GAS PHASE REARRANGEMENTS OF 2-PYRONES

by

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DOCTOR OF PHILOSOPHY

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DECLARATION

I declare that this thesis is my own composition, that the work of which it is a record was carried out by myself and that it has not been submitted in any previous application for a higher degree.

This thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. H. McNab since 1st October 1988, the date of my admission as a research student.

DEDICATION

This thesis is dedicated to my wife Patricia and my sons Kyle and Mitchell.

Special thanks to my parents for their help and support over the past few years, without which this thesis would not have been completed.

ACKNOWLEDGEMENTS

I am most grateful to Dr. H. McNab for suggesting topics of research and his assistance and encouragement over the past three years.

I would also like to thank the technical staff at the Department of Chemistry for providing an efficient service. The excellent typing is the work of Mrs. L. Marouf to whom I am most grateful.

Finally, I would like to thank British Petroleum Company Ltd. for financial support.

LECTURE COURSES

The following courses have been attended:

"Approaches to Synthesis"

Dr. I. Gosney (University of Edinburgh)

"Recent Advances in Organic Chemistry" (three years attendance)

Department of Chemistry (University of Edinburgh)

"Medicinal Chemistry" (two years attendance)

Professor R. Baker and colleagues (Merck, Sharp and Dohme)

"Chemistry and Society: Applications and Consequences"

Royal Society of Chemistry, 1990

"Modern Synthetic Methods"

Dr. G. Tennant (University of Edinburgh)

Attendance at Organic Research Seminars and Colloquia (three years attendance)

Department of Chemistry (University of Edinburgh)

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ABSTRACT

The automerisation and decarbonylation processes of 2-oxo-2*H*-pyran-5-carboxaldehyde have been investigated *via* Flash Vacuum Pyrolysis (F.V.P.) techniques, using ^{18}O and ^{2}H labelled precursors. The products were analysed by ^{1}H, ^{2}H and ^{13}C nmr spectroscopy, and where necessary, by mass spectrometry.

The observed rearrangements can be explained by invoking reversible electrocyclic ring opening of the 2-pyrone system to ketene intermediates with accompanying [1,5]-sigmatropic shifts and carbon-carbon double bond isomerisations.

The mechanism of decarboxylation of 2-oxo-2*H*-pyran-5-carboxylic acids has been investigated and can also be explained by invoking ring opened intermediates.

It was found that a methyl group at C-6 of the 2-pyrone system has two major influences; firstly it blocks the sigmatropic shift process and hence hinders the decarbonylation of the 2-oxo-2*H*-pyran-5-carboxaldehydes.

The temperature dependence of the ring opening process has been investigated by changing the ring oxygen hetero atom of the 2-pyrone system to nitrogen. This pyridone system has been examined using ^{15}N labelled compounds, the ring opening of which was found to occur at much higher furnace temperatures.

A convenient pyrolytic method of making various substituted coumarins from easily synthesised acrylate compounds has also been discussed.

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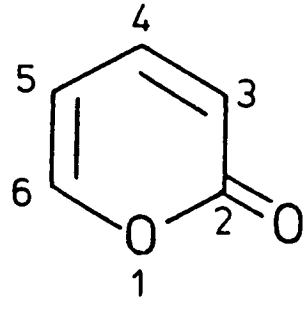
PREAMBLE

This thesis is concerned with the gas phase rearrangements of 2-pyrones and related compounds. Much is known about 2-pyrones and several reviews have been published[1,2,3]. The parent ring system, 1, together with numbering scheme is shown below.



2H-Pyran-2-one

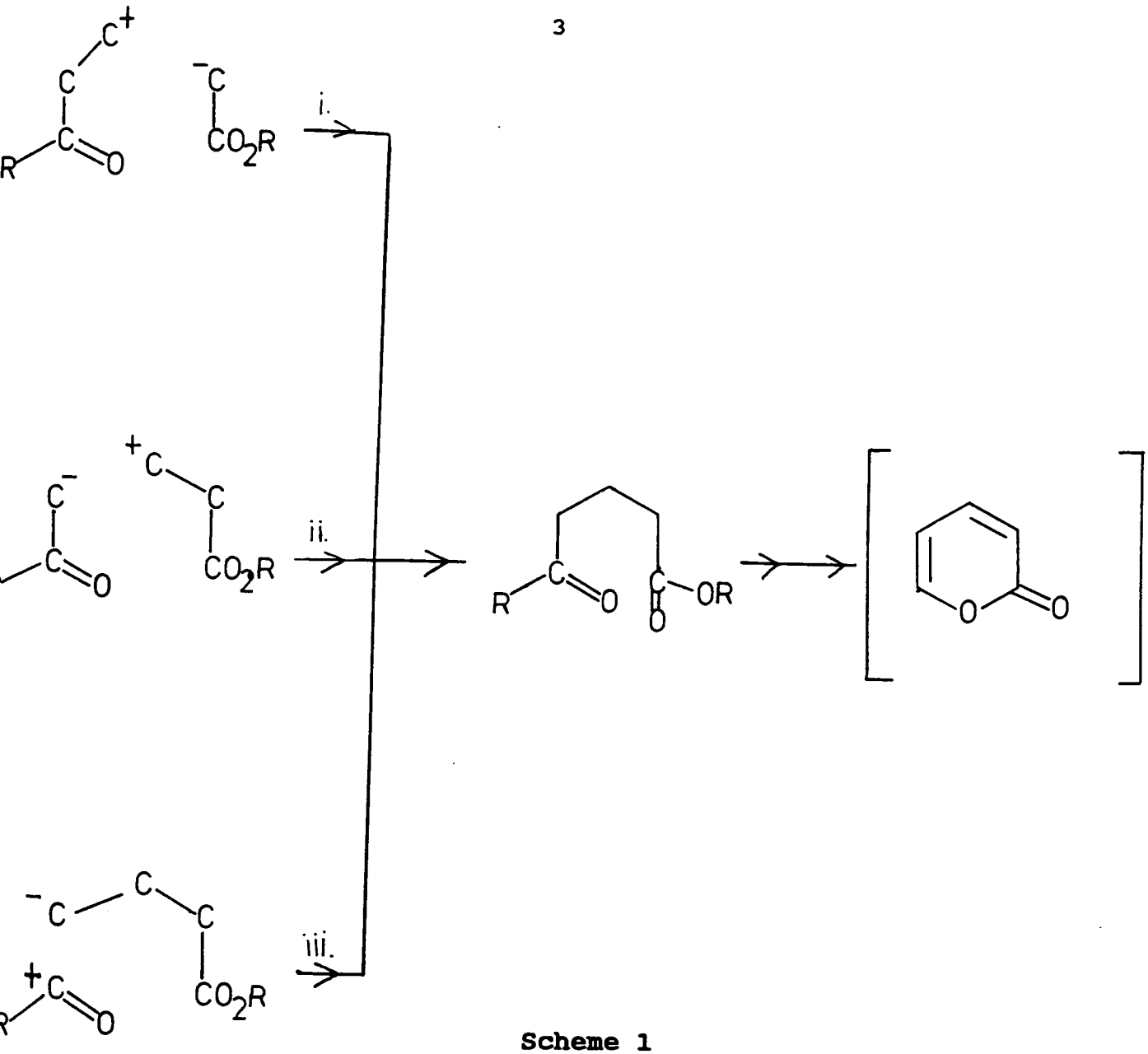
However, due to the nature of the syntheses employed, substituted compounds are produced, with, very typically, electron donating (i.e. hydroxy, alkoxy) and/or electron withdrawing (i.e. esters) groups[2], but surprisingly, very little work has been undertaken on simple alkyl and aryl compounds. Therefore, to limit the scope of the

introductory review, attention will be focussed on the preparation, physical properties and chemistry of these simple alkyl/ aryl compounds. However, a brief overview of the general methods of synthesising 2-pyrones will also be given.

One of the earliest preparations of a 2-pyrone was reported by von Pechmann[4], involving the self-condensation of malic acid in concentrated sulphuric acid, to give a reasonable yield of coumalic acid (discussed later). Historically this was an extremely important discovery, and due to its simplicity became a routine method for synthesising 2-pyrones from a wide variety of unsaturated esters[2].

PREPARATION OF 2-PYRONES

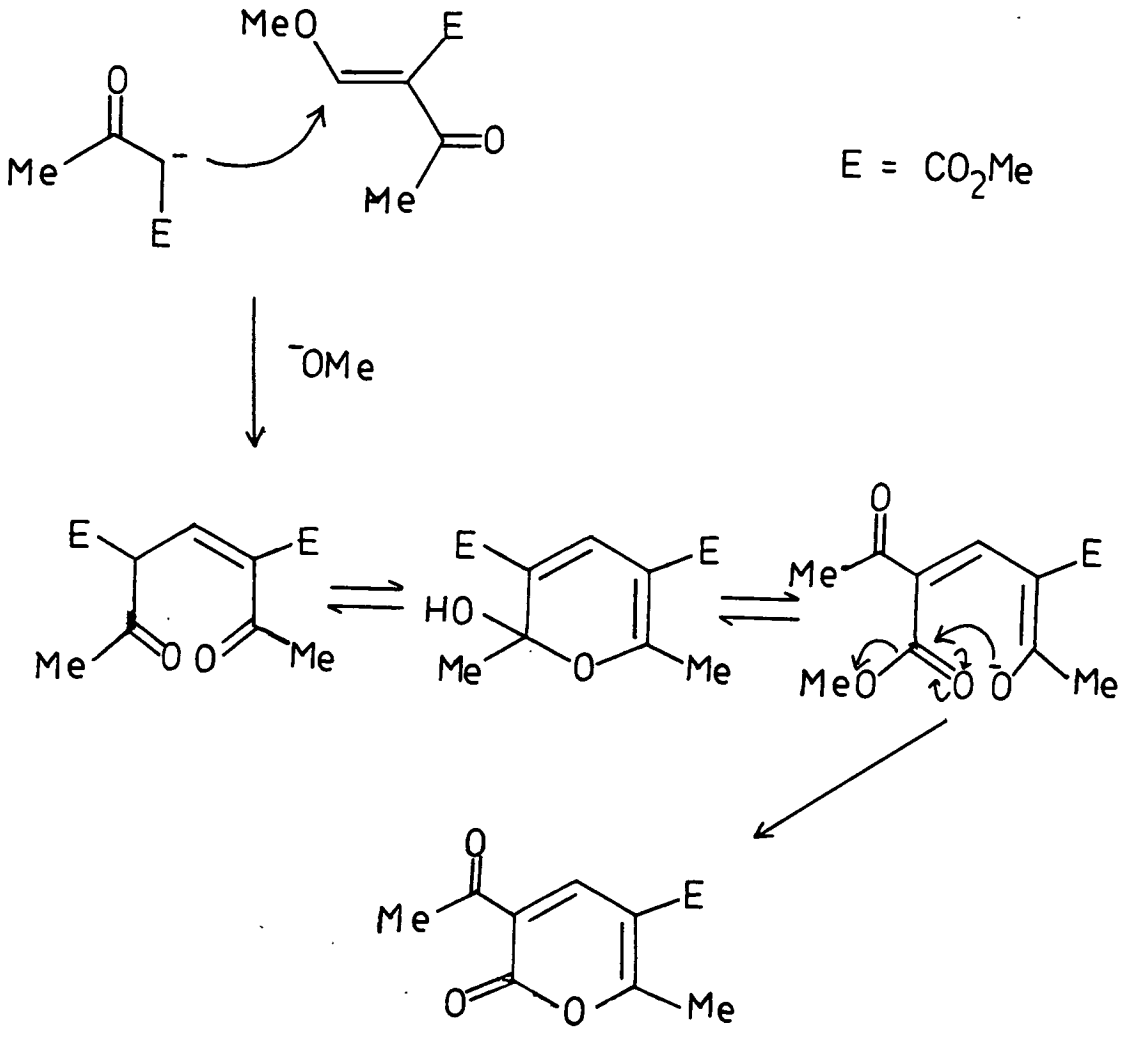
Scheme 1 outlines the three main types of condensation routes to 2-pyrones, albeit in a rather formalised way. All three routes (i, ii and iii) produce a 5-carbon atom unit, which then undergoes cyclisation forming the 2-pyrone ring. Examples of each method will be discussed in turn.



Scheme 1

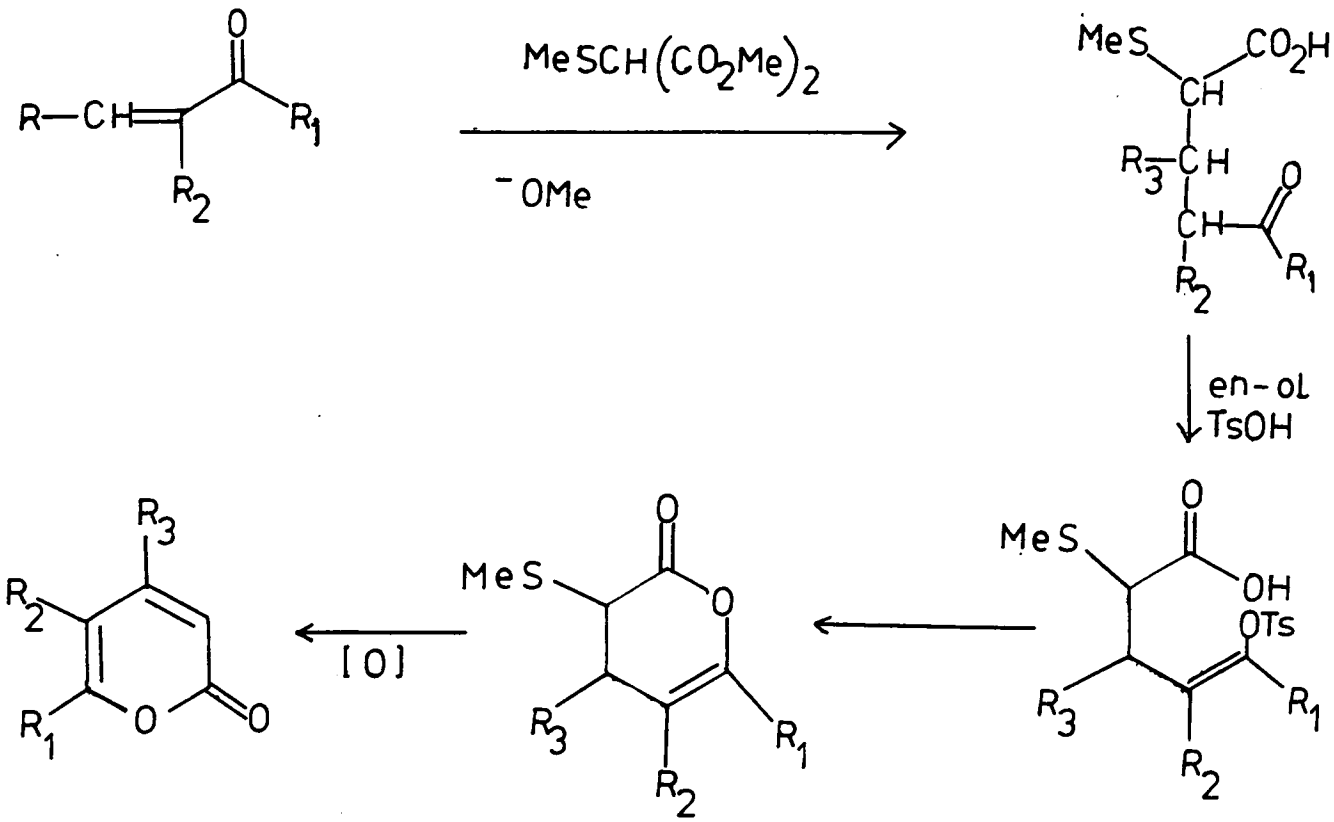
Type (i) Reaction

A typical example is initiated by the Michael addition of a carbanion to an unsaturated carbonyl compound and such a reaction occurs between methyl acetoacetate and methoxymethyleneacetoacetate[5] (Scheme 2). The product has both electron withdrawing and electron donating substituents.



Scheme 2

A more recent variation produces mono methyl substituted compounds[6]. The reaction of dimethyl methylthiomalonate with various α,β-unsaturated ketones has been used to good effect and appears ripe for development for other mono alkyl and mono aryl compounds (Scheme 3).

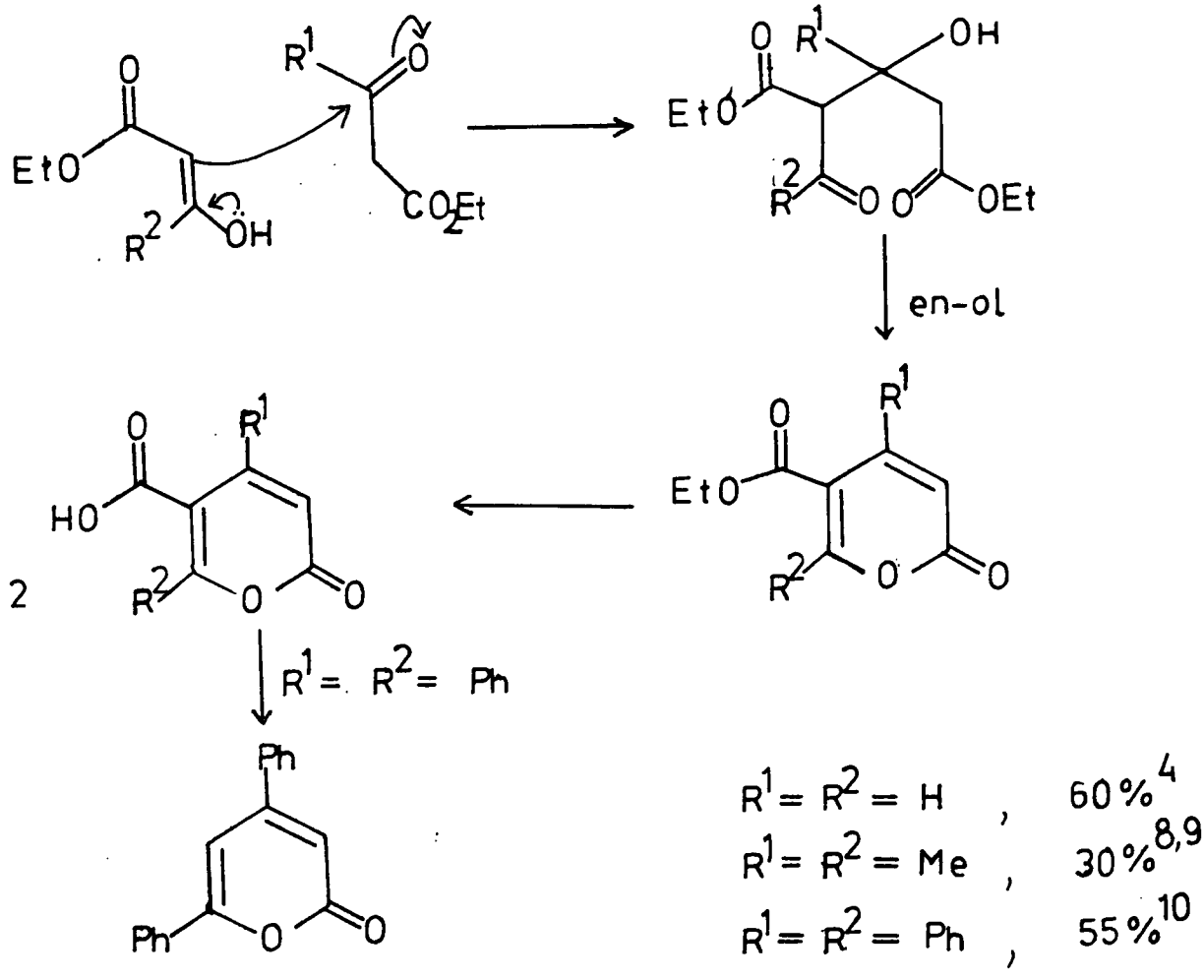


R_3= Me R_2= R_1 = H
R_2= Me R_3= R_1 = H ≈ 60%
R_1= Me R_3= R_2 = H

Scheme 3

Type (ii) Reaction

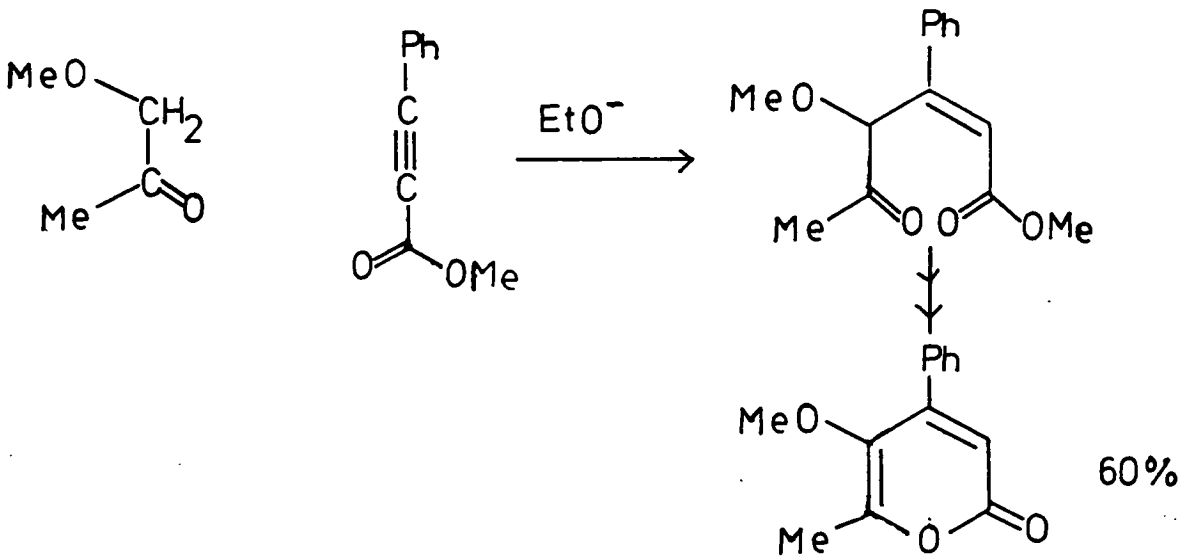
This type of reaction is shown by the self-condensation of β-keto esters[7]. Products have identical groups at C-4 and C-6, and a general reaction scheme is shown below. The basic mechanism involves reaction of an enol tautomer of one molecule with the carbonyl group of a neighbouring molecule (Scheme 4).



Scheme 4

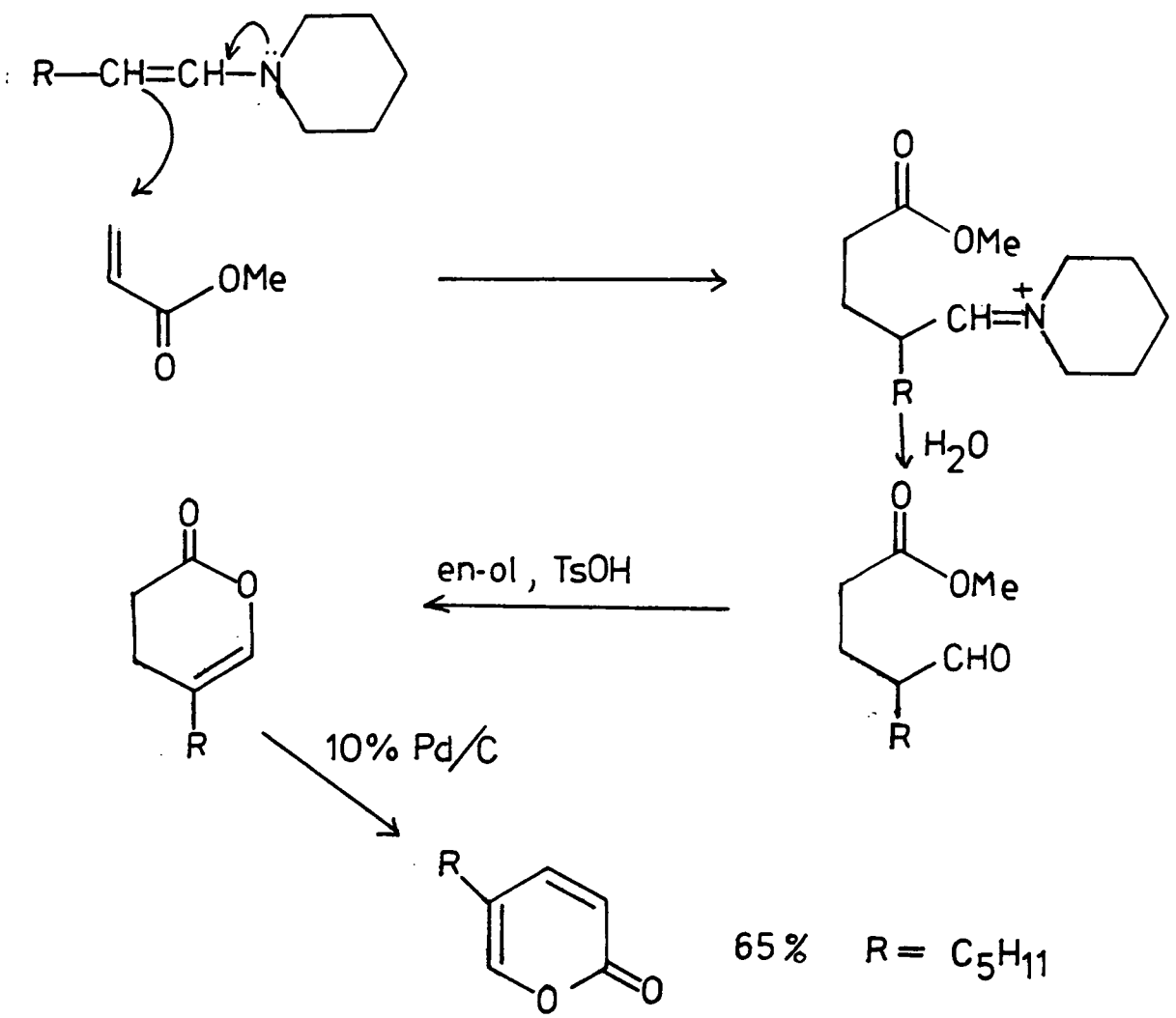
Both coumalic acid 2 (R^1=R^2=H) and isodehydroacetic acid 2 (R^1=R^2=Me) have been decarboxylated *via* various methods[11,12], indeed the mechanism of decarboxylation, during Flash Vacuum Pyrolysis[13] (F.V.P.), of these two compounds will be discussed later in this thesis. A

slight modification of type (ii) reactivity, involves the reaction between an active methylene compound and an alkynic ester[14,15]. This route allows different alkyl or aryl substituents to be introduced at C-4 and C-6. This method appears to have much variation, and could be the subject of further study (Scheme 5).



Scheme 5

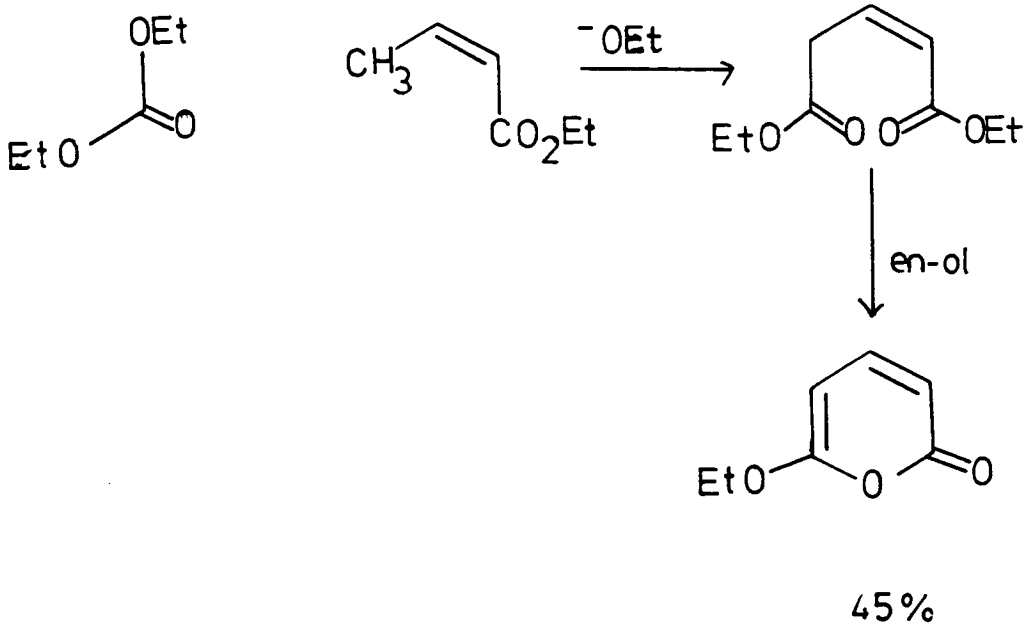
A reaction that has received little attention but produces mono alkyl compounds is shown below in Scheme 6. Only a few examples have been reported. Basically the reaction involves initial alkylation of an enamine by methylacrylate[16]; this reaction could also be developed further.


R—CH=CH—N
OMe
O
O
OMe
CH=N
R
H_2O
O
OMe
CHO
R
en-ol , TsOH
O
O
R
10% Pd/C
R
O
O
65 %
R = C_5H_{11}

Scheme 6

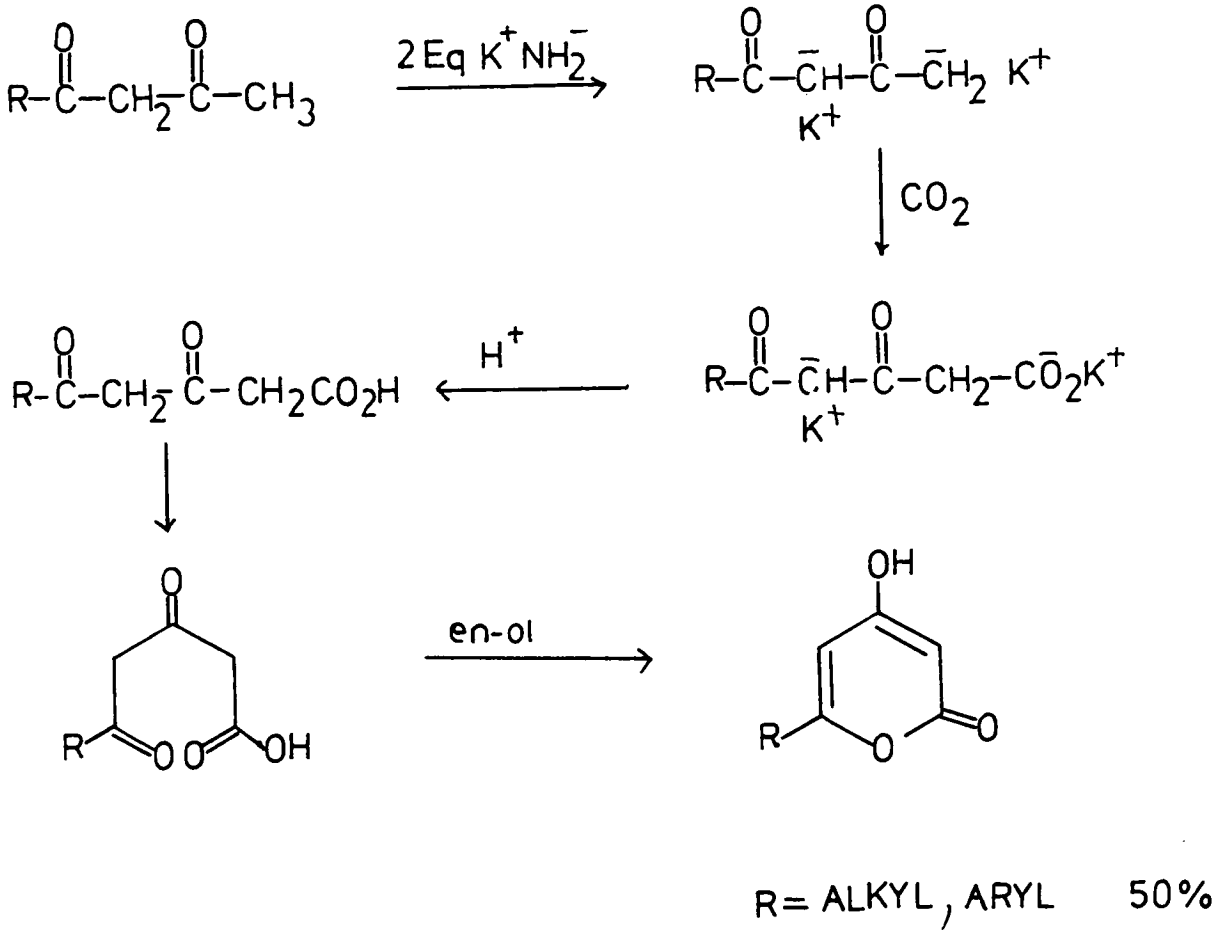
Type (iii) Reaction

This type usually involves reaction of unsaturated esters with diethyloxalate[11] in a cross Claisen type process (Scheme 7).



Scheme 7

A slight variation of (iii) which produces compounds with interesting biological activity[12], involves the carboxylation of the dianion of a diketone, followed by cyclisation (Scheme 8).



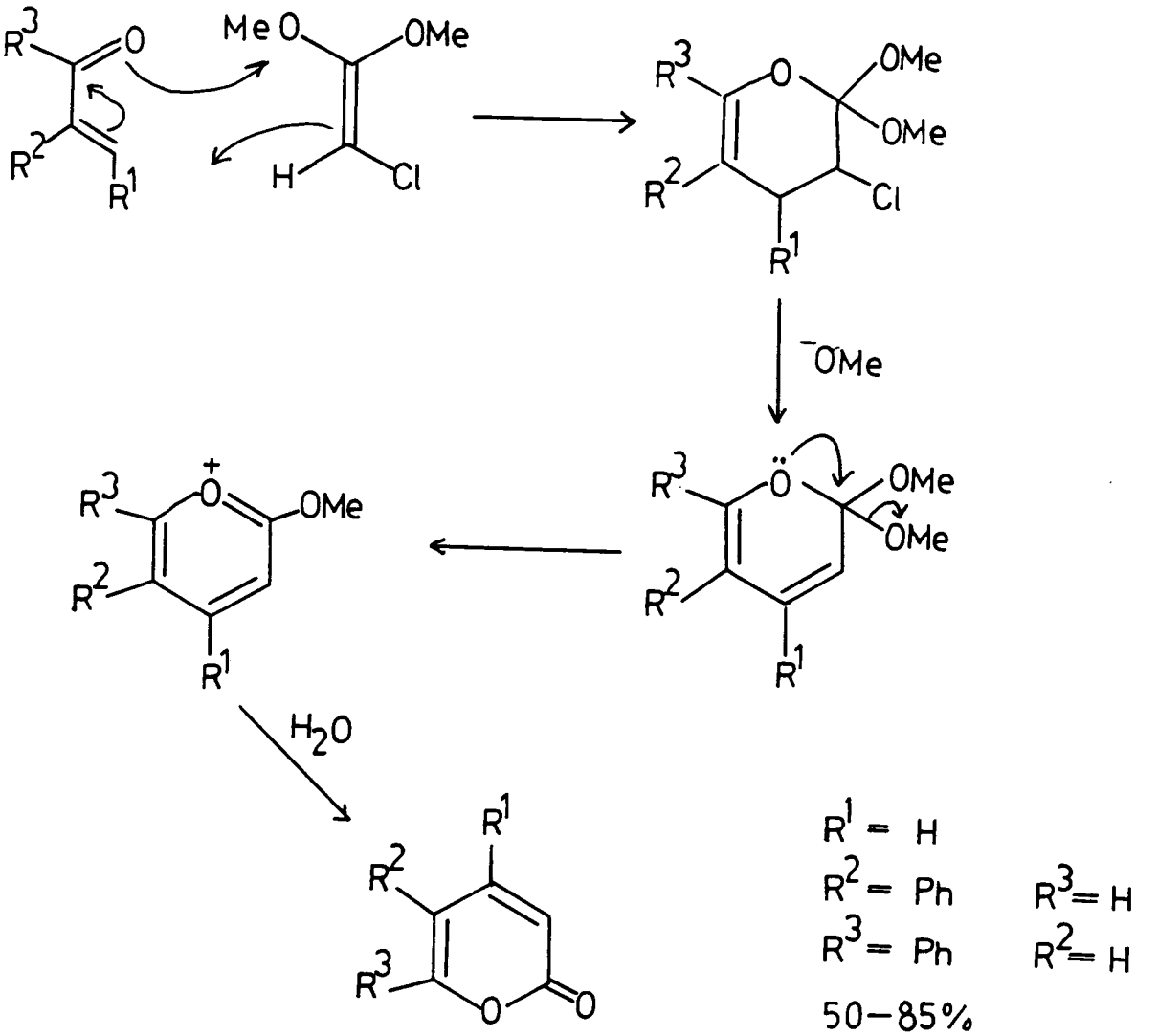
Scheme 8

In addition to the three general methods for synthesising 2-pyrones, there are a few other more modern routes and these will now be discussed.

The reaction between vinyl esters and unsaturated carbonyl compounds, which provides a powerful synthetic

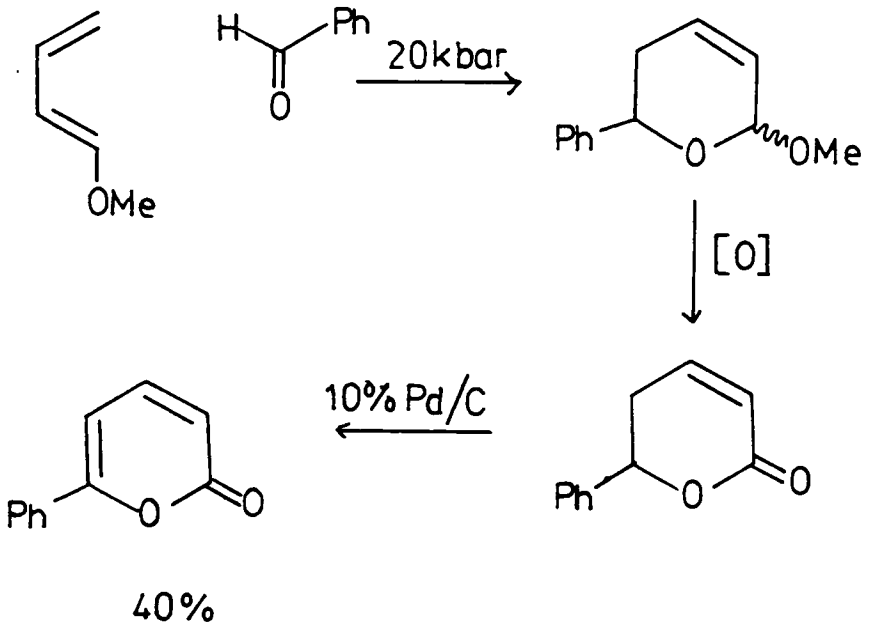
route to dihydropyrans, has been adapted for the synthesis of 2-pyrones.

2-Chloro-1,1-dimethoxethylene, which is a protected form of chloroketene, undergoes cycloaddition with a number of enones[18], a typical example is shown in Scheme 9.



Scheme 9

A more recent report[19] is more specialised and involves the high pressure cycloaddition of 1,3-butadienes and aldehydes (Scheme 10).

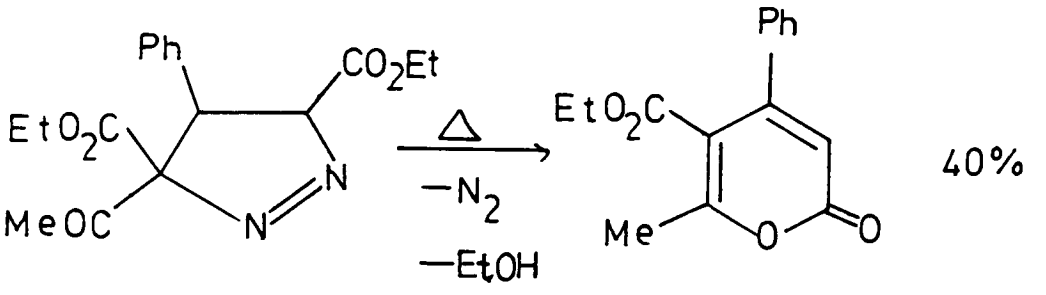


Scheme 10

This reaction appears to be quite useful and could possibly be applied to a whole range of alkyl or aryl aldehydes.

There are also three other less well known syntheses, but nevertheless, they exhibit some interesting chemistry and are worth mentioning. It has been known for quite

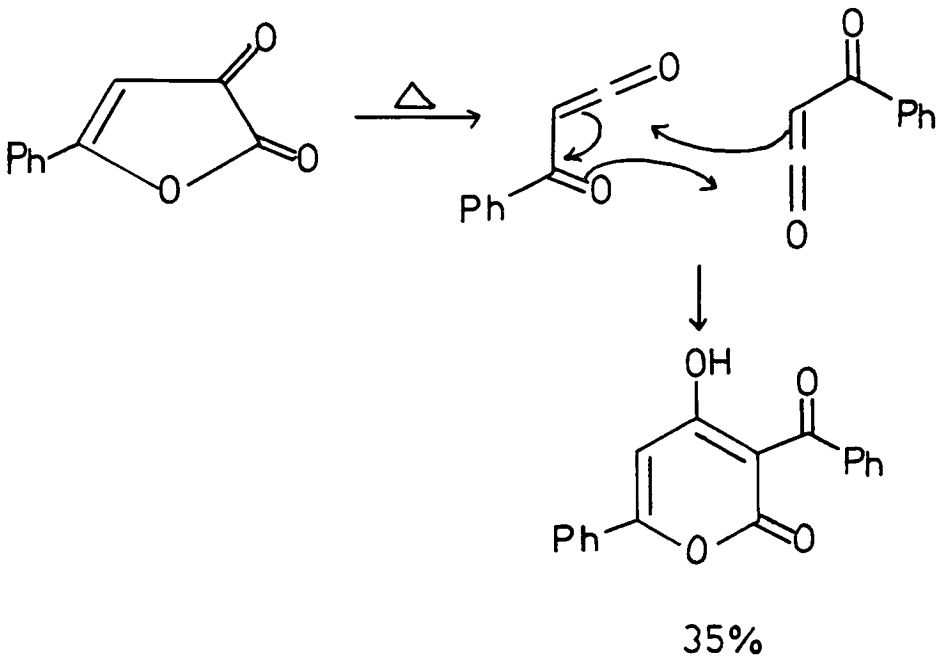
some time that certain pyrazolines undergo thermal ring opening with elimination of nitrogen, to give an intermediate, which cyclises producing the 2-pyrone (Scheme 11). The pyrazolines themselves are produced *via* a 1,3-dipolar cycloaddition of a diazoacetic ester and an unsaturated ketone[20,21].



Scheme 11

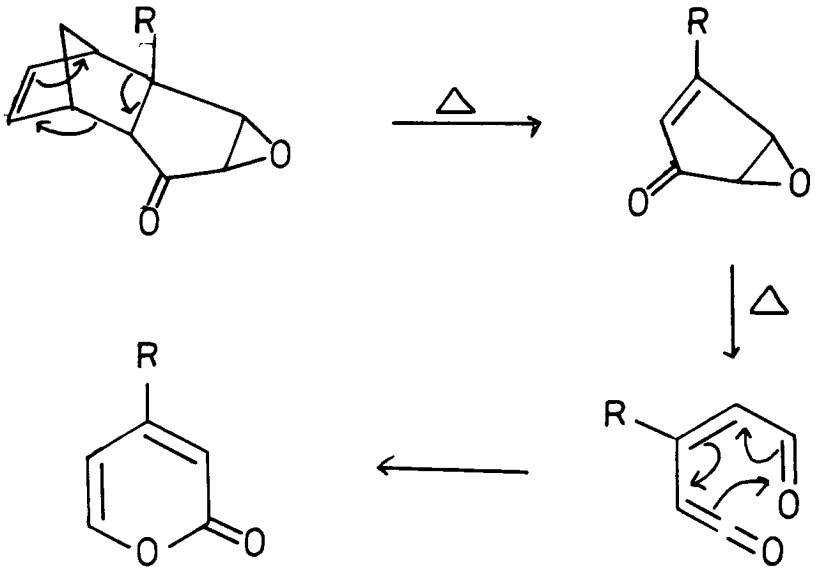
It may be possible to hydrolyse the ethyl ester produced, then decarboxylate to give the 4,6-disubstituted product. This pyrazoline method has received very little attention since these very early reports[20,21].

When heated 5-aryl-2,3-diones readily evolve carbon monoxide to give benzoyl ketenes[22] which dimerise *via* a [4+2] cycloaddition reaction. Studies have inferred that initial chelotropic cycloreversion of the furan is involved[22] (Scheme 12).



Scheme 12

Cyclopentadienone epoxides undergo rearrangement to 2-pyrones when they are subjected to Flash Vacuum Pyrolysis[23] (F.V.P.). A practical synthesis of these epoxides has been reported[24] involving thermal cycloreversion of functionalised tricyclo[5.2.1.$0^{2,6}$] decenone epoxides (Scheme 13).



75% R= CHO, CH_2OH, CO_2Et

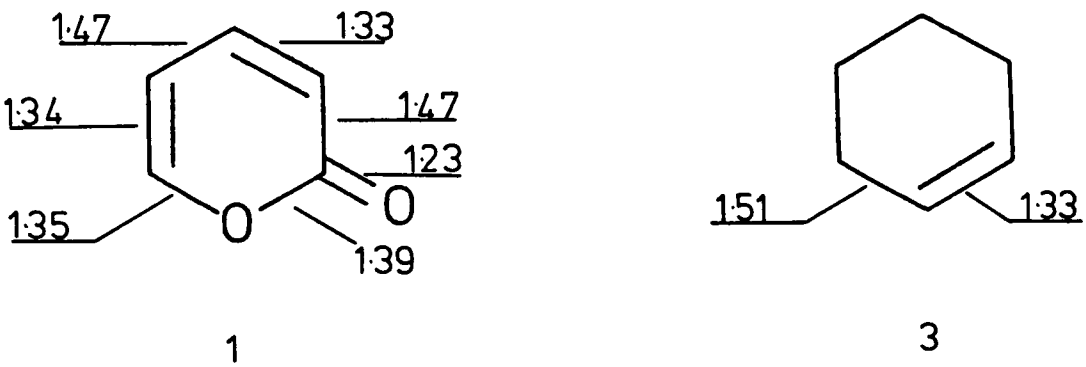
Scheme 13

This reaction is of particular interest as the ketene intermediate which undergoes electrocyclic ring closure has been crucial to the studies undertaken in this thesis and will be discussed later.

PHYSICAL PROPERTIES OF 2-PYRONES

1. Structure Determination

A large number of six membered oxygen containing heterocycles have been investigated by X-ray techniques[25], but there are very few examples concerning simply substituted 2-pyrones. However the structure of the parent, unsubstituted 2-pyrone 1 was determined by microwave spectroscopy[26] (Figure 1).



1 3

Figure 1: Bond Lengths in Å of 2-pyrone 1 and a related model compound 3

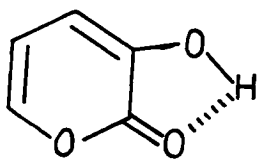
Comparing bond lengths of 1 and 3[27], it appears that there may be some delocalisation associated with the 2-pyrone ring as the single bonds of 1 are somewhat shorter than the unconjugated single bonds of 3.

Also the carbonyl bond length of 1 is 1.23 Å. This is slightly longer than the carbonyl bond length of

acyclic esters, 1.19 Å, again suggesting delocalisation to some extent.

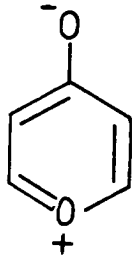
2. Infra Red Spectrometry

2-Pyrones are characterised by absorption at 1730-1704 cm^{-1} associated with the ring carbonyl group[28], which may sometimes be accompanied by a second less intense band at higher frequency[29] (1770-1740 cm^{-1}). The carbonyl stretching frequency is sensitive to substitution and numerous reports have been published[30,31,32,33]. For example a red shift is caused by an α-bromine atom, but the presence of a 3-hydroxy group brings about a more significant shift of the carbonyl stretch to a lower wavenumber (1685 cm^{-1}). This, together with the appearance of a broad band at 3200 cm^{-1}, established that a 3-hydroxy-2-pyrone exists in a hydrogen bonded enolic form 4 rather than the tautomeric pyran-2,3-dione.

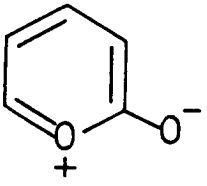


4

In contrast the 4-pyrone system typically absorbs at 1640 cm^{-1}. The different carbonyl stretching frequencies of the 4-pyrone and 2-pyrone system is a reflection of the stronger basicity of 4-pyrone. The effects of substitution on this absorption band are smaller in 4-pyrones, and this feature has been attributed to a more significant contribution of the delocalised structure 5 than the contribution of 6 to the 2-pyrone structure[34].



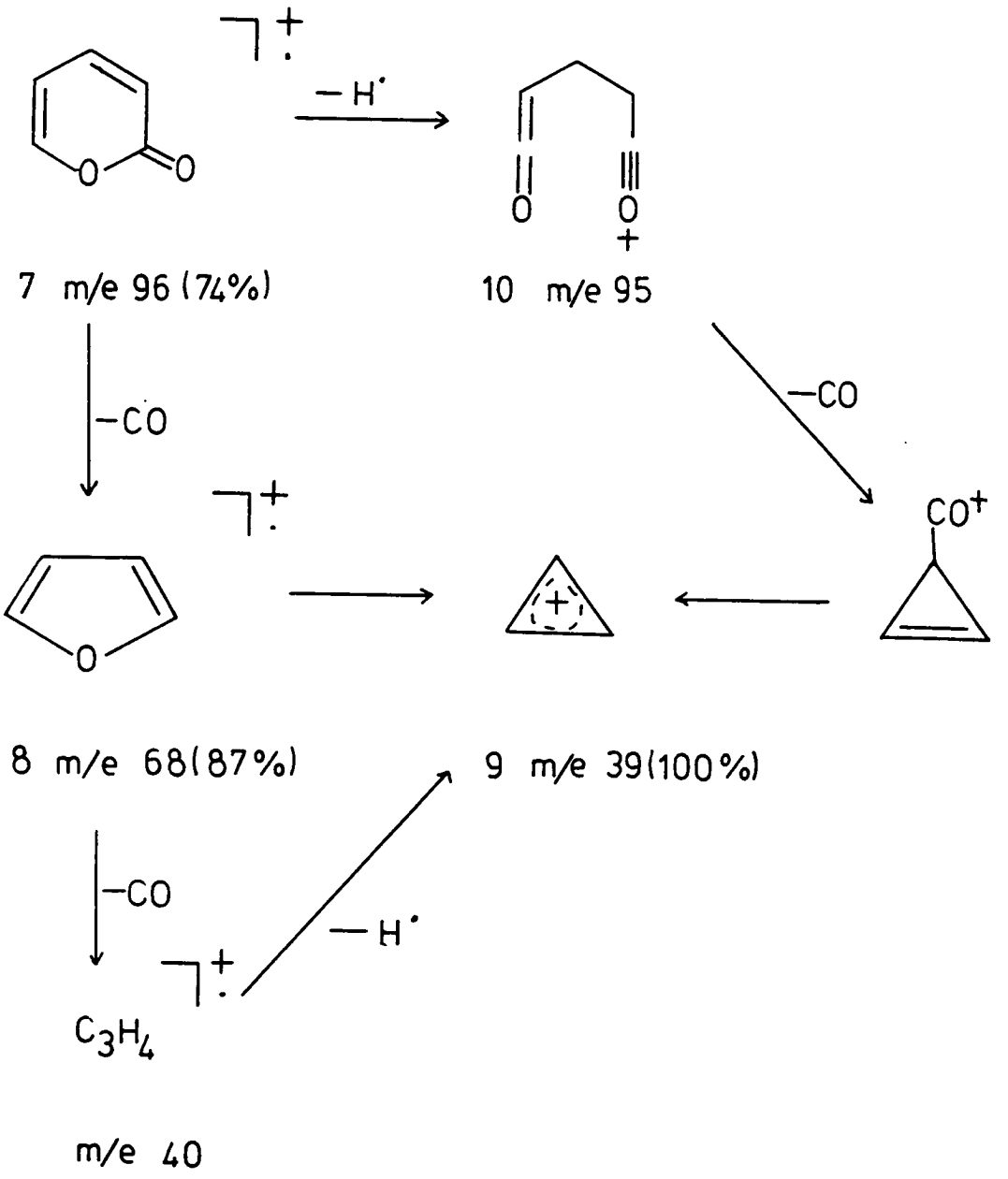
5



6

3. Mass Spectra

The mass spectrum of 2-pyrone has received detailed attention[35], the proposed fragmentation breakdown mechanism is shown below, Scheme 14.



