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SOME REACTIONS OF 2-PYRIDONES AND

ISOQUINOLINIUM SALTS

A thesis presented by

GRAHAM PAUL GISBY

In partial fulfilment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

of the

CITY UNIVERSITY

THE CITY UNIVERSITY

LONDON

MAY 1979

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[REDACTED]

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Finally, I would like to thank my parents for all of their support and encouragement during the long course of my education.

Some Reactions of 2-Pyridones and
Isoquinolinium salts.

Abstract

A review of $[4^+ + 2]$ cationic polar cycloaddition reactions is presented, emphasizing mainly those reactions undergone by large heterocyclic cations. Special attention is paid to the modern mechanistic standpoint for these transformations. The effects that different substituents - on either or both the diene or dienophile - have on the course of the cycloaddition are discussed in relation to the observed regio- and stereochemistries and to the rates of reaction.

The alkylation of the sodium salts of various 2-(1H)-pyridones, and the intermolecular cycloadditions of several 1-methyl-2-pyridones with dimethylacetylenedicarboxylate (DMAD), are described. Attempts to induce intramolecular cycloaddition reactions across the diene backbone of several 2-pyridones are included.

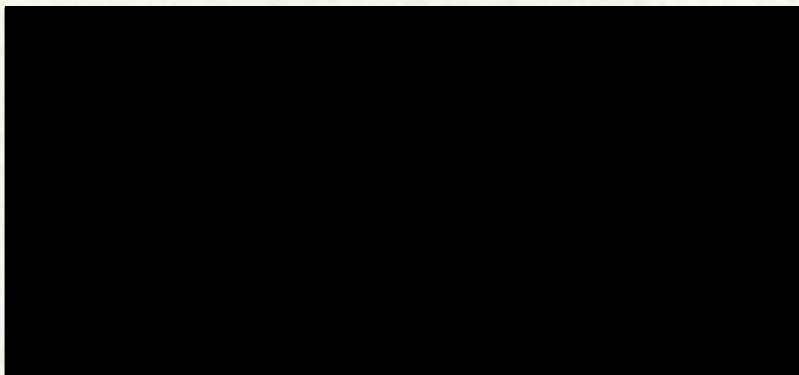
A recently reported synthesis of 6-substituted-4-hydroxy-2-pyridones has been extensively investigated, and the possibility of their alkylation pursued. Their reactions with DMAD are also dealt with.

A novel alkylation procedure of isoquinoline and its 3-methyl analogue is communicated, and has been used in the synthesis of isoquinolinium salts potentially able to undergo intramolecular Diels-Alder reactions. The thermolyses of these salts are described, together with the intermolecular cycloaddition reactions of simple 2,3-dimethylisoquinolinium salts with alkyl vinyl ethers.

Further transformation of the primary adducts obtained has led to several previously unknown structures.

An appendix containing the ^{13}C n.m.r. data of many of the more interesting structures obtained throughout this work has been included.

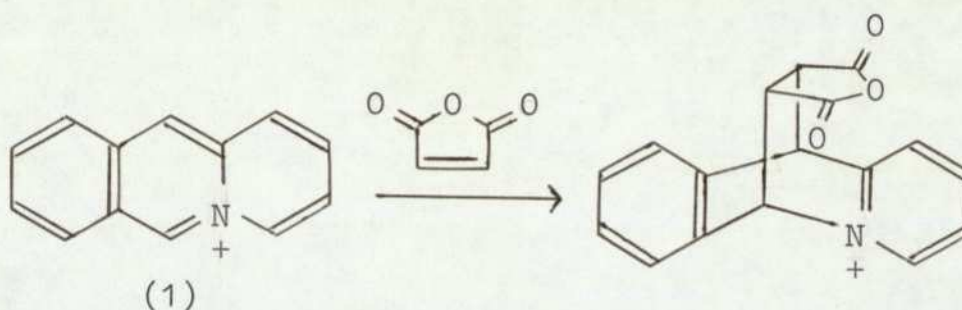
TO MY PARENTS



[4⁺ + 2] Cationic Polar Cycloadditions

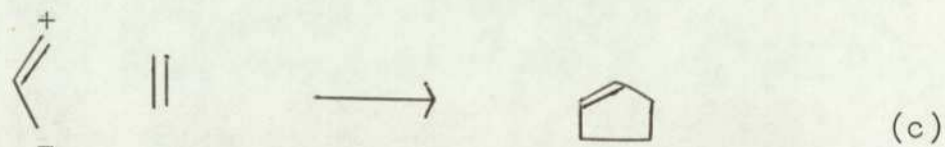
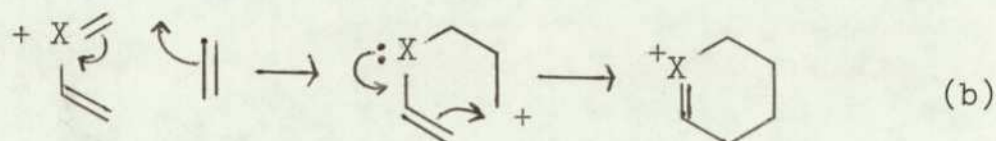
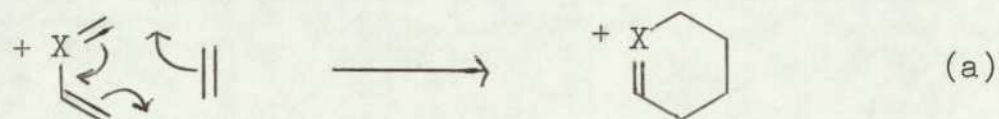
Introduction

Cationic polar cycloaddition reactions have been known since 1958, when Bradsher and Solomons observed that the electron-deficient acridizinium cation (1) was able to couple, in Diels-Alder fashion, with similarly electron-deficient olefinic derivatives, such as maleic anhydride and dimethyl fumarate (Scheme 1).¹



Scheme 1

Until Sauer and Wiest established the tenets of cycloaddition with inverse electronic demand systems four years later, the reaction proved mechanistically confusing.² These cycloadditions are characterised by the presence of a formal positive charge on one of the reacting components (in this case the diene) and therefore lie between the classical Diels-Alder additions (Scheme 2a) and sequented electrophilic additions (Scheme 2b). They also bear comparison to 1,3-dipolar cycloadditions (Scheme 2c).



Scheme 2

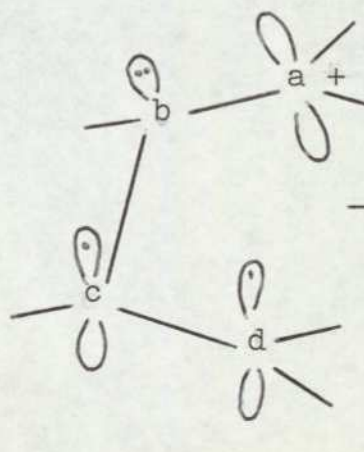
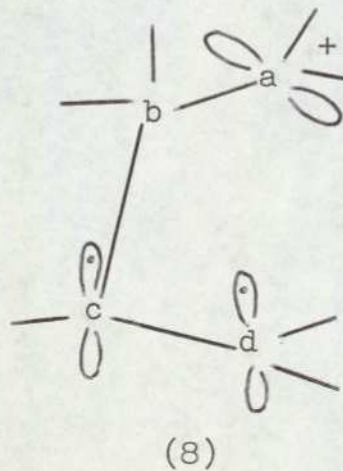
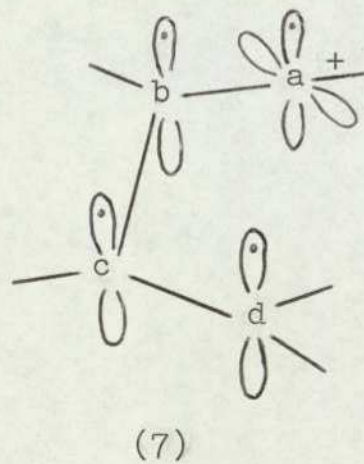
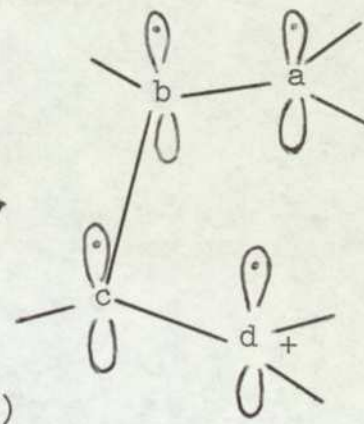
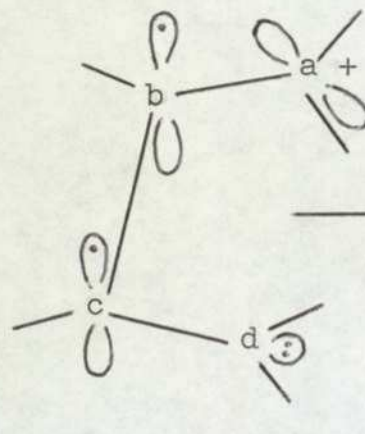
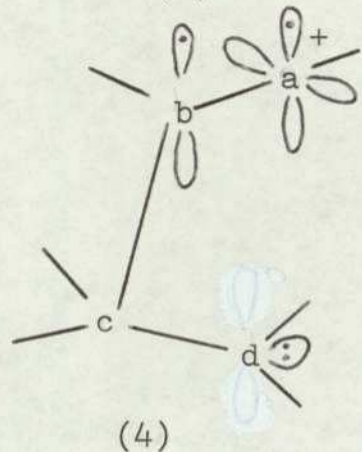
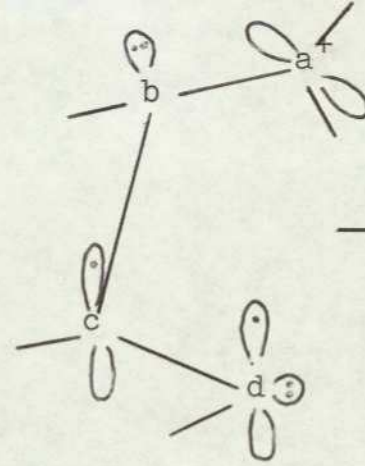
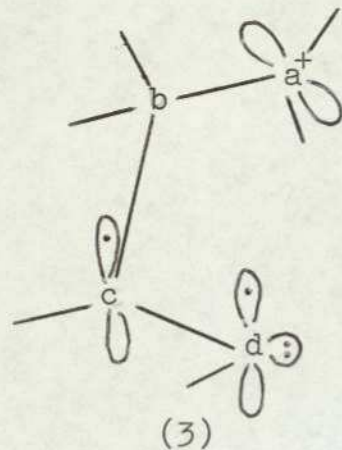
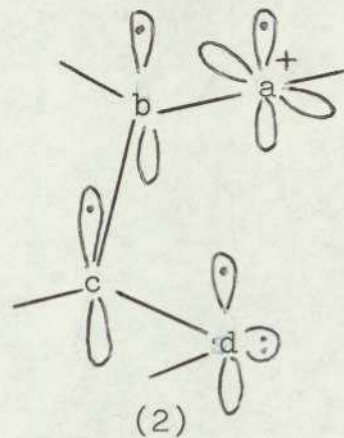
Such reactions appear to be 100% regioselective (up to the last review)³ and where highly polarisable alkenes are involved, very strongly stereoselective. Both of these selectivity effects, to be discussed later, are directly attributable to the electrostatic effects within the initial complex leading to the transition state for the reaction. These repulsive coulombic effects arise between the formal charge on the cation and the developing like-charge on the alkene. For heterocyclic cations one of the addition termini is the most electron-deficient carbon atom in the molecule, while the other cannot support a positive charge in any of the resonance forms that make up the structure. The major advantage of cationic polar cycloadditions is that owing to the 'inverse electron demand' requirements of the cation, reaction can take place quite readily with non-activated olefins. Very often reactions of this type provide a useful inlet to a wide range of unusual heterocyclic systems without recourse to exotic precursors.

The review of Schmidt draws attention to seven structurally different polar 1,4-systems capable of cycloaddition (2)-(8),⁴ and these may be collectively defined

as " compounds a-b-c-d that contain a sextet of electrons and a positive formal charge on a. There is at least one lone pair of electrons on d, or there is a pair of π -electrons between c and d."⁴ The criteria for the cycloadditions employed by Schmidt do not include the requirement that bond formation should occur synchronously (i.e. simultaneously, though not necessarily equally fast) in a concerted fashion, and therefore embraces structures for which a two-step mechanism only is possible.

Structures (3), (4), (6) and (8) all contain tetragonal centres between the reacting termini, and therefore fall into this category. Substitution of the sp^3 centre by a heteroatom then permits charge delocalisation throughout the cation, thus allowing the possibility of synchronous cycloaddition.

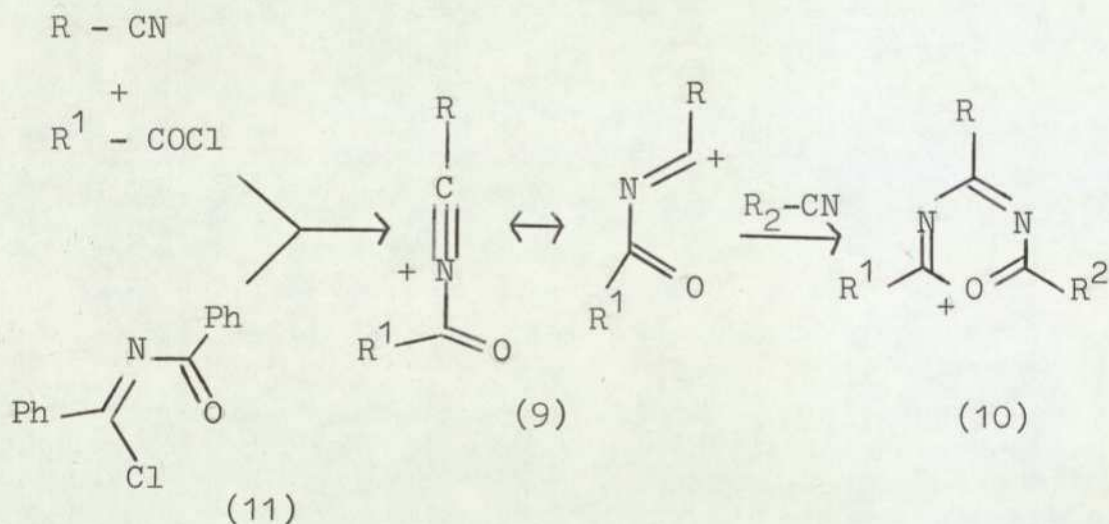
Separate consideration of each system with examples, recent developments and synthetic possibilities will demonstrate the overall generality of these polar cycloaddition reactions. Questions on the mechanism of these cycloadditions will be discussed in a later section. It is proposed that the normal nomenclature be retained throughout this review for the description of these addition reactions,⁵ thus the number of ring atoms provided by each component is listed, and the formal positive charge attached to the moiety bearing the charge.⁴ This review is restricted to $[4^+ + 2]$ cycloaddition reactions.



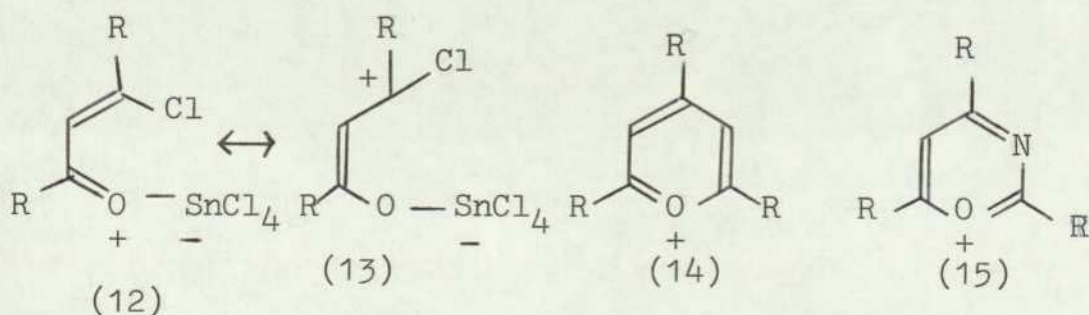
The Reactions

Cycloadditions involving structures of type (2).

Acyl chlorides react with nitriles in the presence of certain Lewis acids in two distinct stages.⁶⁻⁸ The first step consists of formation of the acyl nitrilium salt (9) which is generally not isolated. Reaction with a further molecule of the nitrile ($R^2 = R$) then leads to 1,3,5-oxadiazinium salts (10; $R^2 = R \neq R^1$) in very high yield. Providing evidence of intermediate (9), N-benzoyl benzimidoyl chloride (11) when treated with stannic chloride and p-toluenitrile gave salt (10; $R^1 = R = \text{Ph}$, $R^2 = \text{p-tolyl}$) in 55% yield. The analogous β -chlorovinyl ketone/stannic chloride complex (12) behaved similarly, with acetylenes



they give pyrilium salts (14),^{6,9} and with nitriles they afford 1,3-oxazinium salts (15).

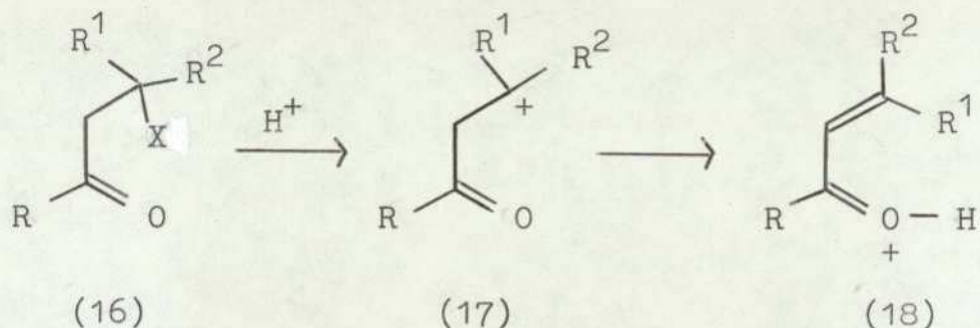


The 100% regioselectivity of addition of the dienophile can be explained in terms of the effect that the complexing Lewis acid has upon the atomic coefficients of the diene LUMO (Lowest Unoccupied Molecular Orbital).^{10,11} The fast rates of reaction observed can similarly be directly ascribed to the influence of the Lewis acid, since formation of complex (12) from β -chlorovinyl ketones produces two major effects on the molecular orbitals involved. Firstly, both the diene HOMO (Highest Occupied Molecular Orbital) and LUMO are lowered in energy and this increases the perturbation energy (see Chapter 1) gained from the initial interaction of the reacting components during cycloaddition. The extra stabilisation is derived from the diminution of the $\text{LUMO}_{(\text{diene})} - \text{HOMO}_{(\text{olefin})}$ energy gap. Since this is the major orbital interaction for inverse demand cycloadditions, depression of the $\text{LUMO}_{(\text{diene})}$ energy level will reduce this energy gap, and thus aid the overall reaction process. The second effect is a large increase in the polarisation of the diene LUMO, due mainly to the stabilisation of the higher energy species (13) by the Lewis acid. Enlargement of the polarisation will increase the regioselectivity of addition, in these extreme cases, to the exclusion of the other isomer.

It is also thought that the acid catalysed trimerisation of aryl isocyanates also proceeds via the $[4^+ + 2]$ polar cycloaddition.⁷

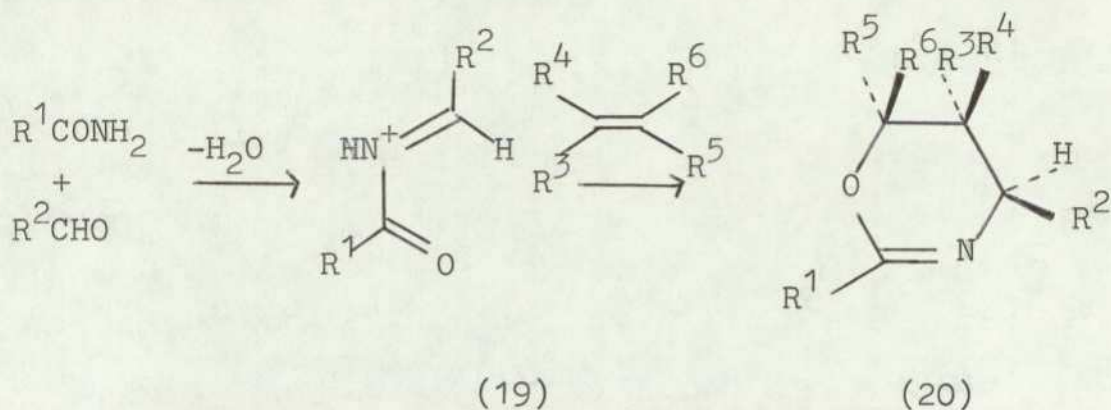
Cycloadditions involving structures of types (3) and (3a).

Much work has recently been reported for cycloadditions via structure (3a), a conjugated system, potentially therefore a Diels-Alder diene.¹²⁻¹⁹ Addition via (3) is restricted to the acid catalysed elimination of the weakly nucleophilic group X (X = OH, Cl) from β -substituted ethyl ketones (16) giving (17), followed by reaction with an acetylene,²⁰ or a nitrile.²¹

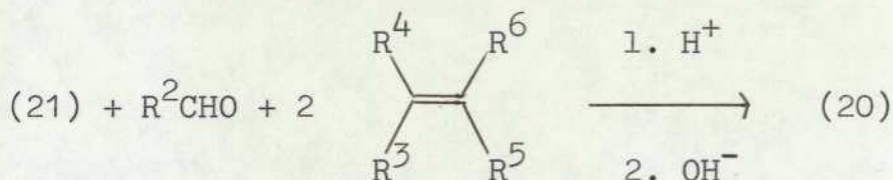
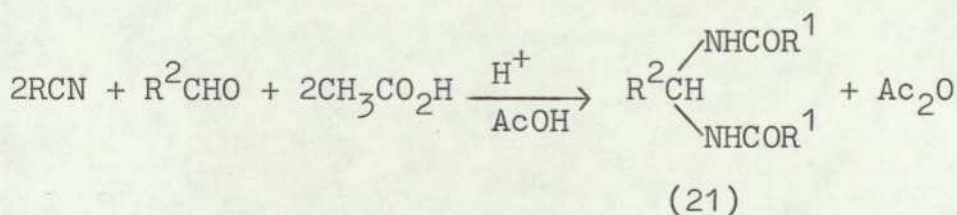


Pyrylium salts, formed by dehydrogenation of the labile dihydro-intermediate, and 4H-1,3-oxazinium salts, respectively, are obtained. Compounds of type (3) cannot cycloadd other than by a two-step mechanism, unless a proton transfer occurs, giving diene (18) from carbonium ion (17).

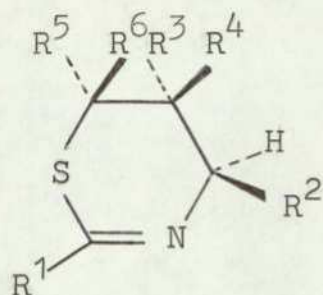
Substitution of carbon atom b of skeleton (3) by a nitrogen atom allows the formation of the amidomethylium cation (19). Giordano has made an extensive study of the preparation and reactions of this ion and its thio-analogue. Treatment of various primary amides, an aldehyde and an olefin with either boron trifluoride etherate in chloroform or glacial acetic acid, followed by mild basic hydrolysis gives 5,6-dihydro-4H-1,3-oxazines (20).¹² The reaction is very general. The same product (20) can be obtained by treating equimolar amounts of a nitrile, an aldehyde and an olefin with acetic acid via the diamidoalkane (21).¹³



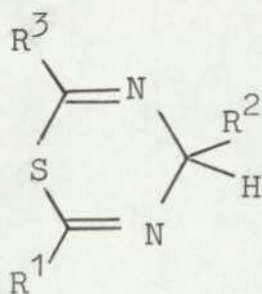
A wide variety of substituents have been employed. The



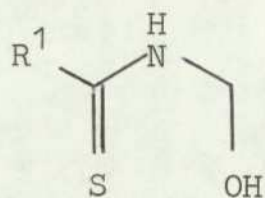
additions are regio- and cis-stereospecific, strongly indicating a concerted mechanism. Also polar effects of the substituents do not influence the stereochemistry of addition. Use of thioamides under the same conditions give the corresponding 5,6-dihydro-4H-1,3-thiazine (22) also with cis-stereospecificity.¹⁴ Structure elucidation was carried out using ¹H n.m.r. spectroscopy. When equimolar quantities of a nitrile, an aldehyde and a thioamide were treated with boron trifluoride etherate, then hydrolysed with dilute base, 40-70% yields of 4H-1,3,5-thiadiazine (23) were realised. Higher yields were consistently obtained, however, when N-hydroxymethylthioamides (24) were treated directly with acid in the presence of the nitrile, giving 4-unsubstituted



(22)

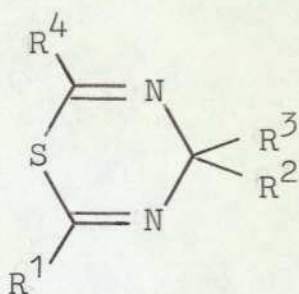


(23)

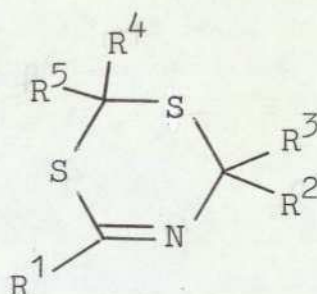


(24)

-4H-1,3,5-thiadiazines (23; $R^2 = H$).¹⁶ A thioamide, a ketone and a nitrile have been shown to give 4,4-dialkyl-4H-1,3,5-thiodiazines (25), while a thioketone instead of the above



(25)

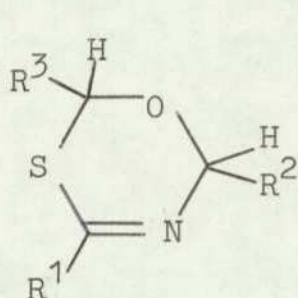


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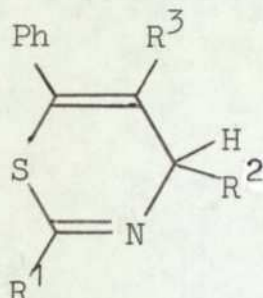
nitrile yields 4,4-dialkyl-4H-1,3,5-dithiazines (26) in good yield.¹⁷ Diastereoisomer ratios for this reaction have not been investigated. The thioketone was generated in situ either from the dithioacetal or from the thioketone trimer. Again better yields were obtained when the N-hydroxymethylthioamide (24) was used directly in the synthesis. Diastereoisomers were observed however, when p-chlorothiobenzamide, benzaldehyde and 2,4,6-trimethyl-2,4,6-triphenyl-1,3,5-trithiane were subjected to the standard treatment; compounds (26; $R^1 = p\text{-ClC}_6\text{H}_4$; $R^2 = \text{Ph}$; $R^3 = \text{H}$; $R^4, R^5 = \text{CH}_3, \text{Ph}$) were obtained.¹⁷ When the dithiazine (26; $R^1, R^2, R^3 = \text{alkyl or H}$, $R^4 = R^5 = \text{Ph}$) was treated with LAH, diphenyl methane was

formed. Acid hydrolysis of the dithiazine caused the formation of benzophenone, while heating above its melting point initiated cycloreversion, and the elimination of diphenyl thioketone.¹⁷

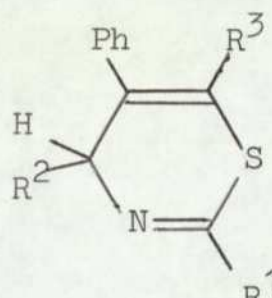
Thioamides and two equivalents of an aldehyde give 6H-1,3,5-oxathiazines (27; $R^2 = R^3$) while a potentially more useful synthetic approach has been evolved following direct treatment of N- α -hydroxyalkylthioamides with acid in the presence of an aldehyde.¹⁸ In this way all three ring substituents can be controlled instead of only two.



(27)



(28)

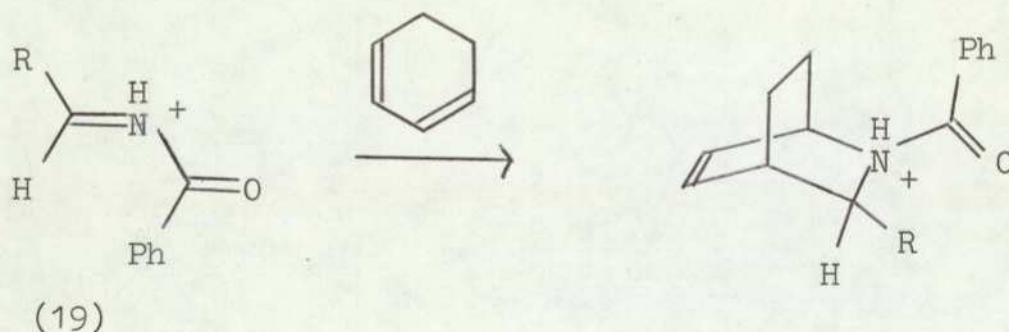


(29)

A non-regiospecific addition resulted when a thioamide, an aldehyde and a phenylalkylacetylene were allowed to interact;¹⁹ two 4H-1,3-thiazines (28) and (29) were obtained. It was proposed that some of the protonated amidomethylum ion may be eliminating a molecule of mineral acid to leave the thioketo-imine to cycloadd in the normal sense, i.e. not by an inverse demand mechanism. The rest of the salt then cycloadds both regio- and cis-stereospecifically.¹⁹ This theory was not tested by performing the reaction with an amidomethylum ion derived from a secondary amine that could not eliminate the same acid.

The character of the amidomethylum ion (19) can be altered such that the iminium function can behave as a

cationic 2π component. Thus Krow et al., have synthesised the protonated ketoimmonium ion (19; $R^1 = \text{Ph}$, $R^2 = \text{H}$ or Ph) and demonstrated its cycloaddition with cyclohexa-1,3-diene (Scheme 3).²²



Scheme 3

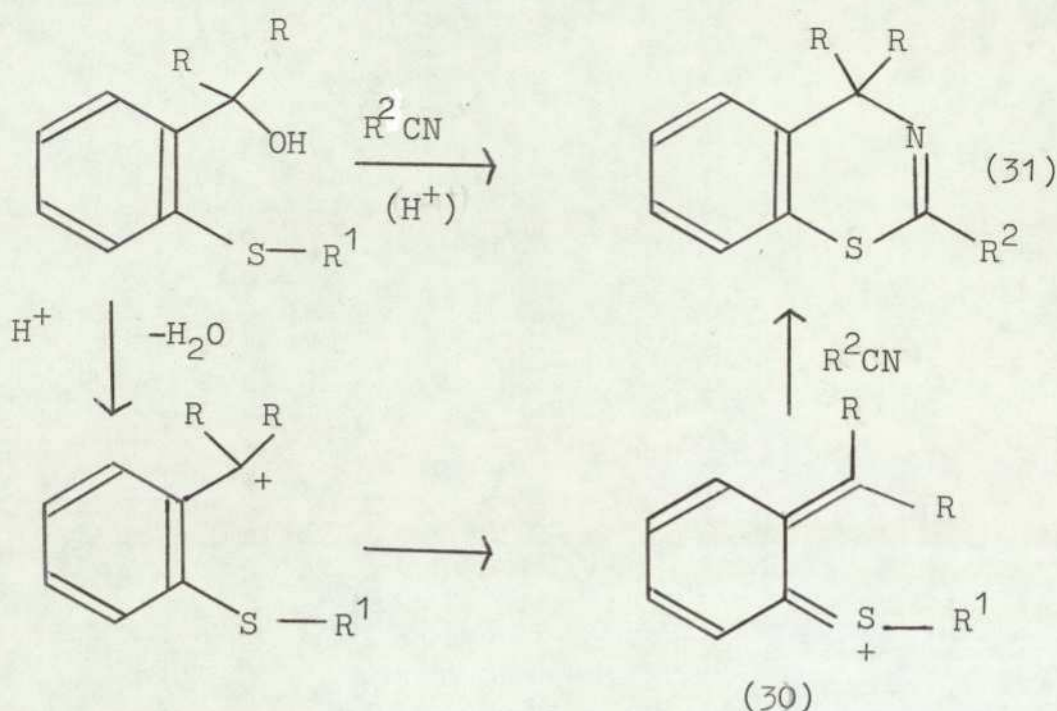
The analogous alkoxycarbonylamidomethylum ions (19; $R^1 = \text{OR}$, $R^2 = \text{H}$ or Ph) undergo the same 2π addition in good yield with a variety of dienes.^{22,23}

Cycloadditions involving structures of type (4).

Reactions of this type have not been reported.

Cycloadditions involving structures of type (5).

Reactions of this type include the acid catalysed dehydrohalogenation, or dehydration of *o*-hydroxybenzyl halides or alcohols. Even protonated quinonemethides have been generated, possessing an electron withdrawing ring nitro-substituent.²¹ Addition of 2-pentenenes to this derivative were found to be non-regiospecific owing to the similarity of the alkyl substituents;²¹ however, the additions were always cis-stereospecific. Recently it has been found that *o*-alkylthiobenzyl alcohols undergo the same transformations



giving, with nitriles, 4,4-dialkylbenzo[e]-1,3-thiazines (31) via the cation (30).²⁴ *o*-Aminobenzyl chloride behaves similarly to give 3,4-dihydroquinazolines in very high yield. Again evidence suggests a concerted mechanism for this last reaction.²⁵

Cycloadditions involving structures of type (6).

Reactions of 1,3-diols,²⁶ or 3-halopropanols,²⁷ with nitriles in the presence of acid gives 5,6-dihydro-4H-1,3-oxazinium salt, i.e. salts of (20). Mercaptoalcohols have been used with success to produce salts of (22): the 5,6-dihydro-4H-1,3-thiazinium cation.^{27,28}

Cycloadditions involving structures of type (7).

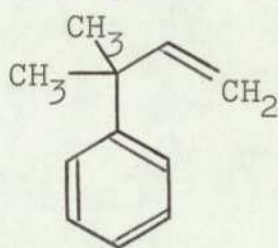
Reactions of this type have not been identified.

Cycloadditions involving structures of types (8) and (8a).

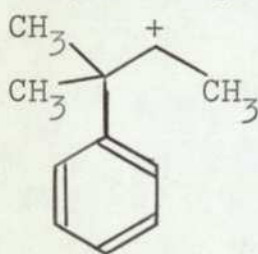
This type (8a) has been the most systematically investigated, since it embraces the vast body of heterocyclic

cationic systems that are capable of undergoing Diels-Alder reactions in the inverse demand sense. A good review of many of these reactions is provided by Bradsher.³ He centres his interest on the acridizinium ion (1) and makes several comments on possible mechanisms operating for these cycloadditions, ultimately favouring the concerted approach. Recent work involving the isoquinolinium and acridizinium (1) ions came out strongly in agreement with this view and many of the reactions that rightfully belong here will be considered in later discussion of the modern mechanistic standpoint.

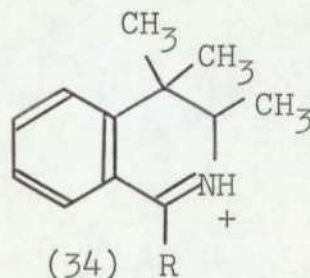
An example of a reaction involving structure (8) is provided by the allylbenzene (32), which on treatment with acid yields carbonium ion (33). Subsequent reaction with nitriles gives the 3,4-dihydroisoquinolinium salts (34) in



(32)



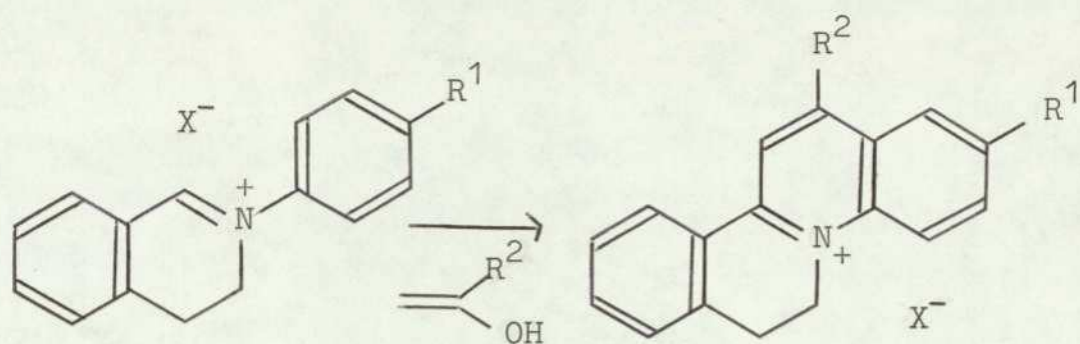
(33)



(34)

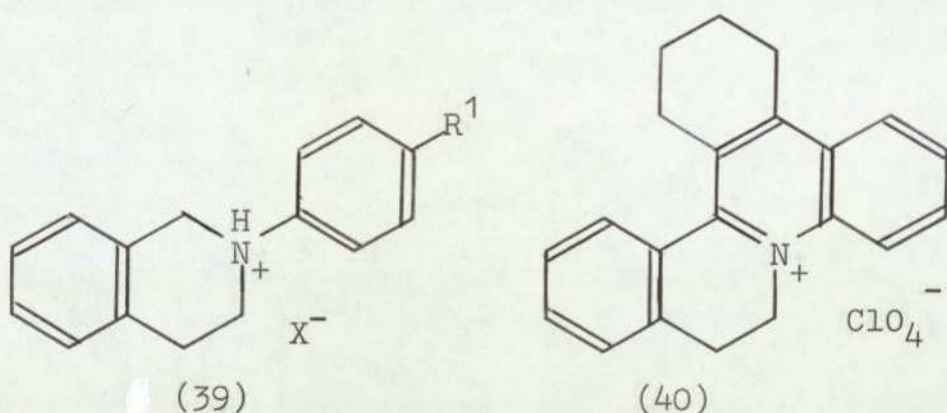
good yields.^{29,30} The mechanism is not concerted because of the lack of conjugation in the system. The stereochemistries of unsymmetrically substituted olefin cycloadditions have not been ascertained.

Certain 1-phenyl-3,4-dihydroisoquinolinium salts have been observed to cycloadd with the enol forms of various ketones and aldehydes via structure (8a).³¹ Thus 6,7-dihydrobenzo[a,f]quinolizinium salts (35)-(38) are obtained from acetone and acetaldehyde enol addition to the precursor, followed by dehydration and oxidative hydride elimination



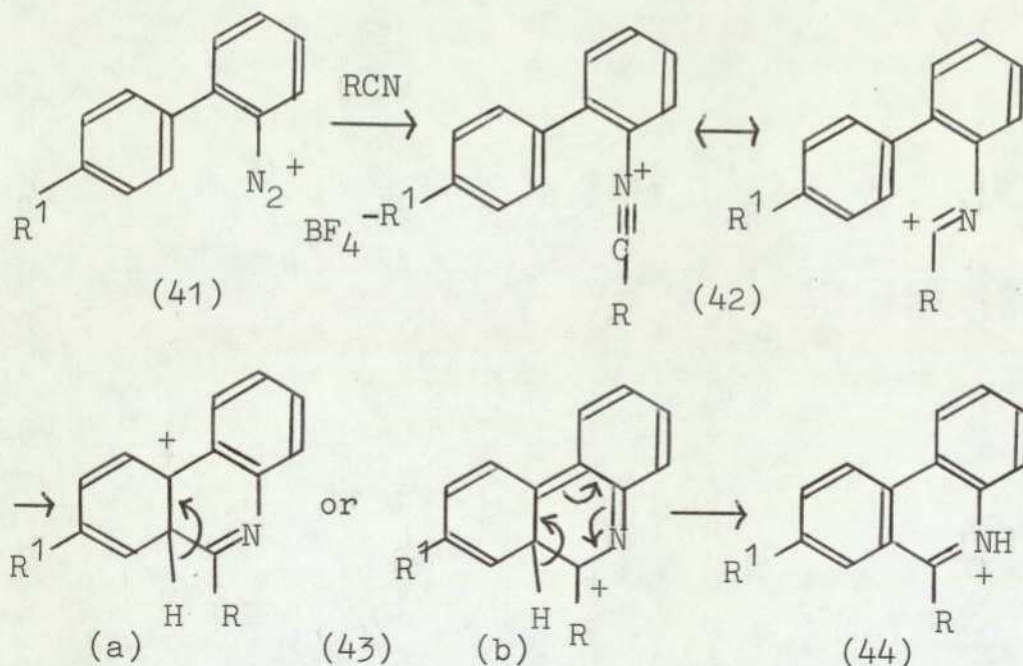
R ¹	R ²	X	
H	CH ₃	Br	(35)
OCH ₃	CH ₃	Br	(36)
H	H	ClO ₄	(37)
OCH ₃	H	Br	(38)

from the intermediate dihydroquinolinium nucleus. Unfortunately the hydride transfer occurs with consumption of the unreacted dihydroisoquinolinium precursor, thus the maximum yield is restricted to only 50%. Large amounts of (39) were always observed. Reaction also occurred with the cyclohexanone enol to afford 1,2,3,4,10,11-hexahydrotribenzo-[a,c,h]-quinolizinium salt (40).³¹

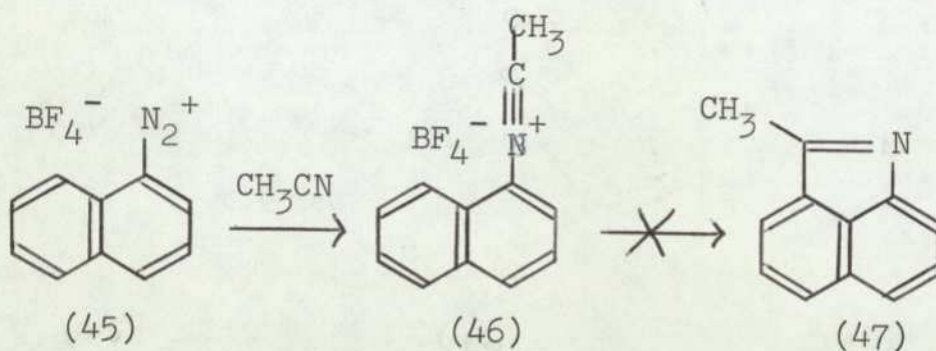


Another important synthesis of polycyclic heterocycles is furnished by the decomposition of *o*-phenylaromatic diazonium salts with nitriles. Petterson *et al.*, treated a range of diazonium tetrafluoroborates (41) with several different nitriles. The nitrilium salt (42) can then intramolecularly cycloadd, perhaps in a concerted fashion to yield, after

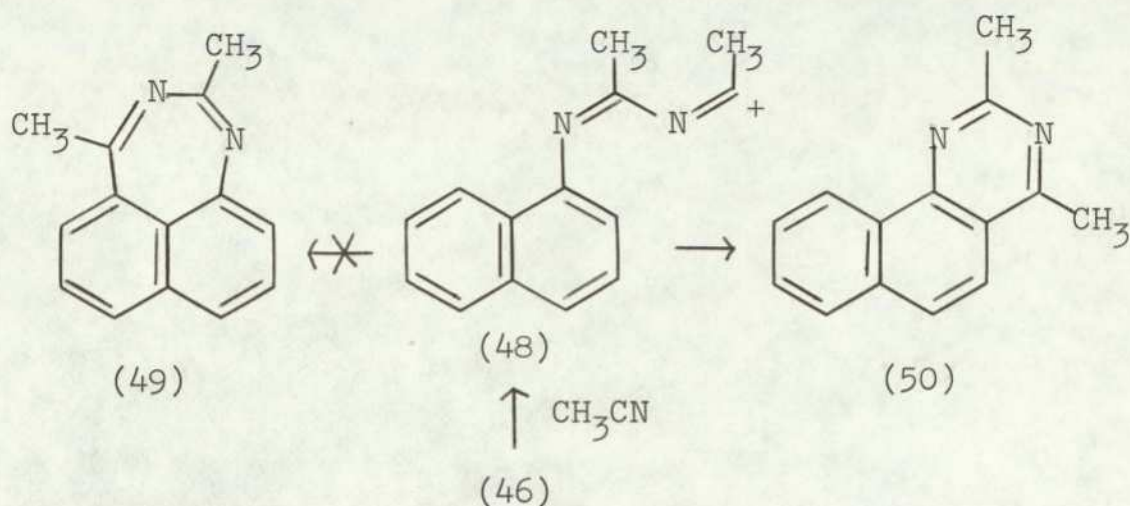
rearomatisation of intermediate (43), phenanthridinium salts (44).^{32,33}



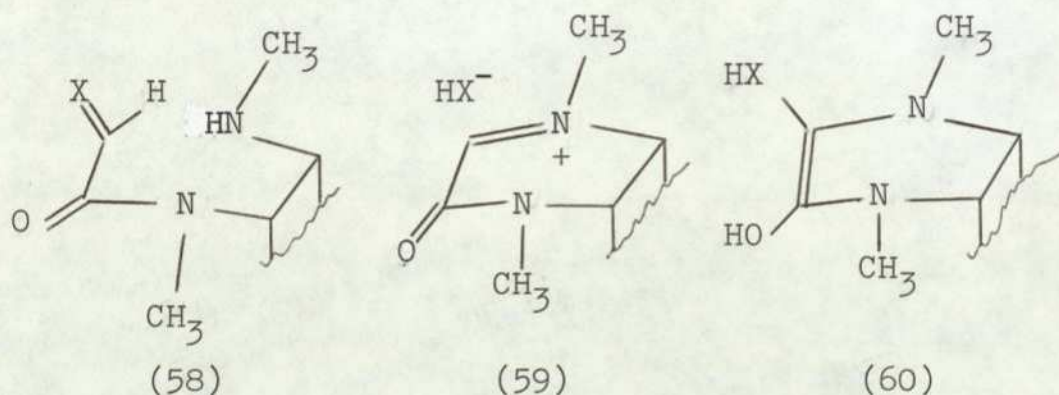
Ion (43b) would be derived from cycloaddition, whereas (43a) from ionic cyclisation. When 1-naphthalenediazonium tetrafluoroborate (45) was treated with an excess of acetonitrile, the expected product 2-methyl-1-aza-acenaphthylene (47) was not formed - an argument against cyclisation. Instead another molecule of the nitrile adds to the salt (46),



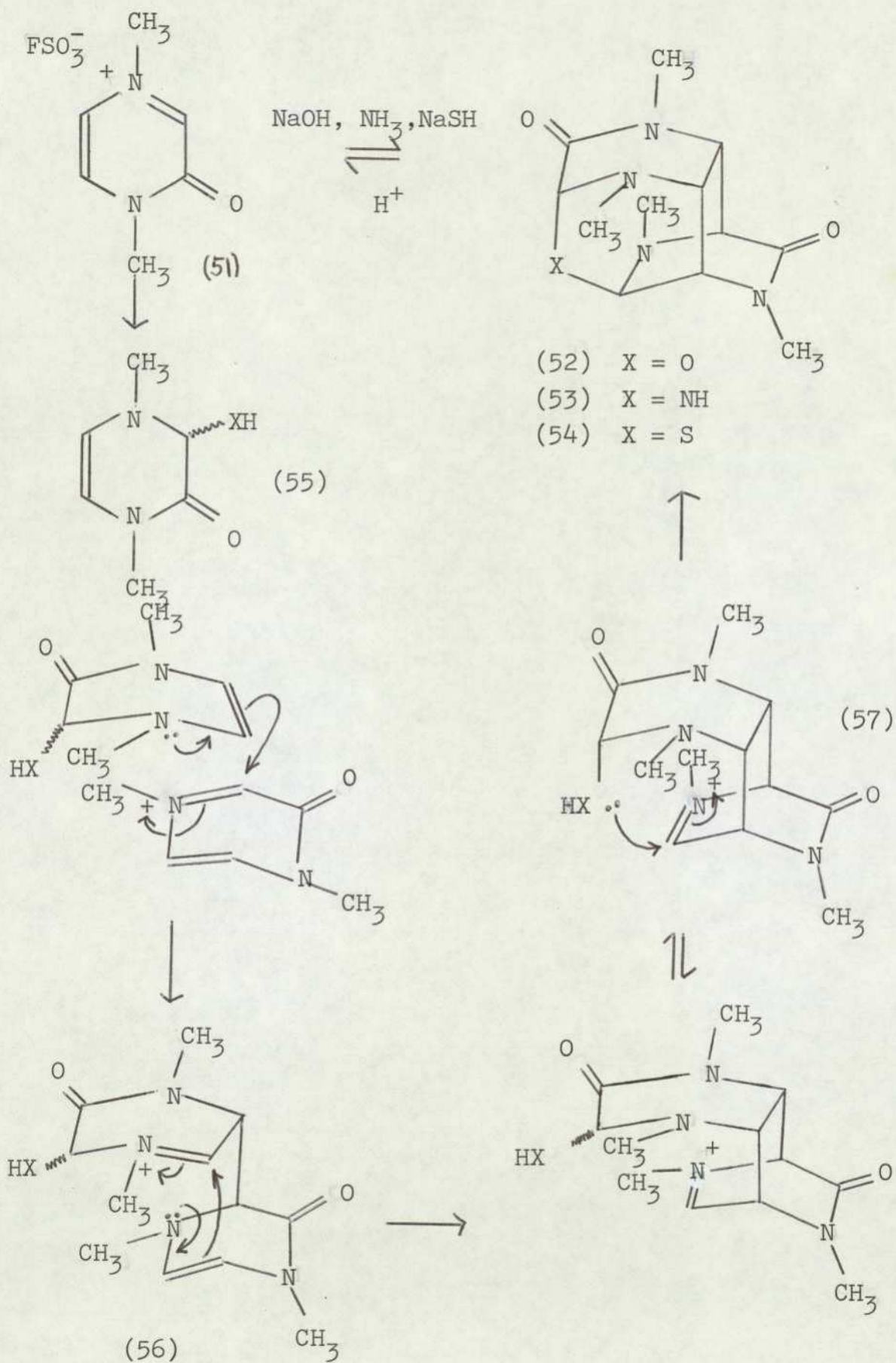
to give the carbonium derivative (48) which cycloadds to give the benzoquinazoline (50) in high yield. The temptation to cyclise towards the C (8) terminus of (48), to give the seven membered ring derivative (49), was resisted.



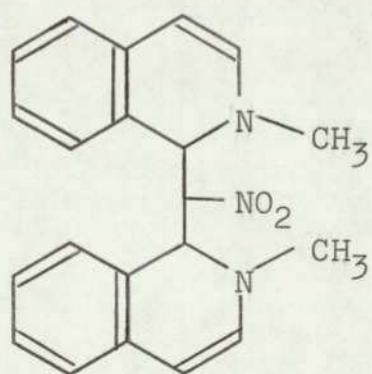
A very interesting cage structure was obtained in 70-80% yield when 1,2-dihydro-1,4-dimethyl-2-oxopyrazinium fluorosulphonate (51) was treated with a nucleophile such as hydroxide, hydrosulphide or ammonia.³⁴ Although Rokach cites the reaction as a polar cycloaddition, he depicts the mechanism as a series of enamine attacks on neighbouring iminium functions following the initial generation of pyrazinone (55).³⁴ The epimerisation of the -XH group to give (57), is postulated as occurring via the ring opened derivative (58), or by the iminium salt (59). The possible enolic mechanism via intermediate (60) can be eliminated since deuterium is not incorporated into the molecule when the cycloaddition is performed with NaOD/D₂O.



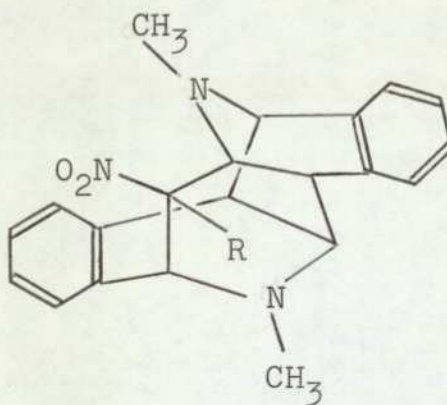
The chemical literature contains two papers where the results could be explained by the concept of polar cycloaddition, but which were not attributed to this type of



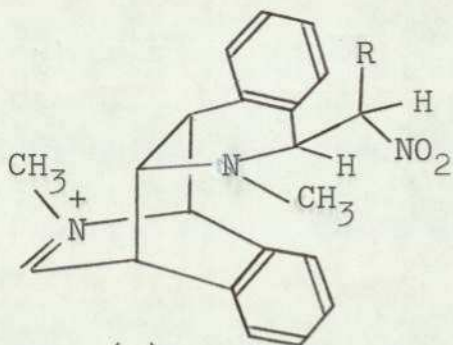
reaction. Kaufmann reported that when a hot basic solution of a nitro-alkane and 2-methylisoquinolinium iodide were allowed to react, a good yield of a species containing two molecules of the isoquinoline to one of the nitro-alkane was isolated.³⁵ Leonard and Leubner reinvestigated these results and determined structure (61) as that of the adduct.³⁶



(61)

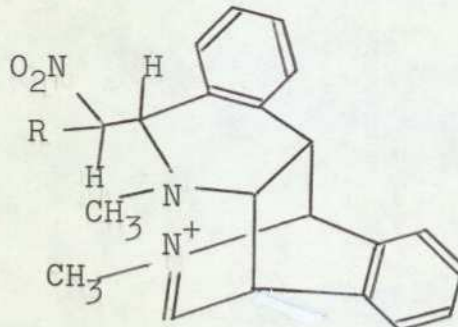


(62)



(a)

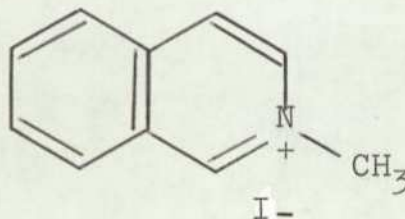
(64)



(b)

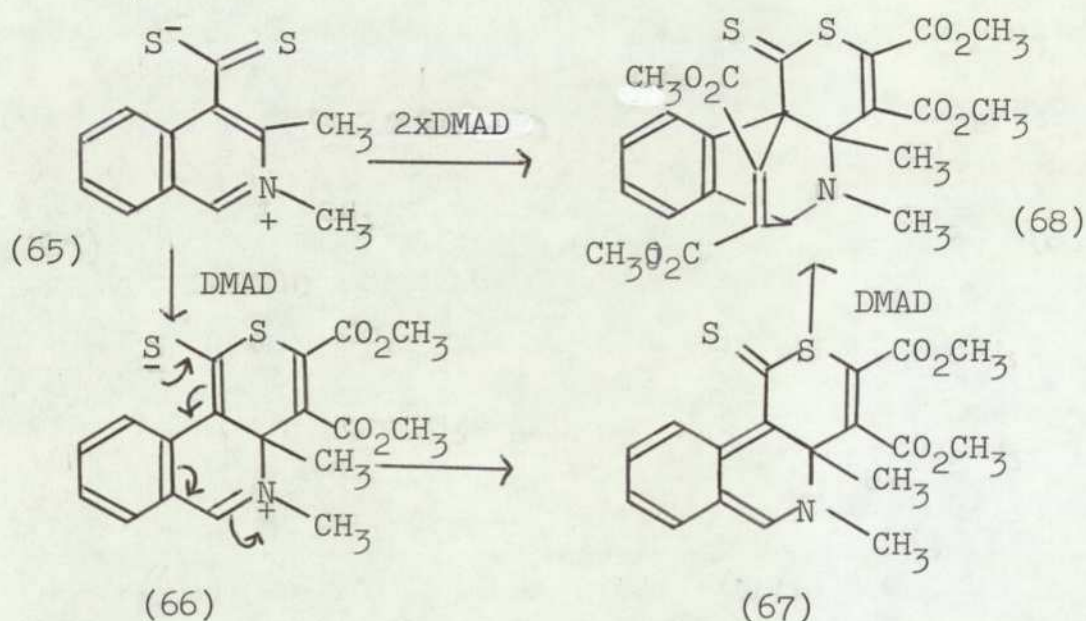


(63)



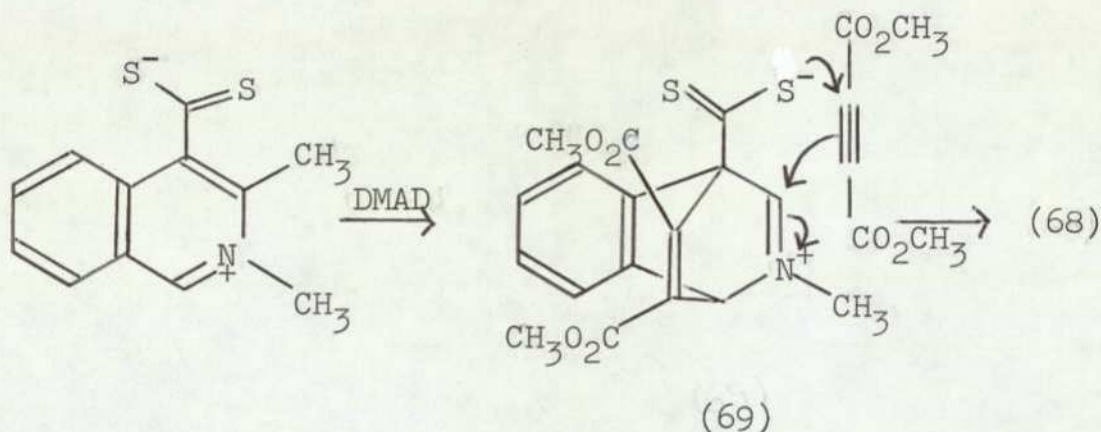
Subsequent ^1H n.m.r. analysis showed this to be incorrect, and results derived from partial deuteration studies suggested structure (62).³⁷ Schleigh's postulated mechanism,³⁷ is a series of enamine attacks similar to the previous example. The probable answer, commences with the creation of the 1,2-dihydroisoquinoline (63) by the base-catalysed addition of the nitroalkane (RCH_2NO_2 ; $\text{R} = \text{H}, \text{CH}_3, \text{C}_2\text{H}_5$). It has been reported that readily polarisable electron-rich olefins cycloadd to the 3-methylisoquinolinium nucleus in a 100% stereo- and regio-specific manner.³ The enamine (63) should be just such a dienophile and with the 2-methylisoquinolinium iodide would be expected to give adduct (64a) in which a maximum distance between the developing positive charges is maintained in the transition state.³⁸ The charge on the cation and that of the alkene during cycloaddition cause the two nitrogen atoms to adopt the orientation allowing their greatest separation, i.e. syn with respect to the phenylene bridge. However, isoquinolinium cycloadditions with enols are known to be reversible at moderate temperatures³⁹ and since the experiment was performed in hot ethanol, the cycloreversion process would be expected to readily occur. The stereospecificity of the reaction is probably compromised at this temperature, permitting the formation of isomer (64b). The nitroalkane group is in the correct orientation now to quench the iminium group, affording cage structure (62). Reduction of the unprotected iminium function, formed after cycloaddition of C(3)-H isoquinolinium species, takes place with even poor nucleophiles.⁴⁰ It seems more probable therefore, that a $[4^+ + 2]$ polar cycloaddition forms part of this synthesis.

Another reaction for which the polar process provides a more reasonable mechanistic pathway is the reaction of the 2,3-dimethyldithio-4-carboxyisoquinolinium internal salt (65) with DMAD.⁴¹ A derivative, assigned structure (68) was isolated that contained two molecules of DMAD for each



one of the isoquinolinium salt (65). It was postulated, without mechanistic evidence, that the first step was a [4 + 2] cycloaddition involving the dithiocarboxy group in a manner similar to that of the 4-vinylisoquinoline addition reported by Dyke *et al.*⁴² Rearrangement of (66) would give what is essentially a dienamine (67) which would very quickly react with another molecule of DMAD affording (68). Previous reports,⁴³ that DMAD did not give an adduct with the acridizinium ion were corrected when it was later found that it did so at 135° in a sealed tube.⁴⁴ The large electron-withdrawing influence of the dithiocarboxy group would have a marked effect on the reactivity of the isoquinolinium ion. The cycloaddition route thus appears to be a more reasonable mechanism. Another advantage gained by

the cycloaddition route would be the non-disturbance of the aromaticity of the benzenoid ring. Investigations of the reactivity of isoquinolinium salts with DMAD have not been carried out. Simple Michael addition of the anion (69) to another molecule of the diester would lead to the 1,4a,6,10b-tetrahydro-3,4,11,12-tetramethoxycarbonyl-4a,5-dimethyl-1-thioxo-6,10b-ethanothiopyrano[4,3-c] isoquinoline (68).



Of the aromatic cations that have been found to undergo cycloaddition, the acridizinium (4a-azoniaanthracene) ion (1) has been the most thoroughly investigated. Between them, Bradsher and Fields, have compiled a large list of dienophiles that react with (1) and Fields has produced a reactivity chart of the alkenes that he used with this ion (Table 1).⁴³ The first and most nucleophilic class gave a 90% completed reaction in less than 4 minutes whereas tetracyanoethylene (TCNE) did not give an adduct under any of the conditions employed.

Various synthetic transformations were possible of the adduct (70) from ketene, diethyl acetal and ion (1). Treatment with dilute acid leads to the unstable ketone (71), which, when heated in acetic anhydride in the presence

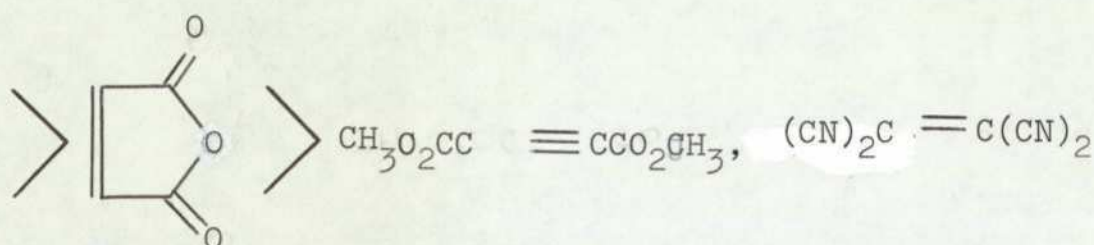
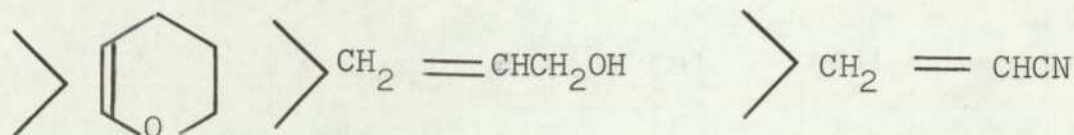
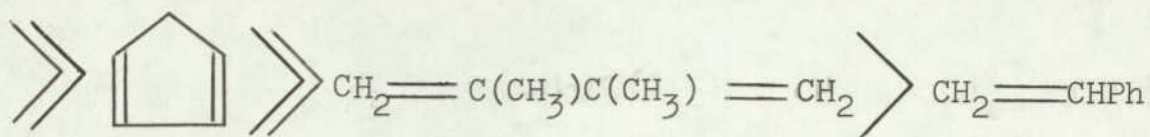
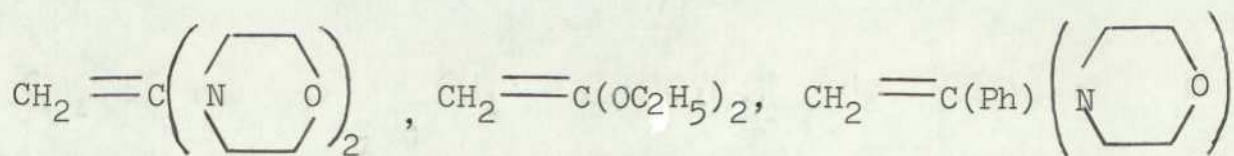
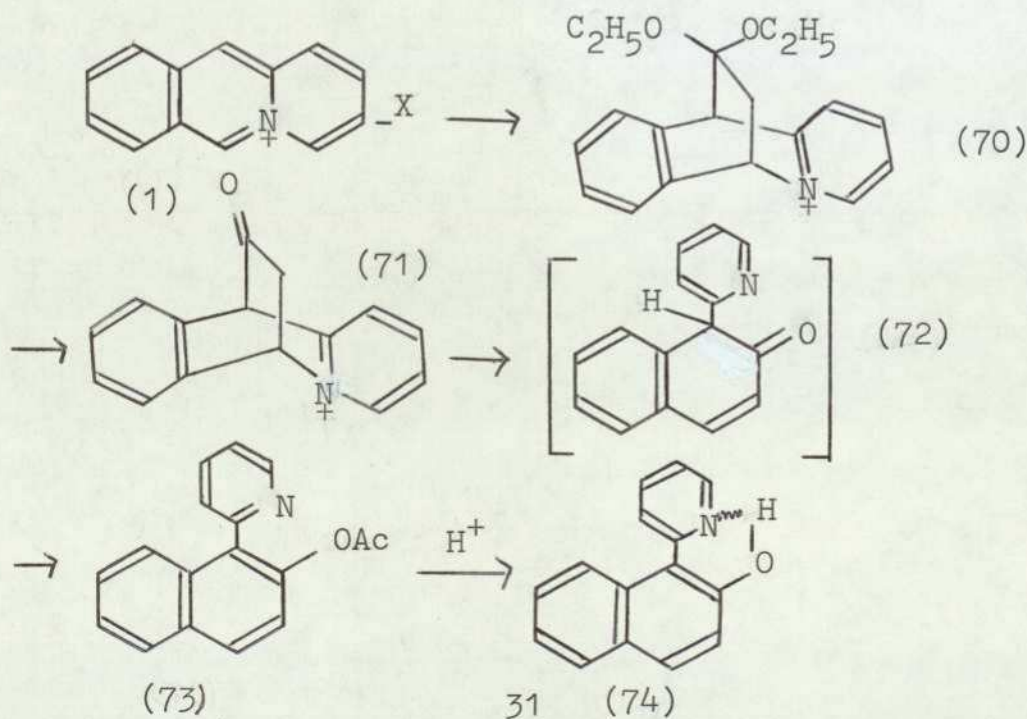


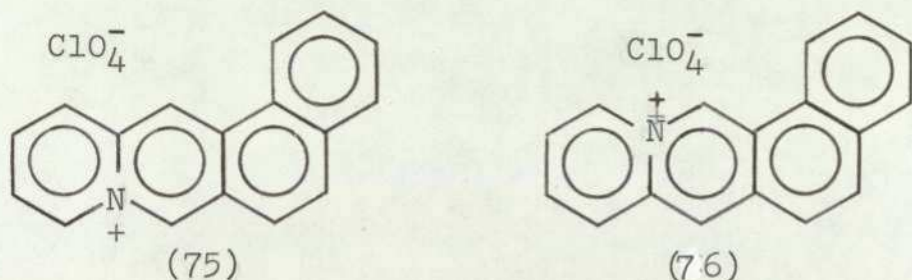
TABLE 1

of sodium acetate, gives the naphthyl ester (73) via intermediate (72).⁴⁵

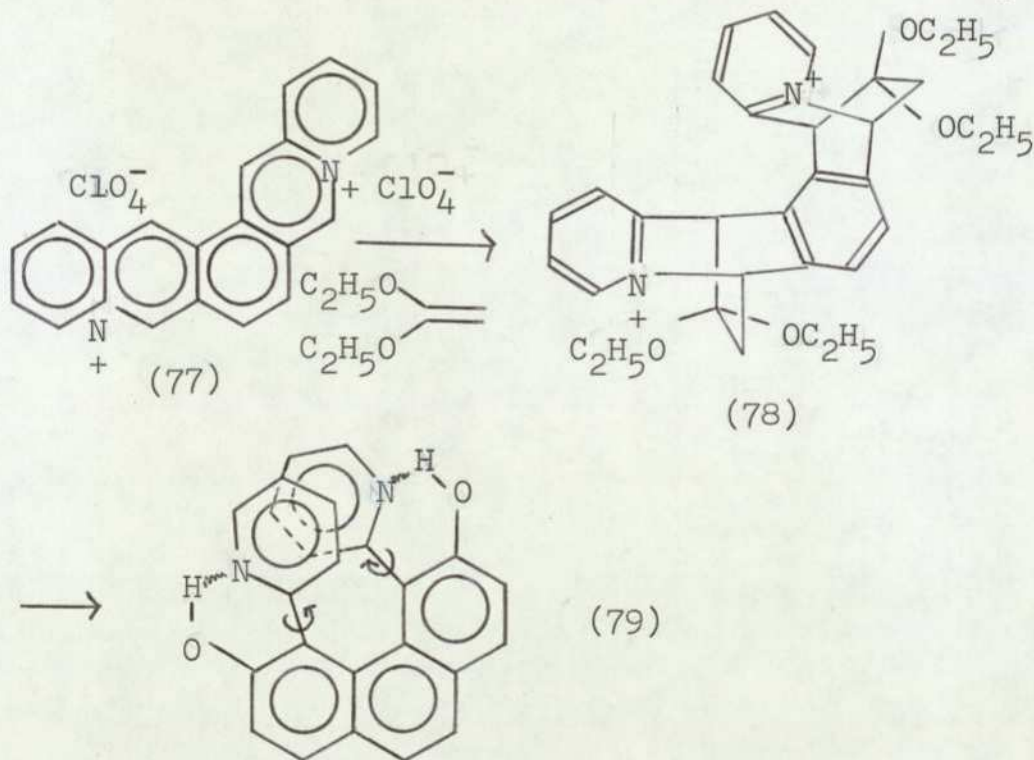
Fields' interest in overcrowded molecules led to the preparation of a derivative of (73) containing a tertiary butyl group peri-to the pyridyl ring substituent.⁴⁵ Hydrolysis of the acetate (73) led to the hydrogen bond



stabilised naphthol (74). The related azoniabenzanthracenes (75) and (76) behaved similarly.⁴⁶ With ketene, diethylacetal, diazoniapentaphene perchlorates give a mixture of

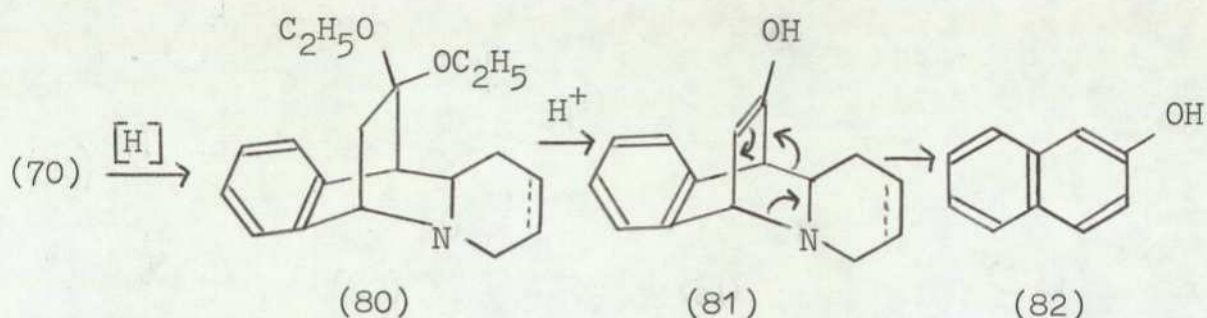


geometrical isomers formed from bis-cycloadditions, in which the olefin has added to both the same side and from opposite sides of the heterocyclic plane. The addition is stereoselective and for unsubstituted ketene acetals is stereospecific.



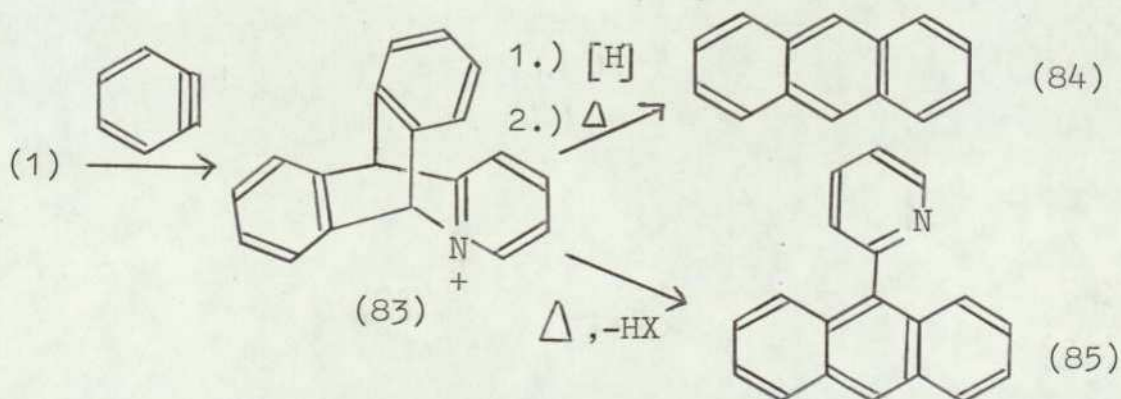
Compound (77) for example gives two adducts of which (78) is one, and acidification of the mixture, followed by heating in acetic anhydride containing sodium acetate led to the phenanthradiol (79) in 88% yield. The isomer obtained

was that shown, there was no evidence for rotamers (see (79) arrows) arising from the different orientations of the pyridyl rings. Hydrogen bonding seems to be the dominant guiding effect.⁴⁶ Catalytic or chemical reduction of the adduct (70) and of many of its derivatives, followed by acidification, then heating affords naphthols (82).⁴⁷ It is not certain whether the pyridinium ring is completely or partially reduced, unidentified amine by-products were formed.

