HETEROCYCLIC COMPOUNDS CONTAINING NITROGEN BRIDGEHEAD ATOMS

by

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TO MY MOTHER

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C O N T E N T S

SUMMARY

Attempts to find a synthesis of quinolizin-4-one more convenient than the previously used route were only partially successful. Although an alternative route was found, the yield was low.

Attempts to obtain derivatives of aza-, oxa- and thiacycl[4,3,3]azines, 10b-azoniapyrene 6H-10b-azapyren-6-one and benzo[a]cycl[3,3,3]-azine from diethyl cycl[3,3,3]azine-1,3-dicarboxylate were unsuccessful.

The chemical shift of the methyl protons in the n.m.r. spectra of diethyl 4-, 5- and 6-methyl cycl[3,3,3]azine-1,3-dicarboxylates should give some indication of the strength of the induced paramagnetic ring current in the ring system. Various attempts to prepare the 4- and 6-methyl derivatives from the diethoxycarbonyl-cyclazine were mainly unsuccessful, though the 6-methyl derivative might possibly have been obtained in one experiment. The 5-methyl derivative was prepared by total synthesis and its n.m.r. spectrum indicated a weak paramagnetic ring current.

Oxidation of diethyl cycl[3,3,3]azine-1,3-dicarboxylate gave a tetraethoxycarbonyl derivative of 10b,14b-diazoniaperopyrene which was shown to be aromatic in nature.

Electrophilic substitution reactions with ethyl cycl[3,3,3]azine-1-carboxylate led to reaction at the 3-position. Attempted addition and oxidation reactions yielded no identifiable products. A further investigation of the properties of cycl[3,3,3]azine was carried out. No identifiable products were obtained from attempted addition and electrophilic substitution reactions but oxidation gave cycl[3,3,3]azine cation and dication.

An e.s.r. spectrum of the cation was obtained, and an interpretation is given. The very low-field values of the proton chemical shifts of the dication gave clear indication of an induced diamagnetic ring current. Attempts to prepare the parent 10b,14b-diazoniaperopyrene dication were unsuccessful, as were attempts to prepare anionic derivatives of cycl[3,3,3]azine and its 1,3-dicyano derivative.

Cycl[3,3,2]azinium perchlorate was prepared from the previously known 2-ethoxycarbonylcycl[3,3,2]azin-1-one. The n.m.r. spectrum of the cation indicated an induced d*a*magnetic ring current but the vicinal coupling constant for the protons of the five-membered ring indicated considerable double bond character in the 1,2-bond. Attempted addition reactions, however, failed to reveal double bond reactivity. A nucleophilic substitution *reaction* was achieved by treatment of the cation with sodium sulphide.

INTRODUCTION

THE ANNULENES

The term 'aromatic' which was originally applied to benzene and its derivatives on account of their characteristic odours gradually became understood to imply a particular and unusual stability of benzene and benzenoid derivatives. Thus although such compounds were formally unsaturated they were nonetheless generally difficult to oxidise and tended to react by substitution rather than addition.

It was recognised by Robinson in 1925 that the behaviour of benzene and its derivatives was in some way due to an association of six valence electrons, the 'aromatic sextet'[1], and this was followed by Hückel's pioneering work[2] in predicting by molecular orbital (M.O.) theory that planar monocyclic systems consisting of trigonally hybridised atoms and containing $(4n+2)\pi$ electrons would show an enhanced stability. Consequently, upon these ideas, the implied meaning of the term aromatic changed yet again, for many compounds which should by the above criteria be considered aromatic are, in fact, highly reactive. However this is only a reflection on the inadequacy of the original definition of aromaticity for the reactivity of a molecule is not a property of the ground state, but depends on the difference in free energy between the ground state and the transition state for the chemical change involved[3]. Thus if the difference is small then the molecule will be reactive irrespective of the energy content of the ground state. We therefore have the presently accepted definition of aromaticity whereby a compound is to be considered aromatic if there is a measurable degree of cyclic delocalisation of the π-electron system in the ground state of the molecule.

A consequence of this delocalisation of π-electrons is that the bond lengths in the aromatic ring or rings tend not to alternate and are of length intermediate between that of single and double bonds[4,5]. Further consequences of this delocalisation of π-electrons may be seen in the "lower-than-classical" energy content of these compounds[6], and in their electronic absorption spectra[7]. More recently the nuclear magnetic resonance (n.m.r.) spectra of aromatic compounds (together with diamagnetic susceptibility measurements) have been found to show a characteristic feature, in that protons joined to the ring and external to it absorb at lower field (benzene 2.81T) than protons of polyolefinic systems (4.1 - 4.6T). This deshielding effect is believed to be due to the freedom of the π-electrons to circulate around the ring under the influence of the applied magnetic field. This ring current is induced in a diamagnetic sense; it gives rise to a secondary magnetic field that opposes the applied field inside the ring and reinforces it outside the ring. On this basis Elvidge and Jackman have defined an aromatic compound as a cyclic conjugated compound that will sustain an induced diamagnetic ring current in an applied magnetic field[8].

The obvious compounds by which the validity of the ideas of Hückel could be investigated are the annulenes. However, until comparatively recently, the only known fully-conjugated monocyclic systems were benzene ([6]annulene) and cyclooctatetraene ([8]annulene)[9], higher vinylogues having resisted classical methods of synthesis. The discovery[10-14], in 1956, of simple methods for the preparation of large-ring hydrocarbons containing 1,3-diacetylenic units and their subsequent prototropic re-arrangement to fully-conjugated cyclic products[15] has resulted in prolific researches by the Sondheimer group leading to the synthesis[16,27] of an entire series of annulenes.
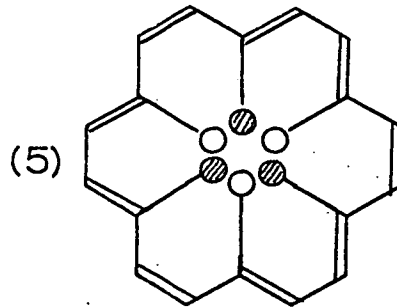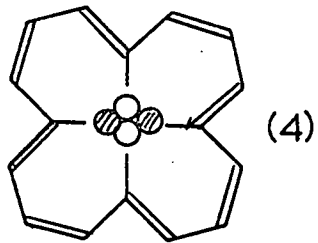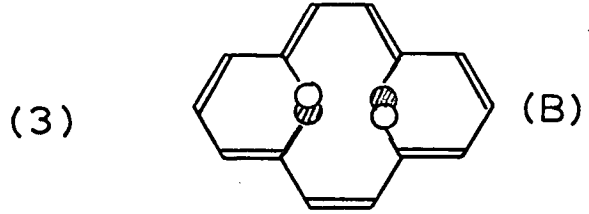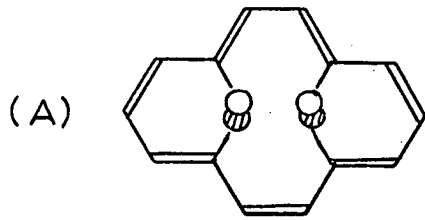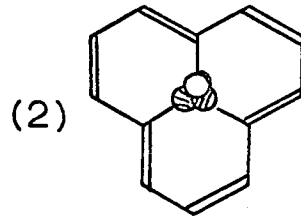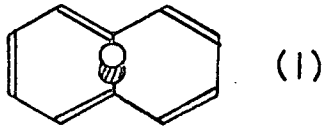
FIG.1

However, one of the requirements for a compound to be able to exhibit delocalisation of its π-electrons is that the ring be planar, or nearly so, and scale drawings[17] (Fig. 1) had suggested that annulenes [10] to [28] would show severe steric interference between the internal hydrogen atoms. It has been pointed out[18] however that some compounds are known which are buckled, or which possess rings distorted from the normally preferred planar geometry, and yet which remain aromatic in character, e.g. di-p-xylylene and di-m-xylylene[19]. In the case of [18]annulene (5) it has been suggested[18,20] that the molecule should be almost, if not completely planar, and should, since it obeys Hückel's rule with respect to the number of π-electrons, show aromatic character.

This view has been substantiated by both physical and chemical means. Thus X-ray crystallography[21,22] has shown that [18]annulene is a centrosymmetric molecule (indicating that there is no bond alternation), and that it deviates from planarity by less than 0.1Å. Low temperature (-60°) n.m.r. studies[23] have shown two regions of absorption, centred at 0.72T (12 protons) and 12.99T (6 protons). These absorptions have been assigned to the external and internal protons respectively and on this basis [18]annulene is considered to be aromatic[24,25]. Heating the solution leads first to broadening of the bands and then to coalesence until at 110° a sharp singlet (4.55T) is observed. The most likely explanation of this behaviour is thought to be rapid conformation al switching of protons between external and internal positions such that averaging of the chemical shifts occurs[26]. Thus the spectrum at 110° is an example of what is termed the "mobile" type while the spectrum at -80° is of the "non-mobile" type[27].

Attempts to bring about electrophilic substitution originally led to
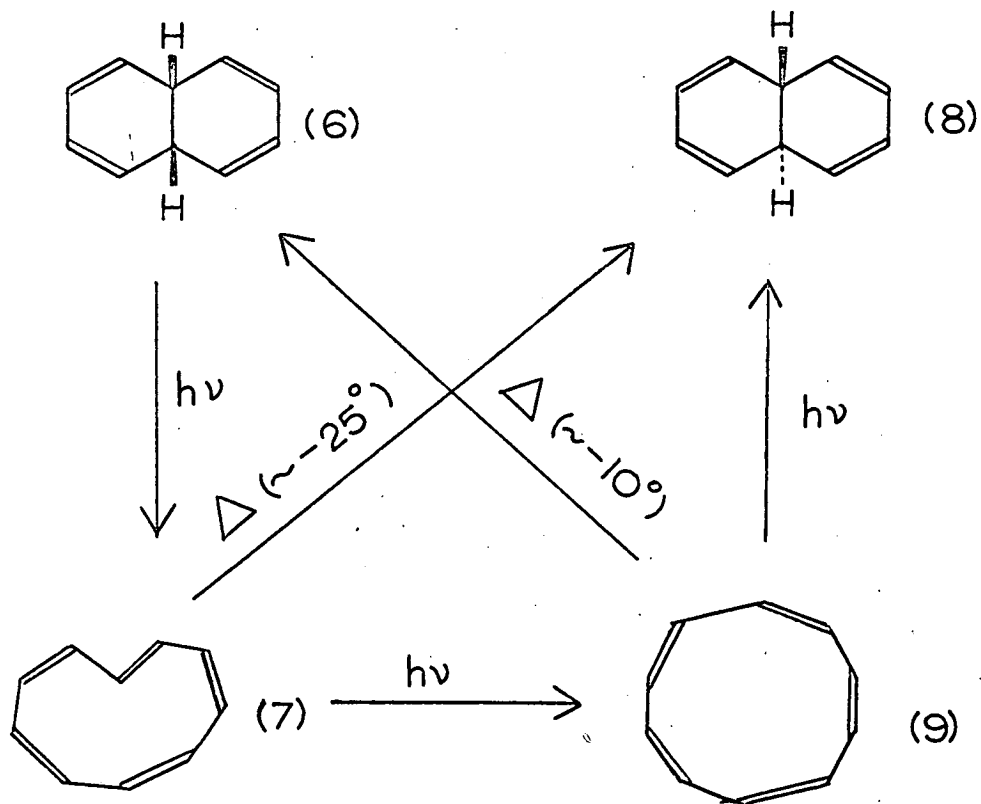
FIG. 2

addition or decomposition,[13,28] but under milder conditions [18]annulene has been shown to yield mononitro and monoacetyl derivatives[29]. With maleic anhydride [18]annulene underwent an addition reaction[13,27].

It would seem that both the classical and modern definition of aromaticity should be applied with caution. In the case of the former, failure to carry out a chemical reaction may merely signify that suitable experimental conditions have not been found, and, in the latter case, that the n.m.r. spectrum at the temperature of observation may not be a good criterion of aromaticity because of the possible occurrence of rapid conformational changes.

The n.m.r. spectrum of [14]annulene[24,25,30] also exhibited temparature dependence, and showed that the molecule existed as two conformers (3 A&B)[23]. These have been separated and shown by n.m.r. studies to equilibrate rapidly in solution[31]. These studies and X-ray analysis[32] have confirmed the aromaticity of one of the conformers (A). Chemical substitution has not yet been achieved, due, in part no doubt, to the instability of the molecule, decomposition occurring on exposure to light and the atmosphere for a period of one day[33].

Until recently [10]annulene had resisted synthetic endeavour[34], but reinvestigation of the low temperature photolysis of dihydronaphthalene (6) gave a solution containing the required product[35] (Fig. 2). The n.m.r. spectrum of this solution showed a temperature dependent signal at 4.16T (-40°) and a sharp temperature independent signal at 4.34T. The signals were assigned on the basis of other experimental data, to structures (7) and (9) respectively. The sharp singlet shown by (9) is taken to indicate all cis-geometry of the molecule, for since the signal is temperature-independent
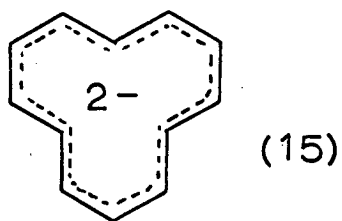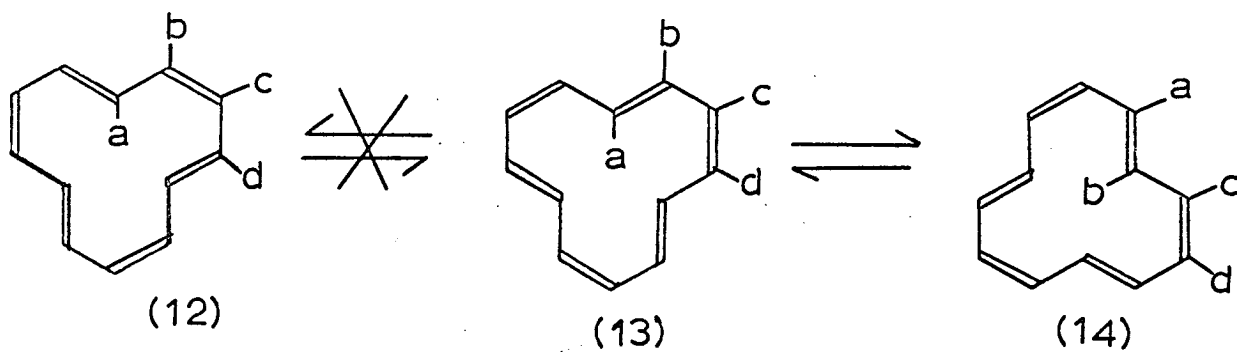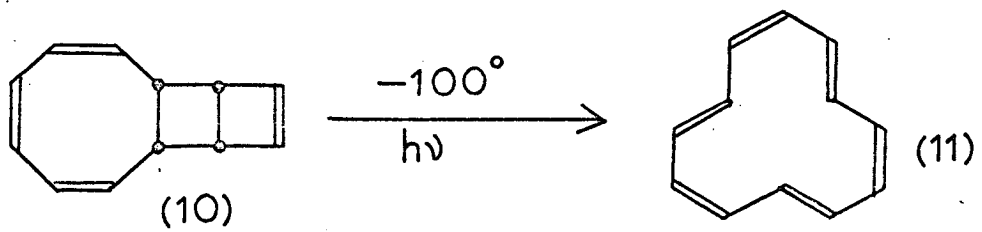
FIG. 3

there is no indication of rapid conformational change. The chemical shift suggests olefinic character which may be due to gross non-planarity.

4n-Annulenes have also been investigated, the synthetic route to [16]-[25,36-38] [20]-[39,45] and [24][40,41] annulene being essentially the same as that used for their 4n+2 analogues. X-ray analysis of [16]annulene (4) has confirmed the non-planarity of the molecule and has also indicated bond alternation between 1.46$\overset{o}{A}$ and 1.34$\overset{o}{A}$. The n.m.r. spectra of these annulenes [36,39-41] showed temperature dependence in a similar manner to [18]annulene.

Thus [16]annulene at room temperature[36] showed a sharp singlet (3.27T), which was still present with slight broadening at -40°, but on cooling to -120° the "non-mobile" type of spectrum was obtained, bands appearing at -0.32T (4 protons) and 4.81T (12 protons)[38]. 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 is called a paramagnetic ring current[27,42-44]. This reversal of position is also exhibited by [24]annulene[46] on cooling to -80°.

[12]Annulene (2) has recently been prepared[47] by u.v. irradiation, at -110°, of syn-tricyclo[6,4,0,0^{9,12}]dodeca-2,4,6,10-tetraene (10) (Fig. 3). At -80°, its n.m.r. spectrum shows two peaks of equal intensity at 3.12T and 4.03T, which are attributed to the configuration (11) in which cis- and trans-bonds alternate. The peaks of equal intensity are explained by rapid conformational mobility as shown (13)⇌(14), π-bond shift (12)⇌(13) not occurring (although it is a characteristic of other 4n π-electron systems) since on account of the drastic interaction of the three inner protons the molecule is unable to become even approximately planar, which is considered to be necessary for π-bond shift[48].

Cooling to -170° [47] gives an n.m.r. spectrum with two broad peaks [48] at 2.12T (3 protons) and 4.07T (9 protons) which is clearly the spectrum of the "non-mobile" type showing a weak paramagnetic current, the weakness being due to the fact that the molecule must deviate appreciably from planarity.

The dianion of [12]annulene (15) has also been prepared[49] and considering the steric interactions that must still be occurring, it shows remarkable stability. Thus while [12]annulene itself undergoes rapid thermal rearrangements at -40° [47] the dianion is stable at +30°.

The n.m.r. spectrum (at -90° or 30°) is also of considerable interest showing three signals at 3.02T (6 protons), 3.77T (3 protons) and 14.6T (3 protons). Thus despite the addition of two electrons the signals due to the external protons have shown a downfield shift and this, together with the very large upfield shift of the internal protons clearly indicates the presence of a diamagnetic ring current.

Although the work on annulenes has contributed much to our understanding of Hückel's rule an inherent defect in the approach is caused by the steric interaction of the internal hydrogen atoms which severely restrict the molecules ability to become planar and thus to exhibit fully developed diamagnetic or paramagnetic ring currents.

One solution to this problem is in the use of dehydroannulenes, an extensive range of which is known from [12] to [30][25,30,31,36,37,39,40,45,50-59] with the exception of [28]. Some examples of these are shown in Fig. 4. Thus (16) is 1,5,9-tridehydro[12]annulene, (17) 1,8-bisdehydro[14]annulene, (18) 1,9-bisdehydro[16]annulene, (19) 1,7,13-tridehydro[18]annulene and (20) is 1,11-bisdehydro[20]annulene. Studies of these compounds have confirmed the pattern already documented for the parent annulenes. Thus the n.m.r.

(16)

(17)

(18)

(19)

(20)
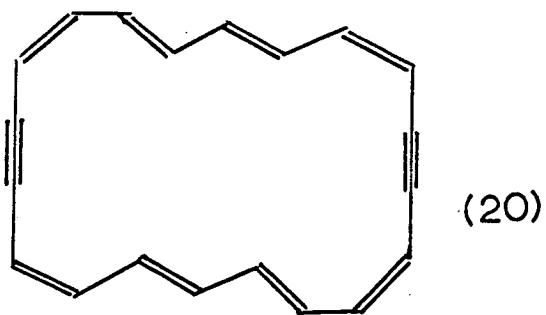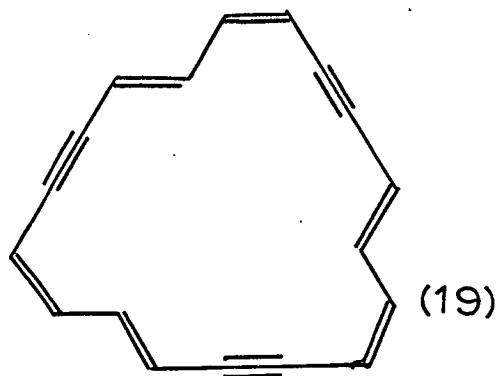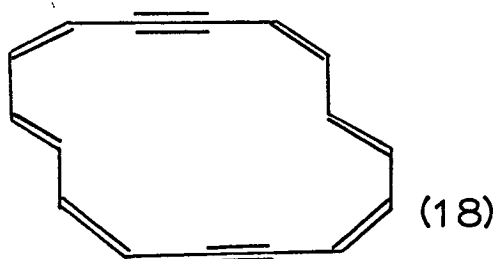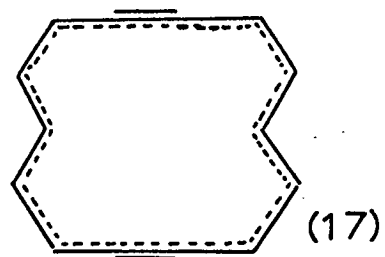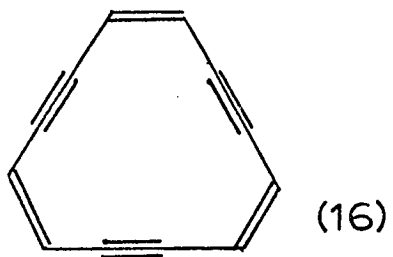
FIG. 4

spectra of the $(4n+2)\pi$-dehydroannulenes[37,38,42] have, with the exception of the [30]dehydroannulenes, shown the effects of a diamagnetic ring current, and their $4n\pi$ analogues have shown a reversal of the chemical shifts of the inner and outer protons owing to a paramagnetic current.

However, where this paramagnetic current is present in the annulenes (e.g. [12]- and [16]annulene) it is seen to be considerably weaker than the diamagnetic current in, for example, [14]- and [18]annulene as shown by the smaller separation of the inner and outer proton signals in their n.m.r. spectra. Part of the reason for this is presumably because there is a much smaller driving force for the $4n$ π-electron annulenes to become planar since they cannot achieve increased stability in this way.

Evidence for this is seen in the fact that much lower temperatures are required to observe the paramagnetic ring current of [12]- and [16]annulene (-170° and -120°) than to observe the diamagnetic ring current of [14]- and [18]annulene (-60° and -20°)[27]. Because of this lack of planarity the annulenes themselves are unable to provide an answer to the question of whether or not the paramagnetic current is intrinsically a weaker current than a diamagnetic one. Because of their lower mobility (due to acetylenic linkages and the reduced numbers of internal hydrogen atoms) a study of suitable dehydroannulenes is more likely to provide a solution.

Thus 1,5-bisdehydro[12]annulene has been synthesised and was assigned structure (21) with one trans double bond[60]. The n.m.r. spectrum showed a two proton quartet centred at $-0.9T$ (together with other absorptions in the region $5-6T$) indicating either that the trans double bond is perpendicular to the plane of the ring[60] (which seems unlikely) or that there is rapid inter-conversion between two equivalent planar conformers[52] which would lead to

averaging of the n.m.r. signals of H^1 and $H^{1'}$. Cooling to $-80°$ had no significant effect[27].
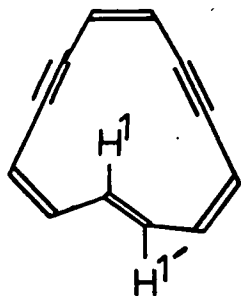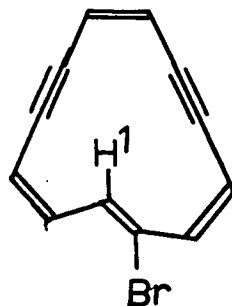
(21)   (22)

The synthesis of 5-bromo-1,9-bisdehydro[12]annulene (22) has since been reported and the n.m.r. spectrum investigated with very significant results[52]. It is clear that no conformational interconversion of this system can occur owing to the size of the bromine atom. The n.m.r. spectrum is therefore that of a single conformer and contains a band at $-6.4T$, unequivocally assigned to the internal proton H^1.

The only other kind of shift of similar magnitude is in the (4n+2) π-electron annulenes. The largest _upfield_ shift among these is found for the inner hydrogens of 1,8-bisdehydro[14]annulene (17) at $15.5T$[61], a shift of ca. 11 ppm compared to cyclic monoolefins (4.4T). The same comparison made with the value of the chemical shift for H^1 in (22) also gives a shift of ca. 11 ppm, but in the _opposite_ direction.

This suggests a strong paramagnetic ring current in (22), and would seem to indicate that any 4n π-electron system (up to n = 6 or 7) would (if held planar or nearly so, and if rapid conformational changes do not take place) probably exhibit an appreciable paramagnetic ring current.

(23)
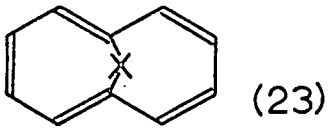
X= CH₂,O,NH,NCH₃,
   C=CH₂,NCOCH₃

(24)

X = O,CH₂

X = O,S   (25)

(26)

(27)

(28) $\xrightarrow[\text{THF}]{\text{K}}$ (29)

$\left[\quad \right]^{2-}$ 2K⁺
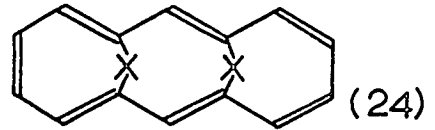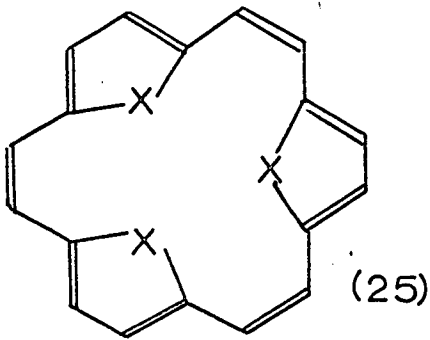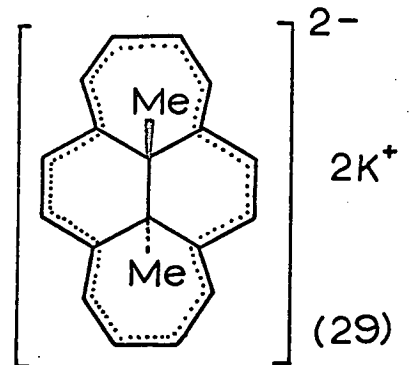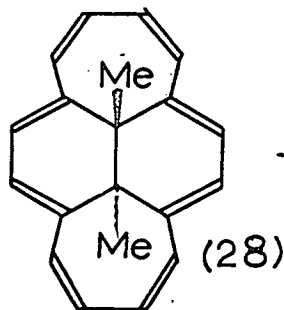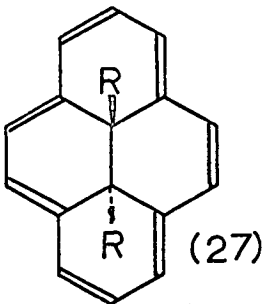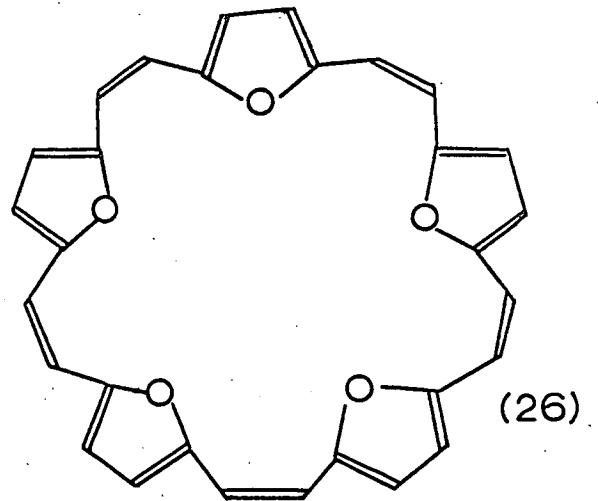
FIG. 5

A further approach to the problem posed by the inwardly directed hydrogen atoms of the annulenes is the synthesis of compounds in which these hydrogens are replaced by saturated carbon bridges or polyvalent hetero atoms. Thus a large number of $(4n+2)\pi$-electron bridged annulenes have been prepared. For example 1,6-bridged [10] annulenes (23)[62-74] and 1,6:8,13-bridged [14] annulenes (24)[68,75] have been synthesised by Vogel and co-workers. Starting from various furfural derivatives, Elix has synthesised a number of large-ring bridged annulenes. To date [18]-, [22]-, [24]-, [30]- and [36]-[75-82] bridged annulenes (25) and (26) have been synthesised in this way. The n.m.r. data are in agreement with Huckel's rule; thus the n.m.r. spectrum of [18] annulene trioxide (25, X=O) shows chemical shifts consistent with the presence of a diamagnetic ring current whereas that of [24] annulene tetraoxide (26) shows evidence of a paramagnetic ring current. The occurrence of absorption bands in the 2.4-4.2T region for the [30]- and [36] annulene polyoxides indicates that neither a diamagnetic nor paramagnetic current is sustained in these large molecules, consistent with the view of Dewar and Gleicher[83] (and others[84]), that $4n+2$ annulenes should be aromatic up to and including [22] annulene, whereas [26] annulene should be non-aromatic.

The dihydropyrene derivative (27) has been synthesised by Boekelheide[85-88] and several derivatives[88,89] are also known. They have been shown to be aromatic by n.m.r. spectroscopy and electrophilic substitution reactions have been accomplished. There has been a recent report of the synthesis of a new bridged [16] annulene (28) and its dianion (29)[89]. The dianion, with 18π-electrons, has been shown to be aromatic, but (28) shows only a weak paramagnetic ring current. It is suggested that this may be due to buckling of the seven membered rings. There has also been a recent report of the synthesis of

(30)

$$\left[\quad CH_2 \quad \right]^+ \quad (31)$$

$$\left[\quad \begin{array}{c} Me \\ Me \end{array} \quad \right]^{2-} \quad (32)$$

$$\left[\quad \begin{array}{c} OCH_3 \end{array} \quad \right]^- \quad (33)$$

$$\begin{array}{c} R \\ CH_2 \quad O \end{array} \quad (34)$$
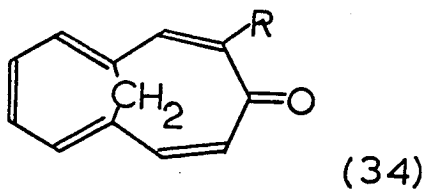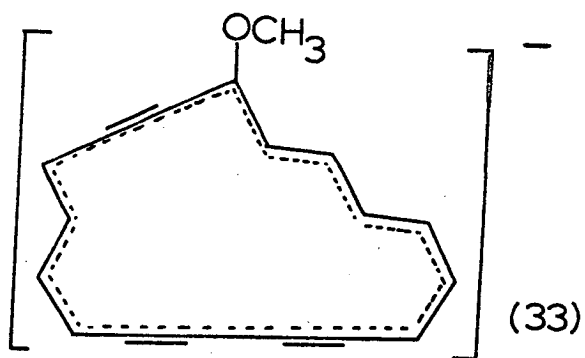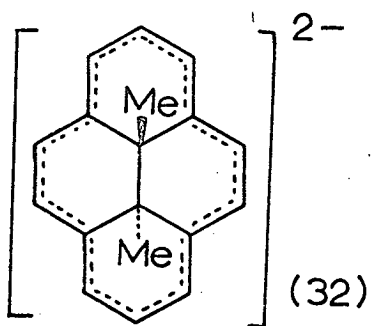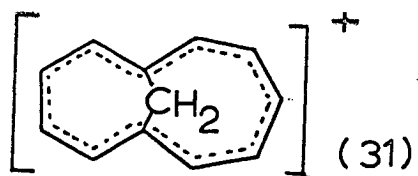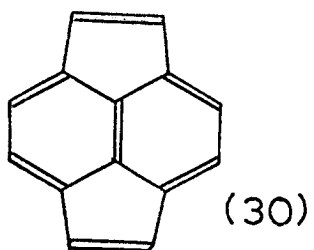
(a) R = H

(b) R = OH

FIG. 6

pyracylene[90] (30) which shows the expected paramagnetic ring current, but it appears to be rather weak.

Present work in this field appears to be concentrating on the synthesis of annulene ions and annulenones (Fig. 6). Bicyclo[5,4,1]dodecapentaenylium cation (31)[91,92], [16]annulene dianion[93], and bicyclo[4,3,1]decatetraenyl anion[94] have been shown to be aromatic, whereas trans-10b, 10c-dimethyl-dihydropyrene dianion (32)[95] and 1-methoxy-2,8,10-tridehydro annulenyl anion (33)[96] demonstrate clearly the effect of a paramagnetic ring current. [13]-[97] and [17]annulenone[98] derivatives are known, and the latter in accordance with prediction,[99] is non-aromatic. One of the more recent additions to the literature of these types of compounds is that of Keto and ketohydroxy derivatives of (34)[74,13]. As expected these show chemical properties analogous to those of tropone and tropolone.

(35)

(36)

(37)

(38)

(39)

(40)
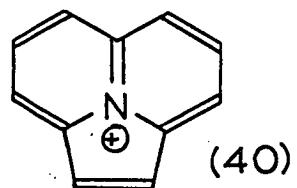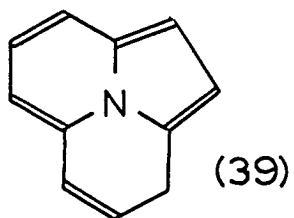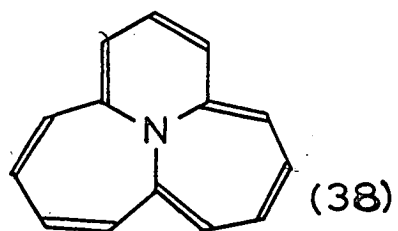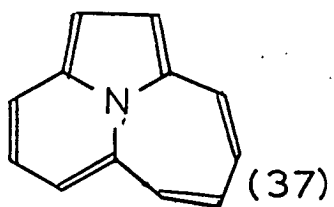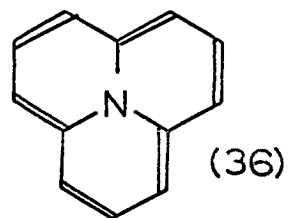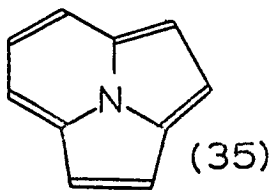
FIG. 7

THE CYCLAZINES

Boekelheide[100] 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. The individual members are distinguished by specifying the number of atoms on the peripheral cycle between points bonded to the internal nitrogen atom. The structures (35)- (38) 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 also accommodates both ionic and partially saturated structures. Thus structure (39) is 3-H-cycl[3,3,2]azine and structure (40) is dehydrocycl[3,3,2]azinium ion. 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 (35) and (36) are thus respectively designated pyrrolo[2,1,5-cd]indolizine and pyrido[2,1,6-de]quinolizine.

While these compounds may be regarded as bridged annulenes, the effect of the nitrogen lone-pair orbital must also be taken into account and separate calculations are necessary for each molecule in order to predict whether or not it is likely to be aromatic. Initial calculations[100,101] indicated that structures (35), (36) and (38) should all possess a resonance energy higher than that of their monocyclic counterparts. Bond orders, π-electron densities and energies of excited states have been evaluated[101], and predictions made regarding the orientation of electrophilic substitution. A more recent calculation[102] has confirmed that cycl[3,2,2]azine should possess considerable resonance energy, but indicated that the most energetically favourable structure of cycl[3,3,3]azine is that containing alternate single and double bonds. It seems possible, therefore, that the number of peripheral
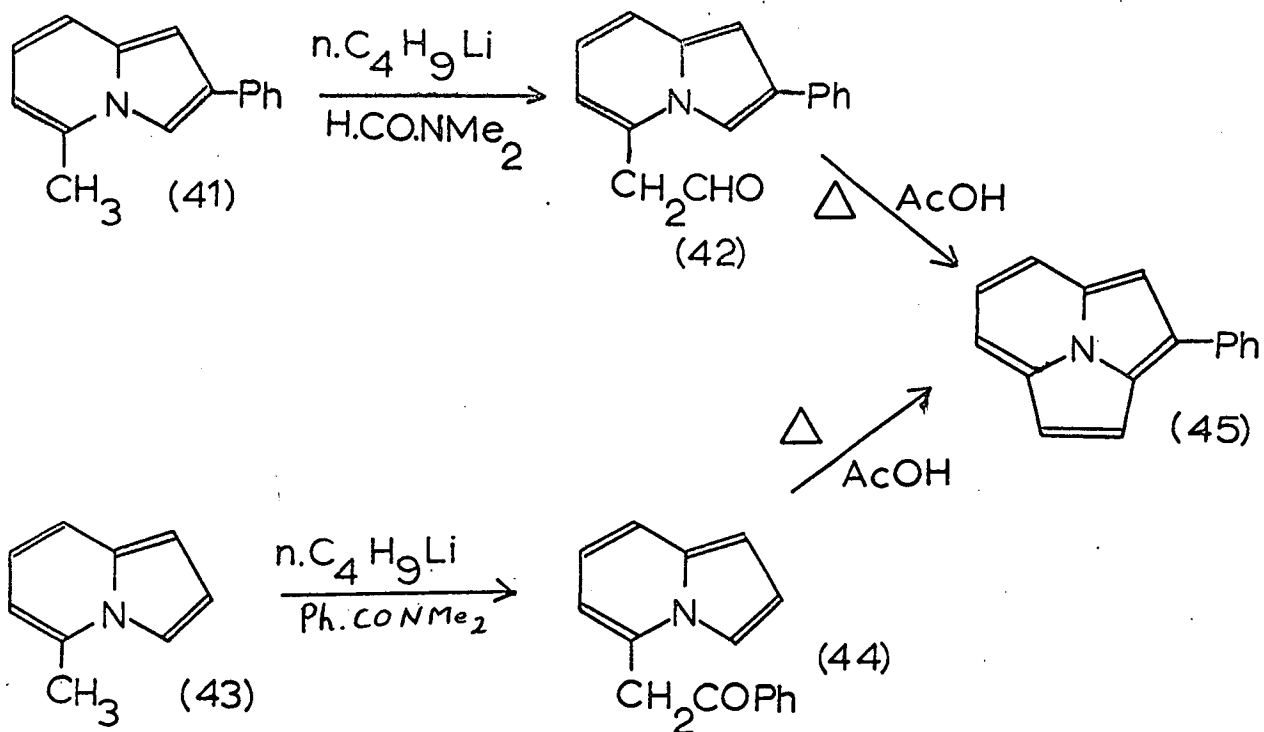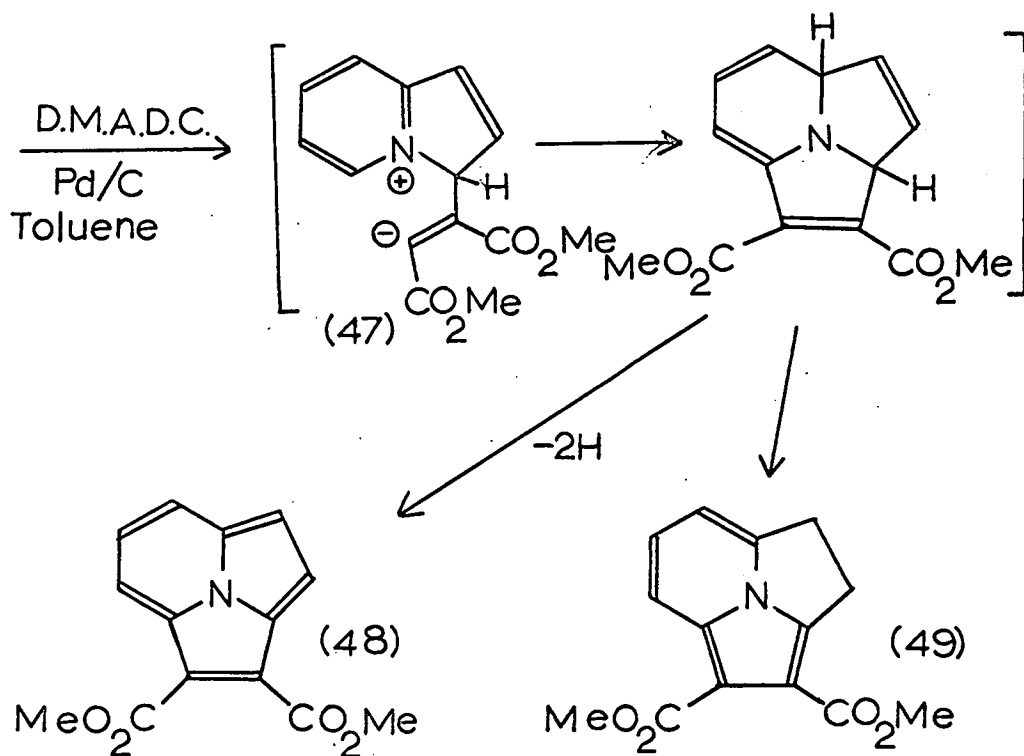
FIG. 8

π-electrons is the most important factor in determining the presence or absence of aromaticity, i.e. that Hückel's rule will still be valid. Experimental results have so far confirmed this possibility.

Until comparatively recently, the only known member of the cyclazine series available for assessment of the validity of these conclusions was cycl[3,2,2]azine[100,103] which has consequently formed the object of several physical[104-109] and chemical[100,103,104,110,111] studies. The tricyclic structure assigned to the molecule has been conclusively demonstrated by X-ray[109] and n.m.r.[104,105] investigations, and also by unambiguous chemical synthesis from indolizine precursors[100,103].

An X-ray analysis of the parent system has unfortunately not been possible owing to the unusual nature of its crystalline structure[109]. An X-ray diffraction study conducted on the 1,4-dibromo derivative[109] has shown that the molecule is almost exactly planar and has also provided details of bond-lengths and bond-angles.

The presence of a plane of symmetry in the molecule is clearly demonstrated by n.m.r. studies[104,105]. Thus the spectrum of the parent system consists of an A_2B multiplet arising from the protons of the six-membered ring (5,7-protons at 2.17T; 6-proton at 2.41T) and two identical AB quartets arising from the protons of the five-membered rings (1,4-protons at 2.81T; 2,3-protons at 2.50T). The chemical shifts of the latter have been unequivocally assigned to their appropriate ring positions by deuteration studies[104] on the 2-methyl derivative.

Synthetic studies confirm the symmetrical nature of the ring system. Thus cyclodehydration of 5-formylmethyl-2-phenylindolizine (42) and 5-phenacylindolizine (44) under mild conditions yielded[112] the same 2-phenylcycl[3,2,2]azine (45).

(a)

D.M.A.D.C.
in dry benzene

D.M.A.D.C.
in methanol

(50)

(51)

(b)

MeO$_2$C   (52)

MeO$_2$C   Ph   (53)

(c)

(54)

(55)

(56)
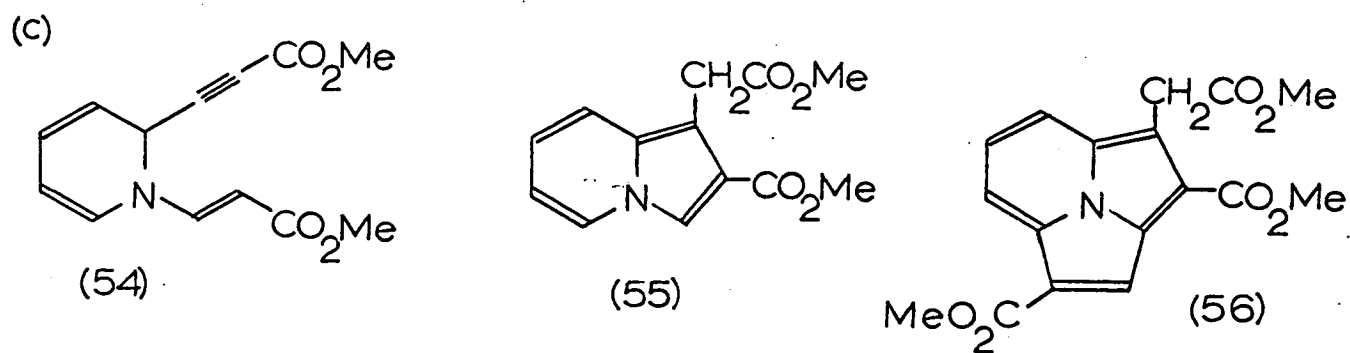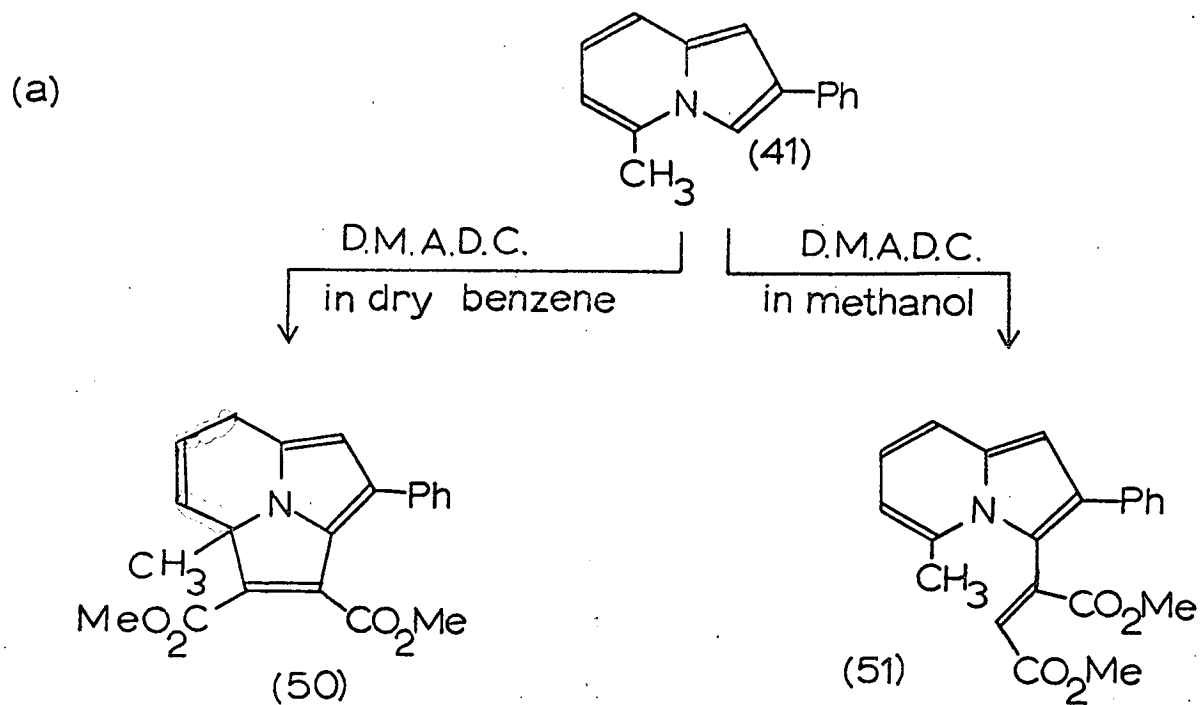
FIG. 9

The parent heterocycle has been synthesised by a similar sequence from 5-methylindolizine (43) and dimethylformamide.

However, a more convenient approach to the system and its derivatives has resulted from the reaction of activated acetylenic esters with indolizines in the presence of a dehydrogenation catalyst[103,104,110,113]. These reactions appear to proceed via zwitterionic intermediates formed as a result of Michael addition to the acetylenic bond. The scheme (Fig. 8b) has been postulated[103] to account for the reaction products from indolizine and dimethyl acetylene-dicarboxylate under aprotic conditions. Alkaline hydrolysis of (48) to the corresponding diacid and subsequent decarboxylation with copper chromite yielded the parent system (35).

Although the intermediacy of the zwitterionic species has not been formally demonstrated, strong support for its existence has been provided by studies on related systems carried out in this Department. Thus, reaction of 5-methyl-2-phenylindolizine (41) with dimethyl acetylenedicarboxylate in methanol as solvent yielded only the red open chain adduct (51) while reaction in anhydrous benzene gave, in addition, the yellow cyclo adduct[114] (50) (Fig. 9a). Formation of the linear adduct as the sole product under protonic conditions may be accounted for in terms of interception, by rapid protonation, of a zwitterionic intermediate. Dihydrocyclazine formation in an aprotic solvent presumably involves change neutralisation of the intermediate by cyclisation, the latter reaction proceeding at a rate comparable with intra- or intermolecular proton transfer.

Addition of activated acetylenic esters to indolizine precursors has been extensively used in the synthesis of a variety of cycl[3,2,2]azine derivatives[103,104,110,111,113]. Thus, the parent indolizine reacts with methyl propiolate[111] and
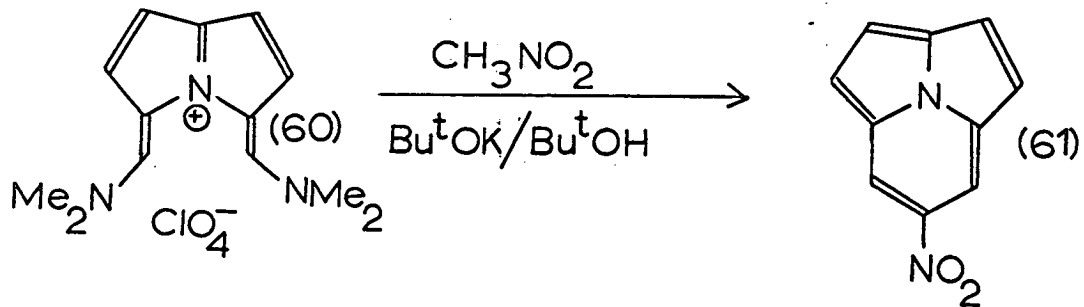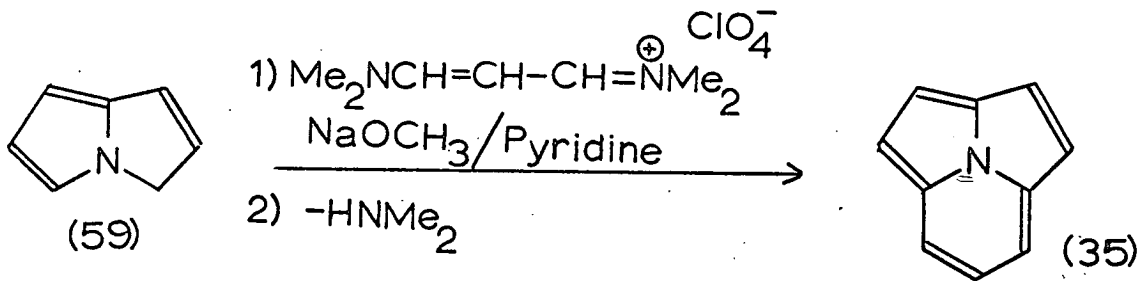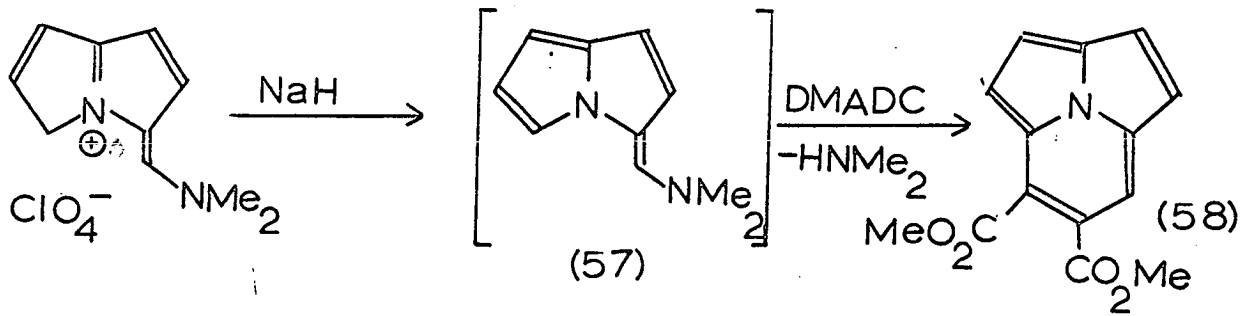
FIG. 10

methyl phenylpropiolate[103] to yield, respectively, 1-methoxycarbonylcycl[3,2,2]-azine (52) and its 2-phenyl analogue (53) (Fig. 9b).

Cycl[3,2,2]azine has recently been prepared in this Department from pyrrolizine derivatives[116] (Fig. 10). 3-(Dimethylaminomethylene)-3H-pyrrolizine (57), (prepared in situ) underwent a cyclo-addition with dimethyl acetylene-dicarboxylate to give a cycl[3,2,2]azine derivative (58) from which the parent system was prepared. Cycl[3,2,2]azine was also obtained in low yield by reaction of 3H-pyrrolizine (59) with 3-dimethylaminoprop-2-en-1-ylidenedimethyl-ammonium perchlorate. 6-Nitrocycl[3,2,2]azine (61) was prepared from 3,5-bis-(dimethylaminomethylene)-3H,5H-pyrrolizinium perchlorate (60) by reaction with nitromethane in the presence of base. Attempts to reduce the nitro-group were unsuccessful. Electrophilic substitution reactions were effected with the 6-nitrocyclazine, reaction occurring at the 1- and 4-positions.

An unusual synthesis of 1-methylcycl[3,2,2]azine has been reported[115] from pyridine and methyl propiolate in acetonitrile as solvent. The triester (56, (Fig. 9c) which is the sole product of the reaction, is considered to result from oxidative addition of the acetylene to an indolizine intermediate (55), the latter being formed from a 1,2-dihydropyridine precursor (54). Hydrolysis to the corresponding tricarboxylic acid followed by decarboxylation with copper chromite in quinoline yielded the 1-methyl derivative.

The physical and chemical properties of cycl[3,2,2]azine have been the subject of a great deal of work. Molecular orbital calculations[100,101,102,117] had suggested that the molecule should show considerable stability, the resonance energy being calculated[102] (0.82 e.v.) to be comparable with that of benzene (0.87 e.v.). These calculations[100] also suggested that electrophilic substitution should occur at position 1.

Experiments have confirmed these results. Thus the parent cyclazine is a non-basic, crystalline, fluorescent, yellow compound exhibiting marked stability towards light, heat and air. Its ultra-violet spectrum in ethanol remains unaffected by added acid, indicating that the nitrogen lone-pair is associated with the conjugated π-electron system and thus not readily available for bonding[103]. Chemically, the cyclazine behaves as a normal, stable aromatic compound undergoing substitution with a variety of electrophilic reagents[103] (Fig. 11).

