

HETEROCYCLIC COMPOUNDS WITH BRIDGEHEAD NITROGEN ATOMS

by

DAVID FARQUHAR, B.Sc.

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TO MY PARENTS

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SUMMARY

The object of this research was to synthesise cycl[3.3.3]azine - a 12π peripheral-conjugated member of the cyclazine series of heterocyclic compounds - and to investigate its chemical properties. Three approaches to the ring-system have been investigated.

1. Attempts were made to effect selective fission of the 1,2-bond of cyclopenta[c,d]cycl[3.3.3]azines using a variety of 'double-bond' reagents. Decomposition product was formed from these reactions which suggested that the reaction intermediates (possibly cycl[3.3.3]azines) were more susceptible to attack by the reagents than the initial cyclazines.

2. A previously projected synthetic route from diethyl 6-methylquinolizin-4-ylidenemalonate has been attempted. The latter compound, together with methyl 6-methylquinolizin-4-ylidenecyanoacetate has been synthesised but attempts to convert them into cyclazines by base-catalysed intramolecular cyclisation has led, in most instances, to the formation of decomposition product.

A reported synthesis of diethyl quinolizin-4-ylidenemalonate is shown to be erroneous.

3. Reaction has been effected between electrophilic acetylenes and several alkyl quinolizin-4-ylideneacetates. The latter compounds were prepared by selective hydrolysis and decarboxylation

of one of the ester groups of dialkyl quinolizin-4-ylidenemalonates. A series of cyclazine derivatives has been prepared and proof of the ring-system has been obtained. Structures are proposed for the reaction intermediates.

The parent cyclazine has been prepared by pyrolysis of the 1,3-di-t-butoxycarbonyl derivative. Although stable under nitrogen it decomposes within minutes on exposure to air. N.m.r. evidence indicates that the system is polyolefinic in character. The proton resonances are amongst the highest observed to date for protons joined to trigonal carbon. This is regarded as evidence of a paramagnetic ring-current in the peripheral, non-aromatic, 12π -electron system. α -Orientated electron-withdrawing substituents exert a stabilising influence on the ring-system and, rather remarkably, cause an increase in the electron density at the second α -position of the ring bearing the substituent. An explanation of this phenomenon has been advanced. Chemical confirmatory evidence for the polyolefinic character of the system has been obtained by cycloaddition reactions conducted on the 1,3-diethoxycarbonyl derivative. Substitution reactions are also possible with electrophilic reagents and are regarded as analogous to those of a typical enamine rather than as evidence of aromaticity.

Cycl[3.3.2]azin-1-one and its 2-ethoxycarbonyl derivative has been prepared by pyrolysis of diethyl/quinolizin-4-ylidenemalonate. The former has been converted into simple derivatives of the hitherto unknown cycl[3.3.2]azinium system.

I N T R O D U C T I O N

OBJECT OF RESEARCH

The continuing investigations directed towards a fundamental understanding of the concept of aromaticity have centred during the past decade on the study of peripherally-conjugated macrocyclic hydrocarbons. The intense activity current in this field has resulted from the potential utilisation of these compounds in investigating the validity of Huckel's $(4n + 2)\pi$ -electron rule.¹ The latter predicts that planar monocyclic conjugated systems incorporating a closed shell of $(4n + 2)\pi$ -electrons should possess an inherent electronic stability.

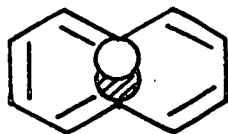
Systems formally constituted of alternating single and double-bonds have been termed annulenes,² the ring size being indicated by a number in parenthesis. These compounds may be further categorised according to their ability to satisfy the Huckel criteria for aromaticity. Thus, planar $(4n + 2)\pi$ peripherally-conjugated systems are potentially capable of exhibiting aromatic properties whereas their $4n\pi$ analogues are expected to be essentially olefinic in character.

The interpretation of the term "aromatic" has long been a source of contradictory and controversial opinion. According to the classical concept, a compound was considered aromatic if it exhibited benzene-like stability and chemical behaviour. However, this definition is no longer considered valid, the latter criteria depending on the free-energy change between the ground-state of the molecule and the transition-state for the chemical reaction involved.³

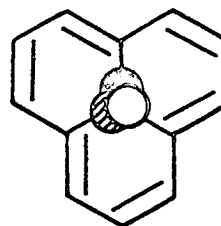
The modern definition considers a compound to be aromatic if there is a measurable degree of cyclic delocalisation of the π -electron system in the ground-state of the molecule. A consequence of such is that carbon - carbon bonds show little alternation in length and the molecule as a whole possesses a lower energy content than would be expected from classical considerations. Delocalisation in $(4n + 2)\pi$ -electron systems further results in the ability of the molecule to sustain a diamagnetic ring-current in an applied magnetic-field.^{4,5} In the case of aromatic annulenes this current shields the inner protons and deshields the outer.⁵ This property can be readily investigated by nuclear magnetic resonance spectroscopy which (together with diamagnetic susceptibility measurements) provides the most convenient means, at present, of determining whether a compound is aromatic or not.

Until comparatively recently the only known fully-conjugated monocyclic systems were benzene ([6] annulene) and cyclooctatetraene ([8] annulene),⁶ higher vinylogues having resisted classical methods⁷ of synthesis. However, the discovery⁸⁻¹¹ in 1956 of simple methods for the generation of large-ring hydrocarbons containing 1,3-diacetylenic units and their subsequent prototropic rearrangement to fully-conjugated cyclic products¹² has resulted in prolific researches by the Sondheimer group, culminating to date in the synthesis¹³ of an entire series of annulenes. Investigations¹³ of the physical characteristics of these compounds have conclusively substantiated the generality of the Huckel π -electron rule.

However, the pursuit of annulene chemistry cannot, within itself, be considered a wholly integral method for the evaluation of the unique chemical characteristics associated with $(4n + 2)\pi$ -electron delocalisation. An inherent defect in the approach arises from molecular distortion consequent on steric interaction of inwardly-directed skeletal protons.^{14,15} Thus, while [10] annulene (1) satisfies the numerical Huckel electron-requirement, realisation of its potential aromatic property appears, at present, to be inhibited by the failure of the molecule to attain planar ring-geometry and hence cyclic delocalisation of the peripheral π -electrons. Similar structural considerations apply to the $4n\pi$ non-Huckel vinylogue [12] annulene.



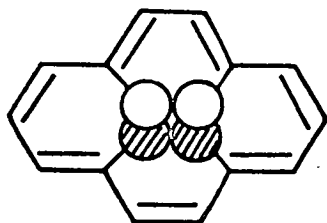
(1)



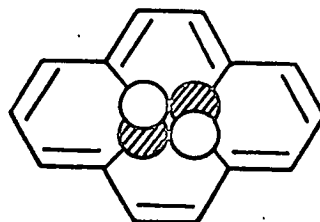
(2)

The importance of the steric factor is clearly demonstrated by the apparent chemical instability of these lower ring-vinylogues. Thus, [10] annulene (1) has resisted synthetic endeavour¹⁶⁻¹⁸ and remains a hypothetical molecule while [12] annulene (2) is still probably unknown.¹⁹⁻²⁰ The [14] Huckel vinylogue cyclotetradecaheptaene (3) has, however, been synthesised²¹ and shown to be

capable of existence²² in two conformationally isomeric forms (A) and (B).



(A)



(B)

(3)

A preliminary X-ray investigation,²³ coupled with a low-temperature ($-60^{\circ}\text{C}.$) n.m.r. study²⁴ has shown at least one of these conformers (A) to be aromatic in character in spite of its apparent non-planar structure. The molecule, however, is very unstable,²¹ undergoing complete decomposition when exposed to light and the atmosphere for a period of one day.

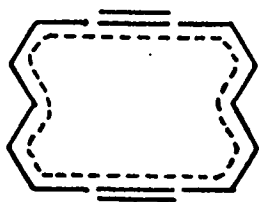
The investigation of the chemical and physical behaviour of annulenes of intermediate ring-size thus presents considerable theoretical and synthetic difficulties. However, the steric nature of the problem lends itself to a readily formulated solution, viz. the avoidance of repulsive forces between inwardly-directed hydrogen atoms. This has been accomplished by two basic approaches.

1) Replacement of one or more double-bonds by linear acetylenic or allenic units.

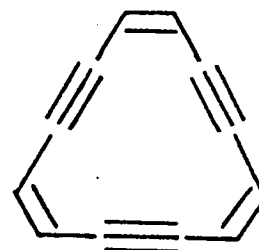
2) Replacement of inwardly-directed protons with saturated carbon-bridges or polyvalent hetero atoms.

Considerable success has attended the work of Sondheimer by

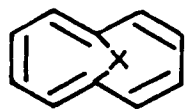
FIG. 1



(4)

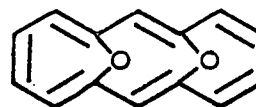


(5)

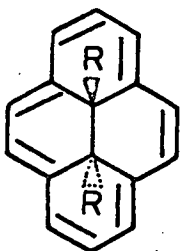


$X = \text{CH}_2, \text{O}, \text{NH},$
 $\text{NCH}_3, \text{NCO}\cdot\text{CH}_3$

(6)

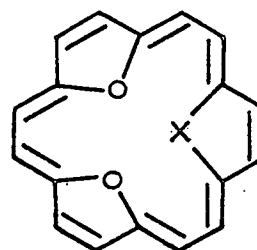


(7)



$R = \text{Me}, \text{Et}$

(8)



$X = \text{O}, \text{S}$

(9)

the former of these approaches, synthesis of an extensive range of dehydroannulenes having been accomplished - e.g. 1,8 - bisdehydro-[14] annulene^{21,25}(4) and 1,5,9 -tridehydro[12]annulene^{26,112} (5).

The second alternative has precipitated prolific researches in a new, but rapidly developing, field of carbocyclic and heterocyclic chemistry, resulting to date in the synthesis of a wide range of novel and unusual chemical structures. Thus bridge-bonded systems (6)²⁷⁻²⁹, (7)³⁰, (8)^{31,32} and (9)^{33,34} are all well authenticated representatives of the $(4n + 2)\pi$ class of annulene derivatives. Their aromatic nature has been amply demonstrated by physical criteria and no significant perturbation of the peripheral conjugated systems has been observed.

However, although a large number of $(4n + 2)\pi$ annulene derivatives have been recognised, no bridge-bonded analogue of the $4n\pi$ class of cyclic polyolefines has been reported. It was the object of the present study to synthesise one such system, the 12π - peripheral-conjugated nitrogen heterocycle - cycl [3.3.3] azine. (11).

THE CYCLAZINES

Conjugated unsaturated molecules formally derivable from the annulenes by replacement of three inwardly-directed valencies by a central nitrogen atom have been assigned the trivial name 'cyclazines'.³⁵ The individual members are distinguished by specifying the number of atoms on the peripheral cycle between points of bonding to the internal nitrogen. Structures (10), (11), (12) and (13) are thus termed, respectively, cycl[3.2.2]azine, cycl[3.3.3]azine, cycl[4,3,2]azine and cycl[4,4,3]azine. The nomenclature equally accomodates ionic and partially saturated structures such as the dehydrocycl[3.3.2]azinium ion (15) and the 3H - cycl[3.3.2]azine (14). The systematic terminology for these compounds, based on 1957 I.U.P.A.C. rules, is derived from the largest nitrogen-containing bicyclic nucleus present in the molecule. Compounds (10) and (11) are thus respectively designated pyrrolo [2,1,5 - cd]indolizine and pyrido [2,1,6 - de]quinolizine

Cyclazine chemistry has to date proved a difficult and relatively unproductive field of research. Despite continuing widespread synthetic endeavour by several research schools the literature of cyclazine chemistry remains sparsely documented. Interest in these compounds stems from their relevance to investigations concerning the validity of current molecular orbital theories of chemical reactivity^{35,36} and chemical shift^{37,38} in heterocyclic systems. Quantum studies^{35,36} have predicted that structures (10) and (11) should be stable once formed and possess a resonance energy higher than that of their monocyclic hydrocarbon counterparts. Bond orders, π - electron densities and energies of excited states

have been evaluated and predictions made regarding the orientation of substitution following reaction with electrophilic reagents.

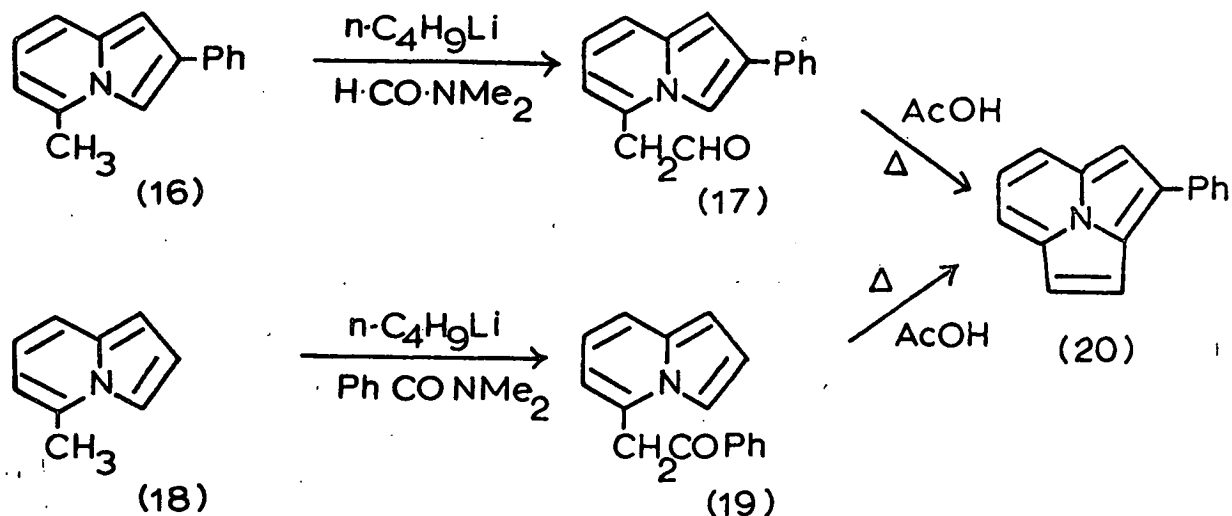
The only known member of the cyclazine series hitherto available for assessment of the relevance of these conclusions, cycl[3.2.2]azine,^{35,39} has consequently formed the object of several physical^{38,42-47} and chemical^{35,38-41} studies. The tricyclic structure assigned to the molecule has been amply demonstrated by X-ray⁴⁶ and n.m.r.^{38,42} investigations and also by unambiguous chemical synthesis from indolizine precursors.^{35,39}

The X-ray diffraction study,⁴⁶ conducted on the 1,4-dibromo derivative, has shown that the molecule is almost exactly planar, deviation from the mean plane of the system being estimated at 0.010\AA . While this finding does not remain inconsistent with apparent planarity resultant on rapid inversion of a pyramidal nitrogen centre, no evidence has been found to support elongation of the centre perpendicular to the plane of the molecule. The supposition must thus be considered remote. An X-ray analysis of the parent system has, unfortunately, not been realised in view of the unusual nature⁴⁷ of the crystalline structure. However, the study of the dibromo-derivative has provided details of important molecular dimensions, viz. bond-lengths and bond-angles.

The presence of a plane of symmetry in the molecule is clearly demonstrated by n.m.r. studies.^{38,42} 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 2.14τ ; 6-proton at 2.41τ) and two identical AB quartets arising from the protons of the five membered rings (1,4-protons at 2.81τ ; 2,3-protons at 2.50τ).

The chemical shifts of the latter have been unequivocally assigned to their appropriate ring positions.

Synthetic studies confirm the symmetrical nature of the ring system. Thus cyclodehydration of 5-formylmethyl-2-phenyl-indolizine (17) and 5-phenacylindolizine (19) under mild conditions yielded³⁵ the same 2-phenylcycl[3.2.2]azine (20)

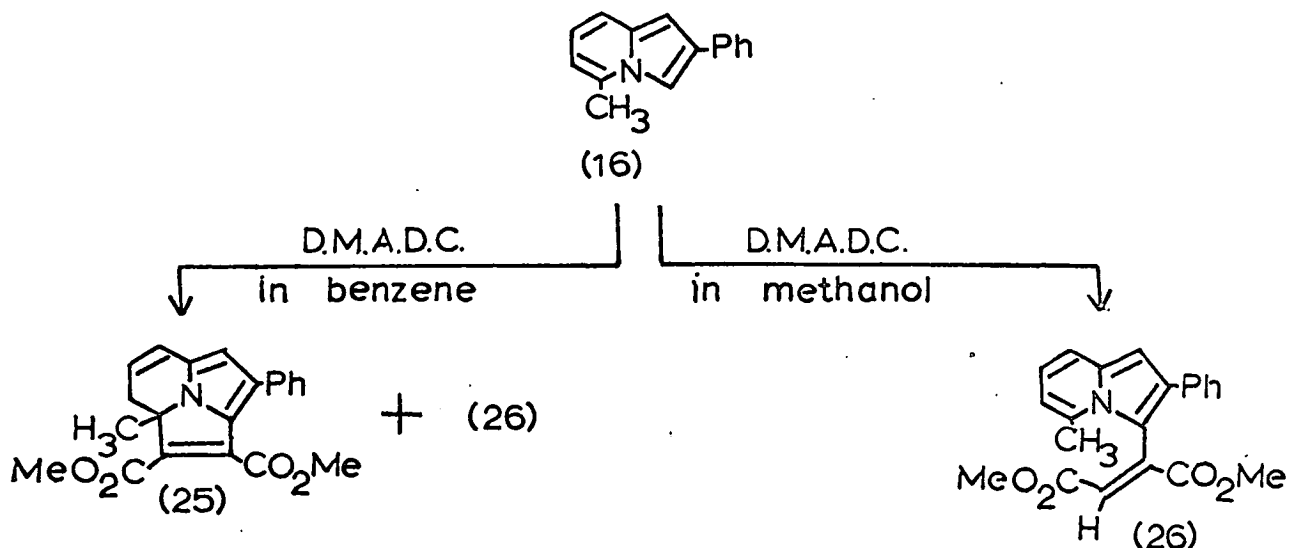


The parent heterocycle has been synthesised by a similar sequence from 5-methylindolizine (18) and dimethylformamide.

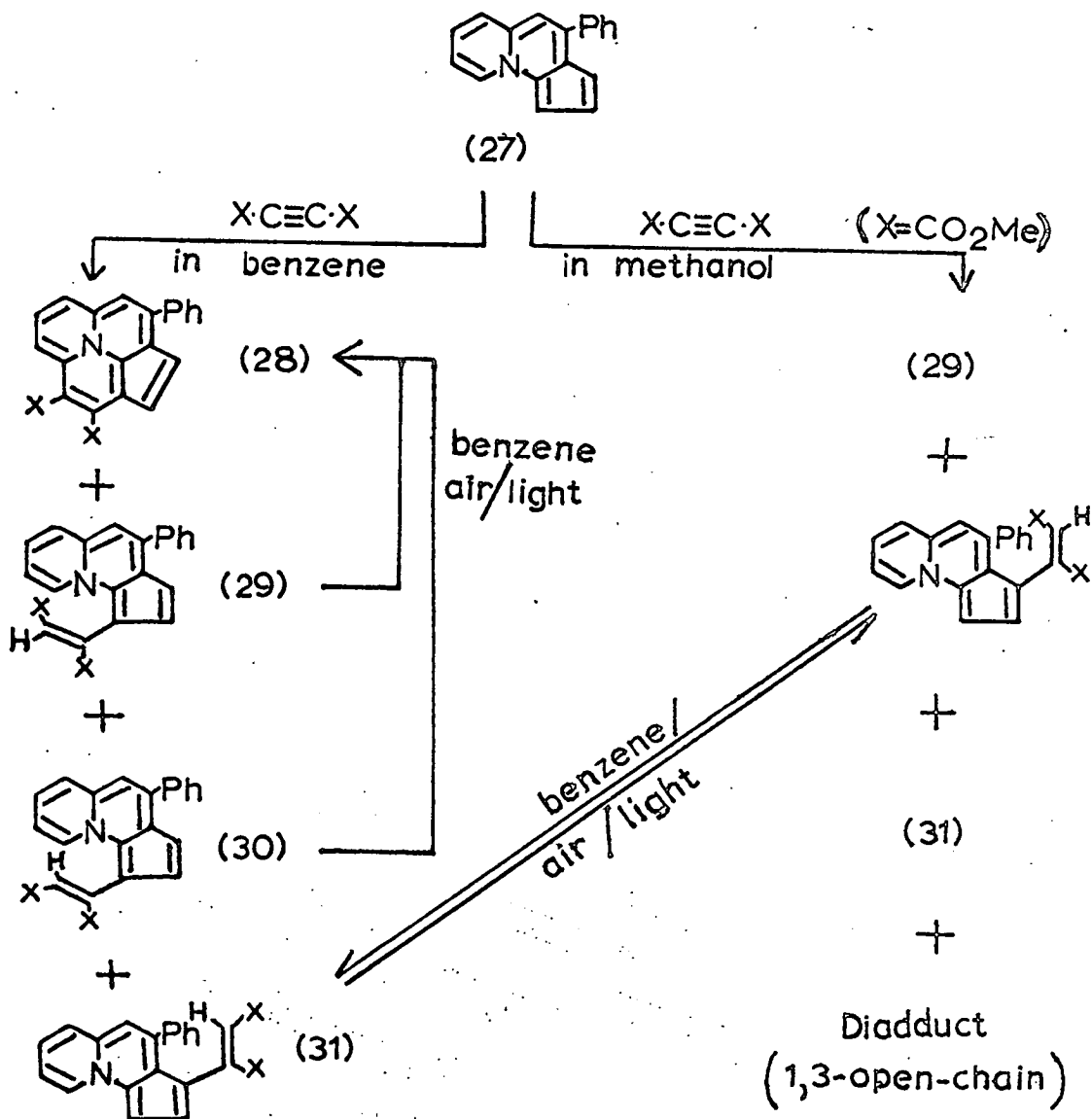
However, a more convenient approach to the system and its derivatives has resulted from the reaction of activated acetylenic esters with indolizines in the presence of a dehydrogenation catalyst.^{38-40,48} These reactions appear to proceed via zwitterionic intermediates formed as a result of a Michael addition to the acetylenic bond. The following scheme has been postulated³⁹ to account for the reaction products from indolizine and dimethyl acetylenedicarboxylate under aprotic conditions.

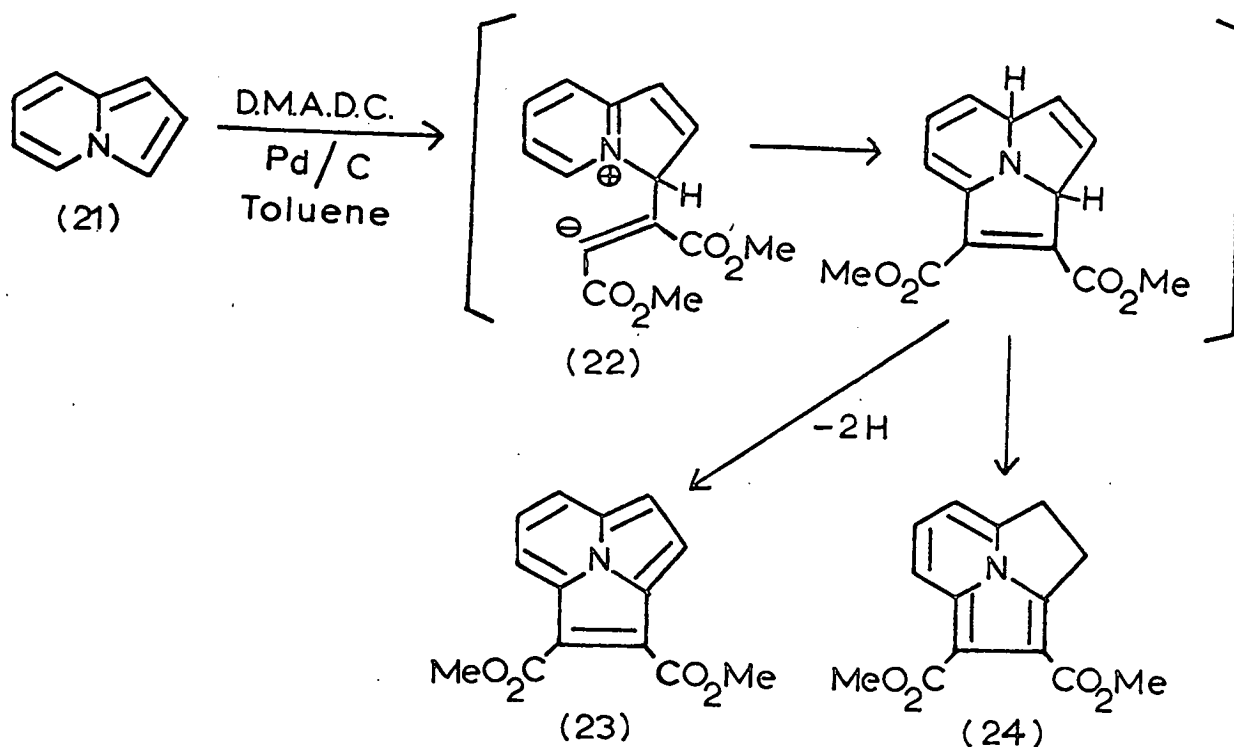
FIG. 3

a.



b.





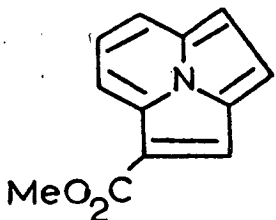
Alkaline hydrolysis of (23) to the corresponding diacid and subsequent decarboxylation with copper chromite yielded the parent system (10).

Although the intermediacy of the zwitterionic species has not been formally demonstrated, strong support for the concept has been provided by studies on related systems carried out in this Department. Thus, reaction of 5-methyl-2-phenylindolizine (16) with dimethyl acetylenedicarboxylate in methanol as solvent yielded only the red open-chain adduct (26) while reaction in anhydrous benzene gave, in addition, the yellow cycloadduct⁴⁹ (25) [Fig. 3a]. 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. Dihydrocycloazine formation in an aprotic solvent presumably involves charge neutralisation of the intermediate by cyclisation, the latter reaction proceeding at a rate comparable with intra- or

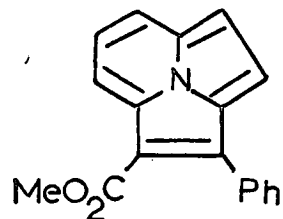
intermolecular proton transfer.

Qualitatively similar results⁵⁰ were obtained following reaction of the acetylenic ester with 2-phenylcyclopenta [c]-quinolizine⁵¹ (27) [Fig.3b.] The absence of tetracyclic ester (28) and the preponderance of open-chain trans-adducts following reaction in methanol is most conveniently rationalised in terms of initial zwitterion formation.

Addition of activated acetylenic esters to indolizine precursors has been widely adopted in the synthesis of a variety of cycl[3.2.2]azine derivatives.^{38-41,48} Thus, the parent indolizine reacts with methyl propiolate⁴¹ and methyl phenylpropiolate³⁹ to yield respectively 1-methoxycarbonylcycl[3.2.2]azine (32) and its 2-phenyl analogue (33)



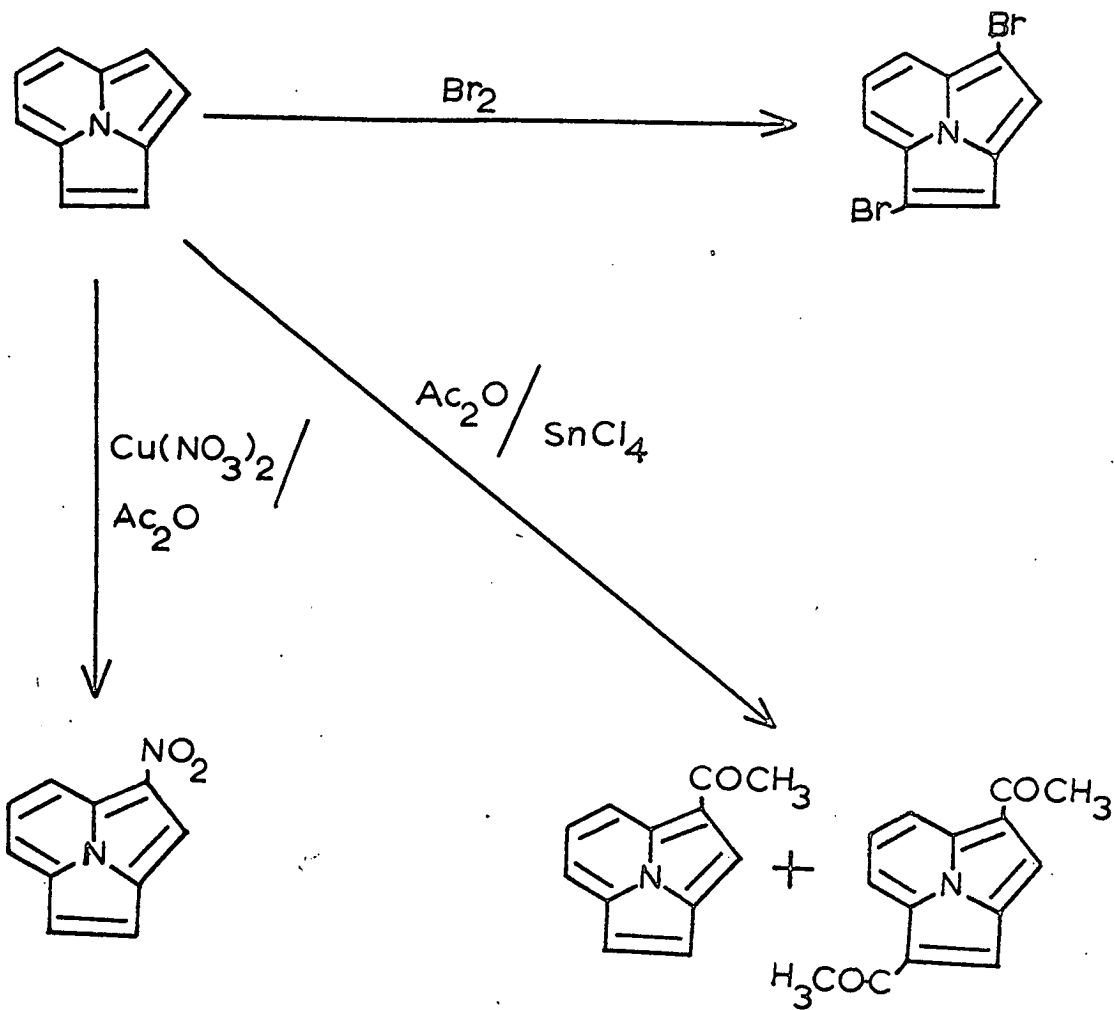
(32)

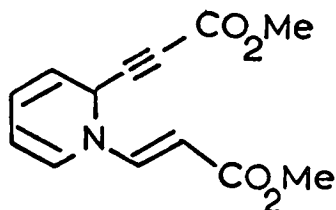


(33)

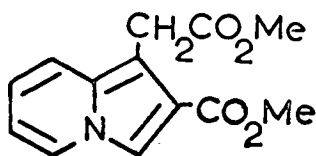
An unusual synthesis of 1-methylcycl[3.2.2]azine (34) has been reported⁵² from pyridine and methyl propiolate in acetonitrile as solvent. The triester (37), which is the sole product of reaction, is considered to result from oxidative addition of the acetylene to an indolizine intermediate (36), the latter being formed from a 1,2-dihydropyridine precursor (35).

FIG. 4

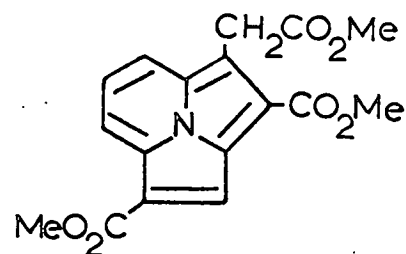




(35)



(36)



(37)

Hydrolysis to the corresponding tricarboxylic acid followed by decarboxylation with copper chromite in quinoline yielded the 1-methyl derivative.

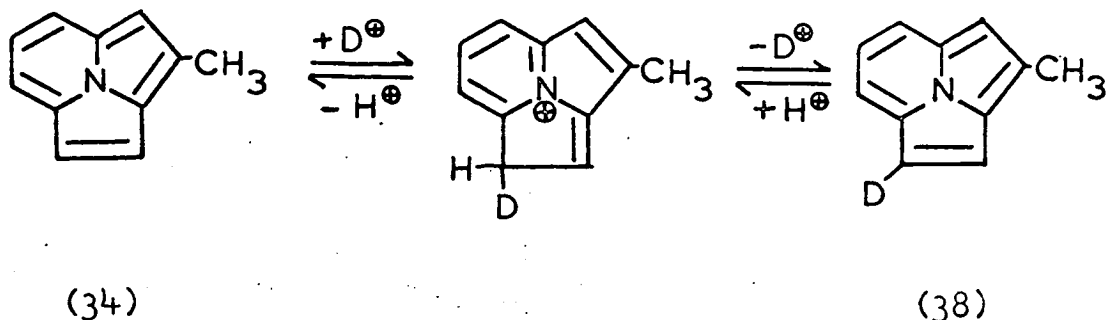
The unsubstituted parent cycl[3.2.2]azine is a non-basic, crystalline, fluorescent yellow compound exhibiting marked stability towards light, heat and air. Its ultra-violet spectrum in ethanol remains unaffected by added acid indicating that the nitrogen lone-pair is completely involved in the aromatic

π -electron system and thus not readily available for bonding. The observed lack of basicity has been theoretically rationalised³⁹ in terms of the loss of resonance energy consequent on isolation of the nitrogen atom following quaternisation.

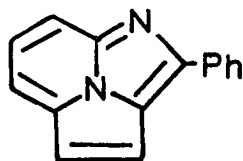
Chemically, the cyclazine behaves as a normal, stable aromatic system undergoing substitution reactions with a variety of electrophilic reagents³⁹ [Fig.4] The orientations of the substituent groups have been experimentally demonstrated⁴¹ and shown to be consistent with an earlier tentative assignment based on molecular orbital calculations.³⁹

Recent n.m.r. studies have confirmed the greater reactivities

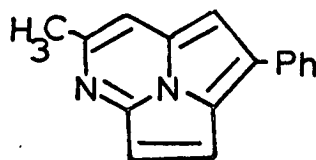
of the 1- and 4-positions towards electrophilic species as evidenced by the formation of a 1,4-dideuterocycl[3.2.2]azine^{38,42} and a 2-methyl-4-deuterocycl[3.2.2]azine³⁸(38)



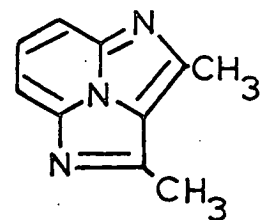
Several interesting cycl[3.2.2]azine systems, (39), (40) and (41), incorporating one or more nitrogen atoms in the peripheral skeleton have been the subject of recent reports.⁵⁴⁻⁵⁶



(39)



(40)



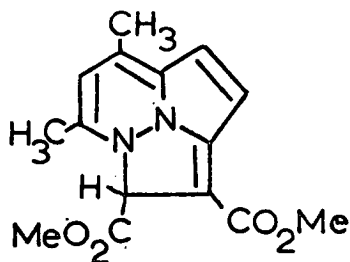
(41)

In addition to their novel appeal they are relevant to studies of the correlation of molecular orbital calculations with experimental data on the basicity and electronic spectra of cyclazines.⁵⁵

All three systems are typically aromatic, their spectroscopic properties being closely similar to that of their mono-aza analogues. However, as opposed to the latter compounds, they are

readily soluble in dilute acids [(41) not specified] thus suggesting that the lone-pairs of electrons on the peripheral hetero-atoms are available for bond-formation.

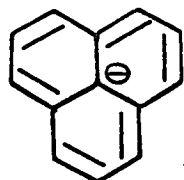
The most recent addition to the literature of cycl[3.2.2]azine chemistry describes the synthesis of the 4,5-dihydro-5-azacycl-[3.2.2]azine derivative (42)



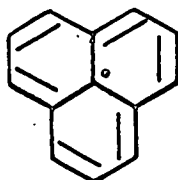
(42)

However, attempts to convert it to the corresponding peripheral-conjugated salt by hydride-ion abstraction have not been realised.

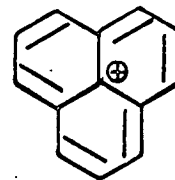
Although considerable success has attended studies in the cycl[3.2.2]azine series, synthetic endeavour in the field of cycl[3.3.3]azine chemistry has, despite continued past and present application by several research schools, resulted in uniform failure.⁵⁸⁻⁶² Molecular orbital calculations, based on a perinaphthenyl anion model, have indicated³⁹ that cycl[3.3.3]azine (11) should possess a resonance energy higher than that of cycl[3.2.2]azine. Further, the perinaphthenyl anion⁶³⁻⁶⁷ (43) together with the corresponding cation⁶⁸⁻⁷⁰ (45) and free radical^{64,71} (44) have been synthesised and all three entities shown to possess moderate stability.



(43)



(44)



(45)

Although the latter criterion does not necessarily reflect on the degree of π -electron delocalisation inherent in these systems, it is relevant to record that all three have been predicted to possess the same resonance energy.^{68,72,73} 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).

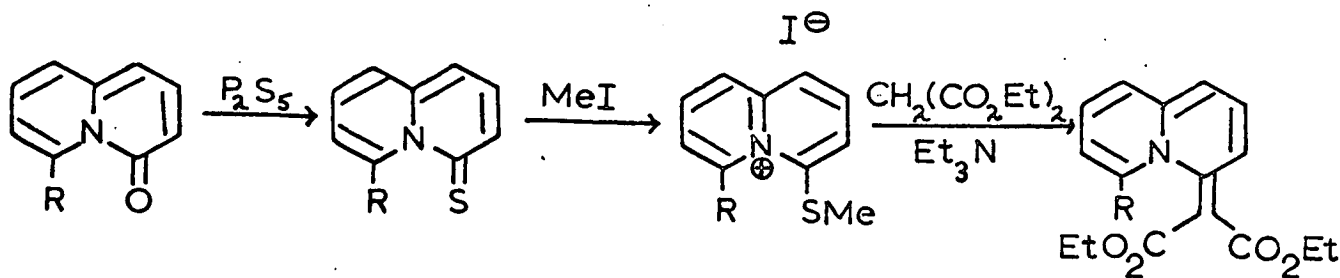
Cycl[3.3.3]azine, which is iso- π -electronic with the perinaphthyl anion, might thus be expected to show similar spectral characteristics and, in particular, possess an enhanced stability by virtue of its uncharged nature.

An important consideration regarding the cycl[3.3.3]azine system arises from its non-conformity with the Huckel $(4n + 2)\pi$ - electron rule. Possessing twelve, peripheral π -electrons (excluding the lone-pair on the nitrogen atom) the system may be considered to be a derivative of the $4n\pi$ class of monocyclic polyenes. Several of the latter have already been reported^{2,3,5,74-76} and the chemical shifts of their outer

peripheral protons shown to occur^{77,78} at abnormally high field-values. The phenomenon, which appears general for all $4n\pi$ systems, has been the subject of theoretical studies^{79,80} and is considered to be a consequence of induced paramagnetic ring-currents. It is therefore interesting to speculate on the nature of the chemical shifts in the cycl[3.3.3]azine system and, further, to consider to what extent these shifts are determined by the presence in the molecule of a central hetero atom.

Several attractive routes to the cycl[3.3.3]azine system have been envisaged and the outcome of their attempted implementation is considered below.

The first reported approach⁵⁸ describes attempts to generate a bicyclic quinolizine precursor (46b). Intramolecular condensation of the spatially-adjacent methyl and ethoxycarbonyl functions would then be expected to yield the basic cyclazine carbon-skeleton.



(46)a: R=H
 b: R=Me

(47)

(48)

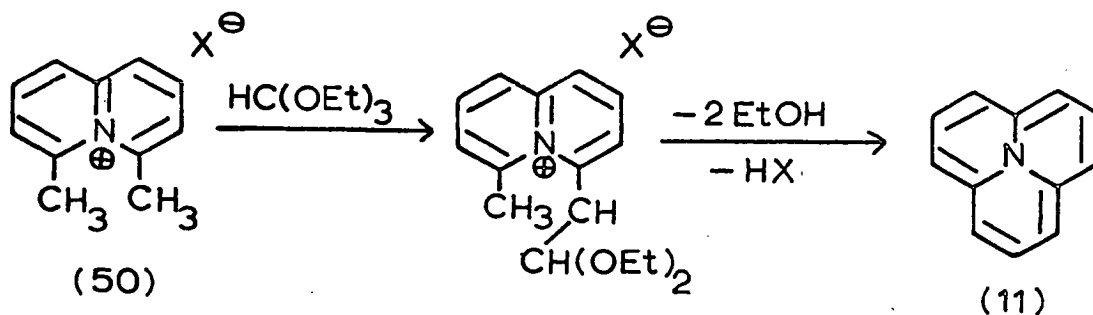
(49)

A preliminary model experiment to assess the feasibility of the projected synthetic route to the methylenequinolizine (49)

utilised the readily accessible quinolizin-4-one (46a) as starting material. Stepwise conversion to the methylthioquinolizinium salt (48a) followed by reaction of the latter with diethyl malonate in the presence of triethylamine was reported to yield the desired quinolizine (49a), structural assignment following from ultra-violet criteria and elemental analysis of the hydrochloride salt. A corresponding sequence from 6-methyl-quinolizin-4-one (46b), with the object of isolating methylene-base (49b), could not be realised since attempts to prepare the intermediate thione (47b) resulted in the formation of decomposition product.

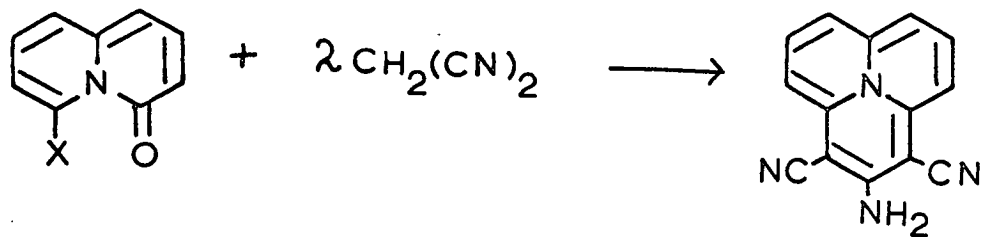
Although the foregoing approach remains mechanistically sound, the attempt to demonstrate its experimental practicability, as will be shown later, is founded on wholly erroneous conclusions. The supposed "methylene-base" (49a) consisted in fact of a mixture of quinolizin-4-one (46a) and quinolozine-4-thione (47a).

An alternative synthetic approach^{59,60} based on the elaboration of 4,6-dimethylquinolizinium salts (50) appeared a particularly promising route to the parent system (11). Thus, treatment of (50) with triethyl orthoformate or some equivalent molecule was expected to yield the parent cyclazine following double condensation with the activated 4,6-dimethyl substituents.



However, despite extensive attempts to effect cyclisation using a wide range of carbonyl compounds and catalytic conditions, only varying amounts of starting material were recovered. The failure to effect the desired condensation is probably due to inhibiting steric repulsion in the transition state of the reaction. However, had a conversion to the parent cyclazine been achieved, isolation of the system under the prevalent conditions would not have been possible. (See discussion section).

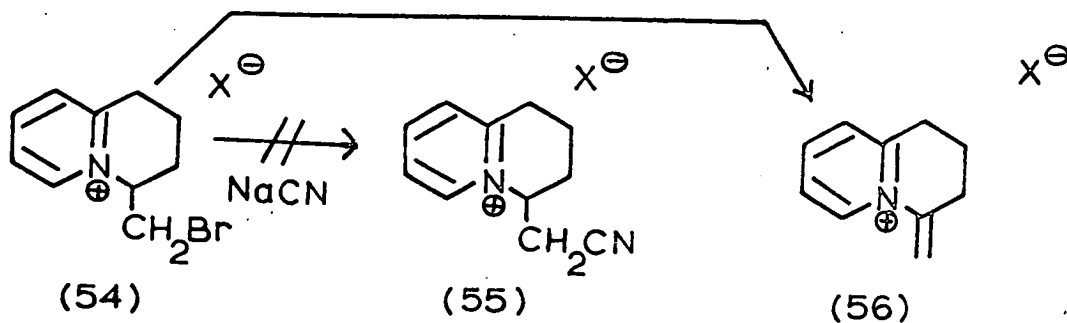
A further attempt⁶¹ to generate the cycl[3.3.3]azine system by reaction of substituted quinolizine derivatives (52) with activated methylene compounds was not realised in view of the difficulties encountered in establishing a suitable electronegative substituent in the 6- position of the molecule.



(52) X=OMe, Cl

(53)

A recent approach⁶² from tetrahydroquinolizinium compounds has met with similar lack of success.



(54)

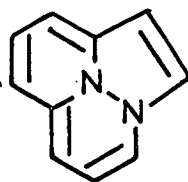
(55)

(56)

Treatment of the salt (54) with sodium cyanide failed to cause the expected nucleophilic displacement at the 4-methyl carbon-centre, but instead resulted in formation of the 6-methyl-4-methylene derivative (56) by elimination of hydrogen bromide. Introduction of the additional carbon-centre was finally accomplished by a different route, but attempted base-catalysed ring-closure yielded only an open-chain lutidine derivative.

Although the last scheme appears rather indirect in method, it serves to illustrate the varying synthetic approaches that have been devised to effect construction of the cycl[3.3.3]azine skeleton.

The continuing interest in the system, coupled with difficulties attendant on its synthesis, has prompted investigation⁸¹ of a closely related isoelectronic structure 10-azacycl[3.3.2]azine (57).



(57)

A protonated dihydroderivative of the latter has been prepared but attempts to convert it to the parent system by dehydrogenation have proved uniformly unsuccessful.

Cycl[3.3.3]azine and its derivatives (except a decahydro compound⁸²) have thus attracted much attention but resisted all

The transitory existence of the cycl[3.3.2]azinium cation (15) has been inferred⁵² from the presence in the mass spectrum of 1-methylcycl[3.2.2]azine (34) of a peak at 154 m/e, the [3.3.2]system supposedly arising from ring-expansion of (34) following loss of an electron and a hydrogen atom. This interpretation, however, is based solely on speculation and no further evidence has been forthcoming to support the suggestion.

Although the parent cycl[3.3.2]azinium ion is as yet unknown, ketonic derivatives were recently reported⁸⁴ by Leaver et al. Thus, reaction of 1,3-diethoxalyl-2-phenyl-5-methylindolizine (61) with sodium ethoxide in dry ethanol yielded the hydroxycycl[3.3.2]azinone (63) or (64) together with the cycl[3.2.2]azine derivative (62) [Fig.5]. Removal of the 1-ethoxalyl function of the former by standard degradative procedures yielded ketone (65) or (66). The latter, a bright yellow, crystalline compound exhibited spectral characteristics consistent with the assigned structure.

The literature of cyclazine chemistry includes one further example⁸⁵ of this tricyclic class of compounds. Preparation of 1-phenyl-8-azacycl[2.2.2]azine (69) has been accomplished from a disubstituted 4,8-diazapentalene (67).

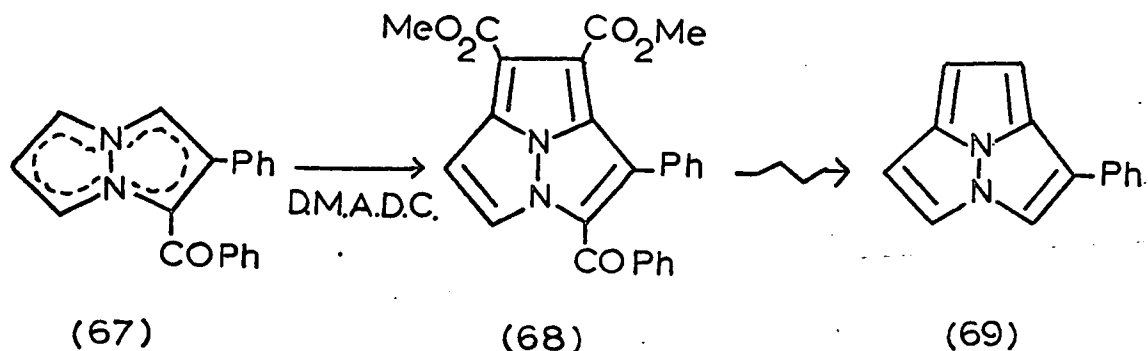
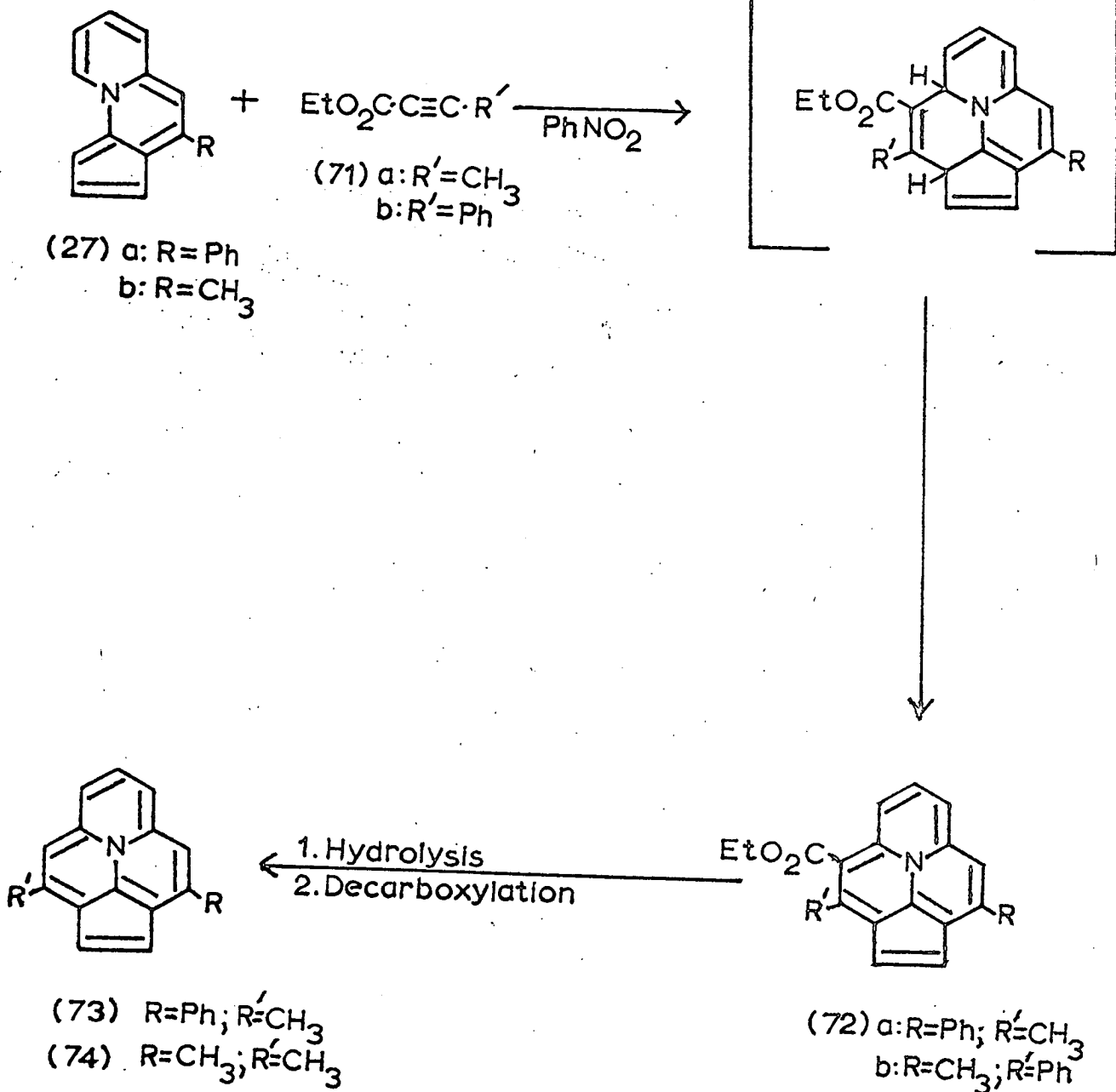
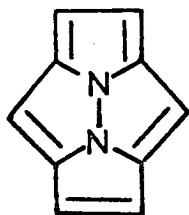


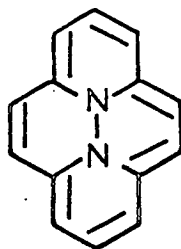
FIG. 6



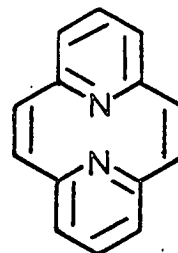
However, the chemical characteristics of the system, which is isoelectronic with cycl[3.2.2]azine, have not been documented and present interest stems from its potential as a precursor to the fully conjugated tetracyclic structure⁸⁵(70) in which the peripheral-conjugated carbon-skeleton (containing 10 π -electrons) is held planar by bonding to two internal adjacent nitrogen atoms. Interest in the latter compound and the related [14] annulene derivative (71) lies in the behaviour of the two nitrogen atoms located within the conjugated peripheral system.



(70)



(71)



(72)

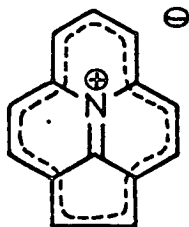
An early attempt⁸⁶ to synthesise 10b, 10c- diazapyrene (71) proved unsuccessful and present calculations⁸⁵ suggest that further synthetic effort will probably yield the more energetically favourable valence-tautomer (72). Although this difficulty is obviated in the potentially aromatic heterocycle (70), no report of its synthesis has been recorded.

At present, only one fully-unsaturated heterocyclic structure incorporating an internal nitrogen atom has been reported. Reaction of 4- substituted cyclopenta[c]quinolizines⁵¹(27) with activated acetylenic esters (71) in boiling nitrobenzene has resulted in the synthesis of a series of cyclopenta[c,d]-cycl[3.3.3]azine derivatives⁸⁷[Fig.6] Confirmation of the structural assignments has been amply provided by chemical and

physical evidence. Thus hydrolysis and decarboxylation of the two different monoesters (72a) and (72b) yielded the same 3-methyl-9-phenylcyclopenta[*c,d*]cycl[3.3.3]azine (73)

The symmetry of the ring-system is apparent from the n.m.r. spectrum of the 3,9-dimethyl derivative (74). The latter shows an AB₂ multiplet at 2.90 - 3.46 τ attributable to the 5-, 6- and 7-protons, and two singlets at 3.04 τ and 3.71 τ attributable to, respectively, the 1,2- and 4,8-protons.

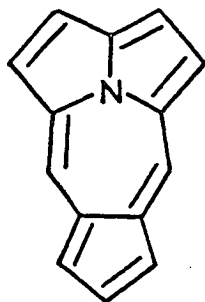
Although electrophilic substitution reactions have met with limited success, the system must be considered aromatic by physical criteria. Thus the chemical shifts of the peripheral protons occur at relatively low τ -values and the ultra-violet spectrum resembles that of the 14 π -electron systems 1,8-bisdehydro[14]annulene (4) and trans-10b, 10c-dimethyldihydro-pyrene (8). It appears probable, and consistent with spectral evidence, that a charge-separated formulation (75) makes a significant contribution to the resonance hybrid.



(75)

Finally, the isomeric tetracyclic compound (76) has been synthesised⁸⁸ within this Department and shown to be aromatic on the basis of n.m.r. criterion. Chemical transformations have not to

date been investigated.



(76)

DISCUSSION

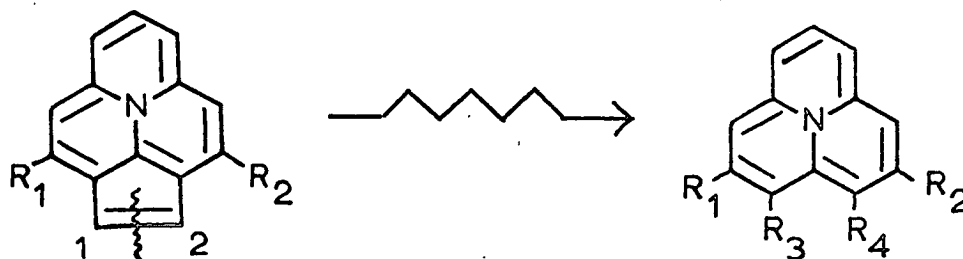
Note.

The u.v. spectra referred to throughout the text are collectively represented in diagrammatic form at the end of each sub-section (i.e. following pp.61, 118 and 124).

N.m.r. spectral data is listed on pp.198 - 208.

ATTEMPTS TO SYNTHESISE CYCL[3.3.3]AZINES BY SELECTIVE CLEAVAGE
OF THE 1,2-BOND OF CYCLOPENTA[c,d]CYCL[3.3.3]AZINES

In view of the failure of several synthetic approaches to the cycl[3.3.3]azine system from bicyclic precursors, it appeared expedient to investigate the possibility of a degradative approach from cyclopenta[c,d]cycl[3.3.3]azines. The latter⁸⁷ are the only known compounds which incorporate a cycl[3.3.3]azine nucleus.

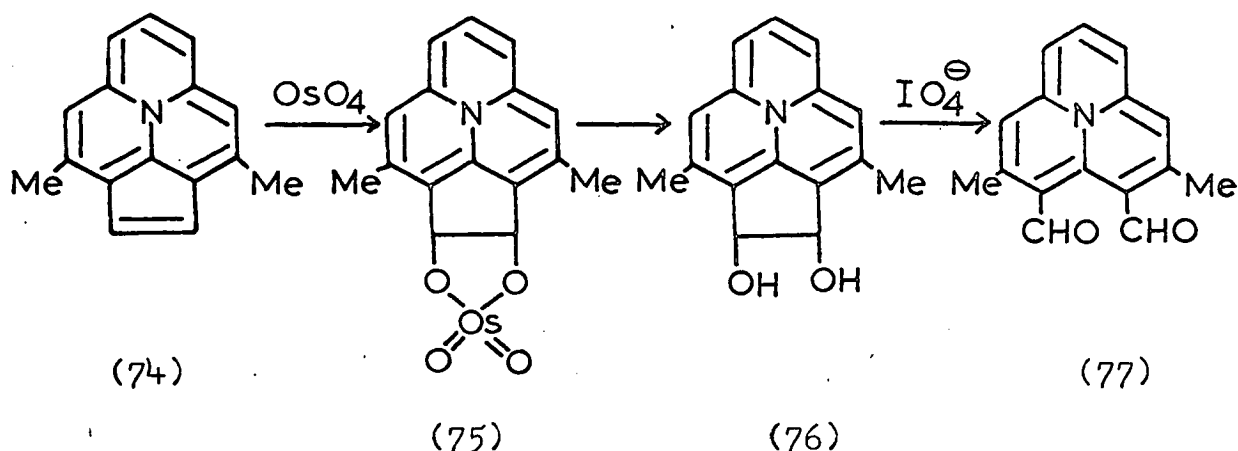


(74)

It seemed possible that selective degradation of the 1,2-bond might be accomplished by initial treatment of the heterocycle (74) with an oxidising species such as osmium tetroxide, potassium permanganate or ozone. These reagents are characterised by their ability to attack double-bonds. They have consequently been termed 'double-bond' reagents. Although normally applied to simple ethylenic molecules, much use has been made of their oxidative properties in the elucidation of the bond-structure of aromatic systems.

Osmium tetroxide appeared particularly appropriate to the present investigation since it has been shown to attack aromatic systems very slowly, and only at the most reactive double-bond.

Thus reaction⁸⁹ with phenanthrene, followed by hydrolysis of the intermediate cyclic osmate ester, yields cis -9,10- dihydroxy - 9,10 - dihydrophenanthrene. A similar sequence with the cyclopenta [c,d] cycl [3.3.3] azine (74) might conceivably have yielded the vicinal diol (76) which on further reaction with periodate should cleave to give the tetrasubstituted cycl [3.3.3] azine (77).



However, reaction⁹⁰ of (74) with a molar proportion of osmium tetroxide in pyridine at room temperature yielded only a small amount of decomposition product. The starting material was returned largely unreacted.

A second attempt to effect bond degradation was made using the permanganate-catalysed periodate oxidation method⁹¹ developed by Lemieux and von Rudloff. This method involves initial hydroxylation of a double-bond, followed by periodate cleavage of the resultant glycol. Catalytic quantities of permanganate are sufficient because periodate oxidises manganese in its lower

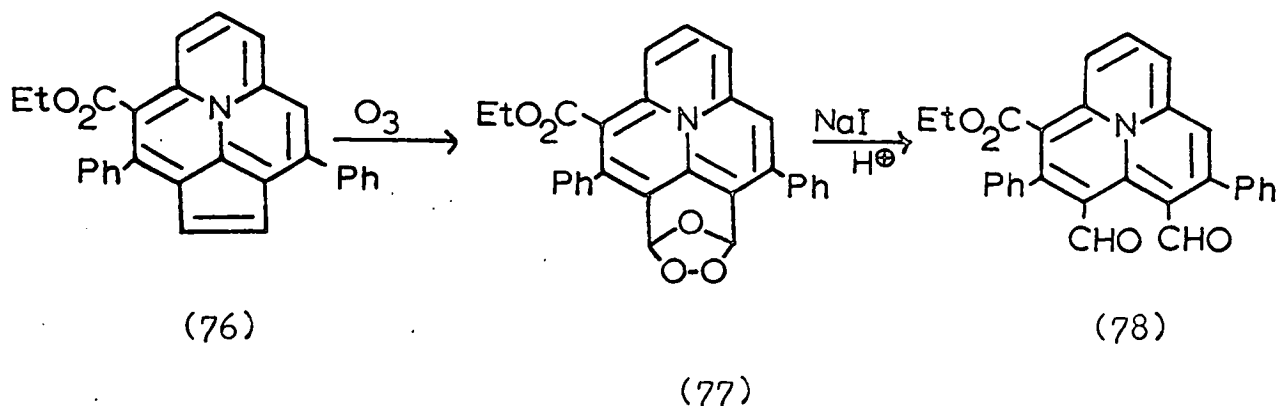
valence states back to the permanganate ion, thus regenerating the hydroxylating reagent. However, when a solution of the cyclopentacyclazine (74) in dioxane was treated with a solution of potassium permanganate - sodium ^{per-}iodate (1:25) in water over a period of 24 hours only black amorphous solid was formed. No starting material remained.

