CYCLAZINES AND RELATED HETEROAROMATIC COMPOUNDS CONTAINING BRIDGE-HEAD NITROGEN ATOMS

David Skinner, B.Sc.

A Thesis presented for the degree of
Doctor of Philosophy

University of Edinburgh 1983
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Declaration

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself, and that it has not been submitted in any previous application for a higher degree.

Post-graduate Courses

The following is a statement of post-graduate courses attended during the last three years:

Homogeneous Catalysis, Dr. T.A. Stephenson
Molecular Interaction in Industrial Food Research, Unilever Research
β-Lactam Antibiotics, Glaxo Group Research
Pulse sequences and their applications to N.m.r. spectroscopy, Dr. G.A. Morris
The Chemistry of Photographic Processes, Dr. L.A. Williams
1,3-Dipoles in Organic Synthesis, Dr. J.T. Sharp & Dr. R.M. Paton
Current Topics in Organic Chemistry, various lecturers
Edinburgh University Chemistry Department Seminars
To Carole
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Abstract

The research contained within this thesis involves the synthesis of various cyclazines containing a pyrrolizine moiety. The syntheses of \([2.2.3\)cyclazines (pyrrolo\([2,1,5-cd\)indolizines), cyclopenta[\(h\)[2.2.4]cyclazines (cyclopenta[4,5]azepino[7,1,2-cd]pyrrolizines), and the new ring system pyrazino[2,1,6-cd:3,4,5-c'd']dipyrrolizine are described.

Two stereoisomeric 3-[2-(N,N-dimethylamino)prop-2-enylidene-3\(H\)-pyrrolizine-7-carboxylates were obtained as by-products in the synthesis of ethyl pyrrolo[2,1,6-cd]indolizine-2-carboxylate. These compounds were shown, however, not to be intermediates in the formation of the cyclazine. A similar type of compound was also obtained during an attempted synthesis of methyl pyrazino[2,1,6-cd]pyrrolizine-1-carboxylate.

Various cyclopenta[2.2.4]cyclazines bearing substituents at C-1 or C-2 have been prepared and their UV-visible spectra have been compared with that of the parent compound, and similarities to azulenes have been noted.

The largest part of this thesis is concerned with pyrazino-[2,1,6-cd:3,4,5-c'd']dipyrrolizine and various possible routes to it are described. Attempts to prepare the pyrazinodipyrrolizine using pyrrolizine coupling reactions were unsuccessful, as was a route from a dipyrrolo[1,2-a:1',2'-d]pyrazine derivative. The synthesis of the pyrazinodipyrrolizine was finally achieved from pyrazino[2,1,6-cd]pyrrolizine via a pyrrolo[2',1':3,4]pyrazino[2,1,6-cd]pyrrolizine derivative.

A route to the parent pyrrolo[2',1':3,4]pyrazino[2,1,6-cd]-pyrrolizine, based on a model reaction involving the preparation
of indolizine directly from pyridine, was unsuccessful. However, a di(methoxycarbonyl) derivative of pyrrolo[2'1':3,4]-pyrazino[2,1,6-cd]pyrrolizine was prepared by another route, and converted into a tetra(methoxycarbonyl)pyrazino[2,1,6-cd:3,4,5-c'd'dipyrrolizine which was hydrolysed and decarboxylated to give the parent pyrazinodipyrrolizine.

The physical properties of this novel bridged[14]annulene have been compared with those of similar systems and it is concluded that the compound exhibits "aromatic character."

Finally, some chemical properties of pyrrolizin-3-one have been investigated briefly.
The trivial name cyclazine was given by Boekelheide to the general case of a conjugated, unsaturated cyclic molecule held planar by three covalent bonds to an internal nitrogen atom. The individual members are distinguished by specifying the number of atoms on the peripheral cycle between points of bonding to the internal nitrogen. Minor modifications of Boekelheide's original proposals for nomenclature are now used. Structures (1), (2), (3), and (4) are thus termed, respectively, [2.2.3]cyclazine, [3.3.3]cyclazine, [2.3.4]cyclazine, and [3.4.4]cyclazine.

The systematic fusion nomenclature for these compounds, based on IUPAC rules, is derived from the largest named nitrogen-containing ring system present in the molecule. Compounds (1) and (2) are thus respectively designated pyrrolo[2,1,5-cd]indolizine and pyrido[2,1,6-de]quinolizine. The following review of cyclazine chemistry is restricted mainly to those containing a pyrrolizine moiety and to cyclazine-like systems containing two internal nitrogen atoms. Systems of these types form the subject of the original research described in the main part of the thesis.
1. [2.2.3]Cyclazines

[2.2.3]Cyclazines, first synthesised by Boekelheide\textsuperscript{1} in 1959, are stable aromatic compounds and may now be synthesised by a variety of methods, most of which involve indolizines.

1.1 Synthesis of [2.2.3]Cyclazines

1.1.1 Intramolecular Condensation of Indolizines

The reactivity of the methyl group in 5-methylindolizine is similar to that of 2-methylpyridine and this allows the introduction of functional groups. Thus, treatment of 5-methyl-2-phenylindolizine (5) with $n$-butyllithium followed by N,N-dimethylformamide yielded 5-formylmethyl-2-phenylindolizine (6)\textsuperscript{1}. Similarly, treatment of 5-methylindolizine (8) with
n-butyllithium and N,N-dimethylbenzamide yielded 5-phenacylindolizine (9). Cyclodehydration by the method of Bradsher\textsuperscript{4,5}, of both (6) and (9) gave good yields of 2-phenyl-[2.2.3]cyclazine (7)\textsuperscript{1}. The parent cyclazine (1) was synthesised by an analogous sequence from 5-methylindolizine, but the yield was much lower at the cyclodehydration stage.

Another similar approach to the system was accomplished by Leaver\textsuperscript{6,7}. Thus, 5-methyl-2-phenylindolizine reacted with ethoxalyl chloride to give the 1,3-diethoxalyl derivative (10).

\[
\begin{align*}
\text{COCO}_2\text{Et} & \quad \text{COCO}_2\text{Et} \\
\text{Ph} & \quad \text{EtOH} \\
\text{CH}_3 & \quad \text{Ph}
\end{align*}
\]

Heating this compound with sodium ethoxide in dry ethanol converted it partly into the [2.2.3]cyclazine (11) and partly into the sodium salt of the hydroxy[2.3.3]cyclazinone (12).

1.1.2 Cycloaddition to Indolizines

The preparation of the [2.2.3]cyclazine derivative (13) by Godfrey\textsuperscript{8} opened up a new preparative path to [2.2.3]cyclazines. This is probably the most extensively used method of preparing [2.2.3]cyclazines to date. For example,
Boekelheide was able to react indolizines with dimethyl acetylenedicarboxylate (DMAD) in the presence of a dehydrogenation catalyst to give 1,2-di(methoxycarbonyl)[2.2.3]-cyclazines (18)\textsuperscript{9-12}. The reaction is thought to proceed either by a concerted [8+2]-cycloaddition to give (17) or by electrophilic attack of the activated acetylenic ester at the
3-position of the indolizine (14) nucleus, to yield a zwitterionic species (16). Cyclisation of this initial adduct would then give (17), and dehydrogenation would lead to formation of the diester (18). The dihydro-derivative (19) was obtained as a by-product and is thought to be formed by hydrogen migration in the intermediate (17). The parent cyclazine was obtained in good yield from the diester (18) by hydrolysis with methanolic potassium hydroxide and subsequent decarboxylation of the acid with copper chromite in quinoline.

Extension of the above [8+2]π cycloaddition of an activated acetylenic ester to various substituted indolizines has led to a large variety of [2.2.3]cyclazine derivatives\(^{13-20}\).

Attempts to react indolizines with other dienophiles including diphenylacetylene and diethyl azodicarboxylate to give [2.2.3]-cyclazines were unsuccessful\(^{10}\).

Extension of the above reaction has led to the synthesis of azacyclazines from azaindolizines. Thus, Boekelheide was able to synthesise 1-aza[2.2.3]cyclazines (20) and 5-aza[2.2.3]-cyclazines (21) from a 1-azaindolizine and a 6-azaindolizine respectively. The 6-aza[2.2.3]cyclazine (22) has also been prepared from 7-azaindolizine\(^{21}\), although no experimental details have been published to date.
1.1.3 Condensation and Cycloaddition Reactions of Pyrrolizines and Methylenepyrrrolizines

Based on the reaction of Jutz and his co-workers\textsuperscript{22}, in which pyrenes (26) were synthesised by the reaction of iminium salts (24) with the phenalenyl anion (23), Leaver\textsuperscript{23} was able
to synthesise the parent [2.2.3]cyclazine from pyrrolizine and the iminium salt (24), using sodium hydride as the base. The yield was too low to be of any real value as a preparative method for [2.2.3]cyclazines.
The reaction of pyrrolizine with N,N-dimethylformamide and phosphoryl chloride gave the Vilsmeier salt (28)\textsuperscript{23,24}. Treatment of the salt with sodium hydride gave the conjugate base which, although unstable, reacted \textit{in situ} with dimethyl acetylenedicarboxylate to give the [2.2.3]cyclazine derivative (29). Similar work by Flitsch\textsuperscript{25} has taken this reaction further, to give 2-chloro[2.2.3]cyclazine (35) (R=H), which cannot be synthesised by electrophilic substitution of the parent compound, and also to give the 4-benzoyl[2.2.3]cyclazine derivative (40). These were obtained by treatment of the salts (34) and (39) with triethylamine in the presence of dimethyl acetylenedicarboxylate. The perchlorate (34) was prepared in good yield by the reaction of 2,3-dihydro-1H-pyrrolizin-1-one (33) with the Vilsmeier complex and the salt (39) was similarly obtained from 2-benzoyl-3H-pyrrolizine (38). Further reaction of the salts (28) and (34) with dimethylthioformamide and acetic anhydride gave mixtures of isomers containing the bismethylene-pyrrolizinium derivatives (30) and (36). These reacted with ammonia to give 6-aza-[2.2.3]cyclazines (31) and (37) respectively\textsuperscript{23-25}. 6-Nitro-[2.2.3]cyclazine (32) was obtained by reaction of the salt (30) with nitromethane in the presence of potassium t-butoxide\textsuperscript{23,24}. 
Cl
R
(35) R=CO₂Me,CO₂H,H.

(33) → (34)

1) POCl₃/DMF
2) NaClO₄

(36) → (37)

NH₃

(38)

(39)

(40)
Johnson and Jones also used the cycloaddition of a methylene-3H-pyrrolizine to obtain a [2.2.3]cyclazine\(^\text{26}\).
Thus, 3-ethoxycarbonylmethylene-3H-pyrrolizine (43), prepared from pyrrolizin-3-one and the Wittig reagent (42), reacted

\[
\begin{align*}
\text{Ph}_3\text{P}=\text{CH-CO}_2\text{Et} & \quad \text{Wittig} \quad \text{DMAD, Toluene} \\
\text{(41)} & \quad \text{(42)} \\
\text{MeO}_2\text{C-CO}_2\text{Me} & \quad \text{CO}_2\text{Et} \quad \text{(44)} \\
\end{align*}
\]

slowly with dimethyl acetylenedicarboxylate to give a mixture of products from which the [2.2.3]cyclazine (44) was isolated.

1.1.4 Direct Formation from Pyridines

Acheson has investigated the reactions of numerous pyridine derivatives with activated acetylenes and has observed the formation of [2.2.3]cyclazines in some cases. Yields are generally low and the reactions are usually thought to proceed via intermediate indolizines, though these have not always been observed directly. Two typical examples are shown in the following Schemes\(^\text{14,27-29}\).
A novel approach to 1-acyl[2.2.3]cyclazines has been reported by Pohjala\textsuperscript{30,31} exploiting the Perkin reaction of pyridine-2-carbaldehyde in the presence of vinylic ketones and esters. A typical example is the reaction of pyridine-2-carbaldehyde (51) with acetic anhydride and potassium acetate in the presence of methyl vinyl ketone to give 1-acetyl[2.2.3]cyclazine (56) in high yield. This reaction was shown to proceed via 3-acyloxyindolizine intermediates (54)\textsuperscript{32} and the proposed mechanism involves a disproportionation step [to form (53)] which has not been fully elucidated.
1.2 Physical and Chemical Properties of [2.2.3]Cyclazines

The physical and chemical properties of [2.2.3]cyclazines have been the subject of a great deal of work. Early simple HMO calculations\textsuperscript{1} predicted that this molecule should show a marked stability and more recent calculations of resonance energy per $\pi$ electron (REPE), using the HMO method together with an appropriate reference structure, have shown that [2.2.3]cyclazine has a value of REPE, 0.040$\beta$\textsuperscript{33}. This is comparable with that of pyrrole (0.039$\beta$) and appreciably greater than that of indolizine (0.027$\beta$). These calculations also suggested that electrophilic substitution should occur at position 1.

Experiments have confirmed these predictions\textsuperscript{1}, the parent cyclazine being a non-basic ($pK_a = -2.8$)\textsuperscript{34}, crystalline, fluorescent yellow compound which is stable to light, heat, and air. In terms of reactivity, [2.2.3]cyclazine shows the normal behaviour of a stable aromatic system, undergoing substitution reactions smoothly and in good yields. The heterocyclic system has been shown to be more prone to electrophilic attack than phenyl groups substituted in the 2- and 3-positions\textsuperscript{1}.

Nitration, bromination and acetylation of [2.2.3]cyclazine yielded 1-mono and 1,4-disubstitution products. Reaction at positions 2,5 and 6 have not yet been observed; attempts at nucleophilic substitution using methyllithium resulted in recovery of starting materials\textsuperscript{12}. 
[2.2.3]Cyclazines are diatropic. The $^1$H n.m.r. spectrum of the parent compound (1) consists of an $A_2B$ multiplet arising from the protons in the six-membered ring and one $AB$ quartet from the two pairs of protons of the five-membered rings. The assignment of the higher-field doublet of the $AB$ spectrum to the 1- and 4-positions was based on the observation that this absorption was absent in the spectrum of dideuterio-[2.2.3]cyclazine prepared by acid-catalysed hydrogen-deuterium exchange$^{35}$. The crystal structure determination for 1,4-dibromo[2.2.3]-cyclazine (59) revealed that the molecule is probably planar or, if not, the nitrogen atom is less than 0.07Å out of the mean plane of the molecule$^{36}$. 
The UV spectrum of [2.2.3]cyclazine in ethanol shows fine structure, and calculations\textsuperscript{34} have assigned electronic transitions to these. The UV spectrum of the conjugate acid of (1) was similar to that of a benzofulvene derivative, confirming that protonation occurs on position 1\textsuperscript{34}.

The REPE value for 6-aza[2.2.3]cyclazine has been calculated\textsuperscript{37} and is comparable to that of the parent [2.2.3]cyclazine.

The \textsuperscript{1}H n.m.r. spectrum of 6-aza[2.2.3]cyclazine is simple, showing a two proton singlet and a four proton AB system\textsuperscript{23}. The low- and high-field components of the AB multiplets being assigned to H-2,3 and H-1,4, respectively.

The UV spectrum of the 6-azacyclazine is similar to that of [2.2.3]cyclazine, the absorptions being virtually the same wavelength and of comparable intensity. However, unlike [2.2.3]cyclazine the azacyclazine showed quite large spectral changes upon addition of small amounts of acid\textsuperscript{23}.

The chemical properties of 6-aza[2.2.3]cyclazine are comparable in certain respects to those of pyridine. Thus, electrophilic substitution at carbon is difficult since protonation (or other electrophile attachment) initially occurs at nitrogen to give a system which is positively charged, so inhibiting further attack by an electrophilic species. Where electrophilic substitution has been successful, eg with Br\textsubscript{2}, substitution has occurred at the 1- and 4-positions\textsuperscript{23}. As in pyridine, quaternisation reactions are possible, e.g. with methyl iodide to give (60)\textsuperscript{23}.
Nucleophilic attack of the 6-azacyclazine with phenyllithium resulted in substitution at the 5- and 7-positions \(^{23}\). 

2.1.1 Synthesis of [2.2.4]Cyclazinylium Salts

Recently Flitsch \(^{38,39}\) reported the synthesis of the 10π-electron [2.2.4]cyclazinium perchlorates (61). These were prepared by two independent routes.

Route a: The parent system (61) was formed by the reaction of a Vilsmeier reagent with 5-(t-butoxycarbonylmethylene)-5H-pyrrolo[1,2-a]azepine (62) followed by electrocyclic ring
closure and elimination of dimethylamine. The \( t \)-butoxycarbonyl group was simultaneously removed by acid catalysed fragmentation. The 5-cyano derivative was also prepared by an analogous route.

**Route b:** Derivatives of [2.2.4]cyclazinium salts are also accessible from 3,5-bismethylenezyrlorolizinium salts \((30)\) and \((36)\) via cycloaddition reactions. Thus treatment of \((36)\) with ethyl vinyl ether or with N-morpholinocyclopentene yielded \((64)\) and \((65)\) respectively.
2.1.2 Physical and Chemical Properties of [2.2.4]-Cyclazinium Salts

[2.2.4]Cyclazinium salts are stable diatropic compounds as expected from PMO-theory. The \(^1\)H n.m.r. spectrum of the parent system (61) shows a four proton AB system and a multiplet for the protons in the seven-membered ring.

2.2.1 Synthesis of Cyclopenta[h][2.2.4]cyclazine

The parent 14π-electron cyclopentacyclazine (66) has been synthesised by Leaver by two routes. The initial route was based on the Jutz synthesis of azuleno[5,6,7-\(\phi d\)]phenalene (67) and \(s\)-indacene (68) by reaction of the cyclopentadiene iminium salt (69) with the conjugate bases of phenalene and cyclopentadiene respectively. Thus, 3\(\phi\)-pyrrolizine (27) reacted with the perchlorate (69) and sodium hydride to give cyclopenta[h][2.2.4]cyclazine. Improved yields were obtained when the pyrrolizinium perchlorate (30) and cyclopentadiene were treated with sodium hydride. More recently Flitsch
reported the use of this second method to synthesise 2-chlorocyclopenta[h][2.2.4]cyclazine.

2.2.2 Physical and Chemical Properties of Cyclopenta[h]-[2.2.4]cyclazine

Cyclopenta[h][2.2.4]cyclazine (66), is a green crystalline solid, has 14 peripheral π-electrons and is an analogue of azulene. Its visible and near UV spectrum is comparable to that of azulene. The ¹H n.m.r. spectrum of the parent system shows a four proton AB system, a 2 proton singlet and a three proton AB₂ system. Protonation in trifluoroacetic acid occurs on position 6 (8). The 6,8-dideuterio-compound was recovered from a solution of the cyclazine in deuteriotrifluoroacetic acid. Other electrophilic substitutions also occur in the 6- and 8-positions.

3. Cyclazine-type Compounds Containing Two Internal Nitrogen Atoms

Cyclazines in which the peripheral cycle contains 14π-
electrons are unknown and the constraints of individual ring size will create obvious difficulties in constructing molecules with more than 14 peripheral π-electrons unless two bridging nitrogen atoms are included.

3.1 Synthesis and Properties of 8b,8c-Diazapyracylenes

Paudler was able to synthesise the parent compound (71) by reaction of the tetraketone (70) with hydrazine followed by dehydrogenation. The crystal structure has been determined and, along with 1H n.m.r. data, has established that this compound is a planar 12π-monocyclic antiaromatic compound.

More recently, Flitsch synthesised the 3,8-dicyano-derivative. Thus, the dinitrile (72) reacted with a Vilsmeier reagent to give the aldehyde (73). Intramolecular condensation afforded the 8a,8b-diaza-as-indacene (74) which was transformed into 3,8-dicyano-8b,8c-diazapyracylene (75) under the conditions of the Vilsmeier reaction.
The chemical properties of 8b,8c-diazapyracylene (71) have not been extensively studied but, as might be expected, hydrogenation takes place only in the 3,4- and 7,8-positions leaving two aromatic pyrrole nuclei.

3.2 10b,10c-Diazadicyclopenta[ef,kl]heptalene.

Attempts to synthesise the parent molecule (77) by dehydrogenation of its dihydro-derivative (76) were unsuccessful. The rearranged, unstable 1,4;8,11-bisimino[14]annulene (78) was obtained when (76) was treated with potassium
t-butoxide in dimethyl sulphoxide\textsuperscript{47,48}. The chemical shift difference between the inside and outside protons of (78) clearly revealed the expected diamagnetic ring current.

The diazadicyclopentaheptalene derivative (80) has been synthesised by Flitsch\textsuperscript{49}. Thus intramolecular condensation of the tetranitrile (79), followed by dehydrogenation and acetylation gave the diatropic 4,9-bis(diacetylamino)-3,8-dicyano-10b,10c-diazadicyclopenta[ef,kl]heptalene.

HMO Calculations show that the HOMO of (77) is antibonding at the N-N bond and this may be responsible for failure to obtain the parent compound. The \( \pi \)-electron density is high at positions 3,5,8, and 10; electron-withdrawing substituents at these positions should therefore stabilise the system.
3.3 Synthesis and Properties of Pyrazino[2,1,6-cd:5,4,3-c'd']diindolizines

Leaver\(^50\) reported the synthesis of cyclazine-like systems in which the two internal bridgehead nitrogen atoms are not directly linked and which possess a [16]annulene periphery. These were synthesised by two routes.

Route a: This was based on the well known synthesis of indolizines from pyridinium ylides, first reported by Boekelheide\(^11\) and later modified by Henrick \textit{et al.}\(^51\) who observed spontaneous dehydrogenation of the intermediate adducts. By using Henrick's procedure, Leaver was able to synthesise the tetraester (82) by treatment of the bisquaternary salt (81) with sodium hydride followed by dimethyl acetylenedicarboxylate.
Route b: This route was based on the indolizine synthesis of Kröck and Kröhnke\textsuperscript{52} which depends on the acylation of 2-methylpyridinium ylides. Thus, treatment of the bis-quaternary salt (83) with triethylamine in acetic anhydride
gave a mixture of the 1,6-dimethyl- and 2-acetyl-1,6-dimethyl-pyrazinodiindolizines (84) and (85).