Orientations of the substituent groups have been experimentally demonstrated[104,105,111] and shown to be consistent with molecular orbital calculations[100].

Several interesting cycl[3,2,2]azine systems, (62), (63) and (64) (Fig. 11b), incorporating one or more nitrogen atoms in the peripheral skeleton have been reported[118-120]. Such compounds are of interest since they may aid the elucidation of the parameter to be assigned to nitrogen in the molecular orbital calculations[119]. All three systems are typically aromatic, their spectroscopic properties being closely similar to those of their mono-aza analogues. However, unlike the latter compounds, they are readily soluble in dilute acids , (64) not specified , thus suggesting that the lone pairs of electrons on the peripheral nitrogen atoms are available for bond formation.

6-Azacycl[3,2,2]azine has recently been prepared in this Department[116] with the intention of investigating further the effect of the peripheral nitrogen atom. The synthesis was achieved by reaction of 3,5-bis(dimethyl-aminomethylene)-3H,5H-pyrrolizinium perchlorate (60) with ammonia. The n.m.r. spectrum was simple, showing a two-proton singlet at 0.79T and an AB system comprising doublets at 2.34T and 2.55T, J_{AB} = 4.5Hz. These absorptions
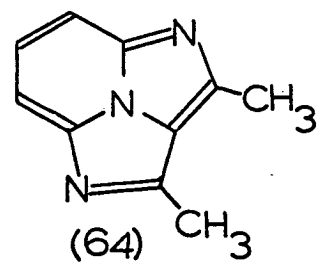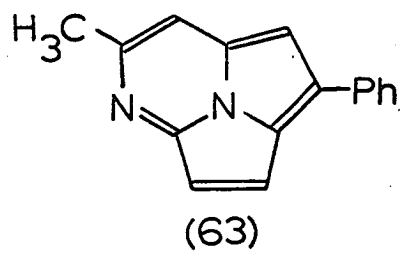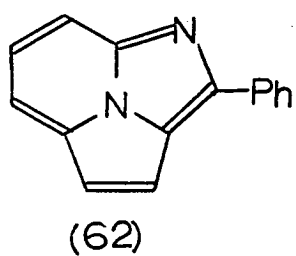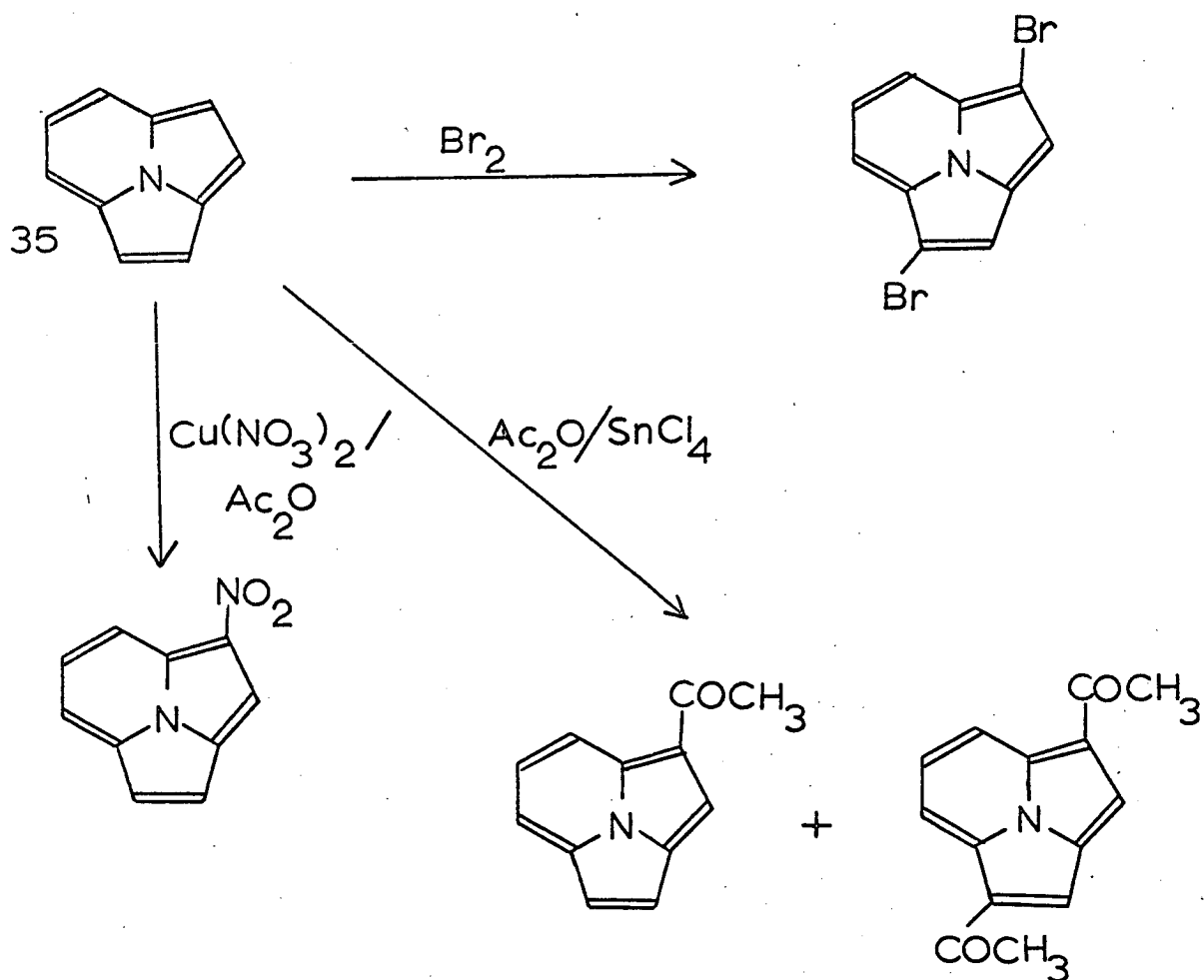
FIG. 11

were attributed to H-5,7; H-2,3; H-1,4 respectively. The u.v. spectrum was very similar to that of cycl[3,2,2]azine, but, unlike cycl[3,2,2]azine, showed quite large spectral changes on addition of small amounts of acid. These changes were larger than for other azacycl[3,2,2]azines[118-120], and are taken to indicate that the structure (65) makes a significant contribution to the resonance hybrid.

(65)
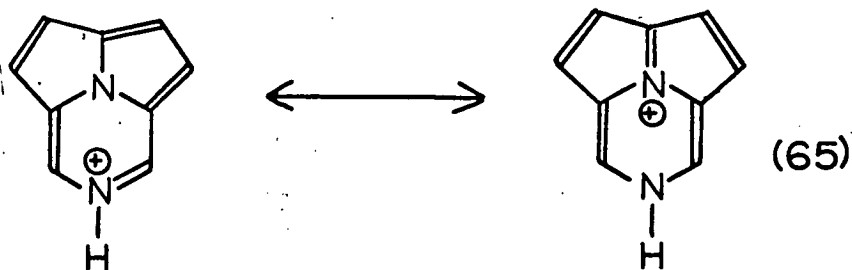
Electrophilic substitution reactions were unsuccessful, with the exception of bromination, when the 1-bromo and 1,4-dibromo derivatives were obtained, and nitration with cupric nitrate in acetic anhydride when the 1,7-dinitro derivative was obtained. The general difficulty in achieving electrophilic substitution reactions was thought to be due to protonation in the acidic conditions and is reminiscent of pyridine. This similarity with pyridine was confirmed when reaction with methyl iodide yielded 6-methyl-6-azacycl[3,2,2]-azinium iodide. Because of this similarity the 5- and 7-positions of the azacyclazine, which are analogous to the 2- and 6-positions of pyridine, were expected to be susceptible to attack by strong nucleophiles. This was confirmed when reaction with phenyl-lithium yielded the 5-phenyl and the 5,7-diphenyl derivatives.

Although work on the cycl[3,2,2]azine system has met with considerable success, attempts to synthesise the cycl[3,3,3]azine system for some time met

(66)   (67)   (68)

$NaCH(CO_2R)CO_2Bu^t/THF$

ClO_4^- Cl

RO_2C CO_2Bu^t

$HCl-PhH$ | (for R=Et)

$CH_3.C_6H_4SO_3H-AcOH$ | (for R=Bu^t)

(69)

$H.C \equiv C.COR$
$\overline{Ph.NO_2 \quad 210°}$

RO_2C CO_2R

CO_2R
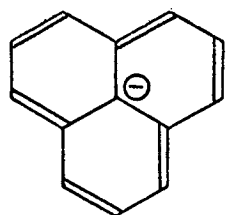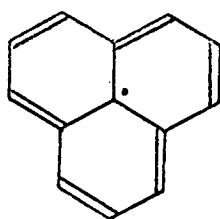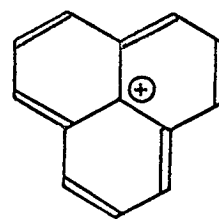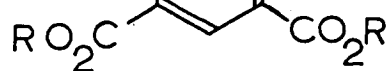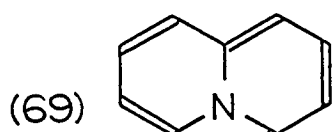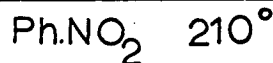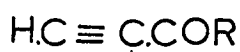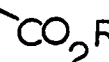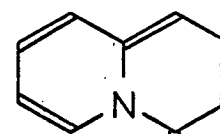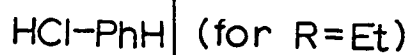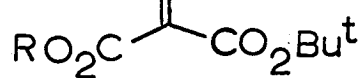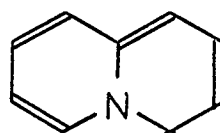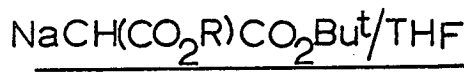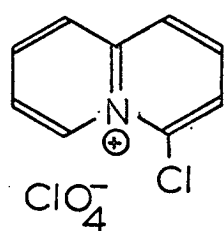
a) R= Et
b) R= Bu^t

$\triangle$ \ R=Bu^t
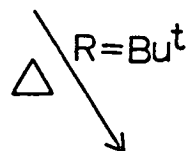
(36)
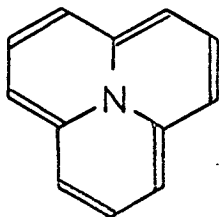
FIG. 12

with uniform failure[121-125], and it was only quite recently that the system was finally obtained. Molecular orbital calculations based on a perinaphthenyl anion model, had indicated[100] that cycl[3,3,3]azine (36) should possess a resonance energy higher than that of cycl[3,2,2]azine, despite the fact that it possesses twelve peripheral π-electrons (excluding the nitrogen lone-pair). The perinaphthenyl anion[126-128] (66) together with the corresponding cation [129,130] (68) and free radical[127] (67) have been synthesised, and all three entities shown to possess moderate stability.

All three have been predicted to possess the same resonance energy[131-133]. This follows from the presence of a zero-energy molecular orbital which can accommodate electrons in excess of those directly involved in bonding. (Respectively 0, 1 and 2 for the cation, radical and anion). The anion is isoelectronic with cycl[3,3,3]azine and it had been hoped that the cyclazine might show a similar enhanced stability. When synthesised, however, by the route outlined in (fig. 12), it was found to be extremely reactive, undergoing extensive decomposition in a few minutes on exposure to the atmosphere or when dissolved in hydroxylic solvents. Under a dry nitrogen atmosphere the purple-brown crystalline solid was stable, and the n.m.r. spectrum of a solution in bis(trimethylsilyl) ether showed a triplet at 6.35T (J=8 c/s) together with a higher field doublet at 7.93T (J=8 c/s). These extremely high-field values are considered to be due to two main factors:-

(a) an induced paramagnetic ring current which may be inferred by comparison with the proton chemical shifts of the cyclic dienamine system, N-phenyl-1,2-dihydropyridine [134], the absorptions of which are 2-3 p.p.m. down-field from those of the corresponding protons in the cyclazine, and

a) R=H, R'=CHO
b) R=CHO, R'=H

a) R,R''=NO₂ ; R',R'''=H
b) R',R''=NO₂ ; R,R'''=H
c) R'=NO₂ ; R,R'',R'''=H
d) R,R'=NO₂; R'',R'''=H
e) R,R'''=NO₂ ; R',R''=H
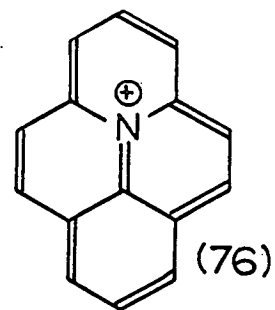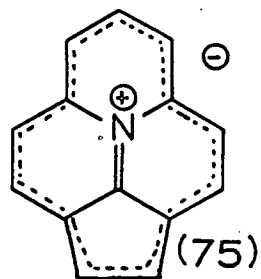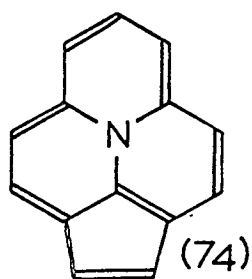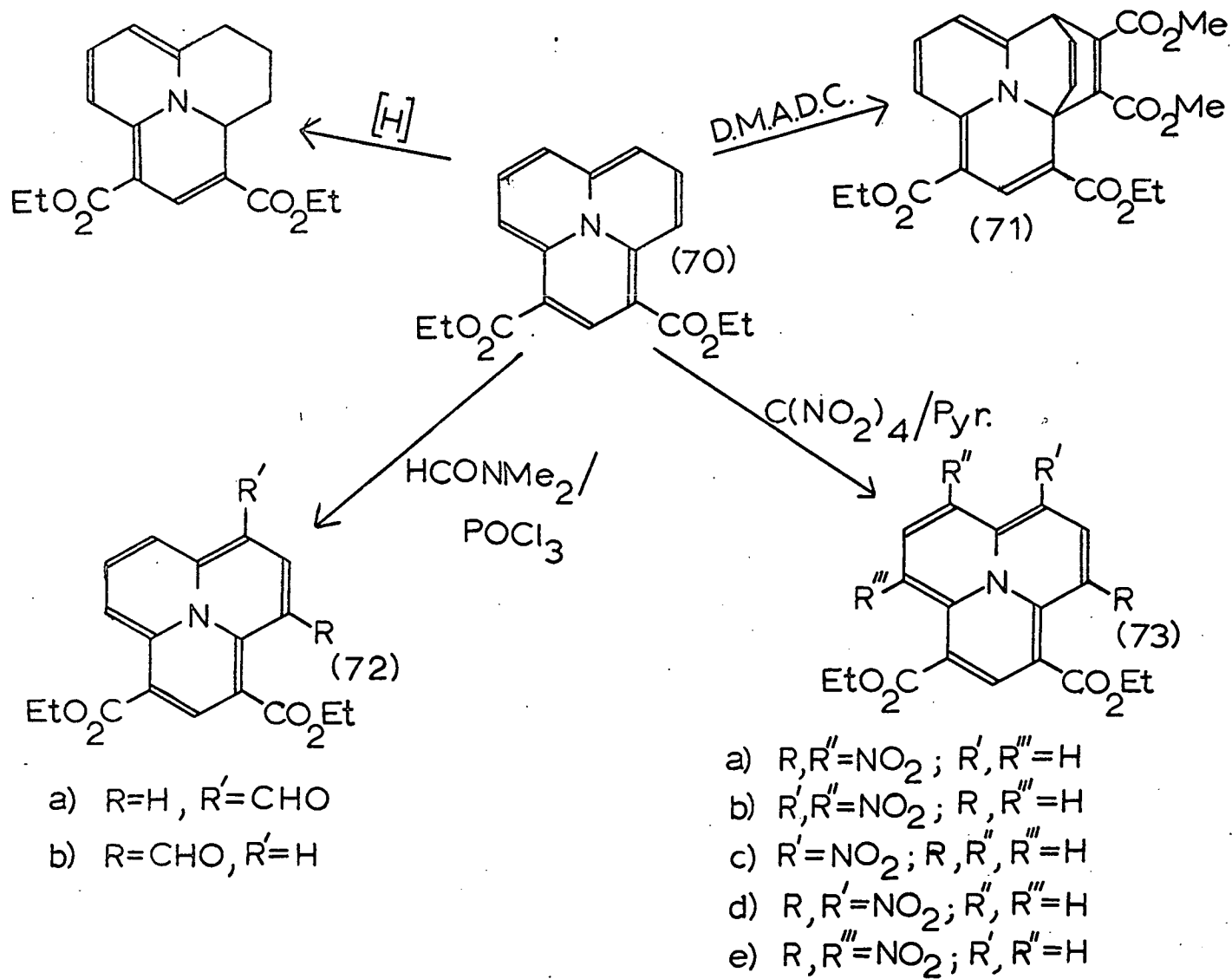
FIG 13

(b) a high electron-density carbon-perimeter consequent on delocalisation of the lone-pair of electrons on the nitrogen atom.
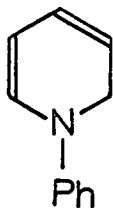
Because of the instability of the parent system, reactions were carried out on the 1,3-di(ethoxycarbonyl) derivative (70). Cyclo-addition with dimethyl acetylenedicarboxylate provided confirmatory evidence of the polyolefinic character of the system. Substitution reactions with electrophilic reagents under mild conditions have also been carried out[135], but were regarded as analogous to those of a typical enamine rather than as evidence of aromatic character (Fig. 13).

Work in this department[140,141] on the reaction of cyclopenta[c]quinolizines with activated acetylenic esters led to derivatives of the first tetracyclic cyclazine structure (74) Evidence from the n.m.r. spectrum and a low value for the coupling constant $J_{1,2}$ indicate that the system is aromatic, possibly with appreciable contribution from the dipolar structure (75) with 14 peripheral π-electrons. An attempt to convert the ring-system into a 10b-azoniapyrene (76) by ring expansion of the five-membered ring with chlorocarbene or with ethoxycarbonylcarbene failed.

Derivatives of 4-hydroxycycl[3,3,2]azin-3-one (77)[136], and of cycl[3,3,2]azin-3-one (78)[137], have been prepared by the routes outlined in Fig. 14. As would be expected, they both show some evidence of aromaticity
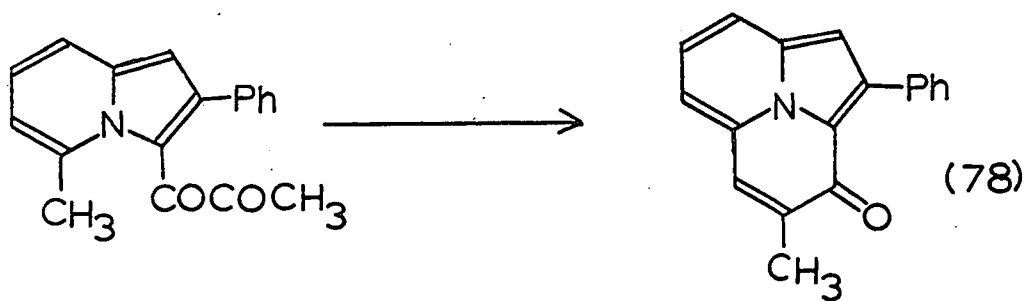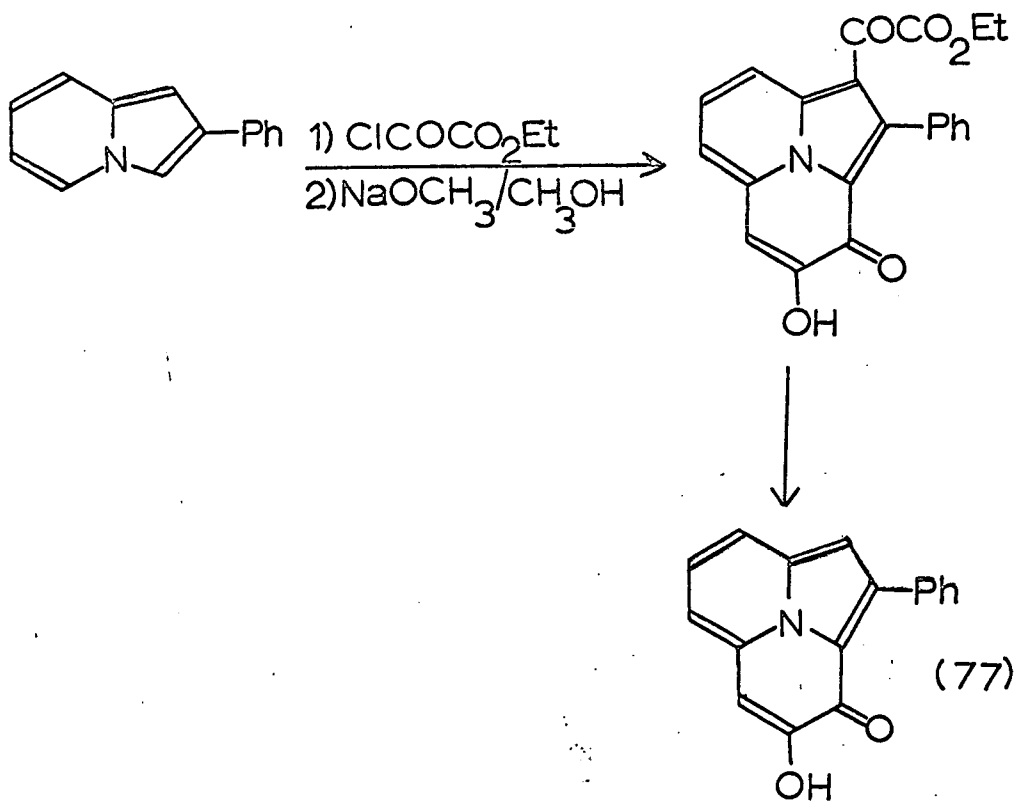
FIG. 14
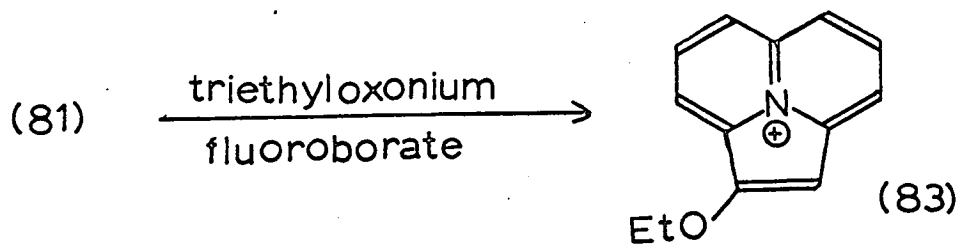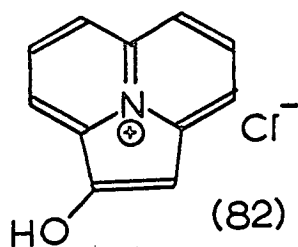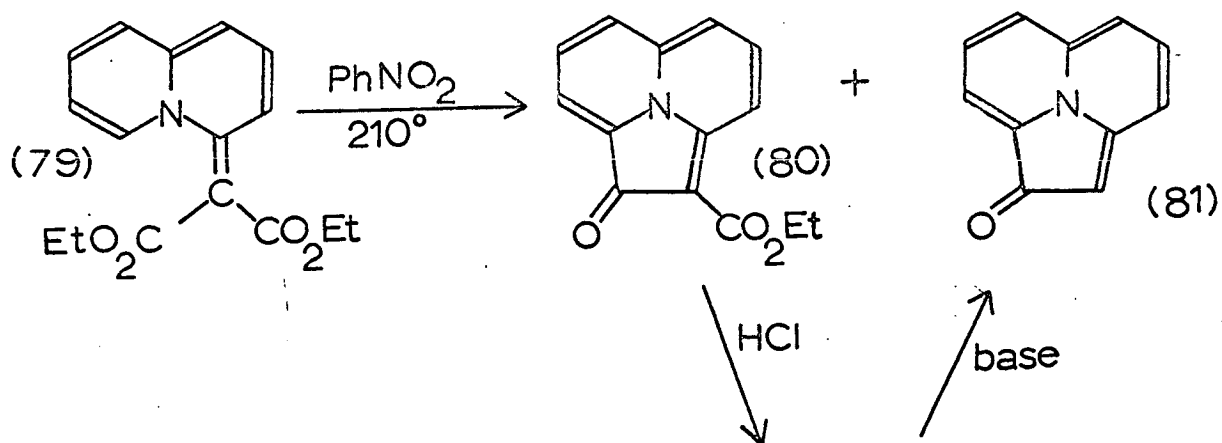
FIG. 15

in a manner analogous to that of tropolone and tropone respectively. A more

convenient method for the preparation of a cyclazinone (cycl[3,3,2]azin-1-one)

was developed later by Farquhar[139] (Fig. 15) (see below).

The cycl[3,3,2]azinium cation may be regarded either as consisting of a

quinolizinium nucleus with a double-bond bridge (40a) or as structure(40b)

which contains 10 peripheral π-electrons, and might therefore be expected,

according to Huckel's rules[2], to exhibit aromaticity.
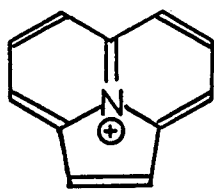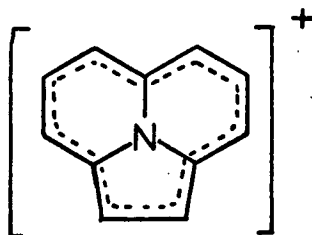
(40a)   (40b)

A measurement of the vicinal coupling constant for the protons of the

five-membered ring, which is related to the π-bond order[138] in the 1,2-bond,

should provide a measure of the extent to which this bond participates in the

aromatic system.

Derivatives of the cycl[3,3,2]azinium cation system have been prepared

in this department[116,139]. Thus it was found that when the quinolizinylidenemalonate

(79) was refluxed in nitrobenzene for 1 hr., two products were obtained. These

were shown to be 2-ethoxycarbonylcycl[3,3,2]azin-1-one (80) (87%) and the

unsubstituted ketone (81) (9%). Heating the ester (80)with dilute acid

followed by evaporation of the solution yielded a pale yellow solid which was

identified as 1-hydroxycycl[3,3,2]azinium chloride (82). Reaction of the

latter with base yielded the cyclazinone (81) which gave the 1-ethoxy

derivative (83) on treatment with triethyloxonium fluoroborate. Attempts
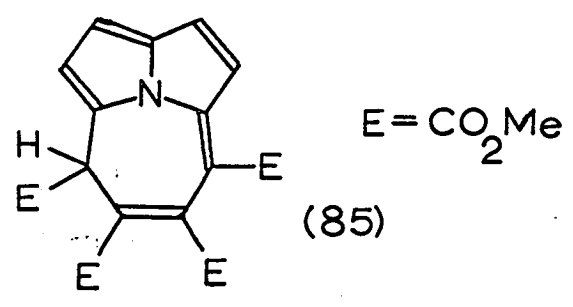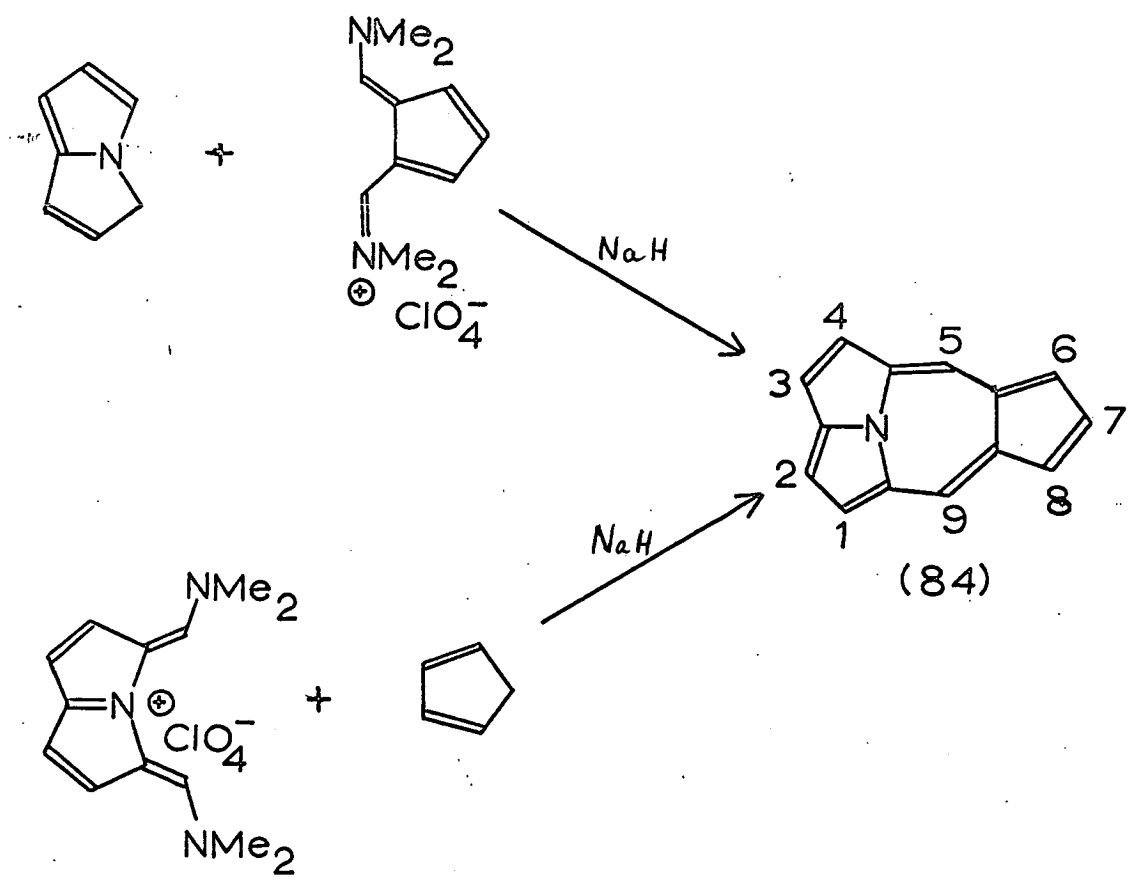
FIG. 16

to remove the ethoxy group proved unsuccessful as did attempts to catalytically hydrogenate (82). The n.m.r. spectrum (in trifluoroacetic acid) of (82) and (83) both showed a complex multiplet in the region 0.8-1.5τ, attributable to the protons in the six-membered rings, and a one-proton singlet at 2.7τ, due to the proton in the five-membered ring. This result shows that the six-membered rings are undoubtedly part of an aromatic system, but it is not clear whether the C_1 - C_2 bond of the five -membered ring belongs to the same aromatic system or whether it is merely an electron-deficient double bond. It was one of the aims of the present investigation to resolve this question through a synthesis and n.m.r. study of the parent cycl[3,3,2]azinium ion.

Cyclopenta[h]cycl[4,2,2]azine (84) (the first derivative of cycl[4,2,2]-azine), has been prepared in this department[116] by two different routes, as outlined in Fig. 16. This compound contains 14 peripheral π-electrons and n.m.r. spectral data indicates, as expected, that it is aromatic in character. Electrophilic substitution reactions were effected with a number of reagents, substitution occurring in the 6- and 8-positions. Failure to react with dimethyl acetylenedicarboxylate confirmed the aromatic character of the compound.

Some derivatives of 5H-cycl[4,2,2]azine, prepared by reaction of 3H-pyrrolizines with an excess of dimethyl acetylenedicarboxylate, have recently been reported[142]. Tetramethyl 5H-cycl[4,2,2]azine-5,6,7,8-tetracarboxylate (85) was obtained by dehydrogenation of the 6,7-dihydro derivative, but could not be oxidised further.

Neither cycl[4,4,3]azine (38) which was predicted to be stable, though showing a tendency to bond alternation[100], nor cycl[4,3,2]azine (37) which is isomeric with cycl[3,3,3]azine (36) have been prepared, although the latter has been the subject of several synthetic studies[143-145].

(86)

(87)

(88)

(89)

(90)

(91)

(92)

(93)
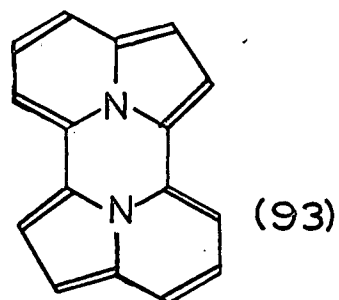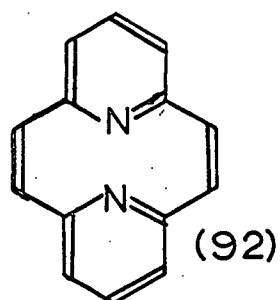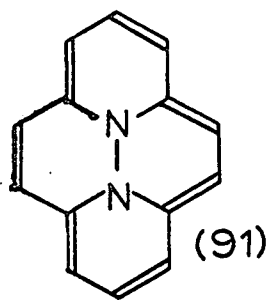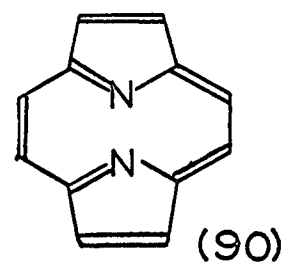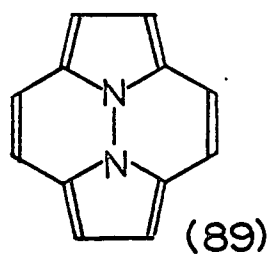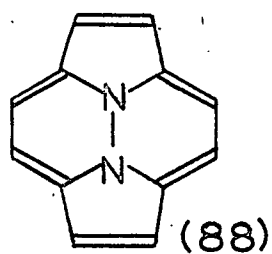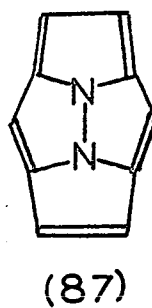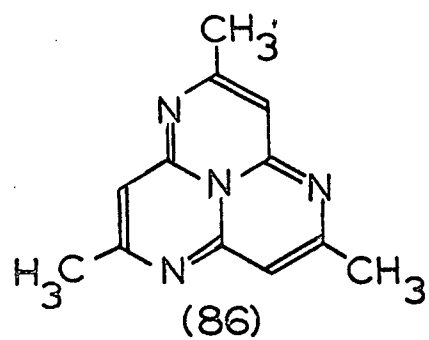
FIG. 17

The preparation of 2,5,8-trimethyl-1,4,7,9b-tetra-azaphenalene (86) has recently been reported[146]. The proton chemical shift for the ring protons is 4.70T and would seem to indicate that the system is not electronically similar to cycl[3,3,3]azine.

The field of cyclazine chemistry may be extended to include tetracyclic compounds of the type (87), (88) and (91) which are related to [10]-, [12]- and [14]-annulene respectively. A report of the synthesis of the second of these (88) has recently been published[147]. In view of the fact that this compound, like cycl[3,3,3]azine, has a 12π-electron periphery, the values for the proton chemical shifts (T4.78 (4H), 4.87 (4H)) are much lower than might be expected. It is possible therefore that either the alternative Kekulé type structure containing two pyrrole rings (89) or the valence tautomer structure (90) are more accurate representations. The preparation of the pyridinophanediene (92) has recently been reported[148]. Earlier work[149] had predicted that it might undergo spontaneous valence tautomerism to 10b,10c-dihydro-10b,10c-diazapyrene. It now appears from n.m.r. evidence that this is not so, but that (92) behaves as a normal bridged pyridine derivative.

Finally, the synthesis of derivatives of the cyclazine (93) which is related to [16]annulene has also been achieved in this department[145]. This system may be regarded either as two indolizine nuclei joined through their 3- and 5-positions, or as a derivative of [16]annulene. Comparison of the n.m.r. spectrum with those of appropriately substituted indolizines suggests the presence of a paramagnetic ring current, the ring protons being shifted upfield ca. 1 ppm. from their positions in the indolizine spectra. This would suggest a non-aromatic system, and hence that it is probably correct to regard it as a derivative of [16]annulene.

DISCUSSION

FIG 18
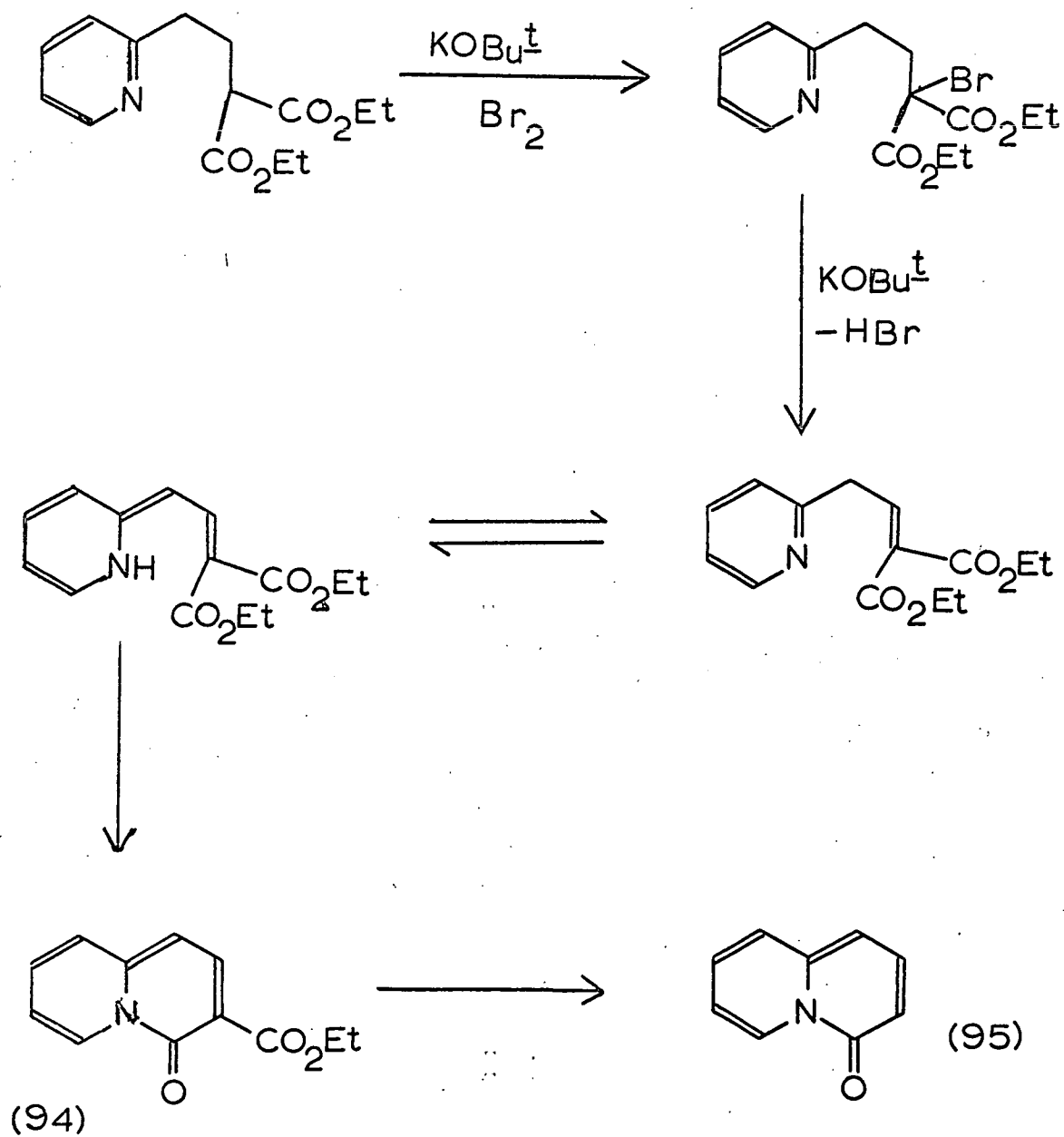
ATTEMPTS TO ACHIEVE A CONVENIENT

SYNTHESIS OF QUINOLIZIN-4-ONE

The method previously used for the preparation of quinolizin-4-one had been by hydrolysis of the products of the reaction of methyl 2-pyridylacetate and diethyl ethoxymethylenemalonate [139]. While the yield from this reaction was reasonable (60%), the preparation of the starting materials was somewhat tedious. An alternative synthesis was thus sought.

The intended reaction scheme was as shown in Fig. 18. Diethyl (2,2'-pyridylethyl)malonate, which is readily available from 2-vinylpyridine and diethylmalonate, was the starting material. Treatment of this with bromine and potassium t-butoxide should result in bromination at the reactive methylene site as shown. It was hoped that dehydrobromination might then occur and that the product would cyclise to yield the 3-ethoxycarbonyl derivative of quinolizin-4-one(94). An authentic sample of this derivative was available for comparison, and could be hydrolysed to the required quinolizone by the usual method.

When the reaction was attempted at 80-90° for 1 hr., only a dark intractable material was obtained. However, solutions of this material, in dichloromethane, showed a strong green fluorescence which is consistent with the presence of a quinolizone derivative. As an alternative approach to the introduction of unsaturation, dehydrobromination was attempted by heating the malonate with an excess of sulphur at 200-210° without solvent for 6 hrs. Chromatography of the product gave a broad fluorescent green band, and from this was isolated an orange-brown solid (23%), which proved to be 3-ethoxycarbonylquinolizin-4-one. This product

was converted into the quinolizone by the procedure used for the hydrolysis of the 1,3-diethoxycarbonyl derivative.[139]

Although the yield from the last stage was reasonable (59%), the overall yield from the malonate was only 14%. It seemed unlikely that this alternative method of preparation could be improved sufficiently, in both yield and convenience, to make it better than the usual method. The attempt was not therefore pursued further.

ATTEMPTS TO PREPARE DERIVATIVES

OF AZA-, OXA- AND THIACYCL[4,3,3]AZINES

Cycl[3,3,3]azine has been shown[139] on the basis of chemical shifts in n.m.r. spectroscopy, to be an antiaromatic system. It thus appears that the interaction between the nitrogen lone-pair and the peripheral electrons is small, and that the properties of the system are determined predominantly by the 12 peripheral π-electrons. Thus compounds (96) which contain 14 π-electrons in the peripheral ring (by utilising the lone-pair on the hetero atom), should be aromatic
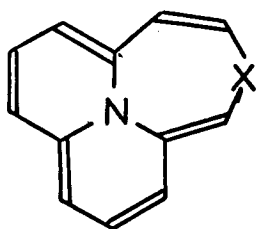
X = O, S, NR
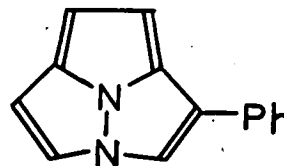
(96)　　　　　　　　　　　　　　(97)

The only cyclazine of a similar nature so far prepared is 1-phenyl-8-azacycl[2,2,2]azine [150](97). N.m.r. data is reported only for dimethyl 1-phenyl-2-benzoyl-8-azacycl[2,2,2]azine-5,6-dicarboxylate, and includes a one proton doublet at 1.6T(J=3 c/s), attributable to the 3- or 4-proton. These values for the chemical shift and coupling constant are typical for the protons of five-membered rings of non-benzenoid aromatic compounds.[151]

The attempted method of preparation of these compounds was by insertion

of the hetero atom into the ring system of cycl[3,3,3]azine, using in all cases the 1,3-diethoxycarbonyl derivative.

Nitrenes are known to readily attack carbon-carbon double bonds to form aziridines. When the double bond forms part of an aromatic system, the resulting aziridine can undergo carbon-carbon cleavage thus effecting the insertion of a nitrogen atom into the aromatic ring. Thus the nitrene formed from ethyl azidoformate can even attack benzene to form, eventually, an azepine, the decomposition of the azidoformate being effected either by photolysis[152] or by thermolysis[153]. It seemed possible that by a similar sequence of reactions, diethyl cycl[3,3,3]azine-1,3-dicarboxylate might yield a derivative of 1- or 2-azacycl[4,3,3]azine. Thermal generation of the nitrene was used in all cases.

An attempted reaction in 1,1,2-trichloroethane at $110° \pm 5°$ yielded after 30 mins. almost entirely decomposition product. Reaction in diglyme and in xylene at $130°$ (the latter with a four-fold excess of the azidoformate) yielded a large number of products as indicated by thin-layer chromatography. While isolation of some of these would probably have been possible, the amounts obtained would have been very small. It seemed possible that a lower reaction temperature together with a proportionately longer reaction time might yield more encouraging results. It has been reported[154] that refluxing ethyl azidoformate in cyclohexene for 40 hrs. yielded mainly the aziridine. The reaction was therefore attempted in benzene with a five-fold excess of the azidoformate and refluxing for 72 hrs. However, thin-layer chromatography during this time indicated increasing decomposition material, and only traces of other products.

On the assumption that the nitrene was being formed (which with the

reaction conditions employed, seems very likely), there are a number of possible reasons for the failure to obtain the required product. The nitrene may attack the solvent, particularly in the case of benzene. If the nitrene attacks the cyclazine and gives a product of the required nature, there would be six possible products following the attack of a single nitrene molecule. Any of these products, even if aromatic in nature, would be susceptible to attack by the extremely reactive nitrene. In view of the first of these possibilities it seemed wise to attempt the reaction using ethyl azidoformate as solvent. Thus the cyclazine was heated at $150\pm5^{\circ}$ with a six-fold excess of the azidoformate for 3 hrs. However, thin-layer chromatography indicated a similar result to that obtained before, viz. mainly decomposition material and only traces of other products.

It seemed that direct attack by nitrene was not likely to yield the required product, but that an alternative route based on deoxygenation of a nitrosocyclazine might prove more suitable.

It has been shown[155] that the intermediate, probably a nitrene, formed from nitrosobenzene by the action of triphenylphosphine, reacts with dialkylamines to form derivatives of 2-amino-3H-azepine.
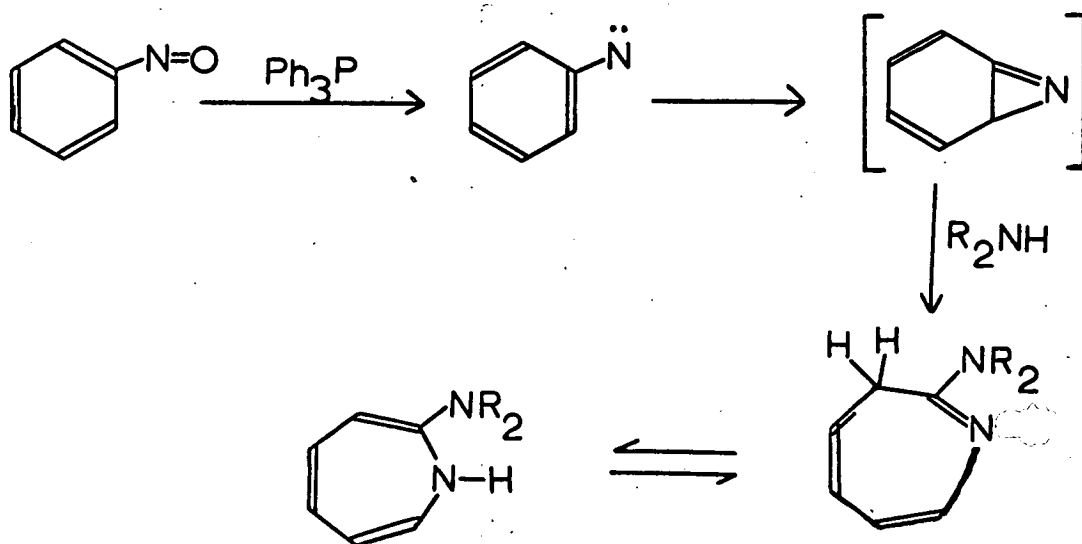
Since nitration of the cycl[3,3,3]azine system is known to occur [139], it seemed probable that nitrosation should also be possible. Attempted nitrosation with iso-amylnitrite and phosphoryl chloride yielded a large number of products in very small yield, none of which was isolated. Attempted nitrosation by the method of Nozoe and Seto[156] using an aqueous solution of sodium nitrite in the presence of acetic acid yielded instead only nitration products. There was obtained the 6-nitro, 4,6-dinitro, 4,7-dinitro, and 4,9-dinitro derivatives, all of which were identified by comparison with authentic samples prepared by Farquhar[139] by treatment of the cyclazine with tetranitromethane in pyridine. One other product was obtained pure, but in very small yield (3.4 mg.). Its mass spectrum had a parent ion at m/e 356, and it therefore seemed possible that it was the 4-nitro derivative which had not been obtained before. To check this possibility a further investigation of the nitration of the cyclazine was undertaken.

In view of the fact that mainly dinitro derivatives of diethyl cycl[3,3,3]azine-1,3-dicarboxylate had been obtained before[139], it seemed that the mildest possible conditions should be employed. The reaction was therefore attempted using cupric nitrate trihydrate in acetic anhydride at room temperature for 2 mins., conditions which were reported to give mononitration with [18] annulene[157]. Three fractions were obtained after chromatography on alumina, the first as dark blue plates (29%). The mass spectrum showed a molecular weight of 356, indicating a mono-nitro derivative. The n.m.r. spectrum was identical with that of the 6-nitro derivative. Thus the 2-, 7-, 8- and 9-protons gave rise to a singlet (2.41T), a doublet (2.24T), a triplet (3.16T) and a doublet (2.56T) respectively. The remaining absorptions in the vinylic region consisted of two doublets at 3.26T and 2.66T. These

were assigned to the 4- and 5-protons respectively. The 5-proton is deshielded as a result of its situation <u>meta</u> to a ring-junction, and <u>ortho</u> to the nitro substituent. The 4-proton despite the presence of the nitro substituent appears at almost the same position as in the cyclazine dicarboxylate (3.23T). This effect was noted, and an explanation advanced in the previous work on the cycl[3,3,3]azine system[139].It was first noted in the n.m.r. spectrum of 1-methoxycarbonylcycl[3,3,3]azine, when the 3-proton resonated at the unexpectedly high T-value of 6.37. This was rationalised in terms of stabilisation of the ring system by significant contributions from the quinolizinium ylide structures (98 a) and (98 b), which can be collectively represented by the structure (98c)
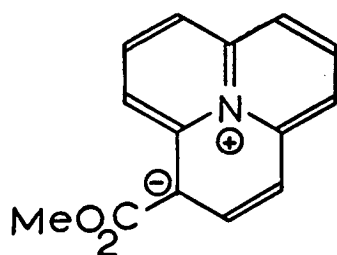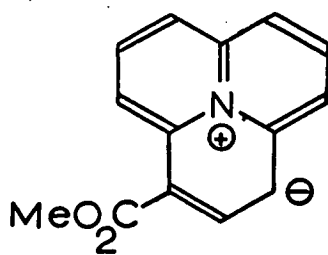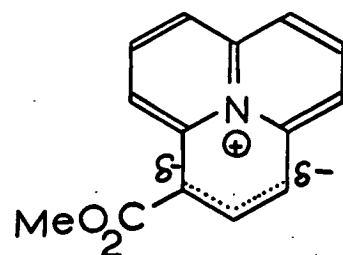
(98a)   (98b)   (98c)

On this basis, in the 6-nitro derivative there must be some contribution from the resonance structure (99)
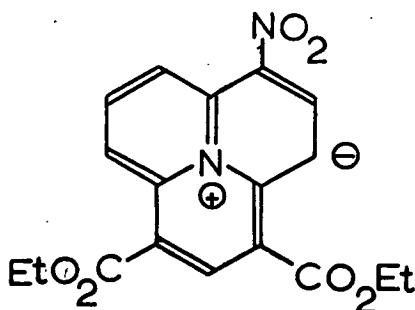
(99)
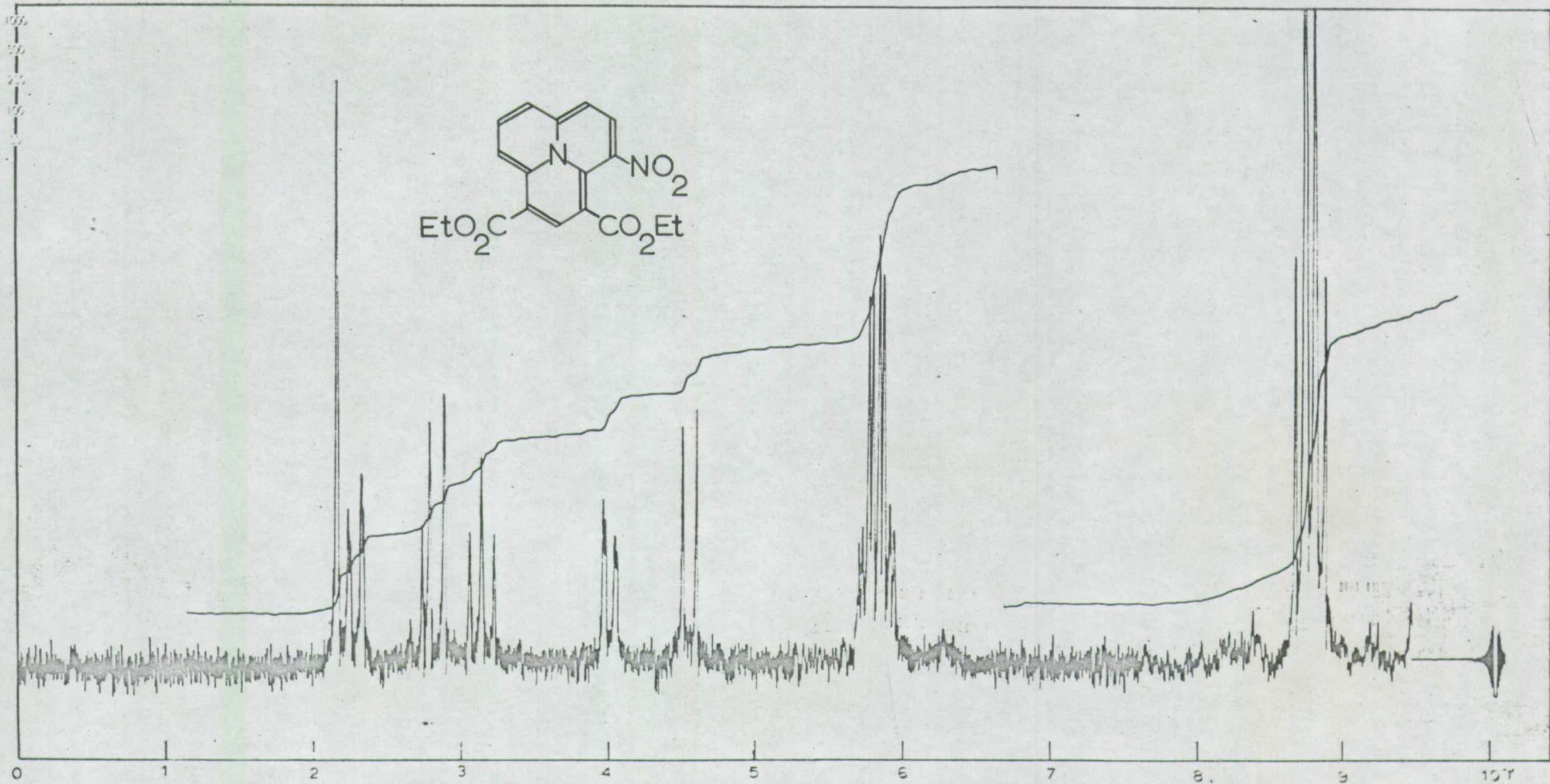
FIG 19

The contribution from such a structure would however be expected to be small, since it has two electron-withdrawing substituents in the quinolizinium part of the molecule.

