# SYNTHETIC APPROACHES TO ALKALOID-SKELETON STRUCTURES VIA INTRAMOLECULAR CYCLOADDITION REACTIONS.

A thesis presented by

LYN BYRON DAVIES

In partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

of the

CITY UNIVERSITY.

THE CITY UNIVERSITY

LONDON

SEPTEMBER 1977

Synthetic Approaches to Alkaloid-Skeleton Structures Via Intramolecular Cycloaddition Reactions

## Abstract

A review of the occurrence and chemistry of the monoterpenoid alkaloids is presented, emphasis being given to current methods of synthesis.

Two principle areas of intramolecular cycloaddition reactions involving heterocyclic systems have been explored. In the first the bimolecular and intramolecular cycloaddition reactions of furan are described. The preparation of various derivatives aimed at extending the scope of the intramolecular cycloaddition process is described. The reactivity of these systems has been explored.

The intramolecular cycloaddition reactions of a series of substituted mono- and dihydroxypyrimidines have been investigated. By substitution of the appropriate alkenyl side chains the cycloaddition process, followed by a retro-Alder elimination of isocyanic acid, yields structures related to the monoterpenoid alkaloid skeleton.

CONTENTS

Acknowledgements.

I sincerely thank Professor Peter G. Sammes for his never-ending help, encouragement and enthusiasm towards the work presented in this thesis.

I thank all my colleagues past and present, for their help and friendship, with special thanks to [redacted] and [redacted].

I gratefully appreciate the advice and assistance given by the technical staff, especially the help of [redacted] in the preparation of starting materials.

Finally, I thank my parents for their unfailing support and encouragement during my years as a student.

TO MY PARENTS

[redacted]

- *Albert Einstein.*

## Introduction.

The major objective of the work presented in this thesis was to develop routes for the synthesis of various alkaloid structures by way of intramolecular cycloadditions across suitable heterocyclic systems.

Much of the work was initiated by R.A. Watt[1], who discovered the ability of olefins to react intramolecularly with certain substituted pyrimidines. It was found that primary cycloadducts could undergo secondary elimination reactions yielding bicyclic products possessing structures similar to those of a specific group of naturally occurring compounds, the monoterpenoid alkaloids.

The occurrence, structure and existing synthesis of these monoterpenoid alkaloids, together with a brief account of their biosynthesis and pharmacology, is discussed in the following literature review.

## The Monoterpenoid Alkaloids.

It is now an established principle that both alkaloids and terpenoids are elaborated by a number of plant families and that, in many cases, the alkaloids consist of terpene conjugates. Terpenoid components may be recognized with varying facility in such alkaloid structures, and the combination of multiples of isoprene units with ammonia, simple amines, and amino-acids frequently occurs in natural products.

Those alkaloids recognized as being conjugates of

modified monoterpenoids (two isoprene units) form the subject of this review. Two previous reviews have appeared[2,3] which cover the literature up to the October 1974 issue (No. 15) of Chemical Abstracts.

Herein a critical summary is made of the literature surveyed up to the July 1977 issue (No. 25) of Chemical Abstracts.

Occurrence and Structure.

Monoterpenoid alkaloids have been found in numerous botanical families and a comprehensive table listing their occurrence has been published.[3]

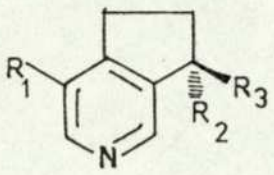
Table (1) lists the main alkaloids subject to the present review together with their proposed structures.

The first monoterpenoid alkaloid to be isolated, gentianine (3:$R^1$=$R^3$=H, $R^2$=CH=$CH_2$), was found more than thirty years ago.[4] Although gentianine is now widely accepted as being an artifact arising from specific isolation techniques,[5] it nevertheless provided a historical basis for structural, synthetic, and biosynthetic research with authentic monoterpenoid alkaloids.

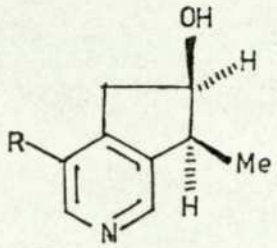
With only a few exceptions, the monoterpenoid alkaloids may be biogenetically related to the iridoid

| ALKALOID | STRUCTURE |
|---|---|
| S-(-)-Actinidine | (1:$R^1$=$R^2$=Me, $R^3$=H) |
| S-(-)-Valerianine | (1:$R^1$=$CH_2OMe$, $R^2$=Me, $R^3$=H) |
| S-(-)-Tecostidine | (1:$R^1$=$CH_2OH$, $R^2$=Me, $R^3$=H) |
| (+)-Boschniakine ≡ (+)-Indicaine | (1:$R^1$=CHO, $R^2$=H, $R^3$=Me) |
| Plantagonine | (1:$R^1$=$CO_2H$, $R^2$, $R^3$=H, Me) |
| Valeriana alkaloid | (1:$R^1$=$CH_2OH$, $R^2$=Me, $R^3$=H) $^+NCH_2CH_2C_6H_4OH$-p |
| Venoterpine ≡ Alkaloid RW47 | (2:R=H) |
| Cantleyine | (2:R=$CO_2Me$) |
| Gentianine | (3:$R^1$=$R^3$=H, $R^2$=CH=$CH_2$) |
| Gentianamine | (3:$R^1$=H, $R^2$=CH=$CH_2$, $R^3$= $CH_2OH$) |
| Gentianadine | (3:$R^1$=$R^2$=$R^3$=H) |
| Gentianidine | (3:$R^1$=Me, $R^2$=$R^3$=H) |
| Gentiatibetine | (4:R=OH) |
| Jasminine | (5) |
| Gentioflavine | (6) |
| Skytanthine | (7) |
| Tecomanine | (8) |
| Arenaine | (9) |
| Bakankoside | (10) |

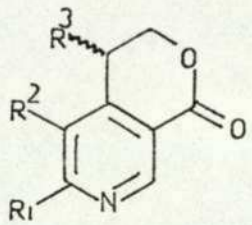
TABLE 1.



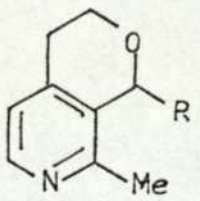
(1)



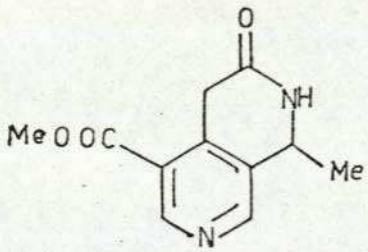
(2)



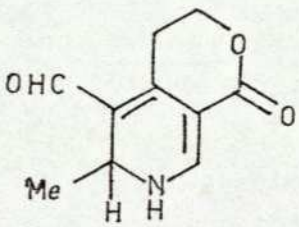
(3)



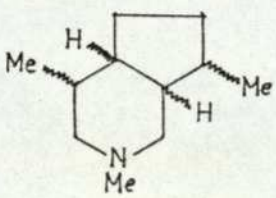
(4)



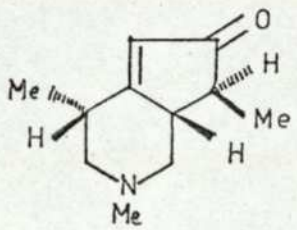
(5)



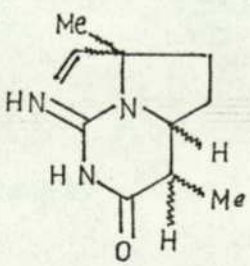
(6)



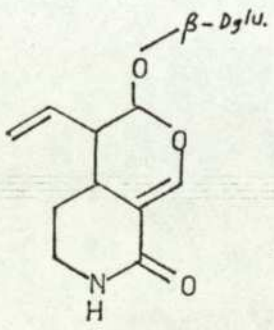
(7)



(8)



(9)



(10)

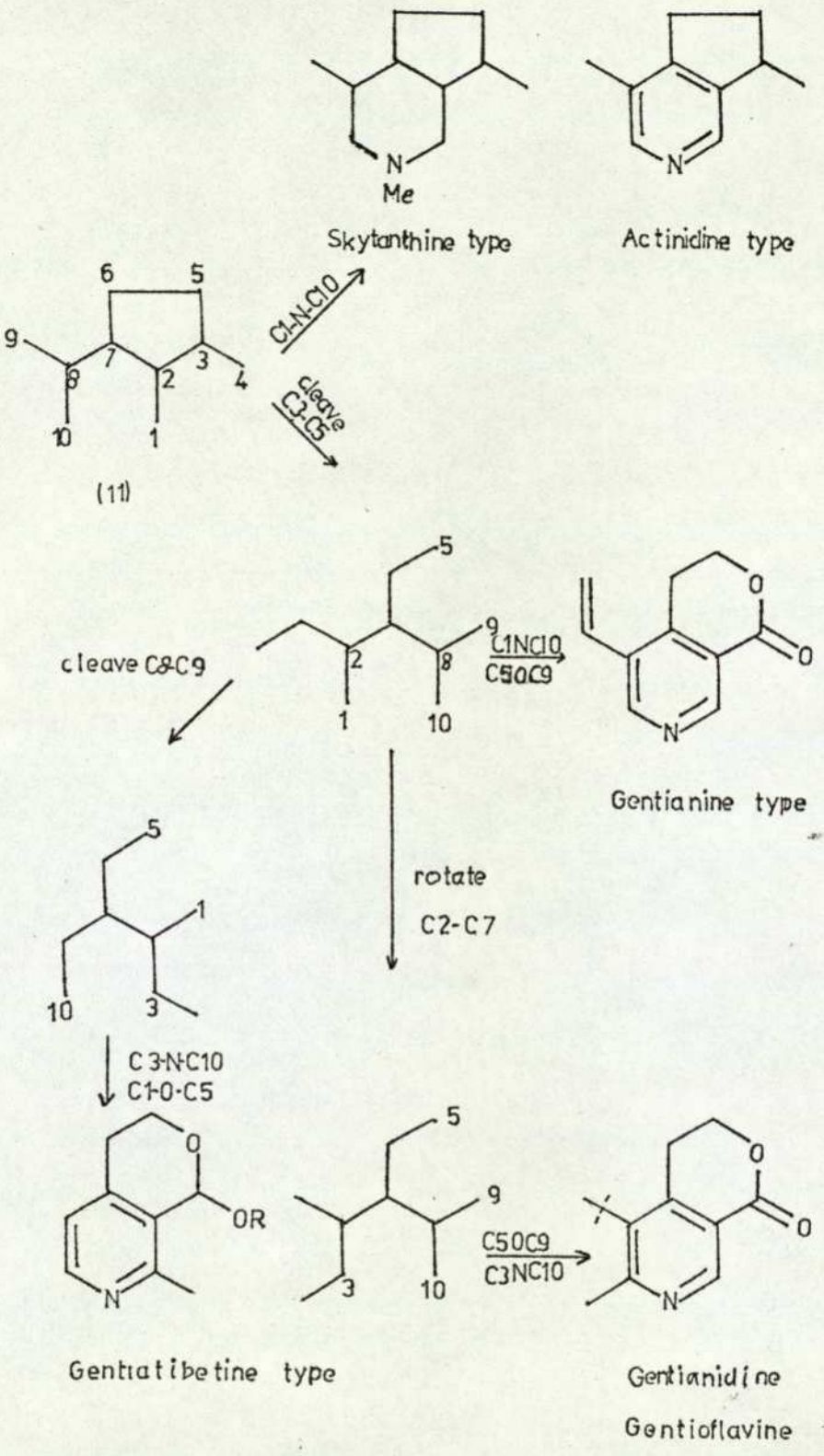

Me
Skytanthine type
Actinidine type
C1-N-C10
cleave C3-C5
(11)
cleave C8-C9
C1NC10
C5OC9
Gentianine type
rotate
C2-C7
C3-N-C10
C1-O-C5
OR
C5OC9
C3NC10
Gentiatibetine type
Gentianidine
Gentioflavine

Figure 1.

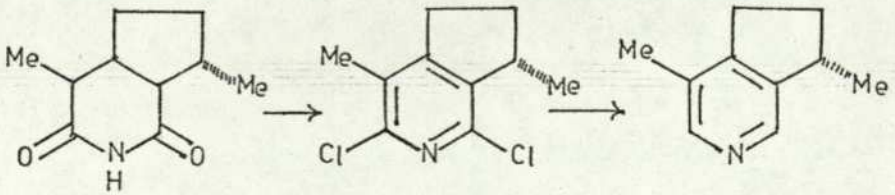
glycoside monoterpenes[6] by the incorporation of ammonia, or its biochemical equivalent. Recognition of this class of alkaloid may, in general, be based on the synthetic structural unit 1,2-dimethyl-3-isopropylcyclopentane (11), which, by appropriate cleavage, nitrogen incorporation at certain sites gives rise to the monoterpenoid family of alkaloids (Figure 1).

## Individual Alkaloids

### Actinidine and related alkaloids.

A relatively large number of alkaloids possessing the pyrindane structure have been isolated and characterised. S-(-)-Actinidine (1:$R^1$=$R^2$=Me, $R^3$=H), was first obtained from Actinidia polygama;[7] more recently from Actinidia arguta[8] and Valeriana officinalis.[8] The structure of actinidine was elucidated on the basis of chemical and spectral evidence and verified by several synthetic routes.

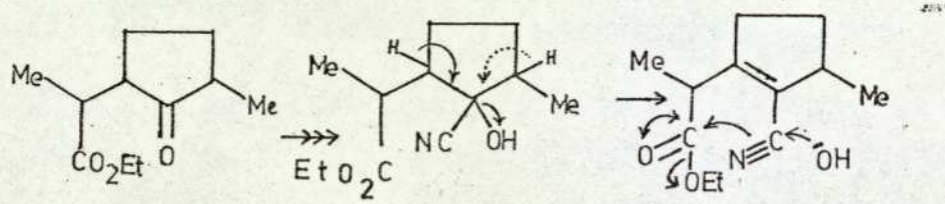
Treatment of nepetalinic acid imide (12) with phosphorus pentachloride gave the dichloropyrimidine (13) which, on reduction in the presence of palladium on charcoal, yielded S-(-)-actinidine.[7]



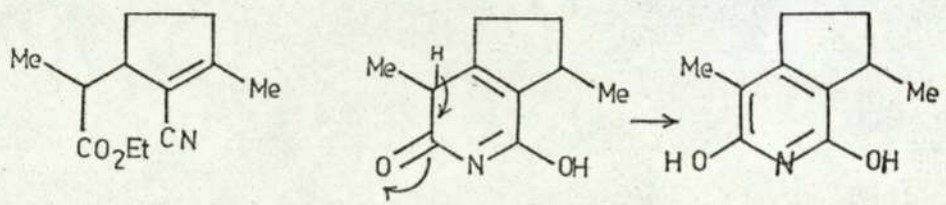

(12) (13) (1,$R^1$=$R^2$=Me, $R^3$=H)

In a second synthesis,[9] ethyl $\alpha$-(3-methyl-2-oxocyclopentyl)-propionate (14) was transformed to the cyanohydrin (15). Dehydration gave a mixtrue of the double bond cyano-ester isomers (16) and (17) which upon hydrolysis led directly to the dihydroxy-pyrimidine (18).

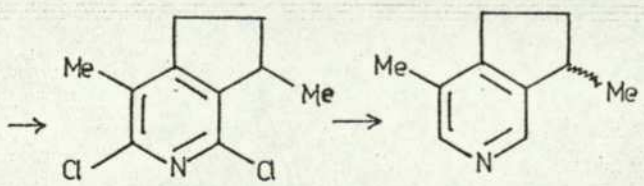
Treatment with phosphorus oxychloride yielded the dichloropyridine (19) which upon reduction led to the isolation of racemic actinidine. Resolution of the monodibenzoyl tartrate salt and regeneration of the free base gave an oil $[\alpha]_D$-8.0° possessing an identical i.r. spectrum and picrate to that of the natural alkaloid S-(-)-actinidine.



(14) (15) (16)

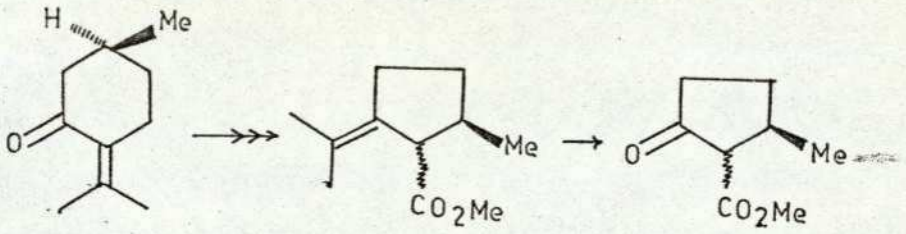


(17) (18)

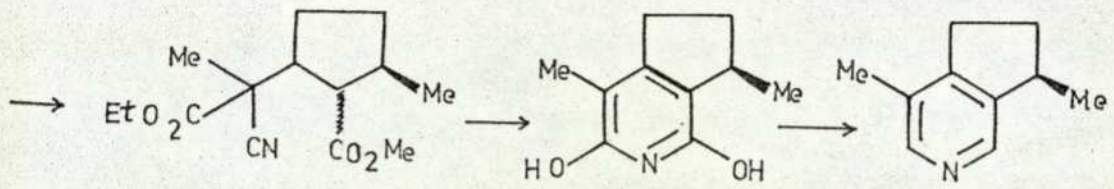


(19)

The enantiomorph of the naturally occurring compound, R-(+)-actinidine, has also been synthesized.[10] Methyl pulegonate (20), derived from R-(+) pulegone (21),[11] was subjected to ozonolysis and the resulting cyclopentanone derivative (22) condensed with ethyl cyanoacetate and then methylated to give (23). Hydrolysis gave a low yield of an optically active dihydroxy-pyridine (24), which, by standard transformations (phosphorus oxychoride followed by reduction), yielded R-(+)-actinidine (25).

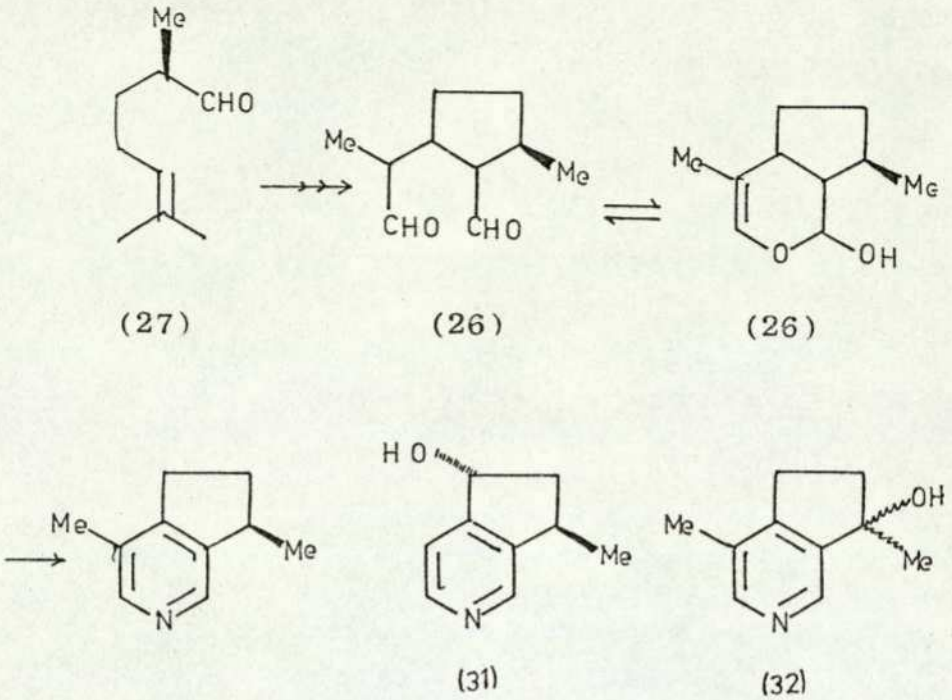



(21) (20) (22)




(23) (24) (25)

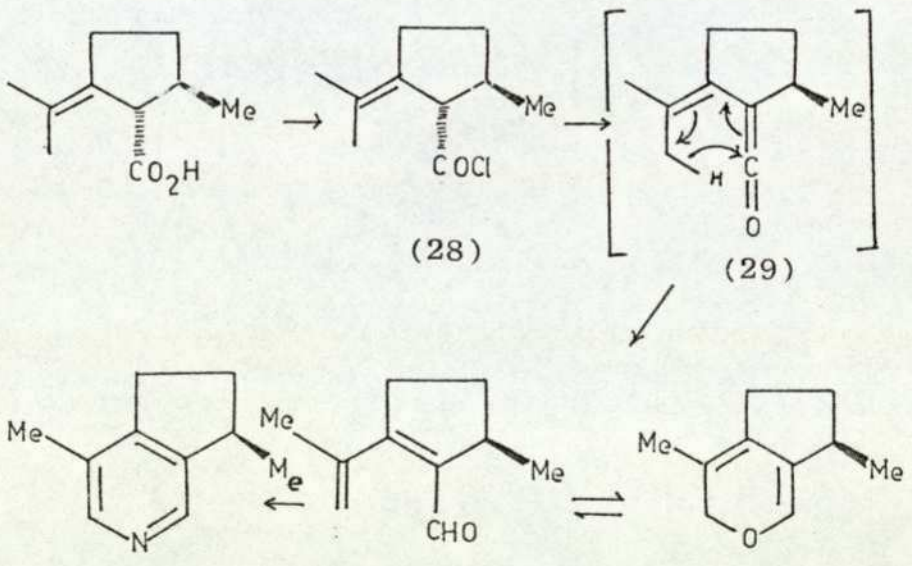
R-Iridodial (26), prepared from R-(+)-citronellal (27)[12], has provided R-(+)-actinidine by reaction with ferric ammonium sulphate in the presence of dilute sulphuric acid.[13]



(27) (26) (26)

(31) (32)

R-(+)-actinidine has recently been synthesized by an interesting route involving a vinyl ketene.[14]



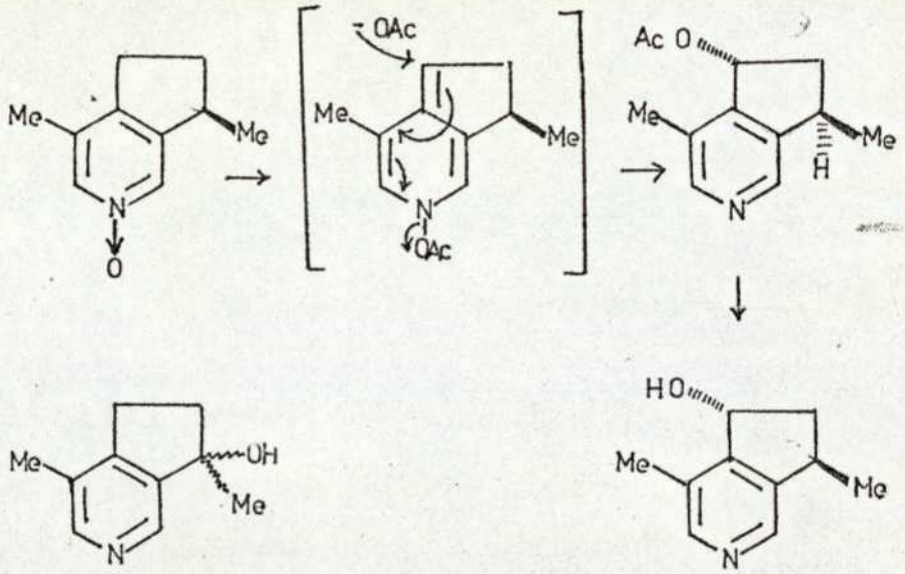
(28) (29)

(30)

(1S,5R)-5-Methyl-2-(1-methylethylidene)-cyclopentane-1-carboxylic acid, prepared from R-(+)-pulegone, was converted to the carbonyl chloride (28). Dehydro-

chlorination led to the vinyl ketene (29) which quickly rearranged by a (1,5)-hydrogen migration, into (R)-5-methyl-2-(1-methyl-ethenyl)-cyclopent-1-ene-1-carboxaldehyde (30). Treatment of the aldehyde with hydroxylamine led directly to R-(+)-actinidine.

Two interesting hydroxyactinidines have been prepared from R-(+)-actinidine.[13] Application of the well-known acetic anhydride promoted rearrangement of pyridine N-oxides[15] followed by hydrolysis gave 5-hydroxyactinidine (31).



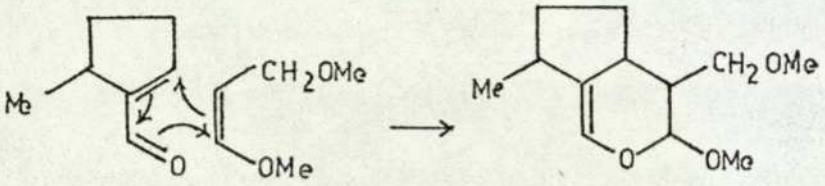

(32) (31)

A single stereoisomer was obtained from this sequence which was assigned the configuration (31), on the basis of the assumed preference for least hindered nucleophilic attack of acetate anion in the intermediate.

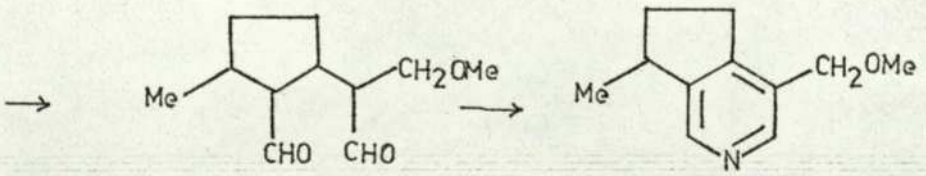
R-(+)-Actinidine was also converted into optically inactive 7-hydroxyactinidine (32)[13], in low yield, by oxidation with cold aqueous potassium permanganate.[13]

S-(-) Methoxyactinidine (1:$R^1$=$CH_2OMe$, $R^2$=Me, $R^3$=H), commonly called valerianine has been isolated from Valeriana officinalis.[16] The proposed structure was consistent with the observed n.m.r. spectral data and was confirmed by an interesting synthesis.[16]

Diels-Alder cycloaddition of 1,3-dimethoxy-propene to the aldehyde (33) provided the dihydropyranyl ether (34) as a mixture of three diastereoisomers. The isomer mixture was converted directly into (±)-valerianine by successive treatment with acid and hydroxylamine (or ferric ammonium sulphate). Resolution of (±)-valerianine was achieved using dibenzoyl tartaric acid and the absolute configuration of the naturally occurring compound assigned on the basis of comparison of its optical rotation with that of S-(-)-actinidine.



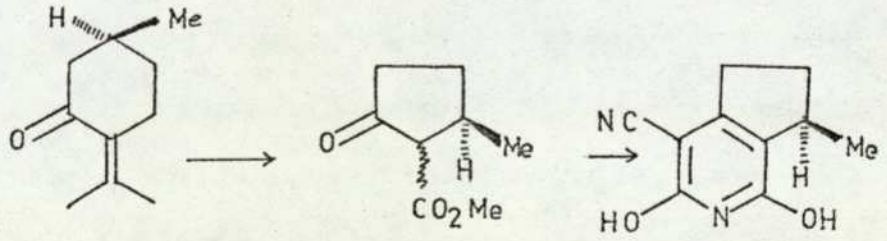

(33) (34)




Valerianine

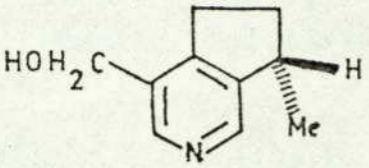
This synthetic route appears to be general, since related alkaloids, e.g. actinidine itself, can be prepared by suitable modification.

S-(-)-11-Hydroxyactinidine (1:$R^1$=$CH_2OH$, $R^2$=Me, $R^3$=H) named tecostidine, was first isolated from Tecoma stans[17] and more recently from Pedicularis rhinantoides.[18] The structure and absolute configuration of tecostidine have been established by the total synthesis of its enantiomer.[13] R-(+)-Pulegone (21) was transformed into 2-carbomethoxy-3-methylcyclopentanone (22) by the previously devised procedure.[11] Condensation (of the keto-ester) with cyanoacetamide in the presence of piperidine gave the dihydroxypyridine (35) which, by conventional transformations (phosphorus oxychloride followed by reduction) led to the cyano-pyridine (36). The nitrile was then converted to the ethyl ester, via the amide, and reduction with lithium aluminium hydride gave R-(+)-tecostidine (37).




(21) (22) (35)

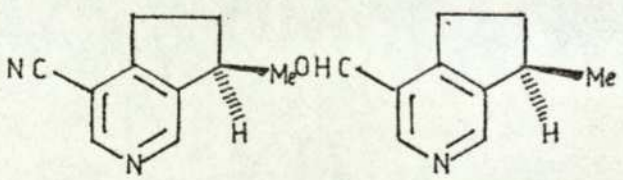

(36) (37)



Tecostidine (1:$R^1$=$CH_2OH$, $R^2$=Me, $R^3$=H)

Attempts to convert tecostidine to actinidine by reduction have so far been unsuccessful because of the inaccessibility of the requisite tosylate.[13]

An alkaloid with the structure (1:$R^1$=CHO, $R^2$=H, $R^3$=Me), named boschniakine, first obtained from Boschniakia rossica,[19] and more recently found in Tecoma stans,[20] is one of the relatively rare actinidine type alkaloids which possess the 7R-configuration. Its structure and absolute stereochemistry were fully established by spectral data and by its synthesis from R-(+)-pulegone.[21] The cyano-pyridine derivative (36) was synthesized as in the case of tecostidine, and was reduced with a large excess of stannous chloride. The resulting aldimine-



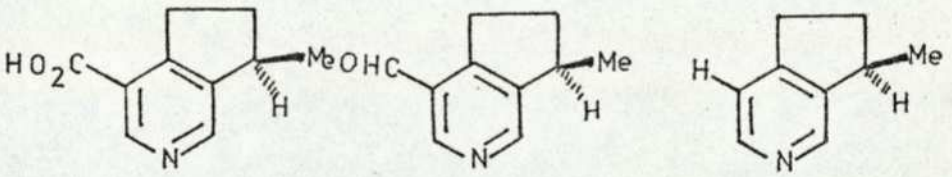
(36) (38)

stannic chloride complex was submitted to steam distillation by which hydrolysis was effected together with the isolation of the required product, boschniakine (38)

(1:$R^1$=CHO, $R^2$=H, $R^3$=Me).

An alkaloid elaborated by Pedicularis olgae[22] and named indicaine, had been earlier isolated by Russian workers and was assumed to be a stereoisomer of boschniakine. It has however, recently been shown[23] to be identical to boschniakine, the earlier difference being due to the formation of a diethyl acetal during picrate derivitisation of one of the alkaloids in ethanolic solution.

Plantagonine, a base closely related to indicaine, was first isolated from Plantago indica,[24] more recently from Pedicularis olgae,[25] and was assigned the structure (1:$R^1$=$CO_2H$, $R^2$=H, $R^3$=Me) possessing the absolute R-configuration [26] on the basis of spectral data and oxidation of indicaine[22] (1:$R^1$=CHO, $R^2$=H, $R^3$=Me), which provided an identical compound.



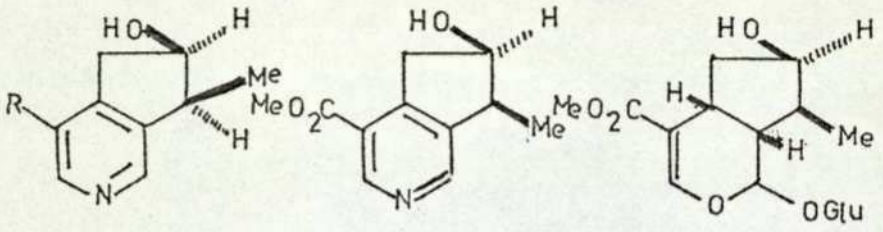

Plantagonine Indicaine (39)

In order to complete the logical oxidation sequence from actinidine ($R^1$=Me) to tecostidine ($R^1$=$CH_2OH$,) boschmakine ≡ indicaine ($R^1$=CHO) and plantagonine ($R^1$=$CO_2H$), only the decarboxylated pyrindane ($R^1$=H)(39) is required.

Such a compound has recently been found in Tecoma stans[20] and Pedicularis macrochilia[27] and given the name 4-noractinidine, although the absolute configuration of

this alkaloid has yet to be determined.

Direct comparison of the physical and chemical properties of alkaloid RW47, isolated from Rauwolfia verticulata and venoterpine (from Alstonia venenata) has established[28] that these two alkaloids are in fact identical and possess the structure and absolute stereochemistry (2:R=H)




(2) (2, R= $CO_2Me$) Loganoside

Although the alkaloid does not contain ten carbon atoms it appears to be closely related, structurally and biogenetically, to the other bases discussed in this review.

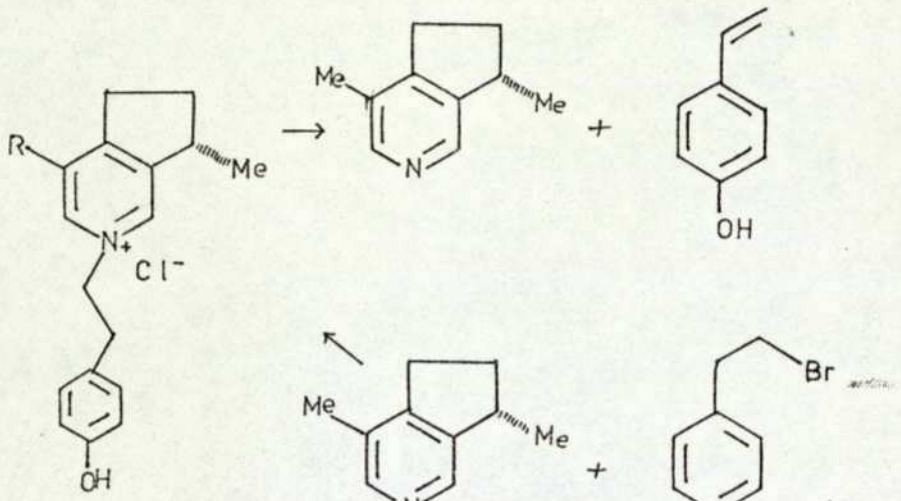
A related alkaloid, named cantleyine, has been isolated from Cantleya corniculata.[29] It has been assigned the structure and relative stereochemistry (2:R=$CO_2Me$) mainly on the basis of an extensive n.m.r. analysis.[28] The proposed structure has been confirmed by its low yield synthesis from loganoside and ammonia. However, further reports have suggested that it is in fact an artifact produced during ammonia treatment of the plant material.[29]

Valeriana Alkaloid.

