REARRANGEMENT AND CYCLOADDITION ROUTES TO NOVEL HETEROCYCLIC SYSTEMS

by

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A thesis submitted to the University of Keele in partial fulfilment of the requirements for the Degree of Doctor of Philosophy.

Department of Chemistry
University of Keele

September 1978

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TO MY PARENTS

The work in this thesis was carried out by the Author under the supervision of Dr. G. Jones.

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CONTENTS

-oOo-

ABSTRACT

Part I of this thesis describes the treatment of tetrahydro-4-oxoisoxazolo[2,3-a]pyridinium, phenyl hydrazone (70) with boiling acetic anhydride to give pyrazolo[4,3-b]pyridine (73) and the pyrrolo[3,2-b]pyridone (74), or on longer heating, further acetylation to give compounds (78) and (79) plus tri-N-(acetyl)phenylhydrazine (75). The Introduction to Part I contains a brief review of the reaction of nucleophiles with differing substituted isoxazolium salts.

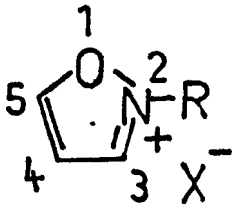
Part II contains the synthesis of pyrido[3,2-c]pyridazine (87) from 2-vinyl pyridine (90) and diesters of azodicarboxylic acid. The synthesis is then extended to include other vinyl heterocyclic systems. The Introduction gives a review of addition of dienophiles to vinyl heterocyclic compounds with a brief summary of cycloaddition and ene reactions of diesters of azodicarboxylic acid.

P A R T I

INTRODUCTION

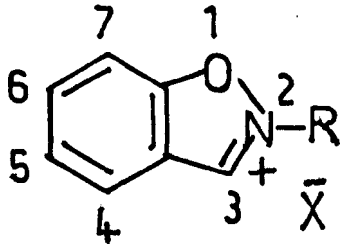
Nomenclature

a. In Part I of this thesis the monocyclic isoxazolium salts will be named and numbered as:

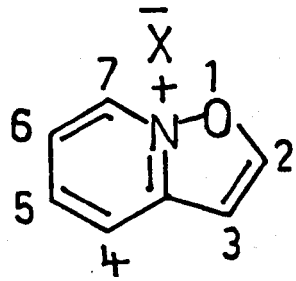


isoxazolium salts

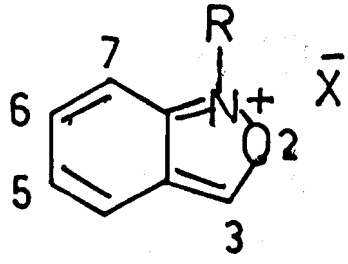
b. The bicyclic systems will be named and numbered according to the rules set down by the American Chemical Society Ring Index.



1,2-benzisoxazolium salts



isoxazolo[2,3-a]pyridinium salts



2,1-benzisoxazolium salts

Preparation of Isoxazolium Salts

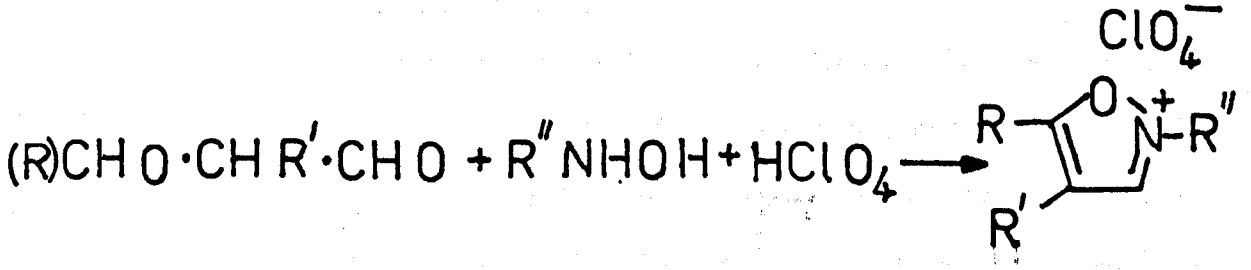
Isoxazolium salts are usually prepared by quaternization of the requisite isoxazole. Alkylation of isoxazoles is complicated not only by their weakly basic nature but to a lesser extent by the vulnerability of their quaternary salts to nucleophilic attack. It is usually advantageous to restrict reaction temperatures to 40 - 50°C but this in turn requires long reaction times with the common alkylating reagents.

The most commonly used reagents are: alkyl p-toluene sulphonates,[1] dialkyl sulphates,[1,2,3] and trialkyl oxonium fluoroborates.[3,4] Occasionally a higher reaction temperature is necessary or a highly reactive reagent such as methyl-2,4-dinitrobenzenesulphonate[1] is used.

A branched quaternizing group is best introduced by treatment of the isoxazole with an appropriate alcohol (which must be a good carbonium ion source) and perchloric acid.[5,6]

Using sulpholane[2] as solvent may improve the alkylation since it tends to reduce reaction times, by-product formation and minimizes the purification problems.

It has been reported[6,7] that in some cases the salts have been prepared by attaching the substituent to nitrogen prior to cyclization, e.g.



The latter route provides a one-step synthesis of isoxazolium perchlorates directly from β-formyl derivatives of carbonyl compounds and N-substituted

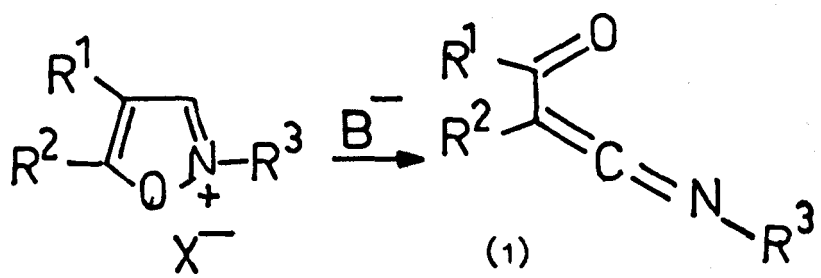
hydroxylamines. It is worth mentioning that isoxazolium perchlorates are explosive on mechanical impact.

Reaction of Isoxazolium Salts with Nucleophiles

A complete review of the reactions between isoxazolium salts and nucleophiles would be very lengthy. This review is intended to show the effect of certain nucleophiles on a range of substituted isoxazolium salts, concentrating on those relevant to the reactions reported in the Discussion (Chapter 1).

1. 3-Unsubstituted isoxazolium salts

3-Unsubstituted isoxazolium salts undergo a number of facile reactions with bases which have been shown[6] to proceed via the intermediate α-ketoketenimine (1).



(1)

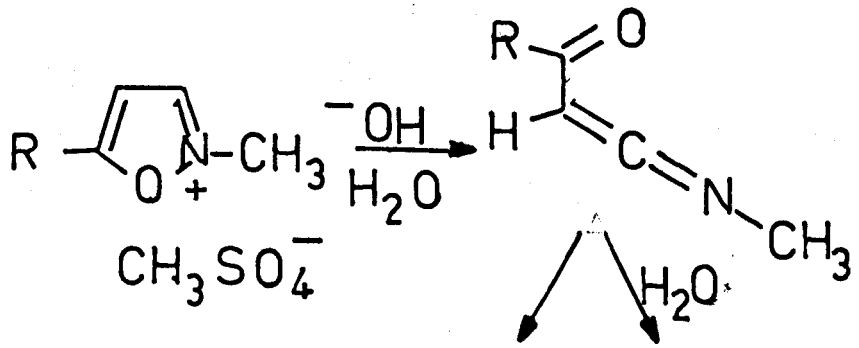
The reaction may be used as a synthesis of many organic compounds.

(i) Reaction with hydroxide ion[8]

Two major products were isolated. The expected acyl amide (2), formed by addition of water to the ketenimine, and a compound of unknown structure whose analysis and molecular weight correspond to a dimer of the ketoketenimine. Two examples of this dimer are described in the earlier literature,

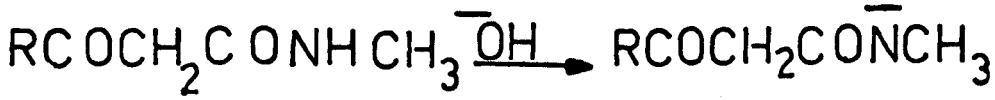
Mumm's dimer where R = Ph

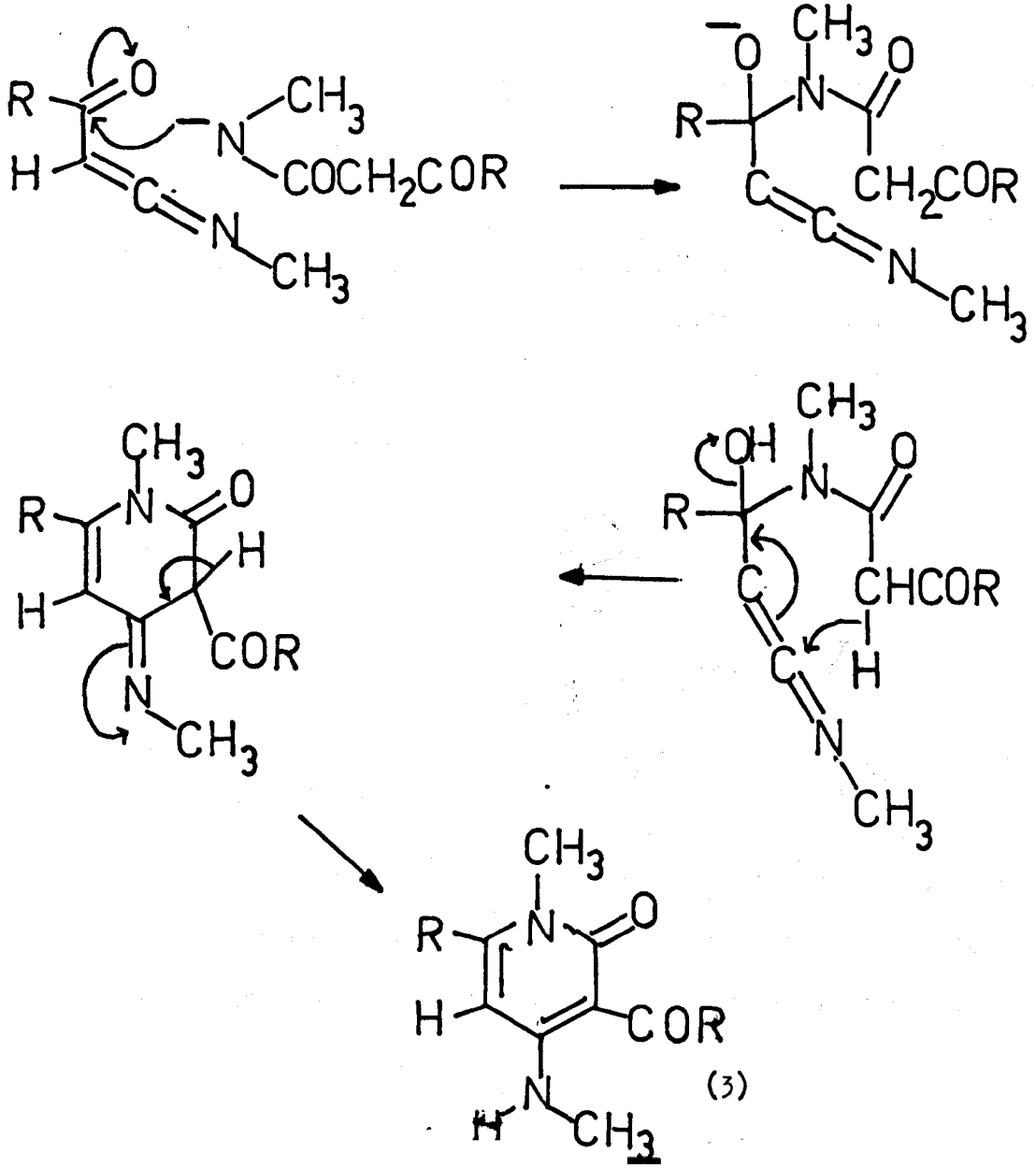
Meyer's dimer where R = CH_3



"DIMER"  (2)

The most probable structure postulated for these dimers is that of the pyridone (3). A possible mechanism for its formation is:

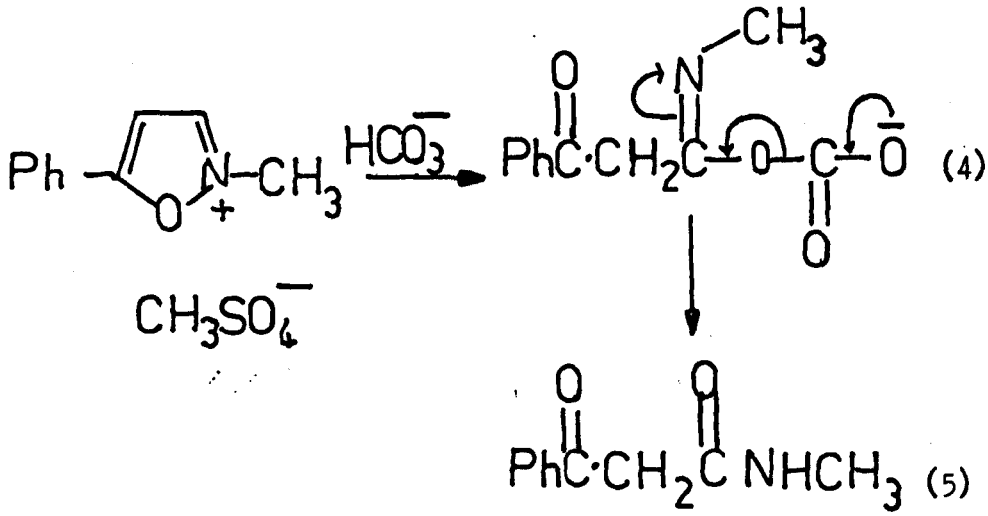




(3)

(ii) Reaction with bicarbonate[8]

The acyl amide (5) is formed in virtually quantitative yield possibly from the intermediate compound (4).



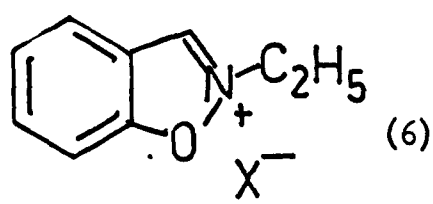
(4)

(5)

Similar reactions occur with other nucleophiles e.g. alkoxide ions and cyanide ions etc.

2. 3-Unsubstituted bicyclic isoxazolium salts

The above examples deal only with monocyclic 3-unsubstituted isoxazolium salts. The 1,2-benzisoxazolium ion (6) is a 3-unsubstituted isoxazolium salt and may react with nucleophiles in a similar manner.



(6)

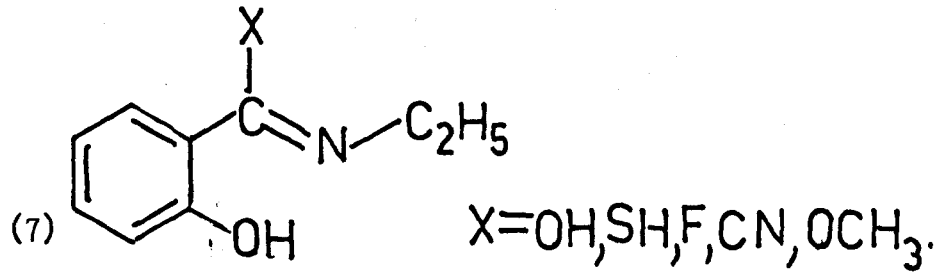
Meerwein's reagent, $(C_2H_5)_3\overset{+}{O}\ \overset{-}{B}F_4$, is used to quaternize benzisoxazole at room temperature in almost quantitative yield,[9] since quaternization of benzisoxazole is not possible with normal alkylating

agents, since it is too weakly nucleophilic and too heat sensitive. The benzisoxazolium salts are stable in acid but very unstable in neutral or basic media.

In an aqueous solution but in the absence of any reactive anions N-ethylsalicylamide is the final product. At pH greater than 7 a yellow polymeric material becomes an important by-product. A similar by-product is obtained when the salt is treated with triethyl amine in an organic solvent.[10] Efforts to detect a ketenimine have failed although the products would indicate such an intermediate.

(i) Products from simple nucleophiles[9]

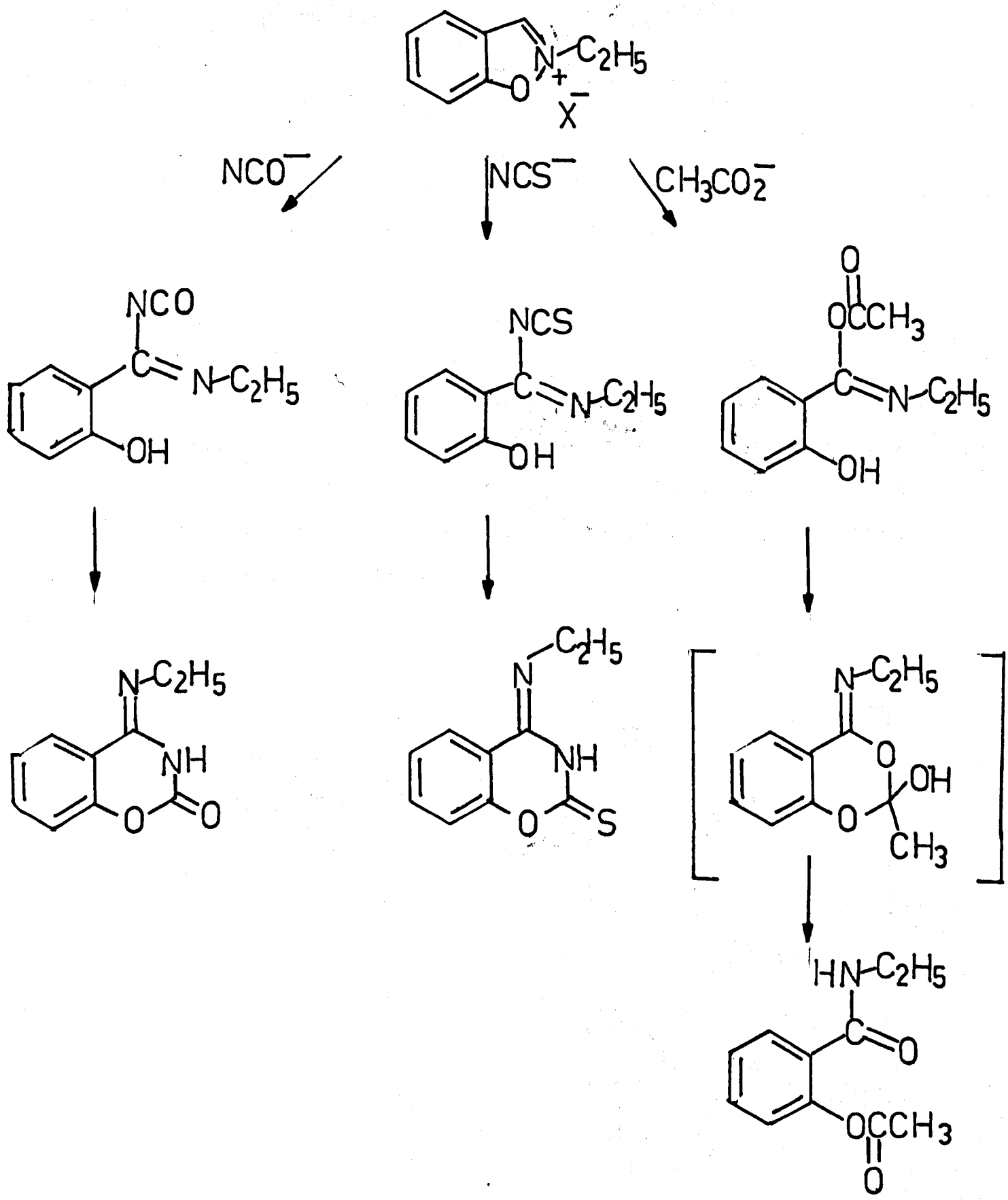
Hydroxide, hydrosulphide, fluoride and cyanide anions in aqueous solution or methoxide anions in methanol give high yields of products with the following structure (7).



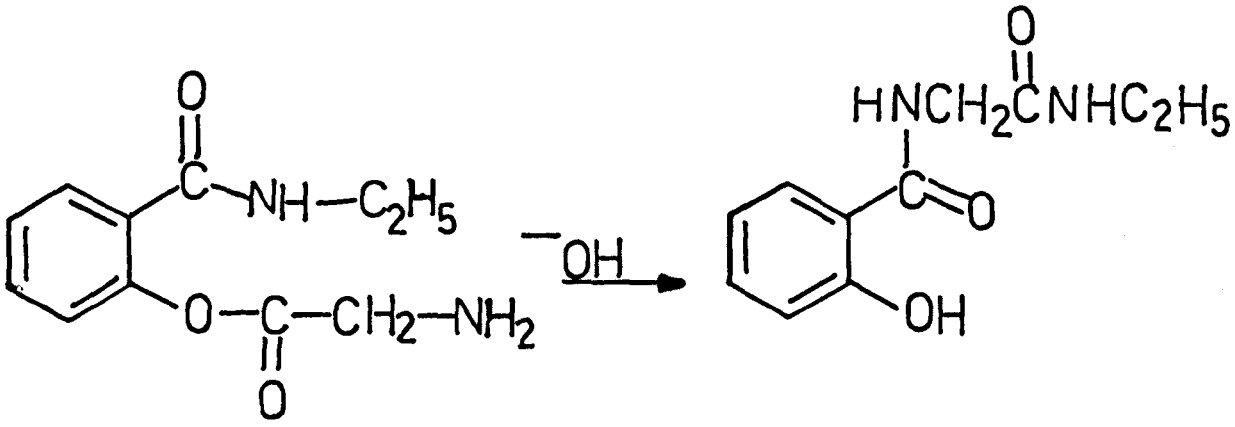
(7)

(ii) Products from cyanate, thiocyanate, and carboxylate anions[9]

These reactions may be summarized as:


NCO⁻
NCS⁻
CH3CO2⁻
X⁻
NCO
NCS
OCCH3
OH
NH
O
S
HN-C2H5

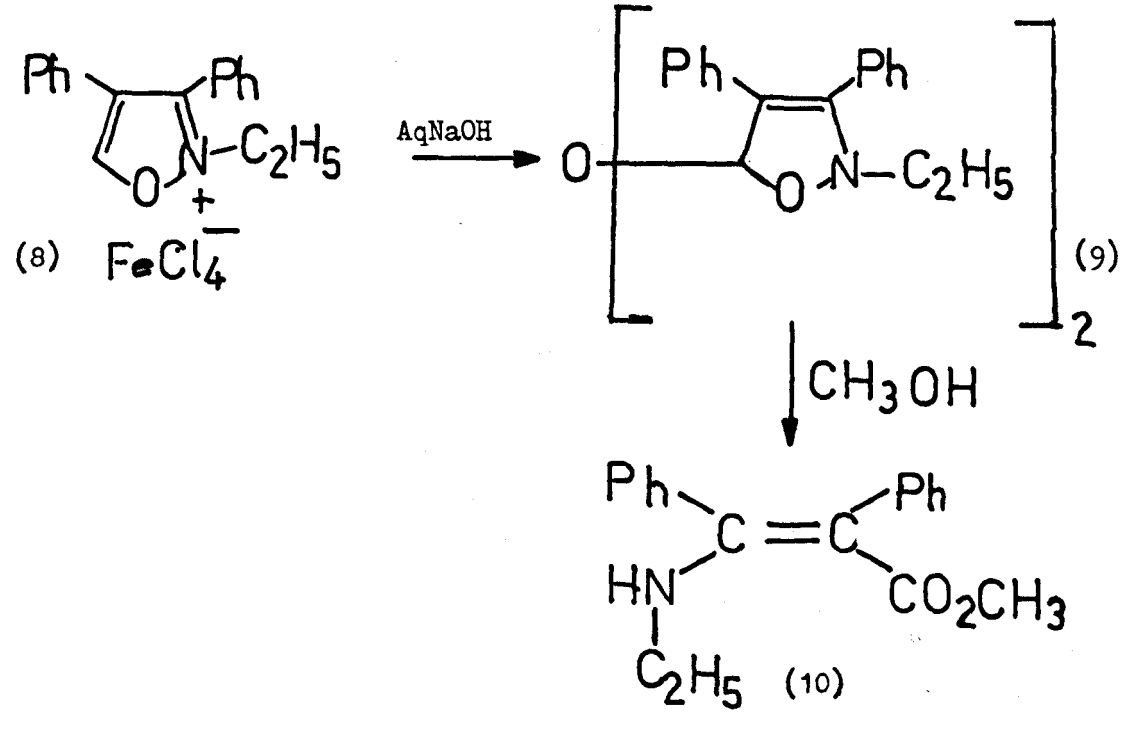
Instead of acetate ion benzoate, methoxyacetate or glycine may be used. With glycine however a further rearrangement occurs as shown below:



Formation of o-acyl-N-ethylsalicylamide may best be rationalized as proceeding from an imino anhydride as shown.

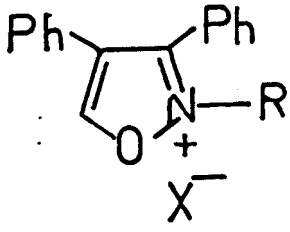
3. 5-Unsubstituted isoxazolium salts

Prior to 1969 only one reference has been made to nucleophilic attack on 5-unsubstituted isoxazolium salts. This paper by Kohler et al.[11] discusses the reaction of 3,4-diphenyl-2-ethylisoxazolium chloroferrate (8) with sodium hydroxide. The authors assigned the structure of the 'bis-molecular anhydride' (9) to the product, which on methanolysis gave β-ethylaminocinnamate (10).

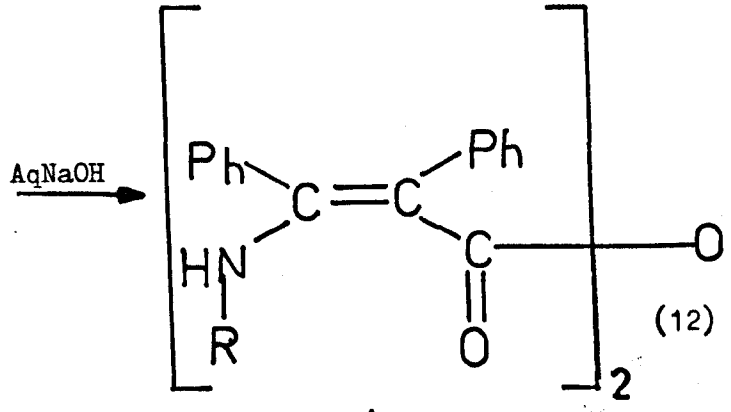


The structure of the compound (9) was not proved and this work was reinvestigated by Adachi and Kano.[10]

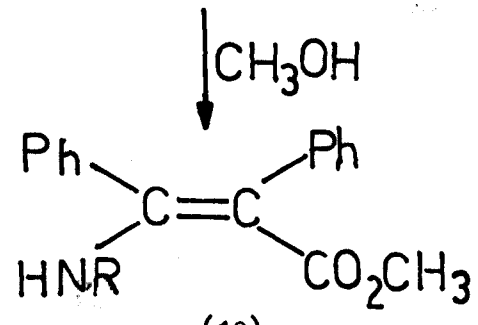
Using the same procedure as Kohler or by an improved method using a mixture of triethylamine, acetonitrile, and water, the isoxazolium salts (8) and (11) gave products whose molecular formulae are those of the "anhydride" (9) or its N-methyl analogue. Infrared and nuclear magnetic resonance studies show the presence of amino groups in the anhydride product, therefore Kohler's postulated structure (9) cannot be correct. Cinnamic anhydride derivatives of type (12) are more in accord with the data. They would also give β-alkyl amino cinnamates (10) on methanolysis.



$R=C_2H_5-$ (8)
$R=CH_3-$ (11)

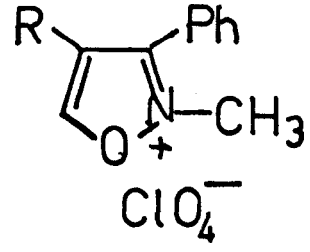


(12)

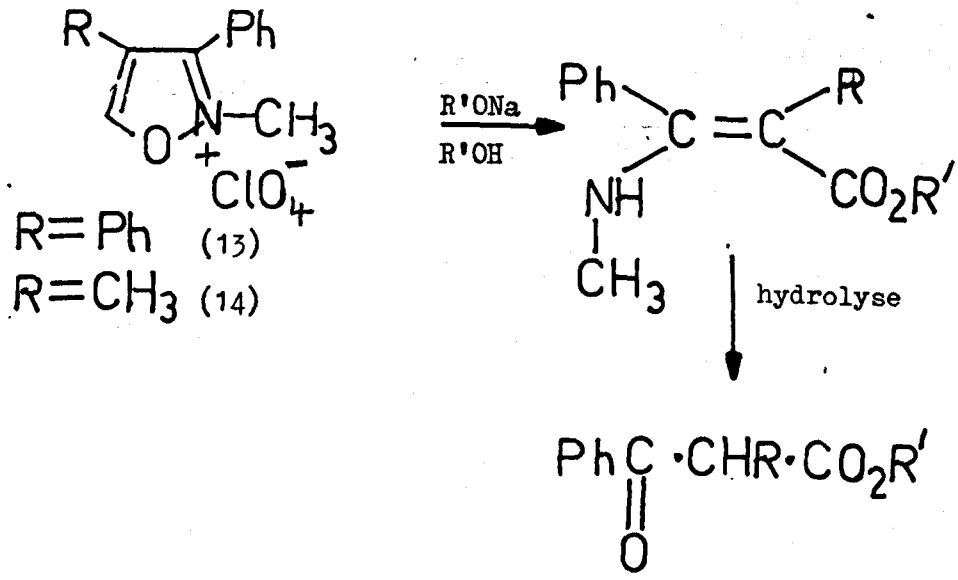


(10)

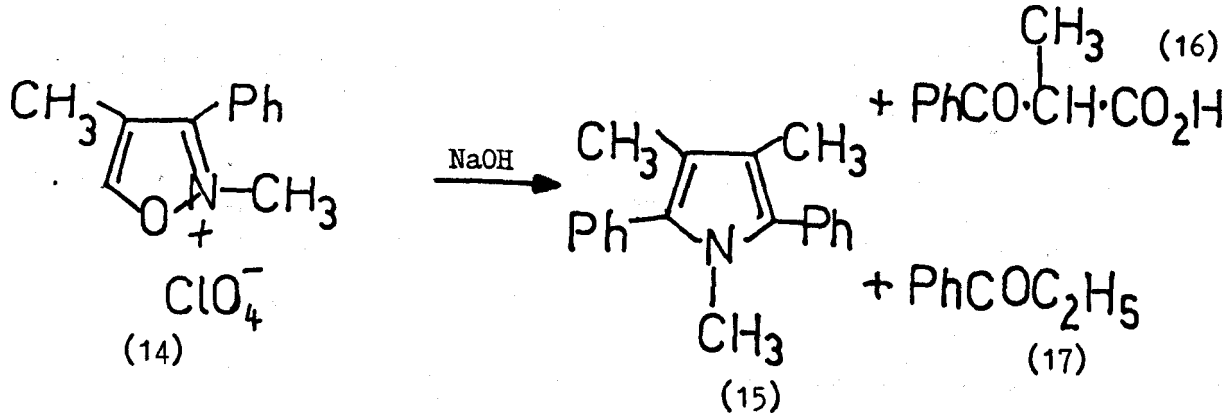
$R=Ph$ (13)
$R=CH_3$ (14)
$R=H$ (15)



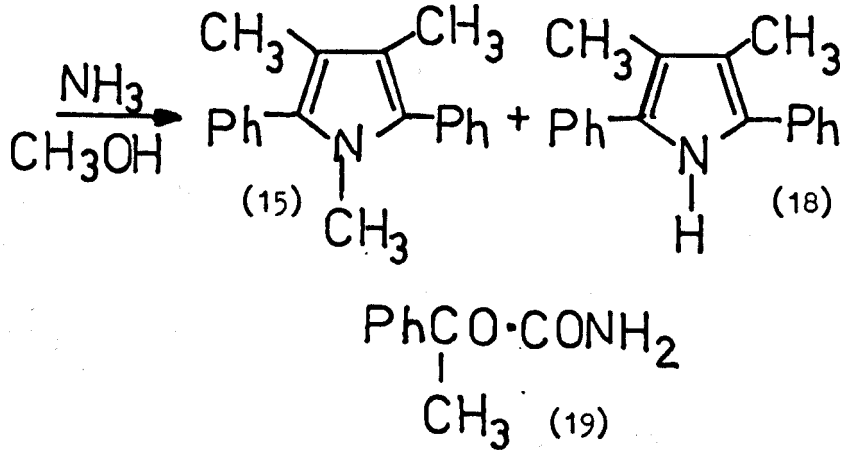
Treatment of salts (13) and (14) with sodium alcoholate gave the corresponding methyl amino cinnamates which could be hydrolysed to give the known β-ketoesters.



The reaction of the salt (14) with cold sodium hydroxide gave an unexpected product (15) in ≃ 30% yield, besides the usual ring cleavage products (16) and (17).

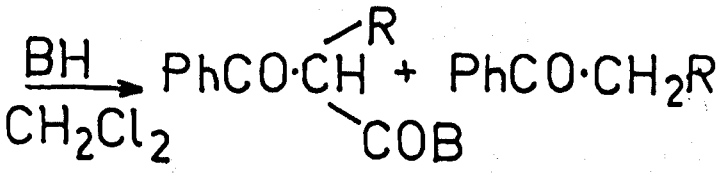


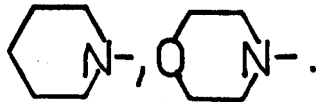
Treatment of the salt (14) with methanolic ammonia gave the two pyrrole compounds (15) (15.4%) and (18) (17.1%) along with the acid amide (19).

(14) 

The structures of (15) and (18) were confirmed by synthesis from 2,3-dibenzoyl butane with ammonia and methylamine.

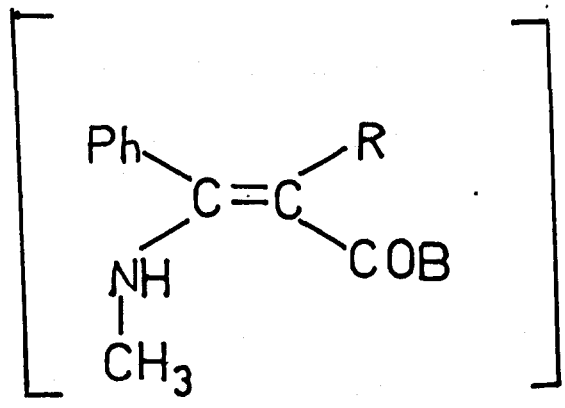
Reaction of the salts (13) and (14) with several primary and secondary amines gave the corresponding β-ketoacid amides and ketones.

(13) or (14) 

B = CH_3NH-, C_3H_7NH-, $PhCH_2NH$-,  .

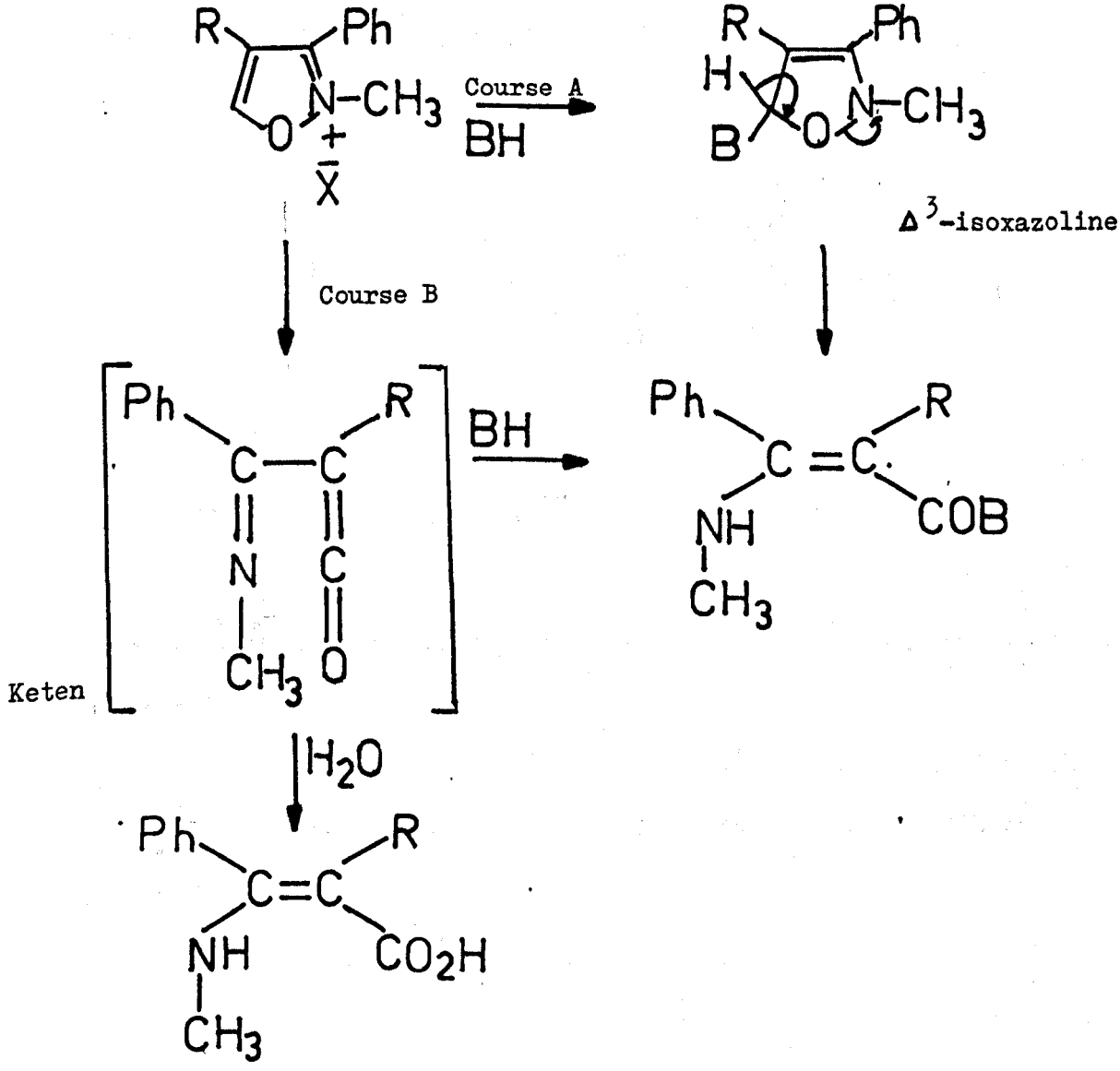
The pyrrole (15) was also isolated from the reaction of (14). None of the pyrrole derivatives could be detected in any nucleophilic cleavage reactions of the salts (13) and (15), which suggests that the methyl group at C_4 may play an important role in the pyrrole formation.

The β-keto acid amides have arisen from the hydrolysis of their p-methyl amino derivatives (20) on passage through an alumina column.



(20)

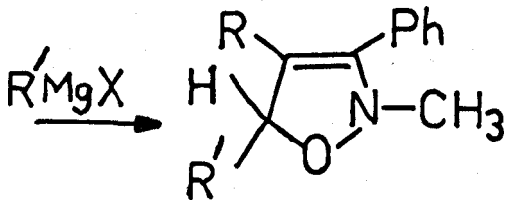
The reaction of these 5-unsubstituted isoxazolium salts with nucleophiles may occur by either addition of the nucleophile at C_5 (course A) or by abstraction of the proton at C_5 (course B).



The pyrrole (15) may arise from reactions involving the keten intermediate though attempts to prove the presence of the keten by i.r. spectroscopy were unsuccessful.

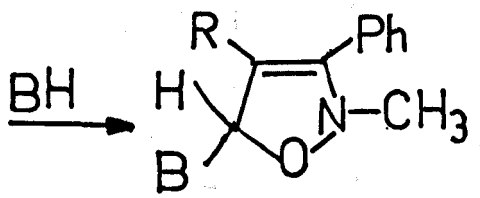
Either pathway may be operating although some 5- substituted Δ^3-isoxazolines have been isolated on reaction of the salts (13) and (14) with some nucleophiles at low temperatures.

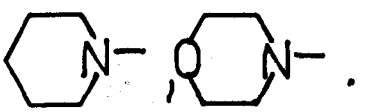
(i) <u>with Grignard reagents at low temperatures</u>

(13) or (14) 

$R' = CH_3, CH_2Ph.$

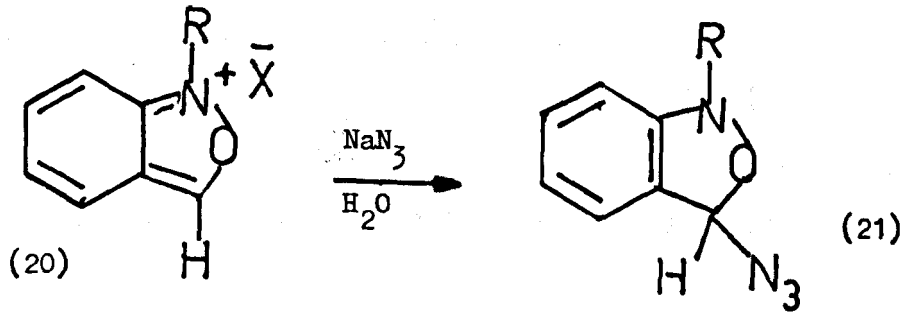
(ii) <u>with piperidine and morpholine at low temperatures</u>

(13) or (14) 

B= 

These Δ^3-isoxazolines revert back to the salts on treatment with perchloric acid.

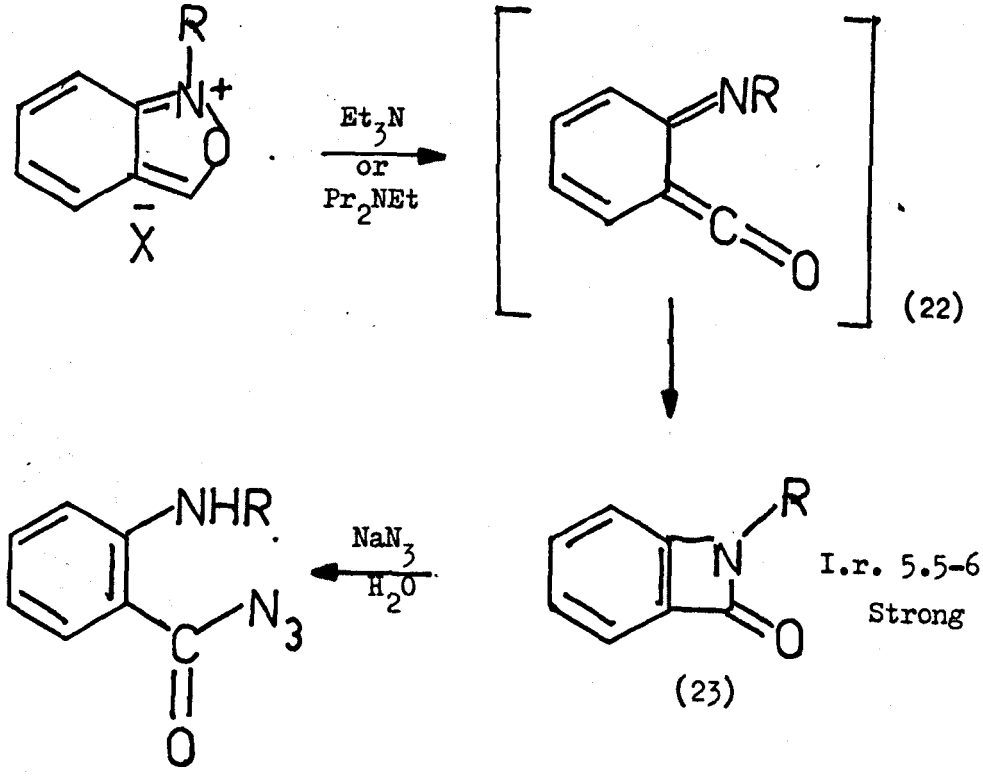
The bicyclic isoxazolium salts (20), the anthranilium salts, also undergo reaction with anions to give the simple C_3 addition products,[12] (21) e.g.



(20) (21)

Cyanide and methoxide ions give similar compounds.

Reaction of the anthranilium salts with amine bases is believed to go via an iminoketen intermediate (22) which then cyclises to the unstable benzoazetinone (23) (N-t-butyl benzoazetinone proved stable enough to isolate). The benzoazetinone compounds may then undergo reaction as shown.



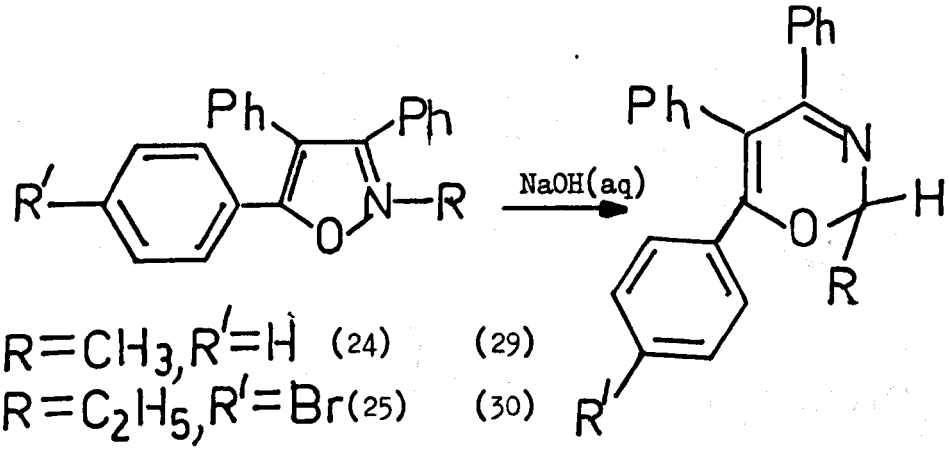
(22)

(23)

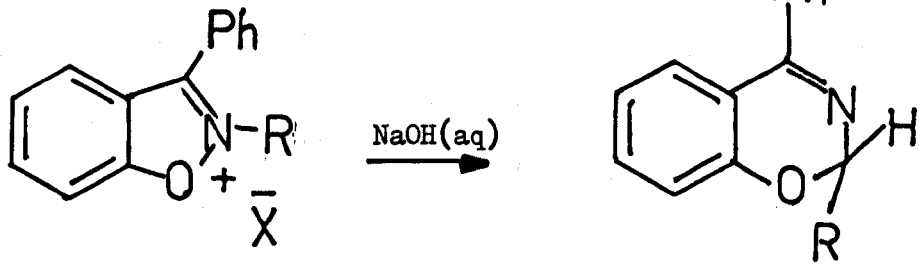
I.r. 5.5-6.6 μ
Strong

4. 2,3,5-Trisubstituted isoxazolium salts

The 2,3,5-trisubstituted isoxazolium salts (24 - 28) undergo reaction[13] with dilute sodium hydroxide. The products are suggested to be the cyclic oxazines (29 - 30) and benzoxazines (31 - 33).



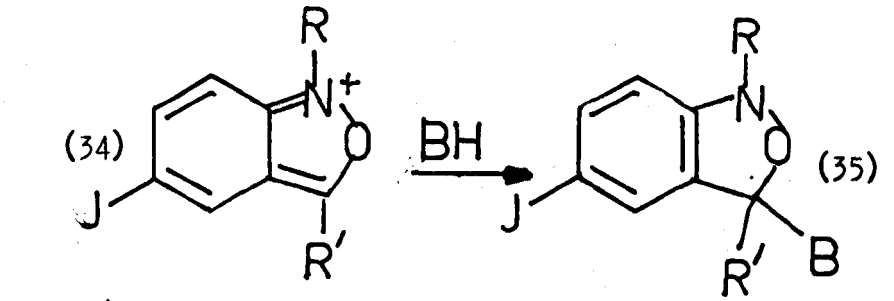
R=CH$_3$, R'=H (24) (29)
R=C$_2$H$_5$, R'=Br (25) (30)



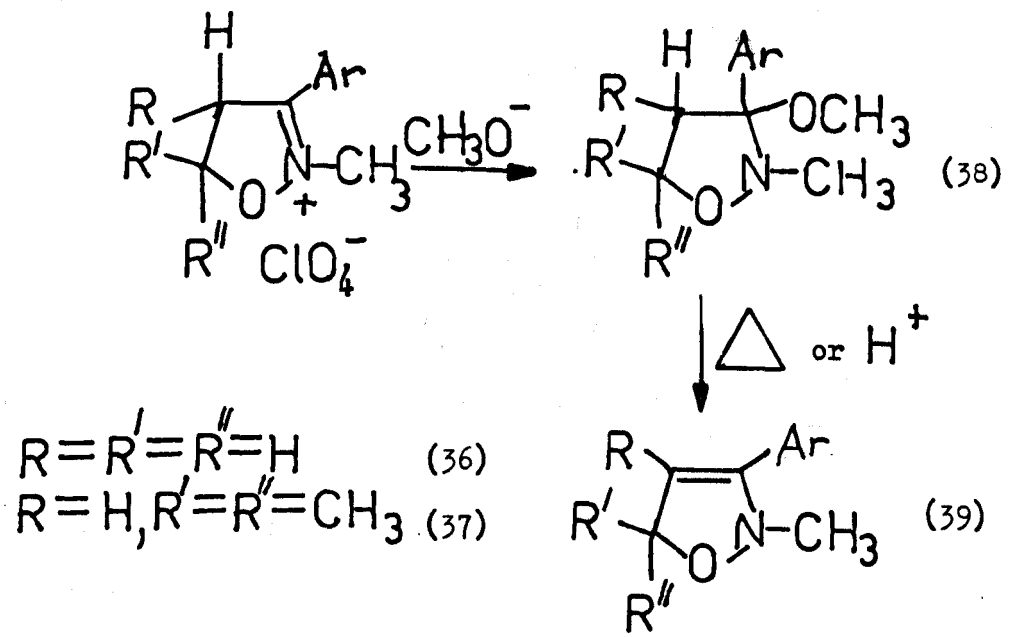
R=CH$_3$ (26) (31)
R=CH$_2$Ph (27) (32)
R=C$_2$H$_5$ (28) (33)

Evidence for the proposed structures comes from i.r. (1620 cm^{-1}, c.f. benzophenone anil 1623 cm^{-1} for X= >C=N), u.v. and proton nuclear magnetic resonance.

It has also been reported[14] that 1,3-disubstituted[2,1 -] benzisoxazolium salts (34) react with nucleophiles to yield 3-substituted-[2,1]-benzisoxazolines (35).



Reaction[15] of the 4,5-dihydro-isoxazolium salts(36), (37) with sodium methoxide yields the unstable isoxazolidine (38), which then may eliminate methanol to give the Δ^3-isoxazolines (39).

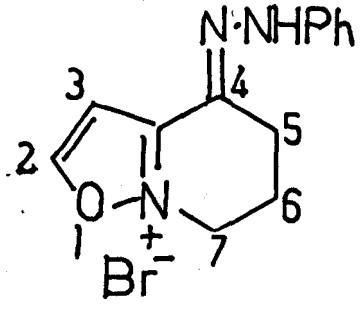


DISCUSSION

(i) Introduction

The isoxazolium salts dealt with in most detail have the general formula and nomenclature shown below:

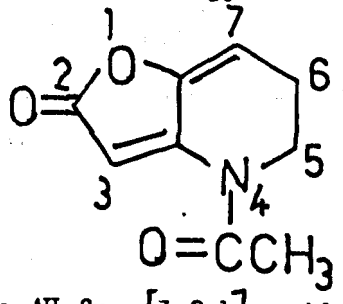
a.



4,5,6,7-tetrahydro-4-oxoisoxazolo[2,3-a] pyridinium bromide phenylhydrazone.

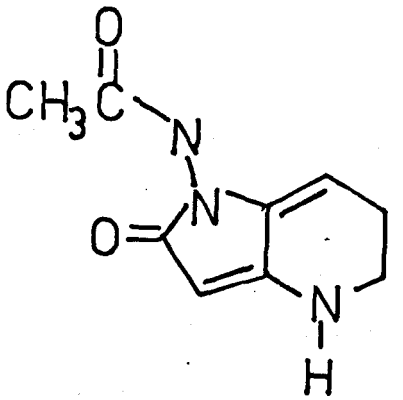
The rearrangement products obtained from these bicyclic salts have the following general formulae and nomenclature.

b. From the parent oxoisoxazolopyridinium salt:

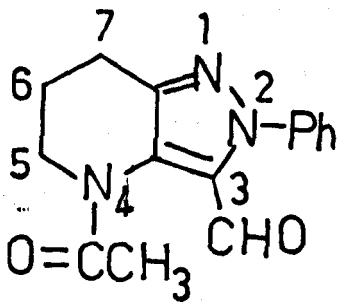


4-acetyl-5,6-dihydro-4H-furo[3,2-b]pyrid-2-one

c. From the oxoisoxazolopyridinium phenylhydrazone salt:

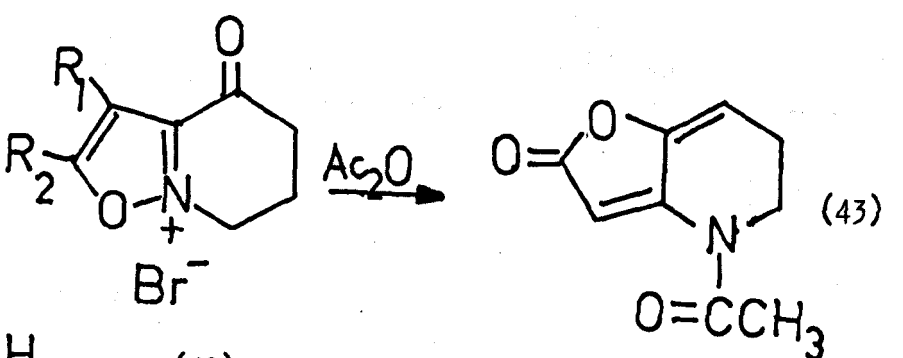


5,6-dihydro-1-(N-acetanilidinyl)-4H-pyrrolo[3,2-b]pyridin-2-one



4,5,6,7-tetrahydro-4-acetyl-2-phenylpyrazolo[4,3-b]pyridine-3-carboxaldehyde

Attempts to aromatise the oxoisoxazolo[2,3-a]pyridinium salt (40) by heating in acetic anhydride led to an interesting rearrangement product (43).[16,17]

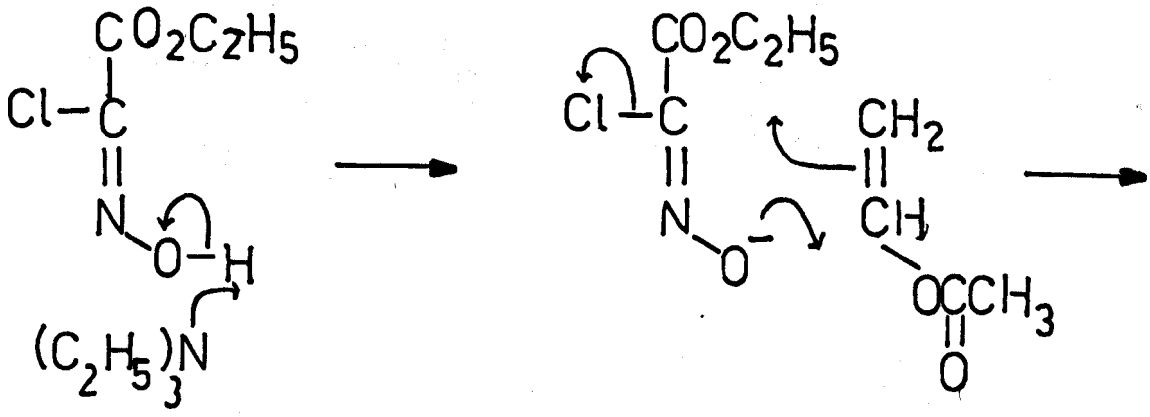


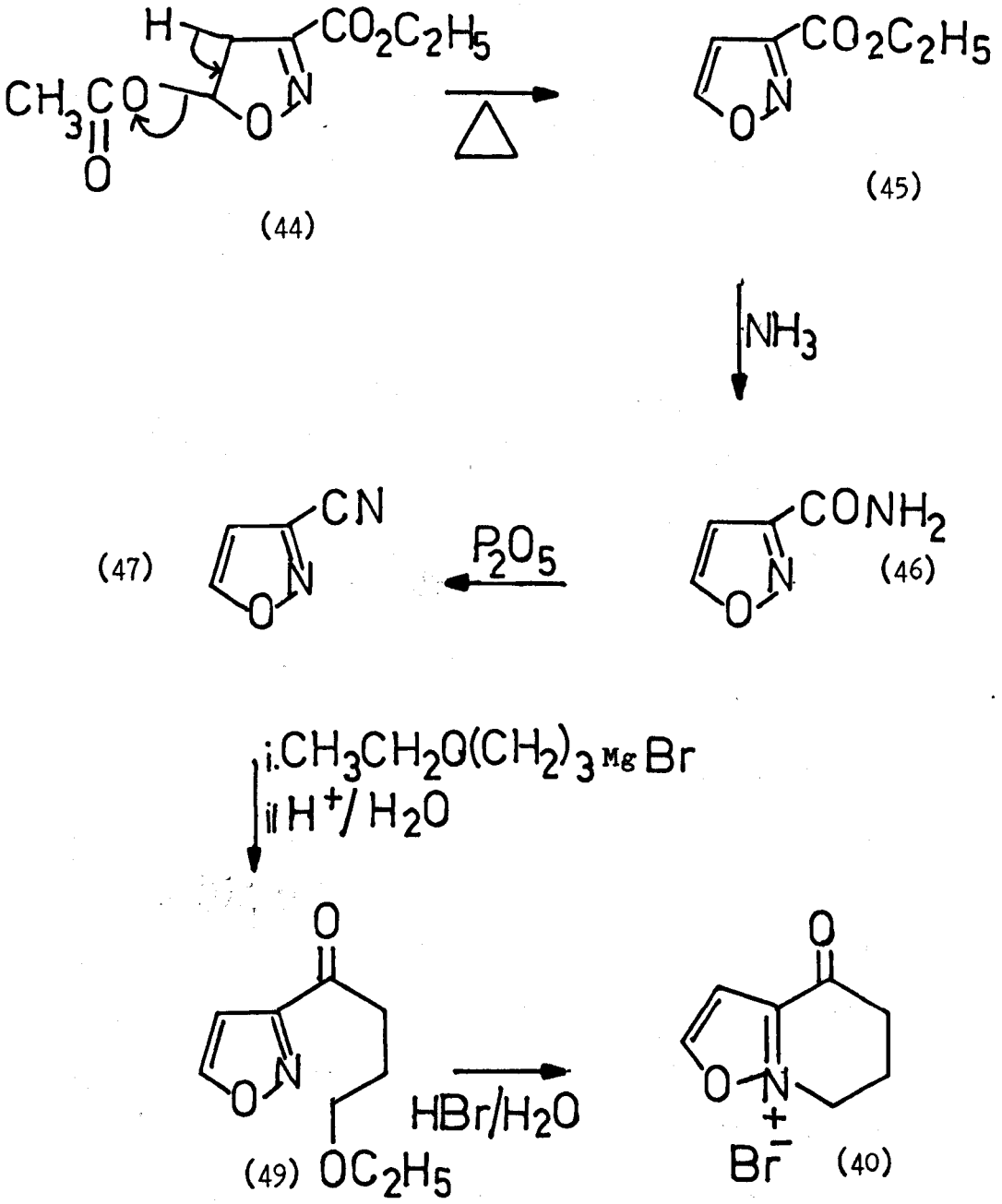
$R_1 = R_2 = H$ (40)
$R_1 = CH_3, R_2 = H$ (41)
$R_1 = H, R_2 = CH_3$ (42)

The cyclic salt (40) was prepared[16] from the 3-carbethoxy isoxazole which was obtained free from the 5-substituted isomer via the isoxazoline (44). Addition of a solution of carbethoxychloracetaldoxime in ether to a heated solution of vinylacetate and triethylamine also in ether. On heating this isoxazoline (44) to between 180 - 190°C the isoxazole (45) distilled over after a fore-run of acetic acid.

Treatment of the 3-carbethoxy isoxazole (45) with an excess of cold ammonia solution converts the ester to the amide (46), which is then dehydrated with phosphorus pentoxide to form the 3-cyano-isoxazole (47). Inverse addition of the Grignard reagent from 3-ethoxypropyl bromide to the nitrile gives the 3-(4-ethoxybutyryl) isoxazole (49) after hydrolysis of the intermediate imine (48). The isoxazole (49) cyclised readily on heating in aqueous hydrobromic acid. The final traces of hydrobromic acid which remained after vacuum distillation were removed by adding absolute ethanol and distillation under reduced pressure.

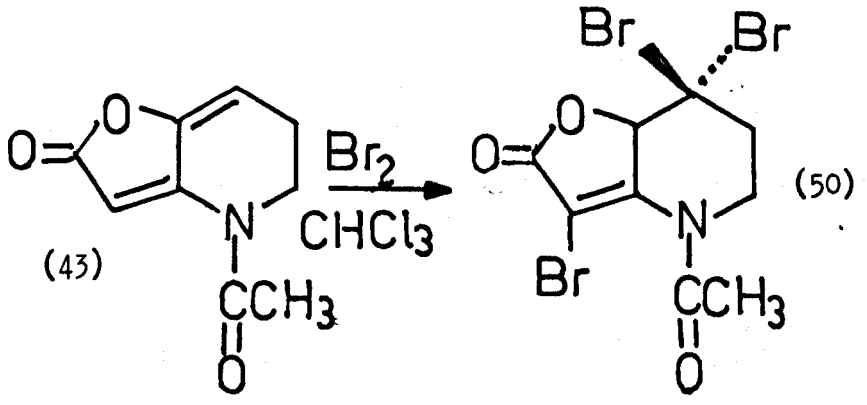
The reaction sequence may be summarised as:



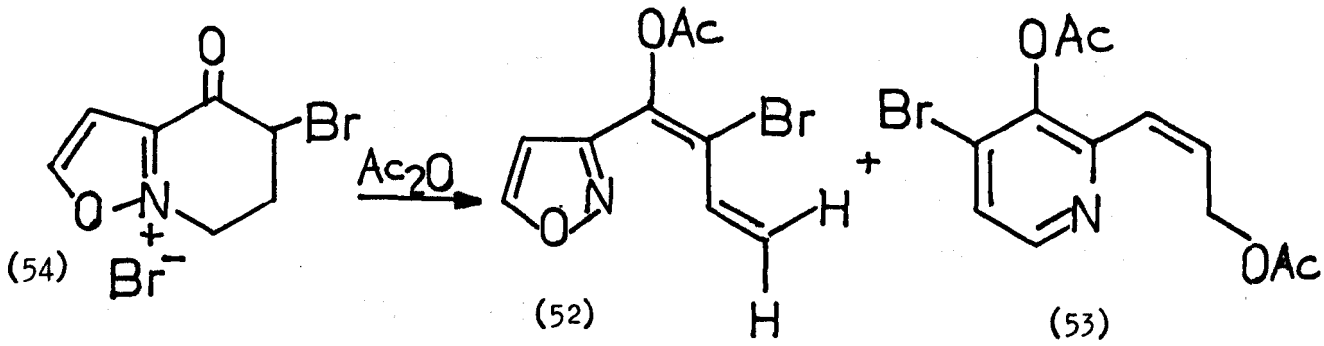

H
$CO_2C_2H_5$
CH_3C
O
O
N
O
(44)
$CO_2C_2H_5$
N
O
(45)
NH_3
CN
N
O
(47)
P_2O_5
$CONH_2$
N
O
(46)
i. $CH_3CH_2O(CH_2)_3MgBr$
ii H^+/H_2O
O
O
N
O
OC_2H_5
(49)
HBr/H_2O
O
O
N
+
Br^-
(40)

A combination[17,18] of spectroscopic, crystallographic and chemical evidence has shown the rearrangement product to be the furo[3,2-b]pyridone (43). This rearrangement product is a novel heterocyclic system which contains an enamino ketone backbone through atoms 2, 3, 3a and 4.

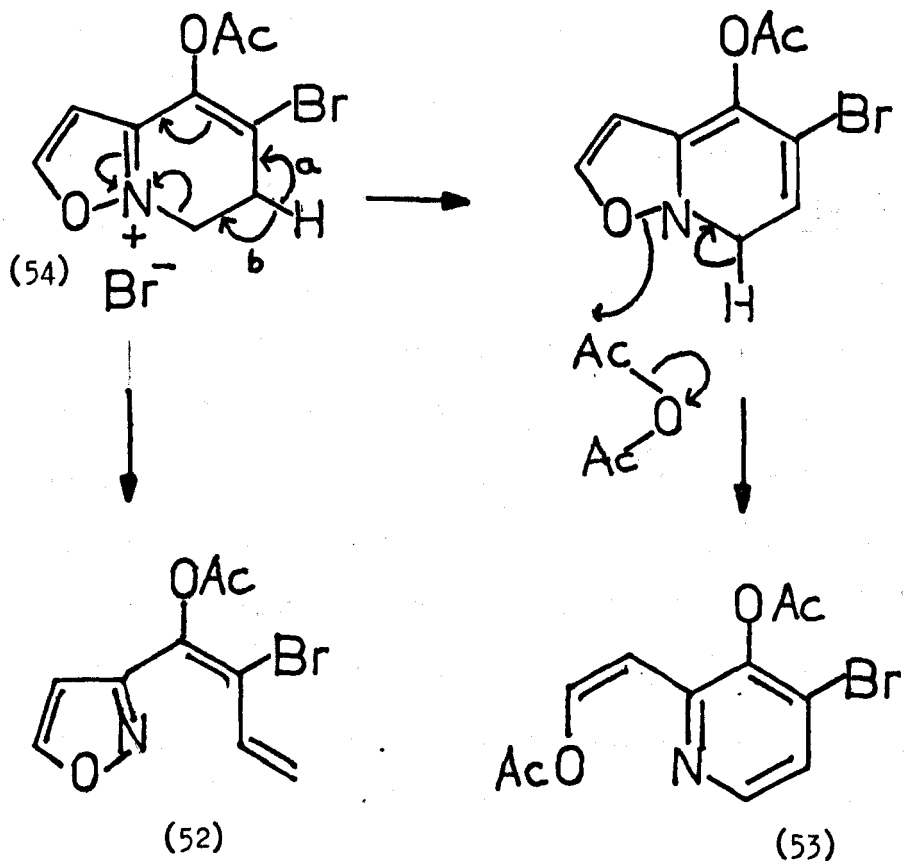
The rearrangement product reacts rapidly with bromine in chloroform giving the brominated product (50),[17] the configuration of which was assigned from ^1H n.m.r. data.



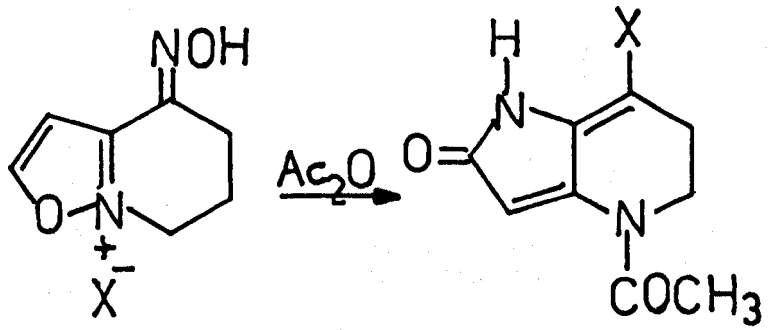
In attempts to clarify the structure of the rearrangement product three other isoxazolo pyridinium salts were treated with acetic anhydride.[17] The 2-methyl derivative (41) gave no identifiable products, while the 3-methyl derivative (42) gave the homologous furopyridone (43) ($R_2 = CH_3$); hence a proton at the 2-position of the cyclic salt is required for the rearrangement to occur. Treatment of the 5-bromo-ketone[17] (51) with acetic anhydride gave no furo pyridone but two products (52) and (53) were isolated, the acetoxyvinylpyridine (53) being the major product.



The mode of attack is similar to that observed by acetic anhydride on oxypyridinium salts. The suggested mechanism involves tautomerism then acetylation to the enolacetate (54), treatment of which with acetic anhydride leads to the isoxazole (52) by Hofmann elimination or to the pyridine (53) by isoxazole ring opening.



The oxime, 4,5,6,7-tetrahydro-4-hydroximino isoxazolo[2,3-a] pyridinium bromide (55) was prepared[19] by heating the salt (40) with hydroxylamine in ethanol. Treatment of the oxime (55) with acetic anhydride gave a major product whose spectroscopic data suggested that it is the pyrrolo[3,2-b] pyridone (58).



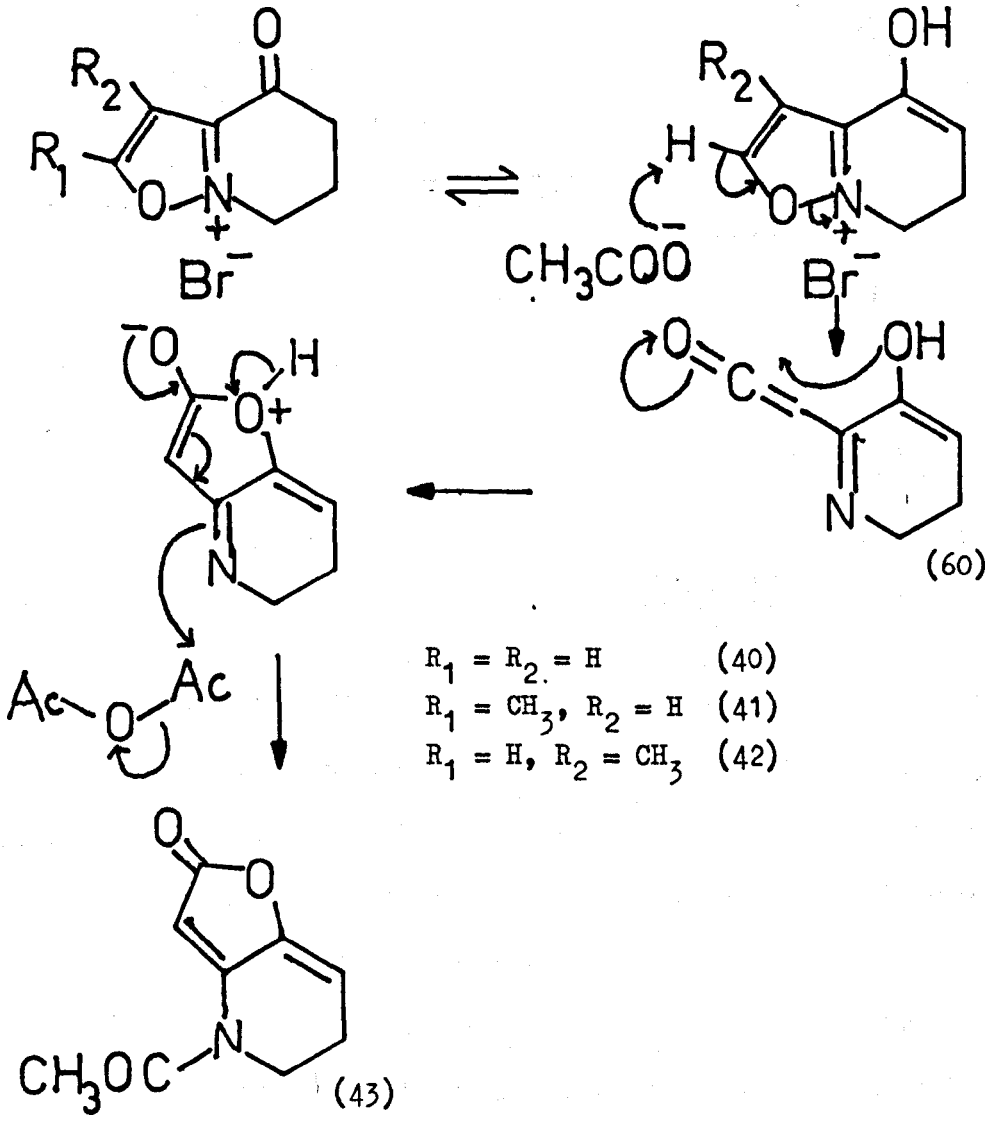
X=Br (55) (58)
X=Cl (56) (59)
X=I (57)

One of the steps in the mechanism of formation of the pyrrolopyridone, is the elimination of water by attack of the counter-ion at position 7. The similarity in yield of compounds (58) and (59) when X = Br^- or Cl^-, indicates that the nucleophilicity of the counterion cannot be rate determining or have any effect on the yield of the pyrrolopyridone, when X = I^- (57); treatment with acetic anhydride gave no isolable product. The sensitivity of the salt (50) perhaps arises because of the reactivity of the product or because the iodide anion caused polymerisation of some reactive intermediate.

Attempts[19] to convert the furopyridone (43) into a pyrrolo-pyridone by treatment with boiling aniline were unsuccessful.

(ii) Mechanism of formation of the rearrangement product

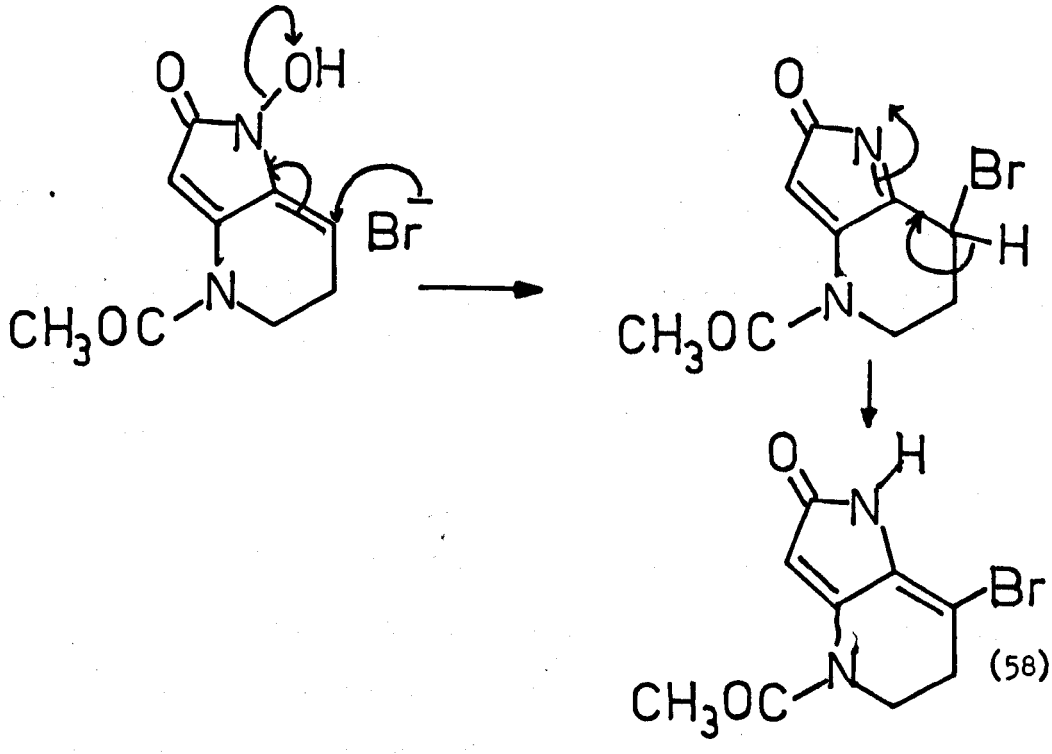
The mechanism of the rearrangement of the bicyclic salt (40) to the furopyridone (43) has been suggested to proceed[19,20] via a keten intermediate. The first step may be



$R_1 = R_2 = H$ (40)
$R_1 = CH_3$, $R_2 = H$ (41)
$R_1 = H$, $R_2 = CH_3$ (42)

considered as enolisation of the carbonyl group, followed by hydrogen abstraction at position 2 of the isoxazolium salt, by an acetate ion, present in small amounts in the acetic anhydride. Bond reorganisation then gives the keten intermediate (60). Attack at the carbonyl carbon atom of the keten by the enolic -OH and subsequent bond reorganisation leads to the furopyridone (43).

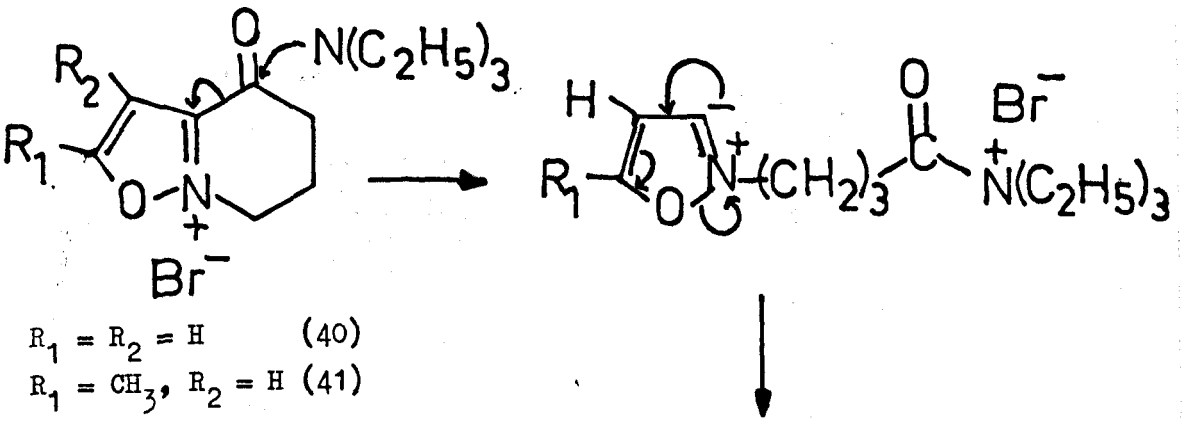
In the case of formation of the pyrrolopyridone water is eliminated by attack of the counter ion at position 7 of the initially formed pyrrolopyridone followed by a [1,3] hydrogen shift to give the required product (58).



(58)

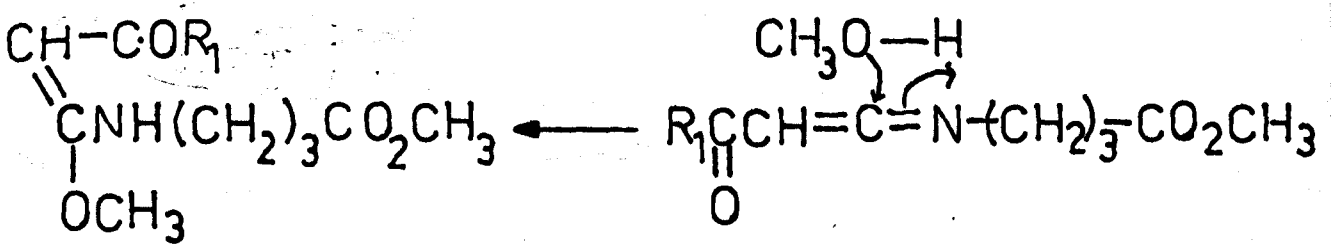
Proof that the proton at position 2 is directly involved in the mechanism of rearrangement comes from the fact that no product was isolated on treatment of the salt (41) ($R_1 = CH_3$) with acetic anhydride whilst the homologous furopyridone was obtained on reaction of the salt (42) ($R_2 = CH_3$) with acetic anhydride.

Attempts[20] to trap the keten intermediate by treatment of salts (40) and (41) with triethylamine in boiling methanol led to non quaternary products whose spectral data left no doubt that a more drastic change had occurred. The proposed structures of the products isolated are those of the enamino-aldehyde (62) and the enamino ketone (63).



$R_1 = R_2 = H$ (40)

$R_1 = CH_3$, $R_2 = H$ (41)



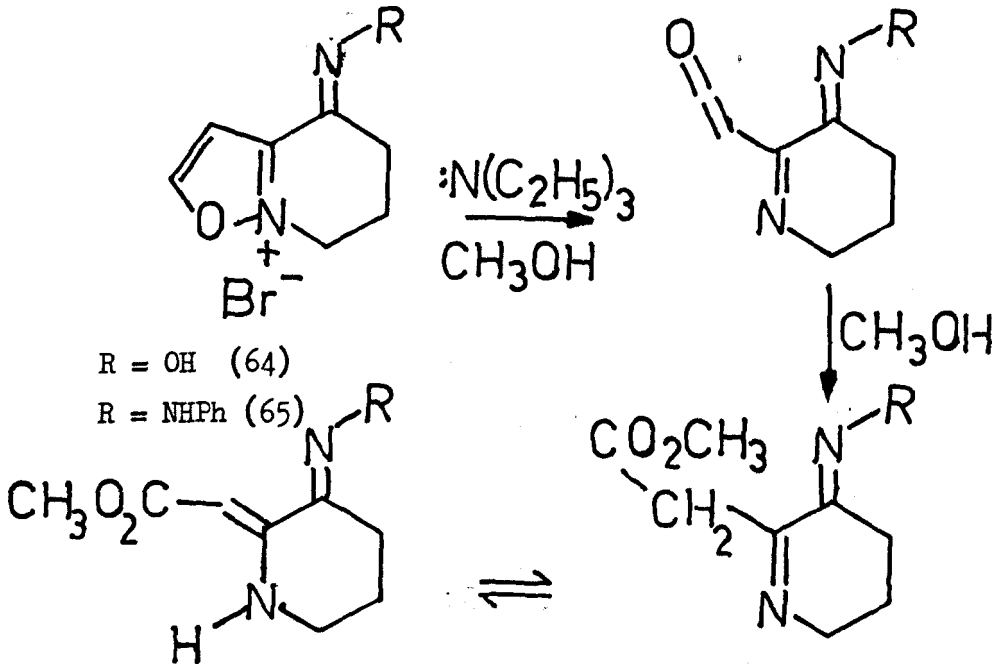
$R_1 = H$ (62)

$R_1 = CH_3$ (63)

The mechanism is thought to involve base catalysed elimination of 3-acyl substituents from isoxazolium salts. The intermediate ketenimine (63) is then analogous to that involved in the Mumm - Woodward - Olofson synthesis of peptides.

The highly electrophilic carbon atom at position 4 of the ketonic salt (40) thus frustrated the trapping of a keten intermediate.

Treatment[20] of the oxime (64) or the phenyl hydrazone derivative (65) (the electrophilic character at C4 is now reduced) of the ketone (40) with triethylamine in methanol led to two products (66) and (67) being obtained whose spectral data were those expected for the tetrahydropyridine.



