STUDIES ON CYCLOADDITION REACTIONS

ACROSS HETEROCYCLIC DIENES

A thesis presented by

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Studies on Cycloaddition Reactions across Heterocyclic dienes

Abstract

A review of the literature on intramolecular cycloadditions is presented.

The cycloaddition reactions of substituted 2-pyridones are examined to elucidate the relative importance of steric and electronic factors for successful addition.

Intramolecular cycloadditions of unactivated olefins to oxazoles have been discovered. The primary adducts are not observed and only the annulated pyridine derivatives are isolated.

A novel rearrangement of 2-pentenyl oxazoles to give pyrrolyl-oxazole derivatives has been discovered and attempts to elucidate its mechanism are described.

Intermolecular cycloaddition reactions of oxazoles with olefinic and acetylenic dienophiles have been investigated to yield the expected pyridine and furan derivatives.

Molecular orbital parameters have been calculated using CNDO/2, MNDO and ab initio (Gaussian 70) methods, the relative merits of these programmes have been evaluated by appeal to known experimentally determined values.

The usefulness of the Frontier Molecular Orbital theory when applied to cycloaddition reactions is considered.

Graham Greene

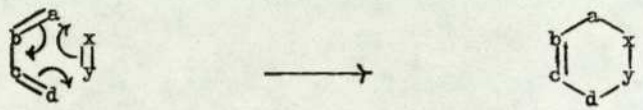
REVIEW

Thermal Intramolecular [4 + 2] Cycloadditions

Thermal Intramolecular [4 + 2] Cycloadditions

The general nature of the intermolecular [4 + 2] cycloaddition process was first recognised by Diels and Alder over fifty years ago.[1] A conjugated diene reacts with an unsaturated component to form a 6-membered ring. (Scheme 1)

Scheme 1

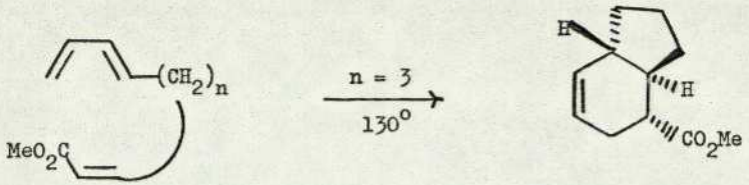


The many variations permitted for both diene and dienophile make this scheme a very attractive one to the synthetic organic chemist. A further refinement was proposed by Alder[2] in 1953 when he considered, without practical verification, the possible fate of the acyclic triene (1).

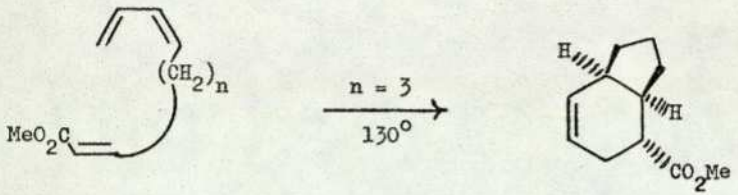
(1) (2)

The spatial proximity of the reacting groups and hence the smaller decrease in entropy on cycloaddition should favour the intramolecular addition over intermolecular dimerisation.

Although some examples of intramolecular cycloadditions were reported in the intervening years[3-14], it was not until House[15] began his investigations in 1965 that a number of important features of the intramolecular cycloaddition were delineated.



(3) (4)



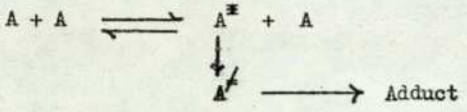
(5) (6)

Significantly, House showed that with a short polymethylene bridge ((3),(5) n = 2), no monomeric product from attempted cyclisation was observed, but that with three carbon atoms separating the addends, both cis- and trans-1,3-pentadiene derivatives ((3),(5) n = 3) underwent stereospecific intramolecular additions. These results highlight the most fundamental difference between the inter- and intramolecular reactions: whereas the former may, subject to limited constraints, adopt a transition state geometry leading to the most favoured product, the latter can generally only adopt one or, at best, a few sterically permitted approaches of the addends; If, for intramolecular cases, the geometry which the unconnected addends can adopt is not included as a favourable case, then the molecule may formally be considered resistant to the electronically favoured pericyclic process; conversely if the most favoured conformation closely approximates to the desired transition state geometry then reaction will occur under relatively mild conditions.

This argument may be clarified by a consideration of the kinetics

of a unimolecular reaction in solution. The reactant (A) gains energy on collision to give an excited species ($A^{\ddagger}$) which is deemed to possess sufficient energy to react when the vibrational energy of the system has rearranged to congregate in the appropriate bonds and generate the activated complex ($A^{\neq}$) (Scheme 2).

Scheme 2



From the RRKM variation of the activated complex theory[16] an equation may be derived for the unimolecular reaction rate constant (k_u) at the high pressure limit.

$$k_u = \left(\frac{RT}{N_o h}\right) \left(Q_v^{\neq}/Q_v\right) \exp\left(-Ec/RT\right) \quad \text{—— (1)}$$

R = Gas constant N_o = Avozadro's number

T = Absolute temperature h = Planck's constant

$Q_v^{\neq}$ = Vibrational partition coefficient for $A^{\neq}$

Q_v = Vibrational partition coefficient for A

E_c = Critical energy that must be accumulated in the appropriate bonds for reaction to occur

A pseudo-equilibrium constant ($K^{\neq}$) for reaction between ($A^{\neq}$) and ($A^{\ddagger}$) may also be derived:

$$K^{\neq} = \left(Q_v^{\neq}/Q_v\right) \exp\left(-Ec/RT\right) \quad \text{——— (2)}$$

Combining (1) and (2) :

$$k_u = \left(\frac{RT}{N_o h}\right) K^{\neq} \quad \text{——— (3)}$$

From thermodynamic principles a free energy ($\triangle G^{\neq}$), enthalpy ($\triangle H^{\neq}$) and

entropy ($\Delta S^{\neq}$) of activation may be defined:

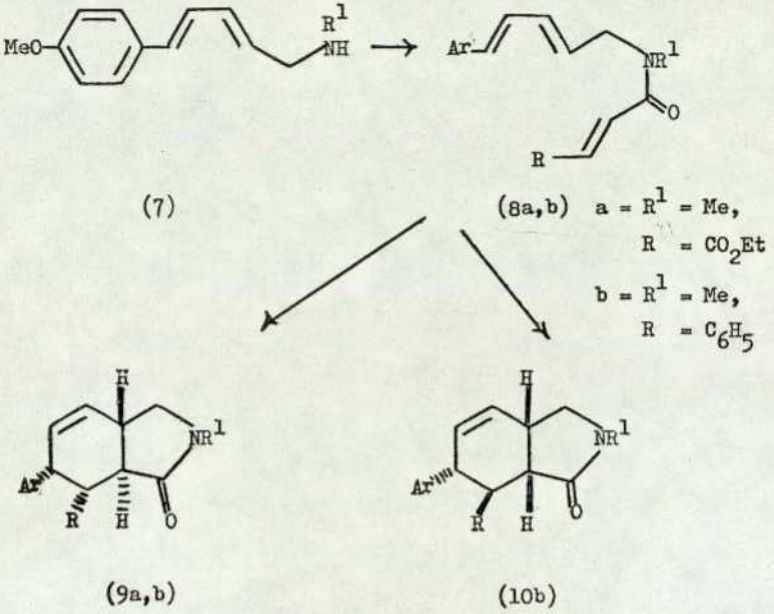
$$\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq} = -RT\ln K^{\neq} \qquad \text{——— (4)}$$

for a unimolecular reaction in solution $\Delta H^{\neq} = E^{\neq}$ where $E^{\neq}$ is the activation energy for the unimolecular process; substituting for $K^{\neq}$ in (3):

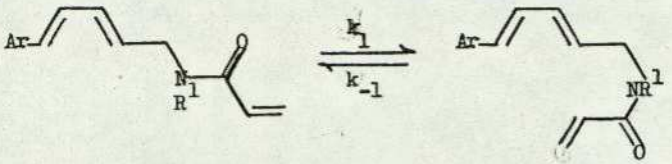
$$k_u = \left({}^{RT}/_{N_o h}\right) \exp\left({}^{\Delta S^{\neq}}/_{R}\right) \exp\left({}^{-E^{\neq}}/_{RT}\right) \text{ — (5)}$$

If the most stable conformation of the molecule corresponds closely to the desired geometry of the transition state then the loss of entropy usually associated with a Diels-Alder reaction will be small and this factor will lead to a greater rate than is observed for an analagous intermolecular reaction. In general, the enforced contiguity of the addends in an intramolecular reaction will lead to a more favourable entropy of activation ($\Delta S^{\neq}$). The effect on the activation energy ($E^{\neq}$) may take one of three forms. Firstly, the bonding and non-bonding interactions arising from the presence of the connecting bridge may have a negligible effect on the conformation of the reactant and thus $E^{\neq}$ will be very similar in magnitude to the value normally associated with an intermolecular addition. Secondly, the bonding and non-bonding interactions may stabilize the transition state geometry with respect to the reactant geometry and hence lower $E^{\neq}$ leading to a significant rate enhancement. Lastly, these interactions may destabilize the transition state with respect to the reactant and so the energy of activation will be greater than for an intermolecular reaction between the unconnected addends which may override the more favourable entropy term.

Confirmation of the smaller entropy loss associated with intramolecular cycloaddition has come from kinetic studies on substituted acrylamide derivatives[17-19a].



The reactive intermediate (8a) is not isolable at 0° but gives exclusively the trans-fused lactam (9a). With the less reactive dienophile, (8b), thermolysis in refluxing benzene gives a mixture (15:2) of the trans-fused (9b) and the cis-fused lactam (10b). By conducting the reaction at different temperatures, a value was determined for the entropy of activation ($\Delta S^{\neq} \simeq$ -16.0 Cal K^{-1} mol^{-1}). This value is much larger than the values usually quoted for intermolecular processes[19b] ($\Delta S^{\neq} \simeq$ -35 Cal K^{-1} mol^{-1}). Another interesting aspect of this study is the observed rate dependence on the size of the N-alkyl group (R^1). For R^1 = H, cycloaddition only occurs above 100°. Since the diene and dienophile are connected the conformational equilibrium is considered to play an important role in determining reactivity.

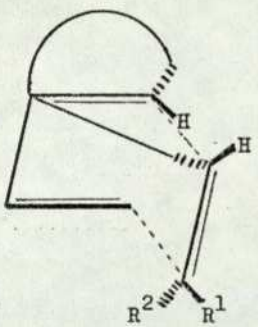


(11) (12)

In addition to the required S-cis-diene conformation, the rate of reaction depends on the concentration of the conformer in which the addends possess a geometry resembling that of the transition state. Presumably, when R^1 is a bulky alkyl group, the desired conformer (12) is stabilised.

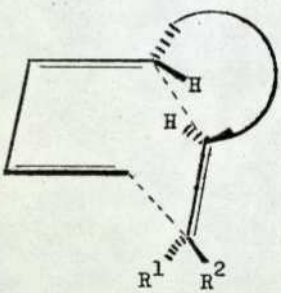
In general, intramolecular additions of acyclic dienes may be categorised according to the orientation of the precursor in the transition state. Trans-dienes can in principle react via three different transition states.

A.



endo - transition state to give cis-fused product.

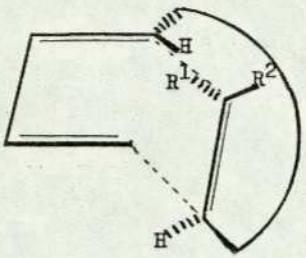
B.



exo - transition state to give trans-fused product.

The terms exo- and endo- are used here to describe the position of the polymethylene bridge with respect to the nascent cyclohexene ring.

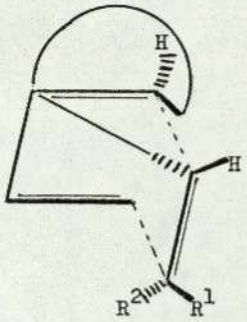
C.



The re-entrant geometry required for case C makes such a transition state energetically unfavourable unless the polymethylene bridge contains more than four carbon atoms; consequently, bridged adducts are not observed. Annulated products arising from either of the former transition states geometries have been isolated. The energy difference between these two transition states depends on the bonding and non-bonding interaction of any substituents present and hence on subtle conformational effects which are hard to predict. Thus terminal ester or phenyl groups usually lead to trans-fused adducts via transition state B which would be the orientation arising from intermolecular addition of the unconnected addends in agreement with the Alder "endo-rule"[19c] for Sp^2 substituents e.g. production of (4) and (9a). When the sidechain contains substituents that destabilize this orientation or strongly stabilize the endo-orientation (A) then the cis-fused adducts are observed e.g. production of (14a). Of course competing cis/trans-isomerisation may make analysis difficult if the reaction is under thermodynamic rather than kinetic control.

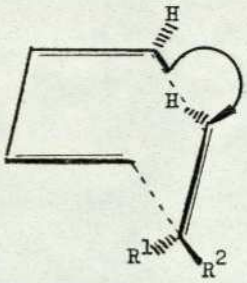
For the thermally less stable cis-dienes, three plausible orientations may be proposed.

D.



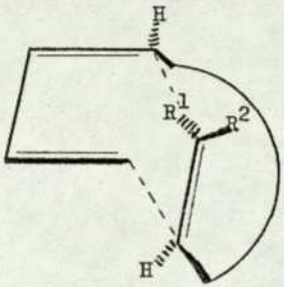
endo-mode

E.



exo-mode

F.

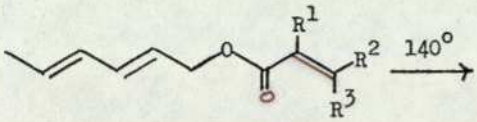


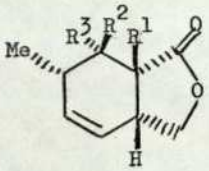
The dienophile chain is now forced into the exo-mode of addition (E) as the endo-mode (D) is too highly strained. Thus cis-adducts are formed with high stereospecificity. It is also possible, however, to produce adducts arising from the re-entrant transition state geometry (F) although the entropically less favoured orientation of the more remote dienophile terminus interacting with the diene terminus closer to the bridge will only be favoured when unusual conformational requirements arise or when the unusual transition state geometry is stabilized by more effective orbital overlap.

The diagrams presented in this thesis, which imply a particular stereochemistry are used primarily to indicate the relative configuration at different centres in the molecule; optical activity is not implied and the formulae therefore represent one of a pair of

enantiomers in a racemic mixture unless stated otherwise.

A good example of the subtle effects that might be expected from an analysis of likely strain in transition state geometries comes from the citraconate acid derivative[20],(13a) which underwent smooth addition at 140° to yield, stereospecifically, the cis-fused adduct (14a).





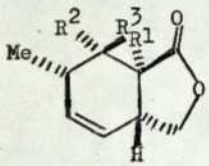
(14a)

(13a) R^1 = H, R^2 = Me, R^3 = CO_2H

b) R^1 = Me, R^2 = H, R^3 = CO_2H

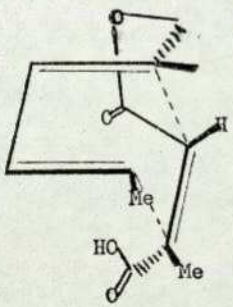
c) R^1 = H, R^2 = Me, R^3 = CO_2Me

d) R^1 = Me, R^2 = CO_2Me, R^3 = H

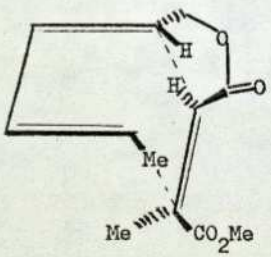


(15c)

For the isomer (13b) no addition was observed when the ester (13c) was thermolyzed only the trans-fused adduct (15c) was isolated. The isomeric ester (13d) failed to cyclise, even at elevated temperatures. The observed stereoselectivity may be explained by considering the favoured transition states.



(14)

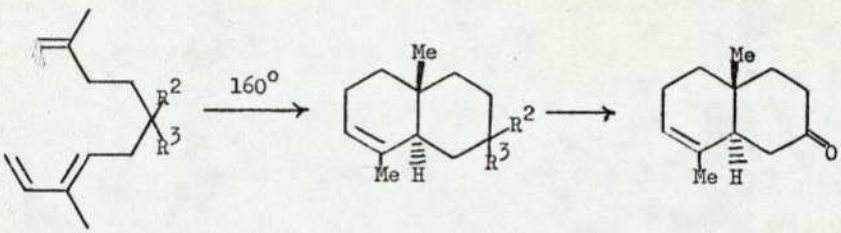


(15)

The intramolecular hydrogen bonding in the acid (14) stabilises the position of the dienophile in the endo-mode, whereas the ester(15)

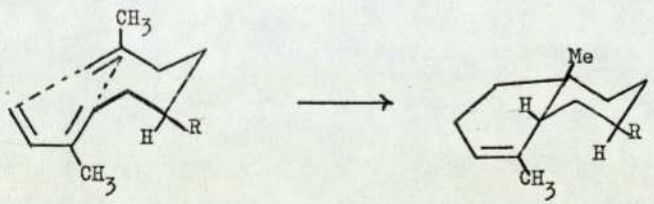
would suffer steric compression of the carboxyl group as cis-fusion proceeded. Even though considerable torsional strain is developed in the exo-transition state it is presumably offset by the diminished interaction of the carbonyl groups. The failure to cycloadd of the isomeric acid (13b) and ester (13d) is inexplicable, a priori, and only serves to underline the importance of steric effects in these processes.

Alicyclic precursors have been used in natural product synthesis. The trisubstituted E-1,3-diene (16) was selectively thermolysed to give the trans-fused adduct (17) which was readily converted to the sesquiterpene eudesmone (18)[21].

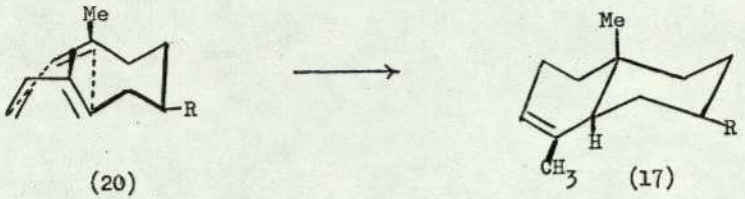


(16) (17) (18)

That only the trans-fused product is obtained may be explained by considering the transition state which would be necessary for the formation of the cis-fused ring (19).



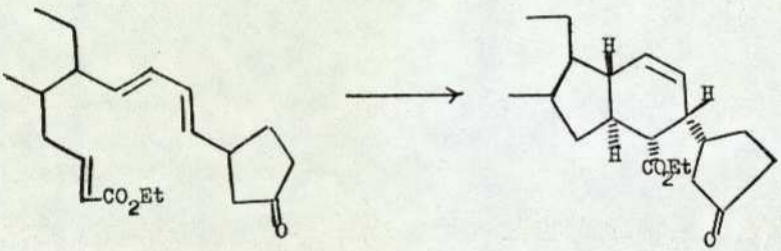
(19)



(20) (17)

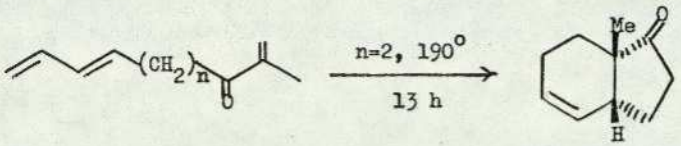
In (19) there is a severe non-bonding interaction between the vinylic methyl on the diene unit and an axial hydrogen in the polymethylene bridge which cannot occur in the transition state (20) leading to the trans-fused product (17).

A recent report has cited the addition of the triene (21) to give a bicyclic ester (22) with moderate stereoselectivity capable of transformation to Ikarugamycin analogues[22].



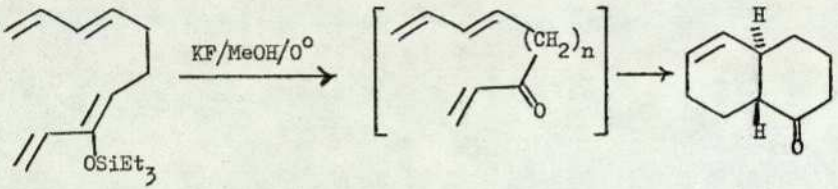
(21) (22)

As the bridge between the diene and dienophile is appreciably extended so the ensuing reaction approximates more closely to the intermolecular case which may enhance or retard the rate of reaction depending upon the greater steric flexibility to be offset against the lesser entropy of activation. Thus the triene (23) required vigorous reaction conditions to produce the cis-perhydroindanone (24) arising from endo-addition[23].



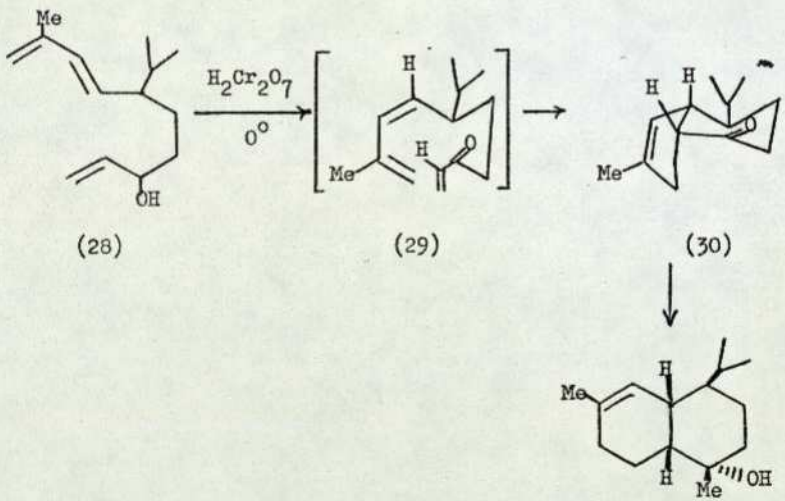
(23) (24)

By contrast the tetraene (25) when treated at 0° with potassium fluoride yielded the trans-octalone (27) as a result of kinetically controlled exo-addition of the unisolable vinyl ketone (26)[24a].



(25) (26) n = 3 (27)

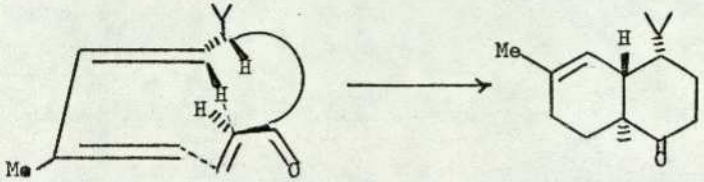
A substituted trienone (29) gave the cis-fused product (30) from endo-addition under mild conditions. This was easily converted to Torreyol (31)[24b].



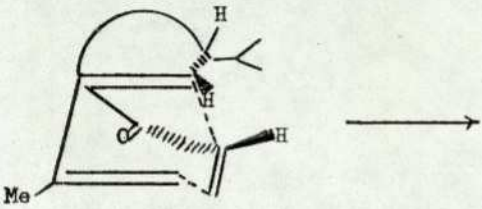
(28) (29) (30)

(31)

Ring fusion occurs such that the isopropyl group is largely syn- to the angular hydrogens. Due to severe non-bonding interaction in the chair transition state (32) the boat conformation (34) is the reactive conformer.



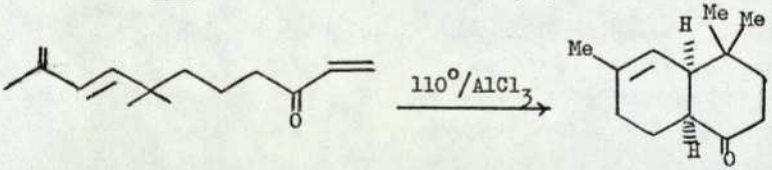
(32) (33)



(30)

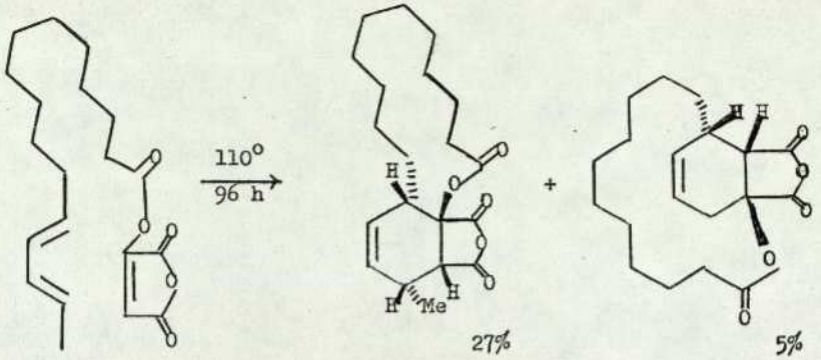
(34)

If a longer polymethylene bridge is present[25] as in the triene (35) then both catalytic and thermal assistance are necessary to produce the cis-annulated cycloheptanone (36).



(35) (36)

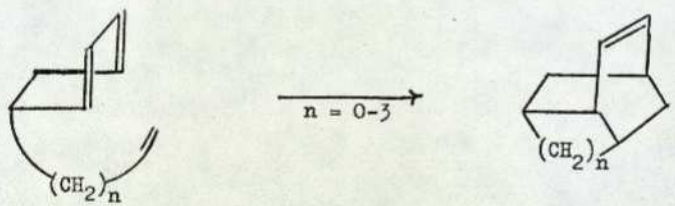
When synthesising macrocyclic structures, the addends should have an electronic compatibility known to be fruitful intermolecularly. Thomas[26] synthesised a cytochalasan analogue (38) from the long-chain diene-anhydride (37).



(37) (38) (39)

The reaction conditions and regioselectivity are similar to those found in the intermolecular reactions of anhydrides with butadiene derivatives[27].

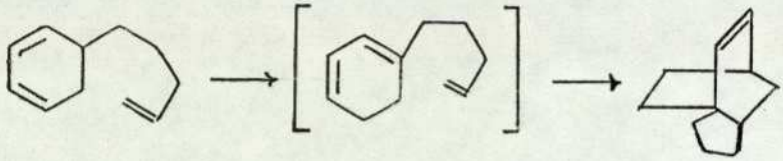
Perhaps the best systematic study on the effect of chain length was conducted by Krantz[28,29], who examined the cyclohexadiene series (40, n = 0-3).