The $^1$H n.m.r. spectra of the pyrazinodiindolizines showed appreciable shielding, relative to analogously substituted simple indolizines, and this was attributed to a paramagnetic contribution to the ring current in the [16]annulene molecular periphery.
SECTION II

DISCUSSION
The research upon which this thesis is based has been largely concerned with the synthesis of cyclazines containing a pyrrolizine moiety. Cyclazines such as pyrrolo[2,1,5-αd]-indolizine (1) and cyclopenta[4,5]azepino[7,1,2-αd]pyrrolizine (66) have previously been synthesised in these laboratories,\textsuperscript{23, 24,41} using 3H-pyrrolizine as the starting material, and derivatives of (66) bearing substituents at C-6 and C-8 have been obtained by electrophilic substitution. Flitsch\textsuperscript{38,39} has prepared the 2-chloro-derivative of (66) but no other examples of (66) with substituents in the pyrrolizine part of the system have been reported. It was our aim, initially, to synthesise and characterise various substituted cyclazines of types (1) and (66) starting from available 3H-pyrrolizines.

Another interesting cyclazine system containing the pyrrolizine sub-unit is the hitherto unknown pyrazinodipyrrrolizine (86) which, like(66), has a [14]annulene periphery. This ring system is also potentially accessible from compounds containing the pyrrolizine nucleus and various routes to this compound were investigated.
For ease of naming the more complicated cyclazines contained in this thesis, the I.U.P.A.C. rules\textsuperscript{3} have been used in the remaining sections.
1. Preparation of Pyrrolizines

3H-Pyrrolizine was prepared by the method of Schweizer and Light\textsuperscript{53} using the Michael-Wittig type condensation of vinyltriphenylphosphonium bromide with pyrrole-2-carbaldehyde. Although it was reported that the clear oil darkened at room temperature, this was prevented by storing the freshly distilled material at \(-30^\circ\text{C}\) under \(\text{N}_2\). Ethyl 3H-pyrrolizine-7-carboxylate was synthesised by an analogous route, starting from ethyl 2-pyrrolylglyoxylate, as reported by Brandange and Lundin.\textsuperscript{54}

Methyl 3H-pyrrolizine-6-carboxylate, first synthesised by Flitsch and Heidhues\textsuperscript{55} in two stages from pyrrole-2-carbaldehyde and methyl acrylate, was obtained in better overall yield by the more recently described three-stage procedure of Kobayashi \textit{et al.}\textsuperscript{56}. Pyrrole-2-carbaldehyde was refluxed with pyrrolidine to give 5,10-dihydro-5,10-dipyrrolidino[1,2-a:1',2'-d]pyrazine (88), a dimer of the azafulvene (87). The action of heat on the dimer caused dissociation to the monomer which underwent cycloaddition in the presence of methyl acrylate to give the dihydropyrrolizine (89). Elimination of pyrrolidine to give the required product was effected by treatment with sodium methoxide. Although it was claimed\textsuperscript{56} that this synthesis gave methyl 3H-pyrrolizine-2-carboxylate, the product obtained was identical to that prepared by Flitsch and Heidhues\textsuperscript{55} who showed unambiguously, by \(^1\text{H}\) n.m.r. spectroscopy, that the compound was methyl 3H-pyrrolizine-6-carboxylate.
2-Phenyl-3H-pyrrolizine and 2-phenylsulphonylpyrrolizine were kindly donated by Professor Wilhelm Flitsch.
2. **Synthesis of [2.2.3]Cyclazines (Pyrrolo[2,1,5-\(\alpha\d\)-indolizines) from Pyrrolizines**

Of the existing routes to pyrrolo[2,1,5-\(\alpha\d\)]indolizines, the original indolizine-based syntheses developed by Boekelheide and his co-workers\(^{19,10}\) remain among the most convenient. It would seem, however, that Jessep and Leaver's\(^{23,24}\) route to pyrrolo[2,1,5-\(\alpha\d\)]indolizines from 3\(\H\)-pyrrolizines, based on the three-carbon annellation procedure of Jutz *et al.*\(^{22}\), ought to offer a shorter alternative synthesis. Although the initial reaction, as carried out by Jessep, gave the parent pyrrolo[2,1,5-\(\alpha\d\)]indolizine in very low yield, it was hoped that conjugatively substituted pyrrolizines would give increased yields and therefore provide a valuable alternative means of entry to the pyrrolo[2,1,5-\(\alpha\d\)]indolizine series.

Accordingly, sodium hydride was added to a stirred solution of methyl 3\(\H\)-pyrrolizine-6-carboxylate (90) and the vinamidinium salt (24) in dimethylformamide. The deep red colour which formed was taken as an indication of the presence of fulvenoid intermediates\(^{57}\) and this was found to be characteristic of these reactions. The reaction was followed
by t.l.c. and this indicated that a longer period of heating was required (35 h) compared with that (5.5 h) given by Jessep for the synthesis of the parent cyclazine. The reaction mixture after chromatography, gave the cyclazine (91) in fair yield (49%) as yellow prisms, which had a $^1$H n.m.r. spectrum identical with that reported by Pohjala.$^{15}$

Since the pentadienium salt (24) was obtained, in two stages, from 1,1,3,3-tetramethoxypropane, it seemed possible that the route to the cyclazine (91) might be shortened by making use of this diacetal itself as the source of the three-carbon unit. The tetraethoxy-compound is known to condense with diethyl malonate, in the presence of acetic anhydride and zinc chloride, to form diethyl ethoxyallylidene-malonate [EtOCH=CH=CH=C(CO$_2$Et)$_2$]$^{58}$ and it seemed possible that a similar condensation with the pyrrolizine derivative (90) would yield an intermediate which should be capable of cyclisation to the pyrrolo[2,1,5-cd]indolizine (91). After an unsuccessful attempt under these conditions, it was found that the condensation occurred without the addition of the zinc chloride catalyst to give in lower yield (26%), the required cyclazine, identical with that prepared by the previous method. Like
the 6-ester (90), ethyl 3H-pyrrolizine-7-carboxylate also reacted with the vinamidinium salt (24) in the presence of sodium hydride to give the required cyclazine (92) in similar yield (48%). The $^1$H n.m.r. spectrum of (92) showed two one-proton doublets at 8.02$\delta$ (H-7; $J_{6,7}$ 7.8Hz) and 7.99$\delta$ (H-5; $J_{5,6}$ 7.8Hz), a one-proton doublet at 7.79$\delta$ (H-1; deshielded by the ester group at position 2; $J_{1,4}$ 0.95Hz), a one-proton triplet at 7.68$\delta$ (H-6; $J_{5,6}=J_{6,7}$ 7.8Hz), a one-proton doublet at 7.82$\delta$ (H-3) and a one-proton doublet of doublets at 7.63$\delta$ (H-4; $J_{3,4}$ 4.5 and $J_{1,4}$ 0.95Hz). All signals showed downfield shifts compared with those of the parent system$^{35}$.

The ultraviolet-visible spectrum showed absorptions at 250 (log $\varepsilon$ 4.26), 295 sh (3.87), 303 (3.97), 420 (3.55), 433 (3.55), and 443 nm (3.51). Comparison of this spectrum with the UV-visible spectrum of the parent cyclazine indicated a small bathochromic shift (23 nm) in the longest wavelength maximum.

Hydrolysis of the ester (92) with methanolic 10% potassium hydroxide gave a yellow solid the melting point of which was identical with that of pyrrolo[2,1,5-cd]indolizine-2-carboxylic
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<th>δ/ppm</th>
<th>3J/Hz</th>
<th>6J/Hz</th>
<th>ASIS</th>
<th>Assignment (93)</th>
<th>Assignment (94)</th>
<th>N.O.E.(%) (value in parentheses indicates proton irradiated)</th>
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a Unless otherwise stated, chemical shifts and coupling constants refer to a saturated solution in CDCl3. b ASIS = δCDCl3 - δC6D6. c Enhancements <3% and those of protons known to be vicinally coupled to the irradiated proton are not reported. d Shown to be mutually coupled by double irradiation (decoupling) experiments. e The resonances due to H-1 and H-2 in (94) are coincident in CDCl3 and appear as a singlet. In C6D6, H-1 is partially obscured by H-6 but H-2 appears as a doublet of triplets (3J1,2 = 5.4Hz, 6J2,6 ≈ 5J2,1, 0.7-0.9Hz). f J refers to solution in C6D6. g Shows additional long-range coupling (5J1,1', ca. 1.4Hz, 6J2,1' ≈ 5J1,3, 0.5-0.7Hz). h Shows additional long-range coupling to H-1. i Average value.
acid, as reported by Boekelheide et al.\textsuperscript{10}.

The reaction of the pyrrolizine-7-carboxylate with the vinamidinium salt, unlike the corresponding reaction of the 6-carboxylate (90), yielded a second characterisable product, in addition to the cyclazine (92). This was obtained as a red brown crystalline solid during chromatographic work-up and more of the same substance was obtained as the sole product if the reaction was carried out without the period of heating.

The product was chromatographically homogeneous (t.l.c.) but its $^{1}$H n.m.r. spectrum (Table 1) showed the presence of two isomeric compounds, the major one of which was assigned the structure (93) on the basis of the following evidence.

\begin{align*}
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{NMe}_2 & \quad \text{NMe}_2 \\
\text{Me}_2\text{N} & \quad \text{Me}_2\text{N} \\
(93) & \quad (94)
\end{align*}

\begin{align*}
\text{CH.CH=CHNMe}_2 & \quad \text{CH.CH=CHNMe}_2 \\
(95) & \quad (96)
\end{align*}
(i) The absence of a $^1$H resonance free from vicinal coupling eliminated the possible structure (95). (ii) Resonances showing low (3.0Hz), intermediate (5.3Hz), and high (12.3Hz) values of the vicinal coupling constant ($^3J_{HH}$) were recognised as due to protons in the aromatic pyrrole ring (H-5 and H-6), the non-aromatic ring (H-1, and 2), and the olefinic side chain ($^5$ (H-1', 2' and 3') respectively. (iii) The resonances due to H-2 and H-6 were recognised from their mutual splitting ($^6J_{2,6}$ 0.9Hz), a similar long range coupling having been reported previously$^{60}$ as a characteristic of other 3H-pyrrroleizines. (iv) Nuclear Overhauser Enhancement (N.O.E.) difference spectra$^{61}$, $^{62}$ showed the proximity of H-2' (5.22$\delta$) to H-5 (7.01$\delta$) and Me$_2$N (2.82$\delta$) and of H-1' (6.18$\delta$) to H-2 (6.36$\delta$).

The proton resonances due to the minor component of the mixture, though less well resolved, were similar in general features to those of the major component (Table 1). N.O.E. difference spectra showed that both double bonds of the side chain have the E-configuration (H-2' close to H-2 and NMe$_2$) but did not yield reliable information concerning the point of attachment of the side chain to the nucleus. A decision in favour of the stereoisomeric structure (94) rather than (96) rests on measurements of aromatic solvent induced shifts$^{63,64}$ (ASIS = $^6$CDCl$_3$-$^6$C$_6$D$_6$) for each of the types of protons in the two components of the mixture (Table 1).

No attempts were made to explain the magnitudes and signs of these shifts in terms of solute-solvent interactions$^{64}$, only the following features were noted. (i) In common with other molecules of "push-pull" type$^{65,66}$, isomer (93) showed
negative ASIS values (-0.49 and -0.52 p.p.m.) for those protons (H-1 and H-6, respectively) close to the negatively polarised group (CO$_2$Et) and positive values elsewhere (except for H-5). (ii) The ASIS values for the protons of the minor isomer correlated well (except for H-5) with those of the corresponding protons in (93); in particular, the value of -0.42 p.p.m. was readily accounted for as being due to H-1 in (94) but was not consistent with H-3 in (96), for which a positive ASIS value would be expected. (iii) The poor ASIS correlation for H-5 in the two isomers was attributed to the differing side-chain configurations, that of (93) being such as to hinder the interaction of solvent molecules with H-5.

It is clear from these structures that compounds (93) and (94) are potential intermediates in the formation of the cyclazine (92) yet both compounds survived during 42 h in refluxing dimethylformamide, either alone or in the presence of sodium hydride or sodium perchlorate, did not yield the cyclazine though some decomposition occurred. A possible explanation of this apparent anomaly is that the true intermediate in cyclazine formation is compound (95) and that when the reaction is conducted at room temperature, either this compound is not formed or it decomposes in preference to forming the cyclazine. The observed fulvenoid products (93) and (94) are more stable since they contain an electronegatively substituted pyrrole ring, this same feature presumably being responsible for inhibition of cyclisation to the cyclazine skeleton.

Since the reactions of the 6- and 7-alkoxycarbonyl-pyrrolizines had required a far longer time at reflux temperature
than had been allowed by Jessep and Leaver in their experiments with the parent 3H-pyrrolizine, it was decided to repeat this work giving a longer period of heating (45 h). This procedure gave a much increased yield (46%) of the parent cyclazine and suggested, together with the results already described, that the pyrrolizine route to pyrrolo[2,1,5-cd]indolizines is one of considerable generality. In further support of this conclusion, Flitsch and his co-workers have recently shown that 1-phenyl- and 1-phenylsulphonylpyrrolo[2,1,5-cd]-indolizines can be obtained, from the corresponding pyrrolizines, using the same annellation procedure.
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<th>Compound</th>
<th>H-1</th>
<th>H-2</th>
<th>H-3</th>
<th>H-4</th>
<th>H-5</th>
<th>H-6</th>
<th>H-7</th>
<th>H-8</th>
<th>H-9</th>
<th>J/Hz</th>
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<td>7.67</td>
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<td>7.44</td>
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<td>8.76</td>
<td>7.94</td>
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<td>J₁₂ 4.6, J₆₇ 3.8</td>
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<td>7.81</td>
<td>7.89</td>
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a In CDCl₃; values in parenthesis refer to protons in substituent groups.

b ref.41.
3. **Synthesis of Cyclopenta[h][2.2.4]cyclazines (Cyclopenta-[4,5]azepino[7,1,2-cd]pyrrolizines) from Pyrrolizines**

To demonstrate the generality of Jessep and Leaver's synthesis of cyclopenta[4,5]azepino[7,1,2-cd]pyrrolizines, the conjugate bases of the substituted 3H-pyrrolizines were reacted with the fulvene-iminium salt (69). The initial reaction at room temperature gave a characteristic burgundy red coloured solution. This was taken as an indication of the presence of intermediates which were slowly converted to the corresponding cyclazines during a subsequent period of heating.

The $^1$H n.m.r. spectra of the cyclazines were easily assigned, each showing two characteristic low-field singlets for H-5 and 9 (Table 2).

The overall appearance of the U.V.-visible spectra were comparable to the parent (Table 3), each showing three main
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<th>(98) 2-CO&lt;sub&gt;2&lt;/sub&gt;Et</th>
<th>(99) 1-SO&lt;sub&gt;2&lt;/sub&gt;Ph</th>
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<td>587 (2.35)</td>
<td>655 (1.82)</td>
<td>586 (2.48)</td>
<td>643 (2.15)</td>
<td>578 (2.23)</td>
</tr>
</tbody>
</table>

<sup>a</sup> In ethanol

<sup>b</sup> ref. 41
regions of absorption. Jessep and Leaver reported\textsuperscript{41} that conjugative electron-\textendash withdrawing substituents at the 6(8)-positions of cyclopenta[4,5]azepino[7,1,2-cd]pyrrolizine caused a marked hypsochromic shift of the long wavelength visible absorption band (HOMO-LUMO transition). This effect may be attributed to preferential stabilisation of the HOMO which, unlike the LUMO, has relatively high one-\textit{\textsigma} electron densities at the 6- and 8-positions\textsuperscript{67}. (Figure 1).

\textbf{FIGURE 1} MO-Diagram and coefficients of the frontier orbitals ($\epsilon_6$ and $\epsilon_3$) of cyclopenta[4,5]azepino[7,1,2-cd]pyrrolizine (relative signs indicated by filled and open circles on the diagram).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
 & HOMO & LUMO \\
\hline
 & $\epsilon_6 = +0.38\beta$ & $\epsilon_3 = -0.42\beta$ \\
\hline
1,4 & 0.1212 & 0.3001 \\
2,3 & 0.3140 & 0.0377 \\
2a & 0.0000 & 0.2843 \\
4a,9a & 0.2245 & 0.0874 \\
5,9 & 0.2245 & 0.4576 \\
\hline
\end{tabular}
\end{table}

In the present work, a small bathochromic shift was observed when the visible spectra of the 1-methoxycarbonyl- and 1-phenylsulphonyl-cyclazines (97) and (99) were compared with that of the parent system. This effect is attributed to differential stabilisation of the LUMO in which the one-\textit{\textsigma} electron density is relatively high at the 1- and 4-positions.
The effect of substitution at C-2 is less clear but a small hypsochromic shift was observed in the longest wavelength peak of the visible spectrum of the 2-ethoxycarbonyl-cyclazine (98). Since the one-π-electron densities at the 2- and 3-positions are higher in the HOMO than in the LUMO, the shift is in the expected direction but it is not apparent in the remaining peaks of the visible absorption band.

These observations serve to further exemplify the previously noted similarity of cyclopenta[4,5]azepino[7,1,2-cd]-pyrrolizines to azulenes, the visible absorption bands of which are hypsochromically shifted by electronegative substituents at C-1,3,5 and 6 and bathochromically shifted by such substituents at C-2,4,6, and 870.
Scheme I

\( \text{Section 4.2.2) \quad \text{d} \quad \text{Section 4.2.1) \quad \text{e} \quad \text{Section 4.2.3) \quad \text{c} \quad \text{Section 4.2.4) \quad \text{b} \quad \text{Section 4.3) \quad \text{f} \quad \text{g}} } \)
4. **Investigation of Routes to Pyrazino[2,1,6-\textit{cd}:3,4,5-\textit{c'\textit{d'}}]-dipyrrolizines**

Pyrazino[2,1,6-\textit{cd}:3,4,5-\textit{c'\textit{d'}}]dipyrrolizine (86) is an interesting ring system containing \(14\pi\)-electrons in the periphery and would therefore be expected to exhibit aromatic properties. The various possible routes for the synthesis of pyrazino[2,1,6-\textit{cd}:3,4,5-\textit{c'\textit{d'}}]dipyrrolizines are outlined, using retrosynthetic symbolism, in Scheme 1.

This shows all known fused ring systems related to (86) and potentially available precursors of it. All the routes implied by the retrosynthetic arrows (with the exception of \(g\)) were investigated to some extent. In principle, a pyrrolizine coupling reaction (retrosynthetic arrow \(a\)) represents the simplest route to (86) but, in practice, the route from pyrazino[2,1,6-\textit{cd}]pyrrolizine via a pyrrolo[2',1':3,4]pyrazino-[2,1,6-\textit{cd}]pyrrolizine derivative (arrows \(c\) and \(b\), respectively) proved more rewarding. A route to the pyrazinopyrrolizine from pyrrolizine (arrow \(d\)) is already known\(^{23}\) but the route from pyrrolo[1,2-\textit{q}]pyrazines (arrow \(e\)) has received scant attention. Some time was therefore devoted to the investigation of this
route and also to the synthesis of pyrrololo[1,2-α]pyrazines themselves. A possible route to (86) from a dipyrrolo[1,2-α:-1',2'-d]pyrazine derivative (arrow f) was also investigated but the indications were not encouraging.

4.1 Pyrrolizine coupling reactions as a potential route to pyrazinodipyrrolizines

The pyrazinodipyrrolizine (86) might in principle be obtainable from two molecules of pyrrolizine by removal of six hydrogen atoms. The first step in such a synthesis would be the oxidative coupling of two pyrrolizine anions to give 3,3'-bipyrrrolizinyl. Such a coupling has been accomplished in the case of the related cyclopentadienide anion by treatment with iodine at -78°C in tetrahydrofuran\textsuperscript{71-73}. The anion derived from methyl 3H-pyrrolizine-6-carboxylate, being delocalised and unsymmetrical, could form a variety of oxidative dimers; one example being (101). The conversion of such a compound into a derivative of the doubly-linked dipyrrolizine system (86) would present further problems but these need not be discussed at this stage.

Deprotonation of the pyrrolizine derivative was carried
out using lithium diisopropylamide in tetrahydrofuran and the resulting solution was treated with iodine. Only a trace of a dimer was obtained, the $^1$H n.m.r. spectrum of which was poorly resolved although a peak corresponding to the dimer (m/e 324) was observed in the mass spectrum. This reaction was repeated several times but on each occasion insufficient material was obtained for spectroscopic characterisation.

Kakehi et al. recently reported a simple synthesis of 3,3'-biindolizines by the treatment of 3-unsubstituted indolizine

![Chemical Structure](image1)

(K102) Pd/C Xylen e

![Chemical Structure](image2)

(K103)
derivatives with palladium-on-charcoal in refluxing xylene. It seemed possible that this procedure might effect a similar coupling of two pyrrolizine nuclei but, in fact, no dimeric product was obtained. Treatment of methyl 3H-pyrrolizine-6-carboxylate with Pd/C in refluxing xylene, yielded a brown crystalline solid, the $^1$H n.m.r. spectrum of which showed it to be the reduced dihydropyrrolizine (105). The mass spectrum showed a parent ion of m/e 165, correct for the dihydropyrrolizine.