Scheme 14

The spectrum displays three prominant peaks. The molecular ion 7 is of high abundance, whilst carbon monoxide loss produces an ion at *m/e* 68, corresponding to $[C_4H_4O]^+$. Collision activation mass spectral studies have demonstrated that the non fragmenting $[M-CO]^+$ ions derived

from 2-pyrones consisted predominantly of furan radical cations[36] 8. The cyclopropenium ion 9 appears as the base peak. A further decomposition mode of 7 involves loss of a hydrogen radical to produce 10, from which the direct elimination of two 'CO' molecules occur in a stepwise manner to furnish 9. It appears that fragmentation by loss of carbon monoxide is of general importance to 2-pyrones, this is of interest as later on in the discussion section of this thesis a proposed decarbonylation mechanism of a 2-pyrone is discussed in detail. Some excellent reviews[37,38,39] concern themselves with various substituted coumarins which fragment giving analogous benzofuran species.

4. NMR Spectroscopy

4.1 ^{1}H nmr

The spectrum of the parent 2-pyrone (1) consists of two multiplets of equal intensity centred at δ7.38 and δ6.25 ppm. Previous work at 60 MHz was unable to resolve the long range couplings by inspection, and computational models were employed[40,41]. However, a sample of 2-pyrone was prepared (see Discussion section) and its 200 MHz ^{1}H nmr recorded (Figure 2).

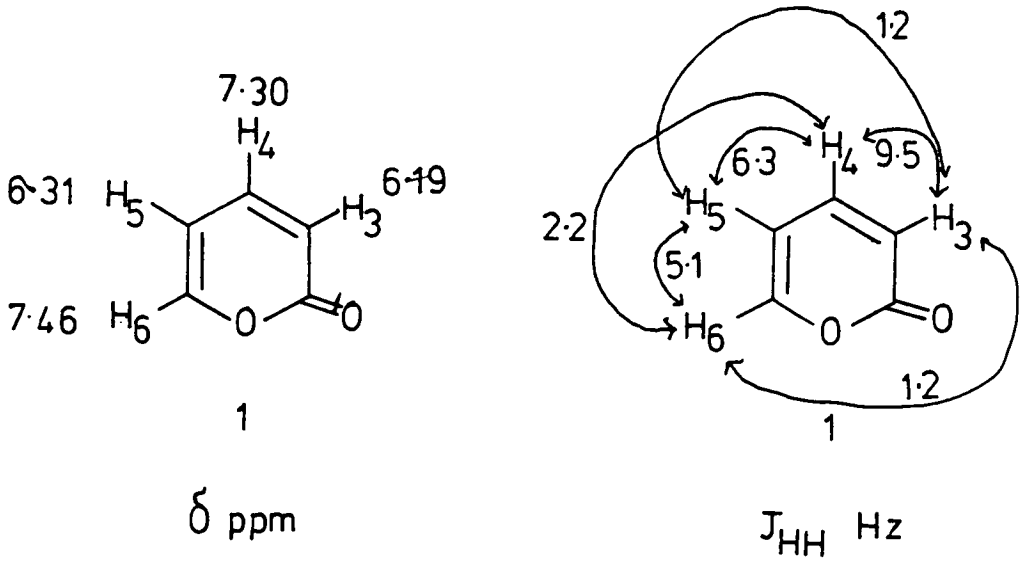


Figure 2. ^{1}H nmr Spectra of 1

The order of ^{1}H shifts, $H_6>H_4>H_5>H_3$ is usually maintained even when positions are substituted; a few examples are shown below (Figure 3).

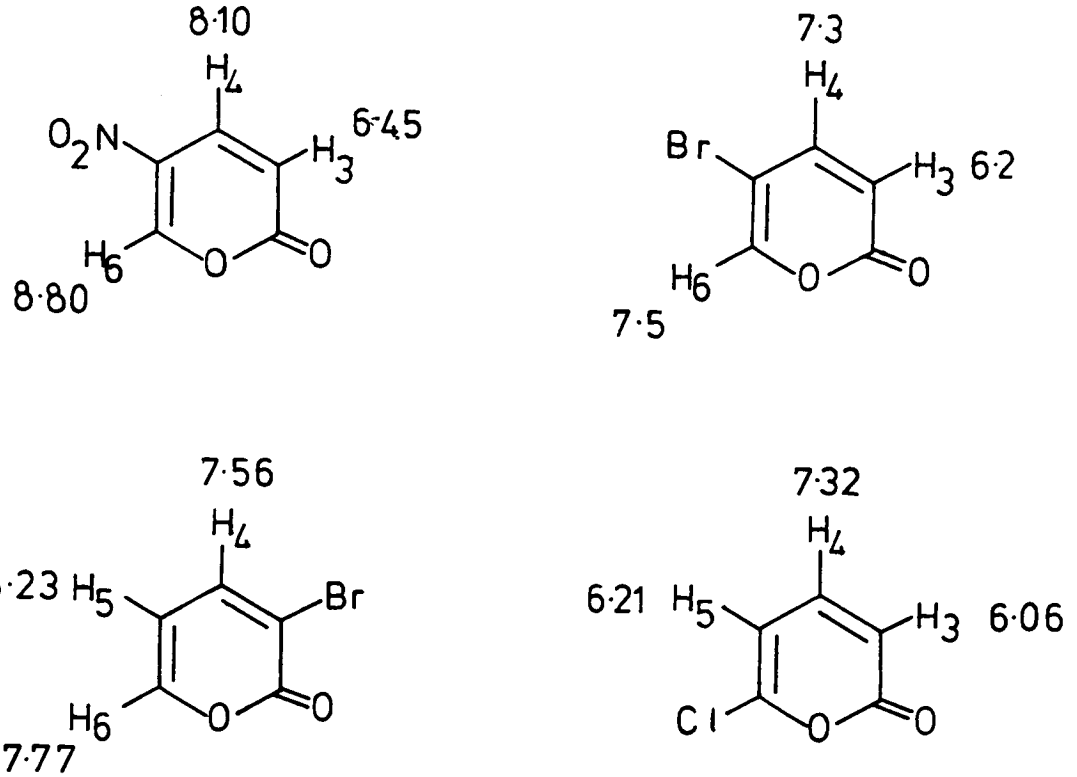


Figure 3. ^{1}H nmr Data of some 2-Pyrones

Various other substituted 2-pyrones have been examined by ^1H nmr spectroscopy[40,41,42] for establishing the position of substituents on the 2-pyrone ring since it was found that their nature has little effect on the coupling constants of the ring protons[40,41]. This consistency of J values has been invaluable to the work undertaken in this thesis and a few examples are shown below (Figure 4).

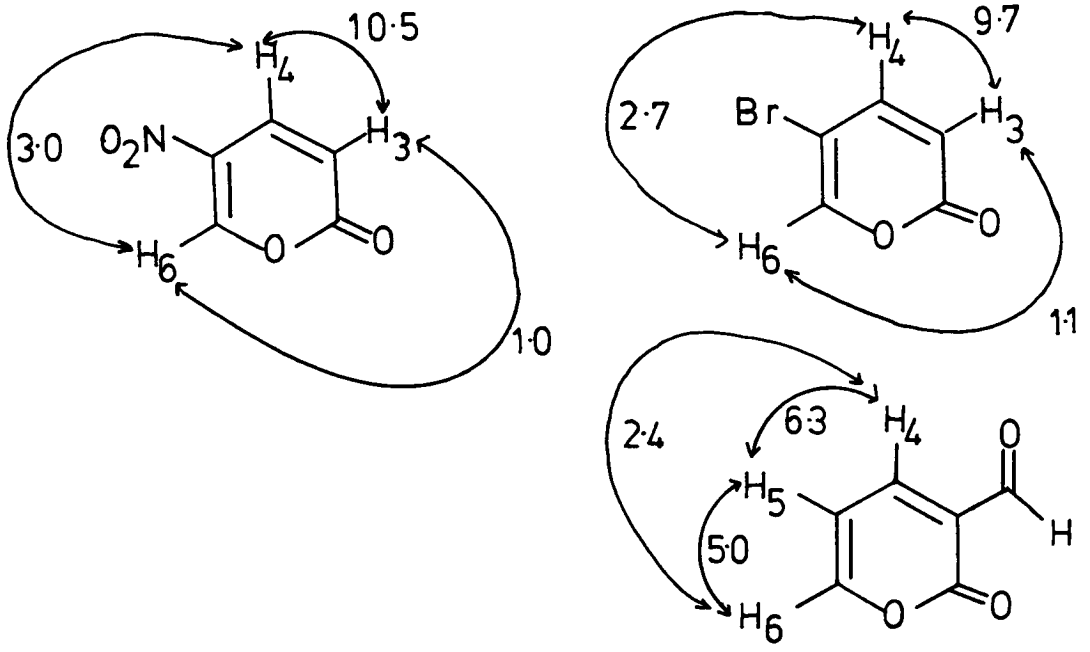
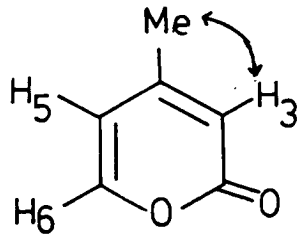


Figure 4. Coupling Constants J_{HH} of some 2-Pyrones

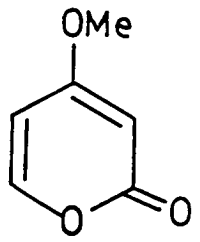
It is also interesting to note that the $^3J_{3,4}$ coupling is quite large (10 Hz) while the $^3J_{5,6}$ coupling is considerably less (5 Hz). Surprisingly the $^3J_{4,5}$ coupling is larger than the $^3J_{5,6}$. Localisation of these double bonds has been suggested[43] by the observation that in the proton spectra of the 4-methyl compound 11, H-3 but not H-5 is coupled to the 4-methyl group.



11

4.2 ^{13}C nmr

Much work has been carried out on the ^{13}C nmr spectra of 2-pyrones and their derivatives, largely because the structural information which accrues can be extrapolated to the many naturally occurring compounds which incorporate these systems. A study of the parent 2-pyrone and a number of its simple derivatives showed that C-6 and C-4 resonances occurred at high frequency relative to those from C-3 and C-5, consistant with localisation of positive charges at the former positions[43], C-6 and C-4. The overall order being C-2>C-6>C-4>C-3>C-5. A comparison of the spectra of 1 and 12 (shown below) indicated that



12

whilst both C-3 and C-5 are deshielded by the introduction of a 4-methoxy group the shift of the former (25 ppm) is much larger than that of the latter (3 ppm). It was thus postulated that the degree of double bond character between C-3 and C-4 is much greater than that between C-4 and C-5. The carbonyl (C-2) resonance is virtually unaffected by substituents. Some ^{13}C nmr data together with $^{1}J_{C-H}$ couplings of various 2-pyrones is shown (Table 1).

Table 1.

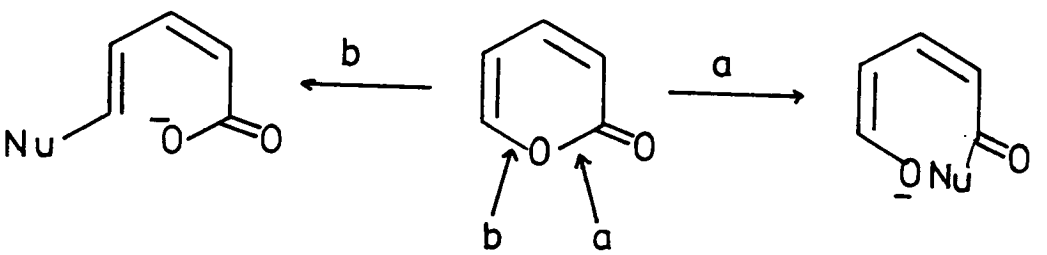
		Chemical Shift (ppm) (J_{C-H}, Hz)						
R	Solvent	C-2	C-3	C-4	C-5	C-6	R	Ref
H	$(CD_3)_2CO$	162.0	116.7(170)	144.3(173)	106.8(173)	153.3(200)		43
4-Me	$CDCl_3$	161.8	113.7(169)	156.1	109.3(169)	151.1(200)	21.1	43
5-Me	"	161.2	115.7(171)	146.5(162)	114.7	148.0(197)	14.4	43
3-CO_2Me	"	157.3	118.0	148.6	105.9	156.6	163.8 52.6	(C=O)44 (Me)

$^{13}C-^{1}H$ coupling constants have been obtained for a number of 2-pyrones. A value of 200 Hz is typical for $^{1}J_{C-H}$ of carbon atoms attached to oxygen in aromatic heterocycles[45]. $^{1}J_{C-H}$ values for C-3 and C-5 are usually around 170 Hz. The parent 2-pyrone shows sixteen long range couplings[46], the five different carbon atoms couple to each of the four non-equivalent protons.

REACTIONS OF 2-PYRONES

5. Reactions of 2-Pyrones with Nucleophiles

Several kinds of nucleophiles react with 2-pyrones and related coumarins; some of these reactions involve ring opening and occasionally, recyclisation into another ring (this recyclisation has been used to good effect in this thesis and will be discussed later). A nucleophile (Nu) which cleaves the ring, attacks to break one of the bonds of the ring oxygen atom as shown below (Scheme 15).

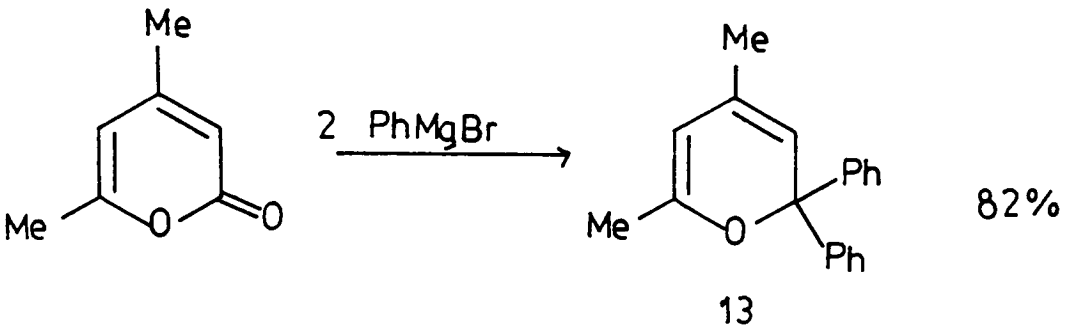


Scheme 15

Much work has been done on these nucleophilic reactions, but the most common reagents used are C, N and O nucleophiles.

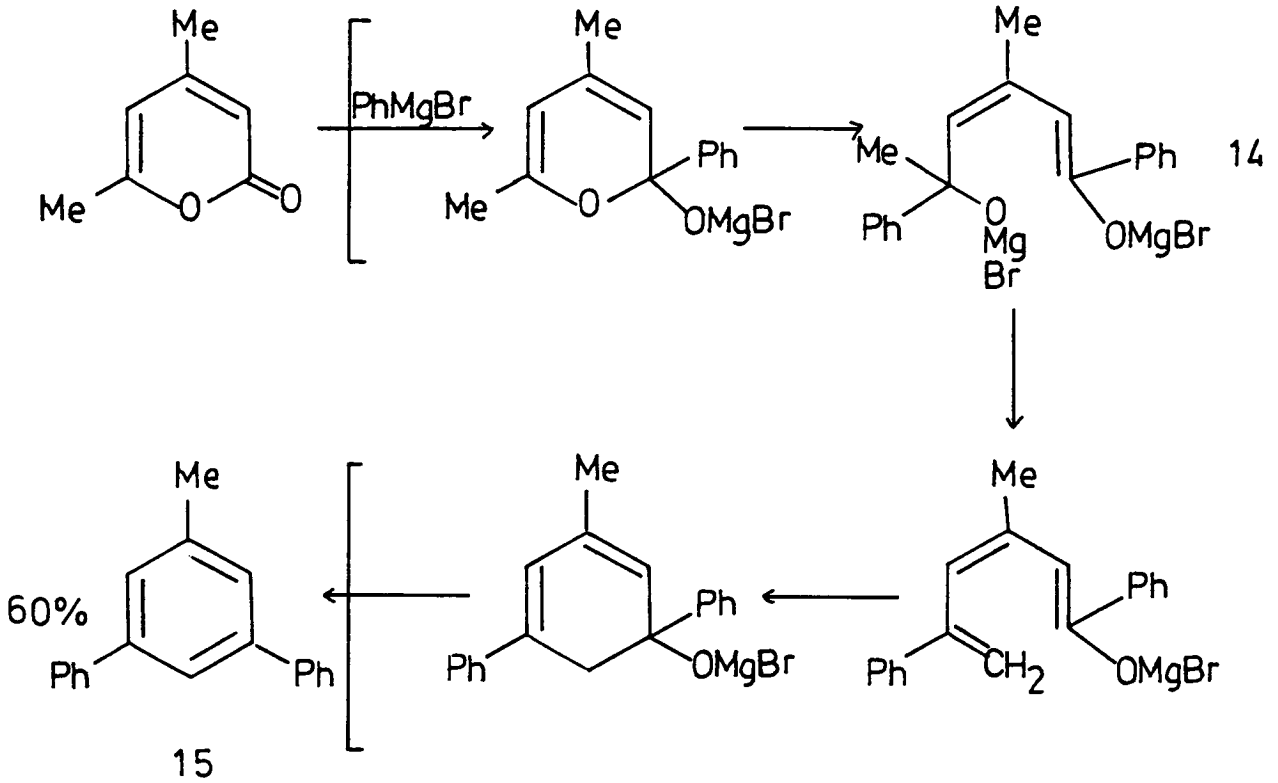
5.1 C-nucleophiles

The most widely used and synthetically useful nucleophilic reactions of 2-pyrones are those of organometallic compounds containing magnesium, lithium or zinc. The products obtained depend on the molar ratio of reagents and on the substituents already present on the ring. With two moles of reagent, a 2,2-disubstituted pyran 13, or chromene, is produced. An example is shown below (Scheme 16).



Scheme 16

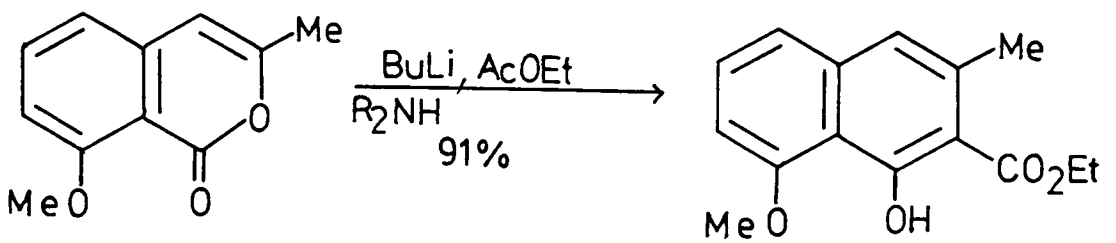
There are many examples of this kind of reaction[47,48,49]. If, however, a larger excess of reagent is used, and provided a methyl group is available at C-6, then the pyrone ring is cleaved to a dienone equivalent 14, which reacts with another molecule of reagent. The methyl group then becomes a member of a newly formed benzene ring[50] 15 (Scheme 17).



Scheme 17

Due to the limitations of obtaining 6-methyl 2-pyrones in the first place the reaction has been seldom used. However, conversion of 2-pyrones into benzene rings can be effected by employment of a Reformatsky reagent, e.g. $BrZnCH_2CO_2Et$, or the corresponding lithium compound ($LiCH_2CO_2Et$). The latter reagent has the advantage that any alkoxy groups present are unaffected by the

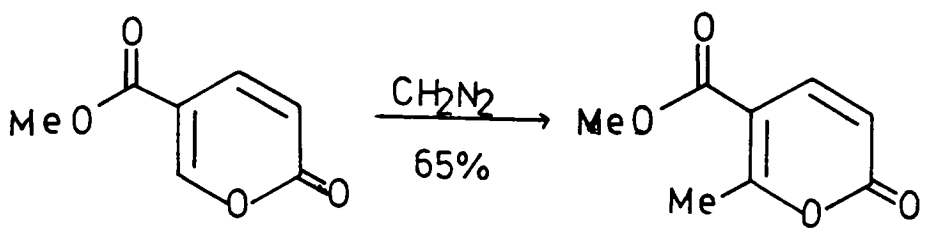
dealkylating action of zinc bromide: the reaction of the isocoumarin 16 is a good example[51] (Scheme 18).



16

Scheme 18

The nucleophilic carbon of diazomethane can also attack the ring of 2-pyrones, especially when electron withdrawing substituents are present. One of the earliest examples is the methylation of methyl coumalate[52,53] 17 (Scheme 19).

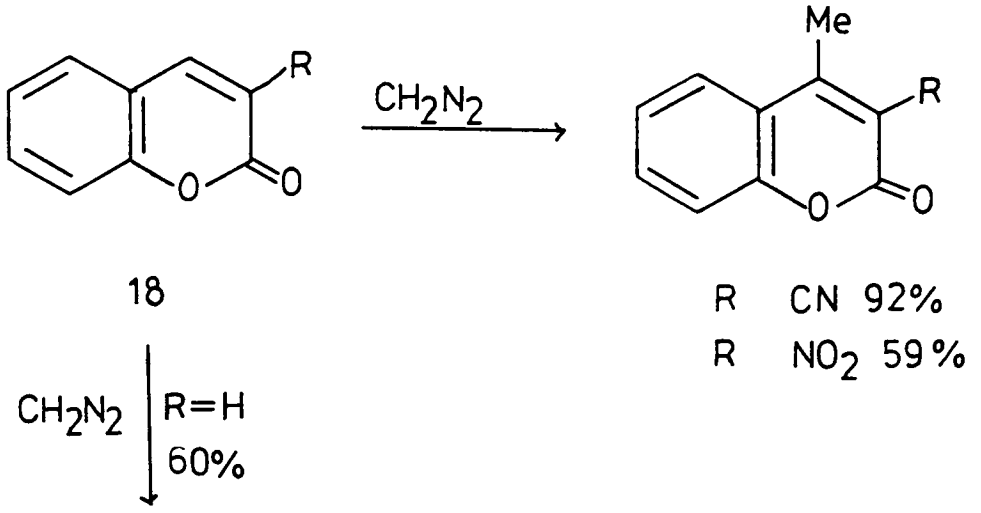


17

Scheme 19

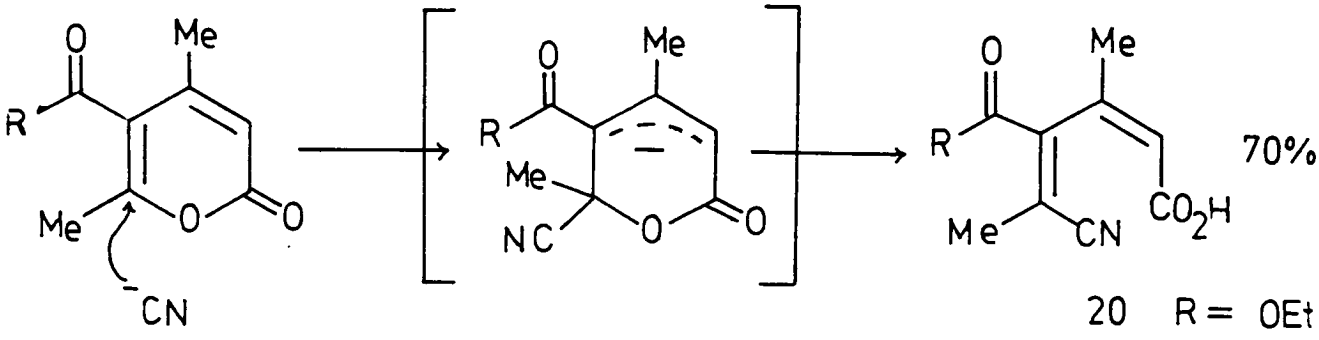
Diazomethane has been used in this thesis for methylation of a similar 2-pyrone derivative, and will be discussed later.

3-Cyano and 3-nitrocoumarin 18 are also readily converted into their 4-methyl homologues[54], but the parent coumarin is transformed to the pyrazolone[55] 19 (Scheme 20).



Scheme 20

Cyanide ion attacks at the 1,6-bond under mild conditions producing a ring opened species 20. A typical example is shown below[56] (Scheme 21).

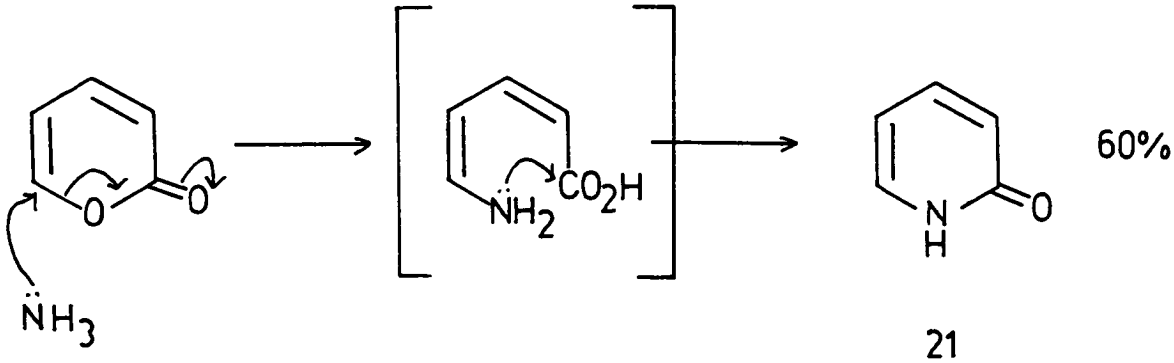


20 R = OEt

Scheme 21

5.2 N-nucleophiles

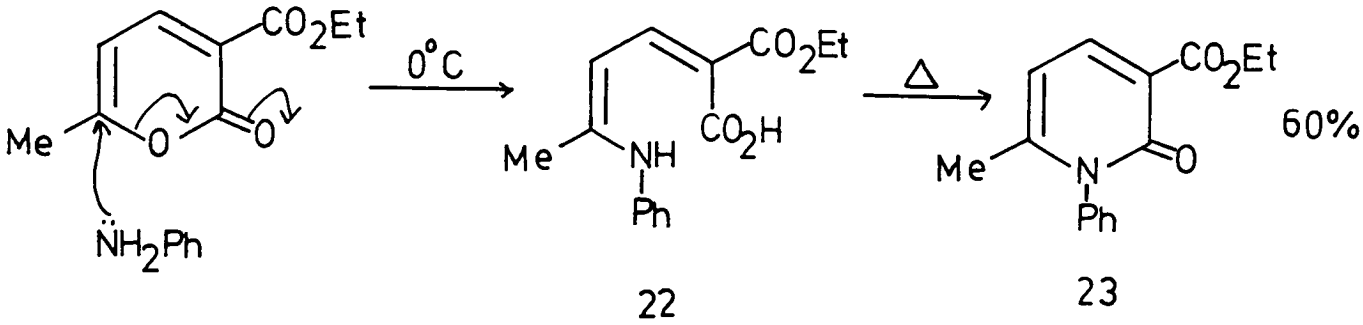
Ammonia and amines cause ring opening of 2-pyrones and the acyclic products may cyclise again to produce pyridones. Treatment of the parent 2-pyrone with ammonia[57], causes attack at the 6-position, followed by immediate ring closure to the pyridone 21 (Scheme 22).



21

Scheme 22

This reaction has been used to good effect in this thesis and will be discussed in detail later. With certain 2-pyrones the "intermediate" acyclic product may be isolated[58] 22 (Scheme 23).

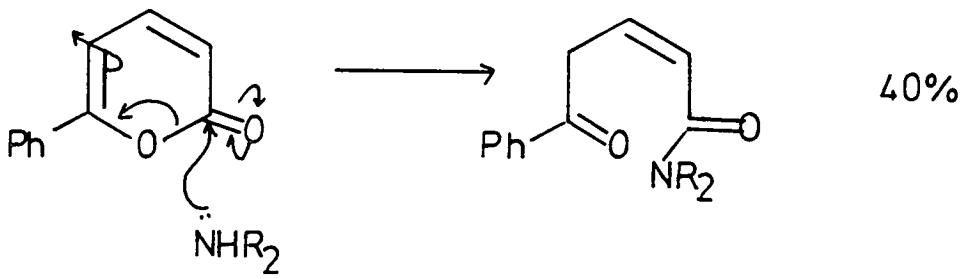


Scheme 23

Increasing the temperature, in this case, affords the ring closed product 23.

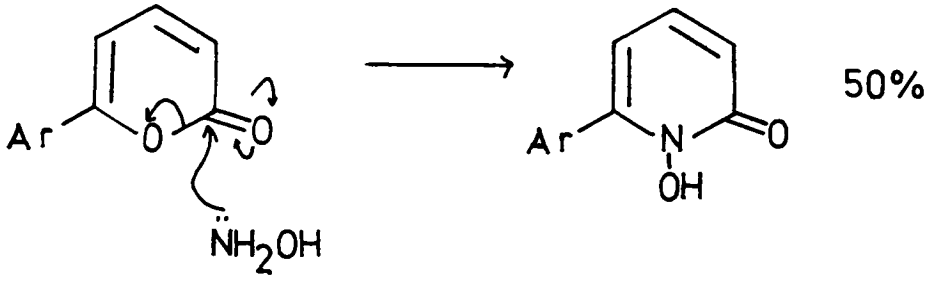
Secondary amines, obviously only produce the initial acyclic product (cf. 22).

If a substituent with large steric bulk is in position 6 then attack of the amine - particularly secondary amines - is directed to the 2 position. A typical reaction is shown below[58] (Scheme 24).



Scheme 24

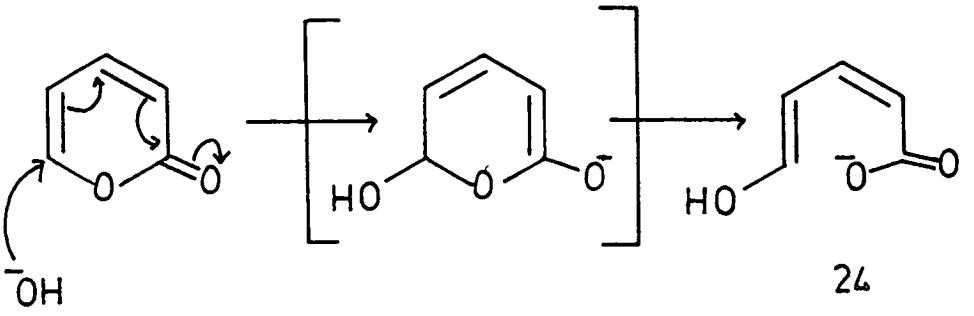
Hydroxylamine converts 2-pyrones into the *N*-hydroxypyridone[59]; the position of initial attack on the ring is uncertain, but it is thought to proceed *via* initial attack at the carbonyl group, when the 6-position is substituted (Scheme 25) (cf. Scheme 24).



Scheme 25

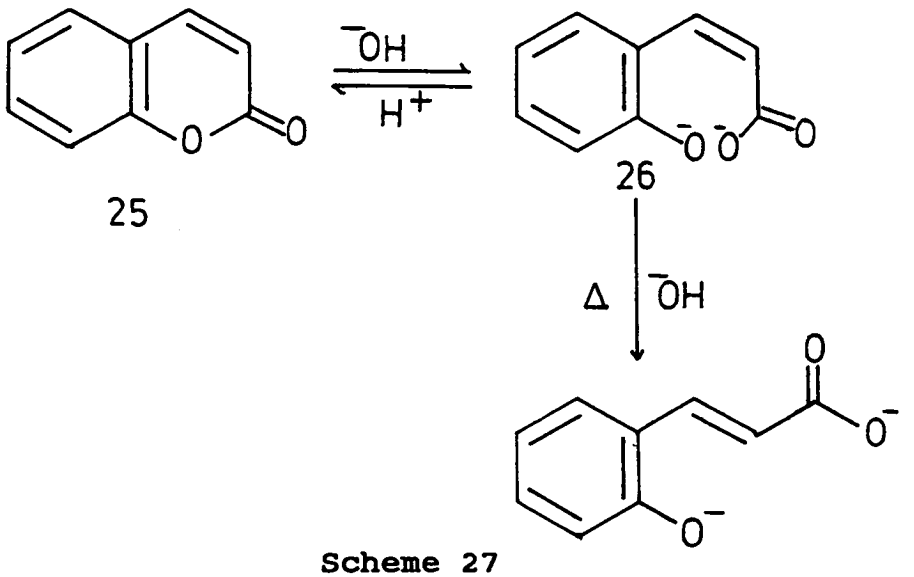
5.3 O-nucleophiles

Aqueous alkali hydrolyses 2-pyrones and the products, i.e. 24 are frequently unstable or recyclise, depending on other substituents present[60] (Scheme 26).



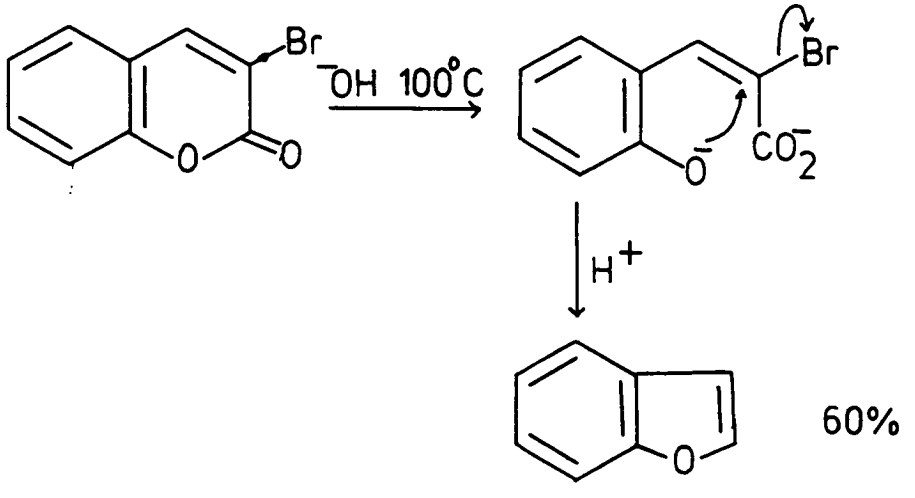
Scheme 26

In the benzofused series these ring opened products are much more stable, thus, coumarin 25 is hydrolysed by dilute alkali first to the yellow *cis* acid (coumarinic acid) salt, 26, which recyclises to coumarin on acidification, but when heated with alkali isomerises to the *trans* acid (coumaric acid) salt[60] 27 (Scheme 27).



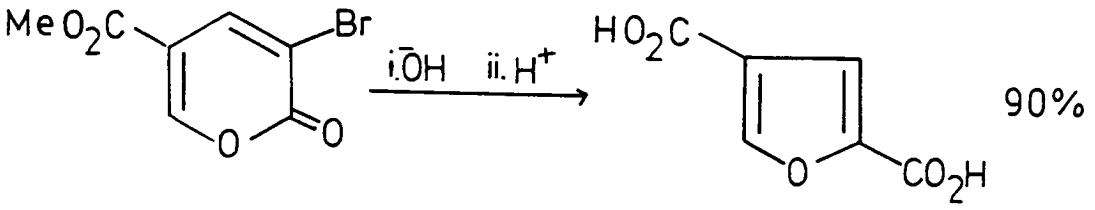
Scheme 27

If however bromine is at position 3 then an alternative pathway is followed - an intramolecular nucleophilic reaction producing a furan[60] (Scheme 28).



Scheme 28

Similarly methyl-3-bromocoumalate 28 gives an excellent yield of the corresponding furan derivative[61] 29 (Scheme 29).



28 29

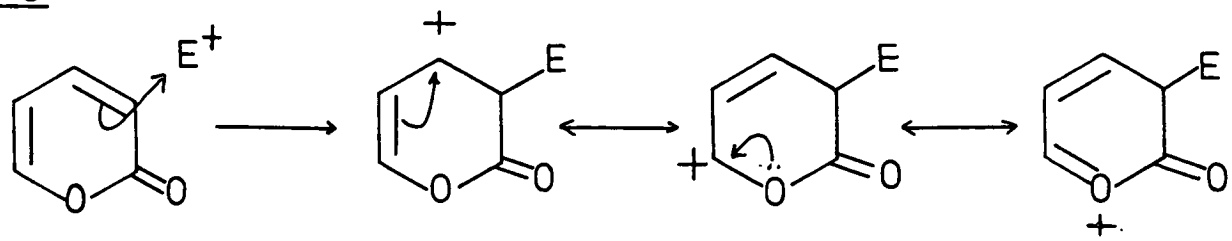
Scheme 29

There are many other examples of hydrolyses of various 2-pyrones and coumarins[62-65].

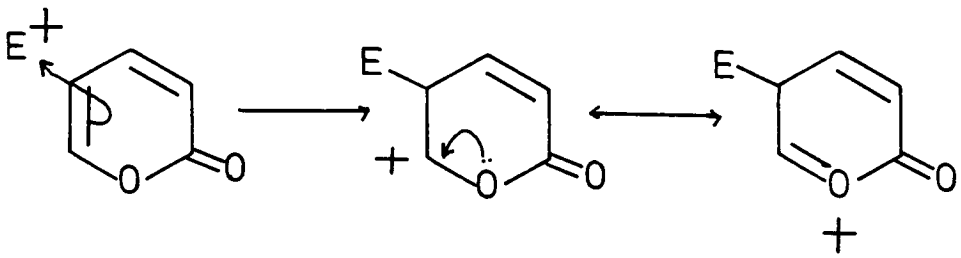
6. Reactions with Electrophiles

Upon examination of the parent 2-pyrone, it appears that electrophiles would react preferentially at C-3 and C-5 rather than C-4 or C-6, due to stabilisation of the positive charge which develops on the pyrone ring (Scheme 30).

C–3



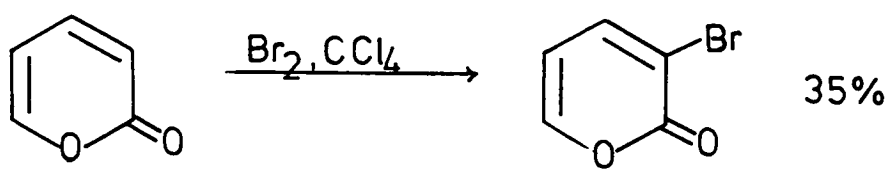
C–5



Scheme 30

As expected on the basis of simple considerations of resonance structures, it is found that C-3 substitution dominates for a variety of electrophilic reagents.

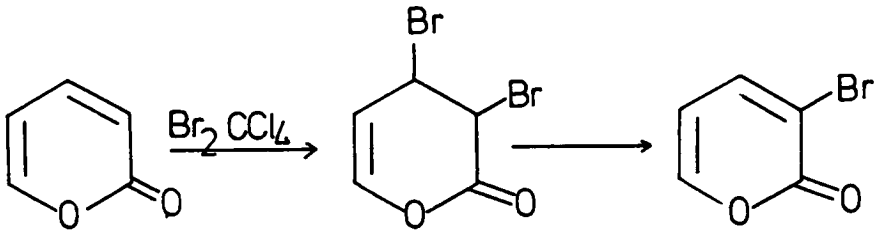
This is indeed found when the parent 2-pyrone 1 is treated with bromine in carbontetrachloride (Scheme 31).



1

Scheme 31

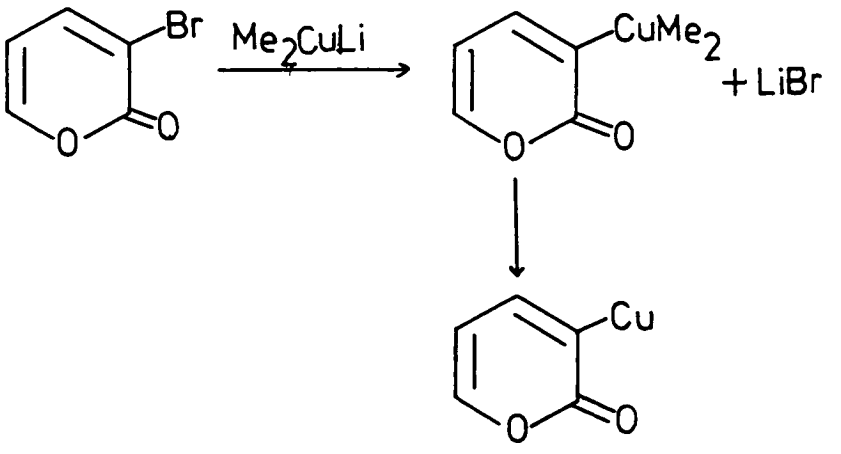
However, Pirkle found that this isolable product was not initially present in the complex bromination product mixture. Further investigations indicated that the mechanism of bromination and chlorination[66] proceeds *via* an addition elimination sequence, quite different from aromatic electrophilic substitution (Scheme 32).



30

Scheme 32

This 3-bromo compound 30 has received much attention as it reacts with (dimethyl copper)lithium[67] to produce 3-cuprio-2-pyrone 31 (Scheme 33).

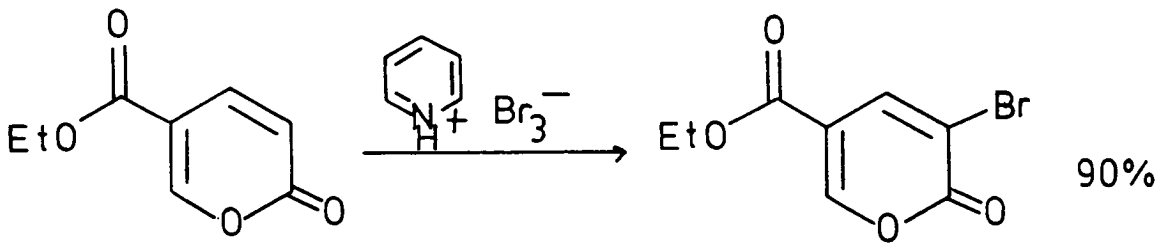


31

Scheme 33

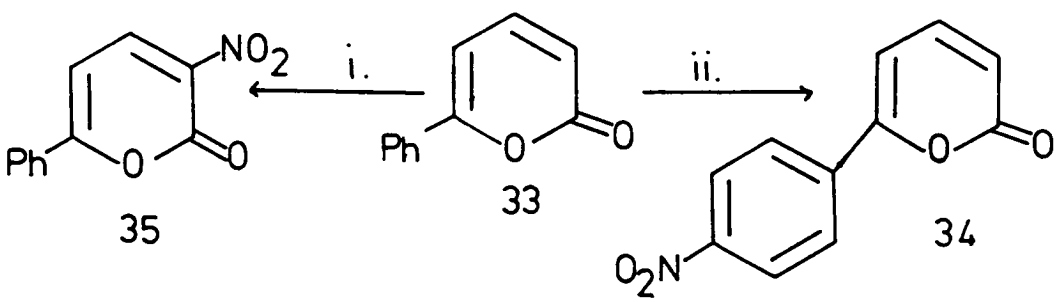
This organo-copper reagent has been the subject of many investigations[67-72] due to its extraordinary behaviour.

Bromination has also been achieved very effectively by the use of pyridiniumhydrobromide perbromide[73] on ethyl coumalate 32 (Scheme 34).



32 **Scheme 34**

The nitration of 6-phenyl-2-pyrone 33 gives an insight into the comparative reactivity of the two rings towards nitronium ion. With 94% nitric acid or mixed nitric and sulphuric acids, the 4-nitrophenyl isomer 34 is formed, but with 67% nitric acid yields the 3-isomer[74] 35 (Scheme 35).



35 33 34

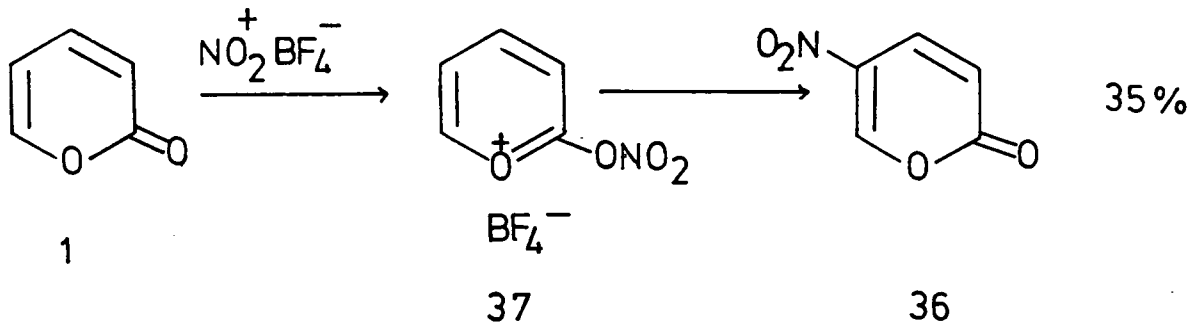
i. 67% HNO_3

ii. 94% HNO_3

Scheme 35

A plausible explanation for these observed differences is that in very concentrated acids the pyrone is protonated at the carbonyl oxygen, thus becoming deactivated thus directing the substitution onto the aromatic ring.

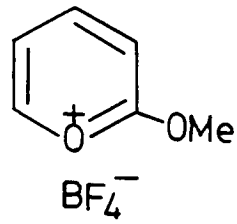
An alternative nitration method, which gives a surprising result, involves the use of nitronium tetrafluoroborate, and gives a moderate yield of the 5-substituted compound 36. It has been postulated that a two stage reaction is involved probably *via* a 2-nitrate ester[75] 37 (Scheme 36).



Scheme 36

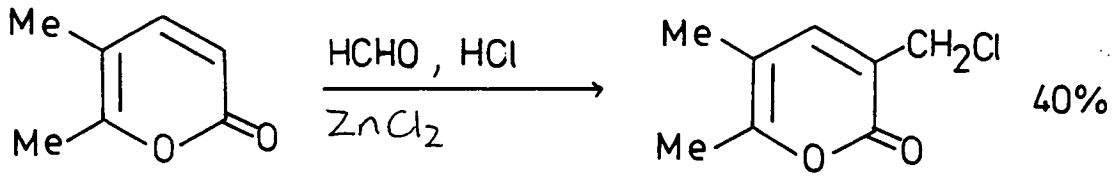
The adduct between 2-pyrone and nitronium ion which forms initially has been very tentatively assigned as 37, since its emerging ^1H nmr spectrum is very similar in appearance and chemical shift to that of the methoxypyrylium salt 38 which in turn is produced by methylation of 2-pyrone with trimethyloxonium

tetrafluoroborate[76].



38

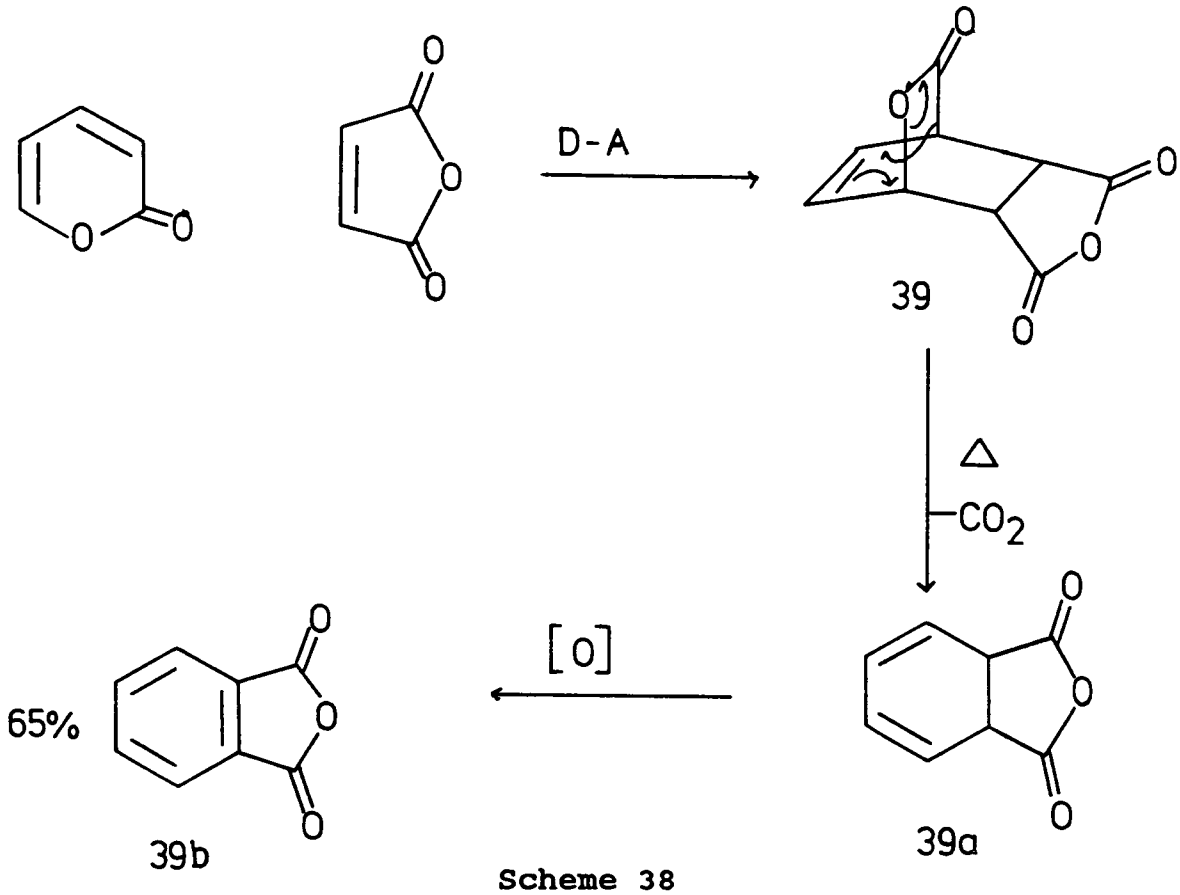
A seldom used reaction is the chloromethylation of 2-pyrones[77], which proceeds at C-3. The mechanism is thought to be analogous to that of benzene type substrates. A typical example is shown below (Scheme 37).