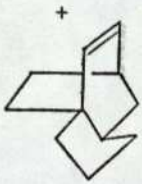
(40) (41)

(42) (43)

Temperatures for effective addition ranged from 158°-275° and for the first three members of the series 40 (n = 0-2) one stereospecific product was isolated for each reaction corresponding to the products 41 (n = 0-2) none of the twistane derivatives (43, n = 0,1,2) was detected. For the member of the series with the largest chain (40) n = 3, products were characterised that arose from an initial [1,5] hydrogen shift followed by addition.

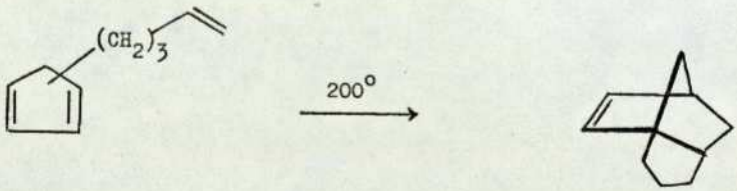


(40) (44) (45)

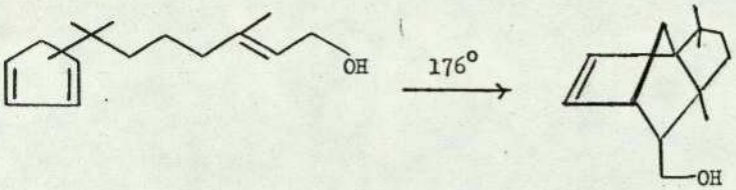


(46)

This parallels closely the observations of Corey[30] and Brieger[31] in the cyclopentadienyl series.

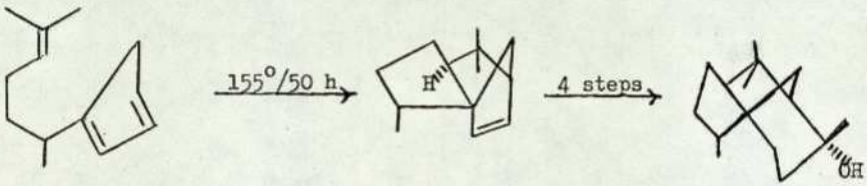


(47) (48)



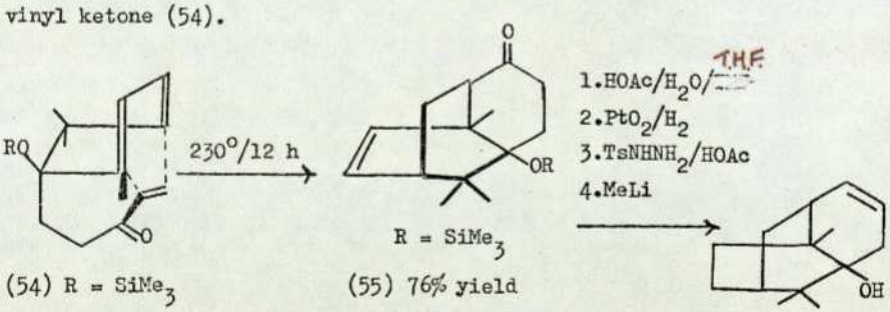
(49) (50)

The stereochemical implications of these studies have been exploited in natural product synthesis, notably by Fallis[32] who synthesised (±) Cedrol (53) from the cyclopentadiene derivative (51).



(51) (52) (53)

The correct exo-orientation was observed for this cycloaddition. Similarly in the cyclohexadiene series, Oppolzer[33] achieved an efficient synthesis of norpatchoulenol (56), the key step being addition of a vinyl ketone (54).

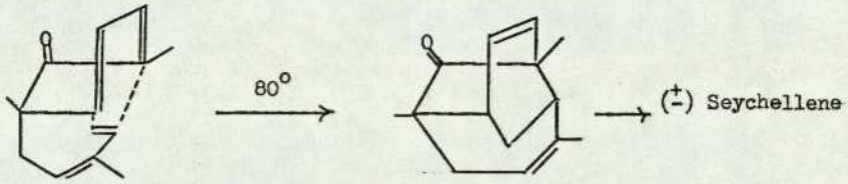


(54) R = $SiMe_3$ (55) 76% yield

R = $SiMe_3$

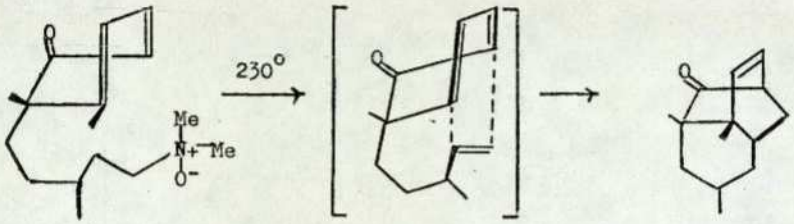
(56)

Other workers[34-36] have concentrated on the synthetic potential of cyclohexadienone derivatives, notably Frater[37] whose synthesis of (±) Seychellene also demonstrates reverse regioselectivity.



(57) (58)

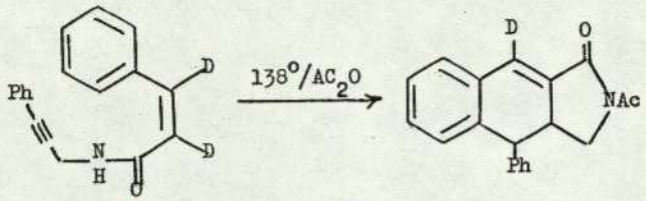
Presumably the orbital overlap within the conjugated dienophile is most stabilising for this orientation. For an isolated olefinic dienophile (60) the more usual orientation is observed[38].



(59) (60) (61)

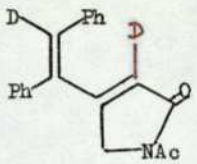
Another feature of the intermolecular reaction of polyenes is the selective formation of a product arising from just one of the thermally allowed pericyclic processes. Such periselectivity is usually explained using the Frontier Molecule Orbital Model[39] which predicts that for simultaneous symmetry-allowed bonding of different centres, those orbitals which overlap best and are closest in energy will interact most and confer the greatest stability on the transition state for the observed product. Once again, if the addends are unable to adopt the desired transition state geometry then unusual periselectivities may arise.

Klemm[40] has studied the intermolecular cycloaddition of N-(phenylpropargyl)-Cinnamamide derivatives to produce cyclolignan lactones and lactams, of particular interest was the deuterated cis-cinnamamide (62).



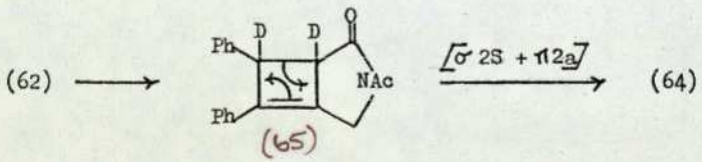
(62) (63) 18%

+

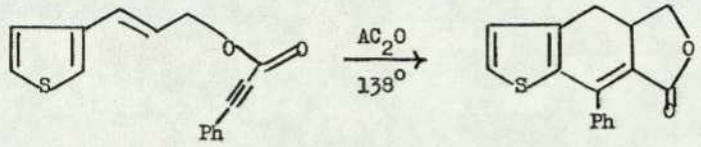


(64) (32%)

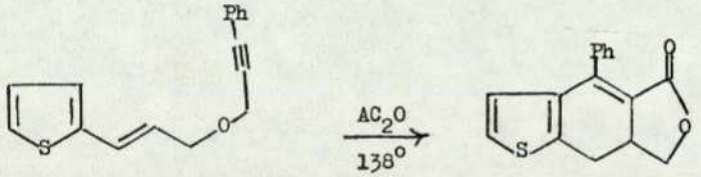
In this instance, competition between the $[\pi 4s + \pi 2s]$ and $[\pi 2s + \pi 2a]$ processes is observed; the former uses the styrene as a diene to form an adduct which aromatises (63) - loss of deuterium probably results from enolisation of the amide carbonyl group. The $[\pi 2s + \pi 2a]$ process produces a cyclobutene intermediate (65) which undergoes conrotatory cycloreversion to yield the N-acetyl lactam (64).



When the trans-cinnamamide was used, the products arose exclusively from the $[\pi 4s + \pi 2s]$ mechanism[41]. Thiophene derivatives (66) and (68) underwent the same type of reaction[42].

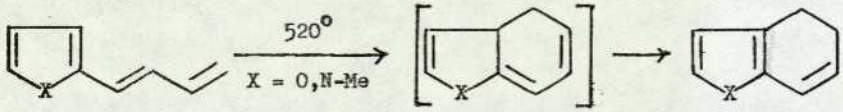


(66) (67)



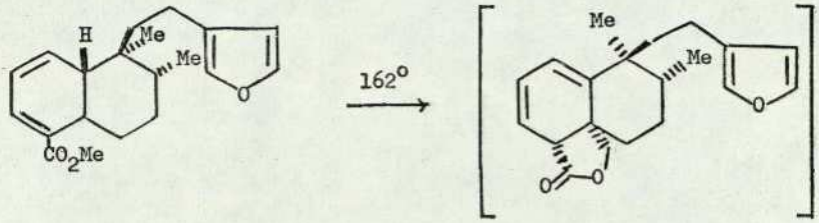
(68) (69)

The distinction between diene and dienophile is sometimes quite arbitrary. Furan and pyrrole derivatives (70) have been shown to undergo electrocyclic ring closure[43].

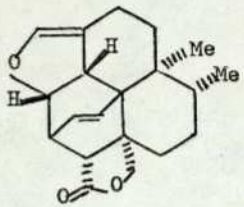


(70) (71) (72)

There are many examples of cycloaddition in which the furan nucleus acts as a diene[44,45], under suitable circumstances it may also participate as a dienophile.[46]



(73) (74)



(75)

Both addends of the precursor (74) would seem to be electron rich implying that the driving force for this reaction arises from steric rather than electronic enhancement.

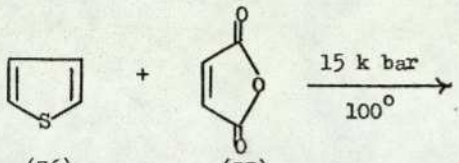
An important, and as yet neglected, area is the influence of pressure on the rate of cycloaddition. For a reaction in which a change of volume occurs, thermodynamic considerations[47] suggest that the rate of reaction will be dependent on the pressure:

$$\Delta V^{\neq} = -RT \left(\partial \ln k / \partial P\right)_T \qquad \text{(6)}$$

Where $\Delta V^{\neq}$ (activation volume) is the difference in partial molal volume between the transition state and the reactants for a bimolecular process. Previous work has demonstrated that for every extra bond created in the transition state, there is a net contraction in volume ($\Delta V^{\neq} \simeq -10\ Cm^3$)[48]. For a concerted mechanism $\Delta V^{\neq} \simeq -20\ Cm^3$,

accordingly an increase in pressure should produce a corresponding increase in rate.

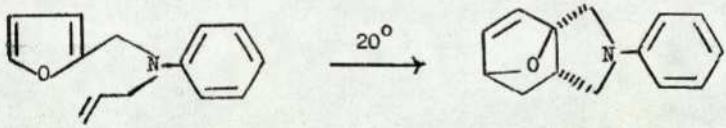
Thus thiophene (76), found previously to be an unreactive diene[49], will react with maleic anhydride (77) at high pressures[50].



(76) (77) endo-adduct (78)

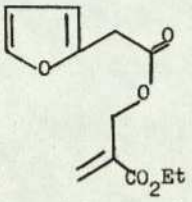
Although formidable problems have been encountered when applying such pressures at elevated temperatures, the potential of this technique is enormous, allowing a switch from thermodynamic to kinetic control or encouraging reactions that could never occur on heating under atmospheric pressure.

Examples of heterocycles as dienes in the Diels-Alder reaction are legion[51], not surprisingly they function well when used as intramolecular dienes. Perhaps the earliest instance[52] occurred with the furfurylamine (79) which underwent spontaneous cyclisation to give the epoxy indole (80).

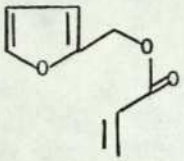


(79) (80)

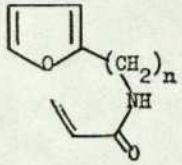
Further investigation[53] revealed a number of stereochemical features that exert considerable influence on the course of the reaction.



(81)

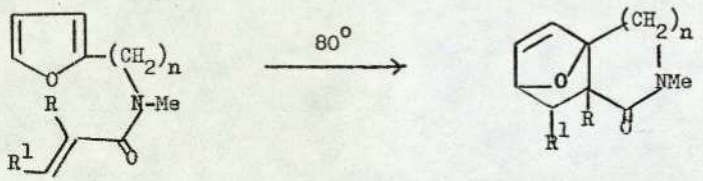


(82)



(83) n = 1-3

Neither the ester-linked chains(81) and (82) nor the secondary amides (83) n = 1-3, showed any tendency to cyclise on heating. Yet a number of tertiary amides (84, a,b,c,e) underwent smooth addition under relatively mild conditions.



(84) a.) n =1,R=R^1=H

b.) n =1,R=Me,R^1=H

c.) n =2,R=R^1=H

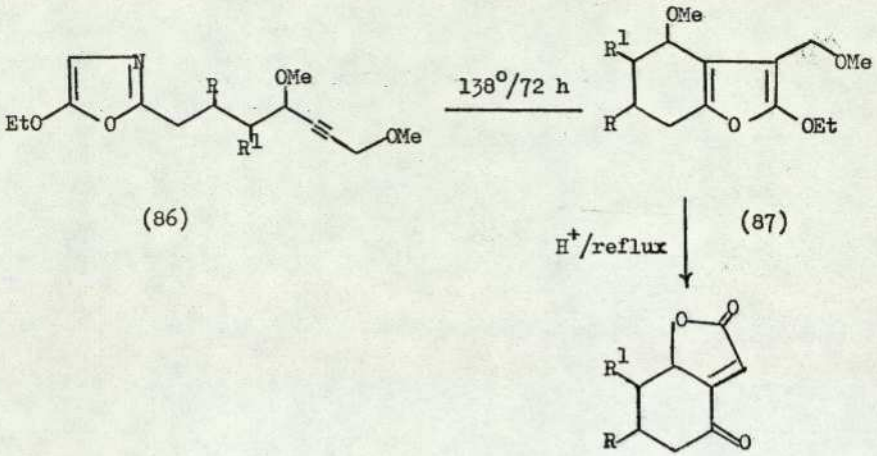
d.) n =3,R=H,R^1=Me no reaction

e.) n =3,R=R^1=H

(85)

The length of the sidechain does not seem to influence greatly the rate of addition, provided the conformation necessary for reaction can easily be adopted. Such observations show some measure of agreement with the kinetic studies on acrylamides mentioned previously.

Another widely used diene, the oxazole group, has recently been used to prepare an ethoxy furan[54] (87).

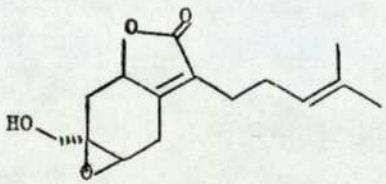


(86)

(87)

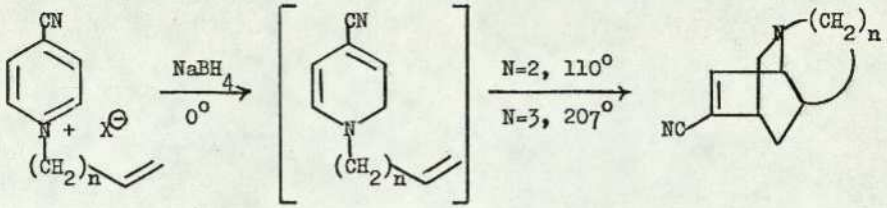
(88)

On refluxing in dilute acid, the methoxybutenolide (88) was formed, which contains many of the structural features of Paniculide C (89).

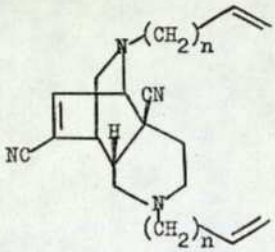


(89)

No intramolecular reactions have been reported for heterocyclic analogues of benzene containing one heteroatom. Although the dihydropyridine (91) has been studied by Greuter [55].



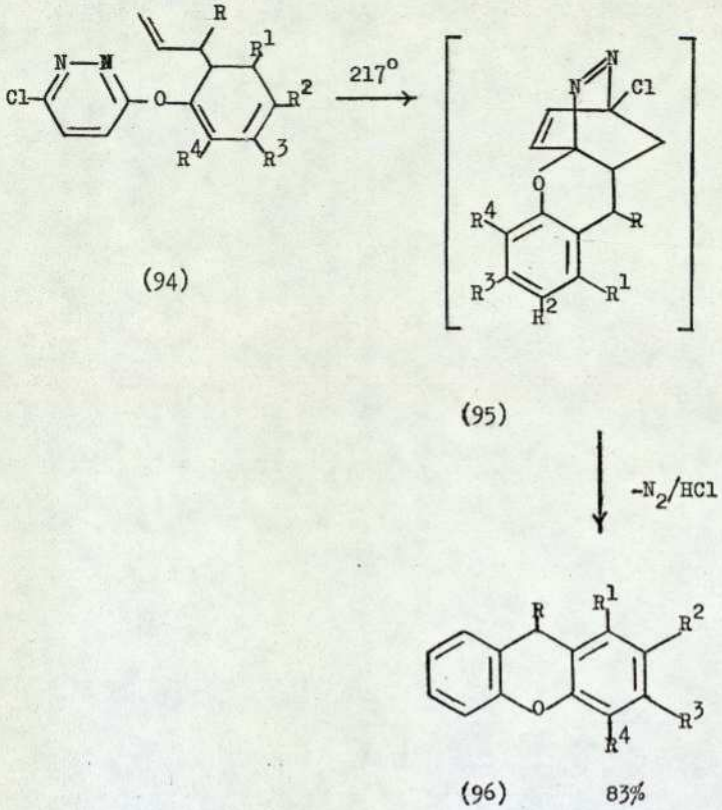
(90) n=2,3 (91) (93) n=2, 48%
n=3, 8%



(92)

In situ preparation of the intermediate(91), isolable as the dimer (92), followed by thermolysis, yielded a stereospecific product (93), proceeding via the exo-transition state. There was a marked decrease in reactivity as the length of the alkyl chain was increased.

A number of cycloadditions involving diazines are known. Under vigorous conditions the chloropyridazine (94) undergoes ($\pi 2s + \pi 4s$) addition with the allylic olefin to produce an adduct which readily eliminates hydrogen chloride and nitrogen to yield the xanthene (96)[56].



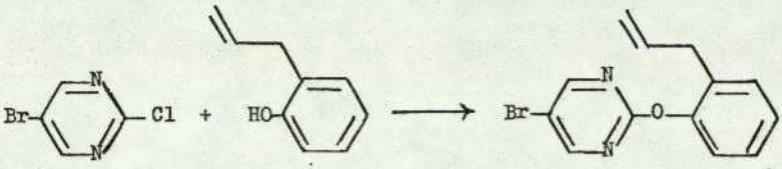
(94)

(95)

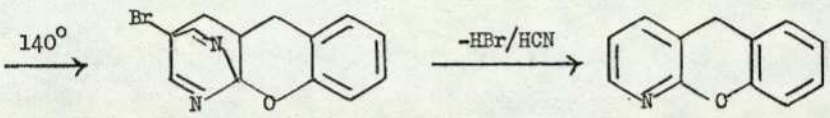
(96) 83%

With no chloro-substituent the corresponding dihydroxanthene was isolated[57].

The same preparative technique provides a pyrimidine derivative (99) that undergoes a similar reaction[58].



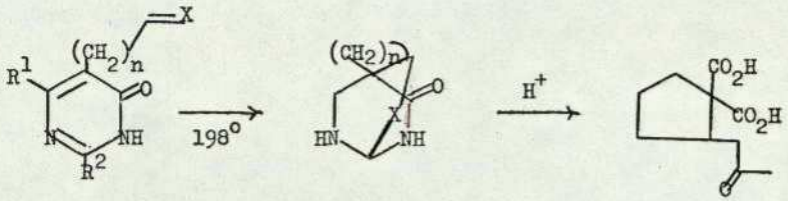
(97) (98) (99)



(100) (101) 27%

Phenolic coupling gives the precursor (99) which, on heating, yields the benzo-pyranopyridine (101)via the adduct (100) which was isolable under the reaction conditions. Substituent effects were marked and without a 5-halo substituent yields of cycloadducts were very poor.

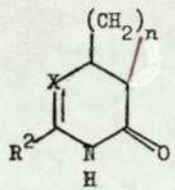
For dihydroxypyrimidines, a number of intramolecular additions have been reported, demonstrating considerable tolerance to variation in dienophile, chain length and substitution in the pyrimidine ring[59].



(102) n=3,4
R^1=OH,Ph
R^2=Me
X =C,N

(103)

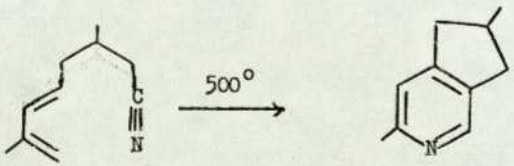
(105)



(104)

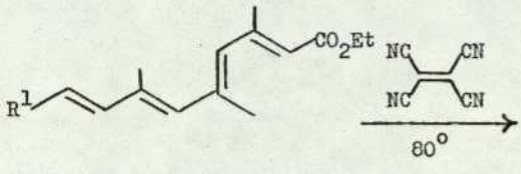
Elongation of the sidechain reduces the reactivity of the molecule. By using a nitrile as the dienophile it was possible to isolate the novel annulated pyrimidones (104, X = N, n = 3). The cycloadducts (103) were isolable and could be hydrolysed to yield the substituted cyclopentane (105).

Use of a nitrile as a dienophile has excellent precedents in intramolecular reactions. Thus the pyrindane (107) was produced from the citronellonitrile derivative (106)[60].

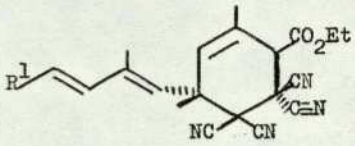


(106) (107)

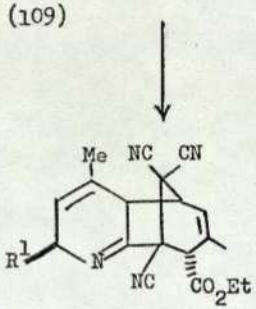
Rather more surprising was the product arising from reaction of a retinoic ester (108) with tetracyanoethylene[61].



(108) $R^1 = C_9H_{15}$



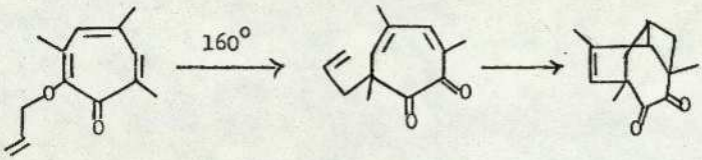
(109)



(110)

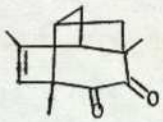
Under the reaction conditions a significant yield (73%) of the annulated dihydropyridine (110) was isolated, arising from [4 + 2] addition of the nitrile indicated in the cyclohexene derivative (109) to the diene present in the side chain.

Certain molecules, whilst notthemselves suitable precursors, have the capacity to rearrange and yield an isomer which can undergo some electrocyclic process. A Claisen rearrangement[62] of the allyl vinyl ether (111) generates an intermediate (112) which can cyclise to produce the isomeric α-diketones (113) and (114).



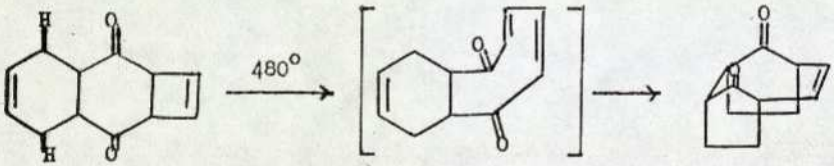
(111) (112) (113) 80%

+



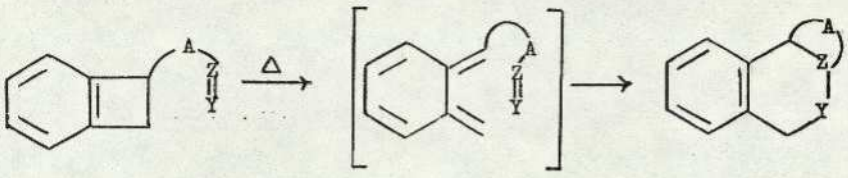
(114) 20%

Electrocyclic ring-opening of the cis-fused tricyclic diene (115) gives an intermediate (116) that can undergo addition to yield the cage compound[63] (117).

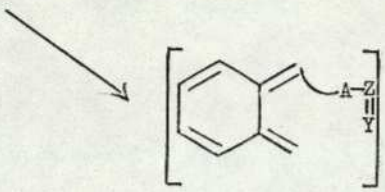


(115) (116) (117)

A particularly fertile area for such processes has been the intramolecular cycloadditions of the quinodimethanes[64] (118).

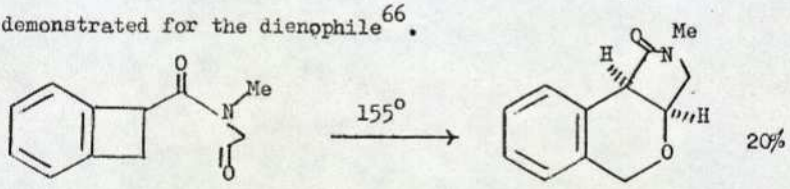


(119) (119) (121)

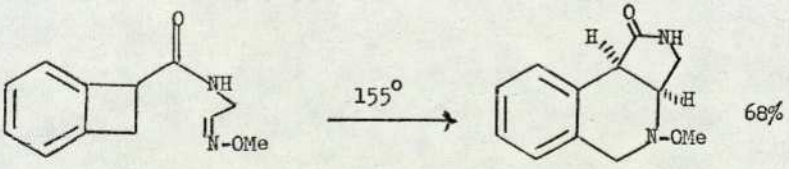


(120)

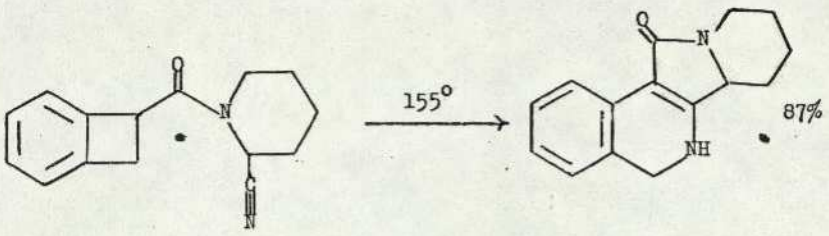
The E-quinodimethanes (119) are formed more readily than the Z-isomer[65] (120) and the regioselectivity imposed by the steric requirements of the side chain make this a very attractive process for building ring systems. Considerable versatility has been demonstrated for the dienophile[66].



