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STUDIES OF HETEROCYCLIC COMPOUNDS CONTAINING BRIDGEHEAD NITROGEN ATOMS.

by

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To Sheila

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I also thank the University of Edinburgh for the provision of laboratory facilities and for my grant.

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EXPERIMENTAL Page

SUMMARY

1, 2 - dimethoxycarbonylcyclopenta [c] quinolizines have previously been synthesised from 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonyl buta - 1, 3 - dien - 1 - yl) indolizines by thermal methods with loss of dimethylamine and a novel ring expansion of the five-membered ring of the indolizine to a six-membered ring. Studies have been made into the synthesis of cyclopenta [c] quinolizines containing a dimethylamino - substituent in the 1 - and 3 - positions by the action of oxidising agents on the 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) indolizine intermediates, and a mechanism proposed for their formation. Application of this procedure to the analogous 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) indoles was unsuccessful.

Attempts to ring expand indolizines to quinolizinium salts also met with failure owing to difficulties in obtaining suitable substituents in the 3 - position of the indolizines.

Studies were carried out into the reaction of 5 - methylindolizines with dimethyl acetylenedicarboxylate in benzene with the formation of dimethyl 7a - methyl - 5, 7a - dihydrocycl [3, 2, 2] azine - 1, 2 - dicarboxylates and tetramethyl 9a - methyl - 5, 9a - dihydrocycl [5, 2, 2] azine - 1, 2, 5, 6 - tetracarboxylates. The latter are believed to be formed by expansion of the six-membered ring to an eight-membered ring in the 2a, 7a - dihydrocycl [3, 2, 2]azines which are the likely initial products of the reaction. When the reaction was carried out in protic solvents, 3 - (1, 2 - dimethoxycarbonylvinyl) indolizines were obtained.

4 - Methyl - 2 - phenyl - 3 - methylthiocycl [3, 3, 2] azinium perchlorate was prepared from 3 - (hydroxyiminoacetonyl) - 5 - methyl - 2 - phenylindolizine but attempts to remove the methylthio group from this,

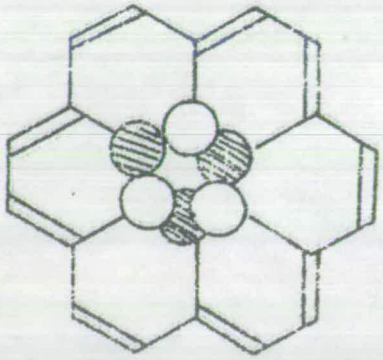
using Raney-nickel, proved unsuccessful. Attempted nitration and formylation of cycl [3, 3, 2] azin - 1 - one proved unsuccessful but the cyclazinone reacted with dimethyl acetylenedicarboxylate to give the 2 - (1, 2 - dimethoxycarbonylvinyl) derivative.

The parent cycl [3, 3, 2] azinium perchlorate, synthesised by a previously reported method, with minor modifications, did not undergo Diels-Alder addition with 1, 3 - diphenylisobenzofuran. This shows that the 1, 2 - bond is less reactive than that in the isoelectronic hydrocarbon, acenaphthylene, though the vicinal proton coupling constants ($J_{1,2}$) are about the same for the two compounds.

Reaction of 1 - methoxycycl [3, 3, 2] azinium perchlorate with sodium sulphide gave a mixture of two cyclazinethiones believed to contain the thione group in the 3 - and 6 - positions, respectively.

The classical definition of an aromatic compound was based on its cyclic nature, stability and chemical reactivity. Chemical reactivity is not a property of the molecule in the ground state, but depends on the difference in free energy between the ground state and the transition state for the chemical change involved[1]. If this free energy difference is small the molecule will be reactive irrespective of the energy content of the ground state. Modern definitions of aromaticity have therefore been made without reference to chemical behaviour but simply in terms of the ground state physical properties of molecules.

The modern definition of aromaticity considers a compound to be aromatic if there is a measurable degree of cyclic delocalisation of the π- electron system in the ground state of the molecule. Consequences of this delocalisation of π- electrons may be seen in the "lower than classical" energy content in the molecule[2] and also in the fact that these delocalised molecules have the ability to sustain a diamagnetic ring-current in an applied magnetic field. The nuclear magnetic resonance spectra of such molecules therefore have the characteristic feature that protons joined to the ring and external to it absorb at lower field (c.f. Benzene 2.81 τ) than protons of polyolefinic systems (4.1 - 4.6 τ). In the case of monocyclic systems formally constituted of alternating single and double bonds, termed annulenes[3] a diamagnetic ring current has the effect of shielding the inner protons and deshielding the outer ones. One other consequence of this property is that marked alternation in bond lengths is not normally a feature of aromatic molecules. Modern techniques for the determination of aromaticity are therefore mainly nuclear magnetic resonance and diamagnetic susceptibility



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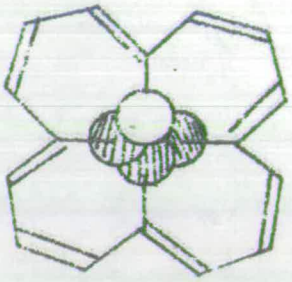

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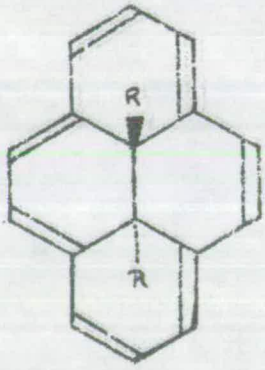
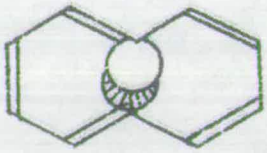


3 R = CH_3, Et.



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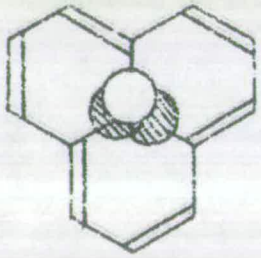

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measurements.

During the 1930's Hückel extended the concept of aromaticity, in terms of electronic structure, from those compounds containing benzenoid rings to non-benzenoid systems e.g. the annulenes. On the basis of molecular orbital theory he concluded that monocyclic planar systems of trigonally hybridised carbon atoms that contain $(4n + 2)\ \pi$ - electrons possess inherent electronic stability[4]. Thus, planar $(4n + 2)\ \pi$ peripherally conjugated systems are potentially capable of exhibiting aromatic properties whereas their $4n\ \pi$ analogues are expected to be essentially olefinic in character.

Until 1956 despite many attempts [5-8], difficulties in the synthesis of annulenes had prevented any test of Hückel's rule. Up to that time only benzene ([6] annulene) and cyclo octatetraene [9, 10] were known, higher vinylogues having resisted classical methods of synthesis [8]. However, the discovery [11-17] in 1956 of simple methods for the generation of large-ring hydrocarbons containing 1, 3 diacetylenic units and their subsequent prototropic rearrangement to fully conjugate cyclic products has resulted in prolific researches by the Sondheimer group culminating to date in the synthesis [18] of an entire series of annulenes, with the substantiation of the generality of the Hückel π - electron rule as may be seen from a comparative study of [18] annulene (1) and [16] annulene [18](2).

Cyclo-octadecanonaene, [18] annulene has been found to display relatively little aromatic character in the classical sense, reacting with Bromine and maleic anhydride to give addition products, but the physical evidence substantiates the view that [18] annulene is in fact aromatic. X-ray crystallography [19, 20] has indicated that [18] annulene is a centro-symmetric molecule, differing from planarity by less than 0.1Å. Bond alteration is not observed, but there is a

variation between the 6 "cisoid" bonds (1.419 Å) and the 12 "transoid" bonds (1.382 Å) and molecular orbital calculations [21], interpretation of electronic spectra [22], and magnetic circular dichroism studies [23] enhance this finding. However, recent modifications of the molecular orbital treatment indicate that in the gaseous state the favoured structure may be one involving alternately long and short bonds [24]. Determination of the heat of combustion [25] and the value of the stabilisation energy calculated from this are found to be in good agreement with a planar model having delocalised π - electrons and equal carbon - carbon bond lengths [26].

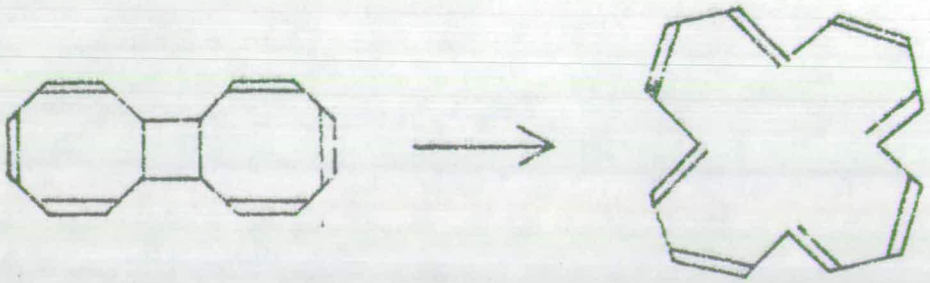
The nuclear magnetic resonance spectrum [27, 28, 29] showed two broad bands, one at a very low field (1.1 τ) (12 protons) and one at a very high field (11.8 τ) (6 protons) assigned to the external and internal protons respectively, and on this basis [18] annulene was taken to be aromatic. The n.m.r. spectrum has since been found to be temperature dependent [30]; at -60° the bands exhibit fine structure; but heating the solution leads first to diffusion of the bands, and then to coalescence, until, at 110°, a sharp singlet (4.55 τ) is observed. It is thought that this is due to a rapid conformational switching of protons between external and internal positions, such that averaging of the chemical shift occurs [31]. This possibility has been confirmed by calculations of the energy barrier to conformational changes (ΔG = 13.4Kcal/mole)[32].

Attempts to bring about electrophilic substitution originally led to addition or decomposition [17, 33], but under milder conditions [18] annulene has been shown to yield mononitro - and monoacetyl derivatives [34]. The n.m.r. spectra of these compounds exhibited essentially the same behaviour as the parent molecule [34]. With

maleic anhydride [18] annulene underwent an addition reaction [17, 33]. These considerations have also been applied to higher vinylogues in the (4n + 2) series, although they are more sparsely documented.

[4n] Annulenes have also been investigated, the synthetic route to [16] [28, 36, 37] [20] [35, 38] and [24] [39, 40] annulenes being essentially the same as that used for their (4n + 2) analogues. Recently, photolysis of dimeric cyclo-octatetraene (4) resulted in a higher yield of [16] [41] annulene. (2). X-ray analysis [42] confirmed the non-planarity (up to 0.57Å from a plane through carbon atoms 3, 7, 11, 15) and indicated bond alternation between 1.46Å and 1.34Å. The n.m.r. spectra [39, 36, 38, 40] of these annulenes showed temperature dependence; that of [16] annulene, for example, showed a sharp singlet (3.27 τ) at room temperature [36], but on cooling to -120°C bands appeared at -0.32 τ (4 protons) and 4.8 τ (12 protons)[41]. These bands were assigned to the internal and external protons respectively, (a reversal in position with respect to the absorptions of (4n +2) annulenes) and are indicative of what has been termed a paramagnetic ring current [43, 44, 45]. This reversal of positions is also exhibited by 24 annulene [43]. The temperature dependence of these n.m.r. spectra has been explained in terms of valence isomerism and conformational mobility [46].

However, the pursuit of annulene chemistry cannot, within itself, be considered a wholly integral method for the evaluation of the unique chemical characteristics associated with (4n + 2) π - electron delocalisation. An inherent defect in the approach arises from molecular distortion consequent on steric interaction of inwardly - directed hydrogen atoms [47, 28]. Thus, while [10] annulene (5) satisfies the numerical Hückel electron - requirement, realisation of its potential aromatic property appears to be inhibited by the failure of the molecule to attain planar ring - geometry and hence



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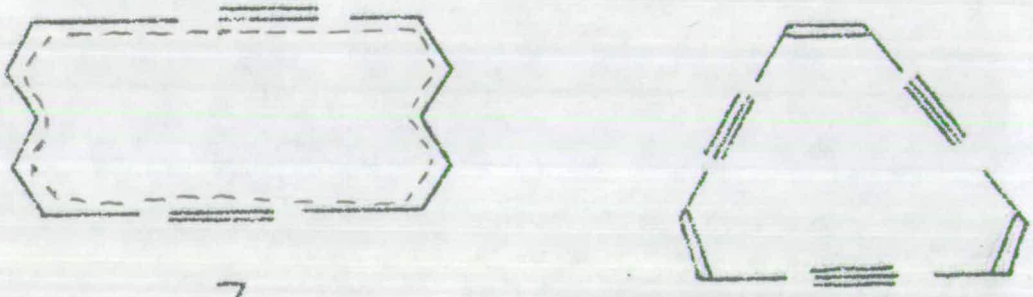

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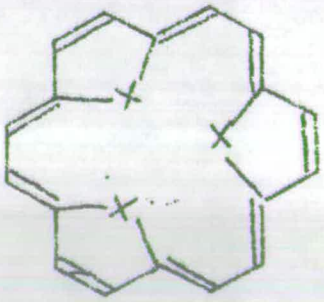
X = CH_2, O, NH, $C{=}CH_2$, NMe_2, $NCOCH_3$



11

X = O, S

10

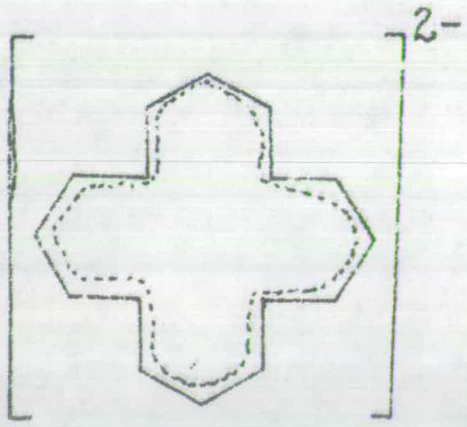
X = O, CH_2

cyclic delocalisation of the peripheral π - electrons. Similar structural considerations apply to the 4n π - non - Hückel vinylogue 12 annulene (6). The approaches used to overcome this problem may be summarised as follows.

1. Replacement of one or more double-bonds by linear acetylenic or allenic units.
2. Replacement of inwardly - directed hydrogen atoms with saturated carbon bridges or polyvalent hetero atoms.

An extensive range of dehydroannulenes is known, covering the range [12] to [30] [1, 3, 28, 36-39, 40, 48, 49-58, 60] with the exception of [28]. Examples containing (4n + 2) and (4n) π - electrons respectively are, 1, 8 - bisdehydro - [14] annulene (7) and 1, 5, 9 - tridehydro [12] annulene (8).

Considerable success has attended the work of Vogel on the synthesis of a range of bridged annulenes. Starting from naphthalene, for example, a series of 1, 6 - bridged [10] annulenes [59-71] has been synthesised and shown, on the basis of nuclear magnetic resonance to be aromatic. 1, 6 - Methanocyclodecapentaene (9; X = CH_2), for example, shows eight external protons centred at 2.9 τ and two bridge protons at 10.5 τ. Other structures studied are doubly bridged [14] annulenes (10) [66, 72], and various multiply - bridged higher annulenes, such as (11; X = O), containing furan rings [73-80]. Further examples of bridge - bonded annulenes are the series of dihydropyrene derivatives based on structure (3), synthesised by Boekelheide [81, 82, 83]. The n.m.r. spectrum of the parent trans - 10b, 10c, - dimethyl - 10b, 10c, - dihydropyrene (3; R = CH_3) [29] shows signals due to the external protons in the range 1.3 - 2.0 τ and a sharp singlet at 14.25 τ due to the internal methyl groups. The displacement of the ring protons to low field, and the remarkable shift



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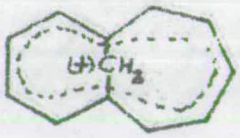

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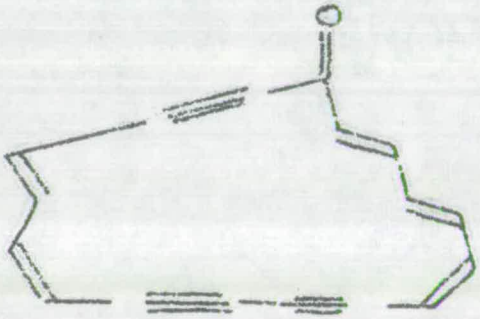

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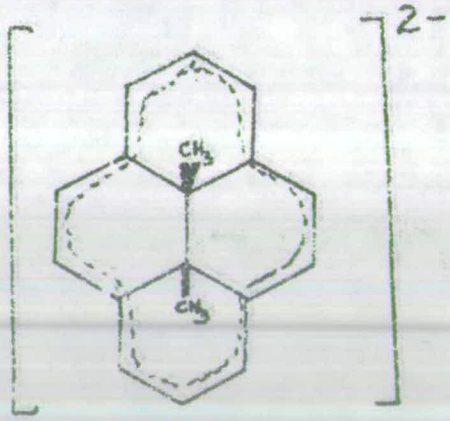

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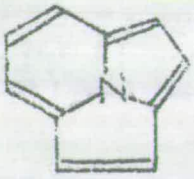
of the methyl protons to high field, provide clear evidence for the existence of a diamagnetic ring current. Electrophilic substitution reactions have also been accomplished.

Present work in this field appears to be concentrating on the synthesis of annulene ions and annulenones. [16] Annulene dianion (12) [84], bicyclo [5, 4, 1] dodecapentaenyl cation (13) [85], and bicyclo [4, 3, 1] decatetraenyl anion [86] have been shown to be aromatic whereas trans - 10b, 10c - dimethyl dihydropyrene dianion (14) [87] demonstrates clearly the effect of a paramagnetic ring current. [13] [88] - and [17] [89] Annulenone (15) derivatives are known and the [17] annulenone, in accordance with prediction [90], is non aromatic.



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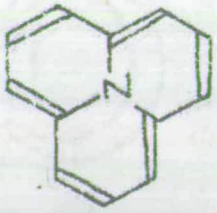

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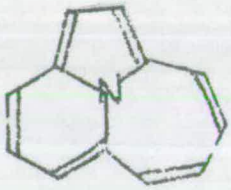

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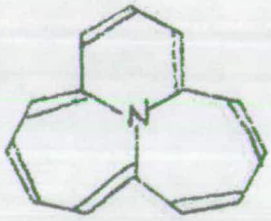

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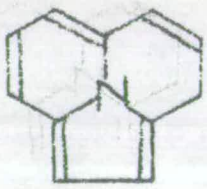

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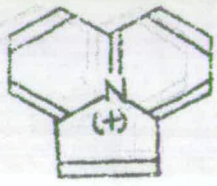

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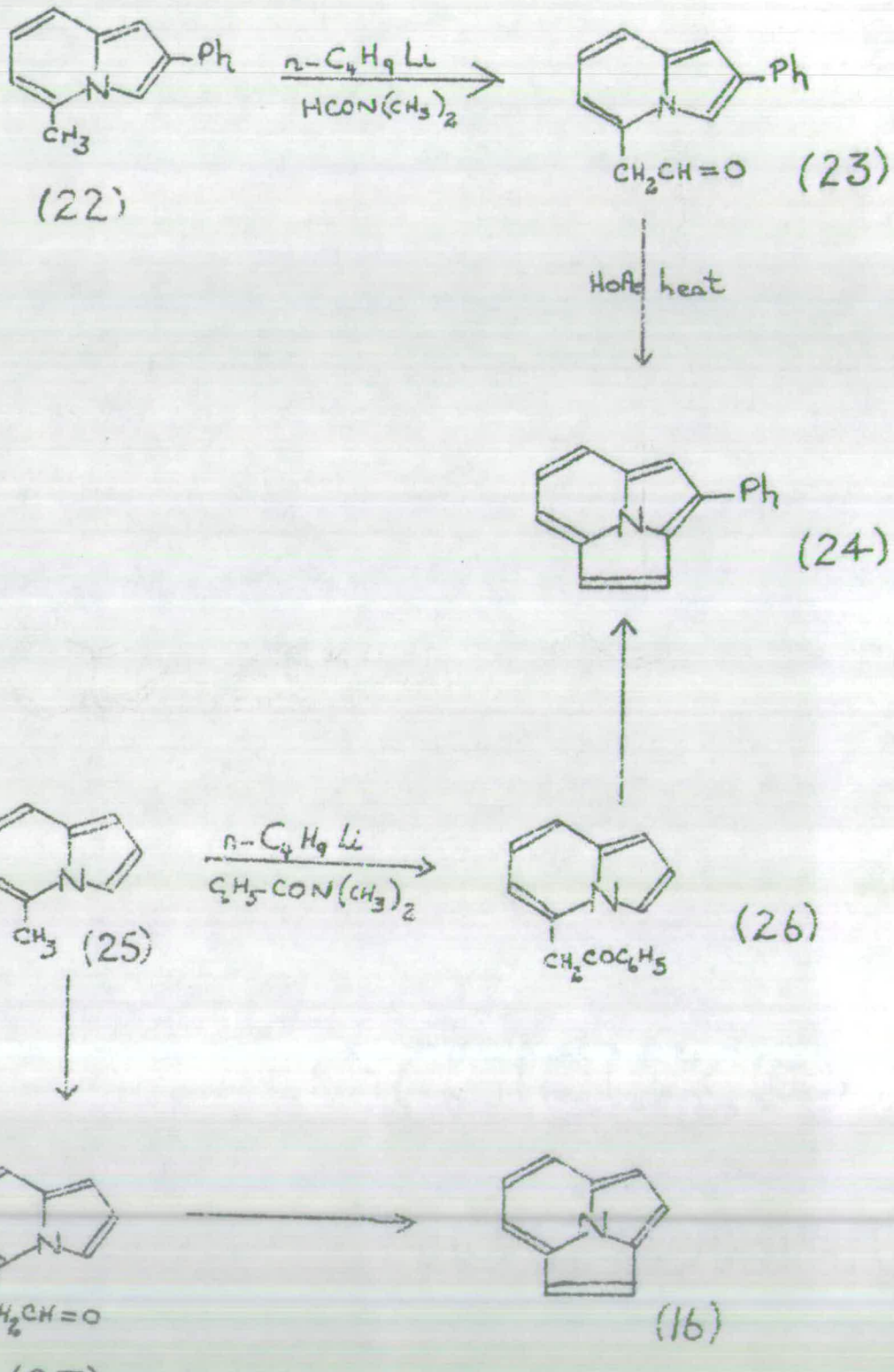
The Cyclazines

Boekelheide [91] has given the name "Cyclazines" to conjugated unsaturated molecules, formally derivable, from the annulenes by replacement of three inwardly - directed hydrogen atoms by a central nitrogen atom. Structures (16) - (19) are thus termed respectively, cycl [3, 2, 2] azine, cycl [3, 3, 3] azine, cycl [4, 3, 2] azine and cycl [4, 4, 3] azine. The nomenclature equally accommodates both ionic and partly saturated structures. Thus structure (21) is the dehydrocycl [3, 3, 2] aziniumion and (20) is 3H - cycl [3, 3, 2] azine. The systematic terminology for these compounds, based on I.U.P.A.C. rules, is derived from the largest nitrogen containing bicyclic nucleus present in the molecule. Compounds (16) and (17) are thus named, respectively, pyrrolo [2, 1, 5 - c, d] indolizine and pyrido [2, 1, 6 - d, e] quinolizine.

The interest in these compounds stems from their relevance to investigations concerning the validity of current molecular orbital theories of chemical reactivity and chemical shift in heterocyclic systems. The systems may be considered as bridged annulenes, but since the effect of the nitrogen lone pair orbital is not easy to predict, then calculations have to be made for each molecule separately in order to predict the presence or absence of aromaticity. Initial calculations [91], [92] indicated that structures such as (16), (17) and (18) should all possess a resonance energy higher than that of their monocyclic hydrocarbon counterparts. Recent calculations [93] have confirmed that cycl [3, 2, 2] azine should show considerable resonance energy but that the most energetically favourable structure for cycl [3, 3, 3] azine is one of alternating single and double bonds, indicating that perhaps the most important factor in determining the presence or absence of aromaticity is the



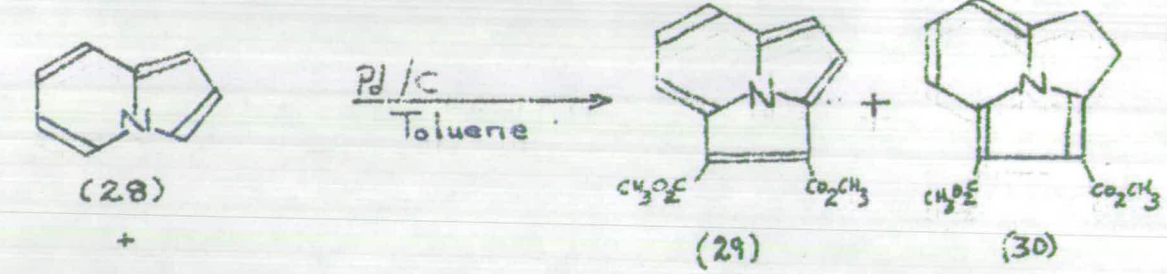
(22) (23) (24) (25) (26) (27) (16)

Scheme i

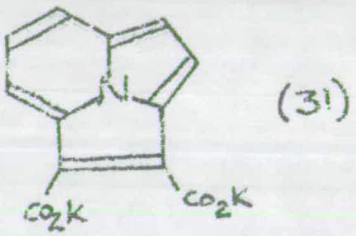
number of peripheral π - electrons. Bond orders, π - electron densities, energies of excited states have been evaluated [91] and predictions made regarding the orientation of electrophilic substitution.

In 1959, Boekelheide achieved the first synthesis of a cyclazine [91] VIZ cycl [3, 2, 2] azine using indolizines as presursors. (scheme 1). Treatment of 5 - methyl - 2 phenylindolizine (22) with n - butyl - lithium followed by N, N - dimethylformamide gave 5 - formylmethyl - 2 phenylindolizine (23). Similarly treatment of 5 - methylindolizine with n - butyl - lithium and N, N - dimethylbenzamide gave the corresponding 5 - phenacylindolizine (26). Cyclodehydration [94, 95] by heating with acetic acid gave a high yield in both cases of 2 - phenyl cycl [3, 2, 2] azine (24). The parent system (16) was synthesised from 5 - methylindolizine by a similar method but in low yield (23%).

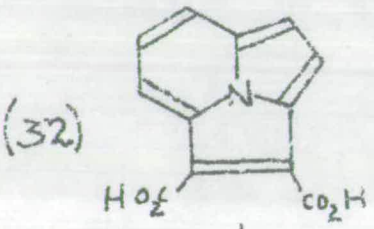
A new preparative path to cycl [3, 2, 2] azine derivatives was opened up when it was found that the reaction of 1, 2, 6, 7 - dibenzoindolizine with dimethyl acetylenedicarboxylate, in the presence of a dehydrogenation catalyst (Pd/C) and a trace of hydroquinone, gave 1, 2, 5, 6 - dibenzo - cycl [3, 2, 2] azine - 3, 4 - dicarboxylic acid in 54% yield [96]. Using this method Boekelheide was ableto prepare cycl [3, 2, 2] azine (16) in high yield via the 1, 2 - di(methoxycarbonyl) derivative (29) (Scheme 2). The reaction is believed [97] to proceed by an electrophilic attack of dimethyl acetylenedicarboxylate at the 3 - position of the indolizine nucleus (28) to give a zwitterionic species (33). Cyclisation of the initial adduct to give (34) and dehydrogenation would lead to the formation of the diester (29). The dihydro derivative (30) was obtained as a by-product in 10-15% yield. It is also believed that hydrogen migration in the intermediate (34) is responsible for the formation of (30). Alkaline hydrolysis



10% Methanolic KOH.

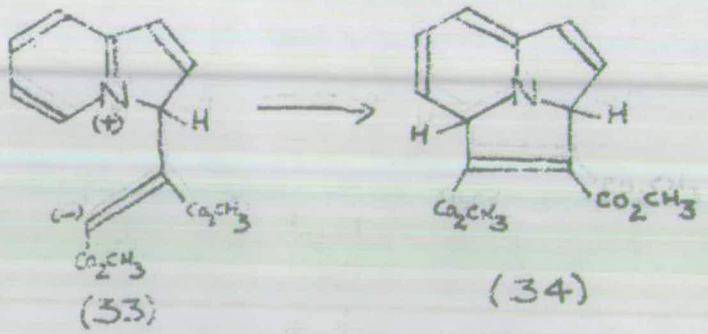


5% HCL

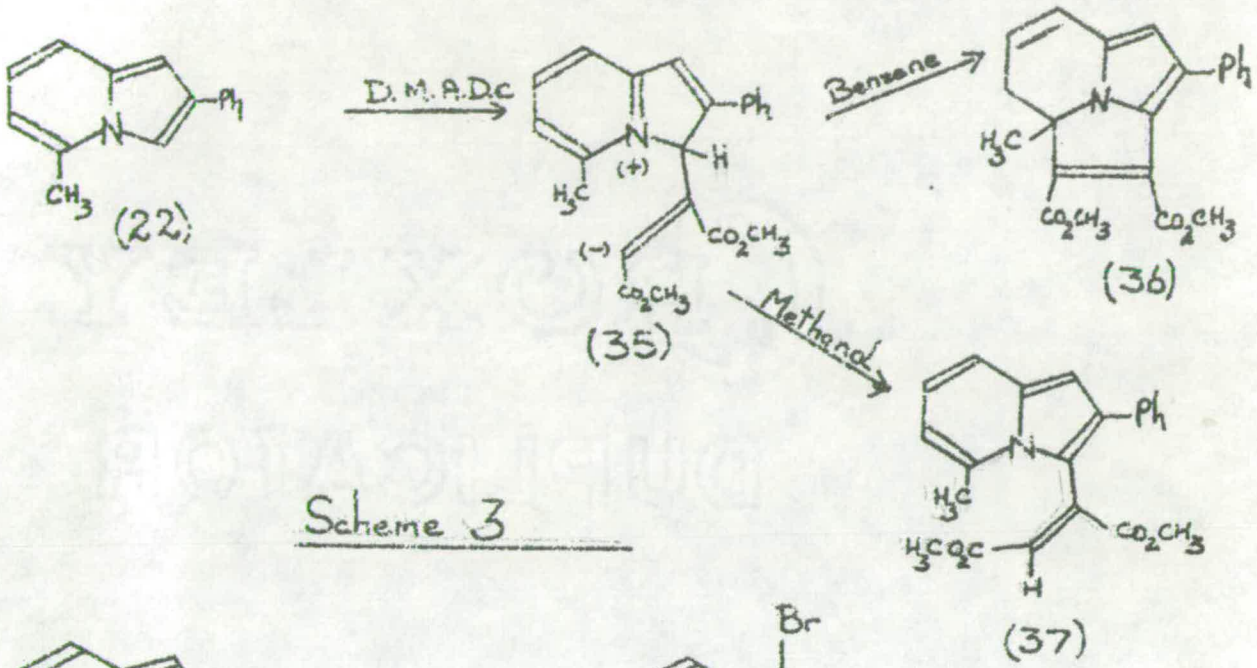


Quinoline — Copper chromite

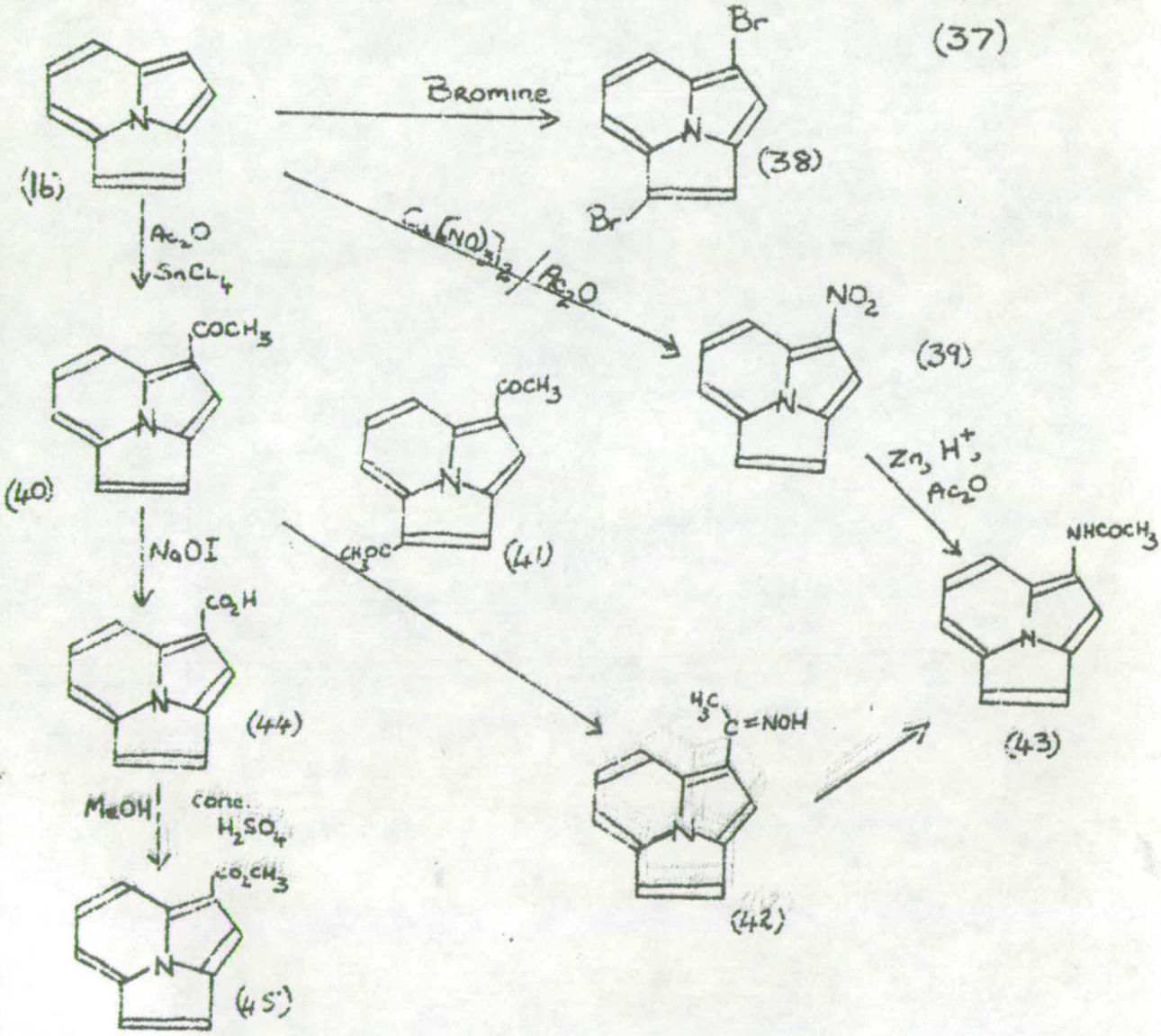
(16)



Scheme 2



Scheme 3



Scheme 4

of (29) followed by subsequent decarboxylation yielded the parent cyclazine (16).

Although the intermediacy of the zwitterionic species has not been formally demonstrated, strong support for the concept has been provided by studies on related systems carried out in this department [108]. Thus, the reaction of 5-methyl-2-phenylindolizine (22) (scheme 3) with dimethylacetylenedicarboxylate in anhydrous benzene "gave a yellow adduct for which the structure (36) was suggested. In methanol, however, a different product, probably the open-chain adduct (37), was obtained." These results remain to be substantiated but can be accounted for on the basis of a zwitterionic intermediate which has a greater chance of cyclisation in the aprotic solvent, whereas under protonic conditions rapid protonation at the anionic site and deprotonation at the 3-position will give the open-chain adduct.

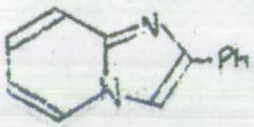
A great deal of work has been carried out into the physical and chemical properties of cycl [3, 2, 2] azine. Molecular orbital calculations [91, 92, 93] suggested that this molecule should show a marked stability, the resonance energy being calculated as [93] (o.82eV) (cf benzene 0.87eV). These calculations [91] also suggested that electrophilic substitution should occur at position -1, nucleophilic attack at position -5 and radical attack at positions -2 and -5.

Predictions of stability and electrophilic attack have been upheld experimentally. Thus the parent cyclazine (16) is a yellow, crystalline, fluorescent compound with a naphthalene-like odour; it is stable to light, heat and air. It is insoluble in aqueous acid and its ultra-violet spectrum remains unchanged by the addition of acid showing that the compound is a very weak base. Electrophilic substitution occurs smoothly and in good yield as is shown by

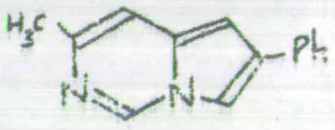
substitution with a variety of electrophiles, (scheme 4) yielding 1 - mono - and 1, 4 - disubstituted cyclazines [91, 99]. The first position of substitution was confirmed by inter-relating the mono-nitro (39) and mono-acetyl (40) derivatives via (42) and (43) and by the fact that the methoxycarbonylcycl [3, 2, 2] azine (45) prepared from the acetylcycl [3, 2, 2] azine (40) was identical with that prepared by the reaction of methylpropiolate with indolizine. Attempted nucleophilic substitution in the cycl [3, 2, 2] azine ring system [99] failed as the initial reaction with methyl-lithium resulted only in recovery of starting material.

The n.m.r. spectrum [100, 101] of cycl [3, 2, 2] azine demonstrates the presence of a plane of symmetry in the molecule. It consists of an A_2B multiplet arising from the protons of the six-membered ring (5, 7 - protons at 2.14 τ; 6-proton at 2.41 τ) and two superimposed AB quartets arising from the protons of the two five membered rings (1, 4 protons at 2.18 τ; 2, 3-protons at 2.50 τ), the coupling constants being $J_{1,2}$ = 4.2Hz; $J_{5,6}$ = 8Hz. Initially there was uncertainty concerning the assignment of chemical shifts to the protons of the five-membered rings but deuteration studies [100], on the 2-methylcycl [3, 2, 2] azine have since confirmed the above data, and also demonstrated the greater reactivity of positions -1 and -4 towards electrophiles. The low field signals of the protons indicate the presence of an induced diamagnetic ring current and therefore the system is regarded as aromatic.

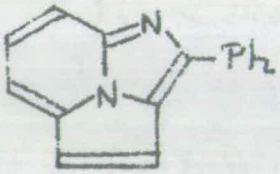
X-ray diffraction studies have been carried out on the 1, 4 dibromo derivative [102]. These indicated that the molecule is essentially planar, deviation from the mean plane being estimated at 0.010^{o}A. It is thought that the configuration of the nitrogen



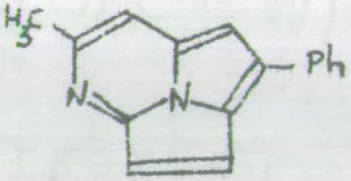
(49)



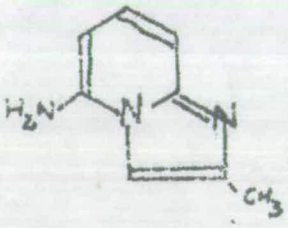
(50)



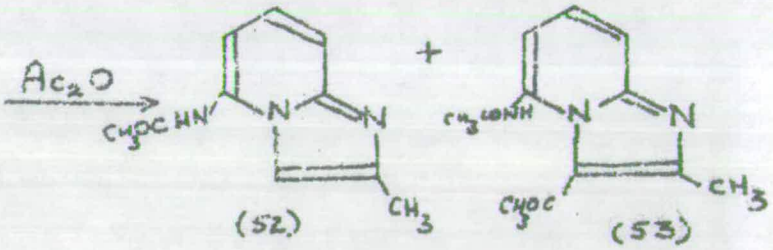
(46)



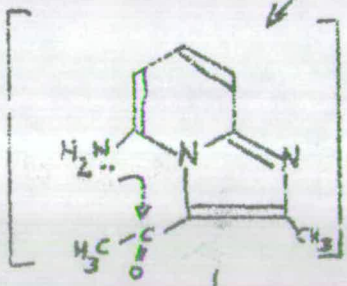
(47)

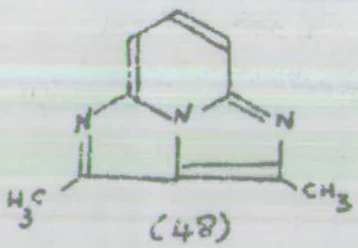


(51)



(52) (53)



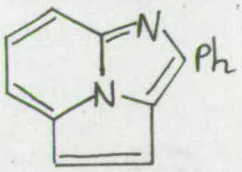


(48)

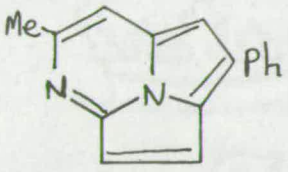
Scheme 5

atom is planar, since this atom and the three carbon atoms to which it is bonded are coplanar. Although this could be accounted for on the basis of a pyramidal nitrogen configuration, the observed planarity being due to alternation of the nitrogen atom between equilibrium positions on either side of the mean plane, such a movement would be expected to give an apparent elongation of the nitrogen atom but this effect has not been detected.

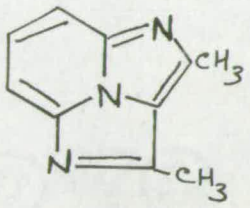
Cycl [3, 2, 2] azine systems with one or more nitrogen atoms in the peripheral skeleton (46), (47) and (48) have been the subject of several reports [102, 103].