Scheme 37

7. Diels-Alder Reactions

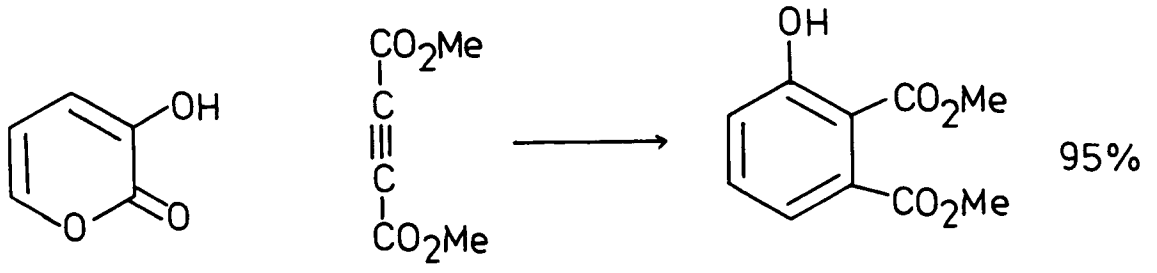
Perhaps the most useful reaction of 2-pyrones is their ability to act as dienes in Diels-Alder reactions[78]. The parent 2-pyrone 1 reacts with maleic anhydride to give the expected *endo* adduct[79,80] 39 (Scheme 38).



Scheme 38

Prolonged heating converts some adducts (cf 39) into benzenoid compounds *via* loss of carbon dioxide[81,84]. Oxidation of these compounds, i.e. 39a produces the aromatic ring 39b.

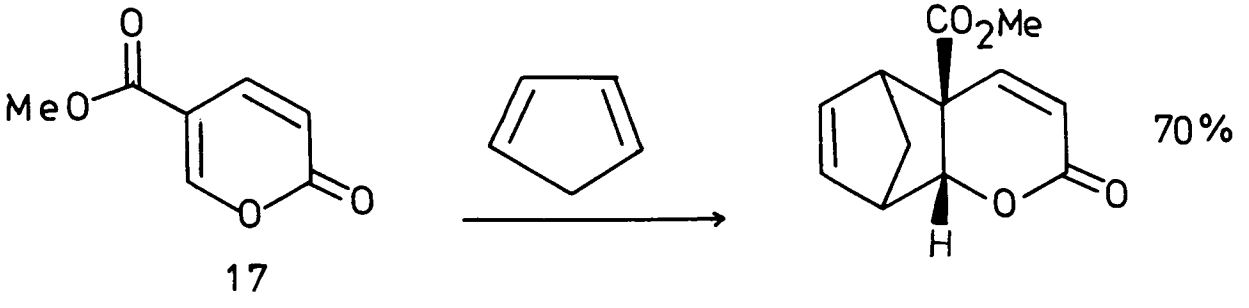
This type of methodology has been extended to Diels-Alder reactions with various acetylenes[82,83], which have the advantage over alkene dienophiles (cf Scheme 38) in that milder conditions are usually employed and no oxidation step is needed to form the benzene ring, one such example is shown below (Scheme 39).



Scheme 39

There are many examples of this type of reaction with acetylenes[85].

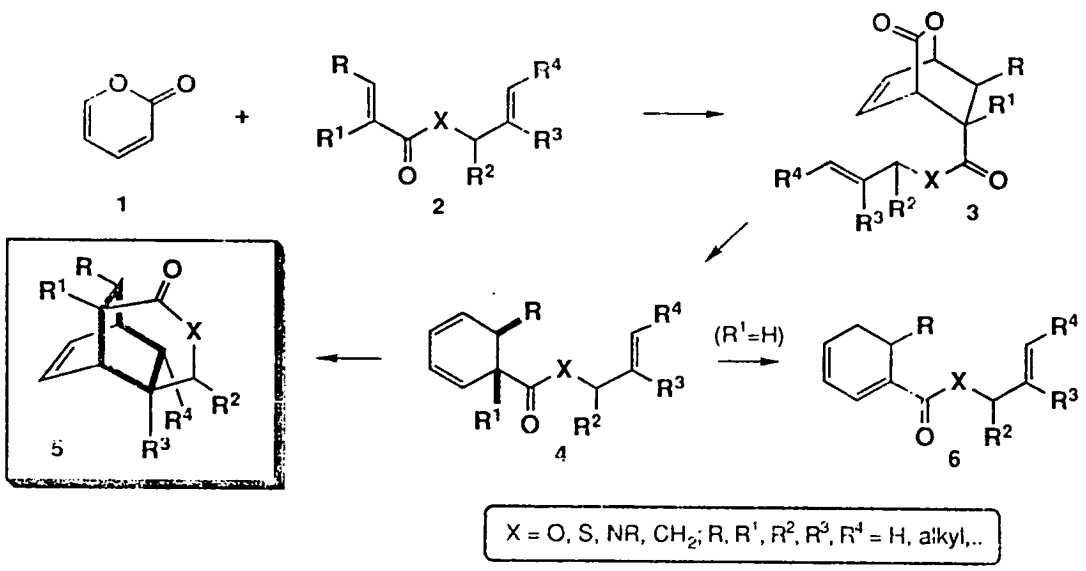
Certain 2-pyrones can also act as dienophiles in Diels-Alder reactions. Few examples are known, but a typical sequence is illustrated by the reaction of methyl coumalate 17 with cyclopentadiene[86] (Scheme 40).



Scheme 40

The balance between the dienic and dienophilic capabilities of 2-pyrone is tipped in favour of the latter by the electron-withdrawing properties of the 5-carboxylic ester group, and this fine balance thus enhances the potential of these compounds.

A more recent study has focussed upon tandem pericyclic processes involving initial Diels-Alder reaction of the parent 2-pyrone[87], followed by an intramolecular cycloaddition reaction. A typical general scheme is shown below (Scheme 41).

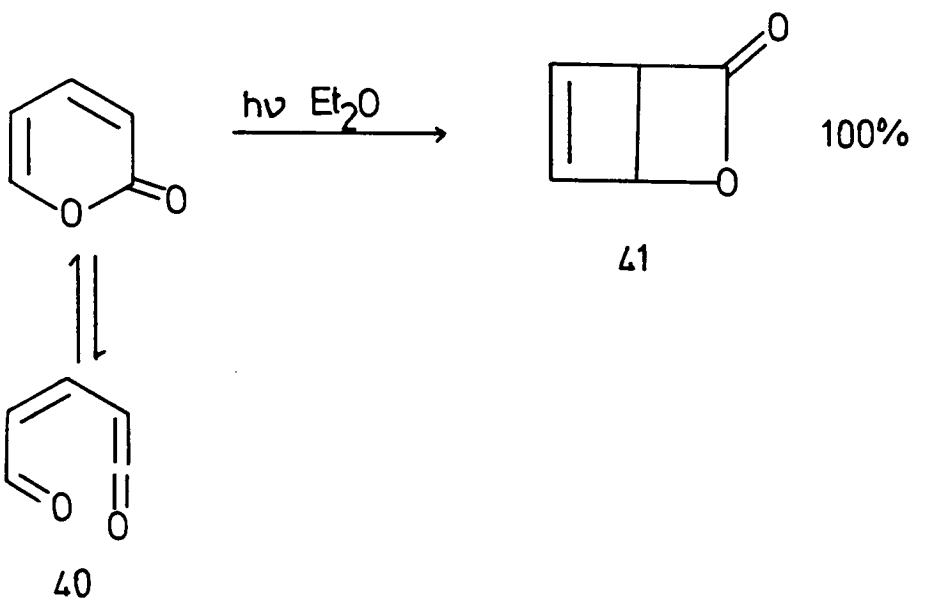


Scheme 41

This technique appears to be extremely useful as all the stereocentres of the central six membered ring are controlled in a single step, and no doubt will receive further attention.

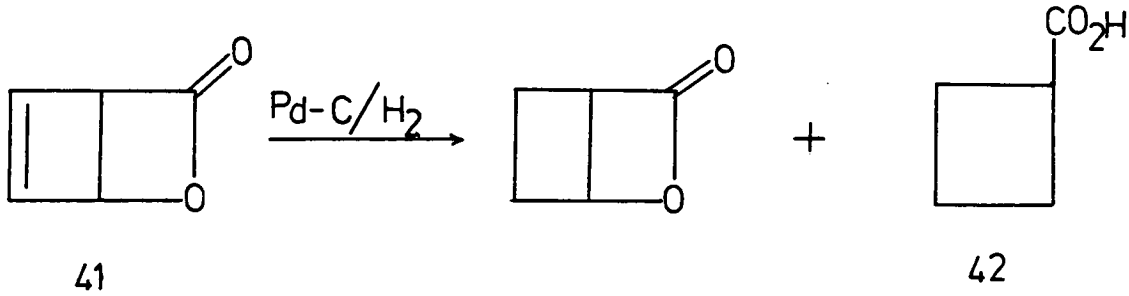
8. Photochemical Reactions

2-Pyrone and its alkyl derivatives are reactive when irradiated and give a variety of interesting compounds, some of which are extremely difficult to obtain using other methods. The presence or absence of dioxygen and the solvent used are important factors in deciding the course of the reaction. When 2-pyrone is irradiated, it is converted, at low temperature (≤ 8K) into ketene 40, but as the temperature is raised a competing reaction leads to lactone 41[88] (Scheme 42).



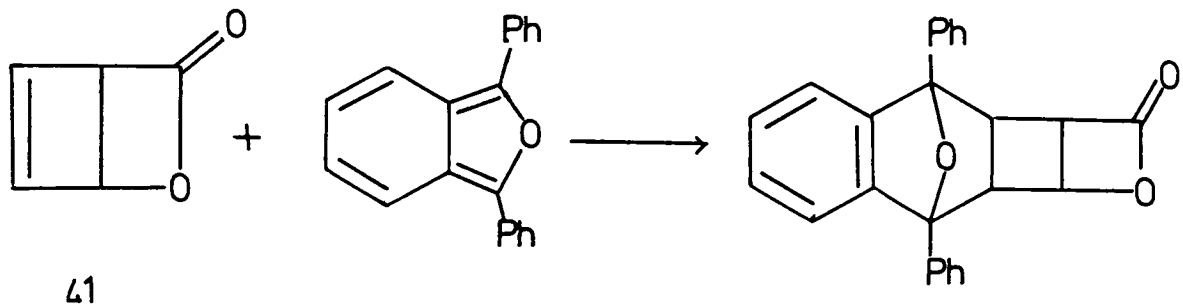
Scheme 42

This photoproduct 41 was used in a variety of reactions, even though it needs careful handling due to its pyrophoric tendencies on contact with air. The double bond can be reduced smoothly using Pd-C catalysts[88]; another product of this reaction is cyclobutane carboxylic acid 42 (Scheme 43).



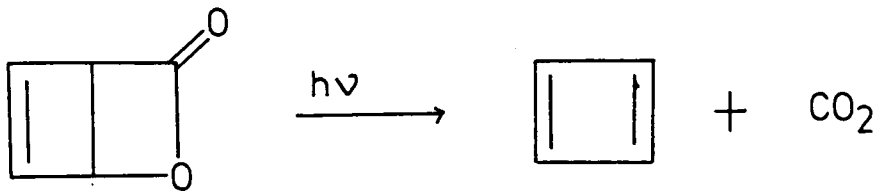
Scheme 43

The photoproduct 41 is able to undergo cycloaddition reactions, but only with quite reactive dienes, such as 1,3-diphenylisobenzofuran[89] (Scheme 44).



Scheme 44

The most interesting reaction of 41 is decarboxylation to give cyclobutadiene, which can be identified spectroscopically[90] (Scheme 45).

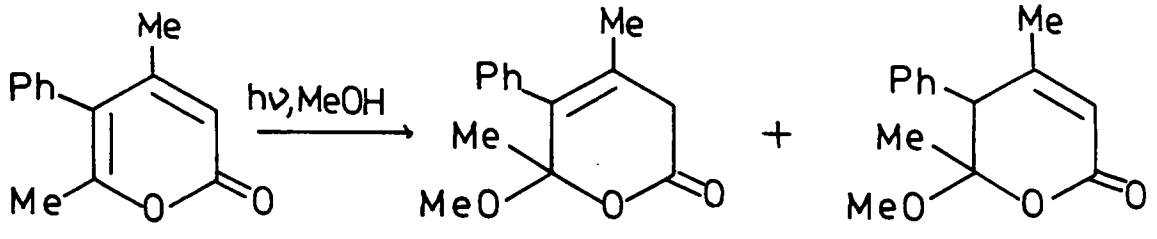


41

Scheme 45

The generation of cyclobutadiene and its derivatives has been the focus of many investigations and several synthetic methods have been developed[91].

In another photolysis study, different intermediates have been shown to be present; for example irradiation of 4,6-dimethyl-2-pyrone 43 in methanol gives two inseparable and reactive lactones 44 and 45 (Scheme 46).

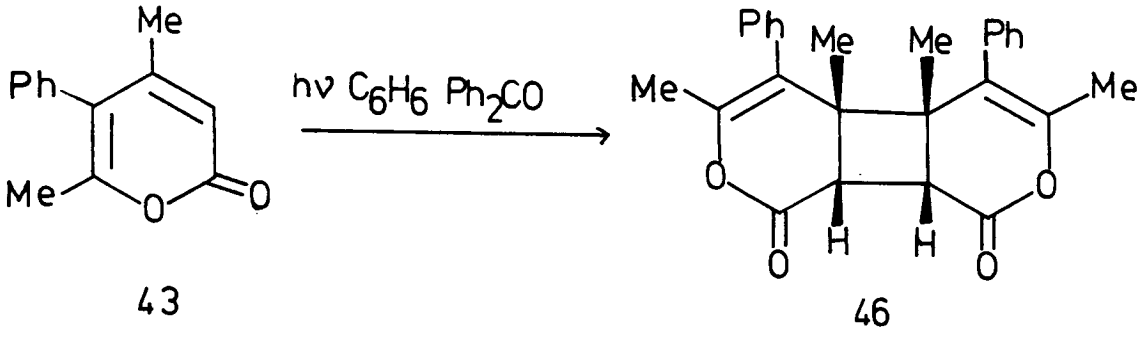


43 44 45

Scheme 46

There is no direct evidence in this case for the presence of ketene intermediates[92], but other workers have obtained spectral evidence of their presence during irradiation of the parent 2-pyrone[93].

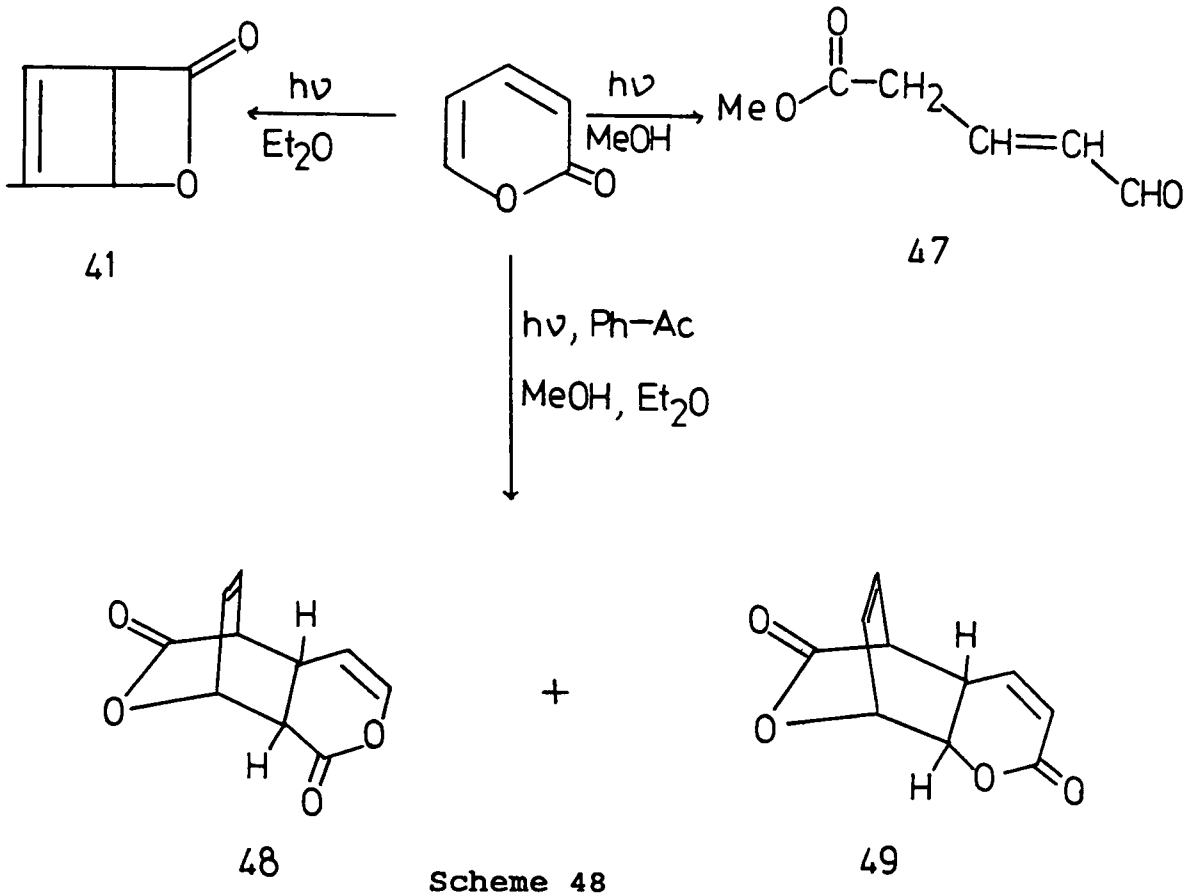
When 43 is irradiated in benzene, with benzophenone as sensitizer, a symmetrical dimer is formed 46 (Scheme 47).



Scheme 47

The effect of solvent and sensitizer on the course of photolysis of 2-pyrone is shown in Scheme 48.

When methanol is present, either the ring is cleaved and an ester 47 is formed, or, with a sensitizer, dimers 48 and 49 are produced in equal amounts.



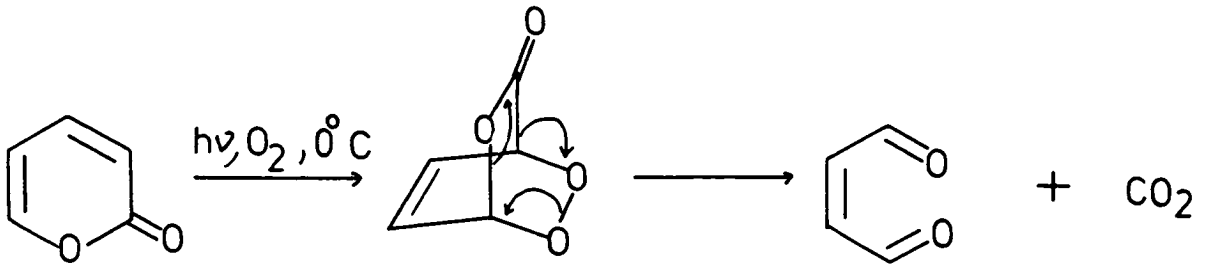
41 47

48 49

Scheme 48

The bicyclic lactone **41** and the ester **47** are believed to be formed *via* the singlet excited states of the 2-pyrone, while the dimers (which are photostable) result from the triplet state[94].

When 2-pyrones and a sensitizer are dissolved in 1,2-dichloroethane and oxygen is bubbled through while the solution is irradiated, a high yield of an *endo* peroxide (e.g. **50**) is formed. Such compounds are described as having hyperenergetic properties; when warmed, they exhibit chemiluminescence and lose carbon dioxide[95] (Scheme 49).

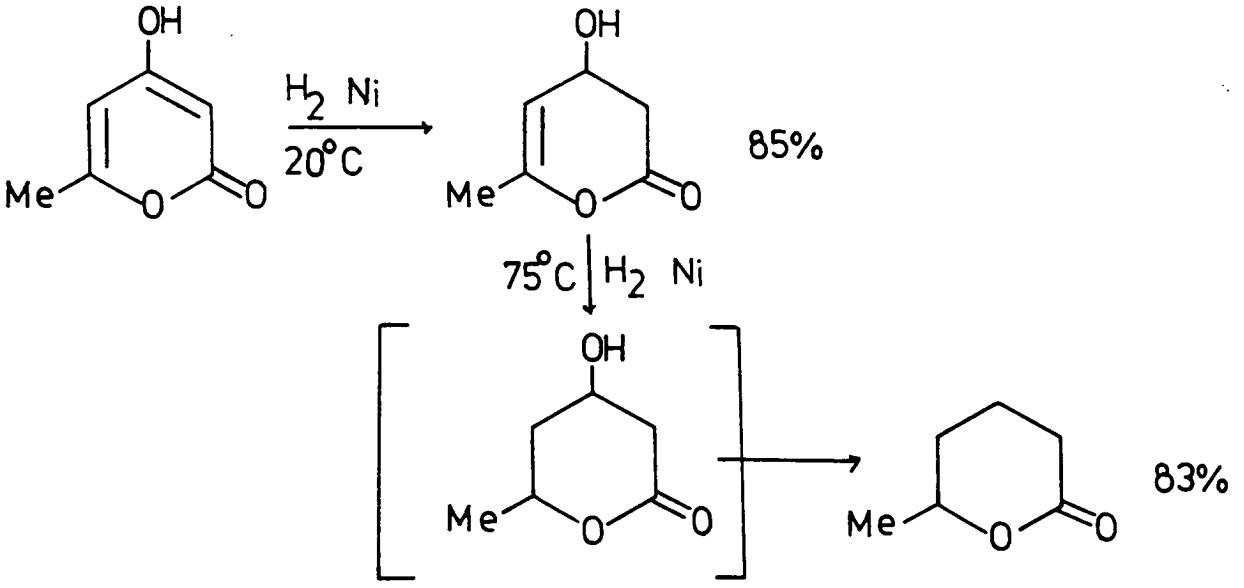


50

Scheme 49

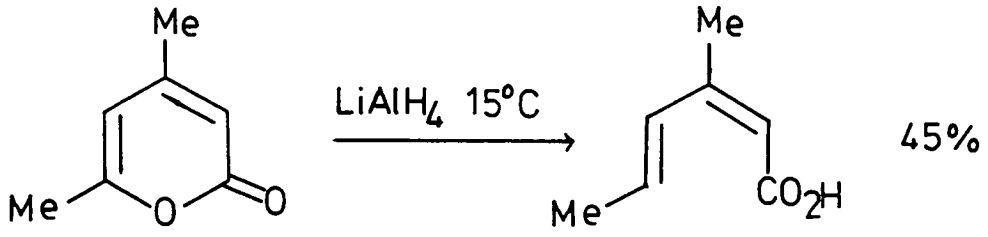
9. Reduction, Oxidation and Radical Reactions

The 2-pyrone ring can be reduced using a variety of reagents. Stepwise catalytic reduction to produce the tetrahydro compound can be achieved by suitable choice of catalyst and reaction conditions, a typical example is shown below[96] (Scheme 50).



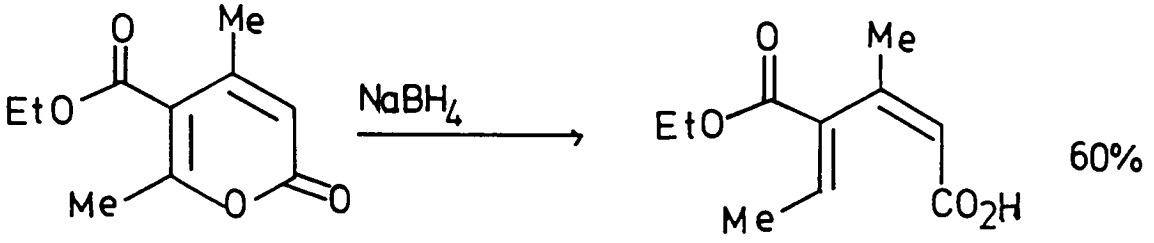
Scheme 50

Nucleophilic reducing agents, such as lithium aluminium hydride attack the 2-pyrone ring at C-6, leading to acyclic species[97] (Scheme 51).



Scheme 51

If, however, various ester groups are present and need to be retained, then the use of sodium borohydride allows selective reduction of the ring[97] (Scheme 52).

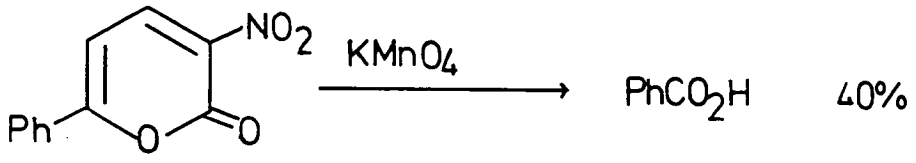


Scheme 52

In addition many methods have been described for the reduction of coumarins[98].

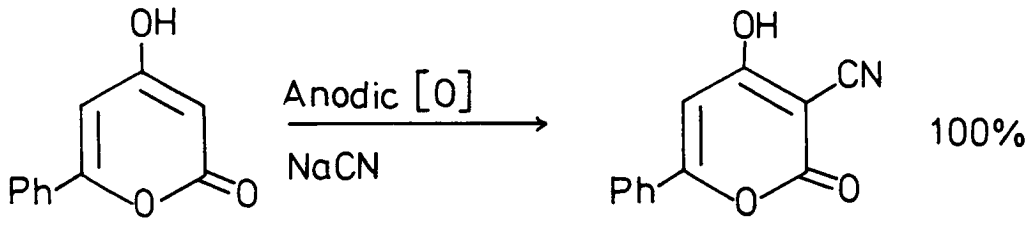
OXIDATION

Much less work has been undertaken on the oxidation of 2-pyrones than the various reduction reactions. Potassium permanganate cleaves the pyrone ring of 3-nitro-6 pheny-2-pyrone to benzoic acid[99] in a rather destructive reaction (Scheme 53).



Scheme 53

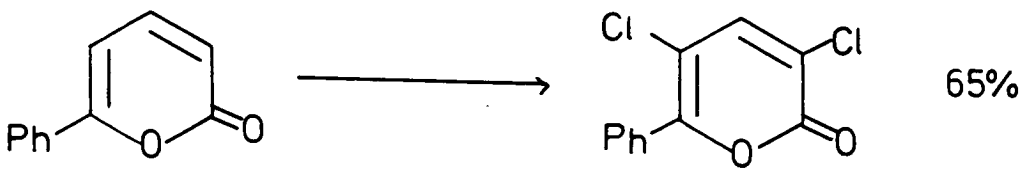
However, more recent studies have shown that by using anodic oxidation techniques[100], the 2-pyrone ring remains intact. An example is shown below (Scheme 54).



Scheme 54

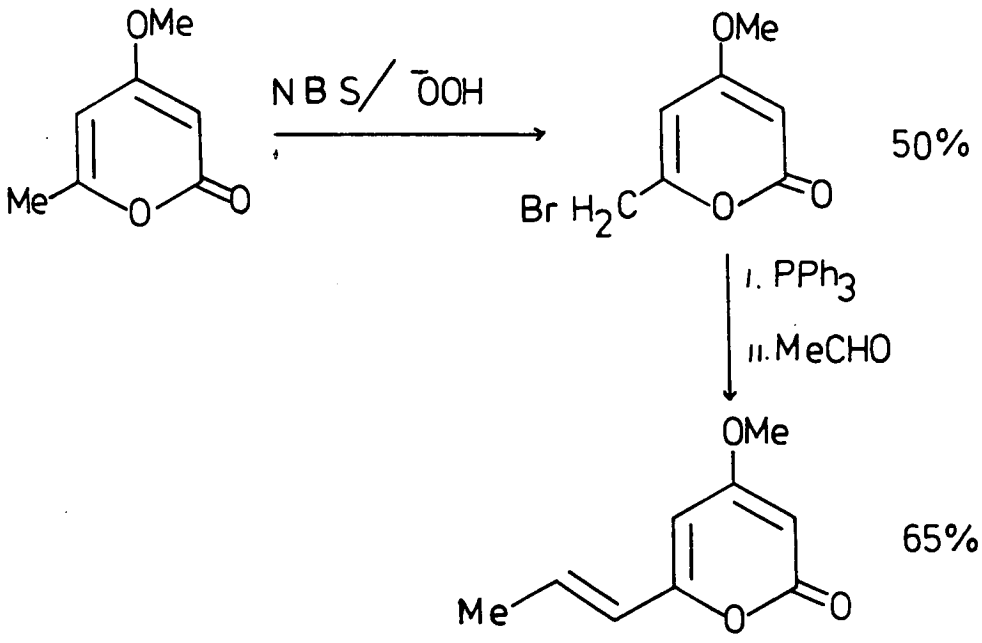
RADICALS

Very little work has been done on the reaction of 2-pyrones with radical type reagents. One such example is the reaction of 6-phenyl-2-pyrone with sulphuryl chloride to give the 3,5-dichloroderivative[101] (Scheme 55).



Scheme 55

Methyl substituents of 2-pyrones are quite easily brominated, using *N*-bromosuccinimide under radical conditions, and this is a useful reaction which can lead to a number of derivatives[102] (Scheme 56).



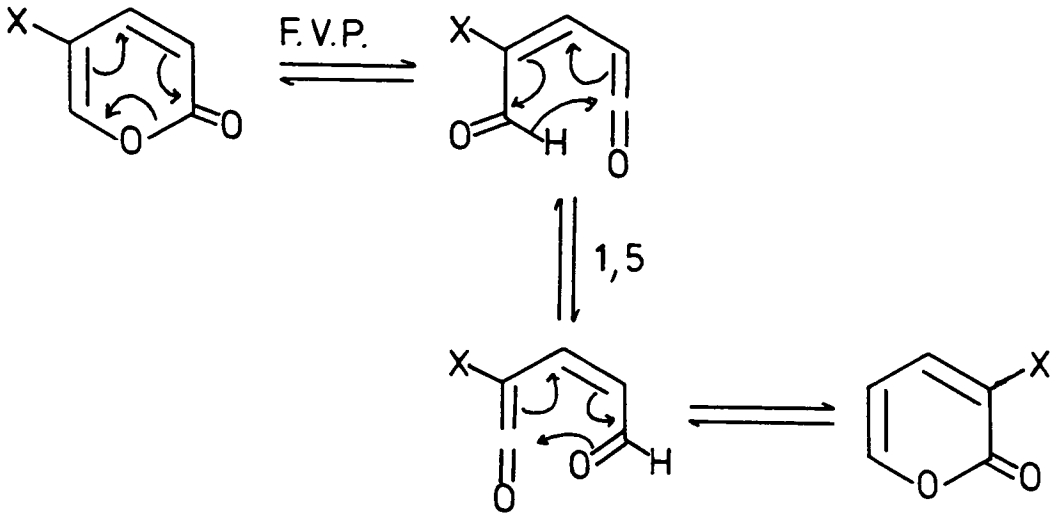
Scheme 56

DISCUSSION

GAS PHASE REARRANGEMENT OF 2-PYRONE-5-CARBOXALDEHYDES

The aim of this thesis was to identify a series of heterocyclic molecules that could produce reactive intermediates upon Flash Vacuum Pyrolysis (F.V.P.), and to subsequently investigate the chemistry of these intermediates, with the strict requirement that there must be no extrusion processes *i.e.* no evolution of gases.

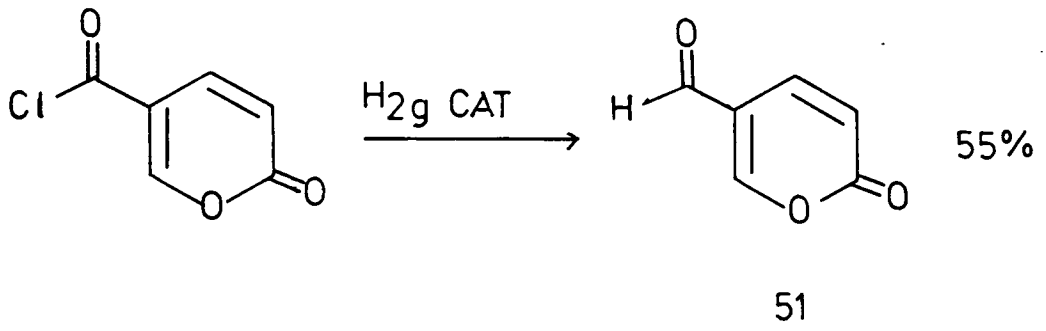
Previous studies by Pirkle[102] have shown that migration of substituents occurs between the 3- and 5-positions of 2-pyrones during gas phase pyrolysis. This was rationalised by invoking electrocyclic ring opening to ketene aldehydes, which undergo reversible [1,5] sigmatropic shifts of the aldehydic hydrogen (Scheme 57).



Scheme 57

A range of 5-substituted compounds were examined (e.g. X = Br, Me, EtO) and it was found that the position of equilibrium favoured the 5-isomer rather than the 3-isomer, probably due to a reduction in steric interactions when X is at the 5-position. Pirkle also found that certain compounds did not rearrange at all. Coumaloyl chloride (2-pyrone-5-carbonyl chloride) was found not to rearrange to its 3-substituted isomer[102], presumably in this particular case the 5-isomer is much more thermodynamically favoured. Pirkle suggested that the carbonyl group was responsible in some way for directing the position of equilibrium to favour the 5-isomer. 3-Carboethoxy-2-pyrone was found to rearrange completely to the 5-isomer[102].

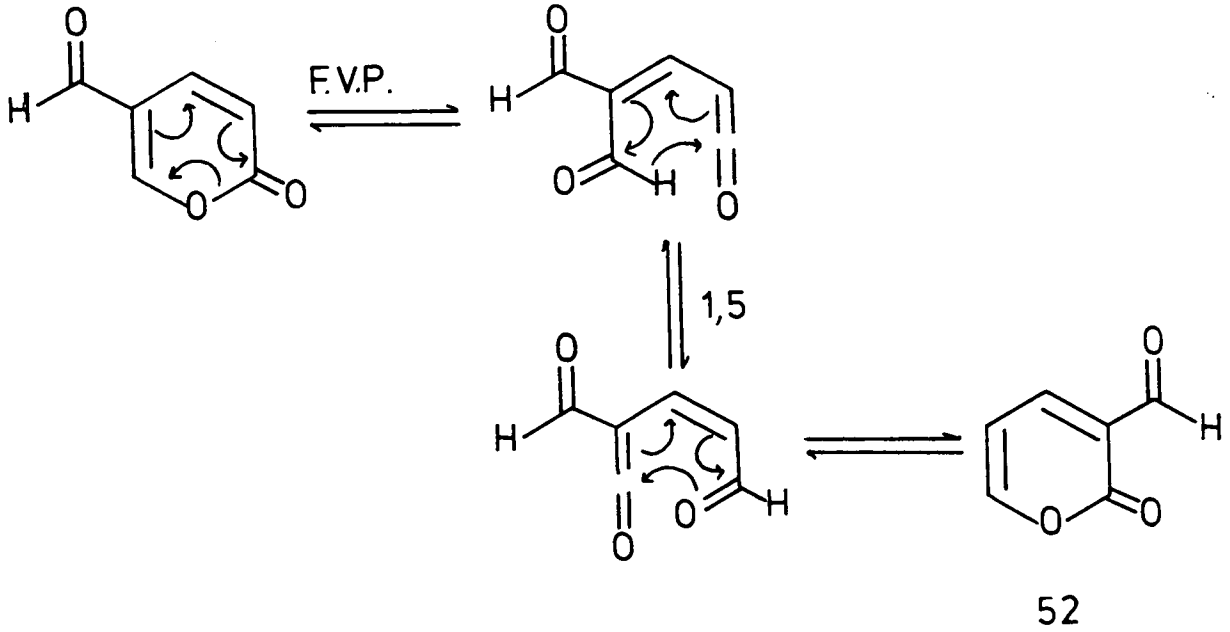
The model compound chosen for our initial investigation was 2-pyrone-5-carboxaldehyde 51 (i.e. X = CHO), prepared *via* catalytic hydrogenation of coumaloyl chloride[42], using a $Pd/BaSO_4$ catalyst. This technique is commonly known as the *Rosenmund* reduction method (Scheme 58). The reaction had to be monitored by t.l.c. to avoid over reduction of the pyrone ring. The yield of 51 generally was 50-60%, dependent upon the reaction temperature and the quality of the catalyst.



51

Scheme 58

Upon Flash Vacuum Pyrolysis (F.V.P.) at a furnace temperature of 600°C, 51 gave some of the rearranged product (≙ 22%) 52, presumably *via* mechanisms suggested by Pirkle (Scheme 59).



52

Scheme 59

The rearranged 3-isomer, 52, was identified by the ^1H nmr (360 MHz) spectra of the pyrolysate mixture. The chemical shift of the hydrogen atoms (δ ppm) and J_{HH} values of 52 are illustrated below, Figure 5. Therefore the isomerisation of 51 to its 3-isomer 52 appears to be in contrast to the work of Pirkle involving various substituted carbonyl containing functional groups.[102] Thus it appears that the isomerisation of such species is dependent upon steric considerations rather than any peculiar properties of the carbonyl group itself.

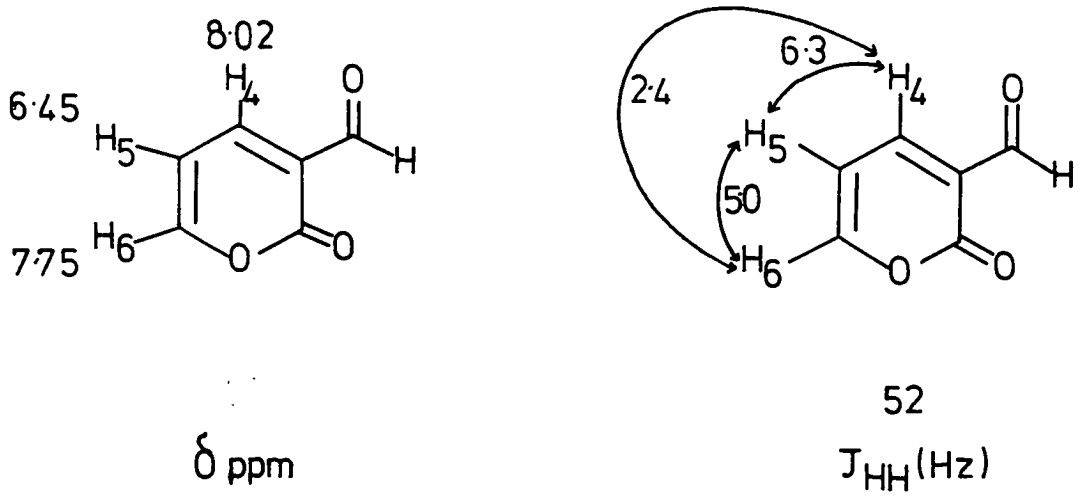
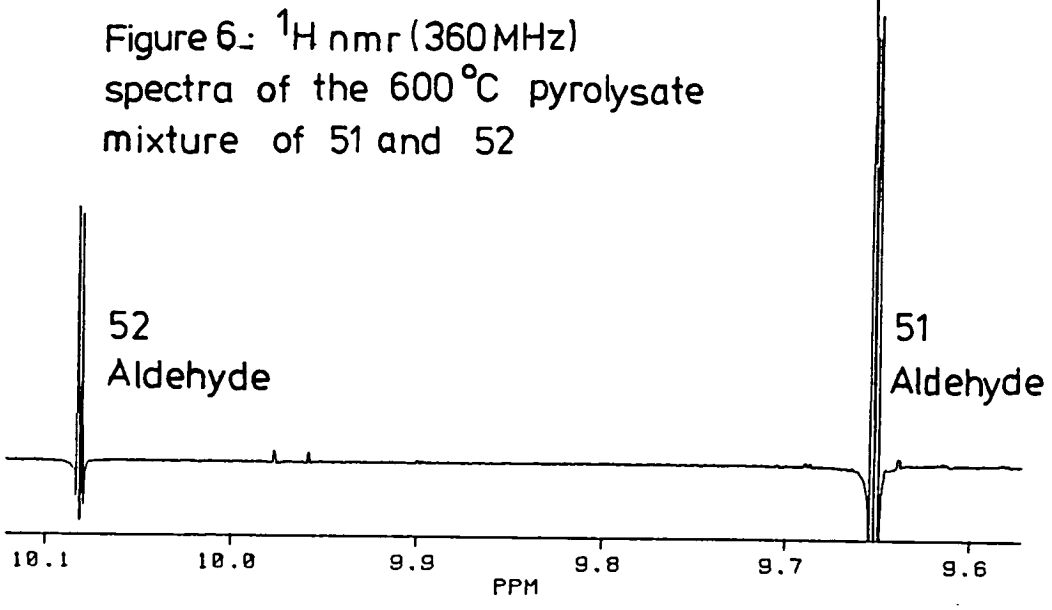
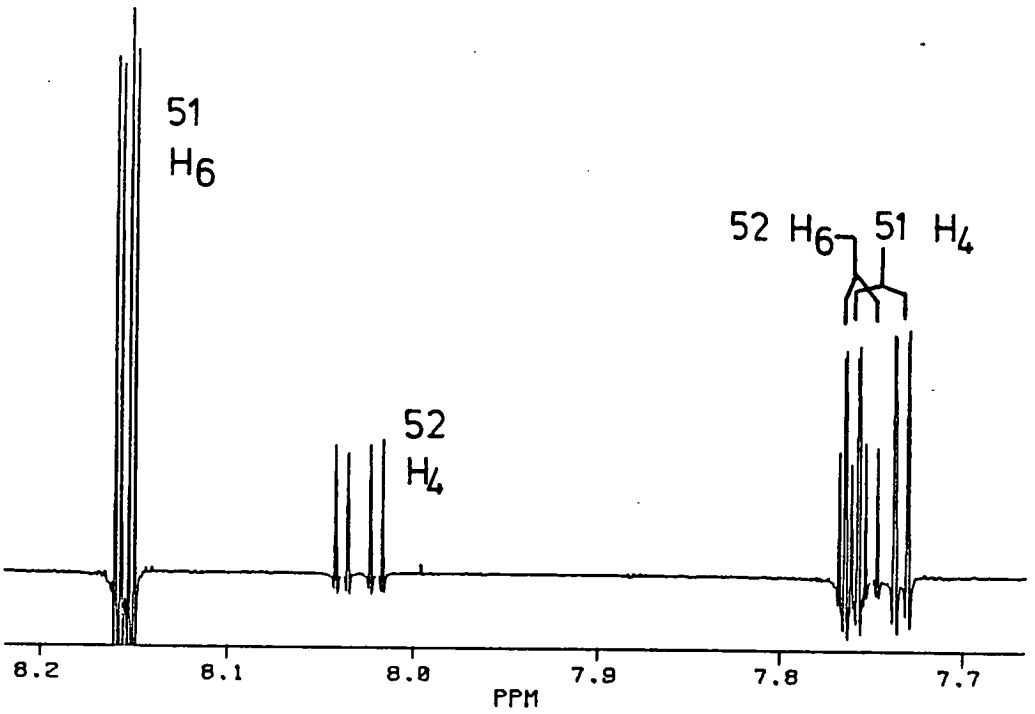
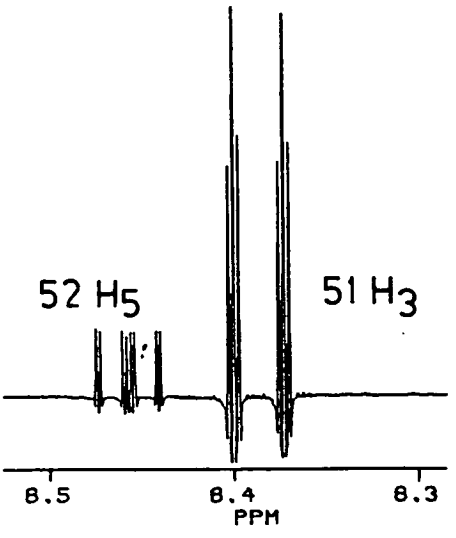


Figure 5: Schematic representation of ^1H nmr data (δ ppm and J_{HH} Hz) of 2-pyrone-3-carboxaldehyde 52

Figure 6.: ^{1}H nmr (360 MHz) spectra of the 600 °C pyrolysate mixture of 51 and 52







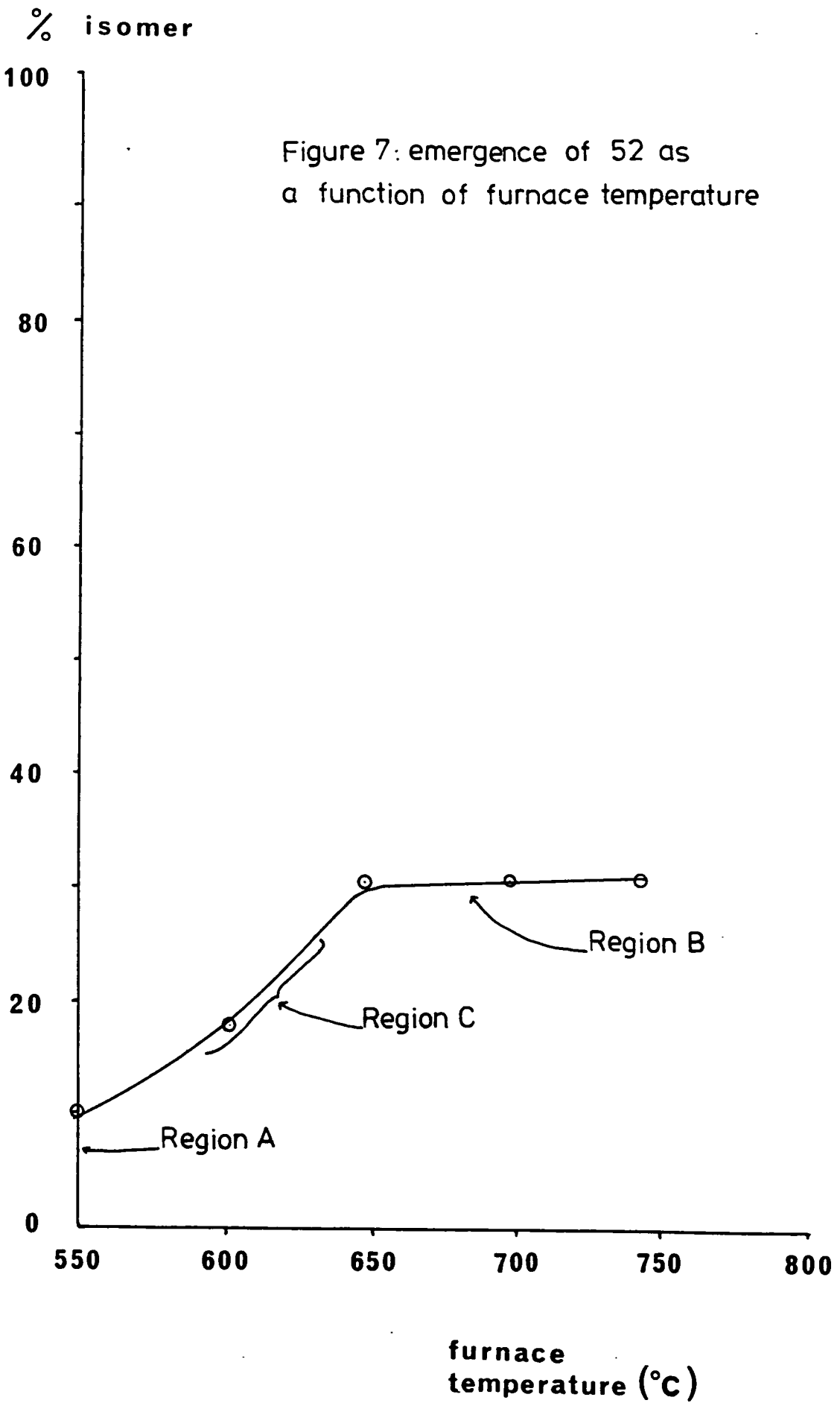
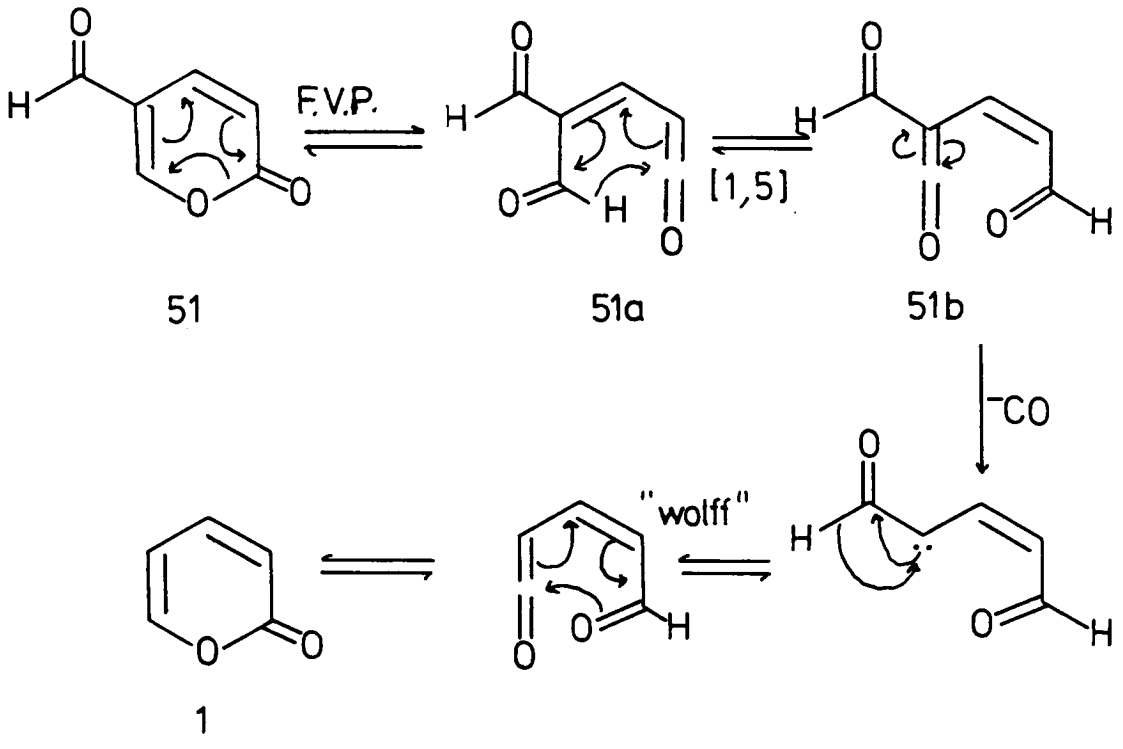


Figure 7: emergence of 52 as a function of furnace temperature

A copy of the 360 MHz spectra is also shown (Figure 6). 51 was subjected to variable temperature pyrolysis and the percentage increase of 52 in the pyrolysate mixture was expressed graphically (Figure 7). The emerging hydrogen atom H-5 of 52 was used to quantify the relative amount of 52. The shape of the graph (Fig. 7) is 'S' shaped in appearance (as well as all subsequent graphs of various 2-pyrone rearrangements). The most plausible explanation for this shape of curve involves direct relationship with the Boltzmann distribution of energies. At the low furnace temperatures, region A Figure 7, only the molecules of relatively high energy can surmount the required energy barrier for electrocyclic ring opening. At the high furnace temperatures, region B Figure 7, the molecules of relatively low energy are now able to surmount this energy barrier. The majority of molecules have energies somewhere inbetween these two extremes and thus form the 'rising' slope of the graph (region C Figure 7). Previous work[103] concerning the very typical shape of these F.V.P. derived graphs, has shown that by differentiating the mathematical equation describing these 'S' shaped curves one obtains a recognisable Boltzmann type distribution curve.

