Synthesis of Benz- and Cyclohepta-pyridines.

by

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

Abstract.

The methods of synthesis of benzocycloheptene-ones are reviewed.

A sequential Claisen - Dieckmann condensation has been used to prepare di-alkyl 5,9-dihydroxy-7H-cyclohepta-[b]-and-[c]-pyridine-6,8-dicarboxylates. These have been converted to the cyclopropaquinoline and cyclopropaisoquinoline-diones.

A review of some of the methods of preparing quinolines and isoquinolines is included.

The sequential condensation was adapted to prepare diethyl 5,8-dihydroxyquinoline-6,7-dicarboxylate and diethyl 5,8-dihydroxyisoquinoline-6,7-dicarboxylate which were oxidised to the corresponding quinones. The quinoline-5,8-dione acted as a dienophile with cyclopentadiene.

Diels Alder adducts of the pyrido-[2,3-d]-and-[3,4-d]-pyridazine-1,4-diones have been prepared.

9H-cyclohepta-[b]-pyridine-9-one has been synthesised.

Ynamine chemistry is reviewed. The reaction of ynamines with carboxylic acids has been studied. An attempt was made to perform a photochemical cycloaddition using an ynamine.

Acknowledgments.

I would like to thank Dr. D. Cohen for his supervision during my first year, Professor H.D. Springall and the University of Keele for provision of laboratory facilities and the S.R.C. for financial support.

I also extend my thanks to Professor C.W. Rees of the University of Liverpool for the provision of laboratory facilities for the pyrolysis experiments.

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Contents.

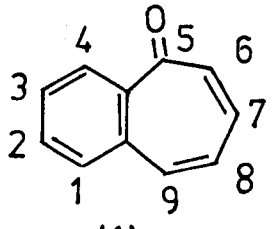
Section I.

Section I.

Introduction

Nomenclature

The method of naming and numbering used in "Chemical Abstracts" will be adopted.



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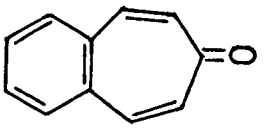

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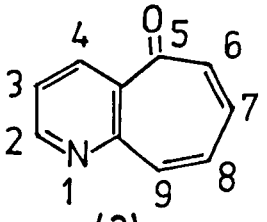

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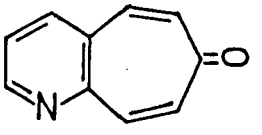

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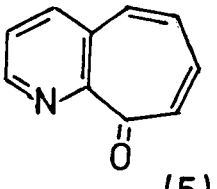

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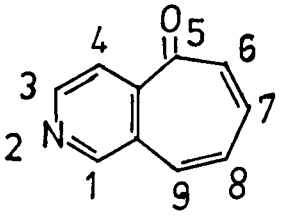

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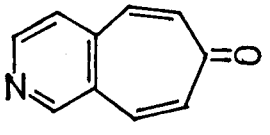

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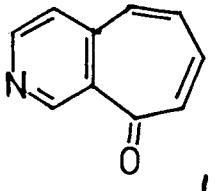


(8)

For the benzene series.

(1) is 5H-benzocycloheptene-5-one.

(2) is 7H-benzocycloheptene-7-one.

For the pyridine series.

(3) 5H-cyclohepta-[b]-pyridine-5-one.

(4) 7H-cyclohepta-[b]-pyridine-7-one.

(5) 9H-cyclohepta-[b]-pyridine-9-one.

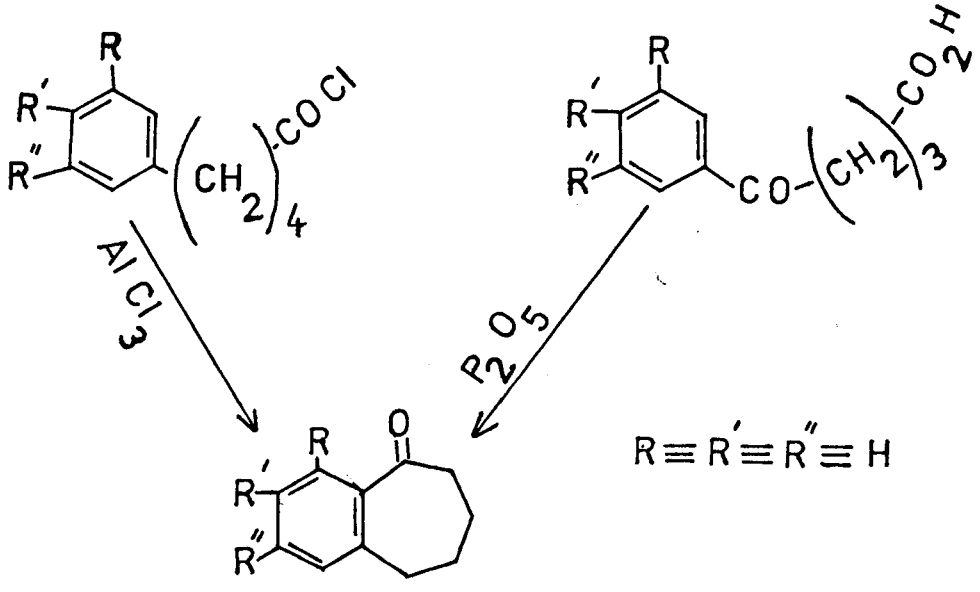
(6) 5H-cyclohepta-[c]-pyridine-5-one.

(7) 7H-cyclohepta-[c]-pyridine-7-one.

(8) 9H-cyclohepta-[c]-pyridine-9-one.

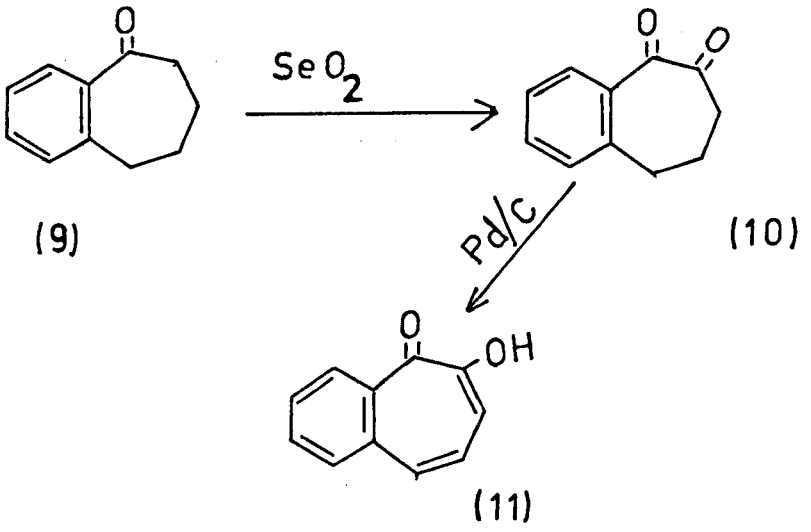
Methods of synthesis of benzocycloheptene - ones and cyclohepta pyridine - ones are reviewed.

The work of Pauson[1] et al and similar work by Barltrop[2] et al on the synthesis of 6,7,8,9-tetrahydro-5H-benzocycloheptene-5-one (9) was adapted and incorporated by Somerville[3] et al in the synthesis of 6-hydroxy-5H-benzocycloheptene-5-one (11).



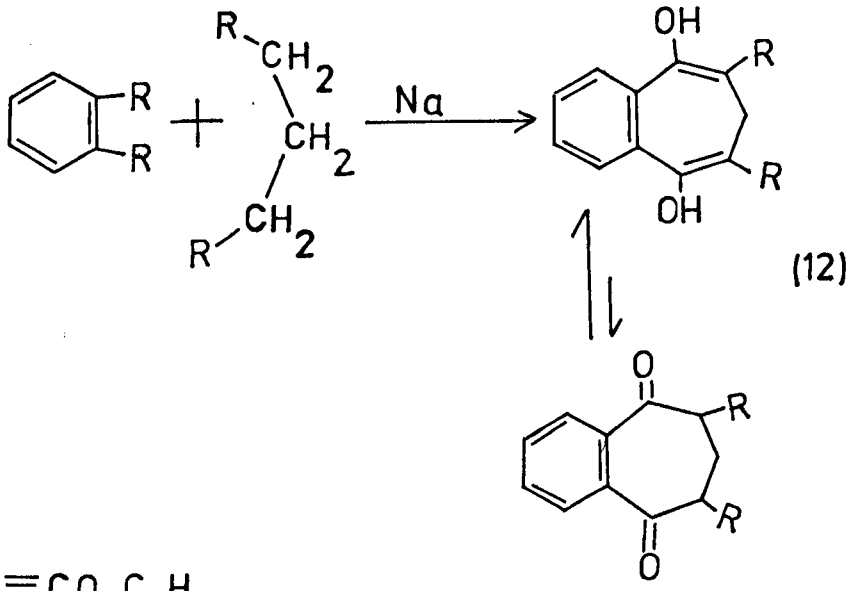
(9)

Selenium dioxide was used to oxidise the ketone (9) to the dione (10). The latter when dehydrogenated with palladium charcoal gave the hydroxy compound (11) in 16% yield.

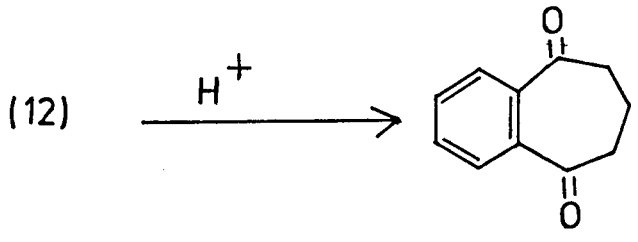


To improve the yield of (11) Somerville[3] et al varied the means of introducing unsaturation. It was found that by brominating compound (10), in glacial acetic acid, then dehydrobrominating the bromoketone with base the yield was improved to 68%.

In 1899 Dieckmann[4] synthesised 6,7,8,9-tetrahydro-5H-benzocycloheptene-5,9-dione (13) from the diester (12) obtained by reacting diethyl phthalate with diethyl glutarate in the presence of sodium metal.

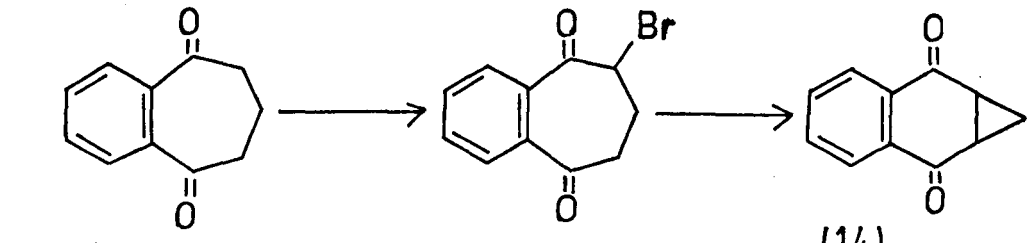


R ≡ $CO_2C_2H_5$

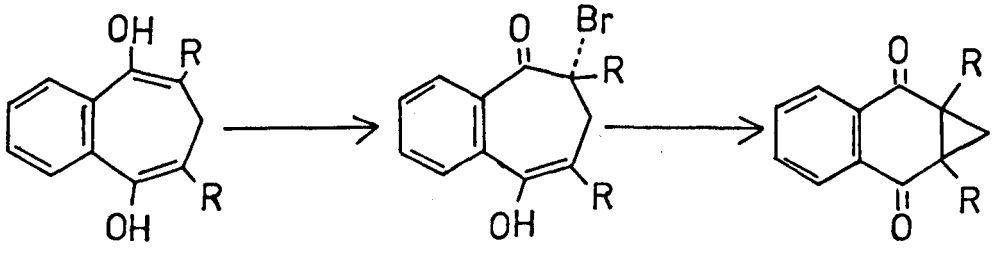


(13)

Buchanan[5] et al attempted to convert the dione (13) to 9-hydroxy-5H-benzocycloheptene-5-one (17). Palladium charcoal dehydrogenation of (13) failed. The bromination dehydrobromination technique used by Somerville[3] gave a compound of the correct molecular formula but wrong structure. This was shown to be the cyclopropane derivative (14). A similar reaction occurred with the diester (12) forming the cyclopropane compound (14a).



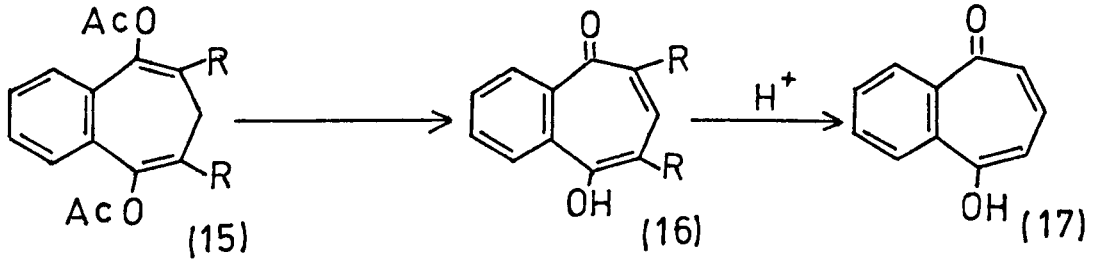
(13) (14)



(12) (14a)

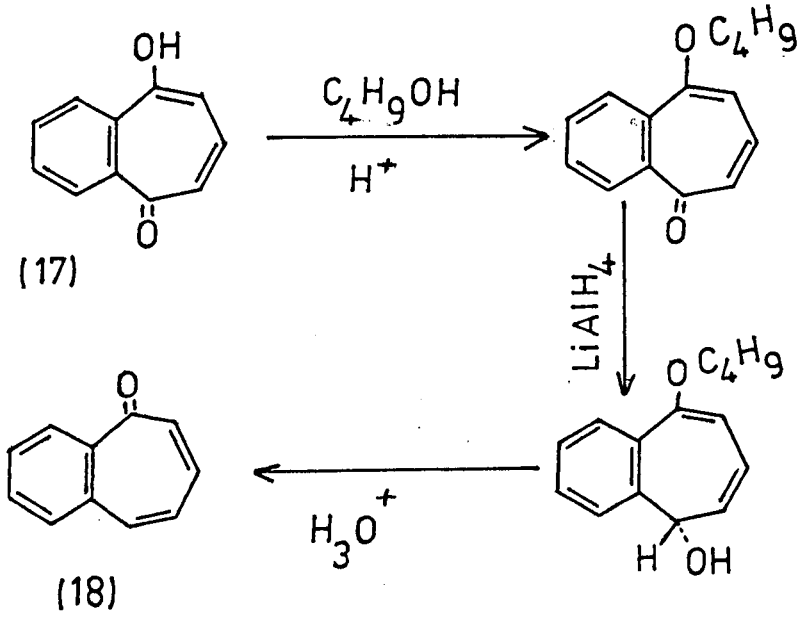
$R \equiv CO_2C_2H_5$

The problem was solved by fixing the dihydroxy compound (12) in the enol form as the 5,9-diacetate (15). When reacted with N-bromosuccinimide and base compound (15) was converted to the keto compound (16) which could be hydrolysed and decarboxylated to yield compound (17).

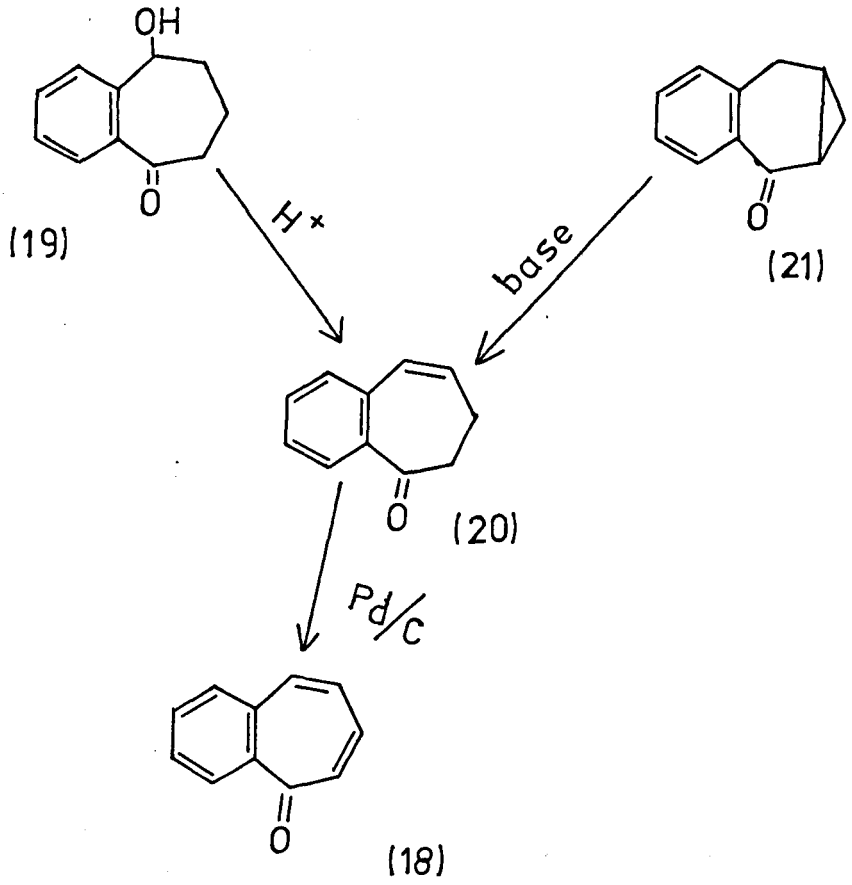


$R = CO_2C_2H_5$

The unsubstituted 5H-benzocycloheptene-5-one (18) was first synthesised by Eschenmoser[6]. The process was however somewhat tedious, requiring the 9-hydroxy compound (17) to be prepared first.



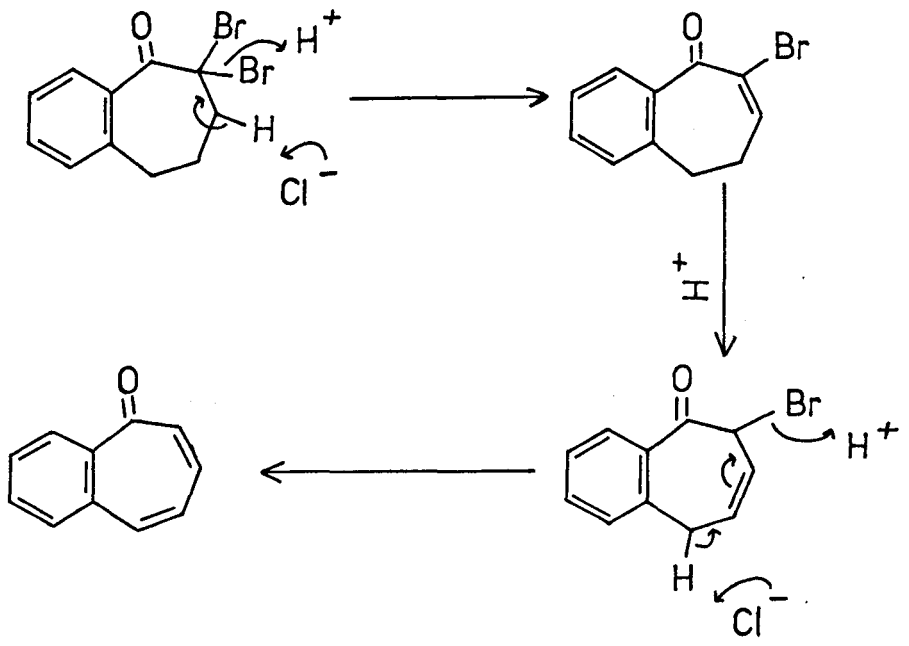
A more practical approach was made by Buchanan[7] et al. They prepared the 6,7-dihydro-5H-benzocycloheptene-5-one (20) from 9-hydroxy-6,7,8,9-tetrahydro-5H-benzocycloheptene-5-one (19) by dehydration with boric acid and from the cyclopropyl ketone (21) by rearrangement with base. The ketone (20) was then oxidised to the compound (18).



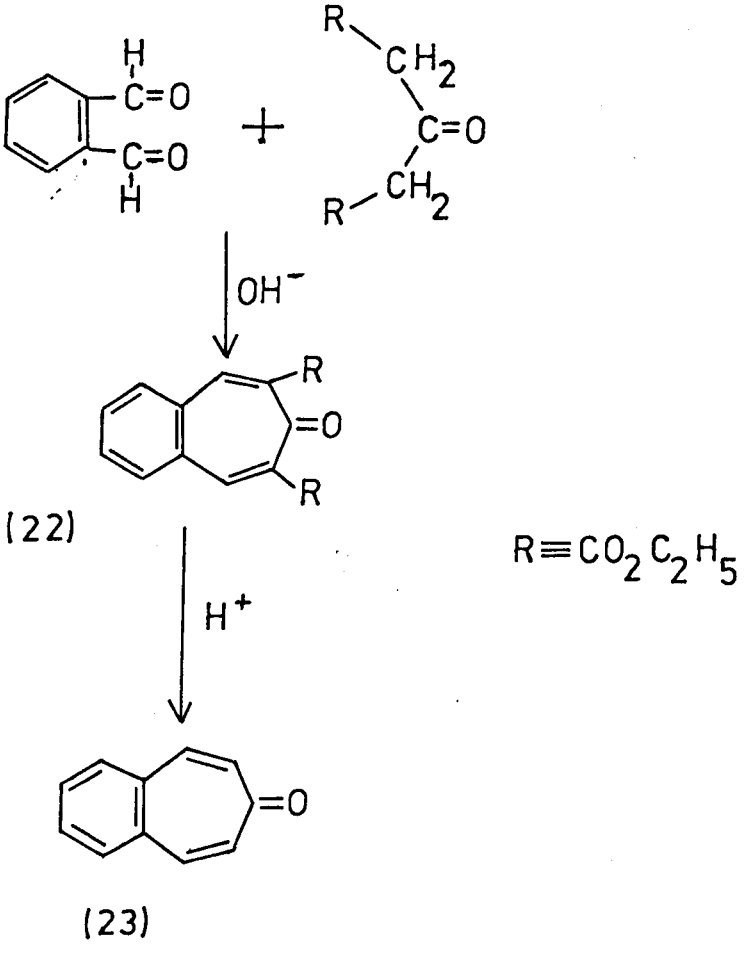
More useful still was the bromination of the tetrahydro compound (9) with N-bromosuccinimide and the subsequent dehydrobromination to give compound (18) in 65% overall yield.

Later syntheses of the ketone (18) have involved improved methods of bromination and dehydrobromination. Jones[8] has shown the usefulness of phenyltrimethylammonium tribromide in tetrahydrofuran as a selective dibrominating agent (α to the ketone) and the value of lithium chloride or carbonate as a dehydrobrominating agent, illustrated by scheme I.

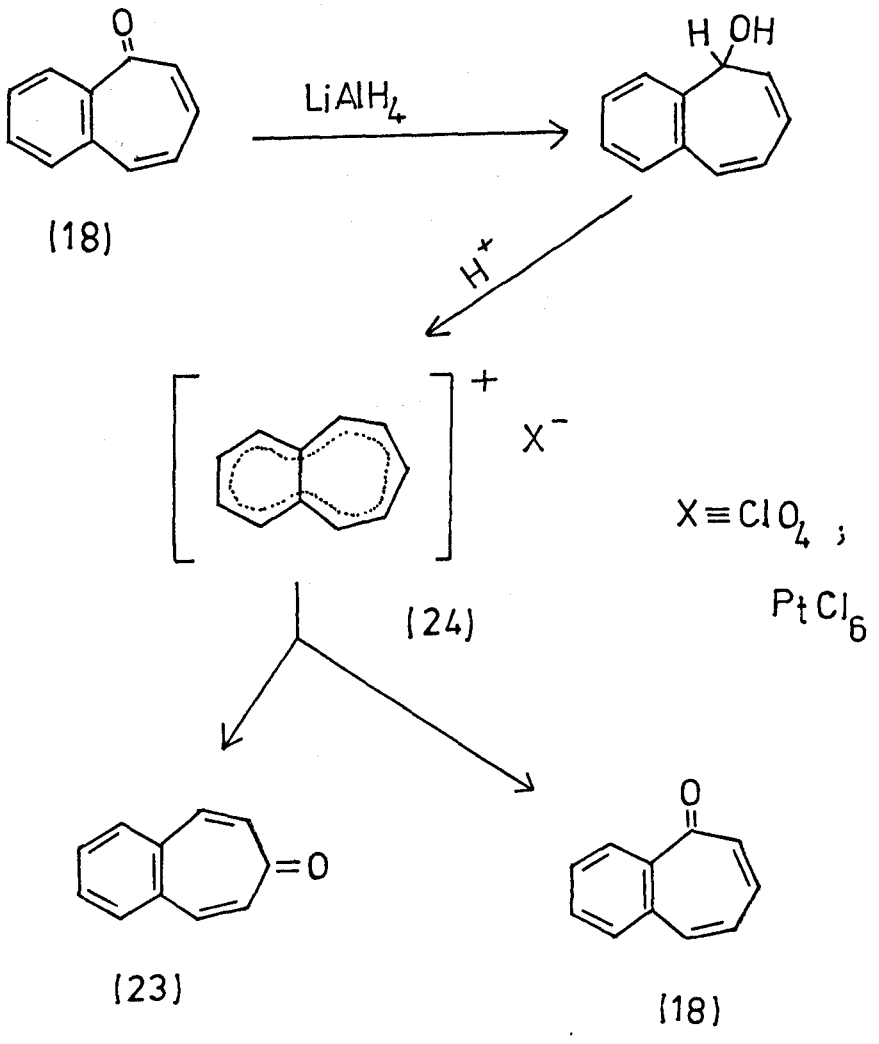
Scheme I.