Another procedure considered to have potential as a route to bipyrrrolizines was based on the known reaction of Na$_2$PdCl$_4$ with olefins to yield π-allyl complexes (106) which can react with carbanions to give allylation products. Assuming that a pyrrolizine derivative would serve as both olefin and carbanion source, the product of such a reaction would be a bipyrrrolizine. Unfortunately, however, treatment of methyl 3H-pyrrolizine-6-carboxylate with Na$_2$PdCl$_4$ in refluxing methanol gave a brown solid which could not be identified by $^1$H n.m.r. or mass spectroscopy.
4.2 The route to pyrazinodipyrrolizines from pyrazino-[2,1,6-cd]pyrrolizines

A useful starting material in the synthesis of pyrazino-[2,1,6-cd:3,4,5-c'd']dipyrrolizine (86) would be the already known pyrazino[2,1,6-cd]pyrrolizine (6-aza[2.2.3]cyclazine) obtainable in three stages from 3H-pyrrolizine. Untch had previously claimed in a private communication to Flitsch that the pyrazino[2,1,6-cd]pyrrolizine could be synthesised by the reaction of pyrrolo[1,2-a]pyrazine with dimethyl acetylenedicarboxylate, although no experimental details were given and none have been published to date. Before attempting the later stages of a route to the pyrazinodipyrrolizine (86) it was appropriate, therefore, to investigate the merits of this alternative route to pyrazino[2,1,6-cd]pyrrolizines from pyrrolo[1,2-a]pyrazines.

4.2.1 Pyrrolo[1,2-a]pyrazines as potential precursors of pyrazino[2,1,6-cd]pyrrolizines

The parent pyrrolo[1,2-a]pyrazine (107) was prepared from N-(2-pyrrolylmethylene)aminoacetaldehyde diethyl acetal by the method of Herz and Tocher.

It seemed likely that the optimum conditions for the preparation of the pyrazino[2,1,6-cd]pyrrolizine would be similar to those used by Boekeheide in his original synthesis of pyrrolo[2,1,5-cd]indolizines. However, when the parent pyrrolo[1,2-a]pyrazine and DMAD in toluene were heated under reflux in the presence of palladium-on-charcoal, chromatographic work-up gave an orange powder, the mass spectrum of which showed a small peak at m/e 406 and another at m/e 375 but no peak at
Shvedov and his co-workers\textsuperscript{77,78} have reported that pyrrolo[1,2-\(a\)]pyrazines were synthesised by the \(N\)-alkylation of 2-acylpyrroles with \(\alpha\)-bromocarbonyl compounds or their acetals, followed by reaction of the resulting dicarbonyl derivatives with ammonium acetate in refluxing acetic acid. This procedure was used to prepare 3-methyl pyrrolo[1,2-\(a\)]pyrazine as outlined in Scheme 2.

The potassium salt of pyrrole-2-carbaldehyde reacted with bromoacetone in dimethylformamide at \(-78^\circ\text{C}\) to give \(N\)-acetonylpyrrole-2-carbaldehyde (109) as colourless needles. Cyclisation was effected by refluxing the dicarbonyl compound (109) and ammonium acetate in glacial acetic acid. 3-Methylpyrrolo-[1,2-\(a\)]pyrazine (110) was then obtained after chromatography as pale yellow plates, the \(^1\text{H}\) n.m.r. spectrum of which was m/e 258, as would be required for (108). The \(^1\text{H}\) n.m.r. spectrum was complex and did not lead to an identification.
identical with that reported by Flament et al.\textsuperscript{79}

The pyrrolo[1,2-\(a\)]pyrazine (110) was also obtained via a similar route using propargyl bromide, in place of bromoacetone. Conversion of \(N\)-propargylpyrrole-2-carbaldehyde (111) into the desired pyrrolo[1,2-\(a\)]pyrazine with ammonium acetate required a catalytic amount of cuprous chloride.

The reaction of 3-methylpyrrolo[1,2-\(a\)]pyrazine with ethyl propiolate in the presence of palladium-on-charcoal gave, in low yield, the required azacyclazine (112). Repetition of the reaction on a larger scale failed to improve the yield and indicated that this method of preparation of the 6-azacyclazine system compared very unfavourably with the route from pyrrolizine.

When the reaction was carried out using DMAD as the
activated acetylene no identifiable products were obtained.

A simple, two-step synthesis of indolizines has been reported by Abramovitch\textsuperscript{80}, involving a modification of the previously known 1,3-dipolar cycloaddition of activated acetylenes to pyridinium ylids. \(p\text{-Tolylsulphonylmethylpyridinium trifluoromethanesulphonates were prepared by the reaction of pyridines with \(p\text{-tolylsulphonylmethyl trifluoromethanesulphonate (113). Deprotonation of these pyridinium}

\[
\begin{align*}
\text{R} \quad & \quad + \quad p\text{-TolSO}_2\text{CH}_2\text{OSO}_2\text{CF}_3 \\ & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \q
It seemed possible that adaptation of this procedure to pyrazines would provide a simple route to the pyrrolo-[1,2-α]pyrazines (119) but attempts were frustrated by failure to obtain the pyrazinium salt (118) by the reaction of pyrazine with p-tolylsulphonylmethyl trifluoromethanesulphonate.

4.2.2 Synthesis of pyrazino[2,1,6-cd]pyrrolizines from 3H-pyrrolizines

Despite the knowledge that pyrazino[2,1,6-cd]pyrrolizine could be obtained from 3H-pyrrolizine according to Scheme 3 shown below, it seemed prudent to investigate the possible use of methyl 3H-pyrrolizine-6-carboxylate (90) as an alternative starting material since this is more stable and possibly more easily accessible than 3H-pyrrolizine itself. Unfortunately, the direct application of Scheme 3 to the pyrrolizine ester (90) failed at the initial Vilsmeier condensation either through lack of reaction (at -30°C) or through instability of
Jessep had attempted, unsuccessfully, to prepare the parent pyrazino[2,1,6-\(cd\)]pyrrolizine by a method based on that used by Jutz to synthesise 4-azapyrene. It was hoped, however, that this reaction would be more successful using methyl 3\(H\)-pyrrolizine-6-carboxylate (90) as the starting material. When the ester (90) was allowed to react with the azavinamidinium perchlorate (121) purple prisms were isolated after chromatography. This product was identified as methyl
3-[3-N,N-dimethylamino-2-azaprop-2-enylidene]-3H-pyrrolizine-6-carboxylate (121) on the basis of the following evidence. The mass spectrum showed a parent peak at m/e 245, correct for the required pyrrolizine derivative (121). The $^1$H n.m.r. spectrum indicated that cyclisation had not taken place and
showed two three-proton singlets at 3.04δ and 3.10δ (NMe₂), one three-proton singlet at 3.78δ (OMe), a two-proton AB system at 6.29δ (H-2) and 6.42δ (H-1), Jₐₕ 5.7Hz, two one-proton doublets at 6.31δ (H-1') and 8.26δ (H-3'), J₁,₃₁=1.1Hz, and two one-proton singlets at 6.78δ (H-7) and 7.59δ (H-5). No other identifiable products were isolated from the reaction mixture.

Attempts to effect cyclisation of (121) using flash vacuum pyrolysis at 1x10⁻³ mm and 700°C and at 800°C were unsuccessful, the pyrolysate being mostly starting material (at 700°C) or a complex mixture of products at (800°C).

Since these reactions using the substituted 3H-pyrrolizine were unsuccessful the perchlorates (28) and (30) were prepared from 3H-pyrrolizine itself, using the method of Jessep and Leaver²³. The final conversion of perchlorate (30) into pyrazino[2,1,6-cd]pyrrolizine was modified slightly by using ethanolic liquid ammonia instead of aqueous ammonia. Concentration of the filtered solution by chromatography gave the desired product in 41% yield. Although the yield was not increased significantly, this method was used in preference to that of Jessep and Leaver because of the easier work-up.
4.2.3 Investigation of the route from pyrazino[2,1,6-cd]-pyrrolizine to pyrrolo[2',1':3,4]pyrazino[2,1,6-cd]-pyrrolizines (including model reactions with pyridine)

A synthesis of the pyrazinodipyrrolizine (86) from pyrazino[2,1,6-cd]pyrrolizine (31) was envisaged as proceeding via the previously unknown pyrrolo[2',1':3,4]pyrazino[2,1,6-cd]-pyrrolizine (122). In order to avoid wastage of the valuable intermediate (31) in exploratory reactions, the conversion of pyridine into indolizine was chosen as a model for this step of the projected synthesis, the chemistry of pyrazino[2,1,6-cd]-pyrrolizine being similar in some respects to that of pyridine (see introduction section 1.2).

Many methods for the synthesis of indolizines from pyridines are already known but most of these give molecules bearing alkyl or aryl substituents and are therefore of limited value for the purpose in hand. Since no syntheses have yet been reported which give a good yield of the unsubstituted indolizine directly from pyridine, it was desirable to devise such a synthesis.

A method that seemed capable of development for this
purpose was one in which the indolizine ring system is obtained via pyridinium $N$-allylides formed by proton abstraction from the corresponding pyridinium salts.\textsuperscript{84-86} For example, treatment of the pyridinium salt (123) with excess potassium carbonate in chloroform gave the substituted indolizine (124). These reactions are thought to proceed via intramolecular 1,5-dipolar cyclisation followed by dehydrogenation. A requirement for such reactions is that the $N$-allyl group should contain a carbanion-stabilising group in the terminal position.

The proposed synthesis (Scheme 4) was based on this work but it was envisaged that the group (Y) would act, not only as a carbanion-stabilising group but also as a leaving group. The elimination of HY could thus serve to generate an unsubstituted indolizine nucleus whilst avoiding the need for
dehydrogenation. It seemed likely that these requirements would be fulfilled in the case $Y=\text{ArSO}_2$ and possibly in the case $Y=\text{Cl}$, though the latter would be a much less effective carbanion-stabiliser.

Accordingly, 3-bromo-1-p-tolylsulphonylpropene (129) and 3-bromo-1-phenylsulphonylpropene (130) were prepared from the corresponding alcohols according to the method reported by Bordwell et al.\textsuperscript{87} and 1,3-dichloropropene (131) was prepared using the method of Hill and Fischer.\textsuperscript{88} These compounds were then used to quaternise pyridine and attempts were made to cyclise the resulting pyridinium salts.
When 1-(3-p-tolylsulphonylprop-2-enyl)pyridinium bromide or 1-(3-phenylsulphonylprop-2-enyl)pyridinium bromide were steam distilled with aqueous sodium bicarbonate, indolizine was obtained as the only isolable product in moderate yield (42%).

\[
\begin{align*}
\text{Br}^- & \quad \Delta \quad \text{NaHCO}_3 \\
& \\
(132) \ R = \text{SO}_2\text{Tol} \\
(133) \ R = \text{SO}_2\text{Ph}
\end{align*}
\]

However, attempts to prepare indolizine by the same method from 1-(3-chloroprop-2-enyl)pyridinium perchlorate, and other attempts to prepare indolizine from the salts (132) and (133), using different bases and solvents were unsuccessful.

In view of these results, the proposed route to pyrrolo-[2',1':3,4]pyrazino[2,1,6-cd]pyrrolizine (122) was attempted using the successfully tested procedure. Quaternisation of pyrazino[2,1,6-cd]pyrrolizine with the allyl bromide (130) gave 6-(3-phenylsulphonylprop-2-enyl)pyrazino[2,1,6-cd]pyrrolizinium bromide (134) in good yield. However, when the salt was heated in aqueous sodium bicarbonate, the solution turned black and extraction of the cooled reaction mixture failed to give any identifiable products. In view of later observations, this disappointing result may well have been due to the instability of the required product rather than to failure of the cyclisation.
As mentioned before in connection with a possible route to pyrrolo[1,2-α]pyrazines, Abramovitch\(^{80}\) has reported a simple two-step synthesis which affords indolizines in good yield from pyridines and \(p\)-tolylsulphonylmethyl trifluoromethanesulphonate (113). Because of the well-known reluctance of \(α\)-halogeno-sulphones to undergo nucleophilic substitution, it is necessary to use the much more effective, but relatively expensive, trifluoromethanesulphonyloxy leaving group rather than halogen in the initial quaternisation reaction. It seemed possible, however, that bromomethyl phenyl sulphone might be a less expensive and more easily accessible reagent than the triflate (113); base-catalysed elimination of benzenesulphenic acid from the initial 3,8α-dihydroindolizine (132) would probably be less effective, as an aromatisation step, than the corresponding elimination of \(p\)-toluenesulphinic acid but an alternative aromatisation pathway is potentially available \(via\) prototropic rearrangement and thermal 1,2-elimination of the sulphenic acid.
Quaternisation of bromomethyl phenyl sulphoxide with pyridine gave the pyridinium salt (138) but attempts to prepare the substituted indolizine (137) by reaction of the salt with triethylamine or sodium hydride in the presence of DMAD were unsuccessful. Only a trace of a yellow-red gum which showed the correct molecular ion at m/e 233 was obtained on both occasions. A similar reaction of the salt (138) and base (NaOEt) with phenyl vinyl sulphoxide as dipolarophile was also unsuccessful. This reaction, modelled partly on an indolizine synthesis (Scheme 5) due to Matsumoto had been designed to yield the parent indolizine by elimination of two molecules of phenylsulphenic acid. In view of the failure
of these exploratory experiments, the indolizine synthesis of Abramovitch was applied in unmodified form to the preparation of the pyrrolo[2',1':3,4]pyrazino[2,1,6-\textit{cd}]pyrrolizine (141). The reaction of pyrazino[2,1,6-\textit{cd}]pyrrolizine with \(p\)-tolylsulphonylmethyl trifluoromethanesulphonate yielded fine yellow needles, the \(^1\text{H}\) n.m.r. spectrum of which showed it to be the desired material by comparison with spectra of other previously prepared salts.\(^{23}\) Treatment of the salt (140) with triethylamine in the presence of DMAD gave the pyrrolopyrazinopyrrolizine (141).

The \(^1\text{H}\) n.m.r. spectrum of the diester (141) indicated that this compound was diatropic and showed two three-proton singlets due to the methyl ester groups, two one-proton doublets of doublets at 7.09\(\delta\) (H-4; \(J_{3,4} 5.14\) and \(J_{1,4} 0.8\text{Hz}\)) and 7.72 (H-1), two one-proton doublets at 7.10\(\delta\) (H-2; \(J_{1,2}\))
3.9 Hz) and 7.45 δ (H-3), and two singlets at 7.94 δ (H-6) and 8.30 δ (H-5). Confirmation of these assignments was obtained by decoupling experiments and by comparison with the $^1$H n.m.r. spectrum of the mono-ester (145) produced by attempted decarboxylation experiments (see later). Thus, irradiation of H-3 (δ 7.45) caused the H-4 signal to collapse to a broad singlet and irradiation of H-1 (δ 7.70) caused the collapse of the H-2 signal to a singlet and the H-4 signal to a doublet.

It was thought initially that the presence of two methoxycarbonyl groups in the pyrrolopyrazinopyrrolizine (141) might inhibit its further elaboration to the pyrazinodi-pyrrolizine ring system. Reactions of the salt (140) with acetylenes containing only one activating group were therefore investigated.
Treatment of the salt (140) with triethylamine in the presence of ethyl propiolate gave only a trace of a compound which showed a molecular ion at m/e 252.090291 (C_{15}H_{12}N_{2}O_{2}
\text{CH}_2\text{SO}_2\text{Tol}
\text{CF}_3\text{SO}_3
(140)
\text{Et}_3\text{N}
X-C≡CH
(142) X=\text{CO}_2\text{Et}
(143) X=\text{CN}
requires m/e 252.089872) and no other identifiable products were obtained. A similar reaction with cyanoacetylene gave a low yield of a yellow fluorescent material which showed a molecular ion at m/e 205. This was consistent with the required product (143) but the $^1$H n.m.r. spectrum could not be assigned to this or any other plausible structure. In view of these disappointing attempts to obtain pyrrolopyrazinopyrrolizines with fewer than two electron-withdrawing substituents, attention was turned to the possibility of removing the methoxycarbonyl groups from the diester (141).

Decarboxylation of carboxylic acids has been achieved by a variety of techniques using various oxidation states of copper as the catalyst. In 1970 a mechanism for the loss of carbon dioxide was postulated in the widely used copper-quinoline decarboxylation. These studies, by Cohen, showed that the reaction was faster if carried out using copper(I) or copper(II) salts as the catalyst. Cohen also reported
that certain chelating agents such as 2,2'-bipyridyl considerably increased the rate of decarboxylation with both types of catalyst. The importance of maintaining a nitrogen atmosphere during the reaction was also reported. Cuprous salts have been utilised in studies by Nilsson,\textsuperscript{92,93} and evidence has been provided that organocopper compounds are intermediates in the reaction. Casini and Goodman\textsuperscript{94} in 1964 reported a much improved method for decarboxylation of indole-2-carboxylic acids using $N,N$-dimethylacetamide as solvent and the copper salt of the acid as a catalyst. Work carried out in this department by Leaver and his co-workers has shown that decarboxylation of various cyclazinecarboxylic acids may be effected by heating the solids, intimately mixed with cuprous oxide, in a sublimation apparatus, the cyclazine being collected on the cold finger. These methods were taken into account in the selection and design of the decarboxylation procedures described below and those used later, for the preparation of the pyrazinodipyrrolizine (86).

Hydrolysis of the diester (141) was carried out with methanolic potassium hydroxide and acidification gave the diacid in good yield. No identifiable products were obtained when decarboxylation of the diacid was attempted in $N,N$-dimethylacetamide with copper chromite or cuprous oxide as the catalyst, according to the procedure reported by Casini and Goodman.\textsuperscript{94} However, a similar procedure using pyrrolidone as the solvent and cuprous oxide as the catalyst yielded traces of two compounds, separated by chromatography. The first compound gave a molecular ion at $m/e$ 180, correct for the parent pyrrolopyrazinopyrrolizine (122), and the second
compound gave a molecular ion at m/e 238, corresponding to a mono-methoxycarbonyl derivative of (122). Despite its initial promise, this procedure proved worthless since increasing the scale of reaction did not increase the amounts of recovered products.

When decarboxylation was attempted using the "sublimation technique" with cuprous oxide only a trace of the mono-methoxycarbonyl compound was obtained. The combined product from three such sublimations was purified by preparative t.l.c. and resublimed to give green micro prisms, identified as methyl pyrrolo[2',1':3,4]pyrazino[2,1,6-cd]pyrrolizine-8-carboxylate (145). The $^1$H n.m.r. spectrum was comparable to that of the diester, the only significant difference being that H-6 was now coupled to H-7 giving an AB system.
Figure 2

(145)

(141)

(146)

(147)
FIGURE 3  UV-visible spectra of (141), (146) and (147).
The formation of the monoester (145) was evidently due to the presence of a small amount of incompletely hydrolysed product (monoester-monoacid) in the dicarboxylic acid. It seems likely that the diacid itself, forming the bulk of the starting material, was also decarboxylated but that the resulting parent pyrrolopyrazinopyrrolizine decomposed under the severe conditions. This new tetracyclic ring system can be compared with the isomeric pyrrolo[1',2':3,4]pyrimido[2,1,6-cd]pyrrolizine (146) and its 8-acetyl derivative (147) prepared by Flitsch and co-workers. The $^1$H n.m.r. spectra of these compare favourably with our system (see Figure 2). The U V-visible spectra of (141), (146) and (147) are depicted in Figure 3 and, although these are not identical, similarities can be seen. Pyrrolo[1',2':3,4]pyrimido[2,1,6-cd]pyrrolizine is reported as being unstable in air and it seems probable that the isomeric compound (122) would exhibit the same limited stability suggested above as a reason for the failure to obtain it by decarboxylation of the diacid.
It had originally been intended that the parent pyrrolo-
pyrazinopyrrolizine (122) would serve as the immediate pre-
cursor of the pyrazinodipyrrolizine (148) by reaction with
dimethyl acetylenedicarboxylate in the presence of palladium-
charcoal catalyst. Since compound (122) was not available

![Chemical structure of 122 and 148](image)

however, this approach was not possible but it was hoped that
the diester (141), though probably less reactive than the
parent compound, might react in a similar manner to give the
tetrasubstituted pyrazinodipyrrolizine (149). Fortunately,

![Chemical structure of 141 and 149](image)

this reaction proved successful, yielding the tetramethylpyra-
zino\[2,1,6-cd:3,4,5-c'd']dipyrrolizine-1,2,3,4-tetracarboxylate
(149) as purple rods in (61\%) yield.
The $^1$H n.m.r. spectrum of the tetraester showed the required pattern of two six-proton singlets and a four proton AB system. The chemical shifts of the methine protons (68.02 and 8.15) suggested that the compound was diatropic.

The tetraester (149) was hydrolysed to tetra-acid (150) by heating with 10% methanolic potassium hydroxide and the parent cyclazine (86) was then obtained by decarboxylation using the following procedure.

Copper bronze, copper(II) acetate and 2,2'-bipyridyl in dimethylacetamide were heated under reflux until a colour change from blue to rusty brown was observed, thus indicating the presence of a copper(I) species. The tetra-acid (150) was added and heating was continued for 42 h. A t.l.c. study of the reaction mixture indicated that two pink coloured compounds were present and these were separated by chromatography.
The first compound was shown to be the required pyrazino-
[2,1,6-cd:3,4,5-c'd']dipyrrolizine (86), the \(^1\)H n.m.r. spectrum of which showed the expected simple AB pattern.

The second compound to be eluted gave a molecular ion at m/e 262 in the mass spectrum which was correct for a cyclazine mono-methylester. Two isomeric structures, (151) and (152), were, therefore, possible.

\[
\text{(151)} \quad \text{(152)}
\]

The \(^1\)H n.m.r. spectrum of the ester showed three two-proton AB systems and a low-field singlet which was easily assigned to the deshielded proton adjacent to the ester group. The ester group also had a deshielding effect on another proton, the resonance of which showed both vicinal (\(J=4.5\)Hz) and long-range (\(J=0.9\)Hz) coupling. The smaller splitting was attributable to six-bond coupling of the type known to be associated with the 2- and 6-positions of the pyrrolizine nucleus and showed that this doubly-split resonance was due H-8 in structure (152) rather than to H-3 in structure (151). Further confirmation of structure (152) was provided by the absence of six-bond coupling in the low-field singlet which is thus shown not to be due to H-1 in structure (151).