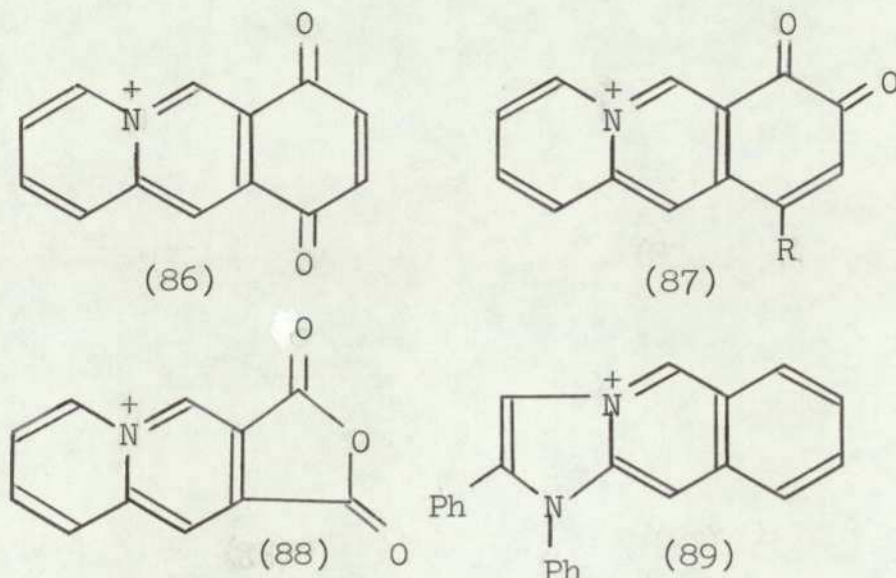


Yields are good to excellent and the reaction very general.⁴⁷ Derivatives of the acridizinium ion (1) also cycloadd with benzyne and reduction of the adduct (83) gives anthracenes in addition to amine by-products; yields are low, however. Thermal elimination of a mineral acid from adduct (83) gives 9-(2-pyridyl)anthracenes (85).⁴⁷ Acetylenes also give good yields of cycloadducts with the acridizinium ion (1) and its derivatives.⁴⁴

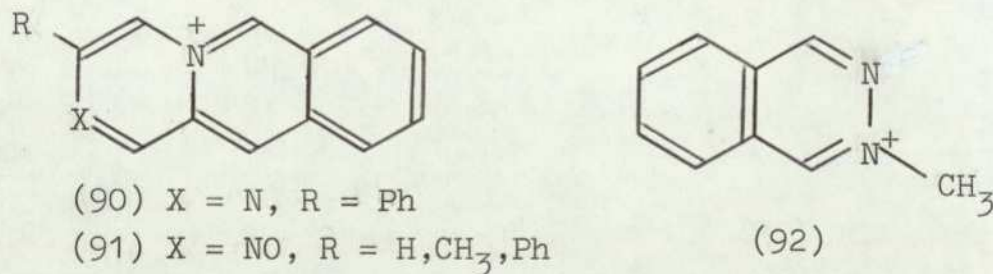
Other aromatic cations able to undergo the $[4^+ + 2]$ cycloadditions include quinones (86) and (87),⁴⁸ and anhydride (88).⁴³



Cations (89), (90) and (91) gave adducts with cyclopentadiene across the pseudo-meso-terminii.⁴⁹ The 2-methylphthalazinium species (92) also formed an adduct with ethyl vinyl ether.⁵⁰

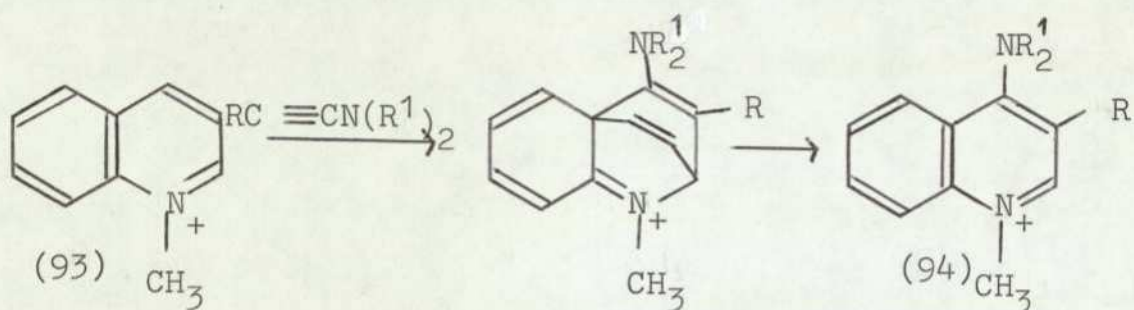


Both isoquinolinium and quinolinium nuclei, when quaternised with various alkyl iodides and sulphates, undergo cycloaddition with nucleophilic olefins. Thus cation (93) reacts with ynamines to yield, after elimination of acetylene, 1-methyl-3-substituted-4-dialkylaminoquinolinium salts (94).⁵¹



Isoquinolinium salts have been studied in great depth, and are known to give excellent yields of adducts with even poor nucleophiles. They react slower than the acridizinium ion (1), and do not react at all with some vinyl ethers that give adducts with cation (1), such as 5,6-dihydro-4H-

pyran. Adducts with alkyl vinyl ethers (95; R = alkyl) are always formed with 100% regio- and stereospecificity, syn with respect to the aromatic ring. Acid hydrolysis of the adduct (95; R = alkyl) gave the 9-hydroxyderivative (95; R = H) still with the syn orientation. The iminium function reacts with potassium cyanide in DMF solution to give a mixture of adducts, exo-(96) and endo-(97) with respect



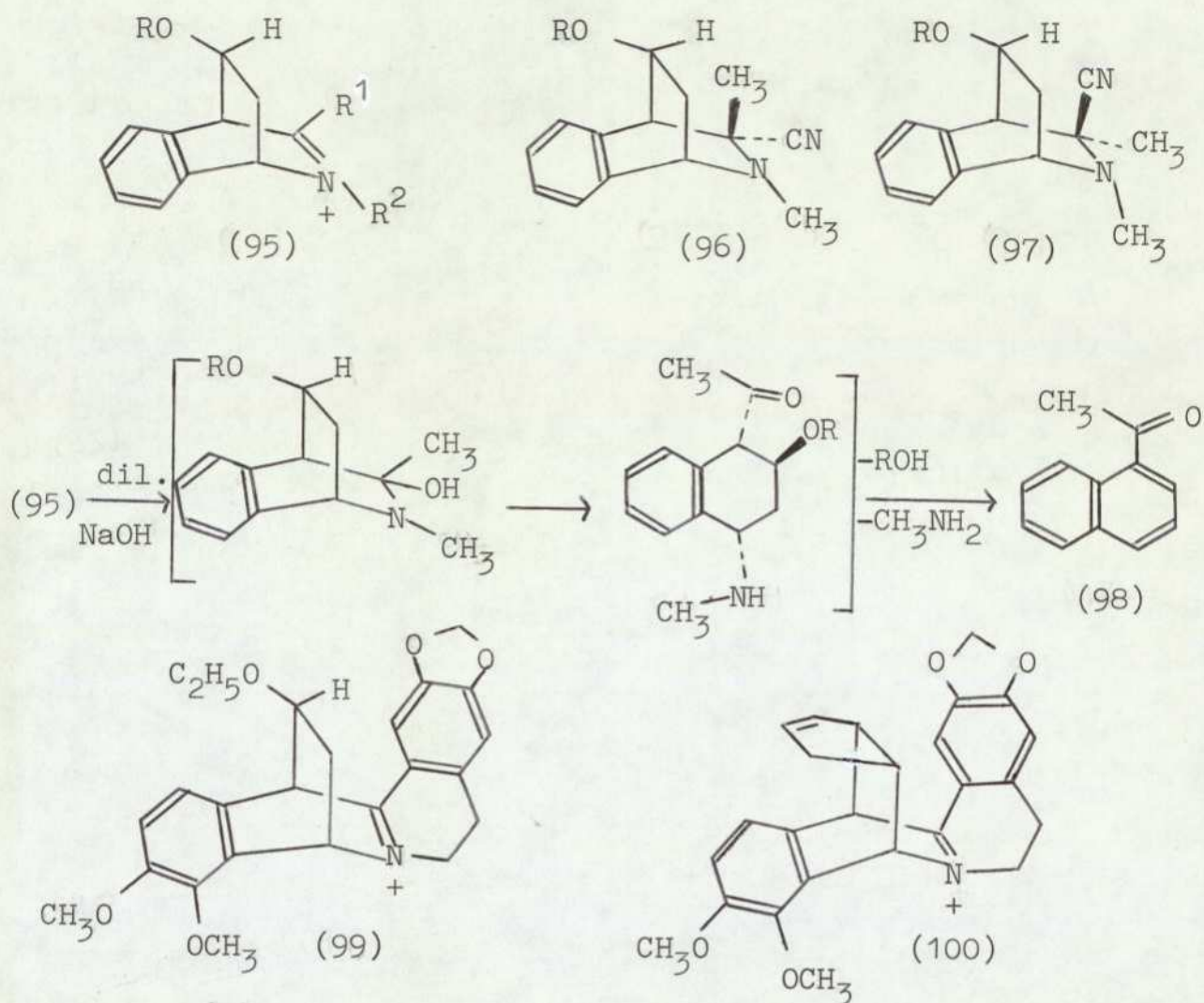
to the ethano bridge, in 93% yield.^{50,52} Under conditions of kinetic control the exo-adduct predominates but on standing the mixture slowly equilibrates to give a solution containing roughly equal amounts of each isomer. The iminium system is easily regenerated following treatment of the cyano-adducts (96) and (97) with silver nitrate.

Hydrolysis of (95; R = CH_3) and (95; R = C_2H_5) with dilute sodium hydroxide solution causes ring opening followed by elimination of an alcohol and methylamine to yield methyl-1-naphthylketone (98).^{50,52}

Berberinium chloride affords adducts (99) and (100) with both ethyl vinyl ether,³⁹ and cyclopentadiene respectively.⁵³

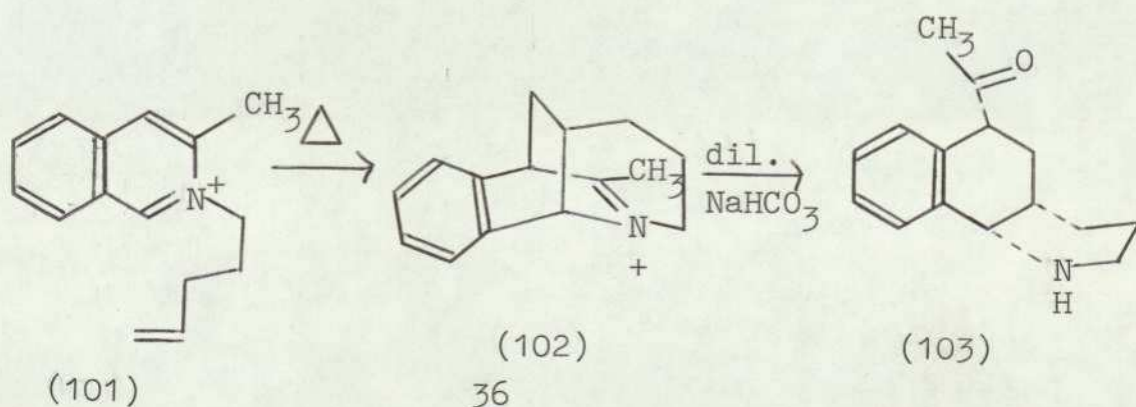
An important development in $[4^+ + 2]$ polar cycloadditions, observed by Watt, was the intramolecular reaction of the isoquinolinium salt (101). Prepared by the quaternisation of 3-methylisoquinoline with pent-4-en-1-yl bromide,

thermolysis gave the adduct (102) quantitatively.⁵⁰

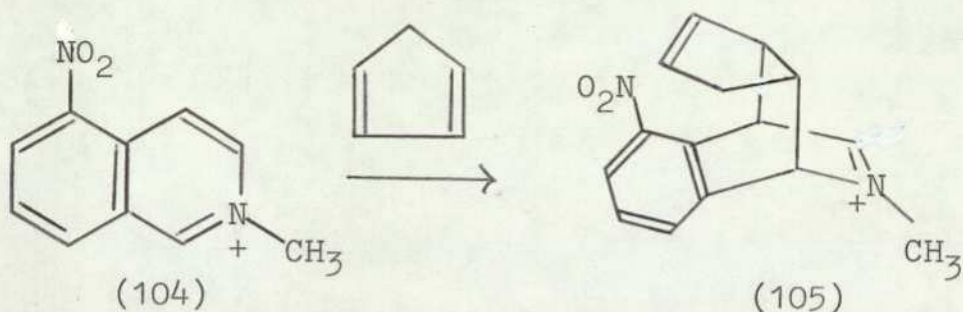


When hydrolysed with weak base the octahydrobenzoquinoline (103) was realised in 56% yield.

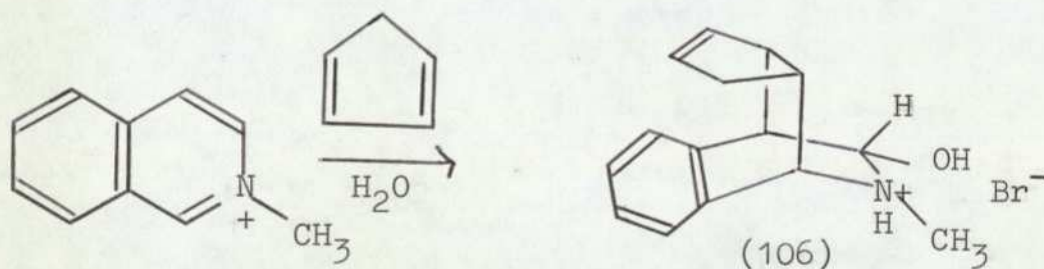
The first preparation of a C(3)-H isoquinolinium salt adduct was provided by the 5-nitro-derivative (104) with cyclopentadiene giving (105).⁴⁰ In the absence of the nitro group the only other reported simple adduct was characterised



as the hydrate (106), after allowing the isoquinolinium salt, the cyclopentadiene and the water more than one year to react.



A cunning development was the quaternisation of isoquinoline with bromoethanol to give the salt (107). Reaction of this with cyclopentadiene gives the usual intermediate which is immediately, intramolecularly quenched by the hydroxyl. It is not known whether the single isolated product (108) has an exo- or endo-configuration.⁵⁴

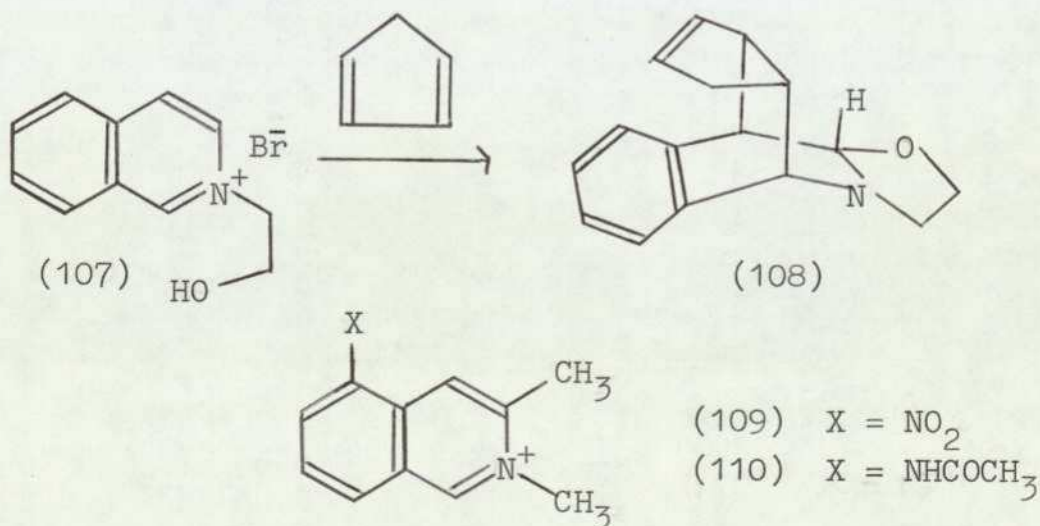


Since the reaction of 2,3-dimethylisoquinolinium salts with alkenes are languid at room temperature, Bradsher sought to improve the overall rate by introducing a C(5) nitro group. This had the desired effect and increased the reactivity of the heterocyclic substrate (109) towards ethyl vinyl ether 120 fold, compared to the parent system. That this enhancement was not totally due to the electron-withdrawing nature of the nitro group was demonstrated by the twofold

increase in rate exhibited by the electron-donating acetamidoisoquinolinium salt (110). The extra ameliorating effect was explained by the peri-interaction between the C(5) substituent and the C(4) proton. The ring methyl will also aggravate the situation. Cycloaddition allows all of these interacting groups to move out of plane away from each other.

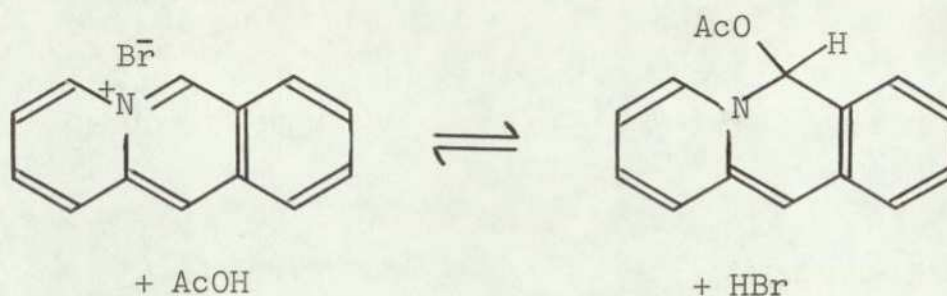
The ethyl vinyl ether adduct of the nitro-isoquinolinium salt (109) gave a cyanide adduct analogous to nitrile (96) and (97). The exo-adduct was the kinetically favoured product, but within 3 days this had partially isomerised to give an equilibrium mixture containing an almost 1:1 mixture of exo- and endo-isomers. The alkenes that give adducts with the nitro-cation (109) include styrene, p-methoxystyrene, ethyl vinyl ether, vinyl acetate, 1,3-cyclohexadiene, indene and norbornene.

The last result is interesting for the reason that only the syn-adduct is observed. With the acridizinium ion (1), the norbornene gives a 60:40, syn:anti isomer mixture, owing to the poor polarisability of the alkene.⁵⁵ Formation of the single isomer with cation (109) points to a more stereoselective process.



On the Mechanism of Cationic Polar
Cycloadditions.

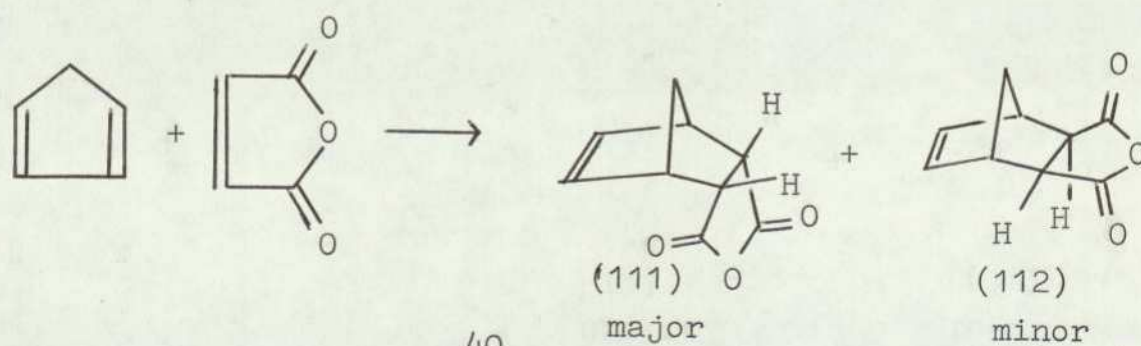
At the time of the last review of this subject,³ the view of the mechanism of the cationic polar cycloaddition was confused. Two major theories predominated, the first being the synchronous and concerted mechanism where bonds are formed at the same time but not necessarily at the same speed. The second postulate was the non-synchronous, two-step mechanism, whereby a discrete carbonium ion was formed following the electrophilic attack of the cation on the electron-rich olefin. It was then envisaged that ring closure occurred by carbonium ion attack on an adjacent pair of π or unshared electrons. Since this review, however, it has become clear that the first postulate is a far more satisfactory explanation of the phenomenon. Re-evaluation of the evidence for the two-step process shows that this too is in favour of the concerted mechanism. In Schmidt's review an equivocal stand was taken, in which a two-step mechanism was preferred.⁴ This stand was on the basis of the apparently non-stereospecific reaction of ethyl maleate to the acridizinium ion (1),⁵⁶ in which a mixture of maleate and fumarate adducts was observed that appeared in violation of the cis-principle.⁵⁷ Bradsher clearly explains this result, however, in terms of an isomerisation of the maleate caused by hydrogen bromide liberated from the acridizinium ion (1), following nucleophilic attack of acetate derived from the solvent acetic acid (Scheme 4). Both isomerised maleate and newly formed fumarate were then supposed to add normally to give a mixture of adducts. Schmidt's interpretation was that the adduct isomers were simply rotamers



Scheme 4

incurred during the second step of his two-step mechanism. Bradsher, however, refuted this type of isomerisation and concluded that undetected fumarate in the maleate used was the cause of the problem.⁵⁸ (A third mechanism is possible, consisting of a diradical two-step cyclisation and will be discussed in due course).

Considering the stereoselectivity of the cycloaddition, the most noticeable effect is derived from the absence of the Endo-Addition rule. The explanation of this rule, given by Woodward and Hoffmann to rationalise the fact that maleic anhydride and cyclopentadiene give the endo-adduct (111) faster than the exo-adduct (112), is based on secondary overlap of the non-bond forming orbitals (Fig. 1).^{59,60} Even though the exo-adduct (112) is the thermodynamically more stable product, the interaction between the π -orbitals on C(2) and C(3) of the diene with those of the two carbonyl carbon atoms of the maleic anhydride provides a symmetry-stabilised lower energy transition state (113) leading to the adduct (111).



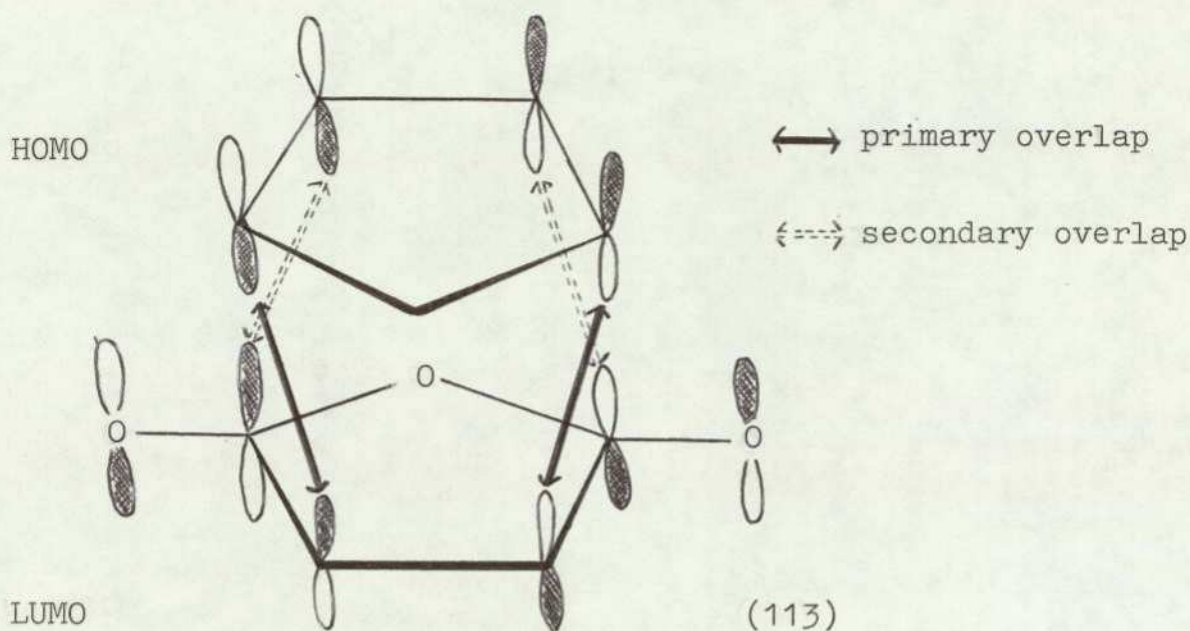
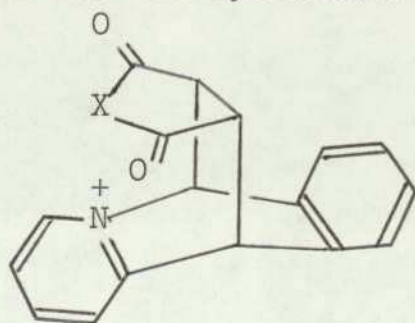


Fig. 1

The effect of secondary overlap of the frontier molecular orbital providing the major interaction in cationic polar cycloadditions is superseded by electrostatic influences originating from the formal positive charge of the cation. Two different processes are operative, depending upon the type of dienophile employed. With maleic anhydride,¹ and N-substituted maleimides,⁶¹ adducts (114) and (115) are always formed anti - with respect to the phenylene bridge. This is rationalised by assuming the formation of a charge transfer complex prior to the transition state for the cycloaddition.

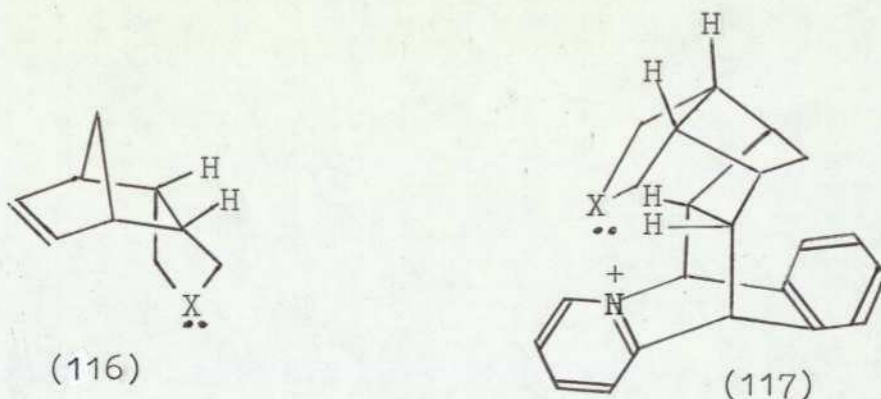


(114) $X = O$

(115) $X = \text{pZC}_6\text{H}_4\text{N}$

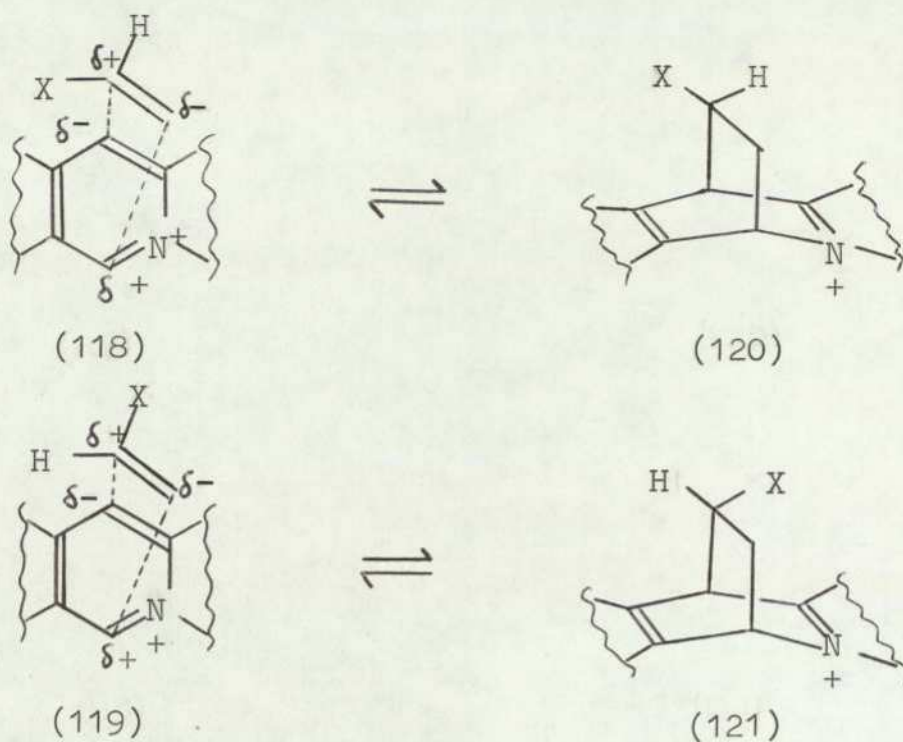
$Z = \text{H}, \text{CH}_3, \text{Cl}, \text{OCH}_3, \text{N}^+(\text{CH}_3)_3$

It is thought that the electrostatic interaction between the positive cation nitrogen atom and the unshared electrons of the dienophile carbonyl groups is the agency by which the stereochemistry is effected. This view finds support from the cycloaddition of norbornene with acridinium ion (1), where a mixture of stereoisomers is observed in a ratio of 60:40 for syn:anti addition. If however, norbornenes of type (116) were employed, where X was an atom containing a lone-pair of electrons then none but the syn-isomer (117) was formed.⁵⁵ A charge transfer complex

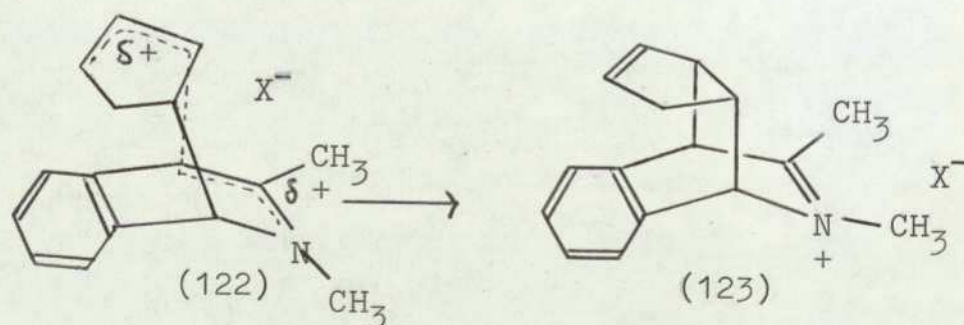


is again invoked between the positive nitrogen and the unshared electrons of the heteroatom X.

Alkyl vinyl ethers are thought to gain both their stereo- and regiospecificity of addition from coulombic repulsions that arise within the charge transfer complex with the cation. If the two electronically most likely complexes, leading to the two stereoisomers (118) and (119) are qualitatively considered, then it can be seen that the energy of complex (118) is marginally lower than that of (119) due to weaker electrostatic repulsions of like charges. Depending on whether the substituent X was more or less electron-releasing, i.e. more or less polarisable, the centre of positive charge in the complex would lie a corresponding



distance down the C-X bond. It is clear that (118) contains fewer repulsions than (119) but the difference is small. It is this factor that allows the formation of stereoisomers from cycloadditions of the heterocyclic cations with olefins containing poorly polarisable substituents.⁵⁸ Stereospecific addition of cyclopentadiene to the 2,3-dimethyl-isoquinolinium ion giving structure (123) is similarly based upon minimum repulsive forces, in the complex leading to, or actually in the transition state (122).



The regioselectivity shown by cationic polar cycloadditions has in the past been interpreted in terms of an electrophilic attack by the most positive carbon atom of the cation on the electron-rich β -carbon atom of the alkene.

Cyclisation is then completed when (in the case of large heterocyclic cations) the remaining terminal of the olefin is electrophilically attached to a ring carbon which does not support a positive charge in any canonical form making up the resonance hybrid. This view was supported until very recently by all but one of the cycloadditions studied - that of acrylonitrile with cation (1).

Several interesting relationships have been observed that give an insight into the mechanism of polar cycloadditions. It has been observed, for example, that an excellent correlation is obtained between the ^{13}C n.m.r. chemical shift of the β -carbon atom of several *p*-substituted styrenes and the relative rates of their cycloaddition reactions with the acridizinium ion (1) (Fig. 2).⁵⁸ Attempts to identify a similar relationship for the α -carbon atom failed, demon-

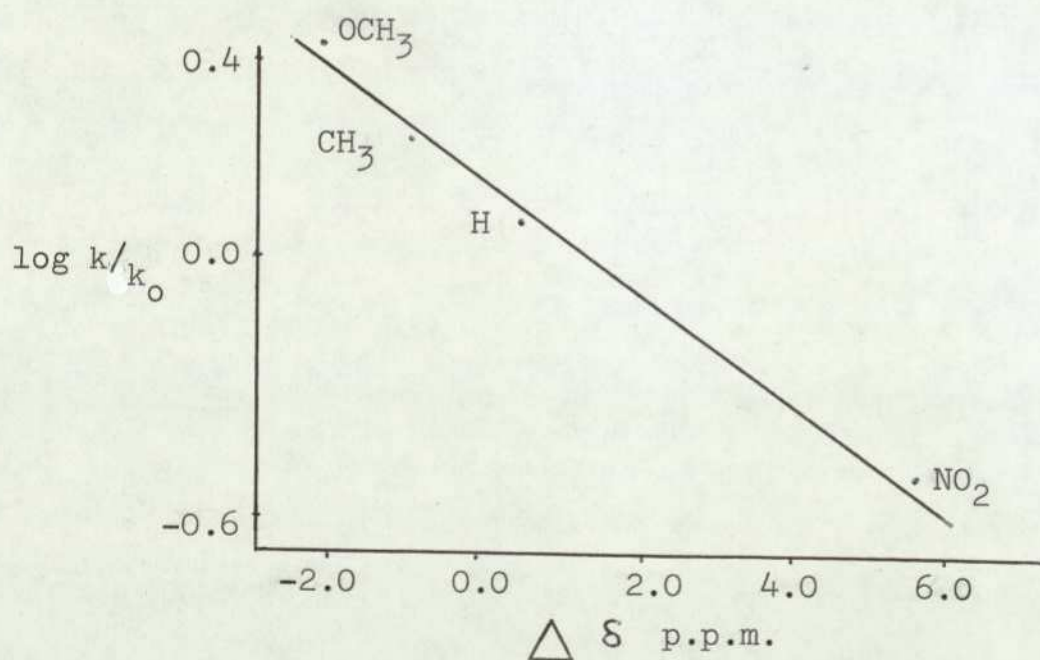
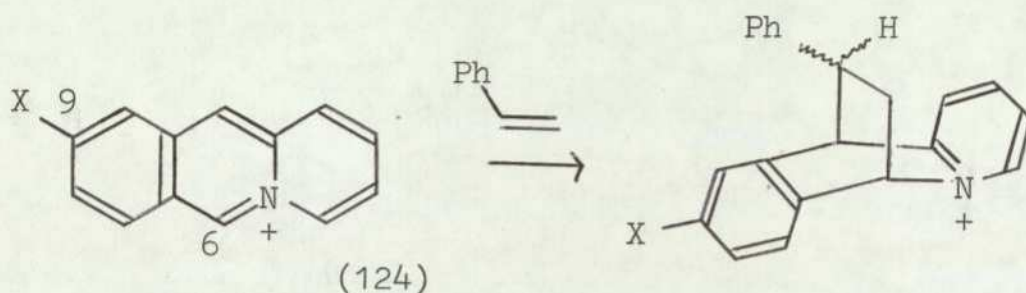


Fig. 2 Plot of the relative rate of cycloaddition of various *p*-substituted styrenes v. the relative ^{13}C n.m.r. chemical shift values for the β -carbon atom.

strating the importance of the unsubstituted olefin terminal.⁵⁸ A series of 9-substituted acridizinium cations (124) were prepared and a Hammett treatment performed on the results of their cycloaddition with styrene. It was observed that a



(X = H, CH₃, CH(CH₃)₂, F, Cl, Br, I, CO₂H, CO₂CH₃, NO₂)

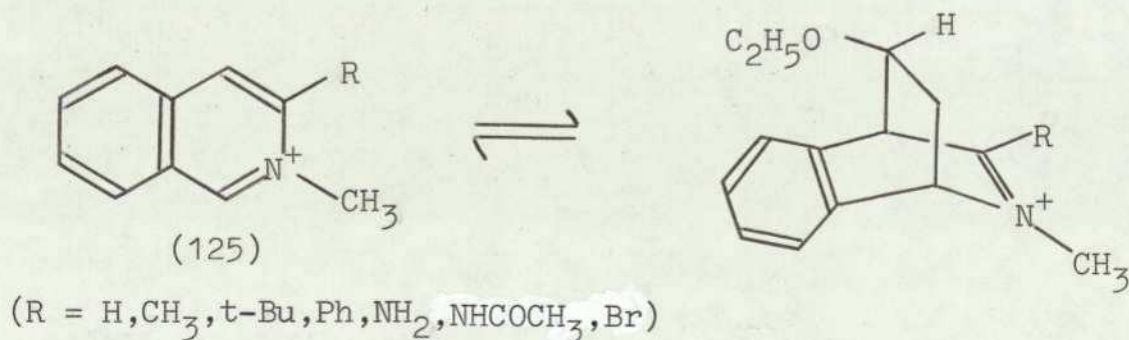
straight line relationship existed between the logarithm of the relative rate of cycloaddition and the σ_p substituent constants. No such relationship was noted for the σ_m values. This is a demonstration of the very important part that C(6) plays in the polar cycloaddition reactions of the acridizinium ion (1). Both styrene at 65° and acrylonitrile at 130° gave the same overall result. The more electron-withdrawing C(9) substituents made C(6) even more electrophilic in its behaviour towards electron-rich olefins. The lack of a relationship between σ_m and the relative rate of reaction shows the subordinate role played by C(11) in the cycloaddition process. A correlation also exists for this series of 9-substituted acridizinium ions (124) between the ¹H n.m.r. chemical shift of the C(6) proton and the relative rate of cycloaddition.⁶²

When the more nucleophilic ethyl vinyl ether was reacted with the series (124), even more dramatic results were observed for the rates of addition, since over the range of substituents employed they varied over 100-fold.⁵⁸ Again a relationship with σ_m was not observed. However, calculated

Hammett reaction constants (ρ) for each of the vinyl components (acrylonitrile 1.13 at 130°, styrene 1.69 at 65°, and ethyl vinyl ether 2.06 at 0°) varied as expected with the nucleophilicity of the olefin, but surprisingly little when the change in polarity of the dienophile is taken into account.⁵⁸ It has been pointed out though, that all of these values are considerably lower than those from reactions which are thought to involve two steps, c.f. the addition of ethyl vinyl ether to TCNE, $\rho(7.1)$.

Bradsher has also studied the polar influences derived solely from the inductive effects on the cycloaddition. Thus, a range of p-substituted phenoxyethylenes were reacted with the acridizinium ion (1). The olefin is separated from the phenyl group by an oxygen atom, thus precluding mesomerism. Again a linear plot was obtained between the relative rate of addition and the substituent constant σ_n ,⁶³ related to σ_p .⁵⁸

Since 2-methyl-3-substituted isoquinolinium ions (125) are known to undergo cycloaddition with ethyl vinyl ethers (Scheme 5), the same Hammett treatment as above was applied.⁶⁴ The expected linear relationship between the relative rate of reaction, and σ_m for the range of 3-substituted cations (125) was not observed. When the result



Scheme 5

for the t-butyl derivative is overlooked, however, a significant correlation is observed (Fig. 3). The omitted value was far too great for the known σ_m and corresponded to a gross enhancement in reactivity. This was rationalised as

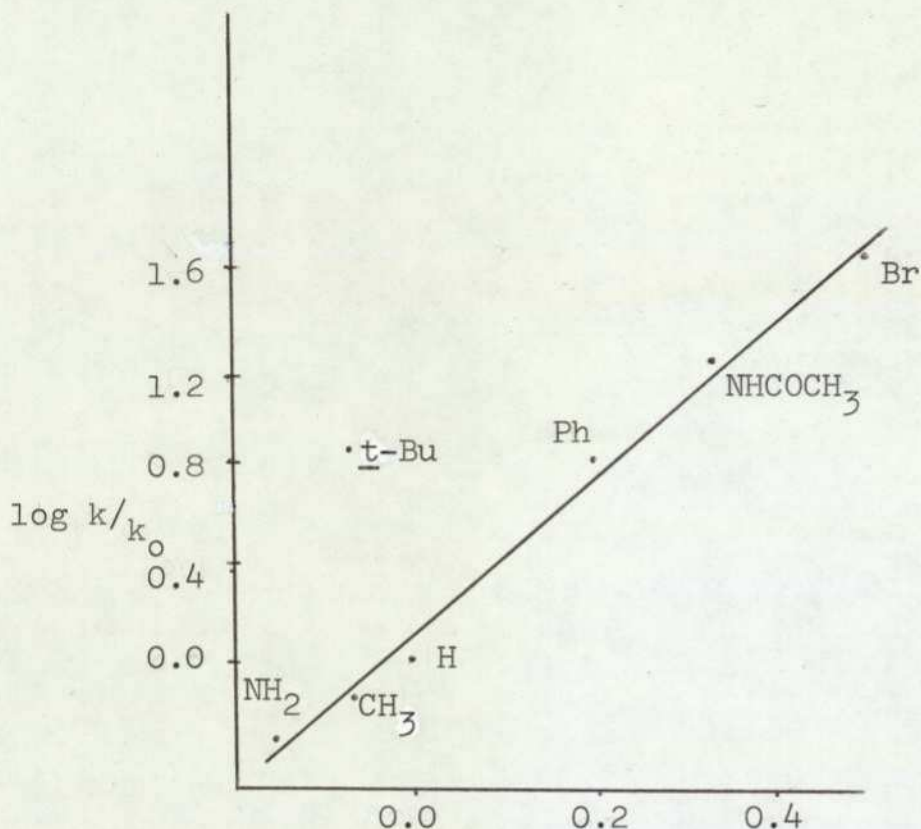
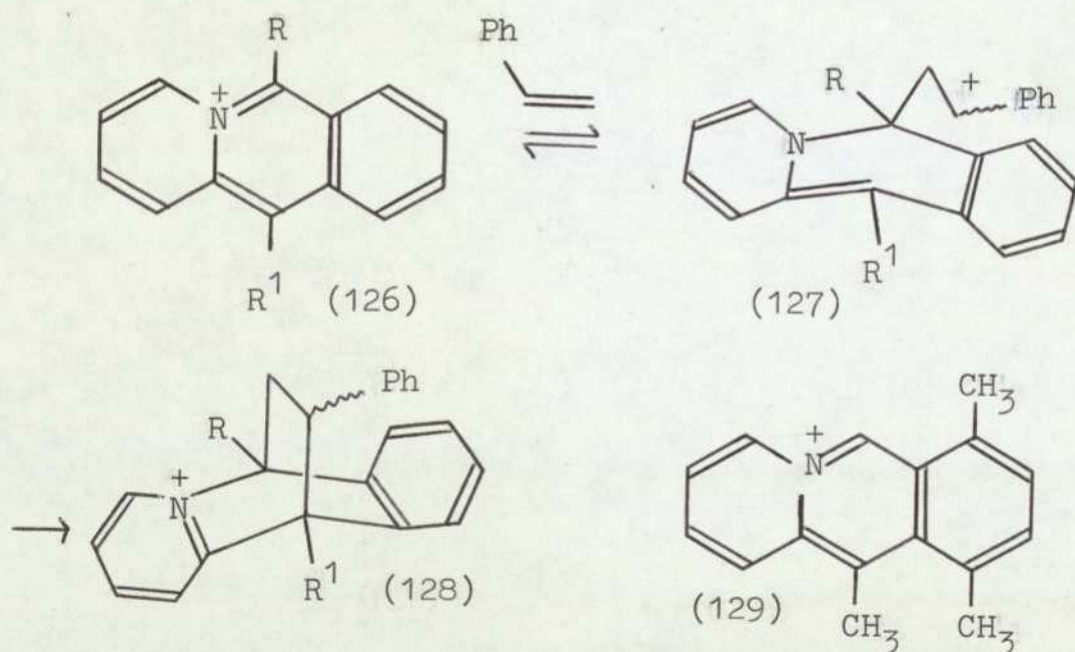


Fig. 3 Plot of $\log k/k_0$ v. σ_m for the cycloadditions of (125) with ethyl vinyl ether.

arising from the relief of the peri-interaction of the C(4) proton with the C(5) proton, and between the former proton and the C(3) substituent especially in the presence of the 2-methyl group. By undergoing cycloaddition these two functions were able to move out of the same plane and to a lower energy state. The bulk of the t-butyl group is sufficient to cause the massive rate enhancement observed.⁶⁴

It had previously been noted that substitution of a methyl group at the meso-C(11) position of the acridizinium ion produced a significant increase in the rate of cycloaddition

with styrene - 13.6 fold compared to the parent ion (1). If however, the methyl group was positioned at the other meso-site C(6) the rate was halved.⁶⁵⁻⁶⁷ The latter observation is predictable if the system is considered as being of an inverse demand nature. Thus, the electron releasing methyl group would raise the heterocyclic LUMO energy, increase the gap between the two frontier molecular orbitals providing the major interaction, and impede the reaction (see Chapter 1). The C(6) methyl retardation could also be answered on steric grounds, i.e. barring the approach of the dienophile. Both C(6) and C(11) methyl monosubstituents however, would qualitatively possess a similar steric environment and so the rate enhancement for the C(11) homologue appeared as persuasive evidence for a two-step mechanism.



That suggested was initiated by formal attack of the nucleophilic olefin on the iminium function at C(6) to give cation (127). It would be reasonable to assume that substitution of a methyl group at C(11) of ion (126; $\text{R}^1 = \text{CH}_3$, $\text{R} = \text{H}$) would make the carbonium ion (127; $\text{R}^1 = \text{CH}_3$, $\text{R} = \text{H}$) more susceptible to nucleophilic attack by the enamine

group.⁶⁵ This view has largely been overtaken by recent measurements concerning the peri-interaction experienced by both methyl substituents. It was observed that the 7, 10,11-trimethylacridizinium ion (129) had a tenfold rate enhancement over the C(11)-monomethyl species (126; $R^1 = CH_3$, $R = H$) towards styrene. These increases are ascribed directly to the relief of peri-strain between the adjacent methyls of (129) and between the methyl and adjacent protons in (126; $R^1 = CH_3$, $R = H$). Similar increases were found by Sauer et al.,⁶⁸ and by Klanderman and Creswell,⁶⁹ for reactions between substituted anthracenes with maleic anhydride and in the latter case also benzyne. When both meso C(9) and C(10) sites were blocked by methyl groups a 218 fold enhancement in reaction rate was observed, compared to anthracene. However, when the same two positions are substituted by methoxyl groups the rate of addition of maleic anhydride was found to be slower than with anthracene itself.⁶⁸ The difference, it is suggested, is derived completely from the steric restrictions imposed by the peri-protons adjacent to each meso-position. Because the methoxyl group is so flexible, and able to bend from these impositions, the rate enhancement already described became redundant in this case. The presence of electron releasing methoxyl groups should improve the rate of addition for this normal demand reaction, in fact they actually inhibit it by presenting a partial barrier to reactive approaches of the dienophile.⁶⁸ This does not explain the reduction in rate experienced by the C(6) homologue (126; $R^1 = H$, $R = CH_3$). The answer to this lies in the activation parameters for the pseudo-first order cycloaddition (Table 2).⁶⁴

(126)	E_A kcal/mol	$\Delta S^\ddagger$ e.u.
$R = R^1 = H$	15.7 ± 0.6	-33.1
$R = H, R^1 = CH_3$	13.4 ± 0.5	-34.7
$R = CH_3, R^1 = H$	14.6 ± 0.4	-37.6

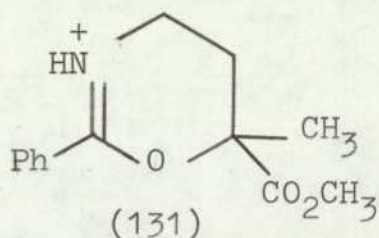
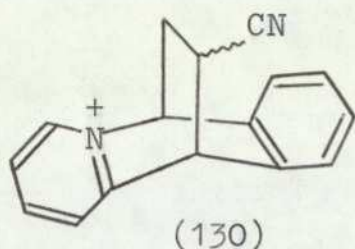
Table 2

The value for the energy of activation, E_A , for the reaction of the parent ion (126; $R = R^1 = H$) with styrene is typical when compared to other Diels-Alder reactions, c.f. 9,10-dimethyl¹anthracene ($17.9 \text{ kcal mol}^{-1}$) and hexachlorocyclopentadiene ($15.2 \text{ kcal mol}^{-1}$) with styrene.⁷⁰ For the C(11) methyl derivative (126; $R^1 = CH_3, R = H$) the lower activation energy is matched by an expected corresponding increase in reactivity. The C(6) methyl compound (126; $R^1 = H, R = CH_3$) similarly has a lower activation energy caused by peri-interaction with the adjacent protons, but has a significantly larger negative entropy of activation. It is thought that this entropy factor overcides the peri-interactions and becomes the dominant effect, thus causing a fall in the observed rate of cycloaddition.

The proposed two-step mechanism, though wrong, provides a useful basis for the understanding of the mechanism of polar cycloadditions. It emphasizes the fundamental significance of the C(6) of the acridizinium ion (1) and the β -carbon atom of the olefin, while at the time shows the relative unimportance of the remaining terminals. As a model it provides a rationalisation of the results obtained from polar cycloadditions with all of the dienophiles used, until very recently, with the exception of acrylonitrile.

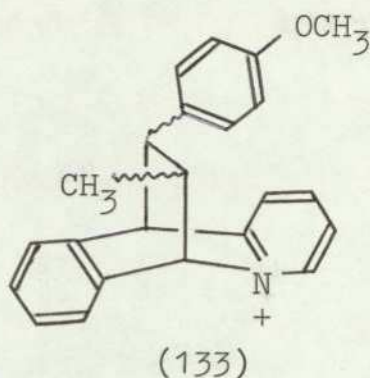
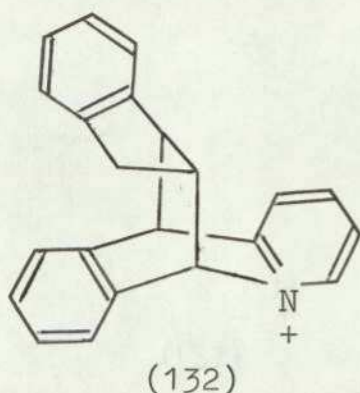
This electron-deficient olefin is found to give stereoisomers (130) with precisely the same regiochemistry as the

adducts obtained from corresponding styrene additions.⁴³ Also when the benzoylamidomethyl cation was treated with methyl methacrylate dihydro-4H-oxazine (131) resulted.⁷¹

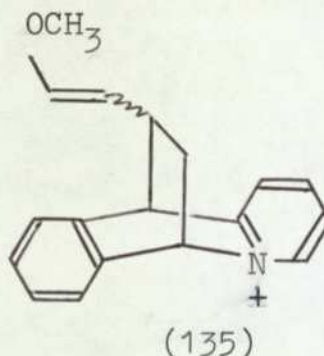
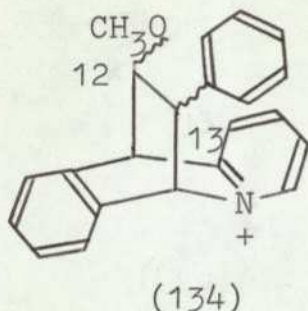


Both adducts (130) and (131) were formed by a mechanism that suggests the most positive diene terminal attacked the most positive site on the olefin, on the basis of ground state polarisation. This clearly is contrary to what should be expected electronically and has been used as evidence for the concertedness of the reaction. Since acrylonitrile behaved in the same manner as styrene towards the 9-substituted acridizinium ion (123) it can be inferred that they undergo addition by a similar mechanism, therefore the nitrile appears to be behaving nucleophilically during the addition.⁶⁷

A demonstration of the regioselectivity of cycloaddition governed by electrophilic parameters was provided by Bradsher for a designed series of dienophiles.⁷² He showed that the direction of addition of asymmetric olefins is virtually always derived from the transition state better able to accommodate a developing positive charge. Styrene had previously been found to add regiospecifically with the β -carbon atom attached to C(6) of the acridizinium ion (1) giving (128; $R^1 = R = H$). Indene was observed to behave similarly, giving a mixture of geometrical isomers of which



(132) is one. Addition of trans- β -methyl p-methoxystyrene gave species (133) with the phenyl group stabilising the developing positive charge. However, cis- β -methoxystyrene gave the regioisomer (134) containing the aryl substituent now at C(13). The methoxyl is now better able to stabilise



the transition state. Even 1-methoxy-1,3-butadiene gives, like the other examples, the adduct (135) best able to support the developing positive charge. Thus, the addition of acrylonitrile with the observed orientation proved perplexing. Similar results have been obtained in related fields and held up as indicating a diradical mechanism.^{73,74} Hypochlorous acid,⁷⁵ nitrosyl chloride,⁷⁶ and nitryl chloride,⁷⁷ all give anomalous adducts with methyl methacrylate. It is suggested that a radical would attack the β -carbon atom of a substituted olefin irrespective of the substituent's polarity. Fleming maintains that the olefin HOMO and LUMO levels

are both polarised in the same direction for C-substituted and electron-withdrawing group substituted olefins (Fig. 4). Even for electron-rich olefins the HOMO is polarised in the same sense as described above. The LUMO is not however,

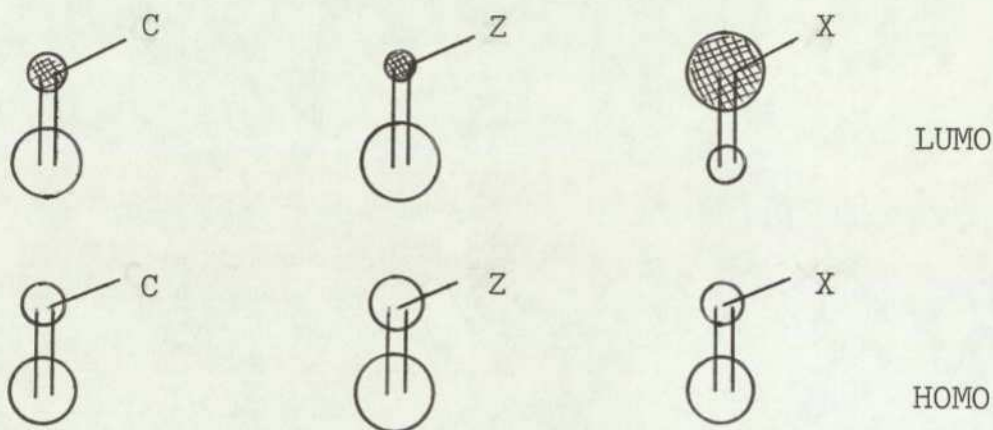
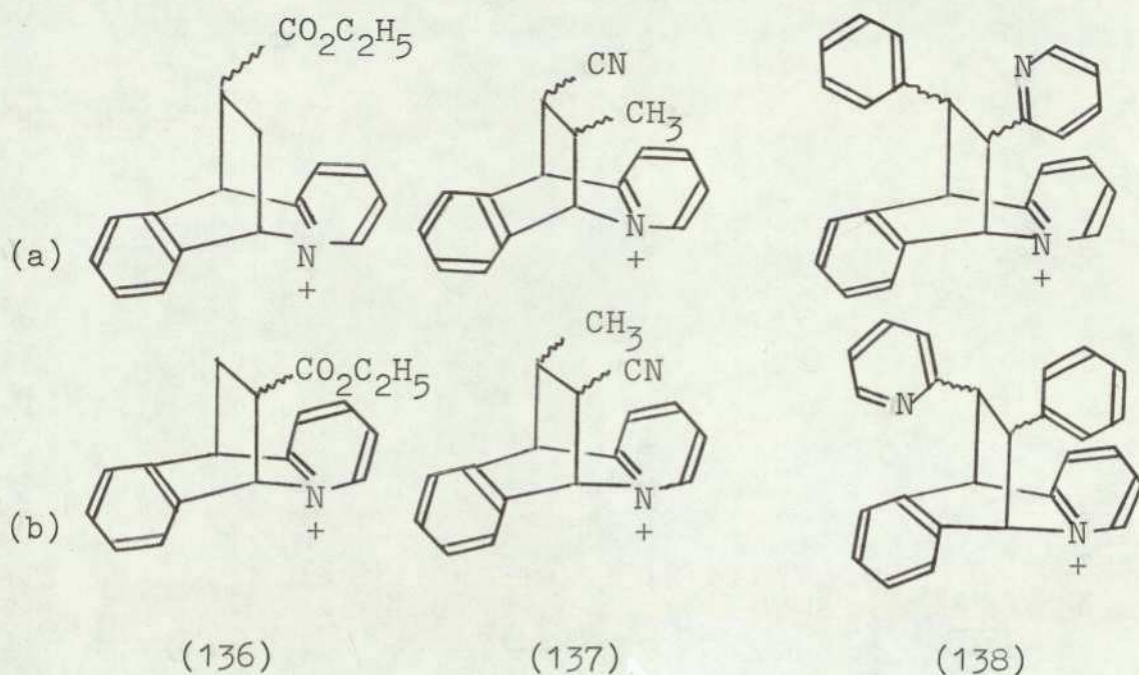


Fig. 4

but is of sufficiently high energy, generally, not to undergo reaction with radicals. Since radicals react with the atom bearing the largest coefficient of an alkene it is far more likely that the site of this reaction will be the β -carbon. The credibility of the diradical mechanism therefore suffered seriously when dienophiles were found that gave a mixture of regioisomers when allowed to react with the acridizinium ion (1). These include ethyl acrylate, cis-crotononitrile, and trans- β -(2-pyridyl)-styrene giving the mixtures (136), (137) and (138) respectively.⁷²

The evidence for isomer formation is based upon ^1H n.m.r. analysis, though the relative stereochemistries were not ascertained. Mixtures containing 80% of (136a), 85% of (137a) and 66% of (138c) were obtained in very high overall yields.



Clearly ground state polarisation is insufficient to explain these mixtures and the anomalous orientations of addition for acrylonitrile and methyl methacrylate⁷² with cation (1).

Since these reactions are of an inverse demand nature it is necessary to consider that molecular orbital interaction which will be dominant during cycloaddition, i.e. between the HOMO_(olefin) and the LUMO_(diene). Considering the HOMO_(olefin) molecular orbital, the olefinic carbon atom bearing the largest coefficient should become attached to the C(6) of the acridizinium ion (1), i.e. the site of the heterocyclic LUMO's largest coefficient (Fig. 5). The biggest atomic coefficient of the olefinic LUMO, as has been shown, resides on the carbon atom β to the substituent (Fig. 4).⁷⁸⁻⁸²

Consideration therefore of the molecular orbitals involved during the cycloaddition gives far greater powers for the prediction of the orientation of the alkene substituent, than if the ground-state polarisation of the olefin only is

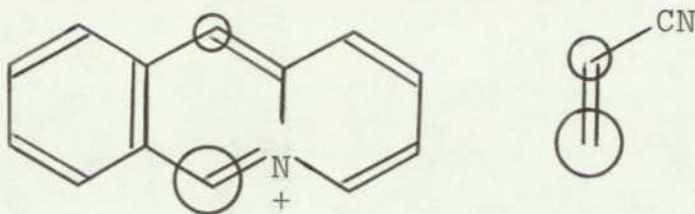
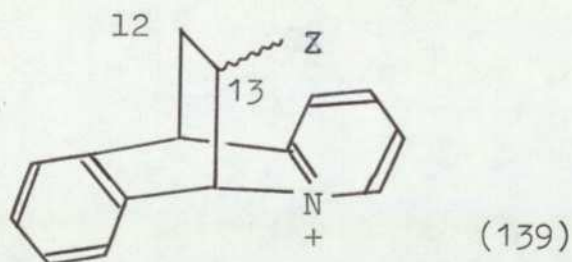


Fig. 5

considered. The electrophilic model, in general, works very well in that the addition gives an intermediate better able to stabilise the developing positive charge of the alkene. Certain olefins will however bear substituents that will modify the atomic coefficients of the alkene HOMO. If this is done in such a way that the coefficient of the α -carbon atom is enlarged or if that of the β -carbon atom is diminished, then the regioselectivity of the cycloaddition will not be so easily predicted. A mixture of regioisomers, or an adduct (139) with reverse regiospecificity - containing the substituent exclusively at C(13) - could then be formed.



Non-regiospecificity has been noted only for very poorly nucleophilic olefins which cycloadd very slowly. The question was therefore raised whether the formation of regioisomers is related to the reactivity of the dienophile. Under similar conditions, the relative rates of adduct formation for these anomalous olefins with the acridizinium ion (1) were obtained: ethyl acrylate, 110; methyl methacry-

late, 93; acrylonitrile, 11; cis-crotononitrile, 1.⁷² Therefore the relationship does not hold. Possibly the site-specificity arises during the first step of a polar cycloaddition, i.e. the charge-transfer complex formation via the HOMO-LUMO interaction. Minute energy differences may be sufficient to control the regiochemistry in what appears to be a borderline situation. It is not impossible to imagine a case where there would be no major influence within the charge-transfer complex thus giving rise to regioisomers. Electrostatic effects are probably most important in this case. Heterocyclic cations are especially prone to charge-transfer complexation,⁸³ and they do so with a variety of donors. 2-Methylisoquinolinium salts give complexes with substrates such as dimethylaniline,⁸⁴ and quinol.⁵⁰

Complexes have previously been invoked in normal Diels-Alder cycloadditions as intermediates, and much work has been undertaken to this end. Konovalov and Kieseler made a study of the ionisation potential, i.e. complexing ability of several aromatic hydrocarbons with respect to the logarithm of the relative rate constant of their reaction with maleic anhydride.⁸⁵ Also investigated was the relationship between the ionisation potential of a series of substituted anthracenes and the logarithm of the rate constant for their reaction with maleic anhydride. In both cases a straight-line relationship was observed and they concluded that "decrease of ionisation potential, i.e. increase of the electron-donating ability, is accompanied by increase of the dienic activity of these compounds." On that basis they continued, "that in the case of compounds of one structural type, when only the electronic effects bringing about altera-

tion of electron-density at the bonds and atoms participating in the reaction are determinative, a parallelism is observed between dienic activity and ability to form charge-transfer complexes."⁸⁵

Bradsher has made a brief study of the charge-transfer complexation of the acridizinium ion (1) with N-vinylcarbazole,⁵⁸ and coupled with the results of Andrews and Keefer,⁸⁶ provides a convincing argument for the existence of the cation almost exclusively as a pre-reaction intermediate, when in the presence of an excess of dienophile. However, they did not determine whether the complex played an intrinsic part in the polar cycloaddition mechanism.

Watt,⁵⁰ was able to isolate the charge-transfer complex between 2,3-dimethylisoquinolinium iodide and quinol. He found that this reacted with a 7-fold rate enhancement over a fresh mixture of components.⁵⁰ The complexation is manifest by intensification of the colour of the heterocyclic cation solution as soon as the quinol is added. This constitutes a tailing in the spectrum of the major absorption to longer wavelengths, and is directly due to a lowering of the energy of the π^* orbital, i.e. the LUMO of the cation.^{87,88} This reduction of the frontier molecular orbital energy level should diminish the energy difference - controlling the actual cycloaddition - between the two levels providing the major interaction, thus increasing the perturbation energy, and the rate of reaction.

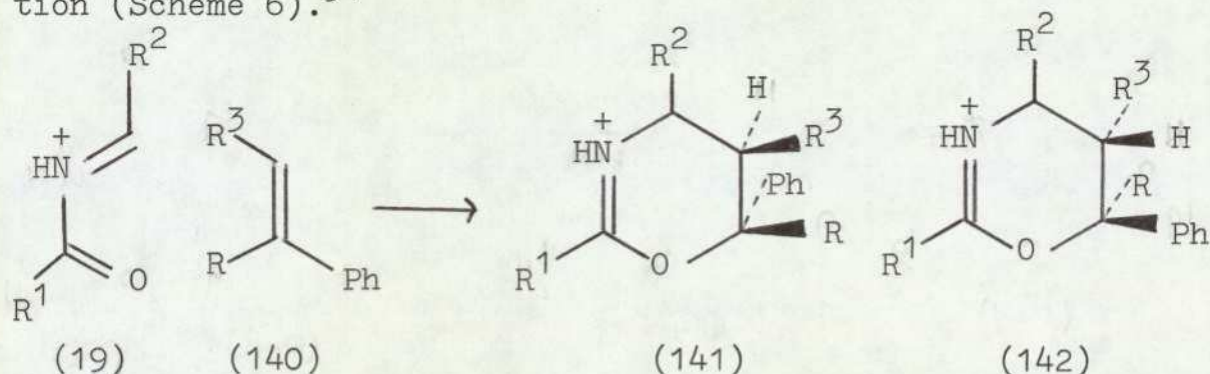
Finally work done on the activation parameters of the reversible reaction between the 2,3-dimethylisoquinolinium cation (125; R = CH₃) and ethyl vinyl ether gives an insight into the geometry of the transition state for the conversion

(Scheme 5).⁵⁸ The forward reaction performed at 0° and 25° gave $\Delta H_f^\ddagger$, the enthalpy of activation for the adduct formation, of 14.6 kcal mol⁻¹, very slightly higher than the value for the average Diels-Alder reaction.^{89,90} The entropy of activation $\Delta S_f^\ddagger$ is -32.2 e.u. and is typical of the classical Diels-Alder values. This suggests a highly ordered transition state for the reaction. It is thought that the structure of the transition state must be very similar to that of the adduct. Figures from measured $\Delta S^\ddagger$ values suggest a cyclic rather than linear arrangement of components for the classical Diels-Alder reaction,⁸⁹ and measurements for the polar case suggest a similar type of mechanism. The first-order reverse reaction, measured at 62.5° and 104° gave the enthalpy of activation for the reverse reaction, $\Delta H_r^\ddagger$, of 26.2 kcal mol⁻¹, within the range of typical Diels-Alder reverse reactions.⁹⁰ The $\Delta S_r^\ddagger$ value of -2.4 e.u. also fits in with measured values for classical reverse reactions. All in all, the activation parameters for cationic polar cycloadditions parallel the classical case forwards and in the reverse sense, suggesting the same cyclic, highly ordered transition state. It has not been possible to totally rule out the two-step mechanism via a discrete or pseudo carbonium ion, but the non-observation of rearrangement products during the cycloaddition with norbornadiene derivatives suggests that any carbonium ion must be exceedingly short-lived. It has been pointed out that the 100% stereoselectivity of some additions would be impossible under these stringent time limits.⁵⁸

The question of the mechanism of $[4^+ + 2]$ cationic polar cycloadditions - at least those involving heterocyclic cations - appears to have been vastly simplified. The

present view supports the initial formation of an intermediate of charge-transfer nature via the $\text{HOMO}_{(\text{olefin})} - \text{LUMO}_{(\text{diene})}$ interaction. In this complex electrostatic and polar effects serve to create the observed regio and/or stereoselectivities through coulombic repulsions existing at, or before the transition state. The initial frontier molecular orbital interaction governs the regiochemistry of addition, and in the case of highly polarisable olefins, where polar effects are greatest, the stereospecificity experienced.

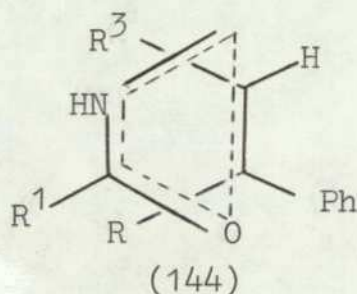
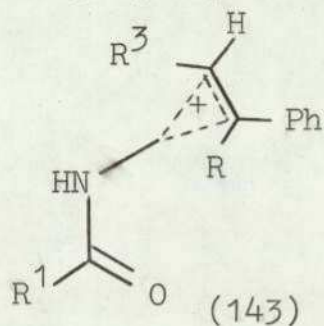
Schmidt has performed much work trying to evaluate the geometry of addition of substituted styrenes (140) to the chiral amidomethyl cation (19; $\text{R}^1 = \text{R-PhCHOCH}_3$, $\text{R}_2 = \text{H}$) generated from the hydroxymethyl precursor in acidic solution (Scheme 6).⁹¹



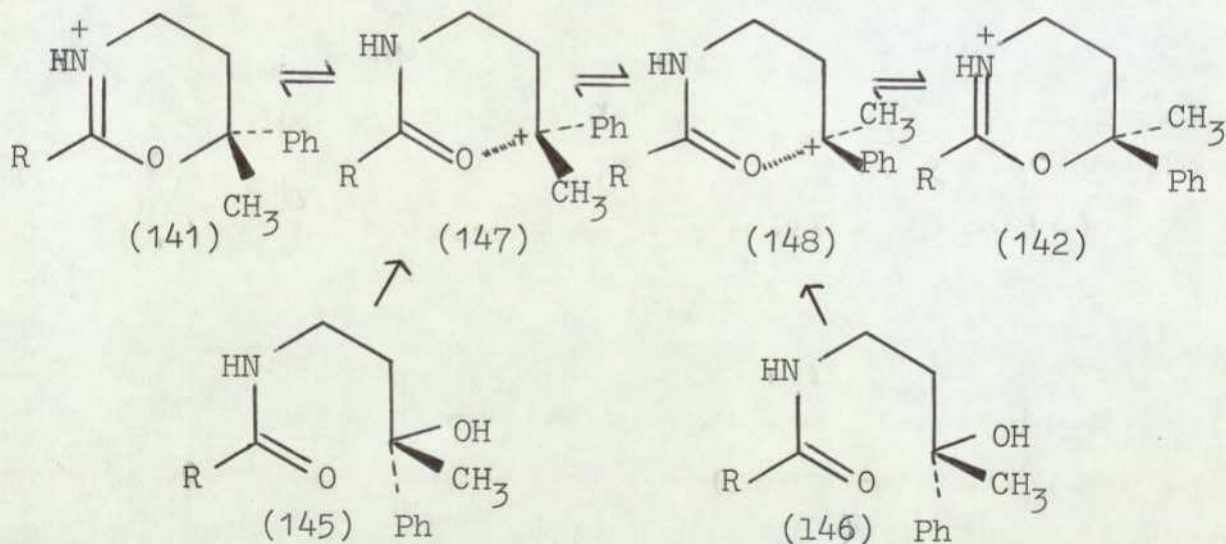
Scheme 6

With β -alkylsubstituents (140; $\text{R}^3 = \text{H}, \text{CH}_3, \text{C}_2\text{H}_5, \text{n-C}_3\text{H}_7$) little effect was observed on the isomer ratios of (141) to (142). However, the styrene (140; $\text{R} = \text{CH}_3$, $\text{R}^3 = \text{H}$) caused a marked difference, altering the ratio from 1.8 to 1.1. It was therefore inferred that in the transition state R is considerably nearer the chiral R^1 group than R^3 . He also maintains that these results eliminate the normal electrophilic attack type of transition state (143) in favour of

a synchronous type of addition via (144), where R has a much more intimate interaction with the chiral R^1 . The product isomer ratios can be influenced in this way, the alkyl group R^3 does not possess that advantage.



It was shown subsequently that a ring-opened equilibrium process was viable and could be considered as the agency leading to the isomers (141) and (142).⁹² The two amido-alcohols (145) and (146) when treated separately in acid both gave (141; $R = \text{CH}_3$, $R^2 = R^3 = \text{H}$) and (142; $R = \text{CH}_3$, $R^2 = R^3 = \text{H}$). These latter compounds must have been



formed via the interchangeable carbonium ions (147) and (148); the suggested ring-opened derivatives. A four species equilibrium was then postulated for the observed thermodynamic equilibrium. Whether or not the formation of the dihydro-oxazines is a polar cycloaddition, in the same sense as

those for heterocyclic cations remains to be seen. Under the conditions of the above reaction, however, it appears that a possible two-step mechanism may be operating.

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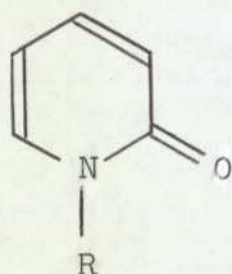
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CHAPTER 1

Attempted Intramolecular cycloadditions of 2-Pyridones.

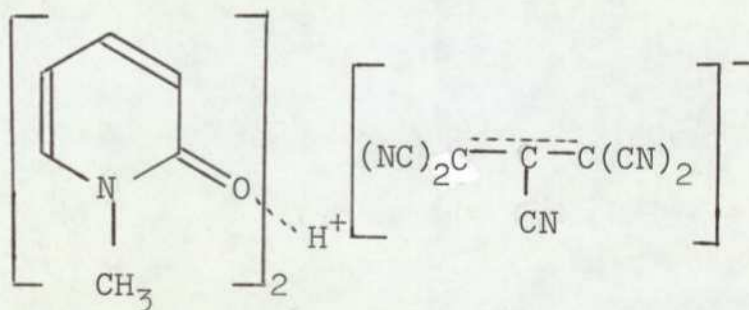
Introduction

Earlier attempts to promote Diels-Alder type reactions, using 2-pyridones as the diene component, met with little success. Elvidge took the initiative by thermolysing 1-methyl-2-pyridone (2) with an equimolar amount of maleic anhydride,¹ but no novel products were isolated. In independent work, two molar equivalents of the anhydride were heated with one of the pyridone under similar conditions to those used by Elvidge, and a 24% yield of an unidentified 2:1 adduct was isolated.²



(1) R = H

(2) R = CH₃

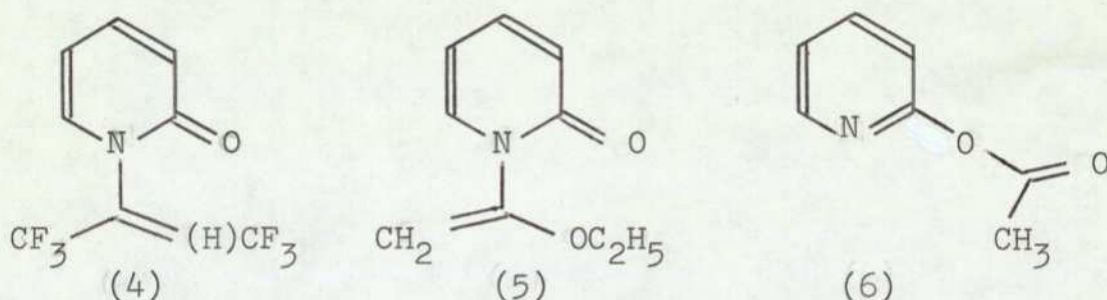


(3)

This compound was apparently not derived from a Diels-Alder addition and contained four acidic protons. During its sublimation 1-methyl-2-pyridone (2) and two equivalents of maleic acid were formed. Unsuccessful results were also obtained when (2) was thermolysed with tetracyanoethylene (TCNE). The evolution of carbon dioxide and hydrogen cyanide from the reaction mixture led to the proposition of structure (3) for the isolated product, containing the resonance

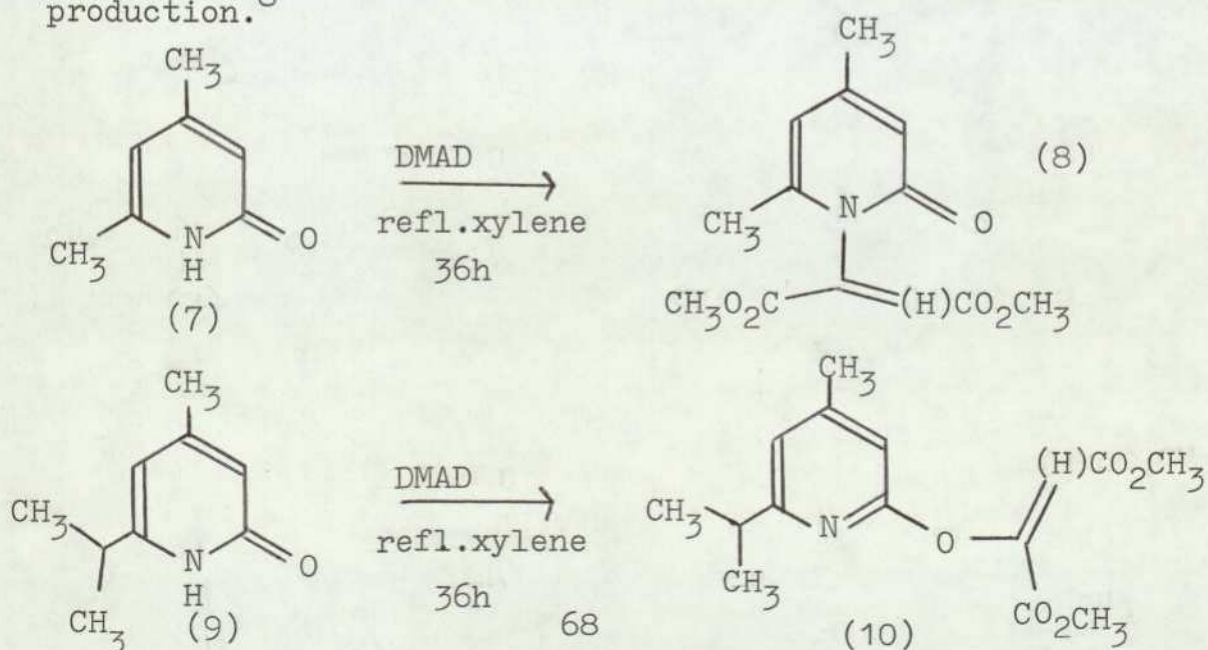
stabilised pentacyanoallyl anion. The spectroscopic data were in agreement with the suggestion.³

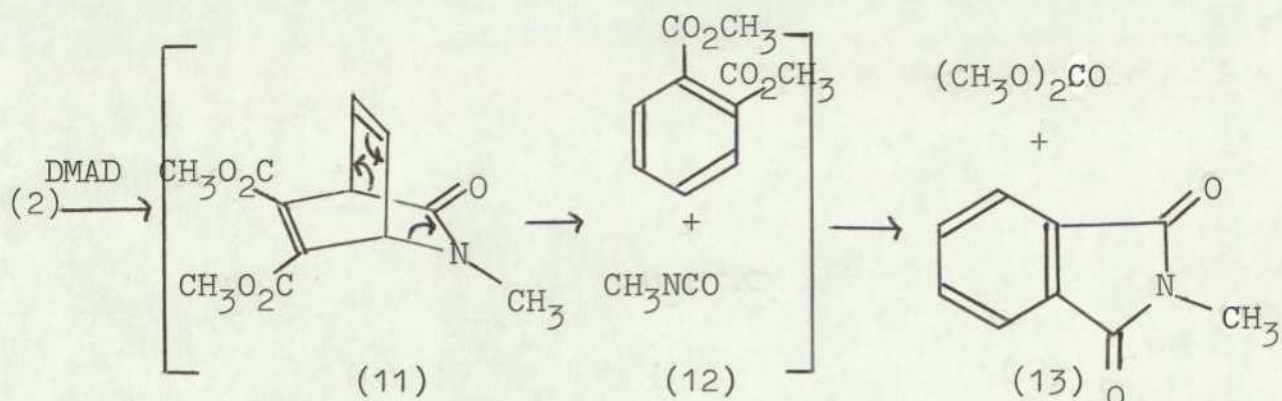
Attempts to involve 2-(1H)-pyridone (1) in Diels-Alder additions have been made assuming the diene possesses classical electron demand requirements. In all cases only products from amide additions were isolated. Hexafluorobut-2-yne gave (4),⁴ while ethoxyacetylene gave derivatives from both N and O alkylation, (5) and (6).⁵ A similar series



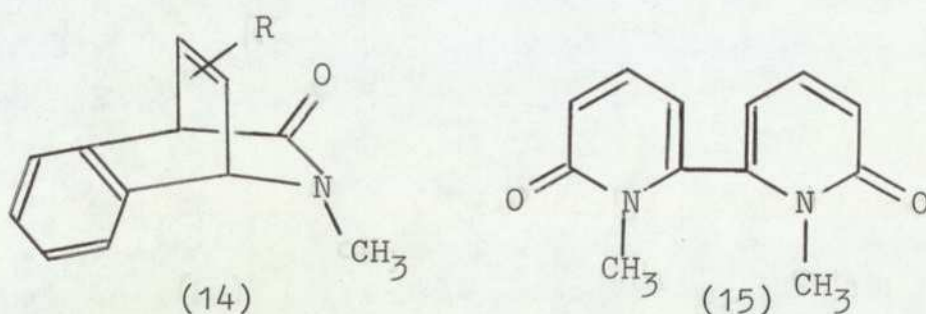
of products were found with dimethylacetylenedicarboxylate (DMAD), (1) and 6-methyl-2-pyridone,⁶ 5,6-dimethyl-2-pyridone and 5,6-tetramethylene-2-pyridone.⁷

Introduction of a bulky group to C(6) of 2-pyridone leads to the isolation of the corresponding pyridine-ether only.⁸ Heep observed that the presence of a 6-methyl group, as in (7), was not sufficient to cause complete oxygen addition, whereas a 6-isopropyl group (9) ensured its exclusive production.⁸

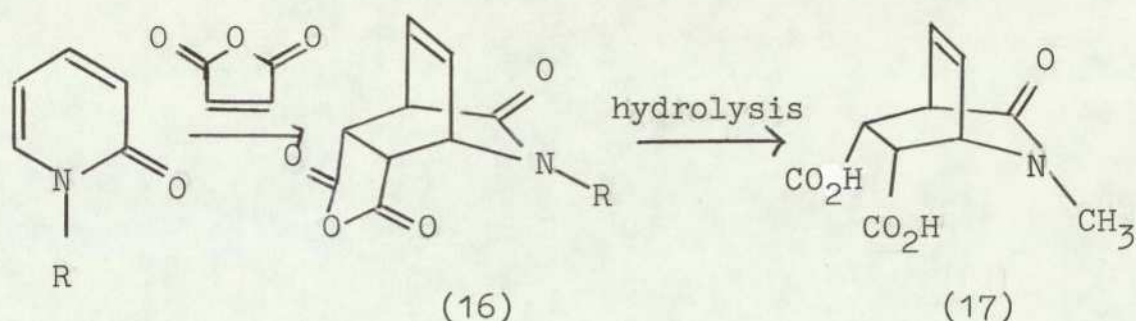




The first successful Diels-Alder 1,4-cycloadditions were observed using only the most reactive dienophiles on N-blocked pyridone (2). Acheson used DMAD and (2), heated at 196° for 4 days, in order to isolate a final product (13) formed from further reaction of the initial adduct (11), in only 4% yield.⁶ At the high temperature employed, the isocyanate and dimethyl phthalate (12) (generated via retro Diels-Alder reaction of intermediate (11)) reacted to give N-methylphthalimide (13).