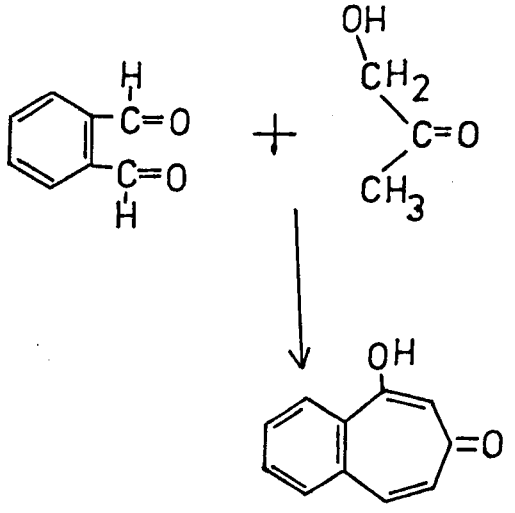
The 7H-benzocycloheptene-7-one (23) was prepared by Thiele et al[9] as far back as 1909. An acetone derivative was condensed with O-phthalaldehyde to give compound (22). When R= CO_2 C_2 H_5 the diester (22) was readily hydrolysed and decarboxylated to compound (23).



Eschenmoser[6] extended the synthesis mentioned (P.6) earlier to give compound (23). The tropylium cation (24) gave both the 5-ol and 7-ol with base. Chromium trioxide in pyridine converted these to the 5 and 7-ones respectively.



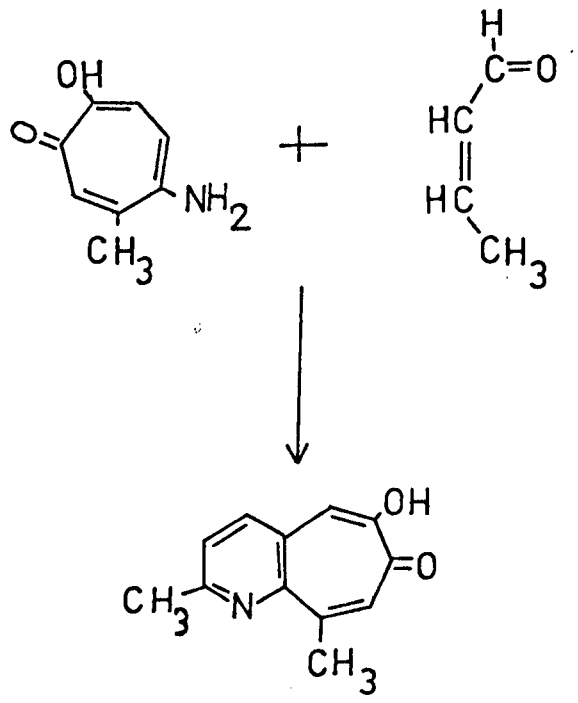
Thiele's method was adapted by Tarbell[10] to give a 6-hydroxy-7H-benzocycloheptene-7-one (25).



(25)

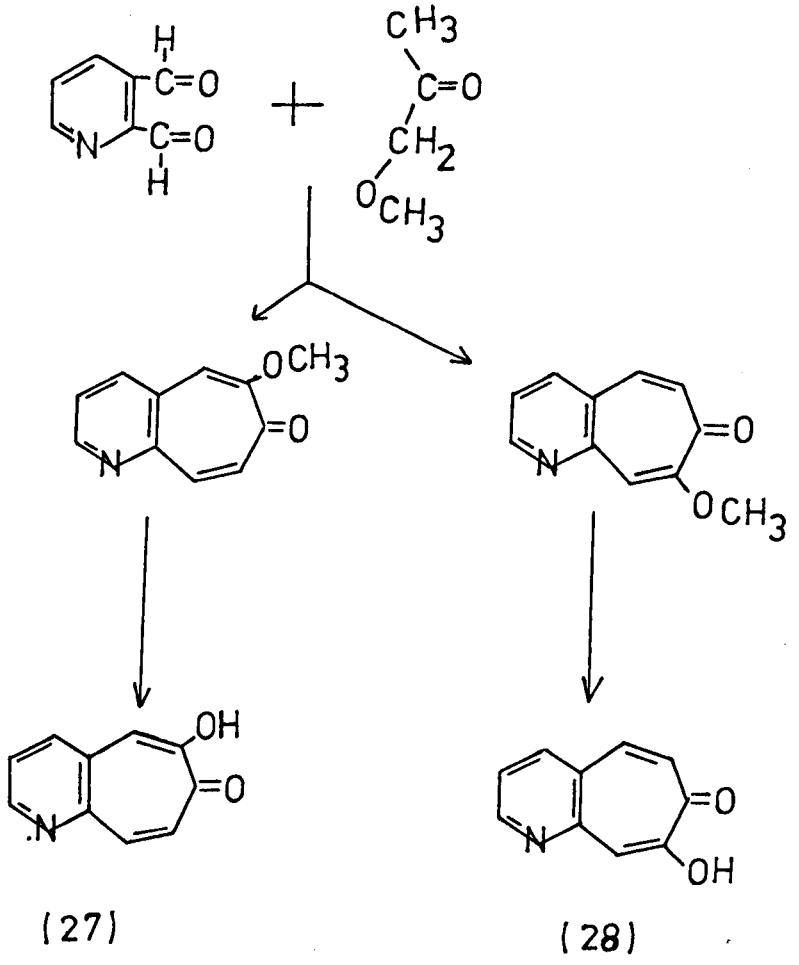
Compounds of the types mentioned above containing a pyridine ring in place of a benzene ring were not prepared until 1954.

Jefferies[11] began his synthesis with a cycloheptatrienone system and built a pyridine ring onto this. Hence by use of either the Doebner-Miller or Skraup[12] reaction he was able to obtain 7H-cyclohepta-[b]-pyridine-7-one derivatives. e.g. 5-amino-2-hydroxy-6-methylcycloheptatrienone with crotonaldehyde yields 2,9-dimethyl-6-hydroxy-7H-cyclohepta-[b]-pyridine-7-one (26).



(26)

More recently Queginer[13] et al using a pyridine-2,3-dialdehyde and Tarbell's[10] synthesis obtained 6-hydroxy-7H-cyclohepta-[b]-pyridine-7-one (27) and 8-hydroxy-7H-cyclohepta-[b]-pyridine-7-one (28).



(27) (28)

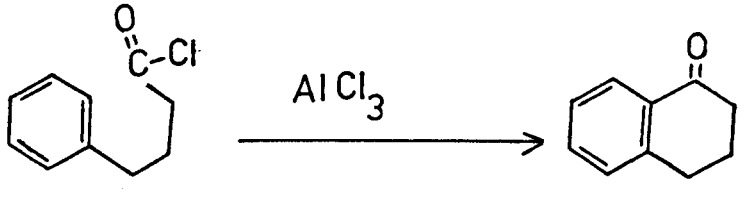
Discussion

The benzocycloheptene-ones illustrated in the introduction were invariably prepared from a benzene derivative. The cyclohepta-pyridine-ones, however, have been prepared from two standpoints. Firstly via the attachment of a cycloheptane ring onto a pyridine ring and secondly through the attachment of a pyridine ring onto a cycloheptane system.

Part I

Synthetic routes from pyridine derivatives.

As benzene, thiophen and furan will each undergo a Friedel-Crafts type reaction, attachment of a ring onto the aromatic nucleus is a relatively simple process. It requires the attachment of an adequate side chain then cyclisation onto the nucleus.



Pyridine will not undergo this type of reaction as the nucleus is much less reactive, towards electrophilic reagents, than the other examples quoted. Hence a synthesis must involve a disubstituted pyridine.

Saper[14] et al had shown that pyridine-2,3-dicarboxylic acid anhydride could be ring opened with amines to generate a carboxyl group in the 3 position and an amide function in the 2 position.

When reacted with a Grignard reagent (γ-ethoxypropylmagnesuimbromide) the anhydride did not give any ring opened product even at low temperatures. For comparison phthalic anhydride[15] was known to give a dialkylated product with alkylmagnesuim iodides.

Sodamide has been used to remove a proton from the methyl group in 2-methylpyridines[16] so generating an anion. This reaction was carried out on ethyl 2-methylnicotinate in the hope that with a halogen compound a side chain would be formed in the 2 position. With ethyl γ-bromobutyrate no reaction occurred.

The most readily available disubstituted pyridines are the diacids, so use was made of these via the esters. Dieckmann's[4] synthesis of 6,7,8,9-tetrahydro-5H-benzocycloheptene-5,9-dione (13) mentioned in the introduction, was adapted and used for the reaction of diethyl pyridine-2,3-dicarboxylate with

diethyl glutarate. The reaction proceeded smoothly and gave diethyl 5,9-dihydroxy-7H-cyclohepta-[b]-pyridine-6,8-dicarboxylate (29) in good yield. The infra red spectrum showed an absorption at 1645 cm^{-1} due to the enol form of the β-ketoester. The n.m.r. (fig 1) had a peak at δ 12.6 p.p.m. (exchangeable with deuterium oxide) due to the enol protons. The protons on carbon 7 appeared as a singlet indicating that they were in identical environments.

The pyridine protons appeared as three sets of doublets of doublets. Proton H_2 at δ 8.9, H_3 at 7.5 and H_4 at δ 8.4 p.p.m. The coupling constants for these were J_{23} 5.1, J_{24} 1.7 and J_{34} 8.5 Hz.

The methyl esters of pyridine-2,3-dicarboxylic acid and glutaric acid reacted similarly to the ethyl esters to give the corresponding dimethyl compound (30). The reaction of diethyl pyridine-2,3-dicarboxylate with dimethyl glutarate also gave the dimethyl ester (30). Except for the ester peaks the n.m.r. of compound (30) was identical with that of compound (29).

n.m.r. of diethyl 5,9-dihydroxy-7H-cyclohepta-[b]-pyridine-6,8-dicarboxylate.

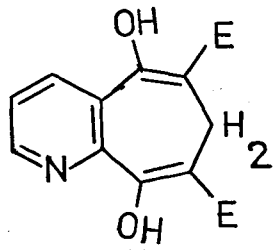
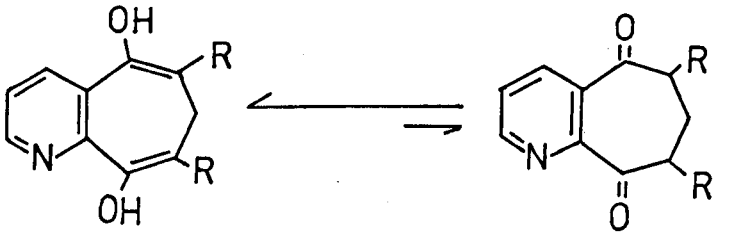
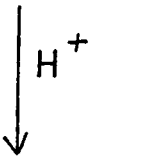


fig. I

Diethyl pyridine-2,3-dicarboxylate when reacted under the usual conditions with di-t-butyl glutarate did not give the expected di-t-butyl ester analogue of compound (29). Instead compound (29) was obtained in good yield. This suggested that a di-t-butyl ester derivative would be sterically unfavourable.

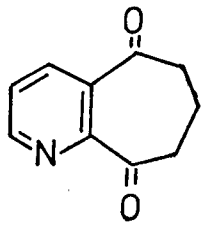
Both the diesters (29) and (30) were readily hydrolysed and decarboxylated by boiling in 48% hydrobromic acid to give 5,6,7,8-tetrahydro-9H-cyclohepta-[b]-pyridine-5,9-dione (31).





(29) $R \equiv CO_2C_2H_5$

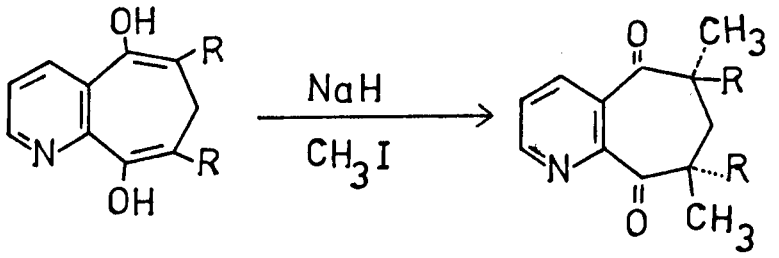
(30) $R \equiv CO_2CH_3$



(31)

An effort was made to reduce one of the ketone functions in compound (31) to a methylene group. The benzene analogue compound (13) had shown that catalytic reduction gave only the 5,9 diol. Hence the Huang-Minlon variation of the Wolff-Kishner reduction was used. On work up only tar was obtained. The same result occurred if one of the carbonyl functions was protected by forming its ketal with ethylene glycol.

The reaction of compound (29) with sodium hydride and methyl iodide in ethanol produced diethyl 5,7-dihydro-6,8-dimethyl-9H-cyclohepta-[b]-pyridine-5,9-dione-6,8-dicarboxylate (32).



(29) (32)

$R \equiv CO_2C_2H_5$

The infra red spectrum showed an ester carbonyl absorption at 1735 cm^{-1} and a ketone carbonyl absorption at 1710 cm^{-1}. This indicated that methylation had occurred on carbons 6 and 8 and not on the oxygen function. The latter would have retained the absorption due to the carbon-carbon double bonds between (C_5 and C_6) and (C_8 and C_9) in compound (29).

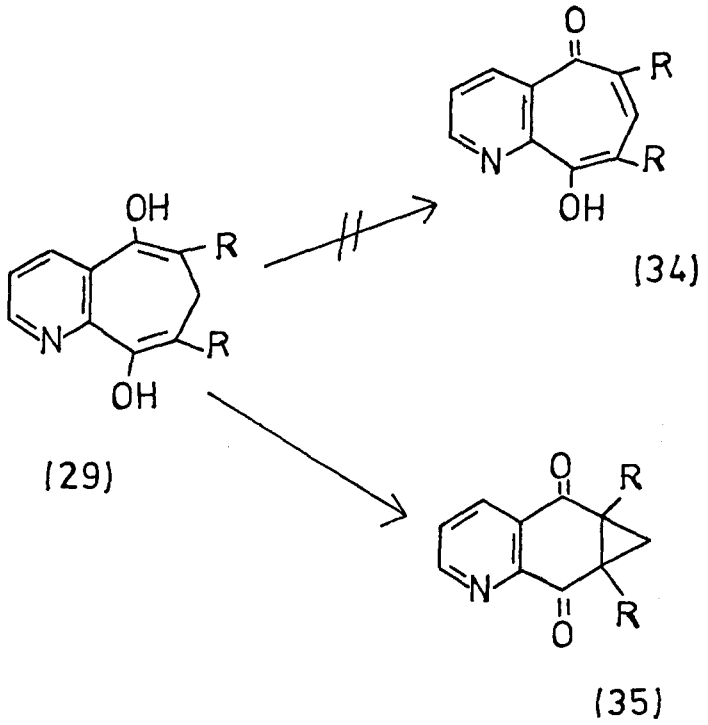
When compound (29) was heated with excess acetic anhydride diethyl 5,9-diacetoxy-7H-cyclohepta-[b]-pyridine-6,8-dicarboxylate (33) was obtained.

The infra red spectrum showed absorptions at 1768 and 1710 cm^{-1} due to carbonyl functions and at 1628 cm^{-1} due to the unsaturation in the seven membered ring. This showed that the reaction had occurred on the enol functions i.e. on oxygen and not carbon.

(29) (33)

$R \equiv CO_2C_2H_5$

It was of interest to see if compound (29) could be oxidised to diethyl 9-hydroxy-5H-cyclohepta-[b]-pyridine-5-one-6,8-dicarboxylate (34). Both lead tetraacetate and dichlorodicyanoquinone were used. The former proved to be the better reagent but both gave the same product diethyl 1H-cyclopropa-[g]-quinoline-2,7-dione-1a,7a-dicarboxylate (35) fig. 2.



(35)

$R \equiv CO_2C_2H_5$

diethyl 1H-cyclopropa-[g]-quinoline-2,7-dione-1a,7a-dicarboxylate.

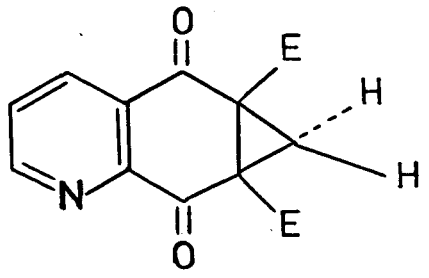
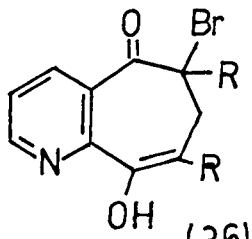


fig. 2.

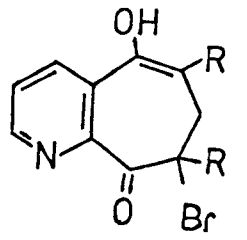
The infra red spectrum showed the ester carbonyl absorption at 1745 cm^{-1} and the ketonic absorption at 1698 cm^{-1}.

The n.m.r. spectrum showed a similar pattern for the pyridine protons as that seen in the spectrum of compound (29) with H_2 at δ 9.2 H_3 at δ 7.8 and H_4 at δ 8.5 p.p.m. The protons forming the methylene group in the cyclopropyl system appeared as two doublets at δ 2.2 and 2.9 p.p.m. coupling constant 6 H_z. The large separation between the two doublets indicated that the ester functions were cis as the trans form would be symmetrical with respect to the esters and the ketone groups alone would not produce such a large separation of the doublets.

An alternative route to compound (34) was to brominate compound (29) and dehydrobrominate the product. Bromination was carried out with N-bromosuccinimide and occurred to the carbonyl group either on C_6 or C_8 to give (36) or (37) respectively. The bromo derivative was not stable. On standing it was converted to compound (35).



(36)



(37)

No compound was isolated from the mixture remaining after the bromo compound had been stirred with 5N caustic soda. Similarly with lithium chloride or carbonate in warm dimethyl formamide no product was isolated. However when treated with 30% aqueous triethylamine the cyclopropyl derivative (35) was obtained.

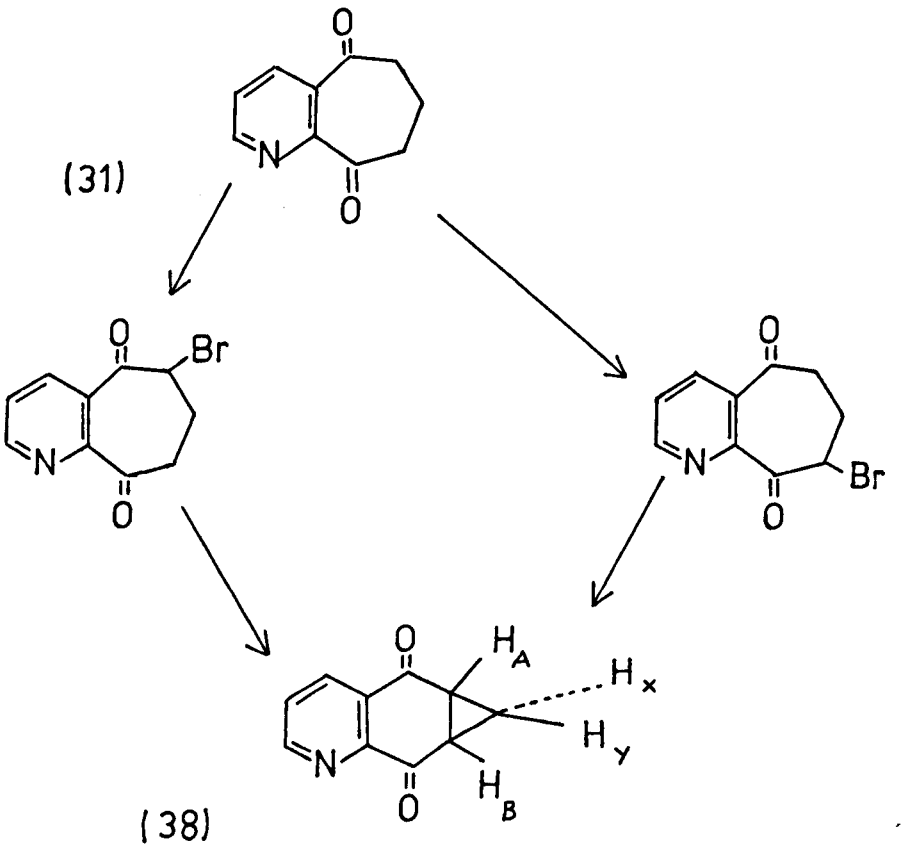
Buchanan[5] experienced similar problems with the benzene analogue. He overcame them by fixing compound (12) in the enol form as the 5,9-diacetate, then brominating and dehydrobrominating to give diethyl 9-acetoxy-5H-benzocycloheptene-5-one-6,8-dicarboxylate. Hydrolysis of the acetate to a hydroxy group gave the required compound.

Under the reaction conditions used by Buchanan the diacetate (33) reacted with N-bromosuccinimide then base to yield not compound (34) but the cyclopropyl compound (35). The intermediate compound was isolated and found to be (36) or (37) , both acetate functions having been removed. Variation of the molar ratios of N-bromosuccinimide to diacetate and variation of times of reaction did not alter the product, only the yield.

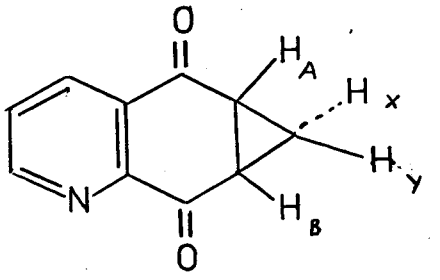
Attempts to rearrange compound (35) by thermal or photochemical means failed. The compound was recovered unchanged or with some decomposition.

Julia[17] had rearranged the compound (21) by proton abstraction. Compound (35) when treated with potassium t-butoxide in benzene gave unchanged material and some decomposed material.

Hydrolysis and decarboxylation of compound (35) was also unsuccessful. Hence in an attempt to prepare the parent cyclopropyl derivative (38) the 5,9-dione (31) was reacted with N-bromosuccinimide. Again bromination occurred α to the carbonyl group and with base the bromo compound yielded the parent compound (38), fig. 3.



1H-cyclopropa-[g]-quinoline-2,7-dione.



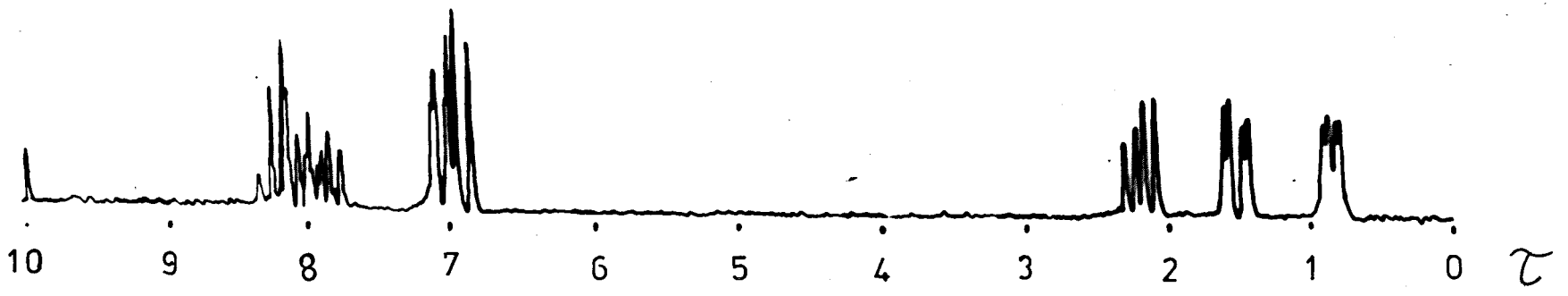


fig. 3.

The n.m.r. spectrum of compound (38) was complex with respect to the cyclopropyl protons consisting of two multiplets, one at δ 2.9 and the other at δ 1.9 p.p.m. The spectrum was simplified by a spin decoupling experiment. Irradiation at δ 2.9 p.p.m. reduced the other multiplet to two doublets 0.3 p.p.m. apart with a coupling constant H_{xy} of 6 H_z.

