ADDITION REACTIONS OF UNSATURATED COMPOUNDS WITH SOME HETEROCYCLIC SYSTEMS, AND FURTHER REACTIONS OF THEIR PRODUCTS.

A Thesis submitted for the
Degree of Doctor of Philosophy
by
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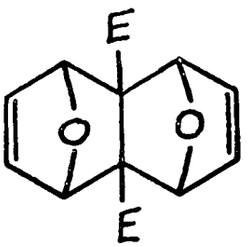
CONTENTS.

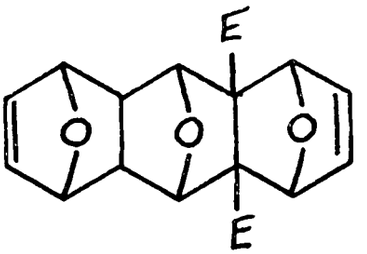
Introduction

The reactivity of the triple bond of dimethyl acetylenedicarboxylate to both electrophiles (e.g. hydrogen halides) and nucleophiles (e.g. sodium ethoxide, diethyl sodiomalonate) led Diels and Alder to investigate the usefulness of this acetylenic ester as one component in their studies of the addition reactions between dienes and dienophiles. Their earliest recorded results of the outcome of the reactions between heteroaromatic compounds and dimethyl acetylenedicarboxylate appeared in 1931, when furan was found to give [1] initially, which with excess furan gave [2] and [3][1].

[1]



[2]



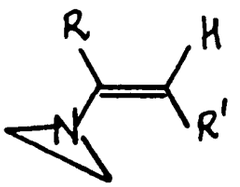
[3]

[The abbreviation E will be used throughout to indicate $COOCH_3$; other ester groups will be written in full. The use of E has precedents in recently published work by Acheson et al[2,3]]

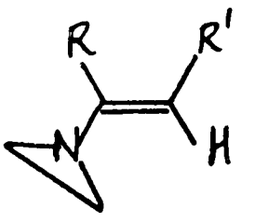
The results of further work in this field between 1931 and 1962 have been reviewed[4], and only more recent results are discussed below.

1. Aziridines

Aziridine reacts with dimethyl acetylenedicarboxylate and ethyl propiolate to give [4] and [5] in comparable proportions when methanol is the solvent, but in dimethyl sulphoxide the cis-isomer [5] comprises 95-100% of the products[5].

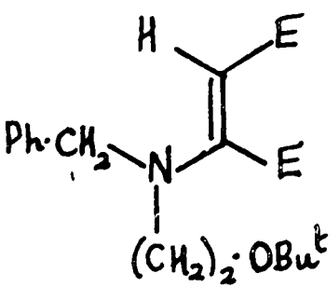


[4] a. R = R' = E.
b. R = H; R' = COOEt.

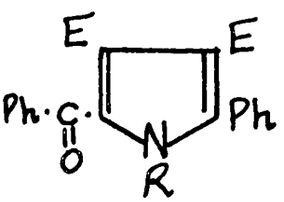


[5] a. as for [4]
b.

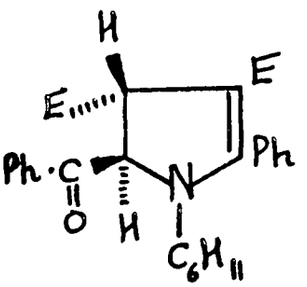
N-Benzylaziridine with dimethyl acetylenedicarboxylate in protic solvents (e.g. tertiary butanol) gives [6] in which the three-membered ring has opened, whilst in aprotic solvents the ester is trimerised to hexamethyl mellitate[6]. Dimethyl (or



[6]



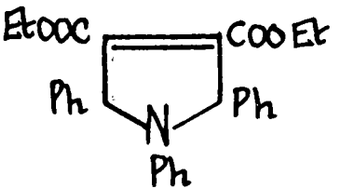
[7a] R = H.
[7b] R = C_6H_{11}.



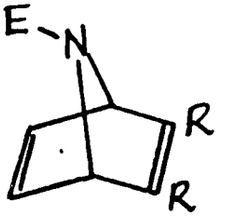
[8]

diethyl) acetylenedicarboxylate yields a product of type [5] with cis-2,3-diphenylaziridine, whilst [7a] and [7b] are the products from trans-2-phenyl-3-benzoylaziridine and its 1-cyclohexyl derivative respectively; in the case of the

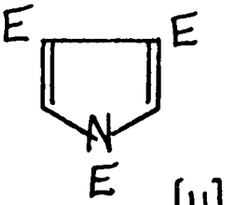
latter precursor product [8] is also isolated[7]. 1,2,3-Triphenylaziridine and diethyl acetylenedicarboxylate in toluene give [9] in 98% yield[8].



[9]



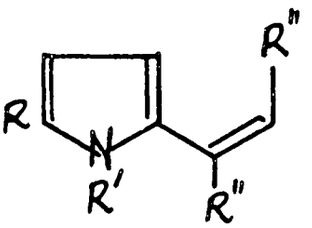
[10a] R = COOH.
[10b] R = E.



[11]

2. Five-membered rings. (one hetero atom).

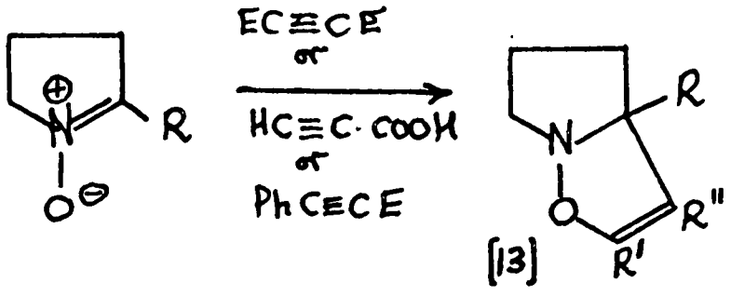
The postulated Diels-Alder adduct [10b] involved in the formation of the isolated product [11][9] from methyl pyrrole-1-carboxylate and dimethyl acetylenedicarboxylate has been isolated as [10a] when the acetylenic acid was employed[10]. Both the acid and its dimethyl ester yield products of type [12] with the above mentioned pyrrole and with 1,2-dimethylpyrrole[10].



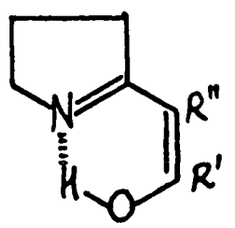
[12] R'' = E or COOH.
R = R' = Me or
R = H, R' = E.

The scheme below outlines recent results with Δ^1-pyrroline N-oxides and acetylenic dienophiles[11]. Acetylenes with a single carboxyl function exhibit this next to the ring-oxygen in the products [13]. Products in which R=H rearrange exothermically at room temperature to [14], whilst heating [13], R=Me, $R' = R'' = E$, at 130° gives [15]. A parallel between this latter process and the cyclisation

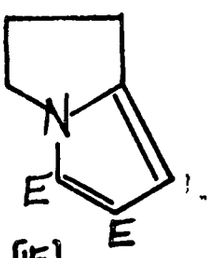
occurring on heating the adduct from 6-methylphenanthridine-5-oxide and dimethyl acetylenedicarboxylate[12,13] has been suggested[12], the alternative formulation of adducts [13] (R=Me) as N-vinyloxides [13a] not being ruled out[12].



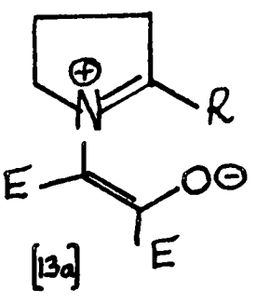
[13]



[14]



[15]

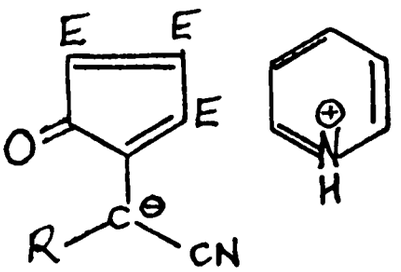


[13a]

3. Pyridines

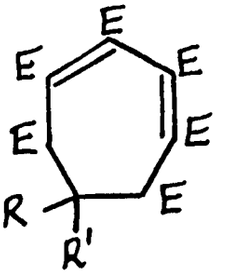
New work in this field is extensive. Two groups[14,15] have established independently that in the presence of ethyl cyanoacetate or malonodinitrile, or malonate diesters, pyridine and dimethyl acetylenedicarboxylate give products, viz. [16a,b] from the first two compounds, and [17] and [18] from malonate diesters, whose formation is accounted for in terms of the pyridine behaving simply as a base, to assist the generation of the initial anion of the active methylene compound or to accept protons eliminated in the reaction or to stabilise the final product as a pyridinium salt. This is in marked contrast to the behaviour of pyridine and the

acetylenic ester in the absence of other reagents.

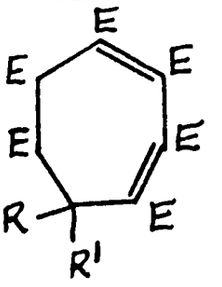


[16a] R = COOEt.

[16b] R = CN.



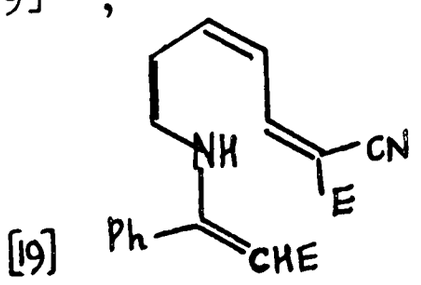
[17]



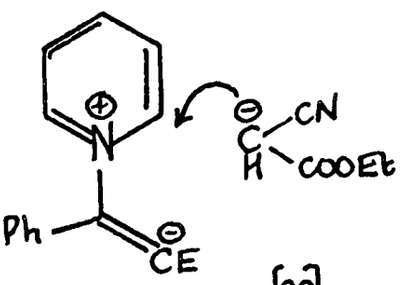
[18]

R, R' = E or COOEt.

Analogues of [17] and [18] having $R=R^1=CH_3CO$ and $R=CH_3CO$, $R^1=E$ have been prepared from acetylacetone and methyl acetoacetate respectively, under similar conditions[15]. In contrast, pyridine (or 3-picoline etc.), ethyl cyanoacetate (or the free acid or the acid amide), and methyl phenylpropiolate yield a series of compounds typified by [19][16],



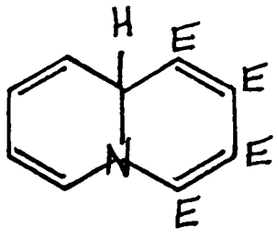
[19]



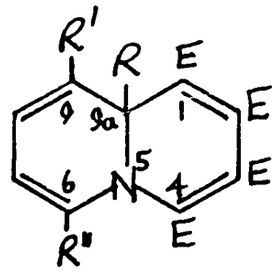
[20]

postulated as arising as indicated by diagram [20].

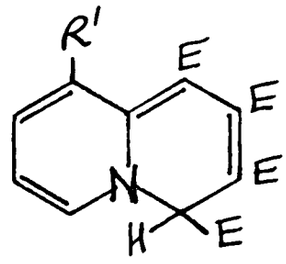
The "red" or "labile" adduct from pyridine and dimethyl acetylenedicarboxylate has been isolated for the first time since 1934[17] and comparison of its nuclear magnetic resonance spectrum with that of analogous "labile" adducts confirmed that it has the 9a<u>H</u>-quinolizine structure [21][18].



[21]



[22]

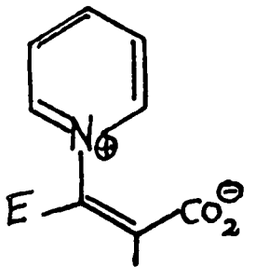


[23]

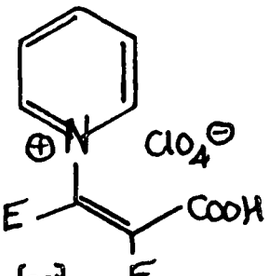
Diels' yellow adduct from 2-picoline[19] and dimethyl acetylenedicarboxylate has been shown[20] to be [22] $R^1=R^{11}=H$, R=Me, and analogous 9a-alkyl-9a<u>H</u>-quinolizines are reported[21] from 2-ethylpyridine, 2,6-lutidine, and 2-ethyl-6-methylpyridine; interestingly, in this last case the ethyl group is at the 9a-position. Also reported in this last reference are the first examples of 9a<u>H</u>-quinolizines isolated which carry no alkyl substituent at the 9-position; 9-alkyl-9a<u>H</u>-quinolizines are sterically less congested in the C9-C9a-C1 region than their corresponding "stable", 4<u>H</u>-isomers, [23], which are the preferred products, owing to their greater conjugation, isolated when steric factors do not intervene.

When the reaction between pyridine (also for alkyl-pyridines, isoquinoline and phenanthridine) and dimethyl acetylenedicarboxylate is carried out at -78^{o} in the presence of excess carbon dioxide, products typified by [24] can be isolated, but are more stable in the form of their perchlorates [25][22]. The initial zwitterion [26] attacks a molecule of carbon dioxide (originally provided

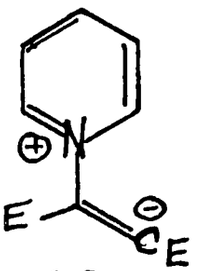
in small amounts by the cooling bath employed) giving [24] but only for pyridine has the trans isomer been isolated as well.



[24]

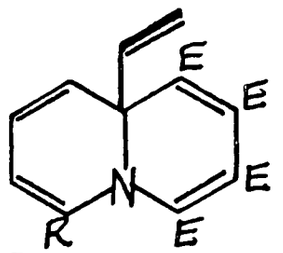


[25]

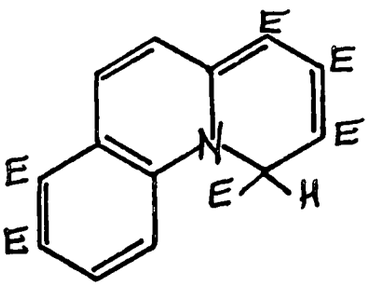


[26]

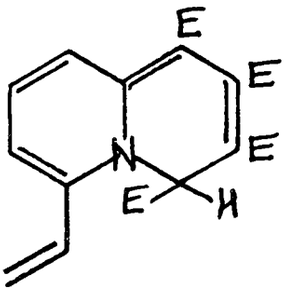
Both 2-vinyl- and 2-methyl-6-vinyl-pyridine with dimethyl acetylenedicarboxylate yield the 9a-vinyl compounds of type [27], whilst a minor product from 2-vinylpyridine



[27] R = H or Me.

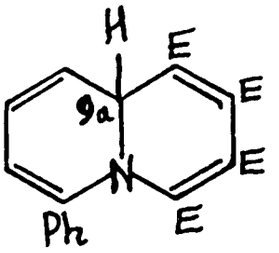


[28]

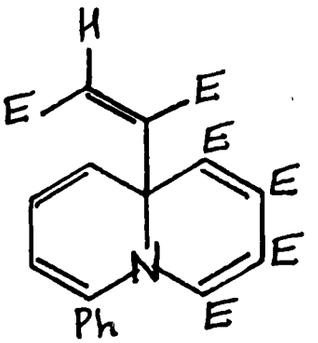


[29]

in this reaction is [28], presumably formed from [29] reacting in true Diels-Alder fashion with a third mole of ester[23]. The only example of a third mole of ester attaching itself at the 9a-position is provided by the reaction of the 9aH-quinolizine [30] from 2-phenylpyridine with excess dimethyl acetylene-dicarboxylate under vigorous heating[23], to yield [31].

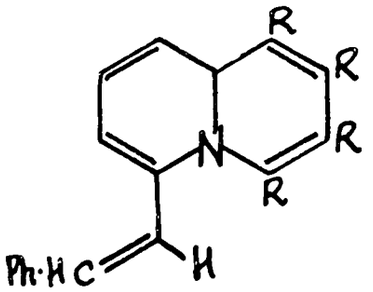


[30]

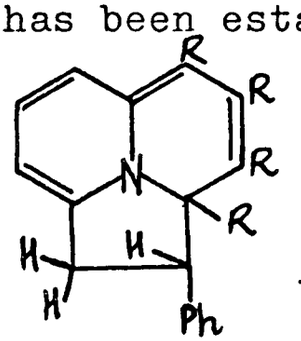


[31]

Stilbazole has provided some interesting results; the reaction of both cis and trans 2-styrylpyridine with dimethyl (and diethyl) acetylenedicarboxylate, and the nature of the products has been intensively studied[2,24]. The 6-styryl-9aH-quinolizines [32] obtained initially, can be isomerised in solution to the "stable" 4H-isomers, and in the case of the quinolizines from trans stilbazole, both isomers can be converted in fair yield to the so-called "2nd stable adduct", which has been established to have



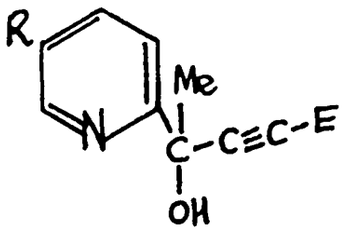
[32] R= E or COOEt.



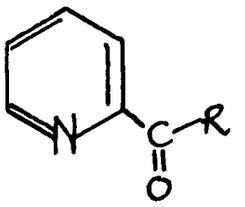
[33]

structure [33], being the first recorded instance of the cycl.[3,3,2] azine system (vide infra).

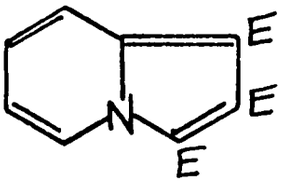
2-Acetyl- and 2-acetyl-5-methyl-pyridine with methyl propiolate in the presence of sodamide in liquid ammonia give compounds [34][25]. However heating dimethyl acetylene-



[34] R= H or Me.

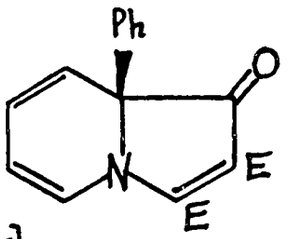


[35a] R= Me.
[35b] R= Ph. [35c] R= CH_2Ph.

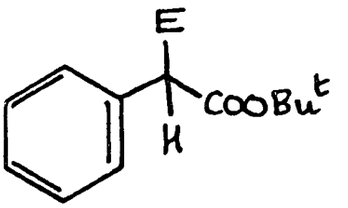


[36]

dicarboxylate in tertiary butanol with the 2-pyridyl-ketones [35a,b,c] gave the same product [36] in each case[26]. To account for the formation of [36], which clearly required appreciable structural rearrangement during reaction, the reaction of the ester with 2-benzoylpyridine [35b] was investigated more closely by chromatographic methods, and compounds [37] and [38] were then also isolated, and a

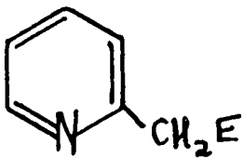


[37]

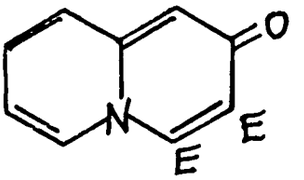


[38]

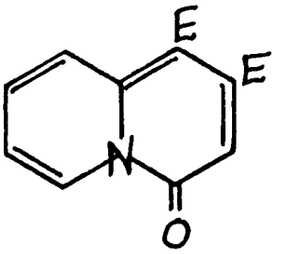
satisfactory mechanism was proposed to account for the three products. Wishing to know whether, in the case of compounds typified by [39], initial attack of the acetylenic ester was at the nitrogen atom or at the activated methylene group of the side chain, Winterfeldt reacted [39] with dimethyl acetylenedicarboxylate in various solvents[26]. In polar solvents, product [40] preponderates (initial attack



[39]

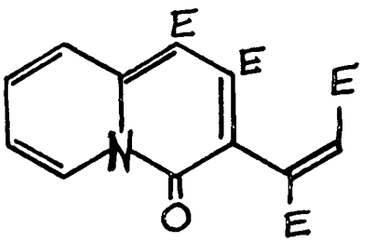


[40]

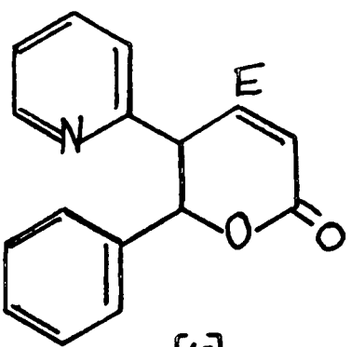


[41]

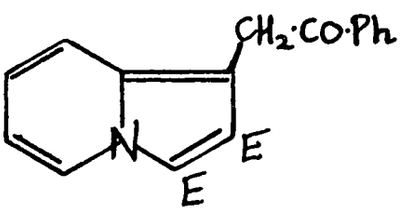
at nitrogen), whilst reaction in non-polar solvents gives rise to [41] as the major product (attack at exocyclic CH_2 group), traces of [42] also being isolated in these latter instances. In polar solvents, 2-phenacylpyridine, predominantly in the enol form[27], gives exclusively [43] the



[42]



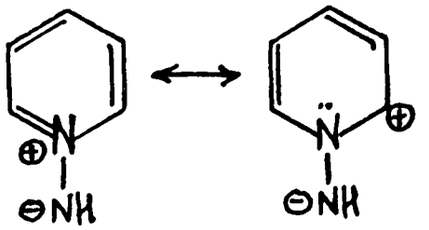
[43]



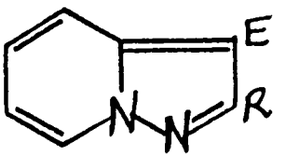
[44]

product of attack at side-chain carbon[26]. 2-(ω-Benzoylvinyl)-pyridine and dimethyl acetylenedicarboxylate are reported to yield the indolizine [44][28].

The zwitterion [45], which has a 1,3-dipolar resonance form, reacts with acetylenic esters to yield compounds [46][52].



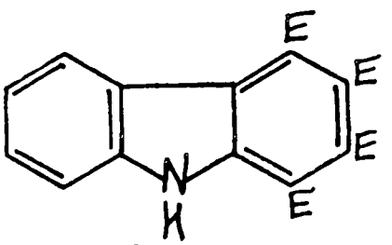
[45]



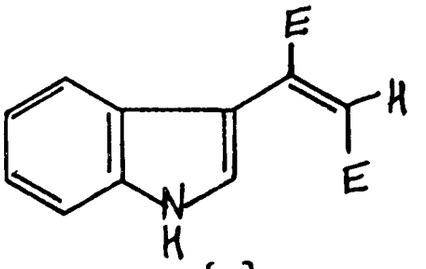
[46] R = E or H.

4. Indole and Indolizine. The Cyclazines.

Only two of the many known[29,30] adducts from indole and dimethyl acetylenedicarboxylate, [47] and [48], have been well characterised in the past[30]. A very recent report[31]

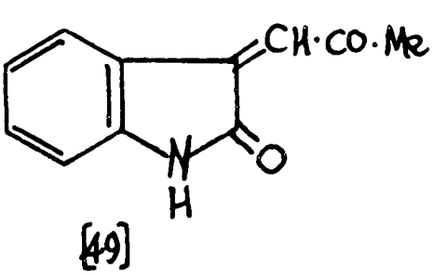


[47]

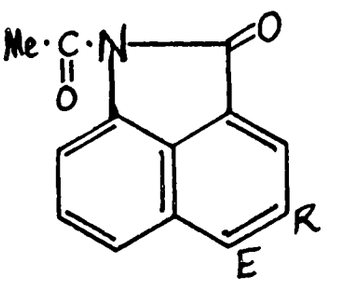


[48]

suggests that phenanthridinones are amongst the products from the reaction of indoles of type [48] with acetylenic carbonyl compounds. Oxindolylideneacetone [49] and acetylenic esters in acetic anhydride give products of type [50][32].

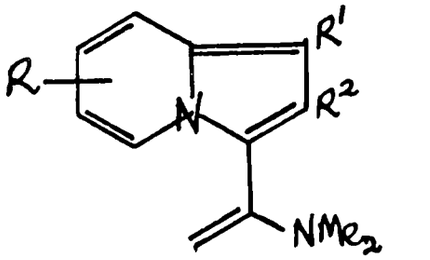


[49]

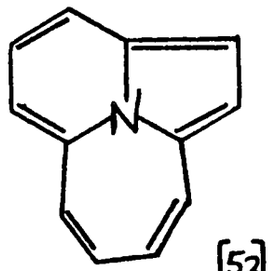


[50] R = E or Ph.

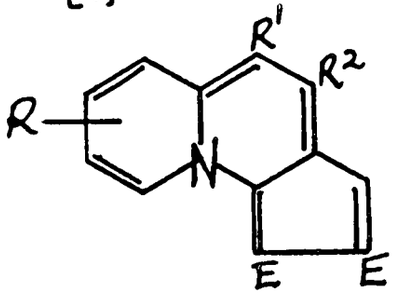
Indolizines of the form [51] have been synthesised as potential precursors to the system cycl[4,3,2]azine, [52],



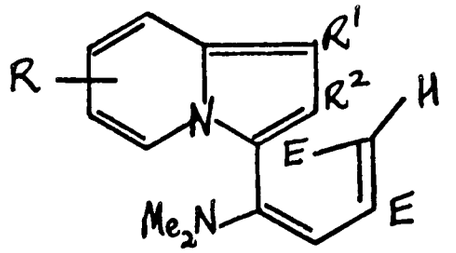
[51]



[52]



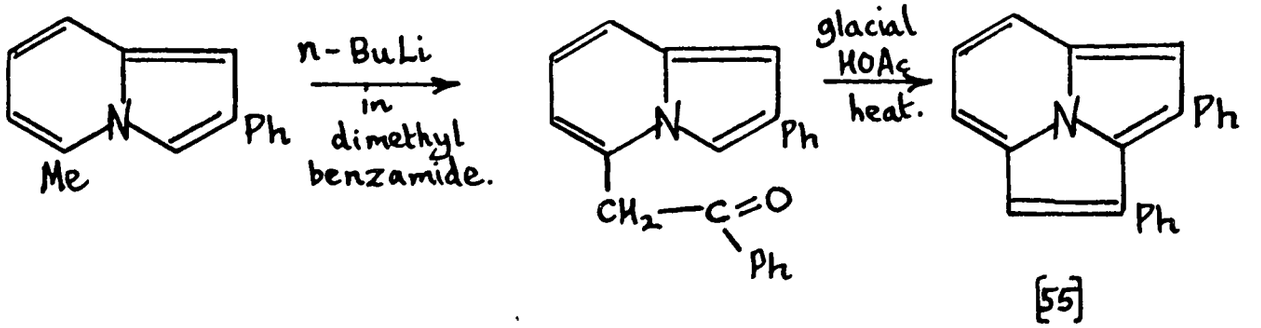
[53]



[54]

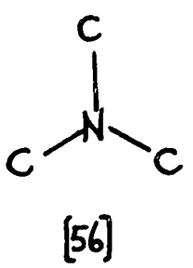
but reaction of compounds [51] with dimethyl acetylenedicarboxylate in boiling toluene gave only the cyclopenta[c]quinolizines [53], whose formation has been accounted for (it involves the unprecedented rearrangement of an indolizine to a quinolizine), the mechanism being substantiated by the isolation of [54] on replacing solvent toluene by methanol[33].

The first recorded instance of a cyclazine in the literature is in 1958, when Boekelheide and Windgassen[34] proposed the trivial name cycl[3,2,2]azine to cover compounds of the class represented by [55], synthesised as indicated below. Molecular orbital calculations suggested[35] that

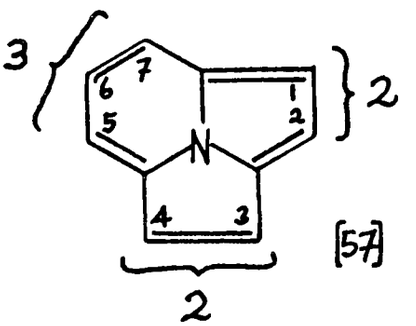


[55]

cycl[3,2,2]azines, cycl[3,3,3]azines and cycl[4,4,3]azines should exhibit considerable aromatic character, and the parent molecule [57] of one class behaved in accord with this view in bromination, nitration, and Friedel-Crafts acylation[35,40]. A cyclazine is defined[35] as referring



[56]

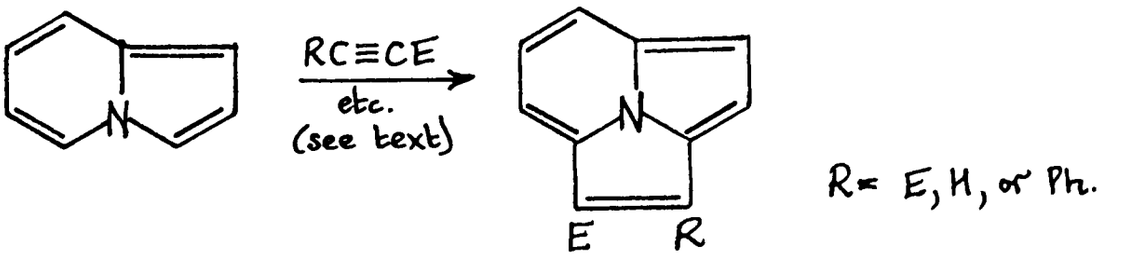


[57]

to the general case of a conjugate, unsaturated cycle held planar by three covalent bonds to an internal nitrogen atom; the numbers appearing in square brackets describe the numbers of carbon atoms between the three consecutive pairs of carbon atoms linked to the central nitrogen atom (see [56]); thus [57] is cycl[3,2,2]azine.

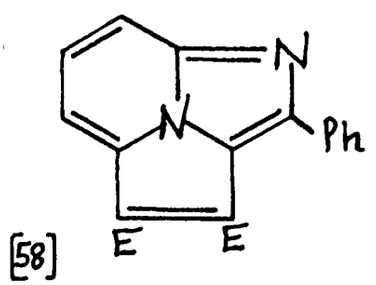
The formation of cycl[3,2,2]azine derivatives by the heating of indolizines with acetylenic esters in the presence of dehydrogenation palladium-charcoal in e.g. toluene solution under an atmosphere of nitrogen was reported in

1959[36,37] and has since been widely generalized[38,40].

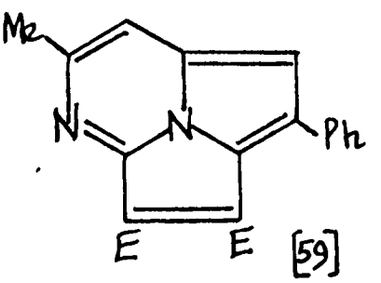


The physical properties of [57] have been given considerable study; the nuclear magnetic resonance spectrum confirms the aromatic character of [57] from the chemical shifts of the protons (2.14 to 2.80τ)[41,42], and ultra-violet[43], nuclear magnetic resonance[41], and theoretical studies indicate that protonation of the ring occurs only under very acid conditions (as predicted[35]) and then at position 1 (or 4); the conjugate acid has a $pK_a = -2.8$[43,44].

Derivatives of both 1-azacycl[3,2,2]azine[45] and 5-azacycl[3,2,2]azine[46], viz. [58], [59], respectively, have been synthesised from the appropriate azaindolizines by the dimethyl acetylenedicarboxylate/palladium-charcoal

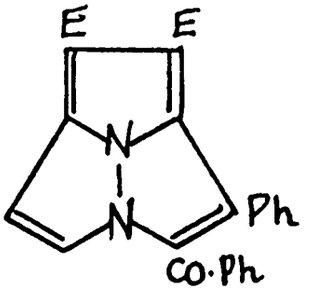


[58]

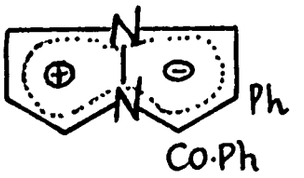


[59]

method. Similarly the first example of a cycl[2,2,2]azine, compound [60], has been synthesised from the diazapentalene [61][47].

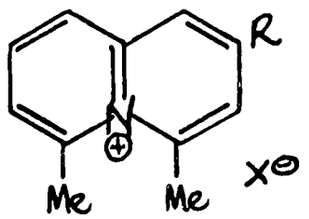


[60]

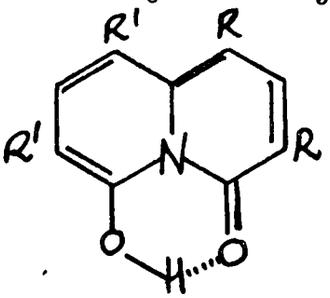


[61]

Attempted syntheses of the cycl[3,3,3]azine system by two independent groups[48,49] by various methods from the 4,6-dimethylquinolizinium salts [62], and the similar efforts of a third group[50] from 6-hydroxy-4-quinolizones [63], were all unsuccessful. However the system cycl[3,3,3]azine was

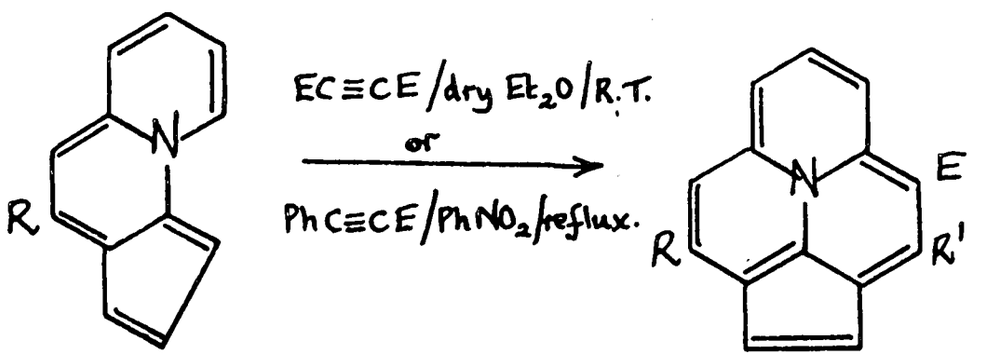


[62] R=H, Me, or Ph.



[63]

realised for the first time recently, when compounds of type [64][33] were reacted with acetylenic esters to give products [65][51]. Hydrolysis and decarboxylation of [65b]



[64] R= Ph or Me.

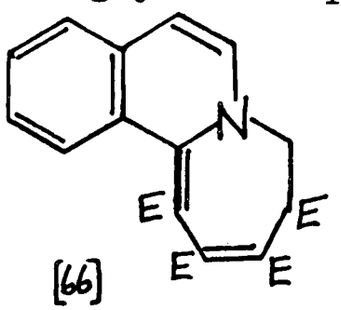
[65] a. R=Me, R'=E.
b. R=R'=Ph.

gave a symmetrical product, as evidenced by its nuclear magnetic resonance spectrum, which confirms the structure.

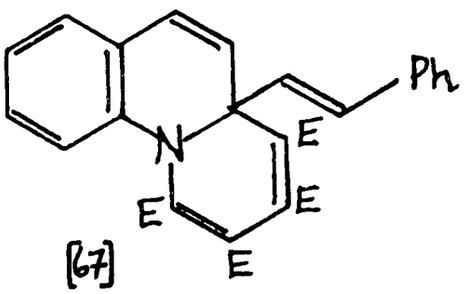
The only known[2,24] cycl[3,3,2]azine is the not fully conjugated compound [33] which has been described earlier.

5. Benzopyridines.

Recent mass spectral studies[3] have supplemented earlier results[53] to establish that azepines (e.g. [66] from 1-methyl-isoquinoline) are the products from various 2-methylquinolines, 1-methyl-isoquinoline, and 6-methyl-phenanthridine with dimethyl acetylenedicarboxylate. The presence of a methyl group at position 1 or 2 in the precursors is essential to the proposed mechanism, and accordingly no azepine type product is observed from

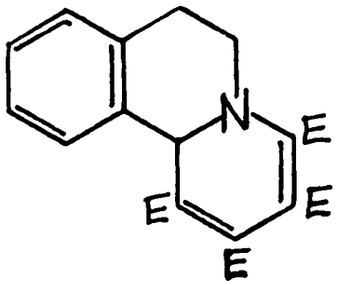


[66]

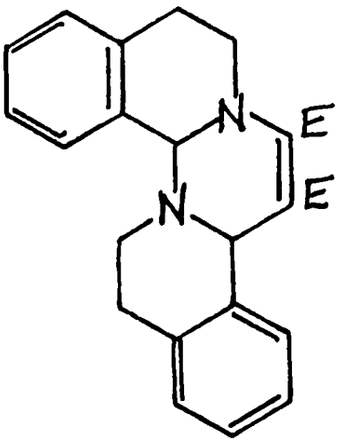


[67]

1-ethylisoquinoline. 2-Styrylquinoline with dimethyl acetylenedicarboxylate in ether is reported to give [67][54]. The product corresponding to [67] is isolated from 1-styrylisoquinoline under similar conditions[55]. In ethereal solution 3,4-dihydroisoquinoline yields compound [68], whilst if the dimethyl acetylenedicarboxylate is very carefully dried, the product is instead [69][56].

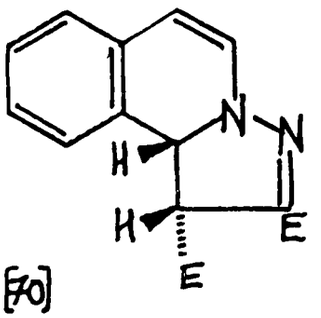


[68]

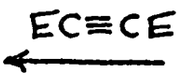


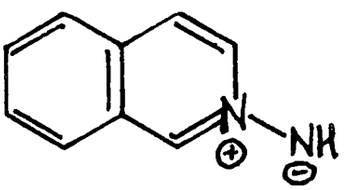
[69]

The product [70] from the zwitterion [71] as shown, is not aromatised in situ in contrast to the reaction in the pyridine series[52], (see [46]).



[70]

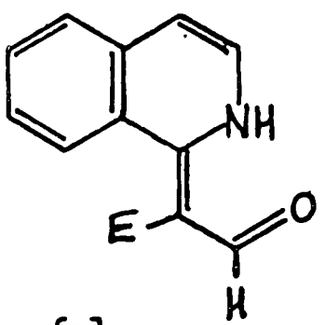




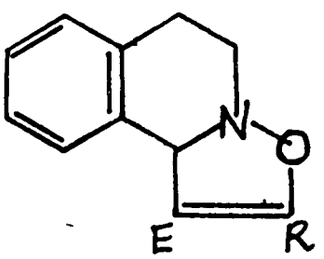
[71]

6. Benzopyridine N-oxides.

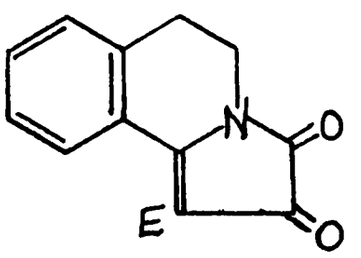
Isoquinoline N-oxide and methyl propiolate gave compound [72], analogous products arising from other acetylenic esters[57], whilst 3,4-dihydroisoquinoline N-oxide gives rise to [73] or [74] dependent upon the acetylenic ester as indicated[58].



[72]

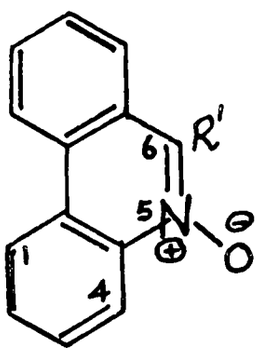


[73] R = H or Ph.

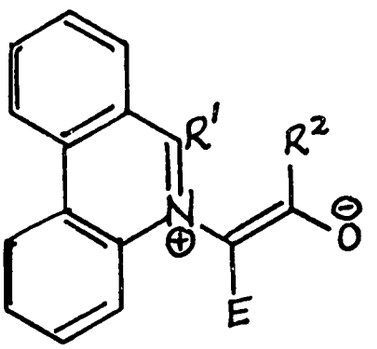


[74] [73], R = E is isomerised

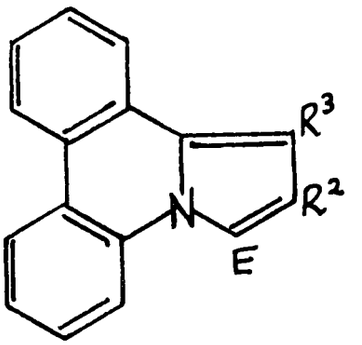
Phenanthridine N-oxides [75] with acetylenic esters give products [76], and where these carry a 6-alkyl group, further treatment with soda-lime in vacuo gives the dibenzo[e,g]indolizines [77], which parallels the observed behaviour of [76, R^1=alkyl] in the mass spectrometer[12,13].



[75]
R'= Me or Et or H.



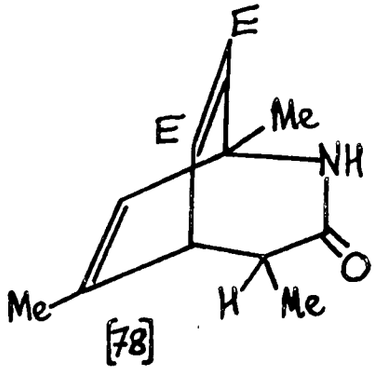
[76]
R'= Me or Et or H.
R²= E or H or Ph.



[77]
R² = E or H or Ph.
R³ = H or Me.

7. Azepines.

3,5,7-Trimethyl-1,3-dihydro-2H-azepin-2-one gives Diels-Alder adducts with typical dienophiles, the product from dimethyl acetylenedicarboxylate being [78][59].

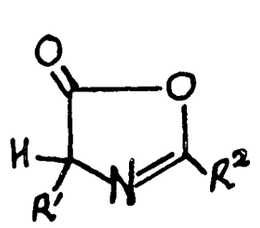


[78]

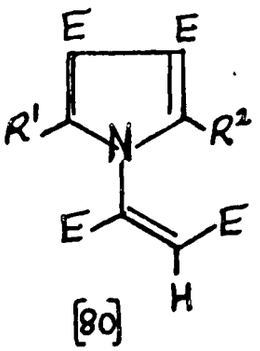
8. Systems containing more than one hetero atom.

The azlactones [79] with acetylenic esters give the pyrrole derivatives e.g. [80][60] by further reaction of the

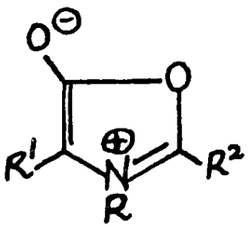
first formed products [82, R = H], similar pyrroles e.g. [82, R = alkyl] being the products when the meso-ionic compounds [81] are precursors[61].



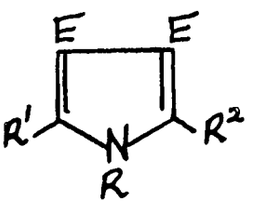
[79]



[80]

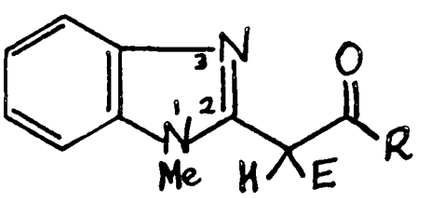


[81]

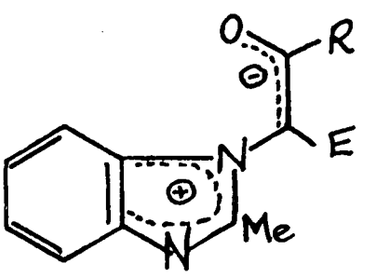


[82]

Acetylenic esters and 1-methylbenzimidazole 3-oxide give the adducts [83][62] whilst blocking of the 2-position with a second methyl group leads to the products [84][63].



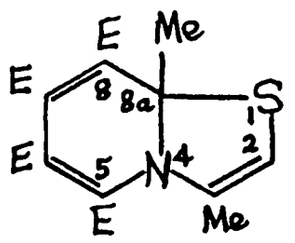
[83] R = H or E.



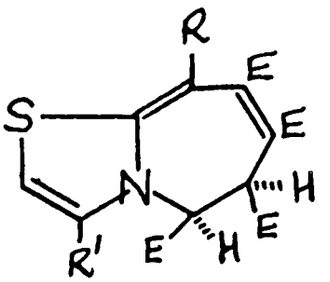
[84] R = H or E.

In dimethyl formamide solution, dimethyl acetylene-dicarboxylate gives compound [85] with 2,4-dimethylthiazole[65], but the products described[65] from thiazole and its 2- or 4-methyl derivative have been reformulated by later workers[64], on the basis of comparative spectral data, as simply further examples of the system typified by [85] and [88] (vide infra). In methanol or acetonitrile solution however, the products proposed from various 2-alkylthiazoles are the azepines [86],

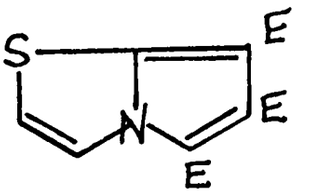
thiazole itself giving [87][65].



[85]

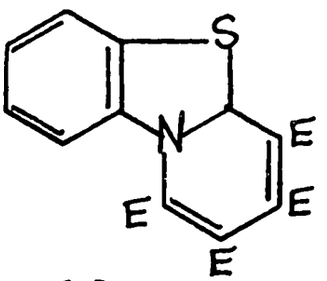


[86] R or R' = H or Me.

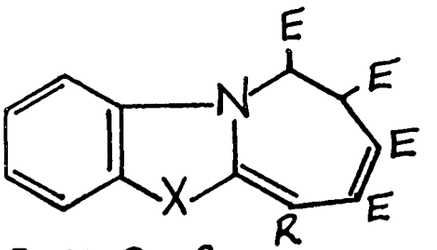


[87]

Acheson and Foxton[64] found that under quite diverse conditions the acetylenic ester combined with thiazole and its 4-methyl derivative, benzothiazole and benzoxazole to give 2:1 molar adducts, e.g. [88] whose spectral properties were not unlike the analogous "labile" adducts in the pyridine series. However azepines of type [89] were obtained



[88]

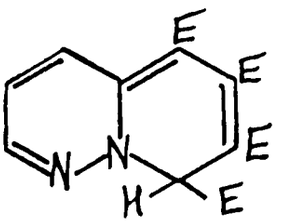


[89] X = S or Se.
R = H or Me.

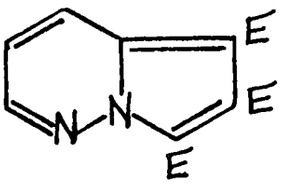
under similar conditions from 2,4-dimethylthiazole, 2-ethyl- and 2-methyl-benzothiazole and 2-methylbenzoselenazole.

Dimethyl acetylenedicarboxylate in acetonitrile with pyridazine, 3-methylpyridazine and 1-methylphthalazine gave pyrido[1,2-b]pyridazines [e.g.90], with smaller amounts of related pyrrolo[1,2-b]pyridazines [e.g. 91]. 3,6-Dimethylpyridazine, however, gave mostly an azepino

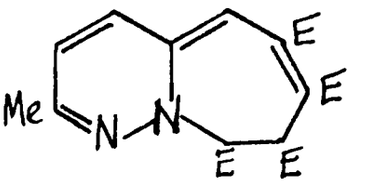
[1,2-b]pyridazine [92]. 2-Methyl- and 2,6-dimethyl-pyrazines gave only low yields of pyrrolo[1,2-a]pyrazines [e.g. 93] under these conditions. In methanol phthalazine gave the adduct [94], phenazine yielding compound [95][66].



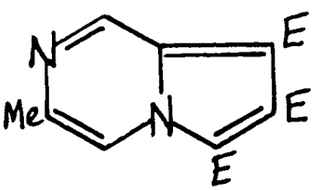
[90]



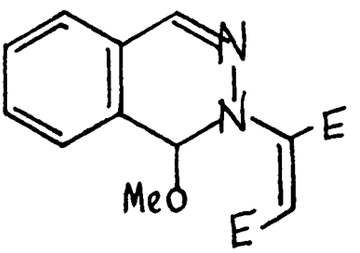
[91]



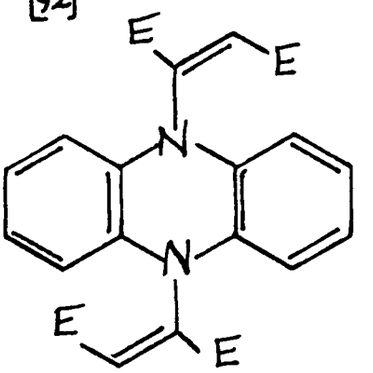
[92]



[93]

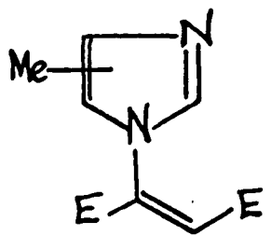


[94]

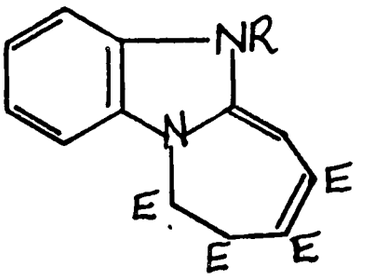


[95]

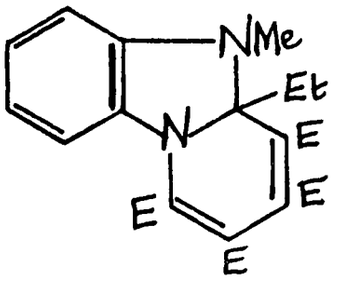
Dimethyl acetylenedicarboxylate with 2- and 4-methyl-imidazole gave the adducts [96]. The major products from 1,2-dimethyl- and 1-ethyl-2-methyl-benzimidazoles were the azepine derivatives [97], but 2-ethyl-1-methyl- and 1-methyl-benzimidazole gave dibenzo[a,d]imidazoles, [e.g.98].



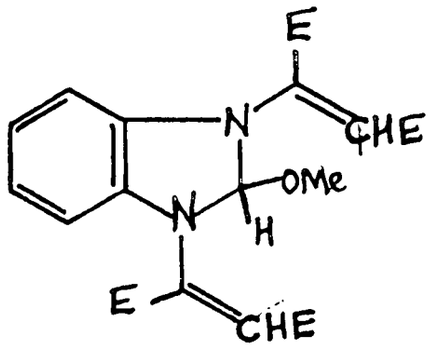
[96]



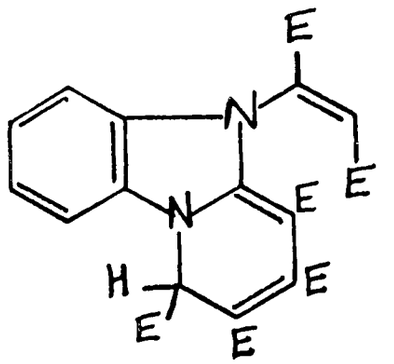
[97] R= Me or Et.



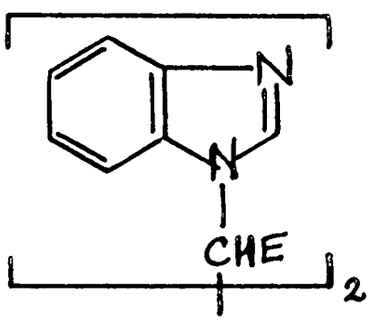
[98]



[99] a. both side-chains trans.
b. one side-chain cis.



[100]



[101]

According to the conditions, benzimidazole itself gave the compounds [99]-[101][67].

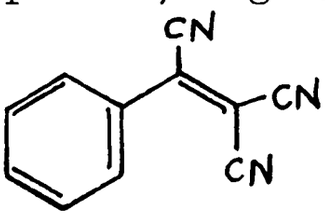
The diversity and extent of the reactions of acetylenic esters, particularly dimethyl acetylenedicarboxylate, with heterocycles should now be apparent.

DISCUSSION

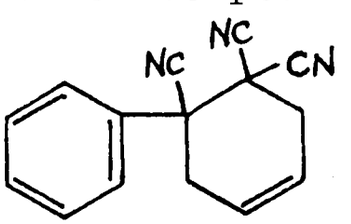
CHAPTER ONE

Reactions of some adducts from dimethyl acetylenedicarboxylate and pyridine or N-methylpyrrole with two dienophiles.