(46)



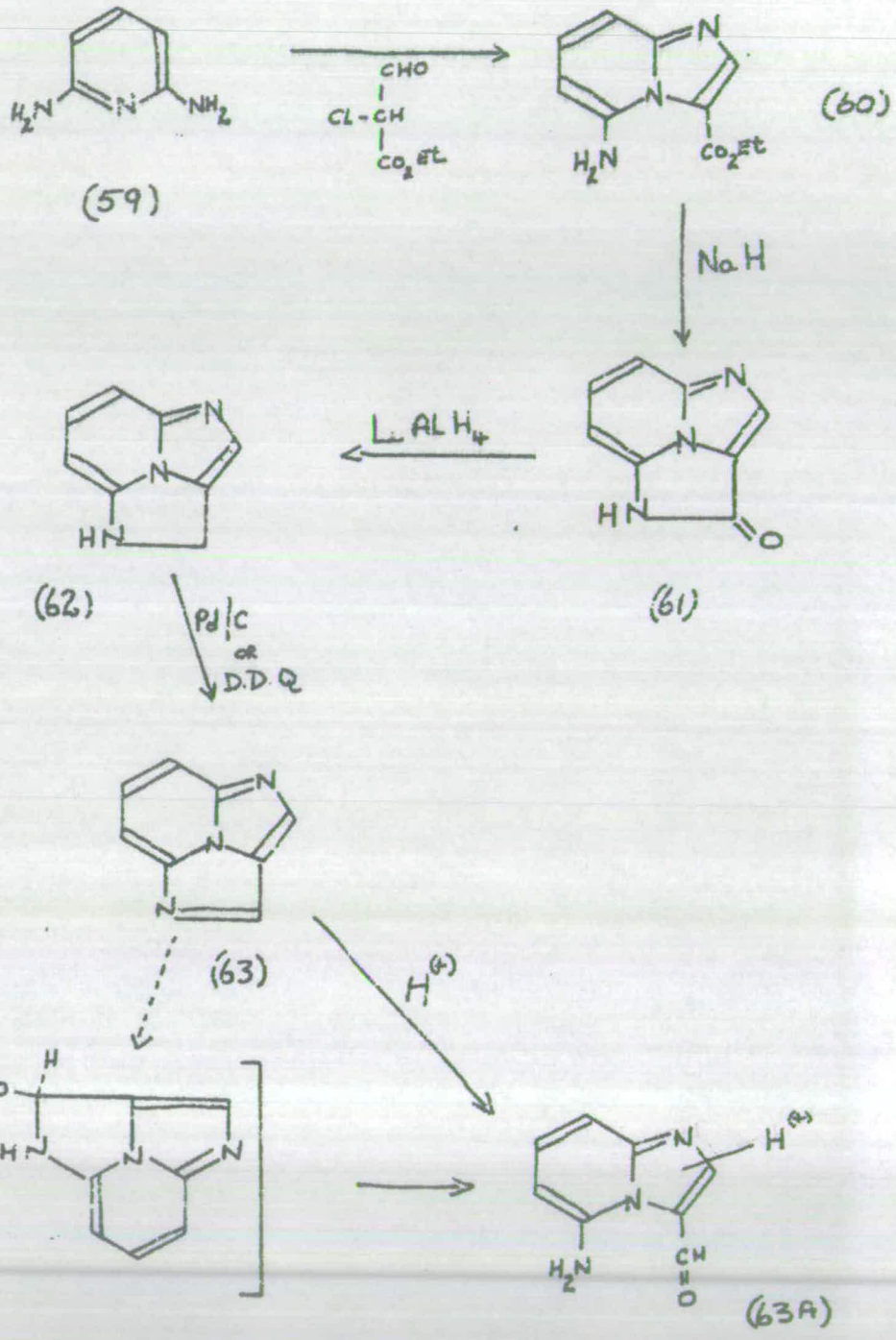
(47)



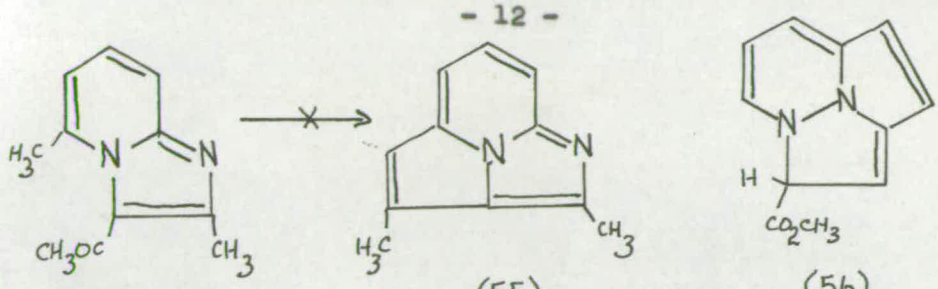
(48)

Starting from 2-phenyl-imidazo [1, 2- a] pyridine (49) (scheme 5) and 7-methyl-2-phenyl pyrrolo [1, 2 - c] pyrimidine (50), Boekelheide and his co-workers obtained 2-phenyl-1-azacycl [3, 2, 2] azine (46) [103] and 6-methyl-2-phenyl-5-azacycl [3, 2, 2] azine (47) [103], respectively, by reaction with dimethylacetylenedicarboxylate and subsequent removal of the dimethoxycarbonyl groups.

In 1966, Valentin and Taurins [104] found that the reaction (scheme 5) of 5-amino-2-methylimidazo [1, 2 a] pyridine (51) with acetic anhydride gave two products, the expected acetamide (52) and the 5-acetamido-3-acetyl compound (53) respectively. On treatment with base (53) cyclised to give 2, 3-dimethyl-1,4 diazacycl [3, 2, 2] azine (48). Attempts to prepare 2, 3-dimethyl-1-aza cycl [3, 2, 2] azine (55) from 3-acetyl-2,5-dimethyl-imidazo [1, 2a] pyridine (54) and to



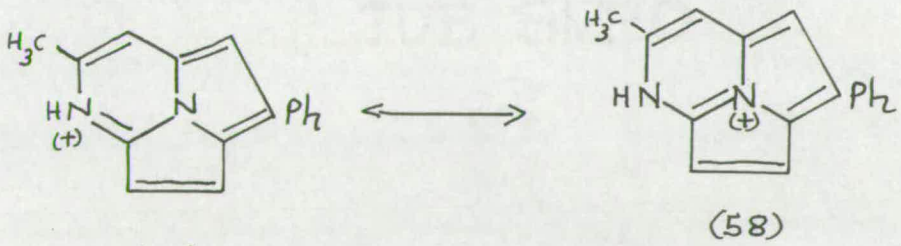
Scheme 6



(54) (55) (56)

convert the 4, 4a-dihydro-4a-azacycl [3, 2, 2] azine derivative (56) to the corresponding 4a-azoniacyclazine [105] failed.

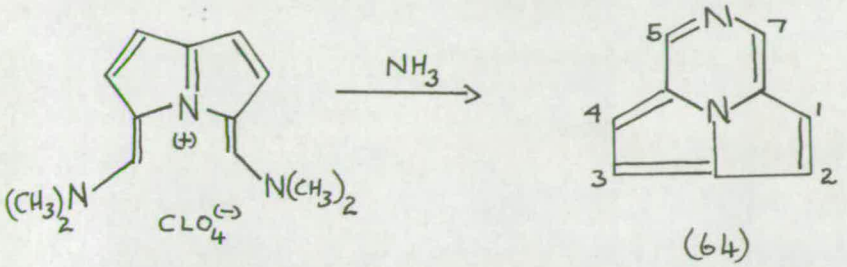
The nuclear magnetic resonance of (46), (47) and (48) all displayed absorptions in the low field region, confirming the presence of an induced diamagnetic ring current. Chemical transformations other than simple salt formation have not as yet been reported. Both (46) and (47) are soluble in dilute acid, unlike their analogues with a completely carbocyclic periphery and a change of ultra-violet absorption to longer wavelengths on the addition of dilute acid is reported [103] for the case of (47). This may be explained on the assumption that (47) is a resonance hybrid in acid solution with (57) and (58) as two contributing forms.



(57) (58)

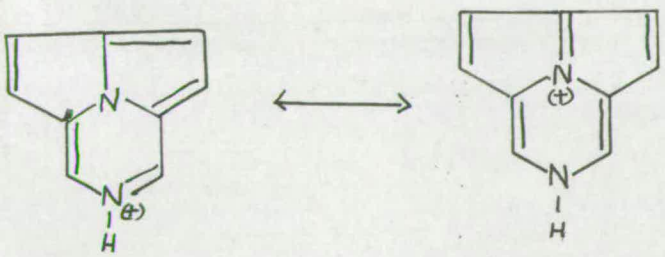
More recently [106] Paudler etal have achieved a synthesis (scheme 6) of the parent 1,4-diazacycl [3, 2, 2] azine (63) from 2,6-diaminopyridine (59). The 1,4-diazacycl [3, 2, 2] azine was found to be unstable to even trace amounts of acid at room temperature being readily hydrolysed to 5-aminoimidazo [1,2a] pyridine-3-carboxaldehyde (63A). Attempts to isolate the intermediate carbinolamine all proved unsuccessful.

Recently [115] 6-azacycl [3, 2, 2] azine (64) has been synthesised in this department by reaction of 3,5-bis (dimethylamino methylene) -3H,5H-pyrrolizinium perchlorate with ammonia.

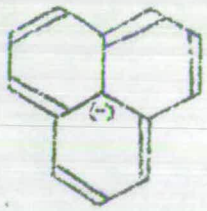


(64)

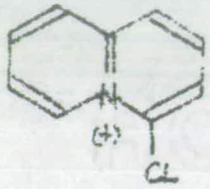
The n.m.r. spectrum showed a singlet at 0.97 τ and an AB system comprising doublets at 2.34 τ and 2.55 τ the coupling constant being J_{AB} = 4.5Hz. These absorptions were attributed to H-5,7; H-2,3; and H-1,4 respectively. The ultra-violet spectra of the 6-azacycl [3, 2, 2] azine was similar to that of cycl [3, 2, 2]azine itself. In acid solution, however, the spectrum showed quite large changes, due to protonation of the peripheral nitrogen, these changes being larger than those observed for the other azacycl [3, 2, 2] azines [102, 103, 104]. The changes were taken to indicate that, like the other azacyclazines, the 6-azacycl [3, 2, 2] azine exists as a resonance hybrid, viz.



The original molecular orbital calculations, based on a model of the phenalenyl anion (65), indicated that cycl [3, 3, 3] azine (17) should possess a resonance energy higher than that of cycl [3, 2, 2] azine (16) [91]. Application of Hückel's rule would lead,



65

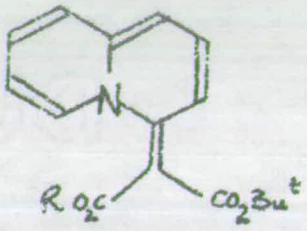


$CLO_4^{(-)}$

(66)

$NaCH[CO_2R]CO_2Bu^t$

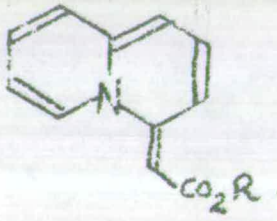
T.H.F.



(67)

HCl/PhH [for R = Et]

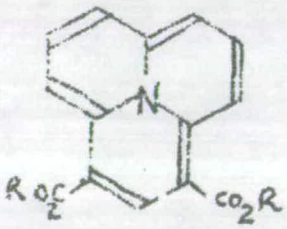
$PhSO_3H/AcOH$ [for R = Bu^t]



[68]

$HC\equiv CO_2R$

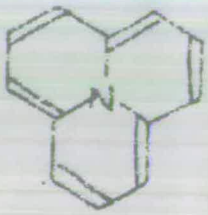
$PhNO_2$ 210°



(69)

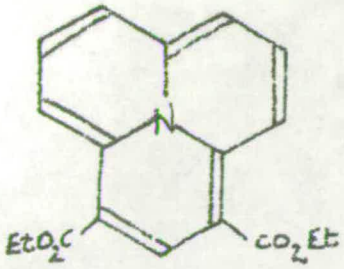
$R = Bu^t$

heat



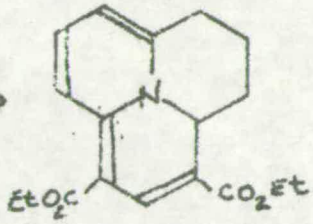
(17)

Scheme 7



(69)

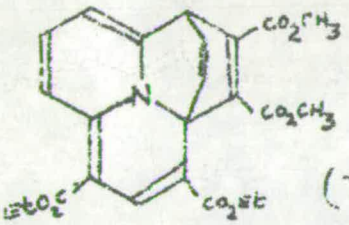
CATALYTIC Hydrogenation →



(70)

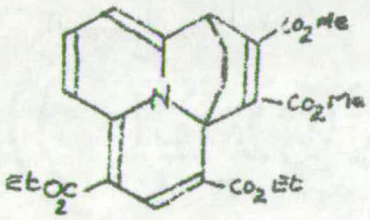
D.M.A.D.C. ↓

1) Tetranitro methane
2) D.M.F. / $POCl_3$
3) Me_2NCOMe / $POCl_3$ → PRODUCTS



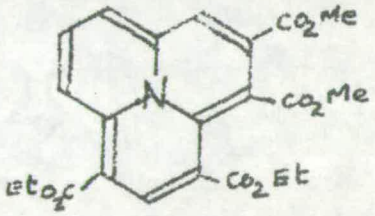
(71)

H_2/Pt ↓



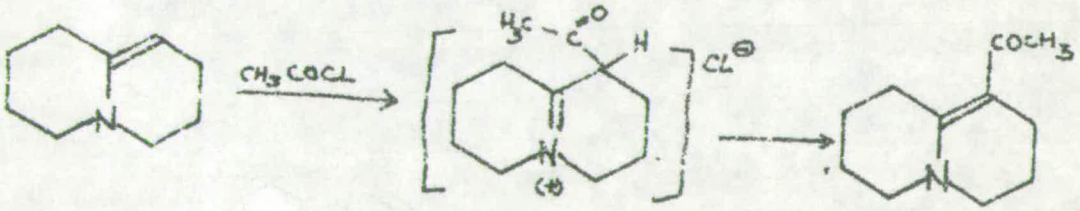
(72)

heat > 220° →

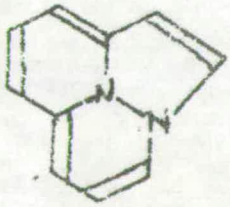


(73)

Scheme 8



Scheme 9



(74)

however, to the conclusion that cycl [3, 3, 3] azine (17) should be non-aromatic, since it possesses a peripheral 12 π - electron system. More recent molecular orbital calculations indicate that the most energetically favourable structure for cycl [3, 3, 3] azine is one containing alternating single and double bonds and that the corresponding "delocalised" structure would possess a negative resonance energy.

After a number of unsuccessful approaches [107-113] the cycl [3, 3, 3] azine system was finally synthesised [114] by the route outlined in scheme 7. Treatment of 4-chloro quinolizinium perchlorate (66) with ethyl t-butylsodiomalonate yielded ethyl t-butylquinolizin - 4 - ylidenemalonate (67). On treatment with dry hydrogen chloride in anhydrous benzene, (67) gave ethyl quinolizin - 4 - ylideneacetate (68). Reaction of this with ethylpropiolate in boiling nitrobenzene gave the diethyl-cycl [3, 3, 3] azine - 1,3 - dicarboxylate (69; R=Et). A range of cyclazine diesters were obtained by variations in the malonates or acetylenic ester used.

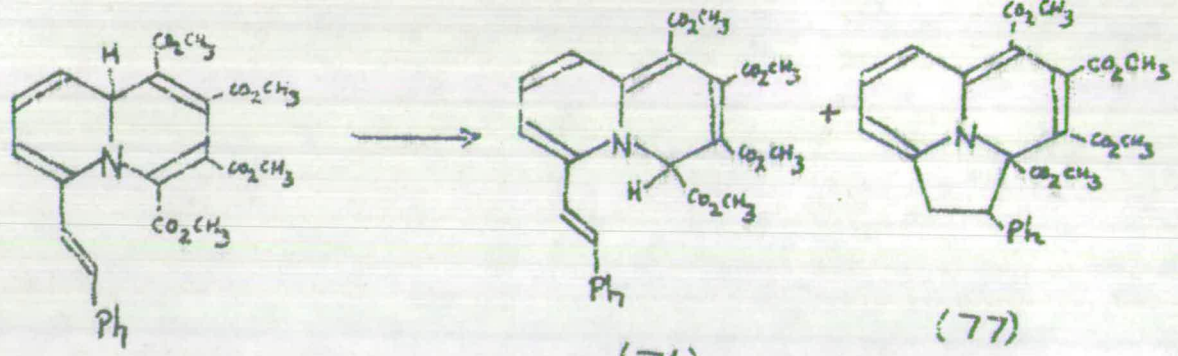
The brown, crystalline esters (69) were stable in the solid state, but in hydroxylic solvents especially, the colour rapidly changes from bright yellow to brown, so precluding hydrolytic methods as a path to the parent system. The parent system was eventually obtained by heating the di-t-butyl ester (69; R=Bu^t) in a sealed, evacuated tube at 250-300° for five minutes and the product was recovered by vacuum sublimation.

The parent cyclazine was a brown, crystalline solid which gave bright yellow solutions in ethers and hydrocarbons. It was stable in a nitrogen atmosphere, but decomposed rapidly in air, or when dissolved in chloroform, carbon tetrachloride, or hydroxylic solvents. The n.m.r. spectrum, obtained in bis (trimethylsilyl) ether, showed

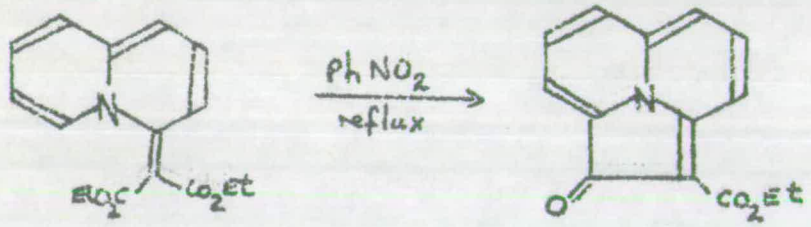
a triplet centred on 6.35 τ (assigned to protons 2, 5 and 8) and a doublet of twice the intensity centred at 7.93 τ (protons 1, 3, 4, 6, 7 and 9), the coupling constant being approximately 8Hz. The chemical shifts in this compound contrast markedly with those of cycl [3, 2, 2] azine [91, 101] (2.1-2.8 τ) and, since they exhibit a high degree of shielding (situated 2.2 and 2.8 p.p.m., upfield of their counterparts in 1,2-dihydropyridines) the system may be regarded as non-aromatic, exhibiting a paramagnetic ring current like a [4n] annulene.

Because of synthetic and stability difficulties the chemical properties of the parent system have not as yet been thoroughly investigated. Most of the work has in fact been carried out on the diethyl ester (69; R=Et). The reactions confirmed the non-aromaticity of the system. On reaction with dimethyl acetylene-dicarboxylate (scheme 8) the Diels-Alder adduct (71) was formed. Catalytic hydrogenation of (71) gave the dihydroderivative (72) which lost ethylene above 220° to give the tetraester (73). Catalytic hydrogenation of the di ester (69; R=Et) proceeded readily at atmospheric pressure and room temperature to yield the tetra-hydroderivative (70). Although the diester (69) reacted with certain electrophilic reagents (e.g. Tetranitromethane, N,N[1] dimethyl formamide/phosphoryl chloride.) to give mono - and di - substituted products, mainly at the 4-and-6- positions [112], this behaviour is not regarded as evidence of aromaticity, but rather as being analogous to that of an enamine as exemplified in scheme 9.

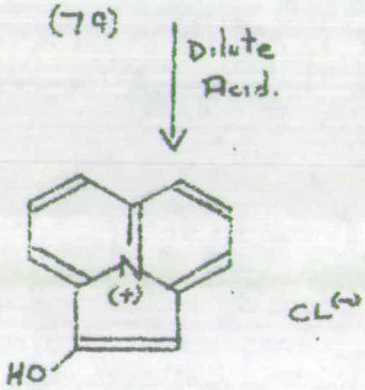
An attempt [116] has been made to synthesise 2a-azacycl [3, 3, 2] azine (74) which is iso- π -electronic with cycl [3, 3, 3] azine but only a dihydroderivative was obtained. Attempts to prepare the



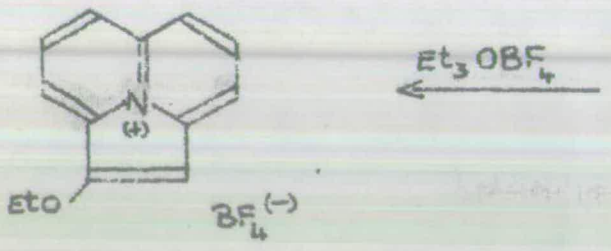
(75) (76) (77)



(78) (79)

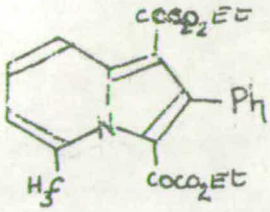


(80)

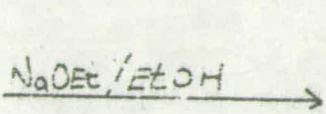


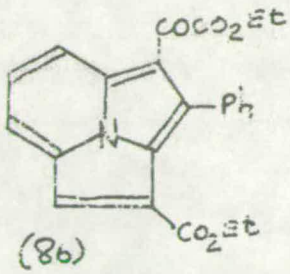
(82) (81)

Scheme 10

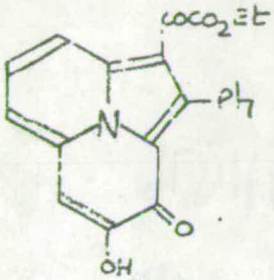


(83)



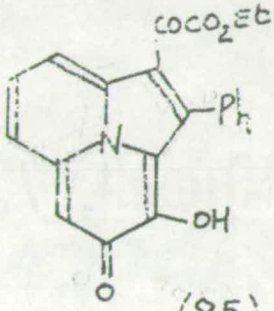


(86)

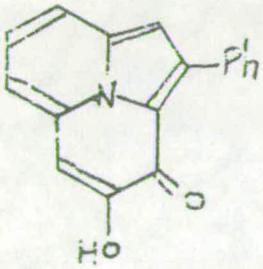


(84)

OR

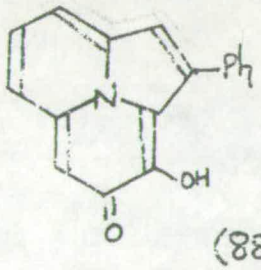


(85)

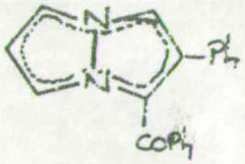


(87)

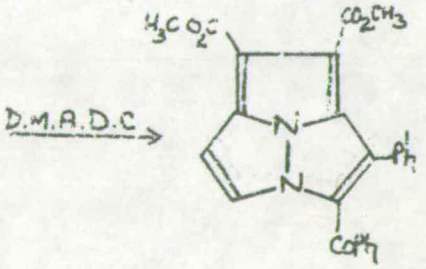
OR

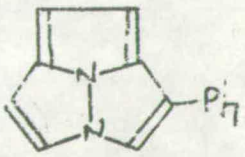


(88)



(89)





(90)

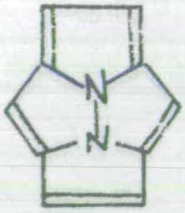
parent system by dehydrogenation proved uniformly unsuccessful.

Neither cycl [4, 4, 3] azine (19) which was predicted to be stable, though showing a tendency to bond alternation [91], nor cycl [4, 3, 2] azine (18) which is isomeric with cycl [3, 3, 3] azine (17), have been prepared although the latter has been the subject of several synthetic studies [117, 118, 119].

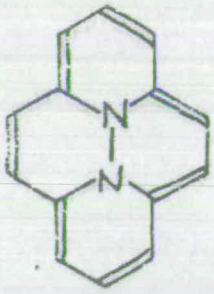
The first reported synthesis of a derivative of the cycl [3, 3, 2] azine system (21) is that due to Acheson [120], who showed that the two products obtained by Diels [121] on heating the initial adduct (75) of dimethyl acetylenedicarboxylate and trans-stilbazole had the structure (76) and (77).

Recently the 1-ethoxy cycl [3, 3, 2] azinium salt (82) has been synthesised in this department [112] by the route shown in scheme 10. When the quinolizinylidenemalonate (78) was refluxed in nitro benzene for one hour, two products were obtained. Chemical and spectroscopic evidence confirmed these as being (79) (80%) and (81) (9%). Heating the ester (79) with dilute hydrochloric acid gave 1-hydroxycycl [3, 3, 2] azinium chloride (80) which was converted into the cyclazinone (81) by treatment with base. Alkylation of the ketone (81) with triethyloxonium fluoborate gave the salt (82). Attempts to remove the ethoxy group proved unsuccessful as did attempts to catalytically hydrogenate (80). The n.m.r. spectra of (80) and (81) in trifluoroacetic acid showed complex multiplets in the region 0.5 - 2.5 τ, indicating that the system may be regarded as aromatic, but as will be shown in this work and from the work of T. T. Gough [122] the n.m.r. spectrum of the parent cycl [3, 3, 2] azinium ion suggests that the 1,2 carbon-carbon double bond is in fact olefinic in nature.

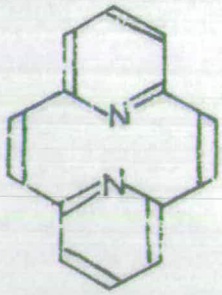
The reaction of 1,3-diethoxalyl-2-phenyl-5-methylindolizine



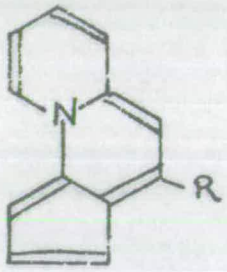
(91)



(92)



(93)



(94)

a) R = Ph

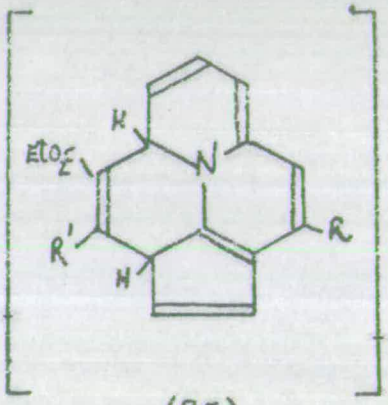
b) R = CH_3

$PhNO_2$

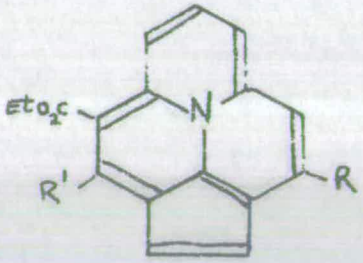
$EtCO_2C \equiv CR'$

a) R' = CH_3

b) R' = Ph



(95)



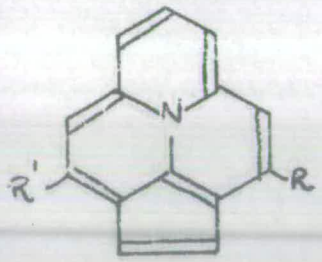
(96)

a) R = Ph, R' = CH_3

b) R = CH_3, R' = Ph

1) Hydrolysis

2) Decarboxylation



(97)

a) R = Ph, R' = CH_3

b) R = CH_3, R' = CH_3

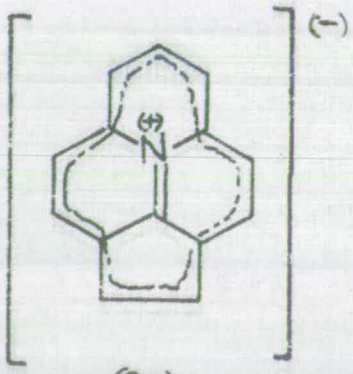
Scheme II

(83) with sodium ethoxide in dry ethanol [123] gave the hydroxy cycl [3, 3, 2] azinone (84) or (85) as well as a cycl [3, 2, 2] azine derivative (86). The 2-phenyl derivative (87) or (88) was then prepared by standard methods of hydrolysis, decarbonylation, and decarboxylation. This system is related to the 3H-cycl [3, 3, 2] azine system in the same way as tropolone is related to cycloheptatriene and like tropolone may be regarded as aromatic. The n.m.r. spectrum of (87) showed a complex multiplet at 1.8 - 2.8 τ, and a singlet (OH) at 1.4 τ.

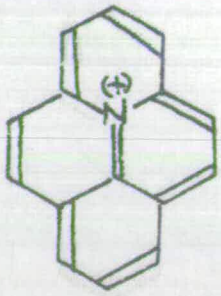
Recently the synthesis of 1-phenyl-2a-aza cycl [2, 2, 2] azine (90) was achieved by the reaction of dimethyl acetylenedicarboxylate with a disubstituted 3a, 6a-diazapentalene [124] (89). The chemical characteristics of this compound, which is iso-electronic with cycl [3, 2, 2] azine, were not reported.

The field of cyclazine chemistry may be extended to include tetracyclic compounds of the type (91) and (92) which are related to [10] - and [14] - annulene, respectively. However work in these fields has proved extremely unproductive, [124, 125, 126] although routes have been proposed to (91) *via* the azacycl [2, 2, 2] azine (90) and to (92) *via* the metacyclophanediene (93) [112].

Work in this department [113, 127] on the reaction of cyclopenta [c] quinolizines [117] (94) with activated acetylenic esters led to the synthesis of the first tetracyclic cyclazine structure, cyclopenta [cd] cycl [3, 3, 3] azine (97) (scheme 11). The structure was confirmed chemically by hydrolysis and decarboxylation of the two monoesters (96a) and (96b) which yielded the same compound (97a). Physical evidence for the structure was provided by the n.m.r. spectrum of the 3,9-dimethyl derivative (97b) in which the symmetry



(98)

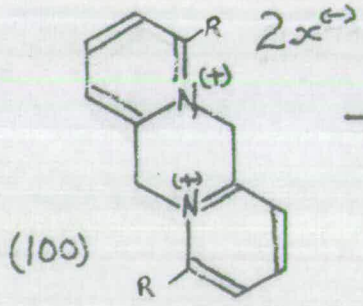


(99)

---

a) R = H

b) R = CH_3

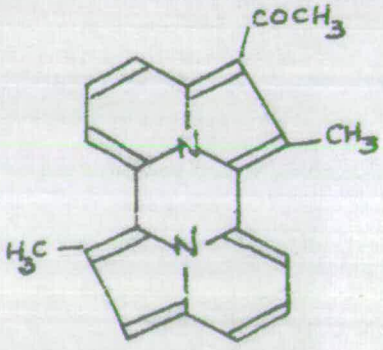


(100)

$2x^{(-)}$

Ac_2O

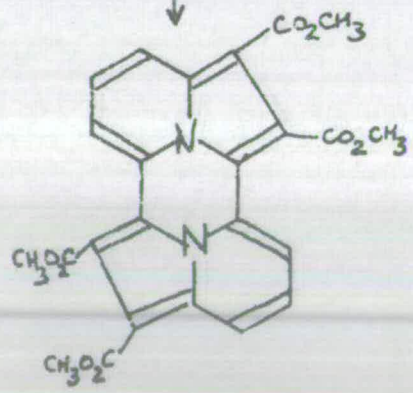
Et_3N



(101)

NaH

excess D.M.A.D.C.



(102)

Scheme 12

of the system was apparent from an AB_2 multiplet at 2.90 - 3.46 τ (5, 6 and 7 protons) and two singlets at 3.04 τ (1, 2 - protons) and 3.71 τ (4 and 8 protons).

Despite limited success in carrying out electrophilic substitution reactions in this system (only benzoylation and deuteration, at position - 1, were successful), spectroscopic evidence suggests that the system is aromatic. The low value of the coupling constant, $J_{1,2}$, is consistent with a low π bond order of the 1,2 - bond and may indicate an appreciable contribution from the dipolar structure (98) with 14 peripheral π - electrons.

An attempt to convert the ring-system into a 10b - azoniapyrene (99) by ring expansion of the five membered ring with chlorocarbene or ethoxycarbonylcarbene failed [113].

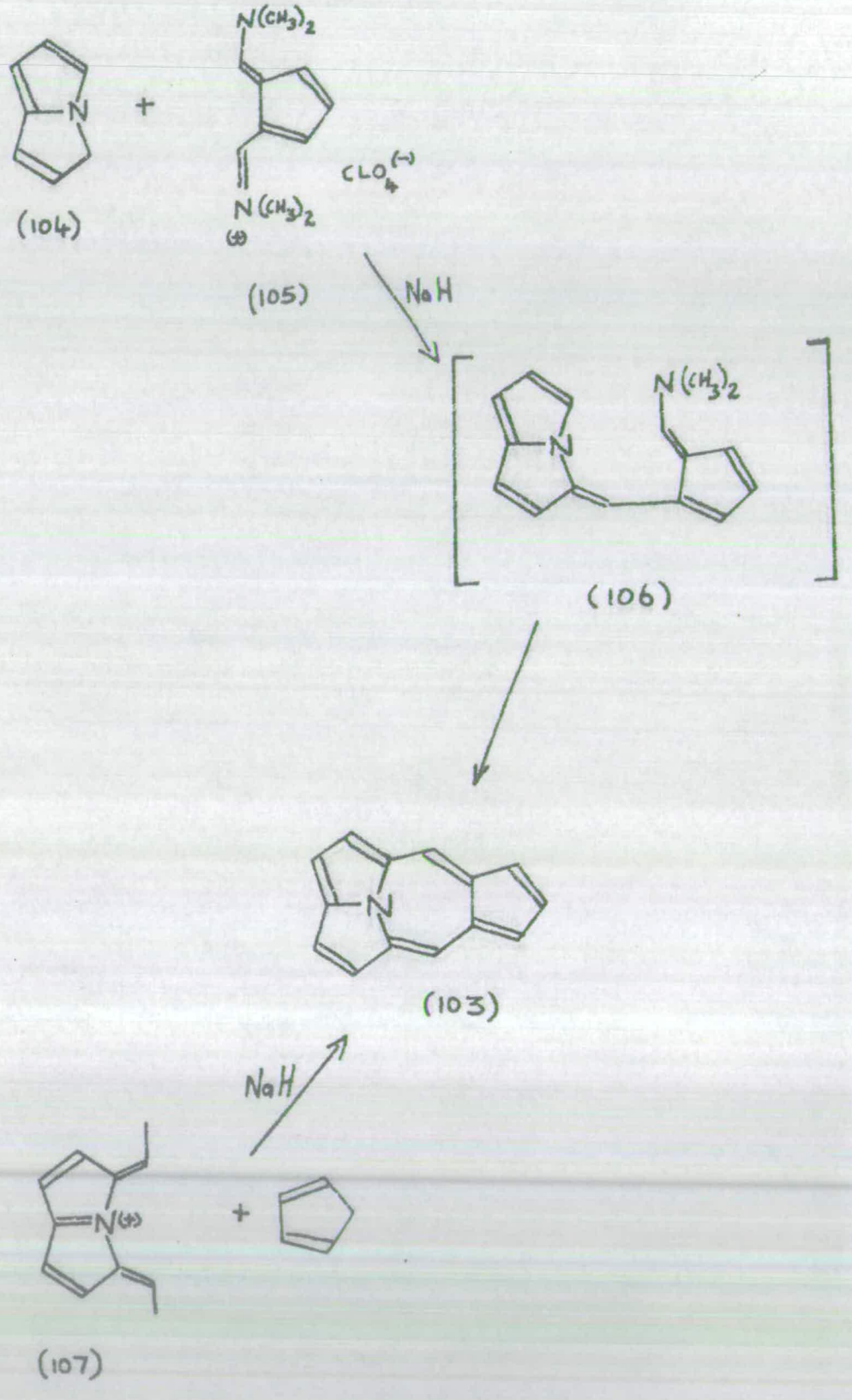
The synthesis of a cyclazine related to [16] annulene has recently been accomplished in this department [119]. Starting from dihydro-dipyrido-pyrazidi-inium salts (100) the cyclazines (101) and (102) were prepared by the routes outlined in scheme 12. This system may be regarded in two alternative ways :-

a) as two indolizine nuclei joined through their 3 and 5 positions.

b) as a derivative of [16] annulene.

Comparison of the n.m.r. spectra with those of appropriately substituted indolizines, suggested the presence of a weak paramagnetic ring current, the ring protons being shifted upfield by approximately 1 p.p.m. from their positions in the indolizine spectra.

Cyclopenta[h]cycl[4, 2, 2]azine, (103), recently synthesised [126] in this department by M. A. Jessep, contains a 14 π - electron peripheral system. The system was prepared by the base-catalysed reaction (scheme 13) of 3H-pyrrolizine (104) with 6-dimethylamino-2-



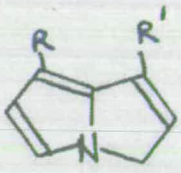
Scheme 13

[N,N - dimethylformimmonium] fulvene perchlorate [128] (105) the cyclazine being obtained as green plates. Alternatively the same compound was obtained by reaction of 3,5 - bis (dimethylaminomethylene) - 3H, 5H - pyrrolizinium perchlorate (107) with sodium cyclopentadienide.

The low values of the proton chemical shifts (1.28 - 2.62 τ) indicate that the system must be regarded as aromatic. No change in the ultra-violet spectra was observed on addition of small amounts of acid showing that, as in cycl [3, 2, 2] azine [100, 101] the lone pair of electrons on the nitrogen atom was not readily available for salt formation being involved with the peripheral π - electron system. One other reason was thought to be that the configuration of the nitrogen atom is probably not tetrahedral (sp^3 hybridised), but planar (sp^2 hybridised), the lone pair of electrons being accommodated in a p-orbital with one lobe above and one below the plane of the molecule.

Cyclopenta [h] cycl [4, 2, 2] azine was found to be stable to light, air and moderate heat. It formed molecular complexes with picric acid, 1, 3, 5 - trinitrobenzene and 2, 4, 7 - trinitrofluorenone. In its chemical behaviour the cyclazine showed a close similarity to azulene, electrophilic substitution occurring in positions 6 and 8 which are equivalent to positions - 1 and 3 - in azulene.

3H - pyrrolizine (104) has also recently been utilised [128] by Johnston and Jones in the preparation of derivatives of cycl [4, 2, 2] azine (scheme 14). The reaction of (104) with active acetylenic esters gave two products, a 1:1 adduct (108) and a 2:1 adduct (109) the structures of which rest largely on n.m.r. evidence. Catalytic hydrogenation of the 2:1 adduct produced the dihydro derivative (110) while dicyanodichlorobenzoquinone gave a didehydro derivative (111).

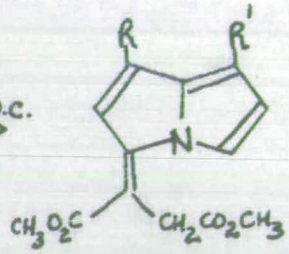


a) R = R' = H

b) R = H, R' = CH_3

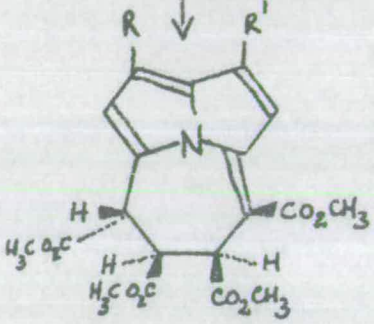
(104)

1 mole D.M.A.D.C.



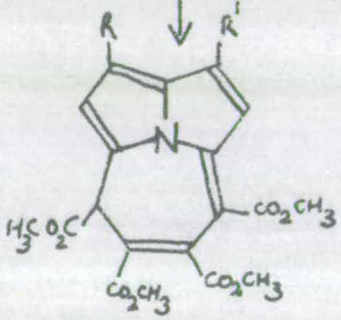
(108)

2 moles D.M.A.D.C.



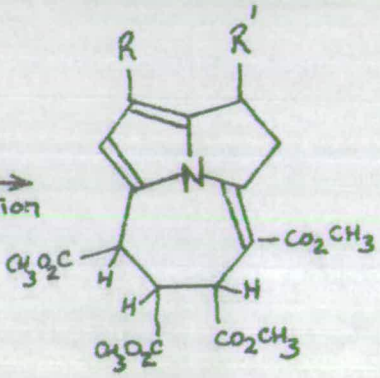
(109)

D.D.Q or N. Bromo Succinamide



(111)

Catalytic Hydrogenation



(110)

$-H^{\oplus}$

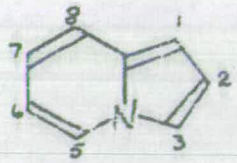
1) Triphenyl methyl perchlorate

2) Phosphoryl pentachloride

3) D.D.Q / $HClO_4$.

Scheme 14

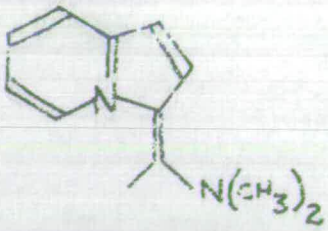
Attempts to remove a hydride ion from (111) with triphenylmethyl perchlorate, phosphorus pentachloride or dichlorodicyanobenzoquinone and perchloric acid failed to give a derivative of the cycl [4, 2, 2] azinium ion which is a 10 π - electron system.



(112)

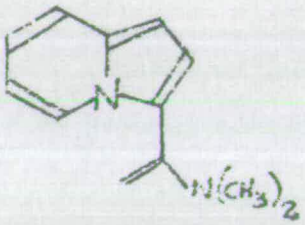
a) 2-Ph
b) 1-Me-2-Ph
c) 1,2-diMe
d) 2,7-diMe
e) 2,6-diMe

D.M.F.
$POCl_3$



(113)

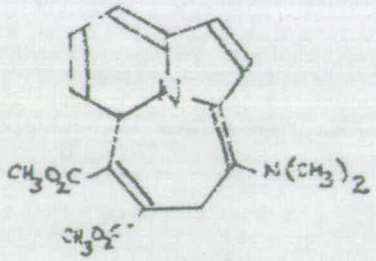
D.M.F | NaOH



(114)

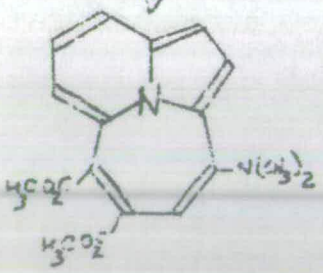
a) 5-Me-2-Ph
b) 2-Ph
c) 1-Me-2-Ph
d) 1,2-diMe
e) 2-Me
f) 2,6-diMe

D.M.A.D.C.
Toluene



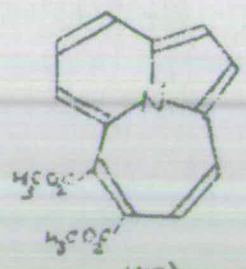
(115)

$-H_2$

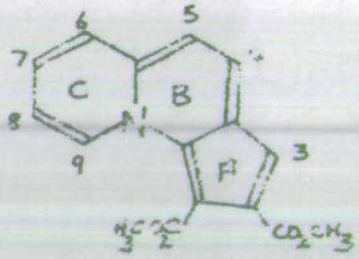


(116)

$-HN(CH_3)_2$



(117)



(118)

a) 4-Ph
b) 4-Me
c) 5-Me-4-Ph
d) 4,5-diMe
e) 4,8-diMe

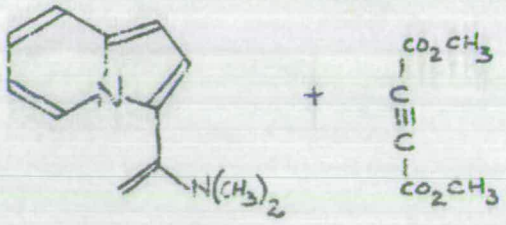
Scheme 15

THE OXIDATIVE CYCLISATION OF 3 -(1 - DIMETHYLAMINO - 2, 3 - DIMETHOXYCARBONYLBUTA - 1, 3 - DIEN - 1 - YL) INDOLIZINES.

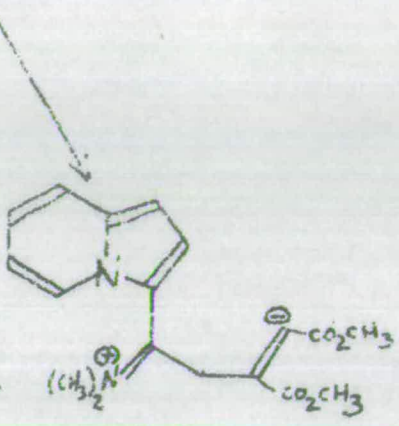
Gibson and Leaver [117], while studying the reaction of the enamine (114 ; scheme 15) with dimethyl acetylenedicarboxylate in boiling toluene found that the product obtained was not the expected cycl [4, 3, 2] azine derivative (116 or 117). Although dimethylamine was evolved showing that cyclisation had occurred, the orange diesters produced showed a low-field n.m.r. absorption (between -0.4 and 0.3 τ), attributable to the α - pyridine proton (position 5 in the original indolizine) since its multiplicity varied in the expected way with the position of the methyl substitution in this pyridine ring. The properties of these compounds could not be explained on the basis of the cycl [4, 3, 2] azine ring system but were explainable on the basis of the cyclopenta [c] quinolizine structure (118), rings A and B of which are iso - π - electronic with azulene.

