SYNTHETIC AND MECHANISTIC STUDIES OF HETEROCYCLIC SYSTEMS

THESIS

Submitted in the Fulfilment of the
Requirements for
the Degree of
MASTER OF SCIENCE

by

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Dedicated to my parents

and Ruth

"Of what strange nature is knowledge! It clings to the mind when it has once seized on it like a lichen on the rock."

Mary Shelley - Frankenstein

Abstract

A series of acrylate esters and selected analogues have been reacted with pyridine-2-, pyridine-3-, and pyridine-4-carboxaldehydes in the presence of diazabicyclo[2,2,2]octane (DABCO) to afford a range of Baylis-Hillman products.

The pyridine-2-carboxaldehyde-derived products have been acetylated using acetic anhydride and the kinetics of the thermal cyclisation of the acetylated compounds to indolizines was investigated using proton NMR spectroscopy. The first-order kinetics of the cyclisation has been confirmed and the influence of substituents on the first-order rate constant, k_{obs}, has been examined. The kinetic data has been shown to be consistent with the previously proposed mechanism in which loss of the acetate group is rate-determining. Each of the cyclisations was also monitored at three different temperatures permitting evaluation of the activation parameters.

The Baylis-Hillman products and related acetylated derivatives were treated at room temperature with sodium methylthiolate; the hydroxy precursors were observed to undergo conjugate addition with a degree of diastereocontrol but the acetylated derivatives favoured an apparent S_N' displacement of the acetate group.

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Acknowledgements

It was with great enthusiasm mixed with a slight feeling of apprehension that I undertook this project at the beginning of the year. I would like to thank my supervisor Prof. Perry Kaye for allaying those feelings of apprehension and guiding me throughout the year. The names of Baylis and Hillman will remain deeply etched on my mind

I would like to thank Mr Aubrey Sonemann and Dr Boshoff of Cape Technikon for collecting MS data.

I would also like to thank my proof readers Heide and Bruce Deane as well as Ruth Whittaker for a job well done.

Thank you to the staff of the Department for your encouragement during the course of the year.

To my colleagues and friends, thank you for an enjoyable year. It was an entertaining experience and a pleasurable one working with you. I hope the smells didn't get to you! Thanks to Catherine Logie and Jeffry Guthrie-Strachan for their help and much appreciated support. A special word of thanks to Ruth Whittaker for always being there when I needed her.

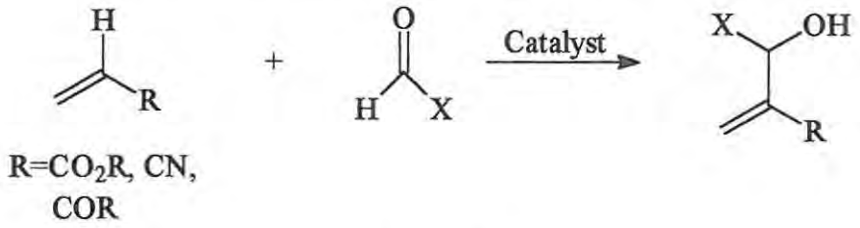
Last, but not least, I would like to thank my parents, without whom none of this would have been possible.

1. INTRODUCTION

1.1 The Baylis-Hillman Reaction

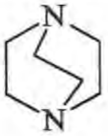
One of the most important processes in organic chemistry is the formation of a carbon-carbon bond.[1] Various classic reactions exist for the formation of such bonds, many of them involving enolate or enolate-equivalent chemistry. Such reactions include: the Stork-enamine reaction, aldol condensation, the Robinson annulation, the Michael Reaction and reactions of silyl enol ethers. Recently, attention has been given to the Baylis-Hillman reaction for the formation of such bonds.

The Baylis-Hillman Reaction (**Scheme 1**) involves attack by an appropriate electrophile (usually an aldehyde) at the α-position of an α,β unsaturated vinylic system. This reaction was patented in 1972 by Baylis and Hillman[2] of the Celanese Corporation of New York. Since then, much work has been done using this reaction and a review has been published by Drewes and Roos.[3] The reaction has also been called the 'DABCO reaction' since 1,4-diazabicyclo[2,2,2]octane (DABCO) is commonly used as the catalyst but, as Drewes and Roos point out, "it implies a restriction to this particular base".[3] Today the reaction is more commonly known as the Baylis-Hillman reaction.



Scheme 1

In their original patent, Baylis and Hillman described the synthesis of a wide range of products from various acrylates and aldehydes, and using DABCO (**1**), pyrrocoline (indolizine) (**2**) or quinuclidine (**3**) as catalysts. The reactions were carried out at temperatures between 10°C and 155°C and gave yields in the region of 70%.



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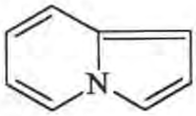

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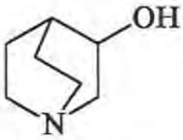

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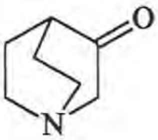

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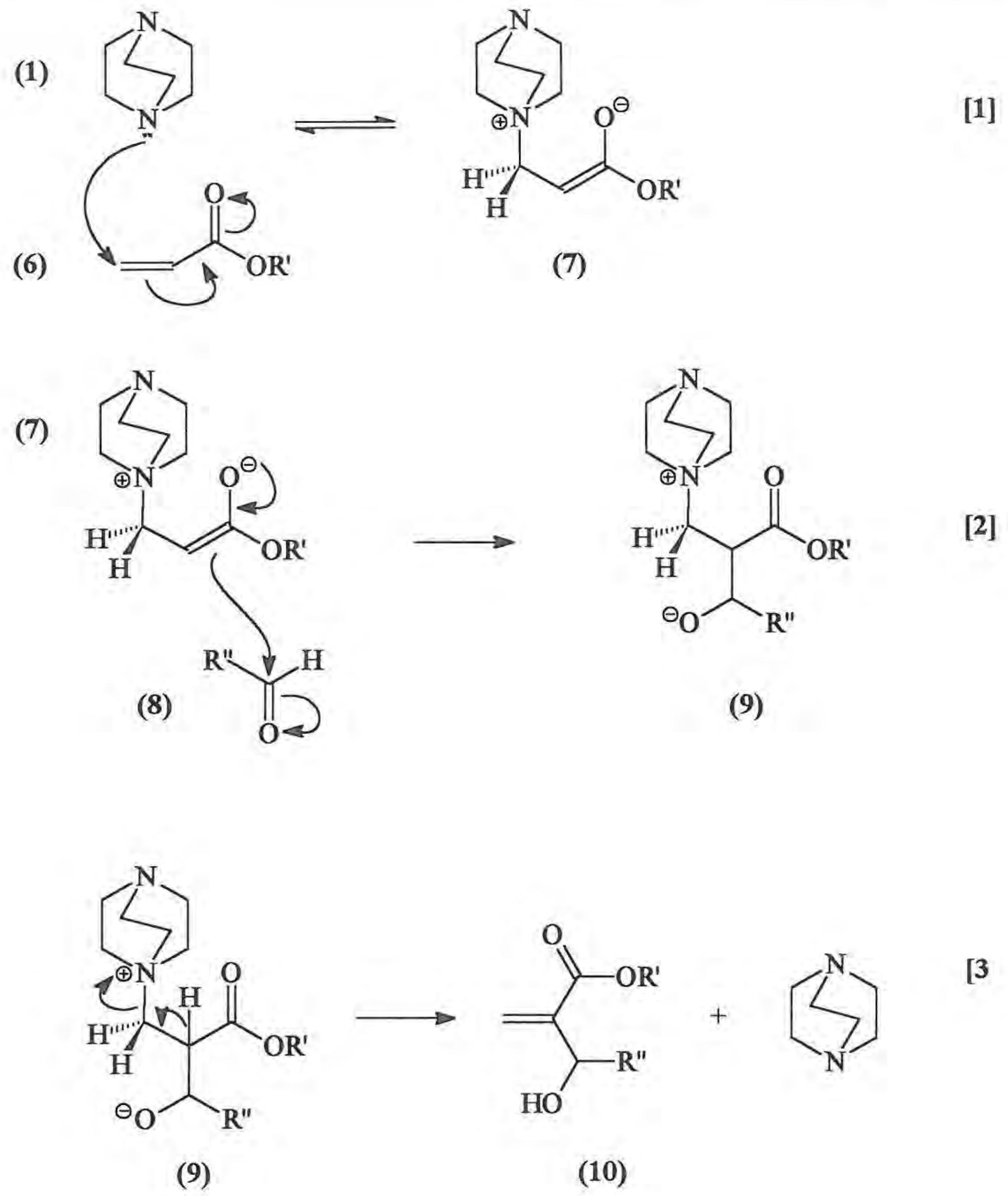
Other catalysts which have been used with varying degrees of success include 3-hydroxyquinuclidine **(4)**,[4] 3-quinuclidone **(5)**,[5] tertiary phosphines,[6,7] an acid-base catalyst consisting of tributylphosphine and triethylaluminium[8] and a rhodium (I) hydride complex.[9] These catalysts will all be discussed in greater detail in section 1.1.3.

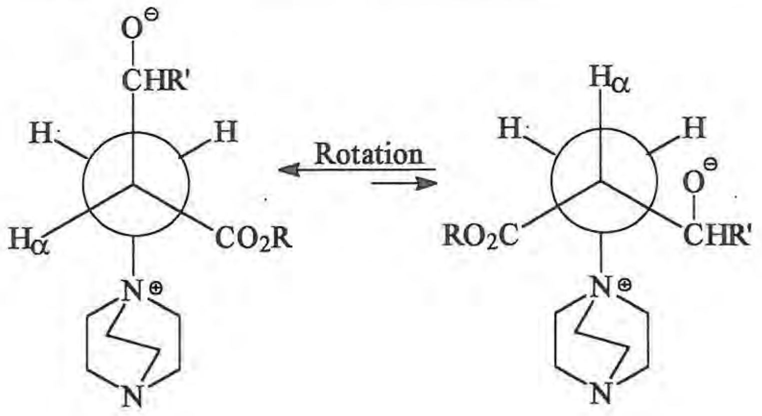
1.1.1 Mechanistic Aspects

Several authors have examined the mechanism for DABCO-[10,11,12] and phosphine-[6,7] catalysed reactions. **Scheme 2** outlines the mechanism proposed by Kaye and Bode,[10] which is very similar to that proposed by Hoffman and Rabe.[11] The reaction is considered to proceed *via* three steps; *viz.*, i) a Michael-type addition to the vinylic substrate **(6)** (step [1]), ii) nucleophlic addition to the aldehyde **(8)** (step [2]) and iii) elimination to afford the unsaturated product in which the double bond resumes its original position (step [3]).



Scheme 2

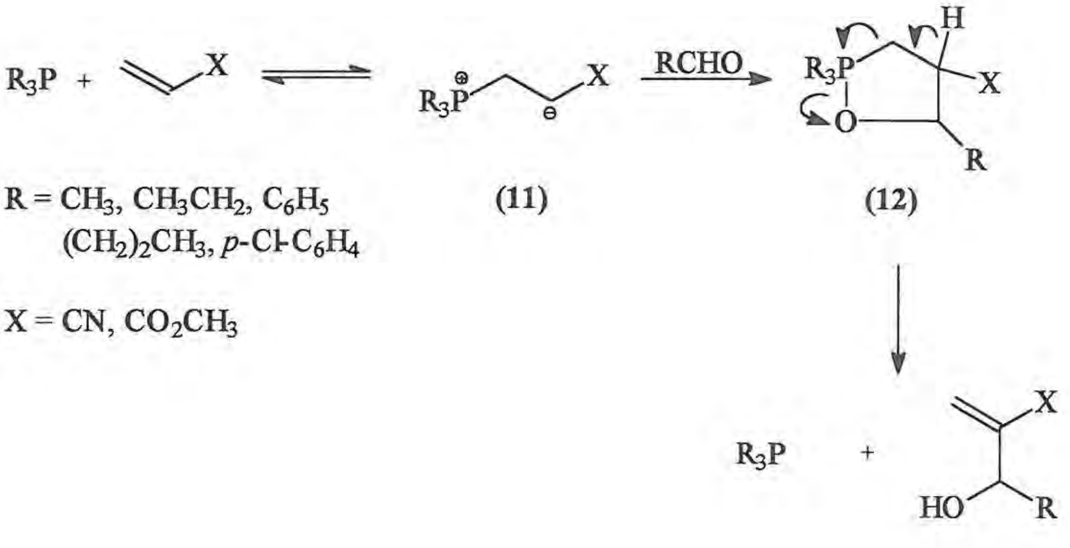
Hoffmann and Rabe go further to suggest that the zwitterionic intermediate (9), formed in the second step, exists as an equilibrium mixture of two conformations (**Scheme 3**). The preferred conformation is **(9a)** as there are fewer gauche interactions.



(9a) **(9b)**

Scheme 3

Morita *et al.*[6] propose a similar mechanism to that of Imagawa *et al.*[8] for reactions involving phosphine catalysts. However, they also put forward a second reaction mechanism **(Scheme 4)** in which cyclisation follows addition of the zwitterionic phosphine intermediate **(11)** to the aldehyde. Electron transfer then occurs and the final product **(13)** is formed.



R = CH_3, CH_3CH_2, C_6H_5
$(CH_2)_2CH_3$, p-Cl-C_6H_4

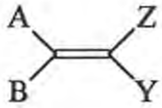
X = CN, CO_2CH_3

(11) **(12)** **(13)**

Scheme 4

1.1.2 Acrylates And Other Systems As Vinylic Substrates

In Baylis-Hillman reactions, the vinylic substrate **(14)** is typically an acrylate derivative. In general A, B and Y are hydrogen, whilst Z is an electron-withdrawing substituent. (*e.g.* Z=COMe, CO_2R,[13] $C\equiv N$[6,8,14-16]). Other vinylic systems, which have been studied, include dienoates [such as compound **(15)**],[17] sulfones [such as compound **(16)**],[18-21] diethlylvinylphosphonate **(17)**[22] and terminal hydroxyalkyl acrylates **(18)**.[1]



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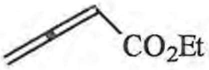

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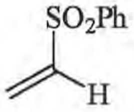

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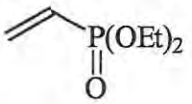

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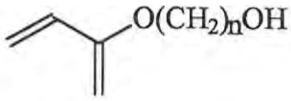

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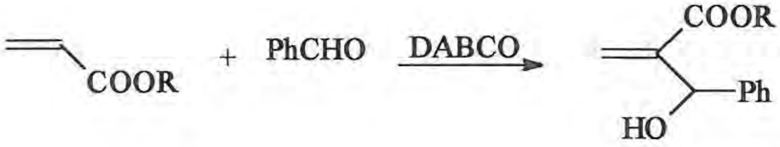
1.1.2.1 Acrylate Esters

In a recent, extensive study by Fort *et al.*[23] it has been shown that the reaction between benzaldehyde and aryl, benzyl, alkyl and functionalised alkyl acrylate esters, with DABCO as catalyst, depends largely upon the electronic and steric effects of the ester functionality. Thus in **Scheme 5**, the reaction rate depends strongly on the electron-withdrawing or donating nature of the sustituent R. Selected results from the first study using *meta-* and *para-*substituted benzyl acrylates are shown in **Table 1**. It was found that electron-donating groups lead to a decrease in the rate of condensation and acrylate destruction. It would also seem that electron-releasing groups, such as the diethylamino group, lead to a decrease in aldehyde destruction but an increase in acrylate destruction and, in general, inhibit the condensation. The authors also tried to correlate the yields of the reactions with σ values but concluded that the correlations were not straightforward.



Scheme 5

Table 1. Data for the reaction between benzaldehyde and a series of benzyl acrylates (**Scheme 5**).

Entry	R	σ[a]	time (h)	Yield (%)[b]
1	p-Me_2N-C_6H_4	-0.63	84	62 (77)
2	p-Me-C_6H_4	-0.14	36	55 (61)
3	m-Me_2N-C_6H_4	-0.10	20	61 (77)
4	m-Me-C_6H_4	-0.06	36	54 (60)
5	C_6H_5	0	5	55 (81)
6	p-F-C_6H_4	0.15	72	39 (51)
7	m-F-C_6H_4	0.34	5	43 (54)

[a] The σ values are values that sum the total electrical effects (resonance and field) of a group attached to a benzene ring.[24]

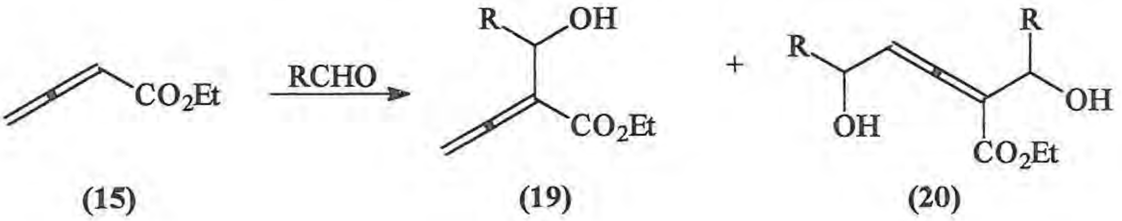
[b] Isolated yield based on benzaldehyde. Values in parentheses are based on converted benzaldehyde.

Another study, carried out by Fort *et al.*[23] involved the use of simple alkyl acrylates. They concluded that increasing the length of the alkyl chain decreases the reactivity of the acrylate system. An increase in the steric bulk of the side chain, *i.e.* going from *n*-C_4H_9 to *i*-C_4H_9, led to a decrease in reaction rate, probably because steric hindrance makes it difficult for reagents to approach. It is also likely that the long chain alkyl groups fold back on themselves creating a bulky group. These results are consistent with results obtained independently by Bode and Kaye,[10] who attributed the decrease in rate to an increase in the electron releasing inductive effect.

Fort *et al.* concluded from their study that: i) the condensation of acrylate esters with benzaldehyde in the presence of DABCO depends strongly on the nature of the acrylate ester; ii) electronic and steric effects are important; iii) it is difficult to accurately determine the exact mechanism of these reactions as a number of side reactions may intervene; and iv) the reaction must be considered to be equilibrated.

1.1.2.2 Ethyl 2,3-butadienoate

Tsuboi *et al.*[17] have used ethyl 2,3-butadienoate **(15)** as a substrate in the Baylis-Hillman reaction with a moderate degree of success (**Scheme 6**).

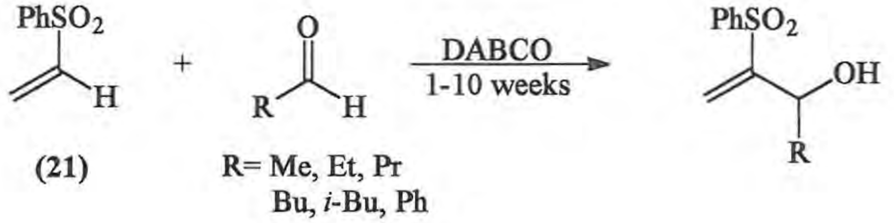


Scheme 6

When DABCO was used as the catalyst only the monosubstituted product **(19)** was obtained, in yields ranging from 41% to 54%. When butyllithium was used instead at temperatures between -75° and -30°C, the monosubstituted product was also obtained as the only product. When the temperature was lowered to -92°C a mixture of both the mono- and di-substituted **(20)** compounds was obtained. The authors attribute the disubstitution to the removal of both α- and γ-olefinic hydrogens in the dienoate species by the strong base, butyllithium. Although the reaction using butyllithium is not a Baylis-Hillman-type reaction, it is interesting to see a Baylis-Hillman-type product being formed *via* a vinylic carbanion. It is, in fact, pertinent to note that in the Baylis-Hillman reaction the acrylate or analogous substrates act as nucleophilic vinylic equivalents.

1.1.2.3 Sulfones

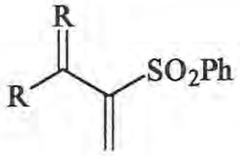
Ando *et al.*[18] have synthesised a series of aromatic and aliphatic sulfones using the Baylis-Hillman reaction. They extended the work of Auvray *et al.*,[19-20] who used phenyl vinyl sulfone **(21)** together with acetaldehyde and other aldehydes (**Scheme 7**).



Scheme 7

The yields for these reactions are fair to very good (54%-84%). However, the reaction is very slow and, in the case of pivaldehyde, was still incomplete after 150 days. The yield is dependent on competition between hydroxyalkylation and aldehyde degradation which leads to aldol or polymer formation. Ando *et al.* went on to synthesise a range of secondary products using the Baylis-Hillman "adducts" as intermediates.

Weichert and Hoffmann[21] have compared α-alkylidine-β-keto **(22)** sulfones to methyl vinyl ketone (MVK). These sulfones were synthesised from phenyl vinyl sulfone and a series of aldehydes, [RCHO:- R=Me, Et, *n*-Pr, CH_2CHMe, Ph, $(CH_2)_2Ph$ and $(CH_2)_3Ph$)] under Baylis-Hillman conditions. It is possible for the resulting β-keto sulfones to undergo a Baylis-Hillman reaction with suitable aldehydes. Although very reactive, the sulfones do not dimerise as does MVK, and Weichert and Hoffmann attribute this to the bulkiness of the benzenesulfonyl group.



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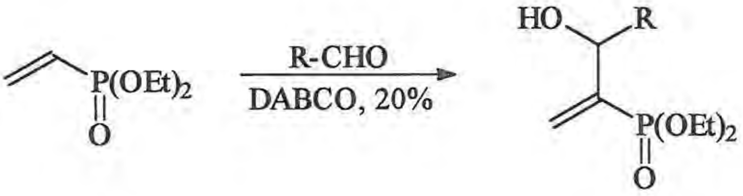
1.1.2.4 Diethyl vinylphosphonate

Amri and co-workers[22] investigated diethyl vinylphosphonate **(17)** as a Baylis-Hillman substrate. They coupled various aliphatic aldehydes with the vinylphosphonate to produce a series of α-hydroxyalkylated diethyl vinylphosphonates **(23)** in very good yields in most cases (**Scheme 8**). The aldehydes used and the corresponding yields are shown in **Table 2**. As can be seen from the data in **Table 2**, the reaction times were long. The authors[22] thought that this may have been due to the reduced reactivity of the vinyl phosphonate substrates, resonance and steric effects decreasing their electrophilicity.



Scheme 8

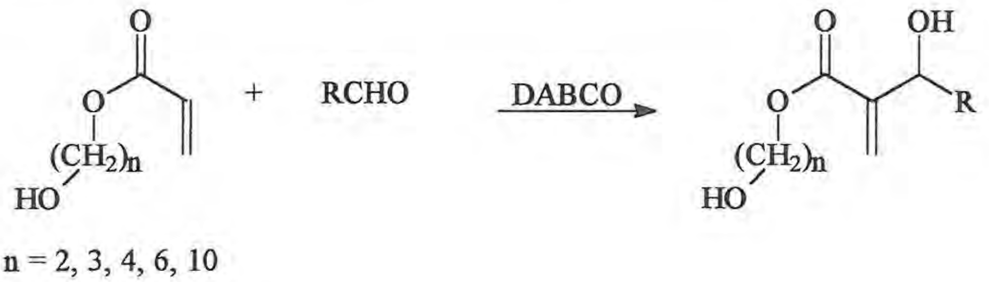
Table 2. Data for the formation of vinylphosphonates **(23)** by the DABCO catalysed reaction between diethylvinylphosphonate and various aldehydes **(Scheme 8)**.[22]

Entry	R	Reaction Time (days)	B.p. (°C/mmHg)	Yield (%)
1	CH_3	7	64/0.65	83
2	C_2H_5	10	58/0.3	78
3	n-C_3H_7	10	74/0.3	73
4	i-C_3H_7	14	81/0.3	74
5	n-C_4H_9	21	97/0.2	68[a]
6	i-C_4H_9	29	102/0.2	54[a]

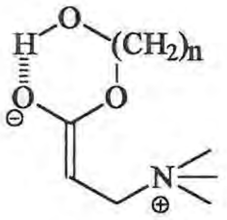
[a] Reactions needing an excess of DABCO (30%)

1.1.2.5 Terminal Hydroxyalkyl Acrylates

Terminal hydroxyalkyl acrylates act as good substrates in the Baylis-Hillman reaction as shown by Basavaiah *et al.* **(Scheme 9)**.[1] The reason for this is the potential for hydrogen bonding stabilisation of the zwitterionic intermediates **(24)** and **(25)**. The reaction was carried out using various aldehydes (propionaldehyde, butyraldehyde, *p*-tolualdehyde and *o*-anisaldehyde) and a series of terminal hydroxyalkyl acrylates. Reaction rates were found to be marginally faster than was the case for analogous acrylates; for instance, the reaction between 2-hydroxyethyl acrylate (n=2) and propionaldehyde was complete in 5 days. A similar reaction carried out using ethyl acrylate took 7 days.[25] This reaction and its mechanism are being studied by Basavaiah and co-workers and these authors have reported the use of chiral hydroxyalkyl acrylates as optical inducers.[26]



Scheme 9



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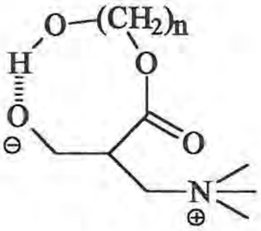

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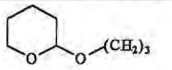
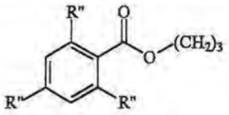
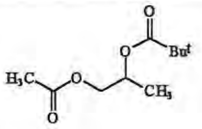
1.1.3 Relative Reactivity of Aldehydes, Ketones and other Electrophiles.

Generally, the Baylis-Hillman reaction is slow with most aldehydes requiring 4-7 days and even longer to run to completion.[10] Aldehydes are more reactive than ketones, and this can be attributed to both electronic and steric factors.[27] A ketone having two bulky substituents will be more sterically hindered than an aldehyde which has hydrogen as one side group. Nucleophilic attack is thus much easier and the tetrahedral intermediate less crowded. Electronically, the carbonyl carbon of an aldehyde tends to be more electrophilic than that of a ketone, making aldehydes more reactive than ketones.

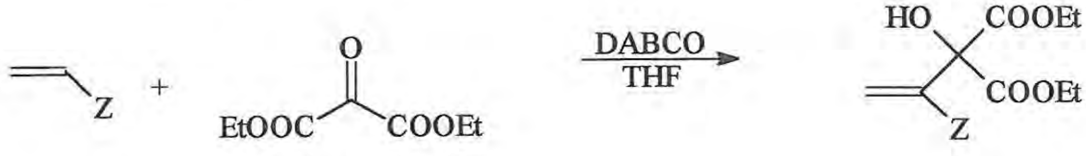
Hoffmann and Rabe,[11] in their synthesis of mikanecic acid, report the coupling of acrylate esters with a wide range of aldehydes. Even the less reactive aldehydes, benzaldehyde and methacrolein can be used, although reaction times are long and the yields are low, as shown in **Table 3**.

Table 3. Summary of results obtained by Hoffmann and Rabe in their DABCO catalysed reactions between acrylate esters and aldehydes.[11]

Entry	R-CHO (R)	$H_2C{=}CHCO_2R'$ (R')	Reaction time	Product yield (%)
1	CH_3	t-Bu	7 d	89
2		Me	7 d	87
				
3	R"=H	Me	7 d	95
4	R"=CH_3	Me	7 d	87
5		Me	7 d	89
6	$Cl(CH_2)_3$	Me	7 d	≈60
7	CCl_3	Me	20 h	>55
8	C_6H_5	Me	6 d	39
9	2-Furyl	Me	18 h	63
10	3-Pyridyl	Me	4 h	>82
11	$H_2C{=}C(CH_3)$	Me	20 d	33

1.1.3.1 Diethyl ketomalonate

In general, ketones tend to be unsuitable substrates for the Baylis-Hillman reaction, being relatively unreactive except under high pressures.[12,28] However, Basavaiah and Gowriswari[29] found that diethyl ketomalonate (**26**) reacted rapidly with acrylate esters, acrylonitrile and methyl vinyl ketone (**Scheme 10**). Results of this study are summarised in **Table 4**. It has been found that similar reactions using aldehydes took between 18 hours and 7 days.[11] The great advantage of this reaction is the synthesis of molecules having five functional groups. Applications of these molecules are under investigation by Basavaiah and co-workers.



(26)

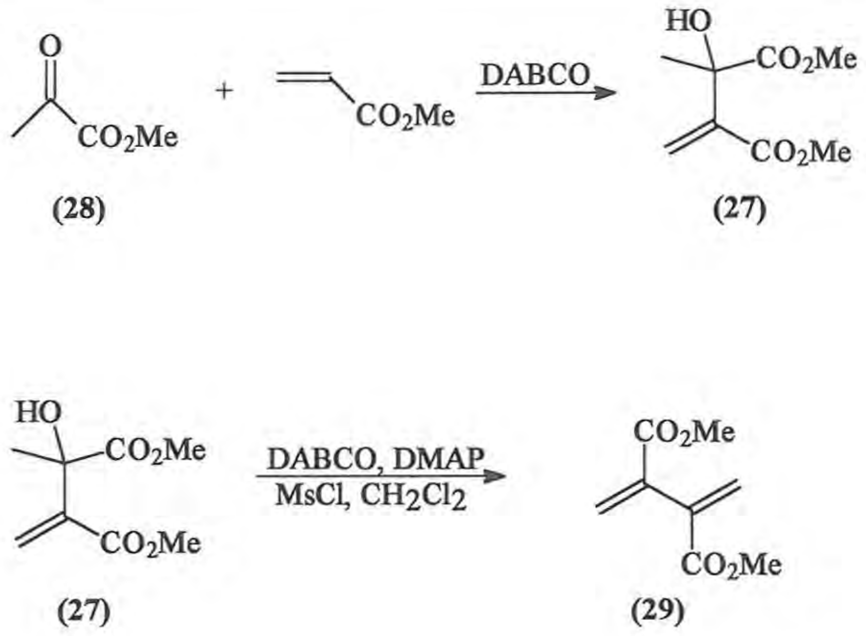
Scheme 10

Table 4. Data for the reaction between diethyl ketomalonate and various acrylates (**Scheme 10**).

Entry	**Z**	**Yield (%) of product**	**Reaction time (h)**
1	COOMe	77	4
2	COOEt	73	6
3	$COOBu^t$	67	36
4	CN	80	3
5	COMe	74	0.5

1.1.3.2 Methyl pyruvate

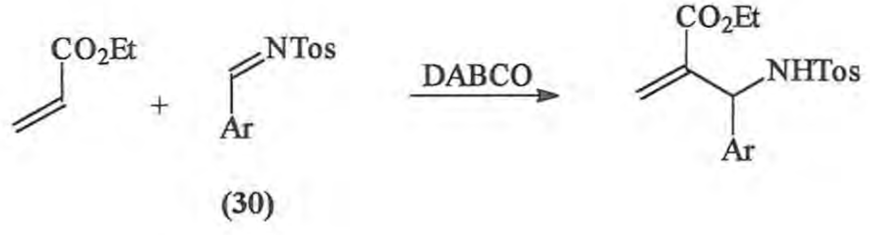
In their synthesis of dimethyl 2,3-dimethylenebutanedioate **(27)**, Grundke and Hoffmann[30] reacted methyl pyruvate **(28)** and methyl acrylate under Baylis-Hillman conditions to give the tertiary allylic alcohol **(29)** in 95% crude yield **(Scheme 11)**. As mentioned earlier, ketones do not readily react with vinylic systems under normal conditions. However, methyl pyruvate reacts readily with methyl acrylate as the ketone is activated by the adjacent ester function. In a subsequent step, the tertiary allylic alcohol was treated with DABCO and 4-(dimethylamino)pyridine (DMAP), followed by methylsulfonyl chloride (MsCl) in dichloromethane to yield the diene **(27)**, which is used as a Diels-Alder diene and as a building block for α-methylene-γ-butyrolactones. This one-pot dehydration, developed by Poly[31] for related compounds, was one of several attempted by Grundke and Hoffmann.



Scheme 11

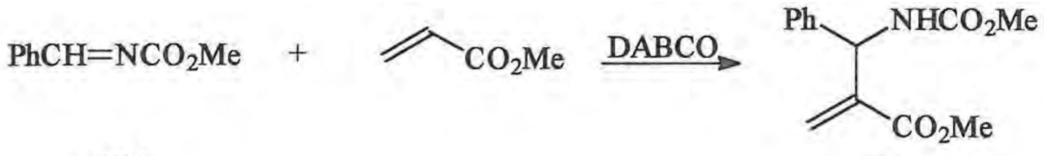
1.1.3.3 Imines

The Bayliss-Hillman reaction is not restricted to aldehydes and ketones. Perlmutter and Teo[32] have shown that analogous systems such as imines can undergo the reaction **(Sceme 12)**. Using a series of aryl tosylimines **(30)** (Ar = phenyl, 4-methylphenyl, 4-methoxyphenyl and 3-nitrophenyl) yields for the reaction ranged from 53% to 80%. The products of this reaction could very well be used in the synthesis of β-lactams. Work on varying the acrylate and imine systems as well as the cyclisation of these compounds is underway.



Scheme 12

Yamamoto *et al.*[33] in their studies into the hydrogenation of 2-[α-(methoxycarbonylamino)benzyl]acrylate **(32)**, synthesised this compound using methyl acrylate and methyl benzylidenecarbamate **(31)**. They found that the reaction proceeded at a greater rate than with aldehydes and they obtained **(32)** in 80% yield.



(31) **(32)**

Scheme 13

1.1.4 Baylis-Hillman Catalysts

A number of Baylis-Hillman catalysts exist, but the one of major interest is DABCO. DABCO is a cyclic tertiary amine and is a relatively strong base.[3] The purpose of the DABCO (and other Baylis-Hillman catalysts) is to activate the vinylic system for nucleophilic attack on the aldehyde.

1.1.4.1 DABCO and Related Compounds

The use of DABCO as catalyst in the Baylis-Hillman reaction is widely documented.[1,2,7,14-22,28-30,32-34] It generally provides a high yielding but slow reaction. However, some DABCO catalysed reactions are complete in less than an hour and Crouch and Nelson[34] report a synthesis suitable for undergraduates that is complete in 45 minutes with a 77% yield.

While other tertiary amine Baylis-Hillman catalysts have been used, DABCO and other bicyclic tertiary amines have the advantage of a rigid ring system. This makes the nitrogen more accessible for nucleophilic attack on an activated alkene.[34]

Kaye *et al.*[4] have used the hydroxylated tertiary amine, 3-hydroxyquinuclidine **(3)**, with a high degree of success. They observed a significant lowering of reaction half-lives compared to those of DABCO catalysed reactions. In a separate study, Drewes *at al.*[35] found that the acetylated 3-hydroxyquinuclidine and 3-quinuclidone were poor catalysts.

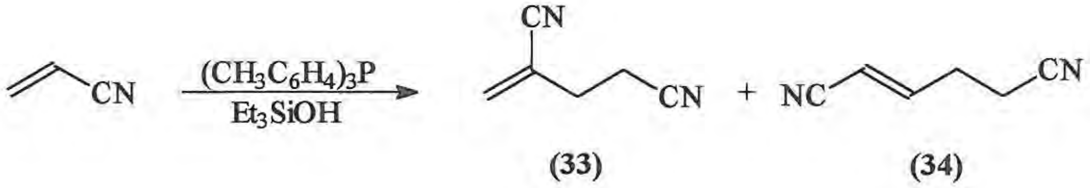
Hill and Isaacs,[28] working at high pressures, found that triethylamine acted as a better catalyst under these conditions. The reaction was better controlled and the reaction time did not seem to be adversely affected. However, triethylamine at room temperature and pressure leads to a slow reaction with poor yields.[35]

1.1.4.2 Tertiary Phosphines

Phosphines are usually associated with the Wittig reaction in which an aldehyde or ketone is treated with a phosphorus ylide to produce an olefin **(Scheme 14).**[36] As early as 1965, tertiary phosphines have been used to catalyse what is now commonly referred to as the Baylis-Hillman reaction. In their paper, Baizer and Anderson[37] reported the synthesis of α-methyleneglutanitrile **(33)** using acrylonitrile and tributylphosphine in acetonitrile containing water or *t*-butyl alcohol. A method previously used by Rauhut and Currier[38] led to polymerisation of the acrylonitrile, hence water or alcohol were added to act as proton donors to inhibit polymerisation; however trimers and an insoluble tar were still isolated along with the required dimer. Baizer and Anderson then varied the reaction conditions by using different concentrations of acrylonitrile, phosphine, acetonitrile and water, but yields for this reaction still varied from only 0.5% to 11%; use of triphenylphosphine led to a slowing of the reaction.

Scheme 14

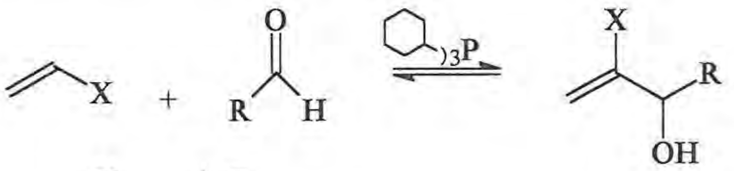
Independently, McClure[39] managed to quadruple the conversion of acrylonitrile obtained by Baizer and Anderson using the reaction outlined in **Scheme 15**. The percentages of the isomers **(33)** and **(34)** obtained vary according to the reaction conditions **(Table 5)**. The catalysts used were tri(*p*-tolyl)-phosphine and triphenylphosphine and the solvents were t-butyl alcohol and triethylsilanol.



Scheme 15

Table 5. Reaction conditions and yields obtained by McClure for the phosphine catalysed dimerisation of acrylonitrile **(Scheme 15)**.

Catalyst	Solvent	T (°C)	t (hours)	% conversion	% (33+34)	% (34)
$(C_6H_5)_3P$	Me_3COH	175	8	15	45	39
$(CH_3C_6H_4)_3P$	Me_3COH	160	8	30	65	30
$(C_6H_5)_3P$	Et_3SiOH	175	8	16	75	40
$(CH_3C_6H_4)_3P$	Et_3SiOH	160	11	36	85	32
$(CH_3C_6H_4)_3P$	Et_3SiOH	160	4	15	90	38



X	R
CN	CH_3
CN	CH_2CH_3
CN	$(CH_2)_2CH_3$
CN	$CH(CH_3)_2$
CN	$(CH_2)_6CH_3$
CN	C_6H_5
CN	p-Cl-C_6H_4
CN	p-$CH_3C_6H_4$
CO_2CH_3	CH_3
CO_2CH_3	CH_2CH_3
CO_2CH_3	$(CH_2)_2CH_3$
CO_2CH_3	C_6H_5

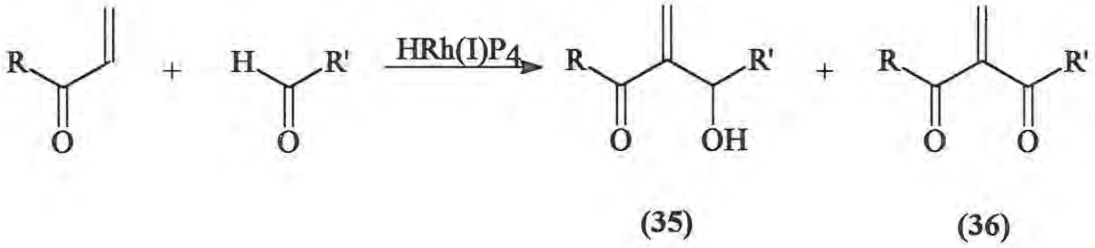
Scheme 16

Morita *et al.*[6] applied the method of Baizer and Anderson in their synthesis of a series of vinylic monomers (**Scheme 16**). In place of tributylphosphine, they used tricyclohexylphosphine, obtaining yields of 70% to 90%, and gave their reaction the name "Carbinol Addition".

Imagawa *et al.*[8] further extended the use of phosphines in their work, in which they made use of tributylphosphine as the catalyst and triethylaluminium as co-catalyst. Although Morita *et al.* obtained high yields in their tricyclohexylphosphine catalysed reactions,[6] the conversion was below 25%. Imagawa *et al.*[8] attributed this to the susceptibility of the phosphine to oxidation; using acrylonitrile and a series of aliphatic aldehydes, Imagawa *et al.*[8] obtained products in yields of 27% to 90%. In their attempts to enhance the reaction further by using other Lewis acids such as diethylaluminium chloride, Imagawa [8] found that only self-condensation of the aldehyde occurred, possibly as a result of the Lewis acid reacting with the phosphine with subsequent loss in phosphine activity. Three possible means of coordination by the Lewis acid have been proposed by Imagawa *et al.*[8]: i) coordination to the phosphorus of the phosphine; ii) coordination with the carbonyl oxygen of the aldehyde; and iii) coordination to the nitrogen of the acrylonitrile. Imagawa *et al.*[8] conclude that the triethyl aluminium catalyst co-ordinates with the carbonyl oxygen of the aldehyde.

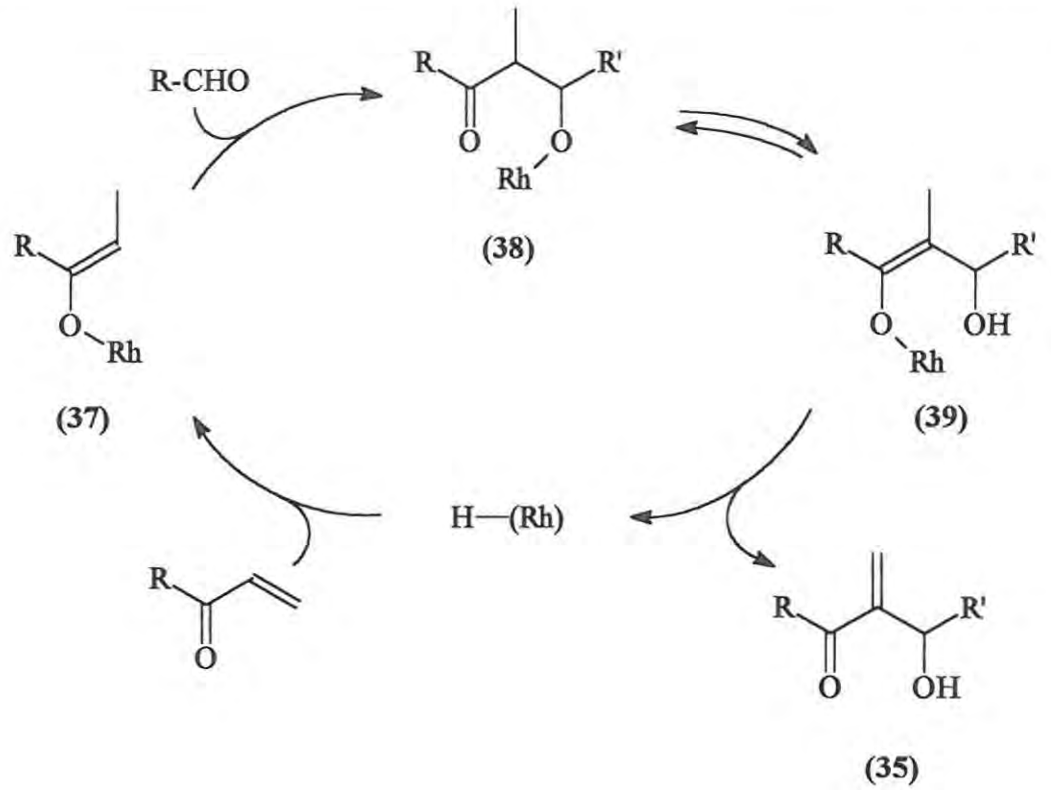
1.1.4.3 Rhodium(I) Hydride Complex Catalysed Synthesis

Several authors have used metal catalysts in the formation of Baylis-Hillman type adducts.[40-43] Such methods are expensive as they require equimolar amounts of catalyst. However, Sato *et al.*[9] have found a more convenient method for the reaction of an aldehyde with an acrylate system using $HRh(PPh_3)_4$ as the coupling reagent (**Scheme 17**). They obtained two coupling products **(35)** and **(36)** (the Baylis-Hillman and Michael-type products respectively) in the ratio 85:15 when reacting 3-buten-2-one and propanal in the presence of a rhodium hydride catalyst. They found that the amount of **(36)** could be decreased by adding a small amount of alcohol to the reaction mixture. Selected results from the study are shown in **Table 6**.



Scheme 17

The formation of intermediate **(37)** is considered to be initiated by hydride attack (**Scheme 18**). As can be seen, the rhodium complexes with the carbonyl of the acrylate species in much the same way as Imagawa's triethyl aluminium catalyst does.[8] Such binding of rhodium has been discussed in previous work published by these authors.[44-46]



Scheme 18

Table 6. Selected results from the study by Sato *et al.*[9] using 3-buten-2-one, propanal and a rhodium hydride catalyst.

Entry	Catalyst	mol % catalyst	Alcohol	Temperature (°C)	Product 35:36	% (35)
1	$HRh(PPh_3)_4$	1.0	none	105	93:7	47
2	$HRh(PPh_3)_4$	0.6	none	40	96:4	17
3	$HRh(PPh_3)_4$	0.9	EtOH	105	90:10	57
4	$HRh(PPh_3)_4$	0.8	*i*-PrOH	105	93:7	62
5	$HRh(PPh_3)_4$	0.8	*i*-PrOH	40	97:3	78
6	$HRh(PPh_3)_4$	0.4	*i*-PrOH	40	97:3	57
7	$HRh(PPh_3)_4$	0.1	*i*-PrOH	40	97:3	58
8	PPh_3	4.2	none	40	77:23	40

1.1.5 Optimisation Studies

Various methods have been employed to enhance the Baylis-Hillman reaction. Different solvents,[47-48] catalysts[4,35,48] and substrates,[4,17,35] the use of pressure,[12,28,47] heat,[49] ultrasound,[49] microwaves[50-51] and tricarbonylchromium complexes[52-53] have all been shown to influence the reaction to some extent.

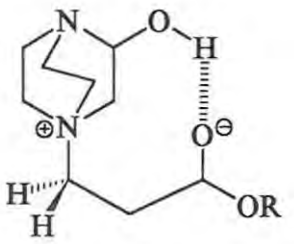
As already mentioned, Kaye *et al.*[4] achieved an overall rate enhancement when substituting the base, 3-hydroxyquinuclidine **(4)**, for DABCO **(1)**, while Drewes *et al.*[36] found a slowing of the reaction when the acetylated 3-hydroxyquinuclidine was used. Selected results comparing the three catalysts are shown in **Table 7**.

Table 7. Influence of catalyst and substrate on the half-life and yield of the Baylis-Hillman reaction.[4,36]

Aldehyde	**Substrate**	**Catalyst** [a]	**$t_{½}$ (min)**	**Yield (%)**
CH_3CHO	$CH_2=CHCO_2CH_3$	acetylated (4)	9750	90
CH_3CHO	$CH_2=CHCO_2CH_3$	(1)	3000	90
CH_3CHO	$CH_2=CHCO_2CH_3$	(4)	<900	90
EtCHO	Methyl acrylate	acetylated (4)	9660-10020	61
EtCHO	Methyl acrylate	(1)	2420-3000	61
EtCHO	Methyl acrylate	(4)	234-300	61
p-C_5H_4NCHO	Methyl acrylate	acetylated (4)	68	83
p-C_5H_4NCHO	Methyl acrylate	(1)	14	83
p-C_5H_4NCHO	Methyl acrylate	(4)	<5	83

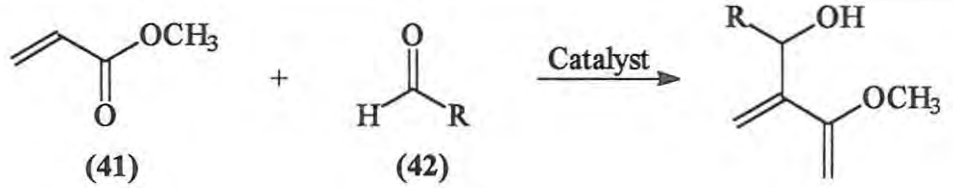
[a] (1) = DABCO, (4) = 3-hydroxyquinuclidine

As can be seen from **Table 7**, 3-hydroxyquinuclidine dramatically decreases the half-life ($t_{½}$) of the reaction, whereas the acetylated derivative increases $t_{½}$. Kaye *et al.*[4] proposed that hydrogen bonding helps to stabilise the catalyst-acrylate intermediate **(40)**.

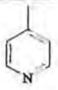
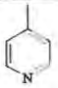
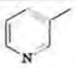


(40)

Table 8. Effects of varying catalyst, solvent and their concentrations on the half-life of the Baylis-Hillman reaction between methyl acrylate and selected aldehydes.[4]



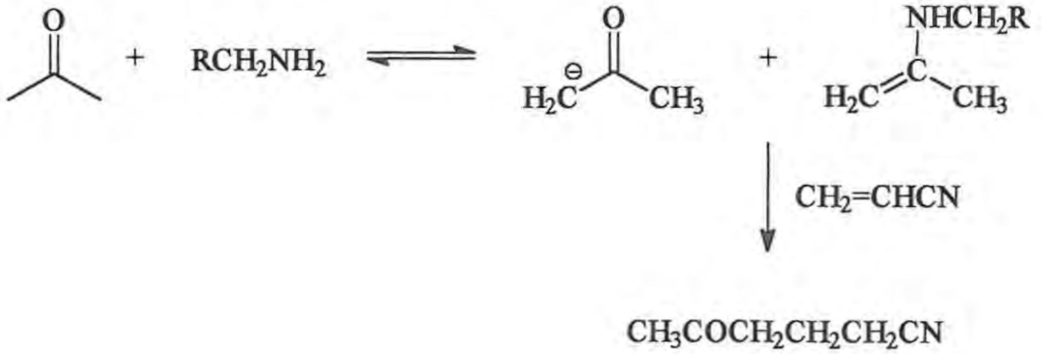
(41) (42)

Entry	**RCHO** **R**	**Catalyst**	**Ratio** **(42):(41):catalyst:MeOH**	**$t_{1/2} \times 10^{-3}$ (min)**	**Solvent**	**Yield (%)**
1	Me	DABCO	1:0.7:0.03	3	-	90
2	Me	DABCO/ MeOH	1:0.6:0.03:0.1	2	-	
3	Me	DABCO/ MeOH	1:0.7:0.1:0.1	1		
4	Me	3-HDQ[a]	1:0.6:0.03	<0.9	-	
5		DABCO	1:1.1:0.05	0.01	$CHCl_3$	83
6		3-HDQ[a]	1:1.1:0.05	<0.005	-	
7		DABCO	1:1.1:0.05	0.06	$CHCl_3$	82

[a] 3-HDQ = 3-hydroxyquinuclidine

Kaye *et al.*[4] also found that increasing the amount of catalyst led to an increase in reaction rate. The effects of changing the catalyst (entries 1 and 4), catalyst concentration (entries 2 and 3) and the effects of solvent (entries 1 and 2) on the reaction rate are detailed in **Table 8**. The role of the substituent R is also apparent if entry 1 is compared with entries 5 and 7.

Hill and Isaacs[12,28] have investigated the effects of pressure on the Baylis-Hillman reaction using, amongst others, acetone and acetonitrile as substrates. The condensation of these reagents is industrially important in the synthesis of pyridine derivatives and is normally catalysed by primary amines **(Scheme 19)**.[28]



Scheme 19

Using various vinylic and carbonyl substrates, Hill and Isaacs showed that an increase in the pressure led to an increase in yield and a reduction of the reaction time. They also found that the reaction was sensitive to changes in the temperature and the catalyst. Selected results are summarised in **Table 9**.