The formation of this monoester must again be attributed
FIGURE 4  UV-visible spectra of [14]bridged annulenes
<table>
<thead>
<tr>
<th>Compound</th>
<th>( \lambda_{max} ) (nm)</th>
<th>( \epsilon ) (log)</th>
</tr>
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<tbody>
<tr>
<td>(86) 252sh (4.30) 347 (4.28)</td>
<td>511 (3.49)</td>
<td></td>
</tr>
<tr>
<td>273 (4.84) 294 (3.59)</td>
<td>522 (3.58) 537 (3.87) 550 (4.11) 565 (2.91)</td>
<td></td>
</tr>
<tr>
<td>(153) 303 (5.17)</td>
<td>361 (3.88) 469sh (2.32) 473 (2.37) 479 (2.39) 487 (2.39) 493 (2.38) 498sh (2.26)</td>
<td></td>
</tr>
<tr>
<td>320 (4.45)</td>
<td>273 (4.84) 347 (4.28) 473 (2.37) 479 (2.39) 487 (2.39) 493 (2.38) 498sh (2.26)</td>
<td></td>
</tr>
<tr>
<td>(154) 306 (5.28) 382 (3.93)</td>
<td>555 (2.89)</td>
<td></td>
</tr>
<tr>
<td>345 (4.16)</td>
<td>518 (2.71)</td>
<td></td>
</tr>
<tr>
<td>(155) 300 (5.15)</td>
<td>330sh (4.24)</td>
<td></td>
</tr>
<tr>
<td>(156) 284 (4.48) 314 (4.76)</td>
<td>518 (2.93)</td>
<td></td>
</tr>
<tr>
<td>(157) 308 (5.31) 339 (4.40) 398sh (3.78)</td>
<td>472 (2.54) 551 (3.57)</td>
<td></td>
</tr>
<tr>
<td>(158) 303 (5.22) 322 (4.36)</td>
<td>362 (3.82) 480 (2.61) 486 (2.64) 492 (2.64) 498sh (2.59) 506 (2.48) 513 (2.36)</td>
<td></td>
</tr>
<tr>
<td>(159) 292 (5.14) 312 (4.38)</td>
<td>365 (3.88) 442 (1.90) 509 (2.48)</td>
<td></td>
</tr>
<tr>
<td>(160) 254 (4.70) 267 (4.99) 285 (4.46) 299 (4.30) 309 (4.28) 334 (4.20) 344 (4.26)</td>
<td>358 (3.64) 387 (2.50) 397 (2.58) 410 (2.89) 423 (2.75) 432 (2.75) 445 (3.84) 444 (3.17) 454 (3.27) 461 (3.21) 471 (3.50) 484 (4.21)</td>
<td></td>
</tr>
<tr>
<td>(161) 335 (5.13) 346 (5.01)</td>
<td>377 (3.54) 397 (3.60) 420 (3.73) 440 (3.79) 445 (3.84)</td>
<td></td>
</tr>
<tr>
<td>(162) 195 (4.28) 304 (5.00)</td>
<td>363 (3.46) 387 (3.70) 399 (4.27) 462 (3.36) 469 (3.44) 485 (3.74) 498 (4.22)</td>
<td></td>
</tr>
<tr>
<td>(163) 338 (4.94) 377 (4.57)</td>
<td>463 (3.78) 528 (1.76) 536 (1.76) 586 (2.04) 598 (2.18) 611 (2.32) 627 (2.36) 634 (2.32) 641 (2.52)</td>
<td></td>
</tr>
</tbody>
</table>
to the presence of partially hydrolysed material as an impurity in the tetra-acid (150).

Pyrazino[2,1,6-cd:3,4,5-c'd']dipyrrolizine (86) was a deep pink crystalline solid, quite stable in air and light. Its visible and near-u.v. spectrum, like those of other bridged [14]annulenes, had three main regions of absorption as shown in Figure 4 together with the spectra of syn-1,6:8,13-bis-methano[14]annulene (153), and trans-15,16-dimethyldihydropyrene (163). The data for other bridged [14]annulenes are shown in Table 4. In view of the differences in topology among this series of compounds, and the presence of potentially conjugating nitrogen atoms in some members, a close correspondence of the electronic spectra is not to be expected. However, the general pattern observed in the spectrum of the pyrazinodipyrrolizine is seen to be consistent with that expected of an aromatic macrocycle.

The $^1$H chemical shifts of the pyrazinodipyrrolizine (86) (67.86 and 7.93) were comparable with those of known bridged [14]annulenes (see Tables 5 and 6) and provided strong evidence of diatropicity. [14]Annulene itself cannot be directly compared since it exists as two conformational isomers, both
<table>
<thead>
<tr>
<th>Compound</th>
<th>$R^1 = R^2$</th>
<th>$\delta(2,5)$</th>
<th>$\delta(3,4)$</th>
<th>$\delta(7,14)$</th>
<th>$\delta(9,12)$</th>
<th>$\delta(10,11)$</th>
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<tr>
<td>(153) $^97$</td>
<td>$R^1=R^2=\text{CH}_2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.0 - 7.9</td>
</tr>
<tr>
<td>(154) $^{108}$</td>
<td>$R^1=R^2=\text{O}$</td>
<td>7.75</td>
<td>7.61</td>
<td>7.94</td>
<td>7.75</td>
<td>7.60</td>
</tr>
<tr>
<td>(155) $^{99,108}$</td>
<td>$R^1=\text{O}, R^2=\text{CH}_2$</td>
<td>7.65</td>
<td>7.34</td>
<td>7.75</td>
<td>7.64</td>
<td>7.43</td>
</tr>
<tr>
<td>(156) $^{100}$</td>
<td>$R^1=\text{NH}, R^2=\text{CH}_2$</td>
<td>7.23 $\leftrightarrow$ 7.58</td>
<td>7.45</td>
<td>7.23 $\leftrightarrow$ 7.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(157) $^{101}$</td>
<td>$R^1=R^2=\text{H}-\text{C}-\text{C}^\text{H}$</td>
<td>8.17</td>
<td>7.82</td>
<td>8.00</td>
<td>8.17</td>
<td>7.82</td>
</tr>
<tr>
<td>(158) $^{102,108,109}$</td>
<td>$R^1=R^2=\text{CH}_2=\text{CH}$</td>
<td>7.74</td>
<td>7.55</td>
<td>7.88</td>
<td>7.74</td>
<td>7.55</td>
</tr>
<tr>
<td>(159) $^{103}$</td>
<td>$R^1=R^2=\text{O}$</td>
<td>$\pm$7.81 - 7.81$\rightarrow$</td>
<td>8.53</td>
<td>$\pm$7.81 - 8.11$\rightarrow$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>X, X =</td>
<td>δ(α)</td>
<td>δ(β)</td>
<td>δ(γ)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>--------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(160)</td>
<td>C=C</td>
<td>8.40</td>
<td>8.68</td>
<td>7.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(161)</td>
<td>CMe-CMe</td>
<td>8.74</td>
<td>8.77</td>
<td>8.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(162)</td>
<td>NH</td>
<td>7.89</td>
<td>8.25</td>
<td>7.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(163)</td>
<td></td>
<td>8.67</td>
<td>8.6</td>
<td>8.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
probably far from planar, and the $^1$H n.m.r. spectrum is variable with temperature. 110

It is probable, however, that the two compounds (161) and (163), which possess peripheral conjugated systems only slightly distorted from planarity, 105,111 provide good approximations to an unperturbed fully "aromatic" [14]annulene. Compared with the protons of these reference compounds, those of the pyrazinodipyrrrolizine show increased shielding to the extent of 0.1-0.9 p.p.m. which, since it does not appreciably exceed the shielding experienced by a benzenoid proton ortho to an amino-substituent, may be attributed entirely to conjugative electron-release from the internal nitrogen atoms. It is reasonable to conclude, therefore, that the pyrazinodipyrrrolizine supports a peripheral diamagnetic ring current of about the same magnitude as that in the bridged annulenes (161) and (163). The bridged annulenes (153)-(159) also show $^1$H resonances somewhat more shielded than those of (161) and (163) but, in the absence of potentially conjugating heteroatoms, this must be attributed to decreased diatropicity consequent upon greater deviations from planarity in their [14]annulene skeletons.

The non-quaternary $^{13}$C resonances of the pyrazinodipyrrrolizine (δ107.3 and 117.4) were in the range typical of electron-rich heterocyclic systems, being notably more shielded than the corresponding $^{13}$C resonances (δ113.6 and 122.5) reported for the pyrrolizine moiety of the cyclopenta-azepinopyrrrolizine (66). Since $^{13}$C chemical shifts are essentially independent of ring current effects (the carbon nuclei being in the null region of the induced magnetic field due to the ring current),
this shielding has no direct bearing on the diatropicity of the annulene ring; it points however to strong conjugation of the carbon π-system with the nitrogen lone-pairs and reinforces the conclusion that the relatively low shielding of the \(^1\)H resonances is due to an induced diamagnetic ring current.

The contrast between the pyrazinodipyrrrolizine (86) and the pyrazinodiindolizine (84)\(^{50}\) is striking; whereas the former is strongly diatropic, the latter is judged to be weakly paratropic (\(\delta_H 5.1-5.9\)) despite the fact that it contains two potentially aromatic indolizine moieties. The conclusion, is therefore, that the aromatic character of these doubly \(N\)-bridged molecules, like that of their singly \(N\)-bridged counterparts (the cyclazines), is governed by the Hückel rule, as applied to the number of \(\pi\)-electrons in their peripheral conjugated systems.

\[\text{Image of structure (84)}\]

4.3 The dipyrrolo[1,2-\(a\):1',2'-\(d\)]pyrazine ring system as a possible precursor of pyrazinodipyrrrolizines

Huisgen and his co-workers\(^{112,113}\) have shown that \(N\)-substituted pyrroles may be synthesised by cycloaddition of
activated acetylenes to mesoionic oxazolium-5-oxides (165) which are generated *in situ* by the action of acetic anhydride on N-acyl-\(\alpha\)-amino acids. The initial cycloadduct (167) loses carbon dioxide spontaneously to form the pyrroles. For example, 3-methyl-2,4-diphenyloxazolium-5-oxide (165), prepared from (164), reacted with DMAD to give the substituted pyrrole (168).

Application of this procedure to suitably \(N\)-substituted prolines has given the dihydro-pyrrolizines (170) and (171).\textsuperscript{113,114}
It seemed possible that this synthesis of the pyrrolizine ring-system might provide an approach to the carbon skeleton of pyrazino[2,1,6-cd:3,4,5-c'd']dipyrrrolizine (86). A direct adaptation of the Huisgen procedure would require, as the starting material, octahydro-5,10-dioxo-5H,10H-dipyrrrolo-

[1,2-α:1',2'-d]pyrazine-3,8-dicarboxylic acid (172).

Preliminary investigations carried out by Copland using the diethyl ester (174) as starting material had shown
promising signs. However, the yields were low and so it was decided to repeat the work using the corresponding dimethyl ester in the hope that the more reactive ester functions might give better yields both during the initial self-condensation and during the subsequent ester hydrolysis.

Dimethyl N-benzylpyrrolidine-2,5-dicarboxylate (175) was prepared, as a mixture of stereoisomers, from dimethyl 2,5-dibromohexanedioate\(^{116}\) using the method reported by Cignarella and Nathansohn\(^{117}\) and this was converted largely to the \(E\)-isomer according to the procedure of Lowe\(^{118}\).
Dimethyl pyrrolidine-2,5-dicarboxylate (176) was obtained from the N-benzyl compound (175) by hydrogenolysis at 40°C and self-condensation of (176) was effected by heating at 180°C.

The hydrolysis of alkyl carboxylic esters is usually carried out under acidic or basic conditions. Anhydrous lithium iodide has also been reported as being a useful method of de-esterification. However, attempts to hydrolyse or cleave the diester (177) using aqueous sodium hydroxide or anhydrous lithium iodide were unsuccessful. The use of iodi trimethylsilane as a mild reagent for the cleavage of esters has been reported and more recently Benkeser et al. reported the catalytic effect of iodine in reactions of this type. It was proposed therefore to attempt the ester hydrolysis using this method.

Treatment of the diester with iodi trimethylsilane in the presence of iodine at 100°C followed by aqueous work-up gave the required diacid (172).

Treatment of the diacid (172) with acetic anhydride in the presence of DMAD failed to give any of the desired product (as shown by mass spectroscopy) after heating the reactants under reflux for five hours. When the reaction was carried
out at 130°C for 1 1/4 hours, starting material was the only identifiable compound obtained from the reaction mixture.

McDermott and Benoiton in 1973 reported\textsuperscript{123} the use of \( N,N \)-dicyclohexylcarbodiimide (DCCI) in tetrahydrofuran for the cyclisation of \( N \)-acylaminoacids. Evidence of the oxazolium-5-oxide intermediate was obtained by trapping it with methyl propiolate at room temperature. It seemed possible therefore that this method might prove useful in the synthesis of the pyrazinodipyrrolizine derivative (173). Treatment of the diacid (172) with DCCI in tetrahydrofuran at 45°C gave two compounds which gave similar \( ^1 \)H n.m.r., mass and infra-red spectra. However, the spectroscopic data were not consistent with the expected structure, nor could any reasonable structure be deduced from the data.
5. Miscellaneous Reactions

5.1 Attempted synthesis of methyl 3-nitroso-3H-pyrrolizine-6-carboxylate

Flitsch\textsuperscript{55} reported in 1968 the preparation of 3-hydroxyimino-3H-pyrrolizine (178) by treatment of the parent 3H-pyrrolizine with amyl nitrite and sodium hydroxide. It seemed possible that methyl 3H-pyrrolizine-6-carboxylate would react in a similar manner to give the nitroso compound (179) which would tautomerise to the oxime (180). This compound would possibly be of synthetic use as a precursor of pyrmidino[2,1,6-cd]pyrrolizine (182) as shown below.

However, attempts to prepare the nitroso compound based on the method of Flitsch\textsuperscript{55} or that of Zambito and Howe\textsuperscript{124} were unsuccessful.
5.2 Attempts to synthesise 6-acyloxyindolizines from \( N \)-acetonylpyrrole-2-carbaldehyde

Sliwa and Blondeau\textsuperscript{125} recently reported the preparation of 8-acyloxyindolizines by treatment of the cyclic hemiacetals (183) with sodium acetate in acetic anhydride. The fact that these somewhat labile compounds were able to survive the reaction conditions suggested that the same conditions might be applicable to a conversion of \( N \)-acetonylpyrrole-2-carbaldehyde (109) into 6-acyloxyindolizine (187). This indolizine derivative, in which both the 3- and 5-positions would be
susceptible to electrophilic attack, might then be a valuable starting point for cyclazine synthesis.
Treatment of $N$-acetonylpyrrole-2-carbaldehyde with sodium acetate and acetic anhydride at room temperature, or at the reflux temperature, failed to give any of the required indolizine. When the reaction mixture was subjected to chromatography, only starting material was obtained. A similar negative result was obtained when 1,5-diazabicyclo[5.4.0]-undec-5-ene (DBU) was used as the base. However, when the reaction was carried out using potassium $t$-butoxide in dimethylformamide at $-20^\circ C$, before the addition of acetic anhydride at $-78^\circ C$ $N$-(2-acetoxyprop-1-enyl)-pyrrole-2-carbaldehyde was obtained. The reaction evidently proceeds via the enolate ion (188) and suggests that deprotonation at the CH$_2$ group is preferred to the required deprotonation at CH$_3$.

\[
\begin{align*}
\text{CHO} & \quad \xrightarrow{\text{KOBu}^+} \quad \text{CHO} \\
\text{CH}_2\text{CHO} & \quad \text{DMF} \\
(109) & \quad (188) \\
\end{align*}
\]
5.3 **Attempted reactions of pyrrolizine-3-one**

The chemical properties of pyrrolizin-3-one (191) are virtually unknown although the compound has been known since 1971. The only reactions which have been reported are those involving stabilised phosphoranes (Scheme 6).

![Scheme 6](image)

More recently a straightforward, high yield synthesis of pyrrolizin-3-one from pyrrole-2-carbaldehyde was reported by McNab. It was proposed, therefore, to synthesise, and investigate the chemical properties of, pyrrolizin-3-one with a view to making use of the compound as a precursor of cyclazines. Thus, pyrrole-2-carbaldehyde was condensed with Meldrum's acid and the resulting product (196) was subjected to flash vacuum pyrolysis to give pyrrolizin-3-one (191) in good yield.

The first objective was to convert the pyrrolizin-3-one into its oxime (197) or tosylhydrazone (198) since these compounds are potential precursors of pyrimido[2,1,6-\(cd\)]pyrrolizine (201) (Scheme 7). This compound is the only unsubstituted
Scheme 7
monoaza-derivative of pyrrolo[2,1,5-cd]indolizine ([2.2.3]-cyclazine) that remains unknown.

Unfortunately, the pyrrolizine did not react directly with tosylhydrazine and attempts to convert it into the potentially more reactive pyrrolizinylium cations (202) or (203) by reaction with phosphoryl chloride or triethylxoxonium fluoroborate, respectively, gave dark, uncharacterisable products.

Attempted reactions with p-tolylsulphonyl isocyanate, Lawesson's reagent [(4-MeOC₆H₄PS₂)₂], Pd(OAc)₂ and formylation reagents were also unsuccessful.
SECTION III

EXPERIMENTAL
### Abbreviations and Symbols

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>b.p.</td>
<td>boiling points</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting points</td>
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<td>t.l.c.</td>
<td>thin layer chromatography</td>
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<tr>
<td>n.m.r.</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>s; d; t;</td>
<td>singlet; doublet; triplet;</td>
</tr>
<tr>
<td>q; m</td>
<td>quartet; multiplet</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
<tr>
<td>p.p.m.</td>
<td>parts per million</td>
</tr>
<tr>
<td>br.</td>
<td>broad</td>
</tr>
<tr>
<td>ν</td>
<td>wavenumber (cm$^{-1}$)</td>
</tr>
<tr>
<td>M$^+$</td>
<td>mass of molecular ion</td>
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<tr>
<td>m/e</td>
<td>mass to charge ratio</td>
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<tr>
<td>h; min</td>
<td>hours; minutes</td>
</tr>
<tr>
<td>M</td>
<td>mol dm$^{-3}$</td>
</tr>
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<td>UV</td>
<td>ultra violet</td>
</tr>
<tr>
<td>sh</td>
<td>shoulder</td>
</tr>
<tr>
<td>quat.</td>
<td>quaternary carbon</td>
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</table>
Melting points of new compounds were obtained on a Kofler hot-stage microscope and are not corrected.

Microanalyses for carbon, hydrogen and nitrogen were carried out on a Perkin-Elmer Elemental Analyser 240 by Mr. J. Grunbaum, University of Edinburgh.

Infrared spectra were recorded on a Perkin-Elmer 157G grating spectrophotometer. Unless otherwise noted, solids were run as nujol mulls and liquids as thin films, both on sodium chloride plates. Characteristic peaks are given and spectra were calibrated with the polystyrene peak at 1603 cm$^{-1}$.

Proton ($^1$H) nuclear magnetic resonance spectra were recorded on a Bruker WP80 instrument (operating at 80MHz) or a Bruker WP200 instrument (operating at 200MHz), operated by Mr. J.R.A. Millar and Mr. L.H. Bell. High resolution and selectively decoupled spectra were obtained on a Bruker WH360 instrument (operating at 360MHz) operated by Dr. I.H. Sadler and Dr. D. Reed. Chemical shift values were recorded on the $\delta$ scale in p.p.m. relative to tetramethylsilane as internal standard ($\delta=0$) or chloroform ($\delta=7.25$). Unless otherwise noted, the solvent used was deuteriochloroform.

Carbon ($^{13}$C) nuclear magnetic resonance spectra were obtained at 25MHz on a Varian CFT-20 instrument or at 50MHz on a Bruker WP200 operated by Mr. J.R.A. Millar.

Mass spectra and exact mass measurements were recorded on an A.E.I. MS902 spectrometer operated by Mr. D. Thomas. The parent ion and major fragmentation peaks are given, together
with the percentage peak heights.

Alumina (Laporte Industries, Type UG) which had been deactivated by shaking with water (6 g per 100 g alumina) was used for column chromatography. Silica was Fisons Scientific Apparatus - Silica Gel for chromatography (60-120 mesh) and was 10% deactivated. For thin layer chromatography, 50x200 mm glass plates covered by 0.3 mm alumina (Merck, Aluminium oxide 60G, type E), or silica (Merck, Kieselgel 60G), with added fluorescent indicator (M. Woelm, Eschwege, Germany), were used. The components were observed under ultraviolet light or by their reaction with iodine vapour. For preparative thin layer chromatography, 1.0 mm layers of the supports mentioned above were used.

Ultraviolet and visible spectra were recorded on a Pye Unicam SP8-400 Spectrophotometer. The abbreviation 'sh' refers to a shoulder on the curve.

Organic solutions were dried by standing over anhydrous magnesium sulphate for an hour and were evaporated under reduced pressure on a rotary evaporator.

Commercially available solvents were used without further purification unless otherwise indicated. Where pure methanol or chloroform were required the commercial Analytical Reagent (A.R.) grade solvent was used. Dry acetonitrile, dimethylformamide, diisopropylamine and nitrobenzene were prepared by storing over freshly activated Linde molecular sieve (Type 4A). Dry benzene, ether and toluene were prepared by addition of sodium wire to the solvent. Super dry ether was prepared by heating the dry solvent under reflux for several hours with lithium aluminium hydride and distilling on to freshly activated
molecular sieve. Pyridine was dried by heating under reflux with KOH for 2 h and then distilling (b.p. 114-117°C) on to freshly activated molecular sieve. Dry tetrahydrofuran was prepared by heating under reflux with calcium hydride in an atmosphere of dry nitrogen for 3 h and then distilling on to freshly activated molecular sieve. Light petroleum refers to the redistilled 40-60°C boiling fraction and was used for both chromatography and recrystallisation.
1. Preparation of Pyrrolizines

Pyrrole-2-carbaldehyde

This was prepared by the method of Silverstein et al. \(^{129}\). Starting from 33.5 g of pyrrole, 38 g (80%) of long white needles, m.p. 44-45°C were obtained.