A quaternary alkaloid isolated from Valeriana officinalis[30] as the chloride has been shown, by chemical and spectral evidence, to be N-$\beta$-(p-hydroxyphenyl)ethyl

actinidine chloride. ((40), $R=CH_3$)[30]

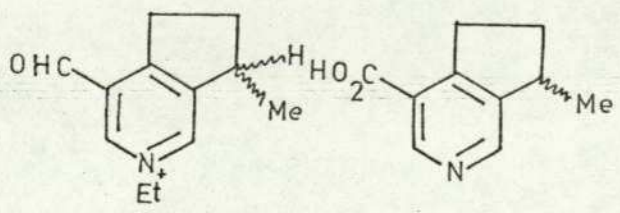
On pyrolysis the alkaloid decomposes into (-) actinidine and p-hydroxy-styrene, and conversely, the alkaloid has been synthesized by the condensation of (-) actinidine with p-β-bromoethyl-phenol,[30] the picrate of the product being identical to that of the natural product.




(40)

The related N-(p-hydroxyphenethyl) derivative of tecostidine ((40) $R=CH_2OH$) has also been obtained from Valeriana officinalis.[30]

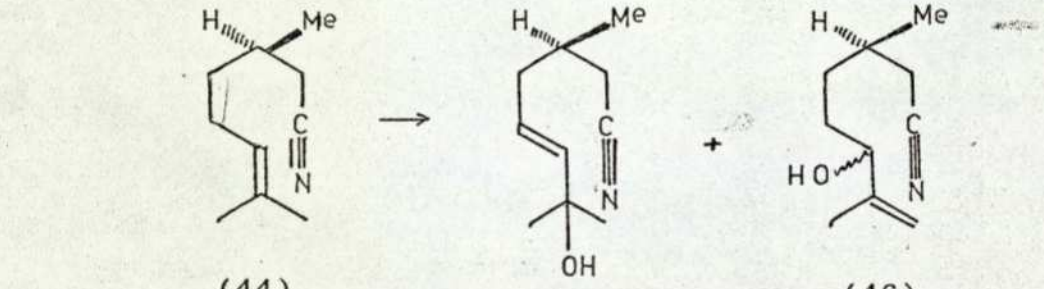
An additional quaternary alkaloid has been obtained from Pedicularis olgae[31] and assigned the structure (41)



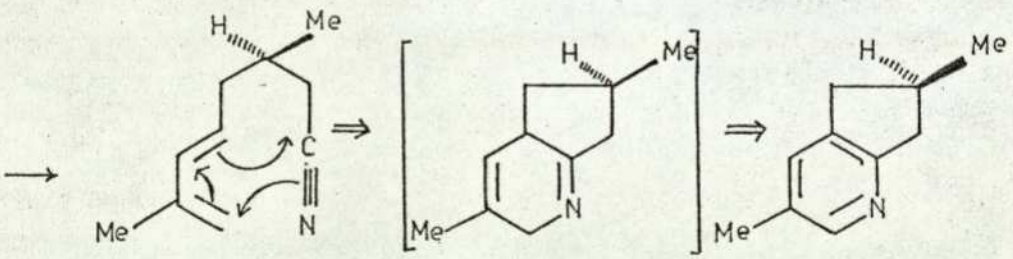

(41) (42)

on the basis of spectral data and an unprecedented selenium dioxide oxidation to plantagonine (42).[31]

Although there has been a lack of extensive synthetic effort on the actinidine type alkaloids an isomer (43) of actinidine has been prepared by an unusual synthetic route.[32] (-)-Citronellonitrile (44) was photooxygenated to give, after reductive work-up, a mixture of allylic alcohols (45) and (46), which upon acid treatment, yielded the diene (47). Upon pyrolysis, the diene suffered an intramolecular Diels-Alder cycloaddition and dehydrogenation, yielding the pyrindane (43).



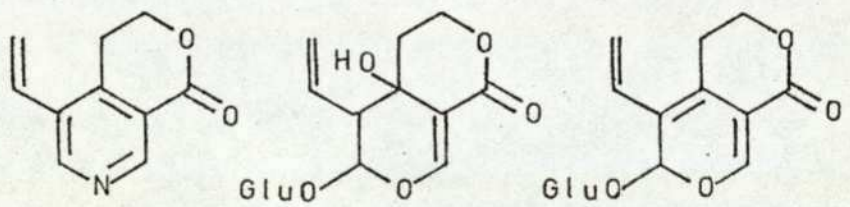
(44) (45) (46)



(43)

Gentianine and related alkaloids.

Gentianine (3:$R^1$=$R^3$=H, $R^2$=CH=$CH_2$), the first monoterpenoid alkaloid isolated, was identified more than thirty years ago.[44] It is now widely accepted that gentianine is in many cases an artifact produced during isolation procedures by the action of ammonia on non-nitrogenous precursors[5] and does not always exist as such in the plant except occasionally in trace quantities. The alkaloid has been isolated frequently from the small family of Gentianaceae,[3] as well as numerous other species.

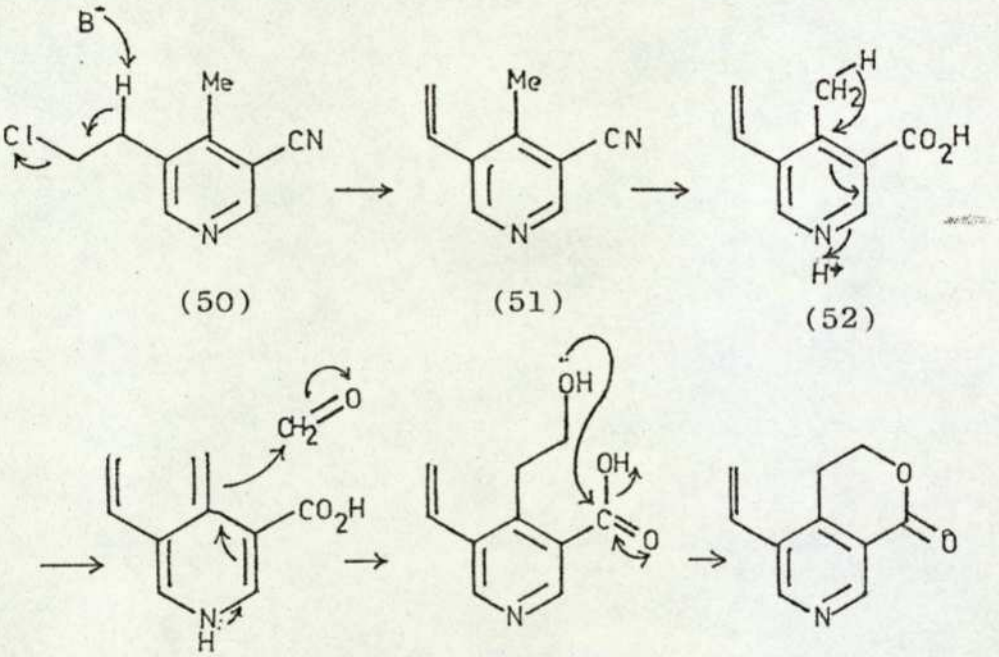



(3:$R^1$=$R^3$=H, $R^2$=CH=$CH_2$) (48) (49)

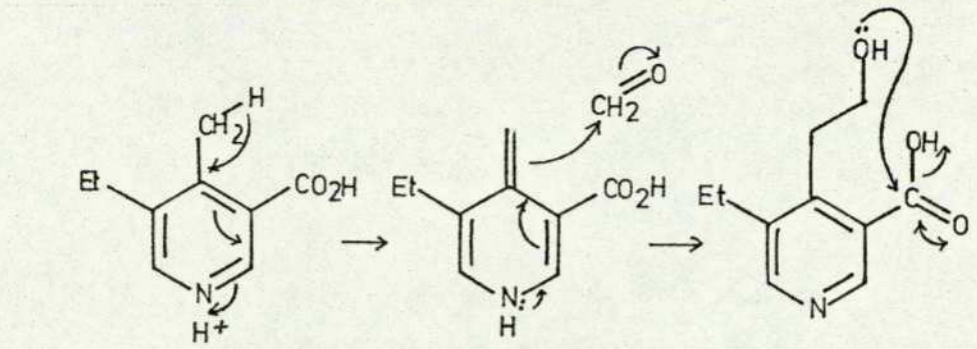
Both swertiamarine (48) a heteroside occurring in Swertia japanoica,[33] and gentiopicroside (49), a common heteroside of the Gentianaceae, are converted into gentianine by treatment with ammonia under very mild

conditions, and have been proposed as precursors for gentianine.[34]

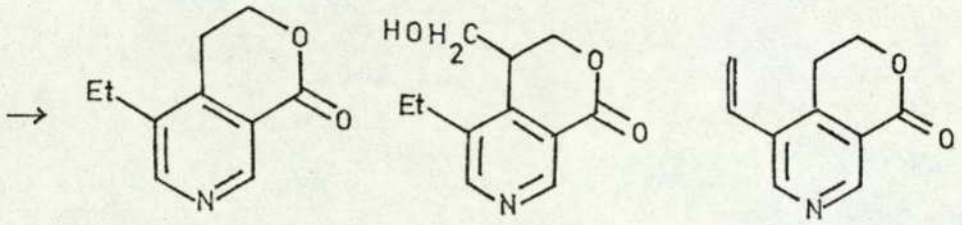
The proposed structure of gentianine has been confirmed by a total synthesis.[9] 5-(2′-Chloroethyl)-4-methyl-nicotinonitrile (50) was transformed into 4-methyl-5-vinyl-nicotinonitrile (51) by use of an excess of diethylamine. Acid hydrolysis then gave the nicotinic acid derivative (52) and treatment of the sodium salt of the acid with formaldehyde gave a moderate yield of gentianine, identical to the naturally occurring compound.




Catalytic hydrogenation of gentianine gives a dihydro derivative (53) lacking absorption at 1634 $cm^{-1}$, identical to the product obtained by the condensation of formaldehyde with the sodium salt of 5-ethyl-4-methyl nicotinic acid (54).[9]



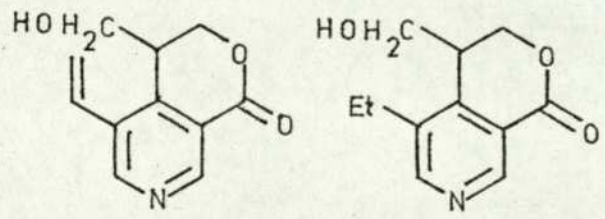
(54)



(53) (55)

Condensation of (54) with two equivalents of formaldehyde produced (55) which was also formed by the action of formaldehyde on dihydrogentianine (53).[9]

A closely related alkaloid, gentianamine (3:$R^1$=H, $R^2$=CH=$CH_2$, $R^3$=$CH_2$OH), has been isolated from Gentiana olivieri[35] and Gentiana turkestanorum.[36] Catalytic hydrogenation of gentianamine has provided dihydrogentianamine[36] (56) identical to the product (55) derived from dihydrogentianine.

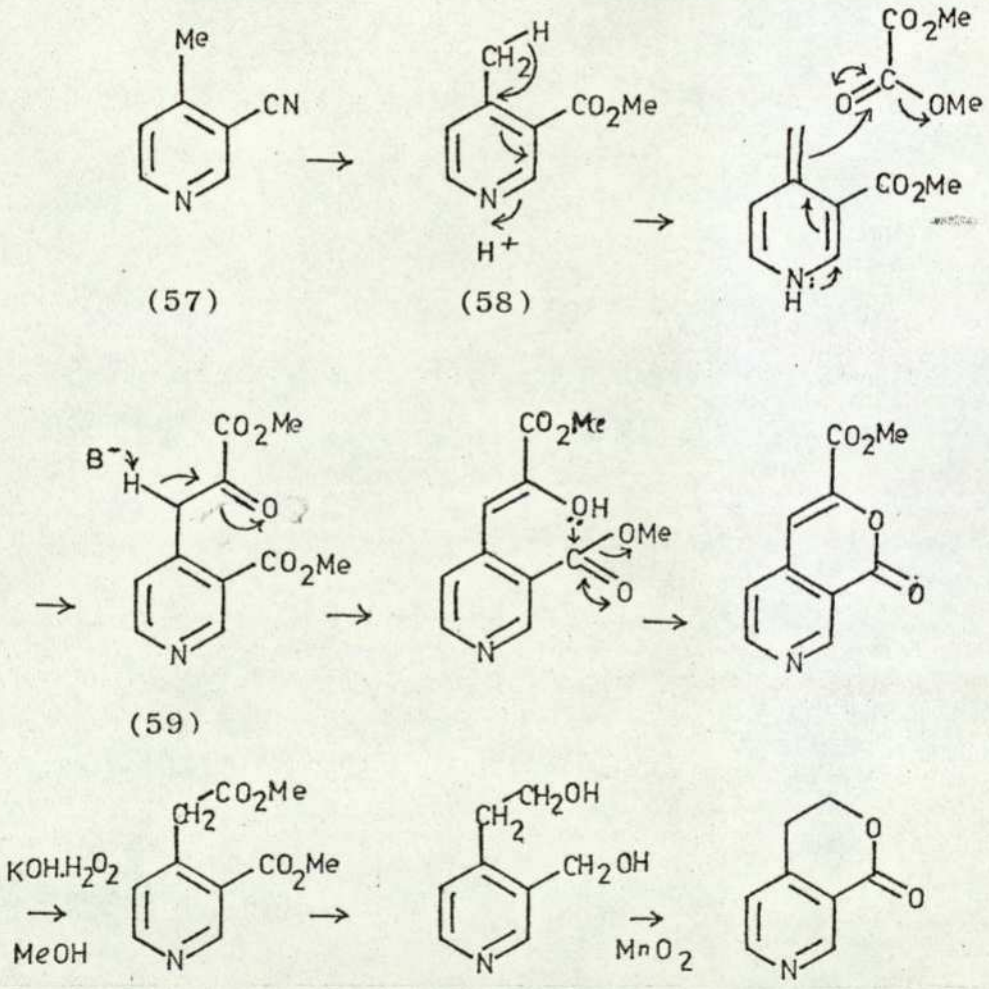


Gentianamine (56)

Gentianadine (3:$R^1$=$R^2$=$R^3$=H), an alkaloid lacking the vinyl moiety of gentianine, has been isolated from several Gentiana species[37] and the proposed structure confirmed

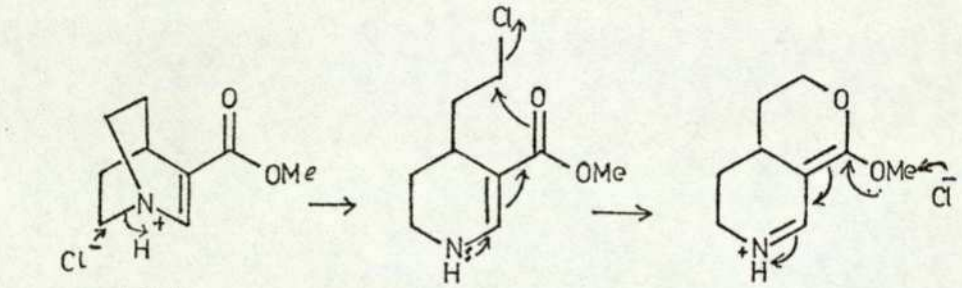
by two synthesis.[38,39]

3-Cyano-4-methyl-pyridine (57) was hydrolysed and esterified to the 3-carbomethoxy derivative (58). Transformation to the diester (59) followed and reduction with lithium aluminium hydride, yielded the dialcohol (60). Treatment with manganese dioxide then produced the lactone (61), identical with naturally occurring gentianadine.[38]

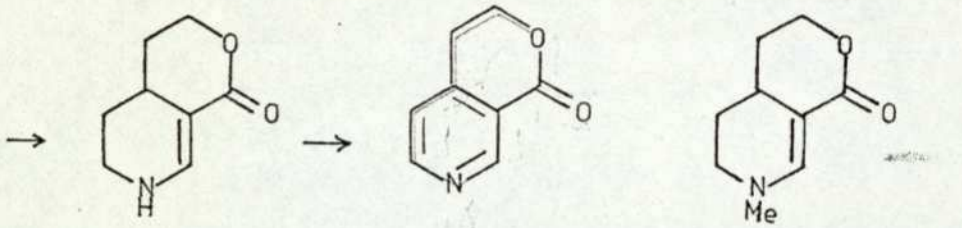



(57) (58) (59) (60) (61)

The second synthesis involved the rearrangement of the quinuclidine hydrochloride (62).[39] Upon thermolysis (62) provided a 70:30 mixture of the tetrahydropyridine derivatives (63) and (64), easily separable by chromatography. Catalytic dehydrogenation of (63) readily provided gentianadine, identical to the authentic natural product.

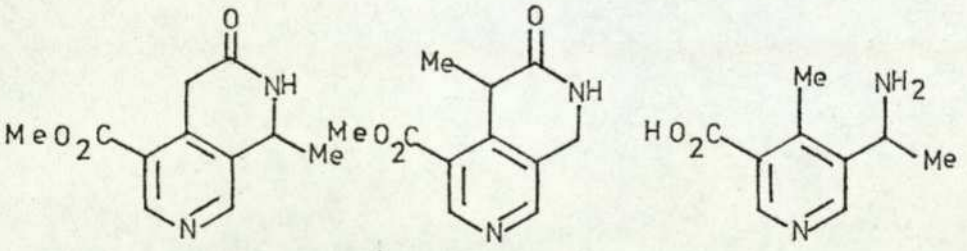


(62)



(63) (64)

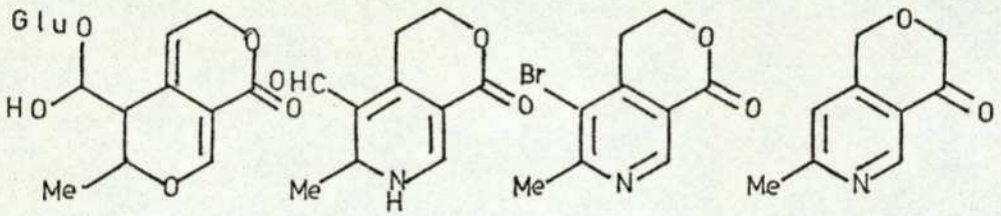
The lactam alkaloid jasminine (5) has been elaborated by several Jasminium species.[40]



(5) (65) (66)

The two alternate structures (5) and (65) were originally proposed but hydrochloric acid treatment of jasminine provided the nicotinic acid derivative (66)[40] conclusively establishing structure (5).

The unusual dihydropyridine alkaloid gentioflavine (6) has been found in several species of Gentianaceae[41,42] and its synthesis from gentioflavoside (67), a monoterpenoid isolated from Gentiana punctata, by treatment with aqueous ammonia has been accomplished.[42]



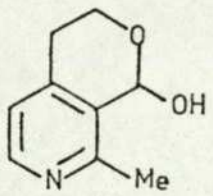

(67) (6) (68) Gentianidine

Reaction of gentioflavine with cold bromine water afforded the basic bromogentioflavine (68), which, upon Raney nickel dehalogenation, afforded a product (69)[42] itself an alkaloid, gentianidine, (3:$R^1$=Me, $R^2$=$R^3$=H).

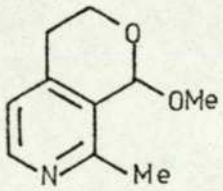
Gentianidine (3:$R^1$=Me, $R^2$=$R^3$=H), formally related to gentioflavine by processes of deformylation and dehydrogenation, was first isolated from Gentiana macrophylla.[43] Its structure was confirmed by synthesis from 4,6-dimethylnicotinic acid[43] and recent studies have suggested that the alkaloid is possibly an artifact.[33]

Gentiatibetine (4:R=OH), elaborated by several Gentiana species, has been characterized mainly on the basis of an extensive n.m.r. analysis.[44] Synthesis of an oxidation

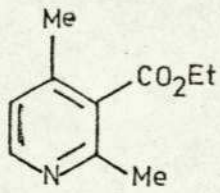
product has also been achieved.[44] Hantzch reaction between crotonaldehyde and ethyl β-aminocrotonate, followed by oxidation, gave the pyridine derivative (70). Condensation with formaldehyde produced a mixture of the lactones (71) and (72) and lactone (71) was shown to be identical to the oxidation product of gentiatibetine.



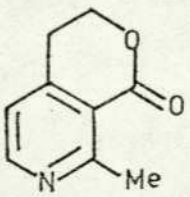
(4, R=OH)



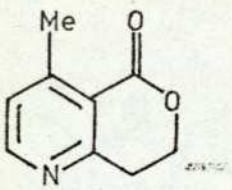
(4, R=OMe)



(70)



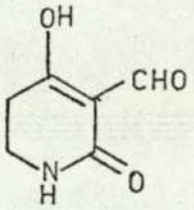
(71)



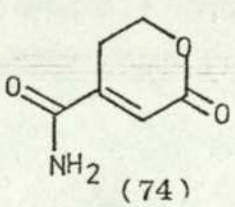
(72)

The related acetal alkaloid, diveridine (4:R=OMe) has been obtained from Gentiana olivieri[35]

It has been noted that certain Gentianaceae plants elaborate compounds which may possibly be degradation products of monoterpenoid alkaloids e.g. gentiananaine (73) and gentiocrucine (74)[45,46]



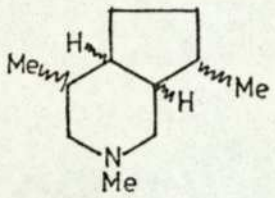
(73)



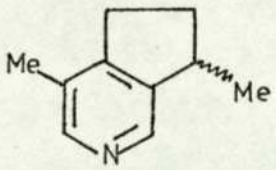
(74)

Skytanthine and related alkaloids.

The skytanthine type alkaloids, possessing the gross structure (7) may be recognized as hydrogenated actinidine-type alkaloids. They were first isolated from Skytanthus acutus,[47] and structure (7) proposed, almost simultaneously by two research groups,[47,48] on the basis of spectral and chemical evidence. The structure was established by catalytic dehydrogenation to a 3,4-disubstituted pyridine which was shown to be identical with (±) actinidine.[47]

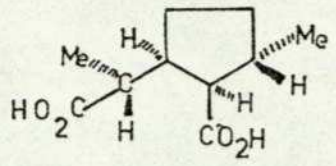



(7)

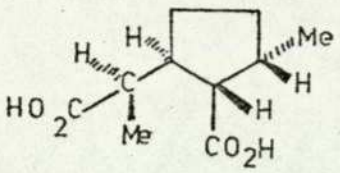



(±) Actinidine

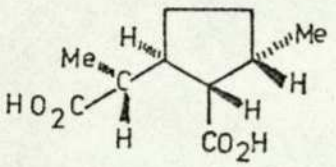
Structure (7) contains four asymmetric carbon atoms and could therefore exist, theoretically, in eight racemic modifications. Skytanthus acutus was originally thought to contain three isomeric skytanthines, proposed as (7α), (7β), and (7δ),[49] the β-isomer predominating. The absolute configuration of each of the naturally occurring stereoisomers was determined by synthesis[49] from the nepetalinic acids (74),+ (75),+ (76),+ (77) of known absolute configuration. Each acid was, in turn, reduced, by lithium aluminium hydride, to the diol, thence to the ditosylate, which upon condensation with methylamine provided each pure isomer.



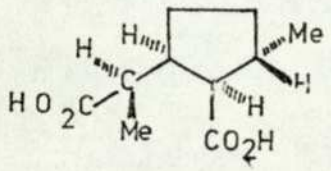
(74)



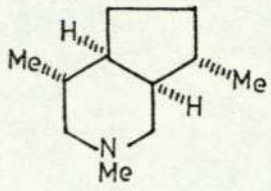
(75)



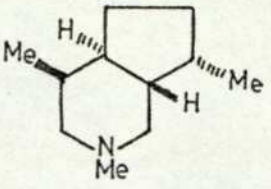
(76)



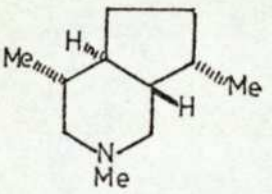
(77)



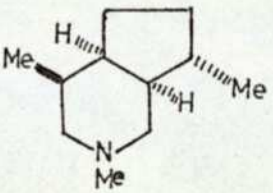
(7 $\alpha$)



(7 $\beta$)



(7 $\gamma$)

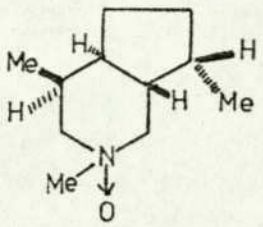


(7 $\delta$)

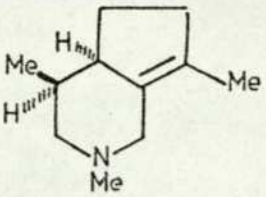
The synthetic and naturally occurring bases were compared by gas phase chromatography and by the melting points of respective picrates. Analysis revealed the presence of $\alpha$ and $\delta$, as well as the $\beta$-isomer, in the mixture of bases regenerated from naturally occurring skytanthine picrate.

Recent evidence has suggested that the $\alpha$ and $\beta$ skytanthines are artifacts, since they are not present in the original extracts of Skytanthus acutus.[50]

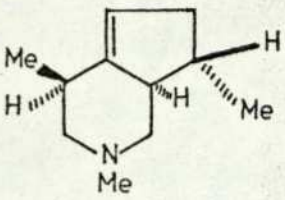
$\beta$-Skytanthine-N-oxide (79) has also been obtained from Skytanthus acutus .[51]



(79)

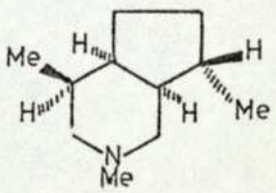


(80)



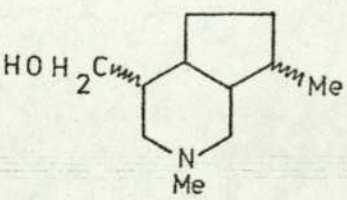
(81)

Two minor alkaloids, proposed as dehydroskytanthines are known: $\Delta^7$-dehydroskytanthine (80) is elaborated by Skytanthus acutus[52] and the $\Delta^5$-dehydroisomer (81) is found in Tecoma stans.[53] Catalytic reduction of $\Delta^5$-dehydroskytanthine (81) has verified the structure by providing $\delta$-skytanthine ($7\delta$).[53]

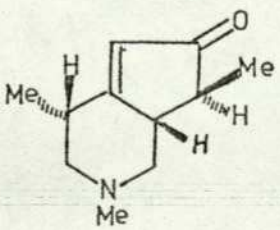


($7\delta$)

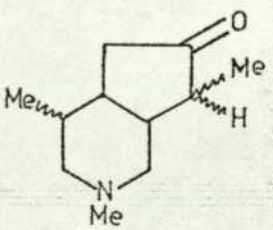
Two other alkaloids possessing the actinidine skeleton, tecomanine (82) and tecostanine (83) have been isolated from Tecoma stans.[54]



(83)



(82)



(84)

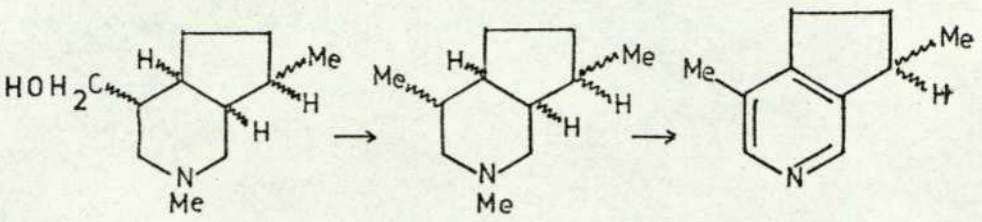
The $\alpha,\beta$-unsaturated cyclopentenone structure of tecomanine was deduced from its U.V. and i.r. (1700,1620 $cm^{-1}$) spectra,[55] whilst catalytic hydrogenation of tecomanine with palladium-charcoal has given predominantly one dihydro derivative (84), possessing a characteristic cyclopentanone i.r. (1740$cm^{-1}$) spectrum.[54]

Catalytic hydrogenation of tecomanine with platinum oxide in glacial acetic acid has given a mixture of saturated ketones, which, on reduction with hydrazine and alkali, gave a mixture of deoxygenated bases.[54] Dehydrogenation of the mixture resulted in the isolation of (±)-actinidine, confirming the proposed structure of tecomanine.

The absolute stereochemistry of tecomanine has recently been determined by a three dimensional X-ray study[56] and is illustrated in structure (82).

Reduction of pure dihydrotecomanine has given an optically active oxygen free base, which is one of the eight possible isomers of skytanthine but which is not identical to any of the four synthetic isomers.[54]

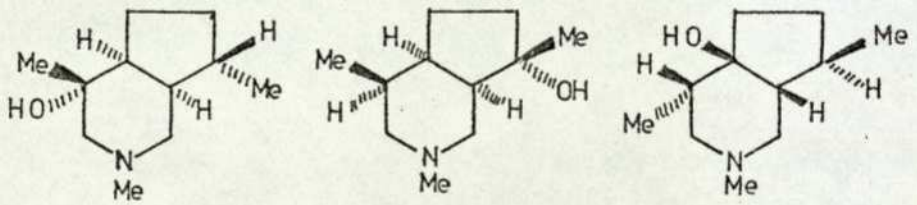
The second alkaloid, tecostanine, has the gross structure (83) but its absolute stereochemistry has yet to be adequately defined. Its structure has been verified by conversion into (±) actinidine by hydride reduction of the tosylate followed by dehydrogenation.[54]



(83) (85)

The deoxybase (85) from hydride reduction, is a further stereoisomer of skytanthine, differing from all those previously observed.

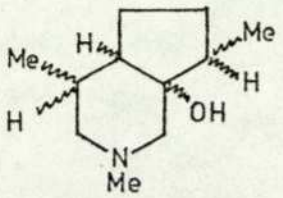
Several hydroxyskytanthines are now known. 4-Hydroxy-skytanthine (86) (also named Alkaloid D, and hydroxysky-tanthine I), was isolated as a minor alkaloid from Tecoma stans[57] and assigned the indicated structure and relative stereochemistry.



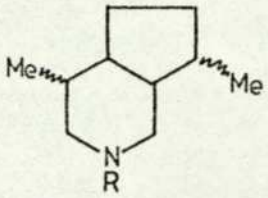
(86) (87a) (87b)

An isomeric alkaloid from Skytanthus acutus,[57] 7-hydroxy-skytanthine (87a)(also named hydroxyskytanthine II) was given the illustrated structure and stereochemistry, whilst another hydroxy skytanthine, found in Tecoma stans[2] has been given the absolute stereochemistry (87b)(named Alkaloid C) on the basis of an X-ray diffraction study of its methiodide.[56]

Subsequently another hydroxyskytanthine has been obtained from Tecoma stans and given the gross structure (88).[58]




(88)



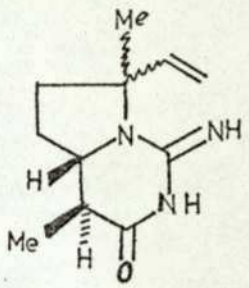

(89)

A further alkaloid, exhibiting no N-methyl absorption in the n.m.r. spectrum has been isolated from Tecoma stans and assigned the N-normethyl skytanthine structure (89, R=H).[58] Upon dehydrogenation it provided (±) actinidine and methylation yielded a "skytanthine", but the absolute stereochemistry has yet to be determined.

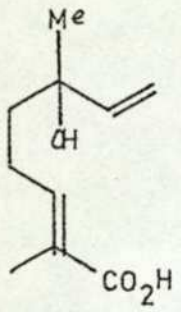
The monoterpenoid alkaloids discussed above all possess fused pyridine type skeletons and have been formed by conjugation of ammonia with a variety of monoterpene units.

Several monoterpenoid alkaloids have been identified as conjugates of urea with monoterpene units and these include arenaine and chaksine.

Arenaine (90) is an unusual monoterpenoid alkaloid isolated from Plantago arenaria.[59,60] It has been assigned the structure and partial stereochemistry indicated mainly on the basis of $^{1}H$ and $^{13}C$ n.m.r. spectra.



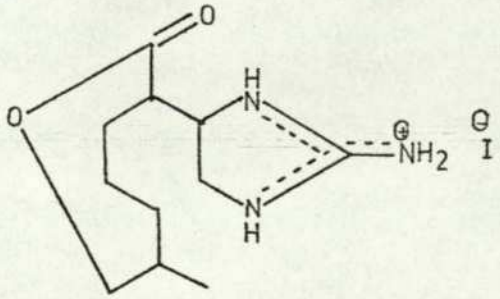

(90)




(91)

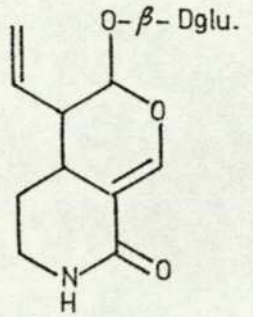
The alkaloid may be dissected, biogenetically, into the acid (91) and guanidine.[60]

A second $C_{11}N_3$ monoterpenoid alkaloid isolated from Cassia absus,[61] and named chaksine, is a cyclic guanido-lactone alkaloid with the structure (92).




(92)

The unique monoterpenoid alkaloid, bakankoside, (93) was isolated from Strychnos vacacoua[62] and characterised as a β-glucoside (93) by hydrolysis with emulsin to D-glucose.




(93)

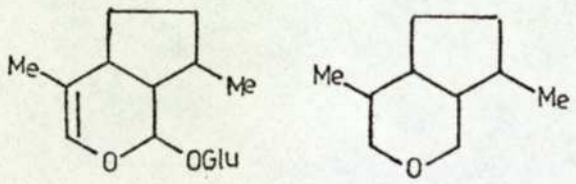
Biogenesis and Biosynthesis.

Despite the common biogenetic origin of the monoterpenoid alkaloids and detailed studies on the non-tryptophan portion of complex indole alkaloids,[63] very few studies on the biosynthesis of the monoterpenoid alkaloids have appeared. Few experiments with radiolabelled precursors have been carried out and most of these have shown only that incorporation can or cannot be achieved without determining the specific sites of incorporation.

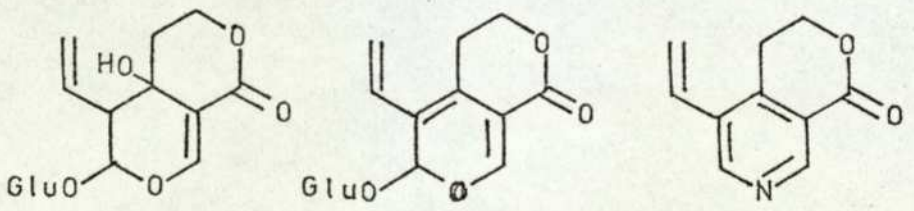
The reasons for this deficiency in the literature may be the lack of systematic degradation sequences which may be used in incorporation studies, problems associated with isolation procedures and the high arti-

fact potential of the alkaloids.

The monoterpenoid alkaloids can be dissected into two isoprene units for which mevalonic acid or isopentenyl pyrophosphate would seem to be precursors. The striking structural similarities between the cyclopentanoid monoterpenes and the monoterpenoid alkaloids suggest that the biosynthesis of both classes of compounds could be similar, involving the intermediacy of the iridoid glycosides, a group of compounds characterized by the cyclopentanopyran ring system (94). Introduction of ammonia (or its biochemical equivalent) at some stage of the biosynthetic process, would appear to be the only major difference in their formation.