Table 9. Selected results from a study by Hill and Isaacs[12] on the effects of pressure and temperature on the Baylis-Hillman reaction.

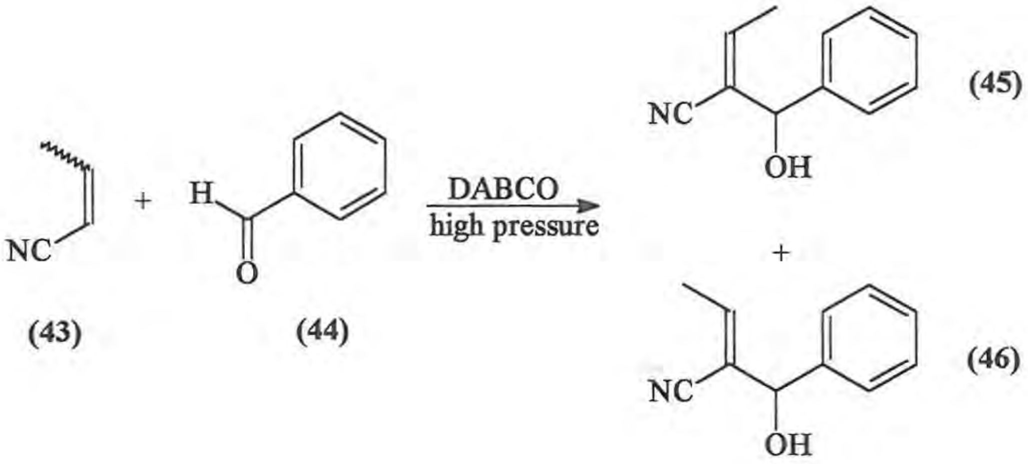
Entry	Vinylic Species	Carbonyl Species	Catalyst	Pressure (kbar)	Temp. (°C)	t (min)	Yield (%)
1	A	MeCHO	DABCO	0.001	42	2900	76
2	A		EDA[b]	5	20	5	78
3	A		EDA[b]	8	20	5	96
4	A	EtCHO	DABCO	0.001	20	7300	75
5	A		EDA[b]	5	46	360	60
6	A		EDA[b]	8	30	5	70
7	A	Me_2CO	DABCO	0.001	40	20160	0
8	A		DABCO	5	40	240	76
9	A		DABCO	10	40	90	65
10	B	MeCHO	DABCO	0.001	40	20160	0
11	B		DABCO	9	50	1080	72 (*Z*) 16 (*E*)
12	A	PhCHO	DABCO	0.001	5	5800	27
13	A		DABCO	0.001	42	4800	85

[a] A = CH_2=CHCN, B = MeCH=CHCN

[b] EDA=Ethyldiethylamine

Roos and Rampersadh,[49] dissatisfied with the generally slow rate of the Baylis-Hillman reaction, studied the effects of temperature and ultrasound on the reaction rate. They found that increasing the temperature slightly (from 22°C to 43°C) increased the reaction rate by between 9% and 97%, while the application of ultrasound produced small to moderate changes in rate (4% to 43%).

Van Rozendal *et al.*,[47] whilst studying the reaction between crotonitrile **(43)** and benzaldehyde **(44)** **(Scheme 20)**, altered the solvent, pressure and catalyst for the reaction. The product formed in this reaction was a mixture of the (*Z*)- and (*E*)-isomers of 2-(hydroxybenzyl)but-2-enenitrile (**45** and **46** respectively). **Figure 1** shows the effects of different solvents have on the *E*/*Z* ratio, while **Figure 2** shows the effects of altering the catalyst; the reactions in these cases were done at 8 kbar. These authors also found that in the presence of an aprotic solvent, such as chloroform, the *E/Z* ratio increased with pressure, whereas with a protic solvent, such as methanol, little or no change in the ratio was observed.



Scheme 20

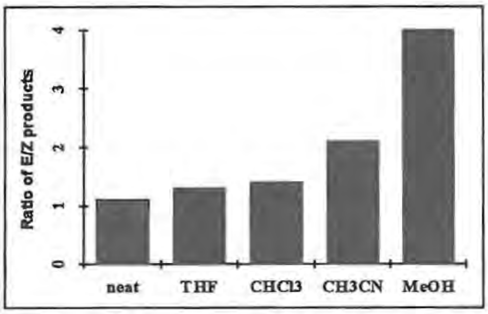


Figure 1. Effects of different solvents on the *E/Z* ratio in the rection between crotonitrile and benzaldehyde.

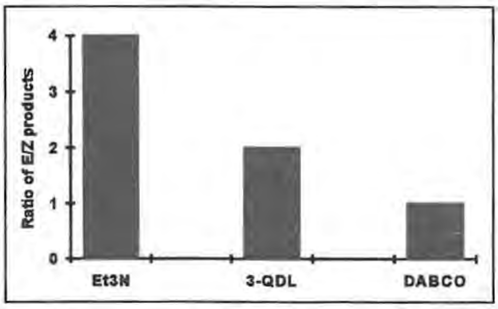
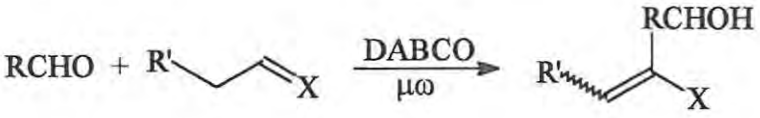


Figure 2. Effects of different catalysts on the *E/Z* ratio in the reaction between crotonitrile and benzaldehyde.

The use of water as a solvent in organic reactions has recently been reviewed by Lubineau *et al.*[54] The fact that most biochemical reactions take place in water suggests its potential as a solvent for use in certain organic reactions.[55] A wide variety of reactions were tested by the authors; these include Diels-Alder reactions, Claisen rearrangements and Michael-Type additions. Augé *et al.*[48] observed an acceleration of the Baylis-Hillman reaction when water was used as the solvent. Augé *et al.* reacted acrylonitrile, benzaldehyde and DABCO in the presence of various solvents, including water, ethylene glycol and formamide to obtain yields of 90-98% in reaction times of 7-8 hours. Use of THF and toluene, however, gave only 15-30% yields, even after a week. It is thought that water and, to a lesser extent, ethylene glycol and formamide may be involved in hydrogen bonding stabilisation of the zwitterionic intermediate.

Since its introduction to organic synthesis in 1986,[56a,b] microwave irradiation has become quite prevalent. Recently, Cablewski *et al.*[50] studied a range of organic reactions using a continuous microwave reactor (CMR). Such reactions included Michael addition, Hofmann degradation and the Mannich, Knoevenagel and Baylis-Hillman reactions.

The preparation of methyl 2-(hydroxymethyl)acrylate has been carried out by Kress *et al.*[57] using a modified Baylis-Hillman reaction. This compound has been used in the preparation of new polymers[58] but, as Cablewski *et al.*[50] state, "these reaction conditions are not conducive to the preparation of kilogram quantities of material." Cablewski *et al.*[50] have carried out this synthesis using CMR techniques at 950 kPa obtaining yields of 30% in 1,5 minutes reaction time. Further applications of this work are under investigation. Kundu *et al.*[51] have also studied the effects of microwave irradiation on the Baylis-Hillman reaction **(Scheme 21)**. It is known that the reaction between unsaturated aldehydes and acrylates is generally slow, but Kundu *et al.* found that microwave irradiation produces a dramatic increase in the rate of reaction **(Table 10)**.



X=CO_2CH_3, $CONH_2$

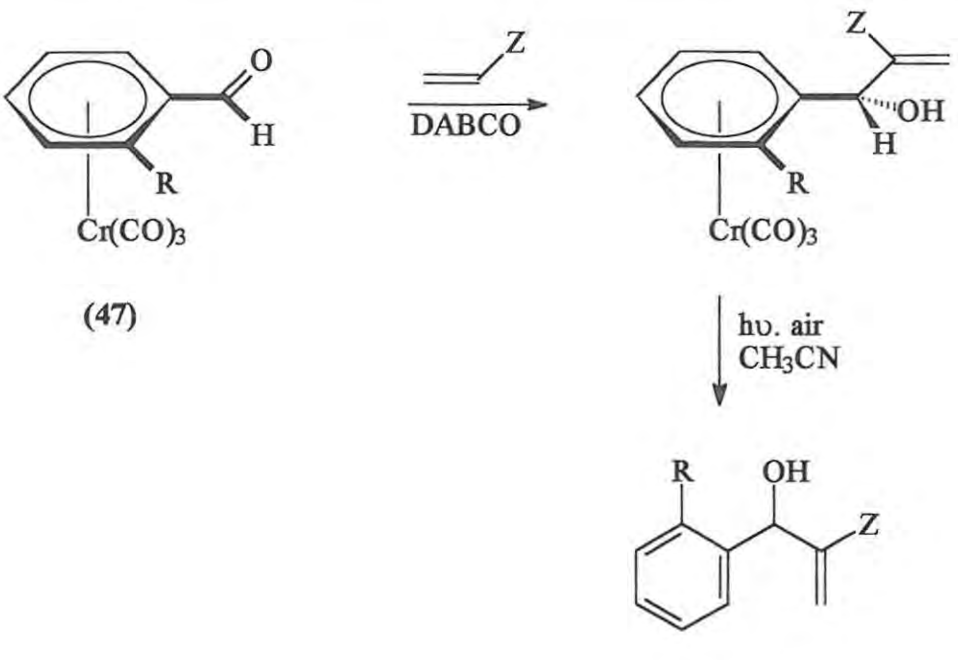
$CO_2C_2H_5$, CN

Scheme 21

Table 10. Comparison of reaction rates and yields under normal and micrwave conditions (see **Scheme 21**)

				Normal conditions		Microwave conditions	
Entry	**R**	**R'**	**X**	**Time (days)**	**Yield (%)**	**Time (mins)**	**Yield (%)**
1	C_6H_5	H	$COOCH_3$	2	25	10	34
2	2-OHC_6H_4	H	$COOCH_3$	3	10	10	70
3	3,4,5-$(CH_30)_3C_6H_2$	H	$COOCH_3$	4	5	30	15
4	3,4,5-$(CH_30)_3C_6H_2$	H	CN	3	80	10	55
5	4-$CH_3OC_6H_4$	H	CN	3	13	10	25
6	4-$NO_2C_6H_4$	H	CN	3	45	10	95
7	3,4,5-$(CH_30)_3C_6H_2$	H	$CONH_2$	3	0	25	40
8	$C_6H_5CH{=}CH$	H	CN	3	10	25	44
9	$C_6H_5CH{=}CH$	H	$COOCH_3$	14	28	45	15
10	CH_3CH_2	H	$COOCH_3$	4	61	10	70
11	CH_3	H	$COOCH_3$	4	90	10	40
12	4-$NO_2C_6H_4$	CH_3	$COOC_2H_5$	-	-	40	10

Kundig and co-workers[52-53] have employed a tricarbonylchromium complexing agent to enhance the Baylis-Hillman reaction. They found that complexing an aryl aldehyde to a tricarbonylchromium group accelerates the reaction with activated olefins (**Scheme 22; Table 11**), while with chiral benzaldehyde tricarbonylchromium complexes, asymmetric synthesis could also be achieved. [52]



(48)

Scheme 22

Table 11. Results from the study by Kundig *et al.*[52] using benzaldehyde, tricarbonylchromium complexed benzaldehyde and a series of acrylates (see **Scheme 22**)

Entry	Aldehyde	R	Z	Reaction time (h)	Yield (%)
1	Benzaldehyde	H	COMe	96	92
2		OMe		384	43
3		Cl		48	90
4	racemic (47)	H		6	94
5		OMe		93	87
6		Cl		6	89
7		F		7	92
8	S-(+)-(47)	OMe		93	85
9		Cl		8	97
10		OMe	CN	11	88

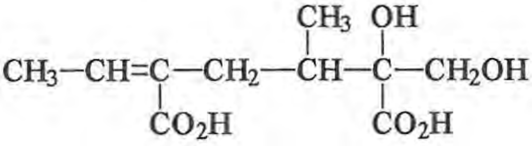
1.1.6 Applications of the Baylis-Hilman Reaction

The Baylis-Hillman reaction has found widespread application in organic chemistry. It can be used as an entry into the synthesis of indolizines,[13] sphingosine analogues,[59] necic acids,[25,28,60-63] terpenoids[64] and trisubstituted alkenes,[64-66] which are useful synthetic building blocks. Work has also been reported on stereoselective applications.[26,67-75]

1.1.6.1 Necic Acids

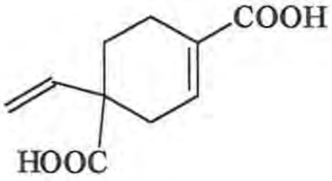
Many natural products contain α-substituted acrylic acid derivatives as sub-units.[76] Certain necic acids such as:- retronecic acid **(49)**, mikanecic acid **(50)** and integerinecic acid **(51)** are examples of such compounds.

In their studies of necic acid synthons, Drewes and co-workers[25,77-80,62] have utilised the Baylis-Hillman reaction to obtain key synthons **(Scheme 23)** for the preparation of various necic acids and analogous compounds. Intermediates **(55)** and **(56)** were subsequently elaborated to afford retronecic **(49)** and isolinecic **(52)** acids.

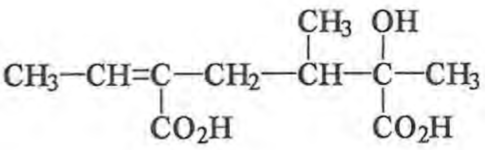


$CH_3{-}CH{=}\underset{CO_2H}{C}{-}CH_2{-}\overset{CH_3}{CH}{-}\overset{OH}{\underset{CO_2H}{C}}{-}CH_2OH$

(49)

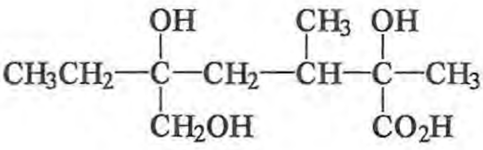


(50)



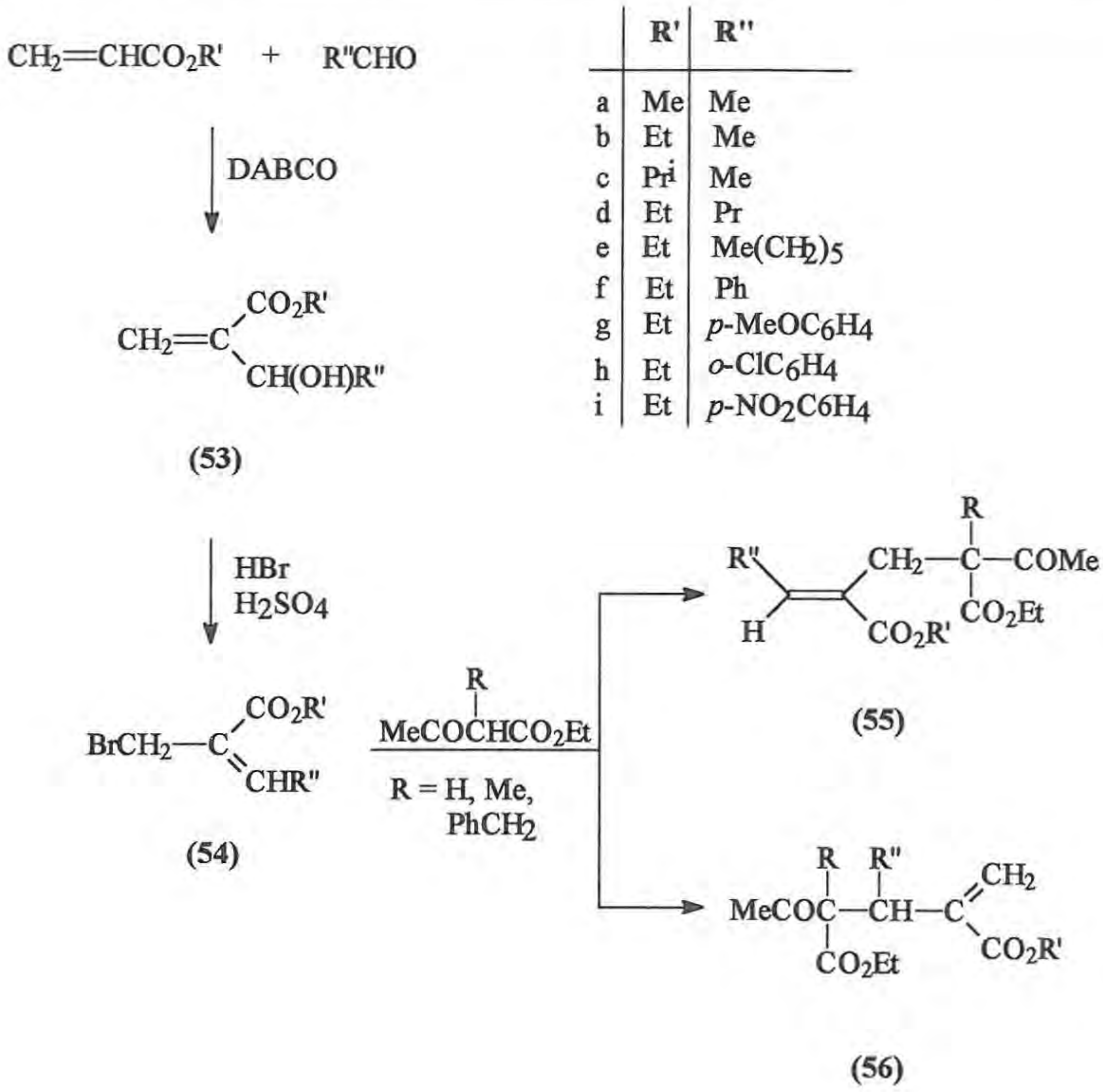
$CH_3{-}CH{=}\underset{CO_2H}{C}{-}CH_2{-}\overset{CH_3}{CH}{-}\overset{OH}{\underset{CO_2H}{C}}{-}CH_3$

(51)



$CH_3CH_2{-}\overset{OH}{\underset{CH_2OH}{C}}{-}CH_2{-}\overset{CH_3}{CH}{-}\overset{OH}{\underset{CO_2H}{C}}{-}CH_3$

(52)



(53)

(54)

(55)

(56)

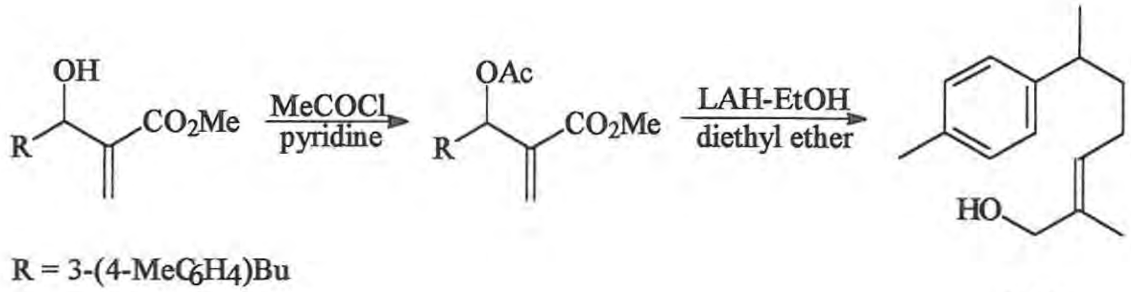
	R'	R''
a	Me	Me
b	Et	Me
c	Pr^i	Me
d	Et	Pr
e	Et	$Me(CH_2)_5$
f	Et	Ph
g	Et	p-$MeOC_6H_4$
h	Et	o-ClC_6H_4
i	Et	p-$NO_2C_6H_4$

Scheme 23

1.1.6.2 Trisubstituted Alkenes

Baylis-Hillman products can be used to synthesise a wide variety of multifunctional molecules.[64] A great number of biologically active compounds contain trisubstituted alkenes as part of their skeleton,[63] and Basavaiah and co-workers[63-64] have synthsised a range of trisubstituted alkenes with defined stereochemistry. In their initial study, Basavaviah *et al.*[63] synthesised (2*E*)-2-ethylalk-2-en-1-ols and (2*Z*)-2-methylalk-2-enenitriles from their respective Baylis-Hillman coupling products and to show applications in the synthesis of natural products, the authors synthesised (*E*)-nuciferol

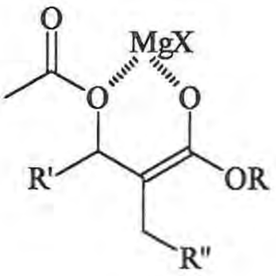
(57) using the method outlined in **Scheme 24**. The starting compound was synthesised using the Baylis-Hillman reaction. Nuciferol has been isolated from the wood oil of *Torreya nucifera*,[81] and the (±)-(*E*) and (±)-(*Z*)- isomers have also been synthesised by Yoneda *et al.*[82]



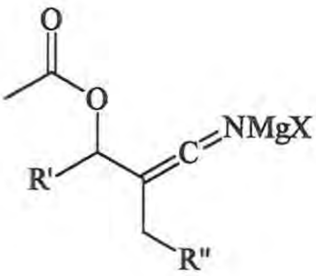
(57)

Scheme 24

In a later study, Basavaiah *et al.*[64] reacted 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylalk-2-enenitriles with Grignard reagents observing, the same reversal in stereochemistry [(*Z*) to (*E*) for alkanoates and (*E*) to (*Z*) for alkenenitriles] as they did in their previous work.[63] They attribute this to the formation of a chelated complex **(58)** in the case of the alkenoates but in the case of the alkenenitriles, the intermediate complex **(59)** is not chelated.

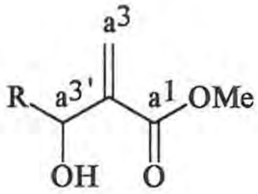


(58)



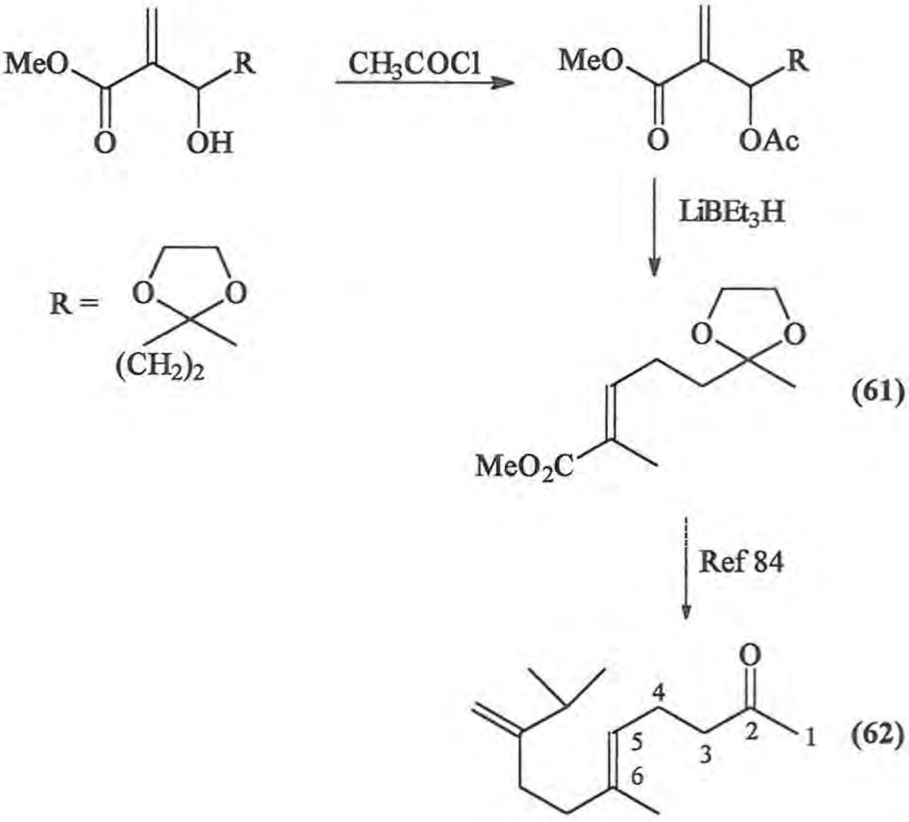
(59)

Hoffmann and Rabe[65] synthesised a series of 2-hydroxyalkyl-2-propenoic esters by coupling methyl acrylate with a number of aldehydes. These esters have the potential for attack at three different sites which makes them useful in synthesis. For example, with the substrate **(60)**, nucleophilic addition can occur at sites a^1 and a^3 and nucleophilic substitution at a^3 or $a^{3'}$.



(60)

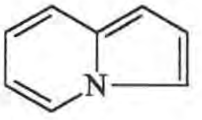
Hoffman and Rabe[65] also found the Baylis-Hillman reaction useful in the synthesis of terpenoids, obtaining the ketone **(62)** with the required (*E*) configuration about the C5-C6 double bond **(Scheme 25)**. The terpenoid ketone **(62)** is found in the root oil of the violet *Costus.*[83]



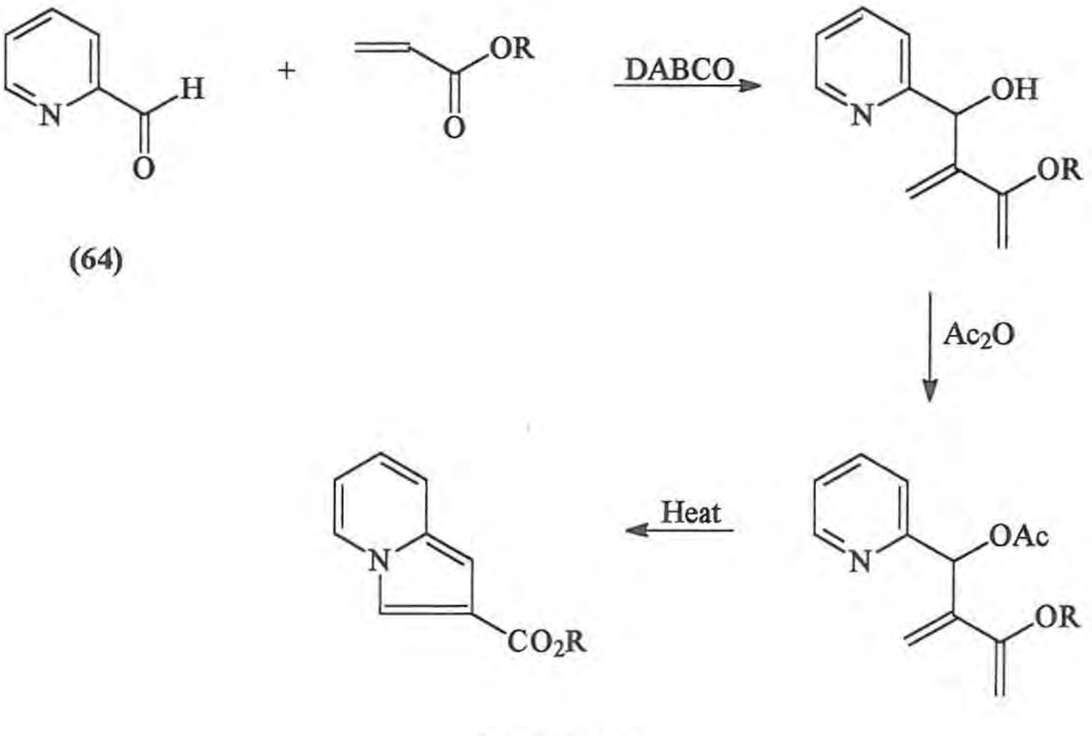
Scheme 25

1.1.6.3 Indolizines

Indolizine **(63)** was discoverd in 1890 by Angeli.[85] The synthesis and chemistry of indolizines is well documented[86] and there are various approaches to synthesising the indolizine skeleton: i) intra-molecular condensation using 1,3-cycloadditions or 1,5-dipolar cyclisations; ii) formation of the six membered ring *via* condensation or Diels-Alder reaction; and iii) simultaneous formation of the five- and six-membered ring *via* condensation. Recently, cyclisation of certain Baylis-Hillman products were shown to afford indolizine derivatives by Bode and Kaye.[13] Reacting a series of acrylates with pyridine-2-carboxaldehyde **(64)** under Baylis-Hillman conditions, the authors obtained intermediates which were then acetylated. Cyclisation occurred upon heating the acetylated compounds **(Scheme 26)**.



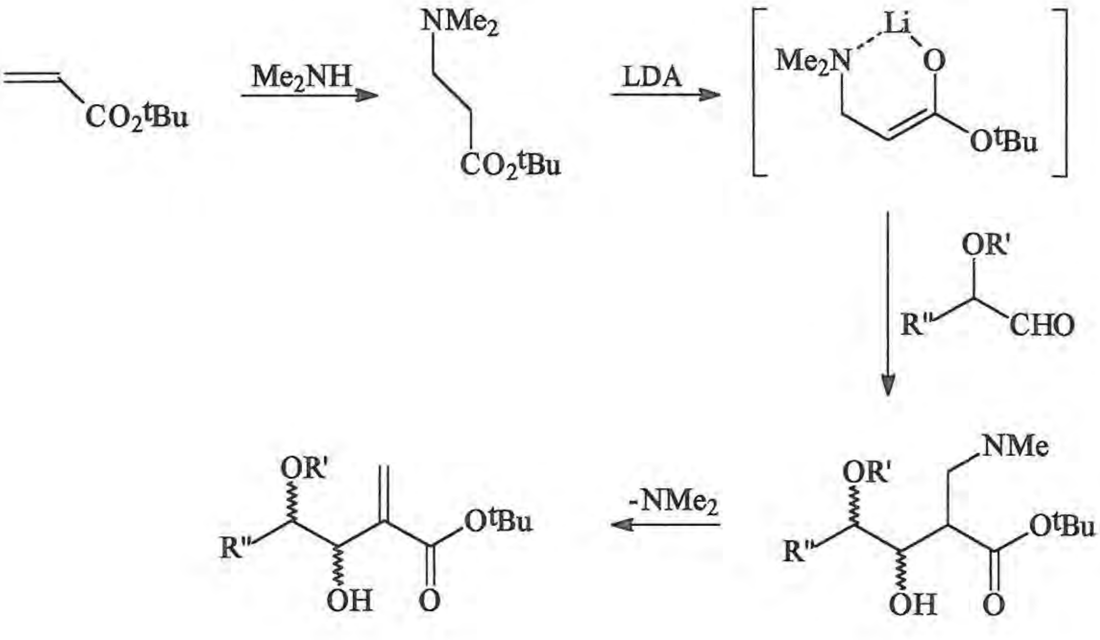
(63)



Scheme 26

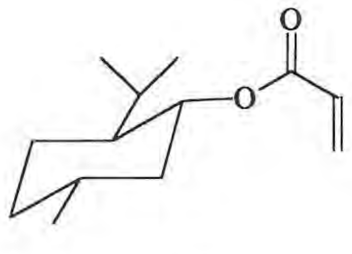
1.1.6.4 Stereoselectivity in the Baylis-Hillman Reaction

Much work has been directed towards stereocontrol in synnthetically valuable aldol-type reactions.[71] Earlier work centred on simple diastereoselectivity, but recently, diasterofacial selectivity (i.e. chirality in one reactant will induce a stereochemical effect in the product) has become the focus of attention. The use of vinylic carbonyl anions is one of the less documented areas of such research, possibly because of the difficulty of generating the anionic species and the need for masked eqivalents. The Baylis-Hillman reaction affords a simple route to the synthesis of α-methylene-β,γ-dioxycarbonyl systems;[68] this approach does not require the low temperatures essential for many aldol reactions, and there is no need to mask and subsequently regenerate the acrylate. **Scheme 27** shows the masked acrylate approach first used by Helquist and Yu[87-88] and subsequently by Scolastico *et al.*[89-91]

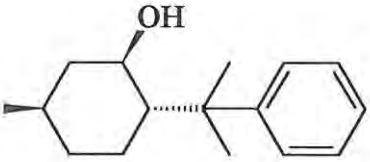


Scheme 27

Stereocontrol has been achieved by a number of authors[26,70-73] using different approaches. These include the use of a chiral acrylate, aldehyde, catalyst or solvent. For example, Basavaiah *et al.*[26] coupled (-)-menthyl acrylate **(65)** with propionaldehyde and found that the coupling reaction not only produced a higher yield, but was also faster when using a molar equivalent of DABCO. The diastereomeric excess ranged from 7% to 20%.



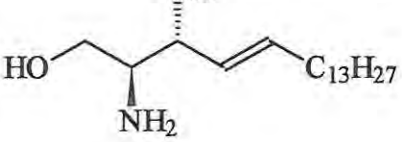
(65)



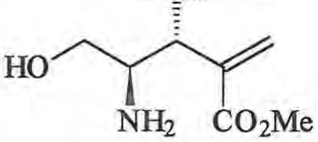
(66)

Drewes *et al.*[73] followed the same approach as Basavaiah *et al.*[26] by using the acrylate ester of 8-phenylmenthol **(66)**, the chiral auxilliary which had been used previously by d'Angelo and Maddulano[92] with a great deal of success. Reacting the chiral ester with a range of aldehydes, Drewes and co-workers obtained diasteromeric excesses ranging from 2% to 70%.

Drewes *et al.*[59] have also used chiral amino aldehydes derived from L-serine and (2*S*)-prolinol in Baylis-Hillman reactions to synthesise sphingosine **(67)** analogues such as **(68)**. Compounds such as **(68)** have been investigated for their anti-tumour activity.[93] When analysing the reaction mixture using ^{1}H NMR spectroscopy Drewes and co-workers[59] found that an *anti* configuration was dominant which is the configuration observed in sphingosine. However, racemisation of the final product can occur if exposure to DABCO is prolonged. The authors suggested the DABCO could remove an α-proton to form an enolate with subsequent racemisation at the α-carbon.



(67)



(68)

1.1.6.5 Miscellaneous Reactions

1.1.6.5.1 Intramolecular Baylis-Hillman Reaction

Roth *et al.*[94] have reported an intramolecular Baylis-Hillman reaction of an α,β-unsaturated ε-keto ester **(69)** in the formation of compound **(70)**. The keto ester was generated through the alkylation of methyl acetoacetate with ethyl 4-bromocrotonate, with subsequent hydrolysis and decarboxylation. Reacting the ester **(69)** with DABCO produced only its *cis*-isomer instead of the expected compound **(70)**; i.e. a reversal in stereochemistry was observed. The reaction was also attempted using sodium ethoxide, quinidine and phosphines as the catalysyts. Selected results are summarised in **Table 12.**

(69) **(70)**

Table 12. Selected results from the study by Roth *et al.*[94] study of an intramolecular Baylis-Hillman reaction.

Entry	**Catalyst, Solvent**	**Reaction time**	**% (69)**	**% (70)**
1	DABCO	32 days	81 [a]	-
2	DABCO, THF	30 days	80 [b]	-
3	Quinidine, C_2H_5OH, THF	10 days	100	-
4	$(n\text{-}Bu)_3P$	1 day	25	75
5	$(CH_3)_2(C_6H_5)P$	1 day	35	65

[a] 19% of the cis isomer of (70) was also isolated

[b] 20% of the cis isomer of (70) was also isolated

1.1.6.5.2 Dimerisations

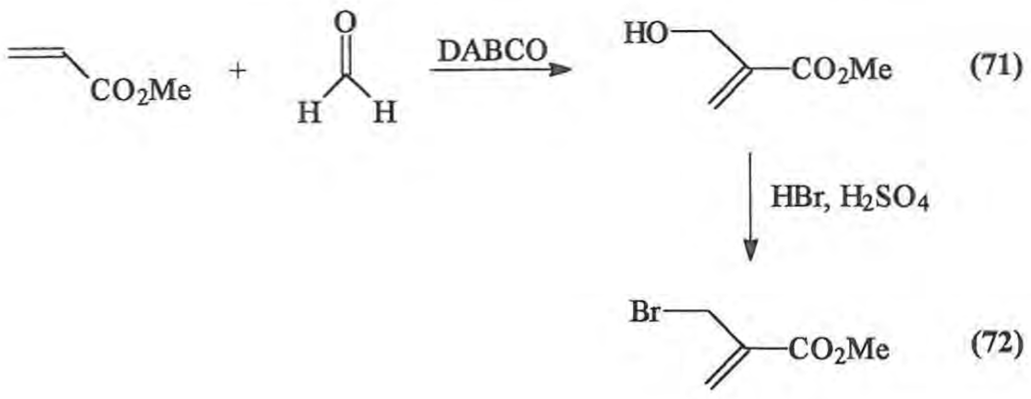
Basavaiah *et al.*[95] have reported the dimerisation of α,β-unsaturated ketones and nitriles under Baylis-Hillman conditions. They had already done work on the reactions of α,β-unsaturated ketones[96] and nitriles[97] with aldehydes and thought that if the aldehyde was left out of the reaction, dimerisation would occur. Their studies confirmed that this is indeed true; their results are summarised in **Table 13**.

Table 13. Results from Basavaiah *et al.*'s dimerisation study of α,β-unsaturated ketones and nitriles.[94]

Entry	Ketone/Nitrile subtrate	Reaction time	Yield (%)
1	p-tolyl vinyl ketone	1 hour	49
2	phenyl vinyl ketone	0.25 hours	62
3	ethyl vinyl ketone	40 hours	60
4	methyl vinyl ketone	4 days	59
5	acrylonitrile	10 days	40

1.1.6.5.3 Alkyl α-halomethyl acrylates

Alkyl esters of α-halomethylacrylic acid have been used widely in organic synthesis.[98] Because of their bifunctional reactivity towards nucleophiles they can be used for the synthesis of bicyclic[99] and spirocyclic ring[100] systems. They can also be used in the preparation of functionalised polymeric dyes.[101] Drewes *et al.*[98] synthesised the most widely used α-halomethylacrylate, ethyl α-bromoethylacrylate **(72)**, by reacting formaldehyde and methyl acrylate under Baylis-Hillman conditions. Subsequent treatment of **(71)** with sulphuric acid and HBr gave the product **(72)** **(Scheme 28)**.

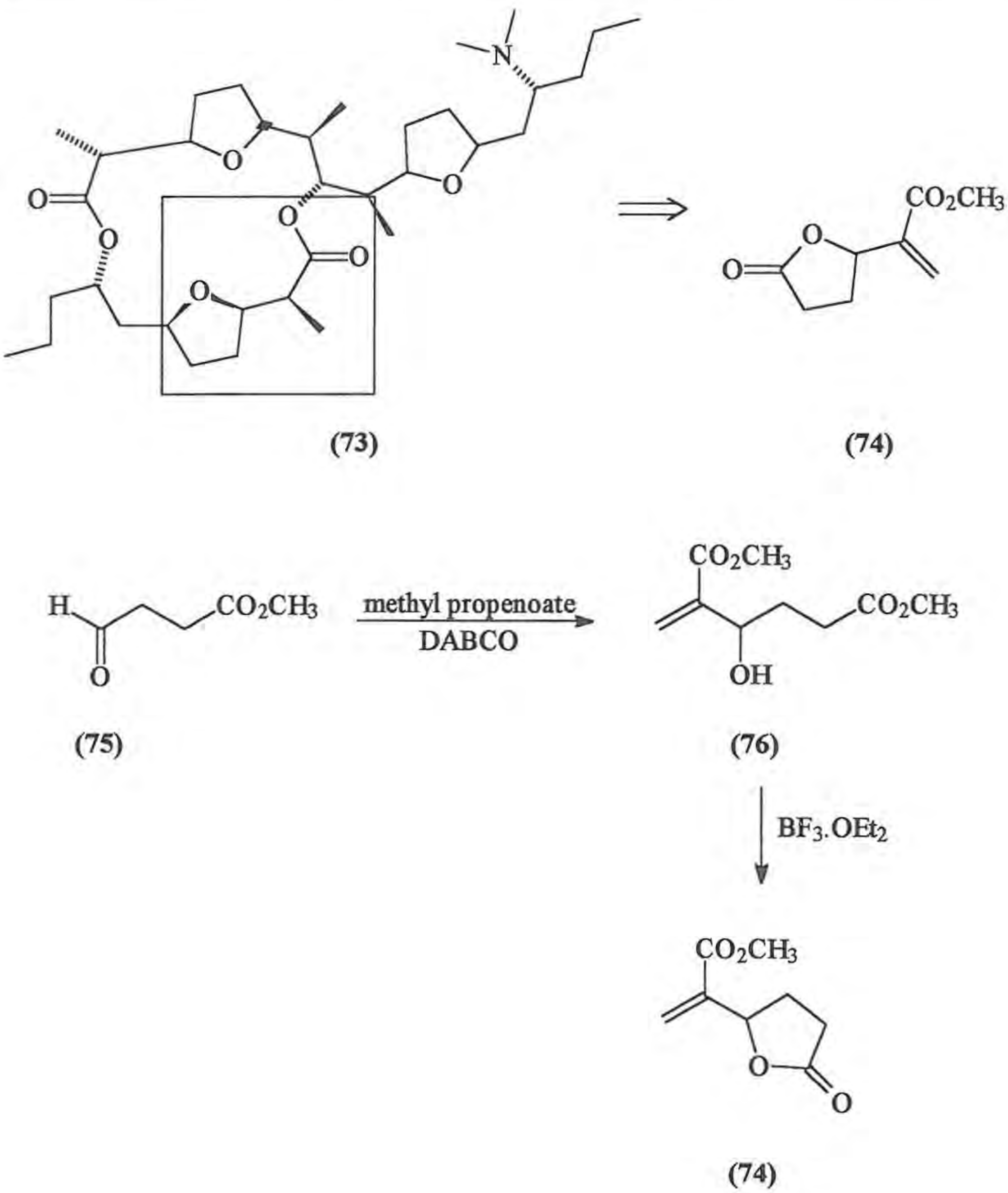


Scheme 28

1.1.6.5.4 γ-Lactones

Pamamycin-607[102] **(73)** is a naturally occurring polyether made up of a number of substituted tetrahydrofurans, which can be derived from 5-ethenyl γ-lactones, such as **(74)**. While Pamamycin-607 fragments have been synthesised from substituted tetrahydrofurans by Walkup and Park,[103-104] Perlmutter and McCarthy[105] have used the Baylis-Hillman reaction as a key step in the synthesis of γ-lactones having an ethenyl substituent at C5 **(Scheme 29)**.

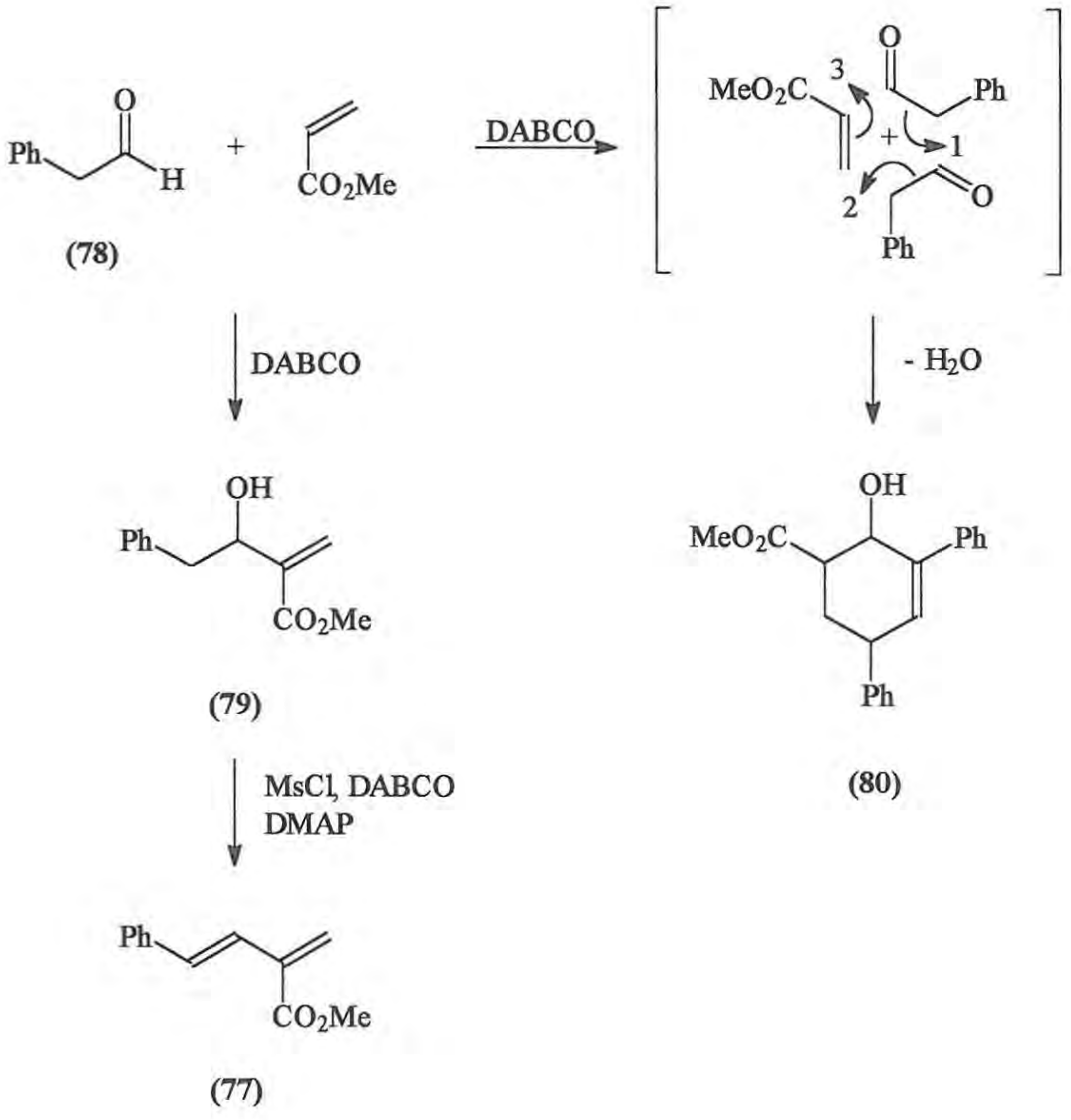
In Perlmutter and McCarthy's approach aldehyde **(75)** was reacted with methyl propenoate in the presence of DABCO to give the intermediate **(76)** in a 40% yield, but some lactonisation occurred [the mixture contained hydroxy ester **(76)** and lactone **(74)** in a ratio of 12:1]. Treatment of the hydroxy ester **(76)** with boron trifluoride etherate then gave the lactone **(74)** in 68% yield.



Scheme 29

1.1.6.5.5 (*E*)-2-Methylene-3-alkenoic acid ester synthesis

The synthesis of (*E*)-2-methylene-3-alkenoic acid esters such as (77) is virtually unknown.[106] Poly *et al.*[107] have reported on the synthesis of such compounds using the Baylis-Hillman reaction as the initial step. An interesting side reaction was observed when suitable aldeydes such as 2-phenylethanal **(78)** were used. 2-Phenylethanal will enolise more readily than simple aliphatic aldehydes and when it was reacted with methyl acrylate under Baylis-Hillman conditions, the formation of the expected product **(79)** as well as a novel compound, the cyclohexenol **(80)**, was obtained. The authors called the reaction a [2+2+2] cycloaddition which involves i) aldol addition, ii) aldol dehydration and intramolecular Michael addition of the d^4-dienolate donor and lastly, iii) intramolecular aldol addition **(Scheme 30)**.



Scheme 30

1.2 Earlier Work and Aims of the Present Study

As already mentioned the Baylis-Hillman reaction has generated considerable interest, but the transformations are generally slow. Efforts have been made to enhance the rate by using novel catalyst systems, various subtrates and reaction conditions. Kaye *et al.*[13] found that use of electrophilic pyridine 2-, 3- and 4-carboxaldehydes resulted in substantial rate acceleration. Upon purification of one of the 2-pyridyl Baylis-Hillman compounds, crystalline material was obtained, which was found to be an indolizine derivative.[13] Attempts were made to extend this novel synthesis of indolizines to other heterocyclic componds and both coumarin[108] and chromone[108] derivatives have been isolated. A study of the kinetics of the cyclisation to indolizines was undertaken with a view to establishing the mechanism,[109] but confirmation of the initial results has been considered necessary. Some preliminary work has also been reported on the reaction of pyridinecarboxaldehyde-derived Baylis-Hillman products with sodium methylthiolate[110] and questions concerning the mechanistic implications have been raised.

The present study flowed from these themes and had the following specific aims:-

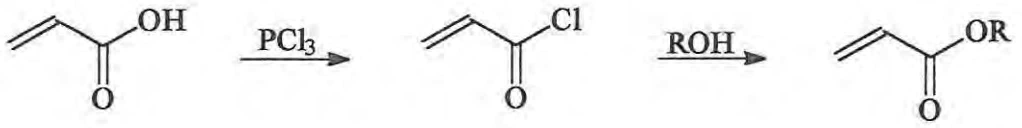
i) to synthesise a series of substituted pyridyl compounds using the Baylis-Hillman reaction;
ii) to undertake a kinetic-mechanistic study of the cyclisation of acetylated derivatives of these compounds to indolizines using ^{1}H NMR spectrscopy; and
iii) to investigate thiomethylation of selected Baylis-Hillman products.

2. DISCUSSION

In broad terms the present study has involved:- the synthesis of a number of acrylate ester systems **(Section 2.1)**; their coupling with pyridine carboxaldehydes using the Baylis-Hillman reaction **(Section 2.2)**; the acetylation and cyclisation of selected Baylis-Hillman products to afford indolizines **(Section 2.3)** and an investigation of thiomethylation of various Baylis-Hillman products **(Section 2.4)**.

2.1 Acrylate Ester Synthesis

The acrylate system forms an integral part of the Baylis-Hillman reaction. Some of the acrylates used in the reactions studied were readily available, while others, *viz.*, isopropyl acrylate **(81)** and *tert*-butyl acrylate **(82)**, were synthesised by reacting acryloyl chloride **(83)** with the relevant alcohols **(Scheme 31)**. Acryloyl chloride was obtained by reacting acrylic acid with phosphorus trichloride. Several reagent systems have been used to convert carboxylic acids to their acid chlorides; these include:- thionyl chloride, phosphorus trichloride, phosphorus pentachloride or oxalyl chloride.[111] Excess reagent is normally removed by distillation when the reaction is complete. Thionyl chloride (b.p. 76-78°C)[112] and phosphorus pentachloride are more commonly used but in the present study phosphorus trichloride (b.p. 76°C) was used for the synthesis of acryloyl chloride(74-75°C).[113] Before distilling the crude acryloyl chloride, cuprous chloride was added to prevent polymer formation. The pure acid chloride was obtained in very good yield (84%), and was susequently reacted with the relevant alcohol in the presence of the base *N*,*N*-dimethylamine; a small amount of hydroquinone was also added to the reaction mixture to inhibit polymerisation.



(83)

	R
(81)	$CH(CH_3)_2$
(82)	$C(CH_3)_3$

Scheme 31

The proton NMR spectra of the acrylate esters are worthy of mention as they can exhibit complex splitting patterns. If the 60 MHz ^1H spectrum is compared with the 400 MHz ^1H NMR spectrum, the effects of field strength can be clearly seen (**Figures** 4 and 5). At low field, (**Figure 4**), acrylates exhibit a typical ABC splitting pattern in the olefinic region (4,5 - 7,5 ppm) due to higher order coupling between the vinylic protons (**Figure** 3). At higher field strengths (corresponding to 400 MHz) first order coupling is evident and, as can be seen in **Figure 5,** a typical AMX pattern is observed.[114]

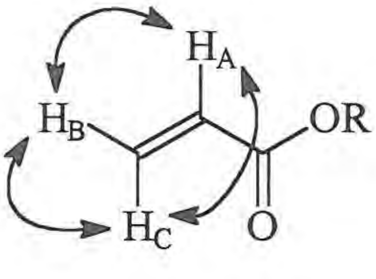


Figure 3. Proton couplings in vinylic systems.