Following prolonged heating at 110° a reaction was observed between (2) and fumaronitrile, giving a mixture of exo- and endo-adducts in 3% yield.⁹ Benzyne has furnished adducts with (2) depending on how the aryne was generated. N- and O-arylation of (1) is obtained with benzyne from diazotised anthranilic acid,^{10,11} while (2) and several dimethylpyridones give low yields of adducts (14).^{10,11}



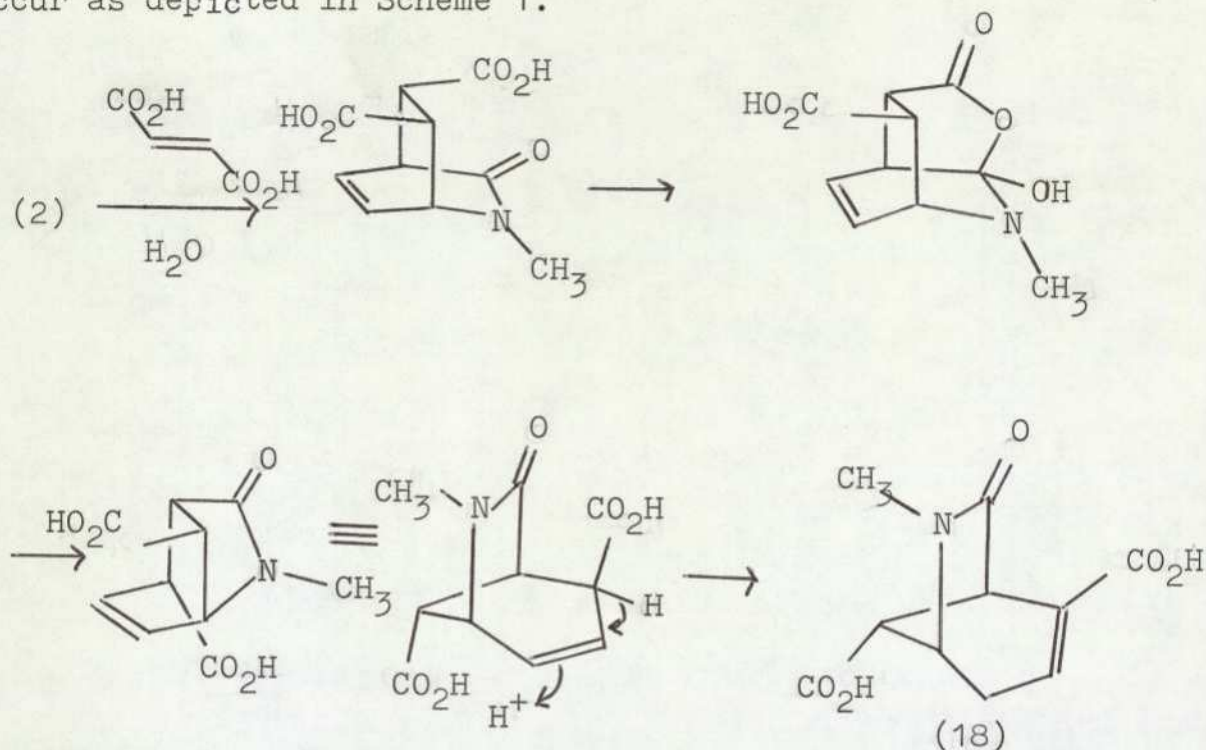
Generated from chlorobenzene and sodamide, benzyne and (2) give 1,1'-dimethyl-6,6'-(bi-2-pyridonyl) (15) and 5% of 1-methyl-3-phenyl-2-pyridone.¹⁰

Compounds structurally similar to (14) have been synthesised as potential pharmaceuticals with various N-substituents.¹² The benzyne was formed from diazotised anthranilic acid.

The reactions of maleimide and N-substituted maleimides with pyridones have given the best results to date, though always with yields less than 40%.^{13,14} Mixtures of exo- and endo-isomers are obtained. N-Phenyl maleimide has even given a Diels-Alder adduct with the parent 2-(1H)-pyridine.¹⁵

Prolonged reactions of (2) with maleic anhydride has furnished several adducts, hydrolysis of which has provided a useful route to the isoquinuclidine skeleton specific to the Iboga alkaloids.^{16,17} Thus, many N-blocked-2-pyridones have yielded the diacid (17) via the isolable intermediate (16).

Reaction of (2) with fumaric acid in water has been described; an unusual rearrangement takes place to give (18) as the major isolable product, in 20% yield.^{18,19} The structure (18) has been verified by ¹H n.m.r. studies on the 3,5-dideutero-derivative of (2), and the mechanism is thought to occur as depicted in Scheme 1.



Scheme 1

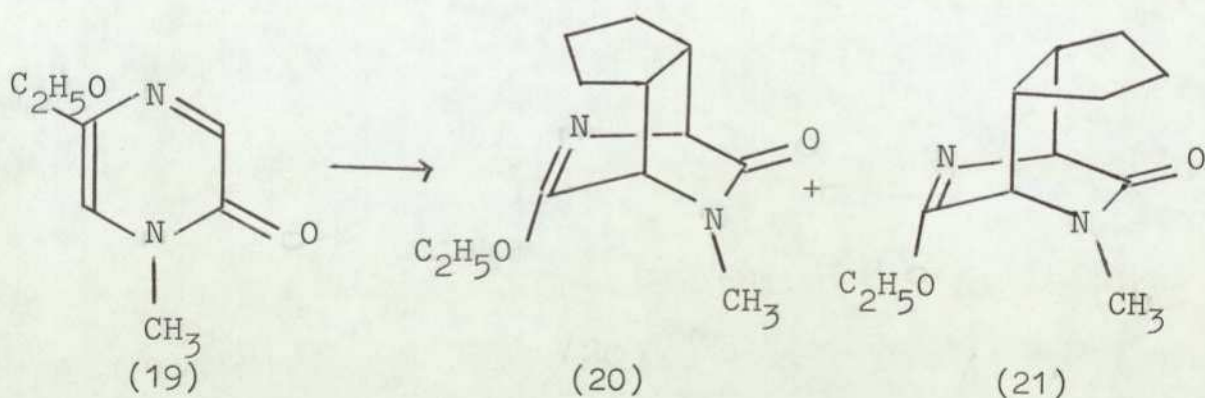
A review of Diels-Alder reactions involving pyridones and covering the literature up to 1974 has been provided by Shusharina, one of the major protagonists in this field.²⁰

The poor yields encountered in this area of research has led to the suggestion that the 2-pyridone system does not exhibit normal electron demand during Diels-Alder cycloadditions.¹¹ If this were so it would mean that instead of the HOMO (Higher Occupied Molecular Orbital) of the diene and the LUMO (Lowest Unoccupied Molecular Orbital) of the olefin providing the major orbital interaction leading to

the transition state, the reverse would be true, i.e. the HOMO(olefin) - LUMO(diene) interaction would predominate (Scheme 2).

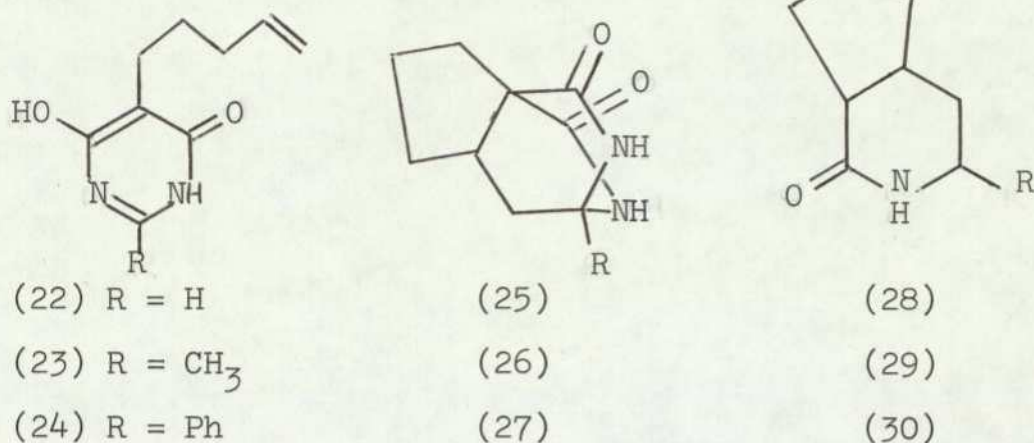
If 2-pyridones were to manifest an inverse electron demand requirement then the diene would, of necessity, be electron deficient. Ideally then, for the Diels-Alder reaction to occur with this diene, the dienophile should consist of an electron-rich alkene or alkyne. All previous thermolyses of the 2-pyridone nucleus, blocked or unblocked, have been undertaken using very electrophilic dienophiles, and, generally, only small amounts of adducts were isolated. This "volte-face" approach could account for the low reactivity observed for 2-pyridones in all of the cycloadditions reported in the literature.

The analogous pyrazine system (19) has been shown to be of the inverse electron demand type.²¹ The "4-aza-2-pyridone" (19) reacted rapidly with the relatively electron rich cyclopentene giving a mixture of primary adducts (20) and (21).



Pyrimidones react similarly in high yield, intramolecularly with non-activated olefins. Thus, pyrimidones (22), (23) and (24) give primary adducts (25), (26) and (27) from which cyanuric acid may be eliminated, giving the respective dihydro-cyclopentano-2-pyridones (28), (29) and (30)

(Scheme 3).

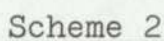


Scheme 3

The cycloadducts were obtained by thermolysing a DMF solution of the precursor at 200° overnight. The intermediates (26) and (27) were isolable, but diminished in concentration as the thermolysis times were extended. Compound (25) was not observed.²²

Substituent effects of both 'ene' and diene components would be expected to play a major role in facilitating 2-pyridone cycloadditions. This can be best understood by considering the perturbations of the relevant orbitals during the initial approach of the reacting species towards each other. The approximations advanced by Fukui to rationalise chemical reactivities, regioselectivities and kinetics of cycloaddition reactions have been generally accepted as providing a basis for the perturbation theory.²³ It must be stressed that the perturbation describes only the preliminary interaction on the mutual approach of the reacting species. It measures the feasibility of the initial approach to the transition state, but does not describe its energy. At best it demonstrates the stabilisation of the newly formed orbitals, provided external factors such as steric

In practice one has only to consider the interactions of the HOMOs and LUMOs for each reacting components. Two perturbations only, need be determined for the reaction between an olefin and a diene, i.e. the $\text{HOMO}_{(\text{diene})} - \text{LUMO}_{(\text{olefin})}$, and $\text{HOMO}_{(\text{olefin})} - \text{LUMO}_{(\text{diene})}$ (Scheme 2).



A diagram of a double bond with four substituents. The left carbon is bonded to 3' (top) and 2' (bottom). The right carbon is bonded to 4' (top) and 1' (bottom). The substituents are arranged such that 3' and 4' are on the same side of the double bond, and 2' and 1' are on the opposite side.

Scheme 4

74

$$\text{Equation 1} \quad + \frac{[(c_{H_1}c_{L_1} + c_{H_4}c_{L_2})\beta]^2}{E_{H_D} - E_{L_O}}$$

β is an expression for the resonance energy and is generally assumed to be constant.

Clearly, the larger the coefficients, the better will be orbital overlap and the larger perturbation energy ΔE . Also, the smaller the difference between the energy levels providing the dominant interaction, the larger again will be ΔE . If one of the pair of interactions is considerably greater than the other, then one of the terms of equation 1 can be neglected completely, reducing it to equation 2(a) or 2(b).

$$\Delta E = \frac{Q}{E_{H_O} - E_{L_D}} \quad \text{Equation 2(a)}$$

$$\Delta E = \frac{Q}{E_{H_D} - E_{L_O}} \quad \text{Equation 2(b)}$$

The assumption has to be made that the atomic coefficients can be taken as constant, (Q), under similar substitution patterns, and this appears to be valid for many cycloaddition series.

For the case of the classical or normal Diels-Alder reaction (a) (Scheme 2), the olefin frontier molecular orbitals are lower in energy compared to those of the diene. The $\text{HOMO}_{(\text{diene})} - \text{LUMO}_{(\text{olefin})}$ energy levels will be closer together than the $\text{HOMO}_{(\text{olefin})} - \text{LUMO}_{(\text{diene})}$ levels. The former interaction will therefore produce the larger perturbation energy, and greater stabilisation to a first approxi-

mation. Substituents on either reactants which will increase the rate of cycloaddition will of necessity have to bring still closer together the two energy levels supplying the dominant interaction. It has been observed that electron-attracting substituents lower both the HOMO and the LUMO of each component, while electron-donating groups raise both of those levels in energy.²⁵ Ideally, normal demand reactions will be enhanced by substituting the diene with the latter type of substituents and the olefin with the former. The largest effects are observed for those reacting species containing the substituent at the atom bearing the largest coefficient in the HOMO or LUMO that takes part in the major interaction.

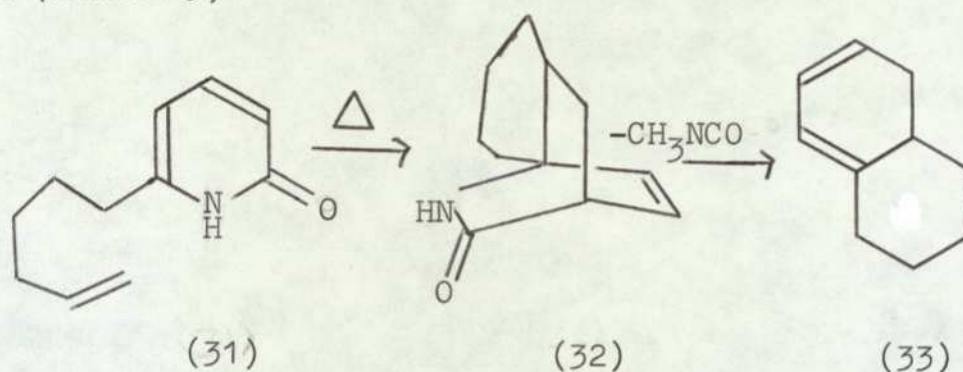
This is equally true for the neutral Diels-Alder reaction (b) (Scheme 2). Here both HOMO - LUMO interactions are of similar magnitude, thus the orbital interactions will depend upon the substituents present.

The inverse demand Diels-Alder situation (c), has, as the major overlapping orbitals, the HOMO_(olefin) and LUMO_(diene) pair. Reactivity may be enhanced by substituting the dienophile with electron-releasing groups and the diene with electron-attracting species. It has been observed that conjugating substituents, such as the phenyl group, will raise the HOMO and depress the LUMO energy levels of both components, thus aiding all three modes of cycloaddition.²⁵

Much numerical data has been collected as part of a study of regioselection in Diels-Alder reactions,²⁶ and also for the Lewis acid catalysis of cycloadditions.²⁷

Preparation and thermolysis of
alkenyl-2-pyridones.

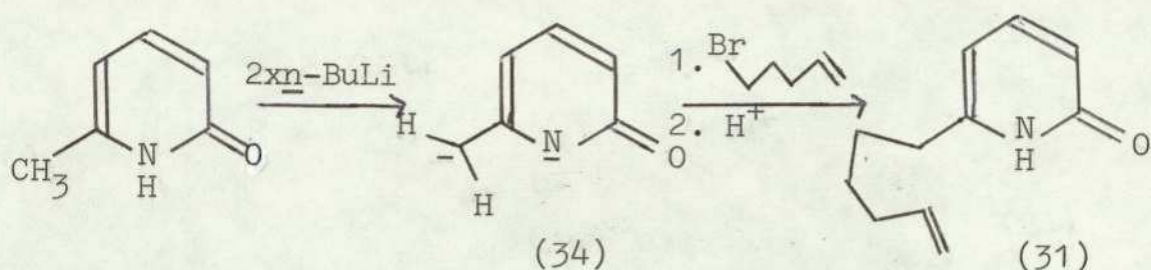
Initially our investigations were directed towards the preparation of a 2-(1H)-pyridone substituted with an alkyl chain containing a terminal olefin. Assuming that the inverse demand requirements exhibited by pyrimidones can be extrapolated to pyridones, the alkenyl pyridone should be capable of undergoing intramolecular Diels-Alder addition (Scheme 5).



Scheme 5

Primary adduct (32) could then be catalytically reduced to a tricycloazaspiro-derivative, or hydrolysed at the amide function to give a dehydrodecalinamino acid. Alternatively elimination of cyanuric acid during thermolysis would give hexahydronaphthalene (33). Compound (31) was prepared by the alkylation of dianion (34) with pentenyl bromide.

Pentenyl bromide was formed by the bromination with phosphorus tribromide of pentenyl alcohol, which was in turn prepared by the method of Brooks.²⁸ The pyridone was generated by the diazotisation and subsequent hydrolysis of 6-amino-2-picoline in a manner similar to that of Adams *et al.*²⁹ The yellow dianion (34) was prepared by the method of Hauser, at 0°, with two equivalents of *n*-butyl lithium.³⁰

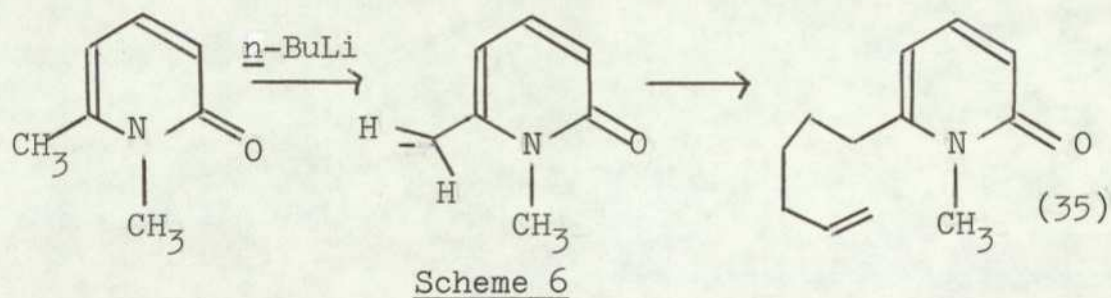


Alkylation with the bromide gave a 50% yield of 6-(hex-5-en-1-yl)-2-pyridone (31). The ^1H n.m.r. spectrum contained, in addition to the expected vinyl absorptions and alkyl envelope, a two-proton triplet at δ 2.65 for the benzylic methylene. The N-H proton is evident at δ 13.35 as a broad singlet which disappears on addition of D_2O . The i.r. spectrum contains the lactam absorption at 1659 cm^{-1} , and the U.V. spectrum, the pyridone band at 306 nm.

Thermolysis of (31) under a variety of conditions was fruitless. Acetonitrile and DMF were used as solvents, for times varying between 1 and 70 h, and at temperatures up to 250° . The substrate was always recovered intact except at the more elevated temperatures where it began to gradually decompose. Even use of Lewis acids, such as boron trifluoride etherate or of catalytic amounts of sodium t-butoxide had little effect. This result is in keeping with the aromatic character of 2-(1H)-pyridone.³¹ For this reason the preparation of the N-methyl derivative of (31) was sought.

1,6-Dimethyl-2-pyridone was prepared from 6-methyl-2-pyridone using a method for the formation of 1-methyl-2-pyridone from 2-pyridone.³² An attempt to prepare the monoanion (Scheme 6), with one equivalent of *n*-butyl lithium, gave a dirty black solution, which when alkylated, gave a

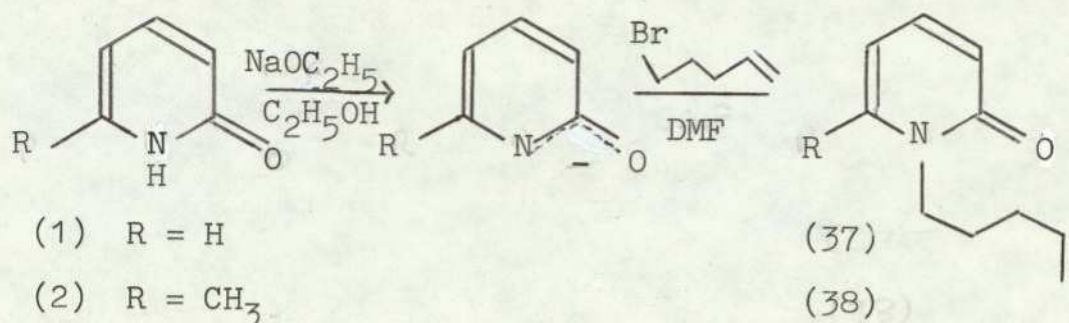
very complex mixture out of which only a 7% yield of 1-methyl-6-(hex-5-en-1-yl)-2-pyridone (35) was isolated. The



^1H n.m.r. spectrum of (35) was very similar to that from (31), though the broad exchangeable singlet is replaced by a three proton singlet at δ 3.56. The carbonyl absorption occurs at ν_{max} 1656 cm^{-1} . Thermolysis of (35) under the conditions described for the thermolysis of (31) gave identical results. In all cases the substrate was recovered after heating, until, at about 200° it decomposed.

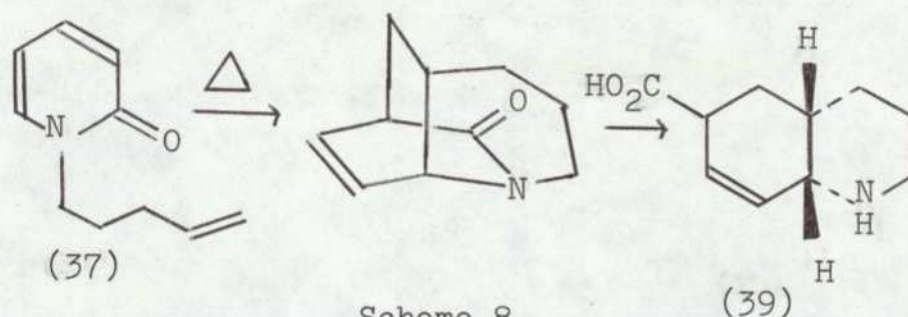
The alternative method of synthesis of (35), *i.e.* direct alkylation of (31), proved to be impracticable. Products of O-alkylation are obtained almost exclusively for any 2-pyridone containing an alkyl group other than a methyl group at position 6. For this reason other N-blocked pyridones were formed (37) and (38) by alkylating 2-pyridone (1) or the 6-methylanalogue (36) with pentenyl bromide (Scheme 7).

These derivatives have the advantage that successful cycloaddition and subsequent hydrolysis, would lead to an amino acid (39) containing the basic skeleton of nor-pumeliotoxin-C. Framework molecular models indicate that use of hex-4-en-1-yl bromide instead of pentenyl bromide would lead to product (40), which contains three of the four asymmetric

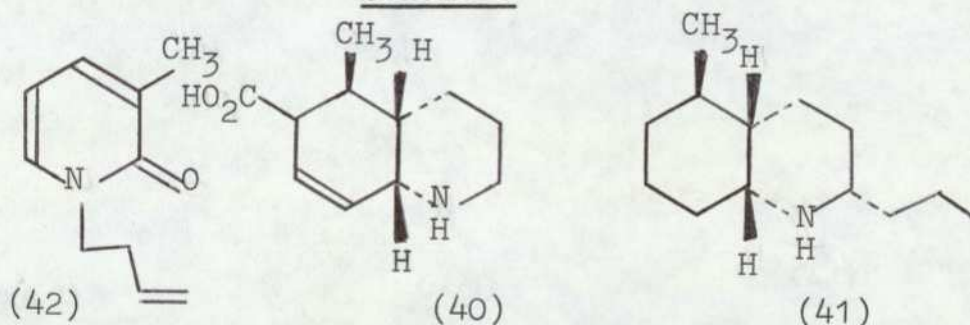


Scheme 7

centres (with the correct stereochemistry) of the parent pumeliotoxin-C (41) - a c.n.s. acting alkaloid isolated from the skins of South American frogs (Scheme 8).



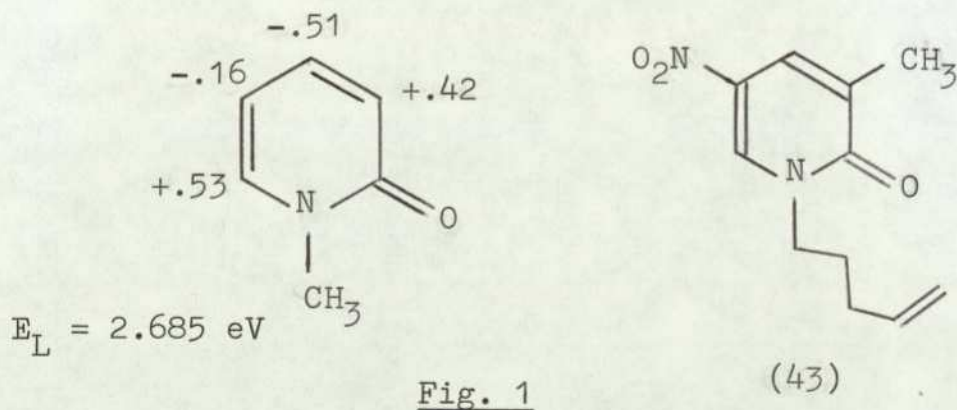
Scheme 8



Using the methylation method of Hopkin *et al.*,³² (37) and (38) were prepared in yields of 39% and 10% respectively. In the latter case the major product was the corresponding pyridine-ether. In both alkylations small amounts of the parent 2-(1H)-pyridones were recovered. Both structures were supported by their spectral and analytical data, and were totally inert to thermolysis under all the conditions that they were subjected to.

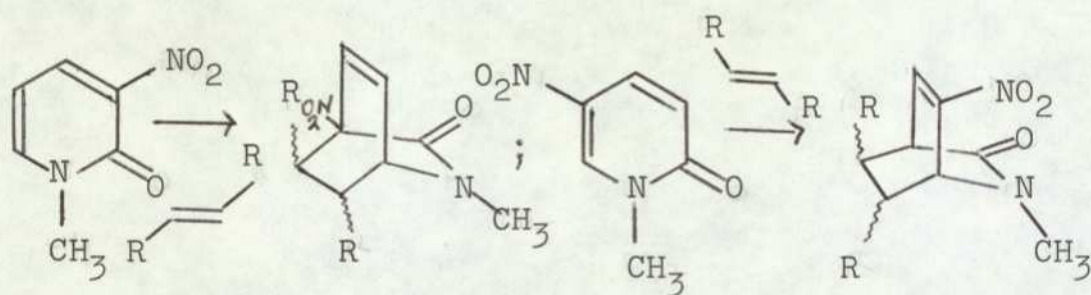
In order to test whether the observed lack of reactivity of alkenyl pyridones was due to the length of the alkenyl chain, pyridone (42) was synthesized via the monoanion of 3-methyl-2-pyridone with butenyl bromide. This, however, also proved totally inert when thermolysed over a wide range of temperatures. It decomposed when heated above 250°.

If the potential cycloaddition was of an inverse demand nature, then two options would exist to induce adduct formation. Firstly, substitution of the heterocyclic ring with an electron withdrawing group would lower the LUMO in energy, whereas replacement of the isolated olefin group with an electron-rich olefin, like an enamine or enol ether, would raise the dienophile HOMO. Either or both of these modifications would tend to bring closer together the energies of the orbitals providing the major interaction. Consideration of the atomic coefficient for each carbon atom of the 2-pyridone LUMO (Fig. 1) shows that the greatest energy lowering effect will be obtained by positioning an electron withdrawing substituent at C(4) or C(6).



The largest atomic coefficient resides on these atom, but unfortunately the preparation of 2-pyridones containing relatively electron deficient groups at C(4) are unknown.

Thus, 4-cyano- or 4-nitro-2-pyridones have not been synthesised. Computer studies have shown that a nitro group substituted at C(3), C(5) or C(6) will still produce a significant lowering effect of the LUMO energy.³³ During the cycloaddition across the pyridone nucleus, C(3) and C(6) lose their sp^2 character as the reaction progresses. The result is that a nitro group in this position would become deconjugated. This is not the case for the C(5) - nitro derivative which would retain conjugation (Scheme 9). Also, since C(3) and C(6) are the diene termini for the cycloaddition, then substituents at either of these sites would sterically interfere with the course of the reaction.



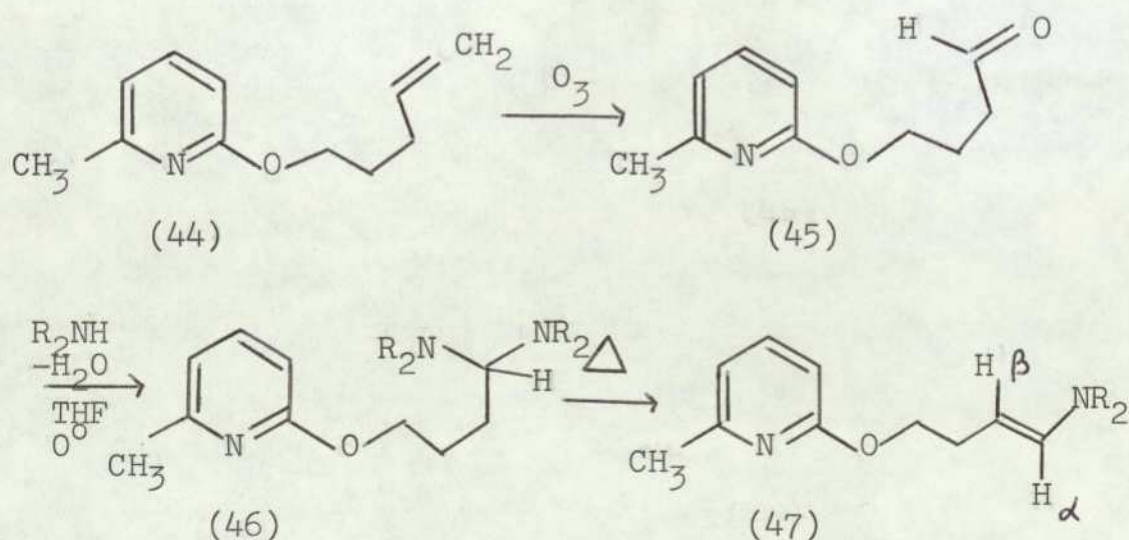
Scheme 9

3-Methyl-5-nitro-2-pyridone was prepared in 62% yield following treatment of 3-methyl-2-pyridone with a mixture of fuming nitric acid and concentrated sulphuric acid. This was converted to 1-(pent-4-en-1-yl)-3-methyl-5-nitro-2-pyridone (43), an orange oil, in 48% yield. The ^1H n.m.r. spectrum contains two aromatic peaks at δ 8.08 (C(4)-H) and 8.69 (C(6)-H) significantly deshielded by the nitro group from their usual positions at about δ 7.20. The lower field signal is a doublet ($J = 3\text{Hz}$), while the other is a broad singlet caused by coupling with the methyl protons. Also deshielded, by 0.4 p.p.m., is a triplet at δ 4.13 ($J = 7\text{Hz}$),

the N-methylene absorption. The i.r. spectrum contains the lactam absorption at 1662 cm^{-1} , and the pyridone peak is present in the U.V. spectrum at 308 (5,800) and 320 nm (5,400), the latter being very broad and tailing off beyond 370 nm.

Thermolysis of this compound led to no cycloaddition products under any of the conditions employed. It decomposed at temperatures as low as 200° to give only intractable tars.

The alternative method of activation was then undertaken, i.e. making the dienophile more electron-rich. It was proposed that enamine formation using a suitable aldehyde would be the best route, following the pioneer work of Stork.³⁴ Since appropriately substituted pyridones had already been conveniently prepared (31), (35), (37), (38), (43), ozonolysis of the terminal olefin should provide a quick route to the required aldehyde. Simple condensation with a secondary amine should then lead to the enamine - an exceedingly electron-rich olefin. As a test of the viability of this method the useless by-product (44) was selected for the precursory attempt (Scheme 10).



Scheme 10

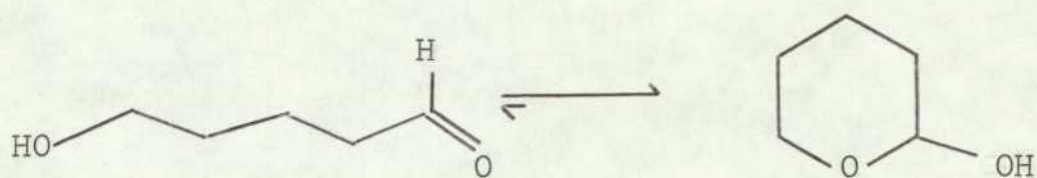
A clean conversion to (45) was obtained, in very high yield. The ^1H n.m.r. spectrum of (45) contained at δ 2.50 a two proton triplet for the methylene adjacent to the formyl group, and a very narrow doublet (J 1Hz) at δ 9.73 for the aldehydic proton. The lowfield doublet should be a triplet, but perhaps the formyl group is held in a specific orientation precluding coupling to both adjacent methylene protons. The ^{13}C n.m.r. spectrum contains the resonance due to the carbonyl carbon atom at 201 p.p.m., and in the i.r. spectrum the carbonyl peak occurs at 1723 cm^{-1} . The i.r. peaks for the aldehydic proton are manifested at 2830 and 2730 cm^{-1} .

Treatment of (45) with piperidine, and anhydrous potassium carbonate gave a clean conversion to (46). Heating at 60° for 30 min. was required to eliminate piperidine from the diaminoacetal intermediate (46) which was evident from ^1H n.m.r. investigations. The spectrum of the enamine (47) showed the incorporation of one molecule of piperidine. A doublet (J 15Hz) is prominent at δ 5.90, and this can be collapsed to a singlet by doubly irradiating a multiplet at 432 Hz, a signal coincident with the absorption for the ether methylene group. The peak at δ 5.90 arises from H_α of (47), and the masked peak from H_β . The i.r. spectrum contains the enamine peak at 1643 cm^{-1} and the N-methylene absorption at 1298 cm^{-1} . When thermolysed at 180° for 12 hrs, an excellent yield of 6-methyl-2-pyridone was obtained, possibly via an intramolecular ene-type reaction.

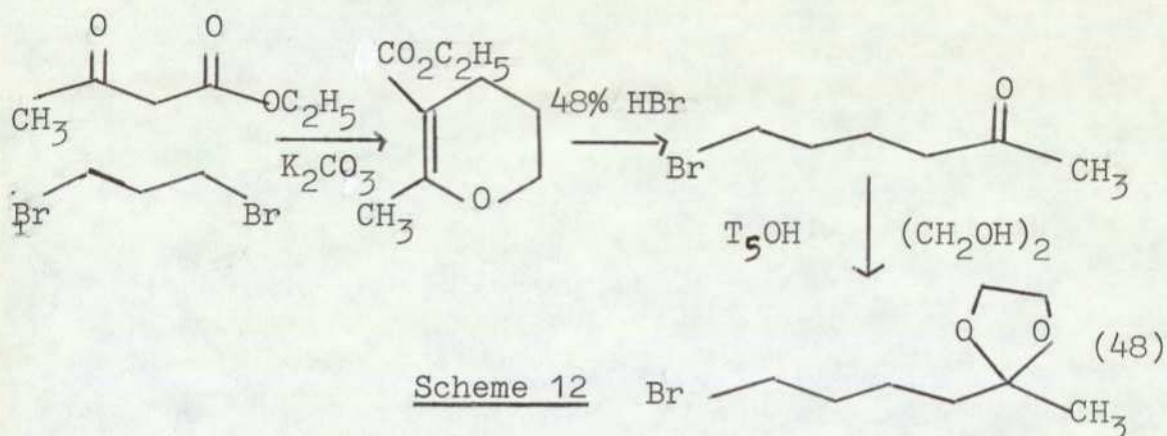
Since the route to enamines appeared successful the nitropyridone (43) was subjected to the same ozonolysis procedure. However, the substrate appeared unstable to this

treatment and general decomposition occurred. DMSO was used to reduce the oxidised solution. Both g.l.c. and t.l.c. analysis indicated a complex reaction and ^1H n.m.r. examination revealed only minor amounts of aldehydic material. Pyridone (31) was then treated similarly, however the reaction could not be followed by the normal g.l.c. method owing to the involatile nature of the substrate (31). The method for monitoring the progress of the reaction due to Slomp was adopted.³⁵ This involved the periodic withdrawal of small aliquots of the ozonised mixture, and observation (by i.r. methods) of the disappearance of the absorption due to the olefin. The bands observed were those for the vinyl bending modes at 911 and 1002 cm^{-1} . The former peak slowly disappeared on commencement of the ozonolysis, as a new peak emerged at about 980 cm^{-1} . Complex changes then swamped the bands being monitored rendering this technique non-viable. A t.l.c. method also indicated the consumption of the substrate (31), but also the formation of only highly complex mixtures. Use of an equimolar amount of pyridine in the reaction mixture to moderate the electrophilic behaviour of ozone made no difference to the outcome.³⁵

Since 5-hydroxypentanal exists more than 99% in the ring-closed form (Scheme 11)³⁶, synthesis of 5-bromopentanal proved elusive. The one reported synthesis requires an involved reaction sequence of many steps.³⁷ 6-Bromohexan-2-one was therefore prepared as an alternative 'handle' using a method similar to that of Bellas et al. from ethyl acetoacetate (Scheme 12).³⁸

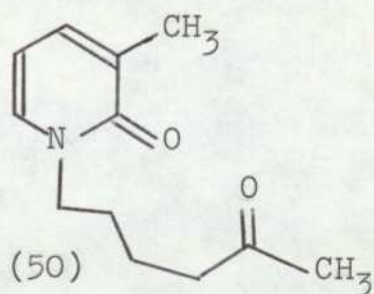
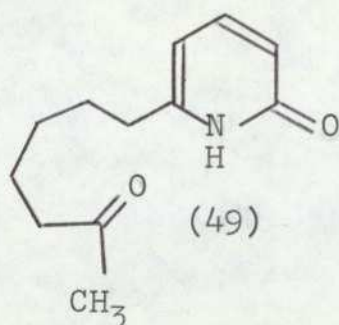


Scheme 11



Scheme 12

Following conversion to the dioxolone (48),³⁸ both 6-(6-oxohept-1-yl)-2-pyridone (49) and 1-(5-oxohex-1-yl)-3-methyl-2-pyridone (50) were synthesised in yields of 67 and 73% respectively.



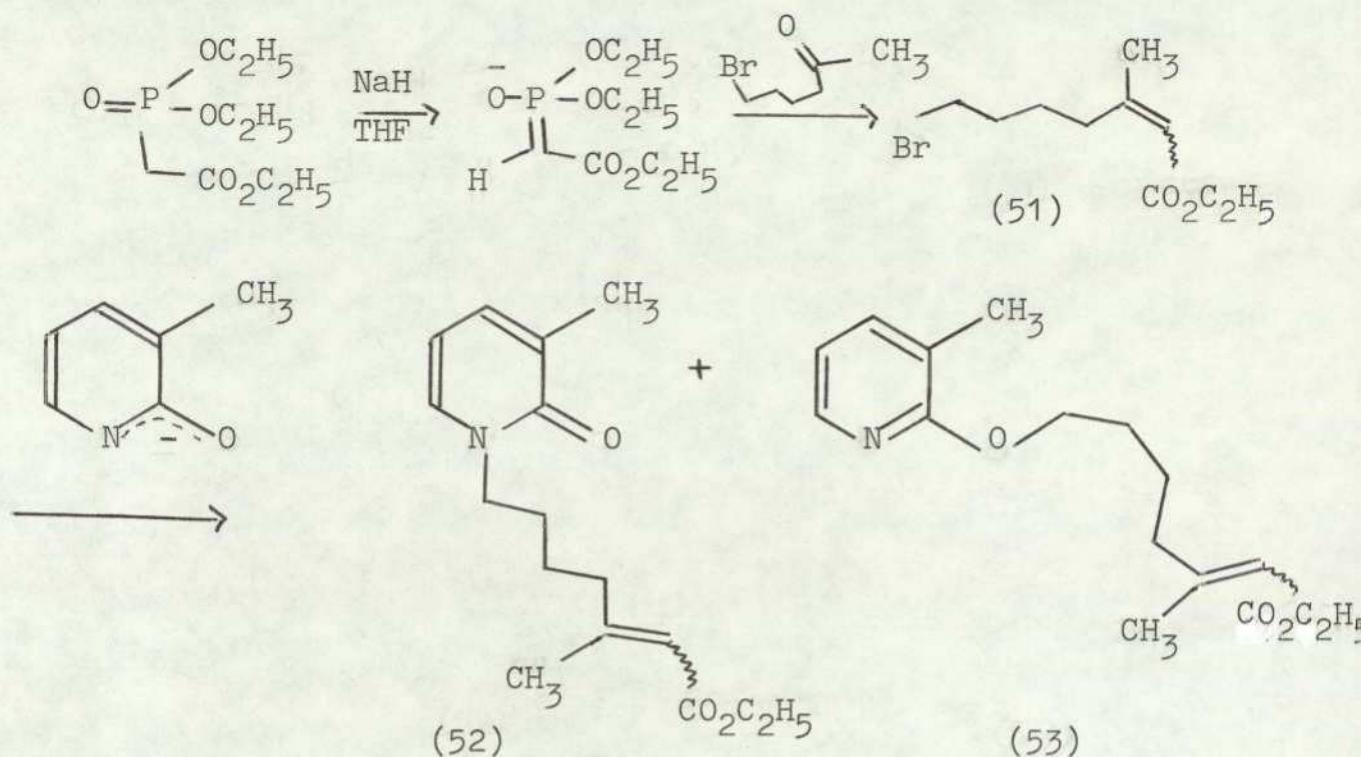
According to Stork the best method for the preparation of monomethyl ketone enamines is to heat with pyrrolidine a benzene solution of the ketone.³⁴ A catalytic amount of tosic acid is required. Low yields are known to be obtained, but in some cases these have been vastly improved, following Soxhlet extraction of the reaction mixture with 4A molecular

sieves as dessicant. When ketopyridone (50) was thus treated, then worked-up as for the aldehydopyridone (45) no enamine could be detected. Changing the solvent to toluene made no difference and only starting material (50) was recovered. This approach was therefore abandoned.

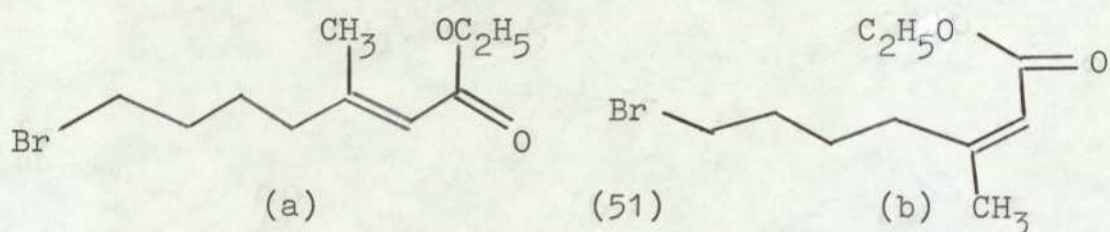
A careful examination of results obtained from intermolecular cycloadditions of variously substituted 1-methyl-2-pyridones, with DMAD (see later) has indicated that pyridones may possess normal electronic demand requirements. Therefore the HOMO of the diene and the LUMO of the olefin would be expected to provide the major interaction during reaction. The extreme sluggishness of the cycloadditions can be interpreted as arising from 2-pyridone tending slightly towards the neutral demand situation. This would make the denominators of equation 1 relatively large, thus reducing the perturbation energy, and indicating low orbital overlap between the diene and dienophile prior to the transition state. In this situation reaction would only occur with difficulty.

In an attempt to test this hypothesis the pyridone (52) was prepared (Scheme 13).

The bromoester (51) was formed as an inseparable mixture of cis-(51b) and trans-(51a) in a ratio of 1 / 9 respectively. It was deduced that the mixture contained predominantly the (E)-isomer as observed for other reactions employing triethylphosphonoacetate,³⁹ and from a Eu (fod)₃ ¹H n.m.r. study of the isomer mixture. Inspection of the structure (51a) indicates that a change in chemical shift induced by the rare earth complex should be greater for the methyl signal than for that of the olefinic methylene.



Scheme 13

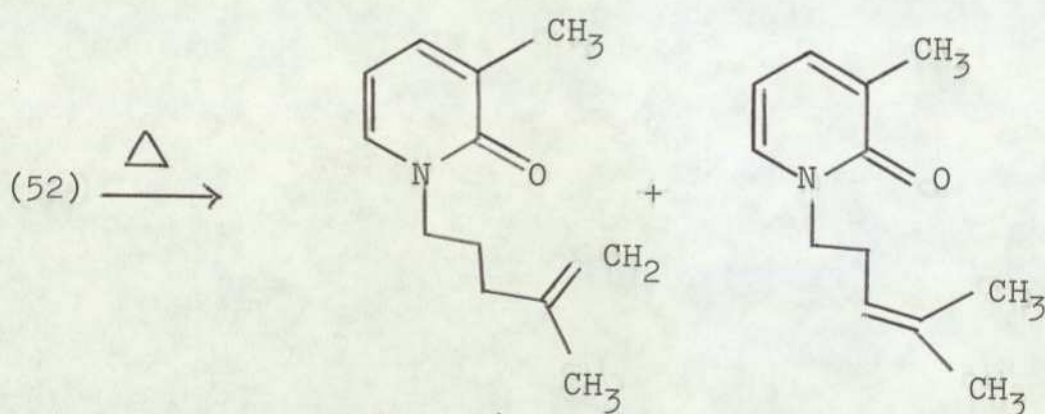


The local magnetic field effect generated by the $\text{Eu}(\text{fod})_3$ complex diminishes proportionately with the inverse cube of the distance of the affected nuclei from the metal.⁴⁰ Therefore to a first approximation the closer the alkyl group is to the position of complexation of (51) with the europium - i.e. the ester function - the greater will be the observed change in chemical shift. The methyl and olefinic methylene group are coincident in the normal spectrum, forming a five-proton multiplet between $\delta 2.11$ - 2.38 . Addition of $\text{Eu}(\text{fod})_3$ to solutions of substrate deshielded the methyl signal more than the methylene peak. This observation confirmed that the isomer mixture contains mainly (51a).

Alkylation of the sodium salt of 3-methyl-2-pyridone

with the bromoester mixture (51) gave a 74% yield of (52). Only minor amounts of (53) were observed after column chromatography, and this was eluted as a mixture with small amounts of unreacted bromide (51). The ^1H n.m.r. spectrum of (52) contains the olefinic proton signal at $\delta 5.74$ as a singlet, and the N-methylene peak as a triplet (J 7Hz) at $\delta 4.07$ overlapping with the ethoxymethylene absorption. The C(5)-H is represented as a triplet (J 7Hz) at $\delta 6.17$ while the C(4)-H and C(6)-H signals overlap to give a distorted triplet at $\delta 7.27$. The i.r. spectrum contains at 1705, 1650 and 1588 cm^{-1} peaks for the ester, pyridone and olefin absorptions respectively. The U.V. λ_{max} occurs at 225 (15,130) and 304.5 nm (5720).

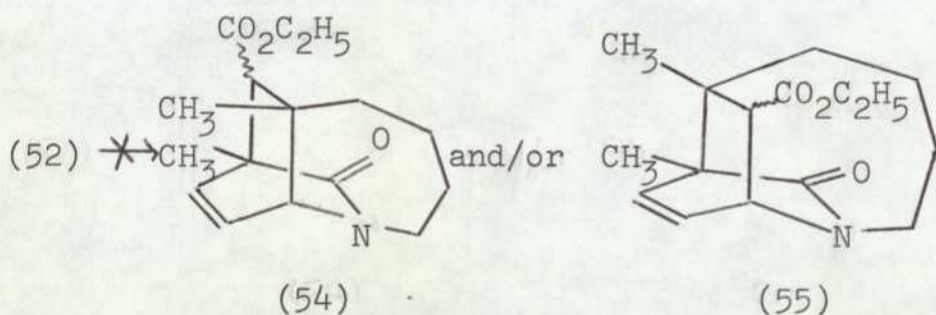
Thermolysis of (52) gave no products of cycloaddition, and only at temperatures in excess of 250° gave what appeared to be a mixture of ester decarboxylated products (Scheme 14).



Two possible explanations exist to account for the lack of reactivity shown by (52), the first being the apparent steric interactions present in the possible adducts due to the substituents. The second reason requires consideration of the effect that the alkyl substituents will

have on the frontier molecular orbitals of the α,β -unsaturated ester.

Two adducts could feasibly form (Scheme 15), the strain-free derivative (54) having fewer steric restrictions than twistane structure (55). The bridgehead methyl in the latter appears framed gauche between the two alkyl substituents adjacent to it from the olefin. This introduces large Pitzer strains in the eight membered rings. Intramolecular Diels-Alder cycloadditions are also known to be considerably slower when involving the production of eight membered rings, whilst seven membered rings are more easily formed. Structure (54) contains a significant reduction in steric strain compared to (55) and is thus the more sterically favourable regioisomer. However, the crowding of substituents present in (54) may be such that cycloaddition is still precluded, explaining the observed inertness.



Scheme 15

Consideration of the terminal atomic coefficients of the model 1,3-dimethyl-2-pyridone (from CNDO/2 investigations) and of a typical olefin substituted with an electron-withdrawing group, shows that (54) should be the more likely adduct. Figure 2 shows a qualitative representation of these coefficients.

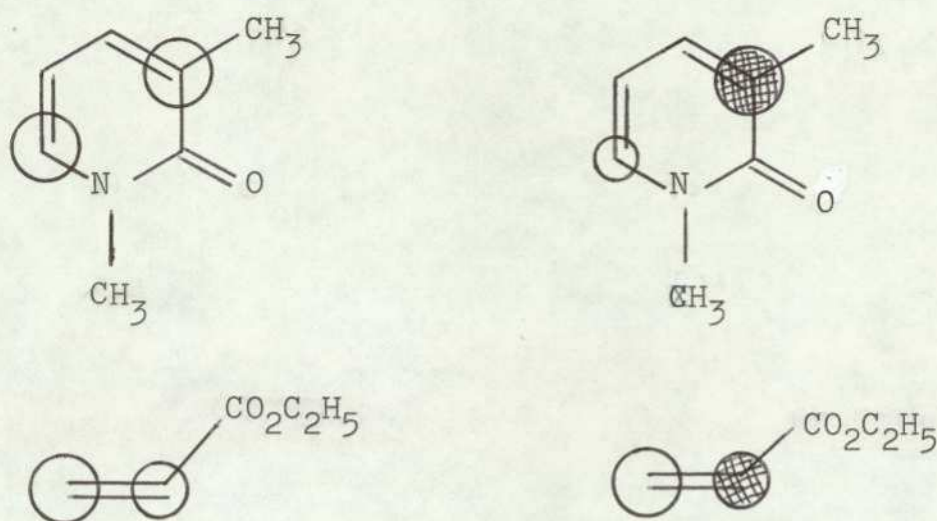
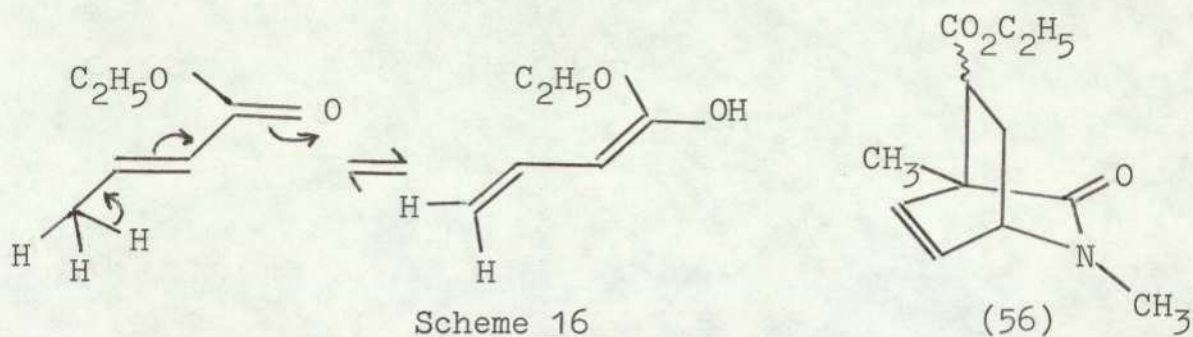


Figure 2

If the cycloaddition were to occur in the inverse sense, then the regioselectivity should be difficult to predict, since the terminal atomic coefficient of both the diene LUMO and the dienophile HOMO are of similar size and phase. Secondary effects should provide the guiding influence in this case.

If however, the pyridone nucleus is treated as a normal demand system, then the HOMO of the pyridone and LUMO of the α,β -unsaturated ester should provide the major interaction. Maintenance of symmetry requirements should lead to adduct (56) in which the bridgehead methyl and electron-withdrawing group are adjacent. This is entirely analogous to the potential formation of (54) from the thermolysis of (52). The effect on the olefin that β -alkyl substitution produces is to diminish the polarisation of the olefin caused by the ester group. This is accomplished through conjugation of the alkyl group with the carbonyl

function via the double bond (Scheme 16).⁴¹ The effect is not considered to be too great, and it is thought that



the largest coefficient of the olefin is still positive and at the β terminal.⁴²

Probably the most deactivating effect due to the alkyl group is the raising in energy of both the olefin HOMO and LUMO. Scheme 2a depicts the frontier molecular orbitals for the normal demand cycloaddition, indicating clearly the major interaction. Substitution of the olefin with electron donating groups will raise both the dienophile HOMO and LUMO, and thus enlarge the difference in energy between the orbitals providing the major interaction. Examination of equation 1 will show that even though the remaining two frontier molecular orbitals have been brought closer together, the overall effect will be a reduction in the perturbation energy. Thus the potential reaction will become more difficult to perform.

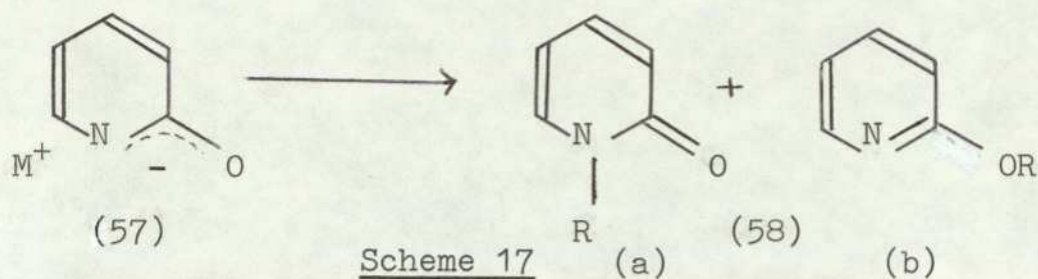
Originally it was hoped that these deactivating effects would not preclude cycloaddition, and that the entropy advantage obtained by attempting the reactions intramolecularly would be of overriding importance. In the light of recent results,^{8,43} it appears that pyridones exhibit normal behaviour tending towards neutral electron demand

requirements during cycloaddition, reacting with only the most electron deficient dienophiles. The inverse demand situation could possibly be generated but this would require a particularly electron-rich olefin to react with a very electron-deficient N-blocked-2-pyridone, a situation totally unprecedented.

Alkylation of 2-pyridones

2-Pyridones have been directly alkylated by three main methods, the most extensively studied being the reaction between a pyridone anion and an alkyl halide. Changes in constituents profoundly affect the course of the reaction unlike the related 2-pyrimidone system where the two ring nitrogens control the π -electron distribution and therefore the polarisability more stringently.⁴⁴ All 2-(1H)-pyridone alkylations give 2-alkoxypyridines and most also give some of the isomeric N-alkylated pyridone (Scheme 17). Since the reaction is subject to kinetic control the ratio of isomers depends upon the reaction conditions, notably the solvent employed, the pyridone cation, and the alkyl halide involved. Because of the lack of specific study on solvent effects etc., generalisations have to be made of the results described in the literature. The solvent effect, it has been suggested, arises from the ion solvation properties of the reaction medium, and this is manifest best in the case of (57, M = Ag).³² In DMF with iodomethane the N-alkylated species (58a, R=CH₃) is the major product, whilst in benzene the pyridine (58b, R=CH₃) is exclusively and quantitatively produced.³² Though not as dramatic, the same

trend is also observed for alkali metal salts, the N-substituted isomer is generally the more predominant species.



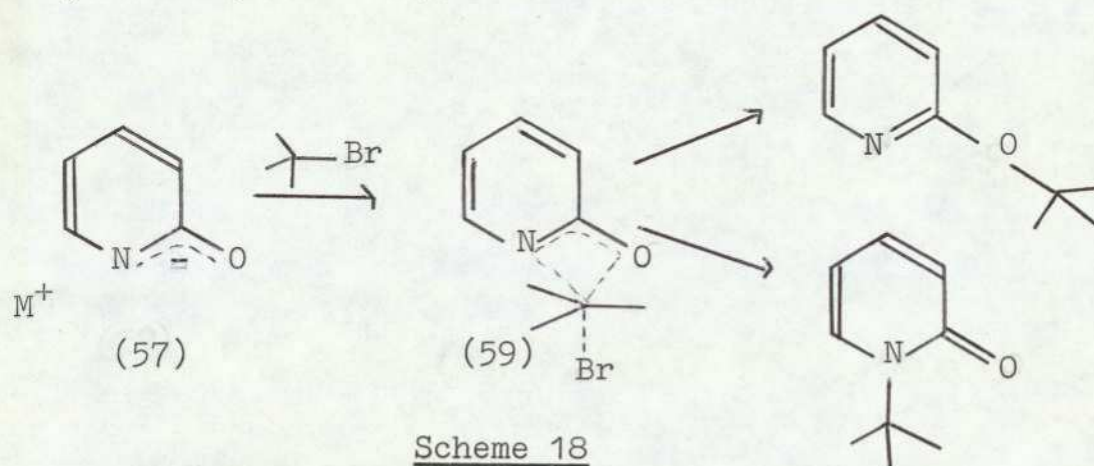
It has been proposed that these alkylations are subject to cation control. Thus, "the sodium salt gives essentially N-alkyl product (2) with n-alkyl halides, whereas silver salts furnish exclusively O-alkylated derivatives (58) in non-polar solvents. The silver ion promotes carbonium character and hence hardens the alkylating agents, thereby favouring attack by the harder oxygen of the ambident anion."⁴⁵ Pyridone substituents also affect the product distribution, especially those in the 3 or 6-position. 1,6-Dimethyl-2-pyridone is obtained in 56% yield when the potassium salt of 6-methyl-2-pyridone is treated with iodomethane in ethanol.⁴⁶ However, the 3-nitro-2-pyridone potassium salt yields 80% of the N-isomer when treated similarly in ethanol/water.⁴⁷

The alkyl halides exert their effect on the product ratios in two ways, firstly depending on the identity of the halogen, and secondly on the degree of substitution of the alkyl group. Subjected to similar reaction conditions primary iodides give better overall yields than the corresponding bromides, and bromides better yields than chlorides.³²

As the degree of branching of the alkyl group increases so does the proportion of O-alkylation in the products, due to steric constraints. This is exemplified by considering

the alkylation in DMF of the sodium salt of 2-pyridone with iodomethane, bromoethane and 2-bromopropane.³² N- to O-isomer ratios of 19, 3.3, and 0.43 are obtained respectively. The same trend is observed for the alkylation of pyridone silver salts, where only 2-pyridone is formed with 2-bromopropane. This is thought to be regenerated by the elimination of hydrogen bromide from the alkyl halide.³² Most pyridone alkylations give moderate yields of regenerated 2-pyridone, especially those involving the silver cation.

It has been suggested that the formation of isomers is caused by small differences in conformation, and energy distribution within a common transition state (59) for the alkylation (Scheme 18).⁴⁸



This view arises from butylation experiments on the sodium salt of 2-pyridone (57, $M = Na$) in DMSO, where the product ratio is independent of pressure over the range of 1-1360 atmospheres. The same is true for the benzylation of the potassium salt (57, $M = K$) in ethanol indicating that the transition states leading to the two isomers have almost identical molar volumes.⁴⁸

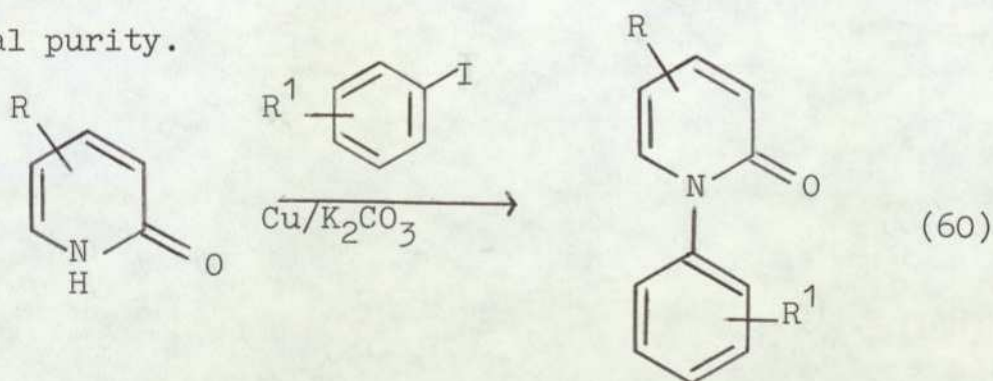
The remaining two methods of direct alkylation are the reactions between the pyridone anion and a dialkyl sulphate,

and between the pyridone and a diazoalkane.

Dimethyl sulphate alkylations give almost equal amounts of both isomers slightly favouring pyridone formation,⁴⁹ except where bulky groups are present at C(6).⁵⁰

Diazoalkanes usually give the products of both N and O alkylation. Diazoethane gives more pyridine than pyridone than does diazomethane, largely owing to steric effects. Another factor suggested is the inclination of diazoethane towards an S_N1 mechanism, rather than that of diazomethane which is thought to be essentially S_N2 .⁵¹

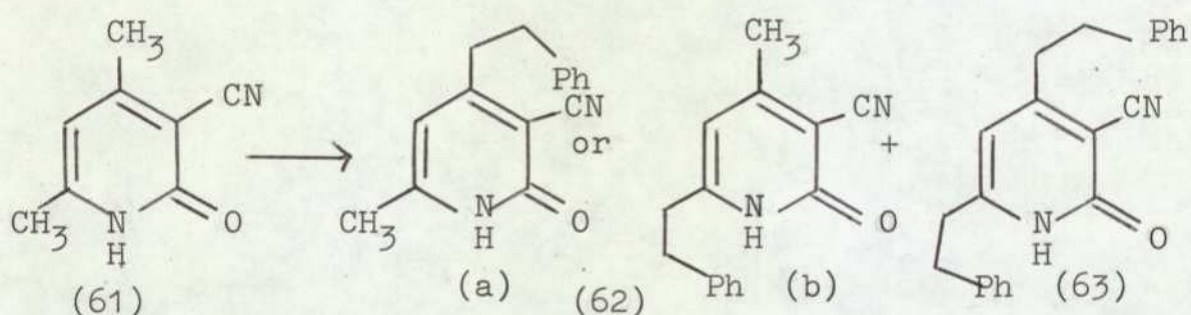
Another method of alkylation involves formation of an O-trimethylsilyl ether which can react with an alkyl iodide, then be desilylated. This gives solely the N-isomer in very good yield, and has found wide application in nucleoside synthesis.⁵² Phase-transfer catalysis methods have been employed, giving mixtures of isomers in reasonable yield.⁵³ Several pyridones have been N-arylated with a mixture of potassium carbonate, an iodobenzene and a catalytic amount of copper (Scheme 19). The copper used needs to be of exceptional purity.



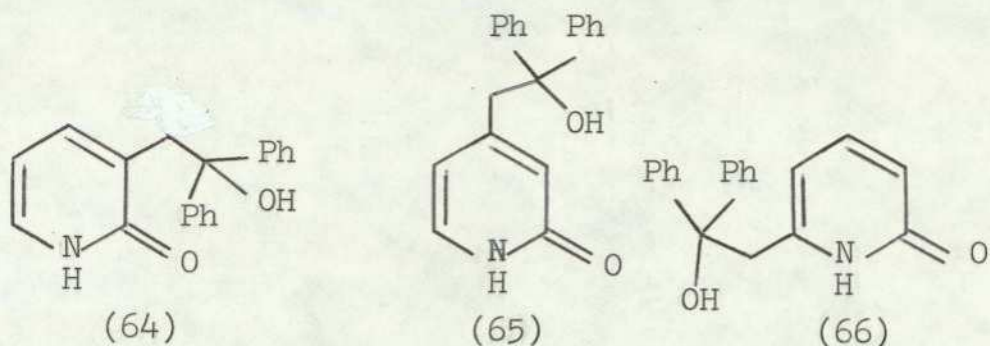
Scheme 19

Compounds of type (60) have been found to possess analgetic, antinflammatory, and anti-pyretic activity. They are also useful in the treatment of dermatitis and of respiratory ailments.^{54,55}

Alkylation of pyridone 3,4- and 6-methyl substituents have also been observed, employing dianions created by potassamide in liquid ammonia.^{56,57} Invariably a C(3) cyano group must be present to stabilise the dianion formed, since by itself potassamide is insufficiently basic. Both 4- and 6-alkyl-3-cyano-2-pyridone dianions have been alkylated, acylated and aroylated in very good yields by this method.^{56,57} 3-Cyano-4,6-dimethyl-2-pyridone (61) has been shown capable of supporting a trianion.⁵⁶ Three equivalents of potassamide followed by an excess of benzyl chloride gave a 35% yield of an unspecified mono-substituted derivative (62(a) or (b)) and 35% of disubstituted product (63). The remainder of the benzyl chloride self-condensed to form stilbene.



Previously the only method to obtain products of methyl alkylation of 6-methyl-2-pyridone involved alkylating 3-cyano-6-methyl-2-pyridone then hydrolysing off the nitrile function.⁵⁷ This clumsy approach has been overcome following the employment of organolithium bases. Using *n*-butyl lithium, 3,4- and 6-monomethyl-2-pyridones have all been alkylated via their respective dianions, conveniently generated in THF or ether.^{30,58} Respective yields of alcoholpyridones (64), (65) and (66), isolated from reactions with benzophenone are 55, 40 and 94%, and these products can be easily dehydrated to vinyl pyridones heated at reflux in 50% sulphuric acid.



This procedure has also been applied to the methyl thiopyridone analogues with success.⁵⁸

Similar results were obtained when 6-methyl-2-pyridone was alkylated via its dianion with certain alkyl halides leading to (31) and (49).

The steric effects reported for the alkylation of 2-pyridone mono-anions cannot be fully appreciated, since only methylations of substituted pyridones have been sporadically and non-systematically reported. No interest seems to have been attached to the nature of the alkyl halide. Also neglected is the effect that a C(3) substituent will exercise during the alkylation. As a result of the alkylations previously reported in this chapter these general trends have been evaluated, and in many cases applied to restrict the production of the unwanted pyridine when using valuable bromides.

That small C(6) substituents do not significantly affect methylations of the sodium salt of 2-pyridones, in DMF, was demonstrated during the preparation of 1,6-dimethyl-2-pyridone, where the corresponding ether was hardly detected in the reaction mixture. The results obtained using substantial alkyl bromides are displayed in Table 1.

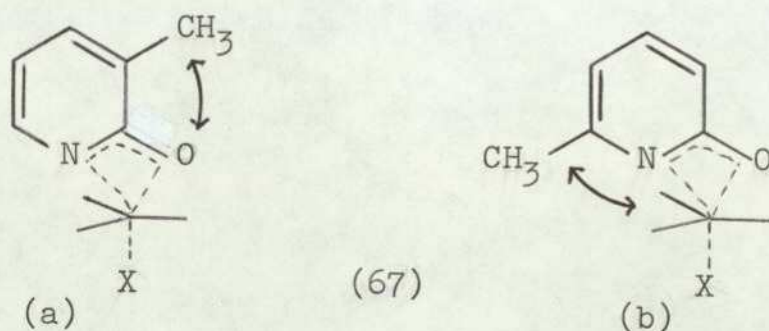
Table 1

2-Pyridone substituent	Bromide	Pyridone	% N-isomer isolated	% O-isomer isolated
-	$\text{CH}_2:\text{CH}(\text{CH}_2)_2\text{CH}_2\text{Br}$	37	39	0
6-methyl	$\text{CH}_2:\text{CH}(\text{CH}_2)_2\text{CH}_2\text{Br}$	38	10	62
6-methyl	$\text{CH}_3(\text{CH}_2)_2\text{CH}_2\text{Br}$	72	13	66
3-methyl-5-nitro	$\text{CH}_2:\text{CH}(\text{CH}_2)_2\text{CH}_2\text{Br}$	43	48	0
3-methyl	$\text{CH}_2:\text{CHCH}_2\text{CH}_2\text{Br}$	42	25	6
3-methyl	$\text{CH}_3\text{C}[\text{O}(\text{CH}_2)_2\text{O}](\text{CH}_2)_3\text{CH}_2\text{Br}$	50	73 ^b	13 ^b
3-methyl	$\text{C}_2\text{H}_5\text{O}_2\text{CH}:\text{C}(\text{CH}_3)(\text{CH}_2)_3\text{CH}_2\text{Br}$	52	74	~8 ^a

(a) Estimated from a mixture of the pyridine and unreacted bromide.

(b) Isolated as keto derivative following treatment of crude reaction mixture with dilute acid in acetone.

The isolated yield of (37) was not high, but was within the ranges reported by Goglimska,^{59,60} and Raczka,⁶¹ for similar alkylations with alkyl halides. The notable feature of this reaction was the virtual absence of the respective ether, it could scarcely be detected by t.l.c. methods, and was not present in isolable quantities. The yield of (43) was also not high but the reaction mixture was again almost totally free from the pyridine. This latter result could be predicted from the directing effect that C(5) electron-withdrawing substituent show in the enhancement of the ratio of pyridone over the pyridine for methylations.⁶² Though the total yield of (42) and its pyridine were low, the results show very well the steric effect produced by a methyl group adjacent to the lactam. Alkylations of (36) consistently gave N to O isomer ratios of about 1 to 6 respectively, in very high overall yield. The situation was reversed for 3-methyl-2-pyridone giving vastly improved yields of the pyridone. Clearly steric in origin, these effects are probably made manifest through interactions within the proposed common intermediate (67) (see arrows).⁴⁸

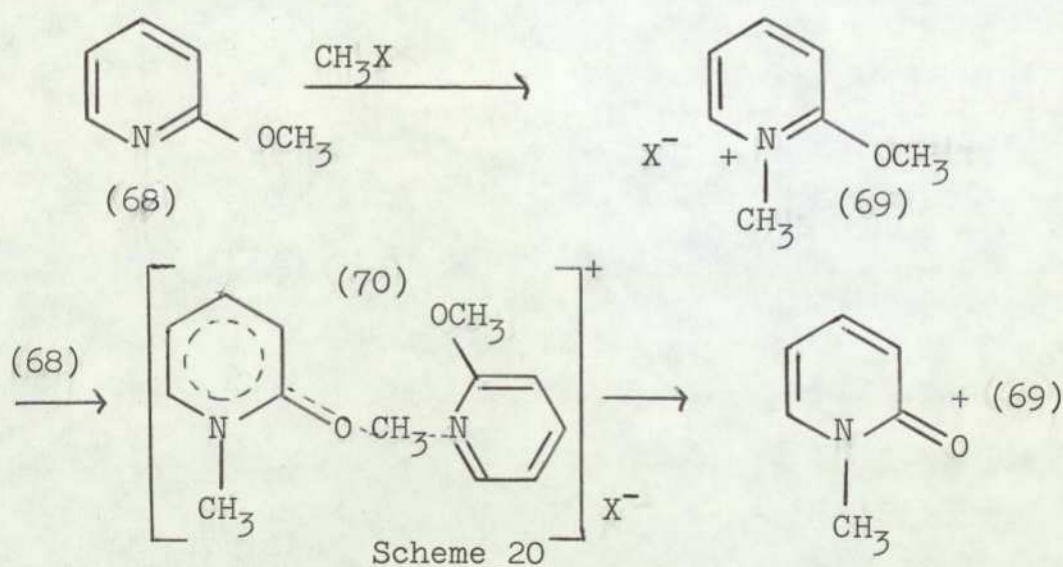


In both (67a) and (67b) the methyl group will try to prevent the total transfer of the alkyl residue to its adjacent heteroatom. In the transition state the non halogen

carbon substituent of the former alkyl halide must adopt a trigonal disposition. Introduction therefore, of a bulky chain into the alkyl halide will intensify the steric repulsions, leading to the product containing the greatest distance between the methyl and alkyl group .

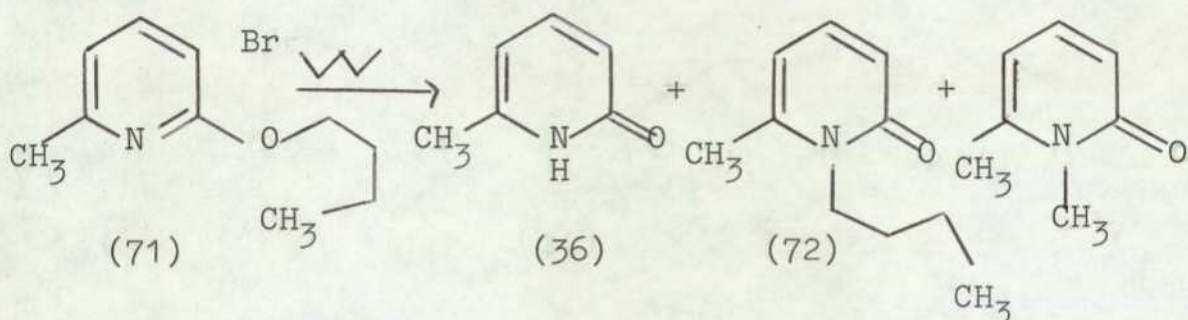
It is not known what effects, if any, will be introduced on the mechanism of alkylation by terminal functionalisation of the alkyl chain of the bromide.

Large yields of unwanted pyridines isolated from the alkylation of 6-methyl-2-pyridone prompted investigation into the viability of oxygen to nitrogen rearrangement. Such processes are known, and have been extensively studied for the conversion of 2-methoxypyridine to 1-methyl-2-pyridone.^{63,64} The rearrangement is catalysed by alkyl halides through a quaternary nitrogen derivative, (69), and is considered to involve an intermolecular ion-pair intermediate (70) (Scheme 20).