(122) (123) 20%

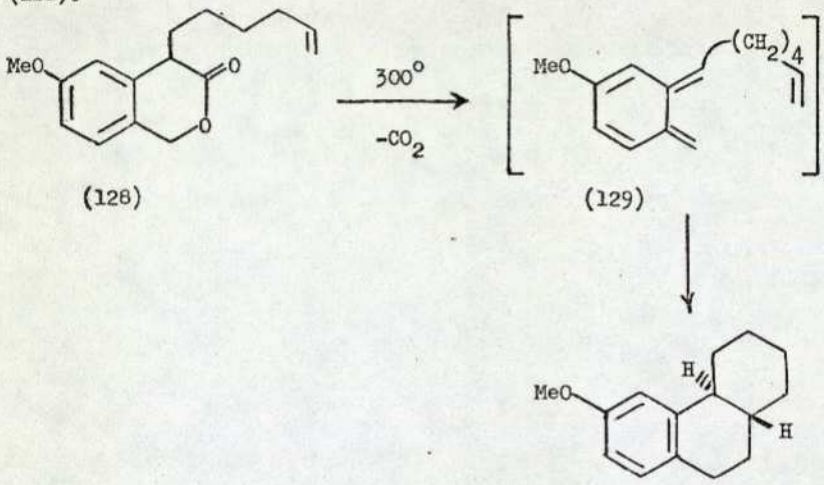


(124) (125) 68%



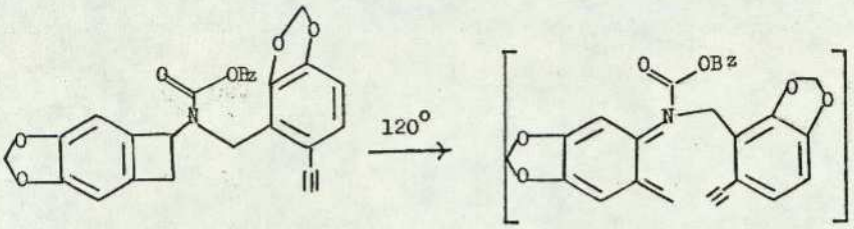
(126) (127)

The same precursors may be generated from 3-isochromanones[67] (128).

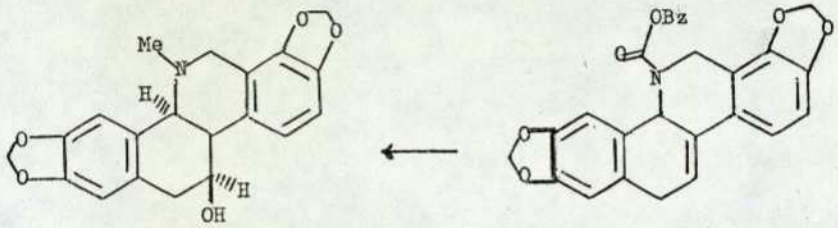


(128) (129) (130)

Such masked dienes have proved useful in natural product synthesis[68].



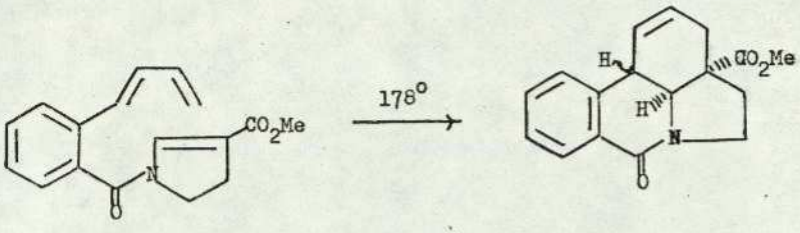
(131) (132)



(125) (±) chelidonine (133) 73%

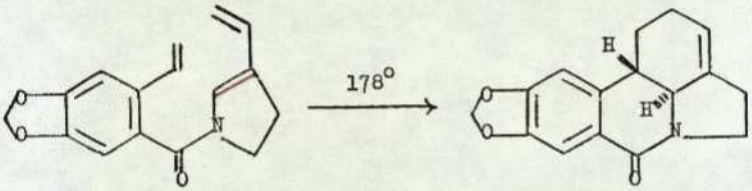
The key step is addition of the acetylene (132) to generate in high yield the adduct (133), which may be manipulated to yield the racemic chelidonine alkaloid (125). The main problem with these systems is the difficulty in making the complex precursors.

The most recent attempt to exploit an intramolecular reaction has been reported by Stork[69]. Synthesis of the phenylbutadiene pyrroline (135) and subsequent thermolysis, yielded a mixture of epimers (136).



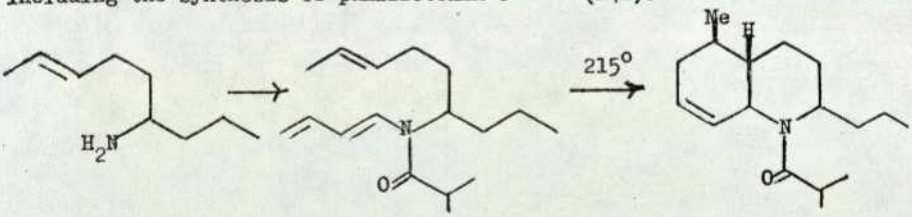
(135) (136)

By reversing the position of the diene and dienophile, however, as in the vinylpyrroline (137) formation of the desired galanthan skeleton (138) occurs stereospecifically.

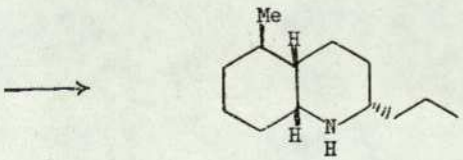


(137) (138)

A number of other interesting reactions have been reported, including the synthesis of pumiliotoxin C[70,71] (142).



(139) (140) (141)



(142)

The amine (139) was readily converted to the dienamide (140) which on heating gave the adduct (141), this could be hydrogenated and hydrolysed to yield the racemic alkaloid (142). The stereochemical features of this scheme along with many other cycloadditions of synthetic utility are all well reviewed by Oppolzer[72].

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CHAPTER 1

1. Computer Models

1. Computer Models

The use of quantum mechanical calculations to explain chemical reactivity has aroused great interest. Although studies on potential energy surfaces may eventually provide a clear understanding of reactivity, the natural desire to interpret experimental results in a satisfactory - if qualitative - manner has led to the development of a number of approximate quantum mechanical methods. Frontier molecular orbital (FMO) theory[1a] is just one of these approximations, in particular it provides a plausible description of the important factors pertinent to a class of reactions known as cycloaddition or pericyclic reactions[1b].

The theoretical framework for the FMO postulates was provided by perturbation theory[2] in which the interaction of a π-system with a reagent was treated as a perturbation of the orbitals on the isolated molecule. In a sense FMO theory is simply a first approximation to a perturbation treatment of chemical reactivity.

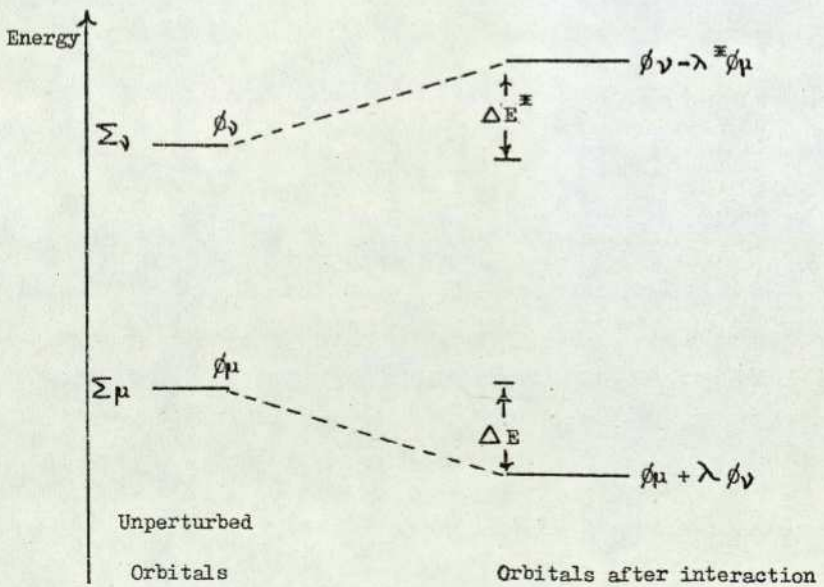


Figure 1

The interaction of 2 orbitals : $\phi\mu$, $\phi\nu$ gives rise to a set of new orbitals : $\phi\mu + \lambda\phi\nu$; $\phi\nu - \lambda^{*}\phi\mu$. The lower energy orbital ($\phi\mu$) will be stabilised by mixing in some of the higher energy orbital ($\phi\nu$) in a bonding combination; meanwhile the higher energy orbital ($\phi\nu$) will be destabilised by mixing in an antibonding combination with $\phi\mu$. The extent of interaction will be inversely proportional to the difference in energy ($E\mu - E\nu$) and directly proportional to the extent of overlap of $\phi\mu$ with $\phi\nu$. Mathematically these observations may be formulated for the interaction of 2 molecules[3].

$$\Delta E = 2\left[\sum_{M}^{OCC}\sum_{N}^{VAC} - \sum_{M}^{VAC}\sum_{N}^{OCC}\right] \frac{\left(\sum_{\mu\nu} C\mu\, C\nu\, \gamma\mu\nu\right)^2}{E\mu - E\nu} \qquad (1)$$

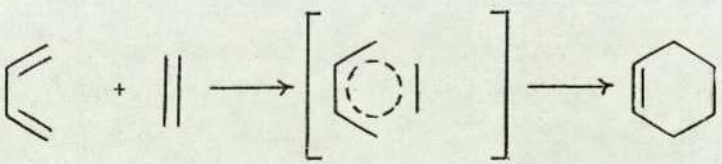
$\gamma\mu\nu$ = resonance integral for atomic orbitals μ,ν in molecular orbitals M,N

$C\mu,\nu$ = atomic orbital coefficients

With reference to Figure 1, the interaction of 2 filled orbitals will be destabilising because $\Delta E < \Delta E^{*}$. However, the interaction of a filled orbital with an empty orbital will result in a lower electronic energy after interaction than for the isolated orbitals because the 2 electrons will both go into a lower energy orbital. Similarly, interaction of a filled orbital with a singly occupied orbital, or a singly occupied orbital with a vacant orbital will lead to stabilisation ($2\Delta E > \Delta E^{*}$).

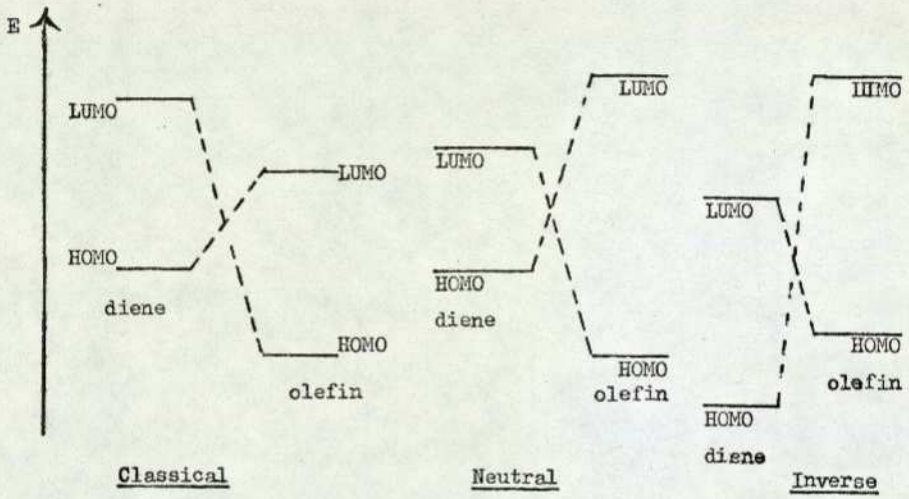
A calculation of the transition state energy for a bimolecular process may be made for an assumed geometry using the molecular orbitals of the reactants as a starting point. From Equation 1 it can be seen that attractive forces will arise from interactions of occupied orbitals on one reactant with vacant orbitals on the other (and vice-versa). The largest stabilisation will be gained when the denominator is a minimum, that is when the orbitals are closest in energy. The greatest interaction will therefore be observed between the highest occupied molecular orbital (HOMO) of one reactant, and the lowest unoccupied molecular orbital (LUMO) of the other (and vice-versa). The FMO theory claims to give an indication of the transition state energy, deduced from the premise that initial stabilising interactions will give a shallower slope for the profile of the reaction coordinate and hence a lower activation energy for the reaction than would be observed without such stabilisation. All of the destabilising interactions such as closed shell repulsion, coulombic repulsion (or attraction) and desolvation energies are neglected. This approximation works quite well for exothermic reactions in which the transition state resembles , and is monotonically related to, the reactants[4].

The simplest allowed[5] Diels-Alder reaction involves 1,3-butadiene (1) and ethylene (2).



(1) (2) (3) (4)

The transition state (3) comes early on the reaction coordinate for the concerted process since the overall reaction is exothermic[6], to predict the effect of substituents on the rate of this reaction, FMO theory may be applied - provided the energy levels of the interacting species are known. In a general sense, three different cases may be distinguished for the relative positions of the important orbitals.



Of the two important interactions one is likely to predominate and any substitution which decreases the energy difference between the two orbitals concerned should enhance the rate of reaction. The most common case promotes reaction between electron rich (high HOMO) dienes and electron deficient (low LUMO) dienophiles[7]. Such a requirement is represented in Figure 2 as the classical demand. It must be stressed, however, that no rigid boundaries exist; indeed butadiene itself may be considered as a conjugated ethylene derivative, as conjugation is known to raise the HOMO energy and depress the LUMO

energy[8], reactions of butadiene (1) will demonstrate neutral demand with most substituted olefins. In general, electron donating substituents will raise both the HOMO and LUMO energies, whilst electron withdrawing groups will lower both levels and so it is possible to construct an empirical hierarchy from which predictions concerning the relative rates of analagous processes may be made.

In each of the many approaches[9-11] to the calculation of orbital interactions, the quantities needed are the difference in energy between the orbitals as well as the symmetry and the magnitude of the coefficients at various centres for each orbital. One approach is to use experimentally determined values where available. Thus an idea of HOMO energies is deduced from ionisation potentials as measured by photoelectron spectroscopy [12] and LUMO energies similarly gleaned from data on electron affinities as obtained from charge-transfer spectra or from reduction potentials[13]. This approach has the considerable drawback that the required data on organic compounds are not prevalent. It also assumes that Koopmans' approximation is totally valid[14], and the orbital coefficients must still be calculated. An alternative approach to obtaining these quantities is to calculate all of them by one of the many molecular orbital methods available.

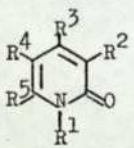
All computer models start by considering the mathematical equations developed by Roothaan[15] and Hall[16] in 1951. Even a precise solution of these equations would be physically inaccurate because of the neglect by the Hartree-Fock[17] method of Coulomb-correlation (the tendency of pairs of electrons to synchronise their motion). Nevertheless, such a solution is attempted by ab initio methods, notably Gaussian 70[18], and (with extended basis sets) the HOMO

energies agree well with experimentally determined values. Unfortunately such a method consumes vast quantities of computer time (for N orbitals the time required is proportional to N^4 seconds).

The second approach is a semi-empirical one which parametrises certain integrals generated by the Roothaan equations rather than solving them explicitly. A simplifying assumption used in most calculations is to consider only the valence electrons and to regard the inner shell electrons as a fixed potential core. Within this approximation various levels of sophistication have evolved and these are conveniently classified by the extent to which 'differential overlap' (the amount two atomic orbitals in space overlap) is neglected in calculating electron interaction integrals for the Roothaan equations. The core approximation is certainly reasonable and the neglect of electron repulsion integrals involving diatomic differential overlap can also be justified[19]. The further neglect of electron repulsion integrals involving one-centre overlap is rather less secure. The total energy of a molecular model should be invariant to rotation in the same way that the total energy of a real molecule is invariant to rotation and so integrals cannot be ignored without considering the effect upon the molecular symmetry[20]. The most common calculations, in order of increasing rigour are: CNDO (complete neglect of differential overlap); INDO (intermediate neglect of differential overlap); and MNDO (modified neglect of differential diatomic overlap). As MNDO is parametrised with a view to examining heterocyclic structures, the HOMO energies of heterocycles are in good agreement with experimentally measured values. All methods, however, rely on the variation principle for energy minimisation, the virtual orbitals are therefore produced as a result of optimising the filled orbitals and not explicitly taken into consideration, consequently LUMO energies are often

unreliably predicted by all methods.

It was decided to examine three of these programmes in the light of experimental observations: CNDO[21], MNDO[22], and ab initio (Gaussian 70)[23]. All programmes require a trial input geometry, the versions used of MNDO and Gaussian 70 will then optimise this geometry using the David$_o$n-Fletcher-Powell method[24] until the total energy of the system is a minimum. A wide-ranging study has estimated the mean absolute error in bond length at 0.014A^o from such methods[24]. The advantage of using this subroutine is that the geometries for desired molecules are frequently unavailable. Geometries from the files of the Cambridge crystallographic data bank[23] were also used as a comparison although it must be appreciated that such data correspond to solid state geometries whereas the computer programmes will calculate geometries for molecules essentially in the gas phase, neglecting interactions with solvent or other molecules. The results from the various investigations (largely on 2-pyridone(5)) are presented in Tables 1 and 2.



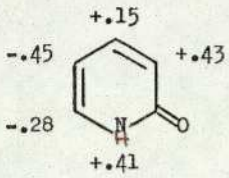
(5)

Table 1. CNDO/2 Orbital Parameters for 2-Pyridones

Substituents					HOMO			LUMO		
R_1	R_2	R_3	R_4	R_5	-E(ev)	C_3	$-C_6$	E(ev)	C_3	C_6
H	H	H	H	H	10.76	.4264	.2849	2.67	.4274	.5305
H	H	H	H	Me	10.52	.4440	.2855	2.70	.4160	.5375
Me	H	H	H	H	10.51	.4075	.2558	2.69	.4231	.5262
H	Me	H	H	H	10.38	.4339	.3078	2.63	.4246	.5097
Me	H	H	H	Me	10.27	.4310	.2573	2.77	.4077	.5363
Me	Me	H	H	H	10.27	.4199	.2832	2.64	.4195	.5065
H	H	H	NO_2	H	9.72	.3507	.2505	2.05	.4474	.5711
H	H	H	H	Ph	10.29	.4400	.2799	1.72	.3296	.4252
H	H	H	CN	H	10.82	.3908	.3038	2.18	.4193	.5942
H	H	H	H	CN	10.87	.4308	.2890	1.65	.4062	.5162
H	CN	H	H	Me	10.55	.4428	.2878	1.95	.3912	.5267
H	Me	H	H	CN	10.53	.4321	.3113	1.66	.4111	.5022
Me	CN	H	H	H	10.61	.4139	.2681	1.94	.4014	.5181
Me	H	H	CN	H	10.59	.3764	.2732	2.20	.4151	.5901
H	H	CN	H	Me	10.79	.2714	.4597	1.87	.4323	.4396
Me	H	OH	H	H	10.60	.4502	.2321	2.87	.3870	.5711

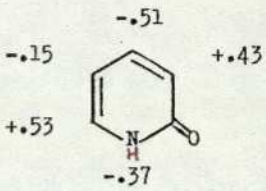
2-Pyridone : CNDO/2

HOMO -10.76 ev



(6)

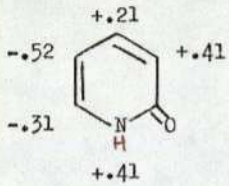
LUMO +2.67 ev



(7)

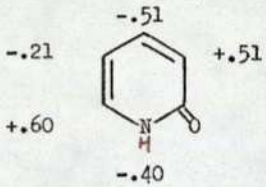
2-Pyridone : ab initio (STO-6G)

HOMO -5.95 ev



(8)

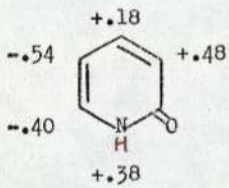
LUMO + 6.09 ev



(9)

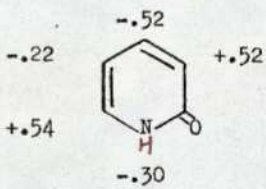
2-Pyridone MNDO

HOMO -8.92 ev



(10)

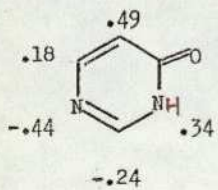
LUMO -0.22 ev



(11)

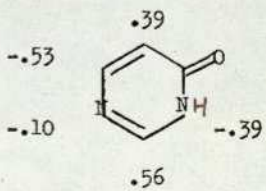
2-Pyrimidone CNDO/2

HOMO -10.86 ev



(12)

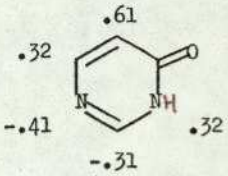
LUMO +2.33 ev



(13)

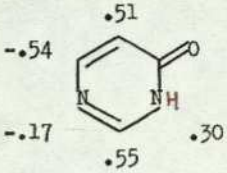
2-Pyrimidone MNDO

HOMO -9.64 ev



(14)

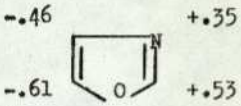
LUMO -.51 ev



(15)

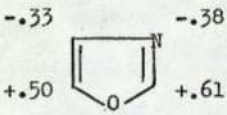
Oxazole CNDO/2

HOMO -12.70 ev



(16)

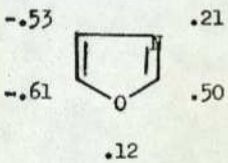
LUMO 4.08 ev



(17)

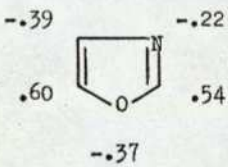
Oxazole MNDO

HOMO -9.72 ev



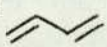
(18)

LUMO 0.27 ev



(19)

Table 2. MNDO, Gaussian 70 (ab initio) Orbital Parameters for Dienophiles

	-HOMO(ev)	C_1	C_2	LUMO(ev)	C_1	$-C_2$
MNDO						
C_2H_4	10.2	.71	.71	1.3	.71	.71
C_2H_2	11.0	.71	.71	2.1	.71	.71
$MeO_2C.C{\equiv}C.CO_2Me$	11.4	.00	.00	-0.8	.45	.45
$CH_3.CH{=}CH_2$	10.0	.56	.67	1.8	.65	.67
$CH_3.C{\equiv}CH$	10.7	.31	.52	1.6	.15	.10
$MeO.CH{=}CH_2$	9.1	.39	.61	2.0	.72	.66
Ab initio						
C_2H_4 (STO-3G)	8.7	.71	.71	5.5	.71	.71
C_2H_4 (6-31G)	10.2	.71	.71	4.7	.71	.71
CNDO/2						
C_2H_4	15.8	.71	.71	5.2	.71	.71
$CH_3.CH{=}CH_2$	14.2	.60	.70	5.9	.60	.70
Experimental Values	-HOMO(ev)[25]			LUMO(ev)		
C_2H_4	10.5			1.55[26]		
C_2H_2	11.4			2.2[27]		
$Me.CH{=}CH_2$	9.9			-		
$Me.C{\equiv}CH$	10.4			-		
	9.08			0.62[26]		

From the CNDO/2 results for 2-pyridones, a number of interesting features may be delineated. Firstly, the effects of electron-donating, withdrawing and conjugating groups are correctly reproduced[8]. More importantly, the effect of a given substituent is dependent on the magnitude of the coefficient at the position of substitution. A substituent placed in the 4-position (R^3) would exert a small effect on the HOMO (C_4 = 0.15) but a large effect on the LUMO (C_4 = -.51). The same substituent in the 5-position (R^4) would now exert an appreciable effect on the HOMO (C = .45) but a minimal effect on the LUMO (C = .15) Provided, therefore, the coefficients are known for the unsubstituted molecule, it is possible to predict which substitution will have the greatest influence on a given orbital. Comparison of the results on 2-pyridones from the three different models used shows that they all predict an antisymmetric HOMO and a symmetric LUMO. The coefficients are also similar in magnitude, of particular interest is the observation that the double bond between C(3) and C(4) has the correct symmetry to act as a dienophile, in particular the large LUMO coefficients make this molecule a good 4 π-electron acceptor[28]. The values for the HOMO energy show far less agreement. The experimentally determined value for pyridine is -9.67 ev[29], as the 2-pyridone structure is a tautomer of 2-hydroxypyridine, its HOMO should be higher than that of pyridine and so the MNDO value (-8.92 ev) would seem to be remarkably accurate. The ab initio value (-5.95 ev) is much too high probably because of the small basis set used in an STO-3G calculation.

For LUMO values again a wide spread is apparent. The difference between the heats of formation of a given negative ion and the corresponding neutral species is, by definition, the adiabatic electron affinity (AEA). In cases where the geometries of the negative ion and

the neutral molecule do not differ significantly, the adiabatic electron affinity and the Koopmans' theorem estimate (vertical or Franck-Condon transition) are similar. Thus for pyridine, MNDO gives an AEA value of 0.22 ev, compared with the experimental[30] value of -0.62 ev. The LUMO energy[31] is given as 0.01 ev and so by Koopmans' theorem the electron affinity would be -0.01 ev agreeing quite well with the experimental value which is itself open to criticism as difficulties arise in identifying the transition to the lowest vibrational level of the negative ion[30], thus values for electron affinities obtained from photoionisation measurements on the negative ion may not always be adiabatic values, but rather an upper limit to them[32]. The CNDO/2 and ab initio values are far too high and reflect their poor correlation for virtual orbitals[33].