At a higher furnace temperature of 800°C, 51 was cleanly decarbonylated to 2-pyrone 1 in 65% yield, identified by its ^1H nmr spectrum (details given in the introduction section of this thesis). For comparison

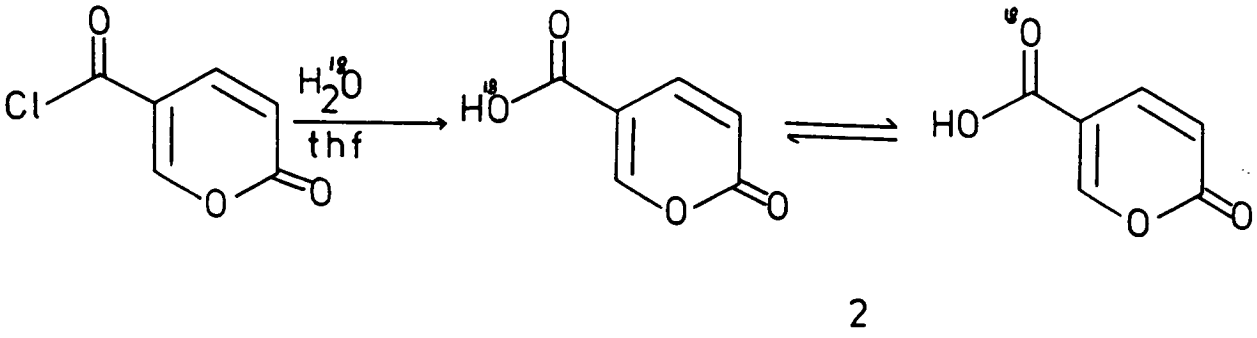
benzaldehyde was pyrolysed at 900°C and was found not to undergo decarbonylation. A plausible mechanism to explain the extrusion process of 51 involves loss of carbon monoxide from a ketene intermediate 51b to generate a carbene which then undergoes a Wolff type rearrangement affording a route to the product 1 (Scheme 60).



Scheme 60

The consequence of this mechanism is that the aldehydic oxygen of 51 is retained in the product 1.

To test whether the decarbonylation mechanism of 51 was correct (Scheme 60), the 2-pyrone-5-carboxaldehyde was prepared isotopically labelled with ^{18}O as the aldehydic oxygen atom. This was achieved by reacting coumaloyl chloride with one equivalent of ^{18}O labelled water in dry tetrahydrofuran, affording the ^{18}O labelled carboxylic acid in quantitative yield. Due to the lability of the acidic proton the ^{18}O was equilibrated between the two oxygen sites (Scheme 61).

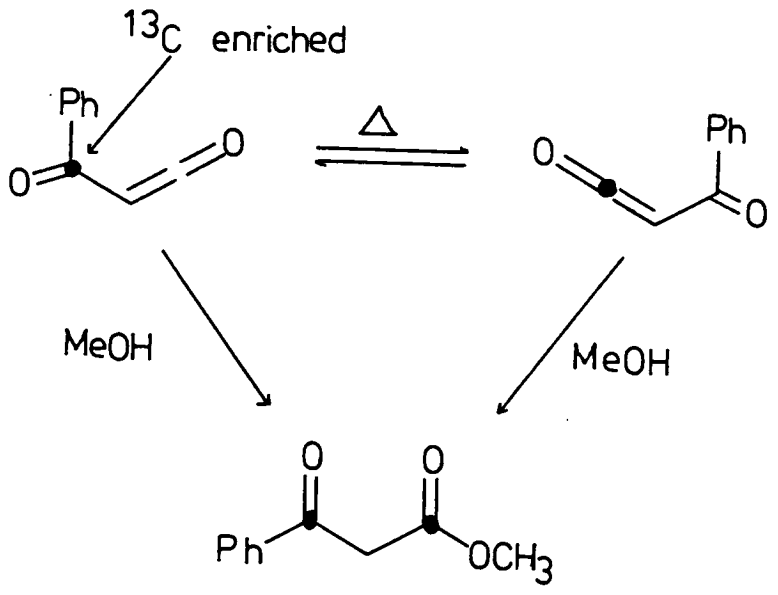


2

Scheme 61

Treatment of the ^{18}O labelled acid 2, with thionyl chloride afforded the ^{18}O acid chloride. Thus, in this reaction half the ^{18}O label was lost. The ^{13}C nmr spectrum (50 MHz) of this acid chloride, showed two signals of the acyl carbon, one resonance due to that atom

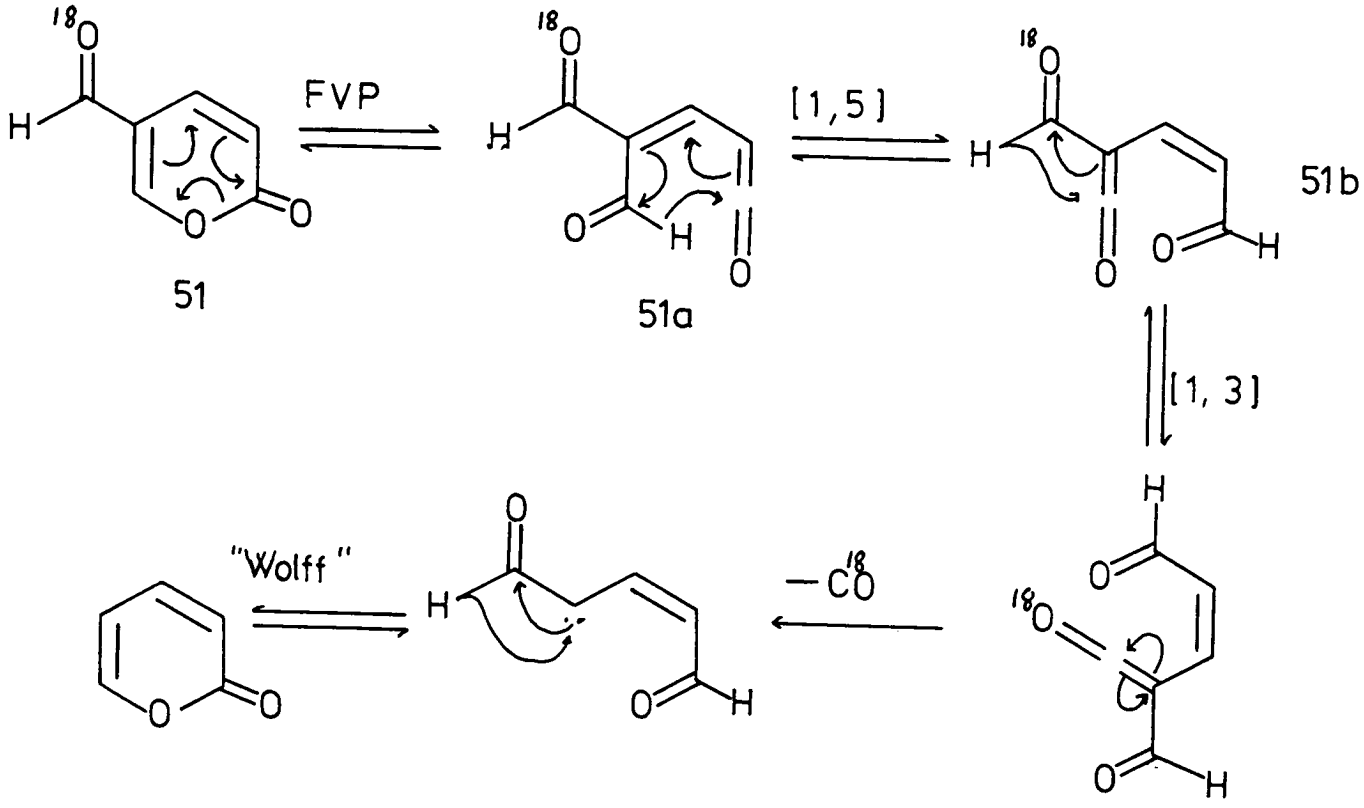
bonded to ^{16}O (8180.570 Hz) and another shifted to slightly lower frequency by ^{18}O[106,107] (8178.498 Hz). The intensity of these signals was approximately the same, indicating that the coumaloyl chloride was approximately 50% ^{18}O labelled. Rosenmund reduction of the acid chloride afforded the ^{18}O labelled aldehyde, which was examined by averaged mass spectrometry which gave *m/z* 126(M^+, 38.4%) (^{18}O compound) and *m/z* 124(M^+, 52.9%) (^{16}O compound). Thus, prior to pyrolysis the aldehyde had 42% incorporation of ^{18}O. This labelled aldehyde was subjected to Flash Vacuum Pyrolysis (F.V.P.) at 800°C to yield the decarbonylated product, 2-pyrone 1. ^{13}C nmr indicated an ^{18}O upfield shift of the C-6 resonance (δ 7638.036 due to ^{16}O, and δ 7636.728 due to ^{18}O) of 1.3 Hz relative to ^{16}O, thus to some extent ^{18}O was retained in the product. Averaged mass spectral analysis gave *m/z* 98(M^+, 20.6%) and *m/z* 96(M^+, 70.0%), thus indicating that the decarbonylated product 2-pyrone had 22.7% ^{18}O incorporation. This corresponds to approximately 50% loss of the initial ^{18}O label, which suggested that some equilibration of ^{18}O was occurring prior to carbon monoxide extrusion. There are two reasonable mechanisms to explain this. The first mechanism invokes the idea of [1,3] sigmatropic shifts to ketenes. It has been shown[104] that acyl ketenes can undergo carbon scrambling *via* a thermal [1,3] shift of a phenyl group (Scheme 62).



Scheme 62

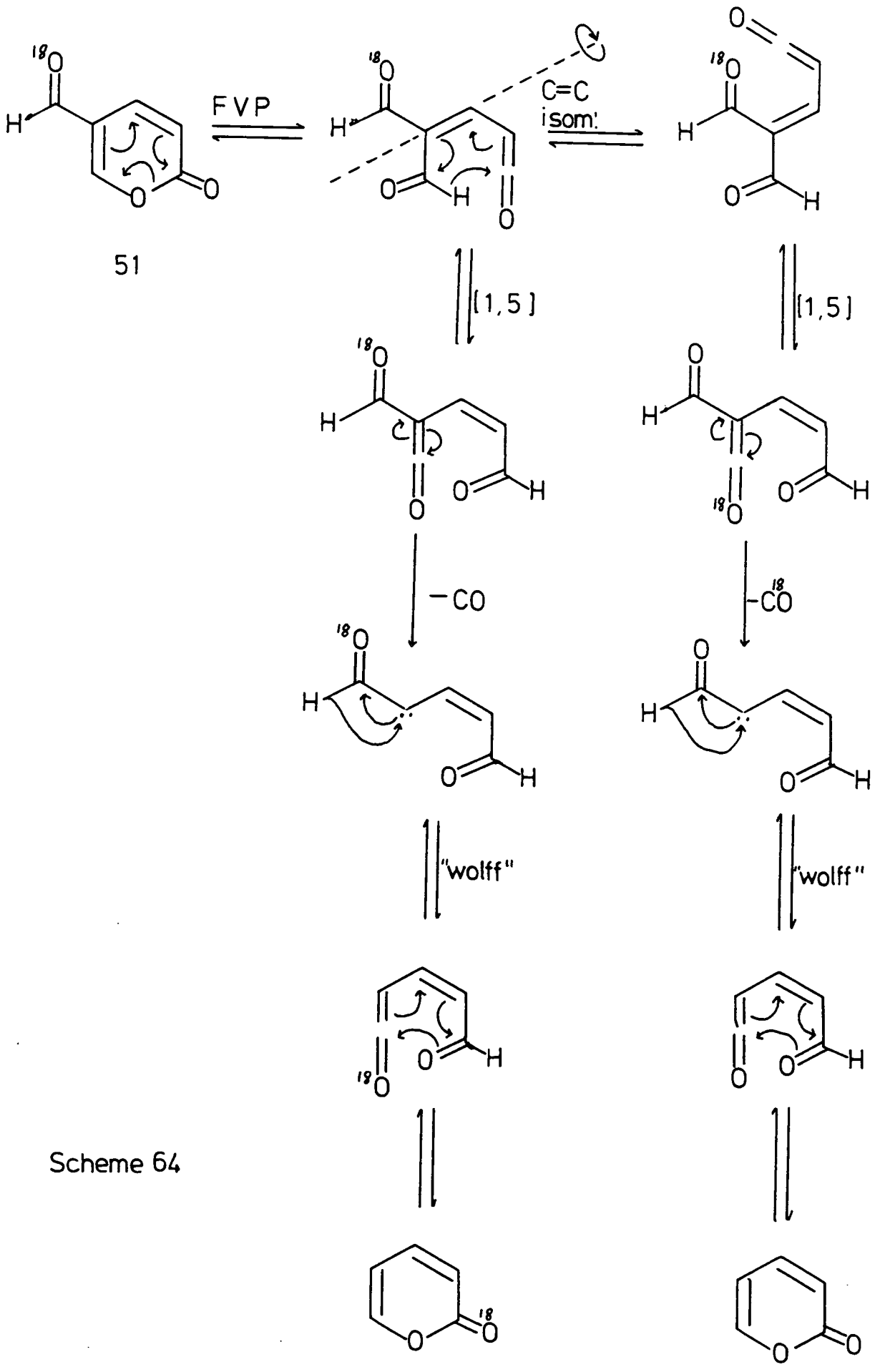
Although suprafacial thermal 1,3-shifts are "forbidden" by the rules of orbital symmetry[105], such shifts become possible in ketenes due to the presence of orthogonal orbitals.

Thus it may be possible that the ketene 51b (Scheme 60) could undergo [1,3] shifts resulting in loss of some of the ^{18}O as carbon monoxide (Scheme 63).



Scheme 63

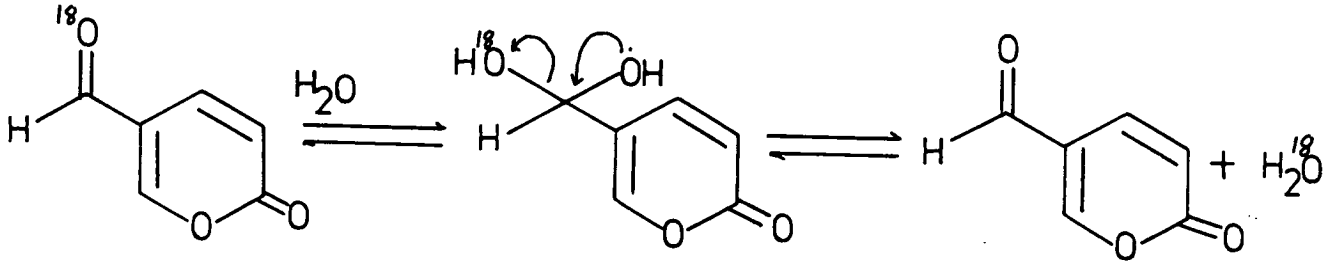
The second mechanism invokes the idea of carbon-carbon double bond isomerisation of the initial ring opened species **51a** to give an alternate competing mechanism. There is precedent for this mechanism as previous work has shown[108] that a wide variety of alkenes can be isomerised to the thermodynamic equilibrium mixtures of *E* and *Z* isomers (Scheme 64).



51

Scheme 64

A necessary control experiment involved the pyrolysis of the ^{18}O labelled aldehyde 51 at a furnace temperature of 600°C (at this temperature no decarbonylation occurs, just rearrangement to the 3-isomer). The pyrolysate was again analysed by averaged mass spectrometry showing *m/z* 126(M^+, 30.9%) and *m/z* 124(M^+, 56.0%). The ^{18}O content of 51 was thus reduced from 42%, prior to pyrolysis, to 36%. The only obvious explanation is that exchange was occurring with water adsorbed on the walls of the inlet or furnace tube very probably *via* gem diol formation (Scheme 65). Such losses are however insufficient to explain the 50% loss observed in the decarbonylation process.

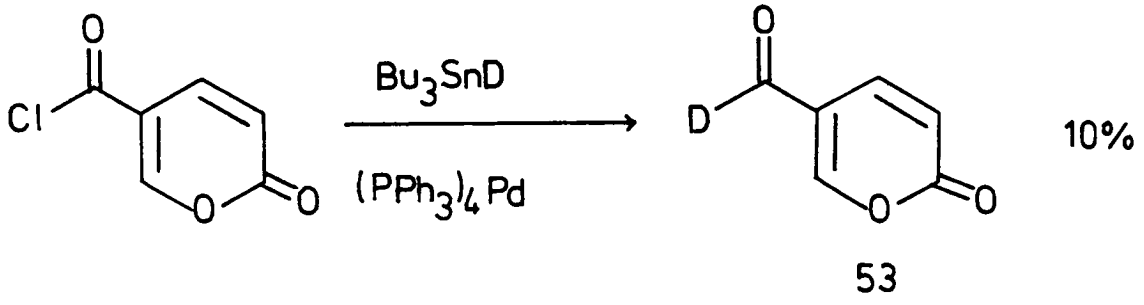


Scheme 65

The following deuterium labelling study was undertaken to prove which of the two previously mentioned decarbonylation mechanisms was operating. Thus if the [1,3]-shift mechanism alone was operating (Scheme 63) a deuterium atom labelled at the aldehyde would not be further scrambled prior to decarbonylation. However, if the double bond isomerisation mechanism takes place

(Scheme 64), this atom would become incorporated at the 6-position of the 3- and 5-carboxaldehydes. 2-Pyrone-5-[^{2}H]carboxaldehyde 53 was prepared by adaptation of known tributyl tin hydride chemistry[109]. This method appears to be applicable to a wide variety of acid chlorides[109], though yields are variable. Work up procedures involve column chromatography of the crude reaction mixture to remove tin residues, tributyltin chloride and hexabutyl-distannane. Due to the toxicity of such residues extreme care must be taken to avoid skin contact and inhalation.

Coumaloyl chloride was treated with tributyltin deuteride in benzene, using tetrakistriphenylphosphine palladium (0) as catalyst (Scheme 66).

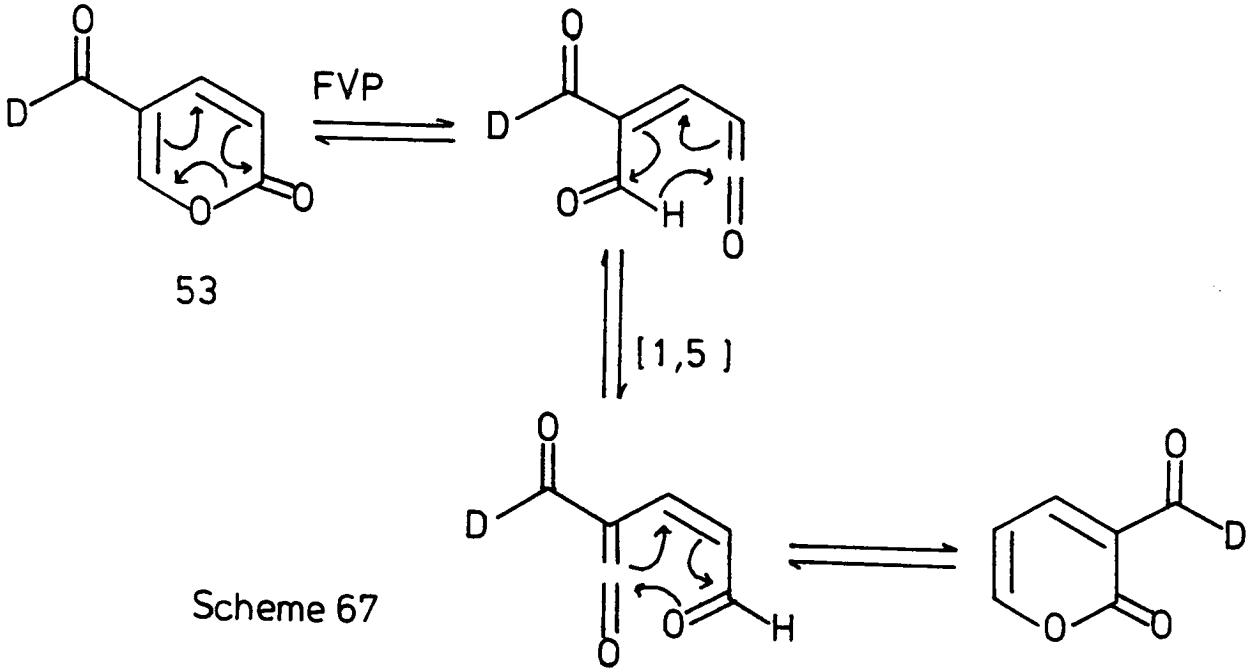


53

Scheme 66

However, in this particular case the reduction was extremely poor and only 52 mgs (10%) of ^{2}H labelled aldehyde was isolated, but this reaction had to be developed to obviate the use of a vast excess of deuterium gas in the *Rosenmund* reduction technique.

The product 53 was examined by ^{2}H nmr spectroscopy, showing the aldehydic deuterium resonance at δ^{2}_{H} 9.65 (*c.f.* unlabelled aldehyde δ^{1}_{H} 9.65). This aldehyde 53, was subjected to variable temperature Flash Vacuum Pyrolysis (F.V.P.). At low furnace temperatures, 550°C and below, the only other observable component in the pyrolysis mixture was the expected 3-isomer 54 (Scheme 67).



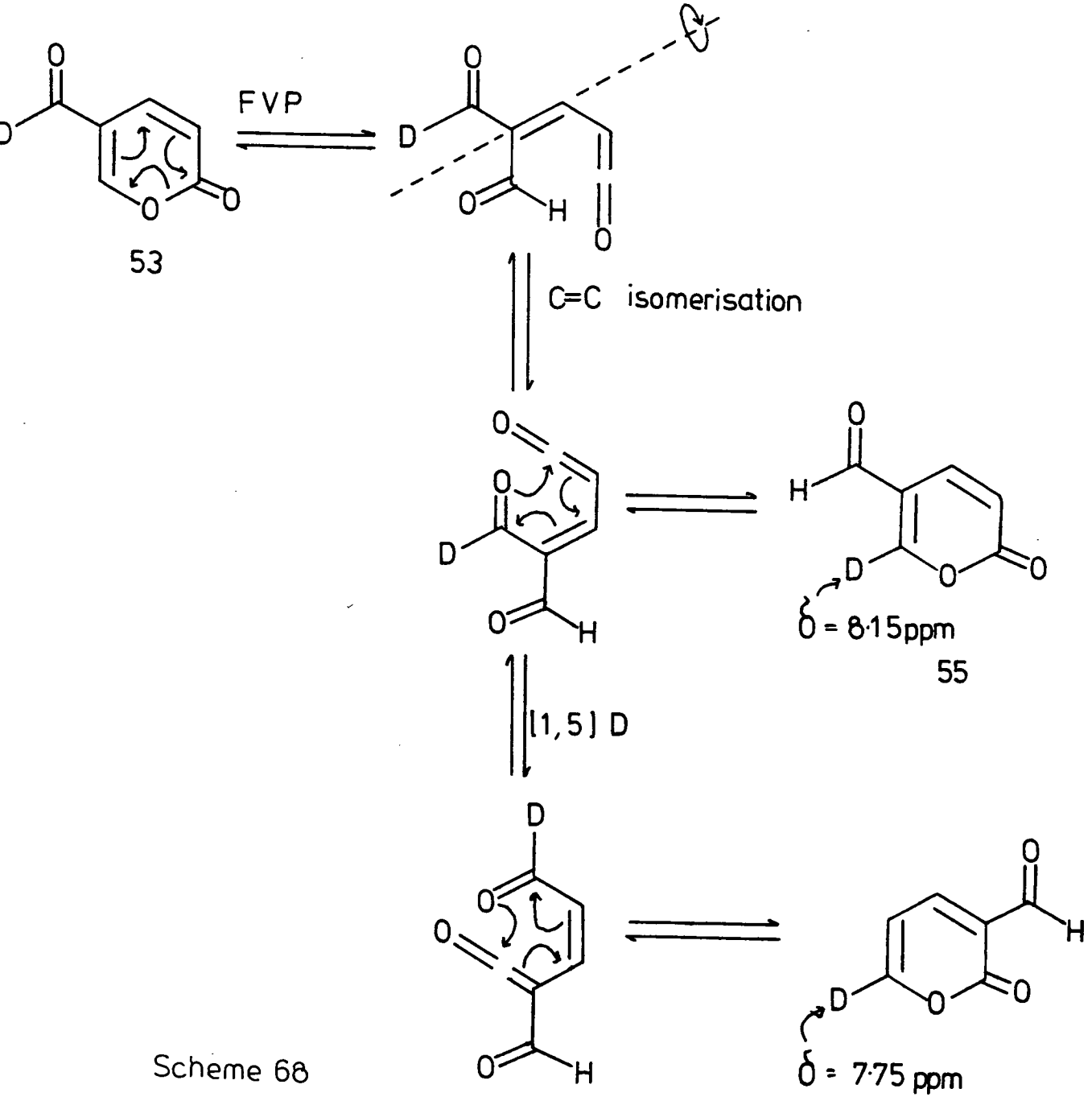
53

Scheme 67

54

54 was identified by its ^{2}H nmr; δ^{2}_{H} 10.0 (*c.f.* unlabelled aldehyde ^{1}H nmr δ^{1}_{H} 10.07). However, at higher furnace temperatures, 600°C and above, other ^{2}H resonances were found at δ^{2}_{H} 8.15 and δ^{2}_{H} 7.75 ppm, corresponding to

the deuterium label being scrambled to position C-6 of the aldehydes 55 and 56 (*c.f.* figure 5 for ^1H nmr data). The simplest mechanism to explain this, invokes carbon-carbon double bond isomerisation as previously explained (Scheme 68).



Scheme 68

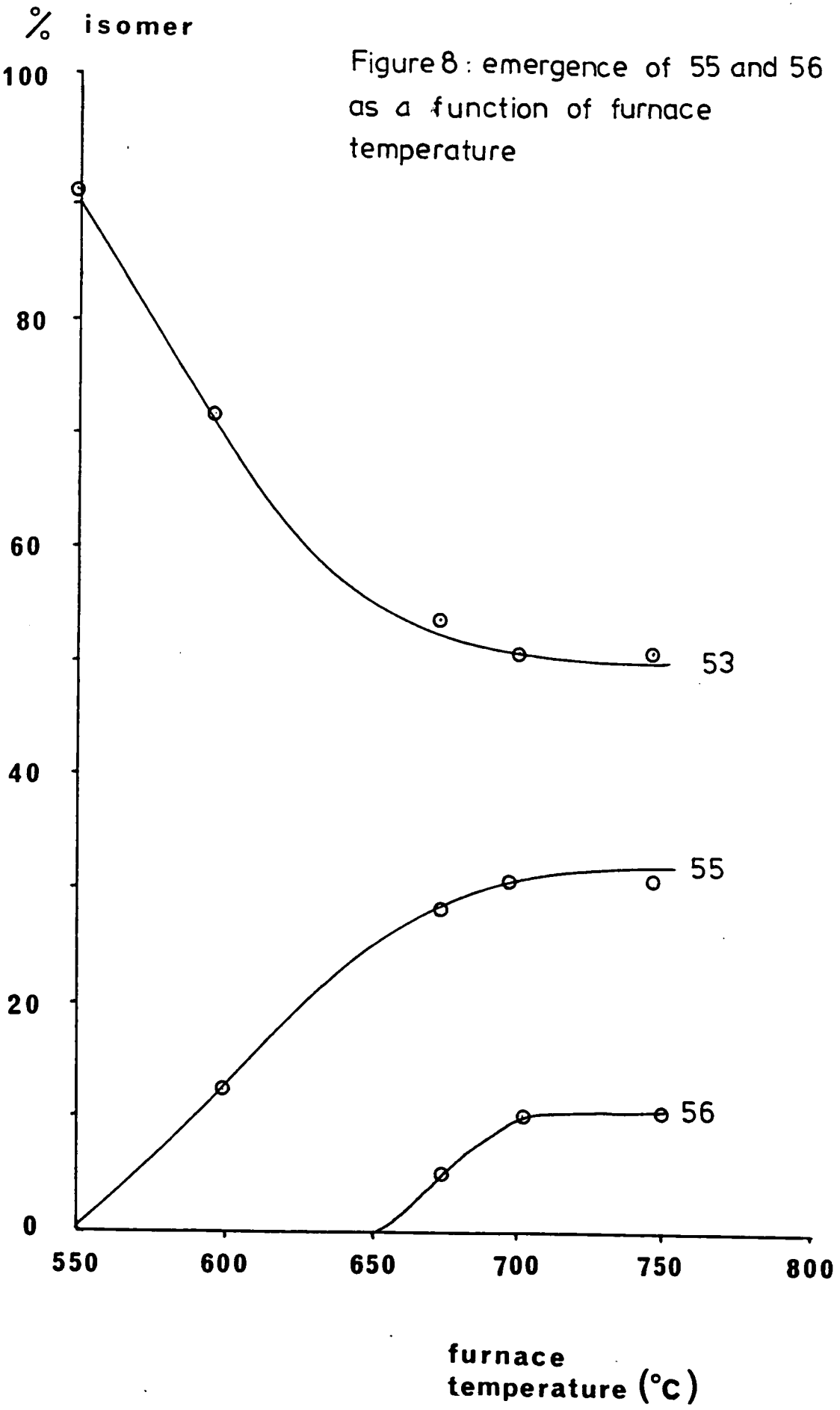
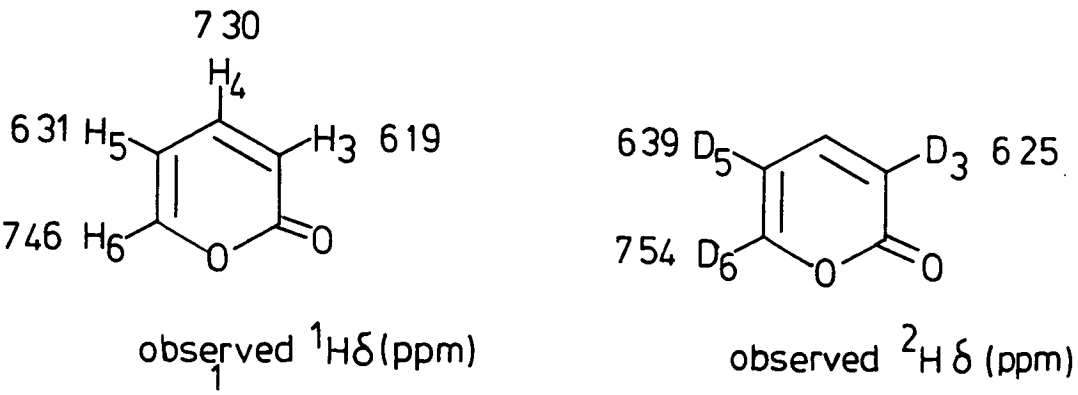


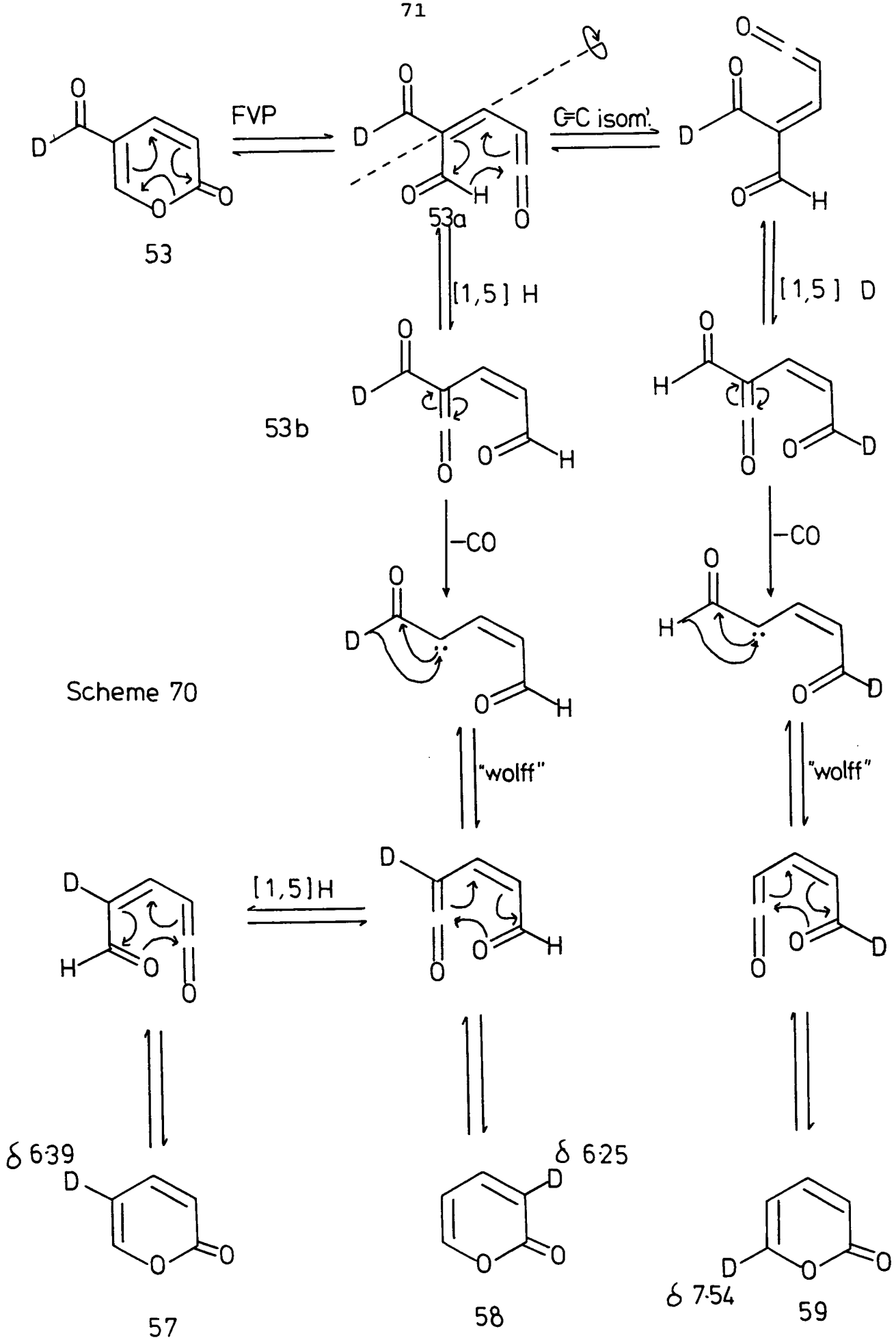
Figure 8 : emergence of 55 and 56 as a function of furnace temperature

The emergence of 55 and 56 as a function of furnace temperature was also expressed graphically. As previously found, the 5-isomer 55 predominates over the 3-isomer 56 (Figure 8). Thus carbon-carbon double bond isomerisation starts to occur, in this case just above 550°C.

At a furnace temperature of 800°C, 53 was cleanly decarbonylated to 2-pyrone, as expected, and the 2-pyrone so produced was examined by ^{2}H nmr. Two resonances were observed at $\delta_{^{2}H}$ 7.54 and 6.39. The signal at $\delta_{^{2}H}$ 6.39 appeared to be quite broad and had a slight 'shoulder' to lower frequency, indicating two unresolved resonances, at $\delta_{^{2}H}$ 6.39 and possibly at $\delta_{^{2}H}$ 6.25. These three resonances fit quite well with the known ^{1}H chemical shift of 1 (Scheme 69).



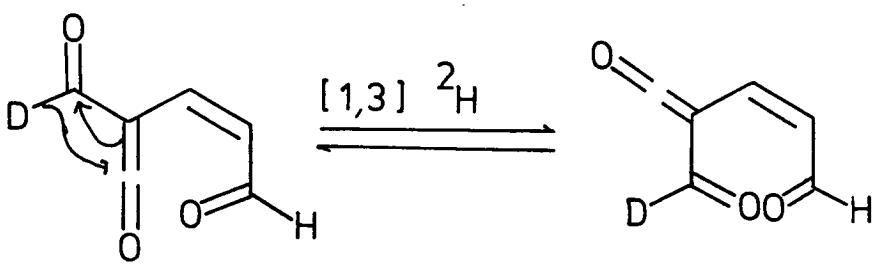
Scheme 69


FVP
C=C isom.
53
53a
[1,5] H
[1,5] D
53b
-CO
-CO
"wolff"
"wolff"
[1,5]H
δ 6·39
δ 6·25
δ 7·54
57
58
59

Scheme 70

A plausible mechanism to explain this scrambling again invokes carbon-carbon double bond isomerisation of the initial ring opened species (Scheme 70).

Examination of the ^2H spectra obtained showed that, to a good approximation, the ratio of 57 + 58 to 59 was 1:1, indicating total equilibration was occurring about the carbon-carbon double bond, i.e. at a furnace temperature of 800°C, carbon-carbon double bond isomerisation competes effectively with the [1,5] hydrogen sigmatropic shift of 53a. If one now considers the possibility of the [1,3] deuterium sigmatropic shift of 53b (Scheme 70), then such a rearrangement could only produce "equivalent" intermediates (Scheme 71) which cannot give rise to the observed labelling pattern.



53b

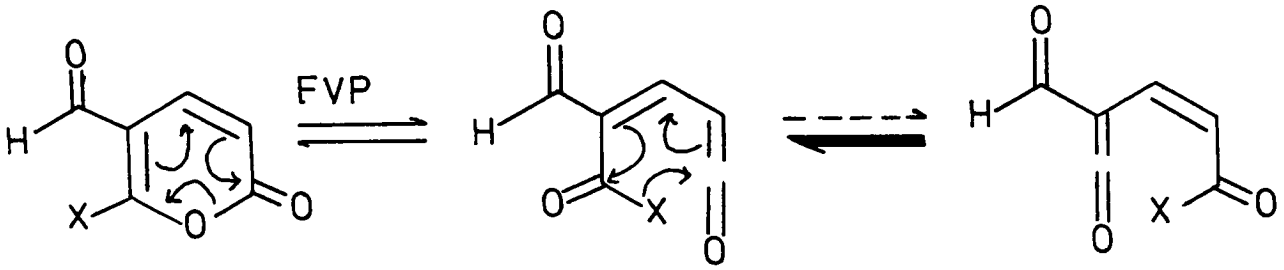
Scheme 71

However, at this stage the [1,3]-hydrogen shift cannot be excluded, though *only* the double bond isomerisation mechanism is *required* to explain the observed [^{2}H] and [^{18}O] labelling experiments.

The following study investigated the decarbonylation of **51** from a different viewpoint.

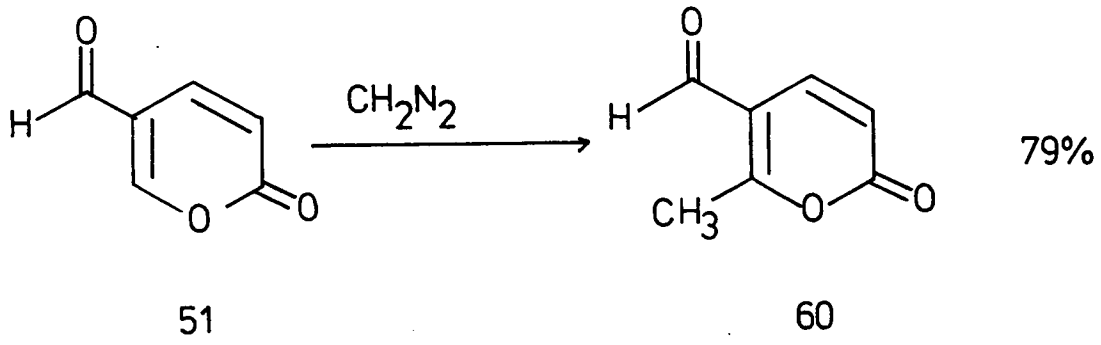
The proposed mechanism for the decarbonylation of the aldehyde **51** was illustrated in Scheme 60. The key step of this process involved a [1,5] hydrogen sigmatropic shift of the initial ring opened species **51a**, which, after loss of carbon monoxide, had a simple Wolff type rearrangement mechanism to give the product 2-pyrone **1**.

It seemed plausible that by preventing this [1,5] hydrogen shift the decarbonylation process would be hindered. What was needed was a suitable group (X) at C-6 of **51**, which had a greatly reduced tendency towards the [1,5] shift (Scheme 72). Simple alkyl groups fulfil this condition.



Scheme 72

6-Methyl-2-pyrone-5-carboxaldehyde 60 was thus prepared *via* reaction of 51 with diazomethane in a rather surprising reaction, in relatively high yield (Scheme 73).



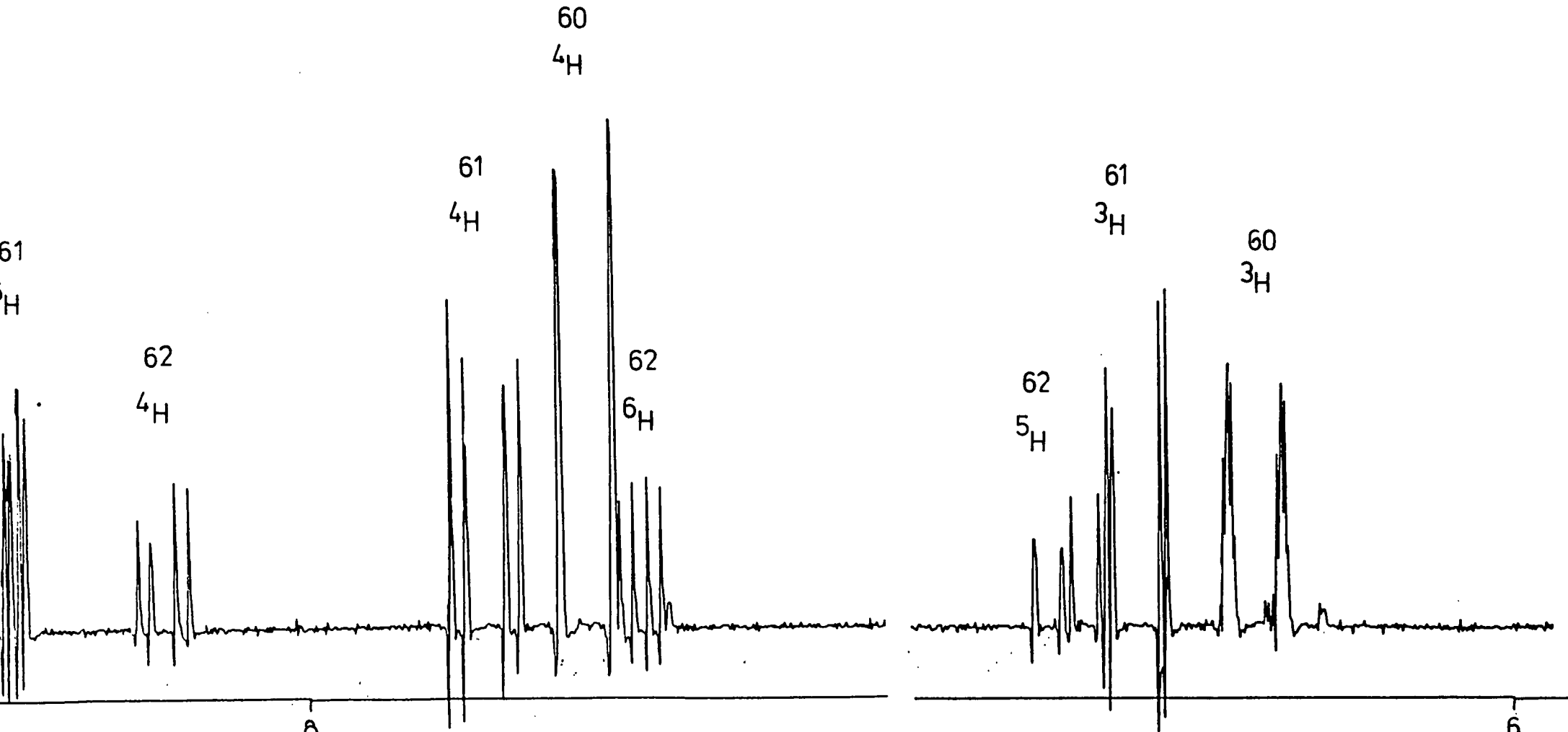
51 60

Scheme 73

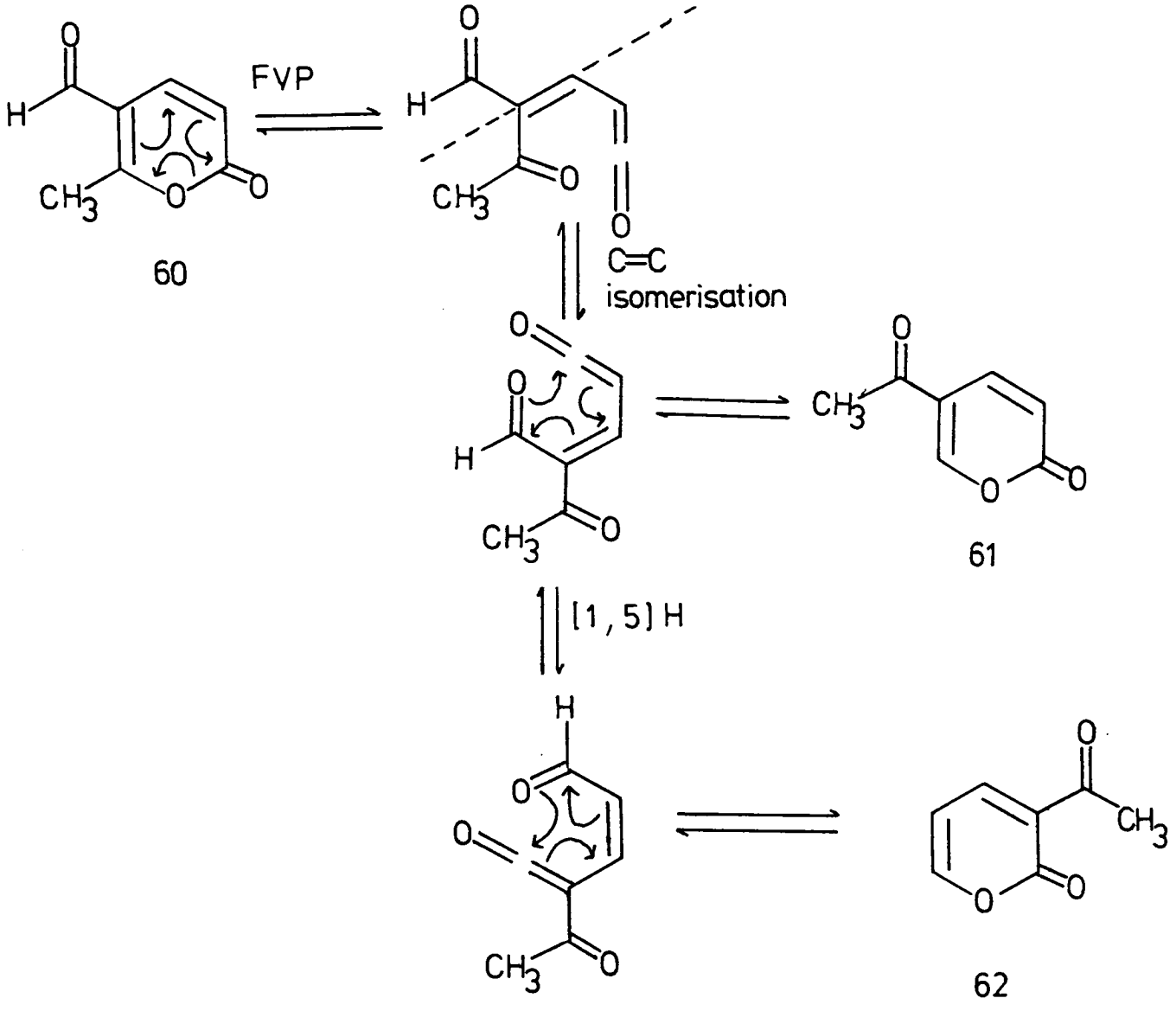
There was precedent for this reaction as methyl coumalate has been shown to react analogously with diazomethane[52,53]. However conditions had to be optimised for the methylation of 51. Dilute conditions using a dichloromethane solution of 51 were employed. A slow rate of addition of the diazomethane solution and rapid stirring of the reaction mixture was necessary to avoid methylation of the aldehyde group.

The 6-methyl derivative 60 was subjected to Flash Vacuum Pyrolysis (F.V.P.) at a furnace temperature of 600°C. Two rearranged isomers 61 and 62 were identified by ^1H nmr of the pyrolysate mixture. The simplest

Figure 9: ^{1}H nmr (200 MHz) spectrum of the 600°C pyrolysate mixture of 60 61 and 62



mechanism explaining the formation of these involves carbon-carbon double bond isomerisation, as previously described (Scheme 74).