The second fraction from the column yielded dark-blue needles (25%). The mass spectrum again showed a molecular weight of 356, indicating a second mono-nitro derivative. The n.m.r. spectrum was entirely consistent with the product being the 4-nitro derivative (Fig. 19). Thus the 2-, 7-, 8- and 9-protons gave rise to a singlet (2.13T), a doublet (3.99T), a triplet (3.11T) and a doublet (2.25T) respectively. The remaining absorptions from the ring-protons consisted of two doublets of an AX system at 2.81T and 4.52T. The higher field of these two doublets is entirely consistent with the expected position of the 6-proton. Thus there is no deshielding from the ethoxycarbonyl group (as there was for the 4-proton in the 6-nitro derivative) and the shielding effect of the β-nitro substituent would be expected to shift the 6-proton to higher field as discussed above. Furthermore the upfield shift of the 7-proton by 1.75T relative to its position in the 6-nitro derivative, is consistent with the absence of a deshielding nitro group from the 6-position.

A third blue-grey fraction obtained in small yield could not be identified. It failed to give either a mass spectrum or an n.m.r. spectrum, but there were indications that it might have been of high molecular weight.

An attempt to synthesise derivatives of 1- or 2-oxa cycl[4,3,3]azine (96 , X=0) also met with no success. The proposed route involved epoxidation with m-chloroperbenzoic acid followed by ring opening. Only a small amount of dark solid, which could not be identified, was obtained from this reaction, together with some recovered cyclazine.

A similar route was envisaged leading to 1- or 2-thiacycl[4,3,3]azine

(96 , X=S), though here it was hoped that the initial episulphidation might be achieved by treatment with elemental sulphur. It was known, from work on vulcanisation processes that persulphenium ions, formed from elemental sulphur at ⌐ ⌐ temperatures near 150°, can interact with olefins to form a variety of organosulphur compounds among which are episulphides
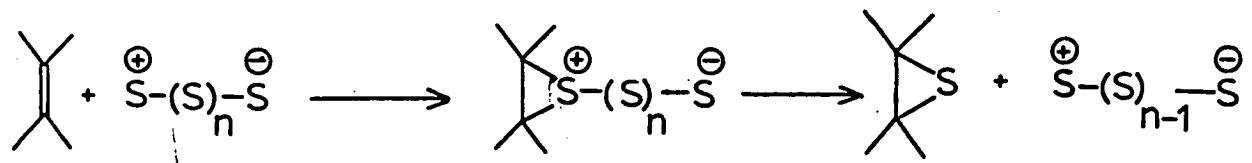
Reaction of the cyclazine with sulphur in boiling pyridine, for 4 hrs. under nitrogen yielded, besides a trace of recovered cyclazine, a number of products all in very small yield. Reaction in dimethylformamide yielded three products. These were, in order of elution from a column, a yellow-brown band, a red band (both in very small yields and neither of which were identified) and an amorphous red-brown solid (10.3 mg.). The mass spectrum of the last product indicated a molecular weight of 389 and also contained a fragment peak of approximately twice the intensity at 373, consistent with loss of oxygen. The molecular weight of the cyclazine dicarboxylate is 311 and so a mass of 389 is consistent with loss of two hydrogen atoms and addition of two sulphur atoms and one oxygen atom. The n.m.r. spectrum showed, besides the presence of the two ethoxycarbonyl and the H-2 singlet groups, two sets of AX systems, both giving rise to two doublets. These were centred at 2.81T and 3.29T (J=8.9 c/s) and 2.90T and 3.14T (J=9.3 c/s). The lower doublets from the two systems partially overlapped to give the appearance of a triplet, but the sizes of the
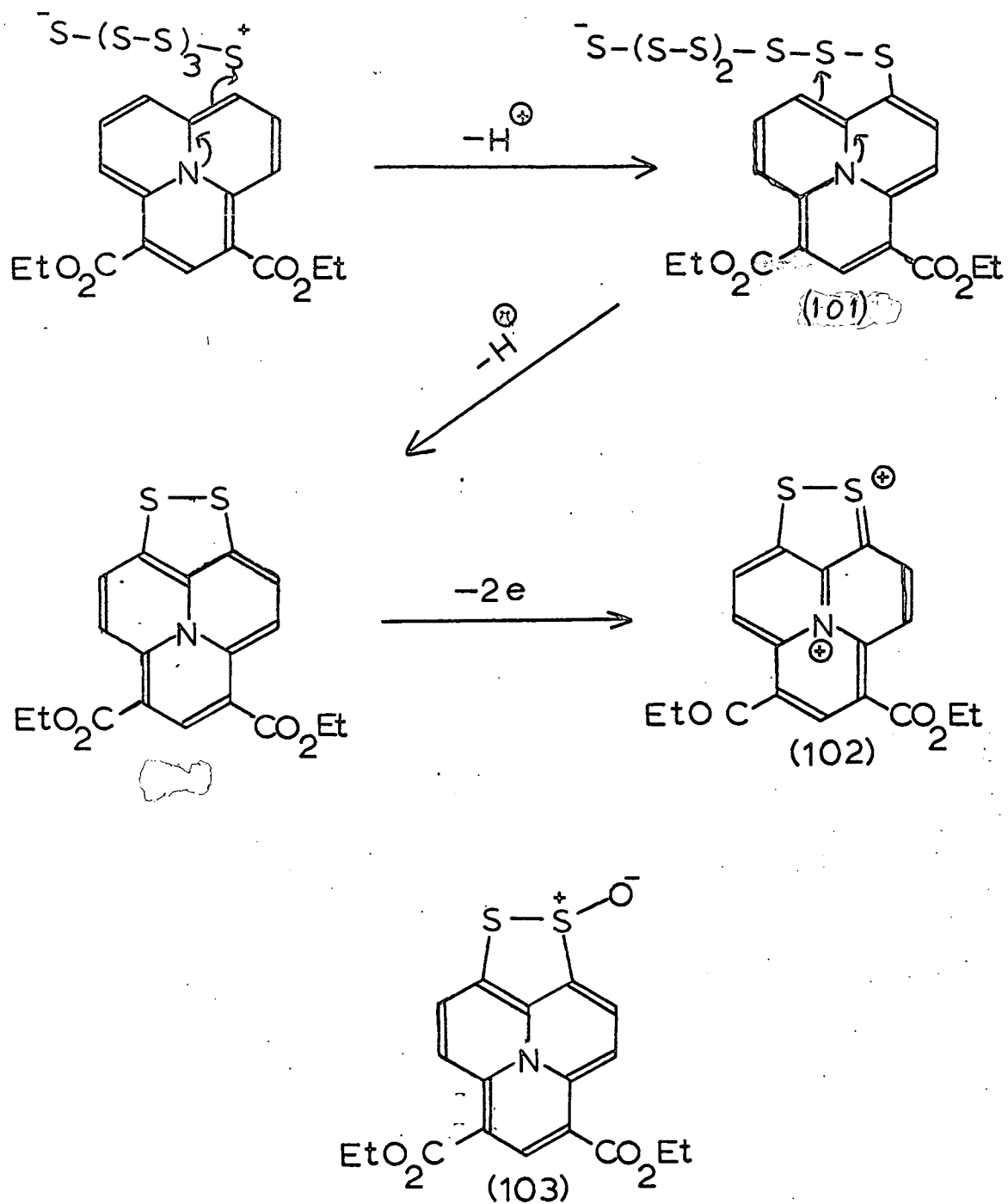
FIG. 20

integrals and the coupling constants pointed to the above interpretation. The presence of two AX systems immediately indicates an unsymmetrical structure and the relatively low field position of these indicates that the protons are in the 4-, 5-, 8- and 9-positions since deshielding of the 4- and 9- protons by the peri-ethoxycarbonyl groups can then take place. It therefore seems that in the 6- and 7- positions we have an unsymmetrical structure composed of two sulphur and one oxygen atoms. A structure such as (103)(Fig.20) would fit with the above observations. The ⬡ structure (101) could be readily formed by electrophilic attack on the cyclazine by a persulphenium ion followed by loss of a proton. Heterolytic cleavage of the penultimate S-S bond could then lead to further substitution in the 7-position, resulting in closure of the dithiole ring. It is necessary then to propose oxidation, perhaps by sulphur. The dication structure (102), if formed, could be expected to have an enhanced stability since it has 14 π-electrons in the peripheral ring. It is known that the thianthrene dication can be converted to the 5-oxide by addition of water and that the process can be reversed by strong acid[158].
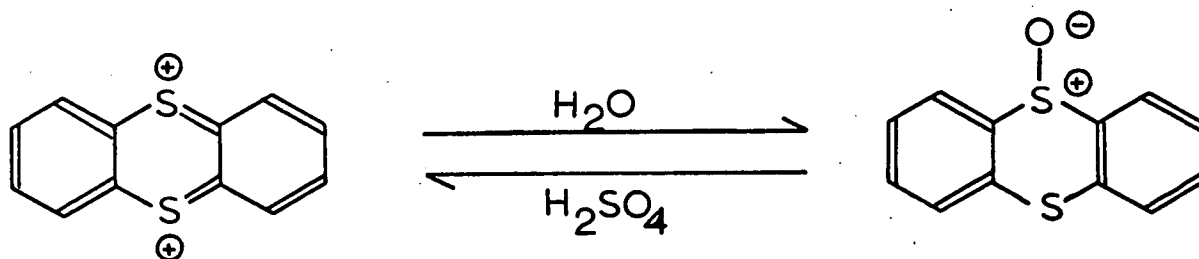
Thus the dication (102) if present would probably be attacked by water during the working up of the reaction to yield the S-oxide. In an attempt to

verify the suggested structure, an n.m.r. spectrum was run on the product in trifluoroacetic acid. It seemed possible that the conversion to the dication might take place, which would yield a symmetrical spectrum with a considerable downfield shift. However, the product appeared to decompose in the acid, and no result was obtained.
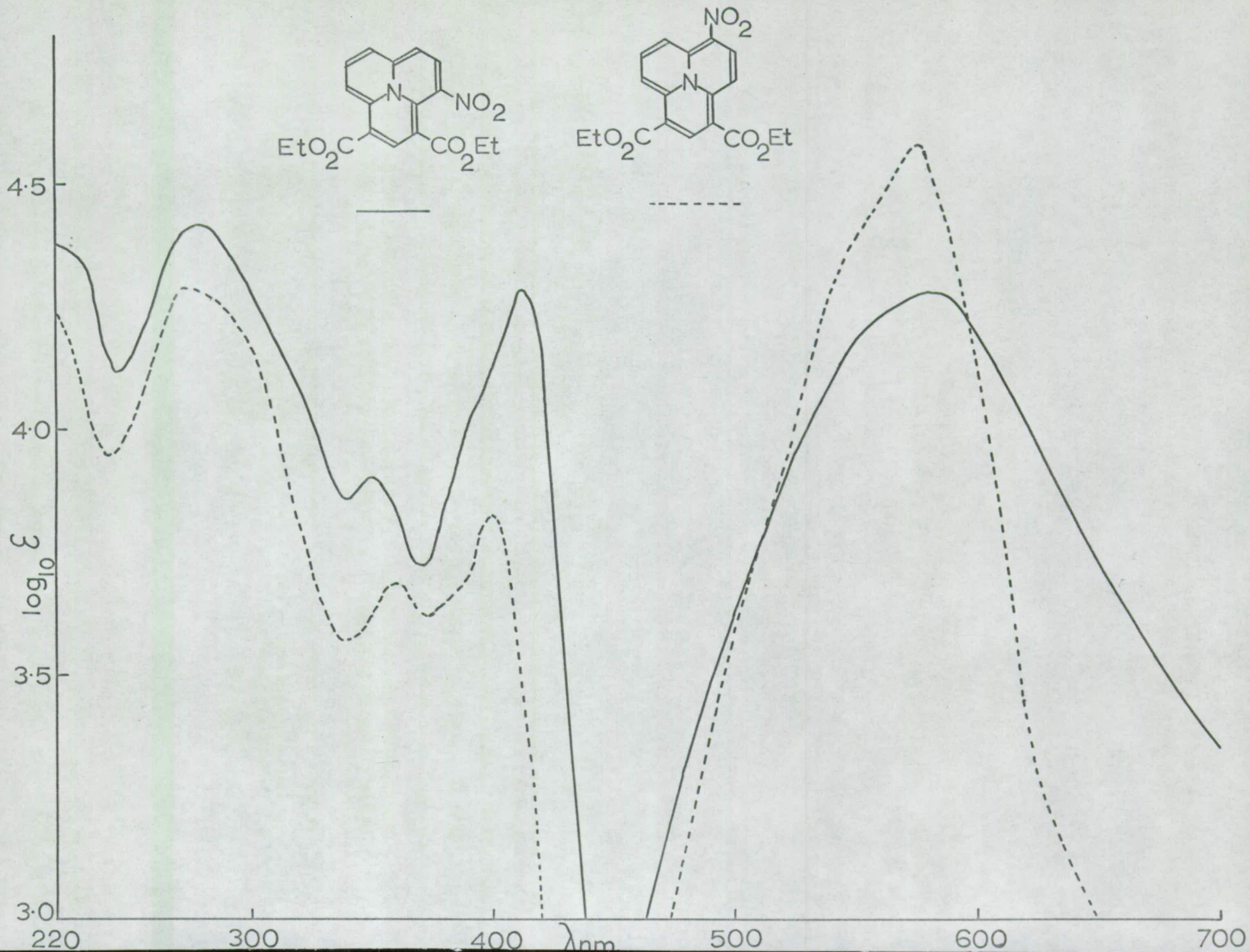
ATTEMPTS TO PREPARE DERIVATIVES OF 10b-AZONIAPYRENE

Derivatives of 10b, 10c-dihydropyrene [85 - 89] have been synthesised, and shown, on the basis of n.m.r. spectra, to be aromatic. A synthesis of the 10b-azoniapyrene system (104) would thus be of interest because of the possibility that it might react with nucleophiles to give 10b-aza-10b, 10c-dihydropyrenes (105) in which the peripheral system of 14 π-electrons in preserved. Efforts were therefore made in this direction, starting from diethyl cycl[3,3,3]azine-1,3-dicarboxylate.

Mathur[145] showed that indolizines add readily to propiolaldehyde, yielding β-indolizinylpropenals and it seemed probable that the cyclazine would react similarly to yield the 4- and 6-adducts. It was hoped that the 6-adduct would be the major product for steric reasons. Cyclodehydration, in the presence of acid could then lead to the desired product.

(104)   (105)
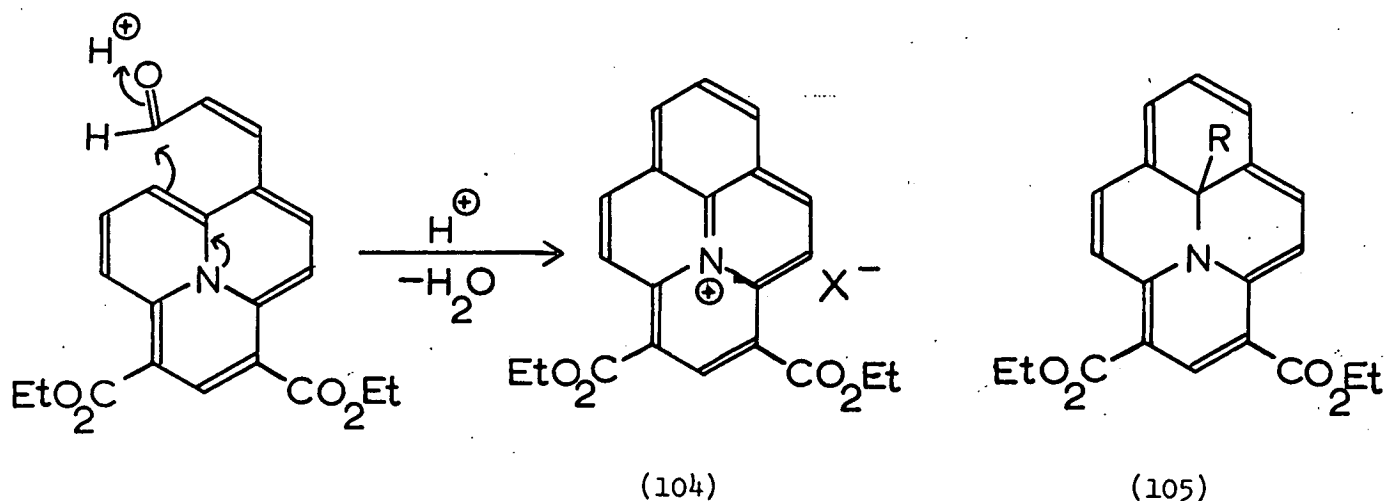
The reaction was first attempted in dichloromethane with a large excess of propiolaldehyde in the presence of methanol as proton donor. Chromatography on alumina yielded, besides a small amount of recovered

cyclazine, only one main product obtained as purple needles (17%). The

mass spectrum showed a molecular weight of 365, consistent with a

monoadduct. The n.m.r. spectrum was consistent with that expected for

the 4-adduct, diethyl 4-(3-oxoprop-1-enyl)cycl[3,3,3]azine-1,3-dicarboxylate (106)
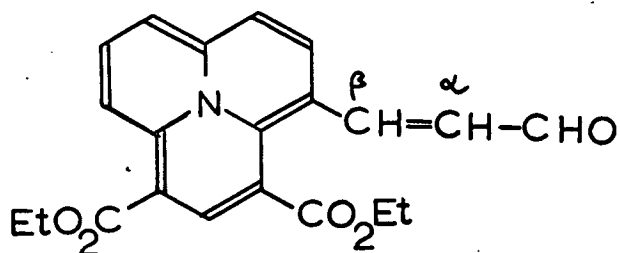
(106)

The aldehyde proton gave rise to a doublet at 0.69T, the α-proton a

doublet of doublets at 3.68T, and the β-proton a doublet at 4.07T. The

values of the coupling constants were typical of propenal systems with

$J_{\alpha,\beta}$ = 15.0 c/s, $J_{\alpha,CHO}$ = 7.4 c/s. The 2-,7-,8- and 9-protons gave rise

respectively to a singlet (2.21T), a doublet (4.06T), a triplet (3.23T)

and a doublet (2.84T). The remaining ring protons gave rise to two

doublets at 3.28T and 4.20T which were assigned to the 5- and 6-protons

respectively, the high-field doublet being insufficiently deshielded for

either a 4- or 5-proton signal. The spectrum is, as would be expected,

very similar to that of the 4-formylcyclazinedicarboxylate[139].

Having failed to obtain the 6-adduct under these conditions, the

reaction was attempted in glacial acetic acid with an excess of

propiolaldehyde. After concentration of the solution and addition of

perchloric acid and ether, a dark perchlorate was obtained. Attempts to

purify and identify this product, which appeared to be a mixture, failed.
The remaining red-purple solution was chromatographed on alumina to yield
a product that crystallised as red needles (6%). The mass spectrum
showed a molecular weight of 293, consistent with loss of an
ethoxycarbonyl group and addition of one molecule of propiolaldehyde.
The n.m.r. spectrum confirmed the loss of one ethoxycarbonyl group and
the presence of a propenal substituent which was shown to be present in
the 3-position (107)
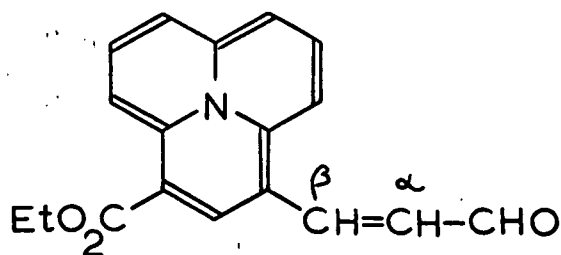
(107)

Thus there was clear evidence of two ABC systems each giving rise to two
doublets and a triplet. Of these only the 9-proton (3.26T) could be
assigned with certainty. The remaining absorptions (two triplets at
3.87T and 3.94T and three doublets at 4.75T, 4.80T and 4.86T) showed
considerable overlapping. The 2-proton gave rise to a singlet at 3.34T.
The aldehyde proton gave a doublet at 0.71T, the α-proton a doublet of
doublets at 4.01T and the β-proton a doublet at 3.70T. The coupling
constants in the propenal chain were close to the values observed in
compound (106) (15.2 c/s and 7.2 c/s) but the change in relative
positions of the α- and β-protons is interesting. The upfield shift of
the α-proton is in accord with the general upfield shift of the ring
protons (due no doubt to the reduced electron withdrawal), although a

contribution to the resonance hybrid from the charge-separated structures collectively represented as (108) would be expected to have a similar effect.

(108)
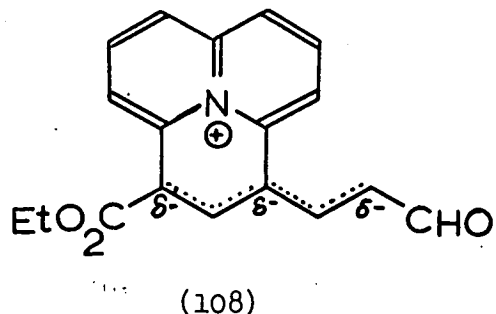
In view of the general upfield shift, the downfield shift of the β-proton becomes all the more difficult to account for; it must be assumed that the β-proton in the 4-adduct (106) is abnormally shielded by the 3-ethoxycarbonyl group which is probably twisted out of the plane of the cyclazine ring.

The replacement of an ethoxycarbonyl group by the oxopropenyl group must proceed via an intermediate (109) which, by base-initiated fragmentation, could lose ethylene and carbon dioxide.

(109)
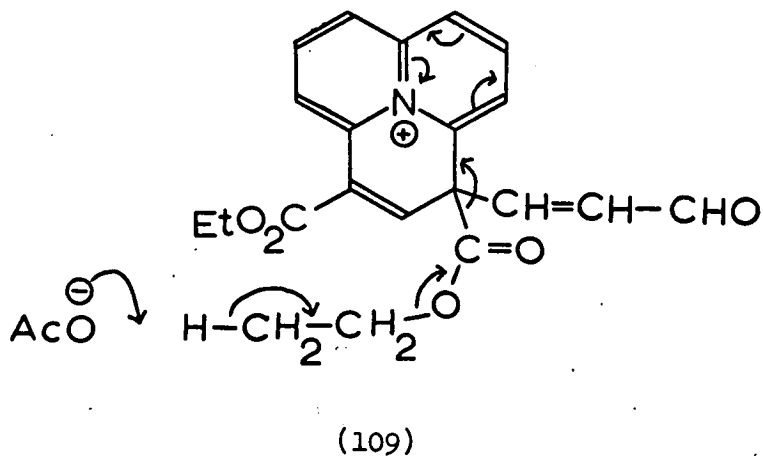
(a)
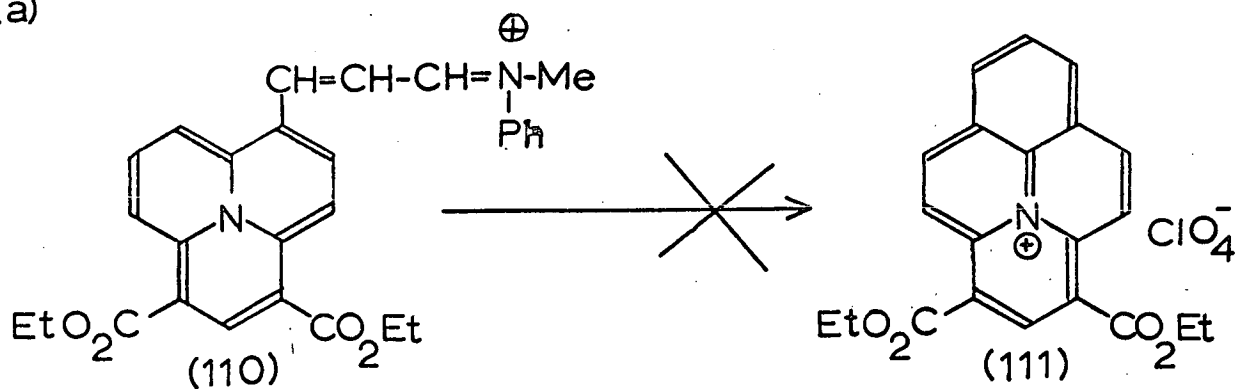
(b)
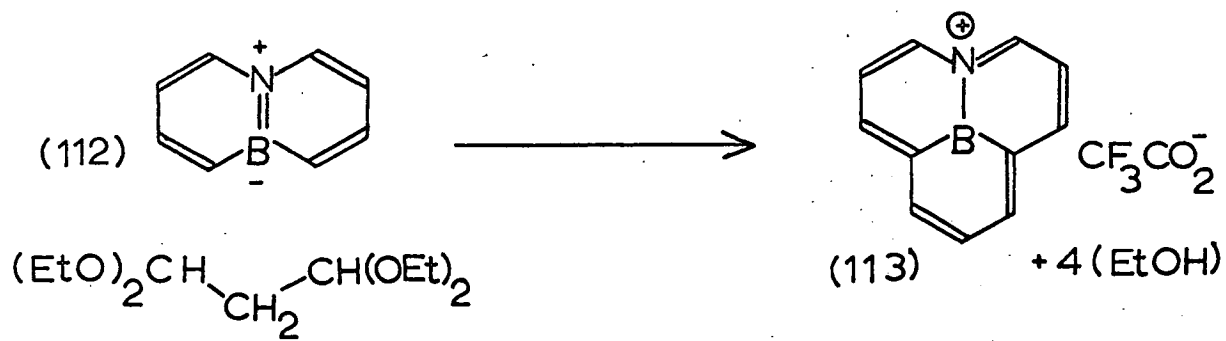
FIG. 21

The rôle of the acetic acid in promoting this type of replacement, rather than the normal 4-substitution which occurs in methanol, is not understood.

Though this product possesses the structural features necessary for cyclisation to an azoniapyrene, the yield was insufficient to allow further reactions to be carried out.

The above products were of some interest in themselves, but the main aim was still to synthesise the 6-adduct and attempt to cyclise it. Formylation of the cyclazinedicarboxylate with N,N-dimethylformamide and phosporyl chloride(Vilsmeier reagent) had been found[139] to yield both the 4- and 6-derivatives, though the latter was the minor product. A corresponding reaction using N-methylanilinoacrolein instead of N,N-dimethylformamide would be expected to yield 4- and 6-propenal derivatives. Indeed the intermediate (110)(Fig.21a) might well cyclise spontaneously to give the required product (111). However, an attempt to isolate such a product from a portion of the reaction mixture, by precipitation as the perchlorate, was unsuccessful. The remainder of the reaction mixture was hydrolysed and chromatographed on alumina to yield a light red solid the n.m.r. spectrum of which showed it to be a 1:1 mixture of the 4-adduct (106) and N-methylanilinoacrolein. Evidently the two were eluted from the column at closely similar rates. Since there was no evidence of the presence of the 6-adduct, no further purification was attempted.

The above method having failed, an alternative route to the azoniapyrene was sought. It seemed possible that the reaction of the cyclazinedicarboxylate with 1,1,3,3-tetraethoxypropane might provide such a route. An analogous reaction has been reported[159] for 10,9-borazaronaphthalene (112) (Fig. 21b) which resembles the cyclazine in undergoing facile substitution in the 4-position by electrophilic reagents

such as D$^+$ and bromine. The reaction with tetraethoxypropane in trifluoroacetic acid gave an intense violet colour which was considered to be the 9b, 9a-borazarophenalenium cation(113), though the evidence for this conclusion appears tenuous. It seemed possible that the cyclazine might undergo a reaction of this nature to yield the desired azoniapyrene system.

The reaction was first attempted in dichloromethane, and yielded a red-brown perchlorate in low yield. This material proved to consist of a complex mixture of products. An attempt in trifluoroacetic acid again yielded a complex mixture of products of which the main component (apart from a small amount of recovered cyclazine) was present in only ca. 2% yield. It seemed, therefore, that even if the desired reaction was taking place, many competing reactions were also occurring, and the attempt was not pursued further.

ATTEMPTS TO PREPARE DERIVATIVES OF
6H-10b-AZAPYREN-6-ONE

Attempts to synthesise the azoniapyrene system having failed, efforts were made to synthesise the azapyrenone system (114). Such a compound would be expected to show aromatic properties in the same way that tropone does, and protonation at the oxygen atom should lead to a fully aromatic system of 14 π-electrons

(114), R=H
(116), R=CN
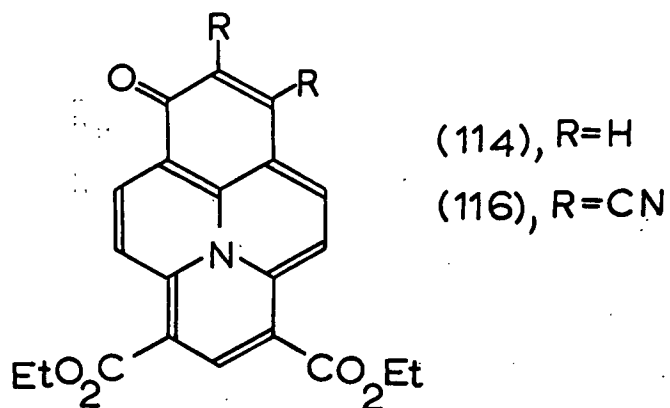
Tetracyanoethylene, besides being a very powerful dienophile[160], can also take part in aromatic substitution reactions. For example, it reacts with N,N-dimethylaniline in dimethylformamide, under mild conditions to form the p-tricyanovinyl derivative[161]. If tetracyanoethylene were to react with the di(ethoxycarbonyl)cyclazine to yield the 6-tricyanovinyl-derivative (which would probably be more likely than the 4-isomer for steric reasons), then this product might undergo ring closure under acidic conditions to yield the imine (115) which would probably hydrolyse readily to the azapyrenone (116).

(a)

(b)
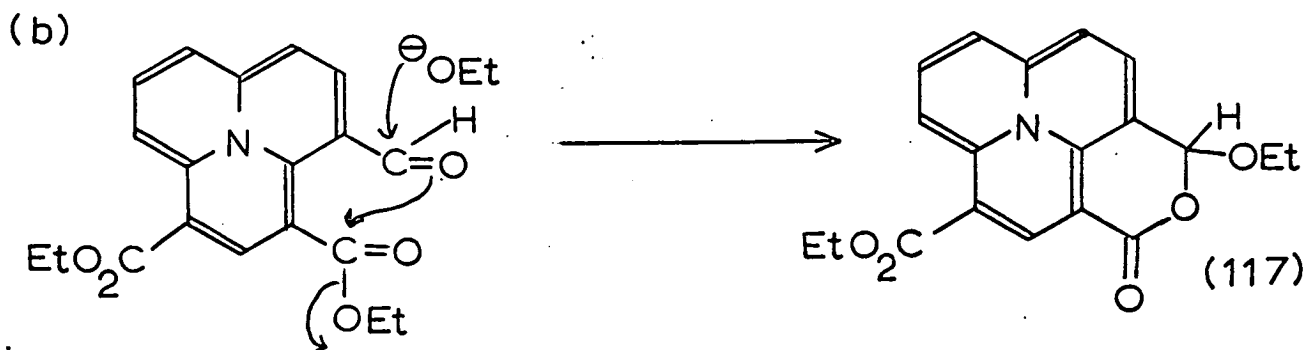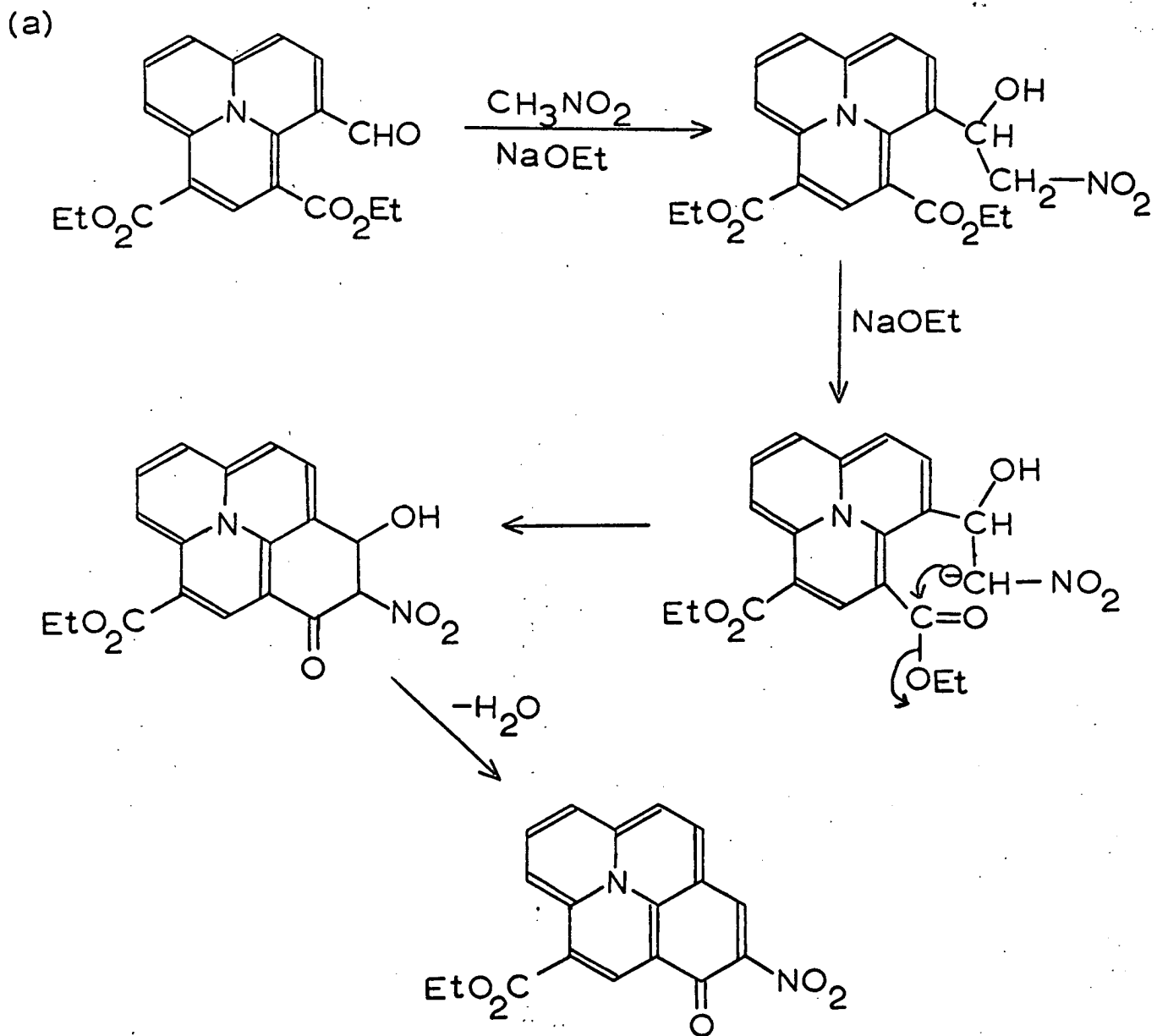
FIG. 22
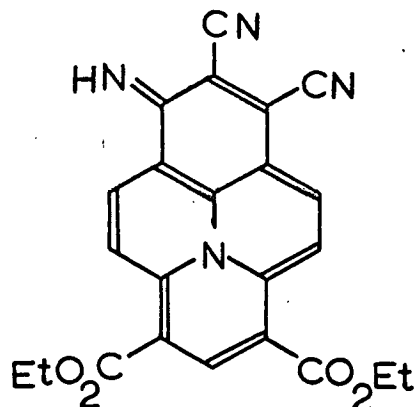
(115)

The reaction was first attempted in dichloromethane at room temperature. A large number of products was obtained, and these were separated by preparative thin-layer chromatography. However, the largest fraction (a purple band) contained only 2 mg. Further attempts were made in both tetrahydrofuran and dimethylformamide, with similar results. It is possible that some of the products were Diels-Alder adducts for the cyclazine is known to undergo such reactions with powerful dienophiles[139]. However, reaction with dimethyl acetylene-dicarboxylate requires refluxing in benzene for 16 hrs. or toluene for 5 hrs., and so although tetracyanoethylene is a very powerful dienophile, it would be a little surprising if it reacted in this way under the very mild conditions used. Nonetheless the results of the attempts did not seem promising and so investigation of the reaction was discontinued.

Another possible route to the azapyrenone system is shown in Fig. 22a. The reaction was attempted using one equivalent of sodium ethoxide in the hope of isolating the initial condensation product. Preparative thin-layer chromatography gave a single main yellow-brown band, from which was

-

obtained an amorphous brown solid. This was identified as the pyrano-
derivative (117). Thus the mass spectrum indicated that the molecular
weight (339) was unchanged. The n.m.r. spectrum showed a singlet (2.92T),
a doublet (3.05T), a triplet (3.71T) and a doublet (4.54T) attributable to
the 2-, 9-, 8- and 7-protons respectively. Two other doublets were
attributed to the 5-proton (3.94T) and the 6-proton (4.68T). This left a
singlet (4.77T), a complex arrangement of quartets (6.01T-6.54T) and the
two triplets (8.81T and 8.84T). The quartets contained a total of four
protons, and the main one appeared to arise from two of these. The
remaining quartets were interpreted as arising from the methylene protons
of the ethoxy substituent in the pyran ring in the following manner. The
ethoxy group is attached to an asymmetric centre and the methylene protons
are therefore nonequivalent. They give rise to an AB system each of the
four peaks of which is further split into a quartet
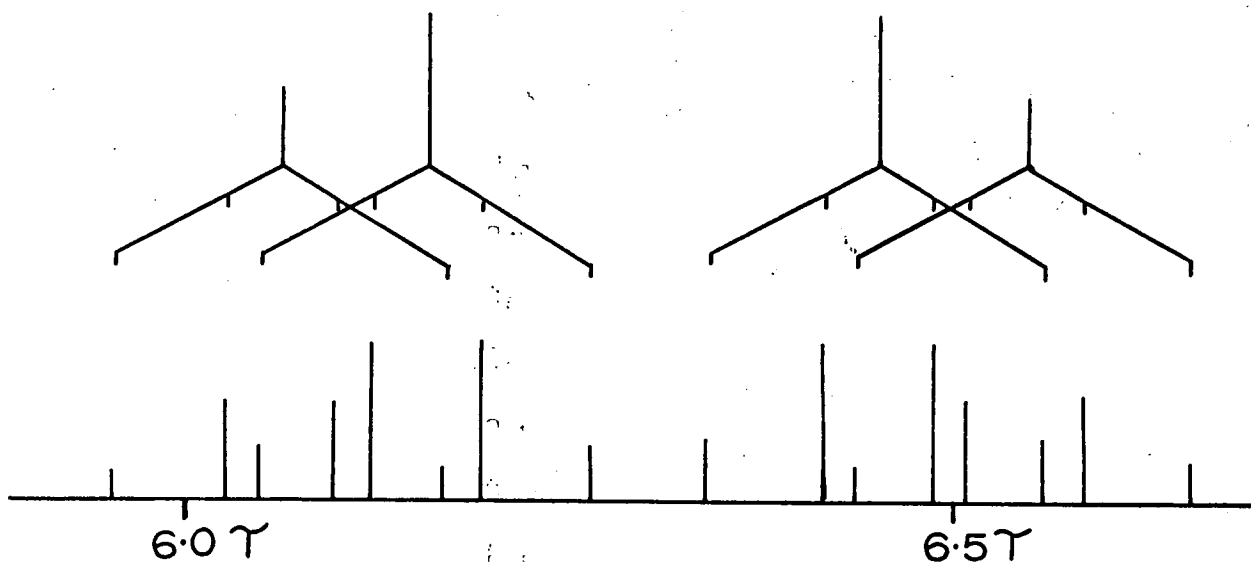
Much of the lower pair of quartets was obscured by the methylene
quartet of the ester group (6.01T) but from the upper quartets and those
parts of the lower quartets visible the above form was clearly indicated.

The formation of this product with ethoxide suggested the possibility of preparing the corresponding hydroxy compound with hydroxide. Such a compound would probably ring open with acid and could then perhaps be decarboxylated to yield a cyclazine with two electron withdrawing substituents in different rings. The n.m.r. spectrum of such a compound would probably be of considerable interest.

(117a)
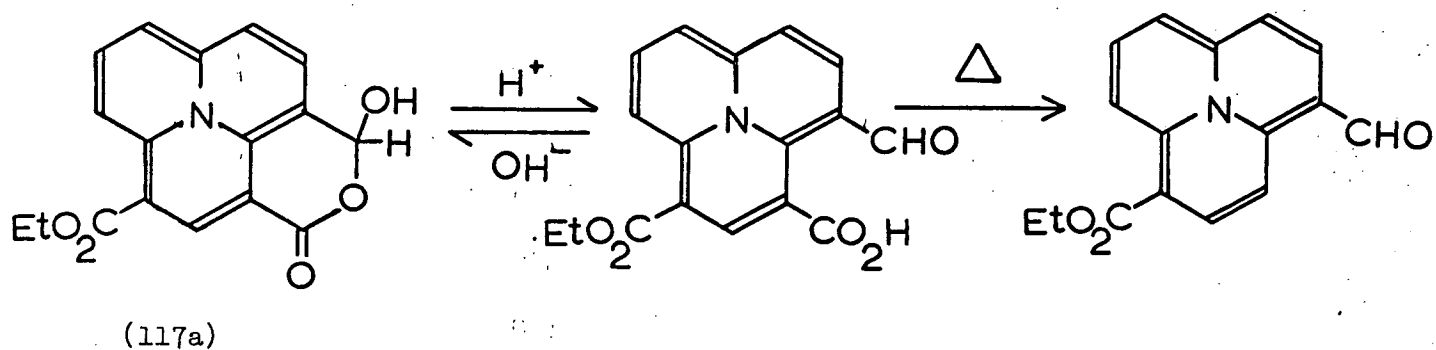
The reaction was attempted using one equivalent of sodium hydroxide in aqueous diglyme. The product, however, proved to consist of a complex mixture from which was obtained (by preparative thin-layer chromatography) a yellow-brown band in low yield (10 mg.). From the mass spectrum there appeared to be a small amount of the ethoxy-compound (117). The remaining peaks indicated masses of 295, 281, 267 and 253. The required compound has a molecular weight of 311, but the mass spectrum contained only a small peak at this position. A mass of 267 would correspond to loss of CO_2, but the peak was not strong. The other peaks are not easy to interpret. The n.m.r. spectrum was similar to that of the ethoxy-compound (117). From the positions and splittings of the ring protons it was apparent that a similar structure had been formed, but the presence of a complex series of absorptions in the region 6.1-6.6T was not consistent with

that expected from the desired compound, nor was the presence of two triplets and a singlet in the region 8.7-8.9T. Although the material could not be identified, it was clear that the expected product had not been obtained.

One further attempt to prepare an azapyrenone derivative was made. Diketene is known to react readily with nucleophiles. It is readily hydrolysed by water to form acetoacetic acid and reacts with alcohols to form the corresponding esters, the latter reactions proceeding at room temperature with a trace of the sodium salt of the alcohol[162]. It seemed possible that the cyclazine might react to form the 6-acetoacetyl derivative (118) which could cyclise and by loss of the elements of water form the desired compound (119).

(118)   (119)
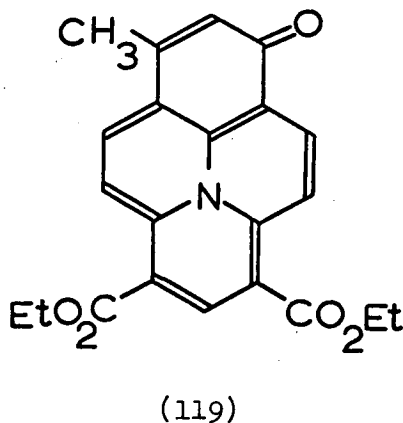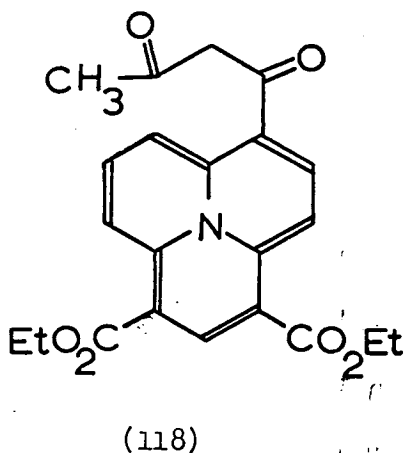
Attempts to perform the reaction in refluxing dichloromethane and in toluene yielded only recovered cyclazine. Refluxing in acetonitrile with a large excess of diketene gave a small amount of reaction, but chromatography indicated the formation of four products in small amounts. A reaction (but not yielding the desired product), was eventually achieved by heating the cyclazine with excess of diketene in a sealed tube at 120° for 1½ hrs.

Chromatography on alumina yielded recovered cyclazine (31%), a very small red fraction, and a purple band obtained as red-brown needles (15%). Mass spectrometry indicated a molecular weight of 461. The n.m.r. spectrum indicated the presence of a keto group in the 6-position. Thus the 2-, 7-, 8- and 9-protons gave rise to a singlet (2.51T), *a doublet (2.03T),* a triplet (3.29T) and a doublet (2.65T), respectively, and the 4- and 5-protons gave rise to an AB system (3.35T and 3.59T). Besides the expected pairs of quartets and triplets from the ester groups, the spectrum also showed a one-proton singlet (3.92T) and two three-proton singlets (7.78T and 7.84T). These were attributed to the protons of a dimethyl α- or γ-pyrone, giving the structure (120 a or b)

(120)　　　　　　　　　　(a)　　　　　　　　　　(b)
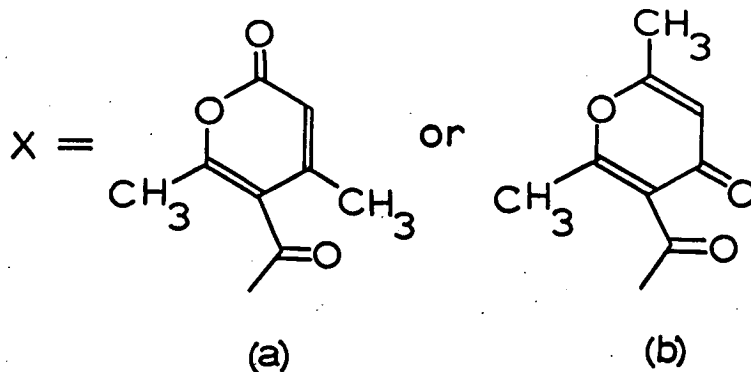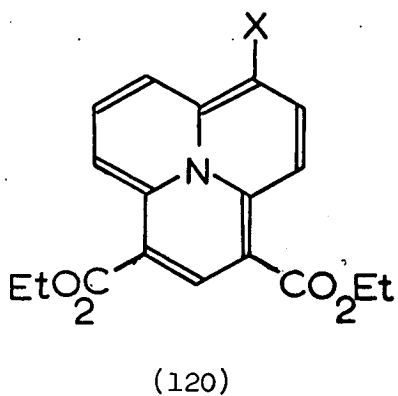
The values for the chemical shifts of the ring protons and methyl substituents of α- and γ-pyrones do not show any marked dependence on their position[163,164], and do not allow a choice to be made between the two possible structures. However, the absorption frequency of the carbonyl group in the infra-red region shows quite a large difference. Thus the

characteristic absorption region for α-pyrones is 1700-1740 cm^{-1} and for

γ-pyrones 1650 cm^{-1} [165]. In this region the i.r. spectrum showed the

following peaks:- 1680 cm^{-1}, 1670 cm^{-1}, 1635 cm^{-1} and 1620 cm^{-1}. The keto

group attached to the ring might cause a slight lowering of the absorption

frequency of the carbonyl group, but nonetheless the fact that there is no

absorption above 1680 cm^{-1} would seem to exclude the possibility of the

α-pyrone derivative. The absorptions at 1680 cm^{-1} and 1670 cm^{-1} will

include the ester groups and the keto group attached to the ring. It

therefore seems probable that the absorption at 1635 cm^{-1} is due to the

γ-pyrone structure (120b). However, this is not certain, and there must

remain some element of doubt.

REACTION OF DIETHYL CYCL[3,3,3]AZINE-1,3-CARBOXYLATE WITH BENZYNE

Diethyl cycl[3,3,3]azine-1,3-dicarboxylate has been shown to react with dimethyl acetylenedicarboxylate to yield the Diels-Alder adduct(71)[139]
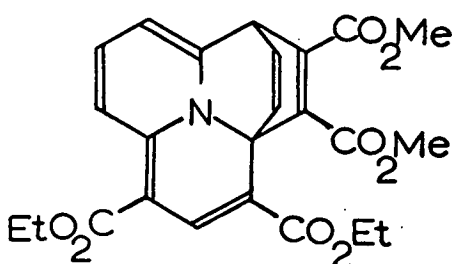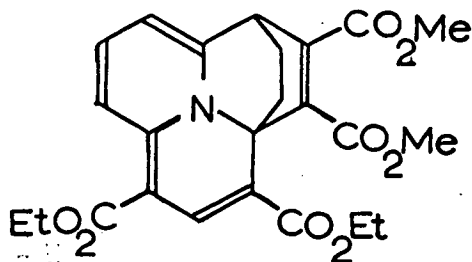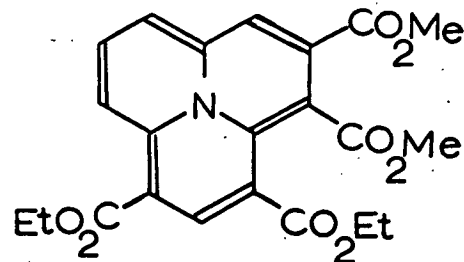
(71)   (121)   (122)

Addition of hydrogen to the adduct yielded the ethano analogue (121) which on pyrolysis lost ethylene by a reverse Diels-Alder reaction to give the tetrasubstituted cyclazine (122).

A similar sequence of reactions using benzyne (generated thermally from diphenyliodonium-2-carboxylate) as the dienophile should lead to the formation of diethyl benzo[a]cycl[3,3,3]azine-1,3-dicarboxylate (123).
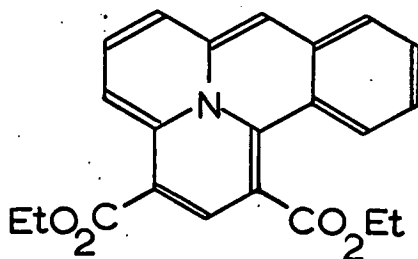
(123)

This is a system containing an aromatic ring fused to an anti-aromatic system, and would be of considerable interest.

However, the reaction when carried out in refluxing triglyme using varying reaction times and amounts of diphenyliodonium-2-carboxylate, yielded a complex mixture of products. It seems probable that the multiplicity of products is due to the high reactivity of benzyne which is very much less selective than dimethyl acetylenedicarboxylate.

Other methods of generating benzyne, at lower temperatures, were considered but rejected because they involve the use of diazonium compounds (which would probably couple with the cyclazine), strong oxidising agents, or strong bases.