For 2-pyrimidones and oxazoles, the MNDO values for the HOMO energies are lower than that for 2-pyridone, reflecting the presence of a heteroatom in the diene - indeed the LUMO energy (-0.51 ev) for 2-pyrimidone is almost as low as that for an acetylenic ester (E_L = -0.8 ev) and consequently would be expected to function well as an electron deficient diene (inverse demand).

For dienophiles, the MNDO agreement with experimental values is very good. The CNDO/2 HOMO energies are far too low and the LUMO values far too high. Ab initio calculations are accurate for the HOMO energies when using large basis sets (6-31G) but again the LUMO energies are much too high.

Of interest is the acetylenic ester which is predicted to have very little π-character in the HOMO or indeed in the subjacent π-orbitals, whilst the low-lying LUMO has large coefficients and should be a good electron acceptor, reacting rapidly with nucleophilic dienes.

As these calculations provided the starting point for laboratory

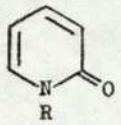
investigations, it is as well to emphasise the implications for the classes of compounds under investigation. Taking butadiene as the yardstick (MNDO, E_{HOMO} = -9.14 ev, E_{LUMO} = 0.39 ev), 2-pyridone, having a higher HOMO and a lower LUMO, should be a better diene. 2-Pyrimidone should be a poor classical diene, but an efficient diene with inverse demand. Finally oxazole is predicted to be a poor diene. The predictions are based purely on the assumption that the FMO model is valid when comparing different systems. The limitations of this premise are assessed in the following discussion.

CHAPTER 2

Cycloaddition Reactions of 2-Pyridones

Cycloaddition Reactions of 2-Pyridones

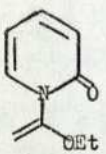
Early studies suggested that 2-pyridones possess about 35% of the aromaticity of benzene as defined by their ability to sustain an induced ring current[34]. The implication that the conjugated system should act as a suitable diene was quickly tested by thermolysing 1-methyl-2-pyridone (21) with maleic anhydride, but no novel products were isolated[34].



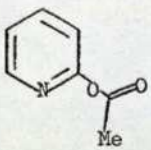
(20) R = H

(21) R = Me

Further attempts generated salts resulting from protonation of the carboxyl group[35]. When 2-(1H)-pyridone (20) was used as the diene, products arose from nucleophilic addition by the amide[36], thus ethoxy-acetylene[37] gave both N- and O-alkyl products (22) and (23).

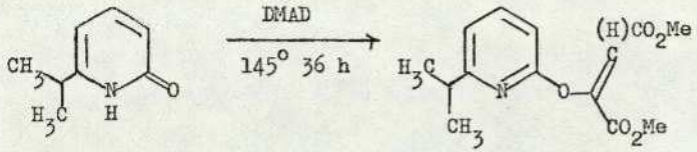


(22)



(23)

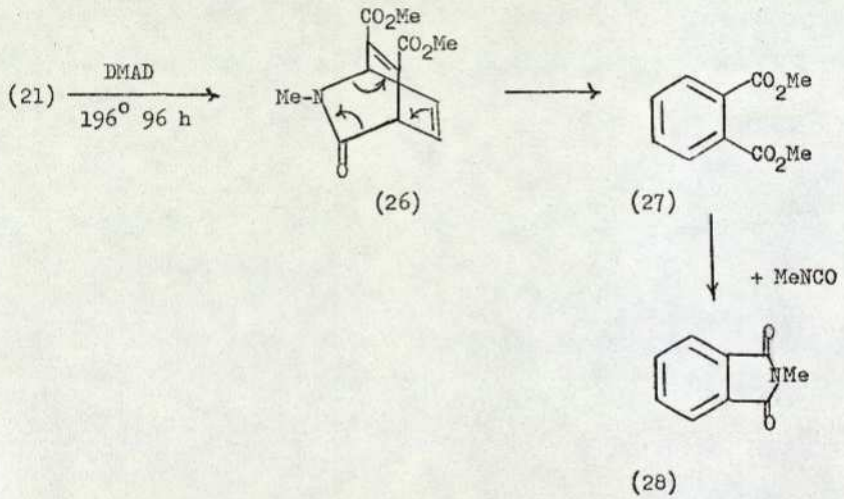
A similar result was obtained by reacting (20) with dimethyl butynedioate[38]. The ratio of N-alkyl to O-alkyl products depends upon the size of the substituent on C(6). Thus 6-isopropyl-2-pyridone (24) gave exclusively the pyridine-ether(25)[39].



(24) (25)

No mention is made of any attempt to isolate the respective cis- and trans-isomers.

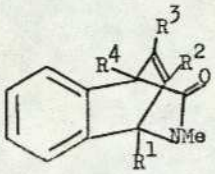
Of greater importance to the present work was the successful addition of DMAD to 1-methyl-2-pyridone (21) under forcing conditions[40].



(26) (27) (28)

The N-methylphthalimide (28) was isolated in very poor yield (4%). Neither the postulated adduct (26) nor the dimethylphthalate (27) were detected and attempts to perform the reaction under milder conditions were unsuccessful.

A mixture of endo- and exo- adducts was obtained in very low yield (3%) from the reaction of (21) with fumaronitrile[41]. Adducts (29 a-d) have also been isolated from reaction of benzyne with 1,3-, 1,4-, 1,5- and 1,6-dimethyl-2-pyridones in very modest yields (4-13%)[42].



(29)

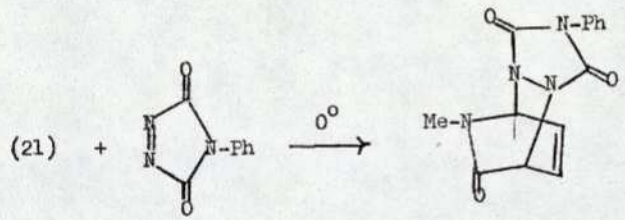
a. R^1 = Me, R^2 = R^3 = R^4 = H

b. R^2 = Me, R^1 = R^3 = R^4 = H

c. R^3 = Me, R^1 = R^2 = R^4 = H

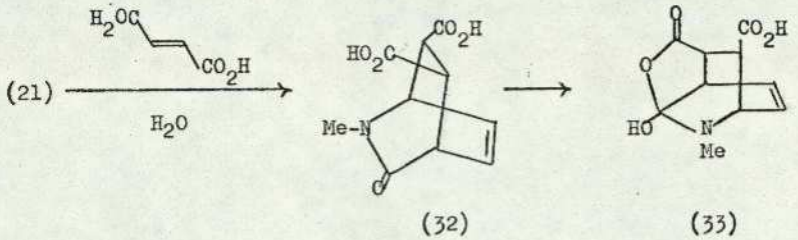
d. R^4 = Me, R^1 = R^2 = R^3 = H

Perhaps the most impressive reports have come from workers using maleimide and N-substituted maleimides to give the desired <u>exo</u>- and <u>endo</u>- adducts in good yields[43-45] (40%) and most recently with 4-phenyl-1,2,4-triazoline-3,5-diene (30) to give a high yield (80%) of the adduct (31).

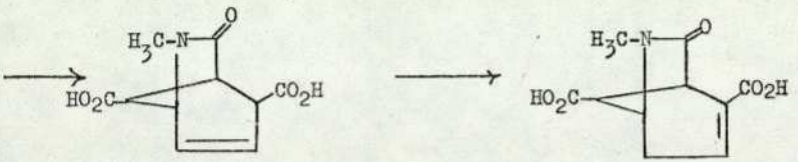


(30) (31)

An unusual rearrangement following addition of (21) with fumaric acid in water has been reported.[48]



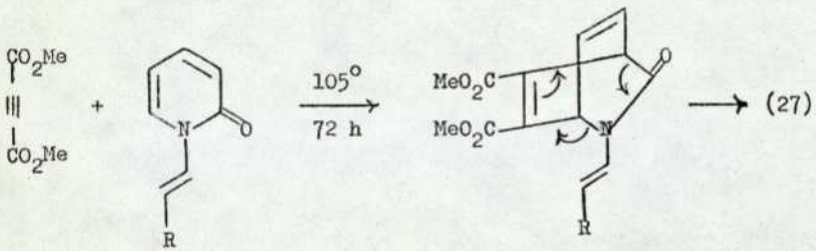
(32) (33)



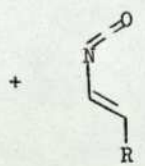
(34) (35)

The bicyclolactam (35) is presumed to form after intramolecular attack by an acid group on the amide.

Reaction of 1-vinyl-2-pyridones (36) has been described[49].

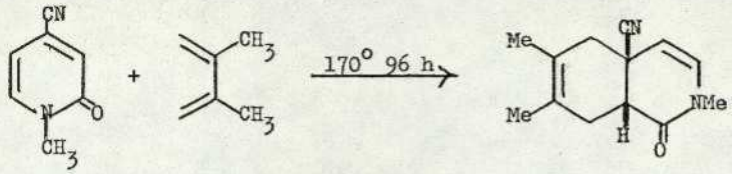


(36) R=Ph,Me (37)



The adducts (37) were isolated in moderate yields (~22%).

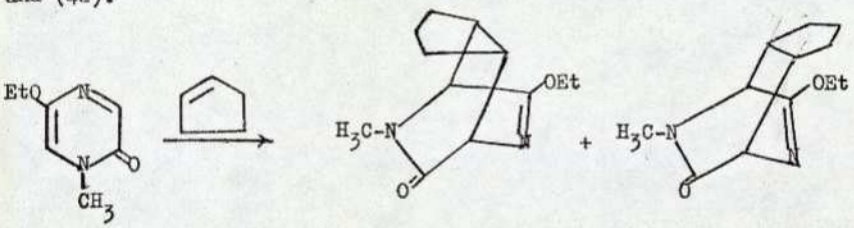
As suggested earlier (see Chapter 1) 2-pyridones have the required orbital characteristics to undergo reactions as 2π-acceptors. Recent confirmation of this observation has come from a report on reaction with 2,3-dimethyl butadiene[28].



(38) (39)

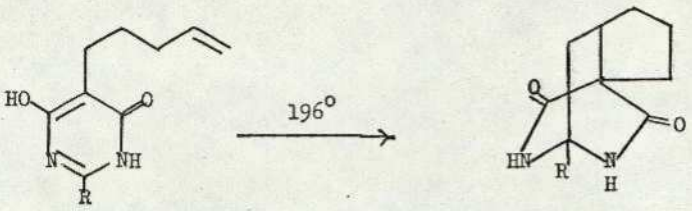
The reaction conditions gave good yields (71.6%) of the cis-fused tetrahydro-2-isoquinolone (39). At higher temperatures the trans-fused adduct was also isolated.

The overall inference is that 2-pyridones are rather unreactive dienes. Certainly an examination of the diazine series shows markedly different propensities. Thus the 1-methyl-2-pyrazinone (40) reacted rapidly with cyclopentene to give a mixture of primary adducts[50] (41) and (42).



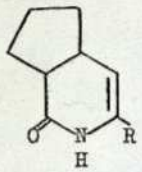
(40) (41) (42)

Similarly 2-pyrimidones (43) will react with an isolated olefinic component in an intramolecular cycloaddition (see Review).



(43) R = H,Me,Ph

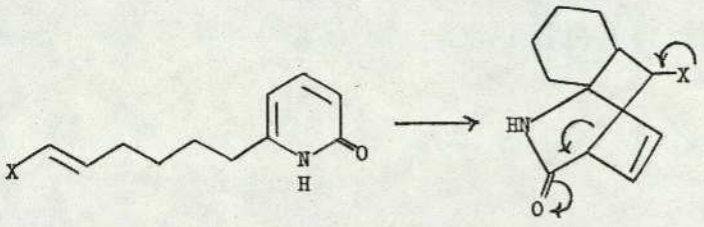
(44)



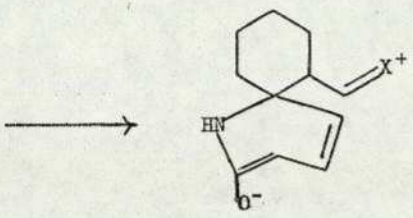
(45)

Both pyrazinones and pyrimidones have low-lying LUMOs (see Chapter 1) and it seems reasonable to infer that any reaction with an electron-rich dienophile will be controlled primarily by the compatibility of the diene LUMO with the HOMO of the dienophile, any substitution which brings these two orbitals closer in energy should enhance reactivity provided other factors are unaltered.

Our initial synthetic interest was centred on the possibility of constructing a substituted 2-pyridone (46) capable of undergoing an intramolecular cycloaddition to give the breakdown product (49) having the general skeleton containing an aza-spiro junction.

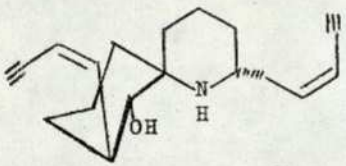


(46) (47)



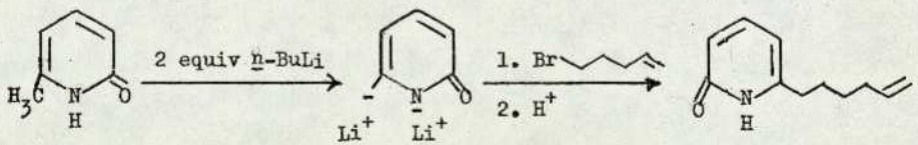
(49)

Such a product would be an analogue of the dendrobatid alkaloid histrionicotoxin[51] (50).



(50)

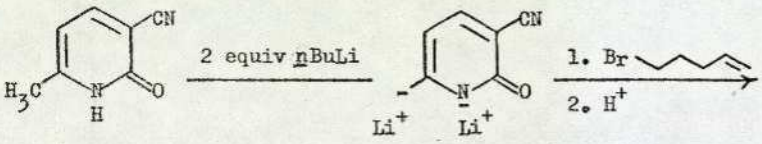
To test the general strategy, the model alkenyl-2-pyridone (53) was synthesised by Gisby[52].



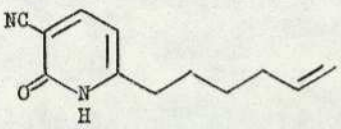
(51) (52) (53)

Pentenyl bromide was prepared by the bromination with phosphorus tribromide of pentenyl alcohol, which was in turn prepared by the method of Brooks[53]. The 2-pyridone (51) was generated by the diazotisation and subsequent hydrolysis of 6-amino-2-picoline in a modification of the procedure of Adams et al[54]. The yellow dianion (52) was prepared by the method of Hauser[55], at -23°C with two equivalents of n-butyl lithium. Alkylation gave a 50% yield of the alkenylated-2-pyridone. Thermolysis up to 250° yielded no products. Evidently this precursor did not possess the necessary electronic compatibility and so a number of variations were examined for both the diene and dienophile.

6-Methyl-3-CN-2-pyridone (54) synthesised by the method of Mariella et al[56] was treated as outlined above.

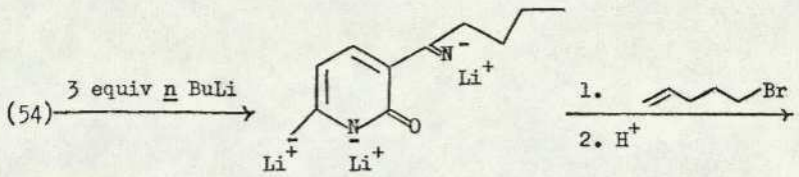


(54) (55)

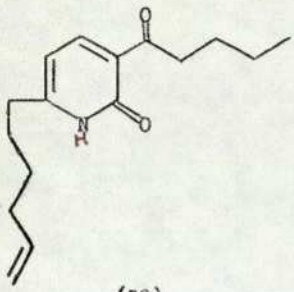


(56)

The brilliant red anion when treated with the bromide gave a product which had lost the nitrile and contained no sidechain. When the reaction was repeated using 3 equiv n-butyl lithium, a single product was obtained.

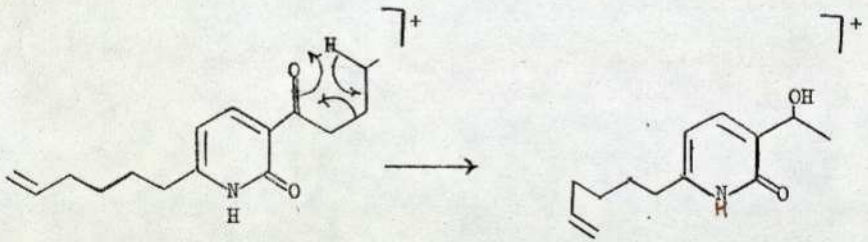


(57)



(58)

The 'H nmr spectrum contained, in addition to the expected vinyl absorptions and alkyl envelope, two triplets at δ 3.16 and δ 2.68 each integrating as two protons. The I.r. spectrum showed loss of a nitrile and the mass spectrum gave a molecular ion at m/e 261, loss of 42 was consistent with a McLafferty rearrangement.



(58) (59)

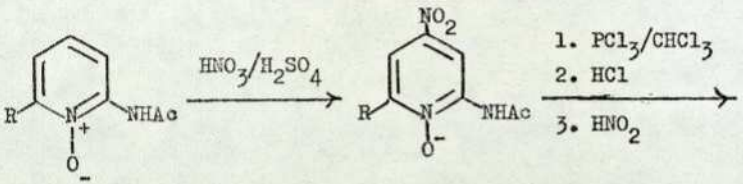
+ $Me.CH{=}CH_2$

The desired dianion (55) could be produced by using two equivalents of a hindered base to avoid the nucleophilic attack by n-butyl lithium. Lithium diisopropylamide (LiDIPA) prepared from diisopropylamine (DIPA) and n-butyl lithium gave a yellow dianion

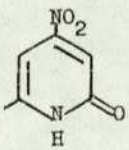
which alkylated smoothly on treatment with pentenyl bromide to give the 6-(hex-5-en-1-yl)-3-CN-2-pyridone (56). The I.r. spectrum showed an absorption at 2220 cm^{-1} and other spectral and analytical data were consistent with (56).

Attempts to thermolyse both (56) and (58) were unsuccessful. Acetonitrile and DMF were used as solvents and temperatures ranged from 110° up to 245°. Slight decomposition was observed at higher temperatures. Even use of Lewis acids, such as boron tri-fluoride etherate or aluminium chloride, failed to induce reaction.

An examination of the 2-pyridone LUMO (7) indicates that an electron-withdrawing group at C(4) should lower the energy of this orbital more than at other positions (C(6) bearing a methyl group to allow introduction of a sidechain). Steric hindrance should also be minimal as the 4-substituent is clear of the diene termini. A report by Brown et al[57] that 2-acetylamino pyridine-1-oxide (60, R=H) was selectively nitrated in the 4-position suggested that the analogue (60, R=Me) would undergo nitration in the same position to allow conversion to the 4-nitro-6-methyl-2-pyridone[59] (62).

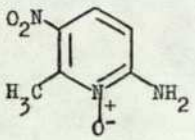


(60) (61)



(62)

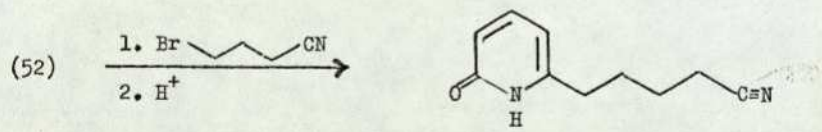
Under suitably mild conditions a product was isolated and analysed by ^{1}H nmr. Of interest were the two aromatic protons which resonated as doublets with a coupling J = 9HZ, typical of an ortho-coupling and much too large for the meta- coupling that should be observed in (61). A comparison with data for analogous nitro-pyridines[60] showed that the nitro group had in fact substituted para- to the amine to give the 5-nitro-derivative (63).



(63)

Synthesis of the nitro-2-pyridone (62) was not pursued as the failure of (56) and (58) to thermolyse suggested that inverse demand compatibility was inappropriate for 2-pyridone cycloadditions. Accordingly a classical approach was examined.

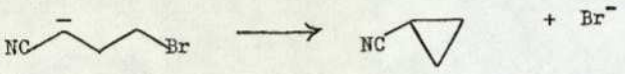
There is ample precedence for the intramolecular addition of a nitrile to a diene (see Review); with this in mind the reaction outlined below was attempted.



(64)

4-Bromobutyronitrile was synthesised by stirring 1,3-dibromo-propane with an aqueous solution of potassium cyanide and benzyl triethylammonium chloride as a phase transfer catalyst, this method was found to be more convenient than the previous literature prepar-

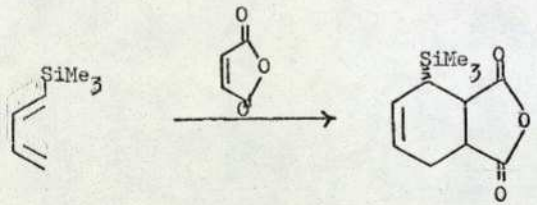
ation[61]. When the bromide was added to the dianion (52) and subsequently quenched, the unreacted 2-pyridone (51) was recovered, together with a novel compound. Analysis by ^{1}H nmr showed that only protons at very high field (δ 1.6- δ 0.9) were present. The i.r. spectrum had an absorption at 2195 cm^{-1} which indicated that a strongly conjugated nitrile was present. A proposed mechanism for the reaction involved the dianion (52) acting as a non-nucleophilic base to generate the anion of the bromobutyronitrile (65).



(66)

An intramolecular displacement would afford the cyclopropanitrile (66). All attempts to circumvent this process were unsuccessful.

A report[62] on the rate of reaction between maleic anhydride and 1-trimethylsilylbutadiene (67) suggested that the trimethylsilyl group slowed the reaction rate by making butadiene a poorer classical diene.

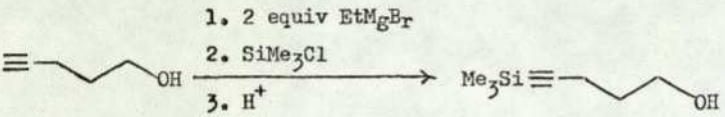


(67)

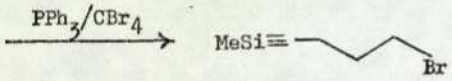
That this was not wholly a steric effect was inferred from a similar study[63] on trimethylsilyl cyclopentadiene addition to maleic anhydride in which the rate of addition diminished as extra trimethylsilyl groups were introduced in the cyclopentadiene ring. The possible

d_π-p_π interaction between the silicon and the adjacent carbon should lead to a partial charge transfer from the alkyne, resulting in an electron deficient dienophile.

A novel sidechain was therefore constructed by taking pent-4-yn-1-ol (68), prepared by the method of Brooks and Snyder[64], and trimethylsilylating the acetylene using the method of Jones et al[65]. The alkynylalcohol (69) was brominated by a variation of the method of Nolan et al[66] using carbon tetrabromide and triphenylphosphine in benzene.

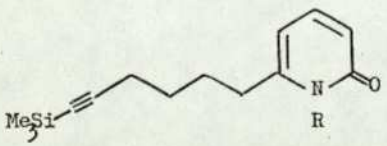


(68) (69)



(70)

Alkylation with the bromide (70) using the dianion (52) afforded 6-(hex-6-trimethylsilyl-5-yn-1-yl)-2-pyridone (71, R=H).

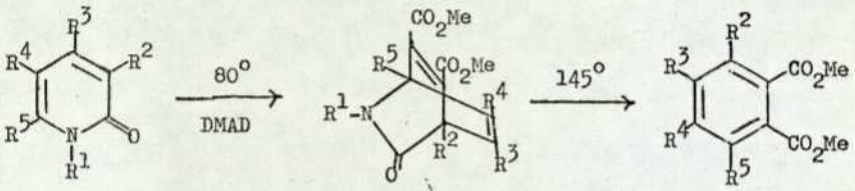


(71) a. R = H, b. R = Me

The ^{1}H nmr spectrum contained a two-proton triplet at δ 2.66 for the benzylic methylene and another at δ 2.26 for the methylene group next to the alkyne, there was also a nine proton singlet at δ 0.12

for the trimethylsilyl group. The i.r. spectrum contained an absorption at 2175 cm^{-1} for the substituted acetylene and an absorption at 1660 cm^{-1} for the lactam. The N-methyl derivative (71, R = Me) was synthesised by the method of Hopkins et al[67]. Both these precursors (71, R = H, Me) proved thermally inert up to 245° (refluxing diethylene glycol.)

The failure of all these alkenylated-2-pyridones, as well as other precursors[52], to react, led to a re-examination of the factors influencing cycloaddition. An independent report[39] claimed to have isolated the adduct (73d) with DMAD.



(72) (73) (74) + R^1NCO

a. $R^1 = R^5 = Me$; $R^2 = R^3 = R^4 = H$

b. $R^1 = R^2 = Me$; $R^3 = R^4 = R^5 = H$

c. $R^1 = R^4 = R^5 = Me$; $R^2 = R^3 = H$

d. $R^1 = R^3 = R^5 = Me$; $R^2 = R^4 = H$

e. $R^1 = Me$; $R^2 = R^3 = R^4 = H$; $R^5 = OMe$

f. $R^1 = Me$; $R^2 = R^4 = R^5 = H$; $R^3 = Ph$

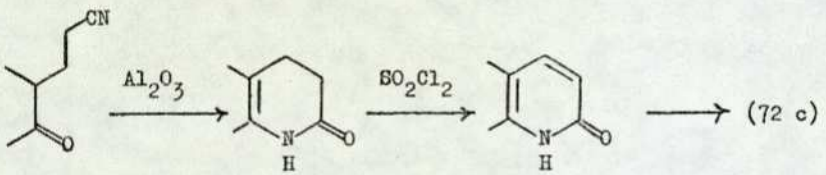
g. $R^1 = R^5 = Me$; $R^2 = R^4 = H$; $R^3 = Ph$

h. $R^1 = OMe$; $R^2 = R^4 = H$; $R^3 = R^5 = Me$

Further heating at elevated temperatures produced the 3,5-dimethyldimethylphthalate (74d) arising from the retro-Alder breakdown of the cycloadduct. The expected electronic enhancement with two methyl substituents is hardly consonant with the dramatic increase in reactivity

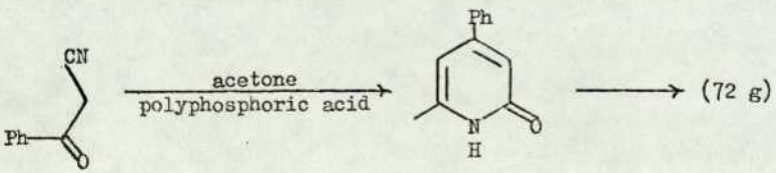
over that observed by Acheson[40] for 1-methyl-2-pyridone (21). We proposed that an important consideration would be the steric interaction between the 1-methyl and the 6-methyl groups for the planar-2-pyridone; any strain present would be relieved on passing to the adduct and thus the activation energy for cycloaddition would be lowered. Accordingly the range of 2-pyridones (72 a-h) was examined to test this hypothesis.