(94)




(48) (49) Gentianine

The facile <u>in vitro</u> conversion of swertiamarine (48) and gentiopicroside (49) to gentianine[33], as well as the occurrence of both metatabilactone (dihydronepetalactone) and actinidine in the same plant support this hypothesis.

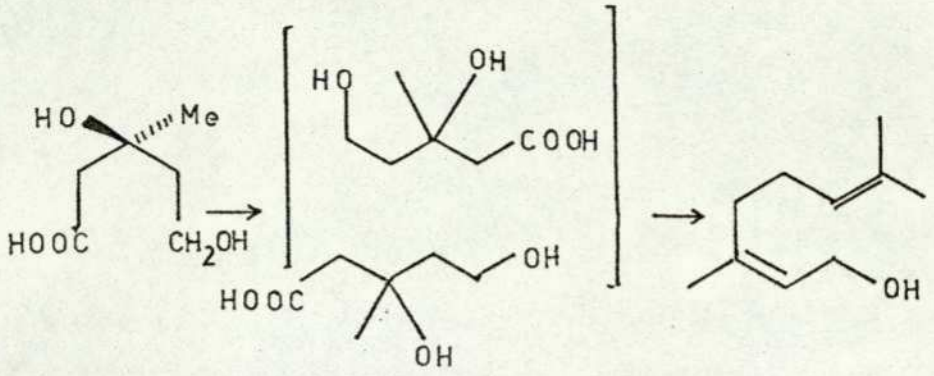
Although the biosynthesis of the monoterpenoid alkaloids seems to correlate directly with that of the iridoids,[64] several questions remain to be answered. The mechanism of closure of the cyclopentane ring and the sequence of various oxidation steps are not completely understood.

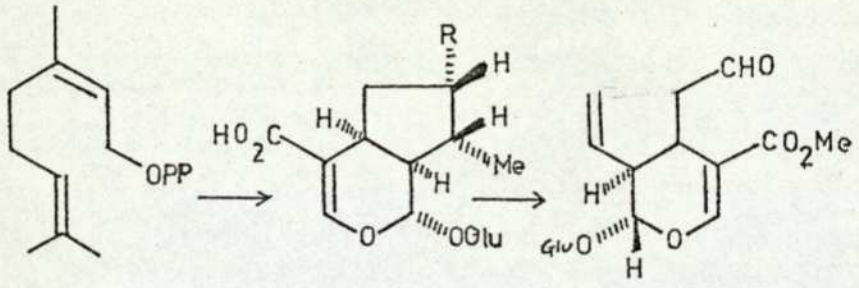
In the absence of knowledge regarding the exact nature of some of the terminal stages of secoiridoid biosynthesis, only a working hypothesis for the biosynthesis of the monoterpenoid alkaloids has been postulated.[3] (Scheme 1.)

Evidence for the isoprenoid origin of actinidine has been provided.[8,64] Good incorporation of [2-$^{14}$C] mevalonate and low incorporation of [2-$^{14}$C] acetate and [1-$^{14}$C] geranyl pyrophosphate into actinidine in Actinidia polygama[8] and Valeriana officinalis[64] have been observed, the results being in agreement with those previously observed in the biosynthesis of the iridoids.

[2-$^{14}$C] Mevalonate has been incorporated in the major alkaloid of Valeriana officinalis.[8]

Mevalonic acid is also an efficient precursor for the skytanthine type alkaloids in Skytanthus acutus.[65] Feeding of [2-$^{14}$C] mevalonate gave radio-labelled $\beta$-skytanthine, the results indicating two biosynthetic pathways: one involving randomization of mevalonate (in young plants), and the second, non-randomisation (in old plants). The explanation put forward was that various amounts of enzyme control occurred, dependent upon the age of the

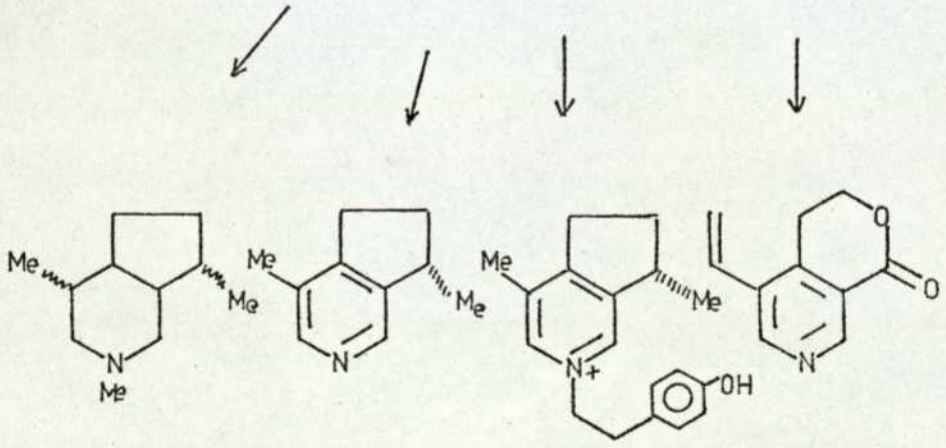



R= H Deoxyloganin

R=OH Loganin

Secologanin




Skytanthine Actinidine Valeriana Alkaloid Gentianine

SCHEME 1.

plant. The former route has been observed for a number of iridoid monoterpenes.

The timing of the introduction of the nitrogen and the possible interconversion of the actinidine and skytanthine type alkaloids remains to be explained.

Although gentianine is in many cases an artifact, biosynthetic experiments have nevertheless been carried out on this alkaloid. [2-$^{14}$C] Glycine has been incorporated into gentianine in Gentiana asclepiadea,[66] and the results suggested a conversion of glycine into acetate, thence via mevalonate into the iridoid monoterpenes.

Several miscellaneous incorporations have also been achieved. [$^{14}$C] Mevalonate has been incorporated into gentioflavine (6) and gentiatibetine (4, R=OH)[67] and [$^{14}CO_2$] has yielded radio-labelled gentioflavine and gentianine in Gentiana asclepiadea.[68]

In summary, actinidine and related alkaloids have been considered to arise from the incorporation of nitrogeneous units in the form of ammonia (or its equivalent from the nitrogen pool) and tyrosine into loganin-type precursors, whilst gentianine and related alkaloids have also been considered to arise from mevalonate through the intermediacy of secologanin by incorporation of ammonia, originating from a nitrogen pool, or in several instances, from the isolation procedure (SCHEME 1).

Pharmacology.

Interest in the monoterpenoid alkaloids has stemmed from their diverse pharmacological effects, reported long before structural elucidation and synthetic work was undertaken.

Injection of crude extracts from Tecoma mollis have been reported to cause a lowering of blood sugar levels.[69]

Gentianine causes a lowering of blood pressure[70] and possesses an anti-inflammatory action as powerful as that of sodium salicylate.[71]

A mixture of crude skytanthines has a stimulating effect on adult male cats[72] and boschniakine may also exhibit physiological effects on Felidae animals.[73]

Valerianine has been reported to possess a sedative action.[16]

Chaksine shows anti-arthritic activity although long term administration leads to toxic effects.[74]

Tecomanine and tecostanine have hypoglycemic effects in the rabbit[75] and gentianine continues to be subjected to other pharmacological examinations.[76]

Summary.

A wide range of conjugates between ammonia and various monoterpene units is found. The example of conjugates from urea and ammonia, such as chaksine, highlights another area of alkaloid chemistry, viz the occurrence of conjugates between amino-acids and monoterpenes. Whilst many of these are found containing rearranged terpene units i.e. loganin-derived systems, relatively few contain unrearranged monoterpene structures.

REFERENCES.


1. R.A. Watt, Ph.D. Thesis, London, 1976.
2. W.I. Taylor and A.R. Battersby. "Cyclopentanoid Terpene Derivatives" Marcel Dekker, New York, 1969. W.C. Wildman, J. LeMen and K. Wiesner. p. 239.
3. V.A. Snieckus. "International Review of Science", Series 2, Volume 9, p. 191.
4. N.F Proskurnina. Chem. Abst. 1946, 40, 7213.
5. D. Gross. Fortsch. Chem. Org. Naturstoffe. 1970, 28, 109.
6. J.M. Bobbitt and K.P. Segebarth. ref. 2. page 1.
7. T. Sakan, A. Fujino, F. Murai, Y. Butsugan and A. Suzui. Bull.Chem.Soc. Japan. 1959, 32, 315.
8. D. Gross, G. Edner, and H.R. Schutte. Arch.Pharm. 1971, 304, 19
9. T. Sakan, A. Fujino, F. Murai, A. Suzui and Y. Butsugan, Bull.Chem.Soc. Japan. 1959, 32, 1155
10. T Sakan, A. Fujino, F. Murai, A. Suzui and Y. Butsugan. Bull.Chem.Soc. Japan. 1960, 33, 712.
11. H. von Rufe and K. Schafer, Helv.Chim.Acta., 1928, 11, 466
12. K.J. Clark, G.E. Fray, R.H. Jaegar and R. Robinson. Tetrahedron. 1959, 6, 217
13. G.W.K. Cavill and A. Zeitlin. Aust.J.Chem. 1967, 20, 349.
14. J D. Wuest, A.M Madonik and D.C. Gordon. J.Org. Chem. 1977, 42, 2111

15. L.A. Paquette. "Principles of Modern Heterocyclic Chemistry." Benjamin, New York, 1968. p.257.

16. B. Franck, U. Petersen and F. Hueper. Angew.Chem. Ind. Edⁿ. 1970, 9, 891.

17. Y. Hammouda and J. Le Men. Bull.Soc.Chim.France. 1961, 2901

18. A.Abdusamatov and S. Yunusov. Chem.Abst. 1970, 72, 51805.

19. T. Sakan, A. Fujino, F. Murai, A. Suzui and Y. Butsugan, Tetrahedron, 1967, 23, 4635.

20. E.M. Dickinson and G. Jones, Tetrahedron, 1969, 25, 1523.

21. L.A. Mitscher, A.B. Ray and A. Chatterjee, Experientia, 1971, 27, 16.

22. K. Ubaev, S. Yunusov and P. Yuldashev, Chem Abst., 1963, 59, 15602.

23. D. Gross, W. Berg and H.R. Schutte, Z.Chem., 1973, 13, 296.

24. A.V. Danilova and R.A. Konovalova, Chem.Abst., 1954, 48, 691.

25. A. Abdusamatov, A. Samatov and S. Yunusov, Chem. Abst., 1976, 85, 74887w

26. K. Torssell. Acta.Chem.Scand., 1968, 22, 2715.

27. A. Abdumatov, A. Samatov, and S. Yunusov, Chem.Abst. 1976, 85, 74887w

28. N.K. Hart, S.R. Johns, and J.A. Lamberton, Aust.J. Chem., 1969, 22, 1283.

29. T. Sevenet, B.C. Das, J. Parello and P. Potier, Bull Soc.Chim.France, 1970, 3120.

30. K. Torssell and K. Wahlberg, Acta.Chem.Scand., 1967, 21, 53.

31. S. Khakimdzhanov, A. Abdumasatov and S. Yunusov, Chem.Abst., 1971, 74, 142118.

32. Y. Butsugan, S. Yoshida, M. Muto, T. Bito and R. Nakashima, Tetrahedron Letters, 1971, 1129.

33. H. Inoye, S. Ueda, and N. Shimokowa, Chem.Abst. 1966, 66, 83102.

34. H.G. Floss, U. Mothes and A. Retting, Z.Naturforsch., 1966, 19, 1106

35. T.U. Ralchmatullaev, S.T. Akramov and S. Yunusov, Chem.Abst., 1970, 73, 84624. Chem.Abst., 1972, 77, 162012.

36. A. Samatov, S.T. Akramov and S. Yunusov, Chem.Abst., 1967, 67, 117007.

37. A. Samatov, S.T. Akramov, S. Yunusov and T. Rakhmatullaev, Chem.Abst., 1971, 74, 136454.

38. J. Dolby, R. Dahlbom, K.H. Hasselgren and J.L.G Nilsson, Acta.Chem.Scand., 1971, 25, 735.

39. J. Dolby, K.H. Hasselgren, S. Castensson and J.L.G. Nilsson, Acta.Chem.Scand., 1972, 26, 2469.

40. N.K. Hart, S.R. Johns and J.A. Lamberton, Aust.J.Chem., 1968, 21, 1321.

41. reference 3, p.206.

42. S.S. Popov and N.L. Marekov, Chem.Ind. (London), 1971, 655.

43. H.T. Liang, T.C. Yu and F.Y. Fu, Chem.Abst., 1965, 62, 5309.

44. F. Rulko, L. Dolejs, A.D. Cross, J.W. Murphy, and T.P. Toube, Roczniki.Chem., 1967, 71, 13247.

45. N. Marekov and St. Popov, Chem.Abst., 1970, 73, 15051.

46. T.U. Rakhmatullaev, S.T Akramov and S. Yunusov, Chem.Abst., 1969, 71, 13247.

47. C. Djerassi, J.P. Kutney, M. Shamma, J.N. Schoolery and L.F. Johnson, Chem.Ind., 1961, 210 and Tetrahedron, 1962, 18, 183.

48. G.C. Casinovi, J.A. Garbarino and G.B. Marini-Bettolo, Chem.Ind., 1961, 253.

49. E.J. Eisenbraum, A. Bright and H.H. Appell, Chem.Ind., 1962, 1242.

50. H.H. Appell and P.M. Streeter., Chem.Abst., 1971, 74, 72815.

51. P.M. Streeter, G. Adolphen and H.H. Appell, Chem. Ind., 1969, 1631.

52. C.G Casinovi, F. Delle-Monache, G. Grandolinie, G.B. Marini-Bettolo and H.H. Appell, Chem.Ind., 1963, 984.

53. D. Gross, W. Berg and H.R. Schutte, Phytochemistry, 1973, 12, 201.

54. Y. Hammouda, M. Plat and J. LeMen, Ann.Pharm.France, 1963, 21, 699.

55. Y. Hammouda and M.M. Motawi, Chem.Abst.,1960, 54, 21646.

56. G. Jones, G. Ferguson and W.C. Marsh, J.C.S. Chem. Commun., 1971, 994.

57. G. Adolphen, H.H. Appell, K.H. Overton and W.D.C. Warnock, Tetrahedron, 1967, 23, 3147.

58. E.M. Dickinson and G. Jones, Tetrahedron,1969, 1523.

59. J. Peyroux, M. Hachem-Mehri, M. Plat, P. Rossignol and G. Valette, Ann.Pharm.France., 1972, 30, 51.

60. A. Rabaron, M. Koch, M. Plat, J. Peyroux, E. Wenkert and D.W. Cochran, J.Amer.Chem.Soc., 1971, 93, 6270.

61. S. Siddiqui and Z. Ahmad, Indian.Acad.Sci., 1935, 2, 421.

62. G. Buchi and R.E. Manning, Tetrahedron Letters, 1960, 5.

63. G.A. Cordell, Lloydia, 1974, 37, 219.

64. H. Auda, G.R. Waller and E.J. Eisenbraun, J.Biol. Chem., 1967, 242, 4157.

65. H. Auda, H.R. Junega, E.J. Eisenbraun, G.R. Waller, W.R. Kays and H.H. Appell, J.Amer.Chem.Soc., 1967, 89, 2476.

66. N. Marekov, M. Arnandov and St. Popov, Chem.Abst., 1970, 73, 11391.

67. N. Marekov and St. Popov, Chem.Abst., 1970, 73, 15051.

68. N. Marekov, M. Arnandov and St. Popov, Chem.Abst., 1970, 73, 970.

69. G.G. Colin, J.Amer.Pharm.Assos. 1926, 15, 556; 1927, 16, 199.

70. E. Steinegger and T. Weibel, Pharm.Acta.Helv., 1951, 26, 259.

71. C.Y. Sung and K.T. Liu, Chem.Abst., 1959, 53, 13415g.

72. H.H. Appel, Scientia, 1966, 33, 1.

73. L.A. Mitscher, A.B. Ray and A. Chatterjee, Experientia, 1971, 27, 16.

74. A. Quayum, K. Khanum and G.A. Miana, Chem.Abst., 1972, 77, 148526.

75. Y. Hammonda and S. Amer, J.Pharm.Sci., 1966, 55, 1452.

76. A.S.C. Wan, E. Macko and B. Douglas, Chem.Abst., 1973, 78, 11686.

# RESULTS AND DISCUSSION

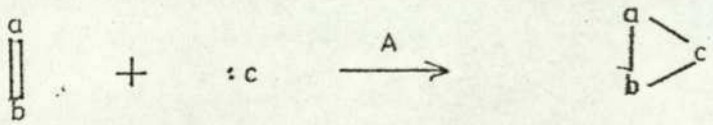
## RESULTS AND DISCUSSION

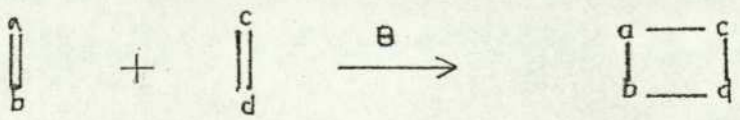
The work presented in this thesis is concerned with the synthesis and attempted intramolecular Diels-Alder cycloaddition reactions of a variety of heterocyclic compounds. Much of this work has originated as a development of previous studies carried out by R.A. Watt[1], who discovered the intramolecular ability of olefins to react with substituted pyrimidine systems.

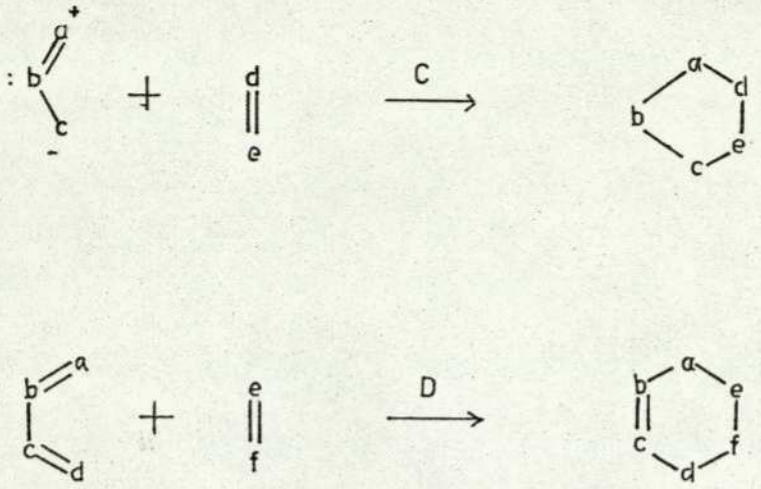
The present study has been restricted to the thermal, ground state, intramolecular combinations of two components in $4\pi + 2\pi$ cycloadditions, and attempts have been made at the incorporation of heterocyclic components into both ene and diene units.

### Cycloaddition Reactions.

Cycloaddition reactions are one of the most important types of reaction used in organic synthesis, giving access to compounds of various ring sizes. Several comprehensive reviews on cycloaddition reactions have appeared.[2,3,4,5]



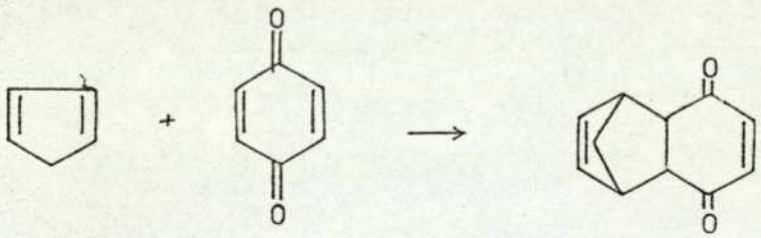





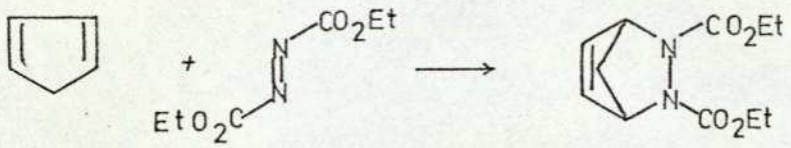

Examples of cycloadditions include carbene and azene additions (A), dimerizations of alkenes and alkynes (B), 1,3-dipolar addition reactions (C) and the Diels-Alder reaction (D). In every case, two new $\sigma$ bond are formed between the reactants at the expense of $\pi$ bonds.

Diels-Alder Reactions in Organic Synthesis

The general applicability of bimolecular (4 + 2)$\pi$ cycloadditions was first recognized by Diels and Alder almost fifty years ago,[6] whose structural elucidations of the 1:1 cycloadducts of cyclopentadiene with p-benzoquinone (1) and diethylazodicarboxylate (2) provided the initial breakthrough to what has now become a very valuable and widely used reaction in organic synthesis.



(1)




(2)

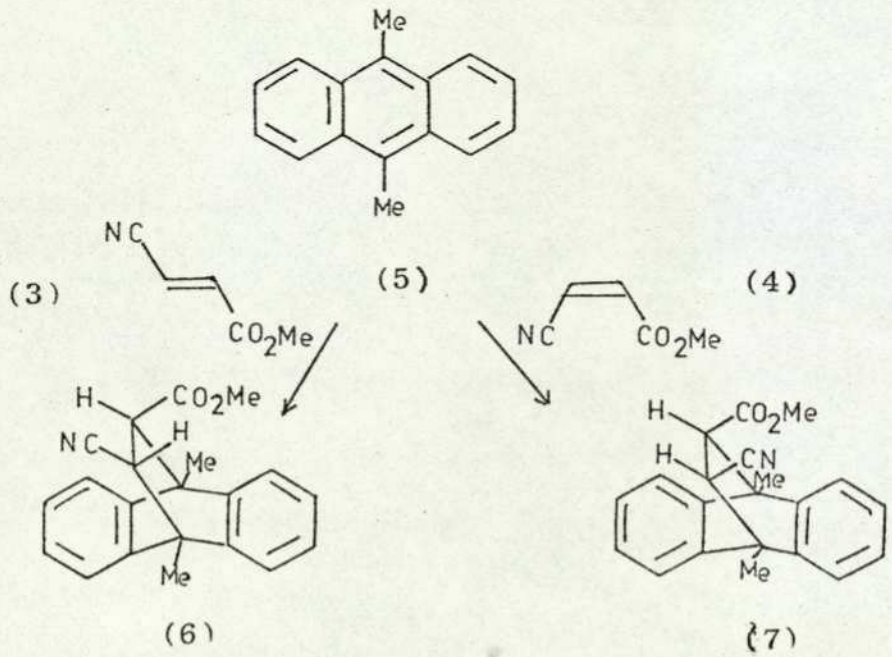
The great attraction of the Diels-Alder reaction, which has since been subjected to several literature reviews,[7,8] is its versatility. Heterocyclic components may be included in either, or both, of the "ene" or "diene" units, which also may, in turn, be linear or part of ring systems.

An inherent advantage of Diels-Alder additions is the control of stereochemistry which can often be achieved. This advantage is particularly valuable in the synthesis of natural products.

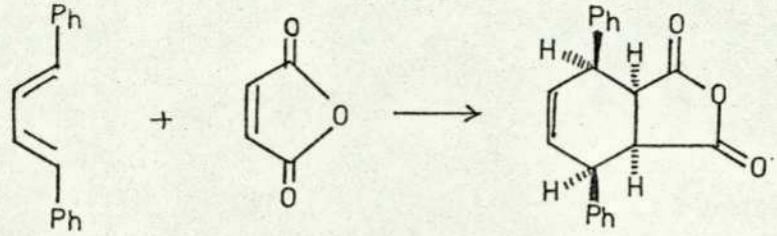
The sterochemical course of single step, concerted cycloaddition reaction is normally governed by the

"Woodward-Hoffmann" Rules,[9] and the concerted nature of the simpler Diels-Alder reactions is confirmed by the observation of the "cis-principle" of product stereochemistry.

Alder and Stein recognized that the steric arrangement of substituents, in both the dienophile and the diene, is preserved in the 1:1 cycloadduct.[10] For example, the isomeric methyl $\beta$-cyanoacrylates (3) and (4) cycloadd with 9,10-dimethyl-anthracene (5) to give the adducts (6) and (7), in which the stereochemistry of the dienophile has been retained, even though the cis-adduct (7) must be thermodynamically less stable than the trans-fused isomer (6) on steric grounds.[11]



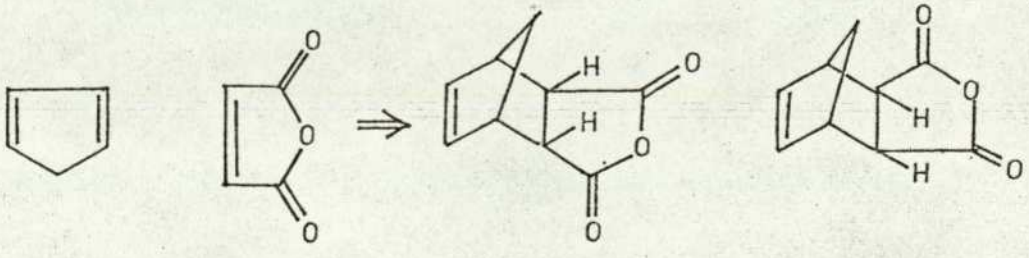

Similarly, the 1:1 adduct from trans, trans-1,4-diphenylbutadiene (8) and maleic anhydride (9), exhibits the stereochemistry in which the phenyl groups are cis to each other.[12]



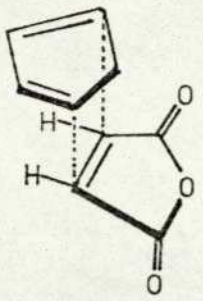
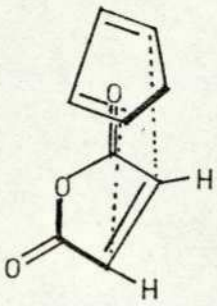
(8) (9) (10)

Observation of the "cis-principle" of product stereochemistry is a confirmation of a concerted reaction because the principle is readily explained by synchronous formation of the bonds between the two components in a one-step reaction. Heterodienophiles also tend to obey the cis-principle.

The course of pericyclic reactions can be determined by several interacting factors, such as substituent effects and secondary orbital interactions. The latter interactions for example, govern the normal preference for endo-transition states leading to cis-fused products in conventional Diels-Alder reactions. This is the Alder Endo Rule and has been illustrated by the cycloaddition of cyclopentadiene and maleic anhydride.[13]



ENDO EXO

EXO ⇍   ⇒ ENDO

After a "sandwich-like" preorientation of the reactants, the dienophile is added in such a way as to give a "maximum interaction" of double bonds in the transition state, including not only the $\pi$ systems directly involved, but also those of the activating ligands.

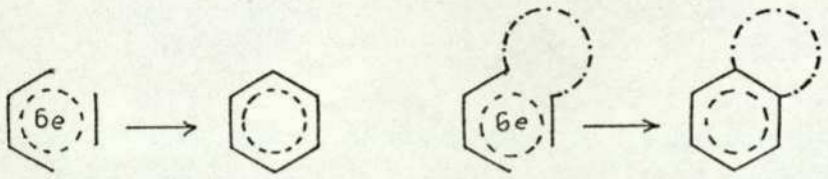
In examining endo-exo product ratios it must however be appreciated that occassionally a facile mechanism for subsequent equilibration of the two products may exist under the reaction conditions.

During the course of preparative experiments, Alder observed that the rate of reaction was often increased by electron-donating substituents (e.g., $N(CH_3)_2$, $OCH_3CH_3$) in the diene and by electron-attracting substituents (e.g., CN, $COOCH_3$, CHO) in the dienophile.[14] This observation was generalised as the "Alder Rule" and the reaction of electron rich dienes with electron deficient dienophiles became an established principle.

It was later observed that reactions formally described as Diels-Alder addition did not always obey this rule. Electron rich dienophiles could add to electron deficient dienes and this process was referred to as an "Inverse Electron Demand" Diels-Alder reaction.[15]

Intramolecular Diels-Alder Cycloadditions.

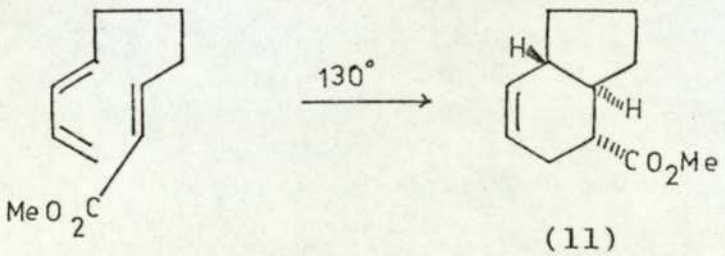
The synthetic scope of the Diels-Alder reaction has been greatly increased in recent years by the principle of intramolecularity.[16,17] Intramolecular Diels-Alder reactions result not only in the simultaneous formation of two rings but also in certain consequences which are superimposed on those of the classical bimolecular variants.



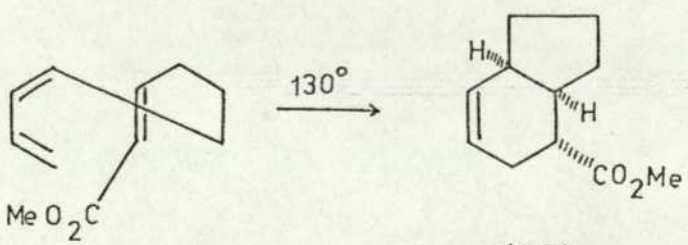

Bimolecular Intramolecular

The first systematic investigation into intramolecular Diels-Alder reactions was carried out by H.O. House in 1965.[18]

Upon heating at 130°, the trans-diene unit in the triene (10) added smoothly to the linked acrylic ester double bond, yielding the trans-annelated hydrindane derivative (11).[18]



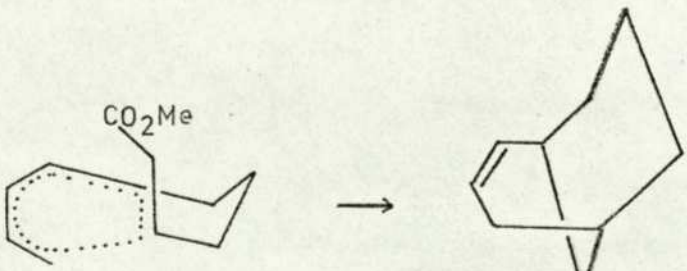

(10) (11)



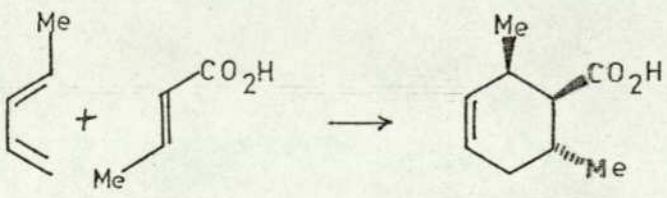

(12) (13)

Surprisingly, under similar reactions conditions, the cis-substituted diene (12) reacted in an analogous manner, but with the exclusive formation of the cis-annelated product (13). Since cis-substituted open chain 1,3-dienes usually undergo bimolecular Diels-Alder reactions only with difficulty, it was concluded that the reaction (12) to (13) profits from entropy factors due to the spatial proximity of the reaction partners, indicating one advantage imposed by intramolecularity. For the same reason, non-activated dienophiles smoothly undergo intramolecular cycloaddition.

Notable features in these intramolecular cycloadditions were the lack of formation of bridged adducts e.g. (15), and the opposite direction of addition compared with that strongly favoured in the bimolecular addition i.e. (16) and (17) to (18)[19]




(14) (15)




(16) (17) (18)

These features were rationalised by a study into the direction and stereochemistry of addition.[18]

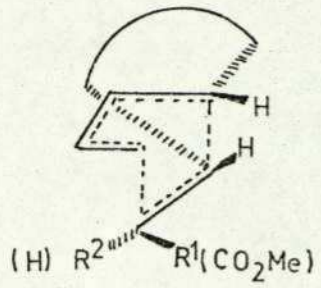
From model considerations, during intramolecular cycloadditions of cis-dienes, the dienophile chain is forced into the exo-position (22), which in this case, is the correct transition state for the observed cis-annelated product.

Two alternative transition states are theoretically possible. The transition state (20) is, however, too strongly strained, thus preventing formation of the trans-annelated product (13). Formation of transition state (24) does not require any deformation of the bond angles and the absence of the bridged adduct (15) from thermolysis of (12) was attributed to entropically favoured easier closure of a 5-membered ring than that of a six membered ring and entropically favoured bond formation between nearer ends of the diene and dienophile.

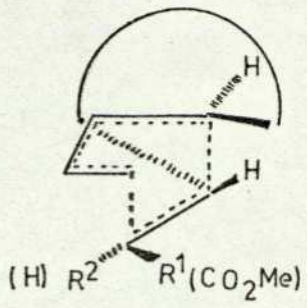
Three feasible transition states also exist for the thermally more stable trans-diene. However the orientation (23) is too highly strained and prevents the formation of a bridge adduct.

The orientations (19) and (21) are both strain free and have a relatively small energy difference which depends upon the bonding and non-bonding interactions, and on other conformational influences that are sometimes less clearly predictable.