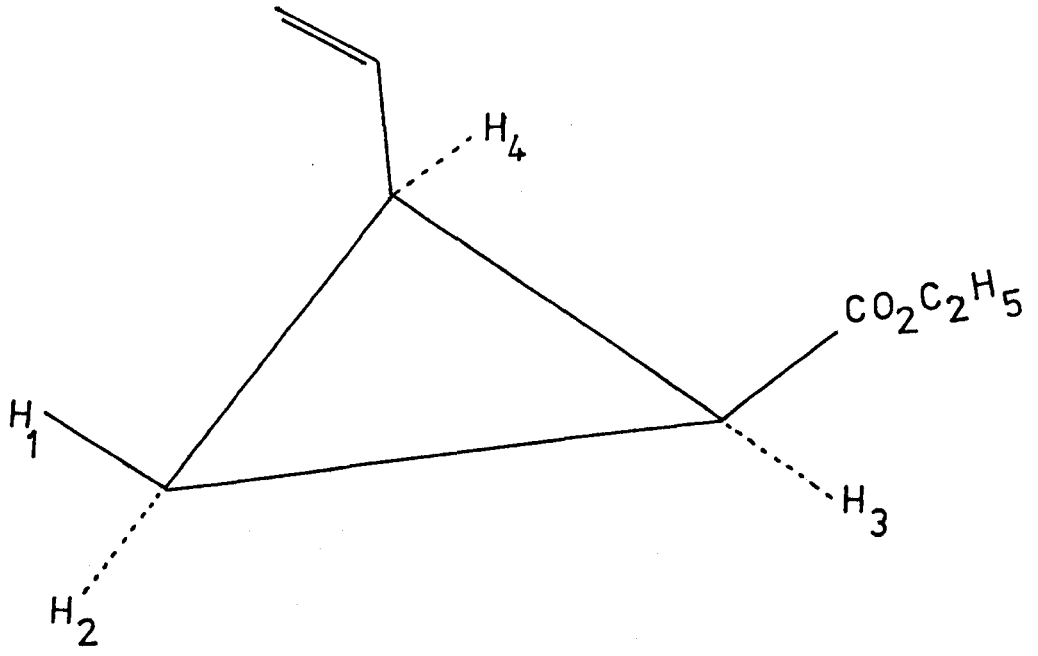
Irradiation at δ 1.9 p.p.m. reduced the other signal to two single peaks indicating that the coupling between H_A and H_B was o-o H_z.

From an expanded spectrum the following coupling constants were obtained.

$J_{AX} = J_{BX} = 10\ H_z$ $\quad J_{AY} = J_{BY} = 6\ H_z$.

For comparison a compound from a paper by Korte[18] was chosen. fig. 5.

fig. 5.



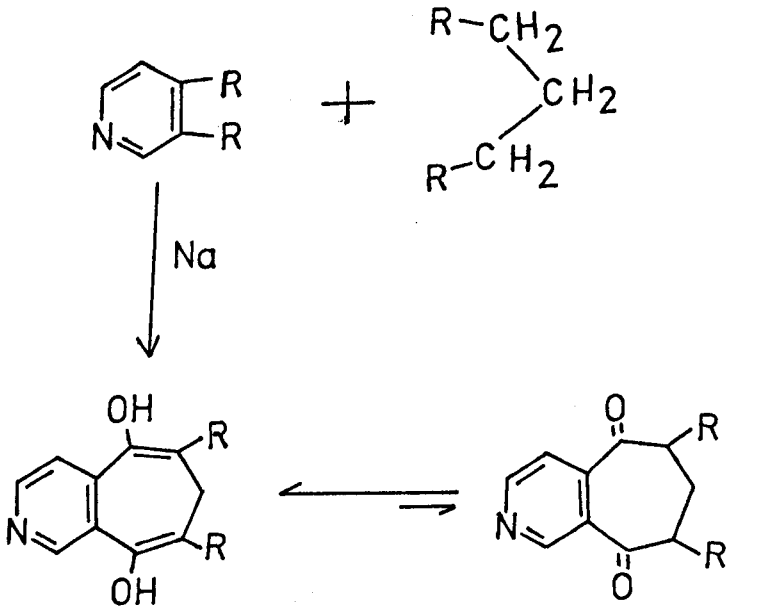
	J (cis) H_z		J (trans) H_z
(2,3)	7.98	(1,3)	4.5
(2,4)	7.6	(1,4)	3.6
(3,4)	0.28		

Compound (38) proved to be as stable as compound (24) being partly unchanged and partly decomposed after thermolysis. Proton abstraction with potassium t-butoxide failed to produce rearrangement.

It was of interest to investigate the analogous cyclohepta-[c]-pyridines to see if the reactions

previously described were unique to the cyclohepta-[b]-pyridines.

The reaction between diethyl pyridine-3,4-dicarboxylate and diethyl glutarate proceeded as expected to the diethyl 5,9-dihydroxy-7H-cyclohepta-[c]-pyridine-6,8-dicarboxylate (39). The yield was slightly lower than that of the cyclohepta-[b]-pyridine (29).



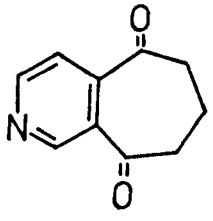
(39)

$R \equiv CO_2C_2H_5$

The infra red spectrum showed an absorption at 1645 cm^{-1} due to the β-ketoester.

The n.m.r. spectrum showed an exchangeable peak at δ 12.6 p.p.m. due to the enol protons. The pyridine protons appeared as a singlet at δ 9.2 p.p.m. (H_1), a doublet at δ 8.8 p.p.m. (H_3) and a doublet at δ 7.8 p.p.m. (H_4). J_{34} was 5.5 Hz. fig. 4.

The ester functions were readily removed from compound (39) by means of 48% hydrobromic acid to give 5,6,7,8-tetrahydro-9H-cyclohepta-[c]-pyridine-5,9-dione (40).



(40)

diethyl 5,9-dihydroxy-7H-cyclohepta-[c]-pyridine-6,8-dicarboxylate.

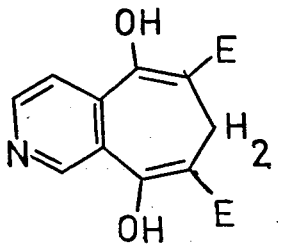
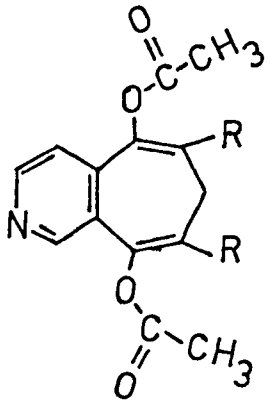


fig. 4.

When heated in excess acetic anhydride compound (39) was converted to diethyl 5,9-diacetoxy-7H-cyclohepta-[c]-pyridine-6,8-dicarboxylate (41) in good yield.

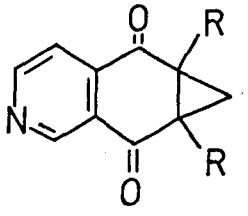


(41)

$R \equiv CO_2C_2H_5$

The infra red spectrum showed carbonyl absorptions at 1775 cm^{-1} (ester) and 1710 cm^{-1} (ester) and an absorption at 1610 cm^{-1} due to the unsaturation in the seven membered ring.

As for the cyclohepta-[b]-pyridine compound (29) oxidation of compound (39) with lead tetraacetate gave a cyclopropyl derivative, diethyl 1H-cyclopropa-[f]-isoquinoline-2,7-dione-1a,7a-dicarboxylate (42).



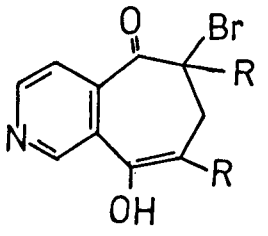
(42)

$R \equiv C O_2 C_2 H_5$

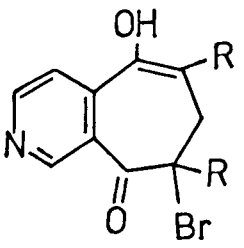
The ester carbonyl and ketonic absorptions appeared at 1748 and 1698 cm^{-1} respectively in the infra red spectrum. The n.m.r. spectrum showed the characteristic two doublets from the protons on carbon 1 at δ 2.9 and δ 2.1 p.p.m. with Jgem $6H_z$.

Bromination of compound (39) with N-bromosuccinimide followed by reaction with aqueous triethylamine also produced (42). The reaction of the diacetate (41) with N-bromosuccinimide produced 50% of the cyclopropane (42) and 30% of the diethyl 6-bromo-6,7-

dihydro-9-hydroxy-5H-cyclohepta-[c]-pyridine-6,8-dicarboxylate-5-one (43) or its isomer the 8-bromo compound (44).



(43)

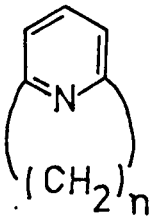


(44)

$R \equiv CO_2C_2H_5$

Attempts to rearrange (42) by thermolysis, deesterification or proton abstraction were all unsuccessful.

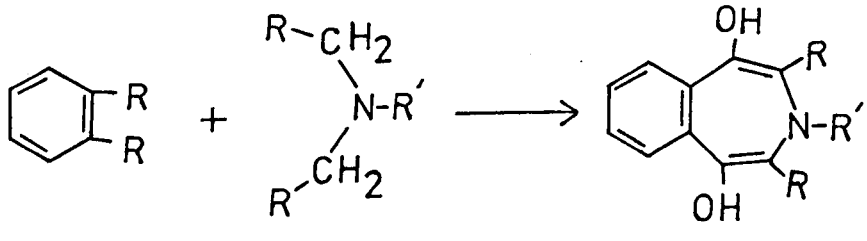
Attempts to prepare the 2,6-pyridinophanes (45) by the Dieckmann[4] reaction from diethyl pyridine-2,6-dicarboxylate and diesters such as diethyl glutarate, adipate or pimelate failed even at high dilution. The aliphatic esters underwent cyclisation-intramolecularly.



(45)

Some of the compounds will now be discussed in more detail. Compounds (29), (30) and (39) showed no peaks in the n.m.r. spectrum corresponding to the keto form and only absorptions due to the enol form in the infra red spectrum. Therefore one may conclude that these compounds exist almost entirely in the enol form. Further support for this statement was found by comparing the ultraviolet spectra of compounds (29), (30) and (39) with those of the diketo compound (32) and the diacetate compounds (33) and (41). The spectra of compounds (33) and (41) showed a greater resemblance to the compounds (29), (30) and (39) than did the spectrum of compound (32). (i.e. enol rather than keto).

A compound similar to compounds (29), (30) and (39) was prepared by Hahn[18], namely a benzo-[4,5]-azepine derivative (46). Hahn concluded from infra red data that compound (46) existed totally in the enol form.



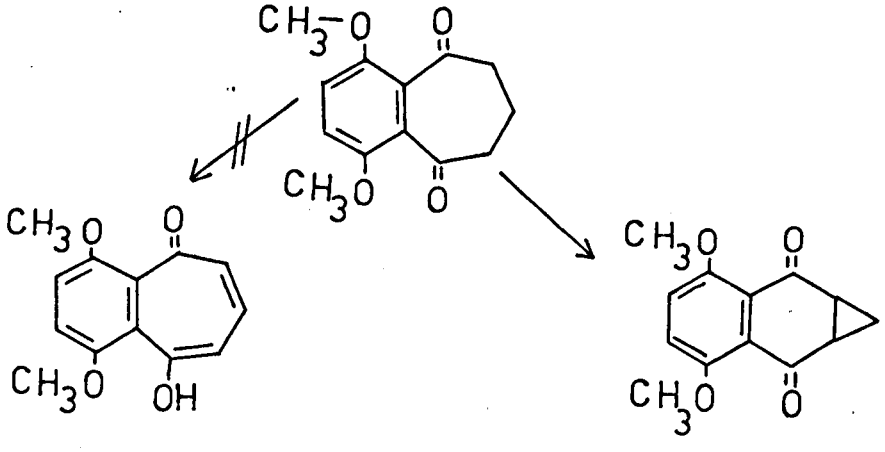
(46)

$R \equiv CO_2C_2H_5$

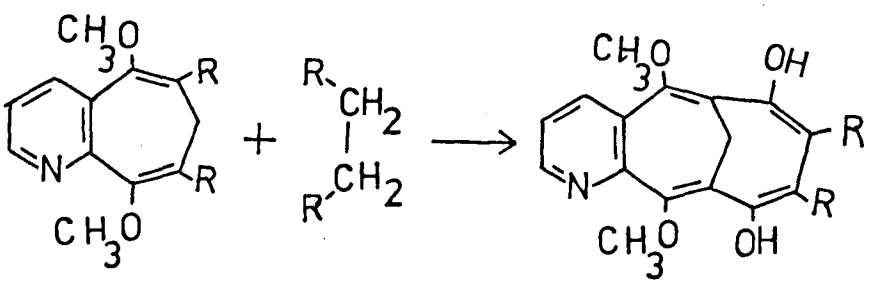
Compounds exhibiting the norcaradiene-cycloheptatriene type of equilibrium[19] provide examples of a seven membered ring becoming a bicyclo-[4,1,0]-heptane system by internal bond formation. Although a particular compound could lie well to one side of the equilibrium it was usually possible to convert it to the other form by moderate thermal means.

Compounds (35), (38) and (42) in the pyridine series may be considered as norcaradiene type structures in which the equilibruim was so far towards this system that reasonable conversion temperatures failed to produce the cycloheptatriene system.

Although the parent benzene compound (13) would form a cycloheptatriene derivative (17) as well as a norcaradiene type compound (14), Thomson[20] showed that substituents (methoxyl) on the benzene ring prevented the cycloheptatriene system being produced.

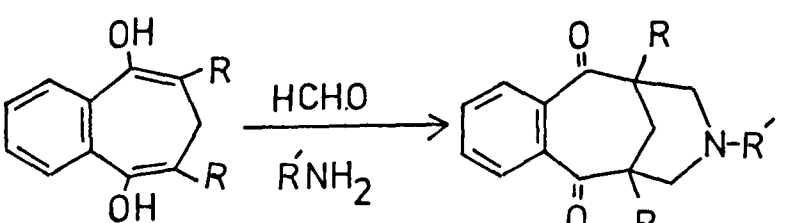


The Dieckmann[4] reaction provided a method of adding a ring onto a pyridine nucleus. The system thus produced may be readily envisaged as one capable of further annelation. For example if positions 5 and 9 were blocked by ether formation a second Dieckmann reaction could be carried out.



$R \equiv CO_2C_2H_5$

Hahn[21] provided an example making use of the Mannich reaction to obtain compound (47). This could be adapted and carried out on the analogous pyridine compound (29).

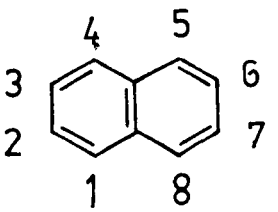


(12) (47)

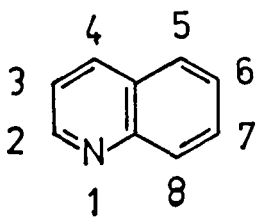
Synthetic routes to derivatives of quinoline and isoquinoline.

Nomenclature

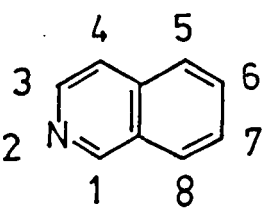
In the benzene series the parent compound was naphthalene (48).



(48)



(49)



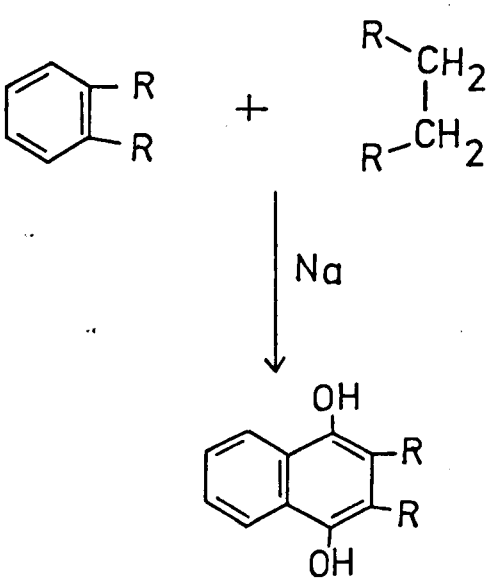
(50)

The parent compounds in the pyridine series were quinoline (49) and isoquinoline (50).

Introduction

The 5,8 oxygenated naphthalenes aroused interest when it was discovered that they had some antihemorrhagic activity. Some of the preparative procedures used are described.

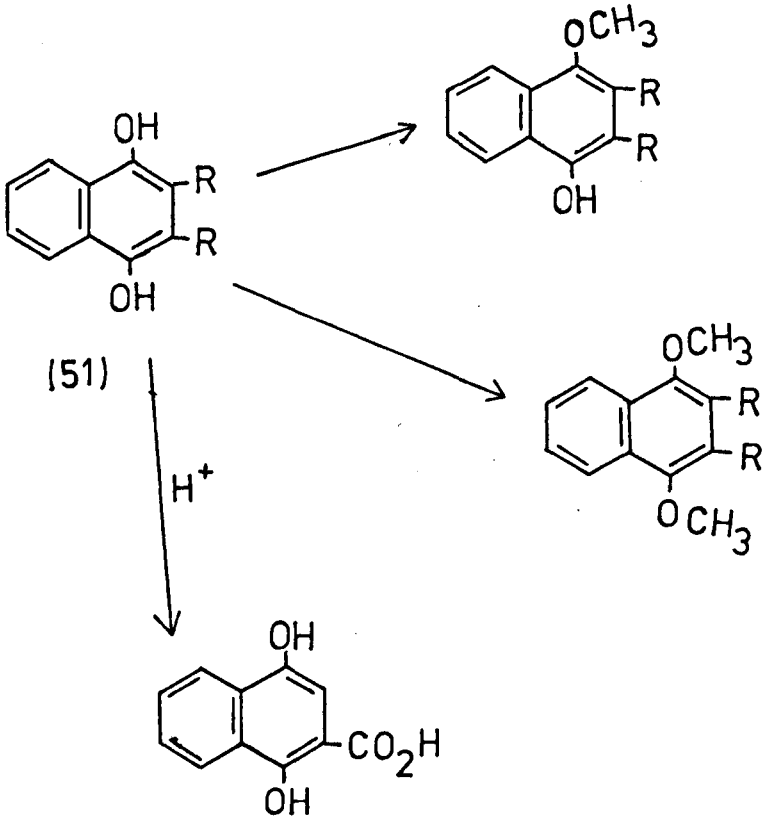
In 1894 Schwerin[22] had obtained diethyl 5,8-dihydroxynaphthalene-6,7-dicarboxylate (51) in 5% yield from a Dieckmann[4] reaction of diethyl phthalate and diethyl glutarate. Later Wallingford[23] adapted this method and thereby increased the yield to 48%. Wallingford was



(51)

$R \equiv CO_2C_2H_5$

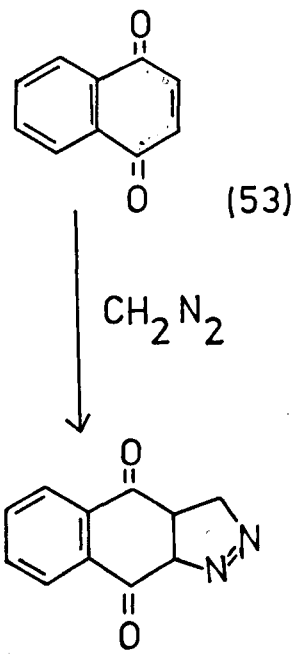
able to obtain both mono and dimethyl ethers of compound (51) but acid hydrolysis and decarboxylation of compound (51) gave a monocarboxylic acid derivative (52) not the expected 5,8-dihydroxynaphthalene.



(52)

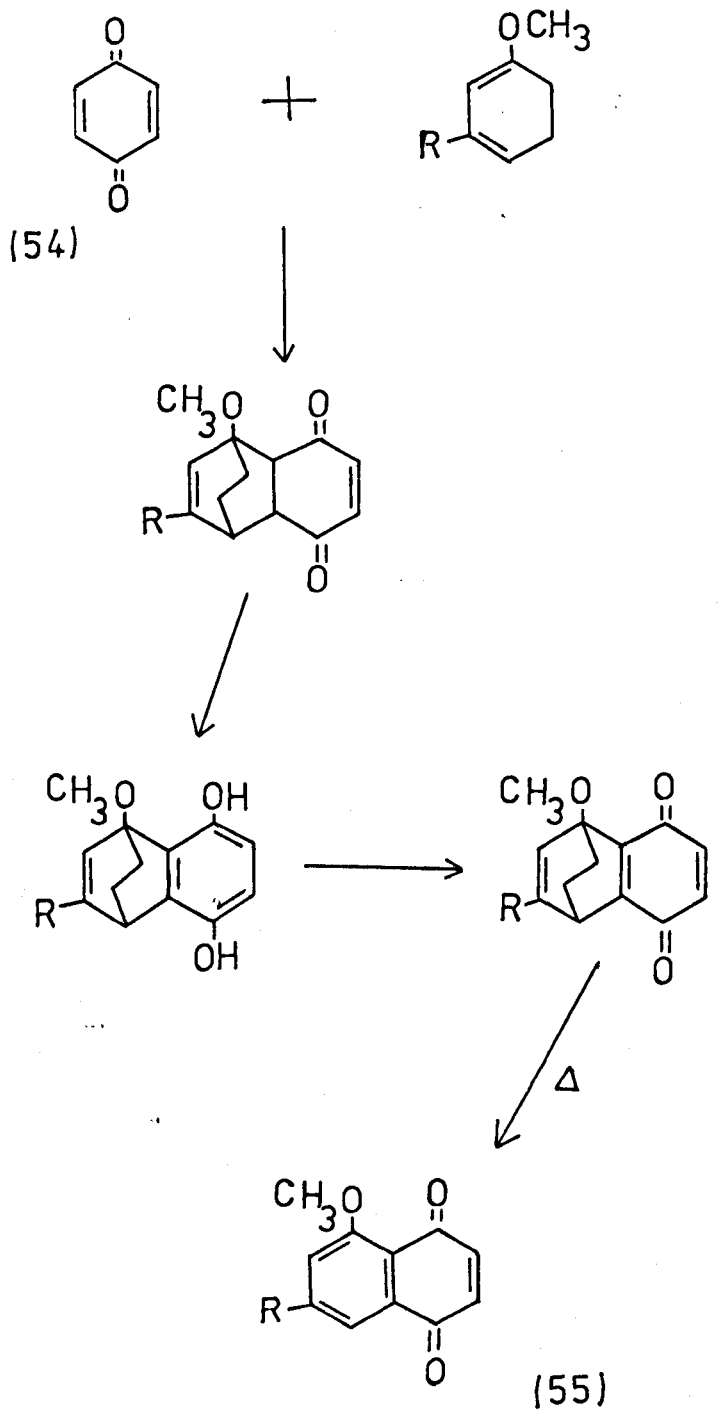
$R \equiv CO_2C_2H_5$

Dihydroxy compounds of the type (51) readily undergo oxidation to the quinone derivative (53).



Quinones will undergo additions with reagents such as amines or diazomethane. They will also undergo the Diels-Alder reaction. Birch[24] provided an example of this in converting a benzoquinone (54) to a substituted 5,8-naphthaquinone (55), as shown in the scheme below.