The formation of decomposition product from both of these attempted hydroxylation reactions, together with the recovery of unreacted cyclazine from only the former, can best be rationalised in terms of the reactivity of the initially-formed adducts.

[e.g. (75)]. It appears probable that decomposition of the ring-system is due to further attack by the 'double-bond' reagent on these adducts, which, as subsequent work has shown, would possess a greater degree of bond localisation, and hence affinity for the attacking species, than the parent heterocycle. The molar equivalent of osmium tetroxide would thus be completely destroyed by further attack on the osmate ester intermediate (75). The permanganate hydroxylating reagent, however, would undergo continuous regeneration by the large excess of periodate co-oxidant and thus progressively degrade the cyclazine system.

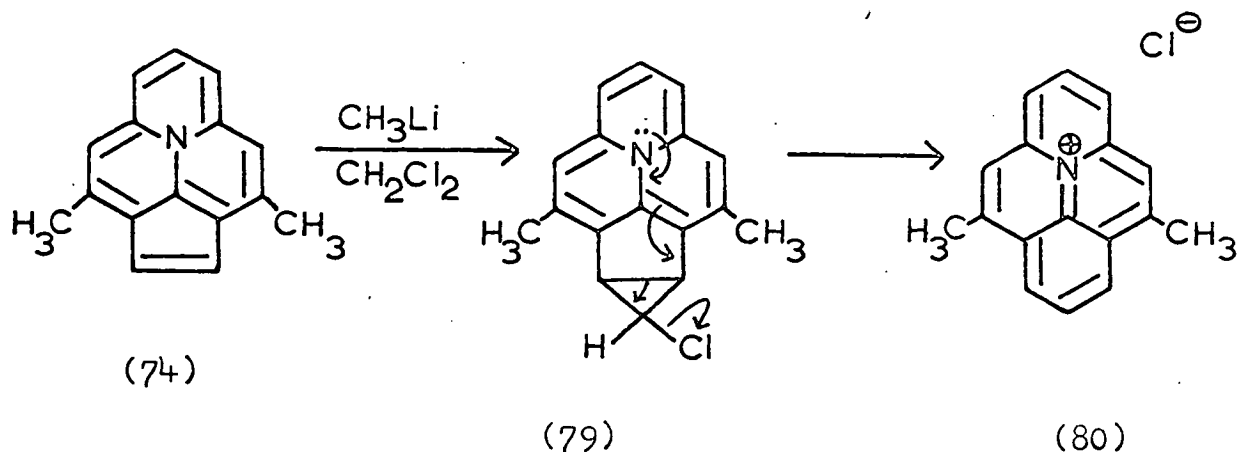
Although the above interpretation suggested that the degradative approach was futile, it was considered desirable to substantiate this view by investigating the behaviour of the system with several other 'double-bond' reagents. One such reagent that has been frequently utilised^{92,93} in aromatic degradative studies is ozone. Reaction with the tetracyclic cyclazine carboxylic ester (76) might conceivably yield a

1,2- mono-ozonide (77) which would be expected to undergo reductive fission to yield the cycl[3.3.3]azine (78).

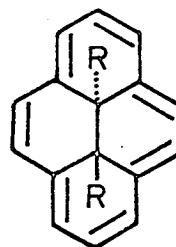
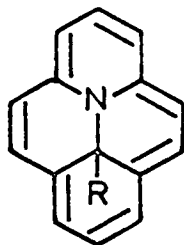


However, since it was appreciated that initial attack of the ozone might yield a system which was comparable in reactivity to the parent, (76), it was considered essential to limit the amount of reagent to one molar proportion. This was accomplished by allowing a solution of the cyclazine (76) in dichloromethane to react with a measured volume of a solution of ozone in dichloromethane, the concentration of the latter having been accurately determined by standard volumetric titration procedures. However, a dark amorphous solid was again isolated from the reaction mixture together with unreacted cyclazine.

A final attempt to evaluate the mode of reaction of cyclopenta[c,d]cycl[3.3.3]azines with 'double-bond' reagents was made using substituted carbenes. Attack on the electron-rich heterocycle can be envisaged at the 1,2- position to yield an intermediate adduct such as (79) which, on further elaboration, might isomerise via ring-expansion to yield the hypothetical 10b - azoniapyrene (80)



The latter compound (80) is of obvious appeal as a potential precursor to the peripheral-conjugated [14] annulene derivative (81), the synthesis of which has become especially desirable in view of the recently reported trans - 10b,10c - dialkyldihydropyrene system (8).

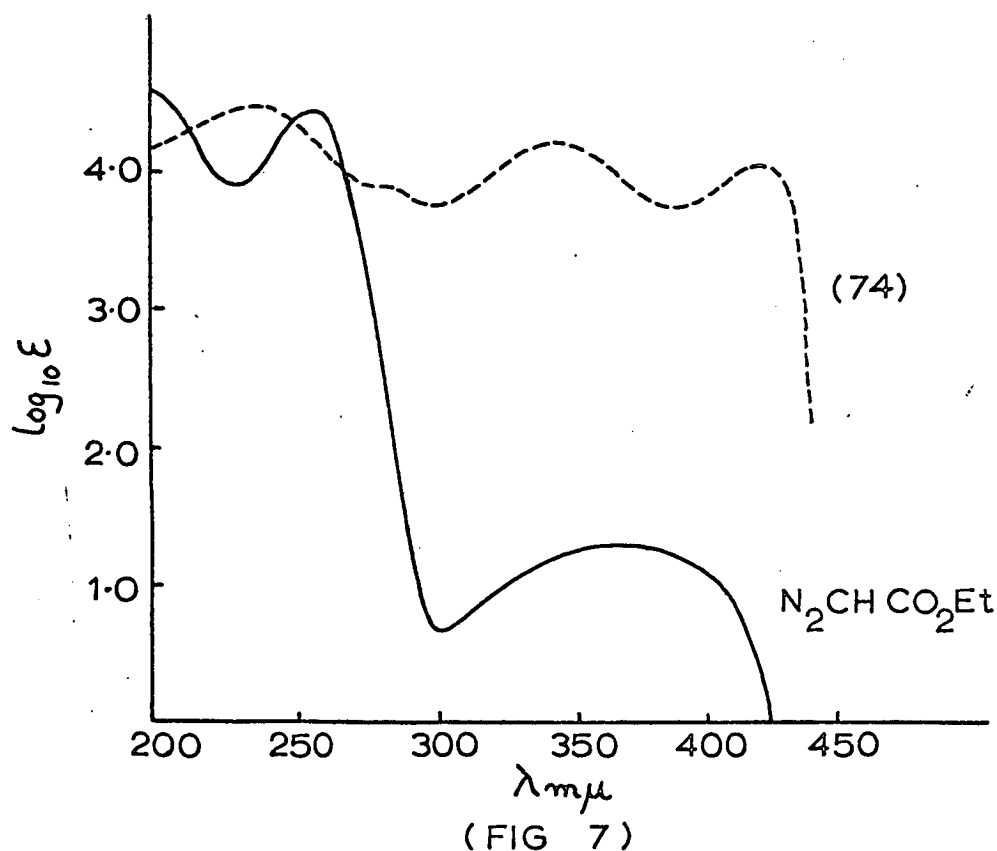


R = Me, Et.

However, once again, only amorphous carbon-like residue could be isolated from the reaction mixture together with unreacted cyclazine, the latter despite having used a three-fold molar excess of the carbene-generating reagents.

Reaction with ethyldiazoacetate under thermal conditions yielded equally disappointing, if not wholly unpredictable, results. However, an attempted photochemically-induced

decomposition of the diazoacetic ester in a cooled solution of tetrahydrofuran containing the cyclopenta[cd]cycl[3.3.3]azine (74) was apparently without effect, the cyclazine being recovered unchanged. This result is best rationalised by inspection of the ultra-violet absorption spectra of the individual reagents (Fig.7).



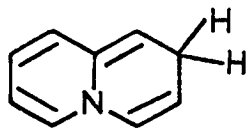
The 300 - 450 mμ. absorption band which normally effects photolytic decomposition of the diazoacetic ester is vastly overshadowed by a strong cyclopentacyclazine absorption in the same wavelength region. The protecting effect of the latter band apparently inhibits radiation-induced decomposition of the ester, thus preventing formation of the carbene.

The approach to the cycl[3.3.3]azine system via selective bond-fission of cyclopenta[c,d]cycl[3.3.3]azines thus appeared invalid. The recurring incidence of decomposition product together with unreacted starting material (with one exception) indicates, as already suggested, the formation of an intermediate species more susceptible to attack by the 'double-bond' reagent than the parent compound. Attempts to generate the cyclazine by the above route were thus discontinued.

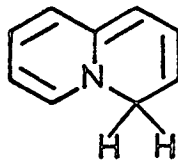
In view of the failure of the foregoing degradative approach to the cycl[3.3.3]azine system, it was decided to investigate the feasibility of a synthetic approach from a suitably substituted quinolizine. The chemistry of the latter class of heterocycles will be briefly reviewed.

QUINOLIZINES, QUINOLIZINONES AND QUINOLIZINIUM SALTS

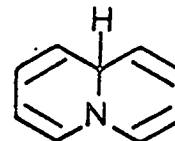
The parent quinolizine ring-system, formerly known as pyridocoline, can theoretically exist in three possible tautomeric forms: 2H - quinolizine (82), 4H - quinolizine (83), and 9aH - quinolizine (84)



(82)



(83)



(84)

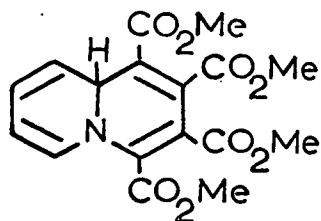
However, none of these isomers is as yet known and present evidence suggests⁹⁴ that attempts to prepare (83) will result in ring-fission

with the formation of open-chain pyridine derivatives, i.e.

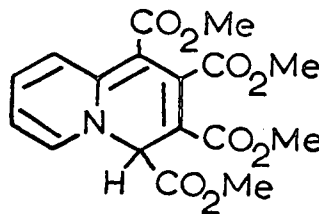


In any event aromatic properties cannot be associated with both rings of the bicyclic system because the presence of the tetrahedral carbon-centre prevents complete delocalisation of the peripheral π -electrons.

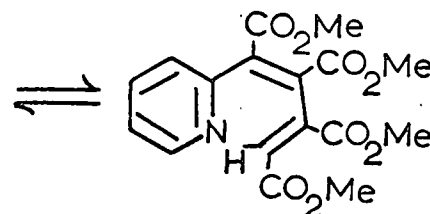
Derivatives of both the 4H- and 9aH- quinolizines, (83) and (84), were prepared⁹⁵ by Diels and Alder in 1932, during their investigation into the adducts from the reaction of pyridine with dimethyl acetylenedicarboxylate. However, these workers assigned erroneous structures to the products, and it was not until 1960 that the true nature of these adducts was rigorously established.⁹⁶ The two major products, a "red" labile and a "yellow" stable adduct have been shown to possess structures (85) and (86) respectively.



(85)



(86)

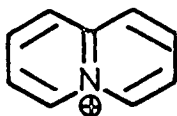


(87)

The former of these compounds, the 9aH- isomer, undergoes rapid

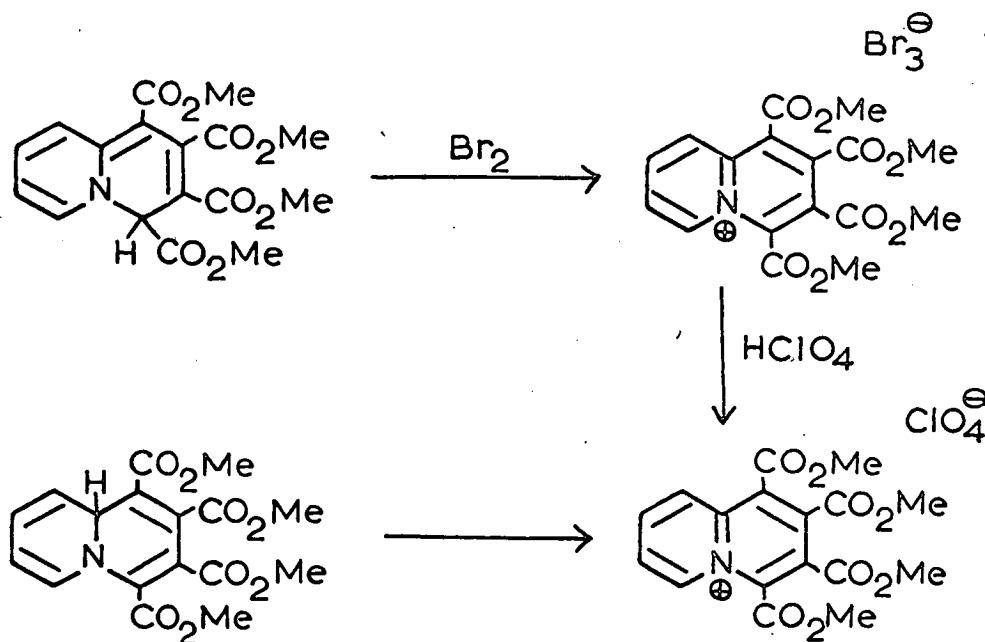
tautomeric conversion to the 4H- analogue when treated with hot polar solvents. It has been suggested,⁹⁷ on the basis of n.m.r. evidence, that even the latter may not exist wholly in the bicyclic form (86), but as an equilibrium mixture in which the open-chain valency-tautomer predominates.

Aromatisation of the quinolizine system can be achieved by conversion, via hydride ion abstraction, to the quinolizinium⁶⁰ (or, more correctly dehydroquinolizinium) cation which is isoelectronic with naphthalene.



(88)

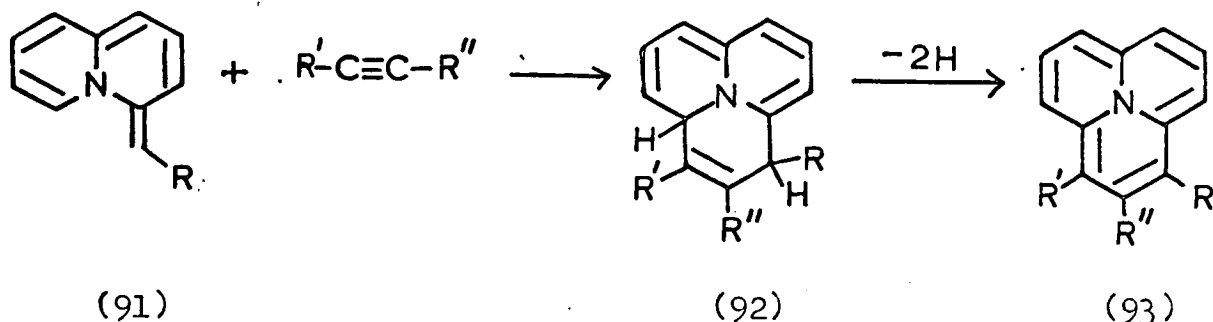
Although the synthesis of the parent cation (88) cannot, at present, be achieved by this route, hydride ion abstraction^{95,96} has been demonstrated for several substituted 4H- and 9aH- quinolizines, e.g.



hybrids to which dipolar structures (89b) and (90b) are major contributors. The observed lack of ketonic reactivity of the 4-oxo function in (89) remains consistent with this interpretation.

Attempts to utilise quinolizine derivatives as potential precursors of the cycl[3.3.3]azine system and the lack of success attendant on these endeavours have already been described. Although further elaboration of these methods can be considered in devising a synthetic route to the tricyclic system, their appeal is limited by the restricted scope for suitable modification of the initial quinolizines. A new approach to the system thus appeared desirable.

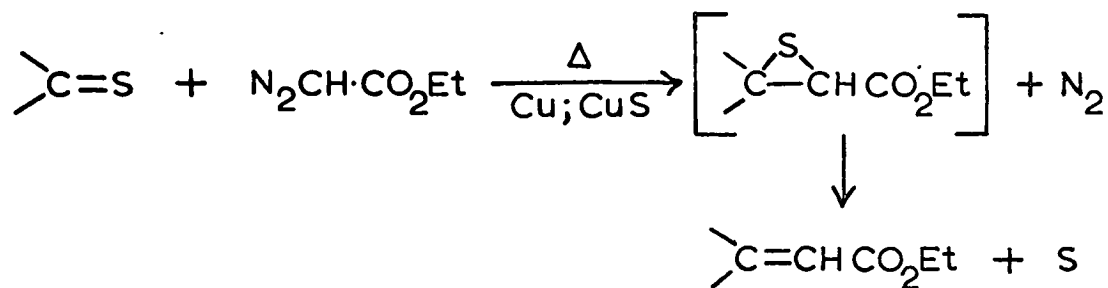
The possibility of a synthetic route from 4-methylenequinolizines seemed particularly attractive. Dipolar addition of an electrophilic acetylene to a methylene base of type (91), followed by dehydrogenation of the resultant adduct (92) might be expected to yield the required system (93)



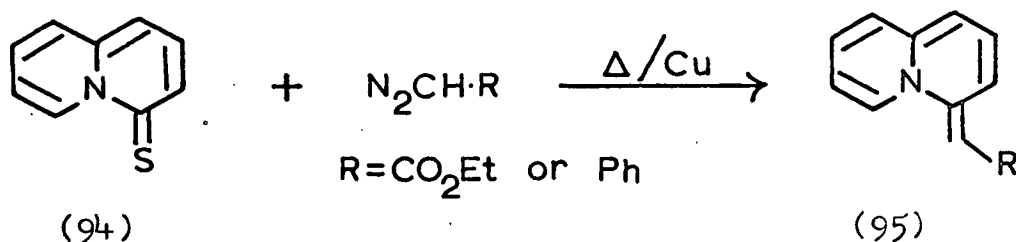
However, except for a reported synthesis⁵⁸ of 4-(diethoxycarbonylmethylene)quinolizine, no account has been given in the literature of methylene-bases derived from 4H-quinolizines. The synthesis of such a system thus constituted a prime objective.

ATTEMPTED SYNTHESIS OF METHYLENEQUINOLIZINES

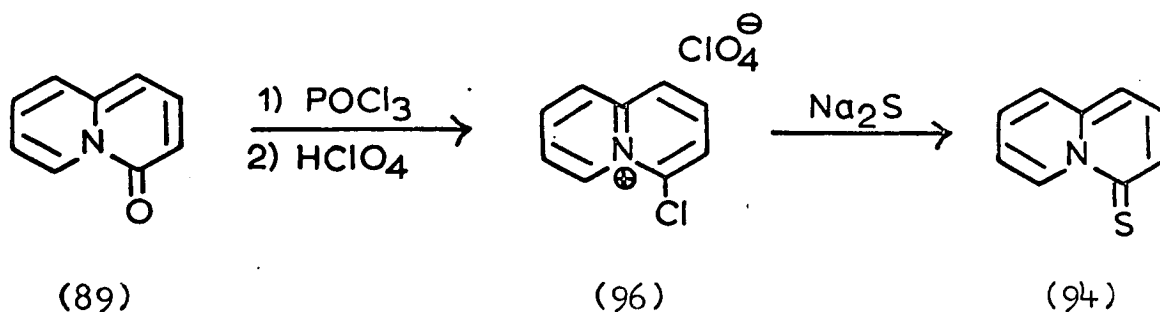
Schonberg and Frese have shown ¹⁰¹ that a number of thiones on treatment with diazoacetic esters, in the presence of copper powder or copper sulphide, yield intermediate episulphides which extrude sulphur with the formation of the corresponding doubly-bonded compounds.



A similar sequence from quinolizine-4-thione might conceivably yield the required base (95)



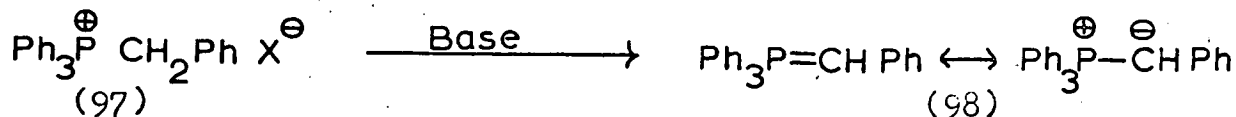
Boekelheide and Gall have reported ⁹⁹ the synthesis of (94) by sulphurisation of quinolizine-4-one with phosphorus pentasulphide. However, a more convenient and reproducible method has been developed ¹⁰² by van Allan and Reynolds



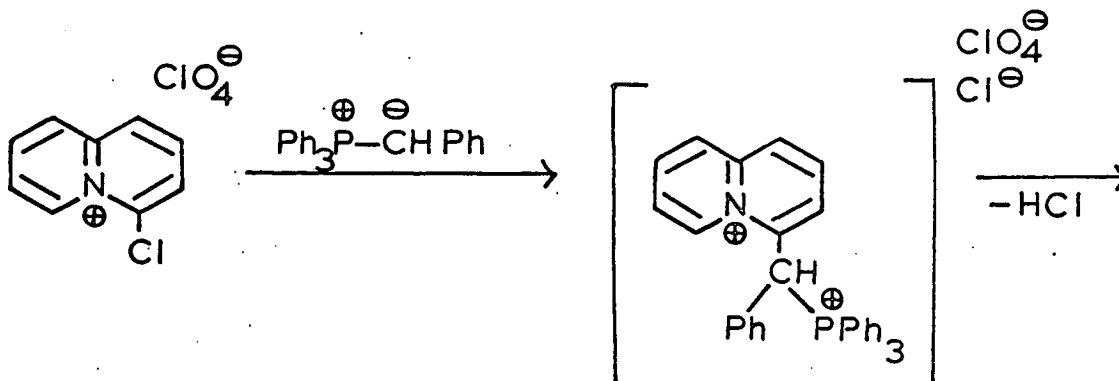
Treatment of the ketone (89) with phosphoryl chloride, followed by perchloric acid, gave an almost quantitative yield of 4-chloroquinolizinium perchlorate (96) which was converted to the thione (94) in 72% yield with sodium sulphide.

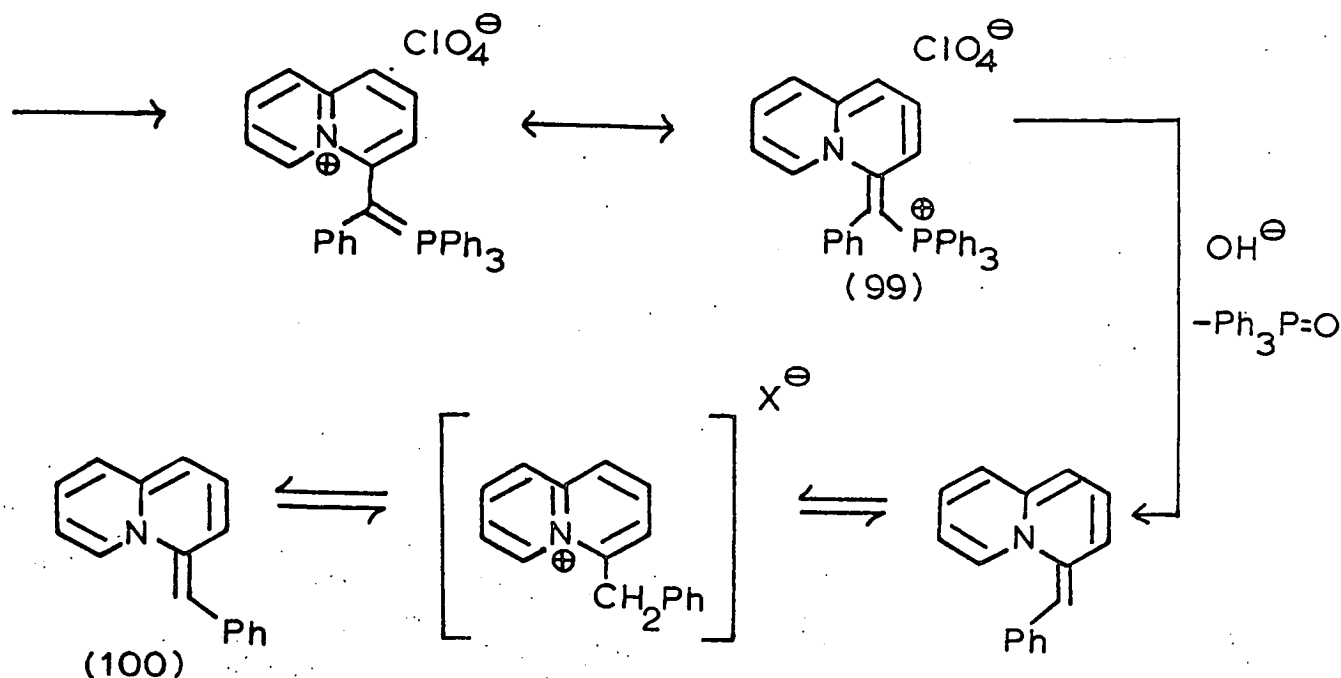
With the required product in hand, reaction with the diazoacetic ester and phenyl diazomethane was attempted. However, despite employing a wide variety of conditions which could not have failed to generate the intermediate carbenes, only unchanged thione was recovered from these reactions.

In view of the failure to synthesise the methylenequinolizine by the above procedure, an alternative route was envisaged using the Wittig reagent benzylidenetriphenyl phosphorane (98).



It seemed feasible that the phosphorane might effect a nucleophilic displacement of the chloride ion from 4-chloroquinolizinium perchlorate to yield, following proton abstraction, the quaternary phosphonium salt (99). Decomposition of the latter with strong base should yield the benzylidenequinolizine (100).

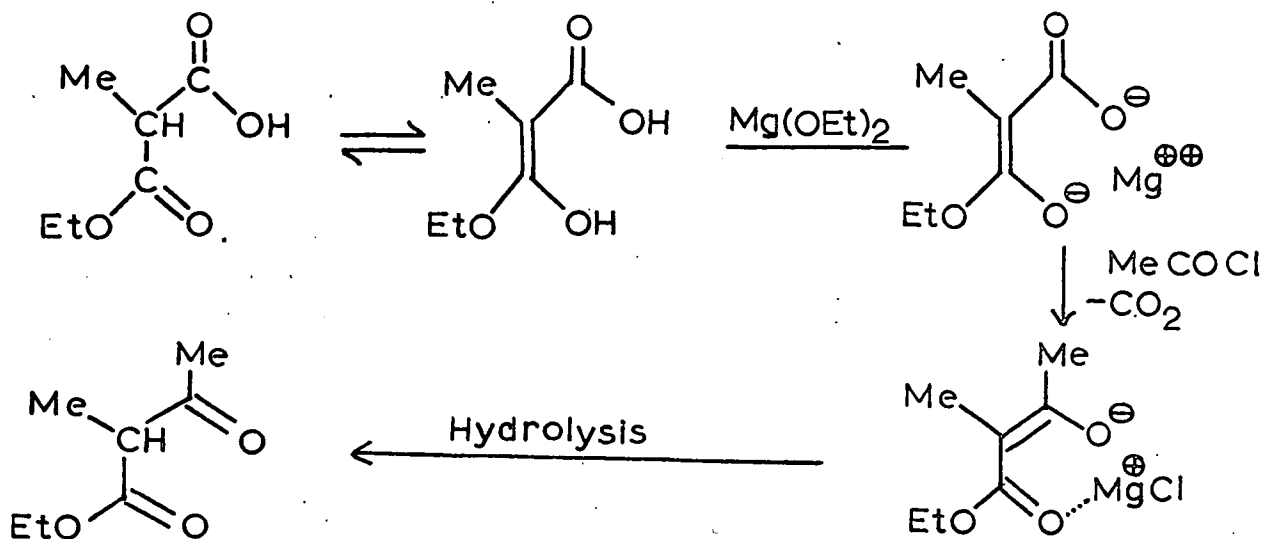




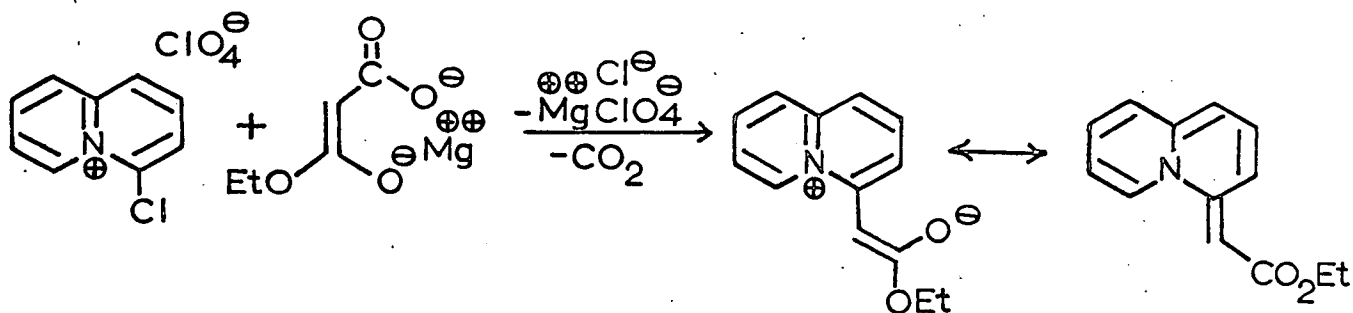
Reaction was first attempted in ethanol as solvent using sodium ethoxide to generate the yellow phosphorane. However, these conditions gave a 70% yield of 4-ethoxyquinolinium perchlorate which was identified from its n.m.r. spectrum. In an attempt to circumvent this difficulty, the phosphonium salt was converted irreversibly into the phosphorane by treatment with methyl lithium in ether. Reaction with the chloroquinolinium salt resulted, however, in progressive formation of a black amorphous solid. No starting material was recovered. It seemed probable, and consistent with later findings, that the reaction had taken the expected course and that the product was unstable under the reaction conditions.

A new approach to the required system was envisaged based on analogy with the formation¹⁰³ of β -ketoesters from alkyl magnesium malonates. When acetyl chloride is added at 0°C . to the chelated magnesium salt of ethyl hydrogen methylmalonate a rapid

evolution of carbon dioxide occurs and a new magnesium chelate is formed. On hydrolysis, the latter gives rise to ethyl α -methylacetoacetate.



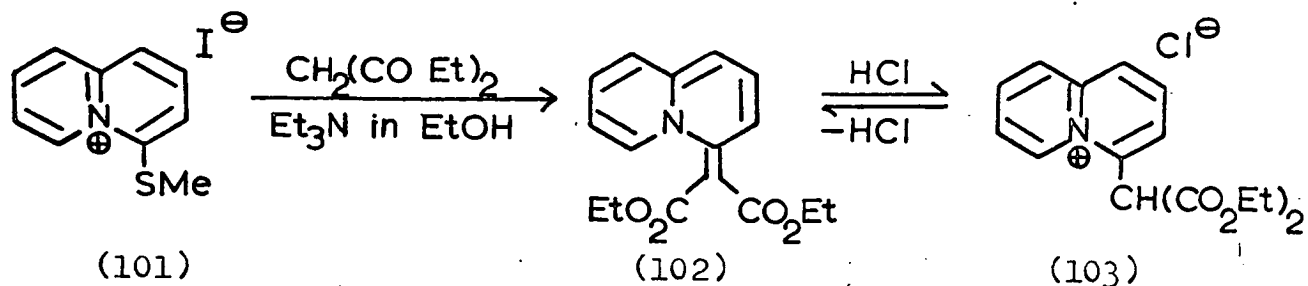
A similar sequence can be envisaged from ethyl hydrogen malonate and 4-chloroquinolizinium perchlorate



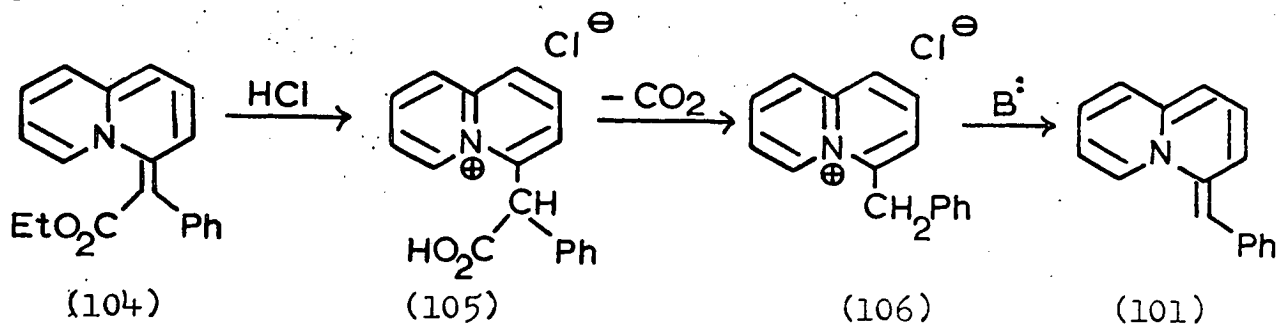
However, when a solution of the perchlorate in dimethylformamide was added to a solution of the magnesium chelate in tetrahydrofuran, the expected evolution of carbon dioxide did not occur. Subsequent warming of the reaction mixture to room temperature followed by reflux for 24 hours yielded only unreacted starting material. The result is best rationalised in terms of the vastly reduced susceptibility of the 4-chloroquinolizinium salt to

nucleophilic attack relative to that of the acid chlorides employed in the original experiments.

The failure of the foregoing approaches to the synthesis of methylenequinolizines prompted an attempted extension, and subsequent reinvestigation, of the method previously used for a reported synthesis of 4-(diethoxycarbonylmethylene)quinolizine (102). Boekelheide and Gall⁵⁸ claimed to have obtained this compound by reaction of 4-methylthioquinolizinium iodide (101) with diethyl malonate, in the presence of triethylamine.



By analogy, reaction of the quinolizinium salt (101) with ethyl phenylacetate might be expected to yield the quinolizine (104). Hydrolysis to the corresponding carboxylic acid (105), followed by decarboxylation and treatment of the resulting benzylquinolizinium salt (106) with base, might then provide the required system. (101).



However, when the reaction was attempted under the conditions of Boekelheide and Gall, no product consistent with the expected structure could be detected. The quinolizinium salt, which had

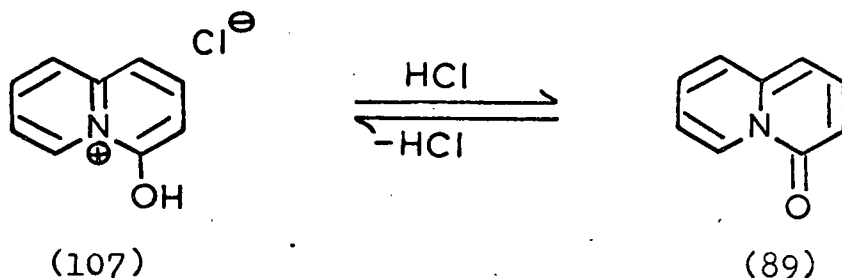
remained largely unreacted, was removed by filtration and a portion of the ethanolic solution was subjected to thin layer chromatography (t.l.c.) on silica. The presence of two reaction products was evident, these being identified as quinolizin-4-one and quinolizin-4-thione by comparison with authentic specimens.

In an attempt to circumvent difficulties caused by demethylation of the methylthio-group and simultaneously to effect more facile elimination of the leaving-substituent, the reaction was repeated using 4-chloroquinolizinium perchlorate. However, the latter was returned unchanged after 5 hours reflux. A further modification of the reaction conditions utilised the stronger base sodium ethoxide in place of triethylamine. Although a slight red colour was initially imparted to the reaction mixture, it gradually gave way to light-green during subsequent reflux. The residue obtained by evaporation of the solvent was recrystallised from ethanol and identified, from its n.m.r. spectrum as 4-ethoxyquinolizinium perchlorate.

The failure to generate the methylene-base (10⁴) by the foregoing procedures prompted a reinvestigation of the reported synthesis of methylene-base (10²). The reaction conditions described by Boekelheide and Gall were exactly duplicated and the resultant product, a yellow oil, was subjected to t.l.c. on silica. Two closely-moving components were discernible on development with ether; a minor pale-yellow band followed by a similar faintly-coloured major band. Trace amounts of a third yellow component were observed on the baseline. Chromatographic comparison of the two main products with authentic samples of

quinolizin-4-thione and quinolizin-4-one suggested identity with these compounds. Treatment of an ethereal solution of the yellow oil with anhydrous hydrogen chloride precipitated a white solid. After recrystallisation from ether/methanol this product possessed physical characteristics (m.p., u.v. spectrum) identical with that attributed by Boekelheide and Gall⁵⁸ to 4-(diethoxycarbonylmethyl)quinolizinium chloride (103).

Likewise the product proved unstable in air and reverted to a yellow compound with loss of hydrogen chloride. This property is characteristic of 4-hydroxyquinolizinium chloride (107).



The yellow oil was separated into its main components by chromatography on silica using ether as eluent and the initial tentative identifications were verified by mixed melting point and i.r. spectroscopy. A u.v. spectrum of the major component, quinolizin-4-one, in acidic ethanol was closely similar [Fig. 8] to that reported for the quinolizinium salt (103). The third component, which was present in only minute yield, was later identified, by comparison with an authentic sample, as the supposed product (102). However, its presence leaves the u.v. spectral properties of the mixture of quinolizin-4-one and quinolizin-4-thione hydrochlorides apparently completely unaffected.

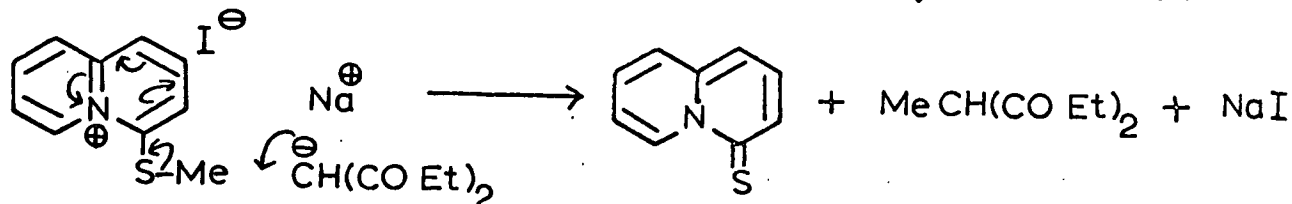
The evidence leaves little doubt that the original authors' conclusions were ill-founded; later findings conclusively

established this fact. Although, in the absence of rigorous spectral evidence, the error should have been revealed by elemental analyses data this was not so, primarily because the authors omitted the nitrogen and chlorine analyses but also because they miscalculated the required hydrogen percentage.

In order to effect the desired condensation, modification of the reaction conditions was attempted. Because of the extremely low solubility of the quinolizinium iodide (101) in ethanol, acetonitrile was substituted as reaction medium. T.l.c. of the product on silica again revealed the presence of a large proportion of quinolizine-4-thione with a smaller amount of the ketone. Traces of the required methylene-base were discernible.

The reaction was finally attempted using potassium *t*-butoxide as base, in *t*-butanol. Under these conditions, conversion of the malonic diester to its conjugate-base should be almost complete and participation of bulky solvent nucleophile in the displacement reaction should be negligible. However, in keeping with previous results, the thione and ketone were the only significant products.

The thione is presumably formed via an S_N2 mechanism involving attack by the malonyl anion at the methyl-carbon atom



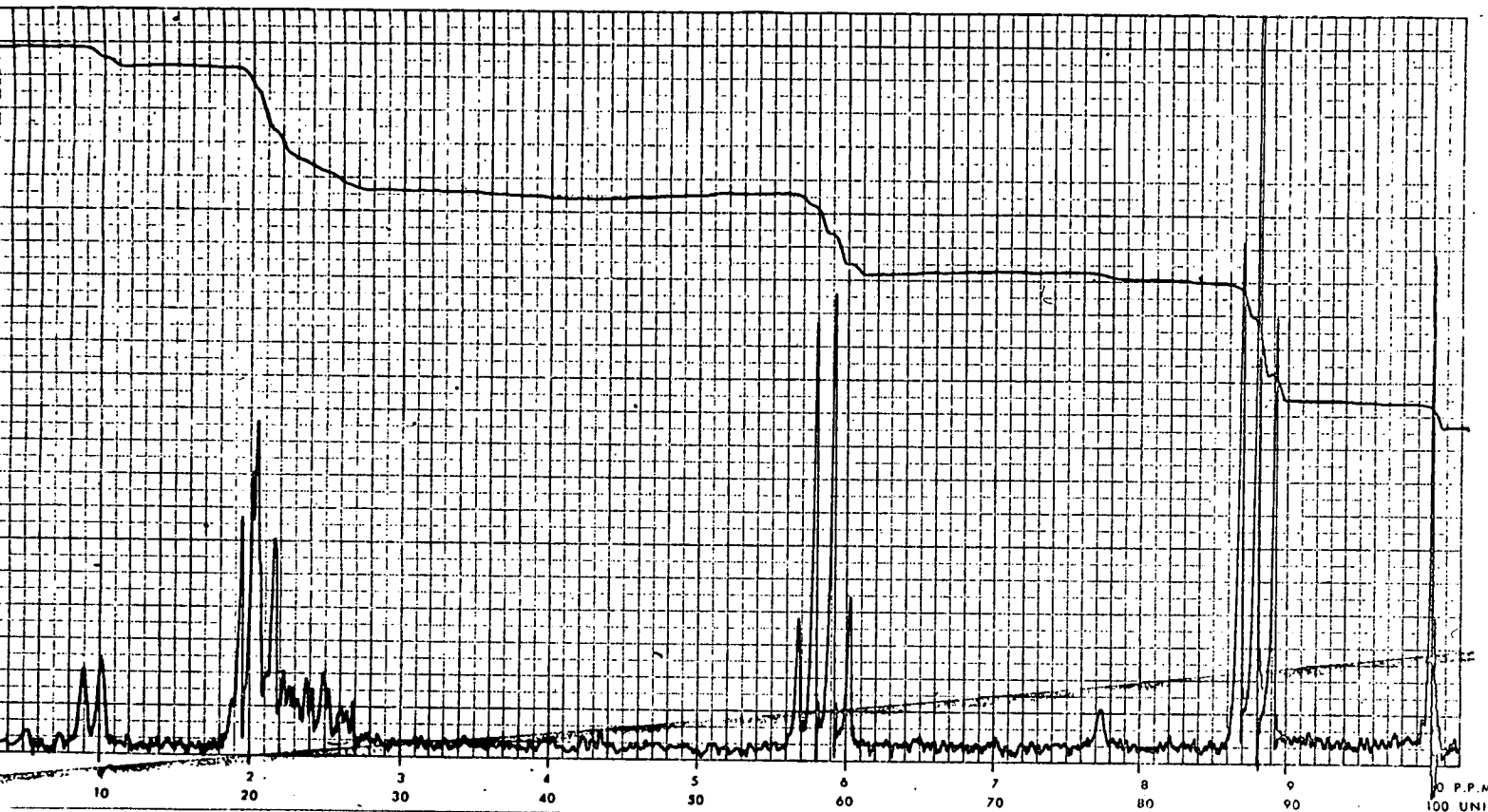
Alternatively, but less probably, a similar displacement may be initiated by the iodide ion. Elimination of methanethiole,

detectable by its odour, during these reactions is in keeping with some displacement at the 4-position of the nucleus. The formation of the ketone as the major product during reaction in ethanol suggests that the attacking nucleophile must be the hydroxide ion. Under anhydrous conditions only minute yields of this product were obtained. That attack by hydroxide ion is favoured rather than by the more strongly nucleophilic malonyl anion must be attributed to steric hindrance in the latter case.

In subsequent attempts to synthesise methylene-bases, 4-chloroquinolizinium perchlorate (96) was used as starting material. As mentioned previously this system is not susceptible to any competing type of nucleophilic displacement and has the advantage of possessing a more electronegative 4-substituent than its methylthio-counterpart (101). Many attempts involving a wide variety of conditions were made to bring the salt into reaction with diethyl malonate and in several instances the desired product was obtained. However, most of these approaches suffered from limitations which seriously inconvenienced their extension to large scale preparations. The nature of these difficulties will be considered at a later stage; at present the most convenient synthesis of the methylene-base (102) will be considered.

In order to eliminate interference from competing solvent nucleophile, a second mole of the malonyl anion was used as proton abstracting base [the initial product is the conjugate acid of (102)]. The anion was generated in anhydrous tetrahydrofuran by using sodium hydride. Addition of the quinolizinium salt resulted in an immediate exothermic reaction with formation of a

FIG. 15

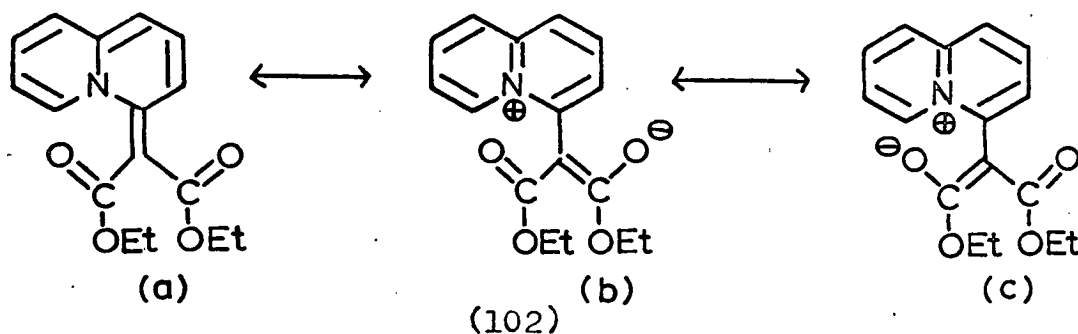


Diethyl quinolizin-4-ylidenemalonate

yellow solution. After 24 hours at 30°C., the yellow crystalline product was isolated in 78% yield; that it possessed structure (102) was amply demonstrated by physical and chemical methods.

The n.m.r. spectrum of the product in deuteriochloroform [Fig.15] showed, in addition to the signals attributable to the ten ethylprotons, a six-proton complex multiplet in the aromatic region (1.85 - 2.70 τ) consistent with that expected for the 1-, 2-, 3-, 7-, 8-, and 9- protons of the quinolizine nucleus. In addition, a low-field doublet (split by ortho-coupling) at 0.94 τ was typical of an α -pyridine proton absorption and was assigned to the 6-position of the molecule. Its slightly low-field value relative to the α -protons of pyridine (1.5 τ) may be attributed to long-range deshielding by the spatially adjacent ethoxycarbonyl group.

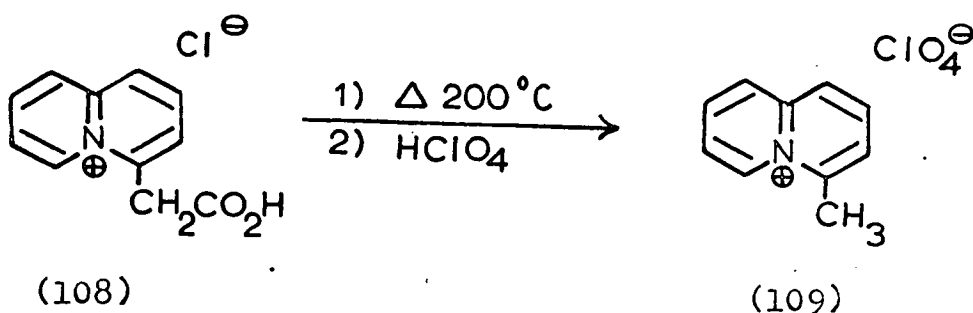
The i.r. spectrum showed a strong absorption band at 1700 cm^{-1} . This value is somewhat lower than expected for an α,β -unsaturated ester (1715-1730 cm^{-1}) and suggests that the carbonyl groups are more polarised than normal. However, the discrepancy can readily be accounted for in terms of dipolar structures (102b) and (102c) which contributed to the resonance hybrid.



The ready availability of the lone-pair of electrons on the nitrogen atom was demonstrated by the ease with which the compound became protonated in dilute acids. Basification of the resultant colourless solutions regenerated the yellow methylene-base. The u.v. spectrum of the perchlorate salt in ethanol was closely similar to that of the parent quinolizinium ion (88) in aqueous solution [Fig.10], showing but a short bathochromic shift of 6-7 m μ . The spectrum attributed to the corresponding hydrochloride salt by Boekelheide and Gall was quite different but strongly resembled that of the 4-hydroxyquinolizinium ion (107) [Fig.8]

A final irreconcilable difference between the product of Boekelheide and Gall and the present compound concerns the nature of their hydrochloride salts. Treatment of a solution of (102) in dry benzene with anhydrous hydrogen chloride deposited not a white solid as previously reported, but a colourless mobile oil. The perchlorate salt exhibited similar characteristics. When refluxed in 6N hydrochloric acid, the quinolizine was converted into a crystalline salt which showed strong carboxyl i.r. absorption bands at 1725 cm.⁻¹ (C=O) and 2750-3500 cm.⁻¹ (OH). The u.v. spectrum remained typical of a quinolizinium system. The n.m.r. spectrum exhibited the expected aromatic multiplet (1.35 - 1.95 τ) and low-field doublet (0.77 τ) attributable to the seven nuclear-protons. In addition, a two-proton singlet at 5.18 τ indicated the presence in the molecule of deshielded methylene-protons. Thermolysis of the salt at 200°C., caused brisk evolution of a gas with the formation of a product which

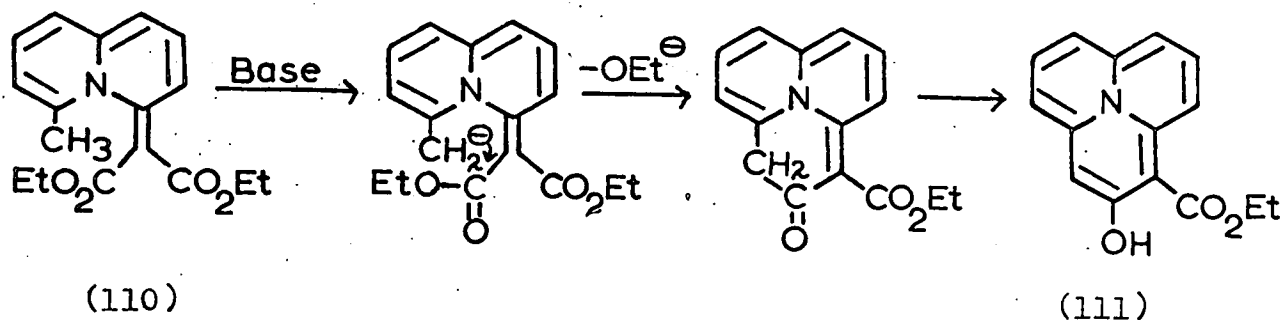
was shown, following treatment with perchloric acid, to be identical with an authentic specimen of 4-methylquinolizinium perchlorate (109). The foregoing evidence leaves no doubt that the compound in question is 4-(carboxymethyl)quinolizinium chloride (108) and that the compound from which it is derived is the methylene-base (102).



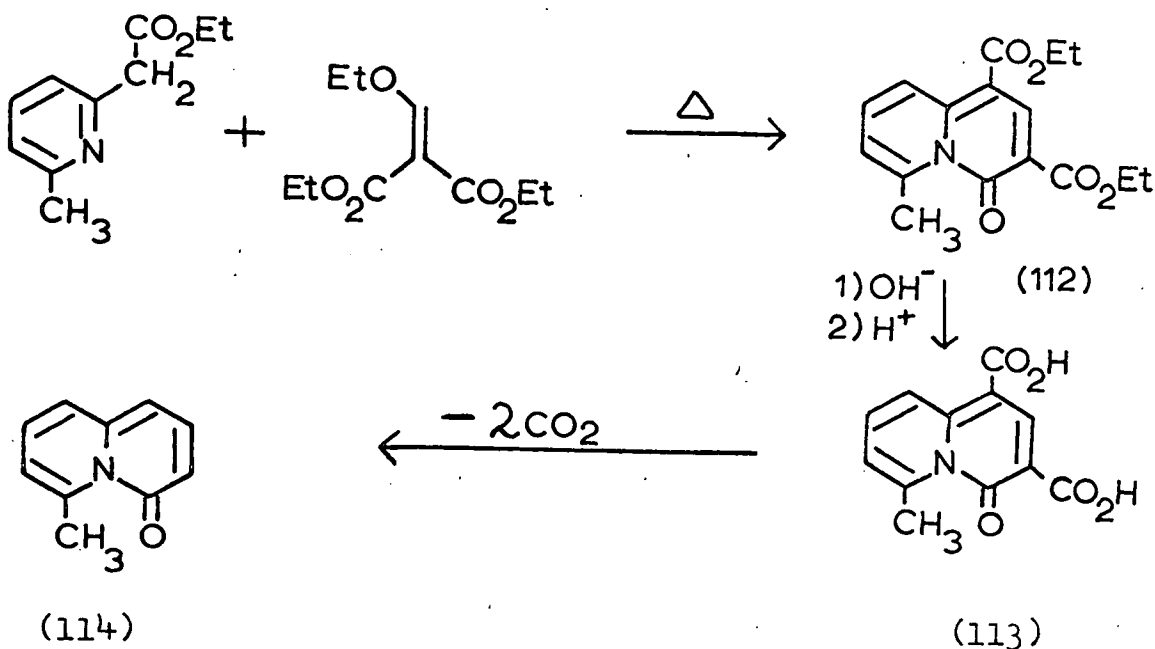
Although several other reaction conditions produced measurable yields of (103) these proved inferior to the procedure already described. Thus triethylamine as base, in ethanol or acetonitrile, gave only a 30% yield of the methylene-base after 5 hours reflux. Sodium ethoxide in ethanol yielded 36% of 4-ethoxyquinolizinium perchlorate in addition to the methylene-base. Potassium *t*-butoxide in *t*-butanol yielded large amounts of decomposition product together with unidentified by-products. The use of dimethylsulphoxide as solvent with its conjugate anion as base presented considerable practical difficulties, purification of the product requiring tedious chromatographic procedures. Similar difficulties were encountered following addition of a solution of the quinolizinium salt in dimethylformamide to a suspension of diethylsodiummalonate in benzene. Although high yields of product were obtained (~80%) the removal of residual solvent proved exceptionally difficult.

It appears that the methylene-base readily forms stable, non-crystalline solvates with high boiling solvents such as dimethylsulphoxide and dimethylformamide. Purification cannot be accomplished by normal procedures (e.g. extraction, evaporation) and chromatographic purification is severely hindered by the comparable rates of elution of the respective components. The initial product obtained from the reaction in tetrahydrofuran appears to be of a similar nature. Evaporation of solvent yielded a yellow viscous residue from which the last traces of diethyl malonate could not be removed even by prolonged evaporation in vacuo. However, the pure crystalline methylene-base was readily obtained after chromatography of the initial solvate on deactivated alumina.

Having successfully developed a practicable synthesis of the methylene-base (102) it appeared of interest to attempt preparation of the 6-methyl analogue (110) and thus investigate the feasibility of Boekelheide's projected route⁵⁸ to the cycl[3.3.3]azine system (111). i.e.



Synthesis of the requisite starting material, 6-methylquinolizin-4-one, was accomplished according to the method⁵⁸ of Boekelheide and Gall.



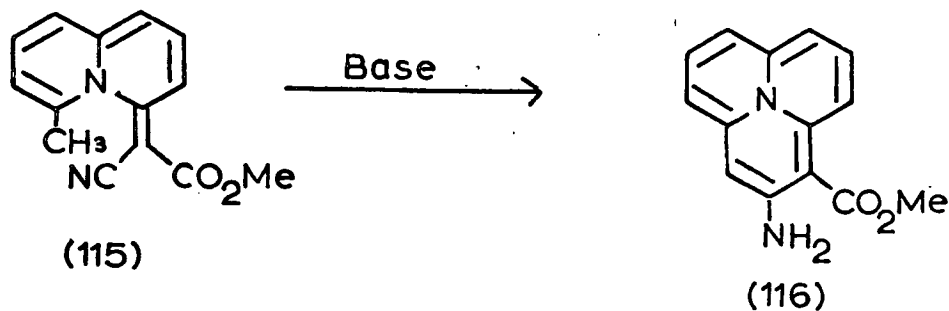
However, the method resulted in yields of the diester (112) much inferior to that claimed by these authors. The initial product from the thermally-induced reaction contained a large amount of decomposition product and subsequent purification proved extremely difficult. The same workers have reported an analogous synthesis of quinolizone from ethyl 2-pyridylacetate, but later workers¹⁰⁴ have obtained much improved yields by catalysis of the reaction with sodium ethoxide at room temperature. Although this procedure was not used in the present instance it would have undoubtedly obviated the practical difficulties inherent in the thermally-induced reaction.

Treatment of the quinolizone (114) with phosphoryl chloride followed by perchloric acid yielded the required 4-chloro-6-methylquinolizinium chloride as colourless needles. Its identity was confirmed by spectral evidence [u.v., Fig. 14] and elemental

analyses. Addition of the salt to a solution of diethyl sodiomalonate in tetrahydrofuran caused immediate formation of a yellow product. However, the solution darkened as the reaction progressed, assuming eventually a deep-brown colour. The yellow product isolated by chromatography on alumina was thermally unstable and required purification by low-temperature recrystallisation. The n.m.r. spectrum was very similar to that of the methylene-base (102) but showed the absence of the α -pyridine low-field doublet. Instead, a three-proton singlet at 7.47τ confirmed the presence of the 6-methyl substituent.

Although various attempts were made to effect the desired intramolecular condensation, no product corresponding to the cyclazine could be isolated from these reactions. Thus, treatment with sodium hydride in warm anhydrous benzene returned unchanged starting material together with a substantial amount of decomposition product. Sodium ethoxide in ethanol or potassium *t*-butoxide in *t*-butanol yielded a dark amorphous product which appeared to be polymeric in nature.

In view of the instability of the methylene-base (110) (presumably a consequence of steric interaction between the 4- and 6- substituent groups), an attempt was made to synthesise the cyclazine nucleus by an analogous route from the related base (115).

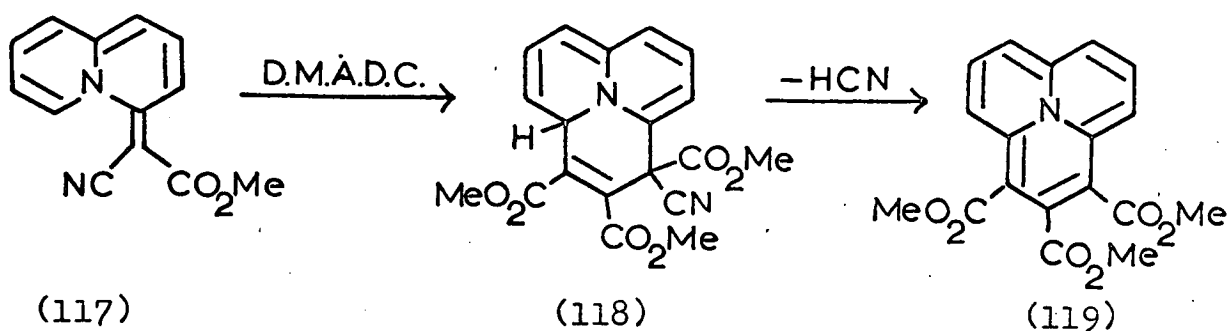


(115) was obtained in 80% yield as a stable orange solid by reaction of the quinolizinium salt with methyl cyanoacetate. Although two structures may be considered for the product because of the possibility of geometrical isomerism about the exocyclic double-bond, that represented is expected to be favoured because of the reduced steric interaction between the more compact linear cyano group and the 6-methyl substituent. Furthermore, this factor can account for the enhanced stability of the system relative to that of methylene-base (110).

(Although a factor of probably equal importance, in this context, is the greater ability of the cyano group than the ethoxycarbonyl group to stabilise negative charge). The n.m.r. spectrum was entirely consistent with the assigned structure and showed no evidence (in common with other spectral and physical properties) for the presence of a second geometrical isomer.

Attempted intramolecular cyclisation of the product, however, yielded products similar to that obtained from the preceding methylene-base (110). Nothing corresponding to the desired cyclazine could be isolated. The amorphous, polymeric-like nature of the products suggested that either an intermolecular condensation reaction had occurred instead of the expected intramolecular cyclisation, or, that the cyclazine had been formed but was unstable under the reaction conditions. By either interpretation the approach lacked promise and was abandoned in favour of alternative methods.

During the progress of the work directed towards a synthesis of monosubstituted methylenequinolizines, the possibility of an approach to the cyclazine system via suitably disubstituted methylenequinolizines was considered. A reasonable choice of starting material for this purpose appeared to be the readily available methylene-base (117). Thus 1,3- dipolar addition of dimethyl acetylenedicarboxylate might yield the tricyclic intermediate (118) which, by loss of hydrogen cyanide, would lead to the cyclazine system (119)



Reaction of (117), in boiling anhydrous toluene, with a two-fold excess of the acetylenic ester resulted in a gradual colour-change of the solution from light-yellow to dark-blue. After 30 hours, the concentrated reaction-mixture was chromatographed on alumina to yield, as major product, a compound which formed intensely blue solutions. Recrystallisation from benzene/light-petroleum yielded lustrous green plates. However, these proved not to be the desired cyclazine. A sharp absorption in the i.r. spectrum at 2190 cm^{-1} indicated the presence in the molecule of a cyano-group. The possibility that a simple 1:1 linear-adduct (i.e. a substituted maleate or fumarate ester) had been formed as a result of electrophilic substitution on the

bicyclic nucleus was inconsistent with the intense colour of the compound. Further, the resistance of the compound to protonation in dilute acids could not be reconciled with such an interpretation. An indication of the complexity of the transformation was obtained from mass spectral evidence. The m/ϵ value of the parent molecular ion was two mass units less than the value expected for a true 1:1 adduct of the individual reactants. This inferred that dehydrogenation had accompanied reaction. The n.m.r. spectrum showed three singlets (at 5.96τ , 6.00τ and 6.12τ) attributable to the methoxy protons (thus confirming that only one mole of acetylenic ester was involved in reaction), together with four doublets and a triplet, corresponding to a total of five nuclear-protons, in the region $0.3 - 2.2\tau$

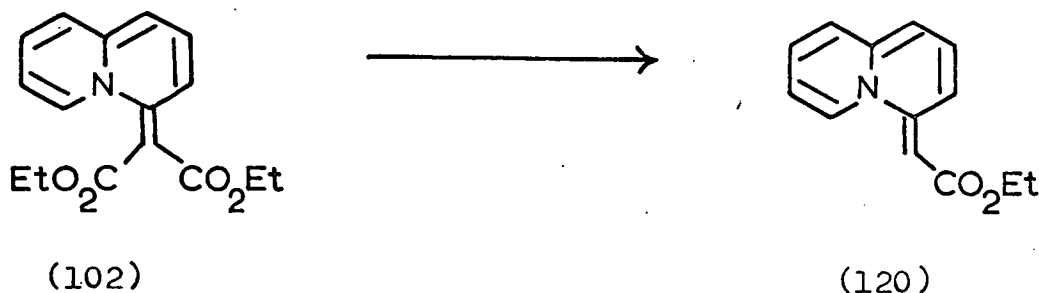
Superficially, it would appear that elucidation of the structure should readily follow from the evidence available. Thus dehydrogenation, unless it leads to an acetylenic linkage, for which there is no evidence, must necessarily involve a cyclisation reaction and consequently the formation of a tricyclic system. The problem would appear to be further simplified by the fact that the elemental constitution of the product (allowing for the loss of hydrogen) corresponds to a 1:1 molar combination of the reactants. That the cyano group and ester groups remain intact, would appear to further limit speculation regarding the nature of the product. However, in spite of these factors, the physical and chemical evidence cannot readily be accounted for in terms of any simple structure. Future work on this compound will require a more elaborate

spectral and chemical investigation.