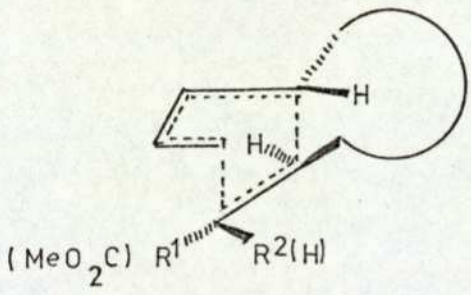
Thermolysis of the trans-diene (10) led to the selective formation of the trans-fused product (11) formed *via* orientation (21), as opposed to the cis-fused product (13) from orientation (19). This observation was rationalised



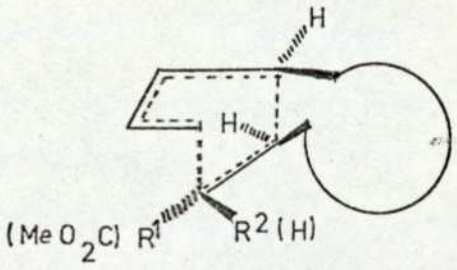

(19)



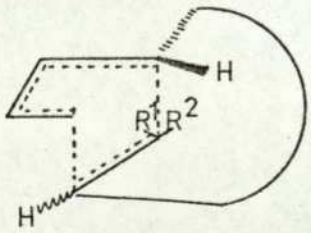

(20)
Strained



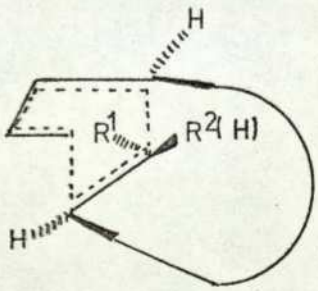

(21)




(22)




(23)
Strained

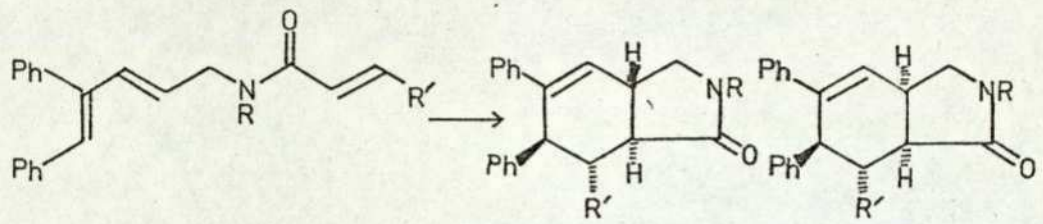



(24)

Figure 2

by a favoured endo-position, of the ester ($\pi$) substituent, as in bimolecular Diels-Alder reactions.[18]

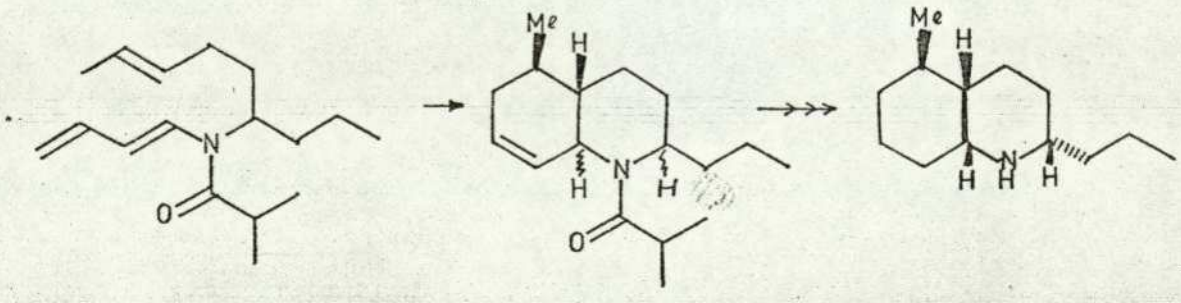
Intramolecular Diels-Alder reactions take place under considerably milder conditions than are required for the analogous bimolecular process.



(25) (26) (27)

The acrylamide((25) R = tert.butyl, R′= H) undergoes an intramolecular Diels-Alder reaction with an activation entropy, $\Delta S^{\neq}$ , which is considerably less negative than that observed in the corresponding bimolecular process.[20,21] As a consequence, not only unactivated dienophiles (e.g. isolated olefins), but also unreactive (e.g. cis-substituted), 1,3-dienes, have been shown to undergo smooth intramolecular additions.

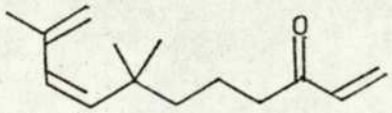
An application of this study has led to the direct synthesis of the physiologically active but almost inaccessible alkaloid pumiliotoxin C (30)[22]



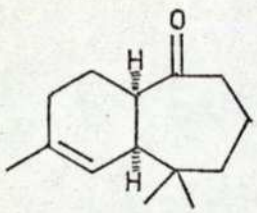
(28) (29) (30)

Upon thermolysis at 215°, the dienamide (28) suffered an efficient intramolecular cycloaddition, giving a stereoisomeric mixture of the adduct (29). Hydrogenation and hydrolysis afforded the alkaloid (30) together with smaller yields of the three alternative stereoisomers.

Bicyclic systems containing seven or more membered rings may be constructed by intramolecular cycloaddition if the distance between the diene and dienophile units is increased. Lewis-acid catalysed conversion of the triene (31) into the annelated cycloheptanone (32) has been achieved.[23]

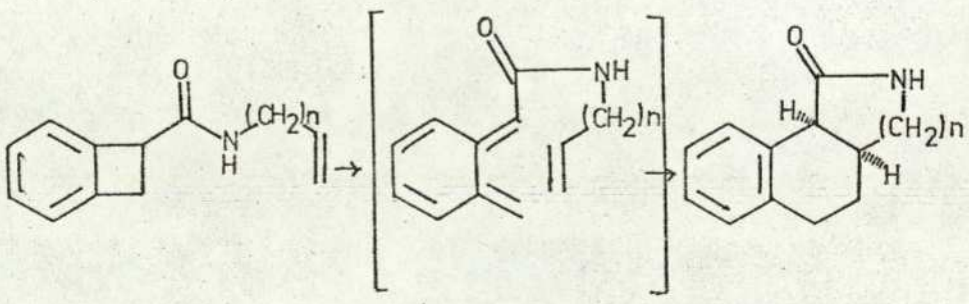



(31)




(32)

However, it must be appreciated that the longer and more flexible the linking bridge, the more the conditions resemble those for bimolecular additions.[24] The validity of this assumption was confirmed by the intramolecular additions of the benzocyclobutenes[24] ((33) a, n = 1, b, n = 2, c, n = 3).[24]

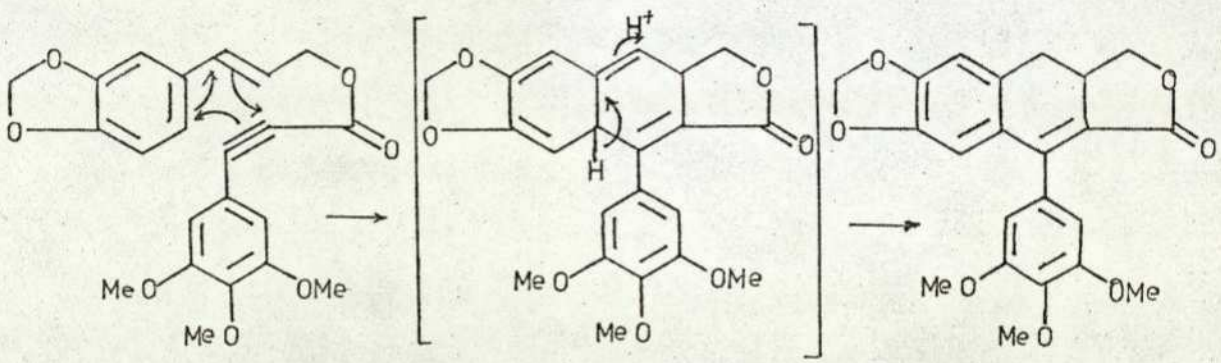



(33) (34) (35)

Upon thermolysis, the benzocyclobutenes underwent a primary reversible opening of the four membered ring giving the non-aromatic (E) - quinondimethane (34) which suffered subsequent irreversible cycloaddition with the linked multiple bond. When n = 1 or 2, the additions occurred smoothly giving ca. 80% yields of the cycloadduct ((35), n = 1 or 2), presumably because of the entropy assistance resulting from the proximity of the reaction partners. The higher homologue ((33) n = 3) however gave the corresponding cycloadduct in a drastically reduced yield (ca. 20%), indicating a loss of reactivity.

Intramolecular cycloadditions of 1,3-dienes which are partly, or wholly, incorporated into a ring may provide complicated ring systems which are only accessible by other routes with difficulty.

A simple synthetic route to the Podophyllum lignans was one of the first applications of an intramolecular $(4 + 2)\pi$ cycloaddition to the synthesis of a natural product.[25,26]




(36) (37) (38)

The naturally occurring lactone (38) was obtained by the thermolysis of the aryl-propargyl ester (36), in which the styrene unit acted as a diene and the triple bond as the dienophile. Aromatization of the intermediate adduct (37) by a (1,3)-hydrogen shift yielded the natural product.

Intramolecular Diels-Alder Reactions of Furans.

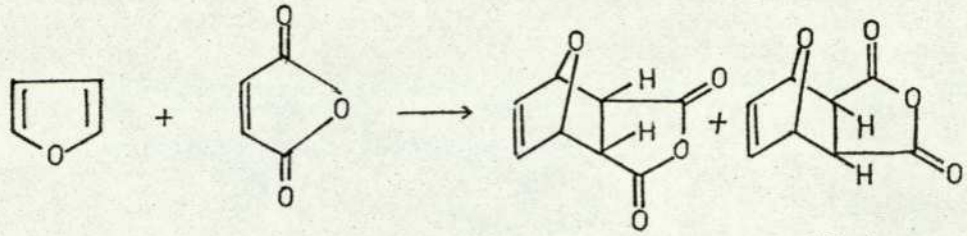
Since the discovery of the Diels-Alder reaction, various heterocyclic nuclei have been thoroughly investigated with respect to their suitability as diene components. Amongst these, the simple heterocycles furan, pyrrole and thiophene have all been studied[8], although their individual behaviours differ considerably.

Furan is one of the more widely used heterocyclic nuclei employed in Diels-Alder reactions, its use dating back to much of the original work carried out on the Diels-Alder reaction.

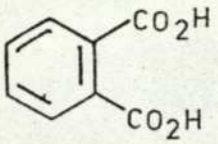
There are numerous examples of bimolecular cycloadditions of the furan nucleus[8] but, at present, surprisingly few examples of intramolecular cycloadditions involving furans have been reported. Furans are particularly useful as diene components in the Diels-Alder reaction since the primary cycloadducts are normally produced under mild conditions and possess numerous possibilities for further modification.

The initial aim of this work was to examine the possibility of increasing the scope of cycloadditions involving the furan nucleus by introduction of the principle of intramolecularity, and to further examine useful modifications of the initial cycloadducts.

Furan itself readily undergoes cycloaddition with maleic acid derivatives yielding oxabicycloheptene derivatives.[27,28] Cycloaddition with maleic anhydride has been shown to produce both the exo-adduct (40) and the less stable endo-adduct (39) which quickly interconverts into the exo-adduct.[27]



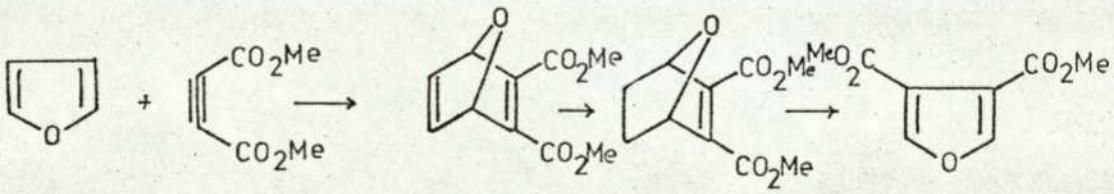
endo (39) (40) exo



(41)

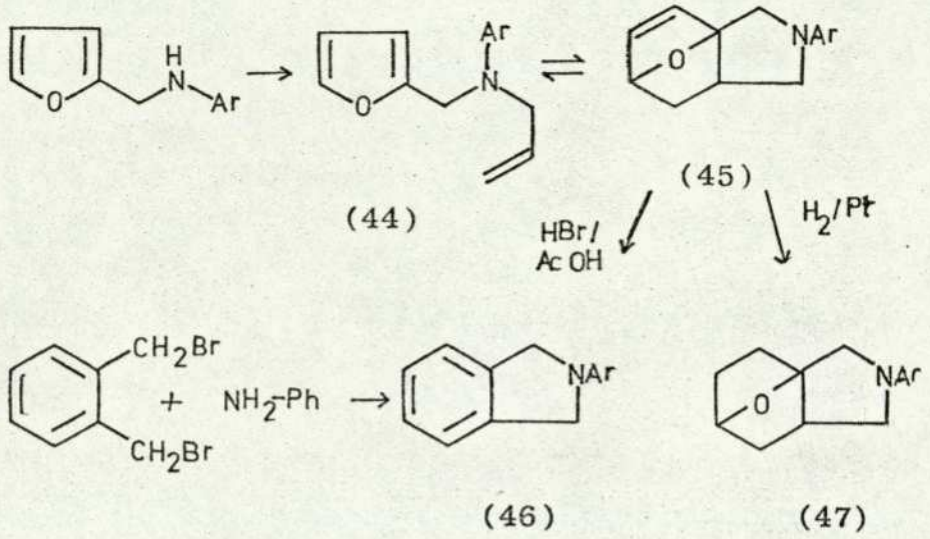
A possible modification of the initial cycloadduct was illustrated by treatment with hydrobromic acid to yield phthalic acid (41).

A notable feature of furan cycloadducts is a pronounced tendency towards redissosciation. Catalytic reduction of the 1:1 cycloadduct of furan and methyl acetylene dicarboxylate produces the dihydro derivative (42), which upon heating undergoes a retro Diels-Alder reaction yielding 3,4-dicarbomethoxy-furan (43) by elimination of ethylene.[29]



(42) (43)

As well as numerous bimolecular cycloadditions[30,31] a facile intramolecular cycloaddition of furan has also been reported.[32]




(46) (47)

Upon standing at room temperature the oily N-allyl-aryl-(2 furfuryl) amines, ((44), Ar = $C_6H_5$, $C_6H_4$-OMe and $C_6H_4$-Me), spontaneously isomerized into crystalline N-aryl epoxyisoindolines (45). The isomerization was rationalised by a mechanism involving an intramolecular Diels-Alder reaction.

The isomerization was found to be completely reversible. An attempt at purification of the isoindoline (45) by vacuum distillation, resulted in the isolation of only the starting amine (44), presumably arising via a retro-Diels-Alder reaction.

The structure of the cycloadduct (45) was confirmed by several reactions; catalytic hydrogenation yielded N-phenylepoxyperhydroisoindole (47) and hydrobromic acid treatment of the adduct afforded N-phenyl-isoindoline (46), identical with an authentic sample prepared from $\alpha\alpha'$-dibromo-o-xylene and aniline.[32]

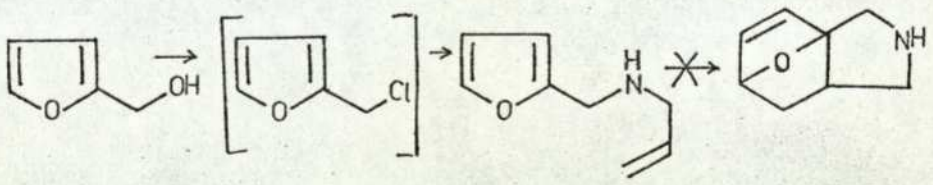
The generality of this cycloaddition was verified to a limited extent by the use of the corresponding toluidine and

anisidine derivatives (Ar = $C_6H_4$-Me and $C_6H_4$-OMe).[32] Although analogous cycloadditions took place, reaction times were considerably larger.

No yields or discussion of stereochemistry were given in the report of these reactions.

Using this reaction as a precedent therefore, it was decided to synthesize alternative N-allyl–furfuryl-amine derivatives, and to investigate their synthetic scope for the preparation of fused heterocyclic rings.

The synthesis of several furfuryl derivatives had been previously reported by Kirner.[33] The method involved formation of unstable furfuryl chloride (48), followed by rapid condensation with amines or alcohols. Adaptation of this method led to the synthesis of (49). Condensation of furfuryl chloride with N-allyl-amine gave a low yield of N-allyl-(-2-furfuryl)-amine (49), a furan capable, by analogy to the published results, of an intramolecular cycloaddition.



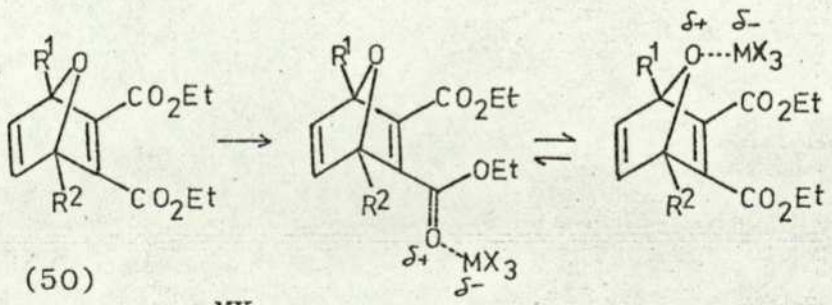

(48) (49)

The infrared spectrum of the reaction product exhibited a broad band centred at 3340 $cm^{-1}$ indicative of a secondary amine (3300-3500 $cm^{-1}$) and a peak at 1615 $cm^{-1}$ which could be assigned to a terminal olefin ($CH=CH_2$) group (1620-1680 $cm^{-1}$).

The $^1H$ n.m.r. spectrum obtained was as expected for the predicted amine, exhibiting a characteristic pattern, consisting of one proton multiplet at $\tau$ 3.90-4.40 and a two proton multiplet at $\tau$ 4.70-5.00, for the olefinic function.

Unlike those previously reported, however, this allyl-amine proved to be indefinitely stable at room temperature; after a period of several weeks no trace of cycloaddition was detected. Consequently, thermolysis of the amine, both neat and in solution, showed no trace of the anticipated cycloaddition; prolonged heating resulting only in the formation of polymerization products.

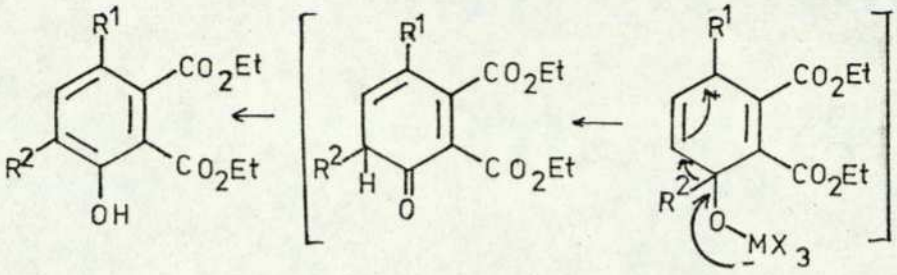
Following this absence of cycloaddition, the effect of catalysts was examined. Intramolecular cycloadditions of the furan nucleus have been shown to be catalysed by the presence of Lewis acids.[34]




(50)

$MX_3$

(especially $BF_3$, $AlCl_3$)



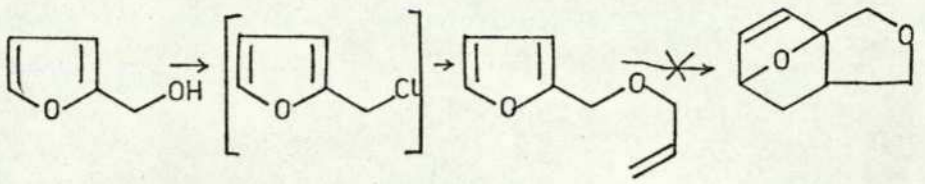
(51)

Upon addition of Lewis acids, a substantial increase in the rate of cycloaddition of diethyl acetylenedicarboxylate, and substituted furans has been observed, yielding the bicyclic adducts (50).[34]

The presence of Lewis acids not only enhanced reactivity of cycloaddition but also promoted the rearrangement of the initial cycloadducts, yielding, in this case, diethyl 3-hydroxyphthalates (51) via the reaction path indicated.

In the case of N-allyl-(2-furfuryl)amine (49) however, addition of Lewis acid (boron trifluoride), failed to promote reaction. Again no trace of cycloaddition was observed, the amine appearing perfectly stable at room temperature, even in the presence of catalysts. Thermolysis of the amine in the presence of catalysts resulted only in the formation of polymeric material.

After the lack of success in this initial attempt at cycloaddition, the incorporation of an alternate heteroatom into the dienophile and diene linking chain was achieved, the oxygen analogue i.e. (52) being the most readily available compound.



(52)

Condensation of furfuryl chloride with allyl alcohol afforded a moderate yield of O-allyl-(2-furfuryl)ether (52).

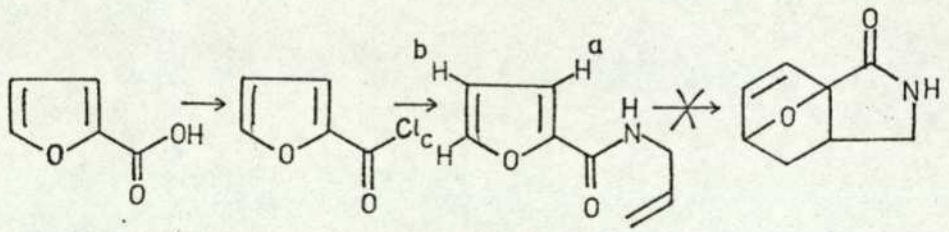
The infrared spectrum of the product showed a band at 1645 $cm^{-1}$ characterisitc for that predicted for a terminal vinyl function (1620-1680 $cm^{-1}$).

The $^{1}H$ n.m.r. spectrum confirmed the proposed structure exhibiting the characteristic one and two proton multiplets at $\tau$ 3.80-4.40 and $\tau$ 4.55-4.97 for the olefinic protons.

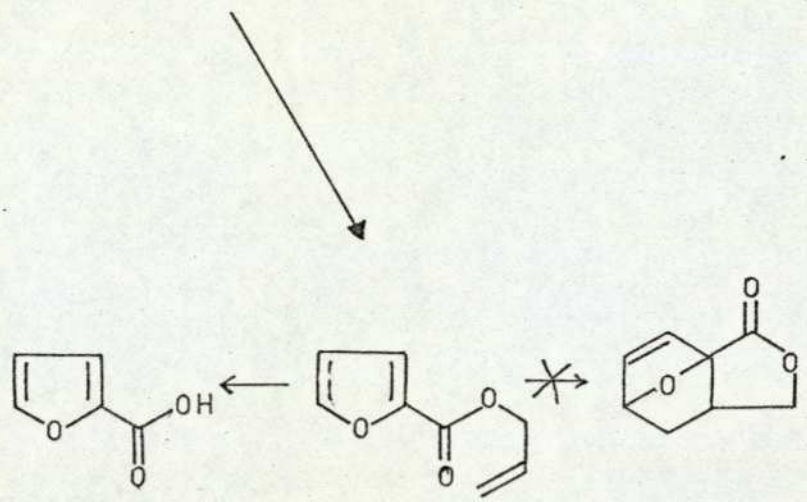
Upon standing at room temperature, the allyl ether was observed to be stable, no trace of cycloaddition being detected. Addition of Lewis-acid catalysts had no apparent effect as did the addition of traces of strong bases[35] and mercuric salts,[36] both of which have been shown to possess some catalytic activity.

Upon thermolysis at 120° in a sealed tube, chromatography and spectroscopy showed no trace of any reaction, whilst thermolysis at 195° resulted only in partial decomposition of the starting material with again no trace of the predicted cycloaddition.

The analogous furoyl-allyl-amine (53) and furoyl-allyl-ether (54) were synthesized by a similar route. Refluxing 2-furoic acid (55) with thionyl chloride afforded the stable acid chloride (56)[37] exhibiting a peak at 1780 $cm^{-1}$ in the infrared spectrum.



(55) (56) (53)



(54)

Condensation of furoyl chloride with allyl amine gave N-allyl-(2-furoyl)amide (53) in good yield.

Synthesis of these furoyl derivatives proved to be more satisfactory than that of the corresponding furfuryl derivatives, mainly because of the extreme instability of furfuryl chloride, which could not be isolated as a pure compound but necessitated use as an ethereal solution. Additionally, furoyl derivatives can normally be trans-

formed into the corresponding furfuryl derivatives by selective reduction, generally using lithium aluminium hydride.[38]

N-Allyl-(2-furoyl)-amine was isolated as an oil, exhibiting a sharp peak at 1680 $cm^{-1}$, characteristic of an amide carbonyl group (1670-1700 $cm^{-1}$), a broad band at 3400-3300 $cm^{-1}$ indicative of the N-H group and a peak at 1645 $cm^{-1}$ confirming the presence of a terminal olefinic group (1620-1680 $cm^{-1}$).

The $^1H$ n.m.r. spectrum exhibited several interesting features. The 3-furoyl proton ($H_a$) existed as a doublet (J= 1.5 Hz), but was downfield by almost 1 p.p.m. relative to the furfuryl derivative. This observation was attributed to the deshielding effect of the adjacent carbonyl group. The chain methylene protons appeared as a triplet indicating coupling to both the adjacent C-H and N-H protons. The olefinic protons were again observed as a one proton multiplet at $\tau$ 3.75-4.40 and a two proton multiplet at $\tau$ 4.60-4.94.

The amide (53) was again very reluctant to participate in an intramolecular cycloaddition reaction, appearing to be indefinitely stable at room temperature even in the presence of catalysts. Thermolysis of the compound, even at relatively low temperatures, resulted only in polymerization with no indication of any cycloaddition processes.

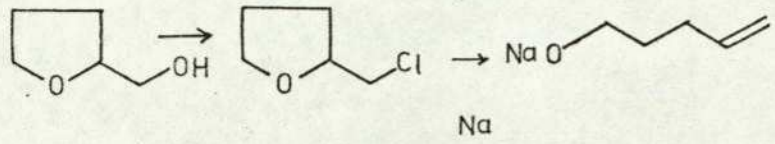
The analogous furoyl allyl ether (54), was prepared by a similar route employing allyl alcohol in place of allyl amine. The compound appeared to be relatively unstable. $^1H$ n.m.r. examination of the crude reaction

mixture indicated the presence of the required product but all attempts at purification of the crude oil by vacuum distillation resulted in the formation of a crystalline material which proved to be identical to an authentic sample of 2-furoic acid, presumably arising from base catalysed hydrolysis.

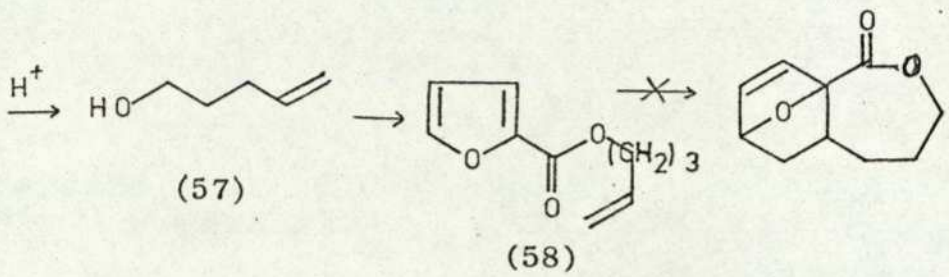
Intramolecular cycloadditions of molecules in which the diene and dienophile linking bridge is flexible and contains more than three atoms tend to follow reaction courses very similar to these observed in the corresponding bimolecular processes.[24] Since the furan nucleus is normally highly reactive towards bimolecular cycloadditions it was thought feasible that the previously attempted intramolecular additions had been prevented by failure of the system in adopting a conformation suitable for addition. Certain torsional strains in the linking chain are possibly eliminated by an increase of chain length.

The synthesis of a furan molecule containing a five-atom linking chain was achieved.

Pent-1-en—5-ol (57) was prepared from tetrahydrofurfuryl chloride by the method of Brooks.[39,40] Treatment of the alcohol (55a) with thionyl chloride yielded the chloride (56a), which, upon treatment with sodium suffered ring opening to provide pent-1-en—5-ol (57). Condensation of this alcohol with furoyl chloride gave N-pentenyl-(2-furoyl)ether (58).



(55a) (56a)



(57) (58)

The infrared spectrum of the furoyl ether exhibited a conjugated carbonyl band at 1720 $cm^{-1}$ together with a smaller peak at 1645 $cm^{-1}$ attributed to a terminal olefinic group.

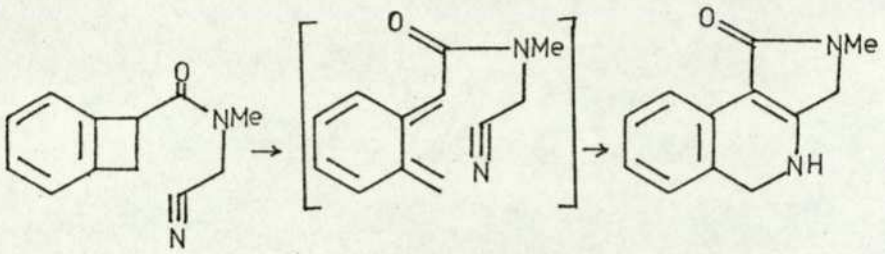
The $^{1}H$ n.m.r. spectrum corresponded to that predicted for the required product.

However, the ether again appeared to be stable at room temperature, both with and without traces of catalysts. Upon thermolysis in a sealed tube, at elevated temperature, only partial decomposition was observed, with no trace of the anticipated cycloadduct.

Following the failure of these attempted cyclo-additions, it was considered that the incorporation of an electron-rich dienophile into the appropriate furan molecule could perhaps increase the chance of a successful reaction.

An excellent precedent, utilising the intramolecular

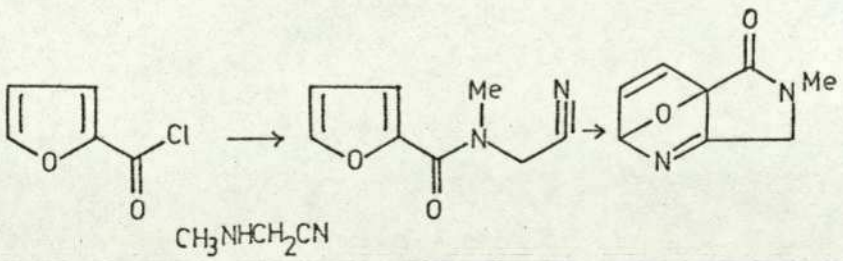
Diels-Alder addition of a nitrile had been reported by Oppolzer.[41] Although nitriles are normally relatively unreactive Diels-Alder species, thermolysis of the benzocyclobutene derivative (59) gave a high yield of the 1,2-dihydroisoquinoline (61). Formation was by way of an intramolecular Diels-Alder cycloaddition of the reactive o-quinonedimethide intermediate (60) and the nitrile component.




(59) (60) 76% (61)

Intramolecular cycloadditions of nitriles have a further advantage in that the incorporation of nitrogen into the cycloadduct increases the synthetic potential of the reaction to an appreciable extent.[42,43]

With this precedent in mind, the nitrile (62) was synthesized by condensation of furoyl chloride with sarcosine nitrile.




(62)

The amide was isolated as a crystalline material m.p. 62-64°, and the infrared spectrum showed the presence of a non-conjugated nitrile ($\nu_{max.}$ 2260 $cm^{-1}$) together with a tertiary amide carbonyl group ($\nu_{max.}$ 1630 $cm^{-1}$), (1630-1670 $cm^{-1}$)).

The $^{1}H$ n.m.r. spectrum showed the presence of a furan nucleus together with the N-Me singlet at $\tau$ 6.64 and a methylene singlet at $\tau$ 5.46.

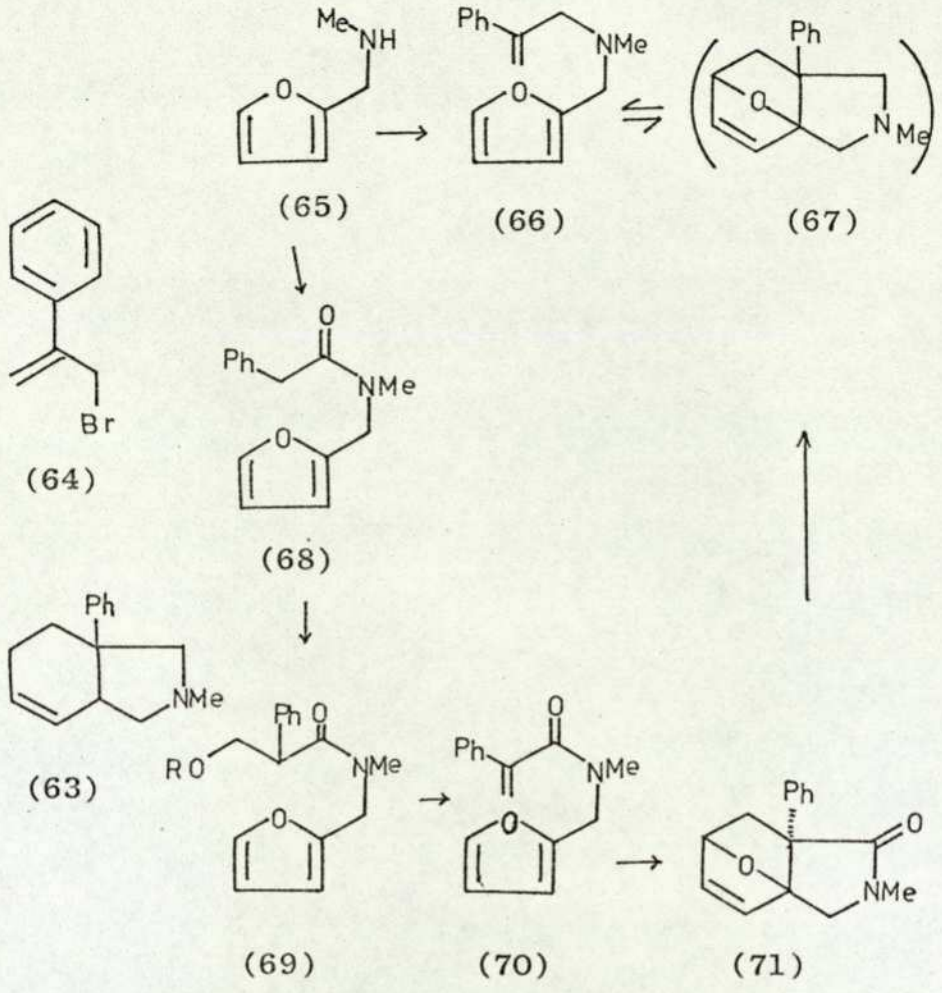
Again, a reluctance of the system towards intramolecular cycloaddition was observed. Thermolysis of the nitrile indicated the molecule to be stable to addition at temperatures up to 200°. No trace of cycloaddition was observed on standing for extended periods at room temperature and introduction of catalysts had no effect. It is possible that cycloaddition was prevented by a lack of flexibility in the linking chain.

After completion of these attempted reactions, a report illustrating some interesting examples of intramolecular additions across furan, together with the instability of certain cycloadducts, has appeared.[44]

In an attempt to synthesize some 3a-phenylisoindolines (63) via intramolecular Diels-Alder cycloaddition, the substrate (65) was prepared readily and in high yield from $\alpha$-bromomethylstyrene (64) and N-furfurylamine. The product however resisted all attempts to effect the cycloaddition reaction leading to (67). Even heating at 230° showed no change in the starting material.

Suspecting an extremely facile retro-Diels-Alder reaction, the temperature was lowered to -60°, but again

no trace of the elusive cycloadduct (67) was observed.




It was concluded that the phenyl substituent in (66) would sufficiently destabilize the $\sigma$ bond to be formed so as to make (67) virtually non-existent.[44]

This destabilizing effect was overcome by the introduction of a carbonyl group adjacent to the dienophile, as in (70), thus providing an electron deficient dienophile capable of undergoing a "normal" Diels-Alder addition with an electron rich diene.

Quenching the anion of the readily accessible phenyl acetamide (68) with paraformaldehyde, produced the alcohol (69, R = H). Acylation, followed by acetic acid

elimination, led directly to the crystalline cycloadduct (71), *via* the intermediacy of (70).

The possibility of the cycloreversion (71) to (70) was also exemplified. Heating a benzene solution of (71) at 120° for 15 hours resulted in an equilibrium of 52% (70) and 48% (71).

Lithium aluminium hydride reduction of the lactam (71) produced an essentially quantitative yield of the styryl amine (66); an observation which firmly established the inherent instability of the intermediate (67).