2-Pyridones (72 a,b,d) were synthesised by diazotisation and subsequent hydrolysis of the required 2-aminopicolines[54], followed by N-methylation[67]. The 6-methoxy-1-methyl-2-pyridone (72 e) was generated by thermally rearranging 2,6-dimethoxypyridine in methyl iodide[68]. The novel 2-pyridone (72 c) was prepared from γ-acetylvaleronitrile (75) by the method of Shusherina et al[69,70].



(75) (76) (77)

The novel 2-pyridone (72 f) was formed from 1-methyl-4-phenyl-pyridinium methosulphate oxidised by alkaline ferricyanide[52]. Finally, the novel 2-pyridone (72 g) was synthesised from benzoylacetonitrile (78) by the method of Hauser et al[71].



(78) (79)

The experimental procedure employed by Heep[39] was rigidly adhered to. All thermolyses were performed at 80° for 72 hours on a solution of the 2-pyridone (1.6 M) in acetonitrile or benzene using 1.1 equiv of the acetylenic ester. Reactions were followed by ^{1}H nmr spectroscopy, comparing the integral of the N-methyl signal in the starting material (typically resonating at δ 3.50) with that of the product in the reaction mixture (typically at δ 2.80). The results are presented in table 3.

Table 3. Data for intermolecular cycloadditions of various 1-substituted 2-pyridones

Pyridone	M.P./°C	% Reaction	Product	Isolated Yield/%
(72 a)	56	22	(73 a)	20
(72 b)	liquid	0	-	0
(72 c)	91	75	(73 c)	70
(72 d)	86	31[a]	(73 d)	31
(72 e)	53	0	-	0
(72 f)	140	0[b]	-	0[52]
(72 g)	106	73	(73 g)	70
(72 h)	-	0[a,b]	-	0

a. From the work of Heep[39], in this paper the yield of product is incorrectly calculated from the experimental data

b. Although no adduct was isolated under the reaction conditions. Prolonged thermolysis (170 h) in neat dimethyl butynedioate gave adducts (73 f) in 36% yield and (73 h) in 8% yield.

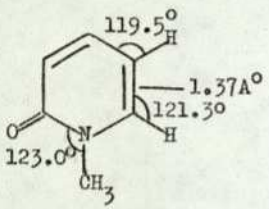
Under the standard conditions the product was generally the bicyclic adduct (73); more vigorous conditions, e.g. 140° for 14 h, gave products arising from the retro-Alder breakdown of the cycloadducts, i.e. the

phthalic esters (74 a-h). The trimerised iso-cyanate residues from the retro-Alder reaction were not pursued[39].

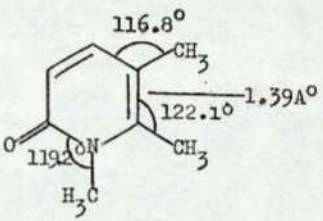
A comparison of the tabulated results reveals a number of striking features. Under the chosen conditions no adduct was isolated unless the 2-pyridone contained methyl substituents at C(1) and C(6). As the acetylenic ester has virtually no π -character in the HOMO (see Chapter 1) the dominant orbital interaction will be between the 2-pyridone HOMO and the LUMO of the ester, i.e. a classical reaction. If such an electronic compatibility were of critical importance to the reaction then a correlation would be found between reaction rate and electron-donating ability. Although methyl substituents are known to promote HOMO energies, the effect is less than that usually observed for a methoxy group[72] yet with a methoxy substituent at C(6) no product was observed. A recent study by Houk[73] has shown that peri-methoxy groups in aromatic molecules adopt a spatial orientation in which the methyl group is orthogonal to the plane containing the oxygen and the ring, thus minimising the steric repulsion between the adjacent substituents and maximising the steric resistance offered to an approaching dienophile. It seems likely, therefore, that the observed reactivity of (72 a) arises from the steric relief afforded when the co-planar methyl substituents adopt a staggered conformation as in the adduct (73 a). Such a consideration is not relevant for either (73 e) or (73 h) when methoxy groups are present. Further evidence for this comes from 2-pyridone (72 b) in which a methyl substituent is situated on C(3), the coefficient of the 2-pyridone HOMO is greater here than at C(6) and the steric hindrance to an approaching dienophile will be of a similar magnitude to (72 a), the only difference arises from the absence of the peri-methyl interaction as a result of which no adduct

is formed. Moreover, vigorous thermolysis of (72 b) at 140 ° for 72 hours produces only traces of the phthalate (74 b) by comparison with the near-quantitative yield of the identical phthalate (74 a) produced from thermolysis of (72 a) at 140° for 14 hours. This diene is therefore little better than Acheson's 1-methyl-2-pyridone (21).

Further corroboration of this hypothesis comes from the 2-pyridone (72 c) with three adjacent methyl groups. MNDO calculations predict a strained geometry to accommodate these bulky groups (see Figure 3).



(80)



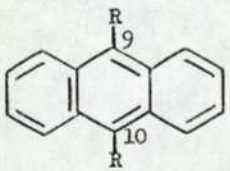
(81)

Figure 3

In addition the 2-pyridone ring is no longer predicted to be planar, with the carbon atoms C(5) and C(6) slightly askew to allow the methyl substituents to be respectively above and below the plane of the other ring atoms. With a HOMO energy of -8.76 ev (72 c) was expected to be a good diene not only because of the steric relief afforded on separation of the methyl groups at C(1) and C(6) but also because of the change in bond order between C(5) and C(6) on passing to the adduct, thus reducing the steric crowding between the methyl groups at these positions. The recorded yield (75%) of the adduct (73 c)

probably represents complete addition as the acetylenic ester tends to polymerise quite readily thus reducing the stoichiometric amount of reactant available. The yield is certainly better than that for the isomeric 2-pyridone (72 d) which shows very little improvement over the first member of the series (72 a). When a conjugating substituent is introduced (72 g) the diene also adds rapidly, as the position of substitution is insensitive to any change in geometry on reaction, the rate enhancement is likely to be from electronic promotion, the removal of the 6-methyl groups as in (72 f) leaves a much less active diene.

A similar effect has been noted for anthracenes (82) substituted with methyl or methoxy groups at the 9- and 10-positions which constitute the diene termini.



(82) R = H

(83) R = Me

(84) R = MeO

Anthracene (83) reacts with maleic anhydride 218 times faster than anthracene (82) whereas the methoxy compound (84) reacts more slowly than (82)[74,75]. This is considered to result mainly from the steric relief afforded on passage from the planar Sp^2 anthracene to the Sp^3 adduct.

From these investigations it would seem that suitable substitution can produce a reactive 2-pyridone, however, such an approach to the

problem of intramolecular addition is unlikely to meet with the same success as the very factors which enhance the 2-pyridone reactivity would hinder the sidechain from adopting a conformation in which the olefinic component was juxtaposed with the ring. Another potential failing of placing the sidechain at C(6) is the limitation imposed on the regioselectivity. For a diene LUMO - dienophile HOMO controlled reaction, the dominant orbital interaction is as shown in Figure 4.

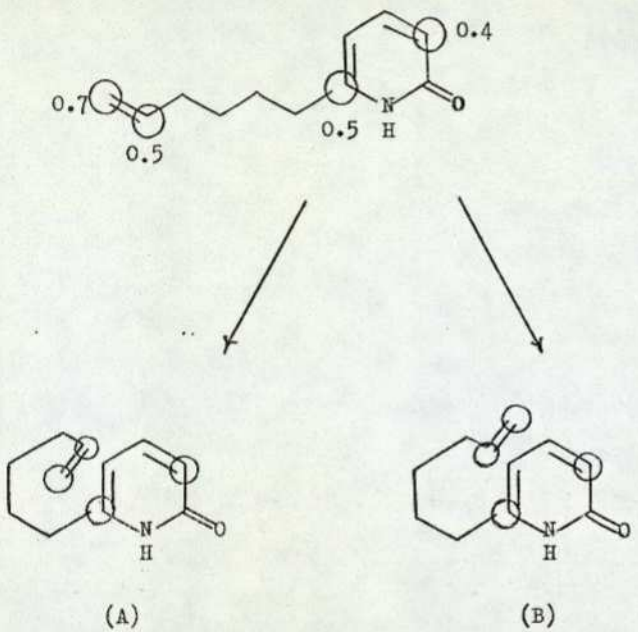


Figure 4

For maximum overlap the large coefficient at the unsubstituted terminus of the olefin should interact with the large coefficient at C(6) of the diene (A), but this requires the chain to twist upon itself which is sterically impossible. As a result the least favour-

able regiochemistry (B) from electronic considerations is the only feasible steric arrangement. Any rate enhancement produced from the smaller entropy loss on addition is likely to be outweighed by the unfavourable activation energy as the transition state will not be significantly stabilised by the weak bonding interactions present in (B).

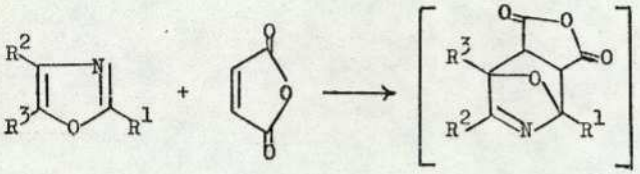
In conclusion, the calculation of molecular orbital parameters provided an adequate description of the electronic considerations relevant to an understanding of pericyclic reactions. Such an approach, however, fails totally to accommodate the observation that 1-methyl-6-methoxy-2-pyridone (72 e) although possessing a higher HOMO energy than 1,6-di-methyl-2-pyridone (72 a) is a worse diene. A satisfactory explanation invokes the steric interference caused by adjacent methyl groups. With this effect present the 2-pyridones so produced are quite reactive towards conventional electron-deficient dienophiles.

CHAPTER 3

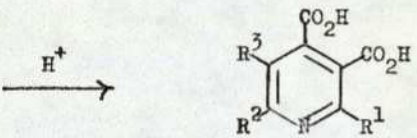
Cycloaddition Reactions of Oxazoles

Cycloaddition Reactions of Oxazoles

The azadiene system present in the oxazole nucleus (85) was first shown to undergo Diels-Alder reactions by Kondrat'eva[76,77]. The bicyclic adducts formed in these condensations with dienophiles underwent facile aromatisation, particularly in acid media.

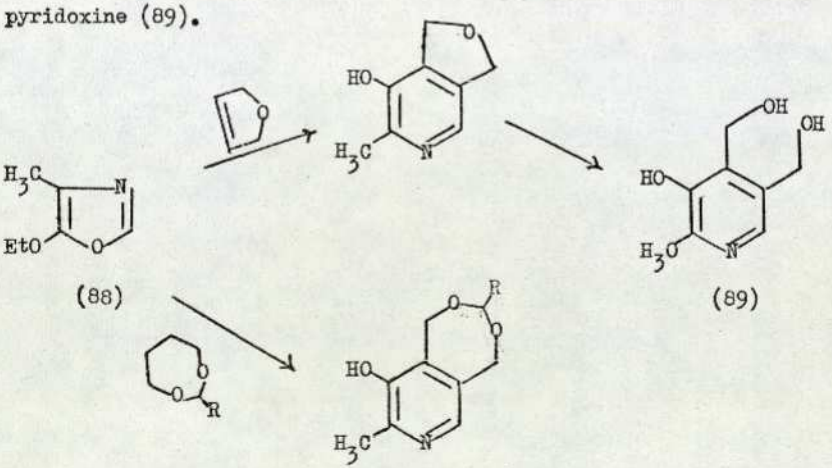


(85) (86)



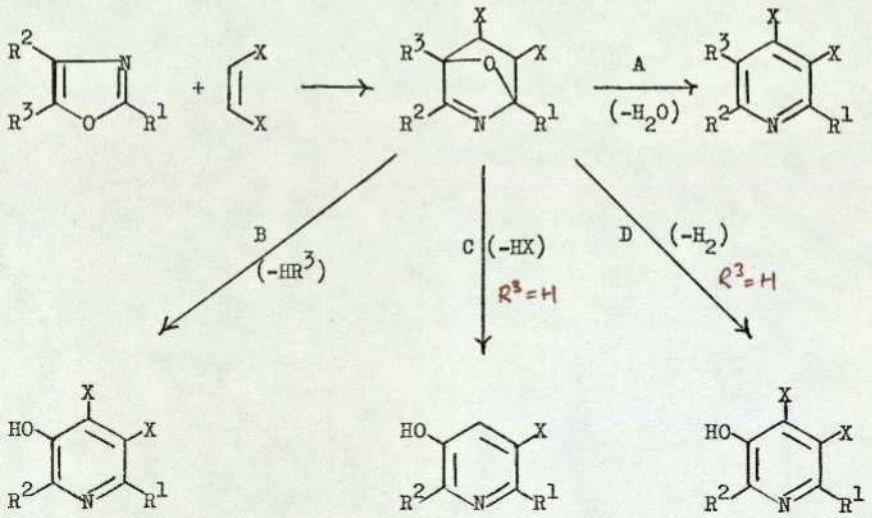
(87)

The realisation that cinchomeronic acid derivatives(87) were readily produced led many workers[78-80] to attempt a synthesis of pyridoxine (89).



(88) (89)

In general, a bicyclic adduct, formed from an oxazole and an olefinic dienophile, can decompose in four principal ways. (see Scheme 1). Generally the reaction proceeds by more than one pathway simultaneously yielding a mixture of products.



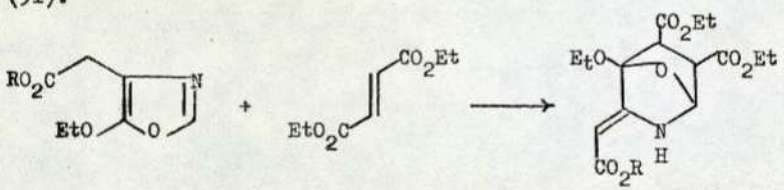
Scheme 1

Of the four mechanisms, pathway D involving removal of hydrogen from the 3- or 4-position of the adduct is energetically less favourable and therefore rare. However, the presence of a hydrogen acceptor, such as hydrogen peroxide or nitrobenzene has been shown to catalyse the reaction and give a better yield of the pyridine[81].

The aromatisation of adducts via pathway A resembles that of furans with dienophiles in acidic media and usually takes place if the substituents R^3 and X in the adduct cannot be eliminated as anions [82,83].

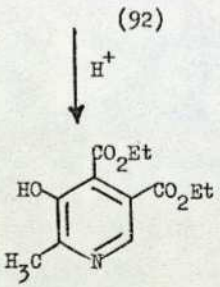
The introduction of a phenyl group in the 4-position of oxazole causes no deterioration in the potency of the diene, but 2- and 5-aryl oxazoles do not take part in cycloaddition[84a] because the loss of conjugation on passing to the adduct coupled with the steric hindrance offered to an approaching dienophile causes a high activation energy for the process. Substituents can be arranged in order of their reactivity: alkoxy > alkyl ~ 4-phenyl > COMe > CO_2Et $\gg$ 2- and 5-aryl, activity decreasing from left to right. If a substituent which is readily eliminated in the form of an anion is present in the 5-position of the adduct, aromatisation occurs via pathway B. Typically this is observed for 5-alkoxy and 5-cyano oxazoles[84 b].

Miki and Matsuo[85] studied the interaction with dienophiles of 5-ethoxy-4-hydroxycarbonylmethyloxazole (90) and its ethyl ester (91).



(90) R = H

(91) R = Et



(92)

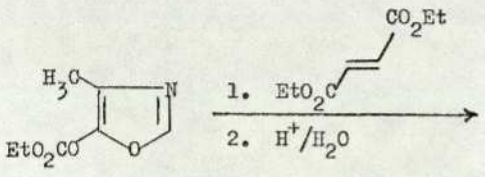
(93)

The condensation of the ester (91) with diethyl fumarate at 10°C leads to the isolable adduct (92) with an exocyclic double

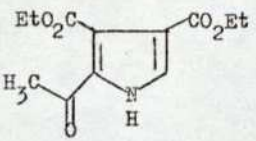
bond stabilised by conjugation with the ester. When the acid (90) is treated in the same way only the aromatised product (93) is observed.

Aromatisation via pathways C and D is characteristic of 5-unsubstituted oxazoles on reaction with dienophiles whose substituents tend to be eliminated as anions[86].

An unusual rearrangement[87] was observed when 5-ethoxycarbonate-4-methyloxazole (94) was condensed with diethyl fumarate.



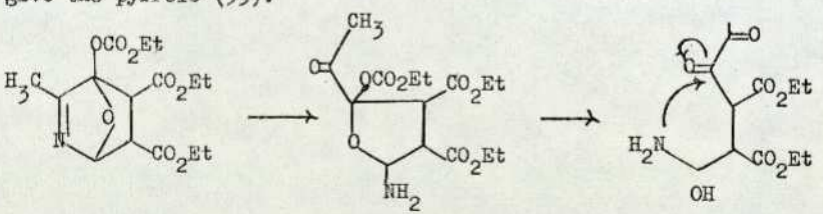
(94) (93)



+

(95)

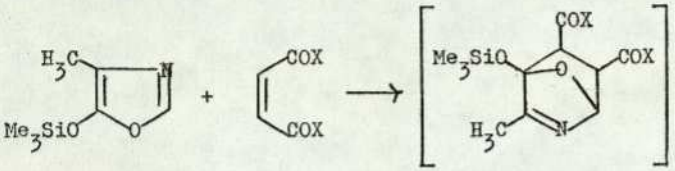
The major product was the pyrrole (95) assumed to have formed from the bicycloadduct (96) by hydrolysis of the imino-bond to give the tetrahydrofuran (97) followed by ring cleavage under the acidic conditions to give the amine (98) which recyclises and aromatises to give the pyrrole (95).



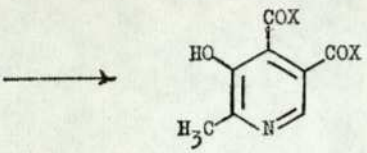
(96) (97) (98)

⟶ (95)

A recent report[88] on the preparation and Diels-Alder reactions of 4-methyl-5-trimethylsiloxyoxazole (99) claimed yields in excess of 90% for condensations with dimethyl maleate and N-phenyl maleimide.

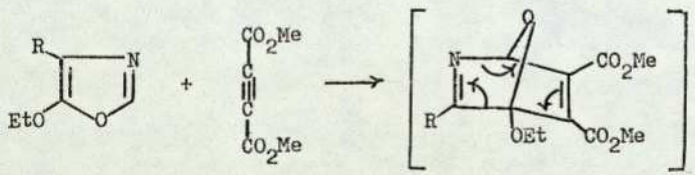


(99) (100)

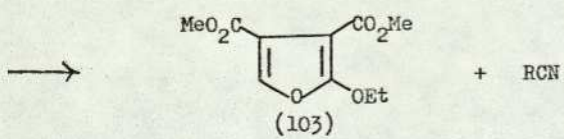


(101)

The fate of the bicyclic adducts derived from condensation with a triple bond is different from those considered above. Ready elimination of a nitrile moiety by retro-Alder reaction of the adduct (102) is usually observed, yielding the substituted furan, e.g. (103). The 5-alkoxyoxazoles usually undergo this process with acetylenic esters at room temperature, less reactive substituted oxazoles require refluxing in benzene or toluene to give the expected furan-3,4-dicarboxylic esters in high yields (90%)[89-91].

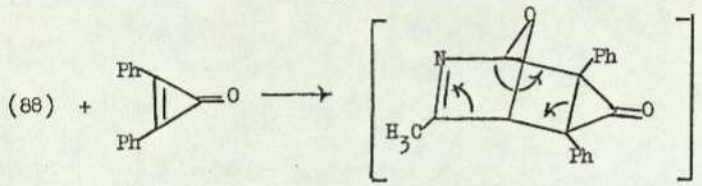


(88) (102)

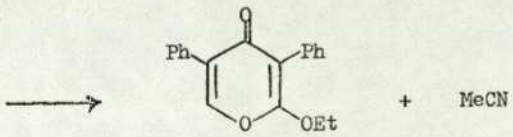


(103)

A reaction has also been reported between diphenylcyclopropenone (104) and (88) to yield a δ-pyrone (106) via a retro-homo-Diels-Alder reaction[91]. No adduct (105) was isolated.

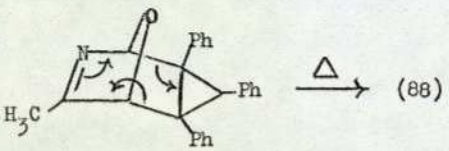


(104) (105)



(106)

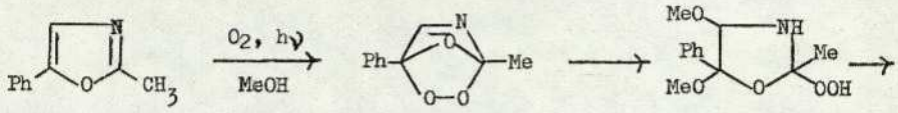
When the same oxazole (88) was treated with triphenylcyclopropene[91], the tricycloadduct (107) was isolated which on pyrolysis gave only the original oxazole (88).



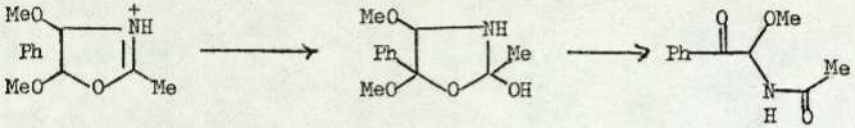
(107)

Singlet molecular oxygen adds readily across the oxazole nucleus. A wide variety of reactions takes place after the initial adduct has formed, depending on the nature of the substituents[92]. 2-Methyl-5-phenyloxazole (108) and singlet oxygen give benzoic acid and the bicyclic ozonide (109) which, after attack by methanol, gives the methoxyhydroperoxide (110). Elimination of the hydroperoxide anion leaves the cation (111) which is attacked by water to yield the

oxazolidine (112). Conversion to the α-acetamide-α-methoxyacetophenone (113) is effected by the cleavage of the oxazolidine ring with elimination of methanol.



(108) (109) (110)

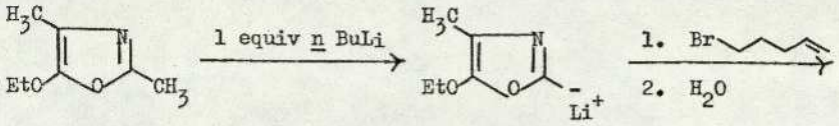


(111) (112) (113)

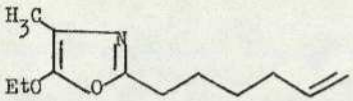
The general chemistry of oxazoles has been thoroughly reviewed by Dewar and Lakhan[94].

The reactivity towards dihydrofuran[80] and other electron rich dienophiles suggested that an intramolecular Diels-Alder reaction with an isolated olefinic component might prove successful. The products generated would be cycloalkylpyridines in which much interest has recently been shown[95-97]. Methyl substituents in the 2-position of oxazole are reactive towards electrophiles in the presence of base, but those in the 4- and 5-positions do not contain acidic protons[98].

Accordingly, 2,4-dimethyl-5-ethoxyoxazole (114), prepared by a variation of the method of Florentiev et al[99], was treated with n-butyl lithium at -78°C in dry THF to form a pale yellow monoanion (115). Alkylation with pentenyl bromide gave a 74% yield of 2-(hex-5-en-1-yl)-4-methyl-5-ethoxyoxazole (116).

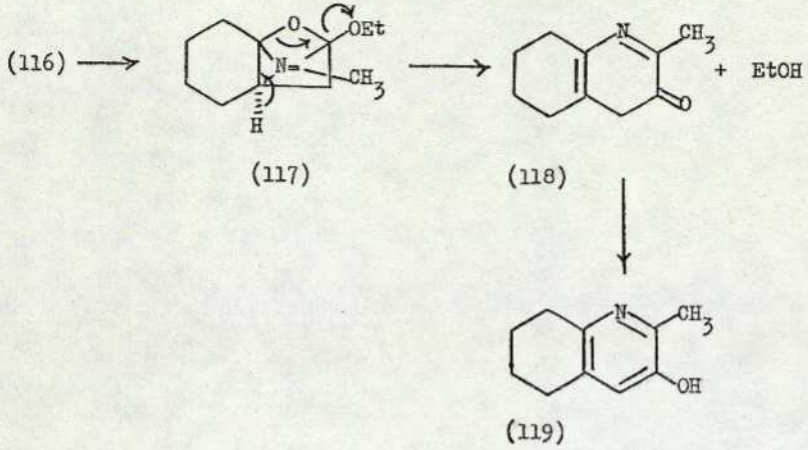


(114) (115)



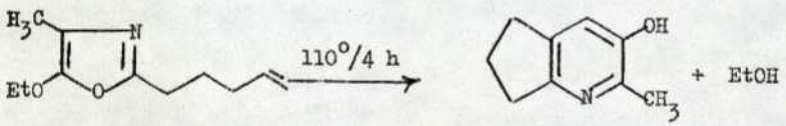
(116)

The ^{1}H nmr spectrum contained, in addition to the expected vinyl absorption and alkyl envelope, a two-proton triplet at δ 2.63 for the benzylic protons, the original 2-methyl signal had disappeared. The I.r. spectrum contained a strong absorption at 1565 cm^{-1} assigned as the N=C-O ring stretching frequency. Thermolysis of (116) at 145° for six hours in toluene produced a microcrystalline solid which gave a positive ferric chloride test for phenols. Analysis by ^{1}H nmr showed that the vinylic protons had been consumed, the product contained an exchangeable proton resonating as a singlet at δ 9.30 another low field singlet resonating at δ 6.80 was also visible, four benzylic protons and a three proton singlet at δ 2.32 as well as four higher-field protons completed the spectrum. The mass spectrum contained a molecular ion at $^m/_e$ 163. These data are consistent with the expected product from intramolecular addition of (116) followed by decomposition (via pathway B, Scheme 1) to eliminate ethanol and aromatise to give the novel 2,3-cyclohexyl-5-hydroxy-6-methylpyridine (119) in 72% yield.