R = OH (64)
R = NHPh (65)

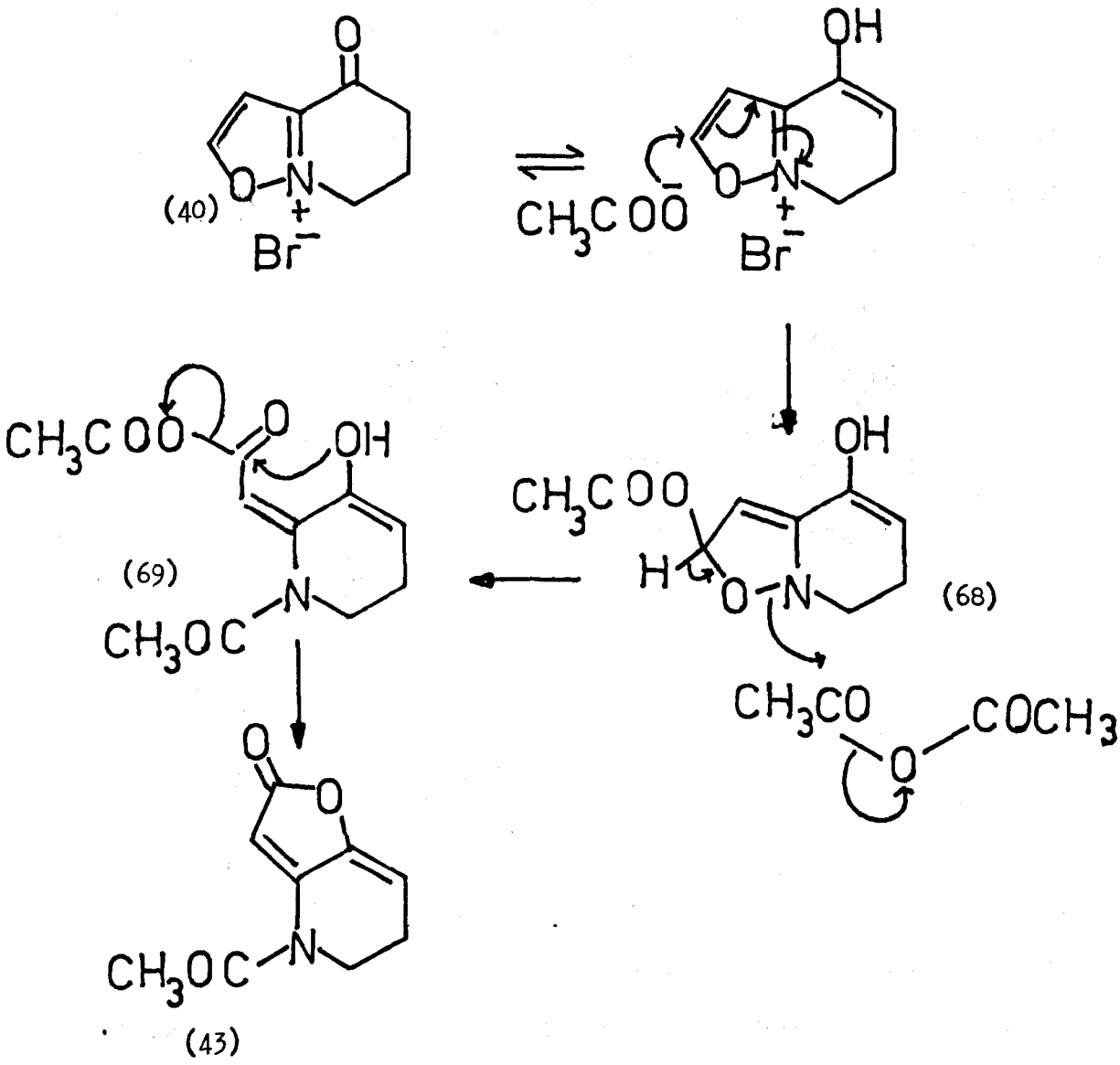
R = OH (66)
R = NHPh (67)

The isolation of these two products favours the existence of the keten intermediate formed by opening of the isoxazole ring, but one cannot rule out, by the isolation of these two products, the Δ^3-isoxazoline route (see below).

When the ring opening reagent is acetic anhydride, acetylation of the piperidine nitrogen increases the electron deficiency at the keten carbon atom, and also possibly enhances the contribution from enol tautomers which can cyclise to give the pyridone ring, such interactions with triethylamine are not possible.

Another possible mechanism involves an intermediate Δ^3-isoxazoline.

Attack of acetate ion at position 2 of the cyclic ketone after enolisation of the carbonyl group forms the Δ^3-isoxazoline (68). Bond reorganisation then leads to the mixed anhydride (69). Cyclisation of (69) with expulsion of acetate ion leads to the furopyridone (43).

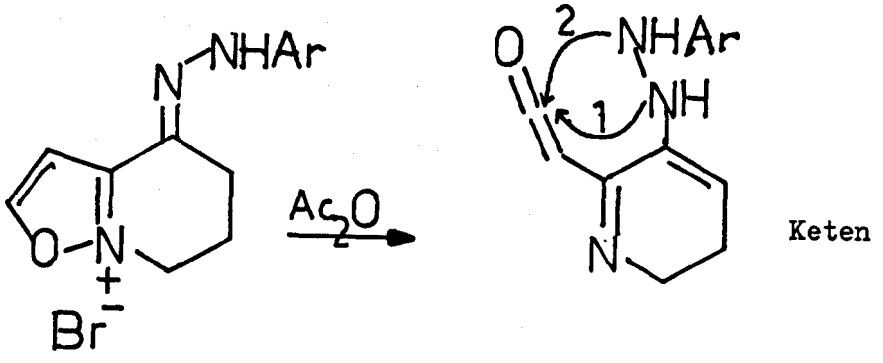


Isoxazolines have been shown[10] to be possible intermediates in the rearrangement of isoxazolium salts but these suggestions do not appear to have been as well substantiated as the proton abstraction mechanism which is more generally favoured.

Attempts to determine the importance of the initial enolisation of the carbonyl group of the cyclic ketone (40) to the enol form have not been successful.

(iii) Rearrangement of isoxazolopyridinium hydrazone salts

Rearrangement of the isoxazolopyridinium hydrazone salts were investigated since there are two different nitrogen atoms present within the system which may attack the carbonyl carbon of the keten.



Keten

Ar = Ph (70)

Ar = 2,4-$C_6H_3(NO_2)_2$ (71)

Cyclisation by route 1 should lead to pyrrolopyridones whereas cyclisation by route 2 may lead to the little studied pyrido-[3,2-c]pyridazinones. Two types of product are indeed formed.

The hydrazones (70) and (71) were obtained in good yield from the ketone (40) and the appropriate hydrazine by heating in either ethanol or acetic acid.

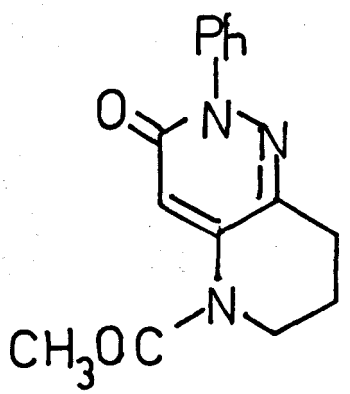
Rearrangement procedure A:

It was found[21] that the best yield of the furopyridone (43) was obtained by heating the ketonic salt (40) in acetic anhydride until the solution boiled, then allowing the solution to cool and then decanting the hot solution from unreacted salt, repeating this procedure until all the salt had gone into solution. Excess acetic anhydride was then removed and the black oily solid extracted with chloroform. The products were then separated by column chromatography.

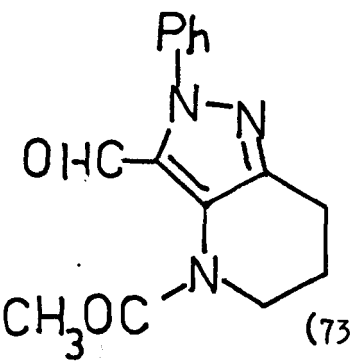
Treatment of the isoxazolo phenylhydrazone salt (70) with acetic anhydride using this procedure gave after column chromatography two major products, isomers of molecular formula $C_{15}H_{15}N_3O_2$.

The first product to be eluted (chloroform : benzene, 3 : 7), after minor uncharacterised solid was a solid recrystallised from absolute ethanol, m. pt 133°C, which has spectral characteristics quite different from the pyrrolopyridones.

This physical data may be accommodated by two structures, that of the pyrido[3,2-c]pyridazinone (72) and that of the pyrazolo[4,3-b]-pyridine carboxaldehyde (73).



(72)



(73)

The mass spectrum shows a molecular ion at 269 a.m.u. and a loss of 42 a.m.u. (CH_2CO), with a strong peak at 77 (C_6H_5) and at 43 (CH_3CO). The ^1H n.m.r. spectrum (Fig. 1) shows a three proton singlet at δ 2.1 p.p.m. assigned to an acetyl group, confirmed by the mass spectrum. Two deshielded two proton triplets at δ 2.75 and 3.1 p.p.m. are attributed to the piperidine ring methylenes adjacent to the double bond and nitrogen atom respectively, the central methylene group occurring as a multiplet at δ 2.0 p.p.m. The signal from the phenyl group is seen as a multiplet between δ 7.1 and 7.5 p.p.m. The most

Fig. 1 ^{1}H N.m.r. spectrum of 4,5,6,7-tetrahydro-4-acetyl-2-phenyl-pyrazolo[4,3-b]pyridine-3-carboxaldehyde (73)

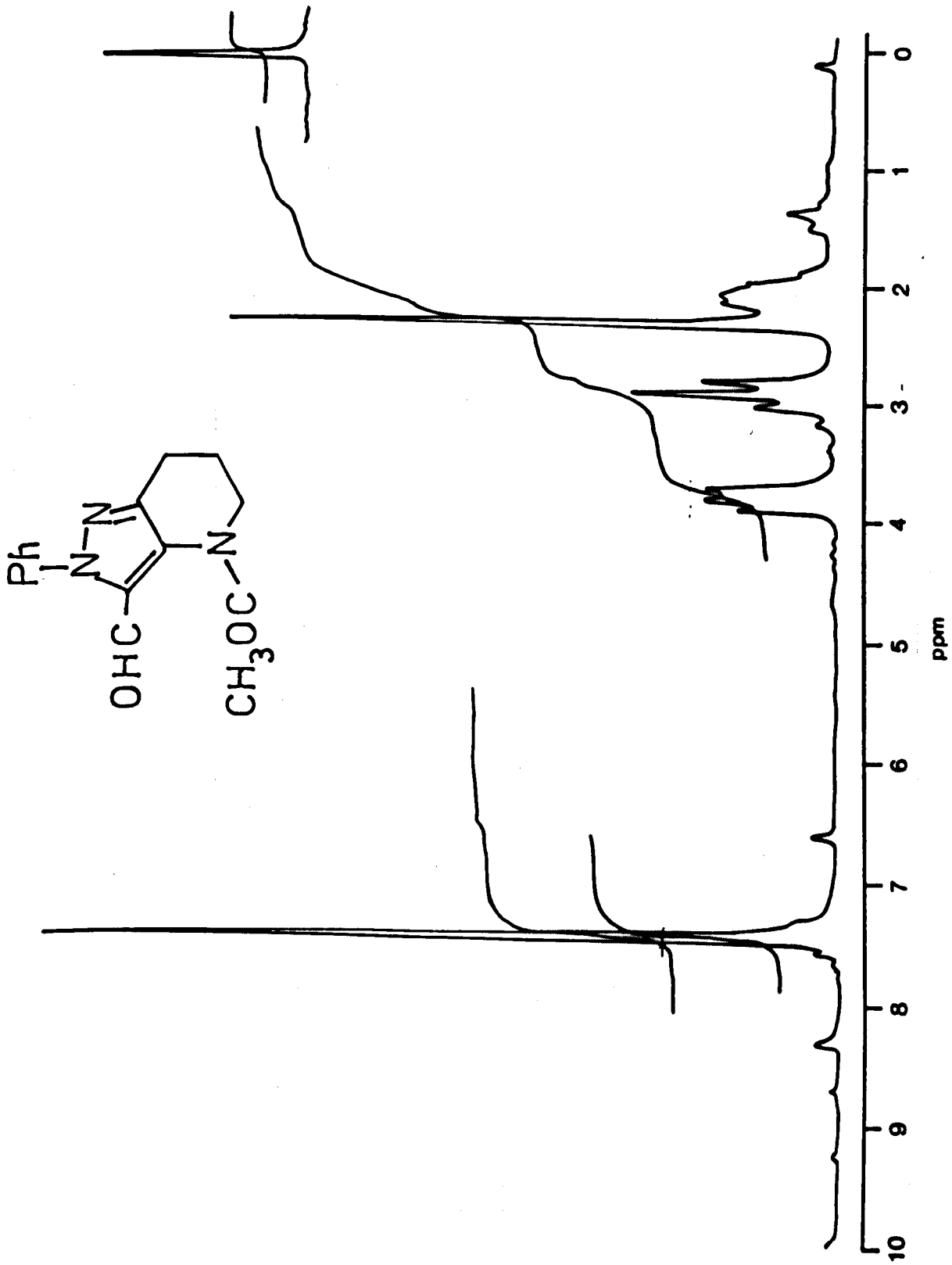
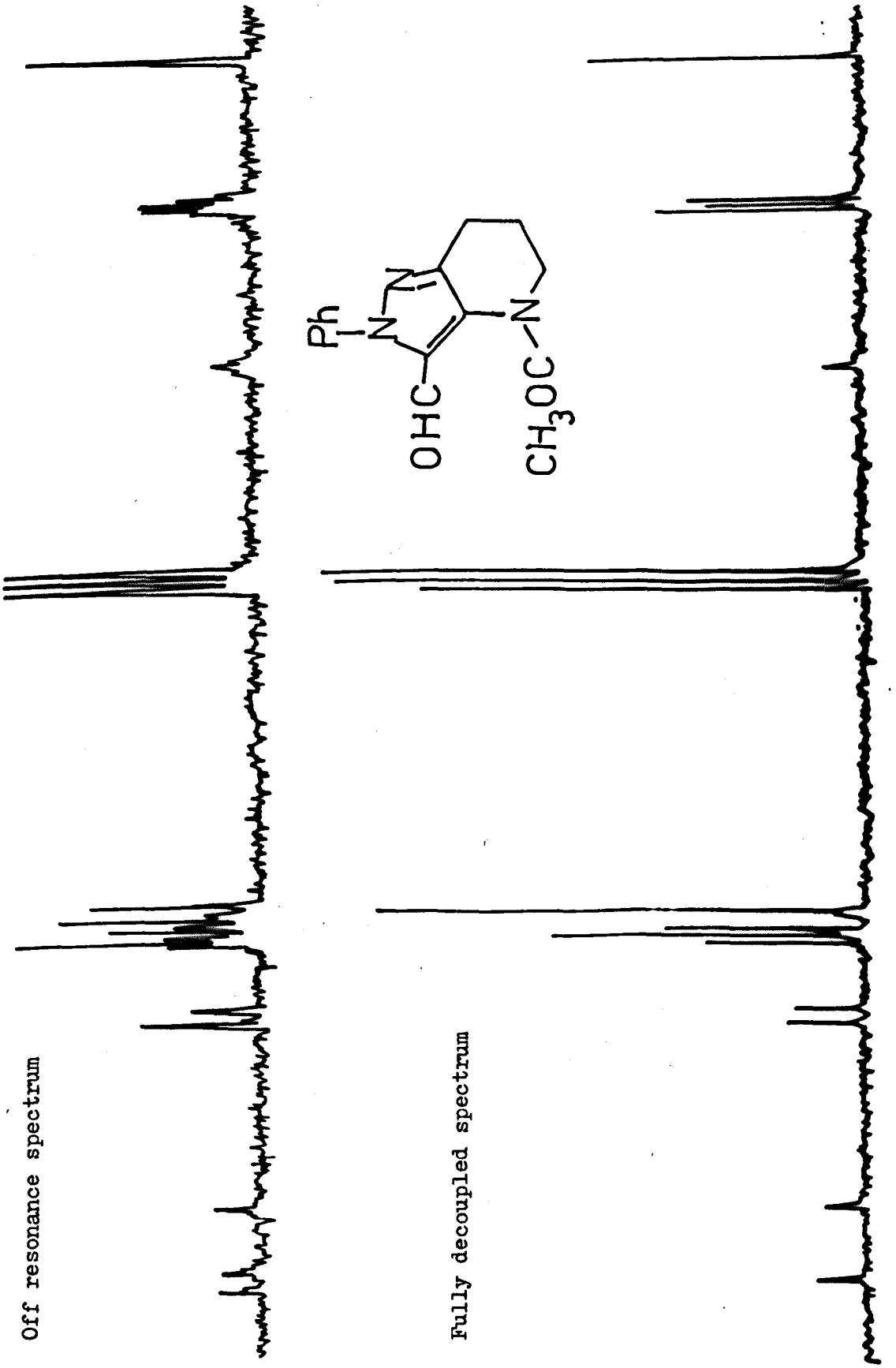


Fig. 2 ^{13}C N.m.r. spectra of 4,5,6,7-tetrahydro-4-acetyl-2-phenyl-pyrazolo[4,3-b]pyridine-3-carboxaldehyde (73)



interesting part of the spectrum concerns the 1 proton singlet peak at δ 9.8 p.p.m. It may be attributed to the aldehydic proton of the pyrazolopyridine (73) or the single proton attached to the double bond of the pyridopyridazinone (72).

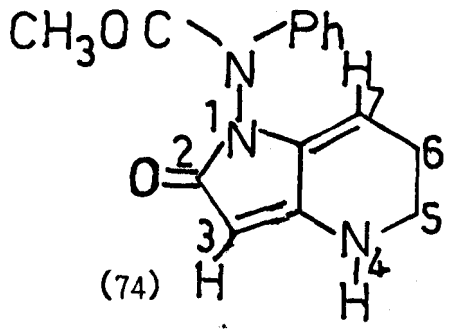
There were no simple models to be found in the literature with which to compare the chemical shift of the olefinic proton of (72), but one would expect it to be quite appreciably deshielded.

The i.r. spectrum showed a broad carbonyl absorption at 1675 cm^{-1}. The u.v. spectrum has $\lambda_{max.}$ at 206, 223, 275 and 323 mm ($\log_{10} \varepsilon$ = 3.34, 3.31, 2.79, 2.82). There was an irreversible change of the spectrum on addition of dilute base, the spectrum becoming more intense and the absorption at 223 nm disappearing.

The ^{13}C n.m.r. spectrum showed that the compound was the pyrazolo[4,3-b]pyridine carboxaldehyde (72). The fully decoupled spectrum which was run with a relaxation time of 60 secs (Fig. 2) showed the presence of two carbonyl absorptions at δ 169.0 and 180.3 p.p.m. from T.M.S. In the off resonance spectrum (Fig. 2a) the signal at δ 180.3 p.p.m. was seen as a doublet, indicating that one of the carbonyl absorptions is due to an aldehyde group. This evidence can only be accommodated by the pyrazolo[4,3-b]pyridine, structure (73). This product is a novel heterocyclic compound.

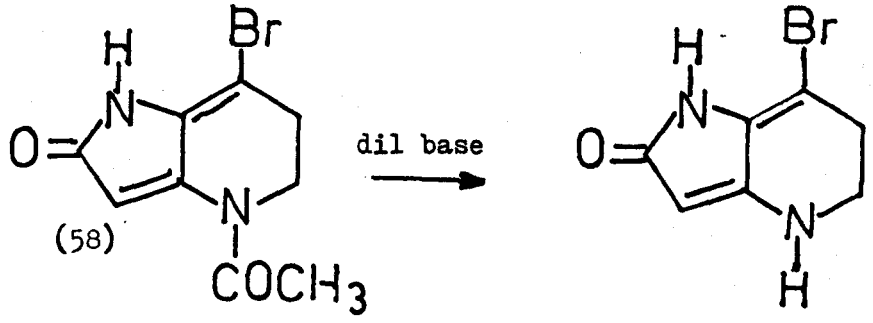
Further elution (1 : 1 $CHCl_3$/benzene) of the products from the column resulted in the second isomer being obtained. The solid was recrystallised from methanol (m.pt 214 - 215°C) and was obtained in yields of up to 58%.

The spectral data from this compound, left no doubt that this product was a derivative of the pyrrolopyridone, and its structure is best represented by (74).



(74)

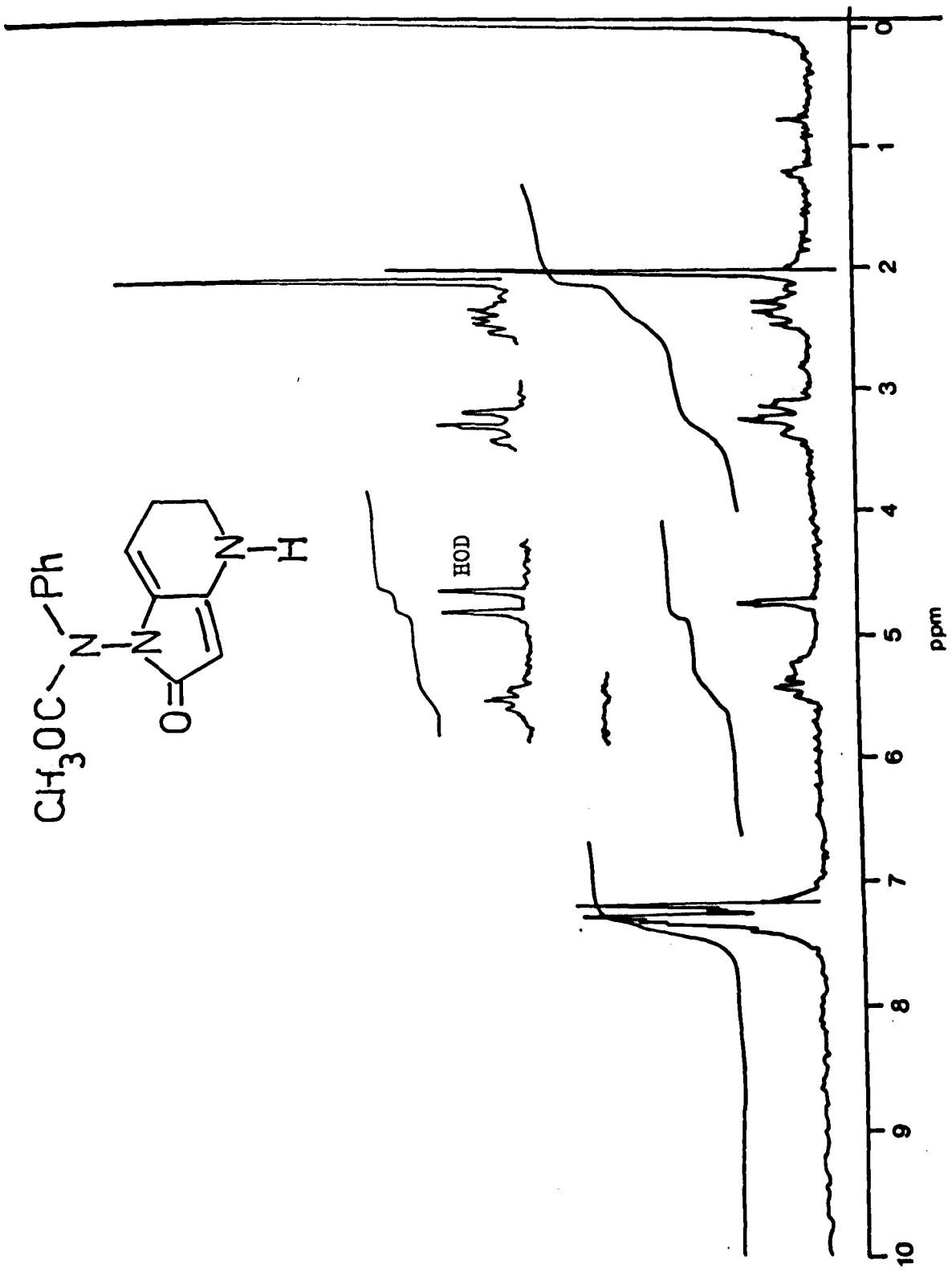
The mass spectrum showed a molecular ion at 269 a.m.u. from which a loss of 42 a.m.u. (CH_2CO) gave the base peak at 227 a.m.u. The spectrum also contained peaks at 77 a.m.u. ($C_6H_5^-$) and 43 a.m.u. (CH_3CO-). The i.r. and u.v. spectra were similar to those obtained after removal of the acetyl group from the pyrrolo-pyridone (58).



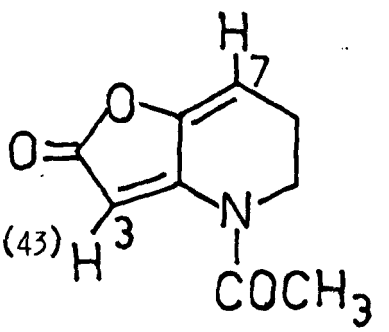
(58)

The ^1H n.m.r. spectrum is shown in (Fig. 3). It shows a 3 proton singlet peak at δ = 2.1 p.p.m. assigned to an acetyl group (confirmed by a peak at 43 a.m.u. in the mass spectrum) and two 2 proton multiplet peaks at δ = 2.4 and 3.3 p.p.m. Three signals are seen which integrate for one proton, the doublet at δ = 4.8 p.p.m. (J = 1 Hz), a broad singlet at δ = 5.5 p.p.m., and a doublet of triplets at 5.5 p.p.m. (J = 1 Hz, 5 Hz). The two signals at δ = 4.8 and 5.5 p.p.m. are attributed to the protons H3 and H7 respectively, and show a cross ring coupling of 1 Hz, which is a characteristic of this pyrrolo[3,2-b] pyridone system. The phenyl group is seen as a 5 proton multiplet between δ 7.1 and 7.5 p.p.m. On addition of D_2O to the spectrum the broad singlet at δ 5.5 p.p.m. disappeared and the signal at δ 3.3 p.p.m. sharpened to a triplet which confirms its position next to the -N-H and

Fig. 3 ^{1}H N.m.r. spectrum of 5,6-dihydro-1-(N-acetanilidinyl)-4H-pyrrolo[3,2-b]pyridin-2-one (74)



adjacent to a $-CH_2-$ group. This observation clears up the position of the acetyl group which must be on the aniline moiety. This evidence is also supported by the fact that the proton H3 in the furopyridone (43) is at a lower field δ = 6.1 p.p.m., in the ^1H n.m.r. spectrum, than H7 (δ 5.8 p.p.m.) due to the anisotropic deshielding effect of the carbonyl carbon of the acetyl group. In the deacetylated furopyridone the singlet peak has moved upfield to δ 4.72 p.p.m. In



the proposed structure (74) H3 is further upfield than H7.

The rest of the material remained at the top of the chromatography column even when the polarity of the eluent was increased.

The yields of the products, the pyrazolo pyridine (73) and the pyrrolopyridone (74), are in a ratio which accords with the basicity of the attacking nucleophile, N_1 being less basic than N_2 (formation of the pyrazolopyridine may proceed via the initially formed pyrido[3,2-c]pyridazine (72), see below).

Rearrangement procedure B:

Using procedure A it was found[21] that some of the isoxazole phenylhydrazone salt (70) had not reacted. It was decided that once all the salt had gone into solution the reaction mixture would be further heated.

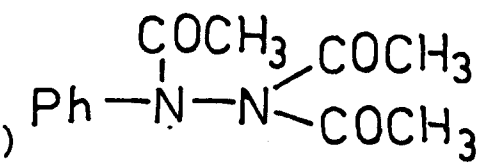
Using this procedure, B, on the hydrazone salt (70), the reaction mixture was heated for approximately 10 mins until the reaction

solution started turning to a dark black/brown colour, probably indicating the formation of polymeric material. Removal of excess acetic anhydride at the pump and then extracting the resultant oil with chloroform left an oil which contained a mixture of products, T.L.C. of which showed three fluorescent spots, one fast moving and two running close together.

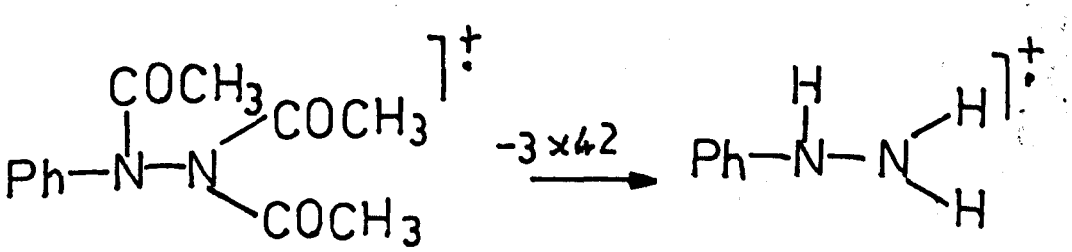
The products of the oil were separated by preparative layer chromatography, eluting with 100% ethyl acetate, to give the three fluorescent bands along with other minor bands. Characterisation of these minor bands was not possible.

Extraction of the fluorescent band of highest R_f gave an oil, micro analysis of which gave its empirical formula as $C_{12}H_{14}N_2O_3$. Its ^1H n.m.r. spectrum (Fig. 4) shows a three proton singlet peak at δ 2.15 p.p.m., a six proton singlet peak at δ 2.45 p.p.m., and a five proton broad peak at δ = 7.4 p.p.m. Its structure is best represented by that of tri (N-acetyl) phenylhydrazine (75).

(75)

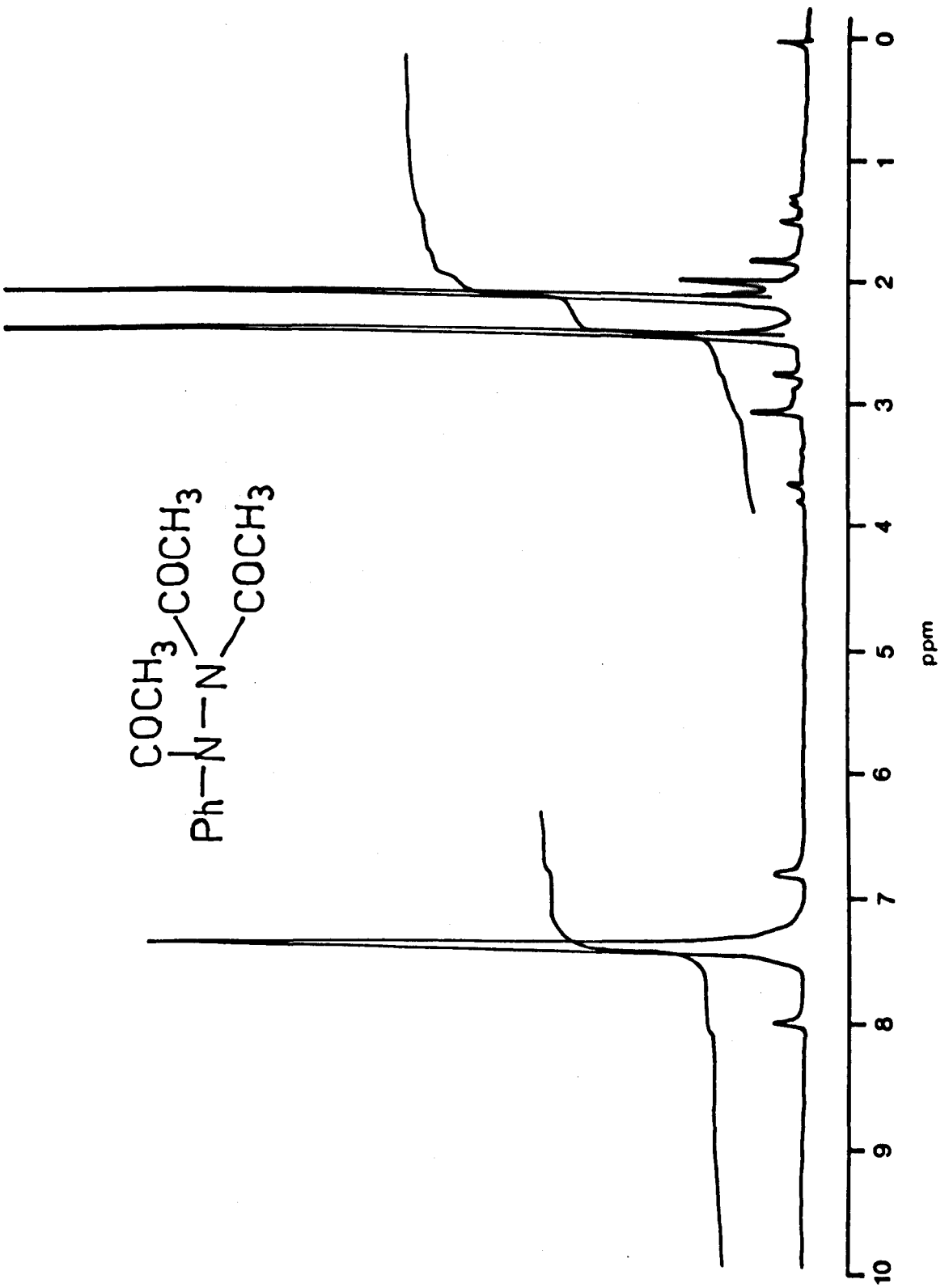


The mass spectrum shows an M^+ at 234 a.m.u. from which three major losses of keten are seen.

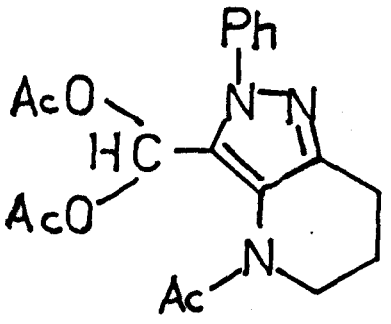


m/e 234 m/e 108 (80.8%)

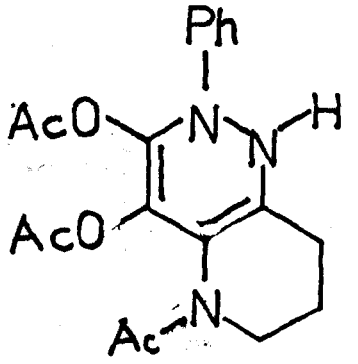
Fig. 4 ^{1}H N.m.r. spectrum of tri-(N-acetyl)phenylhydrazine (75)



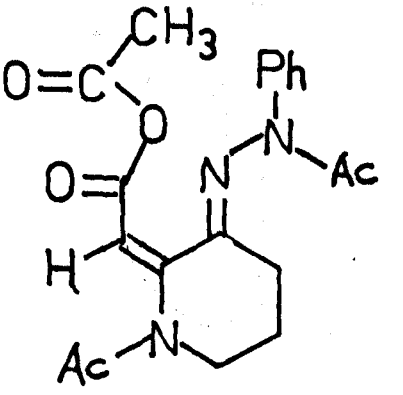
The product with intermediate R_f value was obtained as an oil; trituration and recrystallisation from absolute ethanol gave a yellow solid, m.pt 152 - 154°C (14.0%). Micro analysis gave a molecular formula of $C_{19}H_{21}N_3O_5$. The mass spectrum gave a molecular ion at 371 a.m.u., from which a major loss of 144 a.m.u. (acetic anhydride) to give a peak at 269 a.m.u. and then a loss of 42 a.m.u. to give a base peak at 227 a.m.u.; there were also peaks at 77 ($C_6H_5^+$) and 43 (CH_3CO^+) a.m.u. ^1H and ^{13}C n.m.r. proved that its structure is that of the pyrazolo[4,3-b]pyridine diacetate (76); other structures postulated were those of the pyrido[3,2-c]pyridazinone



(76)



(77)



(78)

(77) and the mixed anhydride (78).

The similarity of the aliphatic region of the ^1H n.m.r. spectrum (Fig. 5) to that of the pyrazolo[4,3-b]pyridine (73) was evident. The spectrum also showed the presence of a six proton singlet peak at δ = 1.85 p.p.m. and a three proton singlet peak at δ 2.20 p.p.m. assigned to the methyl groups of the acetoxy and acetyl groups respectively. The absorption due to the phenyl group is seen between δ 7.1 - 7.5 p.p.m. as a complex signal, adjacent to which is a broad singlet peak, which integrates for one proton, at δ = 7.65 p.p.m., and

Fig. 5 ^{1}H N.m.r. spectrum of 4,5,6,7-tetrahydro-4-acetyl-2-phenyl-pyrazolo[4,3-b]pyridine-3-carboxaldehyde diacetate (76)

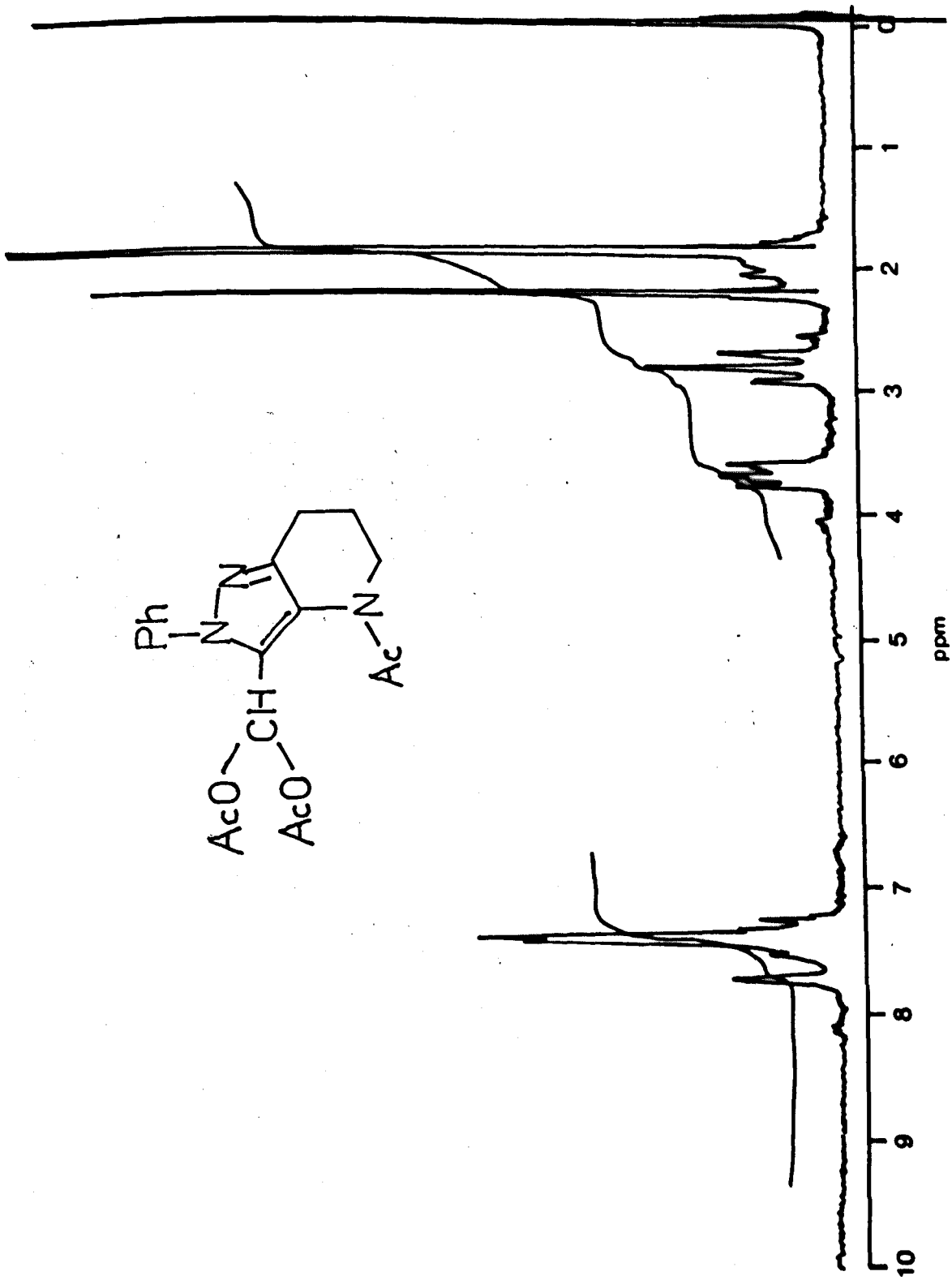
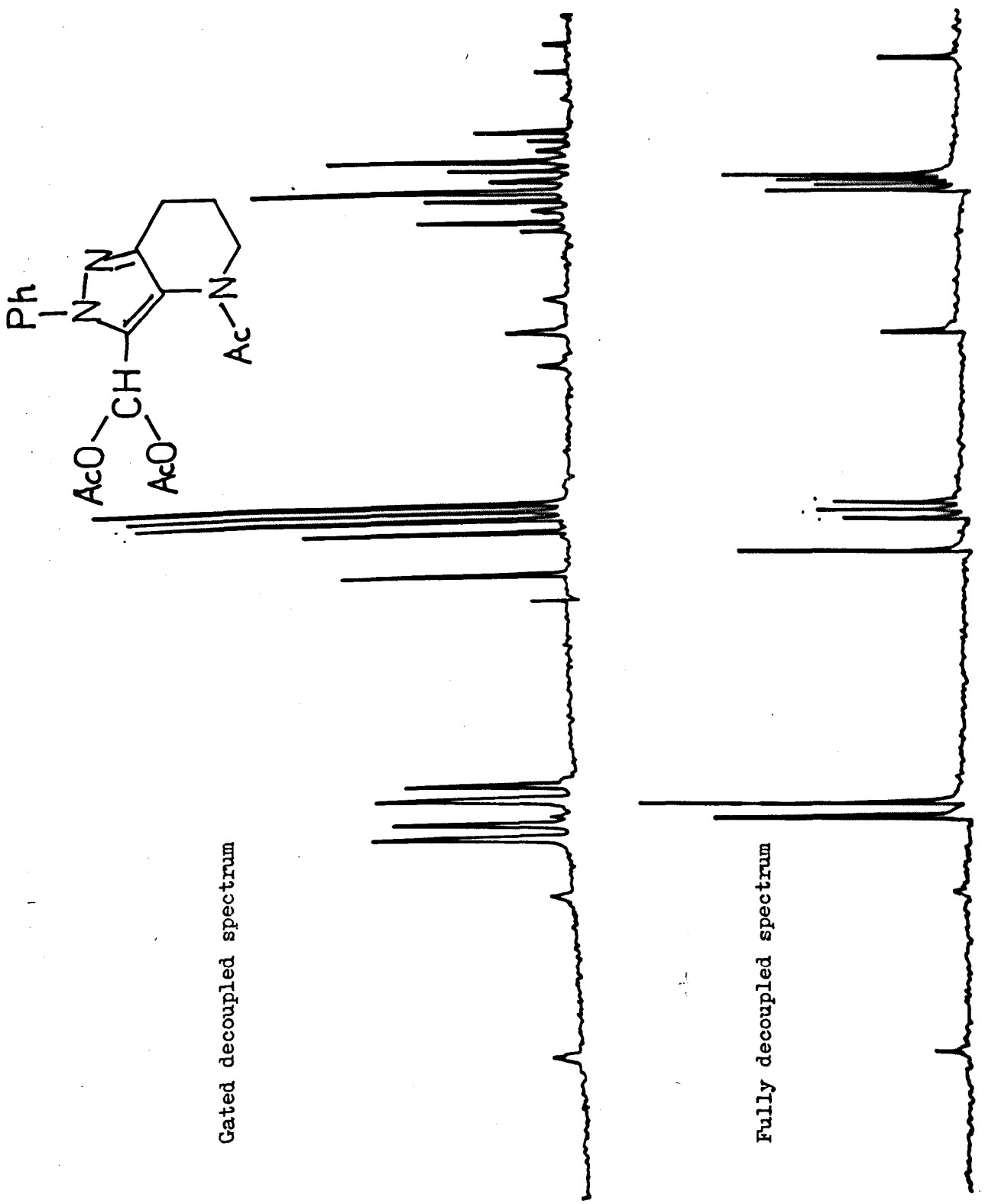


Fig. 5a ^{13}C N.m.r. spectrum of 4,5,6,7-tetrahydro-4-acetyl-2-phenyl-pyrazolo[4,3-b]pyridine-3-carboxaldehyde diacetate (76)



which did not disappear on shaking with D_2O. A gated decoupled ^{13}C n.m.r. spectrum (Fig. 5a) shows a $\rangle C$ - H doublet at δ 83.9 p.p.m. from T.M.S. This evidence rules out the pyrido[3,2-c]pyridazinone (77). The pyrazolo[4,3-b]pyridine structure is favoured over that of the mixed anhydride (78) because:

1. Only one infrared band at 1710 cm^{-1} is seen whereas structure (78) would require two bands around 1850 - 1800 and 1790 - 1740 cm^{-1}
2. The mass spectrum shows an initial loss of 144 a.m.u. which would be difficult to explain from structure (78)
3. The chemical shift of the methine proton (δ = 7.65 p.p.m.) for structure (76) agrees well with a calculated[22] figure of 7.50 p.p.m.

$$\delta_{CH} = 0.23 + C_1 + C_2 + C_3$$

C_1 = - O - COR = 3.1

C_2 $\rangle=\langle$ = 1.3

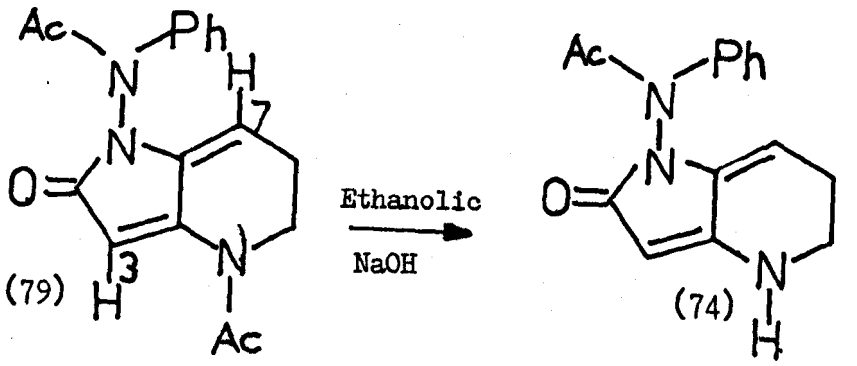
$$\delta_{CH} = 2\,(3.1) + 1.3 = 7.50 \text{ p.p.m.}$$

This diacetate compound (76) is most probably derived from the pyrazolo[4,3-b]pyridine carboxaldehyde (73).

The fluorescent band of lowest R_f from procedure B was obtained as an oil in up to 50% yield, consistent analysis could not be obtained, which was probably due to its sensitivity to hydrolytic conditions. The mass spectrum showed a molecular ion at 311 a.m.u., which is 43 a.m.u. more than that of the pyrrolo pyridone (74).

The ^1H n.m.r. spectrum left little doubt that this

product is the diacetyl pyrrolo[3,2-b]pyridone (79).



The position of the second acetyl group, is confirmed by the fact that in the ^{1}H n.m.r., H3 is seen at lower field, δ = 6.25 p.p.m., than H7 which resonates at δ 5.75 p.p.m., the reverse is true in the monoacetylated compound (74).

Hydrolysis of the diacetyl compound (79) using ethanolic sodium hydroxide was rapid and gave the monoacetyl pyrrolo pyridone (74).

The mechanism of formation of these products will be dealt with later.

On treatment of the isoxazolo pyridinium phenylhydrazone salt (70) with acetic anhydride two types of product, the pyrrolo[3,2-b] pyridone and pyrazolo[4,3-b]pyridine are indeed formed. Attempts to alter the ratio of the products by altering the basic strength of the attacking nucleophile were not successful.

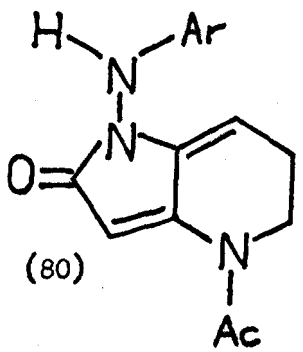
Preparation of simple hydrazones, notably the N,N-dimethyl hydrazone derivative of the ketonic salt (40) failed, which is probably due to the increased basic strength of the aliphatic hydrazine, causing ring opening reactions of the isoxazole moiety as described in the introduction to this chapter.

Treatment of the 2,4-dinitrophenylhydrazone derivative of the ketonic salt, (71), with acetic anhydride, using procedure A, gave

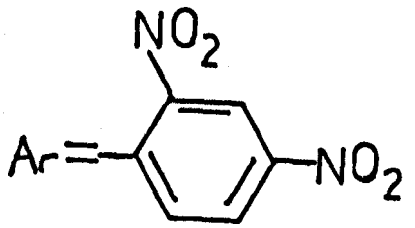
many products which were very difficult to separate and purify, many of them being unstable and also insoluble in common solvents.

After treatment of the dinitrophenylhydrazone derivative (71) with acetic anhydride, the resulting oil contained many products best separated by preparative layer chromatography, using 75% EtOAc, 25% $PhCH_3$ as the eluent. Many brightly coloured bands were seen, but only one band, R_f 0.23, was characterised.

The spectral data obtained from this orange solid left no doubt that it is the acetyl pyrrolo pyridone (80). The position of



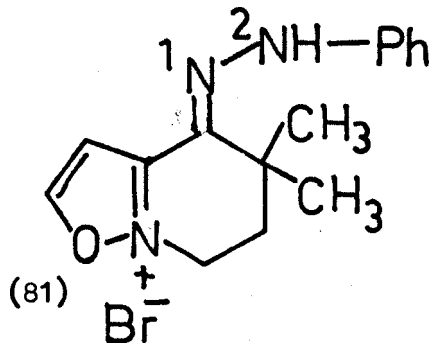
(80)



the N-acetyl group is established by the chemical shift of the -N-H (in compounds of the type (74), where the acetyl group is on the aniline moiety, the N-H shift is δ = 5 - 6 p.p.m.) by the absence of any N-H to $-CH_2-$ coupling, removable by deuterium exchange, and also by the chemical shift of the proton attached to C3.

Thus attempts to influence the ratios of the different types of product formed in the isoxazolo pyridinium salt / acetic anhydride reaction have been thwarted. In the case of the alkyl hydrazines by the instability of the isoxazolium salts towards bases and in the case of the dinitrophenylhydrazone by the difficulty of isolation and purification of the products.

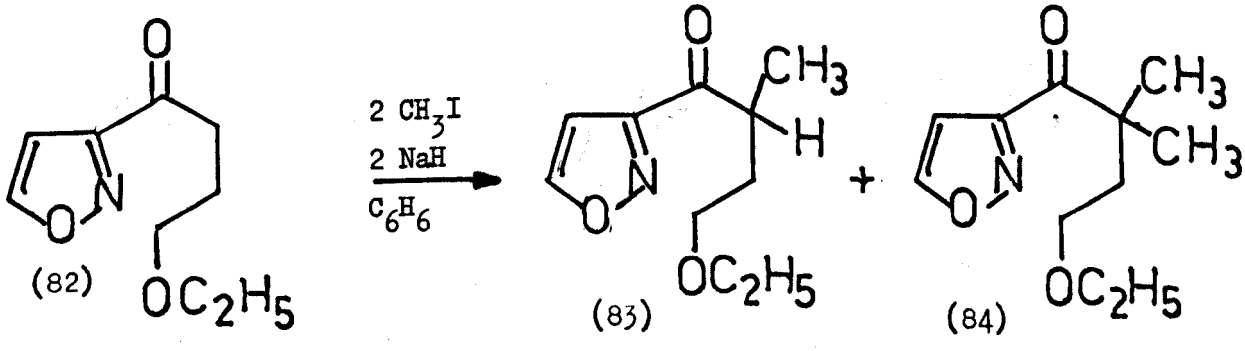
Another possible method of influencing the direction of the reaction would be to prepare and then rearrange the dimethyl isoxazolo pyridinium salt (80).



(81)

Tautomerism of the carbon - nitrogen double bond is prohibited and so only products resulting from cyclisation by ^{2}N will be seen.

Dimethylation of 3-(4-ethoxybutyryl) isoxazole (82) using sodium hydride and methyl iodide proved to be difficult. Using a procedure described by M.D. Soffer, R.D. Stewart et al.[23] a mixture of monoalkyl and dialkyl butyryl isoxazole were formed. It was not



(82) (83) (84)

possible to convert all the monoalkylated product (83) into the dialkylated product (84) without breakdown of the isoxazole ring.

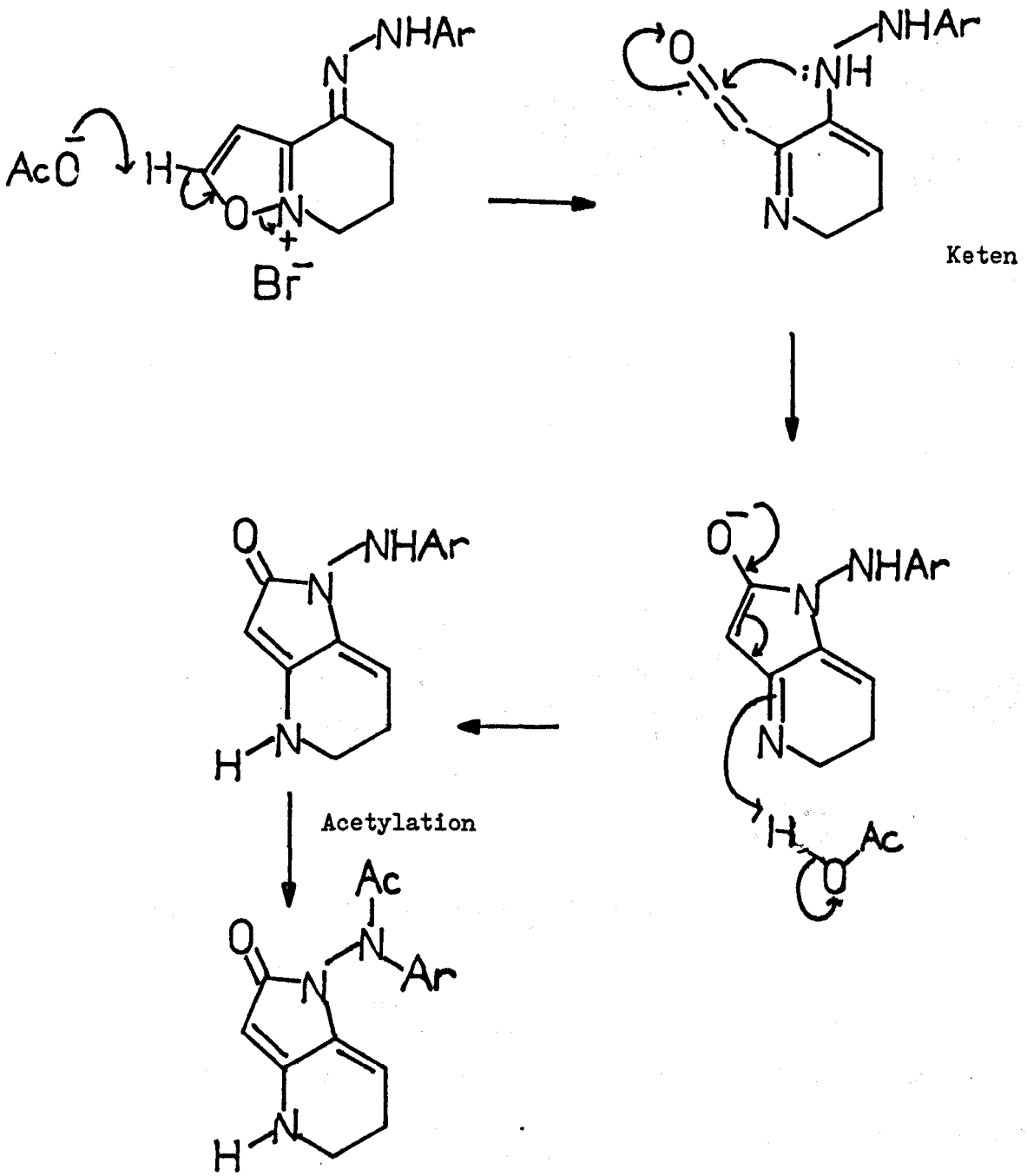
Separation of the two compounds could only be achieved by using preparative gas liquid chromatography. Using this technique the dimethyl butyryl isoxazole (84) was isolated from the mixture.

Because of the tedious nature of isolation of the dimethyl isoxazole this line of work was not pursued further.

(iv) Mechanism of formation of the rearrangement products

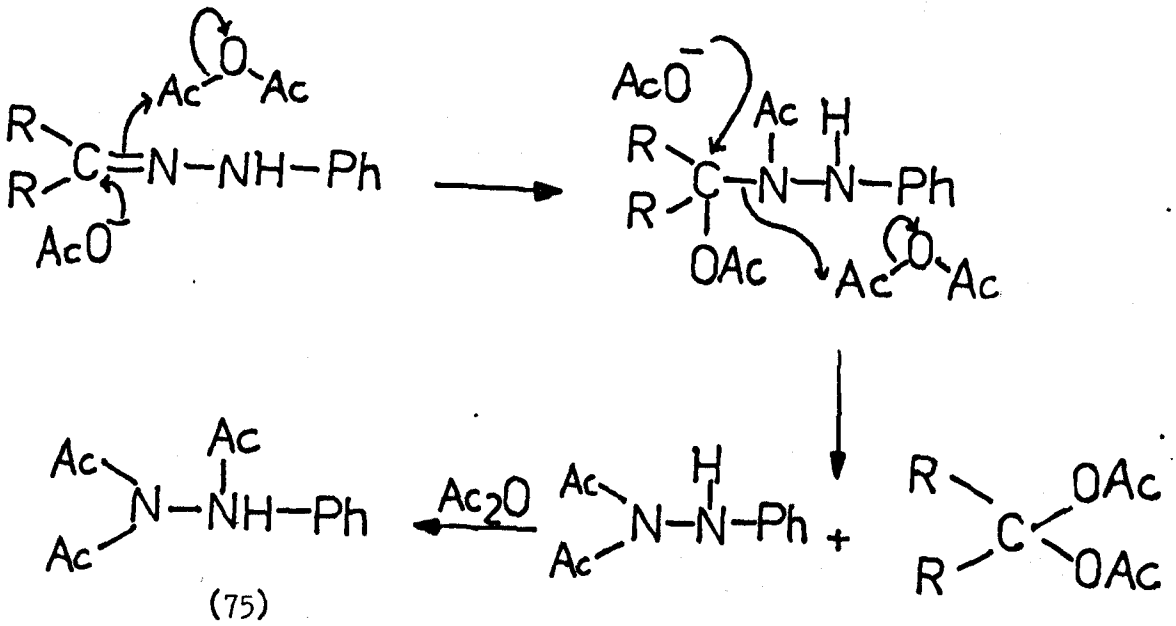
a. Pyrrolo[3,2-b]pyridones

The mechanism has been shown to proceed via a keten intermediate (a more comprehensive discussion is seen earlier) although the path via the Δ^3-isoxazoline cannot be ruled out.



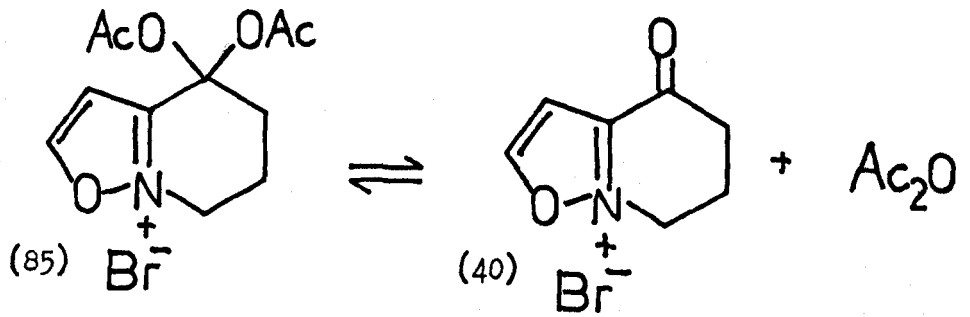
b. Phenylhydrazine triacetate

This compound may probably arise via the scheme shown.



(75)

The acetal (85) formed during the reaction may then be in equilibrium with the ketonic salt, which may then rearrange to the furopyridone (43),



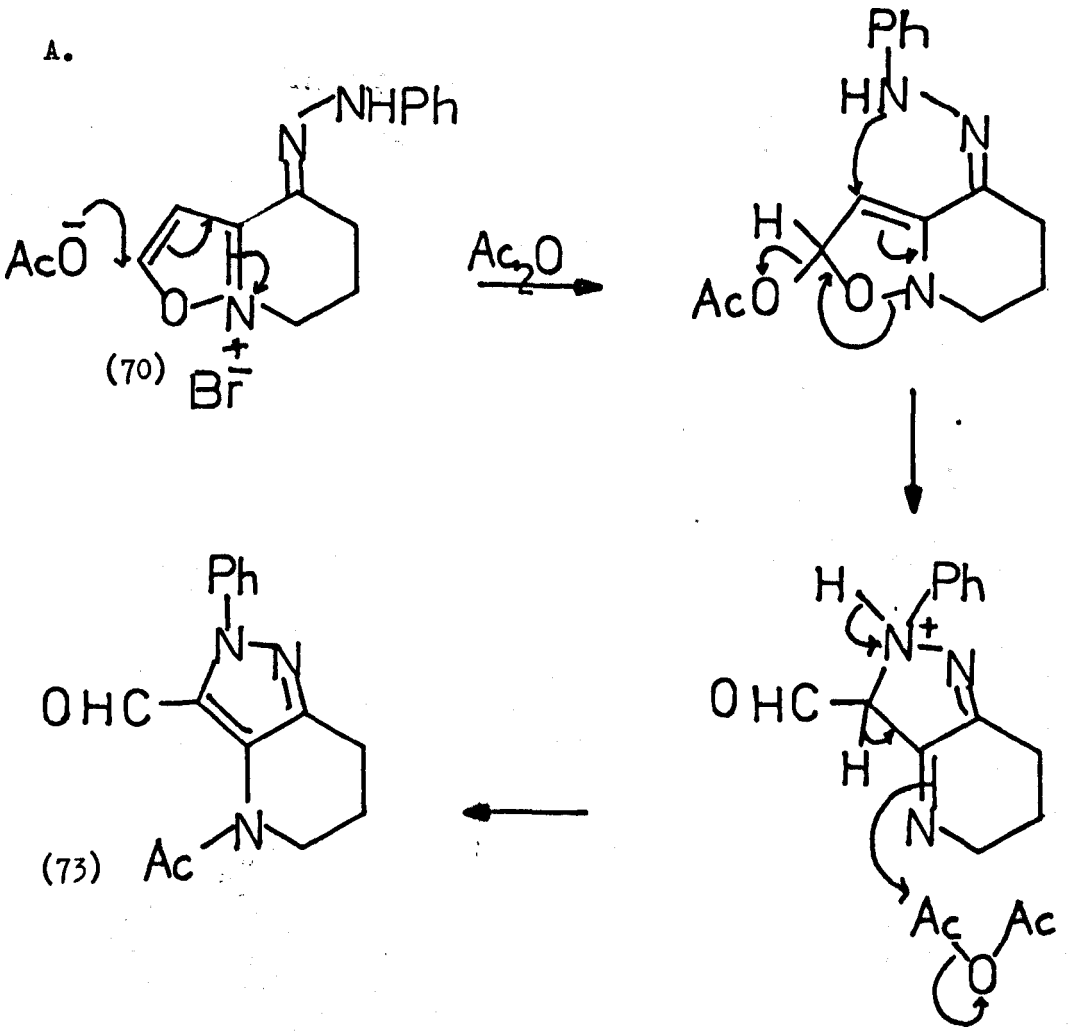
(85) (40)

although this has not been isolated.

c. Pyrazolo[4,3-b]pyridines

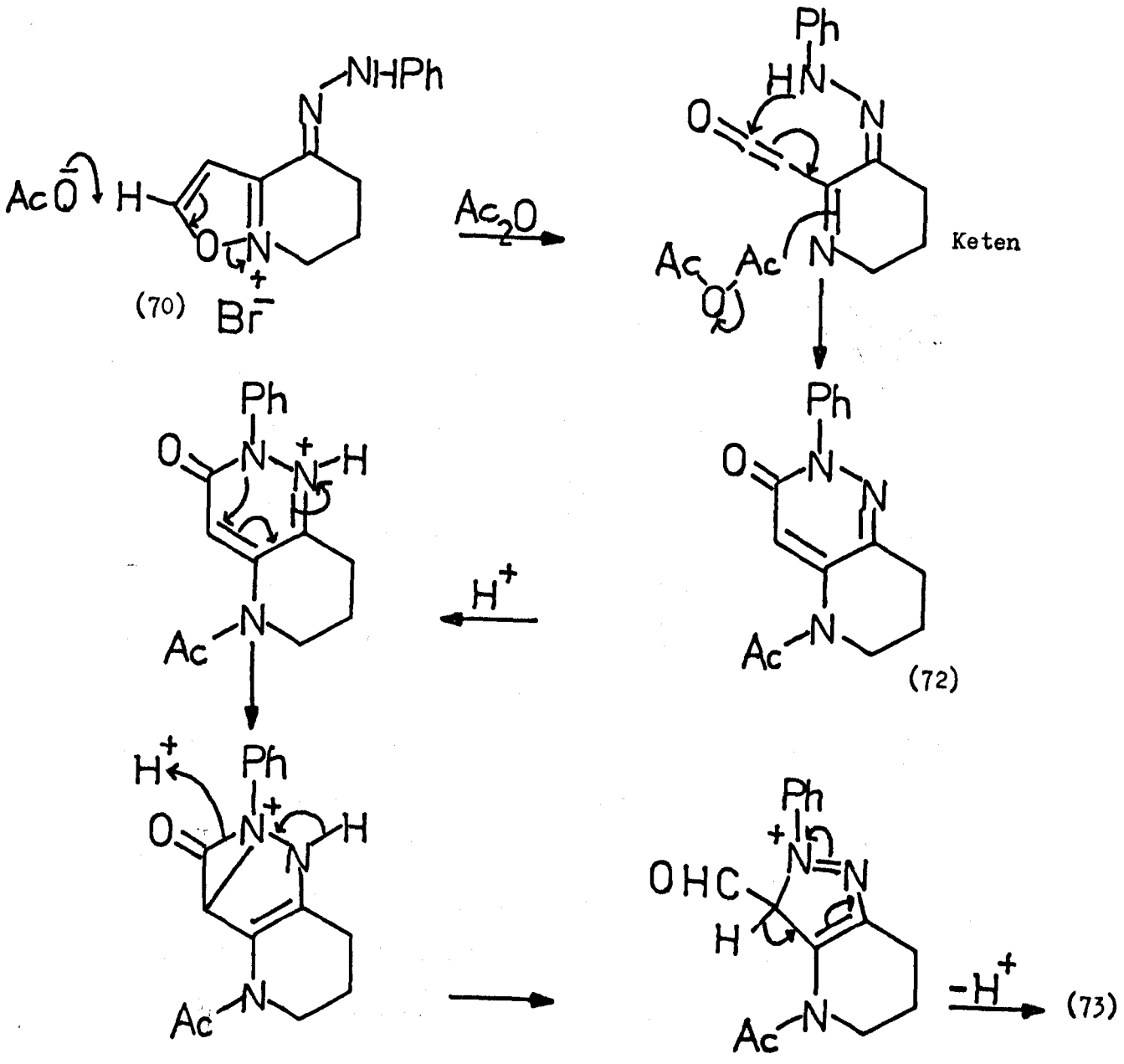
There are two possible routes by which the pyrazolo pyridines might be formed from the salt (73) by hot acetic anhydride.

A.



The first step involves addition of acetate anion to the salt to give the Δ^3-isoxazoline intermediate (86) which can cyclise as shown with subsequent acetylation of the piperidine nitrogen to give the pyrazolopyridine carboxaldehyde (73).

B. The other route involves the keten intermediate, cyclisation by N2 will result in a pyrido[3,2-c]pyridazinone (72). Such compounds, 1-aryl-6(1H)pyridazinones, are known[24] to undergo ring contraction under acid conditions, to give pyrazolo products. Although aldehydes have not been reported, carboxylic acids have. The following mechanism would account for the formation of the aldehyde.



The pyrazolopyridine diacetate (76) may then be formed from (73) by addition of acetate to the aldehyde followed by acetylation of the formed anion.

We have no evidence to favour either of these mechanisms in the systems described.

EXPERIMENTAL

Preliminary Notes.

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Infrared absorption spectra were measured on a Perkin Elmer 257 spectrophotometer and the ν_{max} values are quoted.

Electron absorption spectra were recorded on a Unicam S.P. 800 instrument. The λ_{max} values are quoted with the extinction coefficients expressed as $\log_{10} \varepsilon$ in brackets.

Proton nuclear magnetic resonance (^{1}H n.m.r.) spectra, unless otherwise stated, were recorded on a Perkin Elmer R24 60 MHz instrument and are quoted as 'delta' (δ) values in p.p.m., using a tetramethylsilane standard.

Carbon 13 nuclear magnetic resonance spectra (^{13}C n.m.r.) were recorded on a Jeol F.X. 100-100 Fourier Transform N.M.R. and are quoted as delta (δ) values in p.p.m. using a deutero-chloroform or T.M.S. standard.

The following abbreviations are used in conjunction with n.m.r. spectra: s = singlet, d = doublet, tr = triplet, q = quadruplet, m = multiplet and br = broadened.

Microanalyses were carried out on an F and M carbon/hydrogen/nitrogen analyser at the University of Keele.

Mass spectra were determined on a Hatachi - Perkin Elmer R.M.U.-6 instrument and the exact mass determinations were performed on an A.E.I. MS 902 machine.

Column chromatography was carried out using deactivated Woelm alumina.

Thin layer chromatography was carried out on 20 x 5 cm glass plates or 7.5 x 2.5 cm microscope slides coated with Kieselgel PF_{254} (Merck). The components were visualised under ultraviolet light or developed in iodine vapour.

Preparative layer chromatography was carried out on 40 x 20 cm glass plates coated with a 1.5 mm layer of Kieselgel PF_{254}. The separate components, visualised as for thin layer chromatography were isolated by scraping off the silica and extracted at least three times with boiling methanol. The filtered methanol solution was evaporated to leave a residue which contained silica. The residue was then dissolved in chloroform, filtered and evaporated.

Carbethoxychloraldoxime

Hydrochloric acid (166 cm^3, 1 equiv density = 1.19) was added to a solution of glycine ester hydrochloride in water at $0^{\circ}C$. To this mixture was added dropwise a solution of sodium nitrate (138 g, 1 equiv)in water (200 cm^3) keeping the temperature below $+5^{\circ}C$.

Another equivalent of $NaNO_2$/HCl was then added in the same manner. After complete addition the solution was stirred for 30 mins at $+5^{\circ}C$. The solution was then extracted with 3 x 200 cm^3 of ether, the combined ether extracts were dried over $MgSO_4$.

The $MgSO_4$ was removed by filtration, the solvent then removed and a white solid crystallised out on cooling. The product was then recrystallised from benzene60-80$^{\circ}C$ petroleum ether to give the carbethoxychloraldoxime (190.2 g, 62.8%).

3-Ethoxycarbonylisoxazole (45)

To a boiling vigorously stirred solution of vinyl acetate (215 g) and triethylamine (30 g) in ether (500 mls) was added carbethoxychloraldoxime (37.5 g) in ether (200 mls) over a period of one hour. A precipitate of triethylamine hydrochloride was seen. After complete addition, heating was continued for another hour. Water (400 cc) was then added and the layers of the orange solution separated. The ether layer was dried (magnesium sulphate), filtered and the solvent removed, to leave a red liquid.

The crude product was heated at 100-120°C at approx. 660 mmHg, until all the acetic acid had distilled, the pressure was then gently reduced to approx. 15-20 mmHg, the 3-ethoxycarbonyl-isoxazole (45) then distilled over as a clear liquid (33.3 g, 95.5%).

3-Carboxamido-isoxazole (46)

A cooled solution of 3-carbethoxyisoxazole (45) (34.6 g) in methanol (60 cm^3) was added dropwise to a stirred solution of concentrated ammonia (400 cm^3, Sp.Gr. 0.88) at 0°C. The mixture was then stood for 3 days at 0°C. The white precipitate of amide (46) was filtered, washed with water then dried. A second crop of crystals may be obtained by removing the solvent from the filtrate, the crystals may be recrystallised from ethyl acetate (18.7 g, 68%), m.pt. 145°C.

3-Cyano-isoxazole (47)

Phosphorous pentoxide (56 g) was mixed intimately with 3-amido-isoxazole (46) (28 g) and the flask attached to an apparatus set for vacuum distillation. Using an air bath the reaction flask was heated to 160°C, whereupon the pressure of the system was slowly reduced to 20 mmHg, the nitrile (47) was seen to distil over as a clear liquid and collected in a cooled receiver (12.8 g, 53.6%) b.pt. 96°C at 30 mmHg.

The 3-cyano-isoxazole (47) was pure enough to continue onto the next stage without distillation.

3-(4-Ethoxybutryl)-isoxazole (49)

A solution of the Grignard reagent from 3-ethoxypropyl-bromide (18.4 g) and magnesium (2.88 g) in dry ether (200 mls) was added slowly to a stirred cold solution of 3-cyano-isoxazole (47) (9.4 g) in ether (200 mls) at such a rate that the temperature does not exceed +5°C. The light yellow solution formed may be stirred overnight.

Ice cold hydrochloric acid (12 N, 30 mls) was slowly added to the reaction mixture. A mustard gluey precipitate was seen to be formed. The ether was decanted off and then extracted with more cold hydrochloric acid (12 N, 2 x 10 mls). The combined acid extracts were diluted to dissolve suspended solids and then stirred at room temp. for one hour, to ensure complete hydrolosis of the imine intermediate (48).

The solution was then basified by cautious addition of ammonia solution (approx. 40 mls, Sp.Gr. 0.88) and then ether extracted and dried ($MgSO_4$). The $MgSO_4$ was removed by filtration and the solvent

then removed to leave the desired product (49) (11.1 g, 60.7%). The orange solution is then distilled under vacuum to give the 3-(4-ethoxybutryl)-isoxazole (49) (10.5 g, 57.4%), b.pt. 66°C/ 0.5 mmHg.

4,5,6,7-Tetrahydro-4-oxoisoxazolo 2,3-a pyridinium bromide (40)

Reaction best done on 1 g quantities of 3-(4-ethoxybutryl)-isoxazole (49).

A solution of 3-(4-ethoxybutryl) isoxazole (49) (1 g) in hydrobromic acid (48%, 50 mls) was heated under reflux for one hour; the initially formed bromide was allowed to escape. Evaporation under reduced pressure gave a solid which was dissolved in absolute ethanol; the solution was then re-evaporated. Trituration of the residue with dry acetone gave almost pure cyclic ketone (40) (1.1 g, 91%).

4,5,6,7-Tetrahydro-4-oxoisoxazolo[2,3-a]pyridinium bromide Phenylhydrazone (70)

A solution of phenylhydrazine hydrochloride (0.36 g) in absolute ethanol (10 mls) was added to a solution of the cyclic ketone (40) (0.5 g) also in absolute ethanol (10 mls). The mixture was boiled (20 mins) and evaporated; the residue was crystallised from ethanol to give the isoxazolo-phenylhydrazone (70) (0.68 g, 97%), m.pt. > 300°C.

2,4-Dinitrophenylhydrazone (71) of the cyclic salt

Solutions of the ketonic salt (40) (0.5 g) and of 2,4-dinitrophenylhydrazine (0.45 g) each in glacial acetic acid (10 mls) were mixed and boiled (1 hour) then cooled. The precipitated solid was recrystallised from methanol to give the dinitrophenylhydrazone bromide (71), (0.9 g, 98%), m.pt. $>300^{\circ}C$. (Found: C, 37.5; H, 3.3; N, 16.4. $C_{13}H_{12}BrN_5O_6$ requires C, 38.0; H, 3.25; N, 16.65%) λ_{max}(EtOH) 209, 238 and 253 nm ($\log_{10}\varepsilon$ 3.25, 3.14, 3.28) δ (CF_3CO_2H) 2.9 (2H, m), 3.3 (2H, tr), 5.0 (2H, tr), 7.15 (1H, d, J = 3 Hz, H-3), 8.3 (1H, d, J = 9 Hz, 2,4-DNP), 8.65 (1H, d of d, J = 9 and 2 Hz, 2,4-DNP), 8.95 (1H, d, J = 3 Hz, H-2) and 9.25 (1H, d, J = 2 Hz, 2,4-DNP).

Reaction of Phenylhydrazone (70) with Acetic Anhydride:

Procedure A. The salt (70) (4 g) was heated with acetic anhydride just to the boiling point, the mixture cooled, then the solution was decanted from unreacted salt. This procedure was repeated until all the salt had gone into solution. The combined acetic anhydride solutions were evaporated in vacuo and the black oily residue extracted with chloroform. The chloroform solution was evaporated onto alumina (10 g, Grade IV) and the coated alumina added to the top of an alumina column (150 g, Grade IV). Elution with benzene gave a mixture of products, uncharacterised. Further elution with chloroform/benzene (3 : 7) gave a solid, recrystallised from absolute ethanol, m.pt. 133°C, identified as 4,5,6,7-tetrahydro-4-acetyl-2-phenylpyrazolo[4,3-b]-pyridine-3-carboxaldehyde (73) (0.42 g, 14.5%). (Found: C, 66.6; H, 5.6; N, 15.3. $C_{15}H_{15}N_3O_2$ requires C, 66.9; H, 5.6; N, 15.6%). $\lambda_{max.}$(EtOH) 206, 223, 275 and 323 nm. ($\log_{10}\varepsilon$ 3.34, 3.31, 2.79,

2.82), ν_{max} ($CHCl_3$) 1675 cm^{-1} (broad), δ ($COCl_3$), 2.0 (2H, m), 2.1 (3H, s, CH_3CO) 2.75, 2H, tr, CH_2 C=N), 3.1 (2H, tr, CH_2CO), 7.1-7.5 (5H, m, C_6H_5) and 9.8 p.p.m. (1H, s). M^+ 269 a.m.u. Further elution with chloroform:benzene (1:1) gave a solid, recrystallised from methanol as yellow needles, m.pt. 214-215°C, identified as 5,6-dihydro-1-(N-acetanilidinyl)-4H-pyrrolo[3,2-b]-pyridin-2-one (74) (1.7 g, 58%). (Found: C, 67.1; H, 5.65; N, 15.25. $C_{15}H_{15}N_3O_2$ requires C, 66.9; H, 5.6; N, 15.6%). λ_{max} (EtOH) 272 and 344 nm ($\log_{10} \varepsilon$ 4.11, 3.51). ν_{max} ($CHCl_3$), 3420, 1700 and 1615 cm^{-1}. δ ($CDCl_3$) 2.1 (3H, s, CH_3CO), 2.4 (2H, m, CH_2 C=C), 3.3 (2H, m, CH_2N), 4.8 (1H, d, J = 1 Hz), 5.3 (1H, br, s, NH), 5.5 (1H, d of tr, J = 1 and 5 Hz) and 7.1 - 7.5 p.p.m. (5H, m, C_6H_5). M^+ 269 a.m.u.

Procedure B. As in Procedure A, but when all the salt (70) had dissolved boiling was continued for 10-15 mins, the solution darkening considerably. Evaporation of acetic anhydride gave a black solid, extracted with chloroform. Chloroform soluble material was separated by p.l.c. (eluted with ethyl acetate) giving three fluorescent bands, described in decreasing R_f values: Band 1 when extracted gave a yellow oil, N,N,N'-triacetylphenylhydrazine (75) (Found: C, 61.05; H, 6.15; N, 11.75. $C_{12}H_{14}N_2O_3$ requires C, 61.35; H, 6.0; N, 11.95%). λ_{max} (EtOH) 230 ($\log_{10} \varepsilon$ = 3.80). ν_{max} ($CHCl_3$) 1710 cm^{-1} (broad). δ ($CDCl_3$) 2.15 (3H, s), 2.45 (6H, s) and 7.4 p.p.m. (5H, m, C_6H_5). M^+ = 234. Band 2 This gave solid as crystals from absolute ethanol, m.pt. 153-154°C, identified as the pyrazolo[4,3-b]pyridine-3-carboxaldehyde diacetate (76) (0.39 g, 14.4%). (Found: C, 61.4; H, 5.7; N, 11.45. $C_{19}H_{21}N_3O_5$ requires C, 61.45; H, 5.65; N, 11.3%).

λ_{max} (EtOH) 265 ($\log_{10} \varepsilon$ 3.76). ν_{max} ($CHCl_3$), 1700, 1660, 1400 and 1240 cm^{-1}. δ ($COCl_3$), 1.85 (6H, s, CH_3CO), 2.0 (2H, m), 2.2 (3H, s, CH_3CO), 2.8 (2H, tr), 3.7 (2H, tr, CH_2N), 7.1-7.7 (5H, m, C_6H_5) and 7.9 p.p.m. (1H, s). M^+ = 371 a.m.u. Band 3 Gave an oil which could not be crystallised, and gave irregular analyses, the spectral data showed it to be the diacetylpyrrolo [3,2-b]pyridin-2-one (79). ν_{max} ($CHCl_3$), 1700 and 1615 cm^{-1} δ ($COCl_3$), 2.1 (3H, s, CH_3CO), 2.3 (3H, s, CH_3CO), 2.6 (2H, m), 3.8 (2H, tr, CH_2N), 5.75 (1H, d of tr, J = 1 and 5 Hz), 6.25 (1H, d, J = 1 Hz) and 7.4 p.p.m. (5H, m, C_6H_5). M^+ = 311 a.m.u. Hydrolosis was very rapid with ethanolic sodium hydroxide, hydrolosis procedure: (79) (100 mg) in ethanol (10 mls) was treated with 2N NaOH (2 ml) an immediate colour change was observed (yellow to orange). The ethanol was evaporated in vacuo, and the residue extracted with chloroform, dried ($MgSO_4$), filtered then the chloroform removed. The yellow oily residue was purified by p.l.c. (eluent ethyl acetate). Extraction of the major band, then recrystallisation of the resultant solid (from methanol) gave yellow needles, m.pt. 214°C, identical (mixed m.pt.) with those of compound (74) prepared by Procedure A (70 mg., 80%).

Reaction of 2,4-Diphenylhydrazone bromide (71) with hot Acetic Anhydride:

By Procedure A as described above, the residue from the acetic anhydride being purified by p.l.c. (eluent, ethyl acetate: toluene, 3:1). Only one product was characterised, 5,6-dihydro-4-acetyl-1-(N-(2,4-dinitro)anilinyl)-5H-pyrrolo 3,2-b pyridin-2-one (80), crystals from acetonitrile, m.pt., 221°C, (0.2 g, 11.6%).

(Found: C, 50.45; H, 3.95; N, 19.2. $C_{15}H_{13}N_5O_6$ requires C, 50.15; H, 3.9; N, 19.5%). λ_{max} (EtOH), 216, 269 and 332 nm ($\log_{10}\varepsilon$ 4.20, 4.23, 3.14). ν_{max} (KBr Disc), 1715 cm^{-1} δ (DMSO - d6) 1.85 (3H, s, CH_3CO), 2.0 (2H, m), 3.85 (2H, tr, CH_2N), 5.75 (1H, d of tr, J = 1 and 5 Hz), 6.15 (1H, d, J = 1 Hz), 6.9 (1H, d), 8.25 (1H, d of d), 8.85 (1H, d) and 11.4 p.p.m. (1H, br, exch. D_2O). M^+ = 359 a.m.u.