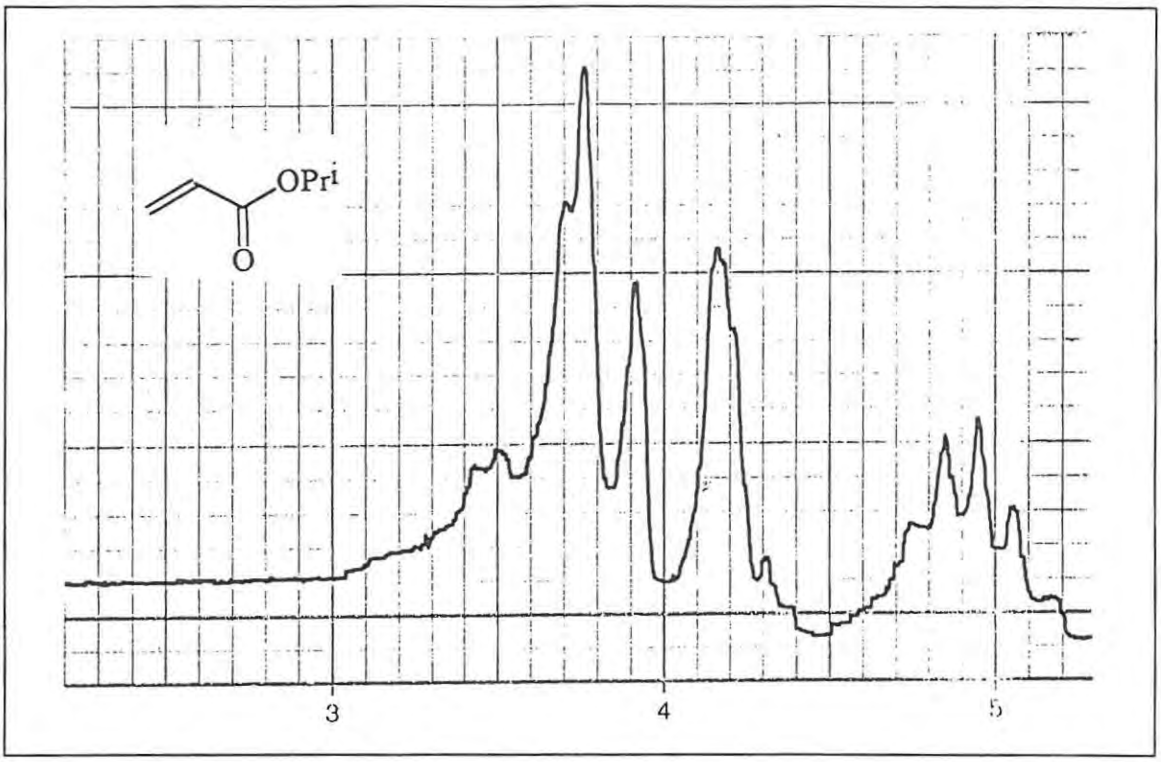


Figure 4. 60MHz ^{1}H NMR spectrum of isopropyl acrylate **(81)** in $CDCl_3$.

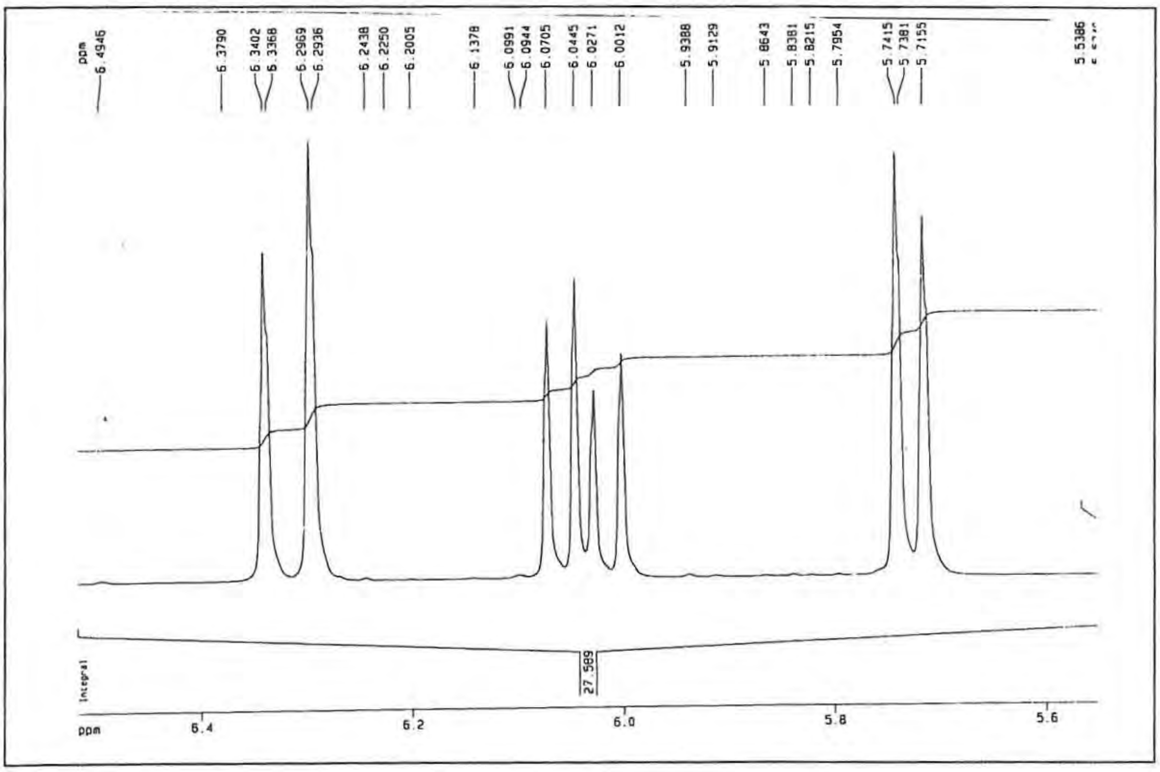
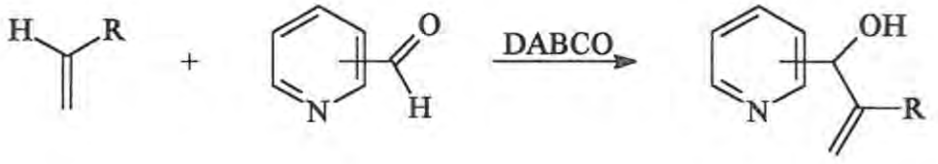


Figure 5. 400MHz ^{1}H NMR spectrum of isopropyl acrylate **(81)** in $CDCl_3$.

2.2 Applications of the Baylis-Hillman Reaction

As indicated in the Introduction, the Baylis-Hillman reaction has found widespread attention in the literature.[49] The currently accepted mechanism **(see Introduction, Scheme 2)** has been substantiated in a kinetic study by Bode and Kaye,[10] and involves nucleophilic attack on an acrylate system by DABCO to afford a zwitterionic intermediate. In the present investigation, a series of acrylate derivatives were reacted with pyridine-2-, pyridine-3- and pyridine-4-carboxaldehyde in the presence of DABCO **(Scheme 32)**.

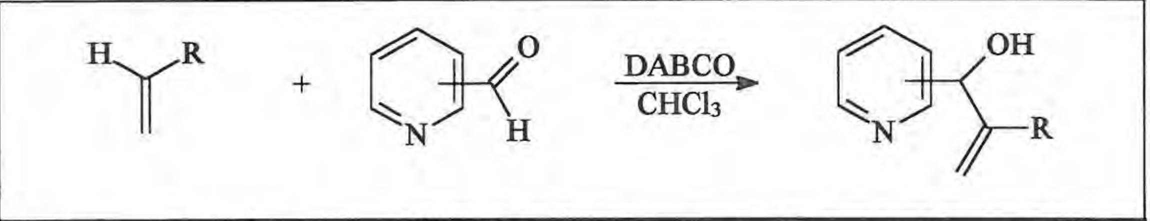
The reactions were all performed in chloroform at room temperature and were generally allowed to proceed for three days followed by appropriate purification. The pyridine-3- and pyridine-4-carboxaldehyde systems seemed to react much faster than the pyridine-2-carboxaldehyde systems, taking as little as one hour for the reaction to go to completion. This could easily be observed as the product formed as a solid mass. **Table 14** summarises the results obtained in these reactions.



R	pyr-2	pyr-3	pyr-4
CN	**84**	**90**	**93**
$COCH_3$	**85**	-	-
CO_2Me	**86**	**91**	**94**
CO_2Et	**87**	**92**	**95**
CO_2Pr^i	**88**	-	-
CO_2Bu^t	**89**	-	-

Scheme 32

Table 14. Results of the Baylis-Hillman reaction of pyridinecarboxaldehydes and acrylate derivatives in the presence of DABCO.



Entry	Pyridine carboxaldehyde	RCH=CH$_2$ R	Reaction time	Product	Yield (%)	Melting Point[d] (°C)
1	pyr-2[a]	CN	1 day	84	91	48-51
2	pyr-2	COMe	3 days	85	78	-
3	pyr-2	CO$_2$Me	3 days	86	80	-
4	pyr-2	CO$_2$Et	3 days	87	72	-
5	pyr-2	CO$_2$Pr^i	5 days	88	45	-
5	pyr-2	CO$_2$Bu^t	3 days	89	44	-
6	pyr-3[b]	CN	1 hour	90	36	93.5-95.5
7	pyr-3	CO$_2$Me	3 hours	91	40	96-98
8	pyr-3	CO$_2$Et	4 hours	92	35	65-67
9	pyr-4[c]	CN	2 fours	93	59	116.5-119
10	pyr-4	CO$_2$Me	2 hours	94	86	143-145
11	pyr-4	CO$_2$Et	3 hours	95	81	109-111

[a] pyr-2 = pyridine-2-carboxaldehyde

[b] pyr-3 = pyridine-3-carboxaldehyde

[c] pyr-4 = pyridine-4 carboxaldehyde

[d] compounds (85) to (89) were isolated as oils

The Baylis-Hillman products **(84-95)** were all identified using ^1H NMR and IR spectroscopy. The ^1H NMR spectra show three peaks in the region δ 5.5 - 6.5 ppm which are common to all the compounds synthesised; these are the signals arising from the proton on C-3 and the vinyl protons. It is interesting to note the lack of complexity of the vinyl proton signals in the products compared to the corresponding signals for the vinylic substrates, the spectra of the former reflecting an absence of coupling between the vinylic methylene protons. The type of substitution of the pyridine ring can also be easily seen in the ^1H NMR spectra **(Figures 6 to 8)**. Generally the 2-pyridyl systems exhibit one peak slightly upfield of the solvent peak (7.25 ppm), with the remaining aromatic signals further downfield **(Figure 6)**. In the 3-pyridyl systems all of the aromatic protons resonate downfield from the solvent signal while the $2'$ proton signal is visible as a doublet **(Figure 7)**. The 4-pyridyl systems only exhibit two peaks in the aromatic region; this is typical of symmetrically substituted aromatic systems **(Figure 8)**.

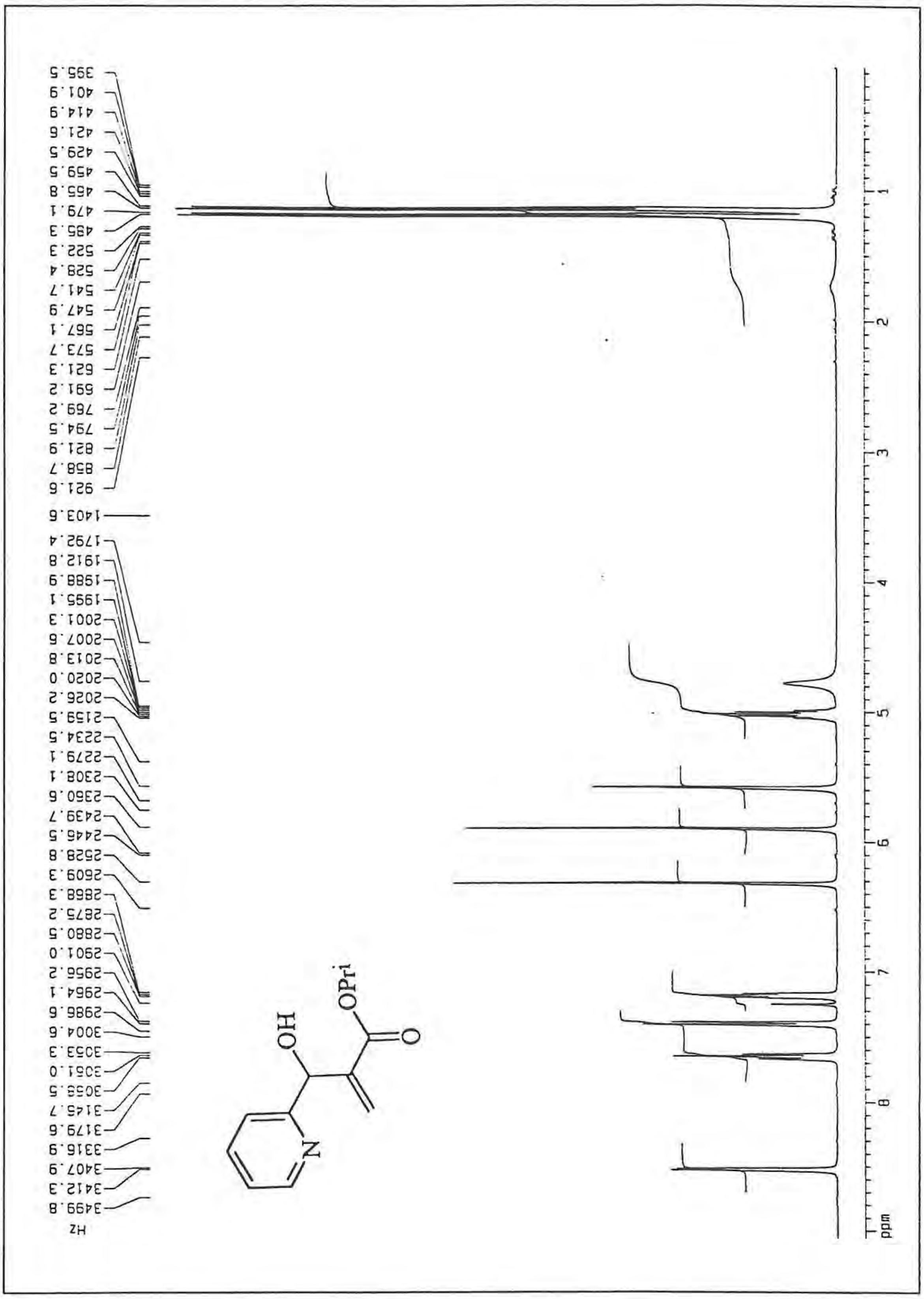


Figure 6. 400 MHz ^{1}H NMR spectrum of isopropyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate (**88**).

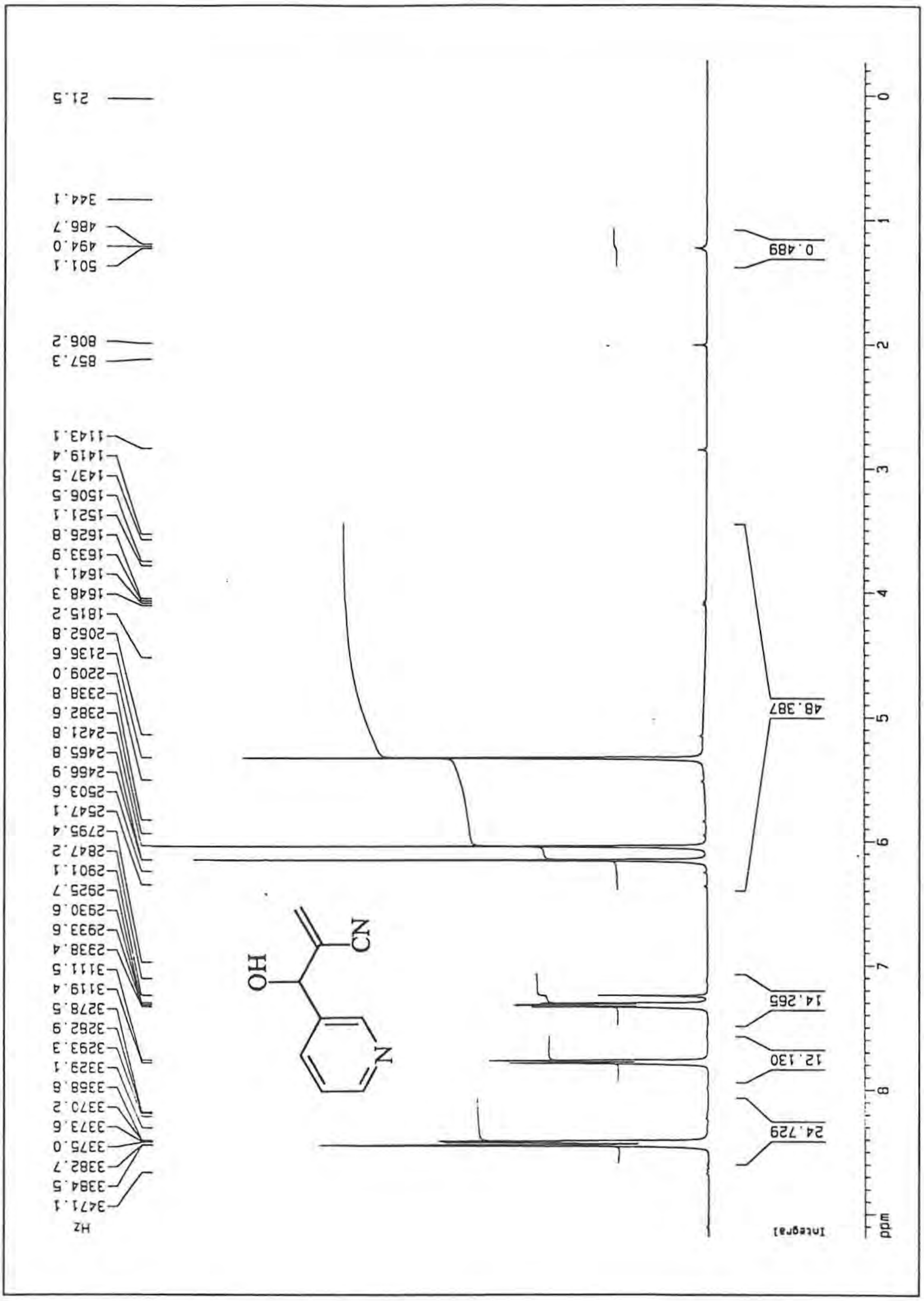


Figure 7. 400 MHz ^{1}H NMR specrum of 3-hydroxy-2-methylene-3-(3-pyridyl)-propanenitrile (90).

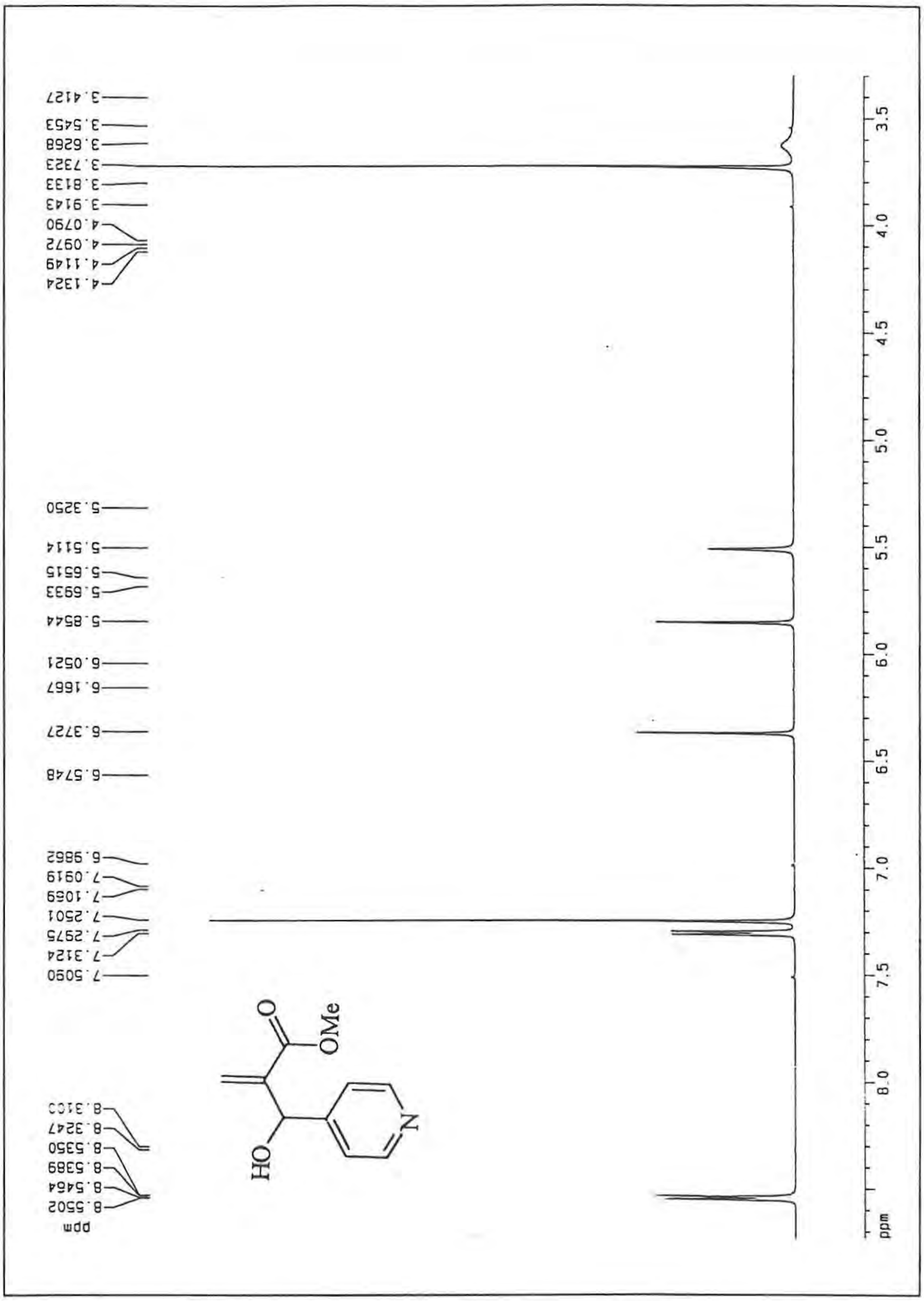
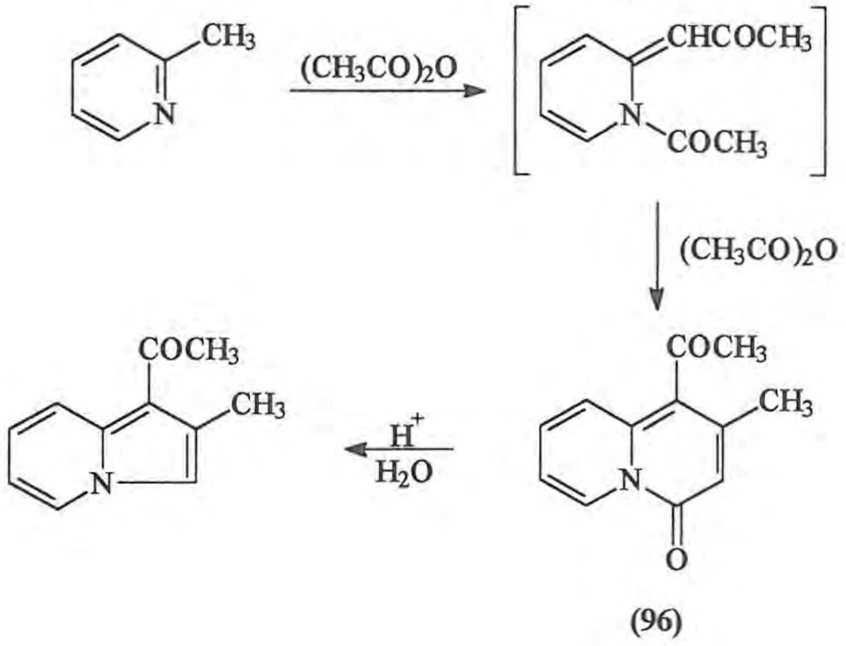


Figure 8. 400 MHz ^{1}H NMR spectrum of methyl 3-hydroxy-2-methylene-3-(4-pyridyl)-propanoate (94).

2.3 Indolizines: Synthesis and Kinetic Studies

Indolizine **(63)** was discovered in 1890 by Angeli,[115] and the preparation and chemistry of these systems is well documented.[116-120] There are various approaches to the synthesis of the indolizine skeleton; these include i) intra-molecular condensation involving 1,3-cycloaddition or 1,5-dipolar cyclisation; ii) formation of the six-membered ring *via* condensation or Diels-Alder reaction and; iii) simultaneous formation of the five- and six-membered ring *via* condensation.[121] There are several classical methods for the synthesis of indolizines which fall into these general categories..

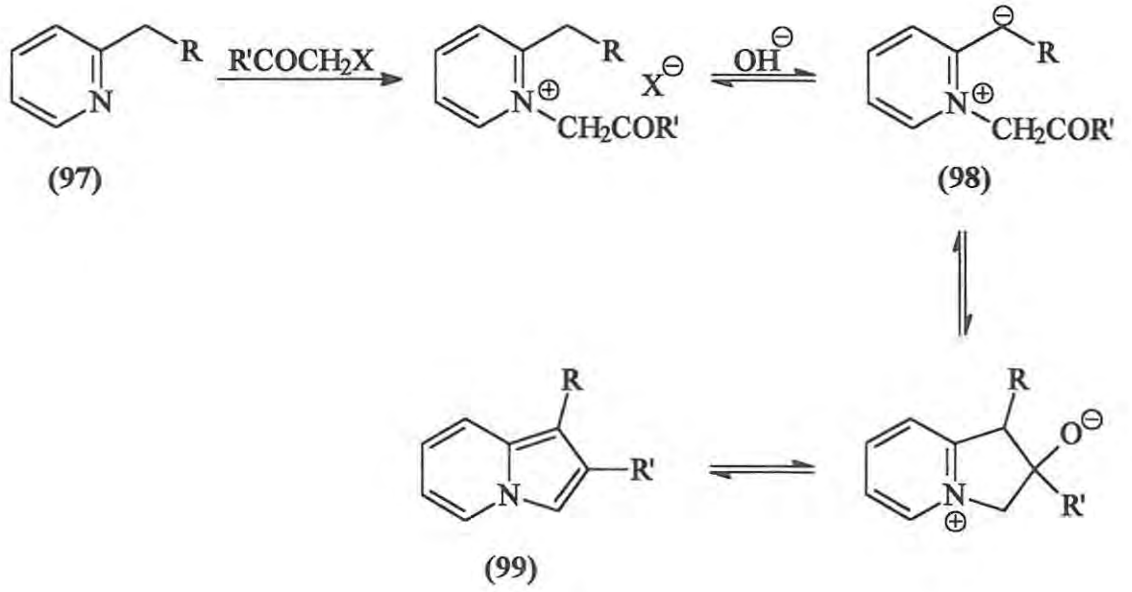
The first to synthesise indolizine was Scholtz.[122] He reacted 2-picoline with acetic anhydride **(Scheme 33)** to produce a compond which he called picolide and for which he proposed (erroneously) the structure **(96)**. Upon hydrolysis of the picolide he obtained the indolizine derivative, the structure of which he correctly proposed.



(96)

Scheme 33

The Tschitschibabin synthesis[123] is a useful and widely-used method for synthesising indolizines. It involves the condensation of 2-picoline **(97)** (or a homologue) with an α-haloketone **(Scheme 34)**. Yields are low (1% in the case of 2-picoline reacting with α-bromoacetaldehyde). Yields can be increased if substituted picolines are used. Thus, the reaction is used mainly in the synthesis of 2-substituted indolizines. The reaction proceeds via the formation of an "betaine" or "methine" intermediate **(98)**. This quaternary salt intermediate cyclises upon treatment with base in an aqueous alcoholic solution to yield the indolizine **(99)**.[124]

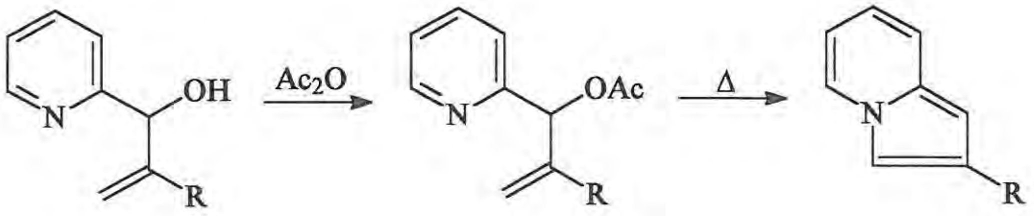


Scheme 34

A large number of indolizines have also been prepared using the method of Barrett.[125] He found that when dehydrating carbinols olefins were produced. Upon refluxing the olefins with acetic anhydride, substituted indolizines were produced. Much work has been done by Diels and co-workers in synthesising indolizines from pyridine and its homologues using acetylenedicarboxylic acid.[126]

As mentioned earlier, Bode and Kaye[13] have found that Baylis-Hillman products derived from pyridine-2-carboxaldehyde cyclise to indolizine upon heating. Prior acetylation of the Baylis-Hillman products facilitates cyclisation. In the current studies, compounds

(84)-(89) were acetylated using a common acetylation method. This involved heating the compounds with acetic anhydride.[13] The reason for acetylation is that the acetoxy group is a far better leaving group than the hydroxyl and thus aids cyclisation. Yields for the acetylation step ranged from 33% to 74%. Attempts to acetylate 4-hydroxy-3-methylene-4-(2-pyridyl)butan-2-one **(85)** gave a complex reaction mixture; in this case, the hydroxy compound is very reactive and tends to cyclise spontaneously to the indolizine derivative **(107)**. Bode and Kaye[13] isolated 5% of the indolizine along with the hydroxy precursor but, in the present study, 4-hydroxy-3-methylene-4-(2-pyridyl)butan-2-one **(85)** was isolated exclusively. The spectrum of the isolated compound **(85)** is shown in **Figure 9**. In general, the acetylated compounds were heated to afford the corresponding indolizine **(Scheme 35)**. The acetylated indolizine precursors were all identified using proton and carbon NMR spectroscopy. Typical of the proton NMR spectra is the appearance of the acetate peak at about 2ppm **(Figure 10)**.



R			
CN	**84**	**100**	**106**
COMe	**85**	**101**	**107**
CO_2Me	**86**	**102**	**108**
CO_2Et	**87**	**103**	**109**
CO_2Pr^i	**88**	**104**	**110**
CO_2Bu^t	**89**	**105**	**111**

Scheme 35

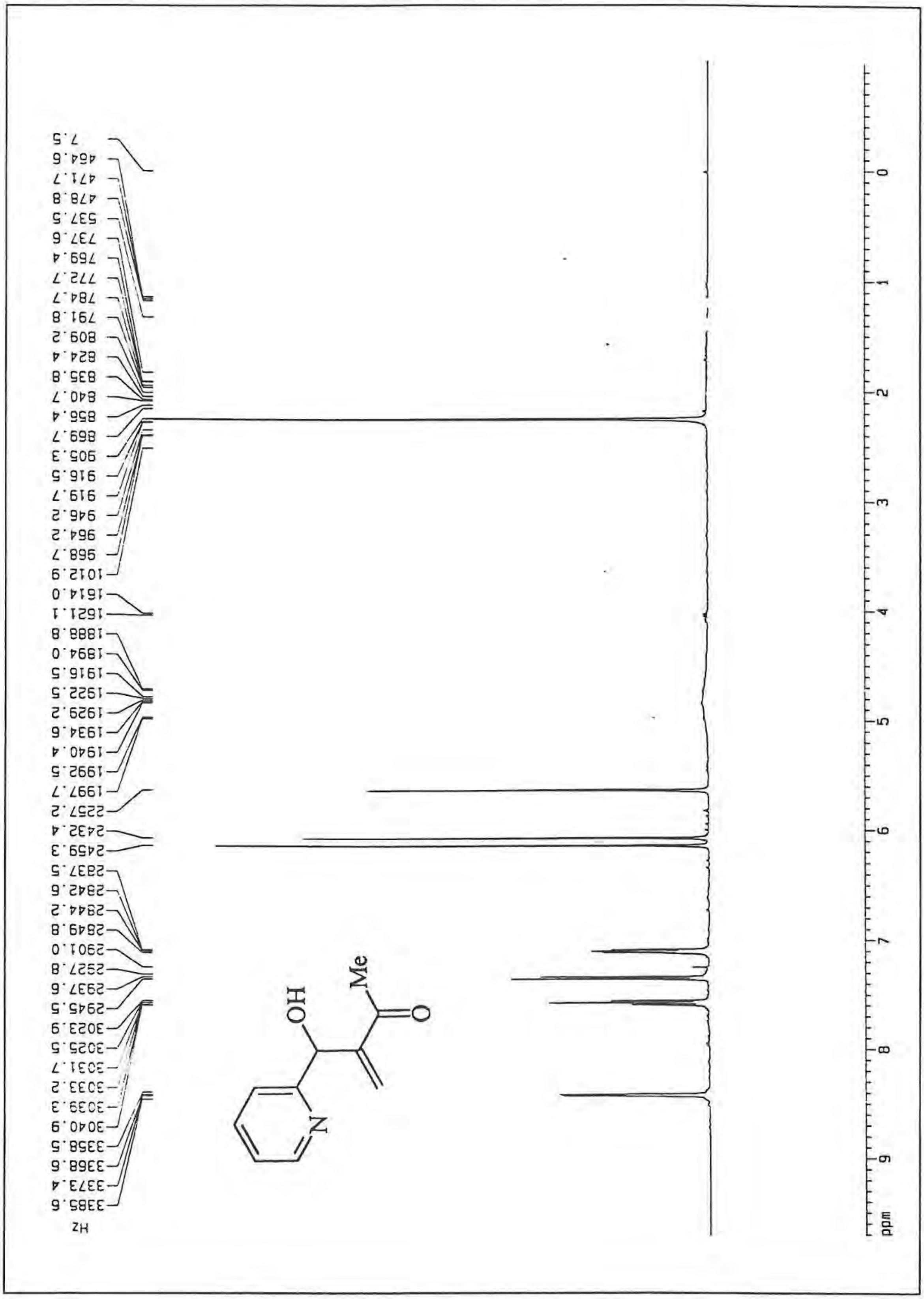


Figure 9. 400MHz ^{1}H NMR spectrum of 4-hydroxy-3-methylene-4-(2-pyridyl)butan-2-one (85)

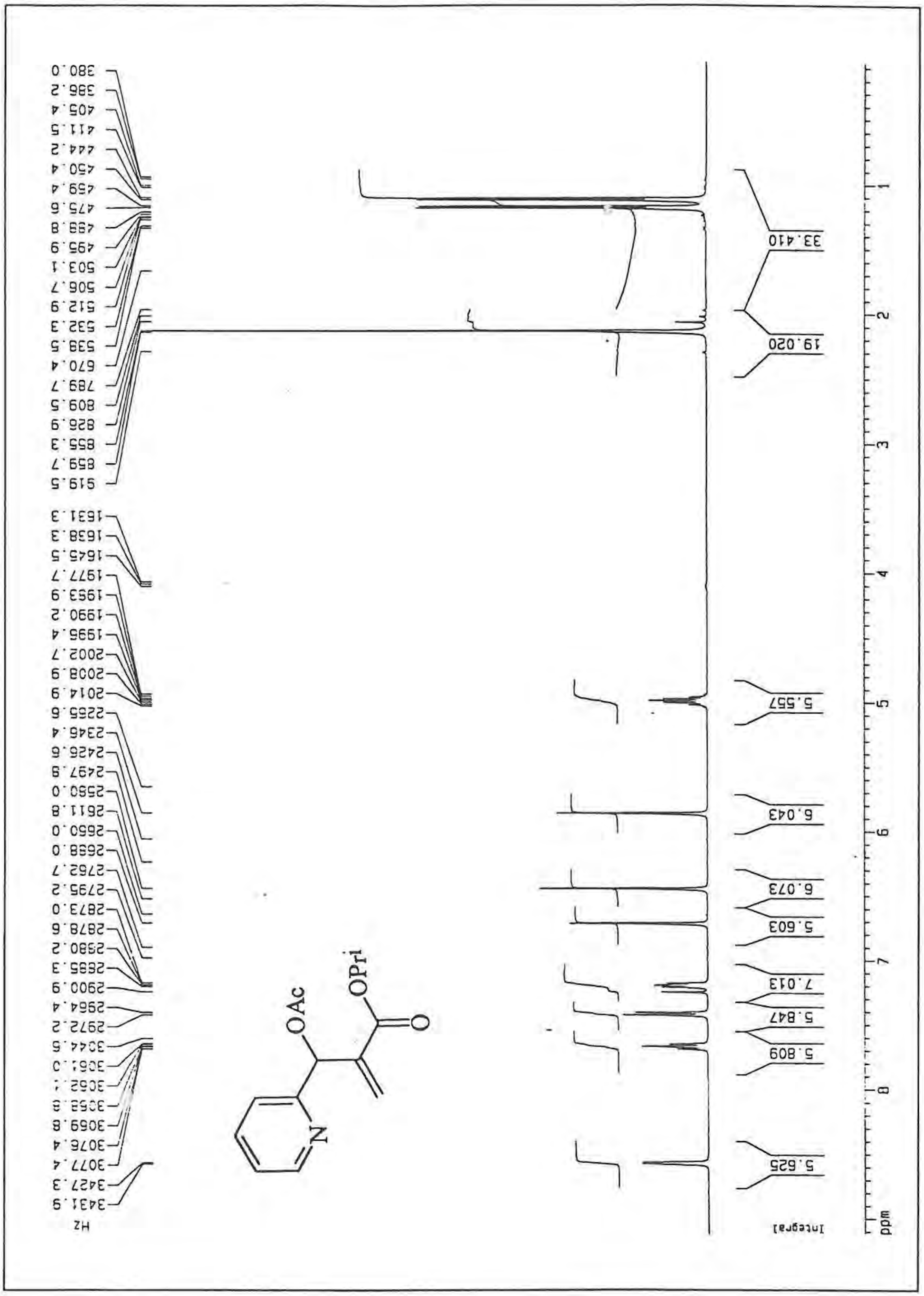


Figure 10. 400MHz ^{1}H NMR spectrum of isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate (**88**).

The mechanism of a reaction can be described as a series of steps in which reactants are converted into products. Although today many reactions have mechanisms to explain the formation of the products, no mechanism is absolute; one can only discard those that do not fit available information about the mechanism. There are several methods used to determine the mechanism of a reaction. These include isotopic labelling, stereochemical evidence and kinetic evidence. Kinetic evidence can further be studied by using periodic or continuous spectral readings, quenching and analysing, calorimetric methods and the removal of aliquots for analysis.[127] In this study proton NMR spectroscopy was used to monitor the cyclisation of the acetylated Baylis-Hillman products to indolizines (**Scheme 35**). Spectra were run at 5 minute intervals and the integrals were used to determine the concentration of starting material. **Figure 11** shows a series of spectra from the cyclisation of isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (**104**) in DMSO-d_6 at 383K.

In order to determine the order of the cyclisation reaction, plots of substrate concentration, [S], against time (**Figure 12**) and ln[S] against time (**Figure 13**) were plotted. Exellent linear correlations were obtained for all first-order plots ($R^2 > 0.99$) and it can be assumed that the reactions are first-order and satisfy the first-order rate equation (**Equation 1**).[128]

$$\frac{\delta[\mathrm{S}]}{\delta t} = k_{obs}[\mathrm{S}] \qquad \textbf{Equation (1)}$$

$$\underline{\text{or}}\ \text{reaction rate} = k_{obs}[\mathrm{S}]$$

$$t_{1/2} = 0.693/k_{obs} \qquad \textbf{Equation (2)}$$

The half-life for such first-order reactions, $t_{1/2}$, does not depend on the concentration of the substrate, [S] (**Equation 2**).[129] Only the the rate of reaction is affected by a change in concentration.

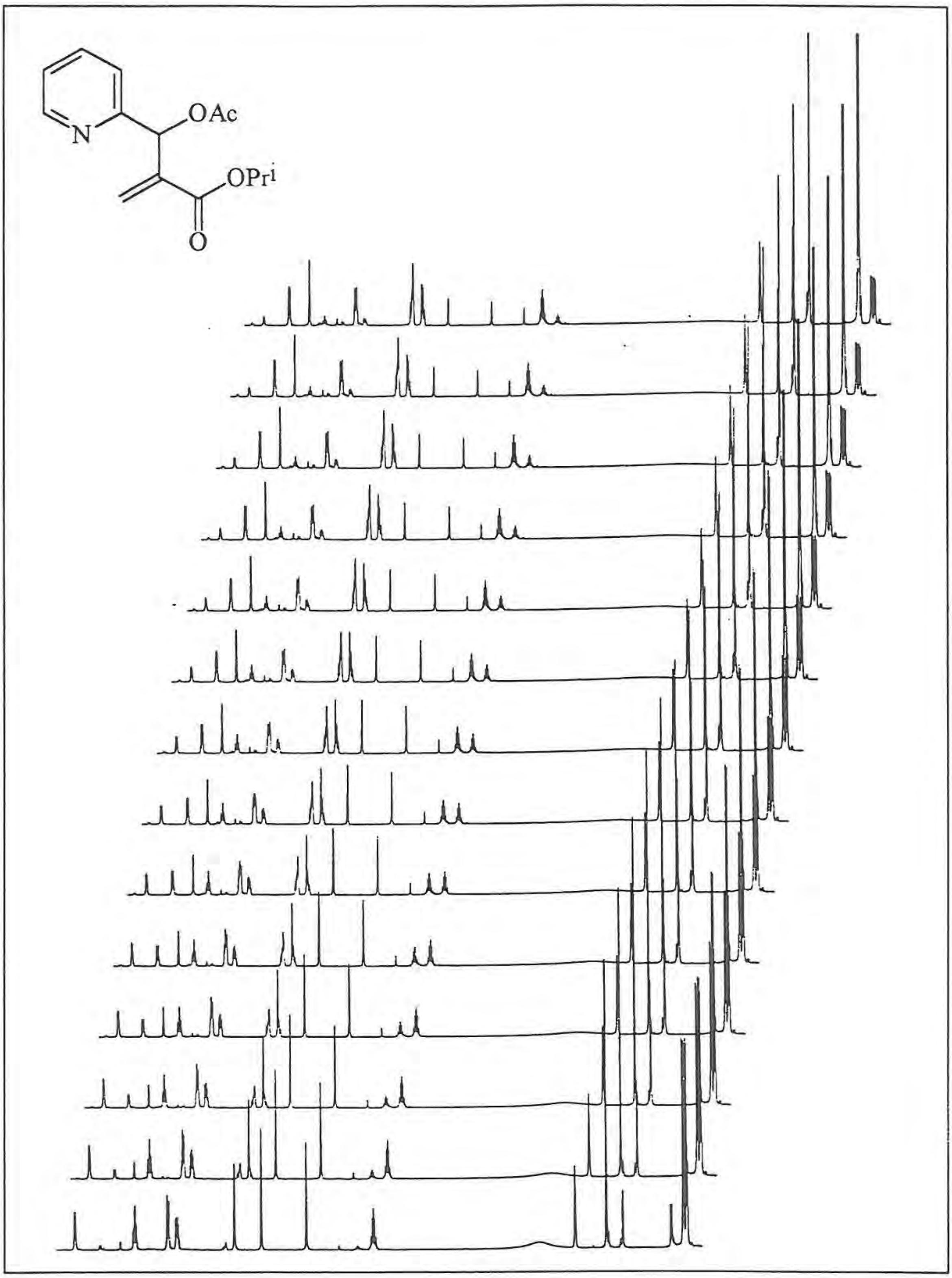


Figure 11. ^{1}H NMR spectra from the cyclisation of isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (104) in DMSO-d_6 at 383K taken at 5 minute intervals.

The first-order character of these reactions was confirmed by varying the reactant concentration. Thus, **Figures 12** and **14** correspond to reactions in which the concentration of reactant differs by a factor of 10, but which nevertheless reflect comparable half-lives and afford effectively the same first-order rate constant.

The cyclisation reaction was also followed, in duplicate, for different substrates and at different temperatures. The results of these experiments are summarised in **Table 15**.

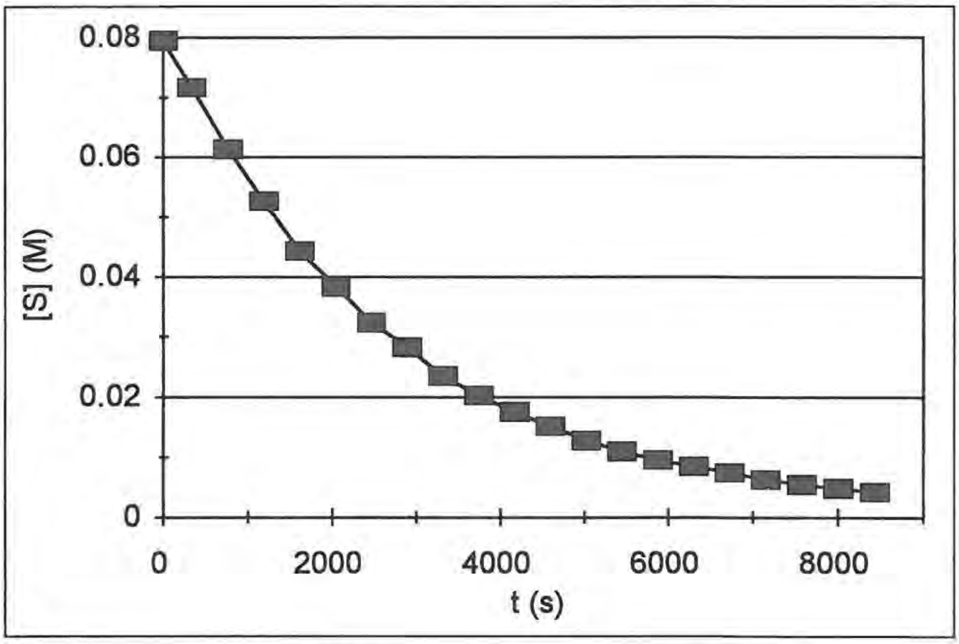


Figure 12. Plot of [S] against t for the cyclisation of ethyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (**102**) at 383K.

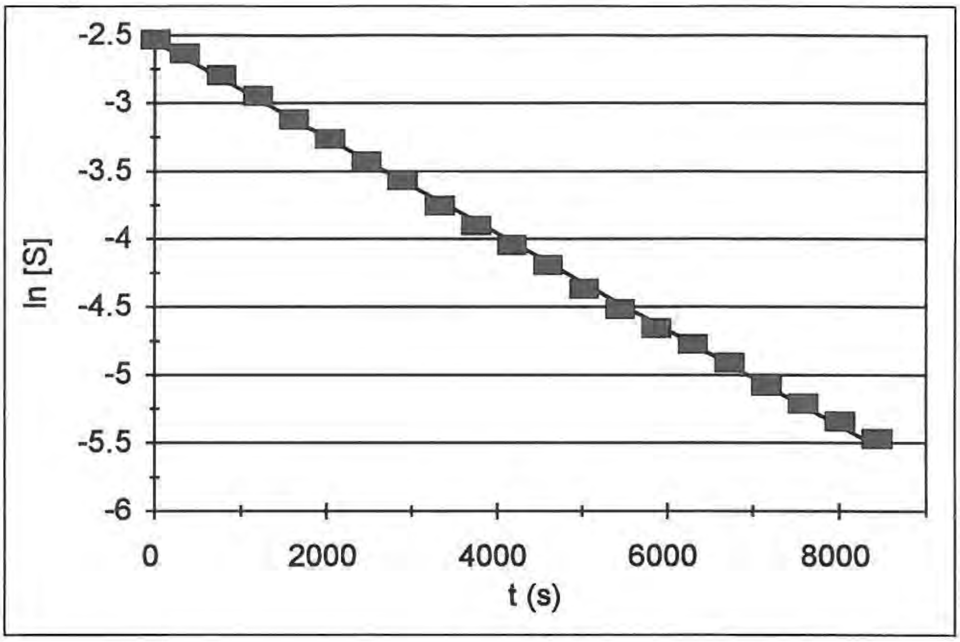


Figure 13. Plot of ln[S] against t for the cyclisation of 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(102)** at 383K

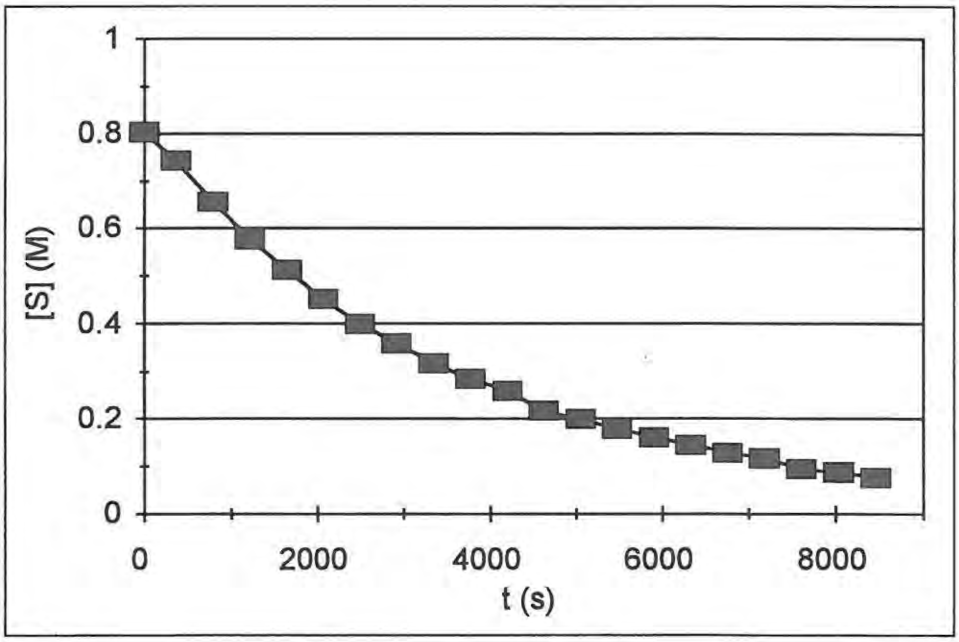


Figure 14. Plot of [S] against t for the cyclisation of 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(102)** at 383K using ten times the normal concentration.

Table 15. Kinetic data for the cyclisation of 2-pyridyl derivatives.