(124) (125) (126)

(69a) ——D.M.A.D.C.——▶ (71)

[H]

(122) ◀——Δ, −C₂H₄—— (121)
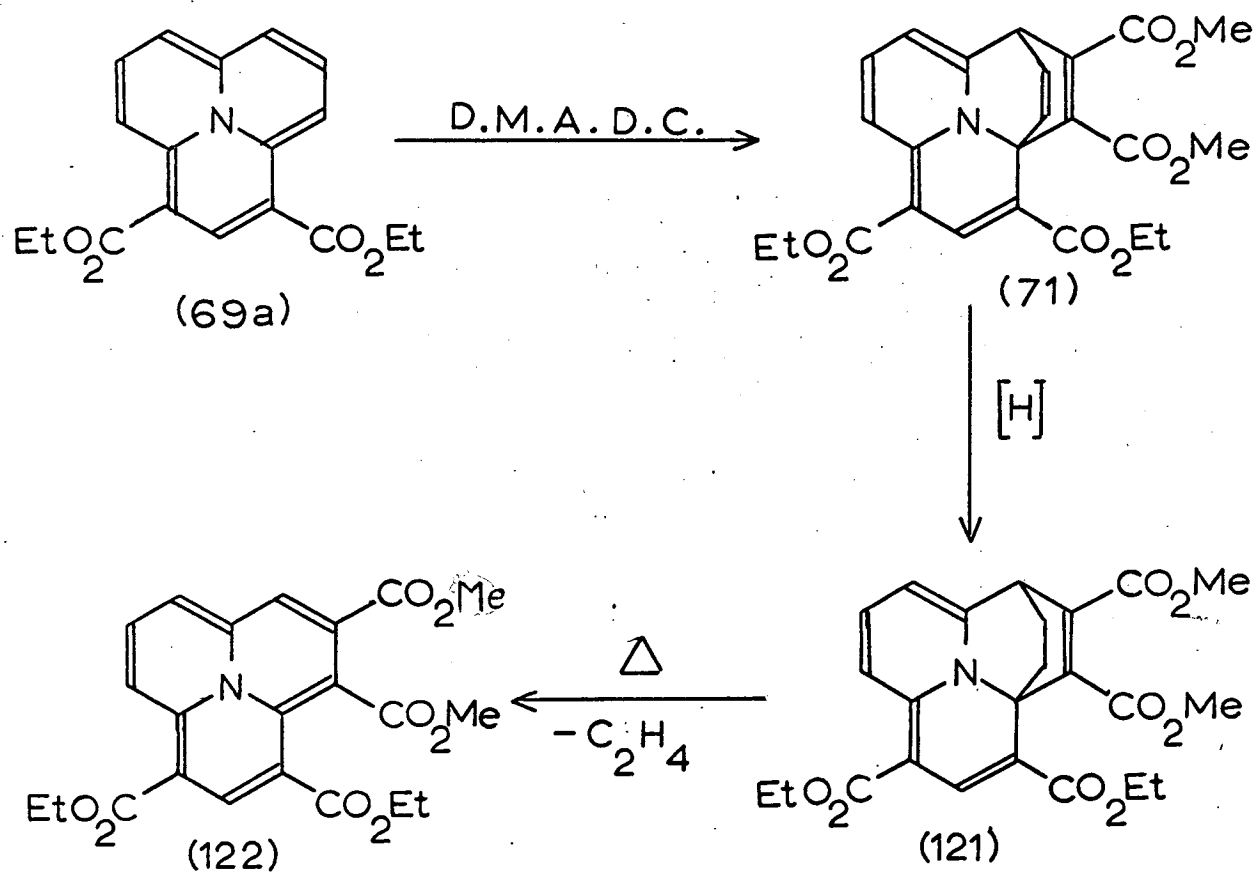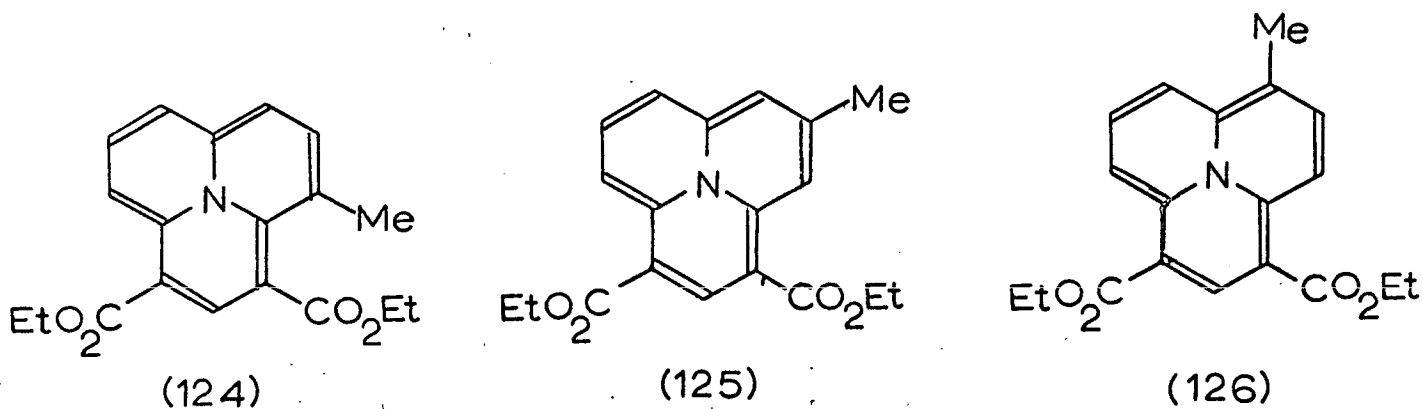
FIG. 23

ATTEMPTED PREPARATION OF 4-, 5- AND 6-METHYL

DERIVATIVES OF DIETHYL CYCL[3,3,3]AZINE-1,3-DICARBOXYLATE

Synthesis of these derivatives (124 - 126) would be useful since measurement of the chemical shifts of the methyl groups in the n.m.r. spectra should give useful information about the paramagnetic ring current in the cycl[3,3,3]azine nucleus. Thus the presence of a paramagnetic ring current would cause the protons of a methyl group directly attached to the ring to resonate at higher field than they would do in a similar chemical environment, but without the ring current. It could be argued that the high-field positions observed for the protons of cycl[3,3,3]azine are due almost entirely to the effect of the electron-rich nitrogen atom. The value of the chemical shift of the methyl group would be affected much less by this cause, and would therefore be a more accurate indication of the presence and magnitude of a paramagnetic current.

Diethyl cycl[3,3,3]azine-1,3-dicarboxylate reacts with dimethyl acetylenedicarboxylate to yield the Diels-Alder adduct (71). Hydrogenation of this product followed by pyrolysis yields the cyclazinetetracarboxylate (122) [139] as shown in Fig. 23. If the corresponding reaction using t-butyl but-2-ynoate could be achieved, then (since the t-butoxycarbonyl group would probably be lost during the pyrolysis stage), it should be possible to obtain the 4- or the 5-methyl derivative, depending on the orientation of the Diels-Alder addition. It was expected that any difficulties with this reaction were likely to arise either from the premature loss of the labile t-butyl group or from failure to obtain the Diels-Alder adduct. The reaction with dimethyl acetylenedicarboxylate requires refluxing for 16 hrs.

in benzene or 5 hrs. in toluene, and the butynoate being a weaker dienophile, would clearly require more vigorous conditions. In an attempt to establish what these conditions would be, the reaction was first tried using ethyl butynoate.

After refluxing in toluene overnight, no reaction occurred, thin-layer chromatography showing only unreacted cyclazine with a small amount of decomposition product. After heating together in a sealed thick-walled glass tube for 6 hrs. at 150° using excess butynoate as solvent, chromatography of the product yielded mainly recovered cyclazine, and only traces of another red band. The previous Diels-Alder product, prepared by Farquhar [139], was bright red and so it is quite possible that this red band was the desired product. However, the amount of it was too small to be worthwhile isolating, or to suggest that a further attempt would be useful. It seemed clear that the reactivity of the butynoate as a dienophile was markedly less than that of dimethyl acetylenedicarboxylate.

Formyl groups have been successfully reduced to methyl groups by the use of diborane, prepared by the action of borontrifluoride-etherate on sodium borohydride, generated either in situ or externally and carried into the reaction mixture by a flow of nitrogen [166,167]. Reaction with diethyl 6-formylcycl [3,3,3] azine-1,3-dicarboxylate yielded an orange product in high yield, which was of a highly polar nature, and was only eluted from 10% deactivated alumina with difficulty. A m. pt. of 212-214° confirmed the high polarity, a considerably lower m. pt. being expected for the 6-methyl derivative. However, the mass spectrum indicated a molecular weight of 325 (together with smaller peaks at 339 and 341), which would be correct for the desired product. It seemed most unlikely, however, that the

6-methyl derivative would show such polar properties. Since the material was only sparingly soluble in chloroform, the n.m.r. spectrum was measured in hexadeutero dimethylsulphoxide (at 120°). The spectrum was largely as would be expected for the 6-methyl derivative. Thus the 2-proton gave rise to a singlet at 2.91T, the 8-proton to a triplet at 3.55T and the 7- and 9-protons to two doublets at 4.39T and 3.25T respectively. The two remaining doublets at 3.35T and 3.55T were assigned to the 4- and 5-protons. Besides those from the ethyl groups, the only remaining absorptions were a three proton singlet at 8.29T and a singlet at 6.33T which, at 120°, integrated correctly for two protons but was much weaker at lower temperatures. It seems likely that this singlet was due to some impurity. If this is so, then the spectrum would be entirely consistent with that expected from the 6-methyl derivative. Furthermore, when compared with the n.m.r. spectrum of the 5-methyl derivative (125) prepared later (see below) the chemical shifts of the 2-, 4-, 7-, 8-, 9- and methyl protons were found to be closely similar. However, despite the evidence from the n.m.r. spectrum it seems, on the basis of the highly polar nature of the material, almost impossible that it could be the 6-methyl derivative. As mentioned above, its m. pt. was 212-214°. That of the 5-methyl derivative was 116.5-117.5°, and it seems unlikely that such a difference could be accounted for on the grounds of different crystal structure alone. Further doubt arises from the fact that the mass spectrum of the material recovered from the n.m.r. sample was considerably changed from the original one, showing four peaks of nearly equal intensity at m/e 369, 355, 341 and 325. Neither of the first two peaks were present in the original spectrum, and it therefore seemed probable that some change had occurred.
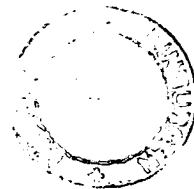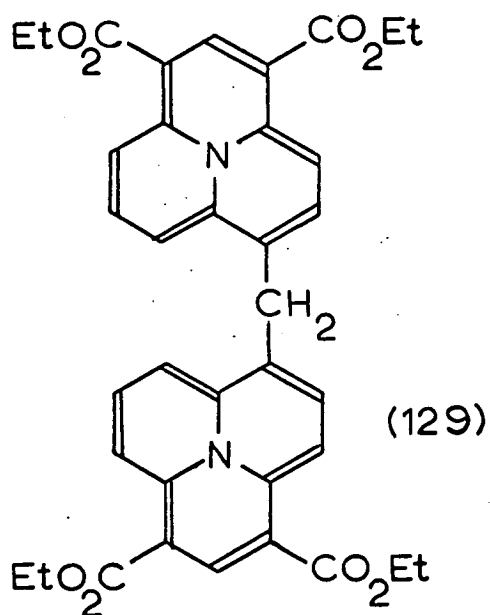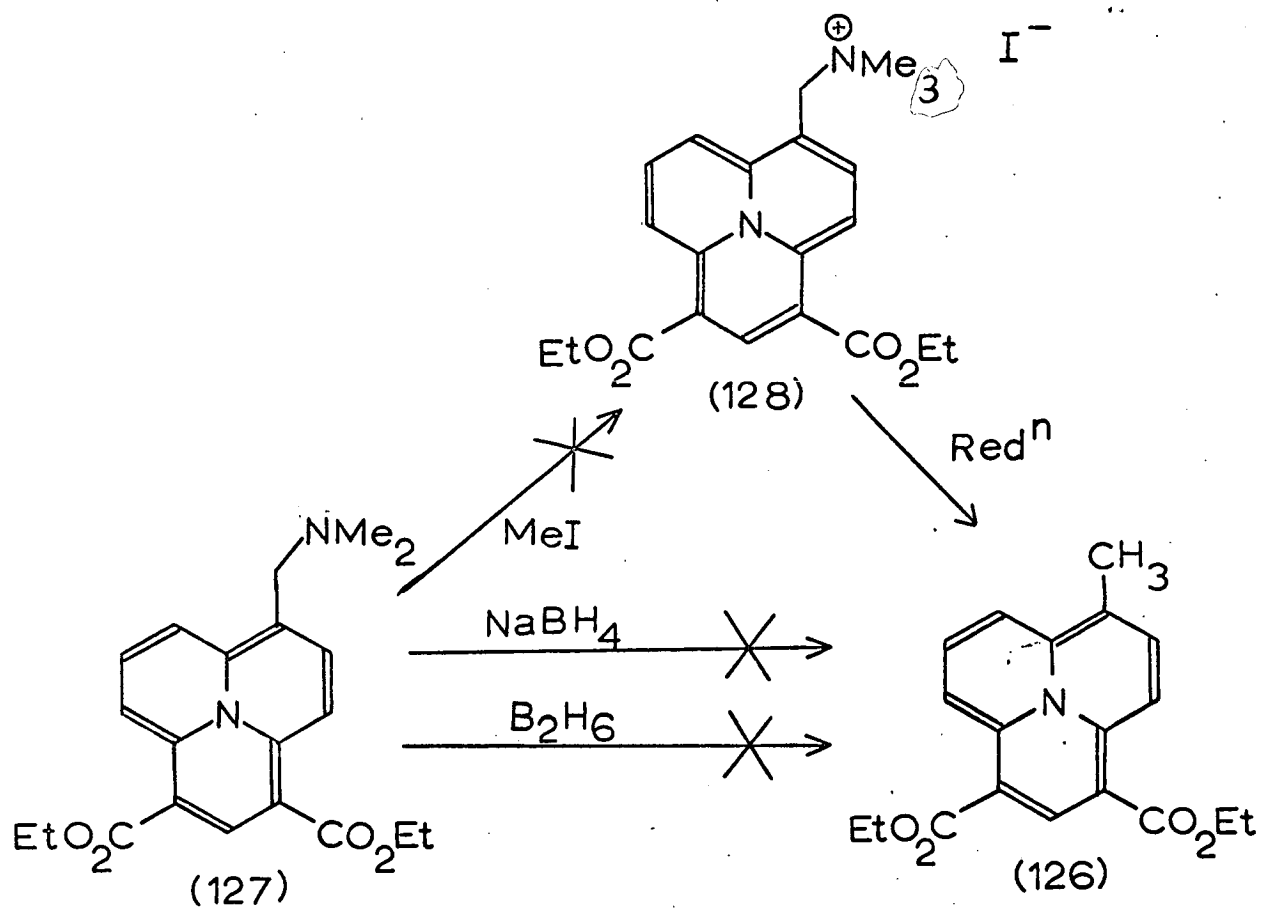
FIG. 24
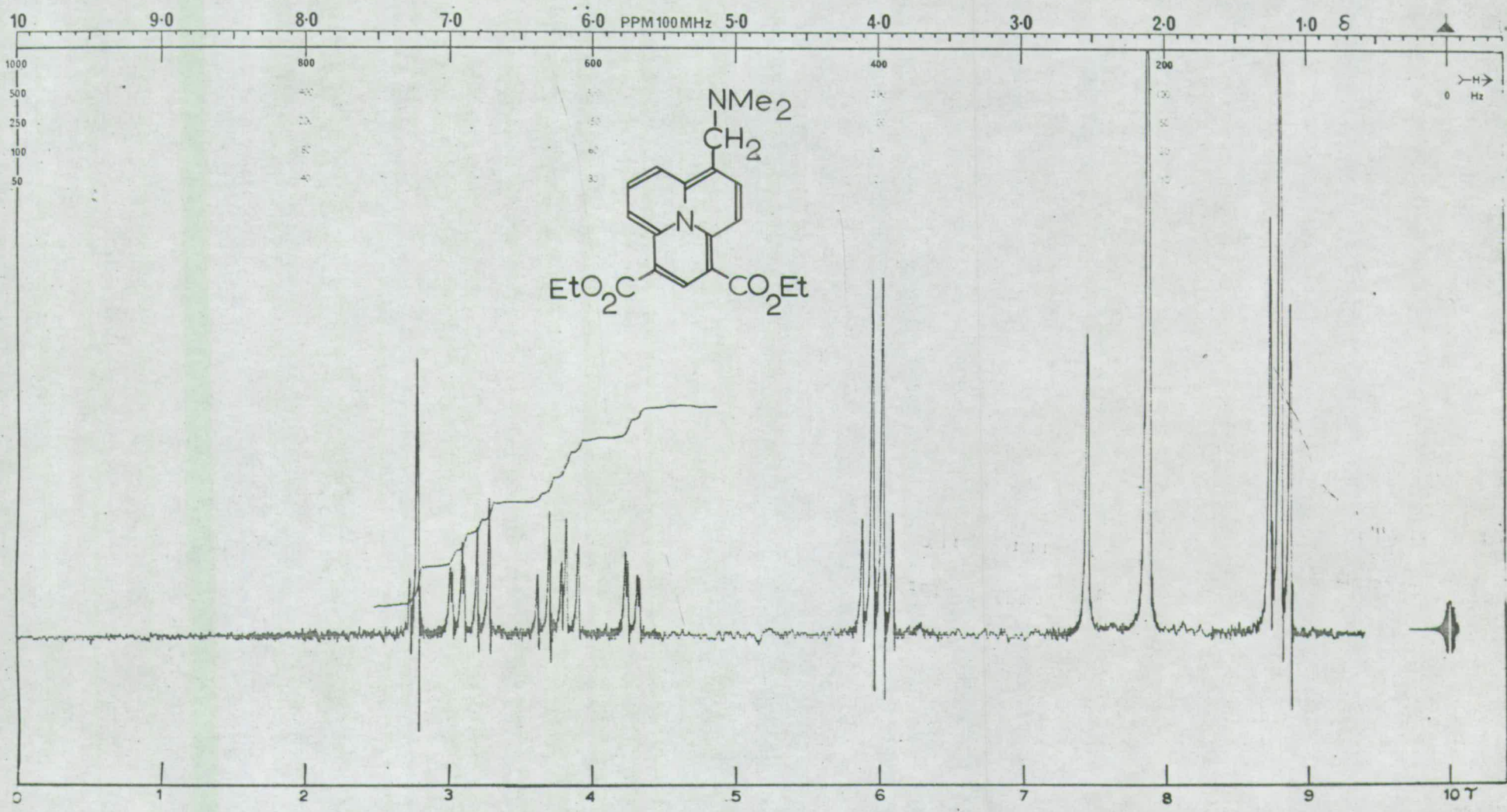
FIG 25

Reduction of the 4-formyl derivative was attempted by the same method, and the reaction appeared to take a similar course. However, during chromatography the product crystallised on the column, and could not be eluted even with warm methanol.

The fact that the n.m.r. spectrum of the reduction product of the 6-formyl derivative is consistent with identification as the 6-methyl derivative while the other properties are not, leads to an inconclusive and unsatisfactory result. Since the 5-methyl derivative was later successfully prepared by total synthesis (see below) it would seem that it may be worthwhile attempting to prepare the 4- and 6-methyl derivatives by a similar route in order to resolve the above doubts.

A dimethylaminomethyl azulene has been obtained by reaction with tetramethyldiaminomethane and paraformaldehyde[168] . Removal of the dimethylamino group to give 1-methyl azulene was then achieved by quaternisation with methyl iodide and reduction of the methiodide with sodium borohydride. It was hoped that a similar sequence with the cyclazine would lead to either the 4- or 6-methyl derivative.

When aminomethylation was attempted, two products were obtained on chromatography. The first of the products was obtained as orange plates (54%) and was shown, by n.m.r. spectroscopy, to be the 6-dimethylaminomethyl derivative (127). Thus besides the pattern of absorptions typical of a 6-substituted derivative (the 4- and 5-protons gave rise to two doublets of an AX system at 3.23T and 3.86T respectively), there was also present a two-proton singlet at 7.46T and a six-proton singlet at 7.89T, attributed to the methylene and methyl protons respectively (Fig. 25).

The second minor product was obtained as orange needles (20%). From
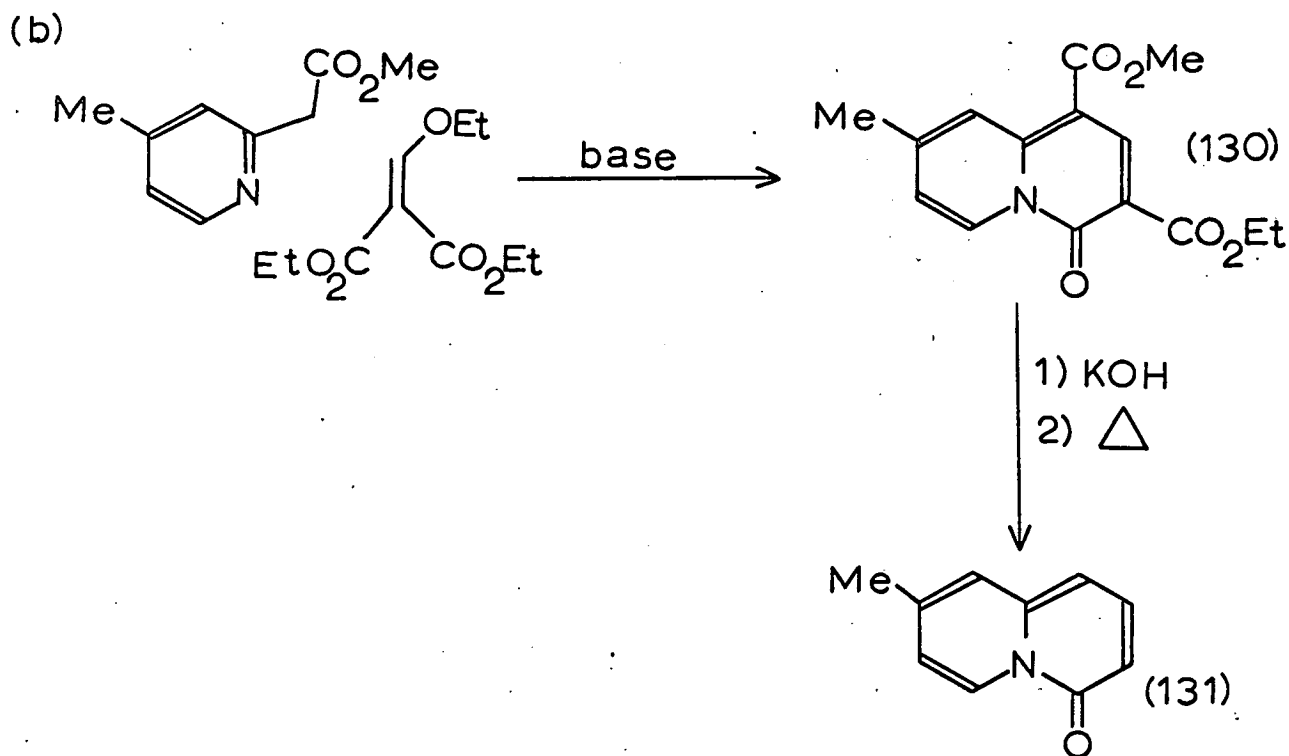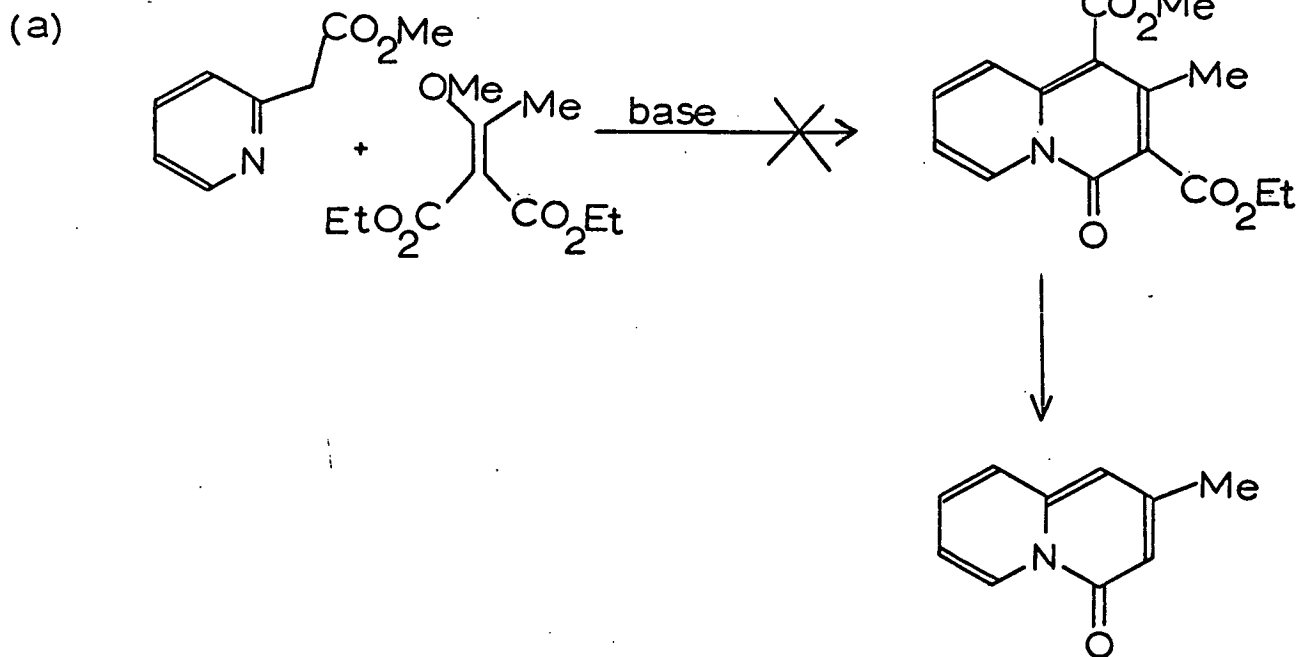
FIG. 26

the mass spectrum (m/e 634) and the n.m.r. spectrum, this was identified as the dicyclazinylmethane (129). The n.m.r. spectrum showed the expected pattern for the ring protons with a two proton singlet at 8.16T attributable to the methylene bridge. The dicyclazinylmethane is presumably formed by nucleophilic attack of the unreacted cyclazine on the protonated aminomethylation product with loss of a molecule of dimethylamine.

An attempt to prepare the methiodide (128) from the aminomethyl product for subsequent conversion to the 6-methyl derivative, failed. Thus the n.m.r. spectrum of the product formed by the reaction with methyliodide was poorly resolved, but showed that the methylene (7.15T) and methyl (7.57T) protons, although they had moved downfield as expected, were weak in intensity, and were apparently part of a minor constituent of a mixture. It was not possible to interpret the remainder of the spectrum. The mass spectrum also indicated a mixture of products.

Direct reduction of the dimethylaminomethylcyclazine (127) was attempted with sodium borohydride, and with diborane, but both yielded only starting material. Further attempts to prepare a methyl derivative of the cyclazine by this route were precluded by lack of material.

Synthesis of diethyl 5-methylcycl[3,3,3]azine-1,3-dicarboxylate

When the above attempts to prepare a methyl derivative of diethyl cycl[3,3,3]azine-1,3-dicarboxylate failed, the possibility of complete synthesis of the 5-methyl derivative was investigated. This would require the preparation of a 2- or 8-methyl derivative of quinolizin-4-one. Using the usual method of preparation of quinolizone [139], this might, in principle, be achieved by either of the routes outlined in Fig. 26.

(131)

HClO₄ →

(132)   ClO₄⁻
Cl

(133)
Bu^tO₂C   CO₂Et

←

(134)
CO₂Et

↓

EtO₂C   (125)   CO₂Et

+

EtO₂C   (135)   CO₂Et
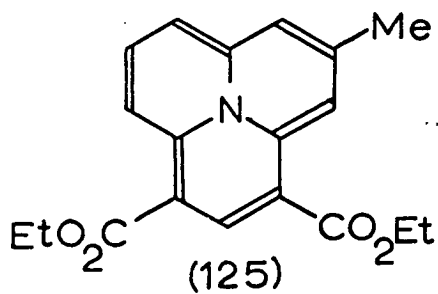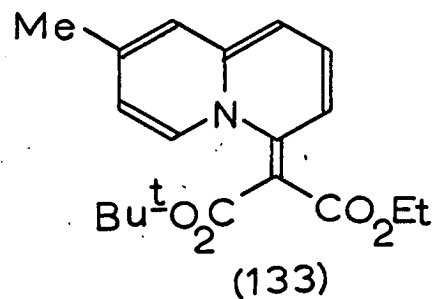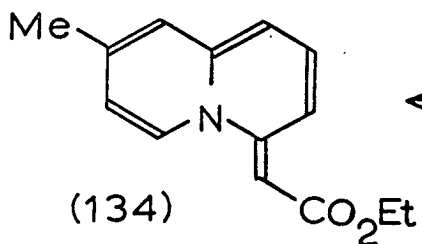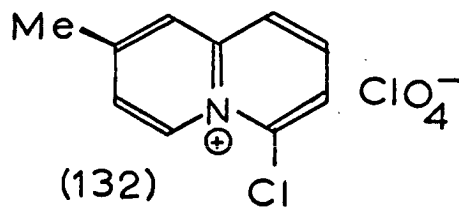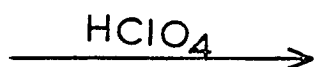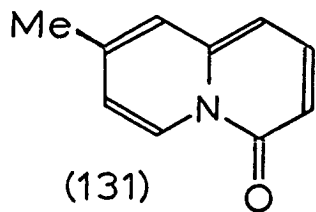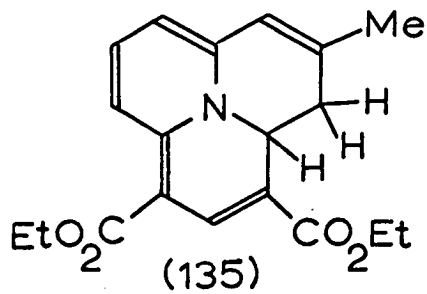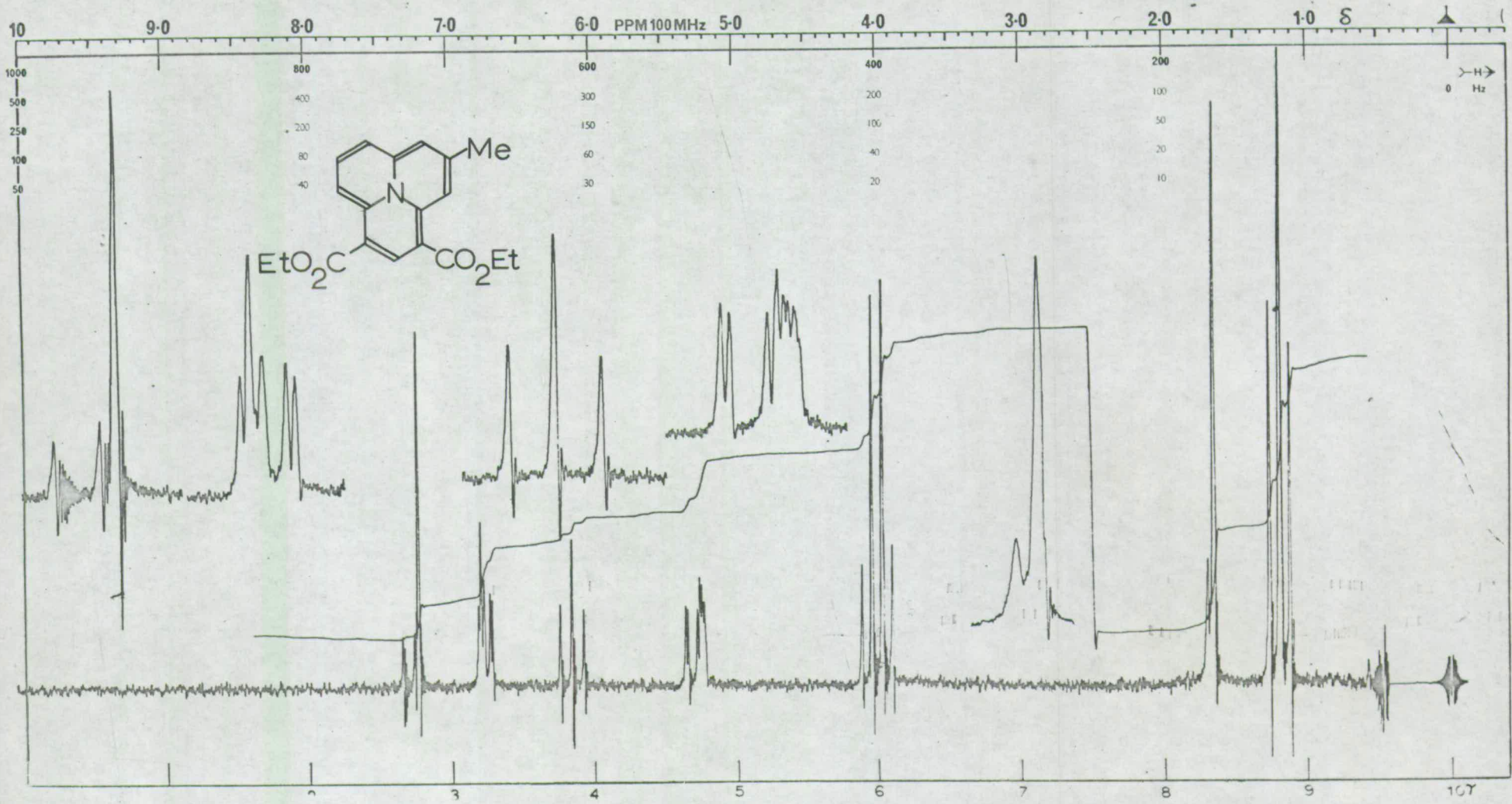
FIG 27

Route (a) was first attempted using diethyl (1-methoxyethylidene)malonate, prepared by treatment of diethyl acetylmalonate with diazomethane. However, the initial condensation failed to occur, perhaps because of the steric hindrance caused by the methyl group.

The initial condensation in route (b) occurred readily but, for an unexplained reason, the expected acid hydrolysis of the condensation product (130) failed. Alkaline hydrolysis to the diacid followed by thermal decarboxylation led to the quinolizone (131), which was obtained by sublimation.

The required diethyl 5-methylcycl [3,3,3] azine-1,3-dicarboxylate was prepared from the 8-methylquinolizin-4-one by the route outlined, the experimental procedures being exactly analogous to those used for the preparation of the diethyl cycl [3,3,3] azine-1,3-dicarboxylate. The final cyclisation reaction yielded, as expected, two products. The first, a yellow-green band on the column, was obtained as dark purple plates (49%). The n.m.r. spectrum showed the expected pattern for the 5-methyl derivative (Fig. 27). Thus the 2-proton gave rise to a singlet at 2.67T, the 7-, 8- and 9-proton to two doublets and a triplet at 4.69T, 3.84T and 3.24T respectively, and the 4- and 6-protons to two singlets with slight splitting at 3.22T and 4.76T respectively. The three-proton singlet due to the methyl group appeared at 8.35T.

The second product, a dark blue band on the column, yielded a dark solid (6.5%), the mass spectrum of which indicated a molecular weight of 327. This was identified as the dihydro derivative (135) by its n.m.r. spectrum. Thus the 2-proton gave rise to a singlet at 2.01T, the 7- and 9-protons to doublets (with further splitting) at 3.77T and 1.37T respectively, and the 8-proton to a doublet of doublets centred at 2.79T. The 6-proton gave rise to a singlet at 3.95T, and the methyl protons

to a singlet at 8.00T. The remaining features of the spectrum, two doublets with further splitting centred at 4.39T and 6.75T a quartet centred at 7.55T were assigned to the 3a, 4β- and 4α-protons respectively (136b).

(a) R=H

(b) R=Me
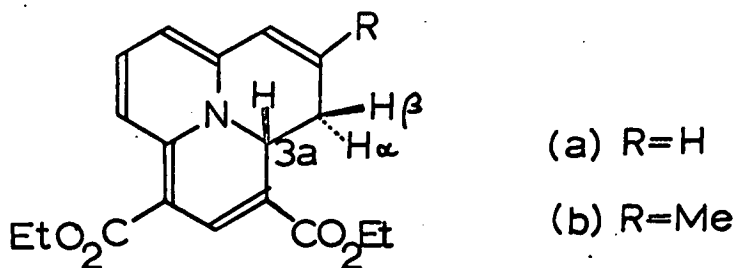
(136)
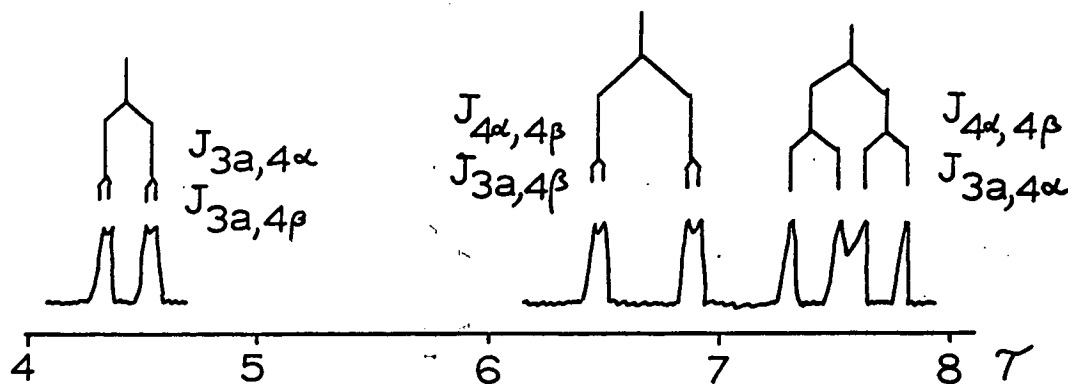
This assignment was confirmed by comparison with the spectrum and interpretation of the dihydro derivative (136a) due to Farquhar[139]. The latter spectrum is slightly more complex due to splitting from the 5-proton, but the remaining splittings are essentially the same.

The chemical shift of the methyl group (8.35T) in the 5-methyl derivative (125) may be compared with those of the corresponding groups
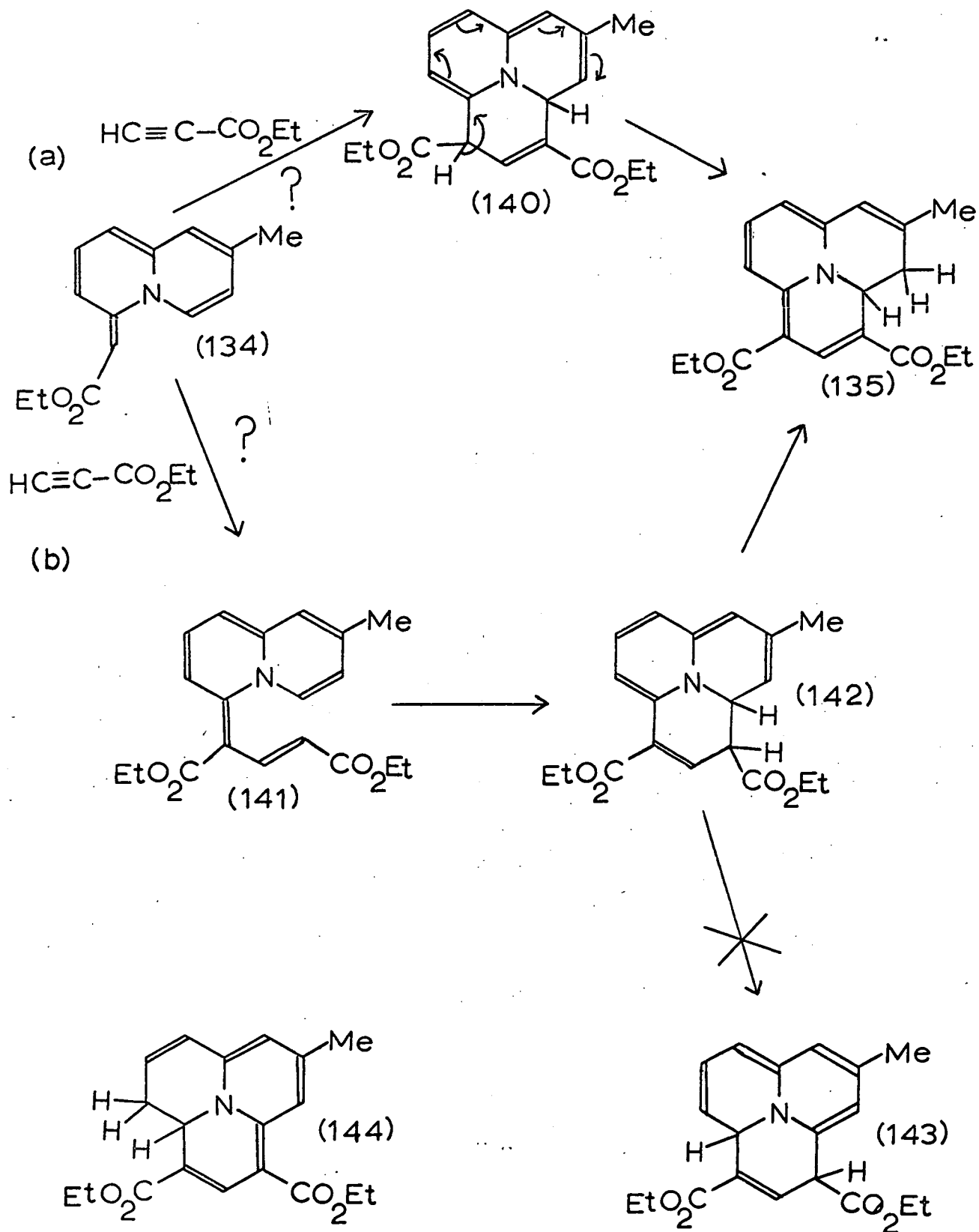
FIG. 28

in such aromatic compounds as (137) (7.70T) and (138) (7.75T)

from which it is ca. 0.6T upfield, and in a typical non-aromatic compound

(139)   (8.29T) from which it is only slightly upfield.

Me—[chemical structure]—Ph   Me—[chemical structure]—Ph   [chemical structure] Me, N—SiMe₃
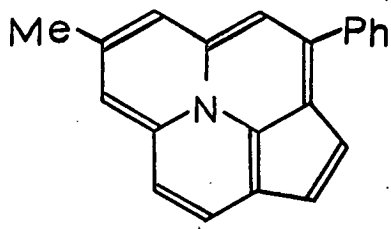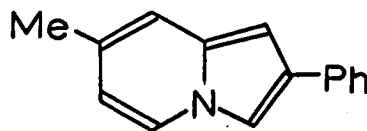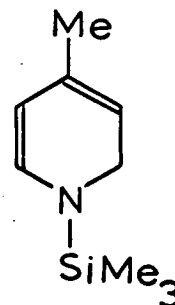
(137)   (138)   (139)

However, perhaps the most valid comparison to be made is with the value

for the methyl group in the dihydro derivative (135) (8.00T) which is

structurally similar, but where there is no possibility of a ring current

in the ring containing the methyl group. This represents an upfield shift

of 0.35T on changing to the fully conjugated structure, and would seem to

be clear evidence for the presence of an induced paramagnetic ring current

in the cycl[3,3,3]azine ring system.

From the observed structure of the dihydro derivative (135)   which

is also an intermediate in the formation of the fully unsaturated cyclazine

(125) [139],   two possible reaction mechanisms may be proposed for its

formation (Fig. 28).   Route (a), proposed earlier by Farquhar, results

from a cyclo-addition of the propiolate to the quinolizinylidineacetate

(134) followed by a 1,9-shift of hydrogen. The driving force for such a

shift was rationalised by Farquhar as arising from the increased stability

of the 4H-quinolizine system of the product (135) over that of its presumed precursor (140). A 1,9-shift of hydrogen is allowed, by the Woodward-Hoffmann rules, as a concerted suprafacial process though, in this case, the large distance between the termini of the nonatetraenyl system might be expected to prevent such a process occurring.

Another possible process is that shown in route (b), involving a two step process of linear addition to form the acrylate (141), followed by cyclisation to yield (142) which would be required to undergo a 1,11-shift of hydrogen. Such a shift can only take place concertedly in the antarafacial mode which again seems unlikely for geometric reasons. The observed product gives no indication of which mechanism is correct, although the fact that none of the open chain acrylate (141) has been found in any of the reactions makes the first one seem more acceptable. The possibility that (144) is formed from (142) via (143), by two 1,9-shifts of hydrogen can, however, be excluded, as none of this product is found.
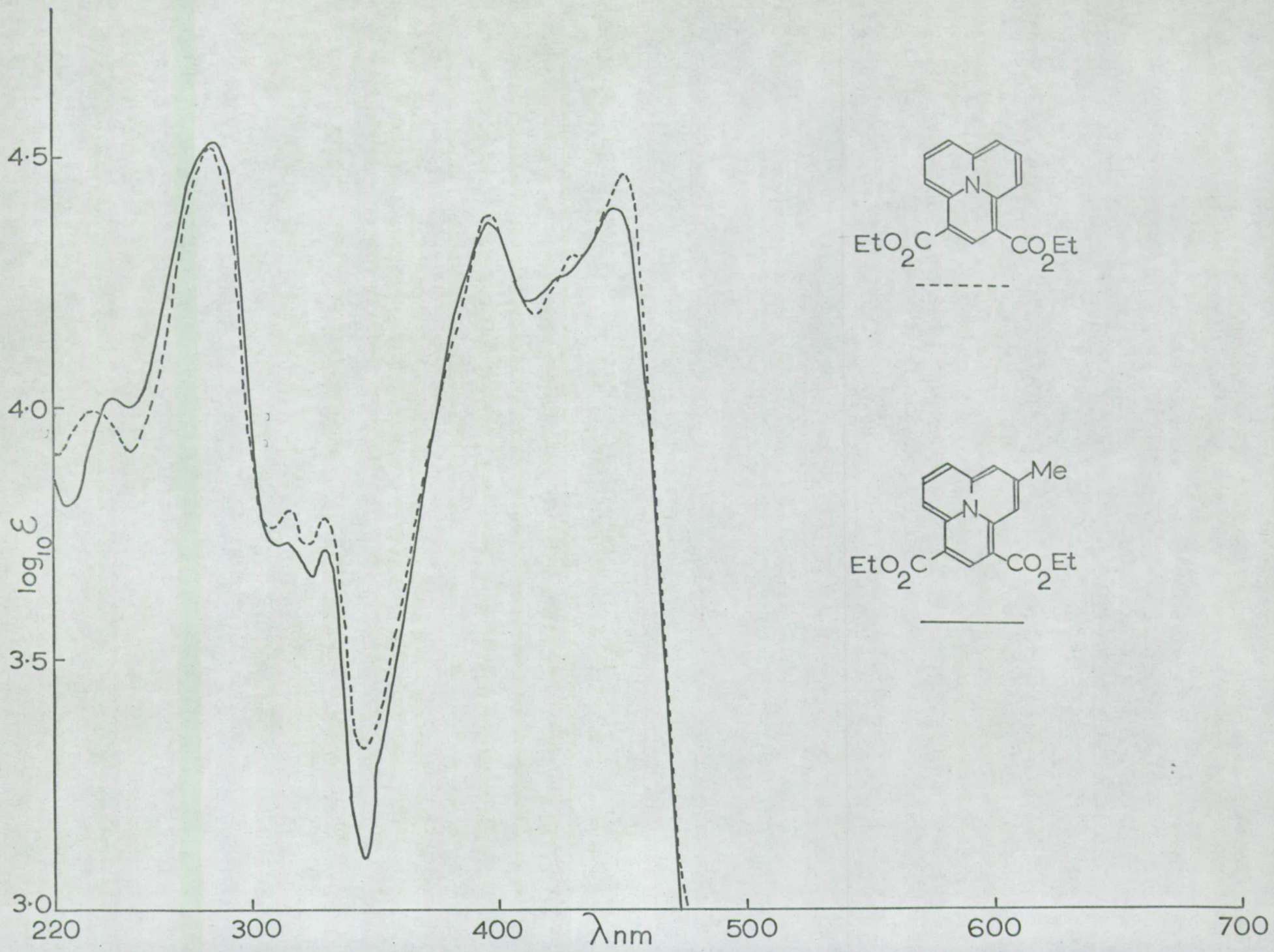
ADDITION AND SUBSTITUTION REACTIONS OF

ETHYL CYCL[3,3,3]AZINE-1-CARBOXYLATE

Dimethyl acetylenedicarboxylate reacts with diethyl cycl[3,3,3]azine-1,3-dicarboxylate in boiling benzene (16 hrs.) or toluene (5 hrs.) to form a red Diels-Alder adduct (71) [139].
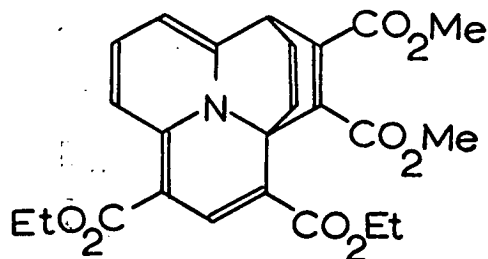
(71)

A similar reaction with ethyl cycl[3,3,3]azine-1-carboxylate could yield two products (or three if reaction occurred in the ring containing the ethoxy-carbonyl group). Since the monoethoxycarbonylcyclazine is more reactive than the diethoxycarbonyl derivative [139], it seemed very likely that milder conditions would be required. This proved to be the case. Thus at 20° in dry benzene the reaction mixture darkened to red-brown in 10 mins., but no product could be isolated. When the reaction was attempted in dry, oxygen-free dichloromethane at -78° for $\frac{1}{2}$hr. with subsequent warming to room temperature, a large number of products was obtained. Separation of these was attempted by preparative thin-layer chromatography, but of the many bands present, only two were isolated. These were a grey band (7.5 mg., ca. 5%) and a purple band (4.3 mg., ca. 3%). The mass spectrum of each contained peaks at m/e 523 and 381, which are correct for the addition of two molecules and one molecule,

respectively, of dimethyl acetylenedicarboxylate to the cyclazine. The
mass spectrum of the second contained, in addition, a peak at m/e 554. An
n.m.r. spectrum of the first product was too weak for the proper assignment of
peaks but indicated that the product was probably a mixture.

It seemed likely that one of the reasons for the large number of
products was the high reactivity of dimethyl acetylenedicarboxylate. The
reaction was therefore repeated using the less reactive ethyl propiolate.
Refluxing for 10 mins. in dry, oxygen-free benzene gave only a trace of
product. Refluxing in toluene for 2 hrs. with a four-fold excess of
propiolate gave a similar result. Refluxing with additional propiolate was
continued for 16 hrs. Chromatography of the product showed mainly
decomposition material with two weak red bands, neither of which could be
isolated. It seemed unlikely that suitable reaction conditions would be found
for the avoidance of a large number of products and for the decomposition of
the cyclazine, and so the attempt was not continued further.

Diethyl cycl[3,3,3]azine-1,3-dicarboxylate undergoes electrophilic
substitution reactions with great ease. Since the monoethoxycarbonyl derivative
is even more electron-rich, it was anticipated that it would be even more
reactive towards electrophiles.

Attempted nitration using cupric nitrate and acetic anhydride in
dichloromethane (conditions which had been reported to give mono-nitration
with [18]-annulene [157], and had already been used to give mononitration of
the diethyl cyclazinedicarboxylate) gave only a complicated mixture of
products, none of which could be isolated in sufficient quantity to identify.

The 4- and 6-formyl derivatives of diethyl cycl[3,3,3]azine-1,3-dicarboxylate
had been obtained by reaction of the cyclazine with N,N-dimethylformamide and
phosphoryl chloride (Vilsmeier reagent) [139]. Reaction at low temperature with
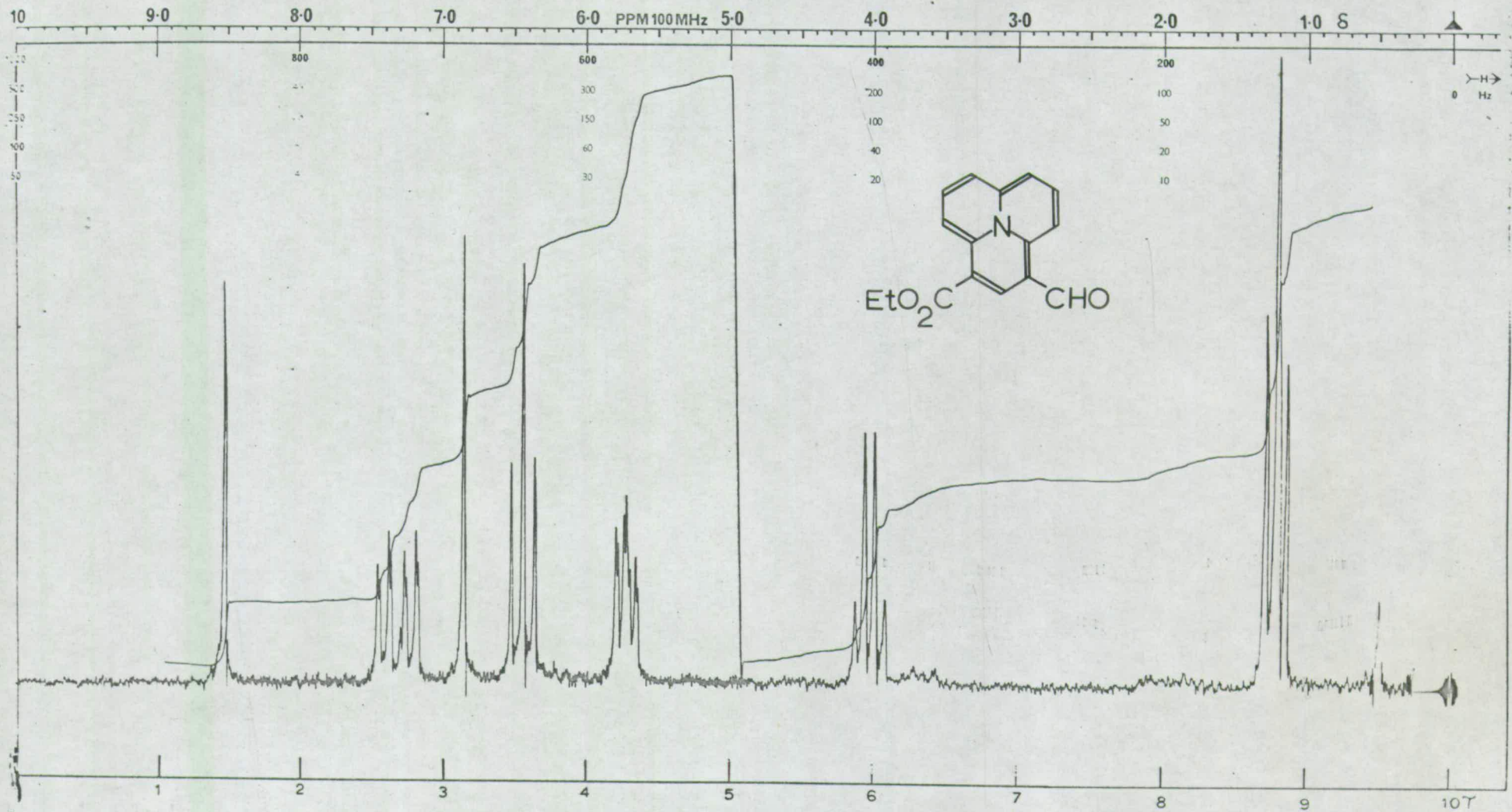
FIG 29

the monoethoxycarbonylcyclazine yielded two products which were separated

by chromatography. The first, a labile red oil, was obtained in only 3.5%

yield. Its mass spectrum indicated a molecular weight of 267, consistent with

a monoformyl derivative, but because of the low yield and instability it could

not be identified. The second product, obtained from a yellow-green band on the

column, was obtained as purple needles (15%). The mass spectrum again indicated

a molecular weight of 267 and the n.m.r. spectrum showed it to be ethyl

3-formylcycl[3,3,3]azine-1-carboxylate (145) Fig. 29.

