"NEW APPROACHES TO THE SYNTHESIS OF AZULENES, PYRROLIZINES AND RELATED COMPOUNDS, AND SOME NEW REACTIONS OF INDOLIZINES."

by

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D.J.C.
DISCUSSION

PART A. The Synthesis of Azulenes and Pseudoazulenes from 6-N,N-dimethylamino-fulvene.

PART B. Approaches to the Synthesis of Pyrrolo[1,2-a]pyrroles (pyrrolizines), a pyrazino[2,1,6-cd;5,4,3-c'd']dipyrrolizine, and pyrrolo[1,2-a]azepines.

PART C. New reactions of indolizines.

EXPERIMENTAL

A. Reactions of 6-dimethylamino-2-(N,N-dimethylformimmonium) fulvene perchlorate.

Synthesis of 3,4-dichlorothiophene-1,1-dioxide and its reaction with 6-dimethylaminofulvene.

Nucleophilic substitution of 5,6-dichloroazulene.

Further reactions of fulvenes.

B. Reactions of pyrrole-2-aldehyde.

Reactions of pyrrolidones (and azepinones).

Preparation and reactions of pyrrolidine-2,5-dicarboxylate.

C. Preparation of indolizines and their reaction with diphenylcyclopropenone.

Preparation and reactions of [2-(indolizin-3-y1)-2-phenylvinyl]triphenylphosphonium salts.
Reactions of 3-(N,N-dimethylamino-
methylen e)-1-methyl-2-phenylindolizinium
perchlorate.
Reactions of indolizines with 2,3,4,4,5-
pentachlorocyclopentenone.

REFERENCES
Heterocyclic analogues of azulene are of two types, formally derived by either replacement of CH by N (or S, etc.), i.e. aza-azulenes (or thionia-azulenes), or by replacement of CH=CH by a heteroatom X. These are known as pseudoazulenes.\(^1,2\)

\[ \text{e.g.} \]

![Structure](image1)

Many of the important syntheses of azulenes and aza-azulenes involve the formation of fulvenes\(^*\), either as stable or as transient intermediates.

For example, Hafner's synthesis of 4,6,8-trimethyl azulene (9) from 2,4,6-trimethylpyrylium perchlorate with

\[ * \text{The synthesis, reactions and physical properties of fulvenes (1) have been reviewed by Day}^3 \text{and, with more specific examples, by Bergmann}^4. \]

Fulvenes with various functional groups on the exocyclic carbon atom (e.g. R\(_2\)N, RO, RCOO, Cl) react with nucleophilic agents to give substitution via an addition-elimination mechanism.
cyclopentadiene proceeds readily at room temperature as follows:

6-Dimethylamino-2-nitrovinyl fulvene has been shown to undergo cyclocondensation with propynal or butynone to give 5-formyl-7-nitroazulene (10; R=H) in 35% yield or 5-acetyl-7-nitroazulene (10; R=CH₃) in 52% yield.

A one-step synthesis of azulenes from 6-aminofulvenes and α-pyrones has been reported by Sato and co-workers. Fulvenes are known to act as 2π or 6π addends and coumalic esters as 4π addends.
The mechanism was represented as going via a \([4+2]\) cycloadduct (11a) or a \([6+4]\) cycloadduct (11b).

![Chemical structure](image)

X was always an amino substituent such as \(NMe_2\), morpholino, pyrrolidino-, or piperidino-.

6-Acetoxyfulvene gave no azulene.

Yields of this synthesis were low however, the highest reported being 12%.

Houk rationalises variations in periselectivity of cycloadditions to fulvenes by application of frontier molecular orbital theory. He has further predicted by this theory and proved experimentally that electron-rich dienes would add \([6+4]\) fashion to fulvenes. 1-Diethylaminobutadiene and 6-phenylfulvene
SCHEME 1

(mixture of isomers)
react to give 4-phenylazulene, via chloranil dehydrogenation of a dihydroazulene mixture. (Scheme 1)

The [6+4] cycloaddition of 6-dimethylaminofulvene with thiophene-S,S-dioxide has been reported\textsuperscript{12} and the adduct with 3,4-dichlorothiophene dioxide is described later in the text. This same observation has been reported by Houk et al.\textsuperscript{15} in a paper which appeared after our work was completed.

Azulenes with a hetero atom in the 7-ring were first reported by Hafner\textsuperscript{14} who described the synthesis of 5-aza-azulene (21), from 6-N,N-dimethylaminofulvene and N,N-dibutylaminoacrolein, via the immonium salt (22).
Hafner further reported the synthesis of 5,7-diaza-azulene (23) from 6-dimethylaminofulvene-2-aldehyde and N,N-dimethylguanidine, in 49% yield. Reaction with N,N-dimethylacetamide hydrochloride (24) gave only the 6-dimethylamino-5-aza-azulene (25).

The synthesis of fulvenotropones (26) has been reported from the condensation of 6-(N,N-dimethylamino) fulvene-3,4-dialdehyde with diethyl acetonedicarboxylate, dibenzyl ketone, or diethyl ketone. When R=phenyl, this fulvenotropone is readily converted, via an iminium salt and alkaline hydrolysis, to 5,7-diphenyl-6-ethoxyazulene-2-aldehyde (27).
Some types of pseudoazulenes have also been made from fulvene derivatives. For example, the reaction of 6-dimethylaminofulvene-2-aldehyde with hydrazine\(^\text{16}\) yields 2H-cyclopenta[d]pyridazine (38) which is isoelectronic with 5-aza-azulene.