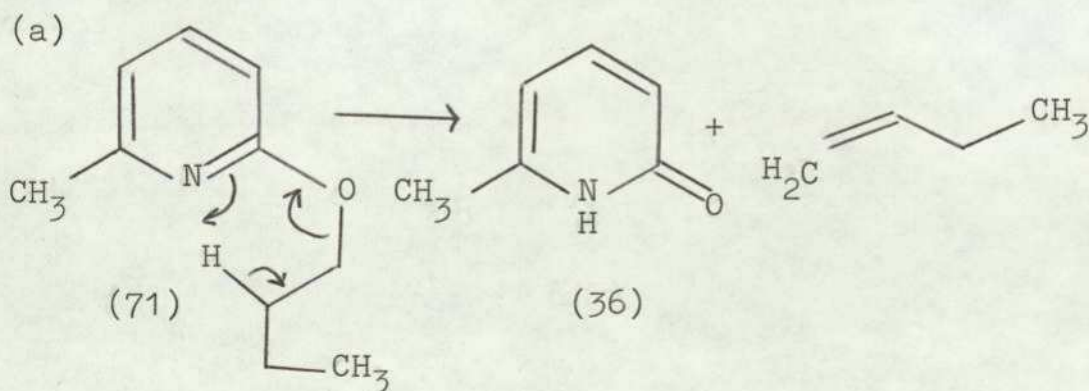
2-n-Butoxy-6-methylpyridine (71) was thermolysed at 140° as a concentrated solution of DMF in a sealed ¹H n.m.r. tube. One drop of n-butyl bromide was added as catalyst,

and the reaction periodically monitored until the absorptions for the pyridine aromatic protons were no longer present. Nineteen days later the reaction was terminated and the products analysed as 6-methyl-2-pyridone (36), (44%); 1-n-butyl-6-methyl-2-pyridone (72), (21%) and 1,6-dimethyl-2-pyridone (19%) (Scheme 21).



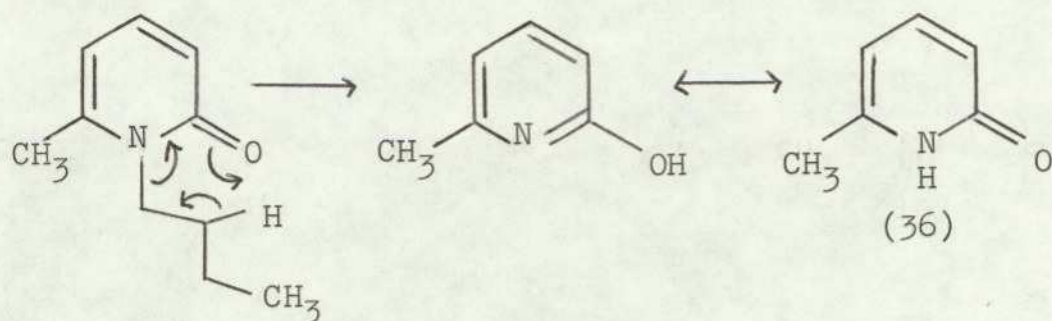
Scheme 21

All of the products were identified by comparison with authentic samples. The very high yield of pyridone (36) suggests that a side-reaction must occur involving the alkyl chain, since other authors have not observed similar rearrangements for methyl ethers. Elimination of but-1-ene from the pyridine ether (71) directly (Scheme 22a) or from (72) once formed (Scheme 22b) must occur to give pyridone (36).

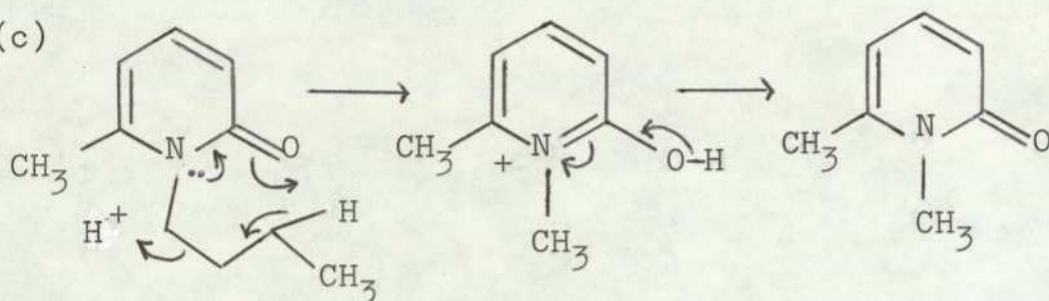


Scheme 22

(b)



(c)



Scheme 22

It seems likely that both processes do occur since the thermolysis of 1-alkenyl-2-pyridones produces minor amounts of the parent pyridone. Also other alkoxy pyridines have given high yields of the parent pyridone. The ample production of (36) from (71), however, suggests that the direct elimination makes the larger contribution, c.f. thermolysis of enamine (47).

The mechanism of formation of 1,6-dimethyl-2-pyridone cannot involve a six-membered transition state and must be derived from (72) - unless propene can be eliminated from the pyridine-ether (71) leaving 6-methyl-2-methoxypyridine to rearrange normally (Scheme 20). A seven-membered transition state, with the reaction promoted by trace acid catalysis seems the most probable mechanism (Scheme 22c). On one occasion 1,6-dimethyl-2-pyridone was isolated from the thermolysis of 6-methyl-2-(pent-4-en-1-oxo)-pyridine in 40% yield.

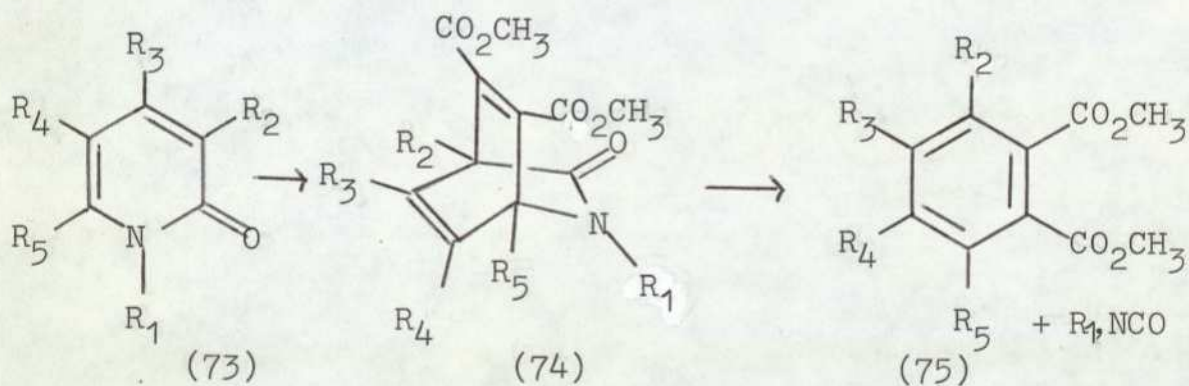
The low yield of the corresponding N-substituted pyridine due to a more favourable irreversible side reaction made the rearrangement non-viable. The bulk of the 6-methyl group may also have had a prohibiting effect on the rearrangement.

CHAPTER 2

Intermolecular cycloadditions of 2-pyridones with dimethyl acetylenedicarboxylate (DMAD)

Previously stated, the major perturbational interaction between 2-pyridones and various dienophiles during cycloaddition, has not been unequivocally established.⁶⁵ Poor yields of adducts from the reaction of 1-methyl-2-pyridone (2) with electron-deficient olefins have caused some investigators to infer that the reaction probably proceeds via an inverse electronic demand mechanism.¹¹

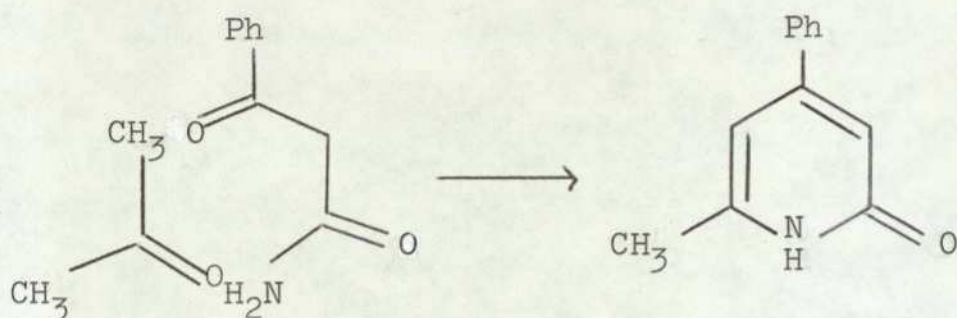
Shortly after our research in this area was initiated,⁶⁸ a claim was published for the isolation of a 31% yield of a primary adduct (74 g), from a mixture of pyridone (73 g) and DMAD when heated under reflux for 72 hours in benzene (Scheme 23).⁸ Heating a solution of (74 g), or a mixture of



Scheme 23

its precursors, in xylene for 10 hours achieved retro-Alder extrusion of methyl isocyanate and dimethyl phthalate (75 g) in high yield. Our interests in intramolecular cycloadditions of 2-pyridones prompted us to undertake a study of possible effects pertinent to reactions of this type.

Pyridones (73a-73d and 73f) (Table 2) were synthesised by alkylating the respective 2-(1H)-pyridone sodium salt by the method of Hopkins et al.,³² while (73e) was formed from 1-methyl-4-phenylpyridinium methosulphate oxidised by alkaline ferricyanide. Pyridone (73; $R_1 = R_2 = R_4 = H$, $R_3 = Ph$, $R_5 = CH_3$) was prepared by polyphosphoric acid dehydration of acetone and benzoylacetamide (Scheme 24).⁶⁷



Scheme 24

All thermolyses were performed for 72 hours at 80° on a 1.6 M solution of the pyridone in acetonitrile. The reactions were monitored, and the percentage conversion of (73) to (74) estimated, by comparing the ¹H n.m.r. integrals for the N-methyl signals of the starting material and product in the reaction mixture. The results are summarised in Table 2. Kinetic parameters for all of the various reactions were not determined. A trial run with pyridone (73a) showed however, that approximate second order kinetics were being followed. In the following discussion the estimated rates of reaction were equated with the degree of reaction after standard times. Accurate kinetic studies were precluded by the tendency of the products to undergo further reactions to the phthalates after prolonged reaction times.

- (a) $R_1 = R_5 = \text{CH}_3$, $R_2 = R_3 = R_4 = \text{H}$;
 (b) $R_2 = \text{CH}_3$, $R_3 = R_4 = R_5 = \text{H}$, $R_1 = (\text{CH}_2)_4\text{COCH}_3$;
 (c) $R_1 = R_4 = R_5 = \text{CH}_3$, $R_2 = R_3 = \text{H}$;
 (d) $R_1 = \text{CH}_3$, $R_2 = R_3 = R_4 = \text{H}$, $R_5 = \text{OCH}_3$;
 (e) $R_1 = \text{CH}_3$, $R_2 = R_4 = R_5 = \text{H}$, $R_3 = \text{Ph}$;
 (f) $R_1 = R_5 = \text{CH}_3$, $R_2 = R_4 = \text{H}$, $R_3 = \text{Ph}$;
 (g) $R_1 = R_3 = R_5 = \text{CH}_3$, $R_2 = R_4 = \text{H}$;
 (h) $R_1 = \text{OCH}_3$, $R_2 = R_4 = \text{H}$, $R_3 = R_5 = \text{CH}_3$

Pyridone	m.p.(°C)	% reaction	Product	Isolated Yield
73a	56	22	74a	(20) ^a
73b	-	0	-	0
73c	83-5	75	74c	(70) ^a
73d	53	0	-	(0) ^a
73e	140	0	-	(0) ^a
73f	106	73	74f	70
73g	86	b	74g	(31) ^c

(a) due to S.E. Royall

(b) not estimated by Heep⁸

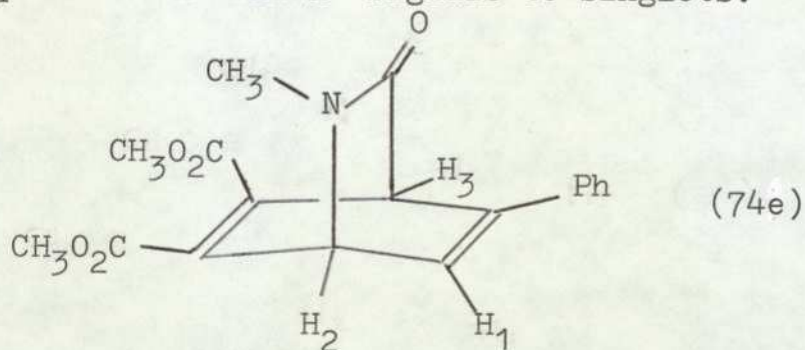
(c) corrected yield⁸

Table 2

Formation of the 2-aza-3-oxobicyclo[2.2.2]-octa-5,7-diene (74h) required prolonged reflux times for reaction to occur (170 h at 80° gave 8% of the primary adduct). All pyridones (73a - 73g), when heated with DMAD under more forcing conditions (140° for 14 h) gave the respective dimethyl phthalates (75a - 75g). Yields of 50% of the phthalates were obtained by this method since the dienophile DMAD readily polymerised at elevated temperatures. However, addition of more DMAD, after successive thermolyses, until the

pyridone had been totally consumed (t.l.c. analysis), gave yields of over 90% for retroproducts (75a - 75g). When pyridone (73; $R_2 = \text{CH}_3$, $R_3 = R_4 = R_5 = \text{H}$, $R_1 = (\text{CH}_2)_4\text{C}(\text{CH}_3):\text{CHCO}_2\text{C}_2\text{H}_5$) was thermolysed under the same conditions as (73b) identical behaviour was observed. No primary adduct could be observed under any circumstances, but high yields of 3-methyl-dimethylphthalate (75b) were isolated following the exhaustive cycloaddition technique described. The trimerised isocyanate residues from the retro-Diels-Alder step were not pursued.⁸ Thermolysis of pyridones (73a - 73g) as neat mixtures with DMAD, rather than in acetonitrile solution, gave much higher yields of the bicycloadducts (74a - 74g).

The ^1H n.m.r. spectrum of primary adduct (74e) contains a three-proton singlet at $\delta 2.99$ (N-CH_3), and a six-proton singlet at $\delta 3.90$ ($2 \times \text{-OCH}_3$), the phenyl group absorbs as a multiplet, $\delta 7.32\text{--}7.61$. Bridgehead proton H^2 couples to H^1 , giving a doublet $\delta 5.30$ (J 6 Hz), while H^3 , allylically coupled to H^1 absorbs at $\delta 5.20$ (J 2 Hz). Double irradiation of the doublet of doublets arising from H^1 , $\delta 6.98$ (J 6.2 Hz), collapses the H^2 and H^3 signals to singlets.

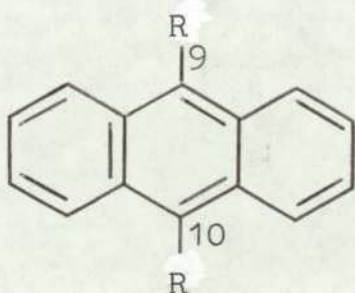


The i.r. spectrum contains peaks for the ester, amide and an olefin at 1720 , 1685 and 1647 cm^{-1} respectively. The phthalides (75b) and (75e) were identified by spectral means.^{68,69}

It is clear from the ease with which some of the pyridone substrates interact with DMAD that steric factors

play a major role in reactivities. If purely electronic effects are considered, then pyridone (73d) should react much faster than (73a), assuming it a classical demand system. However, (73d) is quite inert under the thermolysis conditions employed. The enhancement shown in the rate of cycloaddition of (73c) over (73d) is directly attributable to the steric interaction experienced between the vicinal dimethyl substituent of (73a). Both groups are inclined to move out of plane, away from each other and cycloaddition aids this exigence; the activation energy for the addition is thus lowered. A methoxyl group is smaller and far more flexible than a methyl group, and the small deformation imposed in (73d) by vicinal disubstitution is easily accommodated. The sweeping action of the 6-methoxyl will also reduce the number of fruitful approaches of the dienophile to the pyridone. The absence of such steric effects in pyridone (73h) explains why it is also relatively inert.

Similar differences in the rates of reaction have been observed for anthracenes substituted with methyl or methoxyl groups at the reaction terminii, i.e. positions 9 and 10. Compared to anthracene (76), (77) reacts with maleic anhydride 218 times faster, whereas compound (78) actually reacts slower than (76).⁷⁰



(76) R = H

(77) R = CH₃

(78) R = OCH₃

It has been suggested that this is a result - at least in part - of the steric relief achieved through passage of

the planar sp^2 anthracene to the sp^3 adduct (see review section).⁷⁰

The enhancement of Diels-Alder reactivity observed for pyridone (73c) is considerable and arises purely from steric control. The 6-methyl group is wedged between the 1- and 5-methyl substituents forming a very strained structure that even appears to react with atmospheric oxygen, thus, exposure of the pyridone (73c) to air causes rapid darkening, giving a solid with an indefinite melting point.

A further interesting effect, which also demonstrates the importance of steric factors, is revealed by comparison of the two 4-phenyl-N-blocked pyridones (73e) and (73f). A conjugating phenyl group will lower the LUMO and raise the HOMO energy levels of a potential diene,²⁵ therefore both classical and inverse demand systems will be assisted during cycloadditions. The phenyl group alone, however, is not sufficient to completely compensate for the required energy of activation and so pyridone (73e) is relatively unreactive. The introduction of a 6-methyl substituent, however, has an enormous ameliorating effect on the rate of reaction of pyridone (73f).

The relative sluggishness of all 2-pyridone cycloadditions encountered in our work, and as reported in the literature for systems not containing 6-methyl substituents suggests that this system is not behaving as a classical diene. Molecular orbital calculations (CNDO/2 and ab initio Gaussian 70) have suggested that 2-pyridones more closely approach the neutral demand situation. Thus neither of the two HOMO - LUMO interactions, between the diene and dienophile, is dominant over the other. Substi-

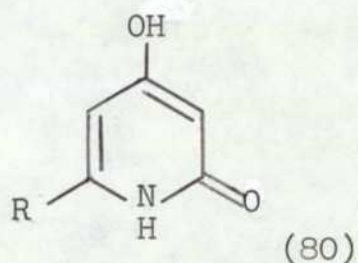
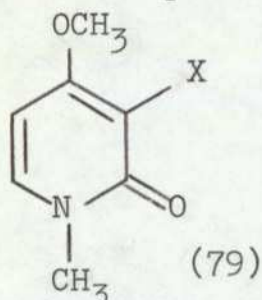
tuent effects will therefore play a major role in facilitating these reactions. Many examples of 2-pyridone cycloadditions approximating to the classical model are known, although none have been observed exhibiting the requirements of an inverse electron demand system. All of the former reactions have been observed to proceed in low yields, even with the most electron deficient dienophiles. A systematic study of reactions between 2-pyridones substituted with highly electron-withdrawing groups, and electron-rich olefins (enol ethers, ketene acetals and enamines) may prove highly illuminating.

CHAPTER 3

Preparation and Reactions of 4-hydroxy-2-pyridones.

Preparations

The synthesis of 4-hydroxy-2-pyridones has received much attention since the identification of ricinine as 3-cyano-4-methoxy-1-methyl-2-pyridone (79, X = CN).⁷¹ Certain 4-hydroxy-2-pyridones have shown cytotoxic activity in vitro and anti-tumour activity in vivo.⁷² For many also, the structural parameters of the π -electron distribution



within the molecules have been calculated and analysed with respect to the sedative and hypnotic activity exhibited by the compounds.⁷³ Formylation of (79, X = H) giving (79, X = CHO) in Vilsmeier fashion forms part of a synthesis of dl-camptothecine and of the total synthesis of ricinine (79, R = CN).⁷⁴

Our interest in 4-hydroxy-2-pyridones was twofold. Firstly, we saw in them an opportunity to synthesise the previously unavailable 4-cyano-2-pyridone, by converting the 4-hydroxyl function to a suitable leaving group. It was then hoped that nucleophilic substitution could be effected by inorganic cyanide ion. Secondly, we wished to investigate the possibility of alkylation of the 4-hydroxy-2-pyridone system with simple alkyl halides, such as pentenyl bromide.

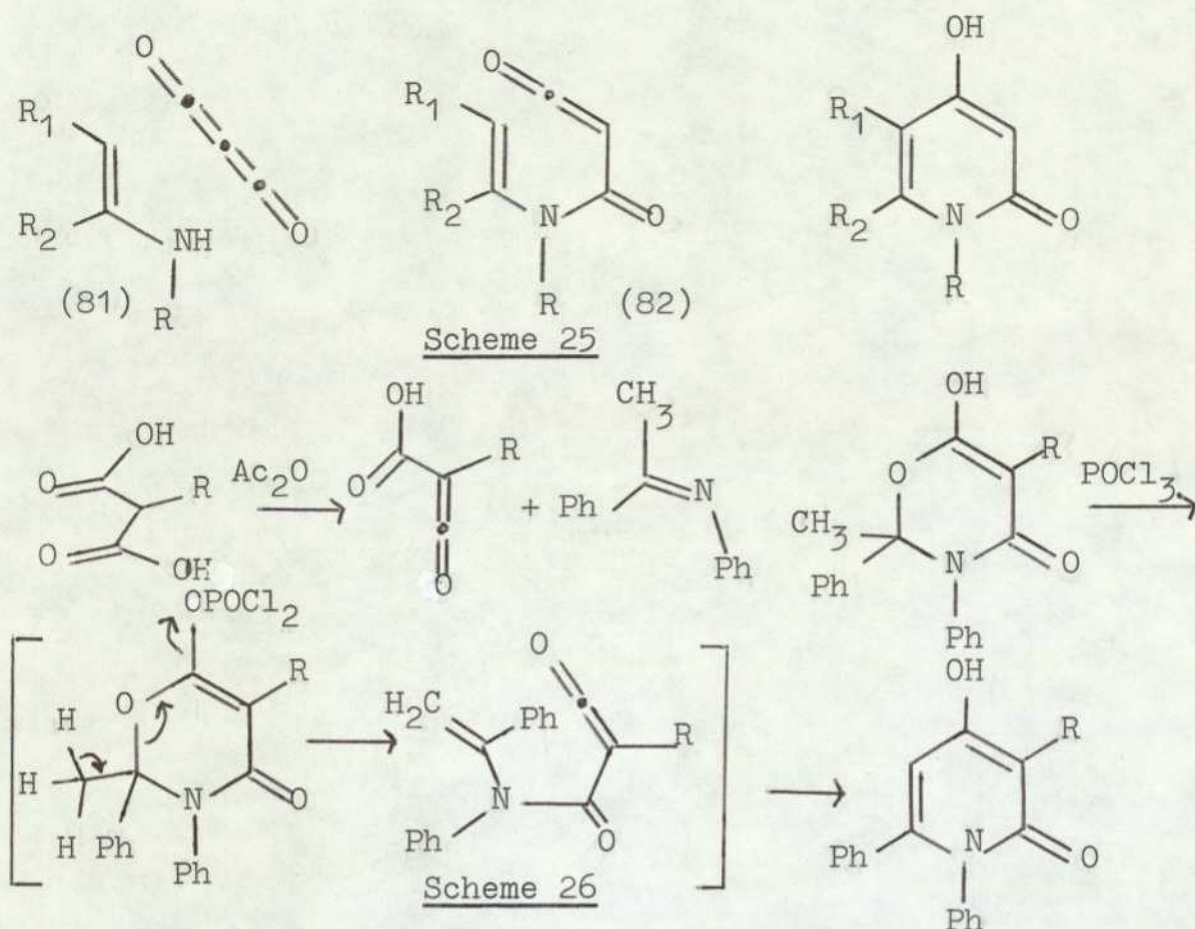
This would yield a substrate potentially able to undergo intramolecular cycloaddition.

The first synthetic route to the parent compound (80, R = H) was due to Errera, who condensed diethyl-1,3-acetonedicarboxylate and ethyl orthoformate in ammonium hydroxide solution.⁷⁵ An acid-catalysed hydrolysis and decarboxylation of the 5-carboethoxy derivative, gave 4-hydroxy-2-pyridone (80; R = H) in low overall yield. Many investigators have used this method, but recently a more efficient route has been developed.⁷⁶ Rearrangement of 4-benzyloxypyridine-N-oxide in acetic anhydride gives the corresponding 4-benzyloxy-2-pyridone which can be catalytically hydrogenated to (80; R = H).

A popular route to derivatives of (80) is the ammonolysis of the appropriate 4-hydroxy-2-pyranone or thio-pyranone,⁷⁷ i.e. via the penultimate step of Errera's method.⁷⁵ Either methylamine or ammonia can be used to generate the N-blocked or unblocked hydroxypyridones in very good yield.⁷⁸⁻⁸³

By far the most favoured synthetic approach however, is the condensation of various three carbon synthons, efficiently producing in 'one-pot' reactions hydroxypyridones bearing a variety of substitution patterns. These include addition of β -ketoenamines (81) to carbon suboxide (Scheme 25), via the very reactive ketene-enamide intermediate (82).^{84,85} Yields are very good for (81; R₁ = CO₂C₂H₅ or COCH₃, R₂R₃ = alkyl or aryl). Ziegler - the major protagonist of this process - has also successfully used ethoxycarbonyl ethyl ketene with enamine (81).⁸⁶ Several carboxyl alkyl ketenes, obtained by the in situ

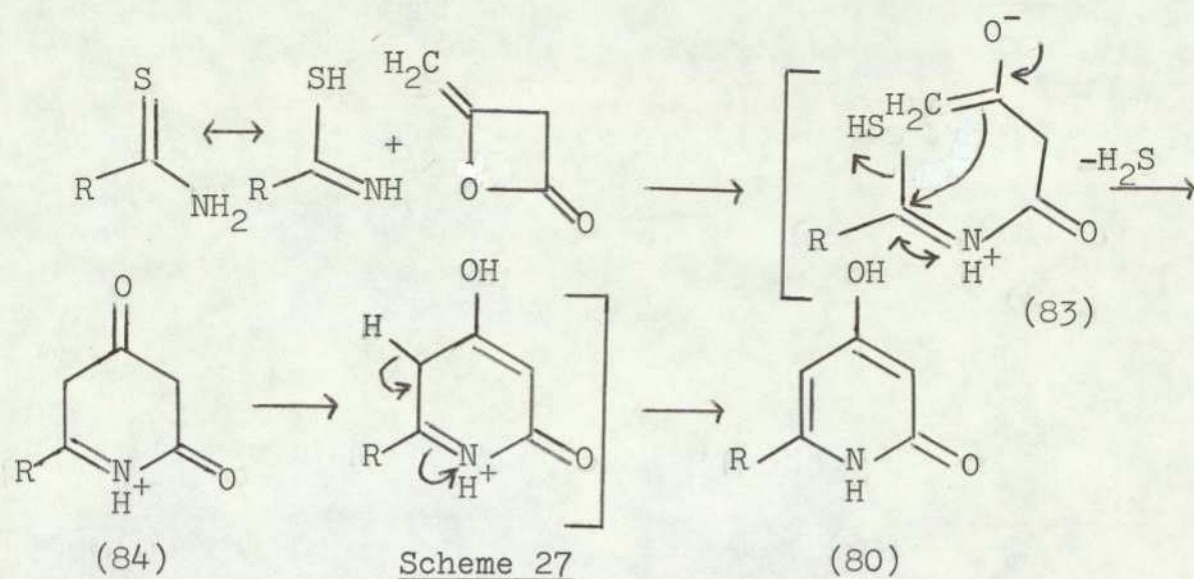
acetic anhydride dehydration of substituted malonic acids, have been reacted with various anils (Scheme 26).⁸



Other condensations have been performed extensively between malonyl chloride and enamines (81),⁸⁸ cyclic anils,⁸⁹ alkyl nitriles,⁹⁰ and O-alkylated oximes.⁹¹

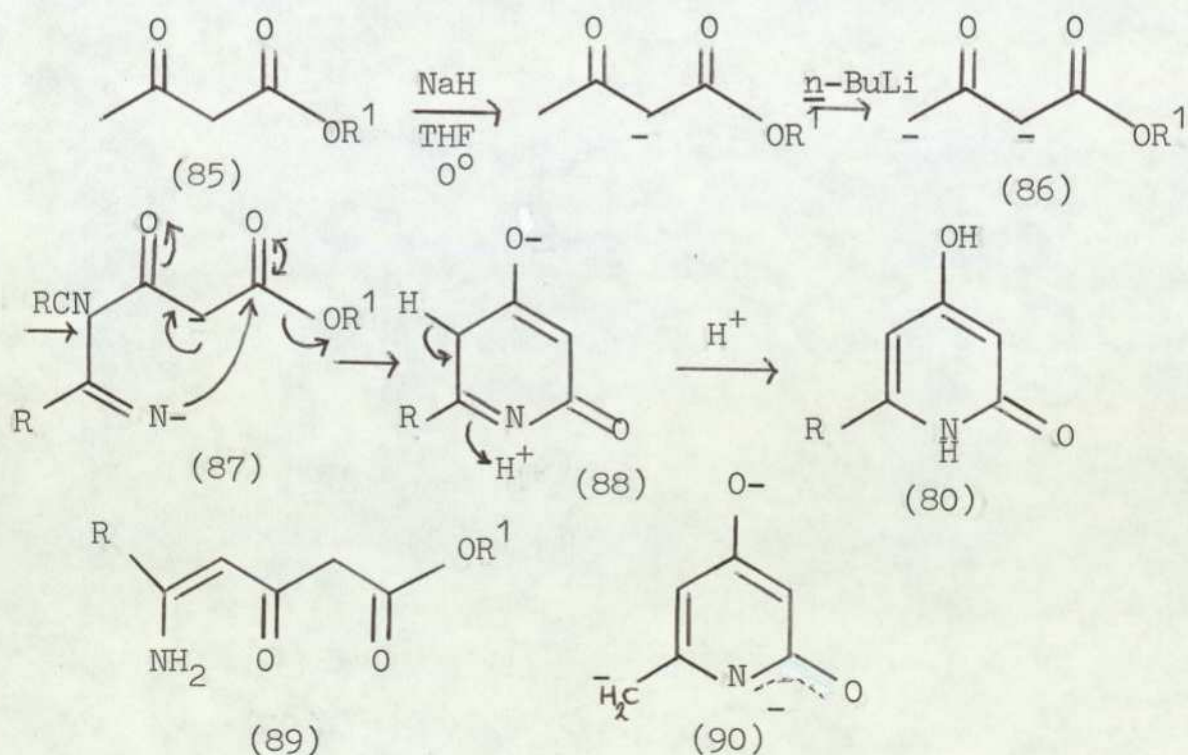
Substituted malonic acids and esters with enamines (81) also react together in high yield,^{92,93} the sodium salt of diethylacetonedicarboxylate is reported to react with phenyl isocyanate yielding 4,6-dihydroxy-1-phenyl-2-pyridone.⁹⁴ Phenyl isothiocyanate gives the analogous 1-phenyl (80; $\text{R} = \text{SH}$).⁹⁴

An interesting condensation is that undergone by several thioamides with diketene (Scheme 27).⁹⁵ Tautomerisation to the imine of the thioamide, followed by attack at the diketene, inducing ring opening, gives the unstable



intermediate (83). Ring closure, then loss of hydrogen sulphide affords (84) which isomerises to (80, R = alkyl, aryl). Yields by this route are only reasonable for R = CH_3 , and are very dependent upon the solvent selected.

Weiler, in an investigation on the acylating properties of β -keto-ester dianions,⁹⁶ recorded a synthesis of 6-phenyl-4-hydroxy-2-pyridone.⁹⁷ The dilithium salt of methyl acetoacetate (86; $R^1 = CH_3$) was prepared by successive additions of one molar equivalent of sodium hydride,



then one of n-butyl lithium to (85, $R^1 = CH_3$) in THF. Two stages for dianion formation were required, since sole use of the organolithium reagent results in reaction at the ester group under the conditions employed. Addition of benzonitrile to (86; $R^1 = CH_3$) followed by acidification gave pyridone (80; $R = Ph$) as a deposit (29%). Analysis of the remaining reaction mixture yielded over 50% of enamine (89; $R = Ph$, $R^1 = CH_3$) which on distillation cyclised to give (80, $R = Ph$) quantitatively. Use of acetonitrile with (86) gave a 66% yield of (89; $R^1 = R = CH_3$) only, this enamine being stable to heat. None of the corresponding pyridone (80; $R = CH_3$) was observed. It was decided to investigate this reaction as a possible preparative route to 4-hydroxy-2-pyridones. The results obtained are displayed in Table 3. It is evident that the large variety of nitriles utilised is mirrored by the wide range in yields of (80) isolated.

Interest was centered on the adduct with acetonitrile since (80a) would give potentially, an extra site for alkylation. Three molar equivalents of n-butyl lithium should create the trianion (90), and reaction with electrophiles should occur at the most reactive point, the 6-methylene anion. Trianions of this type have been observed for 3-cyano-4,6-dimethyl-2-pyridone as giving a reasonable yield of one monoalkylated and the dialkylated derivative.⁵⁶ The absence of the 4-methyl in (80a) should therefore give exclusive 6-methyl alkylation. No reports exist for dianion or trianion formation from 4-hydroxy-2-pyridones.

Quenching of the yellow-orange dianion (86; $R^1 = C_2H_5$) with acetonitrile gave a fluorescent yellow solution

(80)	Nitrile	Yield %	m.p. °C
a	CH_3CN	5-8	312-6
b	$\underline{n}\text{-C}_3\text{H}_7\text{CN}$	7	278-83
c	$\underline{i}\text{-C}_3\text{H}_7\text{CN}$	7	280-4
d	$(\text{CH}_2)_2\text{CHCN}$	40	292-4
e	$(\text{CH}_3)_3\text{CCN}$	0	-
f	$\text{C}_6\text{H}_5\text{CH}_2\text{CN}$	0	-
g	$\text{C}_6\text{H}_5\text{CN}$	30	310-4
h	$\underline{p}\text{-CH}_3\text{C}_6\text{H}_4\text{CN}$	8	280-5
i	$\underline{o}\text{-CH}_3\text{C}_6\text{H}_4\text{CN}$	2	299-303
j	$\underline{p}\text{-ClC}_6\text{H}_4\text{CN}$	30	320-2
h	$\underline{p}\text{-CNC}_6\text{H}_4\text{CN}$	72 ^a	379-82
l	$\underline{p}\text{-CH}_3\text{OC}_6\text{H}_4\text{CN}$	7	258-76
m	$\underline{p}\text{-FC}_6\text{H}_4\text{CN}$	36	345-9
n	$\underline{p}\text{-NO}_2\text{C}_6\text{H}_4\text{CN}$	0	-
p	$\underline{o}\text{-cyanopyridine}$	32	232
q	$\underline{m}\text{-cyanopyridine}$	0	-
r	$\underline{p}\text{-cyanopyridine}$	72	233-5
s	phenyl isocyanate	0	-

(80)	Nitrile	Yield %	m.p. °C
s	phenyl isocyanate	0	-
t	phenyl isothiocyanate	25	b
u	methyl isocyanate	0	-
v	crotononitrile	0	-
w	ethyl cyanoacetate	0	-
x	trichloro acetonitrile	0	-

(a) based on the nitrile

(b) chars above 100°

Table 3

instantaneously. Left overnight, then hydrolysed, and neutralised (80a) was isolated in 5-8% yield. This is contrary to the observations of Weiler, who unable to isolate any pyridone reported sole formation of (89; $R^1 = R = CH_3$). Analysis of the products in our organic phase, in the manner described by Weiler,⁹⁷ indicated that only ethyl acetoacetate was present, giving approximately 85% recovery of material. This is clearly a result of the competition between the cyano group and its adjacent α -protons for the dianion.

The monoanion of acetonitrile is highly resonance stabilised (Scheme 28) and so its formation is a reasonably facile process. This view is reflected in the low yields observed for all of the nitriles containing α -protons. The situation is taken one stage further with phenyl acetonitrile

since not only the nitrile, but also the phenyl group can stabilise the α -anion. No adduct is observed for this electrophile, recovery of the ethyl acetoacetate was almost quantitative. The obvious exception to the above generalisation is provided by the isolation of 6-cyclopropyl-4-hydroxy-2-pyridone (80d) in 40% yield, owing to the inability of the cyclopropyl group to accommodate the required planar disposition of ~~resonance form~~ form (a) , thus not allowing the nitrile to exert its stabilising influence. Proton abstraction loses its appeal and the nucleophilic attack on the cyano function becomes dominant. Large amounts of ethyl acetoacetate were again recovered (48%), no indication whatsoever was found for the formation of (89; $R^1 = C_2H_5$, $R = (CH_2)_2CH$).

Quenched with benzonitrile a solution of dianion (86; $R^1 = C_2H_5$) immediately turned deep-red. Stirred overnight, then worked up, a 30% yield of (80 g) was observed. This yield was not significantly improved when the reaction mixture was stirred for extended periods either before or after addition of the nitrile. Again, the entire procedure was identical to that described by Weiler, yet no enamine (89; $R^1 = C_2H_5$, $R = Ph$) whatsoever was observed. The 1H n.m.r. spectrum of the organic phase, freed from ether, showed none of the peaks predicted for (89; $R^1 = C_2H_5$, $R = Ph$).

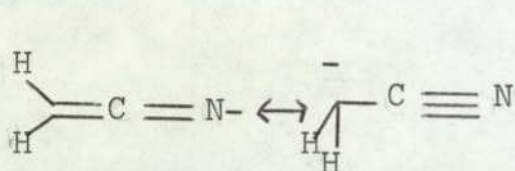
It appears that the sole difference between the two methods was our use of ethyl acetoacetate rather than the methyl ester. It is very hard to believe that so small a difference could have such a marked controlling effect on the course of the reaction; although the experiment was not

repeated using methyl acetoacetate.

The formation of 6-aryl-4-hydroxy-2-pyridones is highly susceptible to electronic influences. Thus pyridone (80r) is obtained in 72% yield. The ring nitrogen makes the nitrile carbon more electron-deficient than the cyano carbon of benzonitrile. The effect is inductive and is similarly manifest by 2-cyanopyridine which leads to (80p) in 32% yield. The case of the meta isomer (80q) is totally different since the ring nitrogen does not similarly assist the nitrile group. It is not understood why none of the pyridone (80q) is formed.

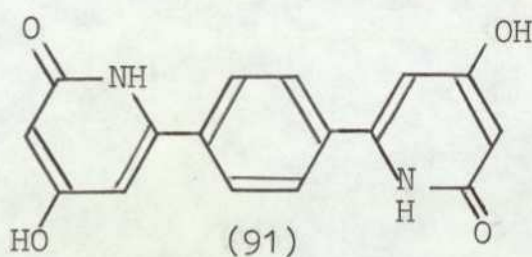
Low yields are also obtained from the o- and p-toluanitriles since the cyano function and the relatively acidic tolyl methyls are both in competition for the dianion (86; $R^1 = C_2H_5$).

In an attempt to prepare phenylene (6,6'-bi-2-pyridonyl)-4,4'-diol (91) from p-dicyanobenzene and (86; $R = C_2H_5$), 6-(p-cyanophenyl)-4-hydroxy-2-pyridone (80k) was isolated, instead, in 72% yield. The peak at 2210 cm^{-1}



(a) Scheme 28

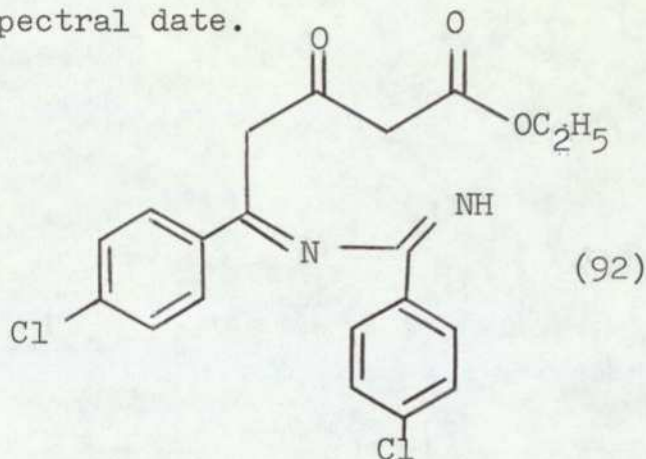
(b)



in the i.r. spectrum confirmed that the nitrile had not been hydrolysed under the conditions of work up. The intermediate imine anion (87; $R^1 = C_2H_5$, $R = p-CNC_6H_4$) must have destabilised the remaining nitrile, after the first had been consumed, even though only one half of a molecular equivalent of the dinitrile had been added.

p-Methoxybenzonitrile predictably gives a very low yield of (80l) while p-chloro and p-fluorobenzonitriles give reasonable yields of (80j) and (80m) respectively, due to the inductive effects of the halogen on the nitrile. The adduct (80m) exhibits fluorine-proton coupling in the ^1H n.m.r. spectrum of J_{HmF} 9 Hz and J_{HoF} 6 Hz.

A detailed analysis of the organic phase obtained in the preparation of (80j) revealed the hydrochloride, of a species m.p. $54-5^\circ$, containing one molecule of ethyl acetoacetate to two of the p-chlorobenzonitrile. The structure was assigned as (92) on the basis of analytical and spectral data.



The derivative (92) was probably formed by attack of intermediate (87; $\text{R}^1 = \text{C}_2\text{H}_5$, $\text{R} = \text{p-ClC}_6\text{H}_4$) on another molecule of the nitrile, and was isolated as the hydrochloride during an acid wash of the organic phase at a yield of 19%. The ^1H n.m.r. spectrum of (92) in $\text{CF}_3\text{CO}_2\text{H}$ shows a four-proton singlet δ 7.30, and an AB quartet,

δ 7.28 and δ 7.54 integrating as two protons each. Two, two-proton singlets exist at δ 3.40 and δ 3.57, no evidence exists for tautomerism to the corresponding enamine. The i.r. spectrum contains two carbonyl absorptions at 1752 and 1729 cm^{-1} , and a broad band at 2680 cm^{-1} , typical for

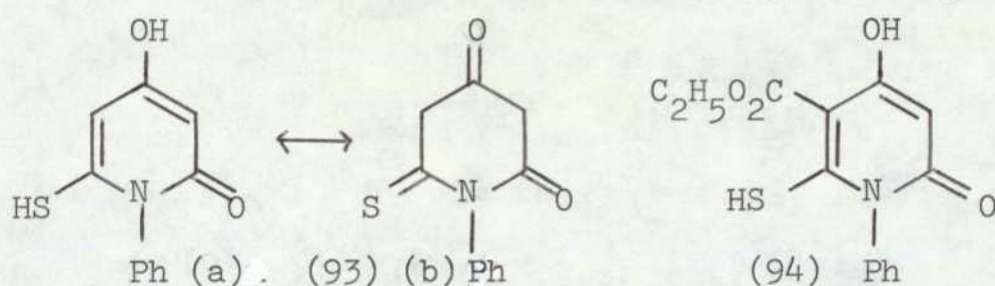
iminium protons (lit. 2700-2250 cm^{-1}).⁹⁸ The peak at 1625 cm^{-1} is probably the protonated imine (lit. 1660-1600 cm^{-1}).⁹⁸

Liberation of the base gave a waxy solid, the ^1H n.m.r. spectrum of which is essentially the same as that of the salt upfield of $\delta 6.00$. The aromatic region was more complex, with only one limb of one of the possible AB quartets being discernable. Between $\delta 9.00$ -10.02 is a broad, one-proton singlet, exchangeable with deuterium and assigned as the imine hydrogen atom.

Why this adduct was formed in this instance is not certain. When it was ascertained that enamines (89) were not forming at all in the earlier experiments it was deemed unnecessary to investigate the organic extract from every alkylation. Of the six that were examined in a more detailed fashion, i.e. those leading to pyridones 80 [(a,c, e,g,h,j)]; only p-chlorobenzonitrile gave the required product. The attempted preparation of (80c) was selected for this trial because it demonstrates the steric control that these alkylations are subject to. None of the pyridone could be isolated even after the mixture of (86; $\text{R}^1 = \text{C}_2\text{H}_5$) and trimethylacetone nitrile was stirred for 48 hr. It appears that the steric imposition of the tert-butyl group must prevent the reactive approach of the dianion to the nitrile, since 90% of the ethyl acetoacetate was recovered.

p-Nitrobenzonitrile was far too reactive because its addition to dianion (86; $\text{R}^1 = \text{C}_2\text{H}_5$) resulted in the immediate deposition of heavy oils and the reaction mixture turned black. T.l.c. analysis of the neutralised reaction

mixture showed nothing but polymeric material. The same result was obtained for trichloroacetonitrile, and methyl thiocyanate, the latter evolving hydrogen sulphide during the reaction. No isolable products were observed for crotononitrile, ethyl cyanoacetate and phenyl isocyanate. Phenyl isothiocyanate however, gave a light red solid in 25% yield which proved to be 1-phenyl-4-hydroxy-6-mercapto-2-pyridone (93a, 80t). General insolubility in a variety of solvents proved a problem in the characterisation of (93a), as with all 4-hydroxy-2-pyridones,



owing to the extensive hydrogen bonding between the N-H, O-H and, in the case of (93a), S-H groups. In DMSO however, the ¹H n.m.r. spectrum of the latter compound contains a doublet (J 2 Hz) at δ5.63 corresponding to C(3)-H and a broadened singlet at δ6.16 typical for the C(5)-H. The C(3) proton for all 4-hydroxy-2-pyridones is exchangeable with deuterium, especially in the presence of a drop of base. For (93), both signals diminish, particularly on heating in DMSO with D₂O, to leave only the aryl absorption. The disappearance of both ring protons seems consistent with the formation of the 6-thioketo-2,4-diketopiperidine tautomer (93b) which would permit the exchange of all the non-aromatic protons in the molecule. The only reported example of a similar structure is the 5-carboethoxy-derivative of (93a),⁹⁴ (94), and like (93a), this derivative eliminated H₂S on heating. The parent

(93a) also loses H_2S slowly in DMSO, this process being observed during the ^1H n.m.r. study. The final product remained unidentified.

The i.r. spectrum showed a broad hydrogen bond absorption present at $3310\text{--}2110\text{ cm}^{-1}$, the keto region containing two peaks at 1619 and 1598 cm^{-1} . Remaining peaks exist at 1233 , 822 , 763 and 694 cm^{-1} . The i.r. spectrum of the analogue (94) of Ziegler is reported to contain the pyridone absorption at 1600 cm^{-1} .

U.V. analysis shows a slight bathochromic shift for the usual phenyl-pyridone band ($305\text{--}15\text{ nm}$) to 327 nm , while mass spectrometry gives a correct accurate mass measurement, and records the extrusion of CO, CS and -SH.

Alkylation of 4-hydroxy-2-pyridones.

Introduction

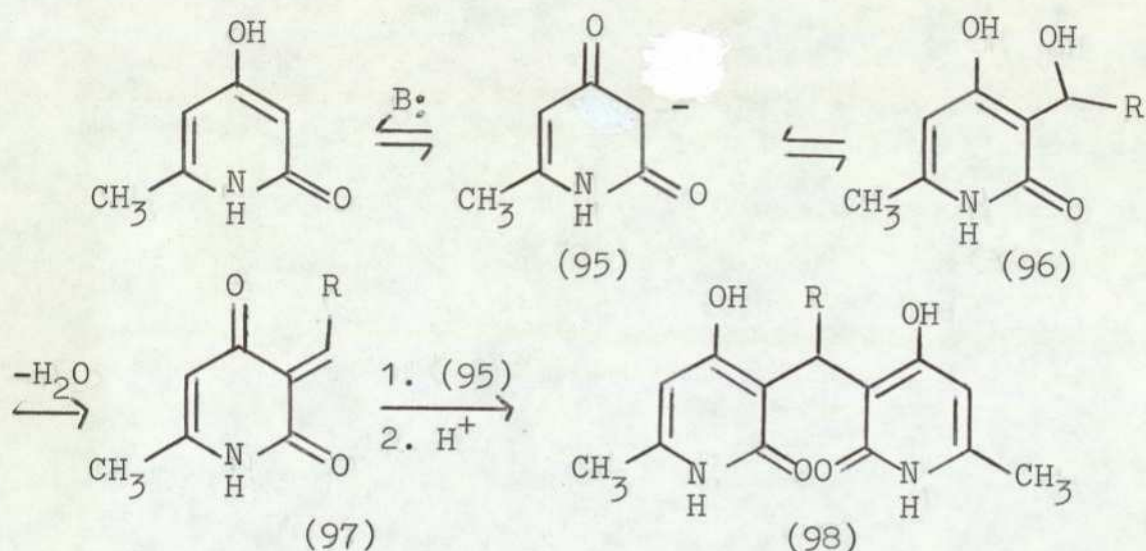
It is well known that electrophiles react at C(3) of 4-hydroxy-2-pyridones, even in the presence of a variety of substituents in the remaining aromatic sites. Thus (80, R = alkyl, Cl) are nitrated with only 50% nitric acid,^{79,81,90,99} and brominated by bromine in ethanol at the 3-position when C(5) is blocked.⁹⁰ Bromination also occurs at C(5).^{81,100}

Acetylation has been reported at the C(3) position of 5-acetyl- (80, R = CH₃), when treated with acetic acid and phosphorus oxychloride.⁸⁵ It has been shown however, that mixtures are produced containing 3-acetyl and 4-acetoxy-6-methyl-2-pyridone, when (80, R = CH₃) is treated with the identical reagents to the 5-acetyl derivative above.^{101,102} The acetoxy pyridone can then be simply converted to the 3-acetyl- (80, R = CH₃) with aluminium chloride in a Fries rearrangement.¹⁰² Possibly the former instigators effected the total conversion to the 3-acetyl derivative via the 4-acetoxy-6-methyl-2-pyridone with phosphorus oxychloride acting as catalyst for the rearrangement. A further explanation could be the non availability of the 4-hydroxy group of the 5-acetyl derivative owing to extensive hydrogen bonding between the two functions.

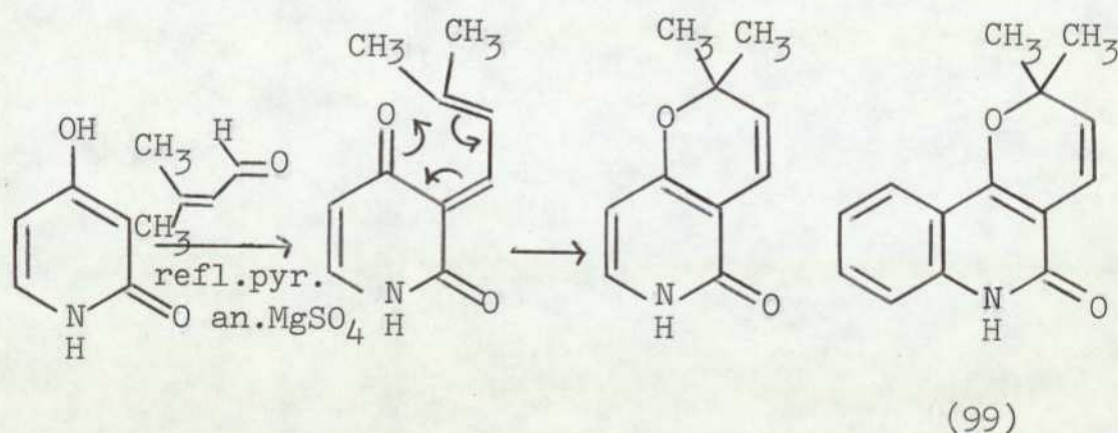
With polyphosphoric acid, acylation of 4-hydroxy-2-pyridones with several carboxylic acids occurs exclusively at the 3-position.¹⁰¹⁻¹⁰⁴ This latter method has been employed during the proof of structure of mocimycin an antibiotic produced by Streptomyces ramocissimus.¹⁰⁴

With a weakly basic solution of piperidine and pyridine many aldehydes have been condensed at position 3 of (80; R = alkyl) giving (96). Dehydration to (97), then permits Michael attack of another anion of (80; R = alkyl) to give (98) in good yield.¹⁰⁵

The reaction of 3-methyl but-2-enal with the parent (80; R = H) has provided a useful model for the total



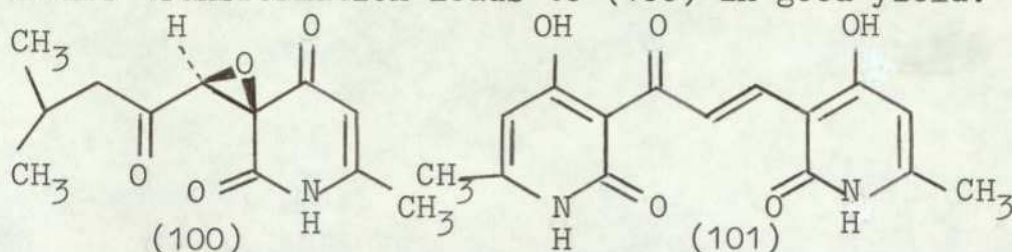
synthesis of the natural product flindersine (99) in 86% yield (Scheme 29).¹⁰⁶



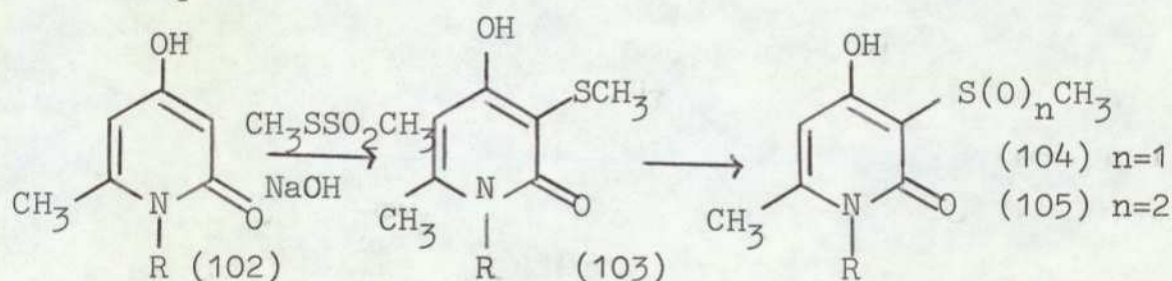
Scheme 29

This condensation has been extended to *d*-ketoaldehydes,¹⁰⁷ and a variation on this development has led to the total synthesis of the natural product ⁺-flavipucine

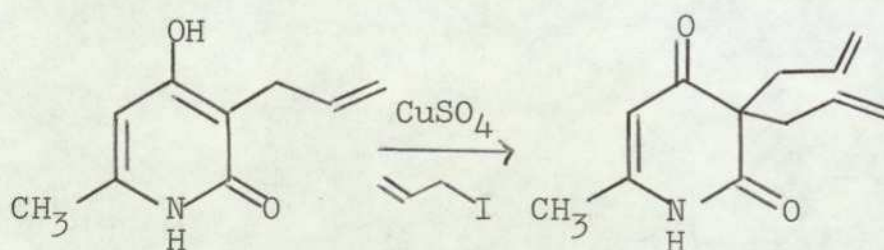
(100).¹⁰⁸ Reaction of the sodium salt of (80; R = CH₃) - prepared from the pyridone and sodium methoxide - with 2-oxo-4-methylpentanal gives (97; R = COCH₂CH(CH₃)₂). Further transformation leads to (100) in good yield.



Dimers can be obtained from the condensation of β -keto-esters with (80; R = CH₃) to yield (101).¹⁰⁹ Thioalkylation of pyridone (102) with CH₃SSO₂CH₃ gives the methyl thioether (103) which can be partially or fully oxidised with hydrogen peroxide to the sulfoxide (104) and sulphone (105).¹¹⁰ Both of these compounds are effective in weed and pest control



The 3-allyl derivative of (80; R = CH₃) has been alkylated with allyl iodide at C(3) in the presence of cupric sulphate. The products are strongly soporific and

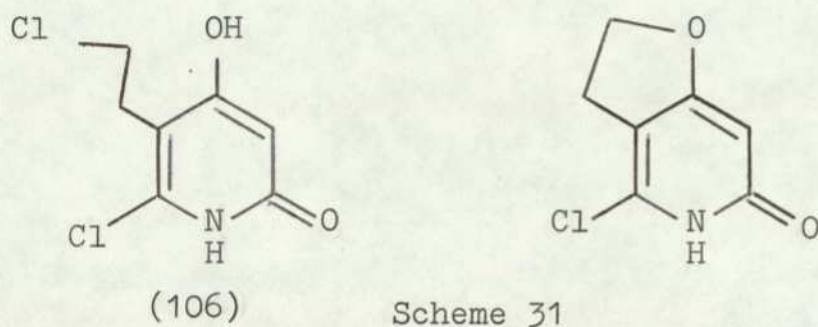


Scheme 30

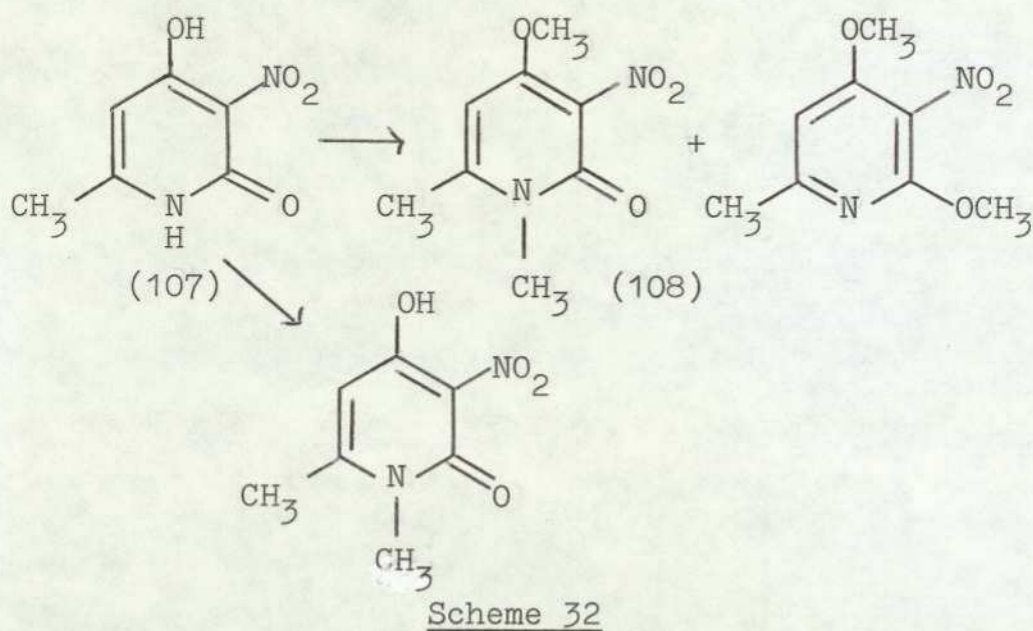
are used as general barbiturate analogues (Scheme 30).

Attempts to alkylate the 4-hydroxyl group include

the intramolecular cyclisation of (106) in ethanolic ammonia (Scheme 31).¹¹¹



Alkylation of nitropyridone (107) with diazomethane produces mixtures of the pyridine and pyridone (Scheme 32).⁹³ The dialkylated pyridone can be obtained pure by first treating the pyridone (107) with a basic



solution of dimethyl sulphate, then isolation of the N-methyl derivative followed by reaction with diazomethane gives the dimethyl pyridone (108) (Scheme 32).

Reactions

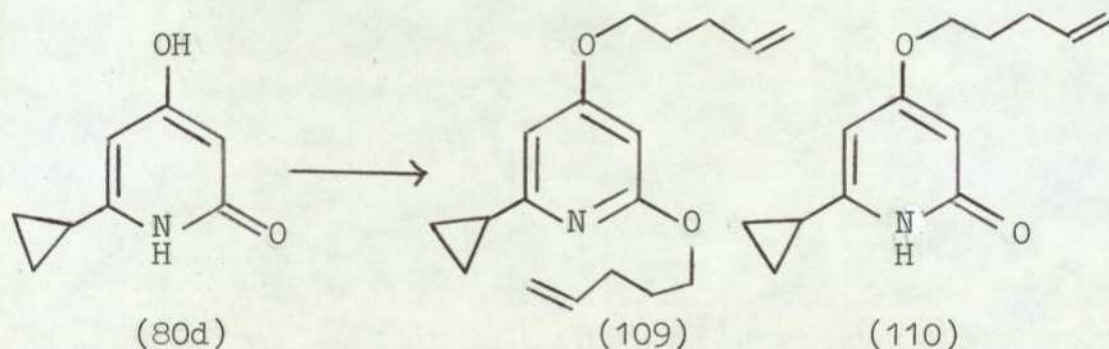
We wished to alkylate the 4-hydroxy-2-pyridone system with simple alkyl halides, especially pentenyl bromide, and our initial investigations followed the method described by Girota for the preparation of the monoanion.¹⁰⁸ It was expected that C(3) would be alkylated from the wealth of examples provided in the literature. Slurried 6-cyclopropyl-4-hydroxy-2-pyridone (80d) was dissolved in ethanol by adding one molar equivalent of sodium ethoxide. Introduction of n-bromobutane and subsequent work-up yielded a quantitative recovery of the starting pyridone (80d). It was thought that perhaps the lactam proton may have been extracted instead of the C(3)-H and that this was insufficiently nucleophilic to react with the bromide. The reaction was repeated with two equivalents of the base in the hope of forming the dianion, but work-up yielded the same result. Whether or not the dianion formed, it appears that the monoanion of (80d) is unable to react in ethanol with weakly electrophilic compounds such as alkyl bromides. The assumption that a monoanion had formed seemed valid since a clear solution was obtained following the basification of the slurried pyridone solution.

The same substrate (80d) was then dissolved in the minimum quantity of dry DMSO and two equivalents of n-butyl lithium slowly added. Immediately the white monoanion precipitated and only efficient stirring maintained a mobile slurry. Left stirring for several hours at room temperature, slightly more than one equivalent of pentenyl bromide was injected. Subsequent work-up indicated two

products which were identified as 2,4-di-(pent-4-en-1-oxy)-6-cyclopropyl-2-pyridone (109) and 4-(pent-4-en-1-oxy)-6-cyclopropyl-2-pyridone (110) in yields of 49% and 17% respectively based on the alkenyl group consumed (Scheme 33).

The ^1H n.m.r. spectrum of (109) contains two, two-proton triplets (J 7 Hz) at δ 3.96 and δ 4.25, and the ring protons appear typically deshielded for protons of this sort. I.r. analysis shows peaks at 1639 and 912 cm^{-1} for the vinyl group as well as normal aromatic absorptions. The U.V. spectrum predictably contains peaks at 225 (ϵ 350) and 268.5 nm (ϵ 150).^{112,113}

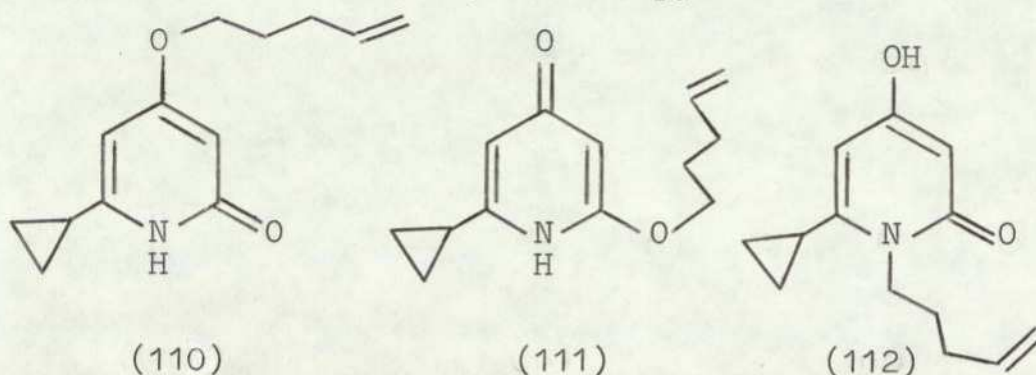
The ^1H n.m.r. spectrum of the pyridone (110) by comparison, has one, two-proton triplet (J 6 Hz) at δ 3.90,



Scheme 33

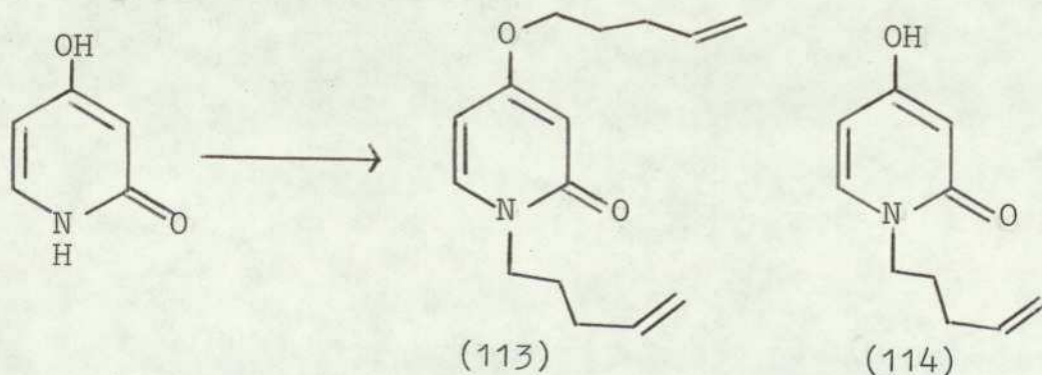
and the ring protons appear as two mutually coupled one-proton doublets (J 2 Hz), δ 5.47 and δ 5.69. The i.r. spectrum contains one major absorption in the carbonyl region 1640 cm^{-1} , with a shoulder at 1625 cm^{-1} . The N-H peak occurs at 3385 cm^{-1} . Three bands appear in the U.V. spectrum at 215.5 (ϵ 23,300), 224 sh (ϵ 4850) and 288 nm (ϵ 7300), the latter in reasonable agreement with values quoted for 4-methoxy-2-pyridone (277 nm) and 1-methyl-4-

hydroxy-2-pyridone (280 nm).⁸¹ Of the possible isomeric monoalkylated structures from this reaction (110), (111) and (112), that of (111) - the 4-pyridone - can at once be



discounted, since 2-methoxy-4-pyridone is known to absorb at 248 nm.¹¹³ The other possible structural isomer (112) can be discounted as a result of ¹³C n.m.r. analysis, the O-methylene of (110) absorbs at 67.3 p.p.m., while the usual range for N-methylene carbon peaks is between 44-50 p.p.m. (see appendix).

When the reaction was repeated using the parent 4-hydroxy-2-pyridone and *n*-butyl lithium, the same type of monoanionic slurry was obtained in DMSO. Alkylation with one molar equivalent of the pentenyl bromide, and work-up again yielded two products. Much regenerated starting material (80; R = H) was filtered from the neutralised reaction mixture. 1-(Pent-4-en-1-yl)-4-(pent-4-en-1-oxy)-2-pyridone (113) was isolated in 26% yield as a mobile oil in addition to 1-(pent-4-en-1-yl)-4-hydroxy-2-pyridone (114) as a crystalline solid.



The dialkylated pyridone gives rise to a ^1H n.m.r. spectrum containing an overlapping pair of two-proton triplets ($J = 7$ Hz and 6 Hz) at $\delta 3.93$ and $\delta 3.98$ respectively. The peak at $\delta 4.25$ in the spectrum of (109) is totally absent, therefore it appears that this latter peak is probably due to the 2-(pent-4-en-1-oxy) O-methylene group. Double irradiation of the alkyl absorption at 186 Hz in the spectrum of (113) causes the collapse to singlets of both triplets. A doublet at $\delta 7.23$ (J 9 Hz) due to C(6)-H collapses to a singlet when part of a multiplet at 597 Hz is irradiated. The multiplet represents both methine and C(3) and C(5) protons. The i.r. spectrum contains a peak at 1657 cm^{-1} and the U.V. shows a band at 284 nm ($\epsilon 250$), both data verifying the basic 2-pyridone structure. The different reaction paths leading to (109) and (113) are clear indications of the steric control exercised by the C(6) substituent. The bulky cyclopropyl group precludes the possibility of the alkenyl chain being able to form a transition state with the lactam function that favours N-alkylation. In the absence of this restriction (80, $R = \text{H}$), the favoured thermodynamically more stable, N-pentenyl isomer can form. None of the N versus O alkylation properties of the lactam that are prevalent throughout 2-pyridone alkylation were observed. The low yields isolated in this work reflect the non-homogeneous nature of the dianions. The second product (114) gave a U.V. spectrum which contained one major peak, λ_{max} 283 nm ($\epsilon 100$), clearly derived from a 2-pyridone. The ^1H n.m.r. spectrum shows a methylene group that could be adjacent to either an oxygen or a nitrogen atom at $\delta 3.89$.

The assignment was based on i.r. evidence, since a very wide band was present between $3490 - 2140\text{ cm}^{-1}$ that occurred in the spectra of all the 6-substituted-4-hydroxy-2-pyridones (80). This is suggestive of an intramolecularly hydrogen-bonded OH group. The absorption for the carbonyl function is present at 1656 cm^{-1} , i.e. the same position as that for pyridone (113) and significantly higher than that for the 4-alkoxy-derivative (110).

That the dianion was not strictly necessary for the alkylations described was demonstrated by repetition of the reaction with (80; R = H), one equivalent of pentenyl bromide and only one of n-butyl lithium. Formed in 20% yield the only isolable product was pyridone (113).

Unless the formation of the dianion is quicker than the monoanion, once the monoanion has formed - and this is unlikely considering the heterogeneous nature of the monoanion mixture - an equilibrium must have been established. It is difficult to believe that the monoanion did not form completely, taking into account the mixing properties of DMSO and n-butyl lithium in hexane. The agent forming the anion was certain to have been the DMSO lithium salt. An equilibrium could then have been set up between the monoanion and the reactive dianion, the monoanion being inert unless it was derived from monoalkylated dianion.

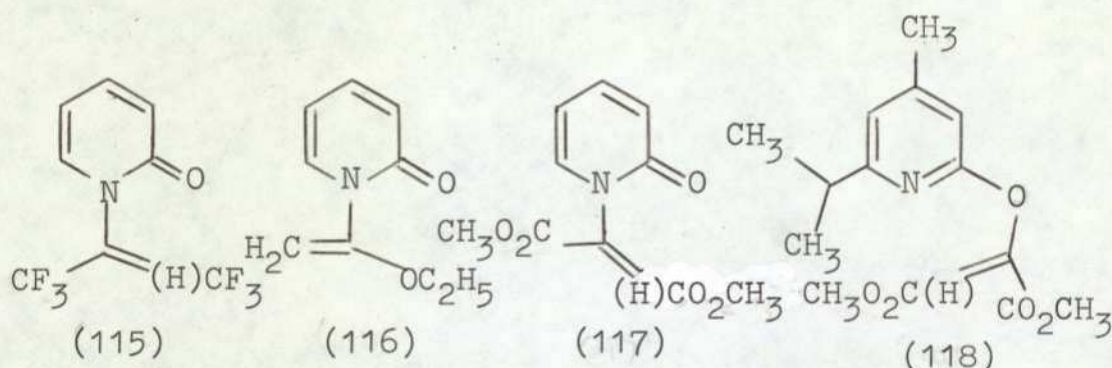
Alternatively the slow step in the process could be the first step, i.e. reaction at the nitrogen of the monoanion. Once the monoalkylated pyridone was formed, the anion of this derivative could have become more easily generated, and if this were more reactive than the monoanion of the original 4-hydroxy-2-pyridone, then the di-

pentenylated product would easily form. This too requires an equilibrium, between the relatively inert non-alkylated monoanion and the reactive, monoalkylated monoanion with the dialkylation step being much faster than the monoalkylation. It appears that, in the absence of a bulky C(6) substituent, the preferred site of monoalkylation will be the lactam nitrogen. If there is a large group present at C(6), then the anion derived from the 4-hydroxyl group becomes more reactive than the amide oxygen.

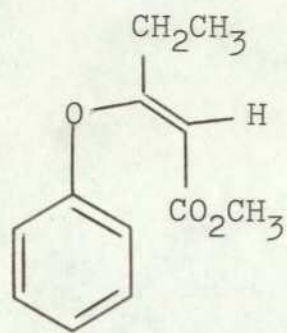
Reaction of 4-hydroxy-2-pyridones with
dimethyl acetylenedicarboxylate (DMAD)

Introduction

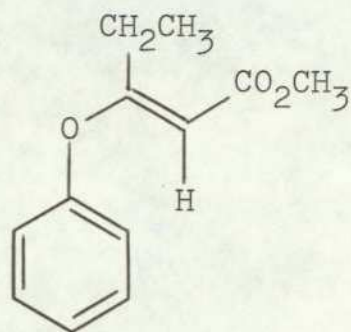
2-Pyridones are known to undergo 1,2-addition to electron-deficient alkynes. Thus, 2-pyridone adds to perfluoro-2-butyne to give (115) with unspecified geometry,⁴ or to ethoxyacetylene to give (116) which rearranges further.⁵ With DMAD (117) is obtained,¹¹⁴ in a geometry "assumed" to be trans.⁶ A bulky 6-isopropyl group causes addition to occur at the oxygen (118),⁷ giving a mixture of the fumarate and maleate.



Likewise phenols are known to add to DMAD,^{115,116} to give a mixture of (119), the fumarate, and (120), the maleate.¹¹⁷ For σ-substituted phenols the fumarate/maleate ratio decreases as the substituent bulk grows. The two isomers were differentiated by the dissimilar resonance positions of the olefinic protons in the ¹H n.m.r. spectrum of the mixture. Buttcrossed between the two ester groups, the fumarate proton absorbs 1.5 p.p.m. lower than that of the maleate.¹¹⁷

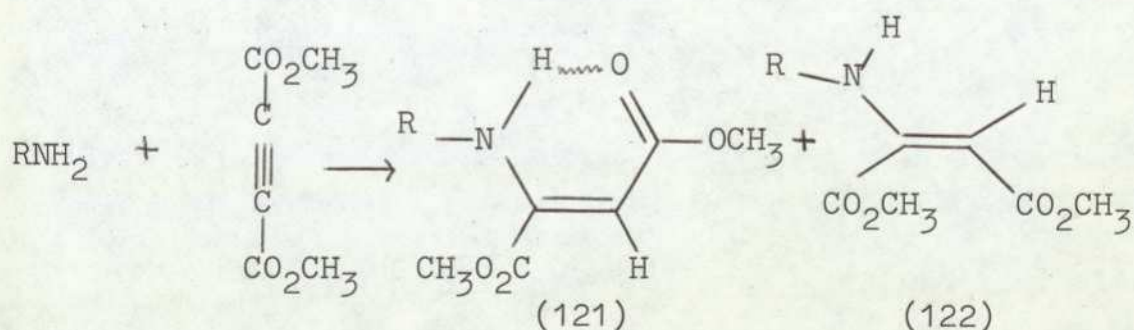


(119)



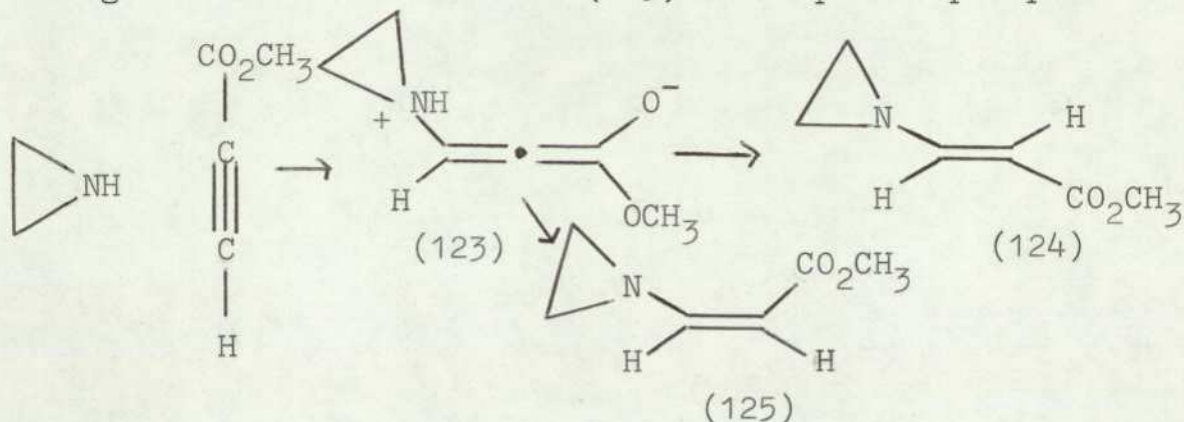
(120)

Addition of small nucleophiles to DMAD is well documented. The attacking species have included thiols,¹¹⁸ and amines.¹¹⁹ The relative yields of the isomers obtained in any addition will depend upon several factors, like the ease of their interconversion, the nature of the attacking nucleophile, the solvent and the reaction conditions. Thus, with primary amines or alcohols and DMAD, the fumarates (121) are formed in larger amounts due to the possibility of forming a 6-membered cyclic transition state. The product, in the maleate case (122), has no such stabilising effect to aid its formation.¹¹⁹ Secondary amines do in fact give much greater proportions of the maleate.