When reaction was attempted between 4-(diethoxycarbonylmethylene)quinolizine (102) and the acetylenic ester, with a view to elucidating the structure of the preceding adduct, a mixture of eight different products was formed. However, because of the small yield of each individual product and the considerable difficulties experienced in effecting their separation, the reaction was not further investigated.

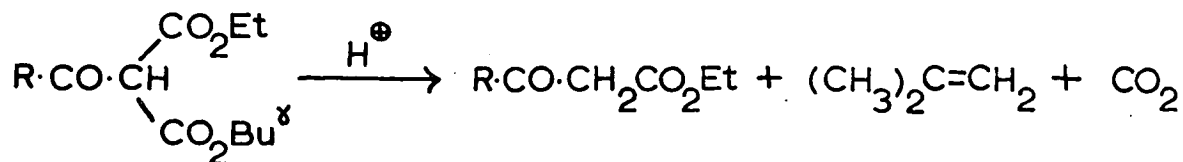
Synthesis of alkyl quinolizin 4-ylideneacetates

An obvious route to monosubstituted methylenequinolizines involves selective hydrolysis and decarboxylation of the methylene-base (102).

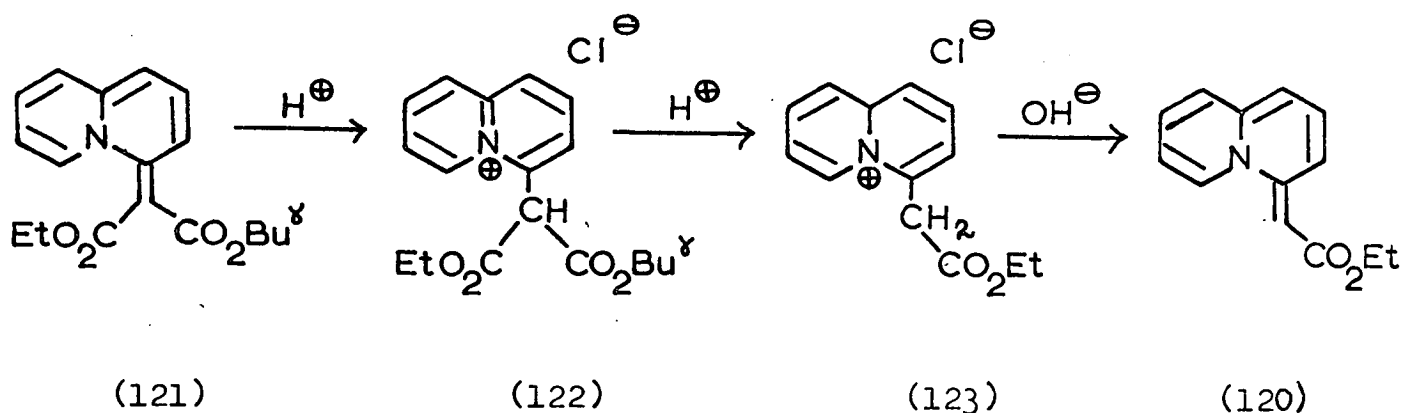


However, conditions cannot be readily devised that result in specific attack by the reagent at only one of the carbonyl centres. Hydrolysis of (102) with 2N hydrochloric acid yielded the 4-(carboxymethyl)quinolizinium salt (108). Attempted alkaline hydrolysis with ethanolic potassium hydroxide returned the quinolizine unchanged. However, a promising means of resolving the problem seemed possible by utilising the lability

of t-butyl esters under mild acidic conditions. It has been shown¹⁰⁵ that acetylated ethyl t-butyl malonates, when refluxed in toluene in the presence of p-toluenesulphonic acid, eliminate isobutene and carbon dioxide to yield the corresponding β -keto esters. i.e.



The t-butoxycarbonyl group of the di(alkoxycarbonyl)-methylquinolizinium salt (122) should, under appropriate conditions, undergo a similar facile cleavage to yield the monoalkoxycarbonyl analogue (123). Treatment of the latter with a suitable base would then liberate the ethoxycarbonylmethylenequinolizine (120).

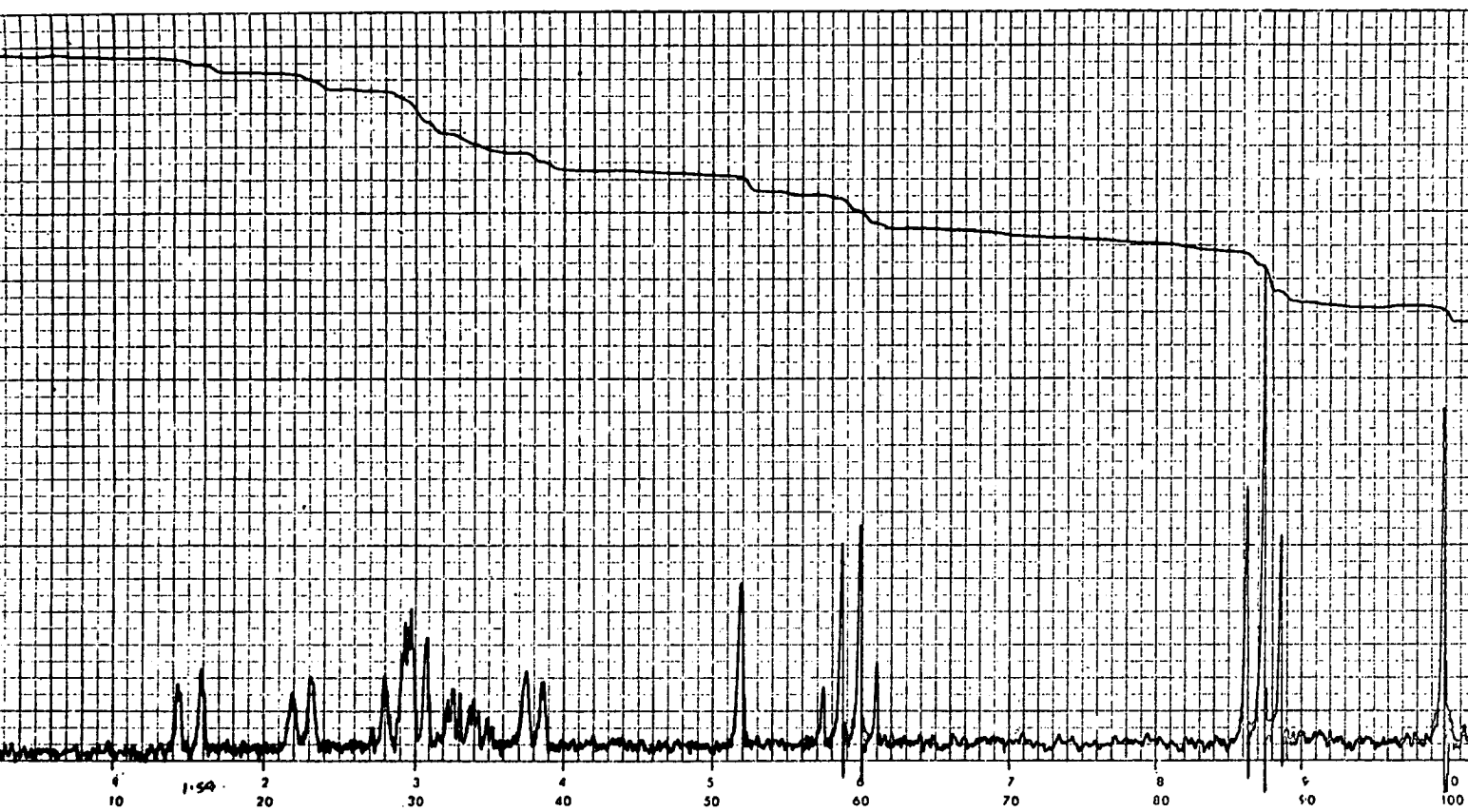


The t-butyl ethyl ester (121) was obtained from t-butyl ethyl malonate and 4-chloroquinolizinium perchlorate by the procedure described previously for the diethyl ester (102).

The conditions under which cleavage of the t-butoxycarbonyl group is normally effected, viz. with catalytic quantities of p-toluenesulphonic acid, are not ideally suited to the methylenequinolizine system because of its basic nature. Instead, it was found convenient to treat a solution of the quinolizine in anhydrous benzene with dry hydrogen chloride. The quinolizinium salt separated as a dense, mobile, colourless oil which rapidly effervesced when heated on a water bath to 60°C. The residual product, a similar colourless oil, liberated a bright orange-red compound when treated in the cold, under a nitrogen atmosphere, with an aqueous solution of 6N sodium hydroxide. The product, however, proved extremely unstable. Extraction with carbon tetrachloride yielded intensely coloured solutions which rapidly darkened on standing, finally depositing a dark tar-like residue. Evaporation of a freshly extracted solution in the cold yielded a viscous oil which solidified after prolonged agitation. Orange-red plates were obtained by low-temperature recrystallisation. Although the compound was more stable in the solid state, exposure to the atmosphere over several days caused formation of a large amount of decomposition product. However, the incidence of the latter was considerably reduced by storing the product under a nitrogen atmosphere at a low temperature (-15°C.). Samples thus preserved remained comparatively free of resinous product for periods of several weeks.

That the product was indeed the ethoxycarbonylmethylenequinolizine (120) was confirmed by physical and chemical evidence.

FIG. 16

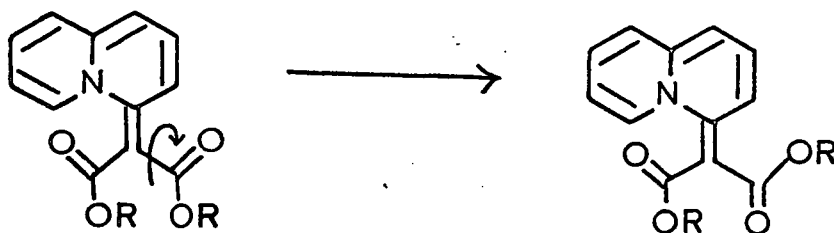


Ethyl quinolizin-4-ylideneacetate

The n.m.r. spectrum [Fig.16] in carbon tetrachloride revealed the presence of only one ester group, the absorption attributable to the methyl protons of the t-butoxycarbonyl group in the precursor compound having completely disappeared. Instead, the spectrum showed a singlet at 5.20τ attributable to the proton joined to the double-bond. Although this chemical shift is somewhat higher than might be expected for a vinylic proton α to a double-bond, the displacement can be accounted for in terms of shielding of the proton consequent on the significant contribution of dipolar structure (120c) (see below) to the resonance hybrid. Allowing for solvent effects (a displacement of approximately $+0.1\tau$ in changing from $CDCl_3$ to CCl_4), the principal aromatic absorptions ($2.7 - 3.6\tau$) showed a general upfield shift relative to those of the parent compound ($1.8 - 2.7\tau$) and were dispersed over a greater frequency range. This difference is consistent with the reduced degree of charge-separation that is expected to ensue within the molecule after removal of the t-butoxycarbonyl group.

A feature of interest in the spectrum of (120) was the appearance of two, low-field, one-proton doublets (each split by further coupling) which were centred at 1.54τ and 2.27 ~~3.82τ~~ , respectively. The doublet at 2.27 ~~3.82τ~~ was assigned to the α -pyridine proton since its coupling-constant ($J=7$ c/s.) was the same as that of the corresponding proton in the parent compound. Although this assignment implies a considerably large upfield shift (1.31τ) for the α -pyridine proton resonance, a

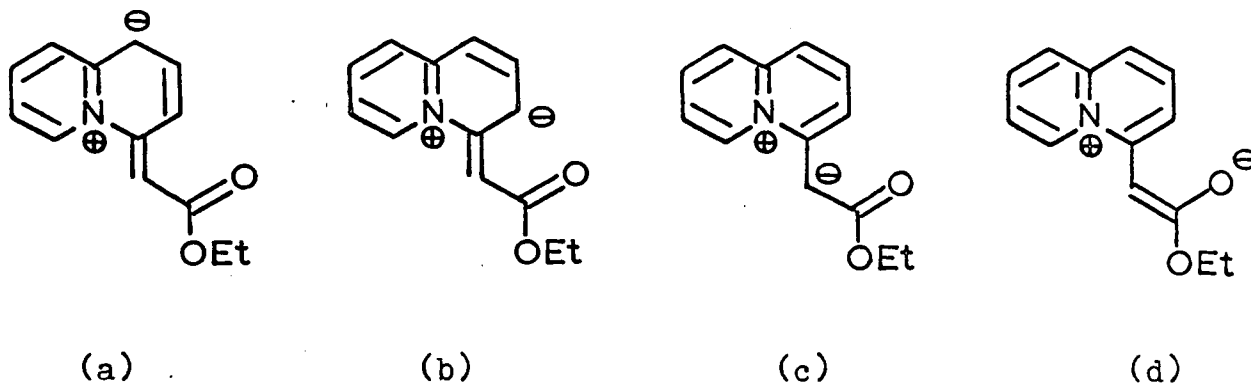
shift of this magnitude is consistent with the elimination of the long-range deshielding influence of the t-butoxycarbonyl group. The remaining low-field signal ($J = \frac{9}{7} \text{c/s.}$) was assigned to the 3-proton. The downfield displacement can then be accounted for in terms of deshielding of the proton by the spatially-adjacent ester group. Although a similar displacement was evident in the spectra of several other similarly constituted quinolizines, it is significant that this was not apparent in the spectra of di(alkoxycarbonyl)-methylenequinolizines. The discrepancy is best rationalised in terms of the conformational orientation of the ester substituents in the latter compounds. It appears that as a result of steric interaction between the alkoxy groups that the ester substituent anti to the ring-system exists preferentially in the conformation shown below.



The long-range deshielding influence of this group on the 3-proton is thus minimised.

The unusually high-field, one-proton doublet which appears in the spectrum of (120) was assigned to the 1-proton.

This assignment may be rationalised from a consideration of the principal contributing structures to the resonance hybrid.



(120)

The significance of each of these structures relative to the corresponding structures in the parent compound is expected to be increased since only four principal dipolar structures are now possible as opposed to five with the latter compound. The 1- and 3-protons will be correspondingly shielded. However, as indicated previously, the 3-proton is also subject to the counter deshielding influence of the adjacent ester group. This latter influence overwhelmingly dominates the direction of the displacement of the resonance signal. [The strong deshielding influence of an ester substituent on a *peri*-situated proton is evident in the spectrum of compound (145). Here, no ambiguity arises in the assignment of the low-field resonance to the appropriate ring-proton].

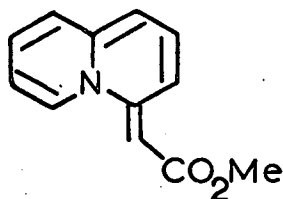
The i.r. spectrum of (120) showed a low-frequency carbonyl absorption band at 1655 cm.^{-1} . This indicates a greater degree

of carbonyl-group polarisation than that which exists in the parent compound. This may be rationalised from a consideration of dipolar structure (120d). Although the degree of charge-separation is less than that which exists in the parent compound the negative charge is now localised on a single oxygen atom rather than shared between two such atoms. The carbonyl group thus assumes a greater degree of single-bond character. The u.v. spectrum of the product in acidic ethanol [Fig.13] was virtually superimposable on that of the protonated diester (103) thus indicating that a quinolizinium salt had been formed.

A significant chemical feature of ethoxycarbonylmethylenequinolizine is its strongly basic character. The compound readily dissolves in water to form colourless solutions from which the free-base cannot be regenerated even by addition of strong alkali. In this connection the formation of the system via proton abstraction from the corresponding hydrochloride salt can only be satisfactorily accomplished by direct addition of alkali. Initial solution of the salt in water followed by addition of alkali gives only a minimal yield of product. This behaviour is rather anomalous but must be a consequence of the strongly basic nature of the system; hence the ease with which it reverts to the quinolizinium salt in protonic media. When applied to silica or alumina, the quinolizine was immediately decolourised thus preventing purification by chromatography. Treatment of the adsorbent with alkali regenerated the product, thus indicating the reversible nature of the transformation.

The strongly basic character of the molecule is further demonstrated by its ready protonation in neutral ethanol. Thus the u.v. spectrum in the latter solvent was changed only slightly by addition of perchloric acid. An authentic spectrum of the methylenequinolizine was obtained by using cyclohexane [Fig.12] in place of ethanol. Although the short wavelength (220-350 m μ .) absorption bands strongly resembled those of the protonated system (but displayed a hypochromic shift of 8 m μ .), a significant difference was the appearance of a strong visible absorption at 450 m μ . The latter band showed a moderate solvent sensitivity, undergoing a blue-shift of 5 m μ . in acetonitrile. This evidence, taken in conjunction with the n.m.r. and i.r. properties, strongly supports the view that ethoxycarbonylmethylenequinolizine is stabilised by dipolar resonance interaction in the ground state.

A similar sequence of reactions, starting from t-butyl methyl malonate, gave methoxycarbonylmethylenequinolizine (124).



(124)

It is noteworthy that when treatment with hydrogen chloride in benzene was prolonged the protonated forms of these monoesters

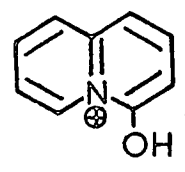
were converted into the corresponding carboxylic acid (108). Although it is possible that traces of water might have promoted partial hydrolysis, complete conversion suggests alkyl-oxygen cleavage, possibly initiated by S_N2 displacement, at the alkyl group, by a chloride ion.

— O —

FIG. 8

Boekelheide's
product

—



- - -

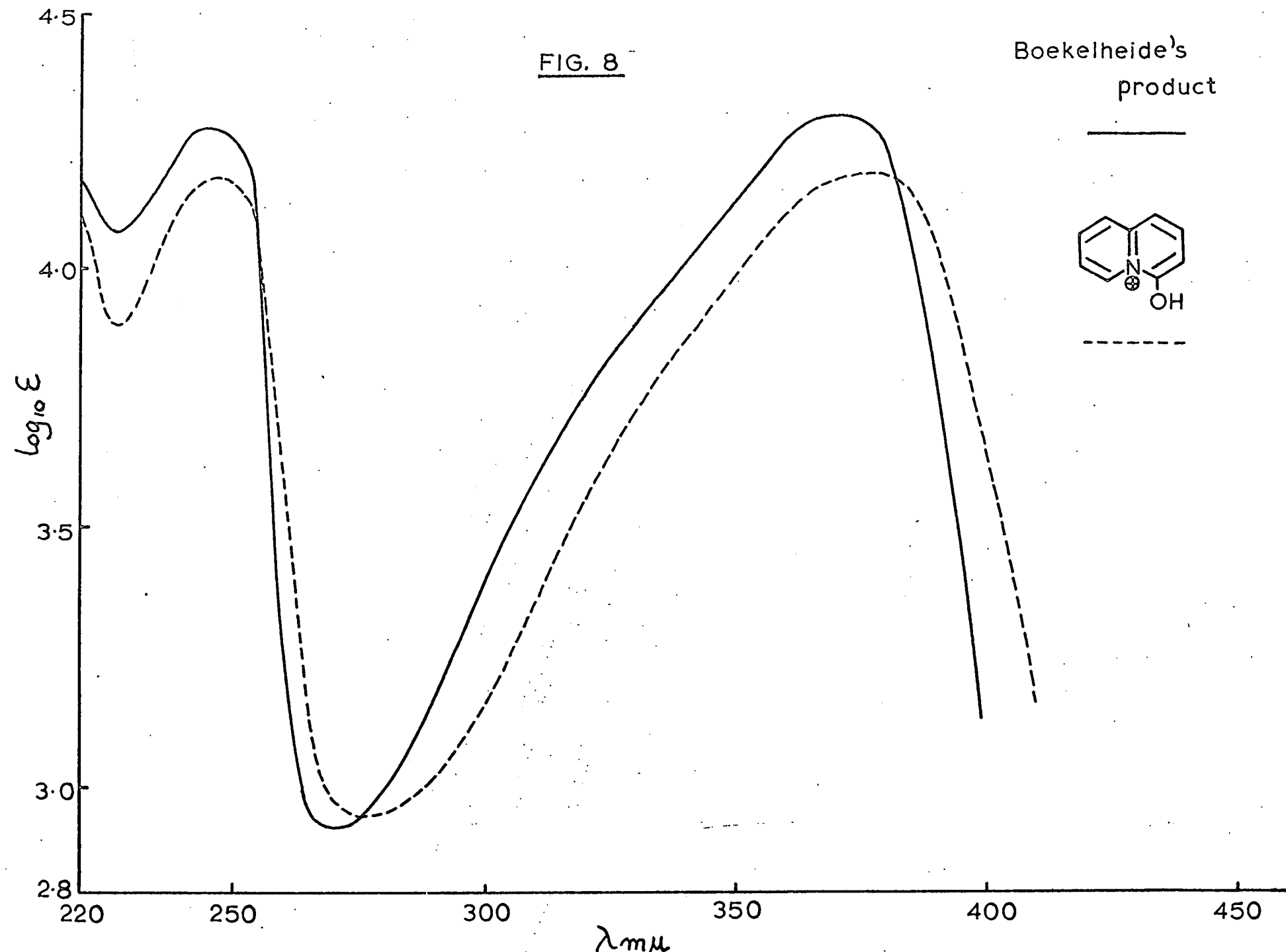


FIG. 9

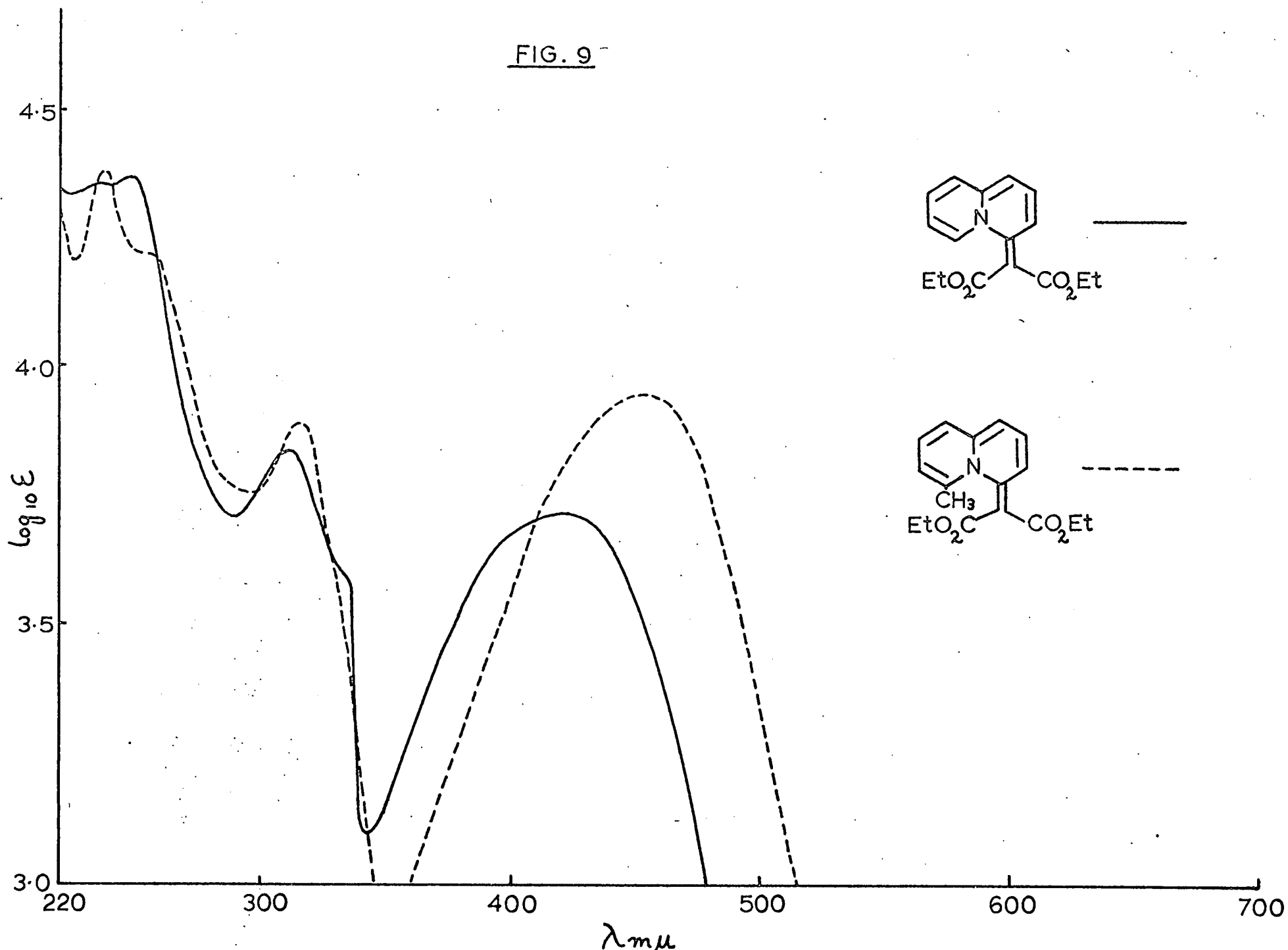


FIG. 10

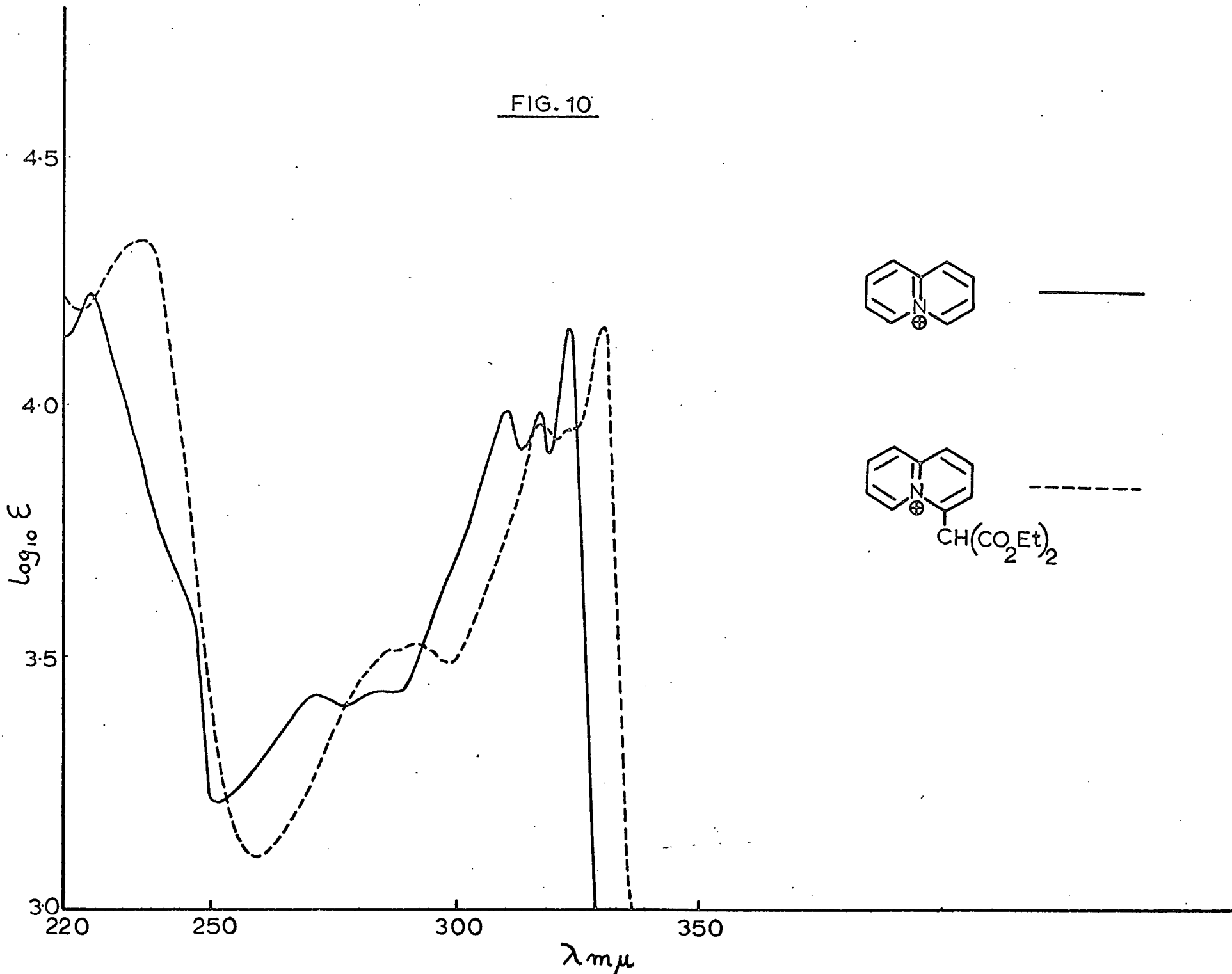


FIG. 11

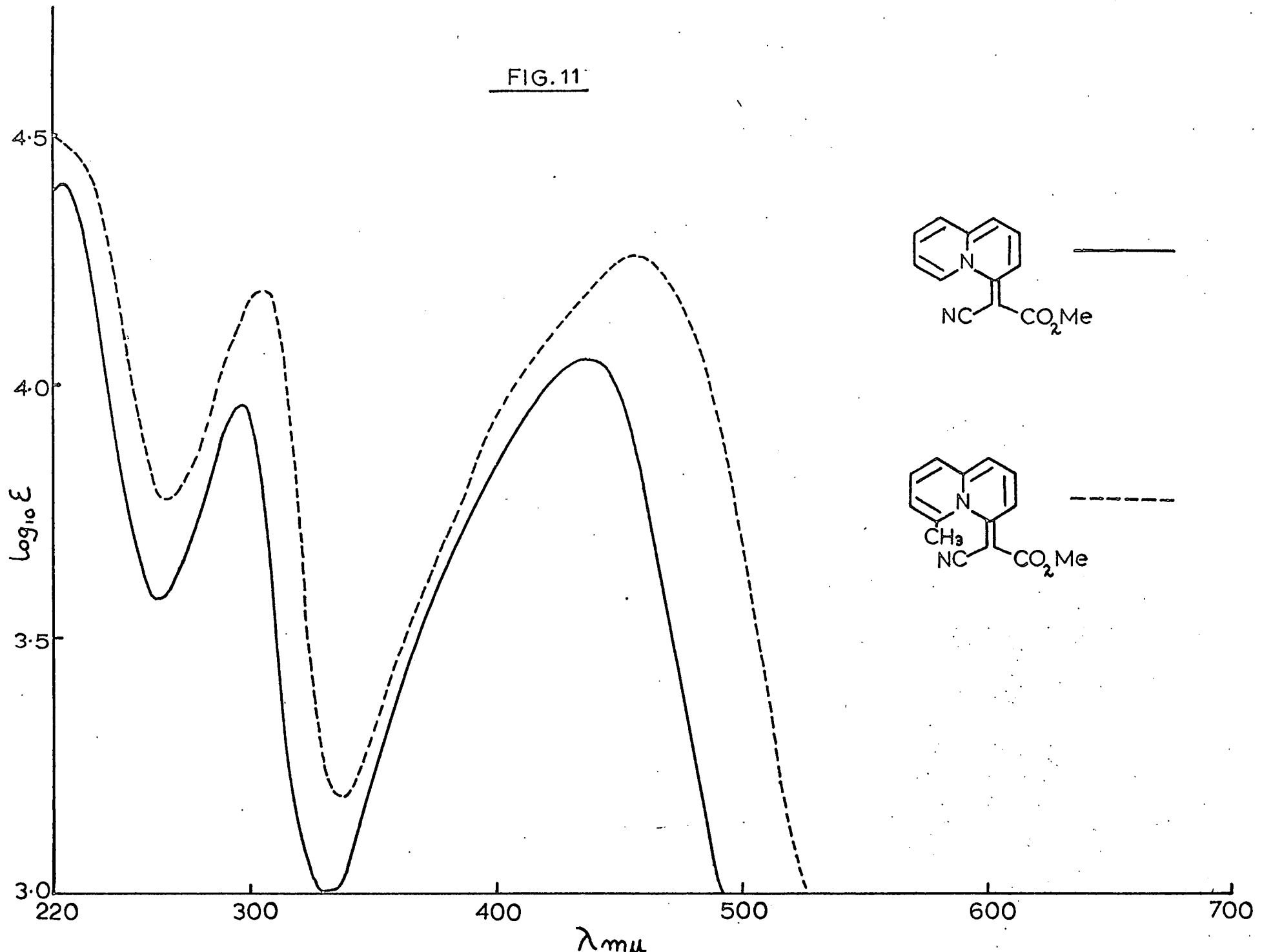


FIG. 12

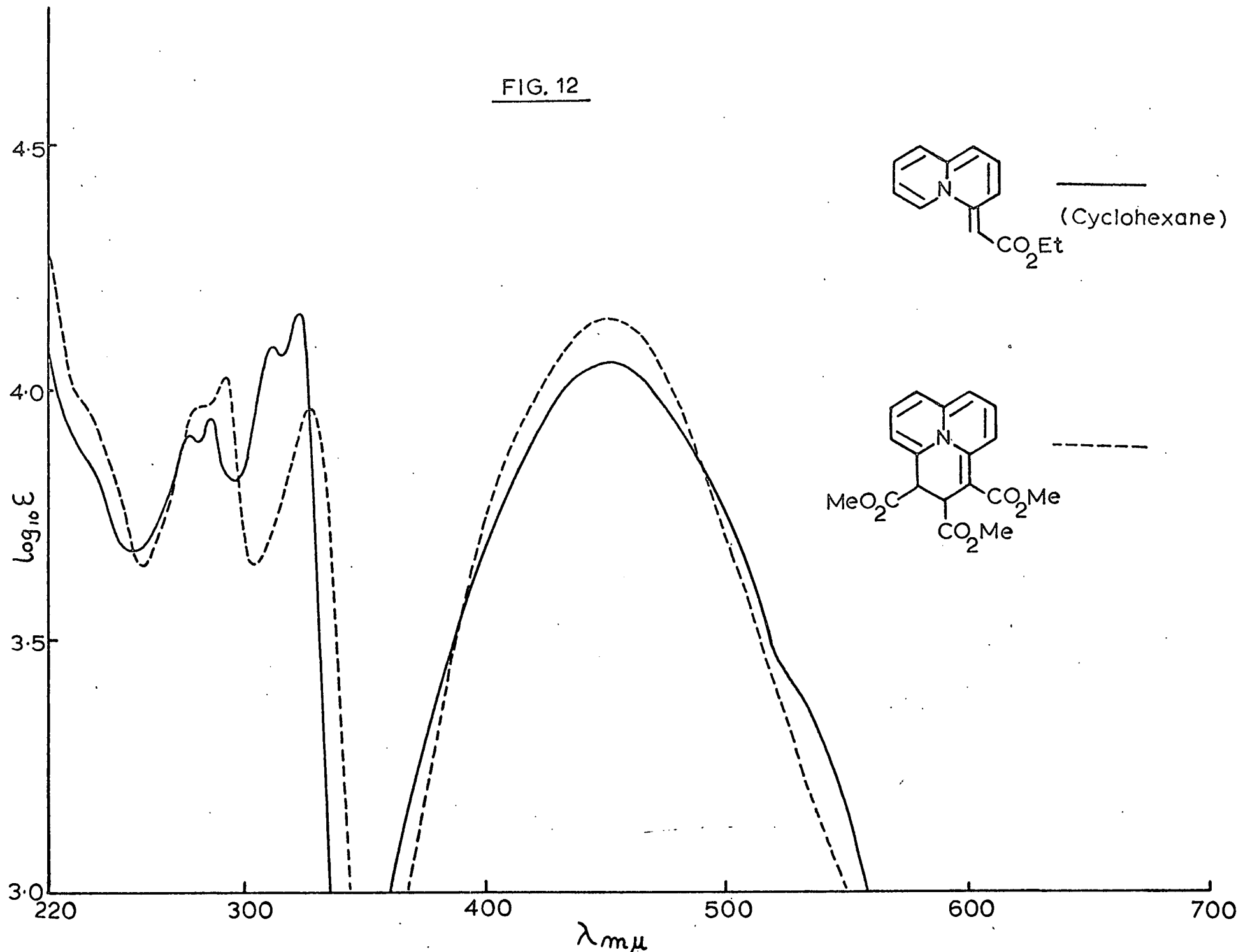


FIG. 13

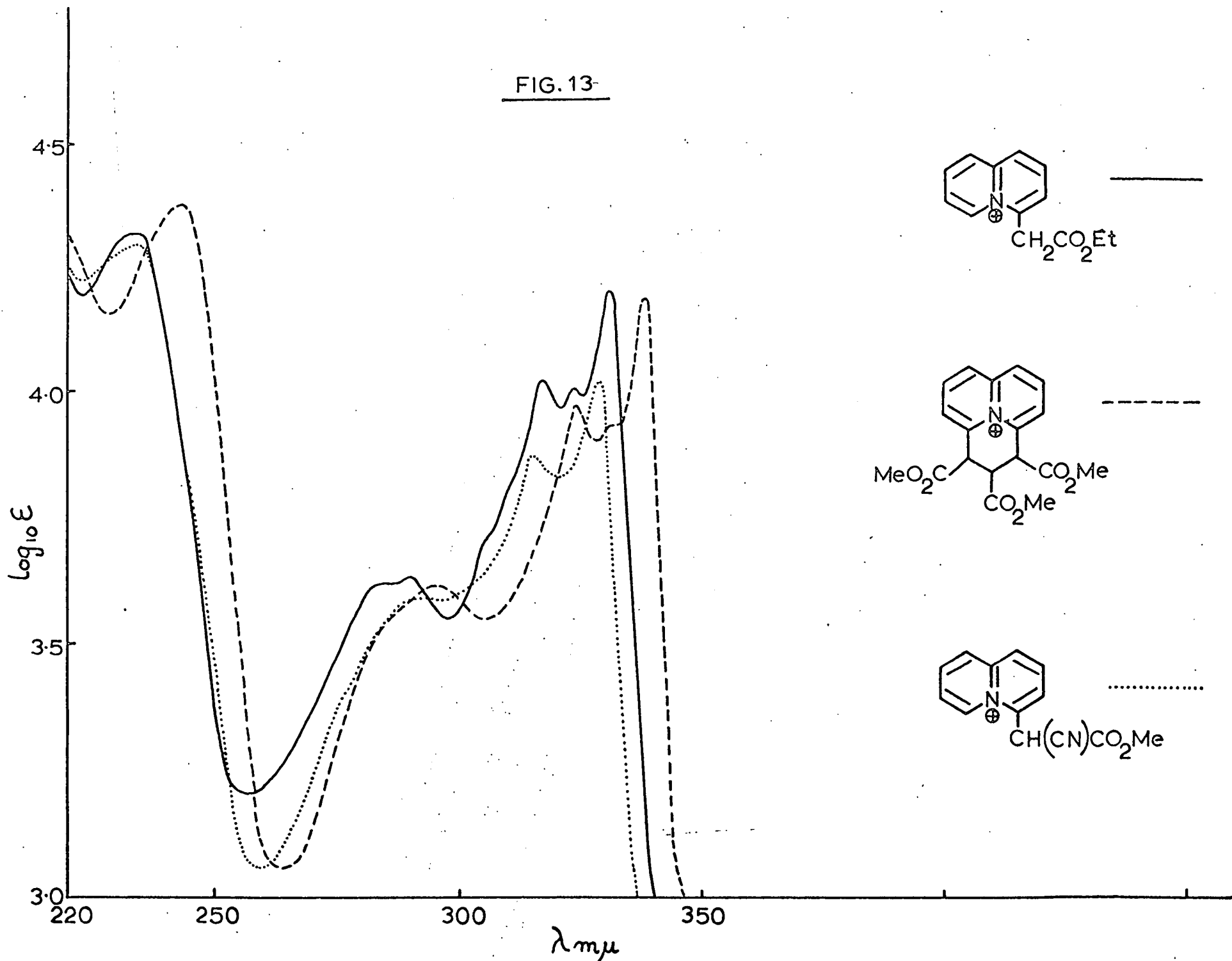
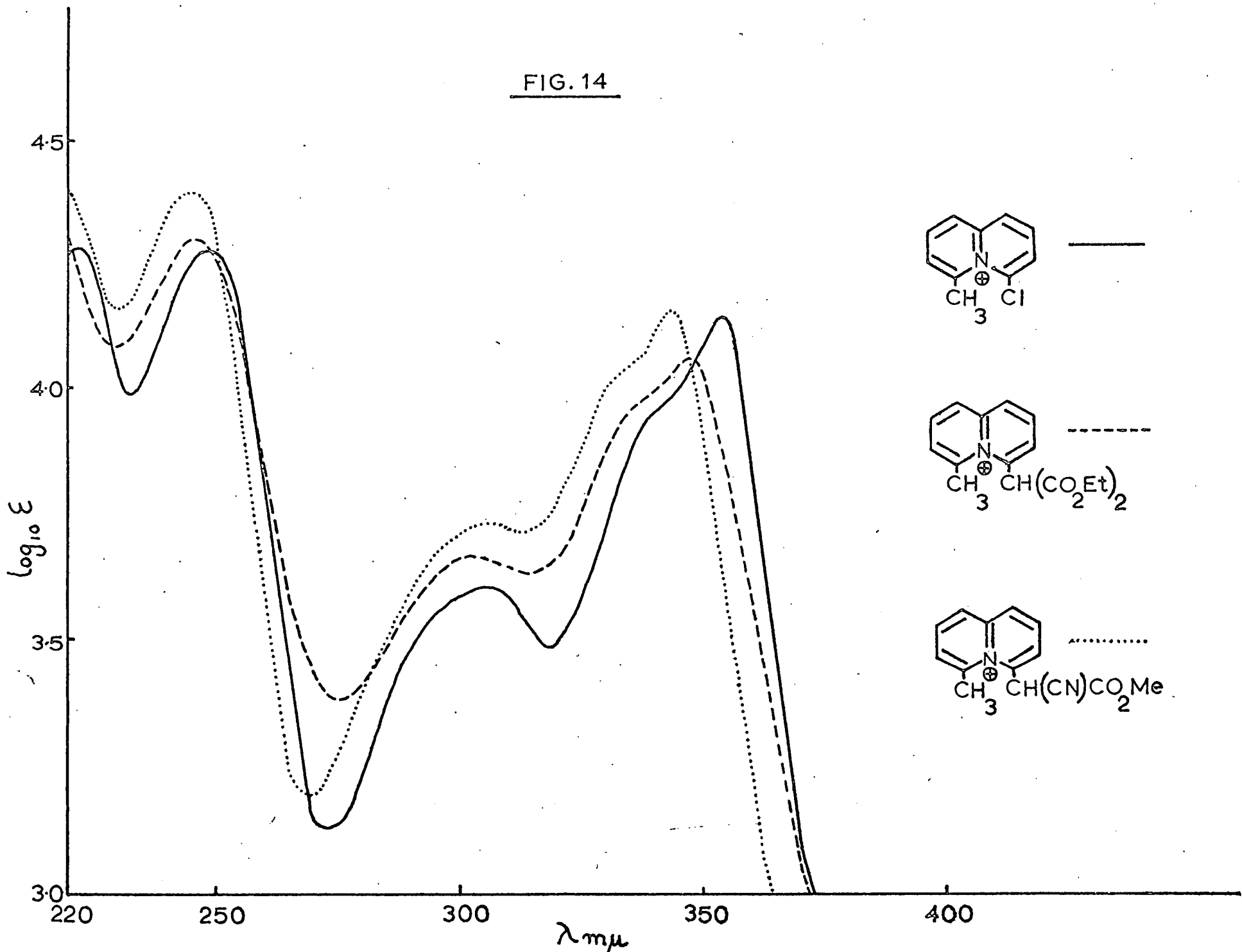
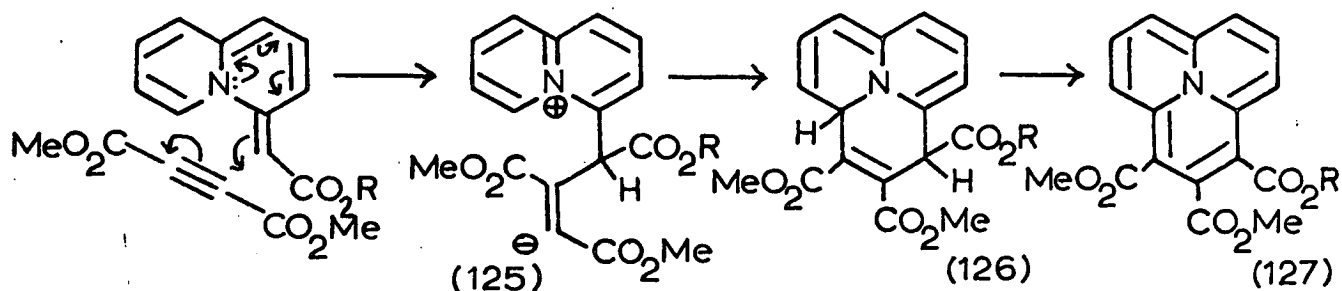


FIG. 14

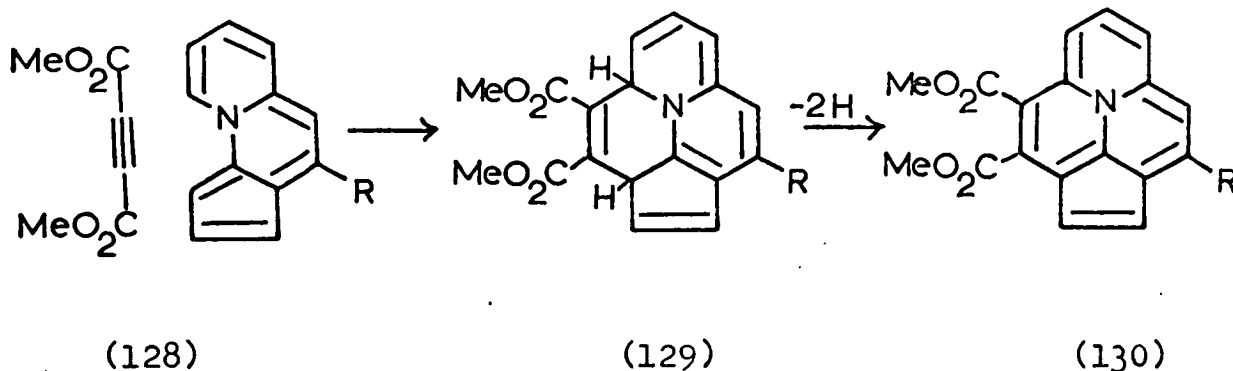


SYNTHESIS OF CYCL[3.3.3]AZINES

With the required monoalkoxycarbonylmethylenequinolizines available, reaction with dimethyl acetylenedicarboxylate was attempted with a view to generating the cycl[3.3.3]azine system. The expected course of reaction involves initial attack by the acetylenic ester at the electron-rich exocyclic carbon atom of the quinolizine. Cyclisation of the resultant zwitterionic species (125) should yield an intermediate adduct (126) which, by loss of hydrogen, should lead to the fully unsaturated cycl[3.3.3]azine (127).



The ease with which oxidative dipolar addition of acetylenic esters to nitrogen-containing heterocycles can be accomplished varies widely depending on the nature of both reactants. Thus, while extended reflux periods in the presence of a dehydrogenating metal catalyst are sometimes necessary, several oxidative additions have been reported which proceed spontaneously in the cold. Leaver et al. have thus found⁸⁷ that cyclopenta[c]-quinolizines (128) react with dimethyl acetylenedicarboxylate at room-temperature to yield fully unsaturated cyclopenta[cd]cycl[3.3.3]azines (130).



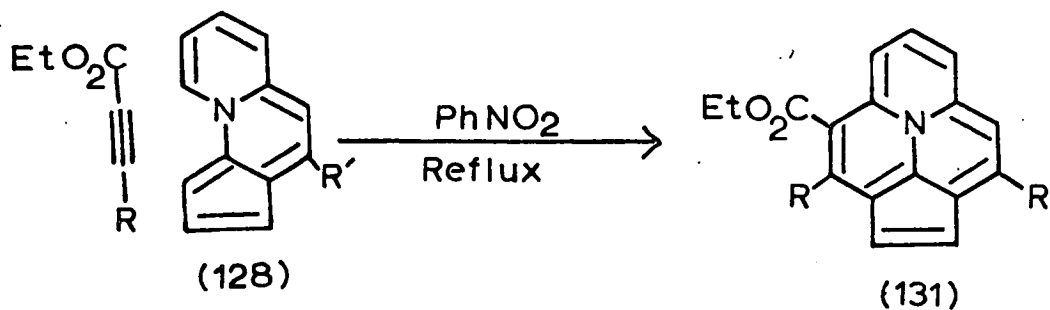
Oxidation of the initially-formed adduct (129) probably occurs by disproportionation or by hydrogen-transfer to a molecule of the acetylenic ester.

When methoxycarbonylmethylenequinolizine (124) was treated with dimethyl acetylenedicarboxylate under conditions similar to the above, an immediate reaction ensued as evidenced by a colour change of the solution from bright-red to dark-brown. After 12 hours at room-temperature the reaction products were separated by chromatography to yield, as major products, a red crystalline solid and a yellow viscous oil. Neither of these products, however, proved consistent with the expected structure. The former product, a true 1:1 adduct, was shown from its n.m.r. spectrum, to contain two saturated carbon-centres. Dehydrogenation, thus, could not have occurred. The latter product, which appeared to have been formed from the reaction of the quinolizine with two molecules of the acetylenic diester, yielded a complex n.m.r. spectrum which proved difficult to interpret. Although the nature of these products was further elucidated by a chemical and spectral investigation, the evidence is best considered in conjunction with the properties of similarly-constituted compounds and will be presented at a later stage.

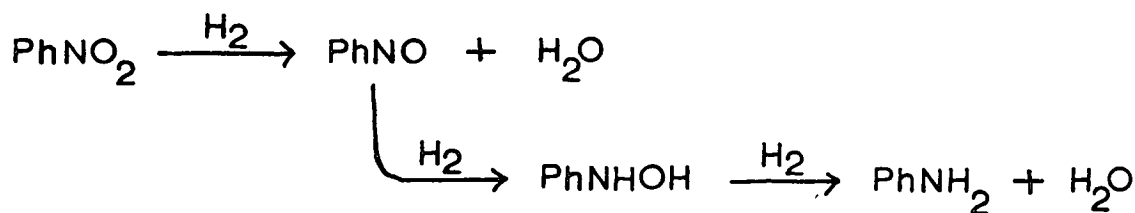
In view of the apparent failure of the dehydrogenation stage in this reaction scheme and the formation of a 1:2 adduct, it was considered desirable to use a more weakly electrophilic acetylenic ester. Conditions might then be devised under which addition could be effected in the presence of an active dehydrogenating reagent.

However, when a solution of the quinolizine (124) in benzene was refluxed with methyl phenylpropiolate in the presence of 10% palladium-charcoal (a catalyst used in the related synthesis³⁹ of cycl[3.2.2]azines from indolizines), the desired reaction did not occur. Continued reflux caused progressive decomposition of the quinolizine. The use of toluene, as higher boiling solvent, in place of benzene met with similar lack of success. However, when the reaction-medium was concentrated by evaporation, a colour-change from red to dark-brown occurred. T.l.c. of a sample of the solution on silica revealed the presence of a complex mixture of components. However, in view of the complexity of this mixture and the small yield of each individual component no further investigation of the reaction was attempted.

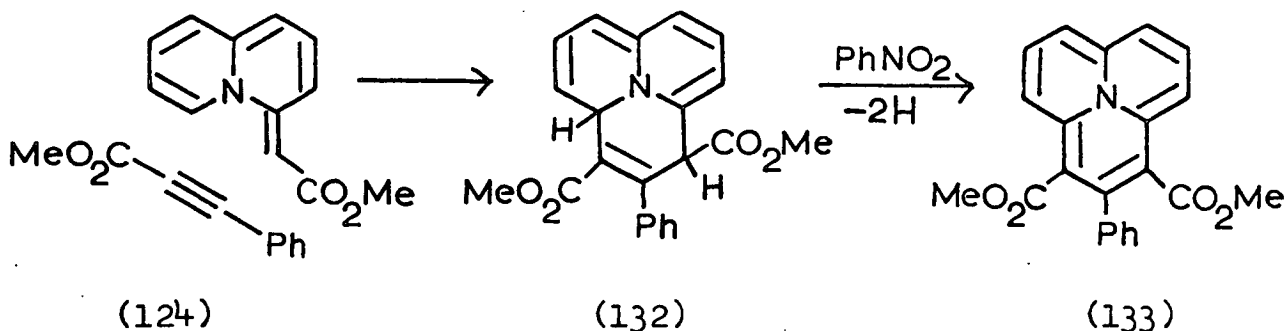
An oxidising solvent that has proved particularly convenient in effecting dehydrogenation reactions is nitrobenzene. Thus, several hydroaromatic products prepared by the Diels-Alder reaction have been oxidised in this medium. However, an example more appropriate to the present work is the preparation¹⁰⁶ of cyclopenta[cd]cycl[3.3.3]azines (131) from cyclopenta[c]-quinolizines (128) and α,β -acetylenic esters.



The formation of water during this reaction is consistent with the interpretation that the solvent acts as the effective oxidising agent. Thus, if reduction to aniline is complete, two molecules of water are produced during the conversion

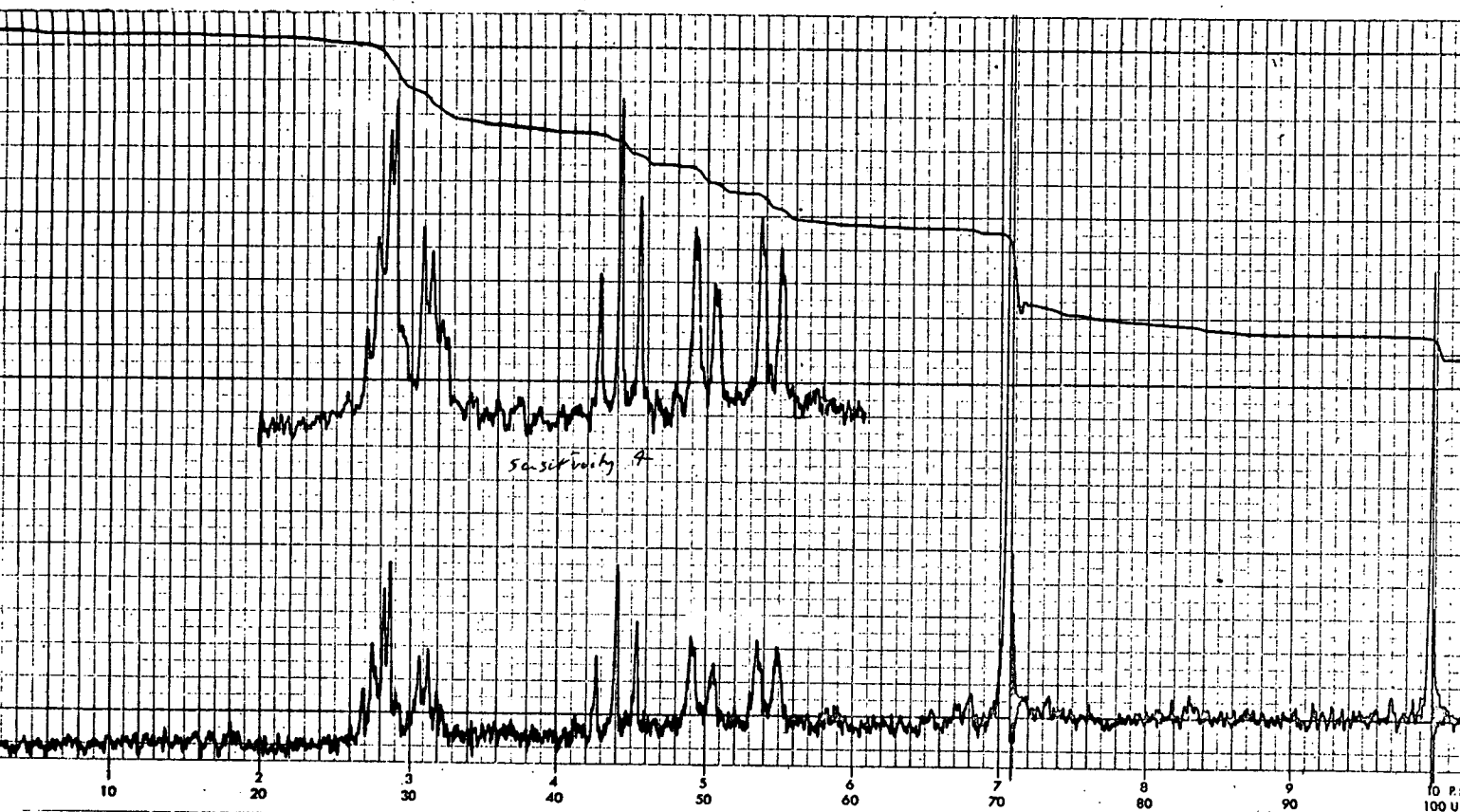


By analogy with the above reaction, the use of nitrobenzene as an oxidising solvent appeared a suitable means of promoting the desired course of reaction between methoxycarbonylmethylenequinolizine (124) and methyl phenylpropiolate. i.e.



When a solution of the quinolizine in nitrobenzene was refluxed for several minutes with a slight molar excess of the

FIG. 24



Dimethyl 2-phenylcycl[3.3.3]azine-1,3-dicarboxylate

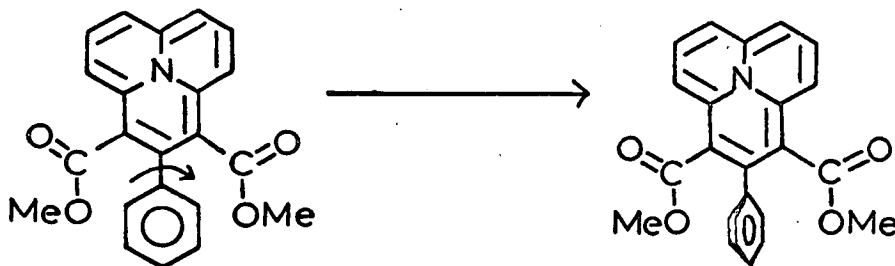
acetylenic ester a progressive colour-change of the reaction medium from deep-red to dark-brown occurred. During this period globules of water formed on the inner walls of the condenser and returned to the refluxing solution with vigorous effervescence and splashing. After 6 minutes the reaction product was chromatographed on alumina to give, in 36% yield, a glistening dark-purple compound. When dissolved in aprotic solvents this compound yielded clear translucent yellow solutions.

The n.m.r. spectrum of the compound [Fig.24] was entirely consistent with the expected structure. Significantly, the low-field absorption attributable to the α -pyridine proton of the quinolizine (124) was absent thus indicating that the proton had participated in the overall reaction. Apart from a five-proton complex multiplet at 2.7 - 3.3 τ , which was assigned to the protons of the phenyl substituent, the low-field region of the spectrum consisted of two doublets ($J=8\text{c/s}$; each two protons) centred at 4.99 τ and 5.44 τ , each of which were split by further coupling, and a lower-field triplet ($J=8\text{c/s}$; two protons) centred at 4.43 τ .

The highest-field doublet was assigned to the 6- and 7-protons, primary splitting being attributed to ortho-coupling, and secondary fine-splitting to meta-coupling. The lower-field doublet, which showed identical subsidiary splitting, was assigned to the 4- and 9-protons. The displacement of the chemical shift of the latter resonance to lower-field values can then be attributed to long-range

deshielding by the peri-methoxycarbonyl groups. The remaining low-field triplet was assigned to the 5- and 8-protons. The coupling-constant was the same as that of the ortho-coupled 4,9- and 6,7-protons; this explains the triplet splitting of the resonance signal.