The extreme susceptibility of some of the Diels-Alder cycloadducts of furan in undergoing cycloreversion could be a possible explanation for the lack of observation of some anticipated cycloadditions proposed in this work.

Monosubstituted furan and furfuryl nuclei are more susceptible to side reactions than are more highly substituted furan nuclei, a fact substantiated by the observation of polymerization in several of the cases studied. An increase in substitution of the furan nuclei with appropriately activating substituents might enhance reactions.

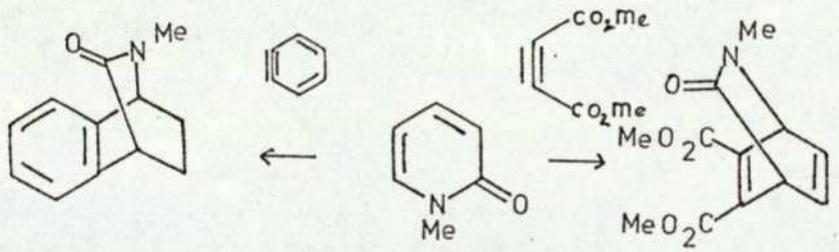
Modification of both the diene and dienophile components with respect to "normal" and "inverse demand" Diels-Alder additions would seem to offer a potential answer.

A further complication in the case of the furoyl systems could be the lack of adoption of the system into a suitable conformation for reaction. Molecular models indicated that in order to twist into the required shape, considerable torsional strain around the ester (or amide) group was necessary.

Because of this lack of success and the reports of similar work by others our attention was turned to the use of other heterocyclic substrates.

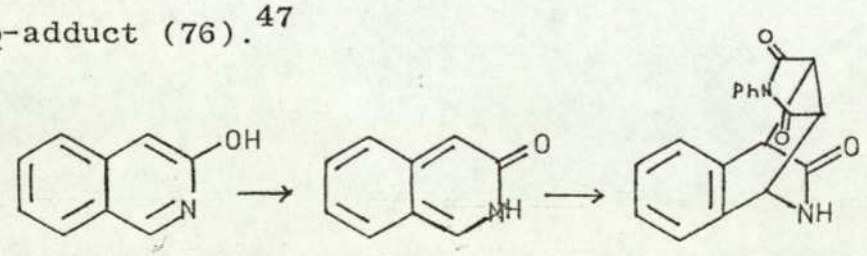
Diels-Alder Cycloaddition Reactions of Mono- and Dihydroxypyrimidines.

A number of heterocyclic systems possessing unsaturated cyclic amide functions have been shown to behave as dienes in conventional cycloaddition reactions. Several 2-hydroxy-pyridines, when blocked in the amide form, undergo this type of reaction. For example, N-methyl-2-pyridone (72) has been shown to undergo cycloaddition with the conventional dienophiles benzyne[45] and dimethyl butynedioate (ADE),[46] yielding the adducts (73) and (74) respectively.



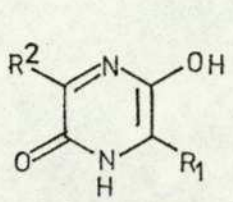
(73) (72) (74)

In a similar manner, 3-hydroxyisoquinoline (75), which can exist in the amide tautomeric form (75a) has been shown to participate in cycloaddition reactions across the 2,5 positions, yielding with N-phenyl maleimide, the endo-adduct (76).[47]

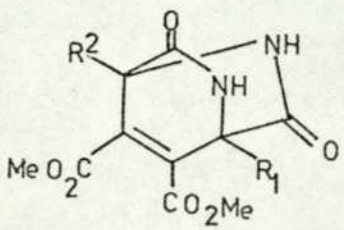


(75) (75a) (76)

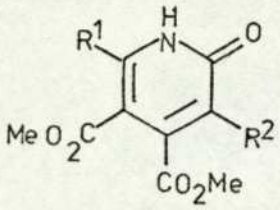
Several intermolecular cycloadditions involving the 2,5-dihydroxy pyrazine nucleus have also been reported.[48]



(77) $R^1$=$CH_2Ph$, $R^2$=$CH_3$
(78) $R^1$=$R^2$=$CH_2Ph$



(79)
(80)



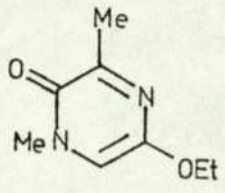
(81) $R^1$=$CH_3$, $R^2$=$CH_2Ph$
(82) $R^1$=$CH_2Ph$, $R^2$=$CH_3$
(83) $R^1$=$R^2$=$CH_2Ph$

The pyrazines ((77), $R^1$ = $CH_2Ph$, $R^2$ = $CH_3$) and ((78), $R^1$ = $R^2$ = $CH_2Ph$) underwent addition with a solution of ADE in DMF at 100°, forming the primary cycloadducts (79) and (80) respectively. The adducts subsequently underwent a smooth decomposition via a retro-Diels-Alder reaction eliminating an isocyanic acid bridge, to yield the pyridones (81), (82) and (83).

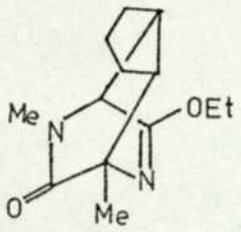
The pyrazines were assumed to react in the keto-hydroxy form rather than in the fully aromatic tautomeric form, since cycloaddition would then result in the formation of two stable amide bonds.

This assumption was validated by the preparation and cycloaddition of the pyrazine (84), blocked in the amide form.[48]

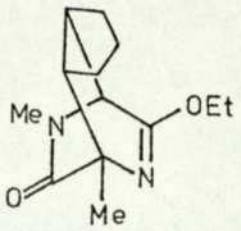
This blocked pyrazine showed enhanced reactivity towards cycloaddition, undergoing rapid reaction even with poor dienophiles such as cyclopentene, producing in this case, a mixture of two isomeric primary adducts (85) and (86).



(84)



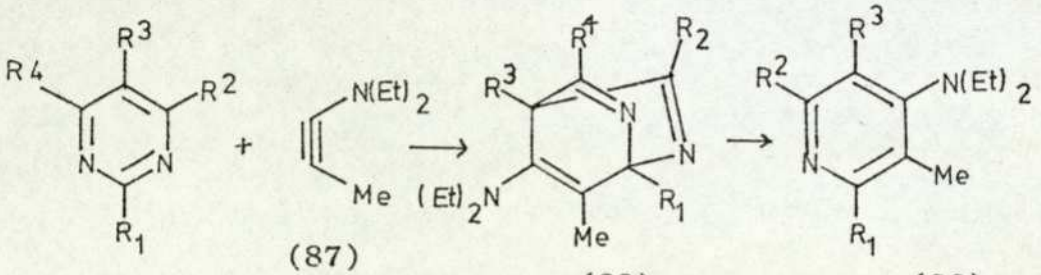
(85)



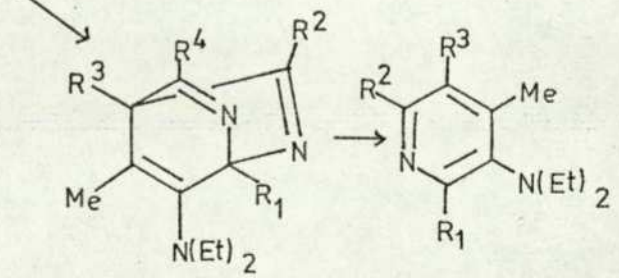
(86)

Some examples of cycloaddition across the pyrimidine nucleus have also been reported.

A series of carbomethoxy substituted aromatic pyrimidines have been shown to react with the electron rich dienophile, N,N-diethylaminomethylacetylene (87).[49] Cycloaddition gave the two primary adducts (88) and (90), which were not isolated but led directly by means of a retro-Diels-Alder reaction to the amino pyridines (89) and (91).



(87) (88) (89)



(90) (91)

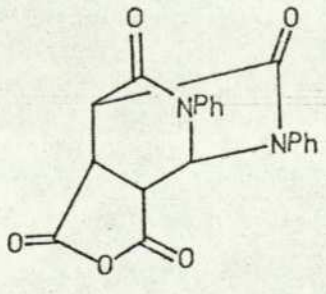
A notable feature was that substitution at different ring positions in the pyrimidine nucleus was shown to influence the cycloaddition.

Substitution in the 4 or 6 positions resulted in low yields or non-regioselective addition, whilst introduction of the carbomethoxy function into the 2 or 5 position gave excellent yields of a single cycloadduct, seemingly to effectively control the orientation of the dienophile approach.

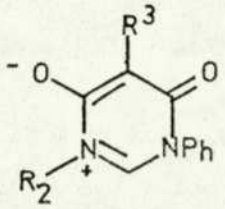
The results were rationalised by electronic interaction between the dienophile and the 2,5-carbomethoxy substituents.[49]

Several pyrimidine betaines have also been shown to participate in cycloaddition reactions.[50,51] The inherent fixed dipolar 4 $\pi$ electron system of the pyrimidine betaine nucleus functions as a diene system, and addition across the 2,5 positions with conventional dienophiles has been accomplished.

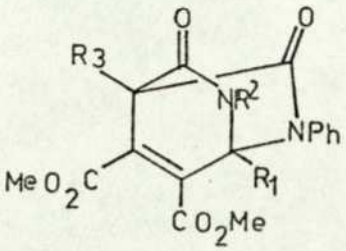
The pyrimidine betaine (92, $R^3$ = H, $R^2$ = Ph) yielded a 1:1 cycloadduct (95) with maleic anhydride [50] whilst cycloaddition with ADE gave the primary adduct (93) in 94% yield. Upon further heating the primary cycloadduct (93) underwent a secondary bridge elimination reaction yielding the pyridone (94).



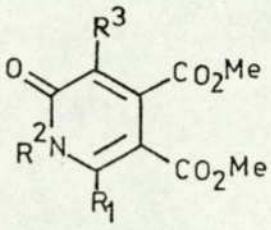

(95)



(92)



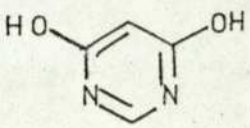
(93)



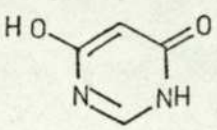
(94)

It is perhaps worthwhile to note that reaction of the betaine (92) with olefinic dienophiles (e.g. dimethyl maleate), as well as ethyl propiolate and N,N′-diethyl-aminophenylacetylene failed to produce well defined adducts.[50]

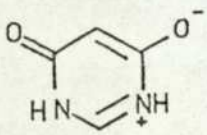
4,6-Dihydroxy–pyrimidines, e.g. (96), which have been shown to exist in a dipolar tautomeric form (98) in polar solvents, and in the keto-enol form (97) in polar organic solvents,[52,53] have also been shown to participate in cycloaddition reactions.[48]



(96)



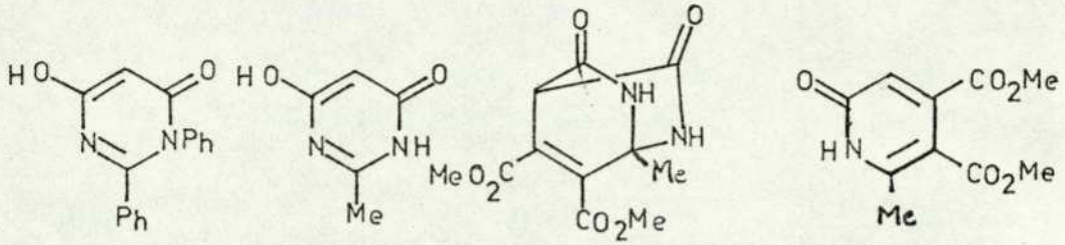
(97)



(98)

2-Methyl-4,6-dihydroxy–pyrimidine (100) has been reported to undergo cycloaddition with ADE.[48] Heating a DMF solution of the pyrimidine and ADE at 60° for 72 hours led to the direct isolation of the pyridone (102). Formation of the pyridone was rationalised by cycloaddition to the

primary adduct (101) followed by a subsequent bridge elimination.[48]



(99) (100) (101) (102)

The cycloaddition of the dihydroxy-pyrimidine (100) with ADE proved to be a highly specific reaction.

Further attempts at intermolecular cycloaddition with the pyrimidine (100) all failed.[1] The pyrimidine was stable in the presence of simple olefins, and even strained olefins, such as norbornadiene, at temperatures up to 200°. Cycloadditions attempts using electron rich dienophiles, such as ethyl vinyl ether, or to activate the heterocyclic system with Lewis acid catalysts were also unsuccessful.[1] Examination of the crude reaction mixtures by mass spectrometry failed to detect even traces of the anticipated cycloadducts.[1]

Reactivity towards cycloaddition can be conveniently and usefully described in terms of molecular orbital theory;[54] in particular through the use of frontier molecular orbital and perturbation theory approximations.[55,56]

For a Diels-Alder reaction involving inverse electron demand, such as the reaction of an olefin with a pyrimidine, reactivity is mainly determined by the HOMO olefin - LUMO pyrimidine interaction. Preliminary CNDO/2 calculations on 2-methyl-4,6-dihydroxy-pyrimidine (100) as the keto-hydroxy

tautomer , indicated that all symmetry, energy levels and atomic coefficient components were all favourable for cycloaddition to take place across the 2,5 positions.

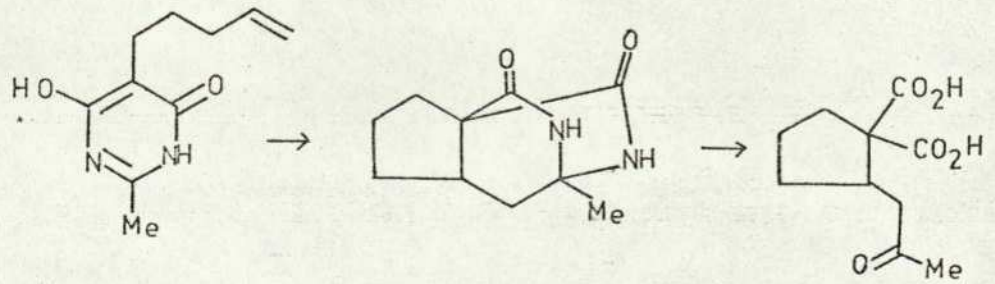
It was therefore predicted that cycloaddition was feasible in terms of electronic energy considerations provided the reaction was neither hindered by steric effects nor inhibited by thermodynamic considerations.

The conclusion was reached that intermolecular cycloaddition processes could well be prevented by a large negative entropy barrier, and one means of overcoming this activation barrier would be to react the diene and dienophile components in an intramolecular sense.

Intramolecular Cycloaddition Reactions of 4,6-Dihydroxypyrimidines.

The model pyrimidine (103) was synthesized and its activity towards intramolecular cycloaddition examined by Watt.[1]

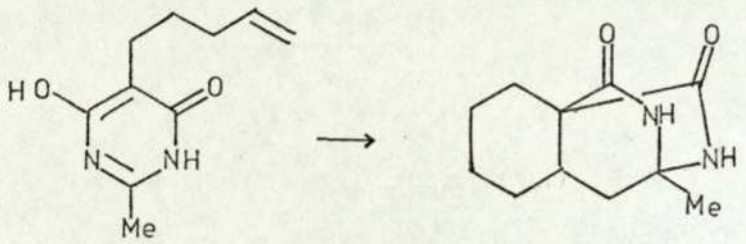
Although the pyrimidine was found to be stable under conditions in which the unalkylated pyrimidine (100) could react bimolecularly with ADE, increasing the reaction temperature from 80° to 200° resulted in efficient intramolecular cycloaddition giving the adduct (104) in good yield.[1,57]



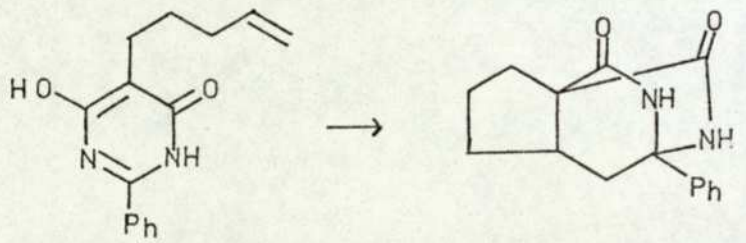

(103) (104) (105)

The cycloadduct, easily isolated as an amorphous solid, was found to be stable at room temperature, and was further characterised by efficient acid hydrolysis into the substituted cyclopentane derivative (105).

Ramifications of this cycloaddition process were examined by application to a variety of derivatives. The homologous hexenyl pyrimidine (106) was synthesized,[1] and upon thermolysis produced the cyclohexano-adduct (107) indicating the possible construction of fused six-membered rings by this route.




(106) (107)



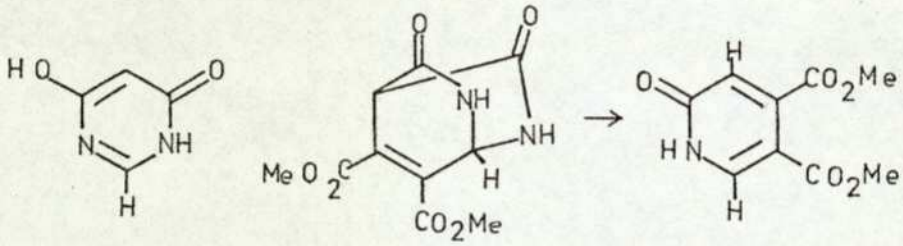

(108) (109)

The 2-phenyl substituted pyrimidine (108) was also synthesized and reacted upon thermolysis to give the anticipated cycloadduct (109)[1] showing that a variety of 2-substituents could be involved in this cycloaddition process.

Because of these encouraging results other 4,6-dihydroxypyrimidines were also examined in order to define more clearly the synthetic potential of these reactions.

The synthesis of 2-unsubstituted pyrimidines by base-catalysed condensation of formamidine with $\beta$-dioxo compounds is a poorly documented reaction, mainly because of the occurrence of several side reactions.

In contrast, 4,6-dihydroxypyrimidine (110) was prepared in moderate yields by the method of Kenner,[58] which involved condensation of diethyl malonate and formamidine. The reactivity of this material towards cycloaddition reactions was tested by heating it with dimethylbutynedioate (ADE) under the same conditions as those reported[48] for the cycloadditions of 2-methyl-4,6-dihydroxypyrimidine.

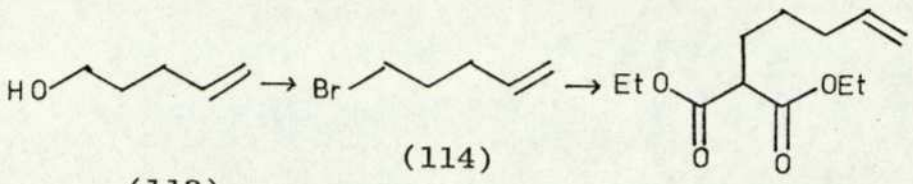


(110) (111) (112)

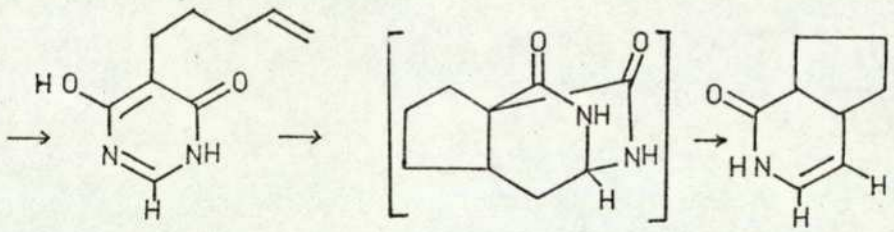
Thermolysis at 80° for a period of three days led to the isolation of the pyridone (112) produced via bridge elimination of cyanic acid from the initial cycloaddition product (111).

Using this precedent, the intramolecular cycloaddition of the 2-unsubstituted 4,6-dihydroxypyrimidine nucleus with an unactivated dienophile (i.e. an isolated C-C double or triple bond) was next investigated.

The model pyrimidine (116) was prepared by the indicated route.



(113) (114) (115)



(116) (117) (118)

Pent-4-en-1-ol (113) prepared by the method of Brooks and Snyder,[39,59] was treated with phosphorus tribromide to give 5-bromo-pent-1-ene (114).

Alkylation of diethyl malonate with this bromide yielded diethyl 2-(pent-4-enyl)-malonate (115),[60] which, upon condensation with formamidine acetate in ethanolic sodium ethoxide, gave 4,6-dihydroxy-5-(pent-4-enyl)-pyrimidine (116).

Upon thermolysis at 198° for 18 hours in DMF, the pyrimidine underwent conversion into a new material. Chromatographic isolation of the reaction product afforded an oil, the $^{1}H$ n.m.r. spectra indicating a unique product which exhibited several interesting features.

A broad, $D_2O$ exchangeable peak integrating to one proton, appeared at $\tau$ 1.84, indicative of a nitrogen-bonded proton. A single proton signal appeared as a double doublet at $\tau$ 4.08, which upon $D_2O$ treatment, collapsed into a sharp doublet (J = 7 Hz). This indicated the presence of

an olefinic proton coupled to both a nitrogen-bonded proton and a second proton.

A third single proton appeared as a double-doublet at $\tau$ 5.15 indicative of a second olefinic proton coupled to two other dissimilar protons.

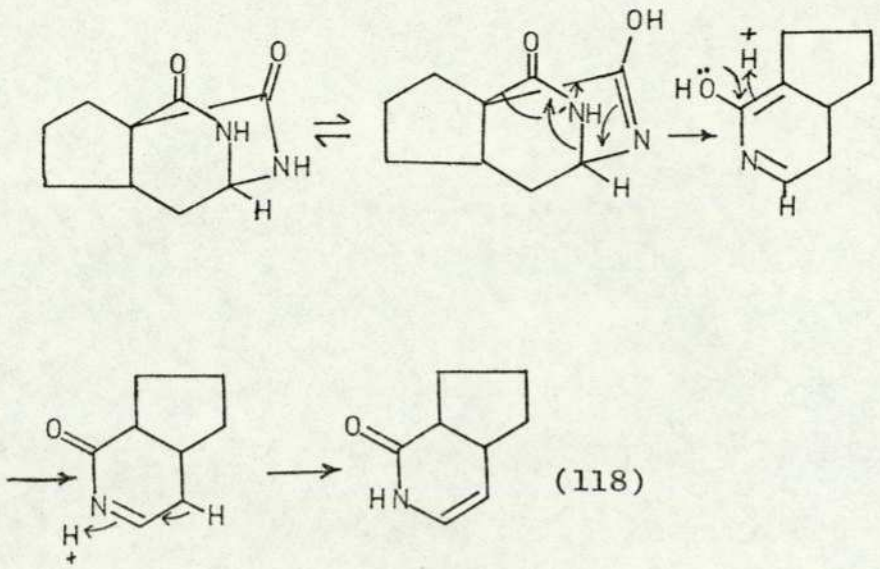
The infrared spectrum showed a broad band at 3200-3400 $cm^{-1}$ together with peaks at 1680 $cm^{-1}$ and 1660 $cm^{-1}$.

On the basis of this spectral evidence, the product was assigned the dihydropyridone structure (118) of unknown configuration.

The proposed structure (118) was confirmed by a $^{1}H$ n.m.r. decoupling experiment. Irradiation of the signal at $\tau$ 5.15 caused the doublet at $\tau$ 4.08 to collapse into a singlet, whereas irradiation of the signal at $\tau$ 4.08 caused the double-doublet at $\tau$ 5.15 to revert into a broadened singlet, thus indicating the mutual coupling of the two protons.

Mass spectrometry also confirmed the proposed structure (118). The molecular ion of the dihydropyridone (118) was observed and an accurate mass measurement substantiated the molecular formula calculated for structure (118).

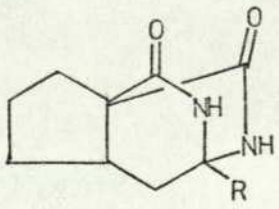
Formation of the dihydropyridone (118) was rationalised by the mechanism illustrated, involving bridge elimination of the primary Diels-Alder cycloadduct (117), which, in this case could not be isolated. Traces were observed by examination of the crude reaction mixture with mass spectrometry. Upon lowering the reaction temperature, either a decreased yield of the dihydropyridone (118) or no cycloaddition at all was observed.



(118)

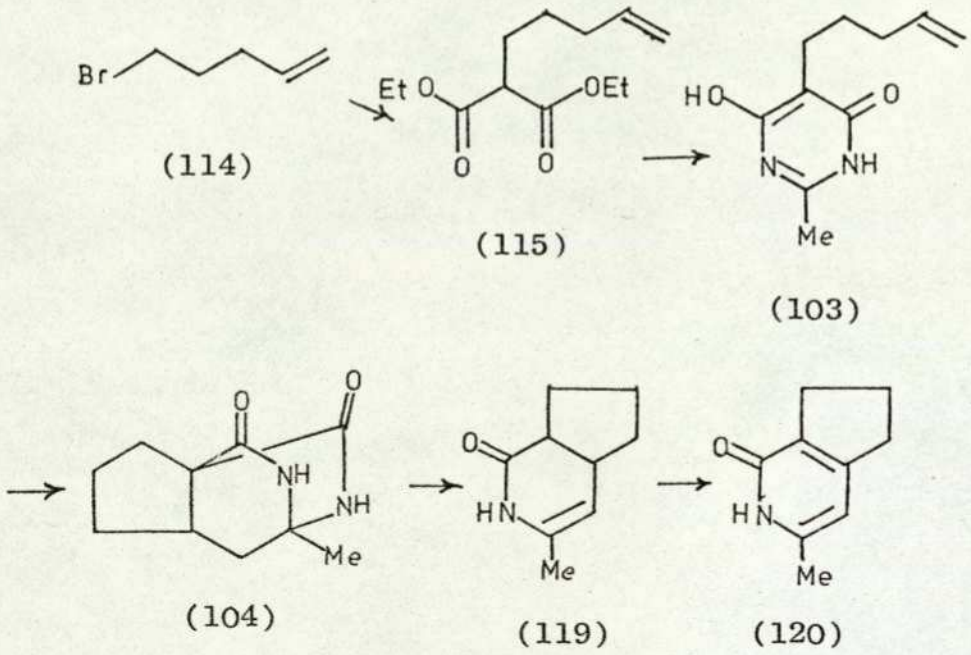
The result of this intramolecular cycloaddition, although performed under identical conditions, contrasts with those observed for the analogous 2-methyl and 2-phenyl substituted pyrimidines, which yielded stable primary cycloadducts as virtually exclusive products.[1] A possible explanation is that 2-substitution increases steric compression in the transition state leading to the dihydropyridones.

The occurrence of facile bridge elimination of the intermediate bicyclic diamide (117) suggested that the other bicyclic diamides, such as (104) and (109), should also be unstable to prolonged thermolysis and this suggestion was therefore put to experimental test.



(117) R = H
(104) R = $CH_3$
(109) R = Ph

4,6-Dihydroxy-2-methyl-5-(pent-4-enyl)pyrimidine (106) was prepared by the method of Watt.[1]




(114) (115) (103) (104) (119) (120)

Alkylation of diethyl malonate with 5-bromo-pent-1-ene (114) yielded diethyl 2-(pent-4-enyl)-malonate (115),[60] which upon base catalysed condensation with acetamidine,[61] led to the required pyrimidine (103).

Upon repeating the thermolysis of the pyrimidine, at 200° in DMF, for an elongated period it was observed that as well as the primary cycloadduct (104) a second product, which increased in concentration as the thermolysis time was extended, could be detected.

Isolation of this second product afforded an oil, the $^1H$ n.m.r. spectrum exhibited a broad $D_2O$ exchangeable peak at $\tau$ 1.60-1.90, characteristic of a nitrogen bonded proton, broad singlet, integrating to one proton, at $\tau$ 5.36-5.44, indicative of an olefinic proton, and a broadened methyl signal at $\tau$ 8.20 along with several multiplets in the

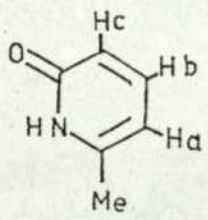
7.8-8.6 region.

The infrared spectrum of the material contained a broad band at 3400 $cm^{-1}$ together with bands at 1660 $cm^{-1}$ and 1595 $cm^{-1}$.

On the basis of spectral evidence, the dihydropyridone structure (119) was proposed for this product although the stereochemistry of the compound was not assigned.

Mass spectrometry verified the existence of a molecular ion at the predicted mass number for the proposed structure (119).

The dihydropyridone (119) was further characterised by catalytic dehydrogenation, using 5% palladium-on-charcoal in refluxing xylene, into the fully aromatic pyridone (120). This crystalline compound possessed a $^1H$ n.m.r. spectrum exhibiting a distinct singlet, integrating to one proton, at $\tau$ 4.0 and a methyl signal at $\tau$ 7.70, characteristic values of pyridones; for example, in the $^1H$ n.m.r. spectrum of 6-methyl-2-pyridone (121), proton (a) occurs as a doublet at $\tau$ 4.04, proton (b) as a double doublet at $\tau$ 2.72, proton (c) as a doublet at $\tau$ 3.68 and the methyl signal is a sharp singlet at $\tau$ 7.69.

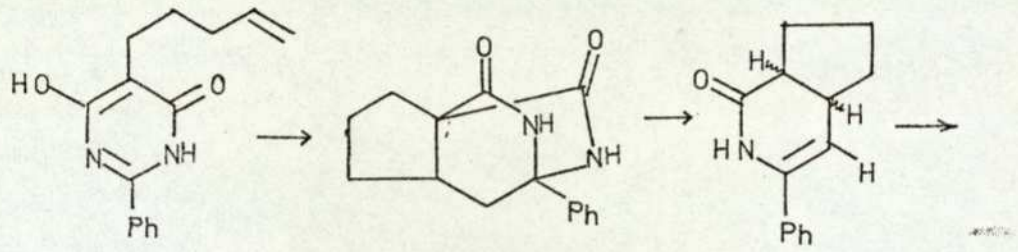



(121)

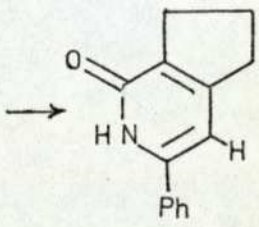
The ultraviolet spectrum of the product was also characteristic of those normally observed in pyridone systems.

It was further observed that thermolysis of a DMF suspension of the primary cycloadduct (104) resulted in the isolation of a material identical to the dihydropyridone (119) obtained from the thermolysis of the pyrimidine (103). The decomposition of the primary adduct (104) was however somewhat hindered by its extreme insolubility.

Following the success in bridge elimination of the methyl substituted bicyclic diamide (104), the phenyl substituted analogue (108) was subjected to further examination.



(108) (109) (122)



(123)

Condensation of diethyl 2-(pent-4-enyl)malonate (115) with benzamidine hydrochloride in the presence of excess base, using the reported method,[1] gave a low yield of 4,6-dihydroxy-5-(pent-4-enyl)-2-phenylpyrimidine (108).

Upon thermolysis the 2-phenylpyrimidine was found to undergo cycloaddition at a far slower rate than the 2-methyl and 2-unsubstituted analogues under comparable conditions. Thermolysis of the pyrimidine (108) at 198° for a prolonged

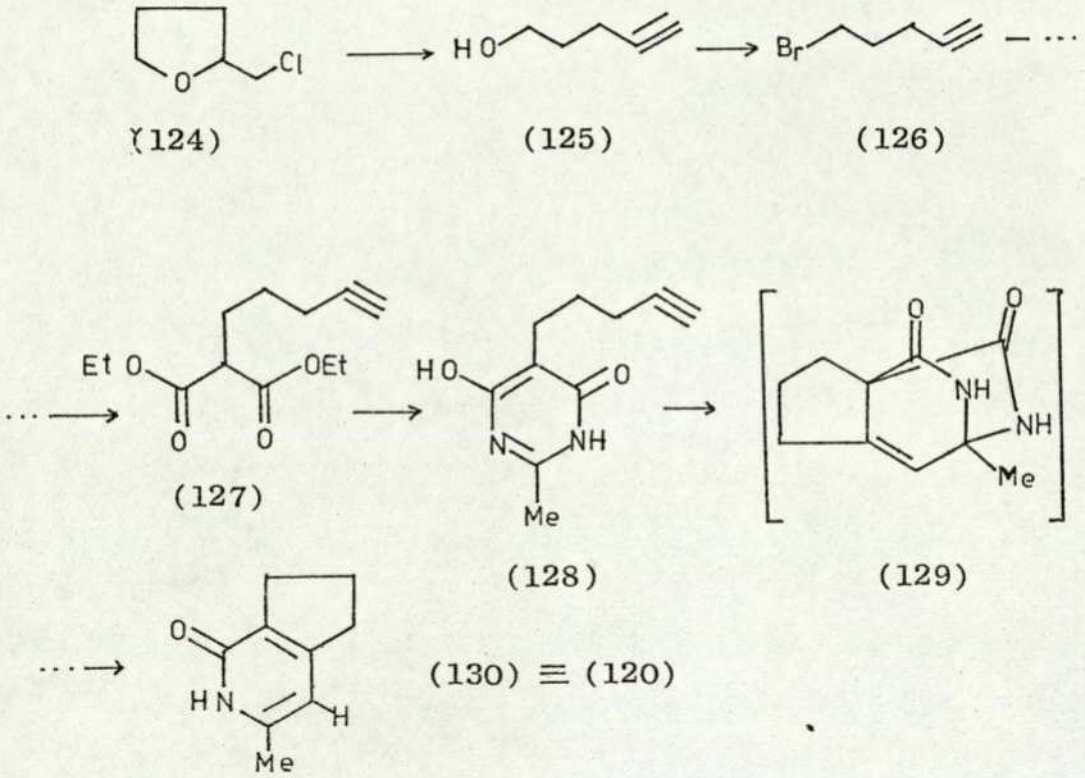
period (48 hours) resulted in a moderate yield of the primary cycloadduct (109). In this case the rate of cycloaddition was so slow that bridge elimination of the intermediate adduct occurred at a comparable rate, giving rise to a second product which was isolated as a crystalline solid and assigned the dihydropyridone structure (122) on the basis of spectral evidence.

The $^{1}H$ n.m.r. spectrum of the material contained a characteristic doublet integrating to one proton at $\tau$ 4.60 which was assigned to the olefinic proton (a).

The dihydropyridone was further characterised by catalytic dehydrogenation to the fully aromatic pyridone (123) in which the corresponding proton (a) appeared as a distinct singlet at $\tau$ 3.48 in the $^{1}H$ n.m.r. spectrum.

The dihydropyridone (122) was obtained in increased yield by prolonged thermolysis of the precursor pyrimidine (108) or by thermolysis of the isolated primary cycloadduct (109).