Hexachlorocyclopentadiene and tetracyanoethylene are amongst the most reactive of dienophiles. As early as 1948[91] the former compound was described as participating in a Diels-Alder condensation, whilst the varied reactivity of tetracyanoethylene was comprehensively reported for the first time in 1958[92] when, in addition to undergoing Diels-Alder condensations, it was also seen to form tricyanovinyl derivatives (e.g. [1]) with aromatic and heteroaromatic precursors, and that these derivatives could themselves act as dienophiles, e.g. formation of compound [2]



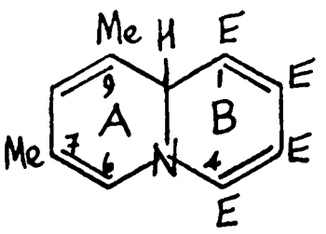
[1]



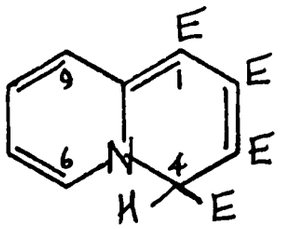
[2]

from derivative [1] with buta -1,3-diene.

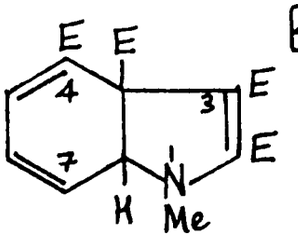
The possibility of further reactions with the above dienophiles of some of the compounds readily available in this laboratory which are themselves products from pyridines and N-methylpyrrole with dimethyl acetylenedicarboxylate[4], but might be considered as potential dienes for Diels-Alder condensations, was investigated.



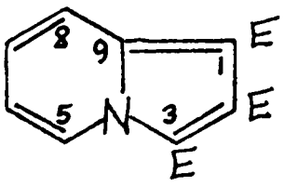
[3]



[4]

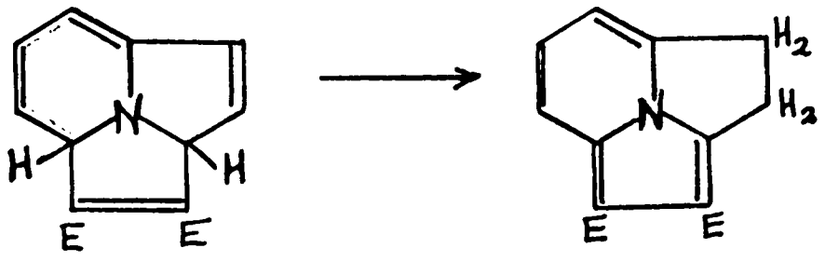


[5]



[6]

The failure of the indolizine [6], (recovered unchanged in all instances), to react with either dienophile confirmed its aromatic character, though by Jackman's criterion[93] indolizine is appreciably less aromatic than pyridine. Furthermore Godfrey states[36] that inspection of accurate molecular models of indolizine and of its possible Diels-Alder adducts clearly indicated that the steric requirements alone of 3,9- or 5,8- adducts should effectively preclude their formation, whilst freedom from steric strain, the resonance energy of the final product, and the localisation energies for simultaneous attack at the 3- and 5- positions make this the most probable mode of reaction. Indolizine and dimethyl acetylenedicarboxylate add in this way[38], but the first formed adduct rearranges as shown below to the form which retains the aromatic indolizine system.

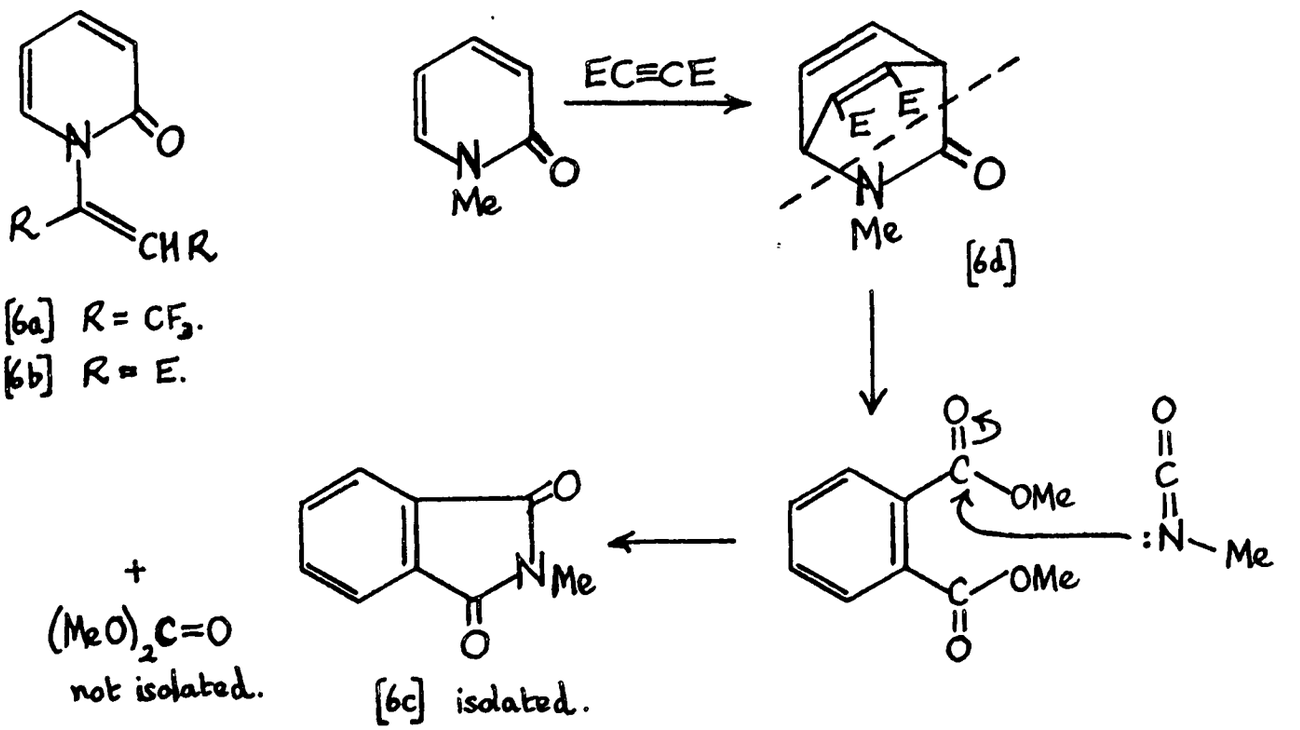


The 3-ester group in the indolizine [6] by virtue both of its bulk and of its electron-withdrawing properties presumably inhibits even this mode of addition in the reactions attempted.

The adducts [3], [4], and [5] each reacted with one or other of the dienophiles in at least one instance as evidenced by the large number of bands obtained when the reaction mixture was subjected to thin-layer chromatography. However unchanged (or in one instance, isomerised) adducts were the only solid products ever isolated from the extraction of such bands.

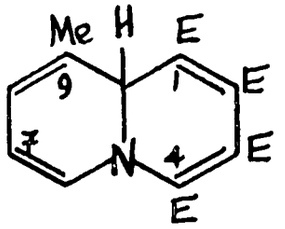
The "stable" adduct [4] had some possibility for reaction since on the evidence of its nuclear magnetic resonance spectrum it is comparably aromatic[68,21] with 2-pyridone of which compound the "stable" adducts may be considered vinylogues[21]. Though Paquette[94] states that 2-pyridone represents a cis-dienoid ring system which has yet to enter into a Diels-Alder reaction, giving only the product [6a] with hexafluorobut-2-yne, Tasker has found that whilst dimethyl acetylenedicarboxylate gives only the analogous

product [6b] with 2-pyridone, the product isolated from N-methyl-2-pyridone, viz. N-methylphthalimide [6c], is accounted for as deriving from a Diels-Alder adduct [6d] as indicated below.[119]

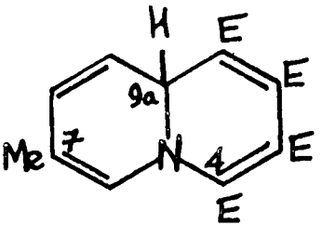


However the nuclear magnetic resonance spectra of the "labile" adducts, the 9a<u>H</u>-quinolizines, e.g. [3], show that the A ring is aliphatic in character[21]. Similarly, parallel studies of compound [5] reveal features consistent with the butadiene-like character of the carbocyclic ring[95]. Furthermore it is already established that heating the sterically congested compound [7] with 3-methylpyridine in methanol gives the less congested isomer [8], isolated in the 4<u>H</u>-quinolizine form owing to further thermal isomerisation.

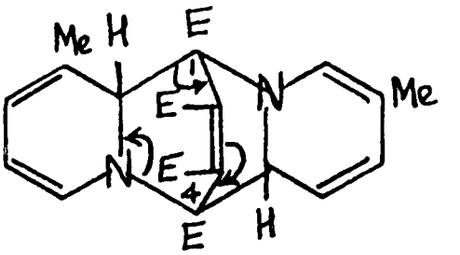
Formation of compound [8] is postulated as involving the intermediate [9] formed via addition of the 3-methylpyridine across the 1,4-positions of [7] in a Diels-Alder manner[68].



[7]

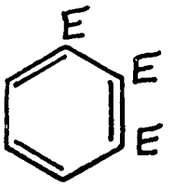


[8]

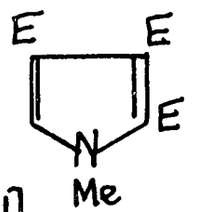


[9]

Heating compound [5] with dimethyl acetylenedicarboxylate gives products [10] and [11] accounted for by postulating a Diels-Alder addition of the ester across the 4- and 7-positions, followed by fragmentation by an alternative mode to the thermodynamically more stable system[69].



[10]



[11]

In view of these precedents, it would seem reasonable to expect compounds [3] and [5] to undergo related reactions with the two dienophiles in question. Thin-layer chromatography indicates complex product mixtures from both compounds. The normal isomerisation of the 9a<u>H</u>-quinolizine [3] to the 4<u>H</u>-quinolizine is the expected side reaction observed under refluxing benzene conditions.

CHAPTER TWO

1. Reactions of Dicyanoacetylene with Heterocycles.

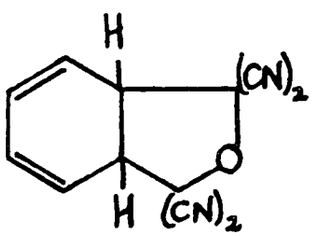
Furans are the only heterocycles whose reactions with dicyanoacetylene have been reported[96], though the products from a number of olefinic, strained saturated[98], and aromatic compounds are also described[97].

The vigour of dicyanoacetylene as a reagent and the apparent lack of study of its reactions with heterocycles led us to begin an investigation in this field. The investigation was however soon abandoned because of the difficulties associated with its preparation and the discouraging results of the reactions undertaken. Two comments should be made regarding the results obtained. It has been reported[99] that sodium hydroxide and anionic catalysts, e.g. butyllithium, cause the polymerisation of dicyanoacetylene. Consequently this may be an important competing reaction in the case of dicyanoacetylene and pyridine. However the tiny quantity of yellow-brown solid isolated from 1 of the 10 bands obtained after large scale thin-layer chromatography of the crude product possessed an ultraviolet spectrum which suggested that the solid could be a definite adduct from the two reagents which would merit further investigation were it obtained in sufficiently large quantities. Secondly, the intractable brown tars obtained with thiophene were most discouraging, particularly in view of the recently reported first ever

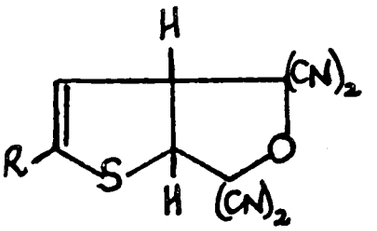
observed examples of the participation of thiophene in Diels-Alder reactions[100]. Any further investigation of this reaction would probably be well advised to employ gas-liquid chromatographic techniques in an attempt to detect possible decomposition products of any initially formed adduct.

2. Reactions of Tetracyanoethylene Oxide with Heterocycles.

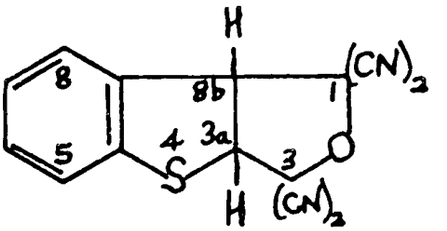
It has been reported that tetracyanoethylene oxide, a potential 1,3-dipole, gives the adducts [1] and [2] with benzene and thiophene respectively[101]. Wishing to know which ring would be attacked when a benzene and a thiophene



[1]



[2a] R=H.
[2b] R=Cl.



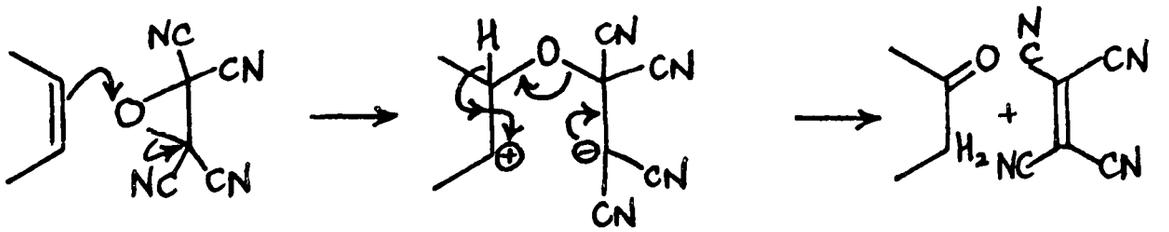
[3]

ring were presented to the reagent simultaneously, we investigated the reaction of benzo[b]thiophene with tetracyanoethylene oxide and obtained the 1:1 molar adduct [3], in which the thiophene ring has been attacked.

The nuclear magnetic resonance spectrum of the adduct [3] shows four aromatic protons at 2.29τ (1 proton) and 2.45 - 2.83τ (3 protons) in acetone, thianaphthene (in deuterochloroform) having six such protons grouped two, centre 2.19τ, and four, centre 2.69τ. Alternative 1:1 adducts to compound [3] would be expected to show only two

aromatic protons and in addition have two olefinic protons. Further support for structure [3] comes from the fact that both the bridgehead protons, H-3a at 3.94τ, H-8b at 4.25τ, $J_{3a,8b}$ = 8.2 c/s, are simple doublets, a feature expected only for structure [3], since in compound [1] both bridgehead protons are at least triplets, and in adduct [2b] one of the bridgehead protons is a doublet with further splitting[101(d)].

In addition to isolating the adduct [3] a small quantity of tetracyanoethylene was also recovered and characterised. The described[101(b)] mode of attack (see diagram below) other than that which yields products of type [3], could account for this, though we did not isolate any characterisable oxidation products of the benzothiophene.



2-Chlorothiophene gives the 1:1 adduct [2b] across the 4,5- positions, and <u>para</u>-xylene adds tetracyanoethylene oxide at the 2,3- positions[101(d)]. Furthermore, durene, 1,2,4,5 - tetramethylbenzene, any 1:1 adduct of which must needs bear at least one bridgehead methyl group, gives only duroquinone and tetracyanoethylene[101(b)]*. There are thus no adducts described which have other than hydrogen atoms at the two bridgeheads. This possibly accounts for the failure to

isolate any parallel adduct of 2,5-dimethylthiophene since the product must needs have a bridgehead methyl group which would lead to severe steric congestion in that area of the molecule.

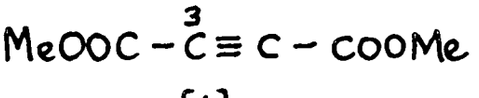
Dibenzo[b,d] thiophene was recovered in good yield from reaction with the oxide. Admittedly neither anthracene nor phenanthrene form adducts involving attachment at either of the terminal benzene rings[101(b)]; as might be expected tetracyanoethylene oxide adds across the 9, 10-positions of anthracene. However naphthalene does add the oxide across the 1, 2-positions[101(b)]. Definite evidence of tetracyanoethylene was again obtained in this reaction, but no oxidation products of dibenzothiophene were characterised.

N-Methylpyrrole and tetracyanoethylene oxide react in an exceedingly vigorous manner in the absence of solvent, though we are unable to say what form this reaction takes as the solids isolated proved uncharacterisable. It is recorded that nucleophilic attack on the oxide is extremely rapid[101(c)], and the 2-position of N-methylpyrrole is very active towards electrophiles.[125] These factors may be of importance in this case.

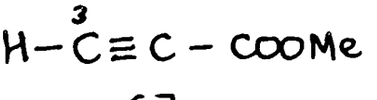
3. Methyl Tetrolate and some Pyridines.

The tarry nature of the evaporated reaction mixtures from pyridines and methyl tetrolate is indicative of some form of reaction, but only trace quantities of any solid products

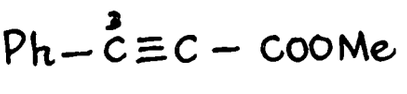
were obtained from column chromatography. Consequently these solids were not characterised. Consideration of the inductive effect of the substituents suggests that in the series of acetylenic esters [4] - [7], methyl tetrolate [7] would be the least susceptible to nucleophilic Michael attack at C-3. This fact may be the reason for the low yields of



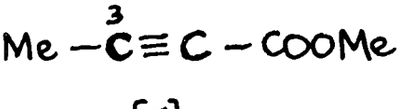
[4]



[5]



[6]



[7]

solid products isolated, though in view of the great structural differences amongst the products from any one pyridine base and the esters [4] - [6], the mode of reaction of methyl tetrolate [7] may be unlike any so far encountered and account for the low yields.

CHAPTER THREE

Reactions of Heterocycles with Methyl Phenylpropiolate.

Pyridine and methyl phenylpropiolate.

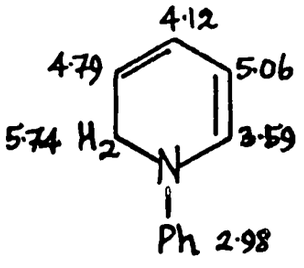
This reaction showed great non-reproducibility and the small quantity of the yellow adduct obtained on two out six attempts has made it impossible to decide on a definite structure for this compound. The data obtained and its implications will be summarised as follows:

(i) Elemental analysis and the mass spectrum established the adduct as having molecular weight 496 corresponding to $C_{30}H_{28}N_2O_5$ containing only two methoxyl groups. This represents an adduct formed from 2 moles of pyridine, 2 moles of methyl phenylpropiolate, and 1 mole of water.

(ii) The most satisfactory interpretation of the integration of the nuclear magnetic resonance spectrum accommodates the 28 protons in keeping with the data in (i) above, and the n.m.r. spectrum is summarised thus: chemical shift (τ), coupling constant (c/s), integration (number of protons): 0.81, singlet, (1); centre 2.52, two singlets and broad multiplet, (11, including two phenyl groups); centre 3.19, multiplet, (3); centre 3.91, multiplet, (2); 4.61, singlet, (1); 5.07, singlet, (1); centre 5.37, multiplet, (3); 6.26, singlet, (6, two ester methyl groups).

The n.m.r. chemical shifts are more in keeping with the presence of 1,2 - rather than 1,4 - dihydropyridine moieties

as the figures[113] below appended to structures [1], [2] and [3] show. Any structure proposed must account for the single



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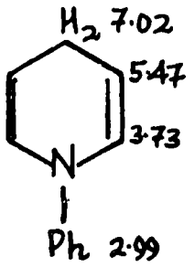

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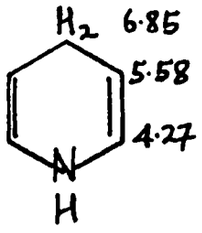


[3]

very low field proton. A symmetrical structure for the yellow adduct is excluded by the n.m.r. spectrum, as are the presence of unreduced pyridine rings.

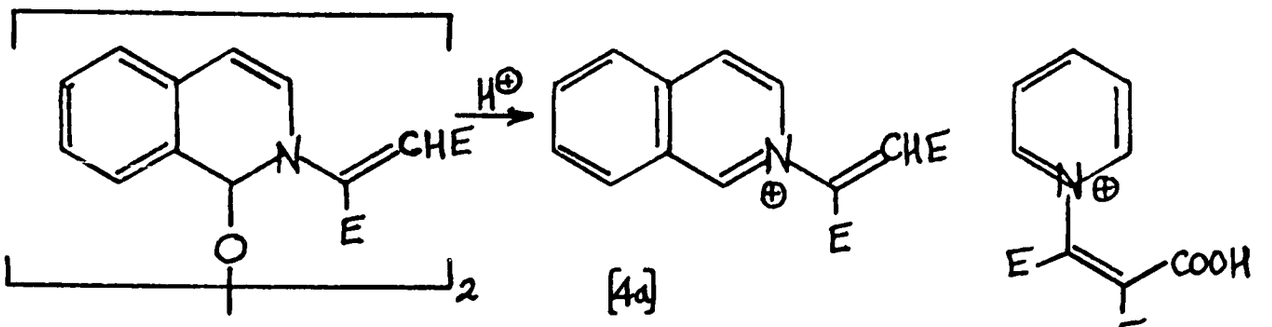
(iii) The ultraviolet spectra of the yellow adduct and some possibly related compounds are set out in Table I below.

Table I

Ultraviolet spectra, λ in mμ (E.10^{-4}).

Compound	Solvent.	Maxima.
Yellow adduct.	(M)	259(3.06) 369(4.69)
[1][113]	?	239(3.9) 350(4.1)
[2][113]	?	286(4.2)
[4][22]	(M)	238(2.66) 303*(1.15) 337(4.21)
Yellow adduct	(P)	260*(2.46) 275(2.75) 345*(0.93) 510 (0.11)
[4a][22]	(W)	237(5.00) 270*(0.30) 280(0.34) 292*(0.18) 344(0.37)
[5][22]	(W)	260(0.63)

(M) = methanol; (W) = water; (P) = methanol : 70% perchloric acid :: 2:1.



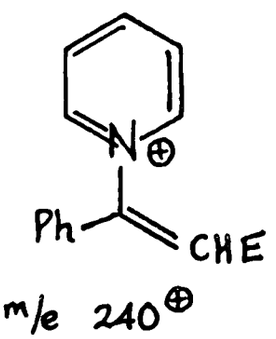
[4] [4a] [5]

The ultraviolet spectrum of the adduct in **methanol shows** similarity to that of the 1,2- but not the 1,4- dihydropyridine structure. The product [4] is obtained[22] when the reaction of isoquinoline and dimethyl acetylenedicarboxylate is carried out in wet ether, and bearing in mind that product [4] is an isoquinoline ether the formulation of our adduct as a pyridine ether is not excluded by its ultraviolet spectrum when compared with that of compound [4]. Comparison of the ultraviolet spectra of these two compounds in acid conditions suggests that if the yellow adduct possesses an ether linkage it is as readily fractured as the ether linkage in compound [4]. The ultraviolet spectral comparisons are hampered by the obvious changes observed in going from pyridinium (e.g. [5]) to isoquinolinium (e.g. [4a]) systems, and by the presence in our adduct of phenyl groups with their own additional spectral features.

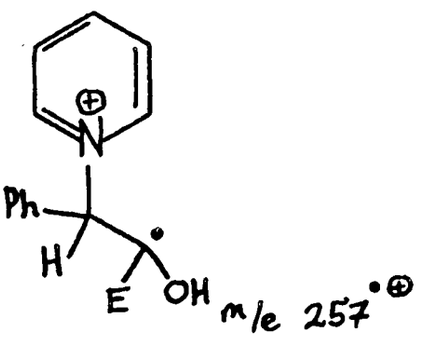
(iv) The infrared spectrum excludes the presence of hydroxyl groups in the adduct.

(v) Finally, any structure for the adduct must explain the

mass spectral features of a very weak molecular ion, m/e 496 (0.58%), and m/e, % age of base peak, 257(31.2), 241(30.4), 240(64.8), 226(19.2), as the only major peaks at m/e $\geqslant$200. It is noted that peaks at 240 and 257 could correspond to 1:1 adducts with the additions of H and H_2O respectively, e.g. [5a] and [5b, or isomer], respectively.



[5a]



[5b]

Uncertainty remains concerning the manner in which the above fragments, should [5a] and [5b] be their correct structures, are linked in the adduct.

3,5- Dimethylpyridine and methyl phenylpropiolate.

Two products have been isolated from these precursors after reaction at room temperature but the small quantities of substance isolated has meant that their structures remain unsolved. The data obtained is presented.

(a) The so-called yellow adduct. Any structure must accommodate the following results:

(i) The absence of the ν(C=O) absorption in the infrared spectrum from the usual ester carbonyl region.

(ii) The nuclear magnetic resonance spectrum can be summarised as follows: chemical shift (τ), coupling constant (c/s), integration (number of protons): 0.75, singlet, (1); 2.51, broad based singlet, (5, the phenyl group); 3.20, broad singlet, (1); 3.46, broad singlet, (1); 4.94, singlet, (1); 6.21, singlet, (3, methoxyl group); 7.83, singlet, (3, C-methyl group); 8.08, singlet, (3, C-methyl group).

Of interest here are the presence of a methoxyl resonance in the region observed for methyl esters or methyl vinyl ethers, and the presence of one very low field proton. The small sample gave a very poor signal-to-noise ratio in the n.m.r. spectrum.

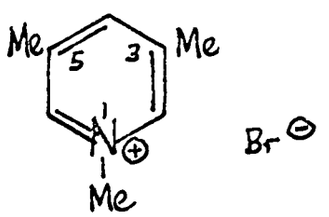
(b) The white crystalline solid. Very little constructive comment can be made regarding this substance. The integration details of the nuclear magnetic resonance spectrum lack internal consistency and are summarised as for (a) thus: 1.52, broad singlet, (?2); 1.75, broad singlet, (?1); 2.47 to 2.98, complex multiplet, (5 - 7 protons, phenyl group etc.); 6.78, singlet, (?2); 7.42, singlet, (?6).

The possible salt-like nature of this substance cannot be excluded, since the addition of D_2O to the n.m.r. solution causes the almost complete disappearance of the spectrum which can be explained in terms of a preferential extraction of the product into the aqueous phase which, surmounting the deuterochloroform in the n.m.r. tube in the spectrometer,

will be out of the region of the R.F. field.

Methyl phenylpropiolate and 3,5- dimethylpyridine under refluxing conditions.

The product obtained in yields of up to 17% from 3,5-dimethylpyridine and methyl phenylpropiolate in refluxing acetonitrile was not an adduct in the usual sense of the word. The results of elemental analysis showed the absence of methoxyl in the compound, and corresponded to $C_8H_{12}NO_5$. It was clear that the analysis data could be equally well accommodated by $C_8H_{12}NBr$, and the probability that the compound was an organic bromide was confirmed by the usual silver intrate test for halide ions in aqueous solution. Comparison of the nuclear magnetic resonance spectra of the compound, 3,5- dimethylpyridine, and 3,5- dimethylpyridinium ion (see below) suggested that the compound was 1,3,5-



[6]

trimethylpyridinium bromide[6].

Table II

Nuclear magnetic resonance data.

Compound	Solvent	Chemical shifts (τ values)					
		1-Me	2-H	3-Me	4-H	5-Me	6-H
Product [6]	(D)	5.32	0.68	7.39	1.88	7.39	0.68
3,5-Dimethylpyridine	(D)	-	1.78	7.77	2.78	7.77	1.78
" " " "	(T)	-	1.42	7.37	1.64	7.37	1.42

(D) = deuterochloroform

(T) = trifluoroacetic acid

All methyl group absorptions appeared as sharp singlets. All ring proton absorptions were slightly broadened singlets (meta coupling only).

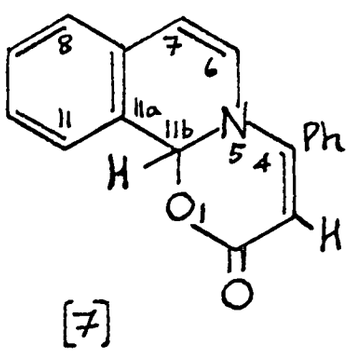
That structure [6] was indeed correct for the product was confirmed as follows. The bromide [6] was converted by means of silver perchlorate into the perchlorate salt, identical in all respects with the perchlorate prepared by the same method from an authentic sample of 1,3,5-trimethylpyridinium iodide obtained from 3,5-dimethylpyridine and methyl iodide. A satisfactory elemental analysis was obtained for the perchlorate prepared from the bromide [6].

It was acknowledged that the methyl phenylpropiolate prepared from methyl 1,2-dibromo-2-phenylpropionate was probably contaminated with some of the oil used to disperse the sodium hydride employed in the dehydrobromination stage of the synthesis. It had not been anticipated that the fractionally distilled methyl phenylpropiolate would contain bromine-containing impurities, i.e. methyl α (or β)-bromocin-

nate, as a result of incomplete dehydrobromination. Such impurity must however be the source of the bromine found in our product [6] since it is feasible for 3,5-dimethylpyridine to be a sufficiently strong base to dehydrobrominate the impurities under prolonged reflux. The source of the N-methyl group in the product is probably the methyl ester group of the acetylenic ester since it seems certain from the control reaction of 3,5-dimethylpyridine and acetonitrile that this latter compound is not the origin of the methyl group. Any proposed mechanism of N-methylation would require alkyl-O fission of the ester group.

Methyl phenylpropiolate and isoquinoline.

The product from these reagents, obtained in almost 33% yield when aqueous methanol was employed as solvent, has been given the structure [7].



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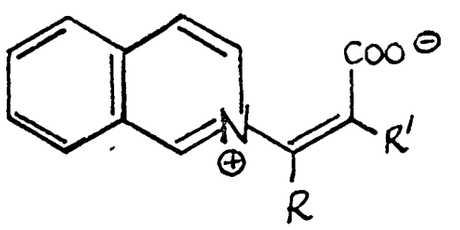

[8] a. $R = R' = E$.
b. $R = Ph$, $R' = H$.

Elemental analysis was in accord with the empirical formula $C_{18}H_{13}NO_2$ and the compound contained no methoxyl group. The infrared maxima attributed to the carboxylate anion at ca. 6.50 and 7.60μ in the adduct [8a][22] are absent from the spectrum of our compound, rendering the alternative

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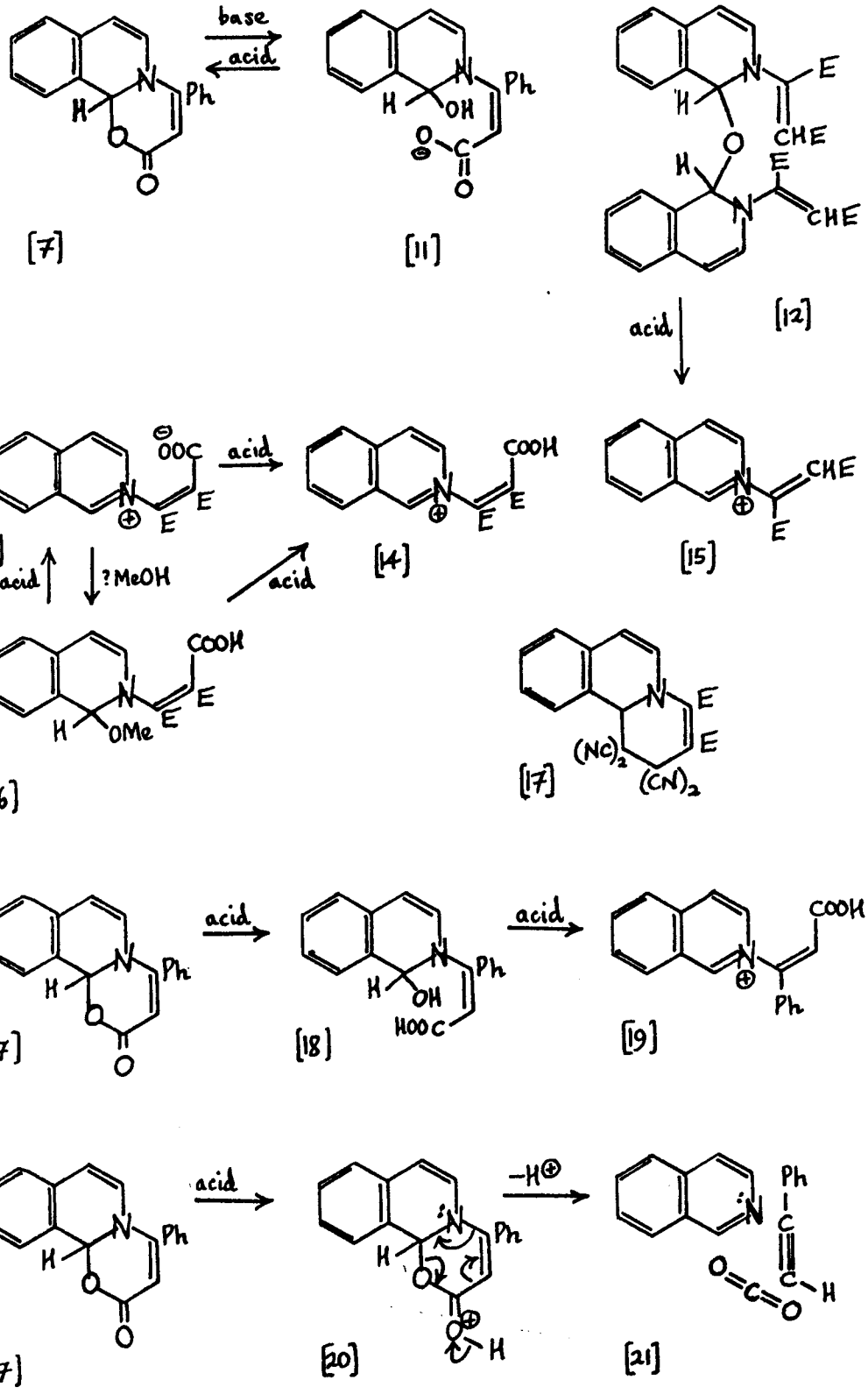
FLOW SHEET. I.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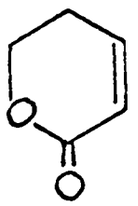
formulation of [7] as [8b] unlikely. Support for the structure [7] is also to be had from the infrared spectrum since the observed carbonyl ν(C=O) position for the compound, 5.88μ, i.e. 1701 cm^{-1}. compares favourably with the value of 1720 cm^{-1}. quoted for the carbonyl group in the lactone [9][102]. A compound [10] very closely related to



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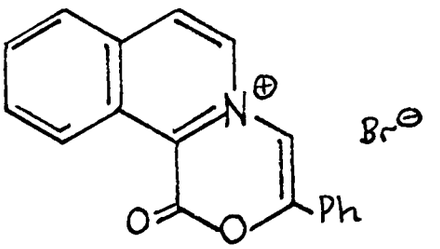


[10]

our adduct has been described, but regrettably no spectral data of any kind was recorded[103].

Comparison of the ultraviolet spectrum of the adduct [7], under various conditions of pH with data available for a series of related compounds (see Flow Sheet I) provides further support for the formulation of the adduct given[22].

Table III

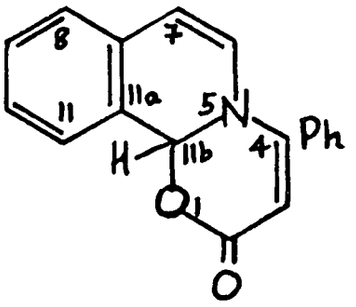
Ultraviolet spectra, λ in mμ ($E.10^{-4}$).

Compound	Solution				
[7]	(M)	234.5(3.36)	270(2.19)		350(0.43)
[11]	(B)	237(1.23)	301(1.20)		331*(0.87)
[12][22]	(M)	238(2.66)	303*(1.15)		337(4.21)
[13 or 16][22]	(M)	236 (1.69)	302*(1.12)		337(2.58)
[14][22]	(W)	237(3.99)	282*(0.53)	295*(0.31)	346(0.42)
[15][22]	(W)	237(5.00)	270*(0.30)	280(0.34) 292*(0.18)	344(0.37)
[17][22]	(M)	245(2.26)	298(0.69)	312(0.68)	363(1.84)
[19]	(A)	236.5(4.86)	270(1.90)		346(0.38)

(M) = methanol; (B) = (M) containing ca. 5% by volume of saturated methanolic sodium methoxide; (A) = (M) containing ca. 5% by volume of perchloric acid (72%); (W) = water.

It is known[22] that in perchloric acid compound [12] gives the salt [15], and adduct [13] gives the salt [14]. It seems reasonable to suggest that in basic solution hydrolysis of [7] will give the anion [11], whilst in acid solution a possible intermediate for products [19] is [18]. Since the ultraviolet spectrum of the very unstable compound [13] in methanol is so like that of [11] and [12] it is suggested that solvolysis (reversed by slight acidification) of [13] to give [16] is in accord with the observations, since now [11], [12], and [16] exhibit the same degree of conjugation. The ultraviolet spectra of [14] and [15] are very similar to that of [19] which supports the formulation of [7] in acid as [19] with the same conjugated system. Some differences between the spectra of these three species [14], [15], and [19] is to be expected since the substituent groups on each are different and are now in conjugation with the remainder of the molecule. The ultraviolet spectra of [7] and [17] bear comparison less well than those of the species described so far.

Finally, support for structure [7] can be adduced from the nuclear magnetic resonance spectrum.



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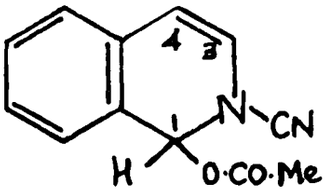

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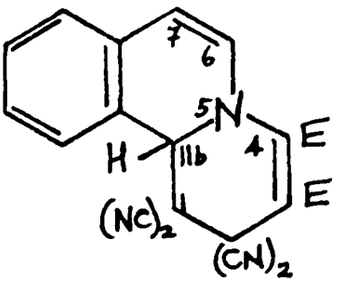


[17]

Nuclear magnetic resonance data for [7]

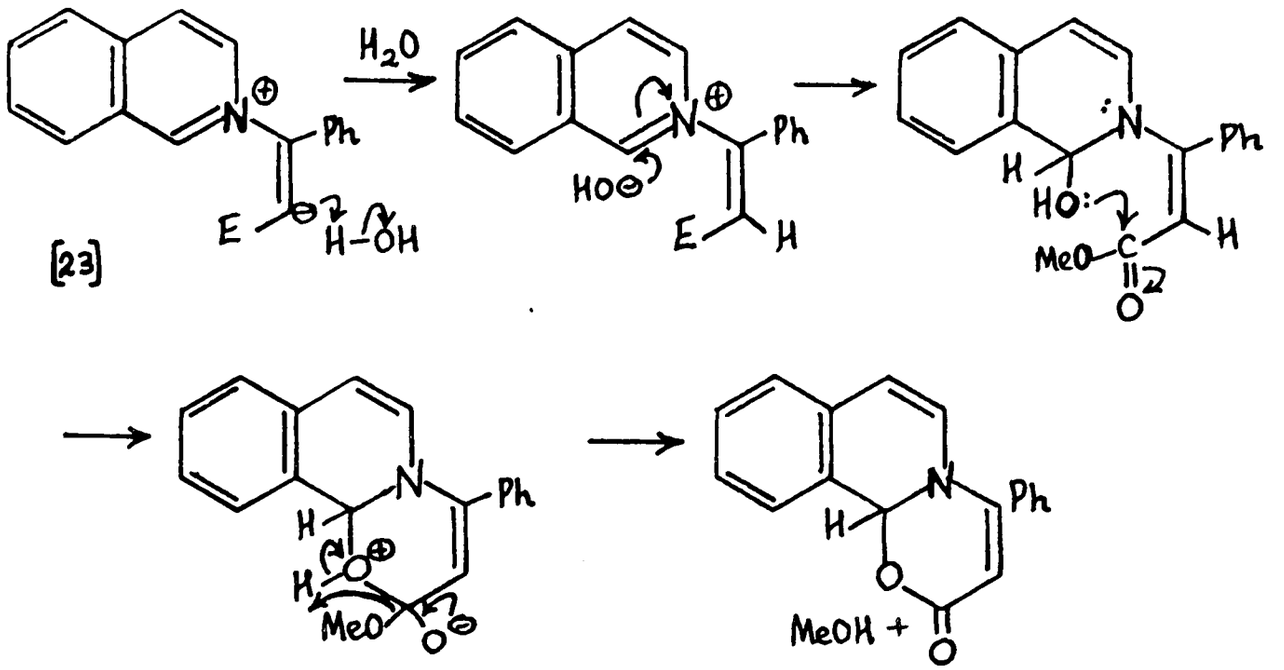
Substituent	Chemical shift (τ)	Coupling constants (c/s.)
4-Ph	2.45	sharp singlet
8,9,10,11-H's	2.32 - 2.90	complex multiplet
3-H	3.12	singlet
6-H	3.55	$J_{6,7}$ = 8.1; doublet
7-H	4.14	$J_{6,7}$ = 8.1; doublet
11b-H	4.16	sharp singlet

Support for the assignments given comes from the data[104] for compound [22], in which H-4 is at 3.95τ (cf. 4.14τ for the equivalent proton in [7]) and H-3 is at 3.56τ, only 0.01τ different from the chemical shift of the corresponding proton in [7]. Further, in compound [22], $J_{3,4}$ = 7.6 c/s, and $J_{1,3} = J_{1,4}$ = 0.0 c/s, in good agreement with our observations. The isolated proton is found as a singlet at 3.72τ, whilst the corresponding proton in [17] is at 4.22τ,[22] both values being in fair agreement with our observed value of 4.16τ for this proton in [7]. Comparison of the remaining proton chemical shifts in [17] with our assignments

in [7], viz. 8 - 11 H's, complex multiplet centred at 2.4τ, H-6, 3.41τ and H-7, 3.86τ, doublets, J = 8.1 c/s, is also very satisfactory.

Acid hydrolysis of the adduct [7] under vigorous conditions gave isoquinoline as the only identifiable product. It has already been suggested (see Flow Sheet I) that the ultraviolet spectrum of [7] in acid is compatible with its hydrolysis to give the salt [19]. The first step in the acid hydrolysis of [7] will probably be protonation to give [20] (see Flow Sheet I) which readily yields [18] after attack at the ring carbonyl group by a molecule of water. On the other hand, electron shifts in [20] as indicated would yield the products [21], viz. isoquinoline, carbon dioxide, and phenylacetylene. This tentative mechanism would account for the isolation of isoquinoline under these vigorous conditions.

The observation that the yield of the adduct [7] was considerably improved by the use of aqueous-methanol as the reaction medium instead of benzene, acetonitrile, or no solvent, is entirely in keeping with the proposed mode of formation of [7] given below. The formation of the intermediate [23] is proposed as a likely first step in the reaction, being parallel to the observed initial Michael



attack of isoquinoline on dimethyl acetylenedicarboxylate[22], and being the intermediate already suggested in the reaction of pyridine, methyl phenylpropiolate and ethyl cyanoacetate[16].

Methyl phenylpropiolate and N-methylpyrrole.

Vacuum fractionation of the reaction mixture after 61 days gave ca.80% recovery of the acetylenic ester which suggests that no reaction has occurred. N-methylpyrrole was not recovered but under the conditions of the distillation it would probably be uncondensed.

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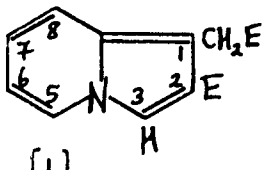

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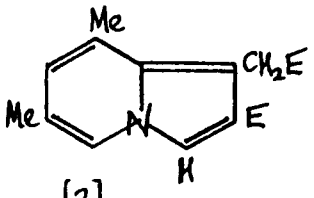

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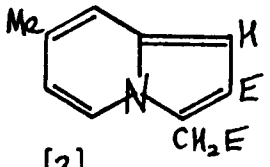

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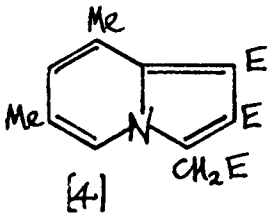

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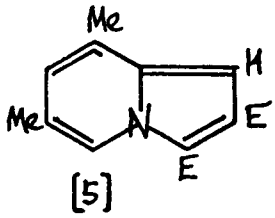

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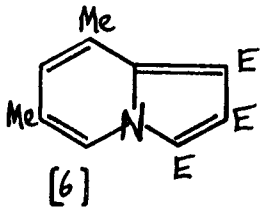

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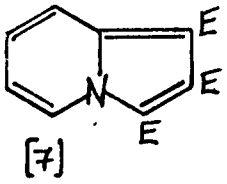

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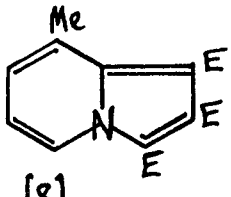

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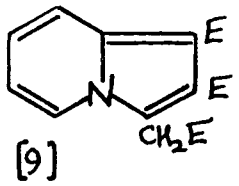

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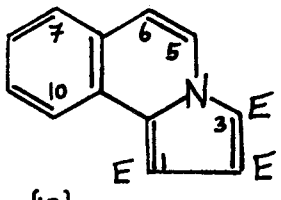

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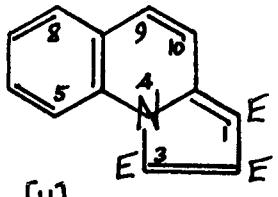

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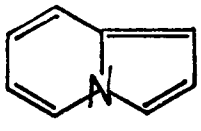

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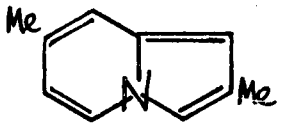
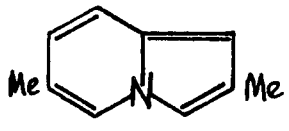


[13]



[14]

CHAPTER FOUR

Reactions of methyl propiolate with pyridines.

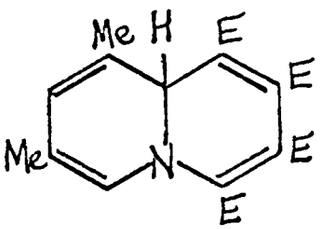
The structure of this chapter will differ somewhat from that of the same chapter in the experimental section. For the purposes of the Discussion it will facilitate the interpretation of the results to group the products into three classes irrespective of their origin, viz.(i) the Indolizines (including those from the subsidiary section of Chapter Four in the Experimental), (ii) the Cycl[3,2,2]azines, and (iii) other Adducts.

(i) The Indolizines.

The interpretation of the data for four indolizines being described here for the first time and for two other known indolizines prepared here by novel routes has been enormously assisted by the fact that the indolizines [6] - [11] were readily available in this laboratory from earlier research workers[68,105,107]. The ultraviolet spectral data used here for [6] - [9] had been recorded previously[105], but the nuclear magnetic resonance spectra of the indolizines [6] - [11] were measured and interpreted for the first time during this research.

The new products, whose formulation we shall hope to justify in this section, are compound [2] obtained from 3,5-dimethylpyridine and methyl propiolate under various

conditions, compound [3] from 4-methylpyridine and methyl propiolate in ethereal solution, and compounds [4] and [5] obtained from the adduct [15][68] and palladium-charcoal in refluxing toluene. This last reaction also yielded the indolizine [6] in very small quantities, identified by comparison with an authentic sample.



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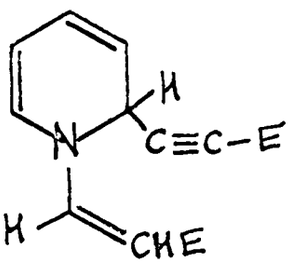

[16]

The indolizine [1] we have isolated directly from the reaction of pyridine and methyl propiolate under rigorously anhydrous conditions. Under these conditions other workers[81] isolated the compound [16] which they cyclised to the indolizine [1] by base-catalysed ring closure with piperidine. Confirmation of the identity of our compound [1] with the indolizine they describe is provided by the ultraviolet spectral data (see Table I) and the melting point, 87 - 88.5° (literature value[81] 88 - 89°). We describe the nuclear magnetic resonance spectrum of compound [1] for the first time.

Elemental analyses in accord with the formulations given were obtained for the products [2], [4], and [5], too

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Table I

Ultraviolet spectra, λ in mμ ($\varepsilon.10^{-4}$) in methanol

Compound	Absorption Maxima									
[1]	235.5(2.49)	240*(2.27)	292.5(0.28)	305.5(0.21)	340*(0.22)	350(0.26)	366(0.25)	385(0.16)		
[1][81]	236 (4.07)		295 (0.22)	306 (0.24)		352(0.26)	367(0.26)	385(0.15)		
[2]	238 (3.03)		297 (0.35)	309 (0.33)	342 (0.26)	355.5(0.25)	373*(0.18)			
[3]	237 (5.19)	241*(4.94)	293 (0.57)	303 (0.57)		352(0.43)	365(0.43)	380*(0.32)		
[4]		242 (3.17)	294 (0.35)	306 (0.46)	339.5(0.46)	346.5(0.46)				
[5]	229 (2.76)	257(2.57)				333*(0.97)	347(1.15)			
[6]		245.5(2.93)	264 (0.86)	275 (0.85)	326 (1.41)	339(1.32)				
[6][105]		245.5(3.47)	264.5(0.97)	274.5(0.97)	324 (1.57)	337(1.48)				
[7][105]		235 (2.66)	264 (1.08)	273 (1.44)	322.5(1.60)					
[8][105]		242 (2.85)	265.5(0.80)	273.5(0.92)	321 (1.42)	334.5(1.37)				
[9][105]	216.5(2.18)	243.5(2.63)	292.5(0.61)	305.5(0.85)		345.5(0.81)				

little material being available for similar data to be acquired for the indolizine [3].

The ultraviolet spectra of these four products provided a strong initial suggestion that they were indolizines. Examination of Table I indicates clear correlations between the structure of the indolizine and its ultraviolet spectrum. All indolizines show 1 or 2 strong absorptions in the region 229-246 mμ. Bands in the range 257-266 and 273-5 mμ indicate that the five-membered ring bears three directly attached ester groups, the latter band disappearing when the 1-ester group is replaced by a proton. Another feature of indolizines carrying only ester substituents directly attached to the five-membered ring is 1 or 2 bands in the regions 321-333 and 335-347 mμ with extinction coefficients (E) of ca. $1\text{-}1.6.10^4$. Indolizines carrying one CH_2E substituent in addition to one or two ester groups attached directly to the five-membered ring show weak absorptions in the regions 292-7 and 303-9 mμ, and also exhibit 1 or 2 absorption bands in the ranges 339-342 and 346-356 mμ with extinction coefficients (E) of ca. $0.2\text{-}0.8.10^4$. The number of directly appended ester substituents in this latter group of indolizines can also be deduced from the data in Table I, since those indolizines carrying but one such substituent show 1 or 2 additional weak bands in the regions 365-373 and 380-385 mμ, features absent from the spectra

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Table II

Proton resonances (τ values) of indolizines

Compound	1-H	2-H	3-H	5-H	6-H	7-H	8-H	Ester-Me
[1]	5.97(CH_2)	-	2.28	2.26	3.23 - 3.69		2.71	6.17, 6.33
[2]	5.70(CH_2)	-	2.34	2.57	7.90(Me)	3.76	7.53(Me)	6.19, 6.31
[3]	3.26	-	5.59(CH_2)	2.27	3.53	7.71(Me)	2.84	6.10, 6.30
[4]	-	-	5.72(CH_2)	2.53	7.77(Me)	3.46	7.60(Me)	6.09, 6.13, 6.32
[5]	3.31	-	-	0.96	7.70(Me)	3.28	7.59(Me)	6.07, 6.10
[6]	-	-	-	0.74	7.69(Me)	3.06	7.37(Me)	6.06, 6.12, 6.18
[7]	-	-	-	0.57	3.06	2.71	1.75	6.07, 6.16(2)
[8]	-	-	-	0.58	3.11	2.92	7.33(Me)	6.04, 6.10, 6.15
[9]	-	-	5.91(CH_2)	2.04	3.18	2.87	1.83	6.05, 6.11, 6.30
[12][106]	3.72	3.36	2.86	2.24	3.69	3.50	2.75	-
[13][106]	4.08	7.76(Me)	3.14	2.44	3.94	7.80(Me)	3.14	-
[14][106]	3.98	7.76(Me)	3.14	2.54	7.86(Me)	3.69	2.96	-

where two such ester groups are present.

The nuclear magnetic resonance data are presented in Tables II - IV. The deductions of the actual structures of the previously unknown indolizines are based largely on these results. The spectra of the indolizines [1] and [6] - [11] whose structures were assured by previous chemical investigations[68,105,107] will be discussed first. The general observations to be made are as follows:

(i) comparison of the chemical shifts of protons in the indolizines bearing ester groups with those of the corresponding protons in the indolizines [12] - [14], reveals that the greater the number of ester groups in conjugation with the ring the lower the field position of the resonances of all protons, including those non-adjacent to such ester groups, (e.g. H-6 or H-7).

(ii) an ester group at the 3-position deshields the adjacent 5-proton very strongly as is clear from comparison of the H-5 resonance in [12] with those for [7], [8].