Attempted Dialkylation of 3-(4-ethoxybutyryl)isoxazole (49)

The ketone (49) (7.2 g, 0.04 mole) was added to a solution of methyl iodide (11.5 g, 0.8 mole) in anhydrous benzene (50 mls), contained in a 3-necked round bottom flask which had been previously flame dried. The solution was then cooled in an ice bath to 0°C, sodium hydride (2 g, 0.8 mole, used as a 50% dispersion in oil) was added in small amounts to the reaction mixture at such a rate that the temperature did not increase appreciably. The solution was then stirred at room temp. for 1 hour and then bought to reflux. The course of the reaction was followed by g.l.c. (3% OV101, Oven Temp = 117°C, N_2 flow rate = 60 mls/min). The dimethylbutyryl isoxazole (84) was isolated by preparative g.l.c. liquid. (Found: C, 62.1; H, 8.30; N, 6.47. $C_{11}H_{17}NO_3$ requires C, 62.55; H, 8.06; N, 6.64%). δ ($CDCl_3$), 1.0 (3H, tr), 1.4 (6H, s, 2 x CH_3), 2.1 (2H, tr), 3.1-3.6 (4H, trand q), 6.6 (1H, d, J = 2 Hz), 8.3 (1H, d, J = 1 Hz). M^+ = 211 a.m.u.

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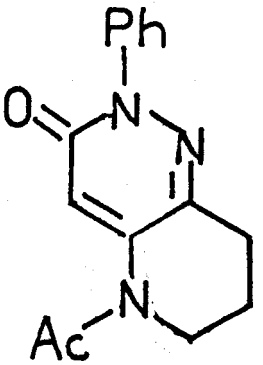
P A R T I I

INTRODUCTION

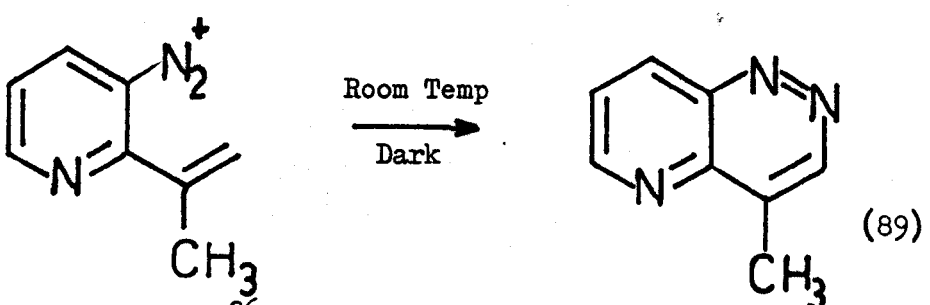
During attempts to establish the structure of the pyrazolo[4,3-b]pyridine (73), one of the proposed structures was that of the pyrido[3,2-c]pyridazinone (72), although this was eventually discounted by ^{13}C n.m.r. spectroscopy.



(72)

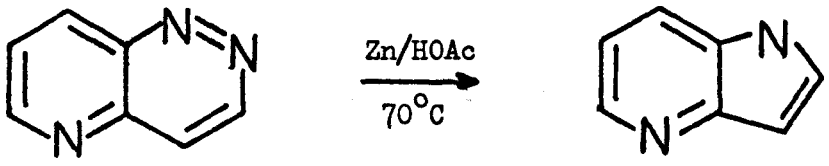
At the time that the structure of the above product was elucidated, there were only two references[25,26] to the parent pyrido-[3,2-c]pyridazine system.

One mentions the isolation of the picrate derivative of the 4-methyl analogue (89) by a modification of the Widman-Stoermer and Boersch synthesis of cinnolines.



(89)

The other[26] by Kost, a Russian chemist, described the reduction of the parent system (87) with zinc in acetic acid to give the pyrrolo-[3,2-c]pyridine (90).

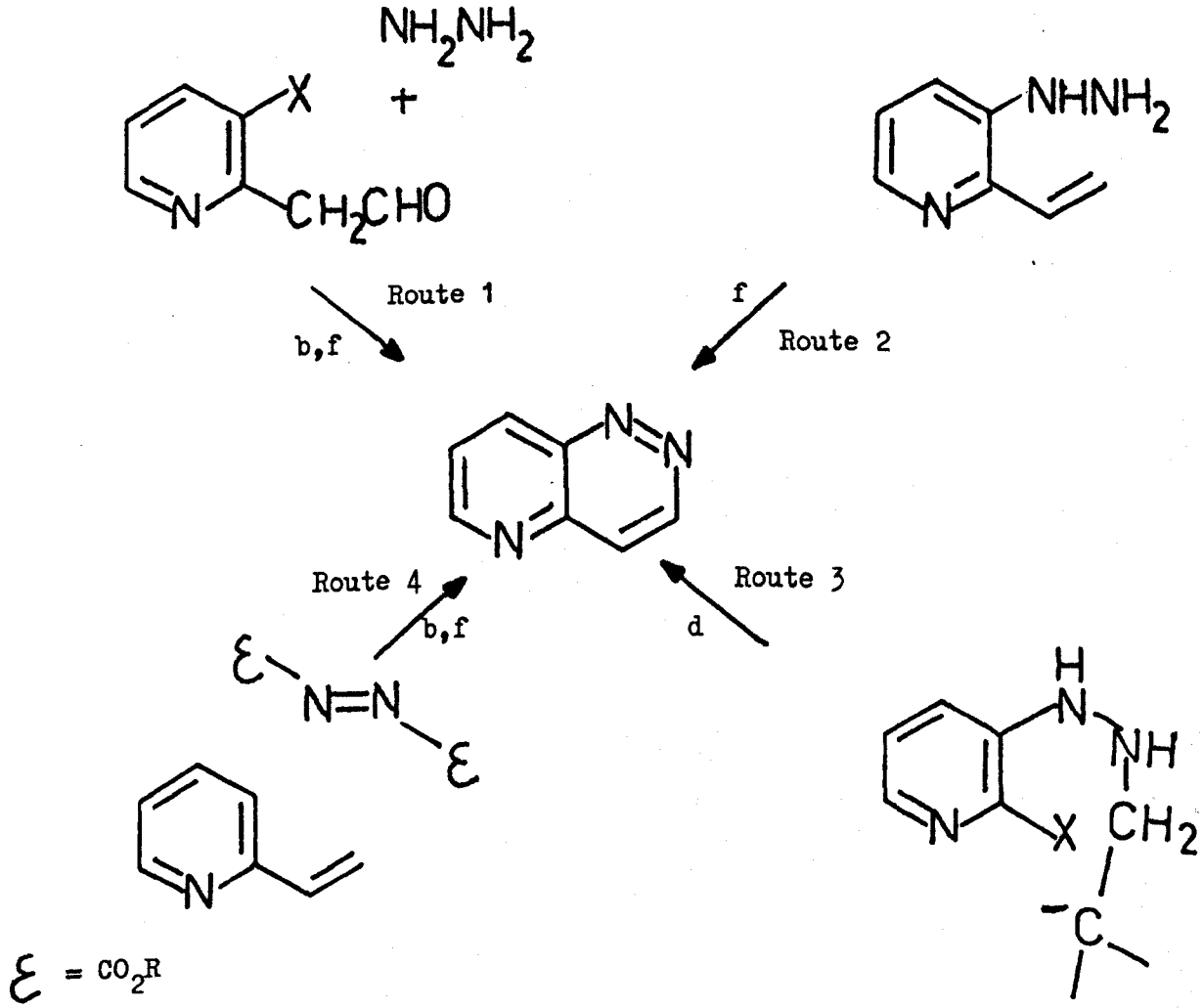


(87) (90)

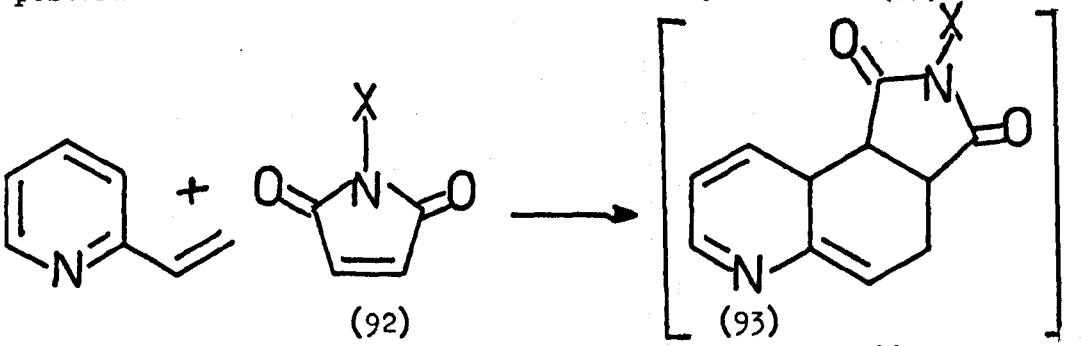
Kost and co-authors later published the synthesis and some reactions of this 5-azacinnoline (87). (See later). The method of synthesis of the azo compound (87), used the same starting materials as our own.

We decided to try to prepare the parent pyrido[3,2-c]pyridazine (87), synthesising the pyridazine moiety, pyridine derivatives being generally more readily available as starting materials.

The routes we considered are shown below.



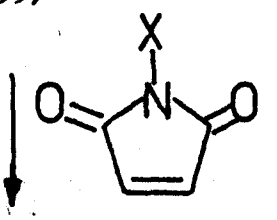
The first route tried was route 4, because of its comparatively short length and the readily available starting materials, 2-vinyl pyridine (90) and diesters of azodicarboxylic acid. It is known[27] that 2-vinyl pyridine (90) undergoes reaction with N-alkyl and phenyl maleinimide (92) to give products which are postulated to be derived from the initial cycloadduct (93).



(92)

X = Ph, Cl

(93)



Further addition

A more detailed account of this reaction will be given on p.74

The remainder of this thesis describes the reactions of 2-vinyl pyridine and its derivatives with esters of azodicarboxylic acid and the conversion of the cycloadducts so obtained to the fully aromatic systems. The synthesis is then extended to include other vinyl heterocyclic systems.

A review of addition of dienophiles to styrene and to vinyl heterocyclic systems is presented which is followed by a discussion of the cycloaddition and ene reactions of azodicarboxylic diesters.

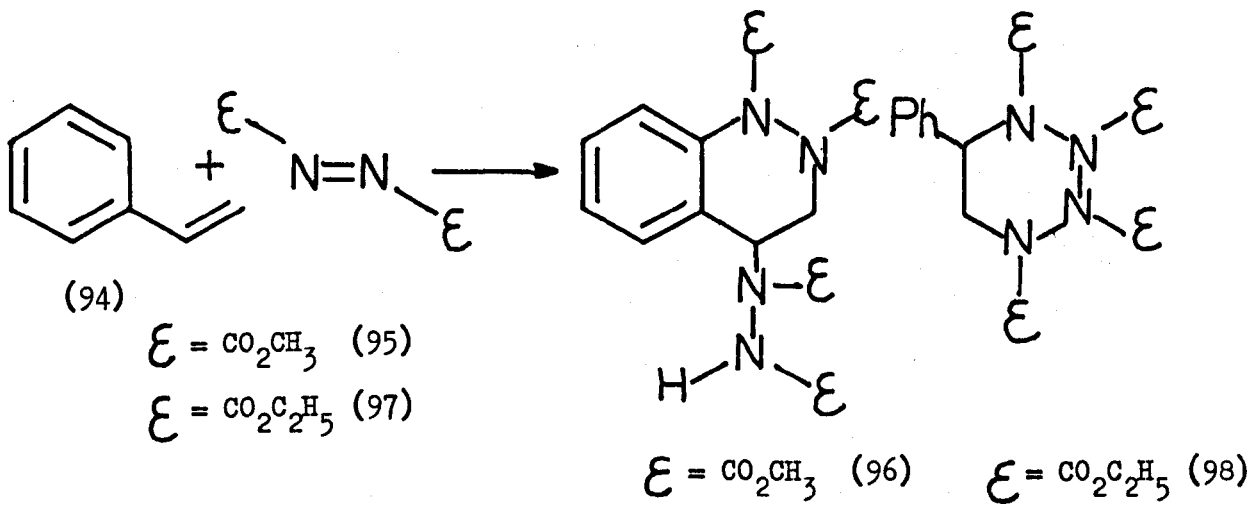
1. Addition of Dienophiles:

(i) To styrene and its derivatives.

Styrene (94) undergoes cycloaddition reactions with a variety of dienophiles, using an aromatic "double bond" and the extra nuclear

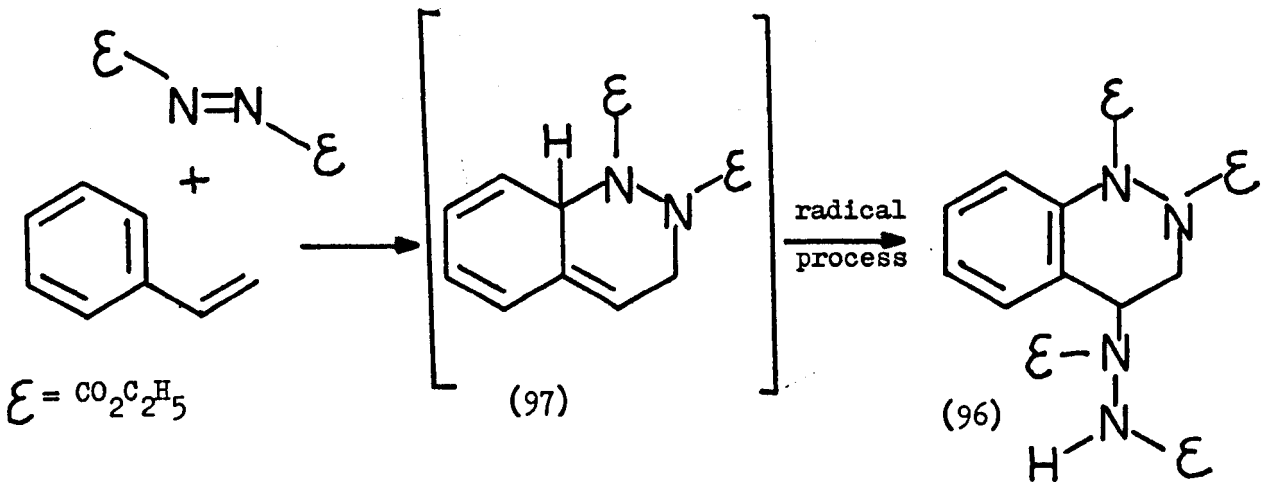
double bond.

Diels and Alder[28] and Ingold and Weaver[29] reported that esters of azodicarboxylic acid react with styrene (94) in the ratio of two moles of the ester to one of the unsaturated compound. The former workers[28] assigned the structure (96) to the product obtained from the condensation of methylazodicarboxylate (95) with styrene (94). Ingold and Weaver[29] suggested the tetrazine structure (98) for the substance they isolated from the reaction of ethyl azodicarboxylate (97) with styrene.



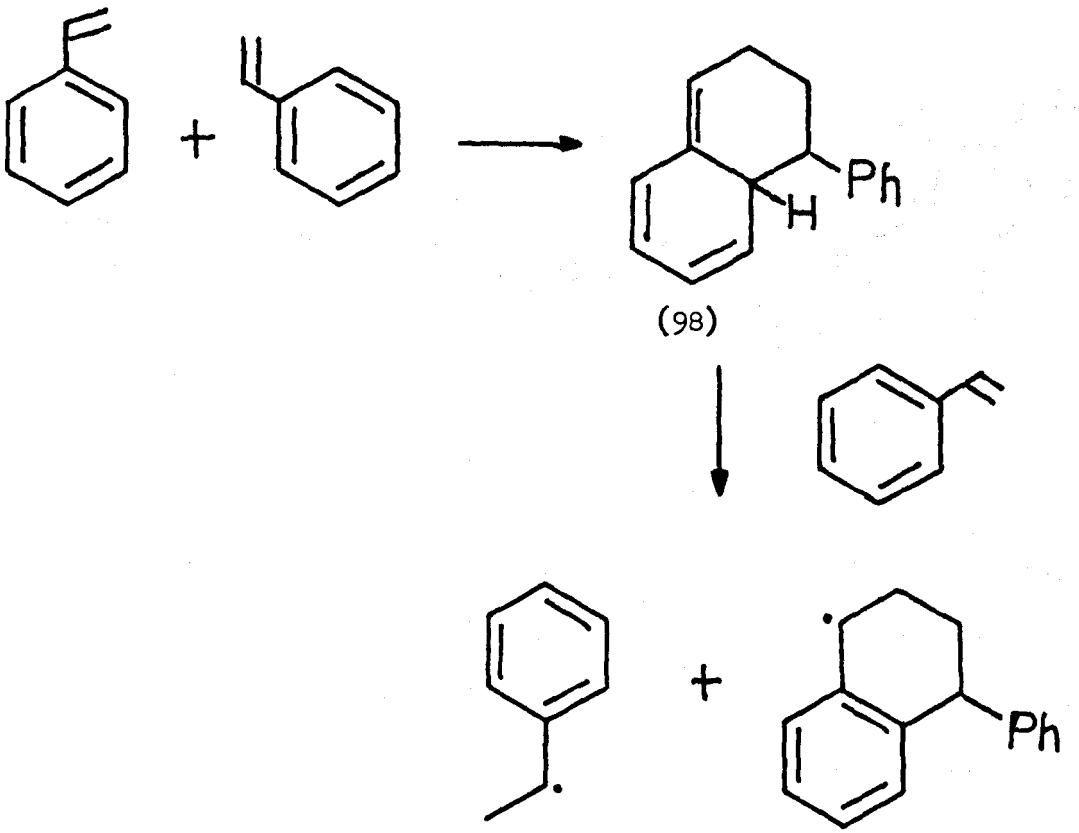
It has been shown[70] that o-chlorostyrene and p-chlorostyrene form adducts with ethyl azodicarboxylate in benzene solution, whereas 2,6-dichlorostyrene fails to react under the same conditions. These results favour the tetrahydrocinnoline structure (96), as the correct structure for the adduct.

This 1 : 2 adduct (96) between styrene and diethyl azodicarboxylate is formed via an ene reaction of the initially formed 1 : 1 cycloadduct (97).

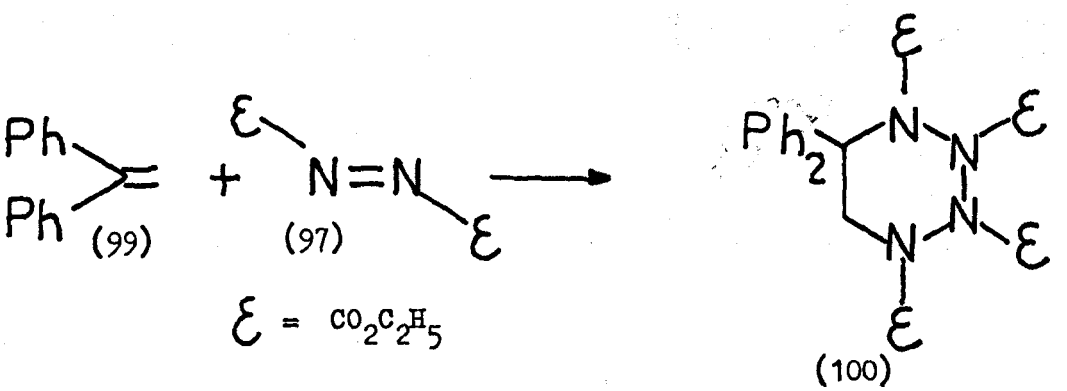


Qualitative kinetic studies now show[31] that the formation of the adduct (96) is strongly inhibited when a radical inhibitor (t-butyl resorcinol) is present in the reaction mixture. An aged mixture of styrene and t-butyl resorcinol fails to give the diadduct (96) with diethyl azodicarboxylate. A kinetic study of the formation of the adduct (96) shows the reaction to be first order in styrene and first order in azodicarboxylate. The disappearance rate of styrene is unaffected by the presence of t-butyl resorcinol in the reaction mixture. Thus the formation of the intermediate (97) is the rate determining step, and attempts to isolate the initial cycloadduct (97) have failed. Furthermore, the effect of the radical inhibitor indicates that the subsequent ene reaction takes place to a significant extent via a radical chain mechanism.

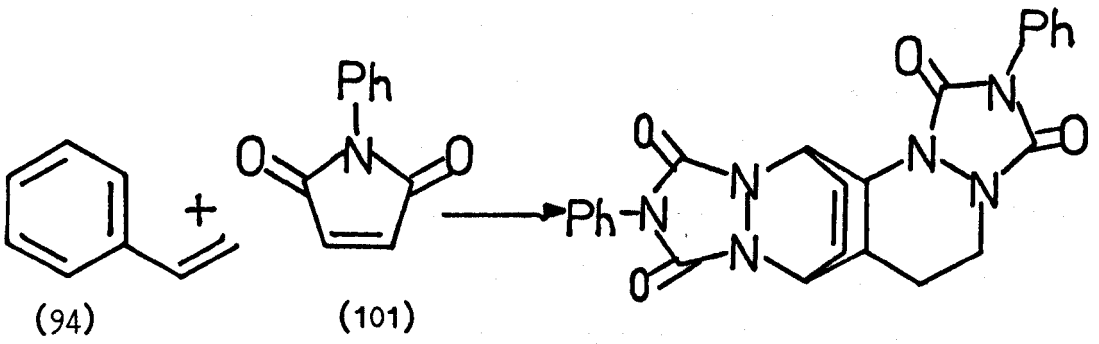
A related process[32] is the spontaneous free radical polymerisation of styrene, where radicals are generated by the reaction of styrene and the cycloadduct (98) of styrene.



Ingold and Weaver[29] also proposed the tetrazine structure (100) for the product from the reaction of 1,1-diphenyl ethane (99) and diethyl azodicarboxylate.

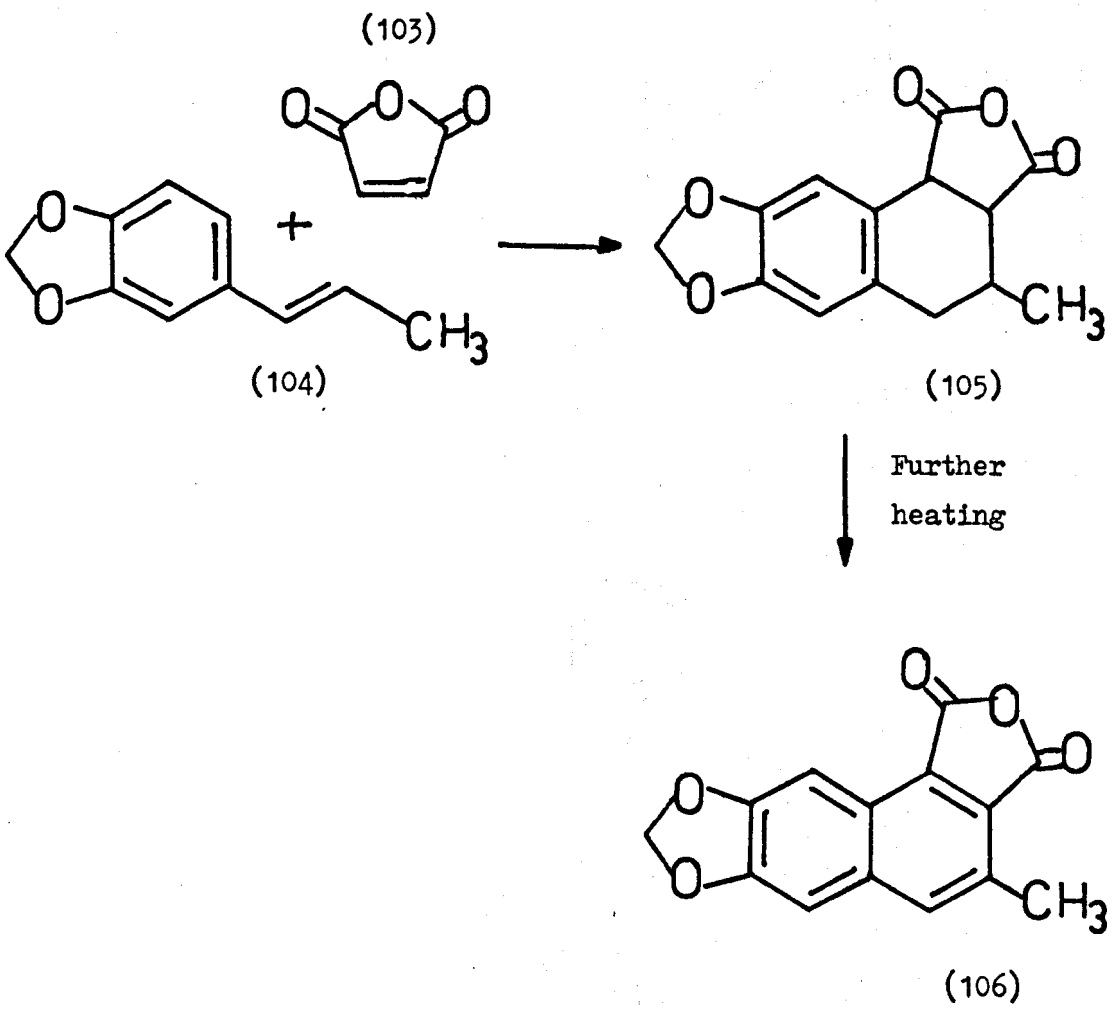


The very reactive 1,2,4-triazoline dione (101) undergoes[33] reaction with styrene at room temperature to give the pentacyclic diadduct (102), isolation of which shows an enhancement of diene character relative to allylic activity.

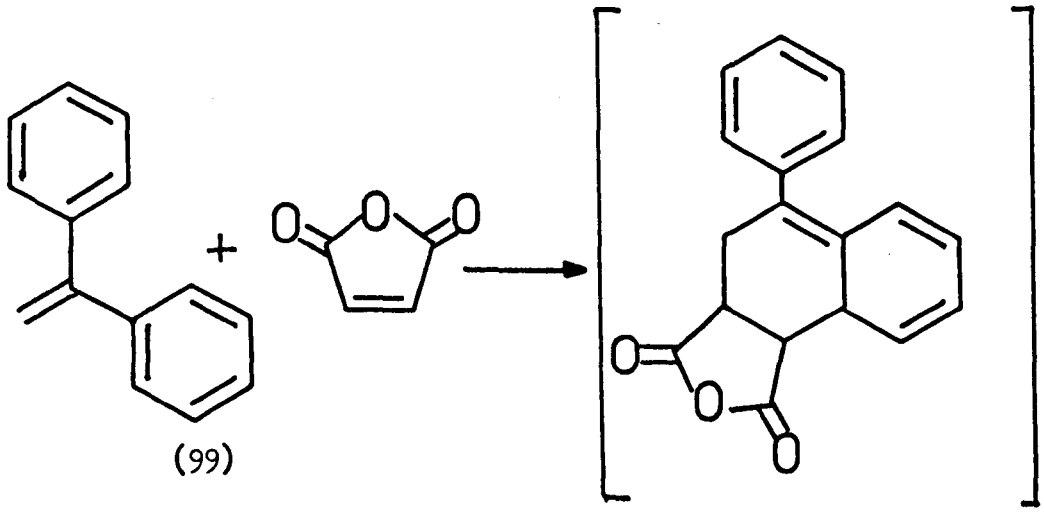


(94) (101) (102)

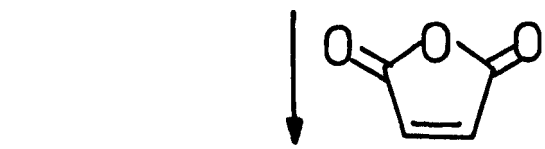
The addition of maleic anhydride (103) to isosafrole (104) gives [34,35] a cycloadduct which rearranges to give the stable aromatic isomer (105). Continued heating of the aromatic isomer (105) results in dehydrogenation to give the naphthalene derivative (106).

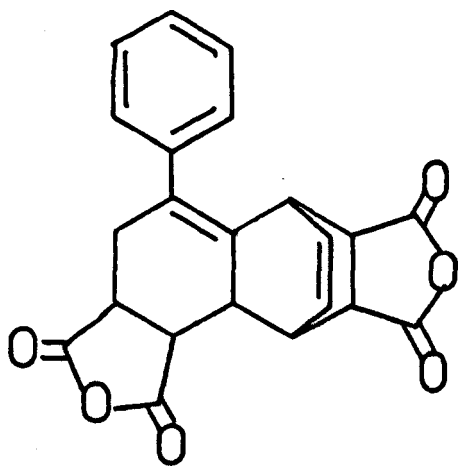


Investigation[34] of a series of styrenes shows that an alkoxy group in the p-position to the unsaturated side chain enhances the tendency to unite with maleic anhydride, an alkoxy group in the m-position has no such effect. Tetrahydronaphthalene derivatives are obtained as adducts only when the styrene is alkylated in the β-position. Maleic anhydride fails to give adducts with m-hydroxystyrene, m-methoxystyrene, m-methoxypropenylbenzene, styrene and stilbene. 1,1-Diphenyl ethane (99) adds two molecules of maleic anhydride to give a crystalline adduct. The following mechanism is proposed for this double addition.



(99)



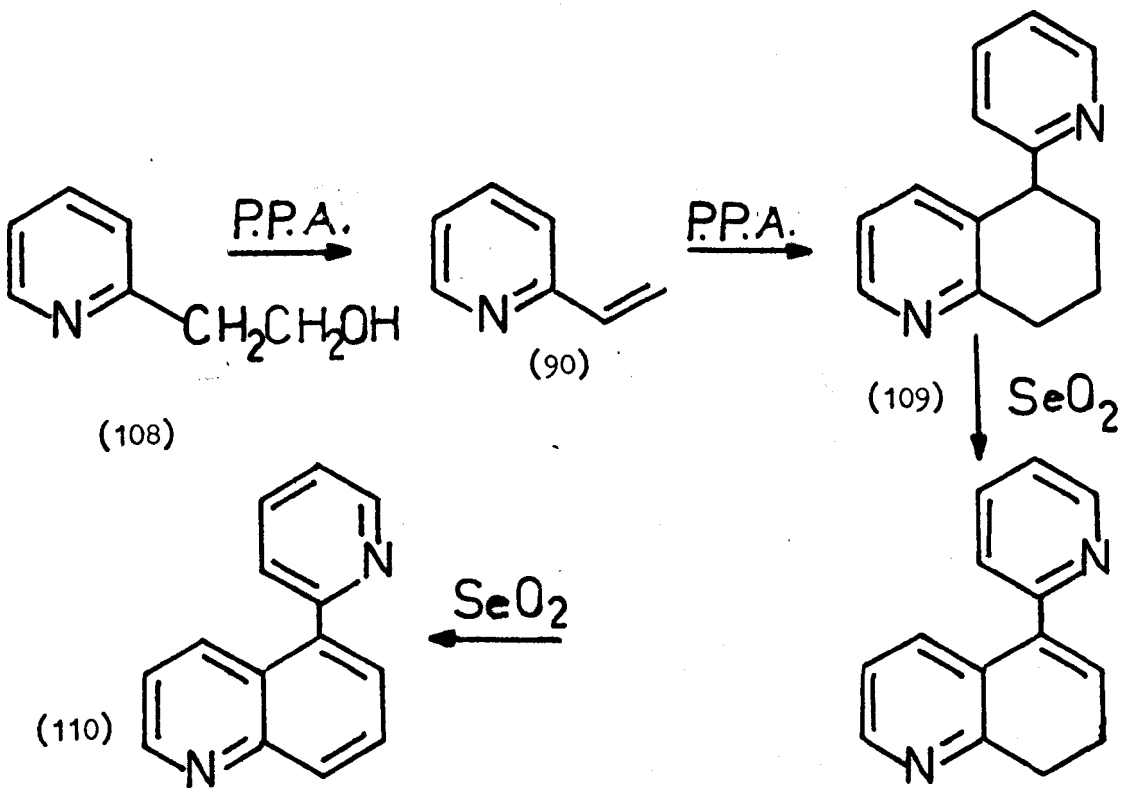


(107)

(ii) To isomers of vinyl pyridine and their derivatives.

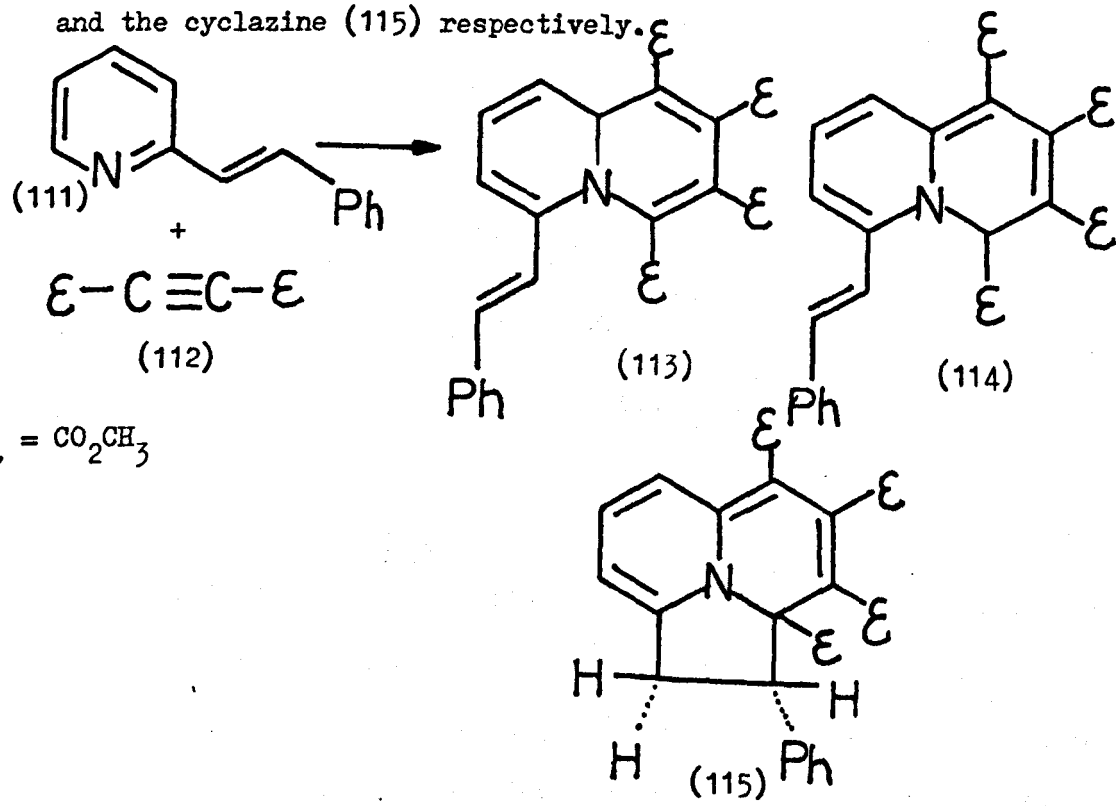
Knieps[36] has shown that by heating 2-(2-pyridyl)ethanol (108) in polyphosphoric acid as well as obtaining polyvinyl pyridine he also obtained a crystalline condensation product $C_{14}H_{14}N_2$ (109).

This condensation product is also obtained[37] by heating 2-vinyl pyridine (90) in polyphosphoric acid (85%) at 200°C. It is shown to be 5-(2-pyridyl)-5,6,7,8-tetrahydroquinoline (109) formed in 36 - 38% yield. The product is formed by combination of 2-molecules of vinyl pyridine either by a radical or molecular mechanism. When heated with selenium dioxide in H_2SO_4 (95%) the adduct is aromatised to the 5-(2-pyridyl)-quinoline (110).

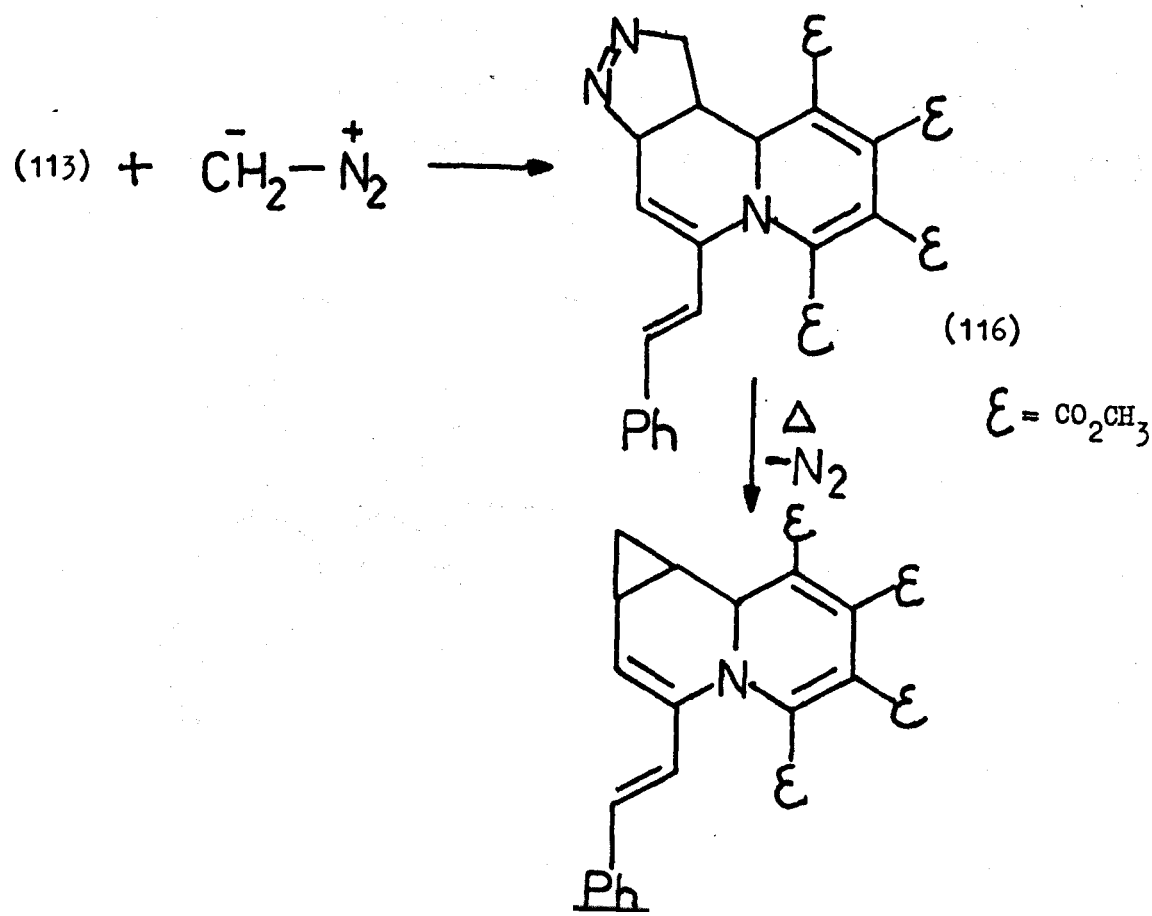


Reaction of 2-stilbazole (111) with dimethyl acetylene dicarboxylate (112) in ether is reported[38] to give a yellow labile adduct (113) which when heated forms a "1st labile adduct" (114) and a "2nd stable adduct" (115).

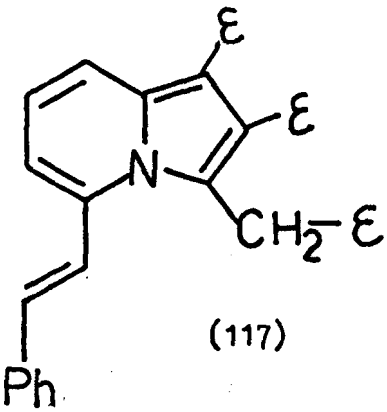
Acheson[39] has shown that the structure of these products are those of the 9aH-styrylquinolizine (113), 4H-quinolizine (114) and the cyclazine (115) respectively.



The olefinic nature of the 9aH-styryl (113) quinolizine was shown by its ready reaction with diazomethane, to give the pyrazoline (116), which on heating loses nitrogen as shown.



The preparation of the 4H-quinolizine (114) from the 9aH-isomer (113) was best effected by heating in phenol; indolizine (117) was also formed in small quantities but became the major product when the reaction time was increased.



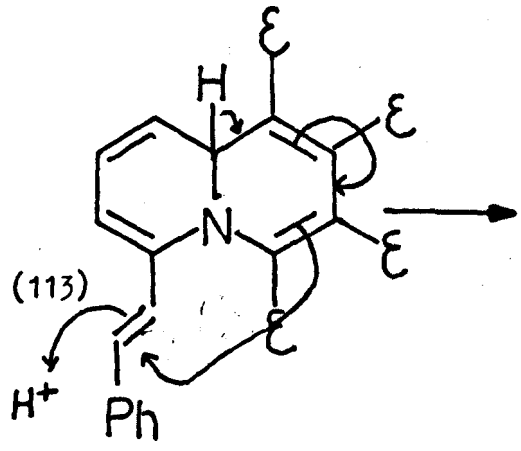
(117)

Ɛ = CO_2CH_3

The 9aH-styryl quinolizine (113) and the 4H-quinolizine (114) when heated under other conditions give the Diels and Meller "2nd stable adduct" (115). This compound (115) proved very resistant to oxidation by potassium permanganate under conditions which gave good yields of benzoic acid with both quinolizines (113) and (114). Catalytic reduction under vigorous conditions caused addition of 5-moles of hydrogen where as the quinolizines (113) and (114) add 6-moles. These results exclude the presence of a styryl group in the "2nd stable adduct" but are consistent with the cyclazine structure (115).

The formation of the cyclazine from the 9aH-quinolizine (113) may take place as shown

Ɛ = CO_2CH_3

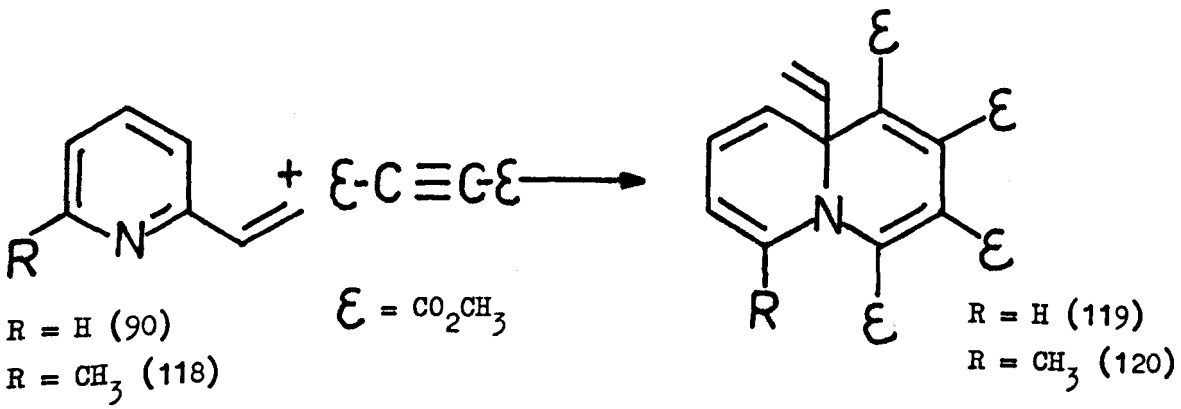


(115)

Competitive attack of a proton at position 4 and loss of the 9aH proton gives the 4H-quinolizine (114), this compound was unlikely to be an intermediate in cyclazine formation since it gives the indolizine (117) in refluxing acetic acid.

With dimethyl acetylene dicarboxylate 5-methyl stilbazole gives analogous products.

Refluxing 2-vinyl pyridine (90) or its 6-methyl derivative (118) with dimethyl acetylene dicarboxylate gives[40] the corresponding 9a-vinyl-9aH-quinolizine (119) and (120).

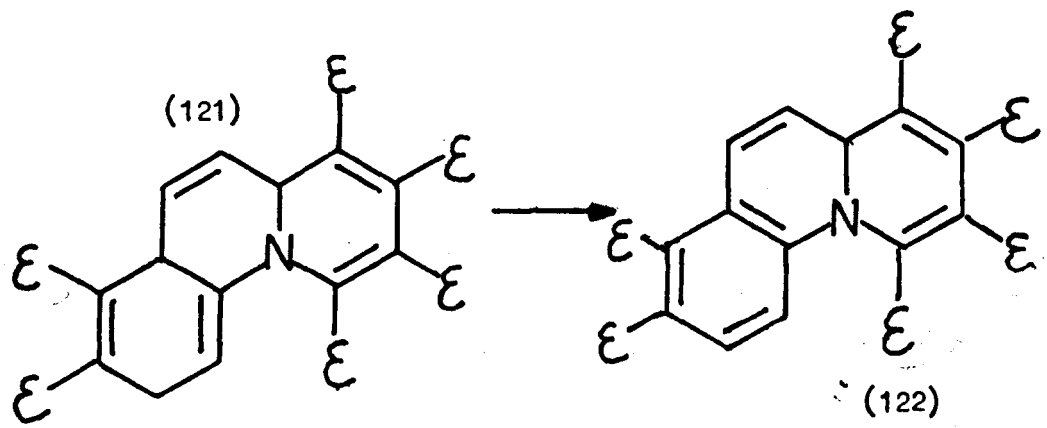


R = H (90)
R = CH_3 (118)

ℰ = CO_2CH_3

R = H (119)
R = CH_3 (120)

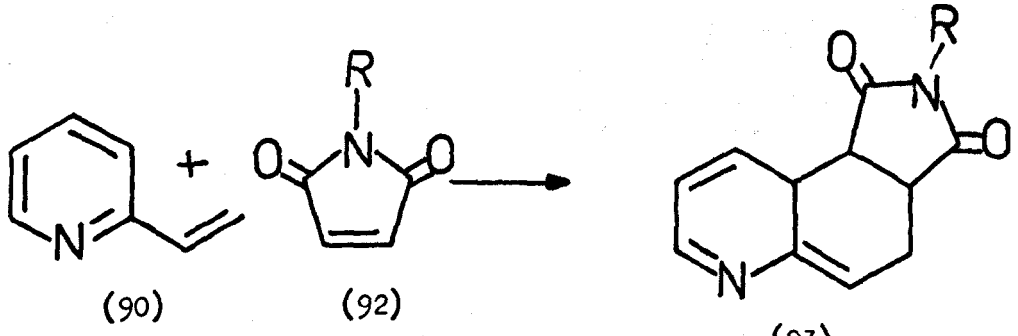
A yellow compound obtained once from the 2-vinyl pyridine reaction rapidly changes into an orange compound which was obtained on every subsequent occasion. The proposed structure for this orange compound was that of the 1H-benzo[c]quinolizine (122).



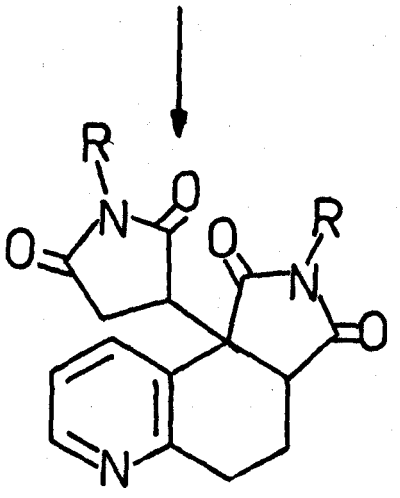
ℰ = CO_2CH_3

The orange compound may be formed by two molecules of the acetylenic ester combining with one of the 2-vinyl pyridine in the opposite orientation to that leading to 9a-vinyl quinolizine (119 - 120) followed by a Diels-Alder reaction of another molecule of the ester building on a third ring of structure (121). This may easily aromatise and isomerise to the benzo[c]quinolizine (122). The mass spectrum supports this structure since the base peak corresponds to the loss of the ester group at position 1 to form the very stable quinolizinium cation.

Heating 2-vinyl pyridine (90) and N-alkyl maleinimides (92) in boiling butanol containing 1 - 5% polymerisation inhibitor gave small yields of 1 : 2 adducts[41] (122). The ^{13}C n.m.r. spectrum shows the presence of a quaternary non aromatic carbon atom, while no signal attributable to an isolated proton is seen in the ^{1}H n.m.r. The structure proposed for this 1 : 2 adduct was that of a tetrahydroquinoline.



(90) (92) (93)

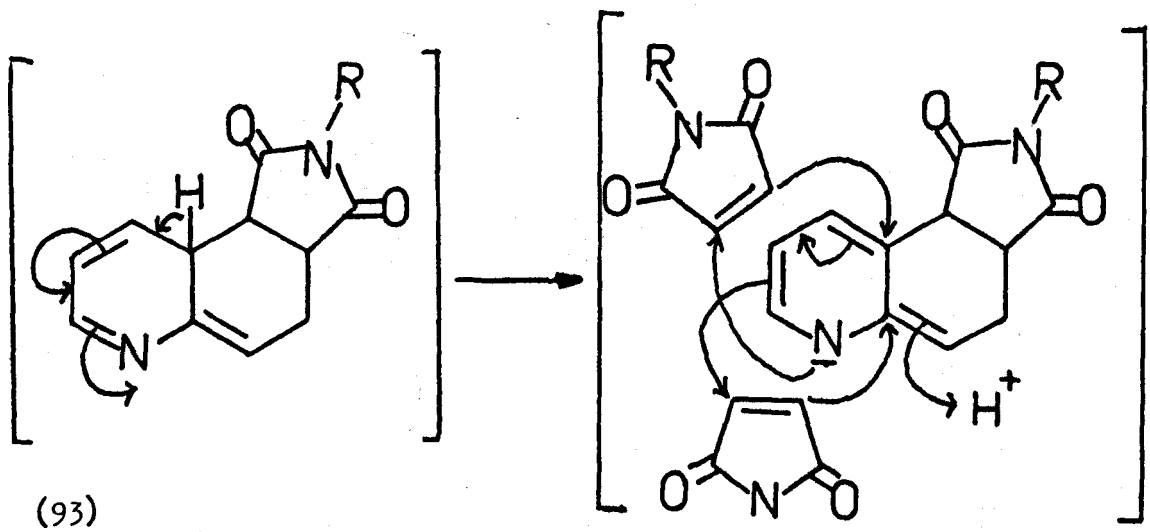


(122)

R = CH_3, C_2H_5, n-bu, cyclohexyl

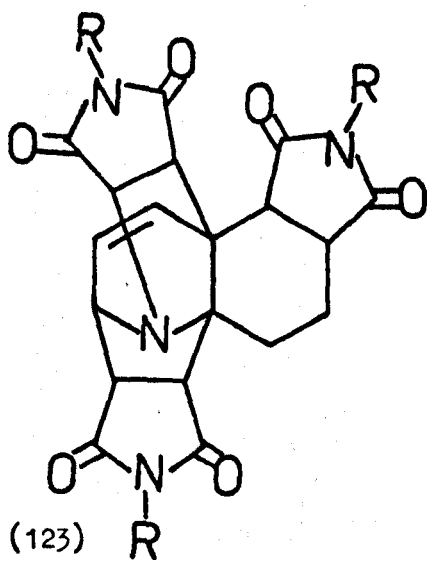
The addition mechanism parallels that of N-butyl maleinimides to styrene in the presence of picric acid, namely combination of a diene synthesis with participation of an aromatic double bond and subsequent indirect substitution.

As well as the 1 : 2 adduct, 1 : 3 adducts (123) were formed and on the basis of ^{1}H and ^{13}C n.m.r. the structure (123) was proposed for the 1 : 3 adducts.



(93)

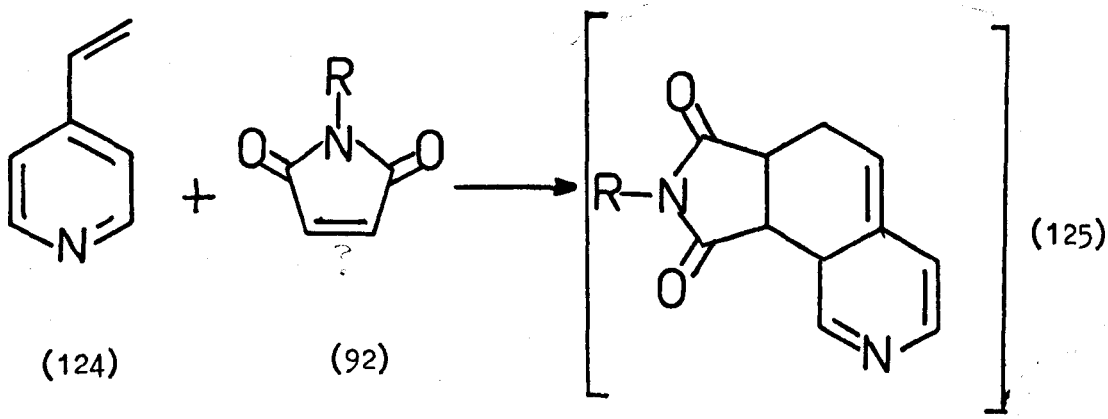
R = CH_3, C_2H_5, n-bu, cyclohexyl



(123)

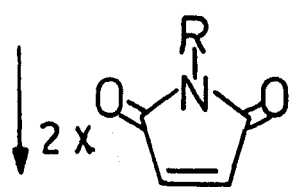
The proposed mechanism for the formation of the 1 : 3 adduct is from the initial cycloadduct followed by "criss cross" addition of two molecules of N-alkyl maleinimide.

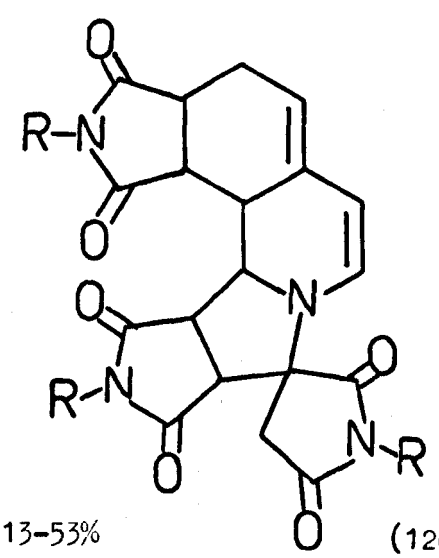
4-Vinyl pyridine (124) adds on 3 molecules of N-alkyl or phenyl maleinimide on heating in boiling acetonitrile or dichloromethane in the presence of 1 - 5% of hydroquinone to give the dihydro pyridine derivative (126).[41]



(124) (92) (125)

R = CH_3, n-Pr, n-bu, cyclohexyl, Ph





13-53% (126)

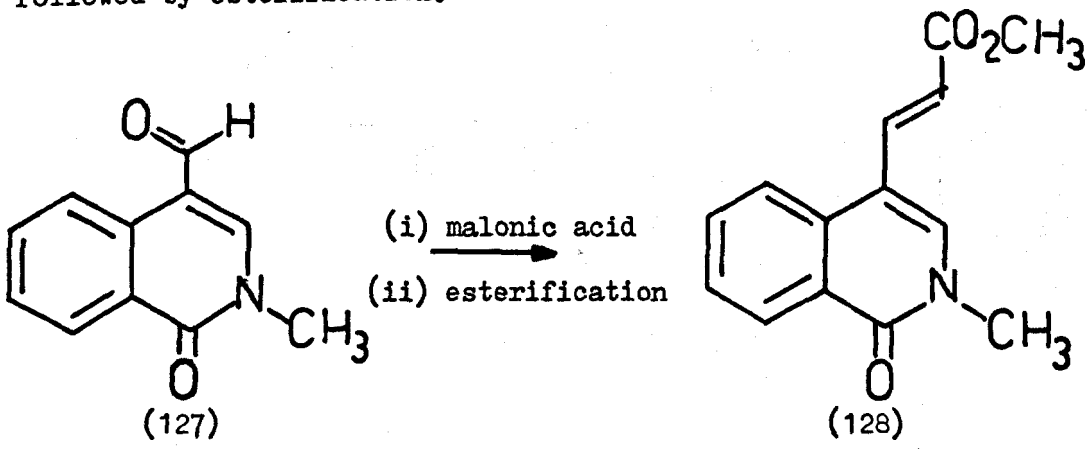
The formation of the 1:3-adduct (126) is via the initially formed cycloadduct (125) which is not isolated. Conjugation of a butadiene moiety with a $\rangle C = N$ causes a dipolar spiro bis addition as the authors describe for addition of maleinimides to Schiff bases.[42]

Reaction[41] of 2-methyl-5-vinyl pyridine with N-alkyl maleinimides in boiling acetonitrile gave a gummy mess, from which a crystalline substance may be isolated in 2 - 5% yield, spectroscopic properties indicate that the compound is a 1 : 2 adduct but no structure was postulated.

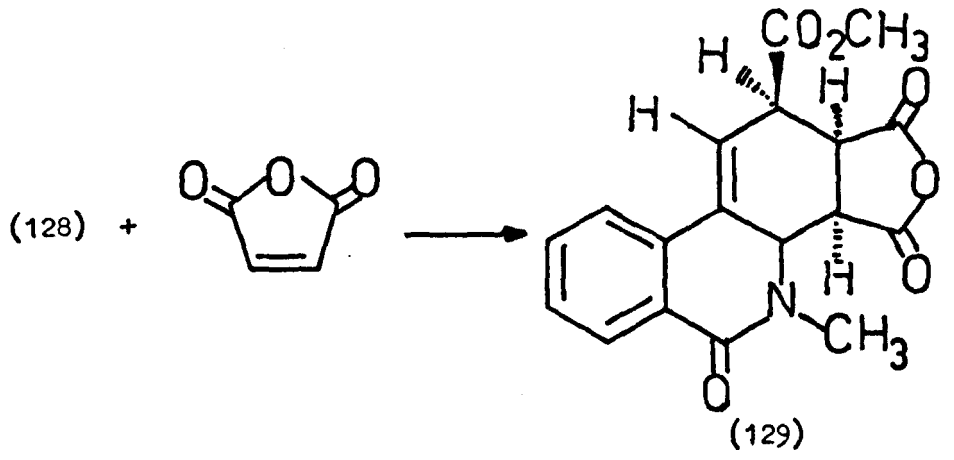
(iii) To vinyl isoquinoline derivatives.

There are no reports in the literature of vinyl quinoline undergoing cycloaddition reactions. However S.F. Dyke et al.[43] describe the reaction of the dihydro vinyl isoquinoline derivative (128) with a variety of dienophiles.

The 1,2-dihydro-4-vinylisoquinoline (128) is best prepared by condensation of the dihydroisoquinoline (127) with malonic acid followed by esterification.

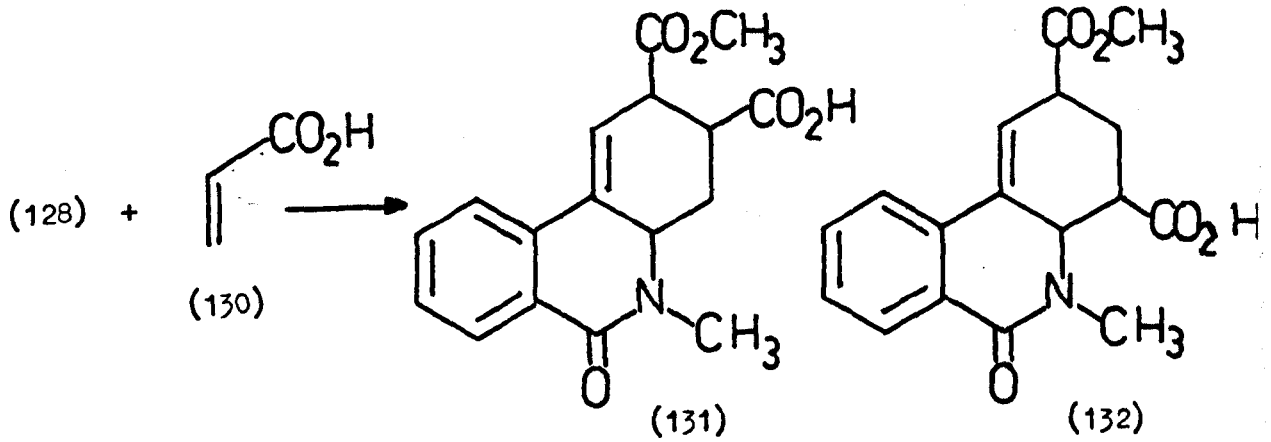


On heating equimolar amounts of the vinyl compound (128) and maleic anhydride in acetonitrile for six hours, a solid was obtained in 89% yield. Spectroscopic evidence indicates that the solid is a cycloadduct (129) having the structure shown.



(129)

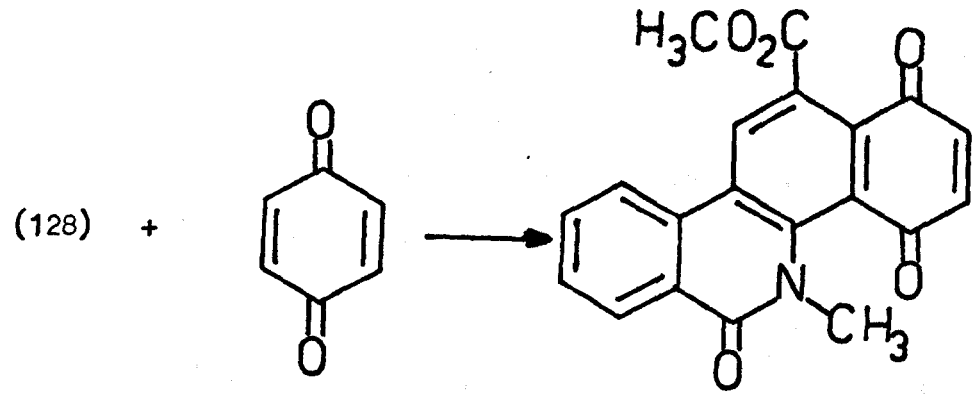
The dihydrovinyl isoquinoline (128) with acrylic acid (130) under the same conditions gave an adduct (131) isolated in 85% yield. Of the two possible isomers the isomer (131) was preferred from a study of the mass spectral fragmentation pattern. A peak at 203 a.m.u. in the mass spectra was assigned to anhydride formation, a transformation which is less likely if the other isomer (132) had been formed.



(131) (132)

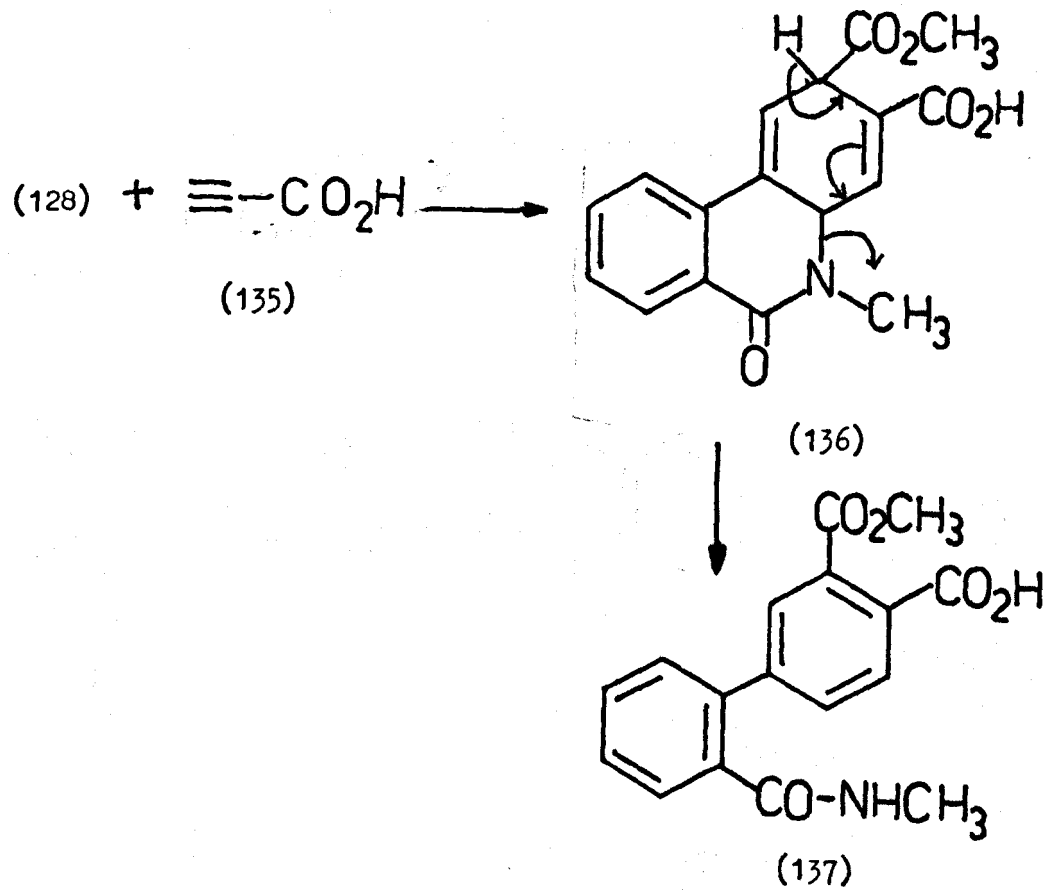
Similar adducts were obtained with ethyl acrylate, acrolein and crotonic acid but acrylonitrile failed to react.

Heating the isocarbostyril (128) with 1,4-benzoquinone (133) in boiling acetic acid gave a dehydrogenated product (134) in 60% yield. Similar dehydrogenation of initially formed cycloadducts has

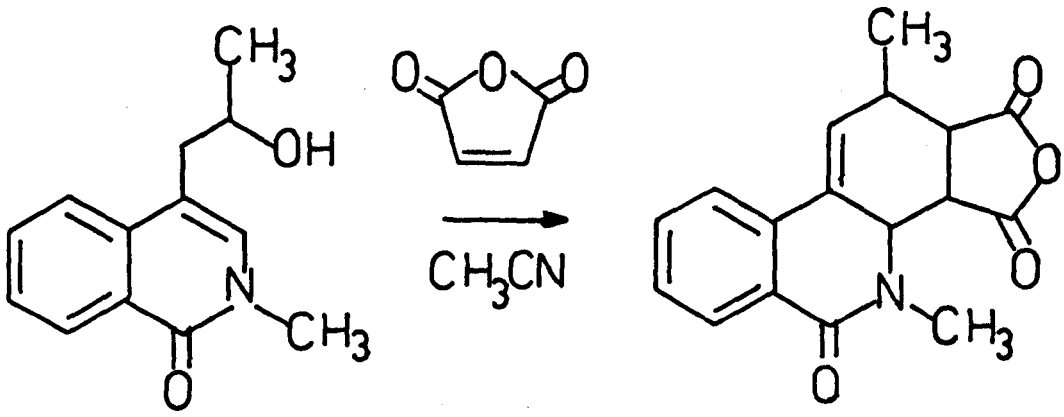


been observed[48] before in diene reactions involving 1,4-benzoquinone. The formation of the adduct (134) represents a synthesis of the benzo [c] phenanthridine ring system.

No reaction occurred between the vinyl isoquinoline (128) and propiolic acid (135) in boiling acetonitrile or acetic acid but in boiling xylene a product $C_{17}H_{15}NO_5$ (137) was formed in 30% yield. The ^1H n.m.r. spectrum indicated that the product was the biphenyl derivative (137) formed by aromatisation of the initially formed cycloadduct (136).



Attempts to dehydrate the secondary alcohol (138) to the vinyl isoquinoline (128) failed, but when the alcohol (138) was heated with maleic anhydride in acetonitrile a 55% yield of the adduct (139) was obtained.

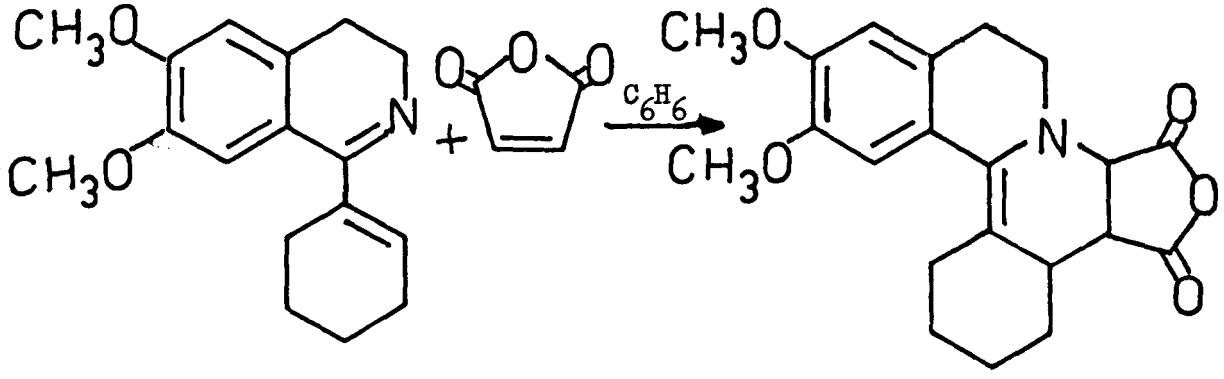


(138) 55% (139)

A similar dehydrogenated adduct was obtained with 1,4-benzoquinone (67%).

This technique has been used before in Diels-Alder reactions.[44]

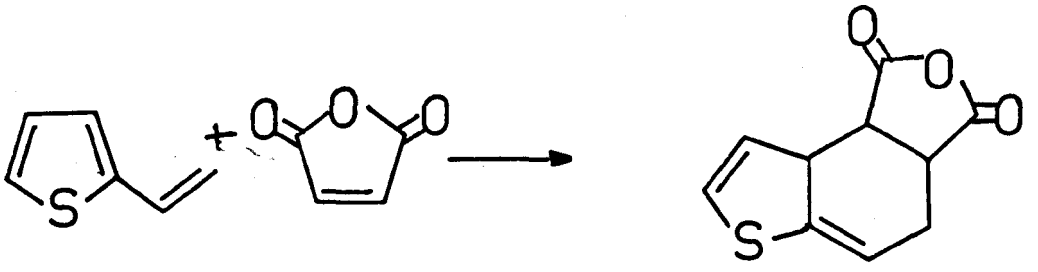
Cycloaddition of 1-(1^1-cyclohexenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (140) with maleic anhydride gave the 6H-dibenzo [a,h]quinolizine (141).[45]



(140) (141)

(iv) To vinyl thiophen, vinyl benzthiophen and their derivatives.

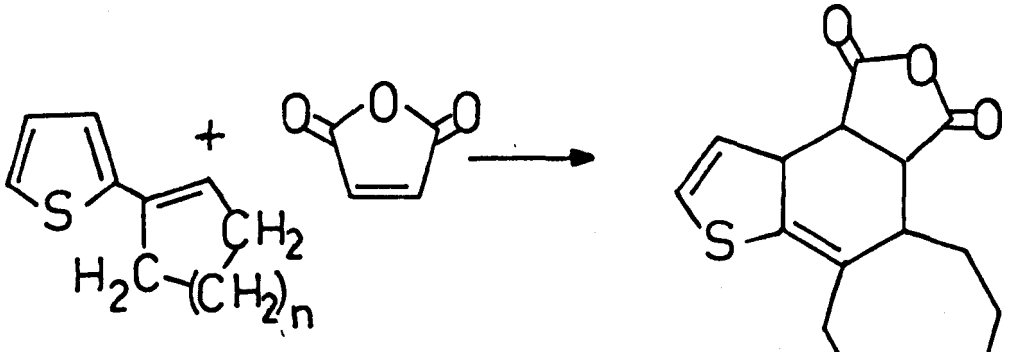
2-Vinyl thiophen (142) undergoes[46] cycloaddition with maleic anhydride (103) when warmed on a steam bath for four hours to give the tetrahydrobenzo[b]thiophen derivative (143) in 35% yield.



(142) (143)

When the reaction mixture was allowed to stand for long periods after heating (overnight), the yield of the adduct (143) decreases and that of the copolymer increases. The yield of the adduct (143) was much lower when the reaction was allowed to proceed at room temperature. Reaction of 2-vinyl thiophen (142) with 1,2,4-triazoline dione gave the analogous adduct (see later p. 153).

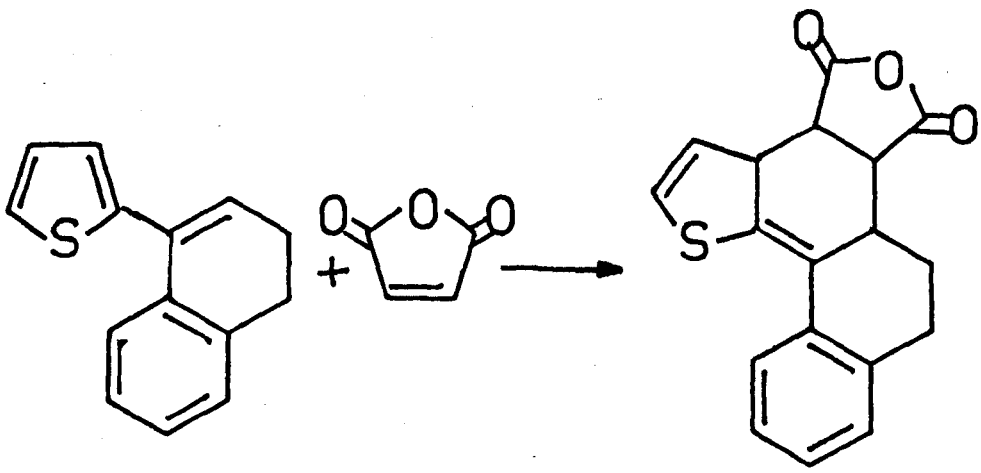
Addition of maleic anhydride to 1-(2[1]-thienyl)cyclohex-1-ene (144) and 1-(2[1]-thienyl)-cyclohept-1-ene (145) gave bis adducts,[47] structures for which were not given, but reaction with 1-(2-thienyl) cyclooct-1-ene (146) gave the mono adduct (147).



n = 2 (144)
n = 3 (145)
n = 4 (146)

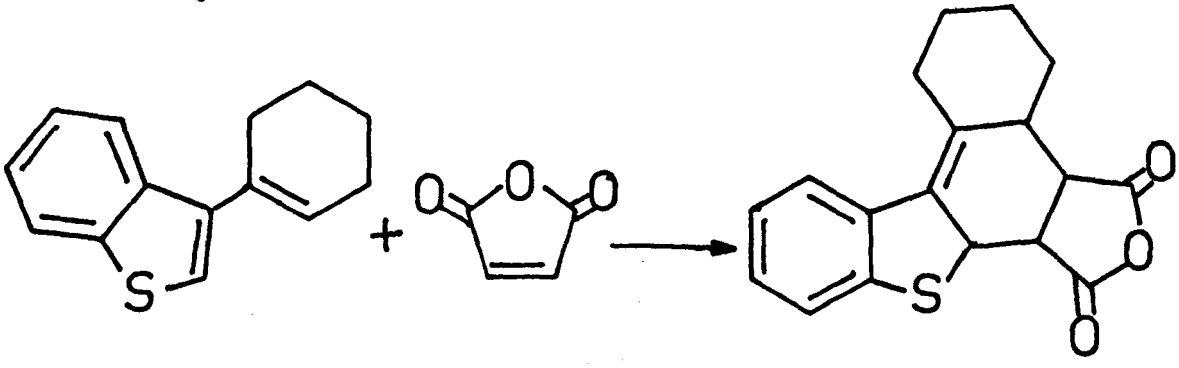
(147)

1-(2-Thienyl)-3,4-dihydronaphthalene (148) also gives[47] a mono adduct (149) on reaction with maleic anhydride, which may be dehydrogenated by sulphur to give the aromatic anhydride.



(148) (149)

A mono-adduct (151) was obtained from 1-(3-thianapthyl)-cyclohex-1-ene) (150) on reaction with maleic anhydride.[47]



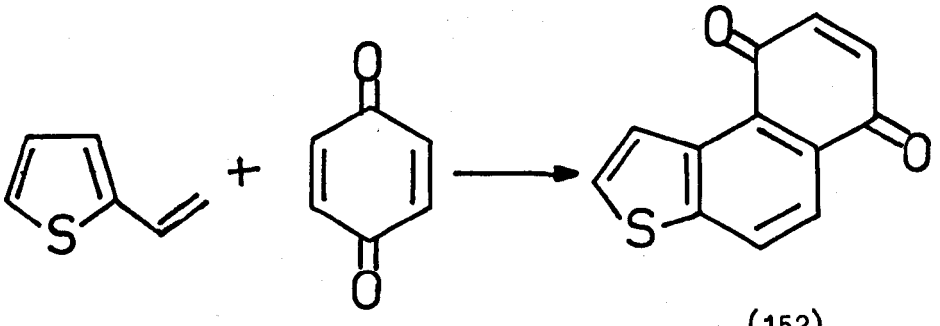
(150)

(151)

A similar mono-adduct was obtained from 1-(3-thianapthyl)-3,4-dihydronaphthalene.[47]

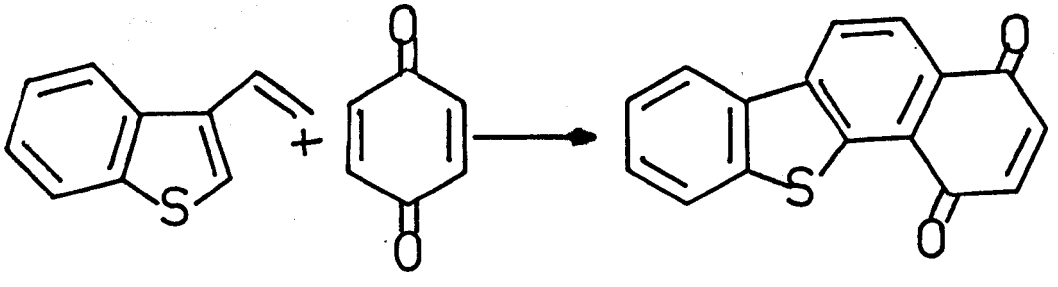
W. Davies and Q.N. Porter have shown[48] that 2-vinyl thiophen (142) reacts slowly with 1,4-benzoquinone (133) to give a 43% yield of 4,5-benzothionaphthen-1^1,4^1-quinone (152), it did not prove possible to isolate an adduct which had not undergone

dehydrogenation by excess 1,4-benzoquinone.



(142) (133) (152)

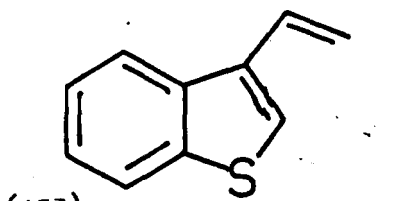
Similarly 3-vinylthionaphthen (153) and benzoquinone gave[49] an 80% yield of the analogous adduct (154). The time required to produce



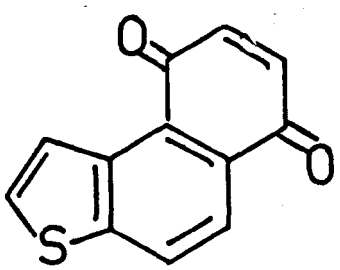
(153) (133) (154)

the adducts (152) and (154) in satisfactory yield shows that 2-vinyl thiophen (143) and 3-vinyl thionaphthen were more reactive than their isosteres styrene and 1-vinyl naphthalene. This was probably due to the lower aromaticity of the heterocyclic compounds and the consequent greater double bond character of their 2,3 double bonds which causes the compounds to approximate more to true dienes. The known greater activity of vinyl naphthalenes than of styrene was paralleled by the superiority of 3-vinyl thionaphthen (153) over 2-vinyl thiophen (142). 2-Vinyl thiophen and 1,4-benzoquinone (133) gave a 43% yield of the adduct (152) in eight hours, but an 80% yield of a similar adduct (154) from 3-vinyl thionaphthen.

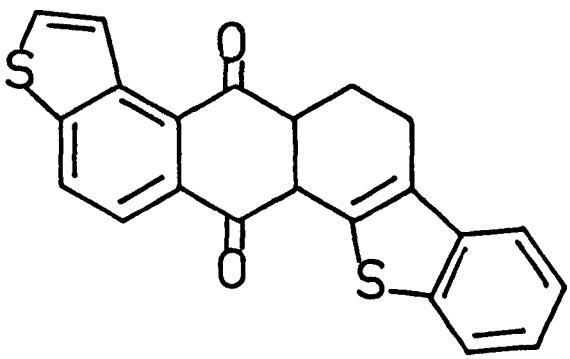
During the preparation of the quinone (152) no bis-adduct from it and another molecule of 2-vinyl thiophen were formed whereas a 61% yield of the adduct (155) or (156) was produced in ten minutes under the same conditions from the quinone adduct (152) and 3-vinyl thionaphthen.



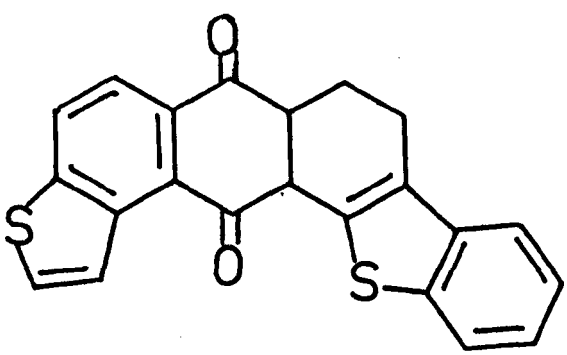
(153)



(152)

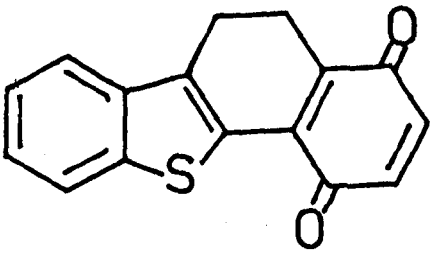


(155)



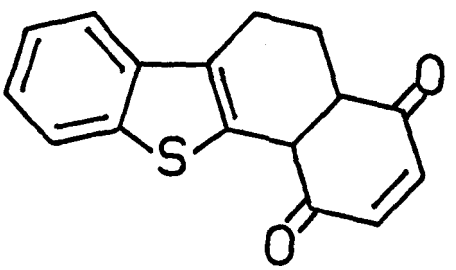
(156)

It was possible[50] to isolate a dihydroderivative (157) by reaction of a weaker solution of 3-vinyl thionaphthen (153) and benzoquinone (133) for three hours.