Aziridines react with methyl propiolate in polar, aprotic solvents like ether, dioxan, DMF, DMSO and acetonitrile to give a mixture of isomers in which the cis-addition was major (~95%). In polar protic solvents like alcohols, the proportion of trans-isomer increased at the

expense of the cis. Huisgens et al. have concluded that the reaction of aziridine with acetylenic esters proceeds through a common intermediate (123) which picks up a proton



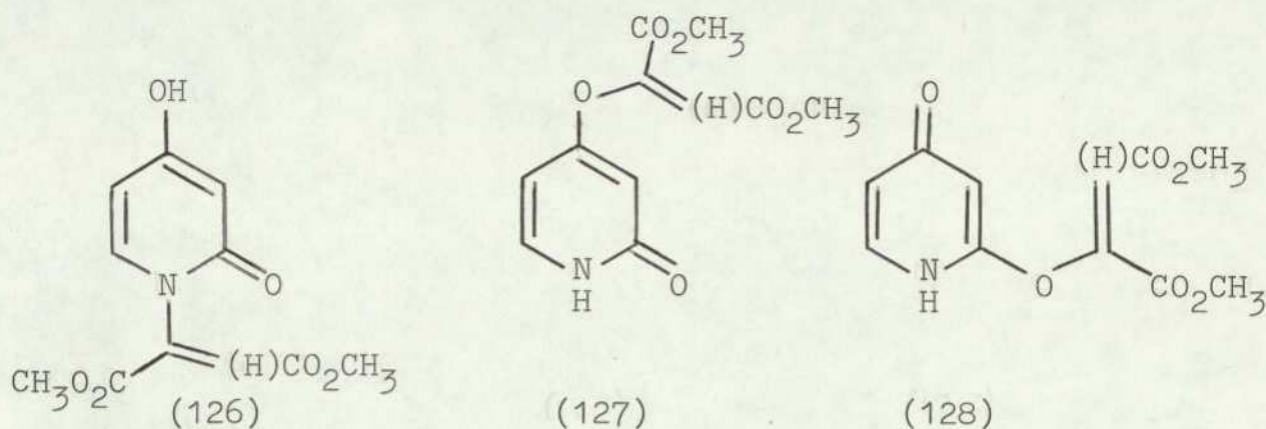
either internally from the attacking nucleophile to give the cis-addition product (124) or externally from the solvent to give the trans-addition product (125). The yield of the latter was directly related to the proton donating ability of the solvent.¹²⁰

Reactions

Thermolysis of (80; R = H) at 70° for 4 hours with a slight excess of DMAD gave an adduct in 47% yield. Due to the insolubility problem encountered with 4-hydroxy-2-pyridones, relatively large amounts of solvent (DMF) were required, and reaction was slow; more than half of the starting material was recovered. A fumarate/maleate mixture was obtained in a ratio of 40/60. The ¹H n.m.r. spectrum of the adducts contained in the aromatic region two olefinic singlets, δ 6.29 (maleate) and δ 7.03 (fumarate). Two doublets, δ 5.89 and δ 5.97 arise from the C(3)-H of both isomers coupled to C(5)-H. The latter proton resonance split also by C(6)-H, occurs as a doublet of doublets (J 7 and 2 Hz) at δ 6.16, the signals from both isomers

being coincident. Two doublets exist at δ 7.05 and δ 7.21 attributable to both of the C(6) protons. Double irradiation of the C(5)-H signal caused the collapse of both C(6)-H doublets to singlets and vice versa. The fine meta-couplings were lost under the conditions required for double irradiation.

It was not certain where the 1,2-addition had occurred, whether at the 4-hydroxyl in a phenolic sense (127), or whether at the N or the O of the lactam in the pyridone fashion of Mariano (126) and (128).¹¹⁴ The i.r. spectrum in addition to the carbonyl absorptions at 1729 and 1662 cm^{-1} shows a broad band between 3480-2300 cm^{-1} reminiscent of the parent 4-hydroxy-2-pyridone. The mass spectrum contains no loss of the unsaturated diester function (-143), but does indicate loss of a mono-oxygenated derivative (-159) as a major fragment. This is contrary to structure (126). The U.V. spectrum is very instructive, since the 4-pyridone (128) can be immediately dismissed, normally absorbing at 240 nm.⁸¹ The novel product absorbs at 299 nm. Another interesting feature is the lack of effect that addition of base has on the chromophore. A shift from 278 to 261 nm is induced when ethanolic potassium hydroxide is added to a solution of (80; R = H). The hypsochromic shift is usually associated with a reduction in conjugation of the chromophore; this effect would not be expected to be significant for (127). For the parent (80; R = H), base addition would induce the formation of 4-keto-3-anion (129), and this effect should also be exhibited by the derivative (126). We have not been able to fully characterise the adduct as (126) or (127), but it



would seem on the evidence presented that it is probably the latter.

6-Cyclopropyl-4-hydroxy-2-pyridone (80d) was thermolysed in the same manner and this too gave only one adduct. From the work of Heep it should be impossible to form the N-isomer for steric reasons.⁸ U.V. analysis suggests structure (130), for the $\lambda_{\max}$ occurs at 299 nm, identical with the previous analogue. The other possible O-adduct - at the lactam - can be eliminated, since as has been mentioned 2-alkoxy-4-pyridones absorb at 240 nm.⁸¹ This result lends support to the assignments of (127).

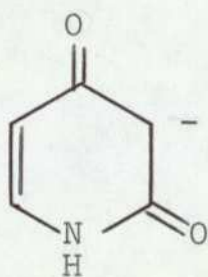
An isomeric mixture was once again obtained, the fumarate/maleate ratio again 40/60. The thermolysis, repeated at 80° instead of 70°, but for the same duration gave a product isomer ratio of 30/70 respectively. As would be expected, the maleate forms to a greater extent as the reaction temperature is increased. The selectivity of the mechanism becomes lower.

The olefinic protons resonate at δ 5.86 (maleate) and δ 6.74 (fumarate) in the ¹H n.m.r. spectrum, the C(3)-H resonance gives rise to two doublets (J 2 Hz) at δ 5.68 and δ 5.63 respectively. The C(5) proton occurs also as two doublets, δ 5.95 (maleate) and δ 5.72 (fumarate). Four separate methoxyl absorptions are in evidence at

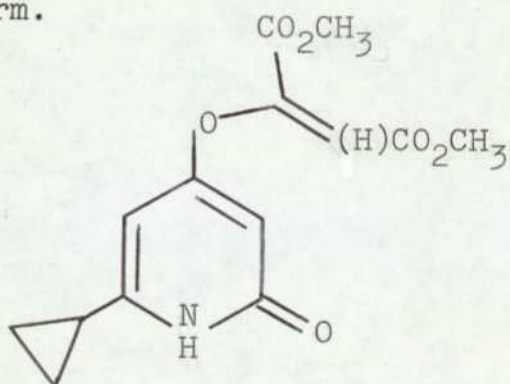
δ3.84 and δ3.92 for the maleate, and at δ3.78 and δ3.88 for the fumarate.

Attempts to perform these 1,2-additions at significantly higher temperatures ($\sim 110^{\circ}$) resulted in decomposition of the starting material. The same loss of precursors was observed for thermolyses of 12 hours or more, at 80° .

The inference for the alkylation of the 4-hydroxyl by DMAD is probably simply that this oxygen atom is the more nucleophilic, neither the N or O of the lactam provide any measureable competition. The protrusion of the 4-hydroxyl from the pyridone probably aids in its nucleophilicity, since for DMAD to react at the lactam a bulky intermediate would need to form.



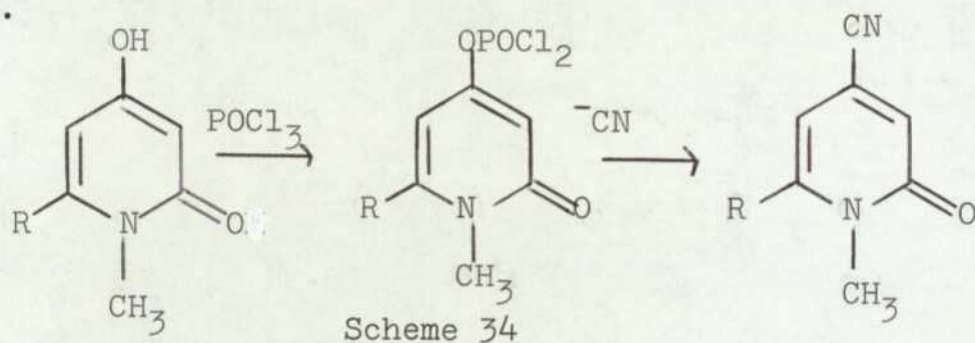
(129)



(130)

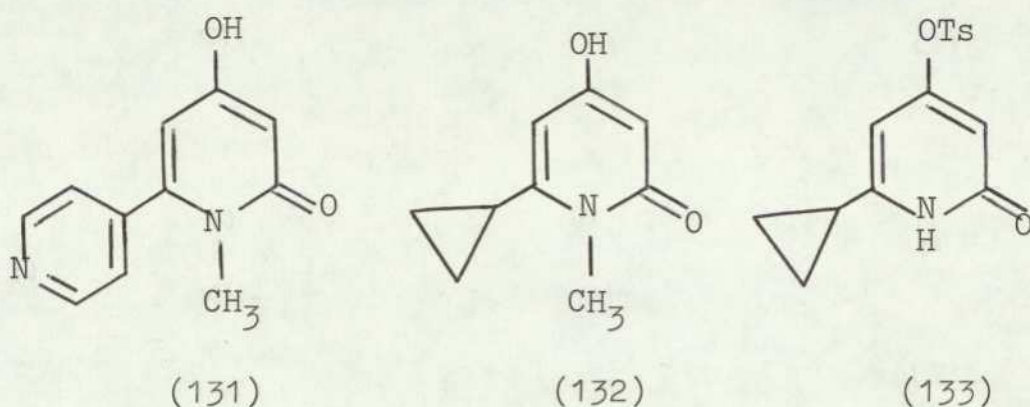
Attempts to prepare 4-cyano-2-pyridones

The basic approach in this investigation was to convert the most readily available 4-hydroxy-2-pyridones into 2-pyridones containing excellent leaving groups at C(4). Nucleophilic displacements are known to occur at the C(2) and C(4) of pyridones, as in the case of chlorination of (80; R = H, alkyl) with phosphorus oxychloride.^{79,81} Both hydroxyl groups are replaced, as phosphoryl esters, by chloride to give dichloropyridines. Our initial attempts revolved around such a nucleophilic displacement (Scheme 34).



Since phosphorus oxychloride reacts with the pyridone oxygen with the same facility shown for the 4-hydroxyl group, it became necessary to block the amide function. It was demonstrated earlier in this chapter that (80; R = H, alkyl) cannot be alkylated in the manner described by Girota,¹⁰⁸ and since this is essentially the method of alkylation of simple 2-pyridones, sodium ethoxide cannot be employed as base.³² The only reported method of direct alkylation was applied.⁹³

This involved the reaction of pyridones (80r) and (80d) with basic dimethyl sulphate. The 4-pyridyl derivative gave less than 20% of the 1-methyl derivative of (80r) (131), while none of the analogous pyridone (132) was observed.



In the latter case, about 50% of (80d) was recovered, t.l.c. analysis of the organic phase from the reaction indicated a very complex mixture. In view of the low conversion of the most readily available pyridones this route was deemed impracticable. It appears that the bulk of the substituents interferes with the alkylation process.

The second approach was to prepare the 4-tosylpyridone (133), in 80% yield, following an improvement in the method of Wang's.⁸¹ A colourless powder was obtained (133), which was triturated free of the minor quantity of ditosylated derivative with ether. The spectral data of (133) were consistent with the assigned structure including the characteristic doublet in the i.r. spectrum at 1176 and 1191 cm^{-1} for the tosyl function.

All attempts to cause the desired nucleophilic displacement failed, the tosylate was very stable. The methods employed included simply stirring a DMF solution of the pyridone and potassium cyanide at room temperature, but this proved fruitless. Heating at 60°, then after no reaction 120° decomposed the substrate. Two solutions were prepared, one in dichloromethane and the other in acetonitrile containing the pyridone, a slight excess of potassium cyanide and a catalytic amount of 18 C 6 crown ether. After a week no reaction could be detected, and so the crown ether was made up to one equivalent. Left stirring

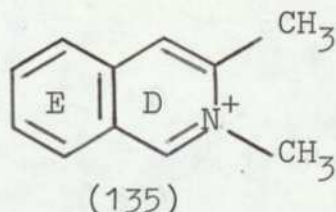
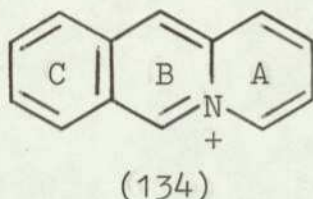
for three months with another DMF solution of the pyridone and cyanide, no reaction was detected in any of the three mixtures. This line of research was discontinued.

CHAPTER 4

Preparation and thermolysis of quaternary pyridinium salts.

Introduction

The acridizinium nucleus (134) was the first aromatic cation to undergo cycloaddition with ethylenic derivatives.¹²¹ It has been reported that with suitable ethylenic substrates cycloaddition is observed even if ring C of (134) is replaced by an anhydride ring, but not if replaced by a pair of methyl groups.¹²²

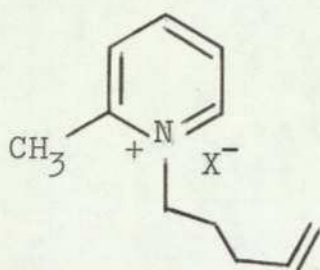
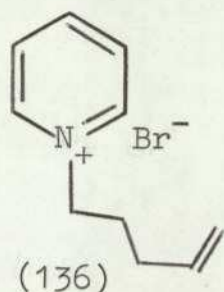


Addition also occurs when ring A is replaced by an imidazo or pyrazino ring.¹²³ Substitution of ring A by two alkyl groups gives the isoquinolinium system (135) which reacts with a wide range of electron-rich olefins (see review).¹²⁴ Taking the situation further, we were interested in how elimination of ring E of (135) would affect the cycloadditive properties of the system. Isoquinolinium salts lacking the C(3) alkyl substituent are known to give very labile adducts with olefins.¹²⁵ The alkyl group is believed to stabilise the iminium salt (produced after cycloaddition) towards attack by even mild nucleophiles.

Reactions

Pyridinium salts (136) and (137) were thus prepared,

by boiling the respective pyridine with pentenyl bromide in acetonitrile. Almost quantitative yields of the very hygroscopic solids were obtained. The ^1H n.m.r. spectra

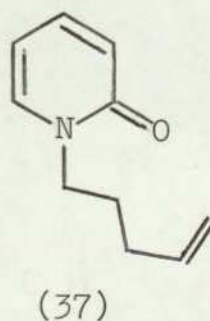
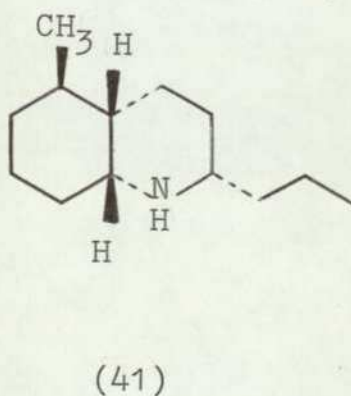
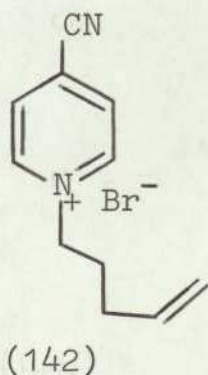
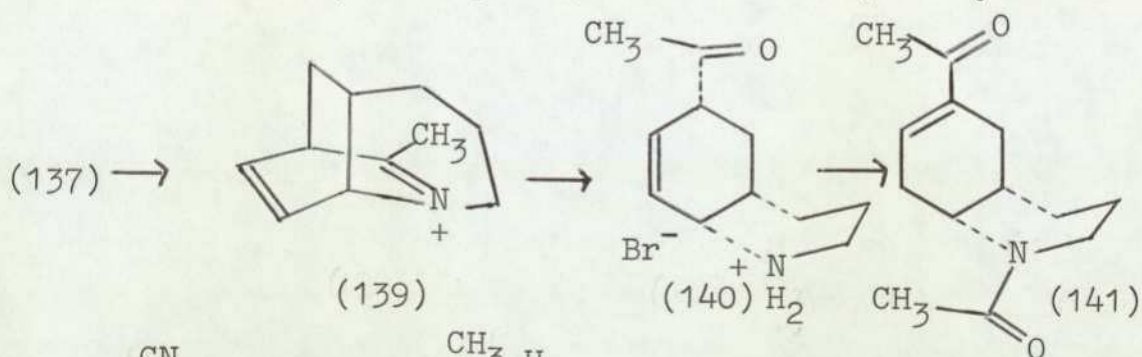


(137) $\text{X} = \text{Br}$

(138) $\text{X} = \text{BF}_4$

of both salts showed the deshielding effect exerted by the quaternary nitrogen on the ring proton's resonance positions, and on the (N^+) -methylene group. The latter signal now absorbs coincident with the peaks arising from the terminal vinyl methylene group, as part of a four proton multiplet ($\delta 4.9 - 5.3$).

Both substrates (136) and (137) proved indefinitely stable to thermolyses below 170° in either DMF or acetonitrile. Heated at 200° for 12 hours however, the starting material was consumed. If cycloaddition had occurred to give adduct (139), then hydrolysis followed by acetylation



should give the bicyclo derivative (141). Under the basic conditions of the acetylation it would be expected that the olefinic link would move into conjugation with the keto-function. A cursory glance at derivative (140) reveals the basic ring skeleton of the alkaloid pumeliotoxin-C (41) containing the correct stereochemistry. This alkaloid was sought previously from the potential intramolecular cycloaddition of pyridone (37). Hydrolytic work-up, followed by acetylation revealed no products derived from cycloaddition. Consistently, almost all of the thermolysed materials remained water soluble, even after boiling the aqueous layer with sodium hydroxide solution for extended periods.

The tetrafluoroborate (138) was prepared as a colourless solid m.p. $144-6^{\circ}$, by the anion exchange of (137) with silver tetrafluoroborate in ethanol. Being non-nucleophilic, this anion would not be expected to attack the azomethine linkage of the pyridinium salt during heating. At elevated temperatures, bromide may be capable of addition, leading to polymerisation of the materials. Thermolysis of salt (138) however, gave results identical to salt (137): formation of unworkable tars.

The pyridinium nucleus is so electron-deficient that it could probably only take part in cycloaddition reactions in the inverse demand sense, if at all. In order to lower the heterocyclic LUMO further, cyanopyridinium salt (142) was prepared. Thermolysis of this derivative however, resulted only in tar formation. Use of water, or potassium cyanide, to trap the cycloadduct, if it formed were equally unsuccessful.

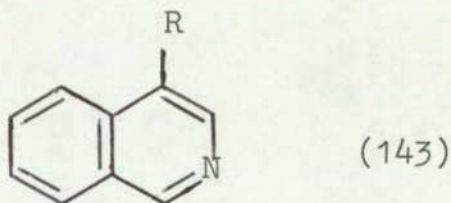
Part of the reason for the inertness of pyridinium salts is probably caused by the resonance energy that the system possesses. The energy of activation for an addition reaction would be high. It was originally hoped that the entropy advantage gained by attempting the addition intramolecularly would be sufficient to help the reaction across this barrier. In the event this did not seem to be so for the reaction to occur in the desired sense.

CHAPTER 5

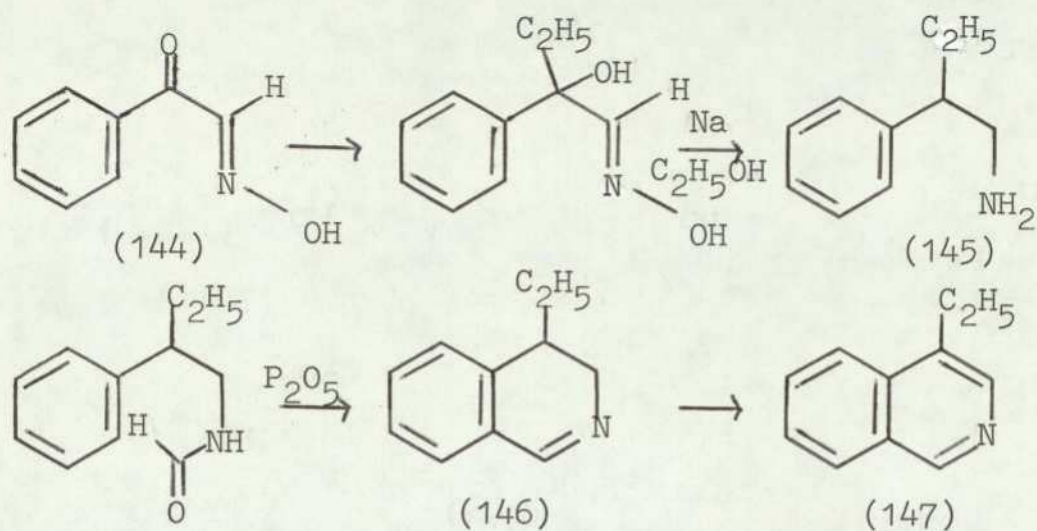
Alkylation of isoquinolines at C(4).

Introduction

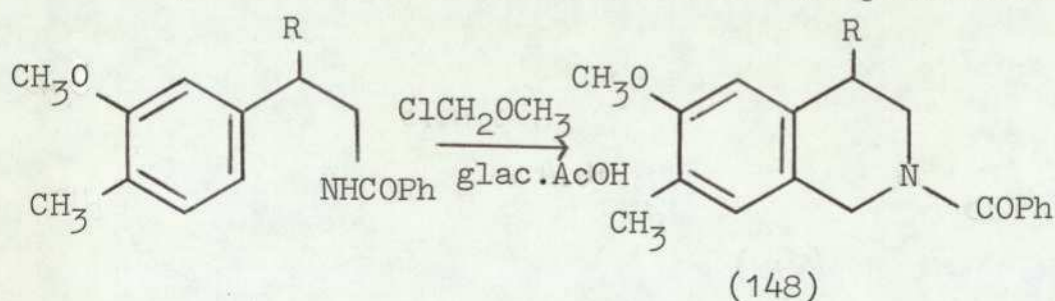
Three methods for the synthesis of 4-substituted isoquinolines (143) exist. The first uses an enamine



attack of a 1,2-dihydroisoquinoline on a suitable electrophile and the second involves formation of an anion at C(4), from 4-bromoisoquinoline and n-butyl lithium via metal-halogen exchange, followed by reaction with a suitable electrophile. The third method requires the preparation of an appropriately substituted β -arylethylamine, which can be formylated and then ring closed in a Bischler-Napieralski manner. Subsequent dehydration yields the isoquinoline. This latter method has been employed by Jones, who has developed a general method for the preparation of 4-alkylisoquinolines starting from α -hydroxyiminoacetophenone (144).¹²⁶ Attack of ethyl magnesium bromide followed by reduction with sodium in ethanol affords the β -phenylbutylamine (145), which can be formylated and cyclised to give the dihydroisoquinoline (146). The fully aromatic base (147) is obtained by mild oxidation of (146). Many 4-alkyl-1,2,3,4-tetrahydroisoquinolines have been produced from alkyl phenylamides following reaction with chloromethyl methyl ether in acetic acid (Scheme 35).¹²⁷

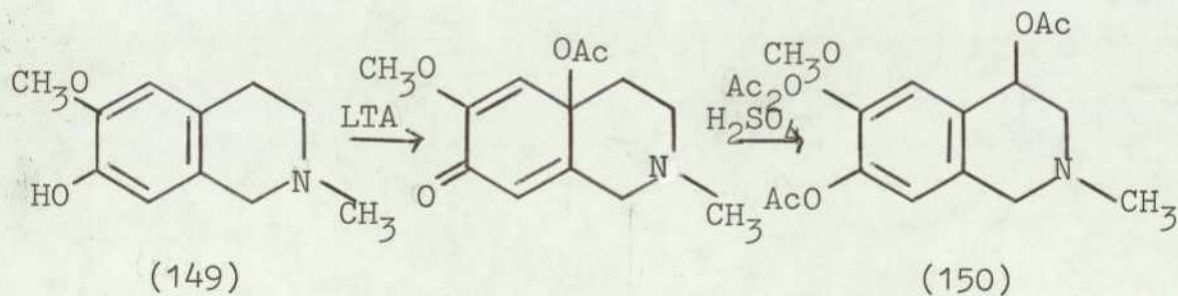


Debenzoylation and oxidation gives the isoquinoline.



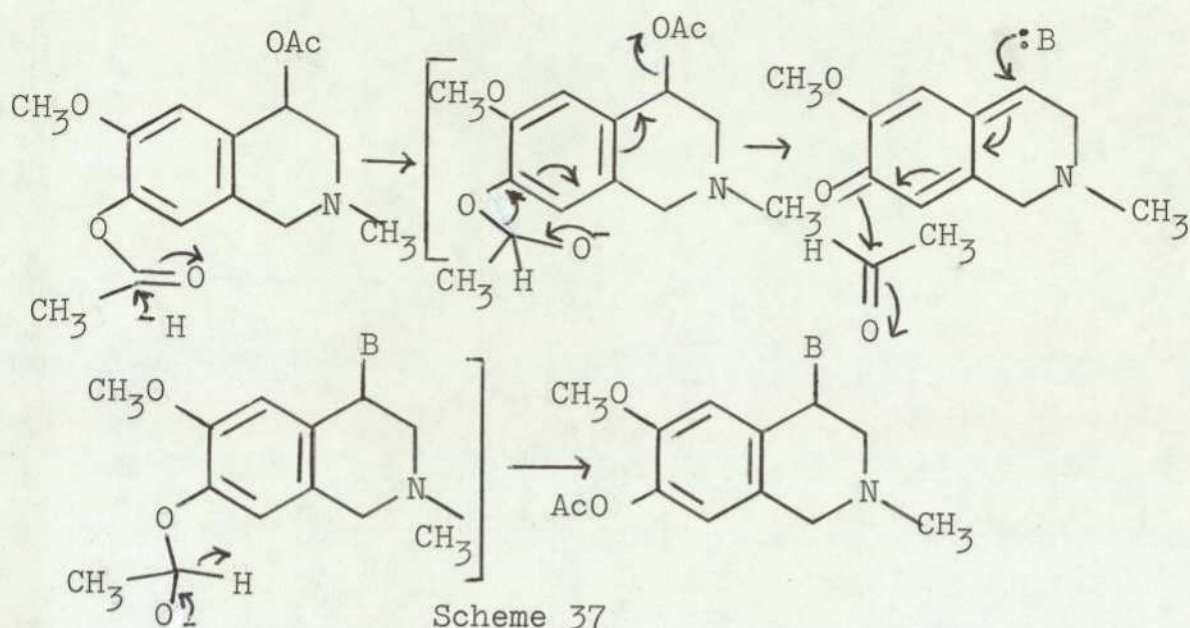
Scheme 35

Interestingly (148, R = OAc) undergoes nucleophilic displacement of the acetate with basic solutions of alcohols, thiols and amines, to give the respective 4-ethoxy, thioethoxy and aminotetrahydroisoquinolines.¹²⁷⁻¹³¹ In a similar fashion compound (150) prepared from lead tetraacetate (LTA) oxidation of tetrahydroisoquinoline (149) (Scheme 36) undergoes substitution by many active methylene compounds in addition to the nucleophiles previously mentioned.¹³² An anhydrous benzene slurry of sodium



Scheme 36

hydride is used. The proposed mechanism was thought to be initiated by hydride delivery to the 7-acetoxy function.

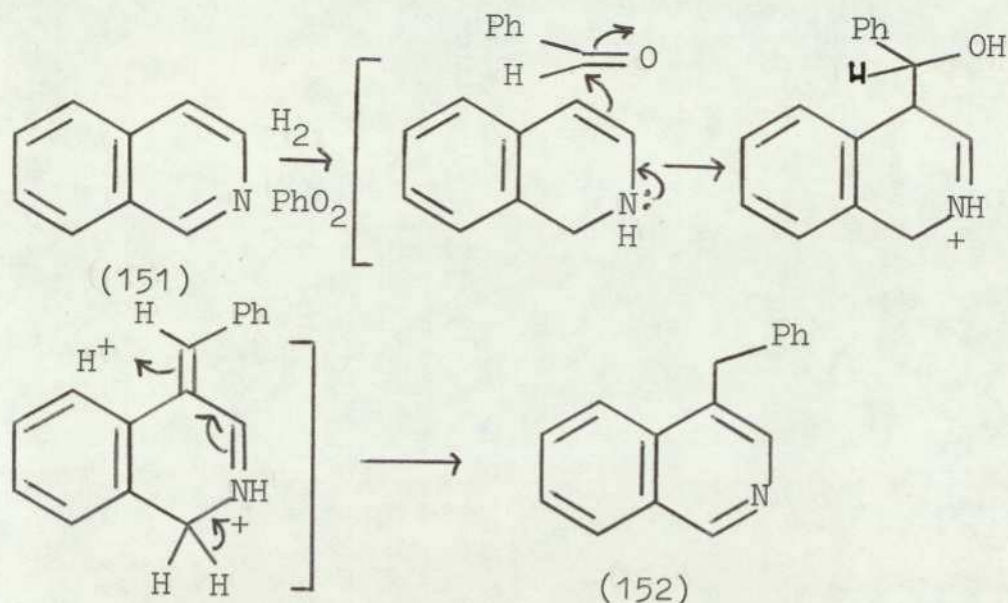


Scheme 37

B = $-\text{CH}(\text{CN})_2$, $-\text{CH}_2\text{COPh}$, Cyclohexanone^- , Cyclopentanone^- , $-\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)_2$, $-\text{CH}_2\text{SOCH}_3$, $-\text{CH}_2\text{NO}_2$, $-\text{CN}$.

(Scheme 37), although such a scheme is unprecedented and unlikely; redox reactions involving hydride loss are virtually unknown. Substitution by nitrile, or nitromethyl can be achieved under aqueous basic conditions. Several other syntheses involving the Bischler-Napieralski reaction have also been reported.¹³³⁻¹³⁶

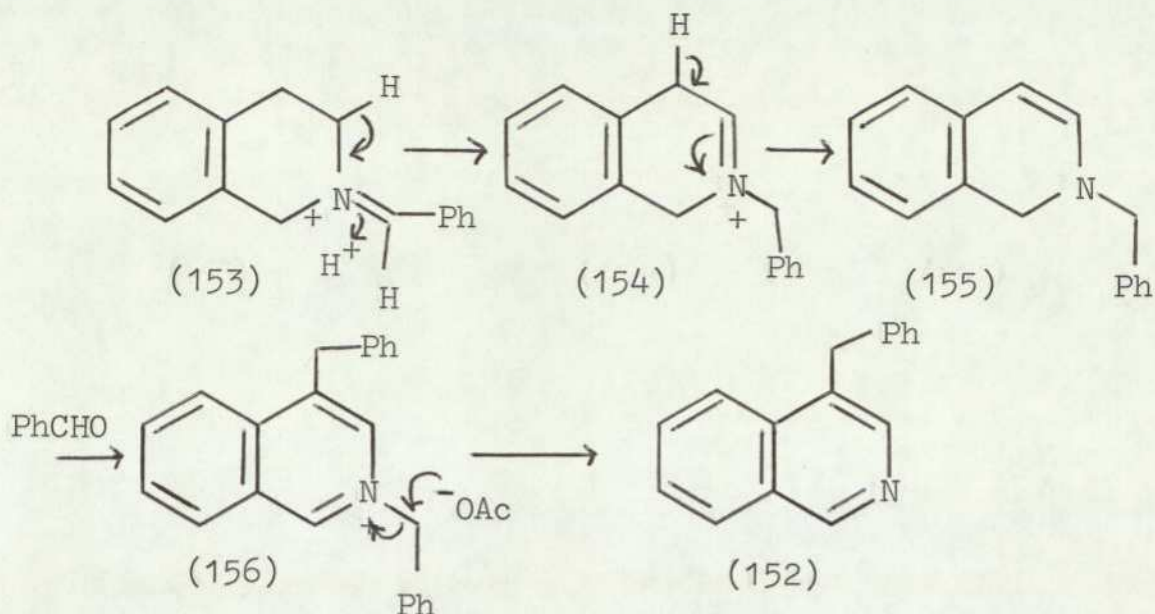
Of the enamine type alkylations the most widely investigated is that in which the isoquinoline is catalytically reduced, *in situ*, to the 1,2-dihydro-derivative, in the presence of an acidic solution of a suitable aldehyde or ketone. In this way 4-benzylisoquinoline (152) has been obtained from benzaldehyde in methanolic acetic acid, by reducing isoquinoline (151) over platinum oxide.¹³⁷⁻¹³⁹



Many mono- and di-substituted partially hydrogenated isoquinolines are formed as by-products, and much controversy exists as to their exact identities.¹³⁹ Yields of (152) rarely exceed 20% by this method, but respectable to good conversion to the 4-substituted isoquinolines have been claimed for anisaldehyde (62%), veratraldehyde (52%), phenylacetaldehyde (37%), and cyclohexanone (83%).¹³⁷

Heating under reflux a toluene solution of tetrahydroisoquinoline with benzaldehyde and acetic acid in conjunction with a Dean and Stark apparatus gave a 34% yield of (152).¹⁴⁰ The mechanistic sequence for this reaction, it is suggested, begins with the formation of Schiff cation (153), followed by double-bond transfer via (154), to the enamine (155), which condenses with another molecule of benzaldehyde giving (156). The final step, to (152), is the nucleophilic displacement of the substituted isoquinoline from its N-benzyl salt. All of the steps in this sequence have been experimentally verified.¹⁴¹

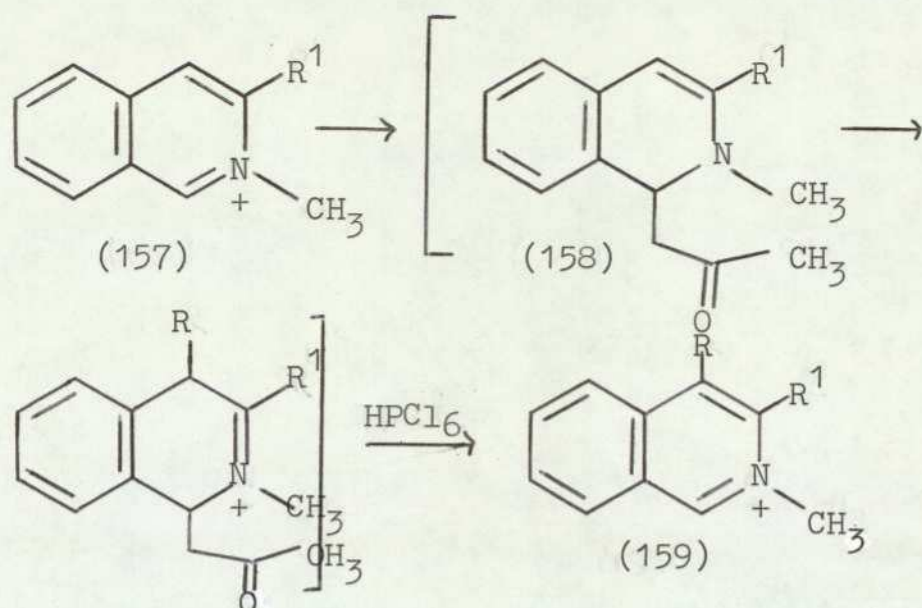
2-Methyl-4-benzyl and 2-methyl-4-benzoyl isoquinolinium salts have been prepared in low to moderate yields, following treatment of 2-methyl-1,2-dihydroisoquinoline with appropriate



benzyl or benzoyl halides, then iodine/potassium carbonate oxidation.^{142,143} The authors, however, were unable to isolate any C(4) alkylated products with ethyl chloroformate, allyl bromide, propargyl bromide, or simple aliphatic halides. With allyl and crotyl halides, the N-substituted 1,2,3,4-tetrahydroisoquinolines were the only identifiable products.¹⁴³

Thermal decomposition of 2-methyl-3-carboethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride in the presence of benzaldehyde or acetophenone gives the corresponding 4-benzyl or 4-(α -methylbenzyl)-derivatives.¹⁴⁹

Bradsher and Chen have obtained respectable yields of 2-methyl-3,4-disubstituted isoquinolinium salts for a very wide range of electrophiles.¹⁴⁵ The experimental procedure consists of stirring an acetone-water mixture of (157; $R^1 = CH_3$) with sodium hydroxide and the halide at room temperature. The product (159; $R^1 = CH_3$, $R = \text{various}$) is collected as a precipitate after treatment of the mixture with hexachlorophosphoric acid. Sodium hydroxide generates the acetone anion which attacks the heterocyclic



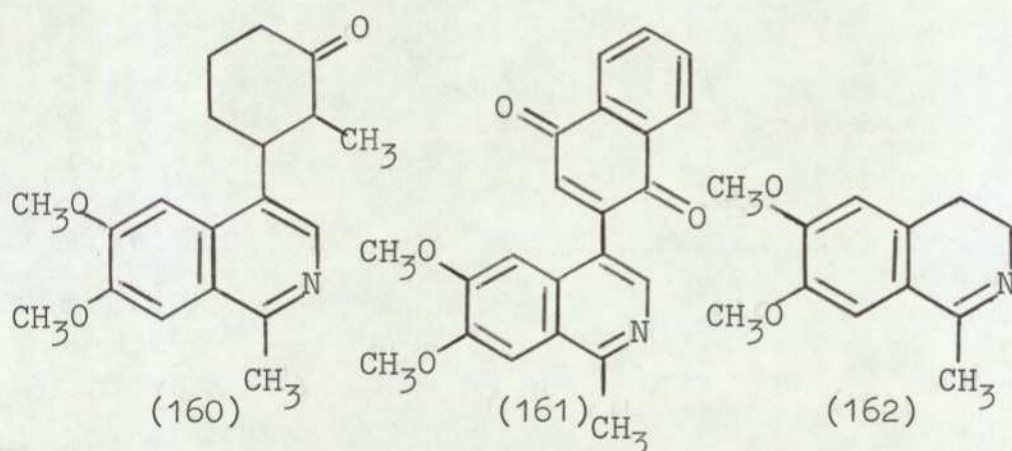
salt at the azomethine linkage giving the enamine (158; $R^1 = \text{CH}_3$). Addition of the bromide or iodide in the usual manner and acidification leads to liberation of (159; $R^1 = \text{CH}_3$, $R = \text{various}$).

Successful additions include iodomethane (41%), allyl iodide (34%), benzyl iodide (54%), bromoacetic acid (41%) and *m*-methylbenzoyl bromide (57%). A yield of 28% of (159, $R = n\text{-C}_4\text{H}_9$, $R^1 = \text{CH}_3$) was obtained by heating under reflux *n*-iodobutane, acetone and (157, $R^1 = \text{CH}_3$) with sodium carbonate as base.¹⁴⁵ This represents the largest realisation to date of an isoquinolinium salt directly substituted by a moderately long alkyl group. Reaction was also observed between (157; $R^1 = \text{H}$) and iodomethane (30%) or benzyl bromide (40%), giving (159; $R = \text{CH}_3$, $R^1 = \text{H}$) or (159; $R = \text{CH}_2\text{Ph}$, $R^1 = \text{H}$).

Another preparation that gives poor, though measureable yields of (143, $R = \text{alkyl}$) is that of Giam and Goodwin,¹⁴⁶ who developed a direct and very efficient alkyl pyridine synthesis. Partial reduction of pyridine with LAH gave lithium tetrakis(*N*-dihydropyridyl) aluminate which reacted

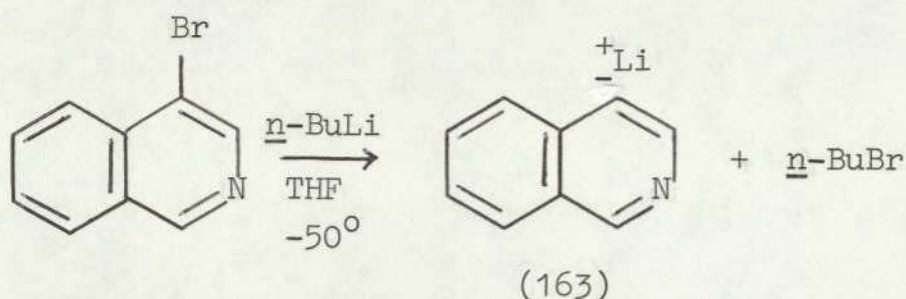
with many alkyl halides to give the 3-substituted pyridine.¹⁴⁷ Applied to isoquinoline however, the comparable mechanism was considered inappropriate, since the yields of alkyl isoquinolines increased in an irregular manner as the initial concentration of halide was increased¹⁴⁶ - the molar ratio of isoquinoline to LAH was maintained throughout the investigations at 4:1 respectively.

Other 4-substituted isoquinoline syntheses have arisen from modification of the Pomeranz-Fritsch reaction.¹⁴⁸⁻¹⁵⁰ Unfortunately owing to the unreliable nature of this conversion, very low yields are encountered; few investigators have employed this method.¹⁵¹ Kametani has developed a route to dimethoxyisoquinolines (160) and (161) from

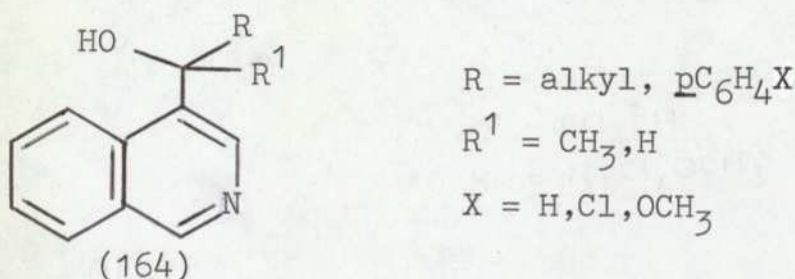


3,4-dihydroisoquinoline (162), which occurs through enamine addition involving electrons in the benzenoid ring.¹⁵²

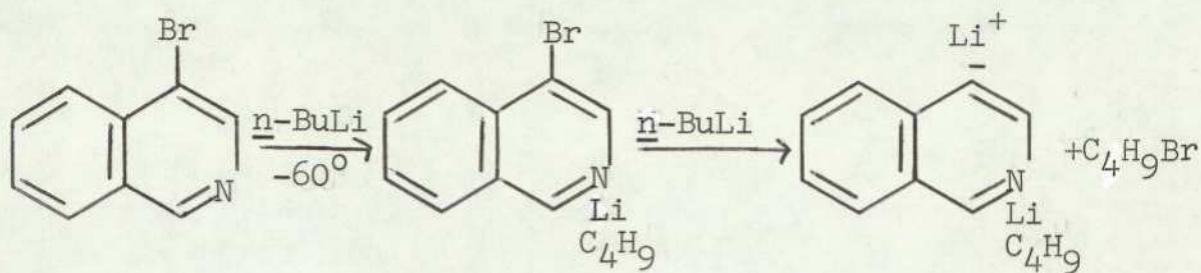
Advances in metallation techniques have enabled a variety of synthetic routes to be opened in the field of heterocyclic alkylations.^{142,153,154} Gilman and Soddy first prepared 4-lithioisoquinoline (163) in THF from 4-bromoisoquinoline and freshly prepared *n*-butyl lithium in a halogen-metal interconversion.¹⁵³



Treatment of anion (163) with carbon dioxide gave the acid (143, R = CO₂H) in 46% yield. The solvent was found to be of critical importance since, for the same reaction use of ether led only to recovery of starting material. Dyke et al. produced anion (163) following Gilman's route and then quenched the anion with many different aldehydes and methyl ketones.¹⁴² Hydroxybenzyl and α -methylhydroxybenzyl isoquinolines (164) were isolated in good yield, and presenting the possibility of further elaboration.



Non-aromatic and heteroaromatic aldehydes and ketones also took part in this reaction. Notable is the preparation of 4-formylisoquinoline (143, R = CHO) from anion (163) and DMF in 70% yield. This follows from the work of Wommack et al. who, unlike Dyke, found that two molar equivalents of n-butyl lithium were required to create the heterocyclic anion (163) from 4-bromoisoquinoline.¹⁵⁴ It was concluded that the first equivalent complexes with the heteroatom, (165); the second equivalent then gives the lithioisoquinoline (166). The anion (166) was formed only at C(4) of the isoquinoline ring. Addition of DMF gave the aldehyde (143, R = CHO) which could be further

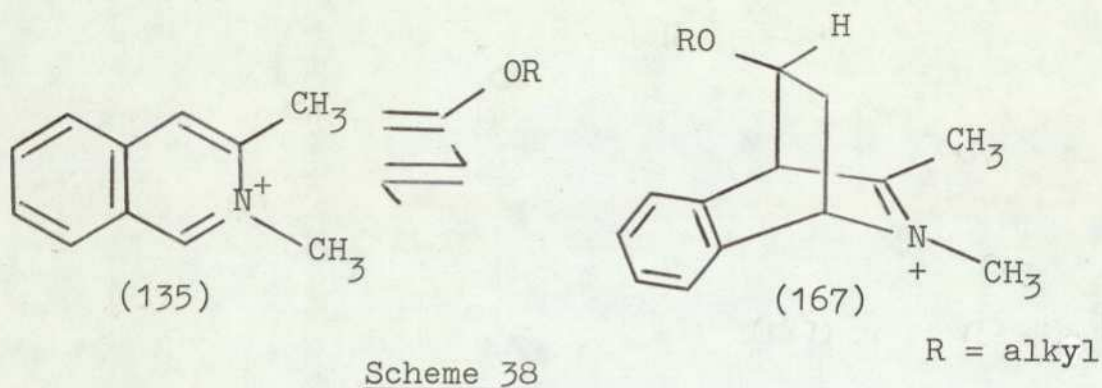


transformed with Grignard-type reagents to give a variety of 4-substituted isoquinolines.

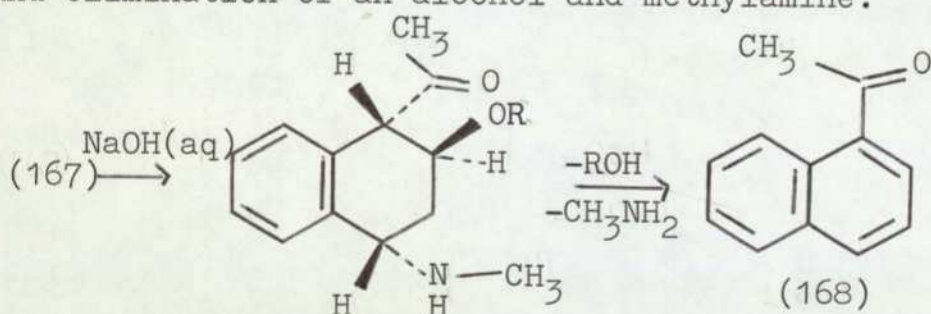
One method of synthesis, noticeable by its absence, is the direct interaction of isoquinoline with very powerful bases. This is probably due to the fact that even bases as weak as Grignard reagents are known to add at the azomethine linkage, though this can only be effected preparatively for allyl magnesium bromide.¹⁵⁵ Other Grignard reagents add only under forcing conditions.¹⁵⁶ Phenyl and *p*-tolyllithium react at C(1) in good yield and even when the 1-position is blocked, e.g. by a bulky phenyl group, aryl addition can still occur.¹⁵⁷ Simple alkyl lithium compounds react almost instantaneously at C(1) and in almost quantitative yields.¹⁵⁸

Alkylation of Isoquinolines

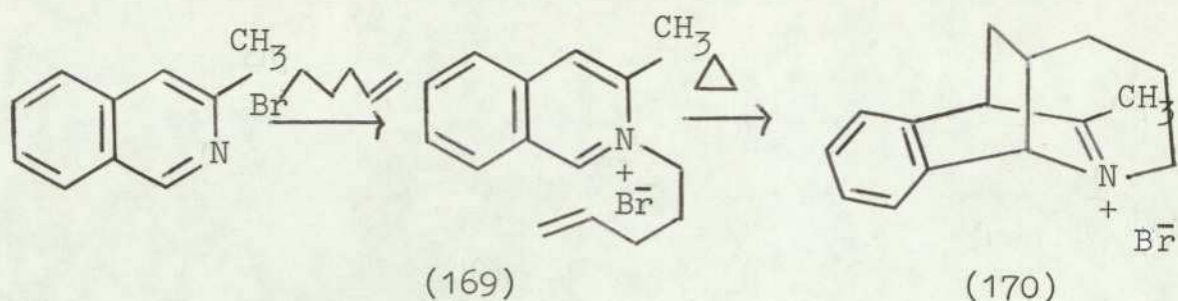
It has been shown that 2,3-dimethylisoquinolinium cations (135) undergo intermolecular cycloaddition reactions at room temperature with simple and electron-rich olefins (Scheme 38).



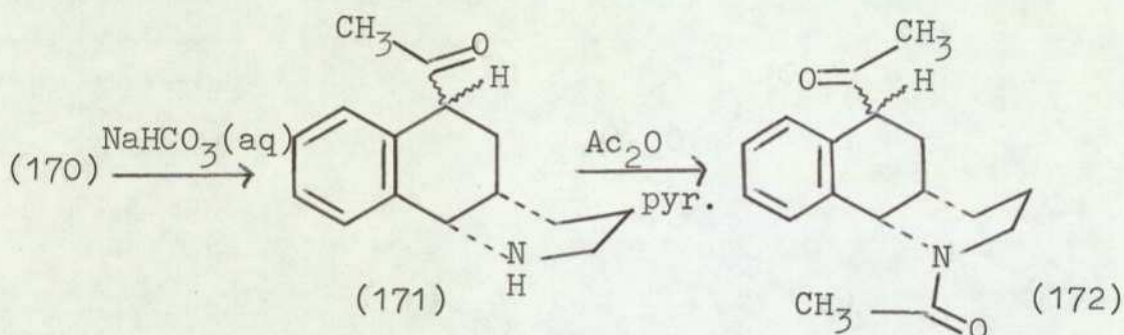
This reaction is both stereospecific and regiospecific as are virtually all known cationic polar cycloadditions involving highly polarisable alkenes (see review).¹²⁵ Hydrolysis of the resultant iminium species (167) yields methyl naphth-1-yl ketone (168) following ring opening and elimination of an alcohol and methylamine.¹²⁴



If the 3-methylisoquinoline is quaternised with pentenyl bromide one has all the requirements, present in the same molecule, for a Diels-Alder cycloaddition. Indeed thermolysis at 145° for 3 hours in acetonitrile converts (169) smoothly and quantitatively to (170).¹⁵⁹

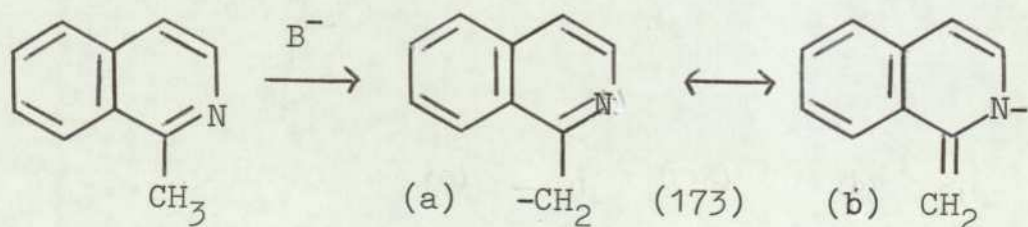


Mild basic hydrolysis opens (170) to the tricyclo-amino ketone (171) which, on acetylation, yields (172). ^1H N.m.r. studies indicate an epimeric mixture, probably about the tertiary ketocarbon.¹⁵⁹



In order to further study of similar reactions it was felt necessary to synthesize more alkenylated isoquinolines. It has been shown that the presence of the 3-methyl group is crucial for the success of these Diels-Alder reactions (see review).

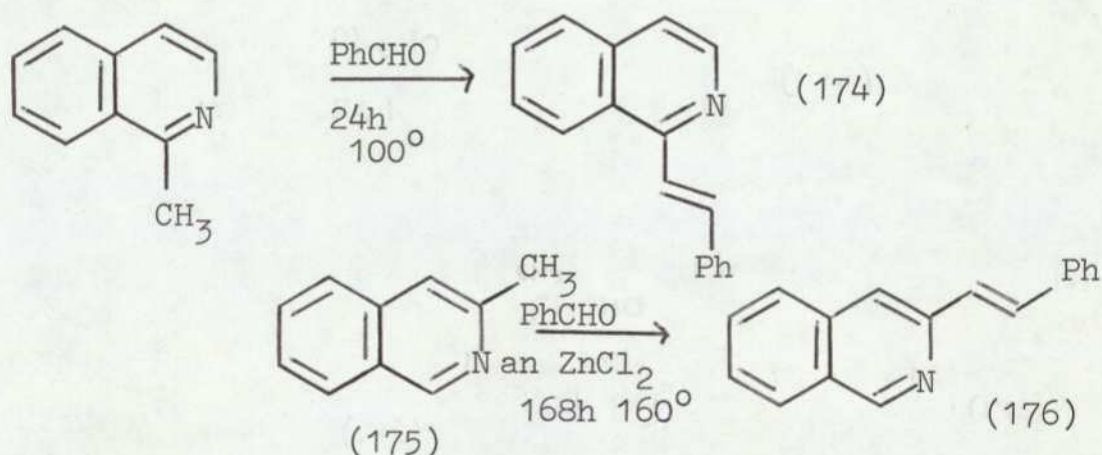
1-Methylisoquinoline can be easily alkylated at the methyl group as a consequence of the assistance provided by the ring nitrogen atom, by directly stabilising the anion formed with moderately strong bases (173).^{160,161}



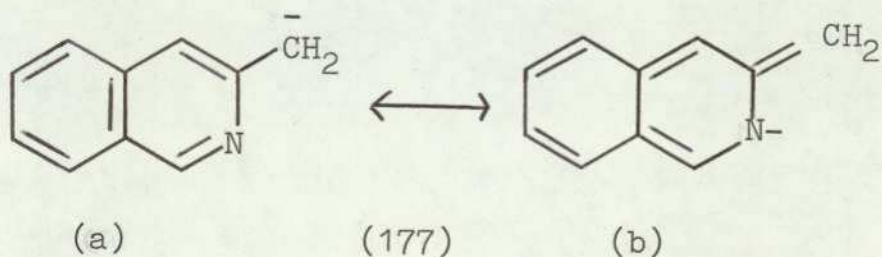
The choice of bases available for anion formation is severely limited for reasons already discussed: serious

losses of substrate can occur by attack of nucleophilic bases at the azomethane linkage.¹⁵⁷ Sodamide can be used with 1-methylisoquinoline, but not for the other methyl isomers because attack occurs at C(1).¹⁶²

The 3-methyl group of 3-methylisoquinoline is also assisted by the ring nitrogen, but here the effect is severely diminished. Thus 1-methylisoquinoline undergoes condensation reactions with benzaldehyde, giving (174) at moderate temperatures (100°) with weak Lewis acids. 3-Methylisoquinoline (175) has to be thermolysed with neat benzaldehyde at 160° for one week in the presence of anhydrous zinc chloride in order to obtain a 3.8% yield of 3-styryl isoquinoline (176).

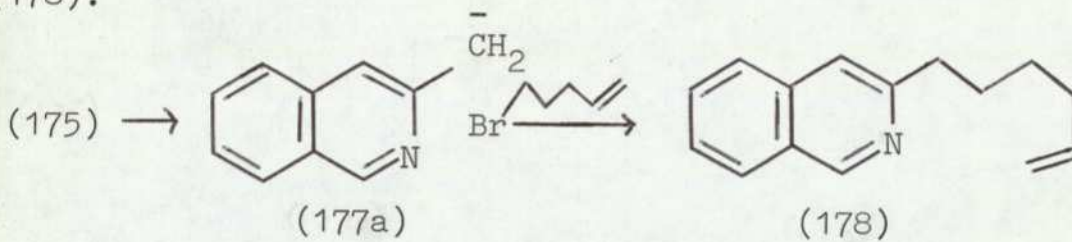


This lack of reactivity is directly due to the loss of resonance energy experienced by (177b) - the canonical structure bearing the negative charge on the nitrogen - compared to the carbanion (177a). The benzenoid ring



resists interference and so the effect transmitted by the nitrogen to the methyl group is minimal. When (175) is quaternised the methyl protons become considerably more acidic and even exchange with D_2O .¹²⁴ Many cyanine-dyes have been formed from the methiodide of (175) condensed with various aldehydes by piperidine.¹⁶³

An attempt to prepare anion (177a) with n-butyl lithium, for reaction with pentenyl bromide at -83° (Scheme 39), gave only the 1-butyl-3-methyl-1,2-dihydro-isoquinoline as shown by 1H n.m.r. study. None of the bromide had been incorporated into the heterocycle to give (178).

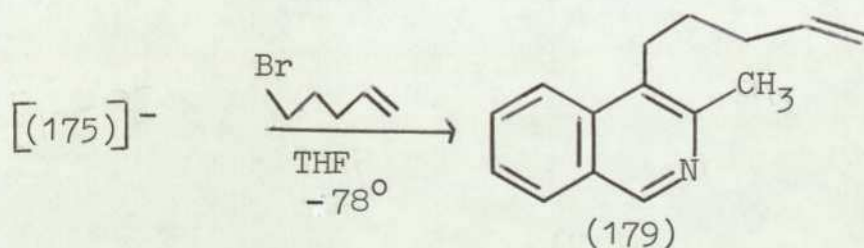


Scheme 39

Lithium diisopropylamide (LiDIA) was prepared from diisopropylamine (DIA) and n-butyl lithium, and addition to (175) caused a light red colouration which deepened considerably on stirring (1 hr). Introduction of n-butyl bromide caused no noticeable change. Analysis of the reaction mixture by t.l.c. showed several new products as well as some regenerated starting material (175). 1H N.m.r. confirmed the presence of (175) in addition to another isoquinoline since two singlets were in evidence at $\delta 9.11$ and $\delta 8.98$ respectively. Both absorptions were assigned to the C(1) protons of each isoquinoline nucleus. Two aromatic methyl signals were manifest at $\delta 2.72$ and $\delta 2.70$, as well as a distorted triplet at $\delta 3.01$. The latter signal

is suggestive of an aryl methylene group, but the two methyls contradict this view. Since much alkyl material was also represented, in an almost indecipherable spectrum, the mixture was deemed too complex to be of preparative value.

Use of lithium isopropylcyclohexylamide (LiICA), as base gave a very clean conversion of (175) to a single alkylated isoquinoline. T.l.c. showed one product less polar than starting material, although separation between the two was very poor. A purified sample of the product gave a ^1H n.m.r. spectrum containing a methyl peak at δ 2.71, a distorted triplet at δ 3.00, a singlet at δ 8.98 and incorporation of a pentenyl group. Five aromatic protons were also present at δ 7.2 - 8.02. The product was thought to be 3-methyl-4-(pent-4-en-1-yl)-isoquinoline (179), i.e. the 3-methylisoquinoline had been directly alkylated at position 4. (Subsequent analysis of the analogous alkylation using butyl bromide indicated a yield of about 10% of the corresponding butyl derivative.) From a preparative standpoint the reaction requires no complex procedures, no exotic starting materials, and gives the product (179) in greater than 50% yield. This yield was not optimised, but even at this level is better



than any previously reported for simple alkylation.

Confirmation of structure (179) was sought from other spectral techniques. The U.V. spectrum of the methiodide

showed the characteristic peaks of an isoquinolinium salt: λ_{max} 224 (43,000), 248 (58,000), 349 nm (6600). Infrared investigation also supported the assignment with peaks in the spectrum of the free base at 3060, 1639, 1623, 1577 and 911 cm^{-1} . Final proof of structure however, was provided by ^{13}C n.m.r. The spectrum of 3-methyl isoquinoline (175) possesses absorptions for C(4) at $\delta 118.4$, and for the 3-methyl at $\delta 24.0$; these are absent in the spectrum of the novel base. In addition, (175) exhibits three-bond coupling between the methyl carbon and the C(4) proton, giving a spectral representation of a wide quartet of narrow doublets (see Fig. 3a).¹⁶⁴ This again is absent in the spectrum of (179), a sharp quartet is observed for the 3-methyl carbon at $\delta 22.1$ indicating that C(4) is not occupied by a proton (see Fig. 3b). No other position of substitution for the alkenyl chain on the isoquinoline ring would give the same result. The ^1H n.m.r. spectrum of (179) did not contain the sharp singlet at $\delta 7.43$ normally associated with the C(4) proton.

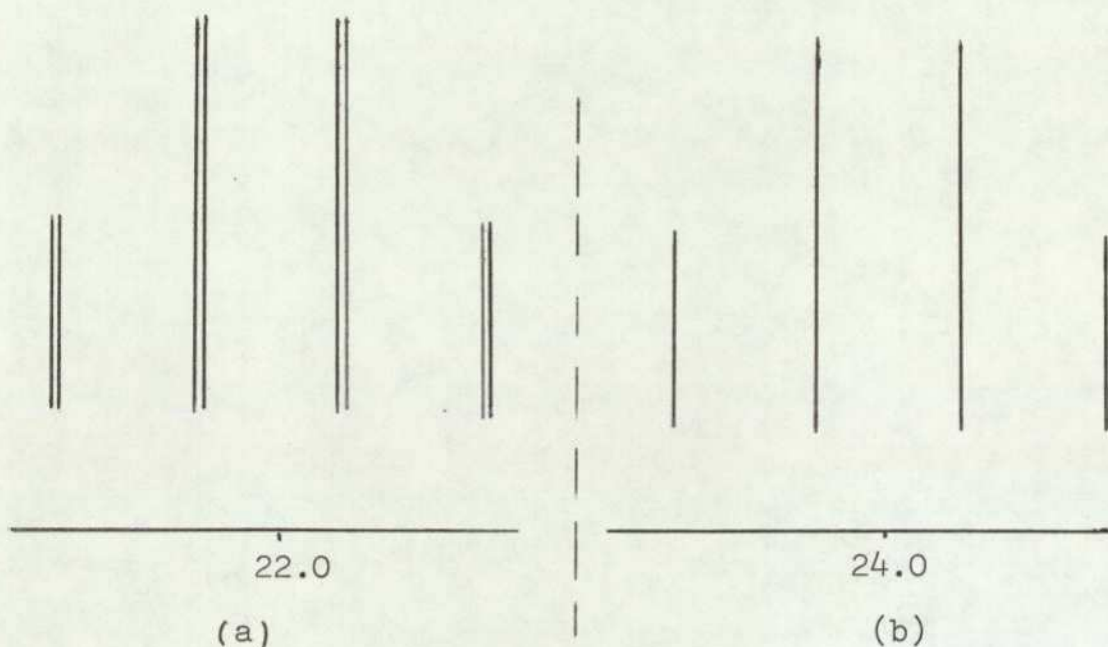
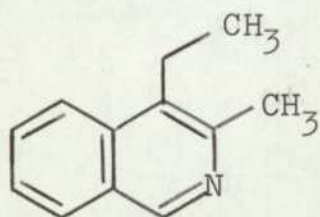
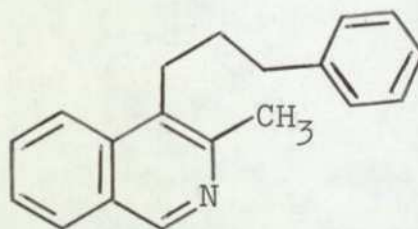


Figure 3. Methyl region of the proton coupled ^{13}C n.m.r. spectrum of 3-methylisoquinoline (175)(a) and 3-methyl-4-(pent-4-en-1-yl)isoquinoline (179)(b).

Similar products were observed using bromoethane and 1-phenyl-3-bromopropane to quench anion (177), giving (180) and (181). Unfortunately separation of (180) and



(180)

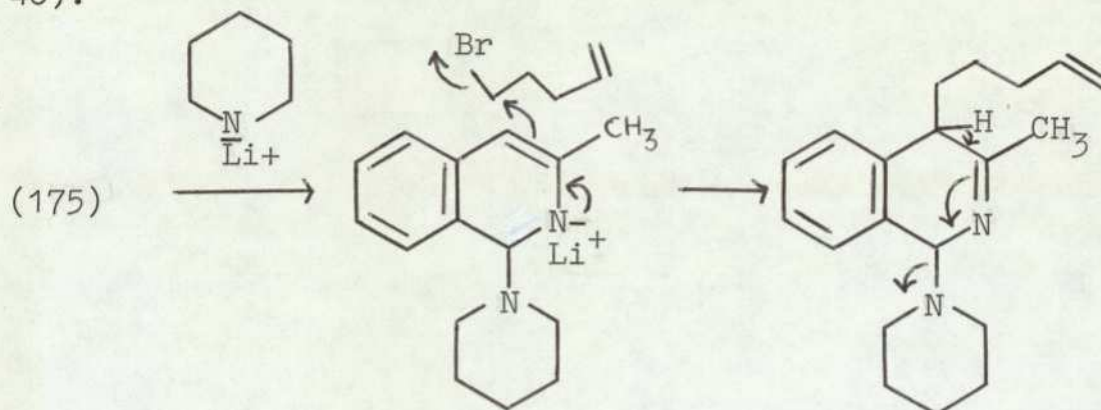


(181)

(181) from regenerated starting material was not achieved since no t.l.c. solvent system employed would effect separation. Both derivatives were isolated as mixtures with (175) and from their ^1H n.m.r. spectra yields were estimated at 41% and 34% respectively. Both compounds exhibited a multiplet at δ 2.99 in their ^1H n.m.r. spectra: a quartet (J 7 Hz) for (180) and a distorted triplet (J 8Hz)

for (181).

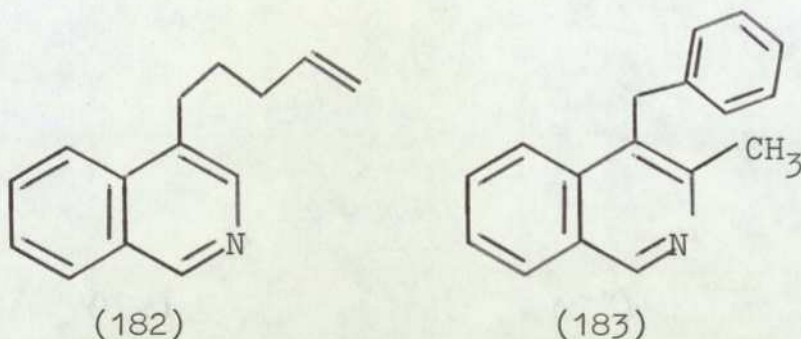
In order to ascertain whether these alkylations were direct, or whether the base was nucleophilically reducing the isoquinoline and causing reaction in an enamine fashion, piperidine was used as a weak amine base (Scheme 40).



Scheme 40

This speculation was not confirmed since the 3-methylisoquinoline was recovered in 95% yield.

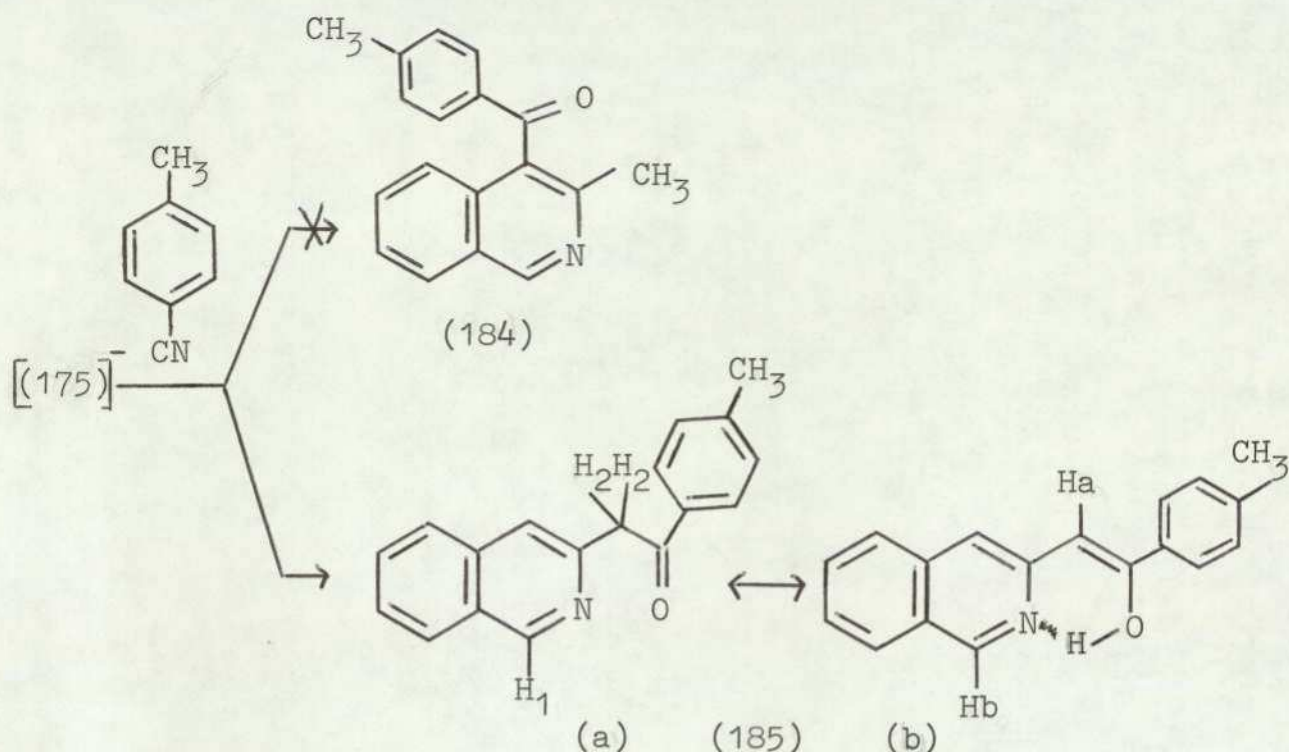
When the parent isoquinoline (151) was treated with LiICA under identical conditions to (175), then quenched with pentenyl bromide, a 33% yield of 4-alkylated isoquinoline (182) was realised.



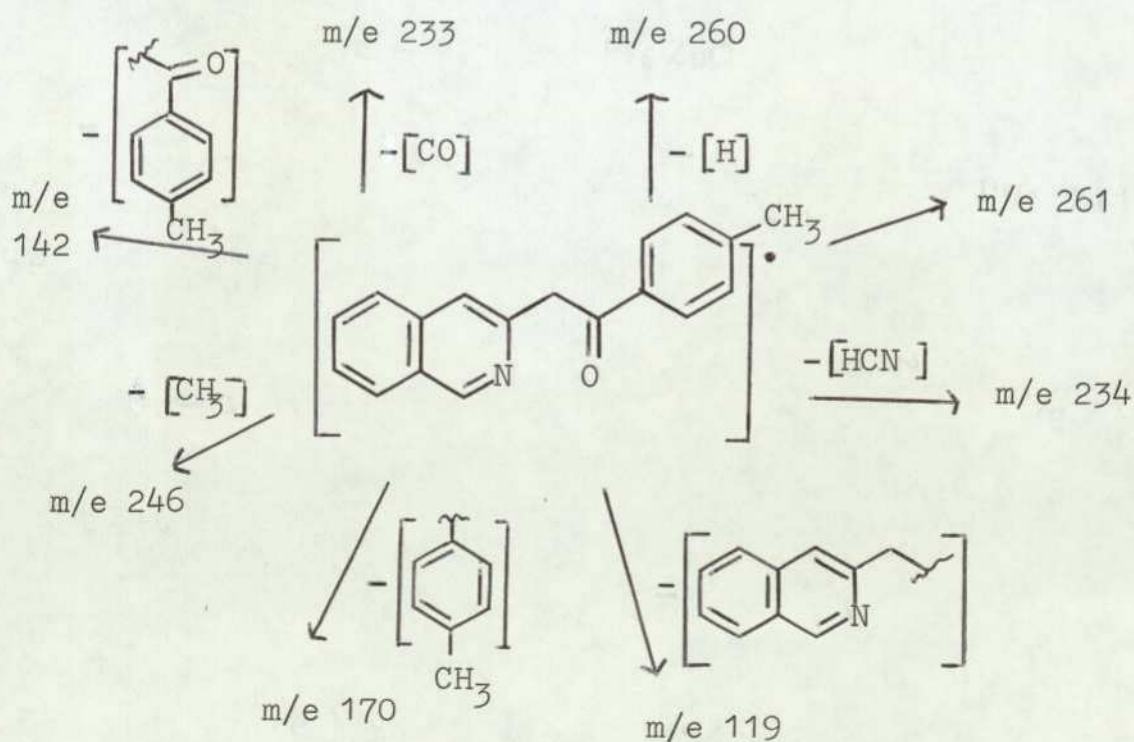
The isoquinolinyl lithium solution was not as intensely red as that for the 3-methyl analogue, even after stirring at -78° for extended periods. Reaction in all cases so far described was not immediate, colour changes occurred at ca. -35° . Alkylation of either anion within this temperature

range did not produce significantly different yields from those at -78° . This was not the case however, when (175) was alkylated in the standard manner with benzyl chloride. At -78° only trace amounts of the 4-benzyl derivative (183) could be observed, the major product was chloroethanobiphenyl. The ^1H n.m.r. spectrum of the reaction mixture clearly indicated the chlorohydrocarbon as a doublet (J 8 Hz) at δ 3.29 and a triplet (J 8 Hz) at δ 5.12.¹⁶⁵ Double irradiation of either signal caused the collapse of the other to a singlet. Repetition of this reaction, alkylating at successively higher temperatures, gave correspondingly larger yields of benzyliisoquinoline (183) until at -20° a yield of 21% was observed. Purification of products again proved difficult, since t.l.c. in many solvent systems could not effect a separation from starting material (175), and microdistillation was impracticable. With 1-phenyl-3-bromopropane only a 2% yield of the corresponding 4-substituted isoquinoline (143, $R = \text{CH}_2\text{CH}_2\text{CH}_2\text{Ph}$) was isolated as a mixture with (151). C(4) Alkylations of (175) with chloroethyl vinyl ether and of 3-methyl-5-nitroisoquinoline with pentenyl bromide were not fruitful.

The transformation of nitrile functions into ketones by treatment with organometallic reagents followed by hydrolysis is well known. Quenching of the anion (177) with *p*-tolylbenzonitrile gave a low yield (11%) of a ketonitrile m.p. $106-110^{\circ}$, but not that expected (184). Its i.r. spectrum contains an absorption at 1678 cm^{-1} , and the ^1H n.m.r. spectrum of this novel compound indicates that the 3-methyl function had been completely consumed, leaving just the tolyl methyl as a singlet at δ 2.38. A two-proton



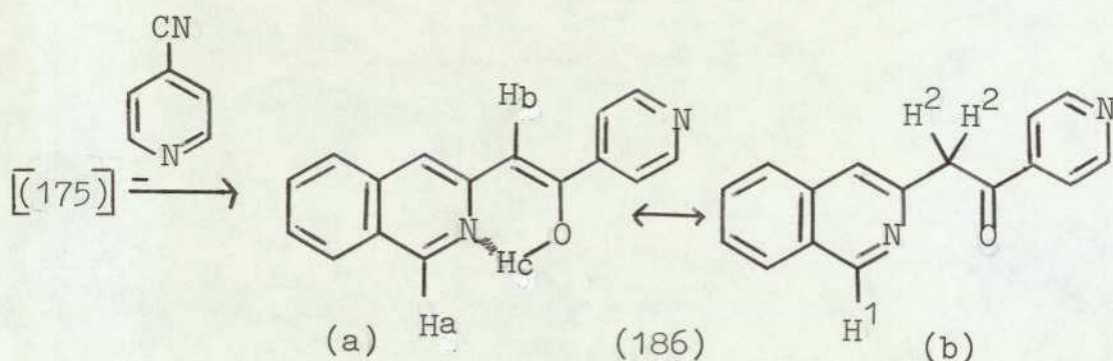
singlet now exists at δ 4.60 (H_2) and a one-proton singlet at δ 9.16 (H_1). Structure (185a) fits the data; there is also evidence for the presence of some of the tautomer (185b), since two small singlets occur at δ 6.17 and δ 9.03 representing H_a and H_b respectively. The majority of support for structure (185a) arises from its breakdown pattern when subjected to mass spectral analysis (Scheme 41).



Scheme 41

The high resolution mass measurement for the molecular ion confirms the composition of the keto-isoquinoline. The low yield of product (185) is explained by competition between the *p*-tolyl methyl, and the nitrile for the anion (177).