Scheme 74

A copy of the ^1H nmr spectrum of the 600°C pyrolysate mixture of 60, 61 and 62, together with J_{HH} values is illustrated (Figure 9). As before 60 was subjected to variable temperature pyrolyses, allowing the emergence of

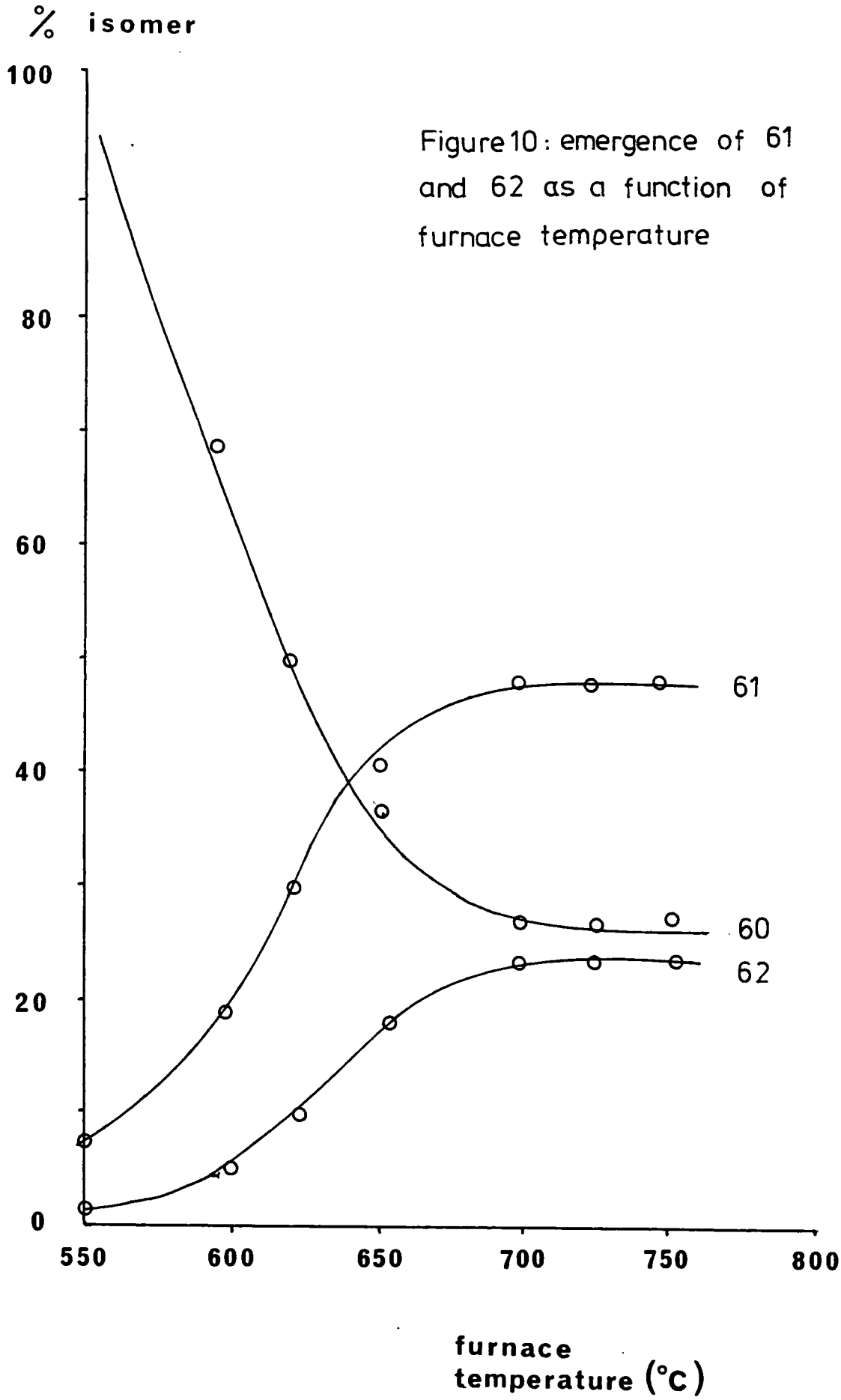
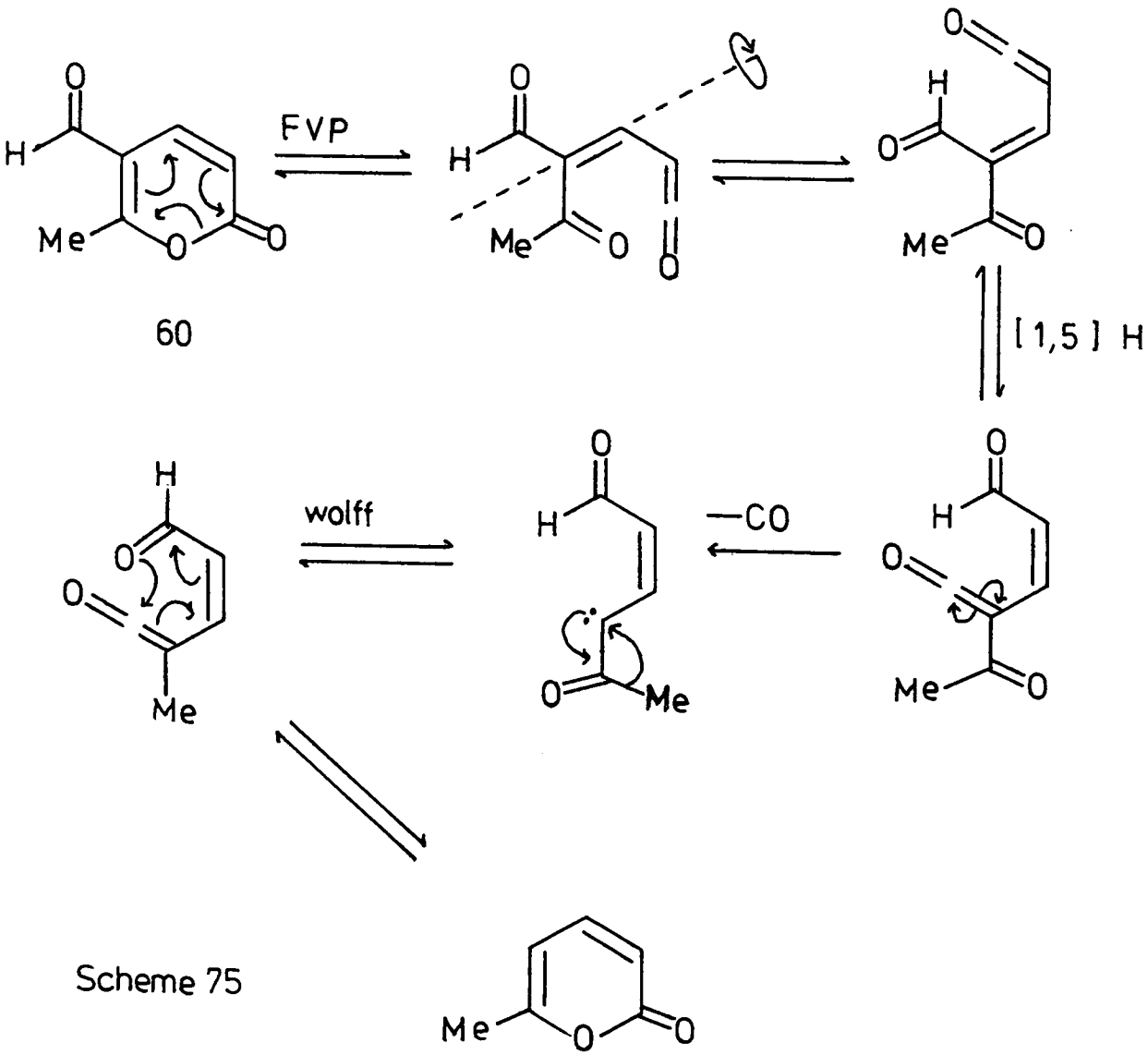


Figure 10 : emergence of 61 and 62 as a function of furnace temperature

61 and 62 to be expressed graphically (Figure 10). Thus this rearrangement further confirms that steric considerations are only needed to explain the equilibria. Indeed in this particular case the least sterically hindered isomer, 61, is the major product.

At a furnace temperature of 800°C, 60, 61 and 62 were all present in the pyrolysate mixture, with no decarbonylated product being observed. Thus the methyl group at C-6 prevents the clean decarbonylation process as observed for 51. This was an extremely interesting result as a reasonable mechanism for the decarbonylation can be envisaged (Scheme 75).



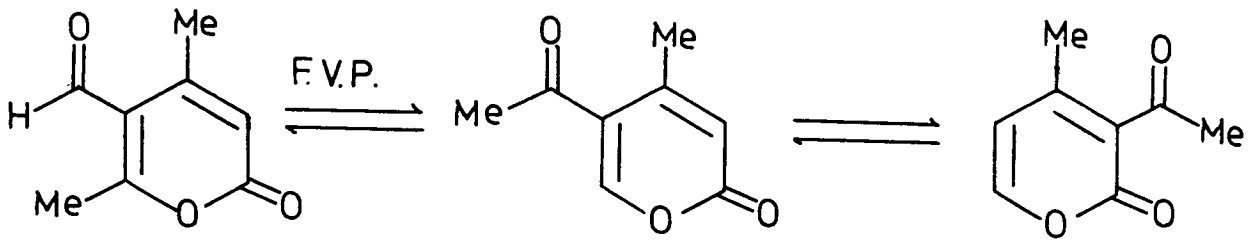
Scheme 75

Thus by comparing this mechanism with the analogous decarbonylation mechanism of 51 (Scheme 60) it appears that the loss of carbon monoxide from the ketene does not involve a free carbene, but is a concerted type process accommodated only when the migrating group is hydrogen, i.e. 51. Thus the proposed mechanism for the carbon monoxide extrusion process of 51 (Scheme 60) is therefore extremely likely, although not involving a free carbene.

The possibility of [1,3]-hydrogen sigmatropic shifts occurring between the aldehydic hydrogen and the adjacent ketene upon Flash Vacuum Pyrolysis was previously mentioned. Comparing the previous graphs obtained for the rearrangement of 51 to 52 (Figure 7) and that of the deuteriated compound 53 to 55 and 56 (Figure 8) with the graph of the isomerisation of 60 to 61 and 62 (Figure 9), it appears that the onset of these rearrangements occurs at approximately the same furnace temperature (550°C); the graphs being virtually superimposable. Thus it follows that the processes involved require similar energy. Since the isomerisation of 60 to 61 and 62 can be explained without the need for [1,3]-hydrogen shifts to ketenes it follows that all the experimental evidence suggests that such migrations do not take place in these systems.

For another example of this isomerisation process 4,6-dimethyl-2-pyrone-carboxaldehyde 63 was prepared *via* the *Rosenmund* reduction of the corresponding acid chloride. The reduction, as for 51, was undertaken in

p-xylene solution but at a slightly higher temperature of 140°C (i.e. reflux conditions) for a longer period. Again the reduction was continually monitored by t.l.c. to avoid reduction of the 2-pyrone ring. The dimethyl compound **63** was subjected to variable temperature pyrolyses and gave analogous rearranged isomers **64** and **65** *via* mechanisms previously described (Scheme 76).



63 64 65

Scheme 76

The emergence of **64** and **65** in the pyrolysate mixture was also expressed graphically (Figure 11).

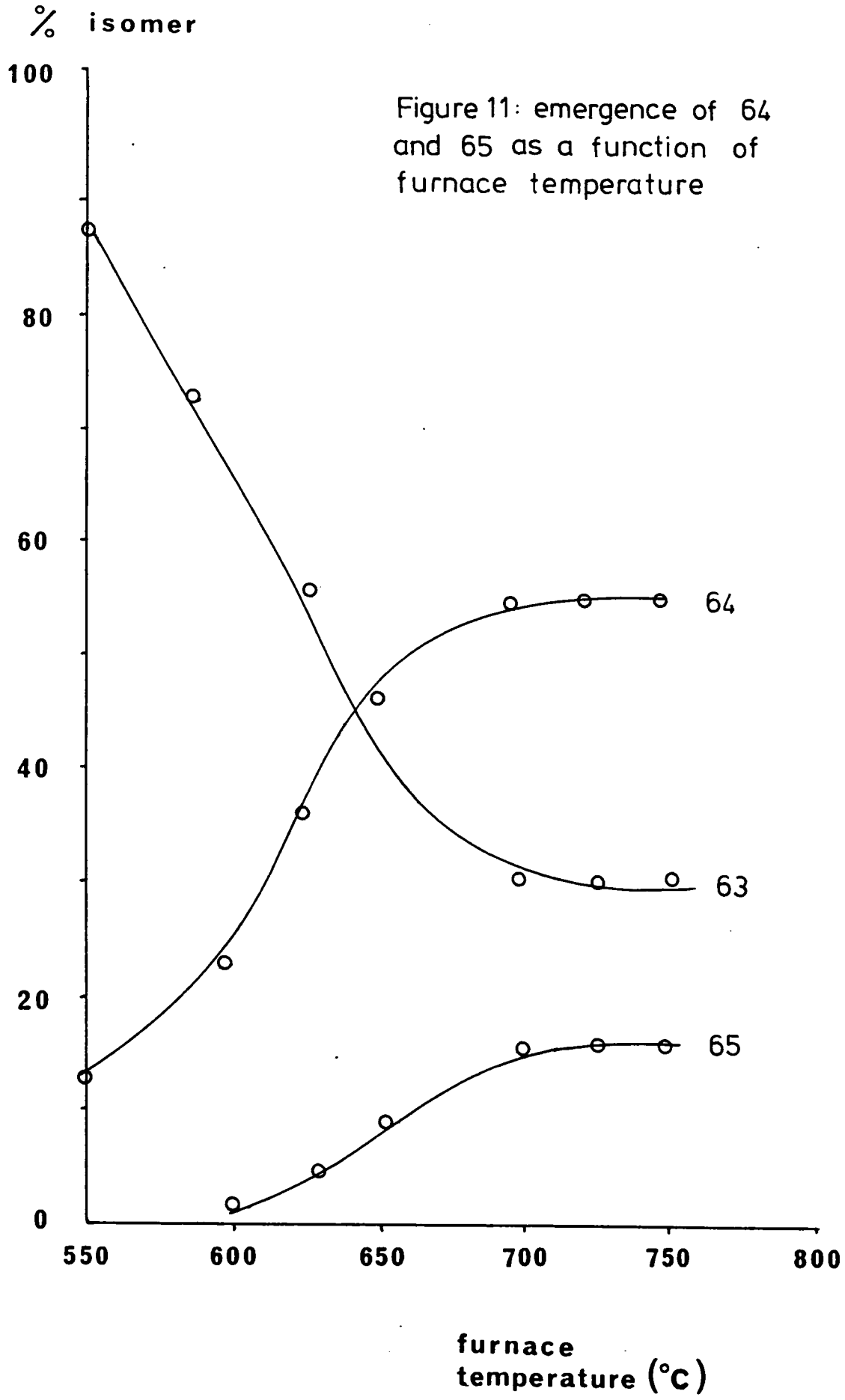


Figure 11: emergence of 64 and 65 as a function of furnace temperature

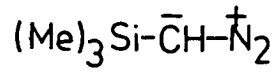
REACTION OF 2-PYRONE-5-CARBOXALDEHYDE 51 WITH OTHER DIAZO COMPOUNDS

The reaction of 51 with diazomethane which gave the 6-methyl compound 60 (Scheme 73) was quite surprising due to its specificity and high yield. Thus it seemed appropriate to investigate this reactivity of 51 with other diazo compounds.

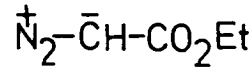
Phenyldiazomethane was generated *in situ* by heating a benzaldehyde tosylhydrazone salt[110] in benzene at a temperature of 80°C. As soon as a pink colour developed in the hot benzene solution, a solution of 51 in benzene was added dropwise. T.l.c. of the hot solution, after 1 hour, indicated the reaction was unsuccessful. Starting material 51, together with stilbene and benzaldazine were identified by comparative t.l.c. analysis and ^{1}H nmr. A slight variation involved the distillation and subsequent condensing of phenyldiazomethane under high vacuum. The contents of the trap containing phenyldiazomethane were dissolved in dichloromethane and were added dropwise to an ice cold solution of 51. This reaction again proved unsuccessful with a high recovery of starting material 51.

Other diazo compounds were reacted with 51 and also with methyl coumalate. Trimethylsilyldiazomethane[111] 66 and ethyldiazonium acetate[112] 67 were employed using a variety of conditions. Room temperature and reflux conditions under $N_{2(g)}$ atmospheres failed to achieve

successful reaction, with a high recovery of starting materials after dry flash chromatography.



66



67

DECARBOXYLATION OF 2-PYRONE-5-CARBOXYLIC ACIDS

Coumalic acid 2 (R_1=R_2=H) has been decarboxylated to 2-pyrone 1 *via* several techniques. However the actual mechanism of the extrusion process has never been investigated. As previously mentioned 2-pyrone-5-carboxaldehyde 51 can be cleanly decarbonylated to 2-pyrone 1 *via* Flash Vacuum Pyrolysis (F.V.P.), at a furnace temperature of 800°C, with the onset of loss of carbon monoxide occurring at a furnace temperature of 650°C. Ring-opened intermediates are probably involved. Coumalic acid 2 (R_1=R_2=H) was subjected to variable temperature pyrolysis and the emergence of 2-pyrone 1 in the pyrolysate mixture expressed graphically (Figure 12). At a furnace temperature of 800°C coumalic acid 2 was completely decarboxylated.

A reasonable mechanism for this extrusion process

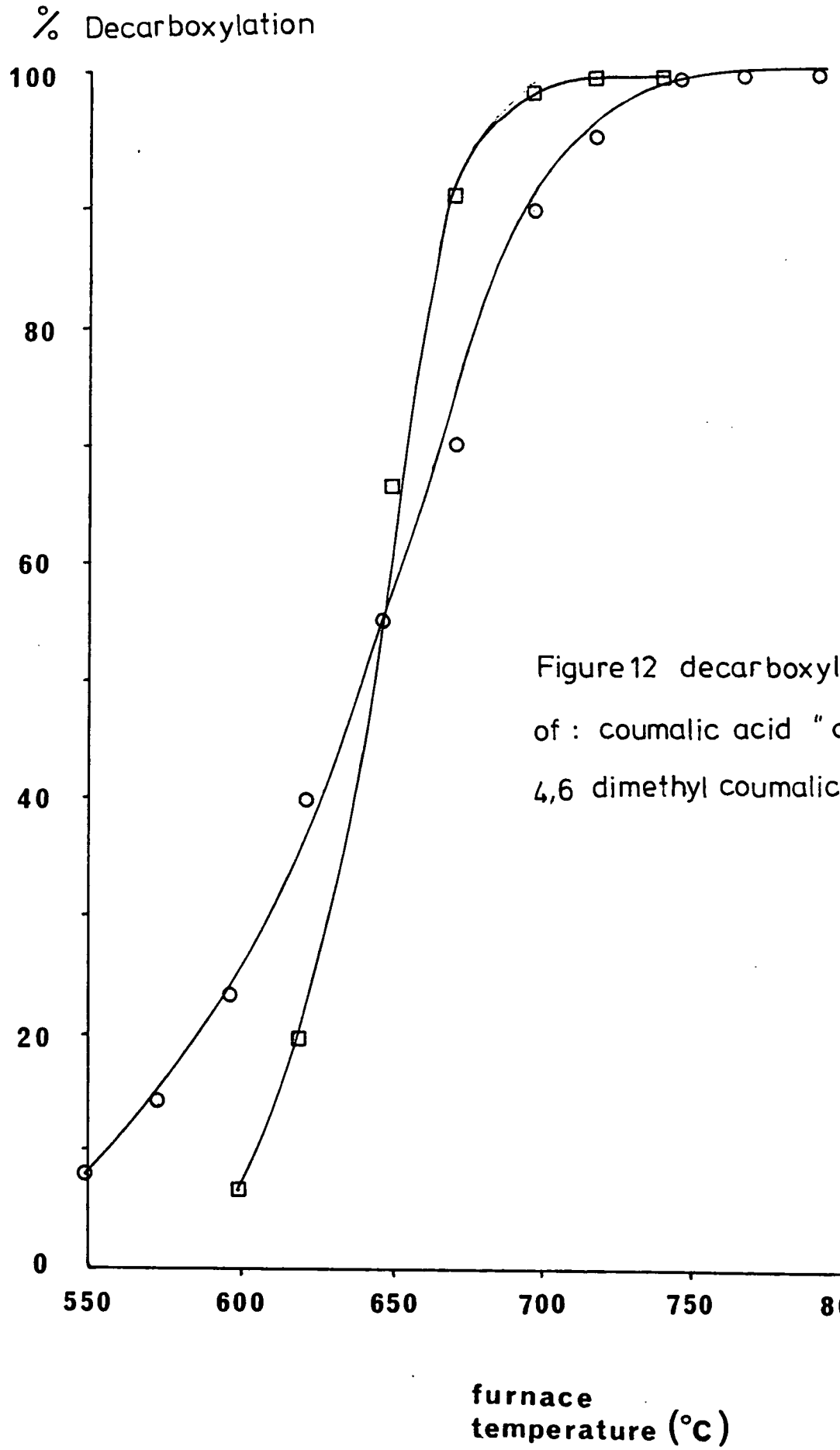
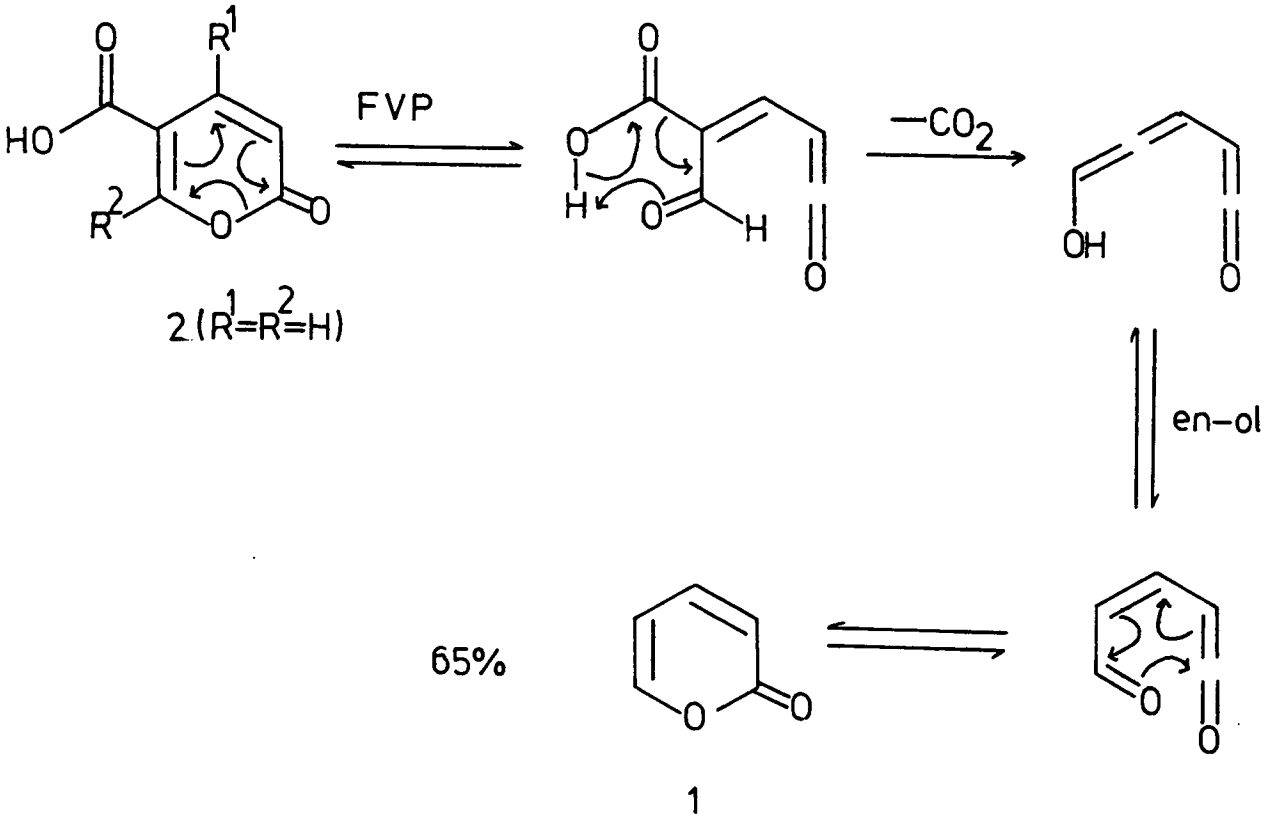


Figure 12 decarboxylation of : coumalic acid "o" and 4,6 dimethyl coumalic acid "□"

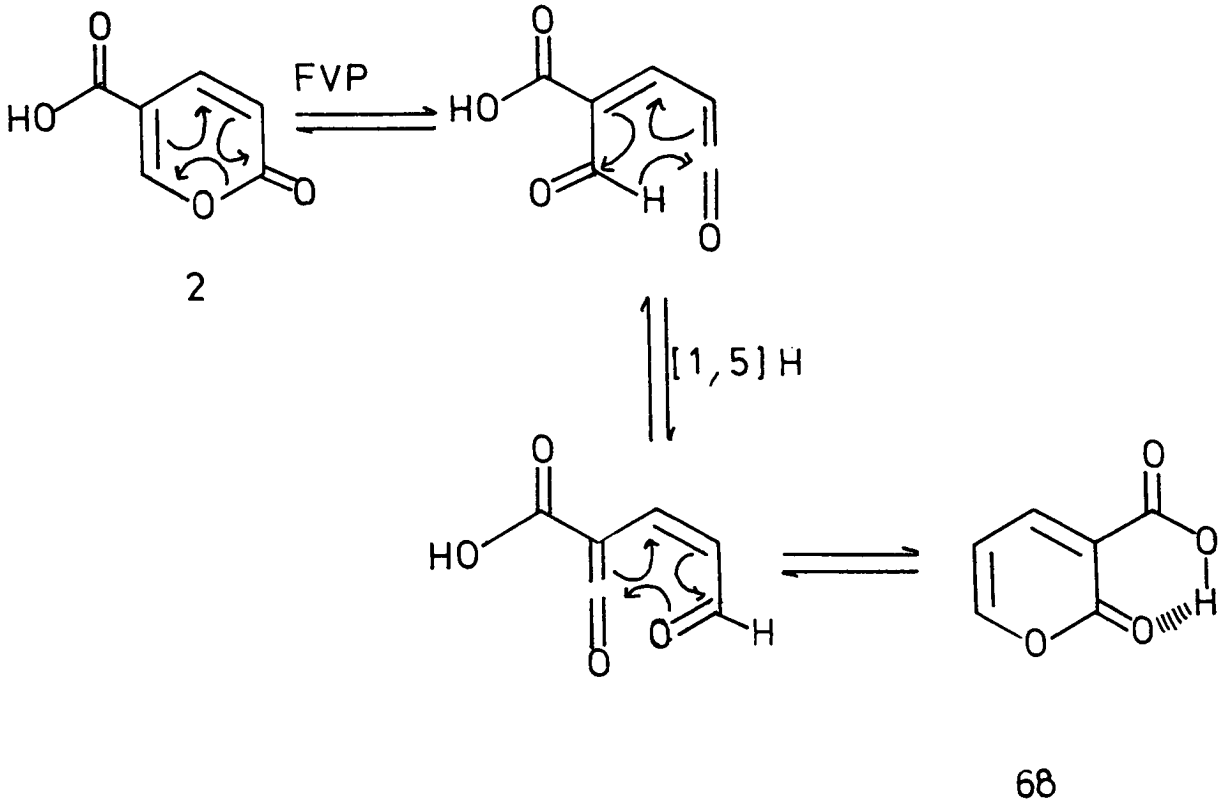
involves an initial ring opened ketene species (Scheme 77).



Scheme 77

The onset of decarboxylation occurred at the relative low furnace temperature of 550°C, previously associated with ring opening. It was extremely surprising to discover that rearrangement to the 3-substituted isomer **68** was not observed, as a very stable hydrogen bonded

structure could be envisaged (Scheme 78).



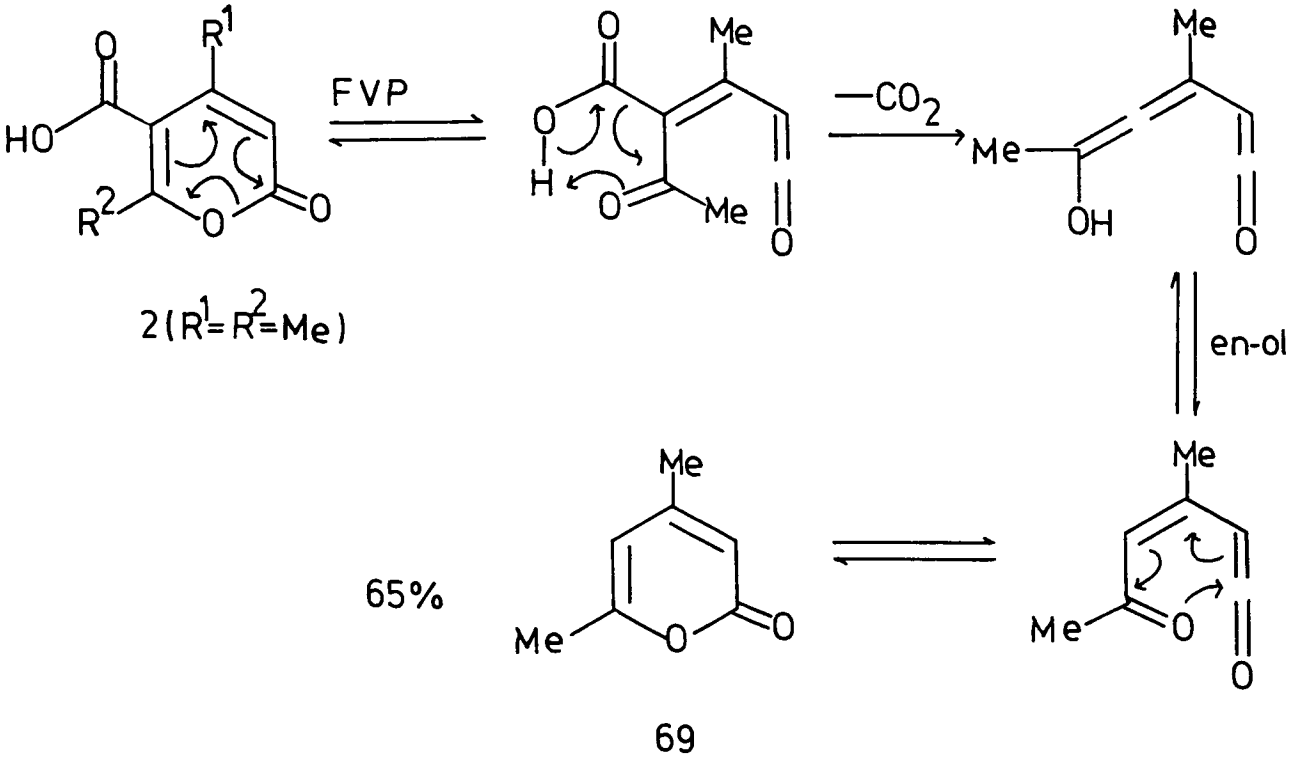
2

68

Scheme 78

The mechanism described above (Schemes 77 and 78) for the decarboxylation process relies only upon initial ring opening of the 2-pyrone system, and appears to be independent of any [1,5] hydrogen shifts. To test this mechanism 4,6-dimethyl-2-pyrone-5-carboxylic acid (isodehydroacetic acid) 2 (R_1=R_2=Me) was subjected to variable temperature pyrolysis. This compound was also cleanly decarboxylated to 4,6-dimethyl-2-pyrone 69 as

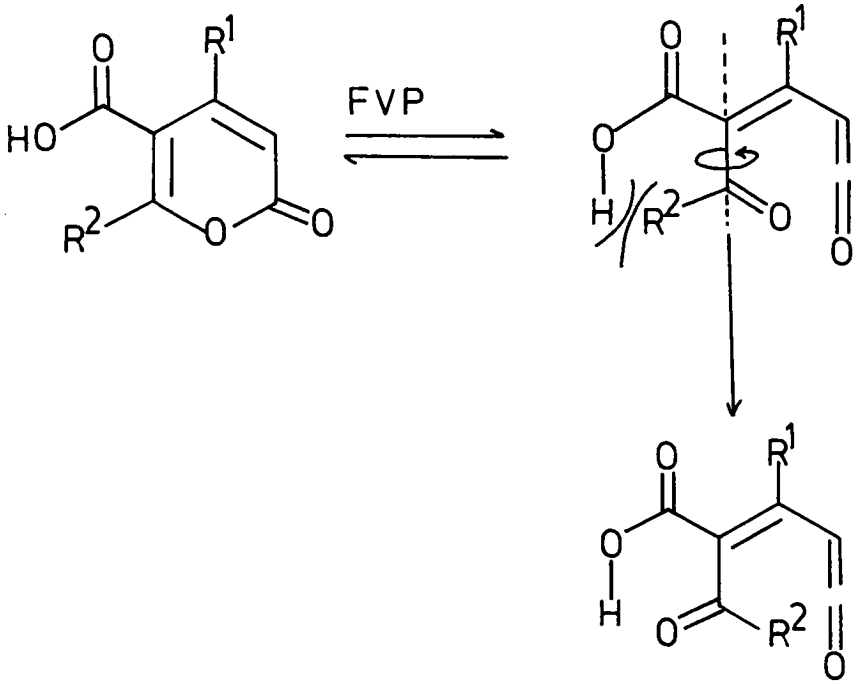
identified by its ^1H nmr spectrum. An analogous mechanism for this process is shown below (Scheme 79).



Scheme 79

The emergence of **69** as a function of furnace temperature was also expressed graphically. For comparison the emergence of **69** is illustrated on the same graph as the decarboxylation of coumalic acid (Figure 12). It can be seen from this plot that the 4,6-dimethyl-2-pyrone-5-carboxylic starts to undergo decarboxylation at a slightly higher furnace temperature than coumalic acid, but then at the higher furnace temperatures decarboxylation of the 4,6-dimethyl acid then "overtakes" coumalic acid. The compositions shown on the graph are

highly reproducible. A reasonable explanation involves closer inspection of the proposed mechanism, which can be defined in two important stages. The methyl groups very probably increase the electron density of the 2-pyrone ring, thus making it slightly more difficult to ring open, hence the increase in furnace temperature needed to initiate ring opening. Also in order for decarboxylation to occur the oxygen hetero atom of the 2-pyrone ring, has to be near the carboxylic acid group, this can be achieved by an internal rotation about a carbon-carbon bond (Scheme 80).

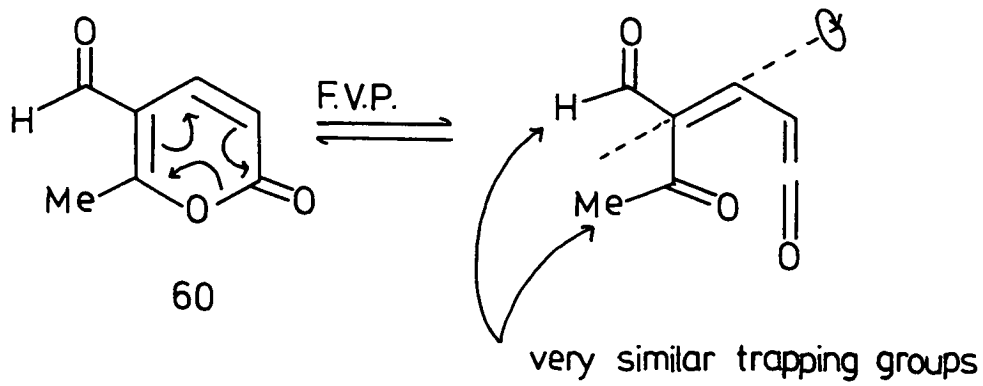


Scheme 80

This internal rotation is probably enhanced when R_2 is a methyl group relative to when R_2 is hydrogen, due to steric repulsion.

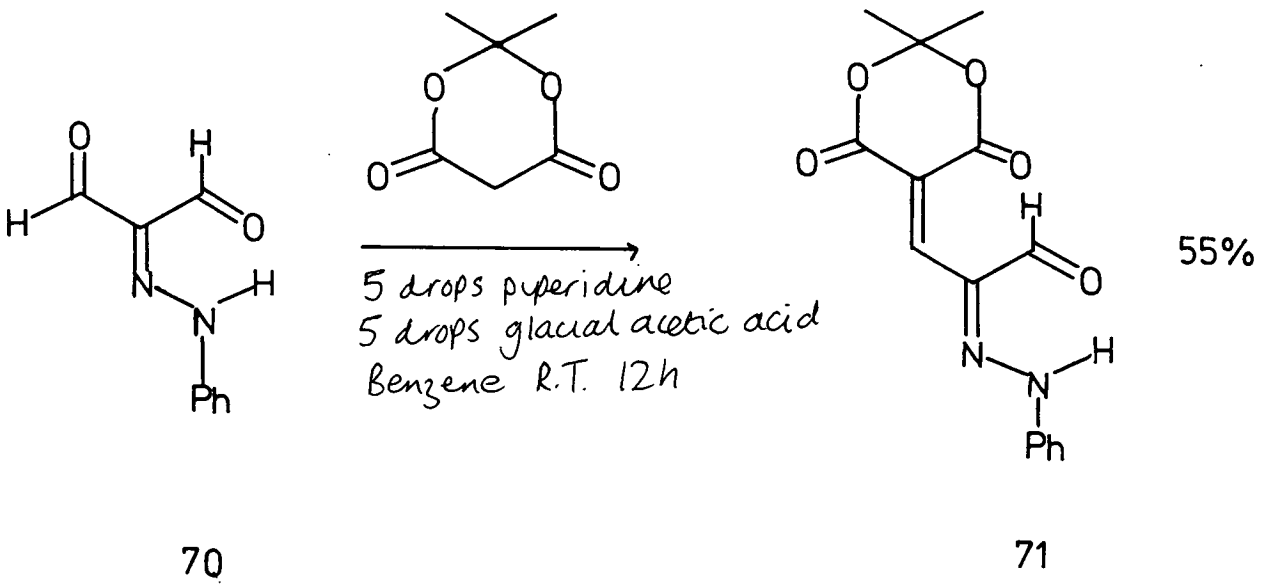
EFFECT OF THE TRAPPING GROUP IN THE 5-POSITION OF 2-PYRONES

It was previously shown that when the 6-methyl-2-pyrone-5-carboxaldehyde 60 was pyrolysed, rearrangement to 61 and 62 occurred (Scheme 74), eventually resulting in the thermodynamic equilibrium mixture. In this particular case, the trapping group in the 5-position was a carbonyl group and is very similar in nature to the methyl ketone group which was produced upon initial ring opening (Scheme 81).



Scheme 81

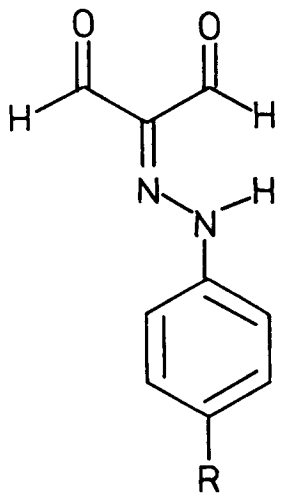
Thus it is not surprising that an equilibrium mixture eventually results, due to this similarity of potential trapping groups. The pyrolysis of a Meldrum's Acid derivative[71] illustrated how the type of trapping group in the 5-position of 2-pyrones can be important in directing the position of equilibrium between isomers. The synthesis of **71** involves condensation of phenylazomalondialdehyde[70] (prepared *via* reaction of phenyldiazoniumtetrafluoroborate $[PhN_2]^+[BF_4]^-$, with 1,1,3,3-tetramethoxy propane[113]) with Meldrum's Acid, under standard Knoevenagel reaction conditions (Scheme 82).



70 71

Scheme 82

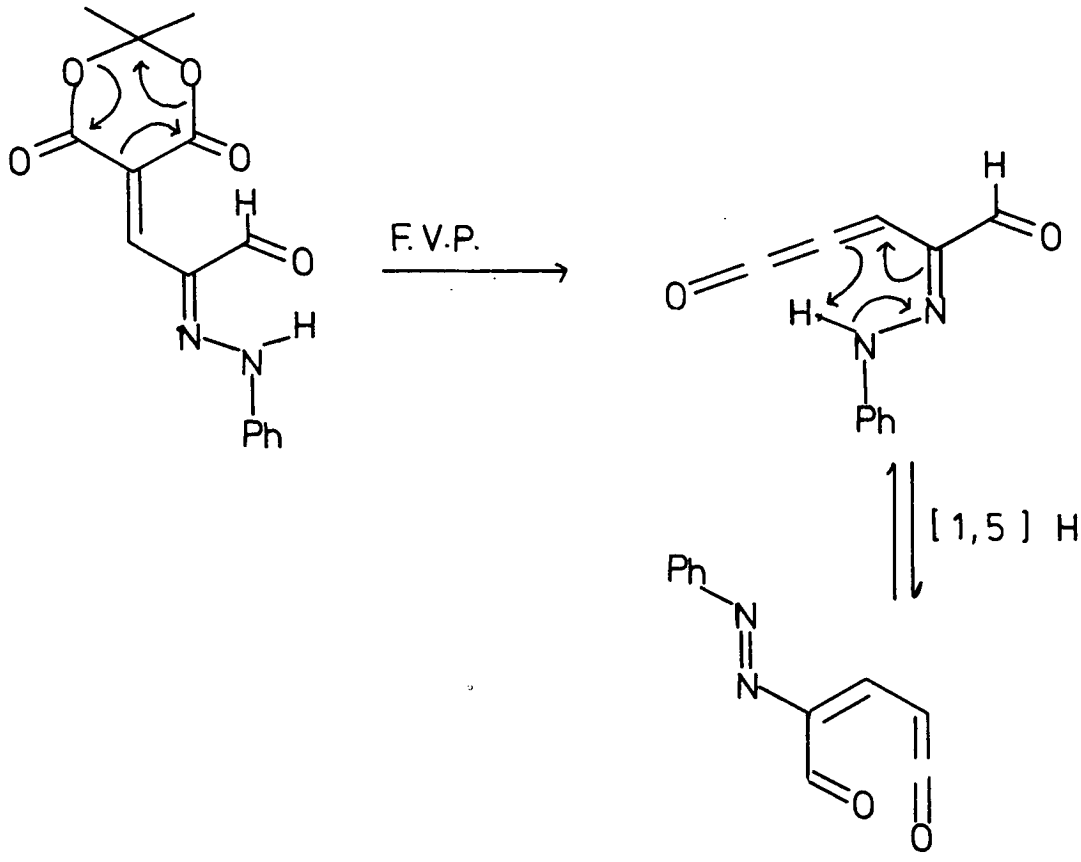
p-Tolylazo- and *p*-nitrophenyl-azo malondialdehydes were also produced (72 and 73).



72 R= Me

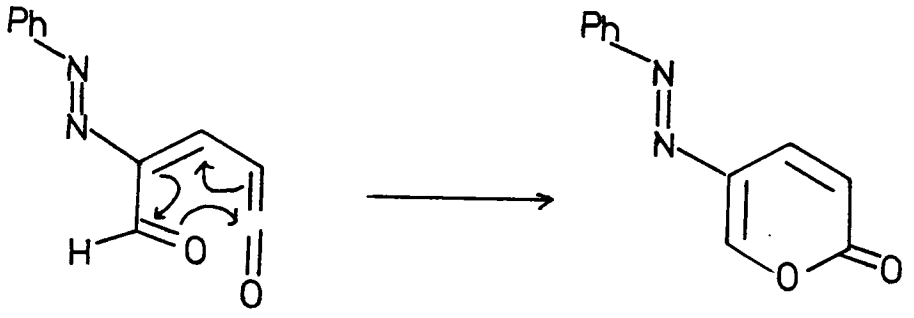
73 R= NO_2

Both 72 and 73 failed to react cleanly with Meldrum's Acid under a variety of conditions[114,115]. Upon Flash Vacuum Pyrolysis, 71 undergoes loss of carbon dioxide and acetone to yield the methyleneketene, which undergoes a [1,5] hydrogen sigmatropic shift affording the recognisable 2-pyrone derived ketene (Scheme 83).



Scheme 83

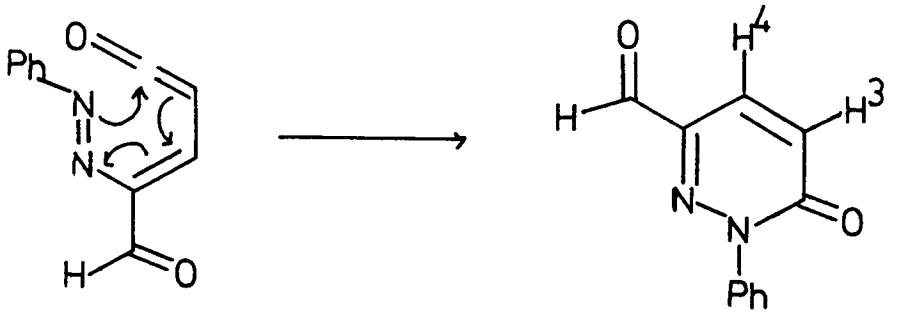
It thus appears that this ketene has two ring closure pathways available. The ketene could be trapped by the aldehyde group (Scheme 84), or alternatively trapping by



74

Scheme 84

the azo group could occur (Scheme 85).



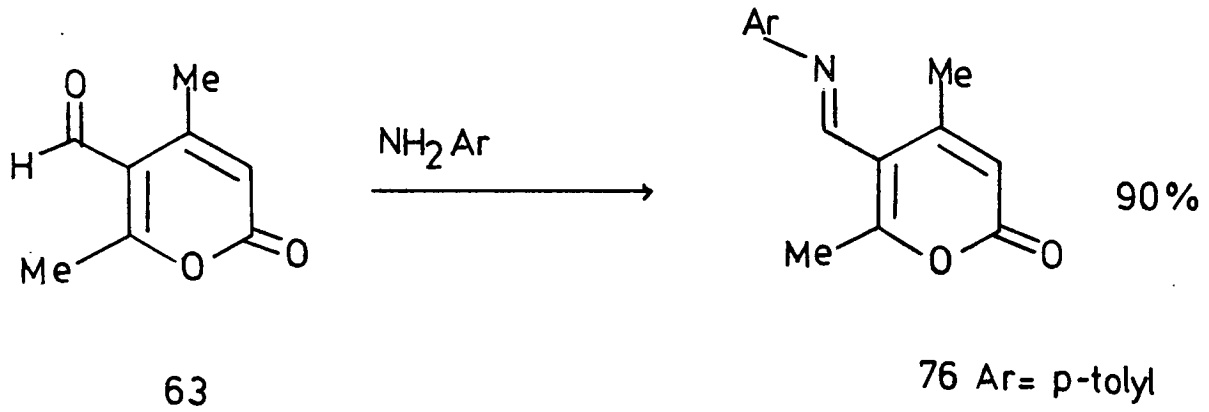
75

Scheme 85

However, a single isomer was obtained in 48% yield. ^{1}H nmr showed an aldehydic resonance at $\delta_{^1H}$ 9.77 ppm and J_{HH} 9.7 Hz indicative of the pyridazinone isomer 75. This pyrolysis was not particularly high yielding with respect to the starting material, since 71 decomposed in the inlet tube upon sublimation. Only *half* of 71 in the inlet tube was actually sublimed through the furnace tube, so the

rearrangement was quite efficient based upon the *actual* amount of 71 successfully pyrolysed.

Thus it appears that 75 is thermodynamically more stable than 74. To test this observation further, the imine 76 was produced *via* reaction of 4,6-dimethyl-2-pyrone-5-carboxyaldehyde 63 with *p*-toluidine. The methyl group at C-6 now hinders nucleophilic attack at this position, thus allowing preferential reaction at the aldehyde (Scheme 86).

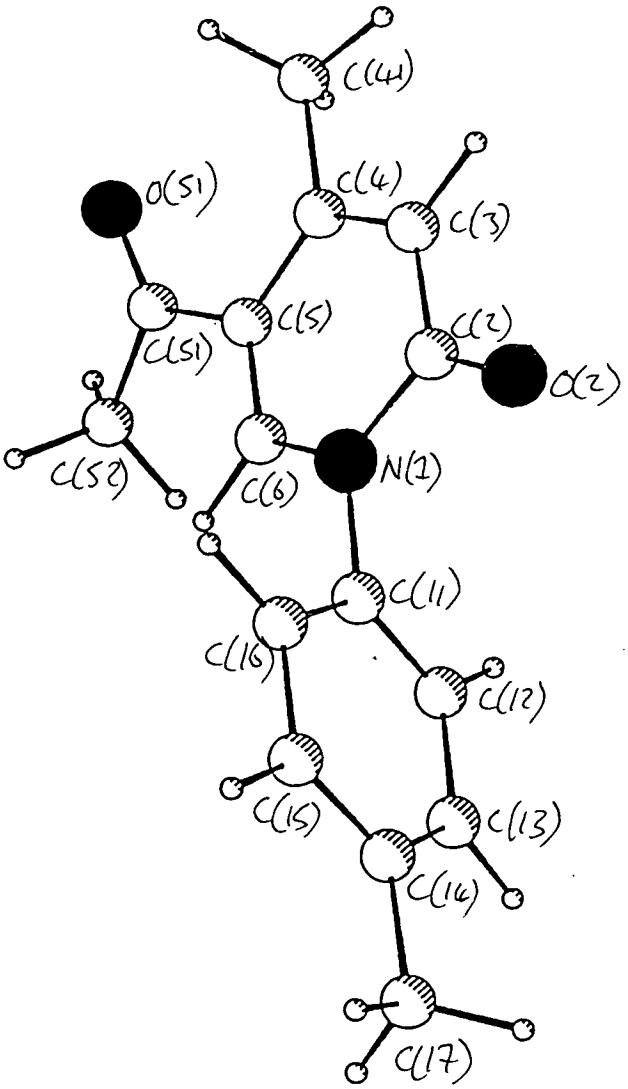


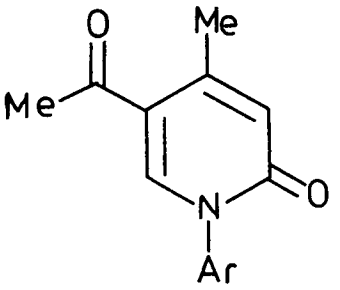
63

76 Ar= p-tolyl

Scheme 86

The imine 76 was subjected to Flash Vacuum Pyrolysis (F.V.P.) at a furnace temperature of 650°C and gave a virtually quantitative yield of the rearranged pyridone isomer 77, identified by ^{1}H nmr (Scheme 87).