(145)
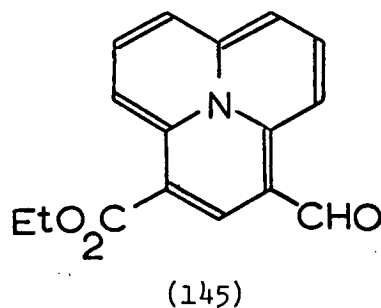
Thus a two-proton triplet at 3.57T was attributed to the 5- and

8-protons (with the same chemical shift) while the 4- and 9-protons gave rise

to two doublets at 2.59T and 2.78T respectively. The two remaining doublets at

4.28T and 4.32T were assigned to the 6- and 7-protons. The ethyl protons gave

rise to the expected triplet and quartet, leaving two singlets at 1.45T and

3.15T. By comparison with the spectrum of ethyl 3-(3-oxoprop-1-enyl)cycl[3,3,3]-

azine-1-carboxylate (107), in which the 2-proton gave rise to a singlet at

3.34T and the aldehyde proton to a doublet at 0.71T, these were assigned to

the formyl- and 2-proton respectively. This was confirmed by comparison with

the spectrum of the 3-benzoyl derivative (146b) prepared later (see below) in

which the 2-proton gave rise to a singlet at 3.07T.
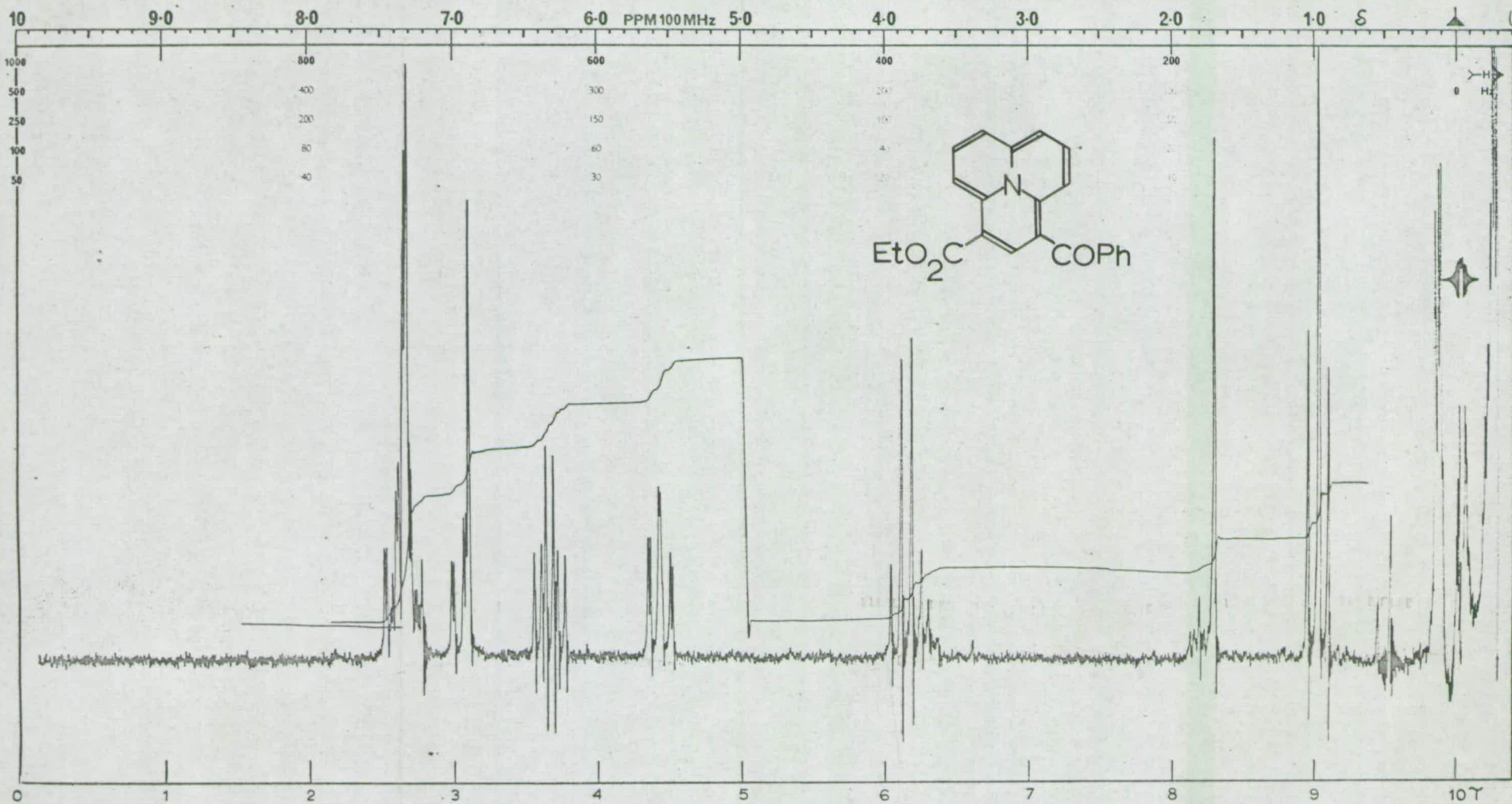
FIG 30

A variation of the above method due to Chong et al.[170] has proved useful where very mild conditions are desirable. In this method benzoyl-chloride is added to a solution, in dimethylformamide, of the material to be formylated. The Vilsmeier complex is hydrolysed as before. These conditions yielded only the 3-formyl derivatives in 41% yield. None of the labile red oil was obtained.

An attempt to prepare the 3-acetyl derivative (146a) by the above method using dimethylacetamide in place of dimethylformamide, resulted instead in formation of the 3-benzoyl derivative (146b) in 39% yield.

(a) R = COMe
(b) R = COPh

(146)
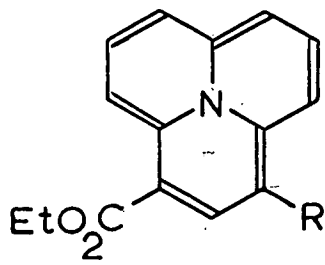
Thus the n.m.r. spectrum (Fig.30) showed a singlet at 3.07T(2-proton), two doublets at 2.54T and 3.00T(4- and 9-protons respectively), two further doublets at 4.37T and 4.44T(6- and 7-protons), two triplets at 3.61T and 3.66T (5- and 8-protons) and a five-proton multiplet in the region 2.55 - 2.75T. *

This result, though surprising, must presumably be due to a faster rate of reaction of benzoylchloride with dimethylformamide than with dimethylacetamide, so that in the second reaction above, reaction of benzoylchloride with the cyclazine

* To prevent collapse of the signals, the n.m.r. sample (in deuterochloroform) was shaken with an aqueous solution of dithionite to remove oxygen. The n.m.r. sample therefore contained traces of water which gave rise to a singlet at 8.15T.

becomes the faster reaction.

Each of the above identified products proved to be the 3-derivative. This may be explained in the following terms:-

It was noted by Farquhar that the 3-proton in alkyl cycl[3,3,3]azine-1-carboxylate resonates at the unexpectedly high-field value of 6.37 - 6.49T. This was rationalised by proposing a significant contribution from structure (98b), to the resonance hybrid as discussed earlier.
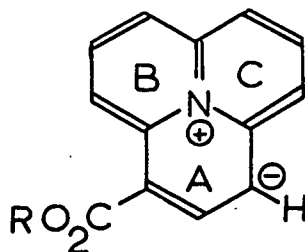
(98b)

Thus the 3-position would be expected to be electron-rich, and hence susceptible to electrophilic attack, while the remaining two rings, B and C, would be relatively electron poor.

It seems quite likely that the labile red oil obtained from the first of the formylation reactions contained a formyl group in ring B or C. If this is so, then its instability is interesting.
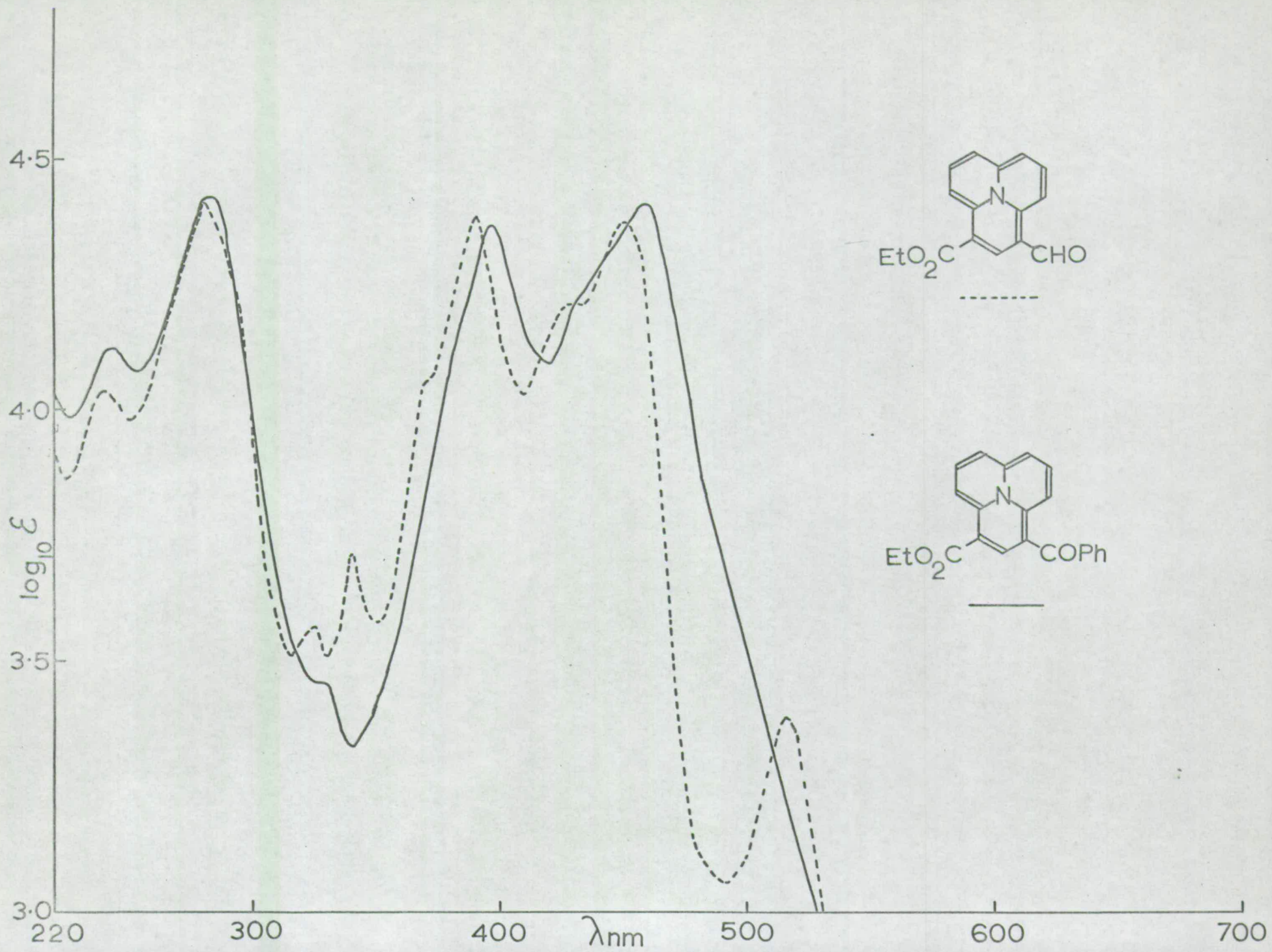
PREPARATION OF CYCL[3,3,3]AZINE, INVESTIGATIONS OF ITS
PROPERTIES, PREPARATION OF IONIC SPECIES DERIVED FROM
IT, AND PREPARATION OF DERIVATIVES OF 10b, 14b-DIAZONIAPEROPYRENE.

The parent cyclazine was prepared from the 1,3-di-t-butoxycarbonyl

derivative by pyrolysis in an evacuated, sealed, thick walled glass tube,

using a technique similar to that of Farquhar in the original preparation[139].

The previously recorded observations on the physical properties and stability

of the parent compound were in agreement with the present investigations.

Thus the product was a dark purple-brown crystalline solid with a metallic

lustre.   Under a dry nitrogen atmosphere it was quite stable but extensive

decomposition occurred within a few minutes on exposure to air.   The initially

light yellow solutions in oxygen-free chloroform, carbon tetrachloride

and trichloroethylene rapidly darkened to yield, within ten minutes, a dark

amorphous solid.   N.m.r. spectra were run in dry oxygen-free benzene and in

tetrachloroethylene, the cyclazine being slightly less stable in the latter

solvent than *in* bis(trimethylsilyl) ether ($Me_3Si.O.SiMe_3$) which was used

previously, fading to a yellow-orange colour in ca. 30 mins.   In

tetrachloroethylene the spectra showed a triplet at 6.37T and a doublet of

twice the intensity at 7.95T. These values are close to those found

previously in bis(trimethylsilyl) ether (6.35T and 7.93T). Solvent shifts

in benzene were found to be small at the concentrations used (ca. 20-30 mg./

ml.), causing only a small upfield shift mainly of the triplet (6.42T and

7.95T). It therefore appears that only a small degree of association between

the solvent and solute molecules occurs.

It seems that the very high-field values for the chemical shifts must

be due to the presence of a paramagnetic ring current, which may be inferred

from a comparison of the proton chemical shifts with those of the cyclic

dienamine system, N-phenyl-1,2-dihydropyridine (147) [171]
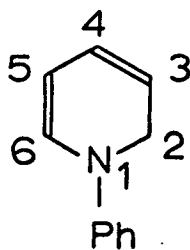
(147)

The 4-proton of (147) gives rise to a multiplet centred at 4.12T while the

3- and 5-protons give higher-field multiplets centred at 4.79T and 5.06T

respectively. These absorptions are 2-3 p.p.m. downfield from those of the

corresponding protons in the cyclazine. Since molecular orbital theory

predicts [102] that the most stable form for cycl[3,3,3]azine is that

containing alternate single and double bonds, it must be concluded that the

system is best represented by rapidly interconverting valence tautomeric

structures.
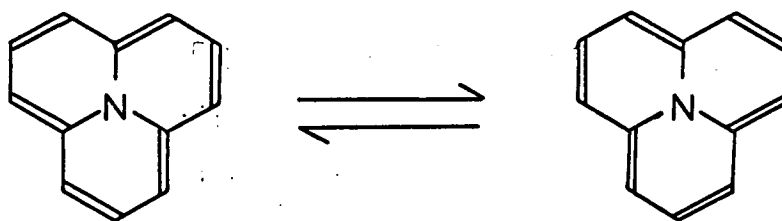
(148)

Attempted preparation of derivatives of cycl[3,3,3]azine

Diethyl cycl[3,3,3]azine-1,3-dicarboxylate undergoes Diels-Alder addition

reactions with acetylenedicarboxylic esters in refluxing benzene (16 hrs.) or

toluene (5 hrs.). Cycl[3,3,3]azine should undergo similar reactions and with

greater ease because of the absence of the electron-withdrawing ethoxycarbonyl groups. Reaction with ethyl propiolate in benzene at room temperature gave a deep red solution, the colour previously found for Diels-Alder adducts. The ultra-violet spectrum however, showed no similarities to those of Diels-Alder adducts, but bore considerable resemblance to that of methyl cycl[3,3,3]azine-1-carboxylate. It seemed possible that a compound of the type (149) might have been formed

CH=CH-CO$_2$Me
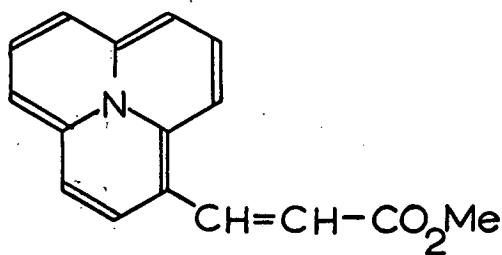
(149)

However, in view of the small yield and formation of a moderate amount of decomposition material, no attempt was made to isolate the product.

Formylation was attempted by the method of Chong et al.[170] which had proved successful for formylation of the ethoxycarbonylcyclazine. Thin-layer chromatography indicated the presence of a considerable amount of decomposition product and only small amounts of several other products. Attempted acetylation in dichloromethane by addition of acetylchloride (with a trace of trimethylamine) yielded a similar result. Neither reaction was investigated further.
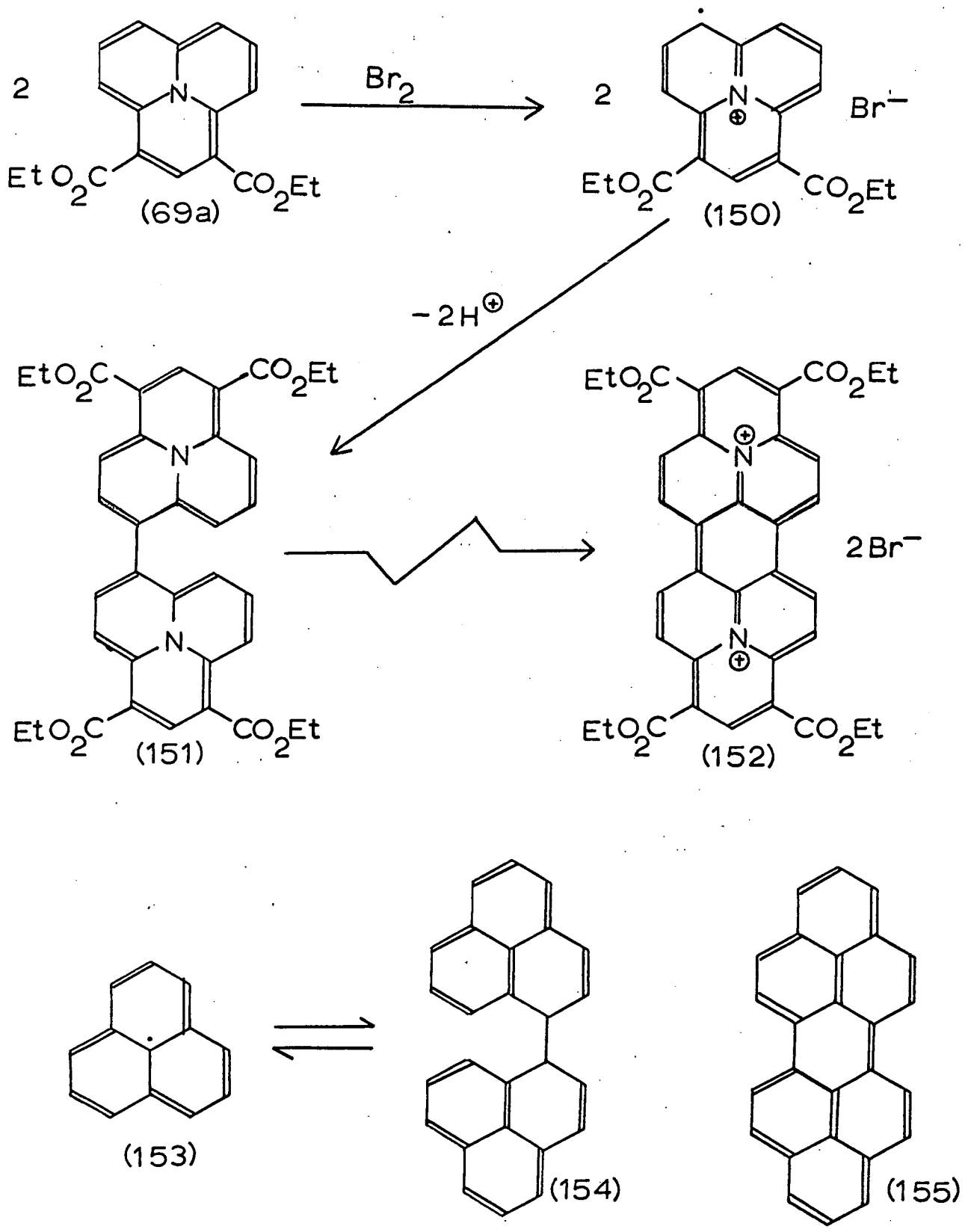
FIG. 31

Cationic species derived from Diethyl
cycl[3,3,3]azine-1,3-dicarboxylate and from cycl[3,3,3]azine

When solutions of the diethoxycarbonylcyclazine (in benzene) were treated with bromine, a blue precipitate was formed immediately. Subsequent heating caused a colour change from blue to a bright red, the yield of the red precipitate being increased (to 68%) by addition of ethanol before heating. The n.m.r. spectrum of the red product in dimethylsulphoxide showed a simple splitting pattern and the signals were shifted about 3-4 p.p.m. downfield from those of the diethoxycarbonylcyclazine. Thus there was seen a quartet arising from the methylene protons of the ester groups (the methyl protons were obscured by the solvent), a singlet (0.31T), and two doublets (-0.31T and 0.38T) in the ratio 4:1:2:2, which is consistent with structure (152).

The proposed ring-system is isoelectronic with the polycyclic aromatic hydrocarbon, peropyrene, and this accounts satisfactorily for the large downfield shift. Further evidence was obtained from the mass spectrum (of the fluoroborate) which indicated a molecular weight* of 618. Such a product could be formed by the route outlined in Fig. 31. Thus oxidation of the cyclazine by bromine to the radical cation (150) followed by dimerisation and loss of two protons would yield (151). Dimerisation through the 4-position would be possible but less likely for steric reasons. Repetition of the process followed by a further two electron oxidation would give the diazoniaperopyrene dibromide (152). A minor product of the above reaction (11%) was obtained

* The peak at m/e 618 is evidently formed by electron-attachment rather than the more usually observed process of electron-expulsion.

from the remaining benzene solution by chromatography. This proved to be the bicyclazinyl (151) which lent support to the above interpretation. This dimer (151) was also prepared by treating a solution of the cyclazine, in dichloromethane, with a slight excess of N-bromosuccinimide (1.2 equiv.) at low temperature and allowing the solution to warm to room temperature. The deep-blue colour of the solution and precipitate formed initially was believed (and later confirmed) to be due to the radical cation. The colour gradually changed to orange-brown on warming and the dimer was obtained, by chromatography, as purple plates (58%). The identity of the product was apparent from its n.m.r. spectrum. Thus a singlet at 2.89T, a doublet at 4.77T, a triplet at 3.77T and a doublet at 3.22T were assigned to the 2,2´-, 7,7´-, 8,8´- and 9,9´-protons, respectively, and two doublets at 3.40T and 4.20T to the 4,4´- and 5,5´-protons. The mass spectrum indicated the expected value of 620 for the molecular weight. A solution of the dimer in benzene, on treatment with bromine, yielded a fine blue precipitate, which was indistinguishable in colour from that obtained from the diethoxycarbonylcyclazine. The diazoniaperopyrene was obtained from it in exactly the same way as before.

The hexachloroantimonate was obtained by treatment of the cyclazine with antimony pentachloride; the method and colour changes being the same as in the preparation of the dibromide.

A series of reactions very similar to those discussed above have been observed with the phenalenyl radical (153)[172]. The radical, which is green in colour and forms blue-green solutions, is in equilibrium with the dimer (154). Solutions of the phenalenyl radical when boiled give peropyrene (155). However it appears that the phenalenyl radical is more readily oxidised to peropyrene (oxygen being sufficient) than the corresponding

reaction with the cyclazine (151 to 152)   when bromine is required.
(Heating (151)   in benzene/ethanol alone without exclusion of oxygen causes
no change). Such a difference is probably due to the presence of the
ethoxycarbonyl groups in the cyclazine rather than to the differences in ring
structure.

Preparation of cycl[3,3,3]azine dication

The ease of the formation of the radical cation of the diethoxycarbonyl-
cyclazine by treatment with bromine, antimony pentachloride etc., is in
agreement with the prediction by Dewar and Trinajstic[102]. Their calculations
indicated that, for the form of cycl[3,3,3]azine (148) containing alternate
single and double bonds, the first ionisation potential would be ca. 7.49 e.v.
This is low compared with typical values for aromatic compounds (8.3 e.v.) and
therefore indicates that the radical cation should be readily formed. If a
second electron could be removed, then the system formed, the cycl[3,3,3]azine dication
(157)   could be regarded as a 10π electron system and would therefore be
expected to show aromatic properties, at least in as much as it should be more
stable than the cycl[3,3,3]azine, and the protons would be expected to resonate
at low field in the n.m.r. spectrum

(156)   (157)
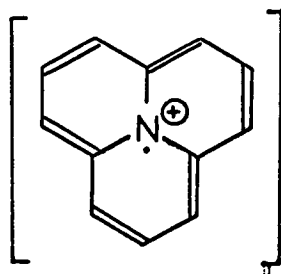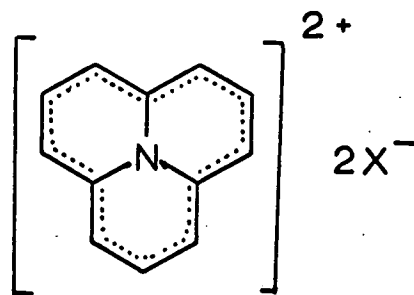
Furthermore phenalene can give rise to a relatively stable anion (66), radical (67)[127] and cation (68)[129,130] which are isoelectronic with the cyclazine parent, radical cation and dication
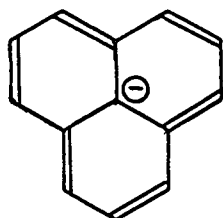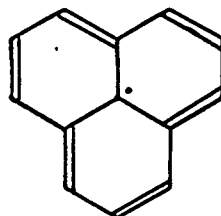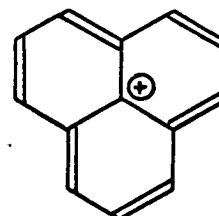
(66)   (67)   (68)

Unfortunately no calculations of the second ionisation potential have been reported, but the fact that a stable system would probably be formed would suggest that it may not be too high. It thus seemed possible that by using a sufficiently strong oxidising agent, the cycl[3,3,3]azine dication might be formed if the intervening radical cation did not dimerise first.

When bromine vapour was passed over a solution of the cyclazine in oxygen-free benzene, a stable blue precipitate was rapidly formed. This was shown to be cycl[3,3,3]azine cation bromide by analysis. Attempts to convert it into diazoniaperopyrene dibromide by heating in benzene with ethanol were unsuccessful, the radical cation being recovered unchanged. When the flow of bromine was continued, the blue precipitate gradually gave way to a light brown oil. Removal of the supernatant liquid, and drying in a vacuum desiccator over sulphuric acid overnight, left a yellow-green solid which reacted rapidly with moisture. This was suspected to be the cycl[3,3,3]azine dication dibromide but some difficulty was experienced in finding a suitable solvent for an n.m.r. spectrum. When run in dry hexadeutero dimethylsulphoxide,

the spectrum showed the following features:- (a) a six-proton multiplet in the region 1.28 - 1.84T, (b) a one-proton doublet at 2.73T(J=9.8 c/s), (c) a one-proton doublet at 4.04T(J=4.8 c/s) and (d) a one proton quartet centred at 3.25T(J=9.8 c/s, 4.8 c/s). Such a spectrum would be consistent with a structure of the type (158)   the signals being assignable as shown:-
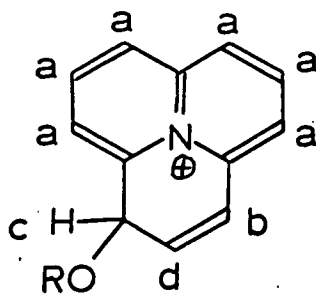
(158)

The chances of isolating such a compound seemed remote, but the observation suggested that the original material probably was the dication. A suitable solvent for the material was eventually found in deutero sulphuric acid* and this yielded a very simple spectrum showing only a doublet at -0.47T(J=8.0 c/s) and a triplet of half the intensity at 0.27T(J=8.0 c/s). The splitting pattern and very low field chemical shifts left no doubt that the cycl[3,3,3]azine dication dibromide had been obtained. Since the n.m.r. spectrum of cycl[3,3,3]azine shows a triplet at 6.37T and a doublet at 7.95T

* Difficulties were experienced in deciding on a suitable standard from which to measure the chemical shifts. 3-(trimethylsilyl)-propanesulphonic acid sodium salt (DSS) decomposed rapidly in sulphuric acid and tetramethylsilane was immiscible. Tetramethylammoniumtetrafluoroborate was used, but the value of its chemical shift (6.84T) was measured from DSS and therefore had to be done in water. Any solvent shift for the tetramethylammonium salt in changing from water to deutero sulphuric acid is not therefore accounted for.

conversion to the dication has resulted in a downfield shift of about 7T. Part
of this shift is doubtless due to the positively charged nature of the dication,
but a large part of the shift (probably the major part) must be due to a
change from a (weak) paramagnetic ring current to a diamagnetic one. It is also
interesting that the relative positions of the doublet and triplet are
reversed with respect to their positions in the parent cyclazine. This is
presumably due to contributions to the resonance hybrids from such resonance
structures as (A) for the parent cyclazine and (B) for the dication
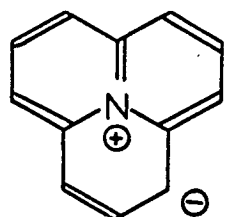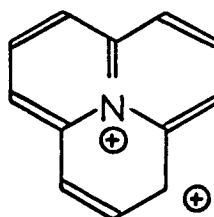
(A)   (B)

Structure (A) would result in an upfield shift for the protons α to
the ring junction, while (B) would result in a downfield shift for the same
protons. Structures similar to (A) have already been proposed to account for
the upfield shift of the 3-proton in ethyl cycl[3,3,3]azine-1-carboxylate
(98c) [139].

These shifts might also be explained in terms of the double occupancy of
the non-bonding molecular orbital in the parent and its vacancy in the dication.
This orbital has electron density only at the α-positions:-
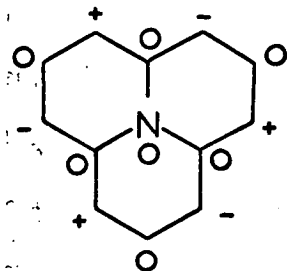
(+) and (-) represent phases of the MO
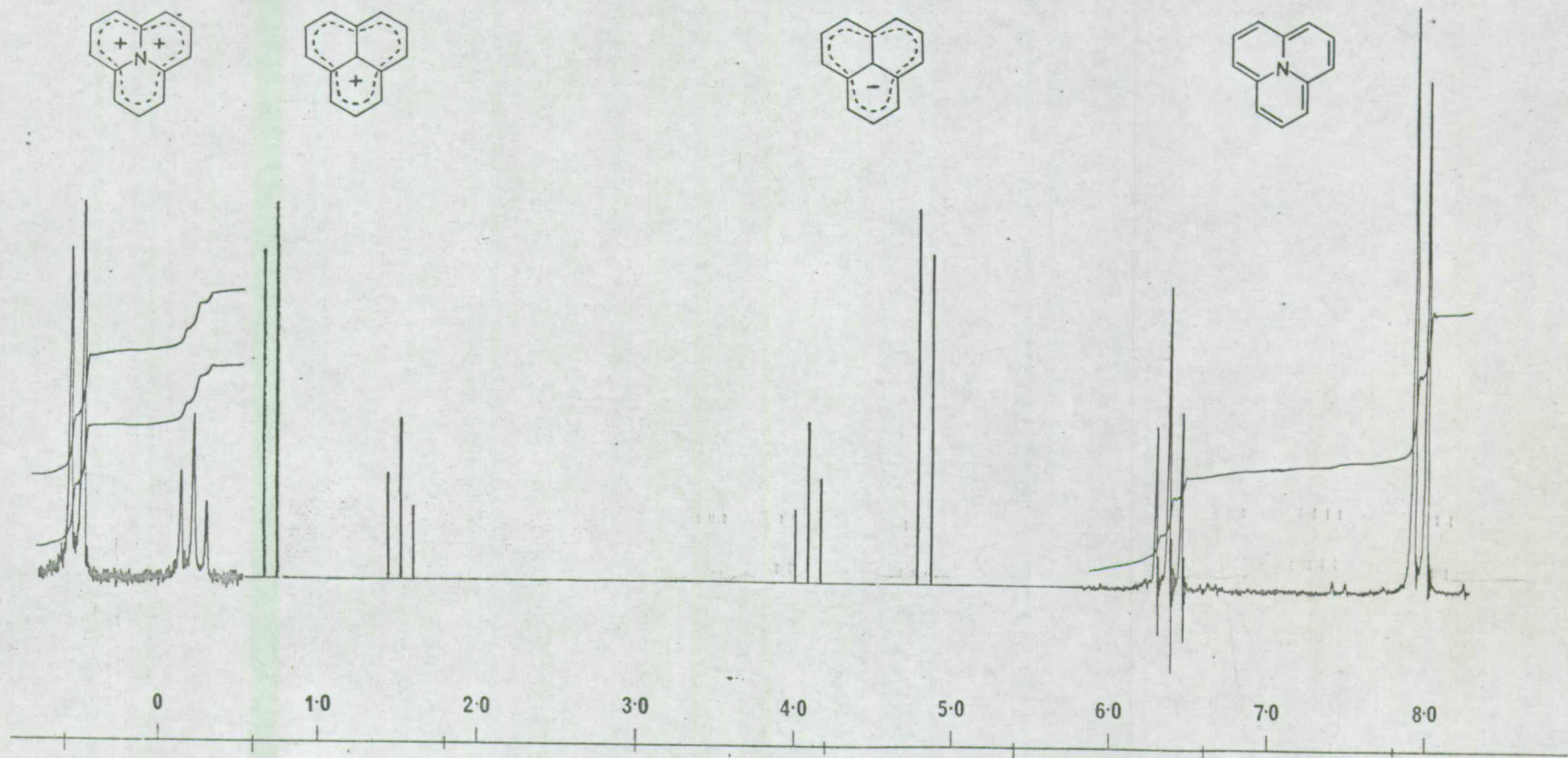
FIG 32

These results for cycl[3,3,3]azine and its dication may be compared with those for the phenalenyl anion[173] and cation[174] (Fig. 32). when striking similarities may be seen. Of particular interest is the fact that the relative positions of the doublet and triplet are interchanged on going from the anion to the cation in the same way as for the cyclazine and its dication. The difference in the chemical shifts of the phenalenyl cation and the cyclazine dication can probably be accounted for by the additional charge of the latter. The reason for the chemical shift of the phenalenyl anion being downfield from that of the cyclazine is less obvious, but is presumably due, at least in part, to contributions to the resonance hybrid from the resonance structure:- (175)
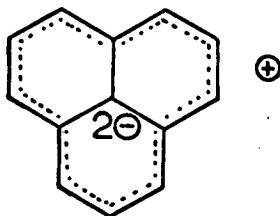
(175)

The cyclazine dication was also prepared by using chlorine gas or antimony pentachloride as oxidising agent. Both of these readily formed the dication, chlorine giving the cleaner product. By using superdry purified benzene as solvent for the cyclazine, an elemental analysis of the cycl[3,3,3]azine dichloride was obtained. Though slightly outside the normally accepted limits, this is regarded as reasonable in view of the preparative difficulties.

Although attempts to prepare substitution products from cycl[3,3,3]azine

had failed, as described previously, it seemed possible that such products might
be obtained from the dication by the route shown below

$$X = CN^-, NO_2^-$$
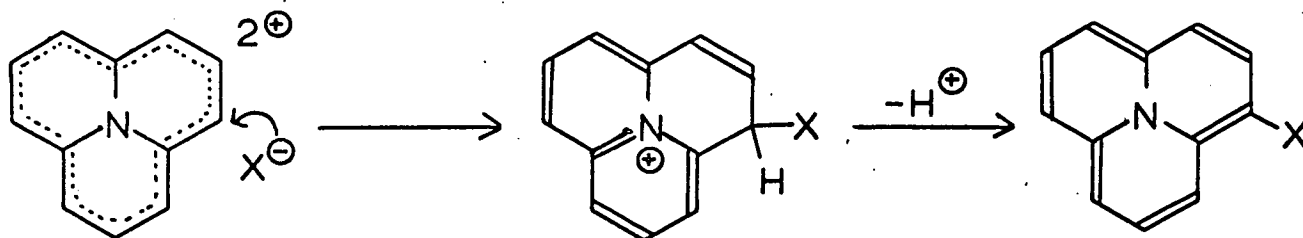
By using sodium nitrite or cyanide, a product with a strongly electron-withdrawing
substituent would be obtained, and might, therefore, be sufficiently stable to be
isolated. Such reactions were attempted in dimethylsulphoxide, dimethylformamide
and acetonitrile, but in each case gradual darkening of the solution occurred
and no product was isolated except from the reaction with sodium nitrite in
acetonitrile, when a gradual change to a bright blue solution occurred during
5 mins. The solvent was evaporated, benzene/ethanol was added, and, after
standing overnight, an orange brown precipitate (ca. 20 mg.) was formed, the
u.v. spectrum of which was very similar to that of peropyrene. It seemed possible
that this might be the diazoniaperopyrene dication. However an attempt to obtain
its n.m.r. spectrum in hexadeutero dimethylsulphoxide yielded no signals. It
seems probable that the blue solution formed contained the radical cation, but
it is strange that it showed signs of having dimerised when the cyclazine bromide
under similar conditions remained unchanged. However identification of the
product is very tentative and no conclusions can be drawn.
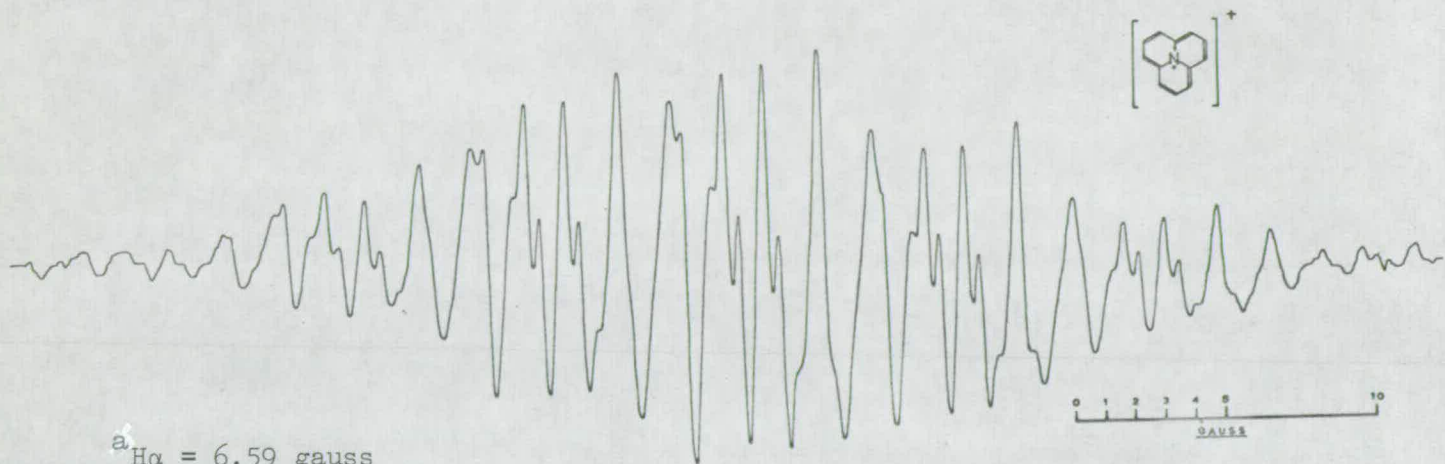
$a_{H\alpha}$ = 6.59 gauss

$a_{H\beta}$ = 1.79 gauss

a_{N} = 1.32 gauss

g = 2.0022 ± 0.0004

SIMULATION
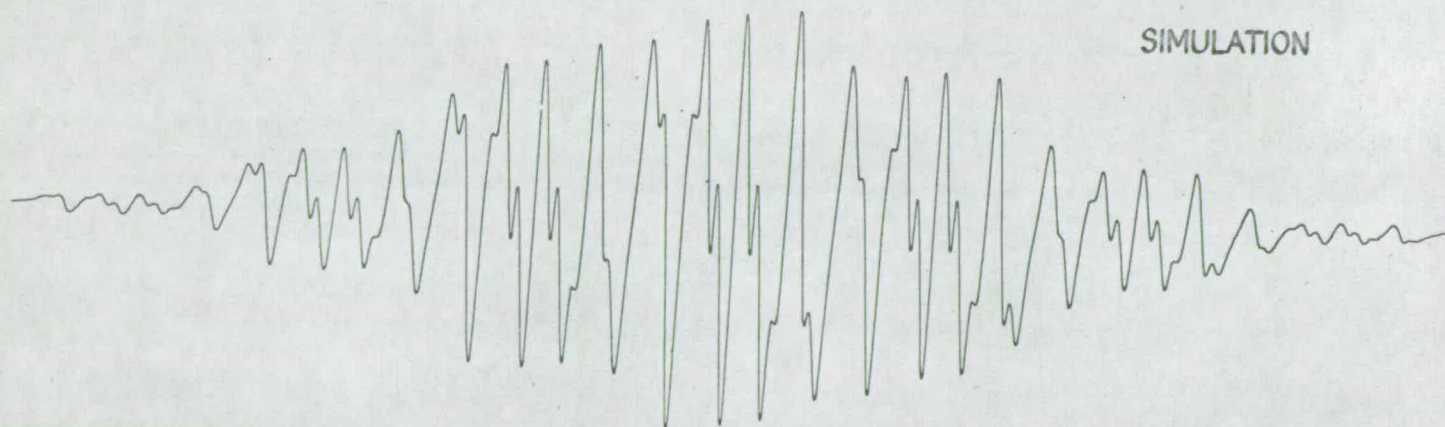
Linewidth = 0.40 gauss

FIG 33

Because of the stability of the radical cation it seemed that it should be possible to obtain an e.s.r. spectrum of it if a suitable solvent could be found.

The bromide was insoluble in benzene, acetonitrile and dichloromethane. Formation of the radical cation by reaction of the parent cyclazine with silver perchlorate seemed promising. Thus silver metal would be precipitated and could be filtered off to leave a solution of the radical perchlorate. When the perchlorate was formed in benzene, it immediately precipitated out, but solutions in acetonitrile were obtained, the e.s.r. spectra of which were not affected by the presence of silver metal. However the resolution was not sufficiently good for an interpretation of the spectrum to be made. It was considered possible that this was due to the polarity of the solvent despite the fact that a fine capillary tube (i.d. ca. 1 mm.) was used. Attempts to prepare the radical cation in less polar solvents (benzene or dichloromethane) by the action of lead tetra-acetate, silver perchlorate or silver p-toluene sulphonate proved unsuccessful. It was eventually found that the poor resolution was primarily due to the use of solutions in which the concentration of the dication was too high. The spectrum is shown in Fig. 33 and an interpretation is given.*

With only a small excess of silver perchlorate the signal due to the radical cation decreased considerably in intensity in a period of 6 hrs. However, it was found that by using a six to ten-fold excess of silver perchlorate, the signal strength remained essentially unchanged for 4-5 days. No explanation for this effect can be offered.

The sample when first prepared was bright blue in colour, but within a few hours it changed to a fluorescent yellow-brown with formation of a

* The values for the hyperfine splittings should be compared with those for the phenalenyl radical (67)[201] (H_α=6.30, H_β=1.82 gauss).

light-brown precipitate. As mentioned above this change did not affect the signal strength, nor did it cause any change in the spectrum itself. The u.v. spectrum of samples which were 4-5 days old still showed a characteristic absorption due to the radical cation in the region 325-350nm. together with two weak bands at 408 and 436 nm. These latter absorptions were not due to the radical cation, but their positions and relative intensities were very similar to those of bands in the spectrum of peropyrene[173] and in the spectrum of the product that might have been the diazoniaperopyrene dication obtained earlier. However, none of the pure product could be isolated and no firm conclusion can be reached.

Attempts to prepare the dianions of cycl[3,3,3]azine and 1,3-dicyanocycl[3,3,3]azine

After the dication of cycl[3,3,3]azine had been prepared, attempts were made to prepare the dianion. Such a species could be considered to possess 14 peripheral π-electrons and would therefore be expected to show aromatic properties.

A common method for the preparation of dianions and radical anions from cyclic conjugated systems is by treatment of a solution of the compound in tetrahydrofuran with metallic sodium or potassium[49,89]. However, on addition of a small amount of sodium/potassium alloy to a dry, oxygen-free solution of cycl[3,3,3]azine in tetrahydrofuran, no change in colour was observed other than a gradual darkening during 1 hr. The radical anion, if it were formed, would almost certainly be strongly coloured, and the dianion probably less so. The absence of any pronounced colour strongly suggested that
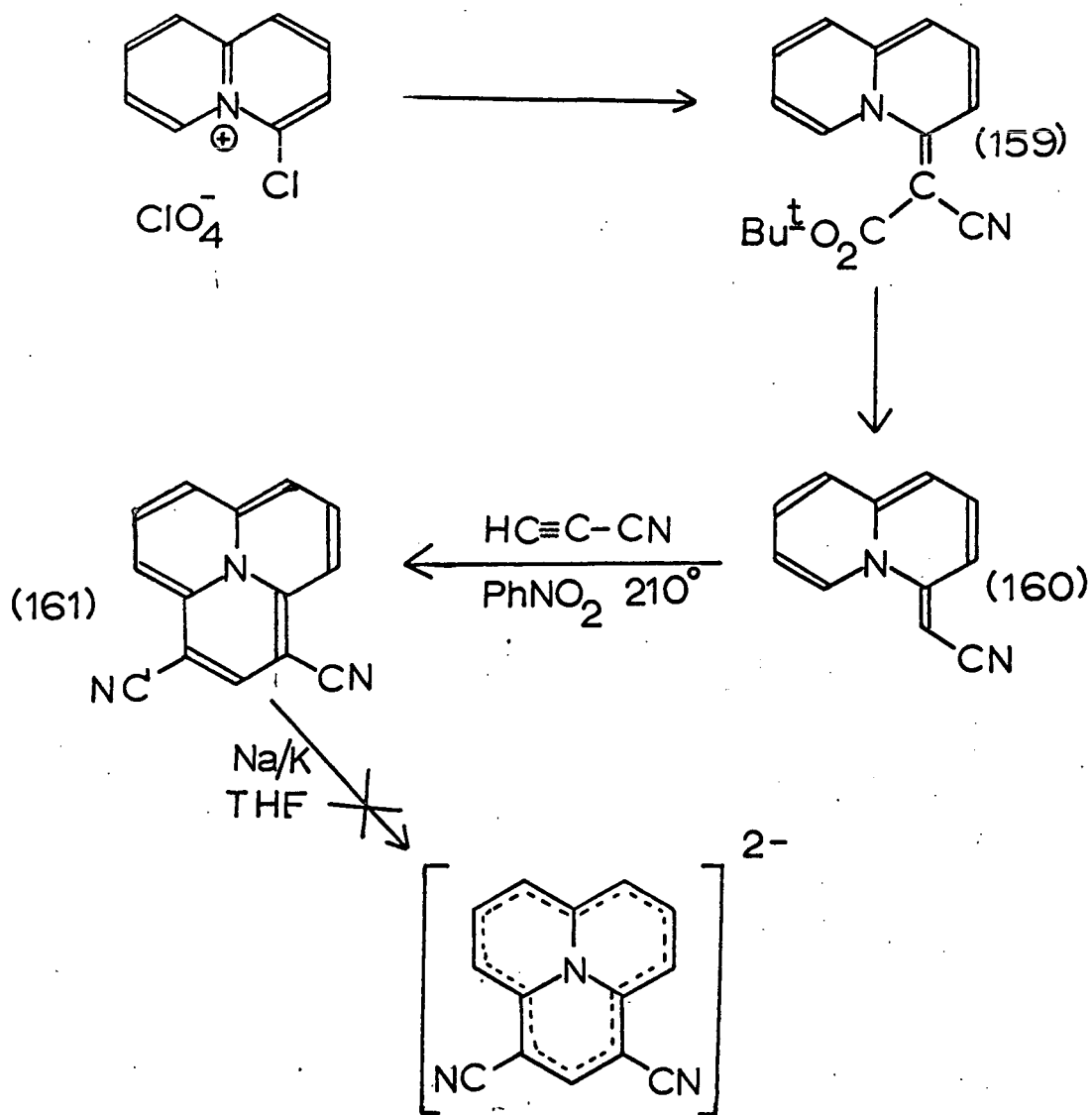
FIG. 34

the desired transformation had not taken place.

The reason for this apparent failure may be due to the fact that the electrons would have to go into what are, in the neutral molecule, anti-bonding orbitals. However, the dianions of (32) and (28) (Figs.5&6) have both been prepared [89,95], and in both of these (particularly in the latter case), a similar situation exists. It therefore seems more likely that the electron richness of the cycl[3,3,3]azine prevents further addition of electrons, although the instability of the molecule may also be a factor. In view of both of these possibilities it seemed that there would be a greater chance of success if the cyclazine contained strongly electron-withdrawing substituents. The diethoxycarbonyl derivative might not be suitable for this purpose as the ester groups would be likely to accept electrons from potassium metal. It was therefore decided to prepare the 1,3-dicyano derivative. This was done by the route outlined in Fig. 34 using a method analogous to that for the preparation of the diethyl cycl[3,3,3]azine-1,3-dicar-boxylate [139]. The 1,3-dicyanocyclazine was obtained as fine purple needles. On account of its high polarity, it had a high m.pt. ($270-273^{\circ}$) and was rather insoluble, the n.m.r. spectrum required to be run in hexadeuterodimethyl-sulphoxide at 100°. This showed the expected features as did the two precursors. The interpretation, chemical shifts, and coupling constants are detailed in the n.m.r. spectral data section.