(iii) an ester group at the 1-position deshields the adjacent 8-proton less strongly than case (ii), as is clear from comparison of the H-8 resonance in [12] with those for [7], [9].

(iv) a methoxycarbonylmethyl substituent at the 3-position has a small uncertain effect on the adjacent 5-proton, as evidenced by the data for [12], [13] compared with that

for [9] and [4].

Exact measures of the effects described in (ii) - (iv) cannot be given since each value obtained from Table II for the difference of chemical shift of two corresponding protons in two indolizines comprises the sum of up to three different effects, viz. (a) the general effect described in (i) which, as a further complication, is not the same for each position of the indolizine ring, (b) the effects (deshielding) described in (ii), (iii) and (iv), and (c) the shielding effect of any neighbouring methyl groups.

Table III

Proton resonance (τ values) for the benzoindolizines.

Compound	5-H	6-H	7,8,9-H	10-H	Ester-Me
[10]	0.79	2.87	2.31-2.54	0.62	6.00, 6.06(2)
	5-H	6,7,8-H	9-H	10-H	Ester-Me
[11]	1.93	2.17-2.60	2.43	1.82	5.97, 6.01, 6.06

Particular comment about the assignments for the indolizines [1] and [6] - [11] are as follows:

(i) Assignments for compound [6] are based on observations made from [12] - [14] that H-5 is always at much lower field than H-7, as are those for the indolizine [8] in which the possible alternative 6-methyl formulation is eliminated by the total splitting (13.2 c/s) of the high field (3.11τ) triplet assigned to H-6. In view of the methyl group absorption in compound [8], the lower field methyl group in

Table IV

Coupling constants in (c/s) for the indolizines

Compound	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{5,7}$	$J_{6,8}$
[1]	7.1	?	9.0	0.9	1.1
[2]	-	-	-	1.0	-
[3]	7.2	-	-	-	1.7
[4]	-	-	-	1.0	-
[5]	-	-	-	1.0	-
[6]	-	-	-	1.2	-
[7]	6.9	6.8	9.1	1.4	1.7
[8]	6.5	6.7	-	1.2	-
[9]	6.9	ca. 7	8.6	1.3	1.5
[10]	7.5	-	-	-	-
[11]	-	-	9.1*	-	-
[12][106]	6.8	6.4	9.0	1.0	1.0
[13][106]	7	-	-	-	2
[14][106]	-	-	8	2	-

* This is the equivalent coupling constant $J_{9,10}$ in [11].

indolizine [6] is assigned to the 8-position.

(ii) Assignments for compound [7] are clear cut if two apparently valid generalisations are observed, viz. (a) that $J_{5,6} < J_{7,8}$, and (b) proton 6 is always at higher field than proton 7 in the absence of the effect of methyl groups. These two generalisations are apparent from observation of the data presented in Tables II and IV, most of which allows of no alternative interpretation and consequently can be used to support these rules.

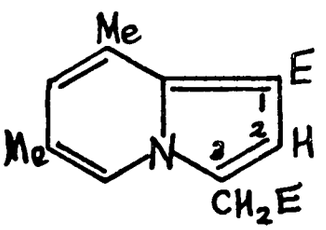
(iii) Application of these same rules results in the assignments presented for compound [9] showing the only case in which H-8 is found at lower field than H-5, these last results being consistent with the nature of the 1- and 3-substituents.

(iv) By analogy with the indolizines, the benzoindolizine [10] has H-5 at much lower field than H-10 in compound [11] (see Table III). The rule regarding $J_{5,6} < J_{7,8}$ is also supported by the data for compounds [10] and [11].

The indolizine [1], by virtue of the chemical shifts of H-5 and H-8, 2.26 and 2.71 τ respectively, values close to those for these protons in indolizine [12] itself, could not have its ester substituent at other than position 2. The lone proton is observed at 2.28 τ and was consequently assigned to position 3 (2.86 τ in [12]) rather than position 1 (3.72 τ in [12]) as a deshielding of 1.44 τ by a single adjacent ester group in the same ring was thought unreasonable.

These assignments are in keeping with the formulation given by previous workers[81].

The formulation of indolizine [2] as the dimethyl analogue of compound [1] is quite obvious from comparison of its nuclear magnetic resonance spectrum with that of [1]. Before compound [1] had been isolated and its spectrum determined, the alternative formulation [17] for the indolizine [2] could not excluded on nuclear magnetic resonance data alone, but the presence of a proton at position 3 was



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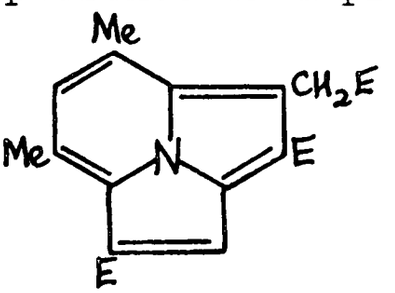

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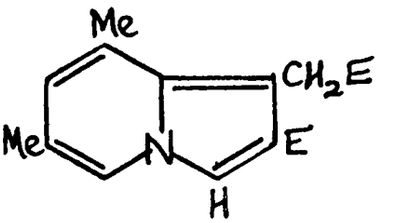


[2]

established by the conversion of indolizine [2] to the compound [18] with methyl propiolate in the presence of dehydrogenation palladium-charcoal (see later).

The spectral data for the indolizine [3] show that it is clearly not an analogue of compounds [1] and [2]. Again the ester group cannot be at positions 1 or 3 because of the chemical shift values for H-5 and H-8. The lone proton however is roughly 1 τ upfield from the lone proton in compounds [1] and [2], entirely in keeping with its assignment to position 1, since in indolizine [12], H-1 is upfield 0.86 τ from H-3.

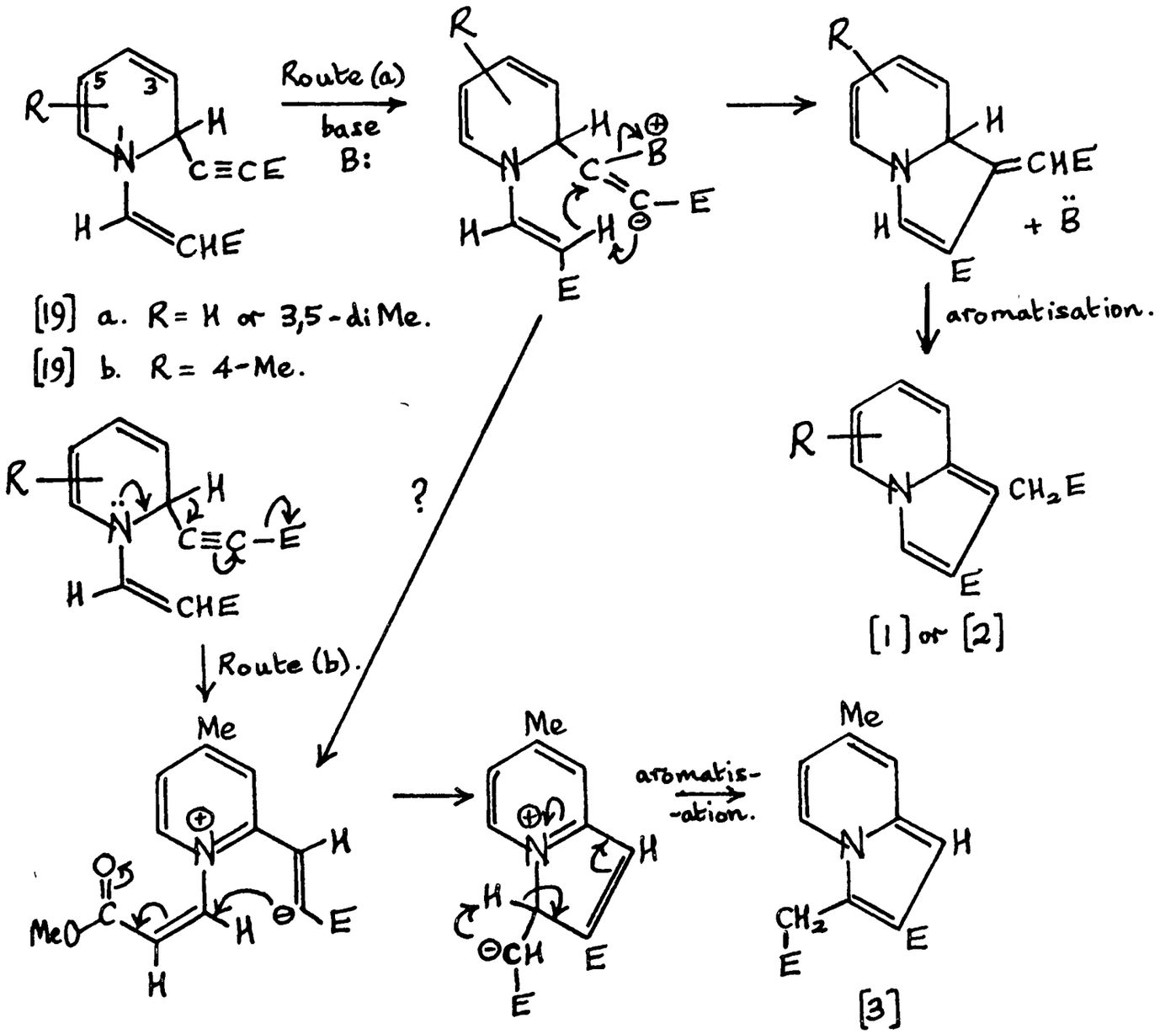
Compound [4] exhibits the spectrum expected in view of the data on the parent indolizine [9], though the shielding of H-5 by the 6- and 8-methyl groups to the extent of 0.49 τ is somewhat higher than anticipated from comparison of the data for compounds [6] and [7].

The last new indolizine, [5], shows a spectrum closely related to that of compound [6]. The effect of the loss of one ester group conjugated with the ring appears as a shift upfield of 0.22 τ for the 5- and 7-protons, whilst the 6-methyl group is virtually unaffected. The 8-methyl group however moves upfield by 0.22 τ which could be supporting evidence for the lone proton being at the adjacent 1-position. Consistent with this view is the observed resonance (3.31 τ), very close in value to that for H-1, 3.26 τ , in compound [3]. Additional support for this assignment is the fact that indolizine derivatives decarboxylate most readily at positions 1 and 3[108], and the loss from position 1 would doubtless be enhanced in the case of compound [5] because of the steric effects of the 8-methyl group.

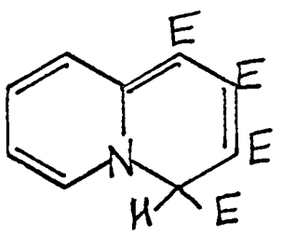
Finally in this section some suggestions will be put forward to account for the formation of the new indolizines described.

The compounds [1] and [2] from methyl propiolate and pyridines are most likely formed by ring closure in situ of first formed intermediates of type [19a]. The ring closure

of such a compound (see [16]) has been effected previously by piperidine[81], and it is feasible that residual unreacted molecules of the pyridines could give rise to similar base catalysed ring closure in situ. The mechanism proposed previously[81] is as shown (Route (a)).



The compound [3] may arise from intermediate [19b] via the scheme indicated above (Route (b)). Why one route should obtain in two cases and the other obtain in a third case cannot be explained, nor can the failure to isolate the intermediates [19a, b] under any circumstances, be accounted for.



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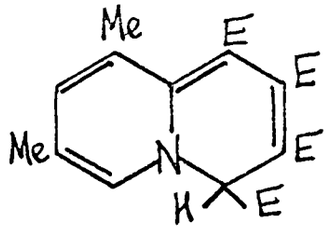

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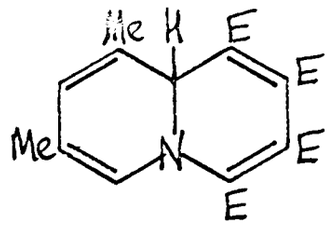


[15]

The oxidation of pyridine "stable" adduct [20] under a variety of conditions[109,68] is reported to yield the indolizine [7], whilst hydrolysis of the adduct [20] with various reagents[105] gave the indolizine [9]. It is possible that in the reaction of the "labile" adduct [15] with dehydrogenation palladium charcoal, some related oxidation process operates to give the indolizine [6], though whether this proceeds via the "stable" adduct isomer [21] is not certain. Trace quantities of isomer [21] were detected in the reaction, but should this be an intermediate which is then oxidised, then the failure of the "stable" adduct [20] to give any indolizine products becomes difficult to explain. The formation of indolizine [4] is unexplained, since it is difficult to imagine any parallel between the action of dehydrogenation

palladium charcoal and the hydrolysis, decarboxylation and ring contraction process involved in the conversion of compound [20] to the indolizine [9]. However, if indolizine [5] derives from its parent [6], and not from an oxidation process alone, some form of hydrolytic process must surely precede the decarboxylation step.

In view of the results of Chapter 1 the failure of the "stable" adduct [20] (recovery yield 71%) to react with phenylacetylene is not unexpected. Dimethyl acetylenedicarboxylate and [20] gave dimethyl fumarate (1.7% yield) and unchanged [20] (36% recovery). The somewhat unexpected products from the "labile" adduct [15] and palladium charcoal would not be expected to react with the phenylacetylene, even were this a sufficiently strong dienophile, since in all cases the 3-position of the indolizines is occupied (see Chapter 1). It is not clear why the "labile" adduct [15], (not recovered), palladium charcoal, and dimethyl acetylenedicarboxylate yield no characterisable products, though similar negative results are known (in the absence of the palladium charcoal)[23].

(ii) The Cycl[3,2,2]azines.

The products obtained from pyridine, 3-methylpyridine, 4-methylpyridine, and 3,5-dimethylpyridine with methyl propiolate have been formulated as the cycl[3,2,2]azine derivatives [22a - d] respectively.

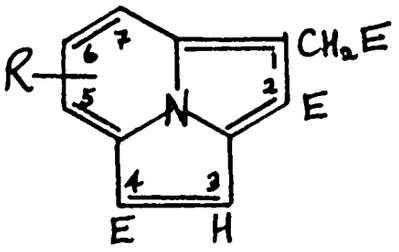
Table V

Ultraviolet spectral data, in $(E.10^{-4})$

Compound		Maxima					
[25]	(M)	234*(1.19)	240*(1.41)	248(1.76)	285.5*(0.36)		
[26a][43]	(E)	242*(3.54)	244(3.58)	248(3.23)	284(0.63)	274*(0.46)	280*(0.57)
[26b][42]			244(1.02)	247*(0.95)	285*(0.15)		
[25]	(contd.)	288(0.37)		403*(0.20)	411(0.23)	420(0.23)	432(0.17)
[26a]	(contd.)	289(0.73)	386*(0.33)	398(0.42)	408(0.45)	419(0.36)	
[26b]	(contd.)	290(0.19)	295(0.21)	299*(0.15)	395(0.10)	405(0.11)	413*(0.08)
[25]	(P)	229(0.95)	233.5(0.90)	244*(0.63)	277(0.34)		
[26a][43]	(P)	230(1.40)	235(1.47)	244*(0.85)	276*(0.44)		
[25]	(contd.)		282(0.33)	293(0.25)	343(0.28)		
[26a]	(contd.)	280*(0.47)	285(0.50)	295(0.34)	339(0.33)		

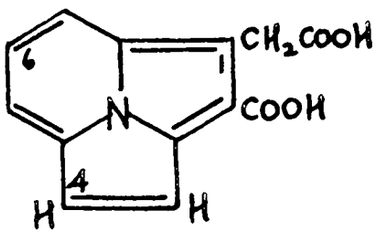
(M) = methanol; (E) = ethanol;

(P) = alcohol : 70% perchloric acid :: 1:4 by volume

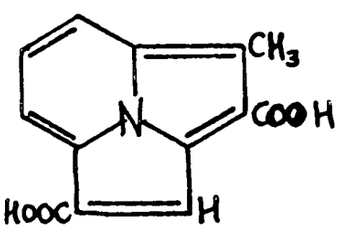


[22] a. R = H.
b. R = 7-Me.
c. R = 6-Me.
d. R = 5,7-di Me.

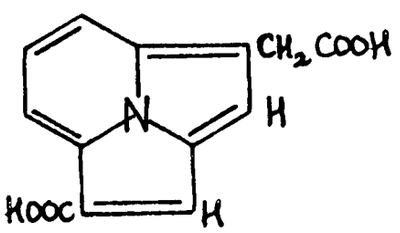
The evidence for this formulation is as follows. The compound [22a] obtained from pyridine and the ester was hydrolysed with methanolic potassium hydroxide at room temperature to give a product which is [23] or [24], identified only by its mass spectrum, the molecular weight and fragmentation pattern corresponding to a diacid derivative of compound [22a]. Isomer [24a] was excluded on previous experience[38,39,108] that 2-(or 3-) carboxyl functions are



[23]



[24]

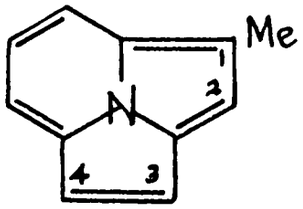


[24a]

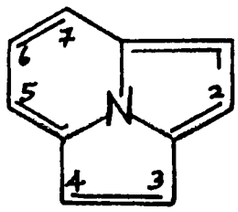
much less readily lost than the 1- (or 4-) carboxyl group. Decarboxylation of this diacid by copper chromite in quinoline gave compound [25] which is assigned the structure 1-methylcycl[3,2,2]azine on the following grounds.

(i) The ultraviolet spectral data for the compound shows a close similarity to the available data for cyclazines [26a] and [26b] as indicated in Table V. The feeble basicity of the cycl[3,2,2]-azine system[43,44] is indicated by

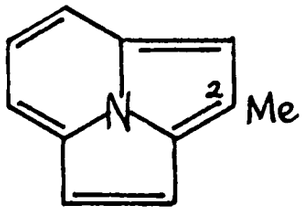
Structures Omitted.



[25]



[26] a.



[26] b.

the extreme acidity required to change its ultraviolet spectral characteristics.

(ii) The nuclear magnetic resonance spectrum of compound [25] shows the expected relationship to those of the known compounds [26a, b][41,42]. The data for these three compounds, for the initial adducts [22a - d], and for two further known cyclazines, are presented in Table VI.

Table VI

Nuclear magnetic resonance spectra (τ values) of cycl[3,2,2]azines.

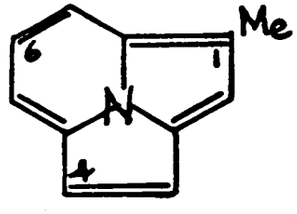
Compound	1-H	2-H	3-H	4-H	5-H	6-H	7-H	Ester - Me
[22a]	5.52 (CH_2)	-	1.85	-	1.56	2.20	1.94	5.94(2), 6.23
[22b]	5.38 (CH_2)	-	1.90	-	1.69	2.42	7.11 (Me)	5.97(2), 6.26
[22c]	5.56 (CH_2)	-	1.89	-	1.73	7.21 (Me)	2.16	5.98(2), 6.27
[22d]	5.41 (CH_2)	-	1.93	-	6.93 (Me)	2.66	7.19 (Me)	5.97, 6.01, 6.27
[25]	7.27 (Me)	2.68	2.53	2.85	2.12	2.43	2.17	-
[26a][42]	2.80	2.49	2.49	2.80	2.14	2.41	2.14	-
[26b][42]	3.07	7.26 (Me)	2.53	2.89	2.31	2.49	2.31	-
[27][42]	-	-	2.37	2.75	2.16	2.31	1.70	?
[28][42]	-	-	?(Me)	3.03	2.31	2.31	1.76	?

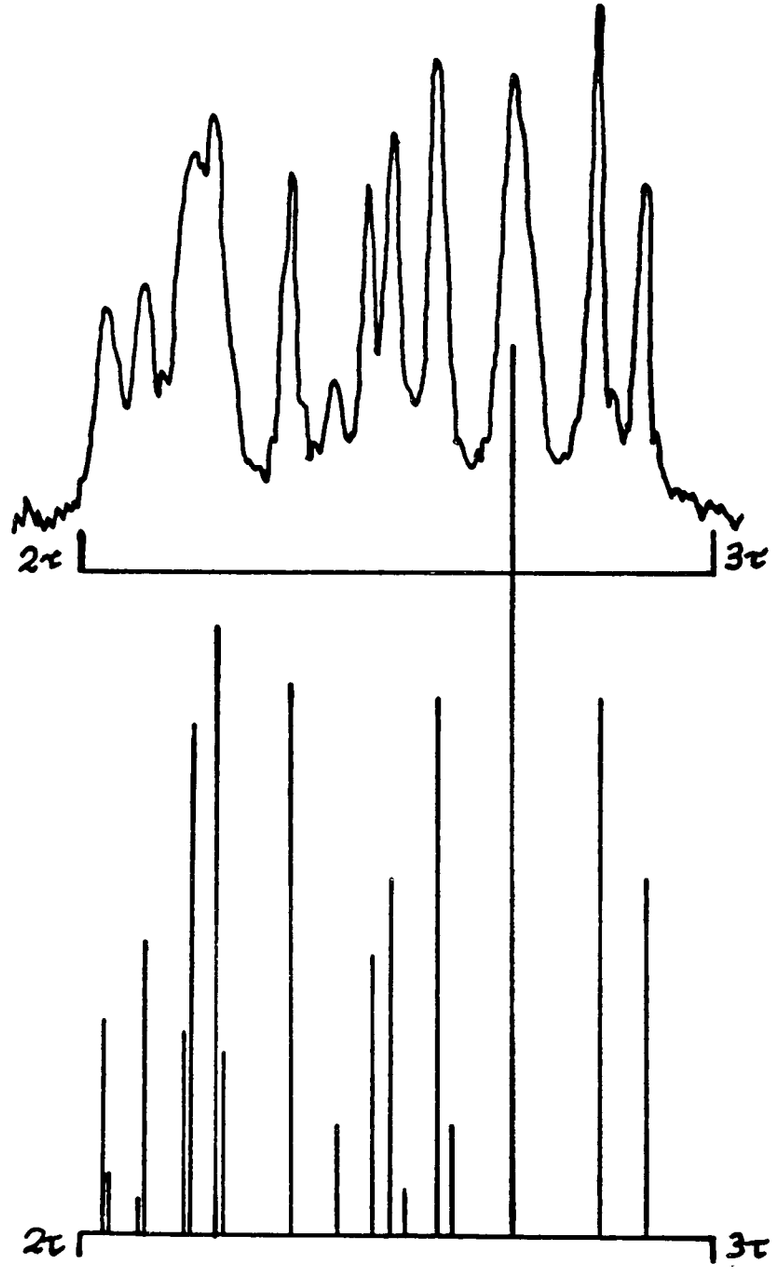
At this point comment will only be made regarding the nuclear magnetic resonance spectrum of compound [25]. This shows

FIGURE I.

Observed (upper)
and
Calculated (lower)

60 Mc/s N.M.R.
spectrum of





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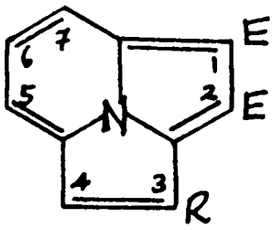
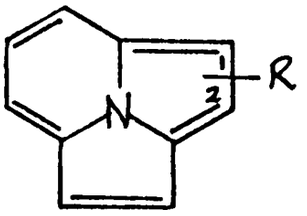
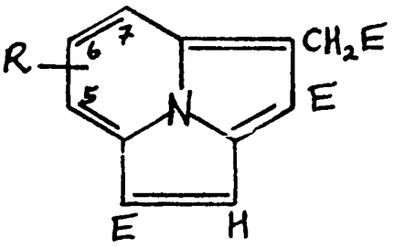


[27] R = H.
[28] R = Me.



[26] a. R = H.
b. R = 2-Me.
[25] R = 1-Me.

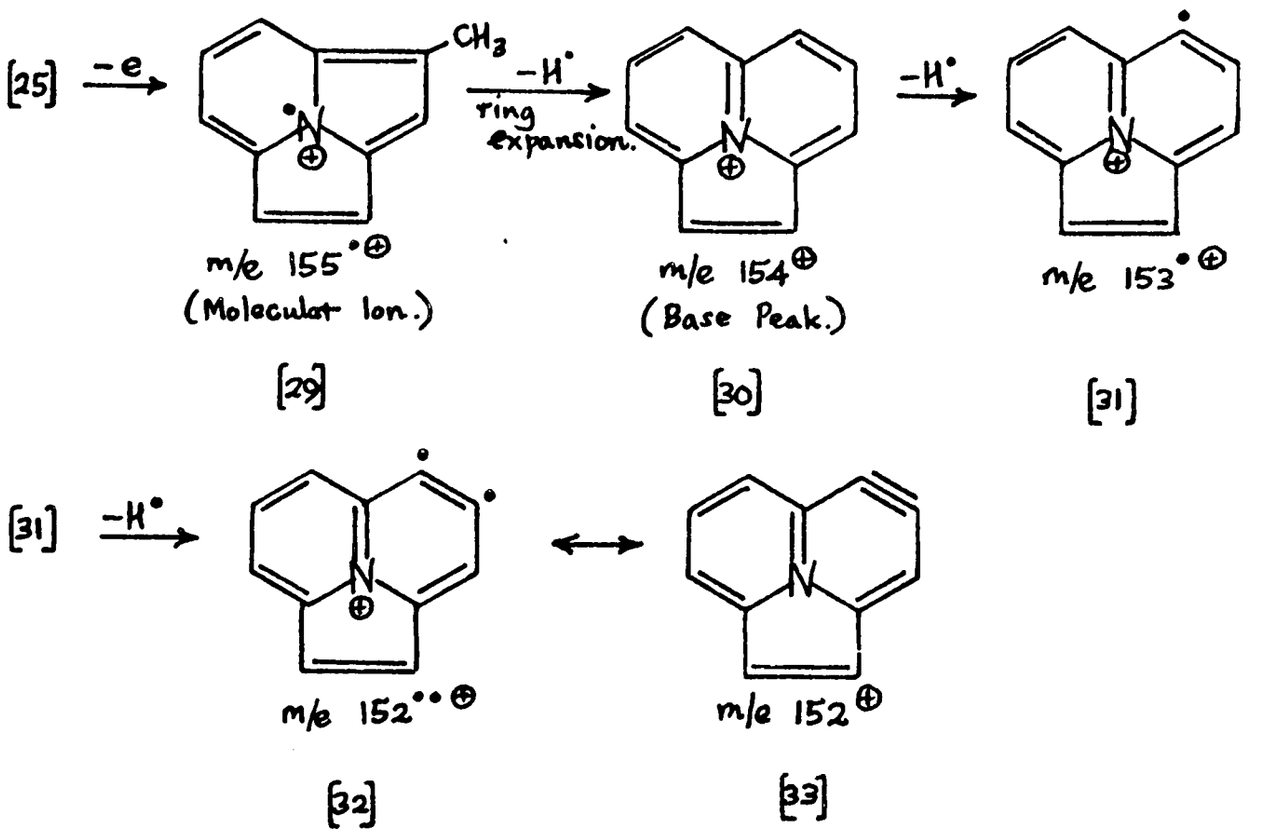


[22] a. R = H.
b. R = 7-Me.
c. R = 6-Me.
d. R = 5,7-di Me

both an AB and X and an ABC spectrum for protons 4,3 and 2, and 5,6,7 respectively. Figure I shows the excellent agreement obtained in both line position and line intensity between the calculated[110] and the observed 60 Mc/s spectra in deuterochloroform. In contrast to 2-methylcycl[3,2,2]-azine [26b], compound [25] must have its methyl group at one of the equivalent positions 1 or 4, since the chemical shifts of H-5 and H-7 are no longer identical, as obtains for compounds [26a, b]. Finally, the coupling constants observed[41] in compound [26a], viz. $J_{1,2} = J_{3,4} = 4.2$ c/s, $J_{5,6} = J_{6,7} = 8.0$ c/s, and no inter-ring coupling, are in good agreement with the values $J_{3,4} = 4.3$ c/s, $J_{5,6} = J_{6,7} = 8.0$ c/s, which were used in the calculation of the optimum theoretical spectrum of our product [25]. In addition $J_{5,7} = 0 - 0.5$ c/s, and all other possible J values are again zero.

(iii) The mass spectrum of compound [25] gives its molecular

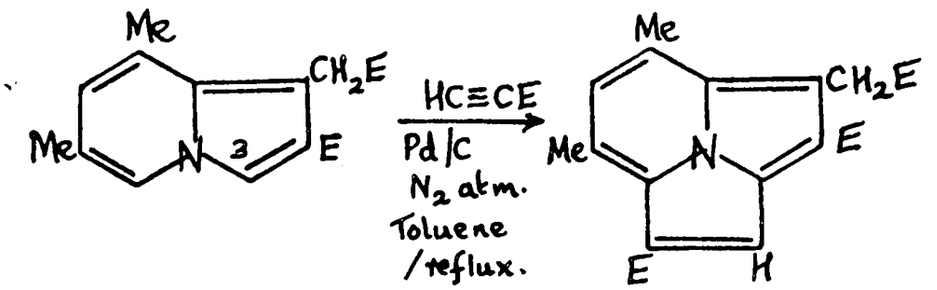
weight as 155 in accord with its formulation and corresponding to $C_{11}H_9N$. Substantiation of the molecular formula from the intensity of the statistical peak at m/e 156 is not readily accessible because of the complication of important peaks at m/e 154, 153 and 152. The spectrum contains only the following significant peaks; m/e (% age of base peak): 156(7.0), 155(61.5), 154(100)-base peak, 153(13.8), 152(8.4), 77.5(5.1), 77(10.6), 76.5(2.4), 76(1.3). No similar data for other known cyclazines has been published so comparisons here are not possible. The great stability of the cycl[3,2,2]azine system expected for an aromatic molecule is apparent from the data presented, no carbon containing fragments being lost from the molecular ion. The last four peaks described are very probably the doubly charged forms of the preceding four peaks. The step-wise loss of three protons may be accounted for by the following scheme:



Each form shown has of course a number of other canonical forms contributing to the resonance system. The most interesting proposal is the ring expansion involved in the 155 → 154 transition which has parallels in the classical instance of the toluene → tropylium transition[134]. The resultant cycl-[3,3,2]azinium cation [30] will be aromatic in the same way as the isoelectronic molecule acenaphthylene[35]. In support of this transition the allegedly aromatic cation [30] shows two much weaker derivative peaks corresponding to the loss of one and two hydrogen atoms. The molecular ion [29] still has the required 10 π - electrons for aromatic character and the

stability is mirrored in the intensity of the peak at m/e 155.

(iv) The final confirmatory evidence for the cycl[3,2,2]-azine nature of the adducts [22a - d] and their degradation products, comes from the synthesis of compound [22d] from the indolizine [34] by the standard indolizine to cycl-[3,2,2]azine method of Boekelheide[38] using methyl propiolate. The synthesis was undertaken in the first place to determine



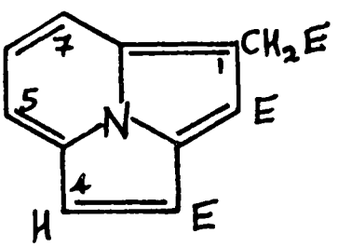
[34] [22d]

whether or not the 3-position of compound [34] was substituted (see section (i) of Chapter 4; also Chapter 1 on the Diels-Alder adducts of indolizine). Synthetic [22d] was identical with the product obtained from the direct action of methyl propiolate on 3,5-dimethylpyridine on all four forms of spectral evidence.

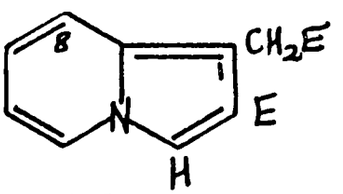
The adducts themselves [22a - d] also require some further comment. That the four products were clearly derivatives of the same parent was clear not only from their nuclear magnetic resonance spectra (see Table VI) but also from their ultraviolet spectral properties. Satisfactory elemental analyses in accord with the formulations given

were obtained for compounds [22a, b, and d], too little material of product [22c] being obtained to allow analysis of a pure sample. No trace of the isomer of product [22b], i.e. the 5-Me derivative, was obtained.

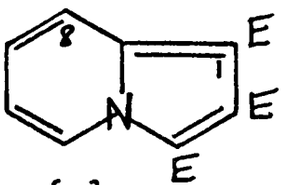
The alternative formulation of the compounds as the isomeric series [35] was rejected for the following reasons: (i) In the nuclear magnetic resonance spectrum of compound [22a] H-5 is deshielded by the ester group at position 4 by 0.38 τ relative to H-7, a value which compares favourably with



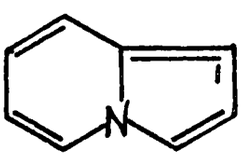
[35]



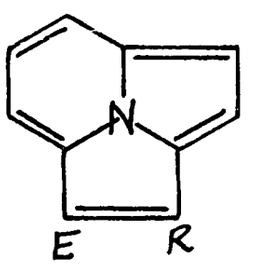
[1]



[7]



[12]



[36] R = Ph or H.

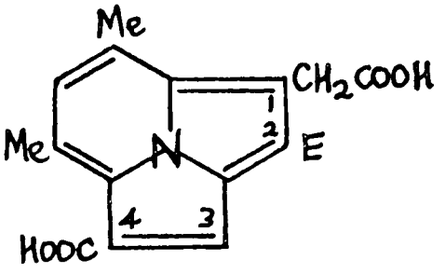
the parallel effect observed for the indolizine[7] in which H-8 is deshielded by the 1-ester group. Similarly in the cyclazine [27] the 1-ester group deshields H-7 by 0.46 τ relative to H-5. For the alternative formulation [35] it would be necessary to postulate that H-7 was deshielded 0.38 τ relative to H-5 by the 1-methoxycarbonylmethyl group in adduct [35]. This would be at variance with experience for the equivalent effect observed in the indolizine series,

particularly for e.g indolizine [1], where (see section (i) of this chapter) the proximity effect of the 1-methoxycarbonylmethyl group on H-8 in compound [1] as compared with the H-8 resonance in indolizine [12] is negligible after other factors have been taken into account. The alternative formulation [35] would require the singlet at 1.85 τ in [22a] to be assigned to H-4, which is a resonance position 1.0τ to lower field than is observed in the parent compound [25]. By comparison of the H-6 resonances for compounds [22a] and [25], a downfield shift of ca. 0.23τ is to be expected for all protons due to the effect of having added two conjugated ester groups to the ring system. This leaves an additional ca. 0.77τ shift to lower field of H-4 in compound [35] to be attributed to the deshielding effect of the adjacent 3-ester group. However with the formulation adopted, the amount of the shift to lower field of H-3 in [22a] which has to be attributed to the deshielding effect of the 4-ester group is ca. 0.45τ , a much more acceptable value in view of our experience with the indolizine series of compounds.

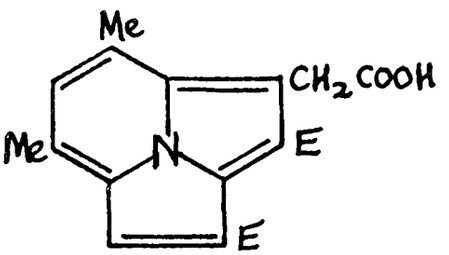
(ii) The mode of orientation of methyl phenylpropiolate and methyl propiolate to indolizine [12] is shown in the product [36][38,40]. It is probable then that the orientation in the addition of methyl propiolate to the indolizine [34] will be the same, so that the synthetic cyclazine will be of the form [22d]. As stated earlier this synthetic material is

identical with [22d] obtained direct from the reaction mixture.

(iii) The hydrolysis product of cyclazine [22d] has been established by its mass spectrum and nuclear magnetic resonance spectrum in pyridine solution to be a mono-ester di-acid, probably the compound [37]. Previous workers found[38] that the 2-ester group of the 3,4-dihydro-derivative of the



[37]



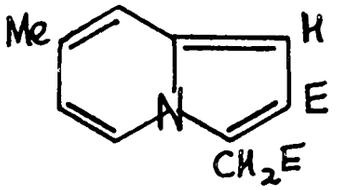
[38]

cyclazine [27] resisted hydrolysis, and it is for this reason that the residual ester group in compound [37] is assigned to position 2. Had the adduct the alternative formulation (type [35]) the hydrolysis product would probably be a di-ester mono-acid, i.e. [38], should a parallel with the above experience occur in this particular instance.

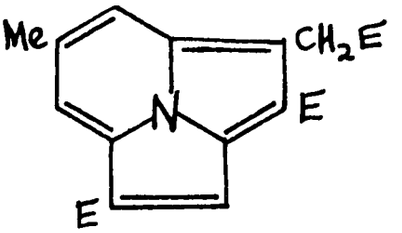
The only fact which can be gleaned from the nuclear magnetic resonance spectrum of the mixture of products obtained from the bromination of compound [22d] is that bromination has occurred at position 6 (if not elsewhere as well), there being no resonance in the spectrum around 2.7τ It has been shown[35,40] that electrophilic aromatic substitution in cycl[3,2,2]azine [26] occurs at positions 1 and/or

4. In compound [22d] these positions are occupied, and the five-membered rings are deactivated for electrophilic substitution by virtue of their ester group substituents.

The mechanism of formation of the cyclazines [22a - d] would seem either to involve the initial formation of the intermediate indolizine (as outlined in the section on Indolizines) with subsequent addition of a third mole of methyl propiolate across the 3,5-positions in situ. Or to involve attack by this third mole of the ester prior to the ring closure of the monocyclic form of the 2:1 adduct, or at least prior to the hydrogen shifts of the first formed bicyclic 2:1 adduct which lead to its aromatisation to the indolizine form. The postulated indolizine intermediate of the first scheme has been isolated in the case of pyridine and its 3,5-dimethyl derivative only. The indolizine [38a] isolated from 4-methyl-pyridine was one incapable of adding



[38a]



[22c]

a third mole of methyl propiolate in the above manner, though the cyclazine [22c] was also isolated. In the case of 3-methylpyridine, no indolizines were detected. These results

are not sufficient in themselves to allow us to favour one mechanistic pathway over its alternative.

2-Methylpyridine and methyl propiolate gave a tar from which no cyclazine-type products were isolated. This result is in accord with the proposed modes of formation since any indolizine from 2-methylpyridine will have a 5-methyl substituent preventing the proposed formal addition of a third mole of methyl propiolate across the 3,5-positions of the indolizine.

(iii) Other adducts from pyridines and methyl propiolate.

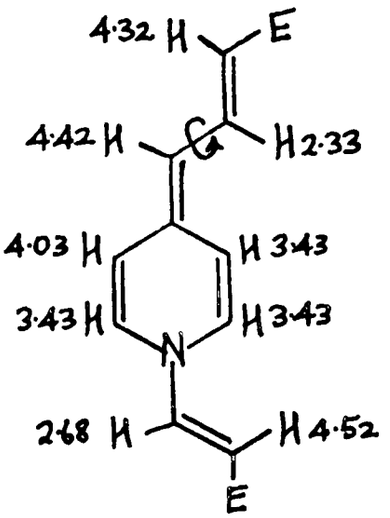
(a) From 3-methylpyridine.

No structure can be suggested for the red-brown adduct described in the experimental section owing to the tiny quantity of material isolated. Its ultraviolet spectrum resembles that of the dark red adduct from 4-methylpyridine (vide infra).

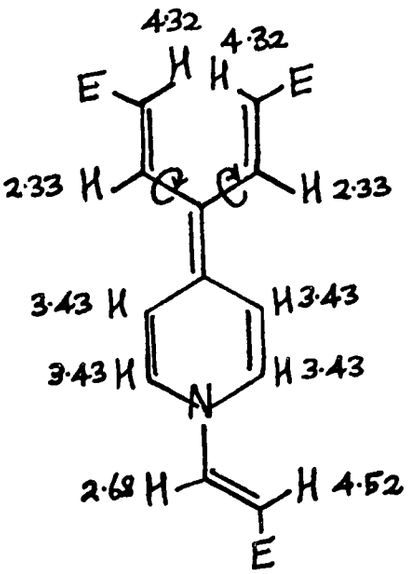
(b) From 4-methylpyridine.

It is not possible to be sure on the evidence of the infrared and ultraviolet spectra whether the two dark red adducts obtained from this pyridine, one from the reaction in ether the other from the reaction in acetonitrile, are one and the same compound in differing states of purity. Most probably they are different, but closely related, compounds. The dark red adduct from the reaction in ether had its nuclear magnetic resonance

spectrum measured, the data being summarised as follows: 2.02 - 2.84 τ , multiplet, 3 protons; 3.09 - 3.60 τ , multiplet, 3 protons; 3.84 τ , broad singlet, 1 proton; 4.13 - 4.54 τ , multiplet, 3 protons; 6.17, 6.23(2) τ , ester groups (3 in all). From these results alone we are not able to suggest a firm structure for the dark red adduct, other than to say that from the integration of the spectrum a total of 19 protons and 3 ester groups corresponds to an adduct from 1 mole of 4-methylpyridine and 3 moles of methyl propiolate. Also the absence of any C-methyl resonance in the spectrum necessitates some involvement of the 4-methyl group in the precursor in the formation of the adduct. In view of the structure [39] proposed (and supported) below for the orange adduct, with the nuclear magnetic resonance assignments (τ) as indicated, the 3:1 adduct [38b] derived from adduct [39], might, on rather superficial reasoning, have the n.m.r. characteristics appended. It is seen that these n.m.r. assignments summarised as 2.33 and 2.68 τ , 3 protons; 3.43 τ , 4 protons; and 4.32 and 4.52 τ , 3 protons, are compatible with observed results for one of the dark red adducts. Thus [38b] is a possible structure for this adduct not excluded by the available data.

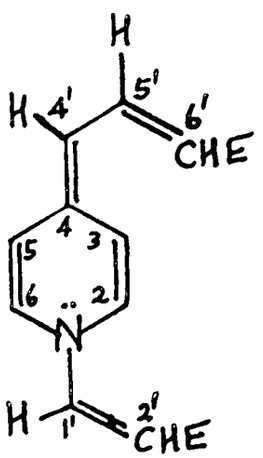


[39]

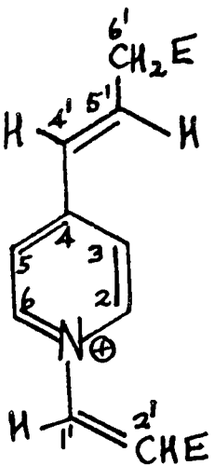


[38b]

The orange adduct isolated from 4-methylpyridine and methyl propiolate has been intensively studied by nuclear magnetic resonance techniques and the structure [39] is proposed to account for the observed results in conjunction with the ultraviolet and mass spectral data.



[39]



[40]

The 100 Mc/s nuclear magnetic resonance spectra were kindly measured by Dr. M. Takeuchi of Japan Electron Optics

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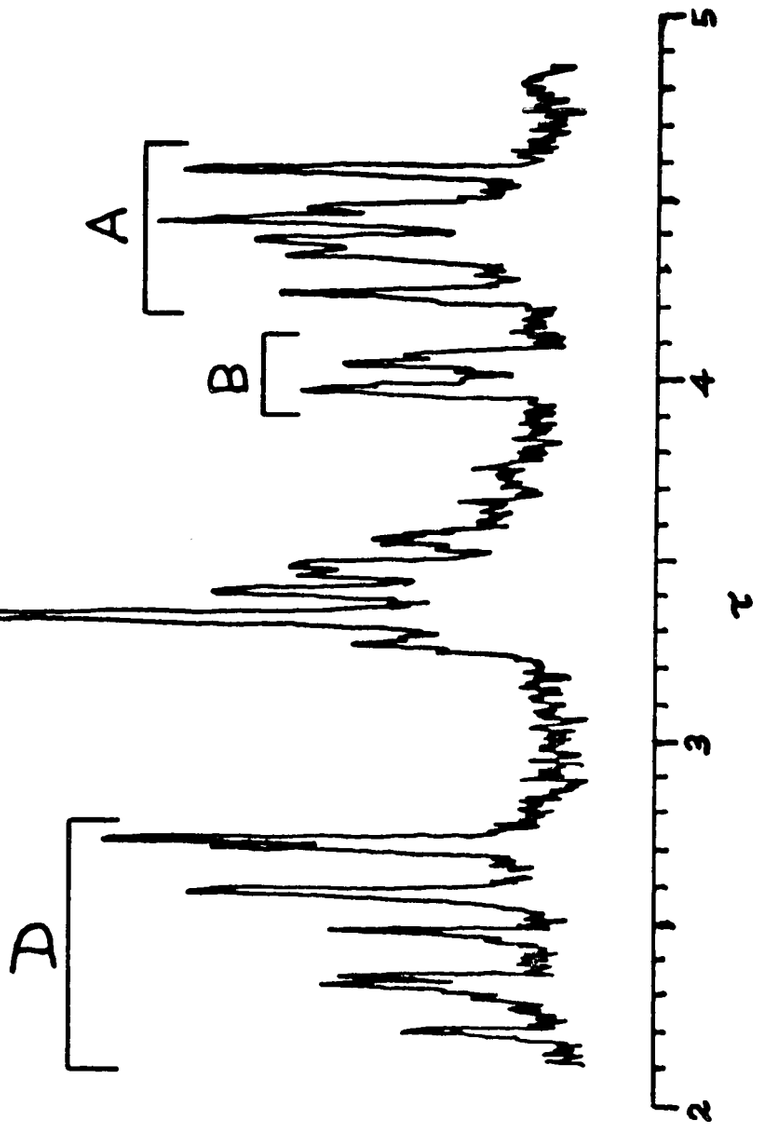
FIGURE II.

100 Mc/s N.M.R. Spectrum of [39].



Laboratory Co. Ltd., Tokyo on the instrument in the Inorganic Chemistry Department at Oxford, and he also carried out the spin decoupling experiments on a similar instrument at JEOLCO (Europe) S.A. in Paris. The spectrum is shown in Figure II with the four groupings of the protons A, B, C, and D indicated

The positions of each resonance line of the protons of compound [39] at both 60 and 100Mc/s (in deuterochloroform) were carefully measured in c/s from TMS, and in conjunction with the integration results for the 60Mc/s spectrum, the first breakdown of the spectrum is as shown in Table VII. The ester-methyl resonances (100Mc/s) in [39] occur at 6.25 and 6.27τ .

The extent of the decoupling investigation was not quite as wide as one would have wished, but the results from the spectra returned from Dr. Takeuchi are summarised in Table VIII.

Table VII

Nuclear magnetic resonance data for compound [39].

Grouping Main	Sub.-	Integration	Chemical shift (τ) and coupling constant (c/s). 60 Mc/s.	100 Mc/s.
D	(i)	1 proton	2.33; J=13 + 14.8	2.37; J=12.2 + 14.3
D	(ii)	1 proton	2.65; J=13.8	2.68; J=13.6
C	-	3 protons	3.42*; complex	3.43*; complex
B	-	1 proton	4.02; J=1.9 + 7.9	4.03; J=2 + 8.5
A	(i)	2 protons	4.35*; 4 lines	4.36*; 4 lines
A	(ii)	1 proton	4.52; J=14.1	4.52; J=13.7

*centre of the complex multiplet.

Table VIII

Decoupling results (100 Mc/s) for compound [39].

Point of irradiation	Effect on remainder of spectrum.
D(i) (scanned)	A(i) decoupled in complex and variable manner.
	A(ii), B, C unaffected; D(ii) not observed.
C* (centre point)	B collapses to a singlet.
	A(i),(ii) unaffected; D not observed.
B (high field doublet only).	C slight change discernible.
	A, D not observed.
A (exact point uncertain).	D(i) affected in complex and variable manner.
	D(ii) unaffected; B, C not observed.

The 4 lines forming the two protons of group A(i) were subjected to further scrutiny as a consequence of the decoupling results, which suggested a coupling between the 4 lines of D(i) with 4 of the 6 lines of the whole group A, the remaining 2 lines of group A, now called A(ii), being, as far as could be discerned, not coupled to any of the protons in groups B and C, being coupled most probably to the proton

denoted by D(ii). The results of the detailed inspection of the lines in A are set out in Table IX with the relevant data for the lines in group D.

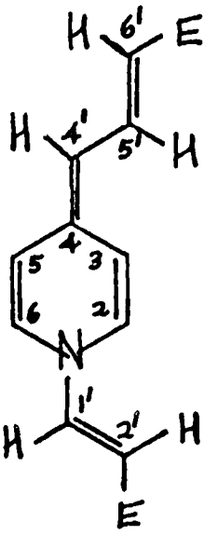
Table IX

Line separations in Groups A and D in compound [39].

Group and lines.		Separation (c/s).	
		60 Mc/s.	100 Mc/s.
A;	lines 1 and 4. (A(i)).	15.1.))27.6	-
A;	lines 2 and 5. (").	12.5.)	-
A;	lines 1 and 3. (").	-	14.7.))26.7
A;	lines 2 and 5. (").	-	12.0.)
D(i);	lines 1 and 4.	13.0+14.8=27.8	12.2+14.3=26.5
A;	lines 3 and 6. (A(ii))	14.1.	-
A;	lines 4 and 6. (").	-	13.7.
D(ii);	2 lines only.	13.8.	13.6.

In view of the excellent agreement between the component splittings of the D(i) quartet and the splittings of the two groups of two lines comprising A(i), the two protons previously described as centred at 4.36 τ were now separately assigned to 4.32 and 4.42 τ in the 100 Mc/s spectrum on the assumption that both coupled only with the proton labelled D(i).

These results led to the following assignments for compound [39] being made to accommodate all the observed data.



[39]

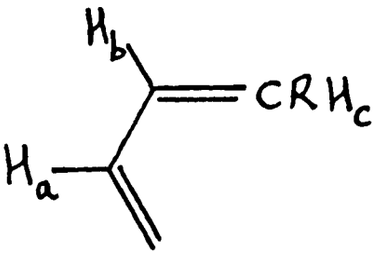
Table X

Proton resonances (τ values) and coupling constants (c/s) in [39].

Group.	Proton position.	Chemical shift and coupling constants. (100 Mc/s)
C	H-2,6 and 3 (or 5).	3.43 (centre); complex multiplet.
B	H-5 (or 3).	4.03; $J_{ortho} = 8.5$; $J_{meta} = 2.0$
D(ii)	H-1^1	2.68; $J_{1^1,2^1} = 13.6$
A(ii)	H-2^1	4.52; $J_{1^1,2^1} = 13.7$
A(i)	H-4^1	4.42; $J_{4^1,5^1} = 12.0$
D(i)	H-5^1	2.33; $J_{4^1,5^1} = 12.2$; $J_{5^1,6^1} = 14.3$
A(i)	H-6^1	4.32; $J_{5^1,6^1} = 14.7$

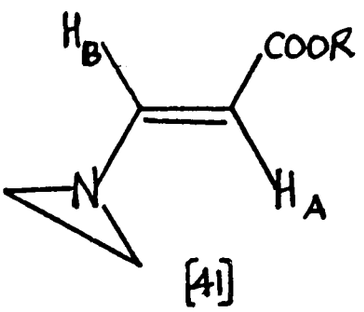
In addition to fitting all the evidence so far available, the following factors support these assignments:

(i) The expected coupling constants for the system illustrated below are $J_{a,b} = 10 - 13$ c/s and $J_{b,c} = 6 - 14$ c/s



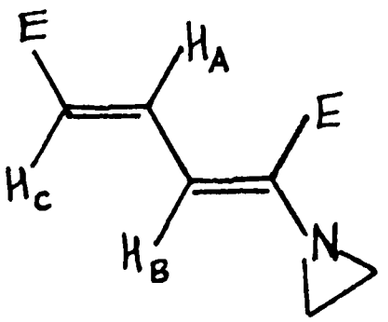
(cis) or 11 - 18 c/s (trans)[111]. For this reason the $5^1,6^1$ - double bond will certainly have the trans configuration and the $1^1,2^1$ - double bond almost certainly so, in view of the observed coupling constants. The observed value for $J_{4^1,5^1}$ is within the range given above for the similar couplin $J_{a,b}$.

(ii) The assignments of H-1^1 and H-2^1 to 2.68 and 4.52 τ respectively is in good agreement with the reported[112] values of 2.60 and 4.75 τ for H_B and H_A in the system [41]. Further, the observed $J_{A,B}$ = 13.5 c/s, is closely similar to our value for $J_{1^1,2^1}$.