That the ester groups in this system occupied positions 1 and 2 in ring A was shown by the abnormally low τ - value of the 9 - proton (c.f. the value of 1.5 for the α - proton in pyridine) which was attributable to long-range deshielding by the 1 - methoxycarbonyl group.

The formation of the cyclopenta [c] quinolizine involves a rearrangement (indolizine to quinolizine) without precedent. Gibson and Leaver therefore studied first the nature of the intermediates in the reaction sequence. In cold aprotic solvents the enamine (114b) and dimethylacetylenedicarboxylate gave a yellow 1 : 1 adduct (121a) which on boiling in toluene gave the cyclopenta [c]

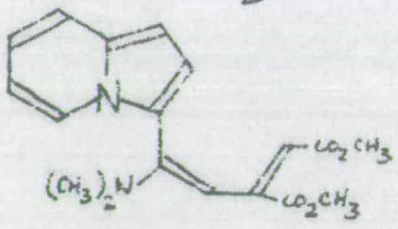


(114)



(119)

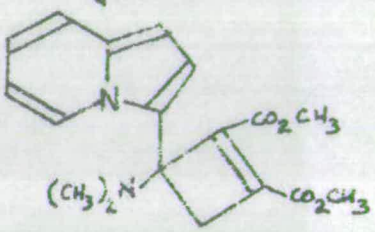
MeOH



(122)

a) 2-Ph
b) 2-Me
c) 1-Me-2-Ph

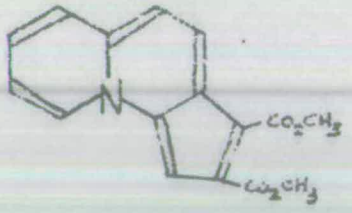
Toluene



(120)

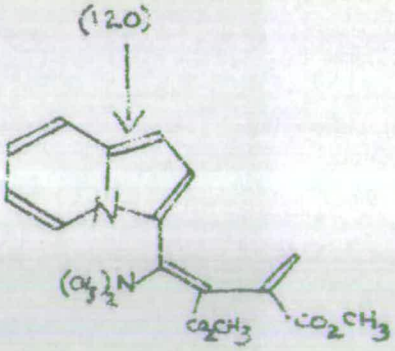
xylene

Reflux



(123)

a) 2-Ph
b) 2-Me
c) 1-Me-2-Ph.

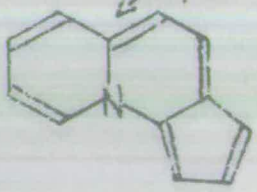


(121)

a) 2-Ph
b) 2-Me
c) 1-Me-2-Ph.

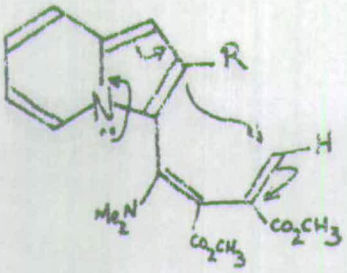
Toluene

Reflux

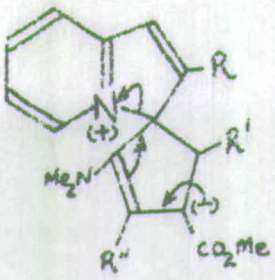


(118)

Scheme 16



(121) or (122)



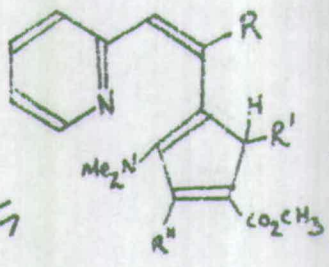
(124)

R = alkyl or Aryl.

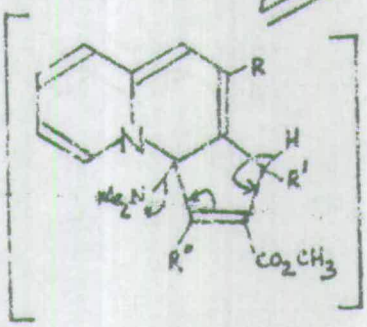
R' = H, R'' = CO_2CH_3

or

R' = CO_2CH_3, R'' = H



(125)



(126)

(118) or (123)

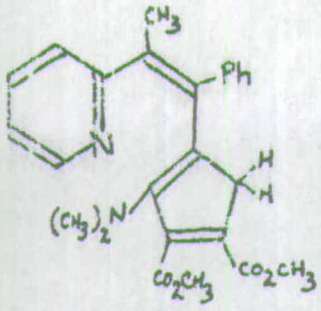
Scheme 17

quinolizine (118a) with loss of dimethylamine (scheme 16). Mechanisms established [129] for related reactions suggested that the adduct was formed by way of the zwitterion (119) and the cyclobutene (120). The intermediacy of the zwitterion was rendered more apparent by carrying out the reaction in a protonic solvent as it was then intercepted by proton transfer to give the isomeric adduct (122a). The latter was converted, by boiling in xylene, into a 2, 3 - dimethoxycarbonylcyclo penta [c] quinolizine in which the 9 - proton signal came at 1.3 τ consistent with the absence of a 1 - methoxycarbonyl group. Partial acid hydrolysis converted the 2, 3 - diester into the 2 - carboxylic acid identical with a specimen obtained from the 1, 2 - diester (118a).

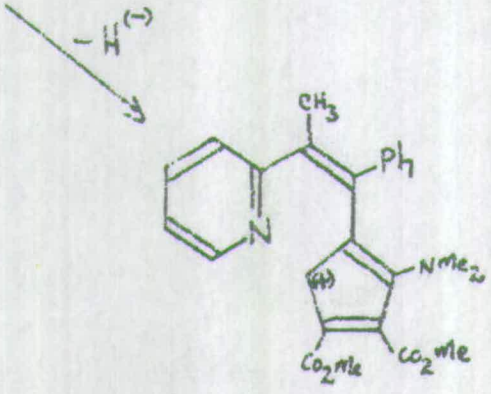
No other intermediates were detectable when the adduct (121b) was heated at 110° in tetrachloro ethylene and the n.m.r. spectrum taken at hourly intervals; no absorptions were observed that could not be attributed to the adduct, final product or dimethylamine.

The most likely mechanism proposed by Gibson and Leaver to account for the transformation is shown in scheme 17. Electron - withdrawal by the ester carbonyl group on the penultimate carbon atom of the side chain creates an electrophilic centre at the terminal carbon atom which is believed to attack position 3 of the indolizine nucleus to give the spiro - zwitterion (124). Charge neutralisation in (124) could then lead to opening of the pyrrole ring to give the substituted pyridine (125). Valence tautomerisation [130] of compound (125) to the 4H - quinolizine (126) and loss of dimethylamine would lead to the cyclopenta [c] quinolizine products.

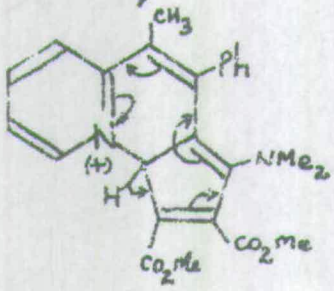
Gibson observed that the adduct (121c) reacted with tetrachloro ortho quinone to give a very low yield of a dehydrogenation product



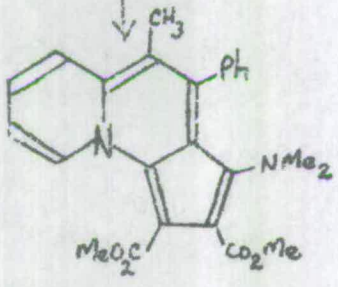
(125a)



(127)



(128)

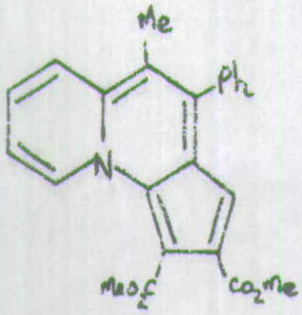


(129)

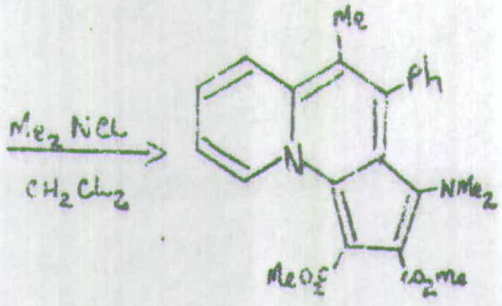
Scheme 18

which, on the basis of spectroscopic evidence, was clearly a di (methoxycarbonyl) cyclopenta [c] quinolizine containing a dimethylamino group. The n.m.r. absorption of the 9 - proton appeared at - 1.44 τ which was much lower than the value for the 1, 2 - dimethoxycarbonyl - 5 - methyl - 4 - phenylcyclopenta [c] quinolizine (118c) (9 - proton occurs at - 0.37 τ). The mechanism proposed initially to account for this is shown in scheme 18. It was thought that the dehydrogenation might have occurred by hydride ion abstraction from the intermediate (125a) to give the carbonium ion (127). Since the five - membered ring of (127) is free to rotate about the single bond joining it to the rest of the molecule, recyclisation could give the cation (128). Proton abstraction would then give the final product which was initially believed to be 1, 2 - di (methoxycarbonyl) - 3 - dimethylamino - 5 - methyl - 4 - phenyl cyclopenta [c] quinolizine (129).

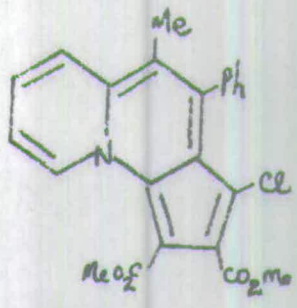
However, work in this department [132] by Farquhar showed that the reaction of 1, 2 - di (methoxycarbonyl) - 5 - methyl - 4 - phenylcyclopenta [c] quinolizine with N - chlorodimethylamine (scheme 19) gave the 3 - dimethylamino - compound (129) as orange crystals which differed from those obtained by Gibson and Leaver. The n.m.r. spectrum showed the 9 - proton absorption at - 0.41 τ close to that of the parent 1, 2 - diester, and the presence of a dimethylamino group (7.70 τ) in addition to the 5 - methyl group. The two ester methyl peaks occurred at 6.10 τ and 6.14 τ , the small separation being characteristic of ester groups in the 1 - and 2 - positions. The ester methyl protons in 3, 4 - dimethoxycarbonyl - 5 - methyl - 4 - phenylcyclopenta [c] quinolizine resonate at 6.2 and 6.8 τ whereas those in the corresponding 1, 2 - diester resonate at 6.10 and 6.15 τ ; the upfield shift of one ester methyl in the 3, 4 - diester is attributed to



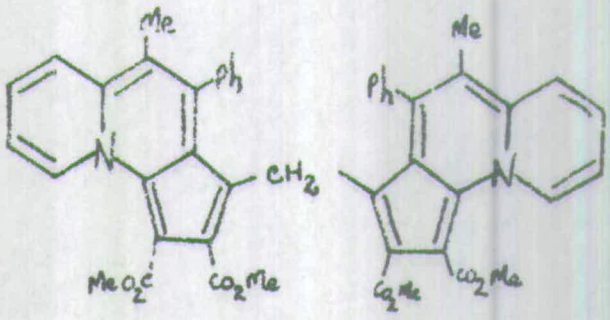
(118c)



(129)

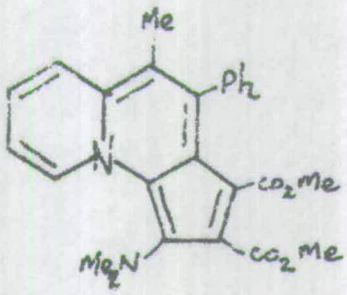


(133)

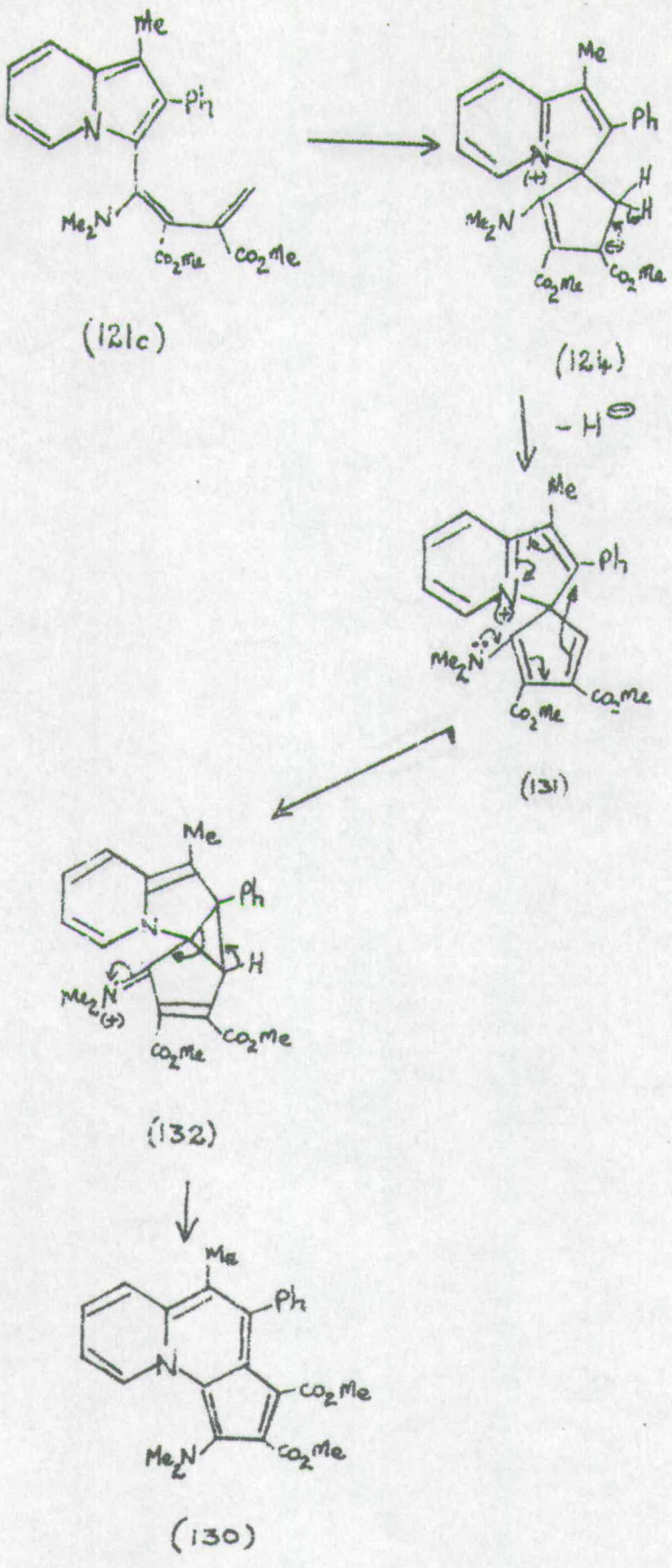


(134)

Scheme 19



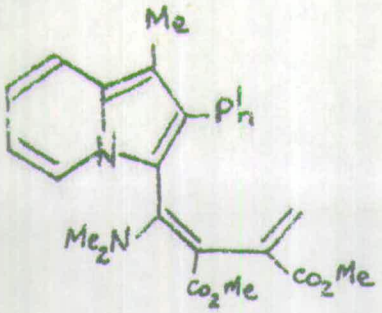
(130)



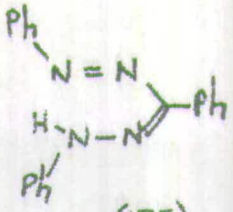
Scheme 20

shielding of the 3 - methoxycarbonyl group by the 4 - phenyl group. The compound that Gibson and Leaver isolated must therefore have been 1 - dimethylamino - 2, 3 - dimethoxycarbonyl - 5 - methyl - 4 - phenylcyclopenta [c] quinolizine. In agreement with this conclusion it showed well separated ester methyl signals at 6.15 τ and 6.8 τ. Further elucidation of the mechanism of this dehydrogenation forms the subject of the present investigation.

Since tetrachloro-orthoquinone is known to react, in many instances, by hydride ion abstraction, a revised hydride - abstraction mechanism was proposed to account for the formation of (130) and is shown in scheme 20. The initial production of the spiro-zwitterion (124a) is the same as in scheme 17 but here, instead of charge neutralisation by opening the pyrrole ring, hydride-abstraction intervenes and the resulting spiro-cation (131) rearranges (one possible mechanism shown) to form the product (130). In order to facilitate further studies of the reaction, a search was made for oxidising agents more effective than tetrachloro-orthoquinone which gives mainly amorphous dark material and very little of the dimethyl-amino-cyclopenta [c] quinolizine. Gibson had already shown that triphenylmethyl perchlorate, a very efficient hydride abstractor, gives none of the required product and, in the present study, tropylium fluoroborate, p - chloranil, and phenanthraquinone were likewise found to be ineffective, all causing extensive decomposition. Finally, a trace of the product (130) was obtained by oxidation with potassium ferricyanide. Thus, the hydride ion - abstractors failed to work but an electron - transfer reagent was partially successful. Attention was then turned to reactions with 2, 3, 5 - triphenyltetrazolium chloride, a mild oxidising agent that reacts by electron transfer (scheme 21).



Triphenyl tetrazolium chloride →



(135)

+

(130) (8%)

a) p-chloranil

b) phenanthraquinone

→ Tars

Potassium ferricyanide →

(130)

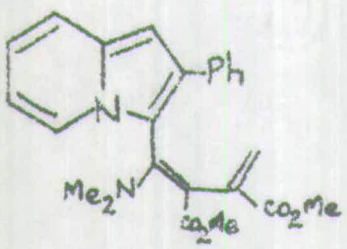
Trace amount

+

(118c) (31%)

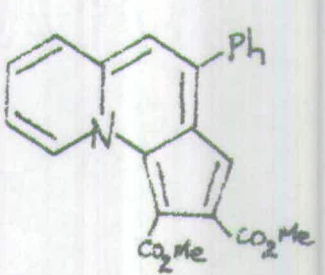
+

(129) (4%)



(121a)

Δ
2-methoxyethanol →

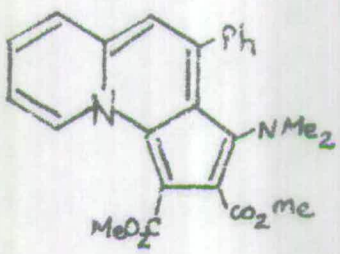


(118a)

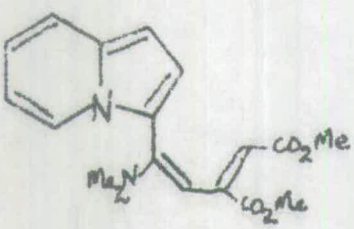
Triphenyltetrazolium chloride ↓

(135) + (118a) 37%

+

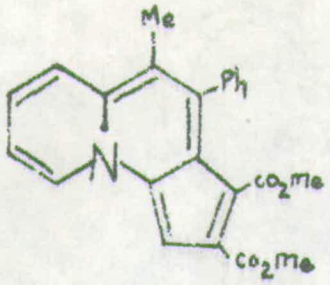


(136) 22%



T.T.C. ✗

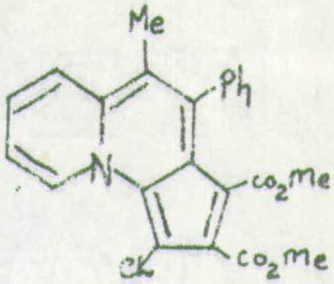
Scheme 21



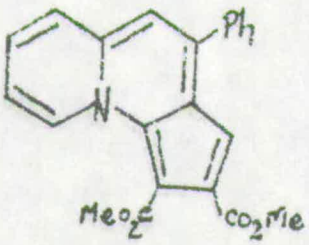
(123c)

Me_2NCl

CH_2Cl_2



(137A)

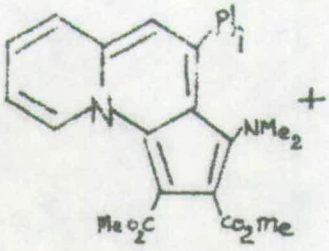


(118a)

Me_2NCl / HOAc ✗

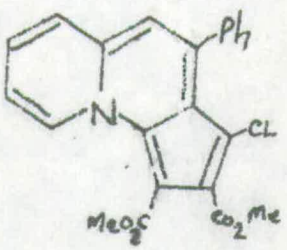
Me_2NCl

CH_2Cl_2



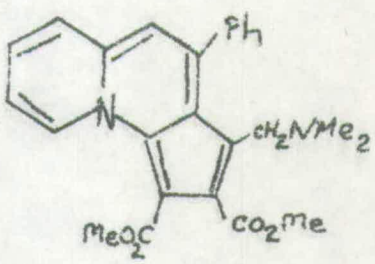
(136)

+



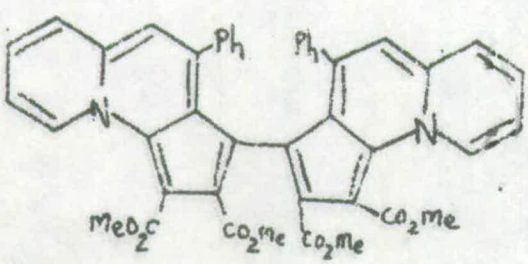
(137)

+



(138)

+



(139)

Scheme 22

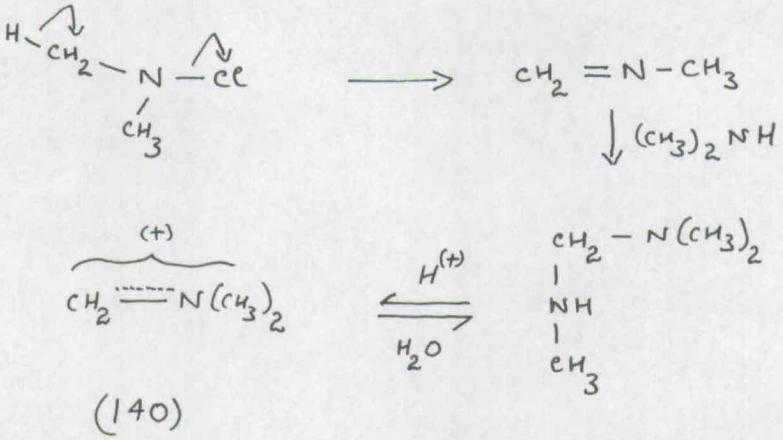
Reaction of (121c) with triphenyltetrazolium chloride in boiling 2 - methoxyethanol gave four products, separated by chromatography on alumina. The initial red band was characterised as triphenyl formazan (135) [133] by comparison with a specimen obtained by reduction of triphenyltetrazolium chloride with sodium dithionite. The remaining three bands produced two red solids and one yellow solid. The yellow solid was shown to be the normal cyclisation product (118c) by n.m.r. comparison. Comparison of the n.m.r. spectra of the two red solids with the n.m.r. spectra of the compounds obtained by Gibson and by Farquhar showed them to be 1 - dimethylamino - 2, 3 - di(methoxycarbonyl) - 5 - methyl - 4 - phenycyclopenta [c] quinolizine (130) and the 3 - dimethylamino analogue, (129) respectively. The 1 - and 3 - dimethylamino - compounds being produced in a 2:1 ratio. An attempt to synthesise the first of these compounds (130), unambiguously from the 2, 3 - diester (123c) and N - chlorodimethylamine yielded only the 3 - chloro - compound (137).

A similar oxidation of (121a) with the tetrazolium salt also produced triphenyl formazan and two other compounds in (37%) and (22%) yields, respectively. The first, a yellow solid was shown, by comparison with an authentic specimen, to be the normal (i.e. thermal) cyclisation product (118a). The n.m.r. spectrum of the second, red solid shows a dimethylamino peak (singlet, 6H, 7.7 τ), two ester methyl peaks (6.1 and 6.15 τ), a singlet due to a H-5 (2.95 τ) and an eight-proton multiplet (2.2 - 2.8 τ) attributable to five phenyl protons and three other aromatic protons. The nine-proton signal of the cyclopenta [c] quinolizine nucleus was present at - 0.59 τ. Whether the dimethylamino group was in position - 1 or - 3 of the molecule was determined by the reaction of the 1, 2 - diester (118a)

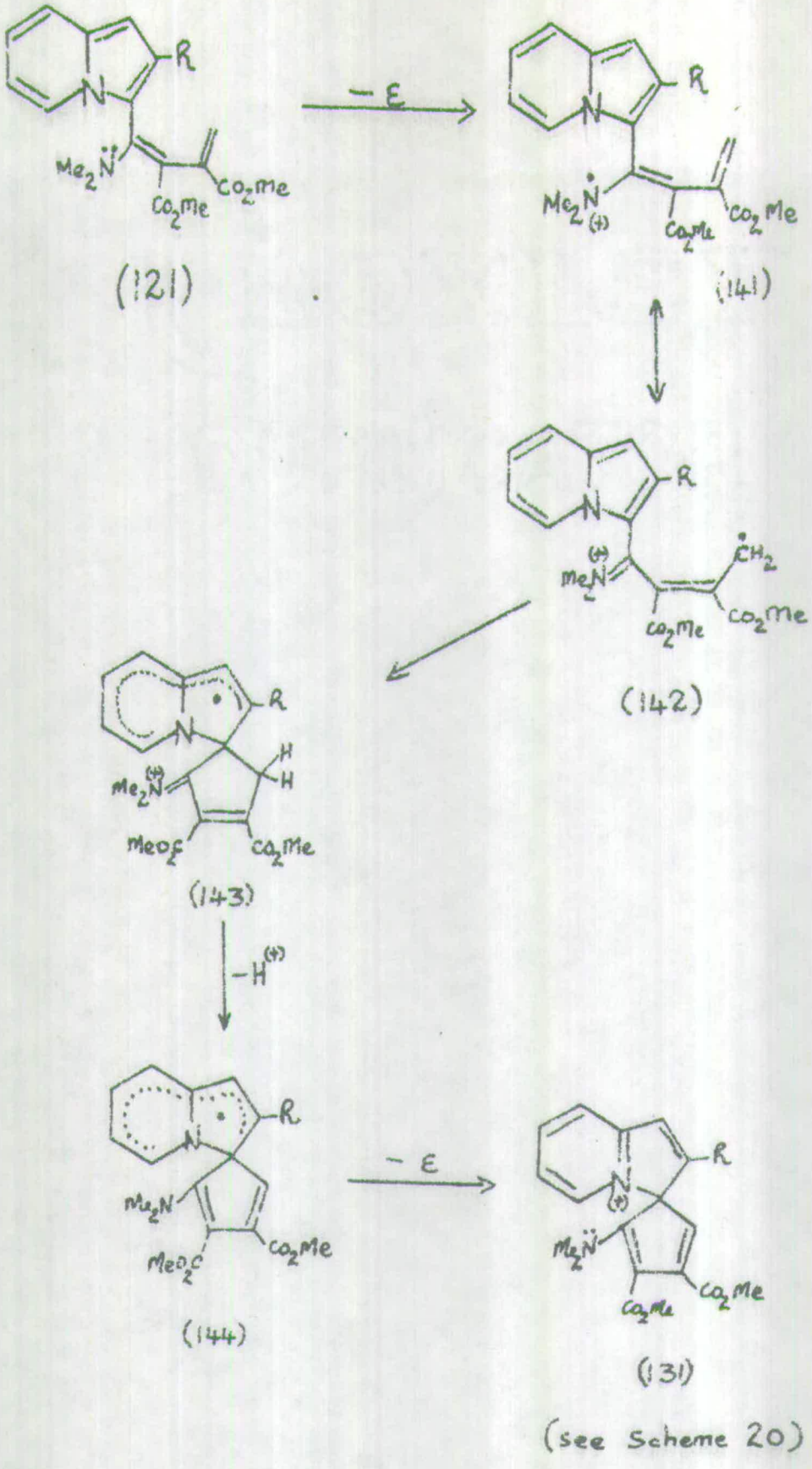
with N - chlorodimethylamine [134, 135] in methylene chloride (scheme 22). The first product was a red solid (M.P. 187°) whose n.m.r. spectrum was identical with that of the red oxidation product (136) thus showing the dimethylamino - group of the latter to be in the 3 - position.

Three other solids were also isolated from the reaction with N - chlorodimethylamine. The first was an orange-red solid and its n.m.r. spectrum showed the nine-proton signal at - 0.31 τ and two ester signals at 6.05 and 6.13 τ. Mass spectrometric data ($^{m}/e$ = 393, 395) and comparison with a previously analysed sample obtained by Farquhar confirmed that this was 3 - chloro - 1, 2 - dimethoxycarbonyl - 4 - phenylcyclopenta [c] quinolizine (137). The second compound, also obtained previously by Farquhar, was lighter coloured (M.P. = 144°), and its n.m.r. spectrum showed the nine-proton at - 0.43 τ, a nine-proton multiplet at 2.2 - 3.0 τ (H-5, 6, 7, 8 and phenyl protons), a six-proton singlet at 6.15 τ (ester methyls), a six-proton singlet at 8.31 τ (NMe_2 grpup) and a two-proton singlet at 6.9 τ (CH_2). These characteristics are accounted for in terms of the structure (138) which could be formed by a Mannich - type reaction of the 1, 2 - diester with the species (140). The following scheme shows a possible route to (140) from N-chlorodimethylamine.

Base



(140)

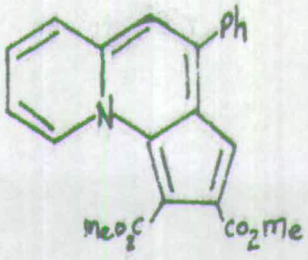

R
N
Me2N
CO2Me
CO2Me
-E
(121)
(141)
(142)
CH2
(143)
H
H
MeO2C
-H(+)
(144)
(131)
(see Scheme 20)

Scheme 23

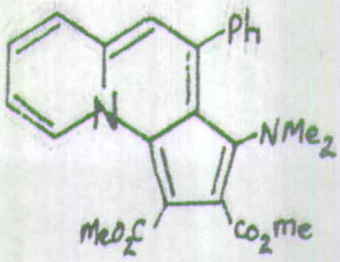
The final product obtained was a red solid, of molecular weight 730, which was identified as the di(cyclopenta [c] quinolizinyl)methane (139) by comparison with a specimen obtained by Farquhar [132] from the reaction of (118a) with bis(dimethylamino)methane. Linkage through the 3 - position is assumed.

Since electron - transfer oxidants were more effective than hydride - abstractors in producing compounds (129, 130 and 136) from the adducts (121c and 121a), scheme 20 required reappraisal. In terms of electron removal from (121) the mechanism shown in scheme 23 was considered. Here the reaction is initiated by removal of one electron from the dienamine system, generating a radical cation, one resonance form of which may be written as (142) with the radical situated on the terminal methylene group. Attack by this radical centre at position - 3 of the indolizine nucleus and delocalisation of the unpaired electron in the indolizine nucleus will give species (143) which, by loss of a proton, produces the spiro - radical (144). A further one - electron oxidation of (144) gives the spiro - cation (131) which was postulated as an intermediate in scheme 20.

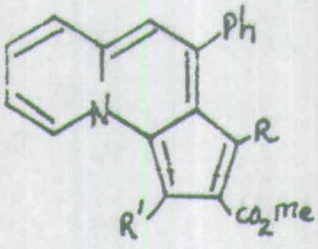
In order to test the hypothesis summarised in scheme 23, the adduct (121a) was subjected to a polarographic study. Dr. B. Woodhall kindly agreed to carry out this work and found that the adduct was oxidised at a rotating platinum electrode with a half-wave potential of +1.1 volts vs S.C.E. (in diglyme with tetra - n - butyl ammonium fluoroborate as supporting electrolyte). This corresponds to an oxidation potential of +1.34 volts and shows that the mechanism of scheme 23 is untenable since triphenyltetrazolium chloride, which is reported [145] to possess an oxidation potential of - 0.08 volts, is not a sufficiently powerful oxidant to remove an electron from (121a).



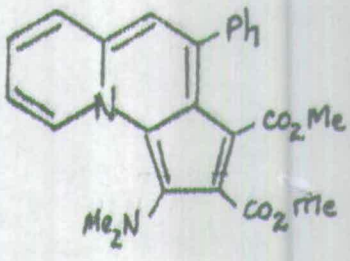
(118a)



(136)



(145)



(146)

a) $R = H$, $R' = CO_2CH_2CH_2OMe$

b) $R = CO_2CH_2CH_2OMe$, $R' = NMe_2$

TABLE 1

Oxidant	Oxidation Potential	Principal Products(%)		Other Products
		121a	136	
Silver Acetate	+0.80	40	1	
Anhydrous Ferric chloride	+0.77	5	1½	(145a) (145b)
$CuCl_2$		Low	Low	(145a)
Copper Acetate	+0.34			
1:1		55	13	
2:1		23	24	
3:1		5	30	
1,1'-dimethyl-4,4'-dipyridylium diiodide	-0.44	70		
+ Sodium Acetate		35		
1,1'ethylene-2,2'-dipyridilium dibromide	-0.35			
+ Sodium Acetate		80		
Manganic Acetate	+1.51	53		
Tris(p-bromophenyl) aminium hexachloro-antimonate	+1.29	6	5½	(145a) (145b)
+ Sodium Acetate		40		
Sodium Ferricyanide	+0.36			
1:1		48	17	146
3:1		0.5	36	146
4:1			11	

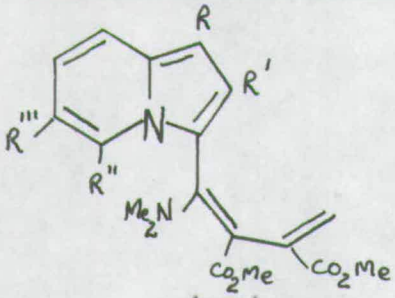
A number of other oxidants, covering a range of oxidation potentials were tested for effectiveness in promoting the oxidative rearrangement of (121a) to (136). The results (see table 1) show that oxidants sufficiently powerful to abstract an electron directly from (118a) are relatively ineffective, whereas cupric acetate and sodium ferricyanide, with oxidation potentials near +0.35 are the most effective oxidants. (The low yield of product mentioned previously as resulting from the use of potassium ferricyanide was probably due to the relatively low solubility of this salt in 2 - methoxy ethanol; the sodium salt is easily soluble). In all cases, the purely thermal reaction leading to the cyclopenta [c] quinolizine (118a) is a competing process and it was necessary to use a three-fold excess of oxidant for optimum yields of the dimethylamino - compound (136).

Subsidiary products were also formed in certain reactions. Thus, sodium ferricyanide - (molar ratio 3:1) in 2 - methoxyethanol produced a second red compound isomeric (parent ion $^{m}/e = 402$) with (136). The n.m.r. spectrum of this compound showed a low field doublet ($\tau = -1.24$) attributable to the nine-proton, two singlets of three protons each at 6.1 and 6.85 τ respectively (ester CH_3) and a six-proton singlet at 7.05 τ (NMe_2 group). Comparison of this spectrum with that of (136) (nine-proton at $\tau = -0.59$; ester CH_3 at 6.1 and 6.15 τ; NMe_2 at $\tau = 7.7$) and with those of (118a) and (123a) showed that the new compound was the 1 - dimethylamino - 2, 3 - diester (146). Ferric chloride, cupric chloride and tris (p - bromophenyl) aminium hexachlorantimonate, in reaction with (121a) all gave small amounts of a yellow solid, the n.m.r. spectrum of which showed the presence of one methylester and one 2 - methoxyethyl ester group on a

Table 2.

Oxidation of 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dienyl) indolizines with sodium ferricyanide in 2 - methoxyethanol.

Substituents in the indolizine ring of 147	Yields of products. (%) 148	149	150
a) 2-Me (≡121b)	18	18	12
b) 2,6-diMe	5	6	6
c) 1,2-diMe	32	5	-
d) 1-Me-2-Ph (≡121c)	-	24	-
e) 5-Me-2-Ph	-	-	Low



(147)

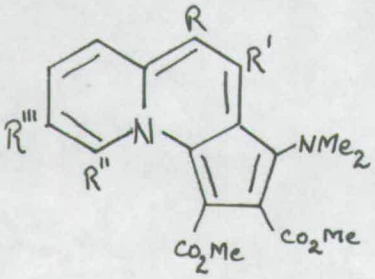
a) R^1=Me, R=R^{11}=R^{111}=H

b) R^1=R^{111}=Me, R=R^{11}=H

c) R=R^1=Me, R^{11}=R^{111}=H

d) R=Me, R^1=Ph, R^{11}=R^{111}=H

e) R^{11}=Me, R^1=Ph, R=R^{111}=H

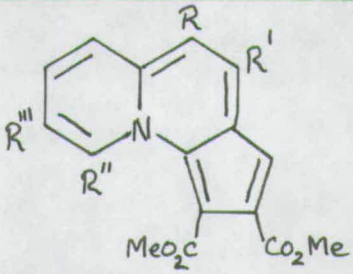


(150)

a)

b)

c)

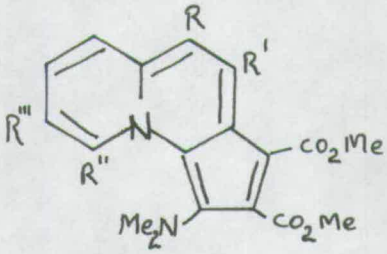


(148)

a) R^1=Me, R=R^{11}=R^{111}=H

b) R^1=R^{111}=Me, R=R^{11}=H

c) R=R^1=Me, R^{11}=R^{111}=H



(149)

a)

b)

c)

d) ≡ (130)

cyclopenta [c] quinolizine nucleus. Since reduction of the oxidant releases one equivalent of HCL, this product is presumably formed by acid-catalysed transesterification of one methoxycarbonyl group in the thermal rearrangement product (118a) .

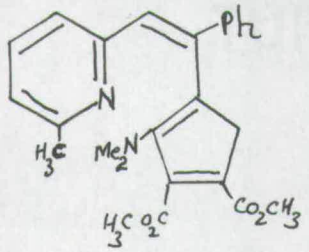
Ferric chloride also produced a second transesterification product which retained the dimethylamino - group in the 1 - position (nine-proton at τ = - 1.2). It is assumed that transesterification occurred at the 1 - or 3 - ester groups since these are known [118] to be more susceptible to acid - catalysed hydrolysis than the 2 - ester group.

Since sodium ferricyanide in a molar ration of 3:1 in 2 - methoxyethanol was the most effective oxidant for (121a), it was utilised in reaction with various substituted 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) indolizines to see if it would produce comparable results. As shown in Table 2, oxidative rearrangement, giving one or more dimethylaminocyclopenta [c] quinolizines, occurred in each of the reactions studied. In three cases, however, thermal rearrangement to (148) was observed as a competing process.

The positions of the dimethylamino and methoxycarbonyl groups in each oxidation product were assigned on the basis of the chemical shift of the nine-proton, this being lower in the 1 - dimethylamino - 2, 3 - diesters (- 0.95 to - 1.3) than in the 3 - dimethylamino - 1, 2 - diesters (ca - 0.3). This method of assignment was not available, however, for the product from (147e) containing a 9 - methyl group. The 3 - dimethylamino - structure (150e) assigned to this compound is based on the small separation of the ester methyl signals (6.10 and 6.26 τ) and on the relatively high τ- value (7.65) of the N - methyl protons

which is attributable to shielding by the 4 - phenyl group. The n.m.r. spectra of the other 3 - dimethylamino - 4 - phenyl compounds (129) and (136) showed similar distinguishing features.

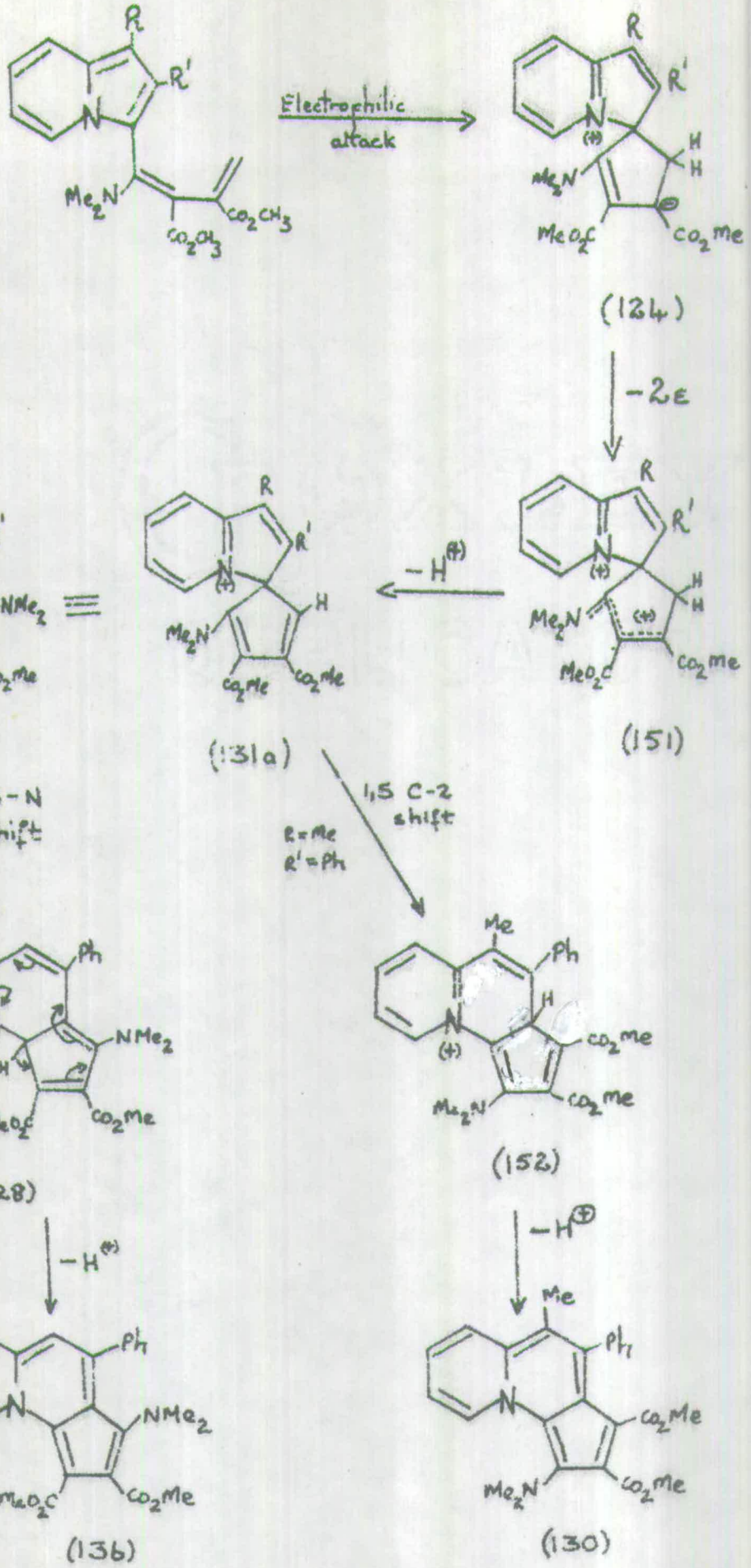
The 5 - methyl - 2 - phenyl compound (147e) was first prepared in the hope that its thermal rearrangement to a cyclopenta [c] quinolizine might be inhibited, by the steric effect of the methyl group, at the ring-open stage (125b). Had it been possible to isolate such an intermediate or a simple transformation product thereof, this would have substantiated the suggested mechanism. In the event, however, apart from recovery of (147e) in low yield, no other characterisable products could be isolated after heating (147e) in 2-methoxyethanol; the thermal rearrangement was certainly inhibited but no positive evidence for the proposed intermediate was forthcoming. It is interesting, however, that the oxidative rearrangement, though giving a low yield, was not entirely inhibited and this is consistent with the view, put forward below, that ring-open intermediates analogous to (125) are not involved in the oxidative process.