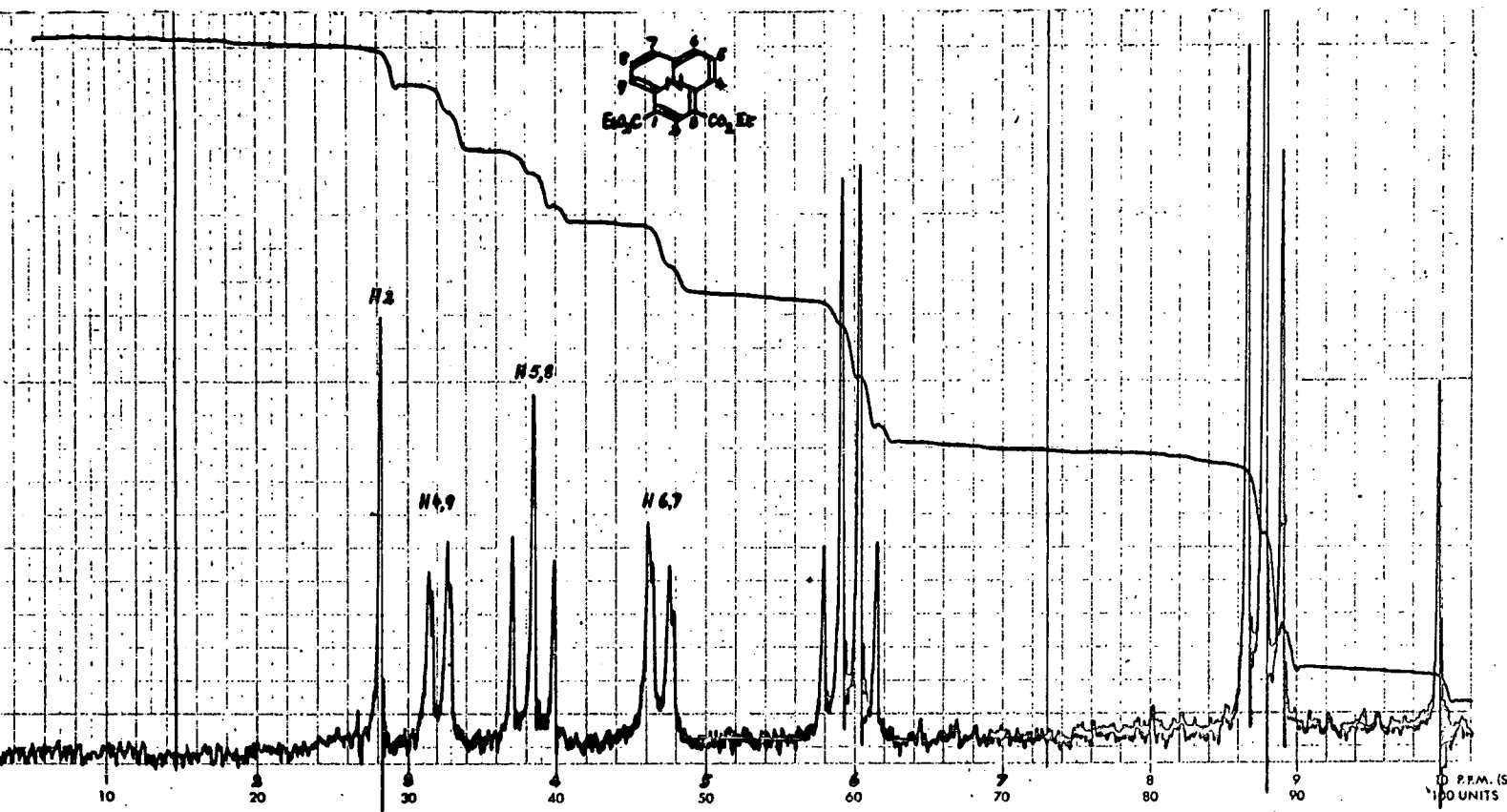
The presence in the spectrum of a six-proton singlet at τ 7.09 is in keeping with the presence in the molecule of two methoxycarbonyl substituents. The chemical shift of this resonance, however, is unusually high, being displaced upfield of that typical of a normal methoxycarbonyl group. This anomalous shift is best rationalised in terms of the steric geometry of the molecule.



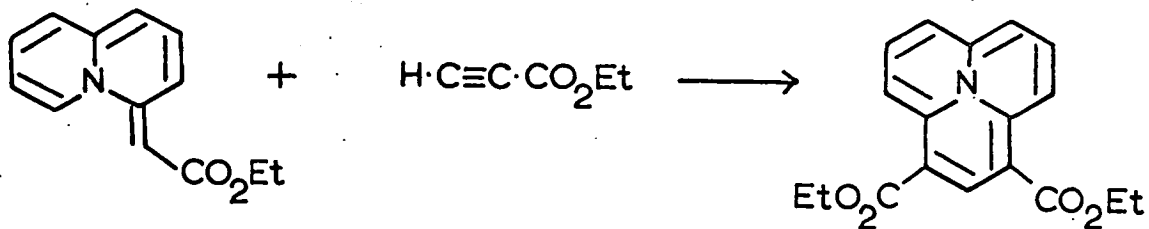
It appears that the 1- and 3- methoxycarbonyl groups overlap with the ortho-hydrogen atoms of the 2-phenyl substituent in a manner analogous to that of 0,0'-substituents in biphenyls. Relief of steric interaction can be achieved by rotation of the phenyl substituent out of the plane of the cyclazine nucleus. The two methoxyl groups may thus be considered to lie on either side of the plane of the phenyl group with the result that they are shielded by the diamagnetic ring-current in that group.

Although the n.m.r. spectrum is fully consistent with the proposed structure (133) it was considered desirable to gain

FIG. 25



Diethyl cycl[3.3.3]azine-1,3-dicarboxylate



(120)

(135)

When quinolizine (120) was reacted with ethyl propiolate in boiling nitrobenzene a blue solution was initially formed which gradually changed to yellow as reflux continued. After 6 minutes the product was chromatographed on alumina to give a yellow solid (75%), which crystallised as purple needles with a metallic lustre, together with a second, blue solid (8%) which crystallised as dark-blue prisms. That the major product was indeed the required cyclazine was apparent from its n.m.r. spectrum [Fig.25]. In addition to the expected two doublets and a triplet, the assignment of which follows from the argument presented for the 2-phenyl compound, a one-proton singlet was present at a comparatively low field (2.84τ). The presence of this singlet is in keeping with the absence of a substituent in the 2-position of the molecule. The displacement of the chemical shift is obviously due to the deshielding influence of the adjacent ethoxycarbonyl groups.

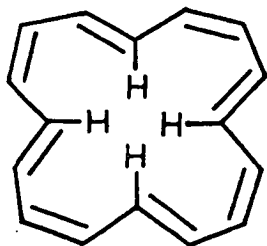
The interesting features of the spectrum relative to that of the phenyl compound were a) the nuclear-proton resonances

had undergone a general downfield displacement and, b) the sequence of the chemical shifts of the 4,9- and 5,8-protons had been reversed. These observations strongly suggest that not only the phenyl group is twisted out of the plane of the cyclazine nucleus in (133) but also, to some extent, the 1- and 3-ester groups. This view allows a rational interpretation of the differences in chemical shift between the two systems. Since (135) does not contain a 2-substituent, the ethoxycarbonyl groups can become coplanar with the cyclazine nucleus and hence exercise a more effective withdrawal of electrons from the conjugated system. The nuclear-protons are consequently deshielded relative to those of cyclazine (133) and hence resonate at lower-fields. A further consequence of the planarity of the system is that long-range deshielding of the 4- and 9-protons by the peri-ester substituents is rendered more effective than in the phenyl compound. Thus, while the 4,9- and 6,7-proton doublets show a difference in chemical shift of 0.45 p.p.m., in the latter compound, the separation is increased to 1.47 p.p.m., in cyclazine (135). The overall effect is that the intrinsically high-field 4,9-proton doublet is displaced to a lower-field value than the intrinsically low-field 5,8-proton triplet. A final difference between the spectra of the two compounds was that the alkoxy protons in (135) resonated as expected at normal τ -values. The essential differences between the chemical shifts of corresponding protons in compounds (133) and (135) are thus well-accounted for in terms of the difference in steric orientation of the substituent groups.

While the foregoing considerations rationalise relative

differences in the shielding and deshielding of individual protons in terms of steric and electronic displacements within the molecule, perhaps the most singularly interesting feature of these spectra is that, despite the deshielding effect of the two ester substituents, the chemical shifts of the nuclear-protons are more typical of an olefinic rather than an aromatic system. By n.m.r. criteria, therefore, the cycl[3.3.3]azine system must be considered polyolefinic in character.

A recently advanced quantum mechanical theory^{79,80} of induced ring-currents predicts paramagnetic electron-circulation in conjugated monocyclic systems containing $4n\pi$ electrons. Under these circumstances the usual diamagnetic rules for $(4n+2)\pi$ systems have to be reversed. The n.m.r. signals of protons outside the ring are thus predicted to be displaced to high field-values, and those of protons inside the ring to low-field values. These predictions have been verified by examination of a number of annulenes and dehydroannulenes.⁷⁹ Thus, the low-temperature (-110°C) spectrum⁷⁷ of [16]annulene consists of a triplet at -0.43τ due to the four inner protons and a multiplet at 4.60τ due to the twelve outer-protons.

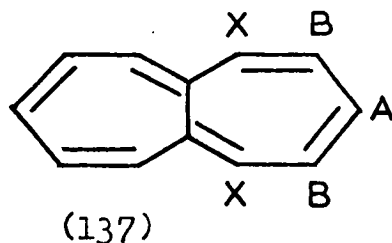


(136)

At room-temperature these protons give rise to a single absorption

centred at 3.29τ , because of rapid conformational inversion of the ring-system. Similar observations⁷⁸ have been made for the higher $4n\pi$ vinylogue, $[2+]$ annulene.

A further interesting example of paramagnetic shielding is apparent in the 12π -electron system heptalene¹⁰⁷ (137).



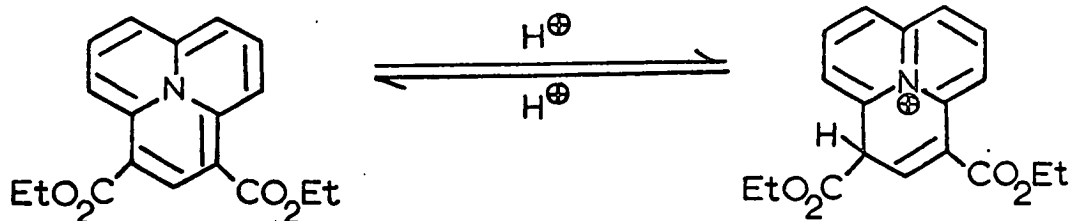
The proton absorptions fall in the vinylic region of the spectrum with the X-protons of the AB_2X_2 system giving rise to a multiplet centred at $\sim 5.0\tau$. This represents an upfield displacement of 0.6 p.p.m. relative to the olefinic protons in cyclohexene (4.40 τ).

However, the presence of paramagnetic ring-currents in the cyclazine systems (133) and (135) cannot readily be demonstrated because it is difficult to assess quantitatively the deshielding effect of the ester substituents. An unequivocal demonstration of paramagnetic shielding in the cycl[3.3.3]azine series requires synthesis of the unsubstituted parent compound (11).

The i.r. spectra of cyclazines (133) and (135) showed carbonyl absorption bands at, respectively, 1660 cm^{-1} and 1680 cm^{-1} . This difference is in keeping with the ester groups being out-of-plane in the 2-phenyl compound. However, both of these absorptions are much lower than expected for normal α,β -unsaturated ester groups; this indicates a high degree of

carbonyl-group polarisation which in turn reflects on the strongly electron-donating character of the cyclazine system. The u.v. and visible spectra of compounds (133) and (135) [Fig.17] showed a marked similarity although that of the phenyl compound possessed less fine-structure and was shifted $\sim 20 \text{ m}\mu$. to longer wavelengths. The latter observation indicates that some conjugation occurs with the phenyl-group despite the non-planarity of the molecule. It is noteworthy that these u.v. and visible spectra were quite different from those of the methylenequinolizine precursor compounds. The cycl[3.3.3]azine system cannot therefore be regarded as simply a vinylogue of the methylenequinolizine system but rather as a fundamentally different molecular species.

Chemically, both cyclazines proved stable in the solid state, remaining unchanged over a period of several months. However, in solution decomposition was evident, the change being accelerated in protonic media. Ethanolic solutions thus yielded dark-brown amorphous products after standing 24 hours at room-temperature. Rather surprisingly, these cyclazines did not possess strongly basic characteristics, as evidenced by their resistance to protonation when shaken in solution with dilute mineral acids. In concentrated acids, protonation occurred readily to give colourless solutions from which the free-base could be regenerated by addition of an excess of alkali. The n.m.r. spectrum of the diethoxycarbonyl compound in trifluoroacetic acid showed that protonation had occurred at the 1-position to yield the vinylquinolizinium cation (138).



(135)

(138)

The presence of a one-proton doublet at 4.31τ , coupled to a lower-field one-proton doublet at 2.35τ , cannot be reconciled with any structure other than (138). The former absorption was assigned to the saturated proton at the 1-position of the molecule. The signal is shifted to a low-field because of the deshielding influence of the gem-ethoxycarbonyl group and the presence of the formal positive charge on the nitrogen atom. The second absorption was assigned to the adjacent vinylic 2-proton. The remaining absorptions, other than those attributable to the two non-equivalent ester groups, were a six-proton multiplet in the aromatic region of the spectrum which was obviously due to the protons of the quinolininium nucleus.

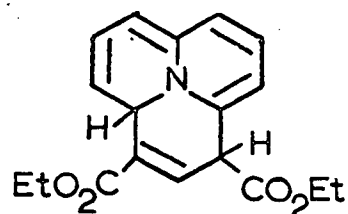
The behaviour of cyclazine (135) under acidic conditions indicates that the system cannot be regarded as a normal tertiary base with the lone-pair of electrons localised on the nitrogen atom, but rather as a cyclic polyeneamine in which these electrons are delocalised around the unsaturated carbon-perimeter. The extended delocalisation of these electrons and

their interaction with the two ethoxycarbonyl substituents can account for the weakly basic character of the molecule. A further analogy with enamines arises from the site of protonation at a β -carbon atom rather than directly on the nitrogen atom. This leads to formation of an aromatic system rather than retention of the polyene system which would result from protonation at the latter site and is thus more favoured on a steric basis. Direct protonation on the nitrogen atom would result in the molecule assuming a tetrahedral configuration thus increasing the degree of bond-strain within the system. By comparison, protonation at the 1-position relieves steric interaction between the 1-ethoxycarbonyl group and the 4-hydrogen atom.

The precise orientation of addition at the carbon periphery is probably controlled by an electronic as well as a steric effect. Thus, of the three structures that are theoretically possible for the conjugate acid, structure (138) is expected to be the most stable since the incorporated quinolizinium nucleus does not, as opposed to the alternative structures, contain electron-withdrawing substituents.

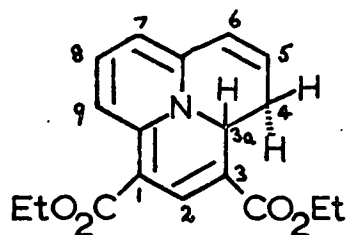
The second product from the reaction of ethoxycarbonylmethylenequinolizine (120) with ethyl propiolate, isolated in low yield as dark blue prisms, proved to be the major product when the reaction was carried out at 160°C for one minute. Elemental analysis indicated the product to be a true 1:1 adduct. Its intermediacy in the formation of (135), which was verified by independent reflux in nitrobenzene, suggested

either a dihydrocylazine structure or, less probably, an open-chain methylenequinolizine structure formed by linear addition at the exocyclic carbon atom. However, this second alternative was eliminated by u.v. and n.m.r. spectral evidence. The possibility that the product was the initially-formed tricyclic adduct (139) was discounted on similar grounds.

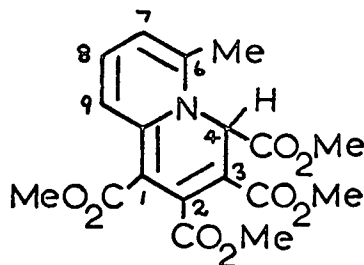


(139)

Thus, the presence in the n.m.r. spectrum of a sharp one-proton singlet at 2.09τ cannot be reconciled with structure (139). This absorption, by virtue of its low chemical shift, appeared to correspond to that of the 2-proton in the fully unsaturated cyclazine (135). This interpretation leaves only one possible structure, (140), fully consistent with the remaining distribution of absorptions.



(140)



(141)

A low-field one-proton doublet (split by further coupling) at 1.26τ can then be assigned to the deshielded 9-proton, and a higher-field one-proton quartet at 2.76τ to the adjacent 8-proton.

The chemical shifts of these absorptions are similar to those of the 9- and 8-protons (respectively 1.33τ and 2.56τ) of 6-methyl-4H-quinolizine-1,2,3,4-tetracarboxylate¹⁰⁸ (141).

A poorly resolved three-proton multiplet in the vinylic region of the spectrum ($3.20 - 3.97\tau$) was assigned to the 7-, [c.f. (141), $7H = 3.22\tau$] 6- and 5-protons. However, the most revealing feature of the spectrum was the presence of a one-proton doublet, split by further coupling, at 4.40τ together with two, one-proton multiplets at $\sim 6.6\tau$ and $\sim 7.6\tau$ respectively. [Fig. 26]

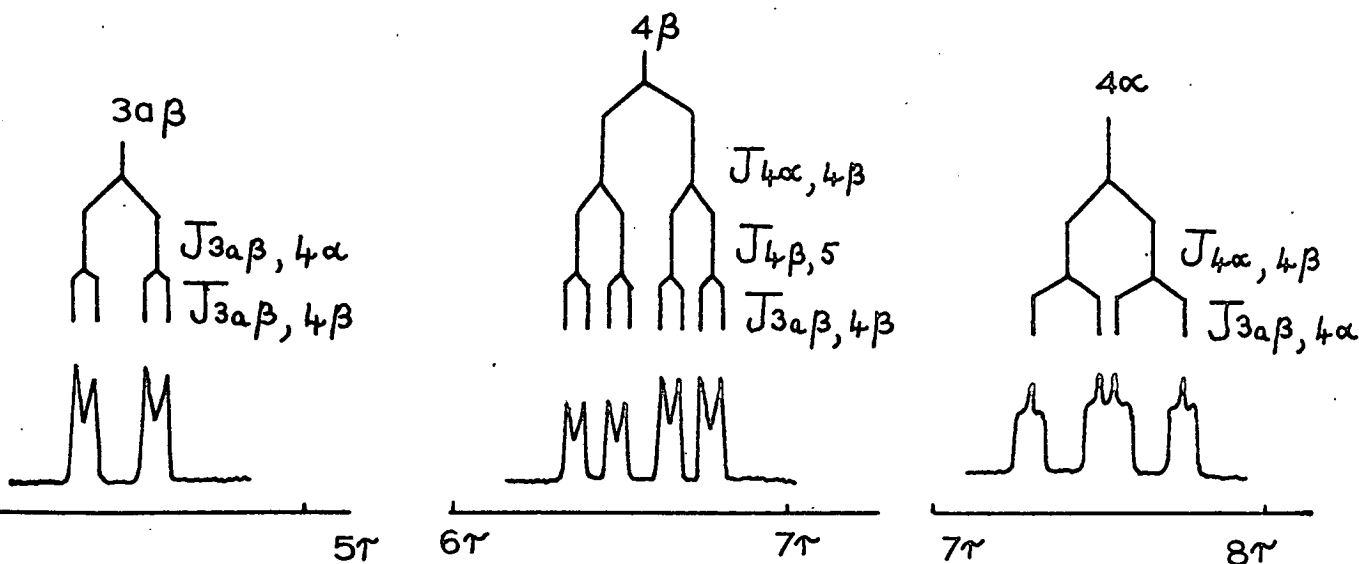
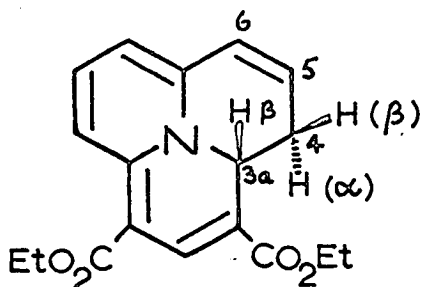
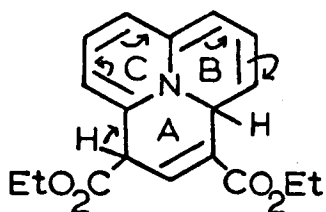


FIG. 26

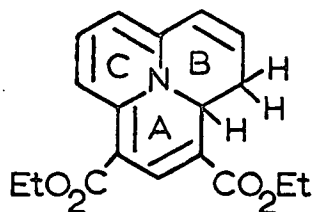
The first of these absorptions was assigned to the aliphatic proton at the 3a-bridgehead position of the molecule. The upfield shift (0.86 p.p.m.) relative to that of the 4-proton in (141) is consistent with the absence of a methoxycarbonyl group joined to the 3a-carbon atom. The primary splitting ($J = 12\text{c/s}$) was attributed to coupling with the trans 4α -proton and secondary splitting ($J = 3\text{c/s.}$) to coupling with the cis 4β -proton. The observed J -values are consistent with the corresponding dihedral angles of $\sim 180^\circ$ and $\sim 50^\circ$ suggested from a study of Dreiding models. The multiplet centred at 6.6τ was assigned to the 4β -proton since it possessed subsidiary splitting ($J = 3\text{c/s.}$) equal to that of the cis 3a-proton doublet. The very large primary splitting ($J = 18\text{c/s.}$) must arise from coupling to a second proton at the same carbon atom (the 4α); this provides confirmatory evidence for the presence of a methylene group within the molecule. The coupling-constant of 18c/s. suggests that the angle between the methylene protons is approximately 106° . The secondary splitting ($J = 7\text{c/s.}$) must be due to coupling to the adjacent 5-proton; unfortunately, this cannot be rigorously verified because of the complexity of the vinylic region of the spectrum. Finally, the high-field multiplet centred at 7.6τ was attributed to the 4α -proton. The absorption consisted essentially of a quartet produced by further splitting ($J = 12\text{c/s.}$) of the primary doublet ($J = 18\text{c/s.}$) [the initial splitting is due to coupling to the 4β -proton]. This subsidiary splitting was the same as the major splitting of the 3a-proton signal, thus confirming the 12c/s coupling of

these two protons. A degree of very fine-splitting ($J = 1-2$ c/s.) which was also evident was attributed to weak coupling to the 5- and 6-protons.

The n.m.r. spectrum is thus fully consistent with the assigned structure and cannot be rationalised in terms of any alternative structure. The formation of 3a, 4-dihydrocycloazine presumably results from prototropic rearrangement of the initially formed adduct (139).



(139)

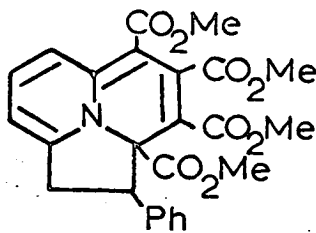


(140)

The driving force for the rearrangement is probably provided by the greater stability achieved by the system in adopting structure (140). Thus, the primary adduct is expected to be extremely labile since the incorporated 4H-quinolizine system (rings B and C) contains no stabilising substituents. By comparison, the 4H-quinolizine system of structure (140) (rings A and C) is stabilised by the two ethoxycarbonyl substituents on the partially-saturated ring, and further by conjugation with the vinyl group. This represents the most stable arrangement possible.

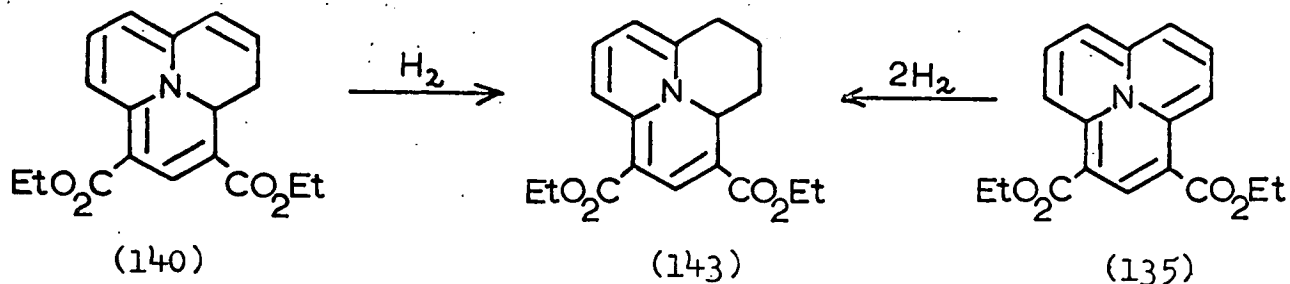
When hydrogenated in ethanol over a platinum catalyst the adduct absorbed a 0.7 molar proportion of hydrogen and the solution underwent a concomitant colour change from deep-blue to bright-red. Chromatography of the product on alumina gave a

forerunner yellow band in 16% yield which was identified as the fully-unsaturated cyclazine (135), together with a second, red band, isolated as red prisms, in 81% yield. Direct hydrogenation of cyclazine (135) by a similar procedure resulted in uptake of two molar proportions of hydrogen with formation of a red solid (the sole product) which was identical to the second solid obtained from the preceding reaction. The n.m.r. spectrum of this solid was closely similar to that of the dihydrocyclazine (140) except that the three-proton multiplet in the vinylic region of the latter spectrum was now replaced by a one-proton doublet ($7H; 3.66\tau$) while a complex six-proton multiplet was present in the $6-8\tau$ region. The visible spectrum showed a close resemblance [Fig.18] to that of the dihydro-compound but was hypsochromically shifted $\sim 25 m\mu$. This is consistent with a shortening of the conjugated system such as would result from the absence of the 5,6- double-bond; it also explains the striking difference in colour between these two compounds. An interesting observation was that the u.v. spectrum showed a striking similarity [Fig.18] to that⁸³ of the cycl[3.3.2]azine system (142) thus providing convincing evidence that the molecule contained a 4H-quinolizine system.

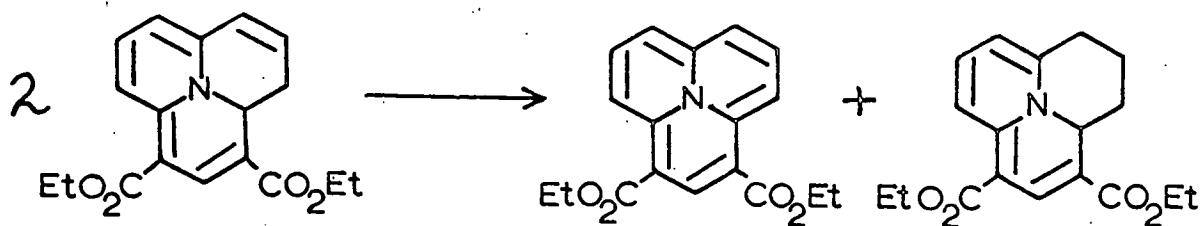


(142)

The foregoing evidence, together with the elemental analysis data, leaves little doubt that the product possesses structure (143).

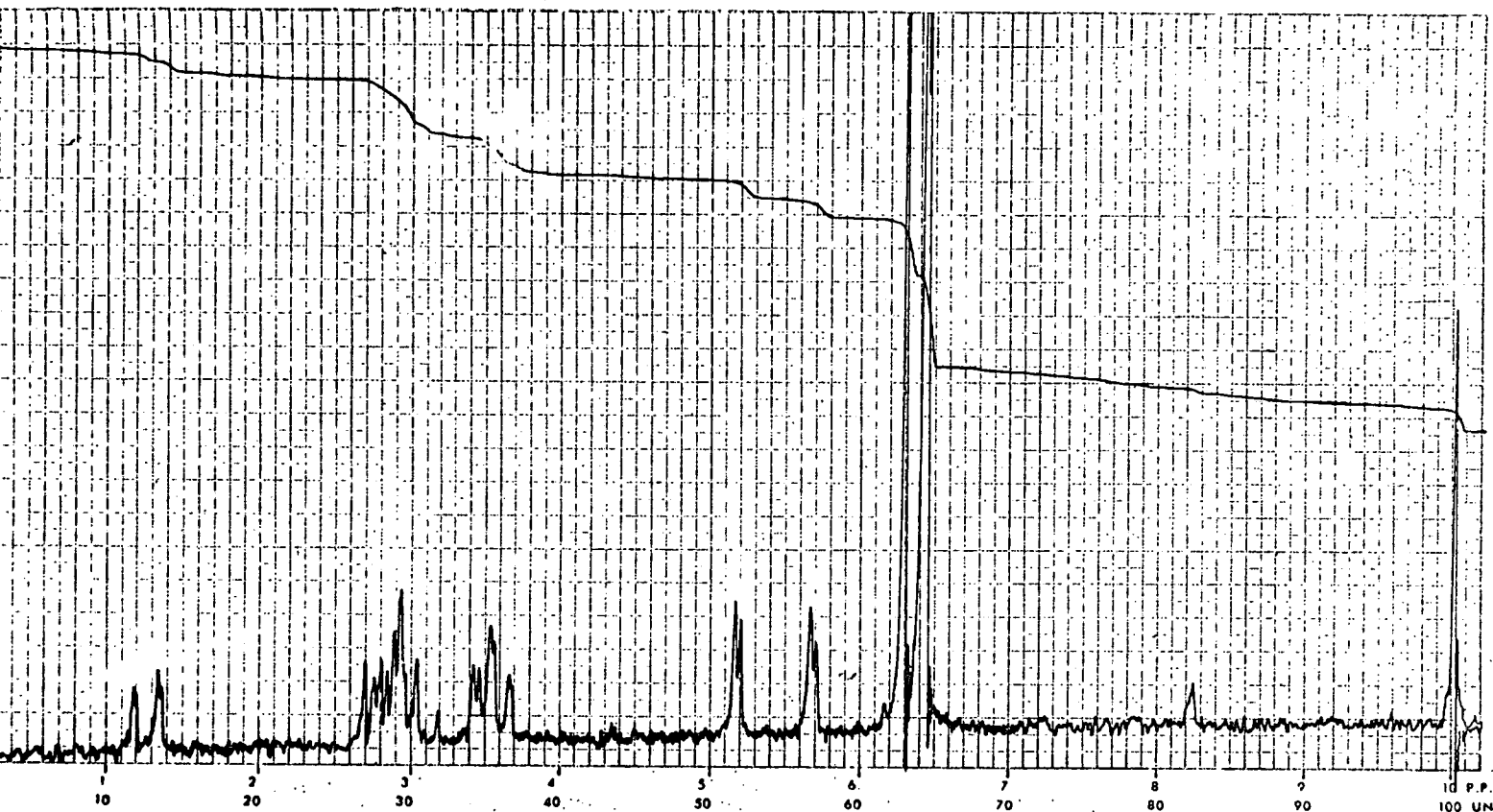


The formation of the cyclazine (135), in addition to its tetrahydro derivative (143), during the hydrogenation of the dihydrocyclazine (140) can only be accounted for in terms of a competing disproportionation reaction, i.e.



The moderate yield of cyclazine (16% ; max. 50%) [the latter is much more resistant to hydrogenation (~7 hours) than the dihydro-compound (~0.5 hours)], suggests that disproportionation occurs to a significant extent. The difference in the susceptibility of these compounds to hydrogenation is further exemplified by the fact that direct reduction of the cyclazine produced no detectable yield of intermediate dihydro-product. Although the latter is presumably the first product of hydrogenation, it must

FIG. 27

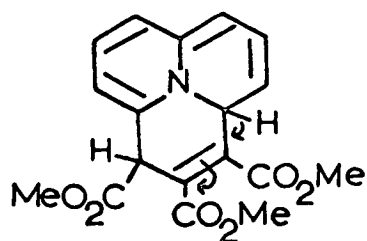


Trimethyl 1,2-dihydrocyclo[3.3.3]azine-1,2,3-tricarboxylate

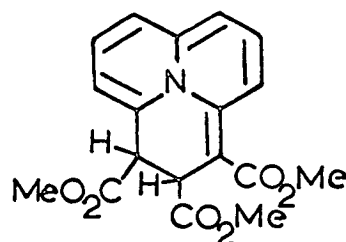
possess only a transient existence before undergoing rapid addition of a second molecule of hydrogen.

The uniquely characteristic spectral properties of cyclazines (133) and (135) provides scope for a discussion of the adducts obtained from the reaction of methoxycarbonylmethylenequinolizine (124) and dimethyl acetylenedicarboxylate. The two major products, a red crystalline solid and a yellow viscous oil, proved extremely difficult to separate, complete resolution being achieved only by dry-column chromatography on silica.

The crystalline compound analysed as a true 1:1 adduct thus indicating that the expected course of reaction had not occurred. The u.v. spectrum [Fig.12] in both neutral and acidic ethanol resembled that of the methylenequinolizine (124) thus suggesting the presence of a similar structural unit in the molecule. Absorption bands at 1645 cm^{-1} and 1730 cm^{-1} in the i.r. spectrum indicated the presence of both saturated and α, β -unsaturated ester groups. The n.m.r. spectrum [Fig.27], in addition to confirming the 1:1 nature of the adduct, showed a broad similarity to that of the methylenequinolizine system, although a significant difference was the absence of the absorptions attributable to the 6-proton and to the exocyclic methylene-proton. These were replaced by two coupled ($J = 2.5\text{ c/s}$) one-proton doublets at 5.15τ and 5.65τ respectively. The foregoing evidence clearly indicates that the adduct possesses structure (145). Its formation can be accounted for by rearrangement of the initially formed adduct (144).



(144)

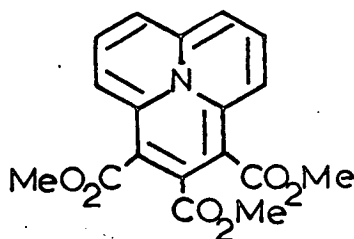


(145)

This mode of rearrangement is presumably more favourable than that observed for the related adduct (139) because it results in less steric interaction between the methoxycarbonyl substituents.

The small coupling between the two saturated protons suggests that they are cis-orientated with respect to each other. The alternative trans-configuration, although more sterically favoured, cannot be considered since the large dihedral angle ($\sim 170^\circ$) would result in a substantially greater degree of coupling ($J \sim 11$ c/s.)

In order to obtain confirmatory chemical evidence for the assigned structure, the adduct was refluxed in nitrobenzene with a view to generating the corresponding 1,2,3-trimethoxycarbonylcyclazine (119).



(119)

FIG. 28



Trimethyl cycl[3.3.3]azine-1,2,3-tricarboxylate

Chromatography of the reaction product on alumina yielded two minor bands, respectively yellow and red, together with a further yellow band as the major product. The first of these products, isolated in 8% yield as brown flakes, was identified as 1,3-di(methoxycarbonyl)cycl[3.3.3]azine by comparison of its u.v. and n.m.r. spectra with that of the diethyl analogue (135). The formation of this product must be due to elimination of the elements of methyl formate from the adduct.

The second product from the reaction, red needles, was isolated in only 2% yield and, as a consequence, it was not possible to investigate its structure. Although the mass spectrum indicated a molecular weight of 341 (this value corresponding to loss of two hydrogen atoms from the adduct) no conclusions could be drawn from the evidence since an identical molecular weight was recorded for the final major product of the reaction. The latter, isolated in 57% yield as brown needles, was identified as the expected triester (119). The u.v. spectrum of the product showed a marked resemblance [Fig.17] to that of 1,3-dimethoxycarbonyl-2-phenylcyclazine (133) thus conclusively establishing the presence of a cyclazine nucleus.

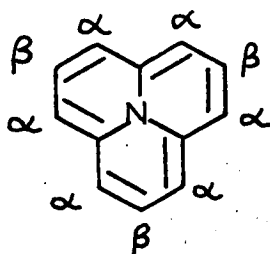
The i.r. spectrum exhibited carbonyl absorption bands at 1670 cm^{-1} and 1730 cm^{-1} thus indicating the presence of two types of ester groups. Since the high-frequency absorption was not present in the spectrum of the phenyl compound (133) it is probably due to the 2-ester group. However, despite the consistency of these properties with those observed for the 2-phenyl compound, the n.m.r. spectrum [Fig.28] was anomalous.

In addition to the absorptions attributable to the three ester groups the spectrum consisted of a four-proton doublet centred at 3.77τ ($J = 5\text{c/s.}$) together with a higher-field two-proton triplet centred at 4.57τ ($J = 5\text{c/s.}$). Although the presence of these absorptions in the vinylic region of the spectrum and the molecular symmetry implied by their multiplicity are consistent with the assigned structure, the relative chemical shifts of the individual protons are completely unexpected. Thus, the magnetic equivalence of the 4-, 6-, 7- and 9-protons, as implied by the four-proton doublet, cannot be reconciled with the previously observed long-range deshielding of the 4- and 9-protons by 1- and 3- ethoxycarbonyl substituents. The anomaly cannot be resolved by assuming that, in this instance, the methoxycarbonyl groups are perpendicular to the plane of the molecule, because the resulting decrease in long-range and conjugative deshielding would be expected to shift the 4,9-proton doublet to a position upfield, rather than downfield, of the 5,8-proton triplet at 4.57τ . The presence of a four-proton doublet downfield of the triplet clearly infers that the 6- and 7-protons, in common with the 4- and 9-protons, are subject to a deshielding influence. However, the origin of such remains obscure. The reduced coupling (5c/s.) between the nuclear-protons relative to that observed for a wide variety of cyclazine systems (8c/s.) is equally anomalous. Although this effect presumably has a common origin with the displaced resonances of the 6,7-protons and is, in some way, associated with the presence of the ester substituent in the 2-position of

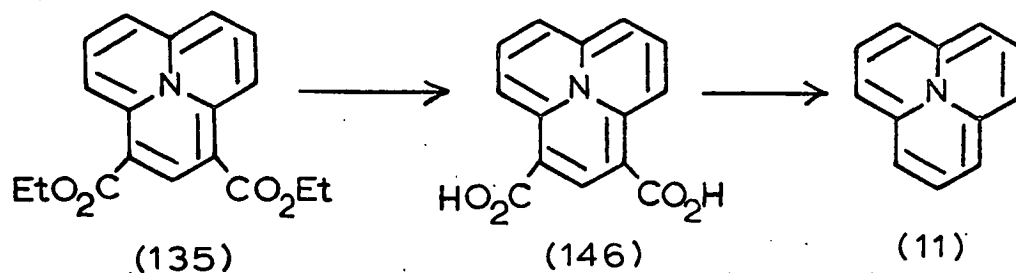
the molecule no rational explanation for its existence can be advanced.

The non-crystalline product from the reaction of methoxycarbonylmethylenequinolizine and the acetylenic ester proved extremely difficult to characterise. Although its u.v. and i.r. spectrum closely resembled that of the triester (119), thus confirming that it was a cyclazine containing two types of ester groups, the n.m.r. spectrum was complex and could not readily be reconciled with any simple structure. However, the intensity ratios of the methyl ester and vinylic proton resonances indicated that the product had been formed by reaction of two molecules of the acetylenic ester with one of the quinolizine. Unfortunately, further analysis of the spectrum was not possible and in view of the difficulties involved in isolating appreciable quantities of the product no further investigation of its structure was attempted.

In the ensuing discussion of the chemistry of the cyclazine ring-system the carbon-positions adjacent to the perimeter ring-junctions will, for convenience, be referred to as the α -positions and the carbon positions sub-adjacent to the ring-junctions as the β -positions. i.e.



The most obvious route to the parent cyclazine (11) appeared to be by hydrolysis and decarboxylation of the 1,3-diethoxycarbonyl derivative (135).

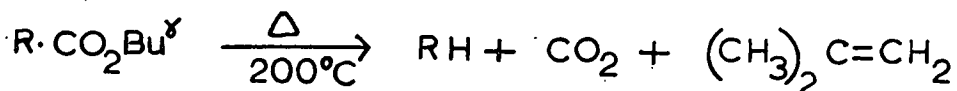


However, attempted acidic hydrolysis under a variety of conditions (dil. and conc. hydrochloric acid, dil. fluoroboric acid, hydrogen chloride in benzene), caused decomposition of the cyclazine system, the rate of decomposition increasing with the severity of the reaction conditions. This behaviour, together with the observed lability of the cyclazine in neutral

hydroxylic solvents, leaves little doubt that the molecule is inherently unstable in protonic media and suggests that attempted acid-catalysed conversion in the cyclazine series is unlikely to be successful.

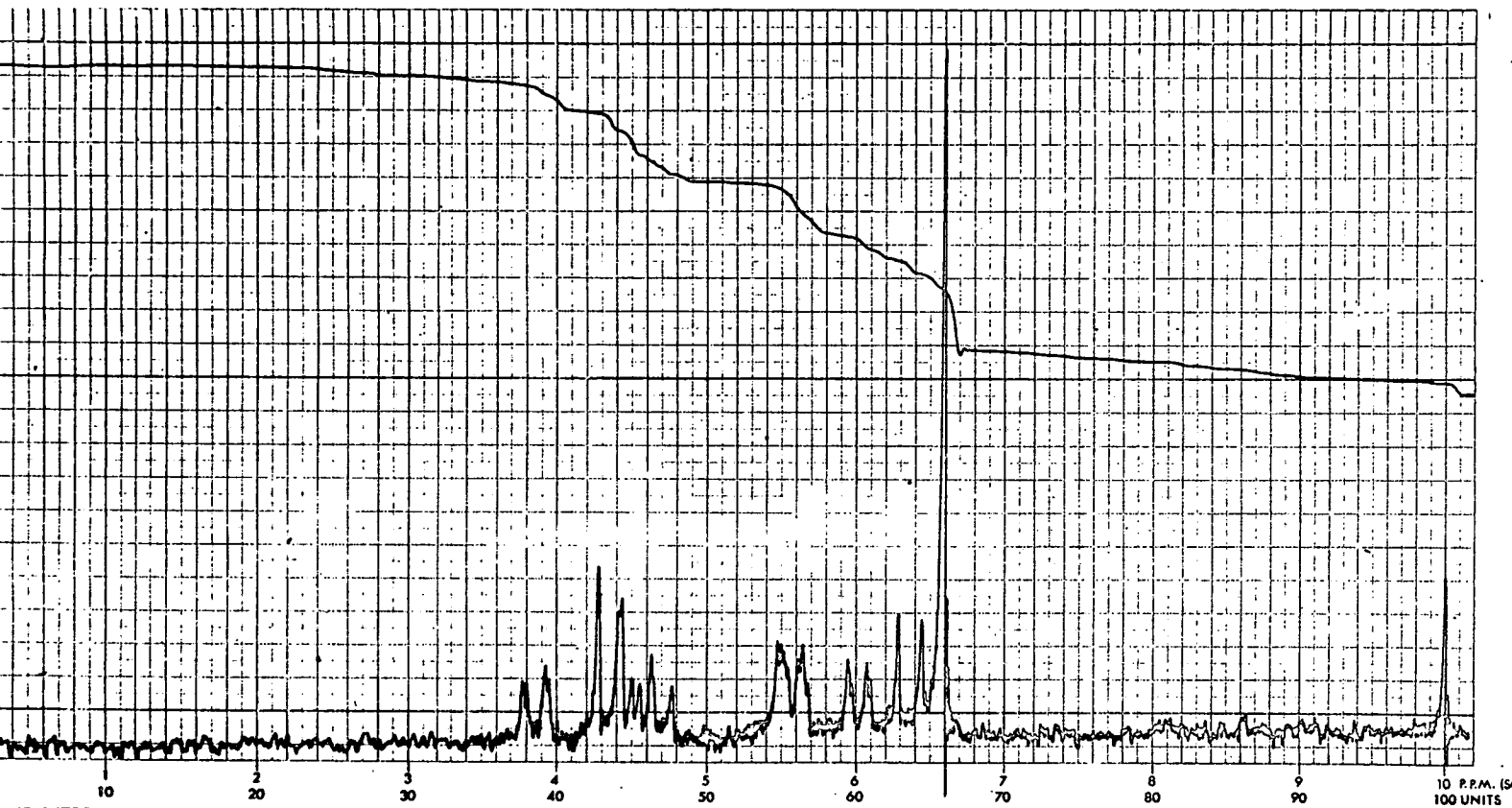
Although more favourable results were expected by the use of basic reagents, the cyclazine was recovered unchanged after treatment with alcoholic potassium hydroxide in the cold. Attempts to force the reaction caused decomposition of the cyclazine. The use of sodium hydroxide in dimethylsulphoxide, a reagent that has been reported¹⁰⁹ to hydrolyse ethyl benzoate quantitatively at room temperature in two minutes, was similarly without effect. Forcing conditions again led to decomposition of the system. The failure of the cyclazine to undergo hydrolysis under basic conditions is possibly due to the comparatively large degree of charge-separation within the molecule, the ester carbonyl groups thus assuming a high degree of single-bond character.

A convenient means of circumventing the foregoing difficulties appeared possible by exploiting the lability of t-butoxycarbonyl groups under thermal conditions.



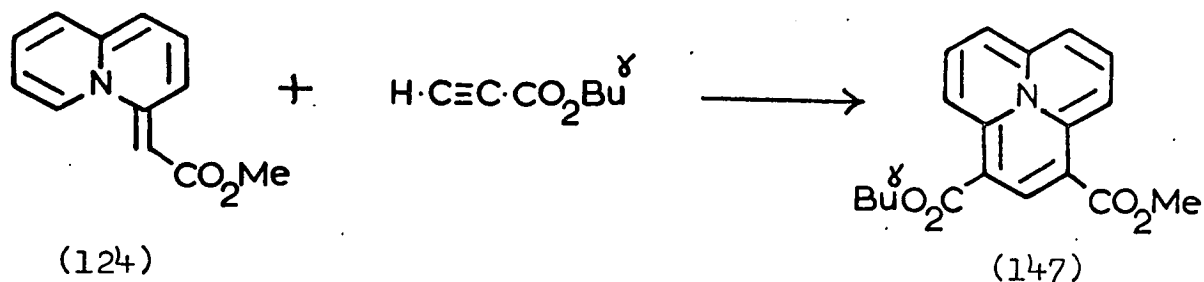
With this object in mind, synthesis of cyclazine (147) was undertaken. Treatment of methoxycarbonylmethylenequinolizine (124) with t-butyl propiolate in boiling nitrobenzene yielded the desired product in 62% yield, its identity as (147) being established from the close similarity of its spectral properties

FIG. 29

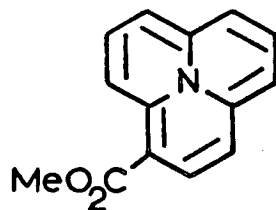


Methyl cycl[3.3.3]azine-1-carboxylate

to those of the diethyl analogue (135).



Pyrolysis of (147) in a sublimation apparatus, under an inert atmosphere at 220°C., caused slow evolution of a gaseous product. When the temperature was further increased to 250°C., a more vigorous effervescence occurred, while a dark violet vapour condensed as a viscous oil on the surface of the cold-finger. Careful resublimation of the product yielded a dark-brown crystalline solid which was identified from its n.m.r. spectrum as the required methoxycarbonylcyclazine (148).



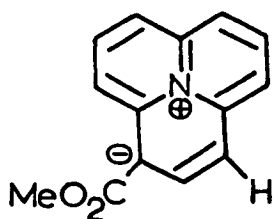
(148)

The u.v. spectrum in cyclohexane [Fig.17] was similar to that of the diethyl ester (135). The n.m.r. spectrum [Fig.29] consisted of a three-proton singlet at 6.6τ attributable to the methoxyl protons, together with six, one-proton doublets and two, one-proton triplets, in the region 3.8 - 6.4τ, attributable to the protons of the cyclazine ring-system. The absorption attributable to the t-butoxyl protons of the precursor

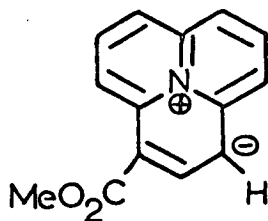
compound was completely absent. Apart from the general upfield-shift of the nuclear-proton resonances, which results from the removal of one of the deshielding ester substituents, the most interesting feature of the spectrum was the presence of one of the doublets at the unexpectedly high τ -value of 6.37 . This value is, in fact, only slightly downfield from that of the methoxyl proton resonance at 6.60 τ . Since the absorption possessed only primary splitting ($J = 9.5\text{c/s.}$), in common with a second lower-field absorption at 4.35 τ ($J = 9.5\text{c/s.}$), it obviously formed part of the AB system attributable to the protons at the 2- and 3-positions of the molecule.

The A signal can only be assigned to the 2-proton, which is relatively deshielded as a result of its situation β to a ring-junction and ortho - to the ester substituent. This leaves the high-field absorption attributable to the 3-proton. However, the displacement of the resonance signal to a higher field than those of, say, the 6- and 7-protons, which are relatively remote from the ester substituent, is completely unexpected. The only logical explanation of these observations is that the high chemical shift of the 3-proton must be a consequence of the electron-withdrawing influence of the ester group.

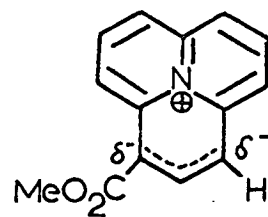
This apparently anomalous conclusion is best rationalised in terms of the stabilisation of the ring-system by the significant contribution of quinolizinium ylide structures (148a) and (148b) [which may be collectively represented by structure (148c)] to the resonance hybrid.



(148a)



(148b)

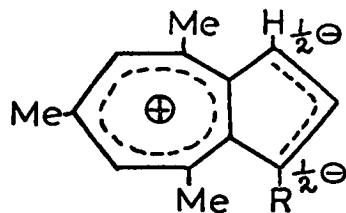


(148c)

The direction of charge-separation within the molecule, which is largely determined by the electron-withdrawing influence of the ester substituent, must result in an increased localisation of negative charge at both the 1- and 3-carbon atoms. The magnitude of the resultant shielding of the 3-proton must be such as to completely over-ride the conjugative deshielding influence of the 1-ester group.

As an extension of this principle, the apparently paradoxical situation arises whereby increasing the electronegativity of the 1-substituent should cause an increase in the shielding of the 3-proton. Although this prediction was not verified for mono-substituted cyclazines, it seemed possible that experimental verification might be gained from a study of the n.m.r. spectra of suitably substituted azulenes. 1-Acetylated derivatives of 4,6,8-trimethylazulene were chosen for this purpose since the resonance signals of the 3-proton in the corresponding 1-substituted parent compounds are generally obscured¹¹⁰ by the complexity of the spectra. The dipolar contributing structures

to the resonance hybrid of 4,6,8-trimethylazulene may be collectively represented as follows:

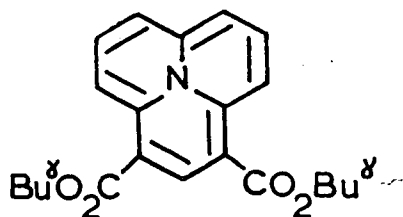


The 1- and 3-proton resonances appear as a doublet at 2.81τ , with the 2-proton giving rise to a triplet at 2.50τ . Introduction of a 1-acetyl substituent ($R = \text{COCH}_3$) causes an upfield shift of the 3-proton resonance to 3.06τ while that of the 2-proton undergoes a downward shift to 2.28τ . The more strongly electron-withdrawing ethoxalyl substituent ($R = \text{CO}\cdot\text{CO}_2\text{Et}$) causes an even greater separation of chemical shift, the 3- and 2-protons resonating at 3.14τ and 2.21τ , respectively. Undoubtedly then, this evidence provides strong confirmatory support for the preceding hypothesis. Although it is probably premature to assume the generality of the concept for all systems that can achieve resonance stabilisation of the type shown, it appears likely that electronegative substituents which enhance the degree of charge separation within such systems will cause shielding, rather than deshielding, of the β -proton.

Chemically, the 1-methoxycarbonylcyclazine proved very unstable, undergoing decomposition within a few hours on exposure to air with formation of a black amorphous surface-residue.

In solution, and especially with hydroxylic solvents, decomposition occurred much more rapidly, the initially-clear, yellow solutions darkening within a few minutes. When applied to either alumina or silica a dark, intractable residue formed within seconds. Although chromatographic purification could not be attempted, the product was obtained in a satisfactory state of purity by resublimation.

The ready susceptibility of the cyclazine to oxidative degradation reflects on the importance of electron-withdrawing substituents in stabilising the electron-rich nuclear system. The parent cyclazine, which cannot achieve stabilisation in such manner, is thus expected to be highly labile in character. Conventional synthetic methods, such as those used by previous workers, would thus appear to be inapplicable. However, the observed thermal stability of the methoxycarbonyl derivative (148) (as inferred by its method of preparation) suggested that extension of the pyrolytic approach might provide a feasible route to the parent compound. The synthesis of the 1,3-di-t-butyl ester (149) was thus attempted.

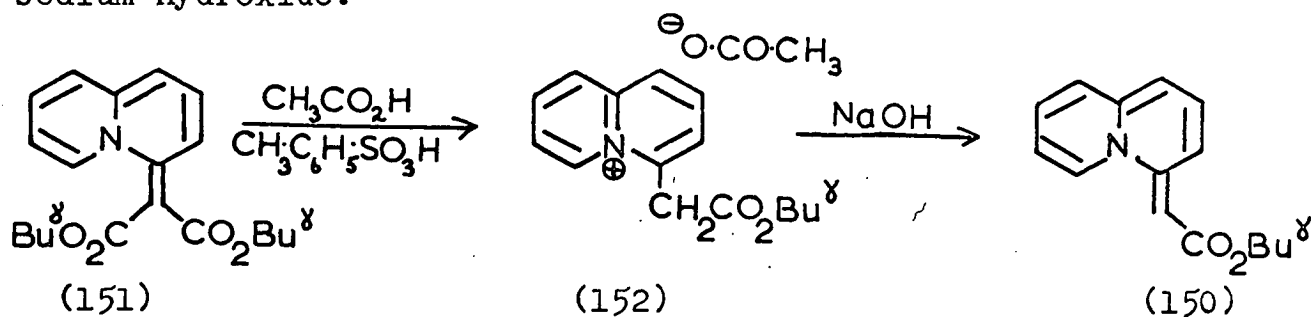


(149)

An immediate obstacle in realising this aim was presented by

the difficulties encountered in synthesising the requisite precursor compound, 4-t-butoxycarbonylmethylenequinolizine (150). The route by which the corresponding ethyl and methyl analogues were obtained appeared to be of doubtful value in view of the susceptibility to acid-catalysed cleavage of both t-butyl ester groups in the quinolizine (151). An attempt to synthesise the product via esterification of 4-carboxymethylquinolizinium chloride (108) was thwarted by the low solubility of the salt in a wide range of solvents. A further experiment to determine the feasibility of condensing ethyl lithioacetate with 4-chloroquinolizinium perchlorate resulted in recovery of starting material.

Synthesis of the required product was eventually achieved by refluxing di-(t-butoxycarbonyl)methylenequinolizine (151) in glacial acetic acid containing a trace of p-toluenesulphonic acid. By extracting samples of the solution at 1 minute intervals it was found that conversion to the monosubstituted methylquinolizinium salt (152) was complete in 6 minutes. Liberation of the free base (150) was accomplished by addition of sodium hydroxide.

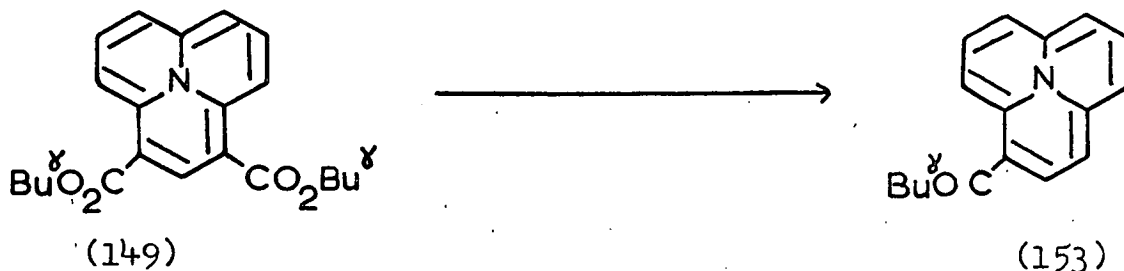


When the reflux period was extended, loss of the second t-butyl group occurred as expected.

Treatment of the quinolizine (150) with t-butyl propiolate in boiling nitrobenzene for 6 minutes gave a 64% yield of the required diester (149), isolated as glistening brown plates, together with a 6% yield of the 3a,4-dihydro derivative.

These products were identified by the close similarity of their spectral properties to those of the ethyl analogues (135) and (140) respectively.

Pyrolysis of the cyclazine under conditions similar to those employed in the preparation of the monomethoxycarbonyl derivative (148) yielded an unstable product, the n.m.r. spectrum of which showed it to be the mono-t-butyl ester (153).



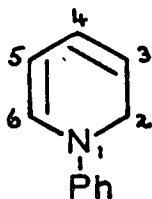
When subjected to further pyrolysis with a view to removing the remaining ester group the system underwent extensive decomposition; only a small amount of unchanged material was recovered. An attempt to generate the parent cyclazine directly by introducing a benzene solution of the diester (149), dropwise, into a vertical tube packed with glass beads at a series of temperatures in the range 250 - 400°C. was also without effect, the cyclazine being recovered unchanged from the final condensate. This appeared a rather incredible result because, at the higher temperatures in this range, some of the benzene was converted into biphenyl. Presumably, the rapid volatilisation of the

solvent carries the cyclazine through the system too rapidly for efficient heat-transfer. Further attempts to generate the parent cyclazine by subjecting the diester to vigorous pyrolysis conditions in a sublimation apparatus yielded a product which, although containing a second highly labile component, consisted mainly of the mono-t-butyl ester (153). In order to avoid this latter complication, it appeared necessary to conduct further pyrolysis reactions in a sealed vessel so that the initially-formed product would not volatilize from the heated zone. This was achieved by sealing the diester in a strong-walled, evacuated glass-tube and immersing the tube in a molten-metal bath at 300°C., for 5 minutes. The tube was then opened and the product was sublimed directly from it. A dark-brown crystalline solid was obtained. Although this solid was quite stable under a dry nitrogen atmosphere, extensive decomposition occurred within a few minutes on exposure to the atmosphere. When dissolved in either tetrachloride or chloroform, the initially-clear, yellow solution darkened within 1 minute with deposition of an amorphous black solid. As a consequence, a satisfactory n.m.r. spectrum of the product could not be obtained in these solvents.

While a slightly enhanced stability was evident in ether, this solvent proved unsuitable for spectroscopy because of interference from the methyl resonances. However, a satisfactory spectrum was eventually obtained in bis(trimethylsilyl) ether (i.e. $\text{Me}_3\text{Si}\cdot\text{O}\cdot\text{Si}\cdot\text{Me}_3$) [although the product was of limited solubility in this medium.]. Two main absorptions were evident;

a triplet centred at 6.35τ ($J = 8\text{c/s.}$) together with a higher field doublet of twice the intensity centred at 7.93τ ($J = 8\text{c/s.}$) A further weak absorption at 8.75τ indicated slight contamination by the mono-t-butyl ester (153). The symmetry of the system, as implied by the simplicity of the spectrum, together with its physical and chemical characteristics (colour, instability) left no doubt that it was indeed the parent cyclazine.

Although the pattern of n.m.r. absorptions is as anticipated with the doublet and triplet being assigned respectively to the protons α - and β - to the perimeter ring-junctions, the chemical shifts are displaced to extremely high field-values. These values are, in fact, the highest observed to date for any peripheral-conjugated system containing $4n\tau$ electrons. The shielding of the nuclear-protons may be attributed to two main factors. The most important of these is undoubtedly an induced paramagnetic ring-current, the presence of which may be inferred from a comparison of the proton chemical shifts with those¹¹¹ of the cyclic dienamine system, N-phenyl-1,2-dihydropyridine (154).

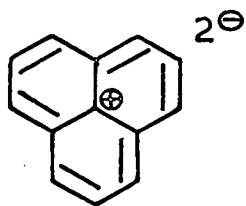


(154)

The 4-proton of (154) gives rise to a multiplet centred at 4.12τ while the 3- and 5-protons yield higher-field multiplets centred at 4.79τ and 5.06τ , respectively. These absorptions

are 2-3 p.p.m., downfield from those of the corresponding protons in the cyclazine. However, in addition to the paramagnetic ring-current, the shielding must also be due, in part, to the high electron-density carbon-perimeter consequent on delocalisation of the lone-pair of electrons on the nitrogen atom. Thus tridehydro[12]annulene, in which the displacement of the chemical shift is solely due to an induced paramagnetic ring-current, gives¹¹² a resonance signal at 5.55 τ ; this value is considerably downfield from that observed for the cyclazine. The unusually high chemical shift of the cyclazine resonances may thus be attributed to the combined effect of these shielding influences.

It is interesting to compare the spectrum of the parent cyclazine with that reported⁶⁶ for the isoelectronic phenalenyl anion (53). The spectrum of the latter consists of a triplet at 4.09 τ together with a higher-field doublet at 4.83 τ . These chemical shifts differ considerably from that of the cyclazine and quite clearly indicate that the anion does not sustain an induced paramagnetic ring-current. It is also noteworthy that the latter shifts are lower than those observed for tridehydro [12]annulene (5.55 τ) despite the fact that the phenalenyl anion possesses a negative charge. The triplet absorption is, in fact, even lower than that of a typical olefinic proton (4.40 τ). It may well be that the phenalenyl anion is more adequately represented⁶⁷ by structure (155) in which 14 π -electrons are delocalised around the carbon-perimeter.



(155)

In view of the considerable development stages involved in the synthesis of the cyclazine it is unfortunate that lack of time has prevented an investigation of the physical and chemical properties of the system.

To conclude this section of the discussion, it may be inferred that, since molecular orbital theory predicts⁷⁹ bond-alternation as an intrinsic property of systems containing $4n$ peripheral π -electrons, the cycl[3.3.3]azine system is best represented by rapidly interconverting valency tautomeric structures.