Unfortunately the dianion of the 1,3-dicyanocyclazine was not obtained. Addition of sodium/potassium alloy to a warm dilute solution of the cyclazine in dry tetrahydrofuran resulted only in a slow darkening of the solution over a period of days. No evidence for formation of the anion or dianion was obtained.
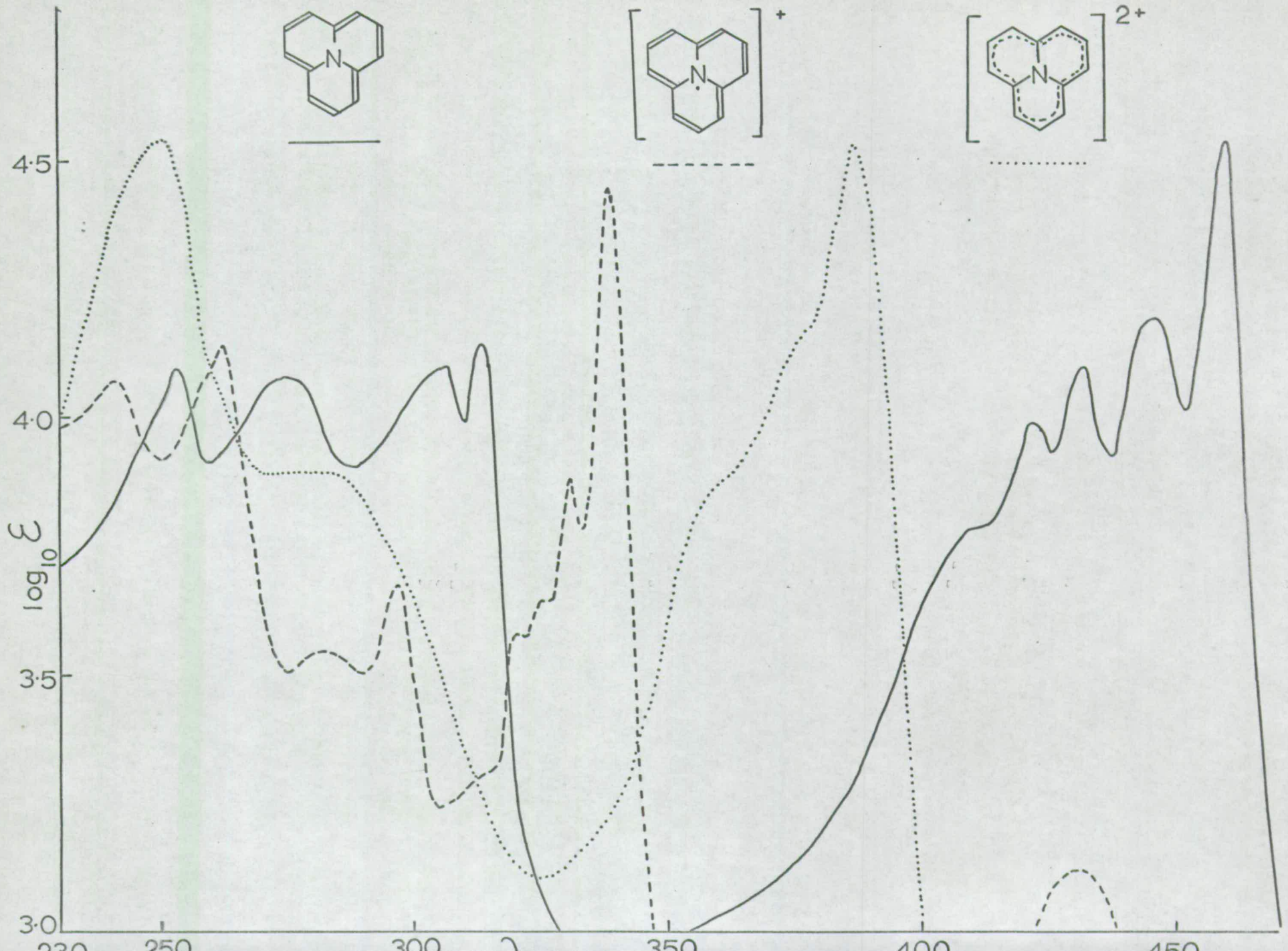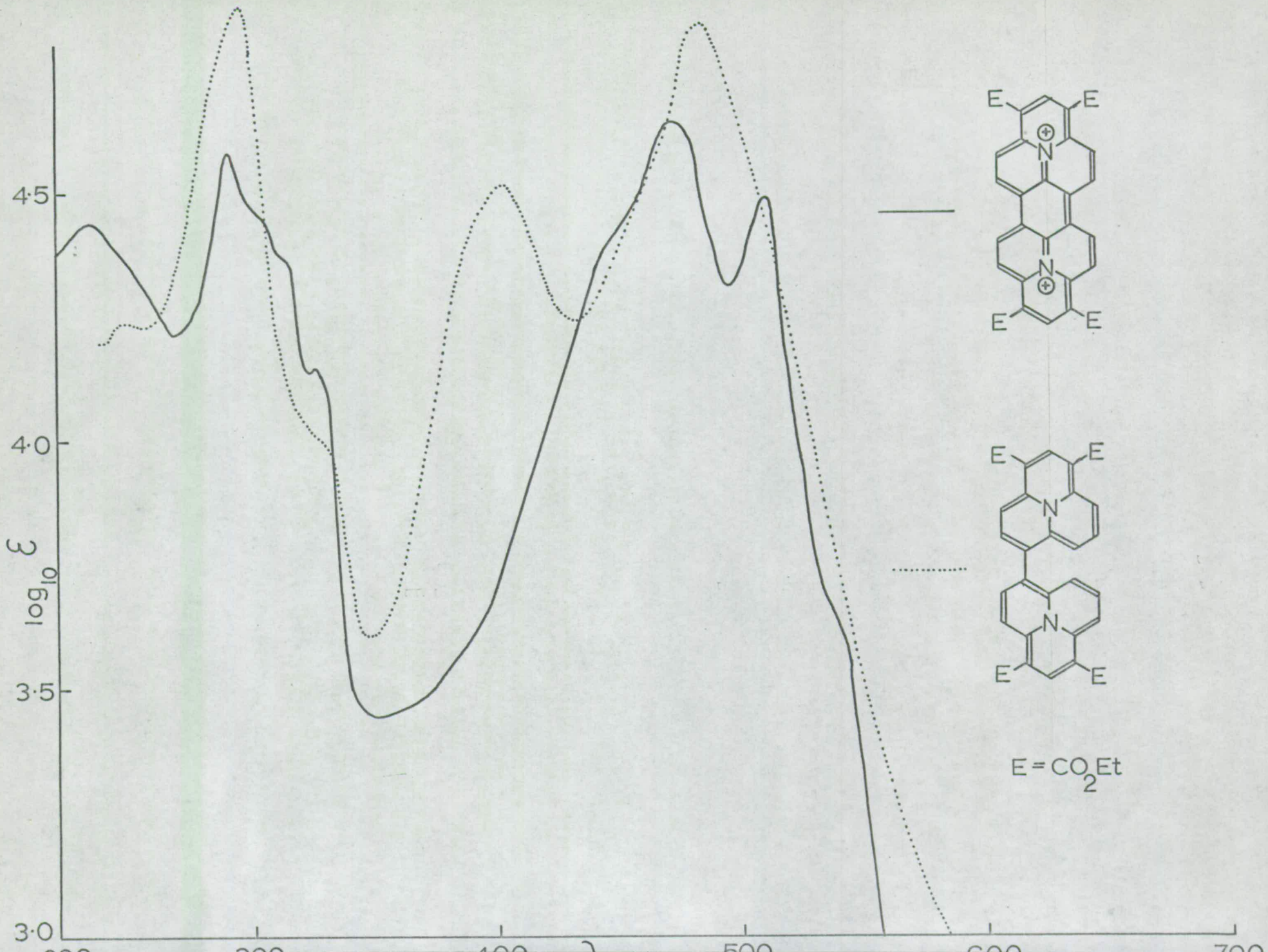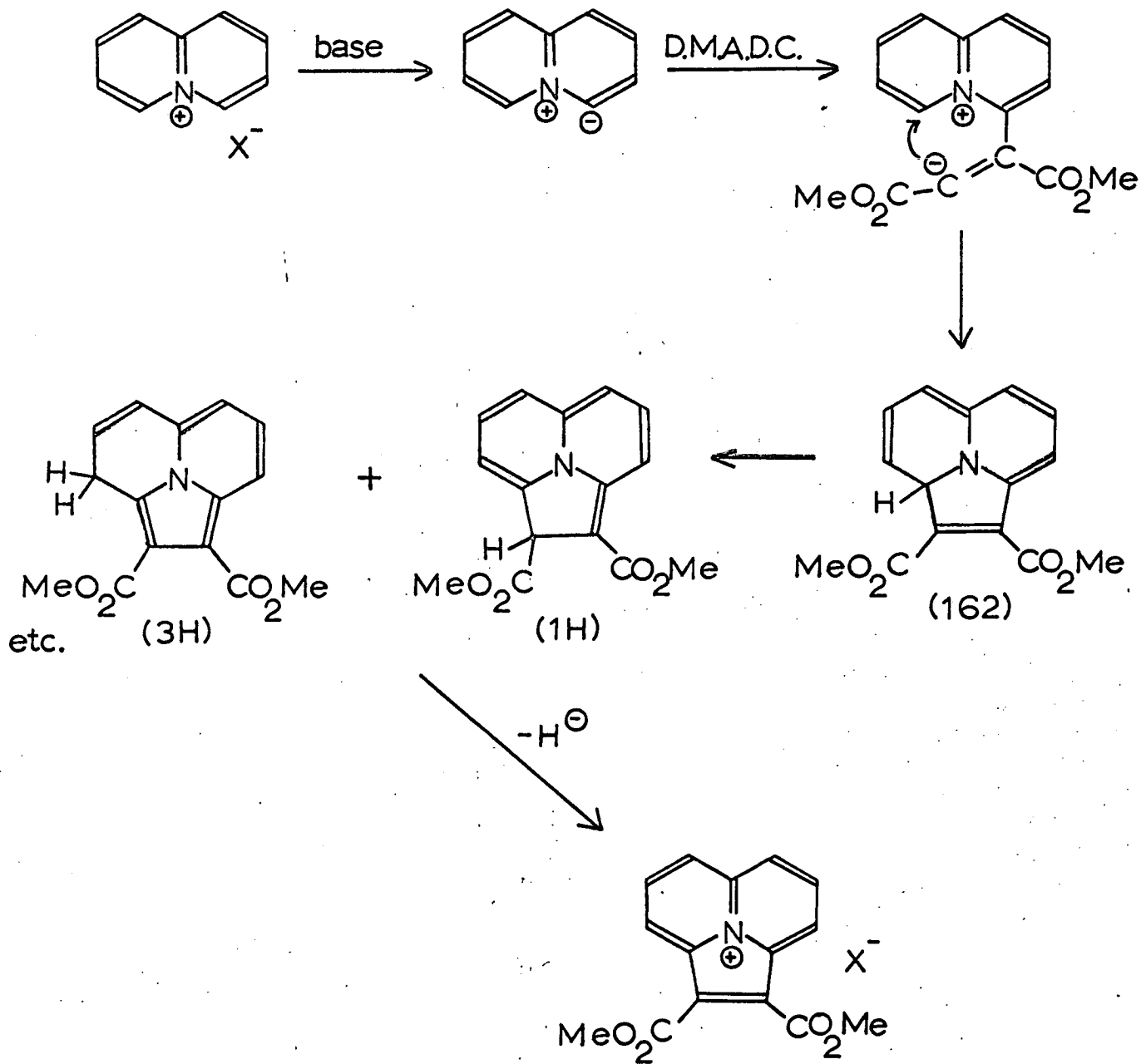
FIG. 35

PREPARATION AND REACTIONS OF CYCL[3,3,2]AZINIUM PERCHLORATE

Farquhar [139] found that refluxing diethyl quinolizine-4-ylidenemalonate in nitrobenzene led to the formation of 2-ethoxycarbonylcycl[3,3,2]azin-1-one which could be hydrolysed to cycl[3,3,2]azin-1-one by refluxing in 6N hydrochloric acid (Fig. 15)   Jessep [116] converted the cycl[3,3,2]azin-1-one into 1-ethoxycycl[3,3,2]azinium perchlorate by reaction with triethyloxonium fluoroborate, but, despite attempts by a variety of methods, was unable to remove the ethoxy group. Because of this difficulty it seemed that an alternative route to the parent system would be required. It seemed possible that quinolizinium salts might react with dimethylacetylenedicarboxylate in the presence of strong base to form a 1,2-dimethoxycarbonyl-2aH-cycl[3,3,2]azine

Such a compound might be expected to tautomerise to a more stable 1H-, 3H- or 5H-cyclazine, from which a cyclazinium salt would be obtainable by hydride abstraction. The α-protons of N-alkylpyridinium salts are known to be somewhat acidic[176] but, before attempting reactions based on the foregoing scheme, it seemed wise to check that the 4- and 6-protons of the quinolizinium ion are similarly activated.

Exchange of the 4- and 6-protons for deuterium was achieved by heating the quinolizinium salt in a dilute alkaline solution of deuterium oxide. Thus the n.m.r. spectrum of the quinolizinium perchlorate in water consisted of a two proton doublet at 0.96T and a six-proton multiplet in the region 1.60-2.05T. After the reaction in deuterium oxide the doublet was entirely absent while the multiplet was little changed, having become slightly less complex, as would be expected with the reduced splitting from the 4- and 6-positions. Despite this favourable result, the attempted reaction of the quinolizinium

(a)

(b)

$(81) \xrightarrow{PSCl_3}$ (X) $\underset{?}{\rightleftharpoons}$ (Y) $\xrightarrow[\text{or } Na_2S]{NaOH}$ (163)
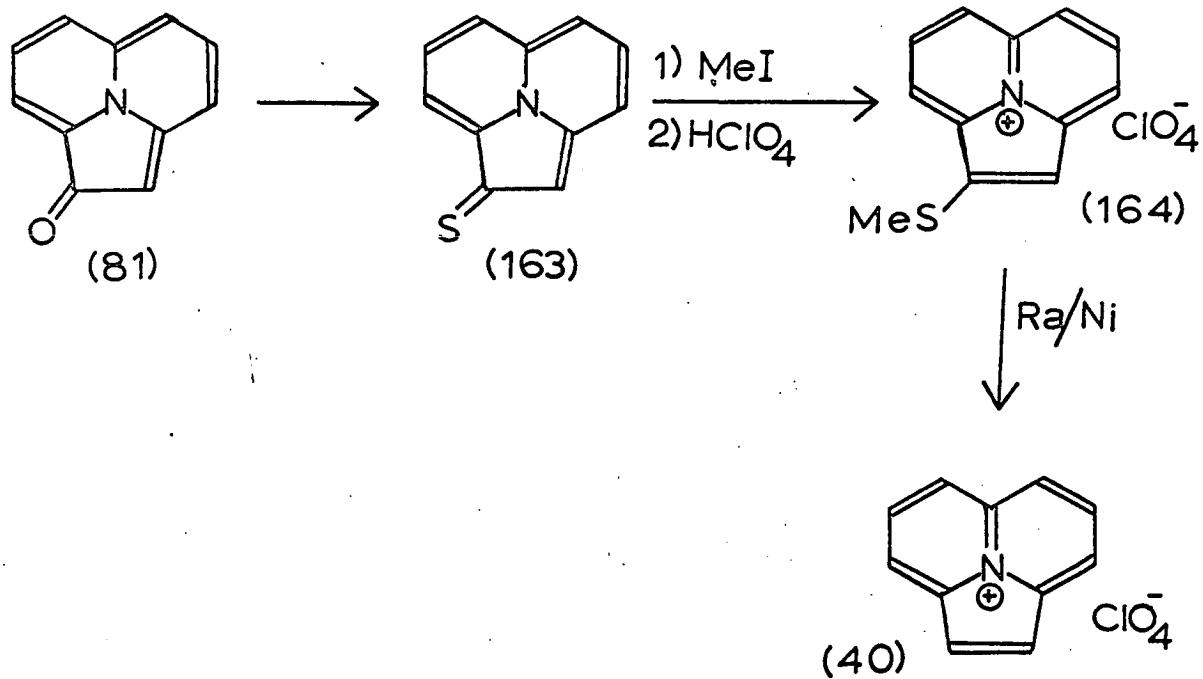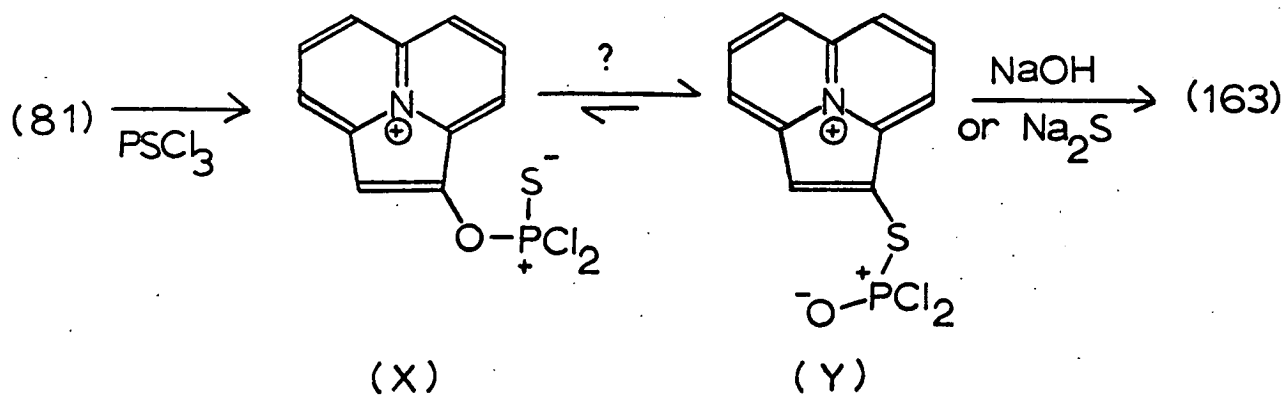
FIG. 36

salt with dimethylacetylenedicarboxylate in dry dimethylformamide, using
sodium hydride as base, yielded an unpromising dark product. Thin-layer
chromatography showed several red-brown bands, none of which was isolated,
and a considerable quantity of immobile decomposition product.

When the above attempt to prepare the cycl[3,3,2]azinium cation failed,
attention was directed again to the approach from cycl[3,3,2]azin-1-one or
its 2-ethoxycarbonyl derivative. It seemed probable that if cycl[3,3,2]azin-
1-one could be converted to the thione (163), then treatment with methyl
iodide, conversion to perchlorate (164) and hydrogenolysis with Raney-
Nickel should yield the parent system (Fig. 36a).

Treatment of the cyclazinone (81) with phosphorus pentasulphide in
refluxing benzene resulted in a change in colour from red to red-purple.
Chromatography of this solution yielded a very light-sensitive blue band and
a red band. Treatment of the eluted blue solution with an excess of methyl
iodide and concentration yielded a light-brown solid which proved to be the
required 1-methylthiocycl[3,3,2]azinium iodide. Thus the mass spectrum
indicated a molecular weight of 200, and the n.m.r. spectrum showed a six-
proton multiplet in the region 0.98-1.40T (H-3,4,5,6,7,8), a one-proton
singlet at 2.10T (H-2) and a three-proton singlet at 7.10T (MeS). The i.r.
spectrum was identical with that of an authentic sample prepared later by a
different route. The second, red band from the column was shown to be
recovered cyclazinone (24%).

Although the required product could be obtained by this route, the yield
was very low (5% based on ^{un}recovered cyclazine). The extreme instability of the
thione to light was not unexpected, and it seems that this (despite careful
shielding of the product from light at all stages) together with possible
thermal instability accounts for the very poor yield. Variation of solvent

and reaction time did not improve the yield, and so an alternative method for the preparation of the thione was sought.

By the use of thiocarbamoyl chlorides, Newman and Karnes [177] have converted a number of phenols and hydroxyheterocyclic compounds into the corresponding thiols by thermal rearrangement of the O-aryl-N,N′-dialkylthiocarbamates to the S-aryl compounds followed by hydrolysis:-

$$ArOH \longrightarrow Ar\underset{O}{\overset{S}{C}}-NR_2 \longrightarrow Ar\underset{O}{\overset{S}{C}}-NR_2 \longrightarrow ArSH$$
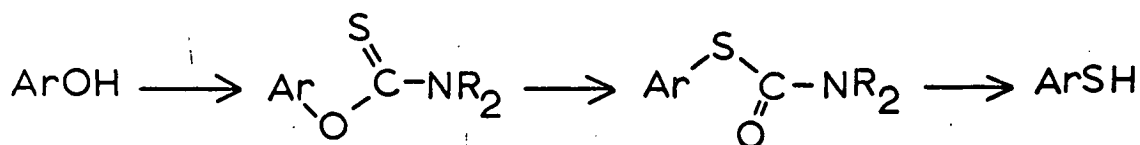
The driving-force for the reaction is the higher bond strength of the carbon-oxygen π-bond relative to the corresponding carbon-sulphur bond. Since the resonance structure (165). [116] (ν C=O = 1610 cm^{-1}) makes a considerable contribution to the resonance hybrid, it seemed possible that the cyclazinone might be converted into the thione by a similar route.

(165)
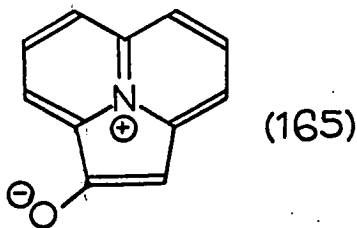
The reaction was attempted in dimethylformamide and in chloroform, and in each case gave a deep blue-purple colour. Chromatography gave a number of weak blue-purple bands which were eluted much less rapidly than the authentic thione. It seemed clear that the thione had not been formed.

Although the above reaction failed, it seemed that thiophosphoryl chloride might prove a suitable alternative to thiocarbamoyl chloride; the very high bond-energy of the phosphoryl group ($\rightarrow$P=O $\leftrightarrow$ $\rightarrow$P$^+$-O$^-$) would provide a strong driving-force for the rearrangement (X) $\rightarrow$ (Y) (Fig. 36b). Dropwise addition of thiophosphoryl chloride to a solution of the cyclazinone in dry dichloromethane caused a rapid disappearance of the red colour and formation of a highly insoluble yellow precipitate. Removal of the solvent left a yellow solid which was only partially soluble in dimethylformamide, treatment with sodium sulphide* resulted in the formation of a strong blue-colour in the solution while a considerable amount of the yellow solid remained in suspension. Filtration and treatment of the blue filtrate with an excess of methyl iodide resulted in a light-brown precipitate which was converted to the perchlorate. This was shown to be the expected 1-methylthiocycl[3,3,2]-azinium perchlorate by its n.m.r. spectrum and by comparison of its i.r. spectrum with that of an authentic specimen prepared later. However the yield was again very low (4.5%). Some attempts were made to identify the insoluble yellow solid, which presumably contained the bulk of the cyclazinone, but these were of limited success. Thus a mass spectrum indicated a molecular weight of 169 which is the value for the cyclazinone, and must, therefore, be attributed to thermal breakdown in the instrument. It was insoluble in all solvents tried and hence no n.m.r. or u.v. spectrum could be obtained, and the i.r. spectrum was of little assistance in identification.

With the failure to achieve a reasonable synthesis of the thione from the cyclazinone, attention was directed towards synthesis of the thione

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* Sodium sulphide was used for hydrolysis in preference to sodium hydroxide because of the possibility that hydrolysis might proceed by attack at carbon rather than at phosphorus, in which case either of the compounds would yield the thione.

from the 2-ethoxycarbonyl derivative which would probably be more stable
towards light and heat than the unsubstituted thione. It was anticipated that
the route to the cyclazinium salt would then follow the scheme outlined
below:-
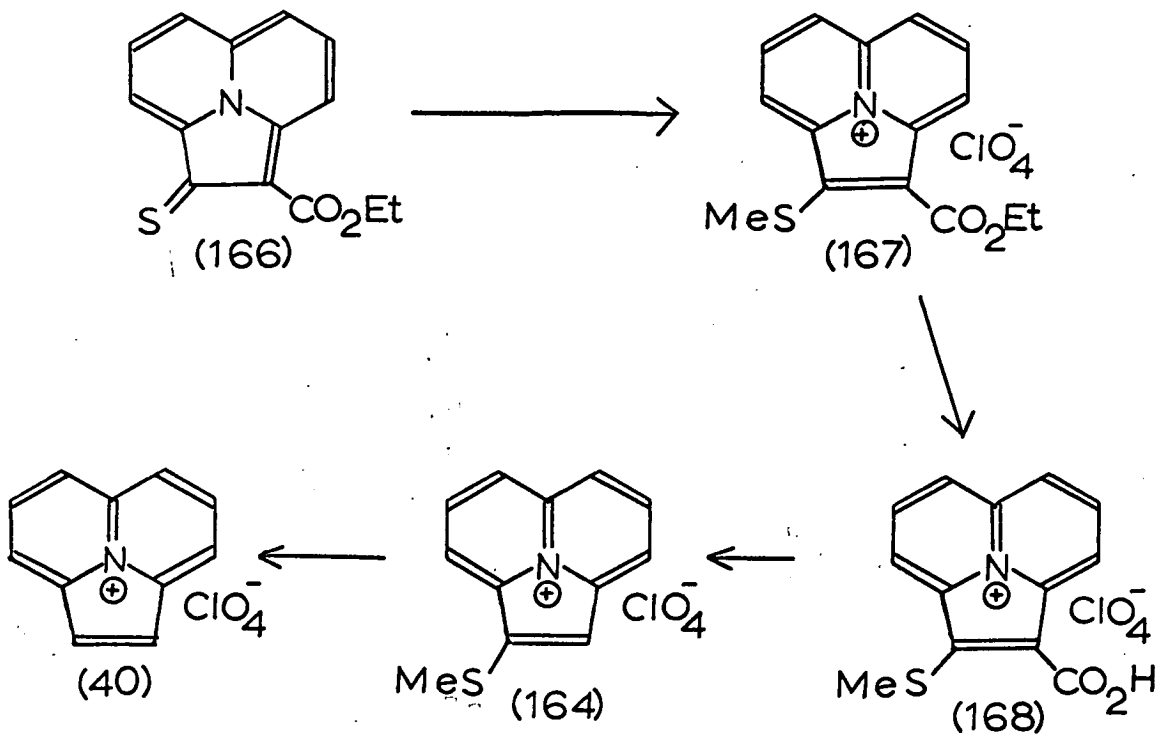
Reaction of the cyclazinone (80) with thiophosphoryl chloride and
treatment of the product with anhydrous sodium sulphide in dimethylformamide
yielded an impure solution of the thione. Treatment with methyl iodide and
conversion to the perchlorate yielded 1-methylthio-2-ethoxycarbonylcycl[3,3,2]-
azinium perchlorate which was identified from its n.m.r. spectrum
This showed a six-proton multiplet in the region 0.60-1.20T(nuclear protons),
a three-proton singlet at 6.86T(MeS) and a triplet and quartet due to the ethoxycarbonyl
group. The yield, although not high (32%) was considerably better than that of
the thione (163) from the unsubstituted cyclazinone (4.5%).

Assuming the initial formation of a dichlorothiophosphoryloxy cyclazinium salt (X), there are at least three possible routes for the ultimate formation of the thione; nucleophilic attack by sulphide ion could occur:-

a)   at carbon in the initial product (X)

b)   at carbon in the rearranged, dichlorophosphorylthio-compound (Y) or

c)   at phosphorus in the rearranged product.
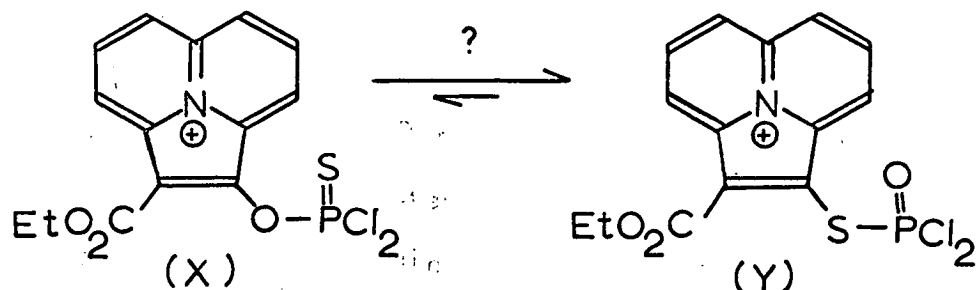
The first of these possibilities does not depend on the use of thiophosphoryl chloride and it was therefore of interest to investigate whether or not the thione could be prepared by the use of phosphoryl chloride. The reaction appeared to take a course similar to that of the previous one, but the product isolated was not the methylthiocyclazinium salt (167). Thus the i.r. spectrum showed considerable differences and the n.m.r. spectrum indicated the absence of a methyl group, but the product could not be identified. This result suggests that the rearrangement postulated initially is indeed an essential step in the synthesis of the thione and that the reaction with sulphide ion occurs via route (b) or route (c).

A very much better yield (82%) of 1-methylthio-2-ethoxycarbonylcycl-[3,3,2]azinium perchlorate was obtained when the thione was prepared by treatment of the cyclazinone (80) with phosphorous pentasulphide. This reaction was carried out in chloroform at 40° and the complex formed was

treated with an aqueous solution of sodium sulphide. Chromatography of the product yielded an intense blue band of the thione (166)   (which was only moderately sensitive to light) and a smaller fluorescent yellow band of recovered ketone. The thione was converted to the 1-methylthio-2-ethoxy-carbonylcyclazinium perchlorate as in the previous preparation.

With the 1-methylthio-2-ethoxycarbonylcycl[3,3,2]azinium perchlorate now readily available it seemed probable that the synthesis of the parent system could be achieved, for it was considered unlikely that the removal of the ethoxycarbonyl and methylthio groups would present any insurmountable difficulties.

Refluxing the cyclazinium perchlorate (167)   in 6N hydrochloric acid effected hydrolysis of the ester group in 78% yield, the product being obtained as fine yellow needles. The mass spectrum indicated a molecule weight of 244, and the n.m.r. spectrum was entirely consistent with the expected product.

Decarboxylations have traditionally been carried out in quinoline but decarboxylation in dimethylacetamide using the copper (I) salt of the acid as catalyst has recently been used with considerable success and simplifies the work-up. A further simplification can be achieved by using freshly prepared cuprous oxide as catalyst instead of the copper salt of the acid[178]. Thus refluxing a solution of the acid in dimethylacetamide with cuprous oxide under oxygen-free conditions resulted in a gradual change in colour from orange-brown to green over a period of only 8 mins. This reaction time is very much shorter than is usually required for decarboxylation and is almost certainly due to the presence of the positive charge in the ring which assists the heterolytic fission of the C-2-carboxyl bond. It was found that higher yields were obtained by using one equivalent of cuprous oxide rather than a catalytic

quantity. Initial formation of a larger amount of cuprous carboxylate

presumably enables the reaction time to be kept short, and thus keeps

decomposition to a minimum.

The 1-methylthiocycl[3,3,2]azinium perchlorate was obtained as yellow-

green needles in 59% yield. When prepared from the unsubstituted cyclazinone

earlier (see above), the product had been yellow and so it seems that this

later product contained a trace of impurity. The amount of impurity must,

however, have been very small since the compound gave good analytical

results and had a reasonably sharp melting point. The i.r. and n.m.r. spectra

were identical with those obtained from the previous specimen.

The final stage in the synthesis of cycl[3,3,2]azinium perchlorate,

hydrogenolysis with Raney-Nickel, proved more difficult than expected. This

was due to difficulty in establishing the correct conditions. The activity of

Raney-Nickel varies according to the method of preparation and is usually

graded on a scale W-1 to W-7 in order of increasing activity [179]. All of

these reagents will effect desulphurisation and also reduction of double bonds

in varying degrees [180]. For purposes of desulphurisation, Raney-Nickel deactivated

by refluxing in acetone before use is more suitable [138]. This treatment

destroys the most active sites in the metal, and decreases its ability to

reduce double bonds. One of the main difficulties with Raney-Nickel when

rather specific conditions are required, is that all the preparations are of

a rather empirical nature, and further that any given sample decreases in

activity with time. Thus a freshly prepared sample even when stored in

a sealed flask in a refrigerator, deteriorates at such a rate that after

about a week its properties are likely to be markedly changed.

Because of these difficulties it took some time to establish suitable
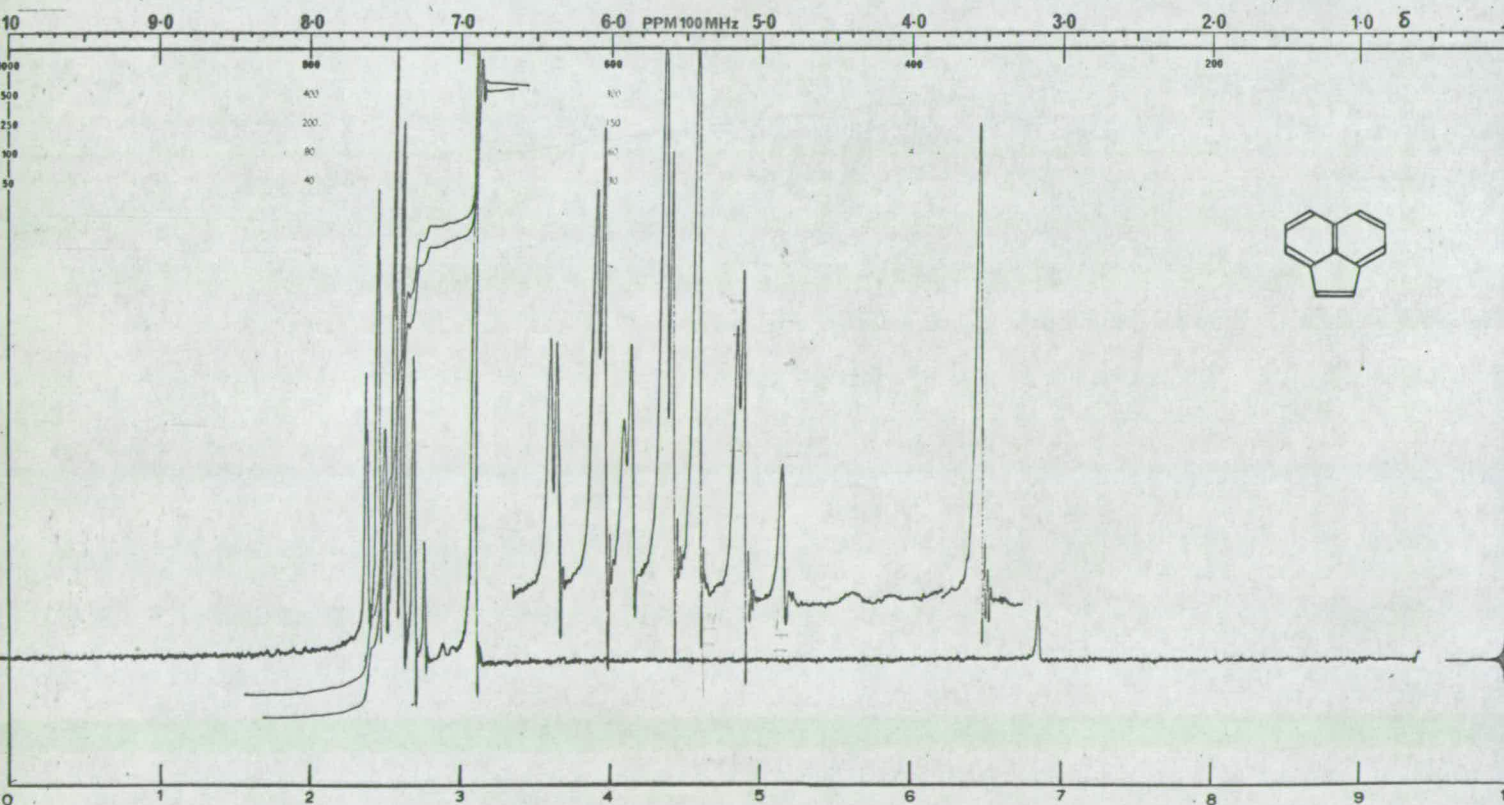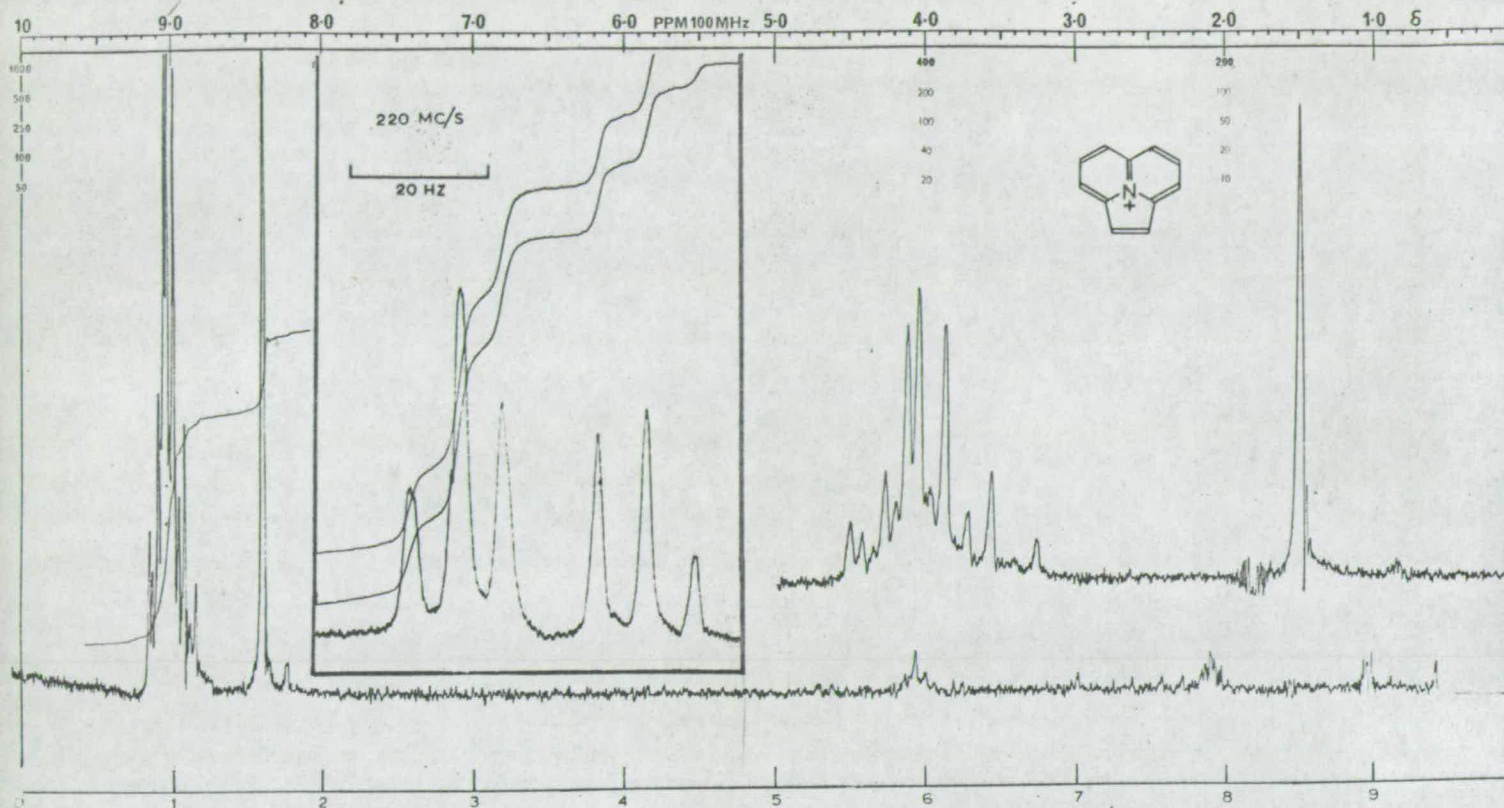
FIG 37

conditions for the required reaction. If the Raney-Nickel was too active, the product, which gave a pale pink colour in ethanol, was probably either a dimer or a partially reduced cyclazinium salt; it was never obtained pure. If the nickel was insufficiently active, removal of the methylthio-group was never complete and separation of product from starting material could not be achieved. The reagent eventually found to be satisfactory was obtained by refluxing approximately W-2 Raney-Nickel (see experimental) in acetone for 1 hr. and carrying out the reaction in ethanol. The product was obtained as a pale grey solid (45-52%).

The n.m.r. spectrum of this material was entirely consistent with that expected for the cycl[3,3,2]azinium perchlorate, containing only a six-proton multiplet in the region 0.86T-1.16T (H-3-8) and a two-proton singlet at 1.61T (H-1,2) (Fig. 37). The downfield shift (of 0.59T) shown by the protons in the five-membered ring is to be expected on loss of the methylthio-group, no trace of which remained. The mass spectrum indicated a molecular weight of 154, but also showed two smaller peaks corresponding to masses of 169 and 141. It seemed possible that these were due to formation of cycl[3,3,2]azin-1-one (by oxidation of the cation by perchlorate ion), the parent ion of which is known[139] to lose carbon monoxide. The salt was therefore converted to the hexafluorophosphate and the mass spectrum re-run. A molecular weight of 154 was indicated with no trace of the peaks at m/e 169 and 141.

The n.m.r. spectrum (100 MHz) of acenaphthylene (Fig. 37) is superficially similar to that of cycl[3,3,2]azinium perchlorate, but the multiplet is just sufficiently widely spread to allow an approximately first order interpretation as two doublets (2.43T and 2.55T) and a triplet (2.70T). A 220 MHz spectrum of the cyclazinium salt was therefore obtained in the hope that the greater separation of chemical shifts would enable a similar pattern to be observed. This was indeed the case (Fig. 37) except

that the two doublets overlapped, thereby preventing the accurate measurement of coupling constants for the 3-, 4- and 5-protons.

However the most important coupling constant (obtained on a 100 MHz spectrometer) is that for the protons in the five-membered ring, since the value for this can give considerable insight into the nature of the 1,2-carbon bond. Thus J_{ortho} in the five-membered rings of non-benzenoid aromatic hydrocarbons is generally 3-4 Hz., but for double-bonds in non-aromatic five-membered rings the value is in the region 5.1-7.0 Hz.[138] The J_{ortho} value thus depends not only on the bond angle[138] (related to ring-size) but also on the bond order, more double bond character giving rise to a larger value for J_{ortho} Thus the 1,2-bond in acenaphthylene, which has been shown to possess considerable double bond character, and to be only weakly involved in the aromatic system, gives a value for $J_{1,2}$ of 5.2±0.1 Hz.[138] This value was determined from the doublet separation in the ^{13}C side-bands of the H-1,2 signal.

The $J_{1,2}$ value for cycl[3,3,2]azinium perchlorate was similarly determined by using a strong solution of the salt (in trifluoroacetic acid). A very weak doublet centred at 2.48T was attributed to the upfield ^{13}C side-band of the H-1,2 signal (J $^{13}C_{-H}$ = 174 Hz). (The symmetrically placed low field doublet would be obscured by the ring protons). The value found for $J_{1,2}$ (5.4±0.2 Hz) is even larger than that for acenaphthylene in which the 1,2-bond is known [181] to be essentially double in character. Furthermore the u.v. spectrum of the cyclazinium salt (λ_{max} (log E) 270(3.96), 282i(3.82), 296i(3.61), 335nm(3.78)) shows some similarities with that of acenaphthylene [182] (λ_{max} (log E) 265(3.31), 293s(3.50), 311s(3.71), 324(3.97), 333(3.59), 339nm(3.60)). It thus appears that there is little

delocalisation of the π-electrons around the peripheral ring; and that the 1,2-bond possesses a high π-bond order. On this basis it seems that the compound is best regarded as an azonia-acenaphthylene (169) rather than as a 10π-electron cation (170) with a central nitrogen atom.
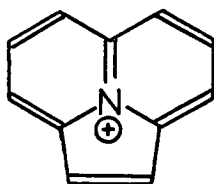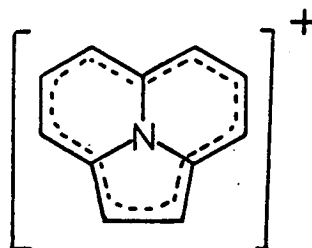
(169)   (170)

Thus the 1,2-bond in cycl[3,3,2]azinium perchlorate might be expected to undergo similar reactions to those of the 1,2-bond in acenaphthylene. However, because of the positive charge in the cyclazinium ion, it is not reasonable to expect an exact analogy with the double-bond reactions of acenaphthylene; electrophilic addition, for example, would presumably be unfavourable. Accordingly, the two reactions chosen for study were Diels-Alder addition and di-imide reduction, both of which, being concerted electrocyclic processes, should be relatively unaffected by changes in electron-density.

When acenaphthylene is heated with isoprene at 170°-175° for 15 hrs., a 43% yield of the Diels-Alder adduct is obtained [183]. Under similar conditions the cyclazinium salt failed to react, only recovered starting material being obtained.

Reduction with di-imide was next attempted. Di-imide generated _in_

situ reduces olefins, alkynes and azo compounds [184,185]. However when the

reaction was attempted using a three-fold excess of di-imide, again only

recovered starting material was obtained.

In view of the evidence from n.m.r. spectroscopy for the double bond

character of the 1,2-bond, these negative results seem surprising. However,

the n.m.r. evidence must be considered the stronger, and so it seems that

the failure of the above reactions was probably due to unsuitable reaction

conditions rather than aromatic character of the 1,2-bond. Unfortunately

lack of material and time prevented further investigation.

Substitution of 1-ethoxycycl[3,3,2]azinium perchlorate with sulphur

(by saturated aqueous sodium sulphide in dimethylformamide) has been

achieved [116] 1-ethoxycycl[3,3,2]azin -6-thione being obtained. A

similar reaction was carried out with the parent cyclazinium salt, and the

thione formed, because of its instability, was converted immediately into the

methiodide. The mass spectrum of this compound showed only a small peak at

m/e 200, but a large one at m/e 185, consistent with the loss of a methyl

group from a methylthiocyclazinium salt. The n.m.r. spectrum showed a five

proton multiplet (1.06-1.39T), two one-proton doublets (1.60T and 1.81T) and

a three proton singlet at 7.00T, which is entirely consistent with a

cyclazinium structure containing a methylthio-group in either the 3- or the

5-position. (A 4-methylthio-group is also possible, but it was considered

likely that the two singlets from the 3- and 5-protons would in that case have

been identifiable). The identification [116] of 1-ethoxycycl[3,3,2]azine-6-thione

rested on the anisotropy of the thione group and its effect on the 5-proton. A

similar method with the parent thione was not possible because of its instability.

Although positive identification was not achieved, the unsymmetrical substitution pattern of the cyclazinium salt allowed an independent measurement of the coupling constant $J_{1,2}$ from the doublet separations of the H-1 and H-2 signals. This was found to be 5.4±0.1 Hz in close agreement with the value found for the parent system.
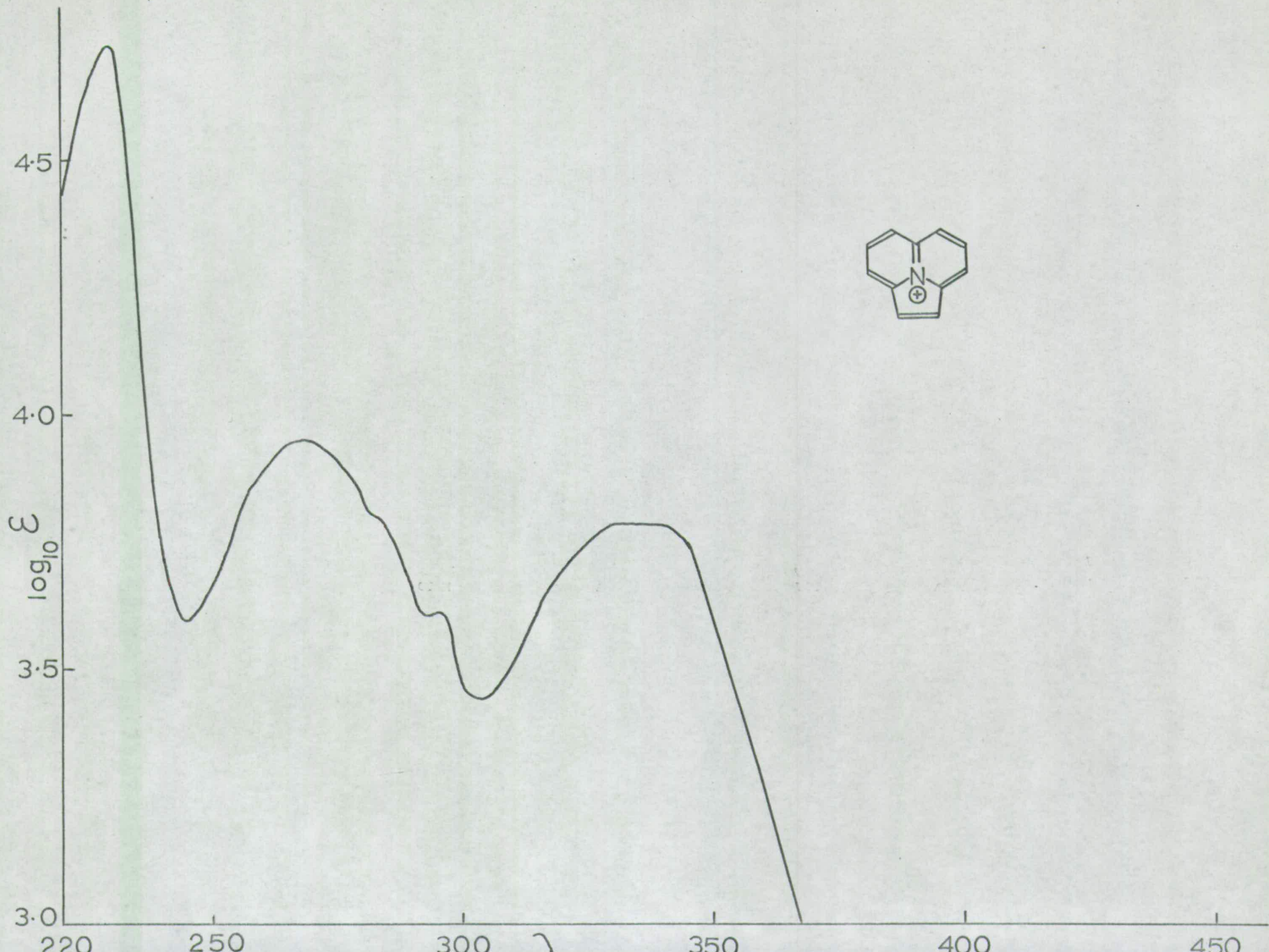
EXPERIMENTAL

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 B. Clark of this Department or by The National Physical Laboratory.

3) Infrared spectra were recorded on a Unicam S.P. 200 Spectrophotometer. Unless otherwise stated nujol pastes were used.

4) Ultraviolet and visible spectra were recorded on a Unicam S.P. 800 Spectrophotometer. The abbreviations 's' and 'i' refer to shoulders and inflexions respectively on the curves.

5) Nuclear magnetic resonance spectra were recorded on a Varian Associates HA. 100 (100 mc/sec.) spectrometer using trimethylsilane as internal standard. Unless otherwise stated, deuterochloroform was used as solvent.

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

7) Electron spin resonance spectra were recorded on a Decca Radar X3 spectrometer employing 100 kc/sec. magnetic field modulation and phase sensitive detection. The microwave klystron operated at a specified frequency of 9270.0 Mc/sec. The magnetic field was provided by a Newport Instruments type F11-inch electromagnet.

   The computer simulated spectrum was obtained using a modified program Q.C.P.E. 83, distributed by the Quantum Chemistry Program Exchange, with an I.B.M. 360/44 computer and a 1327 plotter.

8) Alumina for chromatography was Spence grade 'H'; deactivated alumina refers to alumina which had been shaken for 12 hrs. with 10% (by weight) of 10% aqueous acetic acid.

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

10) Light petroleum refers to the fraction boiling between 60-80°C.

11) Solvents were dried over anhydrous magnesium sulphate or Molecular Sieve type 4A(1/16" pellets).

ATTEMPTS TO ACHIEVE A CONVENIENT SYNTHESIS
OF QUINOLIZIN-4-ONE

Diethyl (2,2´-pyridylethyl)malonate

Prepared by the method of Boekelheide[186]

Attempted preparation of 3-ethoxycarbonylquinolizin-4-one

To a stirred solution of potassium (3.24g., 1 equiv.) in dry t-butanol (50 ml.) was added diethyl pyridylethylmalonate (10g., 1 equiv.), followed by bromine (5.9g., 1 equiv.) and the solution was stirred at 80-90° for 1 hr. During this time the solution darkened considerably. To the cooled solution was added 300 ml. water and the solution was extracted with methylene chloride (3x100 ml.). The combined organic extracts were dried and evaporated under reduced pressure to leave a dark tar. Nothing corresponding to the required product (an authentic sample of which was available for comparison) could be isolated.

Reaction of diethyl (2,2´-pyridylethyl)malonate with sulphur

The malonate (10g.) and sulphur (1.3g., 2 equiv.) were heated to 200-210° for 6 hrs. The resulting dark oil was chromatographed on 10% deactivated alumina, eluting with benzene, to give a broad fluorescent green band which yielded on evaporation of the solvent orange-brown crystals.

Yield = 1.9g. (23%)   (m.p.   112-114°)

(Lit m.p.[187]   115-116°)

The i.r. spectrum of this material was identical with that of authentic 3-ethoxycarbonylquinolizin-4-one.(94)

Preparation of quinolizin-4-one

The product of the above reaction (1.9g.) was dissolved in hydrochloric

acid (50 ml.) and the yellow solution was heated under reflux for 2 hrs.
The resulting pale-yellow solution was cooled in an ice-bath and, with
efficient stirring, neutralised by the addition of powdered potassium
carbonate. The solution was filtered through celite and extracted with
chloroform (4x50 ml.). The combined organic extracts were dried and
evaporated under reduced pressure to leave a yellow-brown solid which was
distilled at $130^{\circ}/0.02$ mm. to yield a yellow hygroscopic solid.

Yield = 0.75g. (59%)   (m.p.   = 70-72°)

(Lit m.p.[188] = 71-72°)

The i.r. spectrum of this material was identical with that of
authentic quinolizin-4-one. (95)

ATTEMPTS TO PREPARE DERIVATIVES OF CYCL[4,3,3]AZINE

1. **With nitrogen in the peripheral ring.**

    Ethyl azidoformate

    Prepared by the method of Forster and Fierz[189]

(i) Reaction of diethyl cycl[3,3,3]azine-1,3-dicarboxylate with ethyl

    azidoformate

    (a) In 1,1,3-trichloroethane

         Ethyl azidoformate (10 mg.), in 1,1,3-trichloroethane (ca.

1 ml.), was added to a solution of the cyclazine (27 mg.) in the same solvent

(5 ml.) and the solution was stirred and heated at $110^{\circ} \pm 5^{\circ}$. When, after $\frac{1}{2}$ hr.,

thin-layer chromatography indicated no traces of material other than cyclazine,

more ethyl azidoformate (40 mg.) was added and the temperature was gradually

raised to $120-125^{\circ}$. During this time, thin-layer chromatography indicated an

increase in decomposition material, a corresponding decrease in the amount of

cyclazine, and only a trace of other material. Nothing corresponding to the

expected product could be isolated from this solution.

    (b) In diglyme

         Ethyl azidoformate (10 mg.), was added to a solution of the

cyclazine (20 mg.) in diglyme (3 ml.) and the solution was stirred and

heated at $130^{\circ} \pm 5^{\circ}$ for $\frac{1}{2}$ hr. More ethyl azidoformate (25 mg.) was added, and

heating continued for a further hour. Thin-layer chromatography indicated

some unreacted cyclazine together with three slower moving orange-brown spots.

The reaction mixture was shaken with water (100 ml.) and ether (20 ml.), and

the organic layer washed with water (50 ml.), separated, dried and

evaporated under reduced pressure. The brown residue was dissolved in benzene

and chromatographed on 10% deactivated alumina, eluting initially with benzene, but gradually changing to ether. A large number of products were shown to be present in the reaction mixture but none of them in sufficient quantity to suggest that reaction on a larger scale would be useful.

(c) In xylene

Ethyl azidoformate (50 mg.) was added to a solution of the cyclazine (27 mg.) in xylene (2 ml.) and the solution stirred and heated at $130°±5°$ for 2 hrs. Thin-layer chromatography indicated a small amount of unreacted cyclazine, together with a large number of yellow and brown spots. The reaction was not pursued further.

(d) In benzene

Ethyl azidoformate (60 mg.) was added to a solution of the cyclazine (20 mg.) in benzene (3 ml.) and the solution refluxed for 72 hrs. Thin-layer chromatography during this time indicated only decreasing amounts of cyclazine, increasing decomposition product, and only traces of other material.

(e) In ethyl azidoformate as solvent

Ethyl azidoformate (80 mg.) was added to the cyclazine (25 mg.) and the mixture was heated at $150°±5°$ for 3 hrs. Thin-layer chromatography indicated a small amount of unreacted cyclazine, traces of other material, and a considerable amount of decomposition product. The reaction was not continued further.

(ii) Reaction of diethyl cycl[3,3,3]azine-1,3-dicarboxylate with iso-amyl nitrite

Phosphoryl chloride (30 mg., 0.96 equiv.) in dry dichloromethane (ca. 1 ml.) was added dropwise to a stirred solution of the cyclazine (60 mg.)

and iso-amyl nitrite (22 mg., 0.97 equiv.) in the same solvent (3 ml.) while

cooling in ice-salt. The colour of the solution gradually changed from yellow

to dark purple. The solution was added to water (50 ml.) and extracted with

chloroform (2x20 ml.). The dark purple organic extract was dried, evaporated

under reduced pressure, and chromatographed on activated alumina (20"x 1"),

eluting initially with ether and gradually increasing to ether/chloroform 1:1.

The column indicated a complex mixture of red-purple and purple bands, all of

them in small amounts. No product was isolated in sufficient quantity or

sufficiently pure for characterisation.

(iii) Reaction of diethyl cycl[3,3,3]azine-1,3-dicarboxylate with sodium

nitrite in the presence of acetic acid

A solution of sodium nitrite (25 mg., 0.95 equiv.) in the minimum

volume of water was added to a stirred solution of the cyclazine (110 mg.) in

a mixture of dichloromethane (2 ml.) and acetic acid (10 ml.) while cooling

in ice-salt. An immediate change from yellow to deep purple took place.