(125b)

In formulating a mechanism to account for the oxidative rearrangement of the adducts (121 a, b, c and 147 b, c and e) it is important to bear in mind :

(a) that the most effective oxidants are insufficiently powerful to react directly with the adducts and


Electrophilic attack
(124)
-2e
(151)
-H(+)
(131a)
(131b)
R=H, R'=Ph
1,5-N shift
R=Me R'=Ph
1,5 C-2 shift
(128)
(152)
-H(+)
-H(+)
(136)
(130)

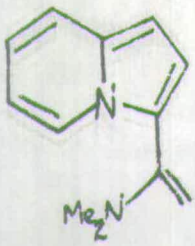
Scheme 24

(b) that the rearrangement may give 1 - dimethylamino - 2, 3 - diesters (147 a - d), 3 - dimethylamino - 1, 2 - diesters (136, 150 a, b), or a mixture of both.

A mechanism that accommodates these observations is shown in scheme 24. It is proposed that the initial stage is the same as that of the thermal rearrangement (scheme 17) giving the spiro - zwitterion (124). Electron-abstraction from the carbanionic centre can then give a cation - radical and, by abstraction of a second electron, a dication (151) in which the new positive charge is stabilised by the dimethylamino - group. Proton loss then leads to the spiro - cation (131 a or b) which was considered as a possible intermediate in scheme 20. The structure of the spiro - cation is represented equally well by formula (131a) or (131b) since the two ring systems are actually orthogonal to each other.

Rearrangement to the cyclopenta [c] quinolizine nucleus can then be achieved by a 1,5 - sigmatropic shift, either of the pyridinium nitrogen atom or of carbon - 2 of the indolizine system. A further proton loss then gives the 3 - dimethylamino - or the 1 - dimethylamino - compound, (136) or (130) respectively.

The fact that no oxidation of the adducts (121 or 147) occurs until the reactants are heated in boiling 2 - methoxyethanol lends further support to the suggestion that the oxidant acts on one of the intermediates of the thermal rearrangement. Moreover, it is not surprising that, under these conditions, the thermal and oxidative rearrangements are competitive. There remains, however, one possibility which must be investigated, namely that the 3 - dimethylamino - 1, 2 - diesters might be produced in a reaction betweenthe thermal rearrangement product (118), dimethylamine (released during

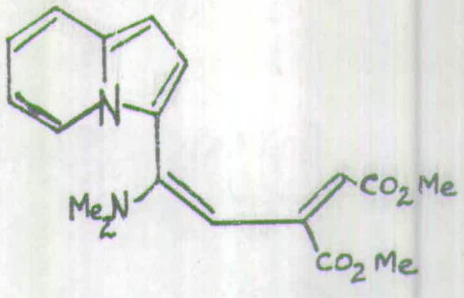


(114)

a) 2-Ph

b) 1-Me-2-Ph.

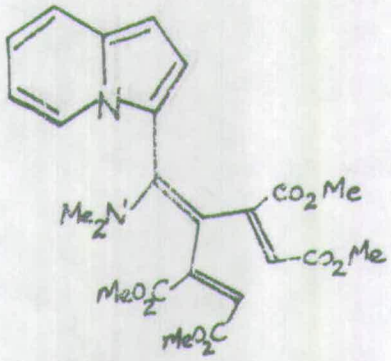
D.M.A.D.C
(MeOH)



(122)

Excess
D.M.A.D.C.
(MeOH)

D.M.A.D.C.
(MeOH)

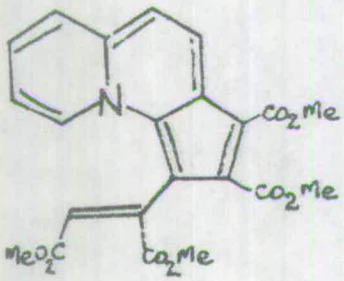


(153)

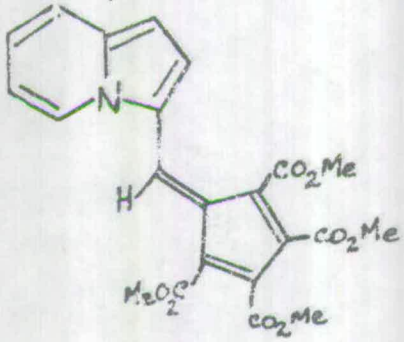
a) 2-Ph

b) 1-Me-2-Ph

Δ



(155)



(154)

a) 2-Ph

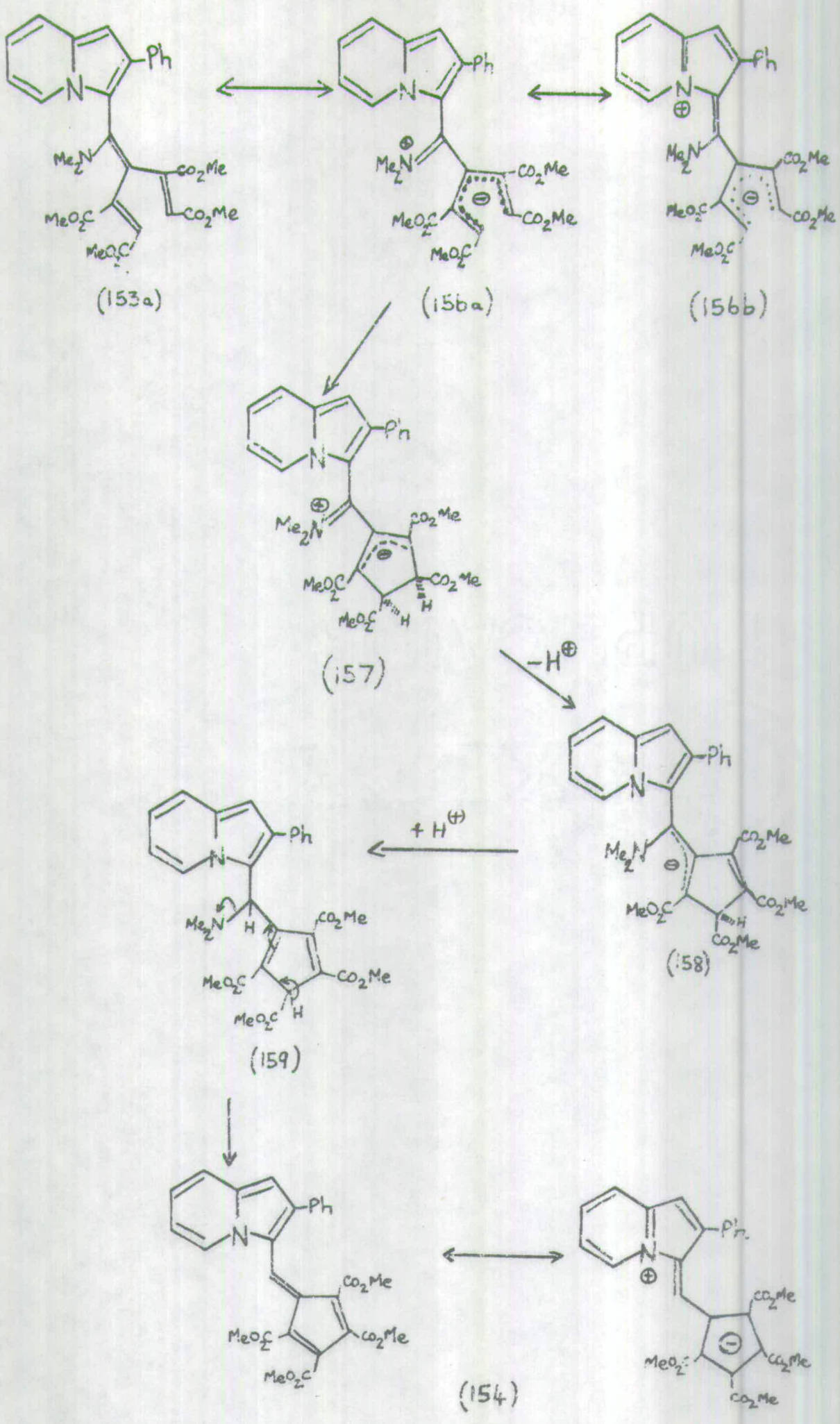
b) 1-Me-2-Ph

Scheme 25

thermal rearrangement) and the oxidant. This possibility was excluded by heating the cyclopenta [c] quinolizine (118a) and dimethylamine, or dimethylammonium chloride, with triphenyltetrazolium chloride in boiling 2 - methoxyethanol. No dimethylamination products were formed.

During the synthesis of the butadienylindolizine (122) by reaction of the enamine (114b) with dimethyl acetylenedicarboxylate in methanol, a second product was isolated as a red crystalline solid. Mass spectrometric analysis ($^{m}/e$ = 546) suggested that this was a 1:2 - adduct of the enamine and dimethyl acetylenedicarboxylate. Its n.m.r. spectrum showed the typical absorption pattern of an indolizine nucleus in the region 2.2 - 3.5 τ, four ester methyl signals (6.2 - 7.1 τ), a dimethylamino signal at 7.25 τ and two olefinic signals at 4.2 and 4.4 τ. From the n.m.r. data the structure proposed was (153a) with a cis - cis configuration of the methoxycarbonyl groups in the penta - 1, 4 - diene system. A similar reaction of the enamine (114c) gave two red solids shown by n.m.r. spectroscopy to be the cis - cis diadduct (153b) (olefinic absorptions at 4.6 and 4.7 τ) and its cis - trans isomer (olefinic absorptions at 5 τ and 3.1 τ). That these diadducts were formed via the butadienylindolizines was shown by reacting (122a) with dimethyl acetylenedicarboxylate to give (153a) as the only product.

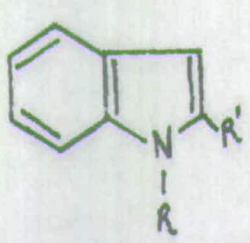
It seemed possible that these compounds might undergo a thermal rearrangement similar to that of the corresponding 1:1 - adducts (122) to give the 1 -(1, 2 - dimethoxycarbonylvinyl) - 2, 3 - dimethoxycarbonylcyclopenta [c] quinolizines (155). Accordingly, the diadducts (153a) and the cis - trans isomer of (153b) were heated in 2 - methoxyethanol and gave orange and yellow solid products,



Scheme 2b

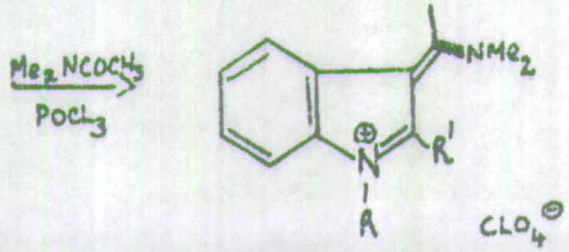
respectively, of the same type. The n.m.r. spectra of these solids showed retention of the indolizine nucleus the pattern of absorptions in the range 2.2 - 3.5 τ being similar to that in the spectra of the starting materials (153). Four ester methyl absorptions were present in the region 6.05 - 6.6 τ but the dimethylamino peak was absent and a one-proton singlet had appeared at 1.95 τ (in the product from 153a) and at 2.05 τ (in the product from 153b). These features suggested that cyclisation, with loss of dimethylamine, had occurred, not in the expected manner (i.e. rearrangement of indolizine to quinolizine) but in the penta - 1, 4 - diene system. The ultraviolet spectra of the products were quite unlike these of cyclopenta [c] quinolizines, thus supporting the idea that the initially expected rearrangement had not occurred. The structures (154a and b) are proposed for these products and the strong deshielding of the single olefinic proton is attributed to electron-withdrawal by the tetra (methoxycarbonyl) cyclopentadienylidene group.

A mechanism that accounts for the formation of the products is shown in scheme 26. The dipolar canonical forms (156a), and (156b), which probably make significant contributions to the structure of the diadducts, contain a pentadienyl anion which can undergo disrotatory cyclisation to a cyclopentenyl anion as in formula (157). Prototropic shift, proceeding <u>via</u> the anion (158), then leads to charge neutralisation and the resulting intermediate (159) can eliminate dimethylamine to give the highly stabilised fulvene structure of the final products.



a) R = R' = Me
b) R = Me, R' = Ph

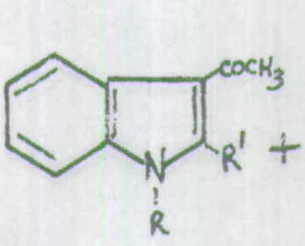
(160)



(161)

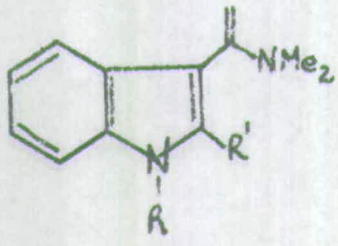
a)
b)

NaOH | D.M.F.



(163)

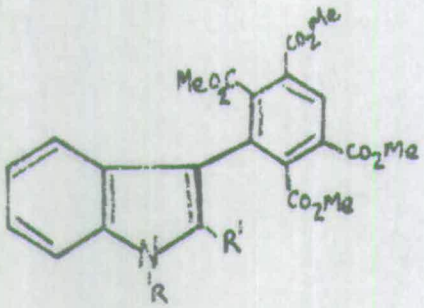
a)
b)



(162)

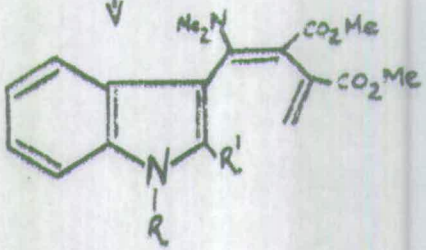
a)
b)

D.M.A.D.C



(165)

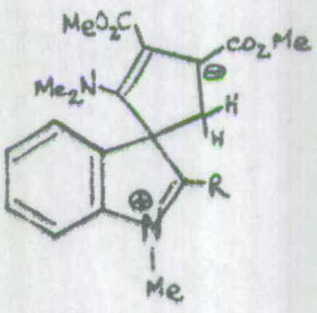
a)
b)



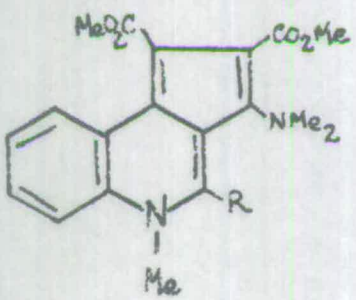
(164)

a)
b)

oxidative cyclisation



(166)



(167)

Scheme 27

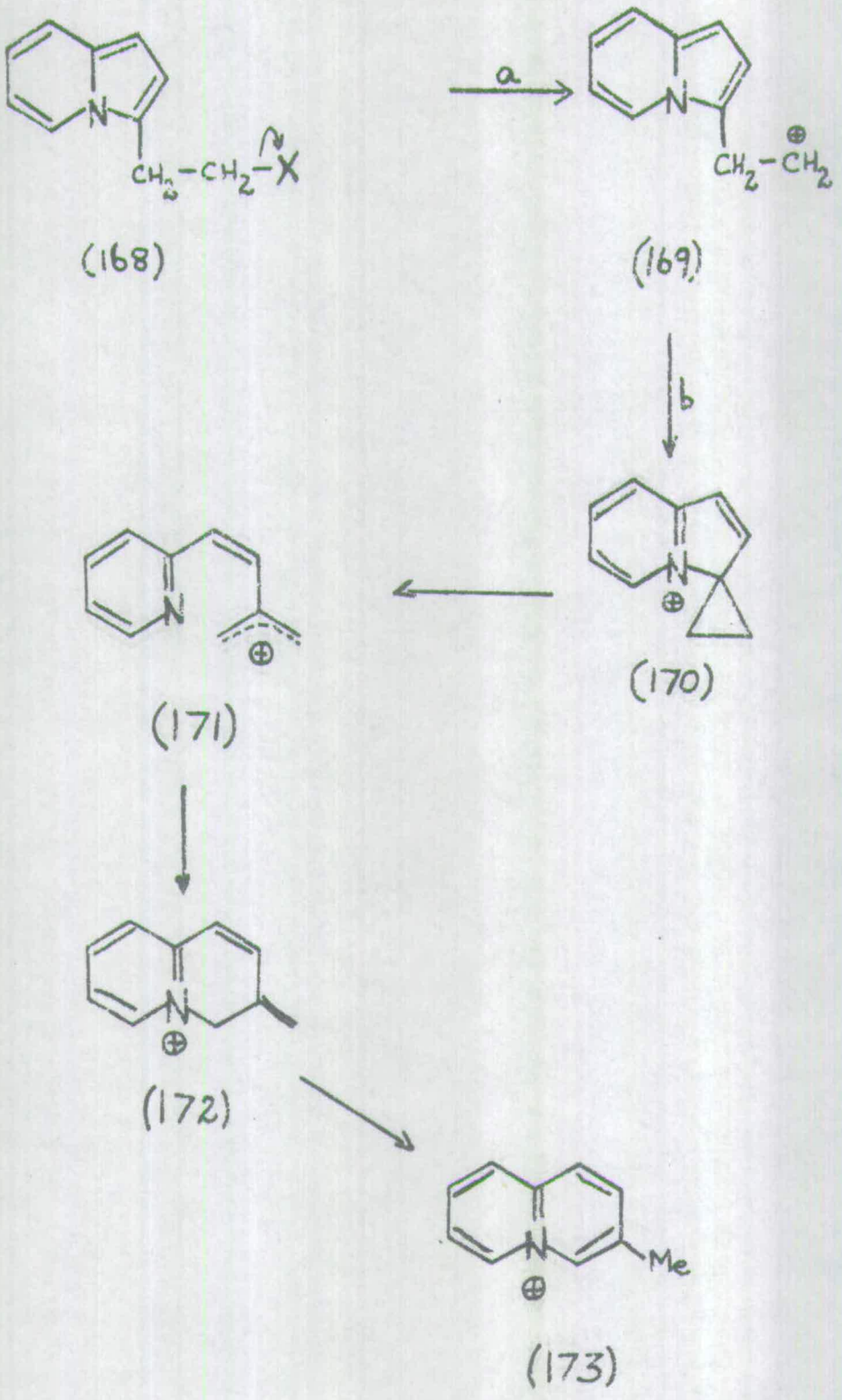
SYNTHESIS AND ATTEMPTED REARRANGEMENT OF 3 - (1 - DIMETHYLAMINO - 2, 3 - DIMETHOXYCARBONYLBUTA - 1, 3 - DIEN - 1 - yl) INDOLES

The type of intramolecular electrophilic attack postulated in schemes 17 and 24 need not be confined to the indolizine series but might conceivably occur in other systems in which the same side-chain is joined to a sufficiently electron-rich carbon atom of an aromatic nucleus. In a 3 - indolyl compound (164), for example, the side-chain might attack at the 3 - position to give a spiro-zwitterion (166) analogous to (124). Oxidative rearrangement, *via* a sequence analogous to scheme 24, could then lead to a cyclopenta [a] quinoline (167). In this case, however, there is no pathway available for thermal rearrangement *via* a ring-opening pathway analogous to scheme 17.

1 - methyl - 2 - phenylindole (160b) and 1, 2 - dimethylindole (160a) were used as starting materials for an experiemental test of this hypothesis. Both compounds reacted with dimethylacetamide and phosphoryl chloride to give the 3 - dimethylaminoethylideneindolium salts, isolated as perchlorates (161b) and 162a), respectively. Treatment of the perchlorates with sodium hydroxide in dimethyl-formamide gave the required 3 - (dimethylaminovinyl) indoles (162), together with the corresponding 3 - acetylindoles (163). Treatment of 3 - (dimethylaminovinyl) - 1 - methyl - 2 - phenylindole in ether, with dimethyl acetylenedicarboxylate gave a pale yellow crystalline 1:1 adduct which, likethe corresponding indolizine compounds [118], was a mixture of stereoisomers; its n.m.r. spectrum showed two sets of terminal methylene protons (3.8 - 5.4 τ), two sets of ester methyl peaks, and two sets of dimethylamino singlets. Analysis and mass spectra confirmed that this was the 3 - (1 - dimethylamino

- 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) 1 - methyl - 2 - phenylindole (164b). Similar treatment of 3 - (dimethylaminovinyl) 1, 2 - dimethylindole (162a) with dimethyl acetylenedicarboxylate gave a yellow solid and a red oil, separated by chromatography. The n.m.r. spectrum of the yellow solid, ($^{m}/e$ = 421) showed a low-field singlet (1 proton) at 1.3 τ, a four-proton multiplet at 2.5 - 3.1 τ, two six-proton singlets at τ = 6.1 and 6.75 due to two sets of two equivalent ester (OMe) groups, and two three-proton singlets at 6.35 τ(NCH_3) and 7.85 τ (2 - CH_3). The compound, which had clearly been formed by reaction with 2 moles of acetylenic ester and loss of dimethylamine, was assigned the structure (165a), the low-field proton being assigned to the ring-proton of the newly-created aromatic ring. The red oil was the required 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) 1, 2 - dimethylindole (164a) and, like the 2 - phenyl analogue, it was a mixture of stereoisomers.

Heating (164a or b) in 2 - methoxyethanol for four hours caused no change and treatment with sodium ferricyanide in 2 - methoxyethanol gave highly complex mixtures of products none of which could be isolated pure, either by column chromatography or by preparative t.l.c.



(168) (169) (170) (171) (172) (173)

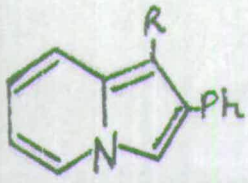
Scheme 28

SECTION 2

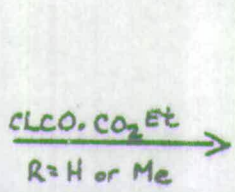
ATTEMPTED RING EXPANSION OF 3 - SUBSTITUTED INDOLIZINES TO QUINOLIZINIUM SALTS

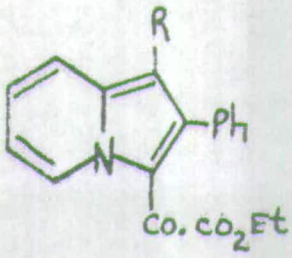
The preparation of cyclopenta [c] quinolizines by Gibson and Leaver [117, 118] involved ring-expansion of an indolizine to a quinolizine nucleus. Another reaction, which might achieve the same result *via* a similar sequence, of intramolecular electrophilic attack, ring-opening, and reclosure, is outlined in scheme 28. It is postulated that a 2 - (3 - indolizinyl) ethyl cation (169) might give rise to the spiro-cation (170). A concerted process [174] involving C - N bond fission and cyclopropyl-allyl rearrangement would then give the carbonium ion (171). Reclosure to form a six-membered ring and aromatisation would then complete the transformation to a 3 - methylquinolizinium cation (173). An indolizine bearing a 3 - substituent (X - CH_2 - CH_2 -) where X is a good leaving group, would be required as the starting material and stages (a) and (b) might possibly be concerted.

In attempting to synthesise such a starting material, the reaction of indolizines with ethoxalyl chloride and the Mannich reaction [151] with N N N^1 N^1 - tetramethyldiaminomethane were studied. The reactions of 2 - phenylindolizine and 1 - methyl - 2 - phenylindolizine with ethoxalyl chloride, in methylene chloride, at room temperature gave 97% and 86% yields of the respective 3 - ethoxalylindolizines (174) as yellow crystalline solids. Attempted reduction of the ethoxalyl compounds to 3 - (2 - hydroxyethyl) indolizines (175) with lithium aluminium hydride proved unsuccessful, giving only compounds which appeared to be mixtures, possibly containing the fully reduced compound (175) together with a partially reduced intermediate. No improvement

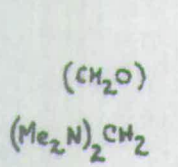


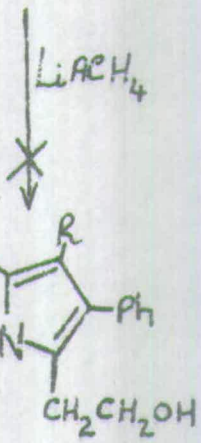
(112)

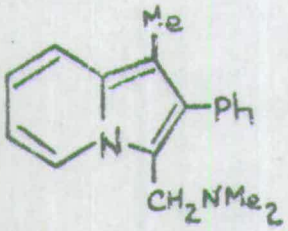




(174)

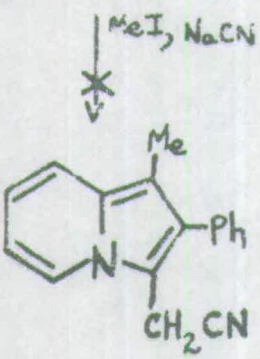




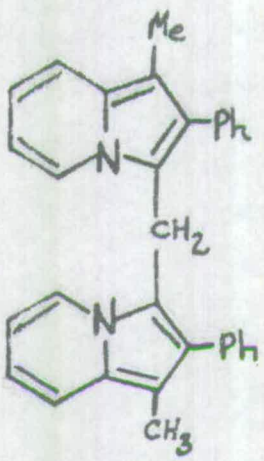


(176)

(175)



(177)



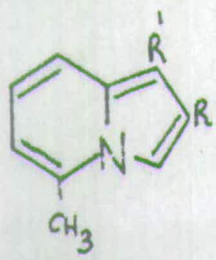
(178)

Scheme 29

was effected by using a larger excess of reducing agent or a longer reaction time.

It is well known that electron-rich aromatic compounds such as indoles [152], azulenes [147, 148], and indolizines [149] will undergo a Mannich reaction [150] with formaldehyde and dimethylamine in the presence of acid. Improved yields have been obtained, in many cases by using formaldehyde together with an excess of N N N^1 N^1 - tetramethyldiamino methane as reagent and solvent. Under these conditions, 1 - methyl - 2 - phenylindolizine gave a green oil whose n.m.r. spectrum showed it to be the required Mannich base (176). It has been found by Rossiter and Saxton [149] that alkylation of the dimethylamino group with methyl iodide, to give the quaternary ammonium iodide, followed by treatment with alcoholic potassium cyanide will give the 3 - cyanomethyl derivative. Reduction of this with lithium aluminium hydride would then give the 3 - (aminoethyl) indolizine. In the present instances, however, the only product isolated was the di-indolizinylmethane (178) which was the same as that obtained as a by-product in the aminomethylation of 1 - methyl - 2 - phenylindolizine.

Owing to these difficulties in obtaining the required starting materials, no further work was carried out into this attempted ring expansion.



(28)

a) $R' = H$, $R = Ph$

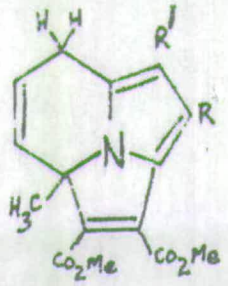
b) $R' = H$, $R = Me$

c) $R = R' = H$

d) $R = Ph$, $R' = COMe$

D.M.A.D.C.

Dilute solution in benzene



(179)

a) $R = Ph$

b) $R = Me$ } $R' = H$

c) $R = H$

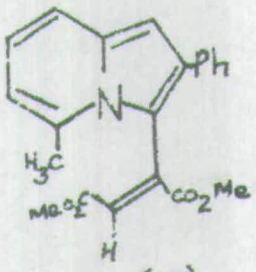
d) $R' = COMe$, $R = Ph$.

+ 1:2- adduct

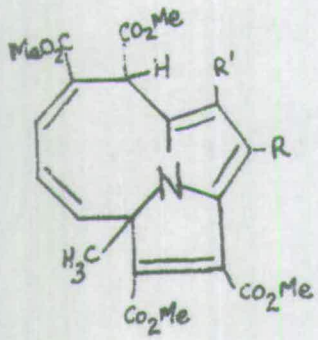
(180)

a) $R' = H$, $R = Ph$

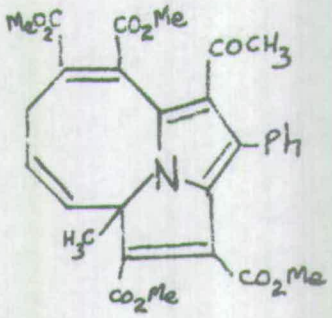
b) $R' = H$, $R = Me$



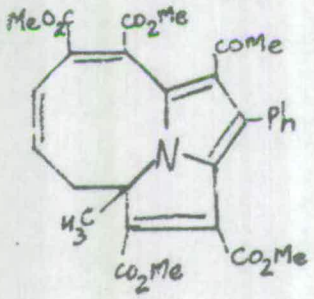
(181)



(180)



(182)



(183)

Scheme 30

SECTION 3

REACTION OF SUBSTITUTED INDOLIZINES WITH DIMETHYL ACETYLENEDICARBOXYLATE

Boekelheide and his co-workers [97, 99, 168] utilised the reaction of indolizine with dimethyl acetylenedicarboxylate, in the presence of a dehydrogenating agent, for the preparation of 1, 2 - dimethoxycarbonyl-cycl [3, 3, 2] azine, obtaining also as a by-product 15% of the 3, 4 - dihydro derivative (scheme 2; compounds 28 - 34). Since these reactions involve the loss of, or migration of, the hydrogen atoms at positions 3 and 5 of the indolizine, it was of interest to investigate the behaviour of indolizines in which one or both of these positions is occupied by a substituent other than hydrogen. Preliminary experiments [108] towards this end have been mentioned in the introduction (scheme 3) but the structures suggested for the products remained to be substantiated.

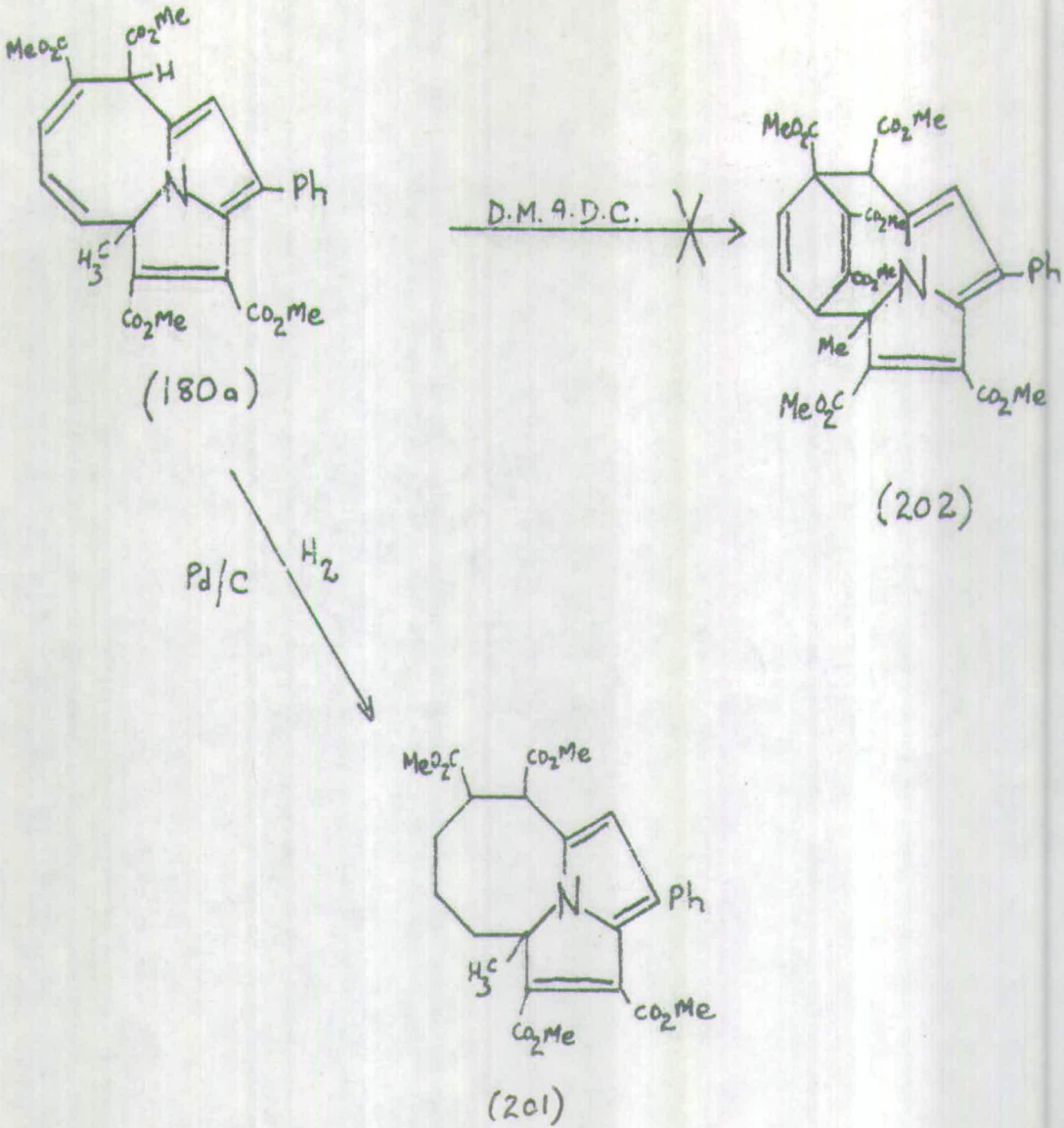
The reaction of 5 - methyl - 2 - phenylindolizine (28a) with dimethyl acetylenedicarboxylate gave two yellow solids, a 1 : 1 - adduct (54%) and a 1 : 2 - adduct (20%). The 1 : 1 - adduct was assigned the structure (179a) on the basis of its n.m.r. spectrum which showed a five-proton multiplet at τ = 2.5 - 2.9 (Ph group), a one-proton, eight-line multiplet centred at 3.32 τ (H-7), a one-proton singlet at 3.7 τ (H-4), and a one-proton, eight-line multiplet centred at 3.95 τ (H-6); the ester methyl groups gave rise to two, three-proton, singlets at 6.25 and 6.35 τ and the C - methyl group to a high-field singlet (8.35 τ), showing that it was no longer joined to an aromatic system; the remaining two protons gave a multiplet centred on 6.65 τ which is attributed to a CH_2 group. From the splitting pattern it could be seen that the two olefinic protons (H-6 and H-7) were coupled to the methylene protons and to each other, accounting for the eight-line multiplets displayed

by the 6 - and 7 - protons and for the fine splitting of the methylene group.

The methylene group was clearly in the six-membered ring andit was assigned to the 5 - position, rather than the 7, largely on the basis of its chemical shift which is considered to be too low for a CH_2 not deshielded by the pyrrole ring. Confirmatory evidence for this assignement was obtained later.

Similarly, the reaction of 2, 5 - dimethylindolizine (28b) under the same conditions, gave a 1 : 1 - adduct and a 1 : 2 adduct as orange-yellow oils. The structure (179b) was assigned to the 1 : 1 - adduct on the basis of its n.m.r. spectrum which showed the same diagnostic features as that of the 1 : 1 - adduct from 5 - methyl - 2 - phenylindolizine; the two C - methyl groups gave singlets at τ 7.85 and 8.45 consistent with their being joined to a pyrrole ring and to a saturated carbon atom, respectively. The ultraviolet spectra of the two 1 : 1 - adducts (179a) and (179b) were also closely similar (Figures 1 and 2). Reaction of 5 - methylindolizine (28c) with dimethyl acetylenedicarboxylate gave only a 1 : 1 - adduct, as a yellow oil, the n.m.r. spectrum being consistent with the structure (179c).

The n.m.r. spectrum of the 1 : 2 - adduct obtained from 5 - methyl - 2 - phenylindolizine showed a five-proton multiplet centred on 2.7 τ (Ph group), two one-proton doublets centred at 3.1 τ and 3.25 τ, two one-proton singlets at 3.25 and 5.05 τ and a one-proton doublet of doublets centred on 3.92 τ. The ester methyl groups gave rise to two six-proton singlets at 6.20 and 6.30 τ and the C - methyl group gave a singlet at 8.25 τ. The high value of the last signal again suggests that the methyl group is no longer joined to an aromatic ring and, in all probability, is similar in environment to the angular


MeO2C
CO2Me
H
Ph
H3C
CO2Me
CO2Me
(180a)
D.M.A.D.C.
MeO2C
CO2Me
CO2Me
CO2Me
N
Ph
Me
MeO2C
CO2Me
(202)
Pd/C
H2
MeO2C
CO2Me
N
Ph
H3C
CO2Me
CO2Me
(201)

Scheme 31

methyl group of the 1 : 1 adducts. The spectrum displayed no absorptions due to saturated protons above the ester methyl absorptions, thus showing the absence of any methylene group in the structure. The doublet of doublets (3.92 τ) showed coupling (J = 6.13 Hz) to both of the one-proton doublets suggesting that there are three olefinic protons present on adjacent carbon atoms. The presence of the one-proton singlet at 3.25 τ suggests that the pyrrole proton on position - 4 (position - 1 in the original indolizine) is still present though its chemical shift is lower than that of H-4 in the 1 : 1 - adducts. The second singlet (5.05 τ) is probably due to a proton joined to a saturated carbon atom bearing one or more deshielding substituents.

The only reasonable structure that is consistent with the n.m.r. data is (180a) in which one molecule of dimethyl acetylenedicarboxylate has added across the 3 - and 5 - positions of the indolizine and the other one has caused expansion of the six-membered ring to an eight-membered ring. Further support for this assignment was provided by the ultraviolet spectrum (Figure 1) which showed absorption bands similar to those of the 1 : 1 - adducts (pyrrolizine chromophore) together with a new band which corresponded in wavelength to the main absorption band of methyl sorbate ($CH_3 \cdot CH = CH-CH = CH-CO_2Me$) and was attributable to the dienoic ester chromophore present in the eight-membered ring. The 1 : 2 - adduct from 2, 5 - dimethylindolizine showed similar n.m.r. and ultraviolet spectra and was assigned the structure (180b).

In an attempt to prove the presence of a 1, 3 - diene unit, the 1 : 2 - adduct was heated with dimethyl acetylenedicarboxylate in boiling xylene. It had been hoped that the Diels-Alder adduct (202) would be formed but the n.m.r. spectrum of the oily product was extremely

complicated in the ester - methyl region (τ = 6 - 6.5) suggesting, in fact, that two moles of dimethyl acetylenedicarboxylate had reacted with (180a). The only conclusion that could be drawn was that the angular methyl was retained (8.6 τ) and the occurrence of a one-proton peak at 5.15τ suggested that the 5 - proton was present. When subjected to catalytic hydrogenation, compound (180a) gave a tetrahydro - derivative (M/e 495) corresponding to saturation of the diene unit as shown in formula (201). The n.m.r. spectrum showed loss of the three olefinic protons and the appearance of a complex series of multiplets (approximately 7H) in the region 6-8 τ. The H-5 absorption remained at 5.2τ but was split into a doublet by H-6. The angular methyl group (8.3 τ) and the H-4 (3.3 τ) remained relatively unchanged. The effect of hydrogenation on the ultraviolet spectrum was to make it more similar to the spectra of the 1 : 1 - adducts (179a and b) (Figures 1 and 2); consistent with removal of the diene chromophore.

Molecular models suggested that the eight-membered ring in (180a) might be capable of changing its conformation. However, variable temperature n.m.r. studies, over the range -60° to +120° showed no significant changes in the spectrum such as might be attributed to a change from a rigid to a conformationally mobile structure.

In an attempt to study the mode of formation of the 1 : 2 - adducts. the monoadducts (179a and b) were treated with one mole of dimethyl acetylenedicarboxylate. In benzene, at room temperature, neither compound reacted, though the diadducts were formed readily from the parent indolizines under these conditions. The dimethyl adduct (179b) also failed to react in boiling benzene but the methylphenyl adduct (179a) was slowly converted into the 1 : 2 - adduct (180a).

When 5 - methyl - 2 - phenylindolizine was allowed to react with a

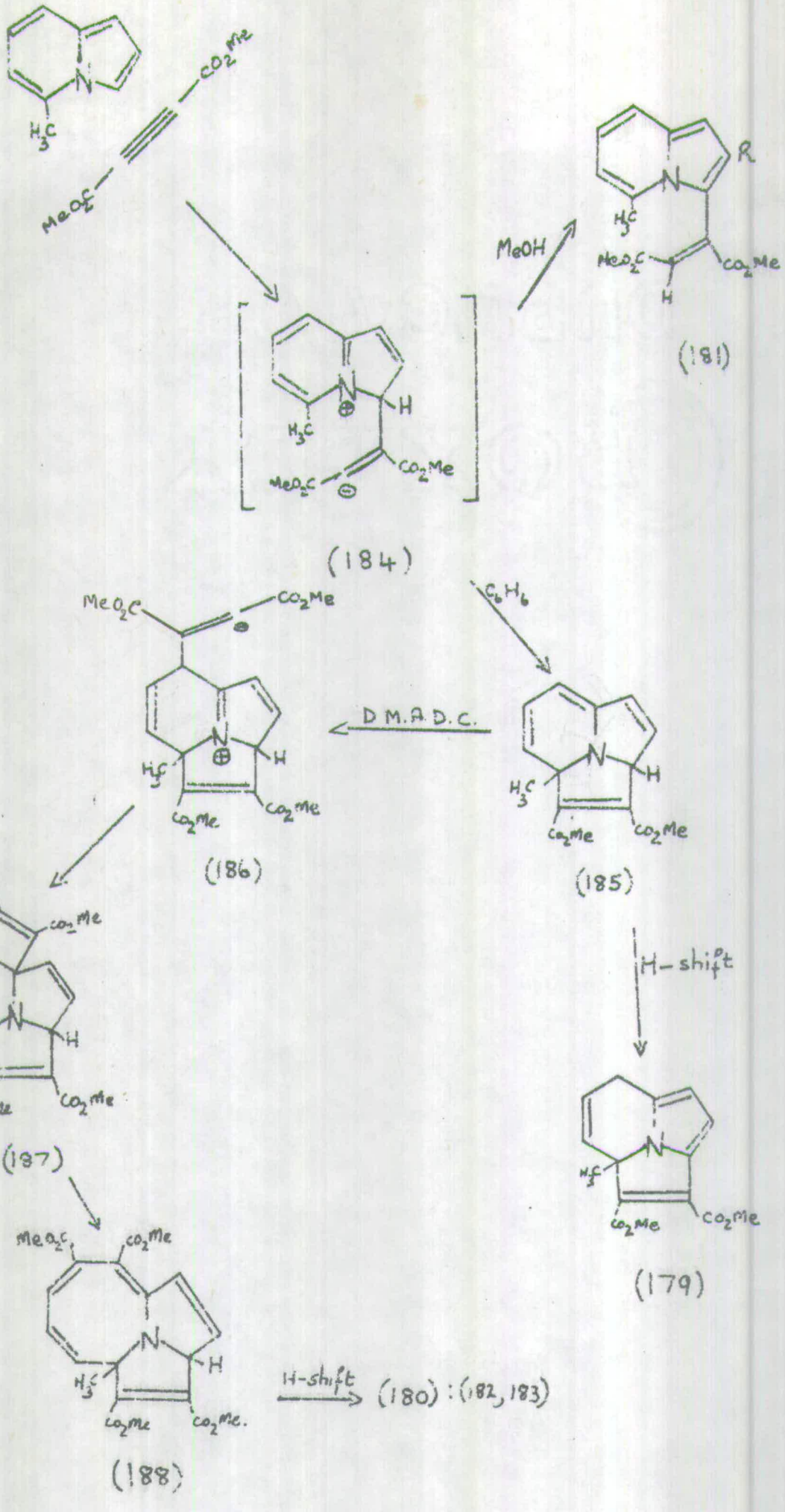
two-fold excess of acetylenic ester, at room temperature, the yield of 1 : 2 - adduct was increased (to 43%) and the yield of 1 : 1 - adduct was reduced to (20%). It would appear therefore that the diadduct is being produced at the expense of the monoadduct but that the latter is not an intermediate in its formation. Evidently the diadduct is formed from one of the intermediates in the formation of the monoadduct, the transformation of intermediate to monoadduct being, presumably, reversible for (179a) in boiling benzene.