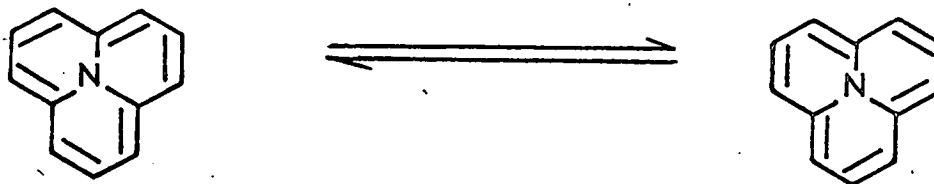
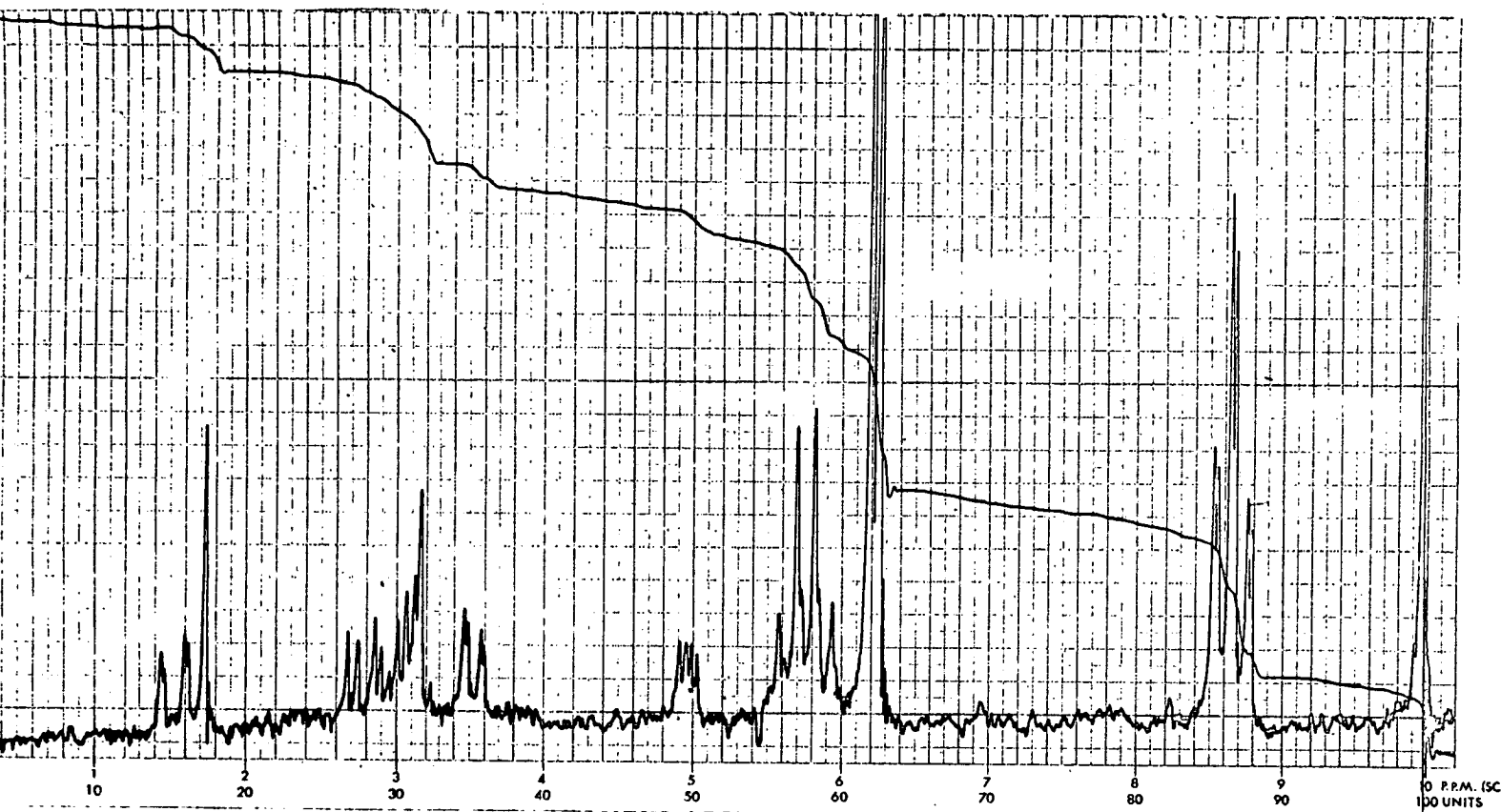


FIG. 30

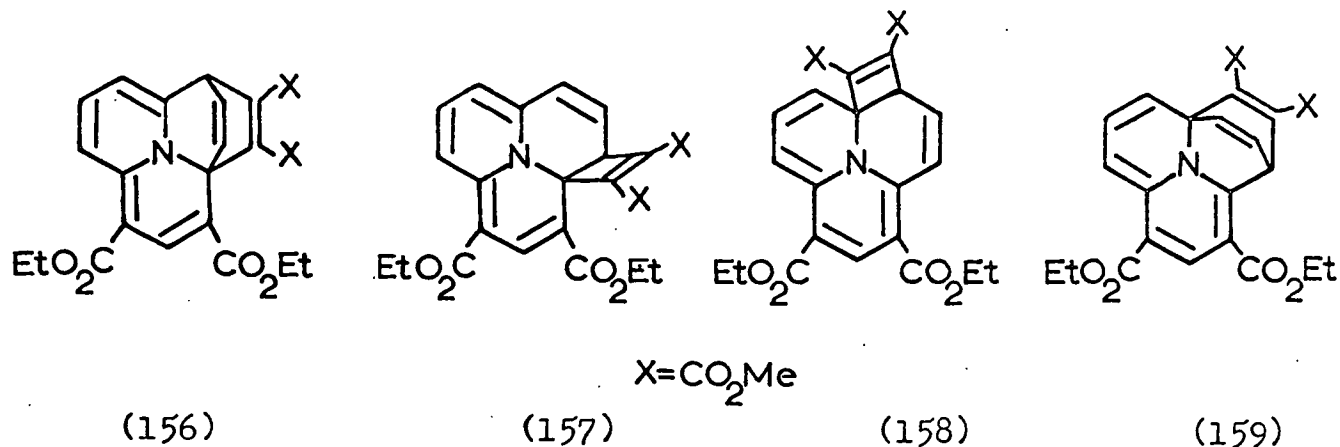


3a,6-Etheno-3a,6-dihydro-1,3-di(ethoxycarbonyl)-4,5-di(methoxy-
carbonyl)cycl[3.3.3]azine

CHEMICAL REACTIONS OF 1,3-DI(ETHOXYCARBONYL)CYCL[3.3.3]AZINE

In order to gain chemical confirmatory evidence for the olefinic character of the cyclazine system, it was of interest to attempt a reaction between the diethyl ester (135) and dimethyl acetylenedicarboxylate and further, if successful, to compare the nature of the product(s) with that obtained from a similar reaction with the related aromatic system cyclopenta [cd] cycl [3.3.3] azine. A special interest in the reaction with the cyclazine arises because the expected cyclo-addition can occur in several different ways.

When the cyclazine was refluxed in benzene for 24 hours with the acetylenic ester, the initial yellow solution turned deep-red in colour. The single product, isolated in 96% yield as red prisms, analysed as a true 1:1 adduct. This was further substantiated by mass spectral evidence which indicated a molecular weight of 453. The u.v. and visible spectrum in ethanol [Fig.19] showed a strong resemblance to that of the tetrahydrocyclazine (143), thus indicating the presence, in the molecule, of a 4H-quinolizine system. The presence, in the n.m.r. spectrum [Fig.30] of a low-field doublet and singlet (each one proton) at 1.77 τ and 1.55 τ , respectively, supported this inference since these absorptions, by analogy with the tetrahydro-compound, can then be assigned to the deshielded protons at the 2- and 9- positions of the cyclazine skeleton. On the basis of this evidence alone, four possible structures may be considered for the adduct.



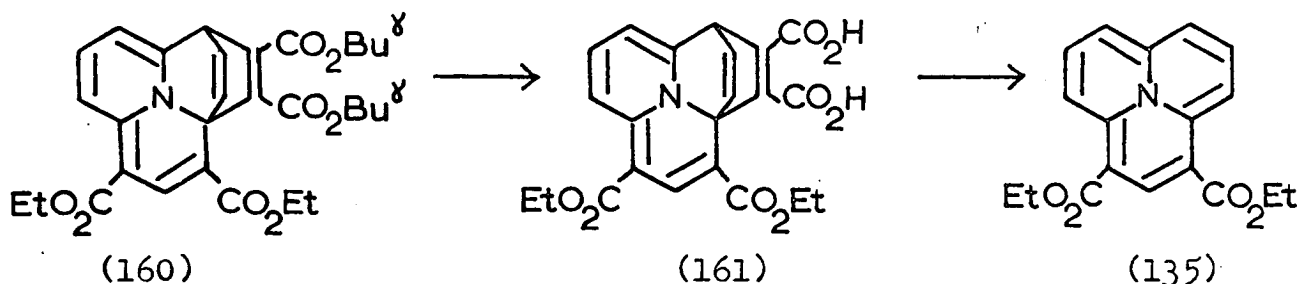
However, structures (158) and (159) appeared very unlikely since the incorporated 4H-quinolizine systems contain no stabilising substituents in the ring bearing the tetrahedral carbon-centre.

Further, these molecules are expected to protonate at either the 7- or 9- position with retention of the n.m.r. singlet attributable to the 2-proton. This singlet was not evident when the spectrum was measured in trifluoroacetic acid.

Structure (157) was also considered unlikely since it possesses a conjugated system similar to the 3a,4-dihydrocycloazine (140) and, by analogy with such, is expected to be intensely blue in colour. This leaves structure (156) as that most consistent with the observed colour and stability of the adduct. On this basis, the remaining absorptions in the n.m.r. spectrum were provisionally assigned as follows:- a multiplet (three protons) at 2.7 - 3.3 τ to the 8-proton together with the two etheno bridge-protons (the latter are deshielded by the adjacent ester groups); a doublet (one proton) at 3.55 τ , further split by m-coupling, to the 7-proton; a quartet (one proton) at 5.00 τ to the saturated bridgehead proton. The multiplicity of the latter absorption arises from coupling to both of the etheno protons.

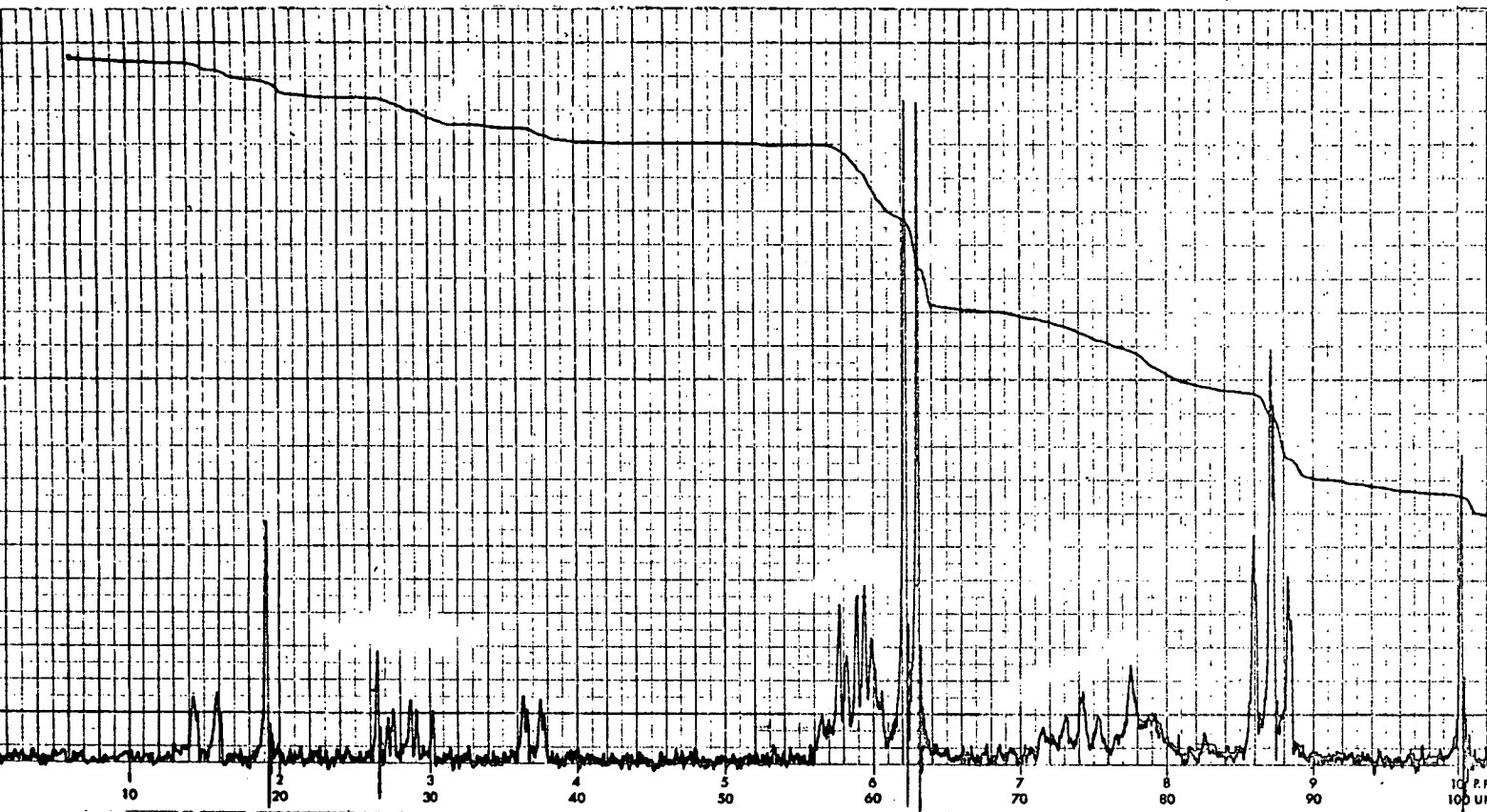
The only additional absorptions present were those attributable to the alkoxy protons of the four ester groups.

When the reaction was repeated using di-t-butyl acetylene-dicarboxylate instead of the dimethyl analogue, a similar red product was obtained. The n.m.r. spectrum proved, as expected, almost identical with that of the preceding adduct except that the methoxyl resonances were replaced by a higher-field absorption attributable to the t-butoxyl protons. Treatment of the adduct with anhydrous hydrogen chloride in benzene yielded a red solid which was identified, from its n.m.r. spectrum in trifluoroacetic acid, as the dicarboxylic acid (161) derived by loss of both t-butyl groups from the adduct (160). When the diacid was sublimed under reduced pressure, a 25% yield of the cyclazine (135) was obtained.



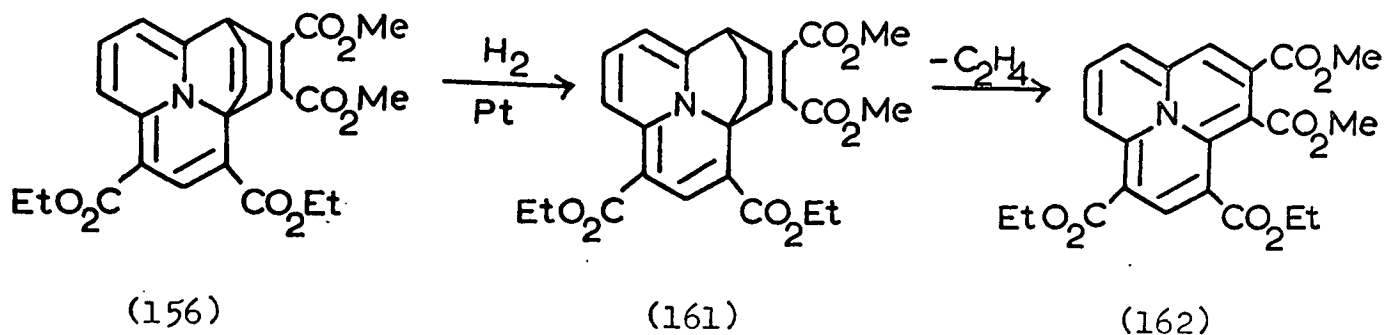
Although the structures given above appear most consistent with the u.v. and n.m.r. evidence, alternative structures derived by addition of the acetylenic ester to the 3a,4-positions of the cyclazine (e.g. 157) might possess similar spectral characteristics and cannot therefore be eliminated with certainty. The chemical evidence provides no criteria for structural assignment since all four structural types are potentially

FIG. 31



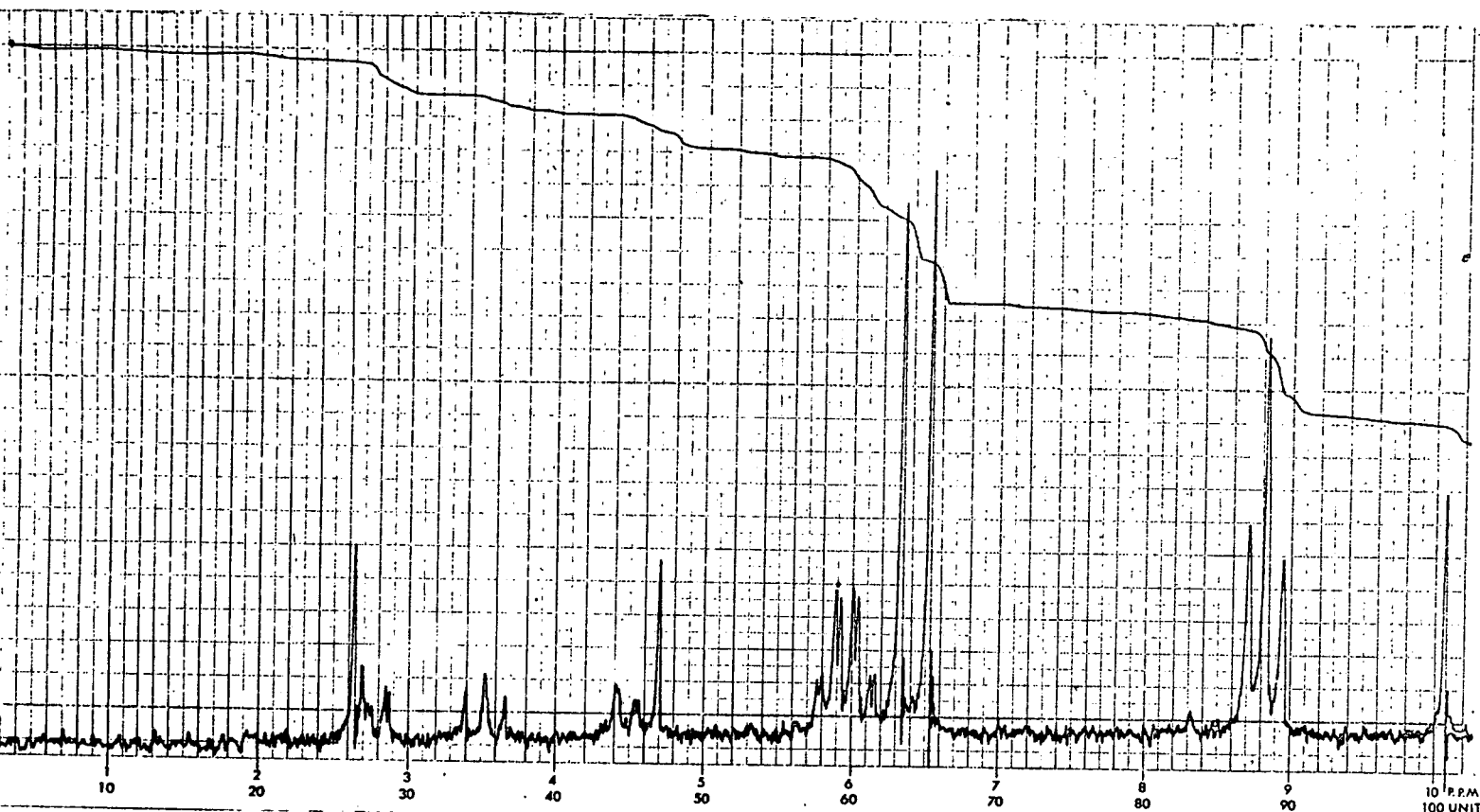
3a,6-Ethano-3a,6-dihydro-1,3-di(ethoxycarbonyl)-4,5-di(methoxycarbonyl)
cycl[3.3.3]azine

capable of undergoing a cyclo-elimination reaction with regeneration of the original cyclazine. It seemed possible that confirmatory evidence for the supposed mode of addition might be gained by attempting the following conversions.



Thus, addition of hydrogen to the adduct, which is expected to occur preferentially at the non-conjugated etheno bridge-bond, should yield the ethano analogue (161) which, on pyrolysis, might lose ethylene by a reverse Diels-Alder reaction to give the tetrasubstituted cyclazine (162). Treatment of the adduct with a molar proportion of hydrogen over a platinum catalyst yielded a red crystalline product which appeared physically similar to the starting material. The u.v. spectrum [Fig.19] was almost superimposable with that of the latter thus indicating that the conjugated system had remained unchanged. The identity of the product as (161) was confirmed from its n.m.r. spectrum [Fig.31] which differed significantly from that of (156) only in the respect that the three-proton multiplet at 2.7 - 3.3 τ (8-proton and etheno bridge-protons) together with the bridgehead proton at 5.0 τ in the spectrum of the latter were now replaced by a one-proton absorption at 2.86 τ (8-proton) together with a five-proton multiplet in the region 6.9 - 8.2 τ (bridgehead proton and ethano bridge-protons).

FIG. 32



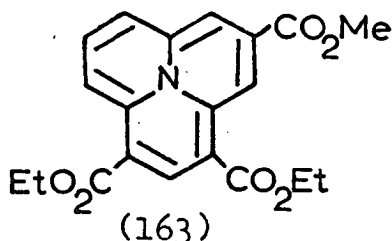
1,3-Di(ethoxycarbonyl)-4,5-di(methoxycarbonyl)cycl[3.3.3]azine

When the product was pyrolysed at 290°C., under a nitrogen atmosphere, a vigorous evolution of gas occurred and the molten residue changed colour from red to light-brown. After chromatography on alumina, a brown crystalline product was obtained in 68% yield, together with a second, lighter-coloured product in 3% yield. The u.v. spectrum of the major product [Fig.20] was similar to that of the diester (135) thus indicating that the product was a cyclazine derivative. This was confirmed from the n.m.r. spectrum [Fig.32] which identified the product as the expected tetracarboxylic ester (162). Apart from the four ester resonances the spectrum consisted of a singlet (2.57 τ), a doublet (4.42 τ), a triplet (3.45 τ) and a further doublet (2.73 τ) which were assigned to, respectively, the 2-, 7-, 8- and 9-protons; a higher-field singlet at 4.63 τ was assigned to the 6-proton. The presence of the methoxycarbonyl groups in the 4- and 5- positions of the molecule follows from the high chemical shift of the latter resonance since the only possible alternative arrangement, viz., with these groups in the 5- and 6- positions, would lead to a much lower shift for the singlet (which would then be attributable to the 4-proton) because of the long-range deshielding influence of the 3-ethoxycarbonyl group. The high chemical shift of the singlet (it is, in fact, the highest-field absorption in the vinylic region of the spectrum despite the fact that the 6-proton lies adjacent to a deshielding group) is undoubtedly due to the strong shielding influence of the 4-methoxycarbonyl group. The spectrum thus provides a further illustration of the remarkable shielding influence of α -orientated electron-withdrawing substituents, in the cycl[3.3.3]azine system, on the proton

attached to the second α -position of the same ring.

The formation of the cyclazine (162) from the pyrolysis reaction leaves the structure of the hydrogenated adduct completely unambiguous and, in turn, firmly establishes the orientation of the addition as that represented in structure (156).

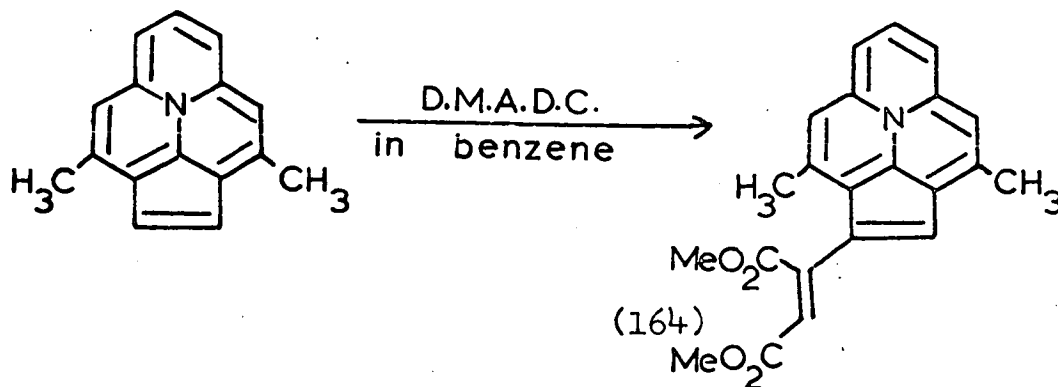
The second component from the pyrolysis reaction, which was obtained in only minute yield, was identified as a cyclazine from the similarity of its u.v. spectrum [Fig.20] to that of the major component (162). The mass spectrum indicated a molecular weight of 369, this value suggesting that the molecule contained only one methoxycarbonyl group. This was confirmed from the n.m.r. spectrum which identified the product as (163).



The nuclear-protons gave rise to a pattern of absorptions similar to that of the corresponding protons in the diethyl ester (135) except for the 4- and 6-protons, each of which gave rise to singlet absorptions (split by m-coupling) which were slightly downfield, because of deshielding by the 5-methoxycarbonyl substituent, from the doublets attributable to, respectively, the 9- and 7-protons. Although the mode of formation of the product is not clear, the driving force for the elimination of the methoxycarbonyl group may be provided by the relief in steric interaction that ensues between the remaining substituent groups.

The structure of the adduct from dimethyl acetylenedicarboxylate and the cyclazine having been established, reaction was attempted between the acetylenic ester and 3,9-dimethylcyclopenta [cd] cycl [3.3.3] azine. The latter compound¹¹³ has been shown by n.m.r. criteria to be aromatic in character, the resonance of the nuclear-protons (2.9 - 3.7 τ) falling within the range expected of an electron-rich aromatic heterocycle. Attempted electrophilic substitution, however, has met with limited success, the system undergoing decomposition under a variety of reaction conditions. Such behaviour does not, of course, reflect on the aromatic character of the system but merely indicates that suitable experimental conditions have not been achieved.

A 1-benzoyl derivative has, in fact, been prepared¹¹³ by reaction with benzoyl chloride in the presence of sodium bicarbonate. When reaction was attempted with the acetylenic ester in refluxing benzene a considerable amount of decomposition material was produced together with a dark-brown product, the latter being isolated in 40% yield after chromatography on alumina. The identity of the product as the linear adduct (164) was apparent from its n.m.r. spectrum.



Thus, the low-field region remained similar to that of the precursor compound except that a two-proton singlet at 3.04τ (1- and 2-protons) in the spectrum of the latter was now replaced by a one-proton singlet at 2.87τ (2-proton) and a further one-proton singlet at 4.12τ (maleoyl proton). The configuration of the exocyclic double-bond is probably that shown since the alternative trans-configuration would be expected to lead to a lower chemical shift for the terminal proton (because of long-range deshielding by the spatially-proximate ester group).

The different modes of reaction of the cyclazine and cyclopentacyclazine with dimethyl acetylenedicarboxylate under similar conditions reflects on the fundamentally different character of the two systems. The fact that the cyclazine, as opposed to the tetracyclic compound, exhibits no tendency to form a linear adduct but, instead, yields a cycloadduct as the sole product of reaction correlates well with the olefinic character of the system as indicated by n.m.r. criteria.

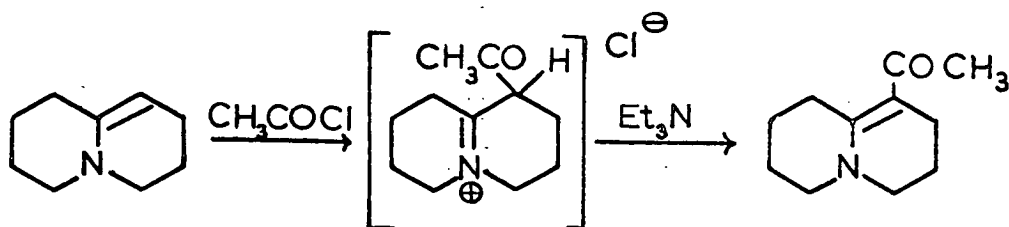
FIG. 33



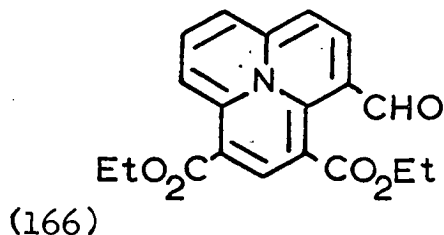
Diethyl 4-formylcycl[3.3.3]azine-1,3-dicarboxylate

ELECTROPHILIC SUBSTITUTION REACTIONS OF
1,3-DI(ETHOXYCARBONYL)CYCL[3.3.3]AZINE

When treated with electrophilic reagents cyclic enamines normally undergo attack at the β -carbon atom to yield immonium salts. Frequently, these eliminate a proton with formation of the corresponding conjugate base such that the overall sequence constitutes an electrophilic substitution reaction. e.g.

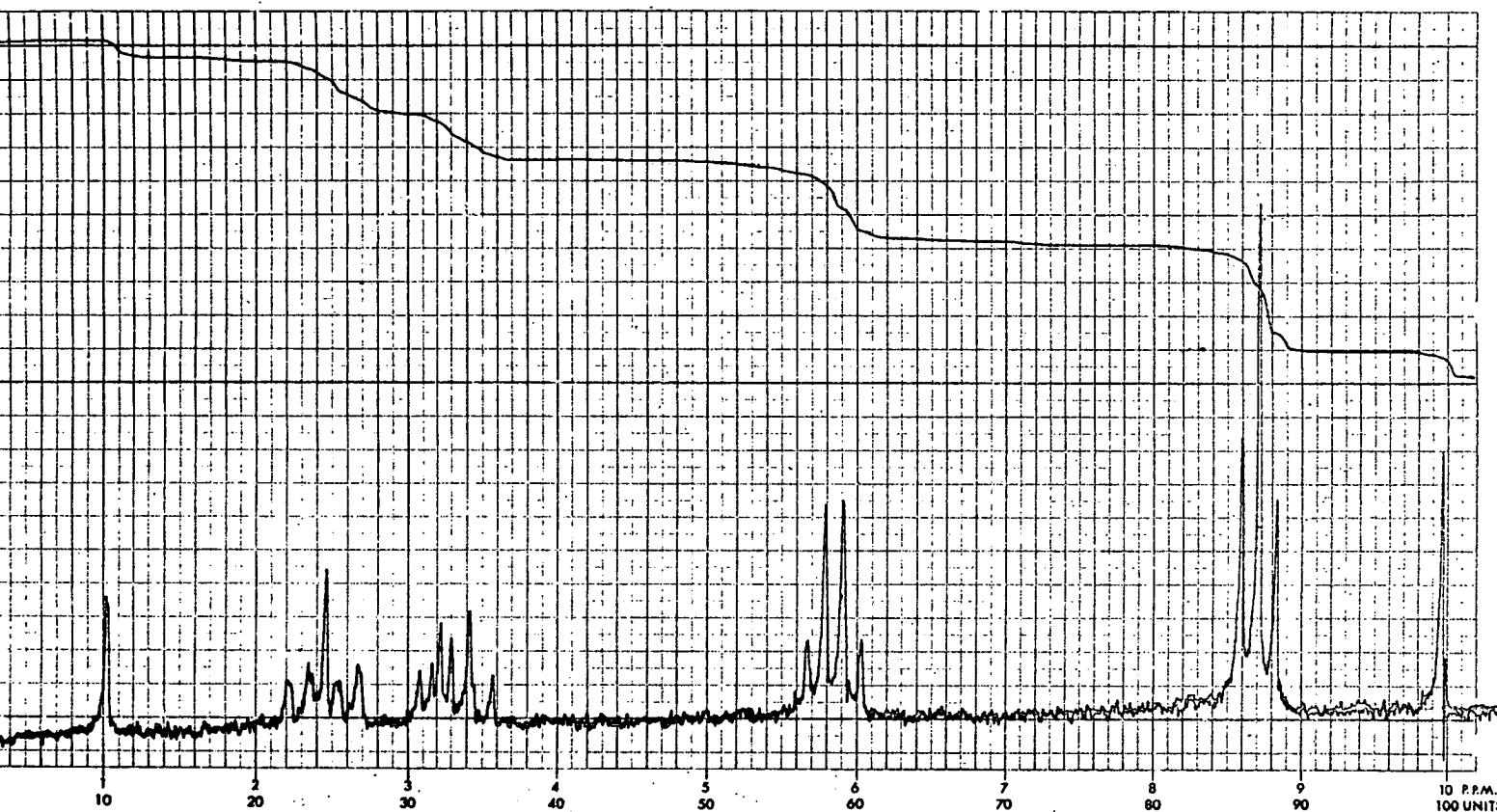


Reaction of the cyclazine (135) with *N,N*-dimethylformamide and phosphoryl chloride (Vilsmeier reagent) yielded two products which were isolated in 12% and 51% yield, respectively, after chromatography on alumina. The major product, obtained as brown needles, was identified from its n.m.r. spectrum [Fig.33] as the 4-formyl derivative (166).



The formyl proton gave rise to a singlet at 1.60 τ while the 2-, 7-, 8- and 9-protons gave rise, respectively, to a singlet (2.23 τ), a doublet (4.07 τ), a triplet (3.23 τ) and a doublet (2.60 τ). The only other absorptions present in the vinylic region of the

FIG. 34

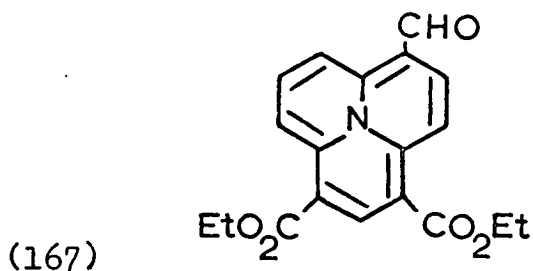


Diethyl 6-formylcycl[3.3.3]azine-1,3-dicarboxylate

spectrum were two doublets, each possessing the same coupling constant (9c/s.), at 3.10 τ and 4.33 τ , these obviously constituting the AX system attributable to the protons at the 5- and 6- positions of the molecule. Two diagnostic features allow an unequivocal assignment of the orientation of the formyl group to be made. Firstly, the high-field resonance of the X part of the AX spectrum can only be interpreted in terms of shielding of the 6-proton by the 4-formyl substituent. The only possible alternative arrangement, with the formyl substituent in the 6-position of the molecule, would lead to a much lower chemical shift for the X resonance, because the shielding influence of the formyl substituent on the 4-proton would then be offset by the long-range deshielding influence of the 3-ethoxycarbonyl group. Secondly, the high-field resonance of the doublet attributable to the 7-proton is inconsistent with the presence of the formyl group in the 6-position of the molecule. Such an arrangement would lead, because of long-range deshielding, to a much lower chemical shift for the doublet.

The expected effects of a 6-formyl group, which, as detailed above, were absent in the spectrum of the major product, were clearly apparent in that of the minor product [Fig. 34]. Thus the AX system now appeared as an AB system (the chemical shifts of the constituent doublets were closely similar) while the doublet attributable to the 7-proton occurred at a lower field than any of the remaining nuclear-proton resonances. The formyl proton gave rise to a singlet at 1.05 τ . Since the spectrum was otherwise similar to that of (166) the product can

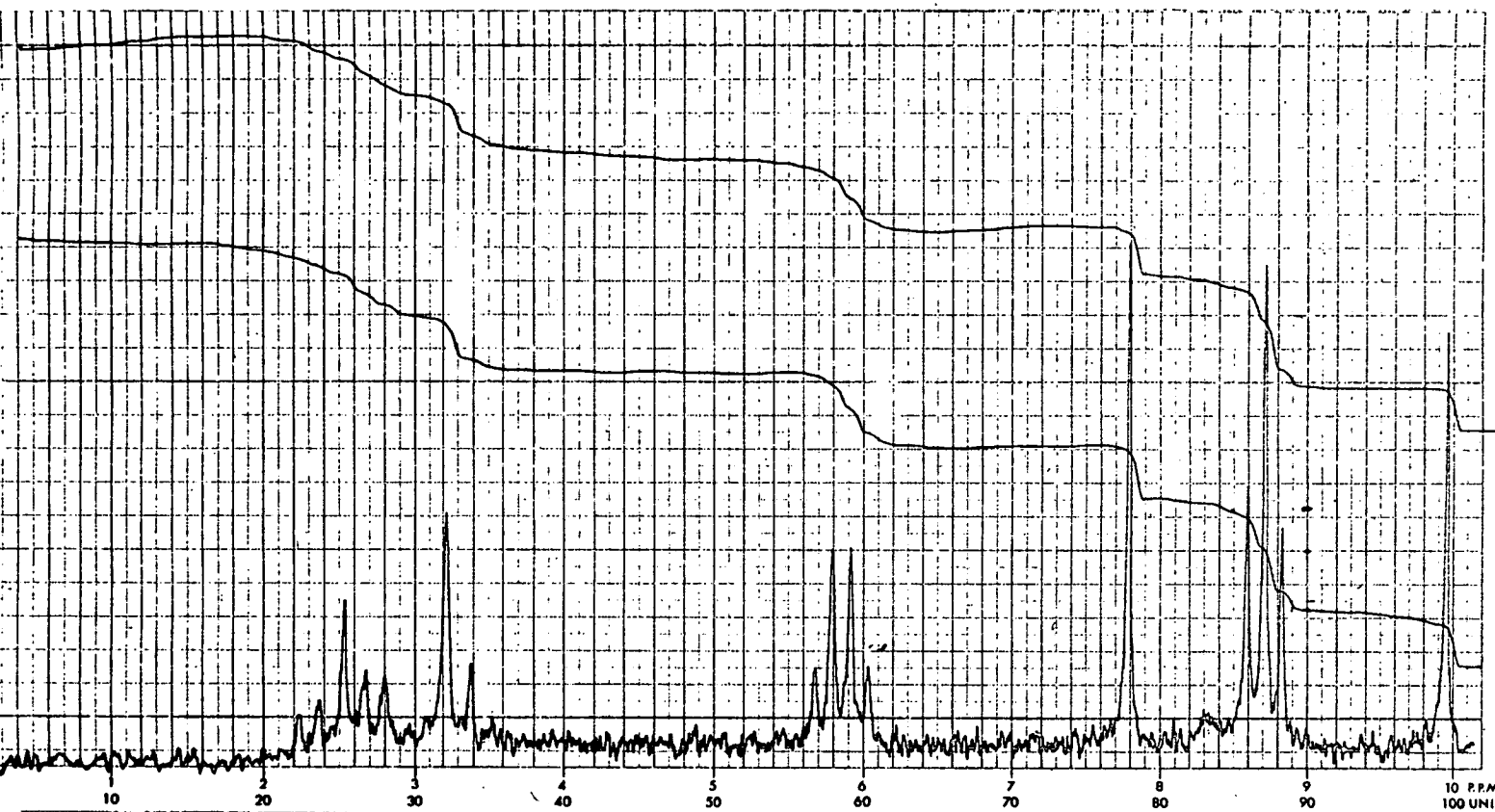
be assigned structure (167).



A feature of interest in the n.m.r. spectra of compounds (166) and (167) is the unusually high-field position of the resonance signal attributable to the formyl protons. It is unlikely that this effect is due to electron-release from the nitrogen atom since the formyl resonance of β -dimethylaminoacrolein is not unusually high. Again the effect is probably due to the paramagnetic ring-current; this is particularly interesting as it seems to be the first observation of a paramagnetic ring-current effect other than on protons attached directly to π -electron systems.

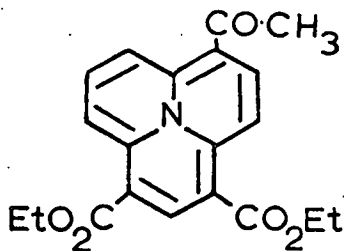
Although the formation of both the 4- and 6-formyl derivatives is consistent with the enamine character of the cyclazine system, the relative proportion of these isomers cannot be readily accounted for. In order to determine whether the system exhibited any consistency in the pattern of electrophilic substitution, an acetylation reaction was attempted using the Vilsmeier reagent derived from N,N-dimethylacetamide and phosphoryl chloride. However, in contrast to the preceding reaction, only one product was obtained in significant yield, this being separated from minute amounts of several other products by preparative t.l.c. on silica. The identity of the

FIG. 47



Diethyl 6-acetylcycl[3.3.3]azine-1,3-dicarboxylate

product as the 6-acetyl derivative (168) was apparent from the similarity of its n.m.r. spectrum to that of the 6-formyl compound (167).



(168)

The only significant difference from the spectrum of the latter, apart from that attributable to the different 6-substituent group ($-\text{COCH}_3 = 7.84\tau$), was that the 4- and 5-protons now gave rise to a triplet absorption comprising an intense inner band and two almost indiscernible outer bands. This difference, which represents a transition from an AB to an approximately A_2 spectrum, is consistent with the reduced electron-withdrawing ability of the 6-substituent; the shielding influence of the latter on the 4-proton is correspondingly reduced thus tending to bring the chemical shifts of the 4- and 5-protons into coincidence.

The absence of the 4-acetyl derivative is anomalous, especially considering that the 4-formyl derivative is the major product in the preceding reaction. No explanation can be offered for this apparent discrepancy and, correspondingly, no conclusions can be drawn regarding the preferred orientation of electrophilic substitution.

Although a further attempt was made to prepare a 4-acetyl-

derivative by heating the cyclazine with acetyl chloride in the presence of sodium bicarbonate, only decomposition material together with minute amounts of two reaction products were formed. The yields of the latter were insufficient for the reaction to merit further investigation. When the cyclazine was treated with benzoyl chloride, with a view to acylating the system, an immediate reaction ensued to yield a complex mixture of products. T.l.c. of a sample of the mixture on alumina revealed the presence of nine components. Unfortunately, these were poorly resolved and attempts to effect a large-scale separation were not successful. Because of this difficulty and the relatively small yield of each individual component, no further investigation of the reaction was undertaken.

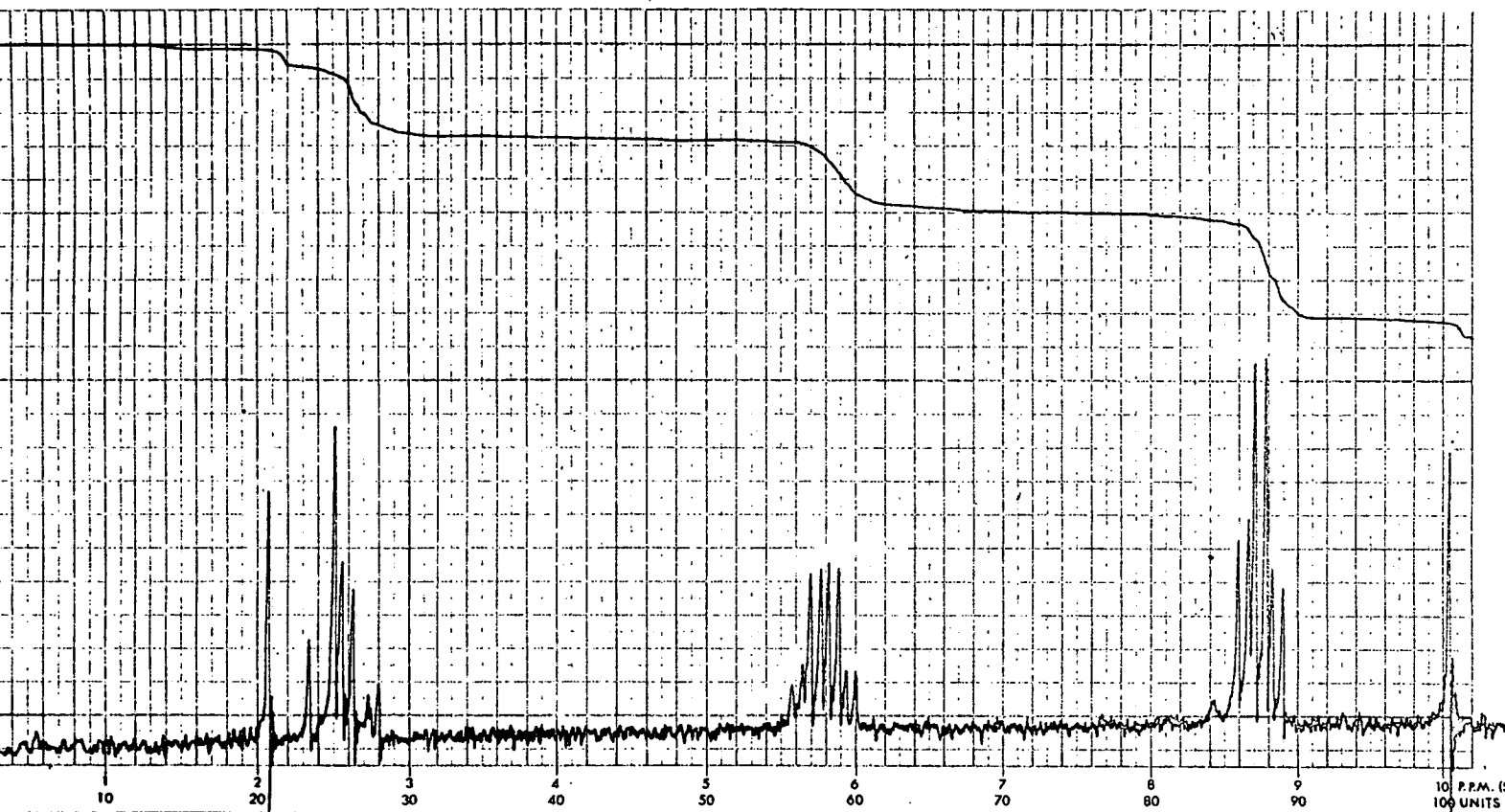
Nitration of the system was next attempted. Although copper nitrate in acetic anhydride is frequently used^{35,114} to nitrate acid-labile systems, the application of the reagent to the cyclazine is severely inconvenienced by the fact that trace amounts of copper caused a collapse of the n.m.r. signals attributable to the α ring-protons. This phenomenon has been observed¹¹⁵ with several other heterocyclic systems and has been theoretically interpreted in terms of the formation of loose complexes with the paramagnetic ion.

In order to avoid this complication, tetranitromethane was employed as the nitrating reagent. When reaction was carried out in pyridine as solvent, the latter also serving to neutralise liberated trinitromethane, a complex mixture of variously coloured products was obtained. Although attempts to

FIG. 36

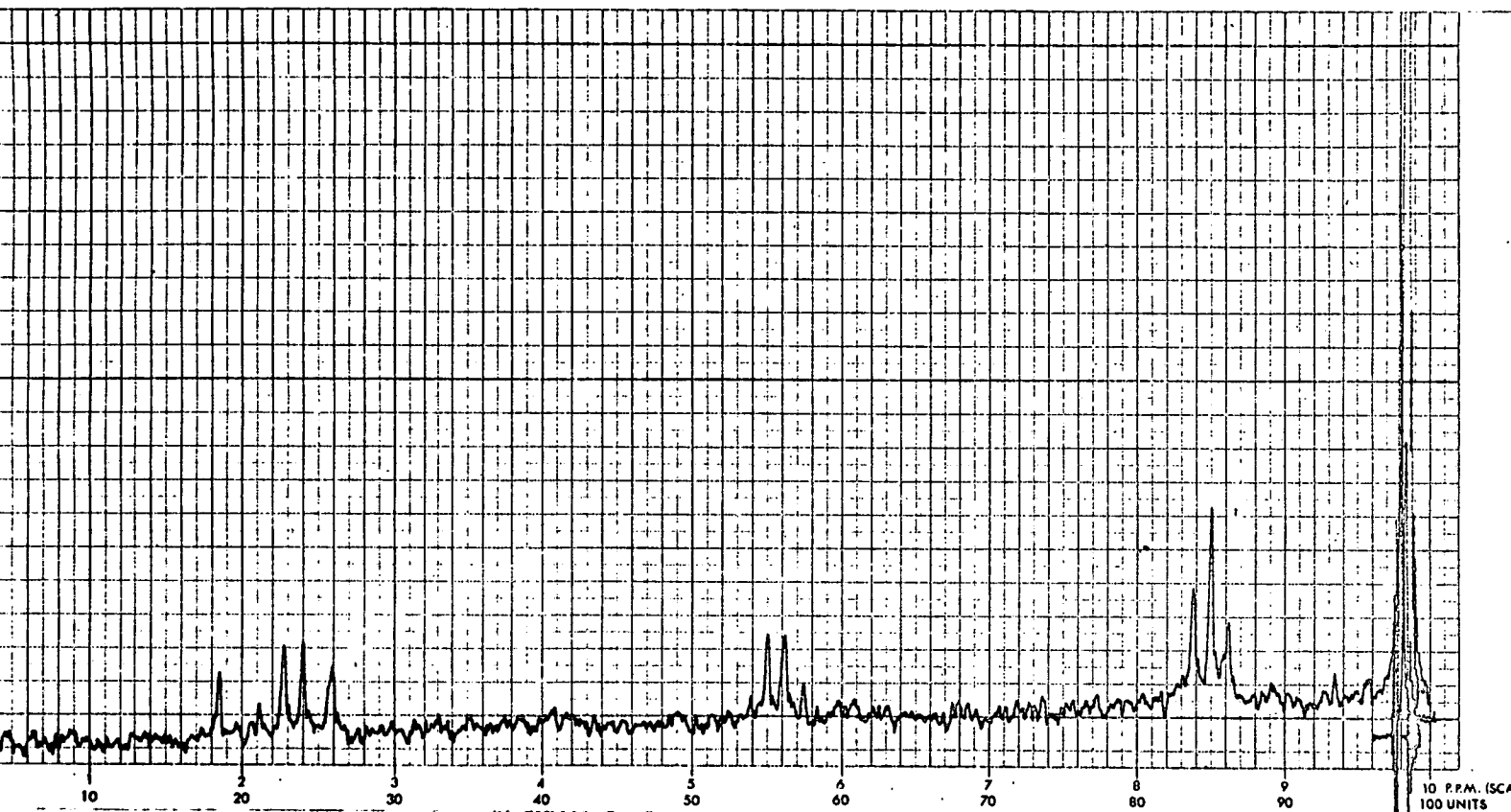


FIG. 37



Diethyl 4,7-dinitrocycl[3.3.3]azine-1,3-dicarboxylate

FIG. 38

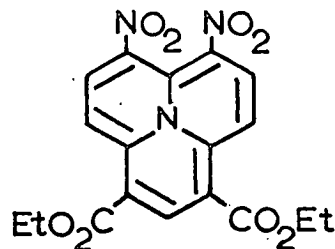


Diethyl 6,7-dinitrocycl[3.3.3]azine-1,3-dicarboxylate

the tendency of the 6- and 9-proton resonances to be displaced to higher fields than those of the 5- and 8-protons by the shielding influence of the electron-withdrawing, meta-situated nitro-groups is offset by the presence of peri-situated electron-withdrawing groups which exert a deshielding influence. The net result is that all four protons possess a similar chemical shift. The only remaining low-field absorption, a singlet at 2.03τ , was assigned to the 2-proton.

Fraction 3

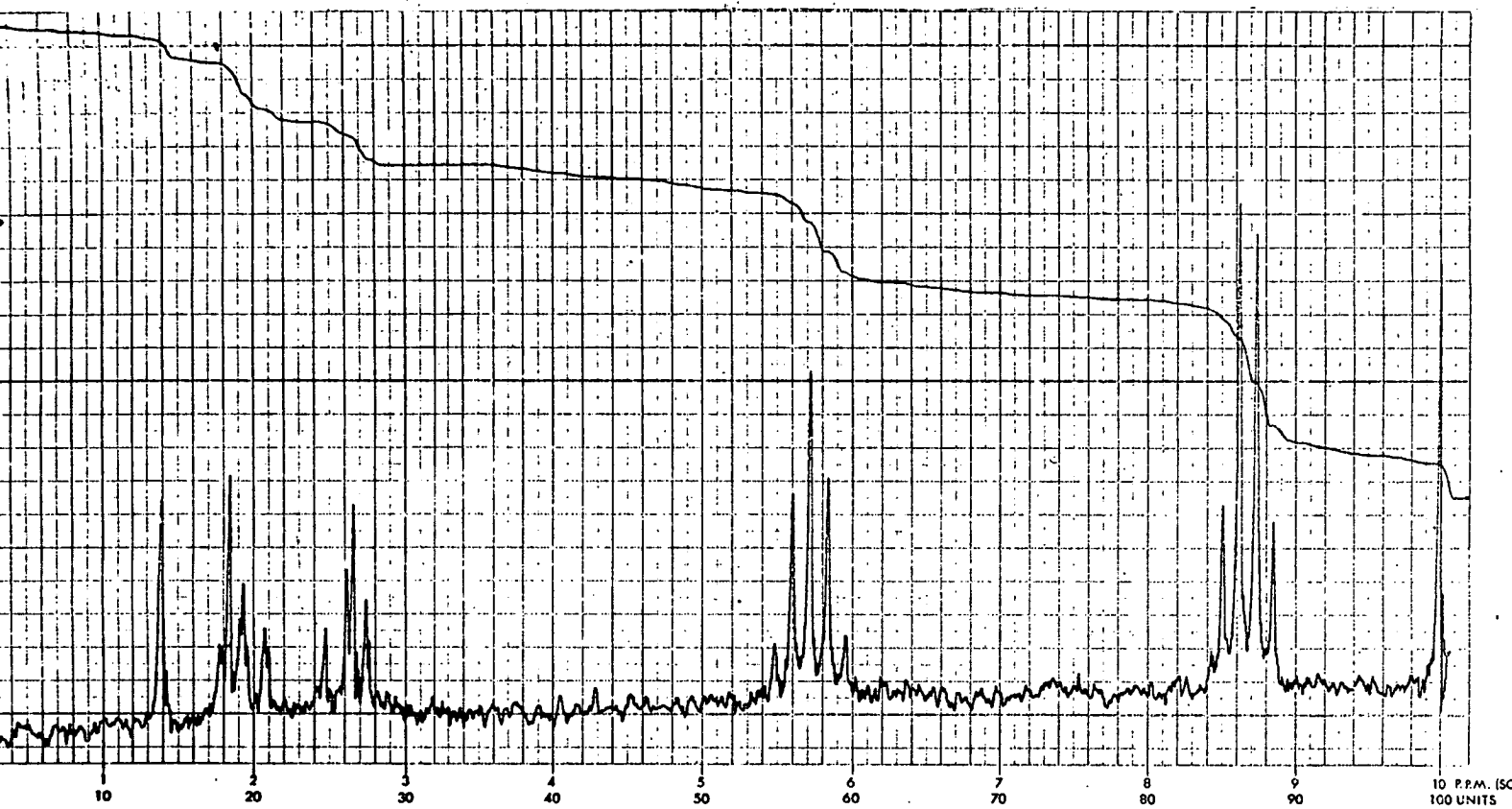
Yield = 5%



(170)

The mass spectrum showed a molecular weight of 401 thus indicating that the product was a dinitro derivative. The symmetry of the molecule was apparent from its n.m.r. spectrum [Fig. 38] The low-field region consisted of a one-proton singlet at 2.02τ attributable to the 2-proton, together with a four-proton quartet (the latter representing two superimposed AB systems) in the region $2.28 - 2.77\tau$, attributable to the 4- and 5-, and 8- and 9-protons. The assignment of the nitro-constituents to the 6- and 7- positions of the molecule follows from the close similarity of the chemical shifts of the constituent doublets of the quartet. The only possible

FIG. 39

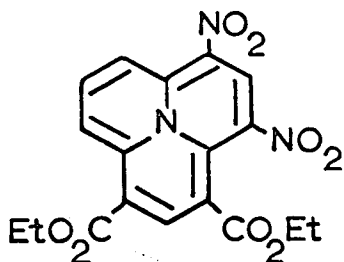


Diethyl 4,6-dinitrocycl[3.3.3]azine-1,3-dicarboxylate

alternative arrangement, with the nitro-substituents in the 4- and 9-positions of the molecule, would be expected to lead to a much larger difference in the chemical shift of the doublets since the shielding influence of the nitro-substituents on the m-protons would then no longer be offset by the long-range deshielding influence of the ester groups.

Fraction 4

Yield = 18%

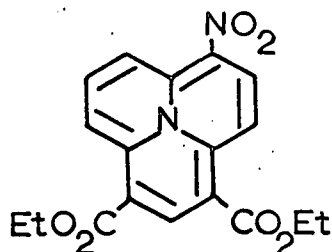


(171)

The mass spectrum showed a molecular weight of 401, thus indicating the product to be yet another dinitro-derivative. The n.m.r. spectrum [Fig. 39] consisted of two one-proton singlets at 1.39 τ and 1.84 τ , these being assigned, respectively, to the 5- and 2-protons, together with two partially superimposed doublets (each further split by m-coupling) in the region 1.85 - 2.00 τ , and a one-proton triplet at 2.62 τ , these being assigned to the 7- and 9-protons and to the 8-proton, respectively.

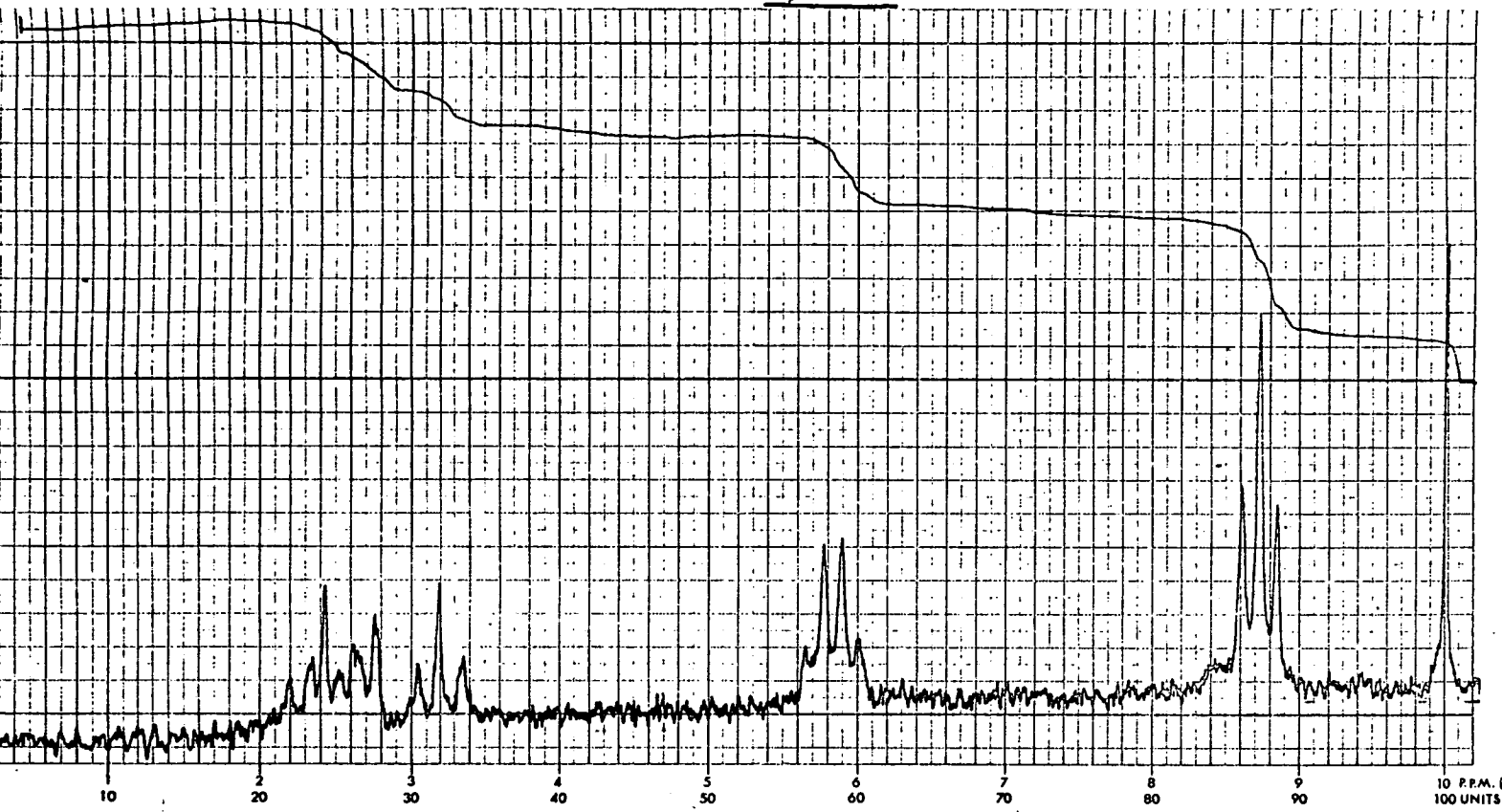
Fraction 5

Yield = 10%



(172)

FIG. 40



Diethyl 6-nitrocycl[3.3.3]azine-1,3-dicarboxylate

FIG. 41

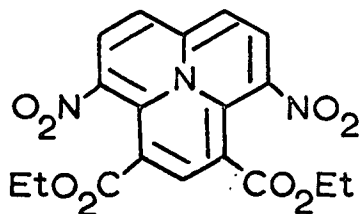


Diethyl 4,9-dinitrocycl[3.3.3]azine-1,3-dicarboxylate

The mass spectrum indicated a molecular weight of 356, this value corresponding to the introduction of one nitro-substituent into the molecule. The n.m.r spectrum [Fig.40] was qualitatively similar to that of the 6-formyl compound (166) [See p.110] thus establishing the identity of the product as (172).

Fraction 6

Yield = 9%



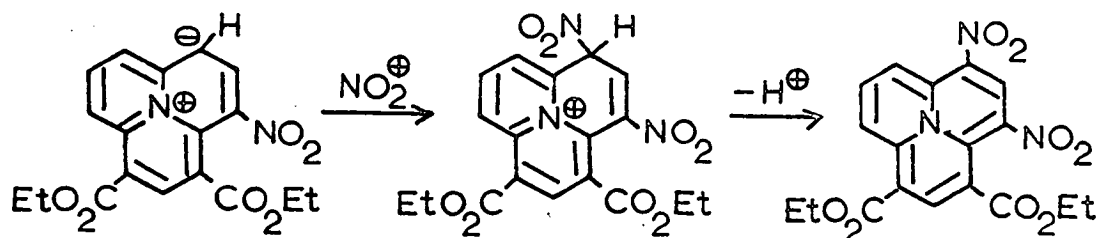
(173)

Although a mass spectrum was not obtained for the product, its identity as the 4,9-dinitro derivative was obvious from the n.m.r spectrum [Fig.41]. Apart from a low-field resonance at 1.91 τ attributable to the 2-proton, this consisted of a four-proton AX spectrum in which the constituent doublets were centred at 2.43 τ and 4.08 τ . These doublets were assigned, respectively, to the 5- and 8-, and the 6- and 7-protons. The high chemical shift of the latter is due to the shielding influence of the nitro-substituents.