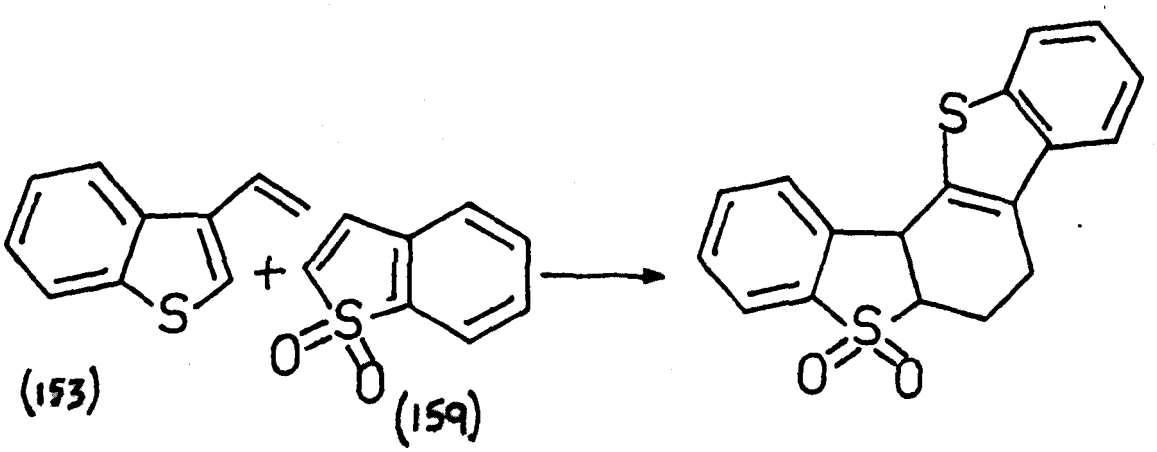
(153) + (133) —Weaker solution 3 hours→ 

(157)

Using a further excess of the vinyl compound (153) and a very short reaction time it was possible to isolate the tetrahydro derivative (158).[50]

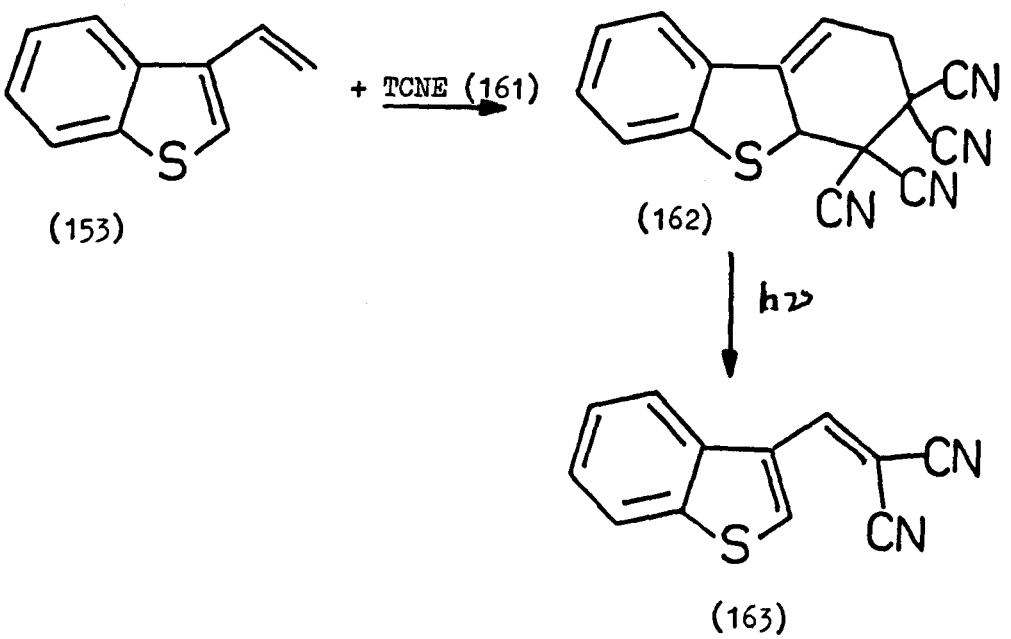


Addition[50] of 3-vinyl thionaphthen (153) to benzo[b]thiophen-5,5-dioxide (159) yields the adduct (160).



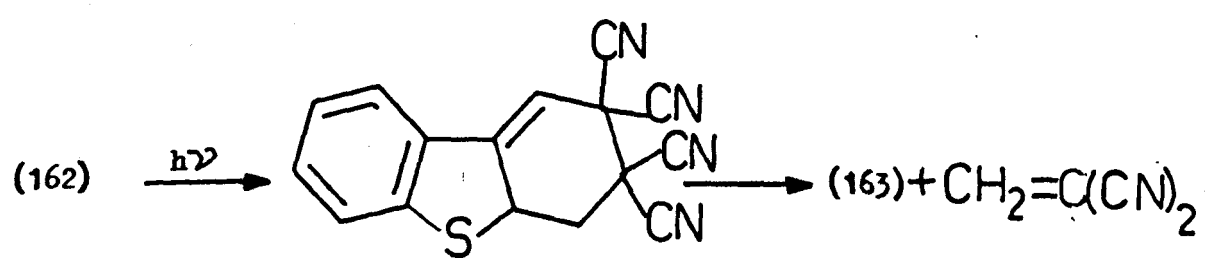
(160)

The adduct (162) from 3-vinyl thionaphthen (153) and tetracyano ethylene (164) when irradiated gave[51] a complex mixture from which one major component may be isolated and characterised. This major component has been assigned structure (163), dicyano-vinyl benzo[b]thiophen, on the basis of n.m.r. and mass spectroscopy, and its synthesis from 3-formyl benzo[b]thiophen and malononitrile.



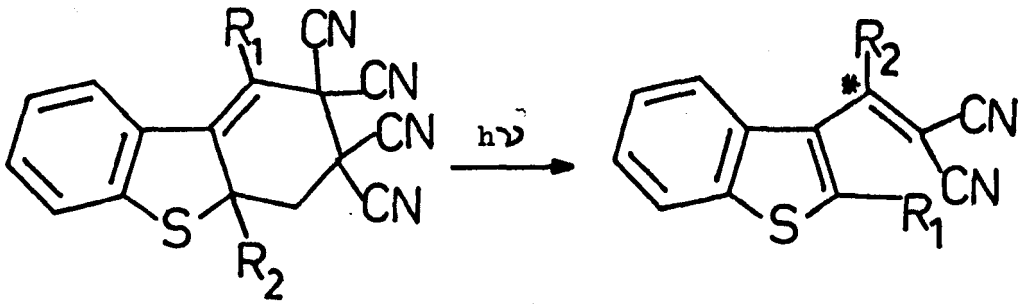
(153) (162) (163)

This rearrangement was best explained as resulting from photochemical conversion of the adduct (162) into its isomer (164) followed by rapid retro Diels-Alder decomposition to (163).



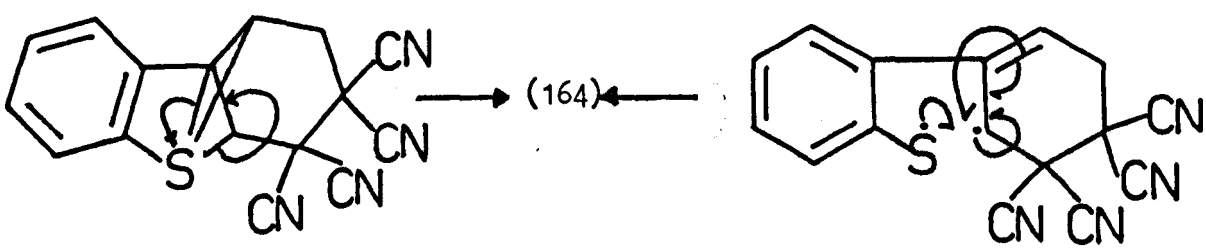
(164)

It was not possible to isolate compound (164). Irradiation of the two cycloadducts (165) and (166) shows that C(4a) in the adduct becomes the α-carbon atom of the β,β-dicyano vinyl group.



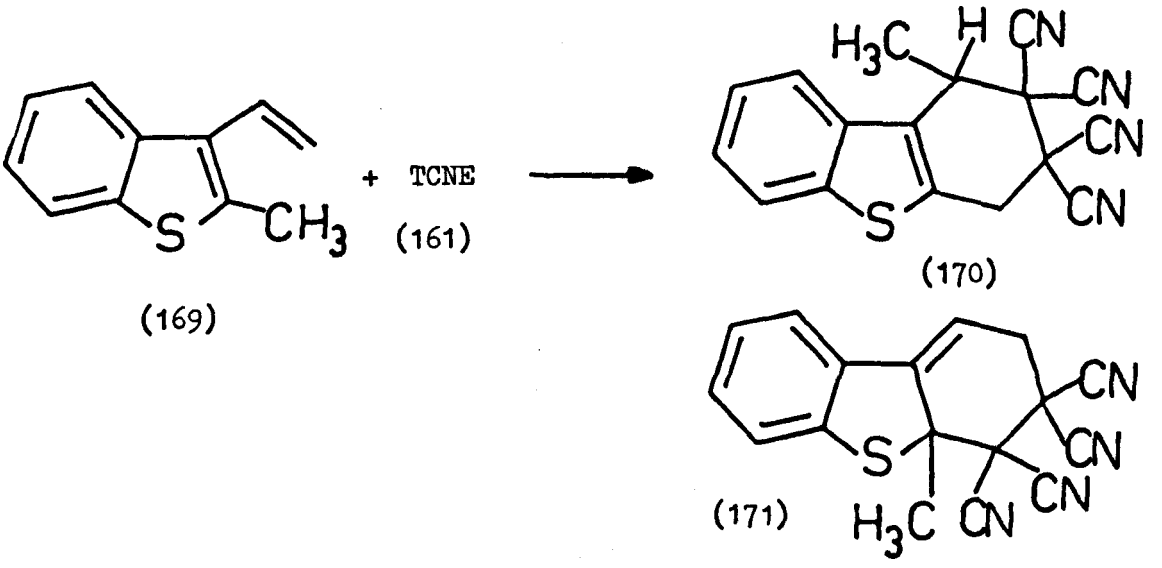
R_1 = H, R_2 = D (165)
R_1 = H, R_2 = CH_3 (166)

The formation of the proposed intermediate (164) may occur via the diradical (167) or the expanded valence shell intermediate (168).

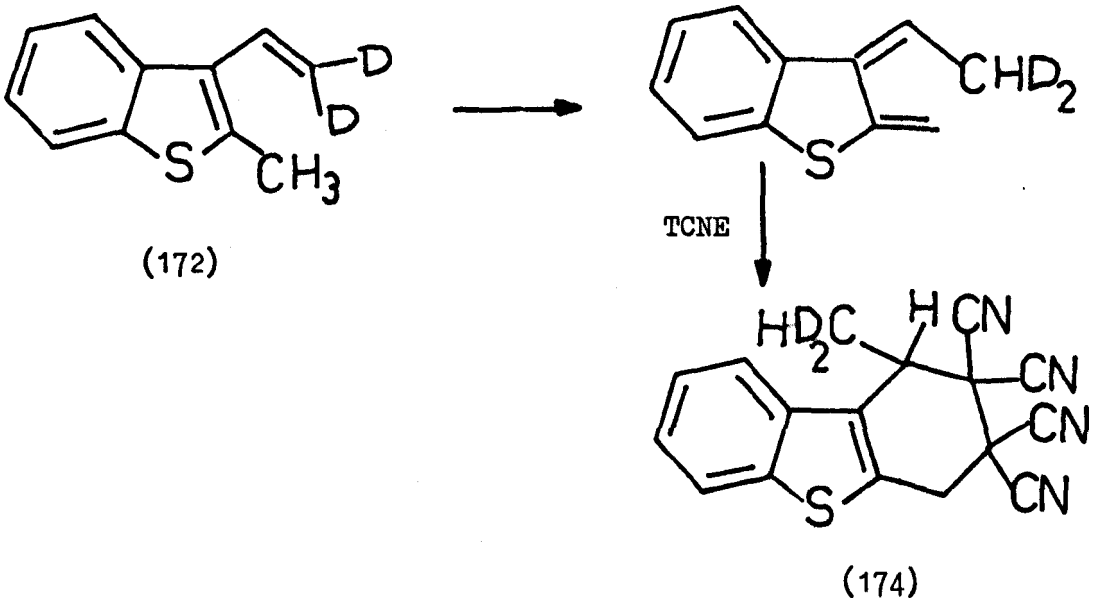


(168) (167)

2-Methyl-3-vinyl benzo[b]thiophen (169) gave[52] an adduct of structure (170) rather than (171) with T.C.N.E. (161).



The course of the rearrangement leading to the adduct (170) was clarified by the structure of the adduct (174) from the dideutero-diene (172) and T.C.N.E.

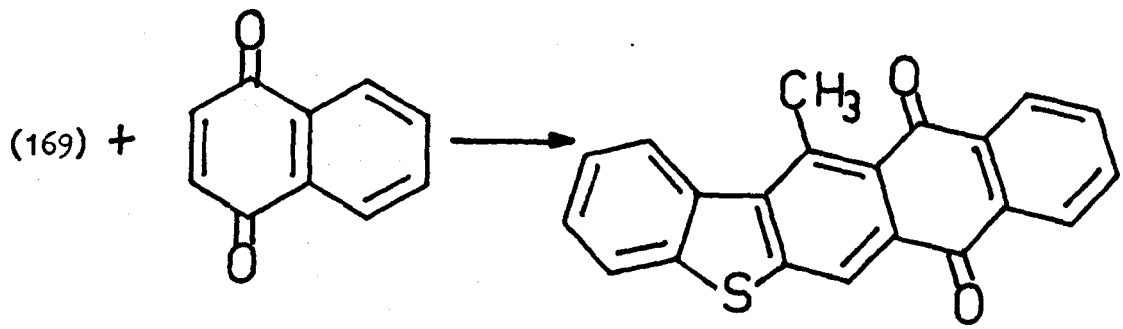


The presence of the dideuteromethyl group in (174) clearly shows that the methyl group in (170) was not the original 2-methyl group of (169) but was formed by hydrogen transfer from presumably that methyl group to the methylene group of the 3-vinyl substituent, to give a reactive dimethylene intermediate (173) which then reacts with T.C.N.E. The detailed mechanism of the hydrogen transfer step remains uncertain. When the dideutero vinyl compound (172) was

heated in the absence of T.C.N.E. no scrambling or deuterium exchange occurred, which counted against the possibility of thermal suprafacial sigmatropic hydrogen shift. Hydrogen scrambling was not catalysed by trace amounts of T.C.N.E. or by non-dienophilic charge-transfer reagents such as 1,3,5-trinitrobenzene.

For steric reasons the 2-methyl vinyl compound (169) was a relatively unreactive diene and it gave no adduct with maleic anhydride or with 1,4-naphthaquinone under non-forcing conditions.

Using an excess of 1,4-naphthaquinone (175) and extended heating, a fully aromatic quinone (176) was formed by the same mechanism as the T.C.N.E. adduct (170).

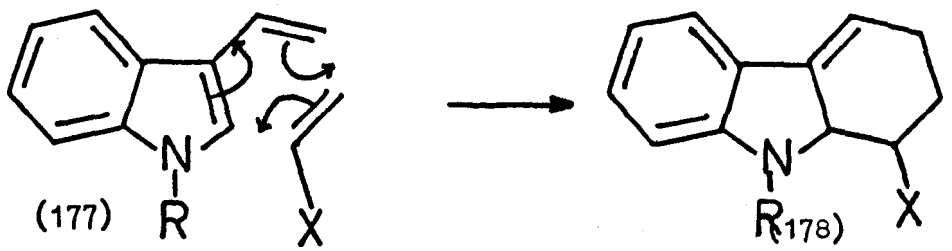


(176)

The structure of the aromatic quinone (176) was confirmed by comparison with other known samples.

(v) <u>To vinyl indoles and their derivatives</u>.

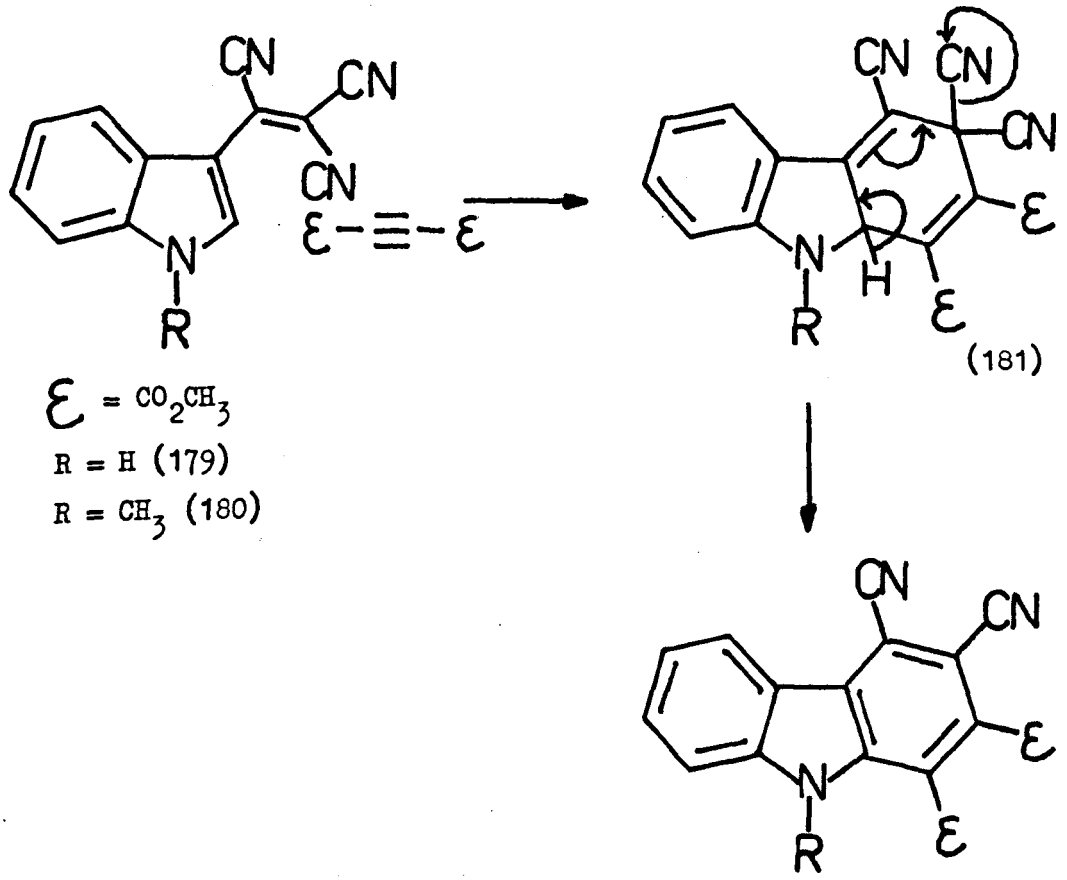
Active dienophiles undergo cycloaddition with 3-vinyl indole (177) yielding carbazole derivatives (178).[53]



(177) (178)

e.g. dienophile = 1,4-benzoquinone

Heating 3-tricyanovinyl indole (179) or the 1-methyl derivative (180) at 220 - 250°C with dimethyl acetylenedicarboxylate resulted in the loss of HCN and gave in 30% and 44% yield respectively the corresponding dimethyl 3,4-dicyanocarbazoledicarboxylates (182) and (183). The reaction was presumed to proceed through an intermediate dihydrocarbazole (181), which subsequently aromatised through the loss of HCN.



(181)

$\mathcal{E}$ = CO_2CH_3

R = H (179)

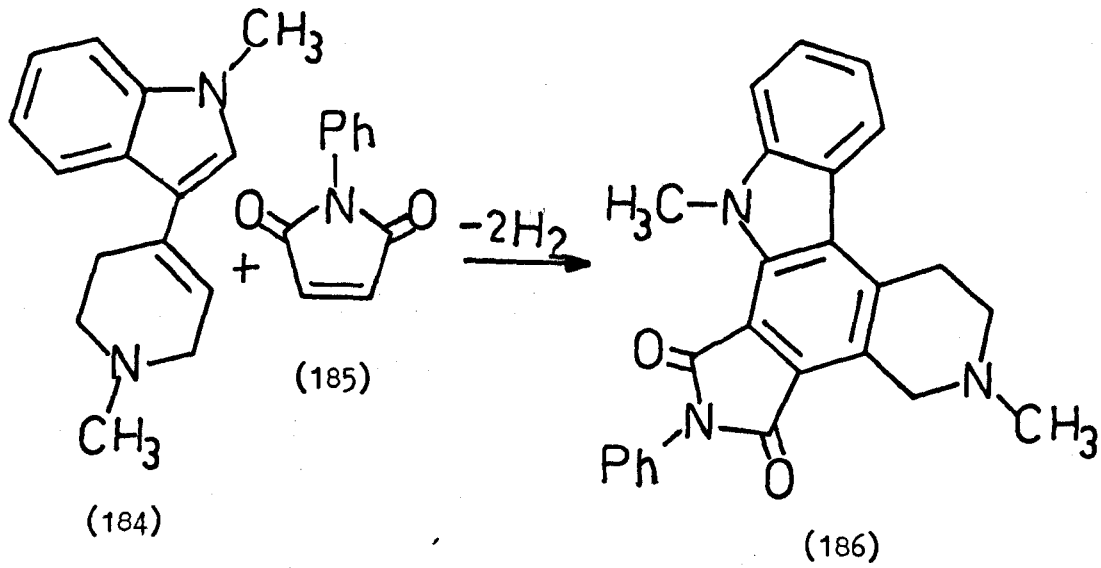
R = CH_3 (180)

R = H (182)

R = CH_3 (183)

The tetrahydropyridyl indole (184) did not react at room temperature with acrylonitrile, dimethyl acetylenedicarboxylate, or 1,4-naphthaquinone.[54] The reaction took place at higher temperatures but formed a complicated mixture from which no isolable products were obtained.

Only in the reaction of the 1-methyl-[tetrahydro-3-pyridyl] indole (184) with N-phenyl maleinimide (185) employing drastic conditions did it prove possible to obtain an adduct (186) (23%) which was thought to have the structure shown.

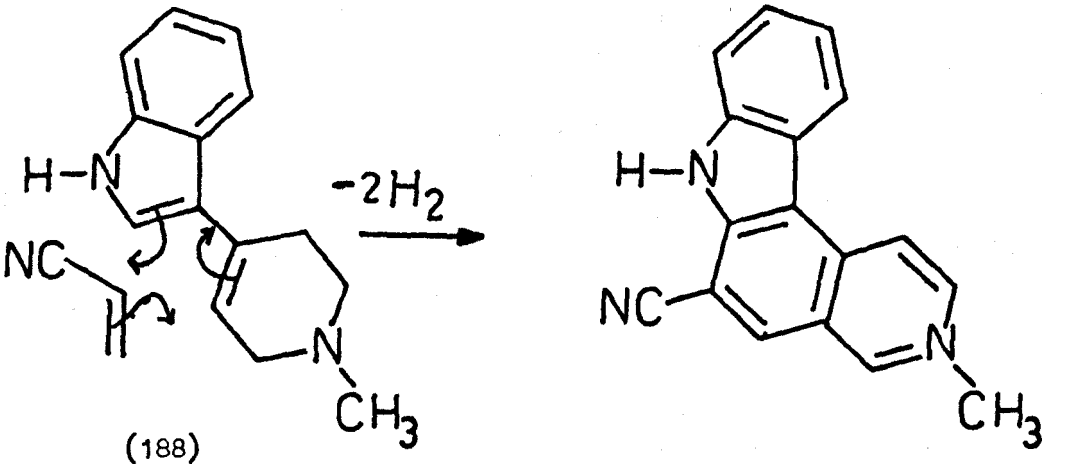


(184) (185) (186)

Similarly the 2-pyridyl isomer (187) proved unreactive. Only with N-phenyl maleinimide (185) did it prove possible to obtain an adduct analogous to (186), in 11.5% yield after chromatography using similar drastic conditions.

The unalkylated indole (188) on reaction with acrylonitrile, maleic anhydride, N-phenyl maleinimide or dimethyl acetylenedicarboxylate gave mixtures which were difficult to separate. The only product isolated was from reaction with acrylonitrile and it was thought to be the carbazole derivative (189). The position of the

cyanide group was suggested but not proved.



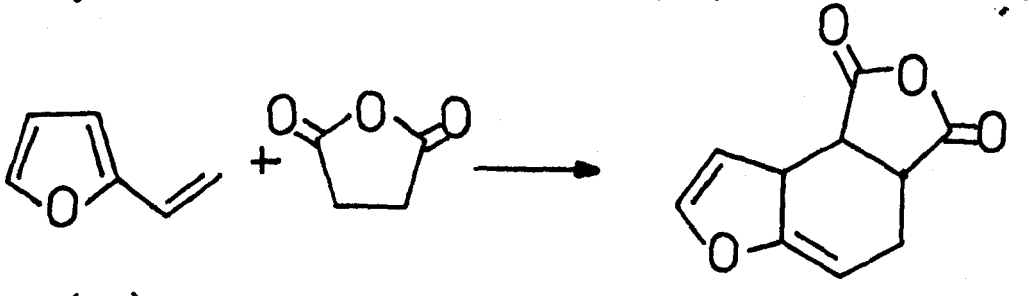
(188)

(189)

(vi) To vinyl furan and its derivatives.

Furan itself participates readily in Diels-Alder reactions.[55] In the case of vinyl furan there are two alternative diene systems, namely the cis-orientated diene of the ring system and the other consisting of the exocyclic double bond and the adjacent furan ring "double bond".

In 1939 R. Paul[56] obtained a 79% yield of the tetrahydrobenzofurandicarboxylic acid anhydride (191) from the reaction of 2-vinyl furan (190) and maleic anhydride (103). Chemical evidence con-

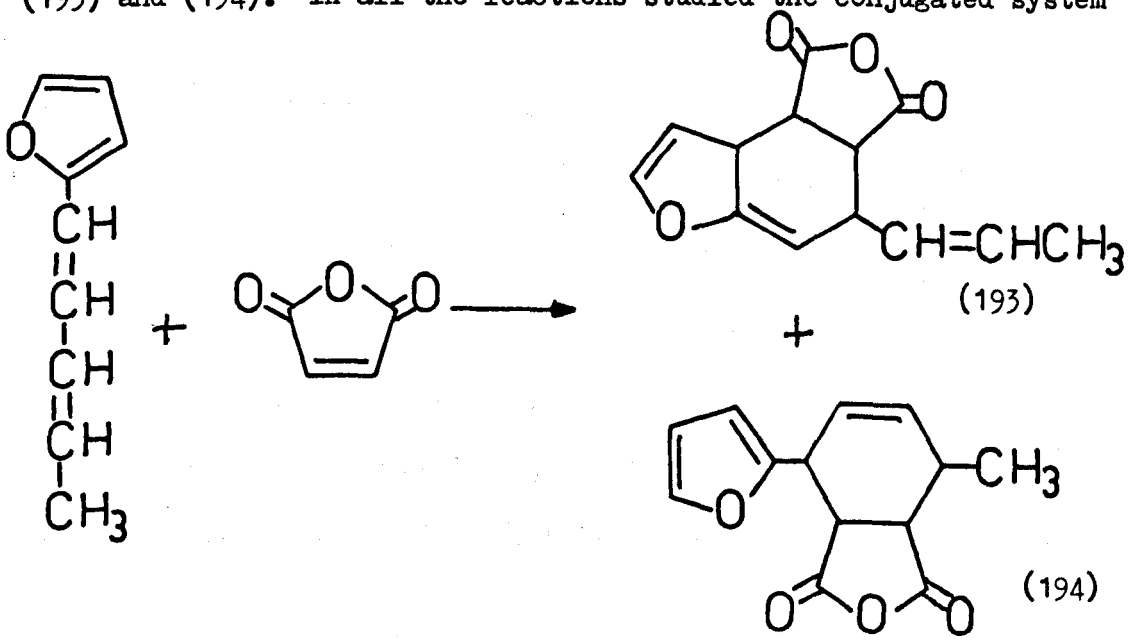


(190)

(191)

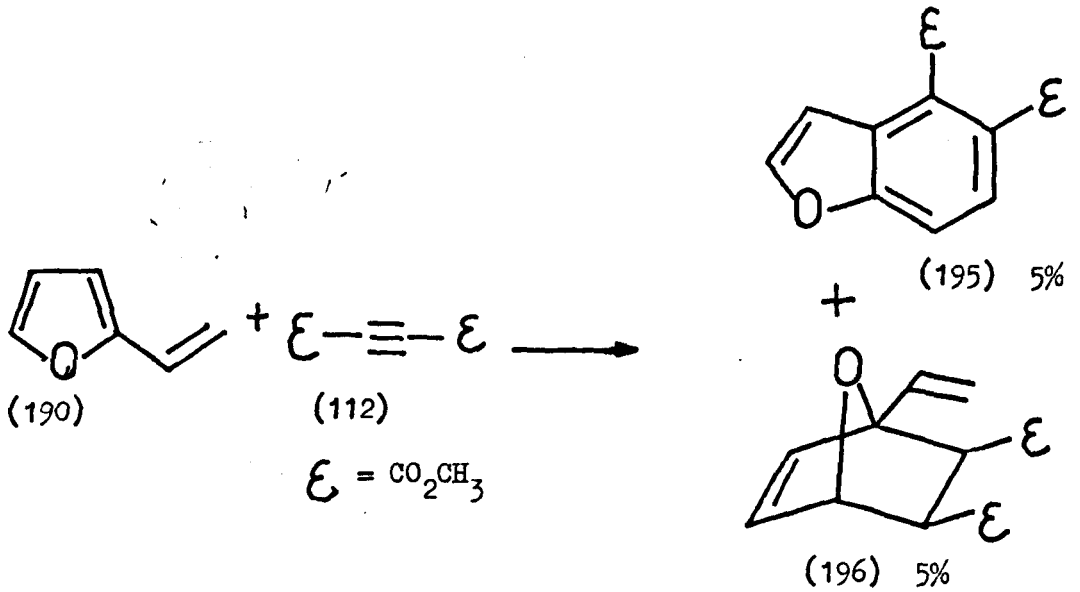
firmed that this adduct (191) was one in which the exocyclic double bond has participated in the diene system.

Schmidt,[57] has extended this work to 2-furylpolyenes, and 1-(2'-furyl)-1,3-pentadiene (192) gave the isomeric adducts (193) and (194). In all the reactions studied the conjugated system

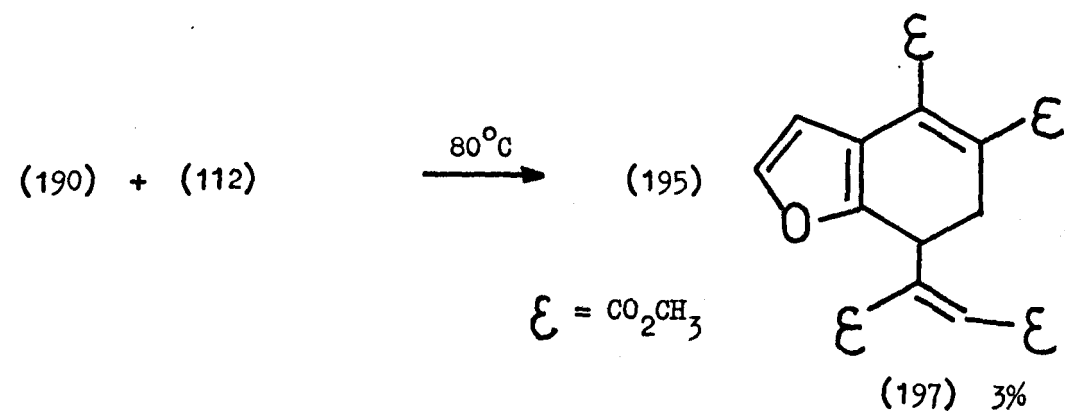


made up of the exocyclic double bond and the adjacent furan ring "double bond" proved to be more reactive than the furan ring system itself. Deactivation of this side chain double bond by powerful electron-withdrawing groups prevented such cycloaddition.[34] Thus 3-(2-furyl) acrylic acid and 2-(β-nitrovinyl) furan did not undergo cycloaddition.

2-Vinyl furan (190) and dimethyl acetylene dicarboxylate (112) reacted at room temperature to give a 1 : 1 mixture of dimethyl benzofuran-4,5-dicarboxylate (195) and dimethyl 3,6-epoxy-3-vinyl-3,6-dihydrophthalate (196).[58]

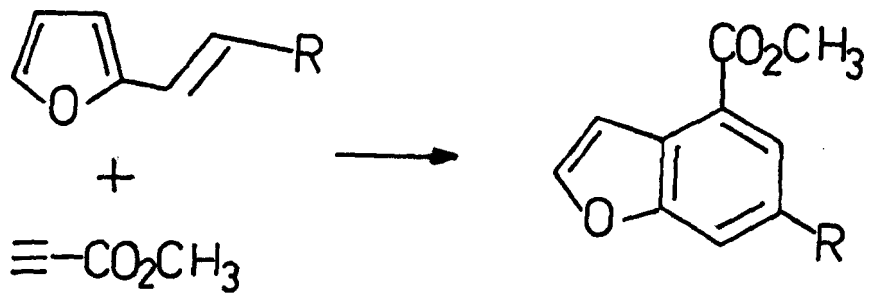


When the reaction was carried out at 80°C (boiling benzene) no epoxy compound, such as (196), was isolated, but the benzofuran (195) and the 1 : 2 adduct (197) were obtained.



The absence of the epoxy compound (196) was probably due to its decomposition under the reaction conditions. The low yield of the products from the reaction is thought due to polymerisation of 2-vinyl furan (190).

The reaction[58] of 2-vinyl furan with methyl propiolate (198) in boiling benzene gave methyl benzofuran-4-carboxylate (199); the reaction did not proceed at room temperature. Only one of the possible isomeric benzofurans was formed (but the authors state that this specificity is not unexpected from a consideration of both the



(198)

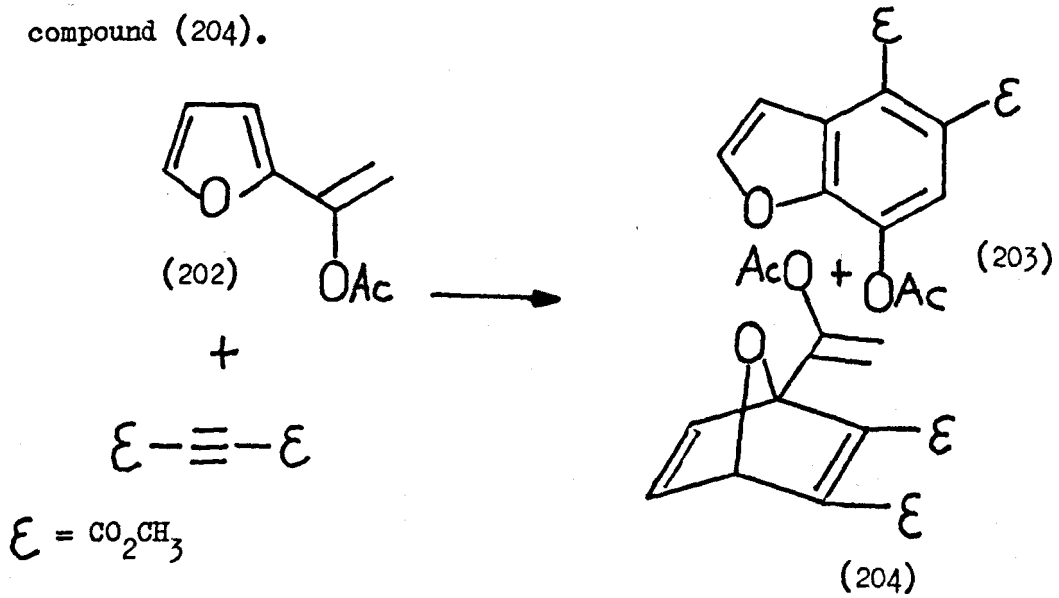
R = H (190)
R = CH_3 (200)

R = H (199) 5%
R = CH_3 (201) 6%

electronic and substituent effects).

In a similar manner, 2-isopropenyl furan (200) reacted with acetylenic esters, to 2-vinyl furan (190), but no adduct was obtained analogous to the epoxy adduct (196). Methyl propiolate with 2-isopropenyl furan (200) gave 3-methyl benzofuran-4-carboxylate (201). In both cases marginally higher yields were obtained than in the corresponding reaction with 2-vinyl furan (190).

2-Acetyl furan may be converted into the enol-acetate (202), reaction of which with dimethyl acetylene dicarboxylate gave a mixture of 1 : 1 adducts, the benzofuran (203) and the tricyclic compound (204).



(202)

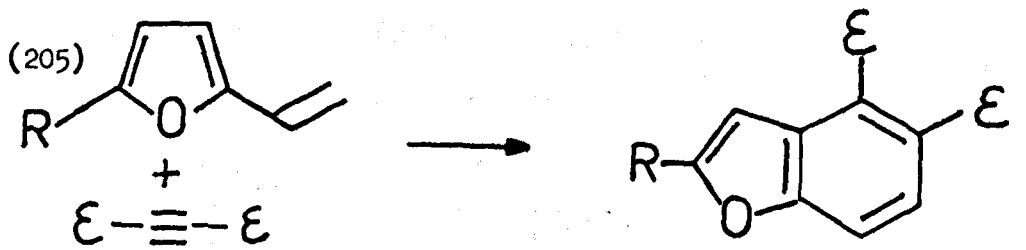
$\mathcal{E} = CO_2CH_3$

(203)

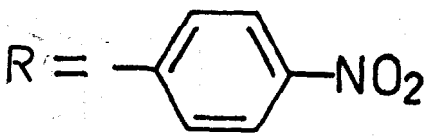
(204)

The yields of the adducts were poor, which the authors ascribe to the rapid polymerisation of 2-vinyl furans even in a nitrogen atmosphere in the presence of an inhibitor.

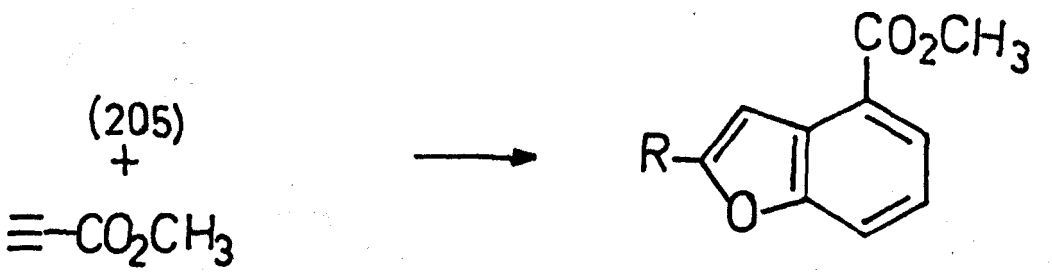
It was thought that 5-(p-nitrophenyl)-2-vinyl furan would be more stable; in fact the reaction of the vinyl furan derivative (205) with dimethyl acetylenedicarboxylate in boiling xylene gave the adduct (206) in 50% yield.



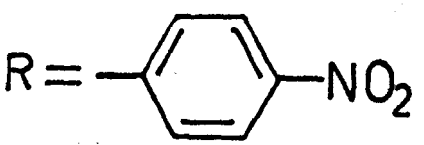
(206) 50%



Similarly the reaction of the stabilised diene (205) with methyl propiolate gave the benzofuran (207) in low yield.



(207)

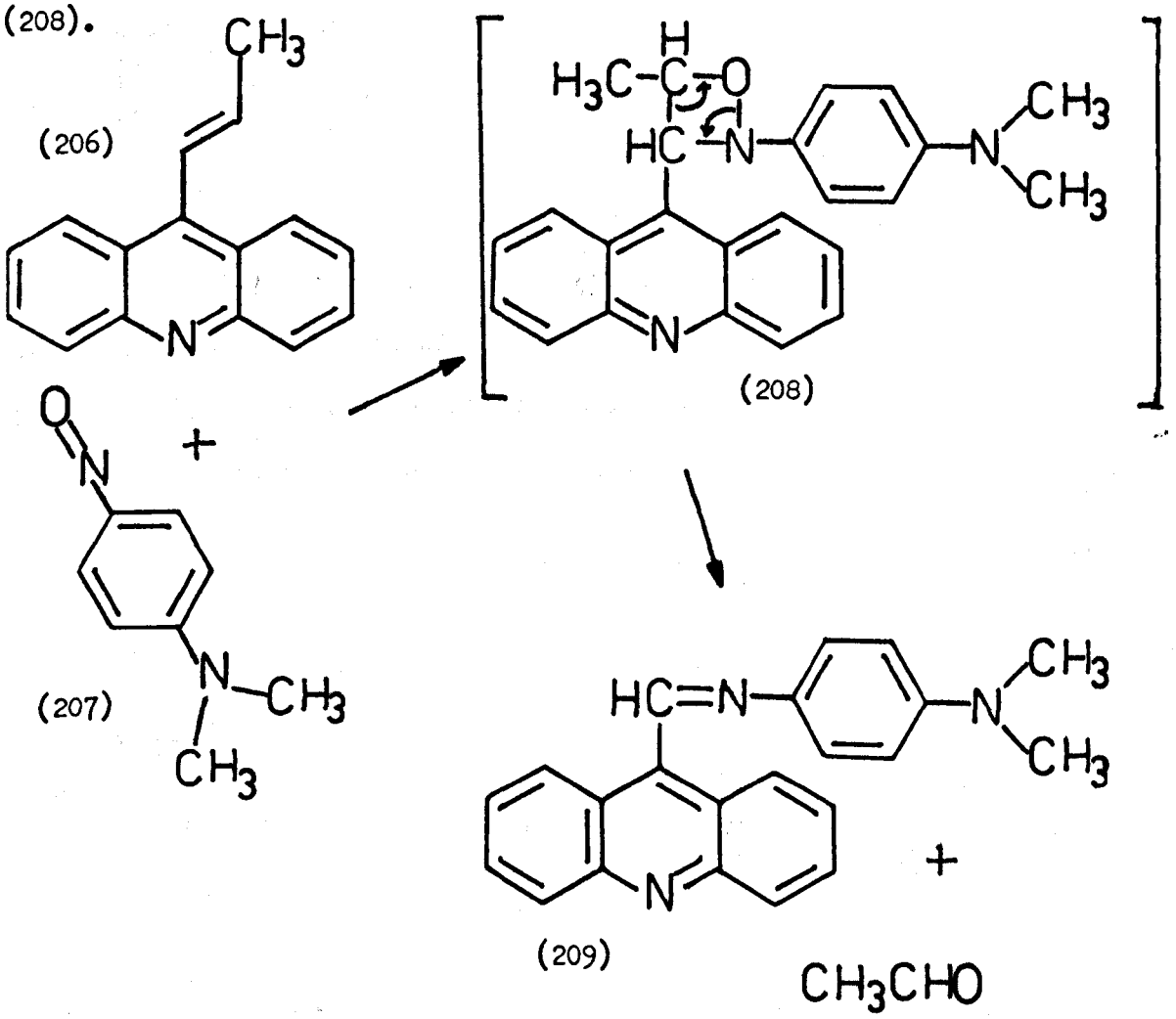


(vii) To 9-vinyl acridine and its derivatives.

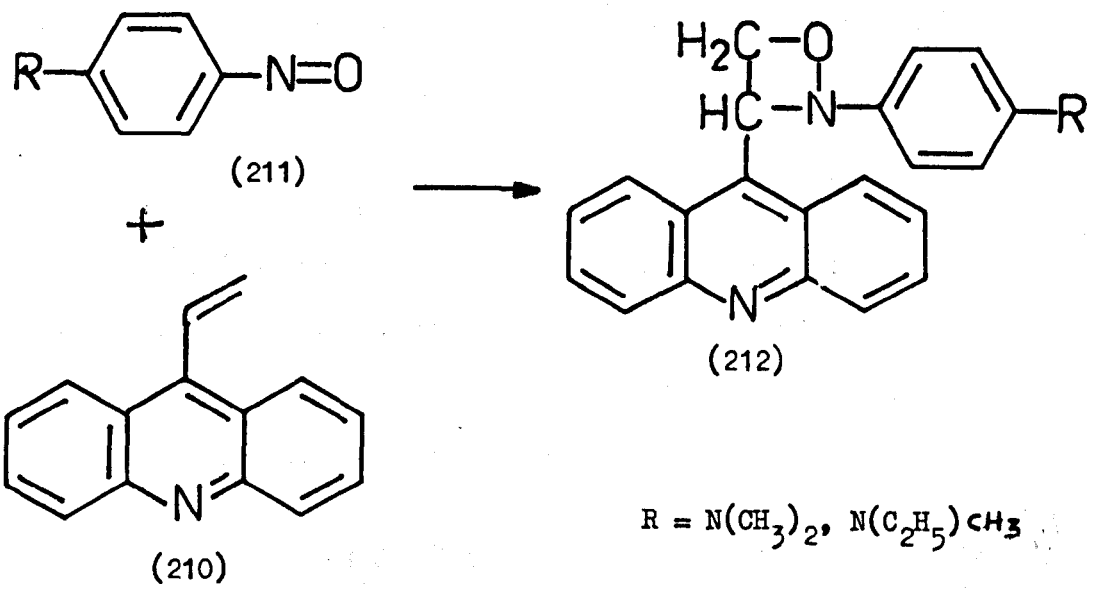
It has been reported[59] that 9-vinyl acridine and its methyl analogue (206) undergo reaction with nitrosobenzenes, and p-substituted nitrosobenzenes.

The reaction of cis or trans 1-(9-acridinyl) prop-1-ene (206) with p-nitroso-N,N-dimethylaniline (207) in the presence of HCl in refluxing ethanol gave the α,β-unsaturated anil (209).

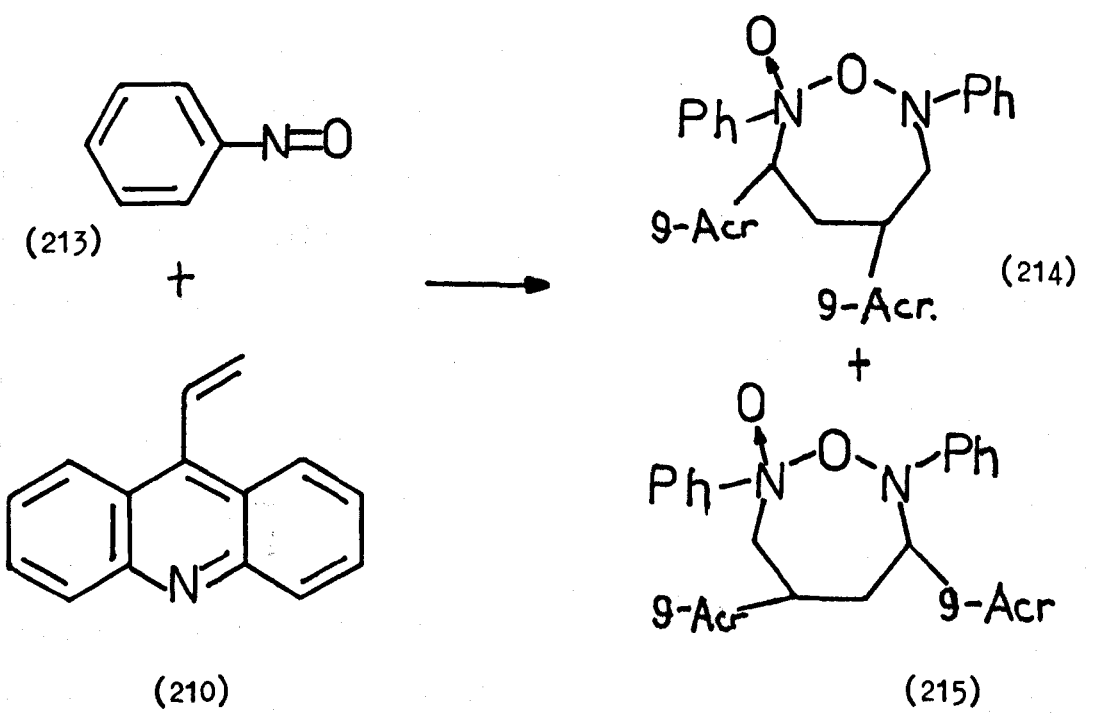
It was thought that the anil may be formed via the oxazetidine intermediate (208) with elimination of acetaldehyde, though it was not possible to isolate the oxazetidine intermediate (208).



The nitrosobenzenes (211) reacted with 9-vinyl acridine (210) at room temperature and in the presence of HCl to give the corresponding oxazetidines (212).



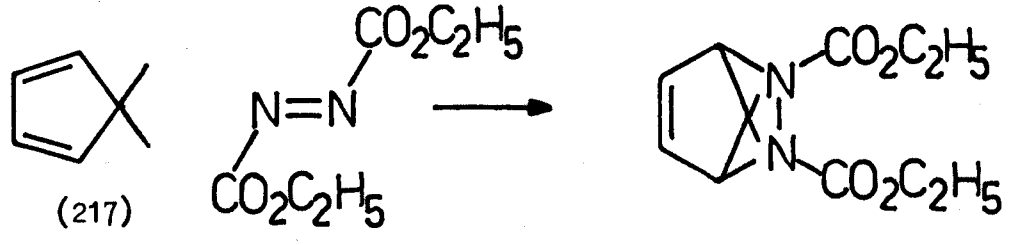
9-Vinyl acridine (210) reacts with nitrosobenzene (213) in the presence of HCl to afford a 2 : 2 adduct as the major product plus a small amount of the oxazetidine. Spectroscopic and chemical evidence support the proposed structures (214) or (215).



2. Example of Cycloaddition and ene reactions of Azodicarboxylic Acid Diester.

(i) Reaction as a dienophile.

α,α'-Dicarbonyl azo compounds are among the strongest dienophiles known. The reaction with dienes was first observed[61] by Diels, Blom, and Koll for diethyl azodicarboxylate (97) and cyclopentadiene (217), to give the adduct (218).



(217) (97) (218)

Detailed kinetic studies show that diene reactions of azodicarboxylates are faster in polar than in non-polar solvents, and that the reaction in non-polar solvents was accelerated by the addition of acid. The reactivities of the azodicarboxylates decrease with increasing size of the alkoxycarbonyl group. Thus the dimethyl ester reacts five to six times as rapidly as the diethyl ester,[62] while the di t-butyl ester reacts only with the more active diene components.[63]

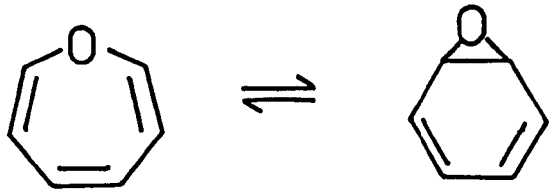
Particularly marked dienophilic activity was shown by cis α,α'-dicarbonyl azo compounds; for example, diethyl cis-azodicarboxylate reacts about thirty times as rapidly as the more stable trans azodicarboxylate. Cyclic azo compounds[33] which contain the cis-azo linkage react even at temperatures below 0°C.

Some recent examples of diesters of azodicarboxylic acid, acting as dienophiles will now be discussed.

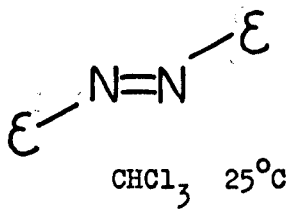
A recent paper by Rastetter[64] concerns the synthesis of

sym-oxepin oxide, because of its interesting chemical properties and the possibility that oxepin oxides may be involved in the biogenisis of naturally occurring dihydro oxepins.

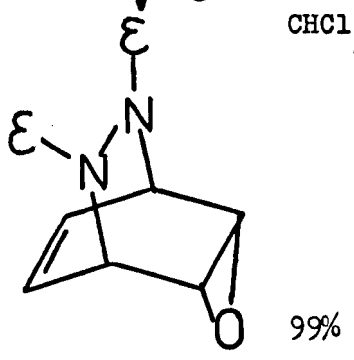
The route to sym-oxepin oxide (224) from benzene oxide - oxepin was accomplished via a protection - epoxidation - deprotection sequence. Protection of the benzene oxide (diene form) (219) was achieved by trapping it as the Diels-Alder adduct (220) with bis-(trichloroethyl) azodicarboxylate. The remaining double bond in the adduct (220) was then set up for the introduction of the epoxide moiety. After epoxidation (p-nitroperoxybenzoic acid) deprotection was achieved by reductive cleavage of the trichloroethylcarbamate ester (221), followed by oxidation of the Cu^{II} to produce the stable, brick red cuprous complex (222). The azoepoxide (223) was then liberated at $-20^{\circ}C$ by $AqNH_3$. A solution of the azoepoxide (223) in aprotic solvents on warming to ambient temperatures lost nitrogen to give in quantitative yield the sym-oxepin oxide (224).



(219) (219)



$CHCl_3$ 25°C

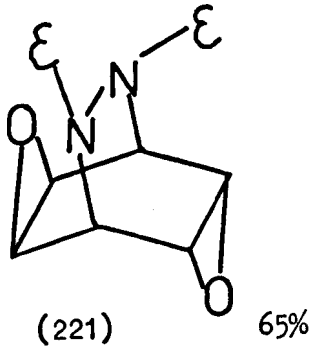


99%

(220)

$\mathcal{E} = CO_2CH_2CCl_3$

$p\text{-}NO_2PhCO_3H$



(221) 65%

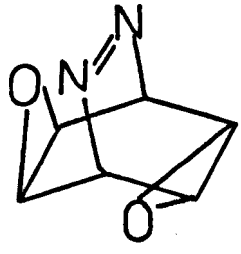
Zn/HOAc
0°C

$CuCl_2$
H_2O

Cu^I
A20

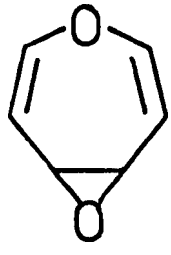
(222)

$NH_3(aq)$
CH_2Cl_2
-20°C



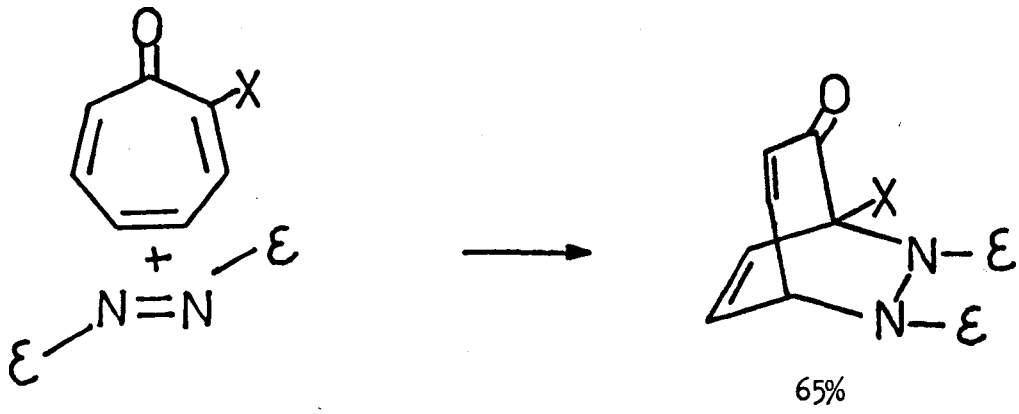
(223)

25°C $CHCl_3$



(224)

Diethyl azodicarboxylate undergoes[65] a formal Diels-Alder reaction on refluxing with tropone in toluene, to give the bicyclic adduct.



65%

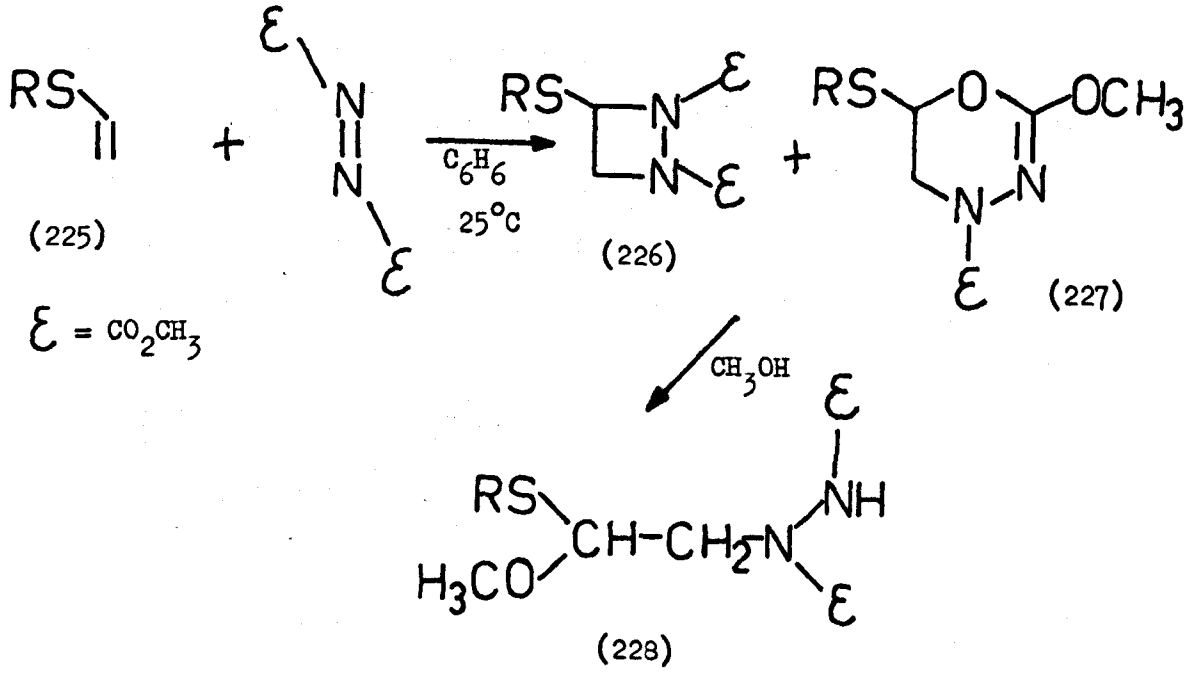
ε = $CO_2C_2H_5$

X = H, OCH_3

(ii) Reaction to form 1,2-diazetidines and 1,3,4-oxadiazine compounds.

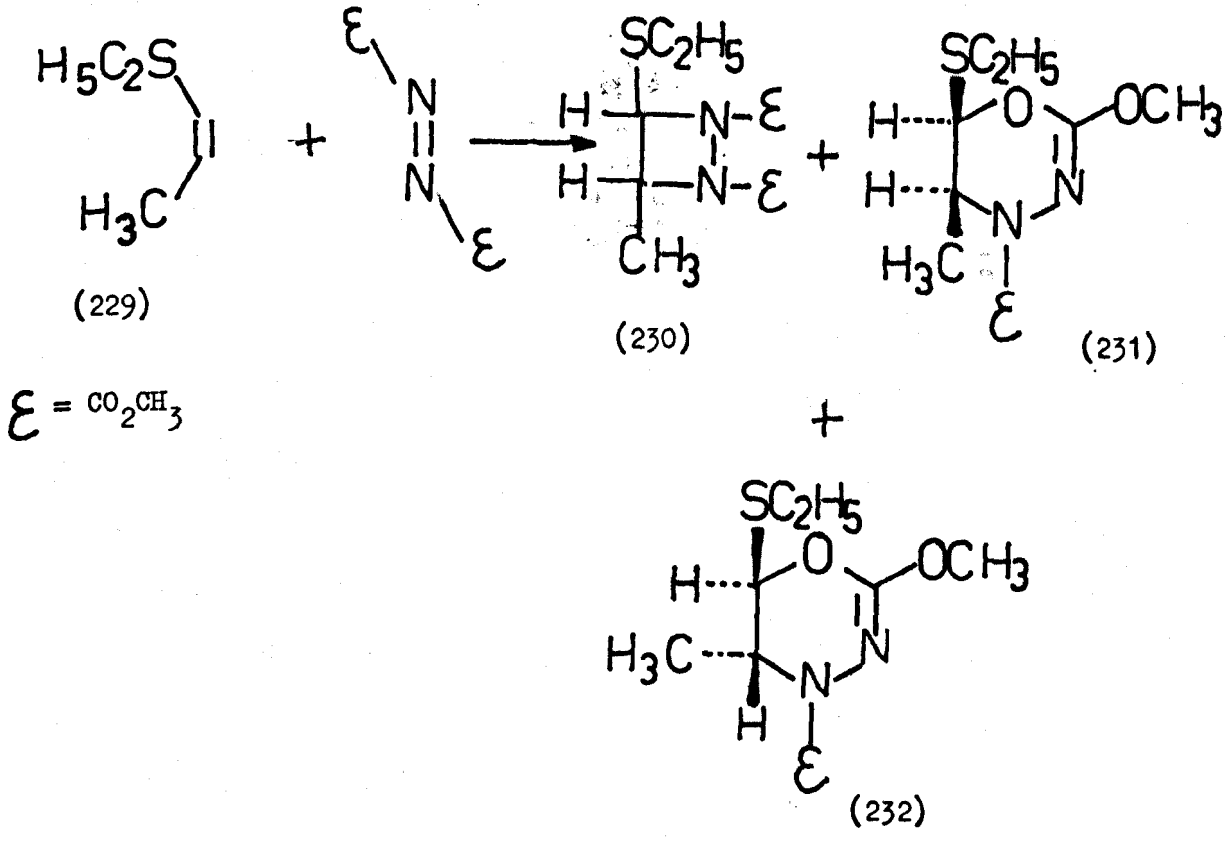
Reaction of enol ethers and enamines with diesters of azodicarboxylic acid give two different types of cycloadducts, those formed by [2 + 2] cycloaddition, the 1,2-diazetidines, and the 1,3,4-oxadiazines formed by [2 + 4] cycloaddition of the azo ester.

Dimethyl azodicarboxylate reacted[66] with ethyl or aryl vinyl sulphides (225) to give a mixture of [2 + 2] (226) and [2 + 4] (227) cycloadducts in overall yield of more than 80%. On solvolysis with methanol the adducts gave the corresponding thio acetal (228) indicating that of the two possible regio-isomers of the 6-membered ring only the adduct (228) was formed.

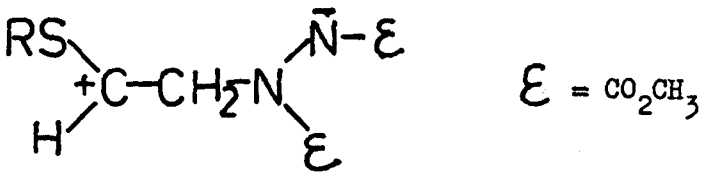


Under the reaction conditions neither of the cycloadducts can be interconverted.

With cis-1-thioethyl propylene (229), dimethyl azodicarboxylate gave three different 1 : 1 adducts, the diazetidine (230) and the isomeric oxadiazines (231) and (232).



The two oxadiazine cycloadducts were not isomerised when exposed to the reaction conditions, therefore the formation of both stereoisomers indicates the presence of an intermediate in the [2 + 4] cycloaddition. The most suitable structure proposed for this intermediate was as a "moreorless free rotating dipole" (233).



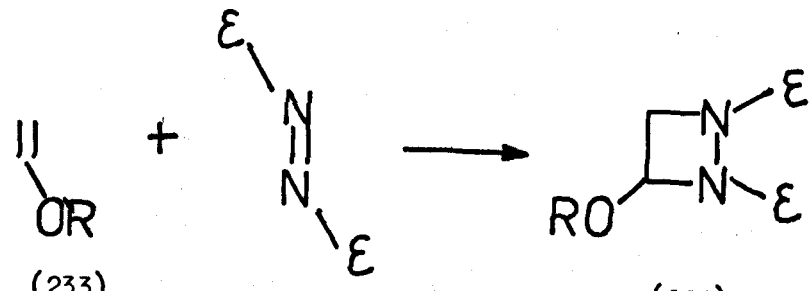
(233)

Such a dipole cannot be intermediate in diazetidine formation since only one stereoisomer was formed. The dipole was trapped by carrying out the reaction in methanol and under these conditions the diazetidine (230) was still formed.

Koerner Von Gustorf[67] et al. propose a concerted [2 + 4] cycloaddition mechanism for the formation of dihydrooxadiazines from dihydro-1,4-dioxine, trans-1,2-dimethoxyethane, vinyl acetate and vinylene carbonate, with dimethyl azodicarboxylate. With cis-1,2-dimethoxyethane the dimethyl azodiester gave the oxadiazine and the diazetidine in a 4 : 1 ratio.

Oxadiazine formation by an electron rich $>C = C<$ bond (dienophile) to the electron poor diene may be thought of as a Diels-Alder reaction having an inverse electron demand. In accord with this Von Gustorf found that all attempted 1,4-additions failed with electron poor olefins.

Dimethyl and diethyl azodicarboxylates add to both ethyl and methyl vinyl ether (233) to give the corresponding diazetidine compounds (234).



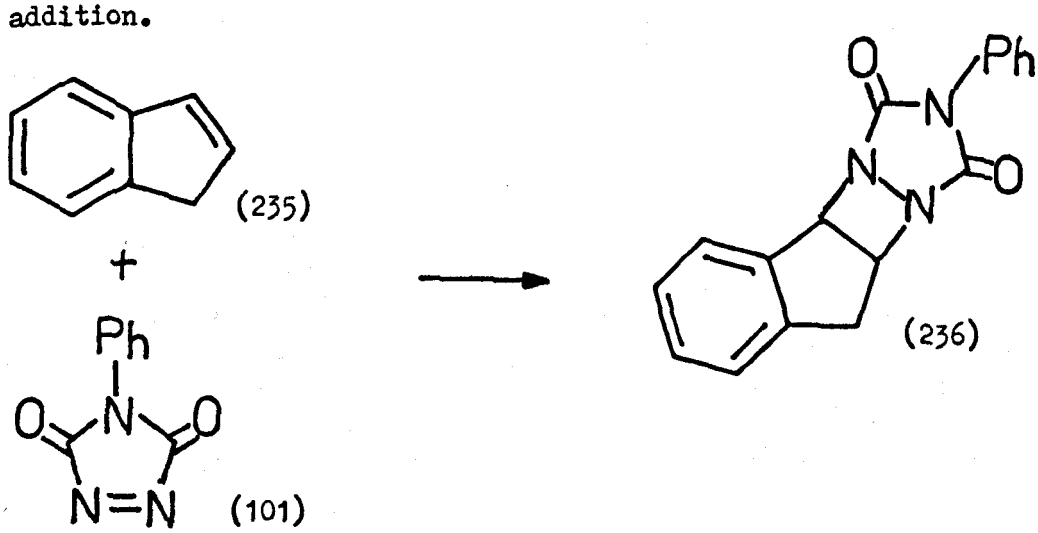
(233) (234)

R = CH_3, C_2H_5

$\mathcal{E}$ = CO_2CH_3, $CO_2C_2H_5$

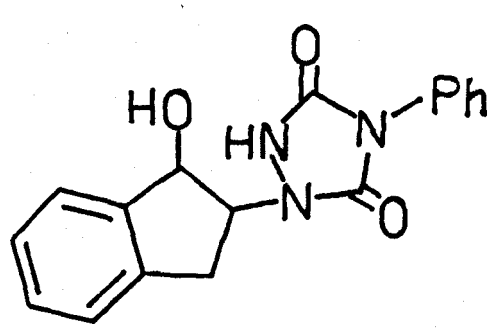
A study of the secondary α-deuterium kinetic isotope effect during the addition of dimethyl azodicarboxylate to ethyl vinyl ether revealed an unsymmetrical transition state. A change of hybridization *in the direction* $sp^2 \longrightarrow sp^3$ *had occurred* at = CH_2 but not at = CH - OR.

Indene (235) reacts with 1,2,4-triazoline-dione (101) to give an adduct which was thought to be the product from a [2 + 2] addition.



(235) (101) (236)

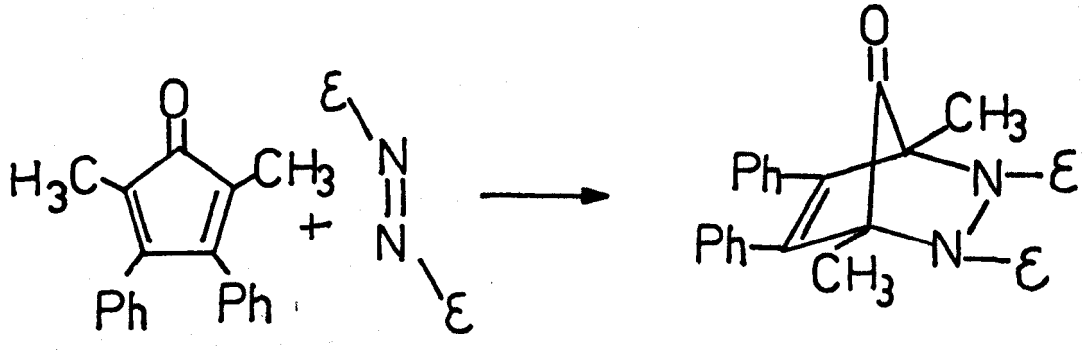
A dipolar intermediate was trapped with water during the above reaction to give the alcohol (237).



(237)

The above observations seem to indicate that a stepwise mechanism may be operating during [2 + 2] cycloaddition. The Woodward and Hoffman rules do not allow concerted thermal [π 2s + π 2s] cycloaddition, although the reaction may proceed, in theory via the higher energy [π 2s + π 2a] route which is allowed as a concerted process by Woodward and Hoffman rules, although stereochemically unfavourable. The authors propose that high polarizability of the olefin coupled with high polarizing power of the cyclophile may reduce the activation energy and make diazetidine formation a more favourable process.

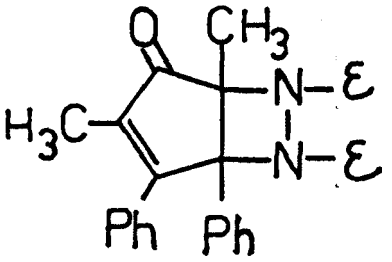
Mackay et al.[68] have shown that reaction of the cyclone (238) (as its dimer) with azodiesters may proceed to give the corresponding adduct (239). The reaction may be followed by ^{1}H n.m.r. spectroscopy which shows the build up of the methyl singlet in the adduct.



(238) (239)

In the later stages of the reaction additional methyl singlets began to appear before the initial reaction was complete. The peaks developing in the n.m.r. spectrum during the later stages of the azodiester reactions were again observed when solutions of the pure adducts were refluxed. When R = Me, the n.m.r. spectrum showed eight new methyl peaks in its spectrum, four of which reached a maximum and

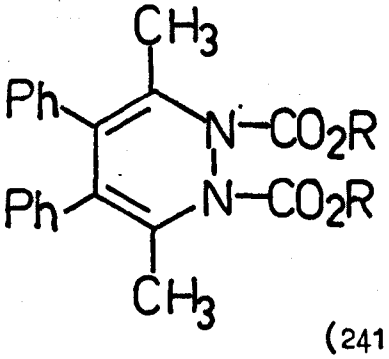
then decreased while the others continued to grow. Repetition of the reaction on a large scale gave quantitative yields of an isomer of the adduct (R = Me). This major product was shown to be the diazetidine (240). Oxadiazine structures was discounted due to the absence of any peaks in the infrared spectrum around 1720 - 1620 cm^{-1}. (Absorption due to $\geq C = N$ occurs in the region 1680 - 1660 cm^{-1}).



(240)

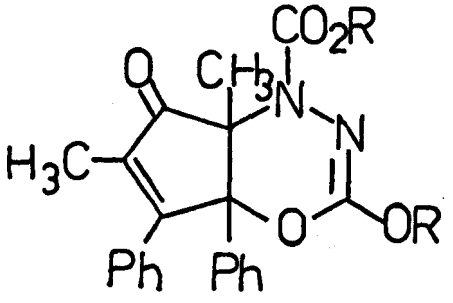
The diazetidine (240) was formed by a [1,3] rearrangement of the original adduct (239). The other adducts all gave the corresponding diazetidine compound except the t-butyl ester which gave only tarry products.

The adducts when R = C_6H_5 or CH_2CCl_3 also gave in addition to the diazetidine compound a dihydro pyridazine derivative (241), formed by decarbonylation of the initial cycloadduct.



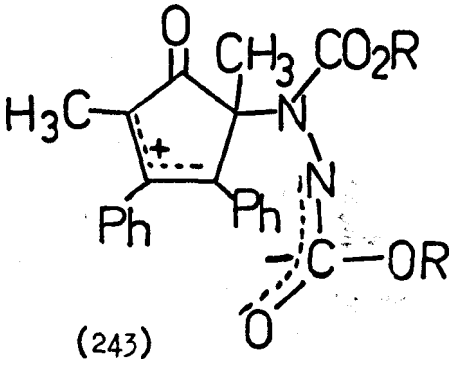
R = Ph, CH_2Cl_3 (241)

The four peaks due to the intermediate noted earlier when the cycloadduct (R = Me) was heated were shown to be due to the oxadiazine (242) (i.r. - 1675 cm^{-1}), the product of a [3,3] sigmatropic rearrangement of the initial adduct, a hetero-Cope rearrangement.



R = Ph, CH_2CCl_3 (242)

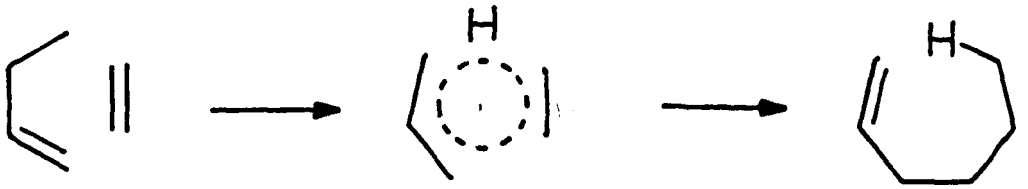
The authors conclude that the initial cycloadduct (239) and the oxadiazine (242) are in reversible equilibrium with one another and the former was transformed slowly into the diazetidine (240). The conversion of the oxadiazine (242) into the azetidine (240) does not occur at all or was very slow. No conclusions were reached about the concertedness of the rearrangements but a possible intermediate (243) may be common to all the transformations taking place.



(243)

(iii) The ene reaction of diesters of azodicarboxylic acid.

The ene reaction[69] is the indirect substituting addition of a compound with a double bond (enophile) to an olefin possessing an allylic hydrogen (ene) and involves allylic shift of one double bond, transfer of the allylic hydrogen to the enophile and bonding between the two unsaturated termini.

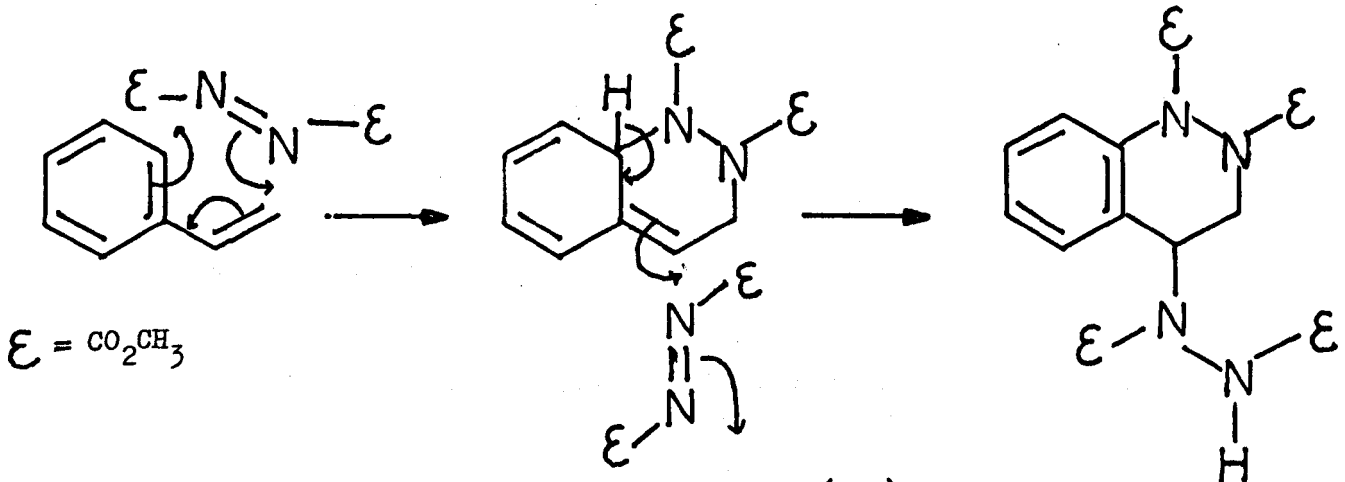


The ene reaction may or may not be concerted. The reaction is not only related to the Diels and Alder addition but may also be regarded as an intermolecular variant of the symmetry-allowed [1,5] hydrogen shift.

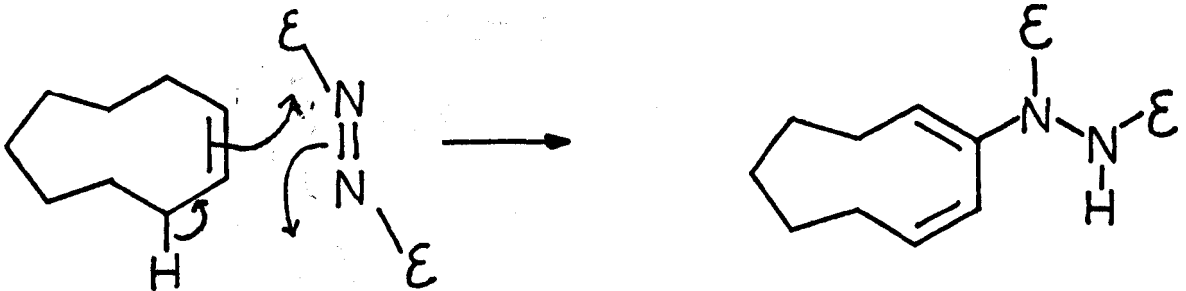
Diesters of azodicarboxylic acid are among the most widely used enophiles. They react under relatively mild conditions with ene components, heating to 80°C for a few hours being sufficient to complete the reaction.

If the azo-linkage is present in the cis-configuration as in photochemically generated azodicarboxylate and in 4-phenyl-1,2,4-triazoline-3,5-dione the addition properties are considerably enhanced.

The formation of the diadduct between styrene and diethyl azodicarboxylate proceeds via an initial cycloaddition followed by an ene reaction which is thought to go via a free radical process[31] (see p. 65 for full discussion.)

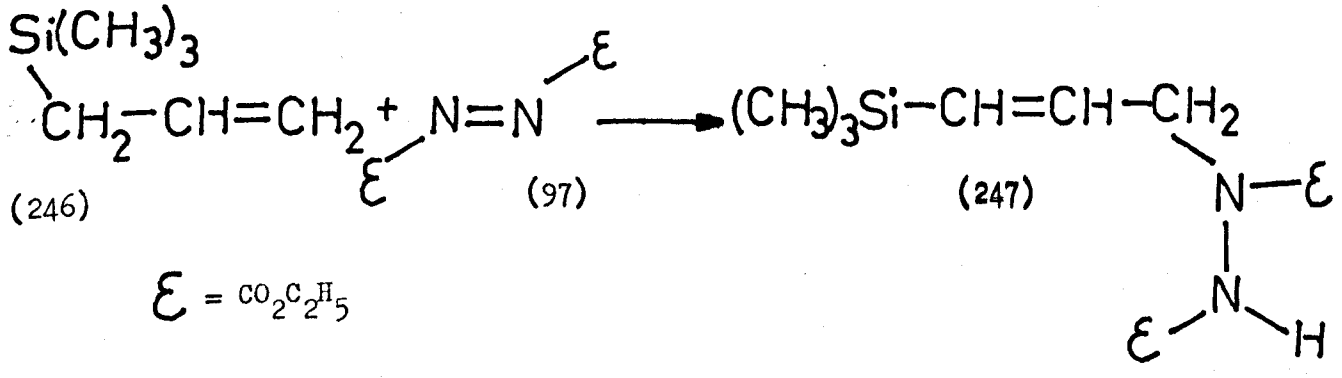


Reaction of cyclonona-1,2-diene (244) with diethylazodicarboxylate gave an 83% yield of an ene insertion product (245).



With other unsaturated compounds cycloaddition was observed to take place.

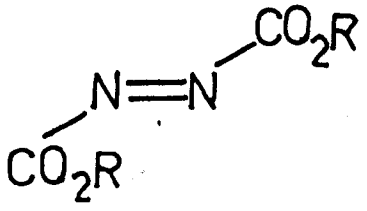
Similarly treating[71] the unsaturated organosilicon compound (246) with diethyl azodicarboxylate gave the ene product (247).



DISCUSSION

(i) Introduction.

The general nomenclature of the azo ester dienophiles used are shown below



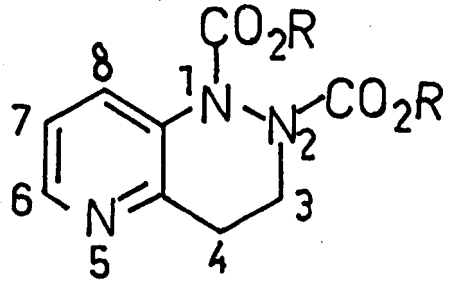
dialkyl azodicarboxylate

azodicarboxylic acid dialkyl ester

diazenedicarboxylic acid dialkyl ester

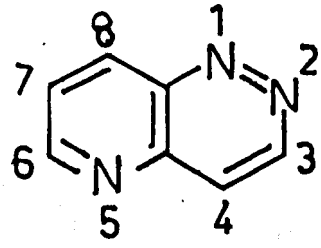
dialkyl azodiformate

The cycloadducts obtained from the reaction of the vinyl heterocycle and the azo ester dienophile have the following general formulae and nomenclature, illustrated by the adduct derived from 2-vinyl pyridine



1,2-dialkoxycarbonyl-1,2,3,4-tetrahydropyrido[3,2-c] pyridazine

The fully aromatic system obtained from this adduct is named as shown below



pyrido[3,2-c] pyridazine

5-azacinnoline

(ii) Pyrido[3,2-c] pyridazine.

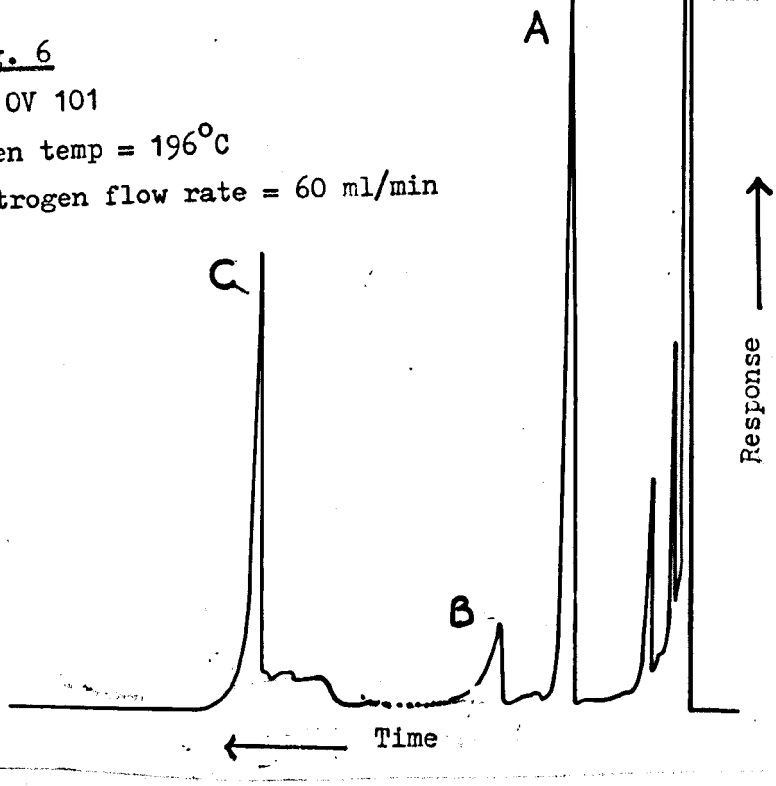
We decided to attempt to synthesise the pyrido[3,2-c] pyridazine system via the reaction of 2-vinyl pyridine and diethyl azodicarboxylate, to give an adduct, which may be de-esterified, decarboxylated then oxidised to give the parent pyrido[3,2-c] pyridazine system (87).

When this work was started there were only two references[25,26] to this pyrido[3,2-c]pyridazine system (described in the Introduction to Part 2 of this thesis) in the literature. After the completion of most of this work, Kost et al. published the synthesis of the 5-azacinnoline system using a method similar to our own.

After boiling 1 : 1 molar ratios of 2-vinyl pyridine and diethylazodicarboxylate in benzene for 26 hours, no azo diester was present in the reaction mixture, although a substantial amount of 2-vinyl pyridine remained.