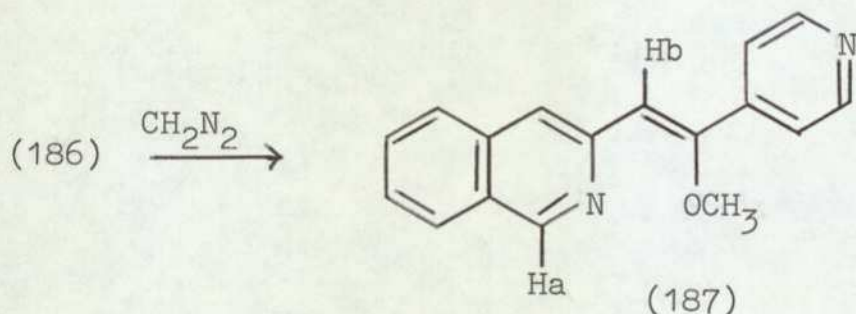
Reaction at the 3-methyl of (175) is similarly noted with 4-cyanopyridine. In this case a rich yellow crystalline product, m.p. 137-8°, was isolated in 34% yield (186). In deuteriochloroform the keto-enol tautomerism was once again exhibited, however the presence of the pyridine nitrogen was enough to maintain the equilibrium almost entirely on the enol side. Again all spectral and analytical data were consistent with these structures (186a) and



(186b). The ^1H n.m.r. spectrum contains two singlets δ 6.35 and δ 9.12, Hb and Ha respectively, the latter has a small accompanying singlet H^1 , δ 9.22. Another singlet at δ 4.59, H^2 , is visible, in addition to a broad exchangeable enolic absorption at δ 14.33. Two pyridyl protons, part of an AX type spectrum at δ 8.67 and δ 8.81, also show duplicity, suggesting an isomeric mixture. The rest of the spectrum is made up of complex aromatic resonances. Infrared analysis shows no carbonyl peaks in the 1680 cm^{-1} region. Two major bands at 1621 and 1596 cm^{-1} correspond to the absorptions for the alkenyl link and the hetero-

aromatic ring system. Structure (186a) is written in the trans-form implying a large intramolecular hydrogen-bonding effect. This view is substantiated by the appearance of a weak, broad band between $3440 - 2260 \text{ cm}^{-1}$, in the i.r. spectrum, typical for stretching modes such as this. The low intensity is also standard.¹⁶⁶ The U.V. spectrum contains several peaks with very large extinction coefficients, notably at 232 (87,000) and 348 nm (115,000).

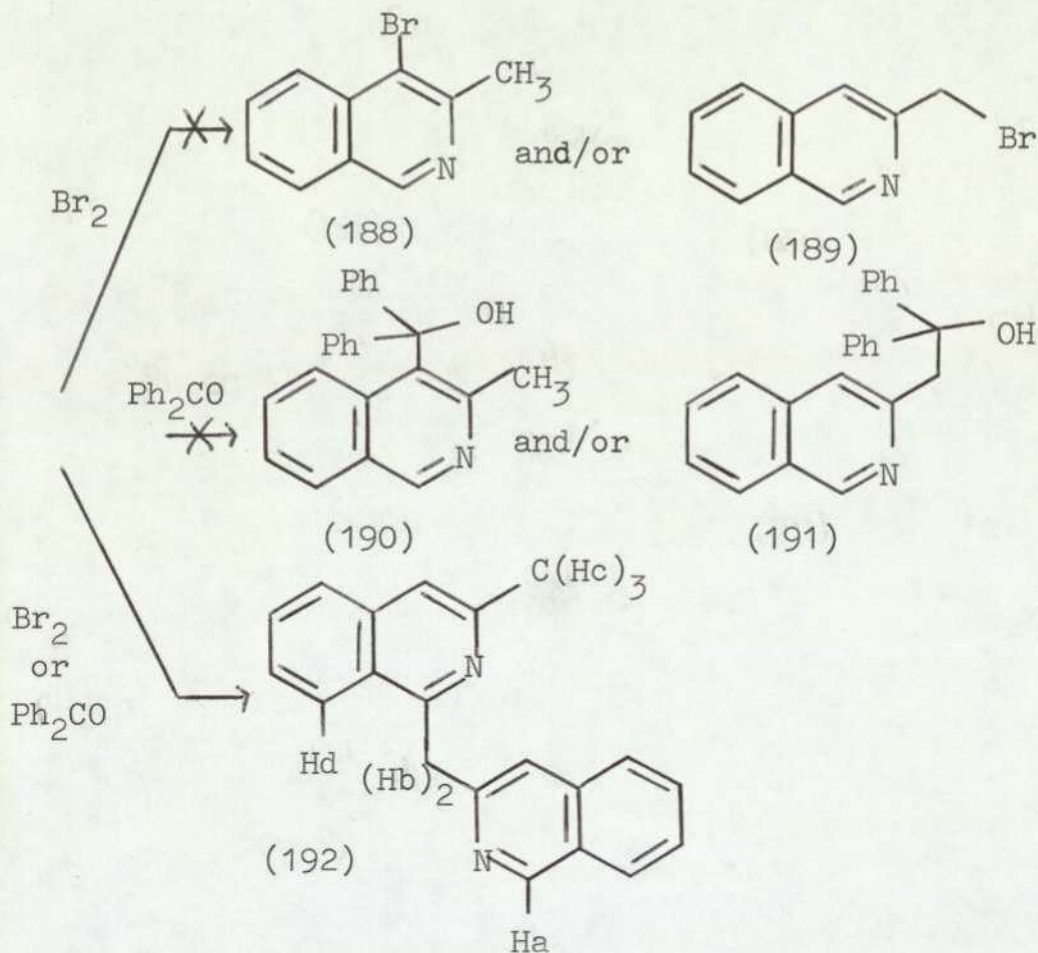
Treatment of (186) with an excess of diazomethane gave a fairly clean conversion to a single compound, (187), whose ^1H n.m.r. spectrum is now devoid of the enolic proton; still present however, are peaks at $\delta 6.10$ and $\delta 9.24$ for Hb and Ha respectively of (187). A new methoxyl absorption at $\delta 3.78$ is also evident.



When isoquinoline (151) itself was treated with LiICA then quenched with p-cyanopyridine an instant reaction occurred at -78° . The red anion swiftly changed through green to black, and work-up indicated consumption of much of the starting material. The only compounds in evidence were intractable tars in addition to some isoquinoline (151). In another attempt the reaction was terminated at its green stage, giving back mainly the isoquinoline (151) and the nitrile. A little polymeric material was also observed, no adducts were isolated.

A further novel reaction was noted when anion (177)

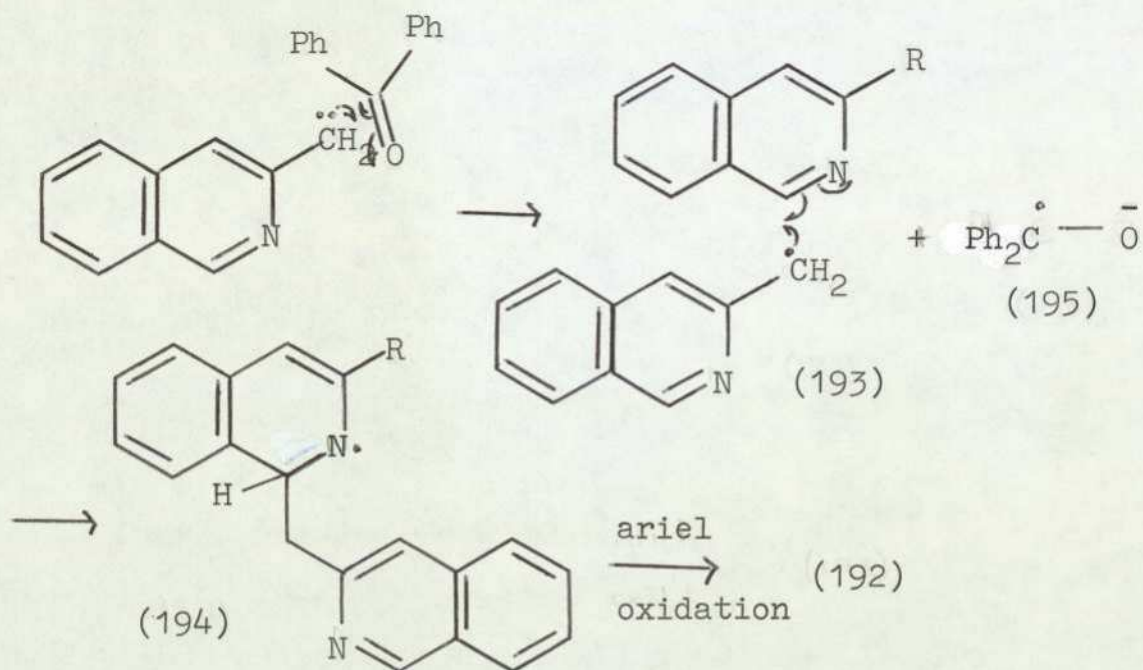
was treated with bromine or benzophenone. The expected products (188), (189), (190) and (191) were not observed, instead a dimeric species was formed in good yield (192).



The spectral data for the diisoquinolyl methane (192) are in accordance with the structure assigned. The ^1H n.m.r. spectrum shows a three-proton singlet Hc, δ 2.74; a two proton singlet Hb, δ 5.00; and a one proton singlet Ha, δ 9.14. In addition to a nine-proton aromatic multiplet a doublet is evident at δ 8.20 (J 9 Hz). This is assigned Hd, and is sterically deshielded from its usual resonance position at about δ 7.90 by the peri-interaction experienced from the adjacent $\text{C}(\text{Hb})_2$ group. Also, deshielding of Hd probably occurs owing to the close proximity of the lower isoquinoline moiety as it rotates around the

$C(Hb)_2$; H(8) of 1-alkenylisoquinolines usually absorb at about $\delta 8.05$. I.r. analysis is not diagnostic in this instance, since only aromatic hydrocarbon multiple-bond absorptions are prominent in the spectrum. Strong bands exist at 748 and 874 cm^{-1} corresponding to four adjacent aromatic hydrogen atoms and one single aromatic hydrogen atom respectively. In the U.V. spectrum typical monomethyl isoquinoline peaks are evident 220 (82,600), 272.5 (8050), 280.5 (6350), 328 nm (7250). Mass spectral data are in accordance with structure (192). In separate experiments, quenching the anion (177) with bromine, the reaction mixture coloured yellow after only 30 sec. Whether worked-up at this point or stirred overnight, a 70% yield of the dimer was observed.

The reaction is believed to involve radicals with bromine and radical anions with benzophenone (Scheme 42).^{167,168}

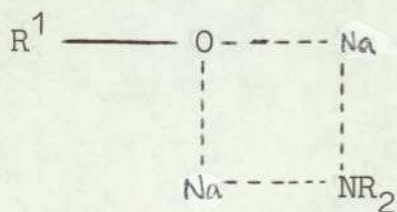


Scheme 42

The mechanism as it stands (Scheme 42; $R = CH_3$) implies that anion formation must, of necessity, be incomplete at

quenching. If radical (193) were to attack anion (177) then radical anion (194; $R = CH_2^-$) would be expected to be unable to participate in ketyl (195) formation. The reaction would thus have to terminate at this point, and work-up provide the required oxidation. The non-observation of trimeric (175) testifies to this view if the reaction proceeds via radical anion (194; $R = CH_2^-$). The length of time allowed for formation of lithioisoquinoline (177) did not seem to be of significance; no improvements in yields were noted following reaction of (177) with simple alkyl halides, after extended periods of stirring at -78° or at temperatures up to -40° . The anion formation is almost certain to be an equilibrium and therefore subject to equilibrium conditions. Anion production may therefore not go to completion.

Recently it has been demonstrated that addition of certain tertiary alcohols to appropriate sodamide reactions, in well defined ratios, is able to increase yields from zero to respectability.¹⁶⁹ The generality of this 'reaction doctoring' was demonstrated on standard benzyne preparation/quenching reactions and various trityl alkylations.¹⁶⁹ It was observed that maximum enhancement was obtained with ratios of amide to alcohol of 2:1. The structure of the reacting species has been tentatively assigned (196), and is denoted a 'complex base'; they are usually formed in situ.



(196)

R_1 = tertiary alkyl

R = H

Since sodamide is unsuitable for reaction with isoquinoline,¹⁶² the base was prepared from n-butyl lithium and ICA in the presence of one-half of a molar equivalent of t-butyl alcohol. The isoquinoline (151), when added, at -78° , caused a colour change to a light orange, i.e. not the red of the reaction mixtures previously described. Alkylation with pentenyl bromide and subsequent work-up gave the isoquinoline (182) in 28% yield. Repetition of the reaction with one-half of an equivalent of the lithium amide in excess, in place of the alcohol, gave virtually the same yield of (182) (25%). The only real difference observed was the overall cleanliness of the former reaction since much tar formation accompanied the other. No starting material (151) was recovered from either reaction. The use of complex bases of this type is therefore shown to be slightly disadvantageous in this instance, compared to the normal alkylation method. Although a marked colour difference was noted between the two alkylations described above, this in no way proves that a 'complex base', as described by Caubère,¹⁶⁹ was present. The bulk of the N-alkyl groups of the amine may have influenced the ability of complex (196) to form. Caubère does not discuss alkylations involving substituted sodamides.¹⁶⁹

Discussion of the mechanism of
alkylation of isoquinolines.

The electrophiles used in attempts to alkylate isoquinoline (151) and, more especially 3-methylisoquinoline (175) can be grouped into three categories: those that do not give an adduct, those that react within 30 sec of addition of the electrophile, and those which react on warming of the reaction mixture after addition of the electrophile. The first class includes dimethyl maleate, 2-chloroethylvinyl ether, ethylchloroformate, dimethyl formamide, 3-phenylpropanal, trimethyl silyl chloride, carbon dioxide and dimethyl sulphate. Several of these substrates are of interest since they have been reported to react with 4-isoquinolyl lithium in other hands.^{142,153,154} Another vitally important point is the description given by Gilman,¹⁵³ and Dyke¹⁴² of the anion. Formed from a halogen-metal exchange of *n*-butyl lithium with 4-bromoisoquinoline, the anion in both cases is described as being a 'bright yellow colour'.¹⁴² In all cases except that of the complex base previously mentioned, the anion of both (151) and (175) was a deep red colour, the latter deeper in intensity than the former. Dyke has already described the reaction of the anion of (151) with DMF as giving a 70% yield of the 4-formylisoquinoline (143, R = CHO), and with various aldehydes - including 2-methylpropanal - giving yields of the corresponding tertiary alcohol (164), in yields consistently greater than 50%.¹⁴² Gilman has performed the carbonation of the anion of (151), obtaining a 46% yield of the 4-carboxylisoquinoline (143, R = CO₂H).¹⁵³

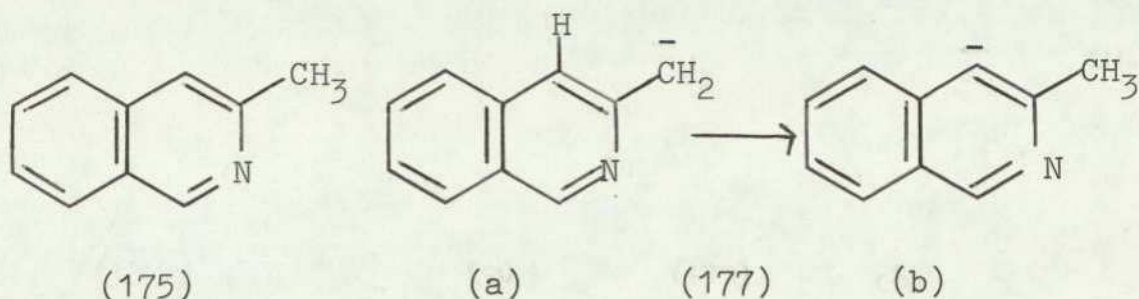
Perhaps the most unanticipated non-reaction was the

total lack of incorporation of deuterium into (175) from D_2O . In an attempt to gauge the percentage conversion of (175) to (177) a solution of the anion was quenched in standard fashion with D_2O .¹⁷⁰ The red solution changed to yellow in seconds and subsequent work-up yielded greater than 90% of the original heterocycle. Also in evidence was a small amount of tarry material which defied spectral analysis. Isoquinoline (151) also did not incorporate deuterium when treated similarly.

There exists precedents in the literature for non-incorporation of deuterium by dianions, especially those generated by hindered amine bases.^{171, 172} Evidence has been produced which indicates that complex formation occurs when o-toluic acid is treated with two equivalents of LiDIA. Removal of all volatile material after preparation of the dianion leaves a red gum, the 1H n.m.r. spectrum of which contains modified resonances for the toluate, and for the DIA groups, in a 1:1 ratio. Treatment of the complex with n-butyl bromide gives good yields of o-pentylbenzoic acid. These results may be understood if the carbanionic intermediate is at least weakly associated with the DIA and that proton transfer on acidification (D_2O) is a complicated process in which the DIA proton is transferred exclusively to the carbanionic site by a non competitive process.¹⁷¹

Pfeffer has shown since, that for this reaction exchange does occur to a very minor degree. He noted only 6% deuterium incorporation into o-toluic acid.¹⁷²

The differences noted between the anion of (175) prepared by metal-halogen exchange or with LiICA, must be derived from the ability of the latter to promote complex formation.



The dissimilarity of colour between the two species can be explained thus, and also the differing reaction paths taken by each with the same electrophile. It would be best to consider both structures (177a) and (177b) as being able to associate with a molecule of ICA.

For those reactions that gave isolable products, the site of alkylation observed can be explained by considering the thermodynamic and kinetic properties of the monoanion of (175). At -78° the most weakly bound protons of the molecule are those of the C(3)-methyl group and it is one of these that is abstracted by LiICA, leading to (177a). Any electrophile that reacts at this depressed temperature with (177a) will therefore react at the methyl. This was observed for *p*-toluanitrile and 4-cyanopyridine. The anion (177a) cannot be very nucleophilic, since addition of alkyl bromides at this temperature has no effect whatsoever. On warming however, abstraction of the C(4) proton of unreacted isoquinoline (175) by (177a), or simple internal rearrangement of the anion (177a) leads to the thermodynamically more stable derivative (177b). The greater proton abstracting ability of (177a) over (177b) was demonstrated during the preparation of 3-methyl-4-benzylisoquinoline (183) from benzyl chloride. Anion (177b), once formed, can react with the alkyl halide at the more elevated temperature to give products of C(4) alkylation. A simple energy profile for the formation of the anions would resemble figure 4.

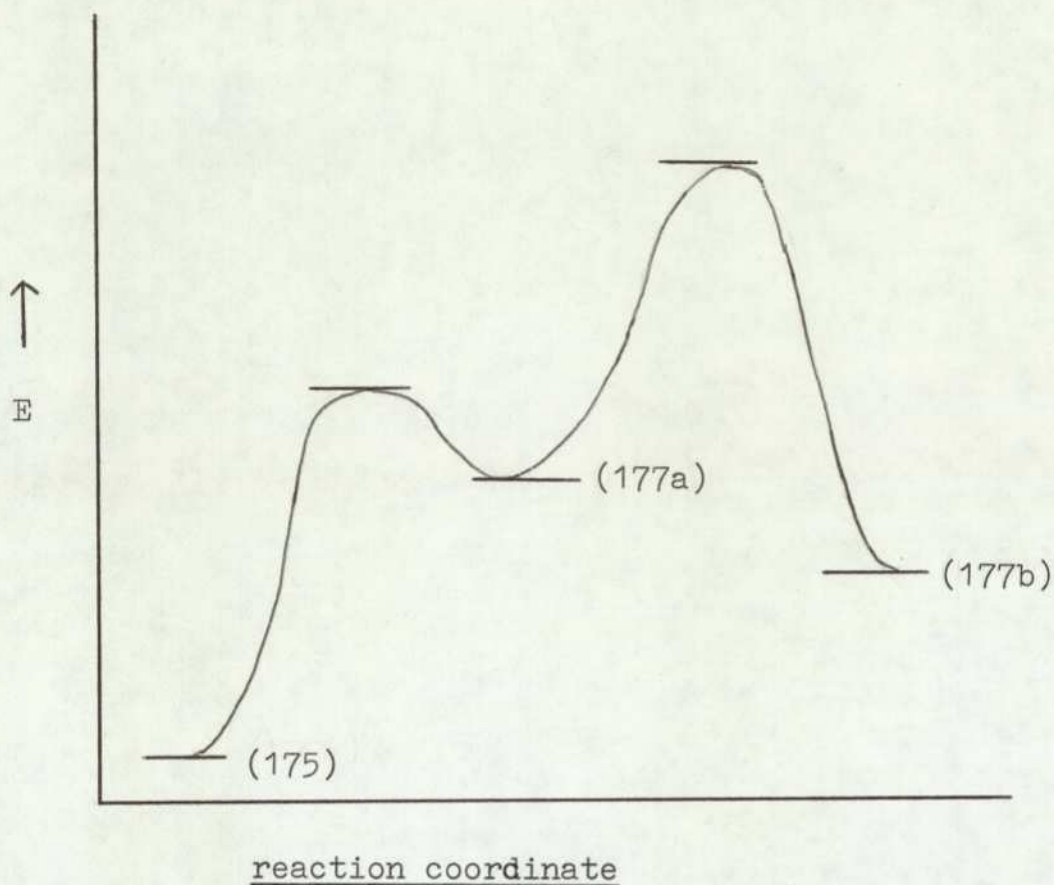


Figure 4 Energy profile for the formation of the anions
of 3-methylisoquinoline (175) with LiICA

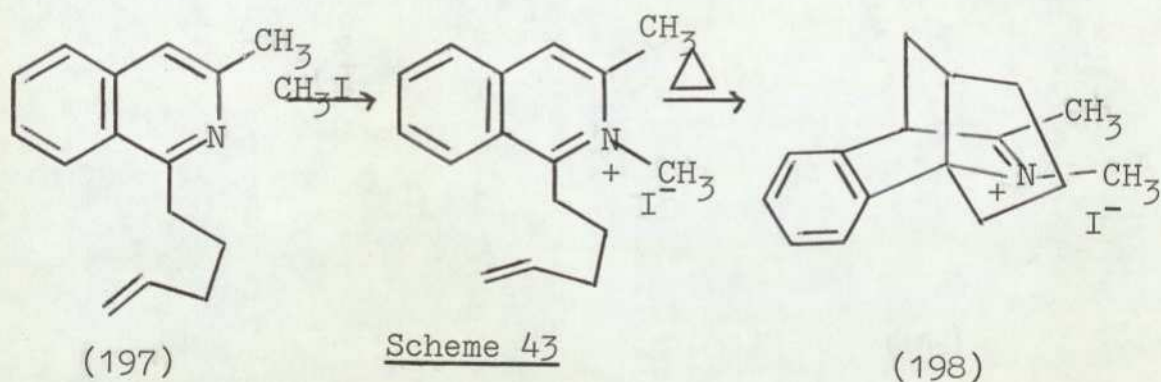
The conversion of (177a) to (177b) may be effected via the hindered base which could be behaving as a proton carrier. Following formation of (177a), raising of the reaction mixture temperature could regenerate the starting isoquinoline (175) and the hindered lithium base. Reaction could again occur between (175) and the LiICA, but this time removing the C(4) proton to give (177b). In this way proton transference could be simply effected.

CHAPTER 6

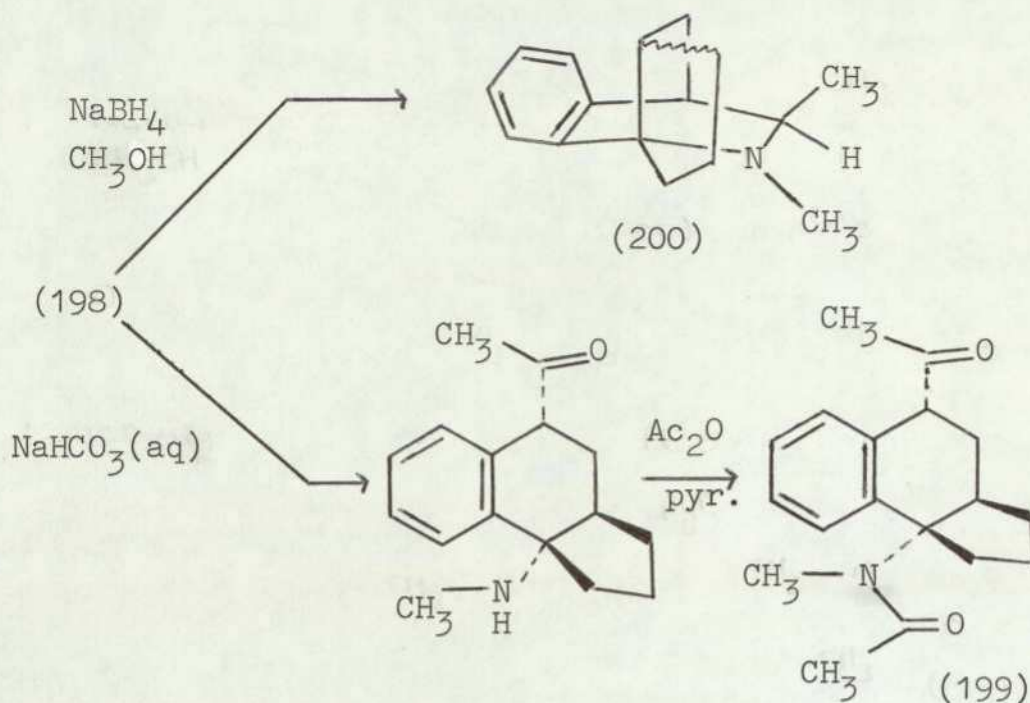
Preparation of 1-alkenyl-3-methylisoquinolines.

The formation of isoquinolines containing uncommon alkyl substituents by classical ring closure methods, e.g. Bischler-Napieralski, Pictet-Gams and Pomeranz-Fritsch syntheses, presents serious synthetic problems. Frequently the available precursors for the cyclisation require considerable modification in order to introduce the unusual substituents needed for the isoquinoline, and this can often only be achieved in low yield after multi-stage reaction sequences. The preparation of 1-pentenyl-3-methyl-isoquinoline (197) presented such a problem.

Interest was centered on this substitution pattern, since quaternisation, with iodomethane would give a substrate potentially capable of undergoing an intramolecular cycloaddition (Scheme 43).



Hydrolysis and acetylation, or reduction of the primary adduct (198) would then lead to structures (199) and (200) of interest as possible pharmaceuticals (Scheme 44).



Scheme 44

The 3-methyl substituent has previously been shown to be necessary in isoquinolinium cycloadditions, to ensure the stability of the adduct.¹²⁵

The most attractive approach to the synthesis of (197) seemed to be the transformation of readily available, and inexpensive 3-methylisoquinoline with an organometallic derivative of pentenyl bromide.

It is known that allyl magnesium bromide gives 1-allylisoquinoline, although low yields are obtained for other alkyl Grignard reagents.¹⁵⁵ Alkylation has been achieved only under the forcing conditions of sealed tube reactions at high temperatures.¹⁵⁶

An attempted reaction of 3-methylisoquinoline with pentenyl magnesium bromide, followed by oxidation of the reaction mixture with nitrobenzene only gave recovered starting material.

Organolithium reagents are known to be reactive towards azoaromatic heterocycles, affording the corresponding

substituted 1,2-dihydro derivatives,^{153,175} although variable yields are often encountered.¹⁷⁴

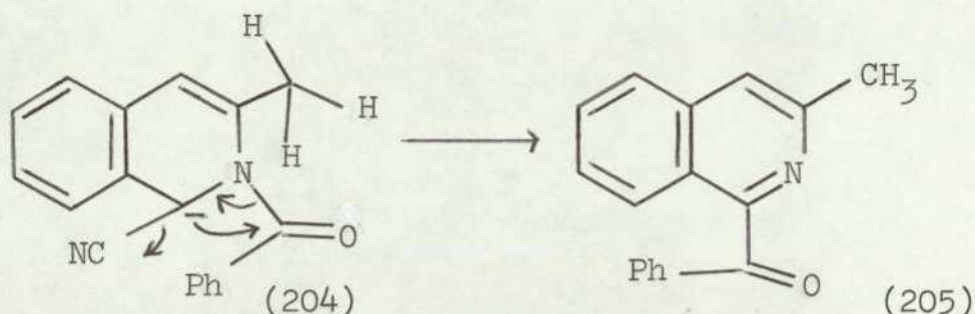
The method of Gilman,¹⁷⁴ was used for the preparation of pentenyl lithium from the bromide, and metallic lithium, in dry ether. The reaction mixture slowly acquired a deep-blue colouration, as it was allowed to warm from -10° and as the organo-lithium reagent formed. On addition of the reagent to an ethereal solution of 3-methylisoquinoline a deep-red mixture formed, which on work-up, including nitrobenzene oxidation,¹⁵⁵ showed conversion to (197) of less than 5%. An excess of the organo-metallic reagent also gave very little of the alkylated isoquinoline. When all of the reagents were scrupulously dried and redried almost no adduct formation was still observed. The stoichiometry of the reaction did not seem to be of importance.

A further method of preparation of (197) seemed to be offered via the alkylation of isoquinoline Reissert compounds. It is known that the Reissert compounds of isoquinoline (201, $R^1 = H$) are capable of supporting a carb-anion at C(1) when treated with sodium hydride in DMF.¹⁷⁵⁻¹⁷⁷ Several reactions with alkyl halides for these anions have been reported giving Reissert compounds (202, $R^1 = H$).¹⁷⁵⁻¹⁷⁷ Treatment with aqueous sodium hydroxide,¹⁷⁶ or methanolic sodium methoxide,¹⁷⁷ gives the 1-substituted isoquinoline (203, $R^1 = H$) in very high yield.

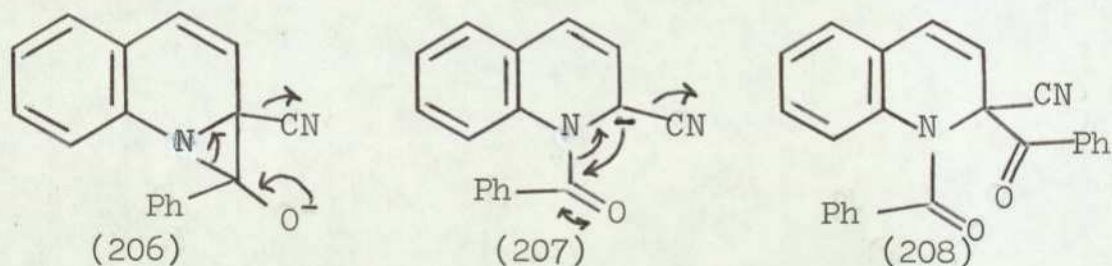


Using the method of Dyke,¹⁷⁷ a solution of (201, R¹ = CH₃) in DMF was added to a slurry of sodium hydride in DMF. Pentenyl bromide was added after the evolution of hydrogen had ceased. Subsequent work-up yielded a new solid, m.p. 100-1^o, spectral analysis of which showed it to be 1-benzoyl-3-methylisoquinoline (205), formed in 68% yield. Alkylations of Reissert compounds sometimes produce small amounts of derivatives of this type (205) as by-products, but rarely as the major product! It was noticeable that during the addition of (201, R¹ = CH₃) the red colour of the anion formed and then quickly dispersed, as if it was being consumed. Anion formation was therefore repeated in the presence of the pentenyl bromide, by adding the sodium hydride to a DMF solution of (201, R¹ = CH₃). Identical colour changes were observed and (205) was again isolated in 68% yield. The latter reaction was then repeated at -40^o. The addition of hydride had no effect and so the solution was allowed to warm slowly to room

temperature. The red colour slowly formed and was retained, but analysis of the reaction mixture again showed the isoquinoline (205) in 65% yield.



This rearrangement has been investigated as part of a study of the interaction of Grignard reagents with quinoline Reissert compounds. It has been proposed that either an intramolecular process was occurring via intermediate (206),¹⁸¹ or (207),¹⁸² or that an intermolecular mechanism approximating to chain reaction was taking place, involving 1,2-dibenzoyl-1,2-dihydroquinaldonitrile (208) as an intermediate.

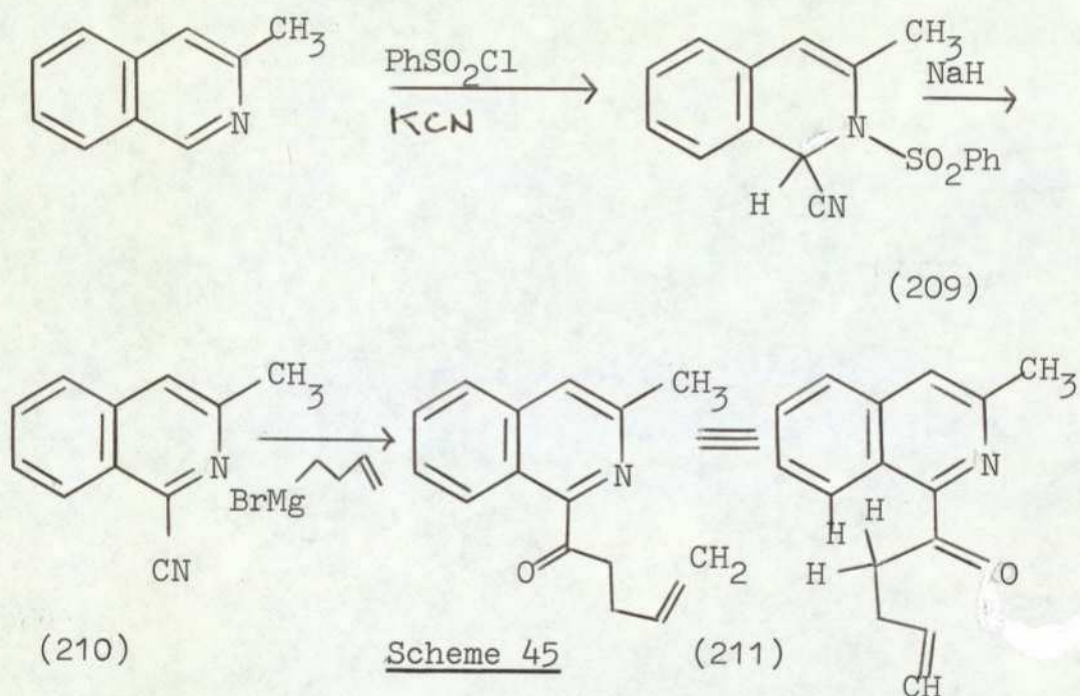


The controversy was settled by McEwen et al. who performed a scrambling reaction between two different quinoline Reissert compounds which possess virtually identical rate data.¹⁸⁰ One of the substrate benzoyl functions was labelled with ^{14}C ; all of the radioactivity remains associated with the nucleus that it began with, demonstrating the intramolecular nature of the rearrangement.

Literature reports describe the Reissert anion,

prepared at low temperatures as stable, the transference of the benzoyl function occurs as the reaction mixture warms to room temperature. The initial presence of the 3-methyl substituent must force the benzoyl function from its normal orientation and closer to the localised anion (204). The rearrangement appears to be instantaneous even at 0°.

Another synthetic route was therefore adopted that would give the ketone (211) instead of the 1-pentenyl-3-methylisoquinoline (197) (Scheme 45).



The synthesis of cyanoisoquinoline (210) by this method is described by Wefer *et al.*,¹⁸³ who prepared the Reissert analogue (209) from phenylsulphonyl chloride and 3-methylisoquinoline. The ^1H n.m.r. spectrum of (209) contains a three-proton singlet at $\delta 2.36$ and a nine-proton multiplet $\delta 6.56$ - 7.66 . A broad, and a sharp singlet, $\delta 6.20$ and $\delta 6.40$ complete the spectrum. Double irradiation of the methyl peak causes the broad singlet to sharpen considerably. As usual the i.r. spectrum did not contain the nitrile band,

but the sulphonamide absorption is evident at 1360 and 1163 cm^{-1} . The conjugated olefin absorbs at 1637 and 988 cm^{-1} .

Heating (209) under reflux in xylene with sodium hydride, as directed, achieved nothing,¹⁸³ since the Reissert analogue (209) was recovered intact. If instead the anion formation was conducted in DMF, liberation of hydrogen was instantaneous and a 63% yield of (210), m.p. 102-4°, (lit. 103-4°)¹⁸³ was realised. The ^1H n.m.r. spectrum consists of a three-proton singlet δ 2.76, a four-proton multiplet δ 7.56-7.87 and a one-proton multiplet δ 8.10-8.34. The singlet corresponding to C(4)-H can be noted in the four proton multiplet at δ 7.70. The nitrile absorption in the i.r. spectrum is evident at 2234 cm^{-1} . It appears that the phenylsulphonyl group is such a good leaving group that the pseudo-Reissert compound (209) cannot support an anion. Restoration of the heterocycles aromaticity occurs with the ejection of the phenylsulphinate anion.

Reaction of cyanoisoquinoline (210) with but-3-en-1-yl magnesium bromide, formed in THF from but-3-en-1-yl bromide, gave a 58% yield of ketone (211) as a pale yellow mobile oil, after acid hydrolysis of the intermediate imine. The ^1H n.m.r. spectrum of the reaction mixture was deceptive, since, at a glance, it closely resembled that of a mixture of (210) and butenyl bromide. The shift in resonance position of 1.15 p.p.m. for the methylene group adjacent to the ketone function is quite considerable. Usually absorbing at ca. δ 2.40 it occurs at δ 3.45 as a triplet (J 7 Hz). This is thought to arise from the

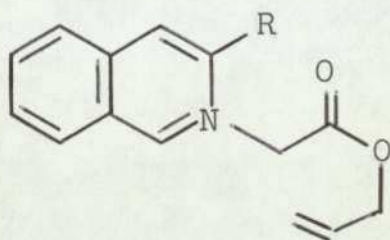
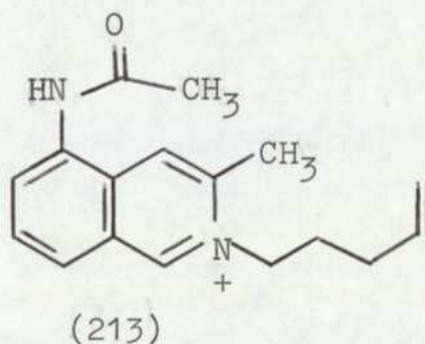
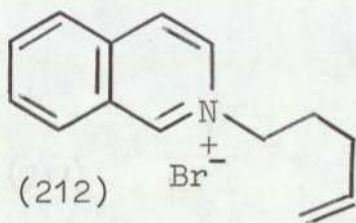
steric environment of these protons due to the close proximity of the C(8) proton, and indeed the latter proton, δ 8.68-8.86, shows a shift of 0.52 p.p.m. from the resonance position for the corresponding proton in cyanoisoquinoline (210). The i.r. spectrum contains the keto absorption at 1693 cm^{-1} and that for the vinyl group at 1639 cm^{-1} .

CHAPTER 7

Intramolecular cycloaddition reactions of isoquinolinium salts

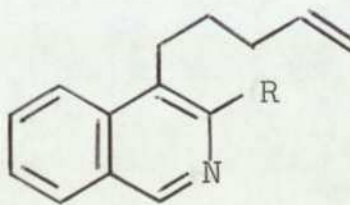
Isoquinolinium salts have been shown to undergo intramolecular Diels-Alder reactions with electron-rich olefins, including vinyl ethers¹⁸⁴ and cyclopentadiene.¹⁸⁵ (See review). An extension of this process has been the intramolecular cycloaddition of pentenyl isoquinolinium salt (169) to give adduct (170), which is capable of further transformation.¹⁵⁹

In an attempt to discover other isoquinolinium systems that would also intramolecularly cycloadd several suitably substituted precursors were prepared (212)-(215), (179), (182), (216), (211).



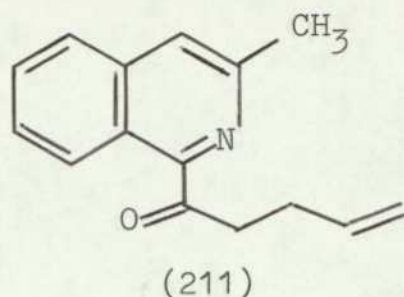
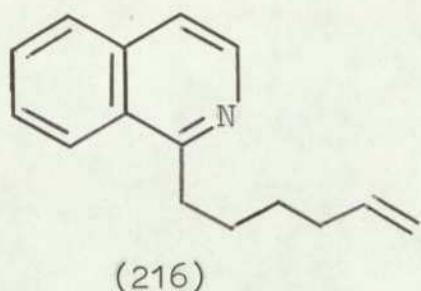
(214) R = H

(215) R = CH₃

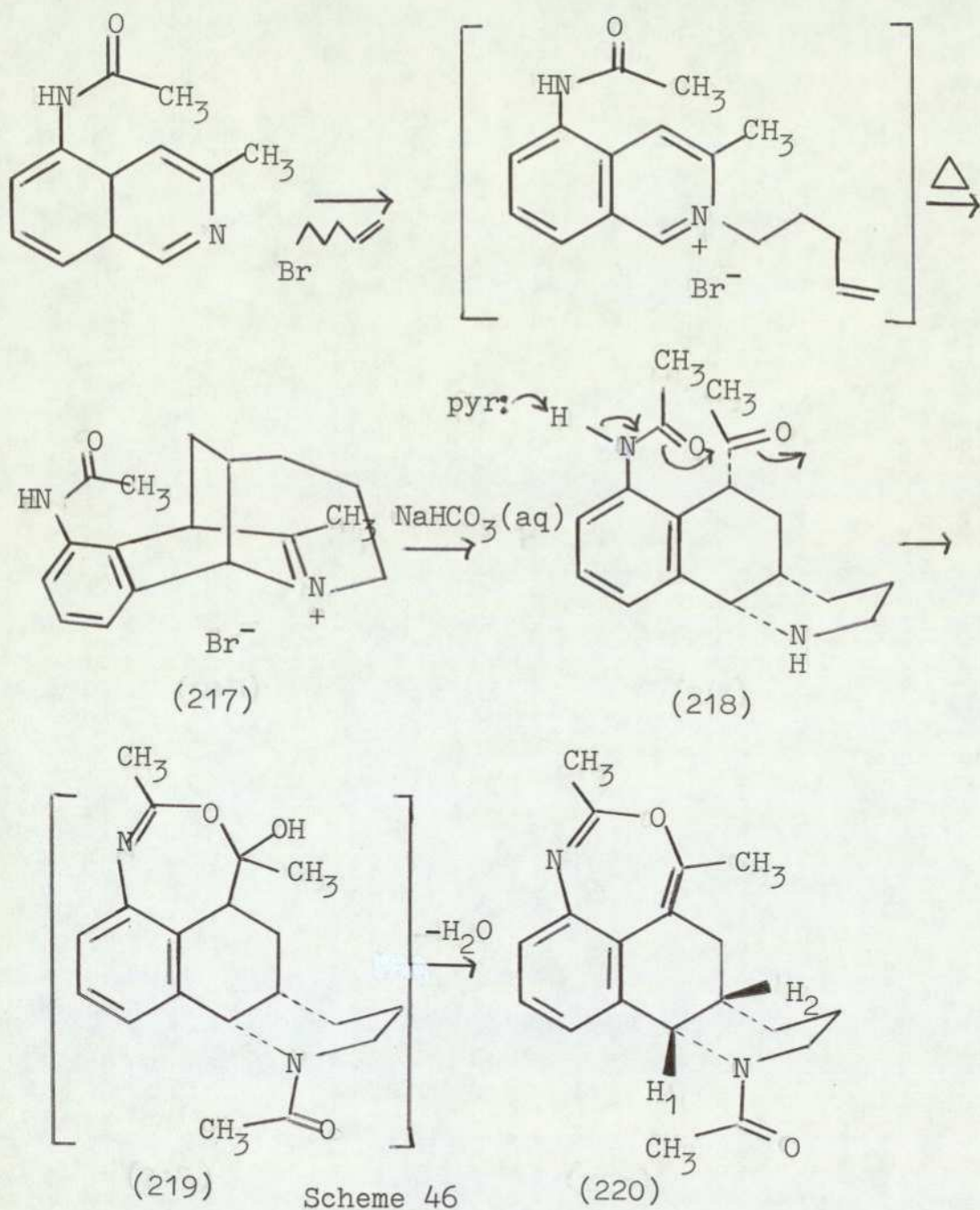


(179) R = CH₃

(182) R = H



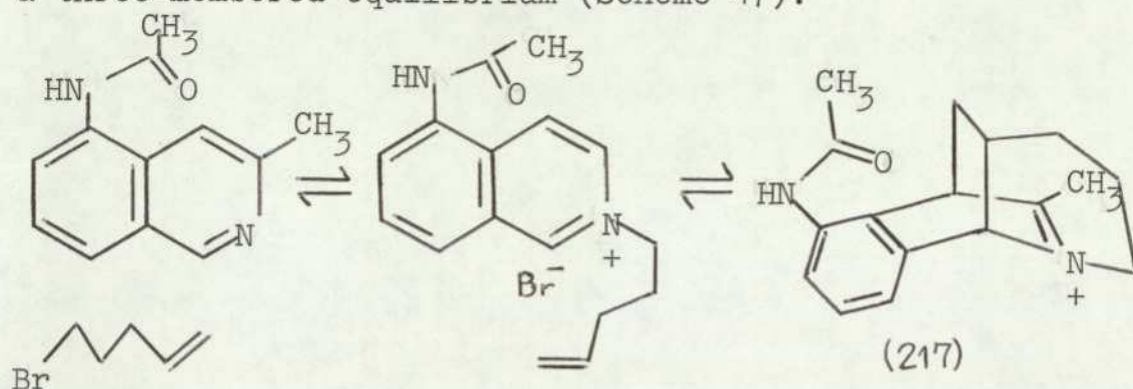
Salts (212)-(215) were prepared from the isoquinoline and the bromide, stirred or heated in acetonitrile. Allyl bromoacetate - prepared from bromoacetic acid and allyl alcohol - proved such a reactive substrate, that quaternisation could be quantitatively effected at room temperature after a couple of hours, or at 50° for 10 min. The mixture of pentenyl bromide and isoquinoline required overnight heating at reflux to produce (212). Acetamidoisoquinolinium salt (213) was not isolated, but rather inferred from the products of its thermolysis. 3-Methylisoquinoline was nitrated,¹⁸⁶ then catalytically reduced over PtO₂ to give the 5-amino-derivative,¹⁸⁶ which was simply acetylated in acetic anhydride. Attempts to prepare (213) in boiling acetonitrile with pentenyl bromide caused a rapid darkening of the solution followed by deposition of a black microcrystalline solid, m.p. 208-212°. Basic hydrolysis of this material, followed by acetylation of the products led to the isolation of one product in low yield as a viscous, pale yellow oil. Accurate mass measurement indicated a molecular ion of 310.1699 and a molecular formula of C₁₉H₂₂N₂O₂, consistent with structure (220). The benzoxazepine is thought to be formed via the primary adduct (217), which when hydrolysed to amine (218), is



able to cyclise under the basic conditions prevailing during the acetylation (Scheme 46). Dehydration of intermediate (219) leads directly to benzoxazapine (220) though in low yield.

The reaction was difficult to monitor, and seemed to be subject to equilibrium conditions. The black solid - believed to be (217) - slowly stopped depositing until the material already formed had been removed from the reaction mixture. A second crop may then be obtained. ^1H N.m.r.

studies show that the 3-methyl-5-acetamidoisoquinoline was always present in the heated solution suggesting perhaps a three-membered equilibrium (Scheme 47).

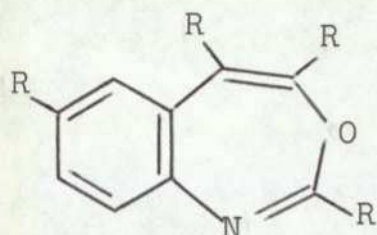


Scheme 47

The initial yield of (217) could be increased by performing the alkylation as a more concentrated solution.

The ^1H n.m.r. spectrum of (220) contains three, three-proton singlets, δ 2.31, 2.59 and 2.76 superimposed on an envelope for part of the alkyl absorption which contains four-protons. Another four-proton envelope is observed between δ 1.32-1.78. Three complex aromatic peaks are present: a triplet (J 7 Hz) at δ 6.94; a multiplet, δ 7.18-7.42 and a doublet of doublets (J 7 and 5 Hz) at δ 7.70. Evidence for isomerism exists for H_1 and H_2 since under basic conditions H_1 can slowly epimerise. Two complementary sets of peaks integrating as one proton each are present, H_1 as two broad doublets (J 5 Hz) at δ 5.34 and δ 6.28, and H_2 as a pair of broad multiplets approximating to doublets (J 13 Hz) at δ 3.79 and δ 4.62. No peaks in the spectrum are exchangeable with deuterium from D_2O . Decoupling investigations were not possible due to the low concentration of the material available, saturation of all absorbing nuclei always occurred. The i.r. spectrum

contains two peaks in the carbonyl region at 1702 and 1624 cm^{-1} , for the enol ether and amide, the latter peak being relatively broad suggesting the presence of a coincident peak - the imino ether. I.r. measurements have not previously been made for the heterocyclic nucleus of (220), however, phenylbenzo-(d)-1,3-oxazapines (221) have been found to contain unassigned peaks at 1670 and 1635 cm^{-1} .^{187,188} These fit well with the peaks measured for oxazapine (220), if one takes into account the lowering effect on the absorption that the phenyl group will exert.

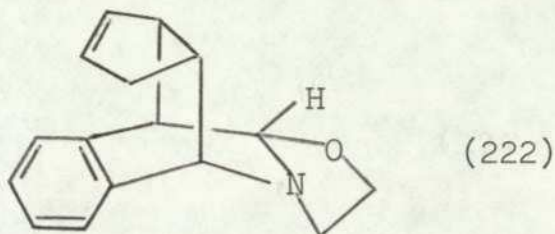


R = Ph, alkyl, H.

(221)

Successful repetition of the work of Watt,¹⁵⁹ led to the preparation of (212)-~~nor-(169)~~- in the hope that this would similarly cycloadd. Under identical conditions of thermolysis however, only starting materials were recovered. Heating for significantly longer times, or at higher temperatures resulted only in the formation of polymeric tars. ¹H N.m.r. analysis of the resultant thermolysis mixtures was impossible due to the limited solubility of the materials. Basic hydrolysis followed by acetylation gave intractable products. The requirement of a 3-alkyl substituent in intermolecular isoquinolinium salt cycloadditions,¹²⁵ has been previously mentioned (see review) and appears applicable to the intramolecular case. A poorly defined cyclopentadiene adduct has been realised with 2-methylisoquinolinium bromide after 65 weeks using

water as a trapping agent.¹⁸⁹ An adduct has been intramolecularly trapped during an intermolecular reaction of cyclopentadiene, with isoquinoline quaternised with 2-bromoethanol.¹⁹⁰



An adduct of unspecified geometry was obtained in 60% yield. 2,3-Dimethyl-5-nitroisoquinolinium salts, have been observed to add to vinyl ethers 120 times faster than the parent salt,¹⁸⁹ and 2-methyl-5-nitroisoquinolinium methosulphate is, to date, the only salt of this type to yield a stable adduct - with cyclopentadiene.¹⁸⁹ Attempts to quaternise 3-methyl-5-nitroisoquinoline,²⁰⁷ with pentenyl bromide were thwarted by the extreme deactivation of the heterocyclic nitrogen by the nitro group. Methylation of this derivative can only be effected by boiling it in acetonitrile with dimethyl sulphate. Endeavours to alkylate the 3-methyl-5-nitroisoquinoline at C(4) with strong base were equally unsuccessful, and so attempts to alkylate the C(3)-H derivative were not pursued.

Thermolysis of (212) in the presence of trapping agents such water or inorganic cyanide gave only tars.

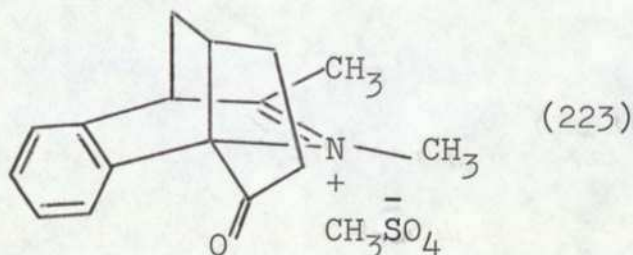
Both isoquinolinium salts (214) and (215) gave results similar to (212) except that they were far more reactive. Heated to 110° the pale-yellow solution turned maroon, and evaporation of the solvents gave only polymeric materials after just five minutes. The presence of

the 3-methyl group made no difference to the results of the thermolyses and again trapping experiments similar to those employed for (212) were totally unsuccessful. The acidic N-methylene function may be at the root of the problem, perhaps hydrogen bromide was eliminated at the elevated temperatures used; no reaction occurred below 110°. Internal salts of this type are known to be deep-red in colour.¹⁹¹⁻¹⁹³

Of the remaining alkenyl-isoquinolines (179) and (182) were formed by the direct alkylation of the respective isoquinoline anion with pentenyl bromide. Substrate (216) was formed by treating the anion of 1-methylisoquinoline with pentenyl bromide. Butenyl ketone (211) was generated by the treatment of 1-cyano-3-methylisoquinoline with butenyl magnesium bromide (Scheme 45) followed by acid hydrolysis. ¹H n.m.r. studies of (211) have shown that considerable steric strain exists about the keto-group (see previous chapter). It was assumed therefore, that - especially in the presence of the C(3)-methyl - access to the ring nitrogen, would be hindered and that quaternisation would be difficult. This proved to be valid, since stirring the isoquinoline in acetonitrile with one equivalent of dimethyl sulphate, proved fruitless. Heated gently under reflux however, ¹H n.m.r. analysis indicated the slow disappearance of the vinyl absorption. Interpreted as indicating immediate cycloaddition as soon as the isoquinoline quaternises, the heating was terminated when the signal had completely vanished. The peak for C(8)-H also disappeared, and a new aromatic multiplet had formed, at the expense of the old, at slightly higher

field. Little could be learned from the alkyl absorptions since the spectra were obtained from neat, acetonitrile reaction mixture. The solvents were removed, and the resultant semi-solid worked-up as usual, but again the only products in evidence were a mixture of tars which defied analysis. The ^1H n.m.r. spectrum of the acetylated mixture was indecipherable and t.l.c. investigations were unable to provide any evidence for discrete products.

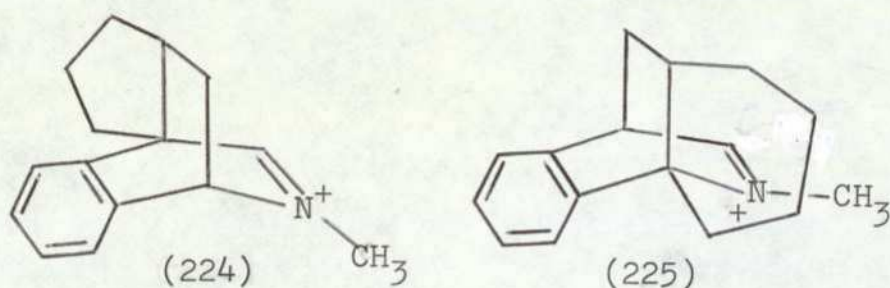
The disappearance of the ^1H n.m.r. resonance for the vinyl group, in addition to the upfield shift of the aromatic absorption (caused by the consumption of the heterocyclic ring of the salt) suggests that the intramolecular formation of (223) did occur. Methylation of the nitrogen would force the carbonyl group orthogonal to the plane of the heterocyclic ring and in this orientation



it should be a very facile process for the vinyl group to assume the geometry required for the formation of the charge-transfer complex intermediate for the cycloaddition (see review). The presence of the keto-group may have been crucial, since under the basic conditions of work-up the relatively acidic α -protons can easily be abstracted. Polymerisation can then occur, especially with the iminium function of another molecule. It would be interesting to reduce the carbonyl group of (211) by either the Clemmensen,¹⁹⁴ or Wolf-Kishner¹⁹⁵ method prior to quater-

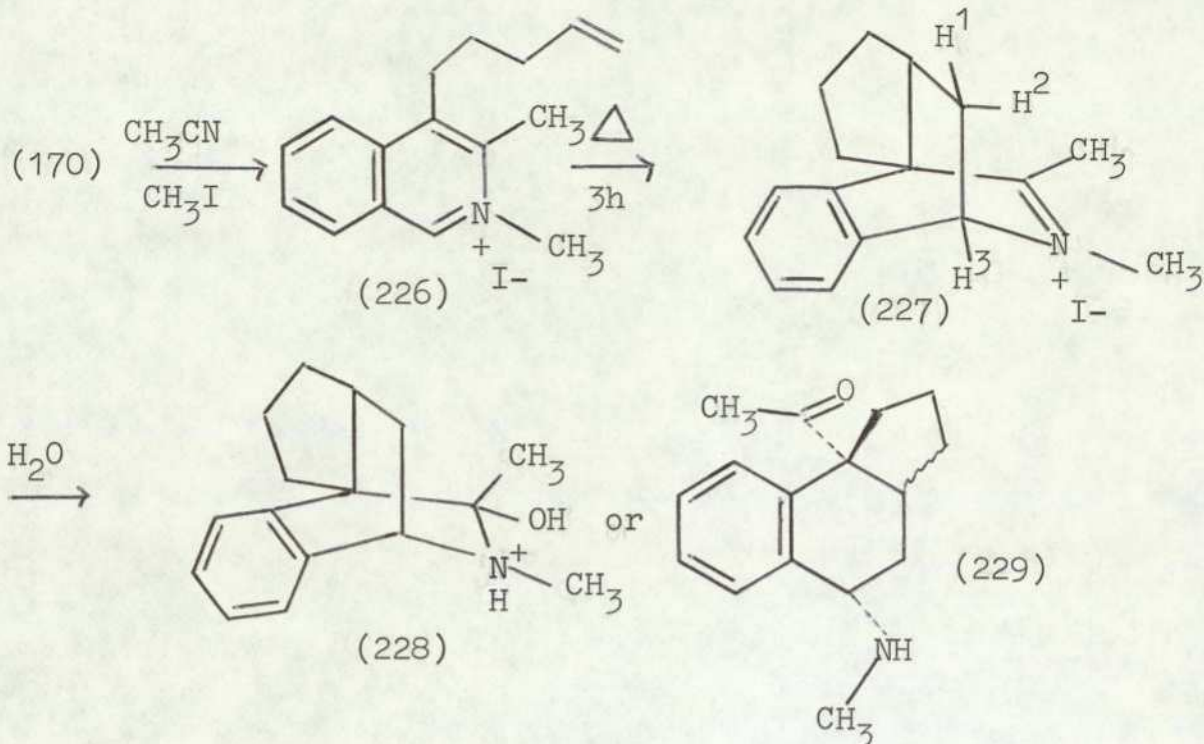
nisation. This would have the added advantage of relieving the steric environment about the nitrogen, thus making methylation a more simple process.

Methylation of (182) and (216) was accomplished quantitatively by stirring an acetonitrile solution of the isoquinoline with iodomethane. Thermolyses of the salts however, gave no isolable primary adducts (224) or (225), and no identifiable products when the reaction mixtures were hydrolysed, then acetylated. In a similar fashion to



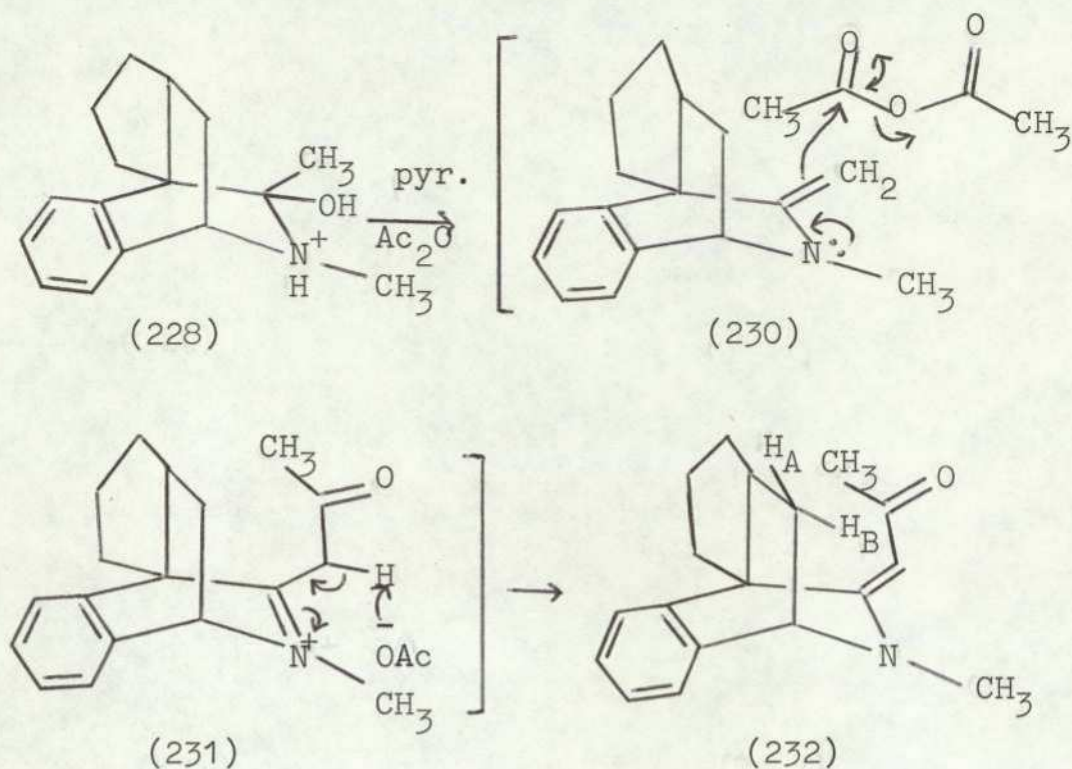
(212), the adducts - if they formed - were consumed by an unidentified agent. No isolable adducts paralleling (170) were observed for either salt. Polymeric tars giving complex ^1H n.m.r. spectra were the result of extended thermolyses, since the 3 hours recommended by Watt for (169),¹⁵⁹ gave only unreacted precursor. Use of higher temperatures was equally unsuccessful.

In contrast to the frustrations encountered for the isoquinolinium nuclei without a C(3) substituent the methiodide (226) gave a very smooth, quantitative conversion to the adduct (227) under the conditions prescribed by Watt.¹⁵⁹ The ^1H n.m.r. spectrum of adduct (227) clearly indicates the consumption of both the vinyl group and the heterocyclic ring. The singlet for C(1)-H of the isoquinolinium salt (226) disappeared, a broad benzylic singlet is



present for H^3 of (227) at δ 5.98. Two methyl signals are present at δ 2.84 and δ 4.00, the latter (N- CH_3) being shielded by 0.70 p.p.m. from the corresponding absorption in (226). Proton H^1 , situated over the phenyl ring occurs as a broad doublet, (J 8 Hz) δ 1.32, while the aromatic absorption occurs as two signals, one of three-protons - a singlet, δ 7.37 - the other a one-proton multiplet δ 7.52-7.78. The separation of the peaks is probably a result of the peri-interaction between C(5)-H and the C(4) substituent.

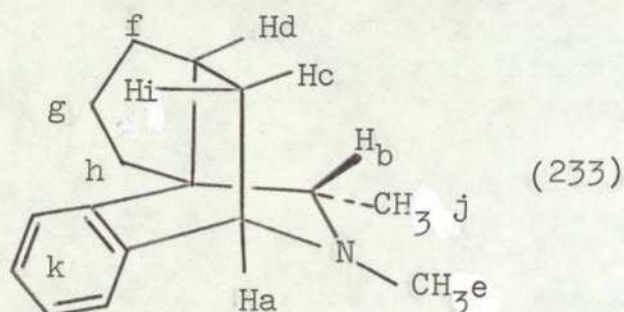
Basic hydrolysis of adduct (227) gave a heavy oil, which on acetylation afforded a single product in 84% yield. A ^1H n.m.r. analysis of this material suggested that ring opening to (229) had not taken place, since only two methyl signals were present in the spectrum. The spectral data fitted tricyclostructure (232), derived from hydroxyisoquinoline (228) (Scheme 48). The ^1H n.m.r. spectrum of (232) contains two, three-proton singlets δ 2.05 and



Scheme 48

δ 3.06 for the methyls, the former being situated in an eight-proton alkyl envelope. The four aromatic protons are present as a broad singlet δ 6.98-7.35, while the olefinic proton exists as a sharp singlet δ 5.01. A broad doublet (J 4 Hz) arising from the proton that was formally C(1)-H of (226) resonates at δ 4.37, and the broad doublet (J 13 Hz) from the proton held over the phenyl ring is present at δ 1.16. This latter coupling constant is considerably increased from the value for the same proton in adduct (227), and is probably caused by a change in the angle between the two geminal hydrogen atoms (H_A and H_B). An accurate mass measurement of the molecular ion of (232) is consistent with the required formula. The i.r. spectrum contains major peaks at 1672 and 1603 cm^{-1} corresponding to the β -amino- α,β -unsaturated-keto function.

Further demonstration of the intramolecular cycloaddition was provided by the borohydride reduction of the primary adduct (227). An 89% yield of a mixture of isomers was obtained exo and endo-(233) with respect to the ethano bridge. The ratio of isomers, exo/endo, was about 1/2, judged by the ^1H n.m.r. integrations for the two sets of doublets arising from the C(3)-methyl of each isomer. No evidence for isomerism was shown by the N-methyl group. Passage of the reaction mixture down a



Assignment	Form	Chemical shift
a	1H, bd, J 4Hz	3.88
b	1H, q, J 7.5Hz	3.63
c	1H, dxdxd, J 13, 9, 4Hz	3.24
d	1H, m	2.10-2.50
e	3H, s	2.24
f,g,h	6H, m	1.40-2.08
i	1H, dxd, J 13, 6Hz	1.08
j*	3H, d, J 7.5Hz	0.79
k	4H, m	7.16-7.46

*the resonance position for the exo-adduct is δ 1.16, d, J 7.5Hz

The ^1H n.m.r. data for the endo-hydride adduct of (227)

Table 4

silica column caused the epimerisation of the former C(3)-proton with the isolation solely of the endo-(233) adduct. The ^1H n.m.r. data is summarised in Table 4.

Double-irradiation experiments demonstrated the mutual coupling of H_j and H_b. Saturation of the signal for H_a collapsed that of H_c to a doublet of doublets (J 13 and 9 Hz), and sharpened that of H_i considerably. Double-irradiation of the H_i absorption turned that of H_c into a distorted doublet of doublets (J 9,4 Hz) and that of H_a into a sharp doublet (J 4 Hz). Saturation of the N-methyl signal and the H_d peak under it caused the H_i absorption to appear as a doublet (J 13 Hz) and that of H_c to resonate as a poorly defined doublet (J 13 Hz). All of the decoupling investigations are consistent with structure (233) in addition to the accurate mass measurement for the molecular ion. The i.r. spectrum contains nothing but alkyl and aryl absorptions.

The smooth cycloaddition of precursor (169), and of (226), under conditions that do not effect (212), or the methiodides of (182) and (216) poses a problem. The adduct formation of the latter group should be considerably faster than the former for two reasons. Firstly, isoquinolinium salts are an inverse demand system,¹²⁵ and so the presence of an electron-donating C(3) methyl group should slightly deactivate the substrate electronically. Secondly, consideration of the geometry of the isolated adducts indicates that the C(2) and C(3) alkyl groups must move into plane with each other as the iminium bond between the nitrogen and C(3) forms. Although the precursor isoquinolinium salt is planar, the localisation of the double

bonds around the heterocycle gives the corresponding C(3)-N bond significant single-bond character, thus allowing greater separation of the substituent.

As part of a study of the rates of reaction of various 3-substituted isoquinolinium salts with ethyl vinyl ether, Bradsher actually demonstrated the retarding effect on the cycloaddition that a C(3) methyl group has relative to a C(3) proton.¹⁹⁶

If one considers methiodide (226) however, it is obvious that the enhancement in rate of cycloaddition arises from the steric relief achieved when the three juxtaposed alkyl groups move out of the same plane. The activation energy of the process is lowered considerably (see review).

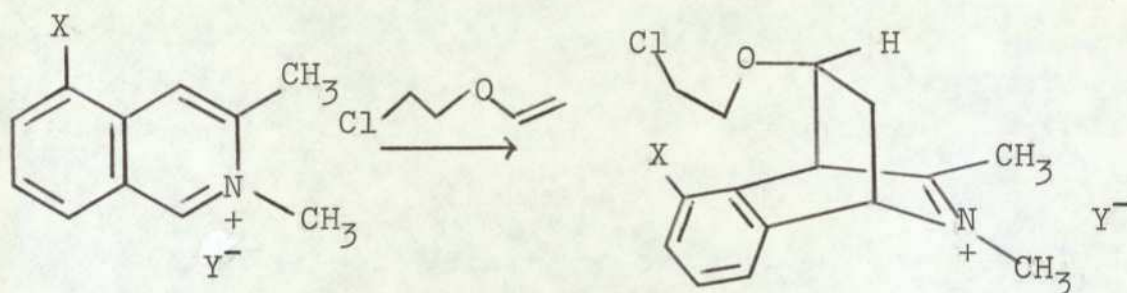
The same is true for salt (169), but slightly more subtly so. If one examines^e the framework molecular model of the adduct (170), then it will be observed that the two alkyl substituents are not in the same plane. The adduct bridge is slightly strained with only the three carbon chain joining it to the nitrogen, so that the alkyl group is able to adopt an orientation away from the C(3) methyl group. A net stabilisation energy is realised by moving the vicinal alkyl groups in (169) out of plane. The long pentenyl chain must exert a measureable steric effect on the C(3) methyl substituent to cause this increase in reactivity.

The alternative answer - i.e. that the cycloaddition does occur at a lower temperature for C(3)-H isoquinolines, but that the adduct then reopens on cooling - can be discounted, since addition of trapping agents had no effect.

CHAPTER 8

Intermolecular cycloadditions of 2,3-dimethylisoquinolinium salts.

The review section of this thesis contains numerous examples of intermolecular cycloaddition reactions with nucleophilic olefins that the 2,3-dimethylisoquinolinium nucleus undergoes. The list of dienophiles has now been extended to 2-chloroethyl vinyl ether (Scheme 49). This electron-rich olefin, in fivefold excess, gave adduct (236),



(234) X = H, Y = I

(236) X = H, Y = I

(235) X = NO₂, Y = CH₃SO₄

(237) X = NO₂, Y = CH₃SO₄

Scheme 49

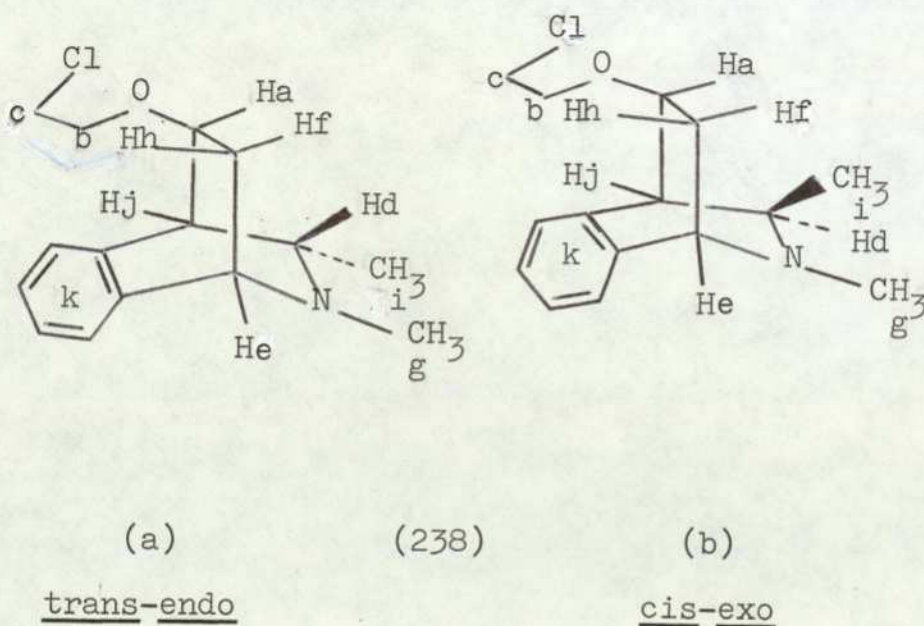
syn with respect to the phenylene bridge, virtually quantitatively from (234) in both acetonitrile and methanol.

In each case a small amount of quinol was added, causing the instant formation of the isoquinoline-quinol charge transfer-complex.¹⁹⁸ The originally pale yellow heterocyclic solution turned green on addition of the dihydroxybenzene. The reaction of (234) with the vinyl ether is completed after 10 days stirring at room temperature, and the adduct (236) can be isolated following precipitation from solution with ethyl acetate. Adducts of this type are thermally unstable and even on mild heating ($\sim 60^{\circ}$)

regenerate the precursors.^{124,184}

The reduction of these adducts has been only briefly investigated, employing Adams' catalyst for hydrogenation studies.¹⁸⁴ A poorly defined compound was isolated and characterised only via mass spectrometry. When adduct (236) was treated with an excess of sodium borohydride in methanol, a mixture of cis and trans-3,4-2,3-dimethyl-9-(2-chloroethoxy)-1,2,3,4-tetrahydro-1,4-ethanoisoquinoline (238) was obtained in 93% overall yield. The product isomer ratio for the reaction was 2:5 for cis (238b) : trans (238a) respectively. The borohydride favoured attack of the slightly more hindered underside of the iminium salt (236). In this case the thermodynamically more stable isomer is preferentially formed.

The assignment of the isomers is based upon the differing chemical shifts, in the ¹H n.m.r. spectrum of the methyl groups of both isomers due to local field effects.



The C(3) methyl of the trans (238) isomer - i.e. the endo adduct with respect to the ethano bridge - experiences

shielding from the o-phenylene group, of 0.53 p.p.m. compared to the corresponding secondary methyl resonance of the exo-adduct (238b). Both resonances are present as doublets (J 7 Hz). The N-methyl group similarly indicates the presence of isomers. In exo-(238b), the steric crowding exerted by the C(3) methyl causes the N-methyl to lie slightly more under the plane of the aromatic bridge than it would normally do so in the absence of the adjacent methyl group. The N-methyl singlet of exo-(238b) resonates 0.36 p.p.m. higher field than that of endo-(238a). The ^1H n.m.r. data are listed in Table 5.

Assignment	Form	<u>endo</u> - (236)	Common	<u>exo</u> - (236)
a,b,c,d	6H, m		3.35-4.27	
e	1H, m		3.08-3.24	
f	1H, m		2.58-2.98	
g	3H, 2xs	2.48	-	2.12
h	1H, m		1.16-1.46	
i	3H, 2xd, J 7Hz	0.88	-	1.32
j	1H, m		2.38-2.58	
k	4H, s		7.48	

^1H n.m.r. spectrum of hydride adducts (238a) and (238b)

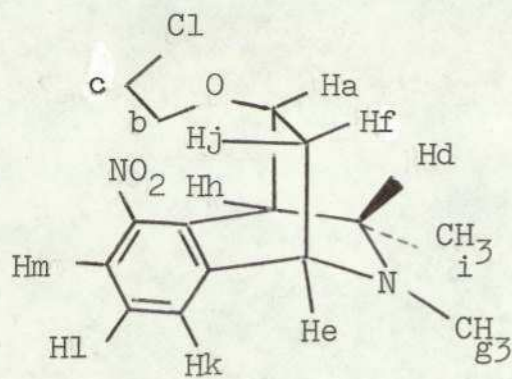
Table 5

Shielding is also observed for Hh which is rigidly held over the phenylene ring. Many of the multiplets are probably caused by the overlapping of the absorptions for the isomers (238a) and (238b).

I.r. analysis of the isomeric mixture shows - in addition to alkyl absorption - peaks for the ether linkage (1109 cm^{-1}), the phenylene group (1477 and 1449 cm^{-1}), and the carbon chlorine stretching (755 cm^{-1}).

When the adduct of 2,3-dimethylisoquinolinium iodide and ethyl vinyl ether was reduced with LAH the endo hydride adduct was the only isolable product in 92% yield.¹⁹⁸ The selectivity, arising from lower reactivity, and/or the reduction in size of the borohydride compared to the LAH allows formation of both isomers from (236).

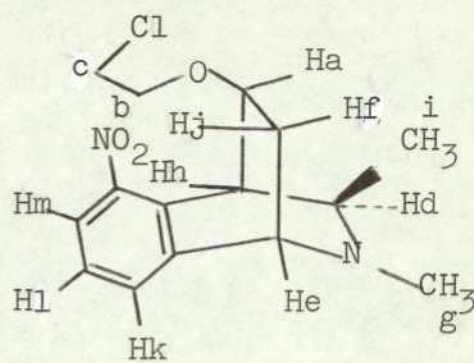
When the 2,3-dimethyl-5-nitroisoquinolinium cation was treated similarly, the reported cycloaddition rate enhancement by the nitro was confirmed.¹⁸⁹ Addition of quinol to the acetonitrile solution of (235) caused an immediate colour change from yellow to intense orange, as the charge-transfer complex formed. Showing clearly the inverse demand nature of this reaction, 2-chloroethyl vinyl ether gave adduct (237) within 1 hour of its addition to a solution of (235). The electron-withdrawing power of the nitro group reduces the energy of the heterocyclic LUMO, thus permitting increased overlap with the HOMO of the olefin. An almost quantitative yield of (237) is observed. Reduction with sodium borohydride in methanol again gave an isomeric mixture of cis- and trans-3,4-2,3-dimethyl-5-nitro-9-(2-chloroethoxy)-1,2,3,4-tetrahydro-1,4-ethano-isoquinoline (239a) and (239b) in 74% yield. The ratio of endo to exo isomers was very slightly in favour of the exo-isomer (239b). The ^1H n.m.r. data are summarised in Table 6.