The products from the nitration reaction thus include all four possible dinitro-isomers that can result from substitution in the α -positions of the molecule, together with one of the two such possible mononitro-isomers. Although it seems possible that the second mononitro-isomer was the forerunner pink-fraction

on the chromatogram, this was not confirmed since the product, in common with several other minor fractions, was present in insufficient yield for characterisation.

Perhaps the most interesting feature of the nitration reaction was the formation of the 4,6-dinitro-derivative as the major characterisable product. This pattern of substitution is in direct contrast to that normal for polycyclic aromatic systems where the introduction of an electron-withdrawing substituent into one of the constituent rings tends to inhibit further substitution in that ring. The formation of the 4,6-dinitro isomer as the major product of reaction is, however, expected since the introduction of the first nitro-group into either the 4- or 6-position of the molecule will lead, as has been demonstrated from n.m.r. evidence, to an increase in the electron-density at the meta-carbon centre thus rendering it readily susceptible to further attack by the reagent.



Since a slight excess of the nitrating reagent was used in the reaction this latter consideration probably accounts for the low incidence of mononitro-product.

SUMMARY

Cycl[3.3.3]azine has been synthesised and shown by n.m.r. evidence to be polyolefinic in character. The chemical shift of

the proton resonances are the highest observed to date for any peripheral-conjugated system. Although stable to heat, cycl[3.3.3]azine undergoes complete decomposition within a few minutes on exposure to air. α -orientated electron-withdrawing substituents exert a stabilising influence on the ring-system and, rather remarkably, cause an increase in the electron-density at the second α -position of the ring bearing the substituent. Chemical confirmatory evidence for the polyolefinic character of the system has been obtained from cyclo-addition reactions conducted on the 1,3-diethoxycarbonyl derivative. Substitution reactions are also possible and are regarded as the reactions of an enamine rather than evidence of aromaticity.

FIG. 17

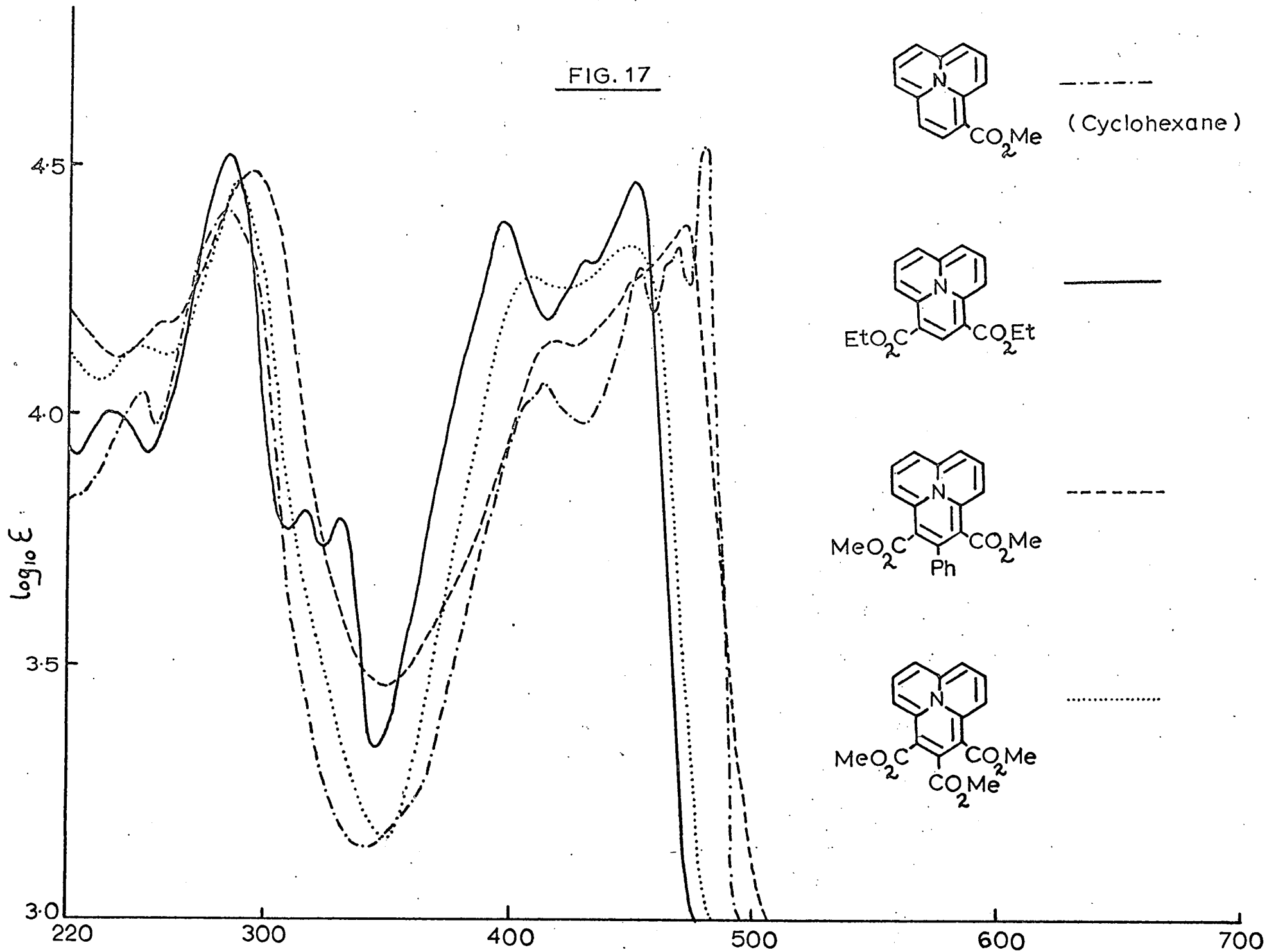


FIG. 18

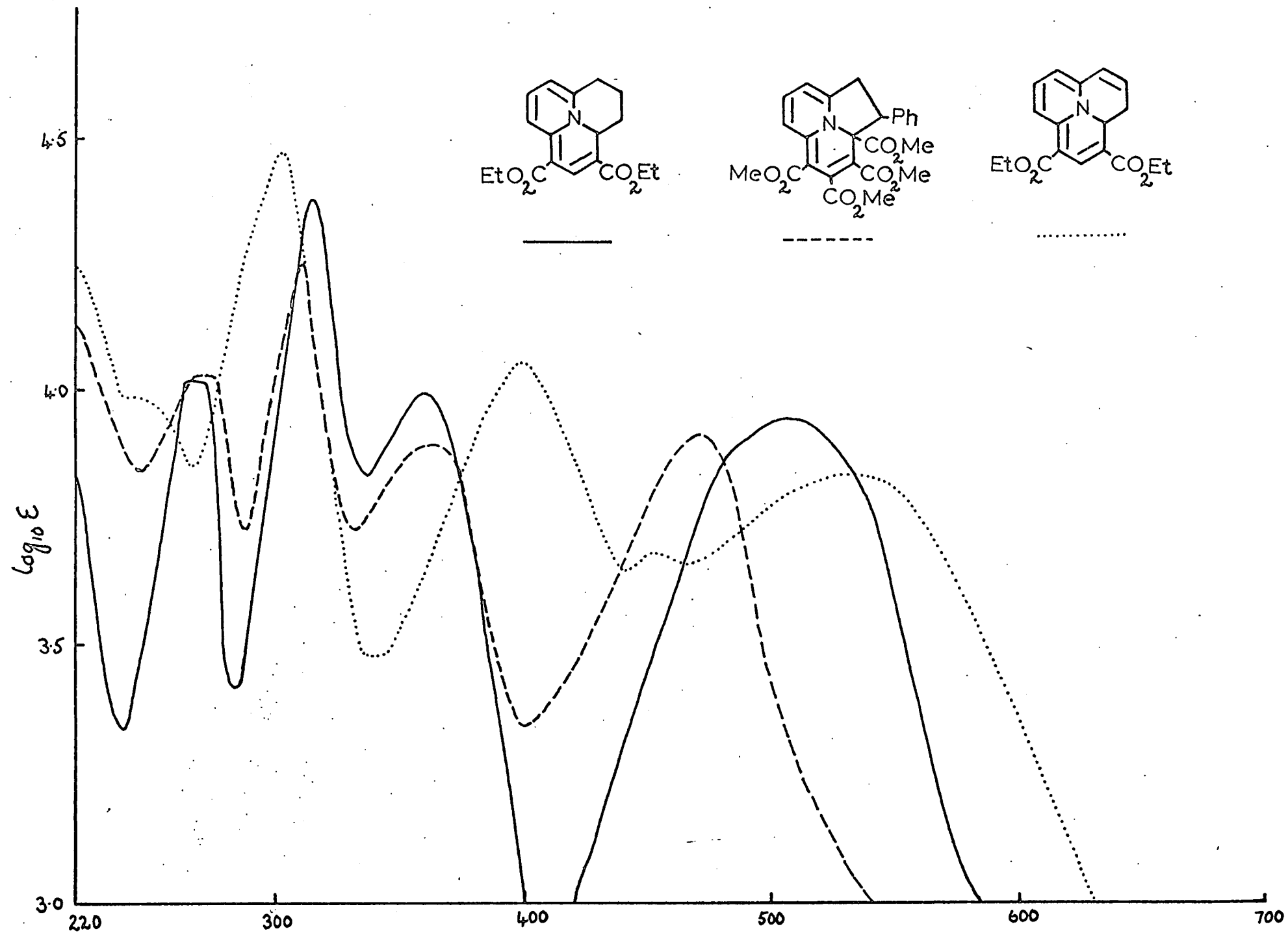


FIG. 19

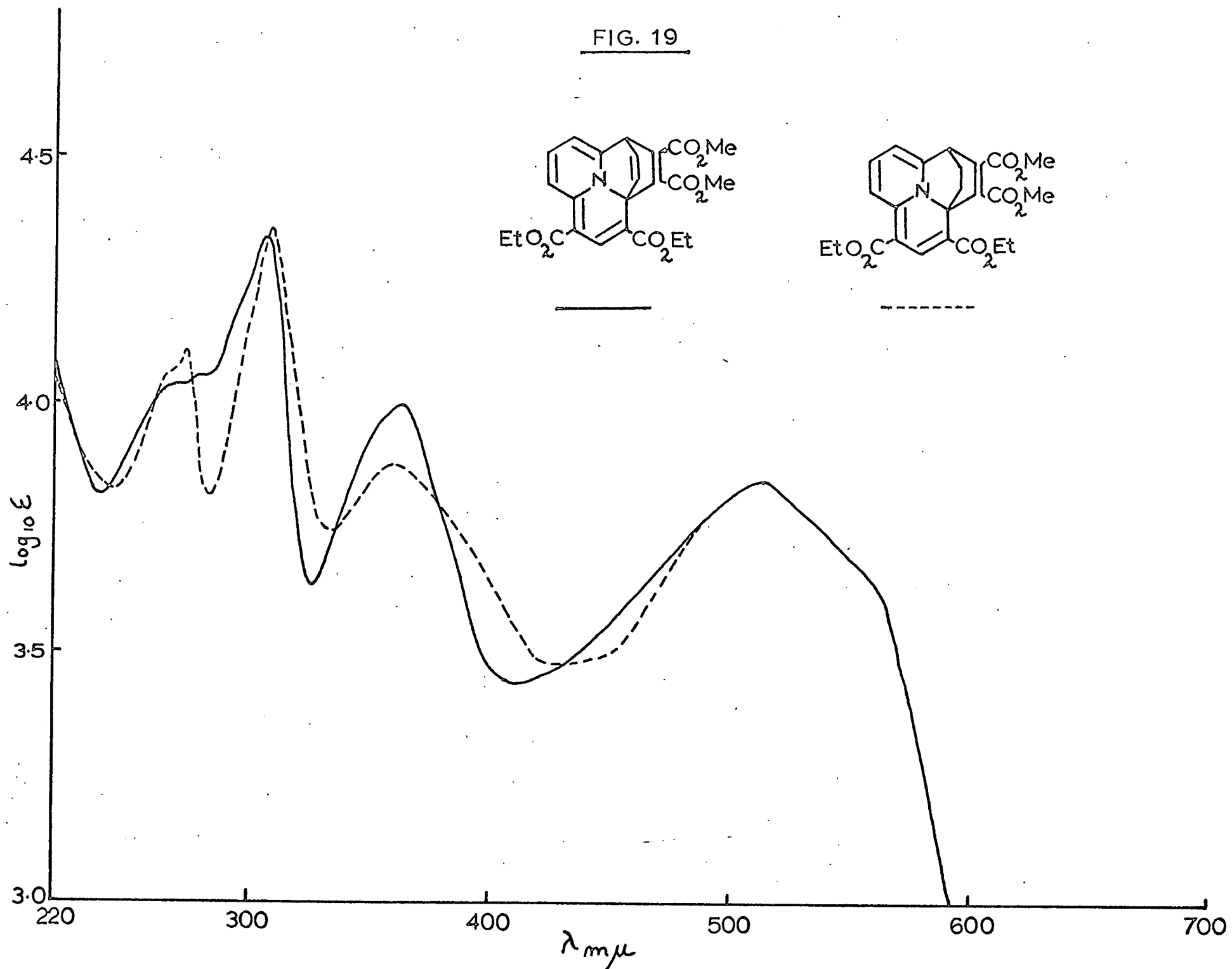


FIG. 20

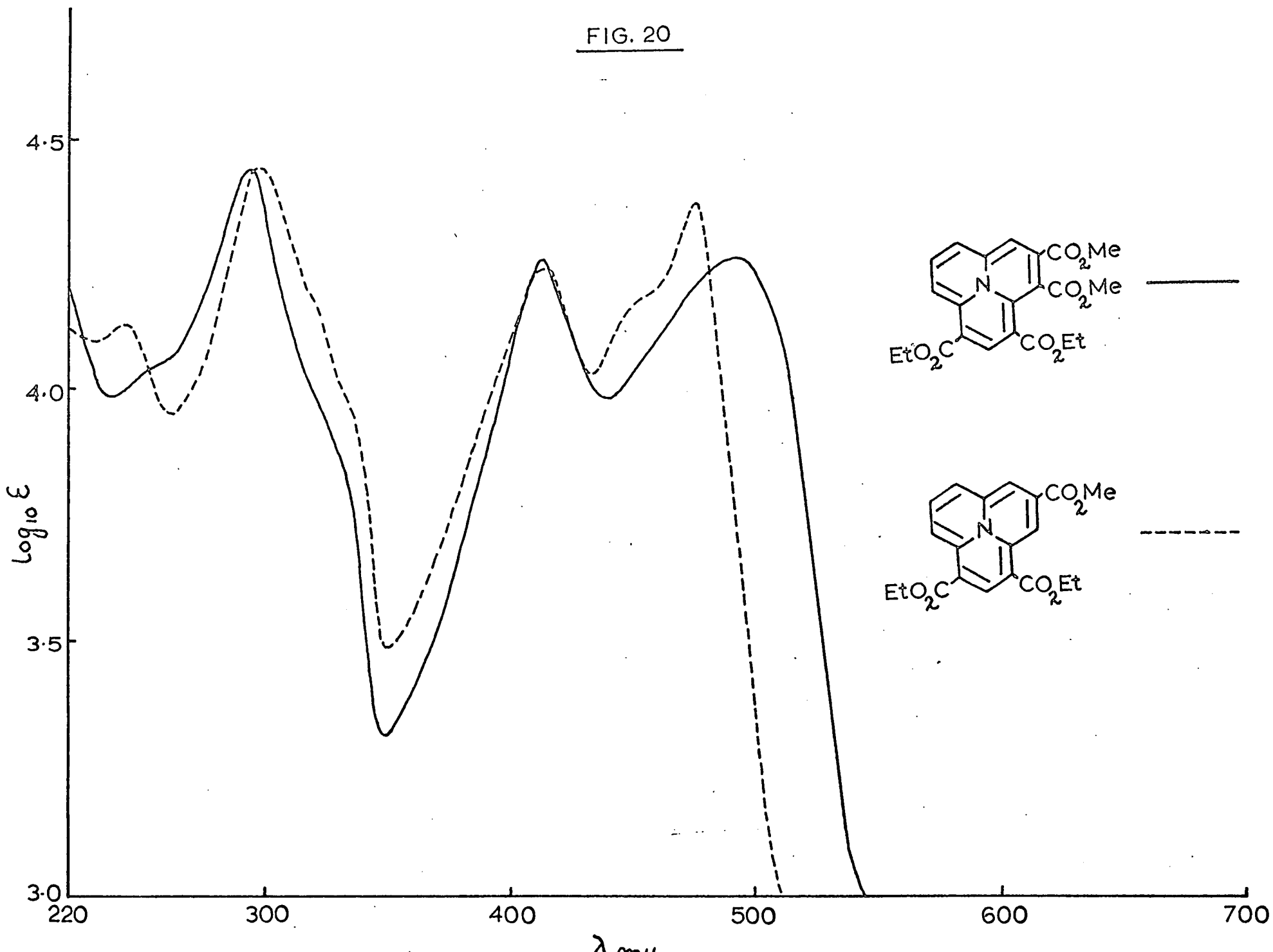


FIG. 21

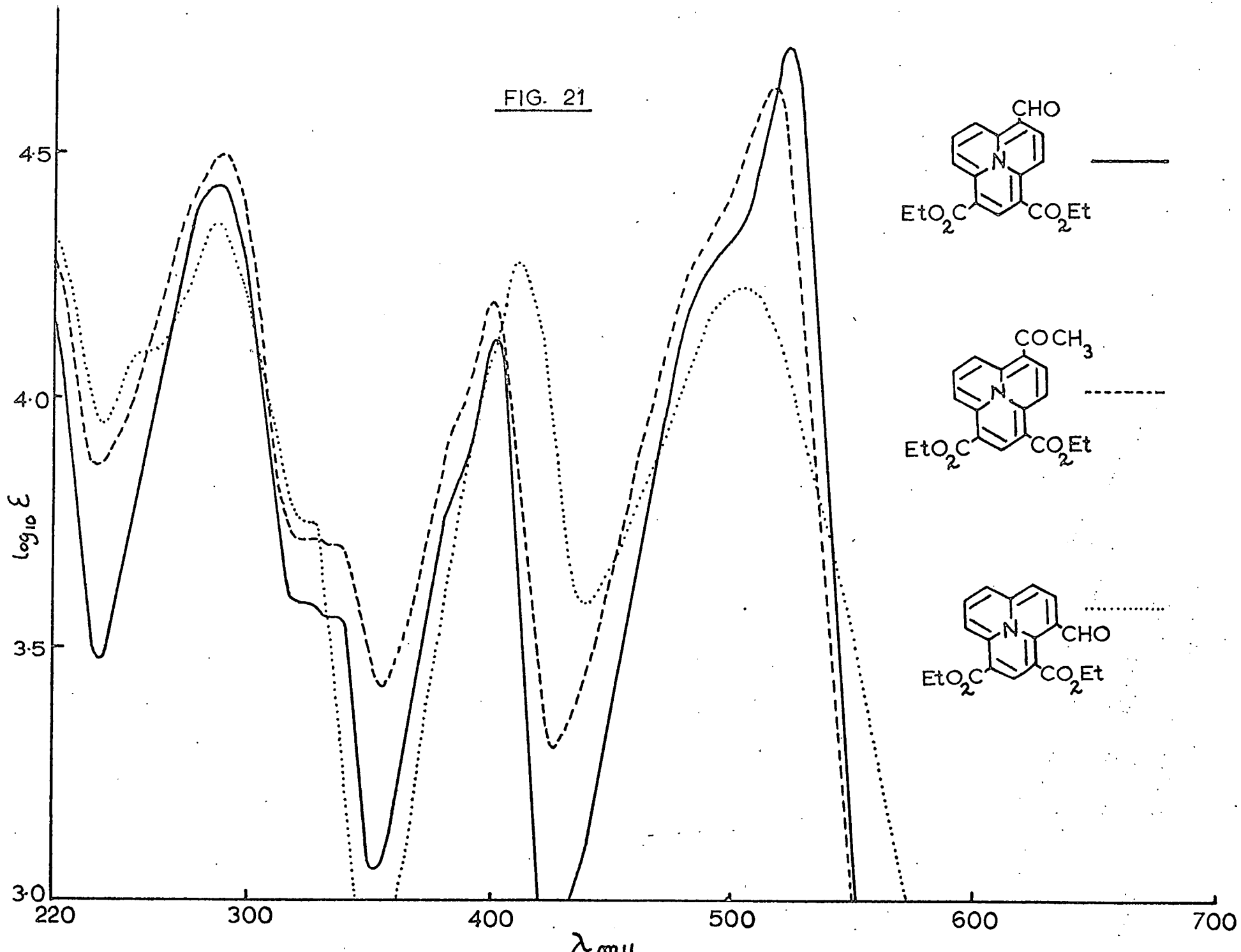


FIG. 22

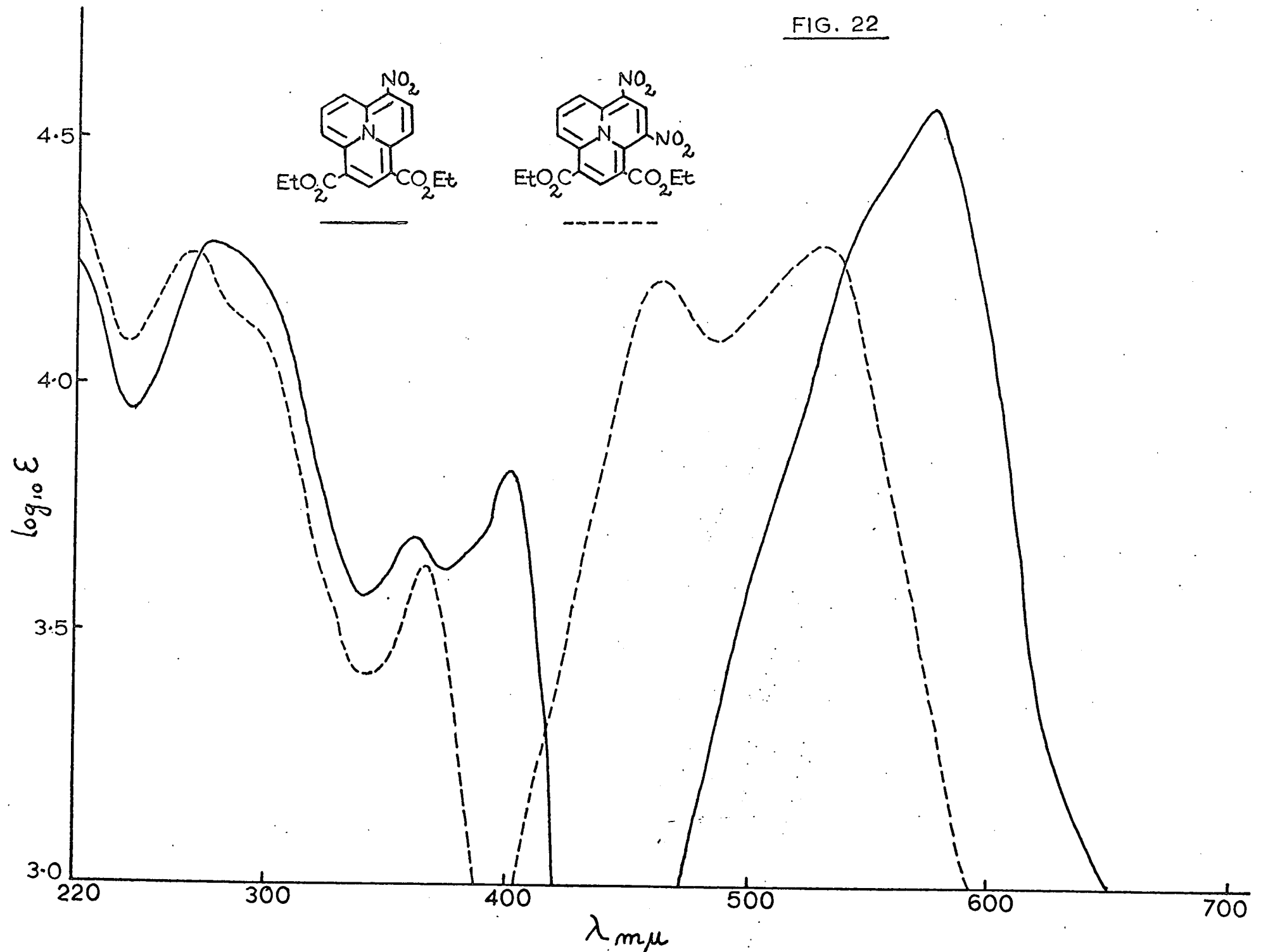
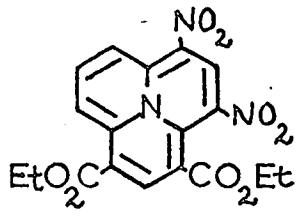
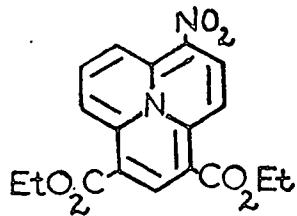
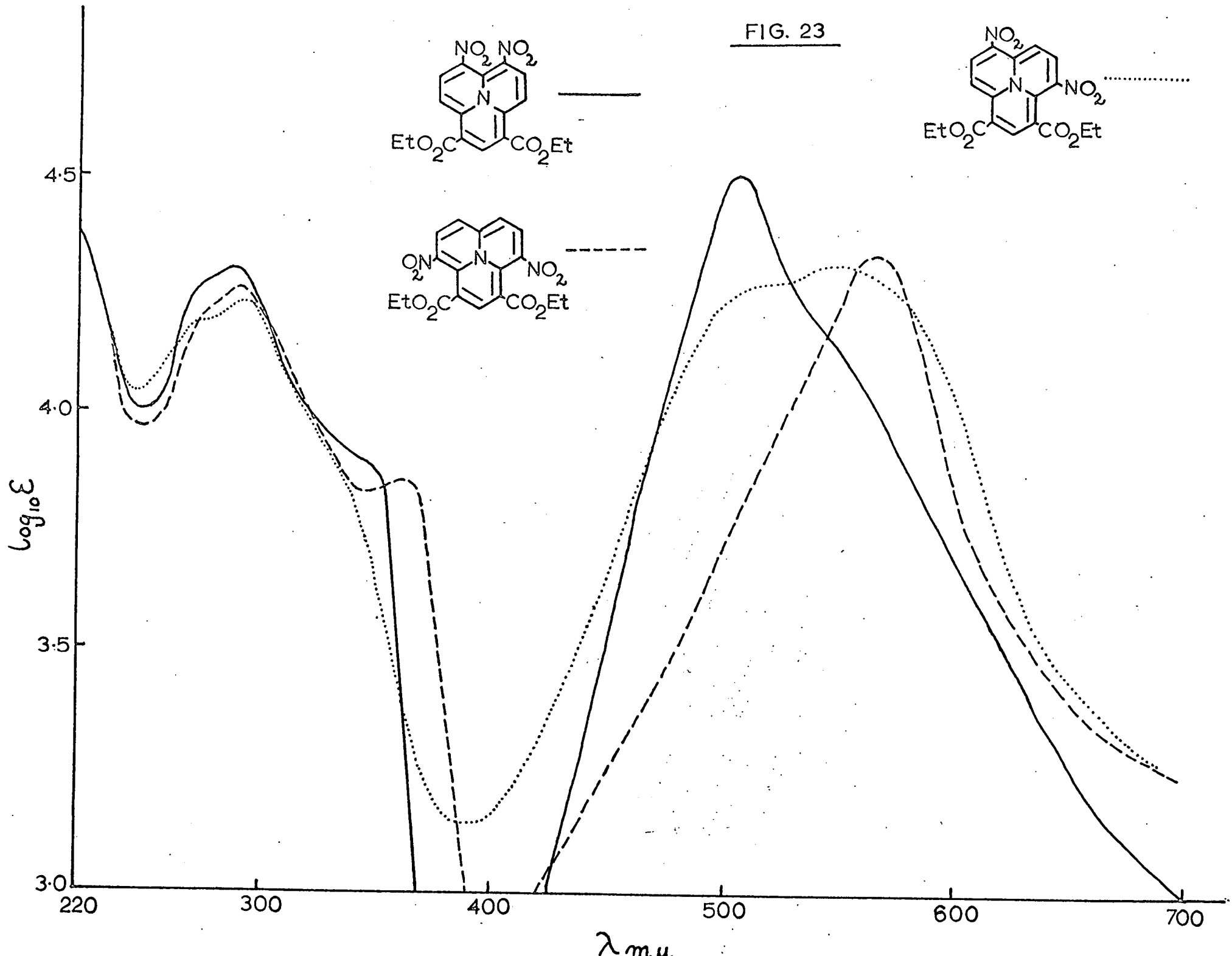
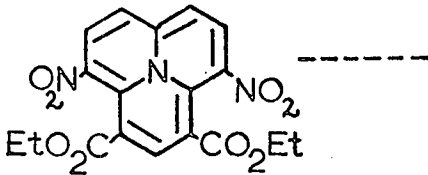
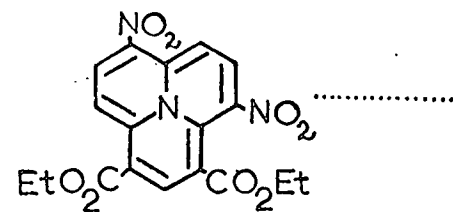
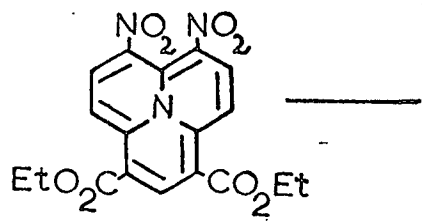


FIG. 23



SYNTHESIS OF CYCL[3.3.2]AZIN-1-ONE AND SOME SIMPLE
DERIVATIVES OF THE CYCL[3.3.2]AZINIUM SYSTEM

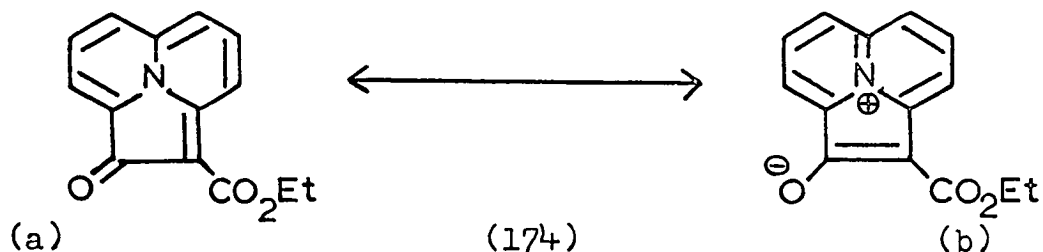
When heated under reflux with nitrobenzene for 1 hour, 4-(diethoxycarbonylmethylene)quinolizine was converted into two products which were isolated, after chromatography on alumina, as a yellow solid (81%) and a red solid (9%).

Although the first of these products, the yellow solid, appeared physically similar to the starting material, it differed markedly from the latter in its chemical and spectral properties. Thus, while the starting material dissolved in aqueous acids to yield colourless solutions, the product under similar conditions yielded solutions which were intensely yellow in colour. Furthermore, the product, as opposed to the starting material, dissolved readily in water to yield, as in acidic media, yellow solutions.

The u.v. spectra of the product in both neutral and acidic ethanol [Figs. 42, 43] were quite different from those of the starting material and no well-defined resemblance was evident to any previously synthesised system containing a methylenequinolizine nucleus. The mass spectrum indicated an M/e value of 241 for the parent molecular ion, this value suggesting that the product had been derived from the precursor compound by the loss of one molecule of ethanol. The n.m.r. spectrum supported this inference, since the only significant difference from that of the precursor compound was that the absorptions attributable to one of the ethoxyl groups and the α -pyridyl proton in the

latter were now absent.

The only structure which is fully consistent with the foregoing spectral evidence is (174).



The system is best regarded as a resonance hybrid to which the dipolar cyclazinium structure (174a) makes a very large contribution. This view is supported by the fact that the i.r. absorption band attributable to the 1-keto group occurs at a comparatively low frequency (1610 cm^{-1}), thus indicating that the group is considerably polarised. The ready solubility in water is further consistent with the view that the molecule exists in a highly polarised ground state. Although the system almost certainly protonates at the carbonyl-oxygen atom this was not directly apparent from the n.m.r. spectrum measured in trifluoroacetic acid, because the hydroxylic proton resonance was not, as expected, observable. (The proton undergoes rapid exchange with the solvent so that its resonance signal merges with that of the carboxyl protons). However, since the spectrum in trifluoroacetic acid was similar to that measured in deuteriochloroform the possibility that the molecule protonates at any alternative site can be discounted.

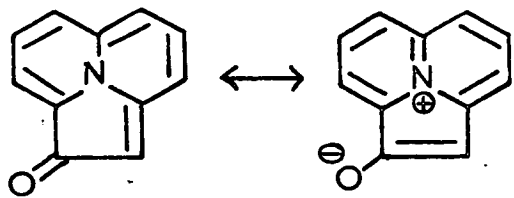
Although the spectral evidence leaves the structure of the product unambiguous, the experimental elemental analysis figures

were in rather poor agreement with those required for structure (174). However, a much closer concordancy was obtained by assuming that the product exists as a monohydrate. This indeed, appears quite probable considering that the product is strongly basic in character.

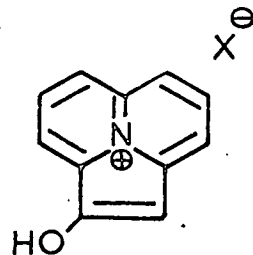
Although the mode of formation of the product presumably involves an intramolecular cyclisation reaction with the elimination of ethanol, the mechanistic sequence by which this process usually occurs (involving electrophilic attack by carbonyl-carbon) cannot be readily accommodated within the electronic framework of the quinolizine. This difficulty arises because the most acceptable reaction scheme involves the non-participation of the lone-pair of electrons on the nitrogen atom, a condition which is contrary to the normal prerequisite for electrophilic attack in the quinolizine series. Notwithstanding this factor, it appears the the α -pyridyl carbon atom is sufficiently nucleophilic to enter into bond-formation with the carbonyl-carbon of the spatially-adjacent ester group.

The second product from the reaction, a red solid, was even more strongly basic in character than the first product. Thus it dissolved readily in water to yield intensely yellow solutions from which the free-base could not be readily recovered by extraction into organic solvents. Its u.v. spectra in neutral and acidic ethanol was similar [Figs. 42 and 43] to the corresponding spectra of the first product thus indicating that the system contained a cycl[3.3.2]azin-1-one nucleus.

The i.r. spectrum differed significantly from that of the first product in two main respects: a) the carbonyl absorption attributable to the ester group was no longer present and b) a new absorption appeared at $2800 - 3500 \text{ cm.}^{-1}$ (thus indicating the presence of a hydroxyl group). Since considerable difficulty had been experienced in purifying the product by recrystallisation (samples melted over a wide temperature-range despite the apparent purity of the original fraction on alumina), the evidence strongly suggested that the product was in fact a mixture of the parent cycl[3.3.2]azin-1-one (175) and a hydroxycyclazinium salt (176), the latter being derived by protonation of the free-base, presumably by water, at the carbonyl-oxygen atom.



(175)

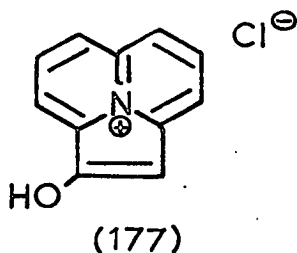


(176)

These conclusions are consistent with the n.m.r. spectrum of the product measured in both deuteriochloroform and trifluoroacetic acid. The former spectrum consisted of a six-proton multiplet in the region $1.41 - 2.60\tau$ which was assigned to the protons of the two six-membered rings, together with two singlets at 3.98τ and 6.47τ which were assigned to, respectively, the five-membered ring-proton and the hydroxyl proton. [The spectrum represents an average of the individual spectra of structures (175) and (176), these being weighted in

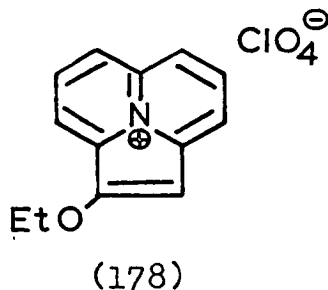
proportion to the relative amount of either product]. The spectrum in trifluoroacetic acid was qualitatively similar to that in deuteriochloroform (six-proton multiplet at 0.80 - 1.48 τ ; one-proton singlet at 2.60 τ) except that the resonance signal attributable to the hydroxyl proton was, as expected, no longer present.

Conclusive evidence for the assigned structure (175) was obtained by establishing the relationship of the product to the 2-ethoxycarbonyl derivative (174). Reflux of the latter with dilute hydrochloric acid followed by evaporation of the solution yielded a pale yellow solid which was identified from its spectral properties [n.m.r. as (175) in T.F.A] as 1-hydroxycycl[3.3.2]azinium chloride (177)



Treatment of an aqueous solution of (177) with base followed by exhaustive extraction with chloroform yielded a red solid which possessed spectral properties qualitatively identical to those of the second product from the pyrolysis reaction. (Slight quantitative differences which were apparent were obviously due to a difference in the proportion of cyclazinium ion contaminant in the respective samples). However, while the identity of the product as (175) is apparent, its mode of formation from the pyrolysis reaction, although presumably involving the loss of the ester group from (174), has not been established.

The 1-hydroxycycl[3.3.2]azinium salt (177) is the first known derivative of the fully-unsaturated cycl[3.3.2]azinium system. A further derivative of this system, 1-ethoxycycl[3.3.2]azinium perchlorate (178), was prepared by treating cycl[3.3.2]azin-1-one (175) with triethyloxonium fluoroborate followed by perchloric acid.



Both of these compounds were obtained as stable, yellow, crystalline solids. Unfortunately, it was not found possible in the time available to investigate the chemical and physical properties of these compounds. However, in conclusion, it is worthy of mention that an attempt to hydrogenate the former salt (177) over a metal catalyst was completely without effect. This behaviour is in contrast to that of the quinolizinium ion which is readily reduced⁵³ under such conditions and suggests that the cyclazinium ion is not to be regarded as simply a vinylogue of the latter but rather as a fundamentally different system, the π 1,2-bonding electrons of which are intimately involved in determining its physical and chemical properties.

FIG. 42

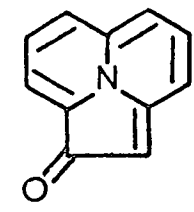
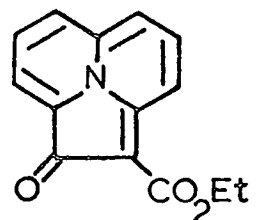
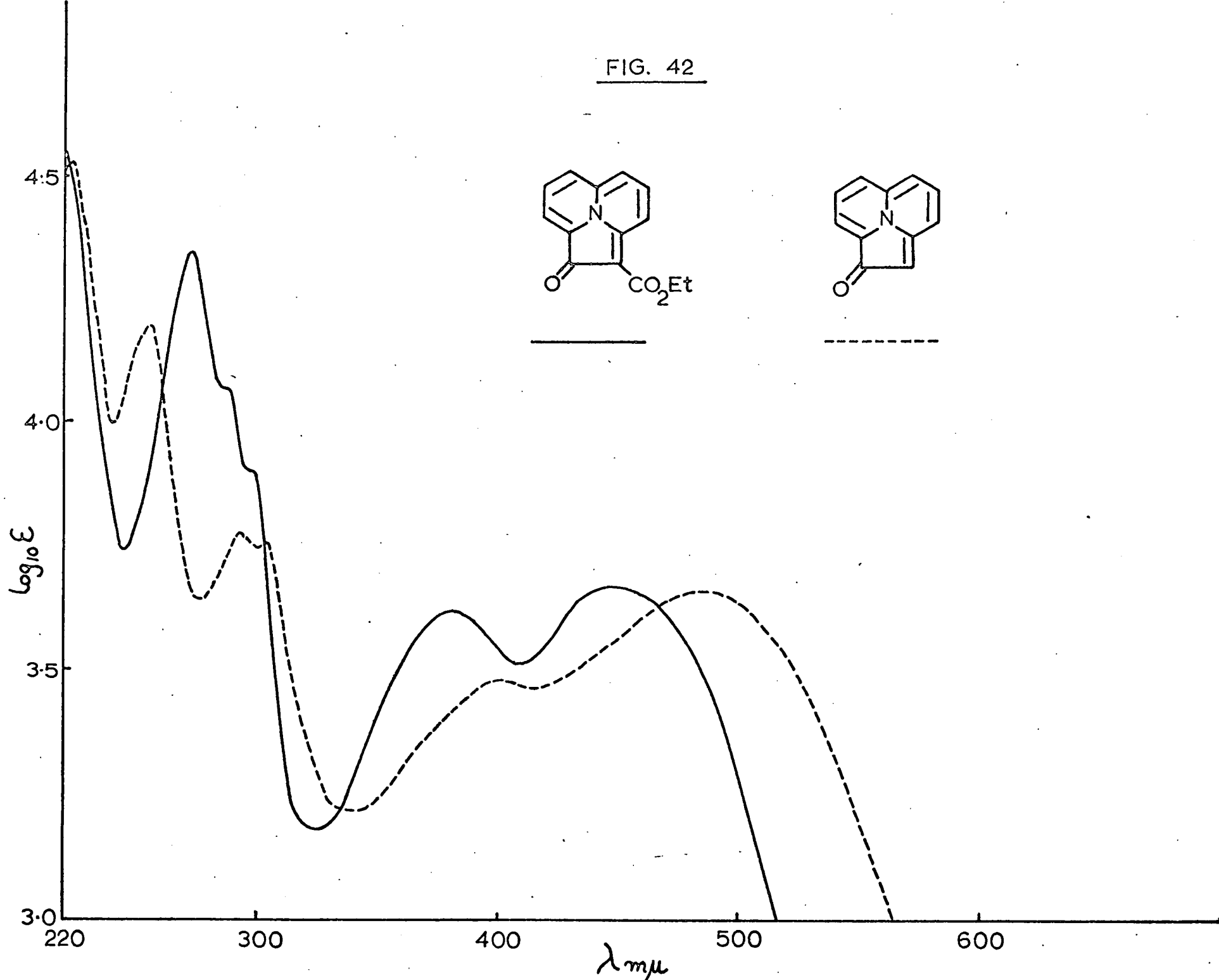
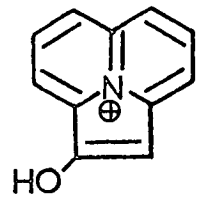
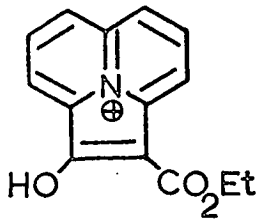
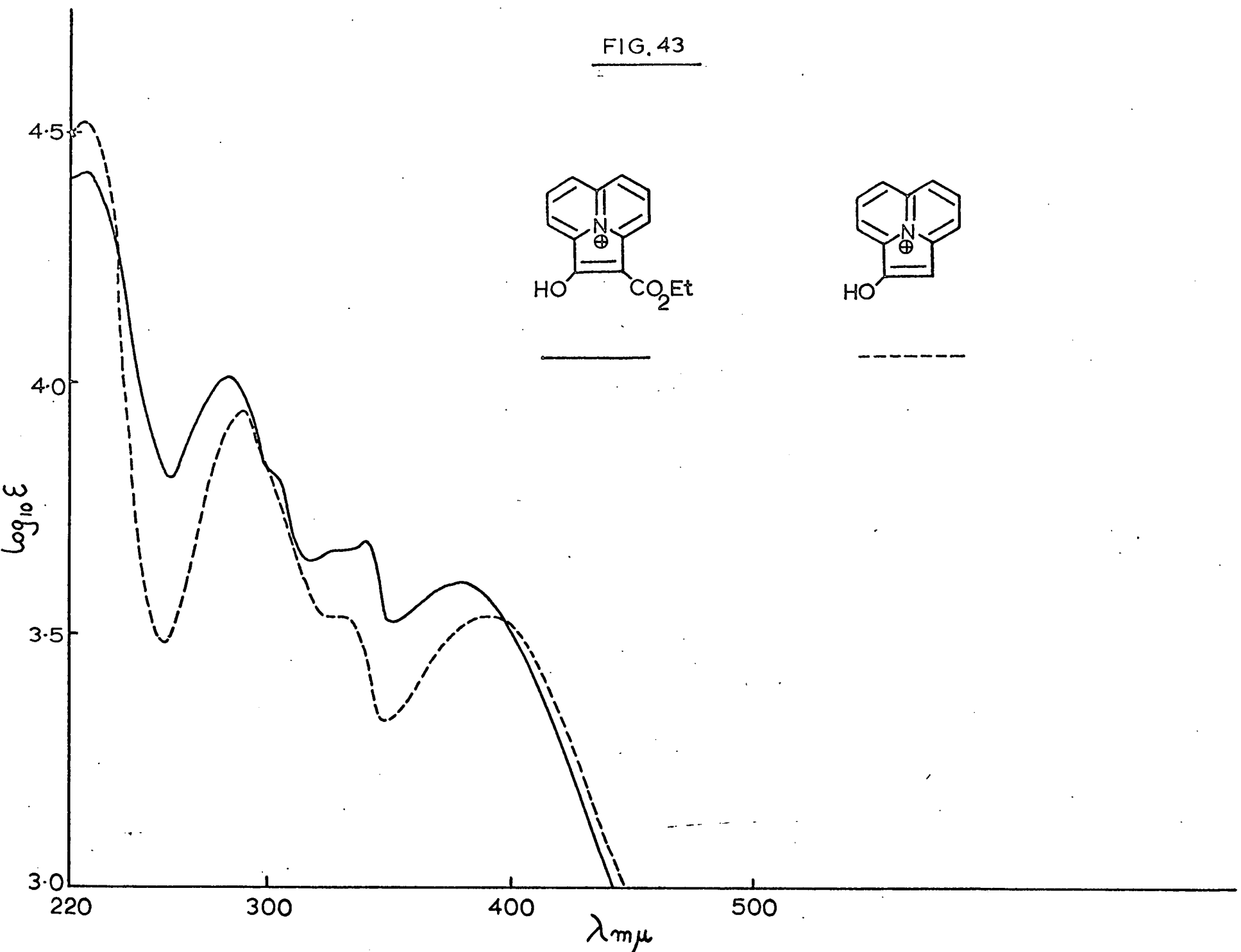


FIG. 43



EXPERIMENTAL

GENERAL NOTES

- 1) Melting points were recorded on a Kofler hot-stage apparatus and, with the exception of the dialkyl quinolizin-4-ylidenemalonate compounds, are corrected. Boiling points are uncorrected.
- 2) Microanalyses were determined by Weiler and Strauss Ltd., Oxford, by Andrew H. Baird Ltd., Edinburgh and by Alfred Bernhardt, Elbach uber Engelskirchen, West Germany.
- 3) Infra-red spectra were recorded on a Unicam SP 200 Spectrophotometer. Unless otherwise stated nujol pastes were used.
- 4) Ultra-violet and visible spectra were recorded on a Unicam SP 200 Spectrophotometer. The abbreviations 's' and 'i' refer to shoulders and inflections, respectively, on the curves.
- 5) Nuclear magnetic resonance spectra were recorded on a Perkin Elmer R10 (60 mc./sec.) spectrometer using tetramethylsilane as internal standard. Unless otherwise stated, deuteriochloroform was used as solvent. The spectra of compounds (135) and (140) were also recorded on a Varian Associates HA.100 spectrometer (100 mc./sec.).
- 6) Mass spectra were recorded on an A.E.I. M.S.902 double-focussing mass spectrometer.
- 7) Alumina for chromatography was Spence grade 'H' and, unless otherwise stated, was deactivated by shaking, for 12 hours, with 10% aqueous acetic acid.

- 8) Thin layer plates for non-preparative chromatography were prepared using Keiselgel G (Merck) or Spence grade H alumina (deactivated).
- 9) Solutions were dried over anhydrous magnesium sulphate.
- 10) Light petroleum refers to the fraction boiling between 60 - 80°C.
- 11) Nitrobenzene was dried over Linde molecular sieve (Type 4A).

ATTEMPTS TO EFFECT SELECTIVE FISSION OF THE

1,2-BOND OF CYCLOPENTA[c,d]CYCL[3.3.3]AZINES

1. Reaction of 3,9-dimethylcyclopenta[c,d]cycl[3.3.3]azine¹¹³
with potassium permanganate / sodium periodate reagent.⁹¹

The cyclazine (0.42 g.) was dissolved in purified¹¹⁶ dioxane (15 ml.) and treated with a solution of potassium permanganate (0.10 g.), sodium periodate (1.71 g.) and potassium carbonate (0.42 g.) in water (5 ml.). The reaction mixture was shaken 24 hours at room temperature then filtered to yield a colourless solution together with a dark amorphous intractible solid. No unreacted cyclazine was recovered.

2. Reaction of 3,9-diphenyl-4-ethoxycarbonylcyclopenta[c,d]
cycl[3.3.3]azine¹¹³ with ozone

A solution of the cyclazine (0.5g.) in dichloromethane (50ml.) was cooled in an ice-acetone bath and treated, with rapid stirring under a nitrogen atmosphere, with a cold (-78°C), saturated solution¹¹⁷ of ozone (0.00805M) in dichloromethane (180ml.). After gradual warming to -30°C. over a period of 30 minutes, the reaction mixture was shaken with a solution of sodium iodide (0.6g.) in methanol (10ml.) / acetic acid (2ml.). After further warming to room temperature the mixture was shaken with a solution of sodium thiosulphate to remove any liberated iodine. Finally,

after neutralisation with sodium bicarbonate the mixture was filtered to yield dark amorphous decomposition product. The filtrate contained only unreacted cyclazine.

ATTEMPTS TO EXPAND THE FIVE-MEMBERED RING OF CYCLOPENTA[c,d]
CYCL[3.3.3]AZINES.

1. Reaction of 3,9-dimethylcyclopenta[c,d]cycl[3.3.3]azine¹¹³
with monochlorocarbene.

The cyclazine (0.4g.) in dichloromethane (15ml.) was treated, over a period of 2 hours, with a solution of methyl-lithium¹¹⁸ (0.12g.) in ether (25ml.). The addition was carried out under a dry nitrogen atmosphere at 25 - 30°C., with vigorous stirring. Filtration of the reaction mixture, however, yielded only decomposition product together with unreacted cyclazine.

2. Reaction of 3,9-dimethylcyclopenta[c,d]cycl[3.3.3]azine¹¹³
with ethyl diazoacetate.¹¹⁹

a) A solution of the cyclazine (1.0g.) in diethyleneglycol dimethyl ether (10ml.), stirred at 140°C., was treated dropwise over a period of 3 hours with a solution of ethyl diazoacetate (0.15g.) in the same solvent (10ml.). The reaction mixture was then diluted with acetone, cooled and filtered. A yield of decomposition product was obtained together with unreacted cyclazine.

A modification of the above procedure involving addition of a solution of the diazo-ester in ether to the molten cyclazine at 145°C., gave a similar result.

b) A solution of the cyclazine (0.3g.) and ethyl diazoacetate (0.045g.) in tetrahydrofuran (30ml.) was irradiated by a mercury-vapour lamp for a period of 24 hours. However, chromatography of the evaporated solution returned the cyclazine unchanged.

PREPARATION OF QUINOLIZIN-4-ONE, QUINOLIZINE-4-THIONE
4-CHLOROQUINOLIZINIUM PERCHLORATE AND 4-METHYLMERCAPTO-
QUINOLIZINIUM IODIDE

Diethylethoxymethylenemalonate

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Quinolizin-4-one

Prepared by hydrolysis of the products of the reaction of methyl 2-pyridylacetate and diethylethoxymethylenemalonate. Since a modification of the literature methods^{99,104} was used, the experimental procedure will be described in detail.

Sodium (9g.) was dissolved in ethanol (220ml.) and methyl 2-pyridylacetate (45g.) was added. The solution was then treated with diethyl ethoxymethylenemalonate (75g.) in ethanol (220ml.) and the mixture was allowed to stand 24 hours at room temperature in a stoppered vessel. The resultant purple semi-crystalline mass, which consisted of a mixture of 1-methoxycarbonyl-3-ethoxycarbonylquinolizin-4-one and the sodium salt of the corresponding 1-carboxy compound, was treated with water (500ml.), and the cooled (10°C.), rapidly stirred, viscous solution was

neutralised by the dropwise addition of concentrated hydrochloric acid. The mixture of ester and carboxylic acid was filtered off and washed with ice-cold ethanol (60 ml.), and dried under reduced pressure in a vacuum desiccator to give 70g. of a pale-yellow solid. The mixed product was boiled under reflux with concentrated hydrochloric acid (1000 ml.) for 1 hour, after which time the solution was transferred to a 5 litre beaker, cooled to 0°C. in an ice-salt bath and neutralised by the addition of powdered potassium carbonate. The resultant pale-yellow solution was filtered to remove precipitated salts and decomposition product, and then exhaustively extracted with chloroform (200 ml. portions) until the organic layer was no longer coloured. The combined extracts were dried and evaporated to yield pale yellow needles of highly hygroscopic quinolizin-4-one. The product was purified by distillation under reduced pressure.

Yield = 27g. (60%) b.p. = 180°C. / 0.02mm.

Quinolizine-4-thione

Prepared according to the method¹⁰² of Van Allen and Reynolds.

4-Chloroquinolizinium perchlorate

Prepared from quinolizin-4-one according to the method¹⁰² of Van Allen and Reynolds

4-Methylmercaptoquinolizinium iodide

Prepared from quinolizine-4-thione by the method⁹⁴ of Boekleheide and Gall.

ATTEMPTED SYNTHESIS OF METHYLENEQUINOLIZINES

1. Attempted reaction of quinolizine-4-thione
with phenyldiazomethane¹²⁰

a) The thione (0.27g.) was dissolved in light-petroleum (100/120°C.), copper bronze (0.48g.) and phenyldiazomethane (0.42g.) were added, and the solution was heated under reflux for 30 minutes. The reaction mixture was then filtered whilst hot, and the filtrate was concentrated and chromatographed on alumina to yield unchanged thione.

Similar experiments with longer reaction times were equally unsuccessful.

b) The thione (0.2g.) was fused with copper-bronze (0.02g.) at a temperature of 140°C., and maintained constant at this temperature while phenyldiazomethane (0.17g.) was added dropwise, under a nitrogen atmosphere, over a period of 1 hour. The temperature was then increased to 200°C., over a 5 hour period. When cool, the reaction mixture was chromatographed on alumina to yield unchanged thione.

2. Attempted reaction of 4-chloroquinolizinium
perchlorate with benzylidenetriphenylphosphorane

a) Benzyltriphenylphosphonium chloride¹²¹ (0.74g.) in ethanol (5 ml.) was treated, under a dry, oxygen-free, nitrogen atmosphere, with a solution of sodium ethoxide (0.18g.) in ethanol (3ml.). The resultant mixture turned a deep-yellow indicating formation of the phosphorane. The quinolizinium salt (0.5g.) in ethanol (5ml.) was then added and the reaction mixture

was refluxed for 2 hours. The residue obtained on evaporation of solvent was recrystallised from ethanol to yield colourless needles which were identified, by comparison with an authentic sample, as 4-ethoxyquinolizinium perchlorate.

Yield = 3.6g. (70%)

b) Benzyltriphenylphosphonium chloride¹²¹ (0.6g.), in dimethylformamide (5ml.), was shaken at room temperature over a period of 1 hour with a solution of methyl-lithium¹¹⁸ (0.037g.) in ether (2ml.). The quinolizinium salt (0.41g.) in dimethylformamide (5ml.) was then added to the yellow phosphorane and the solution was refluxed 2 hours under a dry, oxygen-free, nitrogen atmosphere. The reaction mixture progressively darkened during this period, eventually becoming brown-black in colour. Evaporation of solvent yielded an intractable amorphous residue.

3. Attempted reaction of 4-chloroquinolizinium perchlorate with ethyl magnesium malonate

Ethyl hydrogen malonate¹²² (0.51g.) was added to a solution of magnesium turnings (0.19g.) in dry ethanol (5ml.) and the mixture was shaken for 1 hour at room-temperature. The solvent was then removed under reduced pressure and the residue of magnesium chelate was taken up in benzene (10ml.) and re-evaporated. The product was then dissolved in the minimum amount of tetrahydrofuran and the solution was cooled to 0°C., and treated with a solution of the quinolizinium salt (1g.) in

dimethylformamide (5ml.). However, no reaction was apparent. Subsequent reflux periods of up to 24 hours returned the quinolizinium salt unchanged.

4. Attempted reaction of 4-methylmercaptoquinolizinium iodide⁹⁴ with ethyl phenylacetate

A suspension of the quinolizinium salt (0.5g) in ethanol (10 ml.) was treated with ethyl phenylacetate (0.27 g.) and triethylamine (0.4 g.) and the reaction mixture was heated under reflux for 5 hours. Methanethiol, detectable by its odour, was steadily evolved during this period. Unreacted quinolizinium salt (0.29g.) was filtered off, and the residual solution was evaporated to yield a pale-yellow oil. The latter was taken up in ether and a sample of the solution was subjected to thin layer chromatography on silica. A minor, pale-yellow forerunner band was evident followed by a similar faintly coloured major band, these showing rates of elution identical with those of authentic samples of quinolizine-4-thione and quinolizine-4-one, respectively. Since the same products were obtained from related reactions involving 4-methylmercaptoquinolizinium iodide and were rigorously identified in one such instance, no attempt was made to effect their isolation from the present reaction.

5. Attempted reaction of 4-chloroquinolizinium perchlorate with ethyl phenylacetate

a) The quinolizinium salt (0.5g.) was added to a solution of ethyl phenylacetate (0.32g.) and triethylamine (0.4g.) in ethanol (10ml.) and the reaction mixture was refluxed for 5 hours. The salt was returned unchanged.

b) The preceding reaction was repeated using sodium ethoxide (0.26g.) in place of triethylamine as base. The initial, slightly red, solution gradually turned light-green as reflux continued. After 1 hour, the solvent was evaporated and the residue was recrystallised, after a hot filtration, from ethanol. Greenish-tinged needles were collected and identified, by comparison with an authentic specimen, as 4-ethoxyquinolizinium perchlorate.

6. Reaction of 4-methylmercaptoquinolizinium iodide with diethyl malonate

a) 4-methylmercaptoquinolizinium iodide (0.46 g.) was suspended in ethanol (3 ml.) and boiled under reflux for 5 hours with diethyl malonate (0.35g.) and triethylamine (3 drops). During this period a strong odour of methanethiol was evident. The solution was then evaporated and the yellow residue was taken up in the minimum of chloroform and chromatographed on a column of alumina using ether as eluent. The first yellow fraction, which was found by t.l.c. on silica to consist of a mixture of two components, was rechromatographed on a column of silica (Hopkins and Williams, M.F.C.) using benzene / ether (1/1) as eluent. The first, major component, which was obtained as a hygroscopic yellow solid, was identified, by comparison (i.r. spectrum; i.r. and u.v. spectra of the derived hydrochloride salt) with an authentic sample, as quinolizin-4-one. The second, minor, component which was obtained as a stable yellow solid was identified (i.r., m.p.) as quinolizine-4-thione.

Elution of the original alumina column with chloroform yielded a minute amount of a yellow product. Although present in insufficient yield for independent characterisation, it was later identified, by comparison (i.r., m.p.) with an authentic sample, as 4-(diethoxycarbonylmethylene)quinolizine.

b) The reaction was repeated using acetonitrile (6 ml.), in place of ethanol, as solvent. The quinolizinium salt went into solution readily on warming and the homogeneous reaction mixture was refluxed for 6 hours. Thin layer chromatography of a sample of the product revealed the presence of a large proportion of quinolizine-4-thione together with a small amount of quinolizine-4-one. Only a trace of the required product was evident.

c) The reaction was repeated using potassium t-butoxide¹²⁵ (0.27 g.) as base, in t-butanol (10 ml.) as solvent. Work-up of the reaction mixture after 16 hours at 50°C., yielded a distribution of products similar to that obtained from the preceding reaction.

SYNTHESIS OF METHYLENEQUINOLIZINES

Reaction of 4-chloroquinolizinium perchlorate with diethyl malonate

The malonate (12.1 g.) [dried over a molecular sieve] was added to tetrahydrofuran (150 ml.) [freshly distilled over sodium hydride] contained in a 500 ml., three-necked flask equipped with a magnetic-stirrer, a nitrogen inlet and a condenser and

calcium chloride drying-tube. Powdered sodium hydride (1.82 g.) was then added to the rapidly stirred solution in small quantities such that the evolution of hydrogen did not become too vigorous. When addition was complete, the clear solution was maintained at 50°C., for 1 hour to ensure complete conversion to the sodium salt. The flask was then surrounded by an ice-bath and the quinolizinium salt (10 g.) was added in approximately 1 g. portions such that the temperature of the reaction mixture did not exceed 20°C. When addition was complete and the initial exothermic reaction had subsided, the ice-bath was removed and the yellow suspension was stirred for 24 hours at ~30°C. The tetrahydrofuran was then removed on a rotary evaporator and the viscous yellow residue was shaken with chloroform (100 ml.) and then filtered to remove insoluble salts. The salts were thoroughly washed with chloroform and recrystallised from the minimum amount of boiling water to yield unreacted 4-chloro-quinolizinium perchlorate (1.0 g.). The combined filtrate was concentrated and loaded onto a column (15" x 1 $\frac{3}{4}$ ") of alumina which had been made up in benzene. After elution of excess malonate with benzene, the methylene-base was eluted as a single yellow band with chloroform. Evaporation of the eluate yielded a pale solid which crystallised from ethanol as yellow needles.

Yield = 8.5 g. (78% ; or 88% based on unrecovered perchlorate)

m.p. = 179 - 180°C.

Diethylquinolizin-4-ylidenemalonate

$C_{16}H_{17}NO_4$ requires: C = 66.89% ; H = 5.96% ; N = 4.88%

found: C = 66.84% ; H = 6.24% ; N = 4.88%

I.R. ν (C=O) = 1700 cm.^{-1}

U.V. EtOH : 211(4.54), 250 (4.39), 310 (3.89), 422 (3.73)

EtOH / HClO_4 (0.5%) : 213 (4.44), 236(4.34), 290(3.53), 316(3.97)
322s (3.95), 330 (4.17).