Entry	Substrate	R	Substrate Conc.[a] (mol.dm^{-3})	Temperature [b] (K)	Completion (%)	k_{obs}[c] ($10^{-5}\times s^{-1}$)
1	100	CN	0.08	363 (367.3)	26-29	3.7 ± 0.3
2			0.08-0.09	373 (378.0)	54-57	9.5 ± 0.1
3			0.09	383 (388.8)	84-86	22.8 ± 0.2
4	102	CO_2Me	0.07-0.08	363 (367.3)	42-43	9.2 ± 0.2
5			0.06-0.12	373 (378.0)	71-72	24.3 ± 0.8
6			0.8	373 (378.0)	88-91	26.2 ± 0.2
7			0.06-0.07	383 (388.8)	94	55.5 ± 0.6
8	103	CO_2Et	0.07	363 (367.3)	55-57	6.2 ± 0.3
9			0.07	373 (378.0)	79-89	15.4 ± 0.3
10			0.06-0.08	383 (388.8)	99	34.0 ± 0.1
11	104	CO_2Pr^i	0.06-0.07	363 (367.3)	31-32	4.4[d]
12			0.07-0.08	373 (378.0)	58-60	10.8 ± 0.3
13			0.07	383 (388.8)	89	26.5[d]
14	105	CO_2Bu^t	0.06-0.07	363 (367.3)	12-13	1.5 ± 0.1
15			0.06	373 (378.0)	30-32	4.4 ± 0.1
16			0.06-0.08	383 (388.8)	57-58	9.9 ± 0.1

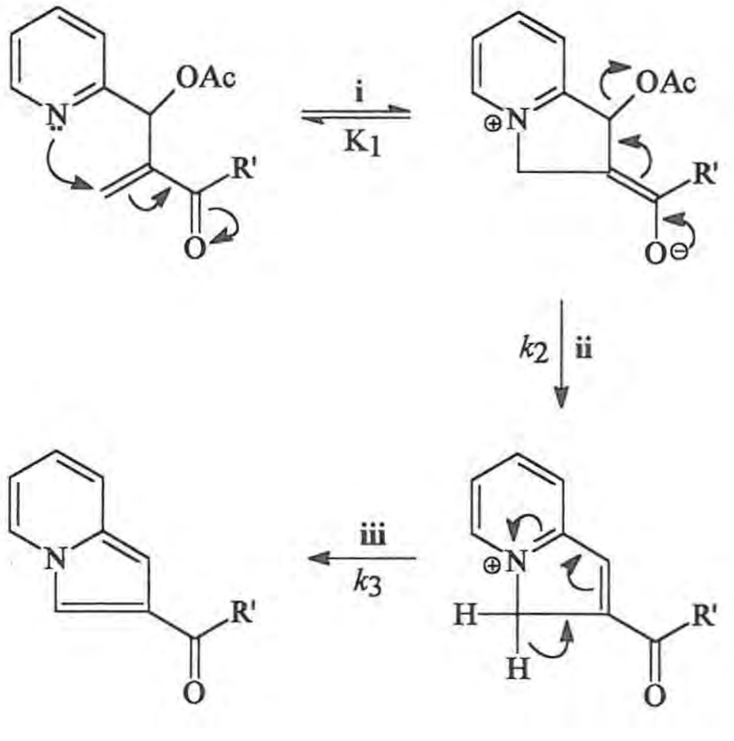
[a] Initial concentration.

[b] Nominal setting followed by the corrected temperature in parentheses.

[c] First order rate constant; mean of duplicate runs.

[d] Duplicate results were identical.

The mechanism for the reaction, which has been proposed by Bode and Kaye,[13] is thought to proceed *via* an addition-elimination sequence (**Scheme 36**). The initial step involves "Michael type" addition of the pyridyl nitrogen to the vinylic carbon (**step i**). This is followed by an elimination step (**step ii**) and it is thought that this step is the rate-determining step. The final step involves deprotonation and aromatisation (**step iii**) and can be ruled out as rate-determining as one can compare it to the rapid aromatisation step in electrophilic substitution. The overall rate constant k_{obs} may then be viewed as a combination of the equilibrium constant, K_1, and the rate constant, k_2 (*i.e.* $k_{obs} = k_2K_1$) K_1 is both concentration and temperature dependent whilst k_2 is temperature dependent. This reaction sequence (**Scheme 36**) is thus consistent with the observed first-order kinetics. Further support for this mechanism is provided by an examination of substituent effects.



Scheme 36

Electron-donating ester substituents, (R), will render the α,β-unsaturated moiety more electron rich and thus less susceptible to nucleophilic attack by the pyridyl nitrogen. Conversely, electron-withdrawing groups will enhance the electrophilicity of the α,β-unsaturated moiety and thus enhance ring formation. From the results summarised in **Table 15** these substituent effects are clearly seen. The rate constant, k_{obs}, decreases as the electron-releasing inductive effect of the *O*-alkyl substituent increases [k_{obs} for R= Me **(102)** > Et **(103)** > Pr^i **(104)** > Bu^t **(105)**]. It has also been found that a methyl group at the 6' position of the pyridyl ring enhances the nucleophilicity of the nitrogen (due to it's electron-releasing effects) and, consequently, increases k_{obs}.[109]

From the data obtained at three different temperatures, the activation parameters, *A* (frequency factor) and E_a (activation energy) could be calculated from a plot of k_{obs} against $1/T$ since,

$$\ln k_{obs} = \ln A - E_a/RT$$ **Equation (3)**[130]

Plots of $\ln k_{obs}$ against $1/T$ (Arrhenius plot) gave a straight line for each of the systems examined **(100-104; Table 15)**, illustrated for methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(100)** **(Figure 15)**. The activation energy can be calculated from the slope of the plot, and using the activation energy and k_{obs} one can calculate the entropy change, ($\Delta S^{\ddagger}$), at a given temperature, *T*, using **Equation (4).**[131]

$$\Delta S^{\ddagger}/19.15 = \log k - 10.753 - \log T + E_a/19.15T$$ **Equation (4)**

Equations **(5)**[132] and **(6)**[131] can then be used to calculate $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$. The activation parameters so calculated are summarised in **Table 16.**

$$\Delta H^{\ddagger} = E_a - RT$$ **Equation (5)**

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$ **Equation (6)**

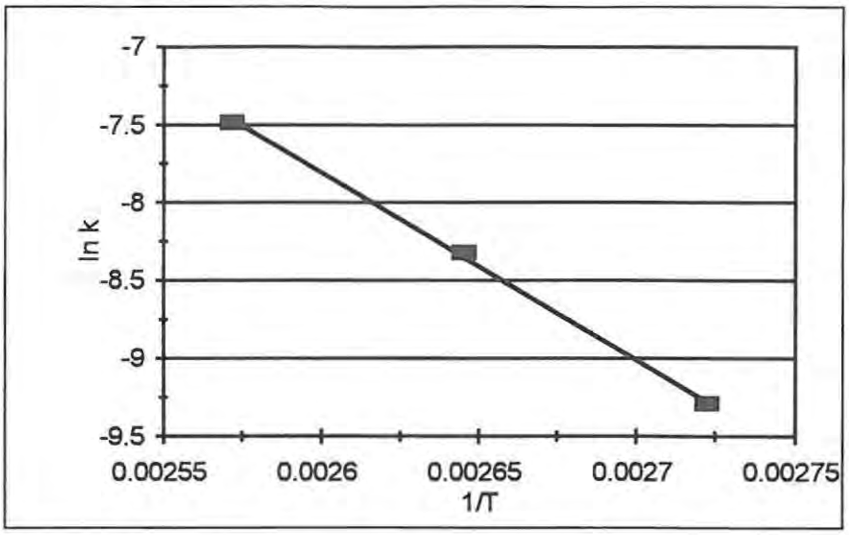


Figure 15. Arrhenius plot for methyl 3-acetoxy-2-methylene-3-(pyridyl)propanoate (**102**)

Table 16. Kinetic parameters for the cyclisation of 2-pyridyl derivatives at 378K.

Entry	**Subtrate**	**$t_{½}$ (s)**	**E_a (kJ.mol^{-1})**	**$\Delta S^‡$ (J.K^{-1} mol^{-1})**	**$\Delta H^‡$ (kJ.mol^{-1})**	**$\Delta G^‡$ (kJ.mol^{-1})**
1	**100**	7295	100.81	65.61 ± 0.09	97.67	122.47 ± 0.03
2	**102**	2852	99.04	62.48 ± 0.27	95.90	119.52 ± 0.10
3	**103**	4500	94.29	78.84 ± 0.16	91.15	120.95 ± 0.06
4	**104**	6417	99.56	67.85 ± 0.23	96.42	122.07 ± 0.09
5	**105**	15750	105.85	58.68 ± 0.19	102.72	124.90 ± 0.07

Since $\Delta G^{\ddagger}$ is positive for all the systems studied, it would appear that the cyclisation is not a spontaneous process at low temperature. It is also interesting to note that the rate constants are more than doubled for every 10°C increase in temperature **(Table 15)**. The positive values obtained for $\Delta S^{\ddagger}$ are also consistent with loss of the acetoxy group in the rate determining step. It should be noted, however, that in these calculations the influence of temperature on the equilibrium constant, K_1, has been ignored.

2.4 Nucleophilic Addition and Substitution Reactions (Thiomethylations)

Thiomethylation reactions of a series of Baylis-Hillman compounds as well as a number of acetylated derivatives were carried out. Nucleophilic attack can proceed *via* a number of different modes (**Fig. 16**). Thus:- a) Michael addition can occur with subsequent loss of the double bond and the formation of two new chiral centres; b) nucleophilic substitution can occur with migration of the double bond and loss of the hydroxyl or acetoxy group (S_N'); c) nucleophilic attack can also occur at the same carbon to which the leaving group is attached (S_N); and d) nucleophilic attack can occur at the carbonyl carbon of the ester functionality.

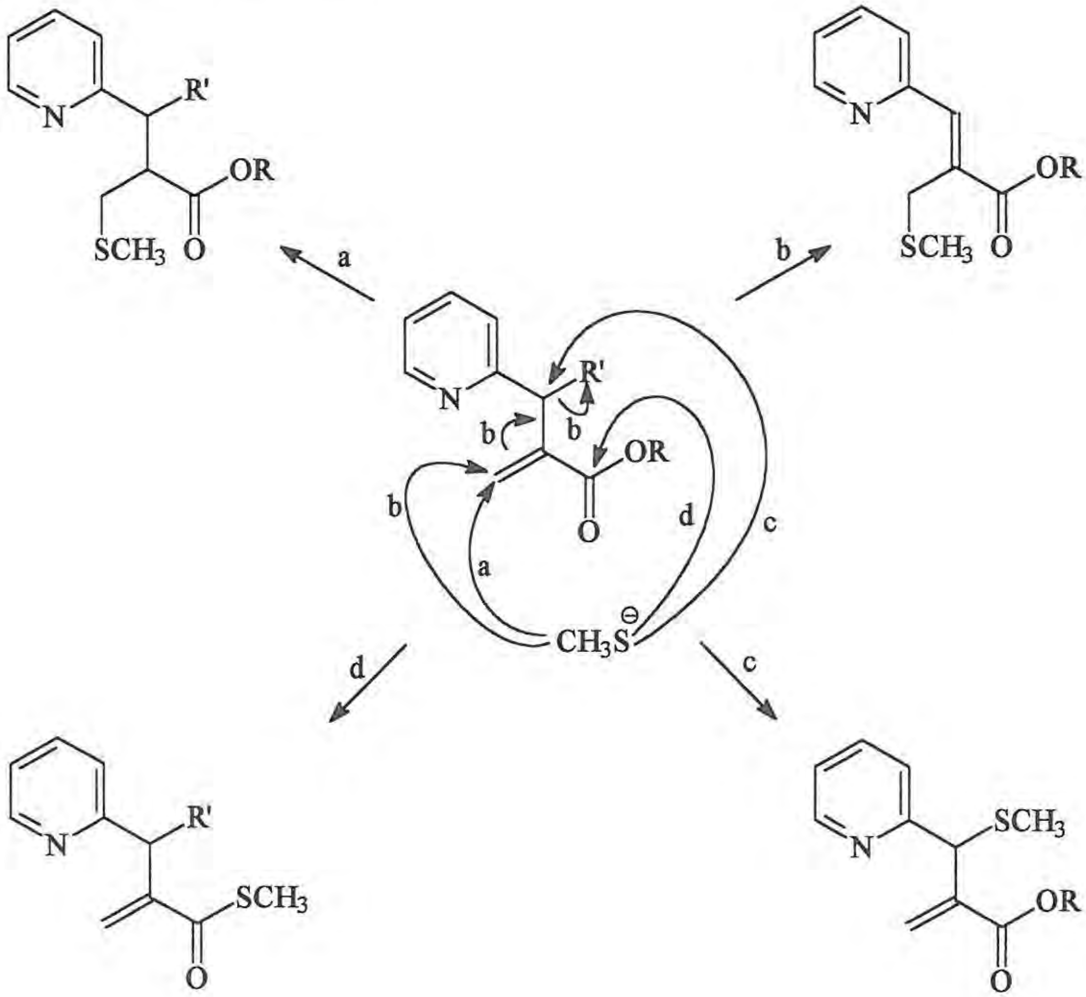
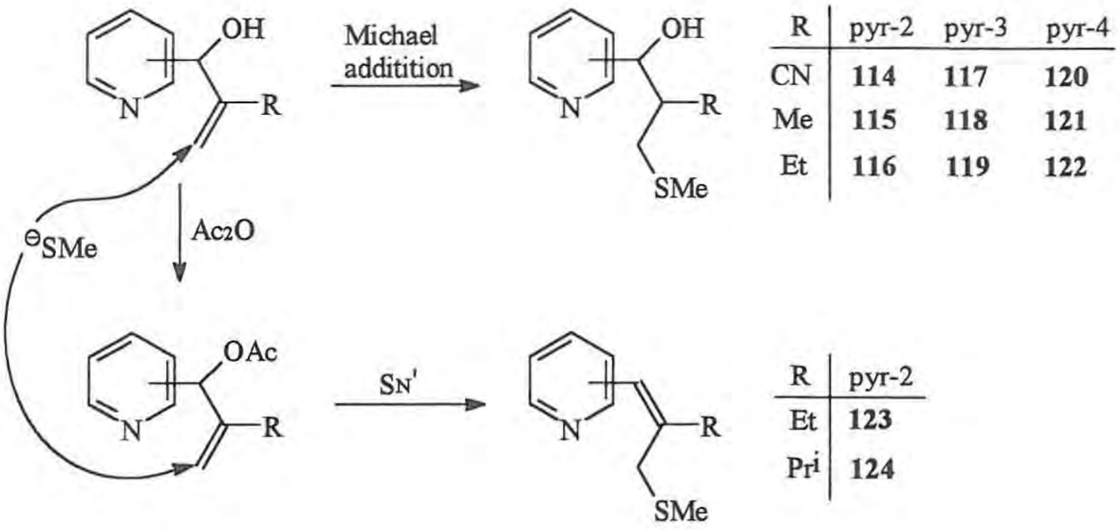


Figure 16

In her synthesis of aldicarb [2-methyl-2-(methylthio)propanal] analogues, Whittaker[110] reacted sodium methylthiolate with pyridine carboxaldehyde-derived Baylis-Hillman products. It was found that several reactions took place. In one case, Michael addition occurred; in another, apparent S_N' displacement was observed and, in a third case, no addition took place but the ester was hydrolysed instead.

In the current study, a slight modification of Whittaker's method was used to thiomethylate a range of substrates (**84, 86-87, 90-95** and **112-113; Scheme 37**).[§] The reaction mixtures were not heated at all, but left to stir at room temperature for 30 to 45 minutes after the addition of the sodium methylthiolate. A rise in temperature (*ca.* 5 C) during the addition period was observed in all cases. Analysis of the products by ^{1}H NMR spectroscopy showed that with Baylis-Hillman products, Michael addition had occurred to afford the thiomethylated compounds **114-122**. Where the hydroxyl group had been replaced by an acetoxy group (by treating the corresponding Baylis-Hillman products with acetic anhydride) S_N' displacement to afford products **123** and **124** was observed. The two product types can be readily distinguished by examining their ^{1}H NMR spectra (**Figures 11 and 12**). It is thought that upon heating of the reaction mixture, the hydroxyl group is lost from the Michael addition product thus giving the appearance of substitution observed by Whittaker. It is interesting to note that substitution occurred at room temperature when the hydroxyl group was replaced by acetate. This would make sense as the acetate moiety is a better leaving group. The results of the thiomethylation reactions are summarised in **Table 17**.

[§] (112) and (113) were not isolated as chemically pure compounds
(see Experimental p. 87).



R	pyr-2	pyr-3	pyr-4
CN	**114**	**117**	**120**
Me	**115**	**118**	**121**
Et	**116**	**119**	**122**

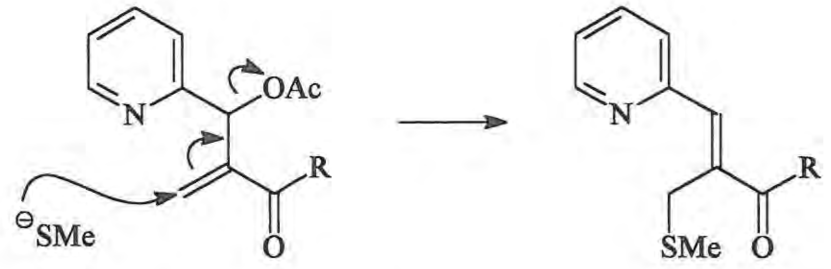
R	pyr-2
Et	**123**
Pr^i	**124**

Scheme 37

Table 17. Results from the thiomethylation of selected Baylis-Hillman products

			High Resolution MS Data		
Entry	Substrate	Product Yield (%)	Formula	Requires	Found
1	**84**	27	$C_{10}H_{12}N_2OS$	208.0670	208.0661
2	**86**	16	$C_{11}H_{15}NO_3S$	241.0772	241.0780
3	**87**	33	$C_{12}H_{17}NO_3S$	255.0928	255.0923
4	**90**	35	$C_{10}H_{12}N_2OS$	208.0670	208.0660
5	**91**	22	$C_{11}H_{15}NO_3S$	241.0772	241.0783
6	**92**	53	$C_{12}H_{17}NO_3S$	255.0928	255.0916
7	**93**	43	$C_{10}H_{12}N_2OS$	208.0670	208.0670
8	**94**	23	$C_{11}H_{15}NO_3S$	241.0772	241.0788
9	**95**	43	$C_{12}H_{17}NO_3S$	255.0928	255.0920
10	**103**	52	$C_{12}H_{15}NO_2S$	237.0823	237.0828
11	**104**	51	$C_{13}H_{17}NO_2S$	251.0999	251.0999

Normally, alkenes do not undergo nucleophilic attack because the π-system is electron-rich. But, if a suitable electron-withdrawing group (*e.g.* ester) is attached to the vinyl system, then the electron density can be lowered rendering the vinylic carbon more susceptible to attack by a nucleophile. Usually, nucleophilic substitution occurs *via* the generation of a vinyl carbanion/enolate ion intermediate. The mechanism for the S_N' thiomethylation reaction is detailed in **Scheme 38**. It is termed S_N' because the leaving group is not attached to the carbon at which nucleophilic attack occurs and the reaction proceeds with allylic rearrangement The reaction is easily followed by proton NMR spectroscopy as the spectra of the products no longer exhibit two signals arising from the vinyl protons; a singlet appearing at about 7.6 ppm confirms the change in position of the double bond **(Figure 17).**



R = CH_2CH_3, $CH(CH_3)_2$

Scheme 38

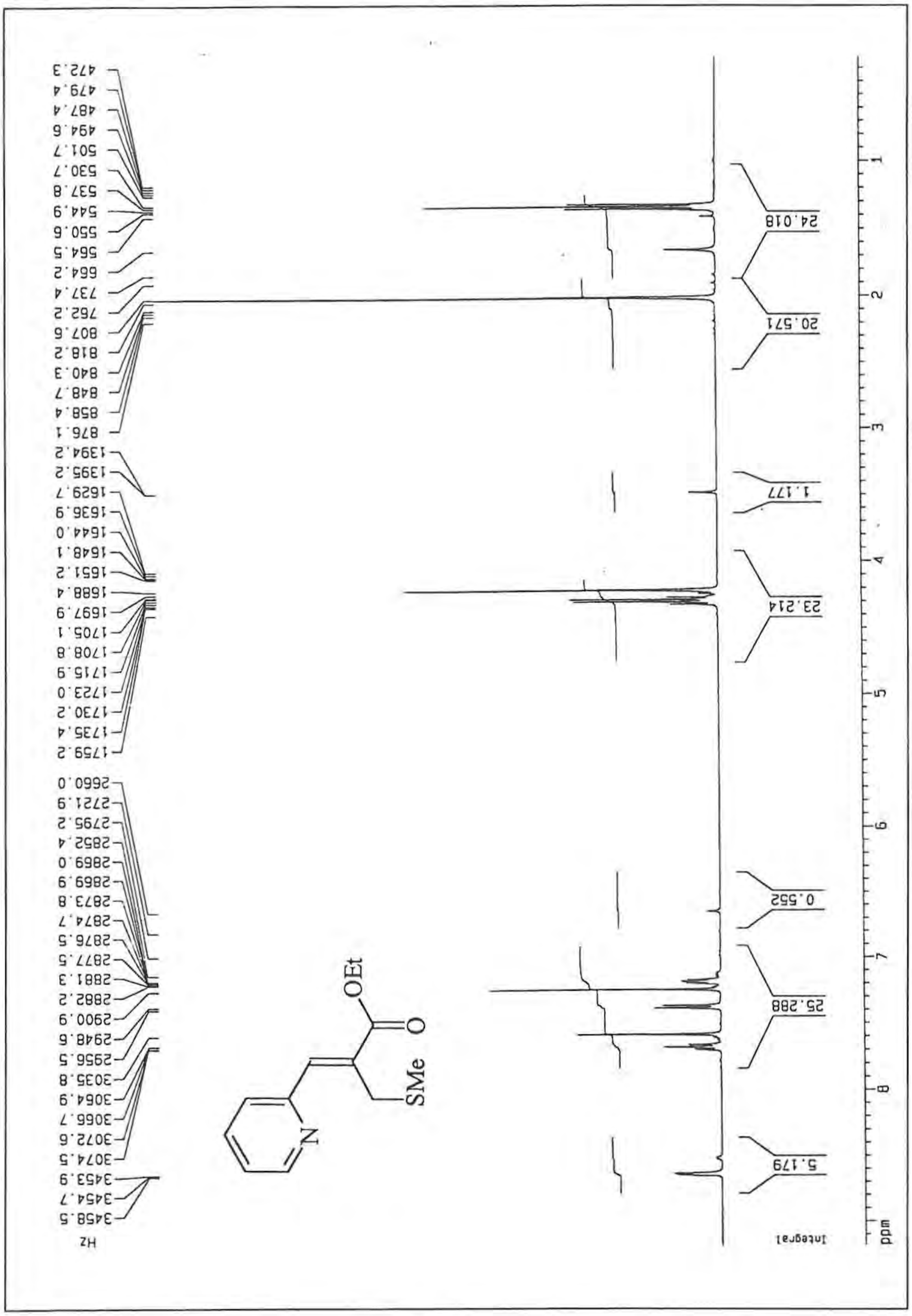
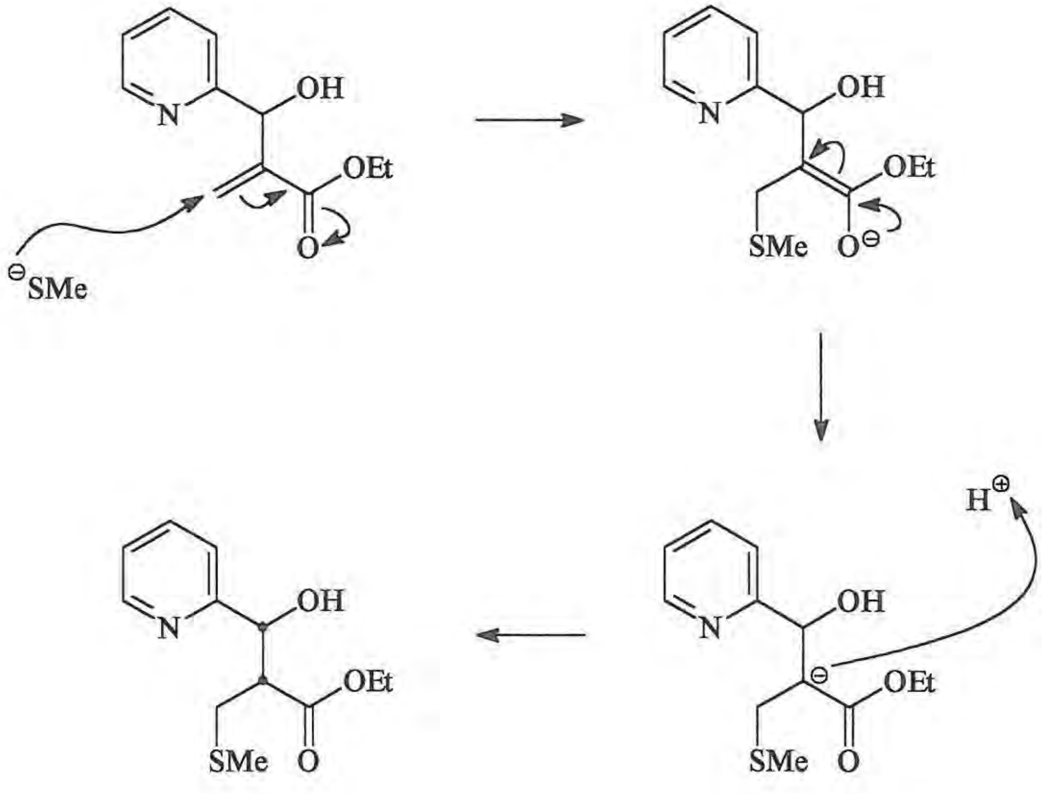


Figure 17. 400 MHz ^{1}H NMR spectrum of ethyl 2-(methylthiomethyl)-3-(2-pyridyl)-2-propenoate (**123**).

Michael (or conjugate) addition, on the other hand, refers to nucleophilic attack on the C-C double bond of an α,β-unsaturated carbonyl system by a carbanion.[133] The attack can occur because, as for the S_N' reaction, the alkene is activated to nucleophilic attack by the conjugated carbonyl group. The general mechanism is illustrated for attack by methylthiolate on the substrates examined here (**Scheme 39**).

From **Scheme 39** it can be seen that two new chiral centres are formed in the conjugate addition, giving rise to four possible stereoisomers, *viz.*, *RR*, *SS*, *RS* and *SR*. The *RR* and *SS* stereoisomers are enantiomeric as are the *RS* and *SR* pair. While the enantiomers cannot be differentiated by ^{1}H NMR spectroscopy, the diastereomers (*RR* and *RS* or *SS* and *SR*) can be.



Scheme 39

Typical peaks in the ^{1}H NMR spectra of the conjugate addition products are found between 2 ppm and 5 ppm (**Figure 18**). The thiomethyl signal appears as two singlets (arising from the diastereomers) at about 1 ppm. The 3-methine doublets appear at *ca.*

5ppm while the 2-methine protons resonate as multiplets at *ca.* 3ppm. The methylene protons are indicated by the multiplet below 3ppm. Splitting patterns in the aromatic region also become more complex. The ^{13}C NMR spectra also show doublets of peaks due to the presence of diastereomeric systems (**Figure 19**). A certain amount of diastereoselectivity was observed when the R group was changed and the diastereomeric excesses were calculated using the ratios of suitable integrals in the proton NMR spectra (**Table 18**). Conclusions about the trend observed (diastereomeric excess for R=CN>Me >Et) cannot be made as a more detailed study is required.

Table 18. Diastereomeric excesses obtained for Michael addition products.

Entry	**Substrate**	**Product**	**d.e. (%)**[a]
1	**84**	114	24.7
2	**86**	115	20.0
3	**87**	116	18.1
4	**90**	117	16.3
5	**91**	118	15.6
6	**92**	119	11.7
7	**93**	120	26.4
8	**94**	121	20.0
9	**95**	122	18.4

[a] Diastereomeric excesses (d.e.) were calculated using the crude product.

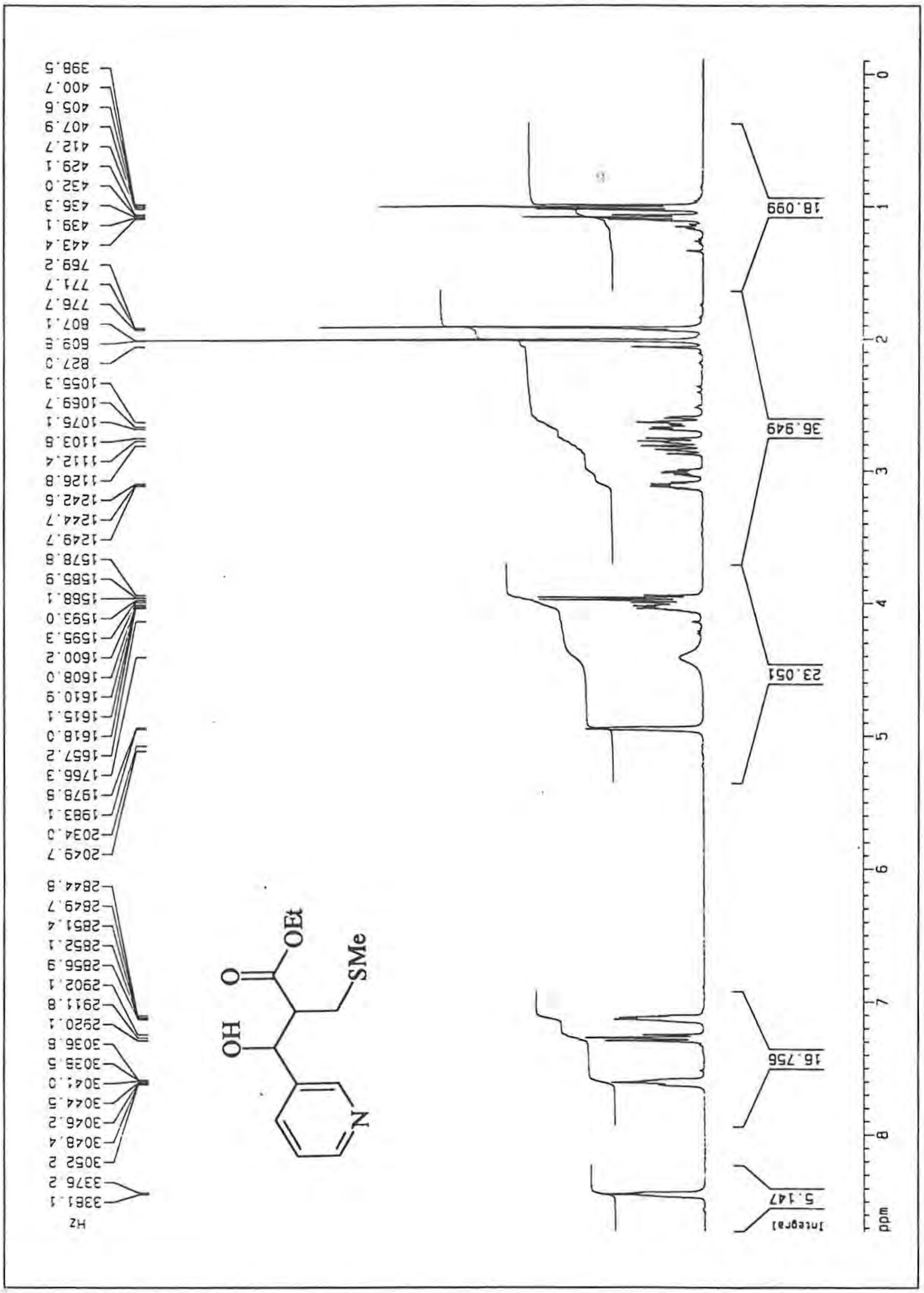


Figure 18. 400 MHz ^{1}H NMR spectrum of ethyl 3-hydroxy-2-(methylthiomethyl)-3-(3-pyridyl)propanoate (119).

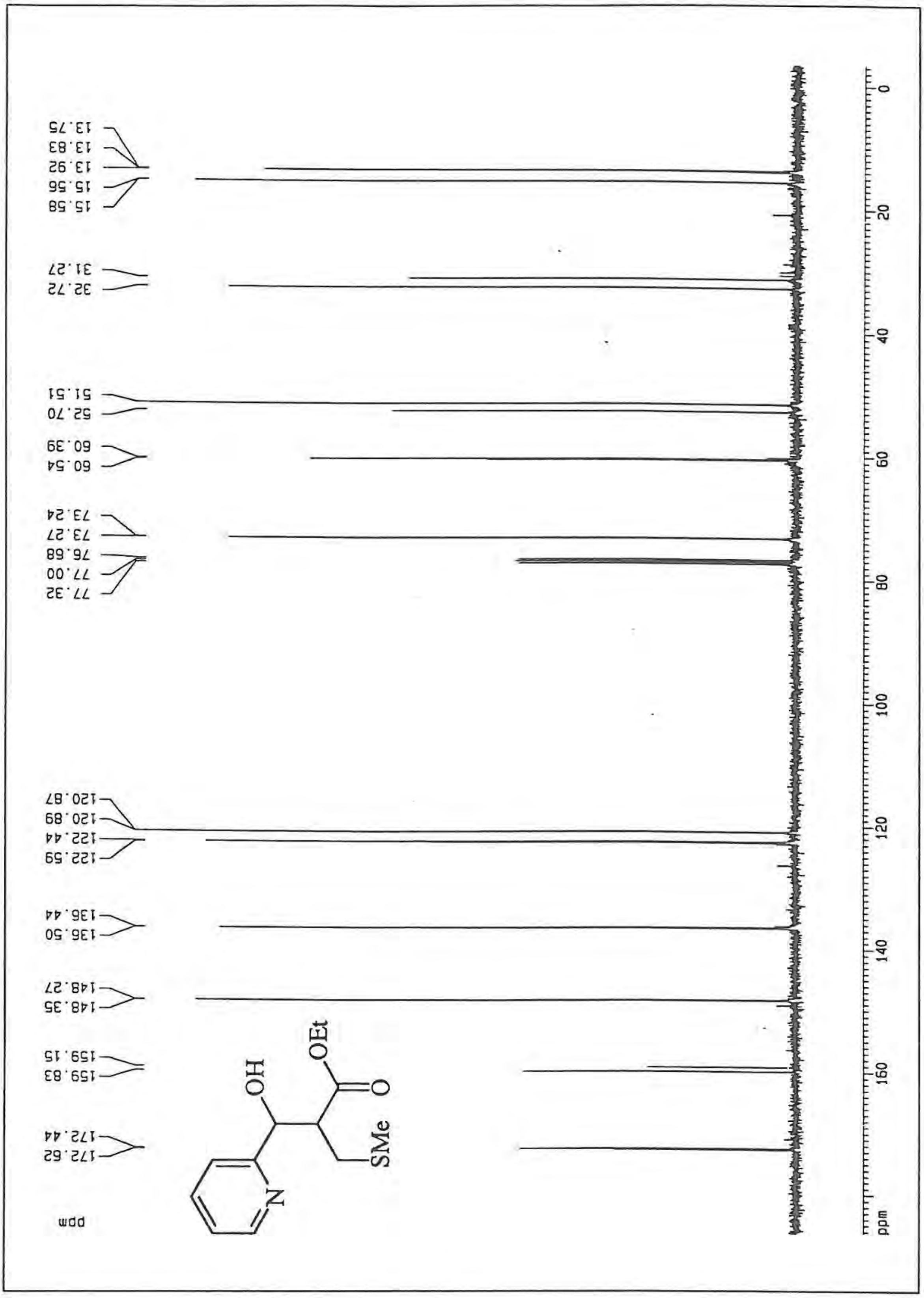
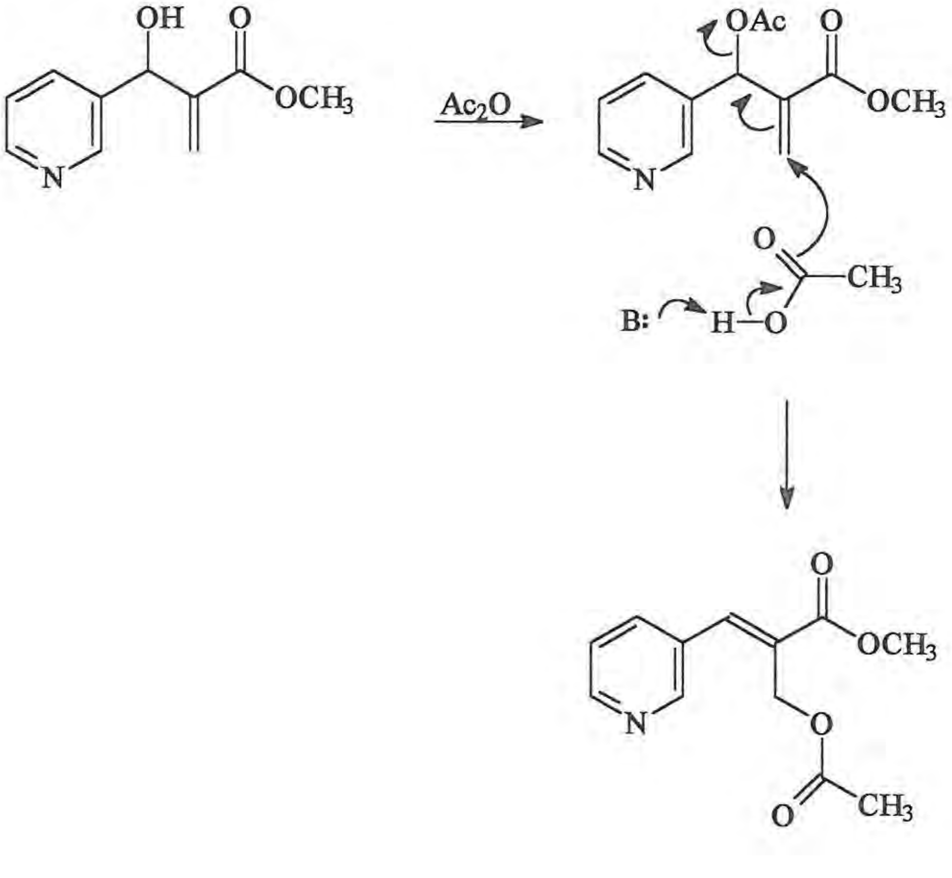


Figure 19. 100 MHz ^{13}C spectrum of ethyl 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate (116).

In order to study the effects of the acetoxy leaving group further, methyl 3-hydroxy-2-methylene-3-(3-pyridyl)propanoate **(91)** and methyl 3-hydroxy-2-methylene-3-(4-pyridyl)propanoate **(94)** were acetylated using the procedure mentioned earlier. In both cases, the fractions isolated from the flash column were shown by proton NMR spectroscopy to have undergone an S_N' type reaction. A mechanism for these particular reactions has been proposed **(Scheme 40)**, but is very speculative as, even after preparative thin layer chromatography, the fractions were still impure. It is thought that acetylation occurs in the normal way but, during work-up, the reaction mixture is basified to remove excess acetic acid and acetic anhydride and, in the basic medium, the nucleophilic acetate anion could attack the double bond with allylic rearrangement and the acetoxy group already present acting as the leaving group.



Scheme 40

2.5 Conclusions

During the course of this research a range of Baylis-Hillman products has been successfully prepared from pyridine-2-, pyridine-3- and pyridine-4-carboxaldehydes and various acrylate systems. The products generated from this reaction with pyridine-2-carboxaldehyde were subsequently acetylated and cyclised to indolizine derivatives. The kinetics of this convenient cyclisation were followed by ^{1}H NMR spectroscopy to confirm previous studies. The reaction was shown to obey a first-order rate equation. Variable temperature studies permitted evaluation of the activation parameters and the observed effects of substituents were accommodated by the proposed mechanism.

The Baylis-Hillman products also proved to be interesting substrates for competing nucleophilic reactions and in reactions with sodium methylthiolate both conjugate addition (in the case of hydroxy precursors) and S_N' (in the case of acetoxy precursors) reactions were found to occur. The conjugate addition route was accompanied by the formation of two new chiral centres and a certain amount of diastereoselectivity was observed.

The objectives identified earlier have been achieved. A detailed examination of transition state conformations and substituent effects will be required to rationalise the observed diastereoselectivities and possibly optimise the stereocontrol. These aspects, however, must form the basis of a future project.

3. EXPERIMENTAL

3.1 General Notes

All melting points were determined using a Kofler hot stage and are uncorrected. NMR spectra were run on Bruker AMX400 and Perkin Elmer 60 MHz spectrometers. Spectra recorded on the 400 MHz spectrometer were calibrated using solvent signals ($CDCl_3$: 7.25 ppm for ^1H and 77.0 ppm for ^{13}C) while spectra recorded on the 60 MHz spectrometer were calibrated using tetramethylsilane (TMS) as an internal standard.

IR spectra were recorded on a Perkin-Elmer 180 grating infrared spectrometer using KBr discs or liquid films. Low-resolution mass spectra were obtained on a Hewlett Packard 5988A mass spectrometer and high resolution mass spectra on a Kratos double-focusing magnetic sector instrument (Cape Technikon Mass Spectrometry Unit).

Thin layer chromatography was performed using precoated Merck Silica gel F_{254} plates and preparative layer chromatography on glass plates coated with Merck Silica gel 60 PF_{254}. Flash column chromatography was performed using Merck silica gel [particle size 0.040-0.063mm(230-400mesh)].

Ether was dried initially over $CaCl_2$ and then refluxed over sodium wire using benzophenone as an indicator.[134]

3.2 Synthetic Procedures

Acryloyl chloride **(83)**[135]

A mixture of acrylic acid (18.03g, 0.25 mol) and PCl_3 (11.45g, 0.08 mol) was heated gently to 60°-70°C in a round-bottomed flask fitted with a reflux condenser and a $CaCl_2$ drying tube. The temperature was maintained at 60°-70°C for 15 minutes. Upon cooling to room temperature the upper liquid layer was decanted off and CuCl (0.25g) added. The crude material was distilled to afford acryloyl chloride **(83)** (19.7g, 84%); b.p. 76°-78°C (lit.,[113] 74°-75°C); ν_{max} (thin film)/cm^{-1} 1805 (CO); δ_H(400 MHz; $CDCl_3$) 6.40 (3H, m, CH_2=CH).

Isopropyl acrylate **(81)**[135]

Acryloyl chloride **(83)** (10g, 0.11 mol) was added slowly over a period of 10 minutes to a stirred solution of isopropyl alcohol (9g, 0.15 mol), *N,N*-dimethylaniline (13.4g, 0.11 mol) and hydroquinone (0.5g) in dry ether (180ml). The mixture was refluxed for 3 days after which the liquid was decanted from the white solid material that formed. The solution was washed with 2*M*-HCl (2×20ml) and 1*M*-NaOH (2×20ml) and then dried (anhyd. $MgSO_4$). The solvent was removed *in vacuo* and the crude material was distilled to afford isopropyl acrylate **(81)** (4.98g, 38%), b.p. 36°-38°C/15-20 mmHg; ν_{max} (thin film)/cm^{-1} 1710 (CO); δ_H (400 MHz; $CDCl_3$) 1.22 [6H, d, $CH(CH_3)_2$], 5.03 [1H, septet, $CH(CH_3)_2$], 5.73 and 6.32 (2H, 2 × d, $CH=CH_2$) and 6.04 (1H, dd, $CH=CH_2$); δ_C (100 MHz; $CDCl_3$) 21.7 (2 × CH_3), 67.7 [$CH(CH_3)_2$]), 129.1 (C-2), 129.9 (C-3) and 156.6 (C-1).

tert-*Butyl acrylate* **(82)**[135]

Acryloyl chloride **(83)** (5.3g, 57.5 mmol) was added slowly over a period of 5 minutes to a stirred solution of *tert*-butyl alcohol (0.63g, 75 mmol), *N,N*-dimethylaniline (7.08g, 0.125 mol), and hydroquinone (0.13g) in dry ether (80 ml). The reaction mixture was boiled under reflux for 7 days and worked up following the procedure for isopropyl acrylate **(82)**. Vacuum distillation of the crude product afforded *tert*-butyl acrylate **(82)** (6.5g, 88%), b.p. 29-30°C/15-20 mm Hg; ν_{max} (thin film)/cm^{-1} 1715 (CO); δ_H (400 MHz; $CDCl_3$) 1.21 [9H, s, $C(CH_3)_3$], 5.67 and 6.25 (2H, 2×dd, $CH{=}CH_2$) and 5.98 (1H dd, $CH{=}CH_2$); δ_C (100 MHz; $CDCl_3$) 21.6 [$C(CH_3)_3$], 67.6 [$C(CH_3)_3$], 129.0 ($CH{=}CH_2$), 129.8 ($CH{=}CH_2$) and 165.4 (CO).

3-Hydroxy-2-methylene-3-(2-pyridyl)propanenitrile **(84)**[13]

Acrylonitrile (1.24g, 29 mmol) was added to a stirred solution of pyridine-2-carboxaldehyde (2.95g, 28 mmol) and DABCO (0.15g, 1.3 mmol) in chloroform (2ml). The reaction mixture was allowed to stir at room temperature for 3 days after which the solvent was removed *in vacuo*. Flash chromatography [elution with dichloromethane-ethyl acetate (7:3) on silica] of the crude material afforded 3-hydroxy-2-methylene-3-(2-pyridyl)propanenitrile **(84)** as creamy-white crystals (4.1g, 91%), m.p. 48°-51°C; ν_{max} (KBr)/cm^{-1} 3300 br (OH) and 2235 (CN); δ_H (400 MHz; $CDCl_3$) 5.28 (1H, s, CHOH), 5.38 (1H, s, OH), 6.00 and 6.16 (2H, 2×s, $C{=}CH_2$) 7.25 (1H, ddd, 5'-H), 7.38 (1H, d, 3'-H), 7.72 (1H, ddd, 4'-H) and 8.52 (1H, d, 6'-H); δ_c (100 MHz; $CDCl_3$) 72.8 (CHOH), 121.2 (CN), 116.9 (C-3'), 121.2 (C-5'), 125.8 ($C{=}CH_2$), 130.8 (C-4'), 137.5 (C-6'), 148.5 (C-2') and 156.0 ($C{=}CH_2$).

4-Hydroxy-3-methylene-4-(2-pyridyl)butan-2-one **(85)**[13]

The procedure used to prepare 3-hydroxy-2-methylene-3-(2-pyridyl)propanenitrile **(84)** was followed using pyridine-2-carboxaldehyde (4.0g, 37 mmol), methyl vinyl ketone (3.27g, 46 mmol) and DABCO (0.112g, 1.07 mmol) in chloroform (3ml). After stirring for three days, the solvent was removed *in vacuo* and the crude material purified using flash chromatography (elution with ethyl acetate on silica) to yield 4-hydroxy-3-methylene-4-(2-pyridyl)butan-2-one **(85)** as an orangey-brown oil (5.70g, 78%); ν_{max} (thin film)/cm^{-1} 3250 (OH) and 1715 (CO); δ_H (400 MHz; $CDCl_3$) 2.33 (3H, s, $CO.CH_3$), 4.76 and 6.13 (2H, 2×d, $C{=}CH_2$), 5.69 (1H, d, CHOH), 6.20 (1H, s, OH), 7.17 (1H, ddd, 5'-H), 7.41 (1H, d, 3'-H), 7.64 (1H, ddd, 4'-H) and 8.50 (1H, d, 6'-H); δ_C

$CDCl_3$) 27.5 (CO.CH_3), 73.2 (CHOH), 99.4 (C-3'), 112.6 (C-5'), 115.2 (C=CH_2), 118.4 (C-4'), 121.0 (*C*=CH_2), 121.1 (C-6'), 137.0 (C-2') and 148.4 (CO).

Methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(86)**[13]

The method used for the preparation of 3-hydroxy-2-methylene-3-(2-pyridyl)-propanenitrile **(84)** was followed using pyridine-2-carboxaldehyde (4.3g, 39 mmol), methyl acrylate (3.4g, 40 mmol) and DABCO (0.21g, 1.84 mmol) in chloroform (2ml). The mixture was stirred for 3 days after which the solvent was removed *in vacuo*. Flash chromatography [elution with hexane-ethyl acetate (3:7) on silica] yielded methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(86)** as a brown oil (6g, 80%); ν_{max} (thin film)/cm^{-1} 3390 br (OH) and 1710 (CO); δ_H (400 MHz; $CDCl_3$) 3.62 (3H, s, $COCH_3$), 4.92 (1H, br s, OH), 5.56 (1H, s, *CH*OH) 5.89 and 6.27 (2H, 2×s, C=CH_2) 7.1 (1H, d, 5'-H), 7.34 (1H, d, 3'-H), 7.58 (1H, d, 4'-H) and 8.43 (1H, s, 6'-H); δ_c (100 MHz; $CDCl_3$) 51.5 (CH_3), 71.9 (*C*HOH), 121.1 (C-3'), 122.4 (C-5'), 126.4 (C=CH_2), 136.6 (C-4'), 141.6 (*C*=CH_2), 148.0 (C-6'), 159.6 (C-2') and 166.3 (CO).

Ethyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(87)**[13]

The method used for the synthesis of 3-hydroxy-2-methylene-3-(2-pyridyl)propanenitrile **(84)** was followed using ethyl acrylate (2.1g, 21 mmol), pyridine-2-carboxaldehyde (2.14g, 20 mmol) and DABCO (0.112g, 1.0 mmol) in chloroform (1ml). The reaction was stirred at room temperature for 3 days after which the solvent was removed. The crude material was purified using flash chromatography [elution with hexane-ethyl acetate (3:7) on silica] to afford ethyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(87)** as a brown oil. (3.05g, 72%); ν_{max} (thin film)/cm^{-1} 3190 br (OH) and 1710 (CO); δ_H (400 MHz; $CDCl_3$) 1.24 (3H, t, CH_2CH_3), 4.12 (2H, q, CH_2CH_3), 4.73 (1H, br s, OH), 5.60 and 6.32 (2H, 2×s, CH_2=C), 5.89 (1H, s, *CH*OH), 7.15 (1H, ddd, 5'-H), 7.37 (1H, dd, 3'-H), 7.62 (1H, ddd, 4'-H) and 8.46 (1H, dd, 6'-H); δ_C (100 MHz; $CDCl_3$) 13.8 (CH_2CH_3), 60.5 (CH_2CH_3), 72.0 (COH), 121.1 (C-3'), 122.3 (C-5'), 126.2 (C=CH_2), 136.6 (C-4'), 141.8 (*C*=CH_2), 148.0 (C-6'), 159.7 (C-2') and 165.8 (CO).

Isopropyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(88)**[13]

The synthetic procedure used for 3-hydroxy-2-methylene-3-(2-pyridyl)propanenitrile **(84)** was followed using isopropyl acrylate **(81)** (2.94g, 26 mmol), pyridine-2-carboxaldehyde (2.14g, 20 mmol) and DABCO (0.206g, 1.84 mmol) in chloroform (2ml). The reaction was stirred at room temperature for 3 days after which the solvent was removed *in vacuo*. Flash chromatography [elution with hexane-ethyl acetate (2:8) on silica] of the reaction mixture afforded isopropyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(88)** as a brown oil (2.28g, 45%); ν_{max} (thin film)/cm^{-1} 3300 br (OH) and 1710 (CO); δ_H (400 MHz; CDCl$_3$) 1.16 and 1.21 [6H, 2×d, CH(CH_3)$_2$], 4.78 (1H, s, OH), 5.02 [1H, sep, CH(CH$_3$)$_2$], 5.58 (1H, s, CHOH), 5.89 and 6.31 (2H, 2×s, CH$_2$=C), 7.17 (1H, ddd, 5'-H), 7.42 (1H, d, 3'-H), 7.64 (1H, ddd, 4'-H) and 8.50 (1H, d, 6'-H); δ_C (100 MHz; CDCl$_3$) 21.7 [CH(CH$_3$)$_2$], 68.3 [CH(CH$_3$)$_2$], 72.3 (CHOH), 121.2 (C-3'), 122.5 (C-5'), 126.5 (C=CH$_2$), 136.7 (C-4'), 142.3 (C=CH$_2$), 148.2 (C-6'), 159.7 (C-2') and 165.6 (CO).

tert-*Butyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate* **(89)**[13]

The method used for the synthesis of 3-hydroxy-2-methylene-3-(2-pyridyl)propanenitrile **(84)** was followed using pyridine-2-carboxaldehyde (2.0g, 21 mmol), *tert*-butyl acrylate **(82)** (2.37g, 21 mmol) and DABCO (0.112g, 1.0 mmol) in chloroform (2ml). The reaction was stirred at room temperature for 5 days after which the solvent was removed *in vacuo*. The crude material was purified using flash chromatography [elution with hexane-ethyl acetate (3:7) on silica] to afford tert-*butyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate* **(89)** as a dark orange oil (1.92g, 44%); (Found: M$^+$ 235.1201. Calc. for $C_{13}H_{17}NO_3$: *M*, 235.1207); ν_{max} (thin film)/cm^{-1} 3360 br (OH) and 1700 (CO); δ_H (400 MHz; CDCl$_3$) 1.26 [9H, s, C(CH$_3$)$_3$], 5.46 (1H, s, CHOH), 5.75 and 6.15 (2H, 2×s, CH$_2$=C), 7.06 (1H, ddd, 5'-H), 7.29 (1H, dd, 3'-H), 7.75 (1H, ddd, 4'-H) and 8.65 (1H, dd, 6'-H); δ_C (100 MHz; CDCl$_3$) 27.9 [C(CH$_3$)$_3$], 72.6 [C(CH$_3$)$_3$], 81.2 (CHOH), 121.0 (C-3'), 122.4 (C-5'), 125.9 (C=CH$_2$), 136.6 (C-4'), 143.2 (C=CH$_2$), 148.1 (C-6'), 160.0 (C-2') and 165.3 (CO); m/z 235.10(M$^+$, 0.29%) and 162(100%).

3-Hydroxy-2-methylene-3-(3-pyridyl)propanenitrile **(90)**[13]

The method used for the synthesis of 3-hydroxy-2-methylene-3-(2-pyridyl)propanenitrile **(84)** was followed using pyridine-3-carboxaldehyde (2.95g, 28 mmol), acrylonitrile (1.54g, 29 mmol) and DABCO (0.15g, 1.3 mmol) in chloroform (2ml). The reaction was stirred at room temperature overnight after which the solvent was removed *in vacuo*. The crude material was recrystallised from ethyl acetate to yield 3-hydroxy-2-methylene-3-(3-pyridyl)propanoate **(90)** as light orange crystals (1.62g 36%), m.p. 93.5°-95.5°C (from ethyl acetate, lit.,[35] 103°C); ν_{max} (KBr)/cm^{-1} 3100 br (OH) and 2230 (CN); δ_H (400 MHz; $CDCl_3$) 4.05 (1H, br s, OH), 5.37 (1H, s, C*H*OH), 6.08 and 6.18 (2H, 2×d, CH_2=C), 7.34 (1H, dd, 5'-H), 7.78 (1H, tt, 4'-H), 8.52 (1H, d, 2'-H) and 8.53 (1H, t, 6'-H); δ_C (100 MHz; $CDCl_3$) 71.7 (CHOH), 116.6 (CN), 124.0 (C-3'), 126.0 (C-4'), 130.3 (C=*C*H_2), 134.9 (C-5'), 136.0 (*C*=CH_2), 147.6 (C-2') and 149.2 (C-6').

Methyl 3-hydroxy-2-methylene-3-3(3-pyridyl)propanoate **(91)**[13]

The method used for the synthesis of 3-hydroxy-2-methylene-3-(2-pyridyl)propanenitrile **(84)** was followed using methyl acrylate (3.43g, 40 mmol), pyridine-3-carboxaldehyde (4.3g, 39 mmol) and DABCO (0.206g 1.84 mmol) in chloroform (2ml). The reaction mixture was stirred at room temperature until it solidified. The solvent was removed *in vacuo* and the crude material recrystallised from ethyl acetate to yield methyl 3-hydroxy-2-methylene-3-(3-pyridyl)propanoate **(91)** as white crystals (3.11g, 40%), m.p. 96°-98°C (from ethyl acetate, lit.,[4] 100°C); ν_{max} (KBr)/cm^{-1} 3200 br (OH) and 1715 (CO); δ_H (400 MHz; $CDCl_3$) 3.71 (3H, s, $COOCH_3$), 3.78 (1H, br s, OH), 5.59 (1H, s, C*H*OH), 5.96 and 6.37 (2H, 2×s, CH_2=C), 7.28 (1H, ddd, 5'-H), 7.71 (1H, dd, 4'-H), 8.46 (1H, dd, 2'-H) and 8.54 (1H, d, 6'-H); δ_C (100 MHz; $CDCl_3$) 52.1 (OCH_3), 71.3 (CHOH), 123.4 (C-3'), 126.6 (C-4'), 134.3 (C=*C*H_2), 137.0 (C-5'), 141.4 (*C*=CH_2), 148.6 (C-2'), 149.0 (C-6') and 166.4 (CO).

Ethyl 3-hydroxy-2-methylene-3-(3-pyridyl)propanoate **(92)**[13]

The procedure used for the synthesis of 3-hydroxy-2-methylene-3-(2-pyridyl)-propanenitrile **(84)** was followed using pyridine-3-carboxaldehyde (2.14g, (20 mmol), ethyl acrylate (2.1g, 21 mmol) and DABCO (0.112g, 1.0 mmol) in chloroform (2ml). The mixture was stirred until it became solid and the solvent was then removed *in vacuo*. The crude material was recrystallised from cold ethyl acetate to yield ethyl 3-hydroxy-2-methylene-3-(3-pyridyl)propanoate **(92)** as cream coloured crystals (1.5g, 35%), m.p. 65 -67 C (from ethyl acetate); ν_{max} (KBr)/cm^{-1} 3300 br (OH) and 1700 (CO); δ_H (400 MHz; $CDCl_3$) 1.21 (3H, t, CH_2CH_3), 3.38 (1H, br s, OH), 4.18 (2H, q, CH_2CH_3), 5.59 (1H, s, CHOH), 5.85 and 6.38 (2H, 2×s, CH_2=C), 7.28 (1H, dd, 5'-H), 7.22 (1H, dd, 4'-H), 8.51 (1H, dd, 2'-H) and 8.59 (1H, d, 6'-H); δ_C (100 MHz; $CDCl_3$) 14.0 (CH_2CH_3), 61.1 (CH_2CH_3), 71.1 (CHOH), 123.3 (C-3'), 126.2 (C-4'), 134.4 (C=CH_2), 137.2 (C-5'), 141.7 (C=CH_2), 148.4 (C-2'), 148.8 (C-6') and 165.9 (CO).

3-Hydroxy-2-methylene-3-(4-pyridyl)propanenitrile **(93)**[13]

The method for the synthesis of 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(84)** was followed using acrylonitrile (1.54g, 29 mmol), pyridine-4-carboxaldehyde (2.95g, 28 mmol) and DABCO (0.15g, 1.3 mmol) in chloroform (2ml). The mixture was stirred at room temperature until it solidified. The solvent was removed *in vacuo* and the crude material recrystallised from ethyl acetate to yield 3-hydroxy-2-methylene-3-(4-pyridyl)propanenitrile **(93)** as light orange crystals (2.67g, 59%), m.p. 116.5 -119 C (from ethyl acetate); ν_{max} (KBr)/cm^{-1} 3300 br (OH) and 1705 (CO); δ_H (400MHz; $CDCl_3$) 3.73 (1H, br s, OH) 5.33 (1H, s, CHOH), 6.08 and 6.16 (2H, 2×dd, CH_2=C), 7.36 (2H, d, 3'-H and 5'-H) and 8.59 (2H, dd, 2'-H and 6'-H); δ_C (100 MHz; $CDCl_3$) 72.8 (CHOH), 116.4 (CN), 121.4 (C-3' and C-5'), 125.59 (C-4') 130.7 (C=CH_2), 149.0 (C=CH_2) and 149.9 (C-2' and C-6').

Methyl 3-hydroxy-2-methylene-3-(4-pyridyl)propanoate **(94)**[13]

The method used for the synthesis of 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(84)** was followed using pyridine-4-carboxaldehyde (4.3g, 39 mmol), methyl acrylate (3.44g, 40 mmol) and DABCO (0.15g, 1.3 mmol) in chloroform (2ml). The reaction was allowed to stir until it became solid. The solvent was removed *in vacuo* and the crude solid recrystallised from ethyl acetate to afford methyl 3-hydroxy-2-methylene-3-(4-pyridyl)propanoate **(94)** as white crystals (6.69g, 86%); m.p. 143 -145 C (from ethyl acetate, lit.,[4] 143 C); ν_{max} (KBR)/cm^{-1} 3100 br (OH) and 1705 (CO); δ_H (400 MHz; $CDCl_3$) 3.62 (3H, br s, OH), 3.69 ($COOCH_3$), 5.50 (1H, s, C*H*OH), 5.84 and 6.35 (2H, 2×s, CH_2=C), 7.28 (2H, d, 3'-H and 5'-H) and 8.52 (2H, dd, 2'-H and 6'-H); δ_C (100 MHz; $CDCl_3$) 52.1 (OCH_3), 72.4 (CHOH), 121.3 (C-3' and C-5'), 127.26 (C=*C*H2), 140.9 (C-4'), 149.8 (C-2' and C-6'), 150.4 (*C*=CH_2) and 166.42 (CO).

Ethyl 3-hydroxy-2-methylene-3-(4-pyridyl)propanoate **(95)**[13]

The method used for the synthesis of 3-hydroxy-2-methylene-3-(2-pyridyl)propanenitrile **(86)** was follwed using ethyl acrylate (2.1g, 21 mmol), pyridine-4-carboxaldehyde (2.14g, 20 mmol) and DABCO (0.112g, 1.0 mmol) in chloroform (2ml). The reaction was stirred until the mixture solidified. The solvent was removed *in vacuo* and the crude product recrystallised from ethyl acetate to yield ethyl 3-hydroxy-2-methylene-3-(4-pyridyl)propanoate **(95)** as cream coloured crystals (3.44g, 81%), m.p. 109 -111 C (from ethyl acetate); ν_{max} (KBr)/cm^{-1} 3050 br (OH) and 1715 (CO); δ_H (400MHz; $CDCl_3$) 1.24 (3H, t, CH_2CH_3), 3.74 (1H, br, OH), 4.20 (2H, q, CH_2CH_3), 5.50 (1H,s, C*H*OH), 5.84 and 6.37 (2H, 2×s, CH_2=C), 7.3 (2H, d, 3'-H and 5'-H), and 8.54 (2H, dd, 2'-H and 6'-H); δ_C (100MHz; $CDCl_3$) 13.9 (CH_2CH_3), 61.0 (CH_2CH_3), 71.6 (CHOH), 121.6 (C-3' and C-5'), 126.4 (C=CH_2), 141.6 (C-4'), 149.3 (C-2' and C-6'), 151.4 (*C*=CH_2) and 165.8 (CO).

3-Acetoxy-2-methylene-3-(2-pyridyl)propanenitrile **(100)**[13]

3-Hydroxy-2-methylene-3-(2-pyridyl)propanoate **(84)** (0.85g, 4.6 mmol) and acetic anhydride (5.0ml, 52.9 mmol) were placed in a round-bottomed flask and heated at 100°C for 0.5h. Upon cooling, the reaction mixture was poured into a $NaHCO_3$-ice slurry and stirred for a further 0.5h. The mixture was then basified (pH 9-10) with 1*M*-NaOH and extracted with ether. The ether extracts were washed with aqueous $NaHCO_3$ (2×30 ml) and satd. brine (2×30 ml) and dried with anhydrous magnesium sulphate. The ether was removed *in vacuo* and the crude product purified using flash chromatography [elution with hexane-ethyl acetate (3:7) on silica] to afford 3-acetoxy-2-methylene-3-(2-pyridyl)propanenitrile **(100)** as a light brown oil (0.60g, 57%); ν_{max} (thin film)/cm^{-1} 3400 br (OAc), 1745 and 1710 (2×CO); δ_H (400 MHz; $CDCl_3$) 2.13 (3H, s, $OCOCH_3$), 6.13 (1H, s, CHOAc), 6.15 and 6.37 (2H, 2×d, $C{=}CH_2$), 7.31 (1H, ddd, 3'-H), 7.47 (1H, d, 5'-H), 7.74 (1H, ddd, 4'-H) and 8.59 (1H, d, 6'-H); δ_C (100 MHz; $CDCl_3$) 20.8 ($CO.\mathit{C}H_3$), 75.3 (CHOH), 115.9 (CN), 121.3 (C-3'), 121.6 (C-5'), 123.8 ($C{=}\mathit{C}H_2$), 133.7 (C-4'), 136.9 ($\mathit{C}{=}CH_2$), 149.7 (C-6'), 154.9 (C-2') and 169.2 (CO).

4-Acetoxy-3-methylene-4-(2-pyridyl)butan-2-one **(101)**[13]

The synthetic method used for the preparation of 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(100)** was followed using 4-hydroxy-3-methylene-4-(2-pyridyl)butan-2-one **(85)** (2.01g, 11.3 mmol) and acetic anhydride (5.0ml, 52.9 mmol). The mixture was stirred at 100°C for 0.5h. The mixture was cooled and poured into a $NaHCO_3$-ice slurry and stirred for a further 0.5h. The mixture was worked up following the method used for 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(100)**. The crude yield was very low and thin layer chromatography showed a very complex reaction mixture.

Methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanenitrile **(102)**[13]

The synthetic method used for the preparation of 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(100)** was followed using methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(86)** (1.0g, 5.2 mmol) and acetic anhydride (5.0ml, 52.9 mmol). The mixture was stirred at 100°C for 0.5h. The mixture was cooled and poured into a

$NaHCO_3$-ice slurry and stirred for a further 0.5h. The mixture was worked up following the method used for 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(100)**. The crude material was purified using flash chromatography [elution with hexane-ethyl acetate (4:6) on silica] to afford methyl 3-acetoxy-2-methylene-3-(4-pyridyl)propanenitrile **(102)** as a brown oil (0.68g, 48%); ν_{max} (thin film)/cm^{-1} 3350 br (OAc), 1730 and 1715 (2×CO); δ_H (400 MHz; $CDCl_3$) 2.01 (3H, s, $CO.CH_3$), 3.57 (3H, s, OCH_3), 5.82 (1H, s, CHOAc), 6.35 and 6.63 (2H, 2×s, CH_2=C), 7.09 (1H, ddd, 3'-H), 7.32 (1H, d, 5'-H), 7.58 (1H, ddd, 4'-H) and 8.44 (1H, d, 6'-H); δ_C (100 MHz; $CDCl_3$) 20.9 ($CO.CH_3$), 50.7 (OCH_3), 72.7 (CHOAc), 121.2 (C-3'), 122.3 (C-5'), 126.5 (C=*C*H_2), 136.7 (C-4'), 141.2 (*C*=CH_2), 147.9 (C-6'), 159.8 (C-2'), 166.3 and 169.9 (2×CO).

Ethyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(103)**[13]

The synthetic procedure used for 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(100)** was followed using ethyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(87)** (2.0g, 9.7 mmol) and acetic anhydride (10ml, 1.1 mol). The reaction mixture was heated at 100°C for 0.5h. Upon cooling, the mixture was poured into a $NaHCO_3$-ice slurry and stirred for a further 0.5h. The mixture was worked up following the procedure for 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(100)**. Flash chromatography [elution with hexane-ethyl acetate (3:7) on silica] of the crude product afforded ethyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(103)** as a dark orange-brown oil (1.8g, 74%); ν_{max} (thin film)/cm^{-1} 3420 br (OAc), 1730 and 1710 (2×CO); δ_H (400 MHz; $CDCl_3$) 1.17 (3H, t, CH_2CH_3), 2.12 (3H, s, $CO.CH_3$), 4.13 (2H, dddd, CH_2CH_3), 5.89 (1H, s, CHOAc), 6.45 and 6.70 (2H, 2×s, CH_2=C), 7.17 (1H, ddd, 3'-H), 7.43 (1H, d, 5'-H), 7.65 (1H, ddd, 4'-H) and 8.56 (1H, d, 6'-H); δ_C (100 MHz; $CDCl_3$); 14.0 (CH_2CH_3), 21.0 ($CO.CH_3$), 60.9 (CH_2CH_3), 73.9 (CHOAc), 122.8 (C-3'), 123.0 (C-5'), 127.3 (C=*C*H_2), 136.7 (C-4'), 138.2 (*C*=CH_2), 149.4 (C-6'), 157.0 (C-2'), 164.9 and 169.6 (2×CO).

Isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(104)**[13]

The synthetic procedure used for 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(100)** was followed using isopropyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(88)** (0.80g, 3.6 mmol) and acetic anhydride (0.90ml, 9.5 mmol). The mixture was stirred at 100°C for 0.5h. After cooling the liquid was poured into a $NaHCO_3$-ice slurry and stirred for 0.5h. The mixture was worked up following the method used for 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(100)** and the crude material purified using flash chromatography [elution with hexane-ethyl acetate (4:6) on silica] to afford isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(104)** as a dark orange oil (0.50g, 53%); ν_{max} (thin film)/cm^{-1} 3420 br (OAc), 1740 and 1700 (2×CO); δ_H (400 MHz; $CDCl_3$) 1.12 and 1.18 [6H, 2×d, $CH(CH_3)_2$], 2.07 (3H, s, $CO.CH_3$) 4.99 [1H, sep, $CH(CH_3)_2$], 5.86 (1H, s, CHOAc), 6.45 and 6.72 (2H, 2×s, CH_2=C), 7.20 (1H, ddd, 3'-H), 7.42 (1H, d, 5'-H), 7.67 (1H, ddd, 4'-H) and 8.57 (1H, d, 6'-H); δ_c (100 MHz; $CDCl_3$) 21.0 (CH_3CO), 21.5 and 21.7 [$CH(CH_3)_2$], 68.5 [$CH(CH_3)_2$], 74.1 (*C*HOAc), 122.8 (C-3'), 123.0 (C-5'), 127.0 (*C*H_2=C), 136.6 (C-4'), 138.6 (CH_2=*C*), 149.4 (C-6'), 157.2 (C-2'), 164.4 and 169.6 (2×CO).

tert-*Butyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate* **(105)**[13]

The synthetic procedure used for 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(100)** was followed using *tert*-butyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(89)** (0.50g, 2.1 mmol) and acetic anhydride (5.0ml, 52.9 mmol). The mixture was heated at 100°C for 0.5h. Upon cooling, the mixture was poured into a slurry of $NaHCO_3$ and ice and stirred for 0.5h. The reaction was worked up following the procedure for 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(100)**. Flash chromatography [elution with hexane-ethyl acetate (2:8) on silica] of the crude product afforded tert-*butyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate* **(105)** as an orange oil (0.2g, 33%); (Found: M^+ 277.1320. Calc for $C_{15}H_{19}NO_4$: *M*, 277.1313); ν_{max} (thin film)/cm^{-1} 3320 br (OAc), 1705 and 1735 (2×CO); δ_H (400 MHz; $CDCl_3$) 1.36 [9H, d, $C(CH_3)_3$], 2.14 (3H, s, OCOCH3), 5.79 (1H, s, CHOAc), 6.34 and 6.69 (2H, 2×s, C=CH_2), 7.20 (1H, ddd, 3'-H), 7.40 (1H, d, 5'-H), 7.67 (1H, ddd, 4'-H) and 8.58 (1H, d, 6'-H); δ_C (100 MHz; $CDCl_3$) 20.3 ($CO.CH_3$), 28.0 [$C(CH_3)_3$], 72.5 (CHOAc), 81.2 [$C(CH_3)_3$], 121.1 (C-3'), 122.4 (C-5'), 125.9 (C=CH_2), 136.6 (C-4'), 136.7 (*C*=CH_2), 143.3 (C-6'), 148.2 (C-2') 160.0 and 165.4 (2×CO); m/z 277.10 (M^+, 0.93%) 108(100%).

Methyl 2-(acetoxymethyl)-3-(3-pyridyl)-2-propenoate **(112)**[13]

The synthetic procedure used for the preparation of 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(100)** was followed using methyl 3-hydroxy-2-methylene-3-(3-pyridyl)propanoate **(91)** (2.0g, 10 mmol) and acetic anhydride (10.0ml, 106 mmol). The mixture was heated at 100°C for 0.5h. Upon cooling, the mixture was poured into a slurry of $NaHCO_3$ and ice. The reaction was worked up as before and flash chromatography [elution with hexane-ethyl acetate (2:8) on silica] of the crude product yielded an impure fraction as well as some starting material. Preparative thin layer chromatography (developed with ethyl acetate) of the impure fraction failed to produce a pure compound and ^1H NMR spectroscopy showed that acetylation had occurred. The acetylation product was tentatively identified as *methyl 2-(acetoxymethyl)-3-(3-pyridyl)-2-propenoate* **(112)**.

Ethyl 2-(acetoxymethyl)-3-(4-pyridyl)-2-propenoate **(113)**

The synthetic procedure used for the preparation of 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(100)** was followed using ethyl 3-hydroxy-2-methylene-3-(4-pyridyl)propanoate **(95)** (2.0g, 10 mmol) and acetic anhydride (10.0ml, 106 mmol). The mixture was heated at 100°C for 0.5h. Upon cooling, the mixture was poured into a slurry of $NaHCO_3$ and ice. The reaction was worked up as before and flash chromatography [elution with hexane-ethyl acetate (2:8) on silica] of the crude product yielded starting material and an impure fraction, ^1H NMR of which showed that acetylation had occurred. The acetylation product was tentatively identified as *ethyl 2-(acetoxymethyl)-3-(4-pyridyl)-2-propenoate* **(113)**.

3-Hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanenitrile **(114)**

3-Hydroxy-2-methylene-3-(2-pyridyl)propanenitrile **(84)** (1g, 5.0 mmol) and THF (5ml) were placed in a three-necked round-bottomed flask fitted with a thermometer, pressure-equalising dropping funnel and condenser. The condenser was connected to a series of three scrubbers; the first one was empty, the second contained saturated aqueous NaOH and the third aqueous sodium hypochlorite solution. A 21% aqueous solution of sodium methylthiolate (1.61ml, 5.3 mmol of $NaSCH_3$) was added drop-wise over a 5 minute period during which the temperature rose from 19° to 23°C. The mixture was allowed to stir for a further 40 minutes after which saturated brine was added. The organic layer was extracted using ethyl acetate, washed with saturated brine and dried (anhyd. $MgSO_4$). The solvent was removed *in vacuo* and the crude material purified using flash chromatography [elution with hexane-ethyl acetate (2:8) on silica] to yield *3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanenitrile* **(114)**[§] as a dark orange oil (0.28g, 27%); (Found: M^+ 208.0661. Calc. for $C_{10}H_{12}N_2OS$: *M*, 208.0670); ν_{max} (thin film)/cm^{-1} 3450 (OH) and 2140 (CN); δ_H (400 MHz; $CDCl_3$)[¶] 2.22/2.23 (3H, 2×s, SCH_3), 2.79-3.02 (2H, m, CH_2SCH_3), 3.11-3.23 (1H, m, CHCN), 4.46/4.82 (1H, 2×d, OH), 4.96/5.07 (1H, d, C*H*OH), 7.31 (1H, t, 5'-H), 7.43 (1H, dd, 3'-H) 7.76 (1H, m, 4'-H) and 8.59 (1H, t, 6'-H); δ_C (100 MHz; $CDCl_3$) 16.0/16.1 (SCH_3) 31.9/33.2 (CH_2SCH_3), 40.6 (*C*HCHOH), 70.9/71.9 (CHOH), 118.5/119.5 (CN), 120.7/121.6 (C-3'), 123.3/123.5 (C-5'), 137.1/137.3 (C-4'), 148.4/148.7 (C-6') and 157.2/157.9 (C-2'); m/z 208(M^+, 1.86%) and 108(100%).

Methyl 3-Hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(115)**

Methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(86)** (1.0g, 4.9 mmol) and THF (5ml) were placed in a three-necked round-bottomed flasked fitted out as described for the synthesis of 3-hydroxy-2-(methylthiomethyl)-3-(-pyridyl)propanoate **(114)**. A 21% aqueous solution of sodium methylthiolate (1.71g, 5.1 mmol of $NaSCH_3$) was added over a 5 minute period. The mixture was stirred for a further 40 minutes during which

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[§] Obtained as pairs of diastereomers.

[¶] The shift values quoted refer to corresponding signals for the diastereomeric pairs and the format is used wherever diastereomeric products occur.

the temperature rose from 17° to 23°C. The reaction was worked up following the method used for 3-hydroxy-2-(methylthiomethyl)-3-(-pyridyl)propanoate **(114)** and the crude product purified using flash chromatography [elution with hexane-ethyl acetate (2:8) on silica] to afford *methyl 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate* **(115)**[§] as a light yellow oil. (0.19g, 16.1%); (Found: M^+ 241.0780. Calc. for $C_{11}H_{15}NO_3S$: *M*, 241.0772); ν_{max} (thin film)/cm^{-1} 3200 br (OH) and 1710 (CO); δ_H (400 MHz; $CDCl_3$) 2.00/2.14 (3H, 2×s, SCH_3), 2.64-2.94 (2H, m, CH_2SCH_3), 3.07-3.21 (1H, *C*HCHCOH), 3.60/3.66 (3H, 2×s, $COOCH_3$), 4.17/4.33 (1H, 2×d, OH), 5.02 (1H, d, C*H*OH), 7.21 (1H, dddd, 5'-H), 7.31 (1H, dd, 3'-H), 7.68 (1H, ttt, 4'-H) and 8.53 (1H, t, 6'-H); δ_C (100 MHz; $CDCl_3$) 15.8 (SCH_3), 31.4/32.9 (CH_2SCH_3), 51.7/51.8 (OCH_3), 52.9 (*C*HCHOH), 73.2/73.4 (OCH_3), 120.9/121.1 (C-3'), 122.7/122.9 (C-5'), 136.7 (C-4'), 148.5/148.6 (C-6'), 159.0/159.7 (C-2') and 173.2/173.3 (CO); m/z 241(M^+, 0.48%) and 109(100%)

Ethyl 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(116)**

Ethyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(87)** (1g, 4.8 mmol) and THF (5ml) were placed in a round-bottomed flask fitted out as described for the synthesis of 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(114)**. A 21% aqueous solution of sodium methylthiolate (1.53g, 5.3 mmol $NaSCH_3$) was added dropwise over a period of 5 minutes during which the temperature rose from 21° to 24°C. The reaction was stirred for a further 40 minutes after which the reaction mixture was worked up following the method used for methyl 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(114)**. Flash chromatography [elution with hexane-ethyl acetate (2:8) on silica] of the crude product afforded *ethyl 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate* **(116)**[§] as a colourless oil (0.42g, 33%); (Found: M^+ 255.0923. Calc. for $C_{12}H_{17}NO_3S$: *M*, 255.0928); ν_{max} (thin film)/cm^{-1} 3200 br (OH) and 1715 (CO); δ_H (400 MHz; $CDCl_3$) 1.10/1.24 (3H, 2×t, CH_2CH_3), 2.01/2.11 (3H, 2×s, SCH_3), 2.66-2.91 (2H, m, CH_2SCH_3), 3.06-3.18 (1H, m, *C*HCHOH), 3.98/4.07 (2H, 2×q, CH_2CH_3), 4.21 (1H, d, OH), 5.03 (1H, q, C*H*OH), 7.21 (1H, dd, 5'-H), 7.33 (1H, dd, 3'-H), 7.68 (1H, m, 4'-H) and 8.54 (1H, t, 6'-H); δ_C (100 MHz; $CDCl_3$) 13.8/15.9 (CH_2CH_3), 15.6

[§] Obtained as pairs of diastereomers.

(SCH_3), 31.3/32.7 (CH_2SCH_3), 51.5/52/7 (CH_2CH_3), 60.4/60.5 (*C*HCHOH), 73.2/73.3 (CHOH), 120.9 (C-3'), 122.4/122.6 (C-5'), 136.4/136.5 (C-4'), 148.3/148.4 (C-6'), 159.2/159.8 (C-2') and 172.4/172.6 (CO); m/z 108(100%).[¶]

3-Hydroxy-2-(methylthiomethyl)-3-(3-pyridyl)propanenitrile (117)

3-Hydroxy-2-methylene-3-(3-pyridyl)propanenitrile **(90)** (1g, 5 mmol) and THF (5ml) were placed in a three-necked round-bottomed flask fitted out as described for the synthesis of 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(114)**. A 21% aqueous solution of sodium thiomethylate (1.75g, 5.3 mmol) was added over a 5 minute period during which the temperature rose from 17° to 23°C. The reaction was stirred for a further 40 minutes and worked up following the procedure used for 3-hydroxy-2-(methylthiomethyl)-3-(3-pyridyl)propanoate **(114)**. Flash chromatography [elution with hexane-ethyl acetate (2:8) on silica] afforded *3-hydroxy-2-(methylthiomethyl)-3-(3-pyridyl)propanenitrile* **(117)**[§] as a yellow oil (0.37g, 35%); (Found: M^+ 208.0660. Calc. for $C_{10}H_{12}N_2OS$: *M* 208.0670); ν_{max} (thin film)/cm^{-1} 3450 (OH) and 2140 (CN); δ_H (400 MHz; $CDCl_3$) 2.15/2.16 (1H, s, SCH_3), 2.67-2.90 (1H, m, SCH_3), 2.97-3.15 (1H, m, C*H*CN), 4.98/5.05 (1H, d, C*H*OH), 6.02 (1H, br s, OH), 7.30 (1H, dd, 5'-H), 7.84 (1H, dd, 4'-H), 8.36 (1H, m, 6'-H) and 8.42 (1H, t, 2'-H); δ_C (100 MHz; $CDCl_3$) 16.2/16.3 (SCH_3), 32.4/33.4 (CH_2SCH_3), 41.3/41.6 (*C*HCHOH), 69.4/70.2 (CHOH), 118.6/119.0 (CN), 123.9 (C-3'), 134.6/135.0 (C-5'), 136.2/136.8 (C-4'), 147.2/147.6 (C-6') and 149.1/149.3 (C-2'); m/z 208(M^+, 1.86%) and 108(100%).

Methyl 3-hydroxy-2-(methylthiomethyl)-3-(3-pyridyl)propanoate (118)

Methyl 3-hydroxy-2-methylene-3-(3-pyridyl)propanoate **(91)** (1g, 4.9 mmol) and THF (5ml) were placed in a three-necked round-bottomed flask fitted out as described for the synthesis of 3-hydroxy-2-(methylthiomethyl)-3-(-pyridyl)propanoate **(114)**. A 21% aqueous solution of sodium methylthiolate (1.72ml, 5.1 mmol $NaSCH_3$) was added dropwise over a 5 minute period, during which the temperature rose from 18° to 23°C.

[¶] No molecular ion peak was detected in the low resolution mass spectrum

[§] Obtained as pairs of diastereomers.

The reaction was stirred for a further 35 minutes and worked up following the method for 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(114)**. The crude product was purified using flash chromatography [elution with hexane-ethyl acetate (2:8) on silica] to afford *methyl 3-hydroxy-2-(methylthiomethyl)-3-(3-pyridyl)propanoate* **(118)**[§] as a colourless oil (0.26g, 22%); (Found: M^+ 241.0783. Calc for $C_{11}H_{15}NO_3S$; *M*, 241.0772); ν_{max} (thin film)/cm^{-1} 3140 (OH) and 1720 (CO); δ_H (400 MHz; $CDCl_3$) 2.04 (3H, s, SCH_3), 2.60-2.91 (2H, m, C*H*CHOH), 2.97-3.02 (2H, m, C*H*$_2$SCH$_3$), 3.57/3.68 (3H, 2×s COOCH$_3$), 4.99 (1H, t, C*H*OH), 7.26 (1H, ddd, 5'-H), 7.69 (1H, dd, 4'-H), 8.42 (1H, dd, 6'-H) and 8.45 (1H, ddd, 2'-H); δ_C (100 MHz; $CDCl_3$) 15.9 (SCH_3), 32.0/33.2 (*C*H$_2$SCH$_3$), 51.9/52.1 (*C*HCHOH), 52.5/53.2 (OCH_3), 71.8/71.9 (CHOH), 123.4/123.6 (C-3'), 134.1/134.2 (C-4'), 137.1/137.3 (C-5'), 147.7/147.8 (C-2'), 148.9/149.1 (C-6') and 173.1/173.6 (CO) ; m/z 241(M^+, 22.9%) and 108(100%).

Ethyl 3-hydroxy-2-(methylthiomethyl)-3-(3-pyridyl)propanoate **(119)**

Ethyl 3-hydroxy-2-methylene-3-(3-pyridyl)propanoate **(92)** (1g, 4.6 mmol) and THF were placed in a three-necked round-bottomed flask fitted out as described for the synthesis of 3-hydroxy-2-(methylthiomethyl)-3-(-pyridyl)propanoate **(114)**. A 21% aqueous solution of sodium methylthiolate (1.61g, 4.8 mmol $NaSCH_3$) was added dropwise over a 5 minute period. During the addition the temperature rose from 21° to 23°C. The solution was stirred for a further 35 minutes during which the mixture became colourless. The reaction was worked up following the method used for 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(114)**. Flash chromatography [elution with hexane-ethyl acetate (2:8) on silica] of the crude material afforded *ethyl 3-hydroxy-2-(methylthiomethyl)-3-(3-pyridyl)propanoate* **(119)**[§] as a colourless oil (0.62g, 53%); (Found: M^+ 255.0916. Calc. for $C_{12}H_{17}NO_3S$; *M*, 255.0928); ν_{max} (thin film)/cm^{-1} 3180 (OH) and 1715 (CO); δ_H (400 MHz; $CDCl_3$) 1.01/1.14 (3H, 2×t, CH$_2$C*H*$_3$), 2.01/2.02 (3H, 2×s, SCH_3), 2.53-2.66 (1H, m, C*H*CHOH), 2.83-2.96 (2H, m, C*H*$_2$SCH$_3$), 3.93/4.05 (2H, 2×dddd, C*H*$_2$CH$_3$), 4.59/4.71 (1H, 2×br s, OH), 4.90/4.93 (1H, 2×d, C*H*OH), 7.19-7.25 (1H, m, 5'-H), 7.67 (1H, ddd, 4'-H) and 8.34-8.42 (2H, m, 2'-H and 6'-H); δ_C (100 MHz; $CDCl_3$); 13.9/14.0 (CH$_2$*C*H$_3$), 15.8/15.9 (SCH_3),

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[§] Obtained as pairs of diastereomers.

32.2/33.1 (CH_2SCH_3), 52.5/53.4 (*C*HCHOH), 60.9/61.1 (CH_2CH_3), 71.7/72.0 (CHOH), 123.3/123.5 (C-3'), 134.1/134.4 (C-5'), 137.4/137.5 (C-4'), 147.7/147.8 (C-6'), 148.8 (C-2') and 172.5/173.0 (CO); m/z 255(M^+, 11.9%) and 108(100%).

3-Hydroxy-2-(methylthiomethyl)-3-(4-pyridyl)propanenitrile **(120)**

3-Hydroxy-2-methylene-3-(4-pyridyl)propanenitrile **(93)** (1g, 5.3 mmol) and THF were placed in a three-necked round-bottomed flask fitted out as described for 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(114)**. A 21% aqueous solution of sodium methylthiolate (1.75g, 5.3 mmol $NaSCH_3$) was added to the solution over a five minute period during which the temperature rose from 21° to 25°C. The reaction was stirred for a further 45 minutes and worked up following the procedure for 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(114)**. Flash chromatography [elution with hexane-ethyl-acetate (2:8) on silica] of the crude material afforded *3-hydroxy-2-(methylthiomethyl)-3-(4-pyridyl)propanenitrile* **(120)**[§] as an orange oil (0.48g, 43%); (Found: M^+ 208.0670. Calc. for $C_{10}H_{12}N_2OS$: *M*, 208.0670); ν_{max} (thin film)/cm^{-1} 3260 br (OH) and 1710 (CO); δ_H (400MHz; $CDCl_3$) 2.15/2.16 (3H, 2×s, SCH_3), 2.63-2.90 (2H, m, CH_2SCH_3), 2.92-3.12 (1H, m, *C*HCHOH), 4.98/5.04 (1H, 2×d, C*H*OH), 7.37 (2H, d, 3'-H and 5'-H), 7.64 (2H, ddd, 2'-H and 6'-H); δ_C (100MHz; $CDCl_3$) 16.2/16.3 (SCH_3), 33.4 (CH_2SCH_3), 40.8/41.1 (*C*HCHOH), 70.1/71.0 (CHOH), 118.2/119.0 (CN), 121.3/121.7 (C-3' and C-5') and 149.5/150.4 (C-2' and C-6'); m/z 255(M^+, 27.2%) and 101(100%).

Methyl 3-hydroxy-2-(methylthiomethyl)-3-(4-pyridyl)propanoate **(121)**

Methyl 3-hydroxy-2-methylene-3-(4-pyridyl)propanoate **(94)** (1g, 4.9 mmol) and THF (10ml) were placed in a three-necked round-bottomed flask fitted as described for the synthesis of 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **(114)**. A 21% aqueous solution of sodium methylthiolate (1.72g, 5.2 mmol $NaSCH_3$) was added dropwise over a five minute period. During the addition the temperature rose from 18° to 21°C. The reaction was stirred for a further 45 minutes and worked up following the procedure

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[§] Obtained as pairs of diastereomers.

used for 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(114)**. The crude product was purified using flash chromatography [elution with hexane-ethyl acetate (2:8) on silica] to afford *methyl 3-hydroxy-2-(methylthiomethyl)-3-(4-pyridyl)propanoate* **(121)**[§] as a pale yellow oil (0.28g , 23%); (Found: M^+ 241.0788. Calc for $C_{11}H_{15}NO_3S$: *M*, 241.0772); ν_{max} (thin film)/cm^{-1} 3140 (OH) and 1730 (CO); δ_H (400 MHz; CDCl$_3$) 2.01/2.09 (3H, 2×s, SCH$_3$), 2.64-2.90 (2H, m, C*H*$_2$SCH$_3$), 2.97 (1H, m, C*H*CHOH), 3.63/3.64 (3H, 2×s, COOCH$_3$), 4.98/5.02 (1H, 2×d, C*H*OH), 7.27 (2H, dd, 3'-H and 5'-H) and 8.51 (2H, ddd, 2'-H and 6'-H); δ_C (100MHz; CDCl$_3$) 15.9 (SCH$_3$), 31.5/33.2 (*C*H$_2$SCH$_3$), 51.9/52.0 (OCH$_3$), 52.7 (*C*HCHOH), 72.3/72.5 (CHOH), 121.1/121.8 (C-3' and C-5'), 149.5/149.6 (C-2' and C-6') and 173.2/173.4 (CO); m/z 241(M^+, 37.9%) and 87(100%).

Ethyl 3-hydroxy-2-(methylthiomethyl)-3-(4-pyridyl)propanoate **(122)**

Ethyl 3-hydroxy-2-methylene-3-(4-pyridyl)propanoate **(95)** (1g, 4.6 mmol) and THF (10ml) were placed in a three-necked round-bottomed flask fitted out as described for the synthesis of 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(114)**. A 21% aqueous solution of sodium methylthiolate (1.61g, 4.8 mmol NaSCH$_3$) was added dropwise over a period of 5 minutes during which the temperature rose from 20° to 25°C. The reaction was allowed to stir for a further 40 minutes and worked up following the method used for 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(114)**. The crude material was purified using flash chromatography [elution with hexane-ethyl acetate (2:8) on silica] to afford *ethyl 3-hydroxy-2-(methylthiomethyl)-3-(4-pyridyl)propanoate* **(122)**[§] as a pale yellow oil (0.51g, 43%); (Found: M^+ 255.0920. Calc. for $C_{12}H_{17}NO_3S$: *M*, 255.0928); ν_{max} (thin film)/cm^{-1} 3350 (OH) and 1720 (CO); δ_H (400 MHz; CDCl$_3$) 1.08/1.12 (3H, 2×t, CH$_2$C*H*$_3$), 1.97/2.06 (3H, 2×s, SCH$_3$), 2.59-2.82 (2H, m, C*H*$_2$SCH$_3$), 2.90 (1H, m, C*H*CHOH), 3.70/3.80 (1H, 2×br s, OH), 4.02/4.10 (2H, 2×q, C*H*$_2$CH$_3$), 4.98 (1H, d, C*H*OH), 7.21 (2H, dd, 3'-H and 5'-H) and 8.48 (2H, d, 2'-H and 6'-H); δ_C (100 MHz; CDCl$_3$) 13.9 (CH$_2$*C*H$_3$), 15.8/15.9 (SCH$_3$), 31.5/33.3 (*C*H$_2$SCH$_3$), 51.6/52.5 (*C*HCHOH), 61.2/61.2 (*C*H$_2$CH$_3$), 72.1/72.5 (CHOH), 121.4/121.6 (C-3' and C-5'), 148.6 (C-2' and C-6') and 172.7/172.9 (CO); m/z 208(M^+,

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[§] Obtained as pairs of diastereomers.

65%) and 108(100%).

Ethyl 2-(methylthiomethyl)-3-(2-pyridyl)-2-propenoate **(123)**

Ethyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(103)** (1g, 4.0 mmol) and THF (5ml) were placed in a three-necked round-bottomed flask fitted out as described for 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(114)**. A 21% aqueous solution of sodium methylthiolate (0.42g, 6.0 mmol $NaSCH_3$) was added to the solution over a five minute period during which the temperature rose from 21.5 to 26 C. The reaction was stirred for a further 30 minutes and worked up following the procedure for 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(114)**. Flash chromatography [elution with hexane-ethyl-acetate (2:8) on silica] of the crude material afforded *ethyl 2-(methylthiomethyl)-3-(2-pyridyl)-2-propeneoate* **(123)** as an orange oil (0.49g, 52%); (Found: M$^+$ 237.0828. Calc. for $C_{12}H_{15}NO_2S$: *M*, 237.0823); ν_{max} (thin film)/cm^{-1} 1715 (CO); δ_H (400MHz; $CDCl_3$) 1.37 (3H, t, $CH_2\mathit{CH}_3$), 2.03 (3H, s, SCH_3), 4.12 (2H, s, CH_2SCH_3), 4.31 (2H, q, CH_2CH_3), 7.20 (1H, dddd, 5'-H), 7.39 (1H, d, 3'-H), 7.6 (1H, s, C=CH), 7.69 (1H, ddd, 4'-H) and 8.65 (1H, dd, 6'-H); δ_C (100MHz; $CDCl_3$) 13.8 ($CH_2\mathit{CH}_3$), 14.1 (SCH_3), 28.8 (CH_2SCH_3), 61.1 (CH_2CH_3), 122.9 (C-3'), 126.4 (C-5'), 133.5 (C=*C*H), 136.2 (C-4'), 136.3 (C-6'), 154.2 (*C*=CH) and 167.4 (CO); m/z 237(M$^+$, 52%) and 117(100%).

Isopropyl 2-(methylthiomethyl)-3-(2-pyridyl)-2-propenoate **(124)**

Isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(104)** (0.4g, 1.5 mmol) and THF (5ml) were placed in a three-necked round-bottomed flask fitted out as described for 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(114)**. A 21% aqueous solution of sodium methylthiolate (0.23g, 3.3 mmol $NaSCH_3$) was added to the solution over a five minute period during which the temperature rose from 20 to 23.5 C. The reaction was stirred for a further 35 minutes and worked up following the procedure for 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate **(114)**. Flash chromatography [elution with hexane-ethyl-acetate (2:8) on silica] of the crude material afforded *isopropyl 2-(methylthiomethyl)-3-(2-pyridyl)-2-propeneoate* **(124)** as an orange-brown oil (0.19g, 51%); (Found: M^+ 251.0999. Calc. for $C_{13}H_{17}NO_2S$: *M*, 251.0999); ν_{max} (thin film)/cm^{-1} 1715 (CO); δ_H (400MHz; $CDCl_3$) 1.33 [6H, d, $CH(CH_3)_2$], 2.03 (3H, s, SCH_3), 4.20 (2H, s, CH_2SCH_3), 5.16 [1H, sep, $CH(CH_3)_2$], 7.19 (1H, dddd, 5'-H), 7.39 (1H, d, 3'-H), 7.57 (1H, s, C=CH), 7.66 (1H, ddd, 4'-H) and 8.64 (1H, d, 6'-H); δ_C (100MHz; $CDCl_3$) 15.1 (SCH_3), 21.6 [$CH(CH_3)_2$], 28.8 (CH_2SCH_3), 68.5 [$CH(CH_3)_2$], 122.8 (C-3'), 122.8 (C-5'), 133.9 (CH=C), 135.9 (C-4'), 136.2 (C-6'), 154.2 (C-2') and 166.9 (CO); m/z 251(M^+, 38.5%) and 117(100%).

3.3 Kinetic Studies

3.3.1 General procedure

All kinetic runs were recorded on a Bruker AMX400 spectrometer fitted with a variable temperature unit. The spectra were calibrated using the solvent peak (DMSO-d_6; δ_H 2.50 ppm), and were collected, phased and calibrated using automatic routines. Where necessary, individual peaks were integrated manually.

Samples were prepared by weighing out the required amount of material in a 1ml graduated NMR tube and the samples were made up to 0.6 ml with DMSO-d_6. Prior to insertion of the sample the probe was heated to the desired temperature and allowed to equilibrate for 5 minutes. The sample was inserted into the probe at t_0 and 32-scan spectra were acquired every 5 minutes. Twenty spectra were run for each sample.

The ratios of product to reactant were obtained by measuring the integrals of suitable pairs of peaks in the spectra. The *O*-alkyl peaks and the acetate peaks were usually used because they were well separated. Using the concentration of substrate [S], plots of [S] against t and ln[S] against t were obtained. For plots of ln[S] against t excellent linear correlations ($R^2 \geq 0.99$) were obtained.

3.3.2 Kinetic Data and Graphs

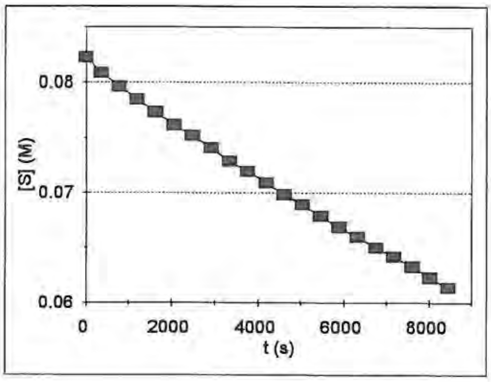
a)

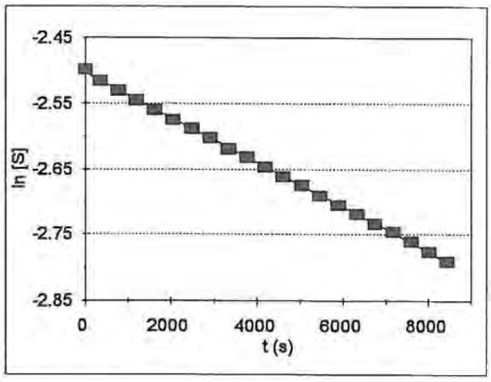
Expt. No.	**t (s)**	**[S] (M)**	**ln[S]**	**Regress.**
	0	0.08226	-2.49787	-2.502996
100	355	0.0808616	-2.515016	-2.515108
101	781	0.0796277	-2.530394	-2.529643
102	1207	0.078476	-2.544962	-2.544178
103	1633	0.0773244	-2.559746	-2.558713
104	2059	0.0761728	-2.574751	-2.573248
105	2485	0.0751856	-2.587795	-2.587783
106	2911	0.0741163	-2.60212	-2.602317
107	3337	0.0728824	-2.618909	-2.616852
108	3763	0.0719775	-2.631402	-2.631387
109	4189	0.0709081	-2.64637	-2.645922
110	4615	0.0698387	-2.661566	-2.660457
111	5041	0.0689339	-2.674607	-2.674992
112	5467	0.0678645	-2.690242	-2.689527
113	5893	0.0668774	-2.704894	-2.704061
114	6319	0.0659725	-2.718517	-2.718596
115	6745	0.0649854	-2.733593	-2.733131
116	7171	0.0641628	-2.746332	-2.747666
117	7597	0.0632579	-2.760535	-2.762201
118	8023	0.0622708	-2.776262	-2.776736
119	8449	0.061366	-2.7909	-2.79127

Regression Output:

Constant	-2.502996
Std Err of Y Est	0.001504
R Squared	0.9997347
No. of Observations	21
Degrees of Freedom	19

X Coefficient(s)	-3.41E-05
Std Err of Coef.	1.28E-07





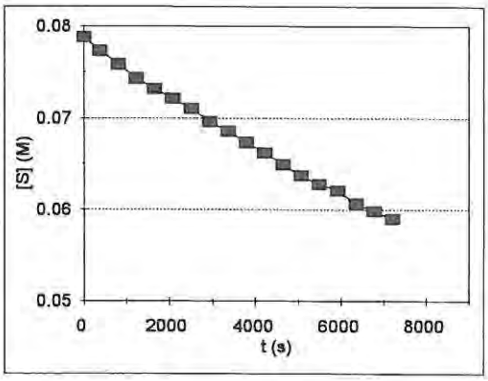
b)

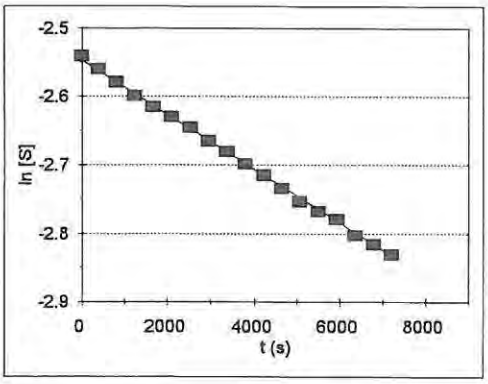
Expt. No.	**t (s)**	**[S] (M)**	**ln[S]**	**Regress.**
	0	0.0788	-2.540842	-2.502996
100	389	0.0773107	-2.559923	-2.516268
101	815	0.0758371	-2.579167	-2.530803
102	1241	0.0743005	-2.599637	-2.545338
103	1667	0.0731422	-2.61535	-2.559873
104	2093	0.0721099	-2.629564	-2.574408
105	2519	0.0709909	-2.645203	-2.588943
106	2945	0.0695962	-2.665046	-2.603478
107	3371	0.0685402	-2.680334	-2.618012
108	3797	0.0673267	-2.698198	-2.632547
109	4223	0.0662078	-2.714958	-2.647082
110	4649	0.0649391	-2.734306	-2.661617
111	5075	0.0637177	-2.753293	-2.676152
112	5501	0.0627721	-2.768245	-2.690687
113	5927	0.0620865	-2.779226	-2.705221
114	6353	0.0606366	-2.802857	-2.719756
115	6779	0.0598565	-2.815806	-2.734291
116	7205	0.0589739	-2.83066	-2.748826
117	7631	0.0580126	-2.847096	-2.763361
118	8057	0.0572403	-2.860497	-2.777896
119	8483	0.0561056	-2.88052	-2.792431

Regression Output:

Constant	-2.547227
Std Err of Y Est	0.0031274
R Squared	0.9991487
No. of Observations	21
Degrees of Freedom	19

X Coefficient(s)	-3.96E-05
Std Err of Coef.	2.65E-07





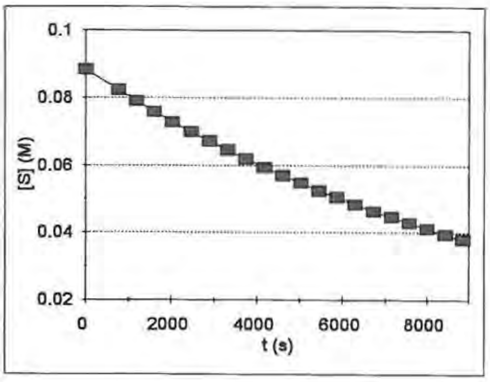
Kinetic data for duplicate runs for the cyclisation of 3-acetoxy-2-methylene-3-(2-pyridyl) propanenitrile **(100)** at 363K using the CO.CH_3/acetic acid integrals.