A Gas Liquid Chromatography (g.l.c.)trace (Fig. 6) of the reaction products showed the presence of at least three major components, two peaks A and B of similar retention time and a peak C at longer retention time.

Fig. 6
3% OV 101
Oven temp = 196°C
Nitrogen flow rate = 60 ml/min

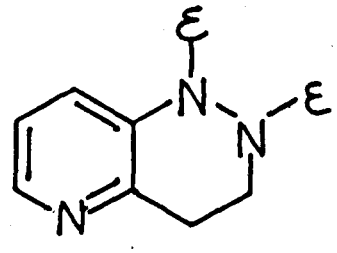


The products from the reaction were separated by column then preparative layer chromatography.

After initial elution of unreacted 2-vinyl pyridine from the column an oil was eluted which contained two major components. These two components (corresponding to the peaks A and B in the g.l.c. trace of the reaction products), were then separated by preparative layer chromatography, compound A as a yellow oil in 13% yield and compound B as a light yellow solid in 2.5% yield.

Heating compounds A and B separately in benzene for 48 hours produced no change in their chemical structure, thus indicating that they are not interconvertible nor intermediates in the production of some other compound.

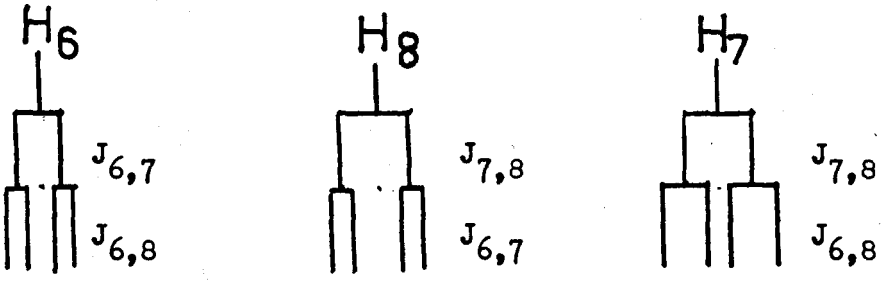
The product with the smaller R_f value, compound A, has an M^+ at 279 a.m.u., indicating that it is a 1 : 1 adduct formed between 2-vinyl pyridine and diethyl azodicarboxylate. Microanalysis after bulb distillation confirmed the empirical formula as $C_{13}H_{17}N_3O_4$. It is proposed that compound A is 1,2-diethylcarbonyl-1,2,3,4-tetrahydro-pyrido[3,2-c]pyridazine (248).



(248)

$\epsilon = CO_2C_2H_5$

The ^1H n.m.r. spectrum (Fig. 7) shows three downfield signals attributed to the protons H-6, δ = 8.3 p.p.m., H-8, δ = 8.05 p.p.m., and H-7 at δ = 7.15 p.p.m. The signals due to H-6 and H-8 are seen as expected for the above structure as two pairs of doublets those attributed to H-7 being a quartet.

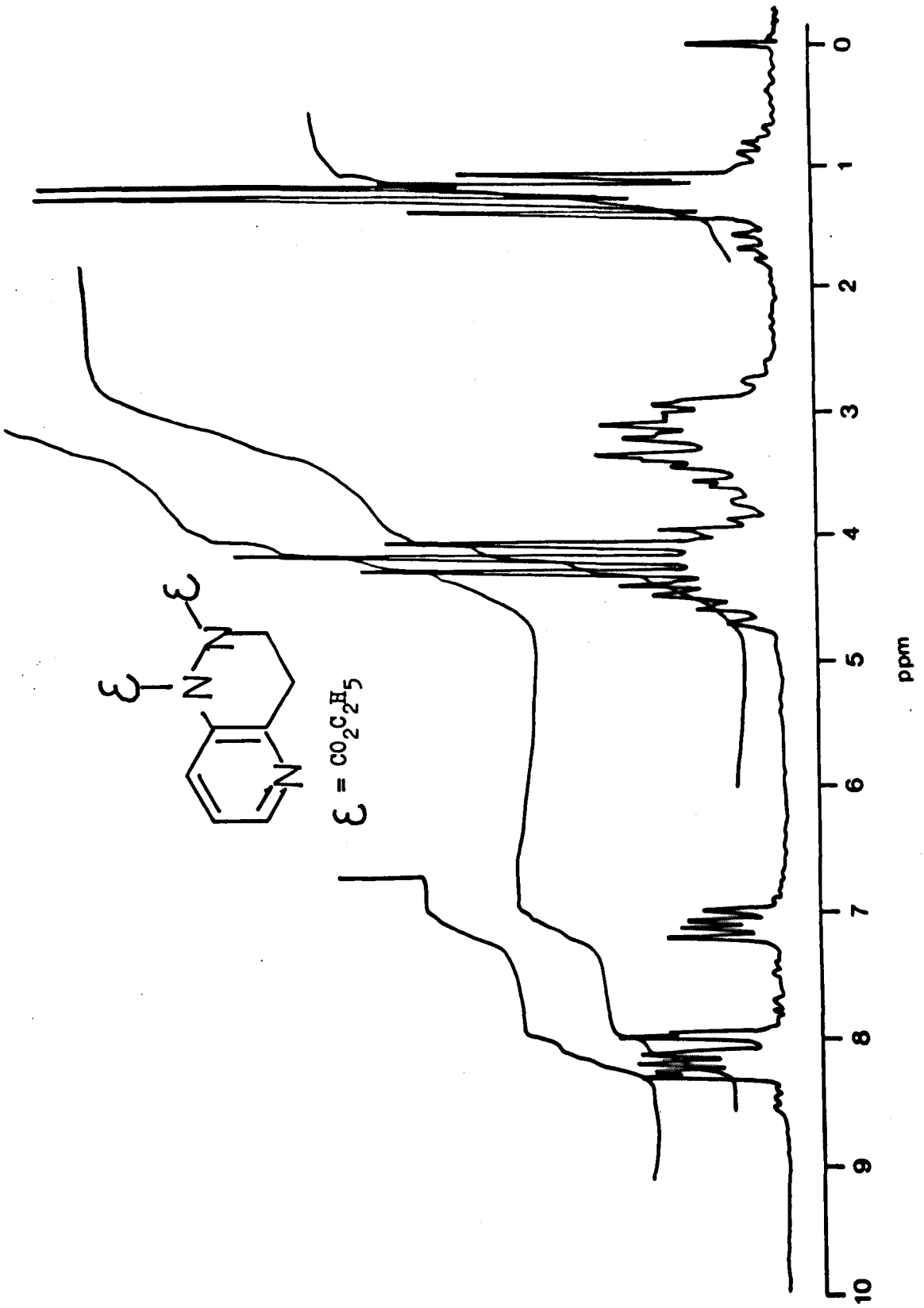


$J_{6,7}$ = 6 Hz, $J_{6,8}$ = 1-2 Hz, $J_{7,8}$ = 9 Hz

Between δ = 3.00 and 4.70 p.p.m. is a complex set of absorptions which integrates for eight protons. Four of these protons are the two methylene groups of the non-equivalent ester substituents, which is the reason why they resonate as a 'distorted triplet' and not as a clean quartet. The remaining four protons are the two methylene groups, C-3 and C-4, they are non-equivalent and resonate as a complex A.B.C.D. system.

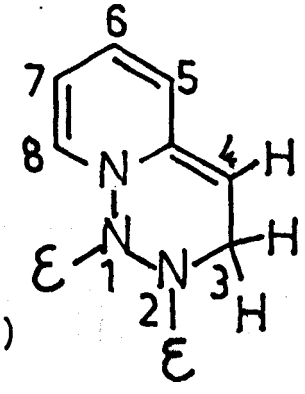
The remaining two methyl groups on the ester substituents resonate as a complex signal between δ = 1.1 and 1.5 p.p.m. It is just possible to make out the distinct triplet structure of each of the signals. (The mechanism of formation of this cycloadduct will be dealt with on p.147).

Fig. 7 ^{1}H N.m.r. spectrum of 1,2-diethoxycarbonyl-1,2,3,4-tetrahydropyrido[3,2-c]pyridazine (248)

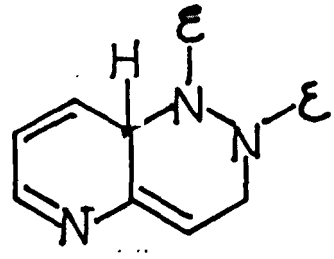


The other product, compound B obtained as a light yellow solid, also had an M^+ = 279 a.m.u. After repeated recrystallisations from cyclohexane, microanalysis confirmed its empirical formula to be $C_{13}H_{17}N_3O_4$.

Two possible structures (249) and (250) were proposed for this product. The compound proved to be the 3H-pyrido[1,2-c]-1,2,3-triazine diester (249).



(249)



(250)

$\mathcal{E} = CO_2C_2H_5$

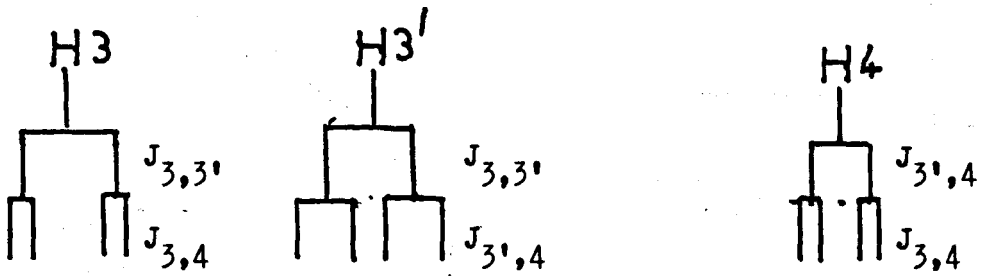
The tetrahydro pyrido[3,2-c]pyridazine (250) should aromatise to the isomer on heating in benzene. The fact that no change was observed on heating in benzene, and the presence of four downfield protons in the ^1H n.m.r. spectrum led us to discount this possibility.

The ^1H n.m.r. spectrum (Fig. 8) confirmed structure (249). It contained four downfield protons (H 5-8) between δ = 7.0 and 8.5 p.p.m. The furthest downfield signal, the 'pyridine-α-proton', H8 is seen as a pair of doublets at δ = 8.5 p.p.m. (J = 4 and 2 Hz). The other three downfield protons have similar chemical shifts and lie virtually on top of one another. The olefinic proton H-4 resonates at δ = 5.35 p.p.m. as a pair of doublets, which is the expected pattern for a single proton next to two non-equivalent protons. The signal between δ = 4.00 and 4.8 p.p.m. integrate for five protons, attributed to the two methylene groups of the ester substituents which overlap one of the methylene protons at position-3.

The other proton of the C-3 methylene group is seen as a quartet at δ = 3.5 p.p.m. The remaining complex signal between δ = 1.1 and 1.7 p.p.m. integrates for six protons and is attributed to the two methyl groups of the ester substituents.

On addition of a sample of lanthanide shift reagent, $Eu(fod)_3$ to the n.m.r. solution, the methylene proton signal under the ester absorptions was moved out into 'open space'. It resonates as a pair of doublets as expected (see Fig. 8).

The 'pyridine type' protons are all moved downfield, H-8 far

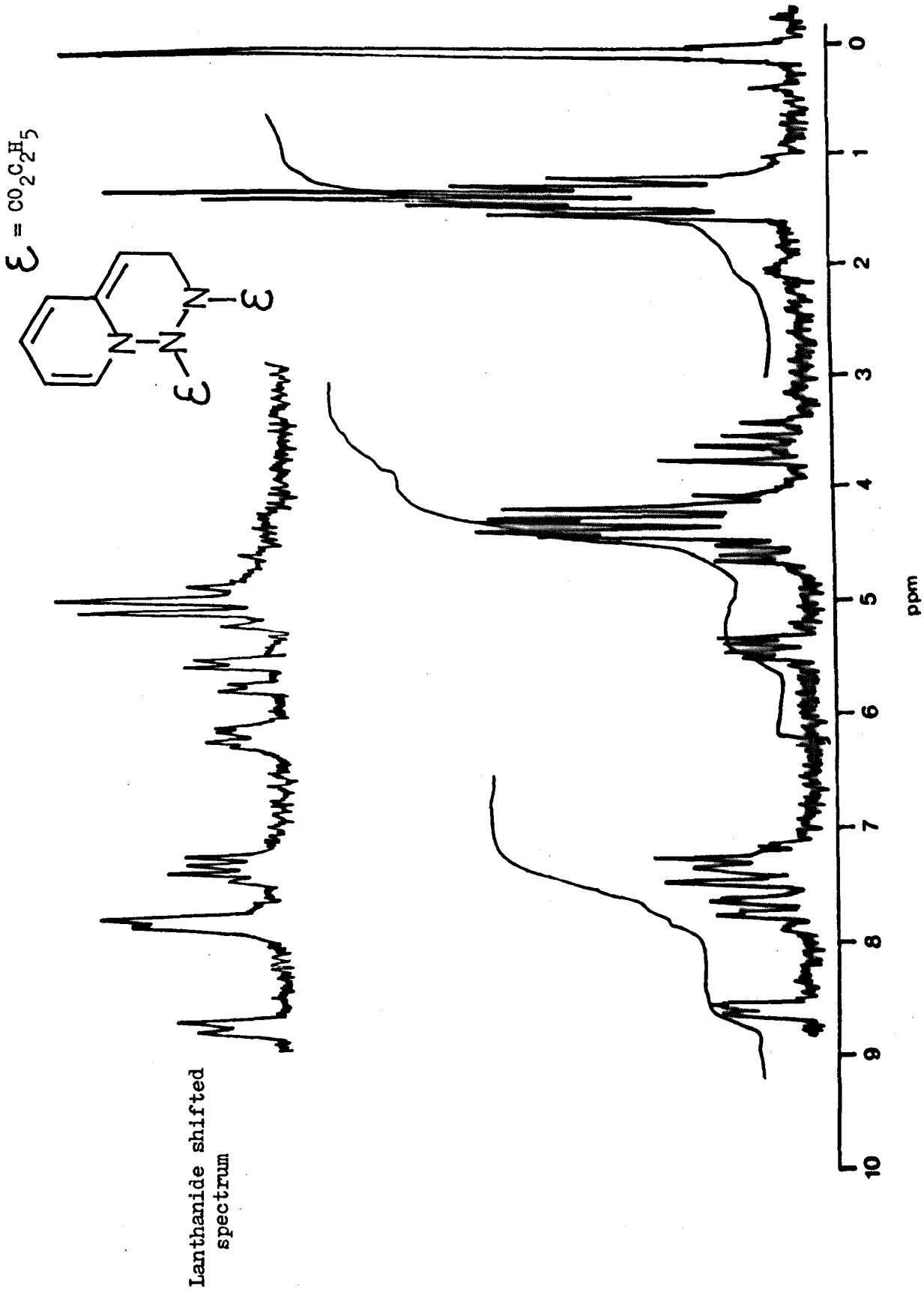


$J_{3',4}$ = 8 Hz, J_{trans}, $J_{3,4}$ = 3 Hz, J_{cis}, $J_{3,3'}$ = 12 Hz, J_{gem}

more than the other three. The protons H-6 and H-7 are seen as a two proton doublet (J = 8 Hz), this is due to H-6 and H-7 having the same chemical shift in the lanthanide affected spectrum and therefore they do not couple. The proton H-5 resonates as a quartet (J = 8, 3-4 Hz) as expected. On addition of more $Eu(fod)_3$ to the n.m.r. solution the signals become distorted which could be due to the $Eu(fod)_3$ complexing all over the molecule.

It was not possible to isolate any pure compounds from the remainder of the reaction products on the column. Repeated chromatography gave non-characterisable fractions. Mass spectra of some of these fractions gave results which indicated that higher adducts were formed, possibly by the reaction of two or more molecules of

Fig. 8 ^{1}H N.m.r. spectrum of 3H-pyrido[1,2-c]-1,2,3-triazine diethyl ester (249)



diethylazodicarboxylate with one of 2-vinyl pyridine. It is not uncommon for reactions of dienophiles with vinyl heterocyclic compounds to give small yields of the desired products plus uncharacterisable material. Sometimes it has proved possible to characterise some higher adducts as was the case when 2-vinyl pyridine reacts with derivatives of N-alkyl maleinimides[27] (see p. 74).

Removal of the ester groups from the tetrahydro pyrido [3,2-c] pyridazine diester (248), then subsequent oxidation should lead to the parent pyrido[3,2-c] pyridazine system.

Boiling the cycloadduct (248) in ethanolic KOH led to the formation of many products. The major product formed albeit in low yield gave ^{1}H n.m.r. and mass spectra which suggest that it is the fully aromatic pyrido[3,2-c] pyridazine system (87).

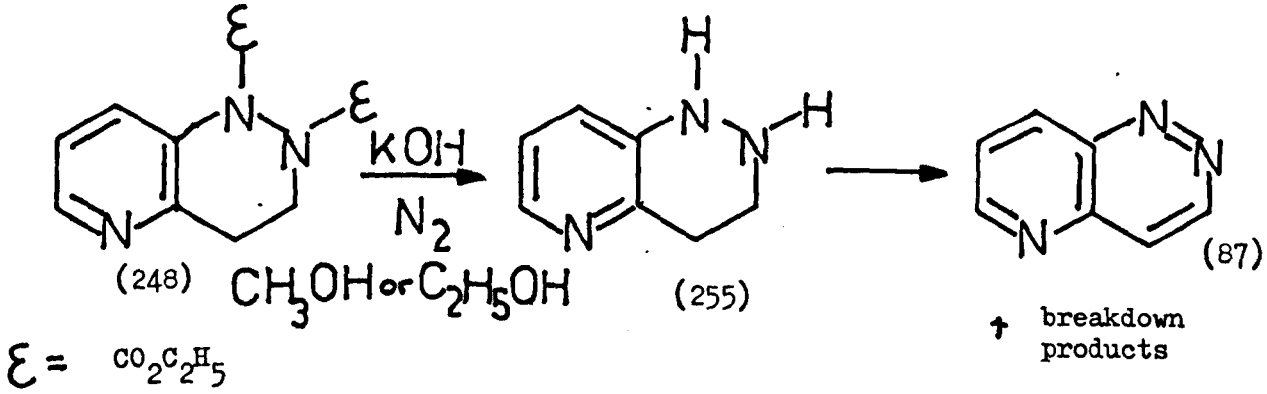
The ^{1}H n.m.r. spectrum (Fig. 13, p.132) contained five down-field protons with the correct splitting pattern for the postulated structure. The mass spectrum has an M^+ of 131 a.m.u. which is 95% of the base peak at 76 a.m.u.

During the course of the reaction many colour changes were observed, notably changes from green to purple and back again.

Carrying out the reaction in either methanol or ethanol under nitrogen also leads to a variety of products. When the hydrolysis reaction was done under nitrogen the boiling reaction solution was a light yellow colour. On removing a sample the colour rapidly darkens to a brown/black solution, which was probably due to the oxidation of the hydrazo compound by air coupled with its probable instability to the alkaline conditions employed.

Using an inert nitrogen atmosphere during the hydrolysis it was possible to isolate and characterise the pyrido[3,2-c] pyridazine (87) after preparative layer chromatography, in very poor yield. The

many other products formed during the hydrolysis were not characterised.



Aerial oxidation and formation of many products during hydrolysis of ethyl azo ester adducts has been encountered by previous workers.[72]

It was found that the best conditions for the reaction which gave the maximum yield of the diethoxycarbonyl tetrahydro pyrido[3,2-c]pyridazine cycloadduct (248) were to reflux equimolar amounts of the starting materials, diethylazodicarboxylate and 2-vinyl pyridine in acetonitrile. The yield of the desired product based on unrecovered 2-vinyl pyridine was 18.2%. The yield of the triazene compound is reduced, and it can only be detected by g.l.c.

If the reaction is carried out in higher boiling hydrocarbon solvents, toluene or xylene, more products were formed resulting in a decrease in the yield of the tetrahydro pyrido[3,2-c]pyridazine (248) adduct.

Table 1 shows the solvents (B. pt. $\simeq 80^{\circ}C$) used in the reaction of equimolar quantities of 2-vinyl pyridine and diethyl azodicarboxylate, the yields of the adduct obtained and the reaction times for the disappearance of the azo ester.

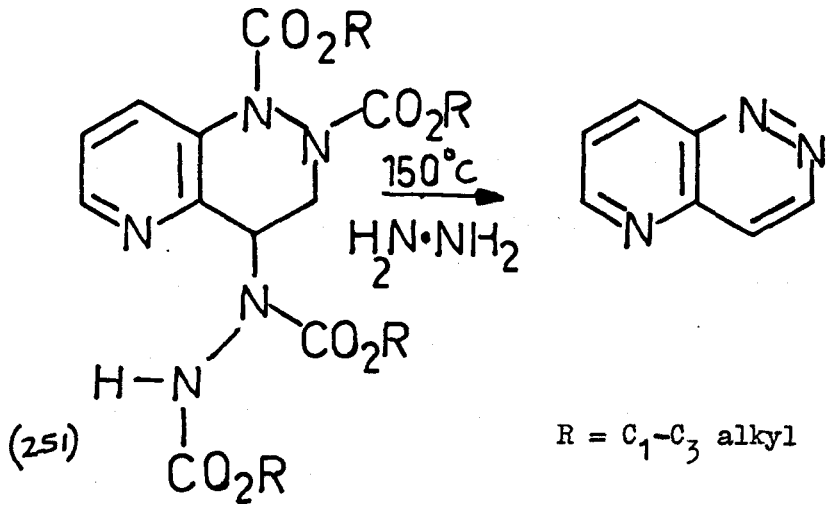
TABLE 1

Solvent	Yield of adduct	Reaction time
Benzene	13.0%	26 hrs
Acetonitrile	18.2%	6½ hrs
Chloroform	18.0%	19 hrs
Ethyl alcohol	6.0%	3½ hrs

Acetonitrile was subsequently used as the reaction solvent during the reaction of diethyl azodicarboxylate and vinyl heterocyclic compounds.

If one uses higher molar ratios of 2-vinyl pyridine to diethyl azodicarboxylate in the reaction, exactly the same amount of the required product, the tetrahydro-5-azacinnoline (248) was obtained in each case. Using higher molar ratios of diethyl azodicarboxylate to 2-vinyl pyridine gave very long reaction times. Since the azo esters are relatively expensive it was thought best to use 1 : 1 molar ratios of reactants and base the yield of the adduct obtained on unrecovered 2-vinyl pyridine.

After the completion of this work Kost et al. have published,[73] in a patent, a similar synthesis to the one described. The abstract of the paper says that the 1,2-dialkoxycarbonyl-tetrahydro pyrido[3,2-c] pyridazines (248) were obtained by cyclising vinyl pyridine with dialkyl azodicarboxylates (R = C1 - C3, alkyl) in a 2-4 : 1 ratio by heating between 50 - 150°C in an organic solvent (e.g. Benzene), and the products isolated by an adsorption method. No yields were given. A later abstract[74] reports the conversion of a diadduct (251) into the fully aromatic pyrido[3,2-c]pyridazine (87) by heating the diadduct (251) at 50 - 150°C with hydrazine hydrate or 20% NaOH or 3% HCl; again no yields were given.



Since the yield of the aromatic pyrido[3,2-c]pyridazine (87) was very poor, it was decided to try to prepare the t-butyl ester analogue of the cycloadduct (248), which ought to undergo facile cleavage using trifluoroacetic acid (T.F.A.)

It was found that after boiling equimolar quantities of 2-vinyl pyridine (90) and di-tert-butyl azodicarboxylate (252) in benzene for eight days no di-tert-butyl azo-ester remained. (The reaction could not be followed by g.l.c. as the di-tert-butyl azodicarboxylate proved unstable in the g.l.c.) The reaction was followed by t.l.c., (observing the yellow spot with the highest R_f value, attributed to the di-tert-butyl azo-ester dienophile).

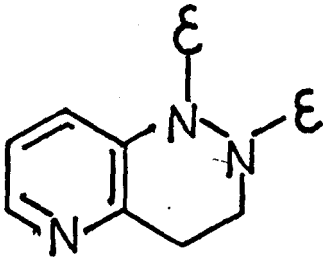
When acetonitrile was used as the solvent for the reaction, a black tar was obtained, probably due to the acidic solvent de-esterifying the cycloadduct as the reaction was in progress. Removal of acid from the solvent using a method described in D.D. Perrin, W.L.S. Armarego and D.R. Perrin, Purification of Laboratory Chemicals, Pergamon Press, p.58, 1966, and use of this 'pure solvent' in the reaction still, however, gave breakdown products. Hence benzene was used as the solvent for the reaction of di-tert-butyl azodicarboxylate (252) with vinyl heterocyclic compounds.

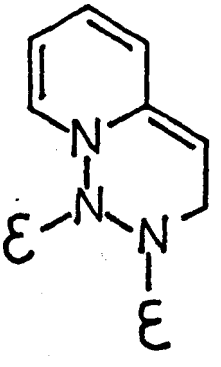
T.l.c. of the reaction products from 2-vinyl pyridine (90) and di-tert-butyl azodicarboxylate (252) showed that the viscous brown

oil contained many compounds. Using column and then preparative layer chromatography it was possible to isolate and characterise two components, isomers with empirical formula of $C_{17}H_{25}N_3O_4$ formed by combination of one molecule of 2-vinyl pyridine (90) and one of di-tert-butyl azodicarboxylate (252).

After elution of unreacted 2-vinyl pyridine (90) from the column an oil was eluted which contained two components separated by p.l.c. The major component of lowest R_f value was obtained as a clear yellow oil (23.1%) which would not crystallise. The mass spectrum gave a weak molecular ion at 330 a.m.u. due to McLafferty rearrangement of t-butyl esters, which leads to the expulsion of isobutylene. A ^1H n.m.r. spectrum (Fig. 9) leaves no doubt that this compound has structure (253).

(253)





(254)

$\mathcal{E}$ = CO_2t-bu

The other minor component was also obtained (2.7%) as a clear yellow oil. A weak molecular ion at 330 a.m.u. was observed in the mass spectrum. The ^1H n.m.r. spectrum (Fig. 10) left no doubt that this compound is the 3H-pyrido[1,2-c]-1,2,3-triazine di-tert-butyl ester (254).

The remainder of the reaction products again were not characterised.

Fig. 9 ^{1}H N.m.r. spectrum of 1,2-di-tert-butoxycarbonyl-1,2,3,4-tetrahydropyrido[3,2-c]pyridazine (253)

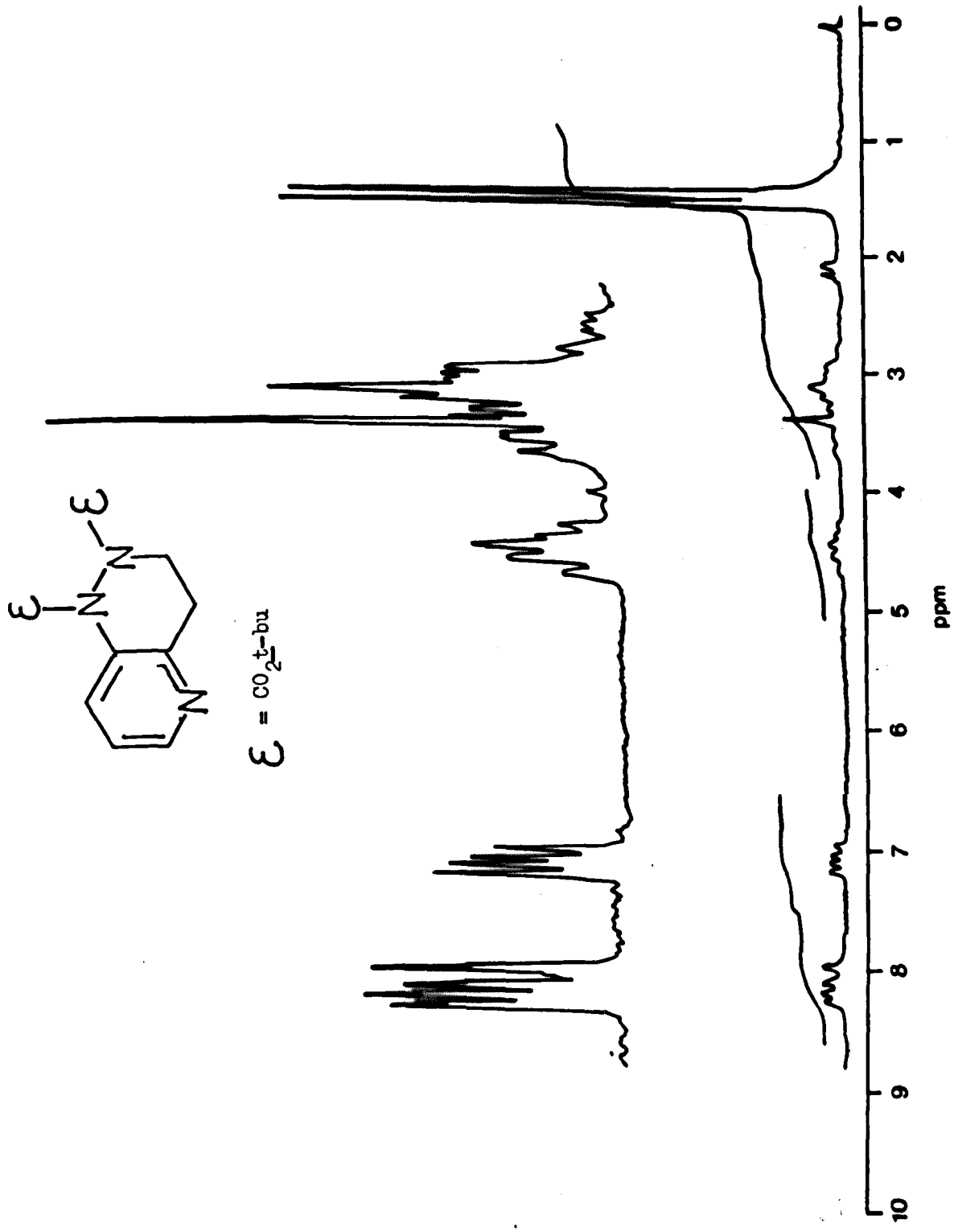
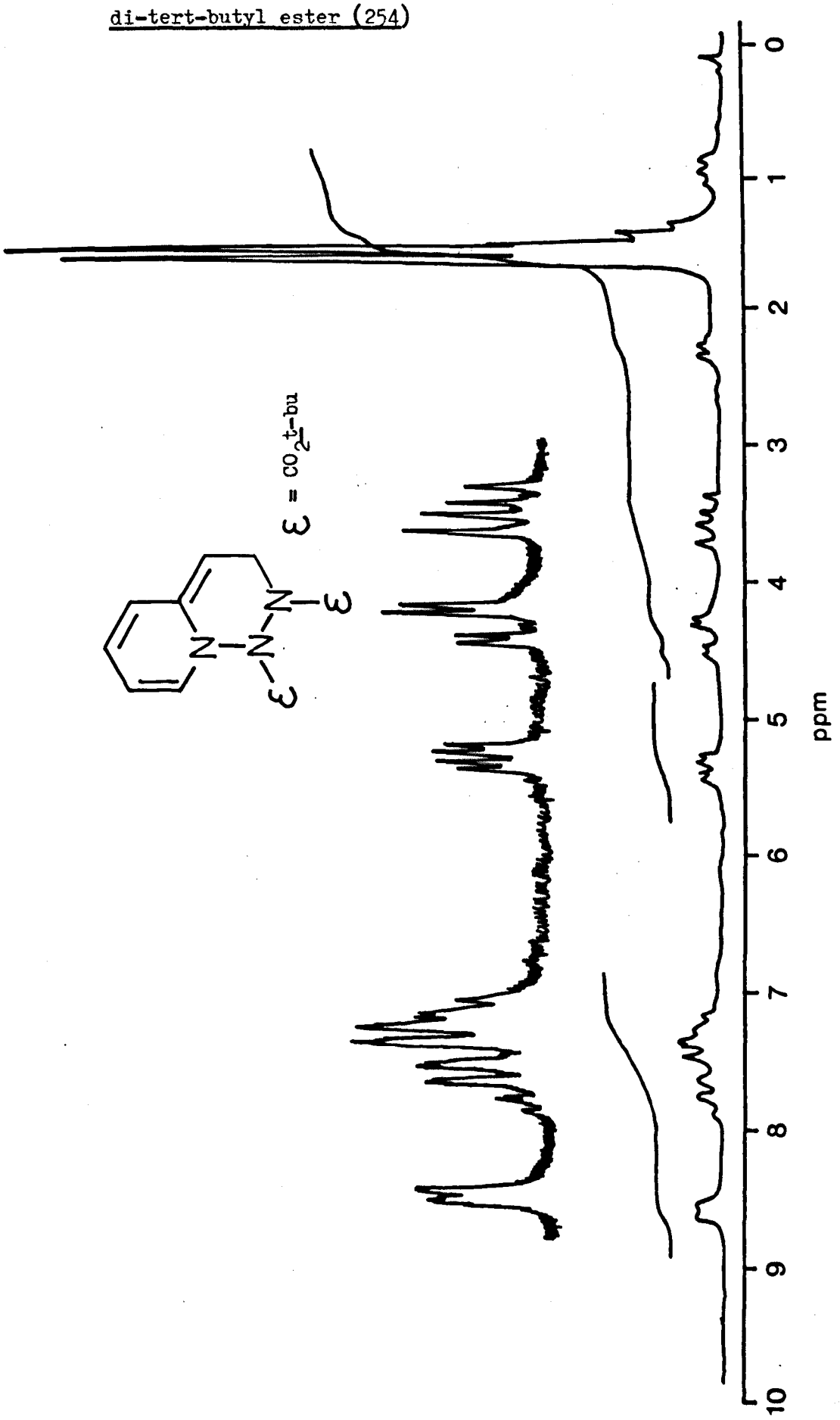


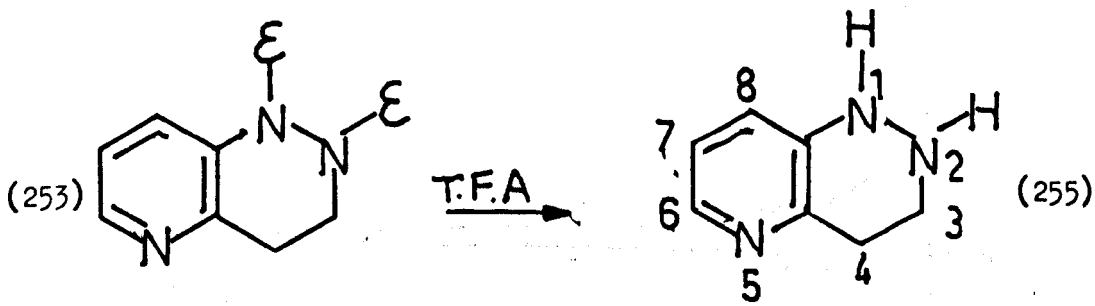
Fig. 10 ^{1}H N.m.r. spectrum of 3H-pyrido [1,2-c]-1,2,3-triazine di-tert-butyl ester (254)



As was expected removal of the t-butyl ester groups from the pyrido[3,2-c]pyridazine di-tert-butyl ester (253) proved to be easy. Treatment with T.F.A. at room temperature gave after work-up the 1,2,3,4-tetrahydro pyrido[3,2-c]pyridazine (255) in virtually quantitative yield.

This hydrazo compound (255) was unstable. It did not prove possible to obtain correct analysis figures for the compound; the carbon and hydrogen values were correct but the nitrogen value was always very low.

The tetrahydropyrido[3,2-c]pyridazine (255) was obtained as a yellow oil, but if when removing solvent from the product using a rotavapour, the flask is not removed immediately the solvent has evaporated, the oil turns to a purple/white solid/oil, whose colour is reminiscent of the colour changes seen on removal of the ethyl ester groups from the adduct.

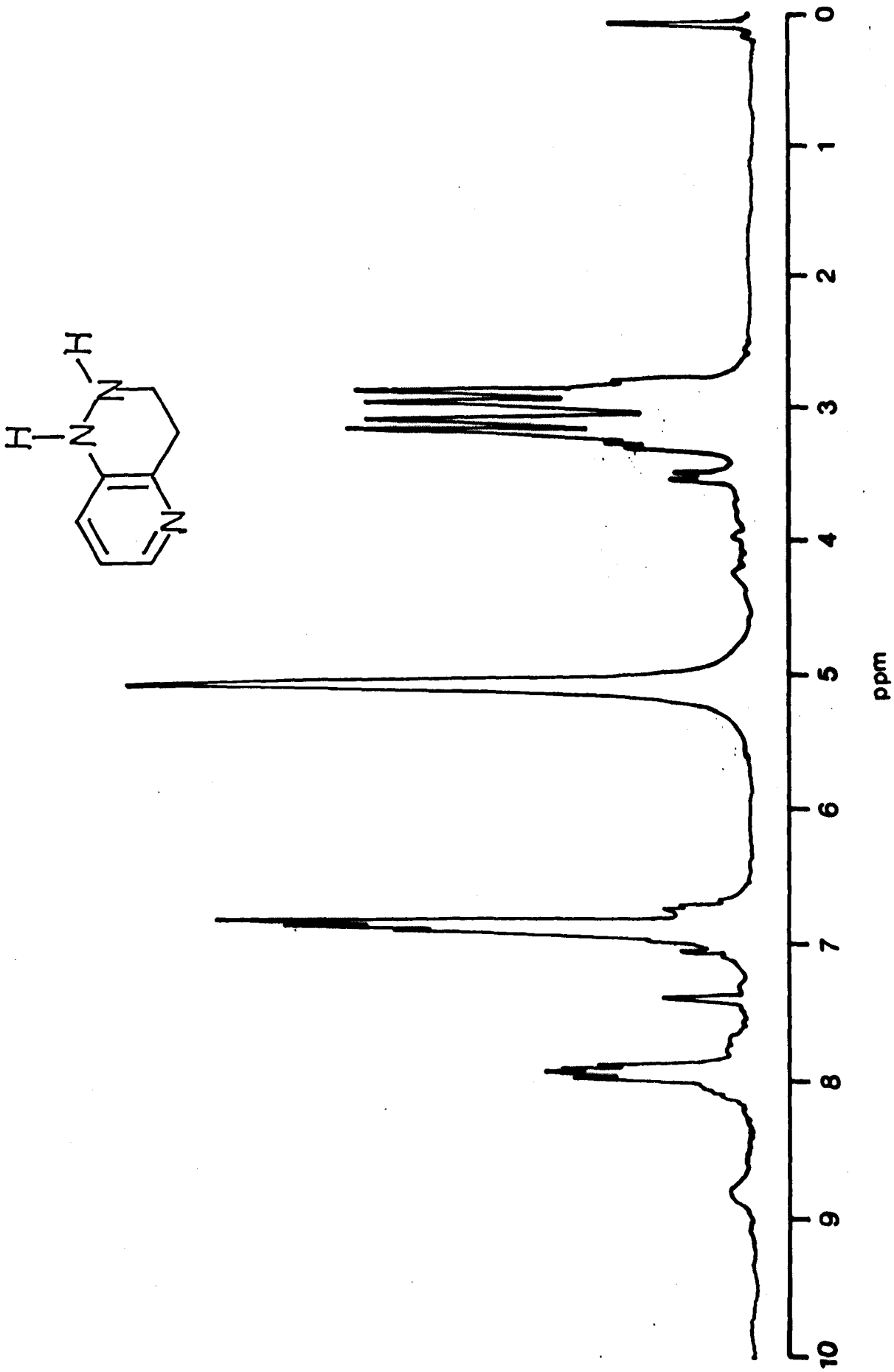


$\mathcal{E}$ = CO_2t-bu

Proof of the structure of the hydrazo compound (255)comes from mass and ^{1}H n.m.r. spectra. An M^+ = 135 a.m.u. was observed in the mass spectrum. The ^{1}H n.m.r. spectrum (Fig. 11) contained three downfield aromatic protons, two N-H protons exchangeable with D_2O and four protons upfield which were strongly coupled.

The protons H-6-8 form an A.B.X. system, the furthest downfield signal is at δ = 7.9 p.p.m. and is attributed to H-7. It

Fig. 11 ^{1}H N.m.r. spectrum of 1,2,3,4-tetrahydropyrido[3,2-c]-pyridazine (255)



integrates for one proton and is observed as four lines of approximately equal intensity. It is coupled to H-6 and H-8 with coupling constants of 3 and 4 Hz respectively. The mesomeric effect of the pyridazine nitrogen causes H-6 and 8 to have the same chemical shift and occur at higher field, δ = 6.85 p.p.m. than H-7. The signals are observed as a broad signal, in which it is just possible to make out eight lines. This gives a total of twelve lines for the H-6,7 and 8 resonances which is the usual number observed in an A.B.X. system.

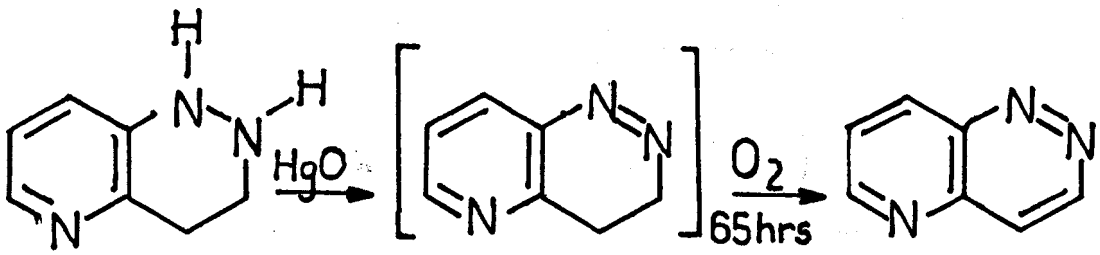
The two N-H protons were seen as a broad singlet at δ = 5.05 p.p.m., they disappear on shaking with D_2O. The two adjacent methylene groups at C-3 and C-4 are strongly coupled and resonate between δ = 2.6 and 3.6 p.p.m.

The tetrahydropyrido[3,2-c]pyridazine (255) was slowly oxidised by the air to the fully aromatic pyrido[3,2-c]pyridazine (87) plus some black material. Bubbling oxygen through a chloroform solution of the hydrazo compound (92 hours) increased its rate of conversion, but the reaction was still not very clean. A purple/black solid was formed during the oxidation which was insoluble in chloroform, but soluble in methanol or ethanol. This method gave an overall yield of 8% for the conversion of 2-vinyl pyridine (90) to the pyrido[3,2-c]pyridazine (87).

The best method found to date for dehydrogenation of the hydrazo compound (255) uses a two-stage procedure; first using mercuric oxide (red) to oxidise the NH-NH functional group to give the 'azo compound' (256) then oxidation of this 'azo compound' (256) by bubbling oxygen through a chloroform solution.

The intermediate azo compound (256) was slowly oxidised by the air to the parent pyrido[3,2-c]pyridazine (87) and could not be characterised. An ^1H n.m.r. spectrum of the oily intermediate showed

the absence of N-H protons. The spectrum was very complex and complete identification of all peaks was not possible; but absorptions which could be attributed to the pyrido[3,2-c]pyridazine (87) system were present.



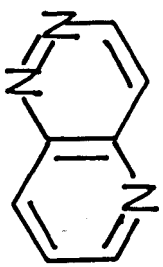
(255) (256) (87)

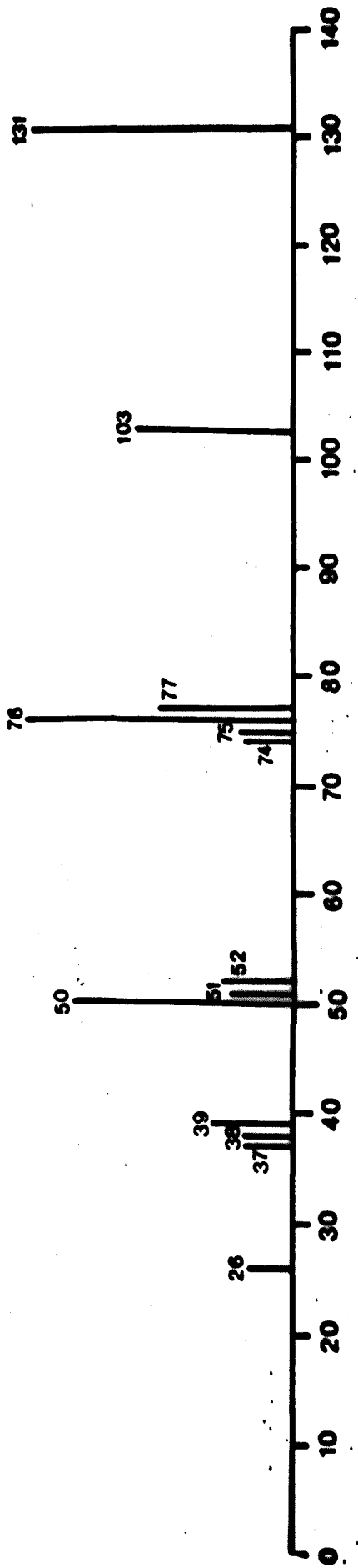
This procedure gave a cleaner conversion, though some chloroform insoluble material was still formed, and a shortened oxidation time of 65 hours in the second stage. An overall yield of 9.7% of pyrido[3,2-c]pyridazine (87) from 2-vinyl pyridine (90) was observed.

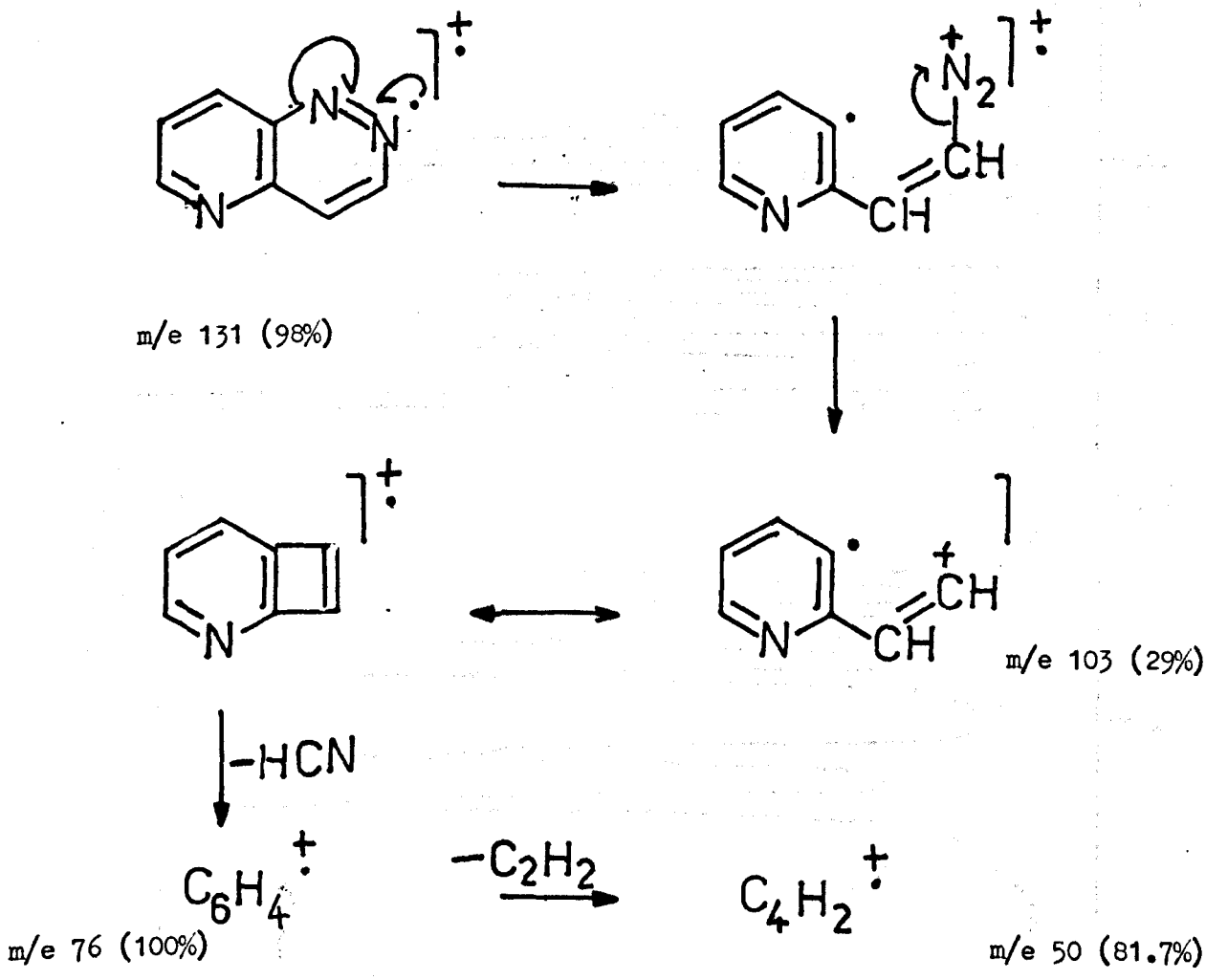
The parent pyrido[3,2-c]pyridazine (87) could be purified by recrystallisation from cyclohexane, m.pt. 89 - 91°C. Microanalysis confirmed its empirical formula to be $C_7H_5N_3$.

The fully aromatic pyrido[3,2-c]pyridazine (87) is a π-deficient heterocycle. The mass spectrum (Fig. 12) shows an M^+ = 131 a.m.u. and a base peak at 76 a.m.u. The following scheme is suggested for the breakdown pattern of the 5-azacinnoline (87).

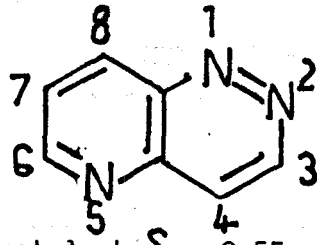
Fig. 12 Mass spectrum of pyrido[3,2-d]pyridazine (87)







The ^1H n.m.r. spectrum (Fig. 13) showed H-3 as the furthest



downfield proton situated at δ = 9.55 p.p.m. It resonates as a doublet, being coupled to H-4 with a coupling constant of 6 Hz. H-4 resonates as a pair of doublets centred at δ = 8.15 p.p.m., coupled to H-3, $J_{3,4}$ = 6 Hz, and also weakly coupled across the ring to H-8 with

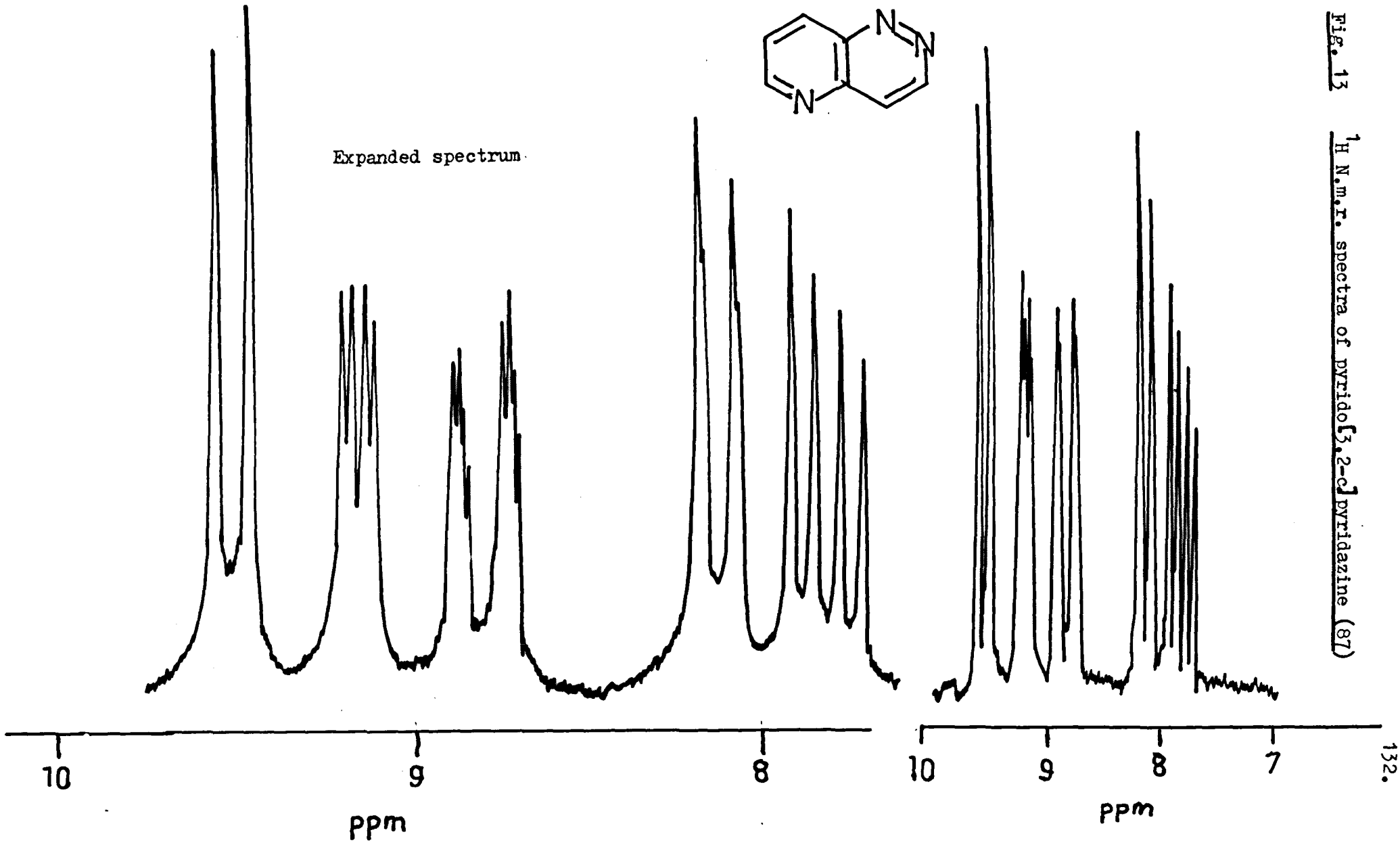


Fig. 13 ^{1}H N.m.r. spectra of pyrido[3,2-c]pyridazine (87)

a small long range coupling constant of approximately 1 Hz. As expected, H-6 and H-7 resonate as a pair of doublets ($J_{6,7}$ = 4, $J_{6,8}$ = 2 Hz) and as a quartet ($J_{7,8}$ = 5, $J_{6,7}$ = 4 Hz) at δ = 9.2 and 7.8 p.p.m. respectively. The complex signal centred at δ = 8.85 p.p.m. is attributed to H-8, it is just possible to pick out eight lines in the expanded spectrum. It shows ortho coupling to H-7 of 5 Hz, meta coupling to H-6 of 4 Hz and also shows the long range coupling of 1 Hz to H-4.

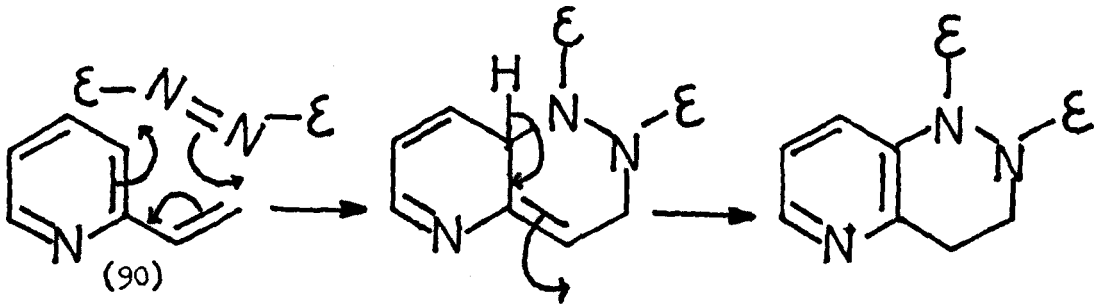
Kost and co-workers have published[74] some physical data of this 5-azacinnoline system (87). They record the same m.pt. as ourselves, the ^{1}H n.m.r. spectrum shows the same chemical shift ordering and the fragmentation pattern obtained in the mass spectrum is similar. The differences are in the recorded data for u.v. spectrum. We found λ_{max} (EtOH 95%) 263 ($\log_{10}\varepsilon$ 3.59), 306 ($\log_{10}\varepsilon$ 3.62), and 318 nm ($\log_{10}\varepsilon$ 3.65). The Russians record λ_{max} (alcohol) 262 ($\log_{10}\varepsilon$ 3.59), 271 ($\log_{10}\varepsilon$ 3.51), 304 ($\log_{10}\varepsilon$ 3.60), 316 ($\log_{10}\varepsilon$ 3.61), and 370 nm ($\log_{10}\varepsilon$ 2.06).

Use of dichlorodicyanoquinone to effect the dehydrogenation of the tetrahydropyrido[3,2-c]pyridazine (255) does not give as clean a conversion to the aromatic 5-azacinnoline (87) and a corresponding decrease in yield was observed.

Thus it is possible to prepare the pyrido[3,2-c]pyridazine system (87) from 2-vinyl pyridine (90) in 9.7% overall yield. The initial formation of the dialkoxy carbonyltetrahydropyrido[3,2-c] pyridazines (248) and (253) may go via a concerted or stepwise mechanism. The next section of this thesis will deal with the experiments carried out to investigate the mechanism of formation of the cycloadducts.

(iii) Mechanism of formation of the cycloadducts.

A complete mechanistic study was not attempted since complete product identification was not possible. We believe however that the initial cycloaddition between 2-vinyl pyridine (90) and diesters of azodicarboxylic acid is concerted, aromatisation of this cycloadduct then proceeds in some stepwise manner. Generally one proves that a reaction is not concerted by carrying out the required experiments and then proposing some stepwise mechanism.



Polymerisation inhibitors (t-butylcatechol, hydroquinone) do not affect the reaction products or the reaction rate of the cycloadduct formation between 2-vinyl pyridine (90) and diethylazodicarboxylate (91). No radicals can be involved either in the cycloaddition step or the stepwise 1,3-hydrogen shift.

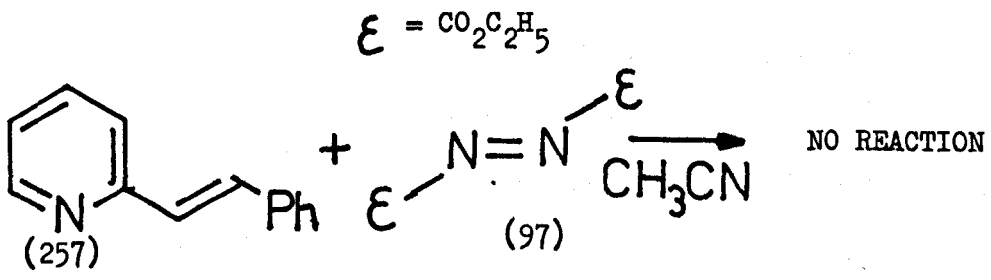
No large solvent effects were observed in the reaction of diethyl azodicarboxylate (97) and 2-vinyl pyridine (90) (see Table 1, p.121). The 'rate of the reaction' in acetonitrile, an aprotic polar solvent of high dielectric constant, was only 3-4 times faster than when the reaction was carried out in benzene, a less polar solvent. One would expect the reaction to be faster in polar solvents since both the 'diene' and the dienophile are polar substrates. Also when the two components in the cycloaddition reaction are polar then bond formation may occur at different rates and hence the transition state may have

some polar character.

No triazine compound was obtained when the reaction was carried out in acetonitrile. When ethanol is used as the solvent for the reaction, there was a decrease in the yield of the cycloadduct but the reaction time is shortened from 26 hours in benzene, to $3\frac{1}{2}$ hours.

Variation of the electronic distribution within the 'diene' system and subsequent reaction with diesters of azodicarboxylic acid can give some clues to the mechanism. One method of varying the electronic availability throughout the system was to prepare trans-2-stilbazole (257).

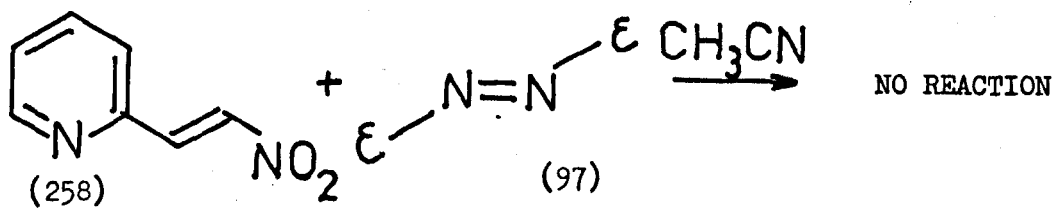
This compound was prepared in good yield by the method of Shaw and Wagstaffe[75] using α-picoline and benzaldehyde as starting materials. In boiling acetonitrile, 2-stilbazole (257) did not react with diethyl azodicarboxylate (97); the solution remained unchanged even after five days. This lack of reaction is probably due to increased conjugation of the 'olefinic double bond' of 2-stilbazole (257) by attaching the phenyl moiety. It parallels the observation that azobenzene is inert as a dienophile.



The addition of azodicarboxylic acid esters to vinyl pyridines is an example of a cycloaddition of an electron deficient dienophile to an electron deficient 'diene' system. One would expect that by attacking electron withdrawing substituents to the diene system the reaction would be even more unfavourable. A Knoevenagel condensation reaction between pyridine-2-aldehyde and nitromethane

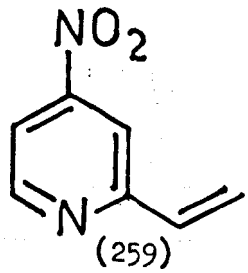
gave 2-(2-nitrovinyl) pyridine (258).[76] On boiling nitrovinyl pyridine (258) with diethyl azodicarboxylate (97) in acetonitrile, the reaction mixture remained virtually unchanged.

$\mathcal{E}$ = $CO_2C_2H_5$



In addition to the electronic effect of the nitro group it may also be that the 'negatively charged' nitro group would not favour approach of the similarly charged ester groups, and this effect could also lead to a decrease in reaction rate.

One possible method of avoiding this steric effect would be to prepare 4-nitro-2-vinyl pyridine (259).



Attempts to prepare the vinyl compound (259) by condensation of 4-nitro-α-picoline with acetaldehyde failed. The 4-nitro-α-picoline was prepared by standard methods from α-picoline via the N-oxide.[77,78,79,80]

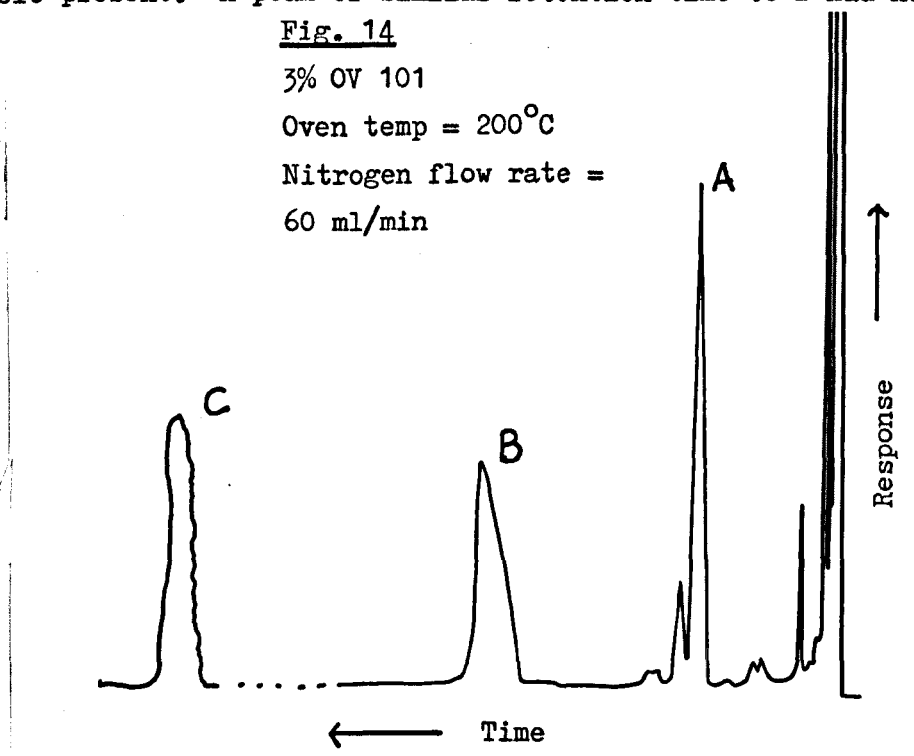
As a further example 2-(1-propen-1-yl) pyridine (260) and 2-(1-propen-2-yl) pyridine (261) were prepared.

The procedure used to prepare 2-(1-propen-1-yl) pyridine (260) was: inverse addition of ethyl magnesium iodide to pyridine-2-aldehyde using a method described by Suzuki,[81] followed by dehydration of the alcohol using concentrated sulphuric acid.[82] 2-(1-Propen-1-yl) pyridine (260) may also be prepared in very poor yield by a method

which involved condensation of α-picoline with chloral followed by reduction of the trichloro-alcohol formed.[83,84]

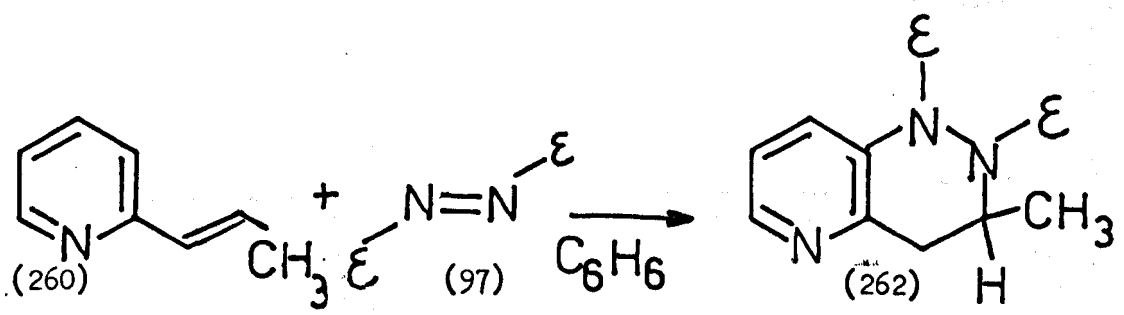
Reaction of 2-(1-propen-1-yl) pyridine (260) with diethyl azodicarboxylate (87) took longer than the corresponding reaction with 2-vinyl pyridine (90) (36 hours in boiling benzene).

A g.l.c. trace (Fig. 14) of the reaction mixture showed three major components A, B and C, although some smaller components were present. A peak of similar retention time to B had not been



seen among the products from 2-vinyl pyridine (90).

Column chromatography was used to separate the components. After initial elution of 2-(1-propen-1-yl) pyridine (260) from the column an oil was eluted from the column which contained one major component and several minor ones. After separation of the components by preparative layer chromatography the major band was extracted $R_f = 0.34$ and an oil was obtained whose spectral data left no doubt that it was 1,2-di(ethoxycarbonyl)-3-methyl-1,2,3,4-tetrahydropyrido [3,2-c]pyridazine (262).



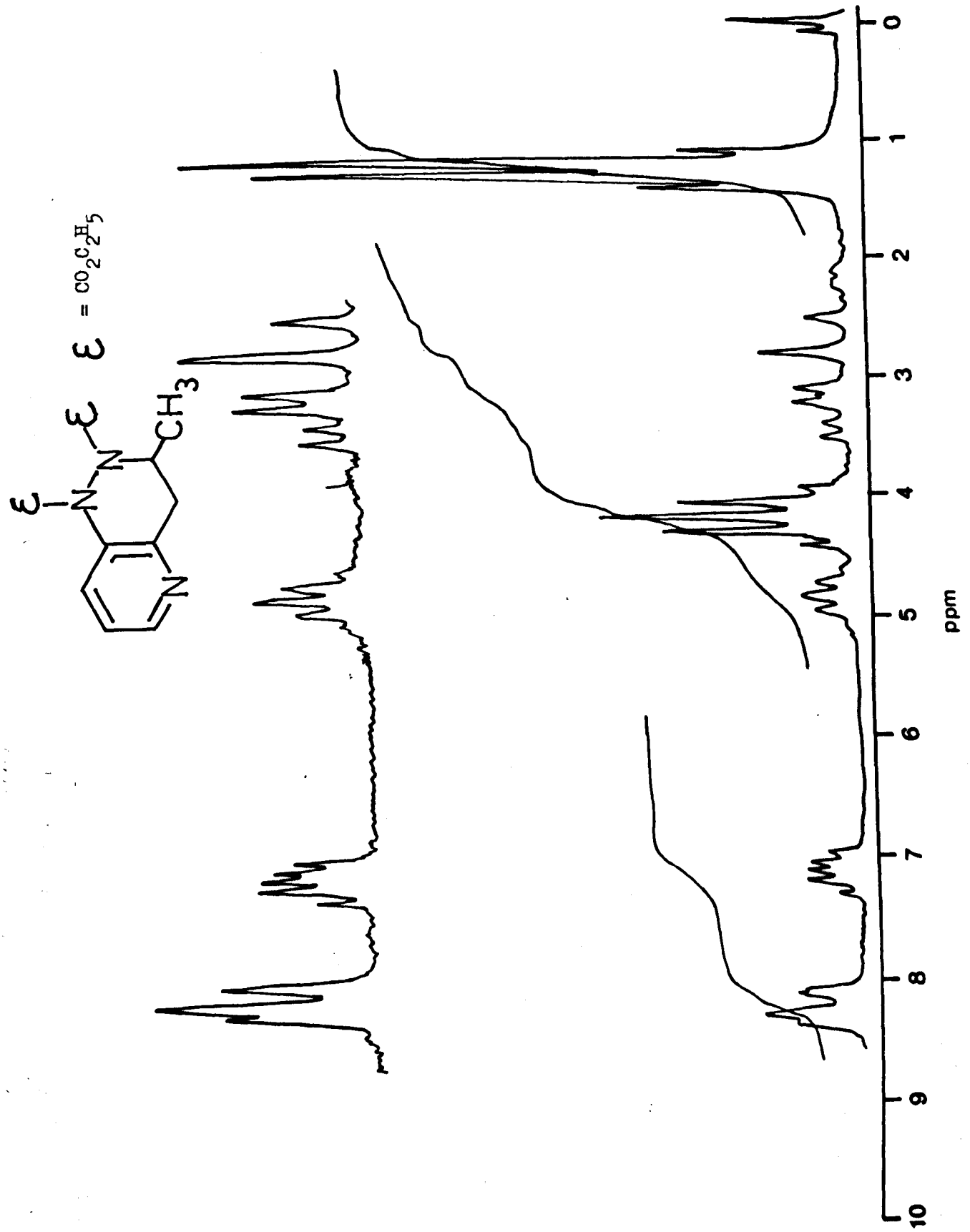
$\mathcal{E}$ = $CO_2C_2H_5$

This peak had the same retention time as peak A in the g.l.c. trace of the reaction products. Microanalysis after bulb distillation confirmed its empirical formula to be $C_{14}H_{19}N_3O_4$. Its mass spectrum contained an M^+ at 293 a.m.u. and a base peak at 148 a.m.u. Its ^1H n.m.r. spectrum (Fig. 14) was similar to that of the ethyl adduct (248) derived from 2-vinyl pyridine (90), except for the difference caused by the 3-methyl substituent. The absorption of the C-3 methyl substituent was located under the absorptions due to the two methyl groups on the ester substituents. This was confirmed by irradiating over this position (δ = 1.4 p.p.m.), the coupling of the C-3 methyl group to the C-3 methine proton were erased and the C-3 proton was observed as the expected pair of doublets at δ = 4.9 p.p.m.

This 3-methyl pyrido[3,2-c]pyridazine diester (263) was obtained in 7.6% yield (the yield was based on unrecovered 2-(1-propen-1-yl) pyridine (260)). This was less than the yield of the parent adduct (248) formed from 2-vinyl pyridine (formed in 13% yield when the reaction was carried out in benzene). This decrease was probably due to hindrance by the methyl group of attachment of the dienophile to the 'diene'.

None of the other minor components on the p.l.c. plate were identified. No triazine compound was isolated from the reaction

Fig. 14 ^{1}H N.m.r. spectrum of 1,2-diethoxycarbonyl-3-methyl-1,2,3,4-tetrahydropyrido[3,2-c]pyridazine (262)



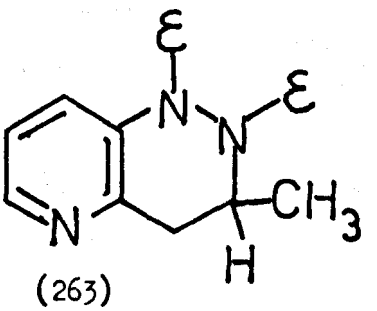
mixture, the same reason of hindrance may be used to explain this anomaly.

The remaining bulk of the material did not yield any pure products even after extensive chromatography. Fractions obtained contained components attributed to the peaks B and C (g.l.c. trace of products).

Hydrolysis of the ethyl adduct (262) was not attempted because of the problems observed with the ethyl adduct (248) derived from 2-vinyl pyridine (90). Instead the di-tert-butyl ester was prepared by refluxing 2-(1-propen-1-yl) pyridine (260) with di-tert-butyl azodicarboxylate (252) in benzene. The reaction took 15 days to go to completion. A g.l.c. trace of the reaction products showed the presence of one major and several minor components; t.l.c. showed a complex mixture to be present.

After the usual chromatographic work up (column and preparative layer) it was possible to isolate an oil (10.4%) whose spectral characteristics showed it to be the di-tert-butyl cyclo-adduct (263).

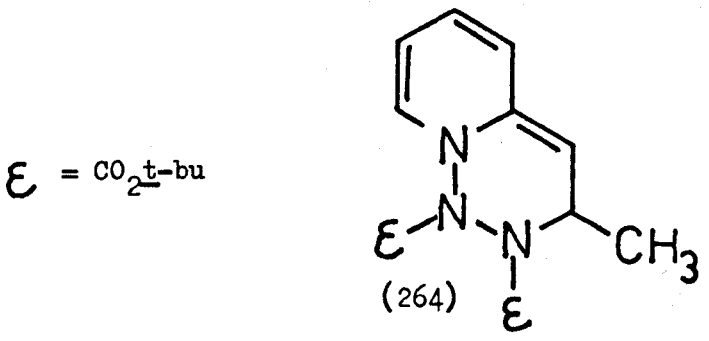
$\mathcal{E}$ = CO_2t-bu



(263)

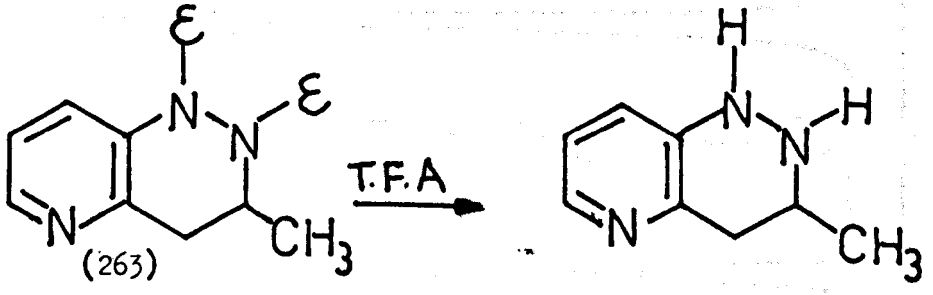
Two other components were also isolated which ran very close together on the preparative layer plate, it was not possible to obtain a pure fraction of one without contamination by the other.

The ^{1}H n.m.r. spectrum of one of the components indicated that it was the triazine compound (264) formed in very poor yield. The remainder of the material on the column was an intractable oil.



(264)

Hydrolysis of the di-tert-butyloxycarbonyl-3-methyl-tetrahydropyrido[3,2-c]pyridazine (263) was easily carried out in virtually quantitative yield, using T.F.A. to give the 3-methyl-1,2,3,4-tetrahydropyrido[3,2-c]pyridazine (265), identified by its ^{1}H n.m.r. (Fig. 15) and mass spectra.



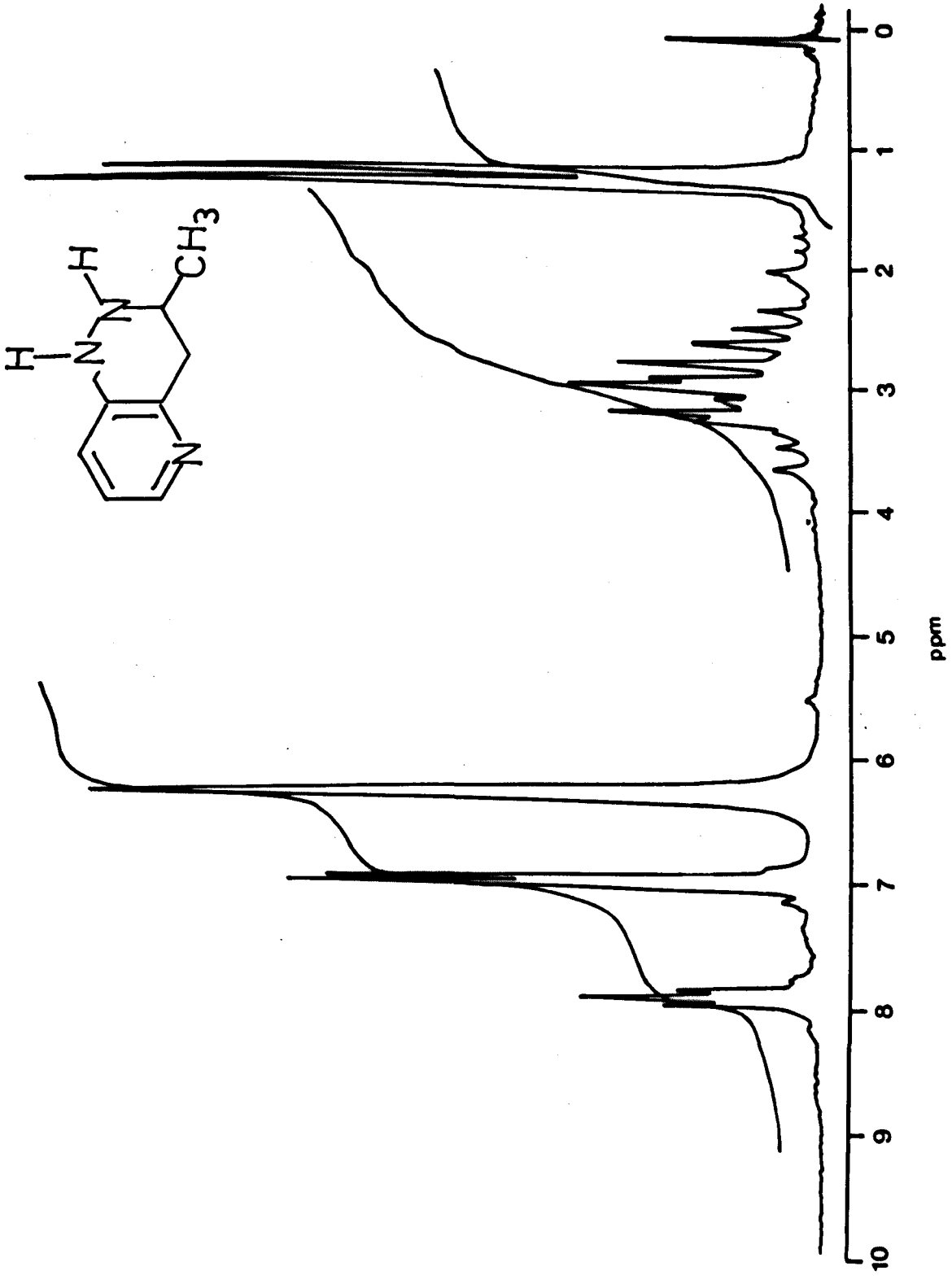
(263)

ε = CO_2t-bu

(265)

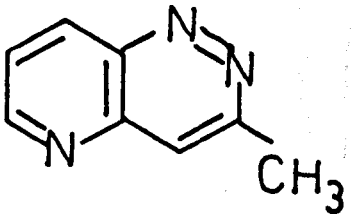
This tetrahydropyrido[3,2-c]pyridazine compound (265) proved unstable. Oxidation first by mercuric oxide then by oxygen (26 hours) afforded the fully aromatic 3-methylpyrido[3,2-c]pyridazine (266). A brown solid was formed during the oxidation by oxygen, which was insoluble in chloroform but soluble in methanol or ethanol. The 3-methyl-5-azacinnoline (266) was obtained as yellow needles,

Fig. 15 ^{1}H N.m.r. spectrum of 3-methyl-1,2,3,4-tetrahydropyrido-[3,2-c]pyridazine (265)



m.pt. 99 - 101°C in 38.7% yield, giving an overall yield of 4% from 2-(1-propen-1-yl) pyridine (260).

Spectral evidence confirmed the proposed structure (266). Microanalysis showed the empirical formula to be $C_8H_7N_3$, the mass spectrum gave the molecular ion at 145 a.m.u., which was also the base peak. The fragmentation followed a similar pattern to that of the parent compound (p.131). The ^1H n.m.r. spectrum (Fig. 16) contained four downfield protons, H's 4-8, and an upfield singlet due to three protons at δ = 2.9 p.p.m.

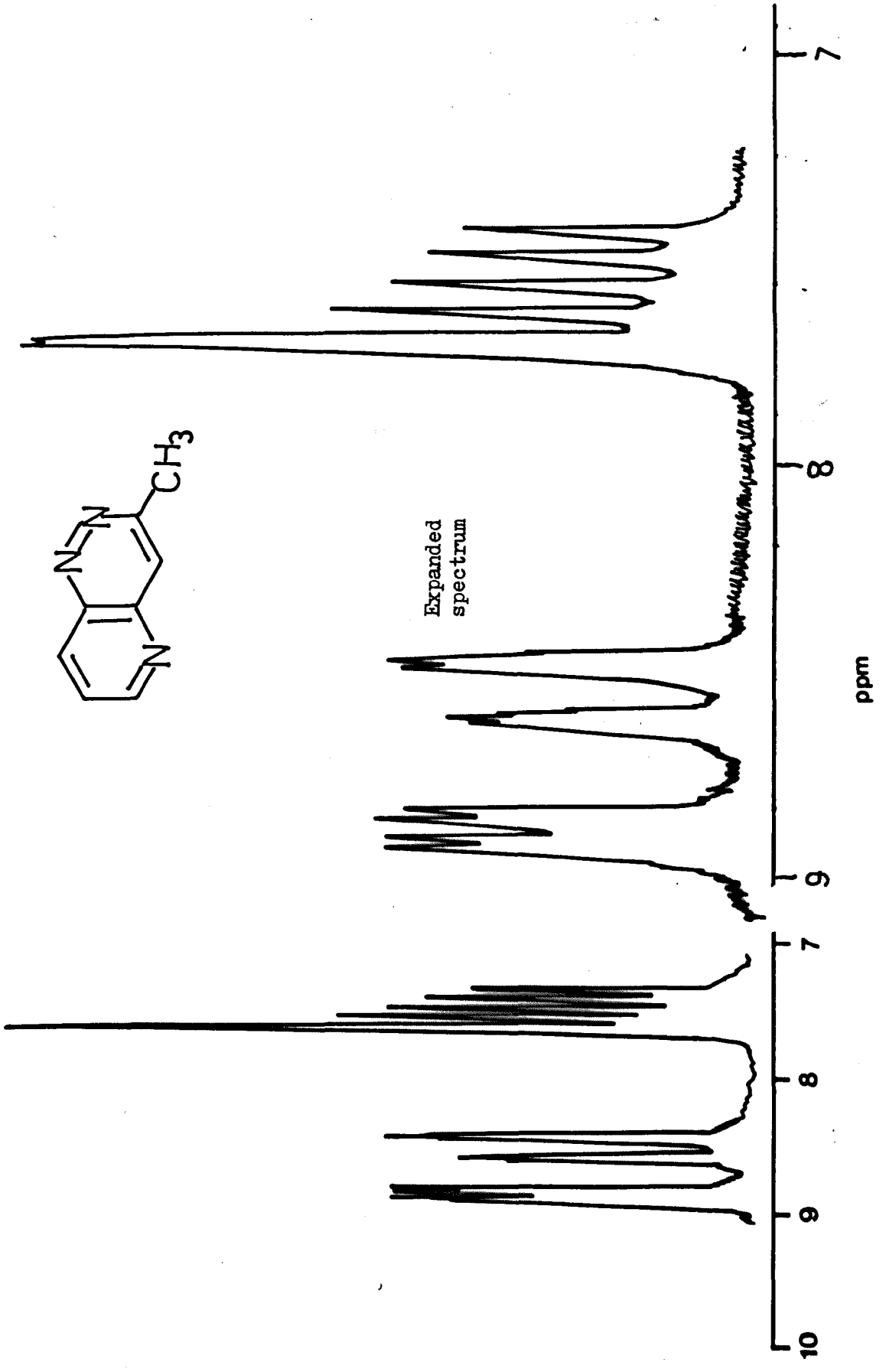
(265) $\xrightarrow[\text{ii } O_2]{\text{i } HgO}$  (266)

Reaction of 2-isopropenyl pyridine (261) with diesters of azodicarboxylic acid should not be subject to hindrance of this type.