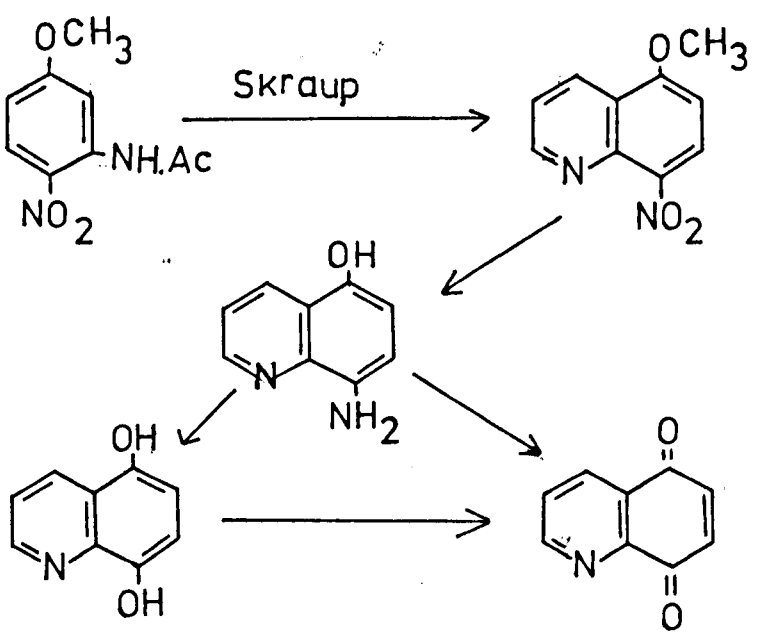
Scheme



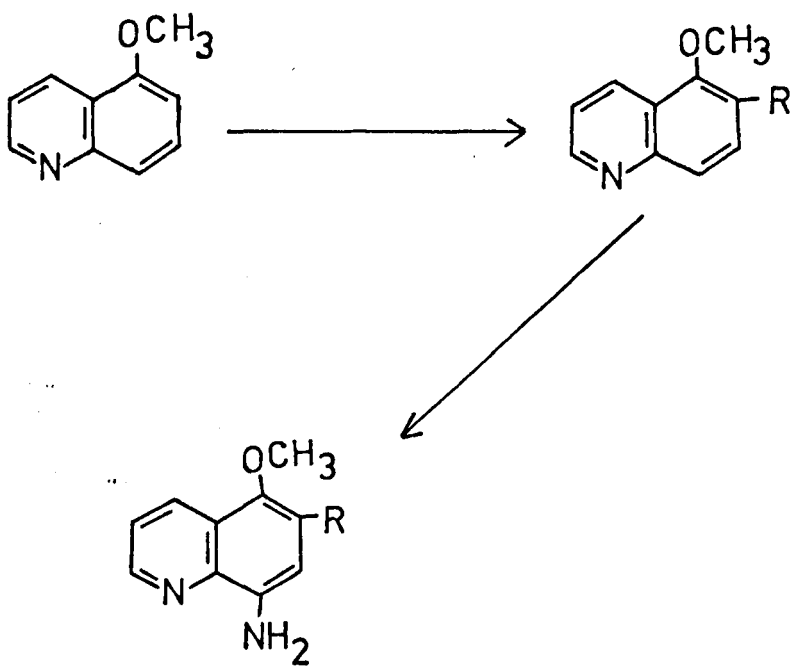
(55)

The pyridine analogues of the quinols and quinones mentioned above were normally prepared by a rather tedious route.

The synthesis of 5,8-dihydroxyquinolines began from aminobenzenes substituted ortho and / or para by nitro or ether functions. These compounds were made to undergo the Skraup[12] synthesis to give quinoline derivatives. The ether groups were converted to phenols directly whereas the nitro groups were first reduced to amino functions which were then converted to phenols. Conversion of the hydroxy -quinolines to the 5,8-diones was achieved by oxidation of the hydroxy functions. The amino groups could be oxidised directly if required.



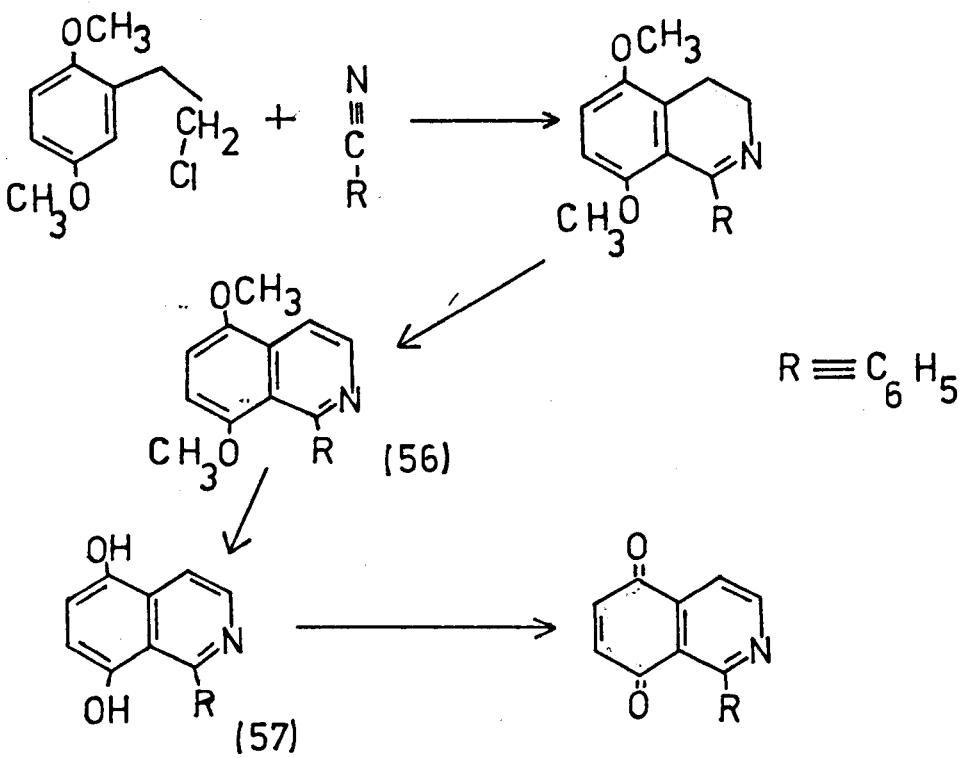
If a synthesis produced a compound containing only one substituent convertible to hydroxy or amino (e.g. 5 methoxyl group) a second could be introduced in the 8 position by means of diazotised sulphanilic acid. The derivative obtained from this reagent could be reduced with stannous chloride to an amino function. One setback with this reaction was the fact that the 6 position was also susceptible to attack and hence had to be blocked.



Schofield[25] used this route successfully in his synthesis of 6 and 7-alkylquinoline-5,8-diones.

The parent compound in this series quinoline-5,8-dione has been prepared by Fischer[26] from the amino, hydroxy derivative.

The reports on the corresponding isoquinoline compounds have been few. An example in this series was the compound (57) prepared by Stud[27]. The isoquinoline derivative (56) was prepared from an alkyl cyanide and a chloro compound, a method described by Munoz[28] et al.

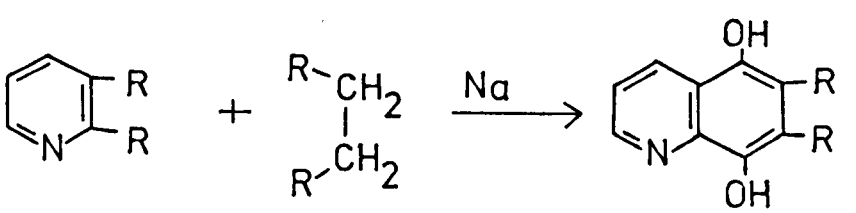


Discussion

The present work was concerned with using the Dieckmann[4] reaction to prepare 5,8-dihydroxyquinolines and isoquinolines then to oxidise these to the 5,8-diones.

The reaction between diethyl pyridine-2,3-dicarboxylate and diethyl succinate gave diethyl 5,8-dihydroxyquinoline-6,7-dicarboxylate (58). The yield was better than that obtained in the reaction with diethyl glutarate since the succinate was less susceptible to intramolecular reaction.

The n.m.r. spectrum showed a peak at δ11.9 p.p.m. (exchangeable with deuterium oxide) due to the hydroxy protons. The pyridine protons occurred as doublets of doublets at δ8.9 (H_2), 8.6 (H_4) and 7.5 p.p.m. (H_3). The coupling constants were J_{23} 4.3, J_{24} 1.7, J_{34} 8.5 H_z. Absorptions were observed at 3420 cm^{-1} (oH) 1725 cm^{-1} (ester carbonyl) and 1665 cm^{-1} (aromatics) in the infra red spectrum.

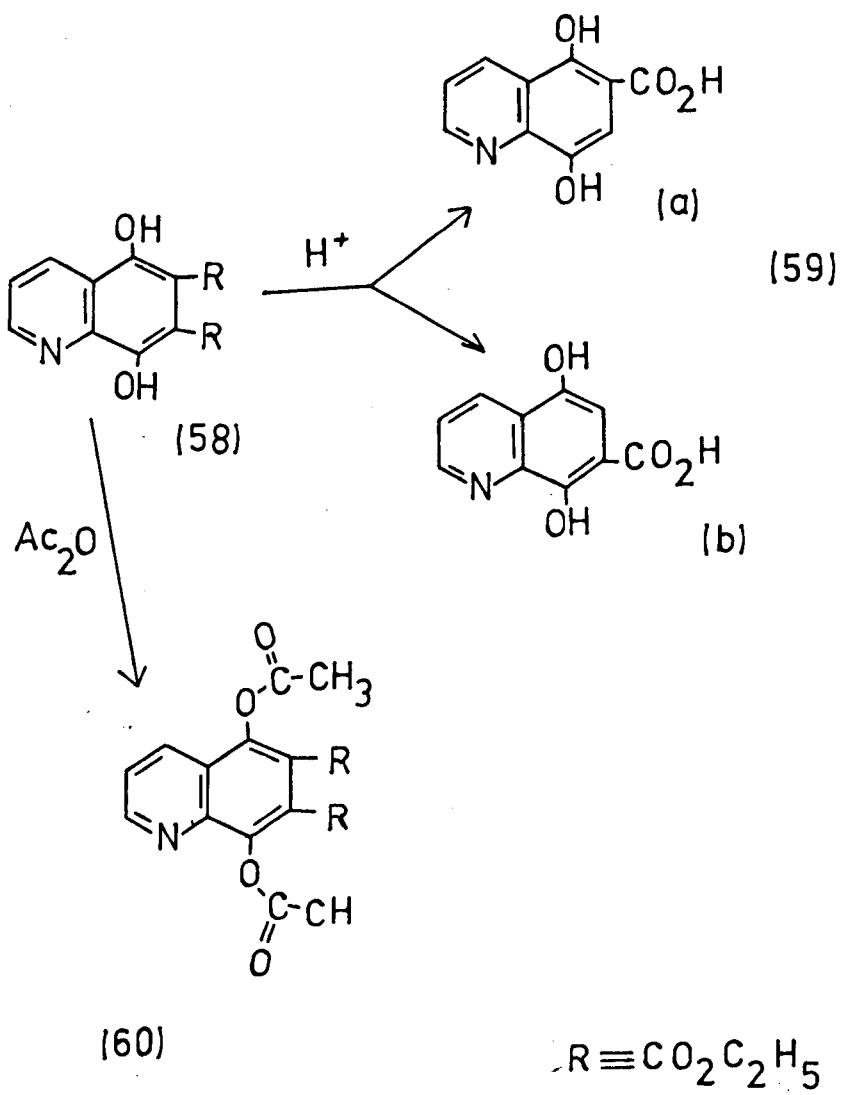


(58)

R ≡ $CO_2C_2H_5$

Compound (58) with 48% hydrobromic acid gave a monocarboxylic acid (59) as its hydrobromide. No attempt was made to distinguish which compound (a) or (b) was produced.

The diacetate (60) of compound (58) was obtained by heating it in excess acetic anhydride.

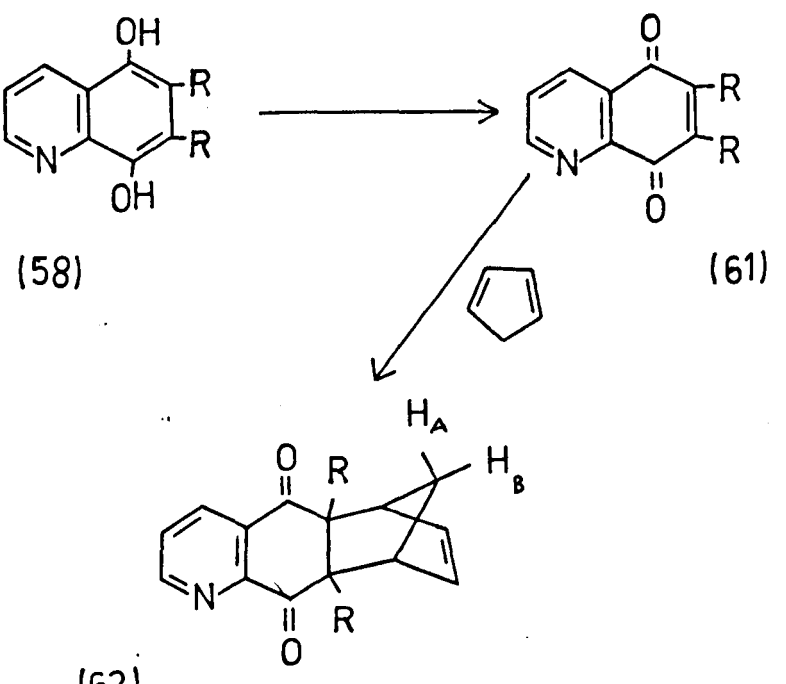


(60)

R ≡ $CO_2C_2H_5$

The structure of the diacetate was confirmed by n.m.r. spectra and C.H.N. analysis. The mass spectrum however gives a peak corresponding to the monoacetate at 347 mass units as the molecular ion. This may be explained as a loss of ketene from the diacetate in the heated inlet of the spectrometer.

Oxidation of compound (58) was readily achieved with lead tetraacetate to give the diethyl quinoline-5,8-dione-6,7-dicarboxylate (61). This underwent a Diels-Alder reaction with cyclopentadiene to give the adduct (62).



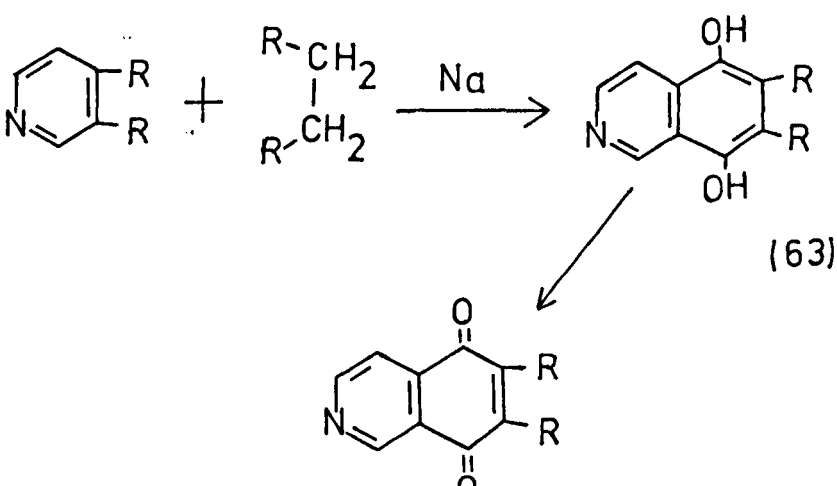
(58) (61) (62)

$R \equiv CO_2C_2H_5$

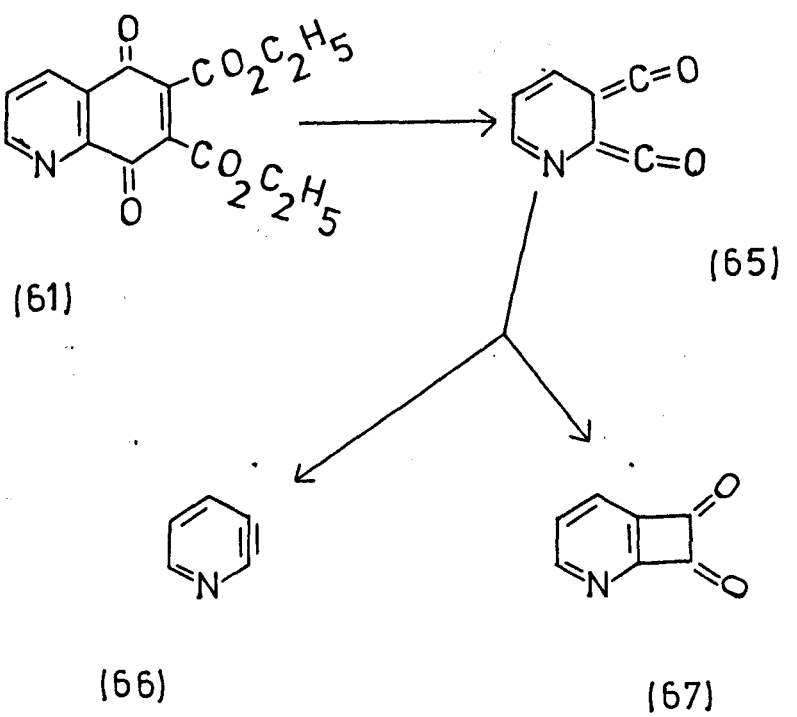
The n.m.r. spectrum of (62) was complex; however the geminal coupling of proton H_A H_B was determined as 10.2 H_z.

Diethyl 5,8-dihydroxyisoquinoline-6,7-dicarboxylate (63) was obtained from the reaction of diethyl pyridine-3,4-dicarboxylate and diethyl succinate. The infra red spectrum showed absorptions at 3400 cm^{-1} (oH) 1728 cm^{-1} (carbonyl of ester) and 1668 cm^{-1} (aromatics). The n.m.r. spectrum showed the pyridine protons at δ 9.7 (H_1), 8.75 (H_3) and 8.05 p.p.m. (H_4). The coupling constant J_{34} was 5.5 H_z.

Oxidation of the dihydroxy compound (63) produced diethyl isoquinoline-5,8-dione-6,7-dicarboxylate (64).



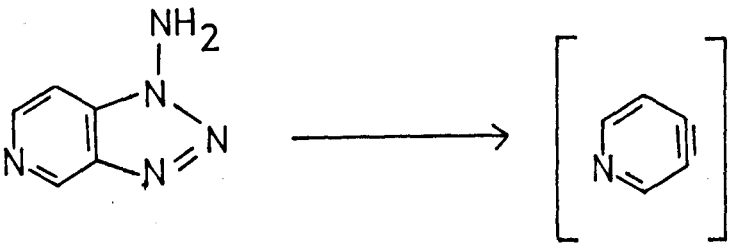
During the work on quinones it was observed that diethyl quinoline-5,8-dione-6,7-dicarboxylate could possibly be made to undergo controlled thermal decomposition via the pathway shown in scheme. Loss of diethyl acetylenedicarboxylate through a reverse Diels Alder reaction would lead to the diketene (65). From compound (65) either loss of carbon monoxide would occur to give the 2,3-pyridyne (66) or intramolecular cyclisation to give a butadione derivative (67).



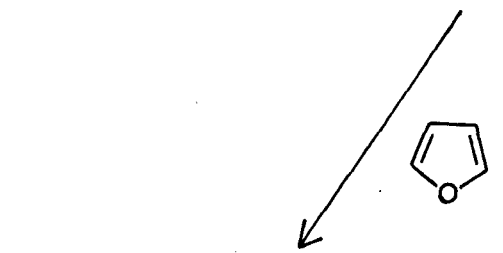
(61) (65)

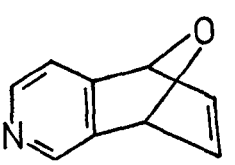
(66) (67)

3,4 pyridyne was known having been obtained by Sasaki[29] from the oxidation of 1-aminotriazolo-[4,5-c]-pyridine (68) with lead tetraacetate. The pyridyne was trapped as a Diels-Alder adduct of furan (69).



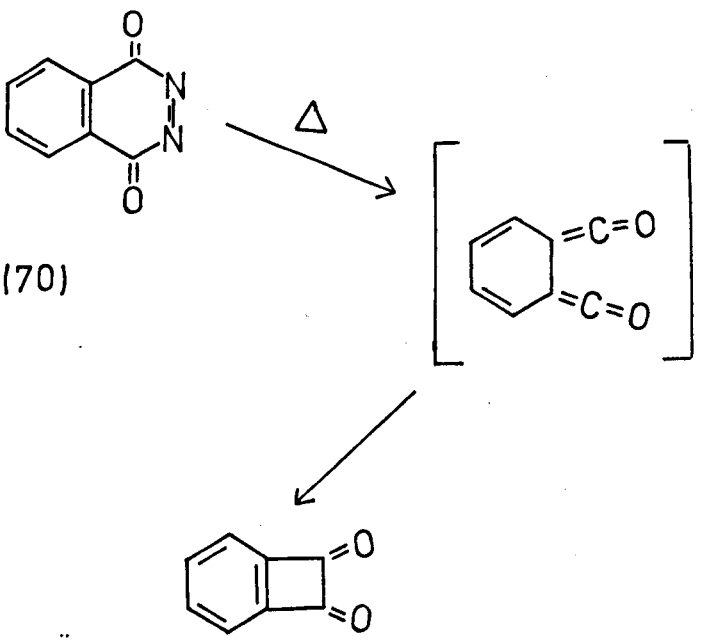
(68)





(69)

At this time Rees[30] et al published some work on the vacuum pyrolysis of phthalazine-5,8-dione (70). Benzocyclobutenedione (71) was obtained in 88% yield but no benzyne or compounds derived from this.

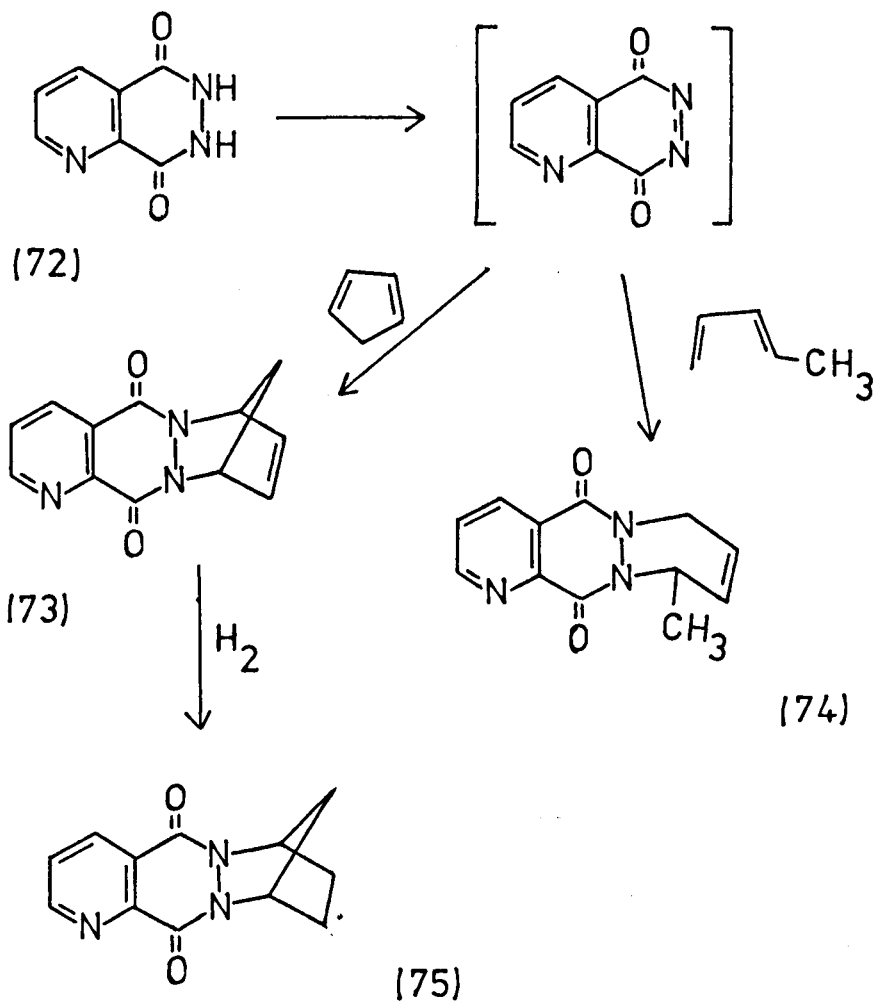


(70)

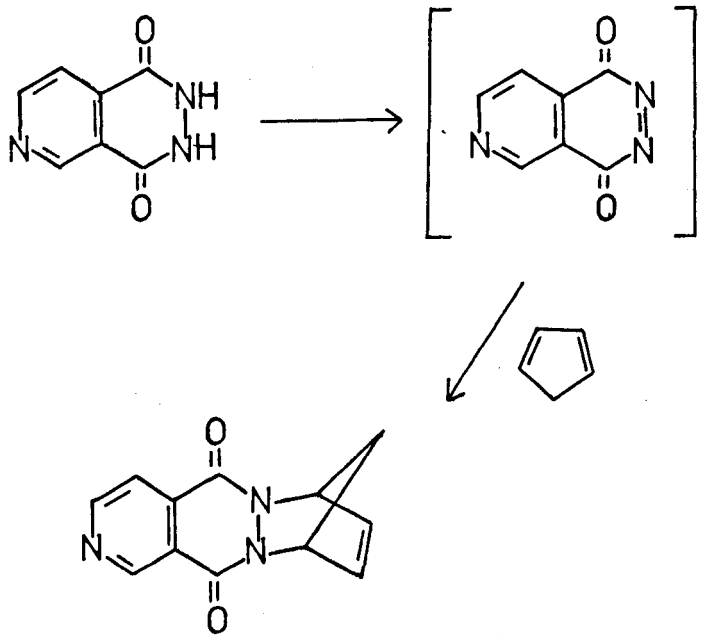
(71)

This work prompted the preparation of the pyridine analogue. The 6,7-dihydropyrido-[2,3-d]-pyridazine-5,8-dione (72) was oxidised by means of lead tetraacetate in the presence of cyclopentadiene to give the adduct (73).

A second adduct (74) was obtained by using penta-1,3-diene as the trapping agent. The isolated double bond in the adduct (73) was hydrogenated with a palladium charcoal catalyst to give compound (75).