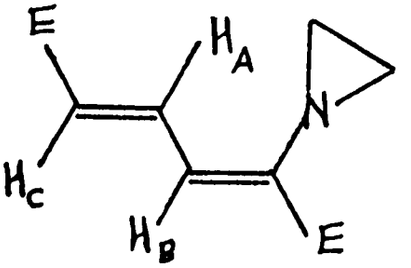


[41]

(iii) Some support for the assignments to H-5^1 and H-6^1 of the resonances at 2.33 and 4.32 τ is found in the data for H_A and H_C respectively, in the molecules [42] and [43], and good agreement with the observed coupling constants is also to be seen.



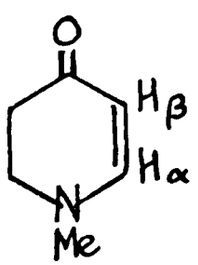
[42]



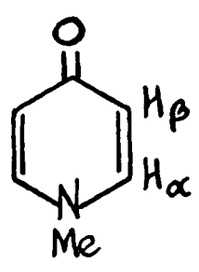
[43]

Compound	Chemical Shifts (τ values).			Coupling constants (c/s).	
	H_A	H_B	H_C	J_{AB}	J_{AC}
[42][112]	2.05	4.05	4.20	11.5	15
[43][112]	2.24	3.70	3.35	12.0	15

The features of the assignments given for compound [39] which are the most difficult to reconcile and for which little justification from the results of other workers is to be found, are the chemical shifts of the ring protons. It is not clear why three of the four ring protons should have such similar τ values; in other words, why one of the protons β to the nitrogen atom is at 0.6 τ to lower field than the other. In a variety of 1,4-dihydropyridines the observed chemical shifts for the α-protons fall in the range 3.30 to 4.49 τ, whilst the β-protons are found at 5.47 to 5.89 τ [113]. The structure [39] however is a more conjugated



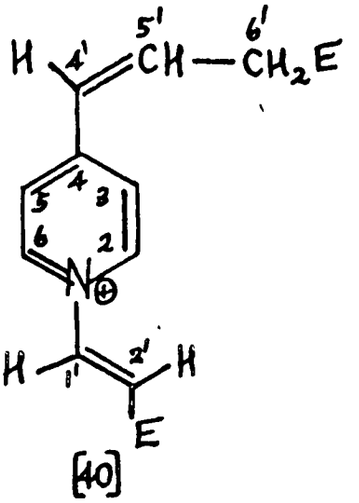
[44]



[44]a.

system than a 1,4-dihydropyridine, and is also more conjugated than the compound [44][112] for which H_α is at 3.0τ and H_β at 5.25τ. An additional double bond in the ring and added conjugation through the 4-position of compound [39] could conceivably be expected to cause the β-protons to move downfield to a value as low as 4.03τ. Supporting evidence for this supposition regarding the effect of additional conjugation is that in compound [44a], of which compound [44] is the dihydro-derivative, H_α is at 1.88τ and H_β at 3.12τ [135], figures representing a shift of 1.12 - 2.13τ to lower field. The observed position of the α-protons in adduct [39] is closer to experience as the above figures indicate.

Strong support for formula [39] being the correct structure of the adduct is found in the nuclear magnetic resonance spectrum in trifluoroacetic acid. Protonation of form [39] would be expected to give the cation [40] as the most conjugated system, and the spectrum observed is in harmony with this formulation as indicated in Table XI. The ester-methyl resonances are found at 5.92 and 6.03τ.



[40]

Table XI

Chemical shifts (τ) and coupling constants (c/s) of compound [40].

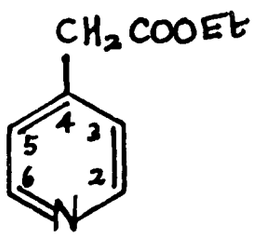
Proton position.	Chemical shift and coupling constants. (60 Mc/s)
H-2,6	0.96, 1.07; J_{ortho} = 6.9; superimposed doublets.
H-3,5	1.84(2 protons); J_{ortho} = 6.9; doublet.
H-1^1	1.55; $J_{1^1,2^1}$ = 14.1; doublet with further splitting of 3.6 c/s.
H-2^1	2.99(?); $J_{1^1,2^1}$ = 14.1; doublet.
H-4^1,5^1	2.84 (centre of complex multiplet).
6^1-H's (CH_2).	6.31; $J_{CH_2,5^1-H}$ = 6.4; $J_{CH_2,4^1-H}$ = ca.2; quartet.

The satisfactory features of the interpretation of the data presented in Table XI are as follows:

(i) The pyridine ring protons in compound [40] are downfield

of the values observed[114] for the related compound [45] by amounts compatible with the effect of going from a neutral molecule to the cationic species (see Chapter 3, Table II, for the observed parallel effect for 3,5-dimethylpyridine).

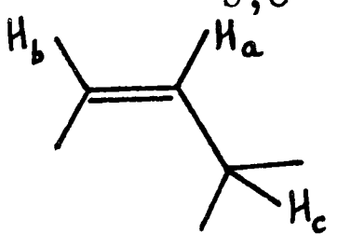
$J_{2,3}$ = 5.4 c/s;
$J_{2,5}$ = 0.8 c/s;
$J_{2,6}$ = 0.4 c/s;
$J_{3,5}$ = 1.5 c/s.



[45]

H-2,6 1.31τ
H-3,5 2.56τ
4-CH_2 5.92τ

(ii) The methylene group proton resonance is at higher field than found for compound [45] in harmony with the indirect attachment of the group to the aromatic ring in compound [40]. The observed[111] coupling constants for the system below are $J_{a,c}$ = 4 - 10 c/s, and $J_{b,c}$ = 0.5 - 2.0 c/s, and our



observations are in agreement with these figures.

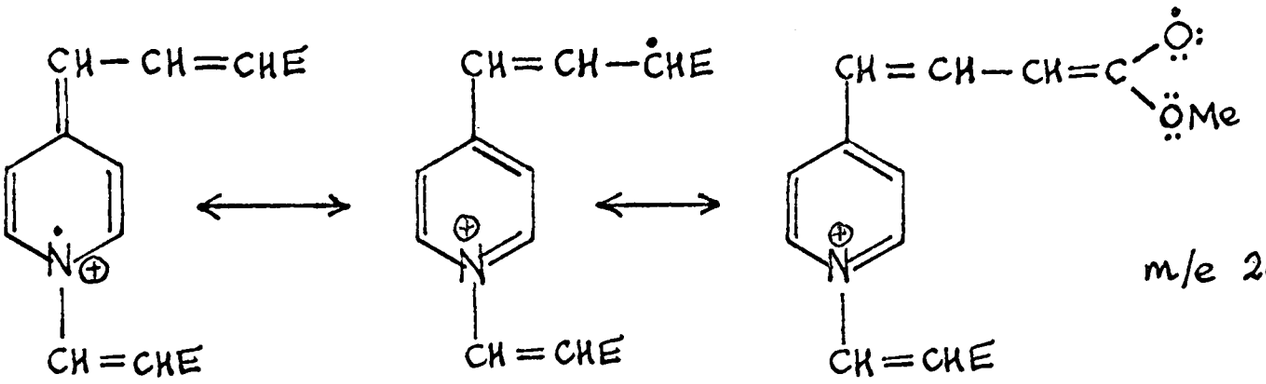
(iii) Of the remaining exo-cyclic protons all except H-5[1] are at lower field in form [40] than in the neutral species [39], in keeping with their attachment in the case of compound [40] to a positively charged aromatic system. It is suggested that in form [39] H-5[1] was strongly deshielded by

the rigidly held 6^1-ester group, whilst in form [40] this deshielding is reduced if not altogether removed by the free rotation possible now about the $5^1,6^1$-carbon-carbon single bond.

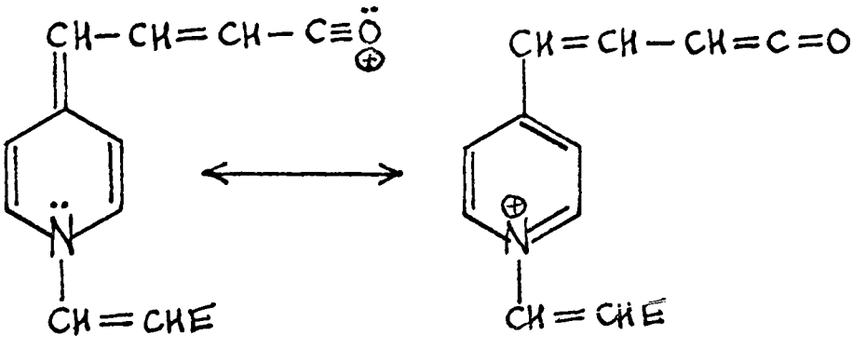
The unsatisfactory features of the spectrum are two. The main reason for these unsatisfactory aspects of the spectrum and its interpretation may be the poor signal-to-noise ratio in trifluoro-acetic acid. Left unexplained by the assignments proposed are the following:
(i) The apparent absence of the $J_{3,5}$ splitting described as 1.5c/s for the model compound [45]. (ii) The apparent further splitting of ca. 3.6c/s of the doublet attributed to H-1^1. This could be spurious owing to the signal-background ratio.

The mass spectrum of the adduct [39] gives the molecular weight as 261 and the intensity of the observed statistical peak at m/e 262 is in good agreement with the value calculated on the basis of the molecular formula $C_{14}H_{15}NO_4$. Major peaks (m/e values) and their intensities as a %age of the base peak are as follows: 261(100), 260(18.0), 246(27.0), 230(73.0), 203(14.2), 202(41.5), 201(11.9), 170(13.1), 117(19.0), 116 (11.5). The great stability of the molecular ion (M) and the fragment at m/e 230, i.e. M-31, corresponding to the loss of methoxyl, may be due to the high degree of conjugation or aromatic character present in the canonical forms which can

be written for those ions:



m/e 261.



m/e 230.

Metastable peaks, and the transitions to which they correspond are observed as follows: 259*, 261 ⟶ 260; 231.5-233* (broad), 261 ⟶ 246, 260 ⟶ 246; 202*(superimposed), 261 ⟶ 230; 156.5*, 261 ⟶ 202. (m/e values).

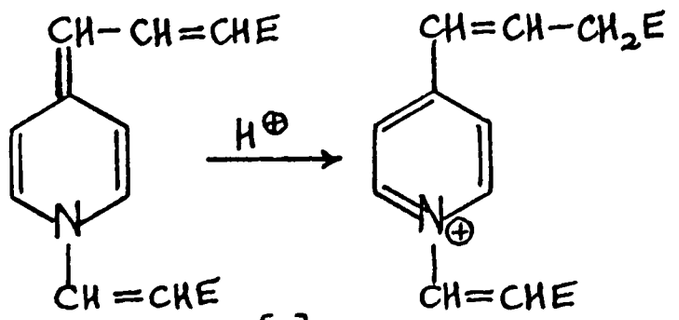
Comparison of the ultraviolet spectrum of compound [39] with that of related compounds shows that the observed longest wavelength absorption moves to longer wavelengths with increasing conjugation (see Table XII), and the data for compound [39] is in keeping with this behaviour. The spectrum of the adduct in acid solution shows a similar relation to the data for the model compounds under these conditions.

Table XII

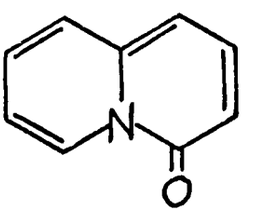
Ultraviolet absorption maxima, λ in $m\mu$, ($E.10^{-4}$).

Compound	Solvent	Maxima			
[39]	(M)		284(0.26)	299(0.26)	440(5.81)
[46][115]	(M)	246(1.39)	251.5*(1.25)	274(0.14)	376(1.41)
[47][116]	(B)	226(1.68)	256*(0.15)	263*(0.11)	367(2.25)
[48][117]	(N)		260(1.89)		
[39]	(A)	233(0.29)			317(2.93)
[47][116]	(S)	224(1.85)	263(0.33)	267(0.40)	
[48][117]	(S)	239(1.18)			

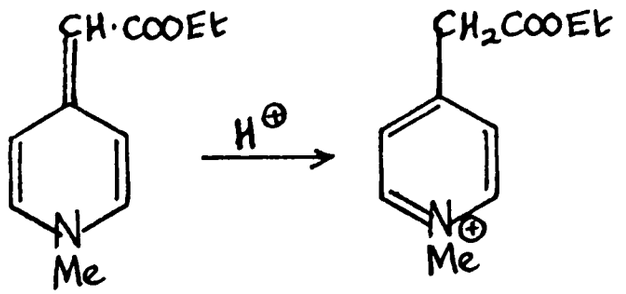
(M) = methanol; (B) = 1N sodium hydroxide; (A) = methanol plus 4 drops 70% perchloric acid; (S) = 1N sulphuric acid; (N) = pH7.



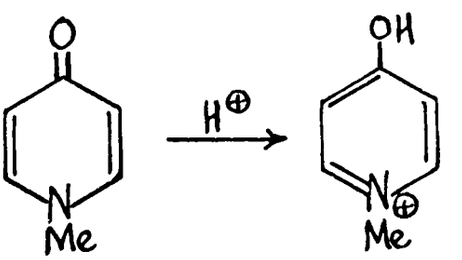
[39]



[46]



[47]



[48]

(c) From 3,5-dimethylpyridine.

An orange adduct from this pyridine and methyl propiolate was isolated for which we can write no structure with any certainty.

The analysis and mass spectrum indicate a molecular weight of 550 corresponding to $C_{30}H_{34}N_2O_8$, which in turn corresponds to an adduct from 2 moles of 3,5-dimethylpyridine and 4 moles of methyl propiolate.

The nuclear magnetic resonance spectrum is summarised thus: chemical shift (τ), coupling constant (c/s), integration (number of protons): 2.50, J = 13.8, (1); 3.83, very broad singlet, (2); 3.99, broad singlet, (1); 4.18, broad singlet, (1); 4.49, broad singlet, (1); 4.71, broad singlet (1); 5.37, J = 13.8, (1); 5.46, J = 3.6, (1); 5.77, J = 3.6, (1); ester methyls, singlets, 6.15, 6.29(2), 6.32; C-methyls, singlets, 8.00, 8.02, 8.21, 8.44.

Any structure for the adduct must accommodate the following features:

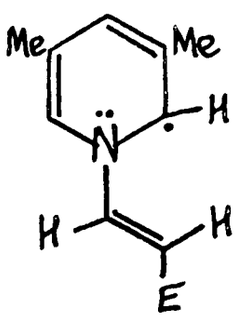
(i) On infrared evidence, no asymmetric carbon-carbon triple bonds are present in the molecule.

(ii) The form of the nuclear magnetic resonance spectrum (and the mass spectrum) precludes a symmetrical structure for the adduct. Furthermore, the presence of 10 protons (other than methyl protons) and the absence of an acetylenic linkage excludes structures involving two dihydropyridine type rings

linked by carbon chains. In other words, one of the initial pyridine molecules must be part of a bicyclic system.

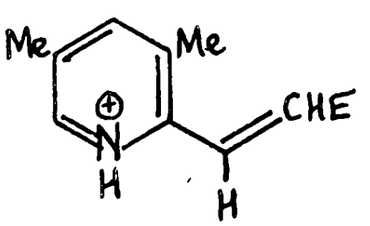
(iii) The presence of two doublets (J = 13.8 c/s) at 2.50 and 5.37 τ requires one acrylic ester moiety to be present in the molecule, possessing the <u>trans</u> configuration.

(iv) The mass spectrum is summarised as follows: m/e, %age of base peak: 550(13.2), 491(10.5), 438(11.3), 358(100), 326(17.0), 298(17.0), 216(12.5), 192(45.0). Any structure must account for a base peak corresponding to (M-192) and only one other major peak at m/e 192, corresponding to (M-358). Metastable peaks are only observed at m/e 297* and 248-9* and correspond to the transitions 358 $\longrightarrow$ 326 and 358 $\longrightarrow$ 298 respectively. No metastable peak in the region of m/e = 233* corresponding to the transition 550 $\longrightarrow$ 358 is, however, observed. The fragment lost of mass 192 and the smallest cation of any importance observed at m/e 192 could be formulated as [49] and [50] respectively, or their isomers.



mass 192°

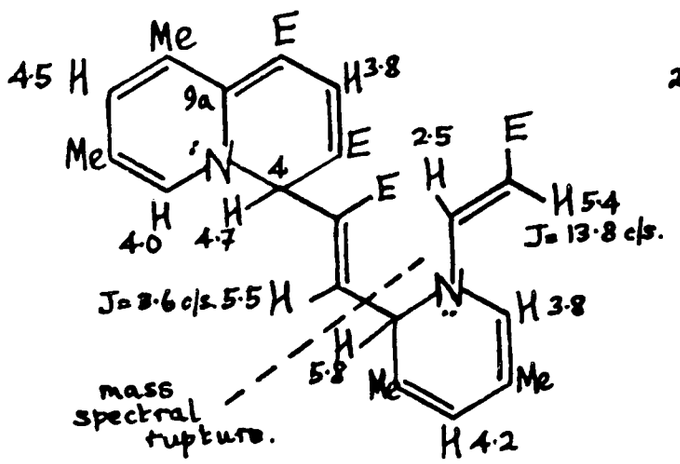
[49]



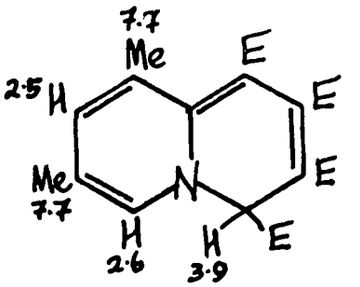
m/e 192⊕

[50]

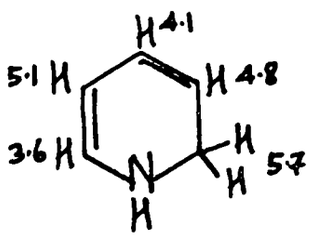
A very tentative structure for the orange adduct is [51] on which the n.m.r. correlations have been appended. These are in fair agreement, considering the differences in the substituents present, with the values for the known compounds [52][21] and [53][113]. In view of the data for adduct [54][21]



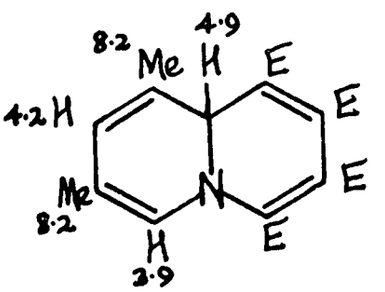
[51]



[52]



[53]



[54]

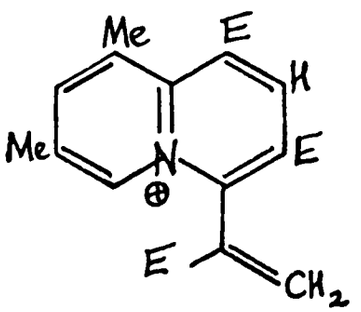
however, attachment of the side-chain at position 9a rather than position 4 (as drawn) in the compound [51] cannot be excluded entirely. The proton τ values are shown on the structural formulae [51]-[54]. The structure [51] satisfies requirements (i)-(iii) outlined above and can readily accommodate the mass spectral observations. Fragmentation of the molecular cation, derived from [51] by the loss of an electron, by rupture of the bond specified in structure [51] can be

represented by the two equation below:

$$550^{\bullet\oplus} \longrightarrow 358^{\oplus} + 192^{\bullet} \quad \text{(a)}$$

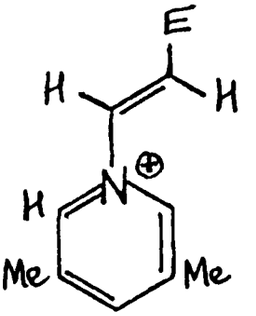
$$550^{\bullet\oplus} \longrightarrow 358^{\bullet} + 192^{\oplus} \quad \text{(b)}$$

Equation (a) will obtain if the lone electron in the molecular ion is associated with the quinolizine ring at the moment of rupture, whilst equation (b) is valid if the lone electron is accommodated by the dihydropyridine moiety at this time. The two possible fragment cations can be represented by the structures [55] and [56], both of which are seen to be aromatic systems which would be in accord with their being the two major peaks of the mass spectrum (vide infra).



m/e 358⊕

[55]



m/e 192⊕

[56]

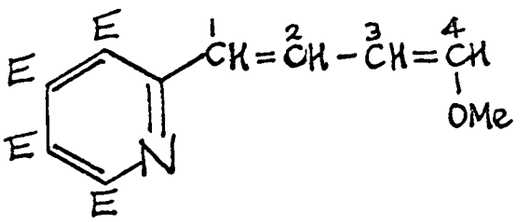
CHAPTER FIVE.

Pyridine and Dimethyl Acetylenedicarboxylate.

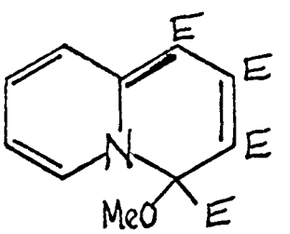
(a) 2-Substituted Pyridines.

(i) The Adducts from 2-Methoxypyridine. Further work.

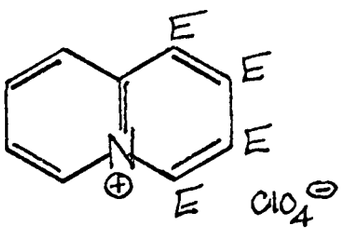
In a previous thesis[126], we have described the adducts from 2-methoxypyridine and dimethyl acetylenedicarboxylate, and these were formulated as [1] and [2], treatment of the reaction tar with perchloric acid prior to chromatography giving the salt [3].



[1]



[2]



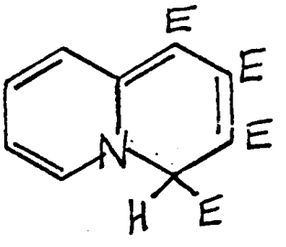
[3]

As some doubt hung over the structure [1] we have undertaken further new work with this compound. Excellent agreement has now been obtained between the observed[126] nuclear magnetic resonance spectral pattern for H-1-4 in adduct [1] and the pattern calculated[110] by successive applications of the ABC n.m.r. programme to the protons grouped 1,2,3 and 2,3,4. The success of this calculation arises from the fact that $J_{1,3} = J_{2,4} = J_{1,4} = 0$.

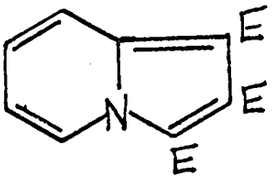
Previously[127] we have converted the adduct [1] into compound [2] by treatment with sodium methoxide as evidenced by the change in the ultraviolet spectrum of the reaction

solution. We also isolated the perchlorate [3] after adduct [1] had stood overnight in methanolic perchloric acid. We now report isomerisation of adduct [1] to the product [2] under the very mild conditions of a short period of boiling in methanol solution. Though the stereochemistry of adduct [1] is unknown these facile transformations strongly suggest that the double bond nearer the pyridine ring has the cis configuration.

The mass spectra of compound [1] and some related compounds [2], [3], [4] and [5] have been measured for the first time, and the results are summarised in Table I.



[4]



[5]

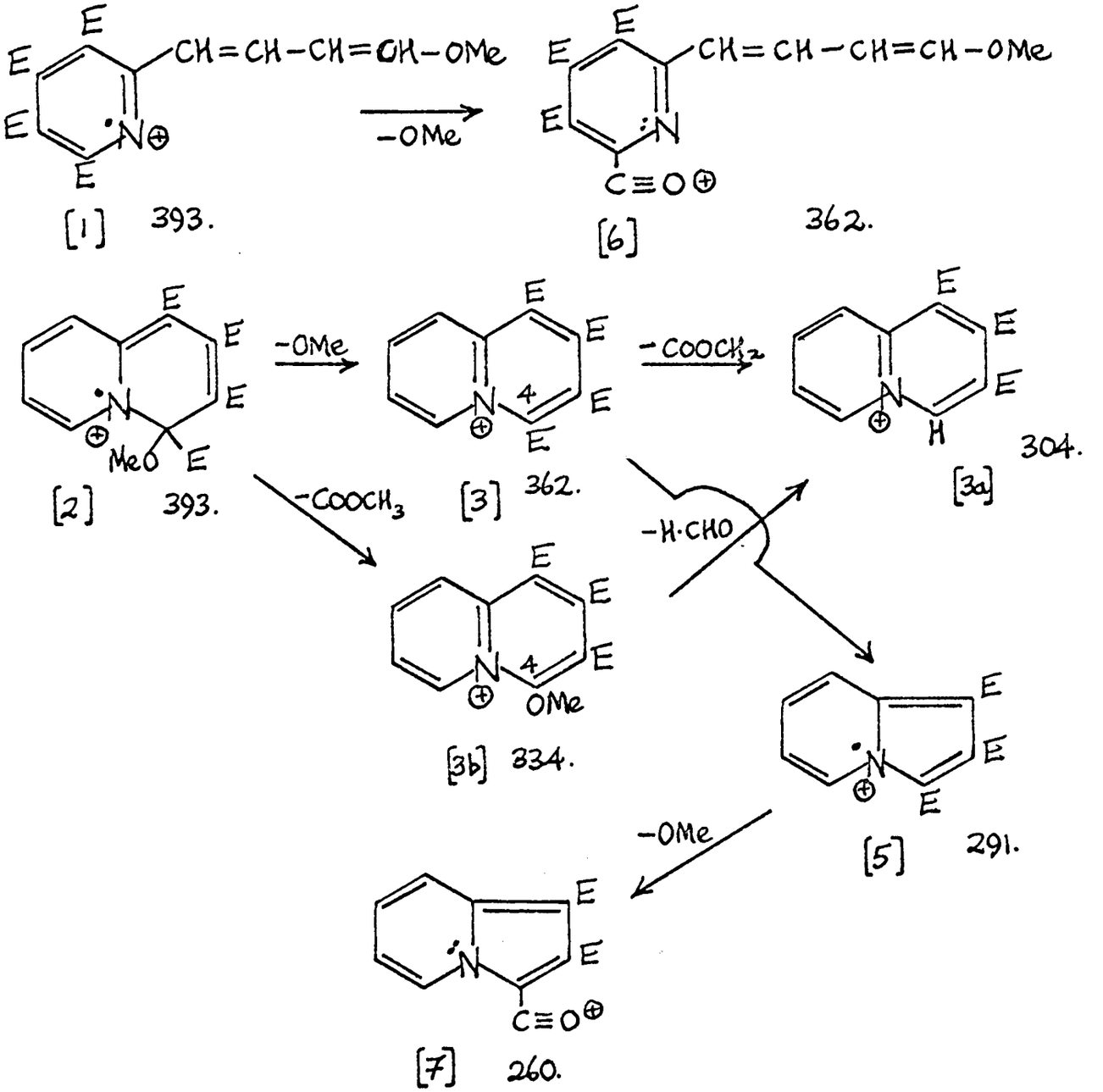
Table I

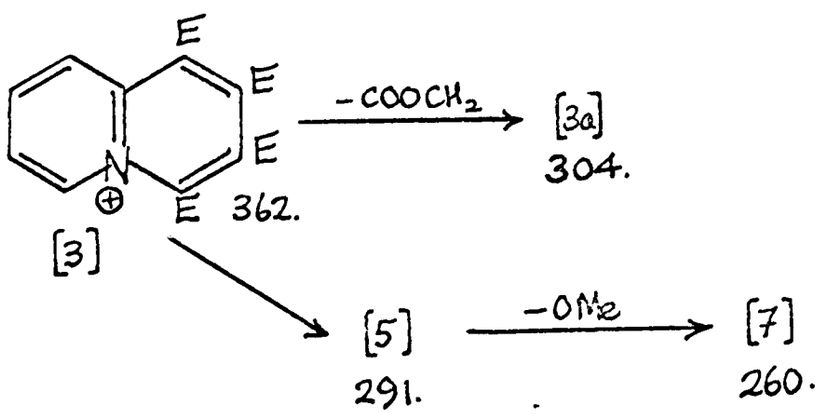
Mass spectral peaks, m/e, %age of base peak.

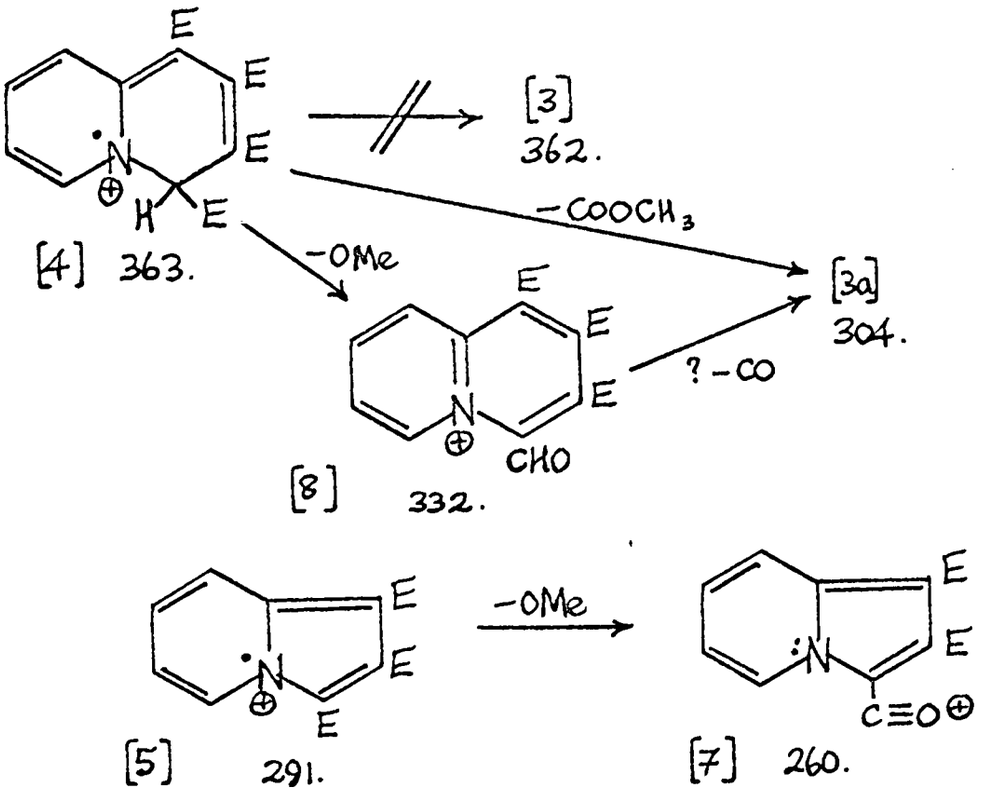
Compound.	m/e values.							
	393	363	362	334	332	304	291	260
[1]	2.7*	s	100	5.2	0.1	1.7	0.3	1.6
[2]	7.0*	s	42	100	<0.2	2.4	10.0	16.7
[3]		s	34*	2.4	1.9	25	69	100
[4]		6.2*	<1	<1	6.5	100	<1	<1
[5]							100*	89.5
Red compound.		22*	100	<1	3.4	48	<1	2.5

* Molecular ion; s = statistical peak only.

The species probably involved in the mass spectral degradation patterns with their m/e values are shown below:

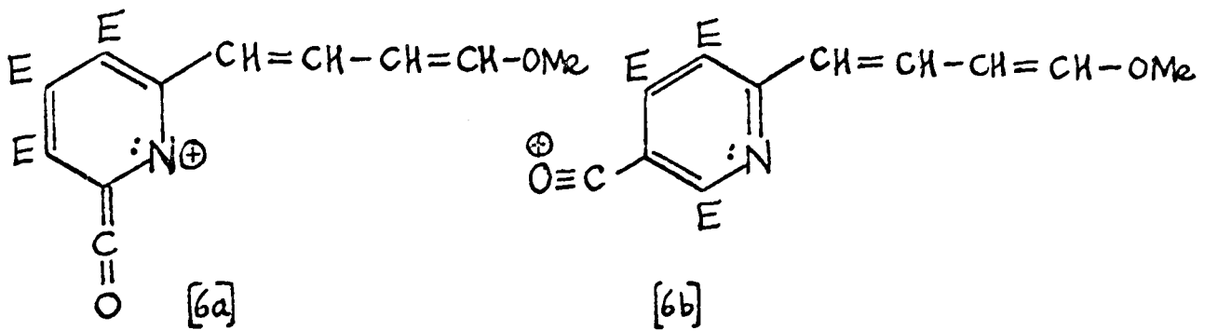




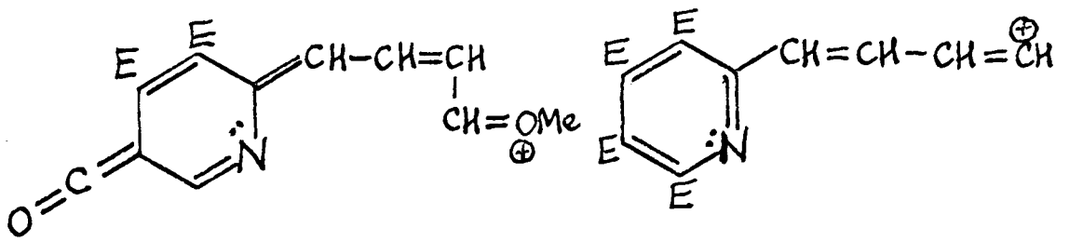


The transitions shown are almost all supported by appropriately situated metastable peaks, and these are absent only in one or two instances where no alternative source (to the one suggested) of the lower mass fragment could be considered as at all likely.

The fragmentation pattern of adduct [1] is noticeably different from that of its isomer [2]. The first fragment m/e 362 attributed with structure [6], has other stabilising resonance forms, e.g. [6a]. However the fragment could on the other hand be [6b] etc., which has resonance forms including [6c]. The structure [6d] is thought less probable. The cyclic form [3] is not favoured because of the low intensity of the derivative peaks expected at m/e 304, 291 and 260. The structure of the fragment at m/e 334 from



[6a] [6b]



[6c] [6d]

compound [1] is not clear, though it seems unlikely that it has the form [3b] since this too is a good source of derivative fragments at m/e 304, 291, and 260. The metastable peaks for compound [1] suggest that m/e 334 derives from fragment [6] and not from the molecular ion [1].

The mass spectra of compounds [2], [3] and [5] are straightforward in their interpretation and very much in accord with the expectation. The alternative fragmentations of the molecular ion [2] to the aromatic species [3] and [3b] are obvious first steps, and the transition [2] ⟶ [3] has been achieved by the simple process of acidification. The oxidation of quinolizinium salts and 4H-quinolizines to the aromatic indolizine system has also been observed under normal laboratory conditions[68], and is now paralleled by the transitions observed in the mass spectrometer; i.e. [3] or

[3b] ⟶ [5]. The loss of an ester group as the fragment $COOCH_2$ (mass 58), as observed here for [3] ⟶ [3a] in two instances, is a known[128] phenomenon particularly characteristic of αβ-unsaturated esters. Pyridine stable adduct [4] as expected predominantly shows the loss of $COOCH_3$ (mass 59) to give the quinolizinium salt [3a]. The much less intense peak at m/e 332 corresponding to the loss of OCH_3 (mass 31) is tentatively formulated as [8], which itself could reasonably be expected to lose carbon monoxide to give [3a]. Whereas species [3] and [3b] can eject plausible fragments, viz. an acetyl radical and carbon monoxide in the former case, and an acetyl radical in the case of [3b], to give the indolizine [5], the generation of [5] from [3a] would involve the less reasonable loss of CH, a carbene radical. This argument assumes a mechanism involving the loss of C-4 in the ring contraction. The acetyl radical and carbon monoxide are themselves products requiring rearrangement either of the ejected carbene radical type fragment or of the prospective fragment prior to its loss.

Finally to describe some further chemical reactions attempted with the adduct [1]. Unfortunately no characterisable product could be obtained from compound [1] and tetracyanoethylene, a reaction which it had been hoped would establish the butadiene nature of the side-chain. Also the reaction with acidified 2,4-dinitrophenylhydrazine was

regrettably inconclusive. The end methoxyl group in structure [1] is in effect a vinyl ether, which compounds are known to be readily hydrolysed by acid, and it was hoped to trap the aldehyde group as it was generated in the form of a familiar derivative. However the competitive reaction in acid media is cyclisation to the quinolizinium salt[127] and this may have been dominant in this instance.

The adduct [1] with maleic anhydride gave a red compound to which we are unable to append any definite structure. It is clear that the anhydride did not behave as a dienophile as was desired. The following facts must however be accommodated:

(i) On the evidence of mass spectrum and elemental analysis the molecular weight is 363 and corresponds to $C_{17}H_{17}NO_8$ with four methoxyl groups.

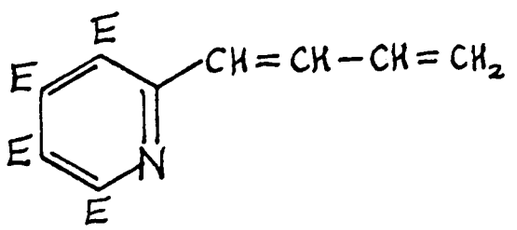
(ii) The product is thus an isomer of pyridine stable adduct [4], but as Table I illustrates, possesses a quite different mass spectrum. Any structure must account for the dominant fragmentation which is the loss of a hydrogen atom, the loss of an ester group being the only other major decay.

(iii) The nuclear magnetic resonance spectrum is summarised as follows: chemical shift (τ), coupling constant (c/s), integration (number of protons): 2.71, J = 10.3 + 1.7, double doublet, (1); 4.10, J = 10.5 + 5.4 (approx.), quartet, (1); 5.31 - 5.97, complex multiplet, (>2 but <3);

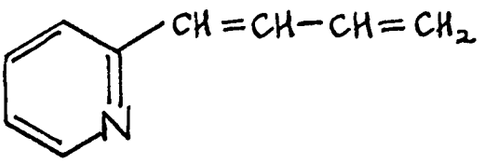
6.14, 6.19, 6.24, 6.29, singlets, methoxyl groups, (12).

The integration of this spectrum presents problems. It is difficult to accommodate a whole third proton in the 5.3 - 6.0τregion which integrates for just under 2½ protons. Also the integration in the methoxyl region cannot be constrained to be equivalent to 13 rather than 12 protons. The spectrum was scanned through negative τ values and no peak is reported in this area, though if it were very much broadened it could well have been missed on the oscilloscope. The problem of not knowing where the missing proton actually has its resonance has been a major factor in the failure to settle on a structure for this compound.

It is certain however that a structure such as [9] must be ruled out since the n.m.r. spectrum is vastly different from that of the precursor [1][126], and the compound [10][129]



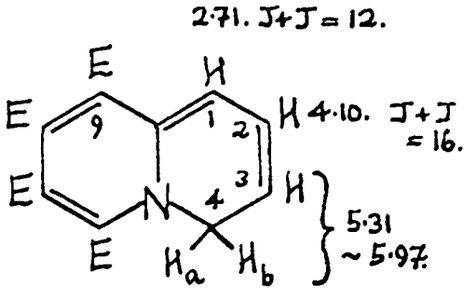
[9]



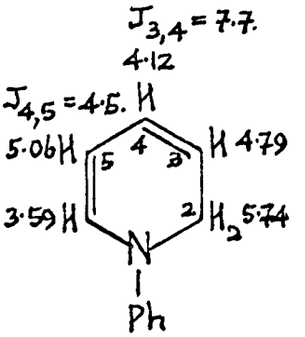
[10]

whose n.m.r. spectrum we have also recorded, has no resonances centred at field positions greater than 4.77τ . If there are in fact five protons to be accommodated in the region 2.6 - 6.0 τ , then the structure [10a] might be expected to give rise to a resonance pattern similar to the one observed.

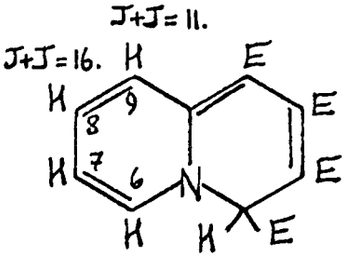
We suggest very tentatively that the red compound has structure [10a], with the n.m.r. assignments as appended on the diagram, the methylene protons being non-identical. The



[10a]



[10b]

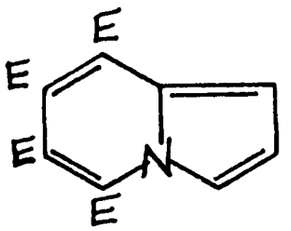


[4]

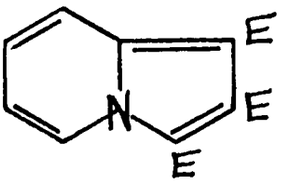
assignments (τ values) for protons 2,3, and 4 in [10a] are in good agreement with the values[103] for the equivalent protons 4,3, and 2 respectively, in compound [10b]. The presence of the second ring and the deshielding effect of the 9-ester group in [10a] could account for the discrepancy in the values of the equivalent protons H-1 in [10a] and H-5 in [10b]. The total coupling constants for protons 1 and 2 in [10a] are in good agreement with the average values found[21] for the equivalent protons 9 and 8 respectively, in adduct [4] and its analogues.

(iv) The ultraviolet spectrum of the red adduct, now described as [10a], is quite different from those[68] of the 4H-quinolizines typified by structure [4]. However adducts of type [4] all possess four ester groups in the other ring compared with structure [10a] and this may account for the

observed differences in the spectra. Thus the ultraviolet spectra of compounds [10c] and [10d] are very different[105],



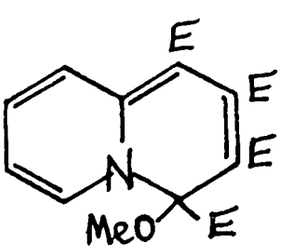
[10c]



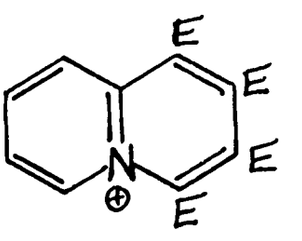
[10d]

(though the analogy is not entirely valid since structures [10c] and [10d] carry differing numbers of ester groups.)

The results which we cannot as yet reconcile with structure [10a] are the mass spectral details (see Table I), since loss of one mass unit from the molecular ion to give the base peak would suggest cation [3] as the base peak species. However the intensities of the peaks at m/e 291, 260, for the red compound are 40 - 70 times smaller than those found in the mass spectrum of the perchlorate salt of [3]. A discrepancy factor of 6 - 7 was observed for these two peaks (m/e 291, 260) when the fragmentations of compounds [2] and [3] were compared, whose peak intensities at m/e 362 were 42 and 34% respectively (vide supra.)



[2]

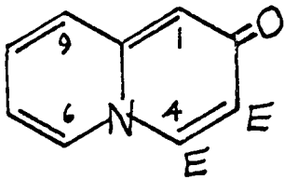


m/e 362

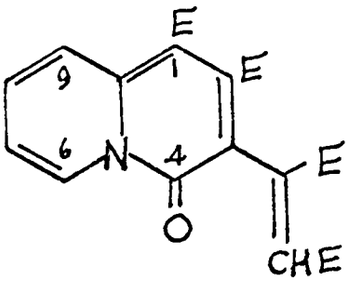
[3]

(ii) Adducts from and syntheses of various 2-Pyridylacetates.

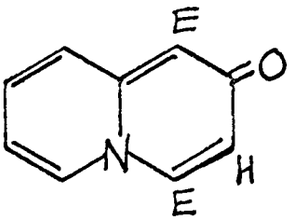
In a previous thesis[118] we proposed the structures [11] and [12] for two adducts obtained from methyl 2-pyridylacetate and dimethyl acetylenedicarboxylate. That the former



[11]



[12]

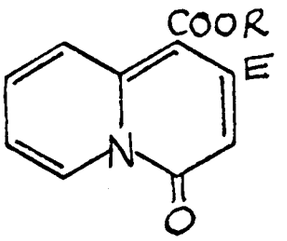


[13]

adduct did not possess the alternative structure [13] was based entirely on the chemical shift of H-9, 2.83 τ , which was thought sufficiently high to exclude the presence of a 1-ester group. However we were not entirely satisfied with our interpretation of the nuclear magnetic resonance spectrum of the compound [11] for which the assignments were made as follows: H-6, 2.13; H-7, 3.33; H-8, 2.83; H-9, 2.83 τ . The second adduct [12], isolated in tiny yield, was formulated on the evidence of its nuclear magnetic resonance and ultraviolet spectra as a 4-quinolizone derivative.

Additional work has thus been carried out to attempt to substantiate the above structures. After this work, to be described, had been completed, the work of Winterfeldt published[26] in December 1965, was uncovered. From the same reagents he reports obtaining the adducts formulated as [11] and [12], in agreement with our structures, and in addition

describes a third adduct [14a], and its analogue [14b] from ethyl 2-pyridylacetate. The obtaining of the analogue [14b]



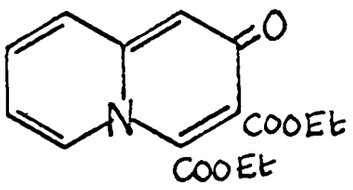
[14] a. R= Me.
b. R= Et.

is taken as proof of the non-involvement of the pyridylacetate ester group in the formation of type [14]. Structure [12] is supported as a 4-quinolizone on the evidence of the ultraviolet spectrum and the chemical shifts of H-6 and H-9. Structure [11] is proposed since the ultraviolet spectrum and chemical shift of H-6 in the product preclude its formulation as a 4-quinolizone. The protons 7,8 and 9 of this compound [11] were not assigned in the nuclear magnetic resonance spectrum. The alternative form [13] was not considered by this discussion.

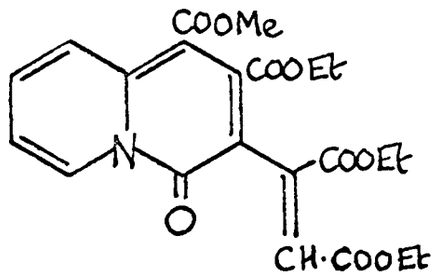
The new work on these adducts will now be described. An attempt to solve the effectively ABMX spectrum of protons 6 - 9 of adduct [11] by successive applications of the ABC nuclear magnetic resonance spectrum programme[110] was not successful, only in the case of H-6 was agreement between the observed and calculated line pattern satisfactory, though the general overall appearance of the theoretical spectrum for H-7,8,9 was recognisably like the observed pattern, particularly when the parameters employed used the same chemical

shift value for H-8 and H-9.

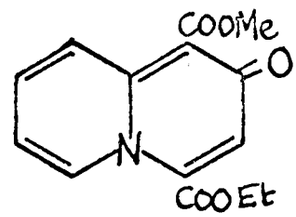
The reaction of methyl 2-pyridylacetate with diethyl acetylenedicarboxylate was next investigated. The products, not previously described, were the compounds [15] and [16].



[15]



[16]



[17]

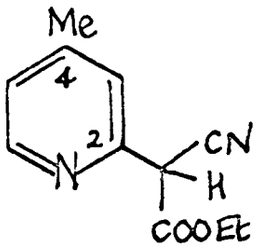
The ester region of the nuclear magnetic resonance spectrum of adduct [15] clearly showed two ethyl and no methyl ester resonances, thereby excluding the form [17] which would involve a different mode of formation. Apart from this fact, the elemental analysis corresponded to structure [15] and not to the form [17]. The resonances for H-1 and H-6 - 9 formed an exact replica of the spectrum observed for compound [11], the chemical shifts of H-1,7,8, and 9 being upfield by 0.07τ , and that of H-6 by 0.04τ , from the corresponding values found for adduct [11]. Adduct [15] is thus undoubtedly an analogue of the product [11], and the alternative form [13] for this latter compound is consequently eliminated. Unfortunately the virtual duplication of the resonance pattern for H-6 - 9 in adduct [15] of that found for adduct [11], in no way clarifies the doubts surrounding these assignments.

The adduct [16] on the evidence of its ultraviolet spectrum and the nuclear magnetic resonances of protons 6 - 9 is the analogue of adduct [12] and possesses the 4-quinolizone form carrying an ester group at the 1-position. Characteristic of 4-quinolizones, H-6 is at very low field, 0.77τ , and the 1-ester group pulls H-9 down to 1.24 τ . The resonances of protons 6 - 9 and of the olefinic proton differ from the corresponding values found[118] for adduct [12] by only 0.04 to 0.09 τ (upfield.) The formulation of adduct [12] is supported by the fact that on the evidence of the ester resonances and elemental analysis, the analogous adduct [16] contains the expected one methyl and three ethyl ester groups in accord with the postulated mode of formation[118] in which the ester group of the original pyridylacetate is not involved, in contrast to the mode of formation of the adducts [11] and [15].

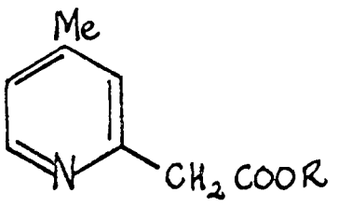
A new approach to the verification of the assignments for H-6 - 9 in adducts [11] and [15] was to attempt to synthesise a pyridylacetate containing a methyl substituent in the pyridine ring, since any adduct from this precursor analogous to compounds [11] and [15] would have a different and simplified proton resonance pattern for protons 6 - 9, the simplicity of which should be greatest for the 8-methyl derivative of compound [11].

Adapting a described synthesis[86], ethyl cyanoacetate and

4-methylpyridine 1-oxide were reacted together and gave a compound for which elemental analysis was in accord with the formula [18], the expected and desired product of the first stage of an attempted synthesis of the compound [19].

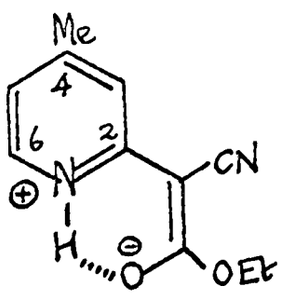


[18]

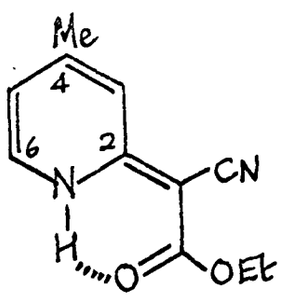


[19] R= Et or Me

However the nuclear magnetic resonance spectrum (see Table II below) of the new compound excludes its formulation as [18], owing to the absence of the one-proton singlet from the region expected for the lone hydrogen atom of the 2--substituent, and owing to the resonance attributed to H-6 appearing as a triplet and not as the expected doublet. The product is consequently given the structure whose resonance forms are [20] and [20a].



[20]



[20a]

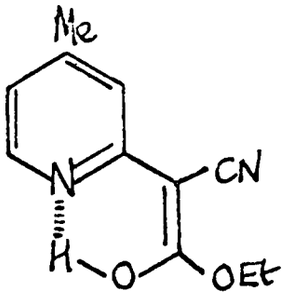
Table II

Nuclear magnetic resonance data for compound [20] in deuterochloroform

Proton	Chemical shift (τ) and coupling constants (c/s)
N - H	-3.8; broad low hump.
H-3	2.88; $J_{3,5}$ = ca. 1.1
4-Me	7.63; singlet.
H-5	3.45; $J_{5,6}$ = 6.5; $J_{3,5}$ = ca. 1.1
H-6	2.40; $J_{5,6} = J_{6,N-H}$ = 6.4. (triplet).
Ethyl-CH_2	5.75; quartet, J = 7.0.
Ethyl-CH_3	8.67; triplet, J = 7.0.

The n.m.r. spectrum shows features which reflect the contributions of each of the resonance forms [20] and [20a] to the actual structure. Thus the chemical shifts of H-3 (deshielded by the adjacent nitrile group) and H-5, both protons being shielded by the 4-methyl group, are at lower field than the corresponding protons in 2-pyridone[114], (which is without a 4-methyl substituent), indicative of contributions from form [20]. On the other hand, the shift of H-6 is ca. 0.9 τ to higher field than the values found for this proton in pyridine (1.50 τ)[120] and methyl 2-pyridylacetate (1.49 τ), and is close to the value observed[114] for H-6 in 2-pyridone (2.27 τ), suggestive of contributions from form [20a]. The strong coupling of H-6 with N-H eliminates the tautomer [20b] as the structure of our product; this form of coupling is

reported[113] for 1,4-dihydropyridine.

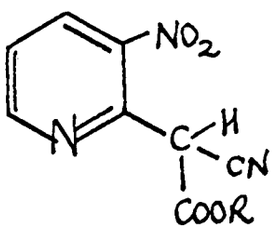


[20b]

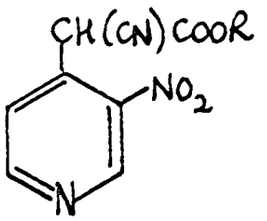
Addition of D_2O to the solution in the spectrometer led to the immediate loss of detection of the resonance at -3.8 , but only a small extent of exchange would be necessary to achieve this effect as the original signal was only just distinguishable from the noise. The triplet at 2.40 τ shows immediate partial collapse to a doublet superimposed on a much less intense form of the original triplet, no other change occurring in the spectrum. After 15 minutes the doublet-to-triplet ratio of the complex at 2.40 τ is appreciably increased in favour of the doublet, and a peak for HOD has appeared in the spectrum (5.35 τ). After 16 hours the intensity of this peak at 5.35 τ has increased, and the signal at 2.40 τ is a doublet (J = 6.8 c/s) with only the slightest traces of the triplet form present.