Stirring was continued for 20 min., and the solution was then poured into

ice-cold 2N potassium carbonate solution (50 ml.) and extracted with

chloroform (3x20 ml.). The organic extracts were combined, washed once with

water (30 ml.), dried, and concentrated under vacuum to approx. 1 ml.

The deep purple solution was separated by preparative thin-layer chromatography

eluting with chloroform, A very complex series of bands was obtained of which

only the main ones could be identified. They all proved to be mono- and

dinitro derivatives of the cyclazine by comparison with authentic samples.

Fraction 1:   Orange-brown on the plate giving purple solutions

Yield = 12.0 mg.   (8.5%)

By comparison with authentic sample prepared by Farquhar

(n.m.r., m/s, m.p. 152-154° (153-154°)) shown to be:-

Diethyl 4,7-dinitrocycl[3,3,3]azine-1,3-dicarboxylate.(73a)

Fraction 2:   Purple on plate and in solution

    Yield = 6.8 mg. (5.0%)

By comparison with authentic sample prepared by Farquhar (n.m.r., m/s, m.p. 209-211° (211-212°)), shown to be:-
Diethyl 6-nitrocycl[3,3,3]azine-1,3-dicarboxylate.(73c)

Fractions 3 & 4:   Two very small bands, orange and grey respectively. Not identified.

Fraction 5:   A grey-purple band giving purple solutions

    Yield = 10.8 mg. (7.5%)

By comparison with authentic sample prepared by Farquhar (n.m.r., m/s, m.p. 230-232° (233-234°)), shown to be:-
Diethyl 4,9-dinitrocycl[3,3,3]azine-1,3-dicarboxylate.(73e)

Fraction 6:   A blue-grey band giving blue-purple solutions

    Yield = 3.4 mg. (2.5%)

Not identified for certain at the time, but by comparison with sample prepared later (see below), shown to be:-
(n.m.r., m/s, m.p. 192-194° (193-194°)):-
Diethyl 4-nitrocycl[3,3,3]azine-1,3-dicarboxylate.(100)

After a large number of small bands of various colours (mostly light brown or purple) there was obtained one further fraction in sufficient quantity to identify:-

Fraction 7:   A purple band giving purple solutions

    Yield = 9.0 mg. (6.5%)

By comparison with authentic sample prepared by Farquhar (n.m.r., m/s, m.p. 226-227° (225-226°)) shown to be:-
Diethyl 4,6-dinitrocycl[3,3,3]azine-1,3-dicarboxylate.(73d)

Nitration of diethyl cycl[3,3,3]azine-1,3-dicarboxylate

A solution of the cyclazine (140 mg.) in acetic anhydride (25 ml.) was added to a solution of powdered cupric nitrate trihydrate (100 mg.) in the same solvent (10 ml.) with stirring. The solution immediately changed colour from yellow to deep blue. After stirring at room temperature for 2 mins., the solution was poured into ether and sodium carbonate solution. The organic extract was washed with sodium carbonate solution and water and was then dried and evaporated under reduced pressure. The blue-black residue was dissolved in benzene (ca. 5 ml.) and chromatographed on 10% deactivated alumina (20" x 1") eluting with light-petroleum/benzene (1:2). The first fraction, a blue-purple solution, yielded dark blue crystals.

Yield = 46 mg. (29%)

By comparison with an authentic sample prepared by Farquhar (n.m.r., i.r., m.p. 210-212° (211-212°)) shown to be:-

Diethyl 6-nitrocycl[3,3,3]azine-1,3-dicarboxylate.(73c)

A second blue band yielded a dark blue solid which was crystallised from ethanol/benzene as fine needles.

Yield   = 40 mg. (25%)

m.p.   = 193-194°

Mass spectrum: m/e (parent) = 356

Diethyl 4-nitrocycl[3,3,3]azine-1,3-dicarboxylate (100)

$C_{18}H_{16}N_2O_6$ requires   C=60.68%;   H=4.49%;   N=7.87%

found   C=60.62%;   H=4.54%;   N=7.65%

ν_{max} (C=O)   = 1690 cm^{-1}

λ_{max} (log E) EtOH: 212(4.40), 279(4.42), 350(3.90) 413(4.28),

581 nm(4.27).

A third grey-blue fraction yielded dark crystals (9 mg.) which could not be identified.

2. <u>With oxygen in the peripheral ring.</u>

<u>Reaction of diethyl cycl[3,3,3]azine-1,3-dicarboxylate with</u>

<u>m-chloroperbenzoic acid</u>

m-chloroperbenzoic acid (66 mg.) was added to a solution of the

cyclazine (100 mg.) in dichloromethane (5 ml.) with stirring. After 4 hrs.

(with continued stirring at room temperature), excess peracid was destroyed by

the addition of 10% sodium sulphide solution (5 ml.). Dichloromethane (15 ml.) was

added, and the organic layer was separated and washed with sodium bicarbonate

solution (10 ml.) and water (2x10 ml.). The solution was dried, evaporated

under reduced pressure, and chromatographed on 10% deactivated alumina

(15" x $\frac{3}{4}$") eluting initially with chloroform, but gradually changing to

chloroform-methanol (4:1). After a small amount of unreacted cyclazine (8 mg.),

there followed a weak red-brown fraction. This yielded a dark solid (7 mg.)

that could not be identified. Most of the material remained at the top of

the column as intractable decomposition product.

3. <u>With sulphur in the peripheral ring.</u>

(i) <u>Reaction of diethyl cycl[3,3,3]azine-1,3-dicarboxylate with sulphur</u>

    (a) <u>In pyridine</u>

        The cyclazine (53 mg.) and sulphur (10 mg., 2 equiv.) were
heated in dry refluxing pyridine (4 ml.), under nitrogen, for 4 hrs. During
this time the solution darkened slightly. The cooled solution was added to
dilute hydrochloric acid (50 ml., 0.5N), and the resulting solution extracted
with ether (3x20 ml.). The combined organic extracts were dried, concentrated,
and chromatographed on activated alumina, eluting with ether. An initial small
fraction of unreacted cyclazine (4 mg.) was eluted first, leaving a complex
series of weak bands from which no product could be isolated in reasonable
quantity.

    (b) <u>In dimethylformamide</u>

        The cyclazine (99 mg.) and sulphur (19 mg., 1.9 equiv.) were
heated in dry refluxing dimethylformamide under nitrogen for 5 hrs. The
cooled solution was added to dilute hydrochloric acid (40 ml., 0.5N), and the
resulting solution extracted with chloroform (2x20 ml.). The combined organic
extracts were concentrated under vacuum, and the resulting red-brown solution
was separated by preparative thin-layer chromatography, eluting with chloroform.
A complex series of bands were obtained from which only one fraction could be
satisfactorily isolated.

Fraction 1 & 2:   A yellow-brown band and a red band respectively which
                   were only partially separated. Fraction 1 may have been
                   recovered cyclazine, but could not be obtained pure. The
                   amounts of each band were very small.

Fraction 3:   A red band from which was obtained a red-brown amorphous

solid

      Yield   = 10.3 mg.

      m.p.   = 211-214°

      Mass spectrum m/e = 389, 373, 345, 317

The product was not identified with certainty, though some

tentative conclusions can be reached concerning its structure

(see discussion).

(ii) <u>Reaction of ethyl cycl[3,3,3]azine-1-carboxylate with sulphur</u>

      The cyclazine (135 mg.) and sulphur (30 mg., 1.8 equiv.) were heated

in dry refluxing dimethylformamide under nitrogen. Thin-layer chromatography

indicated only a fairly rapid decrease in the amount of cyclazine, a

corresponding increase in decomposition product and only traces of other products.

After 10 min. no cyclazine remained. No product could be isolated.

ATTEMPTS TO PREPARE DERIVATIVES OF 10b-AZONIAPYRENE

1. (i) Reaction of diethyl cycl[3,3,3]azine-1,3-dicarboxylate with propiolaldehyde

    (a) In dichloromethane

        Propiolaldehyde (200 mg.) was added to a stirred solution of the cyclazine (110 mg.) and methanol (100 mg.) in dry methylene chloride (5 ml.) and the solution heated to $35°\pm2°$ for 20 mins. The solvent was removed under reduced pressure, and the crude reaction product was chromatographed on activated alumina (20" x $\frac{3}{4}$") eluting with ether. After a small amount of recovered cyclazine (12 mg.) the main band of blue-purple material was eluted, and crystallised from methanol as fine purple needles.

    Yield   = 14 mg. (17% based on unrecovered cyclazine)

    m.p.   = $199-202°$

    Mass spectrum m/e (parent)   = 365

    Diethyl 4-(3-oxoprop-1-enyl)cycl[3,3,3]azine-1,3-dicarboxylate(106)

    $C_{21}H_{19}NO_5$ requires: C=69.04%;   H=5.21%;   N=3.84%

                  found: C=69.00%;   H=4.92%;   N=4.04%

    ν_{max} (C=O)   = 1670 cm^{-1}

    λ_{max} (log E) EtOH: 207(4.30),   244(4.29),   262(4.29),   298(4.33),   322s(4.26), 429(4.26),   535 nm(4.40).

    Two later bands (pink and orange respectively), were present in insufficient quantity for identification. Considerable decomposition material remained at the top of the column.

    (b) In acetic acid

        Propiolaldehyde (22 mg.) in acetic acid (1 ml.) was added to a solution of the cyclazine (103 mg.) in the same solvent (60 ml.) and the

solution stirred and heated to 65°-70° for 15 mins., during which time the solution darkened to dark purple. The cooled solution was evaporated to small volume under reduced pressure, and the dark residue was treated with perchloric acid (2 drops) followed by ether. Filtration yielded a black sticky solid which, after being dried under vacuum, became a black amorphous powder (105 mg.). This solid could not be identified. The purple-pink filtrate was concentrated and chromatographed on activated alumina (20"x $\frac{3}{4}$") eluting with ether/chloroform (1:1). After a very weak purple band, there was eluted the main pink fraction which crystallised from ethanol/benzene as red needles.

Yield   = 7.1 mg. (6%)

m.p.   = 186-189°

Ethyl 3-(3-oxoprop-1-enyl)cycl[3,3,3]azine-1-carboxylate (107)

$C_{18}H_{15}NO_3$ Exact mass. requires: 293.1052

found: 293.1035

λ_{max} (log E) EtOH: 206(4.21),   245s(4.09),   263(4.12),   293s(3.99),

305s(3.96),   326s(3.93),   436(4.20),   523 nm(4.46).

(ii)   <u>Reaction of diethyl cycl[3,3,3]azine-1,3-dicarboxylate with N-methyl</u>
<u>anilinoacrolein</u>

Phosphoryl chloride (70 mg., 1.1 equiv.) was added to N-methyl anilinoacrolein (70 mg.) with stirring and cooling in ice. Stirring was continued for 5 min. at 0° and 15 mins. at room temperature. Dry dichloromethane (2 ml.) was added, and the solution again cooled in ice. This solution was added dropwise to a cooled solution of the cyclazine (130 mg., 1.0 equiv.) in dry dichloromethane (5 ml.) with stirring. The solution darkened rapidly to orange-brown. Stirring was continued for 15 min. with

warming to 30°. (A small portion of this solution was treated with excess of sodium perchlorate in methanol, but even after concentration under reduced pressure and trituration with ether, no precipitate resulted).

The bulk of the solution was added to 2N sodium carbonate (10 ml.), and heated under reflux with vigorous stirring for 10 mins. The organic layer was separated, and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried, evaporated and chromatographed on 10% deactivated alumina (20"x ¾"), eluting initially with benzene and gradually changing to benzene/ether (1:1). A single red-purple fraction was eluted, but from an n.m.r. spectrum it appeared to consist of a 1:1 mixture of diethyl 4-(3-oxoprop-1-enyl)cycl[3,3,3]azine-1,3-dicarboxylate (106) , and N-methyl anilinoacrolein. No other material was obtained.

2. <u>Reaction of diethyl cycl[3,3,3]azine-1,3-dicarboxylate with 1,1´,3,3´-tetraethoxypropane</u>

(a) <u>In dichloroethane</u>

Tetraethoxypropane (25 mg. 1.2 equiv.) and trifluoroacetic acid (0.3 ml.) in dry dichloromethane (5 ml.) was added to a stirred solution of the cyclazine (29 mg.) in the same solvent (10 ml.) with cooling in ice. Stirring, in ice, was continued for 1 hr. (during which time slight darkening took place), and for a further ½ hr. at room temperature (with considerable darkening). The solvent was removed under reduced pressure, the dark residue dissolved in acetic acid (3 ml.) and perchloric acid (3 drops) added followed by trituration with ether. A red-brown solid (11 mg.) was filtered off. Thin-layer chromatography of this solid (eluting with chloroform/methanol (4:1) and of the brown filtrate showed both to consist of a complex mixture of components. Since it seemed unlikely that any of these could be isolated in reasonable yield, the investigation was discontinued.

(b) <u>In trifluoroacetic acid</u>

Tetraethoxypropane (140 mg., 2 equiv.) was added to a solution of the cyclazine (102 mg.) in trifluoroacetic acid (2 ml.) and the reaction mixture left at room temperature for 4 hrs. The solvent was removed under reduced pressure and the residue, dissolved in chloroform, was washed with 2N potassium carbonate (20 ml.) and water (2x20 ml.). The solution was then dried, concentrated and separated by preparative thin-layer chromatography, eluting with chloroform. This showed a complex series of bands the most intense of which was purple but yielded only 2 mg. of material.

ATTEMPTS TO PREPARE DERIVATIVES OF 6H-10b-AZAPYREN-6-ONE

1. <u>Reaction of diethyl cycl[3,3,3]azine-1,3-dicarboxylate tetracyanoethylene</u>

Tetracyanoethylene (64 mg., 1.03 equiv.) in dichloromethane (1 ml.) was added to a solution of the cyclazine (150 mg.) in the same solvent (10 ml.). The reaction mixture was stirred in ice for 10 mins. and then at room temperature for 1 hr., during which time the solution darkened. After concentration the dark residue was separated by preparative thin-layer chromatography, eluting with chloroform. A very large number of bands were obtained, of which the largest (a purple band) contained only 2 mg. The reaction was not investigated further.

Similar results were obtained when the reaction was carried out in tetrahydrofuran or in dimethylformamide.

2. <u>Attempted reaction of diethyl 4-formylcycl[3,3,3]azine-1,3-dicarboxylate with nitromethane</u>

A dilute solution of sodium ethoxide (1 equiv.) in ethanol was added to a stirred solution of the cyclazine (100 mg.) and nitromethane (30 mg., 1.6 equiv.) in the same solvent (25 ml.). The solution darkened slightly, during 1 hr., to yellow-brown. The solution was washed with water (2x30 ml.), dried, concentrated, and separated by preparative thin-layer chromatography, eluting with chloroform. A large number of bands were obtained, all in small yield with the exception of one yellow-brown band. The product from this was obtained as an amorphous brown solid for which a satisfactory solvent for crystallisation could not be found.

Yield   = 62 mg. (62%)

m.p.   = 96-100°(with decomposition)

Ethyl 5-ethoxy-3-oxo-3H,5H-pyrano[3,4,5-c̲d̲]cycl[3,3,3]-
azine-1-carboxylate (117)

$C_{19}H_{17}NO_5$ Exact mass requires: 339.1107

                        found: 339.1113

λ_{max} (log E) EtOH: 207(4.36),   242(4.13),   281(4.52),   315s(3.87)

                330s(3.70),   407(4.40),   452 nm(4.39).

3.   Reaction of diethyl 4-formylcycl[3,3,3]azine-1,3-dicarboxylate with

sodium hydroxide

     A solution of sodium hydroxide (1 equiv.) in water was added to a
stirred solution of the 4-formylcyclazine in diglyme (3 ml.) and water (1 ml.).
The product was extracted with dichloromethane (4x50 ml.) and the extract was
washed with water (3x50 ml.), dried and concentrated. Separation of the
products by preparative thin-layer chromatography yielded a very complex
series of bands from which was isolated a yellow-brown band. This yielded a
brown amorphous solid.

                 Yield   = 10.6 mg.

The mass spectrum and the n.m.r. spectrum were not consistent with the
expected structure (117a) of the product (see discussion)..

Reaction of diethyl cycl[3,3,3]azine-1,3-dicarboxylate with diketene

     Cyclazine (174 mg.) and diketene (0.5 ml.) were sealed in a thick
walled pyrex tube and heated at 120° for 1½ hr. The tube was cooled, opened,
and the product chromatographed on activated alumina (20"x ¾"), eluting with
ether/chloroform (1:1 increasing to 1:3). After elution of unreacted
cyclazine (54 mg.) there followed a small red fraction which was not identified.
The main purple band was eluted next, and the product crystallised from ethanol

as red-brown needles.

Yield	=	26 mg. (15% based on unrecovered cyclazine)
m.p.	=	257-260°
Mass spectrum m/e (parent)	=	461

Either   4,6-di(ethoxycarbonyl)cycl[3,3,3]azin-1-yl-2,6-dimethyl

-2-oxopyran-5-yl ketone   (120a)

Or   4,6-di(ethoxycarbonyl)cycl[3,3,3]azin-1-yl-2,6-dimethyl

-4-oxopyran-3-yl ketone   (120b)

$C_{26}H_{24}NO_7$ requires: C=67.69%;   H=4.99%;   N=3.04%

found: C=67.57%;   H=4.73%;   N=3.34%

ν_{max} (C=O)   = 1680 cm^{-1}, 1670 cm^{-1}

λ_{max} (log E) EtOH: 213(4.48), 254s(4.27), 286(4.47), 338s(3.61)

382s(3.90), 397(4.09),   498s(4.30), 531nm(4.77).

Two other very small bands (pink and orange) were eluted next, but not identified, leaving intractable red-brown material at the top of the column.

REACTION OF DIETHYL CYCL[3,3,3]AZIN—1,3-DICARBOXYLATE WITH BENZYNE

Diphenyliodonium-2-carboxylate[190,191] (320 mg. 2 equiv.) (Note 1) was added to a refluxing solution of the cyclazine (150 mg.) in triglyme (10 ml.) under nitrogen. A vigorous effervescence immediately occurred. Refluxing was continued for $\frac{1}{2}$ hr. and the solvent was removed at the oil-pump. Separation of the products was attempted by preparative thin-layer chromatography eluting with chloroform. However, a large number of variously coloured products was obtained. No attempt was made to isolate any of these. The reaction was repeated using shorter reaction times. After refluxing for 30 secs. with 1 equiv. diphenyliodonium-2-carboxylate thin-layer chromatography indicated that a considerable quantity of cyclazine remained. Refluxing for 3 mins., with 4 equiv. diphenyliodonium-2-carboxylate yielded a simpler mixture than originally obtained with only a trace of unreacted cyclazine. However, the amounts were small, and the mixture still complex and so no product was isolated.

Note 1:   Prepared by the method of Fieser and Haddadin[192].

ATTEMPTED PREPARATION OF 4-, 5- AND 6-METHYL DERIVATIVES
OF DIETHYL CYCL[3,3,3]AZINE-1,3-DICARBOXYLATE

1. Attempted reaction of diethyl cycl[3,3,3]azine-1,3-dicarboxylate with
    ethyl but-2-ynoate

    (a) The cyclazine (51 mg.) and the butynoate (31 mg.) were refluxed in
toluene overnight. Thin-layer chromatography indicated that no reaction had
taken place.

    (b) The cyclazine (17 mg.) and butynoate (98 mg.) were heated at
$150^{\circ}\pm 5^{\circ}$ in an oil bath for 6 hrs. in a sealed, thick-walled glass tube (5 cm x
1 cm). The product was chromatographed on 10% deactivated alumina eluting with
benzene. Cyclazine (10.7 mg.) was recovered together with only a trace of red
material.

2. Reduction of diethyl 6-formyl-cycl[3,3,3]azine-1,3-dicarboxylate with
    diborane

    (By variation of the methods of Breazeale[166] and Jackson[167])

        Sodium borohydride (80 mg.) in dry tetrahydrofuran (3 ml.) and
borontrifluoride-etherate (38 mg.) in the same solvent (2 ml.) were added
separately but at the same time to a vigorously stirred solution of the
cyclazine (76 mg.) in the same solvent (10 ml.). The colour of the solution
changed from red-brown to yellow-green in a few seconds. After stirring for
15 mins., cold dilute potassium hydroxide solution (30 ml.) was added, and the
organic material extracted with dichloromethane. The organic extract was
washed with water, dried and chromatographed on 10% deactivated alumina eluting
with chloroform-methanol (4:1). A red-brown band, which showed signs of

crystallising on the column, was eluted. From it was obtained brown needles

Yield   = .77 mg.

m.pt.   = 212-214°

Mass spectrum (parent?) m/e   = 325 with smaller peaks at 339 and

341.

Although the n.m.r. spectrum was largely consistent with that expected for

the 6-methyl derivative (126), positive identification of the product could not

be achieved (see discussion).

3.   Reduction of diethyl 4-formyl-cycl[3,3,3]azine-1,3-dicarboxylate with

diborane

The reaction was carried out in the same way as with the 6-formyl

derivative above. The reaction appeared to follow a similar course with the

exception that the change in colour from red-brown to yellow-green only

occurred after 20-30 mins. The product was chromatographed as above, and a

red-brown band was seen on the column. After travelling a short distance,

however, crystallisation occurred, and the band could not be eluted further, even

with warm methanol.

The reaction was repeated, and separation of the products was

attempted by preparative thin-layer chromatography. However, only traces of

material were obtained and no product was isolated.

4.   Aminomethylation of diethyl cycl[3,3,3]azine-1,3-dicarboxylate

A mixture of N,N,N´,N´-tetramethyldiaminomethane (44 mg., 0.99 equiv.),

paraformaldehyde (14.0 mg., 0.54 equiv.) and acetic acid (5 ml.) were heated

until a clear solution was obtained. The solution was cooled and added

dropwise to a cold (ice bath) solution of the cyclazine (263 mg.) in

dichloromethane (10 ml.) The mixture was swirled occasionally with continued

cooling for 1 hr. and then allowed to stand in a refrigerator overnight. After

dilution with water (20 ml.), dilute hydrochloric acid (2N., 10 ml.) was added,

the mixture shaken and the separated aqueous layer washed with dichloromethane

(4x20 ml.). The combined organic extracts were washed once with water. The

combined aqueous layers were made alkaline with 10% sodium hydroxide solution,

and twice extracted with ether. The combined ethereal extracts were washed with

water until the washings were neutral to pH paper and were then dried over sodium

sulphate. The product was chromatographed on a column of 10% deactivated

alumina, eluting with benzene. Two yellow-green fractions were obtained.

Fraction 1 was obtained as orange plates after crystallisation from ethanol

Yield   = 164 mg. (54%).

m.p.   = 126-127°

Mass spectrum (parent) m/e   = 368

Diethyl 6-(N,N′-dimethylaminomethyl)-cycl[3,3,3]azine-1,3-

dicarboxylate (127)

$C_{21}H_{24}N_2O_4$ requires: C=68.48%;   H=6.52%;   N=7.61%

                 found: C=68.52%;   H=6.35%;   N=7.29%

ν_{max} (C=O)   = 1665 cm^{-1}

λ_{max} (log E) EtOH: 205(4.26),   248s(3.99),   283(4.58),   313s(3.77)

                           328i(3.68),   400 nm(4.31).

Fraction 2 was obtained as orange needles after crystallisation from benzene

Yield   = 54 mg. (20%)

m.pt.   = 248-250°

Mass spectrum (parent) m/e   = 634

Di(4,6-diethoxycarbonylcycl[3,3,3]azinyl)methane (129)

$C_{36}H_{36}N_2O_8$ requires: C=70.03%;   H=5.36%;   N=4.42%

found: C=70.10%;   H=5.34%;   N=4.10%

ν_{max} (C=O)   = 1670 cm^{-1}

λ_{max} (log E) EtOH: 250i(4.20), 292(4.86), 330i(3.98) 403(4.62),

452s(4.62), 477 nm(4.88).

5.   Reactions of diethyl 6-(N,N´-dimethylaminomethyl)-cycl[3,3,3]azine -1,3-dicarboxylate with:-

(a) Methyl iodide

Excess of methyl iodide was added to a solution of the cyclazine (56 mg.) in acetonitrile, and the light brown solution stirred at room temperature overnight.

An orange solid (74 mg.) was obtained. Its mass spectrum and n.m.r. spectrum indicated that this material contained only small amounts of the required product (see discussion).

(b) Sodium borohydride

Sodium borohydride (10 mg.) in dry diglyme (2 ml.) was added dropwise to a stirred solution of the cyclazine (50 mg.) in the same solvent (5 ml.). An immediate change from light brown to green was observed. After stirring at room temperature for 10 mins., the solvent was removed at the oil pump, and the product taken up in chloroform. The solution was washed with water, dried, and chromatographed on a column of 10% deactivated alumina eluting with benzene. A yellow-green band was eluted, the n.m.r. spectrum of which was identical with that of the starting material.

The reaction was repeated with warming to 40° for 4 hrs. Again only starting material was obtained.

(c) <u>Diborane</u>

Boron trifluoride etherate (15 mg.) in diglyme (2 ml.) was added dropwise to a stirred solution of the cyclazine (15 mg.) and sodium borohydride (5 mg.) in diglyme (4 ml.). An immediate effervescence occurred. The reaction mixture was stirred at room temperature overnight, the solvent removed at the oil pump, and the residue was taken up in chloroform. The solution was washed with water, dried and separated by preparative thin-layer chromatography eluting with chloroform. Several weak brown bands were obtained and one yellow-green band. Only the last band was isolated to yield a brown solid (1 mg.). The mass spectrum of this indicated a molecular weight of 368. It was, therefore, almost certainly recovered starting material.

Preparation of diethyl 5-methylcycl[3,3,3]azine-1,3-dicarboxylate

Diethyl acetylmalonate

      Prepared by the method of Lund[193]

Preparation of diethyl methoxymethylmethylenemalonate

      Diazomethane (ca. 5.5 g.) in ether was added to diethyl acetylmalonate

(25 g.) and, after gentle swirling, the reaction mixture was allowed to stand

at room temperature until all effervescence had ceased (about 1 hr.). The

product was distilled at the oil pump through a fractionating column to yield:-

(i)   diethyl acetylmalonate (b.p. 50-52°/0.2 mm. Hg.) 8.0 g. and

(ii)   a clear oil (b.p. 85-87°/0.2 mm. Hg.)

      15.4 g. (84% based on unrecovered acetylmalonate)

      This was identified from its n.m.r. spectrum as the required material.

Attempted preparation of 2-methylquinolizin-4-one (Fig. 26a)

      (a) The method used was the same as that for the preparation of

quinolizin-4-one [139], but the initial condensation failed to take place, only

a light brown solution resulting (instead of a purple semicrystalline mass)

after standing for 24 hrs.

      (b) The reaction was attempted in dimethylformamide (40 ml.) using

malonate (4.3 g.), methyl 2-pyridylacetate (3.0 g.) and solid sodium ethoxide

(1.5 g.). After 1 hr. at room temperature a few traces of pale-yellow

crystals were seen. The reaction mixture was refluxed for 5 hrs., cooled, and,

after addition of water (200 ml.) neutralised with 2N hydrochloric acid. A

sticky red-orange material was obtained which was dissolved in conc. hydrochloric

acid (50 ml.) and refluxed for 1½ hrs. The solution was worked up as for the

quinolizin-4-one, but only a trace of yellow solid was obtained. It was not

identified.

Methyl 2-(4-methylpyridyl)acetate

The method used was the same as that for the preparation of methyl

2-pyridylacetate [194], except that 2,4-lutidine was used instead of α-picoline.

Reagents:

Ether	350 ml.
Lithium	6.0 g.
Bromobenzene	45 ml. (67 g.)
2,4-Lutidine	49.5 ml. (45 g.)
Methanol	250 ml.
Potassium carbonate	100 g.

The product was obtained as a light yellow oil (b.p. 82-86°/0.2 mm. Hg.)

Yield = 25.3 g. (33% based on lithium)

The product was identified as the required material by its n.m.r. spectrum

and the similarity of its i.r. spectrum to that of methyl 2-pyridylacetate.

Preparation of 8-methyl quinolizin-4-one (131)

The quinolizone was prepared by alkaline hydrolysis and thermal decarboxyl-

ation of the products of reaction of methyl 2-(4-methylpyridyl)acetate and

diethyl ethoxymethylenemalonate. Since a modification of the literature methods

[139,195] was used, the experimental procedure will be described in detail.

Sodium (2.0 g.) was dissolved in ethanol (50 ml.) and methyl

2-(4-methylpyridyl)acetate (11.0 g.) was added. The solution was cooled in

an ice-bath, and treated with diethyl ethoxymethylenemalonate (16.5 g.) in

ethanol (50 ml.). The mixture was swirled, allowed to stand in ice for ½ hr.

and then at room temperature for 16 hrs. in a stoppered flask. The resultant

red-purple semi-crystalline mass, which consisted of mainly

1-methoxycarbonyl-3-ethoxycarbonylquinolizin-4-one[130] was treated with water

(100 ml.), and the cooled (10°C), rapidly stirred, viscous solution was neutralised by dropwise addition of conc. hydrochloric acid. The crude product was filtered off, washed with ice-cold ethanol (15 ml.) and dried in a vacuum desiccator to give 21 g. of red solid.

Hydrolysis of the diester

The crude diester (8.1 g.) and methanol (70 ml.) were added to 10% potassium hydroxide solution (50 ml.) and the reaction mixture heated under reflux for 18 hrs. The solution was transferred to a 600 ml. beaker, cooled to 0°C in an ice-bath, and, with efficient stirring, neutralised by dropwise addition of 6N hydrochloric acid. Further hydrochloric acid was added until the pH of the solution was about 2. The crude product was filtered off and washed with ice-cold water (20 ml.)

Yield	=	5.7 g. (78%)
m.p.	=	230-250° with vigorous evolution of gas.

Decarboxylation of the diacid

The crude 8-methyl-4-oxoquinolizine-1,3-dicarboxylic acid (5.7 g.) was heated in a sublimation apparatus immersed in a Wood's metal bath at 230-240° for 30 mins. at 1 mm. Hg. By the end of this period the initial vigorous evolution of gas had ceased, and some of the product had sublimed onto the cold finger. The sublimation was completed by heating in an oil-bath at 170° at 0.01 mm. Hg. for 1 hr. The yellow hygroscopic product was crystallised from ether as yellow prisms

Yield	=	1.20 g. (33%)
m.p.	=	128-135°

Mass spectrum (parent) m/e $\qquad$ = $\qquad$ 159

8-methyl-quinolizin-4-one (131)

$C_{10}H_9NO$ requires: C=75.48%; H=5.66%; N=8.80%

found: C=75.70%; H=5.91%; N=9.10%

ν_{max} (C=O) $\qquad$ = $\qquad$ 1650 cm^{-1}

λ_{max} (log E) EtOH: 207(4.36), 215s(4.20), 244(4.11), 250s(4.09)

270s(3.53),368s(4.08), 383 nm(4.15).

8-Methyl-4-chloroquinolizinium perchlorate (132)

(Prepared by a slight variation of the method of Van Allen and Reynolds[196]

for the preparation of 4-chloroquinolizinium perchlorate).

The quinolizone (1.15 g.) was dissolved in phosphoryl chloride (5 ml.)

with heating to 90° for 10 mins. The excess phosphoryl chloride was removed

under reduced pressure, the resulting solid dissolved in water (10 ml.) and

the perchlorate precipitated by the addition of perchloric acid. The product

was crystallised from water (containing a trace of perchloric acid) as

colourless needles

Yield $\qquad$ = $\qquad$ 1.38 g. (69%)

m.p. $\qquad$ = $\qquad$ 166-169°

Mass spectrum (parent) m/e $\qquad$ = $\qquad$ 194 and 196

8-Methyl-4-chloroquinolizinium perchlorate (132)

$C_{10}H_9NO_4Cl_2$ requires: C=43.17%; H=3.24%; N=5.04%

found: C=43.30%; H=3.02%; N=5.04%

ν_{max} (ClO_4^-) $\qquad$ = $\qquad$ 1060-1140 cm^{-1}

λ_{max} (log E) EtOH (2% $HClO_4$) 215(4.17), 235(4.01), 285(3.39)

322(3.71), 339 nm(3.91).

Ethyl t-butyl 8-Methylquinolizin-4-ylidenemalonate (133) ..

The experimental procedure was exactly analogous to that of the corresponding reaction with 4-chloroquinolizinium perchlorate[139].

Reagents:

Methyl t-butyl malonate	= 1.45 g.
Sodium hydroxide (50% oil dispersion)	= 0.20 g.
8-Methyl-4-chloroquinolizinium perchlorate	= 1.15 g.
Tetrahydrofuran	= 20 ml.

The product was obtained as yellow needles after recrystallisation from ethanol

Yield	= 0.96 g. (75%)
m.p.	= 198-199°
Mass spectrum (parent) m/e	= 329

Ethyl t-butyl 8-methylquinolizin-4-ylidenemalonate (133)

$C_{19}H_{23}NO_4$ requires: C=68.14%; H=7.25%; N=4.42%

found: C=68.10%; H=7.50%; N=4.08%

ν_{max} (C=O) = 1690 cm^{-1}

λ_{max} (log E) EtOH: 214(4.51), 230s(4.32), 251(4.31), 312(3.79) 420 nm (3.67)

Ethyl 8-methylquinolizin-4-ylideneacetate (134)

Prepared from the preceding product (0.90 g.) by a procedure exactly analogous to that used for the preparation of ethyl quinolizin-4-ylideneacetate[139].

The product was crystallised as a red solid

Yield	= 0.345 g. (55%)

Because of the known instability of similar compounds, the product was not characterised. After drying overnight over conc. sulphuric acid in a vacuum desiccator, the acetate was used without further purification.

Diethyl 5-methylcycl[3,3,3]azine-1,3-dicarboxylate (125)

The experimental procedure was exactly analogous to that used for the corresponding reaction with ethyl quinolizin-4-ylideneacetate[139].

The course of the reaction was followed by thin-layer chromatography which showed essentially complete reaction after refluxing for 8 mins.

Reagents:

Quinolizinylideneacetate	=	0.345 g.
Ethyl propiolate	=	0.15 g.
Nitrobenzene	=	15 ml.
Anhydrous potassium carbonate	=	0.3 g.

The first fraction from the column, which was yellow in colour, was evaporated to give a dark purple-brown solid. Crystallisation from benzene/light petroleum yielded dark purple plates

Yield	=	240 mg. (49%)
m.p.	=	116.5-117.5°
Mass spectrum (parent) m/e	=	325

Diethyl 5-methylcycl[3,3,3]azine-1,3-dicarboxylate (125)

$C_{19}H_{19}NO_4$ requires: C=70.15%; H=5.85%; N=4.32%

found: C=70.08%; H=5.68%; N=4.69%

ν_{max} (C=O) = 1660 cm^{-1}

λ_{max} (log E) EtOH: 205(4.28), 240(4.02), 285(4.54), 315(3.74)

330(3.70), 396(4.34), 426s(4.27), 446 nm(4.40).

The second fraction, a dark blue band on the column, was obtained as
a dark solid

Yield   =   32 mg. (6.5%)

m.p.   =   84-86°

Diethyl 5-methyl-3a,4-dihydrocycl[3,3,3]azine-1,3-dicarboxylate(135)

$C_{19}H_{21}NO_4$ Exact mass. requires: 327.1470

found: 327.1466.

ADDITION AND SUBSTITUTION REACTIONS OF ETHYL CYCL[3,3,3]AZINE-1-CARBOXYLATE

Ethyl cycl[3,3,3]azine-1-carboxylate

Prepared by the method of Farquhar [139]

(Because of the instability of this material it was prepared, from ethyl t-butyl cycl[3,3,3]azine-1,3-dicarboxylate, as required and used immediately).

Reaction with dimethyl acetylenedicarboxylate

Dimethyl acetylenedicarboxylate (60 mg., 1 equiv.) in dry, oxygen-free, dichloromethane (3 ml.) was added dropwise to a stirred solution of the cyclazine (89 mg.) in the same solvent (10 ml.) under nitrogen and with cooling to -78°. The solution, which gradually changed colour from yellow to dark red-purple, was stirred at -78° for 15 mins., and was slowly allowed to warm up to room temperature. The solution was concentrated under reduced pressure and separated by preparative thin-layer chromatography to yield a large number of variously coloured bands, and a considerable amount of decomposition product. The only bands present in reasonable quantity were:-

(a) A grey band 7.5 mg.

Mass spectrum, m/e = 523, 381

The masses would be consistent with one molecule of the cyclazine together with two molecules and one molecule respectively of dimethyl acetylenedicarboxylate. The n.m.r. spectrum was very weak, but seemed to indicate the presence of more than one product.

(b) A purple band 4.3 mg.

Mass spectrum, m/e = 554, (523*), 381 (*weak)

The masses 523 and 381 may be explained as above. The product of mass 554 cannot be a simple adduct. An n.m.r. spectrum was not attempted.

Reaction with ethyl propiolate

(a)   In benzene

A slight excess of ethyl propiolate (20 mg., 1.25 equiv.) was added
to a solution of the cyclazine (40 mg.) in dry, oxygen-free, benzene and the
solution heated under reflux for 10 mins. Thin-layer chromatography indicated
mainly unreacted cyclazine, some decomposition and a very faint pink band.

(b)   In toluene

The reaction was attempted in toluene with a large excess of ethyl
propiolate, heating under reflux for a total of 18 hrs. Chromatography indicated
some unreacted cyclazine, two very weak red bands, and a considerable quantity
of decomposition product.

Attempted nitration

A solution of cupric nitrate trihydrate (76 mg., 1 equiv.) in
oxygen-free acetic anhydride (3 ml.) was added to a stirred solution of the
cyclazine (153 mg.) in dry, oxygen-free, dichloromethane (10 ml.) with cooling
in ice. The colour of the solution gradually changed from yellow to purple-red.
After 15 mins. the solution was shaken with dilute potassium carbonate solution,
extracted with chloroform, and the organic layer dried and concentrated.
Attempted separation by preparative thin-layer chromatography, eluting with
chloroform, indicated a very large number of products, mainly purple in colour,
none of which were present in sufficient quantity to identify.

Formylation I

Phosporyl chloride (105 mg., 1.0 equiv.) was added to dimethylformamide
(48 mg., 1.0 equiv.) with stirring and cooling in ice. Stirring was continued
for 5 mins. at 0° and 15 mins. at room temperature. Dry dichloromethane (3 ml.)

was added, the solution cooled to -78°, and treated with a solution of the

cyclazine (155 mg.) in the same solvent (4 ml.). The reaction mixture, which

had immediately darkened to red-brown, was stirred at -78° for 10 mins. and

then allowed to warm up to room temperature. A solution of sodium acetate

(400 mg.) in water (10 ml.) was added, and the solution heated under reflux

with vigorous stirring for 15 mins. After cooling to room temperature, the

organic layers were separated, and the aqueous layer extracted with chloroform

(3x15 ml.). The combined organic extracts were dried, concentrated, and the

products separated by preparative thin-layer chromatography eluting with

chloroform.

Fraction 1   yielded unreacted cyclazine (4 mg.)

Fraction 2   (a red band) yielded a labile red oil which could not be

               crystallised

                   Yield   = 6 mg.

                   Mass spectrum (parent) m/e   = 267

     Because of its instability and low yield, the product could not be

identified (see discussion)

Fraction 3   was a yellow-green band of similar colour to the diethoxycarbonyl-

               cyclazine, which yielded a purple solid that was crystallised

               from ethanol/benzene as purple needles.

                   Yield   = 25.3 mg. (15%)

                   m.p.   = 260-262°

                   Mass spectrum (parent) m/e   = 267

                   Ethyl 3-formylcycl[3,3,3]azine-1-carboxylate(145)

                   $C_{16}H_{13}NO_3$ requires: C=71.91%; H=4.87%; N=5.24%

                                     found: C=71.90%; H=5.11%; N=5.10%

$$\nu_{max} \text{ (C=O)} = 1680 \text{ cm}^{-1}$$

λ_{max}(log E) EtOH   206(4.25),   239(4.04),   281(4.42),   293s(4.24),

323(3.58),   341(3.72),   372(4.07),   390(4.38),

430i(4.21),   452 nm(4.38).

Formylation II   (By the method of Chong et al.[170]).

Benzoyl chloride (95 mg., 1.1 equiv.) was added dropwise to a stirred solution of the cyclazine (150 mg.) in dry dimethylformamide (5 ml.). The solution was stirred for 20 mins. at room temperature, during which time it gradually darkened from yellow to red-brown. Dichloromethane (15 ml.) and a solution of sodium acetate (0.6 g.) in water (15 ml.) were added and the reaction mixture heated under reflux for 10 mins. with vigorous stirring. Water (100 ml.) was added to the cooled solution, the organic layer separated and the aqueous phase extracted with dichloromethane (2x20 ml.). The combined organic extracts were washed once with water (50 ml.), dried, concentrated, and the product separated by preparative thin-layer chromatography eluting with chloroform. A single yellow-green band was isolated.

Yield   = 68 mg. (41%)

This was shown (n.m.r., i.r.) to be identical with an authentic sample of ethyl 3-formylcycl[3,3,3]azine-1-carboxylate. (145)

Attempted acetylation (leading to benzoylation)

(By a variation of the method for formylation of Chong et al.[170])

Benzoyl chloride (130 mg. 1.0 equiv.) was added dropwise to a stirred solution of the cyclazine (220 mg.) in dry dimethyl acetamide (6 ml.) while cooling in ice. There was a rapid change in colour to red-brown. Stirring was continued for 5 mins. in ice and then for 5 mins. at room temperature.

of sodium

Dichloromethane (10 ml.) and a solution acetate (0.8 g.) in water (10 ml.)

was added and the reaction mixture heated under reflux for 10 mins. with vigorous stirring. Water (100 ml.) was added to the cooled solution, the organic layer separated, and the aqueous phase extracted with dichloromethane (2x20 ml.). The combined organic extracts were washed once with water (50 ml.), dried, concentrated, and chromatographed on 10% deactivated alumina (30"x 1") eluting initially with benzene-light petroleum (4:1), gradually changing to benzene. After traces of unreacted cyclazine there was eluted a weak purple band (5 mg.) which was not identified, followed by a light orange-brown band which was crystallised from ethanol/benzene as orange-brown needles.

Yield	=	122 mg. (39%)
m.p.	=	185-186°
Mass spectrum (parent) m/e	=	343

Ethyl 3-benzoyl cycl[3,3,3]azine-1-carboxylate (146b)

$C_{22}H_{17}NO_3$ requires: C=76.96%; H=4.97%; N=4.08%

found: C=76.83%; H=5.07%; N=4.10%

ν_{max} (C=O) = 1675 cm^{-1}

λ_{max}(log E) EtOH: 206(4.32), 244(4.12), 283(4.43), 398(4.37) 435s(4.23), 458 nm(4.42).

(a)

reaction sample

heating block

heavy metal
tube

thermometer

(b)

water

to oil pump
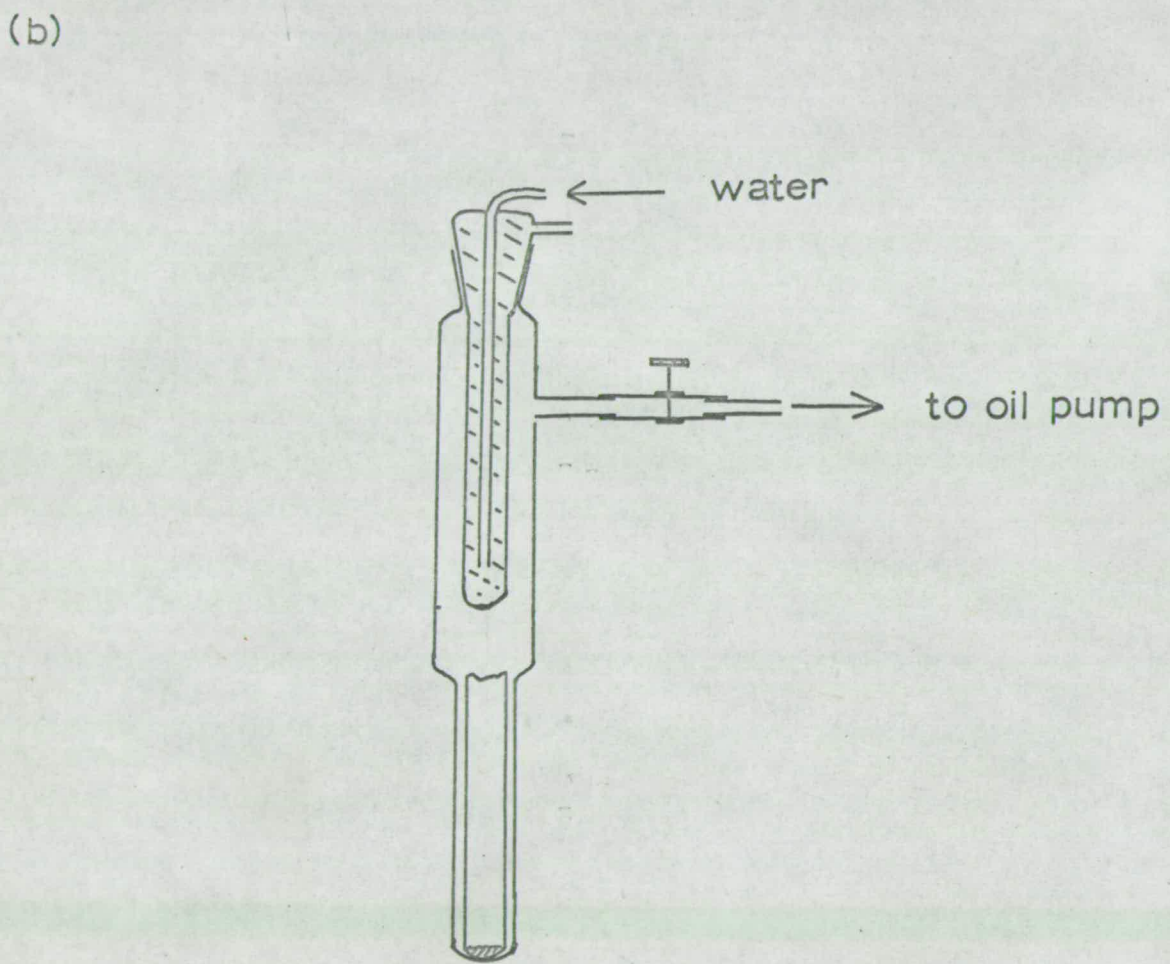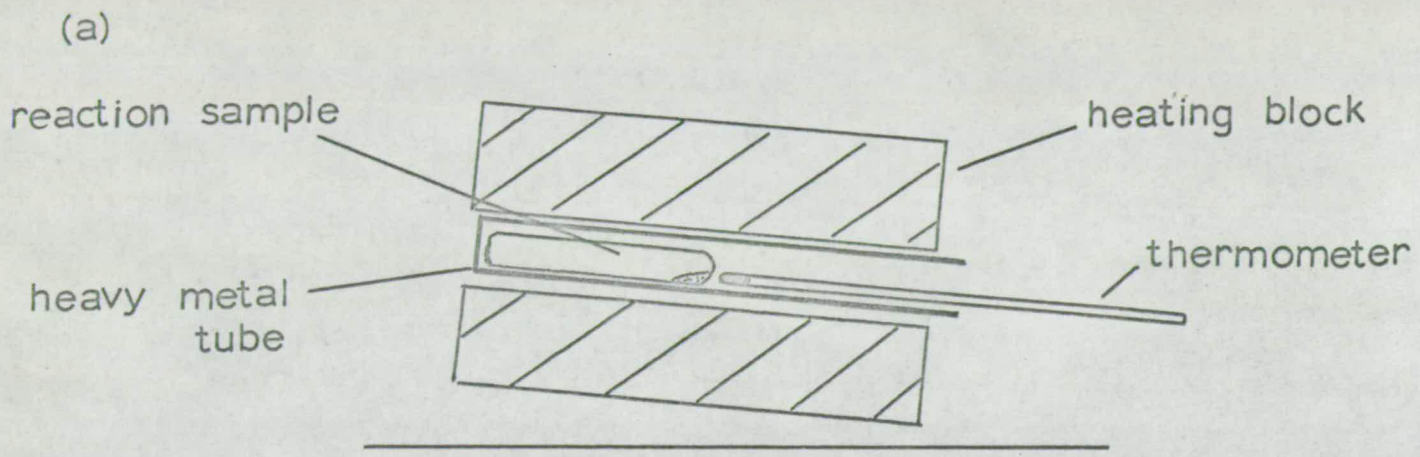
FIG. 38

SYNTHESIS AND REACTIONS OF CYCL[3,3,3]AZINE

Pyrolysis of di-t-butyl cycl[3,3,3]azine-1,3-dicarboxylate: preparation of
cycl[3,3,3]azine

The diester (0.2 g.) was sealed under high vacuum in a thick-walled,
cylindrical, pyrex-glass tube (inner dimensions 12 cm x 0.6 cm) (Note 1). The
Carius tube was slid into a heavy metal tube in a heating block (Fig. 38a)
where the temperature was initially $270\pm2^{\circ}$ and a thermometer was inserted to
monitor the temperature (Note 2). The temperature fell rapidly to ca. 245°
and, within 2 mins., rose again to ca. $255^{\circ}-260^{\circ}$. After a total of 8 mins.
the tube was tipped out into a cloth, (Note 3) allowed to cool to room
temperature and then immersed in ice. The tube was again wrapped in a cloth
and the internal pressure released by melting a small area of an end section
(Note 4) with a small blow-pipe flame. The tube was then stored immediately
under a dry nitrogen atmosphere (Note 5) and, when the end section had cooled,
the opening was sealed with a plug of plasticine. The tube, together with
the sublimation apparatus (Fig. 38b) and necessary accessories (Note 6)
was then transferred to a dry-nitrogen bag and the perforated end-section
(ca. 1 cm) was sheared off with a glass-cutter. The tube was then placed in
the socket section of the sublimation apparatus, the cold finger inserted and
the screw-clip firmly closed. The apparatus was then removed from the
nitrogen-bag and the socket section was immersed, completely, in an oil-bath.
The outlet was connected to an oil-pump and, with the screw-clip still
closed, the vacuum-assembly was evacuated to 0.01 mm. The screw-clip was
opened and the temperature of the oil-bath raised to 120°. Sublimation was
continued at 0.01 mm for 1 hr. A purple-brown crystalline solid collected

on the cold finger. The apparatus was allowed to cool, the flow of cooling

water disconnected, and the water inlet and outlet suitably sealed. The

screw-clip was closed, and the apparatus was disconnected from the pump,

and re-transferred to the nitrogen-bag, together with all apparatus

necessary for the experiment to be carried out (Note 7)

$$Yield = 22 \text{ mg } (24\%) \qquad (\text{Note } 8)$$

$$m.p. = 140\text{-}142^{\circ} \qquad (\text{Note } 9)$$

$M^{\oplus}$ (mass spectrum), 167.0727. $C_{12}H_9N$ requires M, 167.0735

λ_{max} (log E), 254(4.09), 275(4.08), 306(4.10), 410i(3.78),

422(3.99), 431(410), 446(419), 458nm(4.45) in

oxygen-free cyclohexane.

Note 1   It was found most convenient to prepare a number of tubes at one

time and keep them for use as required.

Note 2   The diester was, as far as possible, retained at the lower end of

the tube. The heating block was thus arranged on a slight slope and the tube

inserted as shown.

Note 3   Care being taken not to invert the tube.

Note 4   The pressure in the tube is approximately 5-10 atm. The tube is

therefore opened with due care behind a safety screen.

Note 5   The tube was placed inside a wider tube through which dry nitrogen

was passing.

Note 6   A glass-cutter and a pair of pliers.

Note 7   Details of these experiments follow. Because of the known extreme

reactivity [139] of the product, only dry, oxygen-free, non-hydroxylic solvents

could be used, and even then reactions were carried out as quickly as possible.

Note 8   N.m.r. spectra were run in oxygen-free benzene. Measurement of the

yield was carried out by using benzene containing a suitable known quantity of

cyclohexane and measuring the integrals.

Note 9   In a melting-point tube, filled in the dry nitrogen-bag and sealed with plasticine.

Cycl[3,3,3]azine cation bromide

The cyclazine (ca. 20 mg.) prepared according to the preceeding account was dissolved in dry, oxygen-free benzene (ca. 3 ml.) in the dry nitrogen-bag. The pale yellow-green solution was placed in a 100 ml. 2-necked flask equipped with a magnetic stirring-bar and a calcium chloride drying tube. The flask was stoppered, removed from the nitrogen-bag, and connected up as quickly as possible to a supply of dry nitrogen containing bromine vapour (Note 1). A slow stream of these gases was passed over the gently stirred solution. A blue precipitate of the cation bromide was rapidly deposited leaving a clear solution. The flow of gas was then stopped. The supernatant liquid was removed with a dropping pipette, and the blue solid was washed with a few ml. of dry benzene. The product, still in the flask, was dried overnight in a vacuum desiccator over conc. sulphuric acid. The resulting blue solid was stable to air and moisture. The cycl[3,3,3]azine cation bromide (Found: C=57.9%; H=3.61%; N=5.84%, $C_{12}H_9NBr$ requires: C=58.30%; H=3.65%; N=5.68%), did not melt below 300° and further heating caused gradual decomposition.

Mass spectrum m/e (parent) = 167

λ_{max} (log E)   229i(3.99), 241(4.07), 262(4.14), 297(3.70),
320i(3.38), 325i(3.65), 331(3.88),
338(4.44), 430 nm(3.15) in water.

Note 1   This was achieved by passing the dry nitrogen over bromine. Since bromine reacts with rubber, plastic tubing was used.

Preparation of a solution of cycl[3,3,3]azine radical
cation for e.s.r. spectrum

A large excess (Note 1) of anhydrous silver perchlorate was added to a solution (Note 2) of the cyclazine in dry, oxygen-free acetonitrile in a nitrogen-bag. A blue solution was formed immediately together with a precipitate of silver metal. A sample for e.s.r. spectrum was drawn into a melting-point tube (Note 3) by capillary action. The tube was removed from the nitrogen-bag and the ends were sealed in a small flame.