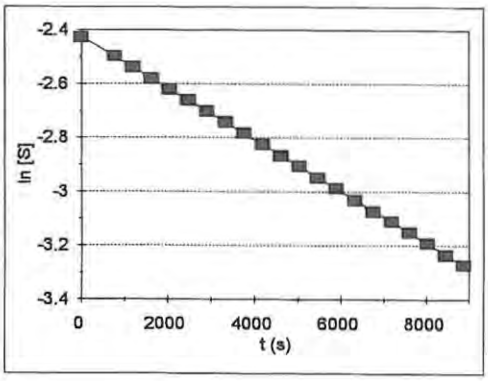
a)

Expt. No.	t (s)	[S]	ln[S]	Regress.
	0	0.08833	-2.426675	-2.42422
100	776	0.0823236	-2.497098	-2.49849
101	1202	0.078967	-2.538725	-2.539262
102	1628	0.0756988	-2.580993	-2.580034
103	2054	0.0727839	-2.62026	-2.620806
104	2480	0.069869	-2.661133	-2.661578
105	2906	0.0671308	-2.701112	-2.70235
106	3332	0.0644809	-2.741386	-2.743122
107	3758	0.061831	-2.78335	-2.783894
108	4184	0.0593578	-2.824172	-2.824666
109	4610	0.0568845	-2.866732	-2.865438
110	5036	0.0547646	-2.904711	-2.90621
111	5462	0.0523797	-2.949236	-2.946982
112	5888	0.0504364	-2.987042	-2.987754
113	6314	0.0483165	-3.029982	-3.028526
114	6740	0.0462849	-3.072939	-3.069298
115	7166	0.0446067	-3.109872	-3.11007
116	7592	0.0428401	-3.150282	-3.150842
117	8018	0.0411618	-3.190245	-3.191615
118	8444	0.0393952	-3.234112	-3.232387
119	8870	0.0379819	-3.270646	-3.273159

Regression Output:

Constant	-2.42422
Std Err of Y Est	0.0016409
R Squared	0.9999609
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-9.57E-05
Std Err of Coef.	1.37E-07



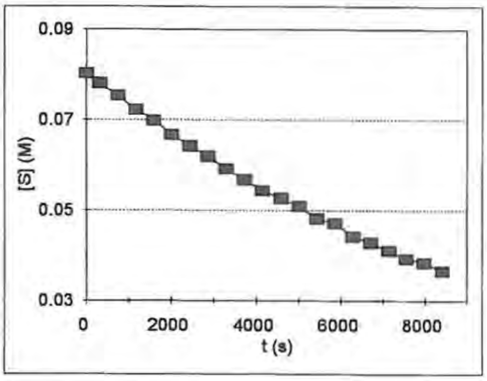


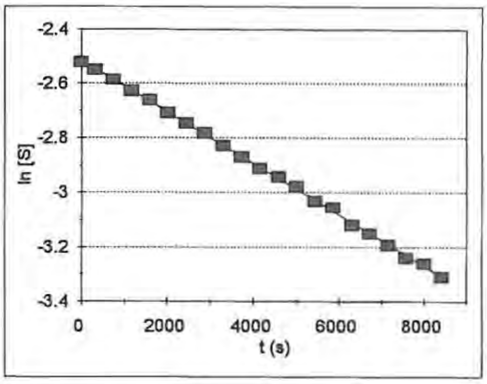
b)

Expt. No.	t (s)	[S]	ln[S]	Regress.
	0	0.0802	-2.523232	-2.42422
100	321	0.0780346	-2.550603	-2.454942
101	747	0.0752276	-2.587237	-2.495714
102	1173	0.07218	-2.628592	-2.536486
103	1599	0.069774	-2.662494	-2.577258
104	2025	0.0666462	-2.708357	-2.61803
105	2451	0.06416	-2.746375	-2.658802
106	2877	0.0619144	-2.782002	-2.699575
107	3303	0.0591074	-2.828399	-2.740347
108	3729	0.0567816	-2.868543	-2.781119
109	4155	0.0543756	-2.91184	-2.821891
110	4581	0.0526914	-2.943303	-2.862663
111	5007	0.050927	-2.977362	-2.903435
112	5433	0.0482002	-3.032392	-2.944207
113	5859	0.0471576	-3.05426	-2.984979
114	6285	0.0441902	-3.119252	-3.025751
115	6711	0.0428268	-3.150591	-3.066523
116	7137	0.0410624	-3.192662	-3.107295
117	7563	0.0392178	-3.238625	-3.148067
118	7989	0.0384158	-3.259286	-3.188839
119	8415	0.036491	-3.31069	-3.229611

Regression Output:

Constant	-2.517128
Std Err of Y Est	0.0065362
R Squared	0.9993396
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-9.41E-05
Std Err of Coef.	5.55E-07





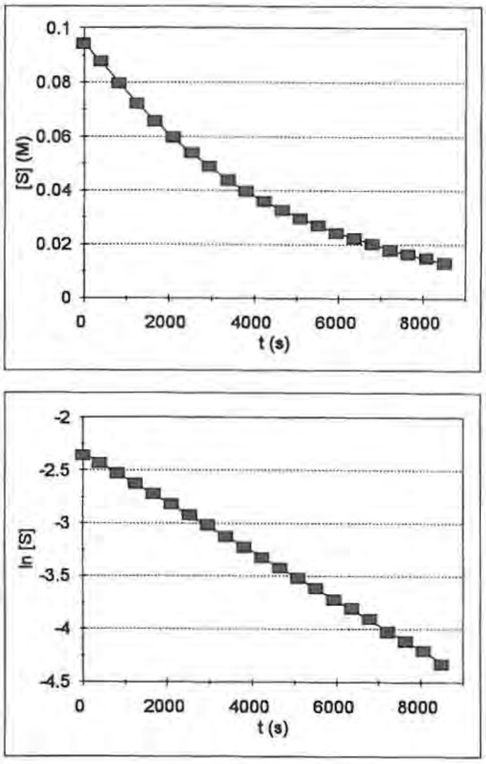
Kinetic data for duplicate runs for the cyclisation of 3-acetoxy-2-methylene-3-(2-pyridyl) propanenitrile **(100)** at 373K using the CO.CH_3/acetic acid integrals.

a)

Expt. No.	t	[S] (M)	ln [S]	Regress.
	0	0.0942	-2.362335	-2.337632
100	408	0.0876625	-2.434261	-2.432458
101	834	0.079712	-2.529335	-2.531468
102	1260	0.072176	-2.628647	-2.630478
103	1686	0.065582	-2.724453	-2.729488
104	2112	0.0595438	-2.821043	-2.828497
105	2538	0.0538447	-2.921651	-2.927507
106	2964	0.0490028	-3.015877	-3.026517
107	3390	0.0438407	-3.127193	-3.125527
108	3816	0.0396865	-3.226745	-3.224537
109	4242	0.035975	-3.324932	-3.323546
110	4668	0.032612	-3.423074	-3.422556
111	5094	0.0296353	-3.518788	-3.521566
112	5520	0.0269506	-3.613749	-3.620576
113	5946	0.024134	-3.724132	-3.719585
114	6372	0.0222124	-3.807106	-3.818595
115	6798	0.0201023	-3.906922	-3.917605
116	7224	0.0178038	-4.028343	-4.016615
117	7650	0.0162589	-4.119114	-4.115625
118	8076	0.0148836	-4.207495	-4.214634
119	8502	0.0131221	-4.33346	-4.313644

Regression Output:

Constant		-2.337632
Std Err of Y Est		0.0096631
R Squared		0.9997648
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000232	
Std Err of Coef.	8.18E-07	

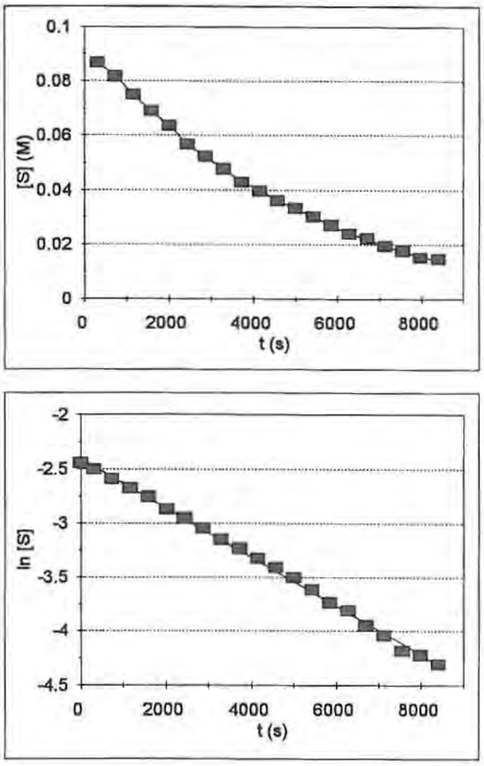


b)

Expt. No	Time	[S] (M)	ln [S]	Regress.
	0	0.08675	-2.444725	-2.409645
100	311	0.0816925	-2.504793	-2.479977
101	737	0.0748739	-2.59195	-2.576317
102	1163	0.0688188	-2.676279	-2.672656
103	1589	0.0634576	-2.757383	-2.768995
104	2015	0.0565784	-2.872129	-2.865334
105	2441	0.0521541	-2.953552	-2.961673
106	2867	0.0476344	-3.0442	-3.058013
107	3293	0.0428892	-3.149135	-3.154352
108	3719	0.0396014	-3.228891	-3.250691
109	4145	0.0360186	-3.32372	-3.34703
110	4571	0.0331819	-3.405751	-3.443369
111	4997	0.0301543	-3.501428	-3.539709
112	5423	0.0269879	-3.612366	-3.636048
113	5849	0.0238649	-3.735345	-3.732387
114	6275	0.0221473	-3.810041	-3.828726
115	6701	0.0192759	-3.948902	-3.925065
116	7127	0.0175929	-4.04026	-4.021405
117	7553	0.0152333	-4.184271	-4.117744
118	7979	0.0146781	-4.221399	-4.214083
119	8405	0.0134723	-4.307121	-4.310422

Regression Output:

Constant		-2.409645
Std Err of Y Est		0.0259563
R Squared		0.9981996
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000226	
Std Err of Coef.	2.2E-06	



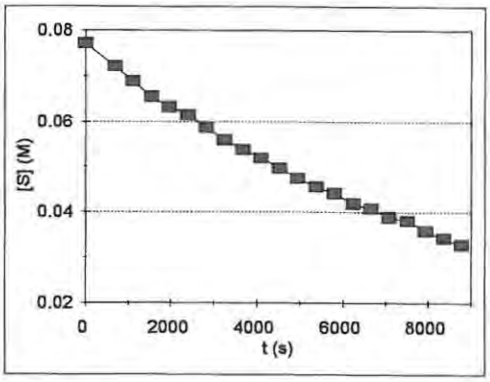
Kinetic data for duplicate runs for the cyclisation of 3-acetoxy-2-methylene-3-(2-pyridyl) propanenitrile **(100)** at 383K using the $CO.CH_3$/acetic acid integrals.

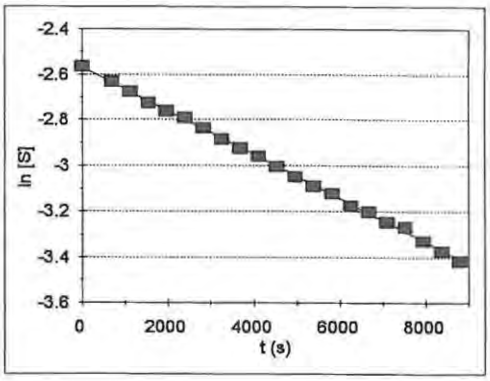
a)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.07716	-2.561874	-2.567504
100	698	0.07211	-2.629563	-2.63448
101	1124	0.06888	-2.675389	-2.675357
102	1550	0.06547	-2.726163	-2.716234
103	1976	0.06317	-2.761926	-2.757111
104	2402	0.06144	-2.789694	-2.797988
105	2828	0.05868	-2.835656	-2.838865
106	3254	0.05587	-2.884728	-2.879742
107	3680	0.05372	-2.92397	-2.920619
108	4106	0.05186	-2.959207	-2.961496
109	4532	0.04959	-3.003966	-3.002373
110	4958	0.0474	-3.049133	-3.04325
111	5384	0.04554	-3.089164	-3.084127
112	5810	0.04409	-3.121522	-3.125004
113	6236	0.04179	-3.175098	-3.16588
114	6662	0.04072	-3.201036	-3.206757
115	7088	0.03889	-3.247018	-3.247634
116	7514	0.03804	-3.269117	-3.288511
117	7940	0.03584	-3.328691	-3.329388
118	8366	0.03427	-3.373485	-3.370265
119	8792	0.0328	-3.417327	-3.411142

Regression Output:

Constant	-2.567504
Std Err of Y Est	0.0069435
R Squared	0.9993005
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-9.6E-05
Std Err of Coef.	5.82E-07



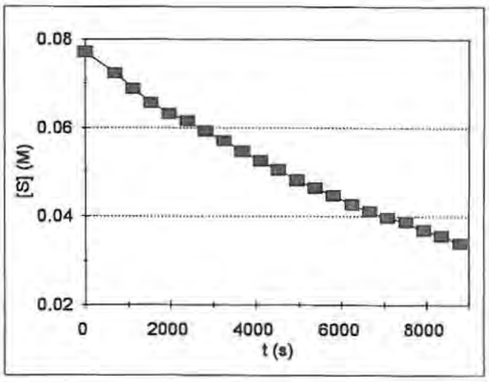


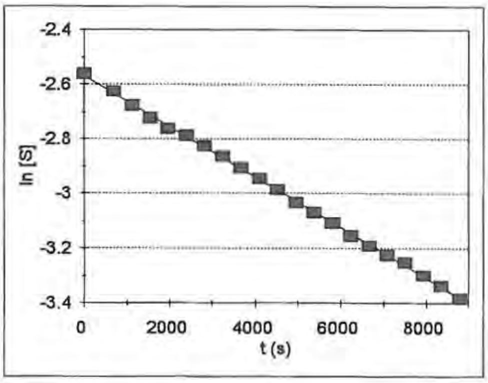
b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.07716	-2.561874	-2.569113
100	698	0.07234	-2.626378	-2.633574
101	1124	0.06882	-2.676261	-2.672916
102	1550	0.06564	-2.72357	-2.712257
103	1976	0.06315	-2.762242	-2.751599
104	2402	0.0616	-2.787093	-2.79094
105	2828	0.05924	-2.826158	-2.830282
106	3254	0.05707	-2.863477	-2.869623
107	3680	0.05471	-2.905709	-2.908965
108	4106	0.05254	-2.94618	-2.948306
109	4532	0.05051	-2.985584	-2.987648
110	4958	0.04817	-3.033019	-3.026989
111	5384	0.04643	-3.069809	-3.066331
112	5810	0.04473	-3.107111	-3.105672
113	6236	0.04267	-3.154259	-3.145014
114	6662	0.04113	-3.191017	-3.184355
115	7088	0.03976	-3.224894	-3.223697
116	7514	0.03869	-3.252174	-3.263038
117	7940	0.03691	-3.299273	-3.30238
118	8366	0.03556	-3.336534	-3.341721
119	8792	0.03395	-3.382866	-3.381063

Regression Output:

Constant	-2.569113
Std Err of Y Est	0.0064289
R Squared	0.9993526
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-9.24E-05
Std Err of Coef.	5.39E-07





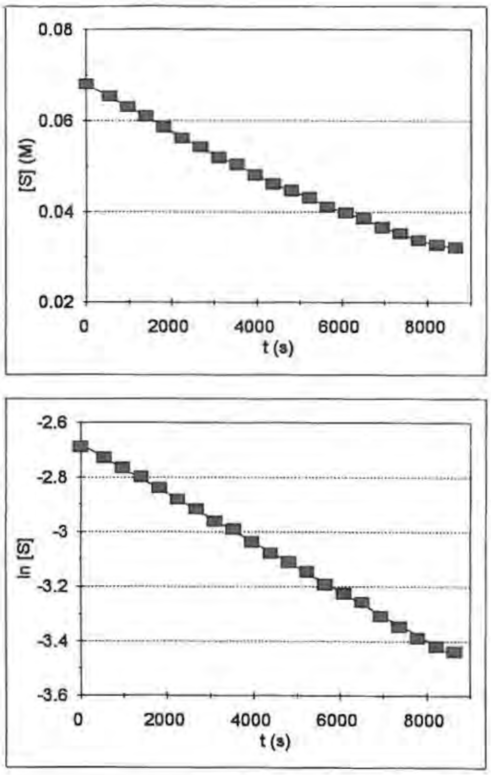
Kinetic data for the cyclisation of methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(102)** at 363K using a) the CO.CH_3/acetic acid and b) the OCH_3 integrals.

a)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.06802	-2.687953	-2.678938
100	553	0.06533	-2.728304	-2.728513
101	979	0.06293	-2.765732	-2.766703
102	1405	0.06093	-2.79803	-2.804892
103	1831	0.05851	-2.838558	-2.843082
104	2257	0.05607	-2.881154	-2.881271
105	2683	0.05416	-2.915813	-2.919461
106	3109	0.05178	-2.960751	-2.957651
107	3535	0.05027	-2.990347	-2.99584
108	3961	0.04798	-3.036971	-3.03403
109	4387	0.04606	-3.07781	-3.07222
110	4813	0.04464	-3.109125	-3.110409
111	5239	0.04311	-3.144	-3.148599
112	5665	0.0411	-3.191747	-3.186789
113	6091	0.03975	-3.225145	-3.224978
114	6517	0.03856	-3.25554	-3.263168
115	6943	0.0366	-3.307707	-3.301358
116	7369	0.03524	-3.345573	-3.339547
117	7795	0.03374	-3.389071	-3.377737
118	8221	0.03277	-3.418242	-3.415927
119	8647	0.03214	-3.437654	-3.454116

Regression Output:

Constant	-2.678938
Std Err of Y Est	0.0066091
R Squared	0.9992673
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-8.96E-05
Std Err of Coef.	5.57E-07

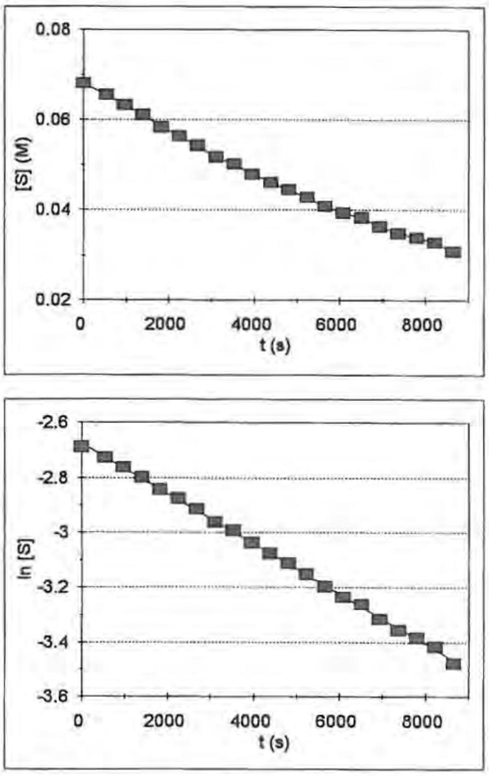


b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.06802	-2.687953	-2.674351
100	553	0.06544	-2.726622	-2.72492
101	979	0.06318	-2.761767	-2.763876
102	1405	0.06096	-2.797537	-2.802832
103	1831	0.05828	-2.842496	-2.841787
104	2257	0.05636	-2.875996	-2.880743
105	2683	0.05427	-2.913784	-2.919699
106	3109	0.05174	-2.961524	-2.958655
107	3535	0.0502	-2.99174	-2.99761
108	3961	0.04799	-3.036763	-3.036566
109	4387	0.04615	-3.075858	-3.075522
110	4813	0.04451	-3.112041	-3.114477
111	5239	0.04279	-3.151451	-3.153433
112	5665	0.04089	-3.19687	-3.192389
113	6091	0.03937	-3.234751	-3.231345
114	6517	0.03836	-3.26074	-3.2703
115	6943	0.03636	-3.314286	-3.309256
116	7369	0.03491	-3.354982	-3.348212
117	7795	0.03392	-3.38375	-3.387168
118	8221	0.03284	-3.416108	-3.426123
119	8647	0.03089	-3.477323	-3.465079

Regression Output:

Constant	-2.674351
Std Err of Y Est	0.0064369
R Squared	0.999332
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-9.14E-05
Std Err of Coef.	5.42E-07



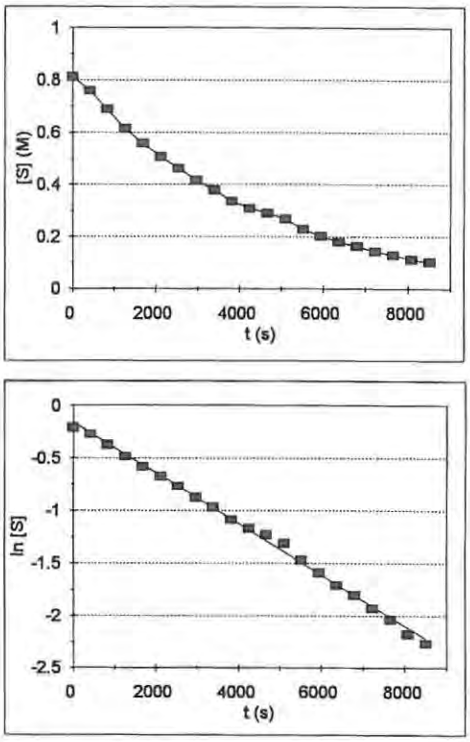
Kinetic data for the cyclisation of methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(102)** at 363K using a) the CO.CH_3/acetic acid and b) the OCH_3 integrals (duplicate run).

a)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.8118	-0.208501	-0.155505
101	415	0.7598	-0.2747	-0.256129
102	841	0.6884	-0.373385	-0.359419
103	1267	0.6145	-0.486946	-0.462709
104	1693	0.5585	-0.582501	-0.566
105	2119	0.5074	-0.678456	-0.66929
106	2545	0.4619	-0.772407	-0.77258
107	2971	0.4156	-0.878032	-0.875871
108	3397	0.3791	-0.969955	-0.979161
109	3823	0.337	-1.087672	-1.082452
110	4249	0.3101	-1.17086	-1.185742
111	4675	0.2914	-1.233058	-1.289032
112	5101	0.2695	-1.311187	-1.392323
113	5527	0.2297	-1.470981	-1.495613
114	5953	0.2038	-1.590616	-1.598903
115	6379	0.181	-1.709258	-1.702194
116	6805	0.1648	-1.803023	-1.805484
117	7231	0.1453	-1.928955	-1.908775
118	7657	0.1307	-2.034851	-2.012065
119	8083	0.1136	-2.175072	-2.115355
120	8509	0.1039	-2.264326	-2.218646

Regression Output:

Constant	-0.155505
Std Err of Y Est	0.040327
R Squared	0.99625
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-0.000242
Std Err of Coef.	3.41E-06

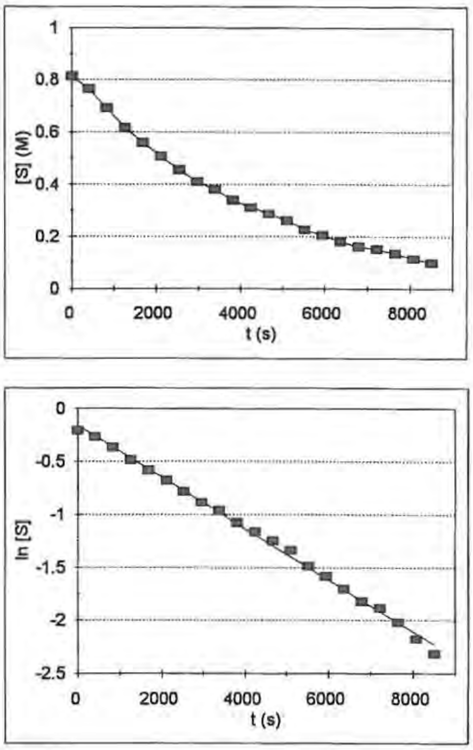


b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.8118	-0.208501	-0.16181
101	415	0.7639	-0.269318	-0.262549
102	841	0.6908	-0.369905	-0.365957
103	1267	0.6145	-0.486946	-0.469366
104	1693	0.5577	-0.583934	-0.572775
105	2119	0.5066	-0.680034	-0.676183
106	2545	0.4554	-0.786579	-0.779592
107	2971	0.41	-0.891598	-0.883001
108	3397	0.3807	-0.965744	-0.986409
109	3823	0.3401	-1.078516	-1.089818
110	4249	0.3117	-1.165714	-1.193227
111	4675	0.2874	-1.24688	-1.296635
112	5101	0.2622	-1.338648	-1.400044
113	5527	0.2257	-1.488549	-1.503453
114	5953	0.2054	-1.582796	-1.606862
115	6379	0.1818	-1.704848	-1.71027
116	6805	0.1615	-1.82325	-1.813679
117	7231	0.1518	-1.885191	-1.917088
118	7657	0.1331	-2.016655	-2.020496
119	8083	0.1137	-2.174192	-2.123905
120	8509	0.099	-2.312635	-2.227314

Regression Output:

Constant	-0.16181
Std Err of Y Est	0.03413
R Squared	0.997317
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-0.000243
Std Err of Coef.	2.89E-06



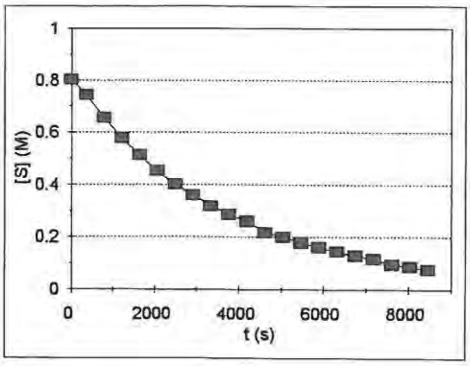
Kinetic data for the cyclisation of methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(102)** at 373K using a) the CO.CH_3/acetic acid and b) the OCH_3 integrals (10× normal concentration).

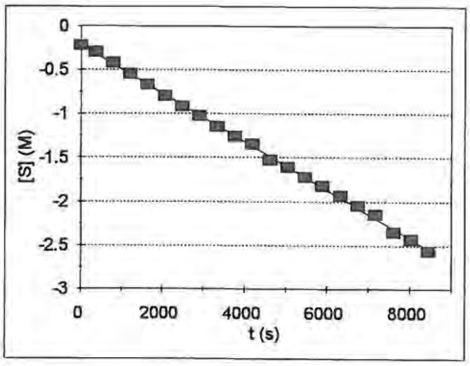
a)

Expt. No.	Time (s)	[S] (M)	ln [S]	Regress.
	0	0.8037	-0.218529	-0.213493
101	363	0.7437	-0.296118	-0.313502
102	789	0.6564	-0.420985	-0.430868
103	1215	0.5775	-0.549047	-0.548234
104	1641	0.5134	-0.6667	-0.6656
105	2067	0.4521	-0.793852	-0.782966
106	2493	0.4001	-0.916041	-0.900332
107	2919	0.3597	-1.022485	-1.017698
108	3345	0.3177	-1.146648	-1.135064
109	3771	0.2851	-1.254915	-1.25243
110	4197	0.2602	-1.346305	-1.369796
111	4623	0.2174	-1.526016	-1.487162
112	5049	0.2	-1.609438	-1.604528
113	5475	0.1786	-1.722607	-1.721894
114	5901	0.1616	-1.822631	-1.83926
115	6327	0.1451	-1.930332	-1.956626
116	6753	0.1292	-2.046394	-2.073992
117	7179	0.1173	-2.143021	-2.191358
118	7605	0.0952	-2.351775	-2.308724
119	8031	0.0878	-2.432694	-2.42609
120	8457	0.0768	-2.566551	-2.543456

Regression Output:

Constant		-0.213493
Std Err of Y Est		0.022406
R Squared		0.999098
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000276	
Std Err of Coef.	1.9E-06	



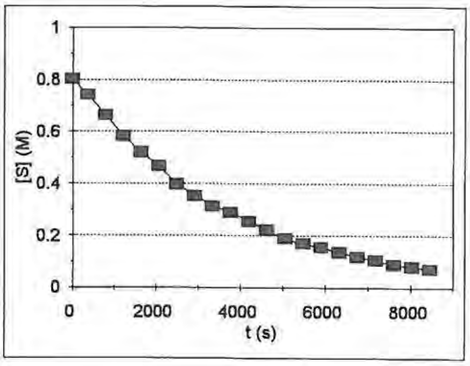


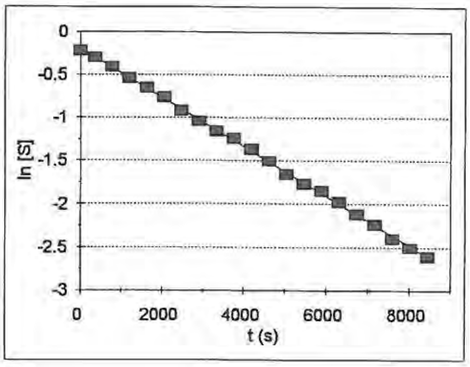
b)

Expt. No.	Time (s)	[S] (M)	ln [S]	Regress.
	0	0.8037	-0.218529	-0.190113
101	363	0.7431	-0.296925	-0.294008
102	789	0.6639	-0.409624	-0.415934
103	1215	0.5839	-0.538026	-0.537861
104	1641	0.5207	-0.652581	-0.659788
105	2067	0.4675	-0.760356	-0.781714
106	2493	0.3981	-0.921052	-0.903641
107	2919	0.353	-1.041287	-1.025567
108	3345	0.3138	-1.158999	-1.147494
109	3771	0.2895	-1.2396	-1.26942
110	4197	0.2555	-1.364533	-1.391347
111	4623	0.2225	-1.502828	-1.513273
112	5049	0.1903	-1.659154	-1.6352
113	5475	0.1705	-1.76902	-1.757126
114	5901	0.1574	-1.848965	-1.879053
115	6327	0.1383	-1.97833	-2.000979
116	6753	0.1201	-2.119431	-2.122906
117	7179	0.1068	-2.236797	-2.244833
118	7605	0.0907	-2.400198	-2.366759
119	8031	0.0813	-2.509609	-2.488686
120	8457	0.0735	-2.61047	-2.610612

Regression Output:

Constant		-0.190113
Std Err of Y Est		0.019908
R Squared		0.99934
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000286	
Std Err of Coef.	1.69E-06	





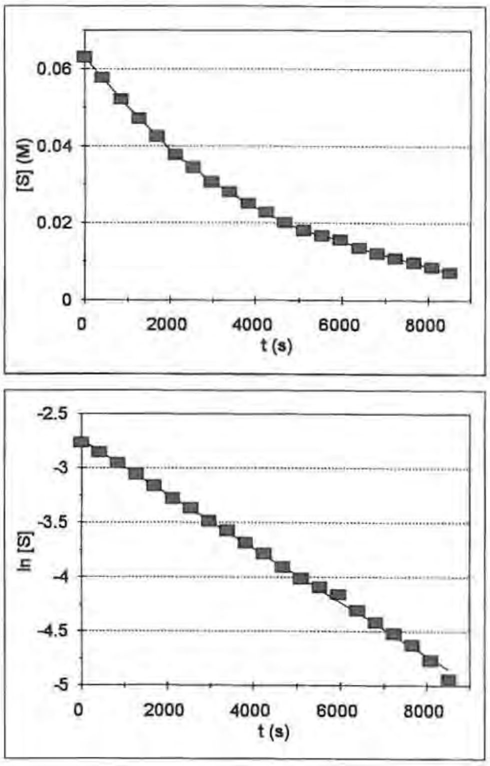
Kinetic data for the cyclisation of methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(102)** at 373K using a) the CO.CH_3/acetic acid and b) the OCH_3 integrals (10× normal concentration; duplicate run).

a)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.06303	-2.764144	-2.738107
100	423	0.05778	-2.851113	-2.84314
101	849	0.05223	-2.952098	-2.948918
102	1275	0.04711	-3.05527	-3.054697
103	1701	0.04246	-3.159193	-3.160475
104	2127	0.03772	-3.277565	-3.266253
105	2553	0.03448	-3.367376	-3.372031
106	2979	0.03068	-3.484144	-3.477809
107	3405	0.02811	-3.57163	-3.583587
108	3831	0.02509	-3.685286	-3.689366
109	4257	0.02273	-3.78407	-3.795144
110	4683	0.02011	-3.906538	-3.900922
111	5109	0.01807	-4.013502	-4.0067
112	5535	0.01672	-4.09115	-4.112478
113	5961	0.01565	-4.157284	-4.218256
114	6387	0.01348	-4.306548	-4.324034
115	6813	0.01209	-4.415377	-4.429813
116	7239	0.01087	-4.521749	-4.535591
117	7665	0.00979	-4.626394	-4.641369
118	8091	0.0085	-4.767689	-4.747147
119	8517	0.00715	-4.940643	-4.852925

Regression Output:

Constant		-2.738107
Std Err of Y Est		0.0276465
R Squared		0.9983169
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000248	
Std Err of Coef.	2.34E-06	

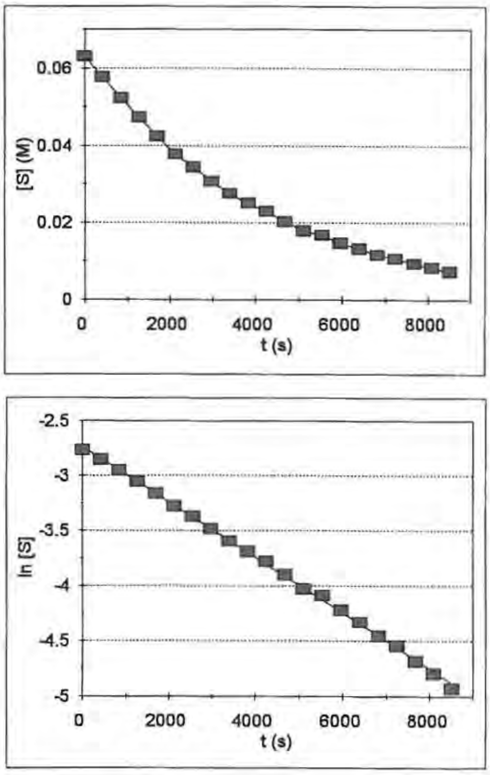


b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.06303	-2.764144	-2.733429
100	423	0.05769	-2.852671	-2.840096
101	849	0.0523	-2.950759	-2.94752
102	1275	0.04727	-3.051879	-3.054943
103	1701	0.04236	-3.161551	-3.162367
104	2127	0.03772	-3.277565	-3.26979
105	2553	0.03436	-3.370862	-3.377214
106	2979	0.03069	-3.483818	-3.484637
107	3405	0.0275	-3.593569	-3.592061
108	3831	0.02497	-3.69008	-3.699484
109	4257	0.02284	-3.779242	-3.806908
110	4683	0.02026	-3.899107	-3.914332
111	5109	0.01781	-4.027995	-4.021755
112	5535	0.01675	-4.089357	-4.129179
113	5961	0.01467	-4.221951	-4.236602
114	6387	0.01315	-4.331334	-4.344026
115	6813	0.01162	-4.455028	-4.451449
116	7239	0.01065	-4.542195	-4.558873
117	7665	0.00926	-4.682051	-4.666297
118	8091	0.00828	-4.793912	-4.77372
119	8517	0.00725	-4.926754	-4.881144

Regression Output:

Constant		-2.733429
Std Err of Y Est		0.0196538
R Squared		0.9991746
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000252	
Std Err of Coef.	1.66E-06	



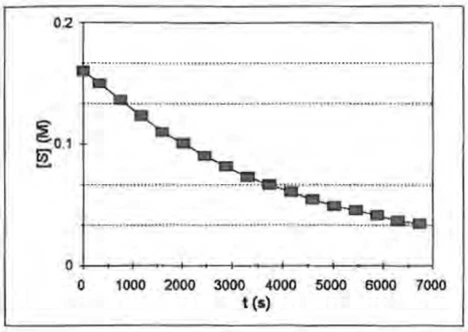
Kinetic data for the cyclisation of methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(102)** at 373K using a) the CO.CH_3/acetic acid and b) the OCH_3 integrals.

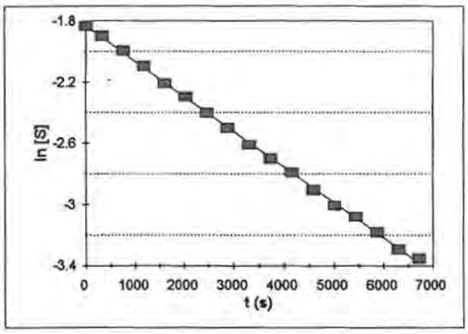
a)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.16	-1.832581	-1.830214
100	333	0.1499	-1.897787	-1.907305
101	759	0.1361	-1.994365	-2.005926
102	1185	0.1232	-2.093946	-2.104547
103	1611	0.1098	-2.209095	-2.203168
104	2037	0.1005	-2.297598	-2.301789
105	2463	0.0903	-2.404618	-2.40041
106	2889	0.0818	-2.503478	-2.499031
107	3315	0.0732	-2.61456	-2.597652
108	3741	0.0669	-2.704556	-2.696273
109	4167	0.0612	-2.793608	-2.794894
110	4593	0.0546	-2.907721	-2.893515
111	5019	0.0493	-3.009831	-2.992136
112	5445	0.0459	-3.08129	-3.090757
113	5871	0.0414	-3.184474	-3.189378
114	6297	0.037	-3.296837	-3.287999
115	6723	0.0349	-3.355268	-3.38662

Regression Output:

Constant		-1.830214
Std Err of Y Est		0.0128535
R Squared		0.9993706
No. of Observations		17
Degrees of Freedom		15
X Coefficient(s)	-0.000232	
Std Err of Coef.	1.5E-06	



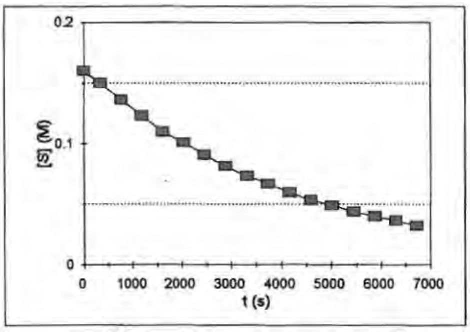


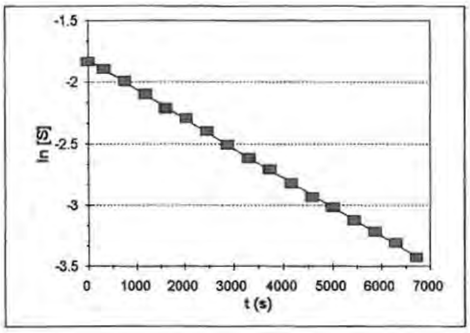
b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.16	-1.832581	-1.818399
100	333	0.15	-1.89712	-1.897857
101	759	0.1363	-1.992897	-1.999506
102	1185	0.123	-2.095571	-2.101154
103	1611	0.1096	-2.210918	-2.202803
104	2037	0.1011	-2.291645	-2.304452
105	2463	0.091	-2.396896	-2.406101
106	2889	0.0816	-2.505926	-2.50775
107	3315	0.0734	-2.611831	-2.609398
108	3741	0.0669	-2.704556	-2.711047
109	4167	0.0596	-2.8201	-2.812696
110	4593	0.0533	-2.931819	-2.914345
111	5019	0.049	-3.015935	-3.015993
112	5445	0.044	-3.123566	-3.117642
113	5871	0.0401	-3.216379	-3.219291
114	6297	0.0366	-3.307707	-3.32094
115	6723	0.0325	-3.426515	-3.422588

Regression Output:

Constant		-1.818399
Std Err of Y Est		0.0090803
R Squared		0.9997042
No. of Observations		17
Degrees of Freedom		15
X Coefficient(s)	-0.000239	
Std Err of Coef.	1.06E-06	





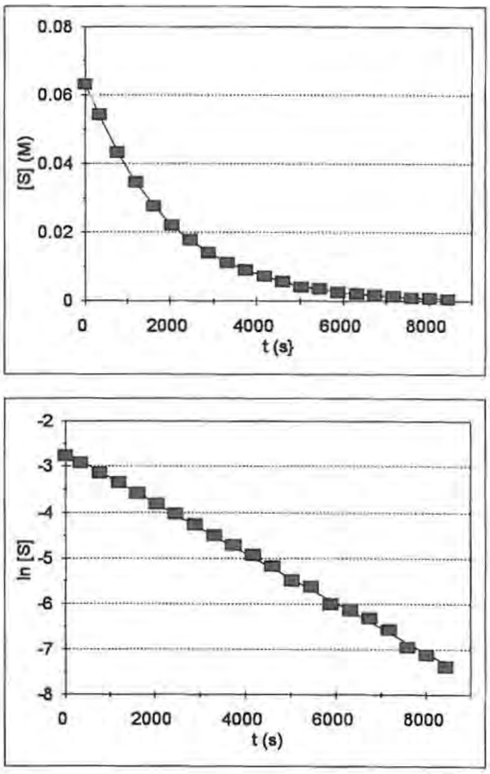
Kinetic data for the cyclisation of methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (102) at 373K using a) the CO.CH_3/acetic acid and b) the OCH_3 integrals (duplicate run).

a)

Expt. No.	t (s)	[R] (M)	ln [S]	Regress.
	0	0.06314	-2.762401	-2.694832
100	345	0.05424	-2.914337	-2.884025
101	771	0.04322	-3.141452	-3.117637
102	1197	0.03466	-3.362169	-3.351249
103	1623	0.02761	-3.589577	-3.584862
104	2049	0.02197	-3.818077	-3.818474
105	2475	0.01781	-4.027995	-4.052086
106	2901	0.01409	-4.26229	-4.285699
107	3327	0.01124	-4.488276	-4.519311
108	3753	0.00907	-4.702783	-4.752923
109	4179	0.00727	-4.923999	-4.986536
110	4605	0.00565	-5.1761	-5.220148
111	5031	0.00415	-5.484647	-5.45376
112	5457	0.00362	-5.621281	-5.687372
113	5883	0.00246	-6.007594	-5.920985
114	6309	0.00215	-6.142287	-6.154597
115	6735	0.00182	-6.308919	-6.388209
116	7161	0.00141	-6.564166	-6.621822
117	7587	0.00095	-6.959049	-6.855434
118	8013	0.00081	-7.118476	-7.089046
119	8439	0.00062	-7.385791	-7.322659

Regression Output:

Constant		-2.694832
Std Err of Y Est		0.0537164
R Squared		0.9986907
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000548	
Std Err of Coef.	4.56E-06	

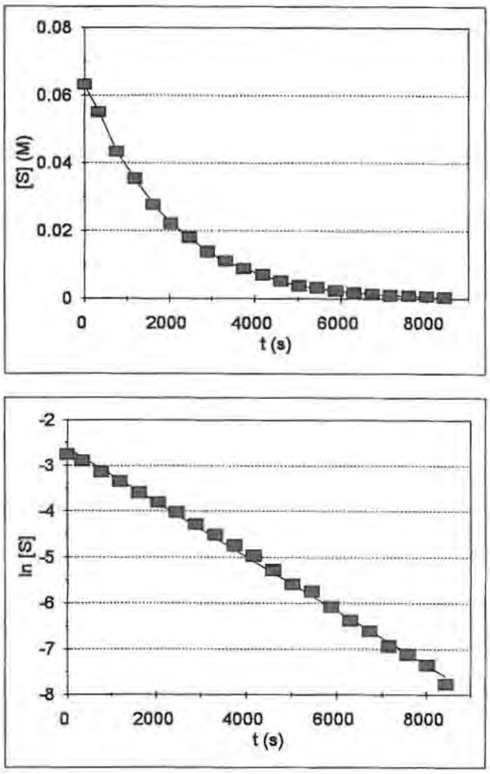


b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.06314	-2.762401	-2.617622
100	345	0.05512	-2.898243	-2.821616
101	771	0.0434	-3.137296	-3.073504
102	1197	0.03537	-3.341891	-3.325392
103	1623	0.02762	-3.589215	-3.577281
104	2049	0.02208	-3.813083	-3.829169
105	2475	0.01791	-4.022396	-4.081057
106	2901	0.01376	-4.285989	-4.332946
107	3327	0.01097	-4.512591	-4.584834
108	3753	0.00876	-4.737559	-4.836722
109	4179	0.007	-4.961845	-5.08861
110	4605	0.00513	-5.27265	-5.340499
111	5031	0.00376	-5.583336	-5.592387
112	5457	0.0032	-5.744604	-5.844275
113	5883	0.0023	-6.074846	-6.096164
114	6309	0.0017	-6.377127	-6.348052
115	6735	0.00135	-6.607651	-6.59994
116	7161	0.00097	-6.938214	-6.851828
117	7587	0.00081	-7.118476	-7.103717
118	8013	0.00064	-7.354042	-7.355605
119	8439	0.00042	-7.775256	-7.607493

Regression Output:

Constant		-2.617622
Std Err of Y Est		0.0795213
R Squared		0.9975347
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000591	
Std Err of Coef.	6.74E-06	



Kinetic data for the cyclisation of methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(102)** at 383K using a) the CO.CH_3/acetic acid and b) the OCH_3 integrals.

a)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.06618	-2.715377	-2.687873
100	328	0.05668	-2.870334	-2.869513
101	754	0.04532	-3.094007	-3.105423
102	1180	0.03549	-3.338504	-3.341333
103	1606	0.02856	-3.555748	-3.577244
104	2032	0.0228	-3.780995	-3.813154
105	2458	0.01815	-4.009085	-4.049064
106	2884	0.01434	-4.244702	-4.284974
107	3310	0.01103	-4.507136	-4.520884
108	3736	0.00897	-4.71387	-4.756795
109	4162	0.00632	-5.064036	-4.992705
110	4588	0.005	-5.298317	-5.228615
111	5014	0.00408	-5.501658	-5.464525
112	5440	0.00329	-5.716868	-5.700435
113	5866	0.00247	-6.003537	-5.936345
114	6292	0.00206	-6.185049	-6.172256
115	6718	0.00163	-6.419175	-6.408166
116	7144	0.00123	-6.700741	-6.644076
117	7570	0.00112	-6.794427	-6.879986
118	7996	0.00083	-7.094085	-7.115896
119	8422	0.00068	-7.293418	-7.351807

```
             Regression Output:
Constant                              -2.687873
Std Err of Y Est                      0.0449882
R Squared                             0.9990981
No. of Observations                          21
Degrees of Freedom                           19

X Coefficient(s)           -0.000554
Std Err of Coef.            3.82E-06
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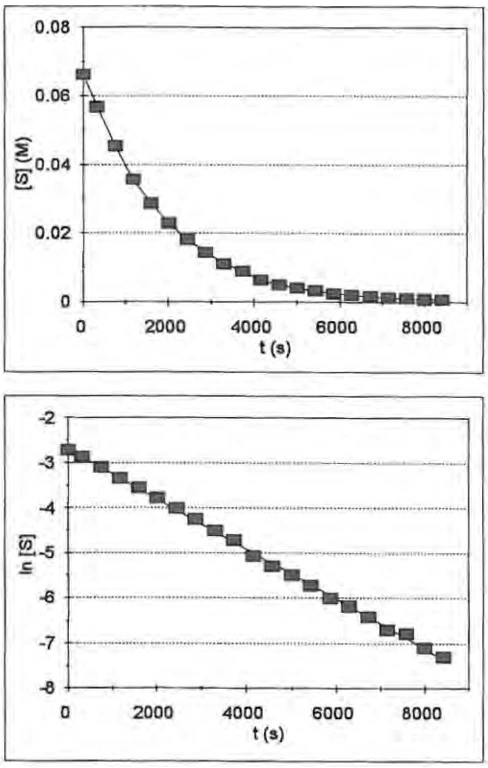

b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.06618	-2.715377	-2.695728
100	328	0.05714	-2.862251	-2.878438
101	754	0.04522	-3.096216	-3.115739
102	1180	0.03541	-3.340761	-3.353039
103	1606	0.02857	-3.555398	-3.590339
104	2032	0.02267	-3.786713	-3.827639
105	2458	0.01766	-4.036453	-4.064939
106	2884	0.01416	-4.257334	-4.302239
107	3310	0.01067	-4.540319	-4.53954
108	3736	0.00882	-4.730733	-4.77684
109	4162	0.0063	-5.067206	-5.01414
110	4588	0.00447	-5.410367	-5.25144
111	5014	0.00389	-5.549346	-5.48874
112	5440	0.00305	-5.792614	-5.726041
113	5866	0.00256	-5.967748	-5.963341
114	6292	0.00198	-6.224658	-6.200641
115	6718	0.00154	-6.475973	-6.437941
116	7144	0.00131	-6.637728	-6.675241
117	7570	0.00094	-6.969631	-6.912541
118	7996	0.00085	-7.070274	-7.149842
119	8422	0.0007	-7.26443	-7.387142

```
             Regression Output:
Constant                              -2.695728
Std Err of Y Est                      0.0621149
R Squared                             0.9983022
No. of Observations                          21
Degrees of Freedom                           19

X Coefficient(s)           -0.000557
Std Err of Coef.            5.27E-06
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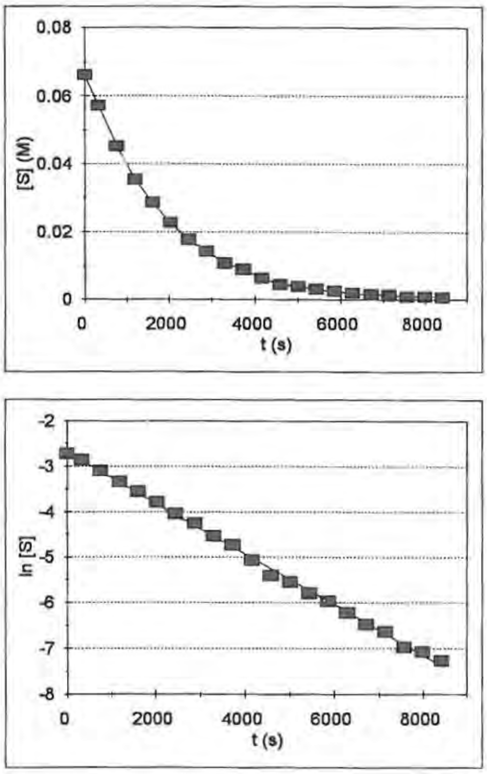


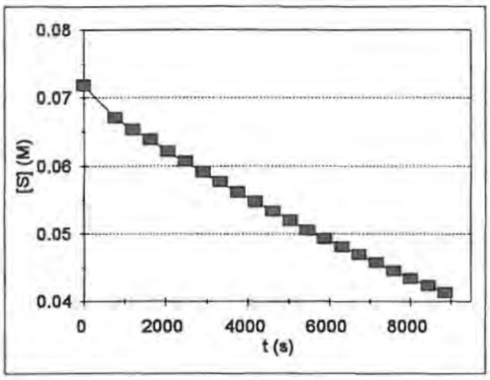
Kinetic data for the cyclisation of methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(102)** at 383K using a) the CO.CH_3/acetic acid and b) the OCH_3 integrals (duplicate run).