The slow hydrogen-deuterium exchange process is in harmony with strong intramolecular hydrogen bonding as indicated by the dotted lines on structures [20] and [20a]. The infrared spectrum of the product accords with this explanation.

The synthesis of the required product [19] from the cyanoacetate [18 etc.] could not be completed as the first product [18] resisted all attempts either to convert the nitrile group into an ester group or to hydrolyse the ester and/or nitrile group to the free acid. In this respect if resembled the behaviour recorded[121] for compounds [21] and [22] which resist hydrolysis under basic and acidic conditions.



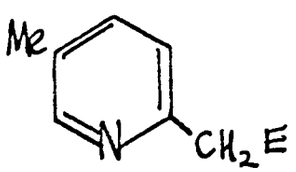
[21]



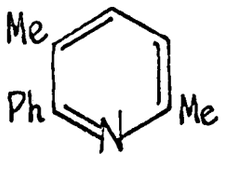
[22]

In one instance compound [18 etc.] gave a small quantity of an unknown substance which on the evidence of its infrared spectrum could have been a hydrolysis product. However the yield of this substance and the difficulties attendant on its isolation, precluded the process as a practicable procedure.

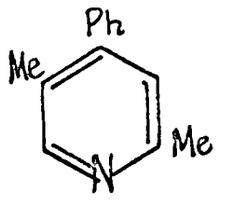
The pyridylacetate [23] was however successfully synthesised by adaptation of literature methods[87,88] from 2,5-dimethylpyridine and phenyllithium inter alia. The product



[23]

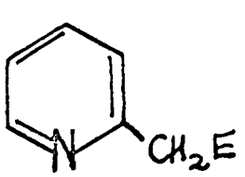


[24]



[25]

[23], which has not been described previously though its ethyl ester analogue is known[88], was identified by means of its nuclear magnetic resonance spectrum. This spectrum could not be completely interpreted, as the required compound [23] was contaminated with approximately 0.25 molar proportions of compound [24] or possibly of a mixture of isomers [24] and [25]. The isomer [24] has been described previously as a by-product of reactions involving 2,5-dimethylpyridine and phenyllithium[88,122]. The nature of the impurity was presumed entirely on this precedent and on the observed resonances at 2.4 - 3.2 τ (phenyl group and pyridine ring protons) and at 7.48 and 7.84 τ (methyl groups). The part of the nuclear magnetic resonance spectrum of compound [23] away from impurity resonances showed peaks at 1.69, 6.21, 6.39 and 7.82 in the ratio (integration) 1:2:3:3, and these were assigned to H-6, 2-CH_2, ester-Me, and 5-Me protons, respectively. The lowest field resonance showed $J_{4,6}$ = 1.7 c/s. These assignments were supported by measurements made by us of the nuclear magnetic resonance spectra of the model compounds [26] and [27]. The data for these models



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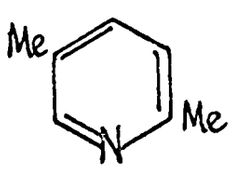
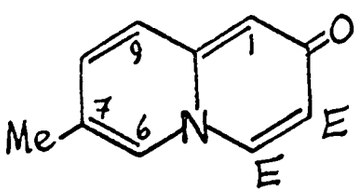


[27]

also supported the proposition that the H-3 and H-4 resonances in compound [23] were obscured by the impurity complex at 2.4 - 3.2 τ .

Compound [23] in its impure state gave an adduct formulated as [28] with dimethyl acetylenedicarboxylate. On the evidence of the ultraviolet spectrum this appeared to be the desired analogue of compound [11]. The nuclear magnetic resonance spectrum confirmed these hopes and as is described below completely vindicates the previous assignments of protons 6 - 9 in compounds [11] and [15]. The ester resonances and lone proton resonance in adduct [28] are very close



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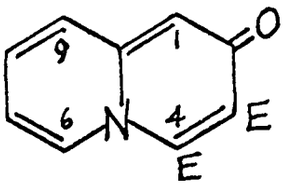


[11]

Table III

Nuclear magnetic resonances (τ) in deuterochloroform.

Compound	1-H	6-H	7-H	8-H	9-H	Ester-Me.
[11][118]	3.32	2.13	3.33	2.83	2.83	5.96, 6.05.
[28]	3.39	2.44	7.80(Me)	2.81 - 3.17		5.98, 6.08.

to the values found for adduct [11] as Table III shows. The nature of the precursor necessitates the product having its methyl group at position 7, and the absence of the multiplet at 3.33 τ in compound [11] from the spectrum of compound [28]

supports the assignment of H-7 to 3.33τ . As expected, if the structures are correct, H-6 in adduct [28] is moved to higher field by the adjacent methyl group compared with the value found for adduct [11]. Finally, the 7-methyl group also causes H-8 and H-9 to have slightly different chemical shifts and the resonance in the 2.81 - 3.17τ region has the pattern expected for an AB system for which $J_{AB}/(\tau_B - \tau_A)$ = ca. 1.4[123]. This pattern, particularly the two small outer peaks, shows the additional superimposed small splitting expected from the <u>meta</u> and <u>para</u> coupling with H-6. Inspection of the resonance for H-6 suggests that $J_{meta} + J_{para} \leqslant 2.3$ c/s.

A by-product from the reaction of crude compound [23] and dimethyl acetylenedicarboxylate is the so-called <u>white adduct</u>. No structure can be proposed for this compound as we cannot be certain of its heterocyclic precursor which could be compound [24] or its isomer [25]. The following data will be quoted however:

(i) Mass spectrum and elemental analysis are in accord with the molecular formula $C_{24}H_{21}NO_7$, molecular weight 435, corresponding to an adduct from 1 mole of compound [24] or [25] and 2 moles of dimethyl acetylenedicarboxylate with loss of methanol.

(ii) The mass spectrum contains three major peaks: m/e, %age of base peak: 435(100), 404(42.5), 403(47.5).

(iii) The nuclear magnetic resonance spectrum is summarised as follows: chemical shift (τ), coupling constant (c/s), number of protons (integration): 2.47, singlet, (5), possibly the phenyl group; 2.17 to 2.68, partially obscured multiplet, (4); 6.08(6), 6.16(3), singlets, three ester methyls; 7.56 (3), an aromatic C-methyl group. These resonances in deuterochloroform are unaffected by the addition of D_2O to the sample.

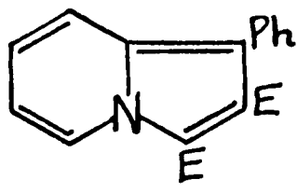
The aromatic nature of the product suggested by the nuclear magnetic resonance data is supported by the great stability of the molecular ion in the mass spectrum.

(iii) 2-Phenoxypyridine.

The failure of 2-phenoxypyridine to form adducts with dimethyl acetylenedicarboxylate could possibly be due to the weakness of this pyridine as a base which renders as energetically unfavourable the initial Michael attack of the nitrogen lone pair on the activated triple bond of the acetylenic ester. A previous attempt[124] to correlate the obtaining of or lack of adducts from numerous pyridines and this ester with the pK_a values for the pyridines was quite successful. It seems unlikely that steric hindrance can be entirely blamed for altering the course of the reaction since adducts have been obtained from 2-phenylpyridine[23]. That some form of reaction has occurred is clear from the tarry nature of the reagent mixture before chromatography.

(iv) Adducts from 2-Benzylpyridine.

Two adducts were obtained from 2-benzylpyridine and dimethyl acetylenedicarboxylate. The first we formulate as the indolizine [29] for the following reasons:



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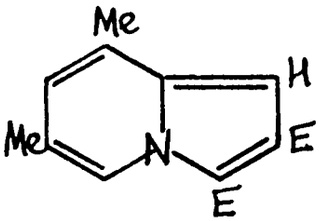

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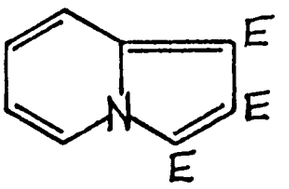


[31]

(i) Its ultraviolet spectrum is approximately a mixture of the spectra of the indolizines [30] and [31].

Table IV

Compound	Absorption maxima, λ in mμ ($E.10^{-4}$), in methanol.				
[30]†	229(2.76)	257(2.57)		333*(0.97)	347(1.15)
[31]†	235(2.66)	264(1.08)	273(1.44)	322.5(1.60)	
[29]		250(2.92)	271*(1.36)		350(1.54)

†Data from Table I, Chapter 4.

(ii) The nuclear magnetic resonance spectrum of the adduct [29] closely resembles that of the indolizine [31] (see Table V), with the exception that the H-8 resonance is 0.65τ to

Table V

Proton resonances (τ) of the indolizines in deuterochloroform.

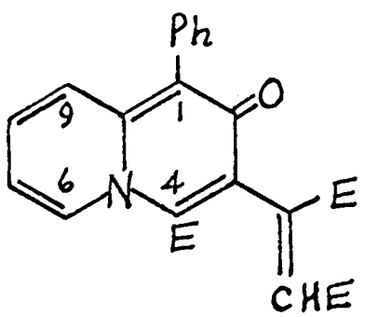
Compound	5-H	6-H	7-H	8-H	Ester-Me, etc.
[29]	0.59	ca.3.17	ca.2.94	2.40	6.12, 6.19; 1-Ph, 2.62.
[31]†	0.57	3.06	2.71	1.75	6.07, 6.16(2)

†Data from Table II, Chapter 4.

higher field compared with H-8 in compound [31], in keeping with the absence of an ester group at the 1-position. The coupling constants follow the pattern established in Table IV of Chapter 4.

(iii) The mass spectrum gives the molecular weight as 309 in harmony with the formulation [29] and shows strong resemblance to the mass spectrum measured by us of the related indolizine [31]. The stability of the indolizines in both instances, particularly in the case of compound [29], is reflected in the fact that the molecular ion forms the base peak. In the spectrum of the indolizine [31], the peak at m/e 260 corresponding to loss of methoxyl has an intensity of 89.5%, whilst in compound [29], the equivalent peak at m/e 278 has an intensity of only 24%. In both cases these are the strongest peaks other than the molecular ion.

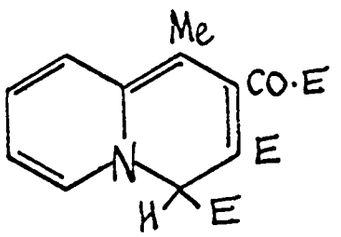
The second adduct obtained is formulated as compound [32].



[32]

In seeking information to clarify the structure of the product its mass spectrum was measured, and the mass spectra of the possibly related adducts described by Gagan[53,21] from 2-ethylpyridine and 1-ethylisoquinoline, formulated by him as

[33] and [34] respectively, were also recorded for the first time. These compounds were thought to be related to our product [32] since their precursors, like 2-benzylpyridine, contain an activated methylene group absent from the product on the evidence of the nuclear magnetic resonance spectra (vide infra). The mass spectra of adducts[118] [35] and [36]



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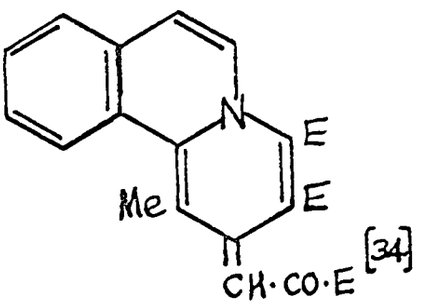

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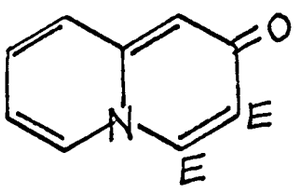

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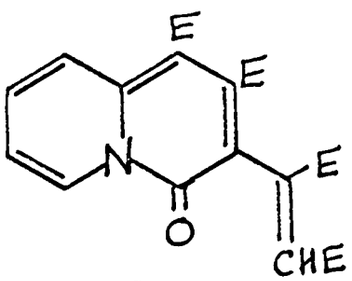

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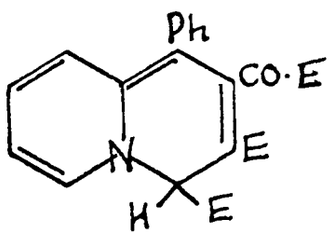
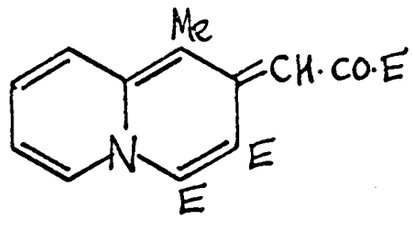


[37]

were also measured.

Two somewhat surprising features were found. Analyses obtained by Gagan[53] were in accord with structure [33], molecular weight 347, whilst those we have obtained for our adduct from 2-benzylpyridine gave perfect agreement with the theoretical values calculated for structure [37], analogous to [33], of molecular weight 409. The mass spectral molecular weights however for these two products were found to be 359 and 421 respectively, representing structures containing one

extra carbon atom and consequently increased unsaturation. Hence structures [33] and [37] must be discarded. The adduct [34] on the other hand, for which mass spectrum and elemental analysis are in agreement, represents a possible formulation with the required degree of unsaturation. Formulation of the adducts from 2-ethyl- and 2-benzyl-pyridine as [38] and [39] respectively might therefore be suggested. We



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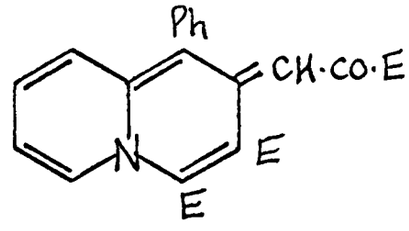
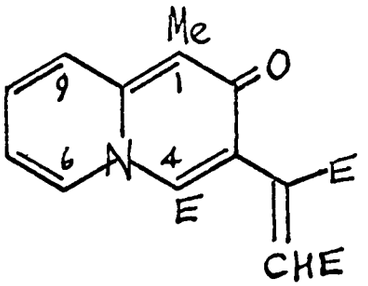


[39]

do not favour these structures, nor structure [34], on the grounds that all three adducts represented as such would be expected to protonate readily to give the aromatic quinolizinium or benzo-quinolizinium cations, whilst in fact all three adducts only protonate under conditions of extreme acidity (methanol : 70% perchloric acid :: 2:1) and their ultraviolet spectra under these conditions, particularly in the case of the adducts from 2-ethyl- and 2-benzyl-pyridine, are difficult to relate to the spectra of known quinolizinium salts[68].

The reformulation of Gagan's adducts as analogues of our product [32] with structures [40] and [41] is therefore proposed and the evidence in favour of these structures will now be discussed.



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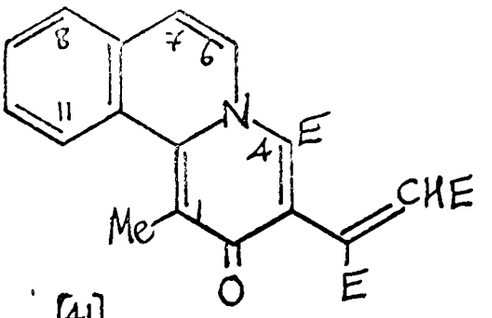


[41]

(i) The nuclear magnetic resonance spectra (see Table VI) of the three adducts, particularly compounds [32] and [40], closely resemble that of the 2-quinolizone derivative [35], and are at the same time quite different from that of the 4-quinolizone derivative [36], which shows the very low field resonance for H-6 typical of 4-quinolizones, making their alternative formulation as 4-quinolizones unlikely.

Table VI

Nuclear magnetic resonance data (τ values) in deuterochloroform.

Compound	6-H	7-H	8-H	9-H	lone H	Other resonances.
[32]	*	3.43	3.08	*	4.00	6.01, 6.20, 6.29(esters); Ph, see*
[35][118]	2.12	3.33	2.83	2.83	3.32	5.96, 6.05(esters).
[36][118]	0.70	2.71	2.22	1.15	3.62	6.09(2), 6.18(2)(esters).
[40][53]	2.25	3.47	3.12	2.78	3.99	6.01, 6.20, 6.32(esters); 1-Me, 7.81.
[41][53]	2.32	3.17	benzo group.		3.89	5.95, 6.13, 6.26(esters); 1-Me, 7.41.

* A complex multiplet at 2.13 - 2.76 τ integrating for 7 protons is attributed to H-6, H-9, and 1-Ph.

† Benzo group resonance observed as a three proton multiplet at 2.15 - 2.70 τ with in addition one low field further split doublet attributed to H-11 at 1.67 τ .

The lone proton resonance positions are closer to the value found in adduct [36] which the adducts resemble in respect of the environment of the isolated hydrogen atom, than with the value observed in adduct [35] in which the hydrogen atom in question has a quite different environment.

(ii) The mass spectra of the adducts [32], [40] and [41] show identical cracking patterns and each contains only one peak, the base peak itself, apart from the molecular ion, with an intensity greater than 10%. The base peak in each case corresponds to the loss of mass 59, i.e. a $COOCH_3$ group. In this respect the mass spectra of the adducts resemble that of compound [36] whilst being quite different from the complex cracking pattern of the 2-quinolizone derivative [35]. This feature suggests that the presence of the side-chain common to [32], [36], [40] and [41], and absent from [35], is an all important factor in the mass spectral cracking pattern, rather than the 2- or 4-quinolizone form of the nucleus. The data is summarised in Table VII.

Table VII

Mass spectral peaks and %ages of the base peak.

Compound	Molecular ion, M.	(M-59) fragment.
[32]	10.8	100
[35]	85.0*	53*
[36]	15.0	100
[40]	11.0	100
[41]	10.2	100

* base peak at (M-116), m/e 145.

These results can still be in keeping with the 2-quinolizone formulations given if the loss of mass 59 and the stability of the resulting fragment is accounted for by the schemes shown below.

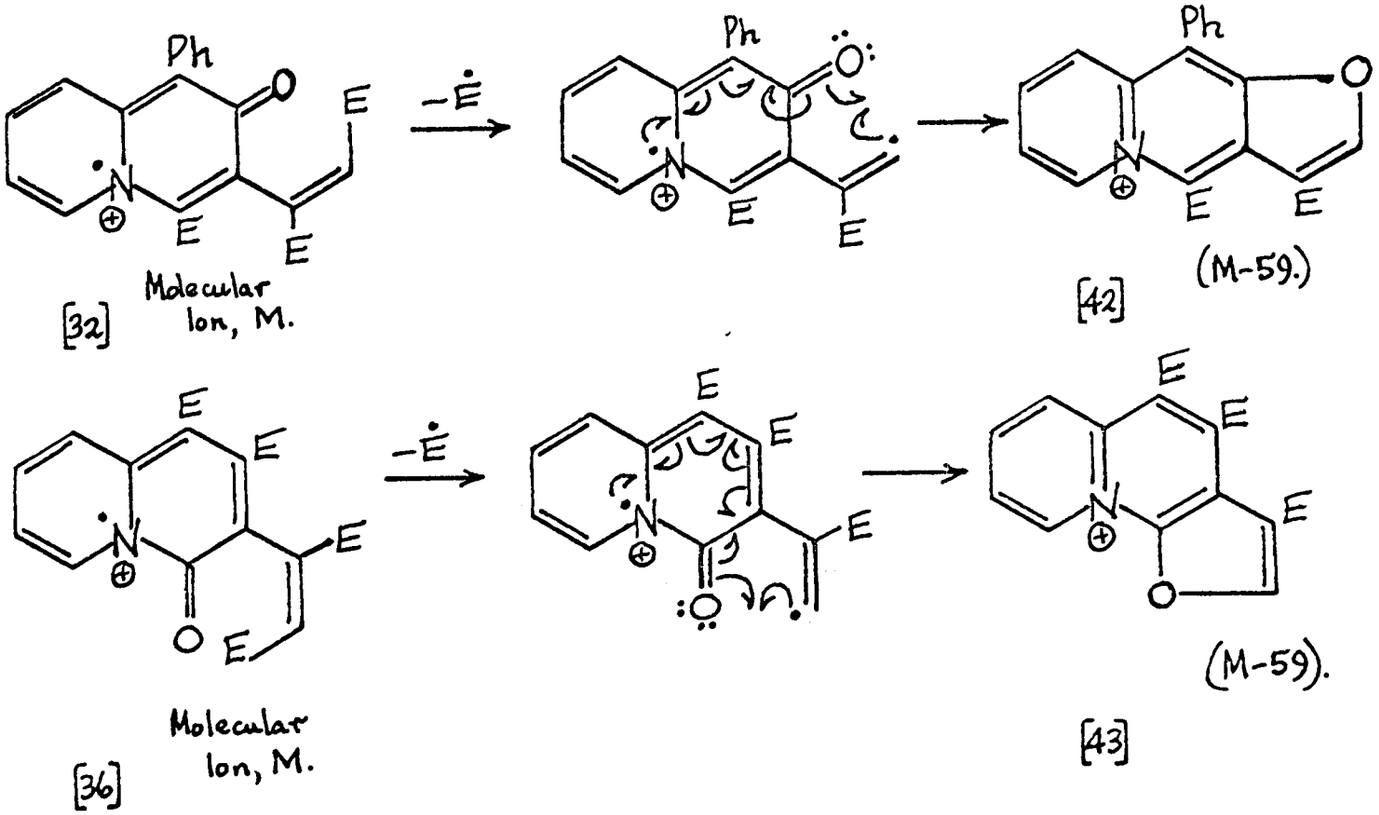


Table VIII

Ultraviolet spectra, λ in $m\mu$, ($E.10^{-4}$)

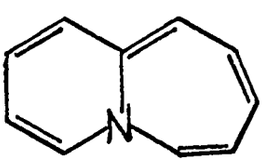
Compound	Solvent	Maxima					
[32]	(M)			267(1.71)	304.5(1.07)	343(1.08)	437(2.03)
[40][53]	(M)			266(1.10)	278*(0.76)	339(0.59)	440(2.40)
[41][53]	(M)	214(1.65)	230(1.28)	275(2.08)	283*(1.85)	300*(0.82)	430(2.62)
[32]	(P)			265.5(2.63)		308*(1.12)	512(0.38)
[40][53]	(P)			267(1.96)		306(0.68)	490(0.29)
[41][53]	(P)			276(2.48)		352(1.44)	555(0.30)

(M) = Methanol; (P) = Methanol: perchloric acid (70%) :: 2:1 by vol.

The proposed breakdown in the cases of adducts [32], [40] and [41] is typified by the upper scheme shown for the case of [32]. The parallel process feasible for adduct [36] is shown in the lower scheme. No such process can of course operate in the case of adduct [35]. The stability of the (M-59) fragments, e.g. [42] and [43], is explained in terms of the aromatic nature of the proposed formulations for these fragments.

(iii) Attempts to substantiate the 2-quinolizone form proposed for the three adducts by comparisons of their ultraviolet spectra with the spectra of possible model compounds was not successful, not least because of the remarkable variations amongst the spectra of related possible model compounds of known structure which occur when quite small modifications are made to the substituent groups of these compounds.

However the observed ultraviolet spectra of the three compounds confirm their inter-relation and exclude alternative formulations involving the indolizine system (see Chapter 4) or the pyrido[1,2-a]azepine system[130], i.e. [44].



[44]

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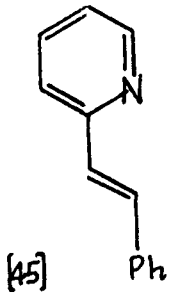

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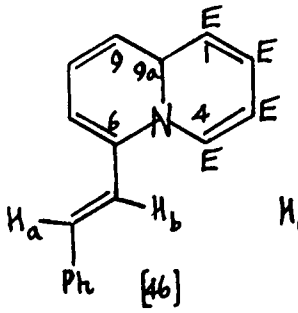

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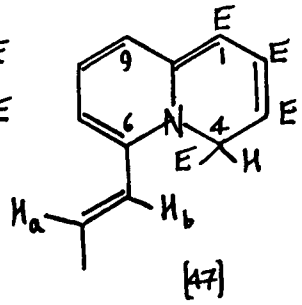

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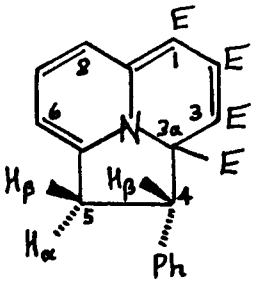

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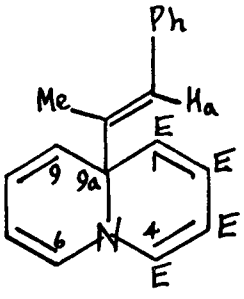

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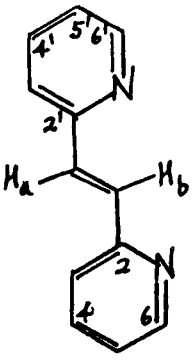

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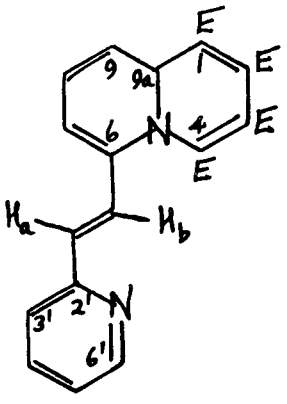

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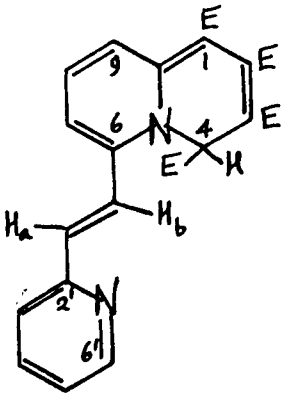

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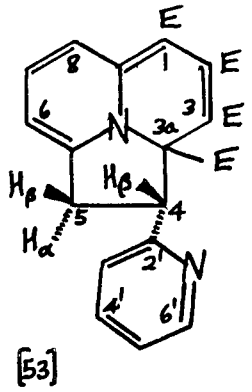

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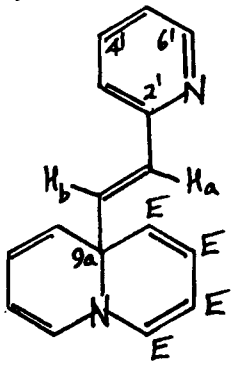

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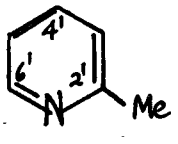


[55]

(v) 4-Benzylpyridine.

The failure to isolate adducts from 4-benzylpyridine and dimethyl acetylenedicarboxylate is not understood, since the pK_a(5.59)[131] of the base compares well with that of 3-methyl--pyridine (5.67)[131] which readily enters into the reaction involving the Michael attack of the pyridine lone pair on the activated triple bond of the ester[68]. Extensive tar formation indicates definite reaction and no precursors were recovered.

(vi) Trans 1,2- bis (2-pyridyl)-ethylene adducts.

The structures used in this section are found on the fold-out page opposite.

Acheson and Feinberg[24] have reported their investigations of the reactions of stilbazole [45] with dimethyl acetylenedicarboxylate and describe the adducts [46], [47], and [48]. The adduct of type [49] was only obtained in the instance shown. We will concern ourselves only with adducts from the trans isomer of the precursor [45].

It was thought interesting to investigate the products which might be formed from the similar compound [50], in which the phenyl group has been replaced by a second pyridine moiety. By comparison of the spectral properties of the compounds described above we are readily able to formulate four analogous adducts from trans 1,2-bis(2-pyridyl)-ethylene [50] and dimethyl acetylenedicarboxylate, viz. [51] - [54].

Table IX - Nuclear magnetic resonance data (τ values) in deuterochloroform.

Compound	3^1-H	4^1-H	5^1-H	6^1-H	H_a	H_b	4-H	6-H	7-H	8-H	9-H	9aH	Ester-Me.
[46][24]	←——	2.61	phenyl —→		3.10*	3.42*	-	-	3.65 —	3.85	4.22	4.88	6.08, 6.20, 6.36, 6.57.
[47][24]	←——	2.49	phenyl —→		2.83	2.83	3.33	-	2.95	ca. 2.5†	1.35	-	6.05, 6.18, 6.22, 6.30.
[49][24]	←——	2.72	phenyl —→		3.32	8.12 (Me)	-	3.41	4.55	3.80	3.95	-	6.01, 6.15, 6.18, 6.30.
[50]	2.63	2.36	2.89	1.40	2.30	-	-	-	-	-	-	-	-
[51]	2.81[4]	2.32	2.81[4]	1.38	2.75*	3.20*	-	-	3.64 —	3.92	4.27	4.91	6.08, 6.22, 6.36, 6.55.
[52]	2.74[5]	ca. 2.30†	2.74[5]	ca. 1.40	2.74[5]	2.74[5]	3.38	-	2.74[5]	2.74[5]	ca. 1.43	-	6.09, 6.23, 6.27, 6.36.
[54]	ca. 2.82	2.47	ca. 2.97	1.55	←3.56[2]→		-	ca. 3.59†	4.50	←3.96[3]→		-	6.04, 6.22(2) 6.34.

Compound	3^1-H	4^1-H	5^1-H	6^1-H	4β-H	5β-H	5α-H	6-H	7-H	8-H	Ester-Me.
[48][24]	←2.86(3)[6], 3.08(2)[6]→				5.55	6.17	7.05	3.31	2.48	1.48	6.23(2), 6.31, 6.73.
[53]	2.98[5]	2.48	2.98[5]	1.63	5.35	ca.6.20†	7.01	3.33	2.52	1.56	6.23(2), 6.30, 6.68.
[55]	3.04[5]	2.57	3.04[5]	1.59							2-Me, 7.51.

* reverse assignment possible; † obscured; [2] centre AB quartet; [3] centre further split AB quartet; [4] centre 2 proton multiplet; [5] centre 6 proton multiplet; [6] centres, 3 and 2 proton multiplets comprising phenyl group.

The adducts [51] and [54] were obtained from chromatography of the reaction tar, products [52] and [53], being obtained only from isomerisation of compound [54] under a variety of conditions of solvent and temperature (vide infra).

The structures of our products are based mainly on the comparisons of their spectral properties with those of the corresponding analogues. The data used for these comparisons are presented in Tables IX and X, and will only be discussed briefly as the results are largely self-supporting.

(i) The nuclear magnetic resonance comparisons - Table IX.

(a) In the case of the labile adducts [51] and [54] comparison of the spectra with that of the precursor [50] clearly indicates the presence of one aromatic pyridine moiety.

(b) Throughout the observed spectra of the new quinolizine-type adducts the coupling constants of the protons of the pyridine moiety resembled those observed in the precursor [50], whilst those of the protons of the quinolizine part of the molecules showed the values expected from comparison with the results found[24] for the products [46], [47], and [49]. The difference between the coupling constants $J_{8,9}$ = 8.9 c/s and $J_{5^1,6^1}$ = 4.3 c/s enables the unambiguous assignments of the chemical shifts of protons 6^1 and 9 in adduct [52]. In the one case where comparison can be made, the olefinic protons in the adduct [46] show a coupling constant $J_{a,b}$ = 16 c/s,

whilst in our product described as [51], the value found is $J_{a,b}$ = 15.7 c/s.

(c) The cycl[3,3,2]azine spectra deserve some mention. It will be seen from Table IX that the protons of the pyridine moiety in adduct [53] are at slightly higher field than observed for the precursor [50] or the quinolizine-type adducts, and are close to the values we have found for 2-methylpyridine, results in keeping with the loss of further conjugation of the pyridine moiety in the adduct [53]. The saturated protons of the five-membered ring of compound [53] show the same coupling behaviour as found for analogue [48], viz. $J_{4\beta,5\beta}$ = 7.6 c/s (7.5), $J_{4\beta,5\alpha}$ = 0.0 c/s (0.0), and $J_{5\alpha,5\beta}$ = 17.2 c/s (17.5). The values in parentheses are those calculated for compound [48] which gave exact agreement of line position and intensity with the observed spectrum[24] This confirms that adduct [53] must possess a very similar geometry to that of compound [48], and further support of this fact is the presence of one very high field ester group (6.68 τ) parallel to the resonance (6.73τ) assigned to the 3-ester group in compound [48]. Molecular models established[24] that in the most favourable disposition of substituents in the adduct [48], the methyl portion of the 3-ester group lay at right angles to and just above the plane of the 4-phenyl group and would consequently be expected to be shielded by the circulating π-electron cloud of the phenyl moiety.

Table X

Ultraviolet spectral data, λ in mμ ($E.10^{-4}$)

Compound	Solvent	Maxima				
[46][24]	(M)	231(1.71)	295*(1.39)	339(2.28)	417(0.46)	
[47][24]	(M)	228(2.07)	311(2.92)	365(0.99)	465(1.07)	
[48][24]	(M)	271(1.01)	311(1.69)	360(0.84)	468(0.85)	
[49][24]	(M)	243(1.93)		330*(0.44)	414(0.57)	
[51]	(M)	227(1.67)	287(1.37)	340(2.51)	426(0.43)	
[52]	(M)	225(1.84)	307(3.05)	380.5(1.01)	467(0.94)	
[53]	(M)	269(1.29)	312.5(1.79)	360(0.97)	466(0.90)	
[54]	(M)	239(2.07)	285(2.30)	336*(0.42)	417(0.53)	
[47][24]	(A)	226*(1.90)	309(2.04)	390(1.65)	480*(0.36)	
[48][24]	(P)		276(0.48)		318(0.18)	330*(0.16)
[52]	(A)	220*(1.67)	307.5(2.63)	352*(1.14)	489(0.37)	
[53]	(P)	263.5(1.22)	270*(1.09)	283*(0.49)	319.5(0.60)	330*(0.54)

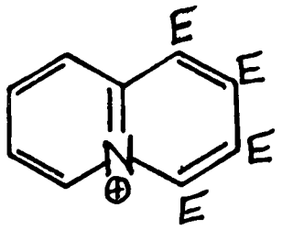
(M) = methanol; (A) = methanol containing ca. 5% by volume of perchloric acid (70%).

(P) = methanol : 70% perchloric acid :: 2:1.

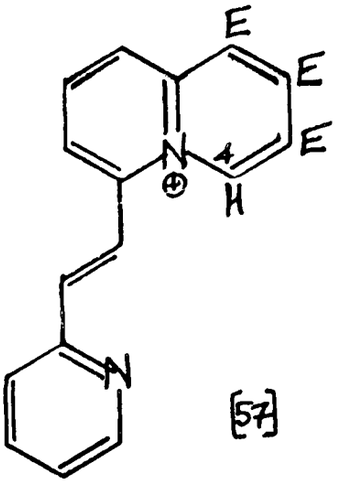
A smaller similar shielding of the 4-ester group is observed in the adducts [46][24] and [51].

(ii) The ultraviolet spectra of the adducts [51] - [54] when compared with their analogues, [46] - [49] respectively, see Table X, strongly support the formulations given.

(iii) The mass spectra of the adducts [51], [53] and [54] gave their molecular weights as 466 in further support of the structures proposed. Adduct [54] showed only three peaks in the mass spectrum of intensity greater than 10%, viz. m/e, %age of base peak : 466(10.3), 407(12.1), 362(100). The stability of the residue of m/e 362 is explained in terms of the loss of 9a-pyridylvinyl group (mass 104) from the molecular ion to give the aromatic quinolizinium tetraester cation [56]. The statistical peak at m/e 363, intensity 19.8%,



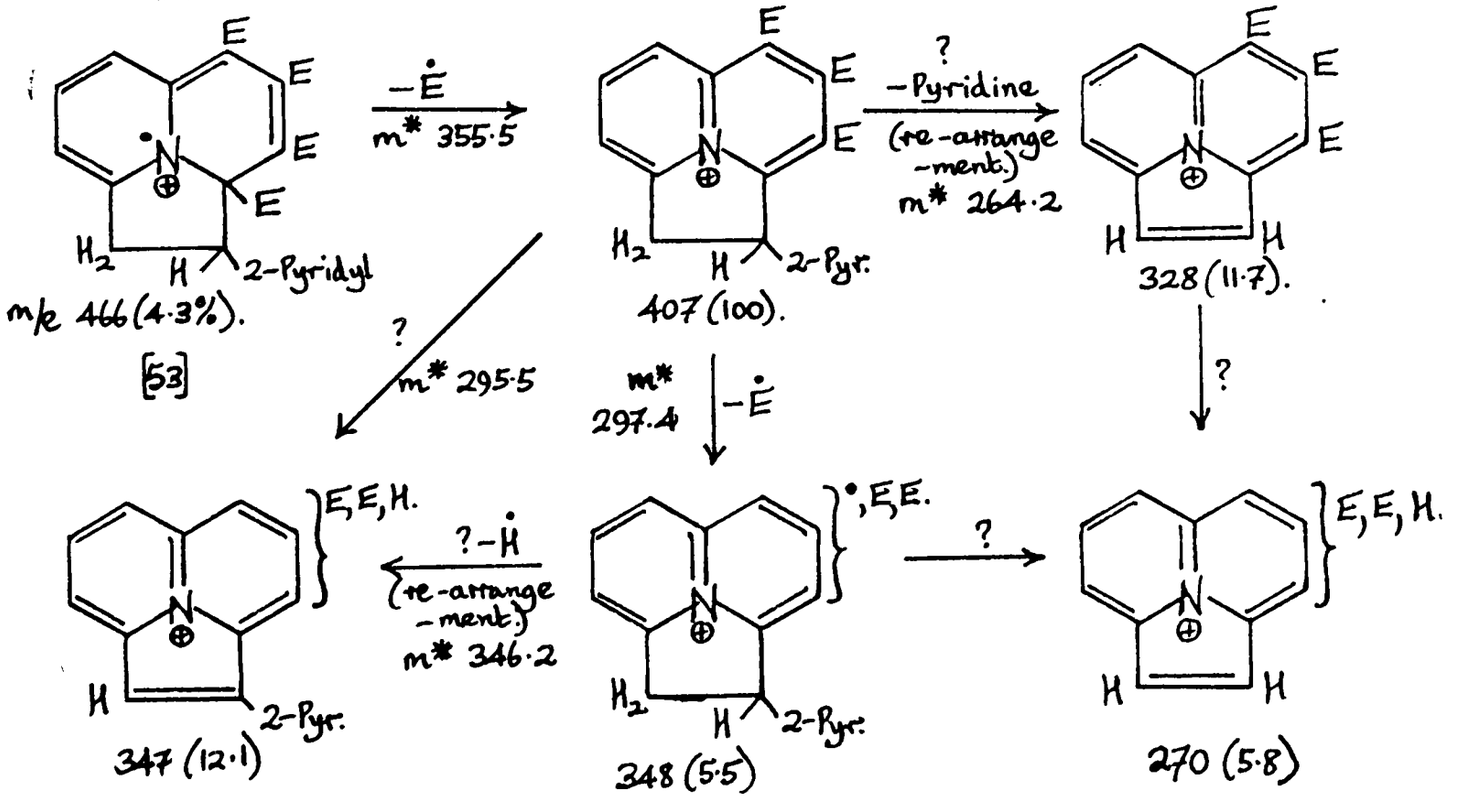
[56]



[57]

supports the molecular formula assumed since the calculated intensity based on $C_{17}H_{16}NO_8$ is 19.78%. The mass spectrum of adduct [51] is more complex which is probably to be expected in view of the adduct's facile thermal isomerisation

(vide infra). Loss of the 6-pyridylvinyl group is only a weak fragmentation (14.1%) since aromatisation to the quinolizinium salt would require additional rearrangement. Loss, presumably of the 9a-hydrogen, is also only observed as a weak peak (10.5%), and the base peak at m/e 407 corresponding to the loss of an ester group is interpreted in terms of thermal rearrangement to the 4H-quinolizine form [52] followed by loss of the 4-ester group to give the aromatic cation [57], though alternative explanations cannot be excluded in view of the mass spectrum of the cycl[3,3,2]azine [53]. A possible scheme of transitions in accord with the mass spectrum of adduct [53] is shown below:-



The base peak m/e 407 contains the aromatic quinolizinium cation which is shown as undergoing further fragmentation (but only to a small extent) to cations formulated as cycl-[3,3,2]-azinium derivatives. This system has already been proposed (see Chapter 4) to account for the mass spectrum of 1-methyl-cycl[3,2,2]azine.

As described in the experimental section the isomerisation of the adducts [51] and [54] was investigated under a variety of conditions mainly with the aid of thin-layer strip chromatography. As would be expected for an adduct possessing no mobile hydrogen atom, the compound [54] was unchanged by all the reaction conditions attempted. The conditions employed were based on those used by Acheson and Feinberg[24], and in general our observations followed the pattern described by them for their parallel family of adducts. Prolonged heating of the "labile" adduct [51] in solvents whose boiling points are lower than its melting point gave mainly the "stable" adduct [52], whilst heating either the "labile" adduct [51] or the "stable" isomer [52] above their melting points gave only the cycl[3,3,2]azine derivative [53].

It will have been noted that elemental analyses were not obtained for these four adducts. The adducts [51] and [54] could only be recrystallised satisfactorily from n-butanol, and even with this solvent attempted further recrystallisations after the initial one gave only tarry oils. The

adduct [53] was only prepared in small quantity and again was crystallised only with difficulty. The adduct [52] however was readily recrystallised from methanol but elemental analytical results after three recrystallisations were in poor agreement with those calculated for the molecular formula assumed on the basis of the mass spectra and n.m.r. integrations for the adducts [51], [53] and [54]. The result of a repeat analysis for compound [52] after four recrystallisations was partly satisfactory.

(vii) 2,6-Dimethoxypyridine.

In view of the previous isolation of adducts from 2-methoxypyridine and dimethyl acetylenedicarboxylate[126] and the alleged dependence of adduct formation on the pK_a of the pyridine precursor[124], it might be expected that 2,6-dimethoxypyridine, presumably a stronger base than 2-methoxypyridine, would also give rise to related adducts. No adducts were isolated, but all reaction conditions gave rise to tar formation and no starting materials were characterised after chromatography. It may be that the steric environment of the introgen atom in 2,6-dimethoxypyridine has affected the course of the reaction, particularly the feasibility of initial Michael attack of the nitrogen lone pair on the acetylenic ester. It is known that 2,6-di-t-butylpyridine is a much weaker base than expected from calculations and observed trends, and this is explained in terms of steric

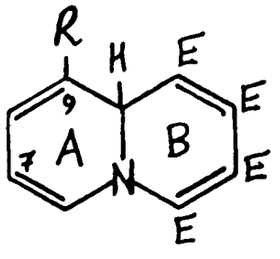
hindrance to the proton, a very much smaller approaching species[132].

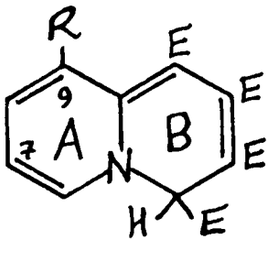
The 3-Substituted Pyridines.

Methyl 3-Pyridylacetate and 3-Cyanopyridine.

(i) The Quinolizine-type adducts.

Reaction of methyl 3-pyridylacetate and dimethyl acetylenedicarboxylate at room temperature in ether gave the adduct [58], purification of which by recrystallisation from n-butanol gave only the isomer [59]. 3-Cyanopyridine and the acetylenic ester in acetonitrile at room temperature gave the adduct [60] whose melting point behaviour on attempted purification suggested probable partial isomerisation to compound [61], though this product was not isolated in the pure state. The structures [58] - [60] proposed are based





[58] $R = CH_2E$

[60] $R = CN$

[62] $R = Me$

[59] $R = CH_2E$

[61] $R = CN$

[63] $R = Me$

entirely on the evidence of the nuclear magnetic resonance and ultraviolet spectral comparisons with the data available[21,68] for the known compounds [62] and [63].

The nuclear magnetic resonance results are set out in Table XI and comment is made as follows:

(i) The form of the spectra of the adducts [58] - [60], viz.

Table XI

Nuclear magnetic resonance data (τ) in deuterochloroform.

Compound	4-H	6-H	7-H	8-H	9-R	9a-H	Ester-Me
[58]	-	3.65	ca. 4.15	ca. 3.95	6.84 (CH_2)	4.97	6.09(2), 6.26-6.29(3).
[59]	3.92	2.28[1]	2.98	2.28[1]	*	-	6.07, 6.22-6.32(4[2]).
[60]	-	3.33	3.96	3.27	-	4.92	6.08(2), 6.17, 6.28.
[62][21]	-	3.78	4.05-4.22		8.19 (Me)	5.01	6.09(2), 6.24, 6.29.
[63][21]	3.89	2.48	3.07	2.33	7.72 (Me)	-	6.06, 6.24, 6.27, 6.31.

* obscured by ester-Me; [1]centre 2 proton multiplet;
[2]integration (14 protons) includes obscured 9-methylene group.

two doublets with J = 5-7 c/s, and a quartet with J = 11-13 c/s, relating to the A-ring protons excludes the alternative forms with the substituent R at position 7 which are always possible from 3-substituted pyridines but less often isolated, at least in the 9a<u>H</u>-quinolizine forms.

(ii) The 9-cyano-substituent in adduct [60] strongly deshields the adjacent 8-hydrogen and moves the other resonances of the A-ring to lower field also, as compared with adduct [62]. The doublet associated with H-8, $J_{7,8}$ = 5.4 c/s, shows additional coupling $J_{8,9a}$ = 1.6 c/s, a feature absent from

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Table XII

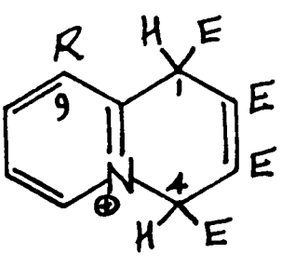
Ultraviolet spectral data, λ in mμ , ($E.10^{-4}$)

Compound	Solvent	Maxima					
[58]	(M)	236(1.51)	291(1.38)	297*(1.32)			444(0.45)
[59]	(M)	263(0.78)		318(1.09)		362(1.26)	437(0.81)
[60]	(M)	247(1.61)	272.5*(0.99)	305(0.85)	312.5(0.86)	340*(0.43)	450(0.43)
[62][68]	(M)	235(1.48)	289(1.48)				441(0.46)
[63][68]	(M)	262(0.74)		311(1.0)		360(1.3)	439(0.97)
[59]	(A)		274(0.62)	305(0.12)			
[63][68]	(A)		272.5(0.91)	316.5(0.07)			

(M) = methanol; (A) = methanol containing ca. 5% by volume of perchloric acid (72%).

the doublet ($J_{6,7}$ = 5.7 c/s) associated with H-6, thereby permitting the unambiguous assignments of H-6 and H-8 in adduct [60]. The 9a-proton shows the expected splitting of 1.6 c/s.

The results set out in Table XII show clearly the great similarity of the ultraviolet spectra in neutral solution of compounds [58] and [59] with the spectra of the established adducts [62] and [63] respectively. Only the spectrum of the "stable" adduct [59] changes on acidification where it again closely parallels the behaviour of the stable adduct [63]. Both these adducts in acid solution show a long wavelength absorption of very small extinction coefficient typical of the form [64] being the major protonated species and indicative of substitution at position 9[68].



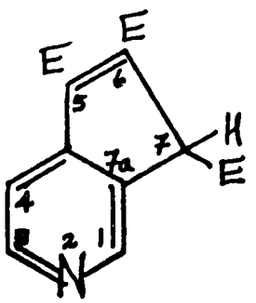
[64]

The adduct [60], by virtue of its 9-cyano group, carries one additional substituent conjugated to the ring system by comparison with the other adducts described here, and this factor may account for the apparently more tenuous relationship, as seen in Tables XI and XII, of its u.v. and n.m.r. spectra to those of the allegedly analogous products.

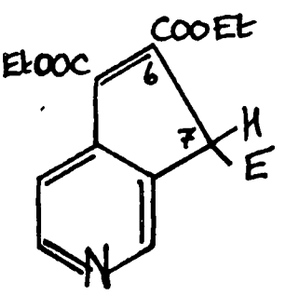
Elemental analyses in support of the structures proposed were not obtained owing to (a) the small quantities of material available and (b) the difficulties (vide supra and in Experimental section) associated with the purification of the compounds.

(ii) The low-temperature adducts.

When methyl 3-pyridylacetate [68] and dimethyl or diethyl acetylenedicarboxylate were reacted in acetonitrile solution for 4-7 days at temperatures of -10° rising in the later stages to $+5^{\circ}$, tiny quantities of adducts tentatively formulated as [65] and [66] respectively, were isolated.



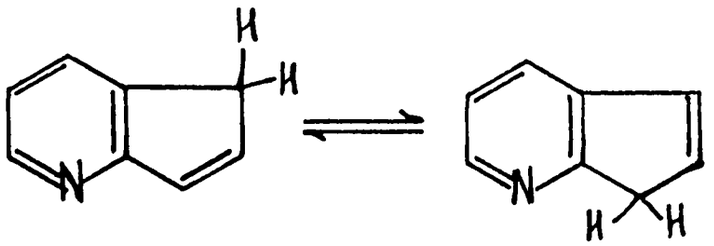
[65]



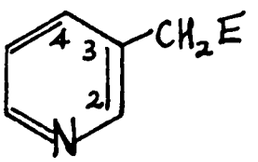
[66]

That the two adducts [65] and [66] were analogues was evident from their spectral characteristics (vide infra). The nuclear magnetic resonance spectrum of [65] is summarised as follows: proton, chemical shift (τ), coupling constant (c/s): H-1, 1.00, singlet; H-3, ca. 1.85, half of AB quartet, J = ca. 6.4; H-4, ca. 2.05, half of AB quartet, J = ca. 6.4; ester-methyl, 6.19, 3 protons, singlet;

ester-methyls and H-7, 6.24, 7 protons, singlet. The integration in the region 6.19 - 6.24 τ could accommodate 10 protons, and in seeking to substantiate the suggestion that H-7 was obscured in this region, the preparation of the ethyl ester analogue [66] was achieved. The n.m.r. spectrum of this compound is thus (notations as above): H-1, 0.96, singlet; H-3, ca. 1.79, half of AB quartet, J = ca. 6.5; H-4, ca. 2.00, half of AB quartet, J = ca. 6.5; 5- and 6- ethyl ester CH_2 groups, 5.67 and 5.77, quartets, J = 7.0; 5- and 6- ethyl ester CH_3 groups, 8.68 and 8.71, triplets, J = 7.0; 7- ester methyl group, 6.21, singlet; H-7, 6.67, singlet. Both spectra were run in DMSO-d_6. The peak attributed to H-7 (6.67τ) in adduct [66] gave a satisfactory integration for 1 proton and supports the view that the resonance for H-7 in adduct [65] is obscured in the region of 6.24 τ . Increased steric congestion in the C6-C7 region in adduct [66] may be the reason for the upfield shift (ca. 0.4 τ) of H-7 in [66] from the value observed in compound [65]. The methylene protons in the tautomeric system [67] are alleged to be non-identical and occur at 6.64 and 6.78 τ in the measured n.m.r. spectrum[133].