(a)

(239)

trans-endo



(b)

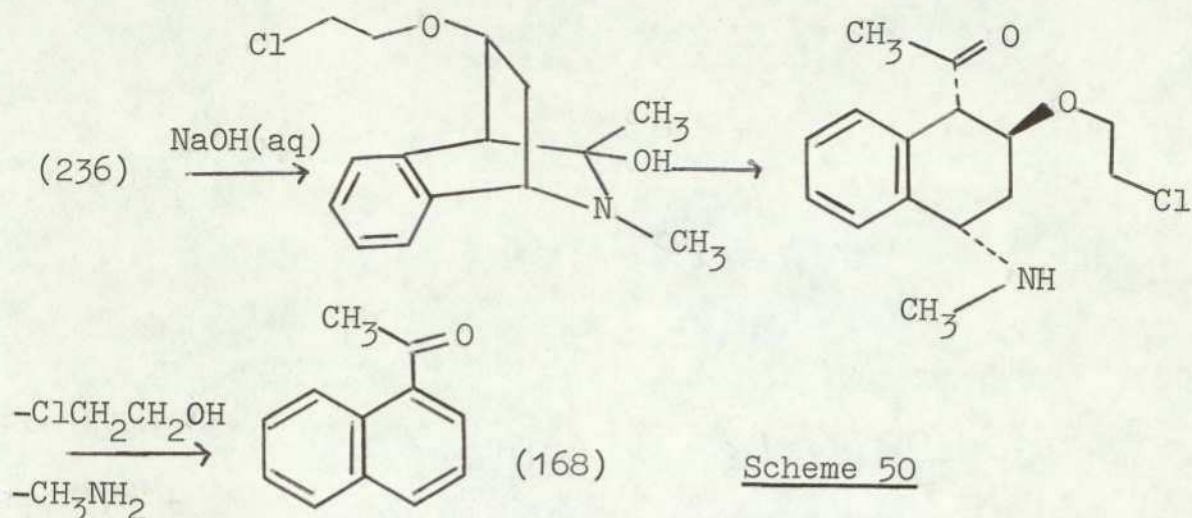
cis-exo

Assignment	Form	<u>endo-</u> (239a)	Common	<u>exo-</u> (239b)
a,b,c,d	7H, m		3.34-4.50	
e,h				
f	1H, m		2.50-3.96	
g	3H, 2xs	2.47	-	2.10
i	3H, 2xd, J 7Hz	0.92	-	1.32
j	1H, m		1.16-1.60	
k,l	2H, m		7.42-7.68	
m	1H, dxd, J 7,3Hz		8.06	

¹H n.m.r. spectrum of hydride adducts (239a) and (239b)

Table 6

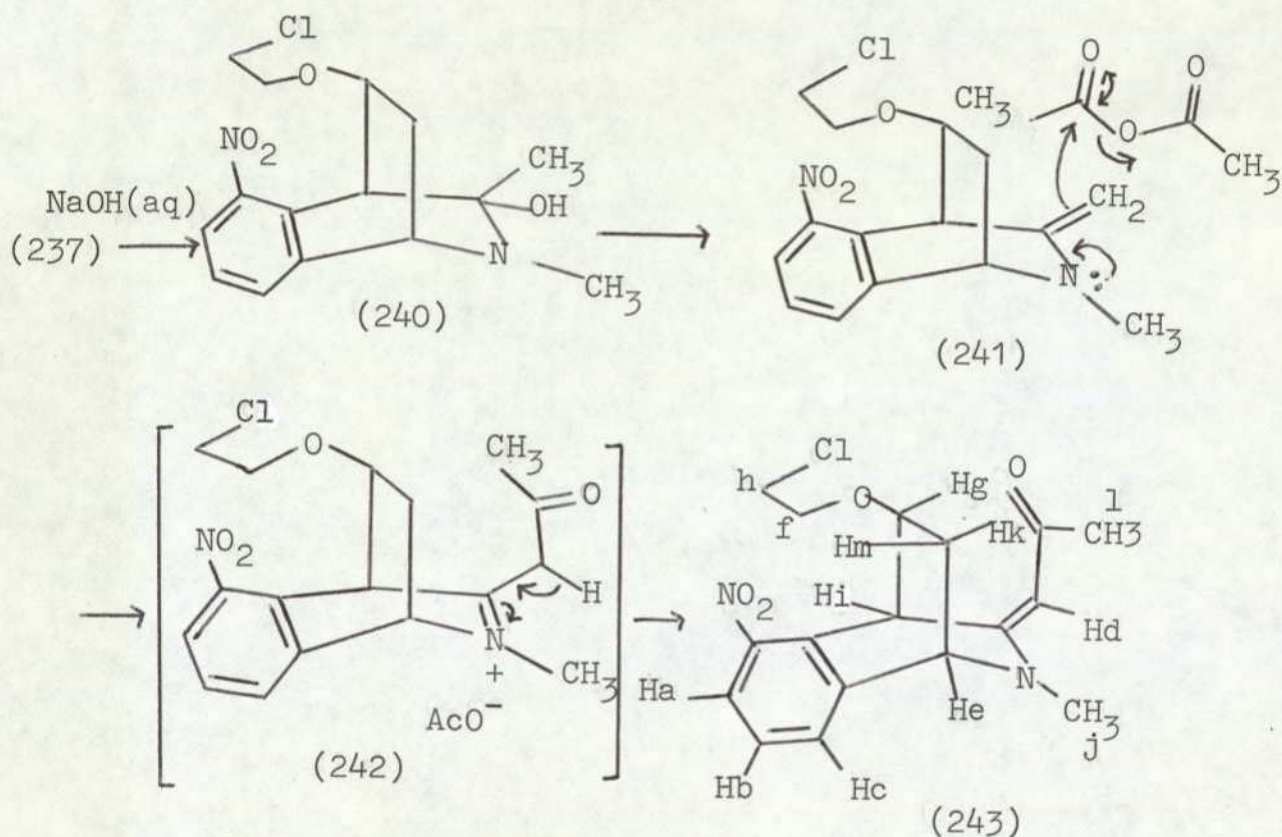
Treated with boiling dilute sodium hydroxide, primary adduct (236) underwent attack at the iminium function, followed by ring opening, and elimination of methylamine and 2-chloroethanol (Scheme 50). This is consistent with previous observations, where alkyl vinyl ether adducts



always give methyl-1-naphthyl ketone (168).^{124,199} The yield of 88% from the 2-chloroethyl vinyl ether adduct compares favourably with those reported.¹²⁴ Prominent in the i.r. spectrum of (168) is the aromatic keto absorption at 1673 cm^{-1} , and in the ^1H n.m.r. spectrum an acetyl methyl peak at $\delta 2.69$. All spectral data are in agreement with literature values.^{124,199}

Treated similarly, primary adduct (237) gave a deposit of intractable indigo oils and tars. However, by omitting the boiling step, a light orange oil could be obtained, t.l.c. examination of which indicated one major and polar product that did not resemble ketone (168). ^1H N.m.r. analysis indicates the same aromatic pattern observed for (239), and also a similar absorption to H_j of (239). Only one methyl peak is present, $\delta 2.69$, and it appears that this is coincident with a peak similar to H_g of structure (239). A doublet (J 3Hz) exists at $\delta 5.18$ in addition to a large complex multiplet between $\delta 3.22$ -4.26. T.l.c. behaviour was very reminiscent of that observed for amine (171), obtained following thermolysis of salt (169), then hydrolysis.

The orange oil was treated with a slight excess of acetic anhydride in dry pyridine. T.l.c. analysis indicated only one product, and spectral data for this compound suggested structure (243) similar to the intramolecularly formed analogue (232). It was thought that the dehydration step would have occurred during the acetylation but the ^1H n.m.r. for the hydrolysed adduct



Scheme 51

suggests that this is not so. The absence of a second methyl signal and the appearance of a doublet (J 3 Hz) at δ 5.18 supports the presence of enamine (241) (Scheme 51). Tables suggest that the range in chemical shift for olefinic protons β to an amino group occur between δ 3.7-5.0 and that the geminal coupling likely to be observed would lie between 0 - 3.5 Hz.²⁰⁰ Acetylation of (241), then dequaternisation of the iminium salt (242), gives (243) as

a pale yellow solid m.p. 127-135°. The ^1H n.m.r. data for (243) are summarised in Table 7.

All multiplicities and coupling constants are consistent with structure (243) and all resonance positions occur within predicted ranges - except Hi. However, examination of a framework molecular model of (243) reveals that Hi is sterically hindered. The peri-interaction exerted by the nitro function will lower its resonance position, as shown in the difference between the corresponding protons

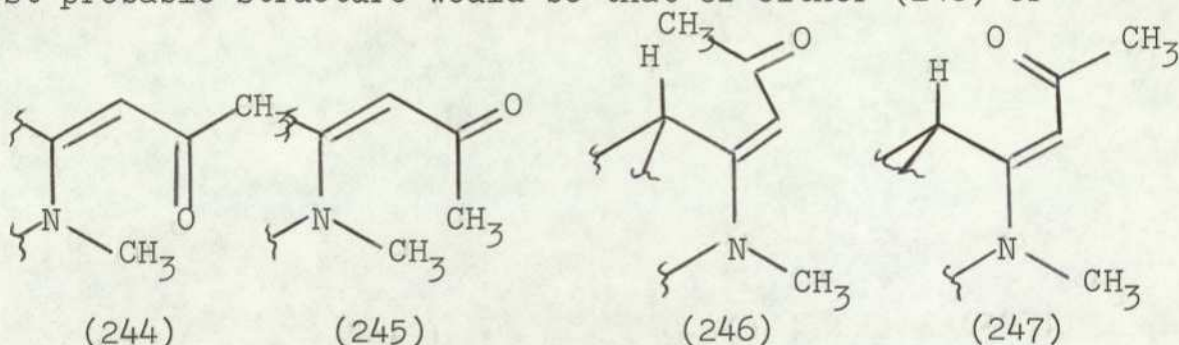
Assignment	Form	Resonance Position
a	1H, d, J 8 Hz	8.04
b,c	2H, m	7.32-7.72
d	1H, s	5.03
e	1H, m	4.64-4.79
f,g,h	5H, m	3.36-4.32
i	1H, d, J 4 Hz	7.80
j	3H, s	3.01
k	1H, dxdxd, J 13, 9, 4 Hz	2.67
l	3H, s	2.12
m	1H, bd, J 13 Hz	1.45

^1H n.m.r. spectrum of (243).

Table 7

of (238) and (239). Perhaps the largest effect will arise from the conformationally fixed α,β -unsaturated ketone. There are four possible orientations of the carbonyl with respect to the amine group, (244)-(247). The two (244) and (245) can be straightway eliminated due to the very

demanding steric requirements imposed by the N-methyl group on the acetyl function in either orientation, if the system is to remain planar and thus maintain conjugation. The most probable structure would be that of either (246) or



(247), the former producing the greatest steric resistance when held planar. Structure (247) would be better able than (246) to accommodate the necessary geometry and would significantly deshield the bridgehead proton due to anisotropic effects.

^1H N.m.r. decoupling experiments show that H_i is adjacent to H_g , since double irradiation at 400 Hz (inside the complex absorption for the strongly deshielded ether and chloroalkyl protons) not only collapses the peak at $\delta 7.80$ to a singlet, but also reduces the signal for H_k and H_m , at $\delta 2.67$ and $\delta 1.45$, to a distorted doublet and a sharp doublet respectively. Irradiation at 780 Hz has no noticeable effect on the aforementioned complex absorption (probably due to the overlapping of signals) or on any other part of the spectrum. No other position of double irradiation has any influence on the peak at $\delta 7.80$.

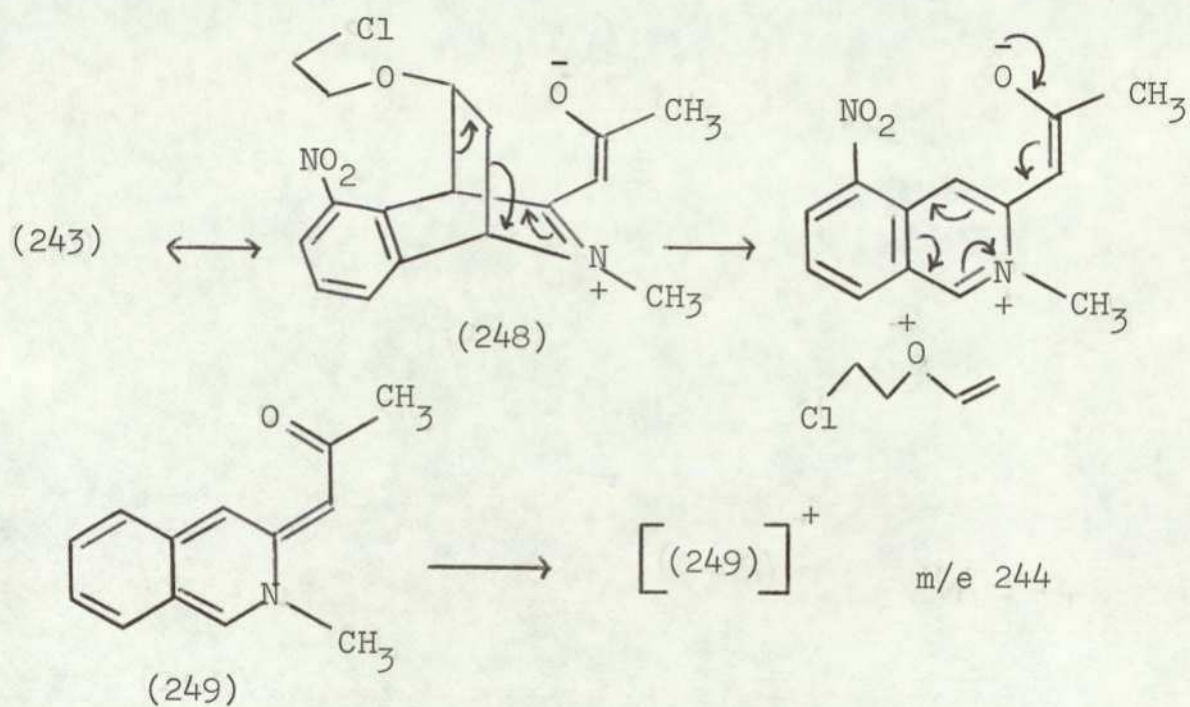
The ^{13}C n.m.r. spectrum of (243) does not indicate anything unusual since the carbon atom to which H_i is attached absorbs at 38.0 p.p.m. (see appendix) showing that any effect on H_i must be purely anisotropic.

The i.r. spectrum supports structure (243) with the ν_{max} occurring at 1548 cm^{-1} , within the range quoted for β -amino- α,β -unsaturated ketones ($1640\text{--}1540\text{ cm}^{-1}$).²⁰¹

This band is very strong and quite wide, and coincides with one of the absorptions for the aromatic nitro group. The other nitro peak is evident at 1352 cm^{-1} , and is considerably weaker, relatively, than the carbonyl peak. Both nitro absorptions are usually of comparable intensity. The olefin absorbs at 1638 cm^{-1} and the ether linkage is represented at 1107 cm^{-1} . This very low carbonyl absorption is not evident in the i.r. spectrum of the analogue (232), which seems to indicate that the carbonyl group has adopted another orientation in this latter molecule, probably that of (246), i.e., unless the presence of the C(4) proton is of vital importance to the i.r. spectrum of (243). It is not known why this difference in the reaction paths of (236) and (237), on hydrolysis, is observed.

Mass spectrometry furnishes a correct accurate mass measurement for the molecular ion and gives the retro-Diels-Alder loss of chloroethyl vinyl ether ($m/e\ 244$) as the major fragment. Presumably this is accomplished via zwitterionic species (248) (Scheme 52). Loss of $\text{C}_2\text{H}_4\text{ClO}$ is evident at $m/e\ 271$ and extrusion of nitrobenzyne leads to the second most abundant fragment ($m/e\ 229$).

In conclusion, it appears that from analysis of all available data, that structure (243) is the most likely, adopting the carbonyl orientation of (247). An exceptional deshielding effect must operate on H_i , probably as a result of the unique arrangement of atoms within the molecule.



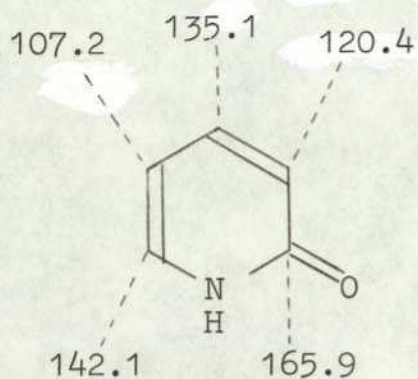
Scheme 52

Appendix

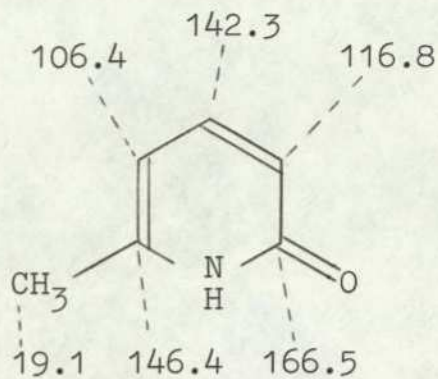
^{13}C n.m.r. Spectra

The following ^{13}C n.m.r. data 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.

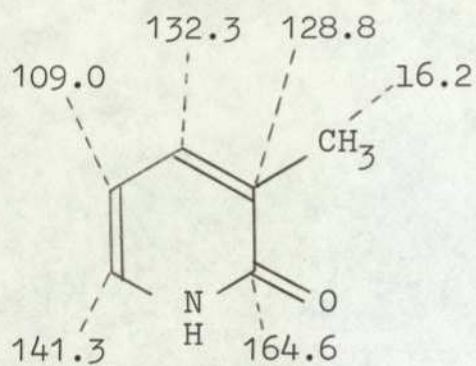
All spectra were obtained from a deuteriochloroform solution of the substrate, except for the 4-hydroxy-2-pyridones in which cases pure DMSO was used. The chemical shifts for the deuteriochloroform solutions were measured relative to an internal standard (TMS), those for the 4-hydroxy-2-pyridones relative to the DMSO signal.



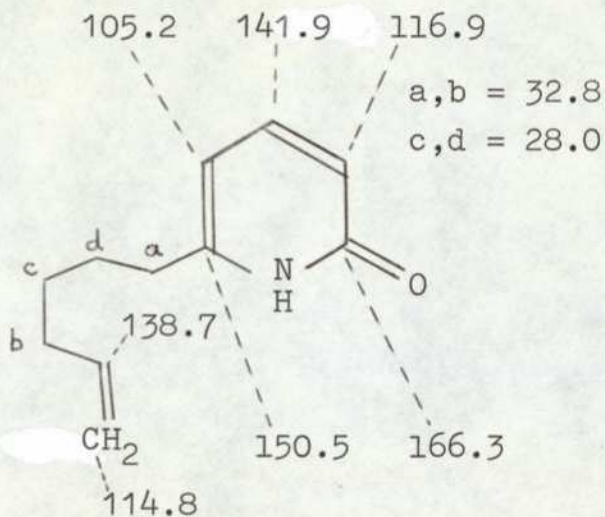
(1)



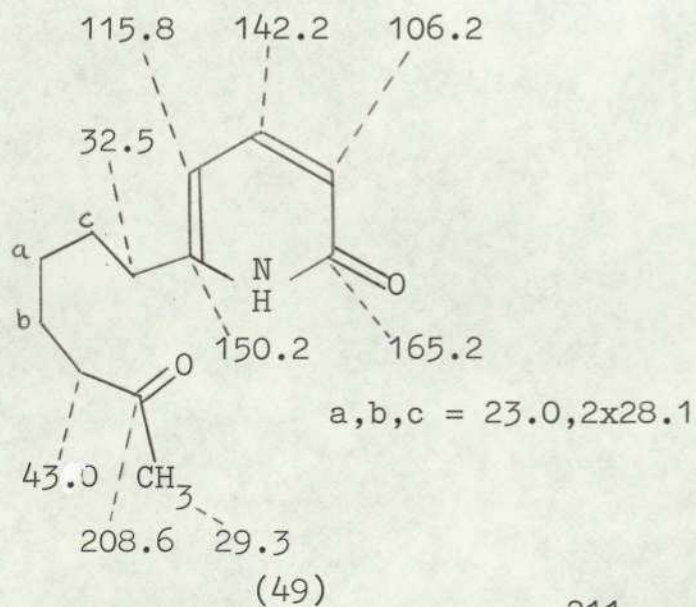
(36)



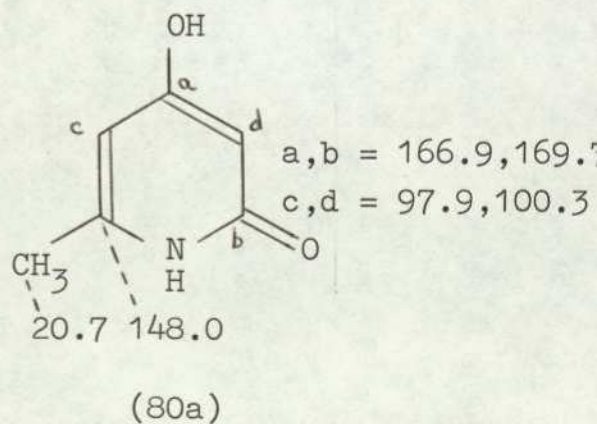
3-methyl-2-pyridone



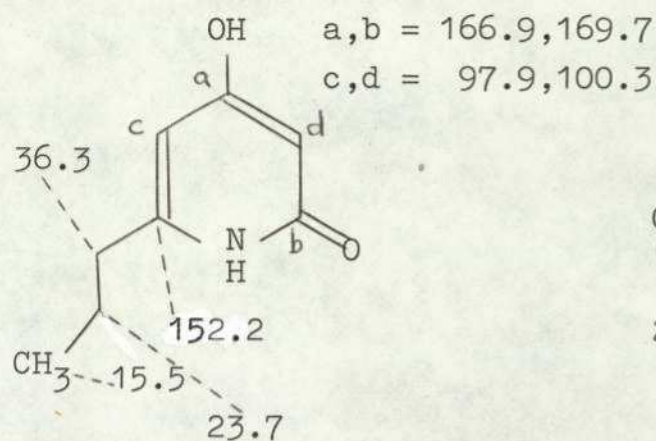
(31)



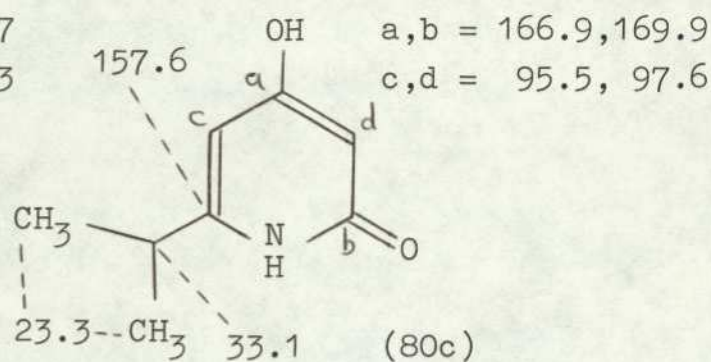
(49)



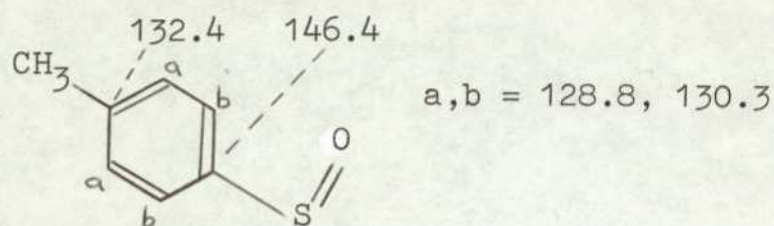
(80a)



(80b)

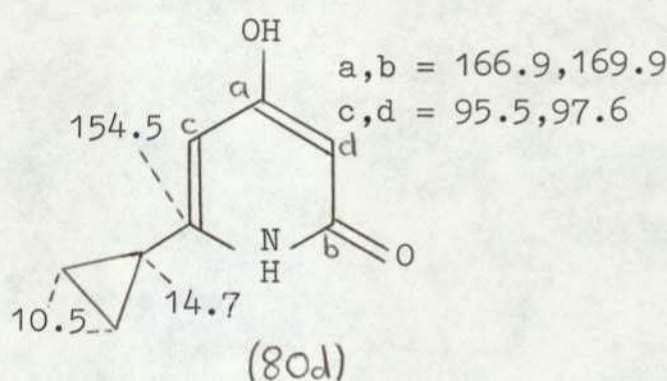


(80c)

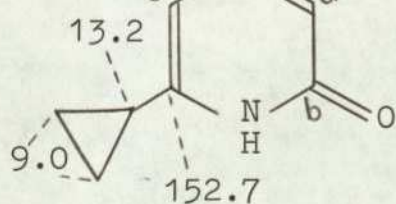
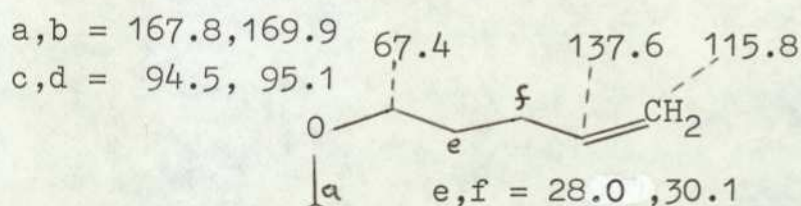


a,b = 128.8, 130.3

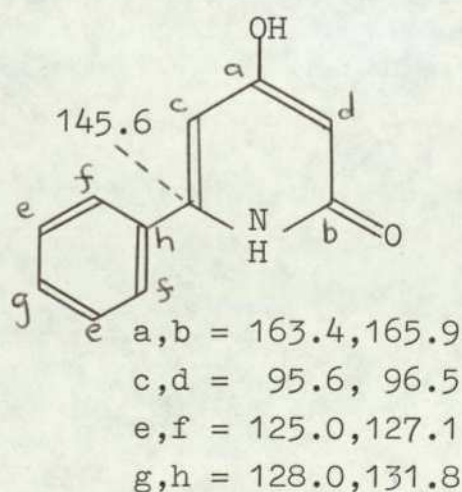
(133)



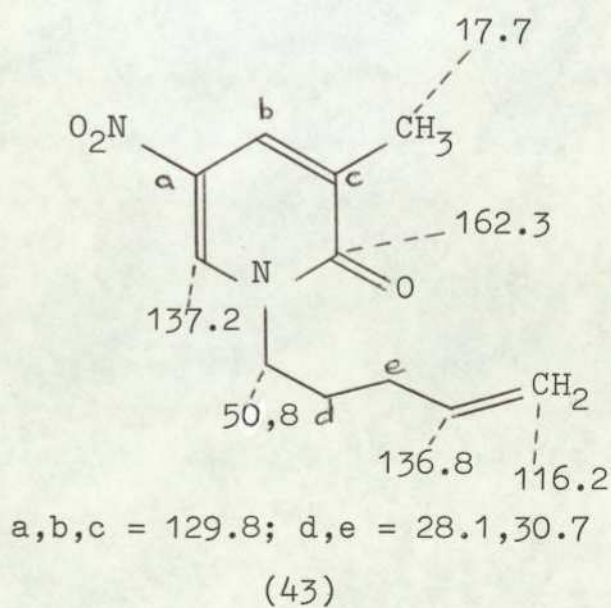
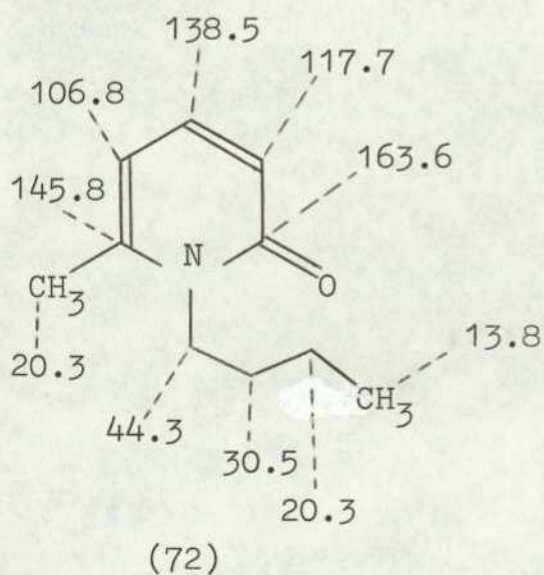
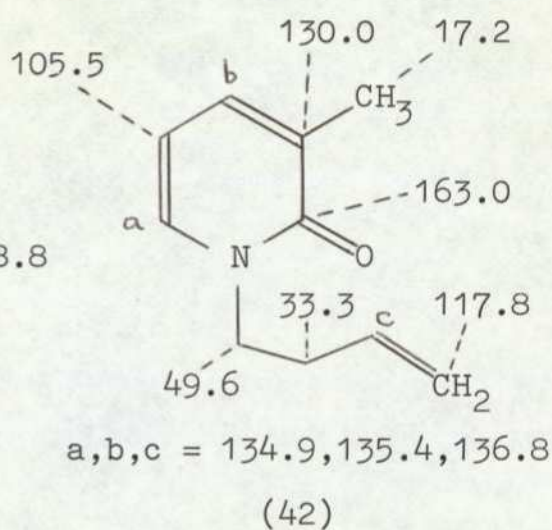
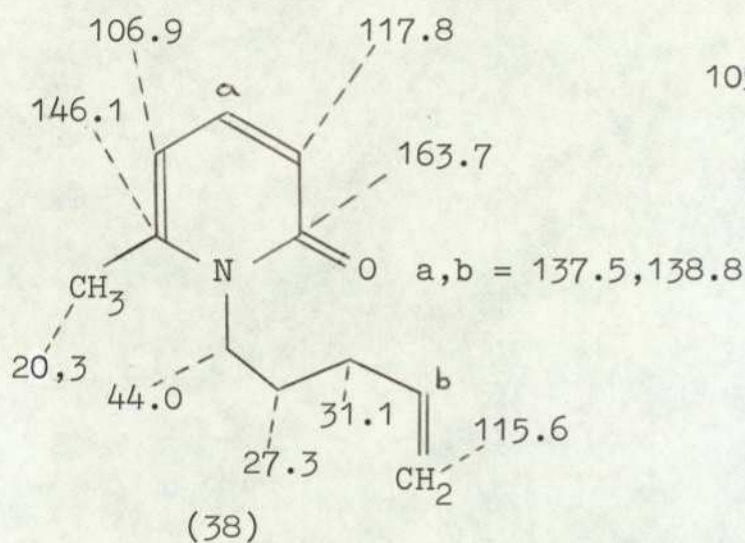
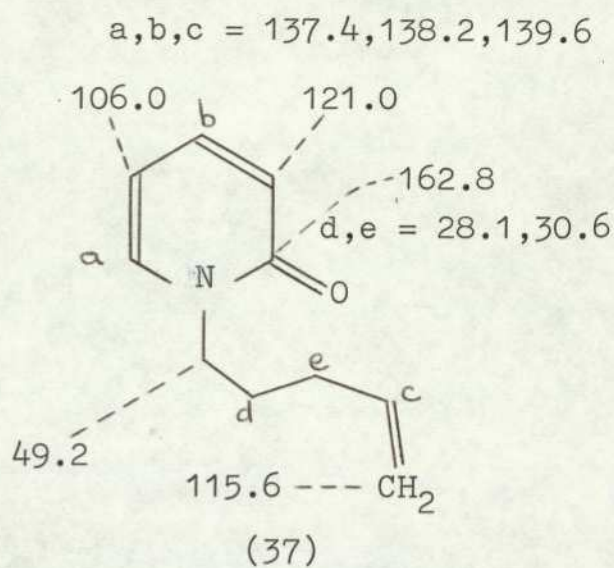
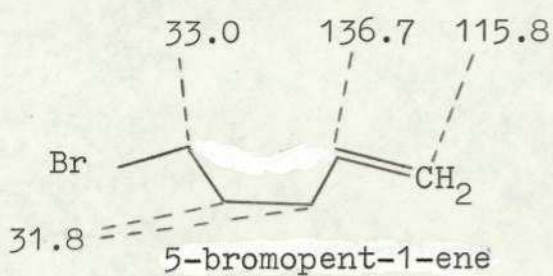
(80d)

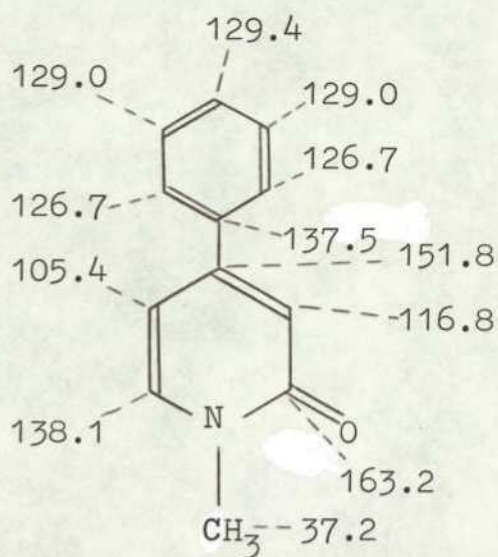
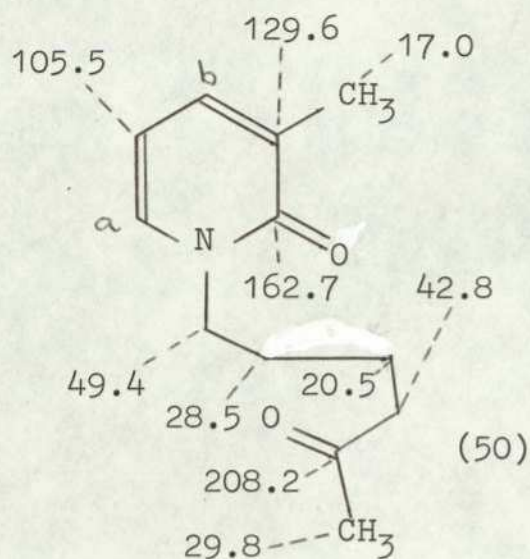


(110)

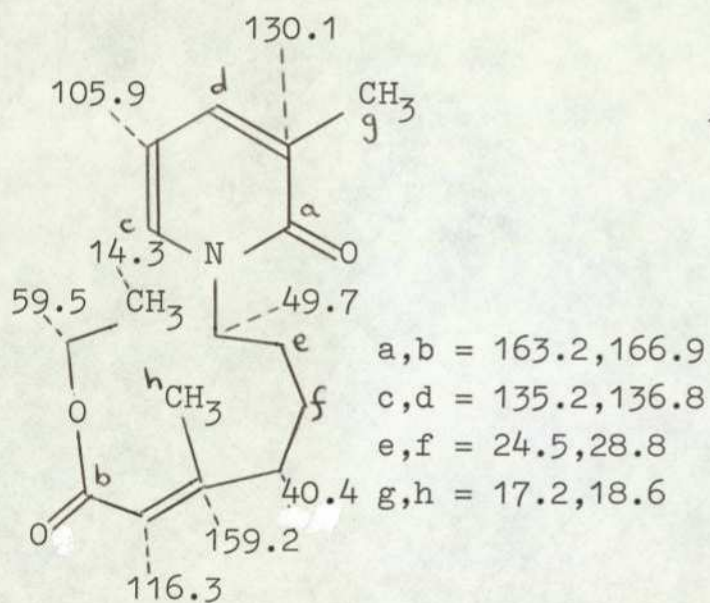


(80g)

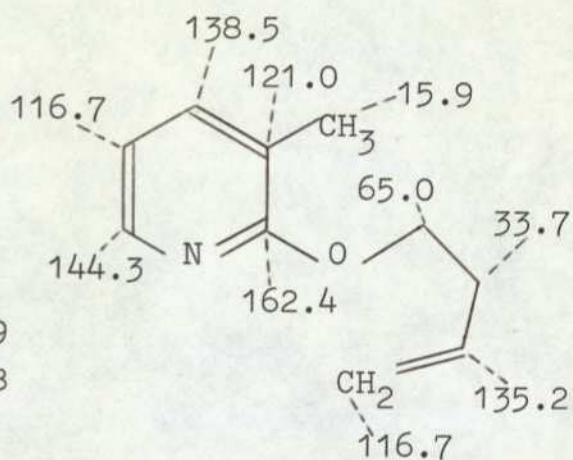




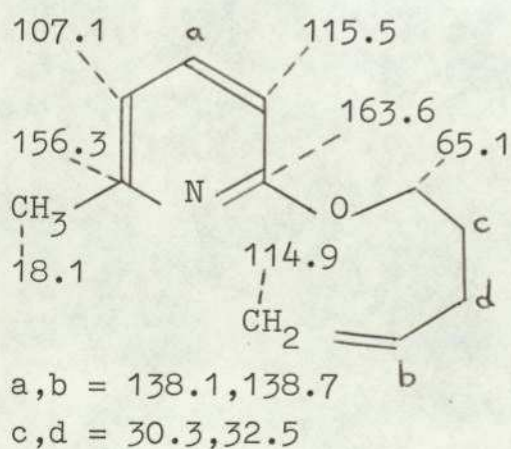
(73e)



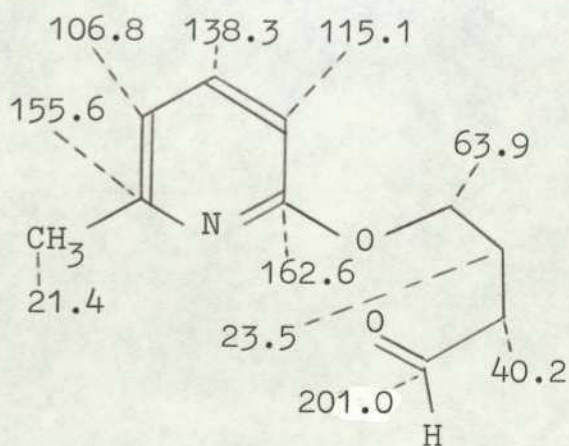
(52)



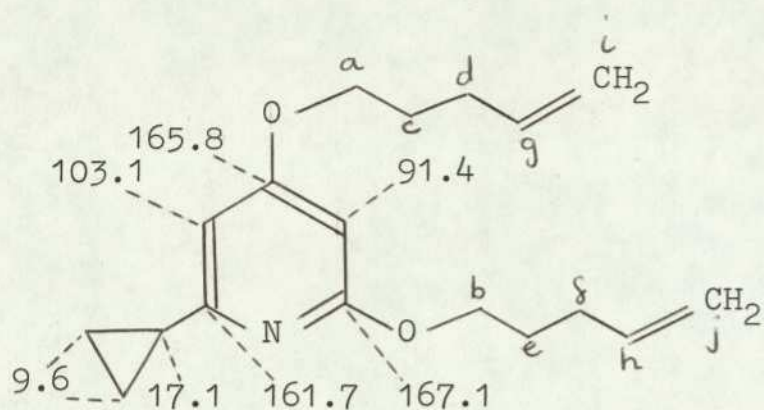
2-(but-3-en-1-oxo)-
3-methyl-2-pyridone



(44)

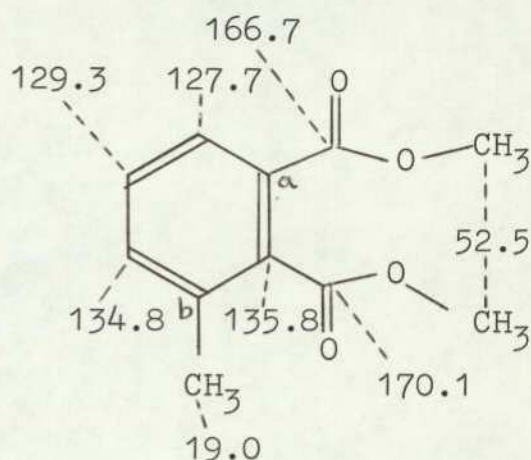


(45)

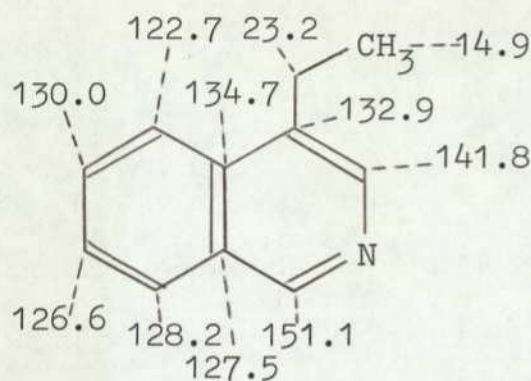


a,b = 65.1, 67.2, c,d,e,f = 28.2, 28.5
30.3, 30.3, i,j = 115.1, 115.6

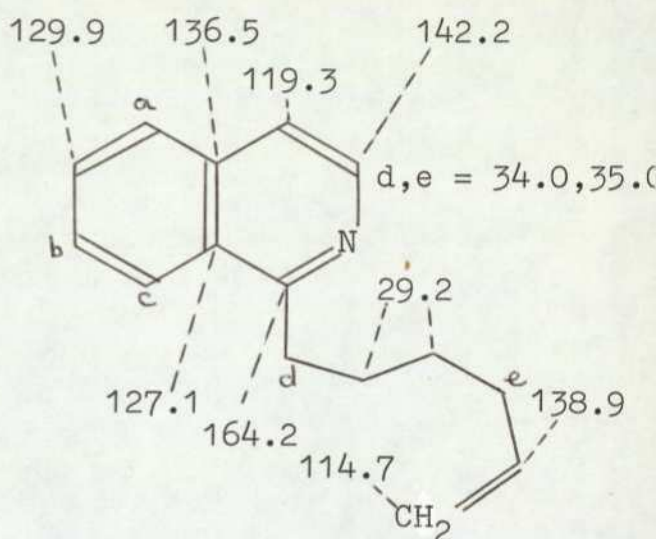
(109) g,h = 138.5, 137.9



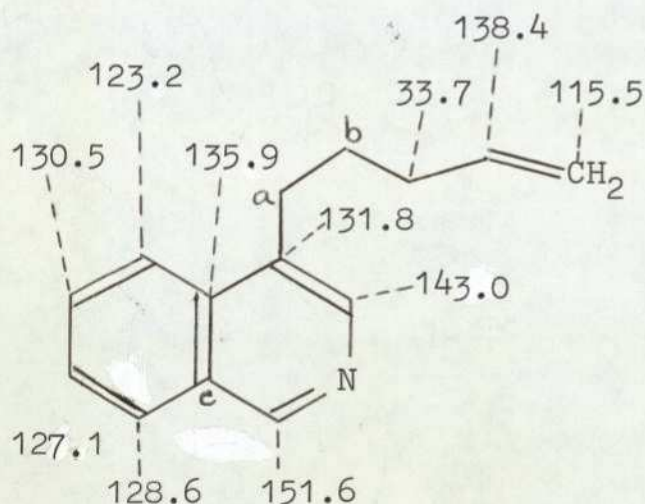
a,b = 128.1 and obscured
(85b)



4-ethylisoquinoline

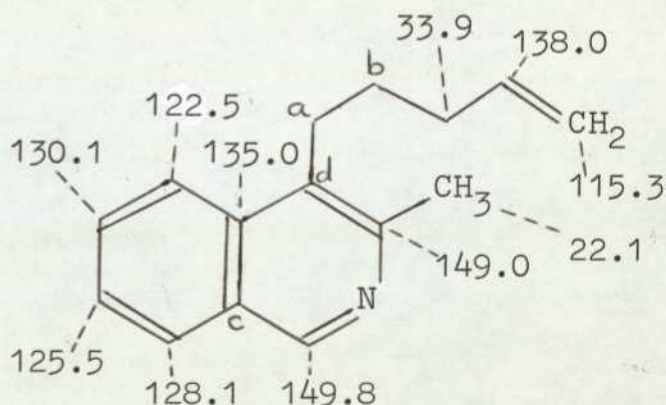


a,b,c = 127.6, 127.1, 125.5
(216)



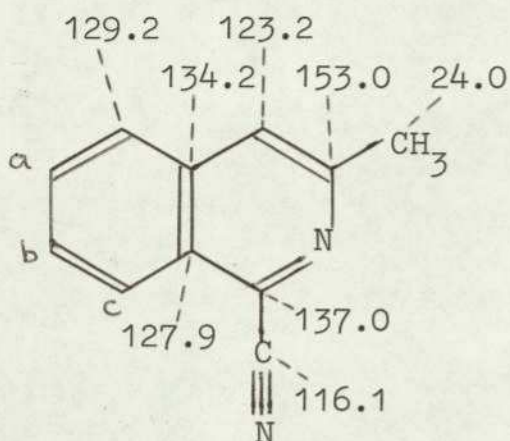
a,b = 29.6, 29.8 c obscured

(182)



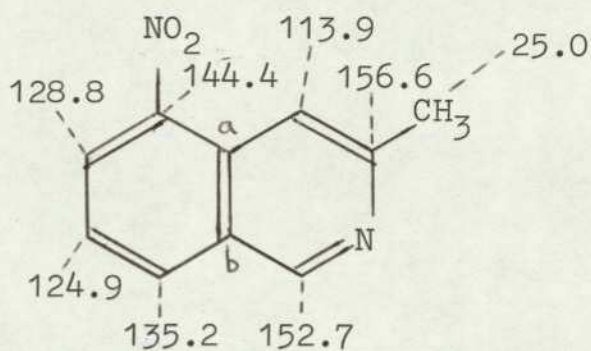
a,b = 27.4, 28.8; c,d obscured

(179)



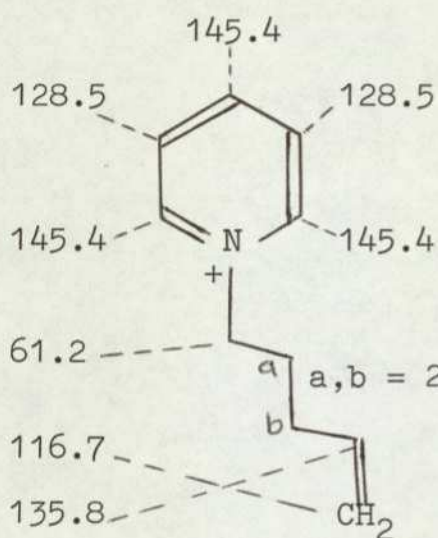
a,b,c = 131.9, 125.3, 127.1

(210)



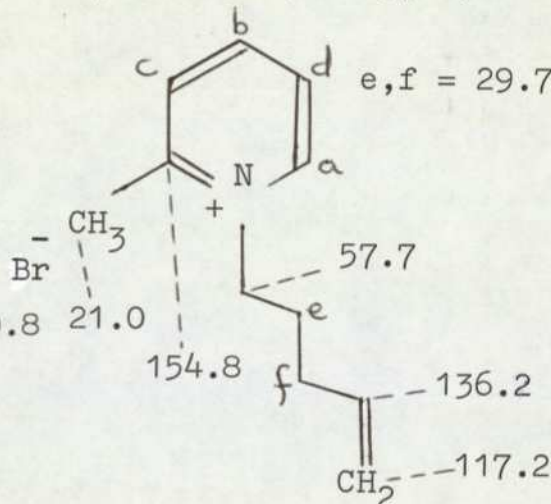
a,b = 127.6, 128.8

3-methyl-5-nitroisoquinoline

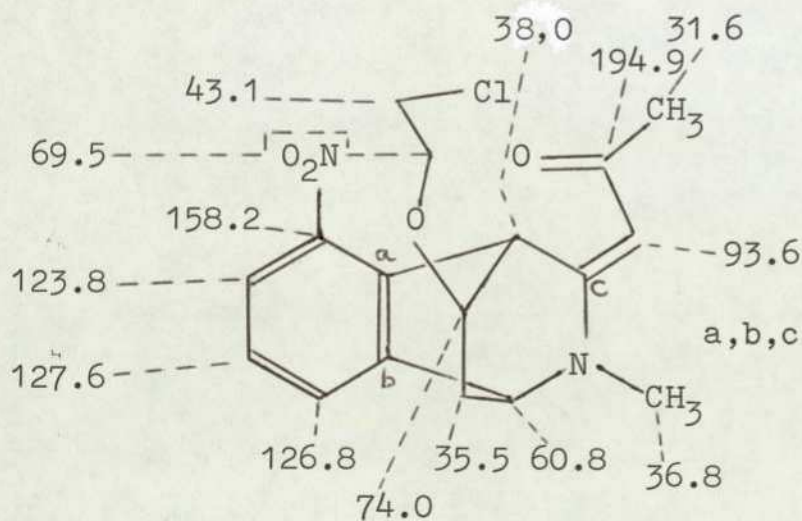


(136)

a,b = 145.8, 146.7; c,d = 127.0, 130.9
e,f = 29.7, 30.1



(137)



a,b,c = 130.7, 143.2, 148.2

(243)



EXPERIMENTAL SECTION

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

Infrared (i.r.) analysis was performed on a chloroform solution of the substrate, unless otherwise stated, on a Perkin-Elmer 157G spectrometer. Materials insoluble in chloroform were analysed as nujol mulls, and oils were generally run neat as thin films between sodium chloride plates. Frequencies of maximum absorptions are quoted ($\nu_{\max}$) in wavenumbers (cm^{-1}) using a polystyrene film as a reference.

Ultra-violet (UV) analysis was performed in all cases on ethanolic solutions of the substrate in quartz cells. Wavelengths of maximum absorbance ($\lambda_{\max}$) are given in nanometers (nm) along with the molar extinction coefficients at those points (ϵ).

Mass spectra data were obtained from the Physical and Chemical Measurement Unit (P.C.M.U.), Harwell or from an AEI MS30 instrument.

Proton nuclear magnetic resonance (^1H n.m.r.) analyses were performed on a Jeol MH 100 instrument. Deuteriochloroform solutions of the substrate were usually employed using tetramethylsilane (TMS) as an internal standard. Values of chemical shift are in δ values where δ is the magnitude of the frequency change in parts per million from the TMS signal.

Abbreviations s = singlet, d = doublet, t = triplet, q = quartet, dxd = doublet of doublets, m = complex multiplet, b = broad, exch. = disappears on addition of D_2O , are employed. Coupling constants (J) are quoted in units of Hz.

All solvents used were commercial reagent grade unless otherwise stated. Ethanol was dried by the addition of sodium followed by distillation immediately before use. Tetrahydrofuran (THF) was obtained dry by distillation from lithium aluminium hydride (LAH) prior to use. Acetonitrile and dimethylformamide were purified by distillation from calcium hydride, then were stored over 4A molecular sieves. Anhydrous magnesium sulphate was used to dry organic extracts and volatile solvents were evaporated in vacuo on a Büchi rotary evaporator. Moisture sensitive reactions were performed under an atmosphere of dry deoxygenated nitrogen.

Analytical t.l.c. investigations were carried out on 0.2 or 1.0 mm thin layers of Merck Kieselgel GF₂₅₄ silica and were monitored under a U.V. lamp or by development in iodine vapour. Large scale chromatographic separations were carried out using columns packed with MFC-120 mesh silica. A silica to compound weight ratio of between 30:1 and 70:1 was used.

Thermolyses were carried out on approximately 1-2 molar solutions of the substrate (unless stated otherwise) sealed in thick walled pyrex tubes. Prior to sealing the solution was degassed by freezing it solid, then remelting it under reduced pressure. The tube was sealed in a flame with its contents frozen and the upper part of the tube at reduced pressure. The products were obtained, after being heated, by breaking the upper part of the tube while the contents were frozen solid.

Butyl lithium was used as a 1.6M solution in cyclohexane. Unless otherwise indicated solvents employed in chromatographic separations were ethyl acetate/petroleum ether mixtures or methanol/chloroform mixtures.

General method for the preparation and
alkylation of 2-pyridone monoanions.

One equivalent of sodium ethoxide was prepared by dissolving the appropriate amount of sodium in freshly distilled ethanol. Added with stirring to an anhydrous solution of the pyridone in ethanol, the solvent was evaporated after 2 hours to yield a powder that was washed with ether. The electrophile (1.05-1.10 equivalents) was added neat, below the surface of a solution of the salt in dry DMF. This sometimes caused the immediate deposition of the sodium halide. Stirred overnight, the mixture was poured into cold water and washed with dichloromethane (3 x 30 ml). The combined organic fractions were washed free of DMF with water, then dried (MgSO_4), filtered and evaporated, in vacuo, to give a viscous oil. The t.l.c. of the crude mixture generally indicated the formation of two, new products, in addition to some regenerated starting pyridone. Specific details follow, listed according to the isolated substituted pyridone.

1,6-Dimethyl-2-pyridone

6-Methyl-2-pyridone (36), (7.83 g, 71.8 mmole) and iodomethane gave, after distillation, 1,6-dimethyl-2-pyridone as a white deliquescent low melting solid (4.05 g, 46%), m.p. $54-6^\circ$, (lit. $55-8^\circ$).²⁰⁶ All spectral data are in agreement with the literature values.²⁰⁶

1-(Pent-4-en-1-yl)-2-pyridone (37)

2-Pyridone (1), (3.72 g, 34.1 mmole) and 5-bromo-

pent-1-ene gave a black oil which, when chromatographed on silica with methanol/chloroform, afforded 1-(pent-4-en-1-yl)-2-pyridone (37) as a light-red oil (2.43 g, 39%) (Found: C, 73.45; H, 8.00; N, 8.51. $C_{10}H_{13}NO$ requires C, 73.59; H, 8.03; N, 8.58); $\nu_{\max}$ 3000-2825, 1659, 1586, 1145, 914 cm^{-1} ; $\lambda_{\max}$ 229.5 (6,300), 235 sh (4,750), 305 nm (5,050); δ 1.41-2.26 (4H, m), 3.90 (2H, t, J 7 Hz), 4.83-5.12 (2H, m), 5.52-5.97 (1H, m), 6.09 (1H, t, J 7 Hz), 6.44 (1H, d, J 9 Hz), 7.11-7.36 (2H, m); $n_D^{18} = 1.5417$. The O-alkylated isomer was not isolated.

1-(Pent-4-en-1-yl)-6-methyl-2-pyridone (38)

6-Methyl-2-pyridone (36) (3.00 g, 27.5 mmole) and 5-bromopent-1-ene gave a dark oil which, when chromatographed, first eluted 2-(pent-4-en-1-oxy)-6-methyl-2-pyridine (44) (3.02 g, 62%) as a pale yellow oil (Found: M^+ , 177.1152. $C_{11}H_{15}NO$ requires M^+ 177.1153); $\nu_{\max}$ (Neat) 3070, 2942, 1641, 1599, 1578, 1449, 1307, 1234, 790 cm^{-1} ; $\lambda_{\max}$ 219.5 (7,250), 275.5 nm (5,300); δ 1.71-1.97 (2H, m), 2.06-2.28 (2H, m), 2.39 (3H, s), 4.29 (2H, t, J 7 Hz), 4.87-5.13 (2H, m), 5.58-6.04 (1H, m), 6.40-6.64 (2H, dxd, J 9, 8 Hz), 7.28 (1H, t, J 7 Hz). The second product eluted was 1-(pent-4-en-1-yl)-6-methyl-2-pyridone (38), (0.49 g, 10%) as a dark oil (Found: M^+ 177.1152. $C_{11}H_{15}NO$ requires M^+ 177.1153); $\nu_{\max}$ 2963, 2920, 2882, 1657, 1570, 1552, 1436, 1411, 1128, 992, 914 cm^{-1} ; δ 1.54-1.93 (2H, m), 1.95-2.26 (2H, m), 2.36 (3H, s), 3.91 (2H, t, J 8Hz), 4.79-5.11 (2H, m), 5.51-5.98 (2H, m), 6.24 (1H, d, J 8Hz), 6.92-7.12 (1H, m).

1-(Pent-4-en-1-yl)-3-methyl-5-nitro-2-pyridone (43).

3-Methyl-5-nitro-2-pyridone (3.81 g, 24.7 mmole) and 5-bromopent-2-ene gave a brown oil which, when purified by column chromatography gave the title compound (43) (2.64 g, 48%) as an orange oil (Found: C, 59.46; H, 6.53; N, 12.43. $C_{11}H_{14}N_2O_3$ requires C, 59.45; H, 6.35; N, 12.60); $\nu_{\max}$ 3120-2795, 1662, 1624, 1584, 1505, 1344, 910 cm^{-1} ; $\lambda_{\max}$ 214 (4,850), 226 (5,000), 308 (5,800), 320 nm ϵ (5,450); δ 1.84-2.48 (7H, m), 4.13 (2H, t, J 7 Hz), 5.00-5.32 (2H, m), 5.69-6.16 (1H, m), 8.08 (1H, bs), 8.69 (1H, d, J 3 Hz); $n_D^{29} = 1.5830$. The O-alkylated isomer was not observed.

1-Butyl-6-methyl-2-pyridone (72)

6-Methyl-2-pyridone (36) (1.26 g, 11.6 mmole) and n-bromobutane gave a light red oil which was purified by column chromatography to yield 2-(but-1-oxy)-6-methyl-pyridine (71) (1.03 g, 66%) as the first product eluted (Found: C, 72.77; H, 9.47; N, 8.70. $C_{10}H_{15}NO$ requires C, 72.64; H, 9.15; N, 8.48); $\nu_{\max}$ (Neat) 3070, 2955, 2868, 1596, 1576, 1447, 1305, 1231, 788 cm^{-1} ; $\lambda_{\max}$ 218.5 (8,100), 275.5 nm (5,350); δ 0.96 (3H, t, J 7 Hz), 1.27-1.89 (4H, m), 2.38 (3H, s), 4.28 (2H, t, J 7 Hz), 6.51 (2H, t, J 8 Hz), 7.29 (1H, t, J 8 Hz); $n_D^{22} = 1.4865$. The second product eluted was 1-butyl-6-methyl-2-pyridone (72) (0.21 g, 13%) (Found: M^+ 165.1152. $C_{10}H_{15}NO$ requires M^+ 165.1154; $\nu_{\max}$ (Neat) 2951, 2928, 2864, 1656, 1575, 1549, 1411, 1153, 1127, 788 cm^{-1} ; δ 0.95 (3H, t, J 7 Hz), 1.18-1.85 (4H, m), 2.36 (3H, s), 3.99 (2H, t, J 7 Hz), 5.99 (1H, d, J 6 Hz), 6.34 (1H, d, J 9 Hz), 7.14 (1H, dxd, J 9,6 Hz).

1-(But-3-en-1-yl)-3-methyl-2-pyridone (42).

3-Methyl-2-pyridone (3.00 g, 27.0 mmole) and 4-bromobut-1-ene gave a pale yellow oil which, when chromatographed, gave as the first eluted product 2-(but-3-en-1-oxy)-3-methylpyridine (0.25 g, 6%) as a pale yellow oil (Found: M^+ 163.0993. $C_{10}H_{13}NO$ requires M^+ 163.0997);

$\nu_{\max}$ (Neat) 3078, 2979, 2948, 1644, 1596, 1587, 1465, 1449, 1425, 1254, 1115, 783 cm^{-1} ; δ 2.06 (3H, s), 2.30-2.61 (2H, m), 4.30 (2H, t, J 7 Hz), 4.87-5.16 (2H, m), 5.58-6.04 (1H, m), 6.56 (1H, dxd, J 7,5 Hz), 7.13 (1H, d, J 7 Hz), 7.83 (1H, d, J 5 Hz). The second product was 1-(but-3-en-1-yl)-3-methyl-2-pyridone (42) (1.04 g, 25%) (Found: M^+ 163.0994. $C_{10}H_{13}NO$ requires M^+ 163.0997); $\nu_{\max}$ (Neat) 3070, 2975, 2941, 2918, 1656, 1650, 1595, 1560, 1448, 1384, 1219, 771 cm^{-1} ; δ 2.09 (3H, s), 2.34-2.66 (2H, m), 3.94 (2H, t, J 7 Hz), 4.68-5.14 (2H, m), 5.50-6.09 (2H, m), 7.12 (2H, dxd, J 8,6 Hz).

1-(5-oxohex-1-yl)-3-methyl-2-pyridone (50).

3-Methyl-2-pyridone (2.00 g, 18.3 mmole) and 2-methyl-2-(4-bromobut-1-yl)-1,3-dioxolane (48) (4.30 g, 19.3 mmole) gave an orange oil which was stirred overnight in acetone with an excess of 2NHCl solution. The acetone was removed at the pump and the organic materials dissolved in dichloromethane. Neutralised with sodium bicarbonate solution, the aqueous layer was twice washed with dichloromethane and the organic portions combined. Dried ($MgSO_4$), filtered and evaporated to dryness the resultant oil was chromatographed to yield as the first eluted product 2-(5-oxohex-1-oxy)-3-methylpyridine (0.49 g, 13%) (Found:

C, 69.27; H, 8.32; N, 6.02; M^+ 207.1261. $C_{12}H_{17}NO_2$ requires C, 69.54; H, 8.27; N, 6.76; M^+ 207.1259); $\nu_{\max}$ (Neat) 2940, 1715, 1600, 1456, 1434, 1257, 1118, 792 cm^{-1} ; $\lambda_{\max}$ 217.5 (7,600), 274 nm (4,700); δ 1.47-1.97 (4H, m), 2.14 (3H, s), 2.18 (3H, s), 2.32-2.72 (2H, m), 4.34 (2H, t, J 7 Hz), 6.80 (1H, dxd, J 9,7 Hz), 7.45 (1H, d, J 9 Hz), 8.04 (1H, d, J 7 Hz). The second product eluted was 1-(5-oxohex-1-yl)-3-methyl-2-pyridone (50) (2.76 g, 73%) (Found: M^+ 207.1258. $C_{12}H_{17}NO_2$ requires M^+ 207.1259); $\nu_{\max}$ (Neat) 3030, 2790, 1740, 1648, 1593, 1562, 1214, 773 cm^{-1} ; $\lambda_{\max}$ 223 (4,850), 238 sh (3,950), 302 (5,450), 322 nm sh (3150); δ 1.37-1.94 (4H, m), 2.12 (6H, s), 2.50 (2H, t, J 7 Hz), 3.94 (2H, t, J 7 Hz), 6.06 (1H, t, J 7 Hz), 7.16 (2H, d, J 7 Hz).

1-(5-Methyl-6-carboethoxyhex-5-en-1-yl)-3-methyl-2-pyridone (52)

3-Methyl-2-pyridone (2.00 g, 18.3 mmole) and ethyl 7-bromo-3-methylhept-2-enoate (51)²⁰³ gave a brown oil which, when chromatographed on silica with ethyl acetate, gave as the first fraction unreacted bromide mixed with 2-(5-methyl-6-carboethoxyhex-5-en-1-oxy)-3-methylpyridine (53). The second fraction was 1-(5-methyl-6-carboethoxyhex-5-en-1-yl)-3-methyl-2-pyridone (52) (3.77 g, 74%) as a pale yellow oil (Found: M^+ 277.1668. $C_{16}H_{23}NO_3$ requires M^+ 277.1678); $\nu_{\max}$ 2976, 2913, 2860, 1705, 1650, 1588, 1563, 1373, 1151, 863 cm^{-1} ; $\lambda_{\max}$ 225 (15,130), 304.5 nm (5,720); δ 1.31 (3H, t, J 7 Hz), 1.40-2.03 (4H, m), 2.08-2.43 (8H, m), 4.01 (2H, t, J 7 Hz), 4.21 (2H, q, J = 7 Hz), 5.74 (1H, s), 6.17 (1H, t, J 7 Hz), 7.27 (2H, t, J 6 Hz).

n_D^{22} 1.5255. Both derivatives existed as a cis-trans mixture, 1/9 respectively, about the olefin.

Ethyl 7-bromo-3-methylhept-2-enoate (51).

Freshly distilled THF (40 ml) was added with stirring and ice-bath cooling to sodium hydride (2.68 g, 55.8 mmole), as a 50% oil dispersion, under a nitrogen atmosphere. Over a period of 40 min. triethyl phosphonoacetate (12.51 g, 55.8 mmole) in THF (10 ml) was dropwise added causing copious evolution of hydrogen; the temperature did not rise. Stirred for 1 hour at 0°, 6-bromohexan-2-one (10 g, 55.8 mmole) in THF (10 ml) was added dropwise over 45 min. with no obvious effect. The mixture was stirred to room temperature overnight. The brown phosphate deposit was dissolved in water and the non-aqueous products extracted into dichloromethane (3 x 20 ml). The organic portions were combined, dried (MgSO₄), filtered, then evaporated in vacuo. Distillation of the residue yielded 7-bromo-3-methylhept-2-enoate (51) (10.81 g, 85%) as a colourless oil b.p. 85° (2 mm); $\nu_{\max}$ 2970, 2930, 2858, 1710, 1643, 1447, 1208, 1143, 1045, 853 cm⁻¹; $\lambda_{\max}$ 224 nm (6,060); δ 1.30 (3H, t, J 8 Hz), 1.54-2.06 (4H, m), 2.11-2.38 (5H, m), 3.49 (2H, t, J 6 Hz), 4.21 (2H, q, J 8 Hz), 5.76 (1H, s). See text for behaviour when treated with Eu(fod)₃.

6-(Hex-5-en-1-yl)-2-pyridone (31).

6-Methyl-2-pyridone (36) (2.02 g, 18.5 mmole) was dissolved with stirring in THF (35 ml), and cooled to -23° (dry ice/CCl₄) under a slow current of nitrogen. n-Butyl lithium was added dropwise over 30 min. The solution

turned deep orange, then stirred briskly for a further 30 min. 5-bromopent-1-ene was slowly added. Left overnight the reaction mixture had turned to pale orange, and quenched with water the organic products were extracted into dichloromethane (3 x 20 ml). The organic portions were combined, dried (MgSO_4), filtered, concentrated in vacuo and chromatographed on silica with acetone/toluene to give 6-(hex-5-en-1-yl)-2-pyridone (31) (1.62 g, 50%), m.p. $52-4^\circ$, as a colourless solid (Found: C, 74.37; H, 8.89; N, 7.79. $\text{C}_{11}\text{H}_{15}\text{NO}$ requires C, 74.54; H, 8.53; N, 7.90); ν_{max} 3580, 2934, 2859, 1659, 1625, 1469, 1159, 912 cm^{-1} ; λ_{max} 230 (5,850), 306 nm (5,950); δ 1.09-2.24 (6H, m), 2.65 (2H, t, J 7 Hz), 4.81-5.16 (2H, m), 5.58-5.98 (1H, m), 6.07 (1H, d, J 7 Hz), 6.42 (1H, d, J 9 Hz), 7.24-7.50 (1H, m), 13.35 (1H, bs exch.).

6-(6-Oxohept-1-yl)-2-pyridone (49)

6-Methyl-2-pyridone (36) (2.00 g, 18.3 mmole) was dissolved with stirring in THF (35 ml) and cooled to -23° (dry ice/ CCl_4) under a slow stream of dry deoxygenated nitrogen. n-Butyl lithium (2.47 g, 38.8 mmole) was slowly introduced, producing the orange dianion, and after $1\frac{1}{2}$ hour 2-methyl-2-(4-bromobutyl)-1,3-dioxolane (48) (4.30 g, 19.3 mmole) was injected into the solution. Stirred to room temperature and acidified with 2N HCl (30 ml), then stirred overnight, the THF was evaporated at the pump and the products partitioned between water and dichloromethane. The aqueous layer was twice washed, then the organic extracts combined, dried (MgSO_4), filtered and the solvents evaporated in vacuo to yield a heavy brown oil. Silica

column chromatography with trichloromethane as eluent afforded 6-(6-oxohept-1-yl)-2-pyridone (49) (2.56g, 67%) as a colourless solid m.p. 76-9° (Found: C, 69.13; H, 8.33; N, 6.37. $C_{12}H_{17}NO_2$ requires C, 69.54; H, 8.27, N, 6.76); $\nu_{\max}$ 3470-3360, 2960-2740, 1709, 1647, 1610, 1155 cm^{-1} ; $\lambda_{\max}$ 229 (7,250), 308 nm (7,050); δ 1.08-1.90 (6H, m), 2.12 (3H, s), 2.45 (2H, t, J 7 Hz), 2.62 (2H, t, J 7 Hz), 6.07 (1H, d, J 7 Hz), 6.38 (1H, d, J 9 Hz), 7.35 (1H, dxd, J 9,7 Hz). 12.86-13.33 (1H, bs exch.).

1-Methyl-6-(hex-5-en-1-yl)-2-pyridone (35).

1,6-Dimethyl-2-pyridone (4.03 g, 32.8 mmole) was dissolved in THF (50 ml) with stirring and external cooling to -23° (dry ice/ CCl_4). Under a nitrogen atmosphere, n-butyl lithium (2.10 g, 32.8 mmole) was slowly introduced causing the solution to turn black. Stirred for 1½ hours 5-bromopent-1-ene (4.88 g, 32.8 mmole) was added and after a further period of stirring (2 hours) the mixture was allowed to warm to room temperature. Water was added, the resulting mixture ^{was} extracted with dichloromethane (3 x 20 ml), and the organic portions combined, dried ($MgSO_4$), filtered and evaporated to give a black oil. From the crude mixture the title compound (35) (0.41 g, 6.6%) was isolated by preparative t.l.c. as a brown oil (Found: M^+ 191.1309. $C_{12}H_{17}NO$ requires M^+ 191.1310); $\nu_{\max}$ 3063, 2921, 2856, 1656, 1647, 1560, 1548, 1432, 1156, 910, 793 cm^{-1} ; δ 1.41-1.84 (4H, m), 1.91-2.33 (2H, m), 2.64 (2H, t, J 7 Hz), 3.56 (3H, s), 4.83-5.18 (2H, m), 5.63-6.08 (1H, m), 6.07 (1H, d, J 7 Hz), 6.47 (1H, d, J 10 Hz), 7.26 (1H, dxd, J 9,7 Hz).

Ozonolysis of 2-(pent-4-en-1-oxy)-6-methyl-2-pyridone (44).

The pyridine (44) (1.01 g, 5.70 mmole) was dissolved in freshly distilled methanol (60 ml). Ozone was bubbled through the solution while the composition of the mixture was monitored by t.l.c. and g.l.c. Both techniques showed a smooth conversion of the substrate to a single product. A slight excess of ozone was added, then the reaction mixture poured into a zinc/acetic acid solution and shaken overnight. Iodine was not liberated from aqueous potassium iodide and so the mixture was neutralised with solid sodium carbonate. The organic products were taken up into dichloromethane and the water layer further washed (3 x 30 ml). Dried (MgSO_4), filtered, then concentrated, 2-(3-formylprop-1-oxy)-6-methyl pyridine (45) (0.80 g, 80%) was obtained in a state of high purity as a colourless oil; ν_{max} 2944, 2896, 2830, 2730, 1723, 1599, 1577, 1449, 1304, 1150, 1082, 990 cm^{-1} ; δ 1.82-2.14 (2H, m), 2.32 (3H, s), 2.48 (2H, t, J 7 Hz), 4.16 (2H, d, J 7 Hz), 6.38 (1H, d, J 8 Hz), 6.58 (1H, d, J 8 Hz), 7.32 (1H, t, J 8 Hz), 9.73 (1H, d, J 1 Hz); ^{13}C n.m.r. δ 201.0.

2-(4-Piperidinobut-3-en-1-oxy)-6-methylpyridine (47).

Freshly distilled piperidine (0.14 g, 1.65 mmole) and THF (20 ml) were mixed at 0° under a nitrogen atmosphere. Anhydrous potassium carbonate (41.1 mg, 0.297 mmole) was added with stirring, followed by a solution of the aldehyde (45) (0.145 g, 0.81 mmole) in THF (5 ml). After 3 hours the mixture was filtered under nitrogen and washed with THF. Heating at 60° for 30 min. then evaporation of the solvent yielded a pale yellow oil of pure 2-(4-

Piperidinobut-3-en-1-oxy)-6-methylpyridine (47) (1.06 g, 97%); ν_{max} 2909, 2862, 1643, 1593, 1572, 1440, 1298, 903, 856 cm^{-1} ; δ 1.30-1.68 (6H, m), 2.22-2.54 (5H, m), 2.60-2.93 (4H, m), 4.00-4.52 (3H, m), 5.90 (1H, d, J 15 Hz), 6.47 (1H, d, J 8 Hz), 6.64 (1H, d, J 8 Hz), 7.38 (1H, t, J 8 Hz).

Thermolysis of enamine (47).

A solution of the enamine (47) in acetonitrile was degassed, then sealed under reduced pressure and thermolysed at 150° for 10 hours. The solvents were evaporated at reduced pressure and ^1H n.m.r. examination revealed the enamine largely intact. Redissolved and thermolysed at 180° for 12 hours a complex mixture was obtained. From this 6-methyl-2-pyridone (36) was obtained in 82% yield, following preparative t.l.c. purification.

Attempted preparation of the enamine of 1-(5-oxohex-1-yl)-3-methyl-2-pyridone (50) with pyrrolidine.

The ketopyridone (50) (0.33 g, 1.59 mmole) and freshly distilled pyrrolidine (0.28 g, 3.96 mmole) were mixed together in benzene with a catalytic amount of tosic acid. Heating at reflux overnight, employing a Soxhlet extractor charged with 4A molecular sieves, gave no reaction. The solvent was changed to toluene, but still no reaction was observed following evaporation of the solvent. Starting material was recovered unchanged.

Attempted ozonolysis of 6-(hex-5-en-1-yl)-2-pyridone (31) and 1-(pent-4-en-1-yl)-3-methyl-5-nitro-2-pyridone (43).

When pyridones (31) and (43) were subjected to the same ozonolysis conditions employed for alkenyl pyridine (44), at room temperature or -65° , work-up with either zinc and acetic acid or DMSO gave only polymeric materials. T.l.c. analysis showed a moderately clean conversion of the olefin to another product but this could never be isolated. Following the method of Slomp,³⁵ who monitored the disappearance of the i.r. absorption for the olefin, was not viable in this instance (see text).

Thermolysis of alkenyl pyridones.

All thermolyses were performed under reduced pressure in sealed tubes containing approximately 1.2 molar degassed solutions of the pyridones in either DMF or acetonitrile. The sealed tubes were encased in large lengths of gas piping to protect the oven in the event of an explosion, and these were placed in a preheated oven at the required temperature. The tubes were cooled in a stiff breeze when the thermolysis time had been completed and the upper parts of the tubes broken after the contents had been cooled to liquid nitrogen temperatures.

The solvent was removed at the pump from the freshly thermolysed solution and the crude mixture was examined by ^1H n.m.r. and t.l.c. techniques. At the higher temperatures minor amounts of poorly defined products could occasionally be observed by both methods, but their isolation was not possible. Product formation was always associated with copious streaking due to decomposition

of the precursor. Frequently the parent pyridone was identified following t.l.c. investigations. Low vacuum fractional distillations of these mixtures also proved fruitless. The alkenyl pyridones were remarkably stable over the 50-250° range but they rapidly decomposed at higher temperatures. The 5-nitro-derivative (43) decomposed at 200°. The breakdown of ester pyridone (52) above 250° clearly involves loss of the carboethoxy group, since the i.r. spectrum of the small amount of product isolated retained a pyridone absorption at 1652 cm⁻¹. This peak was associated with a shoulder at 1648 cm⁻¹ which is probably due to a carbon-carbon double bond. The ester absorption, formerly at 1705 cm⁻¹ is totally absent. The ¹H n.m.r. spectrum agrees with the loss of the ester group and shows the appearance of new methyl signals at δ 1.62 and 1.73 indicative of isomers. The pyridone nucleus is intact and still substituted by an N-methylene group. Two poorly defined olefinic peaks are present, as a broad singlet δ 4.60-4.82, and a triplet δ 5.15 (J 6 Hz). It seems likely that these compounds correspond to those proposed in Scheme 14.

Acetonitrile was employed as solvent for the pyrolyses above 200° due to the instability of DMF at these temperatures. Use of DMF often resulted in explosions, dimethylamine could invariably be noted. Other solvents such as toluene and mesitylene were occasionally employed.

Some Lewis acids were utilised as catalysts, including boron trifluoride etherate, and stannic chloride. These too gave no products derived from cycloaddition, they only lowered the temperature at which the substrates

decomposed. Catalytic amounts of sodium t-butoxide gave similar results.

Isomerisation of 2-butoxy-6-methylpyridine (71) to 1-butyl-6-methyl-2-pyridone (72).