Ar= p-tolyl

Figure 13 X ray crystal structure of 77

Torsion angles(degrees) with standard deviations

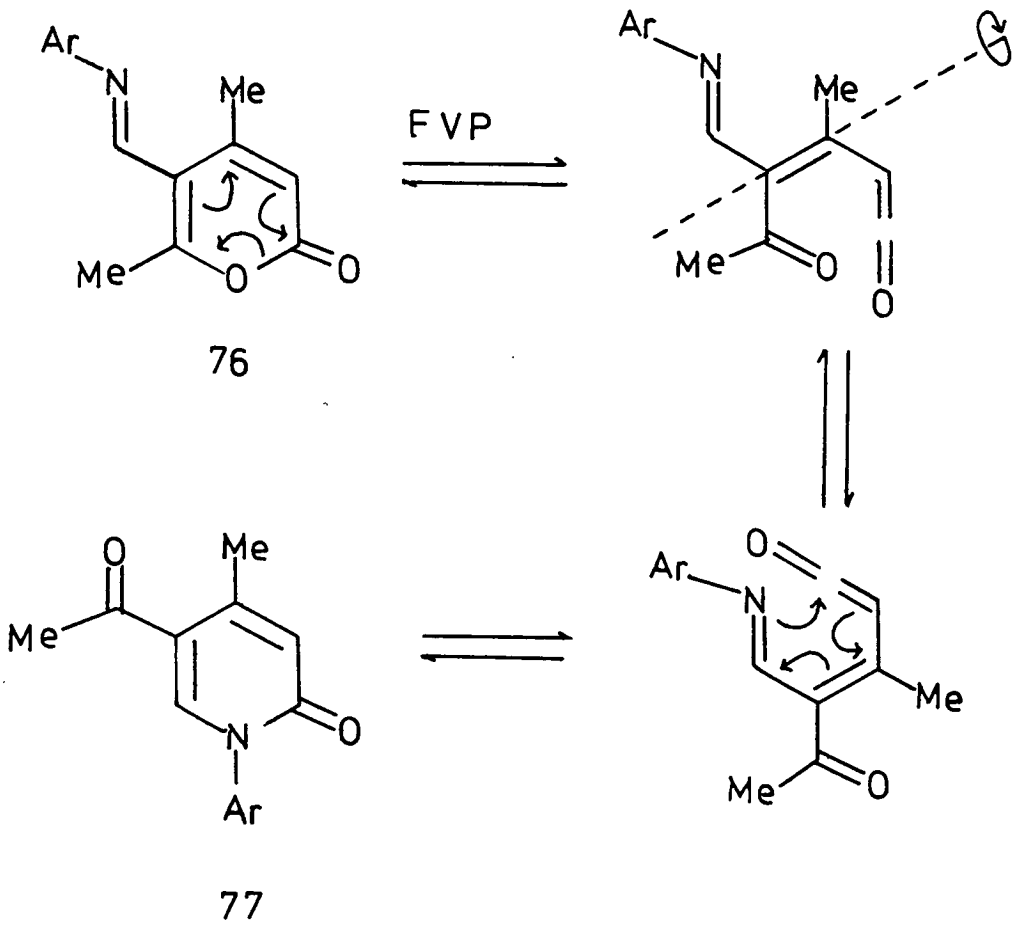
C(6)	N(1)	C(2)	C(3)	-1.7(15)	
C(6)	N(1)	C(2)	O(2)	179.7(10)	
(11)	N(1)	C(2)	C(3)	178.5(10)	
(11)	N(1)	C(2)	O(2)	-0.1(15)	
C(2)	N(1)	C(6)	C(5)	0.9(16)	
(11)	N(1)	C(6)	C(5)	-179.3(11)	
C(2)	N(1)	-C(11)	-C(12)	-82.2(13)	
C(2)	N(1)	-C(11)	-C(16)	97.7(13)	
C(6)	N(1)	-C(11)	-C(12)	98.0(13)	
C(6)	N(1)	-C(11)	-C(16)	-82.1(14)	
N(1)	C(2)	C(3)	C(4)	-0.6(16)	
O(2)	C(2)	C(3)	C(4)	178.0(11)	
C(2)	C(3)	C(4)	C(5)	3.5(18)	
C(2)	C(3)	C(4)	-C(41)	-176.8(10)	
C(3)	C(4)	C(5)	C(6)	-4.3(17)	
C(3)	C(4)	C(5)	-C(51)	-179.3(11)	
C(41)	C(4)	C(5)	C(6)	176.1(11)	
C(41)	C(4)	C(5)	-C(51)	1.1(18)	
C(4)	C(5)	C(6)	N(1)	2.1(17)	
C(51)	C(5)	C(6)	N(1)	177.2(11)	
C(4)	C(5)	-C(51)	-O(51)	13.4(20)	
C(4)	C(5)	-C(51)	-C(52)	-165.6(11)	
C(6)	C(5)	-C(51)	-O(51)	-161.5(13)	
C(6)	C(5)	-C(51)	-C(52)	19.5(17)	
N(1)	-C(11)	-C(12)	-C(13)	177.2(10)	
C(16)	-C(11)	-C(12)	-C(13)	-2.7(18)	
N(1)	-C(11)	-C(16)	-C(15)	-178.0(10)	
C(12)	-C(11)	-C(16)	-C(15)	1.9(19)	
C(11)	-C(12)	-C(13)	-C(14)	-2.5(18)	
C(12)	-C(13)	-C(14)	-C(15)	8.0(20)	
C(12)	-C(13)	-C(14)	-C(17)	-178.2(12)	
C(13)	-C(14)	-C(15)	-C(16)	-8.6(19)	
C(17)	-C(14)	-C(15)	-C(16)	177.3(12)	
C(14)	-C(15)	-C(16)	-C(11)	3.8(18)	

Bond Lengths(A) with standard deviations

N(1)	C(2)	1.426(14)	
N(1)	C(6)	1.347(14)	
N(1)	-C(11)	1.459(15)	
C(2)	C(3)	1.428(16)	
C(2)	O(2)	1.209(13)	
C(3)	C(4)	1.367(16)	
C(4)	C(5)	1.423(17)	
C(4)	-C(41)	1.530(16)	
C(5)	C(6)	1.339(16)	
C(5)	-C(51)	1.481(18)	
C(11)	-C(12)	1.375(17)	
C(11)	-C(16)	1.367(17)	
C(12)	-C(13)	1.409(17)	
C(13)	-C(14)	1.347(18)	
C(14)	-C(15)	1.421(19)	
C(14)	-C(17)	1.492(19)	
C(15)	-C(16)	1.390(17)	
C(51)	-O(51)	1.190(16)	
C(51)	-C(52)	1.497(17)	

Angles(degrees) with standard deviations

C(2)	N(1)	C(6)	122.2(9)		
C(2)	N(1)	-C(11)	117.3(9)		
C(6)	N(1)	-C(11)	120.6(9)		
N(1)	C(2)	C(3)	115.2(9)		
N(1)	C(2)	O(2)	120.5(9)		
C(3)	C(2)	O(2)	124.3(10)		
C(2)	C(3)	C(4)	120.9(11)		
C(3)	C(4)	C(5)	120.7(11)		
C(3)	C(4)	-C(41)	116.5(10)		
C(5)	C(4)	-C(41)	122.8(10)		
C(4)	C(5)	C(6)	118.2(11)		
C(4)	C(5)	-C(51)	121.1(11)		
C(6)	C(5)	-C(51)	120.4(11)		
N(1)	C(6)	C(5)	122.6(10)		
N(1)	-C(11)	-C(12)	115.6(10)		
N(1)	-C(11)	-C(16)	120.7(10)		
C(12)	-C(11)	-C(16)	123.8(11)		
C(11)	-C(12)	-C(13)	116.6(11)		
C(12)	-C(13)	-C(14)	122.4(12)		
C(13)	-C(14)	-C(15)	118.5(12)		
C(13)	-C(14)	-C(17)	121.8(12)		
C(15)	-C(14)	-C(17)	119.4(12)		
C(14)	-C(15)	-C(16)	120.1(11)		
C(11)	-C(16)	-C(15)	118.1(11)		
C(5)	-C(51)	-O(51)	124.4(12)		
C(5)	-C(51)	-C(52)	117.9(11)		
O(51)	-C(51)	-C(52)	117.7(12)		

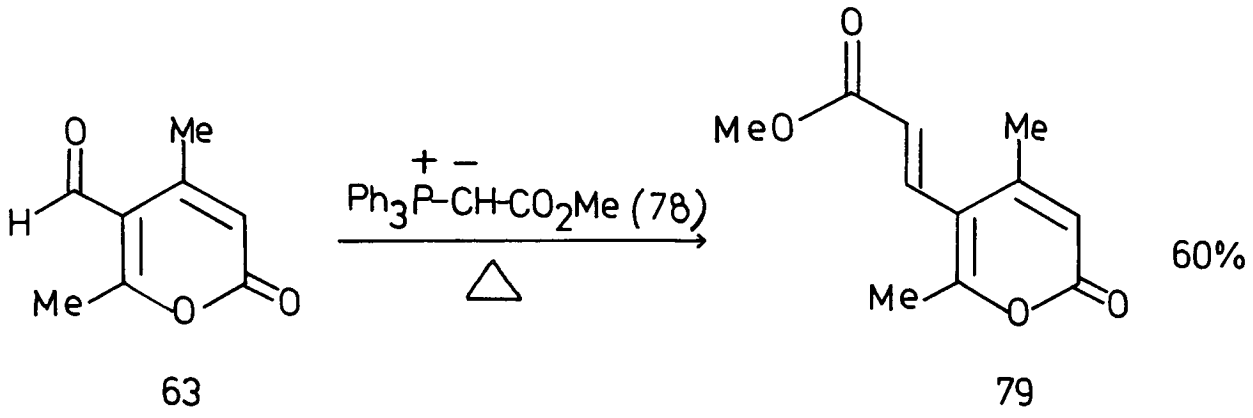


Scheme 87

The imine proton ($\delta_{^1H}$ 8.04) of 76 was absent, with the emergence of a new resonance at $\delta_{^1H}$ 7.98 corresponding to H-6 of rearranged isomer 77. The structure of 77 was further confirmed by X-ray crystallographic analysis (Figure 13).

An alternative trapping group was placed in the 5-position *via* a Wittig reaction of 63 with the stabilised ylid 78[116] affording the olefin 79 in reasonable yield. The reaction was undertaken in toluene solution under

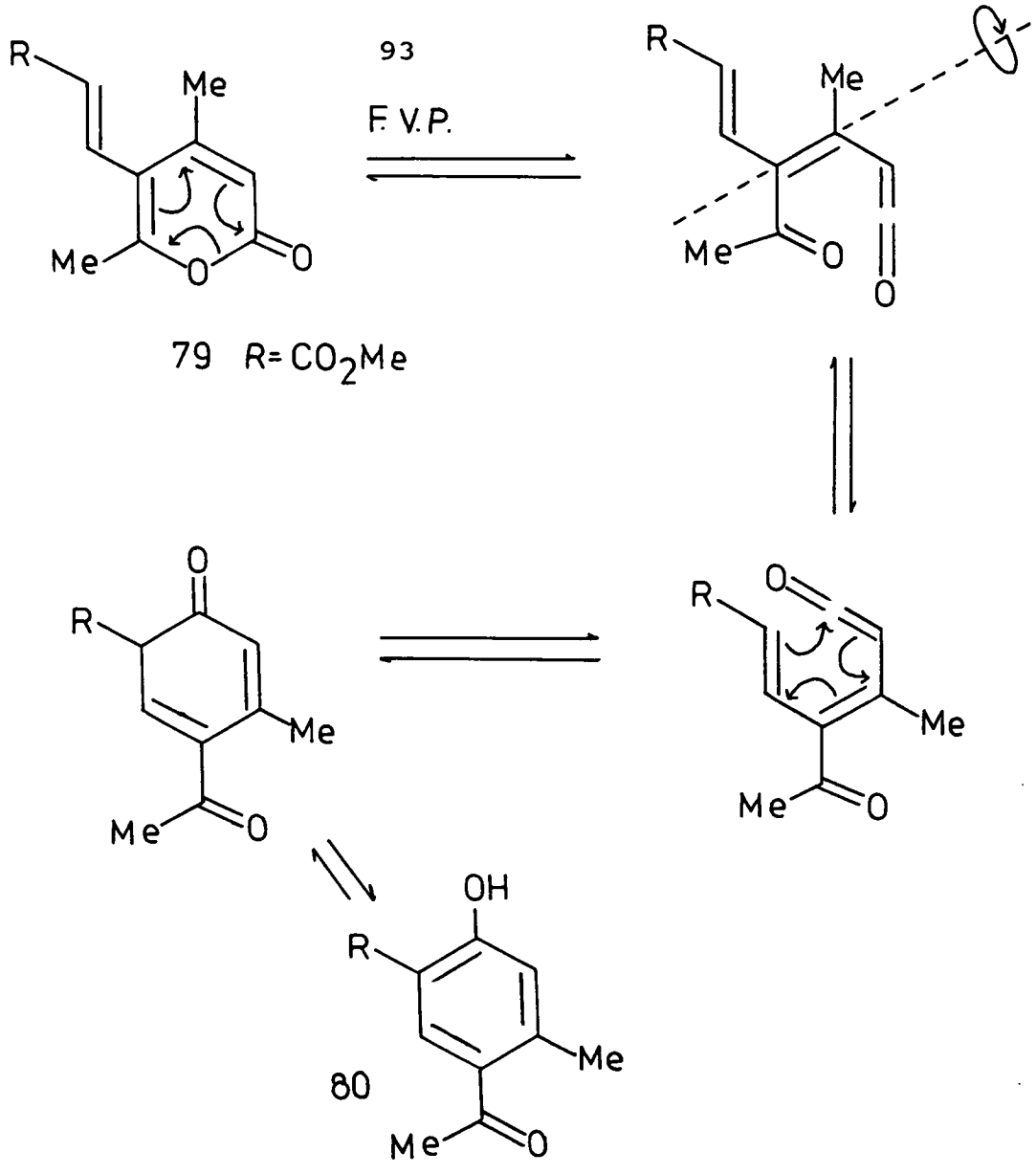
reflux conditions for one hour, followed by dry flash chromatography of the residue so produced after the solution was concentrated to near dryness (Scheme 88).



63 79

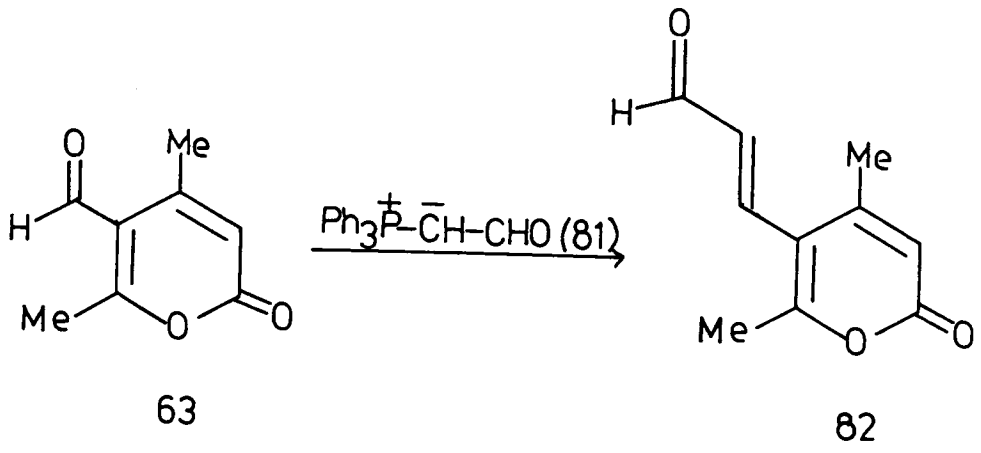
Scheme 88

It was hoped that the olefin **79** would rearrange analogously to the imine **76** (Scheme 87) upon pyrolysis, affording the benzenoid isomer **80** (Scheme 89).



Scheme 89

However, the pyrolysis of 79 at 650°C was not successful, with no clean rearrangement to 80 observed; only an intractable dark viscous material was produced which was not investigated further. The ester function was probably not very robust towards pyrolysis, and to try to overcome this problem an alternative stabilised ylid 81 was employed in the Wittig reaction with 63 (Scheme 90).

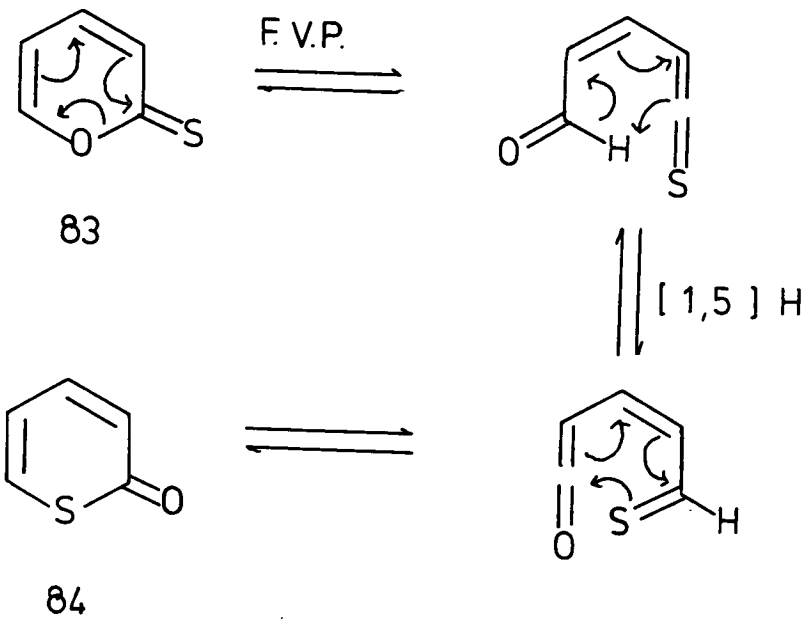


63 82

Scheme 90

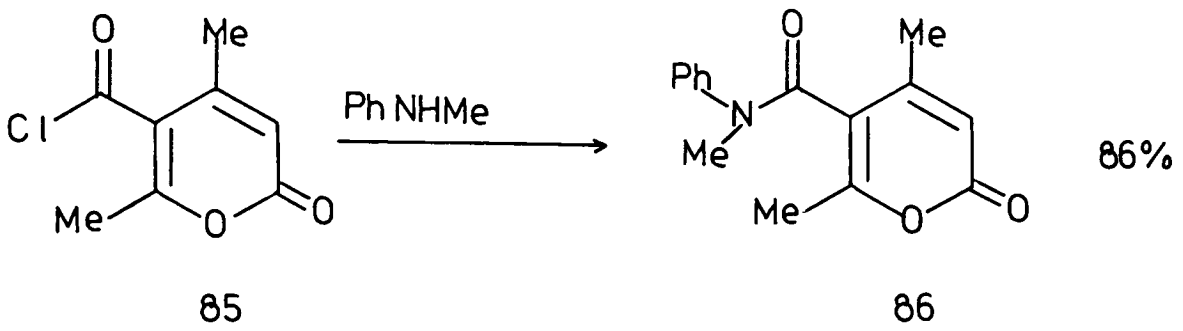
However reflux conditions in toluene solution failed to achieve successful reaction even after eight hours. Longer reaction periods, even when the experiment was conducted under an atmosphere of nitrogen, promoted decomposition of both the reactants, and thus this reaction was abandoned after several attempts.

It was thought very possible that a thio-amide group in the 5-position of the 2-pyrone system would be a good trapping group. Previous work by Pirkle[102] has shown that pyran-2-thione 83 can be isomerised completely to thiapyranone 84 under Flash Vacuum Pyrolysis (F.V.P.) techniques (Scheme 91).



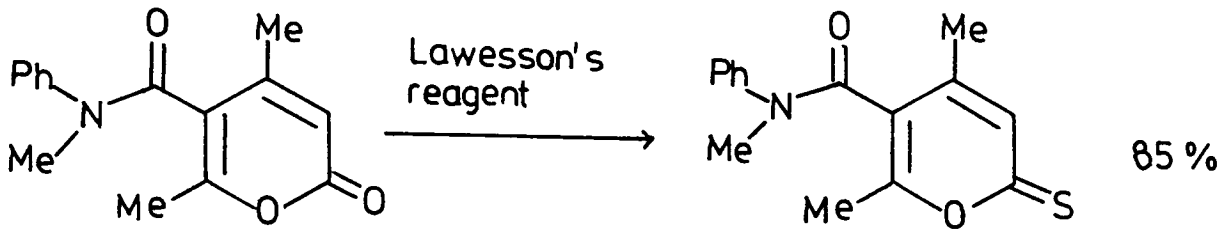
Scheme 91

First the amide 86 was prepared by reacting the acid chloride of isodehydroacetic acid 85 with *N*-methyl aniline (Scheme 92).



Scheme 92

The ^{1}H nmr of **86** showed the chemical shift of 3-H was δ_H 6.15 ppm and the corresponding ^{13}C shift of C-3 was δ_C 111.43 ppm. Previous work[117,118] had shown that smooth thiation of the carbonyl group in both esters and amides could be achieved by the use of Lawesson's reagent. The amide **86** was treated with this reagent under standard conditions[117,118]. A very good yield of a fine yellow microcrystalline material was obtained. Examination of this product by ^{1}H nmr showed that 3-H had shifted to higher frequency (δ_H 6.88 ppm). The ^{13}C resonance had also been shifted to higher frequency (δ_C 127.97 ppm). thus it appears that the amide **86** underwent thiation of the pyrone carbonyl group rather than the amide carbonyl group (Scheme 93).



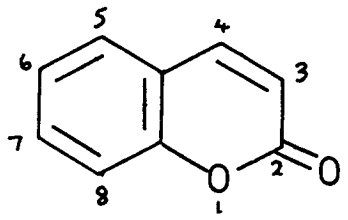
86

Scheme 93

This thiation reaction was not investigated further.

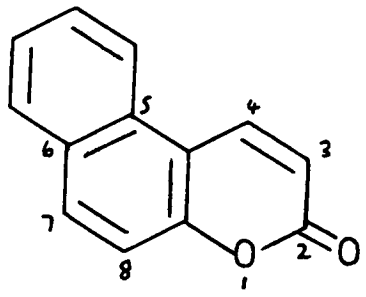
REARRANGEMENT OF BENZOFUSED 2-PYRONE SYSTEMS

It was of interest to investigate how a fused benzene ring affected the ring opening of the 2-pyrone system. One such system is shown below.



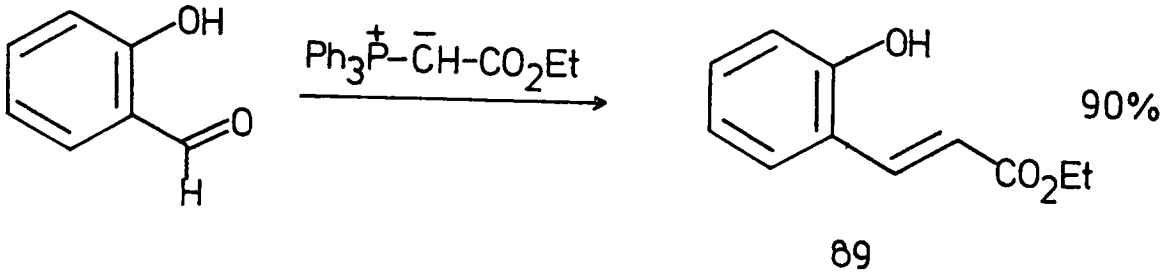
Coumarin 87

However, coumarin has no trapping group in the desired 5-position. A related compound, 5,6-benzocoumarin **88** appeared to have such a trapping group.



88

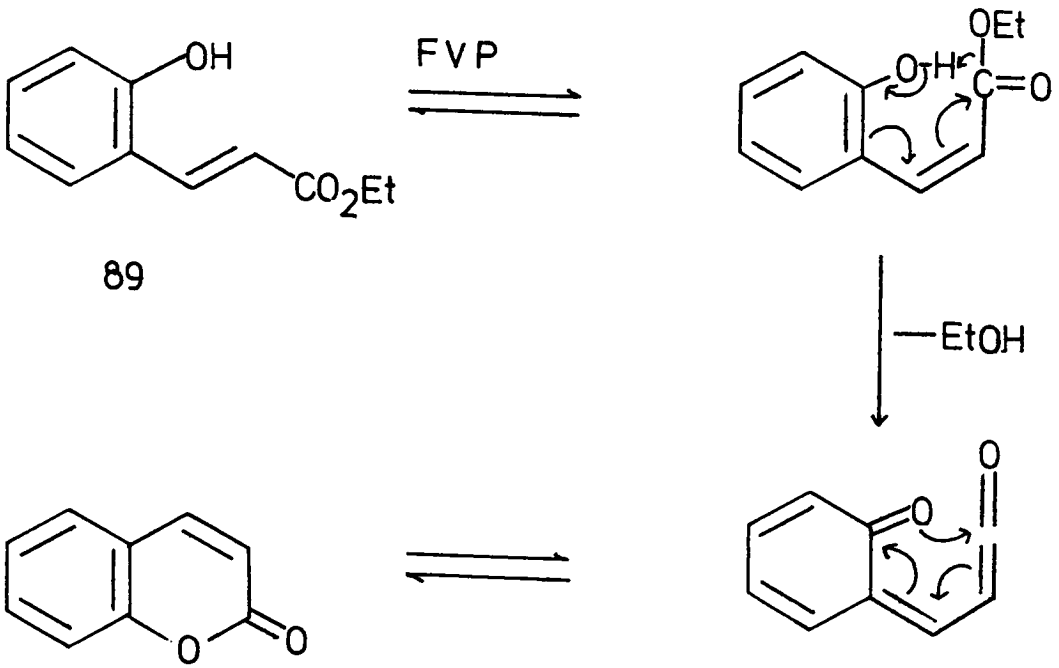
In this particular case the ketene required was generated independently from an acrylate compound. It has been shown[119,120] that *o*-hydroxy benzaldehyde undergoes efficient Wittig reactions with various stabilised ylids. The general reaction is illustrated below (Scheme 94).



89

Scheme 94

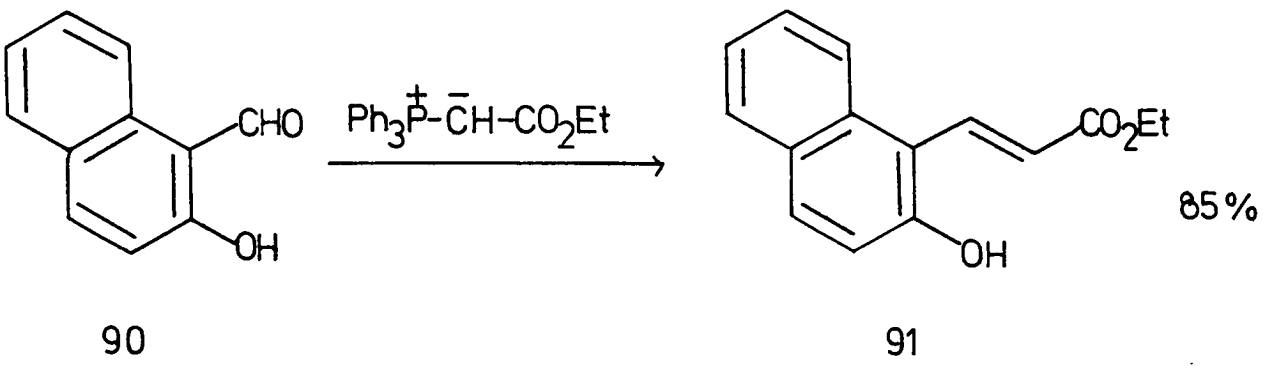
The acrylates (i.e. 89) readily lose ethanol, upon heating in toluene solutions, producing the familiar ketene intermediate which collapses to form the fused 2-pyrone ring 87 (Scheme 95).



89 87

Scheme 95

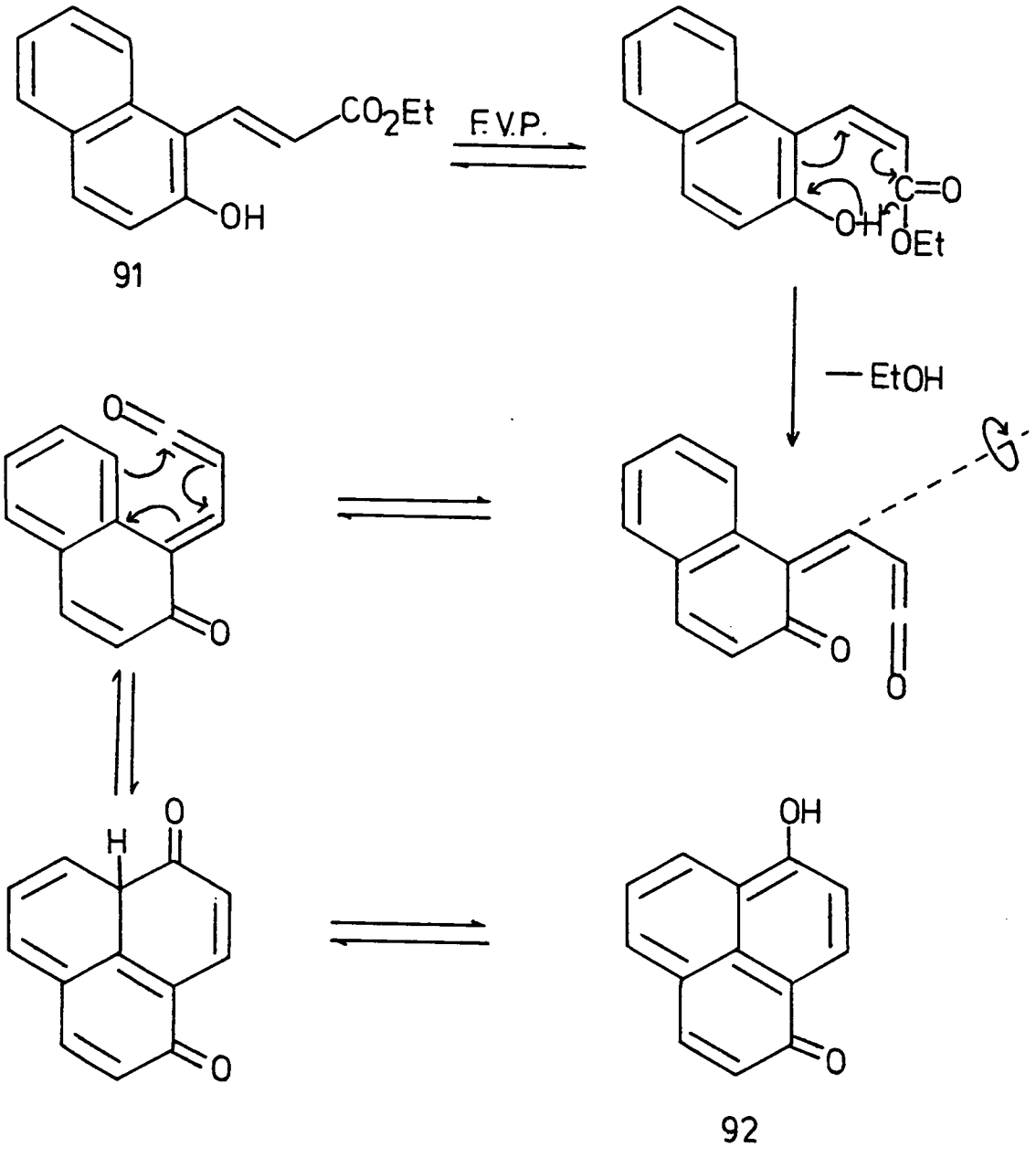
Thus 2-hydroxy-1-napthaldehyde 90 was reacted with the stabilised ylid in dichloromethane under reflux conditions. The acrylate **91** was isolated as a fine white microcrystalline material after dry flash chromatography (Scheme 96). The olefinic double bond protons have a $^{3}J_{HH}$ coupling of approximately 16.0 Hz corresponding to the *trans* configuration.



90 91

Scheme 96

It was considered possible that the ketene derived from **91** could have an alternative ring closure pathway available (Scheme 97).



91

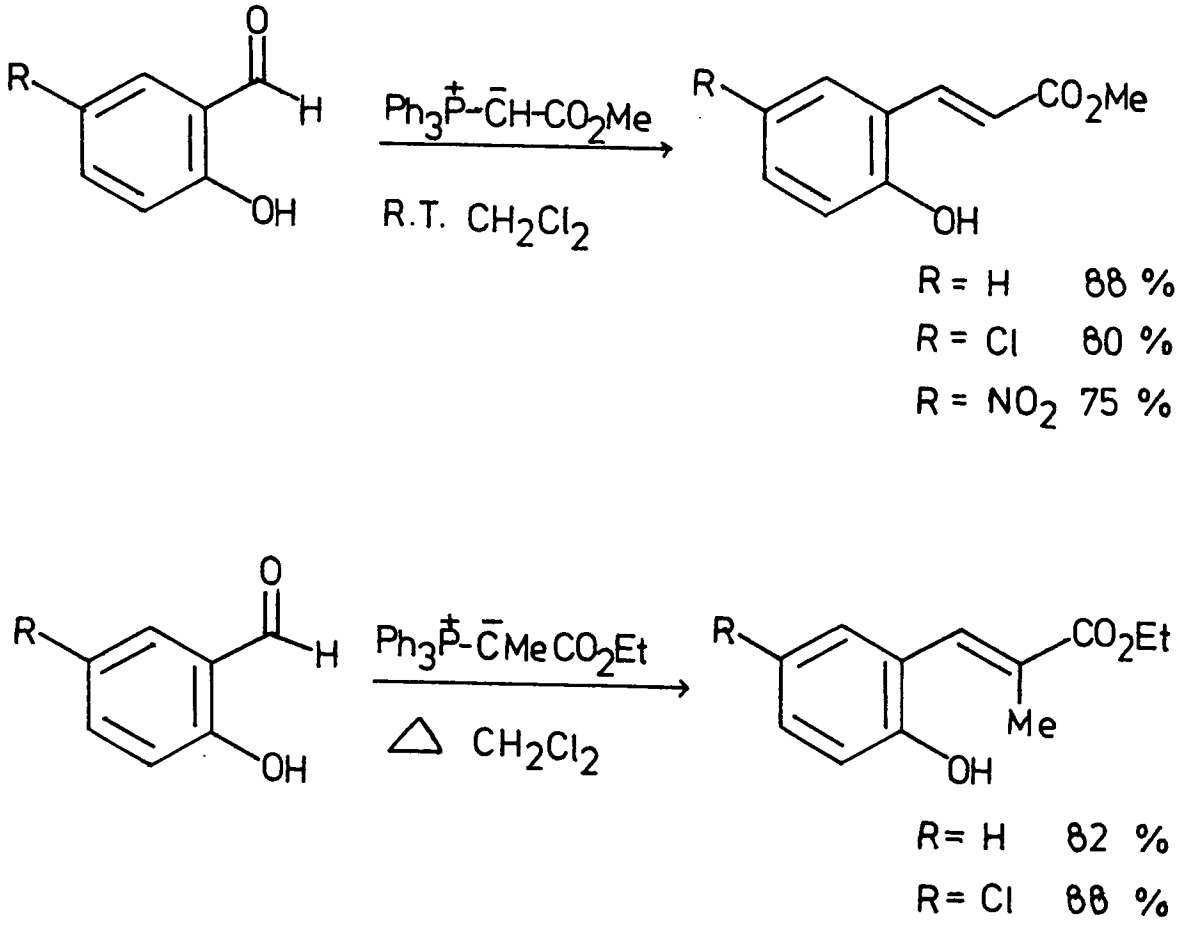
92

Scheme 97

However, upon Flash Vacuum Pyrolyses (F.V.P.) of 91 at a furnace temperature of 750°C a good yield of the 5,6-benzo coumarin 88 was obtained and none of 92. Thus owing to the difficulty in designing suitable trapping

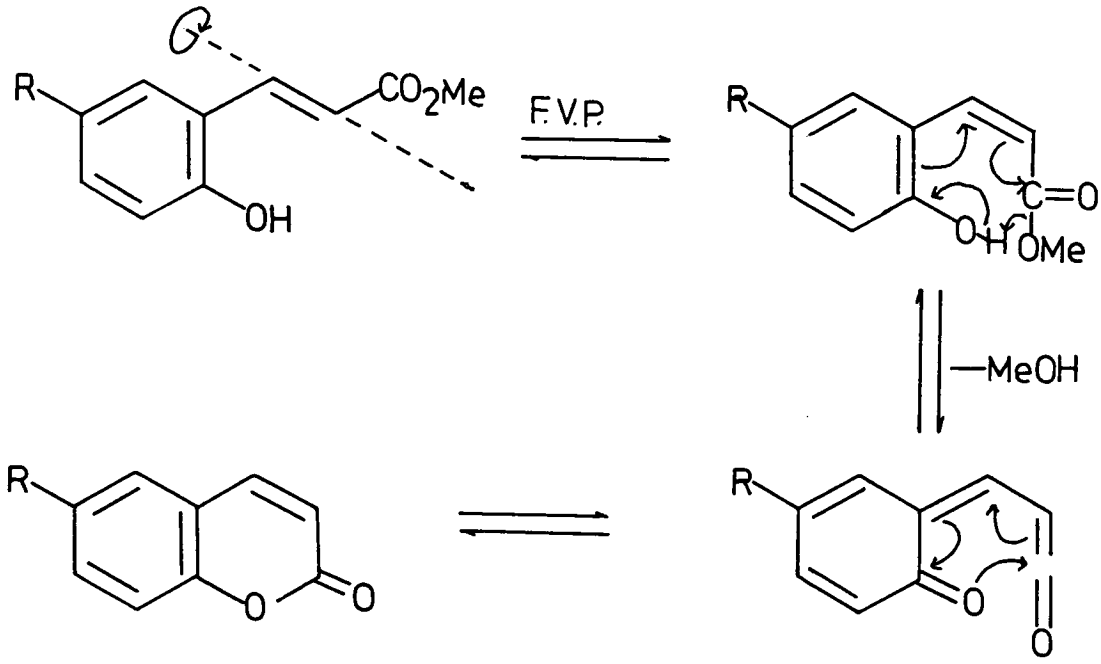
groups for those benzofused 2-pyrones it has not been possible to compare the ease of ring opening of the 2-pyrone and coumarin systems. However the gas phase methodology appeared to be a useful alternative to the solution phase syntheses of coumarins and the syntheses of five such coumarins is discussed.

The Wittig reactions were quite efficient and under mild conditions. The acrylates were obtained as fine white microcrystalline materials isolated by dry flash chromatography (Scheme 98).



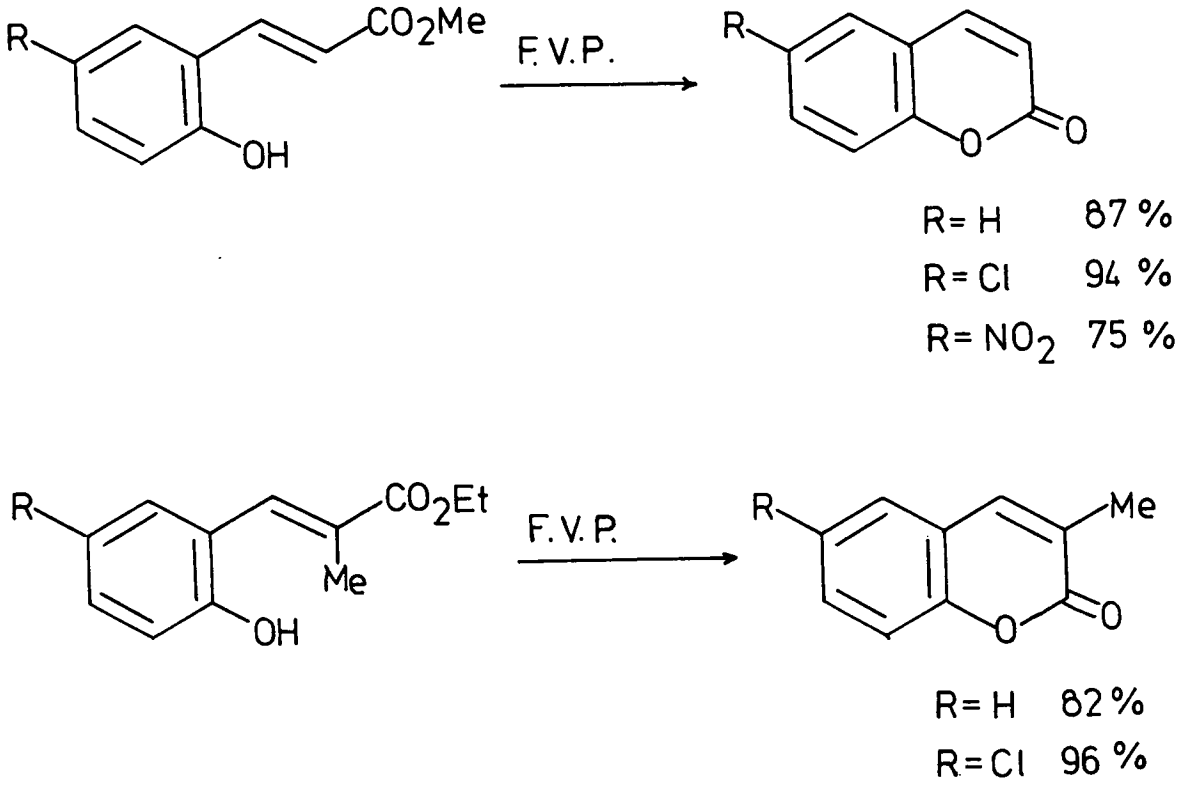
Scheme 98

These acrylates were subjected to Flash Vacuum Pyrolysis (F.V.P.) at a furnace temperature of 750°C. At this temperature the *trans* olefins equilibrate with their *cis* isomers, followed by loss of methanol (or ethanol) in a concerted type process. The ketene intermediates so obtained collapse intramolecularly to afford the fused 2-pyrone ring system. The general mechanism is shown below (Scheme 99).



Scheme 99

The five coumarins synthesised *via* this pyrolytic method are shown below (Scheme 100).



Scheme 100

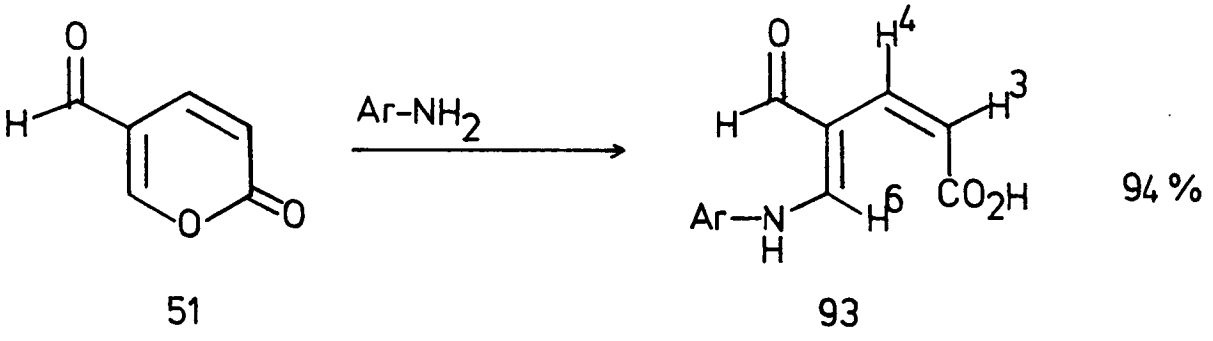
Since this benzofused system was not suitable for these studies, the effect of changing the ring heteroatom rather than ring fusion was therefore investigated.

REARRANGEMENT PROCESSES OF RELATED 2-PYRIDONES

The pyridone ring system is readily obtained *via* reaction of 2-pyrones, which are unsubstituted in the 6-position, with primary amines[121], thus utilising the

very susceptible nature of the C-6 position towards nucleophilic reagents. Previous work[122,123] has investigated such reactivity of 51 with a variety of primary and secondary amines, leading to ring closed pyridines and acyclic species respectively.

When 2-pyrone-5-carboxaldehyde 51 was treated with *p*-toluidine, as a moderately concentrated solution in ethanol (i.e. 0.5 g of 51 in 5 ml of solvent) a rapid reaction ensued, affording a bright yellow crystalline precipitate after only a few minutes. This material was found not to be the required pyridone but the acyclic intermediate 93 (Scheme 101).



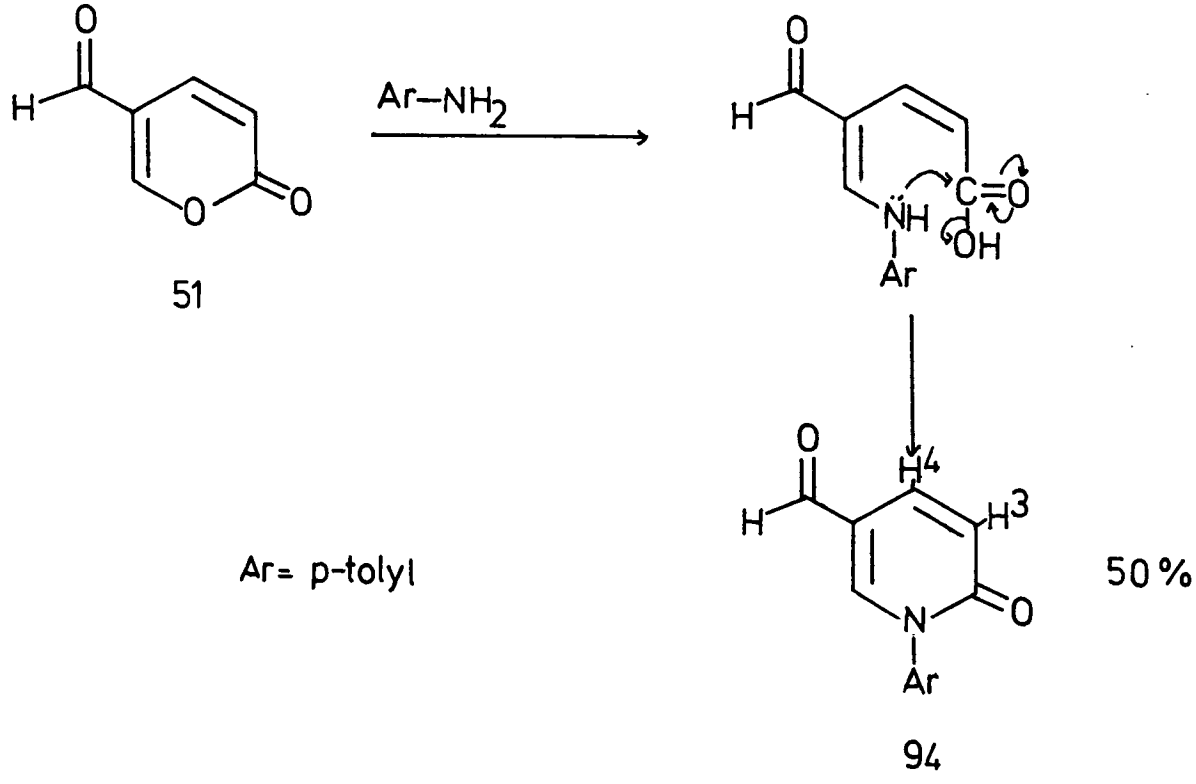
51 93

Scheme 101

The ^1H nmr spectrum of 93 showed an aldehydic proton resonance at $\delta_{^1H}$ 9.41 and also a $^3J_{HH}$ 13 Hz corresponding to H-3 and H-4 coupling. The methylene proton H-6

resonance was coincident with the aromatic proton resonances at δ_{1H} 7.25. The mass spectrum of 93 gave *m/z* 187(M^+-44, 19%) indicating decarboxylation upon ionisation.

This intermediate 93 was found to be extremely labile towards ring closure. A ^1H nmr sample of 93 in $CDCl_3$ rapidly underwent cyclisation to the pyridone 94 in a matter of hours. The reaction of the pyrone 51 with *p*-toluidine was thus repeated in chloroform solution under more dilute conditions (i.e. 0.5 g of 51 in 15 ml of solvent). After 12 hours stirring at room temperature the solvent was removed *in vacuo* affording the yellow microcrystalline pyridone 94 in reasonable yield after trituration with ethanol (Scheme 102).



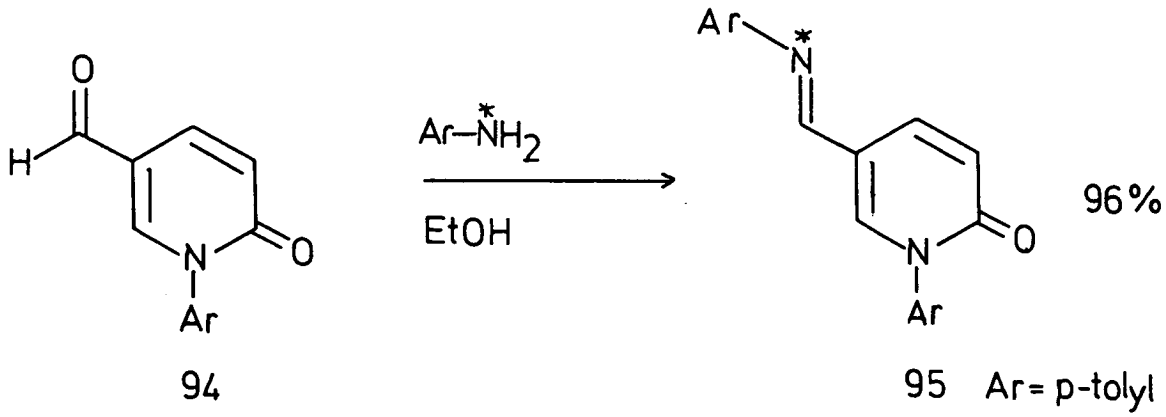
51

94

Scheme 102

The ^{1}H nmr spectrum of 94 showed H-3 and H-4 had a coupling constant of $^{3}J_{HH}$ 9.5 Hz, analogous to the 2-pyrone system. The mass spectrum of 94 gave *m/z* 213(M^{+}, 100%).

The ring opening of the pyridone 94 upon Flash Vacuum Pyrolysis (F.V.P.) was investigated by synthesising a ^{15}N (98%) isotopically labelled derivative 95, by reacting 94 with ^{15}N (98%) *p*-toluidine[124] (Scheme 103). The ^{15}N enriched *p*-toluidine was prepared by firstly reacting ammonium nitrate (^{15}N 98% enriched) with *p*-toluoyl chloride affording the amide in almost quantitative yield. Treatment of this amide with a bromine/sodium hydroxide mixture gave the ^{15}N *p*-toluidine, (*via* a Hofmann reaction) which was removed from the reaction mixture by steam distillation

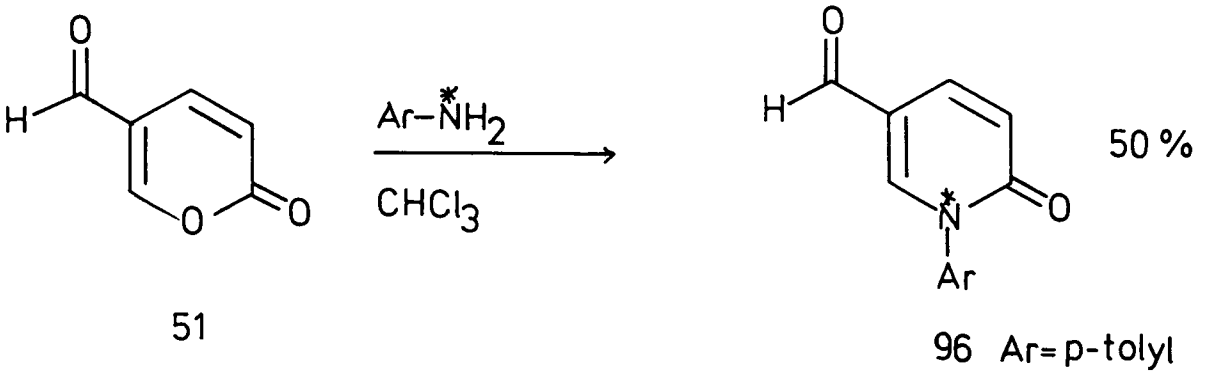


94 95 Ar = p-tolyl

Scheme 103

A sample of the amine **95** was dissolved in dichloromethane and its ^{15}N spectrum recorded[125] (Figure 14). The spectrum consists of one resonance at δ_N -63.7533 ppm corresponding to the imine ^{15}N atom.