(117) (118) (119)

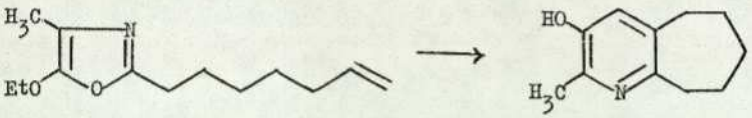
Alkylation of the monoanion (115) with commercially available 4-bromobutene[100] gave 2-(pent-4-en-1-yl)-4-methyl-5-ethoxyoxazole (120) in 78% yield. Thermolysis of (120) at 110° very rapidly produced a yellow microcrystalline solid which was shown to be 2,3-cyclopentyl-5-hydroxy-6-methylpyridine (121).



(120) (121)

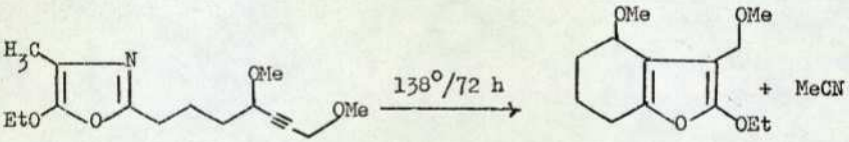
The greater reactivity of the pentenyl sidechain over the hexenyl variant (116) is probably due to the greater ease with which the polymethylene bridge can adopt the desired transition state geometry thus raising the entropy of activation. To test whether or not this trend would obtain for longer chains, the monoanion (115) was alkylated with 6-bromohex-1-ene, prepared by a modification of the method of Snyder et al[101], to give 2-(hept

-6-en-1-yl)-4-methyl-5-ethoxyoxazole (122). After thermolysis for 16 hours at 145° no new products were detected. Attempts to effect cyclisation at higher temperatures were unsuccessful, presumably the sidechain is too long to offer the usual advantage of a high entropy of activation although catalytic assistance might prove of value.



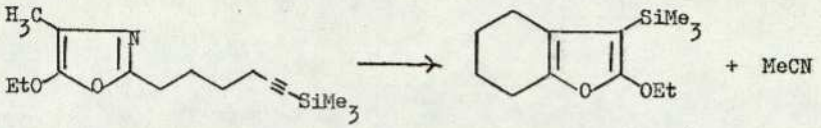
(122) (123)

After this work had been initiated an intramolecular cycloaddition of an acetylene to an oxazole was reported by Jacobi (see Review).



(124) (125)

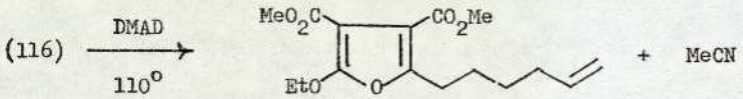
The mild conditions under which this reaction occurred prompted an alkylation of the monoanion (115) with the trimethylsilylacetylene (70) to give 2-(hex-6-trimethylsilyl-5-yn-1-yl)-4-methyl-5-ethoxy-oxazole (126).



(126) (127)

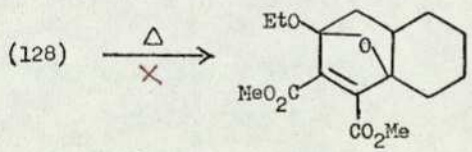
Thermolysis of this compound at 145° for 48 hours produced no reaction, at higher temperatures the compound decomposed to give a polymer. This lack of reactivity suggests that the trimethyl silyl group sterically hinders the attempted addition.

As 5-alkoxyoxazoles condense with acetylenic esters at room temperature[89], whilst the intramolecular olefin addition requires considerable thermal assistance. the precursor (116) might reasonably be expected to undergo conversion to the furan ester (128).



(128)

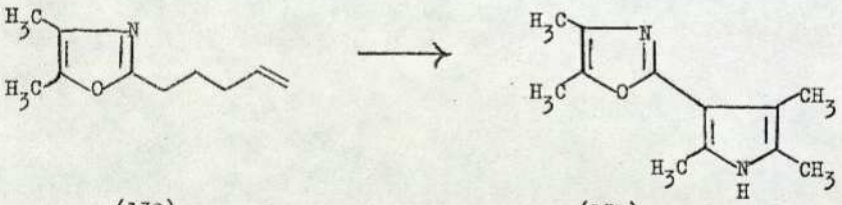
At room temperature the reaction was very slow, but at elevated temperatures the furan (128) was produced in good yield (64%). This sluggishness arising from steric hindrance has previously been noted by Kondrat'eva[102] who found that 2-n-amyl-5-ethoxyoxazole reacted much less rapidly than 2-methyl-5-ethoxyoxazole.



(129)

Thermolysis at 145° for 48 hours produced no novel products. Although the two ester groups should act as electron-withdrawing groups to enhance the inverse demand of the addends, the ethoxy-group aided by the known electron-rich nature of the furan ring exerts the dominant electronic effect and hence no reaction is observed. The methodology, however, must have a certain potential if a suitable substituent can be found to occupy the 5-position on the oxazole.

To examine the generality of these intramolecular cycloadditions, other oxazoles were synthesised. Thus, 2,4,5-trimethyl oxazole, synthesised by the method of Wiley _etal_[103], was treated with one equivalent of _n_-butyl lithium to generate a red monoanion, alkylation with 4-bromobutene gave, by ^{1}H nmr analysis, a good yield of 2-(pent-5-en-1-yl)-4,5-dimethyloxazole (130), purification followed by concentration with heating on a rotary evaporator, gave a white crystalline solid m.p. 190-192° which crystallised from the pale yellow oil.

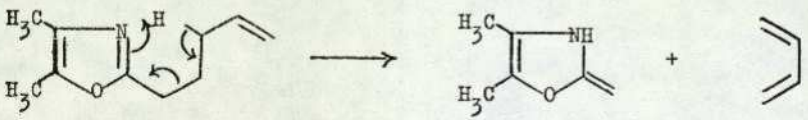


(130) (131)

^{1}H nmr spectroscopy showed the presence of an exchangeable proton at δ 7.20, also five methyl groups resonating as singlets between δ 2.40 and δ 2.06. The i.r. spectrum showed a strong absorption at 3460 cm^{-1} characteristic of a pyrrole and a strong band at 1580 cm^{-1} characteristic of the oxazole ring. The u.v. spectrum

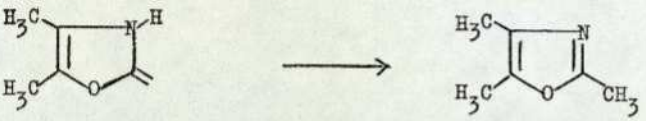
had maxima at 211 (E 9620) and 267 nm (E 12,200) the band at longer wavelength being characteristic of a 2- or 5-aryl oxazole. Microanalysis was consistent with a molecular formula of $C_{12}H_{16}N_2O$. The compound was identified as 2-(3-(2,4,5-trimethyl)pyrrolyl)-4,5-dimethyloxazole (131).

The presence of two nitrogen atoms in the product suggests that at some stage a dimer has been formed, to account for this an initial [1,5] proton transfer of an allylic hydrogen in the sidechain was postulated.



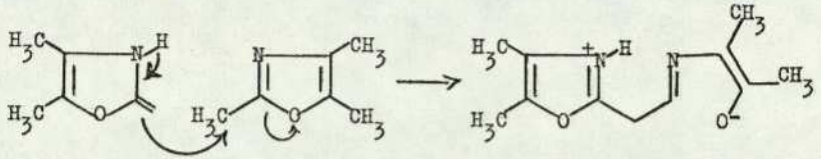
(132) (133)

This could generate the highly reactive enol ether enamine (133) and butadiene. At low concentrations the postulated intermediate (133) could rearrange to the original oxazole (134).

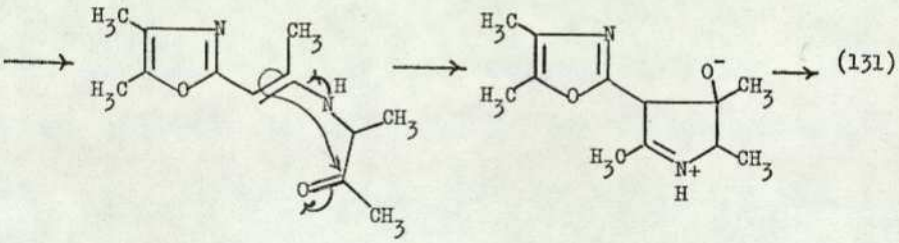


(133) (134)

If, before rearrangement, (133) were able to react with any of the oxazole (134) so produced, then a dimer would be generated. One possibility is nucleophilic addition:



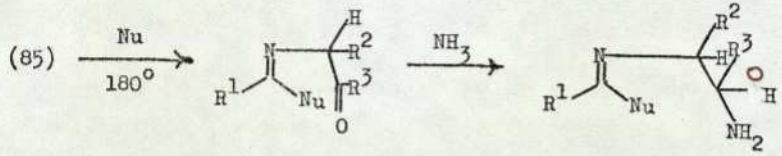
(135)



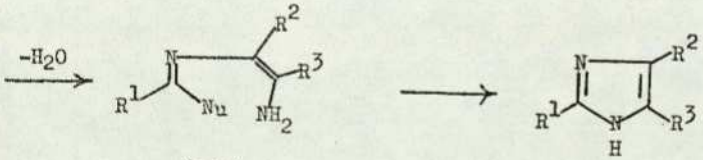
(136) (137)

After ring cleavage the conjugated secondary amine (136) is produced on isomerisation of the imine (135), then intramolecular enamine attack yields the dihydropyrrole (137) which aromatises to the pyrrolyl oxazole (131).

Such a mechanism is consistent with a report[104] on the reaction of oxazoles with formamide at 180°.

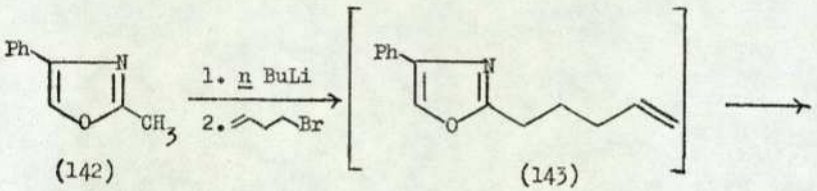


(138) (139)

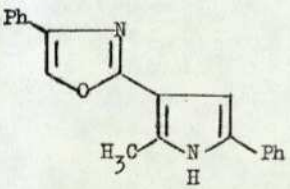


(140) (141)

Cleavage of the oxazole by water or ammonia present in the reaction mixture gives an intermediate (138) which reacts further with ammonia to give after dehydration and cyclisation, the imidazole (141). The ammonia originates from the equilibrium between formamide and ammonium formate in the presence of water. Further investigation of this reaction showed that bulky alkyl groups in the 2- and 5- positions inhibit the reaction, but a 4-phenyl substituent greatly accelerates the process.[105] When 2-methyl-4-phenyloxazole (142), prepared by the method of Lewy[106], was alkylated with 4-bromobutene in the presence of base, no intermediate was observed, only a crystalline solid m.p. 128-130° was isolated.



(142) (143)

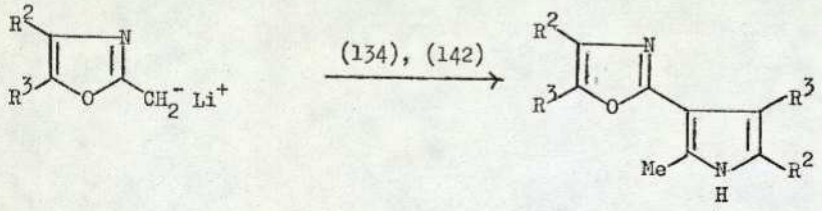


(144)

Of particular interest in the ^{1}H nmr spectrum was a one-proton doublet (J = 2Hz) at δ 6.79, on addition of deuterium oxide the signal collapsed to a singlet and a broad one-proton signal that had resonated at δ 8.20 disappeared. The proton on the oxazole still resonated at δ 7.71 and the methyl group nowresonated as a singlet at δ 2.65 whereas the 2-methyl substituent in (142) resonated

at δ 2.48. The mass spectrum gave a molecular ion at m/e 300 and the i.r. spectrum showed an absorption at 3400 cm^{-1}. This information is consistent with 2(-3-(2-methyl-5-phenyl)pyrrolyl-4-phenyloxazole (144) which would be formed if the rearrangement suggested earlier had also occurred in this instance.

The mild conditions under which the postulated intermediate reacts, suggests that it is a potent nucleophile. The same result should be achieved by adding the parent oxazole (134) to a solution of the monoanion (145) in THF and heating to reflux.



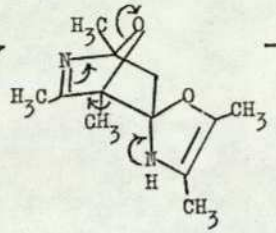
(145) a. R^2 = Ph, R^3 = H
b. R^2 = Me, R^3 = Me

(131) or (144)

Examination by analytical t.l.c. showed that for (145 a) no dimerisation product (131) was produced. Only the starting oxazole (134) was recovered. When (145 b) was treated in the same manner, analytical t.l.c. revealed a product with the same Rf as the previously isolated product (144). The ^1H nmr spectrum, however, did not contain any signals associated with the dimerised product (144), again mainly starting material was recovered, although some polymeric material was also produced.

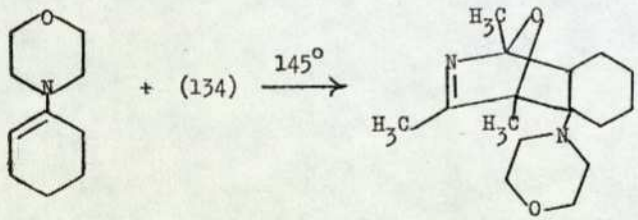
An alternative mechanism for the rearrangement would involve an initial regiospecific cycloaddition of the exocyclic double bond of the postulated intermediate (133) across the diene termini of the

rearranged oxazole (134) to give a tricyclic adduct (146). Ring opening leads to the imine (135), previously postulated for the ionic mechanism, which on rearrangement and ring closure would give

(133) + (134) ⟶  ⟶ (135) ⟶ (131)

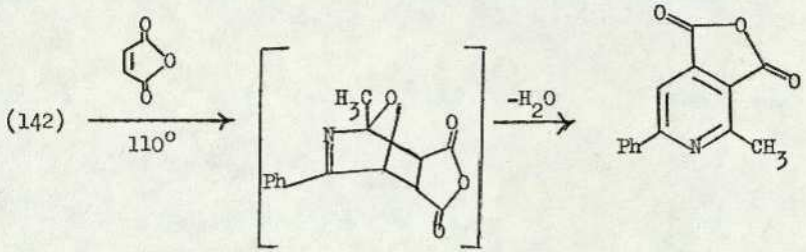
(146)

the observed product (131). If this were the case, then other 2 π-electron donors should react with oxazoles. An attempt to react 1-morpholino cyclohexene (147)[107] with the parent oxazole (134) was unsuccessful, only starting materials being recovered.



(147) (148)

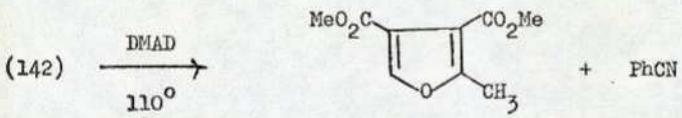
With classical dienophiles (2π electron acceptors), the 4-phenyl oxazole (142) was less reactive than the 5-alkoxyoxazole. Maleic anhydride reacted in dry toluene at reflux to give a good yield of 2-methyl-6-phenyl-3,4-pyridinedicarboxylic anhydride (150).



(149) (150)

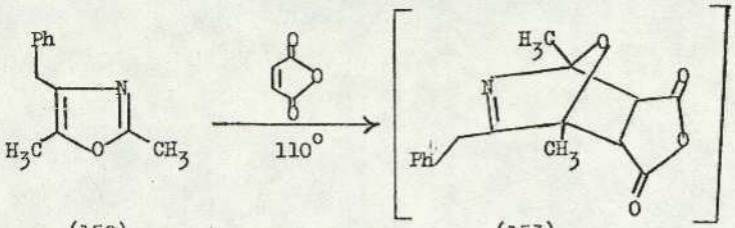
The i.r. spectrum contained anhydride absorptions at 1850,1780 cm^{-1}. The ^1H nmr spectrum contained a one-proton singlet at δ 7.63, five other low field protons and a three proton singlet at δ 2.50. The mass spectrum gave a molecular ion at m/e 239 which was also the most intense peak in the spectrum.

Dimethyl butynedioate reacted under the same conditions to give dimethyl-2-methylfuran-3,4-dicarboxylate (151) and phenyl cyanide.

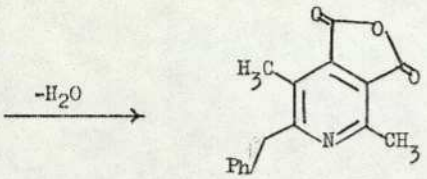


(151)

The spectral and analytical characteristics of this molecule (150) were identical with those reported previously[91]. In neither case was the adduct isolated. It was felt that an isomerised adduct analagous to (92) might possibly be formed from a 4-benzyl oxazole condensation with an olefinic dienophile. Accordingly 2,5-dimethyl-4-benzyl oxazole (152), prepared by a variation of the method of Bredereck et al[104], and maleic anhydride were thermolysed in dry toluene at reflux to give 2,5-dimethyl-6-benzyl-3,4-pyridinedicarboxylic anhydride (154).



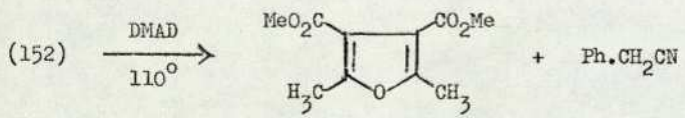
(152) (153)



(154)

The 'H nmr spectrum contained five protons at low field. The benzylic resonance of the starting oxazole at δ 3.70 had disappeared, a two proton singlet at δ 4.19 had appeared. Two singlets each integrating for three protons were recorded at δ 2.55 and δ 2.16 respectively. The i.r. spectrum contained anhydride absorption at 1790, 1730 cm^{-1}. The mass spectrum contained a molecular ion at $^{m}/_{e}$ 267 with a base peak at $(M^{+}-1)$ as a result of the facile loss of hydrogen from the 2-benzyl substituent. No trace of the adduct was detected.

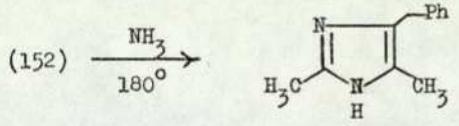
With dimethyl butynedioate at 110° in refluxing dry toluene at reflux the furan (155) was produced in good yield as well as phenyl acetonitrile.



(155)

The 'H nmr spectrum gave a six proton singlet at δ 3.83 and a six proton singlet at δ 2.45, other characteristics were identical with those reported previously[108].

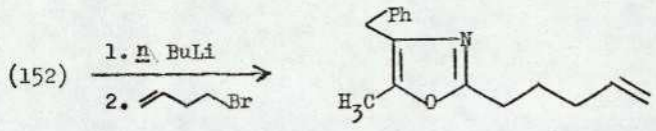
Bredereck reports[104] that this highly substituted oxazole (152) gives poor yields of the substituted imidazole (156).



(156)

If this is the case, then the rearrangement observed earlier should be inhibited for (152).

Alkylation of (152) with 4-bromobutene in base gave 2-(pent-4-en-1-yl)-4-benzyl-5-methyloxazole (157).

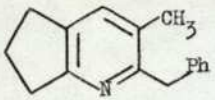


(157)

The 'H nmr spectrum gave a two proton triplet at δ 2.60 as well as vinylic protons characteristic of a monoalkyl substituted olefin. The mass spectrum gave a molecular ion at m/e 241 which was also the most intense peak in the spectrum.

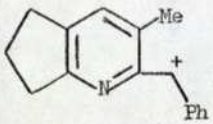
Heating (157) in toluene at 145° for 14 hours produced no product. When glacial acetic acid was used as the solvent, however, reaction occurred very rapidly. The mixture turned black and analysis by t.l.c. on silica showed the presence of a novel product with a much stronger chromophore than the starting oxazole. Purification gave

a novel product. ^{1}H nmr analysis revealed six low field protons resonating between δ 7.30 and δ 7.11, a two proton singlet resonating at δ 4.16, two broadened triplets each integrating for two protons at δ 2.97 and δ 2.89, as well as a three proton singlet at δ 2.18 and a two proton multiplet resonating between δ 2.20-2.08. The mass spectrum gave a molecular ion at $^m/_e$ 223 with the most intense peak at (M^+-1) being the facile loss of hydrogen. The product was identified as 2,3-cyclopentyl-5-methyl-6-benzylpyridine (158).

(157) $\xrightarrow[145^o]{HOAc}$ 

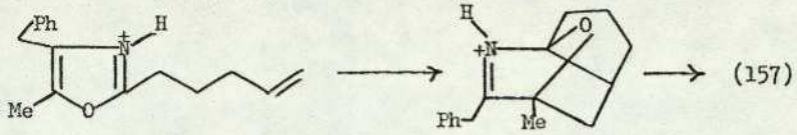
(158)

The base peak in the mass spectrum is probably the stable cation (159), the same type of stabilisation observed for the base peak in the mass spectrum of (154).

(158) $\xrightarrow{-H\cdot}$ 

(159)

The dramatic rate enhancement under acidic conditions is similar to that observed by Naito[109a]. Although oxazole itself has a pKa of 0.8, alkyl substituents - particularly in the 2-position - render the ring nitrogen much more nucleophilic, thus trimethyl-oxazole has a pKa value of 3.6[109b] and therefore in acetic acid (pKa = 4.8) there will be an appreciable concentration of the protonated species (160).



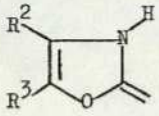
(160) (161)

The protonation of the oxazole nitrogen will greatly lower the LUMO energy (typically to the level of the HOMO of the unprotonated species at -9.7 ev)[31] which will afford a greater stabilisation arising from the orbital interaction with the electron-rich dienophile HOMO (-10.0 ev). The resultant lowering of the transition state energy and hence the activation energy for cycloaddition stimulates a greater rate of reaction. Decomposition of the adduct would also be rapid after protonation and cleavage of the ether bridge.

Of the four 2-pentenyl oxazoles constructed, two ((120) and (157)) gave products arising from intramolecular cycloaddition and two ((130) and (143)) gave products arising from elimination of the sidechain, yields ranging from 32-54%. It seems reasonable to suppose that two competing mechanisms of similar energy requirements exist.

The most reactive diene throughout these investigations was the 5-alkoxyoxazole and it is therefore not surprising that the pentenyl-substituted oxazole (120)underwent cycloaddition most readily.

For products arising from dimerisation, two important factors must be considered: firstly the ease with which the sidechain can be eliminated, this will depend on the nucleophilicity of the oxazole nitrogen and therefore any substituents which enhance this property should facilitate the formation of the postulated intermediate (162).



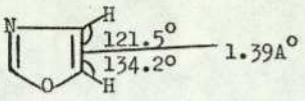
(162)

Calculations (MNDO) on this species predict a symmetric HOMO energy of -8.46 ev and an anti-symmetric LUMO energy of +0.59 ev. (The symmetry is considered solely for the exocyclic double bond.) In addition the orbital coefficients are large so that this species should be an excellent electron-rich dienophile. The presence of the ring should impose considerable regioselectivity. The second important factor arises when considering the possibility of (162) acting as an enamine and attacking the oxazole ring. Bulky alkyl groups in the 2- and 5- position should prohibit such an attack and therefore such oxazoles would be resistant to ring cleavage.

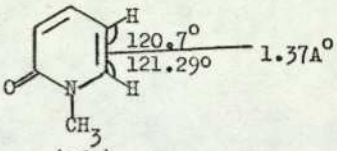
There seems to be no reasonable explanation to account for the lack of reactivity of the 4-benzyl derivative (157) when compared to the trimethyl oxazole derivative (130). Further work is necessary to gain a fuller understanding of this unusual rearrangement.

The MNDO predictions for oxazoles based on calculations of HOMO and LUMO energies were inadequate. Dewar[93] quotes a first ionisation potential of 8.03 ev from MNDO/3 calculations and such a value is certainly in keeping with the observed reactivity of oxazoles towards electron-deficient dienophiles, however this value must be suspect as the experimentally determined value for furan[25] is 8.9 ev and the azadiene would have a greater value than this.

The reactivity of 5-alkoxyoxazoles suggests that the steric effects which obtained for 2-pyridones are unimportant for oxazoles. This is not surprising as the geometry of the oxazole ring permits the substituents to be further apart.



(163)



(164)

Other factors being constant, one would expect steric crowding to become more important as the ring size increases. In general it would seem that FMO theory does not explain the reactivity of oxazoles which perhaps indicates that a concerted mechanism gives a poor description of the transition state involved for its reaction as a conjugated diene.

EXPERIMENTAL

SECTION

Experimental Section

All temperatures are quoted in degrees centigrade. Melting points were determined on a Köfler hot-stage apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin-Elmer 157 G Spectrometer; samples were prepared as nujol mulls or solutions in chloroform for solids and as thin films for oils unless otherwise stated. Frequencies of maximum absorption are quoted (ν max) in wave numbers (cm^{-1}).

Ultraviolet spectra were recorded in ethanolic solution on a Pye-Unicam SP 800 using quartz cells - wavelength of maximum absorbance (λ max) are given in nanometers (nm) together with the molar extinction coefficients (E) at these points.

Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Jeol MH-100 instrument or a Bruker WH-360 instrument. Except where otherwise stated, a deuteriochloroform solution of the material was analysed using tetramethylsilane (TMS) as an internal reference. Values of chemical shift are given in values of δ, the magnitude of the frequency change in parts per million from the TMS signal. Abbreviations : S = singlet, d = doublet, t = triplet, q = quartet, d.d. = doublet of doublets, m = complex multiplet, b = broad, exch. = disappears on addition of D_2O, are employed. Coupling constants are quoted in units of Hz.