By a similar process the pyrido-[c] derivative (76) was also prepared.



(76)

Compounds (73) and (74) were pyrolysed using Rees's[30] apparatus under identical conditions to those used for the benzo compounds. Only starting material and some polymeric material was isolated on the cold trap. Similar results were obtained later when compounds (61) and (76) were pyrolysed. This appeared to suggest that the vacuum was not sufficient to produce adequate sublimation for pyrolysis to occur or that the temperature of pyrolysis was too low.

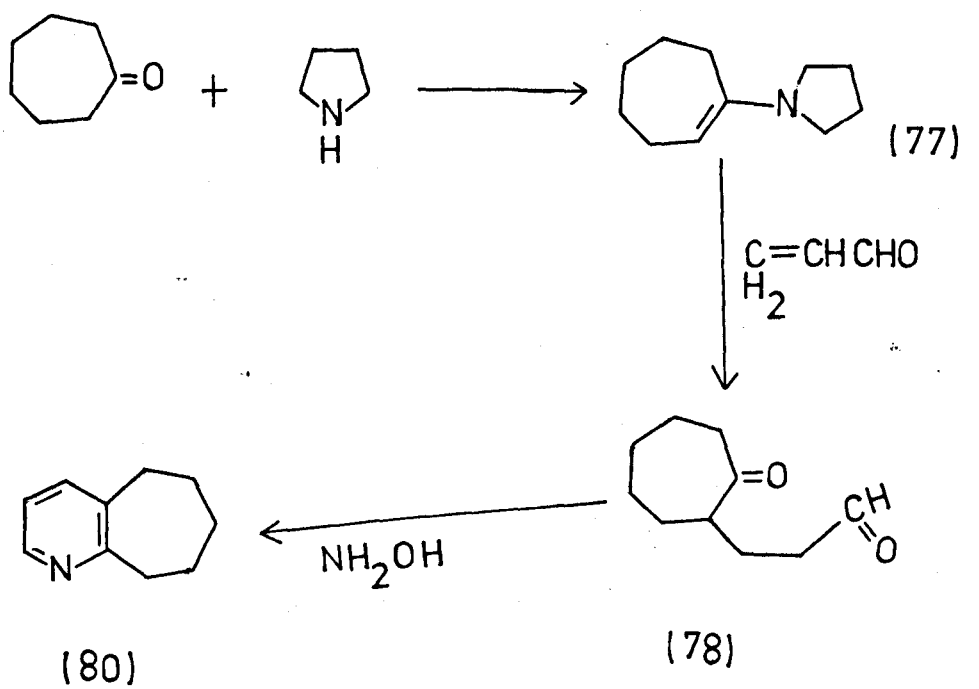
Part II.

A synthetic route from a cycloheptanone.

Jefferies[11] synthesis described in the introduction (P:12) showed how a cycloheptatrienone could be converted to a 7H-cyclohepta-[b]-pyridine derivative (26).

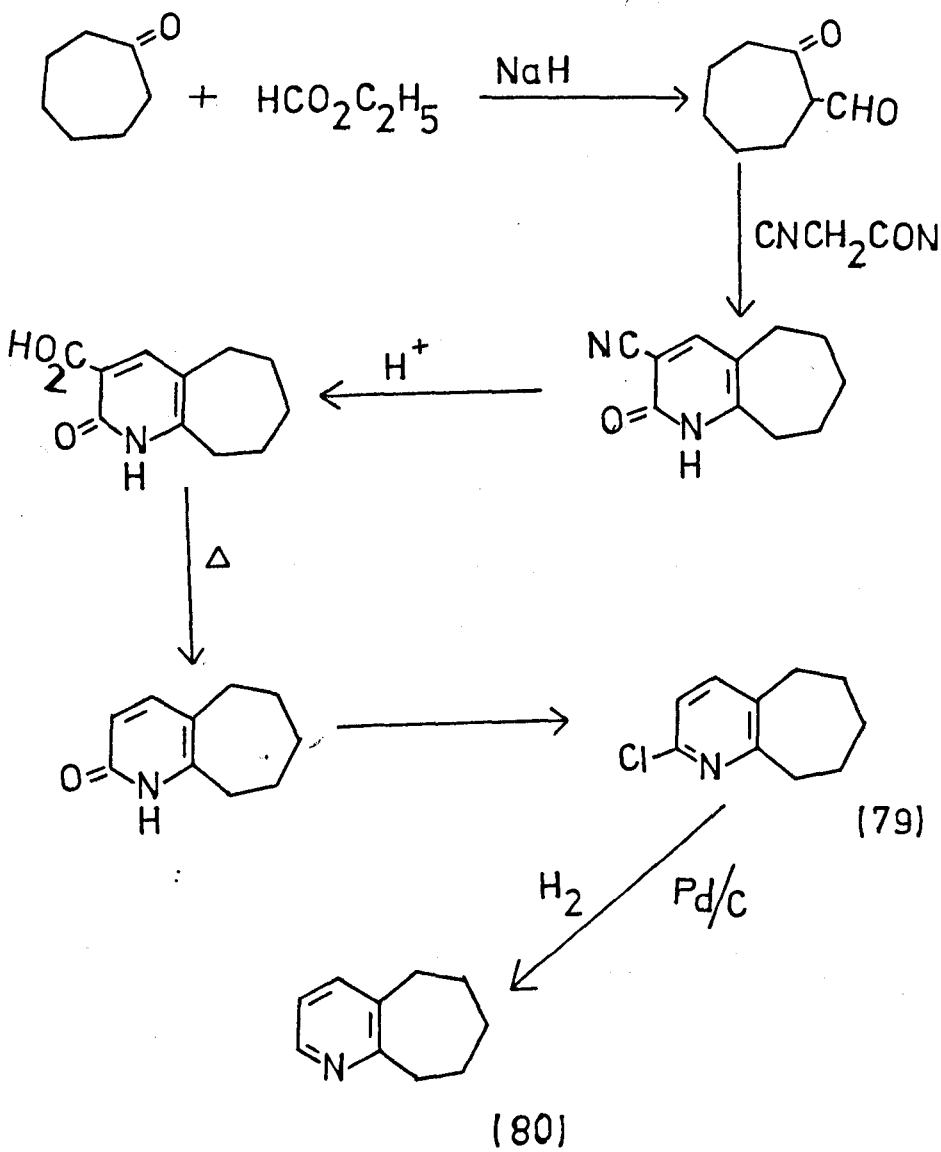
The object of the present work was to prepare the 9H-cyclohepta-[b]-pyridine-9-one (8). The route chosen required the preparation of 5,6,7,8-tetrahydro-9H-cyclohepta-[b]-pyridine (80). This was achieved by two methods.

The first is outlined in the scheme.



The enamine (77) of pyrrolidine[31] and cycloheptanone was reacted at -12° with acrolein to produce some of the required aldehydo-ketone[31] (78) which was readily cyclised to the pyridine compound (80) by heating with hydroxylamine hydrochloride in ethanol.

The second more useful route was that due to Godar et al[32] shown in the scheme below.



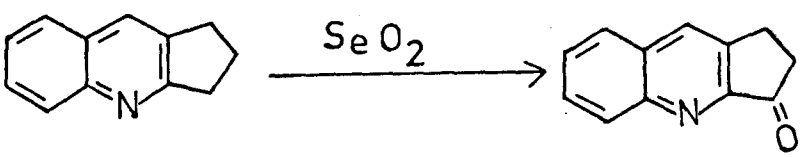
(79)

(80)

It was found difficult to obtain a good yield of the chloro derivative (79) from the pyridone by Godar's method. To improve the yield dichlorophenylphosphine oxide was used.

Once compound (80) had been obtained the next stage required the introduction of a keto function in position 9.

Selenium dioxide has proved useful in oxidising active methylene groups as described by Borsche[34] for 5,6-benzo-7-azahydrindene.



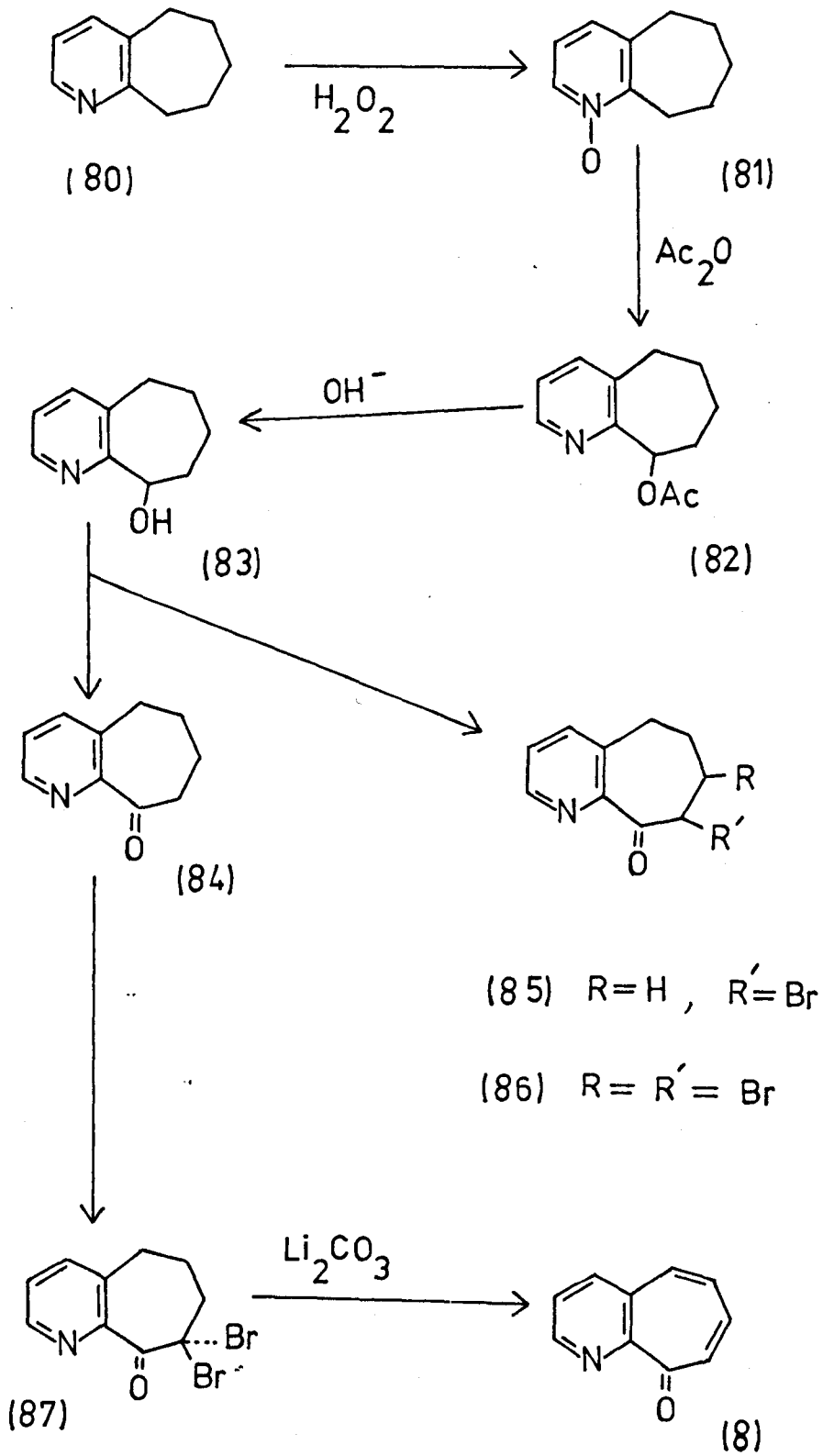
However the cycloheptane derivative (80) was not converted to the keto compound (84) by similar treatment.

As the ketone (84) was not obtainable directly it was decided to introduce a function which was readily convertible to a keto group. This was achieved by utilising a reaction described by Maynard et al[35].

They showed that a pyridine N-oxide would react with a carboxylic acid anhydride to produce an acylated 1-(2-pyridyl)-alkanol.

The cycloheptane derivative (80) was converted in good yield to the N-oxide (81) with hydrogen peroxide in glacial acetic acid[33]. The oxide (81) was then reacted with acetic anhydride[33] to produce the 9-acetyl compound (82). The latter was readily hydrolysed to the alcohol (83) with aqueous base.

The acetyl compound showed an absorption at 1735 cm^{-1} in the infra red spectrum. The n.m.r. spectrum showed the characteristic absorptions for the three pyridine protons at δ 8.4 7.45 and 7.1 p.p.m. (H_2, H_4, H_3). There was a multiplet for the single proton on C_9 at δ 6.0 p.p.m. and a sharp singlet protruding from one of the multiplets at δ 2.2 p.p.m. due to the methyl protons of the acetyl function.


H2O2
(80)
(81)
Ac2O
OH⁻
OAc
OH
(83)
(82)
(84)
R
R′
O
(85) R=H , R′=Br
(86) R= R′= Br
Li2CO3
Br
Br
(87)
(8)

The mass spectrum of the acetyl compound gave no molecular ion, the first visible peak appearing at 163 mass units due to loss of ketene.

The alcohol (83) gave an absorption at 3360 cm^{-1} in the infra red spectrum. The n.m.r. spectrum showed a broad singlet at δ 5.8 p.p.m. (exchangeable) due to the alcohol proton and a broad doublet at δ 4.75 p.p.m. due to the single proton on C_9 (coupling constant 10.5 Hz).

Oxidation of the alcohol (83) to the ketone (84) proved difficult, reagents such as aluminium-isopropoxide, potassium permanganate (neutral) and activatived manganese dioxide were all tried unsuccessfully. However treatment with N-bromosuccinimide did yield up to 50% of the ketone (84) together with 10% of the monobromoketone (85) and 30% of the dibromoketone (86).

In the infra red spectra the ketone (84) gave an absorption at 1695 cm^{-1} and the mono and dibromo derivatives (85) and (86) gave absorptions at 1710 and 1720 cm^{-1} respectively.

The n.m.r. spectra were characterised by an absorption at δ 5.45 p.p.m. for the mono bromo derivative due to the single proton on C_8, the same carbon atom that held the bromine atom. The dibromo compound (86) showed a slightly split doublet at

δ 5.75 p.p.m. and a multiplet at δ 4.87 p.p.m. each containing a single proton. From this data one may conclude that the bromine atoms are on carbons 7 and 8 as no other positions will give the correct coupling assuming that one bromine must be α to the carbonyl function.

An attempt to dehydrobrominate the 7,8-dibromo compound (86) using lithium chloride in dimethyl formamide[8] failed to produce anything except for a tar and some unchanged bromo compound.

The ketone (84) was reacted with a selective brominating agent (phenyltrimethylammonium tribromide) in dry tetrahydrofuran. This did produce a small quantity of the α,α-dibromoketone (87) and on treatment with lithium carbonate in dimethylformamide[8] produced the 9H-cyclohepta-[b]-pyridine-9-one (8). This showed absorptions in the infra red spectrum at 1642, 1612 and 1588 cm^{-1}, in good agreement with the values obtained for the benzo analogue.

The n.m.r. spectrum showed no peaks between δ 6.5 and δ 0.0 p.p.m. indicating the presence of a ring current throughout the two rings.

Experimental.

Experimental

Preliminary notes.

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

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

Ultra violet spectra were recorded on a Perkin Elmer 257 spectrophotometer. The spectra were determined in solution (e.g. $CH Cl_3$) or as liquid films (film).

Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Perkin Elmer R10 60MHz or Varian 100 MHz spectrometer using a tetramethyl silane internal standard (δ 0.00 p.p.m.) and are quoted as 'delta' (δ) values in parts per million (p.p.m.)
The following abbreviations are used:

s = singlet. d = doublet.

t = triplet. q = quartet.

m = multiplet. b = broadened.

r = exchangeable with deuteruim oxide.

Mass spectra were determined on a Hitachi-Perkin Elmer RMU-6 instrument.

Woelm alumina deactivated by the addition of water was used in column chromatography. A number in

brackets is used to denote the activation of the alumina; (1) high, (4) low.

Thin layer chromatography (t.l.c.) was carried out on 7.5 x 2.5 cm microscope slides coated with Kieselgel PF_{254} (Merck). The components were visualised under ultra violet light or developed in iodine.

Preparative layer chromatography (p.l.c.) was carried out on 40 x 20 cm glass plates coated with a 1.5 mm layer of Kieselgel PF_{254}. The separated compounds were visualised under ultra violet light and isolated by scraping off the silica and extracting several times with hot methanol. The filtered methanolic solution was evaporated to leave a residue which contained some silica. This residue was dissolved in chloroform, filtered and evaporated.

Photolytic work was performed using a Hanovia photochemical reactor (medium pressure mercury lamp) which mainly transmitted light of 254, 265, 297, 313 and 366 n.m. wavelength. Irradiations were performed under nitrogen.

Pyridine-2,3-dicarboxylic acid anhydride[48].

Prepared by heating the 2,3-dicarboxylic acid with acetic anhydride. Melting point 161-162° (Lit 161-162°).

γ-Ethoxypropylbromide.

The method of Smith and Sprung[49] was used. Yield 60% B.pt. 146-150° (Lit 147-150°).

Acrolein dibromide.

To one mol of acrolein in three times its own volume of dry carbon tetrachloride was added with stirring one mol of bromine, diluted with carbon tetrachloride. Solvent was removed and the residue distilled, boiling point 86-89° (20mm) (Lit 88° at 18mm).

α-Bromo-β-ethoxypropionaldehydediethylacetal.

Prepared by the method of Fischer and Gielbe[50]. Yield 60% B.pt. 104-108° (20mm) (Lit 103° at 20mm).

β-Ethoxyacroleindiethylacetal.

As described by Price and Moos[51]. Yield 80% B.pt. 94-96° (20mm) (Lit 94° at 20mm).

Ethyl 2-Methylnicotinate.

Prepared as described by Baumgarten and Dornow[52]. Yield 30%. B.pt. 118-121° (20mm) (Lit 118° at 20mm).

Ethyl γ-Bromobutyrate.

Prepared as described in Organic Syntheses Volume 45 Yield 80%. B.pt. 94-99° (20mm) (Lit 97° at 25mm).

Di-tertiarybutyl glutarate.

Prepared as described in Organic Syntheses Collective volume IV. Yield 85%.

Diethyl glutarate.

One mol of glutaric acid was heated overnight with 2.2 mol of ethanol containing a trace of acid. Distillation gave the diester in 90% yield.
B.pt. 140-144° (6mm) (Lit 143° at 7mm).

Diethyl succinate and diethyl adipate were prepared similarly.
B.pt. succinate 106-109° (20mm) (Lit 105° at 15mm)
adipate 131-134° (20mm) (Lit 132° at 20mm).

Dimethyl glutarate.

Prepared as described for the diethyl ester from the acid and methanol.

Yield 92%. B.pt. 68-70° (0.5mm) (Lit 68° at 0.5mm).

Dimethyl Pyridine-2,3-dicarboxylate.

As prepared by Engler[53]. Yield 75%.

Melting point 53-54°. (Lit 53-54°).

Diethyl Pyridine-2,3-dicarboxylate.

Prepared as described for the dimethyl ester[53].

Yield 75%. B.pt. 140-144° (0.6mm) (Lit 140° at 0.6mm).

Similarly prepared were;

diethyl pyridine-3,4-dicarboxylate[54], yield 70%.

B.pt. 168-170° (20mm) (Lit 170° at 20mm).

diethyl pyridine-2,6-dicarboxylate, yield 80%. B.pt. 156-158°(1mm) (Lit 158° at 1mm).

5,6,7,8-Tetrahydro-9H-cyclohepta-[b]-pyridine.

Prepared as described by Godar and Mariella[32] in 30% overall yield.

1-N-pyrrolidinocycloheptene [31].

One mol of pyrrolidine and one mol of cycloheptanone were heated in 300 mls of benzene containing a trace of p-toluenesulphonic acid. A Dean-Stark apparatus was used to remove any water produced. When the production of water ceased the solution was distilled, the required fraction being collected at 130° (15mm). Yield 96%.

β-(2-ketocycloheptyl)-propionaldehyde[31].

One mol of 1-N-pyrrolidinocycloheptene was dissolved in 700 mls of dry diethyl ether and cooled to -12°C. Nitrogen was bubbled through the solution. 1.1 mol of acrolein in 70 ml of dry diethyl ether were added over 2.5 hours and the solution then kept at 0° for 1 hour. 30 mls of water were added with stirring. After 15 minutes the pH was adjusted to 5 with 6N hydrochloric acid. The ethereal layer was separated, washed with saturated soduim bicarbonate and dried. The resulting solution was distilled and the required fraction collected at 110-115° (0.7mm) in 10% yield.

δ ($CD Cl_3$) .

9.75 (1H,s) 2.45 (5H,m).

1.7 p.p.m. (10H,m).

5,6,7,8-Tetrahydro-9H-cyclohepta-[b]-pyridine.

β-(2-ketocycloheptyl)-propionaldehyde (10g) dissolved in its own volume of ethanol was reacted with hydroxylamine hydrochloride (5g). After heating for 3 hours the ethanol was removed the residue neutralised and extracted with diethyl ether. The ether solution was dried and distilled to give a fraction boiling at 107°-109° (15mm) (Lit 108° at 15mm) in 88% yield (9.9g).

5,6,7,8-Tetrahydropyrido-[2,3-d]-pyridazine-5,8-dione[55].

Prepared by heating o.1 mol of hydrazine hydrate with o.1 mol of diethyl pyridine-2,3-dicarboxylate in 100 mls of ethanol. The yellow solid precipitated was filtered washed and dried. Yield 82%. Melting point 313° (Lit 311°).

5,6,7,8-Tetrahydropyrido-[3,4-d]-pyridazine-5,8-dione.

Prepared as described for the [2,3-d]-pyridazine from diethyl pyridine-3,4-dicarboxylate. Yield 78%. Melting point 312° (sublimed).

General procedure for Dieckmann type reactions.

0.5 mols of absolute ethanol were added to 2 mols of sodium wire in a three necked flask equipped with a mechanical stirrer and reflux condenser. The two diesters (1 mol) were diluted 50% with dry xylene then added separately and dropwise onto the vigorously stirred sodium. On completion of the addition the mixture was heated for 1.5 hours, during which time a solid was precipitated.

After cooling the flask in ice, 200 mls of ice cold water were added cautiously. When all the solid had dissolved the aqueous layer was separated and neutralised with 30% glacial acetic acid. The resulting solution was extracted, the solvent dried filtered and removed to leave the product which was then recrystallised .

Diethyl 5,9-Dihydroxy-7H-cyclohepta-[b]-pyridine-6,8-dicarboxylate. (29)

2 mls of ethanol, 2.1g of sodium wire, 10g of diethyl pyridine-2,3-dicarboxylate and 8.5g of diethyl glutarate were used.

3x150 mls of chloroform were used for the extraction. After removing the solvent and recrystallising the residue from 60-80° petrol ether white crystals (7.3g) were obtained in 55% yield. Melting point 117-118°.

δ ($CDCl_3$)

12.6 (1.7H, sbr) 8.9 (1H, d of d) 8.35 (1H, d of d) 7.5 (1H, d of d) 4.4 (4H, q) 3.05 (2H, s) 1.45 p.p.m. (6H, t).

Coupling constants:-

$J_{2,3}$ 5.1, $J_{2,4}$ 1.7, $J_{3,4}$ 8.5 H_z

νmax (CCl_4)

1645, 1615 cm^{-1}

λmax (Et OH)

204, 225 sh, 239, 281, 322 sh n.m. [log ε 4.11, (-), 4.18, 4.35, (-)].

Mass spectrum

m/e 319 (M^+), 274, 246, 200

C.H.N.

For $C_{16}H_{17}NO_6$ required 60.2%C 5.3%H 4.4%N

obtained 60.5%C 5.5%H 4.4%N

Dimethyl 5,9-Dihydroxy-7H-cyclohepta-[b]-pyridine-6,8-dicarboxylate. (30)

2 mls of ethanol, 2.1g of sodium wire, 10g of dimethyl pyridine-2,3-dicarboxylate and 8.1g of dimethyl glutarate were used. The extraction was performed with 3x150 mls of chloroform. The residue obtained from this was recrystallised from benzene to give white crystals (7.6g) in 50% yield. Melting point 139-140°.

δ ($CD Cl_3$)

12.6 (2H, sbr) 8.9 (1H, d of d) 8.35 (1H, d of d) 7.5 (1H, d of d) 3.9 (6H, s) 3.0 p.p.m. (2H, s)

Coupling constants:-

$J_{2,3}$ 5.1, $J_{2,4}$ 1.7, $J_{3,4}$ 8.5 H_z

νmax ($CH Cl_3$)

1730, 1650, 1610, cm^{-1}

λmax (Et OH)

203, 233 sh, 238, 280, 322 sh n.m. [log ε 4.20, (-), 4.17, 4.36, (-)].

Mass spectrum.

$^m/_e$ 291 (M^+), 260, 200.

C.H.N.