3\(H\)-Pyrrolizine

This was prepared by the method of Schweizer and Light \(^{53}\). Starting from 10 g of freshly recrystallised pyrrole-2-carbaldehyde, 9.5 g (89%) of a colourless liquid, b.p. 70-75°C/15 mm were obtained.

5,10-Dihydro-5,10-dipyrrolidino[1,2-a:1',2'-d]pyrazine

Pyrrole-2-carbaldehyde (28.3 g) and pyrrolidine (21.2 g) were heated to 60°C in dry benzene (100 ml) with a catalytic amount of \(p\)-tolylsulphonic acid under dry \(N_2\) for 1 h. The solution changed colour from yellow to red. The solvent was removed and subsequent recrystallisation of the residue from ether gave, as a mixture of E and Z isomers, 5,10-dihydro-5,10-dipyrrolidino[1,2-a:1',2'-d]pyrazine (32.3 g; 73%), as pale orange/pink prisms, m.p. 84-92°C (lit.\(^{130}\) m.p. Z isomer 65-68°C; E isomer 95-98°C). The identity of the mixture was confirmed by comparison of its \(^1\)H n.m.r. spectrum with that reported by Watanabe et al.\(^{130}\).

Methyl 3\(H\)-pyrrolizine-6-carboxylate

5,10-Dihydro-5,10-dipyrrolidino[1,2-a:1',2'-d]pyrazine (8.61 g) was heated under reflux in methyl acrylate (100 ml)
with stirring for 5 h under dry N₂. The solvent was removed and sodium methoxide (from 0.40 g Na) in methanol (25 ml) was added and the reaction heated under reflux for 2 h. After neutralization with dilute HCl and dilution with water, the product was extracted with dichloromethane. The organic extract was dried and concentrated and the residue subjected to chromatography on silica. Elution with ether/light petroleum (2:3) followed by recrystallisation from light petroleum/ethanol gave, methyl 3H-pyrrolizine-6-carboxylate (5.0 g; 53%), as yellow needles, m.p. 92-93°C (lit. 55 m.p. 91°C).

Note:-

This compound was identical with that of Flitsch and Heidhues 55 who showed unambiguously by ¹H n.m.r. that the compound is methyl 3H-pyrrolizine-6-carboxylate and not methyl 3H-pyrrolizine-2-carboxylate as claimed by Watanabe et al. 56.

**Ethyl 2-pyrrolylglyoxylate**

This was prepared according to the method of Brandänge and Lundin 54.

Starting from 10 g of pyrrole, 19.9 g (71%) of a pale yellow liquid, b.p. 105°C/0.1 mm were obtained.

**Ethyl 3H-pyrrolizine-7-carboxylate**

This was prepared according to the method of Brandänge and Lundin 54.

Starting from 5.2 g of freshly distilled ethyl 2-pyrrolylglyoxylate, 2.7 g (49%) of yellow oil were obtained.
2-Phenyl-3H-pyrrolizine and 2-phenylsulphonyl-pyrrolizine

These pyrrolizines were kindly donated by Professor Wilhelm Flitsch, Organisch-Chemisches Institut der Universität Münster.
2. Synthesis of [2.2.3]cyclazines(pyrrolo[2,1,5-<i>cd</i>]-
indolizines) from Pyrrolizines

1,5-Diphenyl-1,5-diazapentadienium perchlorate
This was prepared according to the method of Lloyd <i>et al</i> <sup>131</sup>. 
Starting from 11 g of 1,1,3,3-tetramethoxypropane, 14 g 
(86%) of yellow crystals, m.p. 218–220°C were obtained.

1,1,5,5-Tetramethyl-1,5-diazapentadienium perchlorate
This vinamidinium salt (24) was prepared by the method 
of McNab <sup>132</sup>. 
Starting from 4.8 g of 1,5-diphenyl-1,5-diazapenta-
dienium perchlorate, 3.2 g (98%) of pale buff plates, m.p. 
119°C were obtained.

Methyl pyrrolo[2,1,5-<i>cd</i>]indolizine-1-carboxylate
a) A solution of methyl 3H-pyrrolizine-6-carboxylate (0.5 
g) in dimethylformamide (25 ml) was stirred in a dry N<sub>2</sub> atmos-
phere. 1,1,5,5-Tetramethyl-1,5-diazapentadienium perchlorate 
(0.75 g) was added in one batch at room temperature and the 
resulting suspension was stirred for 10 min. Sodium hydride 
(0.15 g of a 50% oil dispersion) was added, and the solution 
was heated at 60°C for 1 h. The resulting deep red solution 
was then further heated under reflux for 35 h, allowed to cool, 
diluted with water, and extracted with ether. The ethereal 
extract was dried and evaporated and the residue was chromato-
graphed on alumina. Elution with ether/light petroleum (2:3) 
followed by recrystallisation from pentane gave, methyl 
pyrrolo[2,1,5-<i>cd</i>]indolizine-1-carboxylate (0.3 g; 49%), as 
yellow prisms, m.p. 60°C (lit. <sup>12</sup> m.p. 59–61°C). The <sup>1</sup>H n.m.r.
spectrum was identical to that reported by Pohjala.

b) Methyl 3H-pyrrolizine-6-carboxylate (0.5 g) was heated with a slight excess of 1,1,3,3-tetramethoxypropane in acetic anhydride (4 ml) for 6 h. Water was added and the solution was extracted with dichloromethane. Evaporation of the extract and recrystallisation of the residue yielded methyl pyrrolo-[2,1,5-cd]indolizine-1-carboxylate (0.16 g; 26%), m.p. 60°C, identical with the product obtained by method (a).

**Ethyl pyrrolo[2,1,5-cd]indolizine-2-carboxylate**

A solution of ethyl 3H-pyrrolizine-7-carboxylate (0.31 g) in dimethylformamide (25 ml) was stirred under dry N₂. 1,1,5,5-Tetramethyl-1,5-diazapentadienium perchlorate (0.40 g) was added in one batch at room temperature and the resulting suspension was stirred for 10 min. Sodium hydride (0.084 g of a 50% oil dispersion) was added and the solution was stirred for 5 min, warmed slowly to reflux, and heated under reflux for 42 h. The solvent was distilled off, water was added, and the product was extracted into ether. The ethereal extract was dried and evaporated and the residue was subjected to chromatography on alumina. Elution with ether gave first, ethyl pyrrolo[2,1,5-cd]indolizine-2-carboxylate (0.18 g; 48%), as a yellow oil, m.p. close to room temperature (Found: M⁺ 213.077866, C_{13}H_{11}NO₂ requires M⁺ 213.078973); ν max 1720 br (C=O) cm⁻¹; λ max (EtOH) 250, 295 sh, 303, 420, 433, and 443 nm (log ε 4.26, 3.87, 3.97, 3.55, 3.55, and 3.51); δH (360MHz) 1.48 (3H, t, Et), 4.51 (2H, q, Et), 7.36 (1H, dd, H-4), 7.68 (1H, t, H-6), 7.79 (1H, d, H-1), 7.82 (1H, d, H-3), 7.99 (1H, d, H-5),
and 8.02 (1H, d, H-7), J_{1,4} 0.95, J_{3,4} 4.5 and J_{5,6} = J_{6,7} 7.8 Hz; m/e 213 (M^+; 100), 185 (53), 168 (73), 141 (48), 140 (55). Hydrolysis of this product with KOH in methanol gave pyrrolo[2,1,5-cd]indolizine-2-carboxylic acid, as yellow needles, m.p. 231-233°C (from ethyl acetate) (lit.\textsuperscript{10} m.p. 231-233°C) (Found: C, 71.2; H, 4.0; N, 7.3. \text{C}_{14}H_{27}NO_{2} requires C, 71.35; H, 3.8; N, 7.6%).

Further elution of the alumina column with ether and recrystallisation of the eluted material from ethanol yielded, as a mixture of two isomers, (1) ethyl (ZE)-3-[3-(N,N-dimethylamino)prop-2-enylidene]-3H-pyrrolizine-7-carboxylate as the major isomer and (2) the (EE) isomer. (0.098 g; 22%), as red-brown plates, m.p.151-152°C (Found: C, 69.6; H, 6.9; N, 10.6. \text{C}_{15}H_{18}N_{2}O_{2} requires C, 69.7; H, 7.0; N, 10.8%); \nu_{max} 1680 cm\textsuperscript{-1} (C=O); \delta_H (360MHz) (ZE) isomer 1.16 (3H, t, OEt), 2.82 (6H, s, NMe\textsubscript{2}), 4.25 (2H, q, OEt), 5.22 (1H, t, H-2'), 6.18 (1H, d, H-1'), 6.36 (1H, dd, H-2), 6.58 (1H, d, H-3'), 6.63 (1H, d, H-1), 6.69 (1H, dd, H-6), and 7.01 (1H, d, H-5), J_{1',2'} = J_{2',3}, 12.3, J_{1,2} 5.3, J_{5,6} 3.0, J_{2,6} 0.9Hz. \delta_H (360 MHz) (EE) isomer 1.16 (3H, t, OEt), 2.79 (6H, s, NMe\textsubscript{2}), 4.25 (2H, q, OEt), 5.26 (1H, t, H-2'), 6.44 (1H, d, H-3'), 6.51 (1H, d, H-1'), 6.56 (1H, dd, H-6), 6.66 (2H, s, H-1 and 2), and 6.88 (1H, d, H-5), J_{5,6} 3.0; J_{2,6} 0.9Hz and in \text{C}_{6}D_{6} J_{1',2'} 11.8, J_{2',3}, 12.8, J_{1,2} 5.4, J_{2,6} J_{2,1}, 0.7-0.9, J_{1,1} ca 1.4, J_{2,1}, J_{1',3}, 0.5-0.7Hz; m/e 258 (M^+; 100), 230 (9), 213 (36), 185 (14).

A similar mixture of isomers was obtained as the sole product when the same reactants were stirred together in dimethylformamide at room temperature for 16 h; starting from 0.33 g of ethyl 3H-pyrrolizine-7-carboxylate, 0.30 g (60%) of
red brown plates was obtained.

This mixture of compounds, once isolated from the reaction, failed to cyclise on being heated under reflux in dimethylformamide.

Pyrrolo[2,1,5-cd]indolizine

A solution of 3H-pyrrolizine (0.3 g) in dimethylformamide (25 ml) was stirred under dry N₂ and the vinamidinium salt (24) (0.71 g) was added. After 10 min, sodium hydride (0.137 g of a 50% oil dispersion) was added in one portion. The solution was then stirred at room temperature for a further 5 min, heated slowly to the boiling point and held under reflux for 45 h. After being cooled, the solution was diluted with water and extracted with pentane. The pentane extract was dried and evaporated, and the residue was subjected to chromatography on alumina. Elution with ether and vacuum sublimation (2x) of the recovered material yielded, pyrrolo[2,1,5-cd]indolizine (0.185 g; 46%), as pale yellow plates, m.p. 60-61°C (lit. ¹ m.p. 63.5-64.5°C). Comparison of the ¹H n.m.r. spectrum with that reported by Boekelheide et al.¹³,³⁵ indicated that this was the required cyclazine.

6-Dimethylaminofulvene

This was prepared according to the method of Hafner et al.\textsuperscript{133}.

Starting from 21.7 g of freshly distilled cyclopentadiene, 20.1 g (50%) of golden yellow plates, m.p. 65-67°C were obtained.

5-(N,N-dimethylaminomethylene)-1-(N,N-dimethyliminiomethyl)-cyclopenta-1,3-diene perchlorate

This was prepared according to the method of Hafner et al.\textsuperscript{133}.

Starting from 3.6 g of 6-dimethylaminofulvene, 7.0 g (85%) of yellow needles, m.p. 235-236°C were obtained.

Methyl cyclopenta[4,5]azepino[7,1,2-cd]pyrrolizine-1-carboxylate

Methyl 3H-pyrrolizine-6-carboxylate (0.8 g) was dissolved in dimethylformamide (50 ml) in a 100 ml round bottomed flask fitted with a magnetic stirrer, a flow of dry nitrogen and a condenser with calcium chloride drying tube. The fulvene-iminium salt (69) (2.21 g) was added in one batch at room temperature, and the resulting suspension was stirred for 5 min. Sodium hydride (0.39 g of a 50% oil dispersion) was added and the solution was stirred at room temperature for 15 min, and then heated at 70°C for 0.5 h and under reflux for 20 h. Water was added and the product was extracted into dichloromethane.
The extract was dried and evaporated and the residue was subjected to chromatography on silica. Elution with ether/light petroleum (1:4) gave a green solid which was recrystallised from light petroleum to give, methyl cyclopenta[4,5]azepino-[7,1,2-\textit{cd}]pyrrolizine-1-carboxylate (0.35 g; 28%), as green plates, m.p. 135-136°C (Found: C, 76.8; H, 4.4; N, 5.5. C_{16}H_{11}NO_{2} requires C, 77.0; H, 4.45; N, 5.6%); ν_{\text{max}} 1710 (C=O) cm\textsuperscript{-1}; λ_{\text{max}} (EtOH) 245, 264, 282, 302, 340, 354, 388, 425, 453, 580, 625, and 688 nm (log ε 4.34, 4.28, 4.47, 4.45, 4.58, 4.74, 3.92, 3.83, 3.68, 2.81, 2.82, and 2.48);

δ_{H} (100MHz) 3.98 (3H, s, OMe), 7.30 (1H, d, H-3), 7.49 (1H, d, H-4), 7.76 (1H, s, H-2), 7.84 (2H, m, H-6 and 8), 7.97 (1H, t, H-7), 8.54 (1H, s, H-5), and 9.58 (1H, s, H-9); m/e 249 (M\textsuperscript{+}; 100), 218 (13), 190 (32).

**Ethyl cyclopenta[4,5]azepino[7,1,2-\textit{cd}]pyrrolizine-2-carboxylate**

Ethyl 3H-pyrrolizine-7-carboxylate (0.53 g) was dissolved in dimethylformamide (50 ml) in a 100 ml RB flask fitted with a magnetic stirrer, a flow of dry N\textsubscript{2} and a condenser with calcium chloride drying tube. The fulvene-iminium salt (69) (0.91 g) was added in one batch at room temperature, and the resulting suspension was stirred for 5 min. Sodium hydride (0.16 g of a 50% oil dispersion) was then added and the solution was stirred for 15 min. The resulting burgundy red solution was heated slowly to the boiling point and held under reflux for 24 h. The dimethylformamide was distilled off, the residue diluted with water, and the product extracted with ether. The ethereal extract was dried and evaporated and the
product was subjected to chromatography on alumina. Elution with ether, followed by recrystallisation from ethanol gave, ethyl cyclopenta[4,5]azepino[7,1,2-cd]pyrrolizine-1-carboxylate (0.395 g; 50%), as brown micro-prisms, m.p. 124-125°C (Found: C, 77.3; H, 5.05; N, 5.1. C$_{17}$H$_{13}$NO$_2$ requires C, 77.55; H, 5.0; N, 5.3%); $\nu_{\text{max}}$ 1610 (C=O) cm$^{-1}$; $\lambda_{\text{max}}$ (EtOH) 273sh, 307, 331, 345, 402, 425, 455, 526, 544, 564sh, 586 and 643 nm (log $\varepsilon$ 4.18, 4.56, 4.63, 4.82, 3.80, 3.85, 3.90, 2.55, 2.58, 2.53, 2.48 and 2.15); $\delta_{\text{H}}$ (360MHz) 1.50 (3H, t, OEt), 4.50 (2H, q, OEt), 7.61 (1H, dd, H-4), 7.62 (1H, d, H-3), 7.81 (1H, m, H-6), 7.83 (1H, m, H-8), 7.89 (1H, t, H-7), 8.03 (1H, br.s. H-1), 8.61 (1H, s, H-5) and 8.67 (1H, s, H-9), $J_{1,4}$ ca 0.5-0.7, $J_{3,4}$ 4.9, $J_{6,7} = J_{7,8}$ 3.8Hz; m/e 263 (M$^+$ 100), 235 (82), 218 (14), 190 (42).

1-Phenylsulphonylcyclopenta[4,5]azepino[7,1,2-cd]-pyrrolizine

2-Phenylsulphonyl-3H-pyrrolizine (0.2 g) was dissolved in dimethylformamide (20 ml) in a 100 ml RB flask fitted with a magnetic stirrer, a flow of dry N$_2$ and a condenser with a calcium chloride drying tube. The fulvene-iminium perchlorate (69) (0.24 g) was added in one batch at room temperature, and the resulting suspension was stirred for 5 min. Sodium hydride (0.040 g of a 50% oil dispersion) was then added and the resulting burgundy red solution was stirred for 45 min. The solution was heated slowly to the boiling point and held under reflux for 17 h. The dimethylformamide was distilled off, the residue diluted with water and the product extracted with ether. The ethereal extract was dried and evaporated
and the residue was subjected to preparative t.l.c. on silica. Elution with ether followed by recrystallisation from n-butyl acetate gave, 1-phenylsulphonylcyclopenta[4,5]azepino[7,1,2-cd]-pyrrolizine (0.079 g; 30%), as green needles, m.p. 248-250°C (Found: C, 72.3; H, 3.8; N, 4.4. C_{20}H_{13}NO_2S requires C, 72.5; H, 3.95; N, 4.2%; v_{max} 1155 and 1320 (SO_2) cm^{-1}; λ_{max} (EtOH) 275, 295, 301, 337, 349, 386, 424, 432sh, 452, 578, 625, and 687 nm. (log ε 4.38, 4.39, 4.40, 4.51, 4.65, 3.87, 3.72, 3.65, 3.58, 2.34, 2.35, and 2.05); δ_{H} (360MHz) 7.45-7.50 (4H, m, m- and p-Ph protons and H-3), 7.68 (1H, d, H-4), 7.92 (1H, br.d. H-6), 7.93 (1H, s, H-2), 8.01 (1H, br.d., H-8), 8.10 (1H, t, H-7), 8.11-8.14 (2H, m, o-Ph protons), 8.74 (1H, s, H-5), and 9.55 (1H, s, H-9), J_{3,4} = 4.9, J_{6,7} = J_{7,8} 3.8Hz; m/e 331 (M^{+}; 100), 206 (17), 190 (51).

1-Phenylcyclopenta[4,5]azepino[7,1,2-cd]pyrrolizine

2-Phenyl-3H-pyrrolizine (0.28 g) was dissolved in dimethylformamide (20 ml) in a 100 ml RB flask fitted with a magnetic stirrer, a flow of dry nitrogen and a condenser with a calcium chloride drying tube. The fulvene-iminium salt (69) (0.43 g) was added in one batch at room temperature, and the resulting suspension was stirred for 5 min. Sodium hydride (0.074 g of a 50% oil dispersion) was then added and the resulting dark burgundy red solution was stirred for 75 min, heated slowly to the boiling point and held under reflux for 18 h. The dimethylformamide was distilled off, the residue diluted with water and the product was extracted with ether. The ethereal extract was dried and evaporated and the residue was subjected to preparative t.l.c. on silica.
Elution with ether/light petroleum (1:4), gave a dark red solid which was recrystallised from pentane to give, 1-phenyl-
cyclopenta[4,5]azepino[7,1,2-cd]pyrrolizine (0.075 g; 18%), as dark yellow brown needles, m.p. 93°C (Found: C, 89.8; H, 5.2; N, 5.4. \( \text{C}_{20}\text{H}_{13}\text{N} \) requires C, 89.9; H, 4.9; N, 5.2%); 
\( \lambda_{\text{max}} \) (EtOH) 257, 304, 312, 349, 395, 420, 446, 512, 534, 550sh, 578, and 642 nm, (log \( \epsilon \) 4.27, 4.30, 4.31, 4.54, 3.63, 3.68, 3.49, 2.31, 2.32, 2.28, 2.23, and 1.80); \( \delta_{\text{H}} \) (100MHz) 7.30-7.95 (11H, m, Ph and H-2,3,4,6,7, and 8), 8.73 (1H, s, H-9), and 8.88 (1H, s, H-5); m/e 267 (M\(^+\)).
4. Investigation of Routes to Pyrazino[2,1,6-cd:3,4,5-c'd']dipyrrolizines

4.1 Pyrrolizine coupling reactions as a potential route to pyrazinodipyrrolizines

Attempted reaction of methyl 3H-pyrrolizine-6-carboxylate with LDA/I₂

Freshly prepared lithium diisopropylamide (0.39 g) in tetrahydrofuran (2 ml) was added dropwise, under dry N₂, to methyl 3H-pyrrolizine-6-carboxylate (0.59 g) in tetrahydrofuran at room temperature. A colour change from yellow to deep red was observed. The reaction mixture was stirred for 10 min and then cooled to -78°C before the addition of iodine (0.48 g; 5% XS) in tetrahydrofuran (10 ml). The solution was allowed to warm slowly with stirring to room temperature. The solvent was removed, water added and the organic material extracted with dichloromethane. The extract was dried and evaporated and the residue subjected to chromatography on alumina. Elution with ether/light petroleum (2:3) gave a dark yellow red gum (0.03 g). The ¹H n.m.r. spectrum was poorly resolved; however, the mass spectrum of the material showed a peak at m/e 324, the molecular weight of the required dimer. m/e 324 (M⁺; 65), 233 (83), 163 (83), 162 (70), 104 (100).