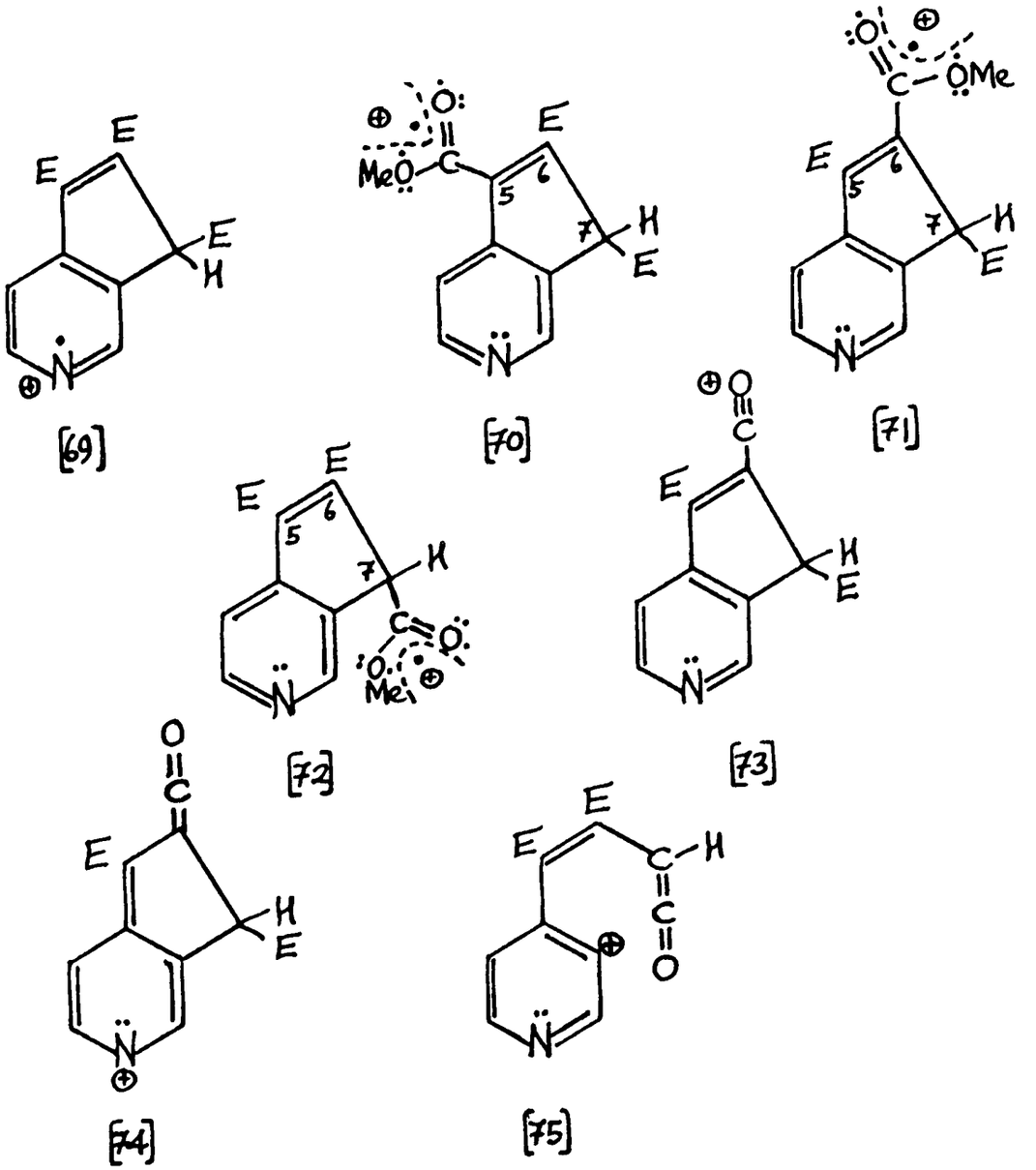
[67]



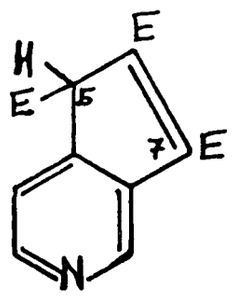
[68]

The form of the resonances associated with the 6-membered ring, viz. an AB quartet and a low field singlet excludes cyclisation across the 2,3-positions of the original pyridine [68], i.e. to forms based on the ring system [67], and is in accord with cyclisation across the 3,4-positions of [68].

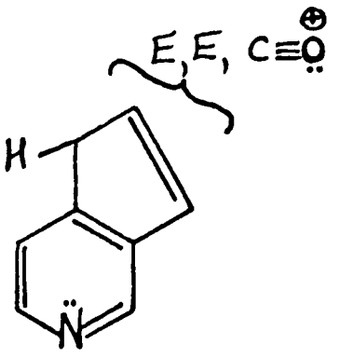
The mass spectra of adducts [65] and [66] give their molecular weights as 291 and 319 respectively, in harmony with the formulations given. The mass spectrum of compound [65] shows only two peaks (other than statistical peaks) with an intensity greater than 10%, viz. m/e, %age of base peak: 291,(93), molecular ion; 260,(100), base peak. The molecular ion includes amongst its resonance forms structures [69] - [72], three of these retaining the fully aromatic pyridine ring. The loss of the methoxyl radical to give the base peak most probably involves the 6-ester group, since the resultant species [73] deriving from the molecular ion form [71] can also have the canonical form [74]. Loss of methoxyl from either the 5- or 7- ester groups however gives cations (positive charge on the oxygen, type [73]) having



other canonical forms (e.g. [75]) whose stabilising contributions to the final system are likely to be much smaller than the contribution from form [74]. Some support for the formulation of the adduct as [65], the 7H-2-pyrindine rather than [76], the 5H-isomer may also be adduced from the mass spectrum, since for none of the base peak cations represented by [77] can canonical forms be written in which the positive charge is delocalised on the nitrogen, as in [74].



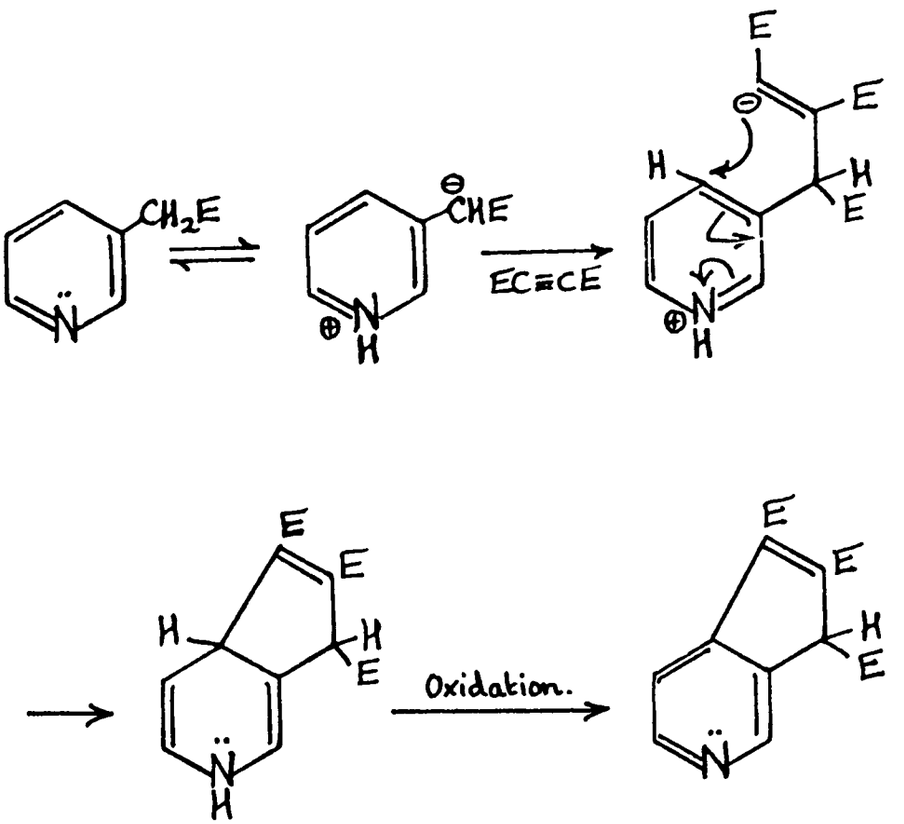
[76]



[77]

In accord with the above interpretation of the mass spectrum of adduct [65], compound [66] exhibits : m/e, %age of base peak: 319,(100), base peak and molecular ion; 274, (40.6), loss of ethoxyl. If parallel fragmentation processes obtain for compounds [65] and [66], the major primary loss of ethoxyl from [66] excludes initial loss of alkoxyl in these adducts from the 7-ester group. The peak at m/e 288 in the mass spectrum of [66] corresponding to the loss of the methoxyl radical has an intensity of only 8.0%.

A possible mode of formation of these low-temperature adducts is shown below. This involves the acceptable process of nucleophilic attack at the 4-position of the pyridinium ion in the cyclisation step.



[65]

EXPERIMENTAL SECTION

GENERAL.

Infrared spectra were measured on a Perkin-Elmer "Infra cord" Spectrophotometer using nujol mulls. The absorption bands at 6.24μ and/or 9.72μ of a polystyrene film were employed as external standards in all cases.

Ultraviolet spectra were obtained from a Perkin-Elmer "137-UV" Spectrophotometer fitted with a deuterium lamp, employing 1 cm. cells and spectroscopically pure solvents. In data given, an asterisk * indicates an inflexion in the absorption curve. The following abbreviations will be used in discussing and presenting data:

(M) Methanol solution.

(A) Methanol solution containing about 5% by volume of perchloric acid (72%).

(P) Methanol: perchloric acid (72%) :: 2:1 by volume.

(B) Methanol solution containing about 5% by volume of a saturated methanolic solution of sodium methoxide.

A Perkin-Elmer Spectrometer operating at 60 Mc/sec. and 34°C. was employed to obtain the nuclear magnetic resonance spectra, deuterochloroform (99.5%) being used as solvent unless otherwise stated, and tetramethylsilane being added as an internal standard.

Mass spectra were measured at low resolution under various conditions using an A.E.I. MS9 Mass Spectrometer. In the

experimental section "M, 371", for example, indicates the molecular weight required by the molecular formula preceding it.

Melting points were measured using a Reichert Microscope "RCH" Kofler Micro Heating Stage and are quoted uncorrected.

Alumina employed for chromatography was grade "H" 100/200's Mesh (P. Spence & Sons Ltd., or Koch Light Ltd.), deactivated by being shaken with 5% of its weight of 10% aqueous acetic acid until no lumps remained in the mixture, thereafter standing at least 12 hours before use. Columns were made up in benzene unless otherwise stated. The mixture to be chromatographed was dissolved in the minimum volume of benzene-chloroform (ca. 3:1 to 1:1 v/v) and poured on to the column. The fractions eluted off the column were evaporated to dryness under reduced pressure, the residue being then dissolved in the minimum volume of hot methanol, and the methanol solutions left to evaporate in small conical flasks. This method was always employed, unless stated to the contrary, and will be described in the following pages simply as "chromatography on alumina", followed by a statement of the volume of alumina used and a description of the eluent.

In a typical preparation of plates for thin-layer chromatography, 30 g. of MN-Silica Gel G (Macherey, Nagel & Co., Düren, Germany) were slurried with distilled water (45 ml.) for 1 minute, and then with more water (25 ml.) for a further 45 secs. Using a special apparatus, 6 plates (20 cm. square) could now have a layer of silica gel deposited on them to a depth of

300μ, which, after setting at room temperature, was baked for 40 minutes at 105°C.

Thin-layer chromatography spot-tests were carried out on strips cut from Eastman Chromagram Sheets Type K301R Silica Gel (100μ thickness) with Fluorescent Indicator (2540Å) using a stoppered test-tube as the chromatography tank. This technique will be described in future as "thin layer strip chromatography".

CHAPTER ONE.

Attempted reactions of some adducts from dimethyl acetylenedicarboxylate and pyridines or N-methylpyrrole with tetracyanoethylene and hexachlorocyclopentadiene.

(i) Tetramethyl 4H-quinolizine-1,2,3,4-tetracarboxylate.[68]

The 4H-quinolizine with tetracyanoethylene or hexachlorocyclopentadiene in benzene solution was unchanged after 5-7 days at room temperature as evidenced by the ultraviolet spectrum of the solution. Refluxing a benzene or acetonitrile solution of the 4H-quinolizine with either dienophile for periods of 21-48 hours gave intractable black-brown tarry solids, separating into 8-16 bands on a thin-layer plate. The only crystalline product obtained on one occasion by extraction of these bands was the 4H-quinolizine precursor.

(ii) Tetramethyl 7,9-dimethyl-9aH-quinolizine-1,2,3,4-tetracarboxylate.[68]

The 9aH-quinolizine was recovered unchanged from a benzene solution containing 1.6 molar proportions of hexachlorocyclopentadiene after 8 days at room temperature, but with tetracyanoethylene under very similar conditions gave rise to a brown tarry solid which separated into five bands on a thin layer plate, amongst which were bands arising from the 9aH-quinolizine precursor and its 4H-isomer, identified by their ultraviolet spectra-after extraction with methanol.

(iii) Tetramethyl 3a,7a-dihydro-1-methylindole-2,3,3a,4-tetracarboxylate.[69]

The ultraviolet spectrum showed no change after the indole and tetracyanoethylene had stood 8 days at room temperature in benzene. Evaporation of the solution resulting from the reaction of the indole and hexachlorocyclopentadiene in benzene for 8 days at room temperature, gave a purple tarry solid. Trituration with methanol led to the recovery of 9% of the indole precursor, whilst the residual purple material separated into 9 bands on a thin layer plate, one band arising from more of the indole, the others being unidentified.

(iv) Trimethyl indolizine-1,2,3-tricarboxylate.[68]

Unchanged starting materials were identified as the only components of reaction mixtures in benzene solution of the indolizine and either of the dienophiles employed above, after prolonged standing at room temperature or refluxing for 49-54 hours.

In all the above instances using thin-layer chromatography the various bands obtained were scraped from the plates, the silica extracted with methanol, and the filtered extracts left to evaporate in an attempt to obtain crystalline materials.

CHAPTER TWO.

1. Reactions of Dicyanoacetylene with Heterocycles. Preparation of Acetylenedicarboxamide.[70]

(a) To 0.880 ammonia solution (120 ml.) maintained at -10°, dimethyl acetylenedicarboxylate (30 ml.) was added in small aliquots shaking the mixture throughout. The creamy reaction mixture was stirred for 1½ hours at room temperature, filtered, the solid obtained being washed with a little ethanol, and dried in vacuo to constant weight. The process was repeated with a second batch of reagents. The combined weight of dry solid "amide" from the two runs, 52.9 g., represents a yield of 111.8% calculated as acetylenedicarboxamide.

(b) Dimethyl acetylenedicarboxylate (30 ml.) was added dropwise over a period of 30 minutes to a vigorously stirred 0.880 ammonia solution (24.5 ml., the stoichiometric quantity), rapid cooling of the reaction mixture taking place whenever the temperature rose above 0°. The solid product (14.4 g.), obtained after a further hour's stirring at room temperature and isolated as in (a), represents a yield of 60.7% calculated as the diamide. A portion of this product was obtained as tiny colourless rhombs from acetonitrile, m.p. decomp. from 200°, unchanged by 295°. (cf. literature[70] value, m.p. 290-2°).

(c) The ester (30 ml.) was added as in (b) to an ammonia solution (35 ml.) over a period of 1 hour. Aliquots of 0.880 ammonia

solution (5 ml. each, total 10 ml.) were added to the reaction mixture stirred at room temperature after a further 30 minutes and again after 3 hours. The yield of solid product (17.6 g.) isolated as in (a) was 74.3% (as diamide).

(d) Adding the 0.880 ammonia solution (35 ml.) to the ester (30 ml.) as in (b) over a period of 40 minutes, and isolating the product as described in (a) gave a cream-pink solid (24.2 g.), 102.2% yield. (as diamide.)

Preparation of Dicyanoacetylene.[70]

(a) Employing the apparatus and procedure described in the literature[71], runs using respectively 6.0, 10.0, and 7.0 g. of the diamide prepared in (a) above with in each case 50 g. of phosphorus pentoxide gave only trace quantities of dicyanoacetylene; the combined yield of product from the first two runs (determined by weighing the receiver) was 0.18 g. (1.6%.)

(b) Using a modified apparatus[72] in which the reaction vessel is a large horizontal tube containing a thin layer of the reagents which can be rotated as a flame is applied slowly along its length gave improved yields. Two runs with respectively 5.0 and 4.0 g. of diamide prepared in (a) above and phosphorus pentoxide (25 g. in each case) were carried out. To establish the yield and authenticity of the dicyanoacetylene, the product of the first run was

reacted immediately after its preparation with furan (4 ml.) in tetrahydrofuran (10 ml.) and left at room temperature for 3 days, when fine white crystals (0.49 g.) of the known[73] adduct, 1,4,5,8-diepoxy-4a,8a-dicyano-1,4,4a,5,8,8a-hexahydronaphthalene, precipitated out, a further batch (0.10 g.) being obtained by evaporation of the mother liquor, the product being identified by comparison of its infrared spectrum with the quoted data. On the basis of a 90% conversion to the adduct (literature[73] 96%), the amount of dicyanoacetylene precursor (0.235 g.) represents a yield of 6.9% from the diamide.

(c) Using the apparatus described in (b), the amide (14.4 g.) from preparation (b) with phosphorus pentoxide (50 g.) gave dicyanoacetylene (2 g.), 20.5% yield (the best observed), determined by weighing the receiver.

Reaction of Dicyanoacetylene with Pyridine.

To dicyanoacetylene (ca. 0.2 g. from preparation (a)) in dry ether (5 ml.) at ca. -50° was added dry pyridine (3 ml., excess) dropwise and an immediate precipitation of a turquoise solid occurred, which was filtered off from the ethereal solution at room temperature. No solvent being found suitable for its recrystallisation, a little of the solid was separated on a thin layer plate (eluent benzene : ethyl acetate :: 1:2 by volume) into 10 bands, of which two were dominant; one, turquoise, R_f 0.10, the other, yellow, R_f 0.42. Separation of

the whole sample of solid with this eluent on 10 plates, and extraction of the bands with methanol, gave ca. 2-5 mg. of a yellow-brown solid from the extract of the yellow band, R_f 0.42, as the only isolable solid product.

U.V. λ in mμ (absorbance values): (M) 223(0.89), 242(0.86), 267.5(0.69), 273*(0.69), 365(0.22), 420(0.54), 442(0.79).

Reaction with Thiophene.

(a) To dicyanoacetylene (ex second run of preparation (b)) cooled in a vessel in a solid carbon dioxide-acetone bath thiophene (5 ml.) was added, the mixture left at room temperature for 7 days, the solution was evaporated in vacuo, the brown residue was dissolved in benzene-ethyl acetate (1:1 by volume) and chromatographed on alumina (100 ml.) with benzene-ethyl acetate (1:3 by volume) as eluent. No solid product was isolated.

(b) Similar negative results were obtained when chromatographic treatment parallel to that in (a) was applied to the dark brown solid residue obtained after refluxing dicyanoacetylene (2 g., ex preparation (c)) in thiophene (12.5 ml.) for 4½ hours and evaporating the liquid phase in vacuo.

2. Reactions of Tetracyanoethylene Oxide with Heterocycles.

Preparation of Tetracyanoethylene Oxide.

The oxide was prepared as described in the literature[74] on two occasions. The yields from 25 g. batches of tetracyanoethylene were 15.5 g. (55%) and 11.1 g. (39.5%), the poorer yield being accounted for in terms of too low a reaction temperature. The authenticity of the product was deduced from comparison of its infrared spectrum with the published[74] data.

Reaction with Thianaphthen.

The general procedural technique is that of the literature[75]. Tetracyanoethylene oxide (2.5 g.) and thianaphthen (7.0 g.) were refluxed in 1,2-dibromoethane (25 ml.) under anhydrous conditions for 30 hours, filtration of the cold reaction suspension yielding an intractable black solid (0.71 g.). Evaporation of the filtrate in vacuo and trituration of the evaporate with dry ether (250 ml.) precipitated a buff solid (0.99 g.), recrystallised from carbon tetrachloride (80 ml.) to yield the adduct, 1,1,3,3-tetracyano-1,3,3a,8b-tetrahydrothianaphthyl [2,3-c] furan, (0.56 g.) as pale buff crystals. Evaporation of the ethereal mother liquor and trituration of the evaporate with carbon tetrachloride precipitated more of the buff solid, which after recrystallisation from carbon tetrachloride gave a further yield (0.49 g.) of essentially pure adduct. The adduct (total 0.96 g., 19.7% yield, once recrystallised), four times recrystallised from carbon tetrachloride as colourless square

plates, decomposed slowly from 177°, and had m.p. 193-4°.

Found: C, 60.7; H, 2.33; N, 20.4; S, 11.4

$C_{14}H_6N_4OS$ requires: C, 60.4; H, 2.16; N, 20.15; S.11.5

I.R. (5-7μ region): 4.43 (v. weak), 6.29 (weak), 6.85.

U.V. λ in mμ ($\epsilon.10^{-4}$): (M) 245(0.79), 278*(0.10), 290(0.09).

Concentration of the carbon tetrachloride solution from which the further yield of adduct had precipitated out gave a dark red syrup which slowly deposited long dark purple needles (0.31 g.), which on spectroscopic and chromatographic evidence comprise a mixture of thianaphthen precursor and tetracyanoethylene, the latter substance being obtained pure (infrared spectrum) when a sample of the needles was recrystallised from cyclohexane.

Reaction with Dibenzo [b,d] thiophene.

Tetracyanoethylene oxide (2.5 g.) and dibenzothiophene (4.83 g.) after being refluxed for 42 hours in 1,2-dibromoethane (40 ml.) gave a suspension of dark solid in a purple solution. Isolation of this solid by filtration, and of three further batches of solid by successive evaporations of the filtrate and trituration with 60-80° petroleum ether or cyclohexane was carried out yielding a total of 5.19 g. of crystalline material, comprising dibenzothiophene and tetracyanoethylene only (73.7% combined yield), identified by their infrared spectra after separation by vacuum sublimation and fractional crystallisation.

Reaction with 2,5-Dimethylthiophene.

When tetracyanoethylene oxide (2.5 g.) and 2,5-dimethylthiophene (5.88 g.) were refluxed in 1,2-dibromoethane (40 ml.) for 22 hours, and the reaction mixture investigated by methods parallel to those described for the last two experiments, no characterisable material was isolated.

Reaction with N-Methylpyrrole.

(a) Tetracyanoethylene oxide (5 g.) and redistilled N-methylpyrrole (8.7 g.), which were seen to undergo violent exothermic reaction in the absence of solvent, were refluxed in 1,2-dibromoethane (50 ml.) under anhydrous conditions for 3 hours. Attempted purification of the brown solid (4.35 g.) isolated from the reaction mixture, by recrystallisation and column chromatography gave no characterisable product.

(b) When a suspension of the oxide (2.5 g.) in 1,2-dibromoethane (10 ml.) at 10° was added to a solution of the pyrrole (2.9 g.) in the same solvent (15 ml.), and the mixture left for 21 days at room temperature, the red-brown solid (0.18 g.) recovered by filtration after this time, could not be characterised, nor was any crystalline product obtained from alumina chromatography of the above filtrate.

3. Methyl Tetrolate and some Pyridines.

Proceeding in accord with the literature[76] the reaction of

chlorine (c. 16 g.), triphenylphosphine (52.4 g.), triethylamine (62 g.) and methyl acetoacetate (24 g.) in benzene solution, gave the phosphorane (50.4 g., 66.9% yield) after recrystallisation from ethyl acetate. Heating the phosphorane (41.8 g.) as described[76] gave methyl tetrolate (6.45 g., 59.3% yield) after purification by vacuum distillation.

Reaction with Pyridine.

To dry pyridine (1.01 g.) was added methyl tetrolate (2.80 g.) and acetonitrile (10 ml.). The mixture after standing 11 days at room temperature gave a viscous brown liquid of pungent odour after concentration in vacuo, which was chromatographed on alumina (200 ml.) but subsequent purification of the column fractions by thin layer chromatography gave an isolable solid in one instance only, obtained as pale yellow rods (ca. 1 mg.), m.p. 113-127°.

U.V. λ in mμ (absorbance values): (M) 255.5(0.18), 261.5(0.19), 380(1.21).

Reaction with 4-Methylpyridine.

When the reaction mixture from 4-methylpyridine (1.0 g.) and methyl tetrolate (2.48 g.) in acetonitrile (10 ml.) after 11 days at room temperature was treated in a manner similar to that described for pyridine above, no solid products were isolated.

Reaction with 3,5-Dimethylpyridine.

Chromatography on alumina (300 ml.), eluent benzene, of the

concentrated reaction mixture from 3,5-dimethylpyridine (0.53 g.) and methyl tetrolate (1.17 g.) in acetonitrile (7 ml.) after 39 days at room temperature gave an impure yellow solid (11.5 mg.) from fractions 4-6. Recrystallisation from ether-methanol gave pale yellow needles (5.8 mg.), m.p. 136-7°.

I.R. (5-7μ region): 6.02*, 6.09, 6.26, 6.85.

U.V. λ in mμ (absorbance values): (M) 266(0.10), 385(1.32).

(A) no maxima at $\lambda > 220$ mμ

CHAPTER THREE.

Reactions of Heterocycles with Methyl Phenylpropiolate.

Preparation of Methyl Phenylpropiolate.

(a) This was prepared on two occasions as described in the literature.[77] From cinnamic acid (200 g. each time) the yields of methyl cinnamate were respectively 190 g. (86.8%) and 188.4 g. (86%). Bromination of the ester, and subsequent dehydrobromination of this product by sodium hydride (isolated from a suspension in oil) and methanol in benzene solution gave after fractional distillations methyl phenylpropiolate described, respectively, as follows: 97 g. (44.9% overall yield), b.p. 127-36°/10 mm. n^{25} 1.5605. 115 g. (53.2% overall yield), b.p. 128-34°/14 mm. (cf. literature data,[78] b.p. 158-9°/48 mm.; 132-3°/16 mm.; m.p. 26°. n_D^{25} 1.5618.)

Both samples of methyl phenylpropiolate were undoubtedly contaminated with the oil from the sodium hydride suspension even though the hydride was presumed to have been freed of this oil by successive washings and decantations with several portions of dry benzene. The physical properties of the oil[79] preclude its complete separation from methyl phenylpropiolate by fractional distillation.

(b) Esterification of phenylpropiolic acid, m.p. 136-7°, (33.0 g.) at room temperature for 48 hours with methanol in

sulphuric acid gave, after fractional distillation, methyl phenylpropiolate (20 g., 55.4% yield), b.p. 123-6°/10 mm., which, in contrast to the samples prepared in (a), solidified on storage at 5°.

Reaction of Methyl Phenylpropiolate with Pyridine.

(a) Pyridine (1.02 g.) and methyl phenylpropiolate (4.58 g.) after 26 days at room temperature in acetonitrile (15 ml.) gave after removal of the solvent in vacuo, a dark red viscous liquid which was chromatographed on alumina (300 ml.), eluting with benzene. Fractions 3 and 4 after standing 7 days gave a yellow adduct (76 mg., 2.4% yield), which twice recrystallised from methanol had m.p. 134-6° (decomp.) and was unstable to light and/or air.

Found†: C, 71.8; H, 5.54; N, 5.85; OMe, 12.3.

$C_{30}H_{28}N_2O_5$ requires: C, 72.5; H, 5.64; N, 5.64; OMe, 12.5, M,496.

Molecular weight†: 496 (by mass spectroscopy).

I.R. (5-7μ region): 5.84, 5.97, 6.04, 6.20, 6.31, 6.35, 6.72, 6.85, 6.98*, 7.05.

U.V. λ in mμ ($\epsilon.10^{-4}$)†: (M) 259(3.06), 369(4.69).

(B) 258.5(3.06), 368.5(3.95), 390*(2.81).

(A) 257*(2.04), 278(2.55), 380(1.15), 470(0.27).

(P) 260*(2.46), 275(2.75), 345*(0.93), 510(0.11).

(b) On another occasion pyridine (3.0 g.) and methyl phenylpropiolate (13.5 g.) after standing 25 days at room temperature in acetonitrile (40 ml.) gave, after chromatography on alumina (500 ml.) with benzene eluent, a crude sample (118 mg., 1.25% yield) of the yellow adduct from fraction 2, which after three recrystallisations from methanol gave yellow microcrystals (28.5 mg.), m.p. 133.5-135.5° (decomp.). The data in section (a) above marked (†) refers to this sample of the adduct.

(c) No solid products were isolated after chromatography on alumina of the evaporated reaction mixtures from (i) a further reaction of pyridine (3.0 g.) and methyl phenylpropiolate (13.5 g.) for a period of 25 days at room temperature in acetonitrile (40 ml.), (ii) the reaction of pyridine (2.0 g.) and methyl phenylpropiolate (9.0 g.) in refluxing acetonitrile (20 ml.) for 66 hours, and (iii) pyridine (2.0 g.) and the ester (7 g.) in methanol (15 ml.) and water (2 ml.) at room temperature for 51 days.

(d) When the evaporated reaction mixture from pyridine (2.0 g.) and methyl phenylpropiolate (9 g.) after 26 days at room temperature in acetonitrile (20 ml.) was chromatographed on alumina (400 ml.) with benzene, fraction 6 after standing 18 days gave a dark red solid (2.9 mg.), m.p. 204-6°.
I.R. (5-7μ region): 6.02, 6.14, 6.22, 6.27, 6.37, 6.51, 6.72* (weak), 6.89, 7.06* (weak).

(e) The same reagents in the same quantities after 68 days at room temperature and chromatography on alumina (400 ml.) with benzene gave very small quantities of solid materials from fractions 2, 3 and 8, respectively dark red needles (8.5 mg.), m.p. 191-4° (decomp.), dark red needles (13.3 mg.), m.p. 193.5-195.5° (decomp.), and scarlet rhombs (7.1 mg.), m.p. 216.5-218.5°, none of which could be characterised further.

Reaction with 3,5-Dimethylpyridine.

(a) The reaction mixture from 3,5-dimethylpyridine (1.03 g.) and methyl phenylpropiolate (3.4 g.) in acetonitrile (15 ml.) after 19 days at room temperature was concentrated in vacuo, and chromatographed on alumina (300 ml.) eluting with benzene (1900 ml.) and then benzene-chloroform (3:1 by volume), to give (from fraction 2 of the benzene elution) a yellow adduct (17 mg.), m.p. 113-7°, after one recrystallisation from methanol.

I.R. (5-7μ region): 6.04, 6.13, 6.27, 6.71, 6.86.

U.V. λ in mμ (absorbance values): (M) 226* (0.18), 264* (0.11), 276 (0.12), 384 (0.76).
(A) 284 (0.16).

(b) Two batches of the pyridine (2.5 g.), the ester (10.0 g.) and acetonitrile (25 ml.) after standing 19 days at room temperature followed by concentration in vacuo, were combined and chromatographed on alumina (600 ml.) with benzene. A brown sticky solid (0.123 g.) was isolated from

fraction 2 after 12 days, which was washed with ether to give a white waxy material (0.108 g.).

Identical treatment of two additional reaction mixtures, the composition of which differed from that of those above only in respect of the quantity of the ester, now 8.5 g., gave, again from the second fraction of the column, a further yield of the brown waxy solid (0.119 g.), isolated after 27 days.

The combined material (0.23 g.) after being ground up beneath acetone gave a white crystalline solid (0.105 g.), m.p. 124-7°. The spectral data below relate to this material. After three recrystallisations from benzene, the product (16 mg.), white rods, had m.p. 120-121.5°, new crystals forming from 126°, which darken (yellow) from 142°, finally melting 182-191° (decomp.). The analytical results relate to this material.

Analysis: Found: C, 70.2; H, 6.45; N, 5.84; OMe, 1.52.

I.R. (5-7μ region): 2.99, 3.12*, 6.08, 6.14, 6.28, 6.40*, 6.49* (weak), 6.69*, 6.85.

U.V. λ in mμ (absorbance values): (M) 263 (1.03). (A) 275 (1.23).

(c) No solid products were isolated after alumina chromatography of the evaporated reaction mixtures from (i) a further reaction of 3,5-dimethylpyridine (2.0 g.) and methyl phenylpropiolate (8.0 g.) for a period of 57 days at room temperature in acetonitrile (30 ml.), (ii) a

similar reaction of the pyridine (1.35 g.) and the ester (5.4 g.) in acetonitrile (15 ml.) at room temperature for 118 days, and (iii) the pyridine (2.0 g.) and the ester (6 g.) in methanol (15 ml.) and water (2 ml.) for 81 days at room temperature.

(d) When 3,5-dimethylpyridine (3.0 g.) and methyl phenylpropiolate (12 g.) were refluxed in acetonitrile (25 ml.) for consecutive periods of 3, 2 and 4 days, the quantities of crystalline solid isolated after each period of reflux were respectively 0.44 g., 0.27 g., and 0.25 g., no more product being isolated after a further prolonged period of reflux either by the method described below or by chromatography on alumina (400 ml.) of the final reaction evaporate. The crude product, isolated by evaporation of the reaction mixture in vacuo, trituration with ether, and filtration, 1,3,5-trimethylpyridinium bromide (0.96 g., 17.1% yield) was obtained as colourless hexagonal plates, hygroscopic, m.p. 305-9° (sublimation and decomposition), after four recrystallisations from ether-methanol.

Found: C, 48.6; H, 6.02; N, 6.86; OMe, 0.24.

$C_8H_{12}NBr$ requires: C, 48.55; H, 5.94; N, 6.93; OMe, 0.00.

I.R. (5-7μ region): 3.97, 4.91, 5.22, 5.35, 5.45 (all v. weak), 6.16, 6.27 (weak), 6.53*, 6.65, 6.73*, 6.88.

U.V. λ in mμ ($\epsilon.10^{-4}$): (M), (B), (P) 271(0.49), 278*(0.42).

In the first isolation of the bromide, the pyridine

(1 g.) and the ester (4 g.) were refluxed in acetonitrile (25 ml.) for 68 hours, the crude product (87 mg., 4.6% yield) being isolated as described above, chromatography on alumina (300 ml.) with benzene of the evaporated filtrate from this single session of reflux giving no further solid products.

On another occasion the final accumulated yield of the bromide was 1.19 g. (15.8%) after the pyridine (4.0 g.), the ester (16.0 g.) and acetonitrile (50 ml.) had been refluxed for a total of 20½ days. Replacing ether by acetone in the isolation procedure gave a cleaner product. No other characterisable products were obtained from chromatography on alumina (600 ml.) of the final evaporated reaction mixture.

In a control reaction, 3,5-dimethylpyridine (3.0 g.) was refluxed in acetonitrile (50 ml.) for 12 days, no solid products being precipitated, evaporation of the solvent in vacuo and vacuum fractionation of the residue giving 3,5-dimethylpyridine (2.1 g., 70% recovery), b.p. 56-7°/13.8 mm., identified by comparison of its infrared spectrum with that of an authentic sample, a very small quantity of brown tar being the residue in the distillation flask.

Reactions of 1,3,5-trimethylpyridinium bromide.

(i) The salt, soluble in water, dissolved more readily in dilute nitric acid, trituration of the solution with silver nitrate solution giving an immediate dense very pale yellow precipitate which was fairly soluble in

concentrated aqueous ammonia solution.

(ii) Warming a little of the salt with 2-3 drops of concentrated sulphuric acid caused the evolution first of an acid gas, fuming in moist air (presumably hydrogen bromide), and later dense brown pungent fumes of bromine were observed.

1,3,5-Trimethylpyridinium perchlorate.

(a) To 1,3,5-trimethylpyridinium bromide (0.113 g., once recrystallised) in distilled water (10 ml.) add a solution of silver perchlorate (0.112 g.) in water (10 ml.) and digest the resulting aqueous suspension of silver bromide for 1 hour at 100°. Cool the solution, remove the silver bromide by filtration and evaporate the filtrate to dryness in vacuo, adding methanol to assist in the removal of the last traces of water. The crude solid evaporate (66.7 mg., 53.8% yield), 1,3,5-trimethylpyridinium perchlorate was obtained as colourless microcrystals (32.7 mg.), m.p. 218-9°, after two recrystallisations from ethanol containing a trace of perchloric acid, identical on the basis of m.p., mixed m.p. and infrared spectrum (2.5-15μ) with an authentic sample prepared as described below.

Found: C, 43.7; H, 5.53; N, 6.05.

$C_8H_{12}NO_4Cl$ requires: C, 43.3; H, 5.41; N, 6.32.

I.R. (5-7μ region): 3.24 (strong), 3.94, 4.95, 5.38, 5.47, 5.63 (all v. weak), 6.11, 6.21 (weak), 6.64, 6.85.

(b) To methyl iodide (3.5 ml., ca. 8.0 g.) in ethanol (50 ml.) was added freshly distilled (from calcium hydride) 3,5-dimethylpyridine (5.5 ml., 5.2 g.) and the mixture refluxed for 3 hours, to give, after filtration and subsequent evaporation, 1,3,5-trimethylpyridinium iodide (11.27 g., 92.4% yield) as a pale yellow crystalline solid, m.p. 268-9°; a portion recrystallised from ethanol was recovered as white needles, m.p. 268-268.5°, turning yellow from 250°. A further portion (0.52 g.) of the iodide was treated with the appropriate quantity of silver perchlorate (0.46 g.) etc. exactly as described in (a), to give an authentic sample (0.41 g., 87.8% yield) of 1,3,5-trimethylpyridinium perchlorate, colourless microcrystals, identical in physical characteristics with the sample described in (a).

Reaction with Isoquinoline.

(a) To isoquinoline (2.5 ml.) was added methyl phenylpropiolate (5 ml.) in methanol (15 ml.) and water (2 ml.), and after standing at room temperature for 31 days, orange-yellow crystals (1.53 g.) were recovered by filtration, a further batch (0.37 g.) being isolated similarly from the filtrate after an additional 24 days. The adduct, (1.90 g., 32.6% yield), 2-oxo-4-phenyl-1,2,5,11b-tetrahydro-isoquinolino-[1,2-b]-1,3-oxazine, after three recrystallisations from acetonitrile was obtained as pale yellow microcrystals,

m.p. 240-241.5°.

Found:	C, 78.6; H, 4.80; N, 5.20; OMe, 0.00.
$C_{18}H_{13}NO_2$ requires:	C, 78.5; H, 4.76; N, 5.09; OMe, 0.00.
I.R. (5-7μ region)†:	5.53 (weak), 5.88, 6.09, 6.24, 6.28, 6.38, 6.71, 6.87, 7.00.
U.V. λ in mμ (ε.10^{-4})†:	(M) 234.5(3.36), 270(2.19), 350(0.43)
	(B) 237(1.23), 301(1.20), 331*(0.87).
	(A) 236.5(4.86), 270(1.90), 346(0.38)
	(P) 238(4.99), 273(2.00), 345(0.40)

The data marked (†) above relate to earlier isolations of the adduct described below.

(b) In the original isolation of the adduct, isoquinoline (1.03 g.) and methyl phenylpropiolate (2.55 g.) were treated as follows:

(i) stood at room temperature in acetonitrile (15 ml.) for 8 days, (ii) this solution refluxed for 24 hours, after which the solvent was removed in vacuo, (iii) residue taken up in benzene (25 ml.) and refluxed for 78 hours, finally (iv) standing for 48 days at room temperature in this benzene solution, when the crude adduct (0.106 g., 5% yield), yellow crystals, m.p. 212-6°, precipitated out and was isolated by filtration, washing with ether. After two recrystallisations from acetonitrile the adduct is obtained as pale yellow microcrystals, m.p. 240-1°, with the

properties marked (†) above.

(c) Isoquinoline (4.0 g.) and methyl phenylpropiolate (6.0 g.) were treated variously in a manner similar to that described in (b), also being left to react in the absence of solvent for a total of 99 days, over a period totalling 117 days, trituration of the final reaction evaporate with benzene precipitating the crude adduct (0.10 g.), a further yield (1.22 g.) of the adduct being obtained from fractions 5-7 after the benzene filtrate had been chromatographed on alumina (400 ml.) eluting successively with benzene and benzene-chloroform mixtures, 7:1 and 3:2 by volume, this last eluent bringing off an orange-brown band in fractions 5-7. The total yield in this experiment was 15.5%.

Reactions of the Isoquinoline-Methyl Phenylpropiolate adduct.

Hydrolysis with concentrated hydrochloric acid.

The adduct (0.43 g.) and concentrated hydrochloric acid (20 ml.) were sealed in a glass bomb and heated at 135° for 28 hours and then at 191-6° for 18 hours. The reaction mixture, from which black carboniferous solid (0.10 g.) was filtered off, was extracted with chloroform (4 x 60 ml.), basified with potassium hydroxide pellets and extracted again with chloroform (4 x 60 ml.), after which the extracts were dried over anhydrous magnesium sulphate. Evaporation of the dry "acid" extract gave an uncharacterisable waxy white deposit, whilst parallel treatment of the "alkaline" extract gave a small volume of liquid

product whose odour and ultraviolet spectrum (in methanol) suggested that this was isoquinoline. Trituration of a portion of a methanolic solution of this product with methanolic picric acid gave the picrate of isoquinoline (96 mg.), which after one recrystallisation from acetonitrile was obtained as yellow needles (64 mg.), m.p. 219-221° and melted undepressed in admixture with an authentic sample of the picrate of isoquinoline of m.p. 219-220°. The infrared spectra confirmed the identity of the two picrates. Assuming a quantitative conversion to the picrate, the calculated yield of isoquinoline picrate from the whole of the "alkaline" extract solution, 0.335 g., represents a yield of 59.6% in the initial reaction.

Hydrolysis with ethanolic potassium hydroxide.

When the crude adduct (0.22 g.) was refluxed for 4 hours in a solution of potassium hydroxide (0.26 g.) in ethanol (15 ml.), extraction of the reaction mixture with chloroform (4 x 20 ml.) after removal of ethanol in vacuo and neutralisation with dilute hydrochloric acid, led to the isolation of a brown solid (57 mg., 25.9% recovery), unchanged starting material, as evidenced by the infrared spectrum of the yellow crystals (30 mg.) resulting from the recrystallisation of the brown product from acetone.

Hydrolysis with aqueous potassium hydroxide.

The adduct (0.38 g.) was refluxed in aqueous solution (30 ml.) with potassium hydroxide (10 g.) for 5 hours, but extraction of the solution with chloroform both before and after acidification

led only to the isolation of an uncharacterisable brown solid (4.5 mg.) and other tarry products.

Oxidation with alkaline potassium ferricyanide.

The adduct (0.59 g.) in 10% W/W aqueous potassium hydroxide solution (10 ml.) was triturated with a solution of potassium ferricyanide (3.1 g.) in water (6 ml.) and the mixture heated for 5 hours at 100°. Filtration of the cold mixture gave a tarry brown solid (0.32 g.), extraction of the filtrate with chloroform under both alkaline and acidic conditions leading only to the isolation of traces of uncharacterisable material in form of a brown liquid (no picrate formation) and a blue-grey powder (66 mg.), probably inorganic matter, which could not be purified. The tarry brown solid was still very impure after precipitation from a chloroform solution by the addition of a large excess of ether and resisted further characterisation.

Reaction with N-Methylpyrrole.

When N-methylpyrrole (1.00 g.) and methyl phenylpropiolate (4.69 g.) in acetonitrile (15 ml.) stood for 61 days at room temperature, removal of the solvent in vacuo gave an orange liquid, vacuum fractionation of which gave unchanged methyl phenylpropiolate (3.8 g., 81% recovery), b.p. 129-141°/14 mm., identified by its infrared spectrum, as the only isolable material.

CHAPTER FOUR.

Reactions of Methyl Propiolate with Pyridines.

Synthesis of Propiolic Acid.[80]

Propiolic acid was prepared as described[80] by the oxidation of propargyl alcohol in acetone with chromium trioxide in concentrated sulphuric acid. Starting with 60 g. aliquots of the alcohol on two occasions the yields of pure propiolic acid after two fractional distillations in vacuo were 36.8 g. (49.1%) and 33.7 g. (45.1%).

Synthesis of methyl propiolate.

Propiolic acid (prepared as above or ex manufacturer) was esterified with methanol in the presence of catalytic quantities of concentrated sulphuric acid at room temperature over a period of 60-119 hours, the longest reaction time giving the best yield. Methyl propiolate, isolated by dilution of the reaction mixture with an equal volume of water followed by ether extraction, evaporation of the dried ethereal extracts and fractionation of the residue at atmospheric pressure, was obtained on four occasions in yields of 41-59%, b.p. 99-102°/744-757 mm.

Methyl Propiolate with Pyridine.

(a) An attempt to repeat the reaction described by Johnson et al.[81] Pyridine (2 g.), distilled from after prolonged reflux over calcium hydride immediately before use, in sodium dried ether (8 ml.) was added dropwise from a constant pressure funnel over a period of 30 minutes,

swirling continually, to a solution of methyl propiolate (4 g.) in dry ether (4 ml.), the reaction vessel being protected from moisture by a calcium chloride drying tube. The reaction, carried out at room temperature, evolved some heat. The reaction mixture after an additional 17 hours at room temperature contained red tar, no crystalline product being discerned. The solution and tar were poured into dry ether (800 ml.), and after scratching the tar for a prolonged period, a brown tar-free solid (1.32 g.) of a very impure nature and different from the product of the literature[81] on the evidence of its infrared spectrum was isolated by filtration. Attempts to purify and characterise this solid by recrystallisation and thin layer chromatography were unsuccessful. The red ethereal filtrate (800 ml.), after evaporation in vacuo, was chromatographed on alumina (450 ml.) with benzene to give, from fraction 1, methyl 1-methoxycarbonylmethyl-indolizine-2-carboxylate, (36.1 mg., 0.6% yield), pale yellow rods, m.p. 87-88.5°, which after one recrystallisation from cyclohexane had m.p. 77-81°. The structure of the product and its identity with that described in the literature[81] is confirmed by its ultraviolet and nuclear magnetic resonance spectra. These latter also establish that the recrystallised material contains approximately 1 part in 8 by weight of the cyclazine adduct (vide infra) which is in accord with the depressed, wide-range m.p. 77-81° (literature[81] value,

m.p. 88-89°.) observed after recrystallisation, and deductions from thin-layer strip chromatography.

U.V. λ in mμ ($\epsilon.10^{-4}$)†: (M) 235.5(2.49), 240*(2.27), 292.5(0.28), 305.5(0.21), 340*(0.22), 350(0.26), 366(0.25), 385(0.16).

(†Extinction coefficients corrected for cyclazine impurity contribution at each appropriate wavelength and for error in sample weight in view of the presence of the impurity.)

(b) Pyridine (2 g.) and methyl propiolate (4 g.) stood at room temperature in acetonitrile (25 ml.) for 135 hours, after which the solvent was removed in vacuo, and the red tar resulting chromatographed on alumina (400 ml.) with benzene to give, from fractions 1-3, the crude yellow adduct, dimethyl 1-methoxycarbonylmethylcycl[3,2,2]azine-2,4-dicarboxylate, 0.24 g., (2.8% yield), obtained as yellow rods, m.p. 181.5-182°, after three recrystallisations from methanol.

Found: C, 62.2; H, 4.66; N, 4.46; OMe, 28.6.

$C_{17}H_{15}NO_6$ requires: C, 62.0; H, 4.59; N, 4.25; 3 OMe, 28.3. M, 329.

Molecular weight: 329 (mass spectroscopy).

I.R. (5-7μ region): 3.30, 5.16 (weak), 5.76, 5.86 (broad), 6.53, 6.66, 6.77, 6.88

U.V. λ in mμ ($\epsilon.10^{-4}$): (M), (B), (A) 252.5(2.19), 273.5(2.00), 295.5*(0.83), 307(1.09), 315.5(1.73), 420*(0.98), 443(1.38).

(P)† 260(1.99), 279.5(1.73), 316*(1.56), 322(1.69), 420*(1.38), 433(1.77).

(†(P) here is methanol: perchloric acid :: 1:4).

In the first isolation of the cyclazine, pyridine (2 g.) and methyl propiolate (4.2 g.) were reacted in sodium dried ether (25 ml.) for 134 hours at room temperature, evaporation followed by chromatography on alumina (400 ml.) with benzene giving the cyclazine, (0.132 g., 1.6% yield), isolated from fraction 2, the eluent from the main yellow band on the column.

(c) In another preparation, pyridine (6 g.) in acetonitrile (20 ml.) was added to methyl propiolate (12 g.) in acetonitrile (20 ml.) and left at room temperature for 116 hours, subsequent treatment as described above giving the cyclazine (0.73 g., 2.9% yield) from the first 2 fractions (1000 ml.) of eluent from the column.

Hydrolysis of dimethyl 1-methoxycarbonylmethylcycl[3,2,2]azine-2,4-dicarboxylate.

The adduct (0.22 g.) in methanol (70 ml.) at room temperature was triturated with potassium hydroxide (5.0 g.) in methanol (30 ml.) and left to stand at this temperature for 22

days. Distilled water (15 ml.) was added, the solution was concentrated in vacuo, and the residue acidified with 5N hydrochloric acid which precipitated a yellow solid, isolated by filtration and washed with excess distilled water to give 1-methylcycl[3,2,2]azine-2,4-dicarboxylic acid (or isomer), 0.191 g., (119% yield calculated as the diacid), m.p. decomp. from 180° without melting by 295°, which was not purified further, but gave negative reactions to tests for halide ions and potassium.

$C_{13}H_9NO_4$ requires:	M, 243
Molecular Weight:	243 (mass spectroscopy).
I.R. (5-7μ region):	2.81 (weak), 3.18, 3.75-3.82, 5.83, 5.89, 5.97 (broad), 6.06 (broad), 6.48, 6.51, 6.69, 6.82, 6.85*
U.V. λ in mμ(ϵ.10^{-4}):	(M) 251(1.93), 270(1.40), 305.5(0.78), 314.5(1.09), 416*(0.69), 436(0.81)
	(P)† 265(1.51), 279*(1.21), 325(1.13), 418*(1.06), 434(1.36).

(†(P) here refers to methanol : perchloric acid :: 1:4).

1-Methylcycl[3,2,2]azine.

(a) The procedure employed was that already successfully applied in cycl[3,2,2]azine chemistry.[42] The quinoline used was carefully purified by the recommended method.[42] The diacid (crude) (95 mg.) and copper chromite (150 mg.) were refluxed in an atmosphere of dry nitrogen in pure quinoline (25 ml.) for 5 hours. After cooling and removal of the

catalyst by filtration, the reaction mixture was acidified with 5N hydrochloric acid, extracted with ether (4 x 60 ml.) and the combined extracts after drying over magnesium sulphate were concentrated in vacuo to ca. 1 ml. of solution. This solution was chromatographed on four thin layer plates eluting with b.p. 40-60° petroleum ether,* the pure material being isolated in a similar petrol solution by extraction of the silica holding the required band on the thin layer plate. The petrol solution was filtered from the silica, dried over magnesium sulphate, and after filtration again was concentrated in vacuo and finally evaporated into a small tared flask, the last traces of petroleum ether* being removed under high vacuum in a desiccator (paraffin wax flakes as desiccant), to give 1-methylcycl[3,2,2]azine, (20.7 mg., 34.1% yield) as a yellow-green oil.

$C_{11}H_9N$ requires: M, 155.

Molecular weight: 155 (by mass spectroscopy).

U.V. λ in mμ ($\epsilon.10^{-4}$): (M) 234*(1.19), 240*(1.41), 248(1.76), 285.5*(0.36), 288(0.37), 403*(0.20), 411(0.23), 420(0.23), 432(0.17).

(P)† 229(0.95), 233.5(0.90), 244*(0.63), 277(0.34), 282(0.33), 293.5(0.25), 343(0.28).

(†(P) here refers to methanol : perchloric acid :: 1:4 by

volume).

(*Note. The 40-60° petroleum ether used initially was the commercial material unpurified. The so-called "non-volatile" impurities in this material grossly contaminated two early measurements of the mass spectrum and the 1-methylcycl[3,2,2]azine was finally obtained reasonably free of these impurities (by mass spectral standards) by repeated separations on thin layer plates using fractionated b.p. 40-50° petroleum ether eluent, extracting the required product from the silica band with sodium dried ether. The R_f values of the impurities (1.00) and the product (ca. 0.9) were too close to allow complete separation.)

(b) On the first occasion when the diacid (ca. 75 mg.) was decarboxylated as described above, the product was lost when it vapourised in a desiccator under high vacuum pumping and concurrent heating with an infrared lamp during the removal of the last traces of volatile solvent impurities.

(c) Only starting material was recovered on two occasions when decarboxylation of the diacid (8-9 mg.) with soda lime at 315° under high vacuum, condensing any sublimate on a cold finger (liquid air cooled), was attempted. Inspection of the ultraviolet spectra of sublimate and residue confirmed the absence of any of the desired product.

Methyl Propiolate with 2-Methylpyridine.

(a) 2-Methylpyridine (1 g.) and methyl propiolate (2 g.) after standing for 6 days at room temperature in dry ether (9 ml.) solution gave no solid products after chromatography on alumina (130 ml.)

(b) The same reactants in the same quantities stood for 7 days in acetonitrile (10 ml.) at room temperature, chromatography on alumina (200 ml.) of the dark red tar resulting from the removal of the solvent in vacuo, giving traces of tarry straw coloured needles (2.8 mg.) from the second 100 ml. fraction of benzene eluent, purified by washing with methanol to give pale yellow needles m.p. 128-134°, resolidifying 135-6°, remelting 153-5°.