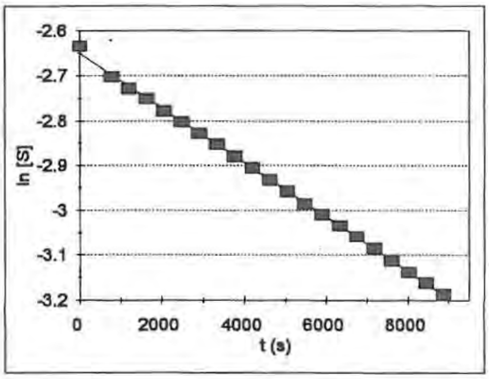
a)

Expt. No	t (s)	[S] (M)	ln[S]	Regress.
	0	0.07176	-2.634428	-2.649938
100	780	0.0670238	-2.702707	-2.697422
101	1206	0.0653016	-2.728739	-2.723356
102	1632	0.0638664	-2.750962	-2.74929
103	2058	0.0621442	-2.778298	-2.775224
104	2484	0.060709	-2.801664	-2.801158
105	2910	0.0591302	-2.828013	-2.827092
106	3336	0.057695	-2.852584	-2.853026
107	3762	0.0561881	-2.879051	-2.87896
108	4188	0.0547529	-2.904925	-2.904894
109	4614	0.0533177	-2.931487	-2.930828
110	5040	0.0519542	-2.957392	-2.956762
111	5466	0.050519	-2.985405	-2.982696
112	5892	0.0492991	-3.009849	-3.00863
113	6318	0.0480792	-3.034906	-3.034564
114	6744	0.046931	-3.059076	-3.060498
115	7170	0.0457111	-3.085414	-3.086433
116	7596	0.0444912	-3.112464	-3.112367
117	8022	0.043343	-3.138609	-3.138301
118	8448	0.0423384	-3.162061	-3.164235
119	8874	0.041262	-3.187813	-3.190169

Regression Output:

Constant	-2.649938
Std Err of Y Est	0.004194
R Squared	0.9993692
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-6.09E-05
Std Err of Coef.	3.51E-07



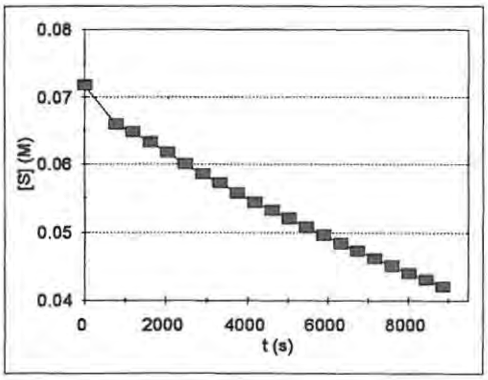


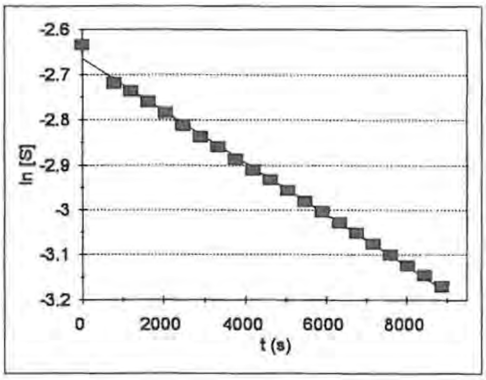
b)

Expt. No	t (s)	[S] (M)	ln[S]	Regress.
	0	0.07176	-2.634428	-2.664636
100	780	0.0659474	-2.718897	-2.709516
101	1206	0.0647993	-2.736461	-2.734027
102	1632	0.0632923	-2.759991	-2.758538
103	2058	0.0617854	-2.784089	-2.78305
104	2484	0.0600631	-2.812359	-2.807561
105	2910	0.0585562	-2.837769	-2.832072
106	3336	0.0572645	-2.860075	-2.856583
107	3762	0.0557575	-2.886743	-2.881095
108	4188	0.0543941	-2.9115	-2.905606
109	4614	0.0532459	-2.932834	-2.930117
110	5040	0.052026	-2.956012	-2.954628
111	5466	0.0507343	-2.981153	-2.97914
112	5892	0.0495862	-3.004044	-3.003651
113	6318	0.0483662	-3.028953	-3.028162
114	6744	0.0472898	-3.05146	-3.052673
115	7170	0.0461417	-3.076039	-3.077185
116	7596	0.0450653	-3.099643	-3.101696
117	8022	0.0439889	-3.123818	-3.126207
118	8448	0.043056	-3.145254	-3.150718
119	8874	0.0419796	-3.170571	-3.17523

Regression Output:

Constant	-2.664636
Std Err of Y Est	0.0080209
R Squared	0.9974224
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-5.75E-05
Std Err of Coef.	6.71E-07





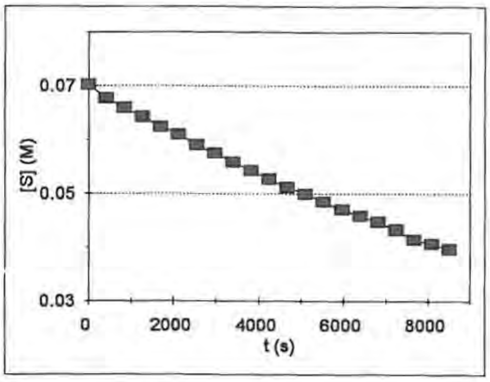
Kinetic data for the cyclisation of ethyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (103) at 363K using a) the $C\mathit{H}_2CH_3$ and b) the $CH_2C\mathit{H}_3$ integrals.

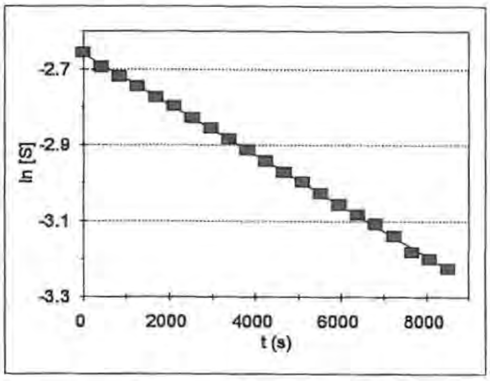
a)

Expt. No.	t (s)	[S] (M)	ln[S]	Regress.
	0	0.07021	-2.656265	-2.659653
100	417	0.0676122	-2.693966	-2.687443
101	843	0.0659272	-2.719204	-2.715832
102	1269	0.0642422	-2.745096	-2.744222
103	1695	0.0624167	-2.773923	-2.772611
104	2121	0.0610125	-2.796677	-2.801001
105	2547	0.0590466	-2.829428	-2.82939
106	2973	0.057502	-2.855936	-2.857779
107	3399	0.0558872	-2.884421	-2.886169
108	3825	0.0542723	-2.913741	-2.914558
109	4251	0.0527277	-2.942614	-2.942948
110	4677	0.0511831	-2.972346	-2.971337
111	5103	0.0499193	-2.997347	-2.999726
112	5529	0.0484449	-3.027328	-3.028116
113	5955	0.0470407	-3.056742	-3.056505
114	6381	0.0458471	-3.082443	-3.084895
115	6807	0.0447238	-3.10725	-3.113284
116	7233	0.0433196	-3.139151	-3.141673
117	7659	0.0414941	-3.182204	-3.170063
118	8085	0.0407218	-3.200992	-3.198452
119	8511	0.0397389	-3.225426	-3.226842

Regression Output:

Constant		-2.659653
Std Err of Y Est		0.004012
R Squared		0.9995072
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-6.66E-05	
Std Err of Coef.	3.39E-07	



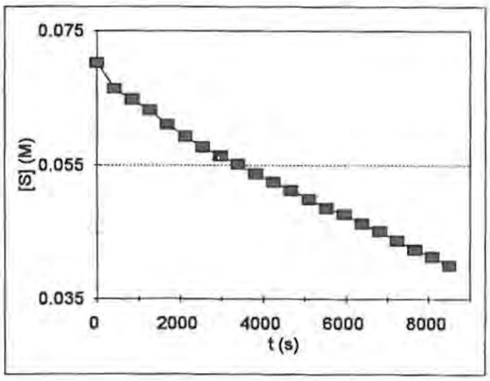


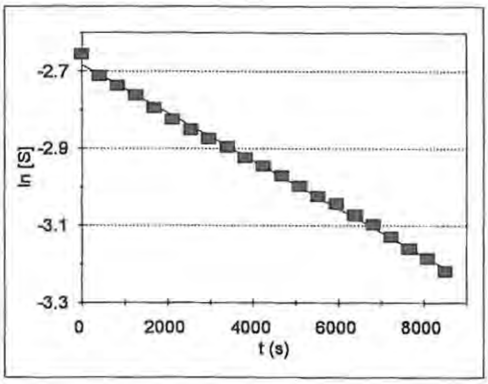
b)

Expt. No.	t (s)	[S] (M)	ln[S]	Regress.
	0	0.07021	-2.656265	-2.683535
100	417	0.0663485	-2.712835	-2.709386
101	843	0.0647336	-2.737475	-2.735794
102	1269	0.0631188	-2.762737	-2.762203
103	1695	0.0610125	-2.796677	-2.788611
104	2121	0.0592572	-2.825867	-2.815019
105	2547	0.0577126	-2.852279	-2.841428
106	2973	0.0563786	-2.875665	-2.867836
107	3399	0.0551851	-2.897063	-2.894245
108	3825	0.0537107	-2.924144	-2.920653
109	4251	0.0525171	-2.946617	-2.947061
110	4677	0.0512533	-2.970975	-2.97347
111	5103	0.0499193	-2.997347	-2.999878
112	5529	0.0485853	-3.024434	-3.026286
113	5955	0.0476726	-3.043399	-3.052695
114	6381	0.0462684	-3.073296	-3.079103
115	6807	0.045145	-3.097875	-3.105512
116	7233	0.0437408	-3.129473	-3.13192
117	7659	0.0424068	-3.160446	-3.158328
118	8085	0.0413537	-3.185594	-3.184737
119	8511	0.0400197	-3.218383	-3.211145

Regression Output:

Constant		-2.683535
Std Err of Y Est		0.0085807
R Squared		0.9974003
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-6.2E-05	
Std Err of Coef.	7.26E-07	





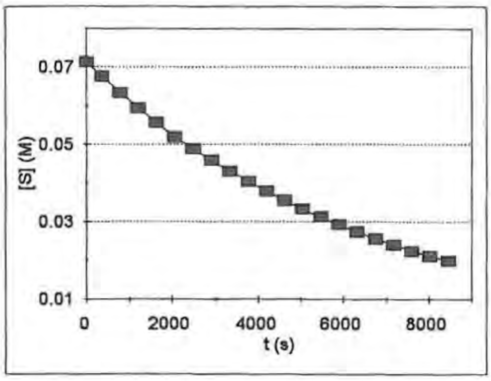
Kinetic data for the cyclisation of ethyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(103)** at 363K using a) the $C\textit{H}_2CH_3$ and b) the $CH_2C\textit{H}_3$ integrals (duplicate run).

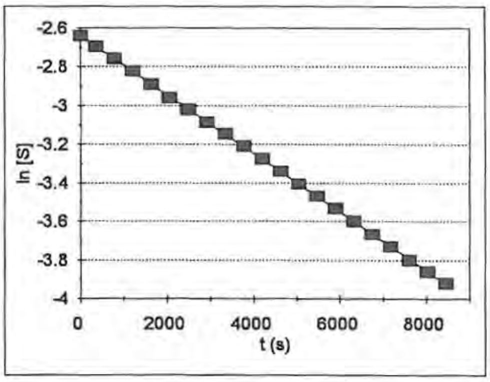
a)

Expt. No.	t (s)	[S] (M)	ln[S]	Regress.
	0	0.07126	-2.64142	-2.640152
100	366	0.0675545	-2.694821	-2.695604
101	792	0.0633501	-2.759078	-2.760145
102	1218	0.0594308	-2.822942	-2.824687
103	1644	0.0555828	-2.889881	-2.889229
104	2070	0.051806	-2.960249	-2.95377
105	2496	0.0488131	-3.019757	-3.018312
106	2922	0.0457489	-3.084587	-3.082854
107	3348	0.043041	-3.145601	-3.147395
108	3774	0.0404044	-3.208816	-3.211937
109	4200	0.0378391	-3.274413	-3.276479
110	4626	0.0354875	-3.338575	-3.341021
111	5052	0.0332072	-3.40499	-3.405562
112	5478	0.0312119	-3.466956	-3.470104
113	5904	0.0292166	-3.533018	-3.534646
114	6330	0.0273638	-3.598533	-3.599187
115	6756	0.0255823	-3.665853	-3.663729
116	7182	0.0240146	-3.729092	-3.728271
117	7608	0.0223756	-3.799782	-3.792812
118	8034	0.021093	-3.858816	-3.857354
119	8460	0.0198815	-3.917964	-3.921896

Regression Output:

Constant		-2.640152
Std Err of Y Est		0.002918
R Squared		0.9999494
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000152	
Std Err of Coef.	2.47E-07	



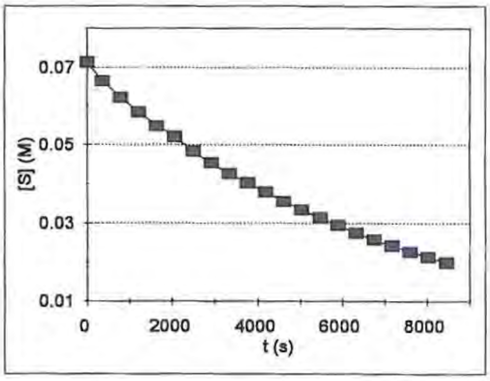


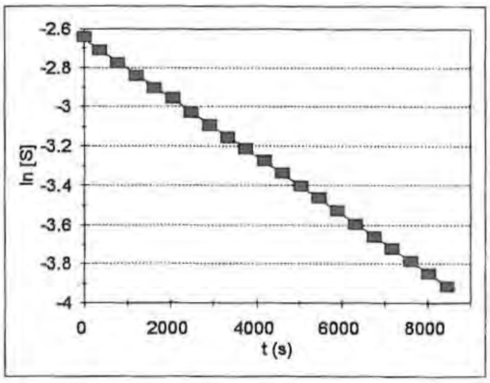
b)

Expt. No.	t (s)	[S] (M)	ln[S]	Regress.
	0	0.07126	-2.64142	-2.653617
100	366	0.0664856	-2.71077	-2.70805
101	792	0.06221	-2.77724	-2.771407
102	1218	0.0583619	-2.841091	-2.834764
103	1644	0.0547989	-2.904084	-2.898121
104	2070	0.0520911	-2.954762	-2.961477
105	2496	0.0483855	-3.028554	-3.024834
106	2922	0.0453926	-3.092406	-3.088191
107	3348	0.0426135	-3.155585	-3.151548
108	3774	0.0402619	-3.21235	-3.214905
109	4200	0.0379103	-3.272532	-3.278261
110	4626	0.0354875	-3.338575	-3.341618
111	5052	0.0332784	-3.402846	-3.404975
112	5478	0.0313544	-3.462401	-3.468332
113	5904	0.0293591	-3.528152	-3.531689
114	6330	0.0274351	-3.595932	-3.595046
115	6756	0.0257249	-3.660297	-3.658402
116	7182	0.0241571	-3.723175	-3.721759
117	7608	0.0226607	-3.787124	-3.785116
118	8034	0.0213067	-3.848732	-3.848473
119	8460	0.0199528	-3.914386	-3.91183

Regression Output:

Constant		-2.653617
Std Err of Y Est		0.0050086
R Squared		0.9998453
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000149	
Std Err of Coef.	4.24E-07	





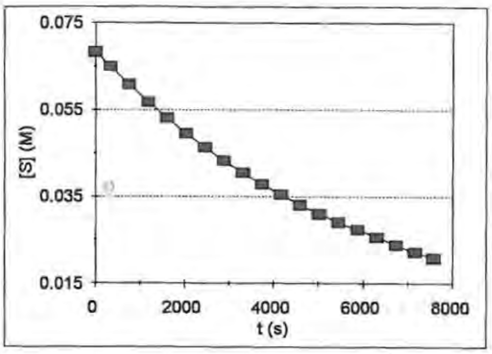
Kinetic data for the cyclisation of ethyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate **(103)** at 373K using a) the $C\mathit{H}_2CH_3$ and b) the $CH_2C\mathit{H}_3$ integrals.

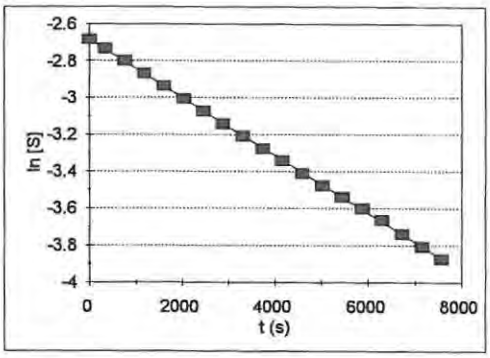
a)

Expt. No.	t (s)	[S] (M)	ln[S]	Regress.
	0	0.06829	-2.683992	-2.68375
100	339	0.0649438	-2.734233	-2.736978
101	765	0.0608464	-2.799403	-2.803865
102	1191	0.0567626	-2.868877	-2.870753
103	1617	0.0530613	-2.936307	-2.937641
104	2043	0.0495103	-3.005576	-3.004529
105	2469	0.0463006	-3.0726	-3.071417
106	2895	0.0432276	-3.141277	-3.138305
107	3321	0.0404277	-3.208241	-3.205193
108	3747	0.0377644	-3.276389	-3.272081
109	4173	0.0353742	-3.341772	-3.338969
110	4599	0.0329841	-3.411731	-3.405857
111	5025	0.0309354	-3.475855	-3.472745
112	5451	0.0290233	-3.539658	-3.539633
113	5877	0.027316	-3.600283	-3.606521
114	6303	0.0256088	-3.664821	-3.673409
115	6729	0.0237649	-3.739545	-3.740297
116	7155	0.0221943	-3.807922	-3.807185
117	7581	0.0207602	-3.87472	-3.874072

Regression Output:

Constant		-2.68375
Std Err of Y Est		0.0037432
R Squared		0.999906
No. of Observations		19
Degrees of Freedom		17
X Coefficient(s)	-0.000157	
Std Err of Coef.	3.69E-07	



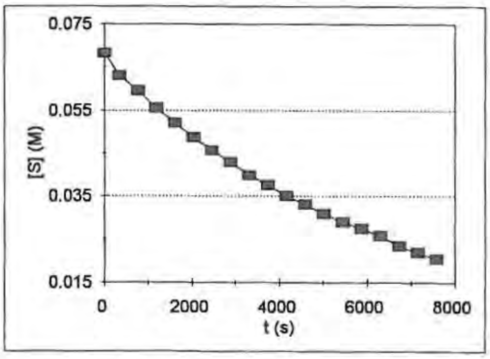


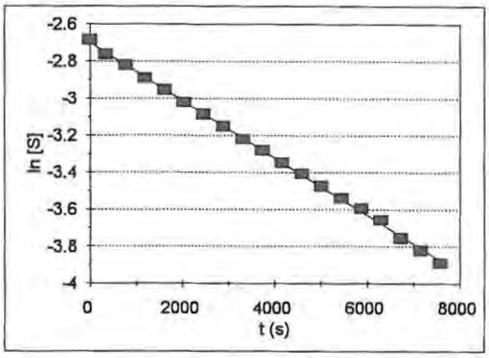
b)

Expt. No.	t (s)	[S] (M)	ln[S]	Regress.
	0	0.06829	-2.683992	-2.70053
100	339	0.0631	-2.763035	-2.753077
101	765	0.0595489	-2.820958	-2.819111
102	1191	0.0555881	-2.889787	-2.885144
103	1617	0.0521053	-2.954489	-2.951178
104	2043	0.0487591	-3.020864	-3.017211
105	2469	0.045686	-3.085963	-3.083245
106	2895	0.0428861	-3.149207	-3.149278
107	3321	0.0398814	-3.221846	-3.215312
108	3747	0.0375595	-3.281829	-3.281345
109	4173	0.0351011	-3.349524	-3.347379
110	4599	0.0331207	-3.407598	-3.413412
111	5025	0.0309354	-3.475855	-3.479445
112	5451	0.0290233	-3.539658	-3.545479
113	5877	0.0274526	-3.595295	-3.611512
114	6303	0.0258136	-3.656853	-3.677546
115	6729	0.0234235	-3.754017	-3.743579
116	7155	0.0219211	-3.820306	-3.809613
117	7581	0.020487	-3.887965	-3.875646

Regression Output:

Constant		-2.70053
Std Err of Y Est		0.0097729
R Squared		0.999343
No. of Observations		19
Degrees of Freedom		17
X Coefficient(s)	-0.000155	
Std Err of Coef.	9.64E-07	





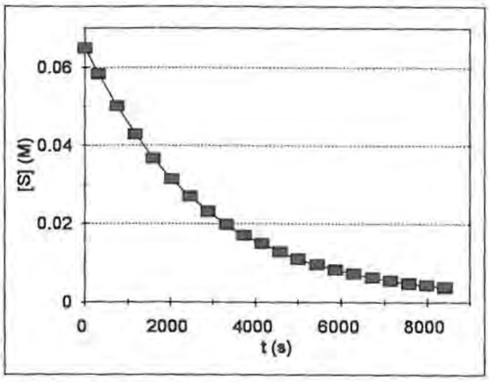
Kinetic data for the cyclisation of ethyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate **(103)** at 373K using a) the CH_2CH_3 and b) the CH_2CH_3 integrals (duplicate run).

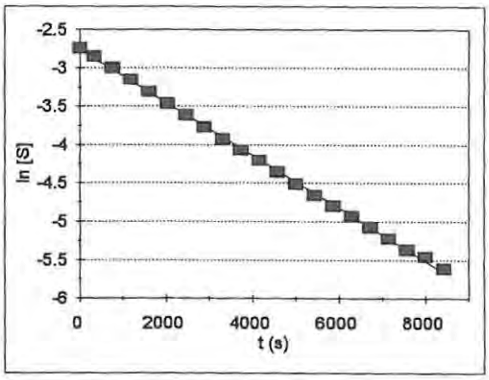
a)

Expt. No.	t (s)	[S] (M)	ln[S]	Regress.
	0	0.06487	-2.73537	-2.758062
100	331	0.0582533	-2.842955	-2.871943
101	757	0.0501445	-2.992846	-3.018509
102	1183	0.0429439	-3.14786	-3.165075
103	1609	0.0366516	-3.3063	-3.311641
104	2035	0.0313971	-3.46104	-3.458206
105	2461	0.0270508	-3.610039	-3.604772
106	2887	0.0231586	-3.76539	-3.751338
107	3313	0.0197854	-3.922814	-3.897904
108	3739	0.0170608	-4.070971	-4.04447
109	4165	0.0149201	-4.205046	-4.191035
110	4591	0.0127794	-4.359922	-4.337601
111	5017	0.0108982	-4.519161	-4.484167
112	5443	0.009471	-4.659519	-4.630733
113	5869	0.0082385	-4.798938	-4.777299
114	6295	0.0072006	-4.933595	-4.923864
115	6721	0.0062794	-5.070478	-5.07043
116	7147	0.0054037	-5.220677	-5.216996
117	7573	0.0046966	-5.360919	-5.363562
118	7999	0.0042814	-5.453471	-5.510128
119	8425	0.0036716	-5.607116	-5.656693

Regression Output:

Constant	-2.758062
Std Err of Y Est	0.0260504
R Squared	0.9992166
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-0.000344
Std Err of Coef.	2.21E-06



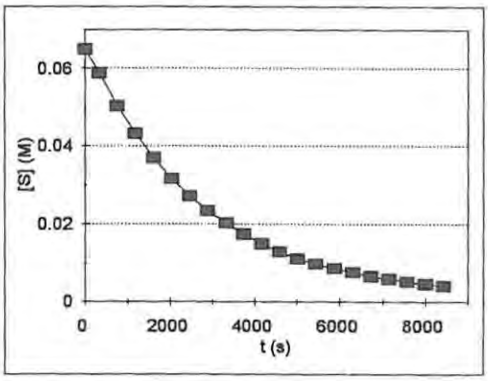


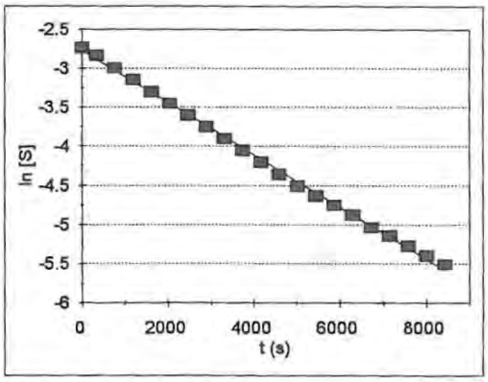
b)

Expt. No.	t (s)	[S] (M)	ln[S]	Regress.
	0	0.06487	-2.73537	-2.769745
100	339	0.0587722	-2.834086	-2.882996
101	765	0.0502094	-2.991553	-3.025311
102	1191	0.0431386	-3.143338	-3.167627
103	1617	0.036911	-3.299245	-3.309942
104	2043	0.0315917	-3.454861	-3.452257
105	2469	0.0271805	-3.605254	-3.594572
106	2895	0.0234181	-3.754247	-3.736888
107	3321	0.0201746	-3.903332	-3.879203
108	3747	0.0173203	-4.055877	-4.021518
109	4173	0.0149201	-4.205046	-4.163834
110	4599	0.0127794	-4.359922	-4.306149
111	5025	0.0110279	-4.507327	-4.448464
112	5451	0.0097305	-4.63249	-4.59078
113	5877	0.0086277	-4.752776	-4.733095
114	6303	0.0075898	-4.880951	-4.87541
115	6729	0.006487	-5.037955	-5.017726
116	7155	0.0058448	-5.142205	-5.160041
117	7581	0.0051377	-5.271149	-5.302356
118	8007	0.0045409	-5.39463	-5.444672
119	8433	0.0040544	-5.507959	-5.586987

Regression Output:

Constant	-2.769745
Std Err of Y Est	0.0385706
R Squared	0.9981813
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-0.000334
Std Err of Coef.	3.27E-06





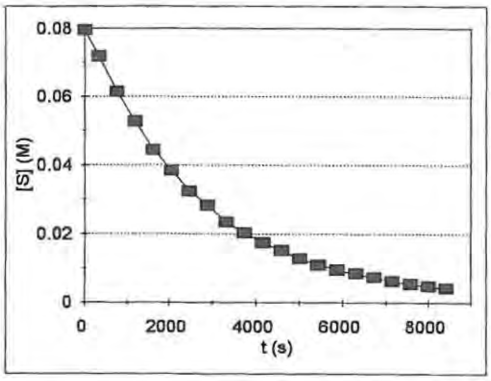
Kinetic data for the cyclisation of ethyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate **(103)** at 383K using a) the $C\mathit{H}_2CH_3$ and b) the $CH_2C\mathit{H}_3$ integrals.

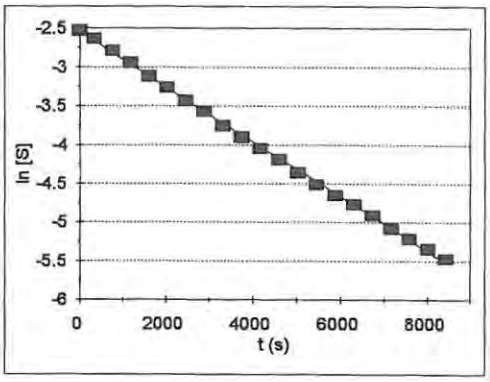
a)

Expt. No.	t (s)	[S] (M)	ln[S]	Regress.
	0	0.07949	-2.532124	-2.546482
100	339	0.0717	-2.635265	-2.66609
101	765	0.0613663	-2.790895	-2.816394
102	1191	0.0527019	-2.943104	-2.966697
103	1617	0.0444349	-3.11373	-3.117001
104	2043	0.0383937	-3.259863	-3.267305
105	2469	0.0324319	-3.428612	-3.417609
106	2895	0.0282984	-3.564949	-3.567913
107	3321	0.023529	-3.74952	-3.718217
108	3747	0.02027	-3.898616	-3.86852
109	4173	0.0175673	-4.041717	-4.018824
110	4599	0.0151826	-4.187606	-4.169128
111	5025	0.0127979	-4.358475	-4.319432
112	5451	0.0109696	-4.512626	-4.469736
113	5877	0.0095388	-4.652388	-4.62004
114	6303	0.0085054	-4.76705	-4.770344
115	6729	0.0074085	-4.905132	-4.920647
116	7155	0.0062479	-5.075508	-5.070951
117	7581	0.0054848	-5.205773	-5.221255
118	8007	0.0048091	-5.337236	-5.371559
119	8433	0.0042289	-5.465821	-5.521863

Regression Output:

Constant		-2.546482
Std Err of Y Est		0.0276741
R Squared		0.9991598
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000353	
Std Err of Coef.	2.35E-06	



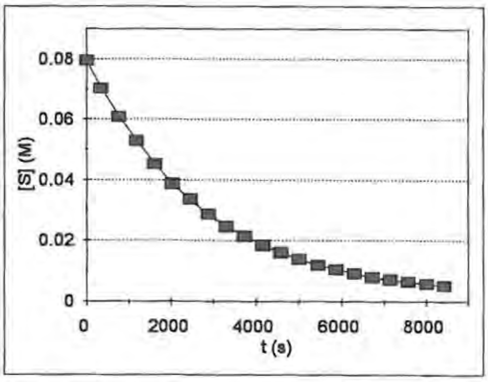


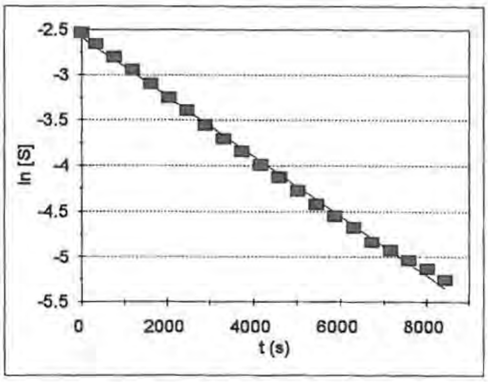
b)

Expt. No.	t (s)	[S] (M)	ln[S]	Regress.
	0	0.07949	-2.532124	-2.580684
100	339	0.0702692	-2.655422	-2.691993
101	765	0.0608099	-2.800003	-2.831869
102	1191	0.0527814	-2.941597	-2.971744
103	1617	0.0451503	-3.097758	-3.11162
104	2043	0.0387116	-3.251615	-3.251495
105	2469	0.0336243	-3.392507	-3.391371
106	2895	0.0286164	-3.553775	-3.531246
107	3321	0.0245624	-3.706538	-3.671122
108	3747	0.0213828	-3.845168	-3.810997
109	4173	0.0184417	-3.993142	-3.950873
110	4599	0.0161365	-4.126673	-4.090748
111	5025	0.0139108	-4.275093	-4.230624
112	5451	0.012003	-4.422599	-4.370499
113	5877	0.0105722	-4.54953	-4.510374
114	6303	0.0093003	-4.677705	-4.65025
115	6729	0.007949	-4.834709	-4.790125
116	7155	0.0072574	-4.925729	-4.930001
117	7581	0.0065102	-5.03438	-5.069876
118	8007	0.005922	-5.12908	-5.209752
119	8433	0.0052384	-5.251741	-5.349627

Regression Output:

Constant		-2.580684
Std Err of Y Est		0.0448123
R Squared		0.9974604
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000328	
Std Err of Coef.	3.8E-06	





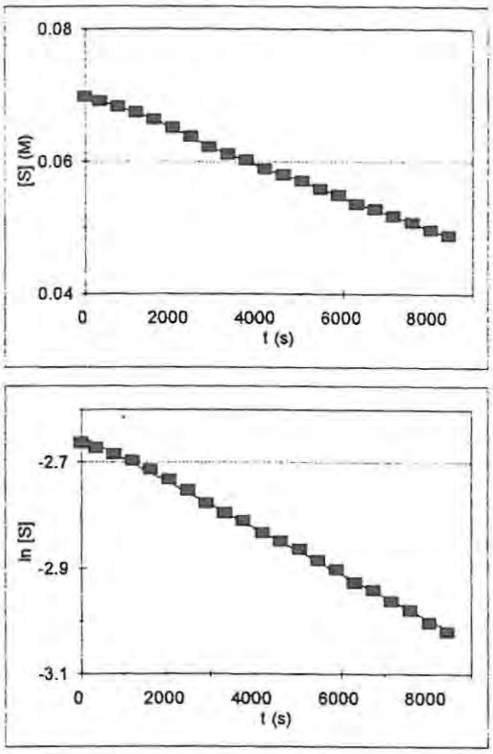
Kinetic data for the cyclisation of ethyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate **(103)** at 383K using a) the $\mathrm{C}H_2\mathrm{CH}_3$ and b) the $\mathrm{CH}_2\mathrm{C}H_3$ integrals (duplicate run).

a)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.06976	-2.662694	-2.649512
100	351	0.0691322	-2.671735	-2.664723
101	777	0.068295	-2.683918	-2.683184
102	1203	0.0674579	-2.696251	-2.701645
103	1629	0.0663418	-2.712936	-2.720106
104	2055	0.0650861	-2.732045	-2.738567
105	2481	0.0637606	-2.752619	-2.757029
106	2907	0.0622259	-2.776984	-2.77549
107	3333	0.0611098	-2.795084	-2.793951
108	3759	0.0602029	-2.810035	-2.812412
109	4185	0.0588774	-2.832297	-2.830873
110	4611	0.0579706	-2.84782	-2.849335
111	5037	0.0570637	-2.863587	-2.867796
112	5463	0.0558778	-2.884589	-2.886257
113	5889	0.0549709	-2.900952	-2.904718
114	6315	0.0535757	-2.92666	-2.923179
115	6741	0.0528781	-2.939766	-2.94164
116	7167	0.0517619	-2.961101	-2.960102
117	7593	0.050855	-2.978776	-2.978563
118	8019	0.0496691	-3.002372	-2.997024
119	8445	0.048832	-3.019369	-3.015485

Regression Output:

Constant		-2.649512
Std Err of Y Est		0.0049975
R Squared		0.9981869
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-4.33E-05	
Std Err of Coef.	4.24E-07	

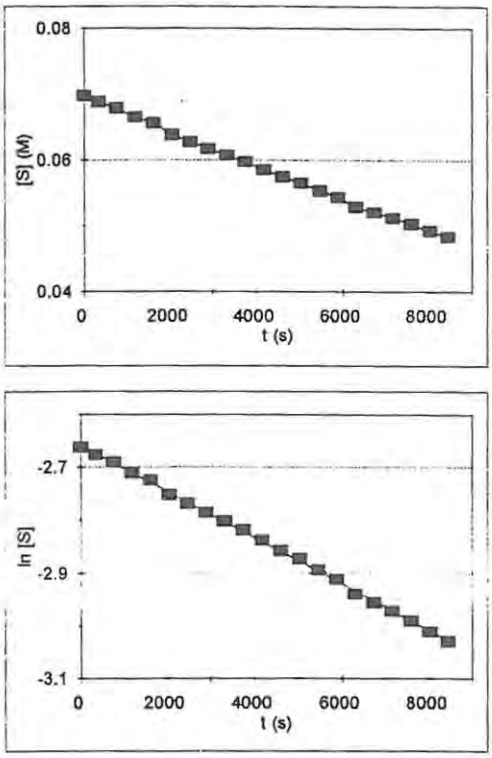


b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.06976	-2.662694	-2.65803
100	351	0.0688531	-2.67578	-2.673381
101	777	0.0678765	-2.690066	-2.692013
102	1203	0.0664813	-2.710835	-2.710644
103	1629	0.0655744	-2.72457	-2.729275
104	2055	0.0637606	-2.752619	-2.747906
105	2481	0.0627142	-2.769167	-2.766537
106	2907	0.0616678	-2.785993	-2.785168
107	3333	0.0606912	-2.801957	-2.803799
108	3759	0.0597146	-2.818179	-2.82243
109	4185	0.0585286	-2.838239	-2.841061
110	4611	0.0574125	-2.857494	-2.859692
111	5037	0.0565056	-2.873416	-2.878324
112	5463	0.0553197	-2.894627	-2.896955
113	5889	0.054343	-2.912439	-2.915586
114	6315	0.0528781	-2.939766	-2.934217
115	6741	0.052041	-2.955724	-2.952848
116	7167	0.0512038	-2.971941	-2.971479
117	7593	0.050297	-2.989811	-2.99011
118	8019	0.0492506	-3.010835	-3.008741
119	8445	0.0483437	-3.02942	-3.027372

Regression Output:

Constant		-2.65803
Std Err of Y Est		0.003284
R Squared		0.9992305
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-4.37E-05	
Std Err of Coef.	2.78E-07	



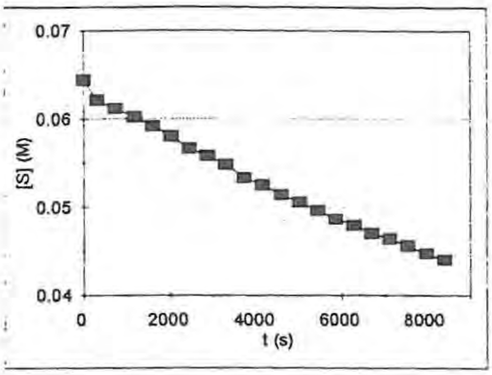
Kinetic data for the cyclisation of isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate **(104)** at 363K using a) the $\mathit{CH}(\mathrm{CH}_3)_2$ and b) the $\mathrm{CH}(\mathit{CH}_3)_2$ integrals.

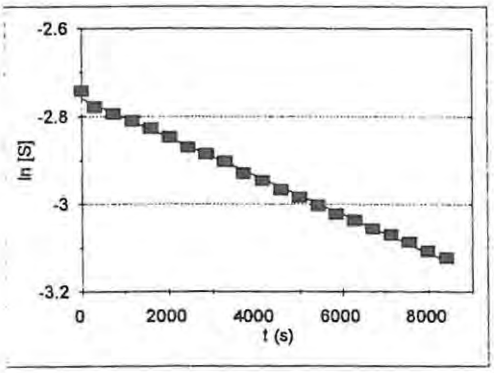
a)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.06439	-2.742797	-2.759431
100	319	0.0621364	-2.778424	-2.773473
101	745	0.0611705	-2.79409	-2.792225
102	1171	0.0602047	-2.810006	-2.810977
103	1597	0.0591744	-2.827266	-2.829729
104	2023	0.0580154	-2.847047	-2.848482
105	2449	0.0566632	-2.87063	-2.867234
106	2875	0.0558261	-2.885513	-2.885986
107	3301	0.0548603	-2.902966	-2.904738
108	3727	0.0533793	-2.930332	-2.92349
109	4153	0.0525422	-2.946138	-2.942242
110	4579	0.0514476	-2.967191	-2.960994
111	5005	0.0505462	-2.984868	-2.979746
112	5431	0.0496447	-3.002864	-2.998498
113	5857	0.0486788	-3.022511	-3.017251
114	6283	0.0479706	-3.037168	-3.036003
115	6709	0.0470691	-3.056139	-3.054755
116	7135	0.0464252	-3.069913	-3.073507
117	7561	0.0456525	-3.086697	-3.092259
118	7987	0.0447511	-3.10664	-3.111011
119	8413	0.0440428	-3.122594	-3.129763

Regression Output:

Constant	-2.759431
Std Err of Y Est	0.0057107
R Squared	0.997702
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-4.4E-05
Std Err of Coef.	4.85E-07



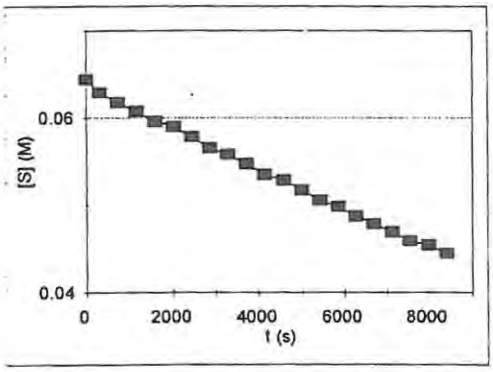


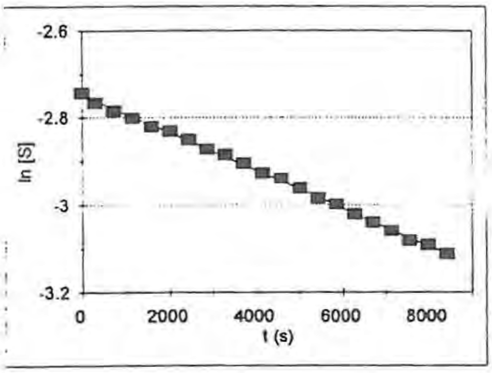
b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.06439	-2.742797	-2.747245
100	319	0.062909	-2.766066	-2.761079
101	745	0.06175	-2.784661	-2.779552
102	1171	0.0607198	-2.801486	-2.798025
103	1597	0.0595608	-2.820758	-2.816499
104	2023	0.0589812	-2.830536	-2.834972
105	2449	0.0578222	-2.850382	-2.853446
106	2875	0.0565344	-2.872906	-2.871919
107	3301	0.0558261	-2.885513	-2.890392
108	3727	0.0547315	-2.905316	-2.908866
109	4153	0.0535081	-2.927922	-2.927339
110	4579	0.0528642	-2.940029	-2.945813
111	5005	0.0517052	-2.962198	-2.964286
112	5431	0.0505462	-2.984868	-2.982759
113	5857	0.0498379	-2.99898	-3.001233
114	6283	0.0487432	-3.021189	-3.019706
115	6709	0.0478418	-3.039856	-3.03818
116	7135	0.0469403	-3.058878	-3.056653
117	7561	0.0459101	-3.081071	-3.075126
118	7987	0.0454593	-3.090937	-3.0936
119	8413	0.0444935	-3.112412	-3.112073

Regression Output:

Constant	-2.747245
Std Err of Y Est	0.0037522
R Squared	0.9989764
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-4.34E-05
Std Err of Coef.	3.18E-07





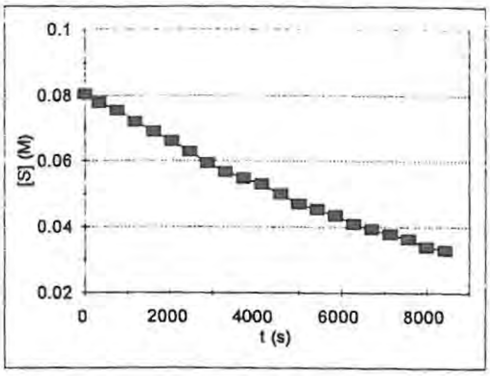
Kinetic data for the cyclisation of isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate **(104)** at 363K using a) the $\mathrm{C}\mathit{H}(\mathrm{CH}_3)_2$ and b) the $\mathrm{CH}(\mathrm{C}\mathit{H}_3)_2$ integrals (duplicate run).

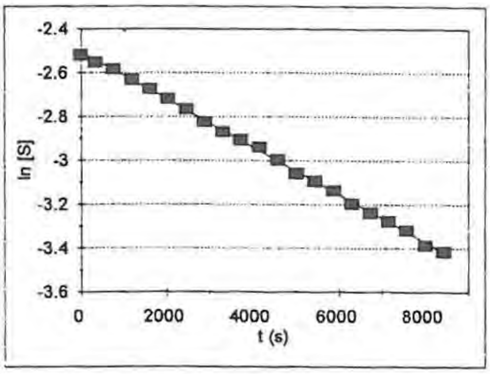
a)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress
	0	0.08055	-2.518877	-2.501041
100	338	0.0778919	-2.552434	-2.537748
101	764	0.0755559	-2.582882	-2.584012
102	1190	0.0720923	-2.629809	-2.630276
103	1616	0.0690314	-2.673195	-2.67654
104	2042	0.066051	-2.717328	-2.722804
105	2468	0.0629096	-2.766057	-2.769068
106	2894	0.0594459	-2.822689	-2.815332
107	3320	0.0567877	-2.868435	-2.861597
108	3746	0.054774	-2.90454	-2.907861
109	4172	0.0530019	-2.937428	-2.954125
110	4598	0.0500216	-2.995301	-3.000389
111	5024	0.0469606	-3.058445	-3.046653
112	5450	0.0453496	-3.093353	-3.092917
113	5876	0.043497	-3.135063	-3.139181
114	6302	0.0409194	-3.196151	-3.185445
115	6728	0.0393084	-3.236317	-3.231709
116	7154	0.037778	-3.27603	-3.277973
117	7580	0.0362475	-3.317385	-3.324238
118	8006	0.033831	-3.386378	-3.370502
119	8432	0.0328644	-3.415365	-3.416766

Regression Output:

Constant	-2.501041
Std Err of Y Est	0.0115335
R Squared	0.9984606
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-0.000109
Std Err of Coef.	9.78E-07



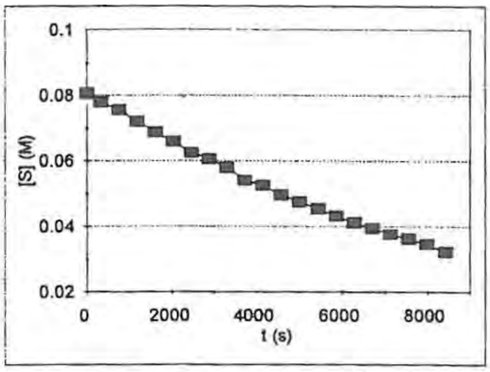


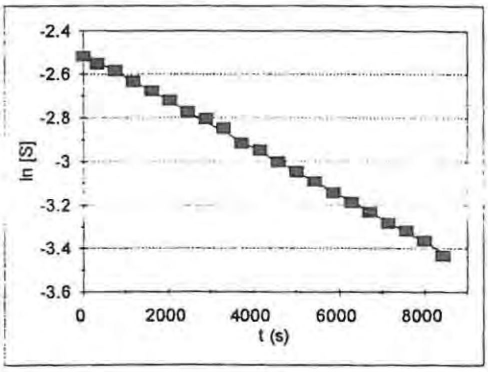
b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress
	0	0.08055	-2.518877	-2.504733
100	338	0.0778919	-2.552434	-2.541353
101	764	0.0754754	-2.583949	-2.587507
102	1190	0.0718506	-2.633166	-2.633661
103	1616	0.0687092	-2.677873	-2.679815
104	2042	0.0658094	-2.720993	-2.725969
105	2468	0.0624263	-2.773769	-2.772123
106	2894	0.0604931	-2.805227	-2.818277
107	3320	0.0579155	-2.848771	-2.864431
108	3746	0.0540491	-2.917863	-2.910585
109	4172	0.0524381	-2.948123	-2.956739
110	4598	0.0495383	-3.00501	-3.002894
111	5024	0.047444	-3.048206	-3.049048
112	5450	0.0453496	-3.093353	-3.095202
113	5876	0.0430943	-3.144366	-3.141356
114	6302	0.0411611	-3.190263	-3.18751
115	6728	0.039389	-3.23427	-3.233664
116	7154	0.0374558	-3.284595	-3.279818
117	7580	0.036167	-3.31961	-3.325972
118	8006	0.034556	-3.365176	-3.372126
119	8432	0.03222	-3.435168	-3.41828

Regression Output:

Constant	-2.504733
Std Err of Y Est	0.0083735
R Squared	0.9991841
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-0.000108
Std Err of Coef.	7.1E-07





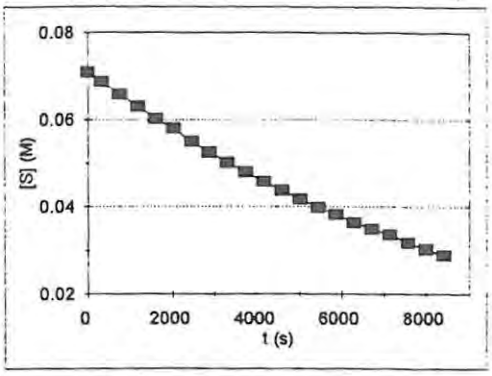
Kinetic data for the cyclisation of isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate (104) at 373K using a) the $C\mathit{H}(CH_3)_2$ and b) the $CH(C\mathit{H}_3)_2$ integrals.