Mass spectral measurements were performed on an AEI MS30 or AEI MS50 instrument. 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 (DMF) were purified by distillation from calcium hydride, then were stored over 4Å molecular sieves[110]. 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 de-oxygenated nitrogen. Analytical chromatography separations were carried out on 1.0 or 0.2 mm thin layers of Merck Kieselgel GF_{254} silica, unless otherwise stated, and were monitored by viewing under u.v. light or by development in iodine vapour. Large scale preparations were carried out using columns packed with MFC 60-120 mesh silica or neutral aluminium oxide (Brockmann Grade 1) using a stationary phase to compound weight ratio of approximately 50:1.

The thermolysis of compounds under pressure was achieved by reaction within a sealed tube. A solution of the material was placed in the bottom of a thick-walled Pyrex tube. The solution was de-gassed by freezing in liquid nitrogen and evacuating the tube. Warming of the solution to room temperature caused evolution of the dissolved gas. The solution was again frozen in liquid nitrogen, the tube evacuated and the upper part sealed in a flame. Tubes so prepared were heated in refluxing stills of appropriate solvents. For the stated temperatures the following solvents were used: benzene (80°), toluene (111°), xylene (145°), ethylene glycol (198°), diethylene glycol (245°).

General Method for the preparation and methylation of 2-pyridone monoanions

One equivalent of sodium ethoxide was prepared by making up a solution of the appropriate amount of sodium in freshly distilled ethanol. This was added with stirring to an anhydrous solution of the 2-pyridone in dry ethanol, after 2 hours the solvent was evaporated to yield a powder which was redissolved in DMF. After 0.5 hours, methyl iodide (1.05 - 1.10 equivalents) was added neat to the solution. Stirred overnight, the mixture was poured onto cold water and extracted with dichloromethane (3 x 30 mls). The combined organic fractions were washed twice with water, then dried ($MgSO_4$), filtered and evaporated in vacuo to give a viscous oil. Purification was effected on silica gel using ethyl acetate/60-80° petroleum ether as eluent. Specific details are listed below.

1,3-Dimethyl-2-pyridone (72b)

3-Methyl-2-pyridone[34] (2.61 g, 23.9 Mmole) and iodomethane gave after purification and distillation, the title compound (72b) as a colourless oil (2.02 g, 69%) b pt 93° (2 mm), lit[54] 78° (0.5 mm). All spectral data are in agreement with the literature values[34].

1,6-Dimethyl-2-pyridone (72a)

6-Methyl-2-pyridone[54] (1.95 g, 18.0 Mmole) and iodomethane gave, after distillation, 1,6-dimethyl-2-pyridone (72a) as a white deliquescent solid (1.10 g, 49%), m.p. 55-57° (lit[110], 55-58°). All spectral data are in agreement with the literature values[110].

1,6-Dimethyl-4-phenyl-2-pyridone (72g)

6-Methyl-4-phenyl-2-pyridone[71] (79), (1.01 g, 5.4 Mmole) and iodomethane gave, after recrystallisation from diethyl ether, the title compound (72g) (560 mg, 52%) as a pale yellow solid m.p. 106-107°,

ν max ($CHCl_3$) 3000, 1660, 1570, 1360 cm^{-1}, δ ($CDCl_3$) 7.60-7.30 (5H, m), 6.60 (1H, bS), 6.20 (1H, bS), 3.48 (3H, S), 2.32 (3H, S).

(Found : C, 78.73; H, 6.42; N, 6.81.

$C_{13}H_{13}NO$ requires : C, 78.36; H, 6.58; N, 7.03%).

1-Methyl-6-(hex-6-trimethylsilyl-5-yn-1-yl)-2-pyridone (71b)

6-(Hex-6-trimethylsilyl-5-yn-1-yl)-2-pyridone (71a) (1.51 g, 6.07 mmole) and iodomethane gave the title compound (71b) as a yellow oil. ν max (neat) 2950, 2180, 1660, 1580, 1500, 1370, 1240, 1045, 1045, 845 cm^{-1}, δ ($CDCl_3$) 7.20-6.88 (1H, d.d. J = 8, 7Hz), 6.16 (1H, d, J = 8Hz), 5.90 (1H, d, J = 7Hz), 3.44 (3H, S), 2.68-2.48 (2H, t), 2.44-2.20 (2H, t), 1.87-1.24 (4H, m).

(Found : M^+ 261.1432. $C_{15}H_{23}NOSi$ requires : M 261.1443).

1,5,6-Trimethyl-2-pyridone (72c)

5,6-Dimethyl-2-pyridone[111] (77), (277 mg, 2.25 mmole) and iodomethane gave after recrystallisation from ethyl acetate, the title compound (72c) (186 mg, 60.2%) as a pale yellow air sensitive solid m.p. 84-85°, ν max ($CHCl_3$) 3020, 1675, 1600, 1540, 1170, 1115, 970, 910 cm^{-1}, δ ($CDCl_3$) 7.00 (1H, d, J = 8Hz), 6.32 (1H, d, J = 8Hz), 3.50 (3H, S), 2.22 (3H, S), 2.02 (3H, S).

(Found : M^+ 137.0846. $C_8H_{11}NO$ requires : M 137.0841).

6-Methoxy-1-methyl-2-pyridone (72e)

2,6-Dimethoxypyridine (3.00 g, 21.6 mmole) taken with iodomethane (6 g) and sealed in a pyrex tube. After thermolysis at 80° for 24 hours the resulting green solution was concentrated and the residue triturated with 40-60° petroleum ether to give the title compound (72e) (2-1 g, 70%) as a white crystalline solid m.p. 52-56° (lit[68] 52-54°). All spectral data are in agreement with the literature values[68].

Thermolyses of N-alkyl-2-pyridones

All thermolyses were performed under reduced pressure in sealed pyrex tubes containing approximately 1.6 molar degassed solutions of the 2-pyridones in acetonitrile with 1.1 equivalents of dimethyl butynedioate. The sealed tubes were placed in refluxing stills of benzene or xylene as appropriate for 72 hours after which time the glass phials were removed from the boiling still and cooled rapidly. The heads of the tubes were broken after the contents had been cooled to -196° in liquid nitrogen. The solvent was removed at the pump from the freshly thermolysed solutions and the crude mixtures were examined by ^{1}H nmr and t.l.c. techniques. Purification was effected on silica gel using ethyl acetate (60-80° petroleum ether as eluent) specific details are appended below.

1,2-Dimethyl-2-aza-3-oxo-5-phenyl-bicyclo[2.2.2]octa-5,7-dien-7,8-dimethyl dicarboxylate (73g)

1,6-Dimethyl-4-phenyl-2-pyridone (72g) (62.9 mg, 0.32 mmole) was dissolved in dry acetonitrile (0.2 ml) with dimethyl butynedioate (76.1 mg, 0.53 mole). The solution was degassed, sealed under reduced pressure and thermolysed at 80° for 72 hours. The reaction mixture was concentrated, analysed and the major product separated from the unreacted 2-pyridone by preparative t.l.c. to yield the title compound (73g) (75.5 mg, 70.1%) as a pale yellow crystalline solid m.p. (diethyl ether) 123-124°, ν max ($CHCl_3$) 2930, 2845, 1735, 1720, 1685, 1650, 1430, 1315, 1130, 1100 and 945 cm^{-1}, δ ($CDCl_3$) 7.60-7.24 (5H, m), 6.58 (1H, d, J = 2Hz), 5.38 (1H, d, J = 2Hz), 3.90 (3H, S), 3.84 (3H, S), 2.88 (3H, S), 1.84 (3H, S). (Found : M^+ 341.1364; $C_{19}H_{19}NO_5$ requires : M 341.1354).

1,2-Dimethyl-2-aza-3-oxo-bicyclo[2.2.2]octa-5,7-dien-7,8-dimethyl dicarboxylate (73a)

1,6-Dimethyl-2-pyridone (72a) (48 mg, 0.39 mmole) was dissolved in dry acetonitrile (0.2 ml) with dimethyl butynedioate (84 mg, 0.58 mmole). The solution was degassed, sealed under reduced pressure and thermolysed at 80° for 72 hours. The reaction mixture was concentrated, analysed and the major product separated from the unreacted 2-pyridone by preparative t.l.c. to yield the title compound (73a) (21.5 mg, 19.8%) as a white crystalline solid m.p. (ethyl acetate) 88-89°, νmax ($CHCl_3$) 2940, 1735, 1720, 1680, 1648, 1435, 1370, 1320, 1120, 1090, 940 and 910 cm^{-1}, δ ($CDCl_3$) 6.97 (1H, d.d., J = 7, 7Hz), 6.49 (1H, d.d., J = 7, 2Hz), 4.89 (1H, d.d., J = 7, 2Hz), 3.88 (3H, S), 3.80 (3H, S), 2.80 (3H, S), 1.82 (3H, S). (Found : M^+ 265.1011; $C_{13}H_{15}NO_5$ requires : M 265.1005).

1,2,6-Trimethyl-2-aza-3-oxo-bicyclo[2.2.2]octa-5,7-dien-7,8-dimethyldicarboxylate (73c)

1,5,6-Trimethyl-2-pyridone (72c) (151 mg, 0.92 mmole) was dissolved in dry acetonitrile (0.5 mls) with dimethyl butynedioate (200 mg, 1.38 mmole). The solution was degassed, sealed under reduced pressure and thermolysed at 80° for 72 hours. The reaction mixture was concentrated, analysed and the major product separated from the unreacted 2-pyridone by preparative t.l.c. to yield the title compound (73c) (213 mg, 71%) as a white crystalline solid m.p. (ethyl acetate/60-80° petroleum ether) 79-81°, νmax ($CHCl_3$) 2930, 1720, 1670, 1650, 1635, 1430, 1380, 1320, 1080 cm^{-1}, δ ($CDCl_3$) 6.41 (1H, bd, J = 6Hz), 4.62 (1H, d, J = 6Hz), 3.80 (3H, S), 3.72 (3H, S), 2.80 (3H, S), 1.83 (3H, d, J = 2Hz).
(Found : M^+ 279.1092; $C_{14}H_{17}NO_5$ requires : M 279.1093).

3-Methoxy-dimethylphthalate (74e)

1-Methyl-6-methoxy-2-pyridone (62.9 mg, 0.45 mmole)was dissolved in dry acetonitrile (0.2 ml) with dimethyl butynedioate (79.6 mg, 0.55 mmole). The solution was degassed, sealed under reduced pressure and thermolysed at 80° for 72 hours. The reaction was concentrated and analysis by ^{1}H nmr and analytical t.l.c. showed that no new products had been formed. The 2-pyridone was then resealed as a neat deoxygenated solution in slight excess of dimethyl butynedioate and thermolysed at 145° for 14 hours. The reaction was concentrated and the major product purified to yield 3-methoxy -dimethylphthalate (74e) (96.7 mg, 96%) as a white crystalline solid m.p. (ether) 75-79° (lit[112] 77°) ν max ($CHCl_3$) 1727, 1588 cm^{-1}; δ ($CDCl_3$) 7.60-7.20 (2H, m), 7.05 (1H, d.d., J = 10, 2Hz), 3.87 (3H, S), 3.84 (3H, S) 3.82 (3H, S). All spectral data are in agreement with literature values[112].

3-Methyl-dimethylphthalate (74b)

1,3-Dimethyl-2-pyridone (72b) (200 mg, 1.63 mmole) was dissolved in dry acetonitrile (0.5 ml) with dimethyl butynedioate (300 mg, 1.75 mmole). The solution was degassed, sealed under reduced pressure and thermolysed at 80° for 72 hours. The reaction was concentrated and analysis by ^{1}H nmr and analytical t.l.c. showed that no new products had been formed. The 2-pyridone was then sealed as a neat deoxygenated solution in a slight excess of dimethyl butynedioate and thermolysed for 14 hours at 145°. The reaction was concentrated and preparative t.l.c. yielded 3-methyl-dimethylphthalate (74b) (67.6 mg, 21%) as a colourless oil. ν max ($_n$eat) 2994, 2948, 2840, 1721, 1593, 1435, 1278, 1196, 1150, 1114, 1072, 1020, 958, 882, 829, 768, 753, 700 cm^{-1}; δ (CCl_4) 8.05-7.62 (1H, m), 7.42-7.16 (2H, m),

3.87 (6H, S), 2.30 (3H, S)[113]. The same compound was obtained in 87% yield from the thermolysis of 1,6-dimethyl-2-pyridone (72a) with an excess of dimethyl butynedioate at 145°.

5-Phenyl-3-methyl-dimethylphthalate (74g)

To 1,6-dimethyl-4-phenyl-2-pyridone (72g) (0.38 g, 1.91 mmole) dissolved in the minimum quantity of dry acetonitrile was added dimethyl butynedioate (0.36 g, 2.10 mmole). Deoxygenated, sealed in a pyrex tube, the mixture was thermolysed at 145° for 14 hours. Analytical t.l.c. indicated that a single product had been formed. Preparative t.l.c. yielded 5-phenyl-3-methyl-dimethylphthalate (74g) (0.48 g, 89%) as a pale yellow solid m.p. (diethyl ether) 88-89°, ν max ($CHCl_3$) 3030, 2940, 1735, 1725, 1610, 1600, 1330, 1105 cm^{-1} δ ($CDCl_3$) 8.00 (1H, b), 7.60-7.30 (6H, m), 3.95 (3H, S), 3.90 (3H, S), 2.40 (3H, S).

(Found : C, 72.10; H, 5.57; $C_{17}H_{16}O_4$ requires : C, 71.82; H, 5.67). The same compound was also obtained following thermolysis of an acetonitrile solution of adduct (73 g) for 14 hours at 145°.

6-Methyl-4-phenyl-2-pyridone (79)

To 125 g of polyphosphoric acid was added benzoylacetonitrile (7.5 g, 0.051 mole), prepared by the method of Hauser[71], and freshly distilled acetone (3.0 g, 0.051 mole). The resulting mixture was stirred at room temperature for 0.5 hours, then on a steam bath for 0.5 hours, after which time a second equivalent of acetone was added and the mixture heated on an oil bath at 140° for 0.5 hours. The dark mixture was then added with stirring to 210 g of crushed ice and diethyl ether (200 mls) was added. The mixture was stirred (0.5 hours) and the two layers separated. The aqueous layer was neutralised with sodium bicarbonate to precipitate the title compound

(79) (6.4 g, 67%) as a pale yellow crystalline solid m.p. (methanol) 201-202° (lit[114] 202-203.5°) λmax 233 (30,000), 260 (16,700), 319 (5900); δ ($CDCl_3$) 13.0 (1H,b,exch.), 7.67-7.35 (5H, m), 6.70 (1H,b), 6.35 (1H, b), 2.43 (3H, S).

5,6-Dimethyl-2-pyridone (77)

Methyl ethyl ketone (72 g, 6.9 mole) was taken in a round-bottomed flask equipped with a mechanical stirrer and cooled to 0° (ice bath). Methanolic potassium hydroxide (1.5 ml of 30% solution) was added and the mixture stirred for 15 m. ACRYLO nitrile (30 g, 0.56 mole) in THF (50 ml) was added dropwise maintaining the temperature below 15°. The yellow solution was stirred for a further 1 hour and then neutralised with cHCl. Water (5 ml) was added to dissolve the potassium chloride. The organic phase was collected and the excess solvent evaporated to give a yellow oil which on distillation gave δ-acetylvaleronitrile (75) (29 g, 41%) b.p. 98-102° (5 mm) (lit[115] 114-115° (15 mm)).

δ-Acetylvaleronitrile (75) (9 g, 0.072 mole) was taken with activated neutral alumina (4.5 g). The slurry was sealed in a pyrex tube under reduced pressure and heated at 200° for 2 hours and a further 3 hours at 220°. After cooling, the tube was opened and the reaction mixture decanted from the vessel. The residue was washed thoroughly with benzene and concentrated in vacuo to yield 5,6-dimethyl-3,4-dihydro-2-pyridone (76) (7.9 g, 87%) as a yellow crystalline solid m.p. (benzene) 128-129° (lit[116] 130°). δ ($CDCl_3$) 7.60-7.20 (1H, b exch.), 2.67-2.04 (4H, m), 1.80 (3H, S), 1.74 (3H, S).

To a stirred solution of 5,6-dimethyl-3,4-dihydro-2-pyridone (76) (2.0 g, 0.016 mole) in $CHCl_3$ (30 ml) at 5° (ice bath) was added dropwise sulphuryl chloride (2.16 g, 0.016 mole) in $CHCl_3$ (10 ml).

After 0.5 hours the solvent was evaporated and the residue heated for 0.5 hours at 120° on an oil bath. The cooled mixture was diluted with water (20 mls) and neutralised with c.NH_4OH to precipitate 5,6-dimethyl-2-pyridone (77) (0.90 g, 45%) as a white powdery solid m.p. (H_2O) 205-207° (lit[116] 206-207°) δ ($CDCl_3$) 13.0 (1H, b, exch), 7.24 (1H, d, J = 10HZ), 6.38 (1H, d, J = 10HZ), 2.34 (3H, S), 2.08 (3H, S).

6-(Hex-5-en-1-yl)-3-(1-oxo-but-1-yl)-2-pyridone (58)

6-Methyl-3-CN-2-pyridone (54) (1.53 g, 11.4 mmole) was taken in dry THF (50ml) with stirring and external cooling to -23° (dry ice/CCl_4) under a nitrogen atmosphere, n-butyl lithium (2.20 g, 34.4 mmole) was slowly introduced to yield a bright red solution, stirred for 0.5 hours, 5-bromopent-1-ene (1.7 g, 11.5 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 extracted with dichloromethane (3 x 20 ml) and the organic portions combined, dried ($MgSO_4$), filtered and evaporated to give a brown oil. From the crude mixture the title compound (58) (1.81 g, 61%) was isolated by preparative t.l.c. as a white crystalline solid m.p. (diethyl ether) 131-132°, ν max ($CHCl_3$) 3450, 2960, 1670, 1640, 1600, 1550, 1160 cm^{-1}, δ ($CDCl_3$) 13.1 (1H, b, exch.), 8.22 (1H, d, J = 8HZ), 6.34 (1H, d, J = 8HZ), 6.06-5.33(1H, m), 5.20-4.87 (2H, m), 3.30-3.02 (2H, t, J = 7HZ), 2.83-2.53 (2H, t, J = 7.5 HZ), 2.30-1.17 (10H, m), 1.15-0.95 (3H, m).

(Found : C, 73.82; H, 8.73; N, 4.90:
$C_{16}H_{23}NO_2$ requires: C, 73.53; H, 8.87; N, 5.36%.)

6-(Hex-5-en-1-yl)-3-CN-2-pyridone (56)

Diisopropylamine (2.05 g, 20.3 mmole) 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 (1.30 g, 20.3 mmole) in cyclohexane and after 0.5 hours the mixture wa s cooled to -23° (dry ice/CCl_4). 6-Methyl-3-cyano-2-pyridone (54) (1.35 g, 10.1 mmole) was added slowly as a slurry in THF, giving a pale yellow solution. Stirred for 0.5 hours then 5-bromopent-1-ene (1.50 g, 10.2 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 extracted with dichloromethane (3 x 20 ml), and the organic portions combined, dried ($MgSO_4$), filtered and evaporated to give a brown oil. From the crude mixture the title compound (56) (1.18 g, 58%) was isolated by preparative t.l.c. as a pale lemon crystalline solid m.p. (diethyl ether) 90-91°, νmax ($CHCl_3$) 2970, 2210, 1670, 1640, 1600, 1145 cm^{-1}, δ ($CDCl_3$) 13.2 (1H, b, exch.), 7.68 (1H, d, J = 8HZ), 612(1H, d, J = 8HZ), 5.95-5.40 (1H, m), 5.08-4.79 (2H, m), 2.76-2.52 (2H, m), 2.16-1.28 (6H, m).

(Found : C, 71.18; H, 6.98; N, 13.60:

$C_{12}H_{14}N_2O$ requires : C, 71.26; H, 6.98; N, 13.85%.)

6-(Hex-6-trimethylsilyl-5-yn-1-yl)-2-pyridone (71a)

6-Methyl-2-pyridone (51) (1.8 g, 16.5 mmole) was taken in THF (50 ml) with stirring and external cooling to -23° (dry ice/CCl_4) under a nitrogen atmosphere, n-butyl lithium (2.14 g, 33.3 mmole) was slowly introduced to generate a yellow solution. Stirred for 0.5 hours, cooled to -78° (dry ice/acetone) and 1-bromo-pent-5-trimethylsilyl-4-yne (70) (3.60 g, 33.4 mmole) was added. After a further period of stirring the violet solution was allowed to warm to room temperature. Water was added, the resulting mixture 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 (71a) (1.99 g, 49%) was isolated as a white crystalline solid m.p. (ethyl acetate) 69°, νmax ($CHCl_3$) 2920, 2175, 1660, 1650, 1620, 1544 cm^{-1}, δ ($CDCl_3$) 13.0 (1H, b, exch.), 7.35 (1H, d.d., J = 8,7Hz), 6.45 (1H, d, J = 8Hz), 6.08 (1H, d, J = 7Hz), 2.66 (2H, t, J = 6Hz), 2.26 (2H, t, J = 7Hz), 1.98-1.46 (4H, m), 0.12 (9H, S).

(Found : C, 67.79; H, 8.55; N, 5.65:

$C_{14}H_{21}NOSi$ requires : C, 67.97; H, 8.55; N, 5.66%.)

Cyclopropanitrile (66)

6-Methyl-2-pyridone (51) (1.1 g, 10.1 mmole) was taken in THF (50 ml) with stirring and external cooling to -23° (dry ice/CCl_4) under a nitrogen atmosphere, n-butyl lithium (1.31 g, 20.4 mmole) was slowly introduced to generate a yellow solution. Stirred for 0.5 hours, cooled to -78° (dry ice/acetone) and 4-bromobutyronitrile (1.65 g, 10.3 mmole) was added. After a further period of stirring the solution was allowed to warm to room temperature. Water was added, the resulting mixture extracted with dichloromethane (3 x 20 ml) and the organic portions combined, dried ($MgSO_4$), filtered and evaporated to give a yellow oil. From the crude mixture was isolated unreacted 2-pyridone (51) (1.04 g, 94%) and cyclopropanitrile (66) (0.54 g, 79%) as a colourless oil. All spectral data are in agreement with literature values[117].

6-Methyl-5-nitro-2-amino-pyridine-N-oxide (63)

6-Methyl-2-acetylaminopyridine-N-oxide (60) (5.0 g, 40.3 mmole), prepared by the method of Brown[58], was cooled with stirring to -23° (dry ice/CCl_4). A cooled mixture of c.HNO_3 (6.1 ml) and c.H_2SO_4 (7.2 ml) was added dropwise over 0.5 hours until complete addition, stirred for 0.5 hours then allowed to warm to room temperature. The

orange reaction mixture was poured onto crushed ice (20 g) to liberate an orange precipitate which was collected. Recrystallisation from water afforded the title compound (63) (3.95 g, 58%) as yellow needles m.p. 210-212° (dec.), ν_{max} (nujol) 2980,1640,1580,1360,1210 cm^{-1} δ (d^6 DMSO) 8.0-7.6 (2H, b, exch.), 7.89 (1H, d, J = 9Hz), 6.92 (1H, d, J = 9Hz), 2.84 (3H, S).

(Found : C, 42.34; H, 4.00; N, 24.61;

$C_6H_7N_3O_3$ requires : C, 42.60; H, 4.17; N, 24.80%.)

Pent-1-en-5-ol

Thionyl chloride (156 g, 1.28 mole) was added dropwise with stirring to an ice-cooled solution of tetrahydrofurfuryl alcohol (118 g, 1.20 mole) and pyridine (103 g, 1.30 mole). After complete addition the mixture was stirred at room temperature for a further 4 hours and then extracted into diethyl ether (5 x 150 ml). The organic portions were combined, washed with water (3 x 25 ml), dried ($MgSO_4$), filtered and evaporated to yield after distillation tetrahydrofurfuryl chloride (70 g, 51%) b.p. 48-50° (16 mm) (lit[53] 41-42° (11 mm)). The chloride (56 g, 0.47 mole) in dry diethyl ether (80 ml) was added dropwise with stirring to a suspension of finely minced sodium (23.0 g, 0.96 mole) in diethyl ether (150 ml). After complete addition the mixture was stirred for 3 hours and decomposed with crushed ice to give two distinct phases. The organic layer was separated, dried ($MgSO_4$) and evaporated. Distillation of the residue gave pent-1-en-5-ol (25.4 g, 59%) b.p. 134-138°, (lit[118] 134-137°) as a colourless oil δ ($CDCl_3$) 6.20-5.58 (1H, m), 5.20-4.90 (2H, m), 3.60 (2H, t), 3.49 (1H, b, exch.), 2.30-1.54 (4H, m).

5-Bromopent-1-ene

Phosphorus tribromide (30.6 g, 0.11 mole) was added with stirring to a mixture of pent-1-en-5-ol (23.3 g, 0.27 mole) and dry pyridine (6.2 g, 0.07 mole) at -23° (dry ice/CCl_4). The mixture was allowed

to warm slowly to room temperature and extracted into dichloromethane. The extracts were washed with 2N sodium hydroxide, water, dried ($MgSO_4$) and evaporated. Distillation of the residue gave 5-bromopent-1-ene (23.2 g, 71%) b.p. 127-131° (lit[118] 128-130°) as a colourless oil δ ($CDCl_3$) 6.20-5.54 (1H, m), 5.22-4.90 (2H, m), 3.44 (2H, m), 2.30-1.85 (4H, m).

Pent-4-yn-1-ol (68)

Tetrahydrofurfuryl chloride (48 g, 0.40 mole), prepared by the method of Brooks and Snyder[64], was added dropwise over 0.5 hours to a stirred suspension of sodamide, made from sodium (31.9 g, 1.38 mole) in liquid ammonia (750 ml). After a further 16 hours stirring, dry ammonium chloride (69 g, 1.28 mole) was slowly added and most of the ammonia allowed to evaporate. The product was extracted into diethyl ether and distillation under reduced pressure gave pent-4-yn-1-ol (68) (31.2 g, 65%) b.p. 56-60° (12 mm) (lit[64] 64-65° (16 mm)); ν_{max} (neat) 3540-3340, 2965, 2878, 2118, 1432, 1348, 1160, 1055, 944 and 903 cm^{-1}; δ ($CDCl_3$) 3.96 (1H, b, exch.), 3.70 (2H, t, J = 5Hz), 2.28 (2H, t, J = 6Hz), 2.00 (1H, S), 1.72 (2H, m).