The versatility of intramolecular cycloaddition across the 4,6-dihydroxypyrimidine was further demonstrated by the incorporation of an acetylenic dienophile in place of the previously employed olefinic moiety. There are numerous precedents for the participation of acetylenic dienophiles in intramolecular cycloadditions.[62]



(124) (125) (126)

(127) (128) (129)

(130) ≡ (120)

Pent-4-yn-1-ol (125) was prepared by the method of Brooks and Snyder, by reactions of sodamide with tetrahydrofurfurylchloride (124).[63] Treatment of the alcohol with phosphorus tribromide gave 5-bromopent-1-yne (126), ( $\nu_{max}$ 2118 $cm^{-1}$ ).[64]

The bromination reaction was however unsatisfactory because of side reactions resulting in the formation of polymeric material. A possible alternative, which was not attempted in this instance, is preparation of the acetylenic tosylate in place of the bromide, followed by the requisite alkylations employing the tosylate.

5-Bromopent-1-yne was used to alkylate diethyl malonate and the reaction product, diethyl-2-(pent-4-ynyl)-malonate (127) condensed with acetamidine hydrochloride in ethanolic sodium ethoxide, to give 4,6-dihydroxy-2-methyl-

5-(pent-4-ynyl)pyrimidine (128), ( $\nu_{max}$ 2116 $cm^{-1}$).

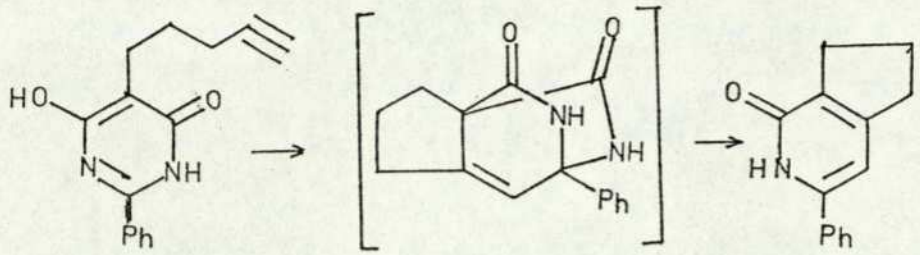
Upon thermolysis of (128) at 198°, intramolecular cycloaddition was observed leading directly to the fully aromatic pyridone (130), easily distinguishable by its characteristic $^1H$ n.m.r. spectrum and by comparison to the material previously obtained by catalytic dehydrogenation of the dihydropyridone (119).

As a synthetic route towards monoterpenoid alkaloid skeleton structures, cycloaddition of the acetylenic derivative possessed certain advantages over the corresponding olefinic additions, since a fully aromatic pyridone, required as a precursor towards the alkaloids, was produced directly from the cycloaddition process.

A further advantage of the acetylenic addition was that the rate of cycloaddition, relative to that of the analogous olefinic addition, was appreciably increased. Thermolysis of (128) at 198° for 4-6 hours resulted in complete reaction whilst the olefinic derivative (106) required at least 20 hours for completion.

Unlike the thermolysis of the analogous olefinic pyrimidine, in which the primary cycloadduct was stable and readily isolable, in this thermolysis no trace of the intermediate bicyclic diamide (129) could be observed from the acetylene (128).

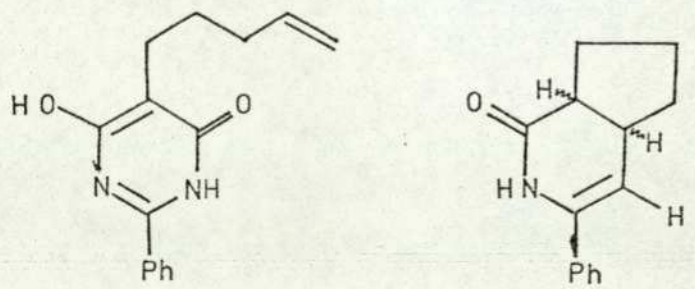
The generality of cycloaddition of an acetylenic dienophile across the 4,6-dihydroxypyrimidine nucleus was demonstrated by the behaviour of the 2-phenylpyrimidine (131).



(131) (132) (133)

Condensation of diethyl-2-(pent-4-ynyl)malonate (127), prepared as previously described, with benzamidine hydrochloride in the presence of an excess of base, gave 4,6-dihydroxy-5-(pent-4-ynyl)-2-phenylpyrimidine (131) in low yield.

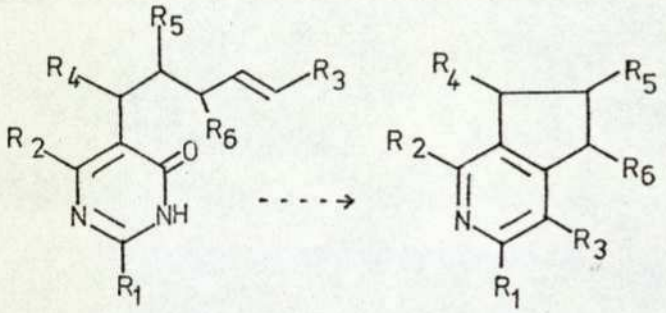
The pyrimidine was again found to suffer intramolecular cycloaddition upon thermolysis at 198°, albeit at an appreciably slower rate than that observed in the 2-methyl pyrimidine (128). Thermolysis led directly to the pyridone (133) identical to the material obtained by the catalytic dehydrogenation of the dihydropyridone (122) from thermolysis of the olefinic pyrimidine (108). Again, no traces of the primary cycloadduct (132) could be detected.



(108) (122)

A relatively large number of alkaloids possess the pyrindane skeletal structure (135). The occurrence and existing syntheses of these natural products has been previously discussed. (See review section).

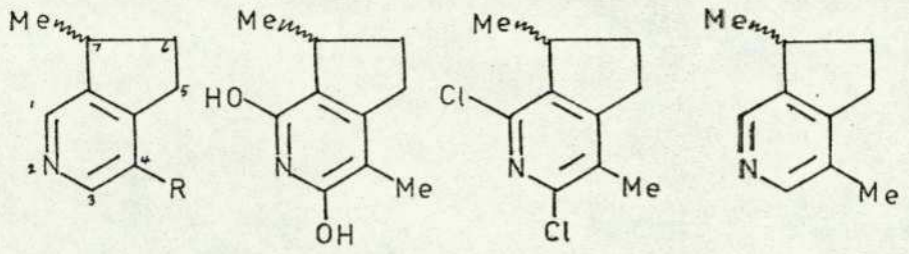
Intramolecular cycloaddition reactions of substituted pyrimidines offer a novel synthetic approach to this class of compounds since incorporation of substituents in the indicated positions (Figure 3) of the pyrimidine precursor should theoretically produce the correspondingly substituted pyrindane skeletal structure (135), capable of further modification by substituent transformations.




(134) (135)

Figure 3

The route to the pyrindane structures achieved by intramolecular cycloadditions of substituted 4,6-dihydroxypyrimidines offers particular promise for the synthesis of the actinidine-type alkaloids (136), a class of compounds for which at the present time, there only exists a minimum of synthetic methods.

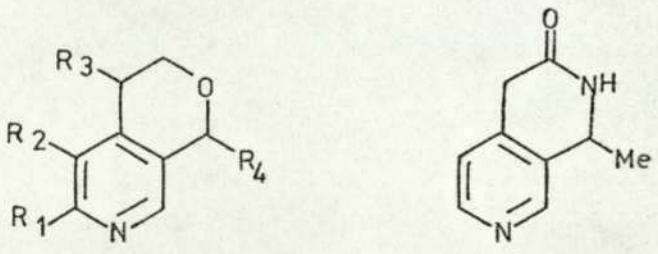


(136) (137) (138) (139)

The fused pyridones produced by the previously described cycloaddition process are ideal precursors to the naturally occurring compounds, as illustrated by existing syntheses which frequently involve annelated pyridones as synthetic intermediates.[65,66]

For example, racemic actinidine (139) has been synthesized by catalytic reduction of the dichloropyridine (138), which in turn, was obtained by treatment of phosphorus oxychloride upon the dihydroxypyrimidine (137).[65]

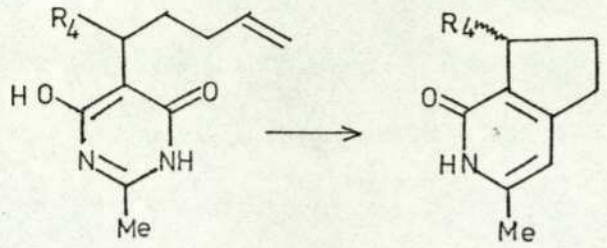
Adaptation of the cycloaddition process could also lead to alternate classes of monoterpenoid alkaloids. Suitable modification in the diene and dienophile linking chain should lead to the gentianine (140)[67] and jasminine (141)[68] type alkaloids.



(140) (141)

The actinidine-type alkaloids all possess a methyl substituent in the cyclopentene ring (in the "7" position). Incorporation of a methyl substituent into the appropriate position ($R^4$) of a dihydroxypyrimidine, followed by intra-

molecular cycloaddition, should theoretically give rise to a pyrindane structure with the cyclopentene ring functionalised in the analogous manner.




(142) (143)

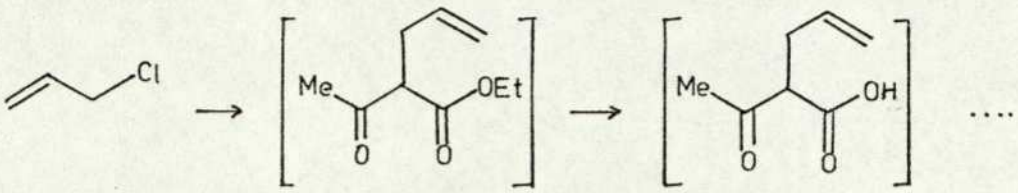
The validity of this proposal was demonstrated by the synthesis and cycloaddition of 4,6-dihydroxy-2-methyl-5-(-1-methyl-pent-4-enyl) pyrimidine (142, $R^4$ = Me).

Allylacetone (146) was prepared by the method of La Forge.[69] Alkylation of ethylacetoacetate with allyl-chloride yielded ethyl(allyl)acetoacetate (144) which upon hydrolysis using concentrated alkali afforded the corresponding acid (145).

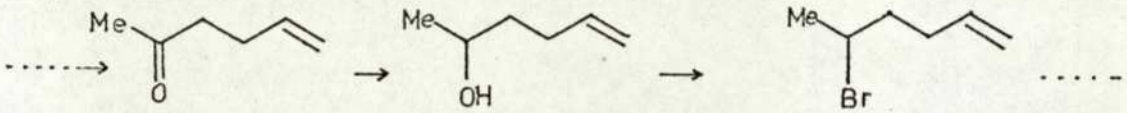
The acid was subsequently decarboxylated, giving hex-1-en-5-one (allylacetone) (146).[69]

Reduction of (146) with lithium aluminium hydride gave hex-1-en-5-ol (147) in high yield, which upon treatment with phosphorus tribromide yielded 5-bromo-hex-1-ene (148).

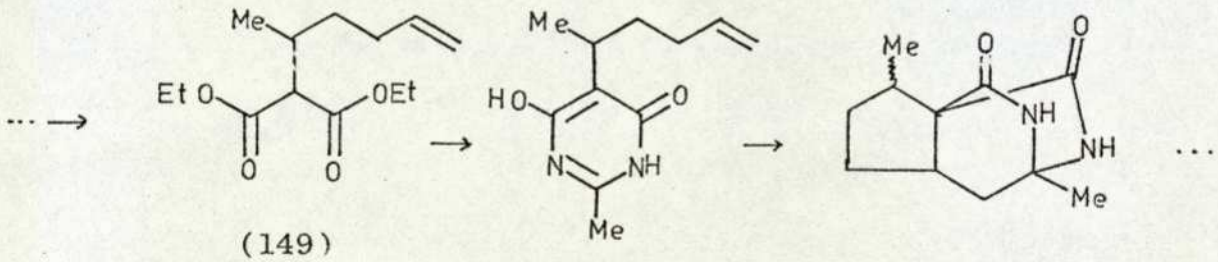
Alkylation of diethyl malonate with this bromide, followed by condensation of the product (149), with acetamidine hydrochloride in ethanolic sodium ethoxide, led to the formation of the required pyrimidine (150).



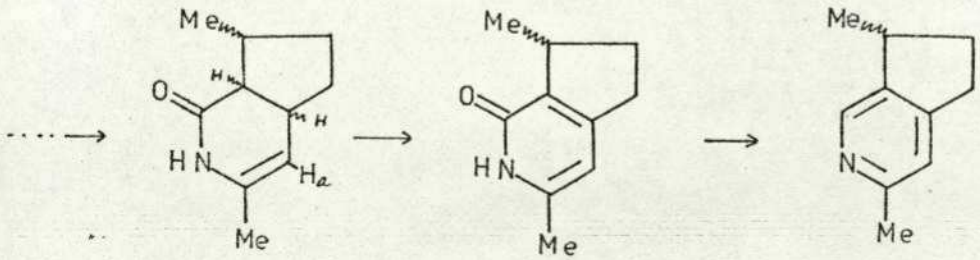

(144) (145)




(146) (147) (148)




(149) (150) (151)




(152) (153) (154)

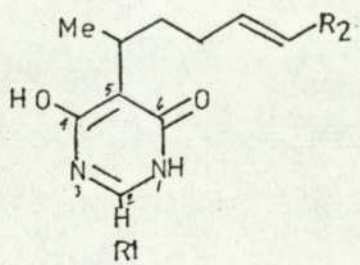
- Scheme 2 -

The $^1$H n.m.r. spectrum of this compound contained a characteristic methyl doublet (J = 6Hz) at $\tau$ 8.65 together with the other anticipated signals.

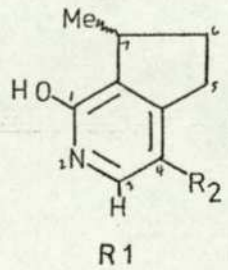
Upon thermolysis at 198$^o$ for 30 hours, the pyrimidine underwent intramolecular cycloaddition giving a moderate yield of the stable primary cycloadduct (151) together with a second product arising from bridge-elimination, identified as the dihydropyridone (152) of unknown configuration.

The $^1$H n.m.r. spectrum of the dihydropyridone exhibited a distinct doublet (J = 6 Hz) at $\tau$ 9.07 which integrated as three protons and was assigned to the methyl function substituted on to the cyclopentene ring. The second methyl function was observed as a broadened singlet at $\tau$ 8.26, indicating allylic coupling, whilst the olefinic proton (Ha) appeared as a multiplet at $\tau$ 5.48.

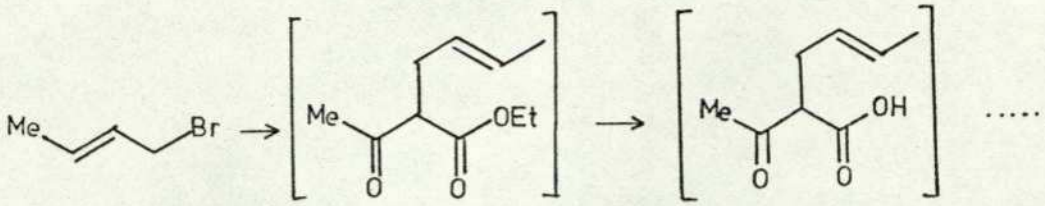
By analogy to reported reactions, the dihydropyridone (152) would appear to be readily amenable to transformation into the pyrindane (154) without loss of functionalisation of the cyclopentene ring, thus illustrating the potential of the cycloaddition process for use in actinidine-type alkaloid synthesis.



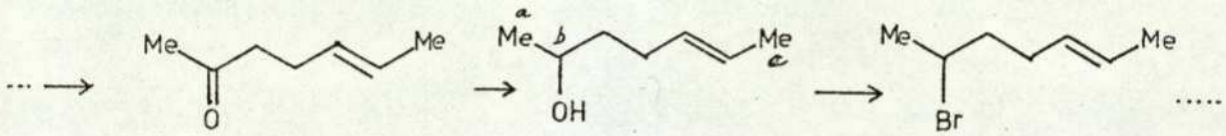

(155)



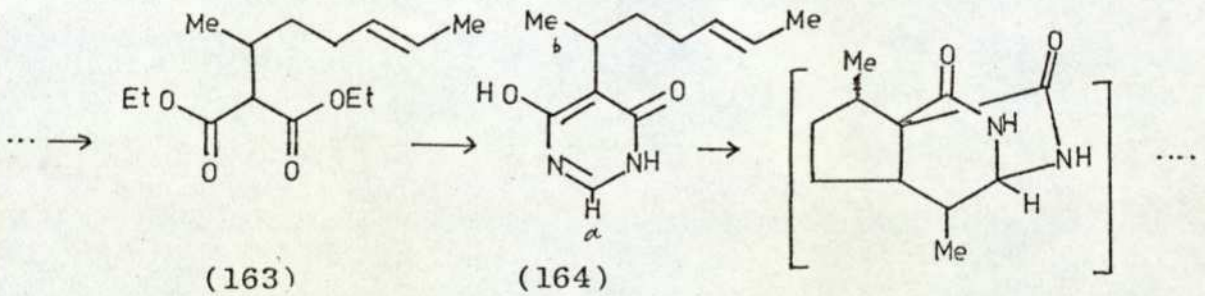

(156)



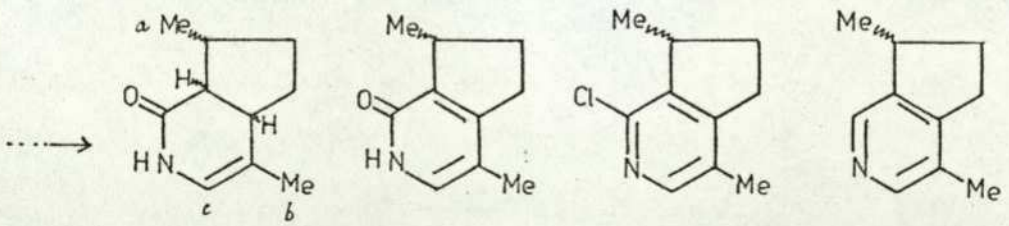
(157) (158) (159)



(160) (161) (162)



(163) (164) (165)



(166) (167) (168) (169)

- Scheme 3 -

Incorporation of a substituent ($R^2$) into the terminal position of the dienophile in the alkylated 4,6-dihyroxypyrimidine, should upon cycloaddition, produce a pyridone substituted in the 7-position (156). Similarly the substituent in the 2-position of the precursor dihydroxypyrimidine should be found in the 3-position of the derived pyrindane (156).

Products related to the actinidine-type alkaloids, of structure (136), should be achieved by cycloaddition of a 2-unsubstituted-4,6-dihydroxypyrimidine with appropriate substituents in the ($R^2$) and ($R^1$) positions.

These proposals were put to experimental test by the synthesis and cycloaddition of an appropriately substituted pyrimidine, 4,6-dihydroxy-5-(-1-methyl-hex-4-enyl) pyrimidine (164), prepared by the synthetic route shown in Scheme 3.

Crotylacetone (hept-2-en-6-one) (160) was prepared by an adaptation of the method of La Forge.[69]

Alkylation of ethylacetoacetate with crotylbromide (157) produced ethyl (crotyl)–acetoacetate (158) which upon basic hydrolysis was transformed into the acid (159). Thermal decarboxylation of the acid (159) gave crotyl—acetone (160).

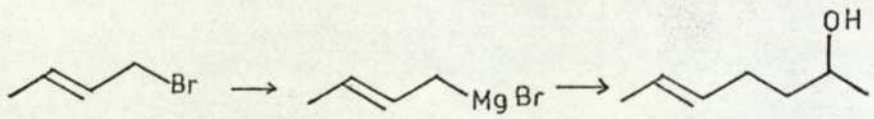
Reduction of the ketone with lithium aluminium hydride gave a high yield of hept-2-en-6-ol (161) which upon treatment with phosphorus tribromide afforded 6-bromohept-2-ene (162).

The $^1H$ n.m.r. spectrum of hept-2-en-6-ol (161) exhibited several characteristic features. The terminal aliphatic methyl group (a) appeared as a distinct doublet

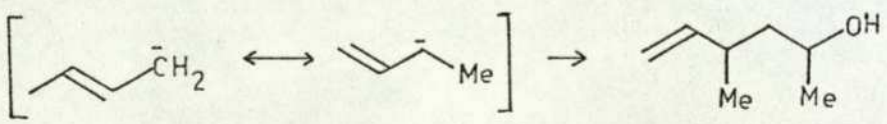
(J = 6 Hz) at $\tau$ 8.84. A second doublet, (J = 1.5Hz), which also integrated into three protons, was observed at $\tau$ 8.36, indicative of a methyl group attached to the olefinic bond, the vinylic protons of which appeared as a 2-proton broad multiplet at $\tau$ 4.48-4.68. A sextet, integrating to one proton, was observed at $\tau$ 6.22 and assigned to proton (b). Irradiation of this signal caused the doublet at $\tau$ 8.84 to collapse into a singlet, indicating coupling to the terminal methyl group.

The $^1$H n.m.r. spectrum of 6-bromo-hept-2-ene (162) was less distinct than that of the precursor alcohol. Introduction of the bromide resulted in a downfield shift of the adjacent methyl group signal, thereby causing overlap of several signals. The terminal methyl group (c) appeared as a doublet (J = 6 Hz) at $\tau$ 8.38 and the second methyl group as a doublet (J = 1.5 Hz) at $\tau$ 8.35.

An alternative method for the preparation of hept-2-en-6-ol was also attempted.




(157) (170) (161)




(171)

Condensation of crotyl magnesium bromide (170) with propylene oxide gave a mixture of the anticipated alcohol (161) ca. 10%, and the rearranged product, 4-methylhex-5-en-2-ol (171) ca. 80%, resulting from the isomerization of the crotyl and allyl-methyl anions.

Alkylation of diethyl malonate with 6-bromohept-2-ene (162) gave the anticipated product (163) which was condensed with formamidine acetate in ethanolic sodium ethoxide to give a low yield of 4,6-dihydroxy-5-(-1-methyl-hex-4-enyl)-pyrimidine (164).

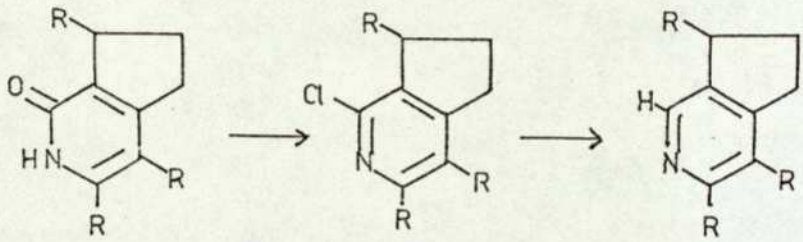
The $^{1}H$ n.m.r. spectrum of the pyrimidine exhibited several characteristic features. The aromatic pyrimidine proton (a) appeared as a distinct singlet integrating to one proton at $\tau$ 0.98, the terminal olefinic methyl function appeared as a doublet (J = 2Hz) at $\tau$ 8.38 whilst the second methyl function (b) appeared as a characteristic doublet (J = 6Hz) at $\tau$ 8.65. The two olefinic protons appeared as a multiplet at $\tau$ 4.56.

Upon prolonged thermolysis at 198° the pyrimidine underwent an inefficient intramolecular cycloaddition giving a low yield of the dihydropyridone derivative (166) of undetermined stereochemistry.

The $^{1}H$ n.m.r. spectrum of the dihydropyridone (166) exhibited a distinct doublet (J = 7Hz) at $\tau$ 9.02 which integrated into three protons and was assigned to the methyl function (a) substituted on to the cyclopentane ring. The second methyl function (b) appeared as a broadened singlet at $\tau$ 8.38 whilst the olefinic proton (c) appeared as a broad signal at $\tau$ 4.50.

The dihydropyridone (166) would seem to be an ideal intermediate towards the synthesis of actinidine (169) by the proposed scheme involving the transformations (166) $\longrightarrow$ (169).

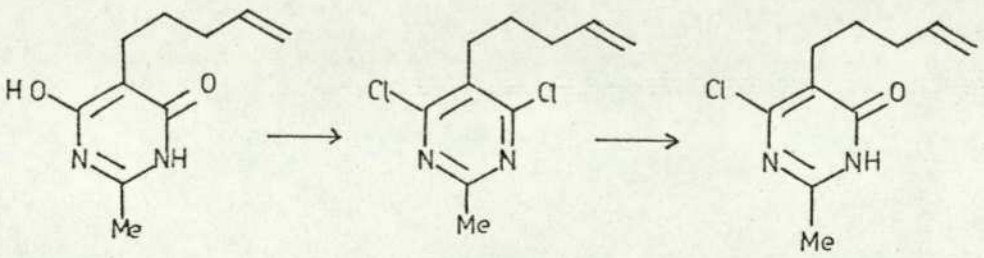
The conversion of the annelated pyridone derivatives formed by means of the intramolecular cycloaddition of dihydroxypyrimidines, into the corresponding annelated pyridine derivatives is desirable from the point of view of the synthesis of the naturally occurring compounds. There are several precedents for this conversion generally involving transformation of the pyridone into the corresponding chloropyridine (173) and subsequent catalytic hydrogenation to give the desired pyridine derivatives (174).[65,66]



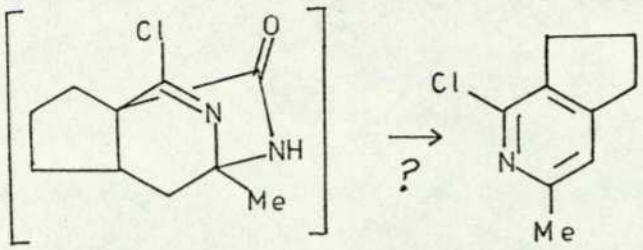
(172) (173) (174)

Since annelated chloropyridines are often utilised as synthetic intermediates for this group of alkaloids it appeared of synthetic use to derive them more directly by the cycloaddition of a suitably substituted pyrimidine.

With this objective, the mono-chlorohydroxypyrimidine (176) was prepared.



(103) (175) (176)




(177) (178)

Treatment of the alkylated dihydroxypyrimidine (103) with phosphorus oxychloride gave the dichloropyrimidine (175) which upon reaction with an equivalent of sodium hydroxide yielded 6-chloro-4-keto-2-methyl-5-(pent-4-enyl)-1,6-dihydropyrimidine (176).

The chloro-hydroxypyrimidine possessed a further advantage in that, unlike the extremely insoluble 4,6-dihydroxypyrimidines whose insolubility hampers reaction, the material was both crystalline and soluble in organic solvents.

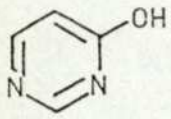
Thermolysis of the chloro-hydroxypyrimidine was predicted to yield the primary cycloadduct (177) capable of several possible bridge elimination processes, one possibility leading directly to the chloropyrindane (178).

In the event thermolysis of the material at various temperatures proceeded in an anomalous manner. No traces of the anticipated primary cycloadduct or bridge elimination products being detected by spectroscopic means.

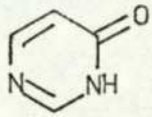
Intramolecular Cycloaddition Reactions of Mono-hydroxy-pyrimidines.

As an extension of the results achieved in the cyclo-addition reactions of 4,6-dihydroxypyrimidines, the intra-molecular cycloaddition reactions of some closely related mono-hydroxypyrimidines have been examined.

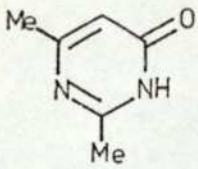
In a similar manner to 4,6-dihydroxypyrimidine, 4-hydroxypyrimidine (179) has been shown to mainly exist in the keto-tautomeric form (180) in polar solvents.[53]




(179)



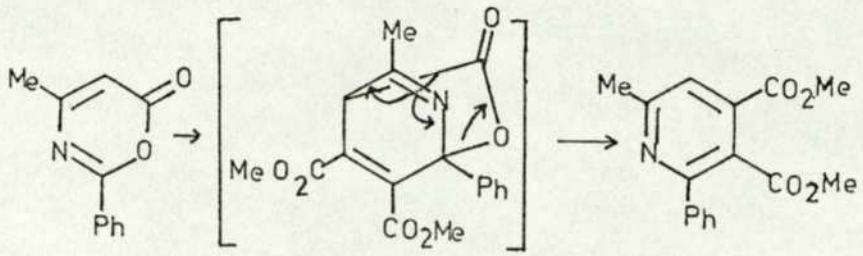

(180)




(188)

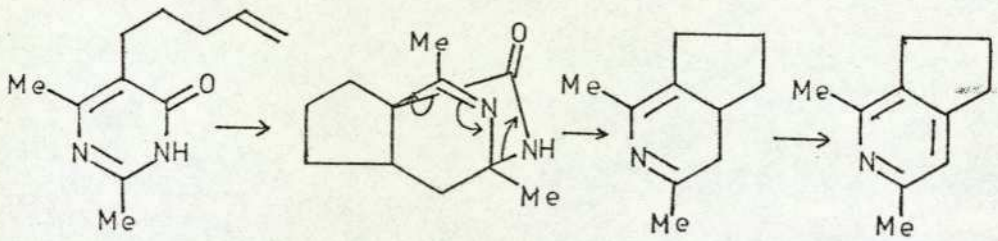
The initial work on attempted cycloaddition reactions of some mono-hydroxypyrimidines has been previously reported.[1] 2,4-Dimethyl-6-hydroxypyrimidine (188) was prepared but unlike the analogous dihydroxy derivative , was found to be inert towards bimolecular cycloaddition. Using a variety of dienophiles at both moderate and elevated temperature offered no trace of cycloaddition.[1]

This observation was perhaps surprising since a related series of compounds, the 1,3-oxazin-6-ones, had been shown to be capable of intermolecular cycloaddition. For example, 2-phenyl-4-methyl-1,3-oxazin-6-one (181) has been shown to undergo cycloaddition with dimethyl butynedioate (ADE) yielding the pyridine (183), formed by decarboxylation of the primary cycloadduct (182).[70]



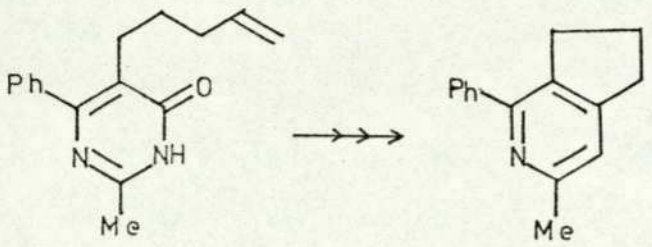
(181) (182) (183)

However, application of the advantages of intramolecularity to the monohydroxypyrimidine system resulted in cycloaddition. The dimethyl-pyrimidine (184) was prepared by Watt[1] and thermolysis at 198° for 18 hours led directly to the annelated pyridine (187).



(184) (185) (186) (187)

The formation of the pyridine (187) was rationalised by a mechanism involving intramolecular cycloaddition to give the primary bridge adduct (185) followed by elimination of cyanic acid to give the dihydropyridine (186) which, after subsequent aerial dehydrogenation, afforded the isolated pyridine (187).

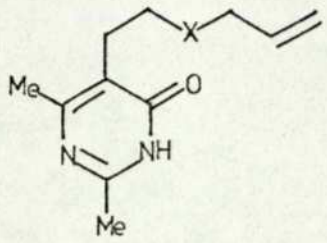



(188) (189)

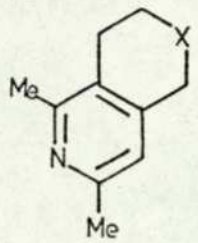
In the same report, the 4-phenylpyrimidine (188) was also prepared and upon thermolysis led to the isolation of the analogous phenyl substituted pyrindane (189).[1]

The generality and scope of the cycloaddition process involving mono-hydroxypyrimidines has been further examined by application to several other derivatives.

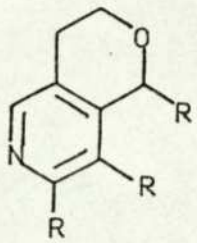
Since intramolecular cycloaddition has been shown to produce annelated pyridines the process again offered potential for use in the synthesis of certain naturally occurring compounds such as the monoterpenoid alkaloids. It was proposed that incorporation of an extra atom into the diene and dienophile linking chain of a mono-hydroxypyrimidine should,upon intramolecular cycloaddition,produce a cyclohexanopyridine structure (191). The synthetic potential of this proposal is as illustrated by the occurrence of a class of alkaloids, the gentianine-type alkaloids, possessing a related skeletal structure (192).



(190)

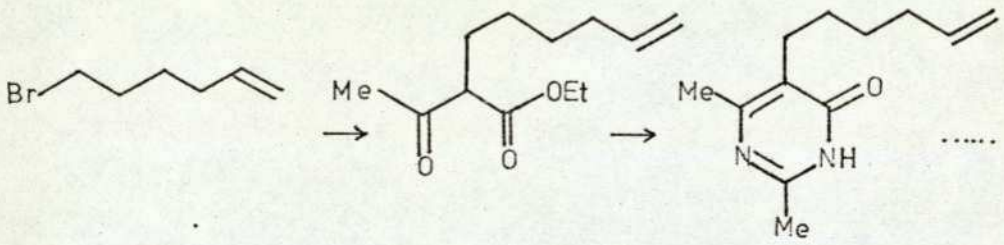


(191)

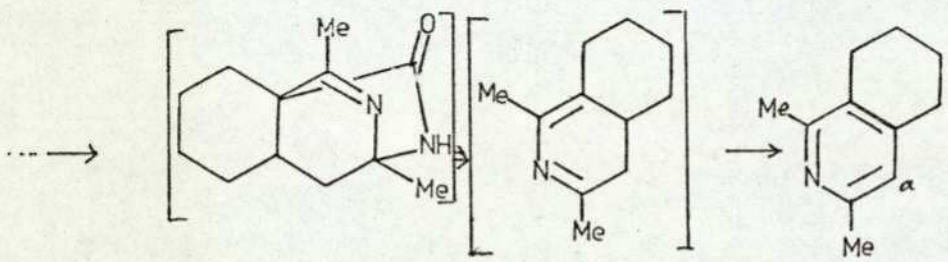


(192)

As a consequence of this proposal, the hexenyl pyrimidine (195) was prepared by the indicated route.



(193) (194) (195)



(196) (197) (198)

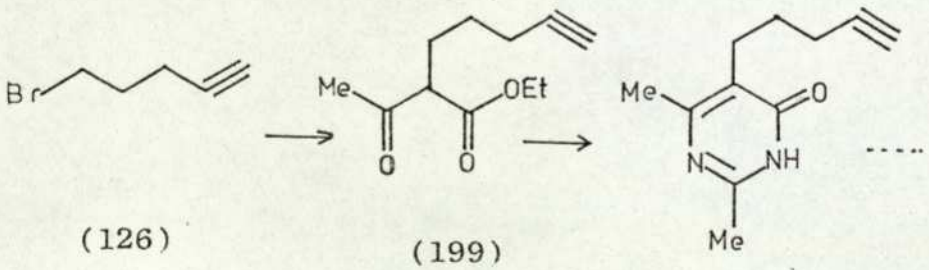
Commercially available 5-hexen-1-ol was treated with phosphorus tribromide to give 6-bromo-hex-1-ene (193).[71] The bromide was then used to alkylate ethyl acetoacetate, giving a moderate yield of ethyl (hex-5-enyl)-acetoacetate (194), which upon condensation with acetamidine hydrochloride in ethanolic sodium hydroxide,[72] produced 2,4-dimethyl-6-keto-5-(hex-5-enyl)-1,6-dihydropyrimidine (195).