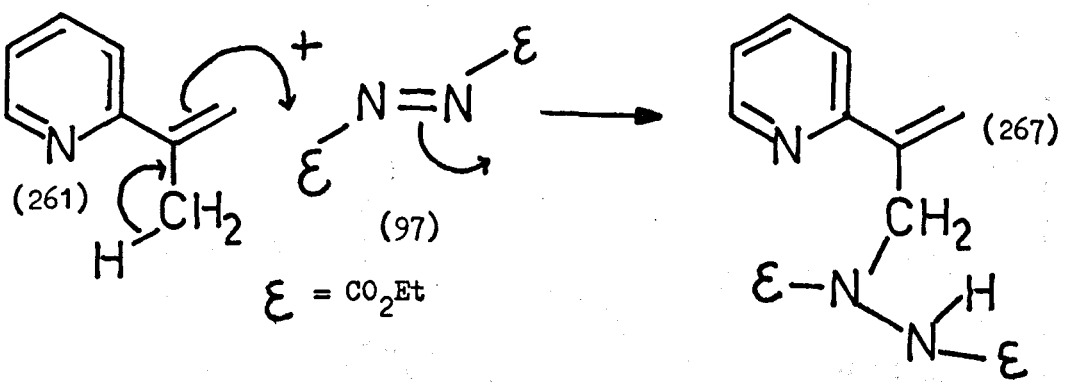
Isopropenyl pyridine (261) was prepared[85] by addition of ethyl picolinate to excess of the Grignard reagent from methyl iodide, followed by dehydration by concentrated sulphuric acid[86] of the alcohol so formed. The reaction between 2-isopropenyl pyridine (261) and diethyl azodicarboxylate (97), in boiling acetonitrile, was complete after five hours. The reaction products contained a major component plus several minor ones (t.l.c.); some unreacted 2-isopropenyl pyridine (261) was also observed.

The products were separated by column chromatography. After initial elution of 2-isopropenyl pyridine (261) (100% 40 - 60 Petrol) an oil began to be eluted from the column (25% C_6H_6, 75% 40 - 60 Petrol), which crystallised from cyclohexane. An ^1H n.m.r. spectrum (Fig. 17) showed the presence of an N-H absorption at δ = 7.95 p.p.m.,

Fig. 16 ^{1}H N.m.r. spectra of 3-methylpyrido[3,2-c]pyridazine



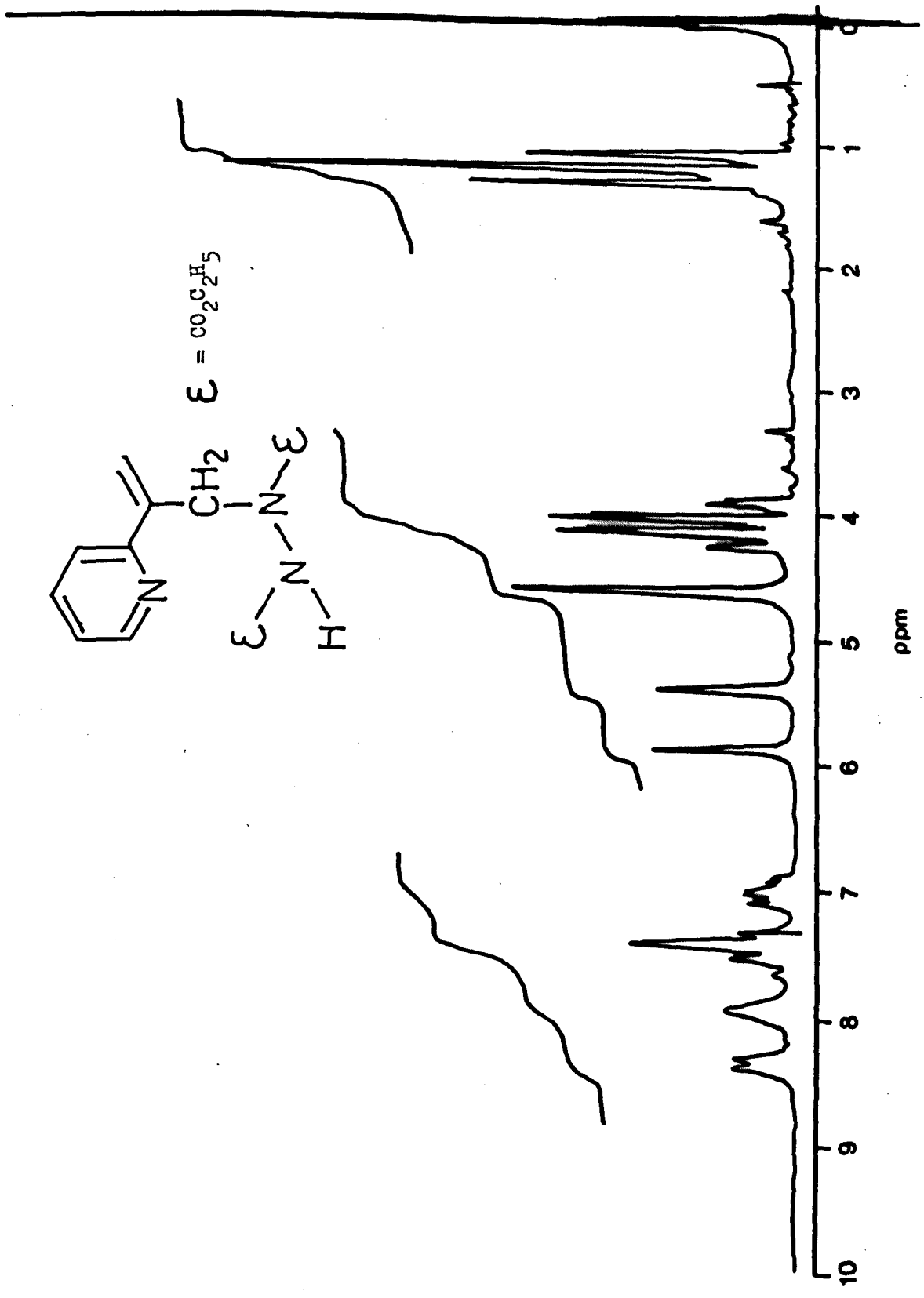
removable on shaking with D_2O, two broad one proton singlets at δ = 5.9 and 5.4 p.p.m. and a two proton singlet at δ = 4.6 p.p.m. This compound is diethyl (2-(2'-pyridyl)-prop-2-ene) hydrazodicarboxylate (267), formed by ene addition of diethyl azodicarboxylate (97) to 2-isopropenyl pyridine (261).



Microanalysis gave the molecular formula as $C_{14}H_{19}N_3O_4$; an M^+ of 293 a.m.u. also agrees well with the proposed structure. The u.v. spectrum of the ene addition product, λ_{max} ($\log_{10}\varepsilon$) 232 (3.88) and 277 nm (3.06) was almost identical with that of 2-isopropenyl pyridine (λ_{max} 209, 248 and 277 nm). Absorptions in the infrared at 3400 cm^{-1} (N-H), and 1720 cm^{-1} (- N - C - O C_2H_5) also confirmed the proposed structure.

The ene addition product may be formed by either a concerted or stepwise mechanism; no work was done to determine which of these paths was followed. Ene addition therefore takes preference over cycloaddition during the reaction between diethyl azodicarboxylate (97) and 2-isopropenyl pyridine (261). Some instances are known when ene addition and cycloaddition compete,[87,88] but no cycloaddition products were obtained from the reaction, indeed no other products were isolated. The ene addition product was eluted slowly from the column even when the polarity of the eluting solvent was increased to

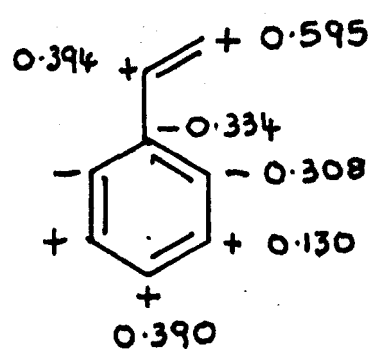
Fig. 17 ^{1}H N.m.r. spectrum of diethyl 2-(2'-pyridyl)-prop-2-ene hydrazodicarboxylate (267)



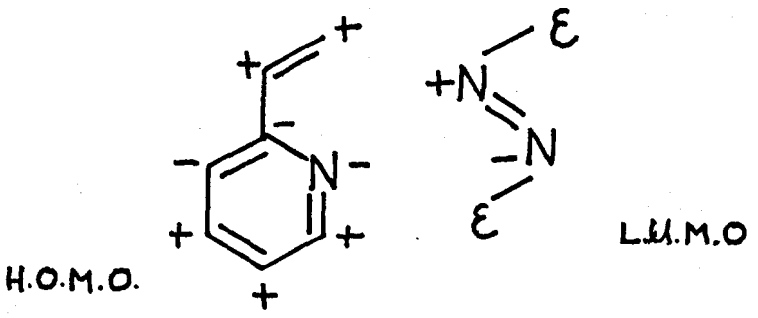
100% benzene.

Since no solvent effects were observed and no free radicals detected it is thought that the initial cycloadduct formation is a concerted process. Concerted cycloaddition involving (8 + 2) electrons is thermally allowed for suprafacial, suprafacial, (s,s), antarafacial, antarafacial (a,a) overlap of the polyene (vinyl pyridine) and the diene (azodicarboxylate diester). Antarafacial, antarafacial approach of the two substrates is stereochemically unlikely.

The highest occupied molecular orbital (HOMO) of 2-vinyl pyridine (90) is equal to that of styrene (94), except that the electron distribution at each particular atom (the c coefficients) will be slightly different because of the electronic effect of the nitrogen. The HOMO and c-values of styrene (94) are shown below.

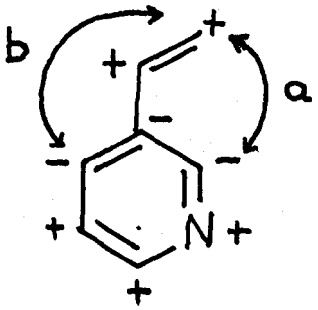


The HOMO, ψ_4, of 2-vinyl pyridine (90) and lowest vacant molecular orbital (LUMO) of the azo ester is shown below.



One can see that the symmetry of the LUMO of the azo ester is such that it may overlap with the HOMO of 2-vinyl pyridine (90), either at the nitrogen atom or at the C-3 position, the reaction is therefore favoured thermally as a concerted process, and is said to be symmetry allowed. In practice both types of cycloadduct are formed.

Isomers of vinyl pyridine may also be treated in the same way. The HOMO of 3-vinyl pyridine is shown below.

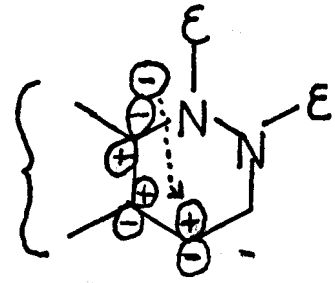


Thermal cycloaddition at the positions a and b ought to be favourable as a concerted process, and was found to occur in practice (see p.173). Similarly 4-vinyl pyridine should undergo thermal cycloaddition reactions with azodicarboxylates to give the pyrido-[3,4-c]pyridazine system (see p.162).

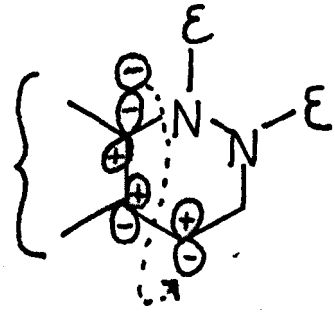
The concerted cycloaddition process to give the intermediate was then followed by aromatisation by a [1,3-H] shift to give the observed product. According to Woodward and Hoffman rules, a [1,3]-sigmatropic rearrangement involving suprafacial shift of the

hydrogen is symmetry forbidden; the process is symmetry allowed for an antarafacial shift of the hydrogen atom. Concerted antarafacial migration is unlikely to be observed since the transition state would be very strained and difficult to attain.

Suprafacial Shift

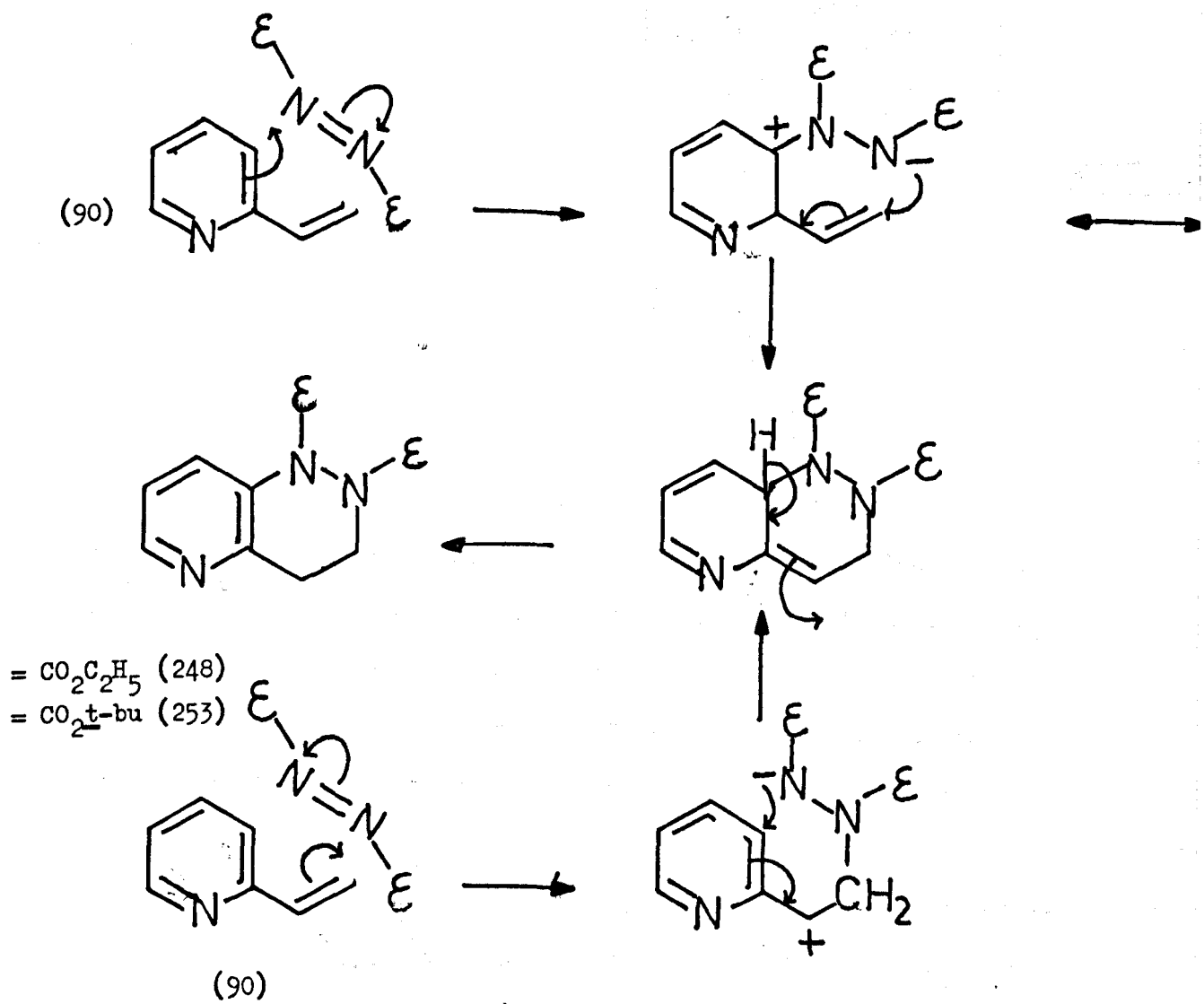


Antarafacial Shift



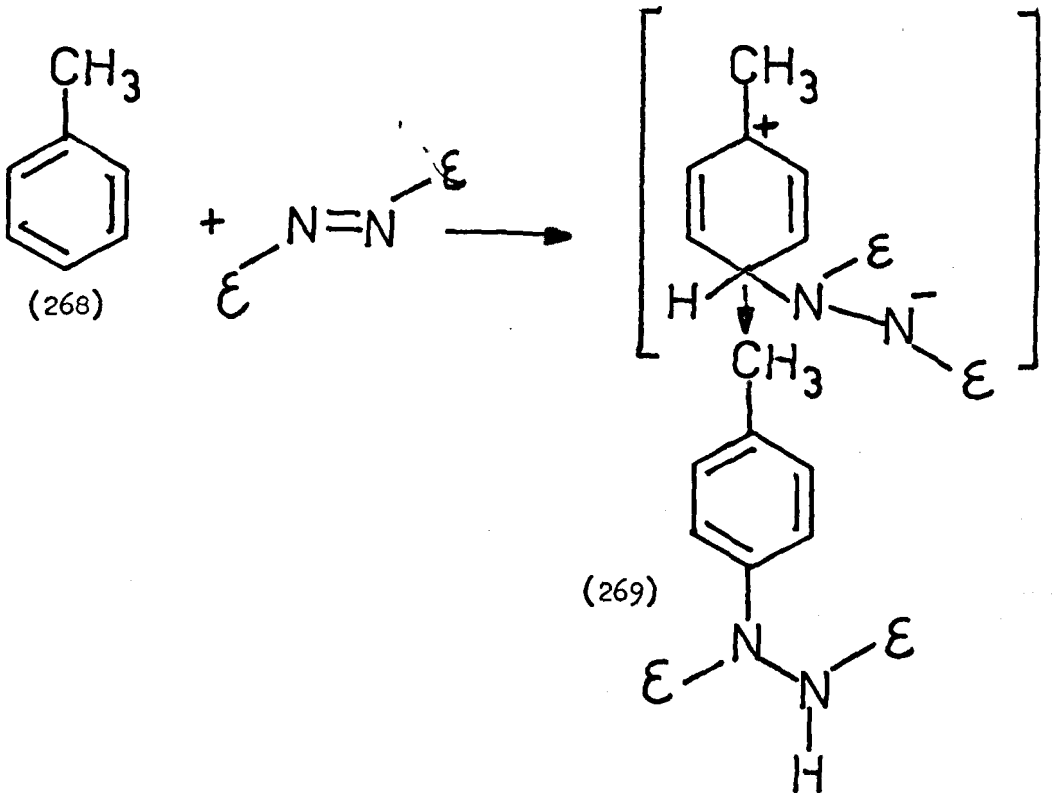
The [1,3-H] shift must go via some stepwise mechanism, the driving force being aromatisation. The process cannot involve radicals since no difference to the rate of the reaction or yield of the product was observed by carrying out the reaction in the presence or absence of radical inhibitors. G. Ahlgren, B. Akermark and co-workers[31] proposed a radical ene addition of diethyl azodicarboxylate to the initial cycloadduct formed between the azo ester and styrene (see Introduction to Part 2 of this thesis, p. 66).

One may write a stepwise electrophilic substitution reaction to the 1,2-dialkoxycarbonytetrahydropyrido[3,2-c] pyridazine (248) or (253), but these mechanisms would be high



energy processes and require forcing conditions. The rate of such reactions would be greatly affected by polarity of solvent.

It is known that α,α^1-dicarbonyl azo compounds undergo electrophilic addition with aromatic compounds to yield the hydrazine-dicarboxylic acid (269) derivative,[89] e.g. with toluene (268).



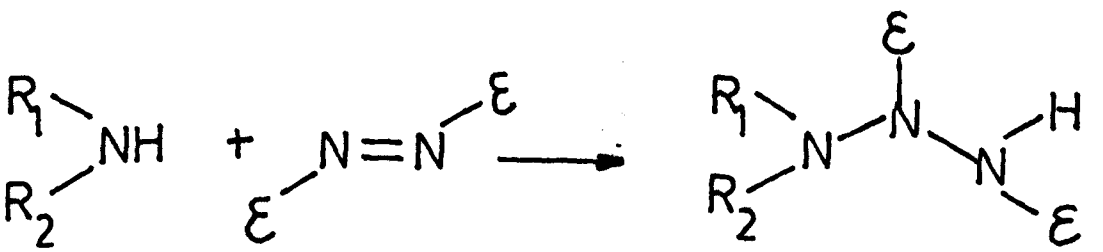
(268)

(269)

Depending on the aromatic system, the reaction sometimes takes place when the reactants were warmed in an inert solvent, but it generally requires the addition of catalytic quantities of acid.

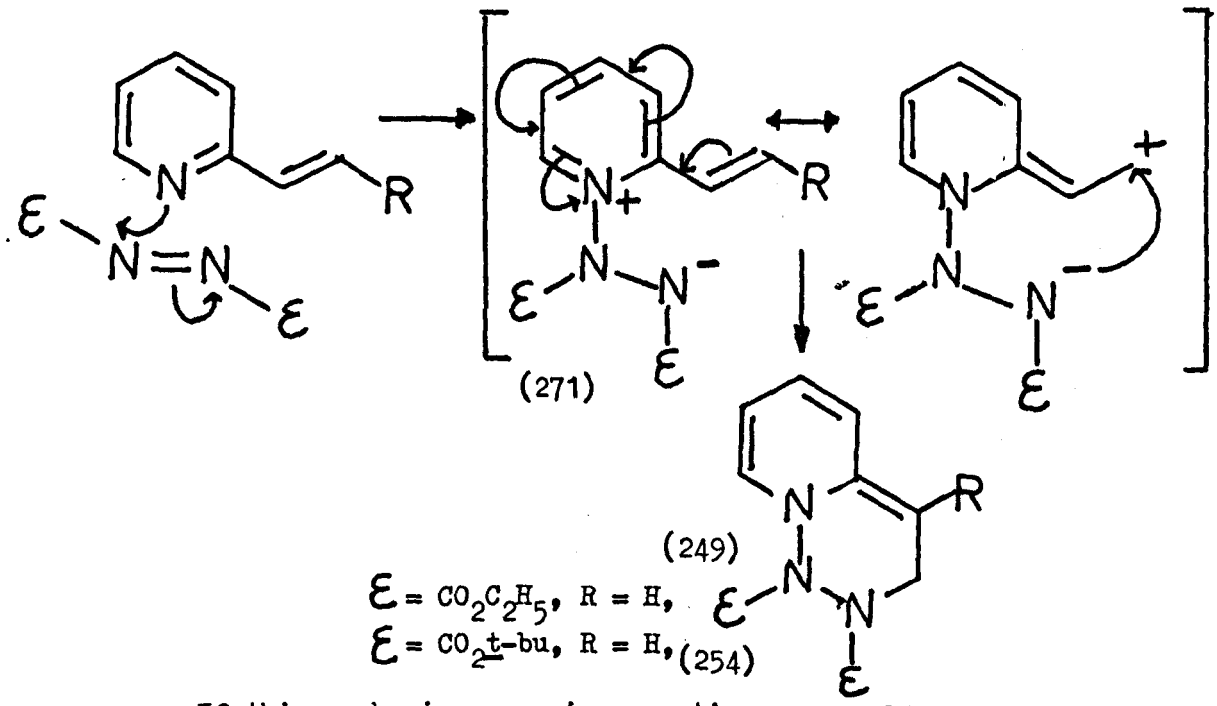
If this electrophilic addition mechanism were in operation, isolation of some intermediates ought to have been possible. The fact that no intermediates were isolated helps to discount this mechanism.

It is possible to write a stepwise mechanism for the formation of the pyrido[1,2-c]triazine diester (249) and (254); based on addition of azodicarboxylates to secondary aliphatic amines (270).



(270)

Electrophilic addition of the pyridine nitrogen to the azo ester to form the zwitterion (271) which may be stabilized by electron delocalisation. Ring closure by intramolecular nucleophilic attack gives the triazine, (249) or (254).



$\mathcal{E}$ = $CO_2C_2H_5$, R = H,
$\mathcal{E}$ = CO_2t-bu, R = H,

If this mechanism were in operation one would expect electron donating groups, such as a methyl substituent, to stabilize the zwitterion (271) and hence promote its formation. Polar solvent should favour the reaction.

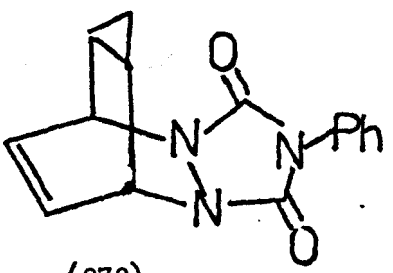
Reaction of 2-(1-propen-2-yl)pyridine (260) with diesters of azodicarboxylate gave no isolable triazine derivatives. In acetonitrile the reaction gave no triazine.

The concerted mechanism is preferred for the formation of the triazine compounds (249) and (254).

(iv) Reaction of 2-vinyl pyridine (90) with 4-phenyl-1,2,4-triazoline-3,5-dione (101).

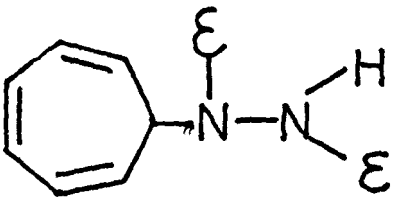
The last variation of the synthesis was in the structure of the dienophile. The title compound, 4-phenyl-1,2,4-triazoline-3,5-dione (101), contains a cis-azo-linkage, and has been shown to be a very potent dienophile. Previous work has shown that it possesses considerable advantages over diethyl trans-azodicarboxylate (97) in the rate of addition and hence suppression of unwanted side reactions of the additive substitution type.[33]

The enhancement of dienophilic relative to allylic reactivity was illustrated[33] by formation of the Diels-Alder adduct (272) from cycloheptatriene, rather than the product of additive substitution (ene reaction) (273) which is formed with diethyl azodicarboxylate (97).



(272)

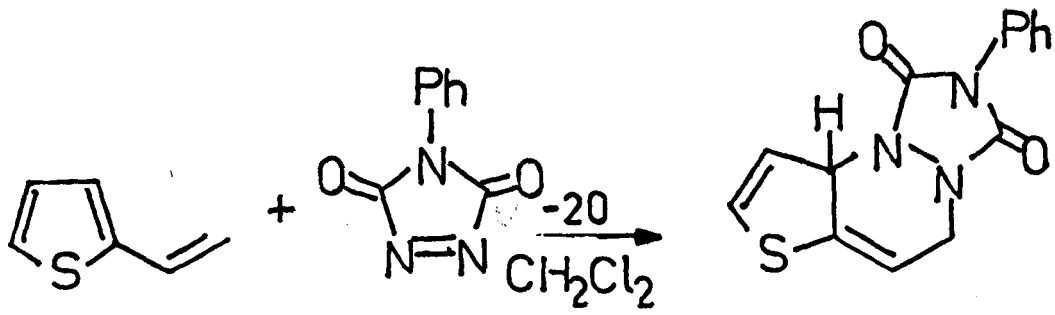
$\mathcal{E} = CO_2C_2H_5$



(273)

Similarly styrene (94) forms the Diels-Alder bis-adduct (102) with the triazoline dione (101) whilst the product (96) with the azoester results from a Diels-Alder reaction followed by additive substitution (see p.65).

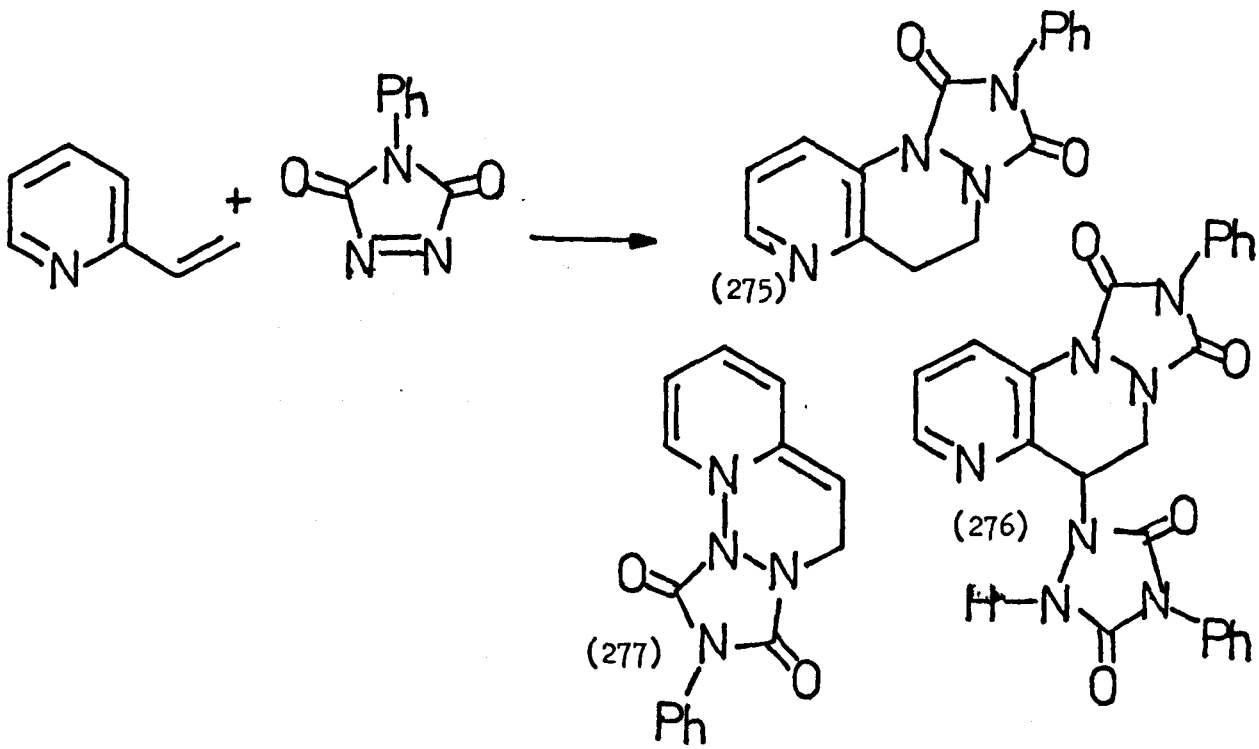
It has also been shown that 2-vinylthiophen (142) underwent reaction with the triazolinedione (101) to give the cycloadduct (274) without further ene reaction.[90]



(142) (101) (274)

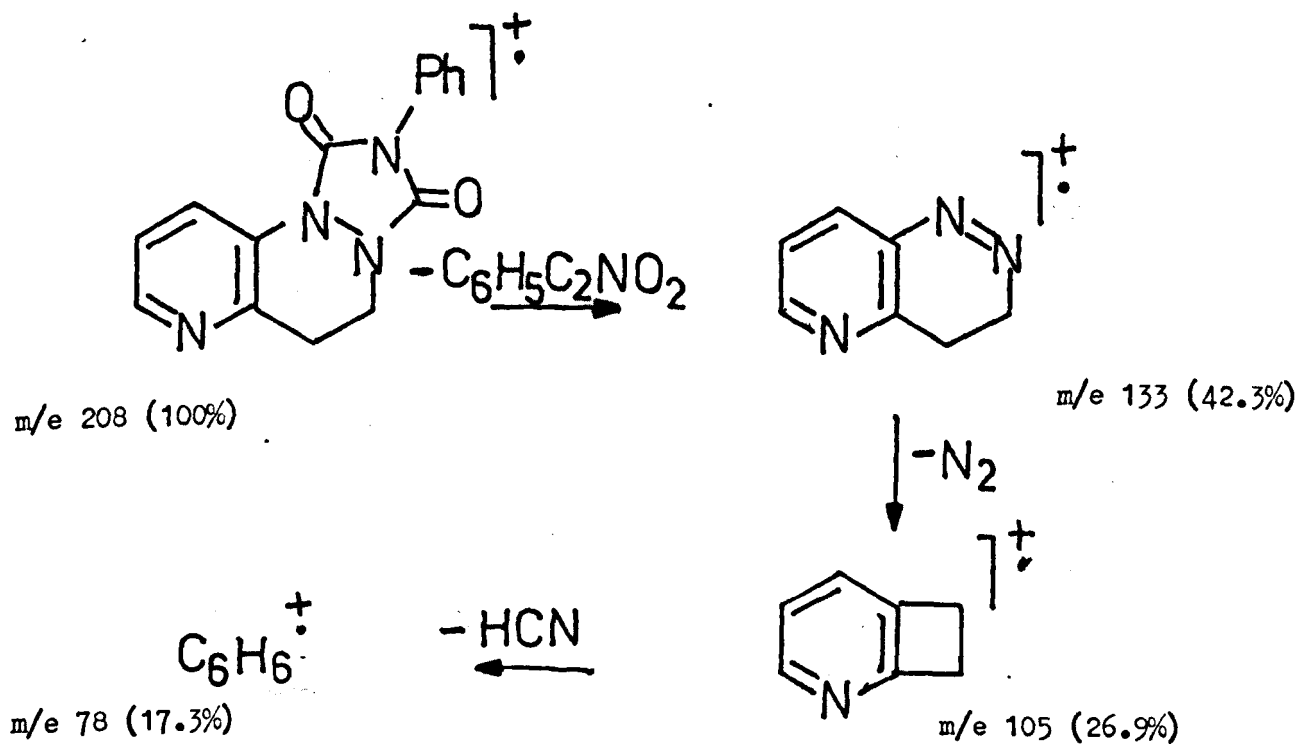
The cyclic azo compound (101) reacts rapidly with a number of dienes at low temperature to give the expected cycloadducts, e.g. with cycloheptatriene at -50°C to give the adduct. It is reported to be decomposed by alkali, acid and water;[91] though stable in the solid state to 160°C, it decomposes slowly at 100°C in solution. It is prepared by oxidation of 4-phenyl-1,2,4-triazolidine-3,5-dione using t-butyl hypochlorite either in acetone at -50°C or in dioxan at room temperature.[33]

Reaction between 2-vinyl pyridine (90) and 1,2,4-triazoline-dione (101) was carried out in dry acetone at -40°C. Addition of freshly distilled 2-vinyl pyridine (90) to the intense red solution of the cis-azo compound (101) produced no immediate colour change, on warming to room temperature then refluxing for one hour the red colour disappeared. A complex mixture of products was present (t.l.c.) Separation of the products by column chromatography gave a fraction which contained a major product plus a minor component. The ^1H n.m.r. spectrum of this fraction seemed to indicate that the major product formed was the 1,2,3,4-tetrahydropyrido[3,2-c]pyridazine-1,2-dicarboxylic acid, N-phenyl imide (275). The minor component of the fraction showed interesting absorption in the ^1H n.m.r. spectrum between δ = 5.1 and 6.7 p.p.m., indicative of one proton adjacent to two non-equivalent protons. This pattern may indicate that a diadduct having structure (276),



or (277) is formed. Separation of these two components was achieved by p.l.c. The major component showed a blue fluorescence on the silica plate. Its spectral data confirmed its structure as that of the mono adduct (275).

The compound (275) was obtained as a white solid, m.pt. 152-153°C, microanalysis gave correct C and H values but the nitrogen value was consistently high. The mass spectrum showed an M^+ at 280 a.m.u., which agrees well with the proposed structure. The fragmentation pattern is shown below.



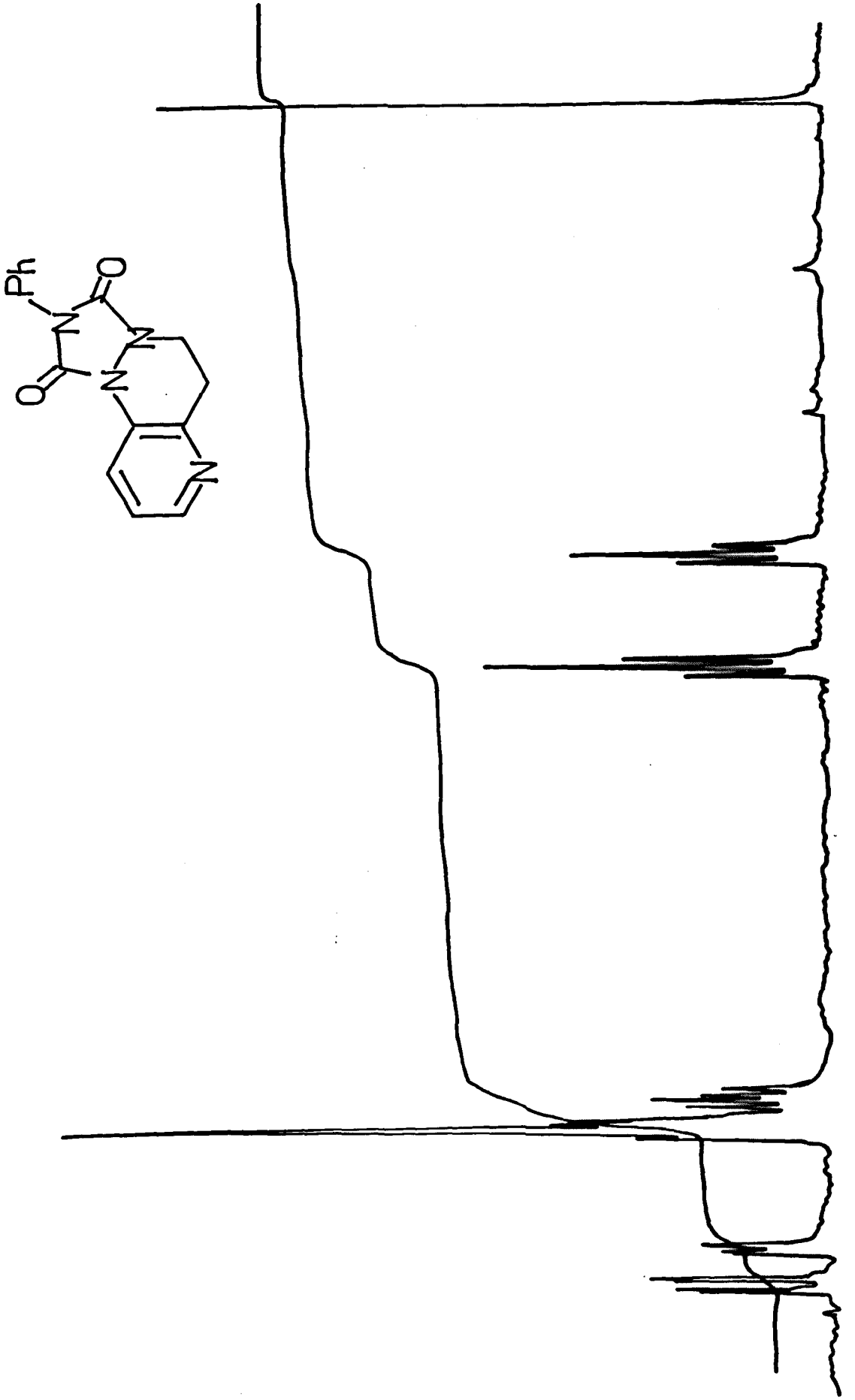
Accurate mass measurements on the peaks at m/e 280 and 133 shows their possible formulae to be $C_{15}H_{12}N_4O_2$ and $C_7H_7N_3$ as expected for the proposed structure. The ^1H n.m.r. spectrum (Fig. 18) showed the presence of eight aromatic absorptions. The furthest downfield is seen as a one proton pair of doublets at δ = 8.65 p.p.m., J = 8.5 Hz. This was attributed to H-8, due to the size of the coupling constant. It was seen further downfield that H-6 due to the anisotropic effect of the carbonyl group of the N-phenyl diimide moiety. H-6 was also seen as a pair of doublets at δ = 8.5 p.p.m., J = 4.5 Hz. A complex singlet which integrates for six protons was between δ = 7.1 and 7.6 p.p.m. This was attributed to the five phenyl group protons and the remaining proton, H-7 on the pyridine ring. It was possible to make out the quartet structure of H-7, J = 8.5 and 4.5 p.p.m. Irradiation at either of the protons at δ = 8.65 or 8.3 causes this quartet to collapse to a doublet. The two two-proton triplets at δ = 4.1 and 3.3 p.p.m. were attributed to the two methylene groups at C-3 and C-4. Absorptions in the infrared at 1765 and 1710 cm^{-1} were similar to reported values for the adducts of 1,2,4-triazolinedione.

The minor component of the fraction was not isolated from the p.l.c. plate.

The remainder of the material remained at the top of the chromatography column, and was not moved even on elution with 100% ethyl acetate.

Attempts to alter the conditions of the reaction to improve the yield of the cycloadduct (275) failed. Allowing the solution to warm to room temperature once the 2-vinyl pyridine (90) was added and then stirring until the red colour disappeared produced a light yellow precipitate. Chromatography of the filtrate after filtration gave the cycloadduct (275) in lower yield of 3.3%. Carrying out the reaction

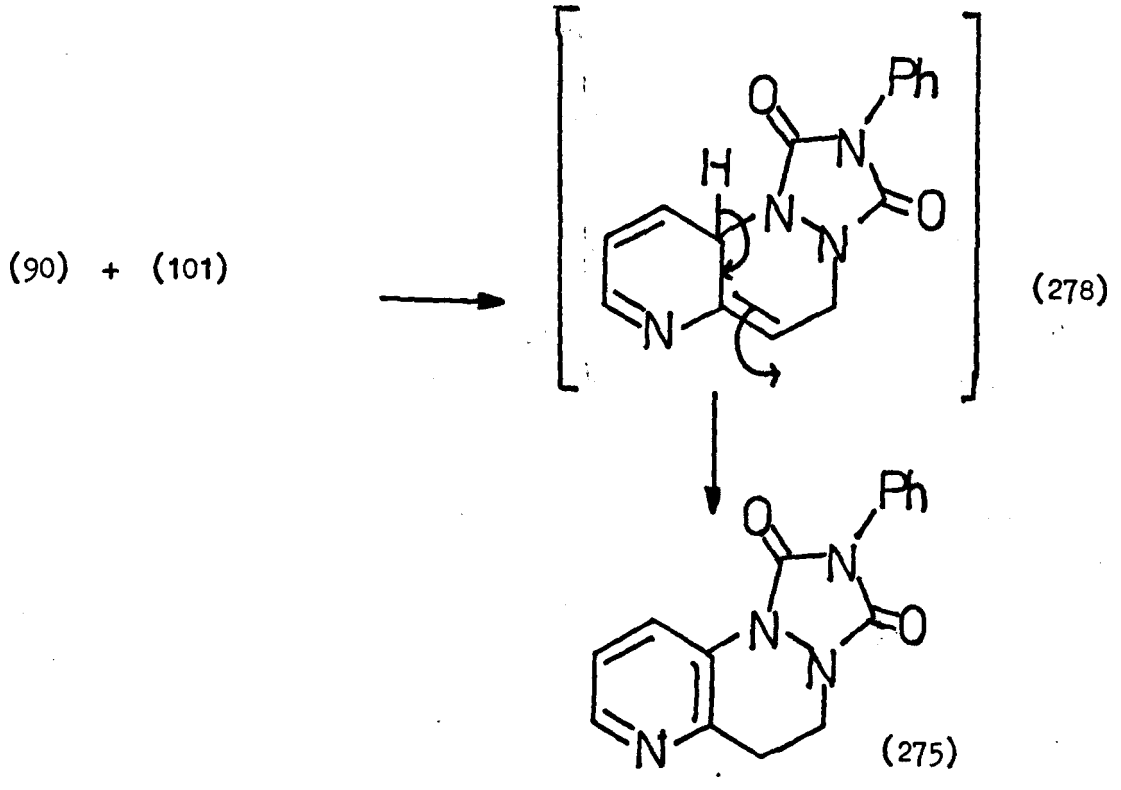
Fig. 18 ^{1}H N.m.r. spectrum of 1,2,3,4-tetrahydropyrido[3,2-c]pyridazine-1,2-dicarboxylic acid, N-phenyl-diimide (275)



in dioxan at room temperature also gave a precipitate; again chromatography of the filtrate gave the 1 : 1 adduct in a lower yield of 4%.

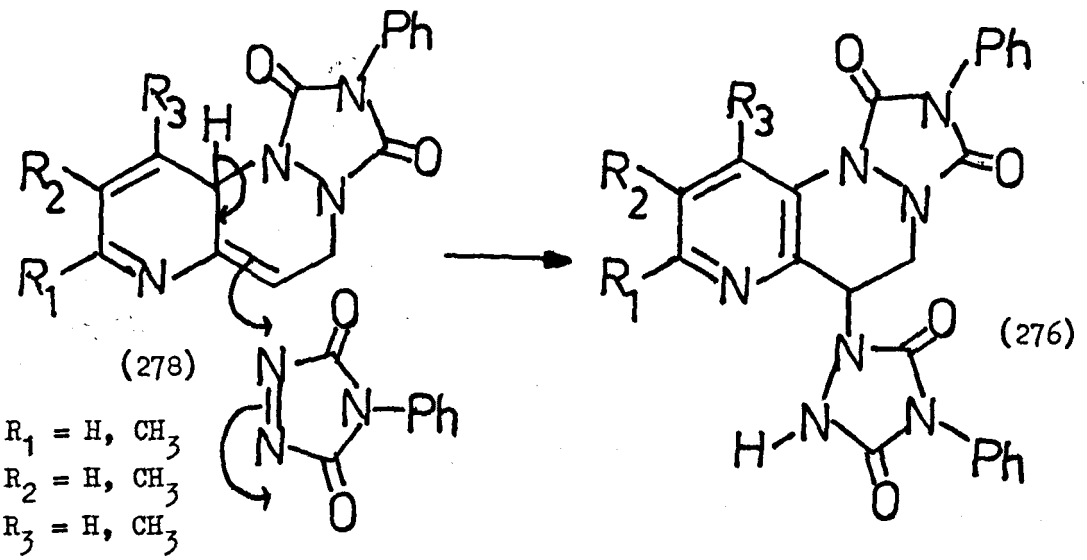
Hydrolysis of the tetrahydropyrido[3,2-c]pyridazine-1,2-dicarboxylic and N-phenyl-imide (275) was not attempted since the yield of this product was low.

Presumably the mechanism of the reaction is initial 1,4-cycloaddition of the cis-azo compound (101) to 2-vinyl pyridine (90) possibly via a concerted pathway, followed by a stepwise[1,3-] hydrogen shift. No work was done to decide the concertedness of the initial process.



After the completion of this section of work, an abstract appeared in 'Chemical Abstracts' referring to a paper by A.N. Kost et al. which describes[92] the preparation of triazoloazacinnolines such as (276) in 60 - 85% yields, by 1,4-cycloaddition of the cis-azo compound (101) to 2-vinyl pyridine and its derivatives, followed by

ene addition of another molecule of the triazolinedione (101) to the initial cycloadduct to give the 2 : 1 adducts.



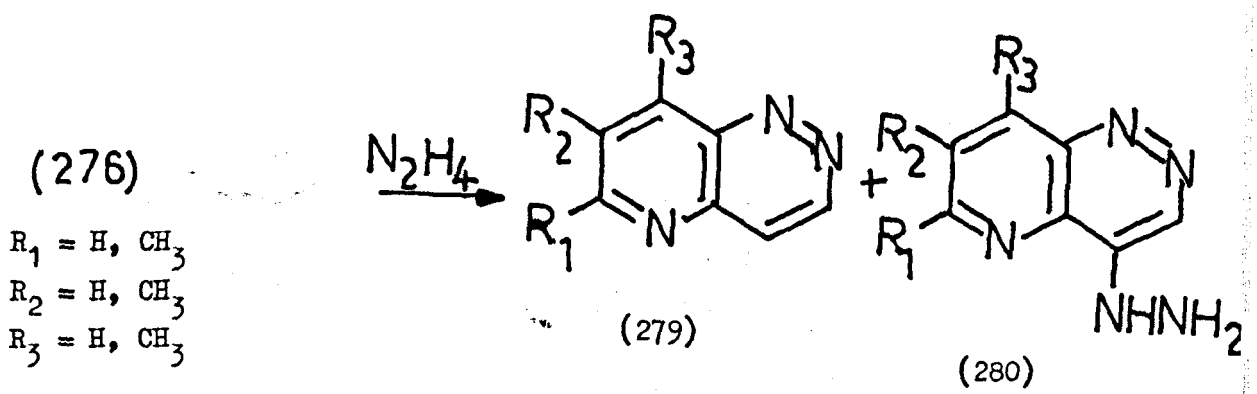
(278)

R_1 = H, CH_3
R_2 = H, CH_3
R_3 = H, CH_3

(276)

The procedure used by the Russians involves adding a slight excess of the cyclic azocompound (101) in ether to the vinyl pyridine compound also in ether and the mixture allowed to stand for one hour at room temperature. The resulting precipitates were removed, then recrystallised from chloroform and shown to be the diadducts (276) by spectroscopic methods.

A second paper[93] by Kost et al. describes the conversion of these diadducts (276) into the 5-azacinnoline derivatives (279) and (280) by heating with hydrazine hydrate for seven hours.



(276)

R_1 = H, CH_3
R_2 = H, CH_3
R_3 = H, CH_3

(279)

(280)

The mechanism of this transformation is not known. Hydrazone derivatives were prepared from compounds (280).

We also obtained precipitates as described above but analysis using ^{1}H n.m.r. spectroscopy did not yield any plausible structures. A minor component was obtained as described (which decomposed on chromatography) which may have been the diadduct (276), but no comparison could be made. These workers did not isolate any monoadducts (275).

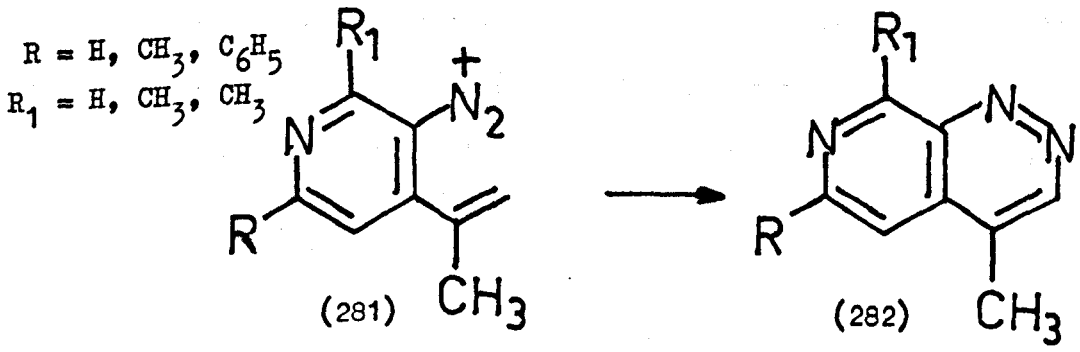
Little work has been done on condensed pyridazines containing heteroatoms in both rings.

By extending our synthesis to other vinyl heterocyclic compounds it is possible to synthesise other relatively inaccessible condensed pyridazines.

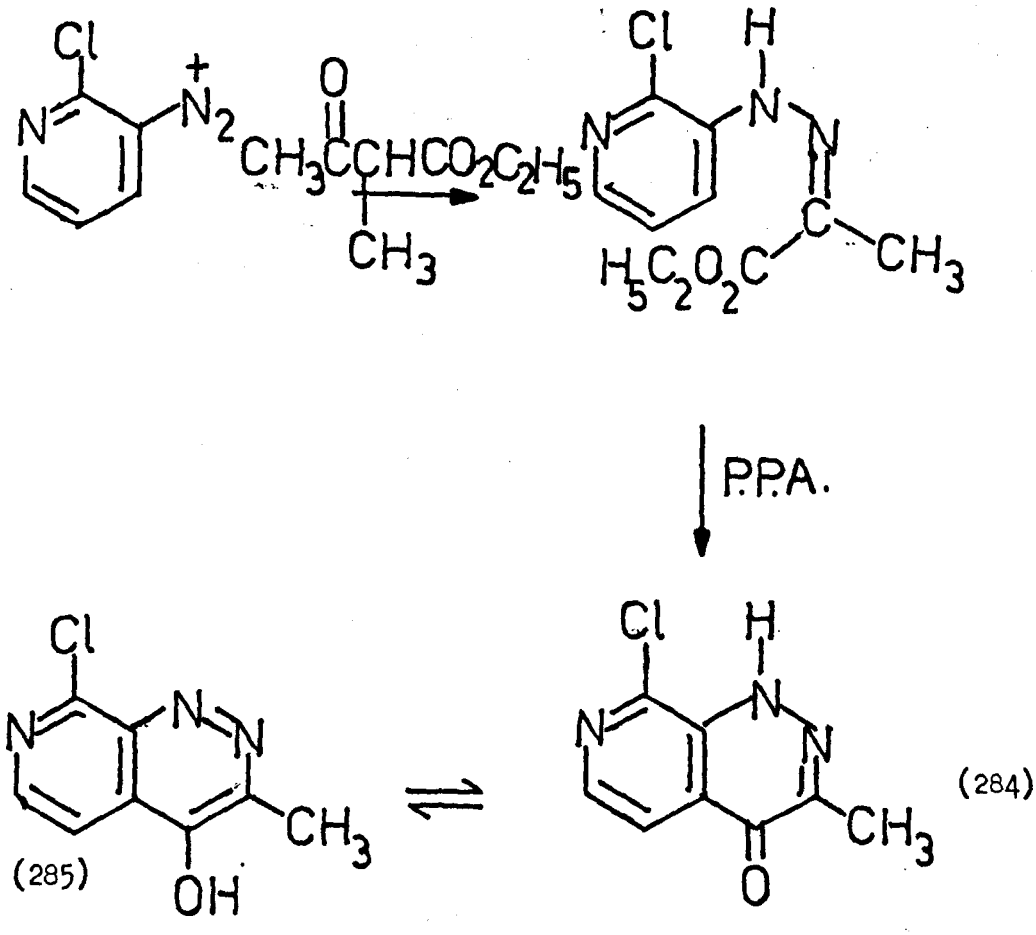
(v) Pyrido[3,4-c]pyridazines.

There are only three references to the pyrido[3,4-c] pyridazines in the chemical literature at this present time.

In addition to preparing the pyrido[3,2-c]pyridazine system, Atkinson and Biddle were able to prepare[25] pyrido[3,4-c]pyridazine (282) by an application of the Widman-Stoermer reaction. The diazotised aminopyridines (281) were left at room temperature for three days. The products were then isolated in low yield.

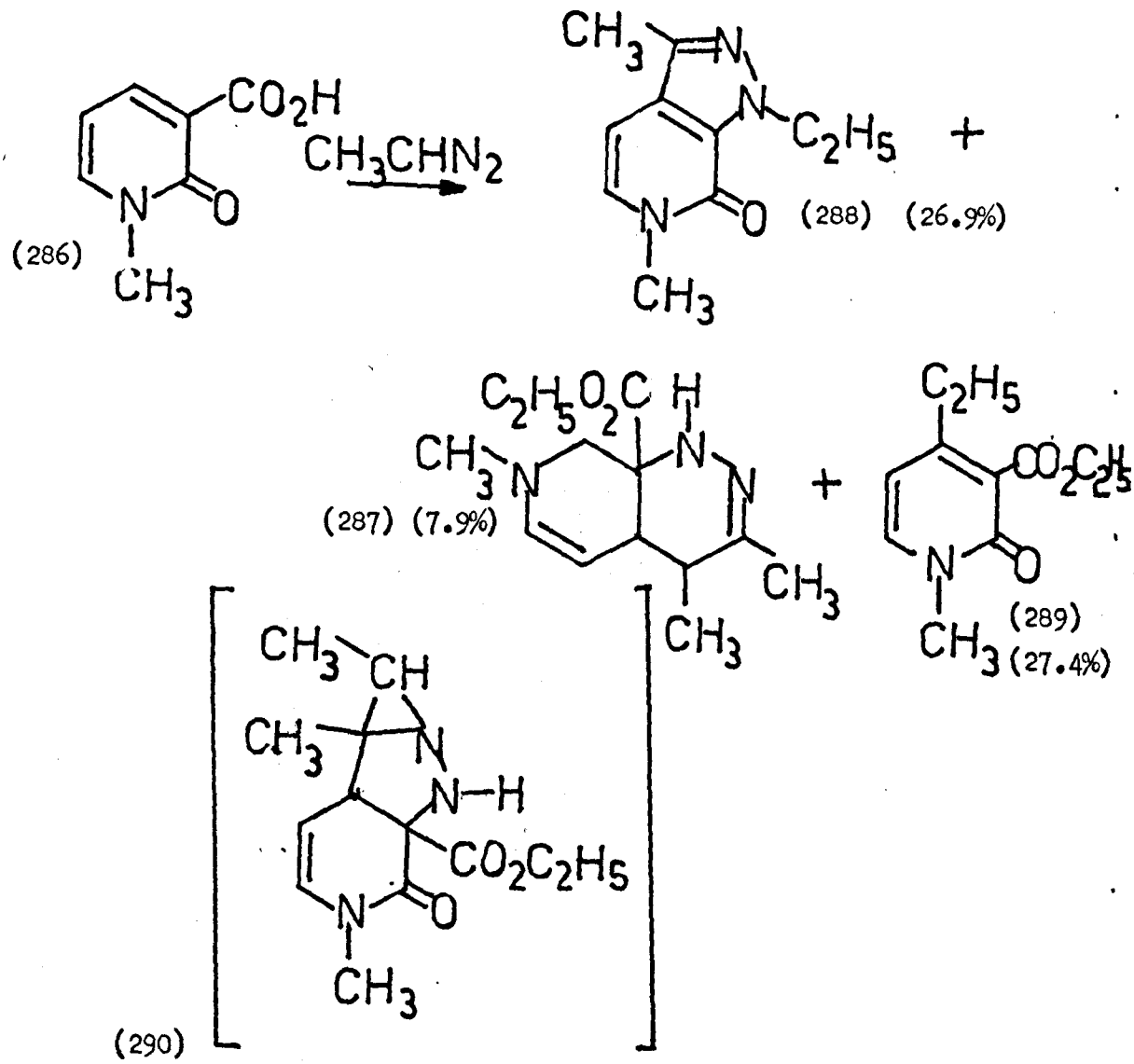


The methyl group of 4-methyl pyrido[3,4-c]pyridazine (282) may be condensed with benzaldehyde in the presence of zinc chloride and the corresponding styryl derivative was obtained. Diazotised 3-amino-2-chloropyridine (283) was coupled to methyl methylacetoacetate and the hydrazone obtained (284) was cyclised in polyphosphoric acid to the pyrido[3,4-c]pyridazine (285).[94]



(284)

Kametani et al.[95] isolated the pyrido[3,4-c]pyridazine after treatment of 3-carboxypyridone (286) with diazoethane in 7.9% yield. They postulate the formation of this 7-azacinnoline (287) via the intermediate (290). Two other products, the pyrazolo[3,4-c]pyridine (288) and the pyridone (289) were also isolated.

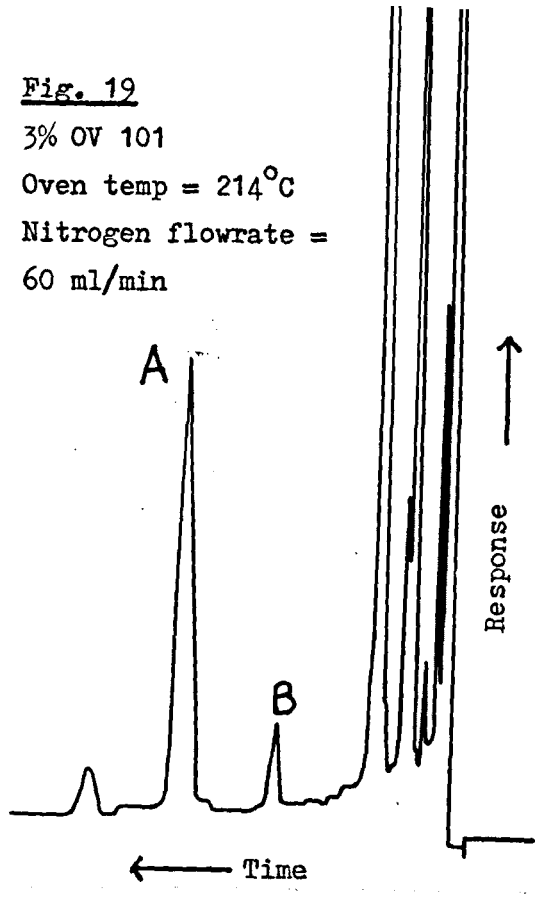


The parent 7-azacinnoline (295) has not been isolated. Using our procedure, starting from 4-vinyl pyridine (291) it was possible to obtain the parent pyrido [3,4-c] pyridazine (295) in 8.0% overall yield from the vinyl heterocyclic compound (291).

Boiling a solution of 4-vinyl pyridine (291) and diethyl azodicarboxylate (97) in acetonitrile (14 hours) gave an oil which was shown by t.l.c. to contain a number of components.

A g.l.c. trace (Fig. 19) of the reaction products showed one major and a minor component present.

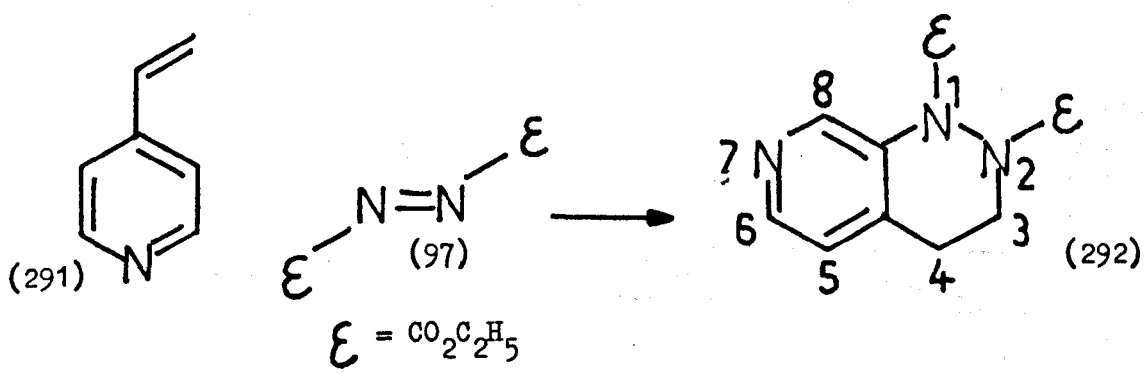
Fig. 19
3% OV 101
Oven temp = 214°C
Nitrogen flowrate = 60 ml/min



The products were separated by column then preparative layer chromatography. After initial elution of unreacted 4-vinyl pyridine (291) from the column an oil was collected which was showed by t.l.c. to contain one major and two minor components.

Separation of these components by p.l.c. gave the major component as a yellow oil (13.2%). Microanalysis after bulb tube distillation gave its empirical formula as $C_{13}H_{17}N_3O_4$. An M^+ of 279 a.m.u. confirmed that this product has been formed by combination of one molecule of 4-vinyl pyridine (291) with one molecule of diethyl azodicarboxylate (97).

The coupling pattern between the aromatic protons in the ^1H n.m.r. spectrum (Fig. 20) leads us to propose the 1,2-diethoxycarbonyl-1,2,3,4-tetrahydropyrido[3,4-c]pyridazine (292) structure for this compound.

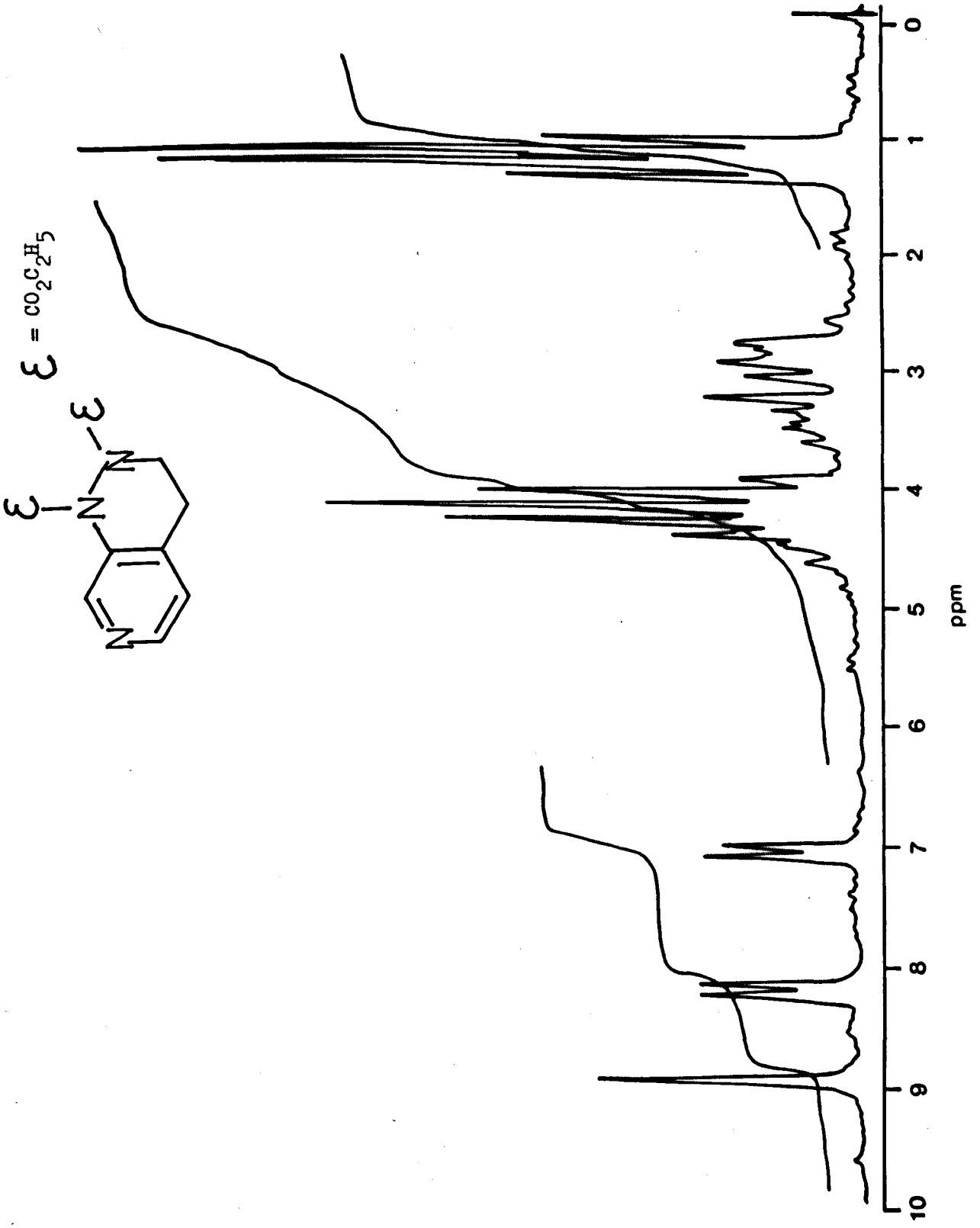


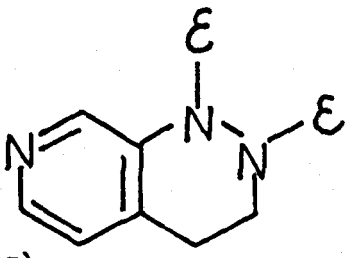
The proton H-8 was seen furthest downfield as a singlet at δ = 9.0 p.p.m., H-6 and H-5 as one proton doublet (J = 5 Hz) at δ = 8.3 and 7.15 p.p.m. respectively. A five proton complex signal was seen between δ = 3.9 and 4.8 p.p.m., this absorption was attributed to the two methylene groups of the non-equivalent ester substituents, which are superimposed on one of the proton resonances of the methylene groups of C-3 or C-4. This proton forms part of a strongly coupled ABCD pattern, the other portion of this pattern was seen as a strongly coupled three proton signal resonating between δ = 2.5 and 3.7 p.p.m. The remaining signal, integrating for six protons was seen between δ = 1.1 and 1.5 p.p.m., attributed to the two methyl signals of the non-equivalent ester groups. The ester absorption in the infrared was seen at 1720 cm^{-1}.

The other components of the mixture were not identified. The remainder of the products were also not identified.

Hydrolysis of the ethyl ester adduct (292) was not attempted, instead the di-tert-butyl cycloadduct (293) was prepared by boiling a solution of 4-vinyl pyridine (291) and di-tert-butyl azodicarboxylate (252) in benzene for eleven days. The di-tert-butoxy carbonyl tetrahydropyrido[3,4-c]pyridazine (293) was obtained in 15.9% yield after column and preparative layer chromatography. Again attempts to isolate any pure products from the remainder of the material on the column failed.

Fig. 20 ^{1}H N.m.r. spectrum of 1,2-diethoxycarbonyl-1,2,3,4-tetrahydropyrido[3,4-c]pyridazine (292)



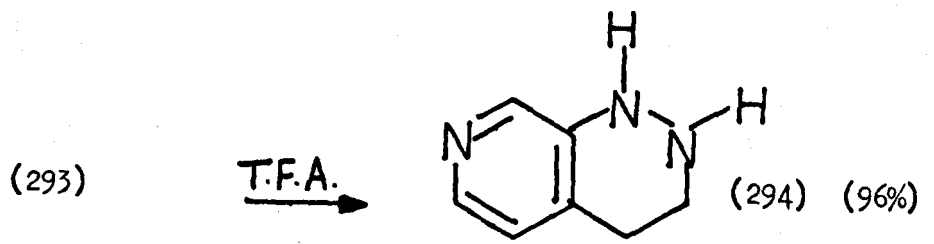


(293)

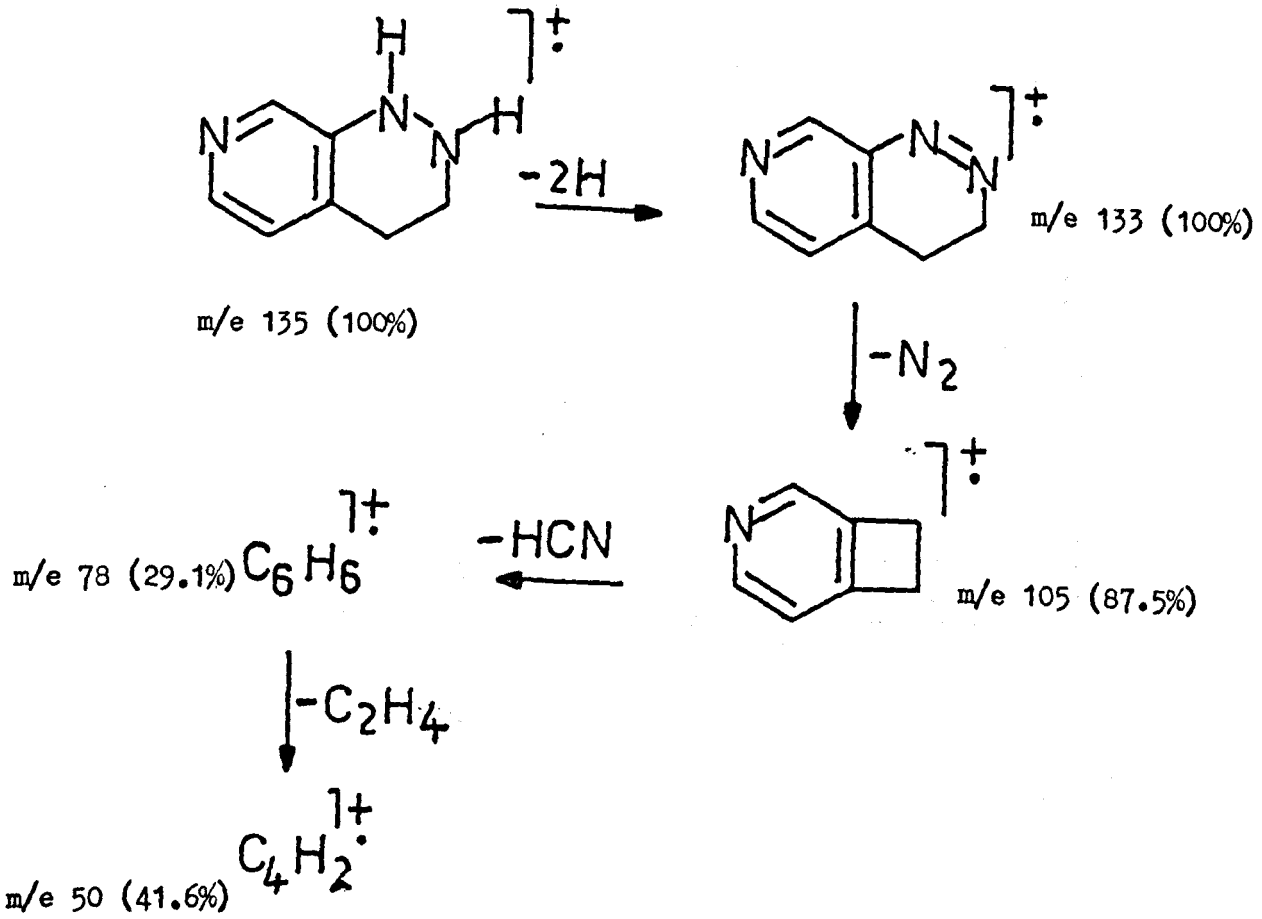
$\mathcal{E}$ = CO_2t-bu

This structure was based on spectroscopic evidence similar to that described for the ethyl adduct (292).

Cleavage of this 7-azacinnoline diadduct (293) with TFA proved very easy. The 1,2,3,4-tetrahydropyrido[3,4-c]pyridazine (294) was obtained in virtually quantitative yield.



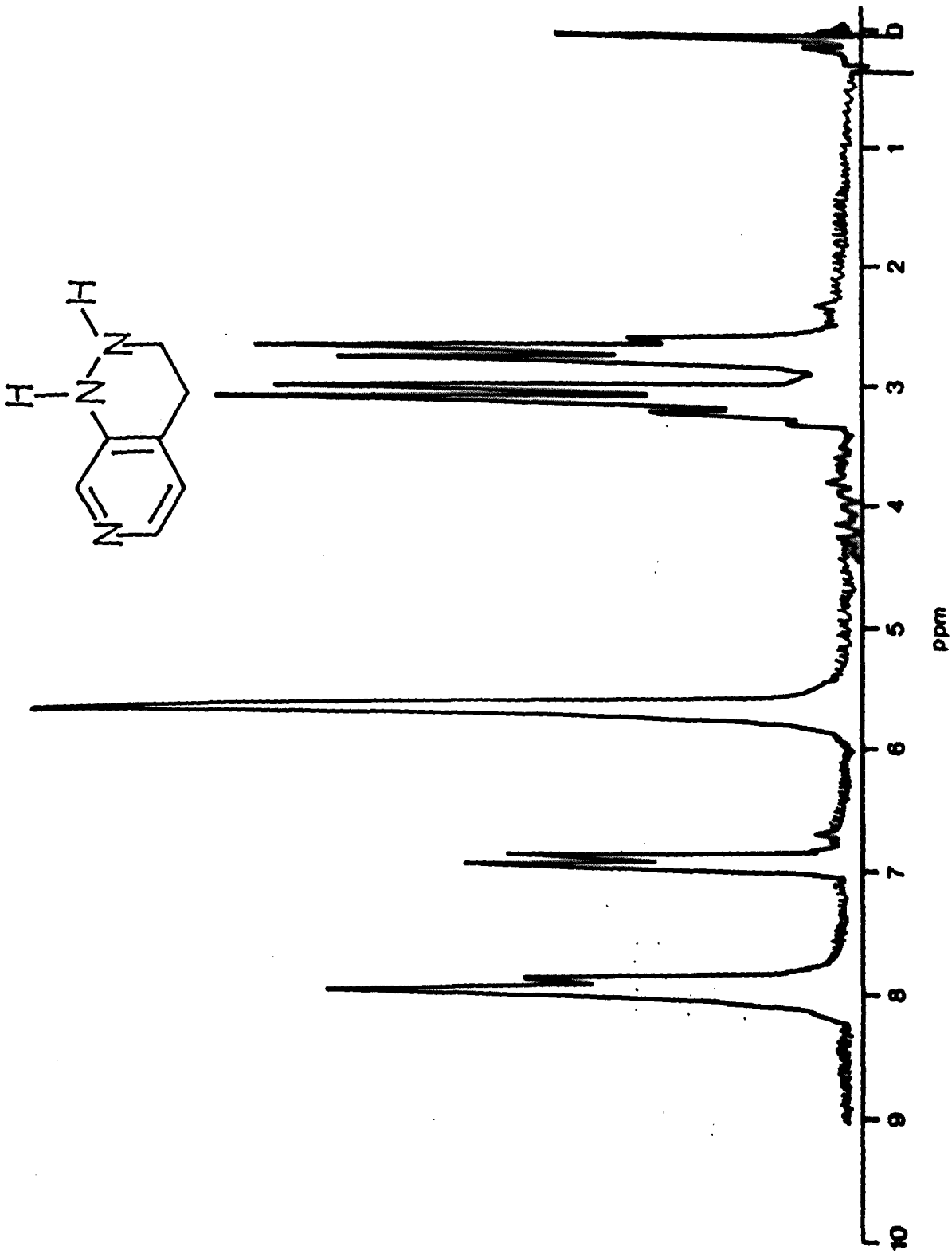
The structure for this 'hydrazo compound' (294) was proposed on the basis of mass and ^{1}H n.m.r. spectra. The mass spectrum showed an M^+ at 135 a.m.u., the proposed breakdown pattern is shown below, it parallels that observed for the parent pyrido [3,2-c] pyridazine (87) and the tetrahydropyrido[3,2-c]pyridazine (255).



The ^{1}H n.m.r. spectrum (Fig. 21) shows a two proton signal centred at δ = 7.9 p.p.m., attributed to H-8 and H-6. The one proton doublet at δ = 6.9 p.p.m. (J = 5 Hz) was assigned to H-5. The signal at δ = 5.65 p.p.m. was exchangeable with D_2O and is due to the two N-H protons. The two methylene groups at C-3 and C-4 are seen as distorted triplets at δ = 3.1 and 2.75 p.p.m. from TMS.

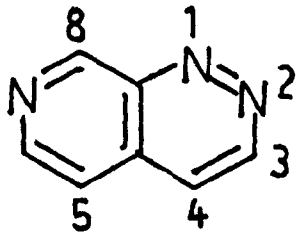
Conversion of the 'hydrazo compound' (294) to the fully aromatic pyrido[3,4-c]pyridazine (295) was carried out, first by oxidation of the NH-NH functional group using mercuric oxide (red) then bubbling oxygen through a chloroform solution of the oil obtained (66 hours). The parent pyrido[3,4-c]pyridazine (295) was obtained as yellow needles, m.pt. 138°C, empirical formula $C_7H_5N_3$. The ^{1}H n.m.r.

Fig. 21 ^{1}H N.m.r. spectrum of 1,2,3,4-tetrahydropyrido[3,4-c]-pyridazine (294)



spectrum (Fig. 22) left no doubt that this product was pyrido[3,4-c] pyridazine (295). The one proton singlet peak at δ = 9.85 p.p.m.

(294) $\xrightarrow[\text{ii } O_2\text{(66hrs)}]{\text{i } HgO}$ (295) (52.6%)



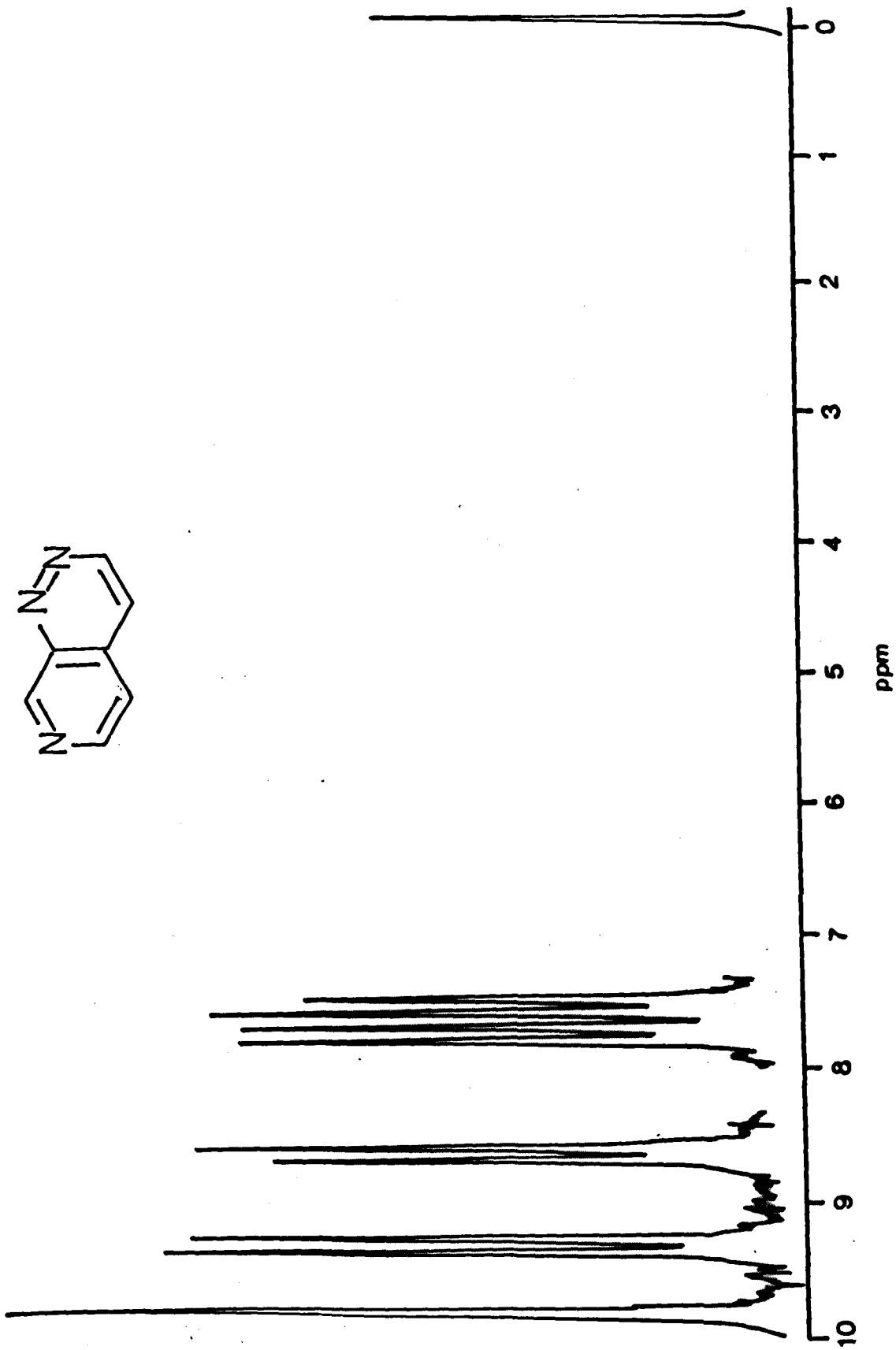
was attributed to H-8. The doublet at δ = 9.35 was assigned to H-3 (J = 5.8 Hz), that at δ = 8.7 p.p.m., also a doublet (J = 6 Hz) was assigned to H-6. Two one proton doublets at δ = 7.8 (J = 5.8 Hz) and 7.6 p.p.m. (J = 6 Hz) were attributed to H-3 and H-5 respectively. Proof of this assignment was obtained by irradiation at δ = 9.35 (at H-3), the signal at δ = 7.8 (H-4) was observed to collapse to a singlet whilst H-5 remained as a doublet, but as expected of lower intensity.