Note:

This reaction was repeated several times, but on each occasion insufficient material was obtained for spectroscopic characterisation.
Reaction of methyl 3H-pyrrolizine-6-carboxylate with Pd/C

Methyl 3H-pyrrolizine-6-carboxylate (0.33 g) and 5% Pd/C (1.0 g) were heated under reflux in dry xylene (30 ml) for 22 h. T.l.c. showed many spots. The Pd/C was filtered off through Celite and the resulting filtrate was concentrated and subjected to chromatography on silica. Elution with dichloromethane gave a brown crystalline solid (10 mg), the \(^1\text{H} \text{n.m.r.} \) spectrum of which suggested that it was the reduced dihydropyrrolizine (105); \( \delta_H \ (200\text{MHz}) 2.43-2.51 \ (2\text{H}, \text{ m, H-2}), 2.80 \ (2\text{H}, \text{ t.d. H-1}), 3.77 \ (3\text{H}, \text{ s, OMe}), 3.94 \ (2\text{H}, \text{ t. H-3}), 6.21 \ (1\text{H}, \text{ q, H-7}), \) and 7.21 \ (1\text{H}, \text{ d, H-5}). \ J_{5,7} 1.3 \text{ and } J_{1,7} 1.1\text{Hz}; \ m/e 165 \ (M^+; 49), 134 \ (100), 106 \ (20).

No other identifiable product was obtained.

Attempted reaction of methyl 3H-pyrrolizine-6-carboxylate with Na\(_2\)PdCl\(_4\)

Sodium chloride (0.24 g) and palladium(II) chloride (0.36 g) were heated under reflux in methanol (20 ml; A.R.) until a homogeneous red brown coloured solution was obtained (1½ h). The solution was allowed to cool to room temperature and methyl 3H-pyrrolizine-6-carboxylate (0.33 g) was added. The solution was stirred for 100 h. A black precipitate (0.27 g) was filtered off. The dark coloured filtrate was diluted with water, extracted with dichloromethane and the extract dried and evaporated to give a black solid m.p. \(>300^\circ\text{C}\). Extraction of this solid with refluxing methanol and hot filtration followed by evaporation of the solvent gave a brown solid (0.52 g) m.p. \(>300^\circ\text{C}\). This could not be identified by \(^1\text{H} \text{n.m.r.} \) or mass spectroscopy.
4.2 The route to pyrazinodipyrrolizines from pyrazino[2.1.6-cd]pyrrolizines

4.2.1 Pyrrolo[1,2-a]pyrazines as potential precursors of pyrazino[2,1,6-cd]pyrrolizines

N-(2-Pyrrolylmethylene)aminoacetaldehyde diethyl acetal

This was prepared according to the method of Herz and Tocher\textsuperscript{76}.

Starting from 6.0 g of pyrrole-2-carbaldehyde, 10.96 g (82\%) of a yellow oil, b.p. 119-125\degree C/2 mm were obtained.

Pyrrolo[1,2-a]pyrazine

This was prepared according to the method of Herz and Tocher\textsuperscript{76}.

Starting from 2.1 g of the foregoing acetal, 0.58 g (49\%) of a clear oil, b.p. 71\degree C/2 mm were obtained.

Note:

1) Cyclisation was also effected by reaction with 0.5M H\textsubscript{2}SO\textsubscript{4} in acetic acid. However the yield was lower (30\%) and the product was contaminated with acetic acid.

2) Attempts to cyclise using BF\textsubscript{3}(Et\textsubscript{2}O) in ether failed to produce any of the required product.

Attempted reaction of pyrrolo[1,2-a]pyrazine with dimethyl acetylenedicarboxylate (DMAD)

The pyrrolopyrazine (0.51 g), 5\% Pd/C catalyst (0.8 g), DMAD (0.81 ml) and dry toluene (54 ml) were heated under reflux
for 22 h. T.l.c. showed the disappearance of starting material. The Pd/C catalyst was removed by filtration through Celite. The filtrate was evaporated and the residue subjected to chromatography on silica. Elution with ether/light petroleum (1:1), gave an orange powder (0.12 g), m/e 406 (M⁺; 5), 375 (100) (C₁₄H₁₂N₂O₄ requires m/e 258). The ¹H n.m.r. spectrum of the product was complex and did not lead to an identification.

N-Acetonylpyrrole-2-carbaldehyde

Pyrrole-2-carbaldehyde (4.0 g) in dimethylformamide (50 ml) was added dropwise to a stirred solution of potassium t-butoxide (4.72 g) in dimethylformamide (50 ml) at room temperature and under dry N₂. The solution was stirred for 2 h and then transferred to a dropping funnel from which it was added dropwise to bromoacetone (3.90 ml; 10% XS) in dimethylformamide (50 ml) at -78°C over a period of 1 h. The solution was allowed to warm to room temperature overnight. The solvent was distilled off, the residue treated with water, and the product extracted into ether. The extract was dried and evaporated and the residue subjected to chromatography on silica. Elution with ether/light petroleum (2:3) gave, N-acetonylpyrrole-2-carbaldehyde (3.36 g; 53%), as colourless needles, m.p.61°C (from light petroleum) (Found: C, 63.5; H, 6.1; N, 9.25. C₈H₉NO₂ requires C, 63.6; H, 6.0; N, 9.3%); νmax 1655 br (C=O) and 1720 br (C=O) cm⁻¹; δH (100MHz) 2.18 (3H, s, -CH₃), 5.06 (2H, s, -CH₂-), 6.22-6.30 (1H, m, H-4), 6.80-6.85 (1H, m, H-3), 6.90-7.0 (1H, m, H-5), and 9.46 (1H, s, -CHO); m/e 151 (M⁺; 42), 109 (94), 108 (100), 94 (7),
100

Note:

1) When the reaction was carried out using chloroacetone and with sodium hydride as the base, yields were much lower (0-10%).

2) If the addition of the salt to the haloacetone was carried out at room temperature the reaction turned dark brown and yields were low.

3) No N-acetonylpyrrole-2-carbaldehyde was obtained using sodium ethoxide as the base.

N-Propargylpyrrole-2-carbaldehyde

Pyrrole-2-carbaldehyde (9.5 g) in dimethylformamide (50 ml) was added dropwise to a stirred solution of potassium t-butoxide (11.2 g) in dimethylformamide (50 ml) at room temperature and under dry N₂. The solution was stirred for 2 h and then transferred to a dropping funnel from which it was added dropwise to freshly distilled propargyl bromide (8 ml; 7% XS) in dimethylformamide (50 ml) at -78°C over a period of 1 h. The solution was stirred under nitrogen for 1 h and then allowed to warm to room temperature overnight. The solvent was distilled off, the residue treated with water, and the product extracted with dichloromethane. The extract was dried and evaporated and the residual liquid was distilled through a Vigreux column to give N-propargylpyrrole-2-carbaldehyde (8.41 g; 63%), as a colourless oil, b.p. 56-58°C /0.05 mm (Found: M⁺ 133.053431, C₈H₇NO requires M⁺ 133.052761); vₓ max 3300 (≡C-H), 2130 (-C≡C-), and 1660 (-CHO) cm⁻¹;
$\delta_H$ (100MHz) 2.43 (1H, t, C=CH-H), 5.15 (2H, d, -CH$_2$-), 6.18-6.28 (1H, m, H-4), 6.86 (1H, m, H-3), 7.18-7.26 (1H, m, H-5), and 9.49 (1H, d, -CHO) $J_{1',3'}$ 3Hz; m/e 133 (M$^+$; 100), 104 (74).

3-Methylpyrrolo[1,2-a]pyrazine

(a) N-Acetonylpyrrole-2-carbaldehyde (1.51 g) and ammonium acetate (0.77 g) were heated under reflux in glacial acetic acid (50 ml) for 45 min. The solvent was removed in vacuo and the residue was diluted with water and extracted with ether. The ethereal extract was dried and evaporated and the resulting solid was subjected to chromatography on silica. Elution with ether/light petroleum (1:1) gave, 3-methylpyrrolo[1,2-a]pyrazine (1.12 g; 85%), as pale yellow plates, m.p. 82-84°C (light petroleum) (lit. 79 m.p. 76-81°C). The $^1$H n.m.r. spectrum was identical to that reported by Flament et al. 79.

(b) N-Propargylpyrrole-2-carbaldehyde (1.73 g) and ammonium acetate (1.0 g) were heated under reflux in glacial acetic acid (50 ml) with a catalytic amount of cuprous chloride for 5 h. The solvent was removed in vacuo, the residue treated with water and the product extracted with dichloromethane. The extract was dried and evaporated and the residue was subjected to chromatography on silica. Elution with ether/light petroleum (1:1) gave, 3-methylpyrrolo[1,2-a]pyrazine (0.82 g; 62%), as pale yellow plates, m.p. 82-84°C (light petroleum) (lit. 79 m.p. 76-81°C), identical with the product obtained by method (a).

Note:

Initial attempts at cyclisation without the cuprous
chloride failed to give any of the desired material.

**Reaction of 3-methylpyrrolo[1,2-a]pyrazine with ethyl propiolate**

The pyrrolopyrazine (110) (0.25 g), ethyl propiolate (0.2 ml) and nitrobenzene (10 ml) were heated under reflux under dry N₂ for 1/4 h. T.l.c. indicated the disappearance of starting material. The solvent was distilled off and the residual oil subjected to chromatography on silica. Elution with ether gave a yellow brown solid (0.06 g), sublimation of which at 0.1 mm 80-90°C gave an initial white solid followed by a yellow solid at higher temperature. A t.l.c. study showed that two compounds were present. These were separated by preparative t.l.c. [silica, dichloromethane/ethyl acetate (4:1)] to give i) a fast moving yellow band which gave a yellow brown gum (m/e 328, 'H n.m.r. spectrum complex and uninformative), and ii) a fluorescent band which gave, ethyl 7-methylpyrazino[2,1,6-cd]pyrrolizine-1-carboxylate (0.010 g; 23%), as fine white needles, m.p. 89°C (after sublimation) (Found: M⁺ 228.089509, C₁₃H₁₂N₂O₂ requires M⁺ 228.089872); νₘₐₓ 1710 (C=O) cm⁻¹; λₘₐₓ (EtOH) 211, 234, 244, 265, 300, 307sh, 376, 385, and 394 nm (log ε 4.20, 4.15, 4.18, 4.34, 3.83, 3.78, 3.57, 3.58, and 3.48); δ_H (80MHz) 1.47 (3H, t, OEt), 3.40 (3H, s, -CH₃), 4.48 (2H, q, -OEt), 7.44 (1H, d, H-4), 7.59 (1H, d, H-3), 8.12 (1H, s, H=2), and 9.09 (1H, s, H-5); J₃,₄ 4.8Hz; m/e 228 (M⁺; 96), 200 (20), 183 (100), 156 (32), 155 (29).

Note:

Further attempts using larger quantities failed to give the desired compound in better yield.
Attempted reaction of 3-methylpyrrolo[1,2-a]pyrazine with DMAD

A solution of 3-methylpyrrolo[1,2-a]pyrazine (0.25 g) and DMAD (0.41 g) in dry toluene (25 ml) containing 5% Pd/C (0.35 g) was heated under reflux for 22 h. The catalyst was removed by filtration and the filtrate was evaporated to give a dark brown residue. This was subjected to chromatography on silica. Elution with ether gave 1) a yellow solid (0.06 g) and 2) a yellow solid (0.04 g), both of which yielded uninformative $^1$H n.m.r. spectra. Mass spectroscopy of both compounds failed to show any peaks corresponding to m/e 272 ($C_{14}H_{12}N_2O_2$ requires 272).

**p-Tolylsulphonylmethanol**

This was prepared according to the method of Bredereck and Bäder.$^{134}$

Starting from 13.7 g of sodium p-tolylsulphinate dihydrate, 9.7 g (81%) of white needles, m.p.95°C were obtained.

**p-Tolylsulphonylmethyl trifluoromethanesulphonate**

This was prepared according to the method of Abramovitch.$^{80}$

Starting from 6.6 g of p-tolylsulphonylmethanol, 8.4 g (74%) of colourless needles, m.p.88-89°C were obtained.

**Attempted reaction of pyrazine with p-tolylsulphonylmethyl trifluoromethanesulphonate**

Pyrazine (0.16 g), p-tolylsulphonylmethyl trifluoromethane sulphonate (0.64 g) and ethanol (2 ml) were heated at 100°C for 10 h. After dilution with ethanol (5 ml) the reaction
mixture was added dropwise, with stirring, to anhydrous ether whereupon a brown solid (0.36 g) was precipitated. The \(^1\)H n.m.r. spectrum of this material was poorly resolved and uninformative.

Note:

1) Attempts to carry out the reaction at 130°C for 1 h gave only black tarry material with starting materials present in the ether solution.

2) Reaction at 110°C for 4 h gave a black solid (0.03 g) which was not identified.

4.2.2 Synthesis of pyrazino[2,1,6-cd]pyrrolizines from 3H-pyrrolizines

1,1,5,5-Tetramethyl-1,3,5-triazapentadienium chloride
This was prepared according to the method of Gold\(^{135}\).
Starting from 10 g of 2,4,6-trichloro-1,3,5-triazine 13.38 g (50%) of yellow crystals, m.p. 103°C were obtained.

Methyl 3-[3-(N,N-dimethylamino)-2-azaprop-2-enylidene]-3H-pyrrolizine-6-carboxylate
A solution of methyl 3H-pyrrolizine-6-carboxylate (0.156 g) and the azavinamidinium perchlorate (121) (0.221 g) in dimethylformamide (10 ml) was stirred under dry N\(_2\) at room temperature. Sodium hydride (0.048 g of a 50% oil dispersion) was added and the solution was stirred at room temperature for 15 h and heated under reflux for 3 h. A t.l.c. study showed disappearance of starting material. The solvent was distilled off, water was added and the solution was extracted with dichloromethane. The extract was dried and evaporated and the
residue was subjected to chromatography on alumina. Elution with ether gave, methyl 3-[3-N,N-dimethylamino)-2-azaprop-2-enylidene]-3H-pyrrolizine-6-carboxylate (0.28 g; 12%), as purple prisms, m.p. 150-151°C (ethyl acetate) (Found: C, 63.6; H, 6.0; N, 17.25 C_{13}H_{15}N_{3}O_{2} requires C, 63.7; H, 6.1; N, 17.1%); ν \text{max} 1700 (C=O) cm\(^{-1}\); δ \text{H} (80MHz) 3.04 (3H, s, -NMe), 3.10 (3H, s, -NMe), 3.78 (3H, s, -OMe), 6.29 (1H, d, H-2), 6.31 (1H, d, H-1'), 6.42 (1H, d, H-1), 6.78 (1H, s, H-7), 7.59 (1H, s, H-5), and 8.26 (1H, d, H-3'). J_{1,2} 5.7, J_{1,3}' 1.1 Hz; δ \text{C} (25MHz) 35.2 (-NMe), 40.4 (-NMe), 50.8 (-Ome), 97.9, 117.6, 118.4 (quat), 122.9, 123.7, 127.7 (quat) 128.9, 139.4 (quat), 157.3, 166.1 (C=O); m/e 245 (M\(^{+}\); 100), 230 (4), 214 (8), 122\(^{\frac{1}{2}}\) (M\(^{++}\); 13).

Note: The title compound was sublimed through a silica tube at 1x10\(^{-3}\) mm and 700°C in an attempt to effect cyclisation. \(^{1}\text{H}\) n.m.r. spectroscopy and t.l.c. of the recovered material indicated that starting material was the major component. Repetition of this experiment at 800°C yielded a complex mixture (as shown by t.l.c.), the \(^{1}\text{H}\) n.m.r. spectrum of which was complex and uninformative.

**Attempted synthesis of 3-(N,N-dimethylaminomethylene)-2-methoxycarbonyl-3H,5H-pyrrolizinium perchlorate**

A solution of methyl 3H-pyrrolizine-6-carboxylate (2.09 g) in tetrahydrofuran (60 ml) was cooled to -78°C under dry N\(_2\) and a previously prepared complex of POC\(_3\)/DMF in tetrahydrofuran (20 ml) was added dropwise with stirring. The yellow solution gradually turned pale pink orange. The
reaction mixture was kept at $-78^\circ\text{C}$ for $\frac{1}{2}$ h and then allowed to warm to $-30^\circ\text{C}$, and a little dry methanol was added. Sodium perchlorate (1.80 g) in methanol (5 ml) was added and, after 15 min, the reaction was cooled to $-78^\circ\text{C}$ before addition of anhydrous ether (100 ml). No precipitate was observed. The solution was allowed to warm to room temperature, water and more ether were added, and the ethereal phase was separated. The extract was dried and evaporated and the resulting residue was subjected to chromatography on alumina. Elution with ether gave yellow needles which were identified as starting material (1.65 g; 79% recovery) by $^1\text{H}$ n.m.r. spectroscopy.

Note:

1) If the reaction was allowed to warm to $-10^\circ\text{C}$, before the addition of sodium perchlorate, some precipitation occurred. This product was filtered off but, unfortunately, decomposed to give a dark solid when recrystallisation from ethanol was attempted. The impure material gave a $^1\text{H}$ n.m.r. spectrum which was poorly resolved and showed many uninformative peaks, inconsistent with the presence of the required product.

2) If the reaction was carried out at $80^\circ\text{C}$ then only dark uncharacterisable products were obtained.

3-(N,N-Dimethylaminomethylene)-$3H,5H$-pyrrolizinium perchlorate

This was prepared according to the method of Leaver$^{23}$. Starting from 3.63 g of freshly distilled pyrrolizine, 9.59 g (quantitative) of a finely divided pink powder, m.p. 158-159$^\circ\text{C}$ were obtained.
3,5-Bis-(N,N-Dimethylaminomethylene)-3H,5H-pyrrolizinium perchlorate
This was prepared according to the method of Leaver. Starting from 4.96 g of the foregoing pyrrolizinium perchlorate, 5.41 g (90%) of a brown powder, m.p. 218-222°C was obtained.

Pyrazino[2,1,6-cd]pyrrolizine
3,5-Bis-(dimethylaminomethylene)-3H,5H-pyrrolizinium perchlorate (3.61 g) was added, with stirring, to a mixture of liquid ammonia (100 ml) and ethanol (100 ml). The solution turned yellow, green and then dark green with a dark suspension. After being allowed to warm to room temperature overnight the solution was heated to 60°C for 2 h, cooled, and filtered through Celite. The filtrate was evaporated carefully, to avoid loss of product, and the residue was subjected to chromatography on alumina. Elution with ether, followed by recrystallisation from pentane gave, pyrazino[2,1,6-cd]pyrrolizine (0.66 g; 41%), as yellow needles, m.p. 52-53°C (lit. m.p. 52-53°C), 1H n.m.r. spectrum identical with that previously reported.

4.2.3 Investigation of the route from pyrazino[2,1,6-cd]pyrrolizine to pyrrolo[2',1':3,4]pyrazino[2,1,6-cd]pyrrolizines (including model reactions with pyridine)
3-p-Tolylsulphonylprop-2-en-1-ol
This was prepared according to the method of Culvenor et al. Starting from 4.6 g of 1-chloro-2,3-epoxypropane and 10.7 g of sodium p-tolylsulphinate dihydrate, 10.45 g (quantitative) of white plates, m.p. 120-122°C were obtained.
3-Bromo-1-p-tolylsulphonylpropene
This was prepared according to the method of Bordwell et al. 87.
Starting from 15.7 g of the foregoing propenol, 15.9 g (79%) of white feathery crystals, m.p. 63-64°C were obtained.

3-Phenylsulphonylprop-2-en-1-ol
This was prepared according to the method of Culvenor et al. 136.
Starting from 5.5 g of sodium phenylsulphinate, 5.4 g (81%) of white plates, m.p. 137°C were obtained.

3-Bromo-1-phenylsulphonylpropene
This was prepared according to the method of Bordwell et al. 87.
Starting from 4.3 g of 3-phenylsulphonylprop-2-en-1-ol, 4.3 (76%) of large feathery white crystals, m.p. 33-34°C were obtained.

1,3-Dichloropropene
This was prepared according to the method of Hill and Fischer 88.
Starting from 50 g of 1,3-dichloropropan-2-ol, 15.5 g (38%) of a clear liquid, b.p. 120-125°C were obtained.

1-(3-p-Tolylsulphonylprop-2-enyl)pyridinium bromide
3-Bromo-1-p-Tolylsulphonylpropene (1.42 g) and pyridine (0.4 ml) were heated at 40°C for 2 h. Ethanol (5 ml) was added and the ethanolic solution was added dropwise to anhydrous ether, with stirring, to give a white precipitate. This was filtered off to give a mixture of both Z and E isomers of 1-(3-p-tolylsulphonylprop-2-enyl)pyridinium bromide (1.5 g;
as a white powder, m.p. 153-154°C; $\nu_{\text{max}}$ 1620 (C=C), 1310 and 1140 (SO$_2$) cm$^{-1}$; $\delta_H$ (100MHz; TFA) 2.50 (3H, s, $-\text{CH}_3$), 4.42 and 5.66 (2H, 2xd, $-\text{CH}_2$ Z and E isomers), 6.70-7.06 (1H, m, H-2'), 7.39-7.56 (2H, m), 7.66-7.96 (3H, m), 8.10-8.30 (2H, m), 8.50-8.76 (1H, m), and 8.88-9.10 (2H, m). $J_{1,2}$, 7Hz.

Reaction with perchloric acid (60%) in ethanol followed by precipitation with ether gave 1-(3-p-tolylsulphonylprop-2-enyl)pyridinium perchlorate as white prisms, m.p. 98-100°C (Found: C, 48.3; H, 4.3; N, 3.7. C$_{15}$H$_{16}$Cl NO$_6$S requires C, 48.3; H, 4.3; N, 3.75%).