2-Butoxy-6-methylpyridine (71) (73.2 mg, 0.44 mmole) and a small drop of n-bromobutane were sealed in a ^1H n.m.r. tube as a solution of degassed DMF. Heated at 140° , until virtually all of the pyridine had been consumed (445 hours, estimated by ^1H n.m.r.), the products were separated by preparative t.l.c.. 6-Methyl-2-pyridone (36) (21.3 mg, 44%), 1-n-butyl-6-methyl-2-pyridone (72) (15.7 mg, 21%) and 1,6-dimethyl-2-pyridone (10.4 mg, 19%) were all identified by comparison with authentic material.

1-Methyl-4-phenyl-2-pyridone (73e).

To 4-phenylpyridine (2.84 g, 18.3 mmole) in acetonitrile (20 ml) was added dimethyl sulphate (2.31 g, 18.3 mmole) with stirring. Heated gently at reflux overnight the pale pink solution was evaporated to dryness giving 5.13 g of the methosulphate. Potassium ferricyanide (13.71 g, 41.7 mmole) was dissolved with stirring and ice-bath cooling into water (30 ml). An aqueous solution of the methosulphate and an aqueous solution of sodium hydroxide were separately, and simultaneously added dropwise over 30 min. After stirring (4 hours), the yellow deposit of the ferricyanide was filtered off and washed with dichloromethane. The aqueous phase was washed with dichloromethane and the combined organic extracts dried (MgSO_4), filtered and evaporated to give highly pure 1-methyl-4-

phenyl-2-pyridone (73e) (2.40 g, 71%) m.p. 139-41° (Found: M^+ 185.0846, $C_{12}H_{11}NO$ requires M^+ 185.0841); $\nu_{\max}$ 2965, 1656, 1588, 1580, 1408, 1341, 869 cm^{-1} ; δ 3.60 (3H, s), 6.48 (1H, dxd, J 7,2 Hz), 6.87 (1H, d, J 2 Hz), 7.39-7.75 (6H, m).

2-Methyl-2-aza-3-oxo-5-phenyl-bicyclo-[2.2.2]octa-5,7-diene-7,8-dicarboxylate (74e).

1-Methyl-4-phenyl-2-pyridone (0.22 g, 1.19 mmole) was dissolved in dry acetonitrile (1 ml) with DMAD (0.194 g, 13.7 mmole). The solution was degassed, sealed under reduced pressure then thermolysed at 80° for 72 hours. Examination of the crude mixture revealed that no reaction had taken place. The solvent and remaining DMAD were removed in vacuo. The pyridone was then sealed neat deoxygenated in a slight excess of DMAD and thermolysed at 80° for 72 hours. The major product was separated from unreacted pyridone by preparative t.l.c. to yield the title compound (74e) (115 mg, 36%) as a pale yellow oil (Found: M^+ 327.1077. $C_{18}H_{17}NO_5$ requires 327.1107); $\nu_{\max}$ 2948, 2845, 1720, 1685, 1647, 1434, 1330, 1121 cm^{-1} ; δ 2.99 (3H, s), 3.90 (6H, s), 5.20 (1H, d, J 2 Hz), 5.30 (1H, d, J 6 Hz), 6.98 (1H, dxd, J 6,2 Hz), 7.32-7.61 (5H, m).

Dimethyl-4-phenylphthalate (75e).

To 1-methyl-4-phenyl-2-pyridone (75e) (0.18 g, 0.973 mmole) dissolved in the minimum quantity of dry acetonitrile was added DMAD (0.159 g, 1.12 mmole). Deoxygenated, sealed in a glass tube, the mixture was thermo-

lysed at 140° for 14 hours. Analytical t.l.c. indicated that a single product formed, although much of the pyridone remained. The crude mixture was resealed in acetonitrile with a further equivalent of DMAD and thermolysed for 48 hours at 145°. This process was repeated until all of the pyridone had been consumed. Preparative t.l.c. yielded dimethyl-4-phenylphthalate (75e) as a heavy pale yellow oil (0.196 g, 75%) (Found: M^+ 270.0900. $C_{16}H_{14}O_4$ requires 270.0892); $\nu_{\max}$ (Neat) 3050, 3025, 2994, 2944, 1721, 1607, 1431, 1271, 1128, 1075, 962, 757, 698 cm^{-1} ; δ 4.00 (6H, s), 7.41-8.03 (8H, m).⁶⁹

The phthalate (75e) was also obtained following thermolysis of an acetonitrile solution of adduct (74e) for 48 hours at 140°.

Dimethyl 3-methylphthalate (75b).

To 1-(5-oxohex-1-yl)-3-methyl-2-pyridone (50) (0.187 g, 0.903 mmole) was added DMAD (0.14 g, 1.11 mmole) in acetonitrile (1 ml). Degassed, the solution was sealed then thermolysed at 150° for 48 hours. Analytical t.l.c. indicated a minor amount of novel product and the decomposition of the DMAD; much of the precursor (50) remained however. Another equivalent of the dienophile was added and the mixture again thermolysed at 150° for 48 hours. This process was repeated until the pyridone had been completely consumed. The solvents were then evaporated in vacuo and volatile materials were distilled under reduced pressure. The distillate was purified by preparative t.l.c. to give dimethyl 3-methylphthalate (75b) (0.171 g, 91%) as a colourless oil; $\nu_{\max}$ (Neat) 2994, 2948, 2840, 1721,

1593, 1435, 1278, 1196, 1150, 1114, 1072, 1020, 958, 882, 829, 768, 753, 700 cm^{-1} ; δ (CCl_4), 2.30 (3H, s), 3.87 (6H, s), 7.16-7.42 (2H, m), 7.62-8.05 (1H, m).⁶⁸

Similarly (75b) was obtained in 86% yield from the thermolysis of 1-(5-methyl-6-carboethoxyhex-5-en-1-yl)-3-methyl-2-pyridone (52) with an excess of DMAD.

General method for the preparation of 4-hydroxy-2-pyridones.

Sodium hydride (1.03 g, 42.7 mmole) as a mineral oil dispersion was added to freshly distilled THF (100 ml) with stirring. A nitrogen atmosphere and ice-bath cooling were applied. Ethyl acetoacetate (5.03 g, 38.8 mmole) was added dropwise causing much evolution of hydrogen. The solution temperature was maintained below 5° during the basification, and during the subsequent period of stirring (30 min.) ensuring total monoanion formation. n-Butyl lithium (2.61 g, 40.7 mmole) was added dropwise, similarly maintaining the solution temperature below 5° for 30 min. as the yellow-orange dianion formed. The nitrile was dissolved in THF (10 ml) and added in one portion. The colour of the reaction mixture changed to deep-red for reacting aromatic nitriles, fluorescent-yellow for alkyl nitriles or not at all for non-reaction. Warmed to room temperature overnight the solution was filtered, then, with 2N NaOH, neutralised to give a fine deposit of the pyridone. This was filtered and washed with water, then acetone. Air drying gave high purity 6-substituted-4-hydroxy-2-pyridones. Specific details follow listed according to the nitrile used. All ^1H n.m.r. spectra were run in DMSO (d^6), except where otherwise stated, and all i.r. spectra in Nujol.

Benzonitrile (4.20 g, 4.07 mmole)

6-Phenyl-4-hydroxy-2-pyridone (80 g) was obtained at a yield of 2.11 g (30%) as a white powder m.p. $311-6^{\circ}$ (decomp.) (lit. $315-22^{\circ}$)⁹⁵ (Found: M^{+} 187.0634. $C_{11}H_9NO_2$ requires 187.0633); $\nu_{\max}$ 3280-2200, 1645, 1618, 1593, 1579, 1276, 1211, 765, 696 cm^{-1} ; $\lambda_{\max}$ 225 sh (18,000), 304 nm (9,250); δ 5.97 (1H, d, J 2 Hz, exch.), 6.53 (1H, d, J 2 Hz), 7.73-8.17 (5H, m), 10.80-11.76 (2H, bs, exch.).

Acetonitrile (1.67 g, 40.7 mmole).

6-Methyl-4-hydroxy-2-pyridone (80a) was obtained at a yield of 0.39 g (8%) as off white crystals m.p. $312-6^{\circ}$ (decomp.) (lit. $315-20^{\circ}$)⁹⁵; $\nu_{\max}$ 3150-2200, 1629, 1598, 1344, 1258, 1227, 1168, 825, 719 cm^{-1} ; δ 2.13 (3H, s), 5.78 (1H, s, exch.), 6.02 (1H, s), 10.80-11.62 (2H, bs, exch.).

p-Chlorobenzonitrile (5.60 g, 40.7 mmole).

6-(p-Chlorophenyl)-4-hydroxy-2-pyridone (80 j) was obtained at a yield of 2.62 g (30%) as a fine white powder m.p. $320-2^{\circ}$ (lit. 324°)⁹⁵; $\nu_{\max}$ 3260-2200, 1648, 1623, 1587, 1564, 1212, 827, 822 cm^{-1} ; $\lambda_{\max}$ 217 sh (21,050), 232 (18,000), 308 nm (10,950); δ 5.55 (1H, s, exch.), 6.15 (1H, s), 7.58 (2H, d, J = 8 Hz), 7.67 (2H, d, J 8 Hz). The aqueous layer was thoroughly washed with ether (3 x 50 ml) which was then combined with the THF phase. Washed with water (2 x 50 ml) the organic solution was shaken with 2N HCl (50 ml). Immediately a buff deposit formed which was separated by filtration and washed with acetone. Air drying yielded ethyl 3-oxo-5,7-di(p-chlorophenyl)-6,8-

diazaocta-5,7-dienoate hydrochloride (2.94 g, 19%); $\nu_{\max}$ (Nujol) 2675b, 1752, 1729, 1625, 1594, 1530, 1250, 1093, 839 cm^{-1} ; δ ($\text{CF}_3\text{CO}_2\text{H}$) 1.07 (3H, t, J 7 Hz), 3.40 (2H, s), 3.57 (2H, s), 4.11 (2H, q, J 7 Hz), 7.30 (4H, s), 7.28 (2H, d, J 9 Hz), 7.54 (2H, d, J 9 Hz). A small sample of this salt was dissolved in 2N sodium bicarbonate solution and the deposited oil collected in dichloromethane. Following drying (MgSO_4), filtering and evaporating, the resultant yellow solid was purified by preparative t.l.c. to yield the free base (92) as a colourless solid m.p. 54-5 $^{\circ}$ (Found: C, 59.36; H, 4.71; N, 7.02. $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_3\text{Cl}_2$ requires C, 59.27; H, 4.47; N, 6.91); $\nu_{\max}$ 3396, 1719, 1712, 1642, 1596, 1092, 1010 cm^{-1} ; δ (CDCl_3) 1.08 (3H, t, J 7 Hz), 2.93 (2H, s), 3.17 (2H, s), 3.99 (2H, q, J 7 Hz), 7.04-7.62 (6H, m), 7.85 (2H, d, J 9 Hz), 9.00-10.02 (1H, bs, exch.).

When treated similarly the organic phases from experiments leading to (80 a,c,e,g,h,j) yielded nothing except regenerated ethyl acetoacetate.

p-Toluonitrile (4.54 g, 38.8 mmole)

6-(p-tolyl)-4-hydroxy-2-pyridone (80h) was obtained at a yield of 0.52 g (8%) as a white powder m.p. 280-5 $^{\circ}$ (decomp.) (Found: M^+ 201.0770. $\text{C}_{12}\text{H}_{11}\text{NO}_2$ requires M^+ 201.0790); $\nu_{\max}$ 3260-2120, 1649, 1619, 1596, 1566, 1513, 1283, 1217, 812 cm^{-1} , $\lambda_{\max}$ 214 sh (22,550), 231 sh (15,250), 308 nm (10,700); δ 2.33 (3H, s), 5.58 (1H, d, J 2 Hz, exch.), 6.13 (1H, d, J 2 Hz), 7.44 (2H, d, J 9 Hz), 7.78 (2H, d, J 9 Hz), 10.52-11.44 (2H, bs, exch.).

σ -Toluenitrile (4.77 g, 40.8 mmole)

6-(σ -tolyl)-4-hydroxy-2-pyridone (80i) was obtained at a yield of 0.13 g, 2% as a colourless powder m.p. 299-303 $^{\circ}$ (Found: M^{+} 201.0763. $C_{12}H_{11}NO_2$ requires M^{+} 201.0790); $\nu_{\max}$ 3280-2280, 3090, 1644, 1621, 1586, 1570, 1356, 1268, 1213, 763 cm^{-1} ; δ 2.24 (3H, s), 5.49 (1H, s, exch.), 5.66 (1H, s), 7.25 (4H, bs), 10.20-11.34 (2H, bs, exch.).

p-Methoxybenzonitrile (5.40 g, 40.7 mmole)

6-(p-Methoxyphenyl)-4-hydroxy-2-pyridone (80l) was obtained as an off-white powder at a yield of 0.59 g (7%) m.p. 258-76 $^{\circ}$ (decomp.) (Found: M^{+} 217.0723. $C_{12}H_{11}N_2O_2$ requires 217.0739); $\nu_{\max}$ 3120-2100, 1632, 1611, 1577, 1510, 1325, 1210, 1175, 1030, 820 cm^{-1} ; $\lambda_{\max}$ 245 (9,200), 311 nm (10,950); δ 3.88 (3H, s), 5.68 (1H, d, J 2 Hz, exch.), 6.20 (1H, d, J 2 Hz), 7.07 (2H, d, J 9 Hz), 7.77 (2H, d, J 9 Hz).

p-Fluorobenzonitrile (4.95 g, 40.7 mmole)

6-(p-fluorophenyl)-4-hydroxy-2-pyridone (80m) was obtained at a yield of 3.12 g (36%) as a colourless powder m.p. 345-9 $^{\circ}$ (decomp.) (Found: C, 64.08; H, 4.03; N, 6.65. $C_{11}H_8NO_2F$ requires C, 64.39; H, 3.93; N, 6.83); $\nu_{\max}$ 3240, 3200-2150, 3100, 1644, 1622, 1600, 1582, 1509, 1285, 1222, 1215, 1160, 844, 830 cm^{-1} ; $\lambda_{\max}$ 228 (21,800), 300 nm (8,950); δ 5.56 (1H, d, J 2 Hz, exch.), 6.09 (1H, d, J 2 Hz), 7.18 (2H, t, $J_{HoHm} = J_{HmF} = 9$ Hz), 7.67 (2H, dxd, $J_{HoHm} = 9$ Hz, $J_{HoF} = 6$ Hz).

p-Dicyanobenzene (2.39 g, 18.7 mmole)

6-(p-cyanophenyl)-4-hydroxy-2-pyridone (80k) was obtained at a yield of 2.86 g (72%) as a buff powder m.p. 379-82° (decomp.) (Found: C, 67.98; H, 3.70; N, 13.27. $C_{12}H_8N_2O_2$ requires C, 67.92; H, 3.80; N, 13.20); $\nu_{\max}$ 3530-2100, 3020, 2210, 1640, 1616, 1588, 1278, 1212, 846, 839 cm^{-1} ; $\lambda_{\max}$ 233 (23,100), 318 (9,750), 349 nm (5,400); δ 5.73 (1H, d, J 2 Hz, exch.), 6.34 (1H, d, J 2 Hz), 7.86 (4H, s).

2-Cyanopyridine (4.24 g, 40.8 mmole)

6-(σ -pyridyl)-4-hydroxy-2-pyridone (80p) was obtained at a yield of 2.36 g (32%) as a buff powder m.p. 232° (decomp.) (Found: C, 64.01; H, 4.25; N, 14.40. $C_{10}H_8N_2O_2$ requires C, 63.83; H, 4.29; N, 14.89); $\nu_{\max}$ 3340, 1659, 1608, 1594, 1491, 1362, 1228, 847, 828, 763, 739 cm^{-1} ; $\lambda_{\max}$ 222 (17,850), 232 sh (15,450), 242 sh (11,300), 324 nm (9,250); δ 5.80 (1H, d, J 2 Hz, exch.), 6.83 (1H, d, J 2 Hz), 7.41-7.72 (1H, dxdxd, J 6,4,2 Hz), 7.85-8.30 (2H, m), 8.66-8.87 (1H, m).

4-Cyanopyridine (4.15 g, 40.7 mmole)

6-(p-Pyridyl)-4-hydroxy-2-pyridone (80r) was obtained at a yield of 5.22 g (72%) as a buff powder m.p. 233-5° (decomp.) (Found: C, 63.60; H, 4.30; N, 14.62. $C_{10}H_8N_2O_2$ requires C, 63.83; H, 4.29; N, 14.89); $\nu_{\max}$ 3620-2380, 3060, 1659, 1629, 1605, 1548, 1347, 1281, 1208, 817, 796 cm^{-1} ; $\lambda_{\max}$ 238 (13,750), 309 nm (5,600); δ 5.68 (1H, d, J 2 Hz, exch.), 6.39 (1H, d, J 2 Hz), 7.71 (2H, d, J 6 Hz), 8.65 (2H, d, J 6 Hz).

n-Butyronitrile (2.81 g, 40.8 mmole)

6-n-Propyl-4-hydroxy-2-pyridone (80b) was isolated as a colourless powder m.p. 278-83° (decomp.) (lit. 279°)⁷⁹
 $\nu_{\max}$ 3320-2140, 3150, 1630, 1589, 1482, 1239, 1229, 1170, 855, 816 cm⁻¹; δ 0.90 (3H, t, J 7 Hz), 1.28-2.00 (2H, m), 2.40 (2H, t, J 7 Hz), 5.50 (1H, d, J 2Hz, exch.), 5.70 (1H, d, J 2 Hz).

i-Butyronitrile (2.81 g, 40.8 mmole)

6-i-Propyl-4-hydroxy-2-pyridone (80c) was obtained at a yield of 0.36 g (7%) as a colourless powder m.p. 280-4° (Found: C, 62.80; H, 7.22; N, 8.99. C₈H₁₁NO₂ requires C, 62.73; H, 7.24; N, 9.14); $\nu_{\max}$ 3320-2090, 3090, 1669, 1628, 1591, 1352, 1246, 1229, 825 cm⁻¹; $\lambda_{\max}$ 212 (16,250), 282 nm (5,750); δ 1.03 (6H, d, J 7 Hz), 2.52 (1H, septet, J 7 Hz), 5.27 (1H, d, J 2 Hz, exch.), 5.52 (1H, d, J 2 Hz).

Cyclopropanitrile (2.60 g, 40.8 mmole)

6-Cyclopropyl-4-hydroxy-2-pyridone (80d) was obtained at a yield of 2.37 g (40%) as a colourless powder m.p. 292-4° (Found: C, 63.25; H, 6.15; N, 9.16. C₈H₉NO₂ requires C, 63.56; H, 6.00; N, 9.27); $\nu_{\max}$ 3600-2100, 3060, 3030, 1630, 1592, 1232, 1200, 849 cm⁻¹; $\lambda_{\max}$ 230 (2,350), 287 nm (7,750); δ 0.57-1.15 (4H, m), 1.59-1.97 (1H, m), 5.25-5.49 (2H, m) integration halved on addition of D₂O, 11.13-12.37 (2H, bs, exch.).

Phenyl isothiocyanate (5.51 g, 40.8 mmole).

1-Phenyl-6-mercapto-4-hydroxy-2-pyridone (93.) was obtained as a light-red solid at a yield of 2.10 g (25%) (Found: M^+ 219.0355. $C_{11}H_9O_2NS$ requires 219.0354); $\nu_{\max}$ 3310-2110, 1619, 1598, 1500, 1233, 1194, 824, 763, 694 cm^{-1} ; $\lambda_{\max}$ 216 (19,650), 327 nm (7,800); δ 5.63 (1H, d, J 2 Hz, exch.), 6.26 (1H, bs, exch.), 7.15-7.59 (5H, m).

Nitriles that did not give a 6-substituted-4-hydroxy-2-pyridone include trimethylacetone nitrile, trichloroacetone nitrile, phenylacetone nitrile, p-nitrobenzotrile, m-cyanopyridine, crotonitrile and ethyl cyanoacetate. Other compounds containing the nitrile function that did not give pyridone products include phenyl isocyanate, methyl isocyanate and methyl isothiocyanate.

Attempted alkylation of 4-hydroxy-2-pyridones.

6-Cyclopropyl-4-hydroxy-2-pyridone (80d) with sodium ethoxide

The pyridone (80d) (0.5 g, 3.31 mmole) was stirred into a slurry with ethanol (30 ml). To this was added a freshly prepared solution of sodium ethoxide [sodium (76 mg 3.31 mmole) in ethanol (15 ml)]. The base caused the total dissolution of the pyridone and stirred for 2 hours, bromobutane (0.45 g, 3.48 mmole) was injected into the mixture. Stirred a further 40 hours the solvents were removed in vacuo and the salt obtained dissolved in water. Neutralisation produced only the starting material (80d).

The same experiment, when repeated employing an extra equivalent of base again gave only regenerated starting material.

6-Cyclopropyl-4-hydroxy-2-pyridone (80d) with *n*-butyl-lithium.

The pyridone (80d) (0.5 g, 3.31 mmole) was dissolved with stirring in dry DMSO (12 ml) under a nitrogen atmosphere. *n*-Butyl lithium (0.44 g, 6.88 mmoles) was added dropwise causing the deposition of the pyridone monoanion. Efficient stirring maintained the mobility of the mixture. After 1½ hours 5-bromopent-1-ene (0.52 g, 3.48 mmole) was slowly added and the mixture stirred overnight. Poured into chilled water, organic products were extracted into dichloromethane and thoroughly washed with water (10 x 20 ml). Dried (MgSO₄), filtered, evaporated and chromatographed on silica, two products were identified. The least polar compound was 2,4-di-(pent-4-en-1-oxy)-6-cyclopropyl-pyridine (109) (0.24 g, 49% based on the amount of the alkyl group incorporated) as a mobile colourless oil. (Found: M⁺ 287.1890. C₁₈H₂₅NO₂ requires M⁺ 287.1885); $\nu_{\max}$ (Neat) 3071, 2999, 2930, 1639, 1600, 1573, 1467, 1439, 1410, 1363, 1181, 1148, 1050, 912, 828 cm⁻¹; $\lambda_{\max}$ 225 (6,350), 268.5 nm (4,150); δ 0.70-1.11 (4H, m), 1.55-2.03 (5H, m), 2.03-2.36 (4H, m), 3.96 (2H, t, J 7 Hz), 4.25 (2H, t, J 7 Hz), 4.91-5.22 (4H, m), 5.65-6.15 (2H, m), 5.97 (1H, d, J 2 Hz), 6.36 (1H, d, J 2 Hz). The second product was 4-(pent-4-en-1-oxy)-6-cyclopropyl-2-pyridone (110) (0.13 g, 17%) as colourless crystals m.p. 80-3° (Found: M⁺ 219.1260, C₁₃H₁₇NO₂ requires M⁺ 219.1259); $\nu_{\max}$ 3384, 2920, 1655 sh, 1649, 1640, 1635 sh, 1438 b, 1378, 1150, 914 cm⁻¹; $\lambda_{\max}$ 215.5 (23,300), 224 sh (4,850), 289 nm (7,300); δ 0.69-1.21 (4H, m), 1.54-2.44 (5H, m), 3.90 (2H, t, 6 Hz), 4.81-5.21 (2H, m), 5.47 (1H, d, J 2 Hz), 5.69

(1H, d, J 2 Hz), 5.60-6.13 (1H, m).

4-Hydroxy-2-pyridone (80, R = H) with *n*-butyl lithium

Treated in a manner similar to that described above, 4-hydroxy-2-pyridone (80, R = H) (1.00 g, 9.01 mmole), *n*-butyl lithium (1.21 g, 18.9 mmole), and 5-bromopent-1-ene (1.48 g, 9.91 mmole) also gave two novel products. The least polar was 1-(pent-4-en-1-yl)-4-(pent-4-en-1-oxy)-2-pyridone (113) (0.32 g, 26% based on the amount of the alkyl group incorporated) (Found: C, 72.39; H, 8.86; N, 5.55; M^+ 247.1578. $C_{15}H_{21}NO_2$ requires C, 72.84; H, 8.56; N, 5.66; M^+ 247.1572); $\nu_{\max}$ (Neat) 3075, 2934, 1657, 1589, 1542, 1337, 1225, 994, 912, 825 cm^{-1} ; $\lambda_{\max}$ 224.5 sh (4550), 284 nm (3250); δ 1.57-2.40 (8H, m), 3.93 (2H, t, J 7 Hz), 3.98 (2H, t, J 6 Hz), 4.97-5.26 (4H, m), 5.68-6.15 (4H, m), 7.23 (1H, d, J 9 Hz). The second product was 1-(pent-4-en-1-yl)-4-hydroxy-2-pyridone (114) (0.11 g, 7%) as a colourless crystalline solid m.p. 140-7° (Found: M^+ 179.0943. $C_{10}H_{13}NO_2$ requires M^+ 179.0946); $\nu_{\max}$ 3508-2100, 2923, 2858, 1656, 1649, 1561, 1539, 1495, 1300, 993, 912, 834 cm^{-1} ; $\lambda_{\max}$ 283 nm (4100); δ 1.46-2.24 (4H, m), 3.89 (2H, t, J 7 Hz), 4.91-5.20 (2H, m), 5.59-6.10 (3H, m), 7.15 (1H, d, J 8 Hz).

Repetition of this reaction using one equivalent only of *n*-butyl lithium gave, as the only isolable product 1-(pent-4-en-1-yl)-4-(pent-4-en-1-oxy)-2-pyridone (113) (0.21 g, 20% based on the amount of the alkyl group incorporated).

Thermolysis of 6-cyclopropyl-4-hydroxy-2-pyridone (80d) with DMAD.

The pyridone (80d) (210 mg, 1.39 mmole) and DMAD (200 mg, 1.41 mmole) were dissolved in dry DMF (3 ml). The solution was degassed, sealed under reduced pressure and thermolysed at 70° for 4 hours. Dichloromethane (5 ml) and water (5 ml) were added and the deposited unreacted pyridone filtered off (110 mg). Preparative t.l.c. purification afforded cis- and trans-6-cyclopropyl-4-(1,2-dicarbomethoxyvinyl)-2-pyridone (130) (0.155 g, 38%) as an inseparable mixture m.p. 127-31° (Found: M^+ 293.0903.

$C_{14}H_{15}NO_6$ requires M^+ 293.0899); $\nu_{\max}$ 2952, 1728, 1641, 1433, 1354, 1275, 1150, 1028, 963 cm^{-1} ; $\lambda_{\max}$ 228 (10,200), 299 nm (6050); δ 0.86-1.38 (4H, m), 1.77-2.15 (1H, m).

3.78, 3.88 (fumarate) and 3.84, 3.92 (maleate) (6H, 4xs), 5.86 (olefinic H_{maleate}) + 6.74 (olefinic H_{fumarate}) (1H, 2xs), 5.63, 5.68, 5.72, 5.95 (2H, 4xd, J 2 Hz). An isomer mixture of fumarate: maleate of 40:60 was obtained. Performed at 80° the isomer ratio altered to 30:70.

Thermolysis of 4-hydroxy-2-pyridone (80, R = H) with DMAD

The pyridone (80, R = H) (0.158 g, 1.42 mmole) and DMAD (0.222 g, 1.56 mmole) were thermolysed and worked-up as directed for the 6-cyclopropyl derivative. A mixture of cis- and trans-4-(1,2-dicarbomethoxyvinyl)-2-pyridone (127) (0.168 g, 47%) was obtained as a pale yellow foam

m.p. 57-8° (Found: M^+ 253.0588. $C_{11}H_{11}NO_6$ requires 253.0586); $\nu_{\max}$ 3480-2300, 2950, 1729, 1662, 1554, 1435, 1354, 1000 cm^{-1} ; $\lambda_{\max}$ 220 (23,500), 299 nm (6,850);

δ [maleate] 2 x CH_3O -(3.80, s), C(3)-H (5.89, d, J 2 Hz),

C(5)-H (6.16, dxd, J 7,2 Hz), C(6)-H (7.12, d, J 7 Hz), olefinic H (6.39, s); δ [fumarate] 2 x CH₃O-(3.80, s), C(3)-H (5.96, d, J 3 Hz), C(5)-H (6.16, dxd, J 7,2 Hz), C(6)-H (7.07, d, J 7 Hz), olefinic H (7.02, s).

1-Methyl-6-(p-pyridyl)-4-hydroxy-2-pyridone (131)

6-(p-pyridyl)-4-hydroxy-2-pyridone (80r) (0.50 g, 2.66 mmole) was mixed with dimethyl sulphate (1.81 g, 14.4 mmole). To this was added slowly 3N sodium hydroxide solution (7 ml) with vigorous stirring. Left 4-5 hours the red solution turned orange, and neutralisation with 2N HCl caused the deposition of a fine solid. Filtered and dried in vacuo over P₂O₅ 1-methyl-6-(p-pyridyl)-4-hydroxy-2-pyridone (131) (0.103 g, 19%) was obtained as an off white solid m.p. 198-205° (Found: M⁺ 202.0740. C₁₁H₁₀N₂O₂ requires M⁺ 202.0742); ν max (Nujol) 3550-2360, 3030, 1645, 1568, 1339, 1209, 830, 794, 748 cm⁻¹; δ (CD₃OD) 3.31 (3H, s), 5.93 (1H, d, J 2 Hz), 6.10 (1H, d, J 2 Hz), 7.46-7.73 (2H, m), 8.01, (1H, txd, J 8,2 Hz resp.), 8.68 (1H, dxd, J 6,1 Hz).

Treated similarly 6-cyclopropyl-4-hydroxy-2-pyridone (80d) gave none of the N-methylated derivative.

6-Cyclopropyl-4-tosyl-2-pyridone

Pyridone (80d) (2.00 g, 13.2 mmole) was dispersed in vigorously stirred trichloromethane (100 ml). To this was added triethylamine (1.34 g, 13.2 mmole), and tosyl chloride (2.52 g, 13.2 mmole). Stirred overnight, the solution was filtered of unreacted starting material (80d) (0.22 g) then washed with water (5 x 50 ml), dried (MgSO₄),

filtered and evaporated to dryness. Trituration with ether removed the small amount of ditosylated pyridine to give 6-cyclopropyl-4-tosyl-2-pyridone (133) (3.30 g, 80%) as a colourless solid m.p. 147.5-148.5° (Found: C, 59.04; H, 4.69; N, 4.44. $C_{15}H_{15}NO_4S$ requires C, 59.00; H, 4.95; N, 4.59); $\nu_{\max}$ (Nujol) 1655, 1649, 1613, 1191, 1176, 1122, 1091, 964, 858, 845, 756, 665 cm^{-1} ; $\lambda_{\max}$ 229.5 (15,700), 276.5 (1,700), 311 nm (7,100); δ 0.65-1.27 (4H, m), 1.70-2.04 (1H, m), 2.46 (3H, s), 6.64 (1H, d, J 2 Hz), 6.95 (1H, d, J 2 Hz), 7.33 (2H, d, J 8 Hz), 7.75 (2H, d, J 8 Hz), 12.55-13.03 (1H, bs, exch.).

Attempts to form 6-cyclopropyl-4-cyano-2-pyridone.

6-Cyclopropyl-4-tosyl-2-pyridone (133) (0.100 g, 3.28 mmole) was dissolved in ^{30 ml of} dichloromethane, acetonitrile and two flasks of DMF as part of four separate experiments. To each was added, with stirring, potassium cyanide (3.5 mmole) and to the first two a catalytic amount of 18 C 6 crown ether. One of the DMF solutions was heated at 60° under nitrogen after one week of fruitless stirring at room temperature. After one week at 60° no reaction had occurred, thermolysis at 120° decomposed the precursors. After one week no reaction could be observed for the crown ether solutions and so the cyclic polyether was made up to one equivalent in both mixtures. Left stirring for three months, with the remaining DMF solution almost no reaction could be perceived.

General method for the alkylation of isoquinoline and 3-methylisoquinoline

Isopropylcyclohexylamine (ICA) was dissolved in freshly distilled THF (40 ml) and cooled to 0° under a continuous flow of nitrogen. To this was added dropwise n-butyl lithium in cyclohexane and after 30 min. the mixture was cooled to -78° (dry ice/acetone). The isoquinoline was slowly added as a solution in THF, causing a light-red colour formation which deepened during the subsequent period of stirring (1 hour) at -78°. The electrophile was added over a period of 15 min., neat if liquid or as a THF solution. Where stated, in the individual details, the reaction mixture was worked-up immediately, otherwise it was allowed to stir to room temperature overnight, then be worked up.

Equal volumes of 2NHCl and dichloromethane (50 ml) were added to the reaction mixture and the nitrogen containing products were extracted with dilute acid in the usual manner. Basification of the acidic extract released the heterocyclic bases and ICA and these were taken up into dichloromethane. Dried (MgSO₄) and filtered, as much of the hindered base (ICA) was evaporated as was possible, in vacuo. The products were then purified, where possible, by silica column chromatography eluting with ethyl acetate/petroleum ether mixtures, or, alternatively a small portion of reaction mixture was purified by preparative t.l.c. in similar solvent systems. Some products proved inseparable from the unreacted isoquinoline and were subsequently worked up as binary mixtures.

Specific details follow listed according to the

electrophile involved, first for 3-methylisoquinoline (175) then the parent isoquinoline (151). The reaction was occasionally performed on one-quarter scale quantities.

3-Methylisoquinoline

5-Bromopent-1-ene: the tan oil obtained from ICA (0.99 g, 6.99 mmole), n-butyl lithium (0.45 g, 6.99 mmole), 3-methylisoquinoline (175) (1.00 g, 6.99 mmole) and the bromide (1.04 g, 6.99 mmole) was 3-methyl-4-(pent-4-en-1-yl)-isoquinoline (179) (0.69 g, 47%); the methiodide was prepared almost quantitatively by iodomethane in acetonitrile giving canary-yellow crystals m.p. 146-8° (with previous surface change 78-80°) (Found: C, 54.42; H, 5.53; N, 3.88. $C_{16}H_{20}NI$ requires C, 54.40; H, 5.71; N, 3.97); $\nu_{\max}$ (Nujol) 3090, 1638, 1607, 1503, 1398, 928, 783 cm^{-1} ; $\lambda_{\max}$ 224 sh (43,200), 248 (58,300), 272 (2,650), 281 (2,800), 292 (1,600), 340 sh (5,750), 349 nm (6,600); δ 1.55-1.94 (2H, m), 2.11-2.42 (2H, m), 2.93 (3H, s), 3.04-3.30 (2H, m), 4.70 (3H, s), 4.97-5.26 (2H, m), 5.60-6.10 (1H, m), 7.67-8.09 (3H, m), 8.52 (1H, d, J 9 Hz), 10.61 (1H, s).

Bromoethane: Prepared from ICA (1.04 g, 7.34 mmole), n-butyl lithium (0.47 g, 7.34 mmole) 3-methylisoquinoline (175) (1.00 g, 6.99 mmole) and the bromide (0.80 g, 7.34 mmole), 3-methyl-4-ethylisoquinoline (180) could only be obtained as a mixture with (175). Estimations by 1H n.m.r. indicated a yield of 0.49 g (41%); δ 1.20 (3H, t, J 8 Hz), 2.68 (3H, s), 2.97 (2H, q, J 8 Hz), 7.36-7.94 (4H, m), 8.96 (1H, s). The methiodide of the mixture was prepared

from the bases and iodomethane yielding a yellow crystalline solid (Found: M^+ 186.1276. $C_{13}H_{16}NI$ requires M^+ 186.1283).

3-Phenyl-1-bromopropane: Prepared from ICA (0.25 g, 1.77 mmole), *n*-butyl lithium (0.11 g, 1.75 mole), 3-methylisoquinoline (175) (0.25 g, 1.78 mmole) and the bromide (0.35 g, 1.76 mmole), 3-methyl-4-(3-phenylprop-1-yl)isoquinoline (181) could only be obtained as a mixture with unreacted (175). 1H N.m.r. estimations indicate a yield of 0.16 g (34%); δ 1.70-2.09 (2H, m), 2.68 (3H, s), 2.46-3.13 (4H, m), 6.98-7.79 (9H, m), 8.87 (1H, s). The mixture was quaternised as previously described (Found: M^+ 261.1516. $C_{19}H_{19}NI$ requires M^+ 261.1518).

Benzyl chloride: The monoanion of (183) was prepared from ICA (1.04 g, 7.34 mmole), *n*-butyl lithium (0.45 g, 7.34 mmole) and 3-methylisoquinoline (1.00 g, 6.99 mmole) and was allowed to warm to -20° . The benzyl chloride (0.93 g, 7.34 mmole) was added and the standard work-up procedure adopted. A solid, inseparable mixture of 3-methyl-4-benzylisoquinoline (183) and (175) was obtained with the benzyl derivative formed at an estimated yield of 0.24 g (21%) (Found: M^+ 233.1214. $C_{17}H_{15}N$ requires M^+ 233.1204); δ 2.69 (3H, s), 4.38 (2H, s), 6.99-7.98 (9H, m), 9.17 (1H, s). 1,2-Diphenylchloroethane was isolated from this reaction in increasing yield as the temperature of addition of the benzyl chloride was lowered.

p-Methylbenzonitrile: a brown oil was obtained from ICA (0.25 g, 1.77 mmole), n-butyl lithium (0.11 g, 1.75 mmole), 3-methylisoquinoline (175) (0.25 g, 1.77 mmole) and p-toluonitrile (0.21 g, 1.79 mmole) which was purified by preparative t.l.c. to give (3-isoquinolylmethyl)-p-tolyl ketone (185a) (50 mg, 11%) as a colourless solid m.p. 106-10° (Found: (M-1)⁺ 260.1066. C₁₈H₁₅NO requires (M-1)⁺ 260.1075); $\nu_{\max}$ 1678, 1622, 1589, 1486, 1451, 1322, 1263, 966, 879 cm⁻¹; δ 2.38 (3H, s), 4.60 (2H, s), 7.11-8.07 (9H, m), 9.17 (1H, s).

4-Cyanopyridine: From ICA (1.06 g, 7.52 mmole), n-butyl lithium (0.48 g, 7.52 mmole), 3-methylisoquinoline (175) (1.02 g, 7.13 mmole) and 4-cyanopyridine (0.78 g, 7.50 mmoles) was obtained yellow crystals, from chloroform, of [3-(2-hydroxy-2-(4-pyridyl))-vinyl]-iso-quinoline (186a) (0.60 g, 34%) m.p. 137-8° (Found: C, 77.59; H, 4.71; N, 11.28; M⁺ 248.0949. C₁₆H₁₂N₂O requires C, 77.40; H, 4.87; N, 11.28; M⁺ 248.0949); $\nu_{\max}$ 3450-3090, 2944, 1621, 1596, 1485, 1451, 1308, 956, 879 cm⁻¹; $\lambda_{\max}$ 232 (87,000), 244.5 (66,000), 274 (46,500), 285 (42,500), 348 nm (115,000); δ 6.35 (1H, s), 7.40-8.04 (7H, m), 8.68 (2H, d, J 6 Hz), 9.12 (1H, s), 14.20-14.50 (1H, bs, exch.). In deuteriochloroform a keto-enol tautomeric mixture is established with the equilibrium position very much in favour of the enol.

An excess of diazomethane in methanol caused the disappearance from the ¹H n.m.r. spectrum of the enolic low field proton, and the formation of a three proton singlet at δ 3.78. A brown oil was obtained which was though to be [3-(2-methoxy-2-(4-pyridyl))-vinyl]-iso-

quinoline (187) (Found: M^+ 262.1087. $C_{17}H_{14}N_2O$ requires 262.1106).

Benzophenone: ICA (1.02 g, 7.23 mmole), n-butyl lithium (0.46 g, 7.23 mmole), 3-methylisoquinoline (175) (1.07 g, 7.06 mmole) and benzophenone (1.36 g, 7.47 mmole) gave a brown oil, which when purified by preparative t.l.c. was identified as 3-isoquinolyl-(3-methyl-1-isoquinolyl)-methane (192) (0.62 g, 61%) (Found: M^+ 284.1292. $C_{20}H_{16}N_2$ requires M^+ 284.1313); $\nu_{\max}$ 3045, 2914, 1625, 1589, 1580 sh, 1562, 950, 873 cm^{-1} ; $\lambda_{\max}$ 220 (82,600), 264.5 (8,000), 272.5 (8,050), 280.5 (6,350), 319 (6,300), 328 nm (7,250); δ 2.75 (3H, s), 5.00 (2H, s), 7.19-7.93 (9H, m), 8.20 (1H, d, J 9 Hz), 9.14 (1H, s).

Bromine: ICA (1.64 g, 11.6 mmole), n-butyl lithium (0.74 g, 11.6 mmole), 3-methylisoquinoline (175) (1.02 g, 7.20 mmole) and bromine (1.73 g, 10.82 mmole) gave 3-isoquinolyl-(3-methyl-1-isoquinolyl)-methane (192) identical to that prepared previously. When this reaction was repeated and worked-up one minute after addition of the bromine the same product (192) was obtained in the same yield.

Electrophiles that did not yield adducts with the 3-methylisoquinoline anion (177) include dimethyl maleate, deuterium oxide, p-chlorobenzonitrile, 2-chloroethyl vinyl ether, ethyl chloroformate, dimethylformamide, 3-phenylpropionaldehyde, trimethyl silyl chloride, carbon dioxide and dimethyl sulphate. Attempts to alkylate 3-methyl-5-nitroisoquinoline with 5-bromopent-1-ene by this method were unsuccessful.

Isoquinoline

5-Bromopent-1-ene: ICA (0.99 g, 6.99 mmole), n-butyl lithium (0.45 g, 6.99 mmole), isoquinoline (151) (0.90 g, 6.99 mmole) and 5-bromopent-1-ene (1.04 g, 6.99 mmole) gave a brown oil, which when purified by preparative t.l.c. yielded 4-(pent-4-en-1-yl)-isoquinoline (182) (0.45 g, 33%). Quaternisation with iodomethane gave yellow needles of the methiodide m.p. 104-5° (Found: C, 52.96; H, 5.37; N, 4.42; M^+ 212.1439. $C_{15}H_{18}NI$ requires C, 53.12; H, 5.35; N, 4.13; M^+ 212.1433); $\nu_{\max}$ (Nujol) 1638, 1607, 1399, 1184, 1155, 992, 867, 782, 632 cm^{-1} ; $\lambda_{\max}$ 232 (44,350), 273 (2250), 280 (2600), 290 (2000), 329 (4450), 340 nm (5050); δ 1.73-2.40 (4H, m), 3.22 (2H, t, J 8 Hz), 4.79 (3H, s), 4.94-5.22 (2H, m), 5.63-6.09 (1H, m), 7.82-8.30 (3H, m), 8.68 (1H, d, J 9 Hz), 8.74 (1H, s), 10.58 (1H, s).

3-Phenyl-1-bromopropane: ICA (1.13 g, 7.98 mmole), n-butyl lithium (0.51 g, 7.98 mmole), isoquinoline (151) (1.00 g, 7.75 mmole), and 3-phenyl-1-bromopropane (1.62 g, 8.14 mmole) gave a yellow oil which yielded, on purification by preparative t.l.c. a mixture of (151) and 4-(3-phenylprop-1-yl)-isoquinoline (143; R = CH₂CH₂CH₂Ph) (0.38g, 20% by 1H n.m.r.); δ 1.89-2.30 (2H, m), 2.77 (2H, t, J 8 Hz), 3.05 (2H, t, J 8 Hz), 7.10-8.07 (9H, m), 8.43 (1H, s), 9.16 (1H, s).

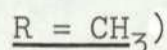
Substitution products were not obtained for deuterium oxide, carbon dioxide, or 4-cyanopyridine.

Alkylation using a "complex base"

tert-Butyl alcohol was mixed with ICA in a molar ratio of 1:2 respectively, to give a 1:2 molar excess of base over isoquinoline when the mixture was fully activated by n-butyl lithium. The alkylation procedure is identical to that of the general method described previously. Alkylation of isoquinoline (151) by this method gave 4-(pent-4-en-1-yl)-isoquinoline (182) (0.43 g, 28%) from ICA (1.15 g, 8.14 mmole), t-butyl alcohol (0.30 g, 4.08 mmole), n-butyl lithium (0.78 g, 12.2 mmole), isoquinoline (1.00 g, 8.16 mmole) and 5-bromopent-1-ene (1.21 g, 8.16 mmole). The isoquinoline anion in this instance was yellow-orange. No isoquinoline was recovered.

Repetition of this reaction using a 1.5 molar excess of ICA and n-butyl lithium, instead of the complex base, yielded 25% of (182) only. The reaction mixture in this instance was far less free of decomposition products than that from the complex base reaction. Yields from both reactions were slightly less than those observed by the normal alkylation method.

1-Cyano-2-benzoyl-3-methyl-1,2-dihydroisoquinoline (201;



To potassium cyanide (8.38 g, 0.129 mole) in water (50 ml) was added finely ground 3-methylisoquinoline (175) (5 g, 0.035 mole) with vigorous stirring. Benzoyl chloride (12.52g, 0.0891 mole) was added dropwise over 30 min. A mobile, orange oil slowly separated out which, after 1 hour solidified to a peach-coloured mass. The supernatant liquid was carefully decanted off and then the

remaining solid was dissolved in dichloromethane, washed with dilute sodium hydroxide solution, dilute hydrochloric acid and then water. The organic extract was dried (MgSO_4), filtered and concentrated in vacuo to a viscous, red oil. The 1-cyano-2-benzoyl-3-methyl-1,2-dihydroisoquinoline (201; $\text{R} = \text{CH}_3$) crystallised from ethanol (7.91 g, 83%) m.p. $125-7^\circ$ (lit. $127-8^\circ$)¹⁷⁸; ν_{max} 1662, 1631, 1607, 1574, 1487, 1447, 1368, 1344, 1287, 1150, 1122, 908 cm^{-1} ; δ 1.82 (3H, s), 6.30 (1H, bs), 6.58 (1H, s), 7.16-7.70 (9H, m)

Attempted preparation of 1-cyano-1-(pent-4-en-1-yl)-2-benzoyl-3-methyl-1,2-dihydroisoquinoline (202; $\text{R}^1 = \text{CH}_3$, $\text{R}^2 = \text{CH}_2(\text{CH}_2)_2\text{CH}:\text{CH}_2$)

Method 1. Sodium hydride (0.44 g, 18.2 mmole) was washed free of the mineral oil with freshly distilled THF. A DMF (10 ml) slurry under nitrogen was formed, with ice-bath cooling. A solution of 1-cyano-2-benzoyl-3-methyl-1,2-dihydroisoquinoline (201; $\text{R}^1 = \text{CH}_3$) (3.00 g, 10.9 mmole) in DMF (50 ml) was added dropwise over 30 min. Each drop caused a deep-red colouration which dissipated immediately. Much hydrogen was evolved and when this ceased 5-bromopent-1-ene (1.79 g, 12.0 mmole) was added over 30 min. at 0° . Stirred for 36 hours the solvents were removed in vacuo, maintaining a water-bath temperature of below 40° . Addition of methanol decomposed the excess of sodium hydride and caused the crystallisation of 1-benzoyl-3-methylisoquinoline (205) (1.85 g, 68%) m.p. $100-1^\circ$ (Found: C, 82.30; H, 5.26; N, 5.67; M^+ 247.9969, $\text{C}_{17}\text{H}_{13}\text{NO}$ requires C, 82.57; H, 5.30; N, 5.66; M^+ 247.9971); ν_{max}

3045, 2955, 1668, 1622, 1596, 1589, 1579, 1563, 1448, 1165, 968, 883 cm^{-1} ; δ 2.62 (3H, s), 7.39-8.23 (10H, m).

Method 2. To the Reissert compound (201; $\text{R}^1 = \text{CH}_3$) (2.00 g, 7.30 mmole) and 5-bromopent-1-ene (1.20 g, 8.03 mmole) in DMF (30 ml) was added sodium hydride (0.19 g, 8.03 mmole) under a nitrogen atmosphere. Much hydrogen was evolved and after stirring for 2 hours, the mixture was poured onto crushed ice. The organic products were extracted into trichloromethane, dried (MgSO_4), filtered and evaporated to give a red oil that crystallised from ethanol to give 1-benzoyl-3-methylisoquinoline (205) identical with previous material (1.23 g, 68%).

Method 3. To the Reissert compound (201; $\text{R}^1 = \text{CH}_3$) (2.16 g, 7.92 mmole), dissolved in DMF (30 ml) with 5-bromopent-1-ene (1.42 g, 8.71 mmole) was added, with stirring, sodium hydride (0.21 g, 8.71 mmole) under a nitrogen atmosphere at -40° (dry ice/acetone). No reaction occurred, the solution was allowed to warm. At -10° hydrogen began to evolve, and when this ceased the red reaction mixture was poured onto crushed ice. The organic products were extracted into trichloromethane, dried (MgSO_4), filtered and evaporated in vacuo to give a red oil which crystallised to yield 1-benzoyl-3-methylisoquinoline (205) (65%, 1.27 g) identical with previous material.

1-Cyano-2-phenylsulphonyl-3-methyl-1,2-dihydroisoquinoline
(209)

To potassium cyanide (7.60 g, 0.117 mole) dissolved in water (60 ml) was added 3-methylisoquinoline powder

(5.00 g, 35.0 mmole) with vigorous mechanical stirring. Phenylsulphonyl chloride (12.89 g, 62.0 mmole) was added dropwise at 0° and this mixture then stirred for 4 hours at room temperature. The black mixture was poured onto crushed ice, extracted with trichloromethane, washed with water, dilute hydrochloric acid, water, dilute sodium hydroxide solution and finally water. After drying (MgSO₄), it was filtered and evaporated at the pump to give a dark oil, which crystallised from ethanol to give the title compound (209) at a yield of 40% (4.33 g) m.p. 131.5-133.0° (lit. 132-4°)¹⁸³; ν_{max} 3050, 2954, 2924, 1637, 1479, 1445, 1360, 1163, 1089, 988, 947, 869 cm⁻¹; δ 2.36 (3H, s), 6.32 (1H, bs), 6.40 (1H, s), 6.56-7.66 (9H, m).

1-Cyano-3-methylisoquinoline (210)

1-Cyano-2-phenylsulphonyl-3-methyl-1,2-dihydroisoquinoline (209) (1.84 g, 5.94 mmole) was dissolved in freshly distilled xylene. Sodium hydride (0.143 g, 5.94 mmole) was added and the system heated at reflux for 2 hours.¹⁸³ Filtration, and evaporation of the solvent gave the starting material as a mixture with mineral oil.

To the Reissert analogue (209) (4.10 g, 13.2 mmole) dissolved in dry DMF was added sodium hydride (0.46 g, 19.0 mmole); hydrogen was vigorously evolved. Stirred overnight, water was added and the deposit taken up in trichloromethane. The aqueous layer was washed twice with trichloromethane (40 ml), the organic portions combined, dried (MgSO₄), filtered and evaporated to yield the title compound (210) (1.20 g, 54%) m.p. 102-4° (lit. 103-4°)¹⁸³; ν_{max} 2957, 2924, 2234, 1628, 1584, 1561, 1408, 1329, 1282,

1154, 887 cm^{-1} ; δ 2.76 (3H, s), 7.56-7.87 (4H, m), 8.10-8.34 (1H, m).

(But-3-en-1-yl)(3-methylisoquinolin-1-yl) ketone (211)

Under an atmosphere of nitrogen, with stirring, 4-bromobut-1-ene (0.67 g, 5.00 mmole) was added dropwise to THF (10 ml) containing magnesium turnings (0.12 g, 5.00 mmole). The temperature rose and the magnesium began to dissolve. When this ceased the mixture was heated at reflux (1 hour), then ice-cooled. The isoquinoline (210) (0.60, 3.57 mmole) in dry THF (2 ml) was introduced over 10 min. causing the mixture to darken. The black solution was stirred at room temperature (2 hours), then acidified (6N H_2SO_4), causing the deposition of material that was taken up in dichloromethane. Washed with water twice more, the organic extracts were combined, dried (MgSO_4), filtered and evaporated to dryness. The resulting heavy brown oil was chromatographed to give the title compound (211) as a pale yellow mobile oil (0.46 g, 58%) (Found: M^+ 225.1130. $\text{C}_{15}\text{H}_{15}\text{NO}$ requires M^+ 225.1154); ν_{max} 3070, 2975, 2918, 2852, 1693, 1639, 1621, 1587, 1438, 1358, 912, 752 cm^{-1} ; δ 2.41-2.82 (2H, m), 2.70 (3H, s), 3.45 (2H, t, J 7 Hz), 4.90-5.26 (2H, m), 5.75-6.21 (1H, m), 7.41-7.80 (4H, m), 8.68-8.86 (1H, m).

1-(Hex-5-en-1-yl)-isoquinoline (216)

To a solution of ice-bath cooled ICA (0.99 g, 6.99 mmole) in THF (30 ml) was added dropwise n-butyl lithium (0.45 g, 6.99 mmole) under a nitrogen atmosphere. Stirred for 20 min. the reaction mixture was cooled to -78°

(acetone/dry ice). A THF solution of 1-methylisoquinoline (1.00 g, 6.99 mmole) was slowly introduced over 10 min. The solution turned black over 40 min., and the 5-bromopent-1-ene (1.04 g, 6.99 mmole) was added with no noticeable change. Stirred overnight, water (30 ml) was added and the deposited oils taken up in dichloromethane. The aqueous layer was further washed (3 x 30 ml), and the organic portions combined, dried (MgSO_4), filtered and evaporated to yield 1-(hex-5-en-1-yl)-isoquinoline (216) (1.30 g, 88%) as a pale yellow oil, following chromatographic treatment; ν_{max} (Neat) 3048, 2921, 2853, 1638, 1622, 1585, 1561, 1499, 909, 801, 744 cm^{-1} ; δ 1.39-2.29 (6H, m), 3.27 (2H, t, J 7 Hz), 4.80-5.16 (2H, m), 5.57-6.03 (1H, m), 7.29-7.78 (4H, m), 7.89-8.19 (1H, m), 8.38 (1H, d, J 6 Hz). The methiodide was prepared almost quantitatively from the base and iodomethane in acetonitrile (Found: M^+ 226.1594. $\text{C}_{16}\text{H}_{20}\text{NI}$ requires M^+ 226.1596; ν_{max} (Nujol) 1639, 1618, 1572, 1148, 998, 923, 818, 763 cm^{-1} ; λ_{max} 230 (49,600), 269 (2,850), 278.5 (2,950), 288.5 (1,550), 340.5 (5,250), 341.5 nm (5,450).

Preparation of quaternary bromide salts of various heterocyclic bases (General Method)

The heterocycle (1 equiv.) was dissolved in dry acetonitrile (25 ml) with stirring. The bromide (1.05 equiv.) was added and the mixture heated under reflux until ^1H n.m.r. analysis indicated consumption of the base. Addition of ethyl acetate to the warm solution caused the crystallisation of the salt. Specific details follow listed according to the heterocycle, firstly for 5-bromo-

pent-1-ene then allyl bromoacetate.

5-Bromopent-1-ene

Pyridine. The bromide (9.80 g, 66.2 mmole) and pyridine (5 g, 63.3 mmole) gave deliquescent crystals of 1-(pent-4-en-1-yl)-pyridinium bromide (136) (14.21 g, 98%) (Found: M^+ 148.1131. $C_{10}H_{14}NBr$ requires M^+ 148.1126); $\nu_{\max}$ 2917, 1633, 1480, 1160, 990, 912 cm^{-1} ; $\lambda_{\max}$ 217.5 (3,420), 255.5 sh (3,820), 260 (4,430), 265 nm sh (3,550); δ 2.13-2.43 (4H, m), 4.91-5.29 (4H, m), 5.60-6.03 (1H, m), 8.25 (2H, t, J 7 Hz), 8.69 (1H, t, J 7 Hz), 9.72 (2H, d, J 7 Hz).

2-Methylpyridine. The bromide (3.30 g, 22.2 mmole) and 2-methylpyridine (2.00 g, 21.5 mmole) yielded 1-(pent-4-en-1-yl)-2-methylpyridinium bromide (137) as colourless deliquescent crystals (4.80 g, 92%); $\nu_{\max}$ 3120-2760, 1631, 1578, 1476, 1168, 993, 917 cm^{-1} ; $\lambda_{\max}$ 218 sh (6,900), 267.5 (11,200), 272.5 nm sh (9,600); δ 1.97-2.47 (4H, m), 3.05 (3H, s), 4.78-5.22 (4H, m), 5.60-6.04 (1H, m), 7.97 (1H, t, J 6 Hz), 8.14 (1H, d, J 8 Hz), 8.51 (1H, t, J 8 Hz), 9.62 (1H, d, J 6 Hz). The tetrafluoroborate (138) was prepared in ethanol from silver tetrafluoroborate and the bromide (137) m.p. 144-6° (Found: M^+ 162.1281. $C_{11}H_{16}NBF_4$ requires M^+ 162.1283).

4-Cyanopyridine. The pyridine (4.80 g, 46.1 mmole) and the bromide (7.20 g, 48.4 mmole) gave 1-(pent-4-en-1-yl)-4-cyanopyridinium bromide (142) as pale yellow feathers

(8.80 g, 75%) m.p. 200-4° (lit. 196-9°); $\nu_{\max}^{202}$ (Nujol) 3090, 1641, 1562, 1348, 1161, 987, 916, 888, 865, 731 cm^{-1} ; $\lambda_{\max}^{230}$ (9,660), 278 (4,250); δ (D_2O) 1.98-2.28 (4H, m), 4.90-5.18 (2H, m), 5.58-6.02 (1H, m), 8.46 (2H, bd, J 6 Hz), 9.11 (2H, d, J 8 Hz).

Isoquinoline (151). The base (2.00 g, 15.5 mmole) and the bromide (2.31 g, 15.5 mmole) gave a heavy oil which crystallised on trituration with ether to give the deliquescent 2-(pent-4-en-1-yl)-isoquinolinium bromide (212)²⁰³ (4.18 g, 97%); $\nu_{\max}^{2935}$ 2935, 1642, 1610, 1581, 1442, 1396, 1282, 1158, 991, 914, 869 cm^{-1} ; δ 1.97-2.52 (4H, m), 4.69-5.30 (4H, m), 4.55-6.01 (1H, m), 7.78-8.25 (3H, m), 8.47 (1H, d, J 6 Hz), 8.74 (1H, d, J 8 Hz), 9.00 (1H, d, J 6 Hz), 11.01 (1H, s).

Allyl bromoacetate

Isoquinoline (151). The base (3.60 g, 27.9 mmole) and allyl bromoacetate (5.00 g, 27.9 mmole) gave, after 10 min., when heated at 50°, allyl (2-isoquinolinio) acetate bromide (214) (8.50 g, 99%) as light orange needles m.p. 133-4° (Found: C, 54.40; H, 4.62; N, 4.62. $\text{C}_{14}\text{H}_{14}\text{BrNO}_2$ requires C, 54.56; H, 4.55; N, 4.55); $\nu_{\max}^{2928}$ 2928, 1750, 1648, 1611, 1396, 1373, 981, 949, 908 cm^{-1} ; $\lambda_{\max}^{215}$ (18,200), 234 (41,200), 272.5 (2,760), 279 (3,080), 288 (2,090), 294 (1880), 335b (3,990), 340.5 nm (4,150); δ 4.72 (2H, d, J 6 Hz), 5.06-5.51 (2H, m), 5.69-6.19 (1H, m), 6.54 (2H, s), 7.81-8.34 (4H, m), 8.47 (2H, t, J 8 Hz), 9.23 (1H, d, J 7 Hz), 10.85 (1H, s).

3-Methylisoquinoline (175). The base (4.41 g, 30.9 mmole) and allyl bromoacetate (5.53 g, 30.9 mmole) gave allyl (3-methyl-2-isoquinolinio) acetate bromide (215) (9.81 g, 98%) as pale-orange needles m.p. 146-7.5° (Found: C, 56.13; H, 5.00; N, 4.21. $C_{15}H_{16}BrNO_2$ requires C, 55.92; H, 5.01; N, 4.35); $\nu_{\max}$ (Nujol) 1758, 1649, 1606, 1194, 971, 920, 774 cm^{-1} ; $\lambda_{\max}$ 234.5 (43,200), 271.5 (2,300), 280.5 (2,500), 290 (1,250), 345b (4,050), 351 nm (4,100); δ 3.97 (3H, s), 4.69 (2H, d, J 5 Hz), 5.11-5.53 (2H, m), 5.59-6.10 (1H, m), 6.35 (2H, s), 7.65-8.59 (5H, m), 10.95 (1H, s).

Thermolysis of alkenyl pyridinium salts

The pyridinium salt (136), (137), (138) or (142) was sealed at reduced pressure, in a thick walled glass tube, as an approximately 1.2 molar, degassed solution in acetonitrile, or DMF. Thermolysis produced little effect at temperatures below 150°, but heating overnight at 200° generally caused the consumption of the substrate. At 160° heating for about 60 hours gave the same result. The reactions were terminated at various degrees of completion, with the precursor between half and fully consumed. The contents of the tubes were pumped free from solvents, then dissolved in water. Boiled for 15 min. an excess of sodium acetate and acetic anhydride was added with further boiling (30 min.). The solution was neutralised with solid sodium bicarbonate and organic products taken up into dichloromethane. Washed twice more, the organic extracts were combined, dried ($MgSO_4$), filtered and evaporated in vacuo. Almost invariably the majority of material had

remained in the aqueous phase, otherwise a poorly defined mixture of intractable tars was obtained in low yield. When water or potassium cyanide was included in the thermolysis as trapping agents no products derived from a cycloaddition reaction were observed.

3-Methyl-5-aminoisoquinoline

To 3-methyl-5-nitroisoquinoline¹⁸⁶ (4.00 g, 21.3 mmole) in the minimum amount of methanol was added platinum oxide catalyst. The mixture was hydrogenated at 1 atm. until 1430 cm³ (63.9 mmole) of gas had been absorbed. Filtered and concentrated, a 91% yield of 3-methyl-5-aminoisoquinoline was realised as a dark solid, m.p. 212-6° (lit. 219.5-221°)²⁰⁴; $\nu_{\max}$ 3434, 3308, 3170, 2918, 2848, 1635, 1581, 1459, 1376, 1302, 859, 751 cm⁻¹; δ 2.63 (3H, s), 5.57-5.99 (2H, bs), 6.87 (1H, dxd, J 7,2 Hz), 7.12-7.43 (2H, m), 7.80 (1H, s), 9.03 (1H, s).

3-Methyl-5-acetamidoisoquinoline²⁰⁵

3-Methyl-5-aminoisoquinoline (0.60 g, 3.80 mmole) was dissolved in acetic anhydride (4 ml), and stirred (2 hours). Poured onto crushed ice and neutralised with solid sodium bicarbonate the organic products were extracted with dichloromethane (3 x 10 ml). Combined, the extracts were dried (MgSO₄), filtered and evaporated to give a pale pink solid m.p. 154-6° of 3-methyl-5-acetamidoisoquinoline (0.69 g, 91%); $\nu_{\max}$ 3420, 3382, 2930, 1688, 1639, 1594, 1467, 1372, 1316 cm⁻¹; δ 2.18 (3H, s), 2.53 (3H, s), 7.15-7.80 (4H, m), 8.71-9.08 (1H, bs, exch.), 8.98 (1H, s).

Thermolysis of alkenylisoquinolinium salts

3-Methyl-5-acetamidoisoquinoline with 5-bromopent-1-ene.

To the isoquinoline (0.54 g, 2.70 mmole) was added 5-bromopent-1-ene (0.48 g, 3.22 mmole) in acetonitrile (10 ml). Heated gently under reflux for 9 hours a black solid formed. The reaction mixture was decanted off and the remaining solid triturated with ether to give dark microcrystals m.p. 208-12°. ¹H N.m.r. and t.l.c. analysis showed that much of the isoquinoline was still present in the decanted solution, therefore the solvent bulk was reduced and the mixture further thermolysed. The second crop of solid was added to the first to give 110 mg of the adduct. Dissolved in 2N sodium bicarbonate solution (1 ml) the deposited oils were taken up in dichloromethane. The aqueous layer was washed (3 x 10 ml) with dichloromethane and the organic portions combined, dried (MgSO₄), filtered and evaporated to give a deep brown oil. Dissolved in the minimum quantity of dry pyridine, excess acetic anhydride (1.2 equivalent) was added and the mixture stirred overnight.

Removal of all volatile materials left a heavy-brown oil that was purified by preparative t.l.c. to give a viscous, pale-yellow oil, 5-H-1-acetyl-6,8-dimethyl-1,2,3,4,4a,12b-hexahydrobenzo [d,e]pyrido [3,2-g](4,2)benzoxazapine (220), (0.121 g, 14%) (Found: M⁺ 310.1699. C₁₉H₂₂N₂O₂ requires M⁺ 310.1681); $\nu_{\max}$ 2982, 2930, 2860, 1702, 1624, 1424, 1355, 1157, 977 cm⁻¹; δ 1.32-1.78 (4H, m), 2.31 (3H, s), 2.59 (3H, s), 2.76 (3H, s), 2.10-3.24 (4H, m), 3.79 and 4.62 (1H, 2xd, J 13 Hz), 5.34 and 6.28 (1H, 2xd, J 5 Hz), 6.94 (1H, t, J 7 Hz), 7.18-7.42 (1H, m), 7.70 (1H, dxd, J 7,5 Hz).

2,3-Dimethyl-4-(pent-4-en-1-yl)-isoquinolinium iodide (226).

The iodide (226) (0.16 g, 0.455 mmole), dissolved in degassed acetonitrile (1 ml) was thermolysed for 3 hours at 145° in a sealed tube. Evaporation of the solvents gave a foam which dissolved in 2N sodium bicarbonate solution. Neutralisation caused the deposition of organic oils which were taken up in dichloromethane. The aqueous layer was further washed, then the organic extracts were combined, dried (MgSO₄), filtered and evaporated at reduced pressure to give a brown oil. Dissolved in the minimum amount of dry pyridine, acetic anhydride (1.2 equiv.) was added and the mixture stirred overnight. The solvents were distilled in vacuo leaving a brown oil which, when purified by preparative t.l.c., gave $\Delta^{2,\alpha}$ -acetonilidene-3-methyl-3-aza-10,11-benzotricyclo[5,2,2^{1,4},0^{1,6}]-undecane (232) (101 mg, 84%) as a heavy oil (Found: M⁺ 267.1619. C₁₈H₂₁NO requires M⁺ 267.1623); $\nu_{\max}$ 2915, 1672, 1618, 1603, 1311, 954, 878 cm⁻¹; δ 1.16 (1H, bd, J 13 Hz), 1.48-2.66 (8H, m), 2.05 (3H, s), 3.06 (3H, s), 4.37 (1H, bd, J 4 Hz), 5.07 (1H, s), 6.98-7.35 (4H, m).

Another sample of the iodide (226) (0.25 g, 0.708 mmole) was thermolysed similarly to obtain a quantitative conversion to the adduct. Dissolved in THF, sodium borohydride (0.0268 g, 0.708 mmole) was added in solid form causing much effervescence. The orange solution turned yellow, and stirred overnight was then poured into water (30 ml). The deposited oil was collected in dichloromethane and after further washings of the aqueous layer the organic portions were combined, dried (MgSO₄), filtered and evaporated in vacuo to give a yellow oil.

Column chromatography gave endo-1,2-2,3-dimethyl-3-aza-10,11-benzotricyclo-[5,2,2^{1,4},0^{1,6}]-undecane (233) (0.143 g, 89%) as a colourless solid m.p. 56-88° (Found (M-15)⁺ 212.1439. C₁₆H₂₀N requires (M-15)⁺ 212.1438; M⁺ = 227) ν_{max} 3023, 2950, 2864, 1475, 1466, 1453, 1377, 1181, 1170, 1148, 1064, 1027, 897, 794, 758 cm⁻¹; δ 0.79 (3H, d, J 8 Hz), 1.08 (1H, dxd, J 13,6 Hz), 1.40-2.08 (6H, m), 2.24 (3H, s), 2.10-2.50 (1H, m), 3.24 (1H, dxdxd, J 12, 9,4 Hz), 3.63 (1H, q, J 8 Hz), 3.88 (1H, bd, J 4 Hz), 7.16-7.46 (4H, m).

2-(Pent-4-en-1-yl)-isoquinolinium iodide (212).

The salt (212) (0.20 g, 0.719 mmole) dissolved in degassed acetonitrile (2 ml), and sealed in a glass tube at reduced pressure was thermolysed for 3 hours at 145°. ¹H N.m.r. analysis indicated that no reaction had occurred. Resealed and reheated for 16 hours at 145° a large brown amorphous solid formed which gave a very poor ¹H n.m.r. spectrum. The supernatant liquid also gave a heavy brown oil on evaporation. Both products were boiled in dilute sodium bicarbonate solution and extracted with dichloromethane. The organic portions were combined, dried (MgSO₄), filtered and concentrated in vacuo. The fraction arising from the solid yielded nothing, but the other gave a viscous oil which was acetylated with pyridine and acetic anhydride. Removal of the solvents yielded a mixture of very polar tars. When the experiment was repeated using water as solvent identical behaviour was observed. The starting material was completely consumed after only 10 hours at 145°.

1-(Hex-5-en-1-yl)-2-methylisoquinolinium iodide.

The methiodide of (216) (0.25 g, 0.708 mmole) was thermolysed in the fashion prescribed for salt (212) at 145° for 3 hours. No reaction had occurred. Heated at 160° for 3 hours most of the precursor had been consumed, and so the resultant brown tar was hydrolysed and acetylated as previously described, but only polymeric tars were obtained. Thermolyses under various conditions were equally unsuccessful.

2-Methyl-4-(pent-4-en-1-yl)-isoquinolinium iodide.

The methiodide of (182) (0.166 g, 0.490 mmole) was thermolysed as previously described, also with no reaction occurring when heated at 145° for 3 hours. Heated at higher temperatures the salt was consumed, but no isolable products were observed on work up. Thermolyses under various conditions were equally unsuccessful, including trapping experiments using water and inorganic cyanide.

Attempted quaternisation of (but-3-en-1-yl) (3-isoquinol-1-yl) ketone (211) with dimethyl sulphate.

The ketone (211) (0.60 g, 2.67 mmole) was mixed with dimethyl sulphate (0.326 g, 2.67 mmole) in acetonitrile (4 ml) and stirred overnight. No reaction had taken place. Heated gently at reflux under a nitrogen atmosphere the ¹H n.m.r. signals for the vinyl group were found to be diminishing in intensity. When these peaks had completely disappeared the solvents were removed to yield a brown foam which was dissolved in saturated sodium bicarbonate solution. The deposited oils were taken up in dichloro-

methane and the aqueous layer washed several times with the organic solvent (3 x 20 ml). The organic portions were combined, dried (MgSO_4), filtered and concentrated in vacuo. The ^1H n.m.r. spectrum of the resultant brown oil was very complex, and acetylation of this material afforded an intractable mixture of tars.

Bromides (214) and (215). Both salts behaved similarly when subjected to heat. Thermolysed in DMF, no reaction occurred until the temperature was raised to 120° . The reaction mixture then turned deep-red, and ^1H n.m.r. analysis indicated consumption of the isoquinolinium nucleus. Evaporation of the solvents gave a heavy, red oil, which when hydrolysed and acetylated gave a complex mixture of tars. Use of water or potassium cyanide as trapping agents was not successful.

syn-1,4-Dihydro-9-(2-chloroethoxy)-2,3-dimethyl-1,4-ethanoisoquinolinium iodide (236).

A solution of 2,3-dimethyl isoquinolinium iodide (234) (0.33 g, 1.15 mmole), 2-chloroethyl vinyl ether (0.56 g, 5.26 mmole) and a catalytic amount of quinol, in the minimum quantity of dry methanol (8 ml) was stirred at room temperature for several days. The gradual disappearance of the resonance for the C(1) proton, in the ^1H n.m.r. spectrum of the reaction mixture (ca. δ 9.9) was the main criteria for judging the progress of the reaction. When the methiodide had been completely consumed (times were variable) the solvent was evaporated in vacuo at room temperature. The resulting salt was tritu-

rated with ethyl acetate to give the title compound (236) (0.41 g, 91%).

Basic hydrolysis of the adduct (236).

To a solution of the chloroethyl vinyl ether adduct (236) (0.236 g, 0.60 mmole) in methanol (2 ml) was added dropwise a 10% aqueous solution of sodium hydroxide (24 mg, 0.60 mmole). The mixture became purple, but the colour was discharged when the solution was boiled for 5 min. The products were taken up in dichloromethane, and the extracts washed with 2N HCl solution, then with water. Drying (MgSO_4), filtration and evaporation of the solvents gave a light-brown oil which was shown to be methyl naphth-1-yl ketone (168) by comparison of its spectral data with those of an authentic sample (0.9 g, 88%)^{124,199}; ν_{max} (neat) 3043, 2919, 1673, 1592, 1572, 1502, 1354, 1278, 1239, 939, 802, 775 cm^{-1} ; δ 2.69 (3H, s), 7.38-7.74 (3H, m), 7.82-8.11 (3H, m), 8.86 (1H, d, J 9 Hz).

Reduction of primary adduct (236) with sodium borohydride.

To an ice-cooled solution of the vinyl ether adduct (236) (0.21 g, 0.54 mmole) in methanol (3 ml) was added excess sodium borohydride (0.03 g, 0.83 mmole) as a solid and in one portion. The green solution turned yellow and after 1 hour water (15 ml) was added, collecting the deposited oils in dichloromethane. The aqueous layer was further washed (3 x 10 ml) and the organic portions combined, dried (MgSO_4), filtered and evaporated in vacuo to give a colourless oil. Purification by preparative t.l.c. gave an inseparable mixture of cis- and trans-3,4-

syn-1,2,3,4-tetrahydro-2,3-dimethyl-9-(2-chloroethoxy)-1,4-ethanoisoquinolines (238a) and (238b) (0.132 g, 93%) (Found: C, 67.56; H, 7.57; N, 5.29. $C_{15}H_{20}ClNO$ requires C, 67.79; H, 7.58; N, 5.27); $\nu_{\max}$ 2915, 2841, 2770, 1477, 1449, 1342, 1109, 755, 732 cm^{-1} ; δ see text.

syn-1,4-Dihydro-9-(2-chloroethoxy)-2,3-dimethyl-5-nitro-1,4-ethanoisoquinolinium methosulphate (237).

A solution of 2,3-dimethyl-5-nitroisoquinolinium methosulphate (235) (0.40 g, 1.27 mmole), 2-chloroethyl vinyl ether (0.68 g, 6.39 mmole) and a catalytic amount quinol, in the minimum quantity of dry methanol (10 ml) was stirred at room temperature overnight. The solvent was evaporated in vacuo while maintaining the solution temperature below 30° . Trituration with ethyl acetate gave the title compound (237) (0.58 g, 95%).

Basic hydrolysis of nitro-adduct (237).

To a solution of the adduct (237) (0.30 g, 0.97 mmole) in methanol (5 ml) was dropwise added sodium hydroxide (0.039 g, 0.97 mmole) as a 10% aqueous solution. An orange oil developed which was taken up in dichloromethane and dried ($MgSO_4$). Filtration and evaporation yielded a brown oil. Dissolved in the minimum amount of dry pyridine, a 1.2 molar excess of acetic anhydride was added and the mixture stirred overnight. All solvents were removed at the pump, yielding a crystallising oil which was purified by preparative t.l.c. to give syn-1,2,3,4-tetrahydro-2-methyl- $\Delta^{3,\alpha}$ -acetonilidene-5-nitro-9-(2-chloroethoxy)-1,4-ethanoisoquinoline (243) (Found: M^+ 350.1010. $C_{17}H_{19}^{35}$

ClN_2O_2 requires 350.1033); ν_{max} 2932, 2878, 1638, 1548, 1405, 1352, 1168, 1107, 966 cm^{-1} ; δ see text.

Reduction of primary nitro-adduct (237) with sodium borohydride.

To an ice-bath cooled methanol (5 ml) solution of the vinyl ether adduct (0.28 g, 0.91 mmole) was added excess solid sodium borohydride (0.052 g, 1.37 mmole) in one portion. The green solution swiftly paled to yellow. Stirred for an hour, water was added and the deposited oils taken up in dichloromethane. The aqueous portion was washed several times (3 x 20 ml) and the organic extracts combined, dried (MgSO_4), filtered and evaporated to give a viscous, black tar. Purification by preparative t.l.c. gave an inseparable mixture of cis- and trans-3,4-syn-1,2,3,4-tetrahydro-2,3-dimethyl-5-nitro-9-(2-chloroethoxy)-1,4-ethanoisoquinolines (239a) and (239b) (0.21 g, 74%) as a colourless oil that quickly darkened (Found: M^+ 310.1110. $\text{C}_{15}\text{H}_{19}^{35}\text{ClN}_2\text{O}_2$ requires M^+ 310.1084); ν_{max} (Neat) 2933, 2857, 2786, 1527, 1451, 1340, 1175, 1109, 824, 796, 784, 742 cm^{-1} ; δ see text.

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