While attempting to prepare the cyclopenta [c] quinolizine (148e) from the enamine (114a) and dimethyl acetylenedicarboxylate Gibson [169] isolated a small amount of a pale yellow solid which appeared to have been formed by addition of the acetylenic ester to 1 - acetyl - 5 - methyl - 2 - phenylindolizine, present as an impurity in the enamine. The n.m.r. spectrum of the compound showed a five-proton singlet at 2.65 τ (Ph), a one-proton doublet of doublets centred at 3.33 τ (olefinic) and a one-proton eight-line multiplet centred at 3.90 τ (olefinic). Two three-proton singlets at 6.2 and 6.55 τ were attributable to ester OMe groups and two three-proton singlets at 7.9 and 8.3 τ to CH_3CO and an angular methyl group, respectively. The remaining two sets of signals (5.6 - 5.9 and 6.4 - 6.7 τ) were due to a CH_2 group, being coupled to each other (J = 21Hz) and to the olefinic protons. This pattern is basically similar to those found in the spectra of the 1 : 1 adducts (179) though one of the methylene protons is shifted downfield, presumably owing to deshielding by the acetyl group. Accordingly, the structure (179d) may be assigned to this adduct. Attempts to obtain more of compound (179d) by reaction of 1 - acetyl - 5 - methyl - 2 - phenylindolizine with dimethyl acetyl enedicarboxylate in refluxing benzene and in refluxing toluene gave a different yellow solid which proved to

be a 1 : 2 - adduct. All attempts to obtain a 1 : 1 - adduct failed.

The n.m.r. spectrum of the 1 : 2 - adduct showed the expected absorptions due to a phenyl group (2.6 τ, singlet, 5H), four ester OMe groups (6.17, 6.20, 6.22 and 6.64 τ), a COMe group (8.1 τ) and an angular methyl group (8.3 τ). The remainder of the spectrum comprised absorptions indicative of the grouping -CH = CH-CH_2-, the two olefinic signals being centred at 3.59 τ (doublet of doublets) and 4.10 τ (eight lines) while the methylene protons (J_{gem}, 14Hz) were centred at 6.85 τ (doublet of doublets) and at 7.40 τ (doublet of quartets). The ultraviolet spectrum (Figure 3) which was similar to those of the previously discussed 1 : 1 - and 1 : 2 - adducts, suggested that the 3H - pyrrolizine chromophore was present. Two structures (182) and (183), both of which are based on the cycl [5, 2, 2] azine ring system, appear to be consistent with this spectroscopic evidence. Molecular models suggest that the potential for extension of conjugation, which is present in both structures, would not, in fact, be realised because the double bonds of the eight-membered ring would not be coplanar with each other (in 183), or with the pyrrolizine π - system, when the conformations of the molecules are such as to minimise non-bonding interactions.

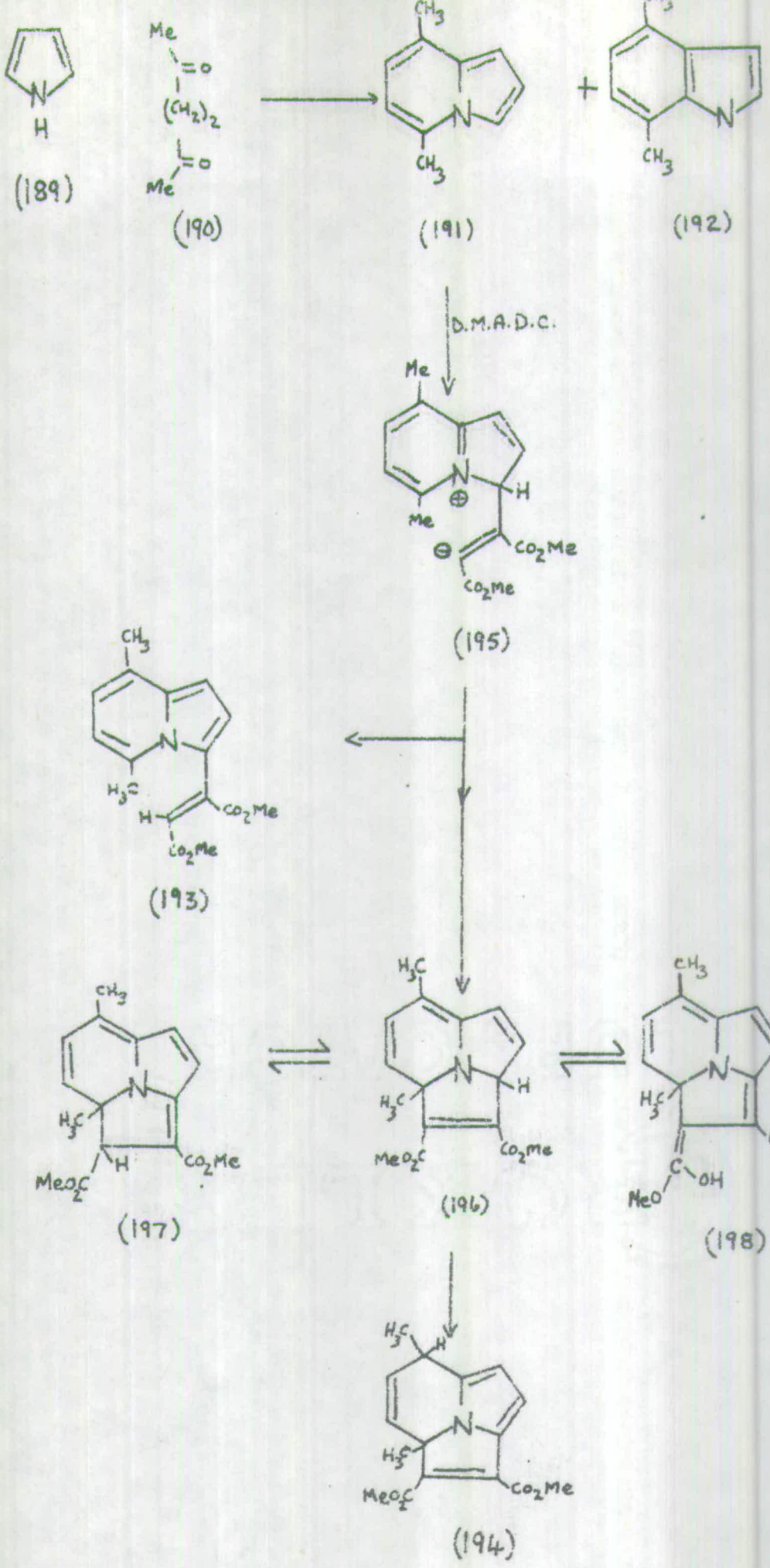
The reaction of 5 - methyl - 2 - phenylindolizine with dimethyl acetylenedicarboxylate in methanol, a proton - donor solvent, gave a red compound which on the basis of the n.m.r. spectrum, was formulated as an indolizinylfumarate; m substitution was assumed to have occurred in the three-position of the indolizine nucleus (181). The n.m.r. spectrum of (181) showed absorptions attributable to the 5 - methyl group (7.6 τ), two OMe groups (6.61 and 6.34 τ), H-6 (doublet, 3.66 τ), H-1 (singlet, 3.38 τ), H-7 (triplet, 3.27 τ), a vinylic proton (singlet, 2.94 τ),


MeOH
(181)
(184)
DMADC
C6H6
(186)
(185)
H-shift
(187)
(179)
(188)
H-shift
(180) : (182, 183)

Scheme 32

H-8 (ca . 2.65 τ, partially obscured by Ph signal) and the phenyl protons (2.72 τ). It is possible that the assignments of H-1 and the vinylic proton should be interchanged but in any event, the low field chemical shift of the latter indicates that it is cis - to a methoxycarbonyl group and that the compound is an indolizinylfumarate rather than the corresponding maleate. The formation of the open-chain adduct (181), at the expense of the cyclazine (179a), in a proton - donor solvent, supports the suggestion that a zwitterionic intermediate (184, scheme 32) is involved in the reaction.

The scheme proposed to account for the formation of the various products is shown in scheme 32. Reaction of dimethyl acetylenedicarboxylate with 5 - methylindolizines will give initally a zwitterionic species (184) which, in methanol, will be protonated and deprotonated to give the open-chain adduct (181). In a non-protonic solvent nucleophilic attack on position - 5 of the indolizine nucleus, by the terminal carbanion, will result in charge neutralisation and formation of a 2a, 7a - dihydro - 7a - methylcycl [3, 2, 2] azine (185). A shift of the 2a - hydrogen atom to position - 5, thereby imparting aromaticity to the pyrrole ring, will lead to the formation of the 1 : 1 - adducts (179; and 194). However, the intermediate (185) contains an enamine system which can react with another molecule of dimethyl acetylenedicarboxylate with the formation of the Zwitterionic species (186). Formation of a cyclobutene system (187) and ring-opening will then lead to the formation of a 2a, 9a - dihydro - 9a - methylcycl [5, 2, 2] azine which, by shift of the 2a - hydrogen atom, thus regenerating the aromatic pyrrole ring, can isomerise to the 2: 1 - adducts. Molecular models suggest that the preference for a 7H - (182) or 9H - Tautomer (183) in the case of the acetyl compound is due to the bulk of the acetyl group



Scheme 33

which would cause serious steric interactions in the normally preferred 5H - Tautomer.

The 1 : 1-adducts (179) were assigned the 5H - Tautomeric structures (179) initially on the basis of their n.m.r. spectra. However, since it would be desirable to provide more conclusive evidence on this point, the synthesis of 5, 8 - dimethylindolizine was undertaken. The adduct of this indolizine with dimethyl acetylenedicarboxylate would have a 5 - methyl substituent which, if the 5H - structure is correct, would show a signal split into a doublet by the 5 - proton.

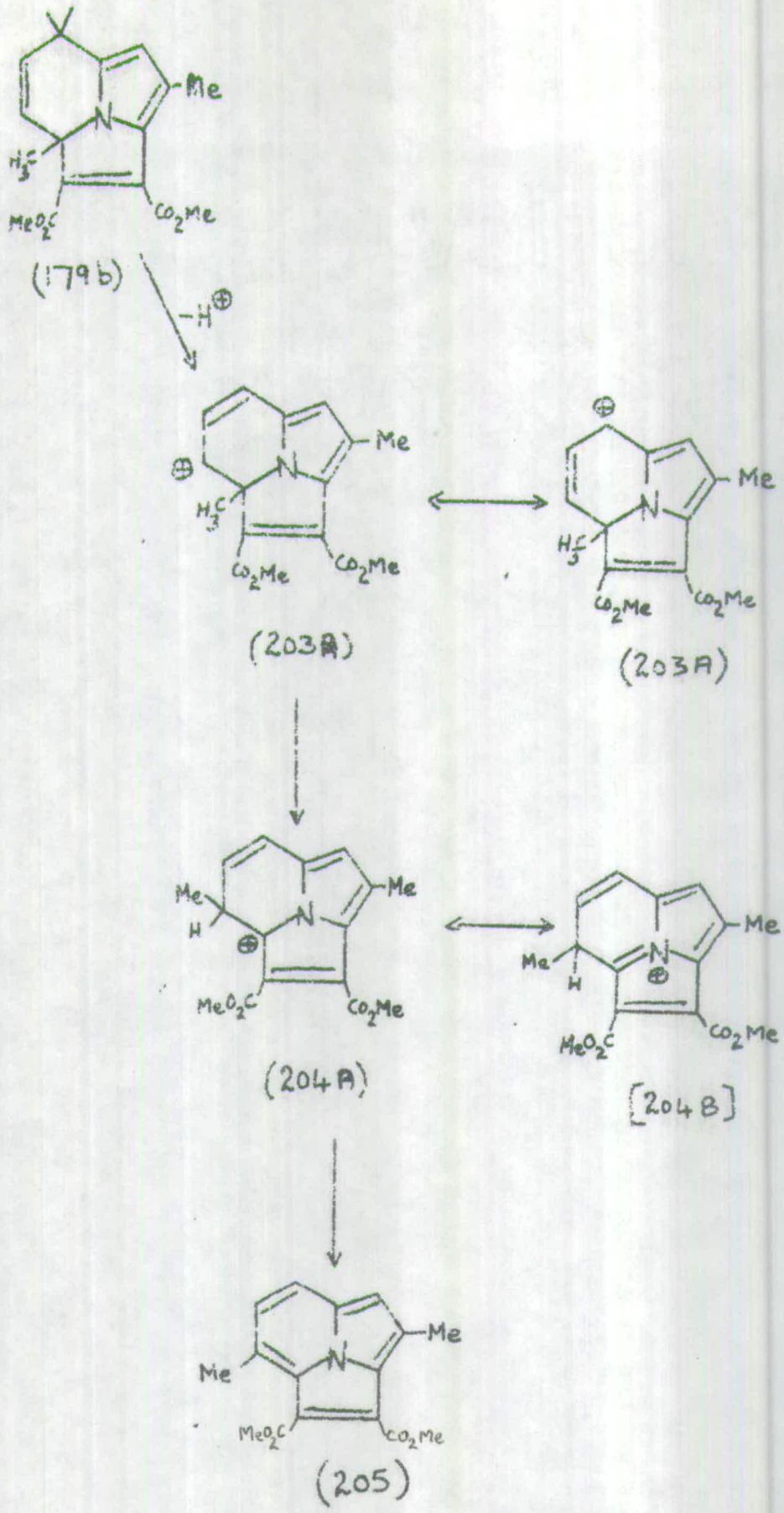
It is known [176] that hexane - 2, 5 - dione will react with 2, 4 - and 3, 4 - dialkylpyrroles to give tetraalkylindolizines; 2, 4 - dimethylpyrrole, for example, gives 1, 3, 5, 8 - tetramethylindolizine. It was therefore thought possible that pyrrole itself (189) might react in an analogous fashion to give the required 5, 8 - dimethylindolizine, although all references to this reaction in the literature mention only the formation of 4, 7 - dimethylindole. Condensation of hexane - 2, 5 - dione with pyrrole in acetic acid, using zinc acetate as a catalyst, gave two products, separated by chromatography on alumina. The first band from the column yielded a dark oil and the second band gave 4, 7 - dimethylindole as a crystalline solid, m.p. 99° (Lit [175] m.p. 101°). The oil was shown to be the required 5, 8 - dimethylindolizine (191) by its n.m.r. spectrum which showed a well-defined aromatic region comprising three doublets of doublets (one proton each) centred at τ 2.9, 3.2, and 3.55 (H-3, H-2 and H-1, respectively) and two one-proton doublets centred at τ 3.6 and 3.82 (H-7 and H-6, respectively). The two methyl groups gave a six-proton singlet at τ 7.62. 5 - Methylindolizine of which an authentic sample was available, gave very similar n.m.r. absorptions in the aromatic region. The 5, 8 - dimethylindolizine

was allowed to react with dimethyl acetylenedicarboxylate and three products were isolated by chromotography, as a yellow oil, an orange solid and a red oil.

The n.m.r. spectrum of the yellow oil showed that this product was the required dihydrocyclazine (194). The low-field part of the spectrum was well-resolved and easily relatable to that of the 1 : 1 - adduct from 2, 5 - dimethylindolizine (179b); there was an additional doublet, due to H-3 at τ = 3.57 and the other signals showed the expected changes in multiplicity, being only slightly shifted from their positions in the spectrum of the isomeric adduct. The single proton at position - 5 was not well-resolved (ca τ = 6.5) but the 5 - methyl group was clearly visible as a doublet (τ = 8.58, J = 7.5Hz) upfield of the 7a - methyl singlet (τ = 8.39). These observations show that the 1 : 1 - adduct from 5, 8 - dimethylindolizine is a 5, 7a - dihydrocyclazine and, since its ultraviolet spectrum is very similar to those of the 1 : 1 adducts from other 5 - methylindolizines, it follows that all these compounds have the same tautomeric structure.

The n.m.r. spectrum of the orange solid showed a well-defined aromatic region consisting of two AB systems at τ 2.95 and 3.45 (J = 4.5 Hz) and at τ 3.35 and 3.59 (J = 7Hz) attributable, respectively, to protons 1 and 2, and to protons 6 and 7, of the indolizine nucleus bearing a 3 - substituent. The ring - methyl signals were at 7.52 and 7.58 τ, typical of Ar-Me groups, and two ester OMe groups at 6.12 and 6.24 τ. The one remaining singlet signal was due to a vinylic proton (4.6 τ) and indicated that the 3 - substituent was a maleate group (formula 193), the cis - configuration of methoxycarbonyl groups being assigned because of the relatively high chemical shift of the vinylic proton.

The red oil, obtained as the third product from the reaction of

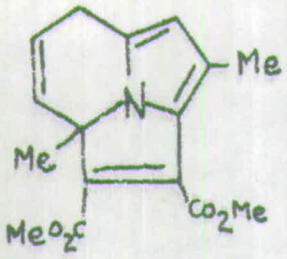

Me
H_3C
MeO_2C
CO_2Me
(179b)
$-H^{\oplus}$
Me
H_3C
CO_2Me
CO_2Me
(203A)
(203A)
Me
H
MeO_2C
CO_2Me
(204A)
[204B]
Me
Me
(205)

Scheme 34

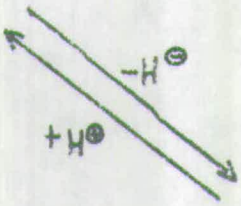
5, 8 - dimethylindolizine with dimethyl acetylenedicarboxylate, also gave an n.m.r. spectrum consisting of two AB systems in the low-field region τ 3.63 and 3.78 (J = 4Hz); τ 3.22 and 4.12 (J = 9Hz) . Two ester OMe signals were present (τ 6.1 and 6.2) and two C - methyl singlets were present at relatively high-field (8.16 and 8.32 τ) showing that neither group was attached to an aromatic ring. This leaves one proton not yet accounted for but the spectrum contained no other sharp signals. A broad hump at τ 6.9 - 7.3 integrated for one proton and had the appearance of an OH proton signal. The infra-red spectrum showed a peak at 3300cm^{-1} which could be attributed to a hydroxyl-stretching band. Owing to the instability of this compound its structure was not verified but it was thought that it might be an intermediate in the formation of (194). Three structures (196) - (198) may be considered as possibilities, all of which would give the observed AB system in the n.m.r. spectrum. Structure (198) is the only possible one containing a hydroxyl group but the enolised ester group seems very improbable and a definite conclusion is not possible without further evidence.

Aromatisation of the 5, 7a - dihydrocycl [3, 2, 2] azines is not likely to occur readily because of the presence of the 7a - methyl group. It seemed possible, however, that abstraction of a hydride ion might be followed by a shift of the methyl group to position - 7 and loss of the 7 - proton to give the aromatic cycl [3, 2, 2] azine system (205; scheme 34).

Accordingly, the 1 : 1 - adduct (179b) was treated with dichlorodicyanobenzoquinone (D.D.Q.) in boiling benzene. Chromatography, after one hour, gave starting material and a new product as a yellow oil. The n.m.r. spectrum of the oil showed that it was an

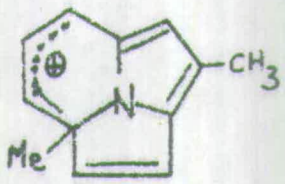


(179b)

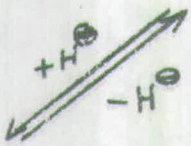


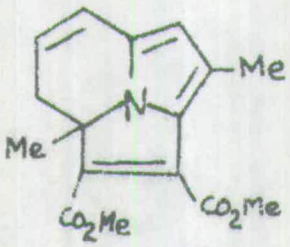
a) 1 mole DDQ

b) catalytic amount



(203)





(199)

Scheme 35

isomer of the starting material to which the 7, 7a - dihydrocyclazine structure (199; scheme 35)may be assigned. The signals due to the pyrrole proton (H-4), andthe C - methyl and O - methyl groups were in essentially the same positions as the corresponding signals in the spectrum of the starting material. The signals due to the -CH = CH-CH_2- grouping of the six-membered ring had, however, shifted appreciably in an upfield direction and the CH_2 protons had become more clearly resolved as an AB system (J_{AB} = 18Hz) with additional splittings from the olefinic protons.

Since the 5, 7a - dihydro - compound (179b) did not isomerise in boiling benzene alone, it is clear that D.D.Q. must act as a catalyst. It seems probable that the carbonium ion (203A$\longleftrightarrow$203B) is formed initially but that isomerisation by methyl shift is not favoured because the resulting cation (204A) would contain an anti-aromatic azoniapentalene system as shown in the canonical structure (204B).

Instead, the cation (203) abstracts a hydride ion from another molecule of (179b), either to regenerate (179b), or to become the 7,7a - dihydro - tautomer (199). Thus, the function of the quinone is seen to be truly catalytic and failure to achieve complete conversion of (179b) into (199) is understandable, the two isomers being merely equilibrated. Relatively small amounts of D.D.Q. were effective in causing the equilibration.

Unfortunately, after the first experiment, later attempts to separate the isomeric dihydrocyclazines were not completely successful and the 7, 7a - dihydro - compound remains incompletely characterised. The 1 : 1 - adduct (179a) did not isomerise when treated with D.D.Q. in boiling benzene.

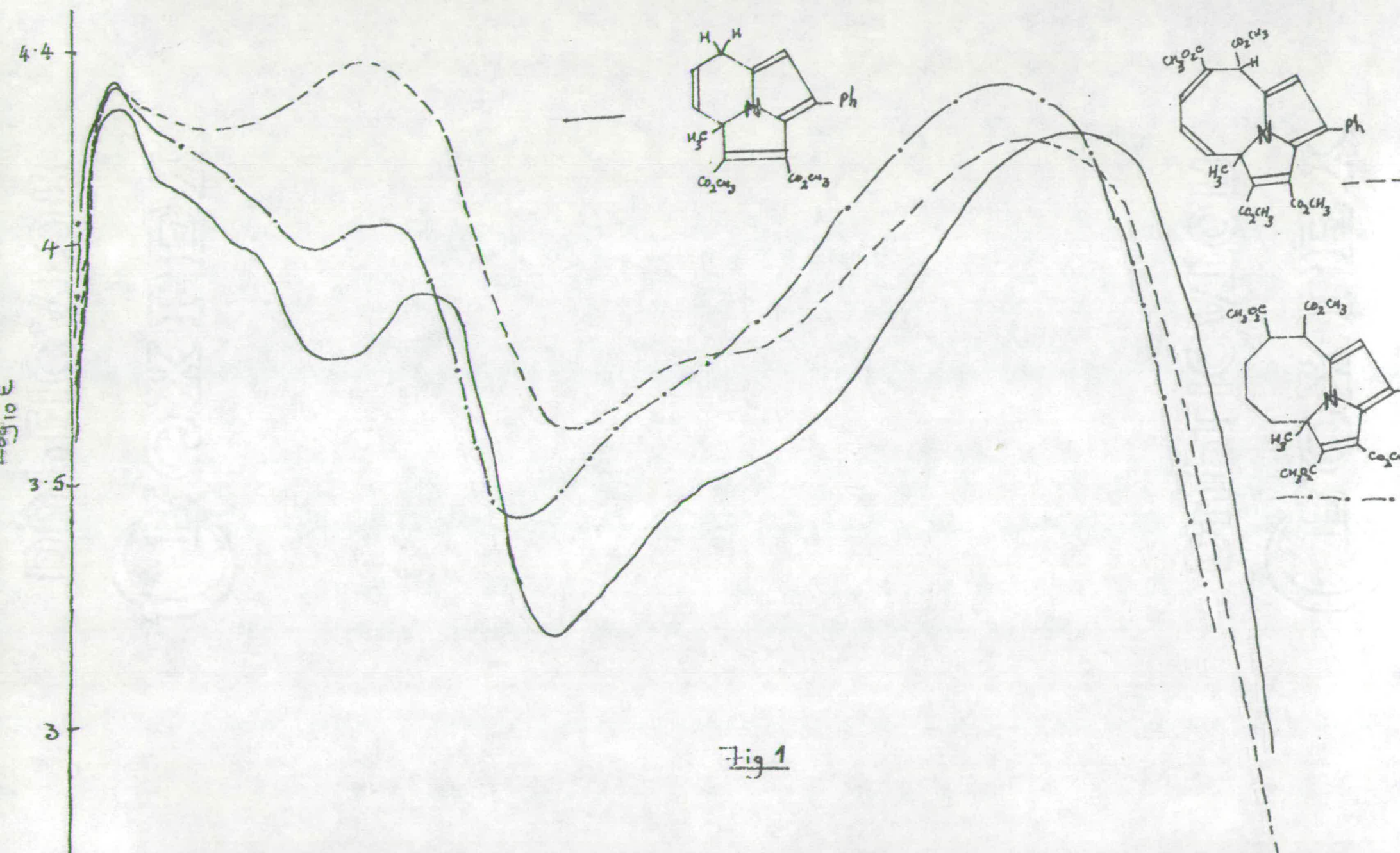


Fig 1

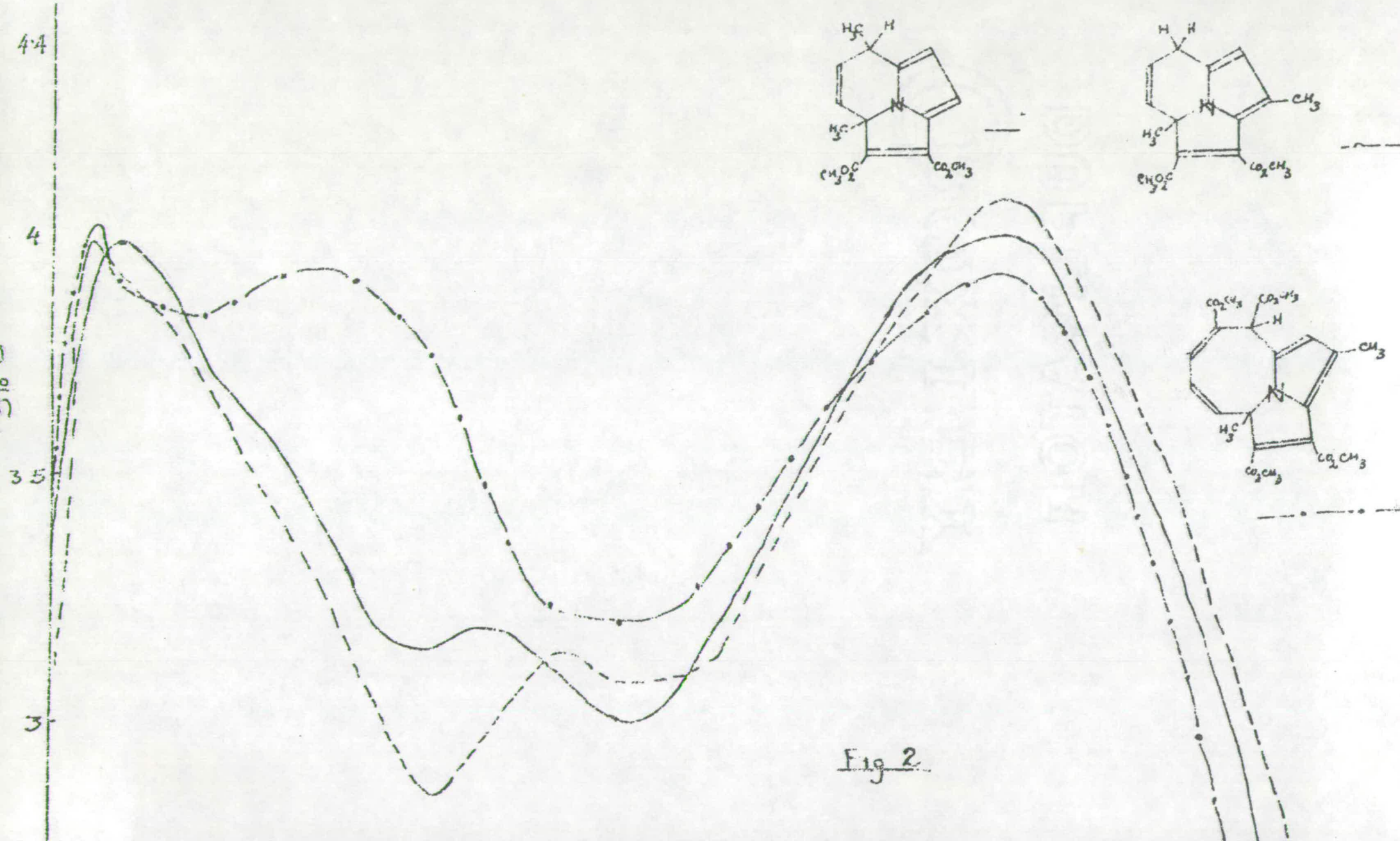


Fig 2.

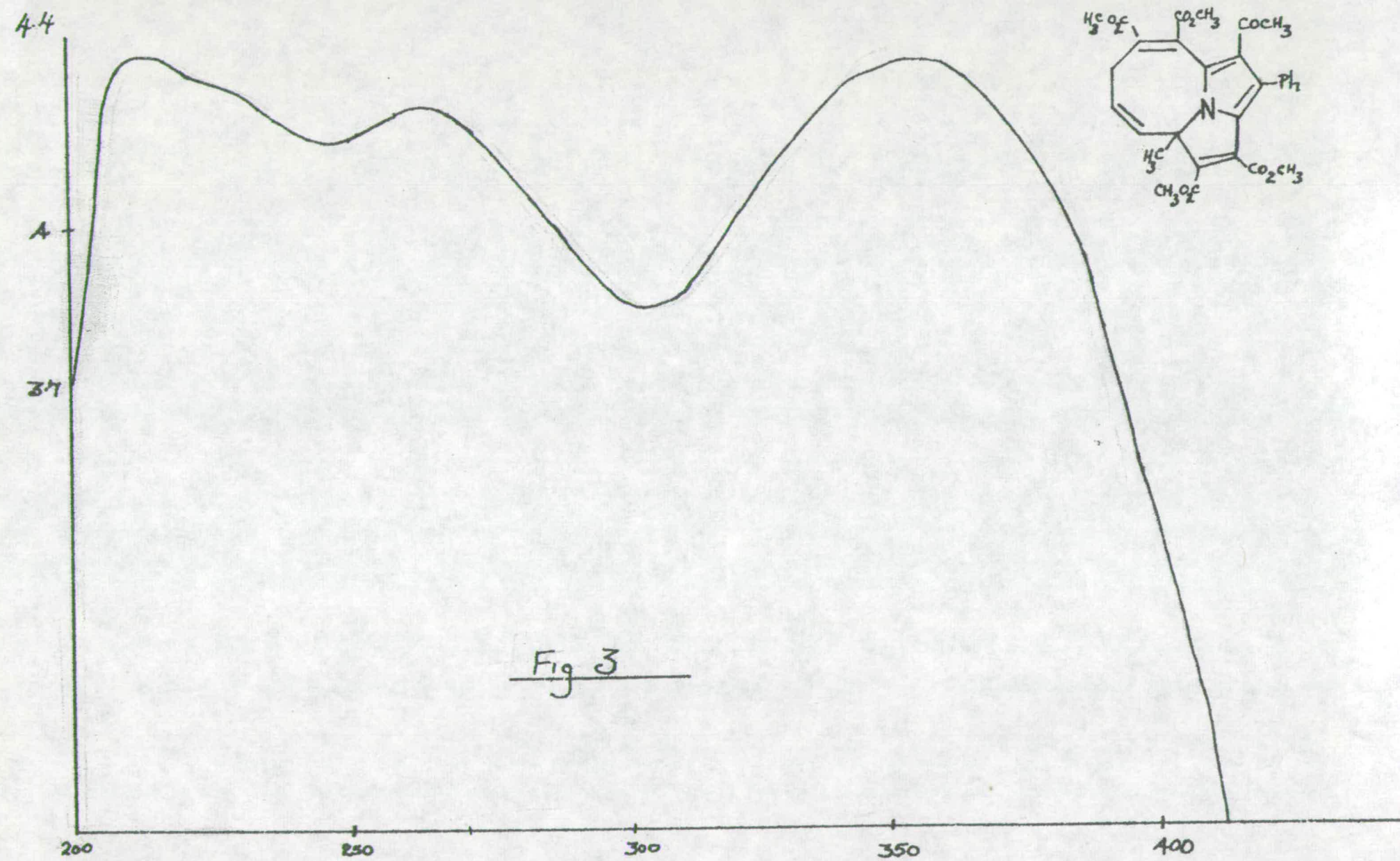

4.4
A
3.7
200
250
300
350
400
$H_3C\,O_2C$
CO_2CH_3
$COCH_3$
Ph
N
H_3C
CO_2CH_3
CH_3O_2C

Fig 3

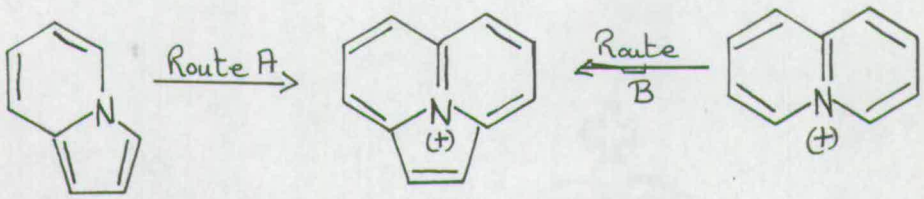
SECTION 4

SYNTHESIS IN THE CYCL [3, 3, 2] AZINE SERIES.

The main aim of the present investigation was to synthesise, and to study the properties of, the parent cycl [3, 3, 2] azinium ion (21) and certain of its derivatives. There are two obvious approaches to this ring system:

(a) starting from indolizines (Route A)

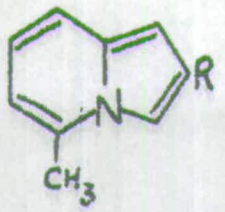
(b) starting from quinolizine derivatives such as quinolizinium - salts (Route B)



(21)

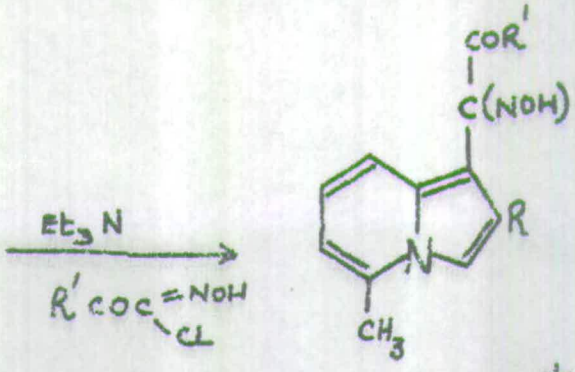
Both of these approaches have been studied previously [126, 159] in this department and a synthesis of the parent ion (21) has been achieved [122] via route B. It seemed likely, however, that route A might prove more adaptable in providing the alkyl and aryl derivatives of (21).

Experimental work [158] has shown that indolizines undergo acylation reactions at the 1 - and 3 - positions, primarily in the 3 - position, and that a methyl group in the 5 - position is comparable in its acidity with that of α - picoline. [91] Previous work by Roff in this department [159] utilised these reactivities in the synthesis of cycl [3, 2, 2] azines and cycl [3, 3, 2] azinones. The principal method of approach was the reaction of indolizines with α - ketonitrile oxides. Thus the reaction of 5 - methyl - 2 - phenyl indolizine (28c) with nitrile oxides generated in situ, by the action of base (triethylamine) on ω - chloro - ω - hydroxyiminoacetophenone and



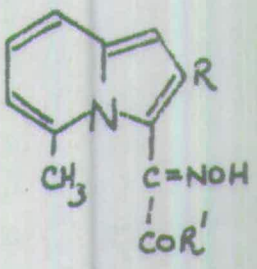
(28)

a. R = H
b. R = CH_3
c. R = Ph



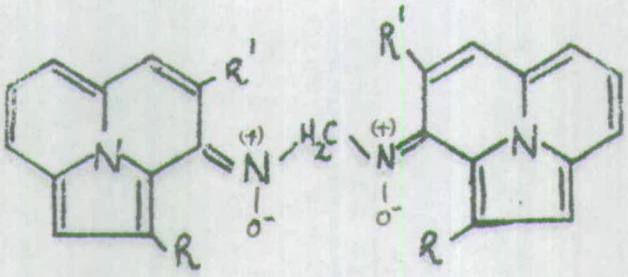
(206)

+

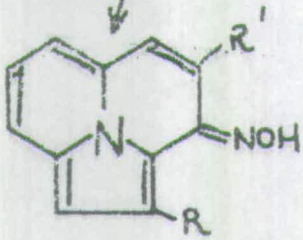


(207)

a. R=H, R' = CH_3
b. R=CH_3, R' = Ph
c. R = R' = CH_3
d. R = R' = Ph
e. R= Ph, R' = CH_3



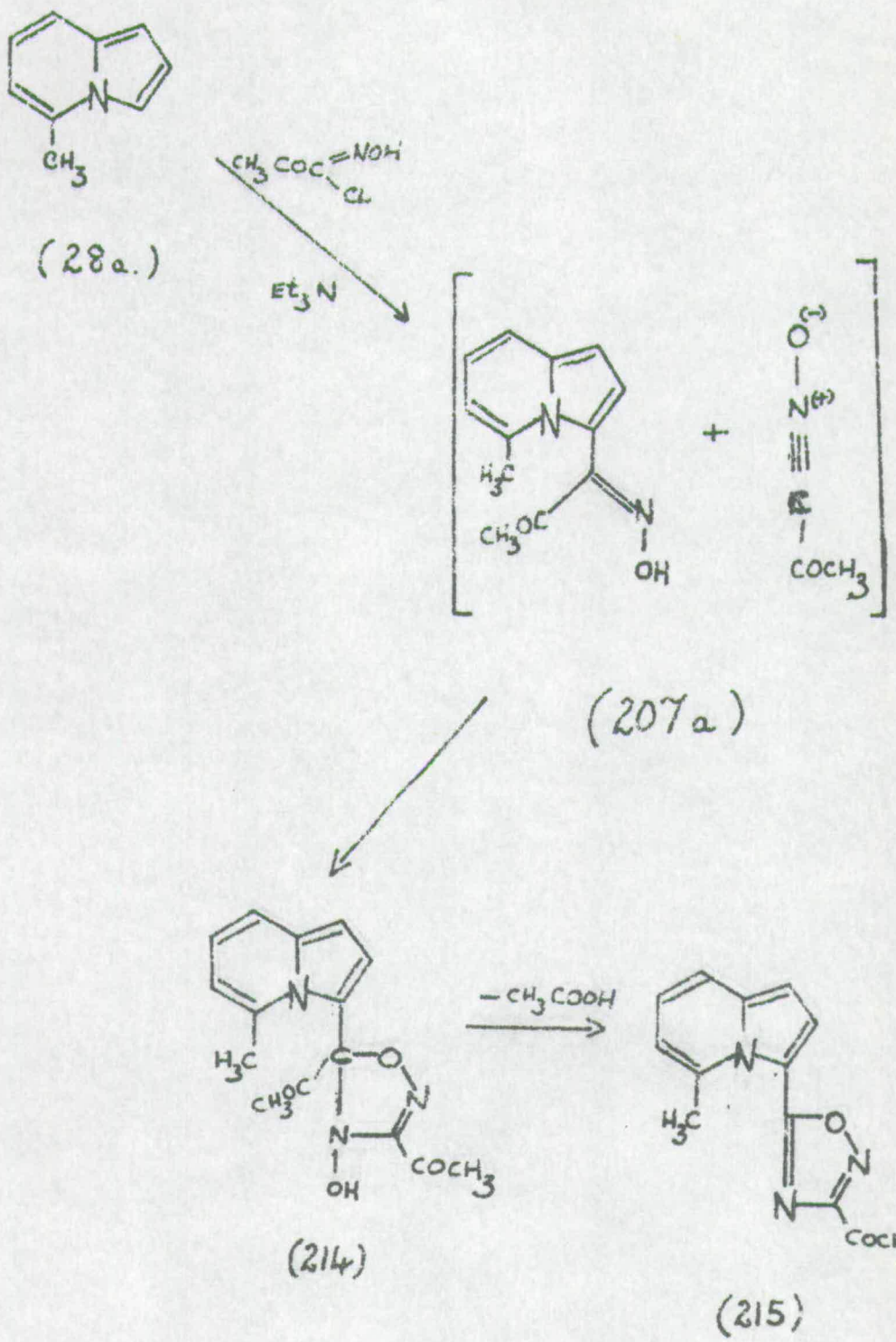
(208)



(209)

a. R = R' = Ph
b. R = CH_3, R' = Ph
c. R = R' = CH_3
d. R = Ph, R' = CH_3
e. R = H, R' = CH_3

Scheme 36


CH3
(28a.)
CH3COC=NOH
Cl
Et3N
H3C
CH3OC
N
OH
+
O
N
COCH3
(207a)
H3C
CH3OC
N
OH
COCH3
(214)
-CH3COOH
H3C
N
O
N
COCH3
(215)

Scheme 37

α - chloro - α - hydroxyiminoacetone gave principally mixtures of 1 - and 3 - (α - hydroxyimino phenacycl) and 1 - and 3 - (α - hydroxyimino acetonyl) derivatives respectively (206, 207d and 206, 207e : R^1 = Ph and R^1 = Me). 2, 5 - Dimethylindolizine (28b) gave a corresponding series of compounds.[159]

In Roff's work, benzene was used as a solvent for these reactions but, in repeating his preparations, it was found that chloroform gave an improved yield. A number of the products, for which satisfactory analytical results had not previously been obtained, were prepared again and obtained analytically pure. The reaction was also extended to 5 - methylindolizine which reacted with α - chloro - α - hydroxyimino acetone to give a mixture of the 1 - and 3 - (α - hydroxyiminoacetonyl) - 5 - methylindolizines (206a) and (207a) as a red oil. A by-product of this reaction, obtained as a yellow solid, is believed to be the 3 - oxadiazolyl - indolizine (215) or the corresponding 1 - isomer. Its n.m.r. spectrum showed absorptions due to a 1, 5 - or 3, 5 - disubstituted indolizine together with two methyl signals at τ = 7.3 (5 - Me) and τ 7.9 (COMe). The mass spectrum showed a parent peak at M/e 241 which corresponds to one molecule of 5 - methylindolizine plus two molecules of pyruvonitrile oxide minus one molecule of acetic acid. This suggests that the compound was possibly formed from the 3 - hydroxyiminoacetonyl compound (207a) and another molecule of the nitrile oxide <u>via</u> a 1, 3 - dipolar addition to the oxime double bond. The resulting oxadiazoline (214) could then aromatise, by loss of acetic acid, to give the oxadiazole (215). Alternatively, a similar reaction with the 1 - hydroxyimino acetonyl compound would give the corresponding 1 - oxadiazolylindolizene.

By the action of potassium <u>t</u> - butoxide on the indolizine - nitrile oxide reaction products (mixed 1 - and 3 - isomers) in dimethyl sulphoxide,

Roff obtained a series of orange compounds which proved to be the 3 - hydroxyiminocyclazines (209) formed by a cyclisation reaction of the 3 - substituted components of the original mixtures.