Isobutene

t-butanol (1000 ml.) , contained in a 2 litre flask equipped with a condenser, was treated with concentrated sulphuric acid (30 ml.). A few boiling chips were then added and the solution was heated to 90 - 100°C. on a water-bath. The liberated isobutene was passed through a calcium chloride drying-tube to remove traces of water and t-butanol and then condensed in a dry-ice/acetone cooled (-78°C.) trap. The required amount of isobutene was collected.

Methyl t-butyl malonate

The product was prepared by the procedure described¹²² for ethyl t-butyl malonate except that dimethyl malonate and methanol were used in place of diethyl malonate and ethanol

Yield = 54% b.p. = 74°C / 3 mm.

Reaction of 4-chloroquinolizinium perchlorate with methyl t-butyl malonate

The experimental procedure was exactly analogous to that of the corresponding reaction with diethyl malonate (p.135). However, as opposed to the latter, the sodium salt of methyl t-butyl malonate was only sparingly soluble in tetrahydrofuran and separated out as^a thick white suspension.

Reagents

Methyl <u>t</u> -butyl malonate	13.2 g.
Sodium hydride	1.82 g.
4-Chloroquinolizinium perchlorate	10.0 g.
Tetrahydrofuran	150 ml.

The product was obtained as yellow prisms after recrystallisation from methanol

Yield = 8.4 g. (74%; 87%^{*}) Recovered perchlorate^{*} = 1.5g.
 m.p. = 192 - 193°C.

Methyl t-butyl quinolizin-4-ylidenemalonate

$C_{17}H_{19}NO_4$ requires: C=67.76%; H=6.36%; N=4.66%

found : C=67.29%; H=6.28%; N= 4.77%

I.R. ν (C = O) = 1695 cm^{-1}

U.V. EtOH: 212(4.51), 227(4.36), 250(4.38), 310(3.90), 429(3.79).

EtOH/HClO₄ (0.5%): 213(4.44), 236(4.34), 290(3.67)
 318(3.99), 331(4.15).

Ethyl t-butyl malonate

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Reaction of 4-chloroquinolizinium perchlorate with ethyl t-butyl malonate.

The experimental procedure was exactly analogous to that described for the corresponding reaction with diethyl malonate (p.135). The sodium salt of ethyl t-butyl malonate was entirely soluble in tetrahydrofuran.

Reagents

Ethyl <u>t</u> -butyl malonate	14.3 g.
Sodium hydride	1.82 g.
4-Chloroquinolizinium perchlorate	10.0 g.
Tetrahydrofuran	150 ml.

The product was obtained as yellow prisms after recrystallisation from methanol.

Yield = 9.2 g. (77%; 86%^{*}) Recovered perchlorate^{*} = 1.0g.
m.p. = 187 - 188°C.

Ethyl t-butyl quinolizin-4-ylidenemalonate

$C_{18}H_{21}NO_4$ requires: C = 68.55%; H = 6.71%; N = 4.44%
found : C = 68.46%; H = 6.95%; N = 4.70%

I.R. ν (C = O) = 1690 cm^{-1}

U.V. EtOH: 212(4.48), 2305(4.27), 251(4.28), 312(3.72), 428(3.66)
EtOH/HClO₄ (0.5%): 212(4.41), 237(4.41), 237(4.29), 291(3.53),
317(3.93), 330(4.11).

Di-t-butyl malonate

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Reaction of 4-chloroquinolizinium perchlorate with di-t-butyl malonate.

The procedure adopted involved a slight modification of the corresponding reaction with diethyl malonate (p.135). The sodium salt of di-t-butyl malonate was soluble in tetrahydrofuran.

Reagents

Di-t-butyl malonate 16.4 g.

Sodium Hydride	1.82 g.
4-Chloroquinolizinium perchlorate	10.0 g.
Tetrahydrofuran	150 ml.

After reaction for 24 hours at 30°C., and evaporation of solvent, the residue was shaken repeatedly with water and chloroform until dissolution of the methylene-base and unreacted 4-chloroquinolizinium perchlorate was complete. The combined aqueous layers were shaken once with chloroform and the combined organic extracts were concentrated, and then triturated with ether to remove unreacted malonate. The precipitated solid was recrystallised from methanol to yield orange-yellow prisms. The residue obtained by evaporation of the aqueous layer was recrystallised from water to give unreacted 4-chloroquinolizinium perchlorate.

Yield = 11.2g. (86%; 92%^{*}) Recovered perchlorate = 0.6g.^{*}

m.p. = 209°C. (decomposes)

Di-t-butyl quinolizin-4-ylidenemalonate

$C_{20}H_{25}NO_4$ requires: C = 69.95%; H = 7.34%; N = 4.08%.

found : C = 69.79%; H = 7.26%; N = 4.24%

I.R. ν (C = O) = 1695 cm^{-1}

U.V. EtOH; 209(4.48), 225i(4.29), 253(4.31), 312(3.87), 434(3.80)

EtOH/HClO₄(1%) : 210(4.40), 235(4.29), 290(3.59), 318(4.00)

331(4.17).

Reaction of 4-chloroquinolizinium perchlorate with methyl cyanoacetate.

The experimental procedure was exactly analogous to that

described for the corresponding reaction with di-t-butyl malonate (p.139)

Reagents

Methyl cyanoacetate	3.0 g.
Sodium hydride	0.73g.
4-Chloroquinolizinium perchlorate	4.0g.
Tetrahydrofuran	60 ml.

The product was obtained as yellow needles after recrystallisation from ethanol.

Yield = 3.9g. (85% ; 89%^{*}) Recovered perchlorate^{*} = 0.2g.

m.p. = 198 - 199°C.

Methyl quinolizin-4-ylidenecyanoacetate.

$C_{13}H_{10}N_2O_2$ requires : C = 69.02%; H = 4.46%; N = 12.38%.

found : C = 68.64%; H = 4.61%; N = 12.36%.

I.R. : ν (C=O) = 1630 cm^{-1} ; (C≡N) = 2130 cm^{-1}

U.V. EtOH: 213(4.45), 223(4.40), 297(3.96), 437(4.06)

EtOH/HClO₄ (3.5%) : 214(4.40), 234(4.30), 293(3.59)
315(3.75), 329(4.03), 435(3.19).

6-Methylquinolizin-4-one

The product was prepared according to the method⁹⁴ of Boekelheide and Gall. Purification was achieved by distillation under reduced pressure.

b.p. = 165°C./0.03 mm.

6-Methyl-4-chloroquinolizinium perchlorate

The quinolizinone (8.7g.) was dissolved in phosphoryl chloride (16 ml.) and heated for 30 minutes on a steam bath

(100°C.). The solid which was deposited on cooling was filtered off using a sintered glass funnel and then dissolved in water and treated with perchloric acid. The precipitated^{it} product was recrystallised from water to yield white needles

Yield = 8.2g. (54%)

m.p. = 316°C. (decomposes)

$C_{10}H_9NCl_2O_4$ requires : C = 43.19%; H = 3.26%; N = 5.04%; Cl=25.51%
found : C = 43.17%; H = 4.30%; N=5.21%; Cl= 25.80%

U.V. EtOH : 222(4.29), 249(4.29), 307(3.61), 340s(3.96), 354(4.15)

Reaction of 6-methyl-4-chloroquinolizinium perchlorate with diethyl malonate .

Diethyl malonate (2.3g.), in tetrahydrofuran (40 ml.), was converted into its sodium salt by the addition of sodium hydride (0.35g.) according to the procedure described on p.135 . When treated with the perchlorate (2.0g.) the solution immediately turned yellow indicating formation of the quinolizine. However, as reaction proceeded the solution gradually darkened suggesting that the product was decomposing. After 24 hours at room temperature the solvent was evaporated and the dark brown residue was taken up in chloroform and filtered to remove insoluble salts together with amorphous decomposition product. The concentrated filtrate was then applied to a column of alumina and eluted, first with benzene to remove residual diethyl malonate, and then with chloroform to remove the quinolizine. The latter separated out as a single yellow band leaving a residue of dark tar-like material at the head of the column. The product, however, was

unstable in solution, the initial clear-yellow eluate gradually darkening on standing. At elevated temperatures, decomposition occurred much more rapidly, a dark intractable residue being deposited. In order to minimise decomposition, the solvent was evaporated under reduced pressure at $\sim 20 - 25^{\circ}\text{C}$., and the residual pale-yellow solid was recrystallised from tetrahydrofuran/light-petroleum by cooling a saturated solution in a dry-ice / acetone bath at $\sim -20^{\circ}\text{C}$.

Yield = 1.28g. (56%).

m.p. = $114-115^{\circ}\text{C}$. (Kofler block preheated to 112°C .)

Diethyl 6-methylquinolizin-4-ylidenemalonate

$\text{C}_{17}\text{H}_{19}\text{NO}_4$ requires: C = 67.76%; H = 6.36%; N = 4.65%

found : C = 64.70%; H = 6.48%; N = 4.72%

I.R. ν (C=O) = 1680 cm^{-1}

U.V. EtOH : 214(4.42), 238(4.29), 257i(4.24), 316(3.93),
455(3.96).

EtOH / HClO_4 (0.5%): 218(4.32), 247(4.30), 303(3.65), 346(4.06).

Reaction of 6-methyl-4-chloroquinolizinium perchlorate
with methyl cyanoacetate

Methyl cyanoacetate (0.93g.) in tetrahydrofuran (20 ml.) was converted into its sodium salt by the addition of sodium hydride (0.23g.) according to the procedure described on p.135. The perchlorate (1.3g.) was then added and the reaction mixture was stirred for 24 hours at room-temperature. The yellow residue obtained by evaporation of tetrahydrofuran was shaken thoroughly with chloroform (50 ml.) and water (25 ml.), and the organic

layer was dried and concentrated and loaded onto a column of alumina. After initial elution with benzene to remove unreacted cyanoacetate, the quinolizine was removed as a single orange-yellow band with chloroform. Evaporation of solvent yielded an orange solid which recrystallised from benzene / light-petroleum as orange plates.

Yield = 0.85 g. (75%)

m.p. = 197 - 198°C.

Methyl 6-methylquinolizin-4-ylidenecyanoacetate

$C_{14}H_{12}N_2O_2$ requires : C = 69.99%; H = 5.03%; N = 11.66%
found : C = 69.78%; H = 4.83%; N = 11.72%

I.R. ν (C = O) = 1660 cm^{-1} ; (C \equiv N) = 2180 cm^{-1}

U.V. EtOH : 217(4.52), 225s(4.49), 306(4.22), 457(4.27)
EtOH /HClO₄(28%): 220(4.41), 245(4.40), 305(3.75),
335s(4.06), 343(4.16)

Attempted alkaline hydrolysis of diethyl
quinolizin-4-ylidenemalonate

The quinolizine (0.3g.) in ethanol (3 ml.) was treated with a solution of potassium hydroxide (0.06 g.) in ethanol (2ml.) and the mixture was allowed to stand 24 hours at room-temperature. The solvent was then evaporated and the residue was shaken with chloroform and water. The dried organic layer was evaporated to yield unchanged quinolizine.

Acidic hydrolysis of diethyl quinolizin-4-ylidenemalonate

The quinolizine (1.0 g.) was dissolved in 2N hydrochloric

acid (20 ml.) and the solution was heated under reflux for 1 hour. Evaporation of the solvent yielded a white residue which was recrystallised from methanol / ether.

Yield = 0.63g. (81%)

m.p. = 168°C. (effervesces)

An identical product was obtained when the hydrolysis was effected with either 6N or 12N hydrochloric acid.

4-(Carboxymethyl)quinolizinium chloride

$C_{11}H_{10}ClNO_6$ requires: C = 45.92%; H = 3.50%; N = 4.87%

found : C = 45.92%; H = 3.80%; N = 4.83%

I.R. ν (C = O) = 1705 cm^{-1} ; (OH) = 2400-3200 cm^{-1}

U.V. EtOH : 213(4.43), 234(4.35), 289(3.63), 306i(3.72)
318(4.08), 325(4.07), 332(4.28).

Decarboxylation of 4-carboxymethylquinolizinium chloride.

The quinolizinium salt (0.57g.) was placed in a 6" x 1" test-tube and the tube was heated, slowly, to 200°C., on an oil-bath. A vigorous effervescence of gas occurred in the 165-175°C., temperature range. The tube was then cooled and the white residue was taken up in ethanol and a few drops of perchloric acid were added. Treatment of the solution with ether precipitated a white solid which was identified, by comparison(m.p., i.r. spectrum) with an authentic sample, as 4-methylquinolizinium perchlorate.

Yield = 0.58g. (94%)

Ethyl quinolizin-4-ylideneacetate

Ethyl t-butyl quinolizin-4-ylidenemalonate (5.0g.) was added

to sodium-dried benzene (200ml.) contained in a 500 ml. R.B. flask equipped with a stirrer, gas inlet-tube and calcium chloride drying-tube. Anhydrous hydrogen chloride was then passed into the rapidly-stirred suspension (Note 1) over a period of 30 minutes. During this time the quinolizine gradually went into solution and was converted into its colourless hydrochloride salt. The latter separated out as a dense, colourless, mobile oil. When conversion to the salt was complete, as evidenced by the absence of the orange quinolizine, the flask was detached from the stirrer and the hydrogen chloride source, and then, suitably stoppered, and equipped with a condenser and calcium chloride drying-tube, it was immersed in a water-bath at 50°C. On addition of a few small pieces of porous pot a vigorous evolution of gas occurred which continued, with progressive abatement, over a period of 50 minutes. (Note 2) During this time the system was occasionally agitated by gentle shaking.

When the effervescence had ceased, the contents of the flask were cooled to ~ 6°C., on an ice-bath and the supernatant benzene was carefully decanted from the colourless, mobile, lower-layer. Carbon tetrachloride (150 ml.) was then added and the flask was immersed in an ice-salt bath. When the internal temperature had reached 5°C., the contents of the flask were vigorously stirred under a nitrogen atmosphere and a chilled 6N aqueous solution of sodium hydroxide (~10 ml.) was added dropwise over a period of 15 minutes. (Note 3). When liberation of the bright orange-red base was complete (Note 4), the organic

layer was separated and the residual aqueous layer was washed twice with 50 ml. portions of carbon tetrachloride (Note 5). The organic extracts were combined, dried, and evaporated on a rotary evaporator at a temperature of 25-30°C. (Note 6). The residual dark-red oil solidified on prolonged agitation. The product was dried for 24 hours over concentrated sulphuric acid in a vacuum desiccator and was used for subsequent reaction without further purification. (Notes 7 and 8). Low-temperature recrystallisation of a sample of the product from benzene / light petroleum yielded orange-red plates (Note 6)

Yield = 2.4g. (71%)

m.p. = 80-81°C. (decomposes; Kofler block preheated to 78°C.)

$C_{13}H_{13}NO_2$ requires: C = 72.54%; H = 6.09%; N = 6.51%

found : C = 72.64%; H = 5.91%; N = 6.27%

I.R. ν (C=O) = 1655 cm^{-1}

U.V. Cyclohexane: 210(4.27), 233s(3.91), 276(3.93), 286(3.97)
311(4.10), 322(4.16), 453(4.06)

Note 1 The quinolizine exhibits only a limited solubility in benzene (~lg./200ml.) and remains largely undissolved.

Although complete solution can be achieved by using a large quantity of benzene, this procedure is practically inconvenient and results in an increased loss of product during the subsequent decantation stage.

Note 2 Prolonged heating or further increase in temperature causes hydrolysis of the second ester group with formation of

4-(carboxymethyl)quinolizinium chloride.

Note 3 The hydrochloride salt must be treated directly with alkali in order to liberate the free-base. Only a small yield of product is obtained if the salt is initially dissolved in water.

Note 4 A large excess of sodium hydroxide is employed; the aqueous layer should be strongly basic at this stage.

Note 5 The solution may require filtration to remove decomposition product.

Note 6 The quinolizine is thermally unstable and must be maintained at a low temperature in order to avoid decomposition.

Note 7 The conventional methods of purification, viz. recrystallisation and chromatography are, respectively, unsatisfactory and inapplicable. Thus low-temperature recrystallisation yields a severely diminished return of product while attempted chromatography on either alumina or silica causes immediate decolourisation of the quinolizine (Treatment of the adsorbent with aqueous alkali regenerates the free-base)

Note 8 Although the quinolizine is more stable in the solid state, extensive decomposition occurs in a few days on exposure to the atmosphere. However, when maintained under a nitrogen atmosphere in the cold (-15°C.), the product remains comparatively free of decomposition material for several weeks.

Methyl quinolizin-4-ylideneacetate

The product was prepared from methyl t-butyl quinolizin-4-ylidenemalonate (5.0g) by a procedure identical with that

employed in the preparation of the ethyl analogue. (See preceding experiment) Low-temperature recrystallisation of a sample of the product from a benzene / light-petroleum solution yielded orange-red plates.

Yield = 2.4g. (72%)

m.p. = 103-104°C. (decomposes; Kofler block preheated to 101°C.)

$C_{12}H_{11}NO_2$ requires: C = 71.63%; H = 5.90%; N = 6.96%

found : C = 71.83%; H = 5.90%; N = 7.20%

I.R. ν (C = O) = 1655 cm^{-1}

U.V. Cyclohexane: 211(4.27), 233s(3.91), 276(3.93), 286(3.98),
311(4.11), 322(4.18), 451(4.08)

EtOH: 212(4.39), 234(4.22), 286(3.74), 317(4.07),
330(4.00), 448(3.74)

EtOH/HClO₄ (0.5%): 235(4.33), 290(3.64), 317(4.03), 324i(4.01)
330(4.21)

Attempted condensation of ethyl lithioacetate with
4-chloroquinolizinium perchlorate

Ethyl bromoacetate (0.63g.) in sodium-dried ether (7ml.) was added, over 2 minutes, to a cold (-78°C.) solution of n-butyllithium¹²³ (0.24g.) in ether (7ml.). The mixture was stirred 8 minutes and then the perchlorate (0.35g.) was added. However, no reaction was evident. After warming to room temperature, the reaction was filtered to give a quantitative return of unchanged perchlorate.

t-Butyl quinolizin-4-ylideneacetate

Di-t-butyl quinolizin-4-ylidenemalonate (5.6g.) and p-toluenesulphonic acid (0.015g.) were dissolved in glacial acetic acid (50ml.) and the solution was heated under reflux for 6 minutes (Note 1). The solution was transferred to a 500 millilitre three-necked flask, then cooled to $\sim 5^{\circ}\text{C}$., in an ice-bath and neutralised, under a nitrogen atmosphere and with rapid-stirring, by the dropwise addition of a chilled 6N aqueous solution of sodium hydroxide (160ml.) (Note 2). During this time the temperature of the solution was maintained at $\sim 10^{\circ}\text{C}$.. The liberated orange-red base was extracted with successive portions of carbon tetrachloride (100ml., 100ml., 50ml., 50ml.) (Note 3) and the combined organic extracts were dried, and evaporated at a temperature of $25-30^{\circ}\text{C}$., on a rotary evaporator (Note 4). The residual red oil solidified on agitation. The product was dried for 24 hours over concentrated sulphuric acid in a vacuum desiccator and was used for subsequent reaction without further purification (Notes 5 and 6). Low-temperature recrystallisation of a sample of the product from benzene / light-petroleum yielded orange-red plates.

Yield = 3.3g. (83%)

m.p. = $111-112^{\circ}\text{C}$. (decomposes: Kofler block preheated to 110°C .)

$\text{C}_{15}\text{H}_{17}\text{NO}_2$ requires : C = 74.05%; H = 7.04%; N = 5.76%

found : C = 74.24%; H = 7.00%; N = 5.35%

I.R. ν (C=O) = 1650 cm^{-1}

U.V. Cyclohexane: 211(4.26), 235s(3.88), 277i(3.96), 282(3.96)
312(4.12), 323(4.18), 455(4.06)

EtOH : 210(4.42), 235(4.29), 288(3.63), 318(4.02),
324i(4.01), 331(4.15), 445(3.13)

EtOH / HClO₄ (1.5%): 211(4.42), 235(4.31), 288(3.59), 318(4.01),
325i(3.99), 331(4.18)

Note 1 The course of reaction was followed by extracting samples at 1 minute intervals. These samples were neutralised with aqueous sodium hydroxide and the liberated base was extracted with chloroform and subjected to t.l.c. on alumina using chloroform / methanol (98/2) as eluent. After 6 minutes no unreacted diester was evident. The presence of the monoester, which decolourises on alumina, was ascertained by treating the baseline of the developed chromatogram with one drop of aqueous sodium hydroxide. The bright red free-base was immediately regenerated. When the reflux period was continued beyond 6 minutes the monoester was progressively converted to the corresponding carboxylic acid.

Note 2 A large amount of sodium hydroxide is required to neutralise the acetic acid. Frequently sodium acetate separates out and has to be removed by filtration. In a subsequent experiment the solution was concentrated (at 30°C. and 0.01 mm.) to approximately one-third of its volume before neutralisation with alkali. A 78% yield of product was obtained.

Notes 3,4,5 and 6 See respectively notes 5,6,7 and 8, page 148.

ATTEMPTED SYNTHESIS OF CYCL[3.3.3]AZINE DERIVATIVESReaction of methyl quinolizin-4-ylidenecyanoacetate
with dimethyl acetylenedicarboxylate¹²⁴

The quinolizine (1.8g.) and dimethyl acetylenedicarboxylate (2.3g.) were dissolved in anhydrous toluene (50ml.) and the solution was heated under reflux for 30 hours. During this period a gradual colour change from pale-yellow to deep-blue occurred. The solution was then concentrated, and chromatographed on alumina using benzene / ether (1/1) as eluent. The initial dark-blue band, which was the major product of reaction, was collected. Several secondary minor bands were ignored. The alumina remained heavily stained suggesting that substantial decomposition of the product had occurred. Evaporation of the eluent yielded a dark-blue residue which crystallised from benzene / light-petroleum as lustrous green plates.

Yield = 0.56g. (19%)

m.p. = 206 - 207°C.

Mass spectrum: m/e (parent) = 366

$C_{19}H_{14}N_2O_6$ requires: C = 62.30%; H = 3.85%; N = 7.65%

found : C = 61.28%; H = 3.47%; N = 7.86%

I.R. ν (C=O) = 1690 cm^{-1} , 1725 cm^{-1} ; (C≡N) = 2190 cm^{-1}

U.V. EtOH: 208, 248, 290, 586

C.HCL : 212(4.33), 241(4.47), 357(4.16)

Reaction of diethyl quinolizin-4-ylidenemalonate with
dimethyl acetylenedicarboxylate¹²⁴

The quinolizine (0.5g.) was dissolved in warm anhydrous

toluene (30ml.), dimethyl acetylenedicarboxylate (0.5g.) was added, and the solution was heated under reflux for 6 hours. The concentrated reaction mixture was then chromatographed on alumina using ether / chloroform as eluent. However, the distribution of products proved extremely complex (eight bands: respectively blue, lilac, yellow, orange, yellow, green, red and yellow) and their complete resolution could not be achieved.

Attempted intramolecular cyclisation of diethyl

6-methylquinolizine-4-ylidenemalonate

a) With sodium hydride

The quinolizine (0.2g.) was dissolved in anhydrous benzene (5ml.) and powdered sodium hydride (8mg.) was added. No reaction was evident. On warming the quinolizine progressively decomposed.

b) With sodium ethoxide

The quinolizine (0.4g.) was dissolved in ethanol (3ml.) and a solution of sodium (30mg.) in ethanol (2ml.) was added. The reaction mixture progressively darkened on warming. After 15 minutes at 40°C., the solvent was evaporated to yield amorphous decomposition product.

c) With potassium t-butoxide¹²⁵

The quinolizine (0.4g.) was dissolved in t-butanol (10ml.) and a solution of potassium t-butoxide (0.16g.) in t-butanol (3ml.) was added. The reaction mixture immediately darkened and a dark-brown solid was deposited. The latter was filtered off but proved to consist of amorphous decomposition product.

Attempted intramolecular cyclisation of methyl
6-methylquinolizin-4-ylidenecyanoacetate

a) With sodium hydride

The quinolizine (0.2g.) was dissolved in anhydrous benzene (5ml) and the solution was heated under reflux for 2 hours with powdered sodium hydride (20 mg.). A quantitative return of unchanged quinolizine was obtained.

b) With sodium ethoxide

The quinolizine (0.26g.) was dissolved in ethanol (5ml.) and a solution of sodium (21 mg.) in ethanol (2ml.) was added. On standing at room-temperature the solution gradually darkened. Evaporation of the solvent after 2 hours yielded a dark solid which consisted of decomposition product, together with some unchanged quinolizine.

c) With potassium t-butoxide¹²⁵

The quinolizine (0.36g.) was dissolved in t-butanol (10ml.) and a solution of potassium t-butoxide (0.17g.) in t-butanol (5ml.) was added. The brown amorphous solid which was deposited was filtered off but proved to consist of decomposition product.

Attempted formation of 1,3-di(methoxycarbonyl)-2-phenyl
cycl[3.3.3]azine from methyl quinolizin-4-ylideneacetate
and methyl phenylpropiolate

a) The quinolizine (1g.) was dissolved in dry benzene (25ml.) and a solution of methyl phenylpropiolate (0.9g.) in dry benzene (5ml.) was added. No reaction was apparent. Palladium-charcoal

(0.15g.) was then added and the solution was refluxed, with stirring, under a nitrogen atmosphere. However, this resulted only in progressive decomposition of the quinolizine.

b) When the reaction was repeated using dry toluene as solvent in place of benzene a similar result was obtained. When the solution was concentrated under atmospheric pressure to a volume of 5-6ml., a colour change from red to dark brown occurred. Thin layer chromatography of a sample of the solution revealed the presence of six different components (respectively yellow, red, brown, orange, mauve and yellow). However, these remained poorly resolved on a variety of silica and alumina adsorbents. In view of the complexity of the product distribution, no further investigation of the reaction was attempted.

SYNTHESIS OF CYCL[3.3.3]AZINES

Reaction of methyl quinolizin-4-ylideneacetate with dimethyl acetylenedicarboxylate¹²⁹

A solution of the quinolizine (2.3g.) in anhydrous benzene (80 ml.) was cooled to 10°C., on an ice-bath and a solution of dimethyl acetylenedicarboxylate (1.8g.) in anhydrous benzene (20ml.) was added, quickly, with rapid stirring. The initial orange-red reaction mixture immediately turned dark-brown in colour. After standing for 2 hours at room temperature, the solution was filtered to remove decomposition product and was then concentrated, and chromatographed on alumina (18" x 1½" column) using benzene as eluent. A forerunner light-brown band separated readily,

leaving several overlapping yellow and brown bands at the head of the column. Despite prolonged development (12 hours) with benzene, the latter could not be successfully resolved. The first band from the column was obtained as a red viscous oil and was shown, by t.l.c., on silica, to contain two components - a forerunner band together with a second red band. However, when applied to a full-scale column of silica (Hopkins and Williams, M.F.C) these bands were eluted together. A partial separation of the red component was achieved by dissolving the residue in hot petroleum containing a little benzene, and allowing the solution to stand for 24 hours at room-temperature. A red crystalline solid (0.6g.) was deposited. The residue obtained by evaporation of the mother liquor was resolved into its individual components using a dry column chromatography technique. A portion of the mixture (200 mg.) was dissolved in ether (3ml.) and applied to a column (12" x 2") of pure precipitated silica (B.D.A.). A constant level of ether (3cm.) was maintained at the head of the column while elution was continued. When the forerunner yellow band had completely separated from the slower-moving red band the column was extruded and cut, and the individual components were extracted with chloroform. This procedure was repeated with successive portions of the mixture until complete separation of the components had been achieved.

Red component

The product was recrystallised from benzene / light-petroleum to yield red prisms. On exposure to the atmosphere over a period

of several months these formed a surface-residue of decomposition product.

Total yield = 0.93g. (23%)

m.p. = 158-159°C.

Trimethyl 1,2-dihydrocycl[3.3.3]azine-1,2,3-tricarboxylate

$C_{18}H_{17}NO_6$ requires: C = 62.97%; H = 4.99%; N = 4.08%

found : C = 62.64%; H = 5.12%; N = 4.16%

I.R. ($CHCl_3$) ν (C=O) = 1645 cm^{-1} , 1735 cm^{-1}

U.V. EtOH : 212(4.41), 235s(4.00), 283s(3.98), 292(3.04),
326(3.97), 452(4.14)

EtOH/ $HClO_4$ (0.5%) : 216(4.36), 243(4.39), 296(3.62).

324(3.95), 332s(3.94), 337(4.19)

Yellow component

The viscous yellow residue obtained by evaporation of the chloroform extracts resisted all attempts at crystallisation. Samples for spectroscopy were freed of residual solvent by drying them under vacuum (0.01mm.) for 24 hours.

Yield = 0.47 g.

I.R. ($CHCl_3$) ν (C=O) = 1670 cm^{-1} , 1730 cm^{-1}

U.V. EtOH : 207, 247, 290, 410i, 457

EtOH/ $HClO_4$ (2%) : 208, 245, 265s, 303i, 331s, 338.

Trimethyl 1,2-dihydrocycl[3.3.3]azine-1,2,3-tricarboxylate with boiling nitrobenzene

The dihydrocyclazine (250mg.) was dissolved in nitrobenzene (25ml.) and the solution was heated under reflux for 10 minutes.

The nitrobenzene was then evaporated under reduced pressure and the residual dark-brown oil was taken up in benzene, filtered to remove decomposition product, and then chromatographed on alumina (10" x 1") using, initially, light-petroleum as eluent to remove residual nitrobenzene and then light-petroleum / benzene (1/1), with an increasing proportion of benzene, to remove the products.

The first fraction (yellow) yielded a brown solid which crystallised from ethanol as brown needles. The compound was identified from n.m.r. and mass spectral evidence as dimethyl cycl[3.3.3]azine-1,3-dicarboxylate.

Yield = 14 mg. (8%)

m.p. = 220-221°C.

Mass spectrum: m/ϵ (parent) = 283

The second fraction (red) yielded a red solid which crystallised from ethanol as needles. This compound was not identified

Yield = 5 mg. (2%)

m.p. = 175-176°C.

Mass spectrum : M/ϵ (parent) = 341.

The final fraction (greenish-yellow), which was the major product of reaction, was obtained as light-brown needles after recrystallisation from ethanol. The compound was identified as trimethyl cycl[3.3.3]azine - 1,2,3-tricarboxylate.

Yield = 141 mg. (57%)

m.p. = 183-184°C.

$C_{18}H_{15}NO_6$ requires : C = 63.34%; H = 4.43%; N = 4.10%
found : C = 63.18%; H = 4.27%; N = 4.20%

I.R. ν (C=O) = 1670 cm^{-1} , 1695 cm^{-1} , 1715 cm^{-1}

U.V. EtOH: 209(4.43), 250(4.16), 288(4.47), 407(4.29), 450(4.35)

EtOH/HClO₄ (3.5%): 210(4.47), 261(4.40), 318i(3.73), 334(3.78),
370(3.78).

Reaction of ethyl quinolizin-4-ylideneacetate with
ethyl propiolate¹²⁶

a) The quinolizine (1.0g.) [Note 1] was dissolved in freshly distilled nitrobenzene (25 ml.) contained in a 100 millilitre three-necked R.B. flask equipped with a stirrer, nitrogen inlet and condenser. Ethyl propiolate (0.6g.), which had been freshly distilled from anhydrous potassium carbonate [Note 2], was then added together with anhydrous potassium carbonate (0.5g.) [Note 2] and the stirred solution was purged with nitrogen for a few minutes. While stirring, and with a continued flow of nitrogen, the solution was brought rapidly to the boil and refluxed for 6 minutes. [Note 3]. During this time the solution changed colour, first to deep-blue and then to brownish-yellow, while water droplets formed in the condenser and returned to the solution with vigorous splashing. The nitrobenzene was then evaporated under reduced pressure on an oil-pump and the dark-brown residue was taken up in chloroform and filtered through a short column of alumina (4" x 1½") to remove potassium carbonate and intractable decomposition product. The residue obtained by evaporation of the chloroform eluate was dried in a vacuum-oven at 0.01 mm./ 80°C., for 24 hours to remove remaining nitrobenzene [Note 4]. The product was then taken up in the

minimum of benzene and was chromatographed on a column of alumina (20" x 1"), which had been made up in light-petroleum, using initially a 1/4, benzene / light-petroleum mixture as eluent. This was progressively changed to a 1/1 mixture as development continued over an approximately 7 hour period [Note 5].

The first fraction, which was yellow on the column, was evaporated to give a brownish-purple solid. Recrystallisation from tetrahydrofuran (or benzene / light-petroleum) yielded brownish-purple needles.

Yield = 1.1 g. (75%)

m.p. = 145-146°C.

Mass spectrum : M/ε (parent) = 311

Diethyl cycl[3.3.3]azine - 1,3- dicarboxylate

$C_{18}H_{17}NO_4$ requires : C = 69.44%; H = 5.50%; N = 4.50%

found : C = 69.69%; H = 5.36%; N = 4.47%

I.R. ν (C=O) = 1660 cm^{-1}

U.V. EtOH: 240(4.00), 285(4.53), 316(3.81), 331(3.81),
399(4.40), 430i(4.31), 453(4.48).

The second fraction, which was dark-blue on the column, was obtained as a dark-blue oil after evaporation of solvent. The product solidified on prolonged agitation and was recrystallised from light-petroleum to yield blue-black prisms.

Yield = 0.12 g. (8%)

m.p. = 99-100°C.

Diethyl 3a,4 - dihydrocycl[3.3.3]azine - 1,3- dicarboxylate

$C_{18}H_{19}NO_4$ requires: C = 69.00%; H = 6.11%; N = 4.47%

found : C = 68.85%; H = 6.00%; N = 4.40%

I.R. ν (C=O) = 1655 cm^{-1} , 1675 cm^{-1}

U.V. EtOH : 210(4.31), 247i(3.97), 302(4.47), 398(4.05),
453i(3.65), 530(3.81)

EtOH/HClO₄ (3.5%): 218(4.22), 261(3.98), 361(3.80)

Note 1 Larger scale reactions (3g. quinolizine) required longer reflux periods (7-8 minutes) and gave reduced yields of product (60-65%).

Note 2 The reaction is sensitive to acidic impurities. The precaution is more important in the synthesis of cyclazines containing t-butoxycarbonyl substituents.

Note 3 The course of the reaction was followed by extracting samples at 1 minute intervals and subjecting these to t.l.c. on alumina using ether as eluent. As reaction continued the proportion of blue intermediate-product progressively decreased, while that of the yellow product correspondingly increased. Longer reaction periods gave reduced yields of product.

Note 4 When this treatment was omitted an inadequate separation of the two products was obtained on alumina and these products remained heavily contaminated with nitrobenzene.

Note 5 The rates of elution of the two fractions are closely similar. Prolonged development is necessary to effect a separation.

b) When the preceding reaction was carried out at a temperature of 160°C., for 1 minute the same two products were obtained, but the relative proportion of these was reversed.

Yield of cyclazine = 0.20 g. (14%)

Yield of dihydrocyclazine = 1.05 g. (72%)

Reaction of diethyl 1,2-dihydrocycloazine-1,3-dicarboxylate
with boiling nitrobenzene

The dihydrocycloazine (0.4g.) was dissolved in nitrobenzene (10ml.) and the solution was refluxed under a nitrogen atmosphere, with stirring, for 6 minutes. The solution was then evaporated and chromatographed (according to the procedure outlined for the previous experiment). A 73% (0.29g.) yield of cycloazine was obtained together with 8% (0.03g.) yield of unchanged starting material.

Preparation of t-butyl propiolate

A heavy-walled pressure vessel was charged with ether (130ml.) and concentrated sulphuric acid (5ml.). The solution was cooled to -5°C ., on an ice-salt bath and propiolic acid (40g.) and isobutene (90ml.) were added. The vessel was then sealed and shaken mechanically for 15 hours. After recooling in an ice-salt bath for 30 minutes, the vessel was opened and the solution was poured into a one litre beaker containing sodium hydroxide (50g.) in water (200ml.) and ice (200g.). The mixture was shaken, the layers separated, and the aqueous layer was extracted three-times with 75 millilitre portions of ether. The ethereal extracts were combined, dried and concentrated. The product was distilled over anhydrous potassium carbonate in a distillation apparatus that had been previously washed with sodium hydroxide solution, rinsed with water and thoroughly dried. The product was collected in a flask immersed in a salt-ice bath

Yield = 40 g. (59%)

b.p. = $30-32^{\circ}\text{C}$. / 0.2 mm.

Reaction of methyl quinolizin-4-ylideneacetate with
t-butyl propiolate

The experimental procedure was exactly the same as that for the corresponding reaction with the ethyl analogues (page 159). The reaction mixture was refluxed for 6 minutes.

Reagents

Quinolizine	1.0g.
t-butyl propiolate	0.7g.
Nitrobenzene	25ml.
Anhydrous potassium carbonate	0.5g.

The first fraction from the column, which was yellow in colour, was evaporated to give a dark purple-brown solid. Recrystallisation from ethanol yielded dark-purple needles

Yield = 1.0g. (62%)

m.p. = 156-157°C.

t-Butyl methyl cycl[3.3.3]azine-1,3-dicarboxylate

$C_{19}H_{19}NO_4$ requires: C = 70.14%; H = 5.89%; N = 4.30%

found : C = 70.02%; H = 6.09%; N = 4.02%

I.R. ν (C=O) = 1655 cm^{-1}

U.V. EtOH : 240(4.00), 286(4.55), 317(3.83), 332(3.83), 400(4.44)
431(4.35), 454(4.51)

EtOH/HClO₄ (30%): 217(4.26), 247(4.31), 279s(4.04), 360(3.97).

Two further fractions, respectively red and yellow, were also evident but these proved inseparable even on prolonged development (Total yield = 0.26g.)

Reaction of t-butyl quinolizin-4-ylideneacetate with
t-butyl propiolate

a) The experimental procedure was the same as that described for the corresponding reaction with the ethyl analogues (page 159). The solution was refluxed for 6 minutes.

Reagents

Quinolizine	1.0g.
t-Butyl propiolate	0.6g.
Nitrobenzene	25 ml.
Anhydrous potassium carbonate	0.5g.

The first fraction (yellow) from the column yielded a brown solid which crystallised from light-petroleum (b.p. 60-80°C.) as glistening brown plates.

Yield = 0.97g. (64%)

m.p. = 166-167°C.

Di - t - butyl cycl[3.3.3]azine-1,3-dicarboxylate

$C_{22}H_{25}NO_4$ requires: C = 71.91%; H = 6.86%; N = 3.81%

found : C = 72.30%; H = 6.72%; N = 4.12%

I.R. ν (C=O) = 1660 cm^{-1}

U.V. EtOH: 240(3.97), 287(4.54), 318(3.80), 333(3.80), 401(4.44)
434(4.33), 456(4.52)

EtOH / $HClO_4$ (18%) : 219(4.30), 249(4.30), 281s(3.99), 370(3.84).

The second fraction (dark-blue) yielded a viscous oil which solidified on prolonged agitation. Crystallisation from light-petroleum yielded dark blue-black prisms.

Yield = 0.09g. (6%)

m.p. = 144-145°C.

Di-t-butyl 3a,4-dihydrocycl[3.3.3]azine-1,3-dicarboxylate

$C_{22}H_{27}NO_4$ requires : C = 71.52%; H = 7.37%; N = 3.79%

found : C = 71.60%; H = 7.21%; N = 3.95%

I.R. ν (C=O) = 1680 cm^{-1}

U.V. EtOH : 206(4.30), 245s(3.93), 303(4.45), 406(3.94)

535(3.74)

EtOH / $HClO_4$ (1.8%) : 205(4.22), 219(4.24), 260(4.02), 363(3.88).

b) When the reaction was carried out at 150°C., for 1 minute the following yields of product were obtained.

Cyclazine = 0.20g. (13%)

Dihydrocyclazine = 0.99g. (66%)

Phenyl propiolic acid

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Methyl phenylpropiolate

Phenylpropiolic acid (120g.) was dissolved in methanol (170ml.) and concentrated sulphuric acid (18g.) was added. The solution was allowed to stand two days at room temperature, then poured into ice-water (600 ml.) and extracted with ether (3 x 150ml.). The combined extracts were washed with sodium bicarbonate solution to remove unreacted phenylpropiolic acid, then dried and concentrated and the product distilled.

Yield = 77g. (59%)

b.p. = 128°C / 14 mm.

Reaction of methyl quinolizin-4-ylideneacetate with
methyl phenylpropiolate

Reagents

Quinolizine	1.0g.
Methyl phenylpropiolate	1.0g.
Nitrobenzene	25ml.

The experimental procedure was identical with that described for the synthesis of the diethyl 1,3-dicarboxylate (Page 159). The solution was refluxed 5 minutes during which time its colour gradually changed from red to dark-brown. Thin layer chromatography of a portion of the solution revealed the presence of an intermediate orange product which gradually disappeared as reaction progressed.

The major product of reaction, which was eluted from the alumina column as a forerunner yellow fraction, was obtained as a dark-brown solid which crystallised from tetrahydrofuran (or ethanol) as dark-purple needles

Yield = 0.46g. (26%)

m.p. = 215-216°C.

Dimethyl 2-phenylcycl[3.3.3]azine-1,3-dicarboxylate

$C_{22}H_{17}NO_4$ requires : C = 73.53%; H = 4.77%; N = 3.90%

found : C = 73.44%; H = 4.60%; N = 4.04%

I.R. ν (C=O) = 1680 cm^{-1}

U.V. EtOH: 204(4.44); 258s(4.18), 294(4.49), 416(4.15)

472(4.39)

A second, orange fraction from the column (0.15g.) resisted all attempts at crystallisation. Investigation of its structure was not attempted.

Reaction of methyl quinolizin-4-ylideneacetate with ethyl phenylpropiolate

Reagents

Quinolizine	1.3g.
Ethyl phenylpropiolate	1.2g.
Nitrobenzene.	30ml.

The experimental procedure was the same as that described previously (Page 159) The solution was refluxed 5 minutes.

The yellow forerunner fraction from the alumina column yielded a brown solid which crystallised from tetrahydrofuran (or ethanol) as dark-purple needles.

Yield = 0.57g. (24%)

m.p. = 186-187°C.

Ethyl methyl 2-phenylcycl[3.3.3]azine-1,3-dicarboxylate

$C_{23}H_{19}NO_4$ requires: C = 73.98%; H = 5.13%; N = 3.75%

found: C = 73.92%; H = 5.36%; N = 3.71%

I.R. ν (C=O) = 1680 cm^{-1}

U.V. EtOH : 205(4.41), 258s(4.15), 294(4.48), 416(4.15)
472(4.40)

Secondary orange bands in minor yield were not investigated.

Reaction of ethyl quinolizin-4-ylideneacetate with methyl phenylpropiolate

Reagents

Quinolizine	1.5g.
Methyl phenylpropiolate	1.2g.
Nitrobenzene	30ml.

The experimental procedure was the same as that described previously (p. 159). The solution was refluxed 5 minutes.

The yellow forerunner fraction from the column yielded a brown solid which crystallised from tetrahydrofuran as dark-purple needles.

Yield = 0.6g. (23%)

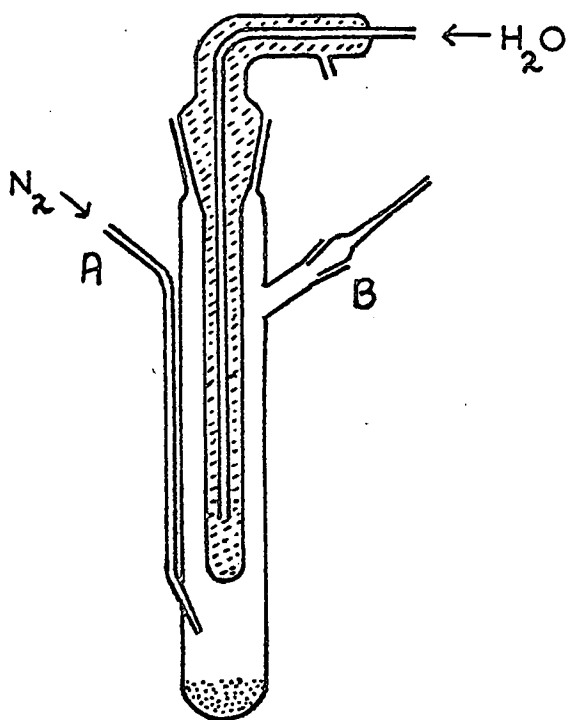
m.p. = 186-187°C.

The product was identical in every respect (n.m.r., i.r., u.v., m.p., m.m.p.) to that obtained from the preceding reaction.

Attempted acidic hydrolysis of diethyl
cycl[3.3.3]azine -1,3- dicarboxylate

The cyclazine (0.4g.) was dissolved in 12N hydrochloric acid (5ml.) and the solution was heated under reflux for 10 minutes. During this time the initially light-brown solution turned dark-brown. Evaporation of solvent in vacuo yielded a black amorphous residue of decomposition product. A similar result was obtained using dilute hydrochloric acid (2N) or fluoroboric acid (6N). Decomposition also occurred when these solutions were allowed to stand in the cold, the rate of decomposition increasing with the strength of the acid. When anhydrous hydrogen chloride was passed through a solution of the cyclazine in anhydrous benzene a light-brown oil was deposited. The product gradually darkened on standing. After 24 hours only black intractable residue remained.

FIG 44



Attempted basic hydrolysis of diethyl
cycl[3.3.3]azine-1,3-dicarboxylate

a) The cyclazine (200mg.) was dissolved in 2-methoxyethanol (10ml.) and a solution of potassium hydroxide (50mg.) in the same solvent (8ml.) was added. After standing for 24 hours at room-temperature, the cyclazine was unchanged. The solution was then refluxed for 1 hour and the dark-brown residue obtained by evaporation of solvent was shaken with water. A large amount of intractable amorphous product was filtered off, and the aqueous filtrate was neutralised with dilute hydrochloric acid. Extraction with chloroform yielded 7mg. of a red solid. However, the small yield of product prevented an investigation of its structure.

b) A solution of the cyclazine (0.4g.) in dimethylsulphoxide (5ml.) was added to a suspension^{lll} of sodium hydroxide (ca. 0.12g.) in the same solvent (3ml.). After standing for 1 hour at room-temperature the cyclazine had remained unchanged. The solution was then heated under reflux for 30 minutes. A black solid was deposited which consisted of amorphous decomposition product.

Pyrolysis of t-butyl methyl cycl[3.3.3]azine-1,3-dicarboxylate

The cyclazine (400mg.) was placed in the socket section of a modified sublimation apparatus (Fig.44). A slow stream of dry, oxygen-free nitrogen was then introduced through side-arm inlet-tube (A) and the apparatus was immersed to a depth of ca. 3cm., in a bath of molten Wood's metal at a temperature of

180°C. The cyclazine immediately liquified. The temperature was then raised to 220°C., at which stage a slow evolution of gas became apparent from the surface of the cyclazine. A mist of violet vapour formed in the sublimation tube. The temperature was then increased to 250°C., over a 5 minute period and was maintained constant at this temperature for a further 5 minutes. During this period a dense cloud of violet sublimate condensed on the cold-finger and the walls of the vessel. A black residue of decomposition product remained in the base of the socket-tube.

The apparatus was then cooled to room temperature and, whilst the inflow of nitrogen was continued, the sublimate was washed back into the socket tube by pipetting a stream of dry ether [Note 1] through side-arm (B) and onto the walls of the vessel and the cold-finger. The resultant solution was evaporated, at room-temperature, by introducing a stream of dry nitrogen through inlet-tube (A) [Note 2]. The cold-finger was then temporarily removed and cleaned, inlet-tube (A) was sealed off, and the dark brown, viscous residue was dried under vacuum (0.04mm.) at room temperature for 30 minutes. [Note 3].

Whilst still under vacuum the apparatus was immersed to a depth of ca. 3cm., in an oil-bath and the temperature of the bath was raised to 140°C., over a 30 minute period [Note 3].

Sublimation was continued at 140°C./0.04mm. for 1 hour.

Dark-brown needles collected on the cold-finger. Trace amounts of unchanged diester which was present in the product (detectable by t.l.c. on silica) were removed by careful resublimation.

[Note 4]

Yield (before resublimation) = 171mg. (62%)

m.p. = 118-119°C. (decomposes; Kofler block preheated to 117°C.)

Methyl cycl[3.3.3]azine-1-carboxylate

$C_{14}H_{11}NO_2$ requires : C = 74.65%; H = 4.92%; N = 6.22%

found : C = 74.76%; H = 5.08%; N = 6.10%

I.R. $\nu = 1630 \text{ cm}^{-1}$ (Shoulder at 1675 cm^{-1})

U.V. Cyclohexane : 202(4.12), 250(4.04), 284(4.41), 413(4.07),
452(4.29), 468(4.34), 479(4.74)

EtOH: 202(4.19), 247(4.10), 282(4.39), 404(3.96), 451(4.21),
467s(4.28), 476(4.49)

EtOH/HClO₄ (2%): 206(4.27), 250(4.22), 327(3.69),
349i(3.77), 360(3.82), 384s(3.62).

Note 1 The ether was previously deoxygenated by refluxing and cooling it under a dry nitrogen atmosphere.

Note 2 The level of the ethereal solution should lie below the entrance of the nitrogen inlet-tube, otherwise splashing occurs.

Note 3 Failure to remove volatile impurities results in decomposition of the product on attempted sublimation.

Note 4 The process was interrupted before completion to prevent resublimation of the diester. Alternative methods of purification are unsatisfactory because of the instability of the product. (See discussion section)

Pyrolysis of di-t-butyl cycl[3.3.3]azine-1,3-dicarboxylate
: preparation of t-butyl cycl[3.3.3]azine-1-carboxylate

Following the procedure described in the preceding experiment

the cyclazine (500mg.) was pyrolysed, over a 10 minute period, at a temperature of 220-250°C. The sublimate was washed from the cold-finger and walls of the vessel with dry ether [Note 1, preceding experiment] and the resultant solution was evaporated under a stream of dry nitrogen. The residual dark-brown oil was dried under vacuum (0.04mm.) at room temperature for 30 minutes. The temperature was then increased to 120°C., over a 30 minute period and sublimation was continued at 120°C./0.04mm. for a further 2 hours. During this time a dark-brown viscous oil collected on the cold-finger. Although it seemed possible that the product had melted because of its close proximity to the hot walls of the vessel, crystallisation did not occur when the vessel was cooled to room temperature, nor when the product was subsequently subjected to prolonged agitation. However, crystallisation was eventually induced by triturating the product with a little light-petroleum (0.5ml.; b.p. 40/60°C.) under a dry nitrogen atmosphere [Note 1]. However, all attempts to effect normal recrystallisation of the resultant impure brown solid caused formation of a large amount of decomposition product. An apparently pure sample was eventually prepared by cooling a room-temperature saturated solution of the product in light-petroleum (40/60°C.) (the solution having previously been filtered under a nitrogen atmosphere) to -20°C., in a dry-ice/acetone bath. The resultant amorphous brown solid was filtered off, washed with a little cold petroleum, and then dried under vacuum (0.01mm.) at room temperature for 2 hours. [Note 2]

m.p. = 108-109°C. (decomposes: Kofler block
preheated to 107°C.)

t-Butyl cycl[3.3.3]azine -1- carboxylate

$C_{17}H_{17}NO_2$ requires: C = 76.38%; H = 6.41%; N = 5.24%

found : C = 75.00%; H = 6.96%; N = 5.5%

Note 1 The product is extremely unstable and decomposes rapidly on exposure to the atmosphere.

Note 2 A representative yield of the product could not be calculated because of the loss involved by decomposition during the crystallisation and recrystallisation stages.

Pyrolysis of t-butyl cycl[3.3.3]azine-1-carboxylate

The cyclazine (0.09g.) was pyrolysed at 250°C., for 10 minutes according to the procedure described on page 169. During this pyrolysis, a cloud of violet vapour condensed as a brown oil on the cold-finger and the surrounding vessel walls. Work-up of the product in the manner described in the preceding experiment yielded a minute amount of an unstable, viscous brown oil. Although the product appeared to consist (on the basis of its rate of decomposition on alumina) of unchanged starting material, its low yield prevented rigorous identification

Attempted pyrolysis of di-t-butyl cycl[3.3.3]azine
-1,3-dicarboxylate over hot glass beads

The apparatus employed consisted of a vertical column (4" x 1") of glass beads (4mm. diameter) which was surrounded by a heating coil and an insulating asbestos jacket. The temperature of the glass-bead chamber was calibrated for several settings of a

Variac transformer which was included in the electrical heating-circuit. When a solution of the cyclazine (200mg.) in benzene (10ml.) was introduced dropwise (1 drop/3 seconds), under a slow current of nitrogen, into the chamber at a temperature of 250°C., the benzene vaporised instantly and a yellow effluent vapour was condensed and collected at the outlet of the chamber.

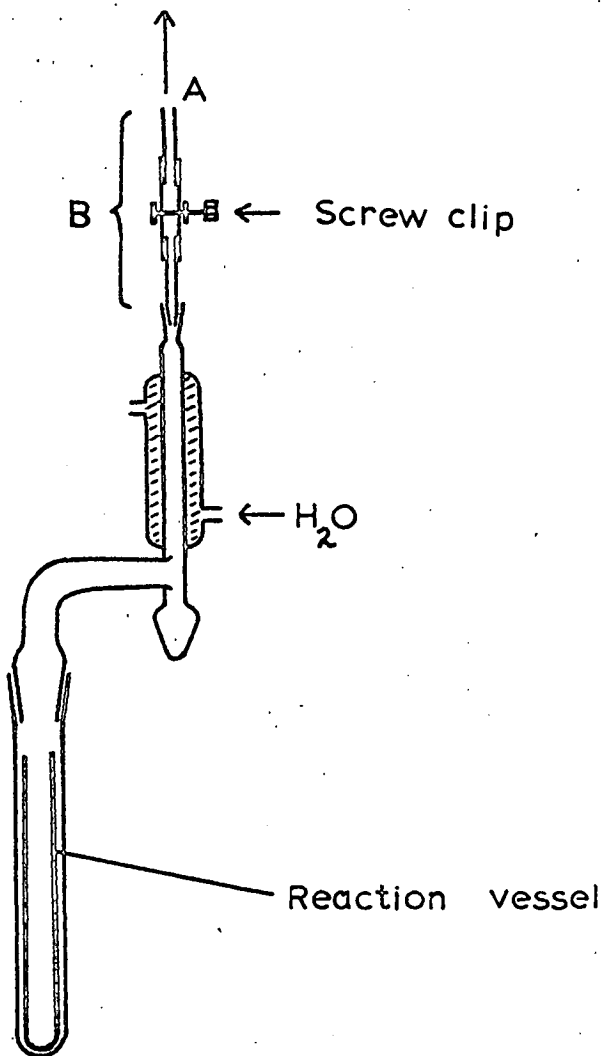
Evaporation of the solution gave a quantitative return of unchanged starting material. The experiment was repeated at progressively increasing temperatures (300, 350, 400°C.) but, in each case, the cyclazine was returned unchanged. However, in the higher temperature range a white solid was also isolated from the condensate. This solid was identified, by comparison with an authentic sample, as biphenyl.

Pyrolysis of di-t-butyl cycl[3.3.3]azine-1,3-dicarboxylate
: preparation of cycl[3.3.3]azine

The diester (0.2g.) was sealed under high-vacuum in a heavy-walled, cylindrical, pyrex-glass tube (inner dimensions 10 cm. x 0.5 cm.). The tube was then immersed, completely, in a bath of molten Wood's metal which was maintained at a constant temperature of 300°C. [Note 1]. After 5 minutes the tube was removed and allowed to cool to room temperature. It was then wrapped in wire-gauze and the internal pressure was released by melting a small area of an end-section [Note 2] with a small blow-pipe flame. The tube was then stored, immediately, under a dry nitrogen atmosphere [Note 3] and, when the end section had cooled, the aperture was sealed with a plug of plasticine.

FIG 45

To vacuum pump



The tube, together with the sublimation apparatus [Fig.45] and necessary accessories [Note 4], were then transferred to a dry-nitrogen box 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, and the condenser section, which was topped by the assembly collectively labelled (B) in the diagram (screw-clip firmly closed), was fitted. The apparatus was then removed from the nitrogen-box and the socket section was immersed, completely, in an oil-bath. Outlet (A) 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 then opened and the temperature of the oil-bath was raised to 120°C. Sublimation was continued at 120°C./0.01 mm. for 1 hour. A brown, crystalline solid collected on the inner walls of the condenser. The screw-clip was then closed and the apparatus was disconnected from the pump and re-transferred to the nitrogen-box. The vacuum within the apparatus was released and bis(trimethylsilyl) ether (1ml.) [Note 6] was pipetted into the condenser section. The resultant yellow solution [Note 7] was transferred to an n.m.r. sample-tube which was then sealed with a cap. The tube was removed from the box and the n.m.r. spectrum immediately measured.[Note 8].

The resonance signal of the solvent was separately calibrated using a trace of benzene as internal standard.

Note 1 An extremely high pressure (15-20 atmos.) is created within the reaction-tube. Full safety precautions are thus necessary. (Safety shield, face visor, protective gloves)

Note 2 It is more convenient to melt the tapered end of the tube, i.e. that end last sealed.

Note 3 The nitrogen was generated by allowing liquid nitrogen to evaporate from a vacuum-flask. It was dried by passage through a calcium chloride drying-tube.

Note 4 The necessary accessories are a glass-cutter, a cloth and a pair of pincers or pliers.

Note 5 All joints were lightly smeared with high-vacuum grease.

Note 6 The solvent had been previously freed of molecular-oxygen by refluxing and cooling it under a dry nitrogen atmosphere.

Note 7 The product was only partially soluble in this medium.

Note 8 The preheat period, necessary for measurement of n.m.r. spectra, was minimised in order to avoid decomposition of the sample.

CHEMICAL REACTIONS OF CYCL[3.3.3]AZINES

1. HYDROGENATION

Hydrogenation of diethyl cycl[3.3.3]azine-1,3-dicarboxylate

The cyclazine (60mg.) was dissolved in thiophene-free benzene (20ml.), platinum oxide catalyst was added (15mg.), and the solution was shaken under hydrogen at atmospheric pressure. After 3½ hours, during which time the rate of uptake of hydrogen had progressively decreased, a sample of the solution was subjected to t.l.c. on alumina. The presence of a pink product

27 ml. of hydrogen were absorbed. The solution was then filtered and evaporated, and the residue was taken up in the minimum of benzene and chromatographed on alumina (15" x $\frac{3}{4}$ ") using benzene / light-petroleum (7/3) as eluent.

The first fraction (yellow) was identified as diethyl cycl[3.3.3]azine-1,3-dicarboxylate (41mg.; 16%) and the second fraction (red) as its 3a,4,5,6-tetrahydro-derivative (210mg.; 81%).

2. DIELS-ALDER ADDITION

Reaction of diethyl cycl[3.3.3]azine-1,3-dicarboxylate with dimethyl acetylenedicarboxylate¹²⁴

The cyclazine (0.3g.), in anhydrous benzene (15ml.), was heated under reflux for 16 hours with dimethyl acetylenedicarboxylate (0.27g.). [Using anhydrous toluene as solvent only 5 hours reflux is necessary]. The solution progressively changed colour from yellow to deep red. The solvent was then evaporated under reduced pressure and the residue was taken up in the minimum of chloroform and chromatographed on a column of alumina (6" x 1") using initially benzene as eluent (to remove excess acetylenic ester) and then chloroform to remove the product. The latter separated as a single red fraction, the residue obtained by evaporation of the eluate crystallised from ethanol as red prisms.

Yield = 0.42g. (96%)

m.p. = 255-256°C.

Mass spectrum: M/ϵ (parent) = 453

3a, 6-Etheno-3a,6-dihydro-1,3-di(ethoxycarbonyl)-3,4-di(methoxycarbonyl)cycl[3.3.3]azine

$C_{24}H_{23}NO_8$ requires: C = 63.57%; H = 5.11%; N = 3.09%

found: C = 65.07%; H = 5.20%; N = 2.99%

I.R. ν (C=O) = 1670 cm^{-1} , 1690 cm^{-1} , 1715 cm^{-1}

U.V. EtOH: 204(4.33), 270s(4.04), 281(4.06), 290(4.19),
307(4.34), 364(4.01), 515(3.85)

EtOH/HClO₄ (56%): 212(4.35), 251s(4.28), 260(4.29), 309(3.61)

Di-t-butyl acetylenedicarboxylate

A heavy walled pressure-vessel was charged with ether (100ml.) and concentrated sulphuric acid (6.5ml.). The solution was cooled to $-20^{\circ}C.$, on a dry-ice / acetone bath and acetylene-dicarboxylic acid (40g.) and isobutene (160ml.) were added. The vessel was closed and shaken mechanically at room temperature for 24 hours. The reaction mixture was then poured into a 2 litre beaker containing a solution of sodium hydroxide (50g.) in water (250ml.), and ice (250g.). The mixture was shaken and the layers were separated and then the aqueous layer was extracted with successive portions (3 x 100ml.) of ether. The organic layers were combined, dried and evaporated, and the residual white solid was distilled over anhydrous potassium carbonate (using an apparatus that had been washed with a solution of sodium hydroxide, rinsed thoroughly with water and dried). The di-t-butyl ester was obtained as colourless prisms

Yield = 45.1g. (57%)

b.p. = $93-94^{\circ}C.$ / 0.07 mm.

m.p. = $37-38^{\circ}C.$

Reaction of diethyl cycl[3.3.3]azine-1,3-dicarboxylate
with di-t-butyl acetylenedicarboxylate

The cyclazine (0.3g.), in anhydrous benzene (10ml.), was heated under reflux for 96 hours (taking care to prevent evaporation of the solvent) with di-t-butyl acetylenedicarboxylate (0.6g.). The solution gradually changed colour from yellow to deep-red. The solvent was then evaporated and the residual red oil was taken up in the minimum of benzene and chromatographed on a column (6" x 1") of alumina using initially light-petroleum as eluent (to remove excess acetylenic ester) and then benzene / light-petroleum (2/1) to remove the reaction product.