For comparison, the pyridone **96** was prepared with the heteroatom ^{15}N (98%) enriched *via* reaction of **51** with [^{15}N] *p*-toluidine (Scheme 104).

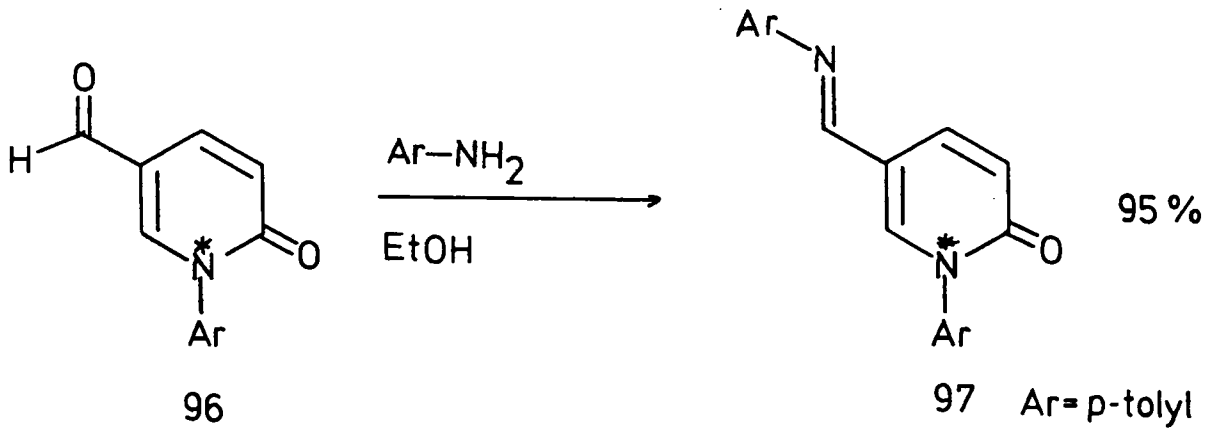


51

96 Ar= p-tolyl

Scheme 104

Compound **96** was then reacted with "unlabelled" *p*-toluidine affording the imine **97** (Scheme 105).



96

97 Ar= p-tolyl

Scheme 105

BRUKER

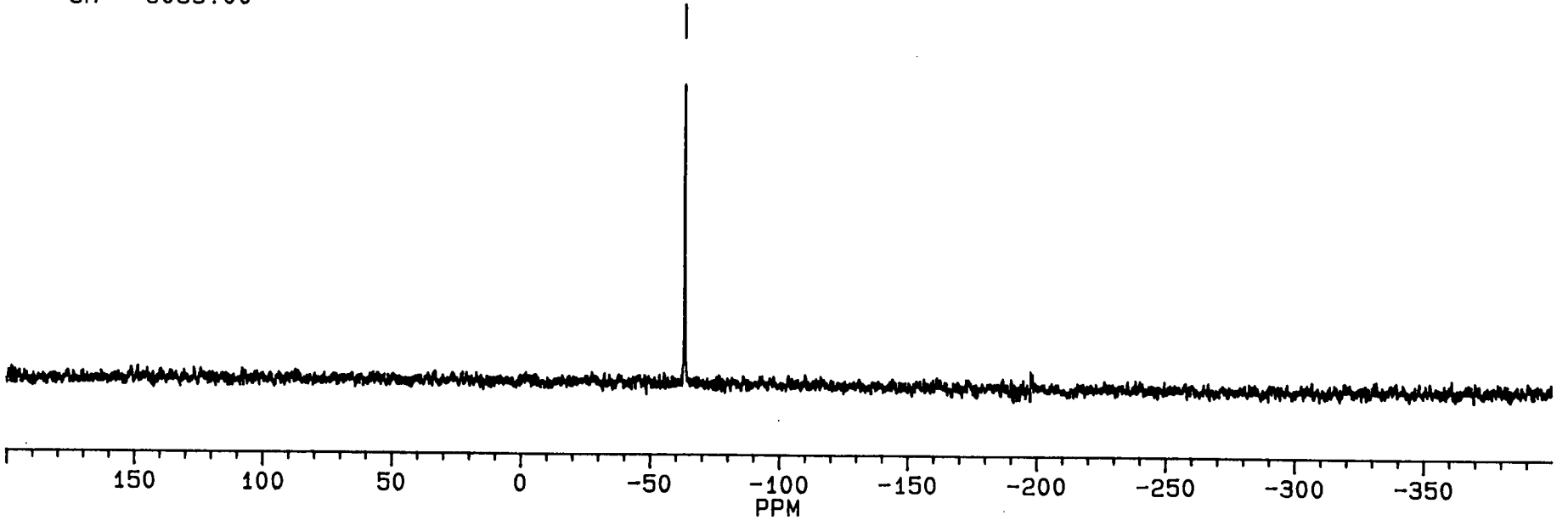
PPM

-63.7553

SHMC111N.100
DATE 27-5-91
TIME 10: 13

SF	36.506
01	4000.000
SI	16384
TD	16384
SW	25000.000
HZ/PT	3.052
PW	2.0
RD	0.0
AQ	.328
NS	2331
TE	298
02	6600.000
DP	15L CPD
LB	5.000
GB	0.0
HZ/CM	912.603
PPM/CM	24.999
SR	8059.00

Figure 14 ^{15}N nmr of 95



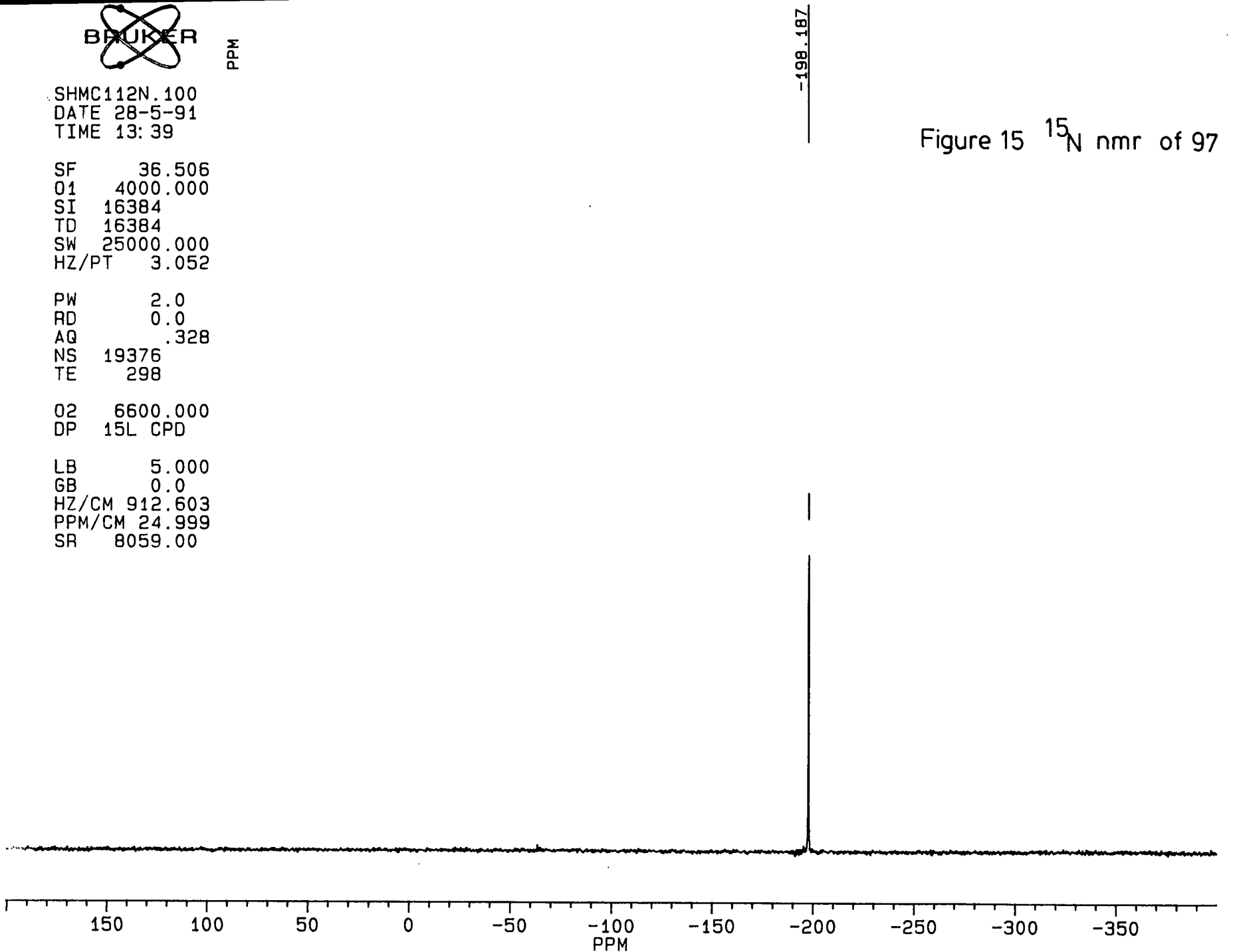


Figure 15 ^{15}N nmr of 97

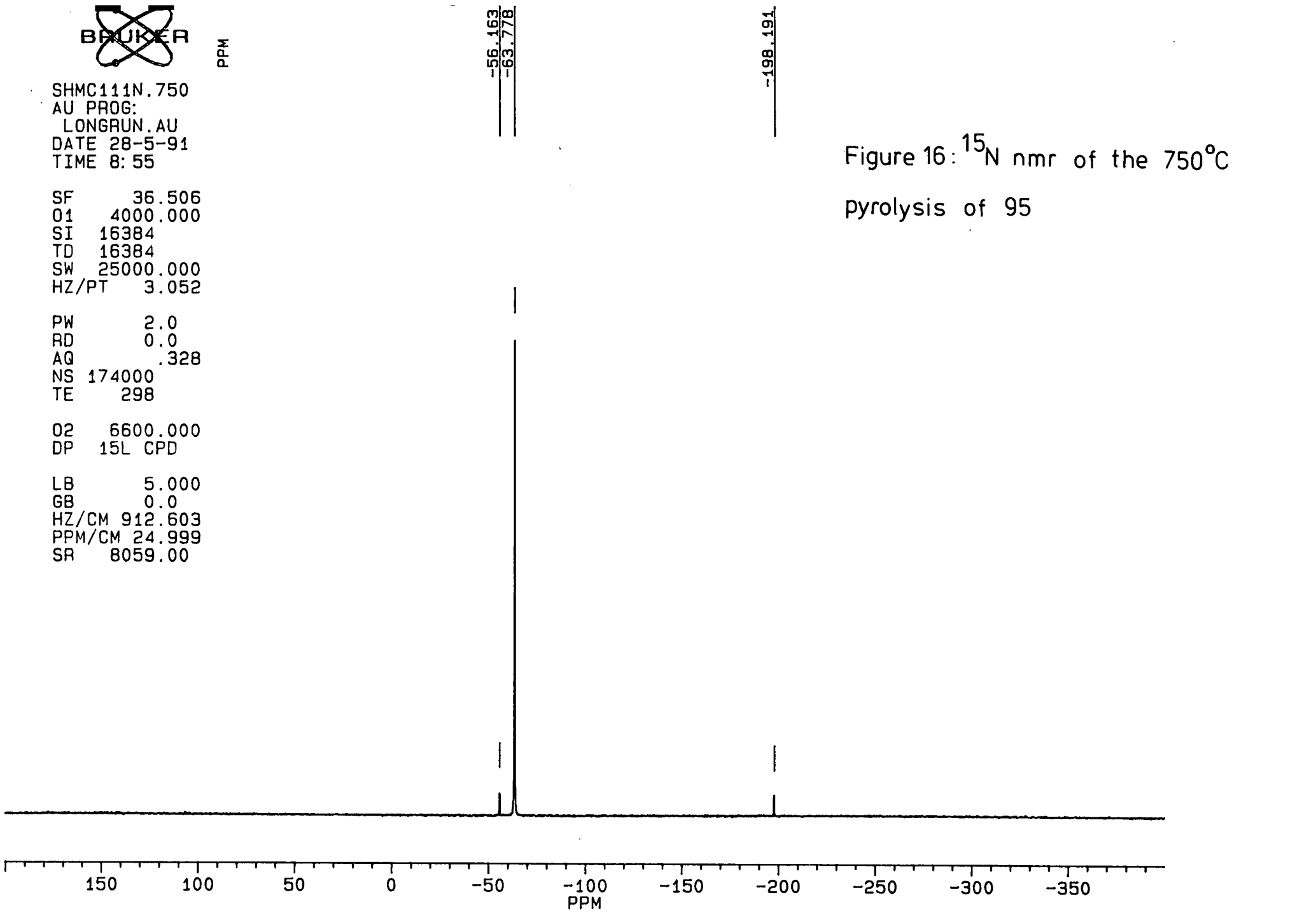


Figure 16: ^{15}N nmr of the 750°C pyrolysis of 95

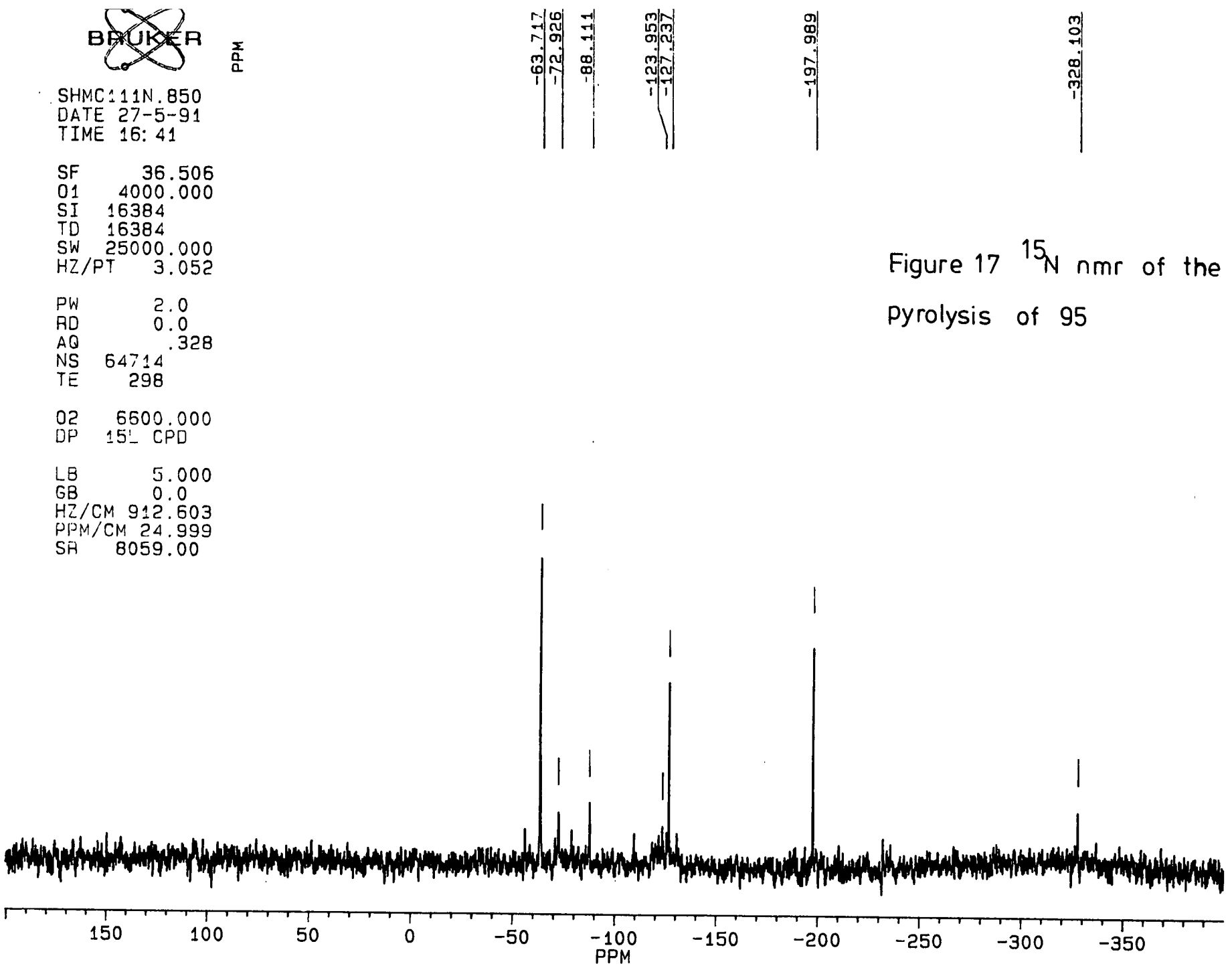
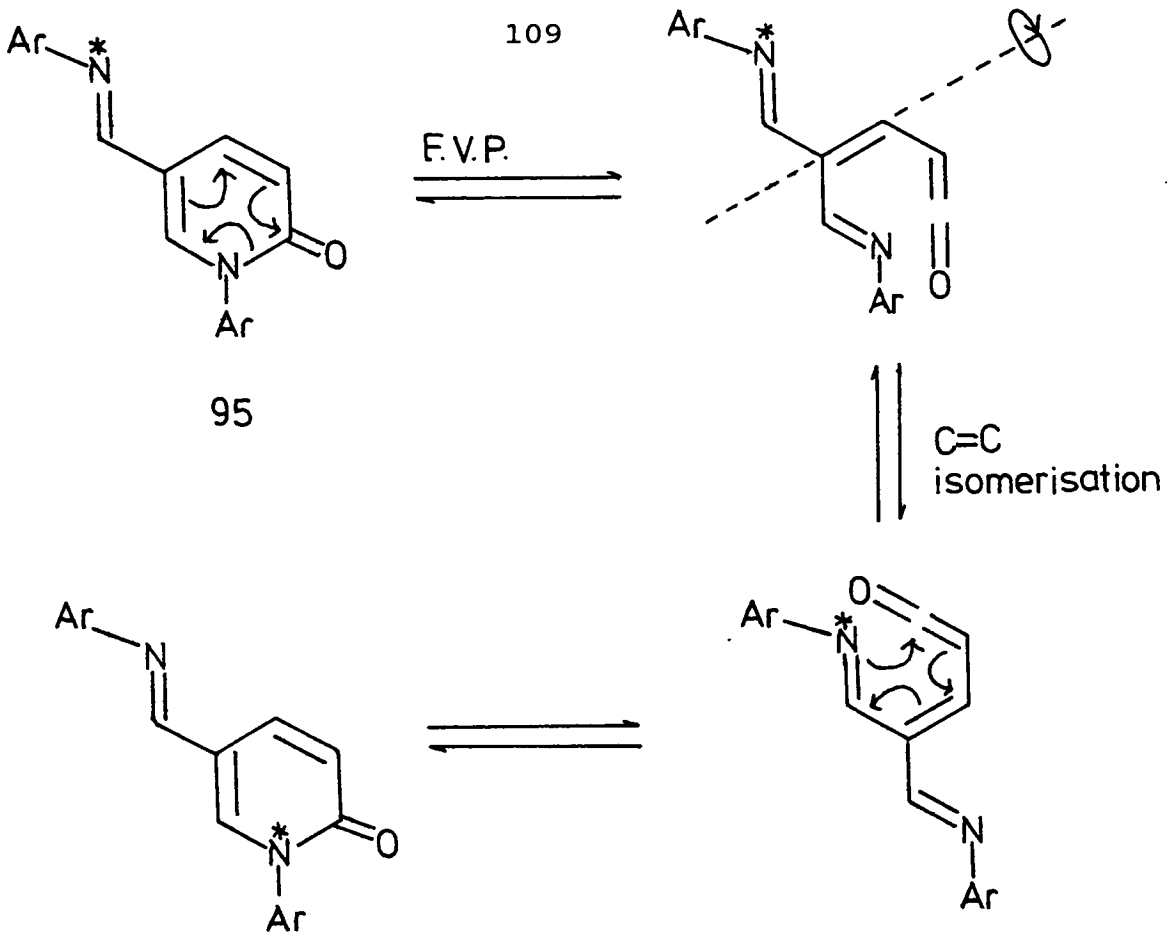


Figure 17 ^{15}N nmr of the 850°C Pyrolysis of 95

A sample of the imine **97** was dissolved in dichloromethane and its ^{15}N spectra recorded (Figure 15). The spectrum consists of one resonance at δ_N -198.187 ppm corresponding to the pyridone nitrogen atom.

A sample of imine **95** was subjected to Flash Vacuum Pyrolysis (F.V.P.) at a furnace temperature of 750°C and the ^{15}N spectrum of the pyrolysate mixture recorded (Figure 16). As can be seen there are two extra resonances developing at this temperature. The peak at δ_N -56.163 ppm may be due to the small amount of *trans-cis* isomerisation of the imine double bond with the *cis* configuration ^{15}N resonance occurring (very typically) slightly to high frequency relative to the *trans* orientation[125]. The developing peak at δ_N -198.191 is much more important and corresponds to the ^{15}N label being scrambled into the pyridone ring. This is indicative of electrocyclic ring opening of the pyridone system, followed by double bond isomerisation and ring closure, as found for the 2-pyrones (Scheme 106).



Scheme 106

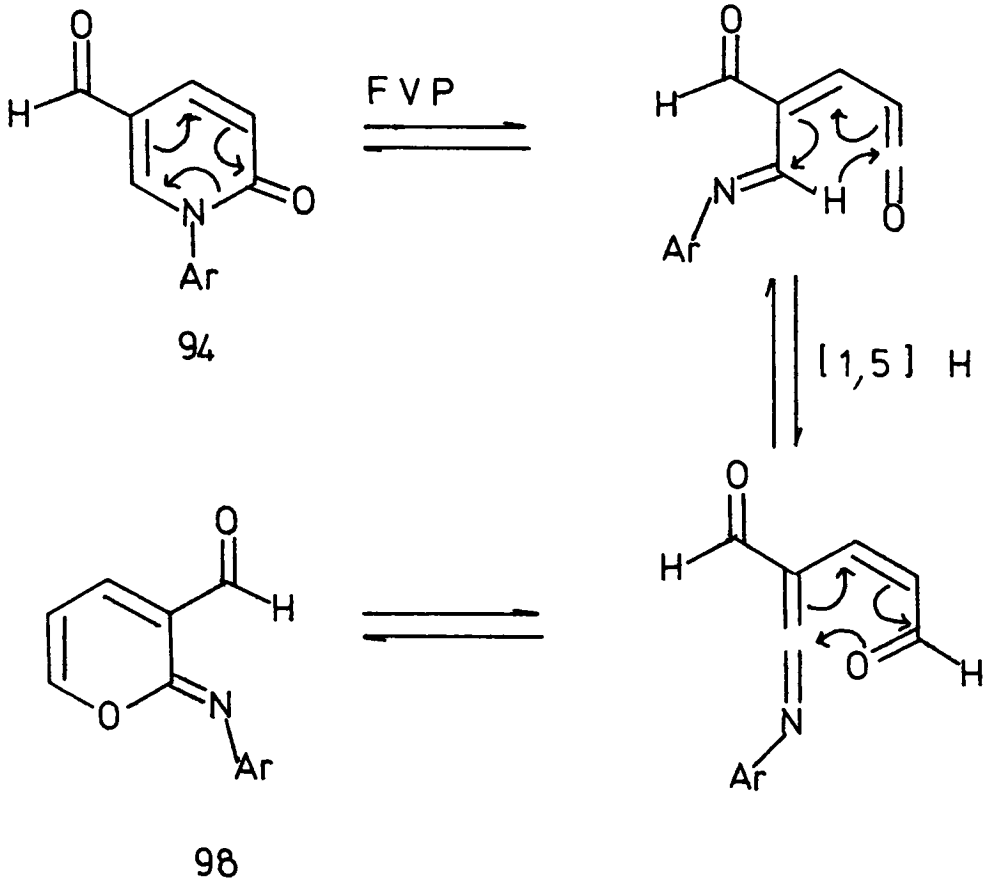
However, with the oxygen-containing rings complete equilibration was reached at a temperature of *ca.* 650-700°C. In this case the extent of rearrangement of the imine/pyridone 95 even at 750°C, was only 4%. The pyrolysis of the imine 95 was repeated at a furnace temperature of 850°C and the pyrolysate was examined by ^{15}N spectroscopy (Figure 17). The rearrangement was much more pronounced (*ca.* 37%) at this temperature, but accompanying decomposition of 95 was also apparent with extra peaks appearing in the ^{15}N spectrum. Of these extra peaks the only easily identifiable one occurs at δ_N

-328.103 and corresponds to *p*-toluidene.

Thus these ^{15}N experiments show that the pyridone system is more difficult to ring open than the analogous 2-pyrone system.

Since samples of the pyridone aldehyde **94** were available, it was decided to investigate the potential rearrangements of such a system.

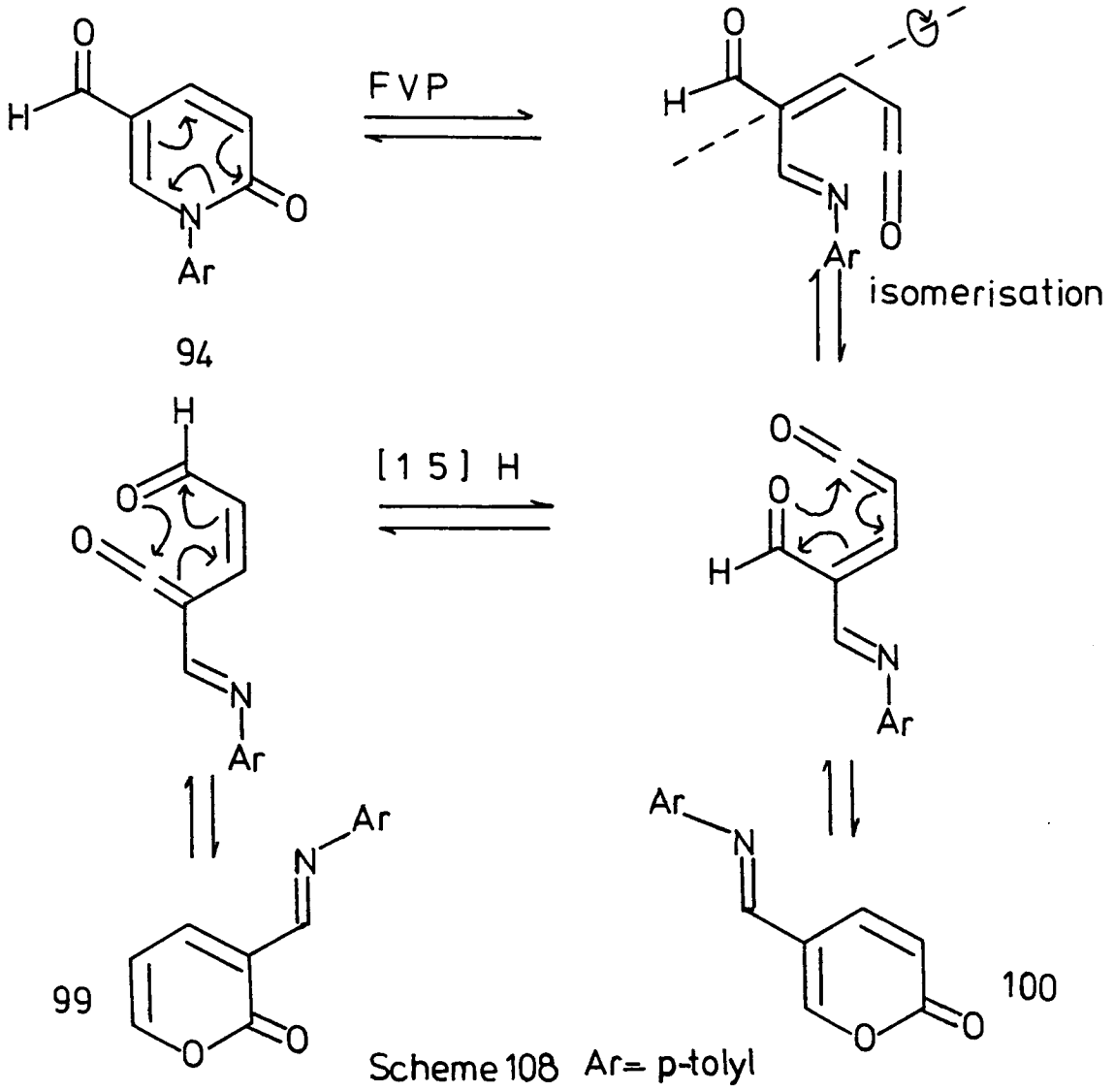
At low furnace temperatures, where extrusion processes are minimal, it is possible that **94** has a number of rearrangement products available, due to the asymmetry of the initial ring opened acyclic species. These possible products are shown below. Firstly if the analogous isomerisation to the 3-isomer occurs as previously encountered for the 2-pyrone-5-carboxaldehyde system **51**, then isomer **98** would result (Scheme 107).



94 **98**

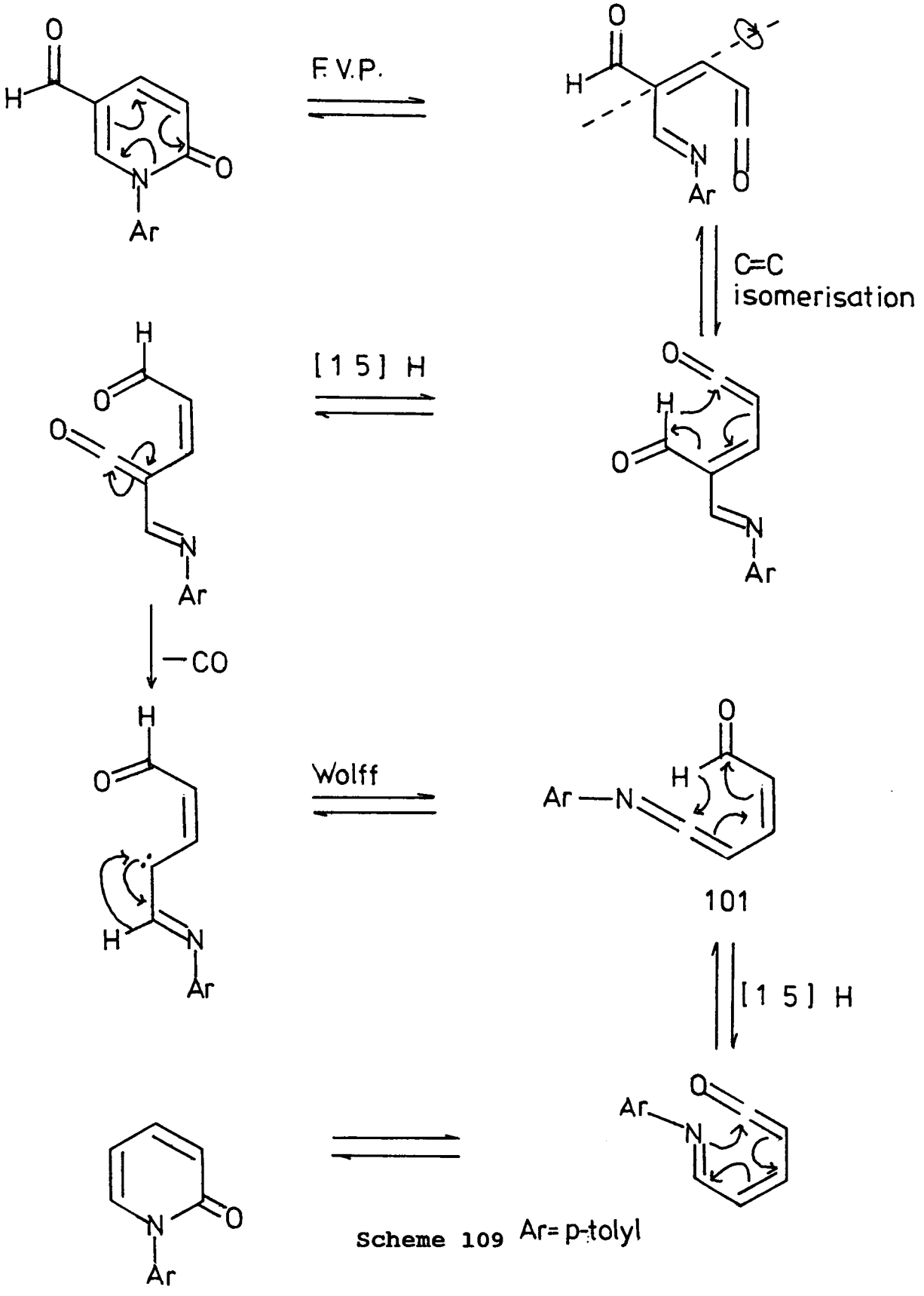
Scheme 107

Two other isomeric products 99 and 100 could also be formed if the initial ring opened species isomerised around the carbon-carbon double bond (Scheme 108).



Scheme 108 Ar= p-tolyl

However, as discussed earlier, the 2-pyridone ring system appears to be more thermodynamically stable than the 2-pyrone system, as the pyrolysis of imine 76 to the pyridone 77 illustrated (*c.f.* Scheme 87). Therefore the formation of 98, 99 and 100 appear to be quite unlikely. This was confirmed experimentally since Flash Vacuum

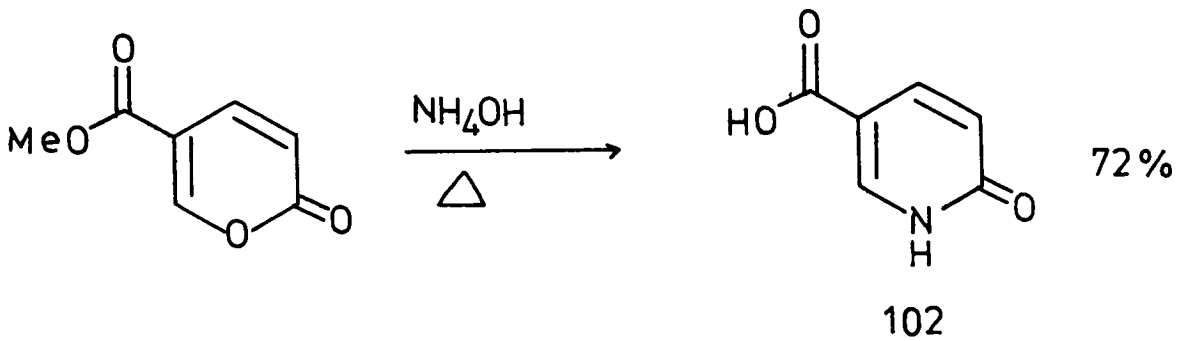


Scheme 109 Ar= p-tolyl

Pyrolysis (F.V.P.) of 94 failed to produce any evidence of isomerisation. Even at a furnace temperature of 900°C the pyridone 94 survived very well indeed without any extrusion processes. The absence of any easily identifiable extrusion process products was somewhat surprising, since a possible decarbonylation mechanism can be envisaged involving ketenimine intermediates 101 (Scheme 109).

This mechanism is analogous to the decarbonylation of 51 to 2-pyrone 1 (*c.f.* Scheme 60), but here ketenimine intermediates 101 need to be invoked, such intermediates may require even higher energies to exist and could explain why the clean decarbonylation process is not encountered.

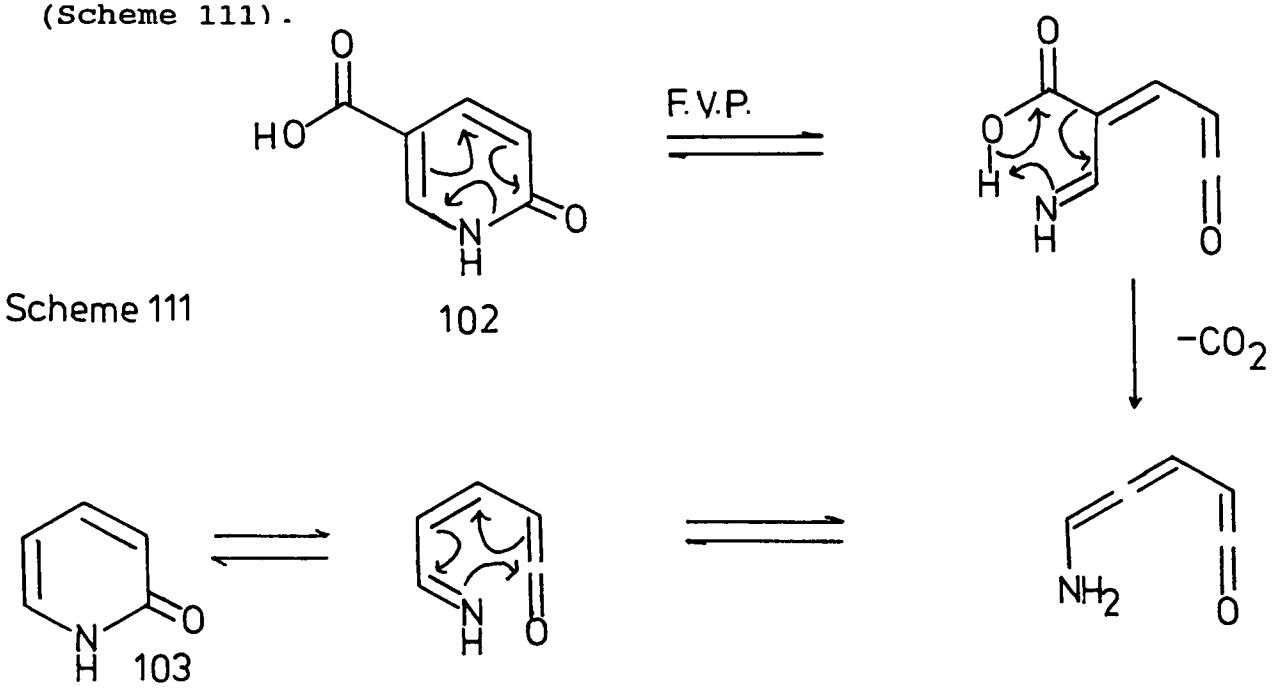
It was also of interest to see if the pyridone carboxylic acid 102 could be decarboxylated under F.V.P. conditions. Compound 102 was prepared readily by the reaction of methyl coumalate with ammonia, followed by *in situ* hydrolysis of the ester function[121] (Scheme 110).



102

Scheme 110

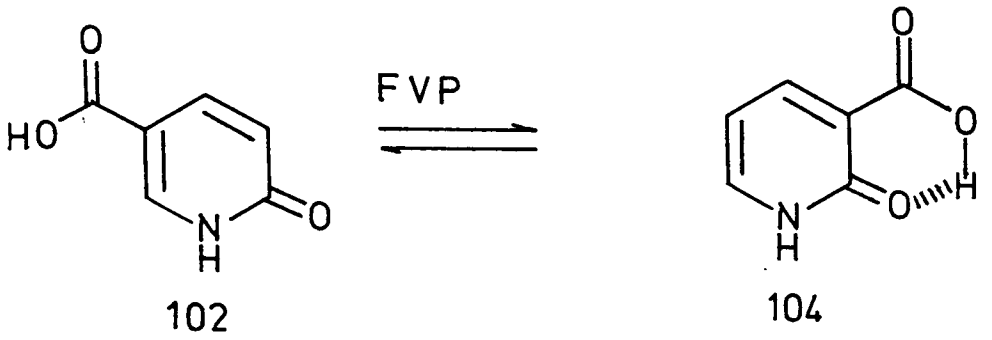
A similar decarboxylation mechanism, as for the decarboxylation of coumalic acid, can be invoked for **102** (Scheme 111).



Scheme 111

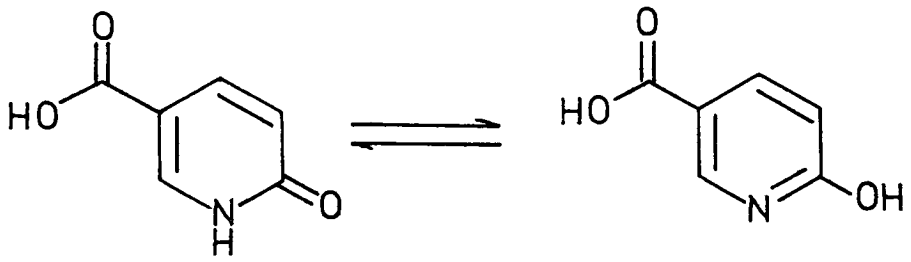
102 **103** **104**

However, Flash Vacuum Pyrolysis (F.V.P.) of **102** at a furnace temperature of 950°C failed to produce any decarboxylated product **103**. An authentic sample of **103** was available for ^{1}H and ^{13}C nmr comparison. It was also surprising that rearrangement to the apparently favourable hydrogen bonded 3-isomer **104** did not occur, even at the high furnace temperature of 950°C (Scheme 112).



Scheme 112

The excellent stability of 102 could be attributed to a high degree of hydroxypyridine tautomer 105 in the gas phase (Scheme 113), since previous work[126] on the parent 2-pyridone 103 has shown that the hydroxypyridine tautomer is favoured in the gas phase. Thus the bond which is initially broken upon electrocyclic ring opening has more 'double bond' character.



102 105

Scheme 113

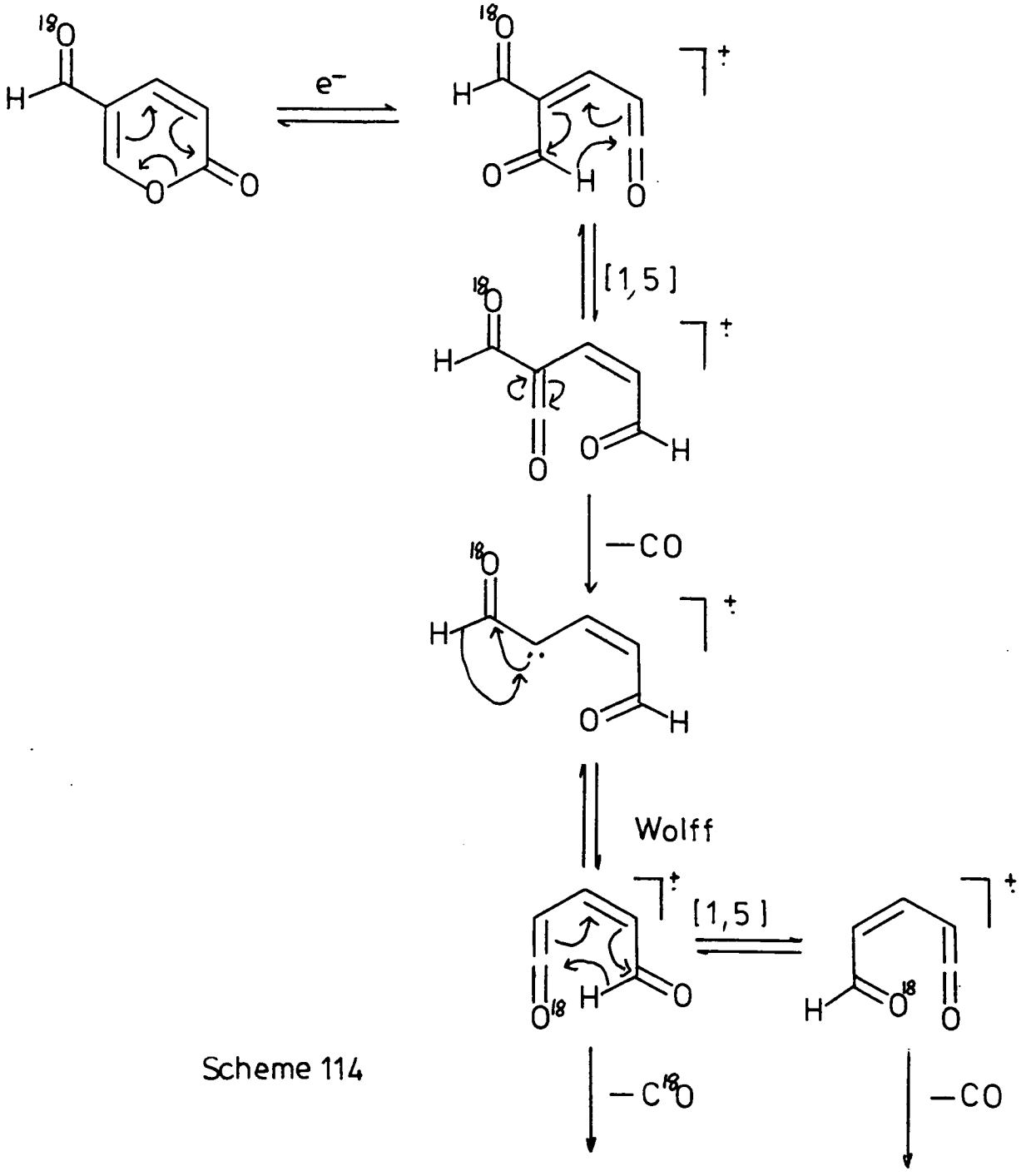
MASS SPECTROMETRY BREAKDOWN OF 2-PYRONE-[^{18}O]-5-CARBOXALDEHYDE

Previously mentioned in the Introduction section of this thesis was the loss of carbon monoxide from the 2-pyrone system upon E.I. mass spectrometry. The extrusion process described initially involves a ring opened intermediate (Scheme 14, p.19).

2-Pyrone-[^{18}O]-5-carboxaldehyde (with the label specifically located at the aldehyde position) was subjected to mass spectral analysis. The parent ions gave M^+ (126, 38.4%) (^{18}O label) and M^+ (124, 52.9%) ("unlabelled"). Thus the 2-pyrone had approximately 42% ^{18}O incorporation. The first loss of 'CO' gave ions of m/e 98 (52.7%) and m/e 96 (75.8%), thus the ^{18}O content was still approximately 41%. This shows that in this particular case the first loss of carbon monoxide involves the ring oxygen atoms *via* ketene intermediates, with almost *complete* retention of the aldehyde substituent. This result was extremely interesting and suggests that in the cation-radical energy surface the initial loss of carbon monoxide precedes any carbon-carbon double bond isomerisation, in contrast to the mechanism associated with the neutral situation (Scheme 64).

The next loss of carbon monoxide, however, involves a significant loss of the ^{18}O label. Ions of m/e 68 (100%) and m/e 70 (34.9%) (^{18}O retained) indicate the ^{18}O content

was reduced to 25%, which is very nearly a 50% loss. This suggests that isomerisation is taking place at a later stage in the process. A reasonable breakdown mechanism is shown below (Scheme 114).



Scheme 114

EXPERIMENTAL

ABBREVIATIONS

n.m.r.	nuclear magnetic resonance
δ	chemical shift
s	singlet
d	doublet
t	triplet
q	quartet (in ^{1}H n.m.r. spectra)
q	quaternary (in ^{13}C n.m.r. spectra)
m	multiplet
br	broad
M^{+}	mass of molecular ion
m/z	mass to charge ratio
t.l.c.	thin layer chromatography
m.p.	melting point
h.	hours
min.	minutes
mol	moles
mmol	millimoles

INSTRUMENTATION AND GENERAL TECHNIQUES

Nuclear Magnetic Resonance Spectroscopy

^{1}H N.m.r. and ^{13}C n.m.r. spectra were recorded by Dr. H. McNab on a Bruker WP200 spectrometer.

^{15}N and ^{2}H spectra were recorded by Dr. D. Reed on a Bruker WH360 spectrometer.

All n.m.r. spectra were recorded for deuteriochloroform solutions unless otherwise stated. Chemical shifts (δ_H, δ_C) were measured in parts per million relative to tetramethylsilane (δ = 0.0). ^{15}N n.m.r. shifts are quoted relative to external nitromethane.

Mass Spectrometry

Mass spectra were recorded by Miss E. Stevenson on an A.E.I. MS902 spectrometer and by Mr. A. Taylor on a Kratos MS50TC instrument.

Chromatography

Thin-layer chromatography was carried out using pre-coated plastic sheets (0.25 mm silica gel) impregnated with a UV fluorescent indicator from Macherey-Nagel.

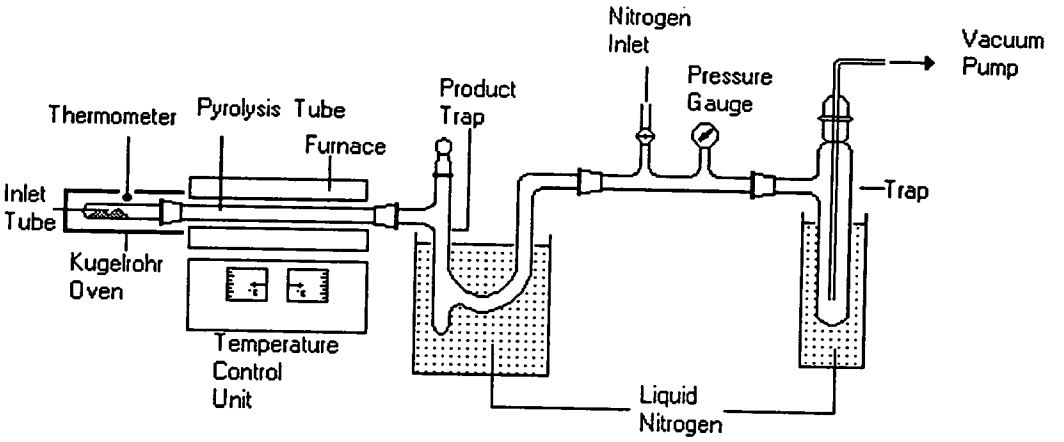
Dry flash chromatography was carried out on silica gel (Merck, grade 60, 230-400 mesh, 60 Å), by the method of Harwood[134]. Ethyl acetate and *n*-hexane was used as the solvent system, with 10% increments in the more polar component per fraction.

Elemental Analysis

Microanalyses were obtained using a Carlo Erba Elemental Analyser, Model 1106, operated by Mrs. E. McDougal.

Pyrolysis Apparatus and General Techniques

Flash vacuum pyrolysis was carried out on apparatus based on the design of W.D. Crow, Australian National University. The important features of the apparatus are shown below.



The sample was volatilised from a horizontal inlet tube, heated by a Büchi Kugelrohr oven, into a silica furnace tube (30 x 2.5 cm). This was maintained at temperatures in the range of 500-1000°C by a Stanton Redcroft Laboratory Tube Furnace LM8100, the temperature being measured by a platinum/platinum 13% rhodium thermocouple situated at the centre of the furnace. The products were collected in a U-shaped trap cooled in liquid nitrogen situated at the exit point of the furnace. The apparatus was evacuated to 10^{-2} - 10^{-3} mbar by an Edwards Model ED100 high capacity rotary oil pump.

PREPARATION OF 2-OXO-2*H*-PYRAN-5-CARBOXYLIC ACIDS

2-Oxo-2*H*-pyran-5-carboxylic acid (coumalic acid) was commercially available.