For $C_{14} H_{13} NO_6$ required 57.7%C 4.5%H 4.8%N

obtained 57.8%C 4.8%H 4.6%N

Diethyl 5,9-Dihydroxy-7H-cyclohepta-[c]-pyridine-6,8-dicarboxylate. (39)

The quantities were the same as those used for the cyclohepta-[b]-pyridine except that 10g of diethyl pyridine-3,4-dicarboxylate was used. Extraction with 3x150 mls of chloroform produced, after removal of solvent, a residue which was recrystallised from 60-80° petrol ether to give white crystals (6g) in 40% yield.

Melting point 93-94°

δ (CD Cl_3)

12.5 (1.7H, sbr) 9.2 (1H, s) 8.75 (1H, d) 7.8 (1H, d) 4.3 (4H, q) 2.95 (2H, s) 1.4 p.p.m. (6H, t).

Coupling constants:-

$J_{3,4}$ 5.5 H_z.

νmax (CH Cl_3)

1645, 1610 cm^{-1}

λmax (Et OH)

206, 218 sh, 252, 272, 320 n.m. [log ε 4.08, (-), 4.27, 4.18, 3.94].

Mass spectrum

m/e 319 (M^+), 290, 273, 246, 227, 200, 199, 172.

C.H.N.

For $C_{16}H_{17}NO_6$	required	60.2%C	5.3%H	4.4%N
	obtained	59.8%C	5.3%H	4.3%N

Diethyl 5,8-Dihydroxyquinoline-6,7-dicarboxylate.[58]

2 mls of ethanol, 2.1g of sodium wire, 10g of diethyl pyridine-2,3-dicarboxylate and 7.8g of diethyl succinate were used. The crude product was extracted with 3x150 mls of chloroform and the oil obtained from this was dissolved in hot 60-80° petrol ether from which cream coloured crystals were obtained (8.4g) in 58% yield.

Melting point 137-138°

δ ($CDCl_3$)

11.88 (1H, sbr) 8.85 (1H, d of d) 8.6 (1H, d of d) 7.45 (1H, d of d) 4.4 (4H, q) 1.4 p.p.m. (6H, t)

Coupling constants:-

$J_{2,3}$ 4.3, $J_{2,4}$ 1.7, $J_{3,4}$ 8.5 H_z.

νmax ($CHCl_3$)

3420, 1725, 1665, cm^{-1}

λmax (Et OH)

208, 232, 268, 341 n.m. [log ε 4.40, 3.98, 4.46, 3.56]

Mass spectrum

m/e 305 (M^+), 261, 260, 231, 230, 159.

C.H.N.

For $C_{15}H_{15}NO_6$	required	59.0%C	4.9%H	4.6%N
	obtained	58.9%C	5.2%H	4.3%N

Diethyl 5,8-Dihydroxyisoquinoline-6,7-dicarboxylate.(63)

Prepared as described for compound (58) except that diethyl pyridine-3,4-dicarboxylate was used. Extraction with 3x150 mls of chloroform produced the product which was recrystallised from 60-80° petrol ether as white crystals (7.0g) in 50% yield.

Melting point 154-155°.

δ(CD Cl_3)

9.68 (1H, s) 8.75 (1H, d) 8.05 (1H, d)

4.4 (4H, q) 1.35 p.p.m. (6H, t).

Coupling constant:-

$J_{3,4}$ 5.5 H_z

νmax (CH Cl_3)

3400, 1728, 1668, cm^{-1}

λmax (Et OH)

219, 248, 254 n.m. [log ε 4.44, 4.25 3.90].

Mass spectrum

m/e 305(M^+), 260, 257, 231, 211, 142, 137.

C.H.N.

For $C_{15}H_{15}NO_6$ required 59.0%C 4.9%H 4.6%N

obtained 59.4%C 4.8%H 4.5%N

The reaction of di-tert-butyl glutarate with diethyl pyridine-2,3-dicarboxylate.

2.1g of sodium wire, 10g of diethyl pyridine-2,3-dicarboxylate and 9g of di-tert-butyl glutarate were used. When ethanol (2 mls) was added as an initial catalyst the product obtained (7g) in 50% yield was diethyl 5,9-dihydroxy-7H-cyclohepta-[b]-pyridine-6,8-dicarboxylate and not the di-tert-butyl ester expected. The nature of the product was determined by n.m.r., t.l.c. and mixed melting point.

Adding tert. butanol as the initial catalyst had no effect on the product obtained.

5,6,7,8-Tetrahydro-9H-cyclohepta-[b]-pyridine-5,9-dione. (31)

Diethyl 5,9-dihydroxy-7H-cyclohepta-[b]-pyridine-6,8-dicarboxylate (2g) was boiled in 20 mls of 48% hydrobromic acid for 1.5 hours. Excess acid was removed under vacuum. The residue was neutralised with aqueous sodium bicarbonate solution and extracted with 3x25 mls of chloroform. After drying the solvent was removed to leave a pale yellow oil. This was chromatographed on an alumina (3) column. Using chloroform as the eluent a fraction was obtained which on removal of the solvent appeared as a pale yellow

viscous oil. Attempts at crystallisation failed but the oil did solidify on standing. Melting point 63-64°. Yield 85%. (0.94g).

δ ($CDCl_3$)

8.85 (1H, d of d) 8.15 (1H, d of d) 7.5 (1H, d of d) 2.9 (4H, m) 2.15 p.p.m. (2H, m).

νmax (CCl_4).

1690 cm^{-1}

λmax (Et OH)

212, 236, 270sh n.m. [logε 4.08, 3.80, (-)] .

Mass spectrum

m/e 175(M^+), 147, 105.

C.H.N.

For $C_{10}H_9NO_2$	required	68.5%C	5.2%C 8.0%N
	obtained	68.4%C	5.6%C 8.0%N

<u>5,6,7,8-Tetrahydro-9H-cyclohepta-[c]-pyridine-5,9-dione</u>. (40)

Prepared from 2g of the diester (39) as described for the cyclohepta-[b]-pyridine derivative. Yield 94% (1.03g). Again attempted crystallisation failed but the oil did solidify on standing. Melting point 64-65°

δ ($CDCl_3$)

9.0 (2H, m) 7.64 (1H, d) 2.85 (4H, m) 2.25 p.p.m. (2H, m).

νmax ($CH Cl_3$)

1688 cm^{-1}

λmax (Et OH)

209, 228, 283, n.m. [log ε 4.02, 3.69, 3.35] .

Mass spectrum

m/e 175(M^+), 147, 119, 105, 91, 77.

C.H.N.

For $C_{10} H_9 NO_2$	required	68.5%C	5.2%H	8.0%N
	obtained	68.5%C	5.3%H	7.8%N

<u>The reaction of diethyl 5,8-dihydroxyquinoline-6,7-dicarboxylate (58) with 48% hydrobromic acid to produce (59).</u>

The diester (58) (3g) was boiled in 30 mls of the acid for 2 hours. Extended heating produced no further effect. On cooling a red crystalline product was obtained. This was filtered, washed with a small quantity of ice cold water and dried. Yield 96% (2.7g).

Melting point above 350°

Mass spectrum

m/e 205(M^+), 189, 188, 160, 103, 82, 80.

C.H.N.

For $C_{10} H_7 NO_4 . HBr$	required	41.9%C	2.8%H	4.7%N
	obtained	41.6%C	3.3%H	4.7%N

Diethyl 5,9-Diacetoxy-7H-cyclohepta-[b]-pyridine 6,8-dicarboxylate. (33)

Diethyl 5,9-dihydroxy-7H-cyclohepta-[b]-pyridine-6,8-dicarboxylate (3g) was heated in 30 mls of acetic anhydride for 12 hours. The excess anhydride was removed and the residue neutralised with aqueous sodium bicarbonate. The resulting solution was extracted with chloroform. After drying, the chloroform solution was concentrated and chromatographed on an alumina (3) column. Elution with a mixture of 80% 60-80° petrol ether and 20% benzene gave a fraction which yielded a solid on removal of the solvent. Recrystallisation from carbon tetrachloride gave white crystals (2.9g) in 75% yield.

Melting point 134-135°

δ (CD Cl_3)

8.8 (1H, d of d) 8.0 (1H, d of d) 7.45 (1H, d of d) 4.3 (4H, q) 3.2 (2H, s) 2.3 (6H, s) 1.35 p.p.m. (6H, t).

νmax (CH Cl_3)

1768, 1710, 1628 cm^{-1}

λmax (Et OH)

205, 236, 252 sh n.m. [log ε 4.09, 4.44, (-)].

Mass spectrum

m/e 403(M^+), 361, 319, 274, 245, 200.

C.H.N.

For $C_{20}H_{21}NO_8$ required 59.6%C 5.3%H 3.5%N

obtained 59.6%C 5.7%H 3.7%N

Diethyl 5,9-Diacetoxy-7H-cyclohepta-[c]-pyridine-6,8-dicarboxylate. (41)

Prepared as described for compound (33) from 3g of the diester (39). The fraction obtained from the column by eluting with a mixture of 90% benzene 10% chloroform yielded a yellow viscous oil on removal of the solvent. The oil could not be crystallised. Yield 85% (3.2g).

δ ($CDCl_3$)

8.92 (1H, s) 8.68 (1H, d) 7.5 (2H, d)

4.24 (4H, q) 3.15 (2H, s) 2.26 (6h, s) 1.3 p.p.m. (6H, t).

νmax ($CHCl_3$)

1775, 1710, 1620, cm^{-1}

λmax (Et OH)

212 sh, 241, 308 sh n.m. [log ε (-), 4.45, (-)].

Mass spectrum

m/e 403(M^+), 361 319, 318, 273.

C.H.N.

For $C_{20}H_{21}NO_8$ required 59.6%C 5.3%H 3.5%N

obtained 59.5%C 5.7%H 3.4%N

Diethyl 5,7-Dihydro-6,8-dimethyl-9H-cyclohepta-[b]-pyridine-5,9-dione-6,8-dicarboxylate. (32)

Sodium ethoxide (1g) and diethyl 5,9-dihydroxy -7H-cyclohepta-[b]-pyridine-6,8-dicarboxylate (2g) were mixed in 15 mls of ethanol. Methyl iodide (2.4g) was added and the mixture stirred overnight. On removal of the ethanol a red oil remained. This was extracted with hot 60-80° petrol ether. On cooling the solution a white crystalline solid (0.44g) was formed in 20% yield. Melting point 154-155°.

δ ($CD Cl_3$)

8.9 (1H, d of d) 8.2 (1H, d of d) 7.5 (1H, d of d) 3.8 (4h, m) 2.6 (2H, s) 1.6 (6H, 2s) 0.7 p.p.m. (6H, m).

νmax ($CH Cl_3$)

1735, 1710 cm^{-1}

λmax (Et OH)

213, 244, 275 sh n.m. [log ε 4.33, 3.84, (-)].

Mass spectrum

m/e 347(M^+), 302, 273, 233.

C.H.N.

For $C_{18} H_{21} NO_6$ required 62.3%C 6.1%H 4.1%N

obtained 62.1%C 6.3%H 4.0%N

Diethyl 6-Bromo-6,7-dihydro-9-hydroxy-5H-cyclohepta-[b]-pyridine-6,8-dicarboxylate-5-one (36).

Diethyl 5,9-dihydroxy-7H-cyclohepta-[b]- pyridine 6,8-dicarboxylate (3g) was heated with N-bromosuccinimide (1.4g) in 40 mls of chloroform for 15 minutes by means of a 200 watt bulb. The resulting solution was cooled in ice and filtered. 2x25 mls of water were used to wash the chloroform solution which was then dried. After removing the chloroform the gum obtained was extracted with hot benzene. On cooling the benzene solution a brown solid (3.2g) was obtained in 85% yield. The solid proved to be unstable, losing hydrogen bromide on standing.

δ (CD Cl_3)

12.6 (1H, sbr) 8.75 (1H, d of d) 8.2 (1H, d of d)
7.38 (1H, d of d) 4.22 (4H, q) 2.9 (2H, s)
1.3 p.p.m. (6H, t).

νmax (CH Cl_3)

1745, 1645, 1610, cm^{-1}

λmax (Et OH)

208, 223, 239, 281, 230 sh n.m. [log ϵ 4.04, 4.09, 4.10, 4.27, (-)].

Mass spectrum

m/e 399, 397(M^+), 325, 320, 274, 273, 247, 245.

Diethyl 5,8-Diacetoxyquinoline-6,7-dicarboxylate (60).

Diethyl 5,8-dihydroxyquinoline-6,7-dicarboxylate (3g) was heated with acetic anhydride (30 mls) for 15 hours. Excess anhydride was removed and the residue neutralised then extracted with 2x25 mls of chloroform. The solution was dried and the solvent removed to leave a red gum. This was recrystallised from benzene to give pale yellow crystals (3.3g) in 95% yield.

Melting point. 167-168°

δ ($CDCl_3$)

8.95 (1H, d of d) 8.15 (1H, d of d) 7.4 (1H, d of d)
4.4 (4H, m) 2.45 (6H, 2s) 1.35 p.p.m. (6H, t)

νmax ($CHCl_3$)

1770, 1738 cm^{-1}

λmax (Et OH)

211, 243, 280 sh n.m. [logε 4.50, 4.64, (-)].

Mass spectrum

m/e 389(M^+), 347, 306, 260, 232

C.H.N.

For $C_{19}H_{19}NO_8$	required	58.6%C	4.9%H	3.6%N
	obtained	58.5%C	4.9%H	3.6%N

Diethyl 1H-Cyclopropa-[g]-quinoline-2,7-dione-1a,7a-dicarboxylate. (35)

Lead tetraacetate (8.9g) and diethyl 5,9-dihydroxy-7H-cyclohepta-[b]-pyridine-6,8-dicarboxylate (3g) were heated in 50 mls of dry benzene for 8 hours. Solvent was removed and the residue neutralised then extracted with 3x50 mls of chloroform. The oil obtained after drying and removing the chloroform was dissolved in hot benzene. On cooling the benzene solution, off white crystals (2.5g) were obtained

Yield 85% Melting point 155-156°

δ (CD Cl_3)

9.1 (1H, d of d) 8.5 (1H, d of d) 7.8 (1H, d of d)

4.3 (4H, q) 2.9 (1H, d) 2.15 (1H, d)

1.3 p.p.m. (6H, t)

Coupling constants:-

Jgem 6 , $J_{4,5}$ 5.1, $J_{4,6}$ 1.7, $J_{5,6}$ 8.5 Hz

νmax (CH Cl_3)

1745, 1698 cm^{-1}

λmax (Et OH)

218, 243 n.m. [logε 4.36, 3.88] .

Mass spectrum

m/e 317(M^+), 272, 244.

C.H.N.

For $C_{16}H_{15}NO_6$ required 60.6%C 4.7%H 4.4%N

obtained 60.7%C 5.0%H 4.5%N

Diethyl 1H-Cyclopropa-[f]-isoquinoline-2,7-dione-1a, 7a-dicarboxylate. (42)

Prepared from diethyl 5,9-dihydroxy-7H-cyclohepta-[c]-pyridine-6,8-dicarboxylate (3g) as described for compound (35). Recrystallisation from benzene gave off white crystals (2,6g) in 90% yield.

Melting point 94-95°

δ ($CD Cl_3$)

9.3 (1H, s) 9.05 (1H, d) 7.85 (1H, d) 4.3 (4H, q)
2.9 (1H, d) 2.1 (1H, d) 1.3 p.p.m. (6H, t)

Coupling constants

Jgem 6, $J_{5,6}$ 5.1 Hz

νmax ($CH Cl_3$)

1748, 1698 cm^{-1}

λmax (Et OH)

212, 238 sh, 297 n.m. [logε 4.33, (-), 3.52] .

Mass spectrum

m/e 317 (M^+), 289, 262, 245, 217, 199.

C.H.N.

For $C_{16} H_{15} NO_6$ required 60.6%C 4.7%H 4.4%N
obtained 60.4%C 4.9%H 4.2%N

Both the cyclopropa-[g]-quinoline derivative and the cyclopropa-[f]-isoquinoline derivative may be prepared by using dichlorodicyanoquinone as the oxidising agent instead of lead tetraacetate. The

yields are however slightly lower and work-ups are complicated by the necessity for chromatography.

1H-Cyclopropa-[g]-quinoline-2,7-dione. (38)

A solution of 5,6,7,8-tetrahydro-9H-cyclohepta-[b]-pyridine-5,9-dione (2g) and N-bromosuccinimide (2.1g) in 40 mls of chloroform was boiled for 20 minutes by means of a 200 watt bulb. The chloroform solution was cooled, filtered then washed with 2x25 mls of aqueous sodium bicarbonate and 1x25 mls of water. After separating the chloroform solution it was stirred for 12 hours with 4 mls of 30% aqueous triethylamine solution. The chloroform layer was removed, concentrated and chromatographed on an alumina (3) column. A band was obtained by elution with chloroform. This was applied to p.l.c. plates which were subsequently eluted several times in a 60% benzene 40% chloroform solvent mixture. The only significant band was removed and the silica extracted to obtain the dione (38) (0.6g) as colourless crystals. These could be recrystallised from carbon tetrachloride.
Melting point 138-139° Overall yield 30%
δ (CD Cl_3)
9.08 (1H, d of d) 8.4 (1H, d of d) 7.7 (1H, d of d)
2.88 (2H, m) 1.85 p.p.m. (2H, m)

Coupling constants:-

$J_{4,5}$ 5.1 , $J_{4,6}$ 0.8 , $J_{5,6}$ 8.5 , Jgem 6.0

$J_{1a,\ 1\ cis}$ 10.0 , $J_{1a,\ 1\ trans}$ 6.0 Hz

νmax ($CH\ Cl_3$)

1690 cm^{-1}

λmax (Et OH)

219, 238 sh n.m. [logε4.08, (-)] .

Mass spectrum

m/e 173(M^+), 145, 117, 116, 106, 105.

C.H.N.

For $C_{10}\ H_7\ NO_2$	required	69.4%C	4.6%H	8.1%N
	obtained	69.5%C	4.4%H	7.8%N

Diethyl Quinoline-5,8-dione-6,7-dicarboxylate. (61)

Lead tetraacetate (4.3g) and diethyl 5,8-dihydroxyquinoline-6,7-dicarboxylate (2g) were boiled in 40 mls of dry benzene for 6 hours. The solvent was removed, the residue neutralised and extracted with 2x25 mls of chloroform. After removing the chloroform an oil remained. This was extracted with 60-80° petrol ether, on cooling the solution yellow crystals (1.8g) were obtained in 90% yield.

Melting point 104-105°

δ ($CD\ Cl_3$)

9.15 (1H, d of d) 8.5 (1H, d of d) 7.8 (1H, d of d)
4.4 (4H, q) 1.3 p.p.m. (6H, t)

Coupling constants:-

$J_{2,3}$ 4.3 , $J_{2,4}$ 1.7 , $J_{3,4}$ 8.5 Hz

νmax ($CH Cl_3$)

1740, 1685 cm^{-1}

λmax (Et OH)

205, 222 sh, 242, 345 sh n.m. [logε 4.03, (-), 4.26, (-)] .

Mass spectrum

m/e 303(M^+), 258, 257, 231.

C.H.N.

For $C_{15} H_{13} NO_6$ required 59.4%C 4.3%H 4.6%N

obtained 59.6%C 4.5%H 4.6%N

Diethyl Isoquinoline-5,8-dione-6,7-dicarboxylate. (64)

Prepared as described for the quinoline derivative (61) from 2g of diethyl 5,8-dihydroxy isoquinoline-6,7-dicarboxylate. The dione (64) was recrystallised as yellow crystals (1.7g) from 60-80° petrol ether. Yield 85%

Melting point 144-145°

δ ($CD Cl_3$)

9.25 (1H, s) 9.05 (1H, d) 7.9 (1H, d) 4.3 (4H, q) 1.25 p.p.m. (6H, t)

νmax ($CH Cl_3$)

1740, 1675 cm^{-1}

λmax (Et OH)

206, 254, 310 sh n.m. [logε 4.15, 4.18, (-)] .

Mass spectrum

m/e 303(M^+), 258, 231, 230, 214, 201, 186, 175.

C.H.N.

For $C_{15}H_{13}NO_6 . 1H_2O$ required 55.9%C 4.9%H 4.3%N

obtained 55.6%C 4.9%H 4.3%N

Diethyl 6,9-Methano-5,5a,6,9,9a,10-hexahydrobenzo-[g]-quinoline-5,10-dione-5a,9a-dicarboxylate. (62)

A solution of cyclopentadiene (0.5g) and diethyl quinoline-5,8-dione-6,7-dicarboxylate (2g) in benzene was stirred at room temperature for one week. The solvent was removed and the residue recrystallised from carbon tetrachloride. The adduct (1.4g) was isolated in 65% yield.

Melting point 119-120°

δ(CD Cl_3)

9.15 (1H, d of d) 8.45 (1H, d of d) 7.8 (1H, d of d)
6.2 (2H, m) 4.05 (5H, m) 2.7 (1H, d) 1.75 (1H, d)
1.2 p.p.m. (6H, t)

Coupling constants

$J_{7,8}$ 5.1 , $J_{7,9}$ 1.7 , $J_{8,9}$ 8.5 , Jgem 10.2 Hz

νmax (CH Cl_3)

1750 1690 cm^{-1}

λmax (Et OH)

216, 243, 275 sh n.m. [logε 4.22, 3.74, (-)] .

Mass spectrum

m/e 369(M^+), 325, 324, 305, 296, 251, 234, 121.

C.H.N.

For $C_{20}H_{19}NO_6$ required 65.0%C 5.2%H 3.8%N

obtained 65.4%C 5.6%H 3.8%N

Attempted reduction of 5,6,7,8-tetrahydro-9H-cyclohepta-[b]-pyridine-5,9-dione.

The method used was the Huang-Minlon modification of the Wolff-Kishner reduction.

The dione (3.5g) was reacted with hydrazine hydrate (1g) in 30 mls of ethanol. After 1 hour a yellow solid was obtained. The ethanol was removed and 70 mls of digol was added together with 3.4g of potassium hydroxide. The mixture was heated at 210° for 1.5 hours, water (150 mls) was added and the mixture extracted with 3x25 mls of chloroform. On removal of the chloroform an intractable tar remained from which nothing was isolated.

A similar result was observed if the monoketal (prepared by heating the diketone in ethylene glycol in the presence of acid) was used.

The reaction of diethyl 5,9-diacetoxy-7H-cyclohepta-[b]-pyridine-6,8-dicarboxylate (33) with N-bromosuccinimide.

A solution of the diacetoxy compound (2g) (33) and N-bromosuccinimide (1.8g) in 30 mls of chloroform were heated for 20 minutes by means of a 200 watt bulb. The solution was filtered, washed rapidly with 25 mls of aqueous sodium bicarbonate and 25 mls of water then dried. The oil which remained after removal of the chloroform was taken up in hot benzene. On cooling the benzene solution a brown solid was obtained. Mass spectrum, t.l.c., and n.m.r. spectrum showed this to be compound (36), the bromo compound obtained from diethyl 5,9-dihydroxy-7H-cyclohepta-[b]-pyridine-6,8-dicarboxylate.

Yield 2g 80%

The reaction of diethyl 6-bromo-6,7-dihydro-9-hydroxy-5H-cyclohepta-[b]-pyridine 6,8-dicarboxylate-5-one with bases: NaoH, LiCl, Et_3N.

Treatment of the bromo compound with 5N caustic soda solution at 100° for 10 minutes gave no isolatable product. Heating with lithium chloride (or carbonate) for 15 minutes at 100° in dimethylformamide gave a black solution. The solvent was removed and the residue shaken with water, checked for basicity and extracted

with chloroform. The tar which remained after removing the chloroform yielded no isolatable product.

An ethereal suspension of the bromo compound (2g) was stirred with 30% aqueous triethylamine for 4 hours. The ether layer was separated, dried, and evaporated to leave an oil which solidified on standing. This was recrystallised from benzene to give a crystalline product (1.4g) in 86% yield. Mixed melting point, t.l.c. and n.m.r. spectrum showed this to be the cyclopropyl derivative (35).
Mixed melting point 155-156°

The reaction of diethyl 5,9-diacetoxy-7H-cyclohepta-[c]-pyridine-6,8-dicarboxylate (41) with N-bromosuccinimide.

The procedure used was that described for the cyclohepta-[b]-pyridine derivative (33).
1g of compound (41) and 0.9g of the N-bromosuccinimide were used. The crude product was applied to p.l.c. plates and eluted with chloroform to produce two main bands. The upper band contained diethyl 1H-cyclopropa-[f]-isoquinoline-2,7-dione-1a,7a-dicarboxylate (400 mgs), confirmed by n.m.r. spectrum, mass spectrum and mixed melting point.