Pent-5-trimethylsilyl-4-yn-1-ol (69)

To magnesium turnings (13.7 g, 0.57 mole) in dry THF (50ml) stirred under a nitrogen atmosphere was added 10 drops of a solution of ethyl bromide (61.8 g, 0.57 mole) in dry THF (50 ml). Addition of an iodine crystal generated a yellow solution for 30 seconds after which time the reaction mixture again became colourless with evolution of gas. A cooling bath (ice/salt) was rapidly applied and the remaining proportion of ethyl bromide added to give a black slurry. After refluxing for 1 hour on a water bath the reaction was cooled and pent-4-yn-1-ol (68) (23.4 g, 0.28 mole) in dry THF (150 ml) was added

dropwise over 0.5 hours. After stirring for 1 hour at ice bath temperature, trimethylsilylchloride (62.1g, 0.57 mole) was added dropwise over 0.75 hours. The thick grey mixture was heated for 1 hour at 50°, stirred at room temperature for 16 hours, poured onto a saturated solution of ammonium chloride (500 ml), extracted with diethyl ether (3 x 500 ml), washed with brine (500 ml), concentrated and poured onto a mixture of ice (29 g)/ethanol (70 ml) and c.HCl (6 drops). After stirring for 2 hours the product was extracted with dichloromethane (3 x 150 ml), dried ($MgSO_4$), filtered and evaporated to leave a yellow oil. Distillation at reduced pressure under an atmosphere of nitrogen gave the title compound (69) (35.2 g 81%) as a colourless oil b.p. 106-108° (14 mm) νmax 3600, 3450, 2950, 2180, 1430, 1160, 1055 and 904 cm^{-1}. δ ($CDCl_3$) 3.75 (2H, t, J = 5HZ), 2.35 (2H, t, J = 6HZ), 1.90 (1H, b, exch.), 1.80-160 (2H, m), 0.15 (9H, S).

1-Bromo-pent-5-trimethylsilyl-4-yne (70)

Triphenylphosphine (58.3 g, 0.22 mols) and carbon tetrabromide (73.8g, 0.22 mole) were taken in dry toluene (400 ml) and cooled (ice/salt bath) with stirring to give a brilliant yellow suspension. Pent-5-trimethylsilyl-4-yn-1-ol (69) (34.3 g, 0.21 mole) in dry toluene (50 ml) was added dropwise. The colour faded rapidly to leave an off-white suspension. After complete addition the reaction was allowed to warm to room temperature, stirred for 2 hours, filtered, 40-60° petroleum ether (200 ml) was added, filtered again and the solvent evaporated to leave a colourless oil. Distillation at reduced pressure under an atmosphere of nitrogen gave the title compound (70) (42.86 g, 89%) b.p. 56-60° (2 mm) νmax (neat) 2960, 2175, 1430, 1272, 1245 cm^{-1}; δ ($CDCl_3$) 3.55 (2H, t, J = 6HZ), 2.40 (2H, t, J = 6HZ), 2.20-1.89 (2H, m), 0.15 (9H, S).

Hexen-1-ol

1,2,6-Trihydroxyhexane (165 g, 1.23 mole) was taken with formic acid (12.5 g, 0.27 mole) and ammonium chloride (0.4 g) in a distillation apparatus, heated slowly until evolution of gas ceased, further heating gave a colourless oil as distillate, more formic acid was added and the process repeated to exhaustion to give 5-hexen-1-ol (71.4 g, 58%) b.p. 154-156° (760 mm) (lit[119] 64° (15 mm)).

6-Bromohex-1-ene

Phosphorus tribromide (39.92 g, 0.14 mole) was added dropwise with stirring to a mixture of 5-hexen-1-ol (20.0 g, 0.2 mole) and dry pyridine (8.4 ml, 0.10 mole) at -23° (dry ice/CCl_4). After complete addition the mixture was allowed to reach room temperature, poured onto crushed ice and extracted with dichloromethane (3 x 150 ml). The extracts were combined, washed with 2N sodium hydroxide, water and dried ($MgSO_4$). Evaporation of the solvent afforded 6-bromohex-1-ene (20.5 g, 63%) as a colourless oil b.p. 156-170° (760 mm) (lit[120] 115-122° (3 mm)) ν max 3074, 2930, 2855, 1640, 1437, 1374, 1282, 1250, 1200, 1098, 990, 965 and 912 cm^{-1}; δ ($CDCl_3$) 5.95-5.60 (1H, m), 5.16-4.84 (2H, m), 3.40 (2H, t, J = 6Hz), 2.20-1.40 (6H, m).

4-Bromobutyronitrile

To a stirred solution of potassium cyanide (0.5 g, 0.16 mole) in water (20 ml) was added 1,3-dibromopropane (30 g, 0.14 mole) and benzyl triethylammonium chloride (0.4 g, 0.02 mole). The reaction was refluxed for 3 hours and the resulting brown emulsion stirred slowly for 1 hour after which time two distinct phases were visible. Separation of the organic phase and extraction of the aqueous phase with methylene chloride gave, on combination and evaporation, a brown

oil which was distilled to give 4-bromobutyronitrile (12.97 g, 59%) as a colourless mobile oil b.p. 68-70 (16 mm) (lit[61] 52-54° (11 mm)).

2,4-Dimethyl-5-ethoxyoxazole (114)

(±)Alanine (50.0 g, 0.57 mole) was taken with absolute ethanol (500 ml) and cooled to 0° (ice/salt bath) with vigorous stirring. Thionyl chloride (43.3 ml, 0.59 mole) was added dropwise over 0.5 hours. The viscous solution was heated to 40° for 1.5 hours, the solvent evaporated to leave DL-alanine ethyl ester hydrochloride[121a] (82.9 g, 95%) as a white powdery solid m.p. 60-63° (lit[121b] 62°dec.).

The ester hydrochloride (80 g, 0.52 mole) was taken in toluene (150 ml) and acetyl chloride (120 g, 1.53 mole) was added dropwise. The resulting solution was refluxed for 6 hours after which time the toluene, excess acetyl chloride and acetic acid were distilled from the reaction vessel at reduced pressure under a stream of nitrogen. The yellow residue was taken up in ethyl acetate (150 ml) and washed with a saturated solution of sodium bicarbonate (3 x 50 ml), dried ($MgSO_4$), filtered and evaporated to leave a clear oil which crystallised on standing to give N-acetyl alanine ethyl ester (65.5 g, 79%) b.p. 104-108° (5 mm) (lit[121g] 120-125°(10 mm)).

To a suspension of phosphorus pentoxide (71.0 g, 0.5 mole) in dry $CHCl_3$ (150 ml) a solution of N-acetyl alanine ethyl ester (39.75 g, 0.25 mole) in dry $CHCl_3$ (100 ml) was added dropwise with stirring. The mixture was gently boiled on a steam bath for 16 hours. To the cooled mixture an aqueous solution of potassium hydroxide (375 ml, 20% solution) was added with vigorous stirring, The mixture was then stirred at room temperature for0.5 hours. The organic layer was separated and the aqueous layer extracted with $CHCl_3$ (2 x 100 ml). The combined extracts were washed with water, dried ($MgSO_4$) and the

solvent evaporated. Distillation of the residue from sodium hydroxide pellets gave 2,4-dimethyl-5-ethoxyoxazole (114) (16.9 g, 48%) as a colourless oil b.p. 65-67° (16 mm) (lit[99] 89-90° (40 mm)). δ ($CDCl_3$) 4.12 (2H, q, J = 7 HZ), 2.30 (3H, S), 2.00 (3H, S), 1.35 (3H, t, J = 7HZ).

2,4,5-Trimethyloxazole (134)

A mixture of pyridine (160 ml, 1.99 mole), acetic anhydride (225 ml, 2.36 mole) and DL alanine (36 g, 0.40 mole) was heated with vigorous stirring on a steam bath for six hours after solution was complete. The excess pyridire and acetic anhydride were removed at reduced pressure and the residue distilled to give 3-acetamido-2-butanone (37.5 g, 72%) as a colourless oil b.p. 120-125° (3 mm) (lit[103] 102-106° (2 mm)).

3-Acetamido-2-butanone (30.0 g, 0.23 mole) was added dropwise to potassium bisulphate (85 g, 0.63 mole) in a distilling flask at 220°. The distillate was collected and on fractionation gave 2,4,5-trimethyloxazole (134) (9.2 g, 36%) as a colourless oil b.p. 50-54° (20 mm) (lit[102] 133-135° (760 mm)) δ ($CDCl_3$) 2.34 (3H, S), 2.16 (3H, S), 2.02 (3H, S).

2-Methyl-4-phenyloxazole (142)

Bromoacetophenone (25.4 g, 0.13 mole) was taken with acetamide (25.1 g, 0.43 mole) and heated at 130° for 3 hours. The brown solution was cooled, made alkaline with sodium hydroxide solution and extracted with diethyl ether (2 x 150 ml). The extracts were combined, dried (K_2CO_3), filtered and distilled to give 2-methyl-4-phenyloxazole (142) (10.6 g, 52%) as a waxy yellow solid m.p. 40-42° (lit[106] 45°) b.p. 92-94° (2.5 mm) (lit[106] 241-242° (760 mm)). δ ($CDCl_3$), 7.80 (1H, S), 7.72-7.20(5H, m), 2.48 (3H, S).

2,5-Dimethyl-4-benzyloxazole (152)

DL-phenylalanine (12.4 g, 0.075 mole) was taken with pyridine (39.3 g, 0.5 mole) and acetic anhydride (65.2 g, 0.64 mole) and heated on a steam bath for 5 hours. The excess pyridine and acetic anhydride were removed at reduced pressure under a stream of nitrogen. The remaining orange oil was poured onto a saturated solution of sodium bicarbonate (200 ml) and extracted with diethyl ether (2 x 250 ml), the extracts were combined, washed with water, dried ($MgSO_4$), filtered and the solvent evaporated to leave an orange solid which on recrystallisation from toluene afforded 1-phenyl-2-acetamido-3-butanone (11.1 g, 72%) as white crystals m.p. 98-99° (lit[122] 99°).

To a suspension of phosphorus pentoxide (14.5 g, 0.1 mole) in dry chloroform (30 ml), a solution of 1-phenyl-2-acetamido-3-butanone (10.5 g, 0.05 mole) in dry chloroform (30 ml) was added dropwise with stirring. The mixture was gently boiled on a steam bath for 16 hours. The cooled mixture was poured onto an aqueous solution of potassium hydroxide (75 ml, 20% solution) with vigorous stirring. The mixture was then stirred at room temperature for 0.5 hours. The organic layer was separated and the aqueous layer extracted with chloroform (2 x 50 ml). The combined extracts were washed with water, dried ($MgSO_4$), filtered and the solvent evaporated. Distillation of the residue afforded 2,4-dimethyl-4-benzyloxazole (152) (7.85 g, 82%) as a pale yellow oil b.p. 114° (3.5 mm) (lit[101] 134° (11 mm)) δ ($CDCl_3$) 7.12-7.04 (5H, m), 3.70 (2H, S), 2.35 (3H, S), 2.13 (3H, S).

General method for the preparation and alkylation of oxazole monoanions

The oxazole (5-10 mmole) was taken in dry THF (20-40 ml) and cooled to -78° (dry ice/acetone) under a steady stream of dry deoxygenated nitrogen with constant stirring. n-Butyl lithium (1.05 equivalents) was added dropwise over 15 m and the bright yellow solution was stirred for a further 15 m without allowing the temperature to rise. The electrophile (1.05-1.10 equivalents) was added neat and after a further 15 m the reaction was allowed to warm slowly to room temperature, stirred for 2 hours, the yellow mixture was poured onto cold water (50-100 ml) and extracted with diethyl ether (2 x 50 ml). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated to leave a yellow oil. Purification was effected by column chromatography on neutral aluminium oxide (Brockmann grade 1) using diethyl ether/40-60° petroleum ether as eluant. Specific details are adduced below.

2-(Pent-4-en-1-yl)-4-methyl-5-ethoxyoxazole (120)

2,4-Dimethyl-5-ethoxyoxazole (114) (1.02 g, 7.2 mmole) and 4-bromobutene gave, after purification, the title compound (120) (1.10 g, 78%) as a colourless oil, ν max (neat) 3080, 2980, 2930, 1665, 1630, 1570, 1435, 1380, 1320, 1220, 1085, 1020, 910 cm^{-1}, δ ($CDCl_3$) 6.30-5.50 (1H, m), 5.31-4.80 (2H, m), 4.12 (2H, q, J = 8HZ), 2.63 (2H, t), 2.20-1.42(4H, m), 2.00 (3H, S), 1.36 (3H, t, J = 8HZ).
(Found : MH^+ 123 196.1214; $C_{11}H_{18}NO_2$ requires :MH 196.1203).

2-(Hex-5-en-1-yl)-4-methyl-5-ethoxyoxazole (116)

2,4-Dimethyl-5-ethoxyoxazole (114) (0.96 g, 6.8 mmole) and 5-bromopent-1-ene gave, after purification, the title compound (116) (1.05 g, 74%) as a colourless oil, ν max (neat) 3080, 2920, 2860, 1660, 1620,

1565, 1430, 1375, 1320, 1220, 1085, 1020 and 910 cm^{-1}, δ ($CDCl_3$) 6.30-5.51 (1H,m), 5.33-4.80 (2H, m), 4.12 (2H, q, J = 8Hz), 2.63 (2H, t), 2.20-1.24 (6H, m), 2.00 (3H, s), 1·36(3H,t,J=8Hz).

(Found : M^+ 209.1504; $C_{12}H_{19}NO_2$ requires : M 209.1495).

2-(Hept-6-en-1-yl)-4-methyl-5-ethoxyoxazole (122)

2,4-Dimethyl-5-ethoxyoxazole (114) (0.66 g, 4.7 mmole) and 6-bromohexene gave, after purification, the title compound (122) as a colourless oil, νmax (neat) 3080, 2930, 2860, 1665, 1630, 1570, 1430, 1380, 1320, 1220, 1090, 1020 and 910 cm^{-1}, δ ($CDCl_3$) 6.31-5.52 (1H, m) 5.34-4.80 (2H, m), 4.11 (2H, q, J = 8Hz), 2.63 (2H, t), 2.20-1.11 (8H, m), 2.00 (3H, S),1.36 (3H, t, J = 8Hz).

(Found : M^+ 223.1595; $C_{13}H_{21}NO_2$ requires : M 223.1592).

2-(Hex-6-trimethylsilyl-5-yn-1-yl)-4-methyl-5-ethoxyoxazole (126)

2,4-Dimethyl-5-ethoxyoxazole (114) (0.95 g, 6.8 mmole) and 1-bromopent-5-trimethylsilyl-4-yne (70) gave, after purification, the title compound (126) (0.83 g, 44%) as a colourless oil, νmax (neat) 2960, 2930, 2175,1665, 1570, 1250, 1220, 1090, 1020, 840, 760 and 735 cm^{-1}, δ ($CDCl_3$) 4.10 (2H, q, J = 8Hz), 2.67 (2H, t), 2.23(2H, t), 2.00 (3H, S), 2.00-1.54 (4H, m), 1.40 (3H, t, J = 8Hz), 0.15 (9H, S).

(Found[123]? MH^+ 280.1871; $C_{15}H_{26}NO_2Si$ requires : MH 280.1860)

2-(Pent-4-en-1-yl)-4-benzyl-5-methyloxazole (157)

2,5-Dimethyl-4-benzyloxazole (152) (0.90 g, 4.80 mmole) and 4-bromopentene gave, after purification, the title compound (152) (0.49 g, 42%) as a yellow oil, νmax (neat) 3030, 2930, 1640, 1630, 1595, 1575, 1495, 1450, 910 and 730 cm^{-1}, δ ($CDCl_3$) 7.17-7.03 (5H, m), 6.24-5.42 (1H, m), 5.20-4.73 (2H, m), 3.70 (2H, S), 2.60 (2H, t), 2.13-1.67 (4H, m), 2.05 (3H, S).

(Found : M^+ 241.1475; $C_{16}H_{19}NO$ requires : M 241.1471)

2-(3-(2,4,5-Trimethyl)pyrrolyl)-4,5-dimethyloxazole (131)

2,4,5-Trimethyloxazole (134) (0.99 g, 9.0 mmole) and 4-bromopentene gave, on purification, the title compound (131) (0.40 g, 44%) as a white crystalline solid m.p. (diethyl ether) 190-192° (dec.), λmax (EtOH)211 (9620), 267 nm (12,120), ν max ($CHCl_3$) 3460, 2920, 1620, 1580, 1070 cm^{-1}, δ ($CDCl_3$) 7.20 (1H, b, exch), 2.40 (3H, S), 2.20 (3H, S), 2.14 (3H, S), 2.08 (3H, S), 2.06 (3H, S).

(Found : C, 70.32; H, 8.03; N, 13.35:
$C_{12}H_{16}N_2O$ requires : C, 70.56; H, 7.90; N, 13.71).

2-(3-(2-Methyl-5-phenyl)pyrrolyl)-4-phenyloxazole (144)

2-Methyl-4-phenyloxazole (142) (2.09 g, 13.1 mmole) and 4-bromobutene gave, on purification, the title compound (144) (0.63 g, 32%) as a yellow crystalline solid m.p. 128-130° (dec.) ν max ($CHCl_3$) 3400, 2920, 1600, 1580, 1100, 940 and 900 cm^{-1}, δ ($CDCl_3$) 8.20 (1H, b, exch.), 7.71 (1H, S), 7.65-7.02 (10H, m), 6.79 (1H, d, J = 2Hz + D_2O, S), 2.65 (3H, S).
(Found : M^+ 300.1273 ; $C_{20}H_{16}N_2O$ requires : M 300.1263).

2-Methyl-6-phenyl-3,4-pyridine dicarboxylic anhydride (150)

2-Methyl-4-phenyloxazole (142) (0.65 g, 4.1 mmole) was taken with maleic anhydride (0.43 g, 4.4 mmole) in dry toluene (2 ml). The solution was degassed, sealed under reduced pressure and thermolysed at 110° for 4 hours. The reaction mixture was concentrated to give a yellow crystalline solid. Recrystallisation from ethyl acetate afforded the title compound (150) (0.63 g, 64%) as a yellow solid m.p. 168°, ν max ($CHCl_3$) 3030, 1850, 1780, 1610, 1595, 1260, 900 cm^{-1}, δ(d^6 DMSO) 7.63 (1H, S), 7.58-7.01 (5H, m), 2.50 (3H, S).
(Found : M^+ 239.0704 ; $C_{14}H_{19}NO_3$ requires : M 239.0692).

2,5-Dimethyl-6-benzyl-3,4-pyridinedicarboxylic anhydride (154)

2,5-Dimethyl-4-benzyloxazole (152) (0.57 g, 3.1 mmole) was taken with maleic anhydride (0.30 g, 3.1 mmole) in dry toluene (2 ml). The solution was degassed, sealed under reduced pressure and thermolysed at 110° for 2 hours. The reaction mixture was concentrated to give a white crystalline solid. Recrystallisation from ethyl acetate gave the title compound (154) (0.58 g, 71%) m.p. 195-196° (dec.), ν max ($CHCl_3$) 2970, 1790, 1730, 1630, 1600, 1580, 1500, 1220 cm^{-1}, δ (d^6 DMSO) 7.30-7.12 (5H, m), 4.19 (2H, S), 2.55 (3H, S), 2.16 (3H, S). (Found : M^+ 267.0735 ; $C_{16}H_{13}NO_3$ requires : M 267.0722).

Dimethyl-2-methylfuran-3,4-dicarboxylate (151)

2-Methyl-4-phenyloxazole (142) (0.83 g, 5.2 mmole) taken with dimethyl butynedioate (0.75 g, 5.3 mmole) in dry toluene (2 ml). The solution was degassed, sealed under reduced pressure and thermolysed at 110° for 2 hours. The red solution was concentrated and distillation of the residue afforded benzonitrile (νmax 2195 cm^{-1}) and the title compound (151) (0.51 g, 49%) as a colourless oil b.p. 112-114° (3 mm) (lit[91] 88-90° (1 mm)) λmax (EtOH) 242 mm (E 5610) ν max ($CHCl_3$) 1737, 1731, 1460, 1350 cm^{-1}. δ ($CDCl_3$) 7.65 (1H, S), 3.78 (3H, S), 3.75 (3H, S), 2.47 (3H, S).

Dimethyl-2,5-dimethylfuran-3,4-dicarboxylate (155)

2,5-Dimethyl-4-benzyloxazole (152) (0.72 g, 3.9 mmole) was taken with dimethyl butynedioate (0.56 g, 4.0 mmole) in dry toluene (2 ml). The solution was degassed, sealed under reduced pressure and thermolysed at 110° for 2 hours. The red solution was concentrated and the crude mixture purified on preparative t.l.c. to yield the title compound (155) (0.41g 51%) as a white solid m.p. 60-62° (lit[108] 63.5°) νmax (neat) 3050, 1725, 1548, 1316, 1279 cm^{-1} δ ($CDCl_3$) 3.83 (6H, S), 2.45 (6H, S).

2-(Hex-5-en-1-yl)-3,4-dicarbomethoxy-5-ethoxyfuran (128)

2-(Hex-5-en-1-yl)-4-methyl-5-ethoxyoxazole (116) (0.81 g, 3.9 mmole) taken with dimethyl butynedioate (0.56 g, 4.0 mmole) in dry toluene (2 ml). The solution was degassed, sealed under reduced pressure and thermolysed at 110° for 6 hours. The red solution was concentrated and the crude mixture purified on preparative t.l.c. to yield the title compound (128) (0.77 g, 64%) as a colourless oil, νmax (neat) 3080, 2950, 1735, 1715, 1635, 1600, 1440, 1320, 1200, 1050, 915 cm^{-1}, δ ($CDCl_3$) 6.30-5.52 (1H, m), 5.33-4.80 (2H, m), 4.31 (2H, q, J = 8Hz), 3.83 (3H, S), 3.80 (3H, S), 2.74 (2H, t), 2.10-1.21 (6H, m), 1.41 (3H, t, J = 8Hz).

(Found : M^+ 310.1540 ; $C_{16}H_{22}O_6$ requires : M 310 1538).

Thermolysis of the oxazole (120)

The oxazole (120) (0.72 g, 3.7 mmole) was dissolved in dry toluene (1 ml) sealed in a pyrex tube under reduced pressure and thermolysed at 110° for 4 hours. The microcrystalline precipitate was filtered off and recrystallised from ethanol to give 2,3-cyclopentyl-5-hydroxy-6-methylpyridine (121) (0.30 g, 54%) as a yellow solid m.p. 290° (dec.), ν max (nujol) 3460, 3070, 2920, 1600, 1580, 1450, 1150, 1110 cm^{-1}, δ ($NaOD/D_2O$) 6.82 (1H, S), 2.61-2.50 (4H, m), 2.08 (3H, S), 1.88-1.80 (2H, m).

(Found : M^+ 149.0762 ; $C_9H_{11}NO$ requires : M 149.0755).

Thermolysis of the oxazole (116)

The oxazole (116) (0.64 g, 3.1 mmole) was dissolved in dry toluene (1 ml) sealed in a pyrex tube under reduced pressure and thermolysed at 145° for 6 hours. The microcrystalline precipitate was filtered off and recrystallised from ethanol to give 2,3-cyclohexyl-5-hydroxy-6-methylpyridine (119) (0.36 g, 72%) as a white crystalline solid

m.p. 340° (dec.), ν max (nujol) 3470-3300, 2920, 1610, 1580, 1460, 1150, 1110 cm^{-1}, δ (d^6 DMSO) 9.30 (1H, b, exch), 6.80 (1H, S), 2.81-2.63 (4H, m), 2.32(3H, S), 1.81-1.72 (4H, m).
(Found : M^+ 163.0989 ; $C_{10}H_{13}NO$ requires : M 163.0997).

Thermolysis of the oxazole (122)

The oxazole (122) (0.18 g, 0.81 mmole) was dissolved in toluene (1 ml) sealed in a pyrex tube at reduced pressure and thermolysed at 145° for 16 hours. No products were detected by analytical t.l.c. or ^{1}H nmr. The sample was resealed and thermolysed at 198° for 6 hours. the solvent was evaporated to leave an intractable tar. No monomeric products were detected by analytical t.l.c. or ^{1}H nmr.

Thermolysis of the oxazole (126)

The oxazole (126) (0.42 g, 1.5 mmole) was dissolved in toluene (1 ml) sealed in a pyrex tube under reduced pressure and thermolysed at 145° for 48 hours. No products were detected by analytical t.l.c. or ^{1}H nmr. The sample was resealed and thermolysed at 198° for 6 hours in which time decomposition occurred to give only polymeric material.

Thermolysis of the oxazole (157)

The oxazole (157) (0.31 g, 1.3 mmole) was dissolved in toluene (1 ml) sealed in a pyrex tube under reduced pressure and thermolysed at 145° for 16 hours. No products were detected by analytical t.l.c. or ^{1}H nmr. The solvent was removed *in vacuo* and the oxazole was then dissolved in the minimum amount of glacial acetic acid (0.5 ml) sealed in a pyrex tube at reduced pressure and thermolysed at 145° for 1 hour. The major product was separated by preparative t.l.c. to yield 2,3-cyclopentyl-5-methyl-6-benzylpyridine (158) (0.15 g, 54%) as a heavy lemon oil, ν max ($CHCl_3$) 3050, 2940, 2850,

1660, 1600, 1560, 1495, 1460, 1430, 1020, 730, 700 cm^{-1}, δ ($CDCl_3$) 7.30-7.11 (6H, m), 4.16 (2H, S), 2.99 (2H, t), 2.89 (2H, t), 2.18 (3H, S), 2.20-2.08 (2H, m).

(Found: M^+ 223. 1378 ; $C_{16}H_{17}N$ requires : M 223.1376).

Thermolysis of the furan (128)

The furan (128) (0.44 g, 1.4 mmole) was dissolved in toluene (1 ml) sealed in a pyrex tube under reduced pressure and thermolysed at 145° for 48 hours. No products were detected by analytical t.l.c. or ^1H nmr. Under more vigorous conditions (198°) a polymeric material was produced.

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