Samples prepared by the above method gradually changed colour to yellow-brown during ca. 6 hrs., but the e.s.r. signal due to the radical cation did not change appreciably during 4-5 days. The ultraviolet spectra of samples after this period showed the characteristic absorptions of the radical cation in the region 325-345nm.

Note 1   With 2 equiv. of silver perchlorate, the signal due to the radical cation decayed considerably during 2-3 hrs. It was found that by using 8-10 equiv. of silver perchlorate, the signal, though no stronger initially, remained of almost constant intensity for several days.

Note 2   A saturated solution of the cyclazine in acetonitrile contained ca. 10 mg. in 1 ml. A more suitable concentration for e.s.r. work contained ca. 10 mg. in 5-10 ml. (approx. 0.01-0.005 molar).

Note 3   The melting-point tube was tapered to a fine capillary at the ends to facilitate the sealing after filling.

Cycl[3,3,3]azine dication dibromide

The apparatus and experimental procedure was exactly the same as for the preparation of the radical-cation bromide (see previous account) with the

exception of the following changes:-

After the precipitation of the blue radical-cation, the flow of nitrogen (and bromine) was continued. The blue colour of the precipitate gradually disappeared to give a heavy light-brown oil, and a pale orange-red solution of bromine in benzene. The flask containing bromine was removed from the nitrogen line which was then reconnected to the flask with a somewhat faster flow of nitrogen. The supernatant liquid was removed with a dropping pipette, and the flask was transferred as quickly as possible to a desiccator and kept at 0.05mm. Hg over conc. sulphuric acid overnight. The residue in the flask had then become a light green-brown solid which reacted rapidly with moisture. An elemental analysis indicated the presence of excess bromine, probably present as perbromide ion. The n.m.r. spectrum in deuterosulphuric acid, with tetramethylammoniumfluoroborate as internal standard showed a doublet (-0.47T) and a triplet (0.27T) in the intensity ratio 2:1 as expected for a salt of the cyclazine dication.

Mass spectrum m/e (parent)   =   167, 167/2

Cycl[3,3,3]azine dication dichloride

The apparatus was similar to that used for the preparation of the dication dibromide. In the nitrogen line was a 1 l. 3-necked flask fitted with a gas inlet and outlet, and also connected to a chlorine cylinder. The flask was swept with dry nitrogen, and the valve of the chlorine cylinder

opened briefly. This chlorine reservoir was then suitably sealed until required.

A solution of the cyclazine in dry benzene (for molecular weight determinations) was treated with chlorine, in a stream of dry nitrogen, as described for the preparation of the dication dibromide. A blue precipitate was very rapidly formed which, with a continued flow of gas, changed fairly quickly to light-brown. As in the preparation of the dibromide, the benzene was removed under dry nitrogen and the product was dried over conc. sulphuric acid in a vacuum desiccator. Analysis samples were prepared by sealing the product (ca. 2 mg.) in previously weighed Voltair Sample Sealer Pans in a dry nitrogen-bag. Because of the method of preparation no completely satisfactory elemental analysis was obtained, the best one being:-

Found: C=61.39%; H=4.05%; N=5.45%

$C_{12}H_9NCl_2$ requires: C=60.55%; H=3.81%; N=5.88%.

Reactions of cycl[3,3,3]azine

1)   Reaction of cycl[3,3,3]azine with ethyl propiolate

A slight excess of ethyl propiolate in benzene (1 ml.) was added to a stirred solution of the cyclazine (21 mg.) in dry oxygen-free benzene (3 ml.) under nitrogen. A rapid change in colour to deep red took place. Thin-layer chromatography indicated a slow moving red spot, several other orange or yellow spots, and a moderate amount of decomposition product. An ultraviolet spectrum of the solution was rather similar to that of methyl cycl[3,3,3]azine-1-carboxylate but bore no resemblance to that of the bridged cyclazine which might have been formed by a Diels-Alder addition. In view of the multiplicity of products and the necessity for small-scale reactions, it did not seem likely that worthwhile amounts of any of the products could be isolated.

2) Attempted formylation

The method was the same as that used for the formylation of ethyl cycl[3,3,3]azine-1-carboxylate [170].   A deep orange-brown solution was initially formed. After working up thin-layer chromatography showed that several minor products were present together with a considerable quantity of decomposition product. Further work-up was not worthwhile.

3) Attempted acetylation

A slight excess of acetylchloride in dichloromethane (1 ml.) was added to a stirred solution of the cyclazine (ca. 20 mg.) in dry oxygen-free dichloromethane (3 ml.) containing a trace of triethylamine. After stirring the solution at room temperature for 30 mins., thin-layer chromatography showed a small amount of material similar in colour to previously prepared mono- and disubstituted cyclazines, several other small fractions, and a considerable amount of decomposition product. No attempt was made to isolate these products.

Reactions of cycl[3,3,3]azine dication dibromide

The dibromide was allowed to react with sodium cyanide and with sodium nitrite in several solvents (all dry and oxygen-free) and the reactions were followed by thin-layer chromatography. A brief summary is given.

a) (i)   Sodium cyanide in dimethylsulphoxide

Initial green solution fading to orange-brown and darkening during $\frac{1}{2}$ hr. T.L.C. indicated two faint red spots.

(ii)   Sodium nitrite in dimethylsulphoxide

Similar to above.

b) (i)   <u>Sodium cyanide in dimethylformamide</u>

      Initial blue solution darkening to deep brown within 10 mins.

T.L.C. showed only decomposition product.

  (ii)   <u>Sodium nitrite in dimethylformamide</u>

      Similar to above but darkening in 2 mins.

c) (i)   <u>Sodium cyanide in acetonitrile</u>

      No initial change in colour. Gradual darkening on standing.

T.L.C. showed only decomposition product.

  (ii)   <u>Sodium nitrite in acetonitrile</u>

      Gradual change through green to bright blue within 5 mins.

The solution was evaporated and benzene (10 ml.) and ethanol

(2 ml.) were added to the residual blue solid. After standing

overnight, an orange-brown precipitate formed, the u.v. spectrum

of which was rather similar to that of peropyrene (see Discussion).

ATTEMPTED PREPARATION OF ANIONIC SPECIES DERIVED

FROM CYCL[3,3,3]AZINE AND FROM

1,3-DICYANOCYCL[3,3,3]AZINE

Treatment of cycl[3,3,3]azine with sodium/potassium alloy

When a small amount of sodium/potassium alloy [197] was added to a solution of cycl[3,3,3]azine in dry oxygen-free tetrahydrofuran a gradual darkening occurred during 1 hr.   No strong colour such as might be expected from the anion or dianion was observed.

t-butyl quinolizin-4-ylidinecyanoacetate (159)

The method was the same as that used by Farquhar [139] for the reaction of 4-chloroquinolizinium perchlorate with diethyl malonate.

Reagents

t-butyl cyanoacetate [198]	4.10g.
50% oil dispersed sodium hydride	1.44g.
Tetrahydrofuran	70ml.
4-chloroquinolizinium perchlorate	4.00g.

The product was crystallised from methanol as yellow prisms.

$$\text{Yield} = 3.09g. \ (76\%)$$
$$\text{m.p.} = 184\text{-}185^\circ$$
$$\text{Mass spectrum } m/e = 268,212$$

$C_{16}H_{16}O_2N_2$ requires:-   C=71.64%; H=5.95%; N=10.45%

found:-   C=71.48%; H=5.87%; N=10.52%

ν_{max} (C=O)   = 1635 cm^{-1}, (CN) = 2220 cm^{-1}

λ_{max} (log E) EtOH = 211(4.40), 224(4.34), 294(4.03)

4.38nm(4.03).

Quinolizin-4-ylideneacetonitrile(160)

The compound was obtained from the preceeding product (2.0g.) essentially as described by Farquhar [139]   for the preparation of ethyl quinolizin-4-ylideneacetate. The following changes were made:-

The product was insufficiently soluble in carbontetrachloride, and was extracted with chloroform. It was purified by chromatography on deactivated alumina, eluting with chloroform to yield a single red band. Following evaporation of the solvent the dark red oil solidified on trituration.

Yield = 0.74g. (59%)

m.p. = 68-72° with decomposition

(On Kofler block preheated to 65°)

Mass spectrum m/e (parent) = 168

$C_{11}H_8N_2$ requires:-   C=78.57%; H=4.77%; N=16.70%; $M^{\oplus}$ 168.06875

found: C=78.67%; H=5.21%; N=16.00%; M 168.06847

ν_{max}(CN) = 2180 cm^{-1}

1,3-Dicyanocycl[3,3,3]azine (161)

The cyclazine was prepared essentially as described by Farquhar [139] for the reaction of ethyl quinolizin-4-ylidinacetate with ethyl propiolate. Alterations to this method are noted below.

Reagents

Quinolizin-4-ylideneacetonitrile   0.70g.

Cyanoacetylene [199]   0.30g.

Anhydrous potassium carbonate   0.2g.

The reaction product was chromatograohed on a column of 5% deactivated alumina, eluting with chloroform. The main fraction, a light yellow-brown

band, proved to be the required material. The product was crystallised from acetonitrile as fine red-purple needles

Yield = 205 mg. (23%)

m.p. = 270-273° (with decomposition)

Mass spectrum m/e (parent) = 217

$C_{14}H_7N_3$ requires:- C=77.41%; H=3.23%; N=19.35%

found:- C=77.04%; H=3.33%; N=19.09%

ν_{max} (CN) = 2230 cm^{-1}

λ_{max} (log E) EtOH = 205(4.15), 239i(3.83), 249i(3.88), 278s(4.57), 287(4.65), 402i(4.20), 425(4.23), 449nm(4.36).

Attempted preparation of 1,3-dicyanocycl[3,3,3]azine dianion

Sodium/potassium alloy was added to a solution of the cyclazine in tetrahydrofuran (freshly distilled over sodium hydride). No change of colour of the solution was observed, but the solution darkened slowly during several days. It appears that no anion or dianion of the cyclazine was formed.

PREPARATION OF DERIVATIVES OF 10b, 14b-DIAZONIAPEROPYRENE AND ATTEMPTED
PREPARATION OF THE PARENT SYSTEM

1,3,8,10-Tetraethoxycarbonyl-10b, 14b-diazoniaperopyrene dibromide [152]

Diethyl cycl[3,3,3]azine-1,3-dicarboxylate (240 mg.) in dry benzene (10 ml.)
was converted into the radical cation by the same method as used for the parent
system (see page 128). The flask was disconnected from the nitrogen line and
ethanol (ca. 1 ml.) added (Note 1). The flask was heated to boiling point in a
water bath with continuous swirling. Within a few seconds the blue precipitate
became bright red. The red solid was separated by centrifugation (Note 2) and
washed with benzene (the supernatant liquid being removed with a dropping
pipette after centrifuging) until the washings were no longer coloured. The
orange-red washings were retained. The product was dried in a vacuum desiccator
to give a fine red powder (206 mg.; 68%), no melting point below 350° then
gradual decomposition.

Mass Spectrum (parent) m/e = 618 (Note 3)

(see below for analysis of hexachloroantimonate)

ν_{max} (C=O) = 1715 cm^{-1}

λ_{max} (log E) = 204(4.57), 230i(4.43), 235(4.44), 291(4.58)

303s(4.45), 313s(4.37), 326i(4.14), 444s(4.39)

471(4.64), 510(4.49), 5.34s nm (3.74) in water

The orange-red benzene washings were evaporated and the residue was
separated by preparative thin-layer chromatography, eluting with chloroform
to give an orange-red band. The product obtained from this band crystallised
from ethanol as purple plates (27 mg.; 11%) decomposition 313-314° (block
preheated to 310°). This was identified by n.m.r. and mass spectroscopy as

tetraethyl 6,6´-bicycl[3,3,3]azinyl-1,1´,3,3´-tetracarboxylate (151)

$C_{36}H_{32}N_2O_8$ requires:-   C=69.68%;   H=5.16%;   N=4.52%; $M^{\oplus}$620

found:-   C=69.73%;   H=5.16%;   N=4.83%;   M 620

ν_{max} (C=O) =   1670 cm^{-1}

λ_{max}(log E) CH_2Cl_2 248(4.25),   295(4.88),   327s(4.00)

403(4.51),   484 nm (4.85.

Note 1   The red product was also formed in the absence of ethanol but less readily and in lower yield.

Note 2   The product was too finely-divided to be separated by filtration.

Note 3   The mass spectrum was obtained from the fluoroborate which was prepared by dissolving a little of the bromide in ca. 0.5 ml. water and adding an excess of fluoroboric acid.

1,3,8,10-Tetraethoxycarbonyl-10b, 14b-diazoniaperopyrene hexachloroantimonate

An excess of antimony pentachloride (2.5 equiv.) in dry benzene (2 ml.) was added dropwise to a stirred solution of the cyclazine (70 mg.) in dry benzene (10 ml.) (Note 1). The resulting blue suspension was treated with ethanol, heated and the red product formed, isolated as in the preceding experiment

Yield   =   100 mg. (69%)

ν_{max} (C=O) =   1715 cm^{-1}

$C_{36}H_{30}N_2O_8Sb_2Cl_{12}$ requires:-   C=33.54%;   H=2.33%;   N=2.17%

found:-   C=33.8%;   H=2.41%;   N=2.05%.

Note 1   With 1 equiv. of antimony pentachloride a less clean product is obtained and in slightly lower yield.

Tetraethyl 6,6-bicycl[3,3,3]azinyl-1,1´,3,3´-tetracarboxylate (151)

N-bromosuccinimide (130 mg., 1.2 equiv.) was added to a stirred solution of the cyclazine (300 mg.) in dry dichloromethane (10 ml.) with cooling to -78°. The deep blue colour, which appears initially, gradually changed to orange-brown when the reaction mixture was allowed to warm to room temperature. Stirring was continued for a further 10 mins. at room temperature and the solution was concentrated and chromatographed on a column of 10% deactivated alumina eluting with benzene.

The first fraction consisted of recovered cyclazine (10 mg.).

The second fraction, an orange band on the column, was shown (i.r., n.m.r., m.p. $271-273^{\circ}$ with decomposition) to be identical with the sample obtained as a minor product in the reaction with bromine

$$Yield = 167 \text{ mg. } (58\%).$$

Conversion of the preceding product into 1,3,8,10-tetraethoxycarbonyl-10b, 14b-diazoniaperopyrene dibromide (152)

The apparatus and method used were the same as in the preparation of the diazoniaperopyrene from the diethoxycarbonylcyclazine. Again an initial blue precipitate was formed which, on being heated to the boiling point with ethanol, changed to bright red.

$$Yield = 20 \text{ mg. } (\text{from } 27 \text{ mg. cyclazinyl})$$

The product was shown (i.r., u.v., n.m.r.) to be identical with the specimen obtained directly from the 1,3-diethoxycarbonyl cyclazine.

PREPARATION AND REACTIONS OF CYCL[3,3,2]AZINIUM PERCHLORATE

Reaction of quinolizinium bromide with dimethylacetylenedicarboxylate in the presence of sodium hydride.

Sodium hydride (0.25g., 50% oil dispersion) was added, in small portions, to a stirred solution of quinolizinium bromide (1.0 g.) and dimethylacetylene-dicarboxylate in dimethylformamide (30 ml., freshly distilled over sodium hydride) under nitrogen and with cooling in an ice-bath. The initially red solution darkened rapidly to deep red-brown. Stirring was continued for 30 mins. in ice and 2 hrs. at room temperature. The solvent was removed at the oil pump, water (50 ml.) was added to the dark residue, and the solution was extracted with chloroform. The extract was dried and concentrated, but thin-layer chromatography indicated only several weak red or red-brown bands and a considerable amount of dark immobile decomposition product.

Reaction of cycl[3,3,2]azin-1-one with phosphorus pentasulphide

Phosphorus pentasulphide (2 g.) was added to a solution of the cyclazinone (81) (1.0 g.) in dry benzene (100 ml.) in a 250 ml. flask (Note 1) fitted with a condenser and a calcium chloride drying tube, and the reaction mixture was refluxed for $2\frac{1}{2}$ hrs. The resulting red-purple solution was decanted from the insoluble residue and the reaction flask was rinsed with hot benzene (50 ml.). The combined solutions were concentrated (Note 1) and chromatographed on a column of deactivated alumina eluting with chloroform. A blue, light-sensitive band was eluted first. The blue solution was treated with an excess of methyl iodide and concentrated to yield a light-brown solid (65 mg.; 3.5%, or 5% based on unrecovered ketone). This was shown (n.m.r., i.r., mass spectroscopy) to be 1-methylthiocycl[3,3,2]azinium iodide, by comparison with a sample of the perchlorate prepared later by a different route (see below).

The second red band was shown to be recovered ketone (240 mg.)

Note 1   The thione is very unstable to light, and must at all times be carefully protected. All flasks and columns were wrapped in aluminium foil.

Reaction of cycl[3,3,2]azin-1-one with N,N-dimethylthiocarbamoyl chloride

a) In dimethylformamide

N-methylmorpholine (0.23 g., 2 equiv.) and N,N-dimethylthiocarbamoyl chloride (0.2 g., 1.5 equiv.) were added to a stirred solution of the cyclazinone (0.2 g.) in dry dimethylformamide, and the solution was heated to 70-80° for 40 mins. During this time the solution became deep blue-purple. The solvent was removed at the oil-pump, and the residue was dissolved in an aqueous solution of sodium sulphide nonahydrate (2g.). The solution was extracted with chloroform, and the extract was dried, concentrated, and chromatographed on deactivated alumina eluting initially with chloroform and later with chloroform/methanol (10:1). Most of the material remained at the top of the column as a blue-grey band, and only a few weak diffuse blue or blue-purple bands moved down the column. It was clear that even if one of these bands was the required thione, the yield would be very poor.

b) In dichloromethane

A reaction on a similar scale was attempted in dry dichloromethane. The product was worked up in an analogous manner, but again none of the required thione was isolated.

Preparation of sodium sulphide (or sodium hydrogen sulphide)

Sodium hydroxide (20 g.) was dissolved in abs. ethanol (300 ml.) and dry hydrogen sulphide passed into the solution until it was saturated. Dry ether (800 ml.) was added, and the white precipitate of sodium sulphide (or sodium hydrogen sulphide) was filtered off, washed with ether, and stored in a desiccator.

(

Reaction of cycl[3,3,2]azin-1-one with thiophosphoryl chloride

Thiophosphoryl chloride [200] was added dropwise to a stirred solution of the cyclazinone (0.28 g.) in dry dichloromethane (30 ml.) until no red colour remained in the solution. The solvent was evaporated under vacuum to leave a yellow solid (0.405 g.) which could not be identified. Dry dimethylformamide (30 ml.) was added but even with warming only a partial solution could be achieved. The solution was treated with an excess of sodium sulphide in dry dimethylformamide and the resulting blue solution was filtered. The filtrate was treated with an excess of methyl iodide, followed by ether (15 ml.), and the resulting yellow-brown precipitate (0.32 g.) was filtered off. (The i.r. spectrum of this solid was very similar to that of the original yellow solid isolated from the dichloromethane). The solid was heated with acetic acid (50 ml.) but only a small amount dissolved. The insoluble portion was separated by filtration and the filtrate treated with an excess of perchloric acid, concentrated under vacuum and treated with ether. A bright yellow solid (22 mg., 4.5%) was precipitated and was shown (n.m.r., i.r., m.p. 224-227°) to be identical with a specimen of 1-methylthiocycl[3,3,2]azinium perchlorate prepared as described later.

Reaction of 2-ethoxycarbonyl[3,3,2]azin-1-one with thiophosphoryl chloride

Thiophosphoryl chloride (0.7 g., 1.2 equiv.) was added to a stirred solution of the ethoxycarbonylcyclazinone (1.0 g.) in dry dimethylformamide (50 ml.). The fluorescent, yellow-orange solution faded to pale yellow during 10 mins. Sodium sulphide was added, until, as far as could be seen, no yellow colour remained and the solution had become a dull red. With continued stirring an excess of methyl iodide was added and the product was precipitated by addition of ether

(150 ml.), filtered off and washed with ether. After drying in a vacuum desiccator the red-brown solid was dissolved in hot acetic acid (40 ml.) an excess of perchloric acid was added, and the perchlorate was precipitated by cooling and addition of ether (100 ml.). The product was crystallised as orange-brown needles from ethanol (containing a trace of perchloric acid)

Yield = 0.51 g. (32%).

This was shown (n.m.r., i.r., m.p. 233-236°) to be identical with a specimen of 2-ethoxycarbonyl-1-methylthiocycl[3,3,2]azinium perchlorate prepared as described later.

Reaction of 2-ethoxycarbonylcycl[3,3,2]azin-1-one with phosphoryl chloride

The reaction was carried out using the same experimental conditions as in the preceding reaction. During the reaction the only difference observed was that the initial fluorescent yellow-orange colour of the cyclazinone faded much faster than previously.

Reagents

Cyclazinone	0.30 g.
Phosphoryl chloride	0.16 g.
Dimethylformamide	20 ml.

A dark orange-brown solid was obtained

Yield = 0.070 g.

The i.r. spectrum of the product, while not dissimilar to that of 2-ethoxycarbonyl-1-methylthiocyclazinium perchlorate, nonetheless showed differences that could not be accounted for on the basis of impurities. It was thus inferred that the required product had not been obtained. This was confirmed by an n.m.r. spectrum (see discussion).

2-Ethoxycarbonyl-1-methylthiocycl[3,3,2]azinium perchlorate

Phosphorus pentasulphide (3.0 g.) was added to a solution of the 2-ethoxycarbonylcycl[3,3,2]azinone (2.0 g.) in chloroform (150 ml.) (Note 1), and the mixture warmed to 40° with stirring. After 20 mins. more phosphorus pentasulphide (2 g.) was added, and stirring was continued at 40°, for a further 30 mins. The chloroform solution was decanted and kept, and the light brown residue was treated with a solution of sodium sulphide nonahydrate (10 g.) in water (100 ml.). The aqueous solution was stirred until all the residue (which consisted of excess phosphorus pentasulphide and thione) had dissolved. The dark solution was transferred to a separating funnel, the chloroform previously decanted was added, and, after shaking, the deep blue organic extract was separated. The aqueous layer was extracted, with more chloroform (5 x 100 ml.), the earlier fractions containing most of the blue thione (Note 2), and the later ones the more water soluble fluorescent yellow ethoxycarbonylcyclazinone. The organic extracts were combined, and, without drying, concentrated under vacuum and chromatographed on a column of deactivated alumina eluting with chloroform. The first fraction, an intense blue band consisting of the thione, was evaporated under vacuum, dissolved in benzene (300 ml.) and stirred with an excess of methyl iodide at $30-35^{\circ}$ for 4 hrs. The resulting solution containing a light brown precipitate, was concentrated under vacuum to ca. 50 ml., ether (100 ml.) was added, and the brown solid was filtered off, washed with ether, and dried in a vacuum desiccator. The dry solid (ca. 2.2 g.) was dissolved in hot acetic acid (50 ml.) and treated with an excess of perchloric acid. The solution was cooled, and the salt precipitated by addition of ether (100 ml.). The 2-ethoxycarbonyl-1-methylthiocycl[3,3,2]azinium perchlorate (167) (2.03 g.; 82%) was filtered off, washed thoroughly with

ether, and recrystallised as orange-brown needles from ethanol (containing a trace of perchloric acid), m.p. 234-237°.

$C_{15}H_{14}NO_6ClS$ requires:-   C=48.45%;   H=3.77%;   N=3.77%

found:-   C=48.57%;   H=3.88%;   N=3.80%

ν_{max} (C=O)   = 1700 cm^{-1}

λ_{max} (log E)   231(4.63),   301(3.90),   358(3.67),   436 nm(3.83)

in ethanol containing 2% $HClO_4$

Note 1   No attempt was made to remove ethanol from the chloroform.

Note 2   The ethoxycarbonylthione, while considerably less sensitive to light than the unsubstituted thione, should nonetheless be protected from strong light, particularly during chromatography.

2-Carboxy-1-methylthiocycl[3,3,2]azinium perchlorate

Ethoxycarbonylmethylthiocyclazinium perchlorate (3.9 g.) was heated under reflux with 6N hydrochloric acid (200 ml.) for $1\frac{1}{4}$ hrs. The solvent was evaporated under reduced pressure and the residue was dried by twice adding benzene (100 ml.) and re-evaporating. The product was dissolved in hot acetic acid (50 ml.) containing a trace of perchloric acid, and the salt was reprecipitated by cooling and adding ether (150 ml.). Recrystallising from ethanol containing a trace of perchloric acid gave 2-carboxy-1-methylthiocycl[3,3,2]azinium perchlorate (168) (2.8 g., 78%) as fine yellow needles, m.p. 223-236°.

$C_{13}H_{10}NO_6ClS$ requires:-   C=45.41%;   H=2.91%;   N=4.08%;   M,244

found:-   C=45.34%;   H=2.90%;   N=4.17%;   M$^{\oplus}$, 244

ν_{max} (C=O)   = 1705 cm^{-1}

λ_{max} (log E)   230(4.61),   300(3.87),   357(3.66),   436 nm (3.81)

in ethanol containing 2% $HClO_4$.

1-Methylthiocycl[3,3,2]azinium perchlorate

Dry redistilled N,N-dimethylacetamide (200 ml.) was heated briefly under reflux in a stream of nitrogen. The solvent was cooled and 2-carboxy-1-methylthiocycl[3,3,2]azinium perchlorate (3.4 g.) and freshly prepared cuprous oxide (2 g.)[202] were added. With a continued flow of nitrogen, and occasional vigorous swirling, the solvent was heated to boiling point and refluxed for 8 mins., during which time the solution changed colour from orange-brown to green. The solvent was removed at the oil pump, and the dark residue crystallised from ethanol (500 ml.) containing a trace of perchloric acid to give 1-methylthiocycl[3,3,2]azinium perchlorate (164) (1.74 g., 59%), as light green needles m.p. 225-227°.

$C_{12}H_{10}NO_4ClS$ requires:- C=48.08%; H=3.34%; N=4.67%; M, 200

found:- C=48.03%; H=3.42%; N=4.92%; M$^{\oplus}$, 200

λ_{max} (log E) 226(4.66), 300(3.88), 319s(3.69), 347i(350),

428 nm (3.79) in ethanol containing 2% $HClO_4$.

Raney-Nickel

Prepared by a variation of the method of Mozingo[203]

Nickel-aluminium alloy (80 g.) was added, in small portions, with efficient stirring, to a solution of sodium hydroxide (200 g.) in water (200 ml.) in a 500 ml. conical flask cooled to 10° in an ice-bath. The alloy was added at such a rate that the temperature remained below 20° during about 40 mins. The ice-bath was removed and the temperature allowed to rise gradually. After a further 20 mins. the temperature was raised slowly such that within a further 2 hrs. it had reached 90°. The temperature was held in this region for 7-8 hrs., by which time the

evolution of hydrogen had become slow. The washing procedure, detailed below, was carried out on the same day. The cooled solution was decanted, and the Raney-Nickel was washed with water into a 1 l. measuring cylinder which was filled and then stirred vigorously for a short time. The Raney-Nickel was allowed to settle, the water decanted, and the process repeated 12-15 times to remove all traces of alkali. The Raney-Nickel was washed with 3x300 ml. comm. ethanol, and stored under ethanol in a tightly stoppered, completely filled flask, in a refrigerator (ca. -5°). This Raney-Nickel corresponds to approximately W-2 specification.

Cycl[3,3,2]azinium perchlorate

Freshly prepared Raney-Nickel (Note 1) (ca. 2 g.) was washed with acetone (3x50 ml.) by decantation, and then refluxed in acetone for 1 hr. with occasional swirling. After being washed three times with ethanol, the deactivated Raney-Nickel was left under ethanol (50 ml.), and the methylthiocyclazinium perchlorate (200 mg.) was added. The solution was heated under reflux with frequent vigorous swirling until the green colour of the solution faded to pale-green or grey. (Generally about 10-15 mins., depending upon the freshness of the Raney-Nickel). A few drops of perchloric acid were added, and, while still warm, the solution was filtered, and the Raney-Nickel washed with acetone (Note 2). The pale-green filtrate was concentrated to yield a light grey solid which was crystallised from acetic acid to yield cycl[3,3,2]azinium perchlorate (91 mg., 52%), decomp. 284-285° (Kofler block preheated to 280°). No satisfactory elemental analysis was obtained.

M^+ (mass spectrum) 154.06625; $C_{11}H_8N$ requires M, 154.06567

λ_{max} (log E), 229(4.73), 270(3.96), 2.82i(3.82), 296i(3.61), 335 nm(3.78).

Note 1 The Raney-Nickel gradually becomes less active and is best used within 3-4 days of preparation. After about a week it becomes noticably less active, and will require boiling with acetone for a shorter period. For example, 9 day old Raney-Nickel was refluxed in acetone for 25 mins. and the reaction time was increased to 20 mins.

Note 2 Raney-Nickel is pyrophoric and must not be allowed to become dry. After use it should be washed down the sink with plenty of water.

Attempted reaction of cycl[3,3,2]azinium perchlorate with isoprene

Cycl[3,3,2]azinium perchlorate (64 mg.) and isoprene (85 mg., 3 equiv.) in acetic acid (3 ml.) were sealed under vacuum in a thick-walled glass tube and heated at 150-155° for 18 hrs. The tube was cooled, opened, and the product obtained as a light-brown solid (45 mg.) by crystallisation from acetic acid. This material was shown (n.m.r., i.r., mass spec.) to be recovered starting material.

Attempted reduction of cycl[3,3,2]azinium perchlorate
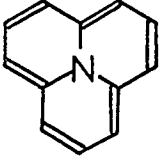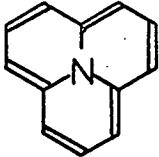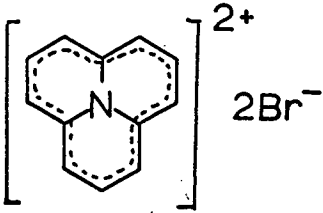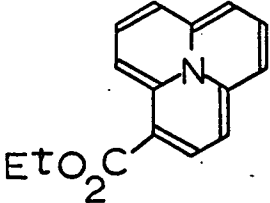
An excess of a solution of hydrazine hydrate (60 mg., 3 equiv.) in water (1 ml.) was added dropwise to an aqueous solution of the cyclazine (58 mg.) containing copper sulphate (5 mg.) in the presence of oxygen. An immediate formation of a blue-grey precipitate took place which changed to brown in 5 mins. After stirring for 1 hr., the solution was evaporated to dryness and the residue was crystallised from acetic acid. A light-brown solid was obtained (40 mg.) which was shown (n.m.r., i.r., mass spec.) to be recovered starting material.
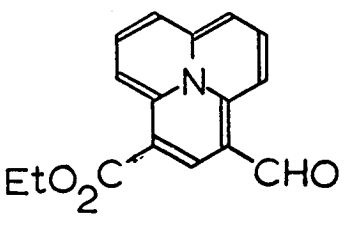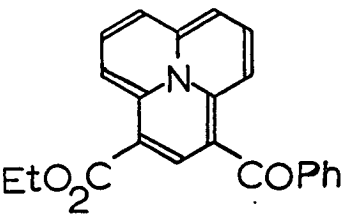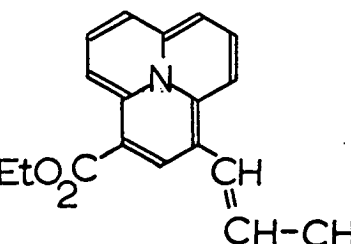
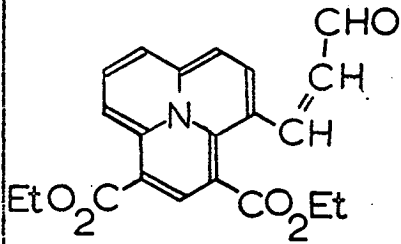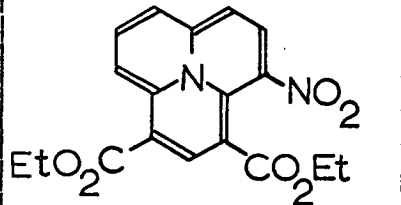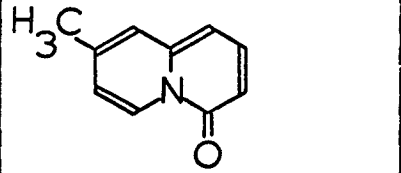## Reaction of cycl[3,3,2]azinium perchlorate with sodium sulphide

Cycl[3,3,2]azinium perchlorate (70 mg.) was dissolved in dimethylformamide (5 ml.) and a saturated aqueous solution of sodium sulphide (5 ml.) was added gradually with stirring (Note 1). A
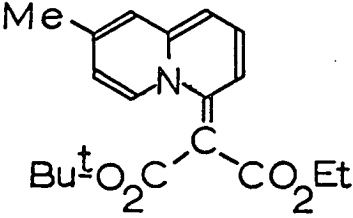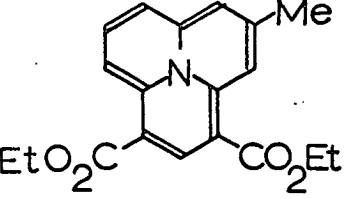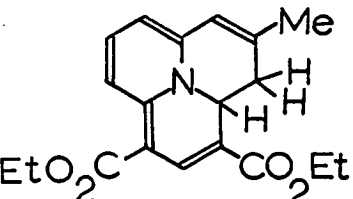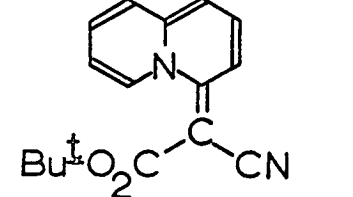
deep purple colour was immediately formed. After stirring for 5 mins.,

water (50 ml.) was added, and the thione was extracted with chloroform.

Without drying the combined organic extracts were concentrated on a rotary

evaporator at room temperature, and chromatographed on deactivated alumina,

eluting with chloroform. The deep blue eluate was treated with an excess

of methyl iodide and the resulting pale-yellow solution was evaporated

to dryness. The residue was taken up in the minimum of hot acetic acid

and converted to the perchlorate by addition of excess perchloric acid.

By cooling and stirring with ether, the product was obtained as a yellow

solid (10 mg., 11%). The product was identified (n.m.r., mass spec.) as

either 3- or 5-methylthiocycl[3,3,2]azinium perchlorate.

Nuclear magnetic resonance spectra were measured at 100 Mc./Sec. with reference to tetramethylsilane as internal standard. All spectra were integrated. Chemical shifts are given as T-values and coupling constants are measured in c/sec. d = doublet, t = triplet, q = quarter, m = multiplet, Ar = aromatic
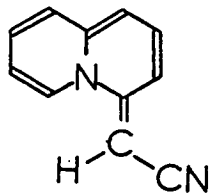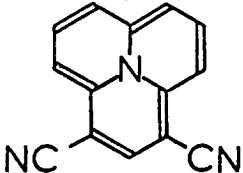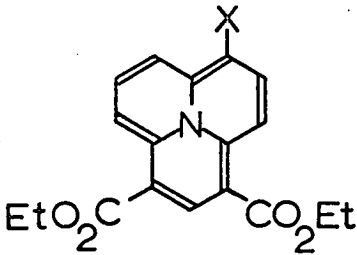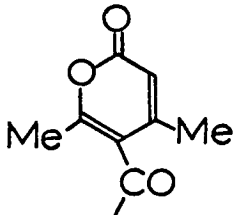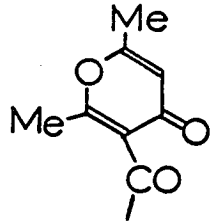
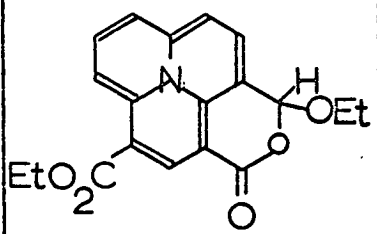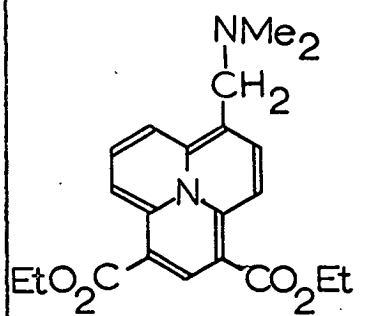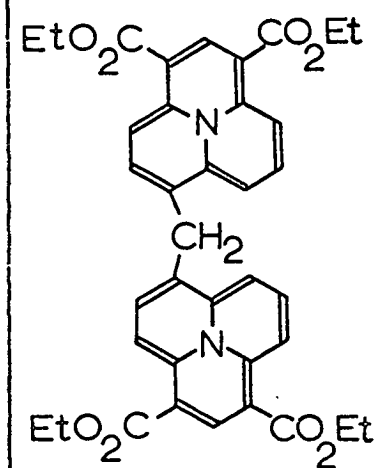| Structure	Solvent	Chemical Shifts	J
(tricyclic amine structure)	C_6H_6	1-H, 3-H, 4-H, 6-H, 7-H and 9-H, 7.95d : 2-H, 5-H and 8-H, 6.42t.	$J_{1,2}=J_{2,3}$ $=7.9$
(tricyclic amine structure)	C_2Cl_4	1-H, 3-H, 4-H, 6-H, 7-H and 9-H, 7.955d : 2-H, 5-H and 8-H, 6.366t.	$J_{1,2}=J_{2,3}$ $=7.9$
(tricyclic dication structure) $[\ldots]^{2+}$ $2Br^-$	D_2SO_4	1-H, 3-H, 4-H, 6-H, 7-H and 9-H, -0.47d : 2-H, 5-H and 8-H, 0.27t.	$J_{1,2}=J_{2,3}$ $=8.0$
(tricyclic amine structure with EtO_2C substituent)	$CDCl_3$	2-H, 4.40d: 3-H, 6.44d: 4-H, 5.69d[a]: 5-H, 4.73t: 6-H, 6.10d[a]: 7-H, 5.65d[a]: 8-H, 4.49t: 9-H, 3.94d[a]: ester-H, 6.16q(CH_2), 8.93t(CH_3).	$J_{2,3}=9.4$ $J_{4,5}=J_{5,6}$ $=7.7$ $J_{7,8}=J_{8,9}$ $=8.5$ $J_{4,6}=J_{7,9}$ $=1.5$

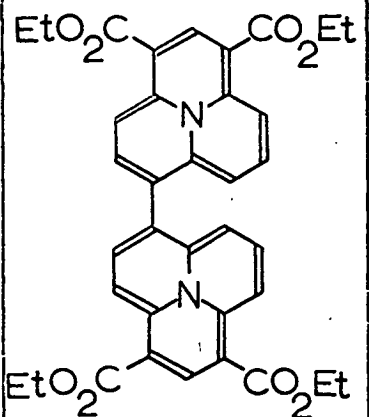| Structure	Solvent	Chemical Shifts	J
EtO$_2$C ... CHO	CDCl$_3$	formyl-H, 1.45s: 2-H, 3.15s: 4-H, 2.59d: 5-H and 8-H, 3.57t[b]: 6-H, 7-H, 4.28d[a,c], 4.32d[a,c]: 9-H, 2.78d: ester-H, 5.98q(CH$_2$), 8.81t(CH$_3$).	$J_{4,5}=J_{5,6}$ $=8.0$ $J_{7,8}=J_{8,9}$ $=8.3$ $J_{4,6}=J_{7,9}$ $=1.5$.
EtO$_2$C ... COPh	CDCl$_3$	Ar-H, 2.55-2.75 m: 2-H, 3.07s: 4-H, 2.54d[a]: 5-H, 8-H, 3.61t[d], 3.66t[d]: 6-H, 7-H, 4.37d[a,e], 4.44d[a,c]: 9-H, 3.00d[a]: ester-H, 6.11q(CH$_2$), 9.00t (CH$_3$).	$J_{4,5}=J_{5,6}$ $=J_{7,8}=J_{8,9}$ $=8.2$ $J_{4,6}=J_{7,9}$ $=1.5$.
EtO$_2$C ... CH CH-CHO	CDCl$_3$	2-H, 3.34s: 4-H, 6-H, 7-H, 4.75d[a,f], 4.80d[a,f], 4.86d[a,f]: 5-H, 8-H, 3.87t[a,g], 3.94t[a,g]: 9-H, 3.26d[a]: aldehyde-H, 0.71d: α-H, 4.01q: β-H, 3.70d.	$J_{4,5}=J_{5,6}$ $=J_{7,8}=J_{8,9}$ $=8.2$ $J_{4,6}=J_{7,9}$ $=1.5$ $J_{ald,\alpha}=7.2$ $J_{\alpha,\beta}=15.2$.
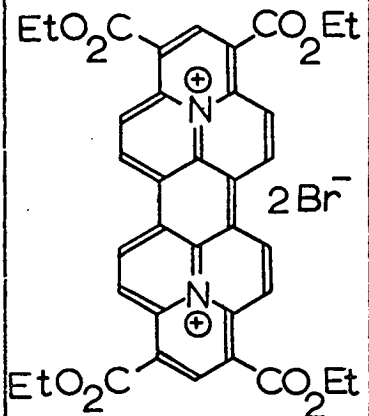
Structure	Solvent	Chemical Shifts	J
	CDCl$_3$	2-H, 2.21s: 5-H, 3.28d: 6-H, 4.20d: 7-H, 4.06d^a: 8-H, 3.23t: 9-H, 2.48d^a: Acetyl-H, 0.69d: α-H, 3.68q: β-H, 4.07d: ester-H, 6.03q (CH$_2$), 6.07q(CH$_2$), 8.71t(CH$_3$), 8.73t(CH$_3$)	$J_{5,6}$=9.0 $J_{7,8}$=8.0 $J_{8,9}$=8.4 $J_{7,9}$=1.5 $J_{acetyl,\alpha}$=7.4 $J_{\alpha,\beta}$=15.0.
	CDCl$_3$	2-H, 2.13s: 5-H, 2.81d: 6-H, 4.52d: 7-H, 3.99d^a: 8-H, 3.11t^h: 9-H, 2.25d^a: ester-H, 5.78q(CH$_2$), 5.82q (CH$_2$), 8.71t(CH$_3$), 8.77t(CH$_3$):	$J_{5,6}$=9.6 $J_{7,8}$=7.6 $J_{8,9}$=8.7 $J_{7,9}$=1.5.
	CDCl$_3$	1-H and 3-H, 3.47d: 2-H, 2.38t: 6-H, 0.93d: 7-H, 3.15d^a: 9-H, 2.75s^i: methyl-H, 7.62s.	$J_{1,2}$=$J_{2,3}$ = 8.5 $J_{6,7}$= 7.5 $J_{7,9}$≈1.
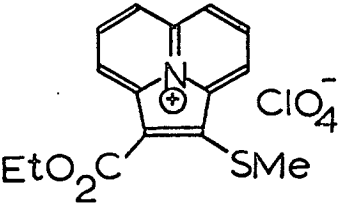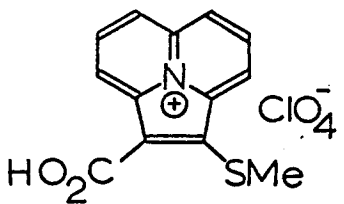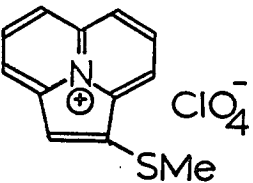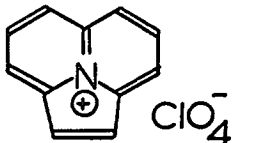
Structure	Solvent	Chemical Shifts	J
	CDCl$_3$	1-H, 2.71d[a,j]: 2-H, 2.13t[k]: 3-H, 2.03d[a,k]: 6-H, 1.05d[l]: 7-H, 2.46d[a]: 9-H, 2.34s[l]: Methyl-H, 7.43s: ester-H, 5.65q(CH$_2$), 8.61s(Bu[t]), 8.75t(CH$_3$)	$J_{1,2}=J_{2,3}$ $=8.0$ $J_{6,7}=7.5$ $J_{1,3}=2.0$ $J_{7,9}=2.4$.
	CDCl$_3$	2-H, 2.67s: 4-H, 3.22s[a,m]: 6-H, 4.76s[a,m]: 7-H, 4.69d[a]: 8-H, 3.84t: 9-H, 3.24d[a]: methyl-H, 8.35s: ester-H, 5.99q(CH$_3$), 8.82t(CH$_3$).	$J_{7,8}=J_{8,9}$ $=8.3$ $J_{7,9}=1.6$ $J_{4,6}\cong 1.5$.
	CDCl$_3$	2-H, 2.10s: 3a-H, 4.39d[a]: 4α-H, 7.55q 4β-H, 6.75d[a]: 6-H, 3.95s[a]: 7-H, 3.77d[a]: 8-H, 2.79q: 9-H, 1.37d[a]: methyl-H, 8.00s: ester-H, 5.81q (CH$_2$), 8.70t(CH$_3$)	$J_{3a,4\alpha}=$ 11.6 $J_{3a,4\beta}=$ 2.8 $J_{4\alpha,4\beta}=$ 18 $J_{7,8}=7.5$ $J_{8,9}=9.3$ $J_{7,9}\cong 1$.
	CDCl$_3$	1-H, 2-H, 7-H, 8-H and 9-H, 2.14- 2.51 m: 3-H, 1.95d[a]: 6-H, 1.59d[a]: ester-H, 8.46s(Bu[t]).	$J_{2,3}=8.4$ $J_{6,7}=7.3$ $J_{2,4}=1.6$ $J_{6,8}=1.0$.
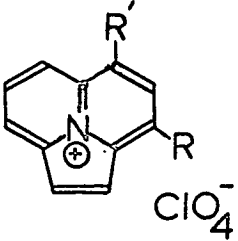
Structure	Solvent	Chemical Shifts	J
	CDCl$_3$	1-H, 2-H, 3-H, 6-H, 7-H, 8-H and 9-H, 2.46-3.64 m: aceto-H, 6.5s.	
	D.M.S.O (100°)	2-H, 4.20s: 4-H and 9-H, 4.71d[a]: 5-H and 8-H, 3.87t: 6-H and 7-H, 5.20d[a]:	$J_{4,5}=J_{8,9}$ $=8.4$ $J_{5,6}=J_{7,8}$ $=7.7$ $J_{4,6}=1.5$
	CDCl$_3$	2-H, 2.51s: 4-H, 5-H, 3.35d, 3.59d: 7-H, 2.65d[a]: 8-H, 3.29t: 9-H, 2.03d[a]: pyrone-H, 3.92s: methyl-H, 7.78s, 7.84s: ester-H, 5.88q(CH$_2$), 5.92q (CH$_2$), 8.76t(CH$_3$), 8.79t(CH$_3$).	$J_{4,5}=9.3$ $J_{7,8}=J_{8,9}$ $=7.5$ $J_{7,9}=1.7.$

Structure	Solvent	Chemical Shifts	J
	$CDCl_3$	1-H, 4.77s: 4-H, 2.92s: 6-H, 3.05d[a]: 7-H, 3.71t: 8-H, 4.54d[a]: 9-H, 4.68d: 10-H, 3.94d: ethoxy-H, 6.05q[n], 6.14q[o], 6.45q, 6.54q(CH_2) 8.84t[p](CH_3): ester-H, 6.01q(CH_2), 8.81t[p](CH_3).	$J_{5,6}=8.8$ $J_{7,8}=8.2$ $J_{8,9}=8.4$ $J_{7,9}\simeq 1$
	$CDCl_3$	2-H, 2.77s: 4-H, 3.23d: 5-H, 3.86d: 7-H, 4.28d[a]: 8-H, 3.65t: 9-H, 3.05d[a] methylene-H, 7.46s: methyl-H, 7.89s: ester-H, 5.99q(CH_2), 8.82t (CH_3).	$J_{4,5}=8.4$ $J_{7,8}=J_{8,9}$ $=8.4$ $J_{7,9}=1.5.$
	$CDCl_3$	2,2´-H, 2.81s: 4,4´-H, 3.27d: 5,5´-H, 3.97d: 7,7´-H, 5.03d[a]: 8,8´-H, 3.73t: 9,9´-H, 3.11d[a]: methylene-H, 8.16s: ester-H, 5.97q (CH_2), 8.80t(CH_3).	$J_{4,5}=8.4$ $J_{7,8}=J_{8,9}$ $=8.4$ $J_{7,9}\simeq 1.$

Structure	Solvent	Chemical Shifts	J
	$CDCl_3$	2,2´-H, 2.89s: 4,4´-H, 3.40d: 5,5´-H, 4.20d: 7,7´-H, 4.77d[a]: 8,8´-H, 3.77t: 9,9´-H, 3.22d[a]: ester-H, 5.96q(CH_2), 8.80t(CH_3)	$J_{4,5}=8.3$ $J_{7,8}=J_{8,9}$ $=8.5$ $J_{7,9}=1.5$
	D.M.S.O.	2-H and 9-H, 0.31s: 4-H, 7-H, 11-H, and 14-H, -0.31d: 5-H, 6-H, 12-H and 13-H, 0.38d: ester-H[q], 5.25q(CH_2).	$J_{4,5}=J_{6,7}$ $=J_{11,12}$ $=J_{13,14}=10.0$

Structures	Solvent	Chemical Shifts	J
	T.F.A.	3-H, 4-H, 5-H, 6-H, 7-H, and 8-H, 0.60-1.20 m: methyl-H, 6.86s: ester -H, 5.21q(CH_2), 8.33t(CH_3).	
	T.F.A.	3-H, 4-H, 5-H, 6-H, 7-H and 8-H, 0.57-1.17 m: methyl-H, 6.81s.	
	T.F.A.	2-H, 2.10s: 3-H, 4-H, 5-H, 6-H, 7-H and 8-H, 0.98-1.40 m: methyl-H, 7.10s.	
	T.F.A.	1-H and 2-H, 1.61s: 3-H, 4-H, 5-H, 6-H, 7-H and 8-H, 0.96-1.17 m.	$J_{1,2}=$ 5.4$\pm$.2.

Structures	Solvent	Chemical Shifts	J
either R=SMe R′= H or R=H R′=SMe	T.F.A.	1-H, 1.60s: 2-H, 1.81s: 4-H, 5-H, 6-H, 7-H and 8-H <u>or</u> 3-H, 4-H, 6-H, 7-H and 8-H, 1.06-1.39 m Methyl-H, 7.00s.	$J_{1,2}=$ 5.4±0.1

a   –   Further split by coupling to a <u>meta</u>-proton.

b   –   The 5-H and 8-H triplets are superimposed.

c   –   The doublets at 4.28T and 4.32T are partially superimposed.

d   –   The assignment of the 5- and 8-protons is uncertain.

e   –   The assignment of the 6- and 7-protons is uncertain.

f   –   The assignment of the 4-, 6- and 7-protons is uncertain.

g   –   The assignment of the 5- and 8-protons is uncertain.

h   –   The triplet shows some signs of further splitting.

i   –   The singlet from the 9-proton is broadened coupling to a <u>meta</u>-proton.

j   –   The doublet is partially obscured by the chloroform peak.

k   –   The signals due to the 2- and 3-protons show partial overlapping and distortion.

l   –   The 6- and 9-proton signals are broadened by further coupling.

m   –   The signals arising from the 4- and 6-protons are partially obscured by those from the 9- and 7-protons. The 6-proton shows signs of <u>para</u>-coupling of 0.7 c/s.

n   –   This quartet is completely obscured.

o   –   This quartet is partially obscured.

p   –   The assignment of these triplets is uncertain.

q   –   Methyl triplet obscured by solvent peak.

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ABSTRACT OF THESIS

Name of Candidate ..... Thomas T. Gough

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Degree ..... Doctor of Philosophy ..... *Date* ..... June 1972.

Title of Thesis ..... Heterocyclic Compounds containing Nitrogen Bridgehead Atoms

SUMMARY

Attempts to find a synthesis of quinolizin-4-one more convenient than the previously used route were only partially successful. Although an alternative route was found, the yield was low.

Attempts to obtain derivatives of aza-, oxa- and thiacycl[4,3,3]azines, 10b-azoniapyrene 6H-10b-azapyren-6-one and benzo [a] cycl[3,3,3]-azine from diethyl cycl[3,3,3]azine-1,3-dicarboxylate were unsuccessful.

The chemical shift of the methyl protons in the n.m.r. spectra of diethyl 4-, 5- and 6-methyl cycl[3,3,3]azine-1,3-dicarboxylates should give some indication of the strength of the induced paramagnetic ring current in the ring system. Various attempts to prepare the 4- and 6-methyl derivatives from the diethoxycarbonyl-cyclazine were mainly unsuccessful, though the 6-methyl derivative might possibly have been obtained in one experiment. The 5-methyl derivative was prepared by total synthesis and its n.m.r. spectrum indicated a weak paramagnetic ring current.

Oxidation of diethyl cycl[3,3,3]azine-1,3-dicarboxylate gave a tetraethoxycarbonyl derivative of 10b,14b-diazoniaperopyrene which was shown to be aromatic in nature.

Electrophilic substitution reactions with ethyl cycl[3,3,3]azine-1-carboxylate led to reaction at the 3-position. Attempted addition and oxidation reactions yielded no identifiable products. A further investigation of the properties of cycl[3,3,3]azine was carried out. No identifiable products were obtained from attempted addition and electrophilic substitution reactions but oxidation gave cycl[3,3,3]azine cation and dication.

Use other side if necessary.

An e.s.r. spectrum of the cation was obtained, and an interpretation is given. The very low-field values of the proton chemical shifts of the dication gave clear indication of an induced diamagnetic ring current. Attempts to prepare the parent 10b,14b-diazoniaperopyrene dication were unsuccessful, as were attempts to prepare anionic derivatives of cycl[3,3,3]azine and its 1,3-dicyano derivative.

Cycl[3,3,2]azinium perchlorate was prepared from the previously known 2-ethoxycarbonylcycl[3,3,2]azin-1-one. The n.m.r. spectrum of the cation indicated an induced diamagnetic ring current but the vicinal coupling constant for the protons of the five-membered ring indicated considerable double bond character in the 1,2-bond. Attempted addition reactions, however, .. failed to reveal double bond reactivity. A nucleophilic substitution/was achieved reaction by treatment of the cation with sodium sulphide.