4,6-Dimethyl-2-oxo-2*H*-pyran-5-carboxylic acid[127] (isodehydroacetic acid)

Concentrated sulphuric acid (98%, 56 ml) was cooled in ice. With continuous stirring ethyl acetoacetate (40 g, 0.30 ml) was added slowly, keeping the temperature close to 0°C. After addition was complete the mixture was allowed to stand at room temperature. After six days the reaction mixture was poured onto crushed ice (150 g). The white solid (a mixture of the required carboxylic acid and its ethyl ester) was collected by filtration and washed with water (200 ml). The solid was dissolved in ether (250 ml) and extracted with saturated sodium carbonate solution (5 x 80 ml). The combined aqueous extracts were acidified with an excess of concentrated hydrochloric acid and the finely divided acid which precipitated was redissolved by heating the solution to its boiling point. The hot solution was filtered and cooled in ice. The resulting solid was collected by filtration and washed with water (50 ml). The crude acid was then dissolved in hot water (40 ml), treated with decolourising carbon, filtered and cooled slowly to effect crystallisation. The yield of acid was 1.77 g (27%) m.p. 154-155°C (lit.[127], 154-155°C). δ_H ([$^2H_6$ DMSO), 6.07 (1H, m), 2.33 (3H, d)

and 2.16 (3H, d).

2-OXO-2*H*-PYRAN-5-CARBOXYLIC ACID CHLORIDES - GENERAL METHOD[128]

The carboxylic acid (70 mmol) was heated under reflux with neat thionyl chloride (20 ml) until solution was complete. The excess thionyl chloride was removed under reduced pressure, leaving a brown residue, which was extracted with several portions of boiling *n*-hexane (4 x 20 ml). The combined hexane extracts were refridgerated at -20°C for four hours. The acid chloride crystallised as fine white needles which were then isolated by filtration and dried. The acid chlorides were pure enough for further use.

The following acid chlorides were made using this method: coumaloyl chloride (7.35 g, 65%), using coumalic acid (70 mmol). m.p. 77°C (lit.[128], 77°C) δ_H 8.60 (1Hdd), 7.84 (1Hdd) and 6.45 (1Hdd). 4,6-Dimethyl-2-oxo-2*H*-pyran-5-carboxylic acid chloride (9.79 g, 75%) using isodehydroacetic acid (70 mmol). m.p. 49-51°C (lit.[129], 52°C) δ_H 5.88 (1H, m), 2.28 (3H, s) and 2.10 (3H, d).

2-OXO-2H-PYRAN-5-CARBOXALDEHYDES - GENERAL METHOD[42,130]

Rosenmund reduction of the corresponding acid chlorides was used. The acid chloride (31.5 mmol) was dissolved in dry p-xylene (50 ml). To this solution was added 5% palladium-barium sulphate catalyst (0.5 g). The solution was stirred vigorously and heated at an appropriate temperature (see below), while hydrogen gas was bubbled through the solution using a capilliary inlet. The excess hydrogen gas was vented high up into a well ventilated fume cupboard, using rubber tubing attached to the top of the condenser. The reaction was monitored throughout by t.l.c. using ethyl acetate and *n*-hexane (1:1). When the reaction was complete, the hot solution was filtered through celite, *n*-hexane (20 ml) was added and the solution cooled at -20°C for 6h. The crystalline material so produced could be recrystallised from ethanol, but was generally pure enough for further use. The following 2-pyrone-5-carboxaldehydes were prepared this way. 2-Oxo-2*H*-pyran-5-carboxaldehyde - Coumalyl chloride (5 g, 31.5 mmol) was heated at 110°C using the above procedure. The yield of aldehyde was 2.14 g (55%) m.p. 93°C (from ethanol) (lit.[42], 93-94°C) δ_H 9.65 (1H, dd, ^5J 1.0 and ^4J 0.3 Hz), 8.15 (1H, dd, ^4J 2.6 and ^5J 1.2 Hz), 7.74 (1H, ddd, ^3J 9.7, ^4J 2.6 and ^4J 0.3 Hz), and 6.38 (1H, ddd, ^3J 9.7, ^5J 1.2 and ^5J 1.0 Hz). *4,6-Dimethyl-2-oxo-2H-pyran-5-carboxaldehyde* - 4,6-Dimethyl-2-oxo-2*H*-pyran-5-carboxylic acid chloride (5.87 g, 31.5 mmol) was

heated at 140°C using the above procedure. The yield of the *aldehyde* was 2.87 g (60%), m.p. 80-82°C (from ethanol). (Found: C, 62.6; H, 5.3. $C_8H_8O_3$ requires C, 63.05; H, 5.3%); δ_H 10.09 (1H, s), 5.97 (1H, m), 2.59 (3H, s) and 2.40 (3H, m); δ_C 187.33, 172.82 (q), 159.40 (q), 155.06 (q) (115.57 (q), 112.23, 20.98 and 18.24; *m/z* 152 (M^+, 45%), 124(68), 109(35), 96(77), 82(13), 43(100) and 39(31).

^{18}O AND ^{2}H LABELLED 2-OXO-2*H*-PYRAN-5-CARBOXALEDEHYDES

2-Oxo-2*H*-pyran-5-[^{2}H]-carboxaldehyde[109]

Freshly prepared coumaloyl chloride (0.491 g, 3.1 mmol) was dissolved in dry benzene (7 ml). Tetrakistriphenylphosphine palladium (o) (0.036 g, 10^{-2} eq) was added. With continuous stirring under an inert atmosphere ($N_{2(g)}$), tributyltindeuteride (1 ml, 1.2 eq) was added slowly over a period of ten minutes. After one hour at room temperature the solution was concentrated and subjected to dry flash chromatography. The yield of labelled aldehyde thus obtained was 0.052 g, (10%). $\delta^{2}H$ ($CHCl_3$), 9.65. m.p. 92-94°C (lit.[42], 93-94°C).

^{18}O LABELLED ALDEHYDE

Coumalic [^{18}O] Acid

Coumaloyl chloride (1.981 g, 12.5 mmol) (prepared as previously described) was dissolved in dry tetrahydrofuran (4 ml). To this solution was added $H_2{}^{18}O$ (250 mg, 12.5 mmol) with continuous stirring. After twelve hours a green precipitate was produced and the solvent was removed *in vacuo* yielding 1.745 g, (98%) of ^{18}O-labelled acid, which was analysed by averaged mass spectrometry *m/z* 142 (M^+, 68%) and 114(100).

[^{18}O] Coumaloyl Chloride

The ^{18}O labelled coumalic acid (1.745 g, 12.28 mmol) was added to thionyl chloride (6 ml) and heated gently until solution was complete. The work up was as described previously for coumaloyl chloride and the yield of [^{18}O] coumalyl chloride was 1.25 g, (64%).

2-Oxo-2H-pyran-5-[^{18}O]carboxaldehyde

Coumaloyl chloride (^{18}O) (1 g) was dissolved in dry p-xylene (20 ml). To this was added palladium/barium sulphate catalyst (0.1 g). The mixture was stirred and gently heated at 110°C, while a continuous stream of hydrogen gas was bubbled through the solution. The reduction was monitored by T.l.c. (1:1 ethylacetate/ n-hexane). After the reaction was complete the hot p-xylene solution was filtered, n-hexane (8 ml) was added. The solution was then cooled at -20°C for 6 h, affording a white, crystalline precipitate. The yield of labelled aldehyde was 0.376 g (40%) m.p. 93°C (from ethanol) (lit.[42], 93-94°C). δ_H 9.65 (1H, dd), 8.14 (1H, dd), 7.75 (1H, ddd) 6.37 (1H, ddd); δ_C 184.92, 184.88 (^{18}O shift) 162.54 (C-6), 159.07 (C-5), 138.04 (C-4), 119.68 (C-2), 116.47 (C-3); Averaged *m/z* 126 (M^+ 38.4%) (^{18}O), 124 (M^+ 52.9), 98(52), 96(75), 70(35) and 68(100). Thus the 2-pyrone contained approximately 42% ^{18}O label.

REACTION OF 2-OXO-2*H*-PYRAN-5-CARBOXALDEHYDE WITH DIAZOMETHANE[131]

The reactions using diazomethane were undertaken using specially designed "*mini diazald apparatus*"[132], with appropriate precautions taken, as carefully described in reference 132. A solution of *Diazald* (*N*-methyl-*N*-nitroso-*p*-toluene sulphonamide) (3.028 g, 14.13 mmol) in freshly distilled ether (25 ml) was decomposed by the dropwise addition into a preformed solution of potassium hydroxide (1.9 g), ethanol (2 ml) and water (2 ml) maintained at 65°C. The diazomethane produced, (approximately 10 mmol in total, assuming 70% conversion from *Diazald*), was distilled (as an ethereal co-distillate) into a separate reaction vessel and allowed to condense dropwise *via* a dry ice/acetone cold finger, into a preformed solution of 2-oxo-2*H*-pyran-5-carboxaldehyde (0.62 g, 5 mml) in freshly prepared dichloromethane (50 ml) maintained at 0°C and vigorously stirred. The solution was bright yellow throughout the reaction. When all the *Diazald* had been consumed, the reaction solution was allowed to warm to room temperature and left to stir for twelve hours (thus allowing excess diazomethane to escape). The dichloromethane was removed *in vacuo*, and the resulting red coloured solid was recrystallised from ethanol. The yield of *6-methyl-2-oxo-2H-pyran-5-carboxaldehyde* was 0.55 g, (79%). m.p. 83-85°C (from ethanol). (Found: C, 60.8; H, 4.45, $C_7H_6O_3$ requires C, 60.85; H, 4.35%); δ_H 9.88 (1H,

d, ^5J 9.7 and ^5J 0.8 Hz), 7.67 (1H, d, ^3J 9.7 Hz), 6.13 (1H, dd, ^3J 9.7 and ^5J 0.8 Hz) and 2.63 (3H, s); δ_C 185.65, 172.92 (q), 159.54 (q), 140.25, 115.79 (q), 113.22 and 16.84; *m/z* 138 (M^+, 64%), 110(43), 95(35), 82(69), 68(31), 43(100), 39(76), 38(30) and 32(50).

ATTEMPTED REACTION OF 2-PYRONE WITH DIAZOMETHANE

The above procedure was repeated for the attempted methylation of the parent, unsubstituted 2-pyrone. However, unreacted starting material was recovered, identified by ^1H n.m.r. spectroscopy. It was of interest to see if other diazo-compounds would react analogously to diazomethane with various 5-substituted 2-pyrones.

REACTION OF ETHYL DIAZOACETATE[112] WITH VARIOUS 5-SUBSTITUTED-2-PYRONES - GENERAL METHOD

The corresponding 2-pyrone (3.24 mmol) was dissolved in freshly distilled dichloromethane (15 ml) and cooled to 0°C, under an atmosphere of $N_{2(g)}$. Triethyloxonium tetrafluoroborate (1.8 g, 9.72 mmol, 3 eq) was added. With continuous stirring, ethyl diazoacetate (0.74 g, 6.48 mmol, 2 eq) was added dropwise over a period of fifteen minutes. The resulting bright yellow solution was maintained at a temperature of 0°C for two hours, then allowed to stand at room temperature for 72 hours. The solution was then vigorously shaken with a saturated solution of sodium bicarbonate (2 x 20 ml) for 1 hour.

The organic layer was isolated, dried over anhydrous sodium sulphate, and concentrated to dryness *in vacuo*. This procedure was carried out using methyl coumalate, 2-oxo-2*H*-pyran-5-carboxaldehyde and the parent unsubstituted 2-pyrone. In all cases a high recovery of unreacted 5-substituted-2-pyrone resulted (> 85%), together with some unidentifiable brown residue.

REACTION OF PHENYLDIAZOMETHANE[110] WITH VARIOUS 5-SUBSTITUTED 2-PYRONES - GENERAL METHODS

Benzaldehyde *p*-Toluenesulphonylhydrazone

p-Toluenesulphonylhydrazide (14.6 g, 0.078 mol) was added to methanol (25 ml). The slurry was swirled as freshly distilled benzaldehyde (7.50 g, 0.071 mol) was added rapidly. The reaction was mildly exothermic and the *p*-toluenesulphonylhydrazide soon dissolved. After 15 min. the mixture was cooled in ice, the product was collected by filtration, washed with methanol (5 ml) and dried. The yield of benzaldehyde *p*-toluenesulphonylhydrazone was 16.0 g (82%) m.p. 122-124°C (lit.[110], 124-125°C).

Benzaldehyde *p*-Toluenesulphonylhydrazone, Sodium Salt

A 1.0M solution (51 ml) of sodium methoxide in methanol was added slowly *via* a syringe to benzaldehyde *p*-toluenesulphonylhydrazone (13.71 g, 0.05 mol). When solution was complete the methanol was removed by rotary

evaporation, to yield the solid *p*-toluenesulphonylhydrazone salt 12.58 g (85%).

REACTION OF 5-SUBSTITUTED-2-PYRONES WITH PHENYLDIAZOMETHANE - GENERAL METHOD

Benzaldehyde *p*-toluenesulphonylhydrazone, sodium salt (0.355 g, 1.2 mmol) was added to dry benzene (30 ml). The benzene solution was slowly heated up to a temperature of 80°C whereupon the solution became red in colour: at this point a solution of the appropriate 5-substituted-2-pyrone (1 mmol) in benzene (20 ml) was added slowly over a period of 5 min. After the addition was complete, the solution was maintained at a temperature of 80°C for a further 15 min. and then allowed to cool to room temperature. After filtration the solvent was removed *in vacuo*, and the residue redissolved in dichloromethane (20 ml). The organic solution was then washed with water (3 x 10 ml) and dried. Removal of dichloromethane yielded a partially crystalline brown oil. The only identifiable components were unreacted starting material, stilbene and benzaldazine, as confirmed by ^{1}H n.m.r. and t.l.c. This procedure was used for 2-oxo-2*H*-pyran-5-carboxaldehyde and methyl coumalate, but in each case the reaction failed.

An alternative method of generating the diazo compound was employed. Thus benzaldehyde *p*-toluenesulphonylhydrazone, sodium salt (0.355 g, 1.2 mmol) was heated at

90°C in a Kugelrohr oven under vacuum (10^{-3} mbar). The phenyldiazomethane thus produced was condensed in a trap cooled by liquid nitrogen. When the distillation was complete the contents of the trap were dissolved in dry dichloromethane, (3 ml) and added dropwise to a solution of the appropriate 5-substituted-2-pyrone (1 mmol in dichloromethane (5 ml)). The solution was left stirring at room temperature for 12 h and then concentrated to dryness to yield a partially crystalline brown oil. The only identifiable components were unreacted starting material, stilbene and benzaldazine - confirmed by comparison of ^{1}H n.m.r. and t.l.c. with authentic materials. The above procedure was used for methyl coumalate and 2-oxo-2*H*-pyran-5-carboxaldehyde.

REACTION OF 2-OXO-2*H*-PYRAN-5-CARBOXALDEHYDE WITH (TRIMETHYLSILYL)DIAZOMETHANE[111]

This reaction was undertaken using glove box techniques under an argon atmosphere. 2-Oxo-2*H*-pyran-5-carboxaldehyde (0.124 g, 1 mmol) was dissolved in freshly distilled dichloromethane (5 ml). With continuous stirring a solution of (trimethylsilyl)diazomethane (2.0 M in hexane, 0.5 ml) was added dropwise *via* a syringe over a period of 3 min. The solution was then left to stir at room temperature for 1 h. The solvent was then removed *in vacuo* and the brown red residue examined by ^{1}H n.m.r. spectroscopy and t.l.c. Many products were detected and

the reaction was not investigated further.

REACTION OF 2-OXO-2*H*-PYRAN-5-CARBOXALDEHYDE WITH *p*-TOLUIDINE

2-Oxo-2*H*-pyran-5-carboxaldehyde (0.062 g, 0.5 mmol) was dissolved in ethanol (1 ml). With continuous stirring *p*-toluidine (0.053 g, 0.5 mmol) was added. The bright yellow crystalline material which formed after 1 minute was filtered and dried. The yield of the ring opened dienoic acid was 0.109 g (94%). m.p. 105°C (from ethanol). δ_H 9.41 (1H, d), 7.25 (5H, m), 6.72 (1H, d, ^3J 13Hz), 5.55 (1H, d, ^3J 13 Hz) and 2.34 (3H, s); *m/z* 187 (M^+-44, 19%), 144(21), 107(80), 106(100), 96(30), 68(31) and 39(44).

The above experiment was repeated on the same scale, but using chloroform (10 ml) as solvent. The mixture was left to stir for 12 h. The solvent was then removed *in vacuo* affording a yellow microcrystalline solid which was recrystallised from ethanol. The yield of *1,2-dihydro-2-oxo-1-p-tolylpyridine-5-carboxaldehyde* was 0.058 g (55%). m.p. 145-147°C (from ethanol) (Found C, 72.80; H, 5.10; N, 6.40; $C_{13}H_{11}NO_2$ requires C, 73.20; H, 5.20; N, 6.55%); δ_H 9.61 (1H, s), 7.95 (1H, d, ^4J 2.4 Hz), 7.86 (1H, dd, ^3J 9.5 and ^4J 2.4 Hz), 7.34-7.23 (4H, m), 6.67 (1H, d, ^3J 9.5 Hz) and 2.41 (3H, s); δ_C 185.90, 162.19 (q), 147.17, 139.38 (q), 137.11 (q), 135.71, 130.06, 125.90, 118.07 (q) and 21.0; *m/z* 213 (M^+, 100%), 212(35), 184(22), 157(22), 131(13), 91(25) and 65(15).

REACTION OF 4,6-DIMETHYL-2-OXO-2*H*-PYRAN-5-CARBOXALDEHYDE WITH *p*-TOLUIDINE

4,6-Dimethyl-2-oxo-2*H*-pyran-5-carboxaldehyde (0.10 g, 0.657 mmol) was dissolved in methanol (3 ml). With continuous stirring *p*-toluidine (0.070 g, 0.657 mmol) was added. After 1 h the solvent was removed *in vacuo* affording a yellow microcrystalline material. This crude imine was recrystallised from ethanol and dried. The yield of the isolated *p-tolylimine of 4,6-dimethyl-2-oxo-2H-pyran-5-carboxaldehyde* was 0.139 g (88%) m.p. 100-102°C (from ethanol). (Found: C, 73.4; H, 6.2; N, 5.3; $C_{15}H_{15}NO_2$ .25 H_2O requires C, 73.3; H, 6.3 and N, 5.7; δ_H 8.40 (1H, s), 7.2-7.0 (4H, m), 6.06 (1H, s), 2.55 (3H, s), 2.40 (3H, s) and 2.36 (3H, s); δ_C 165.07 (q), 155.79 (q), 153.83, 149.13 (q), 136.12 (q), 129.99, 120.32, 114.36 (q), 112.15, 21.54, 20.80 and 18.98; *m/z* 241 (M^+, 100%), 226(48), 212(23), 198(70), 170(18), 91(45), 65(32), 53(27), 43(36), 39(20) and 32(97).

PREPARATION OF 1,2-DIHYDRO-2-OXOPYRIDINE-5-CARBOXYLIC ACID (6-HYDROXYNICOTINIC ACID)[121]

With continuous stirring, methyl coumalate (4.5 g, 0.029 mol) was added to a solution of ammonium hydroxide (12 ml, 14% sol.) keeping the temperature below 20°C. After 45 min. at this temperature the mixture was added to a near boiling solution of sodium hydroxide (60 ml, 17% sol.) and then boiled vigorously for 5 min. and allowed to cool to room temperature. Concentrated hydrochloric acid was then added with stirring, until the solution was strongly acidic. The microcyrstalline solid which separated was collected by filtration and dried. The yield of bright yellow 1,2-dihydro-2-oxopyridine-5-carboxylic acid was 2.9 g (72%) m.p. 299-301°C (lit.[121], 299-300°C).

PREPARATION OF ^{15}N LABELLED COMPOUNDS

i. [^{15}N]-*p*-Toluidine

p-Toluoyl chloride was prepared by heating, under reflux conditions, a mixture of thionyl chloride (9 ml) and *p*-toluic acid until the evolution of gases had ceased (1.5 h). The resulting oil was purified by distillation to give *p*-toluoyl chloride (8.5 g, 90%), b.p. 100°C (15 Torr) (lit.[124], 102°C (15 Torr)).

[^{15}N]-*p*-Toluamide was prepared using the *p*-toluoyl chloride generated above. A solution of ammonium nitrate (1.0 g : 98% $^{15}NH_4NO_3$) in water was cooled in ice and a solution of sodium hydroxide (1.05 g, 0.025 mol) in water (10 ml) was added. The mixture was shaken for 1h with a solution of *p*-toluoyl chloride (1.785 g, 0.0127 mol) in chloroform (100 ml). The chloroform layer was separated and the aqueous layer was extracted with ether (3 x 10 ml). The ether extracts were combined with the chloroform layer, dried ($MgSO_4$) and the solvents were removed *in vacuo*. The resulting solid was washed with light petroleum and was filtered to give the required [^{15}N]-*p*-toluamide (1.55 g, 98%), δ_H 7.70 (2H, d), 7.21 (2H, d), 5.90 (2H, br.s.) and 2.38 (3H, s).

[^{15}N]-*p*-Toluamide was converted to [^{15}N]-*p*-toluidine *via* a Hofmann reaction. A solution of hypobromite was prepared, at 0°C, by the addition of bromine (0.69 g, 5.16 mmol) to a solution of sodium hydroxide (2.79 g,

0.069 mol) in water (20 ml). [^{15}N]-*p*-Toluamide (1.55 g, 0.01 mol) was added and the mixture shaken until solution was complete. The mixture was heated to 70°C, this temperature was maintained for 20 min, then the solution was subjected to steam distillation for 30 min. The amine was extracted from the distillate with ether (3 x 10 ml), the extracts dried ($MgSO_4$) and the solvent removed *in vacuo* to give the required [^{15}N]-*p*-toluidine (0.56 g, 52%), δ_H 7.0 (2H, d), 6.62 (2H, d), 3.50 (2H, br.s.) and 2.24 (3H, s), which was pure enough for further use.

ii. <u>1,2-Dihydro-2-oxo-1-*p*-tolyl-[^{15}N]pyridine-5-carboxaldehyde</u>

2-Oxo-2*H*-pyran-5-carboxaldehyde (0.323 g, 2.61 mmol) was dissolved in chloroform (10 ml). With continuous stirring [^{15}N]-*p*-toluidine (0.282 g, 2.61 mmol) was added, and the solution was left to stir for 12h at room temperature. The solvent was removed *in vacuo* yielding 1,2-dihydro-2-oxo-1-*p*-tolyl-[^{15}N]pyridine-5-carboxaldehyde (0.313 g, 56%) m.p. 145-147°C (from ethanol).

iii. <u>*p*-Tolylimine of 1,2-Dihydro-2-oxo-1-*p*-tolyl-[^{15}N]-pyridine-5-carboxaldehyde</u>

The [^{15}N]-labelled pyridone (0.313 g, 1.461 mmol) was dissolved in methanol (5 ml) and *p*-toluidine (unlabelled) (0.156 g, 1.461 mmol) was added. After 2h the solvent was removed *in vacuo* affording the yellow micro-crystalline

imine, (0.44 g, 96%) m.p. 192-195°C (from ethanol) (Found M^+ 303.1391 $C_{20}H_{18}{}^{14}N^{15}NO$ requires 303.1389); δ_H ($[^2H_2]CH_2Cl_2$) 8.20 (1H, d, ^4J 2.5 Hz), 8.12 (1H, dd, ^3J 9.5 and ^4J 2.5 Hz), 7.75 (1H, d), 7.37-7.05 (8H, m), 6.64 (1H, d, ^3J 9.5 Hz), 2.44 (3H, s) and 2.36 (3H, s); δ_C 162.50 (q), 154.39, 154.25, 149.35 (q), 142.51, 142.45, 139.29, 138.35 (q), 137.40, 136.09 (q), 130.18, 130.07, 126.58, 121.82, 120.98, 120.94, 117.44 (q), 117.30 (q), 21.21 and 21.01; δ_N (CH_2Cl_2)[133] -198.187.

The above procedure was also used to label the imine nitrogen atom with [^{15}N]. This was achieved by first reacting unlabelled *p*-toluidene (0.280 g, 2.61 mmmol) with 2-oxo-2*H*-pyran-5-carboxaldehyde (0.328 g, 2.61 mmol) to yield the unlabelled pyridone (0.31 g, 55%). This pyridone was then treated with [^{15}N]-*p*-toluidine (0.31 g, 1.46 mmol) to afford the *[^{15}N] imine* (0.43 g, 94%) m.p. 193-196°C (from ethanol). (Found M^+ 303.1386 $C_{20}H_{18}{}^{14}N^{15}NO$ requires M^+ 303.1389; δ_N (CH_2Cl_2)[133] -63.7694. Both these [^{15}N] labelled compounds were used in pyrolysis experiments (see Discussion).

THIATION OF A 2-OXO-2H-PYRAN-5-CARBOXAMIDE

i. Preparation of Amide

4,6-Dimethyl-2-oxo-2*H*-pyran-5-carboxylic acid chloride (described earlier) (0.26 g, 1.35 mmol) was dissolved in dry ether (15 ml). To this solution was added a solution of N-methylaniline (0.144 g, 1.35 mmol) and triethylamine (0.136 g, 1.35 mmol) in ether (10 ml). The solution was then left stirring for 12h. The triethylamine hydrochloride was then removed by filtration. The yellow filtrate was concentrated by rotary evaporation, affording a yellow coloured oil which was triturated with ethanol to produce a fine white crystalline *amide*, which was isolated by filtration (0.295 g, 85%). m.p. 150-152°C (from ethanol); Found M^+ 257.1052, $C_{15}H_{15}NO_3$ requires 257.1052; δ_H 7.7-7.15 (5H, m), 5.85 (1H, s), 2.35 (3H, s), 2.19 (3H, s); δ_C 165.74(q), 161.15 (q), 151.95 (q), 153.57 (q), 142.55 (q), 129.33, 127.62, 125.35, 116.37 (q), 111.43, 37.11, 19.87 and 18.61; *m/z* 257 (M^+, 30%), 151(100), 107(23) and 43(21).

ii. Reaction of Amide with *Lawesson's Reagent*[117,118]

This reaction was conducted in a fume cupboard due to the pungent toxic smell of Lawesson's reagent.

The amide prepared above (0.110 g, 0.452 mmol) was dissolved in dry toluene (5 ml). With continuous stirring Lawesson's reagent (0.109 g, 0.271 mmol, 0.6 eq) was added

and the mixture heated at 100°C for 4h. The reaction was monitored throughout by t.l.c. using ethyl acetate and *n*-hexane (1:1). When reaction was complete, the solvent was removed *in vacuo*, and the crude material subjected to dry flash chromatography[134]. The required fractions were combined, and removal of the solvent *in vacuo* afforded *4,6-dimethyl-2-thioxo-2H-pyran-5-(N-methyl-N-phenyl)-carboxamide* as a yellow microcrystalline solid (0.105 g, 85%) m.p. 140-143°C (from ethanol); Found M^+ 273.0820, $C_{15}H_{15}NO_2S$ requires 273.0823; δ_H 7.30-6.96 (4H, m), 6.88 (1H, s), 3.44 (3H, s), 2.14 (3H, s) and 2.10 (3H, s); δ_C 196.06 (q), 164.95 (q), 162.80 (q), 146.62 (q), 142.11 (q), 129.53, 128.08, 127.97, 125.35, 120.44 (q), 37.20, 19.32 and 18.89; *m/z* 273 (M^+, 56%) 167(40), 137(100), 125(40), 107(77), 77(15), 53(10) and 43(48).

MELDRUM'S ACID (2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONE) DERIVATIVES

i. Preparation of Aryldiazonium tetrafluoroborates - General Method[113]

The required amine (250 mmol) was dissolved in fluoroboric acid (110 ml, 40% sol.). To this was added a cold solution of sodium nitrite (17 g, 250 mmol) in water (35 ml) and the resulting mixture was cooled and stirred. The diazonium salt precipitated from solution, and was isolated by filtration, washed once with cold fluoroboric acid (20 ml) and ethanol (30 ml, 95%), and several times with ether to yield the aryl diazonium salt. This procedure was used for aniline producing benzenediazonium tetrafluoroborate (38.25 g, 79%); *p*-toluidine giving *p*-tolyldiazonium tetrafluoroborate (40 g, 81%); *p*-nitroaniline affording *p*-nitro phenyl diazonium tetrafluoroborate (35 g, 61%).

ii. Preparation of Aryl azomalondialdehydes - General Method[113]

1,1,3,3-Tetramethoxypropane (26.3 g, 150 mmol) and hydrochloric acid solution (40 ml, 0.5M) were mixed together for 1.5h resulting in a bright yellow solution of malondialdehyde. To this solution was added ice cold water (375 ml) and the required aryldiazonium tetrafluoroborate salt (100 mmol), and vigorously stirred for 15 min.

A solution of sodium acetate was then added until precipitation occurred. The mixture was stirred for a further 1.5h, filtered, and the resulting solid washed with a large volume of water. The crude material was recrystallised from ethanol affording orange crystalline material of the arylazomalondialdehyde. This procedure was used for the three previously mentioned salts; *p*-tolyl-, *p*-nitrophenyl- and benzene-diazonium tetrafluoroborate to give phenylazomalondialdehyde (13.7 g, 78%) m.p. 110°C (lit.[113], 110-112°C), δ_H 9.96 (1H, s), 9.60 (1H, s) and 7.52-7.23 (6H, m); *p*-tolylazomalondialdehyde (15.6 g, 82%) m.p. 120°C (from ethanol) (lit.[113], 119-121°C); and *p*-nitrophenylazomalondialdehyde (14.3 g, 65%) m.p. 170°C decomp. (from ethanol) (lit.[113], 168°C).

iii. <u>Condensation of Meldrum's Acid with Arylazomalondialdehydes - General Method[113]</u>

A suspension of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's Acid) (1.44 g, 10 mmol) and the phenylazomalondialdehyde (1.76 g, 10 mmol) in benzene (30 ml) was treated with acetic acid (5 drops and piperidine (5 drops). The mixture was stirred for 12h affording an orange precipitate which was isolated by filtration. The yield of 5-(1,2-diazabutadiene-4-ylidene)-3-formyl-2,2-dimethyl-1,3-dioxane-4,6-dione was 1.51 g (50%) m.p. 120°C (from ethanol) (lit.[113], 120°C). δ_H 9.87 (1H, s), 8.78

(1H, s), 7.64-7.25 (6H, m) and 2.15 (6H, s). This procedure was repeated using *p*-tolylazomalondialdehyde and *p*-nitrophenylazomalondialdehyde and in both these cases the condensation failed resulting in formation of black polymeric materials. ^{1}H n.m.r. of these residues showed no required condensation adducts. Other condensation conditions[114,115] were tried, but these also proved unsuccessful, and thus these reactions were not investigated further.

PREPARATION OF METHYL 3-ARYLPROPENOATES VIA A WITTIG REACTION - GENERAL METHOD[119]

The required aldehyde (4 mmol) was dissolved in dry dichloromethane (50 ml). With continuous stirring methyl (triphenylphosphoranylidene)acetate (1.337 g, 4 mmol) was added. After 2h the solvent was removed *in vacuo* and the crude material subjected to dry flash chromatography[134] on silica.

The material isolated was pure enough for further use. The following compounds were made using this procedure. 2-Hydroxy-5-chlorobenzaldehyde gave *methyl 3-(2-hydroxy-5-chlorophenyl)propenoate* (0.68 g, 80%) m.p. 145-147°C (from ethanol). (Found, C, 56.1; H, 3.30 $C_{10}H_9ClO_3$ requires C, 56.40; H, 3.32%); δ_H ([$^2H_6$]DMSO), 7.79 (1H, d, ^3J 16.0 Hz), 7.67 (1H, d, ^4J 2.5 Hz), 7.24 (1H, dd, ^3J 8.7 Hz and ^4J 2.5 Hz), 6.91 (1H, d, ^3J 8.7 Hz), 6.67 (1H, d, ^3J 16.0 Hz) and 3.48 (3H, s); δ_C ([$^2H_6$]DMSO), 116.82 (q), 155.44, 138.50 (q), 130.96, 127.78, 123.02 (q), 122.27 (q), 118.28, 117.69 and 51.29; *m/z* 212 (M^+, 13%), 180(100), 154(33), 152(94), 127(11), 99(12), 89(44) and 63(30); salicylaldehyde gave *methyl 3-(2-hydroxyphenyl)-propenoate* (0.62 g, 88%), m.p. 136-137°C (from ethanol); (Found C, 67.40; H, 5.60 $C_{10}H_{10}O_3$ requires C, 67.35; H, 5.65%); δ_H ([$^2H_6$]DMSO), 7.87 (1H, d, ^3J 16.0 Hz), 7.58 (1H, m), 7.23 (1H, m), 6.91 (1H, m), 6.86 (1H, m), 6.60 (1H, d, ^3J 16.0 Hz) and 3.70 (3H, s); δ_C ([$^2H_6$]DMSO), 167.09 (q), 140.40, 131.88 (q), 131.63, 128.72, 120.56

(q), 119.05, 116.71, 116.05 and 51.20; *m/z* 178 (M^+, 31), 146(100), 118(82), 103(25), 91(34), 65(10) and 32(14); 2-hydroxy-5-nitrobenzaldehyde gave *methyl 3-(2-hydroxy-5-nitrophenyl)propenoate* (0.67 g, 75%) m.p. 198-200°C (from ethyl acetate). (Found C, 53.7; H, 4.01; N, 6.0, $C_{10}H_9NO_5$ requires C, 53.85; H, 4.1; N, 6.35%); δ_H ([$^2H_6$]DMSO), 8.48 (1H, d, ^4J 2.8 Hz), 8.17 (1H, dd, ^3J 9.1 Hz and ^4J 2.8 Hz), 7.80 (1H, d, ^3J 16.3 Hz), 7.07 (1H, d, ^3J 9.0 Hz), 6.80 (1H, d, ^3J 16.3 Hz) and 3.7 (3H, s); δ_C ([$^2H_6$]DMSO) 166.59 (q), 162.35 (q), 139.78 (q), 137.91, 126.80, 124.94, 121.16 (q), 119.91, 116.49 and 51.45; *m/z* 223 (M^+, 26%), 191(100), 163(22), 117(22), 89(24), 63(13) and 32(24); 2-Hydroxy-1-naphthaldehyde gave *methyl 3-(2-Hydroxynaphth-1-yl)propenoate* (0.77 g, 85%) m.p. 145-148°C (from ethyl acetate); (Found C, 73.30; H, 5.30; $C_{14}H_{12}O_3$ requires C, 73.70; H, 5.35%); δ_H ([$^2H_6$]DMSO), 8.29 (1H, d, ^3J 16.0 Hz), 8.16-7.23 (6H, m), 6.88 (1H, d, ^3J 16.0 Hz) and 3.18 (3H, s); δ_C ([$^2H_6$]DMSO) (one quaternary missing), 160.21 (q), 153.47 (q), 140.58, 133.38, 130.04 (q), 128.95, 128.51, 126.26, 122.42, 116.96, 115.49, 113.02 (q) and 48.7; *m/z* 228 (M^+, 50), 196(94), 168(100), 141(31), 140(17), 139(37) and 115(26).

The following compounds were made employing a different ylid, ethyl 2-(triphenylphosphoranylidene)-propionate in dichloromethane solution under reflux conditions for 1h. The same molar amounts of reagents (4 mmol) were used as previously described in the general

method. Salicylaldehyde gave *ethyl 2-methyl-3-(2-hydroxyphenyl)propenoate* (0.67 g, 82%), m.p. 58-61°C (from hexane) (Found C, 69.4; H, 6.8; $C_{12}H_{14}O_3$ requires C, 69.8; H, 6.8%). δ_H ([$^2H_6$]DMSO) 7.74 (1H, s), 7.30-6.79 (4H, m), 4.18 (2H, q), 1.98 (3H, s) and 1.26 (3H, t); δ_C ([$^2H_6$]DMSO) 167.68 (q), 134.36, 129.87, 129.76, 126.62 (q), 122.15 (q), 118.59, 115.76 (q), 115.32, 60.20, 14.07 and 13.92; *m/z* 206 (M^+, 15%), 160(100), 132(40), 131(31) and 77(10). 2-Hydroxy-5-chlorobenzaldehyde gave *ethyl 2-methyl-3-(2-hydroxy-5-chlorophenyl)propenoate* (0.85 g, 88%) m.p. 93-95°C (from *n*-hexane); (Found C, 59.8; H, 5.4; $C_{12}H_{13}ClO_3$ requires C, 59.9; H, 5.4%); δ_H ([$^2H_6$]DMSO) 7.63 (1H, d, ^4J 2.5 Hz), 7.26 (1H, s), 7.21 (1H, dd, ^3J 8.5 and ^4J 2.5 Hz), 6.9 (1H, d, ^3J 8.5 Hz), 4.18 (1H, q), 1.96 (3H, s) and 1.25 (3H, t); δ_C ([$^2H_6$]DMSO) 167.37 (q), 154.66 (q), 138.18 (q), 132.88, 129.40, 128.87, 128.12 (q), 123.85 (q), 116.94, 60.41, 14.07 and 13.87; *m/z* 240 (M^+, 12%), 194(100), 166(38), 131(19), 103(22) and 77(20).

FLASH VACUUM PYROLYSIS (F.V.P.) EXPERIMENTS

Pyrolysis of 2-Oxo-2*H*-pyran-5-carboxaldehyde

0.050 g (0.4 mmol), 60°C, 650°C, 1 x 10^{-3} mbar, 15 min. gave an equilibrium mixture containing starting material and 2-oxo-2*H*-pyran-3-carboxaldehyde; δ_H 10.07 (1H, d, ^5J 0.8 Hz), 8.02 (1H, dd, ^3J 6.3 and ^4J 2.4 Hz), 7.75 (1H, dd, ^3J 5.0 and ^4J 2.4 Hz) and 6.45 (1H, ddd, ^3J 6.3, ^3J 5.0 and ^5J 0.8 Hz). This pyrolysis experiment was repeated at various furnace temperatures and the emergence of the rearranged product was expressed graphically as a function of furnace temperature (see Discussion for detailed explanation). At a furnace temperature of 800°C, clean decarbonylation to the parent 2-pyrone occurred, identified by ^{1}H nmr spectroscopy; δ_H 7.46 (1H, ddd, ^3J 5.2, ^4J 2.3 and ^5J 1.2 Hz), 7.30 (1H, ddd, ^3J 9.5, ^3J 6.4 and ^4J 2.3 Hz), 6.19 (1H, ddd, ^3J 9.5, ^4J 1.2 and ^5J 1.2 Hz) and 6.31 (1H, ddd, ^3J 6.4, ^3J 5.2 and ^4J 1.2 Hz).

Pyrolysis of 6-Methyl-2-oxo-2*H*-pyran-5-carboxaldehyde

0.055 g (0.4 mmol), 60°C, 650°C, 1 x 10^{-3} mbar, 20 min. gave an equilibrium mixture containing starting material and two rearranged isomeric compounds; *5-acetyl-2-pyrone*, δ_H 8.26 (1H, dd, ^4J 2.7 and ^5J 1.1 Hz), 7.84 (1H, dd, ^3J 10.0 and ^4J 2.7 Hz), 6.30 (1H, dd, ^3J 10.0 and ^5J 1.1 Hz) and 2.42 (3H, s); and *3-acetyl 2-pyrone*, δ_H 8.13 (1H, dd, ^3J 6.8 and ^4J 2.4 Hz), 7.70 (1H, dd, ^3J 5.0 and ^4J 2.4

Hz), 6.40 (1H, dd, ^3J 6.8 and ^3J 5.0 Hz) and 2.61 (3H, s). The starting material was also subjected to variable temperature pyrolyses to observe the emergence of the two rearranged isomers (see Discussion section).

Pyrolysis of 4,6-Dimethyl-2-oxo-2*H*-pyran-5-carboxaldehyde

0.060 g (0.4 mmol), 70°C, 650°C, 1 x 10^{-3} mbar, 15 min. gave an equilibrium mixture of starting material and 5-acetyl-4-methyl-2-pyrone, δ_H 8.16 (1H, s), 6.07 (1H, s), 2.37 (3H, s) and 2.20 (3H, s), and 3-acetyl-4-methyl-2-pyrone, δ_H 7.40 (1H, d, ^3J 5.3 Hz), 6.12 (1H, d, ^3J 5.3 Hz), 2.48 (3H, s) and 2.38 (3H, s). Variable temperature pyrolyses of the starting material allowed the emergence of the rearranged isomers to be plotted graphically as a function of furnace temperature (see Discussion).

Pyrolysis of *4,6-Dimethyl-2-oxo-2H-pyran-5-carboxaldehyde-N-p-tolylimine* 0.096 g (0.4 mmol), 70°C, 650°C, 1 x 10^{-3} mbar, 15 min. gave *5-acetyl-4-methyl-p-tolyl-pyridin-2-one* 0.096 g (0.4 mmol) 100%, which was isolated directly from the trap m.p. 150-151°C (from isopropylalcohol); (Found C, 74.70; H, 6.40, N, 5.70; $C_{15}H_{15}NO_2$ requires C, 74.65; H, 6.25; and N, 5.80); δ_H 7.98 (1H, s), 7.32-7.21 (4H, m,), 6.40 (1H, s), 2.48 (3H, s), 2.40 (3H, s) and 2.39 (3H, s); δ_C 194.59(q), 161.23(q), 151.49(q), 143.84, 139.03(q), 137.35(q), 129.97, 126.06, 121.35, 118.53(q), 27.51, 22.14 and 20.98;

m/z 241 (M^+, 100%), 226(47), 212(24), 198(71), 170(19), 19(45), 65(33), 53(38), 43(37) 39(19) and 32(96).

PYROLYSIS OF ^{2}H, ^{18}O ^{15}N AND RELATED COMPOUNDS

Pyrolysis of 2-Oxo-2*H*-pyran-5-[^{2}H]-carboxaldehyde

0.008 g (0.064 mmol), 60°C, 550°C, 1 x 10^{-3} mbar, 5 min. gave some rearranged [^{2}H]-2-oxo-2*H*-pyran-3-carboxaldehyde $\delta_{^{2}H}$ 10.0 (1^{2}H, s). The results of variable temperature pyrolyses are quoted in the Discussion.

Pyrolysis of 2-Oxo-2*H*-pyran-5-[^{18}O]carboxaldehyde

0.050 g (0.4 mmol), 60°C, 800°C, 1 x 10^{-3} mbar, 5 min. gave clean decarbonylation to 2-pyrone δ_{H} 7.46 (1H, ddd), 7.30 (1H, ddd), 6.18 (1H, ddd) and 6.30 (1H, ddd); *m/z* 98 (M^{+}, 20%). ^{18}O label was retained to some degree (see Discussion for interpretation of this result).

Pyrolysis of 1,2-dihydro-2-oxo-1-*p*-tolylpyridine-5-carboxaldehyde

0.015 g (0.07 mmol), 160°C, 900°C, 1 x 10^{-3} mbar, 5 min. gave an almost quantitative yield of starting material. No decarbonylation product could be detected. δ_{H} 9.62 (1H, s), 7.95 (1H, d, ^{4}J 2.4 Hz), 7.85 (1H, dd, ^{3}J 9.5 and ^{4}J 2.4 Hz), 7.34-7.23 (4H, m), 6.66 (1H, d, ^{3}J 9.5 Hz) and 2.41 (3H, s).

^{15}N Labelled Imine Pyrolysis

Imine (95) 0.152 g (0.5 mmol), was subjected to F.V.P. at a furance temperature of 750°C (inlet temperature 140°C), at a pressure of 10^{-3} mbar. Examination of the

pyrolysate by ^{15}N nmr showed a new emerging signal at δ_N -198.191 indicative of the ^{15}N label being scrambled to the ring nitrogen position. The extent of scrambling was only 4%. The experiment was repeated with a fresh sample of **95** at a furnace temperature of 850°C. The pyrolysate was again examined by ^{15}N nmr. The scrambling of the imine ^{15}N label into the ring position was much more pronounced, equilibration to 37%, but with accompanying decomposition to some extent (see Discussion section for details).

PYROLYSIS OF CARBOXYLIC ACIDS

i. Pyrolysis of 2-Oxo-2*H*-pyran-5-carboxylic Acid (Coumalic Acid)

0.050 g (0.36 mmol), 100°C, 800°C, 1 x 10^{-3} mbar, 5 min. gave clean decarboxylation to 2-pyrone (0.027 g, 80%); δ_H 7.46 (1H, ddd), 7.30 (1H, ddd), 6.19 (1H, ddd) and 6.31 (1H, ddd). The starting material was subjected to variable temperature pyrolyses and the emergence of decarboxylated product expressed graphically as a function of furnace temperature (see Discussion).

ii. Pyrolysis of 4,6-Dimethyl-2-oxo-2*H*-pyran-5-carboxylic Acid (Isodehydroacetic Acid)

0.050 g (0.29 mmol), 150°C, 800°C, 1 x 10^{-3} mbar, 5 min. gave clean decarboxylation to 4,6-dimethyl-2-pyrone (0.026 g, 75%) obtained as a yellow oil; δ_H 5.89 (1H, lm), 5.79 (1H, s), 2.14 (3H, m) and 2.04 (3H, m). The starting material was also subjected to variable temperature (see Discussion).

PYROLYSIS OF METHYL 3-ARYLPROPENOATES; FORMATION OF THE 2-PYRONE RING SYSTEM

Methyl 3-(2-hydroxyphenyl)propenoate

0.063 g (0.353 mmol), 100°C, 750°C, 5 x 10^{-3} mbar, 5 min. gave coumarin (5,6-benzo-2-pyrone) (0.051 g, 87%) m.p. 68-69°C (from *n*-hexane) (lit.[135], 68-70°C); δ_H ([$^2H_6$]DMSO) 8.01 (1H, d, ^3J 9.5 Hz), 7.6 (2H, m), 7.34 (2H, m) and 6.47 (1H, d, ^3J 9.5 Hz); δ_C ([$^2H_6$]DMSO) 159.90 (q), 153.39 (q), 144.16, 131.88, 128.35, 124.42, 118.63 (q), 116.18 and 116.10.

Methyl 3-(2-hydroxy-5-chlorophenyl)propenoate

0.060 g (0.28 mmol), 100°C, 750°C, 5 x 10^{-3} mbar, 5 min. gave 6-chlorocoumarin (0.048 g, 94%) m.p. 160-162°C (from ethanol) (lit.[136], 160-162°C); δ_H ([$^2H_6$]DMSO) 8.0 (1H, d, ^3J 9.6 Hz), 7.84 (1H, d, ^4J 2.5 Hz), 7.63 (1H, dd, ^3J 8.9 and ^4J 2.5 Hz), 7.42 (1H, d, ^3J 8.9 Hz) and 6.57 (1H, d, ^3J 9.6 Hz); δ_C ([$^2H_6$]DMSO) 159.39 (q), 152.07 (q), 142.98, 131.42, 128.14 (q), 127.47, 120.03 (q), 118.19 and 117.36.

Methyl 3-(2-hydroxy-5-nitrophenyl)propenoate

0.065 g (0.29 mmol), 140°C, 750°C, 5 x 10^{-3} mbar, 5 min. gave 6-nitrocoumarin (0.042 g, 75%) m.p. 183-184°C (from toluene) (lit.[137], 185-187°C); δ_H ([$^2H_6$]DMSO), 8.67 (1H, d, ^4J 2.7 Hz), 8.35 (1H, dd, ^3J 9.0 and ^4J 2.7 Hz),

8.19 (1H, d, ^3J 9.7 Hz), 7.56 (1H, d, ^3J 9.0 Hz) and 6.65 (1H, d, ^3J 9.7 Hz); δ_C ([$^2H_6$]DMSO) 158.84 (q), 157.14 (q), 143.41 (q), 143.22 (q), 126.44, 124.27, 119.0 (q), 118.0 and 117.75.

Methyl 3-(2-hydroxy-naphth-1-yl)propenoate

0.070 g (0.30 mmol), 140°C, 750°C, 5 x 10^{-3} mbar, 5 min. gave 5,6-benzocoumarin (0.045 g, 75%), m.p. 118-120°C (from ethanol), (lit.[138], 117-118°C); δ_H ([$^2H_6$]DMSO) 8.26 (1H, d, ^3J 9.8 Hz), 8.05 (1H, d, ^3J 8.3 Hz), 7.85-7.45 (4H, m), 7.28 (1H, d, ^3J 8.3 Hz) and 6.44 (1H, d, ^3J 9.8 Hz); δ_C ([$^2H_6$]DMSO) (one quaternary missing), 160.76 (q), 153.49 (q), 138.85, 132.86, 129.96 (q), 128.75, 128.47, 125.87, 121.11, 116.66, 115.23 and 112.67 (q).

Ethyl 2-Methyl-3-(2-hydroxyphenyl)propenoate

0.065 g (0.31 mmol), 100°C, 750°C, 5 x 10^{-3} mbar, 5 min. gave 3-methylcoumarin (0.041 g, 82%), m.p. 90-92°C (from ethanol), (lit.[139], 70°C); δ_H ([$^2H_6$]DMSO), 7.86 (1H, s), 7.63-7.27 (4H, m) and 2.09 (1H, s); δ_C ([$^2H_6$]DMSO), 159.0 (q), 152.56 (q), 139.47, 130.59, 127.41, 124.82 (q), 124.33, 119.24 (q), 115.82 and 16.60.

Ethyl 2-Methyl-3-(2-hydroxy-5-chlorophenyl)propenoate

0.064 g (0.27 mmol), 100°C, 750°C, 5 x 10^{-3} mbar, 5 min. gave 3-methyl-6-chlorocoumarin (0.049 g, 96%), m.p.

158-160°C (from ethanol), lit.[139], 155-158°C); δ_H ([$^2H_6$]DMSO), 7.79 (1H, s), 7.70 (1H, d, ^4J 2.4 Hz), 7.54 (1H, dd, ^3J 8.8 and ^4J 2.4 Hz), 7.38 (1H, d, ^3J 8.8 Hz) and 2.08 (3H, s); δ_C ([$^2H_6$]DMSO) 160.68 (q), 151.15 (q), 138.17, 130.13, 128.04 (q), 126.46, 126.20 (q), 120.62 (q), 117.79 and 16.7.

PYROLYSIS OF THE MELDRUM'S ACID DERIVATIVE, 5-(1,2-DIAZABUTADIENE-4-YLIDENE-3-FORMYL-2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONE

100 mg (0.33 mmol), 120°C, 600°C, 5 x 10^{3} mbar, 45 min. gave *2,3-dihydro-2-phenyl-3-oxopyridazine-6-carboxaldehyde* 31.68 mg (48%), m.p. 80°C (from ethanol); (Found C, 64.8; H, 4.0; N, 13.8; $C_{11}H_8NO_2$ .25 H_2O requires C, 64.5; H, 4.15; N, 13.7); δ_H 9.77 (1H, s), 7.78 (1H, d, ^3J 9.7 Hz), 7.64-7.44 (5H, m) and 7.07 (1H, d, ^3J 9.7 Hz); δ_C 187.62, 159.67 (q), 142.37 (q), 140.63 (q), 130.69, 128.84, 127.54 and 125.12; *m/z* M^+ (200, 100%), 93(43.1), 80(28), 77(51) and 51(21).

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