1-(3-Phenylsulphonylprop-2-enyl)pyridinium bromide

The allylic bromide (130) (1.0 g) and pyridine (0.3 g) were heated at 40°C for 2 h. Ethanol (5 ml) was added and the ethanolic solution was added dropwise to anhydrous ether, with stirring, to give a light brown precipitate. This was filtered off to give a mixture of both E- and Z-isomers of 1-(3-phenylsulphonylprop-2-enyl)pyridinium bromide (1.19 g; 91%), as a highly hygroscopic gum. $\nu_{\text{max}}$ 1630 (C=C), 1360 and 1150 (SO$_2$) cm$^{-1}$; $\delta_H$ (100MHz; TFA) 4.43 and 5.61 (2H, 2xd, CH$_2$ E- and Z-isomers), 6.60-7.02 (1H, m), 7.56-8.30 (8H, m), 8.50-8.77 (1H, br.t., $\gamma$-pyridine proton), and 8.80-9.02 (2H, br.d., $\alpha$-pyridine protons). $J_{1,2}$, 8Hz. Reaction with perchloric acid (60%) in ethanol followed by precipitation with ether gave, 1-(3-phenylsulphonylprop-2-enyl)pyridinium perchlorate, as an off-white solid, m.p. 127-130°C (Found: C, 46.5; H, 3.8; N, 4.0. C$_{14}$H$_{14}$ClNO$_6$S requires C, 46.7; H, 3.9; N, 3.9%). $\nu_{\text{max}}$ 1630 (C=C), 1090br (ClO$_4^-$) cm$^{-1}$.

1-(3-Chloroprop-2-enyl)pyridinium perchlorate

1,3-Dichloropropene (2.0 g) and pyridine (1.5 g) were stirred at room temperature for 3 days. Perchloric acid
(60%); (2 ml) was added and the resulting solution was added dropwise, with stirring, to anhydrous ether. The resulting precipitate was filtered off to give a mixture of both E- and Z-isomers of 1-(3-chloroprop-2-enyl)pyridinium perchlorate (4.41 g; 96%) as an off-white powder m.p. 95°C (ethanol + trace HClO₄). (Found: C, 37.9; H, 3.5; N, 5.7  C₈H₉Cl₂N0₄ requires C, 37.8; H, 3.6; N, 5.5%); \( \nu_{\text{max}} \) 1630 (C=C) and 1100br (ClO₄⁻) cm⁻¹; \( \delta_H \) (100MHz, TFA) 5.34 (E-isomer) and 5.52 (Z-isomer) (2H, 2xd, -CH₂), 6.14-6.46 (1H, m, H-2'), 6.77 (Z-isomer) and 6.88 (E-isomer) (1H, d.t., H-3'), 8.04-8.30 (2H, br. m, β-pyridine protons), and 8.50-9.00 (3H, m, α- and γ-pyridine protons). \( J_{2',3'} \) (Z-isomer) 7, \( J_{2',3'} \) (E-isomer) 12, \( J_{1',2'} \) 7 and \( J_{1',3'} \) 1Hz.

Preparation and attempts to prepare indolizine
(a) 1-(3-p-Tolylsulphonylprop-2-enyl)pyridinium bromide (1.50 g) was dissolved in a saturated solution of sodium bicarbonate in a 500 ml RB flask fitted with a Claisen distillation head. The solution was heated to boiling and the aqueous distillate was collected. This was cloudy and fluorescent and distillation was continued until the fluorescence was no longer present. The aqueous distillate was extracted with ether, and the ethereal extract was dried and evaporated to give a yellow oil which crystallised on standing to give, indolizine (0.20 g; 42%), as yellow plates, m.p. 74°C (lit. 75°C). The \(^1\)H n.m.r. spectrum was identical to that reported by Jackman. 

Note:
No indolizine was obtained when the pyridinium salt was treated with anhydrous potassium carbonate in chloroform or with activated basic alumina.
(b) 1-(3-Phenylsulphonylprop-2-enyl)pyridinium bromide
(1.0 g) was treated as in method (a) and yielded indolizine
(0.16 g; 42%) m.p. 74°C (lit. \textsuperscript{137} m.p. 75°C), identical to that
obtained by method (a).

(c) 1-(3-Chloroprop-2-enyl)pyridinium perchlorate (0.7 g) was
treated as in method (a). The distillate showed no sign of
fluorescence and extraction with ether failed to give any
indolizine.

Note:
Cyclisation was attempted in chloroform using both
anhydrous potassium carbonate and 1,5-diazabicyclo[5.4.0]undec-
5-ene as base. Neither reaction gave any indolizine nor
identifiable products.

\textbf{6-(3-Phenylsulphonylprop-2-enyl)pyrazino[2,1,6-cd]-
pyrrolizininium bromide}

Pyrazino[2,1,6-cd]pyrrolizine (0.132 g) and 3-bromo-1-
phenylsulphonylpropene (0.259 g) were heated in ethanol at 50°C
for 4 h. The ethanolic solution was added dropwise to
anhydrous ether to give a yellow precipitate. This was
filtered off and recrystallised from ethanol to give a mixture
of E- and Z-isomers of 6-(3-phenylsulphonylprop-2-enyl)-
pyrazino[2,1,6-cd]pyrrolizininium bromide (0.32 g; 85%), as
yellow prisms, m.p. 205-207°C (Found: C, 53.5; H, 3.7;
N, 6.9 \textsuperscript{18}H_{15}Br \textsuperscript{15}N_{2}O_{2}S requires C, 53.6; H, 3.75; N, 6.95%);
\nu_{\text{max}} 1660 (C=C) 1325 and 1555 (SO_{2}) \text{ cm}^{-1}. \delta_{H} (100MHz; TFA)
4.54 and 5.98 (2H, 2xd, CH\textsubscript{2} of E- and Z-isomers), 6.80-7.06
(1H, m), 7.36-8.30 (10H, m), and 9.30-9.50 (2H, m) \textit{J} \textsubscript{1,2},
7Hz.
Attempted reaction of 6-(3-phenylsulphonylprop-2-enyl)-pyrazino[2,1,6-cd]pyrrolizinium bromide with NaHCO₃

The cyclazinium bromide (134) (0.32 g) was heated under reflux in a saturated solution of sodium bicarbonate for 1½ h. The solution turned black with a black solid present. The reaction mixture was extracted with ether and the ethereal extract was dried and evaporated to give a dark material (10 mg). A t.l.c. study showed that there were six components to this residue.

Methyl phenyl sulfoxide

This was prepared according to the method of Johnson and Keiser¹³⁹.

Starting from 12.4 g of freshly distilled thioanisole, 12.3 g (88%) of a clear oil, b.p. 78-79°C/0.1 mm were obtained.

Bromomethyl phenyl sulfoxide

This was prepared according to the method of Iriuchijima¹⁴⁰.

Starting from 5 g of freshly distilled methyl phenyl sulfoxide, 5.43 g (66%) of a thick clear oil, b.p. 125-127°C/0.5 mm were obtained.

1-(Phenylsulphinylmethyl)pyridinium bromide

Pyridine (1.68 g) and bromomethyl phenyl sulfoxide (4.22 g) were heated slowly to 140°C and kept at this temperature for ½ h. The red solid which formed was filtered off, washed with ether, and recrystallised from ethanol to give 1-(phenylsulphinylmethyl)pyridinium bromide (2.36 g; 42%), as pale pink prisms, m.p. 213-214°C (Found: C, 48.3; H, 4.1; N, 4.7 C₁₂H₁₂BrNOS
requires C, 48.3; H, 4.1; N, 4.7%; δH (100MHz; TFA) 5.94 and 6.24 (2H, AB system, CH2), 7.18-7.76 (5H, m, Ph), 7.88-8.10 (2H, m, β-pyridine protons), and 8.38-8.70 (3H, m, α- and γ-pyridine protons). J CH2 14Hz. Reaction of perchloric acid (60%) in ethanol followed by precipitation with ether gave 1-(phenylsulphinylmethyl)pyridinium perchlorate, as white micro prisms, m.p. 210-212°C; ν max 1640 (C=C), 1080br (ClO4-) cm⁻¹.

Attempted reactions of 1-(phenylsulphinylmethyl)-pyridinium bromide

(a) with DMAD/Et3N/CHCl3

Triethylamine (0.49 g) in chloroform (2 ml) was added, with stirring, to the pyridinium bromide (138) (0.24 g) and DMAD (0.80 g) in chloroform (15 ml), at room temperature, under dry N2. The solution became orange and then darker on warming to 40°C. The solvent was evaporated and the residue was subjected to preparative t.l.c. Elution with ether gave a trace of a yellow-red gum which showed a molecular ion at m/e 233 (the required indolizine, C12H11NO4 requires m/e 233). No other identifiable products were obtained.

(b) with DMAD/NaH/DMF

Sodium hydride (0.095 g of a 50% oil dispersion) was added to a stirred solution of the pyridinium bromide (138) (0.6 g) and DMAD (0.5 ml) in dimethylformamide (10 ml) at 0°C. The solution was stirred for 15 min under dry N2 and then heated slowly to 60°C and this temperature was maintained for ½ h. The solvent was distilled off and the residue was diluted with water and extracted with ether. The ethereal extract was dried and evaporated and the residue was subjected to
chromatography on silica. Elution with ether/light petroleum (1:1) gave only a trace of the required indolizine.

c) with phenyl vinyl sulfoxide

A solution of sodium ethoxide (from 0.023 g Na) in ethanol (2 ml) was added to the pyridinium perchlorate (138) (0.32 g) and phenyl vinyl sulfoxide (0.15 g) in ethanol (2 ml). After being heated slowly to 40°C, the solution was diluted with water and the organic material was extracted into ether. The ethereal extract was dried and evaporated and the residue was subjected to chromatography on alumina. Elution with ether gave a clear oil (0.15 g) which was identified as phenyl vinyl sulfoxide by 1H n.m.r. spectroscopy. No other product was obtained.

6-(p-Tolylsulphonylmethyl)pyrazino[2,1,6-cd]pyrrolizinium trifluoromethanesulphonate

Pyrazino[2,1,6-cd]pyrrolizine (1.04 g) and p-tolylsulphonylmethyl trifluoromethanesulphonate (2.45 g) were heated in 2-methoxyethanol (5 ml) at 120°C for 2 h. The solution was poured into dry ether (100 ml) and the fine crystalline product was filtered off. Recrystallisation from ethanol gave, 6-(p-tolylsulphonylmethyl)pyrazino[2,1,6-cd]pyrrolizinium trifluoromethanesulphonate (2.84 g; 84%), as fine yellow needles, m.p. 216-218°C (Found: C, 46.75; H, 3.3; N, 5.9. C_{17}H_{15}F_{3}N_{2}O_{5}S_{2} requires C, 46.95; H, 3.3; N, 6.1%); ν_{max} 1370 and 1150 (SO_{2}) cm^{-1}; δ_{H} (100MHz; (CD_{3})_{2}CO) 2.46 (3H, s, -CH_{3}), 6.68 (2H, s, -CH_{2}^{-}), 7.44 (2H, d, Ar), 7.74 (2H, d, Ar), 8.26 (2H, d, H-1 and 4), 8.33 (2H, d, H-2 and 3), and 9.60 (2H, s, H-5 and 7). J_{1,2} = J_{3,4} 4.5Hz.
Dimethyl pyrrolo[2',1':3,4]pyrazino[2,1,6-\(cd\)]pyrrolizine-7,8-dicarboxylate

The salt (140) (1.37 g) and DMAD (1.4 g) in chloroform A.R. (75 ml) were stirred at room temperature under dry N\(_2\). Triethylamine (3 ml) in chloroform (10 ml) was added, dropwise with stirring, whereupon the solution turned dark brown. The solution was heated at 40\(^\circ\)C for 3 h and stirred at room temperature for 15 h. The solvent was evaporated and the residue was subjected to chromatography on silica. Elution with ether gave the required cyclazine which, after recrystallisation from methanol gave dimethyl pyrrolo[2',1':3,4]pyrazino-[2,1,6-\(cd\)]pyrrolizine-7,8-dicarboxylate (0.57 g; 65%), as yellow plates, m.p. 159-160\(^\circ\)C (Found: C, 64.7; H, 4.1; N, 9.15 \(\text{C}_{16}\text{H}_{12}\text{N}_{2}\text{O}_{4}\) requires C, 64.9; H, 4.1; N, 9.45%); \(\nu_{\max}\) 1730 and 1695 (C=O) cm\(^{-1}\); \(\lambda_{\max}\) (EtOH) 208, 227sh, 263sh, 272, 304, 316, 348, 365, 417sh, 438 and 464sh nm (log \(\varepsilon\) 4.28, 4.13, 4.40, 4.50, 4.29, 4.27, 3.76, 3.81, 3.27, 3.34, and 3.23); \(\delta\)\(_H\) (360MHz) 3.90 (3H, s, OMe), 3.96 (3H, s, ONe), 7.09 (1H, d.d, H-4), 7.10 (1H, d, H-2), 7.45 (1H, d, H-3), 7.72 (1H, d.d, H-1), 7.94 (1H, s, H-6), and 8.30 (1H, br.s, H-5), \(J_{1,2}\) 3.9, \(J_{1,4}\) 0.8 and \(J_{3,4}\) 5.14 Hz; m/e 296 (M\(^+\); 100), 265 (47).

Attempts to prepare ethyl pyrrolo[2',1':3,4]pyrazino-[2,1,6-\(cd\)]pyrrolizine-8-carboxylate

The salt (140) (0.050 g) and ethyl propiolate (0.030 g) in chloroform (5 ml) were stirred at room temperature under dry N\(_2\). Triethylamine (0.1 ml) in chloroform (1 ml) was added dropwise with stirring and the solution was stirred at
room temperature for 8 h. The solvent was evaporated and the residue was subjected to preparative t.l.c. on silica. Elution with ether gave a trace of a compound which gave a molecular ion at m/e 252.090291 \((C_{15}H_{12}N_{2}O_{2} \text{ requires } m/e 252.089872)\). No other identifiable products were obtained. Note:

1) Further attempts using larger quantities failed to give the desired product.

2) When the addition of the triethylamine was carried out at \(-78^\circ\text{C}\) no identifiable products were obtained.

3) When the solution was heated under reflux for 30 min, a trace of ethyl 2-p-tolylsulphonylethene-1-carboxylate was identified by \(^1\text{H n.m.r.}\) and mass spectroscopy. No other identifiable products were obtained.

Attempts to prepare 8-cyanopyrrolo[2',1':3,4]pyrazino-[2,1,6-cd]pyrrolizine

The salt (140) (0.124 g) and cyanoacetylene (0.05 g) in chloroform A.R. (16 ml) were stirred at room temperature under dry \(N_2\) and triethylamine (0.2 ml) in chloroform (4 ml) was added dropwise with stirring. The solution darkened and was stirred for 1 h before being filtered through Celite. The filtrate was evaporated and the resulting residue was subjected to preparative t.l.c. on silica. Elution with ether gave a yellow fluorescent material (0.0187 g). Further purification by preparative t.l.c. was necessary to give a compound (<0.005 g) which gave a molecular ion at m/e 205 \((C_{13}H_{7}N_{3} \text{ requires } m/e 205)\). The \(^1\text{H n.m.r.}\) spectrum could not be assigned to a plausible structure.
Note:

Even when the reaction was repeated on a larger scale only a trace of a product showing the required molecular ion was obtained and its $^1$H n.m.r. spectrum was not consistent with the expected structure. $\delta_H$ (200MHz) 7.05-7.11 (2H, m), 7.36-7.47 (3H, m), 7.65 (1H, d, J 4.4Hz), 8.30 (1H, s), and 9.21 (1H, s).

**Preparation and attempted decarboxylation of pyrrolo-[2',1':3,4]pyrazino[2,1,6-cd]pyrrolizine-7,8-dicarboxylic acid**

Dimethyl pyrrolo[2',1':3,4]pyrazino[2,1,6-cd]pyrrolizine-7,8-dicarboxylate (0.053 g) was heated under reflux in 10% methanolic KOH (5 ml) for 4 h. The resulting solution was poured into dilute HCl and the resulting yellow flocculent precipitate was filtered off, to give a yellow solid. This was heated under reflux in pyrrolidone (10 ml), in the presence of copper(I) oxide (0.138 g) and under a N$_2$ atmosphere, for 2 h. After cooling, water was added and the product was extracted into ether. The ethereal extract was dried and evaporated and the residue was subjected to preparative t.l.c. on silica. Elution with ether gave two components: 1) an orange band which yielded enough material (<1 mg) for mass spectroscopy and gave M$^+$ 180 (the required pyrrolocyclazine, C$_{12}$H$_8$N$_2$ requires M$^+$ 180) and 2) a yellow fluorescent band which yielded only enough material for mass spectroscopy and gave M$^+$ 238 which corresponds to a methyl cyclazinemono-carboxylate.
Many attempts at decarboxylation were made but no other method gave any compound which could be identified as the parent cyclazine.

1) When the diacid (presumably containing a trace of its half ester) and Cu$_2$O were heated together in a sublimation apparatus only a trace of the methyl cyclazinemonocarboxylate was obtained on the cold finger condenser. This was combined with the products obtained from two other "sublimation" experiments and these were subjected to preparative t.l.c. on silica. Elution with ether followed by sublimation of the recovered product gave, methyl pyrrolo[2',1':3,4]pyrazino-[2,1,6-cd]pyrrolizine-8-carboxylate, as green micro prisms, m.p. 99$^\circ$C (Found: M$^+$ 238.072259 C$_{14}$H$_{10}$N$_2$O$_2$ requires 238.074222); $v_{\text{max}}$ 1685 (C=O) cm$^{-1}$; $\delta_H$ (100MHz) 3.96 (3H, s, OMe), 7.05 (1H, d, H-4), 7.10 (1H, d, H-2), 7.35 and 7.46 (2H, AB system, H-6 and 7), 7.39 (1H, d, H-3), 7.70 (1H, d.d., H-1), and 8.30 (1H, s, H-5) $J_{1,2}$ 3.7, $J_{3,4}$ 5.2, $J_{6,7}$ 3.5, and $J_{1,4}$ 0.6Hz; m/e 238 (M$^+$; 100), 207 (92), 179 (59).

2) The $^1$H n.m.r. spectrum of the diacid obtained after heating the diester under reflux for 20 min in 10% methanolic KOH failed to show any presence of the methyl ester group.

3) When N,N-dimethylacetamide was used as solvent for the diacid and either copper chromite or Cu$_2$O as the decarboxylation catalyst, no identifiable products were obtained.

4.2.2 Synthesis of pyrazino[2,1,6-cd:3,4,5-c'd']dipyrrolizines

Tetramethyl pyrazino[2,1,6-cd:3,4,5-c'd']dipyrrolizine-1,2,3,4-tetracarboxylate

Dimethyl pyrrolo[2'1':3,4]pyrazino[2,1,6-cd]pyrrolizine-
7,8-dicarboxylate (1.01 g) and DMAD (9 ml) were stirred under dry N\textsubscript{2} in toluene (100 ml). 5\% Palladium on charcoal catalyst (1 g) was added and the solution was heated under reflux for 9 h. T.l.c. indicated the disappearance of starting material. The Pd/C catalyst was removed by filtration through Celite, the filtrate was evaporated, and the residue was subjected to chromatography on alumina. Elution with ethyl acetate gave a purple solid which was recrystallised from methanol to give tetramethyl pyrazino[2,1,6-\textit{cd}:3,4,5-\textit{c'd'}]-dipyrrrolizine-1,2,3,4-tetracarboxylate (0.91 g; 61\%), as purple rods, m.p. 302-305\textdegree C (sublimes) (Found: C, 66.7; H, 3.55; N, 6.6 C\textsubscript{22}H\textsubscript{16}N\textsubscript{2}O\textsubscript{8} requires C, 66.55; H, 3.7; N, 6.4\%); \(\nu_{\text{max}}\) 1740, 1720 and 1695 (C=O) cm\textsuperscript{-1}; \(\lambda_{\text{max}}\) (EtOH) 213, 248, 265, 300, 375sh, 393, and 572 n.m. (log e 4.35, 4.07, 4.02, 4.36, 4.07, 4.21, and 3.68); \(\delta_{\text{H}}\) (200MHz) 4.12 (6H, s, OMe), 4.18 (6H, s, OMe), 8.02 (2H, d, H-6 and 7), and 8.15 (2H, d, H-5 and 8) \(J_{5,6} = J_{7,8} 4.5\text{Hz}\); \(\delta_{\text{C}}\) (90MHz) 52.2 (CH\textsubscript{3}), 52.7 (CH\textsubscript{3}), 113.3 (CH) 115.1 (quat), 118.6 (quat), 121.5 (CH), 121.9 (quat), 122.5 (quat), 124.7 (quat), 128.0 (quat), 163.0 (C=O) and 163.7 (C=O); m/e 436 (M\textsuperscript{+}; 100), 405 (39).

Pyrazino[2,1,6-\textit{cd}:3,4,5-\textit{c'd'}]dipyrrrolizine

The cyclazine tetraester (149) (0.41 g) was heated under reflux in 10\% methanolic KOH (20 ml) for 2 h during which the colour changed from purple to pink. The reaction mixture was poured into dilute HCl (100 ml) and the resulting fine purple green precipitate was filtered off and dried to give a dark purple solid (0.36 g) m.p. >300\textdegree C. This was not purified but used in the next reaction.
Copper bronze (100 mg), copper acetate (150 mg) and 2,2'-bipyridyl (200 mg) in N,N-dimethylacetamide (75 ml) were heated under reflux under dry N\textsubscript{2} for \(\frac{1}{2}\) h. A colour change from blue to rusty brown was observed indicating the presence of Cu(II) species. The "tetra-acid" (159 mg) was added in one batch and heating was continued for 42 h. T.l.c. showed the presence of two compounds. The solvent was distilled off and the resulting residue subjected to chromatography on alumina. Elution with pentane and sublimation of the recovered product gave, pyrazino[2,1,6-cd:3,4,5-c'd']dipyrrolizine (29 mg; 34%), as deep pink plates, m.p. 201-203°C (Found: C, 82.3; H, 4.1; N, 13.45 \(\text{C}_{14}\text{H}_8\text{N}_2\) requires C, 82.3, H, 3.95; N, 13.7%); \(\lambda_{\text{max}}\) (EtOH) 252sh, 273, 294, 347, 511, 522, 537, 550, and 565sh nm (log \(\varepsilon\) 4.30, 4.84, 3.59, 4.28, 3.49, 3.58, 3.87, 4.11, and 2.91); \(\delta\)\textsubscript{H} (360MHz) 7.86 (4H, d) and 7.93 (4H, d) \(J_{1,2} = J_{3,4} = J_{5,6} = J_{7,8} = 4.5\text{Hz}\); \(\delta\)\textsubscript{C} (90MHz) 107.3 (CH), 117.4 (CH), 120.1 (quat), 125.6 (quat); m/e 204 (M\textsuperscript{+}; 100) 102 (M\textsuperscript{2+}; 14).