The lower band contained 320 mgs of a compound which was a derivative of the expected diethyl 6-bromo-

6,7-dihydro-9-hydroxy-5H-cyclohepta-[c]-pyridine-6,8-dicarboxylate-5-one (or its isomer). The mass spectrum showed that it had taken on the elements of water presumably forming diethyl 6-bromo-5,5,9-trihydroxy-6,7-dihydro-5H-cyclohepta-[c]-pyridine-6,8-dicarboxylate.

Mass spectrum

m/e 417, 416, 415, 414, 371, 369, 343, 341, 335, 296.

(Before plates 399, 397, 327, 325, 320)

<u>The reaction of diethyl 5,9-dihydroxy-7H-cyclohepta-[c]-pyridine-6,8-dicarboxylate (39) with N-bromosuccinimide</u>.

The procedure described for the cyclohepta-[b]-pyridine compound (29) was used. 1g of compound (39) and 0.7g of N-bromosuccinimide was used, t.l.c. of the product showed only one product, diethyl 6-bromo-6,7-dihydro-9-hydroxy-5H-cyclohepta-[c]-pyridine-6,8-dicarboxylate-5-one (or its isomer) Yield (1.1g) 88%

δ(CD Cl_3)

9.1 (3H, m) 7.8 (1H, s) 4.7 (1H, d) 4.1 (4H, m) 3.2 (1H, d) 1.1 p.p.m. (6H, m)

After addition of deuterium oxide

9.1 (2H, m) 7.8 (1H, d) remainder unaltered

νmax (CH Cl_3)

1740, 1720, cm^{-1}

Mass spectrum

m/e 399, 397 (M^+), 369, 367, 339, 337, 327, 325, 319, 317

Reaction of diethyl 6-bromo-6,7-dihydro-9-hydroxy-5H-cyclohepta-[c]-pyridine-6,8-dicarboxylate-5-one with aqueous triethylamine.

The procedure described for the cyclohepta-[b]-derivative (36) was used. The crude product was chromatographed on an alumina (3) column. A band was eluted with chloroform which contained diethyl 1H-cyclopropa-[f]-isoquinoline-2,7-dione-1a,7a-dicarboxylate (42) (1.1g) 70% yield. Confirmed by t.l.c. and n.m.r. spectrum.

Reactions on diethyl 1H-cyclopropa-[g]-quinoline-2,7-dione-1a,7a-dicarboxylate (35).

Photolysis

A solution, containing the cyclopropyl compound (35) (1g) and acetophenone (1 ml) in 900 mls of benzene, was irradiated for 24 hours using a pyrex sleeve. The benzene solution was concentrated and chromatographed on an alumina (3) column. Two bands were obtained, the first due to the acetophenone and the second due to unchanged starting material (850 mgs) confirmed by n.m.r. spectrum and t.l.c.

A similar result was observed when a quartz sleeve was used and the compound (35) irradiated for 36 hours, recovery 74%.

Thermolysis

The cyclopropyl derivative (35) (1g) was heated at 210° for 4 hours in 15 mls of diphenyl ether. Chromatography revealed some tar formation and 80% unchanged starting material.

Decarboxylation

Compound (35) (1g) was boiled in 20 mls of 48% hydrobromic acid for 30 minutes. Neutralisation and extraction gave 90% unchanged starting material (t.l.c., n.m.r.).

Heating for 3 hours produced further decomposition, only 30% of the starting material being recovered.

Proton abstraction

Treatment with an equivalent amount of potassium t-butoxide in benzene for up to 45 minutes gave no isolatable material other than unchanged compound (35).

Reactions on diethyl 1H-cyclopropa-[f]-isoquinoline-2,7-dione-1a,7a-dicarboxylate (42).

Thermolysis, decarboxylation and proton abstraction were each tried in turn. As observed for compound (35) decomposition or unchanged starting material was obtained in each case.

Reaction of 1H-cyclopropa-[g]-quinoline-2,7-dione (38) with potassium t-butoxide.

The cyclopropyl compound (38) (200 mg) was dissolved in benzene and base (128 mg) added. The mixture was heated at 40° for 10 minutes. Neutralisation and extracted gave 40% starting material only. The aqueous layer was now first basified and extracted then acidified and extracted. No other product was isolated.

Thermolysis of compound (38).

As described for compound (35). Only starting material was recovered, 175 mg from 200 mgs of starting material.

1,4-Methano-1,4,6,11-tetrahydropyrido-[2,3-g]-pyridazino-[1,2-a]-pyridazine-6,11-dione. (73)

A solution of 5,6,7,8-tetrahydropyrido-[2,3-d]-pyridazine-5,8-dione (2g) in 250 mls of dry methylene chloride was cooled to 0°C.

Cyclopentadiene (0.8g) and lead tetraacetate (5.7g) were added and the solution stirred for two hours the solvent was removed and aqueous sodium bicarbonate was added to the residue until it became neutral. The aqueous mixture was extracted with 3x30 mls of chloroform. After drying, the chloroform was removed to leave a courless oil.

This was crystallised from diethyl ether to give a white compound (1.7g) in 60% yield.

Melting point 220° (decomp)

δ (CD Cl_3)

9.25 (1H, d of d) 8.65 (1H, d of d) 7.85 (1H, d of d) 6.9 (2H, m) 6.2 (2H, m) 2.35 p.p.m. (2H, d)

Coupling constants:-

$J_{8,9}$ 5.1 , $J_{8,10}$ 1.7 , $J_{9,10}$ 8.5 , Jgem 1.7 Hz

νmax (CH Cl_3)

1634 cm^{-1}

λmax (Et OH)

208, 230 sh, 266, 317 n.m. [logε 4.38, (-), 3.68, 3.61].

Mass spectrum

m/e 227(M^+), 105, 77.

C.H.N.

For $C_{12} H_9 N_3 O_2$ required 63.4%C 4.0%H 18.5%N

obtained 63.8%C 4.0%H 18.7%N

<u>1,4-Methano-1,4,6,11-tetrahydropyrido-[3,4-g]-pyridazino-[1,2-a]-pyridazine-6,11-dione</u>. (76)

Prepared as described for the[2,3-g] derivative (73) from 5,6,7,8-tetrahydropyrido-[3,4-d]pyridazine-5,8-dione. The oil obtained was crystallised from diethyl ether to give a white solid (1.5g) in 55% yield.

Melting point 277° (decomp.)

δ ($CDCl_3$)

9.55 (1H, s) 9.05 (1H, d) 8.05 (1H, d) 6.8 (2H, m) 6.0 (2H, m) 2.2 p.p.m. (2H, s)

νmax ($CHCl_3$)

1638 cm^{-1}

λmax (Et OH)

205, 224 sh, 276, 320 n.m. [logε 4.38, (-), 3.63, 3.66].

Mass spectrum

m/e 227(M^+), 105, 79, 77.

C.H.N.

For $C_{12}H_9N_3O_2$ required 63.4%C 4.0%H 18.5%N

obtained 63.0%C 3.7%H 18.3%N

4-Methyl-1,4,6,11-tetrahydropyrido-[2,3-g]-pyridazino-[1,2-a]-pyridazine-6,11-dione. (74)

Prepared as described for the cyclopentadiene adduct (73) from piperylene (0.8g), lead tetraacetate (5.8g) and 5,6,7,8-tetrahydropyrido-[2,3-d]-pyridazine-5,8 (2g). The oil obtained was crystallised from diethyl ether to give a white solid (0.7g) in 25% yield

Melting point 145° (decomp.)

δ ($CDCl_3$)

9.2 (1H, d of d) 8.7 (1H, d of d) 7.85 (1H, d of d) 6.1 (2H, m) 5.6 (1H, m) 5.0 (1H, d of d) 4.4 (1H, d of d) 1.4 p.p.m. (3H, d)

Coupling constants:-

$J_{1,2\ cis}$ 5, $J_{1,2\ trans}$ 1.7, Jgem 18, J_{4,CH_3} 6 Hz.

νmax ($CH Cl_3$)

1638 cm^{-1}

λmax (Et OH)

208, 230 sh, 268, 315 n.m. [logε 4.35, (-), 3.63 3.52].

Mass spectrum

m/e 229 (M^+), 214, 187, 105, 77.

C.H.N.

For $C_{12} H_{11} N_3 O_2$ required 62.9%C 4.8%H 18.3%N

obtained 63.2%C 5.1%H 18.3%N

1,4-Methano-1,2,3,4,6,11-hexahydropyrido-[2,3-g]-pyridazino-[1,2-a]-pyridazine-6,11-dione. (75)

A solution of 500 mg of the tetrahydro compound (73) in 60 mls of ethanol containing 0.5 ml of conc. hydrochloric acid and 100 mg of 5% palladium charcoal catalyst was hydrogenated until the rapid uptake slowed to a halt (5 hours at 1 atmosphere). The solution was filtered and the ethanol removed. The residual oil was neutralised and extracted with 3x25 mls of chloroform. The solution was dried and evaporated to leave a pale yellow oil. This was crystallised from diethyl ether as a white solid (480 mg) in 95% yield. Melting point 206-207°.

δ ($CD Cl_3$)

9.1 (1H, d of d) 8.65 (1H, d of d) 7.7 (1H, d of d)
5.45 (2H, d) 2.05 p.p.m. (6H, m).

Coupling constants

$J_{8,9}$ 5.1, $J_{8,10}$ 1.7, $J_{9,10}$ 8.5, $J_{1,2\ cis}$ 6 Hz

ν_{max} ($CH\ Cl_3$)

1630 cm^{-1}

λ_{max} (Et OH)

205, 229 sh, 258, 315 n.m. [logε 4.34, (-), 3.77, 3.66].

Mass spectrum

m/e 229 (M^+) , 200, 105, 85, 83, 77.

C.H.N.

For $C_{12}\ H_{11}\ N_3\ O_2$ required 62.9%C 4.8%H 18.3%N

obtained 62.6%C 5.1%H 18.0%N

Attempted selenium dioxide oxidation of 5,6,7,8-tetrahydro-9H-cyclohepta-[b]-pyridine.

The pyridine derivative was treated with excess selenium dioxide in several solvents for times up to 6 hours. The reactions were carried out under reflux.

(i) ethyl acetate

Unchanged material recovered.

(ii) acetic acid

Unchanged material recovered.

(iii) dioxan

Up to 4 hours no reaction. After this period some decomposition occurred.

5,6,7,8-Tetrahydro-9H-cyclohepta-[b]-pyridine-N-oxide.(81)

5,6,7,8-tetrahydro-9H-cyclohepta-[b]-pyridine (10g) and 30% hydrogen peroxide (9 mls) were heated in acetic acid (70 mls) at 100° for 9 hours. A further 5 mls of the peroxide was added and the heating continued for 6 hours. The excess peroxide and the acetic acid were removed. The oil obtained was neutralised and extracted with 3x50 mls of chloroform. Distillation gave the oxide (10.5g) in 95% yield.

B.pt. 124° (0.03 mm)

Melting point 107-108°

δ (CD Cl_3)

8.15 (1H, t) 7.05 (2H, s) 3.4 (2H, m) 2.8 (2H, M)

1.8 p.p.m. (6H, m)

λmax (Et OH)

221, 264 n.m. log 4.36, 4.02

Mass spectrum

m/e 163 (M^+), 146, 130, 128.

C.H.N.

For $C_{10}H_{13}NO$	required 73.6%C	8.0%H	8.6%N
	obtained 73.6%C	8.4%H	8.3%N

9-Acetoxy-5,6,7,8-tetrahydro-9H-cyclohepta-[b]-pyridine. (82)

The 5,6,7,8-tetrahydro-9H-cyclohepta-[b]-pyridine-N-oxide (10g) was heated in 40 mls acetic

anhydride at 100° for 2.5 hours.

The solution was distilled to give the required fraction (8.8g) in 78% yield B.pt. 106° (0.6 mm).

Some deoxygenation also occurred to produce the 5,6,7,8-tetrahydro-9H-cyclohepta-[b]-pyridine (1.4g) in 19% yield.

δ (CD Cl_3)

8.4 (1H, d of d) 7.45 (1H, d of d) 7.1 (1H, d of d)
6.0 (1H, m) 2.85 (2H, m) 1.9 p.p.m. (9H, m)

νmax (CH Cl_3)

1735 cm^{-1}

λmax (Et OH)

207, 249, 290, n.m. [logε 3.85, 3.64, 3.46].

Mass spectrum

m/e 163, 162, 155, 154, 153, 134.

<u>9-Hydroxy-5,6,7,8-tetrahydro-9H-cyclohepta-[b]-pyridine</u>. (83)

The 9-acetoxy compound (82) (5g) was heated with aqueous potassium hydroxide solution (5N) (25 mls) at 100° for 3 hours. The solution was extracted (3x25 mls of chloroform) and the oil obtained after removal of the solvent distilled to give a colourless liquid (3.0g) in 76% yield

B.pt. 91-93° (0.4 mm)

δ ($CD Cl_3$)

8.3 (1H, d of d) 7.4 (1H, d of d) 7.0 (1H, d of d)

5.8 (1H, sbr) 4.75 (1H, d) 2.7 (2H m) 1.85 (4H, M)

1.25 p.p.m. (2H, m)

νmax ($CH Cl_3$)

3360 cm^{-1}

λmax (Et OH)

210, 263, 290 sh n.m. [logε 3.75, 3.62, (-)].

Mass spectrum

m/e 163 (M^+) , 162, 145, 144, 135, 134, 106.

C.H.N.

For $C_{10} H_{13} NO$	required	73.6%C	8.0%H	8.6%N
	obtained	73.6%C	8.1%H	8.6%N

5,6,7,8-Tetrahydro-9H-cyclohepta-[b]-pyridine-9-one. (84)

9-hydroxy-5,6,7,8-tetrahydro-9H-cyclohepta-[b]-pyridine (2g) was heated with N-bromosuccinimide (2g) in 40 mls of carbon tetrachloride by means of a 200 watt lamp. The solution turned red, then orange and finally colourless. After cooling the solution it was filtered, washed with aqueous sodium bicarbonate (25 mls) and water (25 mls) and finally dried. On removal of the solvent a colourless liquid remained. This was chromatographed on an alumina (3) column. The fractions eluted with benzene and chloroform were bulked together and applied to p.l.c. plates. After elution with chloroform three main bands were apparent. The lower of these was removed and extracted to give a colourless oil. This was bulb distilled, (500 mg).

n.m.r. δ ($CDCl_3$)

8.65 (1H, d of d) 7.65 (1H, d of d) 7.35 (1H, q)

2.85 (4H, m) 1.9 p.p.m. (4H, m)

J_{23} 5.1 , J_{24} 1.7 J_{34} 8.5 Hz.

νmax (film)

1695 cm^{-1}

λmax (Et OH)

209, 228, 274 n.m. [log 3.64, 3.64, 3.51] .

Mass spectrum

m/e 161 (M^+), 133, 105, 92.

C.H.N.
For $C_{10}H_{11}NO$ required 74.5%C 6.8%H 8.7%N
obtained 74.2%C 6.4%H 8.3%N

8-Bromo-5,6,7,8-tetrahydro-9H-cyclohepta-[b]-pyridine-9-one. (85)

During the preparation of compound (84) p.l.c. of the crude product gave three bands; the central one was found to be compound (85) (100 mg) a colourless oil.

n.m.r. δ ($CD Cl_3$)
8.7 (1H, d) 7.9 (1H, d) 7.4 (1H, q) 5.45 (1H, m) 2.9 (2H, m) 2.25 p.p.m. (4H, m)

νmax (film)
1710 cm^{-1}

Mass spectrum
m/e 241, 239(M^+), 160 160, 133, 131, 119, 117 107, 105.

7,8-Dibromo-5,6,7,8-tetrahydro-9H-cyclohepta-[b]-pyridine-9-one. (86)

The highest of the three bands described in the preparation of compound (84) was found to be compound (86) (500 mg), a colourless viscous oil.

n.m.r. δ ($CD Cl_3$)
8.4 (1H, d of d) 7.5 (1H, d) 7.15 (1H, q) 5.75 (1H,d) 4.87 (1H, m) 2.95 (2H, m) 1.95 p.p.m. (2H, m)

max (film)

1720 cm^{-1}

Mass spectrum

m/e 321, 319, 317(M^+), 307, 305, 303, 228, 226, 224, 222, 149, 147, 145, 143, 131, 119, 117, 105, 103.

8,8-Dibromo-5,6,7,8-tetrahydro-9H-cyclohepta-[b]-pyridine-9-one. (87)

The ketone (84) (0.3g) was stirred with phenyltrimethylammonium tribromide (1.4g) in 30 ml of dry tetrahydrofuran. After 26 hours the solvent was removed, the residue neutralised and extracted with 3x50 mls of chloroform. After drying the solution it was evaporated to leave an oil. This was chromatographed on an alumina (3) column. A band eluted with benzene was evaporated to give a light red oil. A small quantity of methanol was added and the solution cooled to yield pale yellow crystals (0.08g) melting point 83-84° Yield 10%

δ(CD Cl_3)

8.6 (1H, m) 7.5 (2H, m) 2.8 (4H, m) 2.1 p.p.m.(2H,m)

νmax (CH Cl_3)

1718 cm^{-1}

λmax (Et OH)

211, 264, 270 sh n.m. [logε 3.85, 3.58 (-)] .

Mass spectrum

m/e 321, 319(M^+), 317, 240, 238, 161, 159, 157.

C.H.N.

For $C_{10} H_9 NO Br_2$ required 37.6%C 2.9%H 4.4%N

obtained 38.0%C 3.3%H 4.1%N

9H-Cyclohepta-[b]-pyridine-9-one. (8)

The dibromo compound (87) (0.28g) was heated with lithium carbonate (0.15g) in dimethyl formamide (40 mls) under nitrogen. After 2 hours the solvent was removed under reduced pressure and the residue treated with aqueous bicarbonate solution (20 mls). The resulting solution was extracted with 3x50 mls of chloroform. The chloroform was concentrated and chromatographed on an alumina (3) column. Elution with a 90% chloroform 10% benzene solvent mixture produced a band containing compound (8) (0.065 g). Yield 46%

n.m.r. δ ($CD Cl_3$)

9.05 (1H, m) 8.1 (1H, m) 7.7 (1H, m) 7.3 (1H, d)
7.15 (2H, m) 6.9 (1H, m)

νmax ($CH Cl_3$)

1642, 1612, 1588 cm^{-1}

λmax (Et OH)

220, 256 sh, 321 sh, 338 n.m. [log 4.57 (-), (-), 4.20].

Mass spectrum

$^{m}/_{e}$ 157(M^{+}), 129, 102, 83.

C.H.N.

For $C_{10}H_{7}NO$	required	76.4%C	4.5%H	8.9%N
	obtained	76.0%C	4.8%H	8.7%N

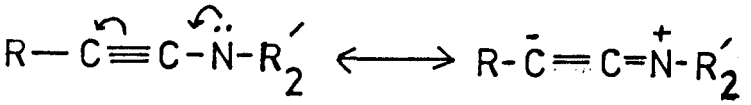
Section II.

This section is concerned with some reactions of alkylaminopropynes. (ynamines).

Introduction

Several heterosubstituted acetylenes are known; thioacetylenes, alkoxyacetylenes[36] (88) alkylamino-acetylenes[37] (89) and nitroacetylenes[38]. The reactions of these compounds have been well studied except for the nitroacetylenes (this is due to their explosive nature).

The reactions of these substituted acetylenes are very similar, each to some extent having two mesomeric forms due to the conjugation of the carbon-carbon triple bond with the lone pair on the hetero atom e.g.



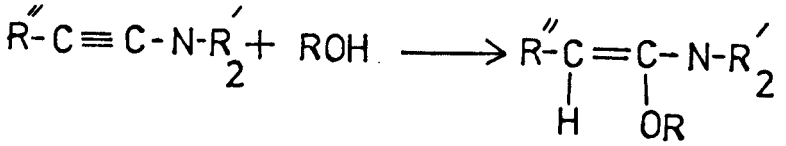
(89)

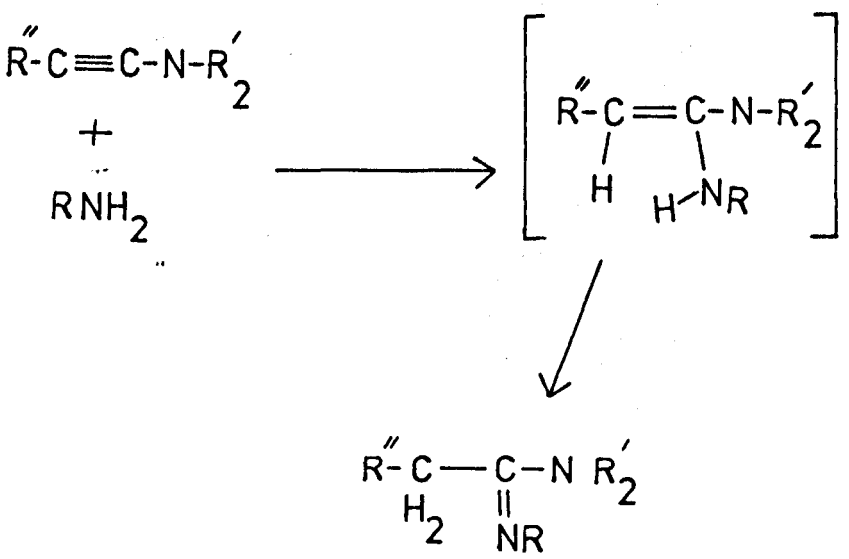
(88)

This conjugation makes the molecules efficient nucleophilic reagents.

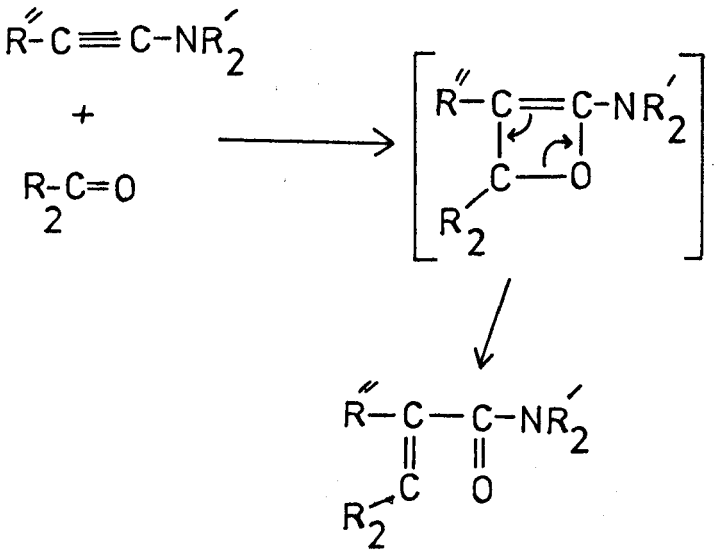
The reactions of the ynamines, as demonstrated by workers such as Viehe, Fuks, Buijle and Ficini,[39] usually involve a a polar or polarisable molecule as the other reagent as illustrated in the following examples.

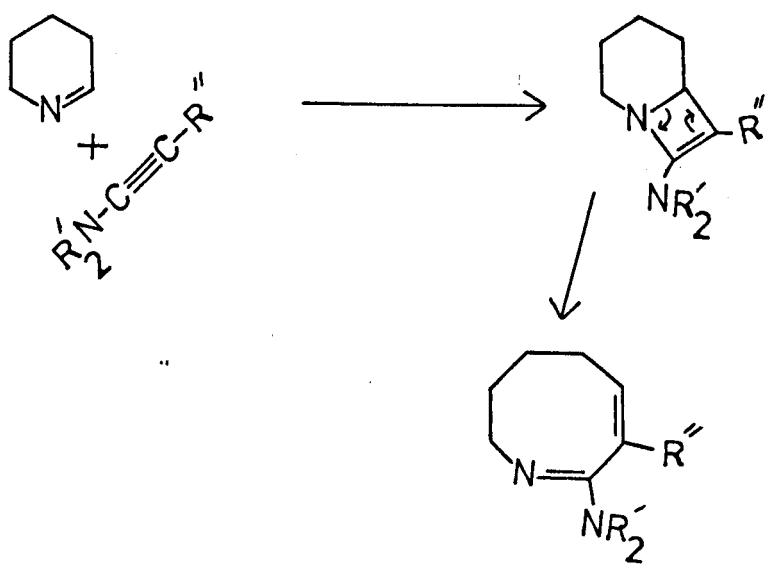
Alcohols and amines



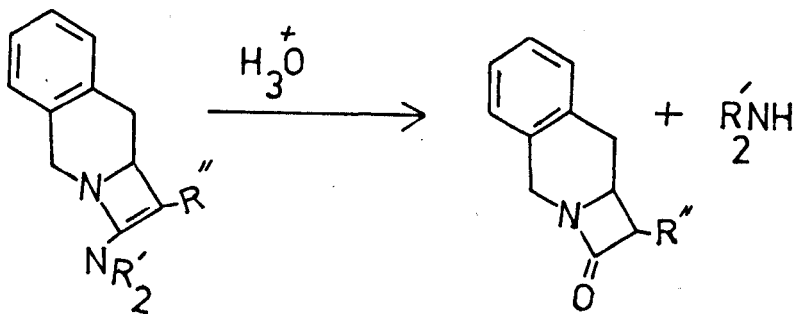


Carbonyl compounds and imines



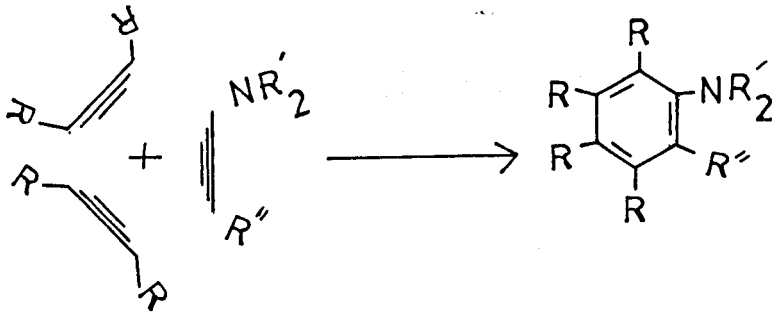


The polar carbonyl and imine bonds are attacked. Evidence for this type of reaction has been provided by hydrolysis of the intermediate enamine to the stable isolatable ketone e.g. compound (90).