Thermolysis of the pyrimidine at 198° led directly to the isolation of the annelated pyridine (198) formed by a mechanism assumed to be identical to that observed for the analogous pentenyl derivative.

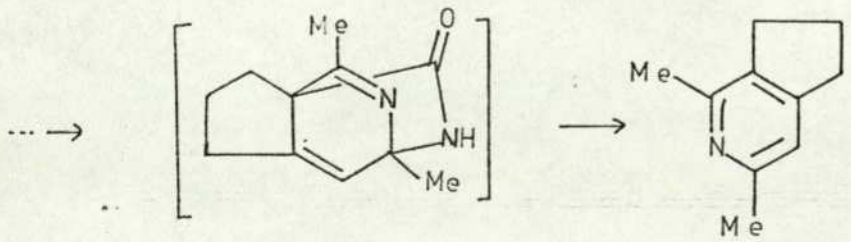
The $^1$H n.m.r. spectrum of (198) showed a distinct singlet, integrating to one proton, at $\tau$ 3.32, characteristic of the aromatic proton (a).

The cycloaddition was however found to progress at a rate somewhat slower than that observed in the pentenyl derivative, a result anticipated because of the tendency of a lengthening of the linking chain to increase the similarity of the intramolecular process to intermolecular additions. The possibility of formation of a fused six-membered ring was nevertheless illustrated.

The versatility of the cycloaddition process was further demonstrated by incorporation of an acetylenic dienophile into a mono-hydroxypyrimidine.




(126) (199) (200)




(201) (202)

5-Bromo-pent-1-yne (126) was prepared by the method previously described[64] (see page —91). The bromide was used to alkylate ethyl acetoacetate and condensation of the product, ethyl(pent-4-ynyl)acetoacetate (199), with acetamidine hydrochloride gave 2,4-dimethyl-6-keto-5-(pent-4-ynyl)-1,6-dihydropyrimidine (200) ($\nu_{max}$ 2120cm$^{-1}$) in moderate yield.

Thermolysis of the pyrimidine at 198° led to the facile formation of the annelated pyridine (202), identical to the product obtained from thermolysis of the analogous olefinic pyrimidine.[1] Formation of the pyridine (202) was rationalised by a mechanism involving cycloaddition to the primary adduct (201) and subsequent bridge elimination, although no traces of the primary cycloadduct (201) could be detected.

The rate of cycloaddition was again substantially increased by the introduction of the acetylene bond in place of an olefinic dienophile, the reaction going to completion in 3-4 instead of 15-18 hours.

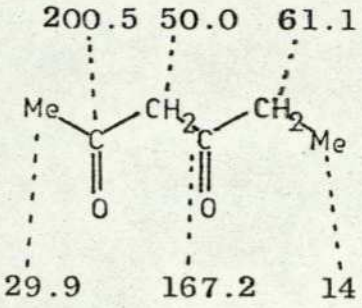
$^{13}C$ n.m.r. spectra.

The $^{13}C$ n.m.r. spectral assignments for various derivatives synthesised in the course of the work described in this thesis are given in table ( 2 ). The spectra were all recorded in deuteriochloroform and chemical shifts are quoted in parts per million from tetramethylsilane.

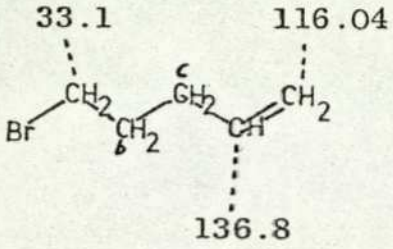
The spectra were recorded on a Jeol FX 60 spectrometer in fully decoupled, partial off-resonance and alternatively pulsed ("Gated") modes; the multiplicities of the signals in the non-fully decoupled spectra were in all cases consistent with the assignments made.

The spectral assignments made were compared with those previously reported for analogous compounds.[73.74,75]

Ethyl Acetoacetate
ref.[73]

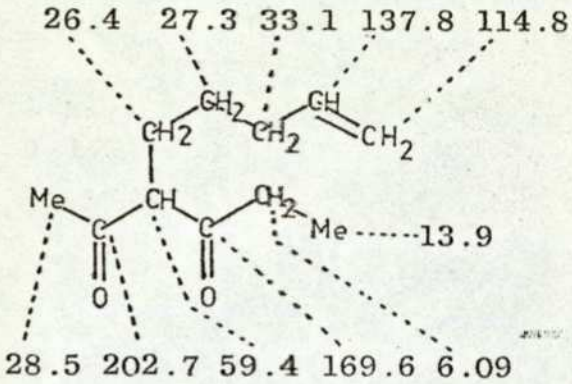



5-Bromopent-1-ene
(114)

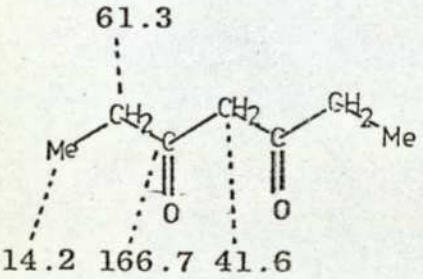



b,c=32.2,31.9

Ethyl 2-(pent-4-enyl)
acetoacetate




Diethyl malonate
ref.[73]




Diethyl-(pent-4-enyl)
malonate (115)

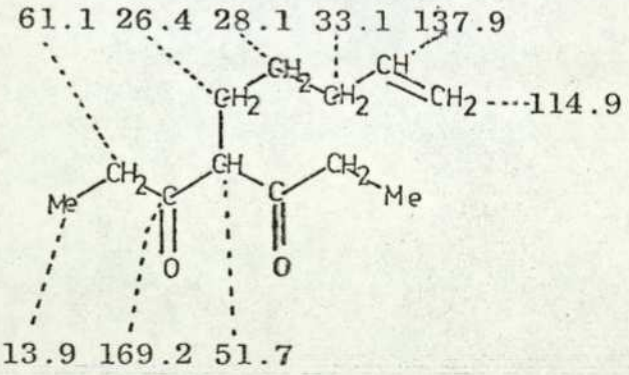
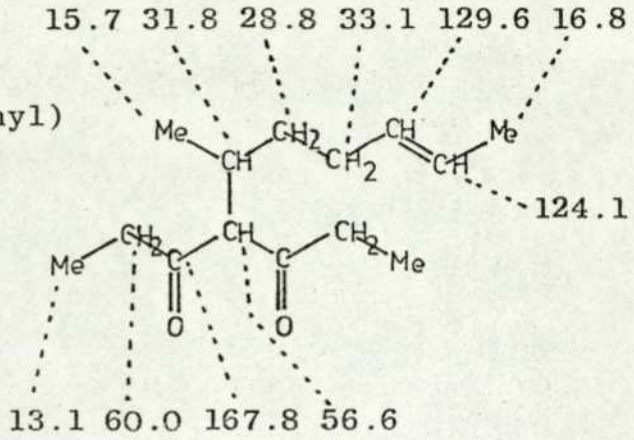
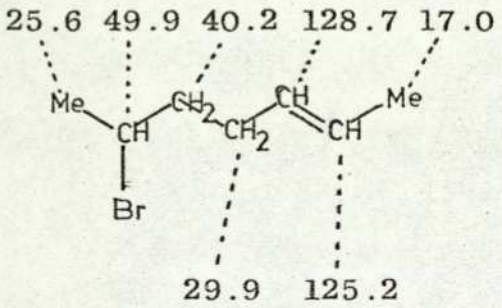



Table 2

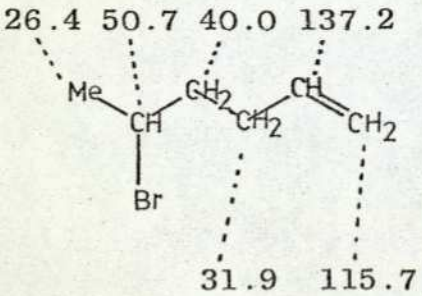
Diethyl(-1-methyl-hex-4-enyl) malonate (163)




6-Bromohept-2-ene (162)




5-Bromohex-1-ene (148)




5-Bromopent-1-yne (126)

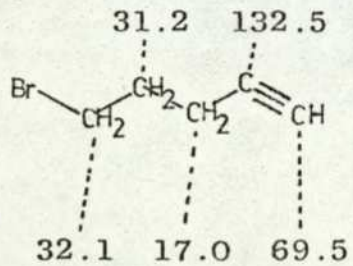
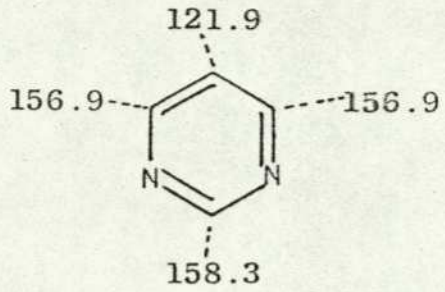
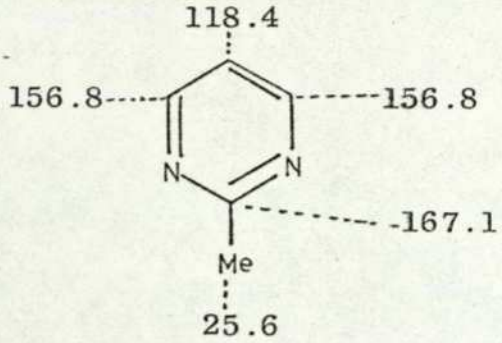



Table 2

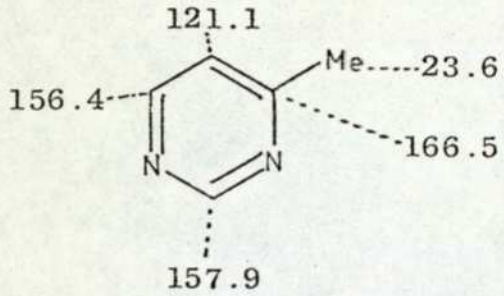
Pyrimidine
ref.[74]




2-Methylpyrimidine
ref.[74]




4-Methylpyrimidine
ref.[74]




2,4-Dimethylpyrimidine
ref.[74]

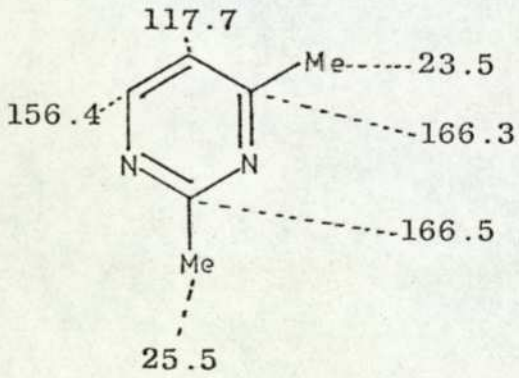
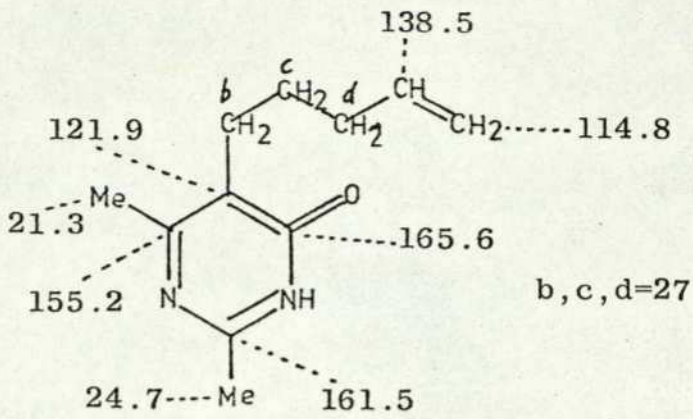
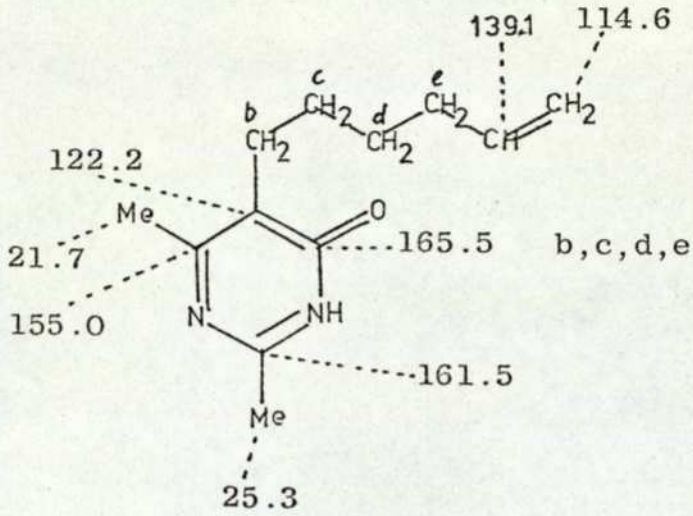



Table 2

(184)




(195)




(200)

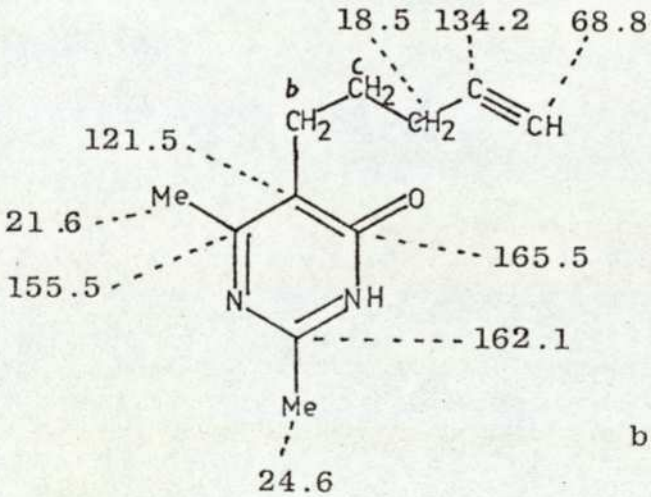
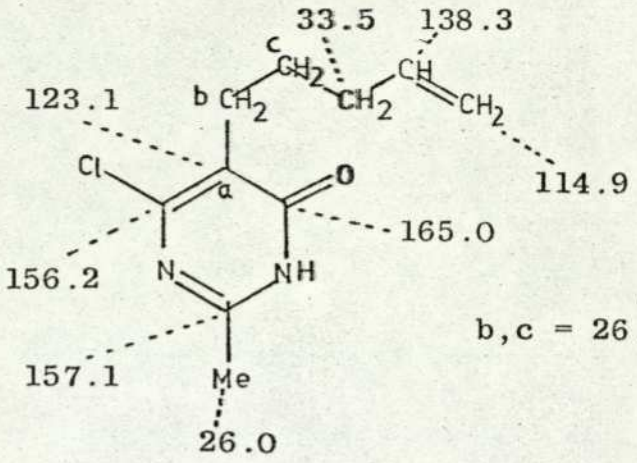


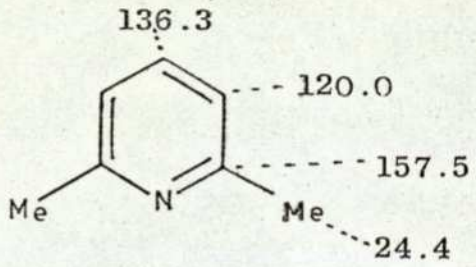

Table 2

6-Chloro-4-keto-2-methyl-5-(pent-4-enyl)-1,6-dihydropyrimidine (176)

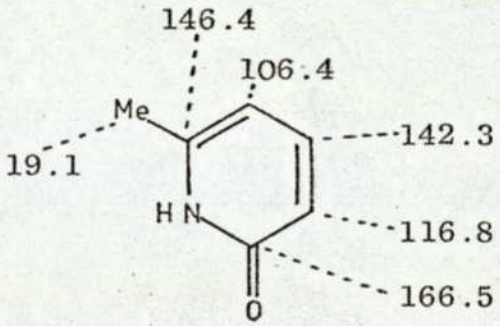



b,c = 26.5,30.9

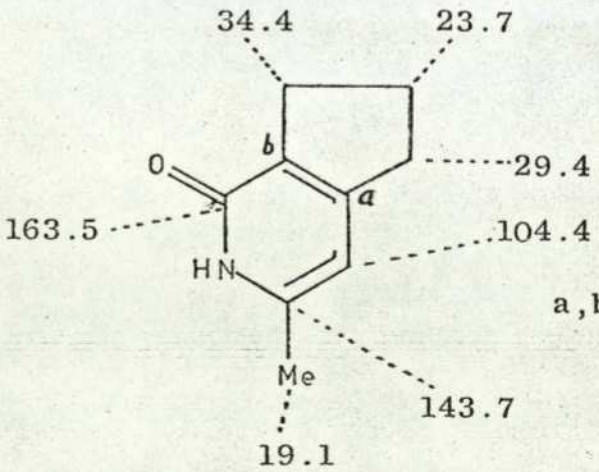
2,6-Dimethyl-pyridine ref.[73]




6-Methyl-2-pyridone



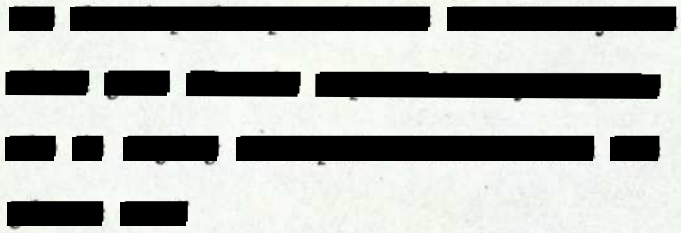

(120)




a,b = 157.1, 158.0.

Table 2

# EXPERIMENTAL SECTION



*James Thurber.*

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. All temperatures are quoted in degrees Centigrade.

Infra-red (i.r.) spectra were recorded on a Perkin-Elmer 157G spectrometer. Samples were prepared as nujol mulls or chloroform solutions for solids, and as thin films for oils, unless otherwise stated.

Ultra-violet (u.v.) spectra were recorded for ethanolic solutions in silica cells with a Pye-Unicam SP 800 instrument, unless otherwise stated.

Proton nuclear magnetic resonance ($^1$H n.m.r.) spectra were recorded on a Jeol MH 100 Spectrometer. Generally, deuteriochloroform was used as solvent with tetramethylsilane (TMS) as internal reference. Trifluoroacetic acid (TFA) was used alternatively as when stated. Coupling constants are quoted as J values in Hz. The abbreviations s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = complex multiplet, b = broadened, exch. = disappears on addition of $D_2O$, are used in connection with n.m.r. data.

Mass spectra were recorded by the Physical and Chemical Measurements Unit (P.C.M.U.), Harwell.

Commercial reagent grade solvents were used unless otherwise stated. Ethanol was dried by distillation immediately before use. Dimethylformamide was purified by distillation under reduced pressure from calcium hydride. Extracts were dried over anhydrous sodium sulphate and were evaporated under reduced pressure on a Buchi rotary evaporator. All reactions liable to be susceptible to water were carried out under an atmosphere of dry nitrogen.

Analytical chromatography separations were carried out on 1.0 or 0.2 mm. thin layers of Merck Kieselgel $GF_{254}$ silica and were monitored by viewing under U.V. light or by development in iodine vapour. Large scale separations were carried out using columns packed with MFC 60-120 mesh silica, with a silica to compound weight ratio of 50:1.

The thermolysis of compounds under pressure was achieved by reaction within sealed tubes. A solution of the material was placed in the bottom of a thick walled pyrex tube. The solution was degassed, frozen to liquid nitrogen temperature, the tube evacuated and the upper part sealed in a flame. Tubes were heated in an oven set at the stated temperatures.

N-allyl-(2-furfuryl)-amine (49).

Thionyl chloride (30.8g, 0.26mole) was added dropwise with stirring to an ice cooled solution of furfuryl alcohol (23.1g, 0.23mole) and dry pyridine (22.4g, 0.28 mole) in dry ether (50ml). After complete addition the mixture was stirred for 30 minutes and the ether layer decanted. The residual brown solid was re-extracted with ether several times. The combined extracts were washed with cold 50% potassium hydroxide solution, water, and dried.

The chloride was not isolated because of its extreme instability but was used as an ethereal solution.

Dry, powdered potassium hydroxide (14g, excess) was added to the ethereal solution followed by the dropwise addition of allyl amine (30g, 0.52mole). The mixture was allowed to stand overnight in a refrigerator, whereupon the ether was removed and the residual dark coloured oil heated at 70-80° for thirty minutes. After cooling, water (100ml) was added and the mixture extracted with ether (3x30ml). The extracts were combined, dried and the solvent removed leaving a residual oil, distillation under reduced pressure gave the title compound (49) as a colourless oil b.pt 50-54°/10mm (5g, 47%) $n_D^{22}$ 1.4848

$\tau$ 2.64 (1H,d), 3.67 (1H,dd), 3.79 (1H,d), 3.90-4.40 (1H,m), 4.70-4.94 (2H, m), 6.25(2H,s), 6.73 (2H,d), 8.27 (1H, broad s, $D_2O$ exch.)

$\nu_{max}$ 3100-3300, 2962, 2850, 1658, 1615, 1518, 1464, 1360, 1157, 1019, 926, 742cm$^{-1}$

O-allyl-(2-furfuryl)-ether (52).

Prepared by the method of Kirner.[33] Dry powdered potassium hydroxide (14g, excess) was added to an ethereal solution of furfuryl chloride, prepared exactly as in the previous experiment, followed by the dropwise addition of allyl alcohol (29g, 0.52mole). The mixture was allowed to stand at 0° overnight, when the solvent was removed and the residue heated at 75-80° for thirty minutes. After cooling, water (100ml) was added and the mixture extracted with ether (3x40ml). The extracts were combined, dried, and the solvent removed. Distillation of the residue at atmospheric pressure gave the title compound (52) as a colourless oil b.pt. 168-169° (lit.[33] b.pt. 173-174°), (7.0g, 63%), $n_D^{20}$ 1.4720, (lit.[33] $n_D^{20}$ 1.4718), $\tau$-2.61(1H,d), 3.70(2H,m), 3.90-4.30(1H,m), 4.55-4.97(2H, m), 5.58(2H,s), 6.00(2H,d), $\nu_{max.}$ 2862, 1645, 1608, 1505, 1362, 1230, 1156, 1018, 930, 744cm$^{-1}$

N-allyl(2-furoyl)-amide (58).

Allyl amine (1.20g, 20 mmole) in dry ether (20ml) was added dropwise with stirring to an ice cold suspension of furoyl chloride (2.80g, 20mmole) and potassium hydroxide (2.09, 100% excess) in ether (30ml). The mixture was stirred overnight at room temperature, water (50ml) added and the mixture extracted into ether (3x50ml). The combined extracts were washed with water (30 ml), dried and the solvent removed to leave an oil. Distillation under reduced pressure gave the title compound (58) as an oil

bpt. 200-210°/5mm. (1.4g,46%) $n_D^{19}$ 1.4880. $\tau$ 2.40(1H,d), 2.75(1H,d), 3.42(1H,dd), 3.80-4.42(1H,m), 4.70-5.02(2H, m), 5.64(2H,t), 7.67-8.26(4H,m).

$\nu_{max.}$ 2960, 1720, 1646, 1574, 1456, 1403, 1300, 1184, 1122, 1019, 920, 768cm$^{-1}$

(Found C, 66.52%, H, 6.68% $C_{10}H_{12}O_3$ requires C, 66.65% H, 6.71%)

N-methyl-(2-furoyl)aminoacetonitrile (62).

Sarcosine nitrile (1.40g, 20mmole) in ether (10ml) was added dropwise with stirring to an ice cold suspension of furoyl chloride (2.80g, 20mmole) and potassium hydroxide (2.0g, 100% XS) in ether (25ml). The mixture was stirred overnight at room temperature, water (30ml) added and the solution extracted with ether (3x30ml). The extracts were combined, dried, and removal of the solvent afforded an oil which crystallized on standing. Recrystallization from benzene/petroleum ether gave the title compound, m.pt. 62-64°. (0.85g, 28%) $\tau$ 2.40(1H,d), 2.76(1H,d), 3.43(1H,dd), 5.46(2H,s), 6.64(3H,s). $\nu_{max}$ 2968, 2260, 1634, 1582, 1487, 1394, 1157, 1075, 892cm$^{-1}$

(Found C, 58.47%, H, 4.95%, N, 17.04%, $C_8H_8N_2O_2$ requires C, 58.53% H, 4.91% N, 17.06%)

Pent-1-en-5-ol (113).

Thionyl chloride (134g, 1.1mole) was added dropwise with stirring to an ice cooled solution of tetrahydrofur-

furyl alcohol (102g, 1 mole) and pyridine (89g, 1.1 mole). After complete addition the mixture was stirred at room temperature for a further four hours and then extracted into ether (7x125ml). The ether extracts were combined, evaporated and the residue washed with water (3x25ml), dried over magnesium sulphate and distilled under reduced pressure to give tetrahydrofurfuryl chloride (59g, 50%) b.p. 60-65° (32mm), (lit[39] 41-42°(11mm)).

The chloride (52g, 0.44mole) in dry ether (75ml) was added dropwise with stirring to a suspension of powdered sodium (21.4g, 0.89 mole) in ether (120ml). After complete addition the mixture was stirred for three hours and decomposed with sufficient ice water to give two liquid layers. The ether layer was separated, dried, and evaporated. Distillation of the residue at atmospheric pressure gave pent-1-en-5-ol (24g 60%) b.p. 134-139° (lit[39] 134-137°) $n_D^{22}$ 1.4280 as a colourless oil. $\tau$ 3.80-4.42 (1H,m), 4.80-5.10(2H,b-t), 6.40(2H,t), 6.51(1H,b, $D_2O$ exch.), 7.70-8.46(4H,m).

5-Bromopent-1-ene (114).

Phosphorus tribromide (26.1g, 0.09mole) was added with stirring to a mixture of pent-1-en-5-ol (19.9g 0.23 mole) and dry pyridine (5.3g 0.06 mole) at -78°. The mixture was allowed to warm slowly to room temperature and extracted into dichloromethane. The extracts were washed with 2N sodium hydroxide, water, dried and evaporated. Distillation of the residue gave 5-bromopent-1-ene (114) (19.0g, 68%) b.p. 126-128°, (lit[59] b.p. 128-130°), $n_D^{22}$ 1.4640,

as a colourless oil. $\tau$ 3.80-4.46(1H,m), 4.78-5.10(2H,b-t), 6.56(2H,t), 7.70-8.15(4H,m).

Diethyl-2-(pent-4-enyl)malonate (115).

Diethyl malonate (5.4g, 0.034mole) was added dropwise to a solution of sodium (770mg, 0.034 mole) in ethanol (15ml). 5-Bromopent-1-ene (5g, 0.034 mole) was then further added and the mixture boiled under reflux with stirring for four hours. The mixture was cooled, evaporated, saturated calcium chloride solution (20ml) added and the product extracted into ether (3x50ml). Evaporation followed by distillation gave diethyl 2-(pent-4-enyl) malonate (5.3g, 70%) as a colourless oil b.p. 85-87° (1.5mm), (lit.b.p.[60] 126-127°(10mm)), $\nu_{max.}$ 1750, 1615, 1469, 1451, 1378, 1160, 1038, and 920cm$^{-1}$, $\tau$ 4.02-4.71(1H,m), 4.95-5.40(2H,m), 6.05(4H,q, J=7Hz), 6.88(1H,t, J=6.5Hz), 7.82-8.95(6H,m), and 8.97(6H,t, J=7Hz).

4-Hydroxy-2-methyl-6-oxo-5-(pent-4-enyl)-1,6-dihydropyrimidine (103).

Diethyl-2-(pent-4-enyl)malonate (2.85g, 12.5mmoles) and acetamidine hydrochloride (1.18g, 1 equivalent) were added to a solution of sodium (864mg, 3 equivalents) in ethanol (50ml). The mixture was stirred and boiled under reflux for six hours. After evaporation of excess ethanol, water (50ml) was added, the liquid neutralised with concentrated hydrochloric acid and buffered to pH 7. On cooling to 0° a white precipitate formed which was filtered off and

dried to give the title compound (2.0g, 83%) as a colourless solid subliming above 200°, $\nu_{max}$ 2600, 1670, 1577, 1446, 1340, 1309, 1155, 1049, 906, 810 and 780cm$^{-1}$, $\tau$(TFA) 4.00-4.95(1H,m), 5.06-5.49(2H,m), 7.51(3H,s), and 7.30-8.92(6H,m), (2H obscured). Identical to the material previously described.[1]

Thermolysis of the Pyrimidine (103).

The pyrimidine (4.0g) was taken up with dry, distilled dimethylformamide (10ml) and heated in a sealed tube at 200° for 72h. On trituration with ether (10ml), the primary cycloadduct, 8,11-diaza-9,10-dioxo-7-methyltricyclo-[5.2.2.$0^{1,5}$]-undecane (104) (440mg, 11%) was isolated as a colourless solid, identical to the material previously described.[1] $\nu_{max}$ 3170, 1707, 1663, 1399, 1320, 1280, 1190, 1182, 1118, 782 and 720cm$^{-1}$, $\tau$(TFA) 1.72-2.00 (2H,b-s), 7.40-8.52(9H,m) and 8.57(3H,s).

On removing the solvent from the filtrate, followed by charcoal treatment and chromatography, a second product was obtained 6-methyl-3,4-dihydro-3,4-trimethylene-2(1H) pyridone (119) ( 820mg, 21%) as a crystalline solid m.p. 137-139° (from EtOAc). $\nu_{max.}$ 3505, 3405, 2920, 2860, 1660, 1595, 1405cm$^{-1}$ $\tau$- 1.40(1H, b-s), 5.38(1H, b-d), 7.15-7.40 (2H,m), 8.20(3H,s) and 7.80-8.80(6H,m). $C_9H_{13}NO$ requires molecular mass 151.0997, Measured Mass, 151.0996

Upon thermolysis of the cycloadduct (104) at 200° for 72 h. the dihydropyridone (119) could be isolated in increased yield (30-40%).

Dehydrogenation of (119) to 6-methyl-3,4-trimethylene-2-(1H)pyridone (120).

The dihydropyridone (119)(200mg) was dissolved in freshly distilled xylene (30ml) and refluxed for 48h. 5% Palladium/charcoal (400mg) was added in aliquots at six-hourly intervals. Removal of the solvent afforded 6-methyl —3,4-trimethylene-2-(1H)pyridone (120) (120mg, 60%) m.p. 180-181°(from EtOAc).
$\nu_{max}$ 3380, 2940, 2860, 1650, 1565, 1458, 1125cm$^{-1}$,
$\tau$2.48(1H,b-s), 4.0(1H,s), 7.0-7.40(4H,m), 7.64(3H,s), 7.98(2H,m).
(Found: C, 72.0; H, 7.5; N, 9.4. $C_9H_{11}NO$ requires C, 72.5; H, 7.4; N, 9.4). Molecular ion, mass 149.0837, calculated for $C_9H_{11}NO$, 149.0841.

Preparation of 4-Hydroxy-6-oxo-5-(pent-4-enyl)-2-phenyl-1,6-dihydropyrimidine (108).

Sodium (230mg, 10mmoles) was dissolved in ethanol (25ml) and benzamidine hydrochloride (786mg, 5mmoles) added. Diethyl 2-(pent-4-enyl)malonate (1.14g, 5mmoles) was then added dropwise to the solution and the mixture boiled under reflux for six hours. The mixture was cooled, evaporated, water (25ml) added to the residue and the solution neutralised with concentrated hydrochloric acid and buffered to pH 7. On cooling to 0° a colourless solid precipitated which was collected, washed, and dried to give the title compound (108) identical to the material previously described[1] (396mg, 31%) m.p. 279-281° (lit[1] m.p. 280-282°) from ethyl acetate. $\nu_{max.}$ 3320, 1610, 1580, 1512, 1351, 1290,

1118, 918, 779 and 701cm$^{-1}$, $\tau$ 2.10-2.90(5H,m), 4.22-4.95 (1H,m), 5.05-5.55(2H,m), 7.50-8.76(6H,m), (2H, obscured). $\lambda_{max.}$ 232(25,000), 306(9,800).

Thermolysis of the Pyrimidine (108).

The pyrimidine (200mg) was taken up in dry distilled dimethyl formamide and heated at 200° in a sealed tube for 72 hours. The solvent was removed and the crystalline residue, containing two products, was purified by preparative layer chromatography.

The first product isolated was 8,12-diaza-9,11-dioxo-7-phenyltricyclo-[5.2.2.0$^{1,5}$] – undecane (109) identical to the material previously described,[1] (44mg, 22%), m.p. 120-121°, $\nu_{max.}$ 3350, 1721, 1659, 1279, 1178, 1031, 917, 754 and 693cm$^{-1}$, $\tau$(TFA) 2.32-2.84(5H,m), 6.78-8.56(6H,m), (2H obscured).

The second product isolated as a crystalline solid was 6-phenyl-3,4-trimethylene-3,4-dihydro-2(1H)pyridone (122) (23mg, 12%), m.p. 155-156° (from ethylacetate,) $\nu_{max.}$ 3490, 3385, 2930, 2860, 1680, 1585, 1450, 1375, and 910cm$^{-1}$, $\tau$ 2.20(1H, b-s), 2.40-2.84(5H,m), 4.42(1H,d, J= 2 Hz), 7.10-7.45(2H,m), 7.60-8.0(4H,m), 8.10-8.20(2H,m).

Dehydrogenation of (122) to 6-phenyl-3,4-trimethylene-2-(1H)pyridone (123).

The dihydropyridone (122)(110mg), was dissolved in freshly distilled xylene (25ml), and refluxed for 48 hours.

5% Palladium/charcoal (250mg) was added in aliquots at six-hourly intervals. Removal of the solvent afforded 6-phenyl-3,4-trimethylene-2(1H)pyridone (123) (74mg, 67%) m.p. 210-211° (from ethylacetate) $\nu_{max.}$ 2960, 1642, 1612, 1596, 1495, 1378, 1156, and 1074cm$^{-1}$, $\tau$ 2.40-2.66(5H,m), 3.48(1H,s), 7.00-7.40(2H,m), 7.98(2H,m).

Preparation of 4-Hydroxy-6-oxo-5-(pent-4-enyl)-1,6-dihydropyrimidine (116).

Formamidine acetate (3.12g, 30mmole) and diethyl 2-(pent-4-enyl)malonate (7.05g, 30mmole) were added successively to a solution of sodium (2.07g, 3 equivalents) in ethanol (100ml). The mixture was boiled under reflux for six hours, cooled and the solvent evaporated. The residue was dissolved in water (100ml) and the solution neutralised with concentrated hydrochloric acid and buffered to pH 7. On cooling to 0° a precipitate formed which was collected, washed, and dried to give 4-hydroxy-6-oxo-5-(pent-4-enyl)-1,6-dihydropyrimidine (116)(2.3g, 74%) as a colourless solid subliming without melting at 190°. $\nu_{max.}$ 2920, 2850, 2630, 1632, 1575, 1455, 1312, 1244, 1138, 913, and 894cm$^{-1}$, $\tau$(TFA) 0.97(1H,s), 4.00-4.36(1H,m), 4.84-5.04(2H,m), 7.32 (2H,t), 7.82(2H,t), 8.29(2H,m), (2H obscured). $\lambda_{max.}$ 249 (4,000), 262(5,200). Calculated for $C_9H_{12}NO$; C,60.00, H, 6.67, Found C, 60.06, H, 6.88%.