Further elution with ether followed by sublimation gave, methyl pyrazino[2,1,6-cd:3,4,5-c'd']dipyrrolizine-1-carboxylate (13 mg; 11%), as deep pink micro-prisms, m.p. 134-135°C (Found: \(M^+\) 262.072440 \(\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_2\) requires \(M^+\) 262.074222); \(\delta\)\textsubscript{H} (360MHz) 4.17 (3H, s, OMe), 7.85 (1H, d.d., H-8), 7.88 (1H, d, H-4), 7.91 (1H, d, H-3), 7.95 (1H, d, H-7), 7.96 (1H, d, H-6), 8.24 (1H, d.d., H-8), and 8.31 (1H, s, H-2); \(J_{3,4} = 4.8, J_{5,6} = 4.6, J_{7,8} = 4.5, \) and \(J_{5,8} = 0.9\text{Hz}\); m/e 262 (M\textsuperscript{+}; 100), 232 (68), 204 (28), 203 (68).
4.3 The dipyrrolo[1,2-a:1',2'-d]pyrazine ring system as a possible precursor of pyrazinodipyrrolizines

**Dimethyl 2,5-dibromohexanedioate**

This was prepared according to the method of Guha and Sankaran\(^ {116} \).

Starting from 167 g of adipic acid, 320 g (84%) of a waxy solid were obtained.

**Dimethyl (ZE)-N-benzylpyrrolidine-2,5-dicarboxylate**

This was prepared according to the method of Cignarella and Nathansohn\(^ {117} \).

Starting from 150 g of dimethyl 2,5-dibromohexanedioate, 109 g (87%) of a clear oil b.p. 160-172\(^\circ\)C/0.2 mm were obtained.

**Dimethyl (E)-N-benzylpyrrolidine-2,5-dicarboxylate**

This was prepared according to the method of Lowe\(^ {118} \).

Starting from 57.5 g of the ZE mixture, 37.2 g (65%) of a clear oil, b.p. 160-165\(^\circ\)C/0.2 mm were obtained.

**Dimethyl pyrrolidine-2,5-dicarboxylate**

The N-benzylpyrrolidine (175) (20 g) was dissolved in methanol (180 ml) and 5% palladium on charcoal (7 g) was added. The suspension was agitated in a hydrogenation apparatus for 4 days at 40\(^\circ\)C under 4 atm. \(H_2\). The Pd/C was removed by filtration through Celite and the filtrate distilled to give, dimethyl pyrrolidine-2,5-dicarboxylate (9.8 g; 72%), as a clear liquid, b.p. 96-102\(^\circ\)C/0.2 mm \(\delta_H\) (80MHz) 1.87-2.19 (4H, m), 2.56 (1H, br.s.), 3.71 (6H, s), and 3.76-3.99 (2H, m).
Dimethyl octahydro-5,10-dioxo-5H,10H-dipyrrlo[1,2-a: 1',2'-d]pyrazine-3,8-dicarboxylate

Dimethyl pyrrolidine-2,5-dicarboxylate (9.6 g) was heated under N₂ at 180°C for 5 h and methanol (5 ml) was added. On cooling white crystals appeared and these were filtered off to give dimethyl octahydro-5,10-dioxo-5H,10H-dipyrrlo-[1,2-a:1',2'-d]pyrazine-3,8-dicarboxylate (0.75 g; 9%), m.p. 166-170°C (Found: C, 54.0; H, 5.8; N, 9.0 C₁₄H₁₈N₂O₆ requires C, 54.2; H, 5.85; N, 9.0%); νmax 1740 (ester C=O) and 1660 (amide C=O) cm⁻¹; δ_H (80MHz) 2.02-2.41 (8H, m, H-1, 2,6 and 7), 3.70 (3H, s, OMe), 3.75 (3H, s, OMe), and 4.30-4.62 (4H, m, H-3, 5a, 8, and 10a); δ_C (50MHz) 25.4 (CH₂), 26.2 (CH₂), 27.5 (CH₂), 28.1 (CH₂), 51.8 (OCH₃), 57.4 (CH), 57.7 (CH), 60.1 (CH), 60.2 (CH), 165.6 (amide C=O), 165.8 (amide C=O), 170.6 (ester C=O), and 171.2 (ester C=O); m/e (M⁺; 33), 251 (100), 223 (57), 128 (100).

Further precipitation was effected by pouring the filtrate into ethyl acetate. The resulting precipitate was filtered off to give a pale yellow solid (1.2 g; 15%). Removal of solvent from the filtrate gave a viscous oil which solidified on standing to give a waxy solid (4.84 g; 61%). All three fractions were shown to be identical by ¹H n.m.r. and infra-red spectroscopy.

Octahydro-5,10-dioxo-5H,10H-dipyrrlo[1,2-a:1',2'-d]-pyrazine-3,8-dicarboxylic acid

The dimethyl ester (177) (1.0 g) and resublimed iodine (0.3 g) were placed in a flame-dried flask fitted with a condenser, rubber septum, stirrer bar and dry N₂ supply.
Iodotrimethylsilane (1.1 ml) was added dropwise using a syringe, stirring under N\textsubscript{2} was continued, and the mixture was heated to 100\textdegree C for 3 h. Water (50 ml) was then added and the solution extracted with chloroform. The chloroform extract was washed with aqueous sodium thiosulphate (10\%), dried and evaporated to give starting material (0.09 g). The water layer was concentrated to 5 ml and the yellow precipitate which formed was filtered off, washed with acetone and dried to give octahydro-5,10-dioxo-5\textsubscript{H},10\textsubscript{H}-dipyrrolo[1,2-\textit{a}:1',2'-\textit{d}]pyrazine-3,8-dicarboxylic acid (0.53 g; 58\%), as a yellow solid, m.p. 278-280\textdegree C (Found: C, 50.8; H, 5.0; N, 9.9\%)

C\textsubscript{12}H\textsubscript{14}N\textsubscript{2}O\textsubscript{6} requires C, 51.1; H, 5.0; N, 9.9\%); \nu\textsubscript{max} 3100-2500 br. (carboxyl OH), 1750 (carboxyl C=O), 1640 (amide C=O) cm\textsuperscript{-1}; \delta\textsubscript{H} (60MHz; (CD\textsubscript{3})\textsubscript{2}SO) 2.0-2.4 (8H, m), and 4.3-4.6 (4H, m); \delta\textsubscript{C} (20MHz; (CD\textsubscript{3})\textsubscript{2}SO) 25.6 (CH\textsubscript{2}), 26.5 (CH\textsubscript{2}), 27.8 (CH\textsubscript{2}), 28.3 (CH\textsubscript{2}), 57.5 (CH), 57.9 (CH), 60.2 (CH), 166.0 (amide C=O), 172.1 (carboxyl C=O), and 172.4 (carboxyl C=O); m/e 282 (M\textsuperscript{+}; 3); 238 (100), 209 (90).

Note: Attempts to hydrolyse or cleave the ester using aqueous sodium hydroxide or anhydrous lithium iodide were unsuccessful.

Attempted reactions of octahydro-5,10-dioxo-5\textsubscript{H},10\textsubscript{H}-dipyrrolo[1,2-\textit{a}:1',2'-\textit{d}]pyrazine-3,8-dicarboxylic acid

a) with DMAD in the presence of Ac\textsubscript{2}O

The diacid (172) (0.054 g) and DMAD (0.1 ml) in acetic anhydride (3 ml) were heated under dry N\textsubscript{2} at 60\textdegree C for 20 min, heated slowly to 130\textdegree C and maintained at this temperature for 1 h. No carbon dioxide evolution was detected using a
barium hydroxide bubbler. T.l.c. failed to detect any mobile material on silica (ether as eluent). Water was added and the solution was extracted with ether. The ethereal extract was dried and evaporated to give recovered DMAD. Concentration of the water layer gave a yellow solid (0.050 g), which was identified as the starting diacid by comparison of its mass and infra-red spectrum with the authentic diacid.

Note:
A similar negative result was obtained when the reaction was carried out under reflux for 5 h. None of the required product (M+ 442) was observed by mass spectroscopy.

b) with N,N'-dicyclohexylcarbodiimide (DCCI) in the presence of DMAD

The diacid (172) (0.056 g) and DCCI (0.120 g) were stirred at room temperature in tetrahydrofuran (5 ml) for 5 min. DMAD (0.12 g) was added and the solution was slowly heated to 45°C, with stirring, over a period of 1 h. This temperature was maintained for a further 2 h. The solvent was evaporated and acetone (20 ml) was added. The solution was cooled to -30°C for 1 h and N,N'-dicyclohexylurea (0.020 g) was filtered off. The filtrate was taken to dryness and the residue subjected to chromatography on alumina. Elution with ether/light petroleum (1:4) gave a clear liquid (0.120 g). This was shown by t.l.c. to comprise two components which were separated by preparative t.l.c. on silica. Elution with ether/light petroleum (1:4) gave 1) a clear oil (20 mg) which could not be identified by ¹H n.m.r., infra-red or mass spectroscopy; νmax 1725 and 1650 (C=O) cm⁻¹; δH (80MHz) 1.86-2.33
(4H, m), 3.68 (3H, s), 3.72 (3H, s), 3.75-3.87 (1H, m),
5.03-5.25 (1H, m), and 6.50 (1H, d, J 1.2Hz); m/e 334 (6),
302 (12), 182 (100) 154 (32); and 2) a clear oil (10 mg)
which could not be identified by $^1$H n.m.r., infra-red or
mass spectroscopy $\nu_{\text{max}}$ 1730 and 1650 (C=O) cm$^{-1}$; $\delta_H$ (80MHz)
1.84-2.03 (4H, m), 3.71 (3H, s), 3.81 (3H, s), 3.86-3.90 (1H, m),
4.50-4.75 (1H, m), 6.08 (1H, d, J 1.7Hz); m/e 336 (14),
182 (100), 155 (48).
5. **Miscellaneous Reactions**

5.1 **Attempted synthesis of methyl 3-nitroso-3H-pyrrolizine-6-carboxylate**

A solution of sodium nitrite (0.20 g) in water (5 ml) was added to methyl 3H-pyrrolizine-6-carboxylate (0.33 g) in acetic acid (5 ml) at 10°C. The solution was stirred for 15 min and then diluted with water. The brown precipitate which formed was filtered off and dried to give a brown powder (0.27 g) which could not be identified by \(^1\)H n.m.r. spectroscopy. Attempts at recrystallisation gave darker material. Mass spectroscopy showed a peak at m/e 193 (C\(_6\)H\(_8\)N\(_2\)O\(_3\) requires m/e 192).

**Note:**

Nitrosation was attempted using amyl nitrite and sodium ethoxide. This gave only the ester exchanged product.

5.2 **Attempts to synthesise 6-acyloxyindolizines from N-acetonylpyrrole-2-carbaldehyde**

a) N-Acetonylpyrrole-2-carbaldehyde (0.38 g) and sodium acetate (0.21 g) were stirred in acetic anhydride (20 ml) for 56 h under dry N\(_2\). The reaction was monitored by t.l.c. and showed only starting material. The solution was then heated under reflux for 10 h, the solvent was distilled off, and the residue was diluted with water and extracted with ether. The ethereal extract was dried and evaporated and the residue was subjected to chromatography on silica. Elution with ether/light petroleum (1:2) gave a white crystalline solid which was recrystallised from light petroleum to give starting material.
(0.16 g; 42%). No other identifiable products were obtained.

b) N-Acetonylpyrrole-2-carbaldehyde (0.25 g) and 1,5-diazabicyclo[5.4.0]undec-5-ene (0.25 g) in acetic anhydride (10 ml) were stirred for ½ h at room temperature under dry $N_2$ in the dark. The solution was then heated slowly to 100°C and this temperature was maintained for 3 h. T.l.c. showed only starting material. The reaction was then heated at 140°C for a further 2 h. T.l.c. showed only starting material and dark immobile material on the baseline.

c) To N-acetonylpyrrole-2-carbaldehyde (0.30 g) in dimethylformamide (20 ml) was added potassium t-butoxide (0.22 g) at -20°C, under dry $N_2$. After 10 min the reaction was cooled to -78°C before the addition of acetic anhydride (10 ml). The solution was stirred at -78°C for 1 h and then allowed to warm to room temperature. The solvent was distilled off and the residue was diluted with water and extracted with ether. The ethereal extract was dried and evaporated and the residue was subjected to chromatography on silica. Elution with ether/light petroleum (1:4) gave, N-(2-acetoxyprop-1-enyl)pyrrole-2-carbaldehyde (0.07 g; 18%), as a clear oil. (Found: $M^+$ 193.071996 $C_{10}H_{11}NO_3$ requires $M^+$ 193.073887); $\nu_{max}$ 1760 (enol ester C=O), 1665 (HC=O); $\delta_H$ (100MHz) 2.03 (3H, s, CH$_3$-C=), 2.10 (3H, s, MeCO), 6.22-6.30 (1H, m, H-4), 6.86-6.98 (1H, m, H-3), 7.10-7.22 (2H, m, H-5 and =CH) and 9.52 (1H, s, CHO); $\delta_C$ (25MHz) 17.8 (CH$_3$), 20.7 (CH$_3$), 110.7 (CH), 113.9 (CH), 123.8 (CH), 129.6 (CH), 131.7 (quat), 140.1 (quat),
167.8 (C=O), 179.2 (HC=O); m/e 193 (M+; 79), 151 (94),
134 (51), 122 (47), 109 (92), 108 (100), 94 (51).

5.3 Attempted reactions of pyrrolizin-3-one

2,2-Dimethyl-5-(pyrrol-2-ylmethylene)-1,3-dioxan-4, 6-dione
This was prepared according to the method of McNab\textsuperscript{128}.
Starting from 4.3 g of pyrrole-2-carbaldehyde, 9.52 g (95\%) of yellow crystals, m.p. 178-180°C were obtained.

Pyrrolizin-3-one
This was prepared according to the method of McNab\textsuperscript{128}.
Starting from 8.13 g of 2,2-dimethyl-5-(pyrrol-2-methylene)-1,3-dioxan-4,6-dione, 3.74 g (81\%) of a deep red mobile liquid, b.p. 130°C/16 mm were obtained.

Attempted reactions of pyrrolizin-3-one

(a) with \textit{p}-tolylsulphonylhydrazide
Pyrrolizin-3-one (0.24 g) in A.R. ethanol (5 ml) at 50°C was added to \textit{p}-tolylsulphonylhydrazide (0.37 g) in ethanol (5 ml) at 50°C. One drop of HCl conc was added and the solution was allowed to cool. No precipitate was observed and t.l.c. indicated only starting materials were present.

Note:
1) When the reaction was carried out with HCl conc (1 ml) and heating under reflux, no reaction took place.
2) When the reaction was carried out using glacial acetic acid as the solvent no reaction took place.
(b) with phosphoryl chloride

Reaction of pyrrolizin-3-one with phosphoryl chloride yielded a black tarry product.

(c) attempted formylation reactions

1) Reaction of pyrrolizin-3-one with POCl₃/DMF gave mostly dark solid with only a trace of the required aldehyde.

2) Pyrrolizin-3-one failed to react with dimethylthioformamide in acetic anhydride.

(d) with triethyloxonium fluoroborate

Pyrrolizin-3-one reacted with triethyloxonium fluoroborate to give an unidentifiable dark solid.

(e) other attempted reactions

1) Pyrrolizin-3-one failed to react with p-tolylsulphonyl isocyanate.

2) Pyrrolizin-3-one failed to react with Lawesson's reagent [(4-MeOC₆H₄PS₂)₂].

3) Pyrrolizin-3-one reacted with Pd(OAc)₂ to give no identifiable products.
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We now report that the Jutz procedure, and modifications of it, are applicable to 3H-pyrrolizines, (2b) and (2c), bearing conjugative substituents in the 2- or 6-position. These substituted pyrrolizines, unlike the parent compound, are quite stable in air and the yields of derived cyclazines, though not yet optimised, are moderately good. We believe, therefore, that this method will provide a valuable alternative means of entry to the [2.2.3]-cyclazine series.

2-Phenyl-3H-pyrrolizine (2b), which is unobtainable by the original Schweizer procedure from pyrrole-2-carbaldehyde and the phosphonium salt (4) was readily prepared by a modification of this route: a toluene solution containing pyrrole-2-carbaldehyde and the phosphine oxide (5) was stirred and heated under reflux with 5M aqueous potassium hydroxide in the presence of a phase-transfer catalyst (Bu₄N); work-up after 100 h yielded the pyrrolizine (2b) [66%, m.p. 179 °C (from CH₂Cl₂-light petroleum), δ(CDCl₃) 4.94 (2H, m), 5.90 (1H, dd, J 3.5 and 1.0 Hz), 6.14 (1H, dd, J 3.5 and 2.7 Hz), 7.00 (1H, m), 7.08 (1H, m), and 7.15-7.60 (5H, m)].

The pyrrolizine (2b) was converted into 1-phenyl[2.2.3]cyclazine (1b) by treatment with the vinamidinium salt (3b) and sodium methoxide in quinoline (0.5 h at 40 °C and 3 h at 160 °C) according to the general procedure of Jutz and his co-workers. Evaporation of the solution, chromatography (SiO₂-CH₂Cl₂), and sublimation yielded the cyclazine (1b) [36%, m.p. 61 °C (from light petroleum), δ(CD₃COCD₃) 7.40 (1H, d, H-4), 7.64 (1H, d, H-3), 7.89 (1H, t, H-6), 7.98 (1H, s, H-2), 8.16 (1H, dd, H-5), 8.42 (1H, dd, H-7) and 7.34-8.00 (5H, Ph)].

6-Methoxycarbonyl-3H-pyrrolizine (2c), first prepared by Flitsch and Heidhues in two stages from pyrrole-2-carbaldehyde and methyl acrylate, was obtained in better overall yield by a more recently described three-stage procedure from the same starting materials. Although it is claimed that the later synthesis gives 2-methoxycarbonyl-3H-pyrrolizine (2d), our product was identical with that of Flitsch and Heidhues who showed unambiguously by 'H n.m.r. that the compound is the 6-methoxycarbonyl isomer. Treatment of the pyrrolizine (2c) with the vinamidinium salt (3a) and sodium hydride in
AN IMPROVED SYNTHESIS OF [2.2.3]CYCLAZINES FROM 3H-PYRROLIZINES

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Abstract: [2.2.3]Cyclazines are obtained in moderate yields by reaction of 3H-pyrrolizines bearing conjugative substituents (Ph or CO₂Me) with vinamidinium salts in the presence of strong bases. Syntheses of the previously unknown 2-phenyl-3H-pyrrolizine and 1-methoxy carbonyl cyclopenta[1] [2.2.4] cyclazine are also described.

Despite considerable activity in the cyclazine field¹ during the past 24 years, the original indolizine-based syntheses of [2.2.3]cyclazines (1), developed by Boekelheide and his co-workers², remain among the most convenient of existing routes to these interesting [10]annulene derivatives. In principle, an approach to [2.2.3]cyclazines starting from 3H-pyrrolizine (2a)³ and based on the three-carbon annellation procedure of Jutz and his co-workers⁴ would seem to offer a shorter alternative route. In practice, however, the yield of the parent cyclazine (1a) obtained⁵ from 3H-pyrrolizine and the vinamidinium salt (3a) was only 2.8%. Condensations⁵,⁶ and cycloadditions⁵,⁶,⁷ starting from 3-methylene pyrrolizines have been somewhat more successful, though less convenient.

![Chemical structures](image-url)
N,N-dimethylformamide (DMF) (1 h at 60°C and 35 h at reflux), dilution with water, ether extraction, and chromatography gave 1-methoxycarbonyl[2.2.3]-cyclazine (1c) [49%, m.p. 60°C (from pentane), (lit.13 m.p. 59-61°C)]. The same product was obtained in lower yield (26%), but somewhat more conveniently, by heating the pyrrolizine (2c) for 6 h with 1,1,3,3-tetramethoxypropane in boiling acetic anhydride.

\[ \text{NMe}_2 \quad \text{ClO}_4^- \quad \text{NMe}_2 \]

(6)

\[ \text{N} \quad \text{Me} \]

(7) a: \( R = H \)
b: \( R = \text{CO}_2\text{Me} \)

6-Methoxycarbonyl-3H-pyrrolizine was also used to prepare 1-methoxycarbonyl-cyclopenta[h][2.2.4]cyclazine (2b) by reaction with the fulvene iminium salt (6) and sodium hydride in DMF (0.25 h at room temp., 0.5 h at 70°C, and 20 h at reflux). Like the parent compound (7a)14 and its methyl14 and halogeno-derivatives14,15, the cyclazine (7b)† was a green crystalline solid [m.p. 135-136°C (from light petroleum)] δ(CDC\textsubscript{3}) 3.98 (3H, s, OMe), 7.30 (1H, d, H-3), 7.49 (1H, d, H-4), 7.76 (1H, s, H-2), 7.84 (2H, m, H-6 and 8), 7.97 (1H, t, H-7), 8.54 (1H, s, H-5), and 9.58 (1H, s, H-9).

We are currently investigating further applications and improvements of these reactions.

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References and Footnote

† Satisfactory elemental analyses were obtained for all new compounds.

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