I.R. (5-7μ region): 5.83, 5.92*, 6.04,* 6.12, 6.31 (weak), 6.64 (v. weak), 6.86, 6.96.

U.V. λ in mμ (absorbance values): (M) 243*(1.08), 250*(1.13), 260(1.37).
(A) 226*(0.63), 242*(0.86), 260(1.28), 285*(0.39).

Traces of tarry solids obtained from the next 300 ml. of eluent (fractions 3-5) separated into 6-11 bands on a thin layer plate and could not be characterised consequently.

Methyl Propiolate with 3-Methylpyridine.

(a) To 3-methylpyridine (1.0 g.) in acetonitrile (9 ml.) was added methyl propiolate (2.0 g.) and the mixture stood for

52 hours at room temperature after which removal of the solvent in vacuo followed by chromatography on alumina (130 ml.) with benzene gave (fractions 1-4) yellow needles, dimethyl 4-methoxycarbonylmethyl-5-methyl-cycl[3,2,2]azine-1,3-dicarboxylate, (84 mg., 2.3% yield), obtained as yellow rods, m.p. 150-1°, resolidifying to needles from 150°, needles m.p. 160.5-161°, after three recrystallisations from methanol.

Found:	C, 63.4; H, 5.23; N, 4.56, 4.61; OMe, 26.7
$C_{18}H_{17}NO_6$ requires:	C, 63.0; H, 4.99; N, 4.08; 3 OMe, 27.1.
I.R.(5-7μ region):	5.78, 5.87, 6.47* (weak), 6.53 (weak). 6.67, 6.77,* 6.87, 6.95.*
U.V. λ in mμ (ε.10^{-4}):	(M), (B), (A). 256(2.23), 276.5(201), 315*(1.09), 325(1.49), 420(0.99), 441.5(1.47)

(b) This reaction was carried out on six other occasions as follows.

(i) no crystalline product was isolated after chromatography from 3-methylpyridine (1 g.) and methyl propiolate (2 g.) in dry ether (9 ml.) after 3½ days at room temperature.

(ii) an exact duplicate of reaction (i) chromatographed after 51 hours gave the cyclazine (36.5 mg., 1.0%

yield.)

(iii) the pyridine (2.0 g.) and methyl propiolate (4.0 g.) in acetonitrile (20 ml.) stood for 46 hours at room temperature, chromatography on alumina (200 ml.) yielding the cyclazine (11.2 mg., 0.15% yield) from the first two fractions (350 ml. benzene), the next two fractions (300 ml. benzene) giving a brown-red solid, which after combination with the material isolated in (iv) below, was recrystallised from acetonitrile to give a red-brown adduct, (3.1 mg.), as red-brown rods, m.p. 160-3°, resolidifying to needles at 163°, needles m.p. 165-8°.

I.R. (5-7μ region): 5.82,* 5.91, 6.03, 6.13, 6.27, 6.39,* 6.47* (weak), 6.86.

U.V. λ in mμ (absorbance values): (M) 266(0.10), 275(0.10), 286*(0.09), 295*(0.08), 445(1.26).

(A) 318(0.59).

(iv) the same quantities and reagents as in (iii) chromatographed on alumina (250 ml.) after 66 hours at room temperature gave the cyclazine (25.6 mg., 0.35%) from the third fraction of benzene eluent, fractions 4 and 5 giving a further very small yield of the red-brown adduct (vide supra).

(v) chromatography after 24 hours at room temperature of the reaction evaporate from the pyridine (1.0 g.),

the ester (1.0 g.) and acetonitrile (20 ml.) gave the cyclazine (30 mg., 0.8% yield).

(vi) the pyridine (2 g.), the ester (4.2 g.) in acetonitrile (20 ml.) after standing 97 hours at room temperature followed by chromatography as before gave the cyclazine (0.122 g., 1.6% yield.)

Bromination of the 5-methylcycl[3,2,2]azine derivative.

(a) Trituration of the cyclazine (0.103 g.) in chloroform (5 ml.) with bromine (0.2 ml.) in chloroform (10 ml.), boiling the mixture for 10 minutes, followed by evaporation in vacuo and recrystallisation of the residue from methanol gave a flocculent yellow solid (94 mg.) which on the evidence of its melting point (141-171°) and thin layer chromatographic inspection (three bands, one arising from unchanged precursor) was a mixture, and was not characterised further.

(b) Boiling a solution of the cyclazine (90 mg.) in chloroform (5 ml.) with bromine (0.3 ml.) in chloroform (15 ml.) for 1 hour followed by treatment as in (a) gave a flocculent yellow solid (76 mg.), a mixture of two products (thin layer chromatography - two bands, precursor band absent), m.p. 165-190°, which was not characterised further.

Methyl Propiolate with 4-Methylpyridine.

(a) To 4-methylpyridine (2 g.) was added methyl propiolate

(4 g.) in sodium dried ether (25 ml.) and the mixture allowed to stand at room temperature for 43 hours. Filtration of the reaction mixture and fragmentation of the tarry solid isolated beneath a large volume of ether gave a brown solid (2.52 g.), which after washing with several aliquots of acetonitrile and finally ether gave an amorphous yellow-brown solid (0.20 g.), purified by being dissolved in chloroform and precipitated by the addition of excess ether, still very impure on the evidence of its infrared spectrum; it could not be characterised further.

Evaporation of the filtrate of the reaction mixture gave a tarry solid which after chromatography on alumina (400 ml.) with benzene yielded (from fraction 4, (1000 ml.), the eluent from a very dark red band) a dark red adduct, (66 mg.), obtained as dark red needles (20 mg.), m.p. 180-1°, after one recrystallisation from methanol.

I.R. (5-7μ region): 5.81, 5.89, 6.05, 6.17, 6.31, 6.40, 6.84,* 6.88, 6.97.

U.V. λ in mμ (absorbance values): (M) 230*(0.18), 250*(0.14), 286(0.18), 444(0.97).

(A) 219(0.38), 256(0.29), 312(0.66).

Evaporation of the acetonitrile washings of the brown solid (vide supra) yielded a dark red tar which was chromatographed on alumina (140 ml.) with benzene to give

from the second fraction (250 ml.) crude methyl 3-methoxycarbonylmethyl-7-methylindolizine-2-carboxylate, (12.9 mg., 0.23% yield) as pale yellow needles, m.p. 155.5-157.5°, identified without further purification on spectral evidence.

U.V. λ in mμ ($\epsilon.10^{-4}$): (M) 237(5.19), 241*(4.94), 293(0.57), 303(0.57), 352(0.43), 365(0.43), 380*(0.32).

(b) To 4-methylpyridine (2 g.) in acetonitrile (15 ml.) was added methyl propiolate (4 g.) in acetonitrile (10 ml.) and the mixture left at room temperature for 39 hours. From the reaction mixture a yellow-brown tarry solid (0.20 g.) was recovered by filtration but no solvent was found satisfactory for its purification. The evaporated filtrate of the reaction mixture was chromatographed on alumina (400 ml.) eluting with benzene, three solid products being obtained as follows: the second fraction (500 ml.) from a yellow band gave dimethyl 1-methoxycarbonylmethyl-6-methylcycl[3,2,2]azine-2,4-dicarboxylate, (26.5 mg., 0.36% yield), obtained as yellow rods (18.9 mg.), m.p. 204-6°, after one recrystallisation from methanol, identified on spectral evidence.

I.R. (5-7μ region): 5.77, 5.86, 5.93, 6.08(v. weak), 6.20(weak), 6.57, 6.70, 6.82, 6.89, 7.01.

U.V. λ in mμ ($\epsilon.10^{-4}$): (M) 252.5(2.03), 276.5(2.10), 297(0.96), 308.5(1.11), 318(1.54), 430*(0.99), 452(1.47).

(P)† 261(1.60), 280*(1.52), 324.5(1.44), 420*(1.04), 440(1.44).

(†(P) here refers to methanol: perchloric acid :: 1:4 by volume).

The third and fourth fractions (1000 ml.) from an orange band gave 1-(2-methoxycarbonylvinyl)-4-(3-methoxycarbonylprop-2-ene-1-ylidenyl)-1,4-dihydropyridine, (0.170 g., 3.0% yield), obtained as red-orange needles (0.121 g.), m.p. 173.5-174°, after one recrystallisation from methanol.

$C_{14}H_{15}NO_4$ requires: M, 261.

Molecular Weight: 261 (mass spectroscopy)

I.R. (5-7μ region): 5.83, 5.92, 6.02,*(weak), 6.13, 6.32, 6.87, 7.02.

U.V. λ in mμ ($\epsilon.10^{-4}$): (M), (RB)†. 284(0.26), 299(0.26), 440(5.81).

(A) 233(0.29), 317(2.93).

(†(RB) indicates that the acidified solution (A) was made neutral (or alkaline) again by the addition of sodium methoxide solution.)

The fifth fraction (500 ml.) from a very dark red

band gave a crude sample of the dark red adduct, (38 mg.), orange-red needles, m.p. traces from 160°, mainly 172-6°, possibly closely related to the dark red adduct described earlier (see p.172) on spectral evidence and on comparison of the R_f values for the two compounds on a thin layer plate.

I.R. (5-7μ region): 5.79,* 5.84,* 5.89, 6.13, 6.17, 6.30, 6.34, 6.41,* 6.86, 6.97.

U.V. λin mμ

(absorbance values): (M) 279(0.05), 444(0.64).

Methyl Propiolate with 3,5-Dimethylpyridine.

(a) To 3,5-dimethylpyridine (2.0 g.) was added methyl propiolate (3.6 g.) in the absence of solvent, and so violent a reaction ensued that some of the brown-red tar produced within 30 seconds was ejected in the manner of a volcanic eruption. The reaction was modified with acetonitrile (10 ml.) and left for 24 hours at room temperature, after which the solvent was removed in vacuo and the resulting tar chromatographed on alumina (200 ml.) with benzene to give from the second fraction of eluent (450 ml.) crystalline solid (0.429 g.), which was in form of a mixture of yellow pellets and hard orange-brown pyramidal crystals. Separation by hand gave yellow pellets (0.196 g., 2.9% yield of the cyclazine derivative - vide infra) and the brown pyramidal crystals, methyl 1-

methoxycarbonylmethyl-6,8-dimethylindolizine-2-carboxylate, (0.233 g., 4.5% yield), which after being freed of superficially adhering yellow solid by rapid washing with chloroform, followed by three recrystallisations from methanol, was obtained as very pale yellow plates m.p. 105.5-106.5°.

Found: C, 65.3; H, 6.19; N, 5.30; OMe, 22.6.

$C_{15}H_{17}NO_4$ requires: C, 65.4; H, 6.18; N, 5.09; 2 OMe, 22.5.

I.R. (5-7μ region): 5.80, 5.88, 6.43, 6.53, 6.64, 6.84, 6.93,* 7.07.

U.V. λin mμ ($\epsilon.10^{-4}$):

(M) 238(3.03), 297(0.35), 309(0.33), 342(0.26), 355.5(0.25), 373*(0.18).

(B) 242(2.59), 264*(0.60), 296(0.18), 309(0.17), 342.5(0.16), 355(0.16), 373*(0.15).

(A) 238(2.45), 297(0.32), 311(0.33), 326(0.31), 340(0.30), 361*(0.17), 381*(0.09).

(P) 227(1.23), 262.5(0.62), 311*(0.48), 325.5(0.73), 339(0.61).

(b) When 3,5-dimethylpyridine (1.0 g.) in acetonitrile (10 ml.)

was cooled in a "cardice"-methanol bath to ca. -70° prior to the addition of methyl propiolate (2 g.) in acetonitrile (11 ml.), and the reaction mixture then allowed to return to room temperature, chromatography on alumina (150 ml.), after 92 hours, with benzene eluent gave, from the first fraction (250 ml.), yellow pellets, dimethyl 1-methoxycarbonylmethyl-5,7-dimethylcycl[3,2,2]azine-2,4-dicarboxylate, (0.125 g., 3.7% yield), obtained as yellow needles, m.p. 178-179.5° after four recrystallisations from methanol.

Found: C, 63.9; H, 5.23; N, 4.12; OMe, 25.9

$C_{19}H_{19}NO_6$ requires: C, 63.9; H, 5.36; N, 3.92;
3 OMe, 26.0. M, 357.

Molecular Weight: 357 (mass spectroscopy).

I.R. (5-7μ region): 5.80, 5.86, 6.28 (v. weak), 6.45 (weak), 6.51, 6.69, 6.88, 6.97.*

U.V. λ in mμ ($\epsilon.10^{-4}$): (M), (B), (A). 265(2.30), 279.5(2.28), 318*(1.29), 329.5(1.90), 411*(0.96), 433(1.58).

(P) 265(2.89), 280(2.75), 321*(1.60), 332(2.02), 413*(1.19), 432(1.73).

(NB. This is the cyclazine derivative referred to briefly

in (a)).

(c) To 3,5-dimethylpyridine (4.0 g.) in dry ether (10 ml.) was added methyl propiolate (5.4 g.) in dry ether (10 ml.). After 96 hours at room temperature, removal of the solvent followed by chromatography on alumina (350 ml.) with benzene gave, from fractions 1 and 2 (1000 ml. total), the cyclazine (0.79 g., 5.9% yield crude), and from fractions 3-5 (1500 ml. total), yellow crystals, the orange adduct, (0.173 g., 0.84% yield), obtained as yellow-orange plates, m.p. 177-177.5°, after three recrystallisations from very small quantities of methanol.

Analysis: Found:	C, 65.4; H, 6.71; N, 5.21; OMe, 22.6.
$C_{30}H_{34}N_2O_8$ requires:	C, 65.4; H, 6.22; N, 5.09; 4 OMe, 22.5. M, 550.
Molecular Weight:	550 (mass spectroscopy).
I.R. (5-7μ region):	5.71, 5.83, 5.90, 6.13, 6.24, 6.43, 6.86, 6.95*.
U.V. λ in mμ ($\epsilon.10^{-4}$):	(M) 250*(1.47), 325(1.44), 384(1.17).
	(A) 256*(0.96), 330(2.14).

The sample of the cyclazine obtained on this occasion, 0.79 g. crude, was, on the evidence of its melting point, infrared, ultraviolet, and nuclear magnetic resonance spectra, a mixture of the cyclazine and the

so-called orange adduct even after being twice recrystallised from methanol.

The reaction between the pyridine and the ester was carried out on five other occasions.

(d) To 3,5-dimethylpyridine (1.0 g.) in dry ether (5 ml.) was added methyl propiolate (1.8 g.) in dry ether (4 ml.) and mixture chromatographed on alumina (100 ml.) as described above after standing 93 hours at room temperature. The crude product (0.57 g.) after separation into its two components by both fractional crystallisation and manual crystal picking gave the cyclazine derivative (0.125 g., 3.7% yield) and the indolizine derivative (0.238 g., 9.3% yield). Neither component could be obtained free of the other even after repeated recrystallisations and attempted separation by thin layer chromatography as evidenced in the case of the cyclazine by its nuclear magnetic resonance spectrum and elemental analysis results and in the case of the indolizine by its melting point behaviour on repeated recrystallisations.

(e) When the pyridine (2.2 g.) and methyl propiolate (3.6 g.) were allowed to react in dry ether (25 ml.) for 135 hours at room temperature and the mixture was chromatographed on alumina (400 ml.) with benzene, separation of the product mixture isolated gave the cyclazine derivative (0.34 g., 4.7% yield) and the indolizine derivative

(0.25 g., 4.4% yield) which was still contaminated with the former compound on melting point evidence after attempted purification as described in (d).

(f) The pyridine (2.2 g.), methyl propiolate (3.6 g.) and 5% dehydrogenation palladium on charcoal (prepared by a slightly modified version of the method of Vogel[82]) (0.5 g) in dry ether suspension (25 ml.) were shaken mechanically in a lightly stoppered flask at room temperature for 140 hours. Chromatography on alumina (430 ml.) with benzene, after filtration and evaporation of the reaction mixture, gave the indolizine derivative (95 mg., 1.7% yield) as the only solid product, obtained pure as pale yellow crystals (60 mg.), m.p. 104-106°, after one recrystallisation from methanol.

(g) The pyridine (2.2 g.) and the ester (3.6 g.) after standing at room temperature in acetonitale (25 ml.) for 66 hours, followed by chromatography on alumina (400 ml.) with benzene gave the cyclazine derivative only, (0.36 g., 5.0% yield).

(h) Shaking a suspension in acetonitrile (25 ml.) of the pyridine (2.2 g.), methyl propiolate (3.3 g.) and 5% dehydrogenation palladium on charcoal (0.5 g.) for 65 hours in the manner described in (f) gave, after chromatography on alumina (400 ml.) with benzene, the crude cyclazine derivative (0.163 g., 2.2% yield) as the

only isolable solid.

Bromination of the 5,7-Dimethylcycl[3,2,2]azine derivative.

The cyclazine (0.103 g.) in chloroform (10 ml.) was heated on a water bath for 10 minutes with a solution of bromine (0.2 ml.) in chloroform (10 ml.), the solvent and excess bromine removed in vacuo and the residue isolated by recrystallisation from methanol as yellow needles (0.104 g.). After four recrystallisations from methanol the product, yellow rods (73 mg.), m.p. 150-8°, resolidifying to needles from 152°, needles m.p. 170-3°, was an inseparable mixture (confirmed by nuclear magnetic resonance spectrum and unsatisfactory elemental analysis) since it also gave only a single band on a thin layer plate with a variety of eluents.

Hydrolysis of the 5,7-Dimethylcycl[3,2,2]azine derivative.

The cyclazine (0.23 g.) in methanol (90 ml.) was triturated with potassium hydroxide (5 g.) in methanol (25 ml.) and left at room temperature for 17 days, after which time the yellow needles which precipitated out slowly from day 6 onwards were filtered off, washed with several aliquots (total 150 ml.) of 4N hydrochloric acid followed by a large volume of distilled water, and isolated as a flocculent yellow mass, methyl 1-carboxymethyl-5,7-dimethylcycl [3,2,2]azine-2-carboxylate-4-carboxylic acid (or isomer), (0.108 g., 50.7% yield), m.p. 256-8° (decomp. from ca. 200°.), giving negative tests for potassium and chloride ions. Acidification of the filtered

reaction mixture gave no further organic products.

$C_{17}H_{15}NO_6$ requires: M, 329.

Molecular Weight: 329 (mass spectroscopy).

I.R. (5-7μ region): 2.90, 3.08*, 3.18 (broad), 3.79 (broad), 5.87 (very broad), 6.27 (weak), 6.43,* 6.51, 6.67, 6.86, 7.03.

U.V. λ in mμ ($\epsilon.10^{-4}$): (M) 262(2.35), 277*(1.95), 301*(0.76), 316.5*(1.20), 326(1.64), 423(1.16).

Reaction of the 6,8-Dimethylindolizine derivative with Methyl Propiolate.

Methyl 1-methoxycarbonylmethyl-6,8-dimethylindolizine-2-carboxylate (58 mg., pure from preparation (f), p.180), methyl propiolate (1.0 g.), and 5% dehydrogenation palladium on charcoal (ca. 100 mg.) were heated under reflux in sodium dried toluene (25 ml.) in an atmosphere of dry nitrogen for 23 hours. The catalyst was removed by filtration and washed with excess benzene and chloroform, and the combined washings and reaction mixture evaporated in vacuo, the residue taken up in the minimum volume of hot acetone and separated on 7 thin layer plates with benzene: ethyl acetate :: 4:1 as eluent. The one major band (bright yellow, R_f 0.63 to 0.75) was recovered from the plates, the silica extracted with methanol (125 ml.) and evaporated in vacuo to give crude yellow solid,

dimethyl 1-methoxycarbonylmethyl-5,7-dimethylcycl[3,2,2] azine-2,4-dicarboxylate, (52 mg., 67.1% yield), obtained as a flocculent yellow solid (39 mg., 50.1% yield), m.p. microcrystals change to clusters of needles at 151-2°, needles have m.p. 180-181.5°. The identity of this product with an authentic sample described earlier was confirmed by its melting point, mixed melting point, infrared, ultraviolet, nuclear magnetic resonance and mass spectra.

$C_{19}H_{19}NO_6$ requires: M, 357.

Molecular Weight: 357 (mass spectroscopy).

I.R. (5-7μ region): 5.79, 5.83, 6.26 (v. weak), 6.43, 6.50, 6.67, 6.84, 6.88, 6.97.*

U.V. λ in mμ ($\epsilon.10^{-4}$): (M) 264(2.09), 279(2.07), 318*(1.22), 328(1.79), 411*(0.89), 431(1.39).

CHAPTER FOUR.

SUBSIDIARY SECTION.

The Reactions of some Quinolizines with Acetylenic Compounds in the presence of Palladium Charcoal (Dehydrogenation).

Reaction of the "labile" adduct from 3,5-dimethylpyridine with phenylacetylene.

(a) To the above "labile" adduct, tetramethyl 7,9-dimethyl-9a*H*-quinolizine-1,2,3,4-tetracarboxylate (2 g.) and 5% dehydrogenation palladium on charcoal (1.0 g.) was added phenylacetylene (2.6 g.) in toluene (50 ml., dry) and the mixture refluxed for 24 hours. The catalyst was removed by filtration and trituration of the evaporated filtrate with methanol precipitated a sand coloured solid (0.127 g.) which could not be characterised further. Evaporation of this methanol filtrate, followed by chromatography on alumina (400 ml.) with benzene of the resulting red tar, led to the isolation of the following three compounds. Fractions 2-4 (850 ml., from an orange yellow band) gave pale brown crystals, dimethyl 6,8-dimethylindolizine-2,3-dicarboxylate, (0.343 g., 25.7% yield) obtained as colourless rhombs, m.p. 144-144.5°, after two recrystallisations from methanol.

Found: C, 64.2; H, 5.65; N, 5.43; OMe, 23.7.

$C_{14}H_{15}NO_4$ requires: C, 64.4; H, 5.79; N, 5.36; 2 OMe 23.75.

I.R. (5-7μ region): 5.79, 5.96, 6.50 (weak), 6.62,*

6.69, 6.86, 6.92, 7.00.*

U.V. λ in mμ ($\epsilon.10^{-4}$): (M) 229(2.76), 257(2.57), 333*(0.97), 347(1.15).

Fraction 5 (500 ml., from an off-white region) gave yellow brown crystals, trimethyl 6,8-dimethylindolizine-1,2,3-tricarboxylate, (20 mg., 1.2% yield), obtained as very pale yellow rods, m.p. 159-159.5°, after one recrystallisation from methanol. An infrared spectrum of an available sample of this known[68] indolizine was identical over the region 2.5-15μ with the spectrum of the above product, confirmation of their identity coming from a comparison of their melting points (literature value[68] 159°) and quantitative ultraviolet spectra.[105]

U.V. λ in mμ ($\epsilon.10^{-4}$): (M) 245.5(2.93), 264(0.86), 275(0.85), 326(1.41), 339(1.32).

Fractions 7 and 8 (1050 ml., from an orange-brown band) gave pale yellow crystals, <u>dimethyl 3-methoxycarbonylmethyl-6,8-dimethylindolizine-1,2-dicarboxylate,</u> (0.127 g., 7.4% yield) obtained as colourless needles, m.p. 126.5-127.5°, after two recrystallisations from methanol.

Found: C, 61.3; H, 5.84; N, 4.21; OMe, 27.8.

$C_{17}H_{19}NO_6$ requires: C, 61.25; H, 5.75; N, 4.20; 3 OMe, 27.9.

I.R. (5-7μ region): 5.74, 5.81, 6.41 (weak), 6.54,

6.61* (weak), 6.82,* 6.86,* 6.91, 6.97.*

U.V. λ in mμ ($\epsilon.10^{-4}$): (M) 242(3.17), 294(0.35), 306(0.46), 339.5(0.46), 346.5(0.46).

Further elution with benzene-chloroform 7:3 (fractions 9-12) and later benzene-chloroform 2:3 (fractions 13-14), followed by extraction of coloured bands still on the column with chloroform, led to the isolation (from fraction 11) of traces (<5 mg.) of a yellow solid whose ultraviolet spectrum suggested that it was the "stable" or 4H-quinolizine isomer of the precursor.

(b) Repeating experiment (a) with all factors and quantities exactly as before except for the omission of phenylacetylene from the reagents, followed by chromatography on alumina (400 ml.) with benzene after removal of the catalyst by filtration and concentration of the filtrate in vacuo, gave the same three indolizines as the only solid products isolated, in the quantities and yields stated below, taking the products in same order as in (a): (i) from fraction 1, (250 ml.), 0.243 g., 18.2% yield; (ii) from fractions 3 and 4, (550 ml.), 11 mg., 0.67% yield; and (iii) from fractions 5-7, (1400 ml.), 0.169 g., 9.9% yield.

Reaction of the "labile" adduct from 3,5-dimethylpyridine with

dimethyl acetylenedicarboxylate.

To the "labile" adduct (2 g.) and 5% dehydrogenation palladium on charcoal (1.0 g.) was added dimethyl acetylene-dicarboxylate (3.6 g.) in sodium dried toluene (100 ml.) and the mixture refluxed for 24 hours. After filtration and concentration in vacuo, the resulting dark viscous liquid was chromatographed on alumina (400 ml.) with benzene (4400 ml.) followed by benzene-chloroform 3:1 (1000 ml.), but gave only trace amounts of two yellow solids, from fraction 1 and from fractions 2 and 4 respectively, which could not be characterised further. The ultraviolet spectral data is shown below.

U.V. λ in mμ (absorbance values):

Solid from fraction 1: (M), (A), 266(0.91), 321*(0.51), 332(0.66), 401*(0.45), 420(0.75).

Solid from fraction 4: (M) 248(0.74), 294(0.93), 378*(0.32), 422(0.47).

(A) 254(0.64), 294(0.96), 378*(0.32), 424(0.48).

Reaction of the "stable" adduct from pyridine with phenylacetylene.

To the "stable" adduct, tetramethyl 4H-quinolizine-1,2,3,4-tetracarboxylate (7.3 g.), and phenylacetylene (10.2 g.) was added 5% dehydrogenation palladium on charcoal (2.0 g.) in dry toluene (150 ml.), and the mixture refluxed for 23½

hours. The hot solution was filtered to remove the catalyst, the catalyst washed free of crystalline solid with hot chloroform, and the combined toluene and chloroform solution evaporated in vacuo to give a tarry brown solid, which on recrystallisation from benzene-chloroform ca. 4:1 by volume (150 ml.) was obtained as orange-yellow crystals of the "stable" adduct precursor, (3.78 g., 51.8% recovery). Evaporation of the mother liquor from the recrystallisation, followed by chromatography on alumina (700 ml.) with benzene of the evaporate, gave no further solid products, but extraction with chloroform of the residual coloured bands on the column after elution gave further orange-yellow crystals of the "stable" adduct precursor (1.40 g., total recovery now 71%.)

Reaction of the "stable" adduct from pyridine with dimethyl acetylenedicarboxylate.

To the "stable" adduct (7.3 g.) and 5% dehydrogenation palladium on charcoal (2.0 g.) was added dimethyl acetylene-dicarboxylate (14.2 g.) in sodium dried toluene (150 ml.) and the mixture refluxed for 24 hours. The catalyst was removed by filtration of the hot solution, and on cooling crude orange crystals of "stable" adduct precursor (2.62 g., 35.9% recovery) crystallised out and were filtered off. The filtrate after evaporation vacuo was chromatographed on alumina (600 ml.) eluting with benzene (fractions 1-5) and

benzene-chloroform 3:1 by volume (fractions 6-7), finally extracting residual coloured bands on the column with chloroform. Fractions 1-3 gave dimethyl fumarate, (0.24 g.), white rods, m.p. 100-2°, identified by comparison of its infrared spectrum with that of an authentic sample, whilst fractions 4-6 gave some dark red plates (6.6 mg.) which could not be characterised further. Measurement of the spectral data below consumed all the available material.

I.R. (5-7μ region):	5.78, 5.91,* 6.12 (weak), 6.28, 6.37, 6.50, 6.87, 6.96.
U.V. λ in mμ	(M) 245*(0.69), 329(1.30).
(absorbance values):	(A) 252(0.36), 330(1.00).

Footnote: The "labile" and "stable" adducts used in the above series of experiments were available in this laboratory as a consequence of earlier researches.[68] When recovered intact from the above experiments they were identified by spectral comparisons.

CHAPTER FIVE.

Reactions of Pyridines with Dimethyl Acetylenedicarboxylate.

(a) 2-Substituted Pyridines.

(i) Further reactions of an adduct from 2-Methoxypyridine.

With Maleic Anhydride.

The adduct, tetramethyl 2-(4-methoxy-1-butadienyl)-pyridine 3,4,5,6-tetracarboxylate[83] (0.61 g.) and maleic anhydride (0.17 g.) were refluxed in benzene solution (15 ml.) for 6½ hours. After standing a further 33 days at room temperature the crude product, washed with several aliquots of benzene, was filtered off as an orange solid, the red compound, (0.223 g., 39·5% yield), obtained as red-orange rods, m.p. 206-8° (decomp.) after purification by thin layer chromatography and three recrystallisations from methanol.

Found:	C, 56.05; H, 4.51; N, 4.02; OMe, 34.4
$C_{17}H_{17}NO_8$ requires:	C, 56.15; H, 4.68; N, 3.86; 4 OMe, 34.15. M, 363.
Molecular Weight:	363 (mass spectroscopy).
I.R. (5-7μ region):	5.74, 5.82, 5.90,* 5.93,* 6.08, 6.24, 6.75, 6.87.
U.V. λ in mμ ($\epsilon.10^{-4}$):	(M) 250(1.25), 269.5*(1.07), 289*(0.90), 472 (0.54).
	(P) 249(1.19), 280(1.15), 456*(0.50), 470(0.53).

The filtrate from the reaction mixture, after concentration

in vacuo, was chromatographed on alumina (300 ml.) with benzene (750 ml.) and benzene-chloroform 3:2 by volume (1450 ml.) but no further solid products were isolated.

Isomerisation of the Butadienylpyridine derivative.

When a sample of the crude adduct (ca. 0.1 g.) m.p. 116-118.5°, identified by its melting point and ultraviolet spectrum,[83] was recrystallised from methanol (20 ml.), concentrating the solution to ca. 5 ml. on a boiling water bath, the product isolated was the isomeric tetramethyl 4-methoxy-4H-quinolizine-1,2,3,4-tetracarboxylate,[84] (80.3 mg., ca. 80% yield), orange rods, m.p. 144-6° (decomp.) obtained in the same form, m.p. 154-7° (decomp.), after a further recrystallisation from methanol. The nature of the product, suggested by its melting point, was confirmed by its ultraviolet and infrared spectra.[84]

Oxidation of the Butadienylpyridine derivative.

(a) The adduct (0.88 g.) dissolved in acetone (100 ml.) was triturated with a solution of potassium permanganate (5.0 g.) in acetone (200 ml.) and the mixture refluxed for 1 hour. The acetone was evaporated on a water bath and finally in vacuo, the residue triturated with water (100 ml.) and the suspension gasified with sulphur dioxide until all the manganese dioxide had been discharged. Extraction of the cloudy yellow resultant solution (excess sulphur dioxide having been boiled off)

with chloroform (4 x 50 ml.), followed by drying and evaporation of the extracts and trituration of the residue with ether yielded the white oxidation product, (73 mg.), obtained as colourless rods, m.p. 172-174.5°, after two recrystallisations from n-butanol. The second analysis results are for a sample, m.p. 171.5-177.5° (decomp.) which was recrystallised a third time from n-butanol.

Found:	C, 46.35; H, 3.74; N, 4.83; OMe, 30.2
Found:	C, 46.1; H, 3.62.
$C_{12}H_{11}NO_9$ requires:	C, 46.0; H, 3.51; N, 4.47; 3 OMe, 29.75.
I.R. (5-7μ region):	5.70,* 5.75, 5.87*(weak), 6.13, 6.23, 6.50 (weak), 6.83, 6.93,* 6.98.
U.V. λ in mμ (absorbance values):	(M), (B). 275(0.81), 232(0.41).
	(A) 250*(0.49), 335(0.33).
	(P) 250*(0.54), 340(0.42).

(b) Repeating procedure (a) in every detail except that the weight of adduct precursor was 0.81 g., gave on this occasion a viscous pale yellow liquid of pleasant odour in trace quantity which could not characterised.

Two small scale reactions of the Butadienylpyridine derivative.

(i) With 2,4-Dinitrophenylhydrazine.

The adduct (ca. 0.1 g.) was dissolved in hot methanol (4 ml.) and triturated with excess 2,4-dinitrophenylhy-

drazine in solution in methanol containing a little concentrated sulphuric acid. The red-brown solid precipitated on cooling the mixture after this had been boiled for 5-10 minutes was, on the evidence of its ultraviolet and infrared spectra, and on the evidence of the ultraviolet spectra and R_f values the two major bands observed when this solid was investigated by thin layer chromatography, possibly a mixture of the two organic precursors. The spectral comparisons were largely inconclusive.

(ii) With Tetracyanoethylene.

The adduct (ca. 0.1 g.) in benzene (4 ml.) and tetracyanoethylene (ca. 0.2 g.) were refluxed for 1½ hours and on cooling, and standing for 10 days, deposited increasing amounts of a very dark red tar which, when subjected to thin layer chromatography, separated into four bands; the major band (R_f ca. 0.4, benzene: ethyl acetate :: 1:2 eluent), yellow in colour, was extracted with methanol but gave no solid product on evaporation. Its ultraviolet spectrum is described below.

U.V. λ in mμ (absorbance values):

(M) 251.5(0.61), 257.5(0.63), 262*(0.61), 346.5(0.21), 428(0.57).

(A) 257(0.64), 347.5(0.22), 405*(0.45), 424(0.59).

(ii) Adducts from and Syntheses of various 2-Pyridylacetates. Methyl 2-Pyridylacetate and Diethyl Acetylenedicarboxylate.

To methyl 2-pyridylacetate (2.0 g.) in dry ether (5 ml.) was added diethyl acetylenedicarboxylate (5.0 g.) in dry ether (10 ml.) and the mixture left at room temperature for 91 hours. The precipitated crystalline solid was recovered by filtration and washed with many portions of dry ether to give, diethyl 2H-quinoliz-2-one-3,4-dicarboxylate, (0.71 g., 18.5% yield), obtained as yellow plates, m.p. 131-131.5°, after three recrystallisations from carbon tetrachloride.

Found: C, 62.2; H, 5.29; N, 4.80; OMe†, 21.8

$C_{15}H_{15}NO_5$ requires: C, 62.3; H, 5.23; N, 4.83; OMe†, 21.45.

(† Total alkoxyl estimated as OMe. Calculated value expressed as OMe corresponding to 2 OEt groups present in the molecule is the figure shown.)

I.R. (5-7μ region): 5.33 (v. weak), 5.73, 6.04, 6.17, 6.26, 6.50, 6.65, 6.88.

U.V. λ in mμ ($\epsilon.10^{-4}$): (M) 232.5(4.76), 245*(3.61), 329(1.65).

(A) 221.5(5.41), 234*(4.09), 326.5(1.77).

(P) 224(3.95), 326.5(1.17).

The reaction mixture filtrate was evaporated in vacuo and the red tar resulting chromatographed on alumina (350 ml.) with benzene. No solid products were obtained from the column fractions, but extraction of a red-orange band still on the column with chloroform led to the isolation of a second adduct, ethyl 1-methoxycarbonyl-3-(1,2-diethoxycarbonylvinyl)-4H-quinoliz-4-one-2-carboxylate, (66.6 mg., 1.1% yield), obtained as pale yellow plates (50 mg.), m.p. 135·5-136.5°, after successive recrystallisations from methanol and ethanol.

I.R. (5-7μ region): 5.78, 5.82, 6.02, 6.14, 6.39, 6.56 (weak), 6.72, 6.84,* 6.89, 6.96.

U.V. λ in mμ ($\epsilon.10^{-4}$): (M) 261(1.19), 277*(0.98), 356*(1.03), 395(1.73).

Attempted syntheses of Methyl 4-methyl-2-pyridylacetate.

4-Methylpyridine 1-oxide.

This was prepared on three occasions by the method described in the literature.[85] 4-Methylpyridine (36.5, 47.8 and 47.8 g.) was oxidised with hydrogen peroxide in glacial acetic acid to yield essentially pure 4-methylpyridine 1-oxide (27.4 g., 64%; 15.5 g., 28%; and 27.9 g., 50% yield, respectively), the product being identified by its melting point and infrared spectrum.

Reaction of the 1-Oxide with Ethyl Cyanoacetate.

This procedure is adapted from parallel syntheses in the literature.[86]

(a) To 4-methylpyridine 1-oxide (3.0 g.) was added a mixture of acetic anhydride (3.5 g.) and ethyl cyanoacetate (3.8 g.) cooled to 0°. The mixture was stirred mechanically under anhydrous conditions at 5° for 1 hour followed by stirring for 90 hours at room temperature. Methanol (5 ml.) was added to destroy any excess anhydride after which the mixture was evaporated in vacuo. The resultant dark red liquid was made alkaline (pH8) with potassium bicarbonate solution then extracted with chloroform (6 x 60 ml.). The combined extracts (at 0°) were extracted with 10% w/w sodium hydroxide solution (also at 0°) (3 x 80 ml.). The combined aqueous extracts were neutralised (cooling when necessary) with dilute acetic acid and at 0° were extracted with ether (3 x 100 ml.) and finally with ether-chloroform 1:2 by volume (140 ml.). The combined organic extracts were washed with saturated potassium bicarbonate solution (2 x 50 ml.) and with distilled water (2 x 50 ml.). The organic phase (ca. 450 ml.) was purified without concentration by passage down an alumina column (100 ml.), the complete elution of the required product being ensured by washing the column with ether (500 ml.). Evaporation of the column effluent and trituration of the residue resulting

with 60-80° petroleum ether, gave ethyl 4-methyl-2-pyridylcyanoacetate, (0.236 g., 4.2% yield), straw coloured needles, m.p. 145.5-146°, after two recrystallisations from carbon tetrachloride.

Found:	C, 64.1; H, 5.71; N, 13.9; OEt, 21.8.
Found:*	C, 63.5; H, 5.82.
$C_{11}H_{12}N_2O_2$ requires:	C, 64.65; H, 5.88; N, 13.7; OEt, 22.1.
I.R. (5-7μ region):	3.18, 3.25, 4.56, 6.12, 6.17, 6.28, 6.67, 6.84, 6.86,* 6.91.*
U.V. λin mμ ($\epsilon.10^{-4}$): (M), (A), (RA)†.	295(2.03), 360(1.14).
(B)	241(1.28), 294.5(1.94), 321*(1.00).

(†(RA) indicates that the basified solution (B) was reacidified with perchloric acid and the ultraviolet spectrum was then remeasured.)

(*These analysis figures relate to a portion of the material prepared in (b) below, m.p. 144-144.8°, after four recrystallisations from carbon tetrachloride.)

(b) Procedure (a) was followed very closely when the experiment was repeated with the oxide (15 g.), the cyanoacetate (19 g.) and acetic anhydride (17.5 g.), allowing the reaction to proceed for 72 hours in this instance. The final process of alumina chromatography was omitted, the final ether extracts being dried over anhydrous magnesium

sulphate, to yield, after evaporation in vacuo and recrystallisation of the dark brown resultant solid from carbon tetrachloride, the pyridylcyanoacetate, (1.53 g., 5.4% yield), as orange brown needles, m.p. 139-43°.

Attempted Hydrolyses of the Pyridylcyanoacetate.

(a) The pyridylcyanoacetate (90 mg.) was refluxed in solution in absolute ethanol (5 ml.) containing concentrated sulphuric acid (0.10 g.) for $5\frac{3}{4}$ hours. Evaporation of the solvent in vacuo, addition of water (5 ml.) to the residue, followed by extraction with ether (5 x 15 ml.) and evaporation of the dried ethereal extracts led to the recovery of the precursor, the pyridylcyanoacetate, (70.3 mg., 78.2% recovery) identified by its melting point and infrared spectrum.

(b) The pyridylcyanoacetate (70.3 mg. ex (a)) was dissolved in absolute ethanol (10 ml.) containing concentrated sulphuric acid (0.7 ml., ca. 1.3 g.) and refluxed for $4\frac{1}{4}$ hours. Isolation of the product as in (a) gave the precursor, (50.6 mg., 72.3% recovery), identified as before, as the only solid isolated.

(c) To the pyridylcyanoacetate (0.23 g.) in ethanol (10 ml.) was added an equimolar quantity (5.5 ml.) of aqueous-ethanolic sodium hydroxide and the mixture left at room temperature for 67 hours, after which it was refluxed for a further $29\frac{1}{2}$ hours. The ethanol was removed in vacuo, the

residual syrup triturated with water (5 ml.) and acidified (pH 1) with concentrated hydrochloric acid. Extraction with ether (4 x 40 ml.) followed by evaporation of the dried extracts gave the precursor, the pyridylcyanoacetate, (0.116 g., 50.7% recovery) as the only solid isolable, identified by its infrared spectrum.

(d) To the pyridylcyanoacetate (0.186 g.) in ethanol (10 ml.) was added aqueous-ethanolic potassium hydroxide solution (10 ml., containing a twice equimolar quantity of the base) and the mixture refluxed for 66½ hours. The ethanol was removed in vacuo, the residue triturated with water (20 ml.) and made strongly acid with concentrated hydrochloric acid. Extraction with ether (4 x 50 ml.) and evaporation of the dried extracts gave the precursor, (20.2 mg., 10.8% recovery) identified as in (c). The aqueous phase was basified with solid sodium hydroxide and extracted first with ether (3 x 50 ml.) and then with chloroform (2 x 50 ml.). These extracts, kept separately, after drying and evaporation in vacuo gave, respectively, traces of a brown viscous liquid which was not characterised, and a white solid, (19.7 mg.), which on the evidence of its infrared spectrum (vide infra) was not the precursor, but could not be identified further owing to the paucity of the sample.

I.R. (5-7μ region): 3.08, 3.16,* 3.21, 5.94 (broad),

6.20, 6.40, 6.75, 6.88.

The aqueous phase was carefully reacidified (pH 3) with concentrated hydrochloric acid, extracted with chloroform (4 x 50 ml.) and finally neutralised (pH 6.1) and extracted with ether (2 x 50 ml.) and chloroform (3 x 50 ml.), combining these latter extracts. Only uncharacterisable trace quantities of brown liquids were isolated from evaporation of these two extracts after drying.

Synthesis of Methyl 5-methyl-2-pyridylacetate.

The synthesis is based on that of the ethyl ester.[87,88]

(a) To sodium dried ether (600 ml.) in a 2 l.3-neck flask was added a suspension of freshly cut beaten sheets of lithium metal (5.9 g.) in dry ether (200 ml.). Freshly distilled bromobenzene (40 ml., ca. 60 g.) was added dropwise over a period of 50 minutes at a rate sufficient to maintain the ether at reflux from the heat of reaction. After refluxing the phenyllithium for a further 3 hours, 2,5-dimethyl-pyridine (44.5 ml., 40 g., freshly distilled from calcium hydride) was added dropwise over a period of 10 minutes to the stirred ethereal solution and the mixture refluxed for 1 hour and then stirred until the temperature had fallen to room temperature. The organo-lithium solution was then poured via a special device which prevents blow back of carbon dioxide gas and protects the reagents from

atmospheric moisture, in small aliquots over a period of 20 minutes on to freshly powdered dried solid carbon dioxide (ca. 600 g.), swirling the reagents vigorously throughout mixing. After standing overnight at room temperature under anhydrous conditions, the slurry of yellow solid was triturated with methanol (100 ml.) to remove excess lithium and the suspension evaporated in vacuo. The residue was taken up in methanol (500 ml.), the suspension cooled to 0^{o} in ice-water and stirred vigorously with continued cooling whilst hydrogen chloride gas was bubbled through the suspension for $9\frac{1}{2}$ hours. After standing overnight at room temperature, the solution was evaporated in vacuo giving a red-brown syrup which was taken up in chloroform (500 ml.) and stirred for 4 hours with an aqueous solution (170 ml.) containing potassium carbonate (250 g.). The chloroform phase was separated in a funnel (facilitated by dilution of the aqueous phase with water (300 ml.) and slight warming), dried over magnesium sulphate, filtered, and evaporated in vacuo to give a viscous dark red liquid (69 ml.). The initial vacuum fractionation of the product led to the isolation of crude unchanged 2,5-dimethylpyridine (4.5 ml., 4.0 g., 10% recovery), b.p. $63\text{-}135^{o}/19\text{-}21$ mm. (mainly $63\text{-}90^{o}$), identified by its infrared spectrum. Two higher boiling fractions collected, (i) 11.2 ml., b.p. $135\text{-}150^{o}/19\text{-}20$ mm.,

(ii) 5 ml., b.p. 153-175°/18-20 mm., had almost identical infrared spectra but differing refractive indices (for white light), viz. (i) $n^{25°}$ 1.5230, (ii) $n^{26°}$ 1.5555. Both fractions were redistilled to give (i) ca. 10 ml., b.p. 75-79°/0.08 mm., $n^{23°}$ 1.5240, and (ii) ca. 4 ml., b.p. 79-81°/0.09 mm., $n^{24-5°}$ 1.5637. Nuclear magnetic resonance spectra revealed that fraction (i) was approximately 80% pure methyl 5-methyl-2-pyridylacetate (ca. 8 g. pure, 13% yield), the remaining 20% of the fraction on the evidence of the nuclear magnetic resonance spectrum and high refractive index[88, 89] being probably 2,5-dimethyl-6-phenylpyridine, the known by-product of syntheses employing 2,5-dimethylpyridine and phenyllithium.[88, 89] Nuclear magnetic resonance investigation suggested that the major component of fraction (ii) was more of the 2,5-dimethyl-6-phenylpyridine, a result supported by the high refractive index.

(b) The first attempted synthesis was largely conducted as in (a) but with the following modifications. Phenyllithium was replaced by butyllithium, prepared as described in the literature[35] from lithium (7.3 g.) and freshly distilled n-butyl bromide (68.5 g.). The quantity of 2,5-dimethylpyridine employed was 54 g. In an attempt to combine the processes of carboxylation and esterification, the synthesised pyridyllithium derivative was triturated with

freshly distilled dimethyl carbonate (45 g.) (a further adaptation of the literature[90]) with which it failed to react. An abortive attempt was then made to revert to the procedure of (a), but problems of transfer and hydrolysis of the organo-lithium compound led to the isolation after the final step of vacuum fractionation of unchanged precursor 2,5-dimethylpyridine, (ca. 20 g., 37% recovery), b.p. 54-60°/15-16 mm., as the only liquid product. The pyridine derivative was identified by its infrared spectrum.

Reaction of Methyl 5-methyl-2-pyridylacetate with Dimethyl acetylenedicarboxylate.

To methyl 5-methyl-2-pyridylacetate (2.0 g. crude from preparation (a)) in dry ether (5 ml.) was added dimethyl acetylenedicarboxylate (4.2 g.) in ether (10 ml.) and the mixture left 66 hours at room temperature. Evaporation of the ether in vacuo and trituration of the resultant red tar with warm benzene crystallised out a sand coloured solid, dimethyl 7-methyl-2H-quinoliz-2-one-3,4-dicarboxylate, (0.268 g., 8.0% yield), obtained as pale yellow rods, m.p. 177-8° (decomp.), after three recrystallisations from benzene.

Found: C, 61.1; H, 4.76; N, 5.20; OMe, 22.4.

$C_{14}H_{13}NO_5$ requires: C, 61.1; H, 4.76; N, 5.09; 2 OMe, 22.55.

I.R. (5-7μ region): 5.73, 6.02, 6.17, 6.29,* 6.49, 6.63,

6.86, 6.92, 7.04.

U.V. λ in mμ($\epsilon.10^{-4}$): (M) 236(3.37), 331(1.10).

(P) 226(3.79), 320(0.93), 330(0.95).

Evaporation of the benzene filtrate gave a red tar which was chromatographed on alumina (450 ml.) with benzene. From the first fraction (500 ml.) were obtained pale yellow crystals, dimethyl fumarate, (41.8 mg., 1.0% yield), identified by its infrared spectrum. After elution had been stopped, residual coloured bands on the column were extracted with chloroform; from the extract of a pink band near the top of the alumina column were obtained off-white crystals of the so-called white adduct, (0.113 g., 2.1% yield), obtained as very pale yellow microcrystals, m.p. 200-1°, after three recrystallisations from methanol.

Found: C, 65.9; H, 5.05; N, 3.60; OMe, 21.6

$C_{24}H_{21}NO_7$ requires: C, 66.2; H, 4.86; N, 3.22;

3 OMe, 21.4. M, 435.

Molecular Weight: 435 (mass spectroscopy).

I.R. (5-7μ region): 5.75, 5.82, 6.33, 6.42*(weak),

6.48*(v. weak), 6.87, 6.99.*

U.V. λ in mμ ($\epsilon.10^{-4}$): (M) 230(3.08), 285*(1.13), 315*(0.93).

(A) 296.5(1.34), 314*(1.07).

(RB)† 239(1.54), 299(1.04), 345*(0.54).

(†(RB) indicates solution (A) basified with 20 drops sodium methoxide solution.)

(iii) 2-Phenoxypyridine.

(a) To 2-phenoxypyridine (4.8 g.) dissolved in acetonitrile (18 ml.) was added dimethyl acetylenedicarboxylate (8.1 g.) and acetonitrile (2 ml.), the mixture being allowed to stand at room temperature for 3 days, after which the solvent was removed in vacuo to give a viscous red tar, which was chromatographed on alumina (520 ml.) with benzene, but yielded no solid products.

(b) Dimethyl acetylenedicarboxylate (8.7 g.), 2-phenoxypyridine (4.8 g.) and acetonitrile (25 ml.) were refluxed for 50 hours, removal of the solvent in vacuo then yielding a viscous red-brown tar, which after chromatography on alumina (510 ml.) with benzene, and further separation of the fourteen column fractions by thin layer chromatography (benzene:ethyl acetate :: 4:1 eluent) gave no solid products.

(iv) 2-Benzylpyridine.

(a) To 2-benzylpyridine (2.38 g.) in dry ether (10 ml.) was added dimethyl acetylenedicarboxylate (4 g.) in dry ether (15 ml.) and the mixture kept at -20° for $2\frac{1}{2}$ hours followed by a period of $20\frac{1}{2}$ hours at room temperature. Removal of the solvent in vacuo, followed by chromatography on alumina (470 ml.) of the resultant red-brown tar with benzene, gave, from fraction 1 (300 ml.), off-white, hard, translucent crystals, dimethyl 1-phenylindolizine-

2,3-dicarboxylate, (63.4 mg., 1.5% yield), m.p. 134-5-135°, freed of superficial yellow impurities by washing with warm methanol.

$C_{18}H_{15}NO_4$ requires: M, 309.

Molecular weight: 309 (mass spectroscopy).

I.R. (5-7μ region): 5.76, 5.92, 6.13 (v. weak), 6.24, 6.35 (v. weak), 6.52, 6.66, 6.73, 6.85,* 6.91,* 6.95, 7.03.

U.V. λ in mμ ($\epsilon.10^{-4}$): (M), (B), (P). 250(2.92), 271*(1.36), 350(1.54).

Fractions 1-4 (950 ml.) gave a flocculent yellow solid, methyl 1-phenyl-3-(1,2-dimethoxycarbonylvinyl)-2H-quinoliz-2-one-4-carboxylate (92.6 mg., 1.6% yield). All subsequent details given now relate to a further isolation of this latter product described below in (b). The adduct is obtained as flocculent yellow needles, m.p. 216-217.5° (? decomp.), after four recrystallisations from methanol, the dry solid exhibiting electrostatic properties.

Found: C, 64.5; H, 4.67; N, 3.43; OMe, 22.4.

Found: C, 64.4; H, 4.59.

$C_{23}H_{19}NO_7$ requires: C, 65.6; H, 4.54; N, 3.32; 3 OMe, 22.1. M, 421.

$C_{22}H_{19}NO_7$ requires: C, 64.5; H, 4.68; N, 3.42; 3 OMe, 22.7. M, 409.

Molecular weight: 421 (i.e. $C_{23}H_{19}NO_7$; mass spectroscopy).

I.R. (5-7μ region): 5.72, 5.78, 5.90, 6.16 (v. weak), 6.23 (weak), 6.35, 6.43, 6.66, 6.79, 6.87, 6.94,* 6.99, 7.04.

U.V. λin mμ ($\epsilon.10^{-4}$): (M) 267(1.71), 304.5(1.07), 343(1.08), 437(2.03).