Thermolysis of the Pyrimidine (116).

The pyrimidine (200mg) was taken up in dry, distilled dimethylformamide (10ml) and heated at 200° in a sealed tube for 18 hours. The solvent was removed and the crystalline residue purified by preparative layer chromatography, using ethylacetate as eluent, to give 3,4-trimethylene-3,4-dihydro-2(1H)pyridone (118) as a crystallizing oil, (63mg, 31%), $\nu_{max.}$ 3210, 2945, 1680, 1660, 1405, 1376, and 1290cm$^{-1}$, $\tau$ 1.84(1H, b-s, $D_2O$ exch.), 4.08(1H,dd), 5.15(1H,m), 7.08-7.40(2H,m), 7.68-8.44(6H,m). Molecular ion 137.0842, Calculated for $C_8H_{11}NO$, 137.0841.

Pent-4-yn-1-ol (125).

Tetrahydrofurfurylchloride (50g, 0.42mole), prepared by the method of Brooks and Snyder,[39] was added dropwise during 30 mins. to a stirred suspension of sodamide, made from sodium (33.25g, 1.44mole), in liquid ammonia (750ml). After a further 16 hours stirring, dry ammonium chloride (72g, 1.34 mole) was slowly added and most of the ammonia allowed to evaporate. The product was extracted into ether and distillation under reduced pressure gave pent-4-yn-1-ol (32g, 64%), b.p. 60-66° (15mm)(lit.[63] b.p. 64-65°(16mm)), $\nu_{max.}$ 3540-3340, 2965, 2878, 2118, 1432, 1348, 1160, 1055, 944 and 903cm$^{-1}$ $\tau$ 6.04(1H,b-s, $D_2O$ exch.), 6.30(2H,t, J=5Hz), 7.72(2H,t, J=6Hz), 8.0(1H,s), 828(2H,dd).

5-Bromopent-1-yne(126).

Phosphorus tribromide (60.5g, 0.22mole) was added dropwise to a mixture of pent-4-yn-1-ol (46.5g, 0.55mole) and dry pyridine (11.2g, 0.14mole) at -70°. After complete addition, the mixture was allowed to reach room temperature, poured into ice/water, and extracted into ether (3x100ml). The extracts were combined, washed with 2N-sodium hydroxide, water, and evaporated. Distillation of the residue under reduced pressure gave 5-bromopent-1-yne (26.5g, 33%), b.p. 78-84° (100mm) (lit.[64] b.p. 80-82°(110mm)), $\nu_{max.}$ 2960, 2840, 2118, 1430, 1272 and 1245cm$^{-1}$, $\tau$ 6.48(2H,t, J=6Hz), 7.60-8.08(5H,m).

Diethyl 2-(pent-4-ynyl)malonate (127).

Diethyl malonate (5.4g, 0.033mole) and 5-bromopent-1-yne (4.85g, 0.033mole) were added successively to a solution of sodium (770mg, 1 equivalent) in absolute ethanol (50ml). The mixture was boiled under reflux for one hour and allowed to stir at room temperature for 18 hours. Ethanol was evaporated, water (30ml) added to the residue and the product extracted into ether (3x25ml). The extracts were combined, dried over magnesium sulphate and evaporated to yield diethyl 2-(pent-4-ynyl)malonate (3.9g, 53%) used without further purification. $\nu_{max.}$ 2930, 2878, 2118, 1720, 1626, 1440, 1364, 1092, 1024, and 852cm$^{-1}$, $\tau$ 5.83(4H, q, J=7Hz), 6.66(1H,t, J=6.5Hz), 7.40-8.52(7H,m), 8.76(6H, t, J=7Hz).

4-Hydroxy-2-methyl-6-oxo-5-(pent-4-ynyl)-1,6-dihydropyrimidine (128).

Acetamidine hydrochloride (1.18g, 12mmole) and diethyl 2-(pent-4-ynyl)malonate (2.85g, 12mmole) were added successively to a solution of sodium (864mg, 3 equivalents) in absolute ethanol (50ml). The mixture was boiled under reflux for 18 hours, cooled, evaporated, and the residue taken up in water (50ml). The solution was neutralised with concentrated hydrochloric acid and buffered to pH 7. Upon cooling to 0°, a white precipitate formed which was collected, washed and dried to give the title compound (0.80g, 35%), as an amorphous solid after sublimation at 200°. $\nu_{max}$ 2610, 2115, 1628, 1560, 1238, 1208 and 1153cm$^{-1}$, $\tau$ 7.14(3H,s), 7.60-8.20(7H,m), (2H, obscured)(TFA) $\lambda_{max.}$ 248(4,600), 263(6,550)

Thermolysis of the Pyrimidine (128).

The pyrimidine (150mg) in dimethylformamide was sealed in a tube and heated at 200° for six hours. Removal of the solvent left a crystalline mass which after treatment with charcoal and chromatographic purification afforded 6-methyl-3,4-trimethylene-2(1H)pyridone (120) (72mg, 46%) identical to the material previously obtained by dehydrogenation of the dihydropyridone (119).

4-Hydroxy-2-phenyl-6-oxo-5-(pent-4-ynyl)-1,6-dihydropyrimidine (131).

Benzamidine hydrochloride (2.77g, 18mmole) and diethyl 2-(pent-4-ynyl)malonate (4.0g, 18mmole) were successivley added to a solution of sodium (820mg, 2 equivalents) in absolute ethanol (30ml). The mixture was boiled under reflux for six hours, cooled and the ethanol evaporated. The residue was dissolved in water (50ml) and the solution neutralised with concentrated hydrochloric acid and buffered to pH 7. The precipated solid formed on cooling to $0^{o}$ was collected, washed and dried to give the title compound, (1.6g, 33%), as a pale yellow solid subliming at $220^{o}$. $\tau$ (TFA), 2.08-2.85(5H,m), 7.50-8.90(6H, m), (2H, obscured). $\nu_{max.}$ 2640, 2116, 1612, 1582, 1374, 1176, and 1110$cm^{-1}$. $\lambda_{max.}$ 232(25,000) and 306(9,800).

Thermolysis of the Pyrimidine (131).

The pyrimidine (110mg) in dimethyl formamide (5ml) was sealed in a tube and heated at $200^{o}$ for 18 hours. Removal of the solvent afforded a crystalline mass, purified by preparative layer chromatography on silica with ethyl acetate eluent to give 6-phenyl-3,4-trimethylene-2(1H)pyridone (123) (42mg, 40%) identical to the material previously obtained by dehydrogenation of the dihydropyridone (122).

5-Hexen—2-one (Allylacetone) (146).

Ethylacetoacetate (186g, 1.43mole) and allyl chloride (99.4g, 1.30mole) were successively added to a solution of sodium (30g, 1.30mole) in absolute ethanol (500ml). The mixture was stirred at room temperature for 18 hours and boiled under reflux for a further one hour. Removal of the solvent and distillation of the residue under reduced pressure gave ethyl $\alpha$-allylacetoacetate, b.p. 90-105°(15mm), (166g, 75%), which was then added to a solution of potassium hydroxide (61.6g 1 equivalent) in water (550ml) at 0°. The suspension was stirred at room temperature for 48 hours, concentrated sulphuric acid (33ml, 1 equivalent) in water (50ml) added and the mixture heated until no more carbon dioxide was evolved. The cooled solution was extracted with petroleum ether (40-60°) (5x100ml) and the extracts combined and washed with 2N sodium hydroxide. After evaporation of the solvent, the residue was distilled to produce 5-hexen—2-one, (34g, 35%), b.p. 127-132°, (lit[69] b.p. 128-132°). $\tau$ 3.94-4.36 (1H,m), 4.82-5.08(2H,m), 7.58(2H,t), 7.82(2H,m), 7.96(3H,s).

Hex-1-en—5-ol (147).

A solution of 5-hexen—2-one (28.0g, 0.28mole) in dry ether (60ml) was slowly added to a suspension of lithium aluminium hydride (2.9g, 0.075mole) in dry ether (300ml). After complete addition, the mixture was refluxed for two hours, cooled, and excess hydride destroyed with ethanol (5ml) and water (10ml). 15% Sodium hydroxide

solution (30ml) was added and the mixture filtered. Extraction of the filtrate with ether afforded hex-1-en-5-ol (20.2g, 89%), b.p. 136-139° (760mm), (lit.[69] b.p. 138-139° (760mm)), $\nu_{max.}$ 3320, 3080 1645, 1110, 990 and 910cm$^{-1}$ $\tau$ 6.25(1H,m), 6.35(1H, b-s, $D_2O$ exch.), 7.90(2H,m), 8.38 (2H,m), 8.72(3H,d, J=7.5Hz), 4.10-4.40(1H,m), 4.82-5.12 (2H,m).

5-Bromo-hex-1-ene (148).

Phosphorus tribromide (18.5g, 0.068mole) was slowly added to a mixture of hex-1-en-5-ol (20.2g, 0.20mole) and pyridine (1.07g, 0.013mole) at -70°. The mixture was allowed to reach room temperature, warmed briefly, and poured onto crushed ice. The solution was extracted with dichloromethane, (3x50ml), and the extracts combined, washed with sodium bicarbonate solution, water and dried. Removal of the solvent followed by distillation at atmospheric pressure gave 5-bromo-hex-1-ene (14.1g, 58%), b.p. 136-144°, (lit.[69] b.p. 138-144°), as a colourless oil. $\nu_{max.}$ 2960, 2918, 1638, 1438, 1374, 1233, 990 and 910cm$^{-1}$, $\tau$ 4.08-4.40(1H,m), 4.84-5.02(2H,m), 5.88(1H,m), 7.60-7.84 (2H,m), 8.0-8.18(2H,m), 8.28(3H,d, J=7.5Hz).

Diethyl 2-(-1-methyl-pent-4-enyl)malonate (149).

Diethyl malonate (5.4g 0.033mole) and 5-bromo-hex-1-ene (5.4g, 0.033mole) were successively added to a solution of sodium (770mg, 1 equivalent), in absolute ethanol (25ml). The mixture was boiled under reflux for six

hours, cooled, ethanol evaporated, and the residue taken up in water (25ml). Ether extraction afforded the title compound, (2.8g, 35%), as an oil used without further purification. $\nu_{max.}$ 2970, 2924, 1730, 1636, 1460, 1366, 1142, 1030 and 910cm$^{-1}$, $\tau$ 4.08-4.46(1H,m), 4.96-5.14 (2H,m), 5.85(4H,q, J=7Hz), 6.78(1H,d, J=7.5Hz), 7.60-8.12 (2H,m), 8.80(6H,t, J=7Hz), 9.02(3H,d, J=7.5Hz).

4-Hydroxy-2-methyl-6-oxo-5-(-1-methyl-pent-4-enyl)-1,6-dihydropyrimidine (150).

Acetamidine hydrochloride (800mg, 8.5mmole) and diethyl 2-(-1-methyl-pent-4-enyl)malonate (2.0g, 8.5-mmole) were added to a solution of sodium (580mg, 3 equivalents), in absolute ethanol (30ml). The mixture was boiled under reflux for six hours, cooled, ethanol evaporated, and the residue taken up in water (30ml). The solution was neutralised with concentrated hydrochloric acid and buffered to pH 7. On cooling to 0°, a precipitate formed which was collected, washed, and dried to give the title compound (1.03g, 56%), as a colourless solid subliming withoug melting above 200°. $\nu_{max.}$ 2600, 1628, 1547, 1438, 1344, 1042, 912 and 782cm$^{-1}$, $\tau$(TFA), 4.04-4.40(1H,m), 4.94-5.10(2H,m), 7.17(3H,s), 7.80-8.34(5H,m) 8.65(3H,d, J=7Hz), (2H obscured). $\lambda_{max.}$ 248(3,380), 264(5150).

Thermolysis of the Pyrimidine (150).

The pyrimidine (200mg) was taken up in dry distilled dimethylformamide (2ml) and heated in a sealed tube at 200° for 48 hours. On trituration with ether a colourless solid formed which was collected, washed and dried to give 2-Methyl-8,11-diaza-9,10-dioxo-7-methyltricyclo-[5,2,2.$0^{1,5}$]-undecane (151), (62mg, 31%), as a colourless solid subliming without melting at 200°. $\tau$ (TFA) 1.68-2.03(2H, b-s), 8.64(3H,s), 8.96(3H,d, J=7Hz), 7.30-8.75(9H,m). $\nu_{max.}$ 3170, 1702, 1658, 1304, 1180, 1144 and 775cm$^{-1}$.

On removal of the solvent from the filtrate a crystalline residue was obtained, which upon purification by preparative layer chromatography on silica afforded 3aza-4,9-dimethyl-2-oxo-bicyclo-[4,2,$0^{1,6}$]-nona-4-ene (152) (44mg, 28%) as an oil. $\tau$ 5.44(1H,m), 8.26(3H,d, J=1.5Hz), 9.02(3H,d, J=7Hz), 7.05-8.60(7H,m), (1H, obscured). $\nu_{max.}$ 3330-3100, 2940, 1664, 1438, 1378, 1308, 1114, 905cm$^{-1}$.

5-Hepten-2-one(crotyl acetone)(160).

Ethyl acetoacetate (87g, 0.68mole) was added to a cooled solution of sodium (7.7g, 0.34mole) in dried methanol (200ml). The solution was stirred at room temperature for thirty minutes and crotyl bromide (46g, 0.34mole) was added dropwise. The mixture was boiled under reflux for one hour, methanol evaporated and excess ethyl acetoacetate removed by distillation under reduced pressure. The residue, ethyl $\alpha$-crotyl-acetoacetate (53g, 84%, 0.28mole) was not purified further but was suspended in hot water (800ml). A solution of sodium hydroxide (70g, 1.75 mole) in water

(500ml) was added in three aliquots, over a period of two hours, with heating and stirring. The mixture was cooled and extracted with petroleum ether (40-60°) (5x100ml). The extracts were combined, dried and evaporated, distillation of the residue giving 5-hepten-2-one (27.8g, 73%), b.p. 151-155°(760mm), (lit.[69] b.p. 151-154° (750mm)). $\nu_{max.}$ 2918, 2870, 1711, 1430, 1359, 1162 and 967cm$^{-1}$, $\tau$ 4.48-4.68(2H,m), 7.96(3H,s), 8.40(3H,d, J=2Hz).

Hept-5-en-2-ol (161).

A solution of crotyl-acetone (10.0g, 0.089mole) in dry ether (20ml) was slowly added to a stirred suspension of lithium aluminium hydride (1.0g, 0.026mole) in dry ether (100ml). After complete addition the mixture was refluxed for a further two hours, cooled, and excess hydride carefully decomposed by addition of water (5ml); 15% sodium hydroxide solution (10ml) was added and the mixture filtered. Ether extraction of the filtrate gave hept-5-en-2-ol (8.0g, 80%) as a colourless oil b.p. 161-162° (760mm) and 40°(2mm), (lit.[69] b.p. 62-64°(12mm)). $\nu_{max.}$ 3440, 2956, 2920, 1638, 1452, 1378, 1112, 1016 and 916cm$^{-1}$, $\tau$ 4.48-4.68(2H,m), 6.22(1H,m, J=6Hz), 7.60 (1H,b-s, $D_2O$ exch.), 7.80-7.98(2H,m), 8.36(3H,d, J=1.5Hz), 8.84(3H,d, J=6Hz), 8.40-8.64(2H,m).

6-Bromohept-2-ene (162).

Phosphorus tribromide (5.4g, 20mmole) was slowly added to a mixture of hept-5-ene-2-ol(5.7g, 50mmole) and

pyridine (1.1g, 14mmole) at -30°. After complete addition the mixture was allowed to reach room temperature, poured onto crushed ice, and extracted into ether. Removal of the solvent and distillation of the residue gave 6-bromohept-2-ene (4.0g, 44%) as a colourless oil b.p. 150-152° (760mm) and 66-67°(22mm), $n_D^{26}$ 1.4592. $\nu_{max.}$ 2956, 2910. 1584, 1486, 1442, 1378, 1242, 970 and 742cm$^{-1}$, $\tau$ 4.52-4.68(2H,m), 5.92(1H,m ), 7.88(2H,m), 8.35(3H,d, J=2Hz), 8.38(3H,d, J=6Hz), 8.08-8.42(2H,m).

Diethyl 2-(-1-methyl-hex-4-enyl)malonate (163).

Diethyl malonate (10.5g, 65mmole) and 6-bromohept-2-ene (11.6g, 65mmole) were successively added to a solution of sodium (1.50g, 1 equivalent) in absolute ethanol (35ml). The mixture was boiled under reflux for 18 hours, cooled, ethanol evaporated and the residue taken up in water (35ml). Ether extraction afforded the title compound (10.5g, 63%), as a colourless oil b.p. 90-92° (0.5mm). $n_D^{27}$ 1.4350. $\nu_{max.}$ 2978, 2930, 1754, 1732, 1448, 1367, 1300, 1235, 1153, 1095, 1034 and 965cm$^{-1}$, $\tau$ 4.58-4.72(2H, m), 5.84(4H,q, J=7Hz), 6.80(1H,d, J=7.5Hz), 7.64-8.12(4H, m), 8.36(3H,d, J=2Hz), 8.78(6H,t, J=7Hz), 9.04(3H,d, J=7.5Hz).

4-Hydroxy-6-oxo-5-(-1-methyl-hex-4-enyl)-1,6-dihydropyrimidine (164)

Formamidine acetate (3.5g, 33mmole) and diethyl 2-(-1-methyl-hex-4-enyl)malonate (8.5g, 33mmole) were added to a solution of sodium (2.3g, 100mmole) in absolute ethanol

(50ml). The mixture was stirred for 18 hours at room temperature and boiled under reflux for a further one hour. Ethanol was evaporated and the residue taken up in water (30ml). The solution was neutralised with concentrated hydrochloric acid and buffered to pH 7. The precipitated solid was collected, washed and dried to give the title compound (3.0g, 44%), as an amorphous solid subliming without melting above 230°. $\nu_{max.}$ 2615, 1626, 1580, 1304, 1240, 1148, 104 and 962cm$^{-1}$; $\tau$ (TFA), 0.98(1H,s), 4.56(2H, m), 8.0(2H,m), 8.38(3H,d, J=2Hz), 8.65(3H,d, J=6Hz), 8.24-8.88(3H,m); $\lambda_{max.}$ 248(3,220), 262(3850).
Molecular mass 208.1210. Calculated for $C_{11}H_{16}N_2O_2$ 208.1211.

Thermolysis of the Pyrimidine (164).

The pyrimidine (200mg) was taken up in dry dimethyl formamide (2ml) and heated in a sealed tube at 200° for 18 hours. Upon cooling, the solvent was removed in vacuo to leave a crystallising residue. Treatment with charcoal followed by chromatographic separation using ethyl acetate as eluent gave 3-aza-5,9-dimethyl-2-oxo-bicyclo-[4,2,0$^{1,6}$]nona-4-ene (166) (49mg, 31%) as an oil, $\tau$ 4.50(1H,m), 8.38 (3H,d, J=1.5Hz), 9.02(3H,d, J=7Hz), 7.40-8.93(7H,m), (1H obscured); $\nu_{max.}$ 3400, 2938, 1655, 1452, 1394, 1142, 964.cm$^{-1}$
$M^+$ = 165.

2-Methyl-4-chloro-5-(pent-4-enyl)-6-oxo-1,6-dihydropyrimidine (176).

4,6-Dihydroxy-2-methyl-5-(pent-4-enyl)-1,6-dihydropyrimidine (103)(4.0g, 20mmoles) was dissolved in phospho-

rus oxychloride (160ml) and the mixture boiled under reflux for one hour. On cooling, excess phosphorus oxychloride was removed in vacuo and the residue poured onto crushed ice. Ether extraction afforded crude 4,6-dichloro-2-methyl-5-(pent-4-enyl)-1,6-dihydropyrimidine (175) which was added to 2N-sodium hydroxide solution (200ml). The mixture was refluxed for three hours, cooled, acidified with concentrated hydrochloric acid and the precipitate was collected, washed and dried to give the title compound (2.6g, 59%) as a crystalline solid m.p. 148-149° (from benzene). $\nu_{max.}$ 3380-2980, 2920, 2870, 1658, 1598, 1433, 1382, 1320, 1138, 1107, 914 and 886cm$^{-1}$, $\tau$ 3.95-4.30(1H, m), 4.82-5.10(2H,m), 7.28(2H,m), 7.47(3H,s), 7.82(2H,m), 8.16(2H,m). [Molecular mass 212.0718, Calculated for $C_{10}H_{13}N_2O^{35}Cl$, 212.0717]

6-Bromohex-1-ene (193).

Phosphorus tribromide (19.96g, 0.07mole) was added dropwise with stirring to a mixture of hex-1-en-6-ol (10.0g, 0.1mole) and dry pyridine (4.2ml, 0.05mole) at -78°. After complete addition the mixture was allowed to reach room temperature, poured onto crushed ice, and extracted into dichloromethane. The extracts were combined, washed with 2N sodium hydroxide solution, water and dried. Evaporation of the solvent afforded 6-bromo-hex-1-ene (10.0g, 61%), as a colourless oil b.p. 156-170° (760mm) (lit.[71] b.p. 115-122 (2.75mm)). $\nu_{max.}$ 3074, 2930, 2855, 1640, 1437, 1374, 1282, 1250, 1200, 1098, 990, 965 and 912cm$^{-1}$, $\tau$ 4.05-4.40(1H,m), 4.84-5.16(2H,m), 6.60(2H,t, J=6Hz), 7.80-8.60(6H,m).

Ethyl 2-acetyloct-7-enoate (194).

Ethyl acetoacetate (6.94g, 0.05mole) and 6-bromo-hex-1-ene (8.7g, 0.05mole) were added dropwise to a solution of sodium (1.23g, 0.05mole) in dry ethanol (30ml). The mixture was boiled under reflux for 18 hours, cooled, ethanol evaporated and the residue taken up in water (30ml). Extraction into ether afforded ethyl 2-acetyloct-7-enoate (8.0g, 74%) as a colourless oil used without further purification. $\nu_{max.}$ 3060, 2915, 2844, 1740, 1714, 1638, 1444, 1368, 1240, 1198, 1026, 995 and 856cm$^{-1}$, $\tau$ 4.10-4.30(1H, m), 4.90-5.12(2H,m), 5.72(2H,q, J=8Hz), 7.82(3H,s), 8.72 (3H,t, J=8Hz), 7.75-8.80(8H,m).

2,4-Dimethyl-5-(hex-5-enyl)-6-oxo-1,6-dihydropyrimidine (195).

Acetamidine hydrochloride (945mg, 10mmole) and ethyl 2-acetyloct-7-enoate (2.10g, 10mmole) were added to a solution of sodium hydroxide (800mg, 2 equivalents) in ethanol (20ml). The mixture was stirred at room temperature for 18 hours, ethanol evaporated and a sodium bicarbonate (400mg) sodium carbonate (400mg) mixture added to the residue. The mixture was taken up in water (15ml) and ether extraction afforded the title compound (1.2g, 54%) as white needles m.p. 89-91° from petroleum ether. $\nu_{max.}$ 2926, 2856, 1650, 1612, 1440, 1382, 1314, 1216, 1160, and 914cm$^{-1}$, $\tau$ 4.1-4.4(1H,m), 4.9-5.1(2H,m), 7.58 (3H,s), 7.68(3H,s), 7.40-8.64(8H,m), $\lambda_{max.}$ 230(5,240) and 274(5,010). (Found: C, 69.80; H, 8.79; N, 13.50; $C_{12}H_{18}N_2O$ requires C, 69.90; H, 8.74; N, 13.59.)

Thermolysis of the Pyrimidine (195).

The pyrimidine (200mg) was sealed in a tube and heated at 180° for 24 hours. On cooling, the residue was purified by preparative layer chromatography on silica to give 3-aza-2,4-dimethyl-bicyclo-[4.4.0]-deca-1,3,5-triene (198) (88mg, 56%), as a pale yellow oil.
$\nu_{max.}$ 1608, 1594, 1448, 1395, 1322, 910 and 854cm$^{-1}$,
$\tau$ 3.32(1H,s), 7.35(4H,b-t), 7.57(3H,s), 7.61(3H,s), 8.08-8.34(4H,m).

Ethyl 2-acetylhept-6-ynoate (199).

Ethyl acetoacetate (4.36g, 0.33mole) and 5-bromopent-1-yne(5.0g, 0.033mole) were added to a solution of sodium (770mg, 1 equivalent) in absolute ethanol (30ml). The mixture was boiled under reflux for four hours, cooled, ethanol evaporated, and the residue dissolved in water (25ml). Ether extraction afforded the title compound (2.7g, 42%) as a colourless oil used without further purification;
$\nu_{max.}$ 2936, 2116, 1735, 1712, 1630, 1533, 1430, 1365, 1252, 1150, 1060, 968 and 892 cm$^{-1}$,
$\tau$ 5.84(2H,q, J=6Hz), 6.60(1H,b-t), 7.78(3H,s), 8.66(3H, t, J=6Hz), 7.42-8.10(7H,m).

2,4-Dimethyl-5-(pent-4-ynyl)-6-oxo-1,6-dihydropyrimidine (200).

Acetamidine hydrochloride (945mg, 10mmole) and ethyl 2-acetylhept-6-ynoate (1.95g, 10mmole) were added to a

solution of sodium hydroxide (800mg, 2 equivalents) in ethanol (20ml). The mixture was stirred at room temperature for 18 hours, ethanol evaporated *in vacuo* and a mixture of sodium bicarbonate (400mg) and sodium carbonate (400mg) in water (15ml) added to the residue. Ether extraction gave the *title compound* (800mg, 42%) as white needles m.p. 107-108° from petroleum ether. $\nu_{max.}$ 2930, 2120, 1650, 1611, 1432, 1384, 1313, 1217, 1160, 887cm$^{-1}$; $\tau$ 7.60(3H,s), 7.64(3H,s), 7.25-7.84(5H,m), 8.24(2H,b-t). $\lambda_{max.}$ 231(5,500), 277(5,250).

*Thermolysis of the Pyrimidine (200).*

The pyrimidine (53mg) was sealed in a tube and heated at 180° for four hours. The residue was purified by preparative layer chromatography on silica to give *3-aza-2,4-dimethylbicyclo [4,3,0]-nona-1,3,5-triene (202)*, (34mg, 64%), as a pale yellow oil, identical to material previously reported.[1] $\nu_{max.}$ 1608, 1580, 1462, 1389, 1221, 1149, 1030, 939, 865 and 764cm$^{-1}$, $\tau$ 3.13(1H,s), 7.16(4H, b-t), 7.32 (3H,s), 7.58(3H,s), and 7.98(2H,t, J=7Hz). $\lambda_{max.}$ 267 (2,700). (Molecular mass 147.1035, Calculated for $C_7H_{15}O_3$ 147.1048).

## REFERENCES.


1. R.A. Watt, Ph.D. Thesis, London, 1976.
2. R.B. Woodward and R. Hoffmann, Angew.Chem., 1969, 81, 797; Angew.Chem.Int.Ed.Engl., 1969, 8, 781.
3. J. Sauer, Angew.Chem., 1966, 78, 233; Angew.Chem., 1967, 79, 76.
4. J. Hamer, "1,4-Cycloaddition Reactions." Academic Press, New York, 1967.
5. R. Huisgen, Angew.Chem., 1963, 75, 604; Angew.Chem. Int.Edn.Engl., 1963, 2, 565; Angew.Chem.Int.Edn. Engl, 1963, 2, 633; J.Org.Chem., 1976, 41, 403.
6. O. Diels and K. Alder, Justus Liebigs Ann.Chem., 1928, 460, 98.
7. J. Sauer. Angew.Chem.Int.Edn.Engl., 1967, 6, 16.
8. J. Sauer. Angew.Chem.Int.Edn.Engl., 1966, 5, 211.
9. R.B. Woodward and R. Hoffmann. Angew.Chem.Int.Edn. Engl., 1963, 2, 565.
10. K. Alder and G. Stein, Angew.Chem., 1937, 50, 510.
11. J. Sauer, H. Wiest and A. Mielert, Chem.Ber., 1964, 97, 3183.
12. K. Alder and M. Schumacher. Liebigs.Ann.Chem., 1951, 87, 571.
13. H. Stockmann. J.Org.Chem., 1961, 26, 2025.
14. K. Alder. Experientia Supplementum II, 1955, 86.
15. W.E. Bachmann and N.C. Deno. J.Amer.Chem.Soc., 1949, 71, 3062.
16. W. Oppolzer. Angew.Chem.Int.Edn.Engl., 1977, 16, 10.
17. R.G. Carlson. Ann.Rep.Med.Chem., 1974, 9, 270.
18. H.O. House and T. Cronin, J.Org.Chem., 1965, 30, 1061.

19. K. Alder and W. Vogt. Justus Liebigs Ann.Chem., 1949, 564, 120.

20. H.W. Gschwend and H.P. Meier. Angew.Chem., 1972, 84, 291.

21. H.W. Gschwend and H.P. Meier. Angew.Chem.Int.Edn. Engl., 1972, 11, 294; Helv.Chim.Acta., 1973, 56, 1763.

22. W. Oppolzer and W. Fröstl. Helv.Chim.Acta., 1975, 58, 593.

23. E. Wenkert and K. Naemura. Synth.Commun., 1973, 3,45.

24. W. Oppolzer. J.Amer.Chem.Soc., 1971, 93, 3833.

25. L.H. Klemm and W. Gopinath. Tetrahedron Letters, 1963, 1243.

26. L.H. Klemm, D.R. Olson and D.V. White. J.Org.Chem., 1971, 36, 3740, and L.H. Klemm, J.Org.Chem., 1976, 41, 2571.

27. R.B. Woodward and H. Baer. J.Amer.Chem.Soc., 1948, 70,1161.

28. H. Kwart and I. Burchuk. J.Amer.Chem.Soc., 1952, 74, 3094.

29. J.A. Berson and R. Swidler. J.Amer.Chem.Soc., 1953, 75, 1721.

30. C.D. Weis. J.Org.Chem., 1962, 27, 3514.

31. H. Krzikalla and H. Linge. Chem.Ber., 1963, 96, 1751.

32. D. Bilovic, Z. Stojanac and V. Hahn. Tetrahedron Letts. 1964, 2071.

33. W.R. Kirner. J.Amer.Chem.Soc., 1928, 50, 1958.

34. A.W. McCulloch, B. Stanovnik, D.G. Smith and A.G. McInnes. Can.J.Chem., 1969, 47, 4319.

35. K.S. Ayer, R.C. Cookson and D.A. Kaji. J.Chem.Soc. Chem.Commun., 1973, 161.

36. L.E. Overman. J.Amer.Chem.Soc., 1974, 96, 597.

37. R.S. Atkinson, D.R.C. Brimage, R. Stephen-Davidson and E. Gray. J.Chem.Soc.Perkin 1. 1973, 960.

38. A.L. Mendzhoyan, A.N. Sukiasyan and A.A. Aroyan. Chem.Abst. 1969, 70, 37581m.

39. L.A. Brooks and H.R. Snyder. Org.Synth.Coll.Vol.III, p. 698.

40. J.I.G. Cadogan, D.H. Hey and S.H. Ong. J.Chem.Soc., 1965, 1932.

41. W.Oppolzer. J.Amer.Chem.Soc., 1971, 93, 3836.

42. Y. Butsugan, S. Yoshida, M. Muto and T. Bito. Tetrahedron Lett., 1971, 1129.

43. K.H. Pfoertner and W.E. Oberhänsli. Helv.Chim.Acta., 1975, 58, 840.

44. H.W. Gschwend, M.J. Hillman and B. Kisis. J.Org. Chem., 1976, 41, 104.

45. R.M. Acheson and P.A. Tasker. J.Chem.Soc.(C), 1967, 1542.

46. E.B. Sheinin, G.E. Wright, C.L. Bell and L. Bauer. J.Heterocyclic.Chem., 1965, 5, 859.

47. D.W. Jones. J.Chem.Soc.(C). 1969, 1729.

48. P.J. Machin, A.E.A. Porter and P.G. Sammes. J.C.S. Perkin 1., 1973, 404.

49. H. Neunhoeffer and G. Werner, Annalen., 1974, 1190.

50. K.T. Potts and M. Sorm. J.Org.Chem. 1972, 37, 1422.

51. T. Kappe and W. Lube. Angew.Chem.Int.Edn.Engl., 1971, 10, 925.

52. G.M. Kheifets, N.V. Khronov-Borisov, A.I. Koltsov and M.V. Volkenskin. Tetrahedron, 1967, 23, 1197.

53. Y. Inoue, N. Furutachi and K. Nakanishi. J.Org.Chem., 1966, 31, 175.

54. R.B. Woodward and R. Hoffmann. Angew.Chem.Int.Edn. Engl., 1969, 8, 781.

55. K.L. Mok and M. Nye. J.C.S. Perkin 1, 1975, 1810.

56. K.N. Houk. Acc.Chem.Res., 1975, 8, 361.

57. P.G. Sammes and R.A. Watt. J.C.S.Chem.Commun., 1975, 502.

58. G.W. Kenner, B. Lythgoe, A.R. Todd and A. Tapham. J.Chem.Soc. 1943, 388.

59. F.B. LaForge, N. Green and N.A. Gersdorff. J.Amer. Chem.Soc., 1948, 40, 3707.

60. J.I.G. Cadogan, D.H. Hey and S.H. Ong. J.Chem.Soc. 1965, 1932.

61. A.W. Dox and L. Yoder. J.Amer.Chem.Soc., 1922, 44, 361.

62. E.J. Corey and R.L. Danheiser. Tetrahedron Letts., 1973, 4477.

63. L.A. Brooks and H.R. Snyder. J.Chem.Soc., 1952, 2873.

64. M. Olomucki. Chem. Abst. 1961, 55, 11294.

65. T. Sakan, A. Fujino, F. Murai, A. Suzui and Y. Butsugan. Bull.Chem.Soc.Japan. 1960, 33, 712.

66. G.W.K. Cavill and A. Zeitlin. Aust.J.Chem., 1967, 20, 349.

67. See review section of thesis - p.18.

68. N.K. Hart, S.R. Johns and J.A. Lamberton. Aust.J. Chem. 1968, 21, 1321.

69. A.W. Friederang and D.S. Tarbell. J.Org.Chem.,1968, 33, 3797.

70. E. Buschmann and W. Steglich. Angew.Chem.Int.Edn. Engl. 1974, 13, 484.

71. J.A. Brockman. Chem.Abst. 1961, 55, 18599a