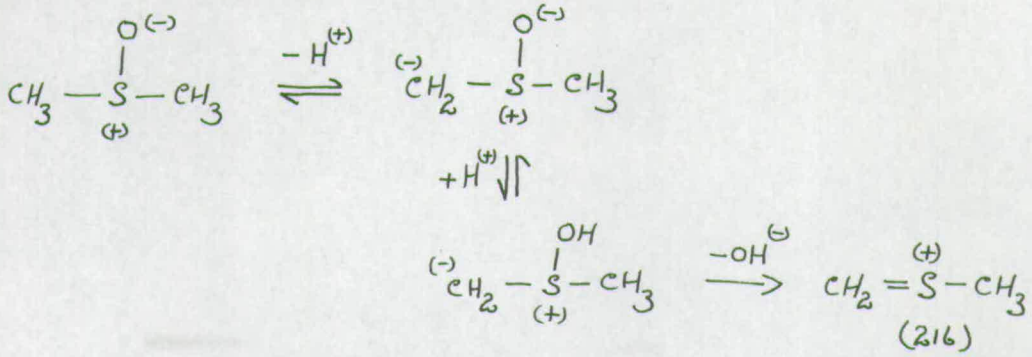
Similar treatment of the mixture of 1 - and 3 - (α - hydroxyiminoacetonyl) - 5 - methylindolizine with potassium t - butoxide in dimethyl sulphoxide gave a poor yield (6%) of the 3 - hydroxyimino - 4 - methylcyclazine (209 : R = H, R^1 = Me). The n.m.r. spectrum of this compound (in trifluoroacetic acid) showed the five - membered ring protons as two doublets ($J_{1,2}$ = 5.5 Hz) at τ 1.18 (H-2) and 2.12 (H-1) and the remaining aromatic protons as a multiplet in the region 1.3 - 1.7 τ. The methyl protons gave a signal at τ 7.29 which was split into a doublet (J = 1Hz) by H-5.

The yields of 3 - hydroxyiminocyclazines, under Roff's conditions, were not easily reproducible; higher temperatures and longer reaction times caused more decomposition but when the conditions were moderated there was a tendency to form a second series of orange compounds, the structures of which remain in doubt.

The ultraviolet - visible spectra of these compounds were almost identical with those of the corresponding 3 - hydroxyiminocyclazines but their n.m.r. spectra (in $CDCl_3$), while generally similar to those of the hydroxyiminocyclazines, showed an additional singlet peak, in the region τ 4-6, which integrated for one proton per cyclazine nucleus. This signal was not due to an OH or NH proton since it did not disappear when the solutions were shaken with deuterium oxide (neutral or alkaline). Moreover, the weak absorption near 3200 cm^{-1} in the infra red spectra of the oximes was absent in the spectra of the new compounds.

One possibility is that these compounds are the N,N^1 - methylenebis (cyclazinimine) N,N^1 - dioxides (208), the methylene bridge being derived

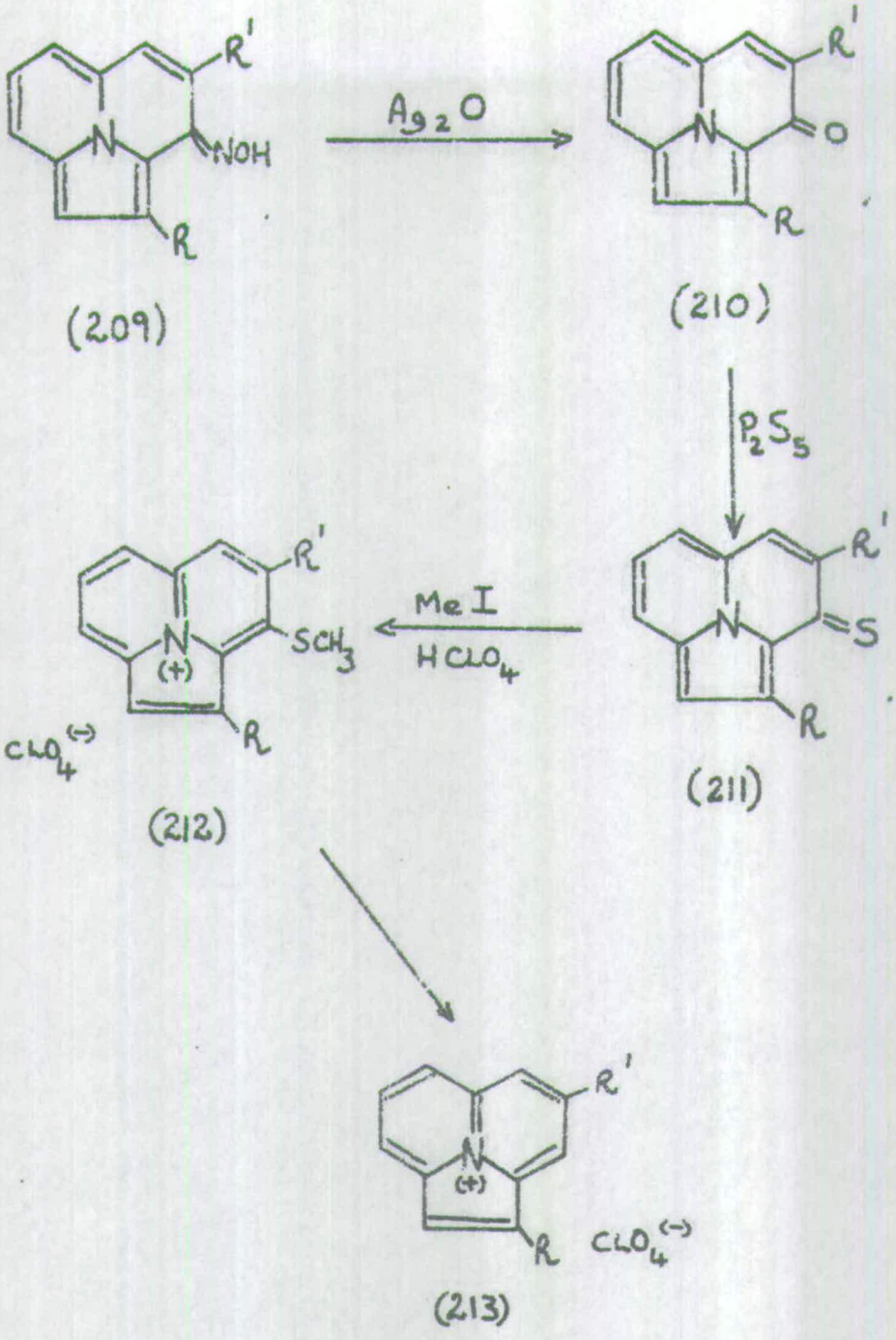
from a formaldehyde - equivalent (216) formed by base - induced decomposition of dimethyl sulphoxide :-



Linkage via the nitrogen atoms of the oxime grouping is considered more likely than linkage via the oxygen atoms since the nitrogen is a more effective nucleophilic centre.

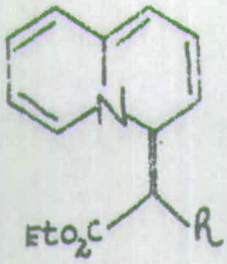
Unfortunately, mass spectrometry failed to confirm the methylene-linked dimeric structure, though the presence of peaks at M/e values higher than the monomer parent peak (e.g. at P + 14 in the spectrum of the diphenyl compound) may be a result of decomposition of such dimeric compounds in the ion - source. The elemental analysis results, though consistent with the proposed structures, were of little diagnostic value since the compositions of the methylene-linked dimers differ from those of the monomers by less than the experimental error.

As in Roff's work, the hydroxyiminocyclazinones were converted into the cyclazinones by treatment with freshly prepared silver oxide in dichloromethane. This reagent gave 60 - 70% yields of the cyclazinones but it had no effect on the compounds believed to be methylene-linked dimers. In view of the low yield of the 3 - hydroxyimino - 4 - methylcyclazine (209e) no attempt was made to convert this compound into the 4 - methylcyclazinone (210e), which would have been the most desirable member of the series for conversion to a cyclazinium salt. Instead the 2 - phenyl - 4 - methyl compound (210d) was selected for further studies towards this objective.


R'
NOH
R
(209)
Ag_2O
R'
O
R
(210)
P_2S_5
R'
S
R
(211)
MeI
$HClO_4$
R'
SCH_3
N
(+)
R
$ClO_4^{(-)}$
(212)
R'
N
(+)
R
$ClO_4^{(-)}$
(213)

Treatment of the cyclazinone with phosphorus pentasulphide in dry benzene gave the corresponding cyclazinethione (211d), as a dark red solid whose infra-red spectrum showed the loss of the carbonyl absorption. The n.m.r. spectrum (in $CDCl_3$) showed a ten-proton multiplet in the region τ 1.9 - 2 (showing the aromatic character of the molecule), and a three-proton singlet at τ 7.3 (ring CH_3 group), the latter showing the expected downfield shift with respect to the corresponding signal (7.6 τ) in the spectrum of the cyclazinone. The ultraviolet spectrum of the thione also displayed a marked change from that of the ketone. Treatment of the 4 - methyl - 2 - phenylcycl [3, 3, 2] azine - 3 - thione with an excess of methyliodide in ether gave the corresponding 3 - methylthiocycl [3, 3, 2] azinium iodide which, on treatment with perchloric acid in methanol, gave a quantitative yield of the perchlorate (212d).

An attempt was then made to remove the methylthio - group by hydrogenolysis with Raney nickel, a reagent which had been used successfully by Gough [122] in the synthesis of the parent cyclazinium perchlorate from its 1 - methylthio - derivative. Unfortunately, however, the desired result could not be achieved; reaction in ethanol gave a dark-coloured, unidentified product and, in methanol, only starting material was recovered. In t - butanol, a low yield of product was obtained which was partly starting material, possibly contaminating the required hydrogenolysed product. The n.m.r. spectrum showed the absorptions of the starting material together with an additional C - Me peak and an additional singlet peak close to the H-1 singlet of the starting material. This difficulty in effecting hydrogenolysis is possibly due to steric hindrance at the C_3 - S bond by the phenyl and methyl substituents at C-2 and C-4.

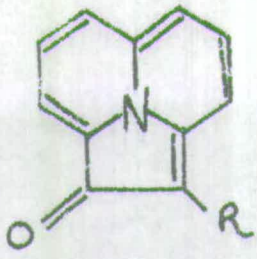


(78)

a. R = CO_2Et

b. R = CN

$PhNO_2$, 210°

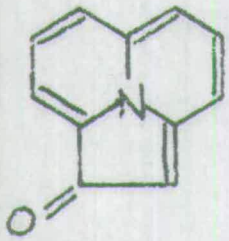


(79)

a. R = CO_2Et

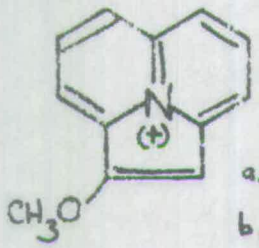
b. R = CN

6N HCL



(81)

CH_3OSO_2F

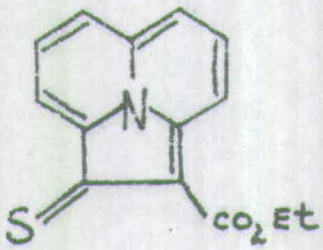


a. $CLO_4^{(-)}$

b. $SO_3F^{(-)}$

(222)

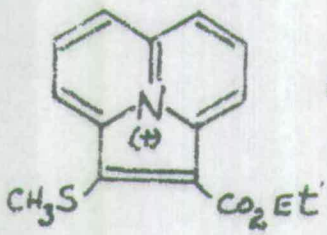
P_2S_5



(216)

1) CH_3I

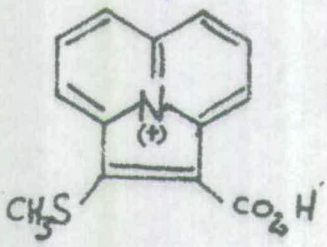
2) $HCLO_4$



$CLO_4^{(-)}$

(217)

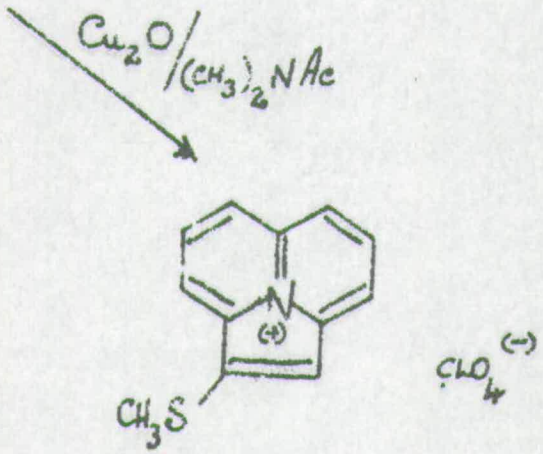
H_2O | HCL



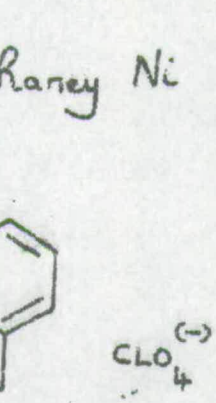
$CLO_4^{(-)}$

(218)

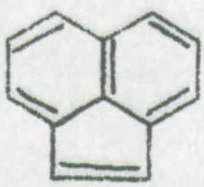
(218)



(219)



(220)



(221)

Scheme 38

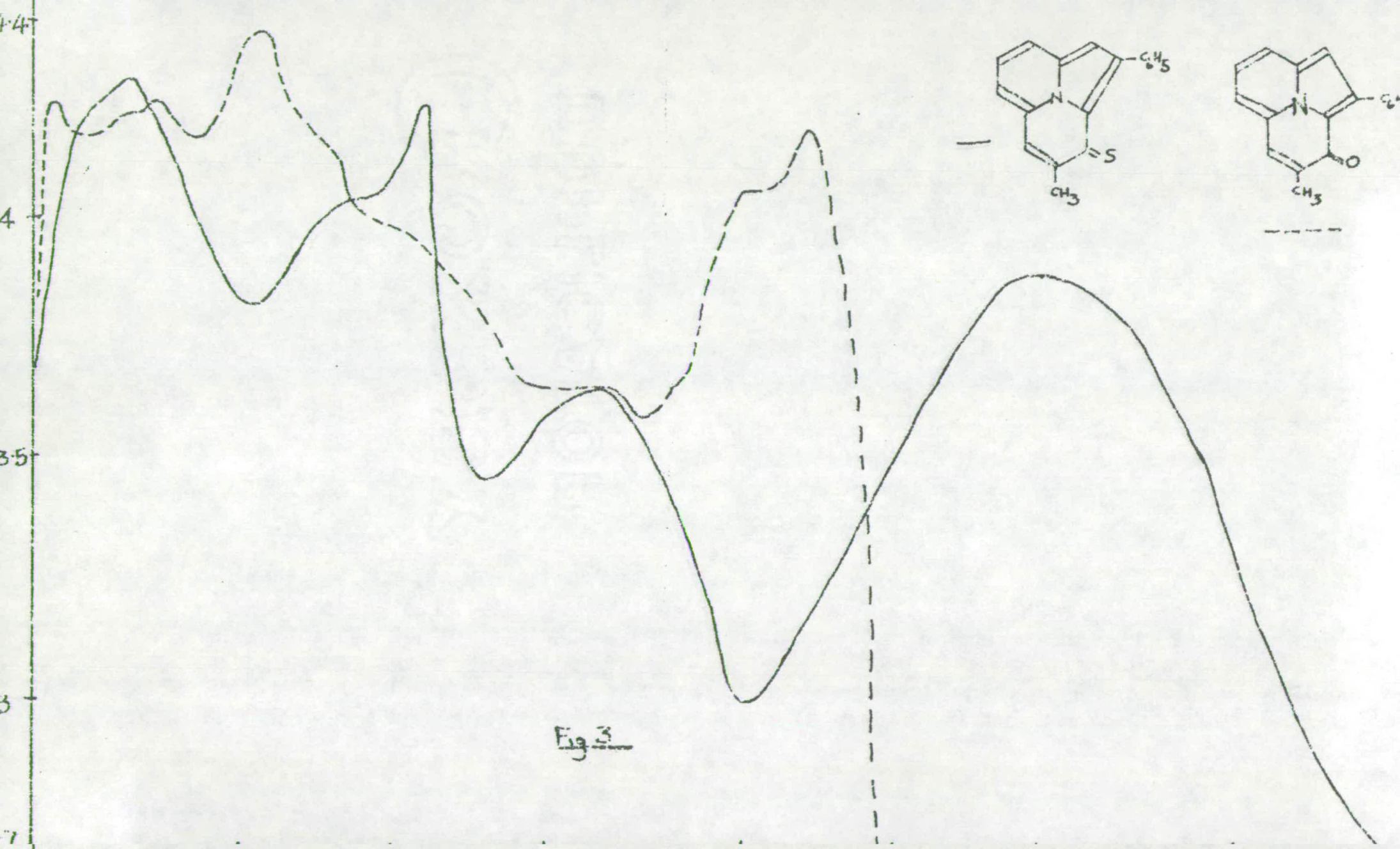


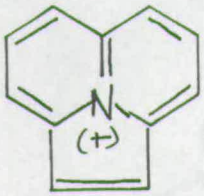
Fig 3

SECTION 4a

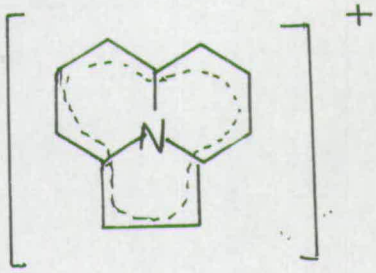
SYNTHESIS OF THE CYCL [3, 3, 2] AZINE SYSTEM FROM QUINOLIZINE PRECURSORS AND REACTIONS OF CYCL [3, 3, 2] AZINIUM SALT.

Farquhar [112] found that heating diethyl quinolizine - 4 - ylidene malonate (78, R = CO_2Et; scheme 38) in boiling nitrobenzene converted it into 2 - ethoxycarbonylcycl [3, 3, 2] azin-- 1 - one (79, R = CO_2Et) which gave the parent cyclazinone (81) when boiled with 6N.HCL. Using (79) as the starting material, Gough [122] was able to synthesise cycl [3, 3, 2] azinium perchlorate (220) by the route outlined in scheme 38. This involved treatment of the cyclazinone (79) with phosphorus pentasulphide, in chloroform at 40° and reaction of the resulting cyclazinethione (216) with methyl iodide followed by perchloric acid to give an 80% yield of 1 - methylthio - 2 - ethoxycarbonylcycl [3, 3, 2] azinium perchlorate (217). Hydrolysis of the ester groups with 6N hydrochloric acid followed by decarboxylation with freshly prepared cuprous oxide [170] in boiling dimethylacetamide gave 1 - methylthiocycl [3, 3, 2] azinium perchlorate (219) in 50% yield. Removal of the methylthio group was achieved by hydrogenolysis with specially prepared Raney-Nickel [122, 173] in ethanol, thus yielding cycl [3, 3, 2] azinium perchlorate (220) as a white solid in moderate yield. The n.m.r. spectrum of 220 showed a six-proton multiplet in the region τ 0.86 - 1.16 (H-3 to H-8) and a two-proton singlet at 1.17 τ (H-1 and H-2). The value of $J_{1,2}$ (5.4 ± 0.2 Hz), found from a ^{13}C side-band of the H-1,2 signal, was even larger than that in the isoelectronic system of acenaphthylene (221) ($J_{1,2}$ = 5.20 ± 0.1 Hz) [153] in which the 1, 2 - bond has been shown to be essentially olefinic, being only weakly involved in the aromatic system. It was also found [122] that the u.v. spectrum of the cyclazinium salt was similar to that of acenaphthylene [172]

suggesting that there is little delocalisation of the π - electrons around the peripheral ring. It would therefore seem that the cycl [3, 3, 2] azinium cation is best regarded as an azonia - acenaphthylene (222) rather than as a 10 π - electron cation (223) with a central nitrogen atom.



(220)



(223)

It would be expected that the 1, 2 - bond in cycl [3, 3, 2] azinium perchlorate should undergo addition reactions similar to those of the 1, 2 - bond in acenaphthylene, except where the positive charge in the cyclazinium ion precludes this, e.g. electrophilic addition should be unfavourable. In view of this Gough [122] attempted to carry out Diels- Alder addition (with isoprene) and di-imide reduction since these are concerted electrocyclic processes in which the double bond of acenaphthylene participates, and they should be relatively unaffected, perhaps slightly facilitated, by a reduction in electron-density. However, in both these reactions the cyclazinium salt was recovered in good yield and no products could be detected.

Nucleophilic substitution, to give a product believed to be a cyclazinethione, was achieved in low yield, using sodium sulphide, but the precise constitution of this product was not elucidated.

In order to obtain more of the cyclazinium salt for studies of its chemical reactivity, the synthesis developed by Gough was repeated. Substitution of 1, 2, 4 - trichlorobenzene for nitrobenzene, in the

conversion of the ylidenemalonate (78) to the ethoxycarbonylcyclazinone (79), gave essentially the same yield (75 - 84%) but all other attempts to improve on Gough's procedures were unsatisfactory. The cyanoester (78, R = CN) was also cyclised in nitrobenzene to give the 2 - cyanocycl [3, 3, 2] azin - 1 - one (60%) as an orange solid.

In view of Gough's failure to obtain a Diels-Alder adduct with isoprene, it seemed desirable to try a reaction with a more reactive, and possibly more electron-rich diene. 1, 3 - Diphenylisobenzofuran was chosen for this purpose but again no reaction occurred, the cyclazinium salt being receovered in good yield after being heated with the diene in boiling 2 - methoxyethanol for twenty-four hours. This negative result does not support the conclusion, based on n.m.r. evidence, that the 1, 2 - bond is essentially double in character and suggests that vicinal proton coupling constants may not, in some cases, give a reliable measure of carbon-carbon bond-order.

A reaction of the cyclazinium salt (220) with sodium sulphide, in dimethylformamide, as described by Gough [122], gave a small amount of red material, which appeared to be the same as Gough's presumed cyclazinethione, but the amount was again insufficient for characterisation.

Jessep [126] prepared 1 - ethoxycycl [3, 3, 2] azinium fluoborate by reaction of cycl [3, 3, 2] azin - 1 - one (81) with triethyloxonium fluoroborate and showed that the salt reacts with sodium sulphide in dimethylformamide to give a mixture of cyclazinethiones. The ethoxy - group was not displaced in this reaction but the position of the thione group in the two components of the mixture was not determined with certainty; it was suggested, on the basis of n.m.r. evidence, that the products were the 1 - ethoxycycl [3, 3, 2] azine - 5 - and 6 - thiones.

In order to study Jessep's reaction further and to determine the positions of substitution in the cyclazine ring, the analogous 1 - methoxycycl [3, 3, 2] azinium fluorosulphonate (222) was prepared by reaction of the ketone (81) with methyl fluorosulphonate. The n.m.r. spectrum of this salt (in T.F.A.) showed a complex, but well resolved six-proton multiplet in the region 0.98 τ to 1.4 τ (H-3, 4, 5, 6, 7 and 8), a one-proton singlet at τ = 2.68 (H-2) and a three-proton singlet at τ = 5.6 (OMe). Treatment of the fluorosulphonate with perchloric acid gave a quantitative yield of the corresponding perchlorate.

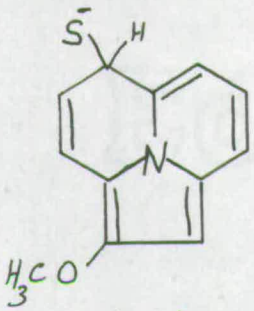
The perchlorate reacted with sodium sulphide in aqueous dimethylformamide to give a deep red - purple solid, the n.m.r. spectrum of which showed a methoxy signal and six other protons. It was thus apparent that, as in Jessep's reaction, a thione group had been introduced at a position other than that occupied by the alkoxyl group. In contrast to Jessep's product, which was oily and highly light sensitive, the methoxy - compound was obtained as a stable solid. The product was believed to be a mixture of the 1 - methoxycycl [3, 3, 2] azin - 3 - and - 6 - thiones based on a more detailed interpretation of the n.m.r. spectrum and other considerations, as detailed below .

(a) A singlet at τ 3.4 which was well-separated from the other signals on the high field side, had less than one-third of the integrated intensity of the methoxyl signal but, when taken together with a smaller singlet at τ 2.5, the total intensity was equivalent to one proton. These two singlets are assigned to H-2 in two isomeric compounds, the deshielding of the smaller one being attributed to the proximity of H-2 to the thiocarbonyl group in the 3 - thione.

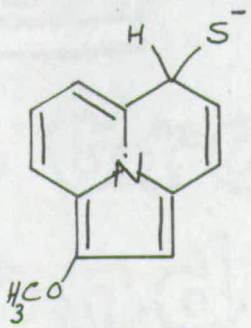
(b) A doublet of doublets at τ 0.95, which was well separated from the

other signals on the low-field side, had the same integrated intensity as the singlet at τ 3.4. Since this signal showed both o - and m - coupling it was clearly due to a proton in one of the six-membered rings and its low-field position is again attributed to proximity to the thiocarbonyl group. This interpretation is applicable to either H-5 of the 6 - thione or H-6 of the 5 - thione.

(c) Consideration of the structures of the presumed Wheland intermediates (224), leading to the 6 - thione and, (225), leading to the 5 - thione, suggests that (224) is the more stable; both intermediates contain an indolizine



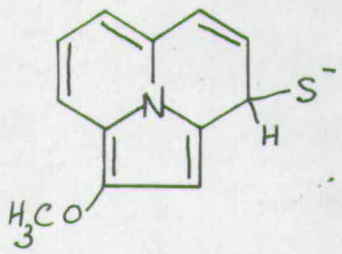
(224)



(225)

system but that of (225) has an electron-releasing methoxyl group attached to the relatively electron-rich 1 - position (indolizine numbering). It follows that the 6 - thione should be formed via a lower energy pathway and it is thus considered to be the more likely product.

(d) The lack of splitting in the methoxyl signal is consistent with the absence of a thiocarbonyl group at the 8 - position in either of the isomers. Had such a group been present in one isomer, it would be expected to have shifted the methoxyl resonance downfield in that isomer relative to the other. The fact that the 3 - thione appears to be formed in preference to the 8 - thione, despite the presence of the electronically unfavourable 1 - methoxyindolizine system in the corresponding Wheland intermediate (226), may

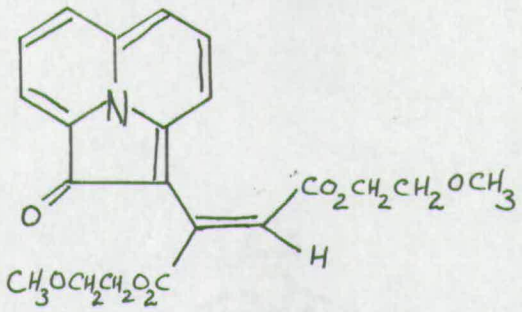


(226)

perhaps be attributed to steric hindrance by the methoxyl groups during attack by sulphide ion at the 8 - position.

As part of the general investigation of reactivity in the cycl [3, 3, 2] azine system, cycl [3, 3, 2] azin - 1 - one was subjected to attempted electrophilic substitution. Attempted nitration with copper nitrate in acetic anhydride or with tetranitromethane in pyridine failed, as did attempted formylation with NN - dimethylformamide - phosphorylchloride in dry benzene. A type of electrophilic substitution that often occurs under mild, non-acidic conditions in electron-rich systems, is the reaction with dimethyl acetylenedicarboxylate. In protic solvents, such reactions usually lead to the introduction of a fumarate or maleate group in place of a hydrogen atom. Aprotic solvents, on the other hand, tend to favour cycloaddition reactions (see section 3). Reaction of cycl [3 3, 2] azin - 1 - one with dimethyl acetylenedicarboxylate in aprotic solvents such as chlorobenzene or Toluene gave only a poor yield of uncharacterised 2 : 1 adduct (M^+ = 453), while in 2 - methoxyethanol a red solid (3%) was obtained (M^+ = 399). The n.m.r. spectrum of this product showed a complex six-proton aromatic region (τ 1.7 - 2.4) and a one-proton singlet at τ 2.76 attributable to the vinylic proton of a fumarate side-chain. The higher field portion of the spectrum showed two triplets at τ 5.38 and 5.68 (two protons each), a five-line multiplet (overlapping triplets) centred at τ 6.28 (four protons),

and two methyl singlets at $\tilde{\tau}$ 6.56 and 6.61. These signals show the presence of two 2 - methoxyethyl groups which must have been introduced by ester exchange with the solvent.



(227)

Structure (227) is assigned to this compound, the fumarate side-chain being placed at position - 2 in order to account for the lack of a second one-proton singlet (H-2) near the vinylic singlet. A similar product was obtained when the reaction was carried out in methanol. In this case there was no possibility of ester-exchange but the product was not obtained analytically pure.

EXPERIMENTAL

GENERAL NOTES

1) Melting points were recorded on a Kofler hot-stage apparatus and are not corrected.

   Boiling points are not corrected.

2) Microanalyses were determined by Mr. B. Clark of this department or by the National Physical Laboratory.

3) Infra-red spectra were recorded on a Unicam S.P.200 spectrophotometer.

4) Ultraviolet and Visible spectra were recorded on a Unicam S.P.800 spectrophotometer.

5) Nuclear Magnetic Resonance spectra were recorded on a Varian Associates H.A.100 (100 MHz) spectrometer using tetramethylsilane as internal standard. Unless otherwise stated deuteriochloroform was used as solvent.

6) Mass Spectra were recorded on an A.E.I. M.S.902 double-focussing mass spectrometer.

7) Alumina for chromatography was Spence Type 'H'; x% deactivated alumina refers to Type H alumina which had been shaken for twelve hours with 5% aqueous acetic acid (x ml per 100g alumina).

8) Thin-layer plates for preparative chromatography were prepared using Kieselgel 0.08mm (Merck).

9) Solvents were dried over anhydrous magnesium sulphate or molecular sieve type 4A ($^1/_{16}$" pellets).

SECTION 1

A) OXIDATIVE CYCLISATION OF 3 - (1 - DIMETHYLAMINO - 2, 3 - DIMETHOXYCARBONYLBUTA - 1, 3 - DIEN - 1 - YL) INDOLIZINES.

Reactions of indolizines with dimethylacetamide and phosphoryl chloride (method slightly modified from that of Gibson [118]).

a) 2 - Phenylindolizine (89.8g) and NN^1 - dimethylacetamide (89.8ml) were dissolved in 1,000cc of sodium-dried benzene in a three-necked flask equipped with a mechanical stirrer, dropping funnel and condenser with a calcium chloride drying tube. Phosphoryl chloride (51.2ml) was added to the refluxing solution, through the dropping funnel, at such a rate that the reaction did not become too vigorous. The refluxing mixture was stirred for a further fifteen minutes, after the addition of the phosphoryl chloride, cooled, and ether added to precipitate as much of the product as possible. The ether-benzene layer was decanted off and methanol (20ml) added to the resultant oil, followed by perchloric acid (70%) until precipitation of the salt was complete. Filtration gave 126.5g (80%) of a yellow crystalline solid shown by infra-red and m.p. (237°C) to be the required 3 - (1 - dimethylamino ethylidene) - 2 - phenylindolizinium perchlorate (lit [118] m.p. 237°).

The same procedure was used in the following cases.

b) 1 - Methyl - 2 - phenylindolizine (18.4g) gave 3 - (1 - dimethylamino ethylidene) - 1 - methyl - 2 - phenylindolizinium perchlorate (11.9g; 50%).

c) 1, 2 - Dimethylindolizine (3g) gave 3 - (1 - dimethylaminoethylidene) - 1, 2 - dimethylindolizinium perchlorate (5.2g).

d) 2 - Methylindolizine (3g) gave 3 - (1 - dimethylaminoethylidene) - 2 - methylindolizinium perchlorate (5.4g).

e) The reaction of 5 - methyl - 2 - phenylindolizine with dimethylacet-

amide and phosphoryl chloride was carried out exactly as described by Gibson [118] to yield a mixture (82%) of the 1 - and 3 - dimethylaminoethylideneindolizinium perchlorates.

Preparation of 3 - (1 - dimethylaminovinyl) - 5 - methyl - 2 - phenylindolizine.

The mixture of perchlorates, from (e) above, was hydrolysed with aqueous - ethanolic sodium hydroxide, as described by Gibson [118], and the resulting mixture of 3 - dimethylaminovinyl and 1 - acetyl compounds was separated by chromatography.

Preparation of other 3 - (1 - dimethylaminovinyl) indolizines. (Method slightly modified from that of Gibson [118]).

a) 3 - (1 - Dimethylaminoethylidene) - 2 - phenylindolizinium perchlorate (121.5g) was dissolved in the minimum amount of dimethylformamide and an excess of cold 2N aqueous sodium hydroxide and 400ml ether added and the mixture well shaken. The ether layer was separated off, and the aqueous layer extracted with 2 x 200ml ether. The ether extracts were combined, washed with water, dried over anhydrous magnesium sulphate, and the ether removed to give the enamine as a cream solid (50g; 80%), m.p. 98-99° (from ethanol) (Lit [118] m.p. 98.5 - 99.5°).

b) The 1 - methyl - 2 - phenylindolizinium salt (113c) was converted by the same procedure into 3 - (1 - dimethylaminovinyl) - 1 - methyl - 2 - phenylindolizine (7g; 95%) as a cream solid.

c) By keeping the temperature of the solution at -7°C, to avoid hydrolysis of the enamines, the same procedure was used to convert 1, 2 - dimethyl - , 2 - methyl - and 2, 6 - dimethyl - 3 - (dimethylaminoethylidene) indolizinium perchlorates into their corresponding enamines in high yield.

Reaction of 3 - (1 - dimethylaminovinyl) - 2 - phenylindolizine with dimethyl acetylenedicarboxylate.

a) In benzene

The indolizine (35g) was dissolved in the minimum amount of benzene and to this solution was added dimethyl acetylenedicarboxylate (20g) in benzene (5ml). The mixture was left at room temperature for twenty-four hours, the resulting dark red solution concentrated, and then chromatographed on 3% deactivated alumina.

Benzene - ether (4 : 1) elution gave a single red band from which a red oil was obtained. Trituration with light petroleum (60/80) - ethanol gave a yellow crystalline solid (36g ; 70%), m.p. 133 - 135°, n.m.r. spectrum idential with that of an authentic sample [118] of 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) - 2 - phenylindolizine (121a).

b) In methanol

The enamine (114b) (5g.) and dimethyl acetylenedicarboxylate (3g) in methanol (30ml) were allowed to react at room temperature for twenty-four hours. Evaporation and chromatography on 3% deactivated alumina with benzene - ether elution gave two bands :

1) an initial yellow band which yielded a yellow crystalline solid, characterised by n.m.r. comparison with an authentic sample [118] as 3 - (1 - dimethylamino - 3, 4 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) - 2 - phenylindolizine (122a), (1.6g ; 20%).

2) a red band which yielded a red crystalline solid (0.8g ; 7%), m.p. 165 - 166° (from ethanol containing a traceeof methanol), M^+546. The n.m.r. spectrum (see discussion) indicated that this was probably tetramethyl 3 - [dimethylamino (2 - phenylindolizin- 3 - yl) methylene] penta - 1, 4 - diene - 1, 2, 4, 5 - tetracarboxylate (153a) with a

cis - cis configuration based on the olefinic absorptions.

Analysis

found : C, 65.8 ; H, 5.6 ; N, 5.3%

$C_{30}H_{30}N_2O_8$ requires : C, 66.0 ; H, 5.5 ; N, 5.1%

Reaction of 3 - (1 - dimethylamino - 3, 4 - dimethoxycarbonylbuta dienyl) - 2 - phenylindolizine (122a) with dimethyl acetylenedicarbox ylate in methanol.

The adduct (122a) (1g) was dissolved in methanol (30ml) and dimethyl acetylenedicarboxylate (0.35g) was added and the mixture left at room temperature for twenty-four hours. Chromatography of the product gave two fractions :

1) starting material (122a) (0.4g)

2) the 2 : 1 adduct (153a) (0.112g)

Reaction of 3 - (1 dimethylaminovinyl) - 1 - methyl - 2 - phenylindolizine with dimethyl acetylenedicarboxylate

a) In benzene

To the enamine (4.5g), in benzene, was added dimethyl acetylene-dicarboxylate (2.1g) and the mixture was left at room temperature for twenty-four hours giving a deep red solution which was concentrated and chromatographed on 3% deactivated alumina. Benzene elution gave a single red band which afforded a red oil (4.5g ; 50%) that could not be crystallised. By spectroscopic comparison with an authentic sample this was identified as 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbon ylbuta - 1, 3 - dien - 1 - yl) - 1 - methyl - 2 - phenylindolizine (121c).

b) In methanol

The enamine (2.5g) was allowed to react, as above, with dimethyl acetylenedicarboxylate (1.5g) in the minimum volume of methanol.

Chromatography with benzene - ether (4 : 1) elution gave two red bands :

1) a red band which yielded a red crystalline solid (0.63g), m.p. 170 - 171° (from methanol), M^+560.

2) a red band which yielded a bright red solid (0.13g), m.p. 150 - 151° (from methanol), M^+560.

The n.m.r. spectra of both solids showed an absorption pattern indicative of an indolizine nucleus at 2.2 - 3.6 τ , four ester - CH_3 absorptions in the region 6.2 - 7.1 τ , one $N(CH_3)_2$ signal at 7.3 τ , one ring - CH_3 at 7.7 τ , and two olefinic absorptions at 4.6 and 4.7 τ [for fraction (2)] and at 3.1 and 5.0 τ [for fraction (1)]. On the basis of the olefinic absorptions the fractions (1) and (2) were assigned the structure (153b) with a 1, 2 - cis - 4, 5 - trans and a 1, 2 - cis - 4, 5 - cis configuration, respectively, of the methoxycarbonyl groups in the penta - 1, 4 - diene system, i.e. tetramethyl - 3 - [dimethylamino - (1 - methyl - 2 - phenylindolizin - 3 - yl) methylene] penta - 1, 4 - diene - 1, 2, 4, 5 - tetracarboxylate.

Analysis

Found for fraction (1) : C, 65.8 ; H, 5.8 ; N, 5.0%

(2) : C, 66.8 ; H, 6.0 ; N, 5.0%

$C_{31}H_{32}N_2O_8$ requires : C, 66.4 ; H, 5.7 ; N, 5.0%

On repeating this experiment the enamine (5.7g) gave mainly the 1 : 1 adduct (122c) (6.7g) as an orange solid, m.p. 108°, (lit. [118] m.p. 108-109°) and smaller amounts of the 2 : 1 adducts (0.2g).

Reactions of the mono - and di - alkyl - 3 - (1 - dimethylaminovinyl) indolizines with dimethyl acetylenedicarboxylate in benzene.

The procedure used was identical with that for the corresponding reactions of 3 - (1 - dimethylaminovinyl) - 2 - phenylindolizine.

a) 3 - (Dimethylaminovinyl) - 2 - methylindolizine (1.2g), on reaction

with dimethyl acetylenedicarboxylate and chromatography, gave

1) a yellow band which gave a yellow solid (0.02g), m.p. 142-143 (from methanol), M^+ 439, τ 2.6 - 3.8 (5H, m, indolizine nucleus), 6.0 (6H, s, 2 x OMe), 6.6 (6H, s, 2 x Ome), 7.95 (3H, s, C-Me), 1.2 (1H, s, ArH ortho to two CO_2Me groups). On this basis the compound was identified as 3 - (2, 3, 5, 6 - tetramethoxycarbonylphenyl) - 2 - methylindolizine, formed by Diels-Alder addition to the initial 1 : 1 adduct and loss of dimethylamine.

Analysis

found : : C, 62.6 ; H, 4.9 ; N, 3.0%

$C_{23}H_{21}NO_8$ requires : C, 62.9 ; H. 4.8 ; N, 3.2%

2) a yellow band that gave a red oil (1.2g ; 60%) characterised by n.m.r. analysis [118] as 3 - (1 - dimethylamino - 2, 3 - dimethoxy carbonylbuta - 1, 3 - dien - 1 - yl) - 2 - methylindolizine (121b).

Similarly the 1, 2 - dimethylenamine (114d), and the 2, 6 - dimethyl enamine (114f) gave good yields of the 1 : 1 adducts (147a) and (147c), and the 5 - methyl - 2 - phenyl compound (114a) gave a 40% yield of (147d). These compounds were oils which were not analysed. Their n.m.r. spectra were consistent with the assigned structures.

Preparation of 1, 2 - dimethoxycarbonyl - 4 - phenylcyclopenta [c] quinolizine. (118a).

The butadienylindolizine (121a) (3g) was dissolved in 2 - methoxyethanol (30ml) and the solution was heated under reflux for three and a half hours. Solvent was removed and the residual oil chromatographed on alumina with benzene - ether (2 : 1) elution. Collection of the orange band, evaporation, and recrystallisation from ethanol gave the required product as an orange solid (1.65g., 60%), m.p. 175-176°

(lit [118] m.p. 175 - 176°). This procedure, using 2 - methoxyethanol, gave a cleaner product in a shorter time than Gibson's method, using toluene.

Preparation of 2, 3 - dimethoxycarbonyl - 5 - methyl - 4 - phenylcyclo penta [c] quinolizine.

The butadienylindolizine (122c) (2g) was heated under reflux in 2 - methoxyethanol (30ml) for nine hours. Subsequent chromatography on alumina and collection of the yellow band gave the required product [118] (123c) as a red solid (0.23g).

Running this reaction in sulphur-free xylene, as described by Gibson [118] produced only decomposition products.

Reaction of 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) - 1 - methyl - 2 - phenylindolizine (121c) with oxidising agents.

a) With potential hydride - abstracting reagents.

Heating the indolizine with chloranil in boiling tetrachloroethylene led to decomposition and no product could be isolated. Heating with phenanthraquinone, under the same conditions, or with tropylium fluoroborate in boiling 2 - methoxyethanol gave only the thermal re-arrangement product (118c).

b) With potassium ferricyanide.

The indolizine (0.74g) and potassium ferricyanide (1.08g) were heated at 100° in dimethyl sulphoxide. (The ferricyanide was not completely soluble). T.L.C. showed a trace of the dimethylaminocyclopenta [c] quinolizine, along with thermalrearrangement product, but the amount was insufficient to be isolated.

c) With 2, 3, 5 - triphenyltetrazolium chloride.

1) In methanol.

Heating the reactants in methanol [as in (2) below] gave only a

low yield of the thermal rearrangement product (118c).

2) In 2 - methoxyethanol.

The indolizine (4.5g) and an equimolar amount of triphenyltetrazolium chloride (3.27g) were heated together under reflux, in 2 - methoxyethanol for two hours. Solvent was removed and the residual oil taken up in the minimum amount of benzene and chromatographed on alumina. Benzene - ether (4 : 1) elution gave four fractions :

i) a red band that gave a dark red solid (m.p. 158 - 160°) identified by melting point and mixed melting point as triphenylformazan [133] (135).

ii) a yellow band that gave (1.05g ; 31%) of the "thermal rearrangement product" (118c).

iii) a brown band that gave a brown crystalline solid (0.14g ; 4%), m.p. 191 - 192° (from ethanol), identified by comparison of its m.p., infra-red, and n.m.r. spectra with those of an authentic specimen prepared by Farquhar [132] (for which good analytical data had been previously obtained) as 3 - dimethylamino - 1, 2 - dimethoxycarbonyl - 5 - methyl - 4 - phenylcyclopenta [c] quinolizine (129).

iv) a red band that gave a red solid (0.335g ; 8%), m.p. 156°, identified by comparison of its n.m.r. spectrum with that of Gibson's specimen [118] as 1 - dimethylamino - 2, 3 - dimethoxycarbonyl - 5 - methyl - 4 - phenylcyclopenta [c] quinolizine (130) (lit. [118] m.p. 156°).