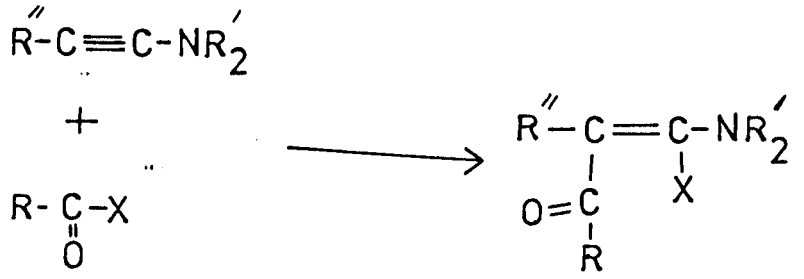
(90)

Polar carbon-carbon triple bonds.



$R \equiv CO_2C_2H_5$

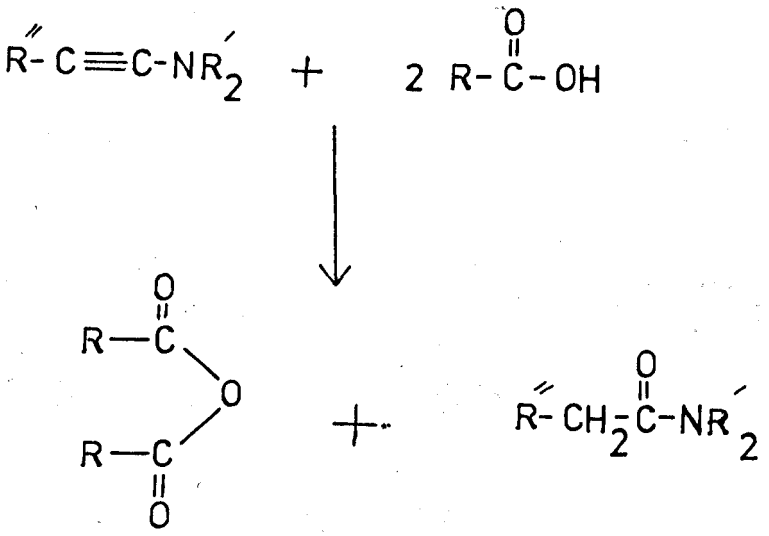
Acylation.



$X \equiv$ R-C(=O)-O ; Cl .

Dehydration

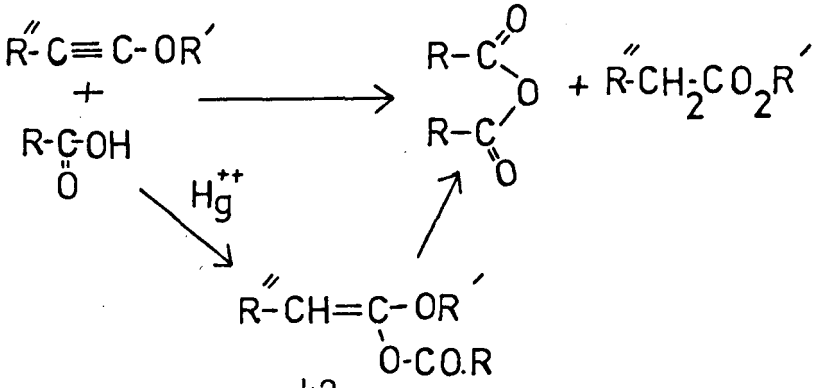
As with all these types of compound the ynamines are excellent dehydrating agents.



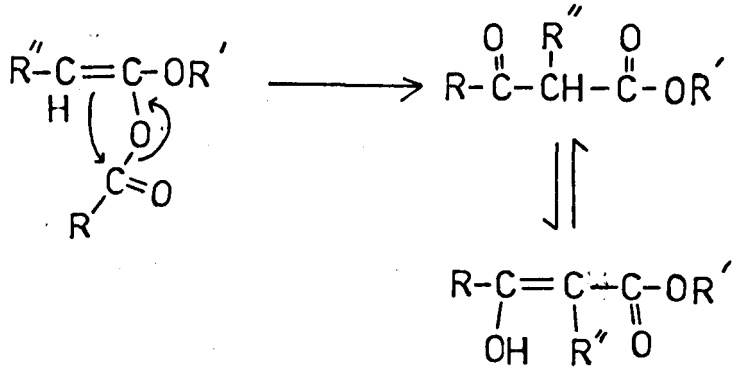
Discussion.

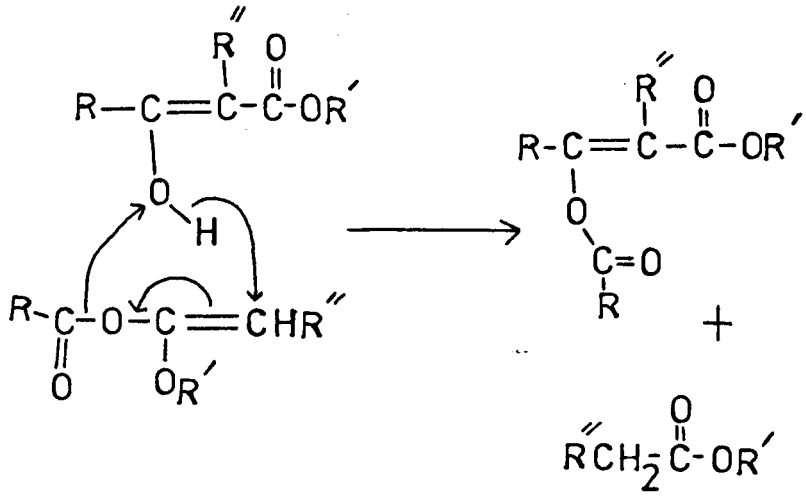
Part I

Arens[40] and later Wasserman[41] et al had shown that a carboxylic acid would react with an alkoxyacetylene (generally ethoxyacetylene) in two ways. Firstly dehydration could occur to produce the acid anhydride, secondly in the presence of a mercuric ion catalyst a vinyl ester was produced (an intermediate in the anhydride formation).



Zwanenburg[42] showed that the alkoxy vinyl esters could be rearranged at temperatures of about 170°, scheme.



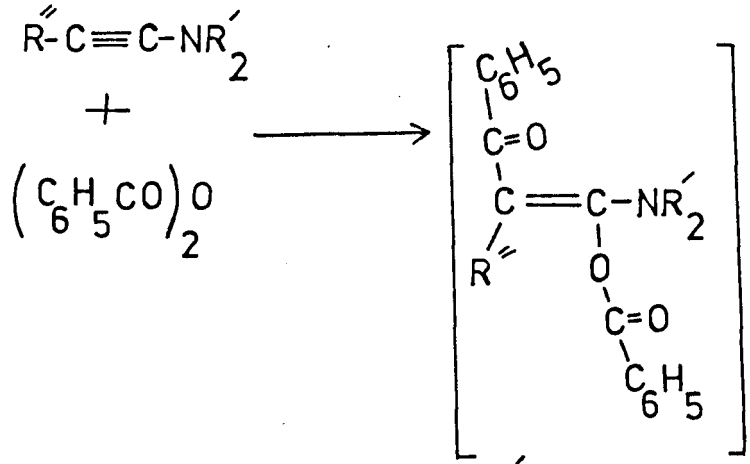


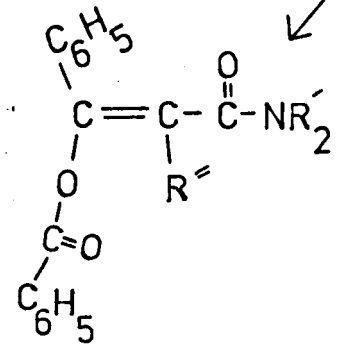
The present work was concerned with the reaction of an ynamine with a carboxylic acid. Viehe[39] had demonstrated the dehydration reaction to produce acid anhydrides in good yield.

The ynamines were far more reactive than the alkoxyacetylenes giving violent reactions with most of the acids used even at -12°. Monochloro, dichloro, and trichloro acetic acids each reacted with the ynamine to give intractable tars from which nothing was isolated except N,N-diethyl propionamide which suggested dehydration had occurred to some extent. A similar reaction was observed with acetic acid.

Benzoic acid also gave a tar, but by extraction

a compound was obtained. It was not a vinylamine but the type of compound one would expect from a Zwanenburg[42] type reaction. However, the reaction was never allowed to reach a temperature greater than room temperature so unless this was a very facile reaction it was not the true pathway. A more plausible explanation would be the formation of an anhydride which then reacted further with the ynamine to give the observed compound (91).



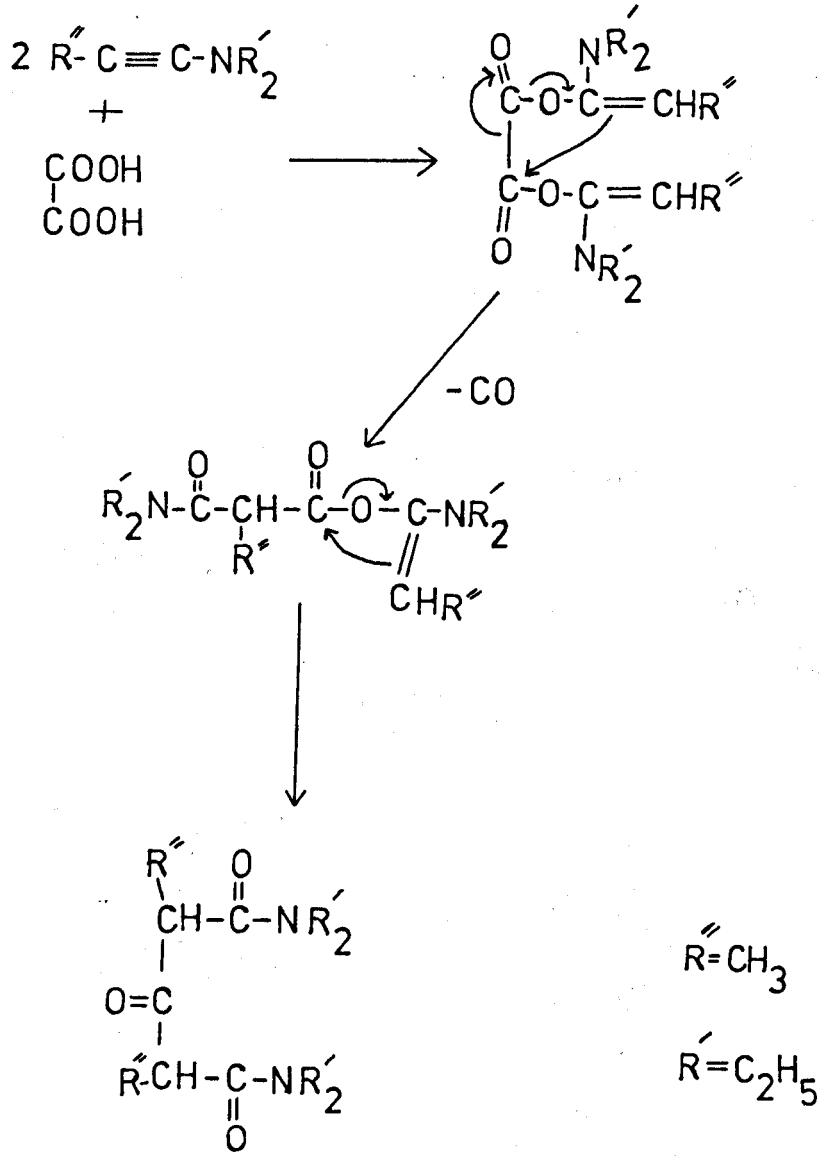


(91)

$R'' \equiv CH_3$

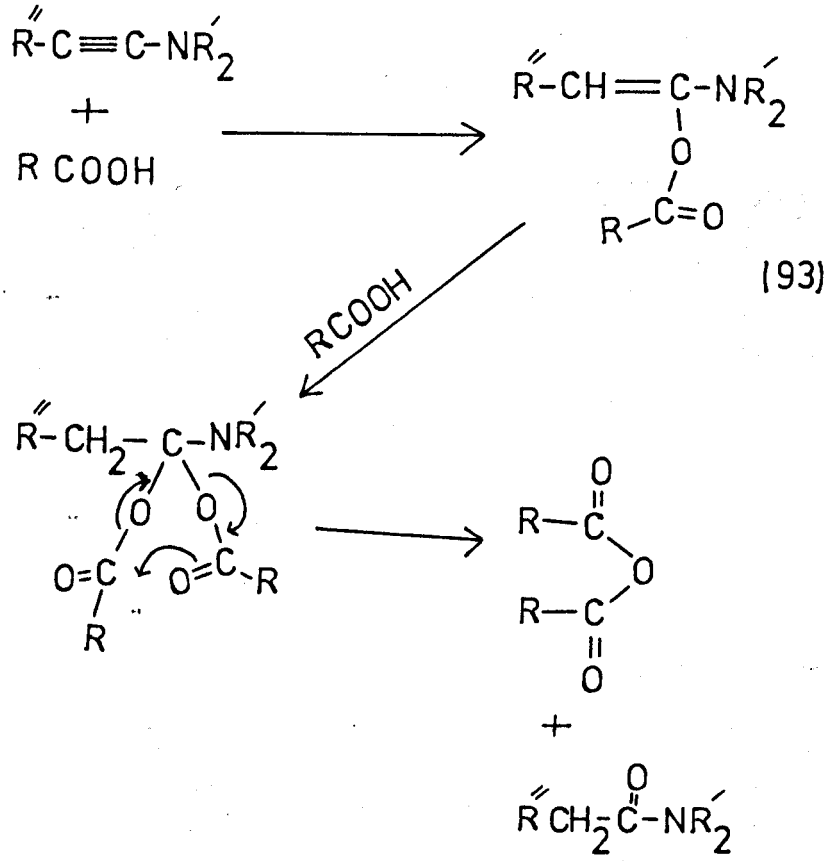
$R' \equiv C_2H_5$

The reaction with oxalic acid was similar to that observed in the alkoxyacetylene series[43]. The yield was small suggesting that dehydration was the main reaction.



(92)

If the above reactions were repeated using a mercuric ion catalyst no changes in the products were observed. The alkoxy series gave the alkoxy vinyl ethers in high yield with mercuric ions present. This suggested that either the reaction pathway was not the same as for the alkoxy series or the reaction was very rapid, perhaps due to the reactive nature of the intermediate enamine (93) that would be formed by analogy with the alkoxy case.

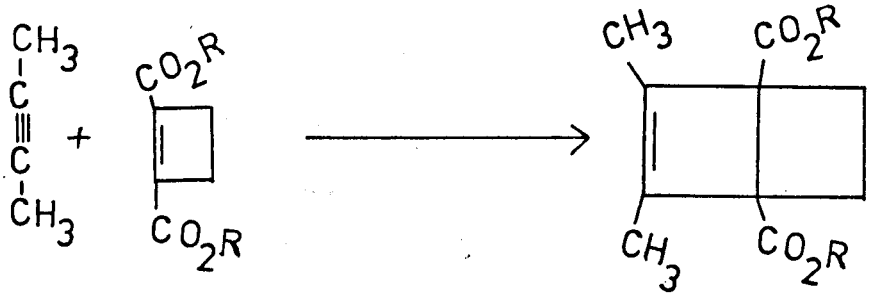


Part II

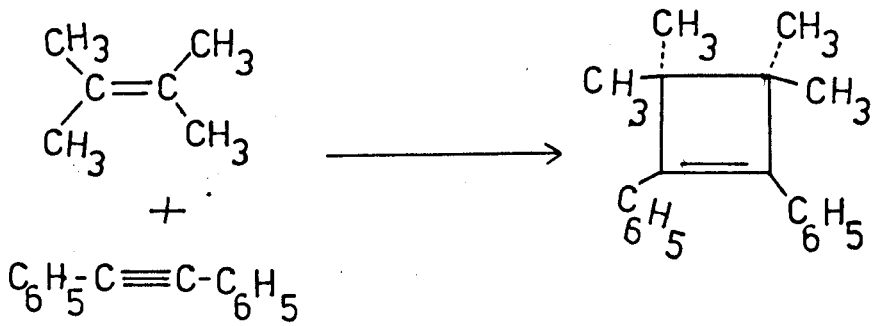
Attempted photochemical additions.

Although symmetrically substituted acetylenes such as dimethylacetylenedicarboxylate, dialkyl and diaryl acetylenes have been studied fairly extensively, there are fewer reports of photochemical reactions involving unsymmetrical acetylenes such as cyano-acetylene, and even less concerning heterosubstituted acetylenes.

Compounds (94) and (95) illustrate the cycloaddition reaction commonly associated with the symmetrical acetylenes[44,45].

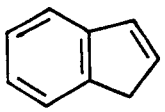


(94)



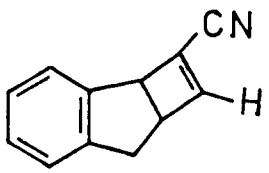
95

Similarly Bowman et al[46] showed that cyanoacetylene (100) would react with an indene derivative to give a cycloadduct.

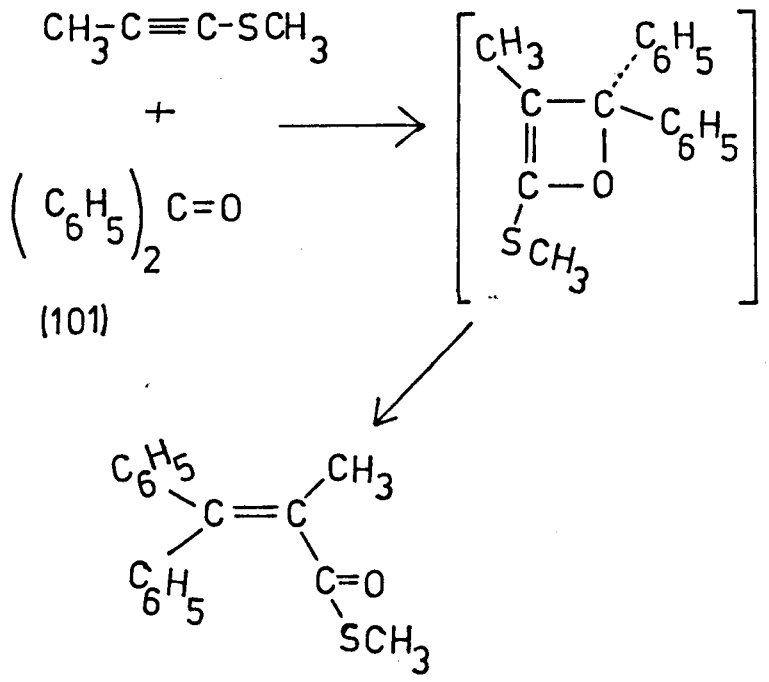


+ NC-C≡C-H

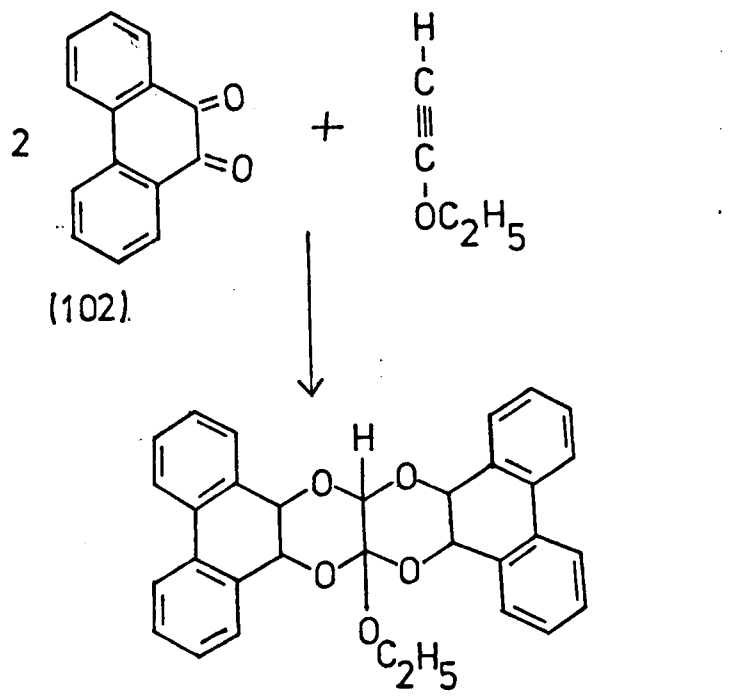
(100)



Two examples of photochemical reactions with the heteroacetylenes were provided by Bos et al[47], both involved the use of aromatic ketones (101) and (102).



(101)



(102)

It was therefore of interest to attempt a photochemical cycloaddition of indene with an ynamine and with ethoxyacetylene.

The results obtained indicated that the cycloaddition would not occur with either of the hetero-acetylenes as the only compounds isolated were unchanged indene and the sensitiser used. As no acetylene starting material was recovered it would appear to have polymerised.

Experimental

General procedure for the reaction of carboxylic acids with an ynamine.

One mol of the acid dissolved in the minimum quantity of methylene chloride was slowly added to 1.5 mol of the ynamine (in its own volume of methylene chloride) cooled to -12^{o}.

The solution obtained was stirred at room temperature for 20 minutes. Solvent was removed under reduced pressure and the residue worked up. This procedure was used both with and without mercuric ions.

All reactions were performed using 1-diethylamino-prop-1-yne.

Reaction with acetic acids.

The mono, di and trichloroacetic acids all reacted exothermically with the ynamine. In each case solvent removal left an intractable tar, from which NN-diethyl propionamide was the sole isolated product.

The reaction with acetic acid itself gave the same result.

Reaction with benzoic acid (91)

Benzoic acid (1g) was reacted with the ynamine (1.5g) to produce a tar. This was triturated with 40-60° petrol ether to give colourless crystals (0.6g) in 20% yield. These were recrystallised from 40-60° petrol ether.

Melting point 111-112°

δ (CD Cl_3)

8.0 (2H,m) 7.4 (8H,m) 3.3 (4H,q) 1.9 (3H,s)

1.1 p.p.m. (6H,t)

νmax (C Cl_4)

1795, 1730, 1635 cm^{-1}

λmax (Et OH)

207, 273 n.m. [log ε 3.36, 3.46.]

Mass spectrum

m/e 337 (M+), 221, 232, 216, 187.

C.H.N.

For C_{21} H_{23} NO_3 required 74.9%C 7.0%H 4.1%N

obtained 74.8%C 6.9%H 4.1%N

N,N,N',N'-Tetraethyl 2,4-dimethyl-3-ketopentan-1,5-diamide. (92)

Oxalic acid (1g) reacted with the ynamine (1.7g) exothermically. The residue obtained on removal of the solvent was triturated with 40-60° petrol ether. Colourless crystals were obtained (0.63g) in 20% yield.

Melting point 114-115°

δ ($CDCl_3$)

(3.5 9H,m) 1.1 p.p.m. (18H,m)

νmax (CCl_4)

1720, 1630 cm^{-1}

Mass spectrum

m/e 284 (M+), 214, 213, 212, 184, 183.

C.H.N.

For $C_{15}H_{28}N_2O_3$	required	63.3%C	9.8%H	9.8%N
	obtained	63.3%C	9.9%H	10.0%N

Reaction of ethoxyacetylene with indene.

12g of ethoxyacetylene and 3.5g of indene in 900 mls of dry benzene were photolysed for times between 3 and 27 hours. Solvent was removed and the residue was chromatographed on a silica column. A fraction was eluted with a 90% benzene 10% chloroform solvent mixture, this was found to be unreacted indene (3.1g).

The results were the same with or without a sensitiser (acetophenone) and with either a quartz or pyrex filter.

Reaction of diethyl 1-aminoprop-1-yne with indene.

The procedure was the same as for the ethoxyacetylene case, using 10g of the ynamine and 2.4g of indene. Again indene was the only compound isolated.

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