The first fraction from the column, a minor yellow band, yielded unchanged cyclazine (70mg.). The second fraction, a purple band, in negligible yield, was discarded. The final fraction, a red band, which was the major product of reaction, yielded a red oil which crystallised on agitation.

Recrystallisation from benzene / light-petroleum yielded red needles.

Yield = 0.27g. (68% based on unrecovered cyclazine)

m.p. = 148-149°C.

3a, 6-Etheno-3a,6-dihydro-1,3-di(t-butoxycarbonyl)-3,4-di(methoxycarbonyl)cycl[3.3.3]azine

$C_{30}H_{35}NO_8$ requires: C = 67.02%; H = 6.56%; N = 2.61%

found: C = 66.81%; H = 6.73%; N = 2.57%

I.R. ν (C=O) = 1675 cm^{-1} , 1695 cm^{-1} , 1710 cm^{-1}

U.V. EtOH: 210(4.26), 269(4.01), 308(4.34), 366(4.00), 5.5(3.84)

EtOH/HClO₄ (56%): 211(4.27), 258(3.53), 295s(3.25).

Hydrogenation of 3a,6-ethano-3a,6-dihydro-1,3-di(ethoxycarbonyl)-4,5-di(methoxycarbonyl)cycl[3.3.3]azine

A solution of the cyclazine (345 mg.) in 2-methoxyethanol (80ml.) containing platinum oxide (40mg.) was shaken under hydrogen at atmospheric pressure until 26.8 ml. of hydrogen had been absorbed [Requires ca. 1½ hours]. The solution was then filtered and evaporated and the residual red solid was crystallised from ethanol. Red rhomboids were obtained.

Yield = 329 mg. (95%)

m.p. = 185-186°C.

Elevation of the temperature to 188°C., caused resolidification of the sample as needles. (m.p. = 206-207°C.) However, no change in the chemical composition of the product had occurred since a sample heated to 200°C., and then cooled and recrystallised from ethanol yielded red rhomboids which were identical (i.r., m.p.) with the product obtained from the original crystallisation

3a,6-Ethano-3a,6-dihydro-1,3-di(ethoxycarbonyl)-4,5-di(methoxycarbonyl)cycl[3.3.3]azine

$C_{24}H_{25}NO_8$ requires: C = 63.29%; H = 5.53%; N = 3.08%

found: C = 63.26%; H = 5.38%; N = 3.25%

I.R. ν (C=O) = 1650 cm^{-1} , 1705 cm^{-1}

U.V. EtOH : 204(4.34), 267s(4.06), 275(4.11), 309(4.36),
362(3.88), 516(3.84).

Pyrolysis of 3a,6-ethano-3a,6-dihydro-1,3-di(ethoxycarbonyl)-4,5-di(methoxycarbonyl)cycl[3.3.3]azine

The dihydrocyclazine (210mg.) was placed in the apparatus diagrammatically represented in Fig. 44 and then, whilst a slow current of dry nitrogen was introduced through side-arm (A), the apparatus was immersed to a depth of ca. 3cm. in a bath of molten Wood's metal at a temperature of 200°C. The temperature of the bath was then raised slowly, over a 5 minute period, to 290°C., and maintained at this temperature for a further 5 minutes. The molten red dihydrocyclazine effervesced vigorously in the 270-290°C. range (effervescence commences ~ 220°C.) and a brown sublimate collected on the cold-finger and the walls of the vessel. After cooling to room temperature, the product was taken up in the minimum of benzene and chromatographed on a column of alumina (12" x 3/4") using benzene as eluent.

The first, yellow, fraction yielded a brown solid which crystallised from ethanol as needles. The product was identified (see discussion) as 1,3-di(ethoxycarbonyl)-5-methoxycarbonylcycl[3.3.3]azine

Yield = 6 mg. (3.5%)

m.p. = 184-185°C.

Mass spectrum : M/ϵ (parent) = 369

U.V. EtOH: 204(4.44), 244(4.13), 298(4.45), 330(4.01), 411(4.25),
452s(4.18), 474(4.38).

The second, yellow-green, fraction yielded a reddish-brown solid which crystallised as similarly-coloured needles from ethanol

Yield = 135 mg. (68%)

m.p. = 226-228°C.

1,3-di(ethoxycarbonyl)-4,5-di(methoxycarbonyl)cycl[3.3.3]azine

$C_{22}H_{21}NO_8$ requires: C = 61.82%; H = 4.95%; N = 3.28%

found: C = 61.79%; H = 4.83%; N = 3.19%

I.R. ν (C=O) = 1675 cm^{-1} , 1695 cm^{-1} , 1710 cm^{-1} , 1725 cm^{-1}

U.V. EtOH: 205(4.48), 292(4.45), 328s(3.89), 413(4.27), 488(4.28)

EtOH/HClO₄ (14%) : 207(4.41), 258(4.28), 382(4.00).

3a,6-Etheno-3a,6-dihydro-1,3-di(ethoxycarbonyl)-4,5-dicarboxycycl[3.3.3]azine

The corresponding 4,5-di-t-butyl ester (100 mg.) was dissolved in anhydrous benzene (20ml.) and dry hydrogen chloride was passed through the solution for 10 minutes. The initial red colour gradually changed to light-brown and a viscous brown oil was deposited in the base of the flask. The solution was then refluxed on a water-bath for 30 minutes and the liberated red solid was filtered off, washed with a little benzene and air-dried. Attempts to recrystallise the product from a variety of solvents (acetic acid, methanol, ethyl acetate) caused decomposition

Yield = 76 mg. (96%)

I.R. ν (C=O) = 1680 cm^{-1} , 1740 cm^{-1} ; (OH) = 2400-3200 cm^{-1}

Sublimation of 3a,6-etheno-3a,6-dihydro-1,3-di(ethoxycarbonyl)-4,5-dicarboxycycl[3.3.3]azine

The title compound (70 mg.) was sublimed under reduced pressure (0.04mm.) on an oil-bath at a temperature of 200°C.

The product, which was crystallised from ethanol, proved identical (m.p., m.m.p., i.r. spectrum) with an authentic sample of diethyl cycl[3.3.3]azine-1,3-dicarboxylate.

Yield = 13 mg. (25%)

Reaction of 3,9-dimethylcyclopenta [c,d] cycl [3.3.3]azine with dimethyl acetylenedicarboxylate¹²⁴

A solution of the cyclazine (300 mg.) and dimethyl acetylenedicarboxylate (600 mg.) in anhydrous benzene (10ml.) was heated under reflux on a water-bath for 30 minutes (Note 1). The solution was then filtered to remove decomposition product and the concentrated filtrate was chromatographed on a column of alumina (16" x 1") using initially light-petroleum / benzene (7/3) as eluent. The first fraction from the column yielded unreacted cyclazine (22mg.). The composition of the eluent was then progressively changed to light-petroleum / benzene (3/7) and the second fraction, a greyish-brown band on the column, was isolated as a dark-brown solid. However, the yield of the product (17mg.) was insufficient for rigorous characterisation. The third fraction from the column, a brown compound, which was the major product of reaction, was eluted with benzene and isolated as a dark-brown solid. Crystallisation from ethanol yielded glistening dark-brown needles.

Yield = 198 mg. (40%)

m.p. = 156-157°C.

1-(α, β -diethoxycarbonylvinyl)-3,9-dimethylcyclopenta [c,d] cycl [3.3.3]azine

$C_{22}H_{19}NO_4$ requires : C = 73.12%; H = 5.30%; N = 3.88%

found: C = 72.25%; H = 5.50%; N = 3.80%

I.R. ν (C=O) = 1700 cm^{-1} , 1725 cm^{-1}

Note 1 The course of the reaction was followed by extracting samples at intervals and subjecting these to t.l.c. on alumina. Although unreacted cyclazine still remained after 30 minutes, further reflux led to formation of an increased amount of decomposition product. A three-fold molar excess of the acetylenic ester was used to reduce the reaction period.

ELECTROPHILIC SUBSTITUTION REACTIONS

Formylation of diethyl cycl[3.3.3]azine-1,3-dicarboxylate

Dimethylformamide (76mg.), contained in a 50 ml. flask equipped with a magnetic stirring-bar and a calcium chloride drying-tube, was cooled to $\sim 5^{\circ}C.$, on an ice-bath. Phosphoryl chloride (160g⁺) was added and the viscous solution was stirred for 5 minutes. The ice-bath was then removed and the solution was stirred for a further 20 minutes. Dichloromethane (3ml.) was then added and the solution was cooled to $5^{\circ}C.$, and treated with a solution of the cyclazine (300mg.) in dichloromethane (6ml.). The reaction mixture, which had immediately assumed a purple colour, was refluxed with stirring for 15 minutes and then cooled to room-temperature. A solution of sodium acetate trihydrate (0.64g.) in water (15ml.) was then added and the mixture was refluxed for a further 15 minutes with vigorous stirring. During this time the organic layer changed colour from

purple to brown. After cooling to room temperature, the layers were separated and the aqueous layer was extracted with successive portions of chloroform until the extracts were no longer coloured. The organic layers were combined, dried and evaporated and the brown crystalline residue was taken up in the minimum of chloroform and chromatographed on a column of alumina (20" x 1") using initially a light-petroleum / benzene (1/1) mixture (to reduce the eluting strength of the chloroform) and then benzene.

The first fraction from the column yielded unreacted cyclazine (3 mg.)

The second fraction, a light-brown band on the column, yielded a brown solid which crystallised from ethanol as brown needles

Yield = 39 mg. (12%)

m.p. = 181-182°C.

Diethyl 6-formylcycl[3.3.3]azine-1,3-dicarboxylate

$C_{19}H_{17}NO_5$ requires : C = 67.25%; H = 5.05%; N = 4.13%

found : C = 67.17%; H = 5.27%; N = 3.98%

I.R. ν (C=O) = 1615 cm^{-1} (formyl); 1660 cm^{-1} (ester)

U.V. EtOH: 209(4.32), 285(4.45), 337s(3.57), 382s(3.84),
400(4.11), 490s(4.29), 521(4.73).

The third, and final, fraction which was slightly darker in colour than the second fraction, was eluted with ether and isolated as a brown solid. Although the product was twice recrystallised from ethanol the resultant finely-divided semi-crystalline solid melted over an extended temperature-range. T.l.c. on silica did not reveal the presence of any impurity.

Yield = 159 mg. (51%)

m.p. = 186-190°C.

Diethyl 4-formylcycl[3.3.3]azine-1,3-dicarboxylate

$C_{19}H_{17}NO_5$ requires : C = 67.25%; H = 5.05%; N = 4.13%

found : C = 66.95%; H = 5.36%; N = 4.25%

I.R. ν (C=O) = 1625 cm^{-1} (formyl) ; 1650 cm^{-1} 1680 cm^{-1} (ester)

U.V. EtOH : 207(4.47), 253s(4.08), 286(4.40), 326s(8.76)
412(4.30), 506(4.24).

Acetylation of diethyl cycl[3.3.3]azine-1,3-dicarboxylate

Dimethylacetamide (77mg.), contained in a 50 millilitre flask equipped with a magnetic stirring-bar and a calcium chloride drying-tube, was cooled to $\sim 5^{\circ}C.$, on an ice-bath. Phosphoryl chloride (136 mg.) was added and the viscous solution was stirred for 5 minutes. The ice-bath was then removed and, after further stirring and with warming to room-temperature for 20 minutes, dichloromethane (5ml.) was added. The solution was then cooled to $5^{\circ}C.$, and a solution of the cyclazine (250mg.) in dichloromethane (6ml.) was added. The reaction mixture, which had immediately assumed a purple colour, was refluxed with stirring for 15 minutes and then cooled to room-temperature. A solution of sodium acetate trihydrate (450mg.) in water (15ml.) was then added and the mixture was refluxed for 15 minutes with vigorous stirring. The organic layer changed colour from purple to light-brown. After cooling to room-temperature the layers were separated and the aqueous layer was extracted with successive portions of chloroform until the extracts were no

longer coloured. The combined organic layers were dried and evaporated. The residue was taken up in chloroform and filtered through a short column of alumina, using chloroform as eluent, to remove intractable decomposition product.

The concentrated eluate (ca. 1 ml.) was then applied, uniformly, along one edge of a rectangular film of silica (20 cm. x 20 cm. x 1 mm.) supported on a glass plate [Note 1] and the chromatogram was developed, using the apparatus diagrammatically represented in Fig.46, by continuous elution with a benzene / ether (97/3) solution over 24 hours.

Only one fraction, a pink compound, was present in significant yield; two preceding yellow fractions, and following brown and yellow fractions were present in only minute yield. The section of the chromatogram containing the pink component was carefully removed from the plate and the product was extracted with chloroform. Evaporation of the extract yielded a light-brown solid which crystallised from ethanol as needles.

Yield = 46 mg. (16%)

m.p. = 211-212°C.

Diethyl 6-acetylcycl[3.3.3]azine-1,3-dicarboxylate

$C_{20}H_{19}NO_5$ requires: C = 67.98%; H = 5.42%; N = 3.96%

found : C = 67.57%; H = 5.85%; N = 3.94%

I.R. ν (C=O) = 1610 cm^{-1} (acetyl); 1680 cm^{-1} (ester)

U.V. EtOH: 210(4.39), 290(4.50), 398(4.30), 515(4.64)

Note 1 Kieselgel G (Merck) (30g.) was shaken with distilled water (60ml.) for 90 seconds and the resultant slurry was coated

to a depth of 1 millimetre on a glass plate (20 cm. x 20 cm.) using a Shandon preparative t.l.c. apparatus. The thin layer of silica was then activated by heating the plate in an oven at 110°C., for 3 hours.

Attempted acetylation of diethyl cycl[3.3.3]azine-1,3-dicarboxylate with acetyl chloride

A solution of the cyclazine (100mg.) in acetyl chloride (20ml.) was heated under reflux with sodium bicarbonate (0.5g.) for 1 hour. The acetyl chloride was then evaporated and the dark residue was shaken for 5 minutes with ether (20ml.) and a solution of 2N sodium hydroxide (10ml.). The mixture was filtered to remove insoluble decomposition product and the ethereal layer was dried and evaporated. T.l.c. of a portion of the dark residue on alumina revealed the presence of a large amount of decomposition product together with some unreacted cyclazine and minor amounts of two reaction products (respectively pink and yellow). However, the yields of these products were insufficient for the reaction to merit further investigation.

Reaction of diethyl cycl[3.3.3]azine-1,3-dicarboxylate with benzoyl chloride

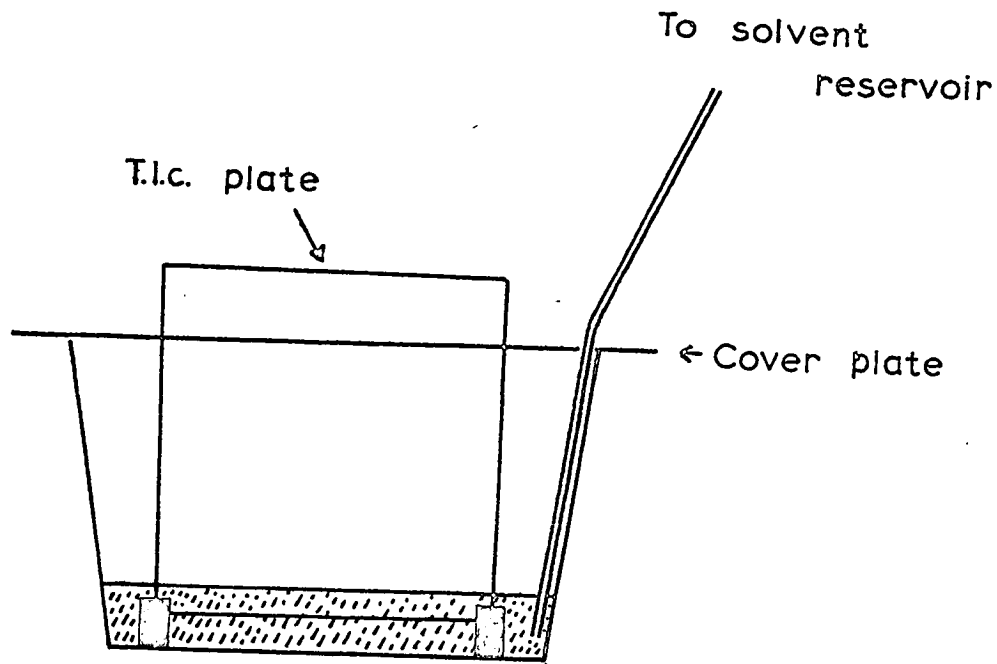
A solution of the cyclazine (100 mg.) in benzoyl chloride (3ml.) was heated under reflux with sodium bicarbonate (0.2g.) for 2 minutes. A colour change from light-yellow to deep-purple occurred. The benzoyl chloride was evaporated under reduced pressure and the residue was taken up in chloroform (15ml.) and

shaken with a 2N solution of sodium hydroxide (10ml.) for 5 minutes. The organic layer was separated, dried and evaporated and the residue was taken up in the minimum amount of benzene and chromatographed on a column of alumina (16" x 1") using benzene / light-petroleum (3/7) as eluent. The proportion of benzene was gradually increased to 70% as development of the column continued. However, the distribution of reaction components proved extremely complex (8 fractions : respectively yellow, purple, brown, olive, purple, dark-purple, purple, dark-brown) and a satisfactory separation could not be achieved.

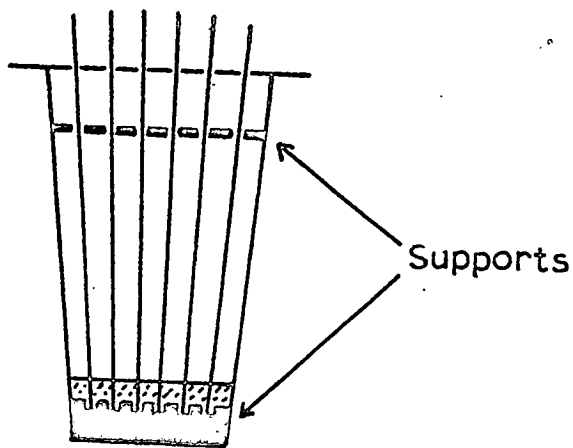
Nitration of diethyl cycl[3.3.3.]azine-1,3-dicarboxylate

A solution of the cyclazine (400mg.) in dry pyridine (30ml.) was cooled to -5°C ., on an ice-salt bath and a solution of tetranitromethane (260mg.) in pyridine (5ml.), which was similarly cooled to -5°C ., was added with rapid stirring. The reaction mixture, which immediately assumed a dark-blue colour, was continuously stirred and allowed to warm to room-temperature over a 30 minute period. It was then evaporated to dryness under reduced pressure on an oil-pump. The residue was taken up in chloroform and filtered through a short alumina column to remove decomposition product. The concentrated filtrate (ca. 3ml.) was then loaded uniformly along the base-line of six separate thin-layer plates of Kieselgel G (each layer 20cm. x 20cm. x 1mm. and each supporting ca. 65 mg. reaction product) [Note 1]. After standing 15 minutes at room-temperature (in order to allow the chloroform to evaporate) the plates were

FIG 46



FRONT VIEW



SIDE VIEW

introduced into a development tank (Fig.46) and were simultaneously developed over a 30 hour period by continuous elution with benzene / ether (50/1). This was achieved by allowing the solvent front to evaporate at the head of the plates, the solvent level within the system being maintained constant by a replenishing device. When development was complete the plates were allowed to dry and the individual fractions (Fig.36) were mechanically separated. Corresponding fractions were then combined and extracted with chloroform. A complete separation, however, of fractions 3,4 and 5 was not initially achieved because these tended to overlap on the chromatogram. The combined chloroform extracts from these overlapping fractions were concentrated and rechromatographed, using the procedure described above, on four separate thin layer plates. A complete separation was then achieved.

Fraction 1

Evaporation of the chloroform extract yielded 3mg.(0.06%) of a light-brown solid. However the extremely low yield of product prevented its characterisation.

Fraction 2

Evaporation of the chloroform extract yielded a dark-purple solid which crystallised from ethanol / benzene as green needles.

Yield = 87 mg. (17%)

m.p. = 153-154°C.

Mass spectrum : M/ϵ (parent) = 401

Diethyl 4,7-dinitrocycl[3.3.3]azine-1,3-dicarboxylate

$C_{18}H_{15}N_3O_8$ requires : C = 53.87%; H = 3.77%; N = 10.47%
found : C = 53.82%; H = 3.86%; N = 10.35%

I.R. ν (C=O) = 1690 cm^{-1} , 1705 cm^{-1}

U.V. EtOH : 207(4.43), 275s(4.20), 292(4.24), 516s(4.30)
548(4.32).

Fraction 3

Evaporation of the chloroform extract yielded a purple solid which crystallised from ethanol / benzene as dark-brown needles.

Yield = 26 mg. (5%)

m.p. = 221-222°C.

Mass spectrum : M/ϵ (parent) = 401

Diethyl 6,7-dinitrocycl[3.3.3]azine-1,3-dicarboxylate

$C_{18}H_{15}N_3O_8$ requires : C = 53.87%; H = 3.77%; N = 10.47%
found : C = 54.08%; H = 4.13%; N = 10.46%

I.R. ν (C=O) = 1680 cm^{-1}

U.V. EtOH : 207(4.49), 284(4.29), 349s(3.84), 504(4.50)

Fraction 4

Evaporation of the chloroform extract yielded a dark-brown solid which crystallised from ethanol / benzene as dark-brown rectangular needles

Yield = 93 mg. (18%)

m.p. = 225-226°C.

Mass spectrum : M/ϵ (parent) = 401

Diethyl 4,6-dinitrocycl[3.3.3]azine-1,3-dicarboxylate

$C_{18}H_{15}N_3O_8$ requires : C = 53.87%; H = 3.77%; N = 10.47%
found : C = 54.75%; H = 4.20%; N = 10.49%

I.R. ν (C=O) = 1700 cm^{-1}

U.V. EtOH : 216(4.42), 276(4.28), 293s(4.13), 366(3.64)
462(4.23), 532(4.31).

Fraction 5

Evaporation of the chloroform extract yielded a dark-purple solid which crystallised from ethanol / benzene as dark-blue microcrystalline plates

Yield = 53 mg. (10%)

m.p. = 211-212°C.

Mass spectrum : M/ϵ (parent) = 356

Diethyl 6-nitrocycl[3.3.3]azine-1,3-dicarboxylate

$\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_6$ requires : C = 60.67%; H = 5.53%; N = 7.86%

found : C = 60.63%; H = 5.23%; N = 8.05%

I.R. ν (C=O) = 1680 cm^{-1}

U.V. EtOH : 206(4.32), 273(4.29), 360i(3.68), 400(3.81),
574(4.59)

Fraction 6

The chloroform extract yielded, on evaporation, a dark blue-purple solid. However, the latter appeared to consist of a mixture of two components since a sample, crystallised from ethanol / benzene melted over a wide temperature range. Slow crystallisation from a slight excess of the same solvent mixture yielded blue-black prisms which possessed a sharp melting-point.

Yield = 45 mg. (9%)

m.p. = 233-234°C.

Diethyl 4,9-dinitrocycl[3.3.3]azine-1,3-dicarboxylate

$C_{18}H_{15}N_3O_8$ requires : C = 53.87%; H = 3.77%; N = 10.47%
found : C = 54.03%; H = 3.91%; N = 10.31%

I.R. ν (C=O) = 1695 cm^{-1}

U.V. EtOH : 209(4.50), 289(4.28), 360(3.87), 563(4.34)

Several other fractions which were present on the chromatogram were in too small yield to be characterised and were ignored.

Note 1 Kieselgel G (90g.) was shaken vigorously with distilled water (180ml.) for 90 seconds and the resultant fluid paste was coated onto three glass plates (20cm. x 20cm. x 1mm.) at a uniform thickness of 1mm. using Shandon t.l.c. equipment. The plates were then dried in an oven at 120°C., for 2 hours.

The procedure was repeated for a further three plates.

SYNTHESIS OF CYCL[3.3.2]AZIN-1-ONE AND SIMPLE DERIVATIVES OF THE DEHYDROCYCL[3.3.2]AZINIUM SYSTEM

Pyrolysis of diethyl quinolizin-4-ylidenemalonate in boiling nitrobenzene

The quinolizine (3.4g.) was dissolved in nitrobenzene (120ml.) and the solution was heated under reflux for 1 hour. The nitrobenzene was then evaporated under reduced pressure on an oil-pump and the residue was taken up in chloroform and chromatographed on a column of alumina (15" x 1½") using chloroform as eluent.

The orange forerunner fraction yielded a yellow solid which crystallised from anhydrous benzene as needles. The product was

readily soluble in water, forming bright-yellow solutions.

Yield = 2.3g. (81%)

m.p. = 287-288°C.

Mass spectrum : M/ϵ (parent) = 241

2-Ethoxycarbonylcycl[3.3.2]azin-1-one monohydrate

$C_{14}H_{11}NO_3 \cdot H_2O$ requires : C = $\frac{64.85}{56.37\%}$; H = $\frac{5.06}{4.31\%}$; N = $\frac{5.41}{5.44\%}$

found : C = 65.32%; H = 4.86%; N = 5.39%

I.R. ν (C=O) = 1620 cm^{-1} (keto); 1660 cm^{-1} (ester)

U.V. EtOH: 219(4.56), 273(4.35), 287s(4.05), 298s(3.89),
380(3.60), 454(3.65).

EtOH/HClO₄ (1%): 218(4.42), 229(4.43), 286(4.01), 305s(3.80),
343(3.69), 386(3.55).

The red, following, fraction from the column yielded a viscous red oil which was obtained as a solid after trituration with ether. The product crystallised from benzene / ethanol (not sufficiently soluble in benzene alone) as red needles. In common with the first fraction, the product readily dissolved in water to yield bright yellow solutions

Yield = 0.18 g. (9%)

m.p. = 90-185°C.

The product consisted of a mixture of cycl[3.3.2]azin-1-one and a 1-hydroxycycl[3.3.2]azinium salt, the latter being derived by protonation of the former at the 1-carbonyl-oxygen atom

I.R. ν (C=O) = 1620 cm^{-1} ; (OH) = 2500-3500 cm^{-1}

U.V. EtOH: 222(4.52), 255(4.20), 293(3.78)
304(3.76), 400s(3.48), 485(3.66)

1-Hydroxycycl[3.3.2]azinium chloride

A solution of 2-ethoxycarbonylcycl[3.3.2]azin-1-one (2.06g.) in 6N hydrochloric acid (35 ml.) was heated under reflux for 1 hour and then evaporated to dryness under reduced pressure. The residual pale-yellow solid crystallised from ethanol to give yellow needles

Crude yield = 1.7g. (97%)

Progressively decomposes when heated $> 150^{\circ}\text{C}$.

I.R. ν (OH) = 2800-3400 cm^{-1}

U.V. EtOH/ HClO_4 (2%): 227(4.53), 291(3.95), 334s(3.54),
395(3.54)

Conversion of the preceding product to cycl[3.3.2]azin-1-one

A solution of 1-hydroxycycl[3.3.2]azinium chloride (1.5g.) in water (10ml.) was cooled ($\sim 5^{\circ}\text{C}$.) on an ice-bath and then treated dropwise, with stirring, with a 4N solution of sodium hydroxide in water (5ml.). The mixture was then extracted with successive portions of chloroform (10-15 x 20ml.) until the extracts were no longer coloured. The combined extracts were dried and evaporated. The residual red oil was obtained as a solid after trituration with ether. The product crystallised from a benzene / ethanol mixture as red needles.

Yield = 1.04g. (83%)

m.p. = $85-190^{\circ}\text{C}$.

The product was identical (i.r., n.m.r., u.v.) with the second product from the pyrolysis reaction, i.e. cycl[3.3.2]-azin-1-one.

1-Ethoxycycl[3.3.2]azinium perchlorate

A solution of cycl[3.3.2]azin-1-one (2.9g.) [Note 1] in dichloromethane (15ml.) was treated with a solution of triethyloxonium fluoroborate ¹²⁷ (3.4g.) in the same solvent. The mixture, which had immediately changed colour from red to yellow, was allowed to stand 15 minutes at room-temperature. The solvent was then evaporated and the yellow residue was taken up in methanol (10ml.) and treated with 70% perchloric acid. Addition of ether precipitated a yellow solid. The product crystallised from ethanol (containing a drop of perchloric acid) as needles

Yield = 3.1g. (55%)

m.p. = 162-163°C.

U.V. EtOH: 229(4.61), 289(4.05), 338s(3.67), 384(3.69)

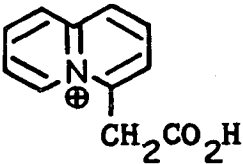
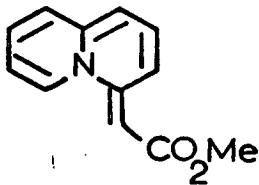
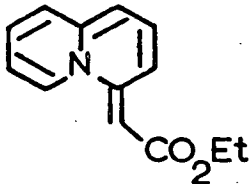
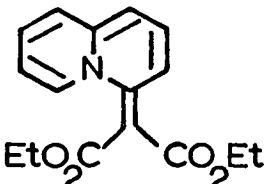
Note 1 The cycl[3.3.2]azin-1-one was chromatographed on alumina immediately before use and dried under vacuum in a desiccator. No attempt was made to crystallise it.

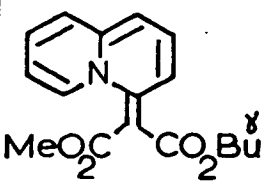
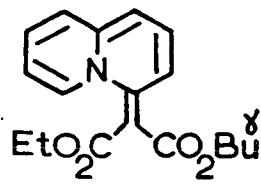
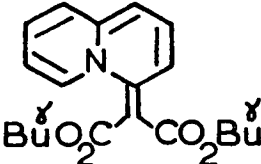
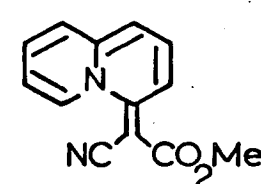
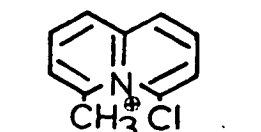
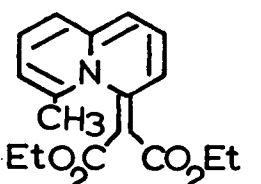
Attempted hydrogenation of 1-hydroxycycl[3.3.2]azinium chloride

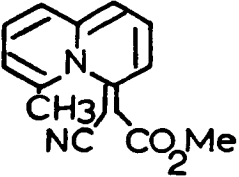
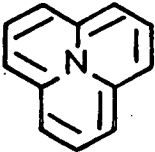
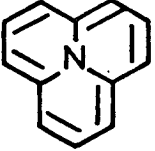
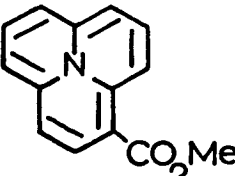
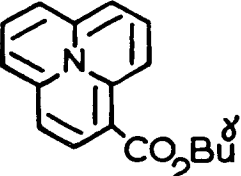
The title compound (0.3g.) was dissolved in glacial acetic acid (35ml.) and the solution was shaken under hydrogen, at atmospheric pressure, with palladium-on-charcoal (35 mg.). However, after 6 hours no hydrogen had been absorbed. The starting material was recovered.

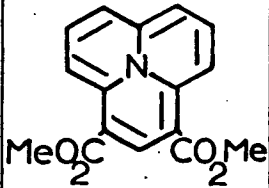
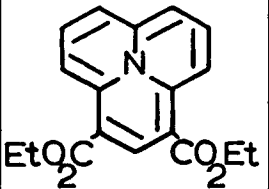
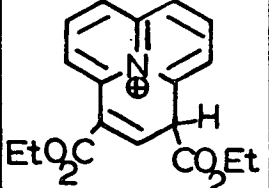
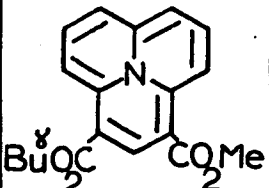
N.M.R. SPECTRAL DATA

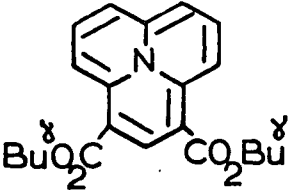

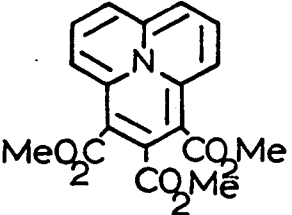
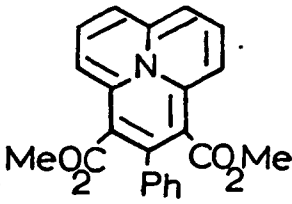
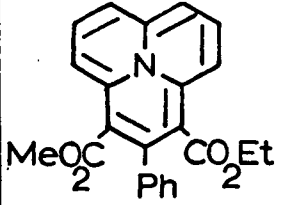
Nuclear magnetic resonance spectra were measured at 60 Mc. / Sec. with reference to tetramethylsilane as internal standard. All spectra were integrated. Chemical shifts are given as τ -values and coupling constants are measured in c. /Sec. d = doublet, t = triplet, q = quartet, m = multiplet, Ar. = aromatic

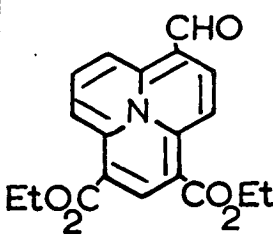
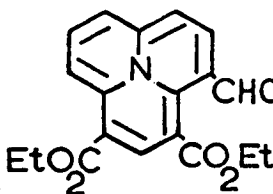
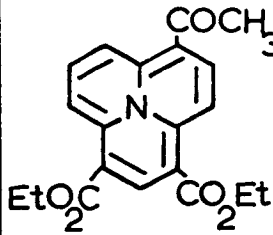
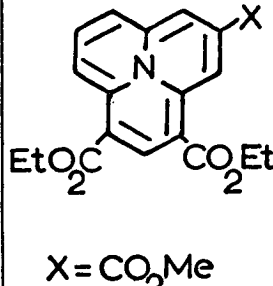
Structure	Solvent	Chemical Shifts	J
	T.F.A.	1-H, 2-H, 3-H, 7-H, 8-H, 9-H, 1.35-2.0m : 6-H, 0.76 d ^a : CH ₂ , 5.19s.	J _{6,7} = 8 J _{6,8} ≈ 1
	CDCl ₃	2-H, 7-H, 8-H, 9-H, 2.65-3.4m: 1-H, 3.60d ^a : 3-H, 1.45d ^a : 6-H, 2.14d ^a : methylene-H, 5.09s: ester-H, 6.33s.	J _{1,2} = 7 J _{2,3} = 9 J _{6,7} = 7 J _a ≈ 1
	CCl ₄	2-H, 7-H, 8-H, 9-H, 2.7-3.55m: 1-H, 3.82d ^a : 3-H, 1.54d ^a : 6-H, 2.27d ^a : methylene-H, 5.20s: ester-H, 5.94q(CH ₂), 8.76t(CH ₃).	J _{1,2} = 7 J _{2,3} = 9 J _{6,7} = 7 J _a ≈ 1
	CDCl ₃	1-H, 2-H, 7-H, 8-H, 9-H, 3-H, 1.85-2.7m : 6-H, 0.94d : ester-H, 5.85q(2 x CH ₂), 8.80t(2 x CH ₃)	J _{6,7} = 7

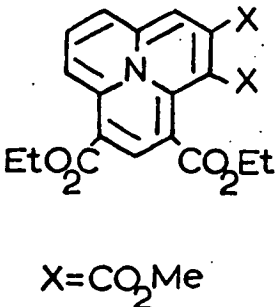
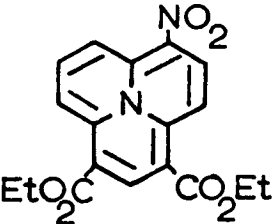
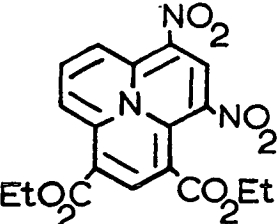
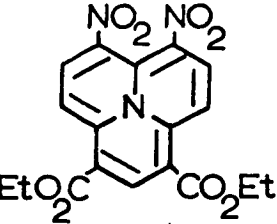
Structure	Solvent	Chemical Shifts	J
	CDCl ₃	1-H, 2-H, 3-H, 7-H, 8-H, 9-H 1.80-2.65m: 6-H, 0.83d : ester-H, 6.27s(Me), 8.65s (Bu ^γ)	J _{6,7} = 7.5
	CDCl ₃	1-H, 2-H, 3-H, 7-H, 8-H, 9-H, 1.85-2.7m: 6-H, 0.95d: ester-H, 5.82q(CH ₂), 8.77t(CH ₃), 8.61s(Bu ^γ)	J _{6,7} = 7.5
	CDCl ₃	1-H, 2-H, 7-H, 8-H, 9-H, 3-H, 1.80-2.75m: 6-H, 1.04d: ester-H, 8.58s(2 x Bu ^γ)	J _{6,7} = 7
	CDCl ₃	1-H, 2-H, 7-H, 8-H, 9-H, 1.96-2.70m: 3-H = 1.86d ^a : 6-H, 1.45d ^a : ester-H, 6.22s(Me).	J _{6,7} = 7 J _{6,8} ≈ 1 J _{2,3} = 8.5 J _{1,3} = 2.5
	T.F.A.	1-H, 2-H, 3-H, 7-H, 8-H, 9-H 1.6-2.15m: CH ₃ , 6.62s.	
	CDCl ₃	1-H, 2-H, 7-H, 8-H, 9-H, 2.07-2.95m: 3-H, 1.93d ^a : CH ₃ , 7.47s: ester-H, 5.89q(2 x CH ₂), 8.86t(2 x CH ₃)	J _{2,3} = 7.5 J _{1,3} = 2

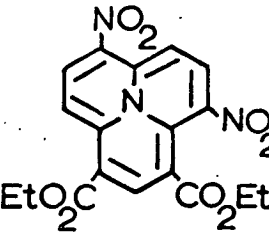
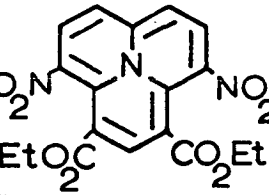
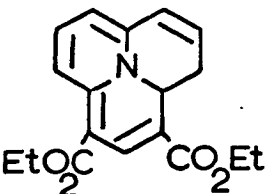
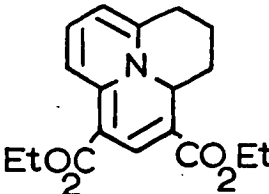
Structure	Solvent	Chemical Shifts	J
	CDCl ₃	1-H, 2-H, 7-H, 8-H, 9-H, 2.1-2.95m: 3-H, 1.77d ^a : CH ₃ , 7.62s: ester-H, 6.28s(Me)	J _{2,3} = 8 J _{1,3} = 2
	(Me ₃ Si) ₂ O	1-H, 3-H, 4-H, 6-H, 7-H, 9-H, 7.93d: 2-H, 5-H, 8-H, 6.35t	J _{1,2} = J _{2,3} = 8
	C ₆ H ₆	1-H, 3-H, 4-H, 6-H, 7-H, 9-H, 8.10d: 2-H, 5-H, 8-H, 6.57t	„
	CDCl ₃	2-H, 4.36d ^b : 3-H, 6.37d: 4-H and 7-H, 5.55d ^{a,c,e} and 5.57d ^{a,c,e} : 5-H, 4.63t ^f : 6-H, 6.01d ^{a,e} : 8-H, 4.42t ^f : 9-H, 3.86d ^a : ester-H, 6.60s.	J _{2,3} = 9.5: J _{4,5} = J _{5,6} = 8: J _{7,8} = J _{8,9} = 9: J _{4,6} = J _{7,9} ≈ 2.
	CDCl ₃	2-H, 4.48d: 3-H, 6.49d: 4-H and 7-H, 5.72d ^{a,c,e} and 5.74d ^{a,c,e} : 5-H, 4.75t ^f : 6-H, 6.17d ^{a,e} : 8-H, 4.54t ^f : 9-H, 4.02d ^a : ester-H, 8.71s	J _{2,3} = 9.5: J _{4,5} = J _{5,6} = 8: J _{7,8} = J _{8,9} = 9: J _{4,6} = J _{7,9} ≈ 2

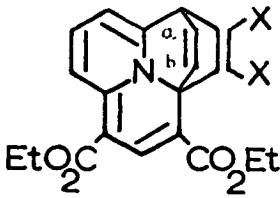
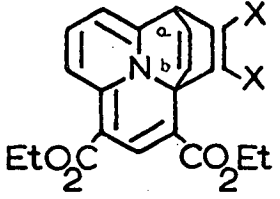
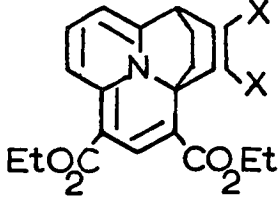
Structure	Solvent	Chemical Shifts	J
 <p>Chemical structure of 2,6-dimethyl-10H-phenanthroline. The structure shows a phenanthroline core with methyl groups (Me) attached to the 2 and 6 positions. The methyl groups are labeled with a subscript '2'.</p>	<p>CDCl₃</p>	<p>2-H, 2.90s: 4-H and 9-H, 3.28d^ad^a: 5-H and 8-H, 3.89t: 6-H and 7-H, 4.76d^ad^a: ester-H, 6.46s(2 x CH₃)</p>	<p>J_{4,5} = J_{5,6} = 8 J_{4,6} = 2</p>
 <p>Chemical structure of 2,6-diethyl-10H-phenanthroline. The structure shows a phenanthroline core with ethyl groups (Et) attached to the 2 and 6 positions. The ethyl groups are labeled with a subscript '2'.</p>	<p>CDCl₃</p>	<p>2-H, 2.98s: 4-H and 9-H, 3.23d^ad^a: 5-H and 8-H, 3.87t: 6-H and 7-H, 4.70d^ad^a: ester-H, 6.00q(2 x CH₂), 8.81t (2 x CH₃)</p>	<p>J_{4,5} = J_{5,6} = 8 J_{4,6} = 2</p>
 <p>Chemical structure of 2,6-diethyl-10H-phenanthroline. The structure shows a phenanthroline core with ethyl groups (Et) attached to the 2 and 6 positions. The ethyl groups are labeled with a subscript '2'.</p>	<p>T.F.A.</p>	<p>1-H, 4.32d: 2-H, 2.35d: 4-H, 1.18t: 5-H, 6-H, 7-H, 8-H, 9-H, 1.4-2.1m: ester-H, 5.40q(CH₂), 5.64q(CH₂), 8.49t(CH₃), 8.68t(CH₃)</p>	<p>J_{1,2} = 7</p>
 <p>Chemical structure of 2,6-diethyl-10H-phenanthroline. The structure shows a phenanthroline core with ethyl groups (Et) attached to the 2 and 6 positions. The ethyl groups are labeled with a subscript '2'.</p>	<p>CDCl₃</p>	<p>2-H, 2.98s: 4-H and 9-H, 3.28d^{a,g} and 3.36d^{a,g}: 5-H and 8-H, 3.91t: 6-H and 7-H, 4.76d^ad^a: ester-H, 6.47s(Me), 8.62s(Bu^δ)</p>	<p>J_{4,5} = J_{5,6} = J_{7,8} = J_{8,9} = 8 J_{4,6} = J_{7,9} ≈ 2</p>

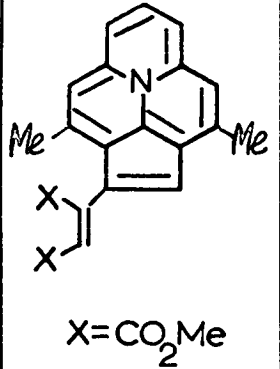
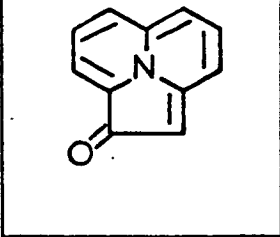
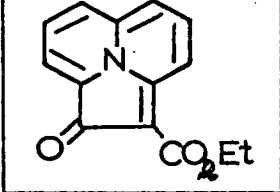
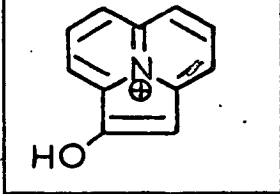
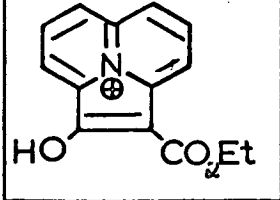
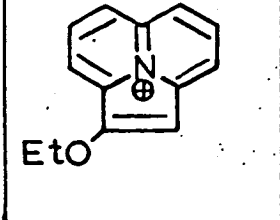
Structure	Solvent	Chemical Shifts	J
	CDCl ₃	2-H, 3.05s: 4-H and 9-H, 3.43d ^a d ^a : 5-H and 8-H, 4.03t: 6-H and 7-H, 4.87d ^a d ^a : ester-H, 8.64s (2 x Bu ^y)	$J_{4,5} = J_{5,6} = 8$ $J_{4,6} \approx 2$
	CDCl ₃	1-H, 5.15d: 2-H, 5.65d: 4-H, 1.23d ^a : 5-H, 6-H, 7-H, 8-H, 9-H, 2.6-3.67m. ester-H, 6.28s(Me), 6.41s(Me), 6.42s(Me)	$J_{1,2} = 2.5$ $J_{4,6} = 9.5$ $J_{5,6} = 1.5$
	CDCl ₃	4-H, 6-H, 7-H, 9-H, 3.77d: 5-H, 8-H, 4.57d: ester-H, 6.35s(Me), 6.49s (2 x Me)	$J_{4,5} = J_{5,6} = 5$
	CDCl ₃	Ar-H, 2.7-3.3m : 4-H and 9-H, 4.99d ^a d ^a : 5-H and 8-H, 4.43t: 6-H and 7-H, 5.45 d ^a d ^a : ester-H 7.09s(2 x Me)	$J_{4,5} = J_{5,6} = 8$ $J_{4,6} \approx 2$
	CDCl ₃	Ar-H, 2.65-3.25m: 4-H and 9-H, 4.97d ^{a,g} and 4.99d ^{a,g} : 5-H and 8-H, 4.42t: 6-H and 7-H, 5.43d ^a d ^a : ester-H 6.57q(CH ₂), 9.47t(CH ₃), 7.08s(CH ₃)	$J_{4,5} = J_{5,6} =$ $J_{7,8} = J_{8,9} = 8$ $J_{4,6} = J_{7,9} \approx 2$

Structure	Solvent	Chemical Shifts	J
	CDCl ₃	Formyl-H, 1.05s: 2-H, 2.40s: 4-H and 5-H, 3.11-3.60q(AB): 7-H, 2.32d ^a : 8-H, 3.33t ^h : 9-H, 2.64d ^a : ester-H, 5.88q(2 x CH ₂), 8.75t(2 x CH ₃)	$J_{4,5} = 9$ $J_{7,8} = J_{8,9}$ $= 8$ $J_{7,9} \approx 2$
	CDCl ₃	Formyl-H, 1.60s: 2-H, 2.23s: 5-H, 3.10d: 6-H, 4.33d: 7-H, 4.08d ^a : 8-H, 3.23t ⁱ : 9-H, 2.50d ^a : ester-H, 5.83q(2 x CH ₂), 8.73t(CH ₃), 8.78t(CH ₃)	$J_{5,6} = 9$ $J_{7,8} = J_{8,9}$ $= 8.5$ $J_{7,9} \approx 2$
	CDCl ₃	Acetyl-H, 7.84s: 2-H, 2.58s: 4-H and 5-H, 3.10-3.35t (~A ₂): 7-H, 2.34d ^a : 8-H, 3.43t ^k : 9-H, 2.78d ^a : ester-H, 5.90q(CH ₂), 8.76t(CH ₃)	$J_{4,5} = 7.5$ $J_{7,8} = J_{8,9}$ $= 8$ $J_{7,9} = J_{4,5}$
 X = CO ₂ Me	CDCl ₃	2-H, 3.13s: 4-H, 3.26s ^a : 6-H, 4.52s ^a : 7-H, 4.94d ^a : 8-H, 4.04t: 9-H, 3.45d ^a ester-H, 6.04q(2 x CH ₂) 8.77t(2 x CH ₃), 6.33s(CH ₃)	$J_{7,8} = J_{8,9}$ $= 8$ $J_{7,9} = J_{4,5}$ ≈ 2

Structure	Solvent	Chemical Shift	J
 <p>X = CO₂Me</p>	CDCl ₃	2-H, 2.57s: 6-H, 4.63s: 7-H, 4.42d ^a : 8-H, 3.45t: 9-H, 2.73d ^a : ester-H, 5.87q(CH ₂), 5.91q(CH ₂), 8.76t(2 x CH ₃), 6.26s(CH ₃), 6.45s(CH ₃)	$J_{7,8} = 8$ $J_{8,9} = 7$ $J_{7,9} \approx 2$
	CDCl ₃	2-H, 2.41s: 4-H, 3.26d ⁿ : 5-H, 2.66d ^o : 7-H, 2.24d ^{a,o} , 8-H, 3.16t: 9-H, 2.56d ^a : ester-H, 5.82q(2 x CH ₂), 8.72t(2 x CH ₃)	$J_{4,5} = 9$ $J_{7,8} = J_{8,9}$ $= 8.5$ $J_{7,9} \approx 2$
	CDCl ₃	2-H, 1.84s: 5-H, 1.39s: 7-H, 1.85d ^{a,p} : 8-H, 2.6 t ^r : 9-H, 2.01d ^{a,p} : ester-H, 5.66q(CH ₂), 5.78q(CH ₂), 8.63t(CH ₃), 8.74t(CH ₃)	$J_{7,8} = J_{8,9}$ $= 8$ $J_{7,9} \approx 2$
	CDCl ₃	2-H, 2.02s: 5-H, 4-H, 8-H, 9-H, 2.27-2.76q ^w (2 x AB): ester-H, 5.73q(2 x CH ₂), 8.66t (2 x CH ₃)	$J_{4,5} = J_{8,9}$ $= 10$

Structure	Solvent	Chemical Shift	J
	<p>CDCl₃</p>	<p>2-H, 2.03s: 5-H, 6-H, 8-H, 9-H, 2.28-2.75m^u (2 x AB): ester-H, 5.71q(CH₂), 5.78q(CH₂), 8.66t (CH₃), 8.73t(CH₃)</p>	<p>J_{5,6} = J_{8,9} = 10</p>
	<p>CDCl₃</p>	<p>2-H, 1.91s: 5-H and 8-H, 2.43dd: 6-H and 7-H, 4.08dd: ester-H, 5.76q (2 x CH₂), 8.72t (2 x CH₃)</p>	<p>J_{5,6} = J_{7,8} = 9</p>
	<p>CDCl₃</p>	<p>2-H, 2.09s: 3a-H, 4.47d^a: 4α-H, 7.3-7.95m: 4β-H, 6.35-6.66m: 5-H, 6-H and 7-H, 3.15-3.85m: 8-H, 2.76q^x: 9-H, 1.26d^a: ester-H, 5.80q(CH₂), 8.70t(CH₃)</p>	<p>J_{3a,4α} = 11 J_{3a,4β} = 3 J_{4α,4β} = 18 J_{4β,5} = 7 J_{7,8} = 8.5 J_{8,9} = 9.5 J_{7,9} \approx 1.5</p>
	<p>CDCl₃</p>	<p>2-H, 2.15s: 3a-H, 4.47d^v: aliphatic-H, 6.7-8.3m: 7-H 3.66d^a: 8-H, 2.80q: 9-H, 1.39d^a: ester-H, 5.79q (2 x CH₂), 8.70t (2 x CH₃)</p>	<p>J_{7,8} = 7 J_{8,9} = 9.5 J_{7,9} \approx 1</p>

Structure	Solvent	Chemical Shifts	J
 <p>X = CO₂Me</p>	CDCl ₃	2-H, 1.77s: 6-H, 5.00q: 7-H, 3.55d ^a : 8-H and etheno-H, 2.65-3.30m: 9-H, 1.55d ^a : ester-H, 6.24s(CH ₃), 6.29s (CH ₃), 5.79q(CH ₂), 5.81q (CH ₂), 6.68t(CH ₃), 6.71t (CH ₃)	J _{7,8} = 7 J _{8,9} = 9.5 J _{7,9} ≈ 1.5 J _{6,a} = 5 J _{6,b} = 2.5
 <p>X = CO₂Bu^γ</p>	CDCl ₃	2-H, 1.78s: 6-H, 5.07q: 7-H, 3.56d ^a : 8-H and etheno-H, 2.55-3.35m: 9-H, 1.56d ^a : ester-H, 8.51s(Bu ^γ), 8.56 (Bu ^γ), 5.78q(CH ₂), 5.80q (CH ₂), 8.69t(CH ₃), 8.71t (CH ₃)	J _{7,8} = 7 J _{8,9} = 9.5 J _{7,9} = 1.5 J _{6,a} = 5 J _{6,b} = 2.5
 <p>X = CO₂Me</p>	CDCl ₃	2-H, 1.89s: 6-H ^y and ethano-H, 6.9-8.2m: 7-H, 3.66d ^a : 8-H, 2.86q ^z : 9-H, 1.50d ^a : ester-H, 6.20s(CH ₃) 6.28s(CH ₃), 5.80q ^y (CH ₂), 8.69t(CH ₃), 8.71t(CH ₃), 5.85q ^y (CH ₂).	J _{7,8} = 7 J _{8,9} = 9.5 J _{7,9} ≈ 1.5

Structure	Solvent	Chemical Shifts	J
 <p>X=CO₂Me</p>	CDCl ₃	2-H, 2.87s; 4-H and 8-H, 3.52s and 3.45s: 5-H, 6-H and 7-H, 2.65-3.25m; maleoyl-H, 4.12s; CH ₃ -H, 7.47s, 7.59s: ester-H, 6.04s(Me), 6.21s(Me)	
	CDCl ₃	3-H, 4-H, 5-H, 6-H, 7-H and 8-H, 1.4-1.6m; 2-H, 3.98s: hydroxyl-H (due to partial protonation), 6.47s	
	CDCl ₃	3-H, 4-H, 5-H, 6-H, 7-H and 8-H, 1.4-2.3m: ester-H, 5.55q(CH ₂), 8.54t(CH ₃)	
	T.F.A	3-H, 4-H, 5-H, 6-H, 7-H and 8-H, 0.8-1.5m: 2-H, 2.65s	
	T.F.A	3-H, 4-H, 5-H, 6-H, 7-H and 8-H, 0.6-1.3m: ester-H, 5.16q(CH ₂), 8.32t(CH ₃)	
	T.F.A	3-H, 4-H, 5-H, 6-H, 7-H and 8-H, 0.85-1.4m: 2-H, 2.70s: Et-H, 5.30q(CH ₂), 8.25t(CH ₃)	

- a - Further split by coupling to a meta-proton
- b - Partially obscured by the triplet attributable to either the 5- or the 8-proton.
- c - The doublets at 5.55 τ and 5.57 τ are partially superimposed.
- e - The assignments of the 4-, 6- and 7- proton resonances may possibly be interchanged.
- f - The assignments of the 5- and 8- proton resonances may possibly be interchanged.
- g - The 4- and 9-proton doublets are partially superimposed.
- h - Partially obscured by AB quartet.
- i - Partially obscured by 5-proton doublet.
- k - Partially obscured by 4- and 5- proton triplet.
- n - The 4-proton doublet is obscured by the 8-proton triplet.
- o - The 5- and 7- proton doublets are partially superimposed.
- p - The 7- and 9- proton doublets are partially superimposed.
- r - Extraneous signals, due to 1) occluded benzene and 2) chloroform impurity in the solvent, overshadow the 8-proton triplet.
- u - Consists of two partially superimposed AB quartets.
- v - Shows poorly resolved fine-splitting.
- w - An extraneous signal, due to occluded benzene, overshadows the highest field component of the quartet.
- x - An extraneous signal, due to chloroform impurity, is present at 2.70 τ .
- y - The methylene resonances integrate for 5-protons. It is possible that the 6-proton resonance is included here.
- z - An extraneous peak, due to occluded benzene, is present at 2.63 τ .

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Synthesis of Pyrido[2,1,6-*de*]quinolizine (Cycl[3,3,3]azine)

By D. FARQUHAR and D. LEAVER*

(Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh, 9)

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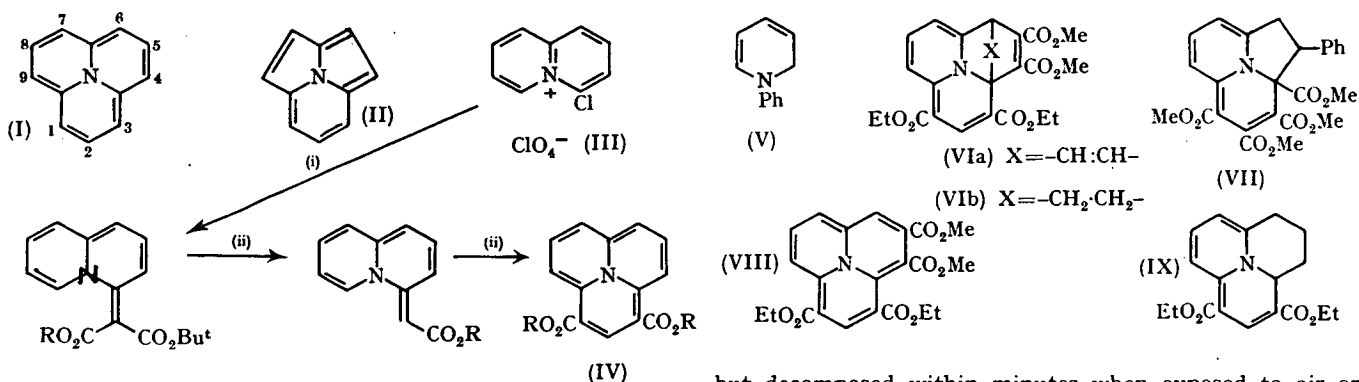
By D. FARQUHAR and D. LEAVER*

(Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh, 9)

PYRIDO[2,1,6-*de*]QUINOLIZINE (I), otherwise known¹ as cycl[3,3,3]azine, has been the subject of theoretical studies^{1,2} which have predicted a resonance energy greater than that of the highly stable and well-known^{1,3} compound pyrrolo[2,1,5-*cd*]indolizine (cycl[3,2,2]azine) (II). Despite considerable effort,⁴ however, the synthesis of the pyridoquinolizine has not hitherto been accomplished.† We now report the synthesis of this ring-system, from 4-chloroquinolizinium perchlorate (III),⁶ by the route outlined below.

(λ_{\max} 453 nm. in EtOH) to dark brown. Hydrolytic procedures were therefore precluded and, in order to obtain the parent compound (I), it was necessary to heat the di-*t*-butyl ester (IV; R = Bu^t) in a sealed, evacuated tube at 250–300° for 5 min. The tube was then opened and the product was recovered from it by vacuum sublimation.

The pyridoquinolizine (I) was a brown, crystalline solid that gave bright yellow solutions (λ_{\max} 458 nm. in cyclohexane) in ethers or hydrocarbons; it was stable in nitrogen



Reagents: (i) NaCH(CO₂R)·CO₂Bu^t·THF; (ii) HCl-PhH (for R=Et) or PhSO₃H-AcOH (for R=Bu^t), NaOH; (iii) HC:C-CO₂R-PhNO₂ at 210°.

Evidence for the structure of the diester (IV; R = Et) was provided by its ¹H n.m.r. spectrum which showed the following signals: τ 2.84 (s, 1H, 2-H) 3.86 (t, 2H, 5-H and 8-H) 3.23 (dd, 2H, 4-H and 9-H), and 4.77 (dd, 2H, 6-H and 7-H). The coupling constants were $J_{4,5} = J_{5,6} = 8.1$ and $J_{4,6} = 1.7$ Hz.

The brown, crystalline esters (IV) were stable in the solid state but their solutions, particularly those in hydroxylic solvents, rapidly changed from bright yellow

but decomposed within minutes when exposed to air or when dissolved in CHCl₃, CCl₄, or hydroxylic solvents. The n.m.r. spectrum‡ of compound (I), in bis(trimethylsilyl) ether, showed a triplet centred at τ 6.35 (protons 2, 5, and 8) and a doublet of twice the intensity centred at τ 7.93 (protons 1, 2, 4, 6, 7, and 9), the coupling constant being *ca.* 8 Hz. These signals are respectively 2.2 and 2.8 p.p.m. upfield of their counterparts in the spectrum of the 1,2-dihydropyridine (V)⁷ and the τ -values are among the highest yet reported for protons joined to trigonal carbon. We regard this high degree of shielding as evidence of a paramagnetic ring-current⁸ in the peripheral, non-aromatic system of 12 π -electrons. The contrast with the typically aromatic pyrroloindolizine (II), which contains

† Cyclopenta[*cd*]cycl[3,3,3]azines are known⁵ but their properties cannot be expected to reflect those of the parent, tricyclic ring-system.

‡ The spectrum also indicated contamination by a trace of *t*-butyl pyrido[2,1,6-*de*]quinolizine-1-carboxylate, a compound that may be obtained in the pure state by pyrolysing the di-*t*-butyl ester under less vigorous conditions.

10 peripheral π -electrons and gives proton resonances⁹ in the range τ 2.1—2.8, is striking.

We have not yet investigated the chemical properties of the parent compound (I) but those of the diester (IV; R = Et) show further evidence of lack of aromatic character. Thus the ester reacted with dimethyl acetylenedicarboxylate, in boiling benzene, to give a red Diels-Alder adduct (VIa), the structure of which follows from the resemblance of its u.v.-visible spectrum to that of the 4H-quinolizine (VII)¹⁰ and from its ready conversion into a dihydro-derivative (VIb) that lost ethylene above 220° to give the tetracarboxylic ester (VIII). Catalytic hydrogenation of the diester (IV; R = Et) proceeded readily,

at room temperature and atmospheric pressure, to give a red tetrahydro-derivative (IX), the u.v. visible spectrum of which was closely similar to that of the adduct (VIa).

Despite its lack of aromatic character according to the foregoing criteria, the diester (IV; R = Et) participated in substitution reactions with certain electrophilic reagents (notably tetranitromethane, *NN*-dimethylformamide-phosphoryl chloride, and acetyl chloride). We do not accept these reactions as evidence of aromaticity but prefer to regard them as analogous to those of a typical enamine.

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