3) In nitromethane.

Only the 1 - dimethylamino - compound (130 ; 3%) was isolated from the reaction mixture.

Reaction of 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) - 2 - phenylindolizine (121a) with triphenyltetrazolium chloride.

The indolizine (3g) and triphenyltetrazolium chloride (2.39g) were heated under reflux in 2 - methoxyethanol (30ml) for ninety minutes. Chromatography on alumina with benzene - ether (4 : 1) elution gave three fractions :

i) a red band that gave triphenylformazan [133] m.p. 156° (0.97g).

ii) a brown band that gave a red solid (0.87g ; 22%) identified as 3 - dimethylamino - 1, 2 - dimethoxycarbonyl - 4 - phenylcyclopenta [c] quinolizine (130), m.p. 157°, mixed m.p. 156 - 158°, infra-red and n.m.r. spectra identical with those of a specimen synthesised by treatment of (118a) with N - chlorodimethylamine.

iii) an orange band that gave an orange solid (1.2g ; 37%) identified from its m.p. (175°), and infra-red and n.m.r. spectra as the thermal rearrangement product [118] (118a).

Reaction of 3 - (1 - dimethylamino - 3, 4 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) - 2 - phenylindolizine (122a) with triphenyltetrazolium chloride.

The reaction was carried out under the same conditions as for the isomeric adduct (121a) (see previous experiment) but, since t.l.c. showed only dark products of decomposition, the reaction mixture was not worked up.

Attempted reaction of 1, 2 - dimethoxycarbonyl - 4 - phenylcyclopenta [c] quinolizine with dimethylamine in the presence of triphenyltetrazolium chloride.

a) The quinolizine (1g) and the tetrazolium salt (0.56g) were heated under reflux in 2 - methoxyethanol and dimethylamine (0.06g), in 2 - methoxyethanol, was added dropwise. Evaporation and chromatography

Reaction of 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) - 2 - phenylindolizine (121a) with triphenyltetrazolium chloride.

The indolizine (3g) and triphenyltetrazolium chloride (2.39g) were heated under reflux in 2 - methoxyethanol (30ml) for ninety minutes. Chromatography on alumina with benzene - ether (4 : 1) elution gave three fractions :

i) a red band that gave triphenylformazan [133] m.p. 156° (0.97g).

ii) a brown band that gave a red solid (0.87g ; 22%) identified as 3 - dimethylamino - 1, 2 - dimethoxycarbonyl - 4 - phenylcyclopenta [c] quinolizine (130), m.p.157°, mixed m.p. 156 - 158°, infra-red and n.m.r. spectra identical with those of a specimen synthesised by treatment of (118a) with N - chlorodimethylamine.

iii) an orange band that gave an orange solid (1.2g ; 37%) identified from its m.p..(175°), and infra-red and n.m.r. spectra as the thermal rearrangement product [118] (118a).

Reaction of 3 - (1 - dimethylamino - 3, 4 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) - 2 - phenylindolizine (122a) with triphenyltetrazolium chloride.

The reaction was carried out under the same conditions as for the isomeric adduct (121a) (see previous experiment) but, since t.l.c. showed only dark products of decomposition, the reaction mixture was not worked up.

Attempted reaction of 1, 2 - dimethoxycarbonyl - 4 - phenylcyclopenta [c] quinolizine with dimethylamine in the presence of triphenyltetrazolium chloride.

a) The quinolizine (1g) and the tetrazolium salt (0.56g) were heated under reflux in 2 - methoxyethanol and dimethylamine (0.06g), in 2 - methoxyethanol, was added dropwise. Evaporation and chromatography

gave starting material but no trace of its 3 - dimethylamino - derivative.

b) The experiment was repeated using dimethylammonium chloride (0.25g) (added initially) in place of dimethylamine and the same result was observed.

Preparation of N - chlorodimethylamine.

To sodium hypochlorite (2.5$\bar{N}$; 240ml), in an ice bath, containing ice (20g) and ether (200ml), was added aqueous dimethylamine (9g ; 36ml), slowly with stirring during five minutes. The two layers were thoroughly mixed and the organic layer was then separated. The aqueous layer was extracted with ether (2 x 100ml). The ether extracts were combined and washed with cold 8% sulphuric acid (25ml) and 5% sodium hydroxide (25ml) and then dried over anhydrous calcium chloride. The dessicant was filtered off and washed with dry ether (50ml) giving a final volume of 435ml.

Titration (iodine - thiosulphate) gave the concentration of N - chlorodimethylamine in this solution as 0.1g/5ml.

Reaction of 1, 2 - dimethoxycarbonyl - 4 - phenylcyclopenta [c] quinolizine (118a) with N - chlorodimethylamine.

[A similar experiment had been carried out previously by Farquhar [132] but he had obtained only compounds (137) and (138)].

N - Chlorodimethylamine (10ml ethereal solution ; 0.2g) was added to the cyclopenta [c] quinolizine (1g) in dichloromethane (20ml) and the mixture was left at room temperature for thirty minutes. The resulting dark solution was washed with aqueous potassiumcarbonate and dried over anhydrous magnesium sulphate. The solvent was removed and the residual oil was taken up in ether and chromatographed on alumina with ether elution to give five fractions :

a) a brown band that gave a brown solid (0.1g ; 10%), m.p. 156 - 158°

(from ethanol), M^+402, identified from its n.m.r. and mass spectra as 3 - dimethylamino - 1, 2 - dimethoxycarbonyl - 4 - phenylcyclopenta [c] quinolizine (136), τ - 0.6 (1H, d, H-9), 2.2 - 2.8 (8H, m, H-6, 7, 8 and Ph), 2.95 (1H, s, H-5), 6.13 (3H, s, OMe), 6.19 (3H, s, OMe), 7.67 (6H, s, NMe_2).

Analysis

found : C, 71.2 ; H, 5.5 ; N, 7.1%

$C_{24}H_{22}N_2O_4$ requires : C, 71.6 ; H, 5.5 ; N, 7.0%

b) a red band that gave a red solid (0.22g), m.p. 186-187° (from ethanol), M^+, 395 ; 393 identified as 3 - chloro - 1, 2 - dimethoxycarbonyl - 4 - phenycyclopenta [c] quinolizine (137), infra-red and n.m.r. spectra identical with those of Farquhar's specimen (m.p. 186-187°) for which good analytical figures had been obtained previously.

c) a red band that gave a red solid m.p. > 250°, (0.015g), (found M^+, 730, $C_{45}H_{34}N_2O_8$ requires : M 730). The compound was identified as di - (1, 2 - dimethoxycarbonyl - 4 - phenylcyclopenta [c] quinolizin - 3 - yl) methane (139) by comparison with a specimen prepared by Farquhar [132]. The latter had been synthesised by reaction of (118a) with bis (dimethylamino) methane, in the presence of sulphuric acid, and satisfactory analytical results had been obtained.

d) a yellow band that gave an orange solid (0.03g), m.p. 143-144° (from ethanol), M^+416, identified as 3 - (N,N - dimethylaminomethyl) - 1, 2 - dimethoxycarbonyl - 4 - phenycyclopenta [c] quinolizine (138) from its n.m.r. spectrum (see discussion) and by comparison of its m.p. and infra-red spectrum with those of Farquhar's specimen which had previously yielded satisfactory analytical data.

e) an orange band that gave starting material (0.19g).

Reaction of 3, 4 - dimethoxycarbonyl - 5 - methyl - 4 - phenylcyclopenta [c] quinolizine (123c) with N - chlorodimethylamine.

[This experiment had been carried out previously by Farquhar [132] but repetition was considered worthwhile in the hope of obtaining an authentic sample of the 1 - dimethylamino - compound (130)].

N - Chlorodimethylamine (2.3ml ethereal solution) was added to a saturated solution of the cyclopenta [c] quinolizine (0.23g) in dichloromethane. After thirty minutes at room temperature, a further quantity (2.3ml) of ethereal N - chlorodimethylamine was added and the solution was left for one hour. Evaporation and trituration with benzene gave starting material (0.056g), the filtrate from which was chromatographed on alumina. Elution with ether gave two fractions :

a) the 1 - chloro - compound (137a), (0.038g), m.p. 168-169°, identical with Farquhar's specimen which had previously yielded satisfactory analytical results.

b) starting material (0.035g).

Preparation of sodium ferricyanide.

Potassium ferricyanide (5g) was dissolved in sufficient water to give a saturated solution. To this stirred solution, a three-fold excess of sodium perchlorate (5.6g) was added and the mixture stirred at room temperature until precipitation of the insoluble potassium perchlorate was complete. The precipitate was filtered off and the filtrate was evaporated to give the required sodium ferricyanide as an orange crystalline solid.

Reactions of 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) - 2 - phenylindolizine (121a) with oxidising agents.

General procedure - The indolizine (1g), in 2 - methoxyethanol (30ml)

was heated under reflux with the oxidant (no. of molecular equivalents as stated) for the time stated. The solvent was evaporated under reduced pressure and the residue was chromatographed on alumina, eluting with ether. The products obtained are detailed below for each experiment.

a) Silver (I) acetate (1 molecular equivalent ; heated for one hour).

Products : (i) 3 - dimethylamino - compound (136) (0.01g ; 1%)

(ii) thermal rearrangement product (118a) (0.04g)

b) Iron(III) chloride (anhydrous) (1 molecular equivalent ; heated for one hour).

Products : (i) 3 - dimethylamino - compound (136) (0.015g ; 1.5%)

(ii) thermal rearrangement product (118a) (0.047g)

(iii) a brown solid (M^+,446) (trace), believed to be a transesterification product (145b) of the 1 - dimethylamino - compound.

(iv) a yellow solid (M^+,403) (0.008g) identified as a transesterification product (145a) of (118a).

c) Copper (II) chloride (hydrate) (1 molecular equivalent ; heated for one hour).

Products : traces of (136), (118a), and (145a).

d) Copper (II) acetate (1 molecular equivalent ; heated for forty minutes).

Products : (i) 3 - dimethylamino - compound (136) (0.13g ; 13%)

(ii) thermal rearrangement product (118a) (0.5g)

e) Copper (II) acetate (2 molecular equivalent ; heated for forty minutes).

Products : (i) 3 - dimethylamino - compound (136) (0.24g ; 24%)

(ii) thermal rearrangement product (118a) (0.23g)

f) Copper (II) acetate (3 molecular equivalent ; heated for forty minutes).

Products : (i) 3 - dimethylamino - compound (136) (0.3g ; 30%)

(ii) thermal rearrangement product (118a) (0.05g)

g) N,N^1 - Dimethyl - 4, 4^1 - dipyridylium di - iodide and N,N^1 - Ethylene - 2, 2^1 - dipyridylium dibromide. (1 molecular equivalent ; heated for one hour).

Product : thermal rearrangement product (118a) only.

h) Sodium ferricyanide (1 molecular equivalent ; heated for forty minutes.)

Products : (i) 3 - dimethylamino - compound (136) (0.17g ; 17%)

(ii) 1 - dimethylamino - compound (146) (trace) [see (i) below].

(iii) thermal rearrangement product (118a) (0.48g)

i) Sodium ferricyanide (3 molecular equivalent ; heated for thirty minutes).

Products : (i) 3 - dimethylamino - compound (136) (0.36g ; 36%)

(ii) 1 - dimethylamino - compound (146) (0.013g ; 1.3%)

(iii) thermal rearrangement product (118a) (0.005g)

Compound (146), m.p. 156-157 (from ethanol), was identified from its n.m.r. spectrum , - 1.22 (1H, d, H-9), 2.2-2.8 (8H, m, H-6, 7, 8 and Ph), 3.00 (1H, s, H-5), 6.11 (3H, s, OMe), 6.87 (3H, s, OMe), 7.08 (6H, s, NMe_2) and from its mass spectrometric molecular weight.

found : M^+, 402·1582

$C_{24}H_{22}N_2O_4$ requires : M, 402·1579

j) Sodium ferricyanide (4 molecular equivalent ; heated for twenty minutes).

Product : (136) only (10%).

k) Manganese (III) acetate [136] (1 molecular equivalent ; heated for one hour).

Product : (118a) only (0.53g)

1) Tris - (p - bromophenyl)aminium hexachloroantimonate [137]

(1 molecular equivalent ; heated for one hour).

Products : (i) 3 - dimethylamino - compound (136) (0.05g ; 5%)

(ii) transesterification product (145b) (trace)

(iii) thermal rearrangement product (118a) (0.006g)

(iv) transesterification product (145a) (0.25g)

m) Tris - (p - bromophenyl)aminium hexachloroantimonate in the presence of sodium acetate [as for (1)].

Products : (i) 3 - dimethylamino - compound (136) (0.002g)

(ii) thermal rearrangement product (118a) (0.4g)

Reactions of 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dienyl) indolizines with sodium ferricyanide.

General procedure - The indolizine (stated amount) and sodium ferricyanide (3 equivalents) were heated under reflux in 2 - methoxyethanol (30 - 50ml) for thirty to forty minutes. The solvent was evaporated and the residue was chromatographed on alumina. The products obtained are detailed below for each experiment.

a) 3 - (1 - Dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl)-1 - methyl - 2 - phenylindolizine (121c) (1.4g).

Product : 1 - dimethylamino - compound (130) (0.4g ; 24%). The column also showed a large amount of decomposition products.

b) 3 - (1 - Dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) 2 - methylindolizine (0.4g) (121b).

Products : (i) a red oil (0.203g ; 27%) identified as a mixture of 1 - dimethylamino - (149a) and 3 - dimethylamino - compounds (150a), which gave H-9 n.m.r. signals (dd) at -1.0 and -0.25 τ respectively. Measurement of the integral ratio of these two signals showed that the isomers were present in the ratio of 3 : 2.

(ii) thermal rearrangement product [118] (0.088g ; 18%)

c) 3 - (1 - Dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 dienyl) 1, 2 - dimethylindolizine (147c) (1g).

Products : (i) a red solid identified as 1 - dimethylamino - 2, 3 - dimethoxycarbonyl - 4, 5 - dimethylcyclopenta [c] quinolizine (149c) (0.045g ; 5%) m.p. 164-165° (from ethanol), τ - 1.3 (1H, dd, H-9), 2.0 - 2.9 (3H, m, H-6, 7 8) 6.15 (3H, s, OMe), 6.20 (3H, s, OMe), 7.15 (6H, s, NMe_2), 7.25 (3H, s, 4-Me), 7.50 (3H, s, 5-Me), the structure being assigned on the basis of the very low-field position of the H-9 signal.

Analysis

found : C, 67.9 ; H, 6.0 ; N, 7.7%, M^+, 354

$C_{20}H_{22}N_2O_4$ requires : C, 67.8 ; H, 6.2 ; N, 7.9%, M, 354

(ii) thermal rearrangement product [118] (148c) (0.324g ; 32%)

d) 3 - (1 - Dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) 2, 6 - dimethylindolizine.(147b) (1g)

Products : (i) a red solid identified as 1 - dimethylamino - 2, 3 - dimethoxycarbonyl - 4, 8 - dimethylcyclopenta [c] quinolizine (0.094 ; 6%) m.p. 164-165° (from methanol), τ - 0.95 (1H, s, H-9), 2.4 - 2.8 (2H, m, H-6, 7), 3.20 (1H, s, H-5), 6.1 (3H, s, OMe), 6.2 (3H, s, OMe), 7.15 (6H, s, NMe_2), 7.30 (3H, s, 4-Me), 7.60 (3H, s, 8-Me).

Analysis

found : C, 68.0 ; H, 6.1 ; N, 8.0%, M^+, 354

$C_{20}H_{22}N_2O_4$ requires : C, 67.8 ; H, 6.2 ; N, 7.9%, M, 354

(ii) a red solid identified as 3 - dimethylamino - 1, 2 - dimethoxycarbonyl - 4, 8 - dimethylcyclopenta [c] quinolizine (150b) (0.09g ; 6%) m.p. 128-129° (from methanol), τ - 0.3 (1H, s, H-9), 2.4 - 2.8 (2H, m, H-6, 7), 3.20 (1H, s, H-5), 6.10 (3H, s, OMe), 6.20 (3H, s, OMe), 7.10 (6H, s, NMe_2), 7.20 (3H, s, 4-Me), 7.58 (3H, s, 8-Me).

Analysis

found : C, 67.8 ; H, 6.0 ; N, 7.9%, M^+ 354

$C_{20}H_{22}N_2O_4$ requires : C, 67.8 ; H, 6.2 ; N, 7.9%, M 354

(iii) thermal rearrangement product [118] (148b) (0.13g ; 5%)

e) 3 - (1 - Dimethylaminovinyl - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dienyl) - 5 - methyl - 2 - phenylindolizine (147e) (0.2g).

Product : a red solid (0.03g ; 15 %) tentatively identified from its n.m.r. spectrum as an impure specimen of 3 - dimethylamino - 1, 2 - dimethoxycarbonyl - 9 - methyl - 4 - phenylcyclopenta [c] quinolizine (150c) τ 2.3 - 3.1 (m, H-5, 6, 7, 8 and Ph), 6.10 (s, OMe), 6.26 (s, OMe), 7.19 (s, 9-Me), 7.65 (s, NMe_2), [the integrated intensity of the aromatic multiplet was too large owing to contamination with benzene] .

found : : M^+ 416·1739

$C_{25}H_{24}N_2O_4$ requires : M 416·1736

Analysis was not attempted as the compound could not be obtained pure.

Attempted thermal rearrangement of 3 - (1 - Dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dienyl) - 5 - methyl - 2 - phenylindolizine (147e).

The indolizine (147e) (0.2g) was heated under reflux in 2 - methoxy ethanol (30ml) for three hours and the recovered material was chromatographed to give only a small amount of starting material and decomposition products.

Thermal rearrangement of the 3 - indolizinylmethylenepenta - 1, 4 - dienes (153a) and 153b).

a) A saturated solution of the indolizine (153a) (0.2g), in 2 - methoxyethanol, was heated under reflux for one hour. The solvent was removed and the residual oil was taken up in benzene and chromatographed on alumina. Elution with benzene gave a yellow band which yielded a pale yellow

solid (0.110g ; 55%), m.p. 163-164° (from ethanol) believed to be tetramethyl 1 - (2 - phenylindolizin - 3 - ylmethylene) cyclopentadiene - 2, 3, 4, 5 - tetracarboxylate (154a), τ 1.92 (1H, s, methine proton), 2.4 - 2.9 (7H, m, H-5, 8 and Ph), 3.1 - 3.7 (3H, m, H-1, 6 and 7), 6.03 (3H, s, OMe), 6.16 (6H, s, 2xOMe), 6.64 (3H, s, OMe), λ_{max} (EtOH), 212, 230, 252 and 355 nm, log ε 4.54, 4.32, 4.59 and 3.44.

Analysis

found ; C, 67.2 ; H, 4.4; N, 2.8% ; M^+, 501

$C_{28}H_{23}NO_8$ requires : C, 67.1 ; H, 4.6; N, 2.8% ; M, 501

b) The indolizine (153b) (0.2g) was treated as in (a) and yielded a yellow solid (0.07g ; 40%), m.p. 161-162° (from ethanol) believed to be tetramethyl 1 - (1 - methyl - 2 - phenylindolizin - 3 ylmethylene) cyclopentadiene - 2, 3, 4, 5 - tetracarboxylate (154b), τ 2.05 (1H, s, methine proton), 2.4 - 2.9 (7H, m, H-5, 8 and Ph), 3.2 - 3.7 (2H, m, H-6 and 7), 6.06 (3H, s, OMe), 6.17 (3H, s, 2xOMe), 6.58 (3H, s, OMe), 7.66 (3H, s, 1-Me), λ_{max} (EtOH) 212, 229, 248 n.m. and 355 n.m., log ε 4.58, 4.41, 4.61 and 3.49.

Analysis

found : C, 67.3 ; H, 5.0 ; N, 2.9% ; M^+ 515

$C_{29}H_{25}NO_8$ requires : C, 67.6 ; H, 4.8 ; N, 2.7% ; M 515

B) SYNTHESIS AND ATTEMPTED REARRANGEMENT OF 3 - (1 - DIMETHYLAMINO - 2, 3 - DIMETHYOXYCARBONYLBUTA - 1, 3 - DIEN - 1 - YL) INDOLES.

Preparation of 1 - methyl - 2 - phenylindole

a) Condensation of acetophenone with 1 - methyl - 1 - phenylhydrazine. Methylphenylhydrazine (20ml ; 20.9g) and acetophenone (19.96ml ; 16.43g) were heated under reflux in dry benzene for nine hours. The solvent was removed and the residual orange liquid was distilled at an oil pump. The first fraction collected proved to be starting materials. The second fraction distilled as a brown viscous liquid that solidified to a yellow crystalline solid (20.8g) on cooling under ice. The first fraction was again heated in benzene in the presence of a small amount of p - toluenesulphonic acid to give more of the hydrazone (6.8g). Total yield = 27.6g (91%) m.p. 43-45°C (lit m.p. 45°).

b) The hydrazone (19.6g) was added to polyphosphoric acid (66.6g), at 100°C, during five minutes with stirring. After the addition was complete the mixture was allowed to cool to 90°C and water (200ml) was added to precipitate the 1 - methyl - 2 - phenylindole (160b) which was filtered off and recrystallised from ethanol.

Yield = 11.8g (77.7%) m.p. 99-100°C (lit m.p. 100°C).

Reaction of 1 - methyl - 2 - phenylindole with dimethylacetamide and phosphoryl chloride.

The indole (3.2g) and dimethylacetamide (1.9ml) were dissolved in dry benzene (100ml) and phosphoryl chloride (1.5ml) was added dropwise to the stirred, refluxing solution, during ten minutes. After the addition was complete the solution was refluxed for a further one hour, cooled in a water bath, and ether added to ensure complete precipitation of the product as an oil. The benzene - ether layer was decanted and the residual oil treated with perchloric acid (2.5ml) until

precipitation of the salt was complete. The precipitate was filtered off and washed with dry ether (20ml) to give 3 - (1 - dimethylamino ethylidene) - 1 - methyl - 2 - phenylindolium perchlorate (2.4g ; 43%), m.p. 243-245° (from acetic acid containing a drop of perchloric acid) τ(in CF_3CO_2H) 2.2-2.7 (9H, m, ArH), 6.16, 6.36, 6.62 (each 3H, s, NMe), 7.30 (3H, s, C-Me).

Analysis

found : C, 60.4 ; H, 5.4 ; N, 7.4%

$C_{18}H_{21}ClO_4$ requires : C, 60.5 ; H, 5.6 ; N, 7.4%

Reaction of 1, 2 - dimethylindole with dimethylacetamide and phosphoryl chloride.

1, 2 - Dimethylindole (3g) and dimethylacetamide (2ml ; 1.8g) were dissolved in dry benzene (100ml) and phosphoryl chloride (2ml ; 3.2g) was added dropwise to the stirred, refluxing solution during ten minutes. After the addition was complete the mixture was heated under reflux for a further thirty minutes. The solution was cooled, ether was added and the benzene - ether layer was decanted off. The resulting oil was taken up in the minimum amount of methanol and the perchlorate salt precipitated by dropwise addition of sodium perchlorate in dry methanol. Filtration gave 3 - (1 - dimethylaminoethylidene) - 1, 2 - dimethylindolium perchlorate (161a) (5.6g ; 86%) as a light brown solid that was re-crystallised from ethanol containing a trace of perchloric acid (m.p. 147-148°).

Analysis

found : C, 53.2 ; H, 5.9 ; N, 8.7%

$C_{14}H_{19}N_2ClO_4$ requires : C, 53.4 ; H, 6.1 ; N, 8.9%

Preparation of 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbutadienyl) indoles.

a) The indolium perchlorate (161b) (0.85g) was dissolved in dimethylformamide (20ml) in a separating funnel at 0°C. Ether (100ml) and an excess of aqueous sodium hydroxide, cooled to 0°C, were added and the mixture was thoroughly shaken. The organic layer was removed and the aqueous layer extracted with ether (2 x 100ml). The ether extracts were combined, dried over anhydrous magnesium sulphate, and evaporated to give 3 - (1 - dimethylaminovinyl) - 1 - methyl - 2 - phenylindole (162b) as a white crystalline solid (0.15g).

The above enamine (2g) was dissolved in ether (50ml) and an equimolar amount of dimethyl acetylenedicarboxylate (1.08g) was added. The mixture was left at room temperature for twenty-four hours, concentrated, and chromatographed on 5% deactivated alumina. Benzene - ether (1 : 1) elution gave two fractions.

(1) a red band that gave 3 - acetyl - 1 - methyl - 2 - phenylindole (163b) (0.07g), M^+, 249, identified from its n.m.r. and infra-red spectra. It must be supposed that this compound was present as an impurity in the original enamine (162b).

(2) a yellow band that gave a pale yellow solid (1.6g ; 50%), m.p. 169-170° (from methanol), M^+ 418, identified as 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) 1 - methyl - 2 - phenylindole (164b) from its n.m.r. spectrum (see discussion). Like the corresponding indolizine derivatives,[118] this substance showed four olefinic signals (each < 1H) with a 2Hz splitting at τ 3.87, 4.51, 4.92 and 5.36 due to the presence of two stereoisomers. The various methyl groups in these isomers gave a total of seven singlets in the range 6.3 - 7.5 τ.

Analysis

found : : C, 71.7 ; H, 6.0 ; N, 6.9%

$C_{25}H_{26}N_2O_4$ requires : C, 71.8 ; H, 6.2 ; N, 6.7%

Ultraviolet spectrum (ethanol) : λ_{max} = 225nm (log ε = 4.517), 252nm (4.19), 265nm (4.23), 295nm(4.41), 350nm(4.02).

b) The indolium perchlorate (161a) (2.1g) was treated with sodium hydroxide as in (a) and gave a white solid (1.25g) that was a mixture of the required enamine (162a) and the corresponding 3 - acetyl compound (163a). Reaction of this solid with dimethyl acetylenedicarboxylate, in dry benzene (50ml), and chromatography on 10% deactivated alumina [benzene - ether (1 : 1) elution] gave a trace of (163a) and two main fractions :

(1) a yellow band that gave a yellow solid (0.2g), m.p. 188-189° (from methanol) M^+, 453, identified on the basis of its n.m.r. spectrum as 3 - (2, 3, 5, 6 - tetramethoxycarbonylphenyl) - 1, 2 - dimethylindole (165a) (see discussion).

Analysis

found : C, 63.3 ; H, 5.0 ; N, 3.4%

$C_{24}H_{23}NO_8$ requires : C, 63.6 ; H, 5.0 ; N. 3.1%

(2) a red band that gave a light red oil (1.5g) identified as 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) 1, 2 - dimethylindole (164a) by comparison of its n.m.r. spectrum with that of (164b). The presence of two stereoisomers was again apparent from the four olefinic doublets (J, 2Hz) and 18Me singlets.

Attempted rearrangement of (164a and 164b).

a) thermally.

Both (164a and 164b) on being heated under reflux in 2 - methoxy ethanol for four hours, gave only starting material.

b) with sodium ferricyanide.

The indoles (164a) and (164b) were treated with sodium ferricyanide molar ratio [(1 : 2) or (1 : 3)] in boiling 2 - methoxyethanol for one

hour. Chromatography of the reaction mixture on an alumina column and preparative thin layer chromatography gave a wide range of compounds, none of which could be isolated pure or identified.

SECTION 2

ATTEMPTED RING EXPANSION OF 3 - SUBSTITUTED INDOLIZINES TO QUINOLIZINIUM SALTS.

Preparation of 3 - ethoxalyl - 2 - phenylindolizine. (174 ; R = H)

Ethoxalyl chloride (0.84g) was added dropwise, with stirring, to a solution of 2 - phenylindolizine (0.85g) in dichloromethane (80ml) at 0°C and the mixture was left at room temperature for twenty-four hours. The resultant green solution was poured into light petroleum (60/80) and refluxed for ninety minutes, cooled, and the solvent removed to give the ethoxalyl compound (1.3g ; 97%), (174a) as a greenish - yellow solid, [118] m.p. 126-127° (from ethanol).

Analysis

found : C, 73.5 ; H, 5.0, ; N, 4.5%

$C_{18}H_{15}NO_3$ requires : C, 73.7 ; H, 5.1 ; N, 4.8%

Preparation of 3 - ethoxalyl - 1 - methyl - 2 - phenylindolizine

Ethoxalyl chloride (0.92g) in dichloromethane (5ml) was added, dropwise with stirring, to 1 - methyl - 2 - phenylindolizine (2g) in dichloro methane (20ml), at 0°C. The mixture was left at room temperature for twenty-four hours, the solvent was removed and the residue was recrystallised from ethanol to give the ethoxalyl compound (2.6g ; 86%) m.p. 147-148° (lit [118] m.p. 147-148°).

Reduction of ethoxalylindolizines

All attempts to reduce (174a) and (174b) with lithium aluminium hydride in varying molar quantities gave only a mixture of products that could not be separated or characterised.

Reaction of 1 - methyl - 2 - phenylindolizine with tetramethyldiamino methane.

A solution of the indolizine (1g), formaldehyde (0.23g) and

tetramethyldiaminomethane (5ml) in glacial acetic acid (1ml) and ethanol (10ml) was stirred at room temperature for forty-eight hours, poured into water, and extracted with ether. The ether extracts were dried over anhydrous magnesium sulphate, ether was removed, and the resultant oil chromatographed on 10% deactivated alumina. Benzene - ether elution gave a colourless, fluorescent eluate which, on evaporation, gave 3 - (N,N^1 - dimethylaminomethyl) - 1 - methyl - 2 - phenylindolizine (176) as a greenish oil (0.2g). The n.m.r. spectrum showed a dimethyl amino absorption at 7.9 τ ; and a methylene absorption at 6.4 τ .

Attempted conversion of (176) to the corresponding 3 - cyanomethyl indolizine (177)by reaction with sodium cyanide and methyliodide gave a small amount of a grey solid the infra-red spectrum of which showed no CN absorption, (M^+ = 426). This product was tentatively identified as di - (1 - methyl - 2 - phenylindolizin - 3 - yl) methane (178) on the basis of (a) its n.m.r. spectrum, which was similar to that of the parent indolizine (112 ; R = CH_3), but with a methylene absorption at 5.4 τ , and (b) the mass spectrometric result.

Analysis

found : C, 86.4 ; H, 5.8 ; N, 6.7%

$C_{31}H_{26}N_2$ requires : C, 87.3 ; H, 6.1 ; N, 6.6%

SECTION 3

REACTION OF DIMETHYL ACETYLENEDICARBOXYLATE WITH 5 - METHYLINDOLIZINES.

Preparation of 5, 8 - dimethylindolizine

Pyrrole (5g), zinc acetate (7.5g) and hexane - 2, 5 - dione (7.5g) were heated under reflux in 90% acetic acid (250ml) for twenty-four hours. Solvent was removed and the residue made alkaline by addition of 2N sodium hydroxide. The resultant mixture was steam distilled and the distillate was extracted with ether. The extract was dried over anhydrous magnesium sulphate, evaporated, and the residue was chromatographed on 5% deactivated alumina. Elution with benzene - ether gave two fractions :

i) a pale blue band that gave a colourless but fluorescent eluate that gave a dark oil (0.714g ; 7%), characterised by n.m.r. as the required 5, 8 - dimethylindolizine (191).

ii) an orange band that gave 4, 7 - dimethylindole (0.28g), m.p. = 99° (lit [199] m.p. = 101°).

The reaction also produced a large amount of decomposition products.

Reaction with

1) 5 - methyl - 2 - phenylindolizine

a) In benzene

The indolizine (0.5g) was dissolved in benzene (100ml) and an equimolar amount (0.35g) of dimethyl acetylenedicarboxylate was added. The mixture was left at room temperature for twenty-four hours. The solution was concentrated to ca 10ml and chromatographed on 10% deactivated alumina. Elution with benzene gave two fractions:

i) an orange-yellow band which, on evaporation and trituration of the residue with methanol, gave a pale yellow solid (0.45g ; 54%), m.p. 107° (from methanol), M^+ 349, identified from its n.m.r. spectrum

(see discussion) as dimethyl 5, 7a - dihydro - 7a - methyl - 3 - phenylcycl [3, 2, 2] azine - 1, 2 - dicarboxylate (179a).

Analysis

found : C, 72.1 ; H, 5.5 ; N, 4.0%

$C_{21}H_{19}NO_4$ requires : C, 72.1 ; H, 5.5 ; N, 4.0%

λ_{max} (log ε) 207 (4.27), 225 (4.06), 250 (3.765), 268 (3.89), 300 (3.28), 325 (3.51), 350 (3.66), 400nm (4.23), in ethanol.

ii) a pale yellow band which, on evaporation and trituration of the residue with methanol, gave a pale yellow solid (0.24g ; 20%) m.p. 168-169° (from methanol), M^+ 491, identified from its n.m.r. spectrum (see discussion) as tetramethyl 5, 9a - dihydro - 9a - methyl - 3 - phenylcycl [5, 2, 2] azine - 1, 2, 5, 6 - tetracarboxylate (180a).

Analysis

found : C, 65.9 ; H, 5.2 ; N, 2.8%

$C_{27}H_{25}NO_8$ requires : C, 66.0 ; H, 5.1 ; N, 2.8%

λ_{max} (log ε) 209 (4.338), 225 (4.24), 257 (4.384), 295 (3.633), 325 (3.787), 390nm (4.225), f in ethanol.

When the reaction was carried out in a smaller volume (30ml) of benzene the yields of 1 : 1 - and 1 : 2 - adducts decreased to 22% and 6% respectively.

When two molar equivalents of dimethyl acetylenedicarboxylate were used the yield of the 1 : 2 - adduct (43%) exceeded that of the 1 : 1 - adduct (20%).

b) In methanol

The indolizine (0.220g) and dimethyl acetylenedicarboxylate (0.154g) were kept at room temperature, in methanol solution, for

twenty-four hours. The solvent was evaporated and the residue was chromatographed on alumina, in benzene, to yield 3 - (1, 2 - dimethoxy carbonylvinyl) - 5 - methyl - 2 - phenylindolizine (181) (0.17g ; 50%), dark red crystals m.p. 95-96° [from light petroleum (60-80°) containing a trace of ethylacetate] . The product was identified from its n.m.r. spectrum (see discussion).

Analysis

found : C, 72.4 ; H, 5.3 ; N, 4.1% ; M^+ 349

$C_{21}H_{19}NO_4$ requires : C, 72.2 ; H, 5.5 ; N, 4.0% ; M 349

2) Reaction with 2, 5 - dimethylindolizine

The indolizine (2g) and an equimolar amount of dimethyl acetylenedicarboxyl ate (1.96g) were left at room temperature, in dry benzene (150ml), for twenty-four hours. The solution was concentrated to ca 15ml and chromatographed on 5% deactivated alumina. Elution with benzene gave two fractions :

i) a yellow band that gave an orange oil (2.28g ; 58%), that could not be crystallised. Identified from its n.m.r. (see discussion) as dimethyl 5, 7a - dihydro - 3, 7a - dimethylcycl [3, 2, 2] azine - 1, 2 dicarboxylate, (179b).

Analysis

found : M^+ 287.1157

calculated : M 287.1164

λ_{max} (logε), 210 (3.965), 225 (3.789), 275 (3.856), 300 (3.156), 325 (3.089), 394nm (4.088), in ethanol.

ii) a pale yellow band that gave a yellow oil (0.7g ; 13%) that could not be crystallised. Identified from its n.m.r. spectrum (see discussion) as tetremethyl 5, 9a - dihydro - 3, 9a - dimethylcycl

[5, 2, 2] azine - 1, 2, 5, 6 - tetracarboxylate.

Analysis

found : C, 61.3 ; H, 5.2 ; N, 2.8% ; M^+ 429.1429

$C_{22}H_{23}NO_8$ requires : C, 61.5 ; H, 5.4 ; N, 3.3% ; M 429.1423

λ_{max} (log ε) 213 (3.965), 230 (3.845), 249 (3.93), 300 (3.267), 320 (3.228), 388nm (3.912), in ethanol.

3) With 1 - acetyl - 5 - methyl - 2 - phenylindolizine.

The indolizine (0.5g) and an equimolar amount of dimethyl acetylenedicarboxylate (0.285g) were heated under reflux, in dry benzene (30ml), for five hours. The solution was concentrated to ca 15ml and chromatographed on 5% deactivated alumina. Elution with benzene - ether gave two fractions :

i) a colourless but fluorescent band that gave a small amount of starting material.

ii) a pale yellow band which, on evaporation and trituration of the residue with methanol, gave a pale yellow solid (0.4g ; 50%) m.p. 189-190° (from methanol) M^+ 533. Identified from its n.m.r. spectrum (see discussion) as tetramethyl 7, 9a - dihydro - 9a - methyl - 4 - acetyl - 3 - phenylcycl [5, 2, 2] azine - 1, 2, 5, 6 - tetracarboxylate (182).

Analysis

found : C, 65.3 ; H, 5.1 ; N, 2.7%

$C_{29}H_{27}NO_9$ requires : C, 65.3 ; H, 5.1 ; N, 2.6%

λ_{max} (log ε) 213 (4.332), 225 (4.295), 245 (4.19), 263 (4.215), 305 (3.84), 360nm (4.308), in ethanol.

When the reaction was carried out in dry benzene at room temperature for twenty-four hours only starting material was recovered.

Running the reaction in toluene (25ml) for five hours gave a low yield 17% of 1 : 2 - adduct as the only isolated product.

4) Reaction with 5, 8 - dimethylindolizine

The indolizine (0.7g) was dissolved in dry benzene (100ml) and dimethyl acetylenedicarboxylate (0.7g), in dry benzene (5ml), was added and the mixture left at room temperature for twenty-four hours. The solution was concentrated to ca 10ml and chromatographed on 5% deactivated alumina. Elution with benzene afforded two fractions and further elution with ether yielded a third fraction :

(i) an orange band that gave an orange oil (0.21g ; 20%) that could not be crystallised. Identified from its n.m.r. spectrum (see discussion) as dimethyl 5, 7a - dihydro - 5, 7a - dimethylcycl [3, 2, 2] azine - 1, 2 - dicarboxylate.

Analysis

found : M^+ 287.1156

calculated : M 287.1157

λ_{max} ($\log \varepsilon$) 213 (3.986), 233 (3.707), 275 (3.146), 290 (3.185), 315 (3.00), 390nm (4.00),

in ethanol.

(ii) an orange - yellow band, travelling close to fraction (i) that gave (0.21g ; 20%) of a red solid. Identified by its n.m.r. spectrum (see discussion) as 3 - (1, 2 - dimethoxycarbonylvinyl) - 5, 8 - dimethylindolizine.

Analysis

found : C, 67.2 ; H, 6.3 ; N, 4.5% ; M^+, 287.1157

$C_{16}H_{17}NO_4$ requires : C, 66.9 ; H, 6.0 ; N, 4.9% ; M, 287.1168

(iii) a red band that yielded an unstable red oil (0.16g), the n.m.r. spectrum of which indicated the presence of two AB systems. The product

was not further characterised.

Reactions of the 1 : 2 - adduct (180a).

1) with dimethyl acetylenedicarboxylate;

The adduct (0.5g) and dimethyl acetylenedicarboxylate (0.145g) were heated under reflux in

a) benzene for twenty-two hours, during which no reaction occurred, and

b) xylene for five hours after which chromatography gave starting material (0.22g) and a red oil (0.25g) the n.m.r. spectrum of which was very complicated in the ester region.

2) Catalytic hydrogenation

The adduct (0.2g) was dissolved in absolute alcohol (25ml) and hydrogenated over palladium - charcoal (0.05g) at atmospheric pressure and room temperature. When absorption of hydrogen ceased, the solution was filtered through Celite and the filtrate was evaporated to give a grey solid (0.15g ; 75%) m.p. 183-185° (from methanol), M^+ 495, identified from its n.m.r. and ultraviolet spectra (see discussion) as tetramethyl 5, 6, 7, 8, 9, 9a - hexahydro - 9a - methyl - 2 - phenylcycl [5, 2, 2] azine - 1, 2, 5, 6 - tetracarboxylate (201).

Analysis

found : C, 64.5 ; H, 5.7 ; N, 2.7%

$C_{27}H_{29}NO_8$ requires : C, 65.4 ; H, 5.9 ; N, 2.8%

λ_{max} (log ε) 208 (4.335), 225 (4.189), 245 (3.99), 260 (4.046), 290 (3.44), 320 (3.72), 385nm (4.335), in ethanol.

Reaction of 1 : 1 - adduct (179b) with dichlorodicyanobenzoquinone.

The adduct (0.1g) and an equimolar amount of D.D.Q. (0.077g) were heated under reflux in benzene (30ml) for one hour during which time,

thin-layer chromatography showed the formation of an orange spot in addition to the yellow spot of the original adduct. Chromatography on alumina with benzene elution gave two fractions :

(i) an orange band from which was obtained a yellow oil (0.02g ; 20%) that could not be crystallised. The n.m.r. spectrum (see discussion) suggested that this was dimethyl 7, 7a - dihydro - 2, 7a - dimethylcycl [3, 2, 2] azine - 1, 2 - dicarboxylate (199).

(ii) a yellow band that gave starting material (0.06g).

Repeating this reaction with varying amounts of D.D.Q. led to the isolation of yellow oils (ca 15%) which were shown by n.m.r. to be mixtures of the 5, 7a - and 7, 7a - dihydro - compounds. No change was observed when the adduct (179b) was heated in benzene in the absence of D.D.Q.

Using chloranil or tetrachloro - orthobenzoquinone gave only decomposition products.

Similar reactions with the 3 - phenyl 1 : 1 - adduct (179a) gave only starting material and decomposition products. Heating in benzene alone caused no change.

Reaction of the 1 : 1 - adduct (179a) with dimethyl acetylene - dicarboxylate.

The adduct (0.37g) and dimethyl acetylenedicarboxylate (0.14g) were heated under reflux in dry benzene (50ml) for five hours. Chromatography on alumina in benzene gave two fractions :-

(i) starting material (0.2g ; 50%)

(ii) 1 : 2 - adduct (180a) (0.18g ; 20%)

A similar reaction in cold benzene led to recovery (100%) of starting material.

Similar reactions with the adduct (179b) in hot or cold benzene led to recovery of starting material (~100%).

SECTION 4.

SYNTHESIS IN THE CYCL [3, 3, 2] AZINE SERIES.

2 - (α - Hydroxypropyl) - 6 - methyl pyridine

Small pieces of lithium (6.9g) were added, in a stream of nitrogen, to dry ether (400 ml) in a 1 litre 3-necked flask fitted with a dropping funnel, magnetic stirrer and condensor with calcium chloride drying tube. The first portion (10 to 15 ml) of a solution of bromobenzene (79g ; dried over molecular sieve) in dry ether (100 ml) was added, with stirring, and the flask was warmed slightly to initiate the reaction. The remainder of the bromobenzene solution was then added at such a rate that a steady reflux of the solvent was maintained. After the addition was complete stirring was continued under nitrogen, until all the lithium had reacted.