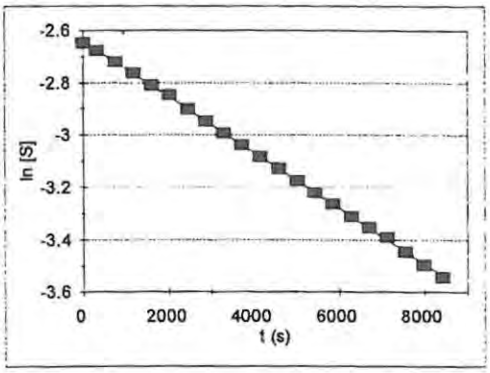
a)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.07083	-2.647473	-2.639736
100	330	0.0687051	-2.677932	-2.674875
101	756	0.0658719	-2.720043	-2.720236
102	1182	0.0631095	-2.762883	-2.765596
103	1608	0.0602055	-2.809992	-2.810957
104	2034	0.0580098	-2.847144	-2.856317
105	2460	0.0549641	-2.901075	-2.901678
106	2886	0.052485	-2.947227	-2.947039
107	3312	0.0501476	-2.992784	-2.992399
108	3738	0.0478811	-3.039035	-3.03776
109	4164	0.045827	-3.082882	-3.083121
110	4590	0.0437729	-3.128739	-3.128481
111	5016	0.0417897	-3.175105	-3.173842
112	5442	0.0399481	-3.220174	-3.219203
113	5868	0.0382482	-3.263659	-3.264563
114	6294	0.0364775	-3.311061	-3.309924
115	6720	0.03499	-3.352692	-3.355285
116	7146	0.0337151	-3.38981	-3.400645
117	7572	0.0318735	-3.44598	-3.446006
118	7998	0.0303152	-3.496105	-3.491366
119	8424	0.0288986	-3.543961	-3.536727

Regression Output:

Constant		-2.639736
Std Err of Y Est		0.0043981
R Squared		0.9997667
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000106	
Std Err of Coef.	3.73E-07	



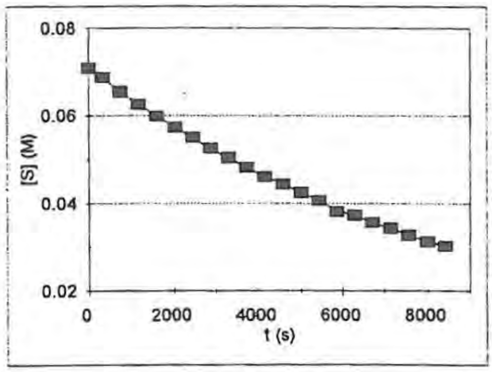


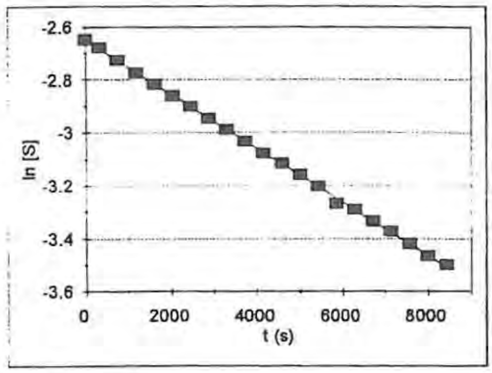
b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.07083	-2.647473	-2.651017
100	330	0.0686343	-2.678963	-2.684631
101	756	0.0654469	-2.726516	-2.728022
102	1182	0.0624721	-2.773036	-2.771414
103	1608	0.0598514	-2.815891	-2.814806
104	2034	0.0573015	-2.859429	-2.858198
105	2460	0.0549641	-2.901075	-2.901589
106	2886	0.0525559	-2.945879	-2.944981
107	3312	0.0503601	-2.988555	-2.988373
108	3738	0.0481644	-3.033135	-3.031765
109	4164	0.0460395	-3.078256	-3.075156
110	4590	0.0443396	-3.115878	-3.118548
111	5016	0.0424272	-3.159966	-3.16194
112	5442	0.0406564	-3.202599	-3.205331
113	5868	0.0380626	-3.268522	-3.248723
114	6294	0.0372566	-3.289927	-3.292115
115	6720	0.0356275	-3.334638	-3.335507
116	7146	0.0342817	-3.373143	-3.378898
117	7572	0.0327235	-3.419663	-3.42229
118	7998	0.031236	-3.466183	-3.465682
119	8424	0.0302444	-3.498444	-3.509074

Regression Output:

Constant		-2.651017
Std Err of Y Est		0.0078939
R Squared		0.9991793
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000102	
Std Err of Coef.	6.7E-07	





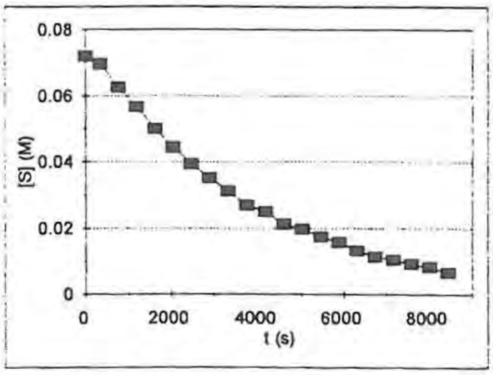
Kinetic data for the cyclisation of isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate **(104)** at 373K using a) the $C\mathit{H}(\mathrm{CH3})_2$ and b) the $\mathrm{CH}(C\mathit{H}_3)_2$ integrals (duplicate run).

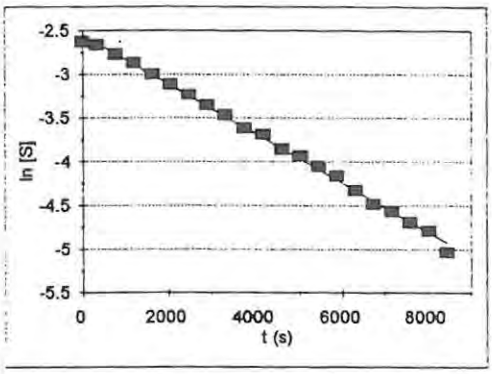
a)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.07208	-2.629979	-2.545579
100	351	0.0696293	-2.66457	-2.64465
101	777	0.0624934	-2.772695	-2.764889
102	1203	0.056727	-2.869506	-2.885129
103	1629	0.0499514	-2.996704	-3.005368
104	2055	0.0444013	-3.114487	-3.125608
105	2481	0.0394278	-3.233285	-3.245847
106	2907	0.035103	-3.34947	-3.366087
107	3333	0.0312827	-3.464689	-3.486326
108	3759	0.0268858	-3.616156	-3.606566
109	4185	0.0250118	-3.688409	-3.726805
110	4611	0.0211915	-3.854154	-3.847045
111	5037	0.0196778	-3.928262	-3.967284
112	5463	0.0173713	-4.052937	-4.087524
113	5889	0.0156414	-4.157837	-4.207763
114	6315	0.0132627	-4.322798	-4.328003
115	6741	0.0113166	-4.481488	-4.448242
116	7167	0.0103795	-4.567921	-4.568482
117	7593	0.0091542	-4.693547	-4.688721
118	8019	0.0082892	-4.792802	-4.808961
119	8445	0.0065232	-5.032384	-4.9292

Regression Output:

Constant		-2.545579
Std Err of Y Est		0.0382639
R Squared		0.997496
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000282	
Std Err of Coef.	3.24E-06	



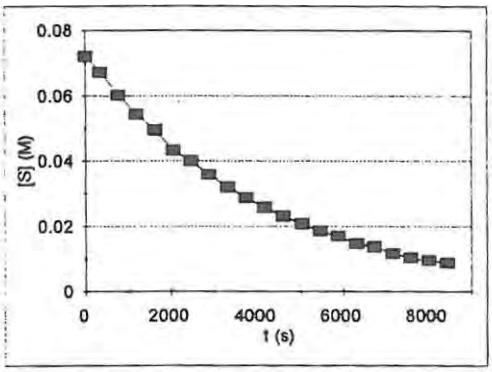


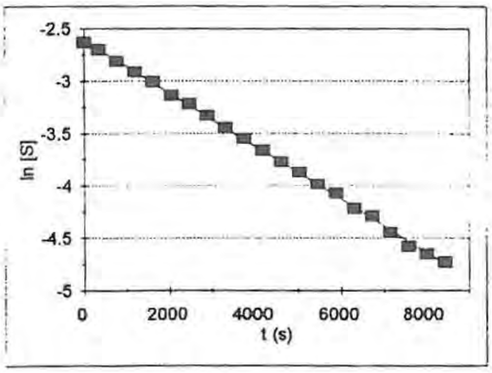
b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.07208	-2.629979	-2.605777
100	352	0.0671065	-2.701475	-2.695149
101	778	0.0600426	-2.8127	-2.803309
102	1204	0.0543483	-2.912342	-2.91147
103	1630	0.0494469	-3.006856	-3.01963
104	2056	0.0431759	-3.142472	-3.12779
105	2482	0.0399323	-3.220569	-3.23595
106	2908	0.0357517	-3.331158	-3.344111
107	3334	0.0319314	-3.444164	-3.452271
108	3760	0.0286158	-3.553798	-3.560431
109	4186	0.0256605	-3.662803	-3.668591
110	4612	0.0229935	-3.772543	-3.776752
111	5038	0.020759	-3.874773	-3.884912
112	5464	0.0185246	-3.988658	-3.993072
113	5890	0.0170109	-4.073902	-4.101232
114	6316	0.0147043	-4.219614	-4.209393
115	6742	0.0136952	-4.29071	-4.317553
116	7168	0.011677	-4.450138	-4.425713
117	7594	0.0102354	-4.581907	-4.533873
118	8020	0.0095146	-4.654932	-4.642034
119	8446	0.0087938	-4.733713	-4.750194

Regression Output:

Constant		-2.605777
Std Err of Y Est		0.018771
R Squared		0.999254
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000254	
Std Err of Coef.	1.59E-06	





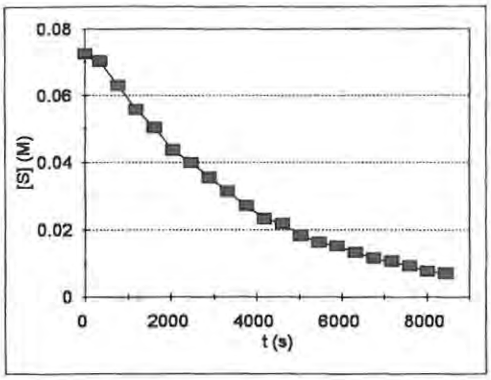
Kinetic data for the cyclisation of isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate **(104)** at 383K using a) the $C\mathit{H}(CH3)_2$ and b) the $CH(C\mathit{H}_3)_2$ integrals.

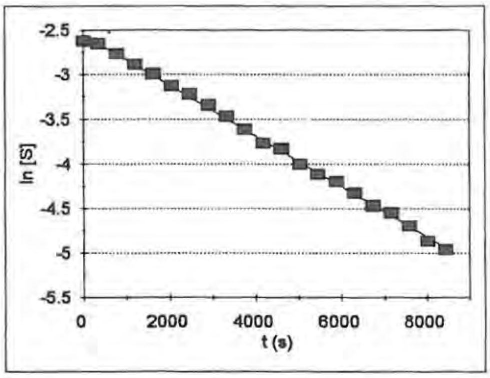
a)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.0724	-2.625549	-2.550261
100	352	0.070228	-2.656008	-2.649984
101	778	0.0628432	-2.767113	-2.77067
102	1204	0.0556756	-2.888213	-2.891357
103	1630	0.0502456	-2.990832	-3.012044
104	2056	0.0435848	-3.133047	-3.13273
105	2482	0.0398924	-3.221569	-3.253417
106	2908	0.0354036	-3.340942	-3.374104
107	3334	0.0312768	-3.464879	-3.494791
108	3760	0.0270776	-3.609048	-3.615477
109	4186	0.023168	-3.764983	-3.736164
110	4612	0.0217924	-3.826194	-3.856851
111	5038	0.0182448	-4.003875	-3.977537
112	5464	0.01629	-4.117204	-4.098224
113	5890	0.0150592	-4.195766	-4.218911
114	6316	0.0131768	-4.329298	-4.339598
115	6742	0.0114392	-4.470709	-4.460284
116	7168	0.0105704	-4.549698	-4.580971
117	7594	0.0091224	-4.697022	-4.701658
118	8020	0.0076744	-4.869865	-4.822344
119	8446	0.0070228	-4.958593	-4.943031

Regression Output:

Constant		-2.550261
Std Err of Y Est		0.0292915
R Squared		0.9985421
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000283	
Std Err of Coef.	2.48E-06	



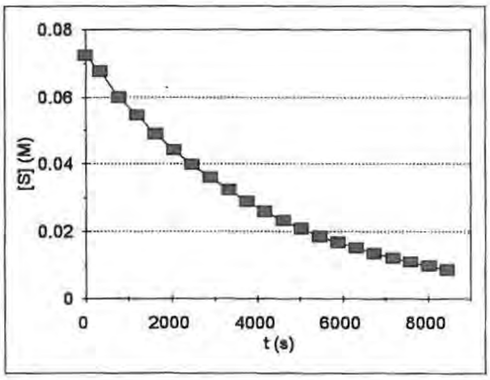


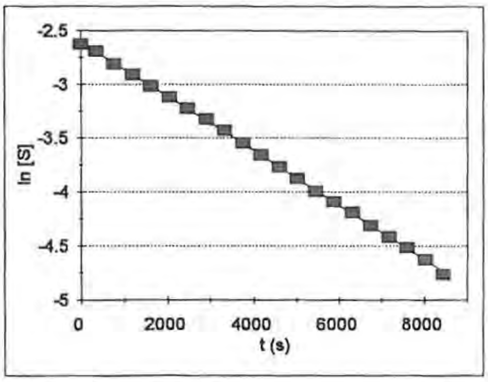
b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.0724	-2.625549	-2.605164
100	352	0.0677664	-2.691689	-2.694079
101	778	0.0600196	-2.813084	-2.801686
102	1204	0.0545172	-2.909239	-2.909294
103	1630	0.0489424	-3.017111	-3.016901
104	2056	0.0440916	-3.121486	-3.124508
105	2482	0.0397476	-3.225206	-3.232116
106	2908	0.0359104	-3.326728	-3.339723
107	3334	0.0322904	-3.432985	-3.447331
108	3760	0.0287428	-3.549368	-3.554938
109	4186	0.0257744	-3.658374	-3.662545
110	4612	0.0230232	-3.771253	-3.770153
111	5038	0.0207064	-3.877312	-3.87776
112	5464	0.0183896	-3.99597	-3.985367
113	5890	0.0167244	-4.090887	-4.092975
114	6316	0.0151316	-4.19097	-4.200582
115	6742	0.013394	-4.312948	-4.30819
116	7168	0.0120908	-4.41531	-4.415797
117	7594	0.0109324	-4.516024	-4.523404
118	8020	0.009774	-4.628029	-4.631012
119	8446	0.0085432	-4.76262	-4.738619

Regression Output:

Constant		-2.605164
Std Err of Y Est		0.0100106
R Squared		0.9997855
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-0.000253	
Std Err of Coef.	8.49E-07	





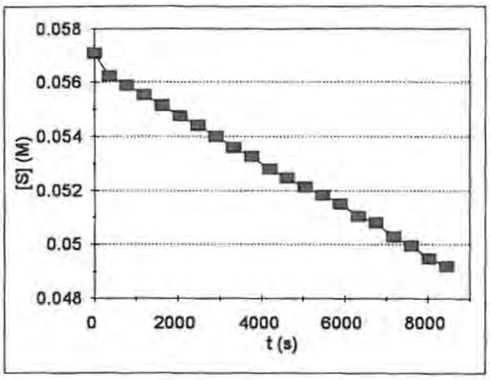
Kinetic data for the cyclisation of isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate (104) at 383K using a) the C*H*(CH3)$_2$ and b) the CH(CH_3)$_2$ integrals (duplicate run).

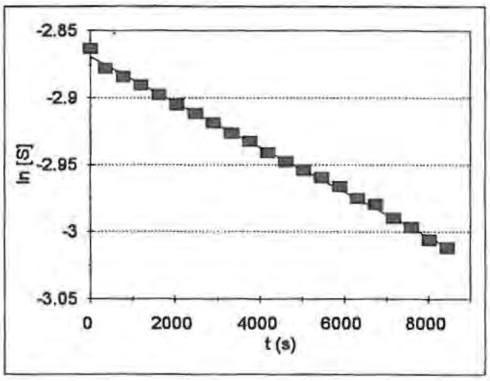
a)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.05708	-2.863301	-2.869572
100	361	0.05624	-2.878127	-2.875621
101	787	0.0558813	-2.884525	-2.882759
102	1213	0.0555388	-2.890673	-2.889898
103	1639	0.0551393	-2.897893	-2.897036
104	2065	0.0547397	-2.905166	-2.904174
105	2491	0.0543972	-2.911442	-2.911313
106	2917	0.0539977	-2.918814	-2.918451
107	3343	0.0535981	-2.926241	-2.925589
108	3769	0.0532556	-2.932652	-2.932728
109	4195	0.052799	-2.941263	-2.939866
110	4621	0.0524565	-2.947771	-2.947005
111	5047	0.052114	-2.954321	-2.954143
112	5473	0.0518286	-2.959812	-2.961281
113	5899	0.0514862	-2.966442	-2.96842
114	6325	0.0510295	-2.975351	-2.975558
115	6751	0.0508012	-2.979835	-2.982697
116	7177	0.0502875	-2.989999	-2.989835
117	7603	0.049945	-2.996833	-2.996973
118	8029	0.0494884	-3.006018	-3.004112
119	8455	0.049203	-3.011801	-3.01125

Regression Output:

Constant	-2.869572
Std Err of Y Est	0.0019529
R Squared	0.9981493
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-1.68E-05
Std Err of Coef.	1.66E-07



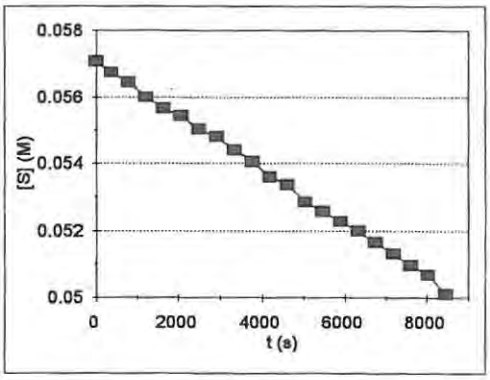


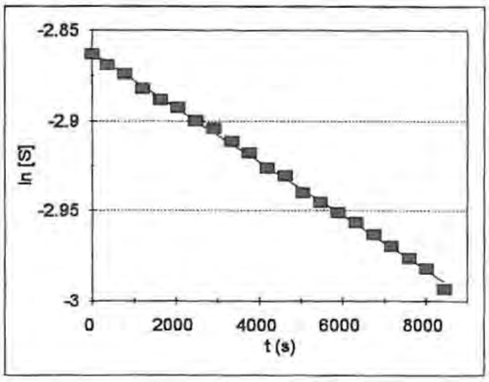
b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.05708	-2.863301	-2.86272
100	361	0.0567375	-2.86932	-2.868133
101	787	0.0564521	-2.874362	-2.874521
102	1213	0.0559955	-2.882484	-2.880908
103	1639	0.055653	-2.888619	-2.887296
104	2065	0.0554247	-2.89273	-2.893684
105	2491	0.0550251	-2.899965	-2.900072
106	2917	0.0547968	-2.904123	-2.906459
107	3343	0.0543972	-2.911442	-2.912847
108	3769	0.0540548	-2.917758	-2.919235
109	4195	0.0535981	-2.926241	-2.925623
110	4621	0.0533698	-2.93051	-2.93201
111	5047	0.0528561	-2.940183	-2.938398
112	5473	0.0525707	-2.945597	-2.944786
113	5899	0.0522853	-2.95104	-2.951174
114	6325	0.0519999	-2.956514	-2.957562
115	6751	0.0516574	-2.963122	-2.963949
116	7177	0.0513149	-2.969774	-2.970337
117	7603	0.0509724	-2.97647	-2.976725
118	8029	0.050687	-2.982085	-2.983113
119	8455	0.0501162	-2.99341	-2.9895

Regression Output:

Constant	-2.86272
Std Err of Y Est	0.0014786
R Squared	0.9986744
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-1.5E-05
Std Err of Coef.	1.25E-07





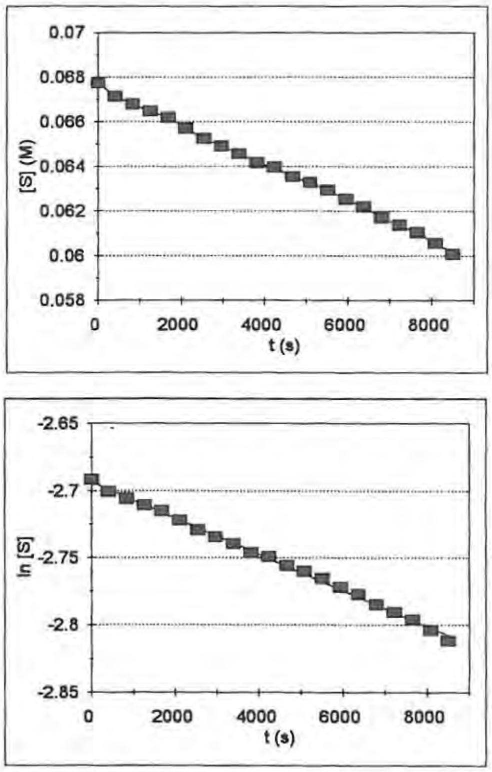
Kinetic data for the cyclisation of *tert*-butyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate (105) at 363K using a) the CO.CH_3/acetic acid and b) the $C(CH_3)_3$ integrals.

a)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.06776	-2.691783	-2.693552
100	411	0.0671502	-2.700824	-2.699081
101	837	0.0668114	-2.705882	-2.704812
102	1263	0.0664726	-2.710966	-2.710543
103	1689	0.0662015	-2.715052	-2.716274
104	2115	0.0657272	-2.722242	-2.722005
105	2541	0.0652529	-2.729485	-2.727737
106	2967	0.0649141	-2.734691	-2.733468
107	3393	0.0645753	-2.739924	-2.739199
108	3819	0.0641687	-2.746239	-2.74493
109	4245	0.0639654	-2.749412	-2.750661
110	4671	0.0635589	-2.755789	-2.756392
111	5097	0.0632878	-2.760062	-2.762123
112	5523	0.062949	-2.76543	-2.767855
113	5949	0.0625425	-2.771909	-2.773586
114	6375	0.0622037	-2.777341	-2.779317
115	6801	0.0617294	-2.784996	-2.785048
116	7227	0.0613906	-2.790499	-2.790779
117	7653	0.0610518	-2.796033	-2.79651
118	8079	0.0605774	-2.803833	-2.802241
119	8505	0.0601031	-2.811694	-2.807973

Regression Output:

Constant		-2.693552
Std Err of Y Est		0.0016429
R Squared		0.9979744
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-1.35E-05	
Std Err of Coef.	1.39E-07	

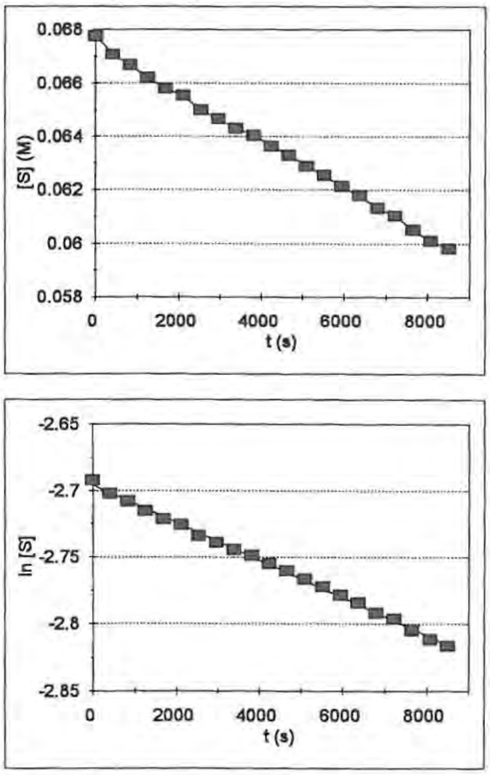


b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.06776	-2.691783	-2.695533
100	411	0.0670824	-2.701834	-2.701332
101	837	0.0666758	-2.707913	-2.707343
102	1263	0.0662015	-2.715052	-2.713353
103	1689	0.065795	-2.721212	-2.719364
104	2115	0.0655239	-2.72534	-2.725374
105	2541	0.0649818	-2.733647	-2.731385
106	2967	0.064643	-2.738875	-2.737395
107	3393	0.0643042	-2.74413	-2.743405
108	3819	0.0640332	-2.748354	-2.749416
109	4245	0.0636266	-2.754723	-2.755426
110	4671	0.0632878	-2.760062	-2.761437
111	5097	0.0628813	-2.766507	-2.767447
112	5523	0.0625425	-2.771909	-2.773458
113	5949	0.0621359	-2.778431	-2.779468
114	6375	0.0617971	-2.783899	-2.785479
115	6801	0.0613228	-2.791604	-2.791489
116	7227	0.0610518	-2.796033	-2.7975
117	7653	0.0605097	-2.804952	-2.80351
118	8079	0.0601031	-2.811694	-2.80952
119	8505	0.0598321	-2.816213	-2.815531

Regression Output:

Constant		-2.695533
Std Err of Y Est		0.001599
R Squared		0.9982551
No. of Observations		21
Degrees of Freedom		19
X Coefficient(s)	-1.41E-05	
Std Err of Coef.	1.35E-07	



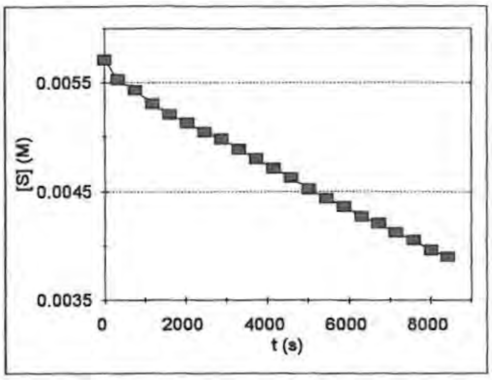
Kinetic data for the cyclisation of *tert*-butyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate (105) at 363K using a) the CO.CH_3/acetic acid and b) the $C(CH_3)_3$ integrals (duplicate run).

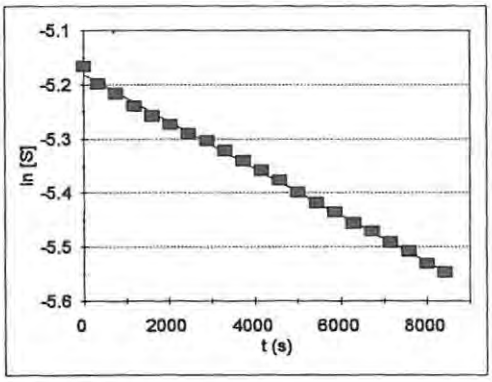
a)

Expt.No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.005708	-5.165887	-5.180562
100	333	0.0055253	-5.19841	-5.195035
101	759	0.0054283	-5.216128	-5.21355
102	1185	0.0053027	-5.239533	-5.232064
103	1611	0.0052057	-5.258002	-5.250579
104	2037	0.0051258	-5.273472	-5.269093
105	2463	0.0050402	-5.290317	-5.287608
106	2889	0.0049774	-5.302852	-5.306123
107	3315	0.004886	-5.321371	-5.324637
108	3741	0.0047947	-5.34024	-5.343152
109	4167	0.0047091	-5.358258	-5.361666
110	4593	0.0046235	-5.376608	-5.380181
111	5019	0.0045207	-5.39908	-5.398696
112	5445	0.0044351	-5.418202	-5.41721
113	5871	0.0043609	-5.435074	-5.435725
114	6297	0.0042696	-5.456239	-5.454239
115	6723	0.0042068	-5.471054	-5.472754
116	7149	0.0041212	-5.491617	-5.491269
117	7575	0.0040527	-5.508377	-5.509783
118	8001	0.0039614	-5.53117	-5.528298
119	8427	0.0038986	-5.547147	-5.546813

Regression Output:

Constant	-5.180562
Std Err of Y Est	0.0048337
R Squared	0.9983115
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-4.35E-05
Std Err of Coef.	4.1E-07



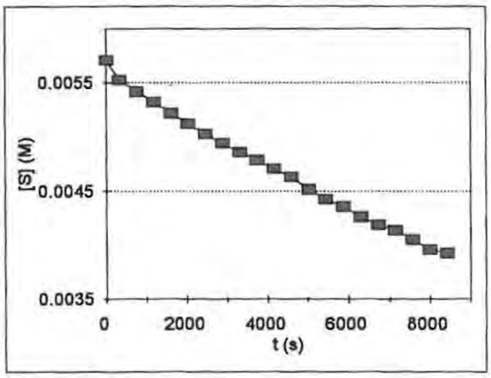


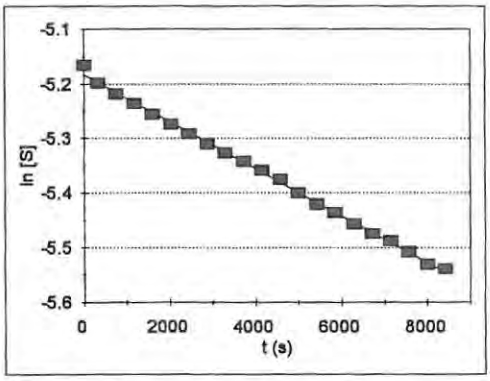
b)

Expt.No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.005708	-5.165887	-5.18246
100	333	0.0055253	-5.19841	-5.19684
101	759	0.0054169	-5.218233	-5.215236
102	1185	0.0053199	-5.236309	-5.233632
103	1611	0.0052171	-5.255811	-5.252028
104	2037	0.0051201	-5.274586	-5.270424
105	2463	0.0050287	-5.292584	-5.28882
106	2889	0.0049374	-5.310912	-5.307217
107	3315	0.0048575	-5.32723	-5.325613
108	3741	0.0047833	-5.342624	-5.344009
109	4167	0.0047034	-5.359471	-5.362405
110	4593	0.0046292	-5.375374	-5.380801
111	5019	0.004515	-5.400344	-5.399197
112	5445	0.0044237	-5.420779	-5.417593
113	5871	0.0043552	-5.436384	-5.435989
114	6297	0.0042639	-5.457577	-5.454385
115	6723	0.0041897	-5.475133	-5.472781
116	7149	0.0041383	-5.48747	-5.491177
117	7575	0.0040527	-5.508377	-5.509573
118	8001	0.0039614	-5.53117	-5.52797
119	8427	0.0039271	-5.539853	-5.546366

Regression Output:

Constant	-5.18246
Std Err of Y Est	0.0050809
R Squared	0.9981106
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-4.32E-05
Std Err of Coef.	4.31E-07





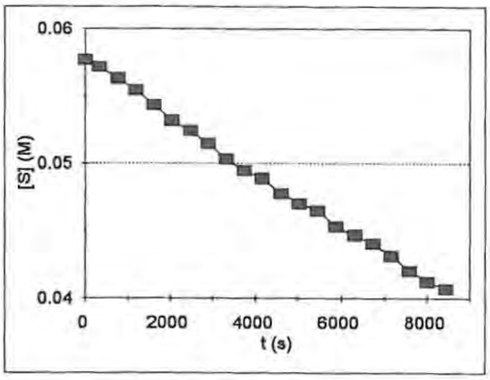
Kinetic data for the cyclisation of *tert*-butyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate (105) at 373K using a) the CO.CH_3/acetic acid and b) the $C(CH_3)_3$ integrals.

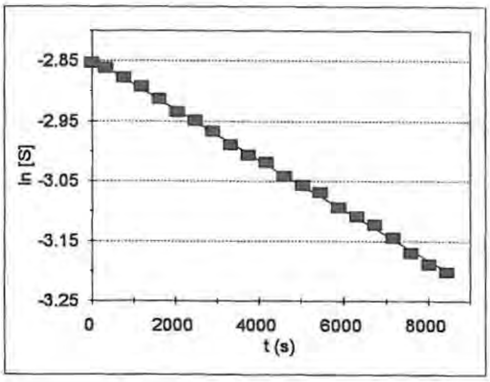
a)

Expt No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.05764	-2.853539	-2.847084
100	341	0.05712	-2.862601	-2.861354
101	767	0.05626	-2.877771	-2.879181
102	1193	0.05539	-2.893356	-2.897007
103	1619	0.0543	-2.913231	-2.914834
104	2045	0.05314	-2.934825	-2.932661
105	2471	0.0524	-2.948849	-2.950488
106	2897	0.05147	-2.966756	-2.968315
107	3323	0.05032	-2.989353	-2.986142
108	3749	0.04946	-3.006591	-3.003969
109	4175	0.04888	-3.018387	-3.021795
110	4601	0.04778	-3.041148	-3.039622
111	5027	0.04703	-3.05697	-3.057449
112	5453	0.04651	-3.068088	-3.075276
113	5879	0.04531	-3.094228	-3.093103
114	6305	0.04467	-3.108453	-3.11093
115	6731	0.04404	-3.122657	-3.128756
116	7157	0.04311	-3.144	-3.146583
117	7583	0.04202	-3.16961	-3.16441
118	8009	0.04121	-3.189074	-3.182237
119	8435	0.04069	-3.201773	-3.200064

Regression Output:

Constant	-2.847084
Std Err of Y Est	0.003852
R Squared	0.9988433
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-4.18E-05
Std Err of Coef.	3.27E-07



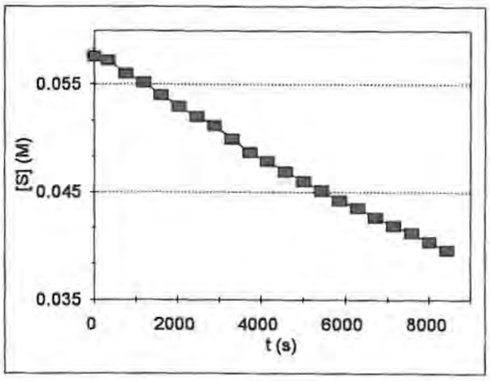


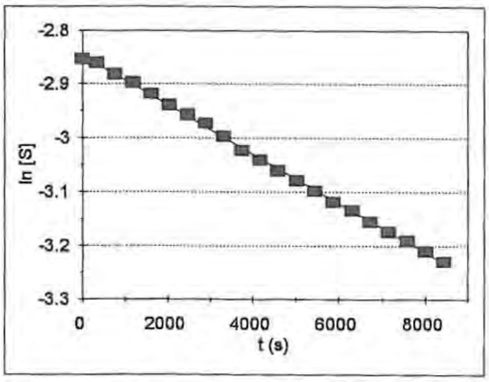
b)

Expt No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.05764	-2.853539	-2.847073
100	341	0.05724	-2.860502	-2.862619
101	767	0.05603	-2.881868	-2.88204
102	1193	0.05516	-2.897517	-2.901462
103	1619	0.05401	-2.918586	-2.920883
104	2045	0.05291	-2.939163	-2.940304
105	2471	0.05198	-2.956896	-2.959726
106	2897	0.05116	-2.972797	-2.979147
107	3323	0.04993	-2.997133	-2.998568
108	3749	0.04866	-3.022898	-3.017989
109	4175	0.0478	-3.04073	-3.037411
110	4601	0.04687	-3.060377	-3.056832
111	5027	0.04601	-3.078897	-3.076253
112	5453	0.04514	-3.097987	-3.095674
113	5879	0.04422	-3.118578	-3.115096
114	6305	0.04353	-3.134305	-3.134517
115	6731	0.04261	-3.155666	-3.153938
116	7157	0.04186	-3.173425	-3.17336
117	7583	0.04117	-3.190045	-3.192781
118	8009	0.04036	-3.209916	-3.212202
119	8435	0.03961	-3.228674	-3.231623

Regression Output:

Constant	-2.847073
Std Err of Y Est	0.0033671
R Squared	0.999255
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-4.56E-05
Std Err of Coef.	2.86E-07





Kinetic data for the cyclisation of *tert*-butyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate **(105)** at 373K using a) the CO.CH_3/acetic acid and b) the $C(CH_3)_3$ integrals (duplicate run).

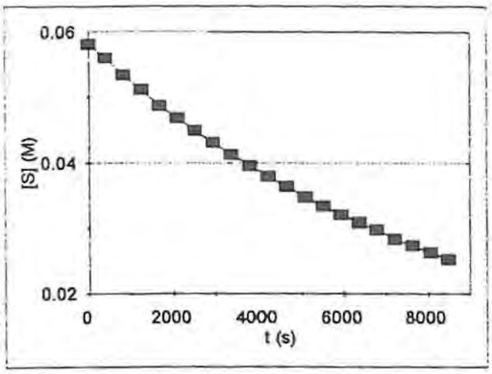
a)

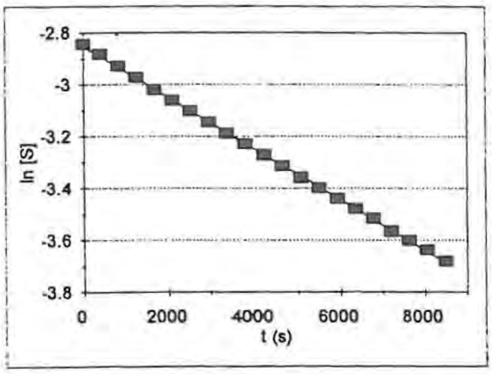
Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.05818	-2.844214	-2.85093
100	398	0.05604	-2.88169	-2.890119
101	824	0.05348	-2.928448	-2.932066
102	1250	0.05126	-2.970845	-2.974012
103	1676	0.04881	-3.01982	-3.015958
104	2102	0.04688	-3.060164	-3.057904
105	2528	0.04495	-3.102205	-3.09985
106	2954	0.04308	-3.144696	-3.141796
107	3380	0.04127	-3.187619	-3.183742
108	3806	0.03958	-3.229431	-3.225689
109	4232	0.03795	-3.271486	-3.267635
110	4658	0.03637	-3.314011	-3.309581
111	5084	0.03479	-3.358425	-3.351527
112	5510	0.03345	-3.397703	-3.393473
113	5936	0.03211	-3.438588	-3.435419
114	6362	0.03088	-3.477647	-3.477365
115	6788	0.02977	-3.514254	-3.519312
116	7214	0.02831	-3.56454	-3.561258
117	7640	0.02732	-3.600136	-3.603204
118	8066	0.02633	-3.637046	-3.64515
119	8492	0.02522	-3.680118	-3.687096

Regression Output:

Constant	-2.85093
Std Err of Y Est	0.0049868
R Squared	0.9996508
No. of Observations	21
Degrees of Freedom	19

X Coefficient(s)	-9.85E-05
Std Err of Coef.	4.22E-07





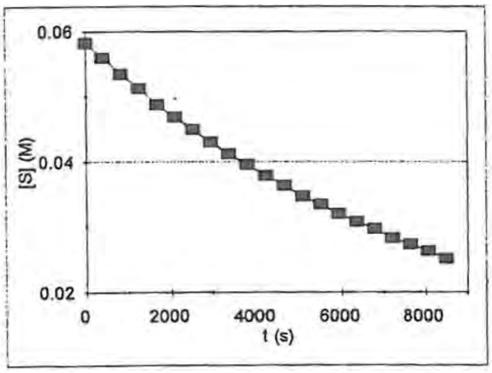
b)

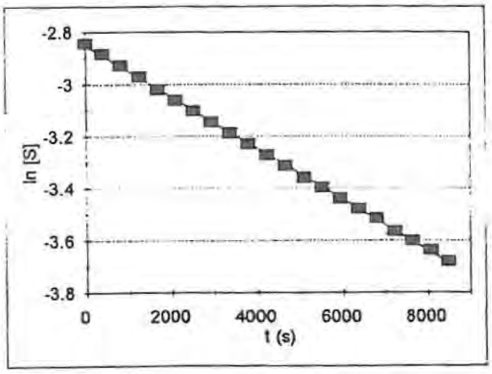
Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.05818	-2.844214	-2.851527
100	398	0.05594	-2.883476	-2.890764
101	824	0.05349	-2.928261	-2.932762
102	1250	0.05124	-2.971235	-2.97476
103	1676	0.04875	-3.02105	-3.016758
104	2102	0.04683	-3.061231	-3.058756
105	2528	0.04492	-3.102872	-3.100754
106	2954	0.04301	-3.146323	-3.142752
107	3380	0.04125	-3.188104	-3.184749
108	3806	0.03955	-3.23019	-3.226747
109	4232	0.03789	-3.273068	-3.268745
110	4658	0.03635	-3.314561	-3.310743
111	5084	0.03472	-3.360439	-3.352741
112	5510	0.03342	-3.398601	-3.394739
113	5936	0.03206	-3.440146	-3.436737
114	6362	0.03081	-3.479916	-3.478735
115	6788	0.02974	-3.515262	-3.520732
116	7214	0.02827	-3.565954	-3.56273
117	7640	0.02729	-3.601235	-3.604728
118	8066	0.02629	-3.638567	-3.646726
119	8492	0.02518	-3.681705	-3.688724

Regression Output:

Constant	-2.851527
Std Err of Y Est	0.0050939
R Squared	0.9996365
No. of Observations	21
Degrees of Freedom	19

X Coefficient(s)	-9.86E-05
Std Err of Coef.	4.31E-07





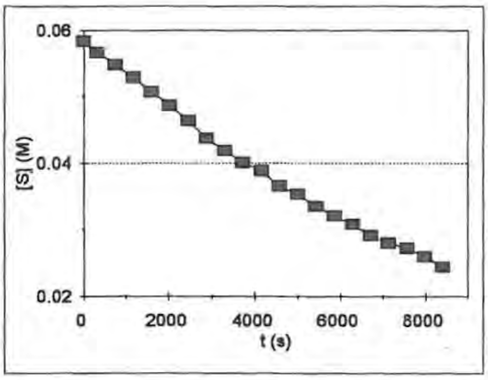
Kinetic data for the cyclisation of *tert*-butyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate **(105)** at 383K using a) the $CO.CH_3$/acetic acid and b) the $C(CH_3)_3$ integrals.

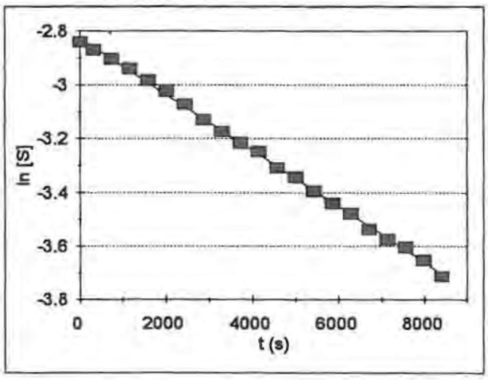
a)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.05838	-2.840782	-2.825529
100	318	0.0566286	-2.871241	-2.858741
101	744	0.0548188	-2.903722	-2.903234
102	1170	0.0528923	-2.939498	-2.947726
103	1596	0.0506738	-2.982345	-2.992219
104	2022	0.0486305	-3.023504	-3.036711
105	2448	0.0463537	-3.071454	-3.081204
106	2874	0.0437266	-3.129798	-3.125696
107	3300	0.0418585	-3.173461	-3.170189
108	3726	0.0401071	-3.216203	-3.214682
109	4152	0.0388227	-3.24875	-3.259174
110	4578	0.0365459	-3.309187	-3.303667
111	5004	0.0353199	-3.343309	-3.348159
112	5430	0.0335101	-3.395908	-3.392652
113	5856	0.0320506	-3.440439	-3.437144
114	6282	0.0308246	-3.479441	-3.481637
115	6708	0.0290732	-3.537937	-3.526129
116	7134	0.027964	-3.576837	-3.570622
117	7560	0.0272051	-3.604352	-3.615114
118	7986	0.0259207	-3.652713	-3.659607
119	8412	0.0244028	-3.713056	-3.704099

Regression Output:

Constant	-2.825529
Std Err of Y Est	0.0087788
R Squared	0.999034
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-0.000104
Std Err of Coef.	7.45E-07



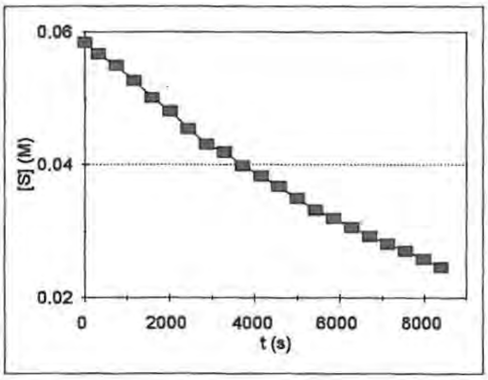


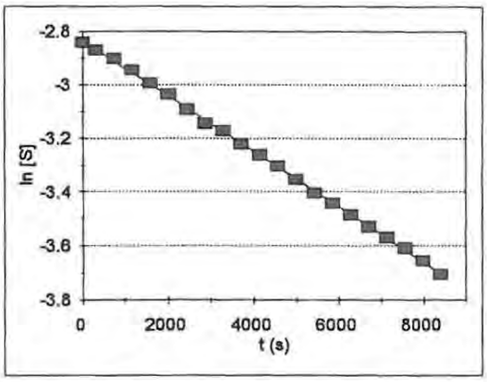
b)

Expt. No.	t (s)	[S] (M)	ln [S]	Regress.
	0	0.05838	-2.840782	-2.833811
100	318	0.056687	-2.870211	-2.866725
101	744	0.0549356	-2.901594	-2.910817
102	1170	0.0526588	-2.943923	-2.95491
103	1596	0.05009	-2.993933	-2.999002
104	2022	0.0480467	-3.035581	-3.043095
105	2448	0.0453613	-3.093097	-3.087187
106	2874	0.0430261	-3.145949	-3.13128
107	3300	0.0418585	-3.173461	-3.175372
108	3726	0.0398152	-3.223508	-3.219465
109	4152	0.0382973	-3.262376	-3.263557
110	4578	0.036721	-3.304406	-3.30765
111	5004	0.0349112	-3.354946	-3.351742
112	5430	0.0332182	-3.404657	-3.395835
113	5856	0.0319922	-3.442262	-3.439927
114	6282	0.0306495	-3.485139	-3.48402
115	6708	0.0293068	-3.529937	-3.528112
116	7134	0.0281392	-3.570593	-3.572205
117	7560	0.0270883	-3.608653	-3.616297
118	7986	0.0258623	-3.654967	-3.66039
119	8412	0.024578	-3.705904	-3.704482

Regression Output:

Constant	-2.833811
Std Err of Y Est	0.0065747
R Squared	0.9994481
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-0.000104
Std Err of Coef.	5.58E-07





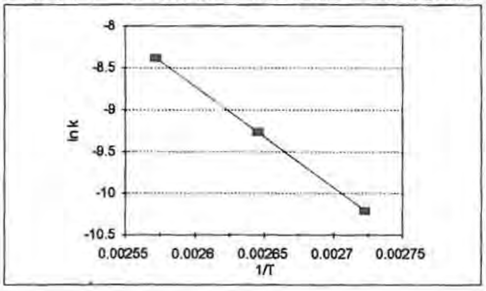
Kinetic data for the cyclisation of *tert*-butyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanoate (105) at 383K using a) the CO.CH_3/acetic acid and b) the $C(CH_3)_3$ integrals (duplicate run)

a)

T (K)	k (run 1)	k (run 2)	ln k1	ln k2	ln k (Ave.)	1/T	Regress.
367.3	3.41E-05	3.96E-05	-10.28621	-10.13668	-10.21145	0.002723	-10.20676
378	9.57E-05	9.41E-05	-9.254292	-9.271153	-9.262722	0.002646	-9.272317
388.8	0.00023	0.000226	-8.377431	-8.394976	-8.386203	0.002572	-8.381292

Regression Output:

Constant		22.80456
Std Err of Y Est		0.011752
R Squared		0.999917
No. of Observations		3
Degrees of Freedom		1
Degrees of Freedom		1
X Coefficient(s)	-12125.06	
Std Err of Coef.	110.3775	

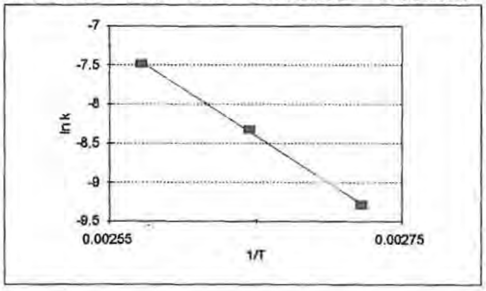


b)

T (K)	k (run 1)	k (run 2)	ln k1	ln k2	ln k (Ave.)	1/T	Regress.
367.3	9.42E-05	9.05E-05	-9.27009	-9.310161	-9.290126	0.002723	-9.27651
378	0.00025	0.000236	-8.29405	-8.351679	-8.322864	0.002646	-8.35076
388.8	0.00057	0.000556	-7.469874	-7.494742	-7.482308	0.002572	-7.468029

Regression Output:

Constant		23.42755
Std Err of Y Est		0.034168
R Squared		0.999287
No. of Observations		3
Degrees of Freedom		1
X Coefficient(s)	-12012.2	
Std Err of Coef.	320.9245	

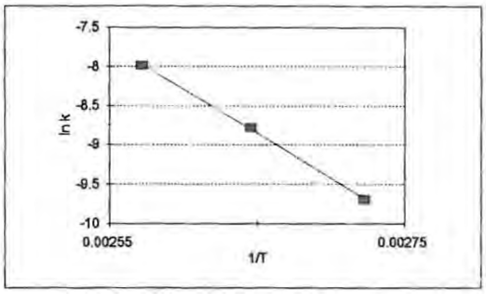


c)

T (K)	k (run 1)	k (run 2)	ln k1	ln k2	ln k (Ave.)	1/T	Regress.
367.3	5.92E-05	6.43E-05	-9.734589	-9.651951	-9.69327	0.002723	-9.681012
378	0.000151	0.000156	-8.798231	-8.765655	-8.781943	0.002646	-8.807057
388.8	0.000339	0.000341	-7.98951	-7.983628	-7.986569	0.002572	-7.973714

Regression Output:

Constant		21.19329
Std Err of Y Est		0.030761
R Squared		0.999351
No. of Observations		3
Degrees of Freedom		1
X Coefficient(s)	-11340.13	
Std Err of Coef.	288.9244	



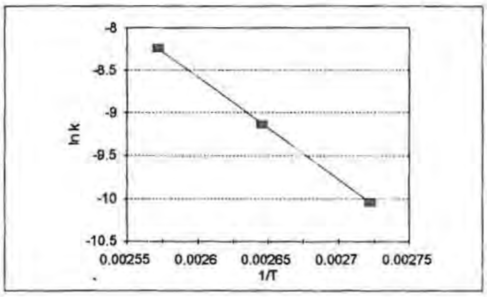
Arrhenius plots for the cyclisation of a) 3-acetoxy-2-methylene-3-(2-pyridyl) propanenitrile **(100)**, b) methyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanenitrile **(102)** and c) ethyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanenitrile **(103)**

a)

T (K)	k (run 1)	k (run 2)	ln k1	ln k2	ln k (Ave.)	1/T	Regress.
367.3	4.35E-05	4.37E-05	-10.04275	-10.03816	-10.04046	0.002723	-10.0475
378	0.00011	0.000105	-9.11503	-9.16155	-9.13829	0.002646	-9.123869
388.8	0.000265	0.000265	-8.235781	-8.235781	-8.235781	0.002572	-8.243163

Regression Output:

Constant		22.58155
Std Err of Y Est		0.017664
R Squared		0.999808
No. of Observations		3
Degrees of Freedom		1
X Coefficient(s)	-11984.65	
Std Err of Coef.	165.9107	

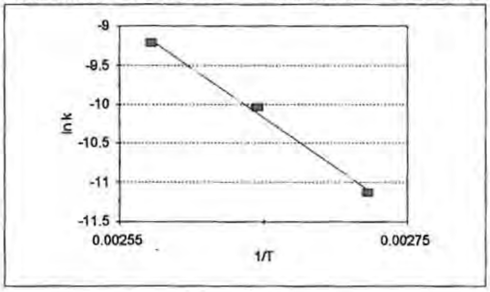


b)

T (K)	k (run 1)	k (run 2)	ln k1	ln k2	ln k (Ave)	1/T	Regress.
367.3	1.55E-05	1.38E-05	-11.07467	-11.19084	-11.13276	0.002723	-11.09629
378	4.35E-05	4.37E-05	-10.04275	-10.03816	-10.04046	0.002646	-10.11517
388.8	9.85E-05	0.0001	-9.225454	-9.21034	-9.217897	0.002572	-9.17965

Regression Output:

Constant		23.56363
Std Err of Y Est		0.091517
R Squared		0.995462
No. of Observations		3
Degrees of Freedom		1
X Coefficient(s)	-12730.59	
Std Err of Coef.	859.5796	



Arrhenius plots for the cyclisation of a) isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanenitrile (104) and b) methyl 3-acetoxy-2-methylene-3-(2-pyridyl) propanenitrile (105).

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