The u.v. data was: λ_{max} (EtOH 95%) 209 ($\log \varepsilon$ = 4.46) and 284 nm ($\log \varepsilon$ = 3.58). There was little change in the u.v. spectrum on addition of dilute HCl (2N) whilst on addition of dilute sodium hydroxide (2N) the extinction coefficient was greatly increased, with a corresponding hypsochromic shift of the absorption at 209 nm to 204 nm.

The mass spectrum contained an M^+ at 131 a.m.u. The breakdown pattern parallels that of the pyrido[3,2-c]pyridazine (87).

This is the first report of the preparation of the parent 7-azacinnoline (295).

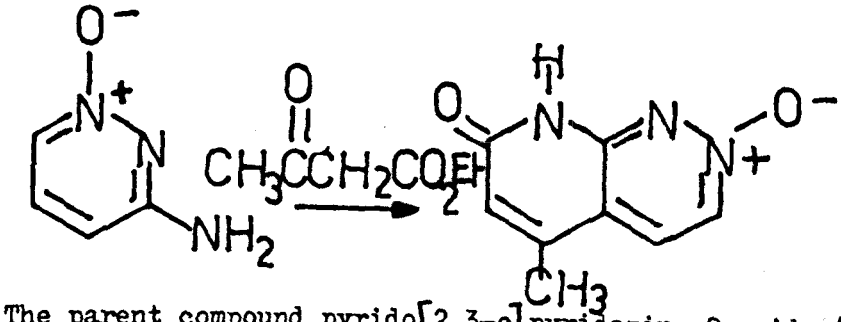
Fig. 22 ^{1}H N.m.r. spectrum of pyrido[3,4-c]pyridazine (295)



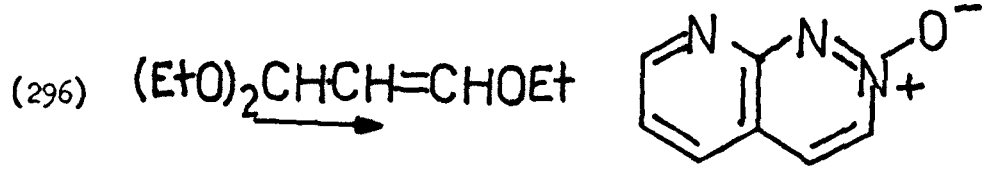
(VI) Pyrido[2,3-c] and [4,3-c] pyridazines.

Only one report[96] appeared in the literature concerning the synthesis of the pyrido[2,3-c]pyridazine system.

The bicyclic products were formed by condensing 3-amino-pyridazine 1-oxide (296) with β-dicarbonyl compounds or with ethoxymethylene malonate in hot diphenyl ether or, preferentially, in the presence of polyphosphoric acid. Thus with ethyl aceto-acetate a product was formed to which the structure of 5-methyl pyrido[2,3-c]pyridazin-7(8H)-one 2-oxide (297) was assigned.



The parent compound pyrido[2,3-c]pyridazine 2-oxide (298) was prepared in low yield by employing 1,1,3-triethoxyprop-2-ene. Attempts to deoxygenate this 8-azacinnoline (298) using phosphorous trichloride failed.

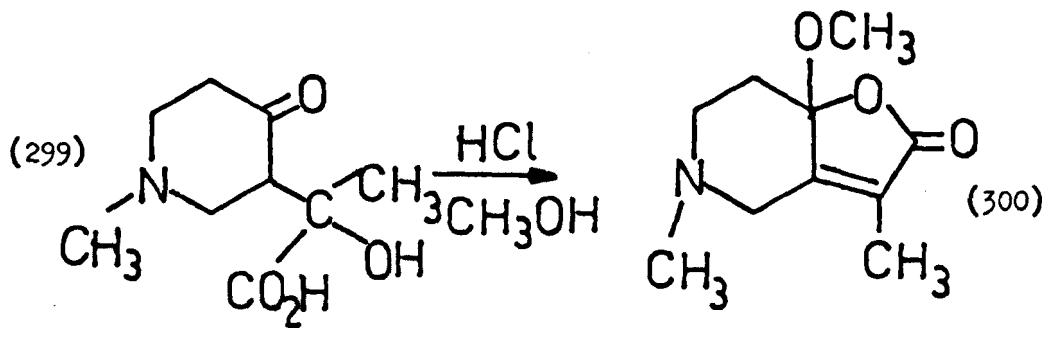


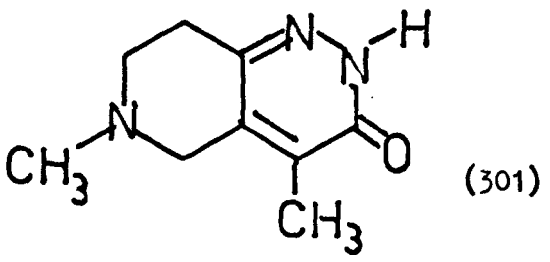
(298)

The pyrido[4,3-c]pyridazine system also has received scant attention; the only references to the system are described below.

A synthesis of the 6-azacinnoline system was reported by Prasad and Wermuth[97] in 1967. They report that the condensation

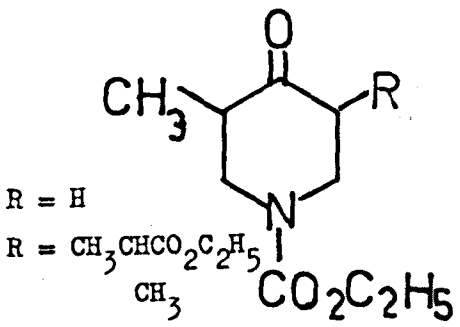
product from N-methylpiperidone (299) and pyruvic acid was transformed into the pseudoester (300) with methanolic hydrogen chloride. The pseudoester (300) was then treated with hydrazine in butan-1-ol to give the 6-azacinnoline derivative (301) in 40% yield.



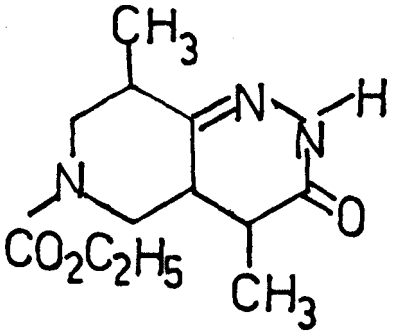


Recently abstracts have appeared of Swiss and German patents,[98] which describe the preparation of various derivatives of the pyrido[4,3-c]pyridazine systems, and their testing as chemotherapeutic agents by the general method shown.

The piperidine derivative (302) was converted to its pyrrolidine enamine and then treated with ethyl 2-bromo propionate to give the piperidine, which was then cyclised with hydrazine to give octahydropyrido[4,3-c]pyridazinone (303).

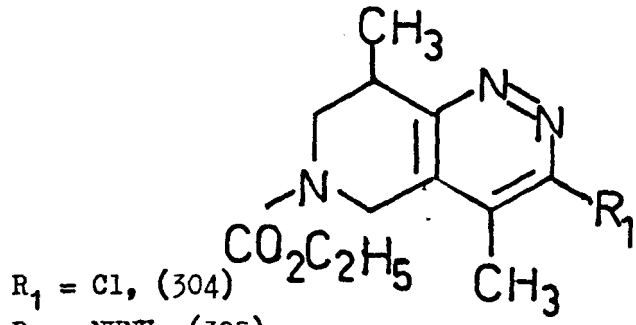


(302)



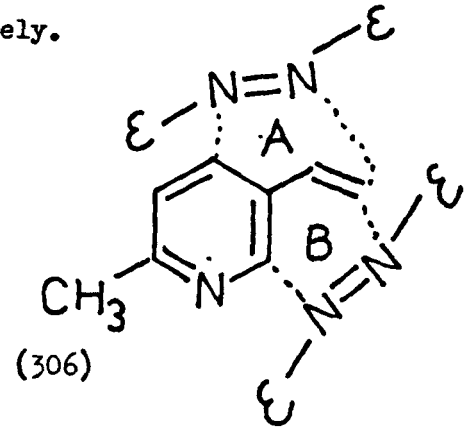
(303)

Dehydration then chlorination gave the pyridazine (304), which may then be treated with hydrazine to give the hydrazino derivative (305).



R_1 = Cl, (304)
R_2 = $NHNH_2$ (305)

The two title pyrido pyridazine isomers may be synthesised from 3-vinyl pyridine or 2-methyl-5-vinyl pyridine (306) which was more readily available. Cyclisation was found to occur via route A and by route B to give the pyrido[4,3-c] and [2,3-c] pyridazine system respectively.



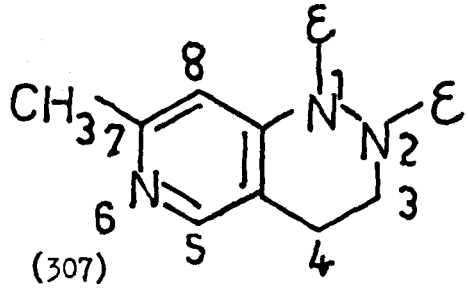
(306)

When boiling equimolar quantities of 2-methyl-5-vinyl pyridine (306) and diethyl azodicarboxylate (97) in acetonitrile the reaction was complete after five hours. The resultant oil was shown by t.l.c. to contain many components. The products were separated by column then preparative layer chromatography.

After initial elution of unreacted 2-methyl-5-vinyl pyridine (306) from the column, an oil was collected which t.l.c. showed to contain three blue fluorescent components. Separation of these fluorescent components was achieved by p.l.c.

The band with the lowest R_f (0.33) was obtained (5.3%) as a solid which crystallised from cyclohexane, m.pt. 103.5 - 105°C. It had an M^+ of 293 a.m.u., and microanalysis confirmed its empirical formula to be $C_{14}H_{19}N_3O_4$.

The ^1H n.m.r. spectrum (Fig. 23) showed this product to be the 1,2-diethoxycarbonyl-7-methyl-1,2,3,4-tetrahydropyrido[4,3-c] pyridazine (307).



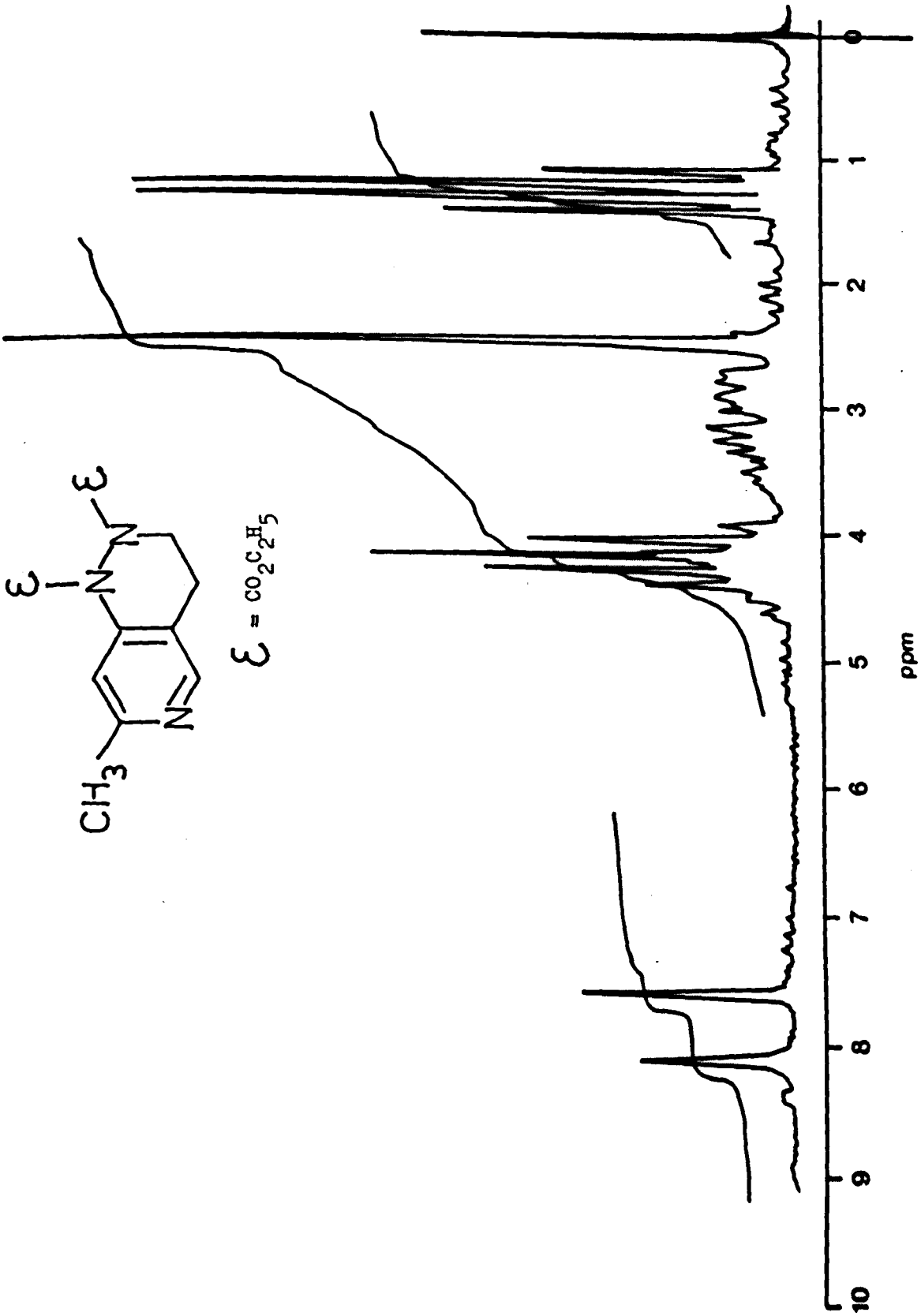
(307)

The one proton singlet signals at δ = 8.1 and 7.6 p.p.m. were attributed to H-5 and H-8 respectively. The complex signal between δ = 4.8 and 3.8 p.p.m. was assigned to the two methylene groups of the non-equivalent ester substituents which are superimposed over the absorption of one of the protons of the methylene groups at C-3 or C-4. The other three protons of these two methylene groups were seen as a complex multiplet between δ = 3.8 and 2.6, the methyl group was seen as a three proton singlet at δ = 2.5 p.p.m., and the remaining six proton multiplet between δ = 1.1 and 1.5 was attributed to the two ester methyl groups. The infrared showed the ester absorption at 1720 cm^{-1}.

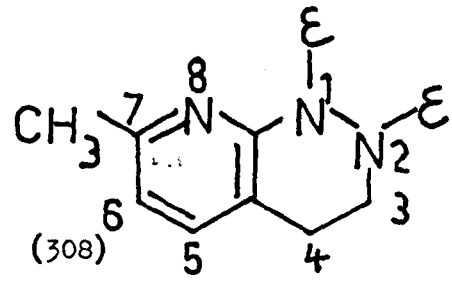
The fluorescent band of intermediate R_f value (0.42) was obtained as an oil (3.7%), spectroscopic data showed that it was the isomeric pyrido[2,3-c]pyridazine (308).

The ^1H n.m.r. spectrum showed the presence of two one proton doublets (J = 7 - 8 Hz) at δ = 7.35 and 6.9 p.p.m. attributed to H-5 and H-6 respectively. The remainder of the spectroscopic data is given

Fig. 23 ^{1}H N.m.r. spectrum of 1,2-diethoxycarbonyl-7-methyl-1,2,3,4-tetrahydropyrido[4,3-c]pyridazine (307)



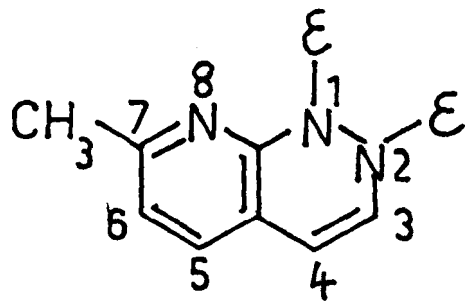
in the Experimental Section.



(308)

$\varepsilon = CO_2C_2H_5$

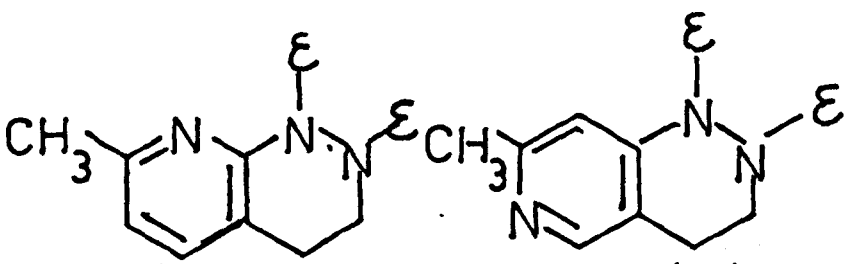
The remaining fluorescent band, $R_f = 0.52$, was also obtained as an oil. A mass spectrum gave an M^+ at 291 a.m.u., indicating that some dehydrogenation had taken place. Microanalysis, after bulb distillation of the oil, gave correct carbon and hydrogen values but a low nitrogen value for an empirical formula of $C_{14}H_{17}N_3O_4$. A ^1H n.m.r. spectrum indicated that the structure of the product was best represented as dihydropyrido[2,3-c]pyridazine (309), since one can see three one



$\varepsilon = CO_2C_2H_5$

proton doublets in the aromatic region of the spectrum and a one proton doublet (J = 6 - 7 Hz) at δ = 5.95 p.p.m., assigned to the olefinic proton H-4. Irradiation at δ = 7.1 p.p.m. causes this doublet to collapse to a singlet. The two ester methylene groups were seen between δ = 4.5 and 3.9 p.p.m., the three proton methyl singlet resonates at δ = 2.55 p.p.m., and the two remaining methyl groups of the non-equivalent ester substituents occur between δ = 1.0 and 1.6 p.p.m. The remainder of the products proved unidentifiable.

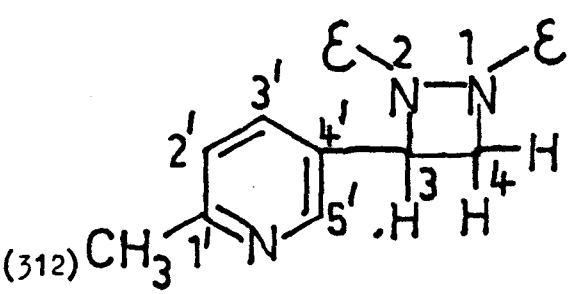
Hydrolysis of these ethyl esters (307 - 9) was not carried out, instead the corresponding t-butyl esters were prepared by boiling the 2-methyl-5-vinyl compound (306) with di-tert-butyl azodicarboxylate (252) in benzene. The reaction took six days to go to completion. Separation of the products by the usual chromatographic procedures gave the di-tert-butyl pyrido[2,3-c] (310) and [4,3-c] pyridazines (311) in 3.7% and 5.5% yields respectively.



(310) (311)

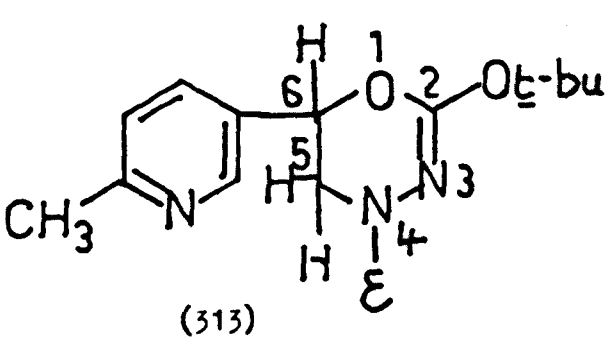
$\varepsilon = CO_2t\text{-bu}$

Also isolated was an oil (1.7%) whose ^1H n.m.r. spectrum indicated that the product was either the diazetidine derivative (312) formed by [2 + 2] cycloaddition or the oxadiazine compounds (313) and (314) formed as a result of the azodiester acting as a hetero diene.

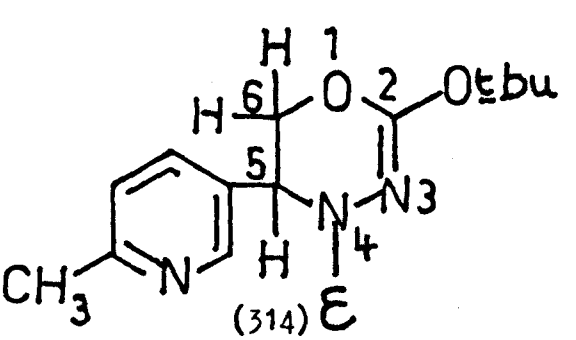


(312)

$\varepsilon = CO_2t\text{-bu}$



(313)



(314)

All three structures would contain in the ^1H n.m.r. spectrum (Fig. 24) three downfield aromatic protons. A broad doublet (J = 2 Hz) at δ = 8.4 p.p.m., a doublet of doublets (J = 7 - 8, 2 Hz) at δ = 7.5 p.p.m. and a doublet at δ = 7.1 p.p.m. attributed to the pyridine protons H-5^1, H-3^1 and H-2^1 respectively. The presence of the $CH-CH_2-$ grouping was suggested by the pattern of absorptions seen at δ = 5.2 (doublet of doublets, H-3, J = 9, 3 Hz), 4.2 (doublet of doublets, H-4, J = 14, 3 Hz) and 3.25 p.p.m. (quartet, H-4, J = 14, 9 Hz). The pyridine methyl group was seen as a three proton singlet at δ = 2.55 p.p.m. and the two non-equivalent tert-butyl groups resonated as two nine proton singlets at δ = 1.5 and 1.55 p.p.m.

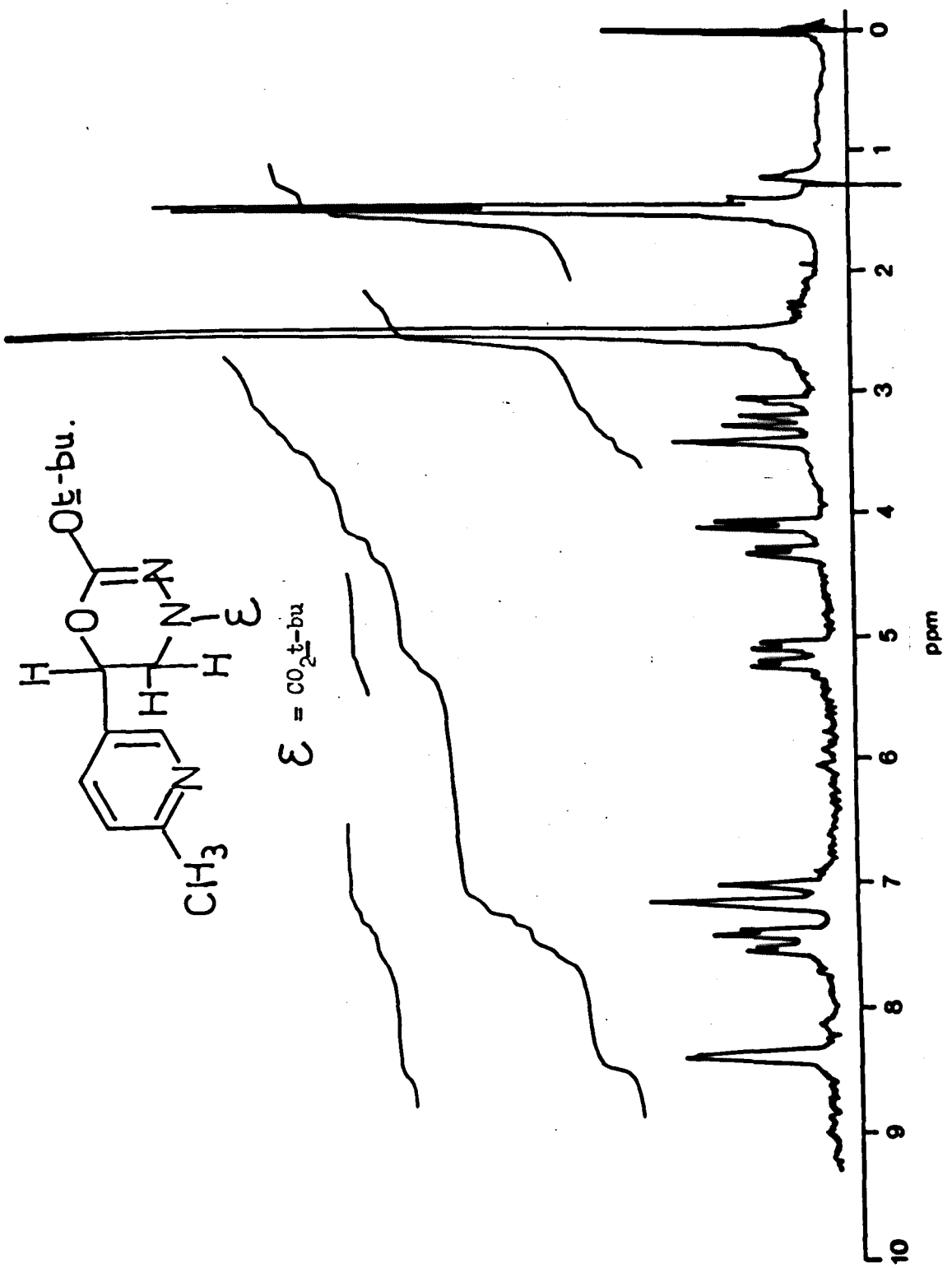
The mass spectrum showed the highest peak at 293 a.m.u. ($M^+ -56$), peaks at 149 ($M^+ - 2 \times CO_2 + CH_2 = C(CH_3)_2$), 131, 119 and 105 a.m.u. were also observed.

Microanalysis after bulb distillation gave correct carbon and hydrogen values but incorrect nitrogen values for an empirical formula of $C_{18}H_{27}N_3O_4$. Exact mass measurements on peaks at 293 and 237 failed.

The favoured structure is that of the dihydro-oxadiazine isomer (313) for the following reasons:

1. The oxadiazine structure is characterised by an absorption in the infrared between 1660 and 1680 cm^{-1}. The infrared spectrum of the product (313) showed a broad carbonyl absorption at 1720 cm^{-1} which contained a shoulder at 1660 cm^{-1}, assigned to the $>C=N-$ stretch. No absorptions around 1660 cm^{-1} have been observed for the initial adducts formed between the vinyl pyridine compound and azodicarboxylate

Fig. 24 ^{1}H N.m.r. spectrum of 2,3-dihydro-6-(2'-methyl-5'-pyridyl)-2-tert-butoxy-4-tert-butoxycarbonyl-oxa-3,4-diazine (313)



diesters. A peak at 1610 cm^{-1} was also observed, due to >C=C< stretch in the pyridine moiety.

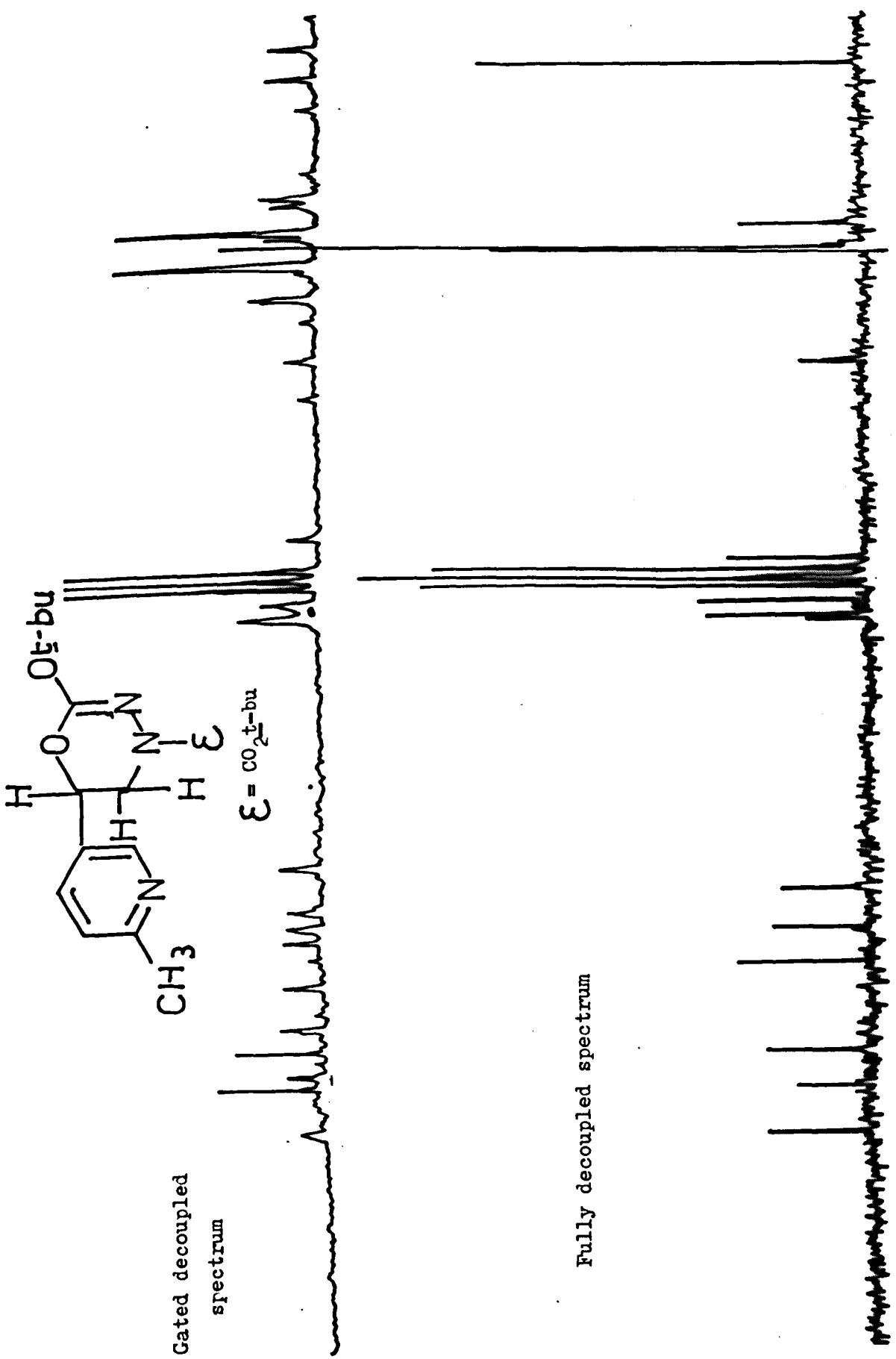
2. The chemical shifts obtained for the $CH-CH_2$ unit agreed with those obtained by Firl and Sommer[66] (see p.102).

The geminal coupling constant found by the above workers for the oxadiazine compound was 13.5 Hz. We observe a geminal coupling constant of 14 Hz. Other coupling constants were in good agreement.

The geminal coupling constant observed for the diazetidine structure by previous workers was always 9 to 9.5 Hz.[66,67]

3. A completely decoupled and gated decoupled ^{13}C spectra (Fig. 25) showed the carbonyl absorption and the C-2 imine-type carbon atom at δ = 152.3 and 147.1 p.p.m. from T.M.S. (The carbonyl group absorption of the carbamate linkages resonate at δ = 157.8 p.p.m. for methyl ethylcarbamate and δ = 154.0 for isopropyl phenylcarbamate).[99] For the oxadiazine structure (313) and (314) one would expect two types of 'carbonyl absorption'. No simple models could be found in the literature for comparison with this ^{13}C data. It was found, however, that the two carbonyl absorptions in the adducts below were different.

Fig. 25 ^{13}C N.m.r. spectrum of 2,3-dihydro-6-(2'-methyl-5'-pyridyl)-2-tert-butoxy-4-tert-butoxycarbonyl-oxa-3,4-diazine (313)



Adduct	δ p.p.m. from T.M.S.
1,2-di-tert-butoxycarbonyl-1,2,3,4-tetrahydropyrido[3,4-c]pyridazine (293)	153.8 152.3
1,2-diethoxycarbonyl-1,2,3,4-tetrahydropyrido[3,4-c]pyridazine (292)	155.2 153.7
1,2-di-tert-butoxycarbonyl-1,2,3,4-tetrahydropyrido[3,2-c]pyridazine (253)	153.7 146.2
diethyl N-[2-(2-pyridyl)prop-1-en-3yl]-hydrazo-N,N'-dicarboxylate (267)	156.4 156.0

The other ^{13}C data of the oxadiazine was in good agreement with the proposed structure (313).

4. Von Gustorf and co-workers report[67] that oxadiazine formation occurred only between an 'electron rich' double bond and an 'electron poor' diene. No products with the oxadiazine structure were isolated from the reaction of 2- and 4-vinyl pyridine (90) and (291) (which contain an electron deficient double bond) and azodicarboxylate diesters.

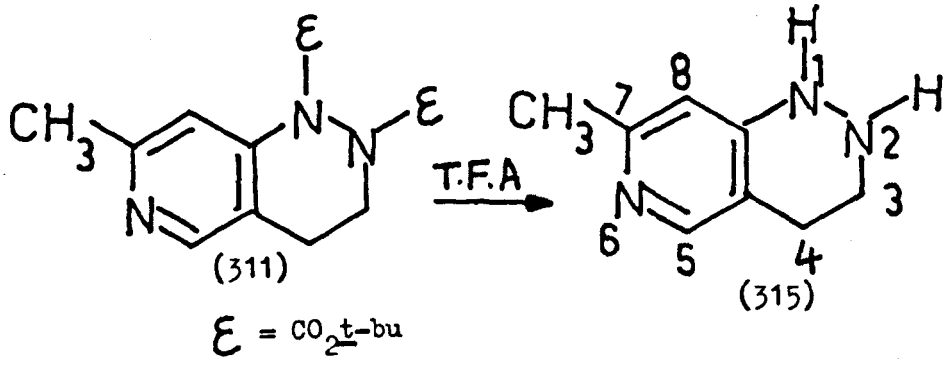
The oxadiazine (313) may be formed via a concerted or stepwise mechanism, from our results it was not possible to differentiate between these two processes.

Removal of the t-butyl ester groups from the adducts (310) and (311) should lead to the little studied parent systems.

Removal of the t-butyl groups from the pyrido[2,3-c]pyridazine adduct (310) was not carried out due to the small amount of material obtained.

Removal of the t-butyl groups from the pyrido[4,3-c] pyridazine (311) and subsequent oxidation posed some interesting problems.

Addition of T.F.A. to the di-tert-butyl pyrido[4,3-c] pyridazine adduct (311), followed by warming at 50°C for ¾ hr. gave the expected 1,2,3,4-tetrahydropyrido[4,3-c]pyridazine (315) in virtually quantitative yield.



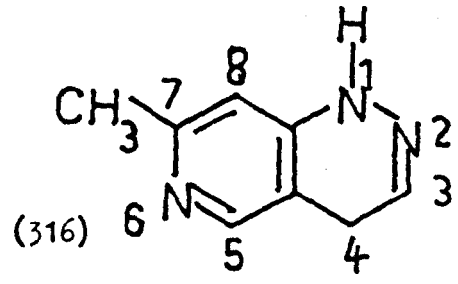
(311) (315)

Ɛ = CO_2t-bu

The mass spectrum showed an M^+ at 149 a.m.u. with a base peak at 145 (M^+ - 4H), corresponding to the parent pyrido[4,3-c] pyridazine, the breakdown pattern then closely follows other aza-cinnolines. The ^1H n.m.r. spectrum showed two downfield one proton singlets at δ = 7.85 and 6.25 p.p.m. A broad singlet at δ = 5.9 p.p.m. which was exchangeable with D_2O was assigned to the two N-H protons. The C-3 and C-4 methylene groups were seen as distorted triplets at δ = 3.1 and 2.65 p.p.m. The methyl group attached to C-7 was seen as a three proton singlet at δ = 2.3 p.p.m.

Treatment of this hydrazo compound (315) with mercuric oxide (red) gave, after work up, an oil which gave an M^+ at 147 a.m.u. (88%) and a base peak at 146 a.m.u.

The ^{1}H and ^{13}C n.m.r. spectrum showed the compound to be the (1H)-1,4-dihydro-7-methylpyrido[4,3-c] pyridazine (316).



The ^{1}H n.m.r. spectrum (Fig. 26) showed a broad singlet (exchangeable with D_2O) at δ = 8.4 p.p.m., and two one proton singlets at δ = 8.0 and 6.4 p.p.m. assigned to H-5 and H-8 respectively. Between these two signals was observed a one proton triplet at 6.8 p.p.m., J = 3 Hz, attributed to H-3. The C-4 methylene group was observed at δ = 3.3 p.p.m. as a doublet (J = 3 Hz). Thus the methylene group must consist of two protons which lie on either side of the double bond, this stereochemistry gives a geminal coupling constant of zero. The C-7 methyl group was observed as a three proton singlet at δ = 2.4 p.p.m.

The ^{13}C n.m.r. spectrum confirmed the postulated structure (316), the completely decoupled and off-resonance spectra are shown (Fig. 27) and respectively.

The most important features of the spectra are the carbon resonance at 105.3 p.p.m. which was assigned to C-3. It was seen as a doublet in the off-resonance spectrum indicating that one proton is attached to C-3. The C-4 carbon atom resonates at δ = 29.7 p.p.m. and was observed as a triplet in the off-resonance spectrum indicating a methylene group present. The other parameters of the ^{13}C n.m.r. spectrum are in good agreement with the proposed structure (316). The N-H absorption was confirmed by the single peak in the infrared

Fig. 26 ^{1}H N.m.r. spectrum of (1H)-1,4-dihydro-7-methyl-pyrido-[4,3-c]pyridazine (316)

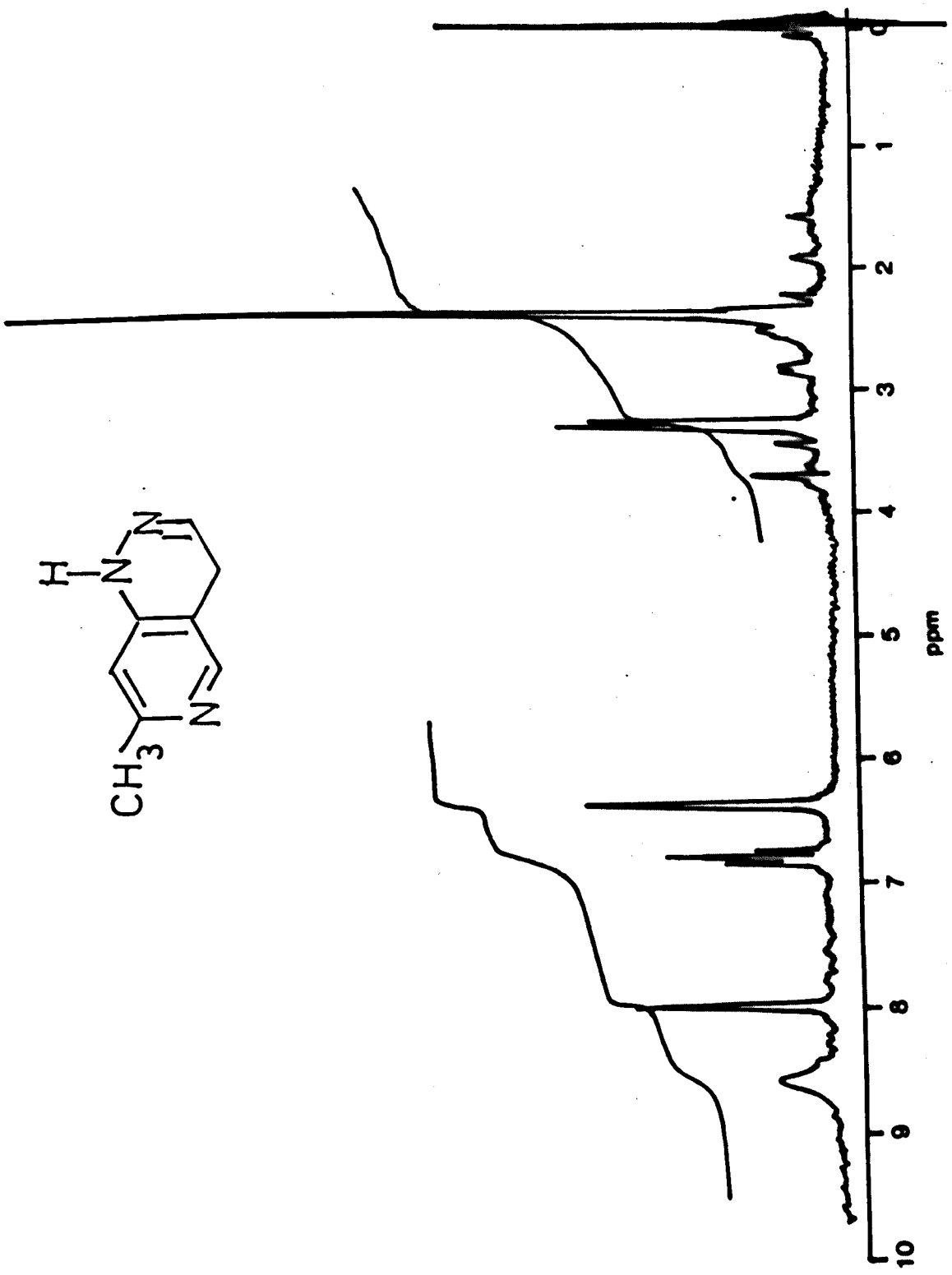
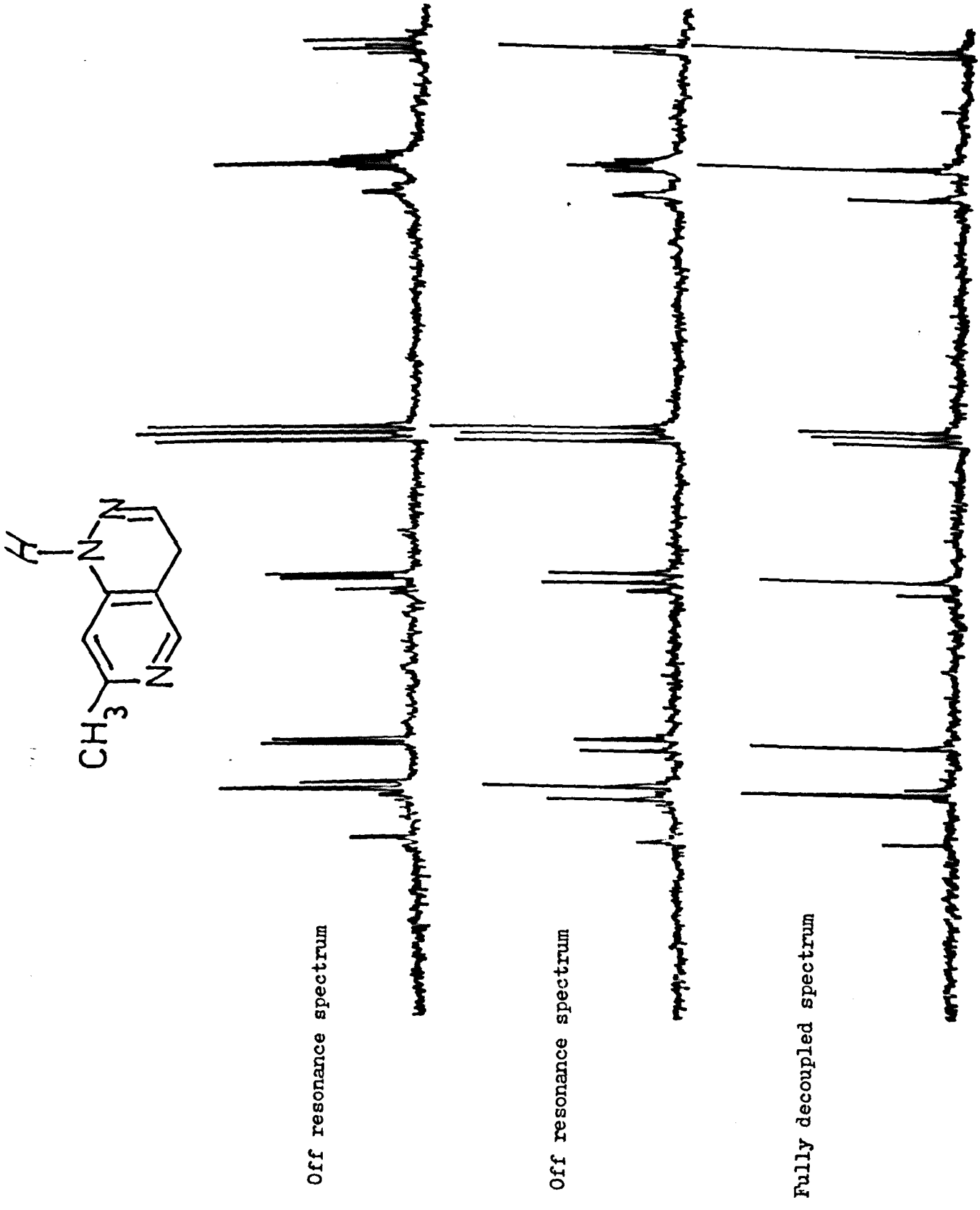


Fig. 27 ^{13}C N.m.r. spectra of (1H)-1,4-dihydro-7-methyl-pyrido-[4,3-c]pyridazine (316)



at 3410 cm^{-1}, which also contained a broad peak at 1660 cm^{-1} which may be assigned to $\geq C=N-$ stretch.

Attempts to purify this product (316) by recrystallisation from carbon tetrachloride, caused a rearrangement to take place to another unidentified product, whose ^1H n.m.r. contained a pair of doublets at δ = 8.2 p.p.m. and other aromatic type absorptions around δ = 7.2 p.p.m.

Crystallisation of compound (316) could be induced by leaving the oil in the fridge overnight, the solid obtained, m.pt. 151 - 153°C (decomp.), gave incorrect microanalysis figures for an empirical formula of $C_8H_9N_3$. A sample submitted for exact mass showed a molecular formula of $C_8H_9N_3$ for the peak at 147 a.m.u.

Reaction of 2-methyl-5-vinyl pyridine (306) with diethyl and di-tert-butylazodicarboxylate (97) and (252) gave the pyrido [2,3-c] and [4,3-c] pyridazines albeit in poor yields. Attempts to prepare the parent aromatic pyrido[4,3-c]pyridazine failed; a partially reduced system (316) was obtained.

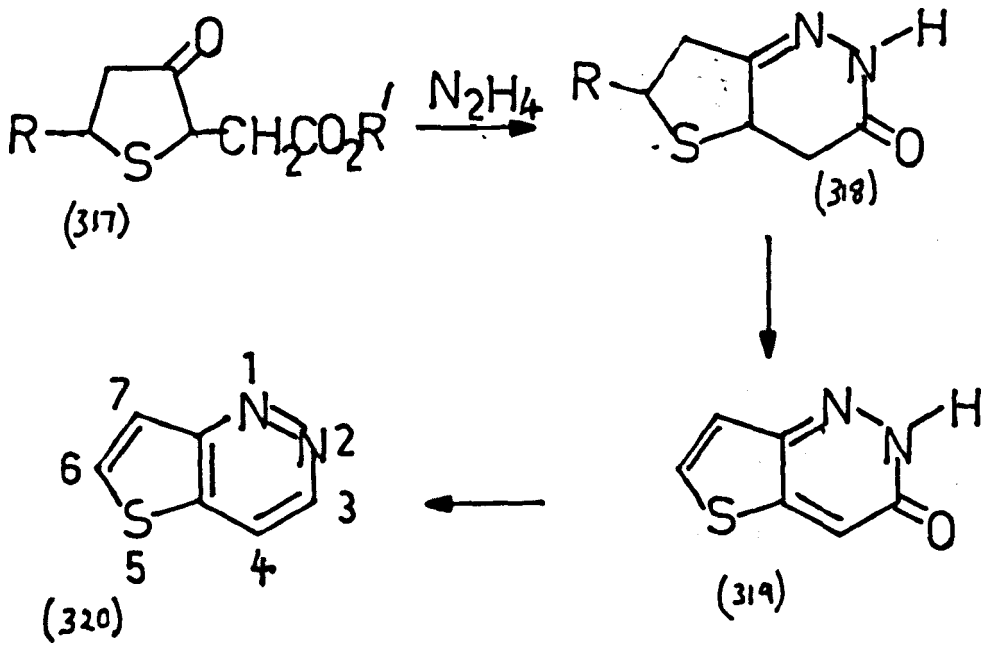
(VII) Thieno[3,2-c]pyridazine.

The cycloaddition of vinyl pyridines, to diesters of azodicarboxylic acid, is an example of interaction between an electron deficient 'diene' and an electron deficient dienophile.

The 'Alder Rule' states that an electron deficient dienophile would prefer to react with an electron rich diene; the reverse is also true.[100]

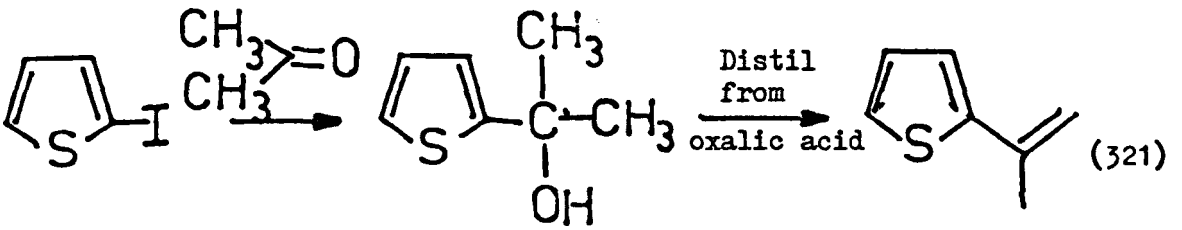
One would expect therefore that addition of azodicarboxylate diesters to vinyl thiophen (142) or vinyl furan (170) would be a more favourable process, the reaction rate being increased, and also the yields of the products may be greater.

There is only one reference at the present time to the thieno[3,2-c]pyridazine system (320). Poole and Rose[101] describe a synthesis leading to some reduced analogues and to the parent compound, in poor overall yield. The tetrahydrothiophen derivative (317) was cyclised with hydrazine to the thieno[3,2-c]pyridazinone (318) (R = H or CO_2Me). The ester (R = CO_2Me) was then dehydrogenated and decarboxylated to thieno[3,2-c]pyridazin-6(5H)-one (319) which after treatment with phosphonyl chloride and dehalogenation afforded the parent thieno[3,2-c]pyridazine (320).



Reactions of 2-vinyl thiophen (142) as a diene are well known and are documented in the Introduction to Part 2 of this thesis.

We first considered the reaction of 2-(2'-thieno)-propene (321) with diesters of azodicarboxylic acid. The vinyl heterocycle was easily prepared by addition of acetone to the Grignard reagent of 2-iodothiophen,[102,103] followed by distillation of the tertiary alcohol so formed from oxalic acid, to give the isopropenylthiophen (321) in good yield.



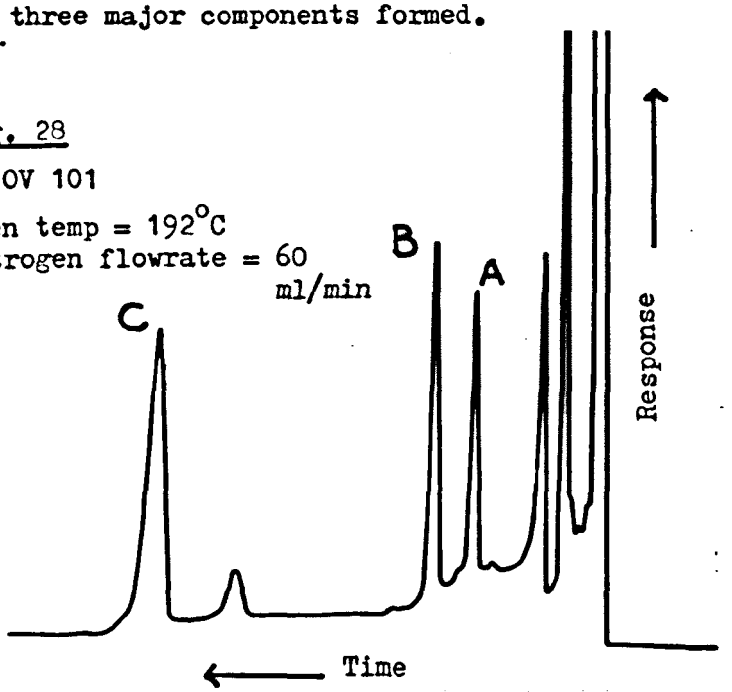
Reaction of 2-(2'-thieno)-propene (321) with diethyl azodicarboxylate (97) in boiling acetonitrile was as expected, much faster than with the pyridine series. G.l.c. (3% OV101, oven temperature = 120°C) showed that after one hour there was no dienophile present in the reaction. Similarly reaction between di-tert-butyl azodicarboxylate (252) and 2-(2'-thieno)-propene (321) in boiling benzene was completed after fourteen hours (cf eight days with 2-vinyl pyridine). A g.l.c. trace (Fig. 28) showed that there were at least three major components formed.

Fig. 28

3% OV 101

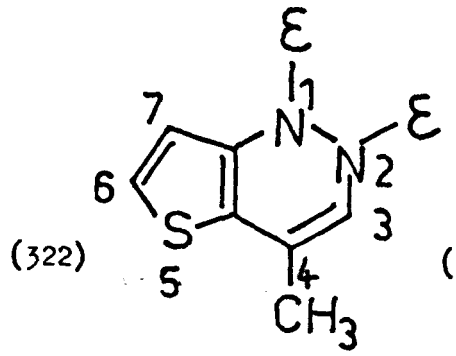
Oven temp = 192°C

Nitrogen flowrate = 60 ml/min



T.l.c. showed three major fluorescent spots. The components of the oil were separated by p.l.c. which gave three fluorescent bands plus some minor bands close to the base line.

The fastest running fluorescent band was extracted and its spectra were consistent with structure (322), 1,2-di-tert-butoxycarbonyl-4-methyl-1,2-dihydro-thieno[3,2-c]pyridazine.



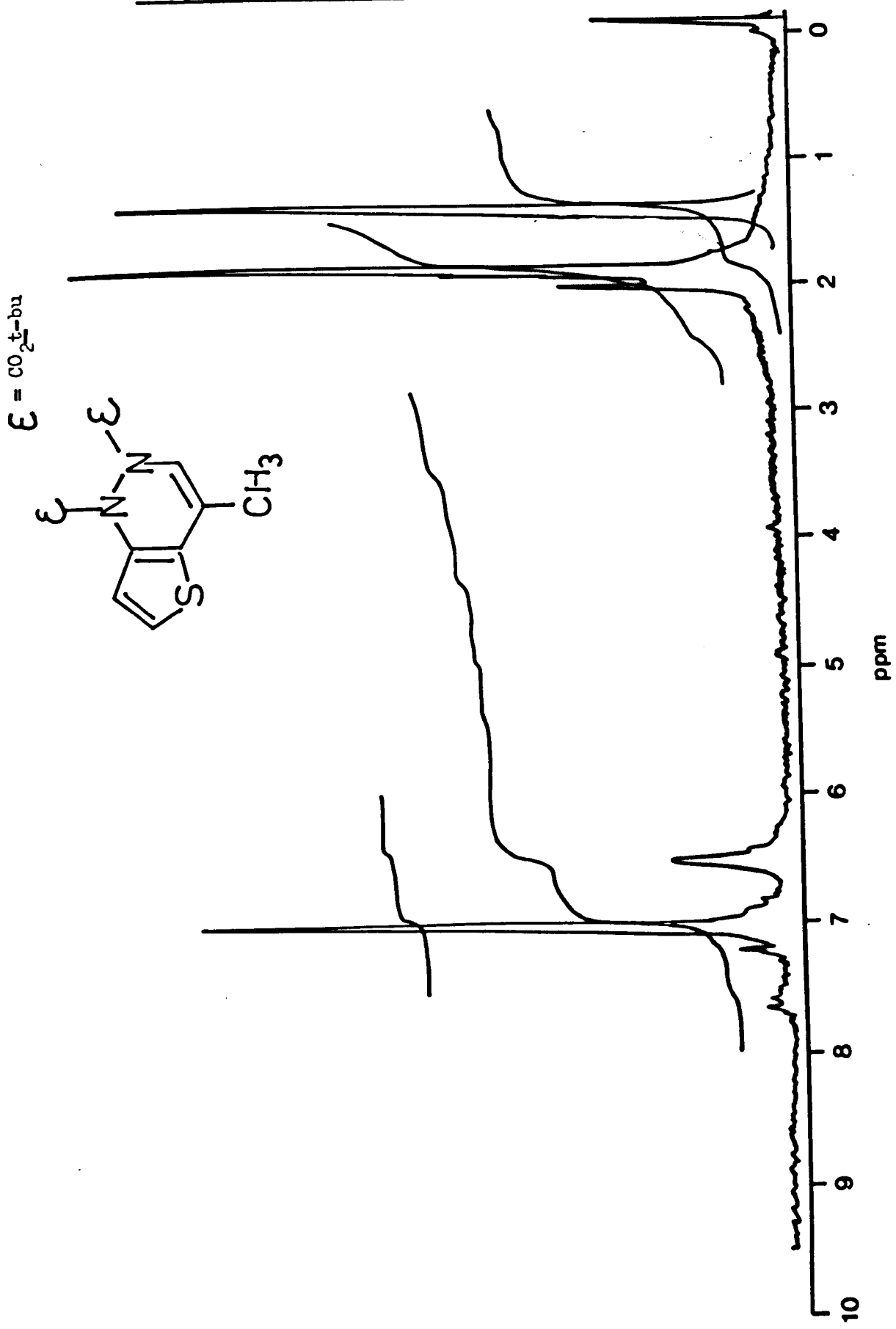
(322) (10%)

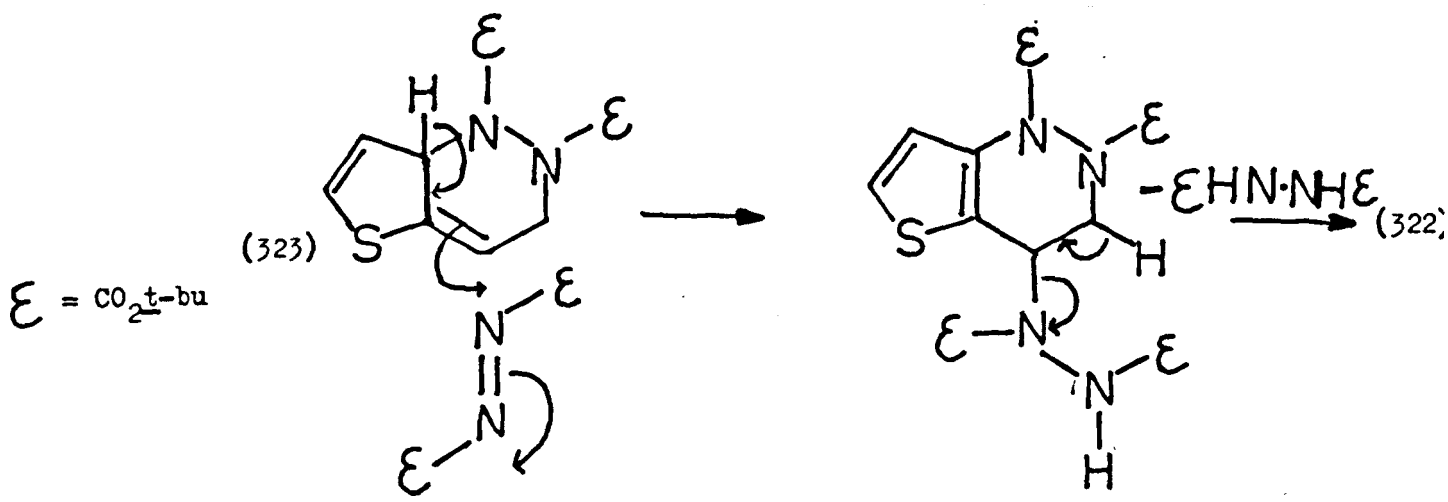
$\mathcal{E}$ = CO_2t-bu

Microanalysis after bulb distillation gave the empirical formula as $C_{17}H_{24}N_2O_4S$. The mass spectrum showed the highest peak to be at 152 a.m.u. $M^+ - [(2 \times CH_2 = C(CH_3)_2 + 2 \times CO_2)]$, the fragmentation pattern also agrees well with the proposed structure (322). The ^1H n.m.r. spectrum (Fig. 29) shows a two proton singlet at δ = 7.1 p.p.m., attributed to the two thiophen protons H-6 and H-7, which have the same chemical shift and therefore do not couple. The broad singlet at δ = 6.6 was attributed to the ring olefinic proton H-3, the broadening was probably caused by allylic coupling to the C-4 methyl group, which was seen as a three proton singlet at δ = 2.0 p.p.m. The two t-butyl groups were seen to resonate at δ = 1.5 p.p.m. as an eighteen proton singlet.

This dihydrothieno[3,2-c]pyridazine compound (322) was formed by cycloaddition of one molecule of 2-(2'-thieno)-prop-2-ene and one molecule of the di-tert-butyl azoester (252) followed by dehydrogenation by some mechanism. One possible mechanism which could account for the dehydrogenation was ene addition of a second molecule of the di-tert-butyl azoester to the initially formed cycloadduct (323), followed by elimination of di-tert-butyl hydrazodicarboxylate, to give the observed product. Diethyl azodicarboxylate (97) is known to possess general hydrogen-abstracting properties, e.g. it oxidises primary and secondary alcohols and hydrazobenzene to aldehydes,

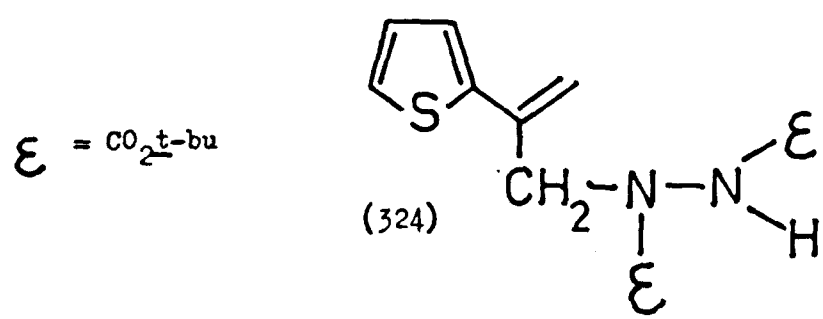
Fig. 29 ^{1}H N.m.r. spectrum of 3,4-dihydro-1,2-di-tert-butoxycarbonyl-4-methylthieno[3,2-c]pyridazine (322)





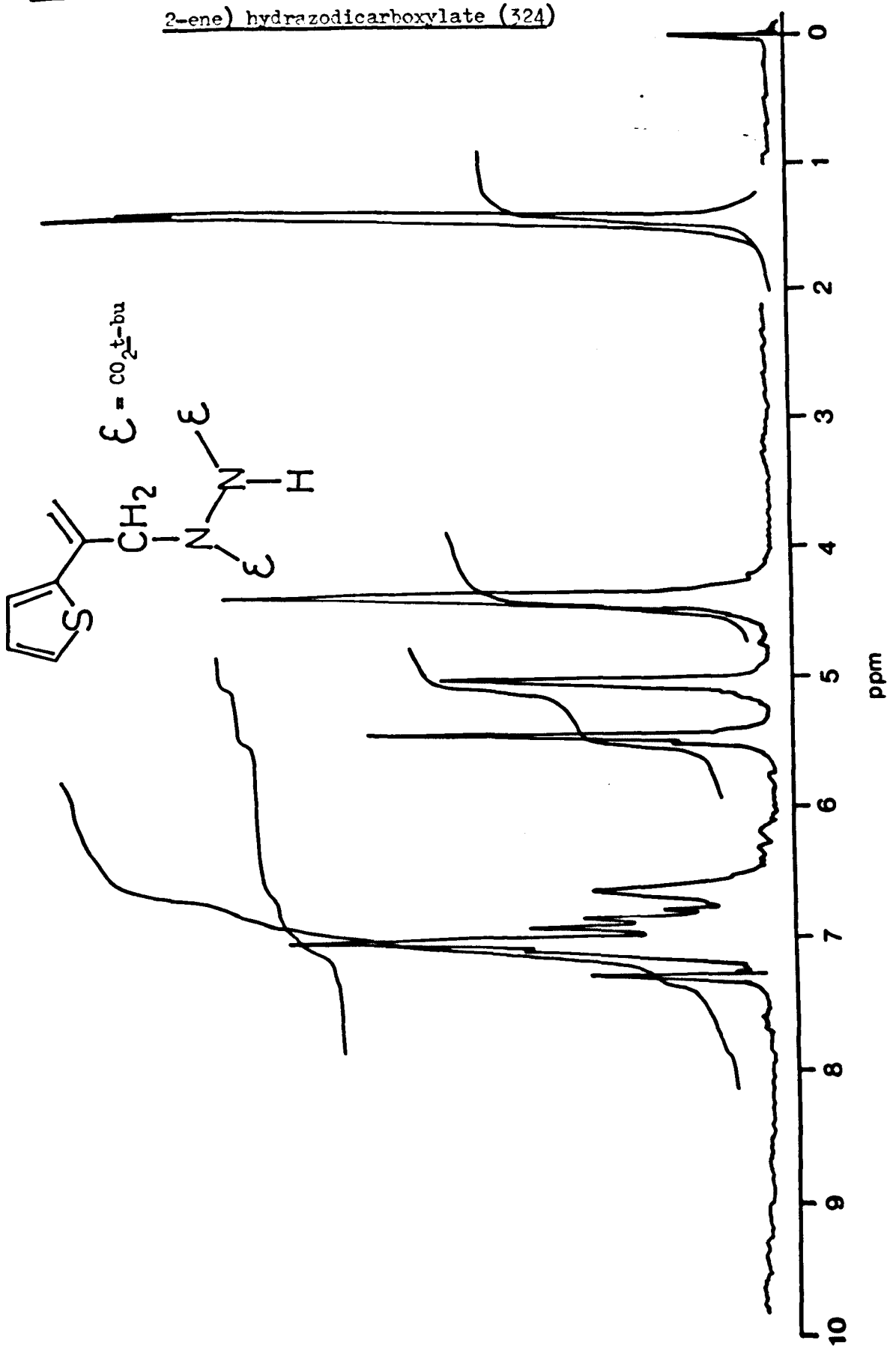
ketones and azobenzene respectively.[69,89]

The middle fluorescent band was also obtained as an oil (23.5%), microanalysis gave its empirical formula as $C_{17}H_{26}N_2O_4S$. The mass spectrum contained the highest peak at 154 a.m.u. $M^+ - (2 \times CH_2 = C(CH_3)_2 + 2 \times CO_2)$, the fragmentation pattern was different from that of the previously described adduct. The ^1H n.m.r. spectrum (Fig. 30) contains three downfield thiophen protons between δ = 7.5 and 6.8 p.p.m. and also a broad one proton signal at δ = 6.65 p.p.m. which was exchangeable with D_2O. The best structure which agrees with the spectroscopic data was that of the di-tert-butyl 2-(2'-thieno)-prop-2-ene-hydrazodicarboxylate (324). The two terminal



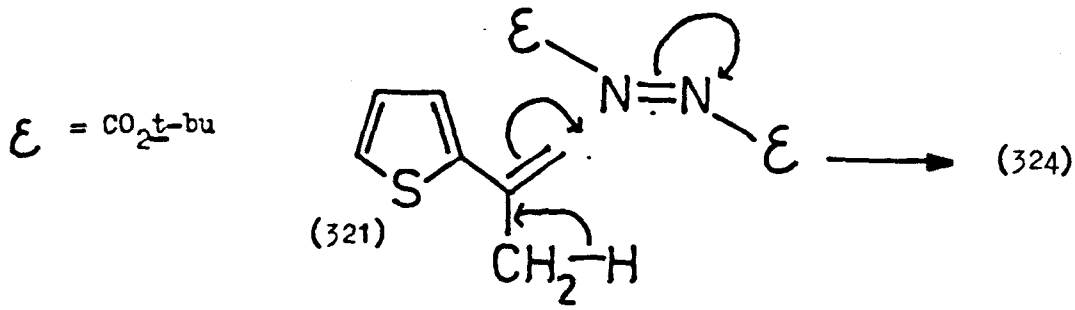
olefinic protons were seen as two singlets at δ = 5.45 and 5.05 p.p.m., the allylic methylene group resonated at δ = 4.40 as a singlet and the remaining t-butyl groups were observed as nine proton singlets at

Fig. 30 ^{1}H N.m.r. spectrum of di-tert-butyl 1-(2-(2'-thieno)-prop-2-ene) hydrazodicarboxylate (324)



δ = 1.50 and 1.45 p.p.m. respectively.

The product (324) was most probably formed by ene addition of di-tert-butyl azodicarboxylate to the allylic double bond. The reaction may be concerted or stepwise, no work was done to determine the mechanism of the reaction.



Other examples are known[87,88] where cycloaddition competes with ene addition.

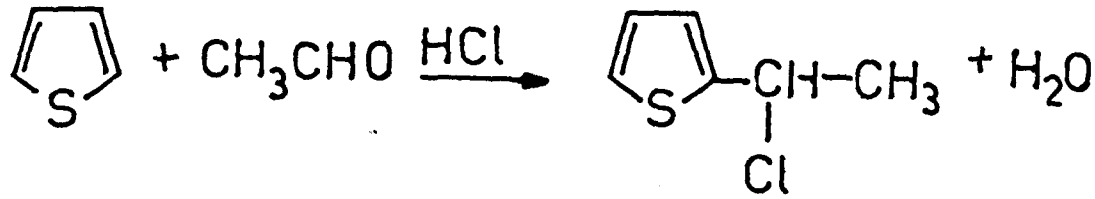
The two characterised products (322) and (324) correspond to the two peaks A and B seen in the g.l.c. trace of the crude reaction products.

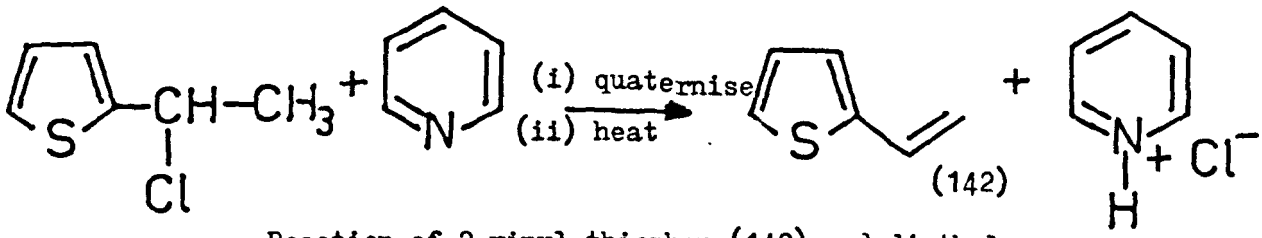
The third fluorescent band (26.0%) which gave the broad peak C plus other minor unidentified products in the g.l.c. trace, contained many components. Repeated chromatography did not yield any purer products and no plausible structures could be proposed from the physical data.

Cleavage of the t-butyl groups of the dihydro cycloadduct was not attempted because of the poor yield of the product.

Attempts to prepare the thieno[3,2-c]pyridazine system from 2-(2'-thieno)propene (321) were less successful than was hoped, due to the ene activity of the vinyl heterocycle employed.

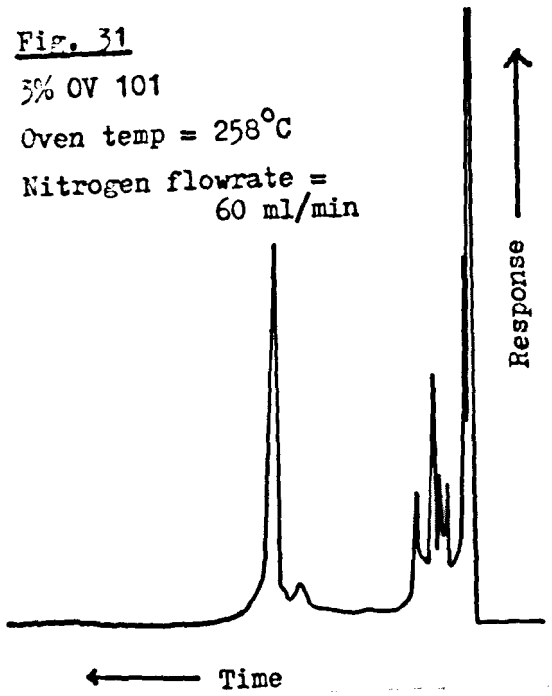
A good method of preparation of 2-vinyl thiophen (142) is reported in "Organic Synthesis".[104]



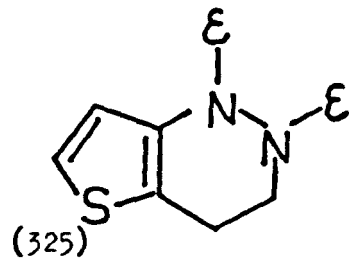


Reaction of 2-vinyl thiophen (142) and diethyl azodicarboxylate (97) was completed after half an hour in boiling acetonitrile.

A g.l.c. trace (Fig. 31) of the crude reaction products showed at least five components present, one major.

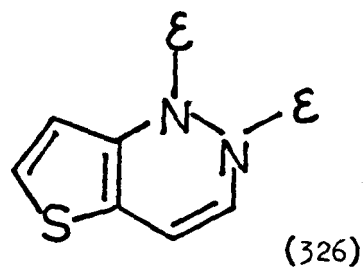


Separation of the products by p.l.c. gave the major component in 36.0% yield. From the ^1H n.m.r. it could be seen that more than one component was present. The mass spectrum contained M^+ values at 282 and 284 a.m.u., which could be attributed to the mixture containing the two cycloaddition products (325) and (326).



(325)

M^+ 284



(326)

M^+ 282

$\mathcal{E}$ = CO_2t-bu

A g.l.c. trace of this major component showed it to contain almost as many products as was seen in the g.l.c. trace of the crude reaction products. Carrying out the reaction:

1. In the presence of a small amount of quinol,
2. Under nitrogen, or
3. In a lower boiling solvent,

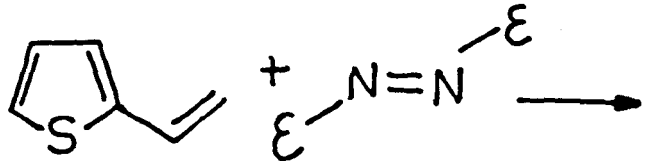
did not alter the ratio of products formed in the reaction, to any great extent.

It was decided to react 2-vinyl thiophen (142) with di-tert-butyl azodicarboxylate (252) and remove the ester groups from the major product using T.F.A., to see if any of the fully aromatic thieno[3,2-c] pyridazine (320) could be obtained.

Reaction of 2-vinyl thiophen (142) with di-tert-butyl azodicarboxylate (252) in boiling benzene was completed in seven hours. Column chromatography gave a major fraction in 35.9% yield, that contained more than one product. Treatment of a sample of this oil (1.04 g) with T.F.A., followed by the usual oxidation procedure (HgO (red), O_2) gave an oil which upon T.L.C. was seen to contain a slow running purple fluorescent spot plus some faster running components.

The products were separated by p.l.c., the purple fluorescent band proved to be the parent thieno[3,2-c] pyridazine (320) (70 mgs).

The faster running bands were not identified.



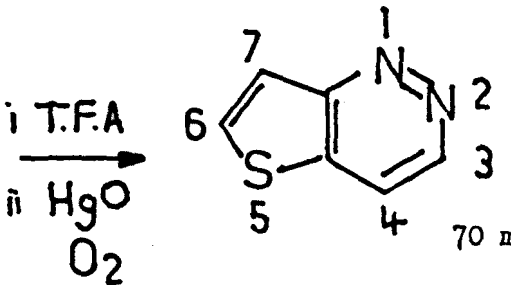
major component

$\mathcal{E}$ = $CO_2C_2H_5$, 36.0%
$\mathcal{E}$ = CO_2t-bu, 35.9%

major component

1.04 g

$\mathcal{E}$ = CO_2t-bu



70 mg

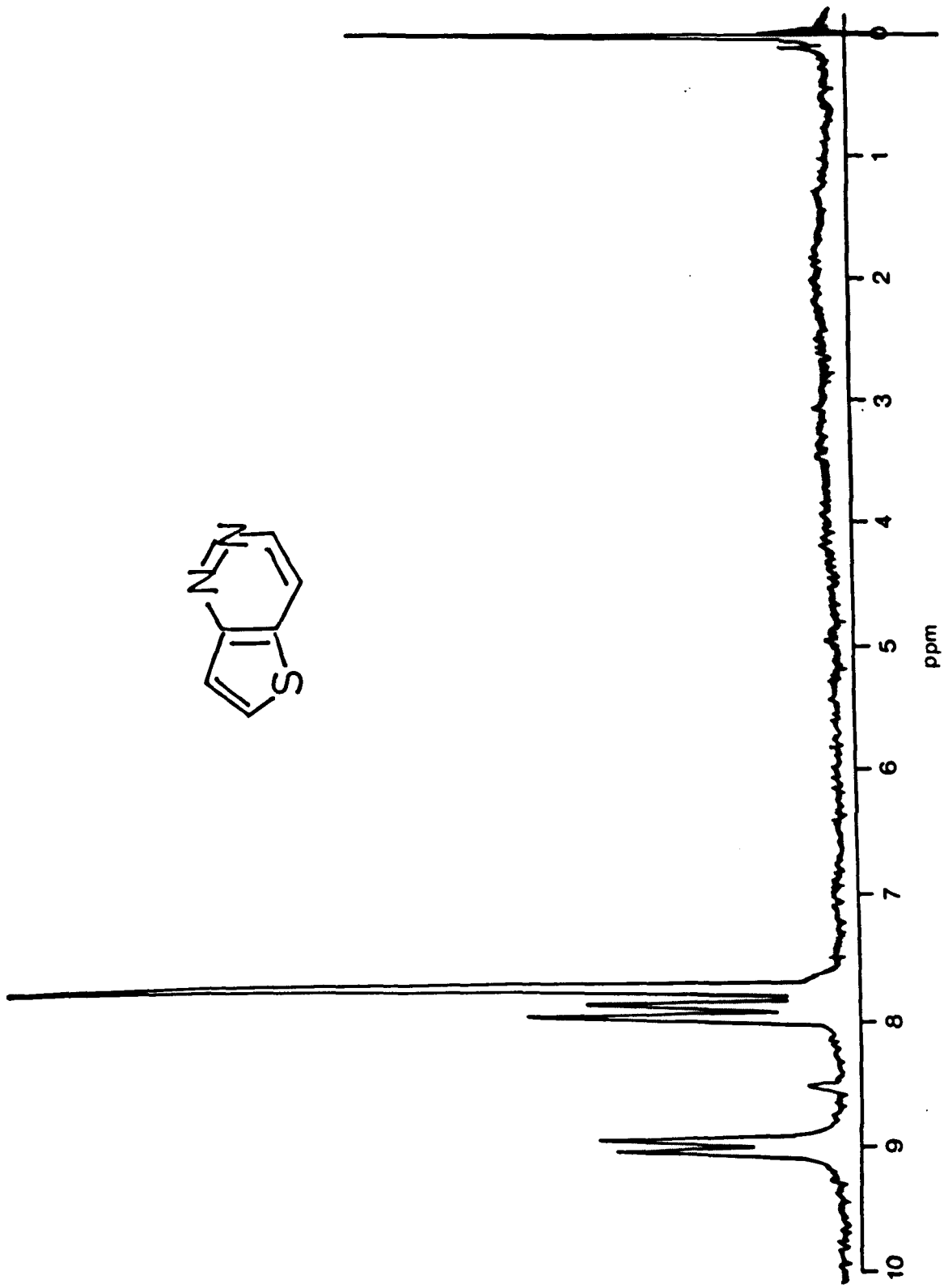
(320)

The thieno[3,2-c]pyridazine (320) was obtained as a crystalline solid, m.pt. 98.5 - 99°C (literature[101] m.pt. 97.5 - 98.5°C). Microanalysis confirmed its empirical formula as $C_6H_4N_2S$. A mass spectrum contained an M^+ at 136 a.m.u., the fragmentation pattern is similar to that of the parent pyrido[3,2-c]pyridazine system (87).

The ^1H n.m.r. spectrum (Fig. 32) was similar to that quoted by F.L. Rose. The two one proton doublets at δ = 9.0 and 7.95 p.p.m. (J = 6 Hz) were attributed to the ring pyridazine protons H-3 and H-4 respectively. The two proton singlet at δ = 7.25 p.p.m. was assigned to the two thiophen protons H-6 and H-7, which have the same chemical shift and therefore do not couple. The u.v. and i.r. spectra obtained agreed well with those quoted in the literature.

The multiproduct formation during the reaction of the vinyl thiophen (142) and the azoester, prevented a good yield of the parent thieno[3,2-c]pyridazine (320). The formation of many products during reaction of vinyl heterocycles with dienophiles has been observed by other workers.

Fig. 32 ^{1}H N.m.r. spectrum of thieno[3,2-c]pyridazine (320)



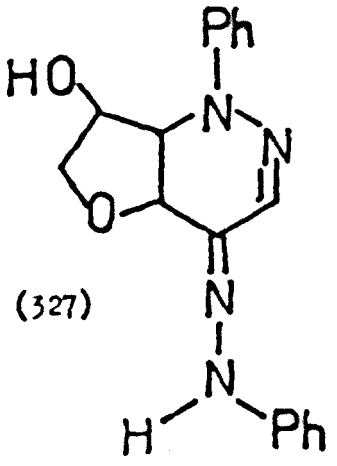
(VIII) Furo[3,2-c]pyridazine.