2, 6 - Lutidine (53.5g ; dried over molecular sieve) was then added dropwise, under nitrogen, to the ice-cooled, stirred solution of phenyl - lithium. The addition took fifteen minutes and gave a red solution which was stirred for one hour after the addition was complete. The flask was cooled in an ice-salt bath and a solution of ethylene oxide (20g) in dry ether (75 ml) was added dropwise, under nitrogen, during forty minutes, the colour of the reaction mixture disappearing as the last drops were added. The solution was stirred for a further sixty minutes and water (100 ml) was then added dropwise, followed by concentrated hydrochloric acid (100 ml).

The mixture was shaken and the aqueous layer removed and added to a warm solution of sodium carbonate decahydrate (300g) in water (100 ml). The oil that separated was taken up in chloroform (300 ml) and after filtering off lithium carbonate, the aqueous layer was extracted with chloroform (3 x 100 ml). The chloroform extracts were combined and dried over anhydrous magnesium sulphate. Filtration and removal of the

chloroform gave a reddish-brown viscous liquid which was fractionated to give :

a) 2, 6 - lutidine (2.4 g) b.p. 35°/0.4 mm

b) 2 - (3 - hydroxypropyl) - 6 - methylpyridine (61.4g ; 82%), b.p. 90-92°/0.4 mm.

5 - methylindolizine

The hydroxypropylpyridine (13.3g) and 10% Pd/C catalyst (0.5g) were placed in a 50 ml 2-necked flask fitted with a nitrogen inlet and a column packed with pellets of molecular sieve (Type 4A). The apparatus was flushed with nitrogen and the liquid was boiled under reflux for eighteen hours and then cooled. Material adhering to the column was washed into the reaction flask with water and the mixture was steam distilled, giving an emulsion which was extracted with ether. The extract was dried and evaporated to give a dark oil which was distilled (water-pump vacuum) to give 5 - methylindolizine (6.7g ; 57%) as a clear oil.

Reactions of Indolizines with - chloro - - hydroxyiminoketones in the presence of triethylamine.

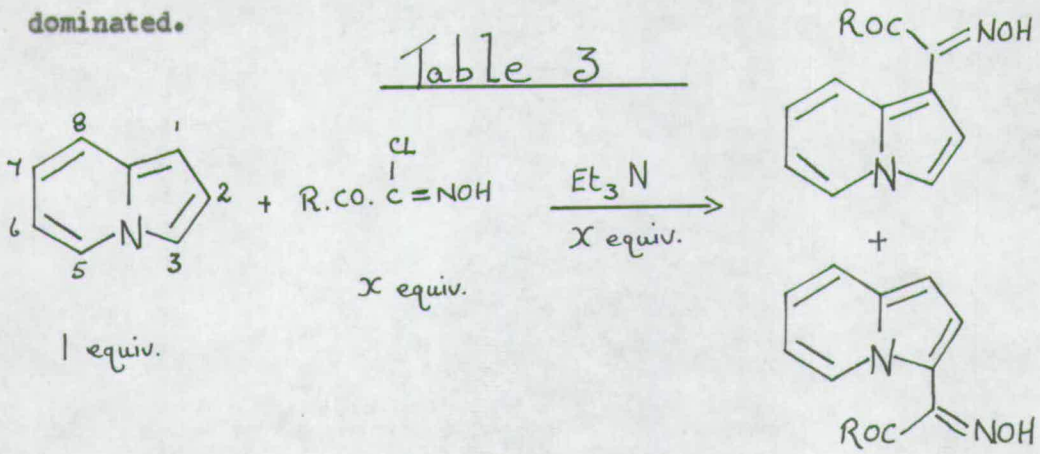
General Procedure

Triethylamine (1 - 2 equivalents) was added dropwise, during 1-3 hours, to a stirred solution of the indolizine (1 equivalent) and the α - chloro - α - hydroxyiminoketone (1 - 2 equivalents) in benzene, methanol, or chloroform. The solution was stirred at room temperature for twenty-four hours and then washed with water or (in the case of methanol solutions) diluted with water and extracted with ether. The non-aqueous fraction was then dried and evaporated and the residue was chromatographed on deactivated alumina. Elution with benzene gave, in some experiments, a small recovery of starting indolizine, and continued elution with benzene - ether (ca. 1:1) gave the product. The quantities

of reactants and solvents and the yields of products are summarised in Table (3).

Unless otherwise indicated in the more detailed accounts following the table, the products (identified by comparison of their n.m.r. spectra with those of Roff's products) were mixtures of the 1 - and 3 - (α - hydroxyimino - β - ketoalkyl) indolizines in which the 3 - isomer predominated.

Table 3



Experiment No.	Indolizine (g)		R	X	Solvent (ml)		Yield (%)
1	5 - Me - 2 - Ph	(1)	Me	1	C_6H_6	(100)	24
2	5 - Me - 2 - Ph	(1)	Me	1	MeOH	(100)	44
3	5 - Me - 2 - Ph	(1)	Me	1	$CHCl_3$	(100)	53
4	5 - Me - 2 - Ph	(1)	Me	2	$CHCl_3$	(100)	36
5	5 - Me - 2 - Ph	(5)	Me	1.8	$CHCl_3$	(120)	66
6	5 - Me - 2 - Ph	(1)	Ph	1	C_6H_6	(120)	15
7	5 - Me - 2 - Ph	(4)	Ph	1	$CHCl_3$	(175)	72
8	5 - Me - 2 - Ph	(1)	Ph	1	MeOH	(100)	32
9	1 - Me - 2 - Ph	(5)	Me	1.8	$CHCl_3$	(120)	70
10	2, 5 - di Me	(5)	Ph	1	$CHCl_3$	(180)	76
11	5 - Me	(2.7)	Me	1.8	$CHCl_3$	(65)	50

Experiment No. 5

Repeated crystallisation of the product from a large volume of benzene gave a pure sample of 3 - (α - hydroxyiminoacetonyl) - 5 - methyl - 2 - phenylindolizine, m.p. 184°.

Analysis

found : C, 73.7 ; H, 5.3 ; N, 9.7% ; M^+ 292

$C_{18}H_{16}N_2O_2$ requires: C, 74.0 ; H, 5.5 ; N, 9.6% ; M 292

Roff's sample of the 1 - isomer was also recrystallised to analytical purity from benzene.

found : C, 73.8 ; H, 5.5 ; N, 9.8% ; M^+ 292

Experiment No. 7

Repeated recrystallisation of the product from a large volume of benzene gave a pure sample of 3 - (α - hydroxyiminophenacyl) - 5 - methyl - 2 - phenylindolizine, m.p. 161°.

Analysis

found : C, 77.7 ; H, 5.2 ; N, 7.8% ; M^+ 354

$C_{23}H_{18}N_2O_2$ requires: C, 77.9 ; H, 5.1 ; N, 7.9% ; M 354

Experiment No. 8

The n.m.r. spectrum of the product showed, by comparison with that of Roff's sample, that it was 1 - (α - hydroxyiminophenacyl) - 5 - methyl - 2 - phenylindolizine

found : C, 78.3 ; H, 4.7 ; N, 8.0% ; M^+ 354

$C_{23}H_{18}N_2O_2$ requires: C, 77.9 ; H, 5.1 ; N, 7.9% ; M 354

Experiment No. 9

The product was recrystallised from benzene to yield 3 - (- hydroxy iminoacetonyl) - 1 - methyl - 2 - phenylindolizine, m.p. 152°.

Analysis

found : C, 74.2 ; H, 5.3 ; N, 9.4%

$C_{18}H_{16}N_2O_2$ requires: C, 74.0 ; H, 5.5 ; N, 9.6%

Experiment No. 10

Elution of the column with benzene - ether (1:1) yielded two fractions :

(i) an orange band that yielded 3 - (α - hydroxyiminophenacyl) - 2, 5 - dimethylindolizine (7.6g), m.p. 142-144° (from benzene).

Analysis

found : C, 73.9 ; H, 5.3 ; N, 9.5% ; M^+ 292

$C_{18}H_{16}N_2O_2$ requires: C, 74.0 ; H, 5.5 ; N, 9.6% ; M 292

(ii) a yellow band that yielded 1 - (α - hydroxyiminophenacyl) - 2, 5 - dimethylindolizine (0.15g) m.p. (from benzene).

found : C, 74.2 ; H, 5.3 ; N, 9.7%

Experiment No. 11

Elution of the column with benzene - ether (1:1) gave two fractions :

(i) a yellow band that yielded a yellow solid (0.1g) m.p. 79 – 80° (from benzene), tentatively identified as 3 - (or 1 -) (3 - acetyl - 1, 2, 4 - oxadiazol - 5 - yl) - 5 - methylindolizine (21b).

Analysis

found : C, 65.2 ; H, 4.6 ; N, 17.1% ; M^+ 241

$C_{13}H_{11}N_3O_2$ requires: C, 64.9 ; H, 4.5 ; N, 17.4% ; M 241

(ii) an orange band that yielded a red oil (2.2g), the n.m.r. spectrum of which suggested that it was the required mixture of 1 - and 3 - (α - hydroxyiminoacetonyl) - 5 - methylindolizines with the 1 - isomer predominating.

Base - catalysed Cyclisation of 3 - (α - hydroxyimino - β - ketoalkyl) - 5 - methylindolizines.

General Procedure

Potassium t - butoxide was prepared by evaporating its solution in t - butanol and heating the resulting solid at 100° in vacuo for one hour.

Previous workers had shown that material prepared in this way contains 1 equivalent of t - butanol.

A solution of the indolizine (1 equivalent) and potassium t - butoxide (2 equivalents) in dry dimethyl sulphoxide was kept at the specified temperature for the specified time [See Table (4)]. After being cooled, the reaction mixture was worked up according to one of the following procedures.

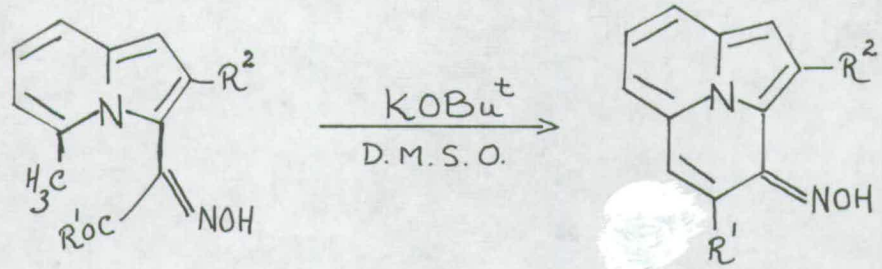
(a) The solvent was evaporated under oil-pump vacuum and the tarry residue was neutralised with dilute hydrochloric acid and extracted with dichloromethane. The extract was dried and evaporated and the residue chromatographed on deactivated alumina in benzene - ether (ca 1:1).

(b) Procedure as in (a) but neutralisation with HCl omitted.

(c) Procedure as in (a) but acetic acid was used in place of dilute HCl and the dichloromethane extract was washed with water before being dried.

(d) The dimethyl sulphoxide solution was neutralised with acetic acid before evaporation. Thereafter the procedure was as in (b).

Quantities of reactants and yields of products are summarised in Table (4).



(and 1-isomer)

Product (A)

x_g

+ NN'-Methylene bis (cyclazinimine) - dioxide. (PRODUCT B)

Experiment No.	R^1	R^2	X	DMSO (Me)	Time	Temp. (°C)	Work up	Yields (%) A	B
1	Me	Ph	1	15	5 minutes	b.p.	(a)	8	-
2	Me	Ph	1	6	5 minutes	100	(a)	37	-*
3	Me	Ph	5	30	5 minutes	100	(a)	-	15
4	Ph	Ph	1	10	5 minutes	100	(b)	36	12
5	Ph	Ph	1	10	5 minutes	100	(d)	27+	-
6	Ph	Ph	1	10	24 hours	R.T.	(b)	-	30
7	Ph	Ph	1	10	48 hours	R.T.	(b)	36	20
8	Ph	Me	1	7	5 minutes	100	(b)	-	30
9	Ph	Me	1	7	48 hours	R.T.	(b)	5	30
10	Me	H	1.2	10	5 minutes	100	(c)	4	0.7

* This result was not easily reproducible; some experiments, under apparently identical conditions, gave mixtures of (A) and (B).

+ Starting material (38%) recovered.

Experiment No. 3

The product was a red solid, m.p. 171-172° (from 2 - methoxyethanol), λ max (log ε) 227 (4.79), 245 (4.75), 267 (4.86), 350 (4.22), 390 (3.97), 435 nm (4.16), in ethanol.

Analysis

found : C, 79.0 ; H, 5.0 ; N, 10.0% ; M^+ 274

$C_{37}H_{28}N_4O_2$ requires : C, 79.2 ; H, 5.0 ; N, 10.0% ;

Experiment No. 4

Chromatography yielded two fractions :

(i) an orange band that yielded a red solid, tentatively identified as N, N^1 - methylene - bis (2, 4 - diphenylcycl [3, 3, 2] azin - 3 - imine) N, N^1-dioxide, m.p. 225-226° decomp. (from 2 - methoxyethanol), λ max (log ε) 218 (4.69), 248 (4.83), 265 (4.90), 325 (4.38), 400 (4.11), 440 nm (4.21), in ethanol.

Analysis

found : C, 82.3 ; H, 4.8 ; N, 8.5%

$C_{47}H_{32}N_4O_2$ requires : C, 82.4 ; H, 4.8 ; N, 8.2%

(ii) a red band that yielded a red-brown solid, identified as 3 - hydroxy imino - 2, 4 - diphenyl - 3H - cycl [3, 3, 2] azine, m.p. 198° (lit m.p.) (from benzene).

Analysis

found : C, 82.3 ; H, 4.7 ; N, 8.7%

$C_{23}H_{16}N_2O$ requires : C, 82.1 ; H, 4.8 ; N, 8.3%

Experiment No. 8

The product was a red solid, m.p. 192-193° (from 2 - methoxyethanol), λ max (log ε) 22.3 (4.58), 260 (4.81), 277 (4.86), 360 (4.21), 395 (3.83), 440 nm (4.12), in ethanol.

Analysis

found : C, 79.2; H, 5.0; N, 9.9%

$C_{37}H_{28}N_4O_2$ requires : C, 79.2; H, 5.0; N, 10.0%

Experiment No.10

Chromatography yielded two fractions :

(i) Elution with benzene gave an orange solid (0.008g), tentatively identified from its n.m.r. spectrum (peak at 4.99) as N, N^1 - methylene bis (4 - methylcycl [3, 3, 2] azin - 3 - imine) N, N^1 - dioxide.

(ii) Elution with benzene - ether gave 3 - hydroxyimino - 4 - methylcycl 3, 3, 2 azine as an orange solid (0.05g), m.p. 199 - 200° (from benzene).

Analysis

found : C, 72.6 ; H, 5.0 ; N, 14.1%

$C_{12}H_{10}N_2O$ requires : C, 72.6 ; H, 5.0 ; N, 14.1%

4 - Methyl - 2 - phenylcycl [3, 3, 2] azin - 3 - thione

4 - methyl - 2 - phenylcycl [3, 3, 2] azin - 3 - one (0.5g) and phosphorus

pentasulphide (1g) were heated together under reflux in dry benzene (70 ml) for ninety minutes (note 1). The benzene was decanted off and the residual complex was heated at 50°C with an excess of concentrated aqueous sodium sulphide with stirring, for thirty minutes. The resultant purple solution was extracted with benzene until the extracts were colourless. The combined benzene solutions were, dried over anhydrous magnesium sulphate, concentrated (to ca 20 ml) and chromatographed on 10% deactivated alumina (note 2). Benzene elution gave two fractions :

(i) a red band that yielded the required thione as a dark red solid (0.35g ; 66%) m.p. 167-168° (from ethanol), λ max (log ε), 224 (4.293), 260 (3.805), 313 (4.235), 330 (3.469), 370 nm (3.645), in ethanol.

Analysis

found :C, 78.4 ; H, 4.6 ; N, 5.3% ; M^+ 275

$C_{18}H_{13}NS$ requires:C, 78.5 ; H, 4.7 ; N, 5.1% ; M 275

(ii) a yellow band that gave starting material (30%).

Note 1. The reaction must be carried out under aluminium foil, to exclude light, as the thione is unstable over a period in light.

Note 2. The column was wrapped in aluminium foil.

3 - Methylthio - 4 - methyl - 2 - phenylcycl [3, 3, 2] azinium perchlorate.

The foregoing thione (0.05g) and an excess of methyl iodide were heated together under reflux, in dry ether (20 ml), for thirty minutes during which time the red colour disappeared and a solid was deposited. The mixture was filtered giving the methiodide (0.07g ; 90%) as a pale orange solid.

The iodide was dissolved in the minimum amount of methanol (with slight warming) and perchloric acid (1 equivalent) was added followed by ether (5 ml). Scratching caused a rapid and quantitative precipitation of the perchlorate salt as a yellow solid, m.p. 199-200° (from ethanol containing a drop of perchloric acid), n.m.r. (H-1 at 1.8 τ; H - 5, 6, 7, 8

as a singlet at 1.2 τ; Ph at 2.1-2.4 τ; CH_3 at 7.79 τ; SCH_3 at 6.8 τ).

Analysis

found : C, 58.6 ; H, 3.8 ; N, 3.9%

$C_{19}H_{16}NS\,Cl\,O_4$ requires : C, 58.5 ; H, 4.1 ; N, 3.6%

Treatment of the perchlorate with an excess of sodium sulphide, in water (100 ml) - chloroform (50 ml) at room temperature for one hour regenerated the thione (83%).

Attempted preparation of 4 - Methyl - 2 - phenylcycl [3, 3, 2] azinium perchlorate by reaction of the 3 - methylthiocyclazinium perchlorate with Raney-Nickel.

The Raney-nickel was prepared by the method of Gough [122] adapted from that of Mozingo [171].

Reaction of the perchlorate with deactivated Raney-nickel [122] in ethanol, or methanol, gave decomposition products and a mixture of compounds (n.m.r. spectrum showed SMe absorption) respectively. In t - butanol a product was obtained which, while grossly impure, showed an increase in the C-Me: S-Me integral ratio in the n.m.r. spectrum.

SECTION 4a

SYNTHESIS OF THE CYCL [3, 3, 2] AZINE SYSTEM FROM QUINOLIZINE PRECURSORS.

2 - Ethoxycarbonylcycl [3, 3, 2] azin - 1 - one (79)

Diethyl quinolizin - 4 - ylidenemalonate [112] (1g) was dissolved in nitrobenzene (40ml) and the solution was heated under reflux for one hour. The solvent was removed at the oil pump and the residual oil was taken up in chloroform and chromatographed on 10% deactivated alumina. Elution with chloroform gave two fractions :

(i) an orange band that gave the ethoxycarbonylcyclazinone (79) (0.64g ; 76%) m.p. 187-189°, infra-red and n.m.r. spectra identical with those of Farquhar's[112] specimen.

(ii) a red band that gave cycl [3, 3, 2] azin - 1 - one (81) (0.006g ; 1%) m.p. 188-190° infra-red and n.m.r. spectra identical with those of Farquhar's specimen.

Running this reaction in 1, 2, 4 - trichlorobenzene gave 85% of (79) and 6% of (81).

2 - Cyanocycl [3, 3, 2] azin - 1 - one

Ethyl quinolizin - 4 - ylidenecyanoacetate [112] (0.5g) was heated under reflux in nitrobenzene (40ml) for one hour. Removal of solvent and chromatography on alumina gave the cyanocyclazinone (0.24g ; 60%) m.p. 262-264° (from Benzene containing a trace of methanol), M^+, 194.

Analysis

found : C, 73.0 ; H, 3.3 ; N, 14.5%

$C_{12}H_6N_2O$ requires : C, 74.2 ; H, 3.1 ; N, 14.4%

The low carbon percentage is probably due to the marked tendency of the compound to absorb atmospheric water. After standing in air for a short time, the same sample gave analytical results as listed below :-

found : C, 68.8 ; H, 3.0 ; N, 13.5%

$C_{12}H_6N_2O - H_2O$ requires : C, 67.9 ; H, 3.7 ; N, 13.4%

Cycl [3, 3, 2] azinium perchlorate

The ethoxycarbonylcyclazinone was converted into the parent cyclazinium salt by the method of Gough.[122] Since satisfactory analytical results had not previously been obtained, the compound was recrystallised carefully from acetic acid.

M.p. 285° (decomposes) (lit[122] m.p. 284-285°)

Analysis

found : C, 51.9 ; H, 3.1 ; N, 5.5%

$C_{11}H_8NClO_4$ requires : C, 52.1 ; H, 3.2 ; N, 5.5%

Attempted Dials - Alder reaction of cycl [3, 3, 2] azinium perchlorate with 1, 3 - diphenylisobenzofuran.

Cycl [3, 3, 2] azinium perchlorate (0.07g) and an equimolar amount of the isobenzofuran (0.07g) were heated under reflux, in 2 - methoxyethanol (30ml), for twenty-four hours, after which T.L.C. analysis showed no apparent reaction. The solution was cooled, ether was added, and the white precipitate was filtered off giving (0.06g ; 85%) recovery of the cycl [3, 3, 2] azinium perchlorate.

Reaction of cycl [3, 3, 2] azinium perchlorate with sodium sulphide.

Gough's procedure[122] was repeated but the amount of red product (probably a thione) was insufficient for characterisation.

REACTIONS OF CYCL [3, 3, 2] AZINIUM SALTS.

Preparation of 1 - methoxycycl [3, 3, 2] azinium perchlorate.

Note : The chloroform used as the solvent had been passed through activated alumina to remove ethanol.

The cycl [3, 3, 2] azin - 1 - one (0.24g) was dissolved in chloroform (30ml) and methyl fluorosulphonate (excess) was added. The mixture was heated under reflux for fifteen minutes during which time a solid was deposited. Filtration gave a light brown solid (0.39g, quantitative yield). The mass spectrum showed a parent peak at M/e 283 corresponding to the methoxycyclazinium ion. The n.m.r. spectrum was very similar to that of the 1 - ethoxy derivative prepared by Jessep [126]. Treatment of the fluorosulphonate, in ethanol, with perchloric acid, and precipitation with ether gave 1 - methoxycycl [3, 3, 2] azinium perchlorate, m.p. 185-186°.

Analysis

found : C, 50.8 ; H, 3.6 ; N, 5.0%

$C_{12}H_{10}NClO_5$ requires : C, 50.8 ; H, 3.5 ; N, 4.8%

Reaction of 1 - methoxycycl [3, 3, 2] azinium fluorosulphonate with sodium sulphide.

An excess of aqueous sodium sulphide was added to the cycl [3, 3, 2] azinium fluorosulphonate (0.9g) in dimethylformamide (50ml) and the mixture was stirred at room temperature for twenty-four hours. The resultant purple solution was extracted with chloroform, the extracts dried over anhydrous magnesium sulphate, concentrated to ca 20ml and chromatographed on 10% deactivated alumina. Elution with dichloromethane and evaporation of the deep red-purple eluate gave a dark red solid (0.21g ; 32%), m.p. 157-160° (from cyclohexane - ethanol), the n.m.r. spectrum of which suggested that it was a mixture of 1 - methoxycycl [3, 3, 2] azin - 3

- thione and the corresponding 6 - thione.

Analysis

found : C, 67.2 ; H, 4.2 ; N, 6.6% ; M^+, 215.0405

$C_{12}H_9NOS$ requires : C, 66.9 ; H, 4.2 ; N, 6.5% ; M, 215.0406

Reaction of Cycl [3, 3, 2] azin - 1 - one with tetranitromethane

The cyclazinone (0.5) was dissolved in dry pyridine (50ml) and the solution cooled to -5°C. To this solution tetranitromethane in dry pyridine (10ml) at -5°C, was added slowly with stirring. When addition was complete the solution was allowed to come to room temperature over thirty minutes. Subsequent chromatography showed only decomposition products.

Reaction of cycl [3, 3, 2] azin - 1 - one with N, N - dimethylformamide and phosphoryl chloride.

Reaction of the cyclazinone with N, N - dimethylformamide - phosphoryl chloride in dry benzene gave a green solution from which no characterisable product could be isolated.

Reaction of cycl [3, 3, 2] azin - 1 - one with dimethyl acetylenedicarboxylate.

a) in chlorobenzene.

A solution of the cyclazinone (0.5g), in chlorobenzene (50ml) was dried by heating under a Soxhlet extractor containing molecular sieve. An equimolar amount of dimethyl acetylenedicarboxylate (0.5g) was added and the mixture was kept at room temperature for twenty-four hours. Chromatography on a column of alumina and preparative T.L.C. (on silica) of the two main bands gave a red solid (0.006g) the mass spectrum of which showed a parent ion at M/e 453, indicating that it was a 2 : 1 adduct of the acetylenic ester and the cyclazinone. The solid was not characterised further owing to the very poor yield.

Running the reaction in toluene gave an identical result.

b) in 2 - methoxyethanol.

Equimolar amounts of the cyclazinone (0.5g) and the acetylenic ester (0.5g) were heated under reflux in 2 - methoxyethanol (40ml), for forty minutes. The solvent was removed and the residual oil taken up in chloroform and chromatographed on 10% deactivated alumina. Elution with ether - chloroform (1:4) gave two fractions :

(i) a red band that gave a red oil which crystallised from methanol as a light red solid (0.04g, 3%) m.p. 147-148°, M^+ 399. On the basis of its n.m.r. spectrum (see discussion) this compound was identified as di (2 - methoxyethyl) (1 - oxo - 1H - cycl [3, 3, 2] azin - 2 - yl) fumarate (227).

Analysis

found : C, 62.6 ; H, 5.7 ; N, 3.3%

$C_{21}H_{21}NO_7$ requires : C, 63.1 ; H, 5.3 ; N, 3.5%

(ii) a light red band that gave recovered cyclazinone (0.13g).

c) in methanol.

The cyclazinone (0.25g) and an equimolar amount of dimethyl acetylenedicarboxylate (0.25g) were heated under reflux, in methanol (50ml), for one hour. Chromatography of the resultant deep red solution on 10% deactivated alumina, eluting with benzene - ether (1:1) gave two fractions :

(i) a brown band that gave a dark red solid (0.033g, 20%) m.p. 209-210°. The n.m.r. spectrum showed a six-proton aromatic region (1.6 - 2.8 τ), an olefinic singlet at 3.1 τ and two ester methyl absorptions at 6.15 and 6.25 τ respectively. On this basis, the compound was identified as dimethyl (1 - oxo - 1H - cycl [3, 3, 2] azin - 2 - yl) fumarate (M^+ 311, $C_{17}H_{13}NO_5$ requires M311) though satisfactory analytical results were not obtained.

(ii) a red band that gave recovered cyclazinone (0.19g).

NUCLEAR MAGNETIC RESONANCE SPECTRA.

Nuclear magnetic resonance spectra were measured at 100Mc/sec with reference to trimethylsilane as internal standard. All spectra are integrated. Chemical shifts are given in τ-values and coupling constants in c/sec.

d = doublet

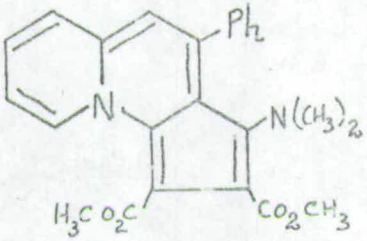
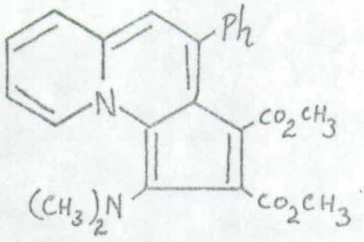
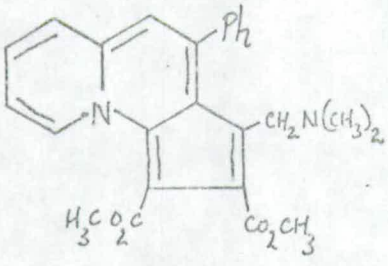
t = triplet

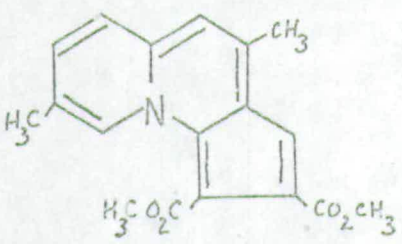
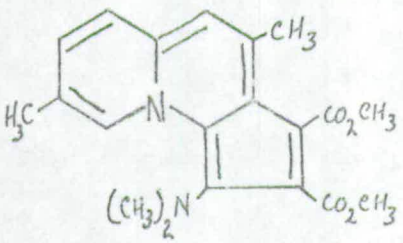
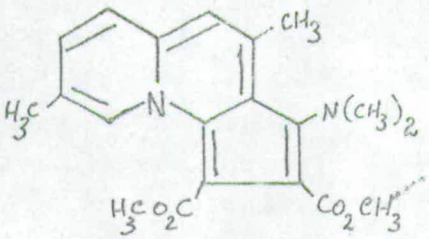
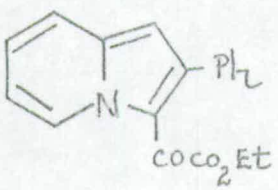
q = quartet

m = multiplet

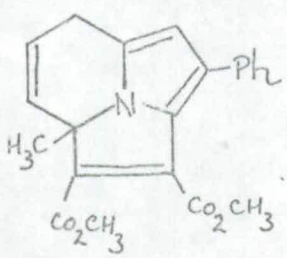
Ph = phenyl

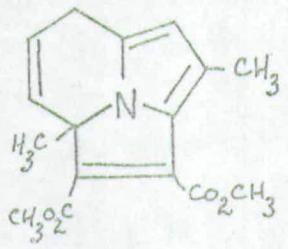
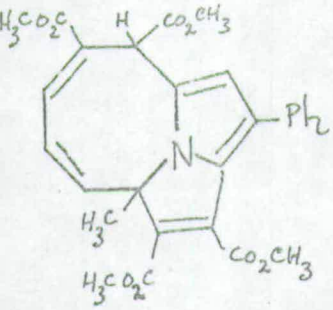
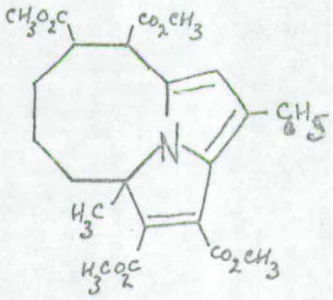
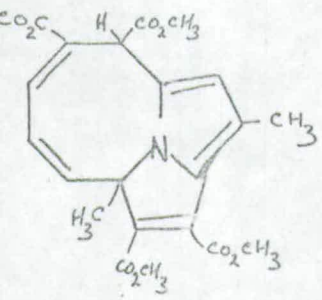
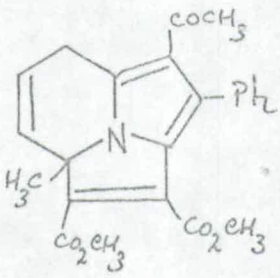
Ar = aromatic

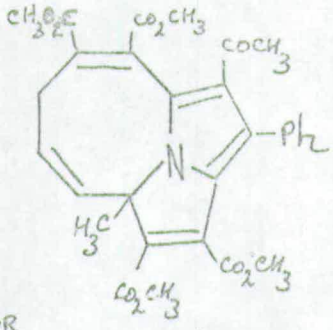
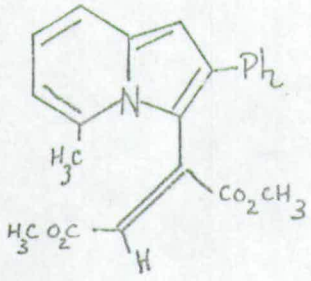
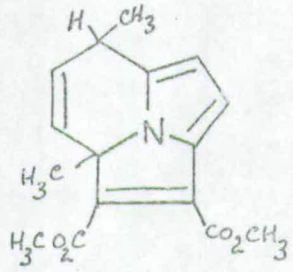
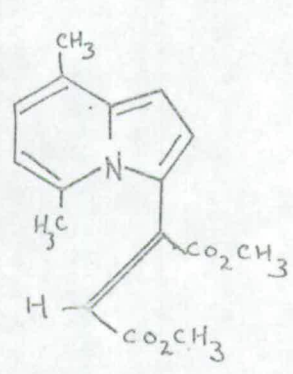
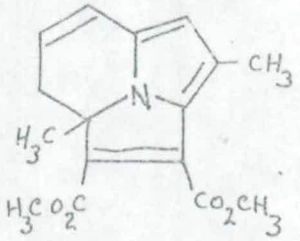
Structure	Solvent	Chemical Shift	J.
		Sections 1 and 2	
	$CDCl_3$	Ar(H-6,7,8 and Ph), 2.2-2.8m; H-5, 2.95s; H-9, -0.6d[a]; (CO_2Me), 6.1s, 6.2s; NMe_2, 7.68s	
	CDCl3	Ar(H-6,7,8 and Ph), 2.2-2.8m; H-9, -1.25d[a]; H-5, 2.98s; (CO_2Me), 6.1s, 6.8s; NMe_2, 7.1s:	
	$CDCl_3$	Ar(H-6,7,8 and Ph), 2.2-2.6m; H-9, -0.43d[a]; H-5, 2.9s; (CO_2Me), 6.15s[b]; NMe_2, 8.3s; (CH_2), 6.9s:	

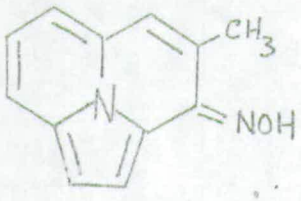
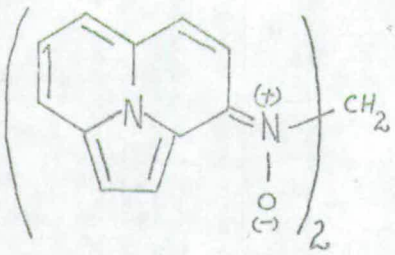
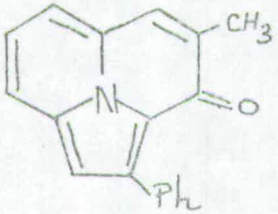
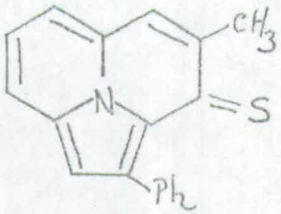
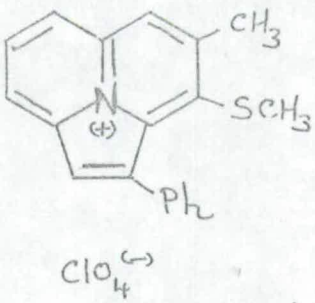
Structure	Solvent	Chemical Shift	J.
	$CDCl_3$	H-6,7, 2.5d, 2.7d; H-9, 0.1s; H-5, 3.08s; H-3, 3.15s; C-Me, 7.4s, 7.6s; (CO_2Me), 6.1s[b]:	
	$CDCl_3$	H-6,7, 2.5d, 2.7d; H-5, 3.20s; H-9, -0.95s; (CO_2Me), 6.1s, 6.2s; (NMe_2), 7.15s; C-Me, 7.3s, 7.60s:	
	$CDCl_3$	H-5,6,7, as above; H-9, -0.3s; (CO_2Me) 6.1s, 6.2s; (NMe_2), 7.1s; C-Me, 7.2s, 7.58s:	
	$CDCl_3$	H-6,7,8, and Ph 2.4-3.1m; H-1, 3.4s; H-5, 0.1d; CO_2Et (CH_2), 6.4q, (CH_3), 8.9t:	

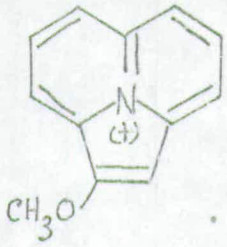
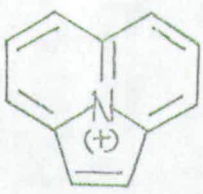
Section 3

	$CDCl_3$	Ph, 2.5-2.9m; H-7, 3.32m[c]; H-4, 3.7s; H-6, 3.95m[c]; (CO_2Me), 6.25s, 6.35s; C-Me, 8.35s; (CH_2), 6.65m[d]:	

Structure	Solvent	Chemical Shift	J.
	$CDCl_3$	H-4, 4.14s; H-6, 4.0m[c] H-7, 3.4m; (CO_2Me), 6.1s, 6.2s; (CH_2), 6.7m[d]; 3-Me, 7.8s; 7a-Me, 8.45s:	
	$CDCl_3$	Ph, 2.6-2.8m; H-9,7, 3.1d, 3.25d; H-4, H-5, 3.25s, 5.05s; H-8, 3.92[e]q; (CO_2Me), 6.2s; 6.3s; C-Me, 8.25s:	$J^{e}_{8,9,7}=6.1$
	$CDCl_3$	H-5, 5.2d; H-4, 3.3s; C-Me, 8.3s; olefinic, 6-8[f]m;	
	$CDCl_3$	H-4, 3.58s; H-5, 5.18s; H-7,9, 3.2[g]; H-8, 4[e]q; (CO_2Me), 6.1s, 6.2t; 3-Me, 7.9s; 9a-Me, 8.4s:	
	$CDCl_3$	Ph, 2.65s; H-7, 3.33[e]q; H-6, 3.9m[c]; (CO_2Me), 6.2s, 6.55s; (COMe), 7.9s; C-Me 8.3s; (CH_2) coupled with H-6,7, 5.6-5.9, 6.4-6.7m;	J=21Hz

Structure	Solvent	Chemical Shift	
 OR 8,9a-dihydro.	CDCl3	Ph, 2.6s; olefinic centred at 3.59[e] and 7.4[h]; (CO_2Me), 6.17s, 6.2s, 6.22s, 6.64s; (COMe), 8.1s; 9a-Me, 8.3s:	
	$CDCl_3$	Ph 2.72s; (CO_2Me) 6.61s, 6.34s: 5-Me, 7.6s; H-6, 3.66d; H-1, 3.38s; H-7, 3.27t; vinylic proton 2.94s; H-8, 2.65[i]:	
	$CDCl_3$	H-3, 3.57d; H-5, 6.5m; H-4, 4.2[e]q; H-6, 3.9; H-7, 3.4[e]q; 5-Me, 8.58d; 7a-Me, 8.39s:	J=7.5H
	CDCl3	H-1,2, 2.95d, 3.45d[J]; H-6,7, 3.35d, 3.59[J]; vinylic proton 4.6s; (CO_2Me), 6.12s, 6.24s; C-Me, 7.52s, 7.58s:	$J_{1,2}$=4 $J_{6,7}$=7
	$CDCl_3$	H-4, 4.1s; H-5, 3.6[e]q; H-6, 4.45[c]; (CH_2) 7.3[J]; (CO_2Me), 6.05s, 6.22s; C-Me, 7.9s, 8.5s:	J_{AB}=18

Structure	Solvent	Chemical Shift
		Section 4
	$CDCl_3$	H-1,2, 1.2d, 2.1d^J; H-5,6,7,8 1.3-1.8m; 4-Me, 7.3s:
	T.F.A.	Ar 1.2-2.2m; (CH_2) 4s; Me 7.1s:
	$CDCl_3$	H-1, 2.8s; H-5,6,7,8 and Ph, 1.9-2.7m; Me, 7.6s:
	$CDCl_3$	H-1, 2.75s; H-5,6,7,8 and Ph, 1.9-2.7m; Me, 7.3s:
	T.F.A.	Ph, 2.3m; H-5,6,7,8, 1.2s; H-1, 1.8s; C-Me, 7.8s s-Me, 6.8s:

Structure	Solvent	Chemical Shift	
	T.F.A.	H-2, 2.68s; H-3,4,5,6,7,8 1.98-2.44m; Me, 5.6s.	
	T.F.A.	H-1,2 1.61s; H-3,4,5,6,7,8 0.9-1.17m:	$J_{1,2}=5.4 \pm 0.2$

a) coupled ortho to H-8, and shows subsiduary splitting due to meta coupling with H-7.

b) two ester signals superimposed to give a six-proton singlet showing splitting at the top of the peak.

c) consists of a one-proton, eight-line multiplet.

d) coupled to H-6 and H-7

e) four peaks made up of a set of doublet of doublets.

f) complex olefinic absorptions of approximately 7H.

g) consists of a triplet and a singlet.

h) doublet of quartets.

i) partially obscured by Ph signal.

j) constitutes an AB system.

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2.	Armit and Robinson	J. Chem. Soc. 1925, 127, 1604
3.	Sondheimer, and Wolovsky	J. Amer. Chem. Soc. 1962, 84, 280
4.	Hückel	Z. Physik, 1931, 31, 204
		Z. Electrochemie, 1937, 43, 754
5.	Wilke	Angew. Chem. 1957, 69, 397
6.	Wittig, Koenig, and Clauss	Ann. 1955, 593, 127
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ABSTRACT OF THESIS

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Title of Thesis Studies of heterocyclic compounds containing bridgehead nitrogen atoms.

1, 2 - dimethoxycarbonylcyclopenta [c] quinolizines have previously been synthesised from 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonyl buta - 1, 3 - dien - 1 - yl) indolizines by thermal methods with loss of dimethylamine and a novel ring expansion of the five-membered ring of the indolizine to a six-membered ring. Studies have been made into the synthesis of cyclopenta [c] quinolizines containing a dimethylamino - substituent in the 1 - and 3 - positions by the action of oxidising agents on the 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) indolizine intermediates, and a mechanism proposed for their formation. Application of this procedure to the analogous 3 - (1 - dimethylamino - 2, 3 - dimethoxycarbonylbuta - 1, 3 - dien - 1 - yl) indoles was unsuccessful.

Attempts to ring expand indolizines to quinolizinium salts also met with failure owing to difficulties in obtaining suitable substituents in the 3 - position of the indolizines.

Studies were carried out into the reaction of 5 - methylindolizines with dimethyl acetylenedicarboxylate in benzene with the formation of dimethyl 7a - methyl - 5, 7a - dihydrocycl [3, 2, 2] azine - 1, 2 - dicarboxylates and tetramethyl 9a - methyl - 5, 9a - dihydrocycl [5, 2, 2] azine - 1, 2, 5, 6 - tetracarboxylates. The latter are believed to be formed by expansion of the six-membered ring to an eight-membered ring in the 2a, 7a - dihydrocycl [3, 2, 2] azines which are the likely initial products of the reaction. When the reaction was carried out in protic solvents, 3 - (1, 2 - dimethoxycarbonylvinyl) indolizines were obtained.

Use other side if necessary.

4 - Methyl - 2 - phenyl - 3 - methylthiocycl [3, 3, 2] azi·ium perchlorate was prepared from 3 - (hydroxyiminoacetonyl) - 5 - [redacted]hyl - 2 - phenylindolizine but attempts to remove the methylthio group from this, using Raney-nickel, proved unsuccessful. Attempted nitration and formylation of cycl [3, 3, 2] azin - 1 - one proved unsuccessful but the cyclazinone reacted with dimethyl acetylenedicarboxylate to give the 2 - (1, 2 - dimethoxycarbonylvinyl) derivative.

The parent cycl [3, 3, 2] azinium perchlorate, synthesised by a previously reported method, with minor modifications, did not undergo Diels-Alder addition with 1, 3 - diphenylisobenzofuran. This shows that the 1, 2 - bond is less reactive than that in the isoelectronic hydrocarbon, acenaphthylene, though the vicinal proton coupling constants ($J_{1,2}$) are about the same for the two compounds.

Reaction of 1 - methoxycycl [3, 3, 2] azinium perchlorate with sodium sulphide gave a mixture of two cyclazinethiones believed to contain the thione group in the 3 - and 6 - positions, respectively.