(P) 265.5(2.63), 308*(1.12), 512(0.38).

(The awkward neutralisation of the pink solution (λ512) (P) with sodium methoxide solution was carried out and the yellow colour (λ437) returned). No solid products were obtained from the chloroform extracts of residual coloured bands on the column on completion of the elution.

(b) To 2-benzylpyridine (7.14 g.) in dry ether (75 ml.) was added dimethyl acetylenedicarboxylate (12 g.) and the mixture left for 40½ hours at room temperature, after which evaporation in vacuo followed by chromatography on alumina (600 ml.) with benzene gave, from fractions 1 and 2 (500 ml.), the 2H-quinoliz-2-one triester (0.158 g., 0.9% yield), the data for which was given in (a) above.

(v) 4-Benzylpyridine.

(a) To 4-benzylpyridine (2.38 g.) in dry ether (10 ml.) was added dimethyl acetylenedicarboxylate (4 g.) in dry ether (15 ml.). After standing for 2½ hours at -20° followed by 21 hours at room temperature, the mixture was evaporated in vacuo, and the resulting dark red gum chromatographed on

alumina (520 ml.) with benzene, but no crystalline solid was isolated from the fractions of eluent nor from the chloroform extracts of residual coloured bands remaining on the column.

(b) With the same quantities of reagents as in (a), the mixture stood 2 hours at -20° followed by $21\frac{1}{2}$ hours at room temperature, but no solid products resulted after chromatography on alumina (530 ml.) with benzene of the reaction evaporate.

(c) The pyridine (2.38 g.) and the ester (4.6 g.) stood for 16 hours at -20° followed by 2 days at room temperature in acetonitrile solution (25 ml.). The solvent was removed in vacuo and the dark red gum resulting chromatographed on alumina (430 ml.), with benzene. The first column gave poor separation of a yellow and two red bands; consequently the eluent fractions from these bands (6500 ml.) were combined, evaporated in vacuo, and the red tar resulting (0.9 g.) chromatographed again on alumina (180 ml.) with benzene:ether :: 1:1 (1270 ml.) and later benzene:chloroform :: 1:1 (750 ml.), but no solid products were isolated.

(vi) Trans 1,2-bis-(2-pyridyl)-ethylene.

(a) The trans 1,2-bis(2-pyridyl)-ethylene (4 g.) was dissolved in dry ether (250 ml.) and triturated with dimethyl acetylenedicarboxylate (6.5 g.) in dry ether (10 ml.) at

room temperature for 5 hours. The solution was then concentrated on a water bath to 100 ml., and thereafter refluxed for 24¼ hours. Removal of the solvent in vacuo and chromatography on alumina (500 ml.) with benzene gave the following crystalline products: from fractions 2-5 (1000 ml.) impure off-white crystals, unchanged 1,2-bis-(2-pyridyl)-ethylene, (0.185 g., 4.6% recovery) identified by their melting point; from fractions 6-10 (3000 ml., from a yellow orange band), the yellow adduct, identified by melting point; from fractions 8-16 (4300 ml.) and the chloroform extract of the residual portion of the orange brown band remaining on the column, the orange adduct, identified by melting point. In the cases of fractions 8-10 which yielded both adducts the crystals were separated manually on the basis of colour, the separation being confirmed by the melting points. Without any further investigation the samples of the two adducts were combined with the appropriate batches isolated as described below in (b).

(b) The pyridine (4 g.) in acetonitrile (35 ml.) was triturated with the ester (6.4 g.) in acetonitrile (20 ml.) and left at room temperature for 45½ hours. Evaporation of the solvent in vacuo and chromatography of the dark brown gum resulting on alumina (520 ml.) with benzene gave the following crystalline products: from fraction 1 (500 ml.), dimethyl

fumarate, (32.2 mg., 0.5% yield), identified by melting point (100-102°) and infrared spectrum: from fractions 3-5 (1500 ml., from an orange-yellow band), the yellow adduct, identified by melting point: from the chloroform extract of the residual orange band remaining on the column after elution, the orange adduct, identified by melting point.

The combined samples of the yellow adduct, tetramethyl 9a-[2-(2-pyridyl)-vinyl]-9aH-quinolizine-1,2,3,4-tetracarboxylate, comprised 1.548 g., an overall yield of 7.6%. The crude adduct, m.p. 124-32°, was recrystallised (a portion only) from n-butanol to give translucent pale yellow parallelipipeds, m.p. 161.5-162.5°, identical on the evidence of nuclear magnetic resonance and mass spectra with the crude material, in spite of the greatly elevated melting point.

$C_{24}H_{22}N_2O_8$ requires: M, 466.

Molecular Weight: 466 (mass spectroscopy).

I.R. (5-7μ region): 5.75, 5.85, 5.89, 6.08 (weak), 6.25, 6.32, 6.40 (weak), 6.58, 6.85,* 6.88, 6.97.

U.V. λ in mμ ($\epsilon \cdot 10^{-4}$): (M) 239(2.07), 285(2.30), 336*(0.42), 417(0.53).

(A) 230.5(1.77), 292.5(2.41), 355*(0.41), 425(0.41).

(P) 230(1.67), 293(2.38), 345*(0.65), 429(0.35).

The combined samples of the orange adduct, tetramethyl 6-[2-(2-pyridyl)vinyl]-9aH-quinolizine-1,2,3,4-tetracarboxylate, comprised 3.241 g., 15.8% overall yield. A portion of this sample recrystallised from n-butanol was obtained as orange microcrystals, m.p. 152-3°.

$C_{24}H_{22}N_2O_8$ requires: M, 466.

Molecular Weight: 466 (mass spectroscopy).

I.R. (5-7μ region): 5.74, 5.80, 5.87, 6.15, 6.22 (v.weak), 6.30 (weak), 6.39 (v. weak), 6.46 (weak), 6.63, 6.78,* 6.86, 6.99, 7.07.

U.V. λin mμ ($\epsilon.10^{-4}$): (M) 227(1.67), 287(1.37), 340(2.51), 426(0.43).

(P) 286.5(1.12), 367.5(2.81).

Isomerisation of the orange adduct under various conditions.

(a) A little of the orange adduct (ca. 30 mg.) was heated in a small flask for 5 minutes at 200-215° in a silicone bath. The reaction was quenched rapidly, the black tarry mass taken up in methanol, and a spot of this solution separated on a thin layer strip (eluent benzene-ethyl acetate 1:1 by volume) showed one major spot, bright orange, R_f 0.33.

The orange adduct (0.426 g.) in a small flask was heated in a silicone bath at 200-6° for 5 minutes, the

reaction quenched rapidly and the black tarry mass dissolved in boiling methanol (50 ml.). A portion separated on a thin layer strip (eluent as above) showed the expected major spot, bright orange, R_f 0.26, with a contaminant, pale yellow-brown, R_f 0.49. The required product did not crystallise out from the methanol solution and it was therefore evaporated in vacuo and the residue taken up in benzene (30 ml.), traces of a tarry brown solid remained undissolved and were rejected after inspection by thin layer strip chromatography. Small scale tests with spots of this benzene solution on thin layer strips suggested that prolonged elution with benzene-ethyl acetate 2:1 by volume gave the best separation of the impurity from the required product. A portion of the benzene solution (1 ml.) was chromatographed on alumina (32 ml., in a burette) with the above eluent, and the separation of the impurities from the required orange band suggested that for alumina the best eluent was benzene-ethyl acetate 3:1 by volume. The benzene solution (concentrated to 12 ml.) was chromatographed on alumina (150 ml.) with the above eluent and gave, from fraction 7 (300 ml., from an orange red band), crude tetramethyl 4-(2-pyridyl)-4,5-dihydro-3aH-cycl[3,3,2]azine-1,2,3,3a-tetracarboxylate, (0.107 g., 25% yield), obtained as brown amorphous plates, m.p. partial melting 185-8°, remainder melting 195-8°, after one

recrystallisation from ethanol.

$C_{24}H_{22}N_2O_8$ requires: M, 466.

Molecular Weight: 466 (mass spectroscopy).

I.R. (5-7μ region): 5.78, 5.90, 6.01, 6.13, 6.35, 6.54, 6.83, 6.95.

U.V. λ in mμ ($\epsilon \cdot 10^{-4}$): (M) 233.5(0.86), 269(1.29), 312.5(1.79), 360(0.97), 466(0.90).

(A) 269*(1.91), 271.5(1.94), 306(1.55), 360(0.92), 477(0.87).

(P) 263.5(1.22), 270*(1.09), 283*(0.49), 319.5(0.60), 330*(0.54).

(b) The orange adduct (0.40 g.) was dissolved in dry toluene (150 ml.) and refluxed for a total of 18½ hours. The progress of the reaction was investigated by thin layer strip chromatography after 5, 10½ and 18½ hours; the final chromatogram showed the required product (vide infra) as the major spot, red-brown, R_f 0.41, only a trace of the precursor, a yellow spot, R_f 0.75, and the presence of some of the cycl[3,3,2]azine derivative, an orange spot, R_f 0.18 (eluent benzene-ethyl acetate, 1:1 by volume.). The nature of the spots was confirmed by the ultraviolet spectra of their extracts (with methanol) when a little of the solution was separated on a full thin layer plate with the above eluent. The toluene was removed in vacuo, and

trituration of the resultant red tar precipitated a dark red crystalline solid which was recrystallised in situ from methanol to give tetramethyl 6-[2-(2-pyridyl)vinyl]-4H-quinolizine-1,2,3,4-tetracarboxylate, (0.212 g., 53% yield), obtained as dark red rods, m.p. first melting 151-3°, resolidification at 152-4°, final melting 179-180° (? decomp.), after three recrystallisations from methanol.

Analysis: Found: C, ; H, ; N, 5.98; OMe, 25.8.

$C_{24}H_{22}N_2O_8$ requires: C, 61.7; H, 4.71; N, 6.00; 4 OMe, 26.6.

I.R. (5-7μ region): 5.74, 5.92,* 6.01, 6.10* (v. weak), 6.21, 6.31,* 6.35, 6.52, 6.82, 6.86,* 6.98.

U.V. λ in mμ ($\epsilon \cdot 10^{-4}$): (M) 225*(1.84), 307(3.05), 380.5(1.01), 467(0.94).

(A) 220*(1.67), 307.5(2.63), 352*(1.14), 489(0.37).

(P) 235.5(1.71), 240.5(1.71), 297(1.59), 355(2.17).

(c) Various other methods of isomerising the orange adduct were investigated (by thin layer strip chromatography, eluent benzene-ethyl acetate, 1:1 by volume in each case) on a small scale only.

(i) A little of the orange adduct (61 mg.) was boiled with phenol (96 mg.) for 100 seconds, quenched rapidly,

and the black resultant tar taken up in methanol and investigated by thin layer strip chromatography. Results: precursor, pale yellow spot, R_f 0.72; 4H-quinolizine derivative, very pale red brown spot, R_f 0.51; cycl[3,3,2]-azine derivative, orange spot (major product), R_f 0.27.

(ii) The orange adduct (ca. 20 mg.) was refluxed in n-butanol (5 ml.) for 35 minutes and the solution examined as in (i). Results: precursor only, yellow spot, R_f 0.84.

(iii) The orange adduct (ca. 20 mg.) was refluxed in n-amyl alcohol (6 ml.) for 32 minutes and then examined as in (i). Results: precursor, yellow spot (major component), R_f 0.81; 4H-quinolizine derivative, pale brown spot, R_f 0.55; cycl[3,3,2]azine derivative, very pale orange spot, R_f 0.27.

(iv) The orange adduct (ca. 30 mg.) was refluxed in xylene (6 ml.) for 105 minutes and the solution examined as in (i). Results: precursor, yellow spot, R_f 0.68; 4H-quinolizine derivative, red brown spot (major product), R_f 0.41; cycl[3,3,2]azine derivative, orange spot, R_f 0.20.

(v) The orange adduct (ca. 20 mg.) was refluxed in toluene (7 ml.) for 180 minutes and the solution examined as in (i). Results: precursor, yellow spot

(major component), R_f 0.77; 4H-quinolizine derivative, red brown spot, R_f 0.48; cycl[3,3,2]azine derivative, very pale orange spot, R_f 0.24.

Isomerisation of the 4H-quinolizine derivative.

The 4H-quinolizine derivative (ca. 20 mg.), material which had been twice recrystallised from methanol and gave a single orange-brown spot (R_f 0.43, usual eluent) on a thin layer strip, was placed in a small test tube and heated for 5 minutes at 195-205° in a silicone bath, the reaction quickly quenched, and the dark residue taken up in acetone and investigated by thin layer strip chromatography. Results: precursor, orange-brown spot, R_f 0.47; cycl[3,3,2]azine derivative, bright orange spot (major component), R_f 0.33.

Reactions of the yellow adduct.

(a) The yellow adduct (ca. 20 mg.) was refluxed in xylene for 105 minutes, after which the solution was investigated by thin layer strip chromatography, eluent benzene-ethyl acetate 1:1 by volume. The strip exhibited but one major spot, the yellow precursor, R_f 0.77; a very pale yellow spot was noticed with R_f 0.69, and some brown residue remained at the strip origin.

(b) In an exact repeat of (a) the results were: precursor, major yellow spot, R_f 0.82; very pale yellow spot, R_f 0.70.

(c) The yellow adduct (ca. 10 mg.) was heated in a test tube

at 200-205° in a silicone bath for 5 minutes, the reaction quenched and the black residue taken up in hot methanol and examined as in (a). The results showed a brown spot remaining at the strip origin as the only detectable band.

Table of R_f values for the four adducts

Eluent: benzene-ethyl acetate 1:1 by volume

Compound	No. of observations	Range of values	Mean value
Yellow adduct	3	0.76-0.82	0.78
Orange adduct	10	0.68-0.84	0.77
4H-Quinolizine derivative	10	0.40-0.58	0.47
Cycl[3,3,2]azine derivative	10	0.17-0.33	0.24

(vii) 2,6-Dimethoxypyridine.

(a) To 2,6-dimethoxypyridine (4 g.) in acetonitrile (10 ml.) was added dimethyl acetylenedicarboxylate (8 g.) in acetonitrile (10 ml.) and the mixture left 11 days at room temperature. Evaporation of the solvent in vacuo, and chromatography of the dark brown viscous evaporate on alumina (450 ml.) with benzene gave no crystalline products.

(b) The same quantities of the above reagents were refluxed in acetonitrile (25 ml.) for 27 hours, the solvent thereafter removed in vacuo and the viscous brown liquid

chromatographed on alumina (480 ml.) with benzene-chloroform 7:3 by volume. No solid products were isolated.

(c) The same quantities of the above reagents were refluxed in N,N-dimethylformamide (25 ml.) for 34 hours, the solvent removed in vacuo, and the black viscous evaporate chromatographed on alumina (530 ml.) with benzene. No solid products were isolated. Further separation of the 7 column effluent fractions on thin layer plates (benzene:ethyl acetate :: 4:1 as eluent) and extraction of the two major bands with methanol gave no crystalline products. The ultraviolet spectrum of the predominant band (yellow), R_f ca. 0.1, is given.

U.V. λ in mμ (M), (A) 232(0.66), 297.5(0.85), 410(0.43).
(absorbance values);

(b) 3-Substituted Pyridines

(i) Methyl 3-Pyridylacetate

(a) To methyl 3-pyridylacetate (4.5 g.) was added dimethyl acetylenedicarboxylate (8.6 g.) in ether (20 ml.) a vigorous exothermic reaction ensuing. The reaction mixture was cooled and then stood 22 hours at room temperature. Removal of the solvent in vacuo, and chromatography on alumina (550 ml.) with benzene of the resulting viscous red tar gave 14 fractions (total volume 7000 ml.)

from the orange brown region of the column. Inspection of spots of each fraction on thin layer plates (eluent benzene-ethyl acetate 4:1 by volume) indicated that fractions 2-6 separated into 6 bands of which 2 only were significant, whilst fractions 7-14 separated into 5 or 6 bands of which only 1 was important. The combined eluent (2500 ml.) from fractions 2-6 was evaporated in vacuo and separated on 14 thin layer plates, the silica from the two significant bands, one, red-orange, R_f ca. 0.28, the other, yellow-orange, R_f ca. 0.08, being extracted with methanol. Evaporation on standing at room temperature of column fractions 7-14 and the thin layer extract of the red-orange band gave tetramethyl 9-methoxy-carbonylmethyl-9a<u>H</u>-quinolizine-1,2,3,4-tetracarboxylate, (0.170 g. crude, 1.3% combined yield), yellow-orange needles, m.p. 90-93°, which was isomerised by any solvents suited to its recrystallisation, and consequently investigated without further purification.

I.R. (5-7μ region): 5.76, 5.80, 5.86*, 6.19, 6.35 (v. weak), 6.62, 6.87, 6.94.*

U.V. λ in mμ ($\epsilon.10^{-4}$): (M), (A) 236(1.51), 291(1.38), 297*(1.32), 444(0.45).

The 9a<u>H</u>-quinolizine derivative (55 mg.) was "recrystallised" from n-butanol (5 ml.), but concentration of the filtered solution to ca. 1 ml. by boiling on a hot plate gave tetramethyl 9-methoxy-carbonylmethyl-4<u>H</u>-

quinolizine-1,2,3,4-tetracarboxylate, (33 mg., 60% yield from isomerisation), red-orange microcrystals, m.p. 187-5.188°.

I.R. (5-7μ region): 5.73, 5.78,* 5.97,* 6.02, 6.18 (weak), 6.35, 6.52, 6.86, 6.95.*

U.V. λ in mμ ($\epsilon.10^{-4}$): (M) 263(0.78), 318(1.09), 362(1.26), 437(0.81).

(A) 274(0.62), 305(0.12).

Repeated evaporation on standing and trituration with methanol of the extract of the yellow-orange band on the thin layer plates (vide supra) gave only a small quantity (30.7 mg.) of a yellow brown amorphous solid contaminated with black tarry particles, which could not be characterised further. The ultraviolet data for the methanol extract of the band immediately after chromatography is given below.

U.V. λ in mμ (absorbance values): (M), 269(0.73), 308(0.61), 345(0.52), 433(0.90).

(A)† 263(0.58), 322(0.53), 430(0.59).

(†(A) here is (M) acidified with 10 drops of perchloric acid.)

(b) To dimethyl acetylenedicarboxylate (8.6 g.) in acetonitrile (10 ml.) at -50° (approx.) was added methyl 3-pyridyl-acetate (4.5 g.) in acetonitrile (10 ml.) cooled to the same temperature. After mixing, the reagents were stored at -10°, but so exothermic was the reaction that further

immersion in a "Cardice"-methanol bath was required after 10 minutes. The mixture was returned to the store at ca. 5° and left there for 94 hours, after which time the solvent was removed in vacuo, and the resultant red tar chromatographed on alumina (460 ml.) with benzene. After elution, residual coloured bands on the column were extracted with chloroform. No solid products were obtained from the fractions of eluent, but the chloroform extract of a brown band near the top of the column gave trimethyl 7H-2-pyrindine-5,6,7-tricarboxylate, (61.3 mg.,) 0.7% yield), pale yellow crystals, obtained as pale brown microcrystals, m.p. 249-50° (decomp.) after one recrystallisation from acetonitrile.

$C_{14}H_{13}NO_6$ requires: M, 291.

Molecular weight: 291 (mass spectroscopy)

I.R. (5-7μ region): 3.07, 3.22 (both weak), 5.77, 5.92, 6.04, 6.16, 6.23,* 6.28* (weak), 6.54, (v. weak), 6.71* (weak), 6.88, 7.06.

U.V. λin mμ ($\epsilon.10^{-4}$): (M) 246.5*(2.27), 250.5*(2.71), 262(4.77), 275(2.07), 305*(0.83), 310.5(0.92), 375(0.66).

(A) 246.5*(2.27), 257.5*(4.19), 262.5(4.62), 275.5(2.01), 311(1.02), 375(0.76).

(c) To diethyl acetylenedicarboxylate (10.2 g.) in acetonitrile

(10 ml.) cooled to ca. -50° was added methyl 3-pyridyl-acetate (4.5 g.) in acetonitrile (10 ml.) at the same approximate temperature. The mixture is kept at ca. -10° for 15 hours and then at ca. 5° for 6 days. Removal of the solvent in vacuo, and chromatography on alumina (520 ml.) with benzene of the red tarry evaporate gave no solid products from the column fractions. Residual coloured bands on the column were then extracted with chloroform, and from a yellow-brown region now near the base of the column, after slow evaporation from ethanol (19 days) there was obtained, diethyl 7-methoxycarbonyl-7H-2-pyrindine-5,6-dicarboxylate, (25.3 mg., 0.27% yield), as a pale yellow amorphous solid, m.p. 219-221° (decomp.).

$C_{16}H_{17}NO_6$ requires: M, 319

Molecular weight: 319 (mass spectroscopy).

U.V. λ in mμ ($\epsilon.10^{-4}$): (M) 246*(2,40), 263.5(5.09), 276.5*(2.28), 312(1.14), 376.5(0.79).

(B) 254(4.33), 278(1.29), 296.5(1.14), 305(1.23), 349*(1.90), 359.5(2.11).

(RA)† 245.5*(2.40), 263(4.88), 276(2.31), 311.5(1.26), 376(0.91).

(P) 246*(2.34), 262(4.48), 276*(2.28), 312(1.37), 375(1.08).

(†(RA) is solution (B) made just acid with 8 drops of perchloric acid.)

(ii) 3-Cyanopyridine.

To 3-cyanopyridine (5 g.) in acetonitrile (25 ml.) was added dimethyl acetylenedicarboxylate (14 g.) and the mixture left at room temperature for 5½ days. Evaporation of the solvent in vacuo, followed by chromatography on alumina (550 ml.) with benzene of the red viscous evaporate, gave, from fractions 4-11 (4000 ml., from an orange-brown band) tetramethyl 9-cyano-9a*H*-quinolizine-1,2,3,4-tetracarboxylate, (0.274 g., 1.5% yield), as impure orange-yellow needles, m.p. 151-3°, which on the evidence of melting points and visual inspection of any crystals isolated, always gave complex mixtures of products when purification was attempted either by recrystallisation or by separation on thin layer plates recovering the material from the silica by extraction with and crystallisations from methanol.

I.R. (5-7μ region): 4.52 (medium), 5.76,* 5.78, 5.84, 6.14, 6.37, 6.62, 6.88,* 6.95, 7.03.*

U.V. λ in mμ ($\epsilon.10^{-4}$): (M), (A) 247(1.61), 272.5*(0.99), 305(0.85), 312.5(0.86), 340*(0.43), 450(0.43).

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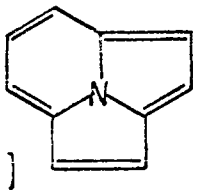
Facing Abstract page 1

STRUCTURES FOR THE ABSTRACT



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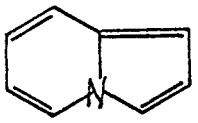

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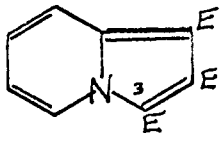

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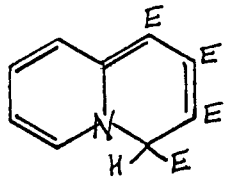

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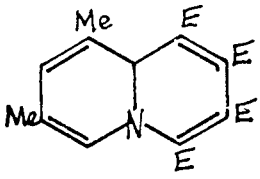

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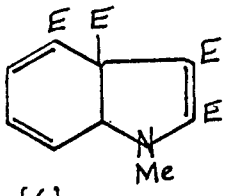

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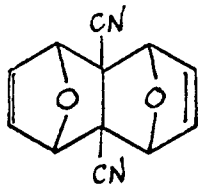

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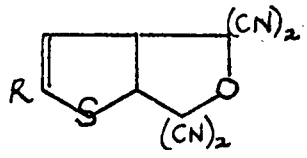

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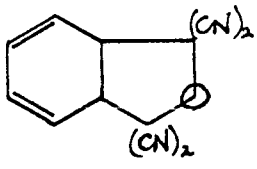

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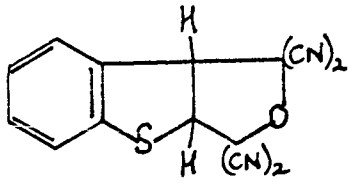

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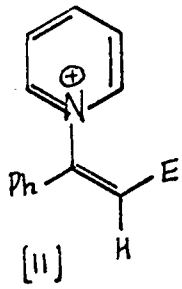

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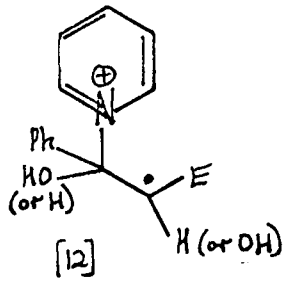

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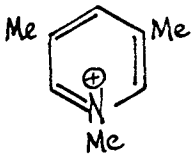

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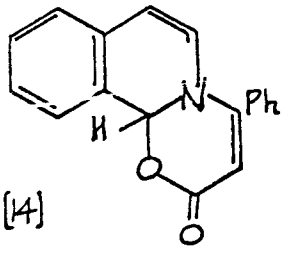

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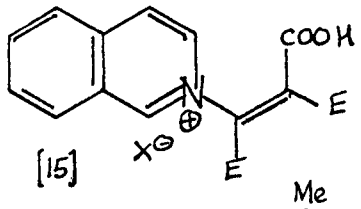

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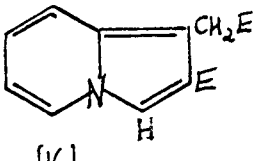

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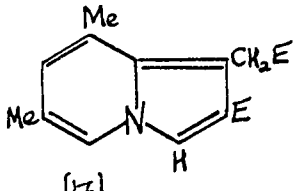

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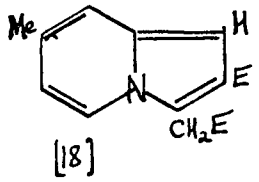

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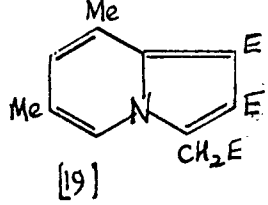

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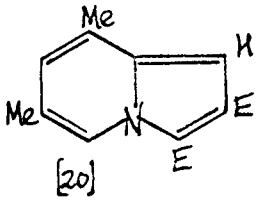

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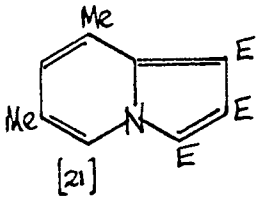

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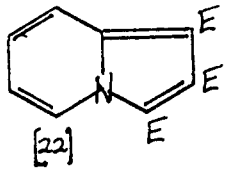

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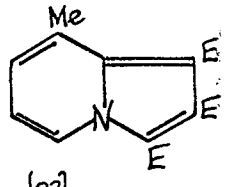

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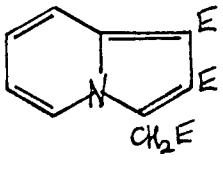

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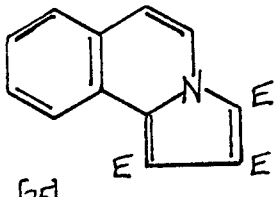

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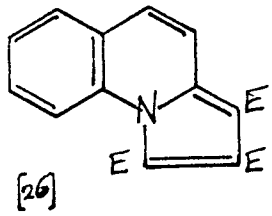

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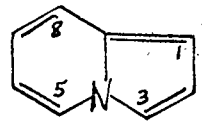

[27]

ABSTRACT

The formulae described in this abstract are to be found on the fold-out flow sheets. Abbreviation E ≡ $COOCH_3$.

The Introduction surveys the results obtained since a 1962 review[1] from investigations of the reactions of heterocyclic compounds and acetylenic esters. The chemistry of the cycl[3,2,2] azine system [1] first described in 1958[2] is discussed and particular mention is made of the syntheses of derivatives of compound [1] from indolizine [2] and acetylenic esters.[3,4]

Chapter One describes the investigation of the reactions of the potentially dienic systems [3]-[6] with tetracyanoethylene and hexachlorocyclopentadiene. The indolizine [3] did not react with either dienophile and this failure is attributed to the steric and electron-withdrawing effects of the 3-ester group. The 4H-quinolizine [4] gave complex mixtures of products with both dienophiles on the evidence of thin-layer chromatography. Parallel treatment of the reaction mixtures from the 9aH-quinolizine [5] and tetracyanoethylene, and from the dihydroindole [6] and hexachlorocyclopentadiene, suggested similar results, whilst compounds [5] and [6] were recovered when the corresponding dienophiles were interchanged.

Chapter Two falls into three sections. Dicyanoacetylene, characterised by formation of the known compound [7] with furan,[5] gave a turquoise solid with pyridine separating into many bands on a thin layer plate but yielding no crystalline solid thereafter.

Thiophene, recently reported[6] as undergoing the Diels-Alder reaction for the first time, gave brown intractable solids with dicyanoacetylene. Section two deals with some reactions of tetracyanoethylene oxide, which is reported[7] to give products [8] and [9] with thiophene and benzene, respectively. Benzo[b] thiophene and the oxide yield an adduct formulated as [10], this structure being supported inter alia by the nuclear magnetic resonance (n.m.r.) spectrum in which the bridgehead hydrogens are simple doublets; in alternative formulations of a 1:1 adduct at least one of these protons would be expected to exhibit further spin-spin splitting. Dibenzo[b,d] thiophene and the oxide gave no isolable adduct, tetracyanoethylene and dibenzothiophene being recovered in approximately 75% combined yield. The oxide gave an uncharacterisable brown fluid with 2,5-dimethylthiophene, and reacted violently with N-methylpyrrole yielding a red-brown solid whose nature could not be determined. Intractable tars or trace quantities of yellow solids are the products described in the final section from the reactions of methyl tetrolate and pyridine, 4-methyl-pyridine, and 3,5-dimethylpyridine.

Chapter Three gives an account of some reactions of methyl phenylpropiolate. Pyridine with this ester gave a yellow solid whose elemental analysis, n.m.r. spectrum, and mass spectrum were in accord with its formulation as an adduct from 2 moles of pyridine, 2 moles of the ester, and 1 mole of water. The major fragments in the mass spectrum at $^{m}/_{e}$ 240 and 257 were tentatively

assigned the structures [11] and [12], or their isomers. The mode of linkage of these fragments in the parent adduct was not established. 3,5-Dimethylpyridine and methyl phenylpropiolate at room temperature on different occasions gave small quantities of a yellow and a white solid whose nature could not be discovered. When this pyridine and the ester were refluxed in acetonitrile however, the salt [13, X=Br] was obtained in up to 16% yield. Its structure was established from its u.v. and n.m.r. spectra, and by conversion to the perchlorate [13, X= ClO_4] which was identical with an authentic sample prepared by standard routes. Impurities in the methyl phenylpropiolate consequent upon its preparation from methyl 2,3-dibromo-3-phenylpropionate are the source of the bromine in the salt [13, X=Br.]. The yield of the adduct [14] was increased from 5 to 33% by carrying out the reaction of isoquinoline and methyl phenylpropiolate in aqueous methanol. The structure of compound [14] is based on its n.m.r. spectrum, comparison of its u.v. spectrum at various pH values with the spectra[8] of [15] and related structures, and its degradation to isoquinoline, identified as the picrate, by concentrated hydrochloric acid at 200°. Methyl phenylpropriolate was recovered in 75% yield after attempted reaction with N-methylpyrrole.

Chapter Four, dealing with the products from Pyridines and methyl propiolate, is divided into three sections. Section one is concerned with indolizines. Pyridine, 3,5-dimethylpyridine,

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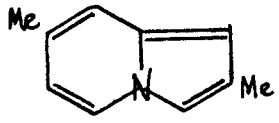
STRUCTURES FOR THE ABSTRACT.



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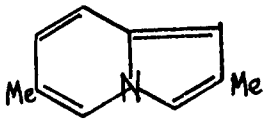

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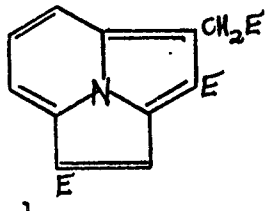

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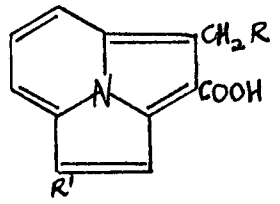
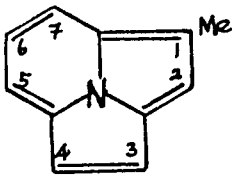


[31] R = H or COOH.
R' = COOH or H.



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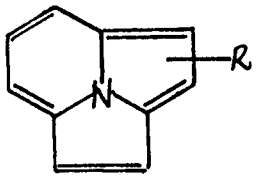
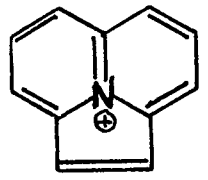


[33] R = H.
[34] R = 2-Me.



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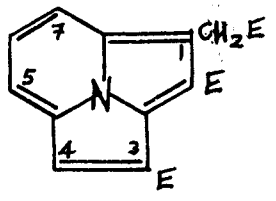

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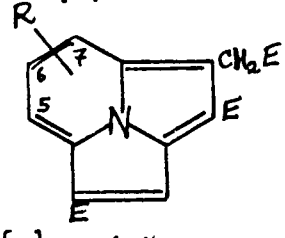
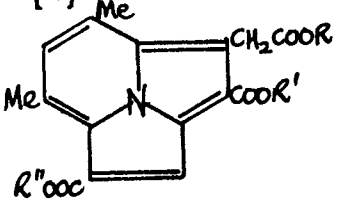
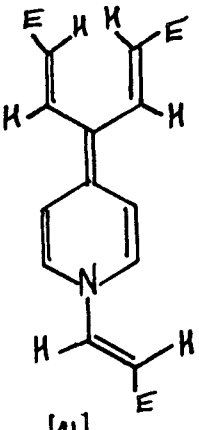


[37] R = 6-Me.
[38] R = 7-Me.
[39] R = 5,7-di-Me.



[40] R, R', R'' = H, H, Me.



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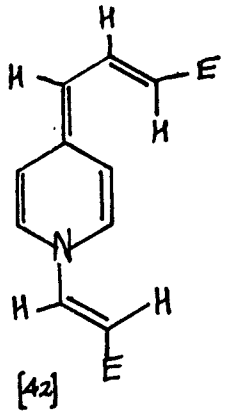

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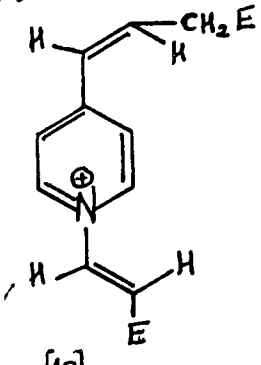

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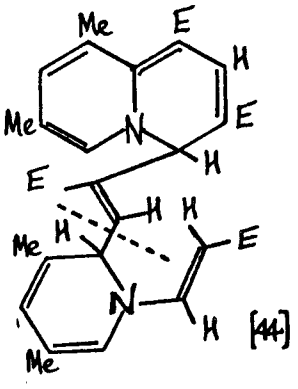

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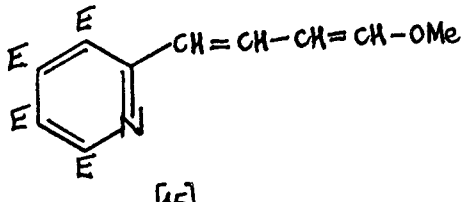

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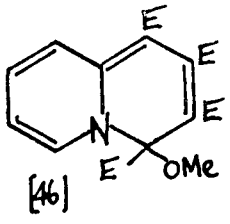

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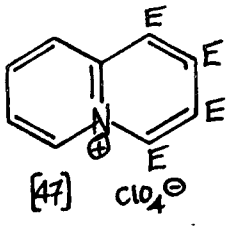
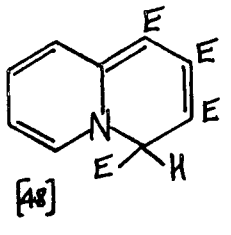


[47] $ClO_4^{\ominus}$



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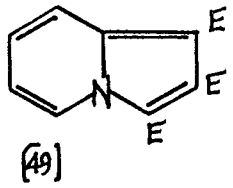

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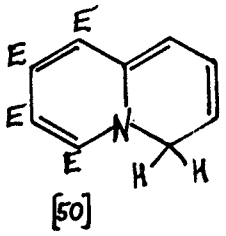

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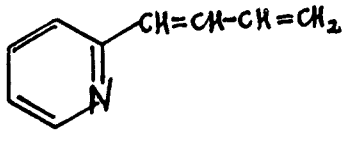

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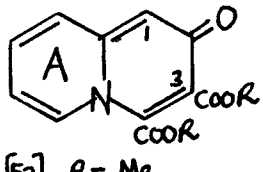

[52] R = Me.
[53] R = Et.

and 4-methylpyridine, with methyl propiolate gave the indolizines [16], [17], [18], whilst heating the 9a<u>H</u>-quinolizine [5] with dehydrogenation (5%) palladium charcoal gave the indolizines [19], [20], and [21]. Compound [16] on the evidenc of its m.p. and u.v. spectrum was identical with an indolizine described previously,[9] whilst indolizine [21] showed the same physical characteristics as an authentic sample of this product available from earlier researches.[10] That the new compounds [17]-[20] were indolizines was suggested from the comparison of their u.v. spectra with those[10] of the known indolizines [16] and [21]-[24], and correlations between the u.v. spectral bands and the nature of the indolizine substituents were deduced. The n.m.r. spectra of all the indolizines [16]-[26] were measured and interpreted for the first time, reference being made to the n.m.r. data recorded[11] for compounds [27]-[29]. The extent of deshielding of protons 8 and 5 by methyl ester substituents at positions 1 and 3, respectively, is discussed since this has bearing on the interpretation of the n.m.r. spectra of the cycl[3,2,2]azines (vide infra).

The cycl[3,2,2]azine adducts are discussed in section two. The product from pyridine and methyl propiolate [30] on hydrolysis (alkaline) gave the di-acid [31] which decarboxylated to give 1-methylcycl[3,2,2]azine [32] identified by comparison of its u.v. and n.m.r. spectra with those for the known compounds [33] and [34].[12,13,14] The mass spectrum of

product [32] was in accord with the formulation given, the base peak corresponding to the loss of an hydrogen atom being assigned to the cycl[3,3,2]azinium cation [35] formed by ring expansion. The alternative formulation of the first formed adduct [30] as [36] was discounted on the basis of the magnitude of the deshielding of H-3 and H-5 by the 4-ester group (cf. the indolizine section) in compound [30] and on the fact that the cyclazine [39] from 3,5-dimethylpyridine and methyl propiolate was identical with a sample prepared from the indolizine [17] and methyl propiolate by an established route[15] for which the orientation of addition of methyl propiolate is certain, i.e. [39] is the expected product. Spectral comparisons with data for [30] and [39] establish the structures [37] and [38] for the cycl[3,2,2]azines obtained from methyl propiolate and 4-methyl-and 3-methyl-pyridine, respectively. Hydrolysis of adduct [39] gave the di-acid mono-ester [40], whilst bromination of [39] yielded a mixture of products all of which were brominated at position 6 (amongst others), these facts being clear from the n.m.r. spectra.

Other adducts from pyridines and methyl propiolate are described in section three. The structure of a minor product, a red-brown adduct, from 3-methylpyridine and this ester was not elucidated. 4-Methylpyridine and the ester gave a dark red adduct, comparison of whose n.m.r. spectrum with that of the orange compound [42], allowed of its tentative formulation as

the product [41]. The major product from 4-methylpyridine and methyl propiolate was the orange adduct [42]. The n.m.r. spectrum in deuterochloroform establishes the involvement of the original 4-methyl group in the adduct formation, and extensive decoupling experiments on the n.m.r. sample supported the structure [42], as did the n.m.r. spectrum in trifluoroacetic acid which was that expected for the protonation product [43] derived from the adduct [42]. An orange compound from 3,5-dimethylpyridine and methyl propiolate is a 2:4 molar adduct on the evidence of its mass spectrum. The n.m.r. spectrum shows no aromatic protons and the i.r. spectrum contains no evidence of carbon-carbon triple bonds, and a very tentative structure proposed with these features is [44]; rupture of the marked carbon-carbon bond would account for the major mass spectral fragments at $^{m}/e$ 358 and 192. No crystalline products were obtained from 2-methylpyridine and methyl propiolate.

Chapter Five is in two sections, the first of which is concerned with the adducts of 2-substituted pyridines and dimethyl acetylenedicarboxylate. In an earlier thesis[16] we described the adducts [45] and [46] from 2-methoxypyridine and dimethyl acetylenedicarboxylate, and additional support for the somewhat tentative structure [45] has been obtained here. Though [45] is both a vinyl ether and a conjugated diene it failed to react with acidified 2,4-dinitrophenylhydrazine and

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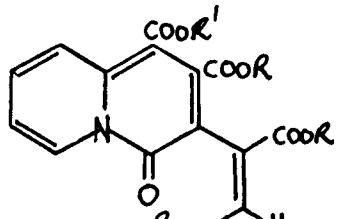
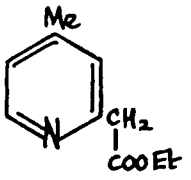
STRUCTURES FOR THE ABSTRACT.



[54] R = R' = Me.

[55] R = Et ; R' = Me.



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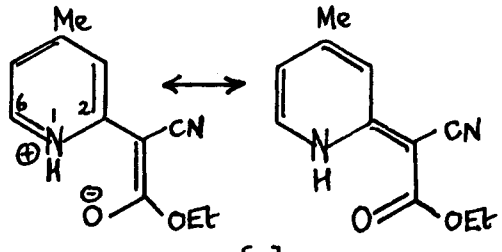

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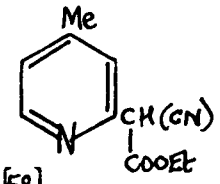

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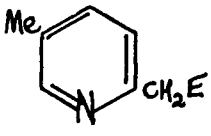

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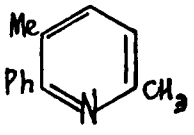

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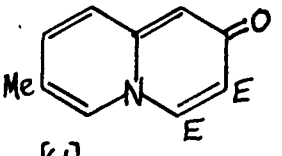

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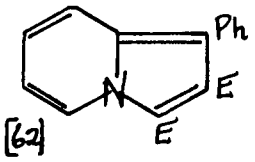

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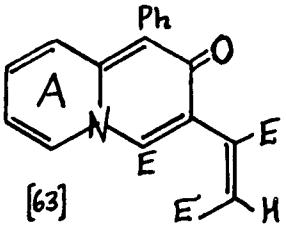

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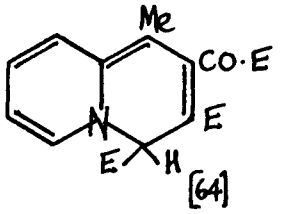

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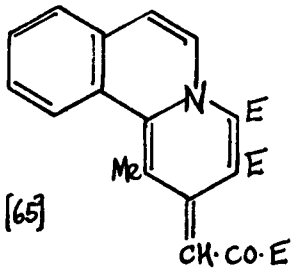

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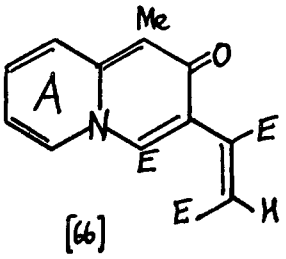

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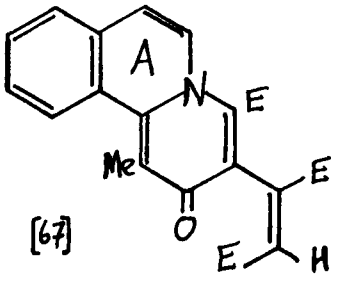

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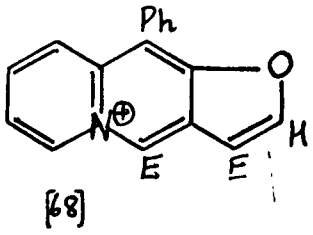

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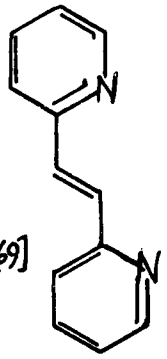

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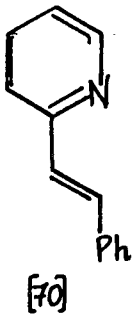

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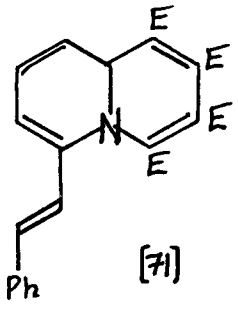

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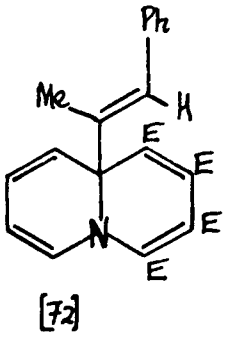

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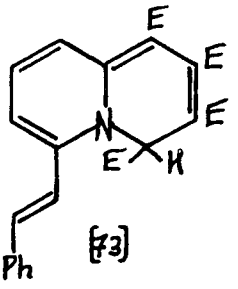

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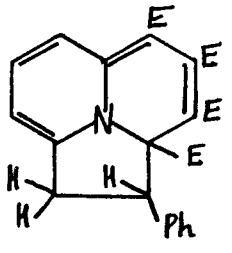

[74]

gave no crystalline adduct with tetracyanoethylene. The facile isomerisation observed here of adduct [45] to the bicyclic isomer [46] on boiling in methanol suggested that the double bond nearest the ring in [45] had the cis configuration. With maleic anhydride adduct [45] gave a red compound tentatively assigned structure [50] on the basis of its n.m.r. spectrum which was quite different from that of the monocyclic systems [45] and [51]. The inter-relations of the mass spectra (measured for the first time here) of compounds [45]-[51] are discussed and this survey provided further support for structures [45] and [50]. Earlier[17] we described the adducts [52] and [54] from methyl 2-pyridylacetate and dimethyl acetylenedicarboxylate, though a recent report in the literature[18] supporting these formulations did not satisfy our uncertainties concerning the n.m.r. spectrum of the A-ring protons of compound [52]. To this end further work was undertaken, and we report analogous adducts [53] and [55] on replacing dimethyl acetylenedicarboxylate by the diethyl ester. These structures confirm the participation of the pyridyl ester group in the formation of adducts [52] and [53], whilst formation of [54] and [55] requires the involvement of the pyridyl 2-methylene group only. An attempt to prepare the pyridine [56] involved the synthesis[19] of the system [57] for which the formulation [58] is discounted because of the observed strong coupling between H-6 and N-H in the n.m.r. spectrum of [57] which slowly disappears on addition of D_2O. Compound [57] resisted all

attempts to hydrolyse it. The pyridine [59] was prepared by parallel methods to established[20] procedures and gave with dimethyl acetylenedicarboxylate the adduct [61] whose n.m.r. spectrum resolved our doubts concerning the spectra of [52] and [53]. A possible contaminant in our prepared sample of [59] is the base [60] and this may be the precursor of an uncharacterisable white by-product obtained in the reaction of [59] with the acetylenic ester. This ester and 2-phenoxypyridine gave only intractable tars.

The indolizine [62], whose structure was determined from it u.v. and n.m.r. spectra, was a minor product from the reaction of 2-benzylpyridine and dimethyl acetylenedicarboxylate, the major product being formulated as compound [63]. The adducts described as [64] and [65] by Gagan,[21] we assign as [66] and [67] for two main reasons:

(i) the n.m.r. spectra of compounds [63], [66], and [67] strongly suggest that they are analogues, and the very close similarity of the A-ring proton resonances to those resonances in adduct [52] supports the 2-quinolizone formulation, the absence of any very low field resonance ruling out the alternative 4-quinolizone structures.

(ii) the mass spectra of compounds [63], [66] and [67] each possess only two major peaks corresponding to the molecular ion (M) and the fragment (M-59) and in

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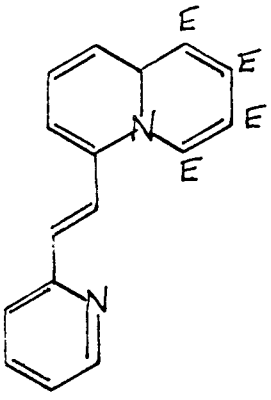
STRUCTURES FOR THE ABSTRACT.



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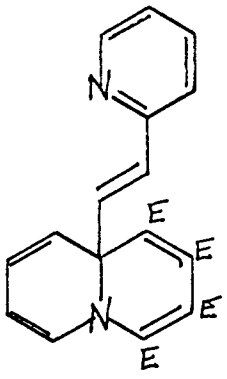

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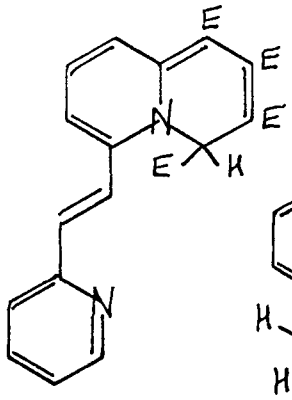

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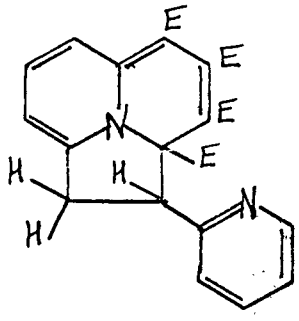

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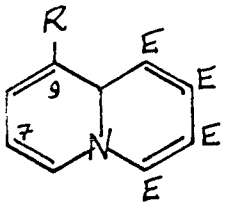
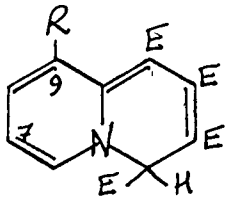


[79] R = CH_2E.

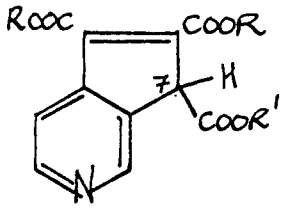
[80] R = CN.

[81] R = Me.



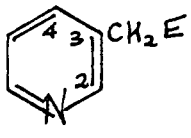
[82] R = CH_2E.

[83] R = Me.



[84] R = R' = Me.

[85] R = Et; R' = Me.



[86]

this respect closely resemble the mass spectrum of adduct [54]. The strong similarities of these four mass spectra is believed to lie in the ability common to the four molecular ions to lose a fragment of mass 59 (COOMe group) to give stable species typified by structure [68] (arising from adduct [63].)

No crystalline products were isolated from 4-benzylpyridine and dimethyl acetylene-dicarboxylate. The acetylenic ester and the pyridine [69] gave rise to a series of adducts [75]-[78] which were readily identified by comparison of their u.v. and n.m.r. spectra with those of the analogous adducts [71]-[74] from the ester and stilbazole [70].[22] The initial products from column chromatography were the adducts [75] and [76], compound [75] isomerising to the adducts [77] or [78] dependent upon the temperature of isomerisation being respectively below or above that of the m.p. of the adduct [75]; under these conditions adduct [76], devoid of a labile hydrogen atom, was quite stable. Features of significance in the n.m.r. and mass spectra of the new adducts are discussed. Intractable tars were the only products from 2,6-dimethoxypyridine and dimethyl acetylenedicarboxylate, a reaction whose course may differ from that of 2-methoxypyridine and this ester[16] for steric reasons.

The second smaller section describes the adducts from 3-substituted pyridines and acetylenic esters. At room

temperature dimethyl acetylenedicarboxylate gave the adducts [79] and [80] from methyl 3-pyridylacetate and 3-cyanopyridine, respectively. These adducts were difficult to purify recrystallisation of [79] yielding the isomer [82]. Identification of these three new compounds resulted from the comparison of their u.v. and n.m.r. spectra with those of the analogues [81] and [83],[10,21] and features of these spectra clearly showed that the substituent R (see [79]-[83]) was at position 9 and not at position 7. At low temperatures the adducts tentatively formulated as [84] and [85] were isolated from methyl 3-pyridylacetate and dimethyl or diethyl acetylenedicarboxylate. The AB and X form of the resonances of the three protons of the six-ring in [84] and [85] was taken to indicate cyclisation across the 3,4-positions of the original base [86]. The n.m.r. spectrum of ethyl analogue [85] revealed the resonance (6.67τ) due to H-7 which was obscured (at 6.24τ) by the three methyl ester resonances in the spectrum of [84]. Some support for the structures proposed was adduced from the interpretation of their mass spectra.

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