The little studied furo[3,2-c]pyridazine system ought to be obtainable by reaction of 2-vinyl furan (190) and diesters of azodicarboxylate. Electronically the reaction should be more favourable, since an 'electron rich diene component' interacts with an electron deficient dienophile.

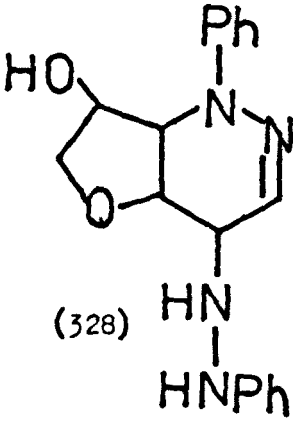
Furan itself readily participates in Diels-Alder reactions. However in the case of 2-vinyl furan (190) there are two alternative diene systems, namely the cis-orientated diene of the ring system and a second consisting of the exocyclic double bond and the adjacent furan ring "double bond".

Previous work has shown that it was always this latter diene system that participated in cycloaddition reactions with maleic anhydride[56] (see Introduction to Part 2 of this thesis, p.92). However Elix and Davidson[58] have shown that products may be obtained, formed by participation of both diene systems of 2-vinyl furan (190) when it reacts with dimethyl acetylenedicarboxylate (112).

There are few reports in the literature concerning the furo[3,2-c]pyridazine system. The first report was contained in a communication by Hensecke, Muller and Badicke.[105] They rejected the structural formula for dianhydrohexosazone proposed earlier by Percival[106] and suggested either of the furo[3,2-c]pyridazine structures (327) or (328).



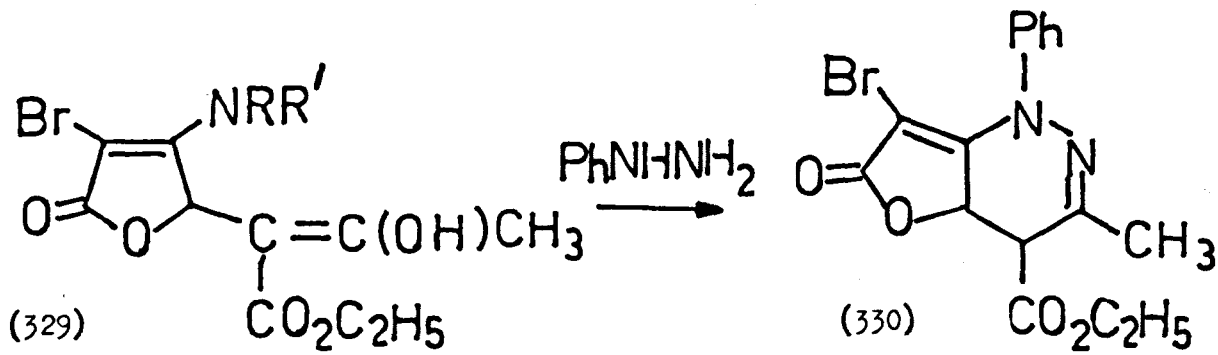
(327)



(328)

The hydrazone and hydrazo groups may be hydrolysed by nitrous acid to give the ketone and enol respectively.

Phenyl hydrazine underwent reaction with the amino butyrolactone (329) to give the furo[3,2-c]pyridazine system (330).[107]

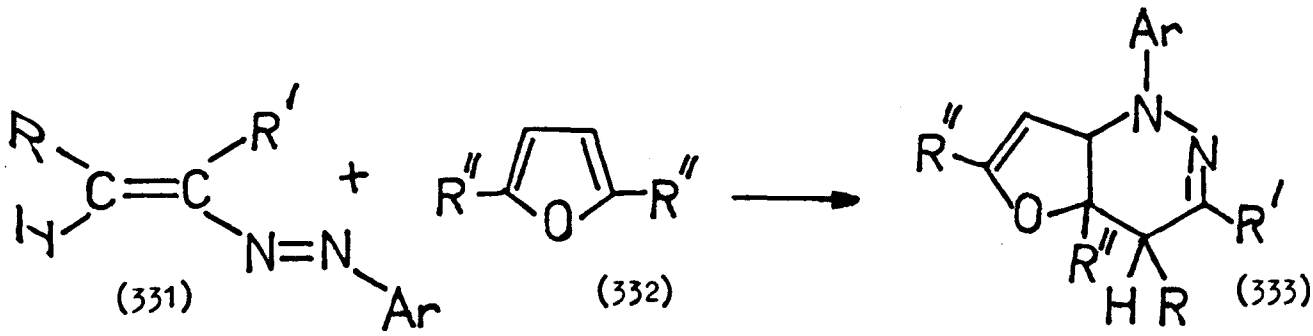


(329) (330)

R = C_2H_5, n-bu, R' H, H

NRR' = piperidino, morpholino

Gilchrist and Faragher[108] have shown that the azoalkene (331) reacts with furan derivative (332) to give the furo[3,2-c] pyridazine (333) derivatives in good yield.



(331) (332) (333)

Ar = $C_6H_3(NO_2)_2$ - 2,4

R	R'	R''	Yield %
H	Ph	H	89
H	Ph	CH_3	87
H	CH_3	H	22

Slow distillation of 2-furanacrylic[109] acid in quinoline in the presence of anhydrous copper sulphate[110] gave 2-vinyl furan (190) in poor yield.

Reaction of 2-vinyl furan (190) with di-tert-butyl azodicarboxylate took three hours to go to completion in boiling benzene.

Separation of the products by p.l.c. gave two major fluorescent bands. The faster running band contained at least six components, further purification of which by chromatographic methods was not achieved.

The slower running fluorescent band also contained a mixture of components. Further separation by p.l.c. gave a mixture of products. No structural assignment for components of this oil was possible, although the size of the t-butyl ester absorption in the ^1H n.m.r. indicated that higher adducts may have been formed. The mass spectrum contained the highest peak at 150 a.m.u.

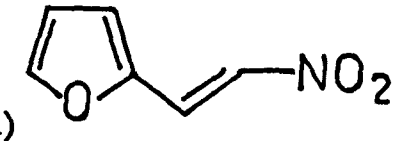
A slight exothermic reaction occurred on stirring 2-vinyl furan (190) and diethyl azodicarboxylate (97) at room temperature, the reaction took one hour to go to completion. The same type of mixture was obtained as was obtained with di-tert-butyl azodicarboxylate (252). Carrying out the reaction at 0°C gave no isolable products.

Many products were observed by Elix and Davidson[58] in the reaction of 2-vinyl furan (190) and dimethyl acetylenedicarboxylate (95). (See p.93). They proposed that 2-vinyl furans were unstable and rapidly polymerised even under nitrogen and in the presence of a polymerisation inhibitor.

We found that 2-vinyl furan (190) was stable at 0°C for two weeks or more. Also the end point of the reaction between 2-vinyl furan (190) and diesters of azodicarboxylate was when g.l.c. or t.l.c. indicated the absence of the azodiesters, which must have undergone

reaction with the vinyl heterocycle. Diesters of azodicarboxylic acid are known to be stable up to 100°C above which they decompose, sometimes explosively, presumably into nitrogen, carbon dioxide and alkyl radicals.[89]

Using a method based on that of Goldfarb and Kalinovskii,[111] 2-(2'-nitrovinyl) furan (334) was prepared, by a Knoevenagel condensation reaction between furfural and nitromethane.

(334) 

Reaction of diethylazodicarboxylate (97) and 2-(2'-nitrovinyl) furan (334) in boiling acetonitrile was completed after 7½ days. Chromatographic separation of the products did not yield any pure isolable compounds.

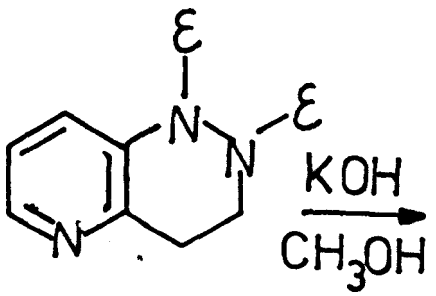
The reaction of the azoester dienophiles with the 'electron rich dienes' 2-vinyl furan and thiophen, led to mixtures of products, which were difficult to separate.

(IX) Cleavage of the ethyl ester adducts using trimethyl silyl iodide.

The parent pyrido[3,2-c]pyridazine (87) was synthesised via the t-butyl adduct (253), by cleavage of the t-butyl groups using T.F.A., followed by oxidation. Preparation of the t-butyl adduct (253) required the use of di-tert-butyl azodicarboxylate (252), which is expensive and produced long reaction times.

Attempts to prepare the pyrido[3,2-c]pyridazine (87) by

basic hydrolysis of the ethyl ester groups of the adduct (248) gave a mixture of products, probably due to their instability towards the basic conditions employed.



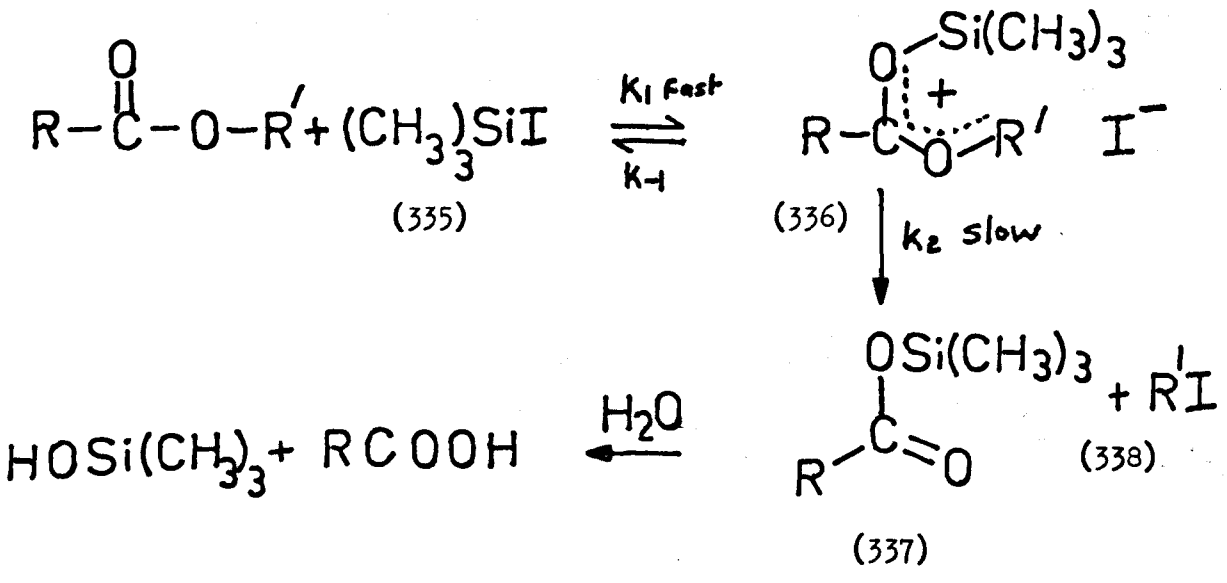
mixture of products

$\mathcal{E}$ = $CO_2C_2H_5$ (248)

Successful cleavage of the ethyl ester groups would give a better synthesis.

Michael Jung has reported[112] an efficient dealkylation procedure, which proceeds in virtually quantitative yield under neutral conditions. It involves the treatment of alkyl carboxylic esters with trimethylsilyl iodide (335), followed by aqueous hydrolysis. The authors have also shown that dealkylation of ethers may be carried out using trimethylsilyl iodide (335).[113]

In the suggested mechanism for the cleavage the ester reacts with the trimethylsilyl iodide in a fast and reversible step to produce the silylated ester iodide salt (336) which can then go on to products (337) and (338) in a slow, irreversible process by either an S_N2 mechanism (R^1 = Me, Et) or an S_N1 mechanism (R^1 = tert-bu, CH_2Ph).



R' = CH_3, C_2H_5, i-Pr, i-bu, CH_2Ph

The authors do not discount the possibility that the reactions may be due entirely to small amounts of hydrogen iodide present in the trimethylsilyl iodide (335), although in the presence of 10-15 mole % pyridine, ester dealkylation does occur, at a slow rate.

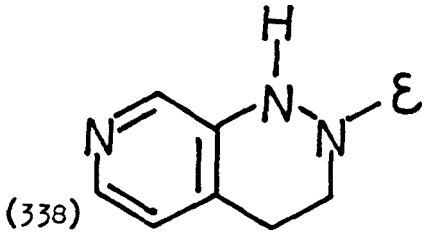
No report of cleavage of carbamates using trimethylsilyl iodide (335) is known.

Trimethylsilyl iodide (335) was easily prepared from trimethylsilyl chloride in two steps.[113]

The conditions of the dealkylation were worked out employing the diethyl ester adduct (248) formed from 2-vinyl pyridine (90), but subsequent work was carried out on the diethyl ester adduct (292) prepared from 4-vinyl pyridine (291) and diethyl azodicarboxylate (97), where larger amounts of material were available.

Dealkylation of diethoxycarbonyltetrahydro-pyrido[3,4-c] pyridazine (292) using trimethylsilyl iodide (335) (ratio 1 : 2 moles) was carried out on a small scale in an n.m.r. tube, at 50°C, following

the decrease of the ethyl ester signal and increase of the ethyl iodide signal. After 24 hours the ratio of the two signals did not alter. After work up the major product was shown to be the mono ester (338).



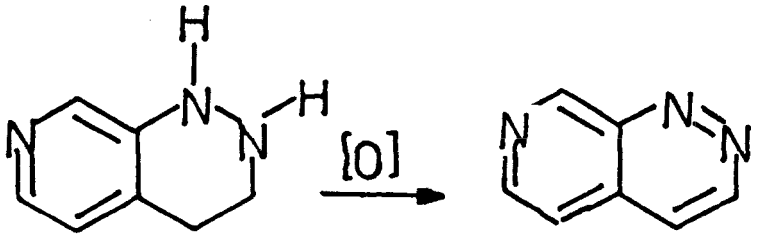
(338)

$\mathcal{E} = CO_2C_2H_5$

Mass spectrum showed an M^+ at 207 a.m.u., the ^1H n.m.r. spectrum showed three downfield protons, a singlet at δ = 8.75 p.p.m., a doublet at 8.1 p.p.m. (J = 6 Hz) and an equivalent doublet at δ 6.95 p.p.m. A signal which integrates for three protons was seen between δ = 4.0 and 4.5 p.p.m., as a quartet, attributed to the methylene group of the remaining ethyl ester substituent which is superimposed on the N-H absorption. The two C-3 and C-4 methylene groups resonate as distorted triplets at δ3.25 and 2.7 p.p.m. respectively. The remaining methyl absorption of the ester substituent was also observed as a distorted triplet. Also present were some high field absorptions, presumably due to hexamethyldisiloxan.

The three aromatic absorptions were all moved upfield in the mono ester compound (338) compared to the diester adduct (292), (cf δ = 9.0 (1H, s), 8.3 (1H, d, J = 6 Hz) and 7.15 p.p.m.(1H, d, J = 6 Hz)), which showed that the ethyl ester group at N-1 has been cleaved.

The remaining ethyl group was cleaved using the same procedure (40 hours) to give an oil, ^1H n.m.r. indicated that it was due mainly to the tetrahydropyrido[3,4-c]pyridazine (294), although high field absorptions were still present.



(294) (295)

Oxidation by the usual procedure (HgO, then O_2) gave the parent pyrido[3,4-c]pyridazine (295), confirmed by ^1H n.m.r., which also showed the continued presence of the high field absorptions. The product was separated from this contamination by p.l.c., to give the pyrido[3,4-c]pyridazine (295)in 30.6% yield from the diethyl adduct (292).

Attempts to scale up the cleavage reaction using trimethylsilyl iodide (335) (on ≃ 0.5g ethyl adduct) gave the monoester, but subsequent treatment resulted in unidentifiable products.

On a small scale, cleavage of the ethyl esters of the adduct (292) was accomplished using trimethylsilyl iodide (335). One ester group was observed to be preferentially cleaved, probably due to steric considerations, after work up, the monoester (335) may be isolated. The remaining ethyl ester group may be then cleaved. On scale up of the reaction, cleavage of the second ethyl ester group failed; problems may be encountered due to silylation of the free nitrogen.

EXPERIMENTAL TO PART II

CONTENTS

-oOO-

EXPERIMENTAL

A General procedure for reaction of vinyl heterocycles with:

1. Diethyl azodicarboxylate (97).

Diethyl azodicarboxylate (97) (0.05 mole) and the vinyl heterocycle (0.05 mole) in acetonitrile (100 mls) were boiled and the reaction followed by g.l.c., (3% OV 101 volume oven temp = 120°C, nitrogen flow rate = 60 mls/min). Reaction times are given below.

Vinyl heterocycle	Reaction time (Hours)
2-vinyl pyridine (90)	6½
2-(1-propen-2-yl) pyridine (261)	5
2-(1-propen-1-yl) pyridine (260)	36 *
4-vinyl pyridine (291)	14
2-methyl-5-vinyl-pyridine (308)	5½
2-(1-propen-2-yl)thiophen (321)	1
2-vinyl thiophen (142)	½
2-vinyl furan (190)	1

* benzene used as solvent

The vinyl heterocycles were all distilled before use.

2. Di-tert-butyl azodicarboxylate (252).

Di-tert-butyl azodicarboxylate (252) (0.05 mole) and the vinyl heterocycle (0.05 mole) in benzene (100 mls) were boiled and the reaction followed by t.l.c. (25% toluene : 75% ethyl acetate, the azoester was the fastest moving yellow spot). The reaction

times are given below.

Vinyl heterocycle	Reaction time
2-vinyl pyridine (90)	8 days
2-(1-propen-1-yl) pyridine (260)	15 days
4-vinyl pyridine (291)	11 days
2-methyl-5-vinyl pyridine (308)	6 days
2-(1-propen-2-yl)thiophen (321)	14 hours
2-vinyl thiophen (142)	7 hours
2-vinyl furan (190)	3 hours

B Isolation of Products from Reaction between:

1. 2-vinyl pyridine (90) and diethyl azodicarboxylate (97) in benzene.

The solvent was removed from the products, chloroform was added and then evaporated onto Alumina (35 g, Grade IV) and the coated alumina added to the top of an alumina column (275 g, Grade IV, length = 17 cm), made up in 40-60°C Petroleum ether. Elution with 25% benzene : 75% Petroleum ether gave unreacted 2-vinyl pyridine (90) (0.61 g, 11.6%). Further elution with 50% benzene : 50% Petroleum ether gave an oil (1.87 g) which contained at least two major products. The products were separated by p.l.c. (12 plates, eluent 25% toluene : 75% ethyl acetate) to give two major fluorescent bands, and one minor band. The fluorescent band with highest R_f when extracted gave a solid, recrystallised from cyclohexane, m.pt. 93-94°C, identified as 3H-pyrido[1,2-c]1,2,3-triazine diethyl ester (249) (0.27 g, 2.3%). (Found: C, 56.35; H, 6.3; N, 15.3. $C_{13}H_{17}N_3O_4$ requires C, 56.25; H, 6.05; N, 15.45%). λ_{max} (EtOH, 95%) 258 (log ε 3.49), 260 (log ε 3.5) and 267 nm (log ε 3.44). ν_{max} ($CHCl_3$) 1700, 1661 and 1300 cm^{-1}.

δ ($CDCl_3$) 1.1-1.6 (6H, m, CH_3CH_2O), 3.5 (1H, d of d, J = 13 and 8 Hz, H-3), 4.0-4.6 (5H, m, CH_3CH_2O and H-3'), 5.35 (1H, d of d, J = 8 and 3 Hz, H-4), 7.1-7.9 (3H, m, H-5, 6, 7) and 8.5 p.p.m. (1H, br d of d, J = 4 and 2 Hz, H-8). The fluorescent band with lowest R_f was obtained as an oil, b.pt. 140°C/5 x 10^{-4} mmHg, identified as 1,2-diethoxycarbonyl-1,2,3,4-tetrahydropyrido[3,2-c]pyridazine (248) (1.55 g, 13.2%). (Found: C, 56.35; H, 6.3; N, 15.3. $C_{13}H_{17}N_3O_4$ requires C, 55.9; H, 6.1; N, 15.05%). λ_{max} (EtOH, 95%) 233 (log ε 3.9) and 269 nm (log ε 3.58) ν_{max} ($CHCl_3$) 1710, 1320 cm^{-1}. δ ($CDCl_3$) 1.0-1.5 (6H, m, CH_3CH_2O), 2.5-5.0 (8H, m, CH_3CH_2O and $-CH_2-CH_2-$), 7.1 (1H, q, J = 8 and 4 Hz, H-7), 8.05 (1H, d of d, J = 8 and 2 Hz, H-8), and 8.25 p.p.m. (1H, d of d, J = 4 and 2 Hz, H-6). Increasing the polarity of the eluent gave an oil, characterisation of which was not possible.

Use of Acetonitrile as solvent gave the same experimental conditions, and a yield of the pyrido[3,2-c]pyridazine diester adduct (248) of 18.2%. No triazine (249) was isolated.

2. 2-vinyl pyridine (90) and di-tert-butyl azodicarboxylate (252).

The solvent was removed from the products, chloroform was added and then evaporated onto Alumina (40 g, Grade IV), the coated alumina was then applied to the top of an alumina column (400 g, Grade IV, 22.7 cm) made up in 100% 40-60 Petroleum ether. Elution with 25% benzene : 75% Petroleum ether gave unreacted 2-vinyl pyridine (90) (1.07 g). Further elution with 50% benzene : 50% Petroleum ether gave an oil (4.98 g), which contained many components. The products were separated by p.l.c. (22 plates, eluent 25% toluene : 75% ethyl acetate) to give two fluorescent bands. Extraction of the fluorescent

band of highest R_f gave an oil, b.pt. 185°C/10^{-4} Hg, identified as 3H-pyrido[1,2-c]-1,2,3-triazine di-tert-butyl ester (254) (0.35 g, 2.7%). (Found: C, 61.21; H, 7.81; N, 12.49. $C_{17}H_{25}N_3O_4$ requires C, 60.89; H, 7.46; N, 12.54%). λ_{max} (EtOH, 95%) 253 (log ε 3.27), 261 (log ε 3.28) and 267 nm ($\log_{10}\varepsilon$ 3.17). ν_{max} ($CHCl_3$), 1710, 1660, 1305, 1295, 1170 and 1140 cm^{-1}. δ ($CDCl_3$) 1.45 (9H, s, $(CH_3)_3$ C-O-), 1.50 (9H, s, $(CH_3)_3$ C-O), 3.5 (1H, d of d, J = 14 and 8 Hz, H-3), 4.35 (1H, d of d, J = 14 and 4 Hz, H-3'), 5.3 (1H, d of d, J = 8 and 4 Hz, H-4), 7.0-7.9 (3H, m, H-5,6,7) and 8.5 p.p.m. (1H, d of d, J = 5 and 1 Hz, H-8). M/e (% base peak), 263 (10.6), 224 (14.9) 223 (66), 222 (10.6), 180 (48.9), 154 (46.8) 131 (10.6), and 56 a.m.u. (100). The fluorescent band of lowest R_f was also obtained as an oil, b.pt. 195-200°C/10^{-4} mmHg, identified as 1,2-di-tert-butoxycarbonyl-1,2,3,4-tetrahydropyrido[3,2-c]pyridazine (253) (3.3 g, 19.7%). (Found: C, 60.78; H, 7.58; N, 12.67. $C_{17}H_{25}N_3O_4$ requires C, 60.89; H, 7.46; N, 12.54%). λ_{max} (EtOH, 95%), 234 (log ε 3.89) and 281 nm (log ε 3.6). ν_{max} ($CHCl_3$), 1710, 1330 and 1156 cm^{-1}. δ ($CDCl_3$) 1.4 (9H, s $(CH_3)_3$ C-O), 1.5 (9H, s, $(CH_3)_3$ C-O-), 2.8-3.8 (3H, m, -, CH-CH_2-), 4.45 (1H, m), 7.05 (1H, d of d, J = 8 and 6 Hz, H-7), 8.0 (1H, d of d, J = 8 and 1 Hz, H-8), 8.2 (1H, d of d, J = 6 and 1 Hz, H-6). M/e (% base peak), 206 (11.8), 180 (27.5), 176 (100), 136 (9.8), 135 (58.8), 134 (66.6), 133 (43.1), 107 (25.5), 105 (19.6), 84 (11.8), 79 (13.7), 58 (29.4), 57 (94.1) and 56 a.m.u.

The remainder of the products were unidentified.

3. 2-(1-propen-1-yl)pyridine (260) and diethyl azodicarboxylate (97).

Reaction carried out in benzene (75 mls) using 2-(1-propen-1-yl) pyridine (260) (3.7 g) and diethyl azodicarboxylate (97) (5.4 g).

The solvent was removed, chloroform was added and then evaporated onto Alumina (20 g, Grade IV), the coated alumina was then added to the top of an alumina column (300 g, Grade IV) made up in 40-60°C Petroleum ether. Initial elution with 40-60°C Petroleum ether (900 mls) gave minor unidentified products. Elution with 25% benzene : 75% 40-60 Petroleum ether gave unreacted 2-(1-propen-1-yl) pyridine (260) (0.7 g, 18.9%). Further elution with 50% benzene : 50% Petroleum ether gave an oil (0.93 g) which contained a blue fluorescent component. Separation of the products by p.l.c. (6 plates, eluent 15% toluene : 85% ethyl acetate) resulted in the major fluorescent band, R_f = 0.34, being obtained as an oil, b.pt. 195-200°C/10^{-4} mmHg identified as 3-methyl-1,2-diethoxycarbonyl-1,2,3,4-tetrahydropyrido[3,2-c]pyridazine (262) (0.56 g, 7.6%). (Found: C, 57.05; H, 6.59; N, 14.44. $C_{14}H_{19}N_3O_4$ requires C, 57.34; H, 6.48; N, 14.33%). λ_{max} (EtOH, 95%) 233 (log ε 4.04) and 280 nm (log ε 3.67). ν_{max} 1710 and 1325 cm^{-1}. δ ($CDCl_3$) 1.1-1.5 (9H, m, 2 x CH_3CH_2O- + C-3 CH_3-), 2.2 (1H, d of d, J = 17 and 1 Hz, H-4), 3.35 (1H, d of d, J = 17 and 7 Hz, H-4'), 3.9-4.5 (4H, m, CH_3CH_2-O), 4.85 (1H, m, H-3), 7.1 (1H, d of d, J = 8 and 5 Hz, H-7), 8.1 (1H, d of d, J = 8 and 1 Hz, H-8) and 8.25 p.p.m. (1H, d of d, J = 5 and 1 Hz, H-6). M/e (% base peak), 293 (M^+, 11.76), 221 (61.76) 220 (38.23), 176 (20.58), 149 (14.7), 148 (100), 147 (38.23), 133 (23.52), 107 (26.5), and 44 a.m.u. (17.64).

Other components of the oil remained unidentified. The remainder of the products on the column also were uncharacterised.

4. 2-(1-propen-1-yl) pyridine (260) with di-tert-butyl azodicarboxylate (252).

The solvent was removed, chloroform was added and then evaporated onto Alumina (50 g, Grade IV), the coated alumina was then applied to an alumina column (400 g, Grade IV) made up in 40-60°C Petroleum ether. Elution with 100% 40-60°C Petroleum ether gave minor unidentified products. Using 25% benzene : 75% Petroleum ether as eluent gave unreacted 2-(1-propen-1-yl) pyridine (260) (0.73 g, 12.2%). Further elution with 50% benzene : 50% 40-60°C Petroleum ether gave an oil (2.4 g) which contained more than one product. The components were separated by p.l.c. (15 plates, eluent 75% ethyl acetate : 25% toluene) giving a major fluorescent band as an oil, b.pt. 190-195°C/10^{-4} mmHg, identified as 3-methyl-1,2-di-tert-butoxycarbonyl-1,2,3,4-tetrahydropyrido[3,2-c]pyridazine (263) (1.94g, 15.1%). (Found: C, 61.89; H, 7.74; N, 12.03. $C_{18}H_{27}N_3O_4$ requires C, 61.83; H, 7.81; N, 12.25%). λ_{max} (EtOH, 95%), 235 (log ε 3.99) 283 nm (log ε 3.66). ν_{max} ($CHCl_3$) 1700, 1340 and 1160 cm^{-1}. δ ($CDCl_3$) 1.45 (12H, s, $(CH_3)_3$ C-O + C-3 CH_3), 1.5 (9H, s, $(CH_3)_3$ C-O), 2.65 (1H, d of d, J = 18 and 1 Hz, H-4), 3.3 (1H, d of d, J = 18 and 7 Hz, H-4') 4.8 (1H, m, H-3), 7.05 (1H, d of d, J = 8 and 5 Hz, H-7), 8.05 (1H, d of d, J = 8 and 1 Hz, H-8) and 8.2 p.p.m. (1H, d of d, J = 5 and 1 Hz, H-6). M/e (% base peak) 193 (32.1), 149 (71.4), 147 (37.5), 145 (33.9), 134 (33.9), 128 (16.0), 118 (16.0), 117 (12.5), 107 (35.2), 105 (12.5), 90 (21.4), 89 (14.2), 80 (12.5), 79 (19.6), 57 (44.6), 56 (100) and 55 a.m.u. (33.9).

The other components of the mixture were uncharacterised. The material left on the column was also unidentified.

5. 2-(1-propen-2-yl) pyridine (261) with diethyl azodicarboxylate (97).

Reaction was carried out in acetonitrile (60 mls) using 2-(1-propen-2-yl) pyridine (261) (3.29 g) and diethyl azodicarboxylate (97) (4.82 g).

The solvent was removed from the products, chloroform was added and then evaporated onto Alumina (25 g, Grade IV), which was then applied to an alumina column (240 g, Grade IV) made up in 40-60°C Petroleum ether. Elution with 40-60°C Petroleum ether (1.8 litres) and then 25% benzene : 40-60°C Petroleum ether, gave unreacted 2-(1-propen-2-yl) pyridine (261) (0.5 g, 15%) plus some minor uncharacterised products. On increasing the polarity of the eluting solvent an oil was obtained, which crystallised from cyclohexane, m.pt. 75-76°C, identified as diethyl N-[2-(2-pyridyl)prop-1-en-3yl] hydrazo-N,N'-dicarboxylate (267) (5.9 g, 90.2%). (Found: C, 57.63; H, 6.80; N, 14.07. $C_{14}H_{19}N_3O_4$ requires C, 57.34; H, 6.48; N, 14.33%). λ_{max} (EtOH, 95%), 232 (log ε 3.88) and 277 nm (log ε 3.6). ν_{max} ($CHCl_3$), 3400, 1720 and 1110 cm^{-1}. δ ($CDCl_3$), 1.2 (6H, tr, CH_3CH_2O), 4.1 (4H, q, CH_3CH_2-O), 4.6 (2H, s), 5.4 (1H, s), 5.9 (1H, s), 7.0 (1H, m), 7.3-7.4 (2H, m), 7.95 (1H, br.s, exch. D_2O) and 8.50 p.p.m. (1H, d of d, J = 5 and 1 Hz). M/e (100% base peak) 293 (10), 249 (10), 222 (10), 221 (10), 206 (18), 205 (100), 205 (28), 133 (54), 119 (60), 118 (44), 105 (10), 79 (16), 78 (20), 52 (10) and 51 a.m.u. (10).

The product was eluted slowly from the column on increasing the solvent polarity to 100% benzene.

6. 4-vinyl pyridine (291) with diethyl azodicarboxylate (97).

The solvent was removed and the products absorbed onto Alumina (35 g, Grade IV), the coated alumina was then applied to an alumina column (400 g, Grade IV). Elution with 100% 40-60°C Petroleum

ether (1.2 lit) followed by 25% benzene : 75% 40-60°C Petroleum ether (0.5 lit) gave unreacted 4-vinyl pyridine (291) (2.08 g, 35%). Elution with 40-60°C Petroleum ether (0.7 lit) gave minor unidentified products. Further elution with 50% benzene : 50% 40-60°C Petroleum ether (1.2 lit) then 75% benzene : 25% 40-60°C Petroleum ether gave an oil (1.64 g) which contained a major blue fluorescent component plus other minor products. Separation by p.l.c. (10 plates, 85% ethyl acetate : 15% toluene) gave the major blue fluorescent band as an oil, b.pt. 175-190°C/10^{-4} mmHg, identified as 1,2-diethoxycarbonyl-1,2,3,4-tetrahydropyrido[3,4-c]pyridazine (292) (1.1 g, 13%). (Found: C, 55.80; H, 6.29; N, 15.05. $C_{13}H_{17}N_3O_4$ requires C, 55.91; H, 6.15; N, 15.05%). λ_{max} (EtOH, 95%) 233 (log ε 4.19) and 277 (log ε 3.74). ν_{max} ($CHCl_3$), 1720, 1325 and 1305 cm^{-1}. δ ($CDCl_3$) 1.1-1.5 (6H, m, CH_3CH_2O-) 2.5-3.7 (3H, m, $-CH_2-CH-$), 3.8-4.8 (5H, m, CH_3CH_2O + -H-3), 7.15 (1H, d, J = 5 Hz, H-5), 8.3 (1H, d, J = 5 Hz, H-6) and 9.0 p.p.m. (1H, s, H-8). M/e (% base peak), 279 (9.6), 208 (11.5), 207 (86.5), 206 (26.9), 179 (19.2), 162 (26.9), 149 (13.5), 135 (23.1), 134 (100), 133 (36.5), 117 (15.4), 107 (46.2), 106 (11.5), 105 (21.2), 104 (13.5), 80 (13.5), 79 (11.5), 78 (23.1), 77 (11.5), 52 (23.5) and 51 a.m.u. (13.5).

The remainder of the products were not characterised.

7. 4-vinyl pyridine (291) and di-tert-butyl azodicarboxylate (252).

The solvent was removed and the products absorbed onto Alumina (335 g, Grade IV, length 10.5 cm) made up in 50% benzene : 50% 40-60°C Petroleum ether. Elution with 50% benzene : 50% 40-60°C Petroleum ether (1 lit) gave unreacted 4-vinyl pyridine (291) (1.7 g, 32.3%) plus some minor unidentified products. Further elution with 75% benzene : 25% 40-60°C Petroleum ether (2.8 lit) gave an oil (2.83 g)

which contained several products. The components were separated by p.l.c. (10 plates, 75% ethyl acetate : 25% toluene), giving a major band, extraction gave an oil, b.pt. 185°C - 195°C/10^{-4} mmHg, identified as 1,2-di-tert-butoxycarbonyl-1,2,3,4-tetrahydropyrido-[3,4-c]pyridazine (293) (1.80 g, 15.9%). (Found: C, 60.88; H, 7.69; N, 12.50. $C_{17}H_{25}N_3O_4$ requires C, 60.89; H, 7.46; N, 12.53%). λ_{max} (EtOH, 95%) 235 (log ε 3.9) and 277 nm (log ε 3.52). ν_{max} ($CHCl_3$) 1715, 1210 and 1150 cm^{-1}. δ ($CDCl_3$) 1.40 (9H, s, $(CH_3)_3C$-O), 1.50 (9H, s, $(CH_3)_3$ C-O), 2.4-3.5 (3H, m, $-CH_2-CH-$), 4.1-4.8 (1H, m, H-3), 7.0 (1H, d, J = 5 Hz, H-5), 8.15 (1H, d, J = 5 Hz, H-6) and 8.9 p.p.m. (1H, br.s, H-8). M/e (% base peak) 149 (40), 131 (96), 103 (28), 76 (96) and 56 a.m.u. (100).

The remainder of the products were not characterised.

8. 2-methyl-5-vinyl pyridine (306) and diethyl azodicarboxylate (97).

The reaction was carried out in acetonitrile (50 mls) using the vinyl pyridine (306) (2.8 g) and the azoester (97) (4.0 g).

The solvent was removed and the products absorbed onto Alumina (20 g, Grade IV), the coated Alumina was then applied to an Alumina column (200 g, Grade IV, length 23½ cm) made up in 40-60°C Petroleum ether. Elution with 100% 40-60°C Petroleum ether (0.6 lit), 25% C_6H_6 : 75% 40-60°C Petroleum ether (0.6 lit) eluted nothing. Elution with 50% benzene : 50% 40-60°C Petroleum ether (1.6 lit) gave unreacted 2-methyl-5-vinyl pyridine (306) (1.27 g, 45.3%). Further elution with 75% benzene : 25% 40-60°C Petroleum ether gave an oil (0.48 g) which contained three fluorescent products. The components were separated by p.l.c., (4 plates, eluent 10% methanol : 90% ethyl acetate) to give three fluorescent bands, described in decreasing R_f

value. The band of largest R_f value (0.53) was obtained as an oil, b.pt. 170-200°C/ 3 x 10^{-4} mmHg, preliminary identified as 7-methyl-1,2-diethoxycarbonyl-1,2-dihydropyrido[2,3-c]pyridazine (309) (70.1 mg 1.9%). δ ($CDCl_3$) 1.0-1.6 (6H, m, CH_3CH_2O-), 2.55 (3H, s), 3.9-4.5 (4H, m, CH_3CH_2O), 5.95 (1H, d, J = 6-7 Hz, H-4), 6.95 (1H, d, J = 8 Hz, H-6), 7.1 (1H, d, J = 6-7 Hz, H-3) and 7.3 p.p.m. (1H, d, J = 8 Hz, H-5). M/e (% base peak) 291 (40), 290 (40), 220 (30), 219 (30) and 143 a.m.u. (100). The band with intermediate R_f value (0.44), obtained as an oil, b.pt. 210-220°C/10^{-4} mmHg, identified as 7-methyl-1,2-diethoxycarbonyl-1,2,3,4-tetrahydropyrido[2,3-c]pyridazine (308) (0.14 g, 3.7%). (Found: C, 57.60; H, 6.68; N, 14.23. $C_{14}H_{19}N_3O_4$ requires C, 57.34; H, 6.48; N, 14.37%). λ_{max} (EtOH, 95%), 228 (log ε 3.97) and 282 nm (log ε 3.79). ν_{max} ($CHCl_3$), 1715 cm^{-1}. δ ($CDCl_3$) 1.0-1.5 (6H, m, CH_3CH_2-O), 2.5 (3H, s, CH_3-), 2.6-4.5 (8H, m, CH_3CH_2O, $-CH_2CH_2$-), 6.9 (1H, d, J = 7-8 Hz, H-6) and 7.35 p.p.m. (1H, d, J = 7-8 Hz, H-5). M/e (100% base peak) 293 (71), 149 a.m.u. (100%). The band with lowest R_f value (0.33) was obtained as an oil which crystallised from cyclohexane, m.pt. 103.5-105°C, identified as 7-methyl-1,2-diethoxycarbonyl-1,2,3,4-tetrahydropyrido[4,3-c]pyridazine (308) (0.204 g, 5.3%). (Found: C, 57.64; H, 6.47; N, 14.43. $C_{14}H_{19}N_3O_4$ requires C, 57.34; H, 6.48; N, 14.37%). λ_{max} (EtOH, 95%), 239 (log ε 4.06), 268 (log ε 3.48) and 277 nm (log ε 3.38). ν_{max} ($CHCl_3$) 1720 cm^{-1}. δ ($CDCl_3$), 1.1-1.5 (6H, m, CH_3CH_2O), 2.5 (3H, s, CH_3), 2.6-3.8 (3H, m, $-CH_2$-CH-), 3.8-4.8 (5H, m, CH_3CH_2O + H-3), 7.6 (1H, s, H-8) and 8.1 p.p.m. (1H, s, H-5). M/e (% base peak) 293 (57.7), 249 (19.7), 222 (40.8), 221 (71.8), 220 (57.7), 193 (69.0), 176 (70.4), 149 (76.0), 148 (100), 147 (71.8), 146 (22.5), 133 (42.2), 119 (67.6), 117 (50.7), 107 (14.5), 105 (14.5), 94 (21.1),

93 (16.9), 92 (16.9), 91 (28.5), 77 (26.8), 65 (28.8), 53 (12.7), 52 (21.1), 51 (19.7) and 50 a.m.u. (14.0%).

9. 2-methyl-5-vinyl pyridine (306) and di-tert-butyl azodicarboxylate (252).

The solvent was removed and the products absorbed onto Alumina (40 g, Grade IV), the coated Alumina was then applied to an Alumina column (400 g, Grade IV), made up in 25% benzene : 75% 40-60°C Petroleum ether. Elution with this solvent system (1.2 lit) gave unreacted 2-methyl-5-vinyl pyridine (306) (1.4 g, 23.5%). Further elution with 50% benzene : 50% 40-60°C Petroleum ether (2.0 lit) gave an oil (2.0 g) which contained more than one component. The products were separated by p.l.c. (10 plates, eluent 75% ethyl acetate : 25% toluene), to give three blue fluorescent bands, described in decreasing R_f value. Band 1: R_f = 0.39, obtained as an oil, b.pt. 170-175°C/10^{-4}mmHg, identified as 7-methyl-1,2-di-tert-butoxycarbonyl-1,2,3,4-tetrahydropyrido[2,3-c]pyridazine (310) (0.46 g, 3.5%). (Found: C, 62.24; H, 7.97; N, 12.41. $C_{18}H_{27}N_3O_4$ requires C, 61.89; H, 7.74; N, 12.03%). λ_{max} (EtOH, 95%), 229 (log ε 3.93) and 282 nm (log ε 3.73). ν_{max} ($CHCl_3$), 1710 and 1150 cm^{-1}. δ ($CDCl_3$), 1.40 (9H, s, $(CH_3)_3CO$-), 1.5 (9H, s, $(CH_3)_3CO$), 2.5 (3H, s, CH_3), 2.6-3.8 (3H, m, $-CH_2-CH-$), 4.1-4.7 (1H, m, H-3), 6.85 (1H, d, J = 8 Hz, H-6) and 7.3 p.p.m. (1H, d, J = 8 Hz, H-5). M/e (100% base peak) 249 (23.4), 193 (100), 149 (95.7), 148 (74.5), 147 (10.6), 146 (21.3), 121 (29.8), 120 (21.3), 119 (10.6), 77 (10.6), 57 (97.7), and 56 a.m.u. (21.3%). The band with intermediate R_f value, Band 2: R_f = 0.29 was obtained as an oil, b.pt. 190-200°C/10^{-4} mmHg, preliminary identified as 5,6-dihydro-6-(2'-methyl-5'-pyridyl)-2-tert-butoxy-4-tert-butoxycarbonyl-oxa-3,4-diazine (313) (0.220 g, 1.7%). P.C.M.U. were unable to obtain

exact masses of peaks at 293 and 237 a.m.u. λ_{max} (EtOH, 95%) 261 (log ε 3.82), 267 (log ε 3.95) and 274 nm (log ε 3.79). ν_{max} ($CHCl_3$), 1720, 1660 (>C=N-), 1610, 1160 and 1140 cm^{-1}. ^1H n.m.r. spectrum, δ ($CDCl_3$), 1.50 (9H, s), 1.55 (9H, s), 2.55 (3H, s, CH_3-), 3.25 (1H, d of d, J = 14, 9 Hz, H-5), 4.2 (1H, d of d, J = 14, 3 Hz, H-5), 5.2 (1H, d of d, J = 9, 3 Hz, H-6), 7.1 (1H, d, J = 7-8 Hz, H-3'), 7.5 (1H, d of d, J = 7-8, 2 Hz, H-4') and 8.4 p.p.m. (1H, br, d, J = 2 Hz, H-5'). ^{13}C n.m.r. spectrum δ ($CDCl_3$), 24.2 (CH_3-), 28.0, 28.1 (tert-butyl groups), 44.9 (C-5), 74.3 (C-6), 80.7, 82.8 (-C-O), 123.2 (C-3'), 129.0 (C-5'), 134.2 (C-4'), 147.2 (>C=O, C-6'), 152.4 (C=O), 159.3 (C-2'). M/e (100 base peak), 293 (46.1), 279 (15.4), 237 (30.8), 193 (83.1), 167 (23.1), 149 (58.5), 146 (24.6), 132 (30.8), 131 (73.8), 123 (24.6), 122 (27.7), 121 (23.1), 120 (100), 119 (46.2), 105 (23.1), 93 (21.5), 57 (80.0) and 56 a.m.u. (43.1%). The band of lowest R_f value, Band 3: R_f = 0.20, was obtained as an oil, b.pt. 150-160°C/10^{-4} mmHg, identified as 7-methyl-1,2-di-tert-butoxycarbonyl-1,2,3,4-tetrahydropyrido[4,3-c]pyridazine (311) (0.73 g, 5.5%). (Found: C, 61.68; H, 7.92; N, 12.20. $C_{18}H_{27}N_3O_4$ requires C, 61.89; H, 7.74; N, 12.03%). λ_{max} (EtOH, 95%) 243 (log ε 4.00), 268 (log ε 3.53) and 277 nm (log ε 3.40) ν_{max} ($CHCl_3$), 1710, 1140 cm^{-1}. δ ($CDCl_3$), 1.4 (9H, s), 1.5 (9H, s), 2.5 (3H, s, CH_3-), 2.6-3.5 (3H, m, CH_2-CH-), 4.2-4.7 (1H, m, H-3), 7.7 (1H, s, H-8) and 8.2 p.p.m. (1H, s, H-5). M/e (% base peak), 181 (18.7), 169 (20.8), 149 (12.5), 145 (64.6), 131 (20.8), 119 (29.2), 90 (14.6), 89 (16.6), 76 (41.6), 69 (91.6), 56 (100) and 55 a.m.u. (52.1%).

The remainder of the products from the reaction remained unidentified.

10. 2-(1-propen-2-yl) thiophen (321) with di-tert-butyl azodicarboxylate (252).

2-(1-Propen-2-yl) thiophen (321) (0.62 g, 5 m.mol) was added to a solution of di-tert-butyl azodicarboxylate (252) (1.15 g, 5 m.mol) in benzene (10 mls) and the solution boiled for 14 hours. The products were separated by p.l.c. (10 plates, eluent, 90% toluene : 10% ethyl acetate) to give three major fluorescent bands, described in decreasing R_f value. Band 1: obtained as an oil, b.pt. 150-170°C/10^{-4} mmHg, identified as 3,4-dihydro-1,2-di-tert-butoxycarbonyl-4-methylthieno[3,2-c]pyridazine (322) (0.17 g, 10%). (Found: C, 58.03; H, 6.75; N, 7.96. $C_{17}H_{24}N_2O_4S$ requires C, 57.95; H, 6.28; N, 7.95%). λ_{max} (EtOH, 95%) 229 (log ε 3.98), 269 (log ε 3.80) and 307 nm (log ε 3.73). ν_{max} ($CHCl_3$) 1725 cm^{-1}. δ ($CDCl_3$) 1.5 (18H, s), 2.0 (3H, s, CH_3-), 6.6 (1H, br.s, H-3), 7.1 (2H, s, H-6 and 7). M/e (% base peak), 178 (24.0), 152 (16.0), 151 (16.0), 150 (100), 149 (32.0), 121 (56.0), 97 (16.0), 96 (36.0), 78 (20.0), 77 (24.0), 70 (20.0), 69 (16.0), 59 (56.0), 57 (24.0) and 56 a.m.u. (96.0%). The fluorescent band of intermediate R_f value, Band 2: was obtained as an oil, b.pt. 170-185°C/10^{-4} mmHg, identified as di-tert-butyl [2-(2-thieno)prop-1-en-3yl] hydrazo-N,N'-dicarboxylate (324) (0.416, 23.5%). (Found: C, 57.93; H, 7.47; N, 8.18. $C_{17}H_{26}N_2O_4S$ requires C, 57.62; H, 7.34; N, 7.91%). λ_{max} (EtOH, 95%), 266 (log ε 3.95) and 279 nm (log ε 3.96). ν_{max} $CHCl_3$, 3400 and 1720 cm^{-1}. δ ($CDCl_3$), 1.45 (9H, s), 1.50 (9H, s), 4.40 (2H, s, $-CH_2-$), 5.05 (1H, s), 5.45 (1H, s), 6.65 (1H, br.s, exch. D_2O) and 6.8-7.5 p.p.m. (3H, m, thiophen protons). M/e (% base peak), 154 (10.6), 151 (8.5), 150 (8.5), 125 (14.9), 124 (85.1), 123 (19.1), 112 (19.1), 111 (25.5), 110 (61.7), 97 (21.3), 84 (17.0), 69 (19.1), 65 (21.3), 59 (25.5), 57 (25.5) and 56 a.m.u. (100%). The fluorescent band of lowest R_f value

was obtained as an oil (0.46 g, 26.0%), which contained many components. Repeated chromatography did not yield a purer product.

Identification of other minor bands seen on the p.l.c. plates was also not accomplished.

11. 2-vinyl thiophen (142) and di-tert-butyl azodicarboxylate (252).

Di-tert-butyl azodicarboxylate (252) (1.15 g, 0.0005 mole) was added to a solution of 2-vinyl thiophen (142) (0.55 g, 0.0005 mole) in benzene (10 mls) and the resulting solution boiled for 7 hours.

The solvent was removed and the products absorbed onto Alumina (5 g, Grade IV), the coated Alumina was then applied to the top of an alumina column (60 g, Grade IV) made up in 40-60°C Petroleum ether. Elution with 40-60°C Petroleum ether (150 mls), 75% Petroleum ether : 25% benzene (150 mls), 50% 40-60°C Petroleum ether : 50% benzene (150 mls), 25% Petroleum ether : 75% benzene (150 mls) gave minor products. Further elution with 100% benzene (450 mls) gave an oil (0.61 g, 35.9%) which t.l.c. showed to contain many components. Further purification of this band by p.l.c. was not possible. The major portion of the reaction products remained at the top of the chromatography column.

12. 2-vinyl furan (190) with di-tert-butyl azodicarboxylate (252).

Di-tert-butyl azodicarboxylate (252) (1.15 g, 0.005 mole) was added to a solution of 2-vinyl furan (190) (0.47 g, 0.0005 mole) in benzene (10 mls) and the resulting solution boiled for 3 hours. The solvent was removed to leave an oil, the components of which were

separated by p.l.c. (9 plates, eluent 80% toluene : 20% ethyl acetate) to give two fluorescent bands. The fluorescent band of higher R_f value was obtained as an oil (0.50 g, 30.9%), and was shown by further p.l.c. to contain at least 6 components. The fluorescent band of lowest R_f value was also obtained as an oil (0.64 g, 39.5%). Further purification by p.l.c. gave an oil (0.36 g, 22.2%), of which complete identification was not possible.

C General procedure for removal of tert-butyl groups from cycloadducts, then subsequent oxidation to the parent compound.

Trifluoroacetic acid (T.F.A.) (approx. 5 mls) was added to the di-tert-butyl cycloadduct (approx. 0.5 g) and the solution left at room temp for 30 mins. Excess T.F.A. was removed under vacuum and the resulting oil basified with a saturated solution of sodium bicarbonate. The product was then repeatedly extracted with chloroform, the combined chloroform extracts were dried over $MgSO_4$. Removal of the drying agent, then the solvent gave the 'hydrazo compound' in virtually quantitative yield.

Mercuric oxide (red) (0.2-0.3g) was then added to a stirred solution of the 'hydrazo compound' in chloroform (5 mls) at room temp. The solution was stirred until a colour change of yellow to green had occurred, usually about 15-30 mins. The solution was filtered to remove black mercurous oxide, the green/yellow solution was then diluted with more chloroform, then oxygen was bubbled through the solution, using an efficient condenser to retain the solvent. After complete conversion to the fully aromatic system, the chloroform insoluble material was filtered off, the solvent removed and the resultant oil extracted with cyclohexane, filtered, then recrystallised from that solvent.

1. 1,2-di-tert-butoxycarbonyl-1,2,3,4-tetrahydropyrido-[3,2-c]pyridazine (253).

(253) (0.40 g) was treated with T.F.A., after work-up an unstable oil was obtained (0.15 g, 94%) which was identified as 1,2,3,4-tetrahydropyrido[3,2-c]pyridazine (255). δ ($CDCl_3$), 2.90 (2H, m, $-CH_2-$), 3.15 (2H, m, $-CH_2-$), 5.05 (2H, br.s, exch. D_2O), 6.85 (2H, m, H-7, 8) and 7.9 p.p.m. (1H, d of d, J = 4 and 3 Hz, H-6). M/e (100% base peak) 135 (100%), 133 (68.7), 132 (93.7), 131 (56.2), 107 (31.2), 106 (37.5), 79 (43.7), 76 (50), 51 (50) and 50 a.m.u. (31.2%).

The 1,2,3,4-tetrahydropyrido[3,2-c]pyridazine (255) (0.15 g) was treated with mercuric oxide (red) (0.2 g), then gaseous oxygen for 65 hours, after recrystallisation of the oil obtained, yellow crystals were obtained, m.pt. 89-91°C, which were identified as the parent pyrido[3,2-c]pyridazine (87) (64.53 mg, 44.2%). (Found: C, 64.4; H, 3.95; N, 31.65. $C_7H_5N_3$ requires C, 64.1; H, 3.8; N, 32.05%). λ_{max} (EtOH, 95%), 263 (log ε 3.59), 306 (log ε 3.62) and 318 nm (log ε 3.65). δ ($CDCl_3$) 7.8 (1H, d of d, J = 8 and 4 Hz, H-7), 8.15 (1H, d of d, J = 6 and 1 Hz, H-4), 8.85 (1H, q of d, J = 8, 2 and 1 Hz, H-8), 9.2 (1H, d of d, J = 4 and 2 Hz, H-6) and 9.95 p.p.m. (1H, d, J = 6 Hz, H-3).

2. 1,2-di-tert-butoxycarbonyl-3-methyl-1,2,3,4-tetrahydro-pyrido[3,2-c]pyridazine (263).

(263) (0.51 g) was treated with T.F.A. After work-up the 3-methyl-1,2,3,4-tetrahydropyrido[3,2-c]pyridazine (265) was obtained as a yellow oil (0.212 g, 97.7%). δ ($CDCl_3$), 1.15 (3H, d, J = 6 Hz, CH_3-CH-), 1.9-3.8 (3H, m, $-CH_2-CH-$), 6.2 (2H, br.s, exch. D_2O), 7.1 (2H, d, J = 3 Hz, H-6, 8) and 8.0 p.p.m. (1H, tr, J = 3 Hz, H-7).

M/e (100% base peak), 149 (100), 147 (27.6), 146 (34.5), 145 (17.2), 134 (37.9), 132 (17.2), 107 (37.9), and 79 a.m.u. (24.1).

The 3-methyl-1,2,3,4-tetrahydropyrido[3,2-c]pyridazine (265) (0.212 g) was treated with mercuric oxide (red) (0.35 g) then gaseous oxygen (26 hrs) to give an oil which was recrystallised from cyclohexane to give yellow needles, m.pt. 99-101°C, identified as 3-methylpyrido[3,2-c]pyridazine (266) (80 mg, 38.7%). (Found: C, 66.18; H, 4.76; N, 29.09. $C_8H_7N_3$ requires C, 66.28; H, 4.83; N, 28.96%). λ_{max} (EtOH, 95%), 265 (log ε 3.67), 276 (log ε 3.60), 314 (log ε 3.75) and 327 nm (log ε 3.80). δ ($CDCl_3$), 2.85 (3H, s, CH_3-), 7.55 (1H, d of d, J = 4, 8 Hz, H-7), 7.75 (1H, d, J less than 1 Hz, H-4), 8.65 (1H, q of d, J = 8, 2 and less than 1 Hz, H-8), and 9.0 p.p.m. (1H, d of d, J = 4, 2 Hz, H-6). M/e (100% base peak), 145 (100), 117 (18.6), 116 (20.9), 92 (13.9), 91 (67.4), 90 (60.5), 64 (20.9), 63 (27.9), 52 (16.3), 51 (20.9) and 50 a.m.u. (18.6%).

3. 1,2-di-tert-butoxycarbonyl-1,2,3,4-tetrahydropyrido-[3,4-c]pyridazine (293).

(293) (0.50 g) was treated with T.F.A. followed by the usual work-up procedure to give an oil, identified as 1,2,3,4-tetrahydropyrido[3,4-c]pyridazine (294) (0.192 g, 96%). δ ($CDCl_3$), 2.75 (2H, tr, $-CH_2-$), 3.1 (2H, tr, $-CH_2-$), 5.65 (2H, br.s, exch. D_2O), 6.9 (1H, d, J = 5 Hz, H-5), 7.85 (1H, d, J = 5 Hz, H-6), and 7.95 p.p.m. (1H, s, H-8). M/e (% base peak) 135 (100), 134 (25), 133 (100), 131 (41.6), 107 (25), 106 (29.2), 105 (87.5), 85 (41.6), 83 (70.8), 80 (25), 79 (37.5), 78 (29.2), 77 (29.2), 76 (37.5), 53 (16.6), 52 (45.8), 51 (41.6) and 50 a.m.u. (41.6).

The 1,2,3,4-tetrahydropyrido[3,4-c]pyridazine (294) (0.192 g) was treated with mercuric oxide (red) (0.30 g) then gaseous oxygen (66 hours), after work-up an oil was obtained which was crystallised

from cyclohexane to give yellow needles, m.pt. 138°C, identified as pyrido[3,4-c]pyridazine (295) (98 mg, 52.6%). (Found: C, 63.8; H, 3.7; N, 32.35. $C_7H_5N_3$ requires C, 64.1; H, 3.8; N, 32.05%). λ_{max} (EtOH, 95%) 284 nm (log ε 3.58). δ ($CDCl_3$), 7.6 (1H, d, J = 5 Hz, H-5), 7.8 (1H, d, J = 6 Hz, H-4), 8.7 (1H, d, J = 5 Hz, H-6), 9.35 (1H, d, J = 6 Hz, H-3) and 9.85 p.p.m. (1H, s, H-8). M/e (% base peak), 131 (93.3), 103 (26.6), 76 (100) and 50 a.m.u. (66.6%).

4. 1,2-di-tert-butoxycarbonyl-7-methyl-1,2,3,4-tetrahydropyrido[4,3-c]pyridazine (311).

(311) (0.400 g) was treated with T.F.A., after the usual work-up an oil was obtained preliminary identified as 7-methyl-1,2,3,4-tetrahydropyrido[4,3-c]pyridazine (315) (0.169 g, 99%). δ ($CDCl_3$), 2.3 (3H, s, CH_3-), 2.65 (2H, tr, $-CH_2-$), 3.1 (2H, tr, $-CH_2-$), 5.9 (2H, br.s, exch. D_2O), 6.25 (1H, s, H-8) and 7.85 p.p.m. (1H, s, H-5). M/e (% base peak), 149 (19), 145 (100), 119 (16.6), 118 (16.6), 117 (16.6), 105 (16.6), 90 (13.3), 89 (20), 76 (23.3), 51 (16.6) and 50 a.m.u. (23.3%).

The 7-methyl-1,2,3,4-tetrahydropyrido[4,3-c]pyridazine (315) (0.169 g) in chloroform (5 mls) was treated with mercuric oxide (red) (0.30 g) after the usual work-up procedure a red/brown oil was obtained which solidified in the cold to give solid, recrystallised cyclohexane, m.pt. 151-3°C, which was preliminary identified as (1H)-1,4-dihydro-7-methyl-pyrido[4,3-c]pyridazine (316) (0.155 g, 93.3%). λ_{max} (EtOH, 95%), 225 (log ε 3.99) and 300 nm (log ε 3.74). ν_{max} ($CDCl_3$), 3410 (N-H) and 1660 cm^{-1} (>C=N-). ^1H n.m.r.: δ ($CDCl_3$) 2.4 (3H, s, CH_3-), 3.3 (2H, d, J = 3 Hz, $-CH_2-$), 6.4 (1H, s, H-8), 6.8 (1H, tr, J = 3 Hz), 8.0 (1H, s, H-5) and 8.4 p.p.m. (1H, br.s, exch. D_2O). ^{13}C n.m.r.:

δ ($CDCl_3$), 23.7 (CH_3-), 29.7 (C-4), 105.3 (C-8), 107.8 (C-4a), 137.8 (C-3), 146.0 (C-8a), 147.4 (C-5) and 158.8 p.p.m. (C-7). M/e (% base peak) 147 (88), 146 (100), 119 (28), 92 (24), 91 (24), 65 (28), 52 (20) and 51 a.m.u. (28%). $C_8H_9N_3$ calculated mass 147.0796, measured mass 147.0789.

5. Treatment of components obtained from reaction between 2-vinyl thiophen (142) and di-tert-butyl azodicarboxylate (252) with T.F.A. then subsequent oxidation.

The major component, an oil (1.04 g) was treated with T.F.A., after work-up an oil was obtained which was then treated with mercuric oxide (red) (0.4 g) then gaseous oxygen (64 hours) to give a yellow oil (0.24 g) the components of which were separated by p.l.c. (2 plates, eluent, 25% toluene : 75% ethyl acetate). The only component identified was a blue fluorescent band, R_f = 0.085, obtained as colourless needles, recrystallised from cyclohexane, m.pt. 98.5-99°C (lit[107] m.pt. 97.5-98.5°C), identified as thieno[3,2-c]pyridazine (320) (70 mgs). (Found: C, 53.20; H, 2.92; N, 20.68. $C_6H_4N_2S$ requires C, 52.94; H, 2.94; N, 20.59%). λ_{max} (EtOH, 95%), 234 (log ε 4.97), 277 (log ε 3.75) and 304 nm (log ε 3.40). ν_{max} ($CHCl_3$) 1720, 1399, 1205 cm^{-1}. δ ($CDCl_3$) 7.25 (2H, s, H, 6 and 7), 7.95 (1H, d, J = 6 Hz, H-4) and 9.0 p.p.m. (1H, d, J = 6 Hz, H-3). M/e (% base peak) 136 (58.8), 108 (11.8), 85 (53), 83 (70.6), 82 (23.5), 69 (29.4), 63 (29.4), 58 (88.2), 57 (100) and 45 a.m.u. (41.1%).

D Reaction of 2-vinyl pyridine (90) with 1,2,4-triazoline-3,5-dione (101).

Freshly prepared tert-butyl hypochlorite (1.4 g) was added to a solution of N-phenyl urazole in dry acetone (90 mls, dried $CaSO_4$, then

distilled), at -40°C, the clear solution immediately assumed a deep red colouration which indicates the formation of the azodienophile (101). Freshly distilled 2-vinyl pyridine (90) (1.05 g, 10 mmol.) was added and the solution allowed to warm to room temp. The solution was then boiled for 1 hour until the red colour had disappeared. The solvent was removed to leave a yellow oil. The crude products were absorbed onto Alumina (Grade IV, 10 g), and the coated Alumina then applied to the top of an Alumina column (Grade IV, 120 g, length = 14 cm) made up in 40–60°C Petroleum ether. Elution with 100% 40–60°C Petroleum ether (400 mls), 50% 40–60°C Petroleum ether : 50% benzene (400 mls), 25% 40–60°C Petroleum ether : 75% benzene (400 mls), 100% benzene (400 mls) gave minor unidentified products. Elution with 25% $CHCl_3$: 75% benzene (100 mls) gave an unidentified product (40 mgs), further elution with this solvent system (750 mls) gave a yellow crystalline solid (0.26 g). The components of this product were separated by p.l.c. (2 plates, eluent 5% methanol : 95% ethyl acetate). The major band, R_f = 0.37, was obtained as a solid, recrystallised from carbon tetrachloride, to give a white crystalline solid, m.pt. 152-153°C, identified as 1,2,3,4-tetrahydropyrido[3,2-c]pyridazine, 1,2-dicarboxylic acid, N-phenyl-diimide (275) (0.19 g, 6.8%). $C_{15}H_{12}N_4O_2$, calculated mass, 280.0960, measured mass 280.0961, $C_7H_7N_3$ calculated mass 133.0640 measured mass 133.0642. λ_{max} (EtOH, 95%) 223 (log ε 4.06), 260 (log ε 4.11) and 292 nm (log ε 3.66). ν_{max} ($CHCl_3$) 1765, 1710 and 1420 cm^{-1}. δ ($CDCl_3$) 3.3 (2H, tr, $-CH_2-$), 4.1 (2H, tr, $-CH_2-$), 7.1-7.6 (6H, m, Ph + H-7), 8.5 (1H, d of d, J = 4.5, 1 Hz, H-6) and 8.65 p.p.m. (1H, d of d, J = 8.5, 1 Hz, H-8). M/e (% base peak) 280 (100), 149 (17.3), 133 (42.3), 105 (26.9), 104 (19.2), 78 (17.3), 44 (10.0) and 40 a.m.u. (10%).

The remainder of the material was not identified, most remaining at the top of the alumina column.

Carrying out the reaction under the same conditions but stirring the solution at room temp overnight (instead of boiling) gave a yellow precipitate (1.27 g, 19.5%) which was not identified. Similar chromatography of the remainder of the reaction products gave the adduct (275) (0.14 g, 3.3%). The bulk of the reaction products remained unidentified.

E 1. Synthesis of 2-(1-propen-1-yl)pyridine (260).

A. Preparation of 1-(2-pyridyl)-propan-1-ol.[81]

To a cooled stirred solution of pyridine-2-aldehyde (26.75 g) (previously distilled in nitrogen under vacuum) in dry ether (500 mls) was added the ether solution (500 mls) of ethyl magnesium iodide (prepared from ethyl iodide (38.0 g), and magnesium turnings (6.6 g)).

The resulting orange solution was refluxed for ½ hr., cooled, acidified with HCl (conc.), then basified with sodium hydroxide (10% solution), the organic material then extracted with ether, the combined ether extracts were then dried over Na_2SO_4. The drying agent and solvent were removed to leave a red oil (49.43 g) which was distilled under vacuum collecting the fraction which boils between 100-106°C/ 9 mmHg, clear liquid shown to be 1-(2-pyridyl)-propan-1-ol (10.5 g, 30.7%) (lit. b.pt.[81] 66-77°C/6 mmHg).

B. Dehydration to 2-(1-propen-1-yl)pyridine (260).[82]

1-(2-pyridyl)-propan-1-ol (5.5 g) was treated in sulphuric acid (conc) (20 mls) for 6 hrs on a water bath. The red solution was cooled and diluted with ice/water, neutralised using sodium hydroxide

(50% solution) with ice cooling, the light brown solution was then extracted with ether (1 lit.) and the combined ether extracts dried over $MgSO_4$. The drying agent and solvent were removed to leave a red oil (3.3 g). This oil was distilled under reduced pressure, major fraction coming over between 70-76°C/15 mmHg, shown to be 2-(1-propen-1-yl) pyridine (260) (3.1 g, 66.0%) (lit. b.pt.[114] 70-74°C/15 mmHg, 189-190°C).

2. Synthesis of 2-(1-propen-2-yl) pyridine (261).

A. Preparation of 2-(2-pyridyl)-propan-2-ol.[84]

Ethyl picolinate (50.3 g, 0.3 mol) in dry ether (200 mls) was added slowly to a well cooled solution of methyl magnesium iodide (prepared from methyl iodide 153.7 g, magnesium turnings (28.6 g) 3.25 mol) in dry ether (1.5 lit). The resulting solution was heated on a water bath until the yellow green solid went into solution (2 hr). After cooling the complex was destroyed by addition of a saturated solution of ammonium chloride in ammonia (100 ml) to the cooled solution, the product was then extracted with ether (600 ml) and the combined ether extracts dried over magnesium sulphate. The solution was then filtered and the solvent removed to give the alcohol (29.3 g, 71.3%), pure enough for the next stage.

B. Dehydration of the alcohol to give 2-(1-propen-2-yl) pyridine (261).

2-(2-pyridyl)-propen-1-ol (1.0 g) was dissolved in sulphuric acid (conc.) (10 mls) with ice cooling. The solution was then heated on a water bath for 4 hrs where it assumed a dark red colour.

The products were then poured onto ice/water (50 ml) and the resulting solution basified with sodium hydroxide (20% solution). The resulting pink solution was extracted with ether (200 mls) and the combined ether extracts dried over $MgSO_4$. The drying agent and solvent were removed to leave a clear oil, identified as 2-(1-propen-2-yl) pyridine (261) (0.56 g, 65.1%) b.pt. 63-67°C/9 mmHg, 170-173°C (lit.[121] b.pt. 60-65°C/9 mmHg).

3. Preparation of 2-stilbazole (257).[75]

A solution of α-picoline (46.5 g, 0.5 mol), benzaldehyde (45.5 g, 0.5 mol, previously shaken with $NaHCO_3$ (10% solution), water and freshly distilled, b.pt. 62°C/10 mmHg) and acetic anhydride (25.5 g, 0.25 mol) were boiled for 30 hrs. The solution was extracted with hydrochloric acid (2N), the acidic solution was then basified with sodium hydroxide (2N) to leave a white turgid solution which was extracted with chloroform, and the combined chloroform extracts dried over Na_2SO_4. The drying agent and the solvent were removed to leave a white solid, identified as 2-stilbazole (257) (63.3 g, 70%), m.pt. 91-93°C (lit. m.pt.[75] 91°C).

4. Synthesis of 2-(2'-nitrovinyl) pyridine (258).[75]

A. Preparation of 2-nitro-1-(2'-pyridyl)ethanol.

An ice cold mixture of pyridine-2-aldehyde (25 g), nitromethane (83 mls) and potassium carbonate (1.25 g) were shaken for 24 hrs at 5°C, then left for 3 days at -20°C. The yellow precipitate was quickly filtered using Whatman fast flowing filter paper, then dissolved in ether (600 mls) and treated with decolourising charcoal,

filtered and the filtrate concentrated to about 100 mls whereupon it was left to cool, the yellow precipitate was filtered and dried at the pump and identified as the alcohol (19.5 g, 46.8%), m.pt. 70°C (lit. m.pt.[76] 68°C).

B. Preparation of the hydrochloride of the pyridine base.

Dry hydrogen chloride was passed through a solution of the alcohol (19.5 g) in ethanol (57 mls). After about 15 mins a yellow precipitate was seen, which was removed by filtration, dried at the pump and identified as the hydrochloride salt (26.5 g), m.pt. 139°C (lit. m.pt.[76] 138°C).

C. Dehydration of the alcohol to the 2-(2'-nitrovinyl) pyridine (258).[75]

A suspension of the hydrochloride salt (20 g) in phosphorus oxychloride (80 mls), were stirred and boiled for 10 mins then stirred at room temperature for 30 mins. The dark green solution was poured onto crushed ice (250 g). The black/green solution was then poured, in small quantities, onto sodium carbonate (100 g) with ice cooling and vigorous stirring. A small amount of a brown oil was removed by filtration. The filtrate was then treated with more sodium carbonate to pH 3, to yield a yellow/brown precipitate, which was filtered, washed with water then dried over phosphorus pentoxide in vacuo. The yellow brown powder was dissolved in ether (200 mls), filtered then treated with active charcoal, filtered then the filtrate concentrated to approx. 25 mls. The solution was then stood in ice, whereupon yellow crystals were seen to precipitate out of solution. The crystals were filtered, washed with ice cold ether (6.2 g, 42.2%), m.pt. 76°C.

5. Synthesis of 2-(1-propen-2-yl)thiophen (321).

A. Preparation of 2-(2'-thieno)propan-2-ol.[103]

The Grignard reagent from 2-iodothiophen,[102] (prepared from 2-iodothiophen (160 g, 0.76 mole), magnesium (20 g) and ether (500 ml)) was transferred to a 3-necked round bottom flask and cooled in an ice/salt bath. Acetone (44.2 g, 0.76 mol, previously dried over calcium sulphate, then distilled) in ether (50 ml) was added at such a rate that the temp of the solution was kept below 5°C. After complete addition the solution was allowed to warm to room temperature and stirred for 2 hrs. The resulting brown/green complex was destroyed by addition of a saturated solution of ammonium chloride in ammonia (200 mls). The ether layer was then decanted and dried over magnesium sulphate.

The drying agent and solvent were removed to leave a red/brown oil. This oil was then distilled under vacuum to give the desired product (64.45 g, 59.7%), b.pt. 105-107/25 mmHg.

B. Dehydration of the alcohol to 2-(1-propen-2-yl)thiophen (321).

2-(2'-thieno)propan-2-ol (10. g) was mixed with oxalic acid (5 g), and the flask attached to an apparatus set for vacuum distillation. Using an air bath the flask was heated to 130°C, whereupon the pressure was slowly reduced to 25 mmHg. A water white liquid was seen to distil over between 71-73°C, which was collected in a cooled receiver.

The water white liquid was shaken with sodium bicarbonate (saturated solution), then dried over magnesium sulphate. The drying agent was removed to leave a clear liquid which was distilled under vacuum to give 2-(1-propen-2-yl)thiophen (321) (7 g, 80%), b.pt. 72-73°C/25 mmHg.

6. Synthesis of 2-vinyl thiophen (142).[104]

Dry hydrogen chloride gas was bubbled into a solution of thiophen (163 g, 2 mol), paraldehyde (88 g, 0.66 mol) and hydrochloric acid (conc) (150 ml) contained in a 1 lit. flask which was cooled by a dry ice/acetone bath to keep the temp between 10-13°C, until the solution became saturated (25 mins).

The contents of the flask were poured onto ice (150 g), the organic layer separated and then quickly washed with three portions of ice water (100 ml).

The organic layer was added with some cooling to a mixture of pyridine (158 g, 4 moles) and α-nitroso-β-napthol (1 g) in a 500 ml distilling flask. (Heat is given out which cracks the quaternary compound). The solution was then distilled under nitrogen at successively lower pressures, ending at 125°C/50 mm collecting the distillate over α-nitroso-β-napthol (½ g) in a cooled receiver.

The distillate was then poured onto a mixture of ice (200 g) and hydrochloric acid (conc) (200 ml), the layers were separated and then washed successively with portions (50 ml) of 1% hydrochloric acid, water, and then 2% ammonia.

The organic layer, a dark red solution, was filtered through 1 cm of anhydrous magnesium sulphate on a sintered glass funnel into a distilling flask (250 ml).

The aqueous layer from above was extracted with two portions of ether (50 ml). The combined ether extracts were then passed through the sinter, dried with magnesium sulphate, filtered, then the ether removed by distillation at atmospheric pressure on a water bath under nitrogen.

The remaining organic residue was added to the distilling

flask (250 ml) and the mixture distilled through a 2 cm column, 35 cm high, packed with 6 mm glass helices. After a forerun of thiophen (20 g), b.pt. 34-38°C/150 mmHg, then an intermediate fraction, (4 g), b.pt. 34-39°C/100 mmHg, 2-vinyl thiophen (142) (80 g) was collected in a cooled receiver, b.pt. 65-68°C/50 mm.

7. Preparation of 2-vinyl furan (190).[110]

Furan-2-acrylic acid[109] (20 g), quinoline (50 g) and copper sulphate, anhydrous (2.5 g), were placed in a distilling flask (100 mls) and distilled under a nitrogen atmosphere. At an oil bath temp of 220-230°C two immiscible liquids were slowly collected, in a cooled receiver, separated, the lower yellow liquid being quinoline, the upper colourless liquid being 2-vinyl furan (190) (7.4 g, 21.8%). The 2-vinyl furan (190) was pure enough for immediate use.

8. Preparation of 2-(2'-nitrovinyl) furan (334).[111]

Furfural (38.4 g, 0.4 mol), nitromethane (24.4 g, 0.4 mol), methylamine hydrochloride (2.6 g), sodium carbonate (0.8 g) and ethanol (absolute) (30 ml) were stood at room temperature in a stoppered conical flask for 2 weeks. The yellow precipitate was filtered, treated with decolourising charcoal then recrystallised from ethanol (absolute). The product may be further purified by recrystallisation from methanol to give the desired product as yellow crystals, (44.5 g, 80%), m.pt. 73-74°C.

9. Removal of ethyl ester groups from 1,2-diethoxycarbonyl-1,2,3,4-tetrahydropyrido[3,2-c]pyridazine (248).

Potassium hydroxide pellets (1.2 g) were added to a solution of the adduct (248) (1.7 g) in methanol (50 mls) and the solution boiled for 5 hrs in an inert nitrogen atmosphere. The solution was then filtered, the solvent removed to leave an oil which was extracted with boiling chloroform. The chloroform was removed to leave an oil (0.88 g), the components of which were separated by p.l.c. (6 plates, eluent, 10% methanol : 90% ethyl acetate). Many brightly coloured bands were seen. Band of R_f = 0.47 was extracted (0.29 g) then replated (2 plates, eluent 10% methanol : 90% ethyl acetate). A band of R_f = 0.40 was extracted and identified as pyrido[3,2-c] pyridazine (87) (0.52 mg, 6.5%) m.pt. 90°C, spectroscopic data as given before. None of the other products were identified.

10. Preparation of α-picoline-N-oxide.[77]

A mixture containing α-picoline (46.5 g, 0.5 mol), glacial acetic acid (300 ml) and a 30% aqueous solution of hydrogen peroxide (100 vols, 50 ml) was heated between 70 and 80°C for 3 hrs. An additional portion of 30% hydrogen peroxide (35 ml) was added and the mixture refluxed for a further 9 hrs.

The mixture was then concentrated to a volume of 100 ml. (Distilling off acetic acid at atmospheric pressure). An equal volume of water was added and the remains of acetic acid and water were removed under water pump pressure. The remaining black oily liquid was taken up in chloroform (250 ml) and was shaken with a paste of potassium carbonate until no more carbon dioxide was evolved. The chloroform layer was removed and dried with magnesium sulphate. The

drying agent and chloroform were removed and the crude product distilled under vacuum. The desired product distilled over as a clear liquid between 123-128°C/15 mmHg (41.38 g, 77%).

11. Preparation of 4-nitro- ∝ -picoline-N-oxide.

4-Nitro- ∝ -picoline-N-oxide (45 g) was slowly added to cold conc. sulphuric acid (Sp. Gr. 1.84, 158 ml) immersed in an ice/salt bath. The mixture was then cooled to below 10°C and fuming nitric acid (124 ml) was added in 50 ml portions with constant stirring. The solution was then heated for 2 hrs between 100 and 105°C, care!

The mixture was cooled to 10°C and then poured onto crushed ice (500 g). Sodium carbonate (0.4 kg) was then added with vigorous stirring, during the addition a yellow solid was seen to precipitate. Once added the mixture was allowed to stand for 3 hrs to expel nitrogen oxides. The yellow solid was collected by suction filtration, thoroughly washed with distilled water and rendered as dry as possible on the filter.

The collected solid was extracted twice with two portions of boiling chloroform (200 ml), the filtrate was also extracted. The combined chloroform extracts were dried over magnesium sulphate.

The dried solution was filtered and the chloroform removed to leave a yellow solid, which was recrystallised from acetone, shown to be 4-nitro- ∝ -picoline-N-oxide (33 g, 51.9%), m.pt. 152-154°C.

12. Deoxygenation to form 4-nitro-α-picoline.

Phosphorous trichloride (10 g) was added to a stirred solution of 4-nitro-α-picoline-N-oxide (10 g) in chloroform (200 ml) with ice cooling. The reaction mixture was warmed for 20 mins at 50°C, cooled then poured onto an ice/water mixture (200 g).

The resultant mixture was neutralised with a saturated solution of sodium bicarbonate, then extracted with chloroform. The chloroform extracts were dried over sodium sulphate.

The dried solution was filtered and the chloroform removed to leave a waxy yellow solid, identified as 4-nitro-α-picoline (7 g, 78.1%), m.pt. 35°C.

13. Attempted condensation of 4-nitro-α-picoline with formaldehyde.

4-Nitro-α-picoline (1 g), formalin (0.7 g) potassium persulphate (50 mg) and hydroquinone (50 mg) were heated in a carius tube between 150 and 210°C for 70 mins. Analysis of the products showed no reaction had taken place.

14. Preparation of hexamethyldisiloxane.

N,N-dimethylaniline (24.2 g, 0.2 mol) and water (3.6 g, 0.2 mol) were placed in a 3-necked round bottom flask. Chlorotrimethyl silane (21.8 g, 0.2 mol) was added slowly as the mixture was vigorously stirred and cooled in ice. A gas was seen to be given off and a white solid precipitated out of solution.

The white solid/solution was filtered using a fast flowing filter paper (Whatman Grade 90), the filtrate contained two immiscible

liquids, the upper clear layer was separated and dried with magnesium sulphate. The drying agent was removed by filtration, and the clear solution distilled at atmospheric pressure, fraction collected between 98–101°C, shown to be hexamethyldisiloxane (25.9 g, 80%) (lit. b.pt. 100°C).

15. Preparation of trimethylsilyl iodide (335).[112,113]

Iodine (50.8 g, 0.2 mol) was added piece-wise over a period of 45–55 mins, via a solid addition funnel, to a stirred mixture of aluminium powder (5.6 g, 0.21 mol) and hexamethyldisiloxane (16.2 g, 0.1 mol) at approx. 60°C. Nitrogen was blown through the apparatus at intervals. The solution assumed a violet colouration. After complete addition the solution was refluxed for 1½ hrs during which time the violet colour had disappeared.

The solution was then distilled at atmospheric pressure, a very light pink liquid distilled over between 104 and 107°C, shown to be trimethylsilyliodide (335) (14.2 g, 70.6%), (lit. b.pt.[112,113] trimethylsilyliodide 106°C), δ $CDCl_3$ 0.8 p.p.m.

16. Treatment of 1,2-diethoxycarbonyl-1,2,3,4-tetrahydropyrido[3,4-c]pyridazine (292) with trimethylsilyl iodide (335).

Trimethylsilyl iodide (335) (0.1 ml, 0.75 mmol) was added (via a dry syringe in a dry box) to a solution of the adduct (292) (0.1022 g, 0.75 mmol) in deuterated chloroform (1 ml) containing 1% T.M.S., contained in an n.m.r. tube fitted with a drying tube, and the reaction maintained at 50°C for 26 hrs.

The contents of the n.m.r. tube were hydrolysed by pouring onto water (5 ml) containing 5 drops hydrochloric acid (2 N) and stirring for 30 mins. The yellow/green solution was basified with a saturated sodium bicarbonate solution and then repeatedly extracted with chloroform. The combined chloroform extracts were dried over magnesium sulphate. The magnesium sulphate then the chloroform were removed to leave a green oil, preliminary identified as 1-ethoxycarbonyl-1,2,3,4-tetrahydropyrido[3,4-c]pyridazine (338) (73 mg, 96.3%). δ ($CDCl_3$), 1.2 (3H, q, CH_3CH_2-), 2.8 (2H, tr, $-CH_2-$), 3.25 (2H, tr, $-CH_2-$), 4.25 (5H, q, CH_3CH_2- plus N-H), 6.95 (1H, d, J = 6 Hz, H-5), 8.1 (1H, d, J = 6 Hz, H-6) and 8.75 p.p.m. (1H, s, H-8).

Using the same procedure the second ester group was hydrolised by warming at 50°C for 40 hrs. After work-up a yellow/green oil was obtained (68.5 mg), ^1H n.m.r. spectrum showed a number of low field absorptions plus some high field absorptions. The material was oxidised by bubbling oxygen through a chloroform solution of the oil for 64 hrs. The solution was filtered, the solvent removed to give an oil, the components of which were separated by p.l.c., (1 plate, eluent 10% methanol : 90% ethyl acetate). Blue fluorescent band, R_f = 1.0 shown to be pyrido[3,4-c]pyridazine (87), (15 mg, 30.6%), m.pt. 139°C, mixed m.pt. 139°C.

Attempts to scale up the ester hydrolysis to 0.5 g quantities of the 1,2-diethoxycarbonyl-1,2,3,4-tetrahydropyrido[3,4-c]pyridazine (292) failed.

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