![Chemical structure of 6-dimethylaminofulvene-2-aldehyde reacting with hydrazine](image)

With bases the system easily produces the anion which reacts with alkylating agents to yield \(N\)-alkyl derivatives (39), which may also be obtained directly from monosubstituted hydrazines.

Cyclopenta[d][1,2]oxazines (38a; \(X=0\)) have been obtained by reaction of diaroylcyclopentadienes with hydroxylamine.\(^\text{17}\) The properties of these pseudoazulenes have been reviewed by Lloyd and Preston.\(^\text{18}\)
In the present work, attempts were made to reach the 5-aza-azulene (21) and 5,7-diaza-azulene (4) ring systems starting from a fulvene precursor.

Starting from 6-dimethylamino-2(N,N-dimethylformimmonium)fulvene perchlorate (5) prepared from 6-dimethylaminofulvene it was anticipated that cyanoacetamide would react in the presence of base to give the dihydro aza-azulenone (7) via the open intermediate (6). Aromatisation might then have been effected with, for example, phosphoryl chloride, to give the aza-azulene (8). In practice (Expt. A.2), the product obtained from the reaction with cyanoacetamide was incompletely characterised, although its mass spectrum showed strong evidence for the presence of the open-chain product (6).
Although fulvene derivatives have been used in the synthesis of cyclopenta[d]pyridazines (36) and cyclopenta[d]1,2-oxazines (38a; X=O), the corresponding cyclopenta[d]1,2-thiazines (38b) are not accessible in the same way because of the non-existence of thio-hydroxylamine (R₂N.SH).

The same problem is encountered in the preparation of isothiazoles which, until recently, had not been studied to the same extent as the pyrazoles and isoxazoles. The synthetic problem is overcome, for isothiazoles, by creating the S-N bond oxidatively as the final ring-closure step:

\[
\begin{align*}
\text{[0]} & \quad \rightarrow \\
\text{or (for } R=H) & \quad \rightarrow
\end{align*}
\]

A similar procedure might be possible in the synthesis of cyclopenta[d][1,2]thiazines, starting with the fulvene derivative (5) and introducing the required nitrogen and sulphur functions in a stepwise manner, followed by oxidation.
However, on reaction of the fulvene perchlorate(5) with aniline in a 1:1 molar ratio (Expt. A.1) the disubstituted product (12) was obtained in 80% yield (from aniline).

No monosubstituted product was apparently formed at all, as deduced from the absence of any methyl absorption in the $^1$H nmr of the crude products.

In the hope that this product might be used in the synthesis of a cyclopenta[d]pyridazinium salt, an attempt was made to ring-close by creating a N-N bond
by the action of bromine, as outlined below. However only starting material was recovered, along with some decomposition material.

Previous work,\textsuperscript{20} as outlined earlier, had shown a novel route to azulene itself from 6-dimethylaminofulvene and thiophene-1,1-dioxide, via Diels-Alder addition followed by the loss of $SO_2$ and dimethylamine.

The instability of the thiophene, and thus the necessity to generate and use it as a solution, leads to relatively poor yields of azulene, but the analogous reaction with the 3,4-dichloro derivative of thiophene-1,1-dioxide, which is a stable compound, gave a good yield (40-50\%) of 5,6-dichloroazulene (17) (Expt. A.5). This is a useful source of other substituted azulenes since the chlorine in the 6-position is susceptible to nucleophilic substitution.
A possible extension of the above reactions with thiophene dioxides was investigated via the reaction of a cyclopentadienone (18) with 6-dimethylaminofulvene. The bridged intermediate (29) from such a reaction would be expected to lose dimethylamine and carbon monoxide.

Tetrachlorocyclopentadienone (20) is unstable as a monomer but may be prepared in situ from 2,3,4,5-pentachlorocyclopentadienone (19) by treatment of the pentachloro-compound with base.
An attempt to prepare $4,5,6,7$-tetrachloroazulene (30) by treatment of a solution of 6-dimethylaminofulvene and $2,3,4,4,5$-pentachlorocyclopenta-2-enone in benzene with sodium ethoxide (Expt. A.7) produced only tarry decomposition products and subsequent tests with a range of bases showed the pentachloro-compound to be rather unstable in the presence of base.

Hafner\textsuperscript{21} reports a range of nucleophilic substitutions of the halogen in 6-chloro- and 6-bromo-$4,8$-dimethyl azulene including piperidine, ethoxide and sodium azide (to give the amino-azulene).

Unlike the 1 and 3 substituted azulenes, the 6-halo-$4,8$-dimethyl azulene undergoes nucleophilic
substitution with copper(I) cyanide and silver acetate, an observation which may be rationalised by the greater stability of the resonance form 'b' in the 6-substituted azulene.

Nucleophilic substitution of 5,6-dichloroazulene at the 6-position by various nucleophiles (Expts. A.6a-l) produced a colour change in the substituted azulene due to the electron releasing or attracting properties of the substituent relative to chlorine, thus:

Referring to Fig.A, an electron releasing (relative to chlorine) substituent at any 'o' position produces a hypsochromic shift, decreasing \( \lambda \), (producing a more reddish blue colour), while a relatively electron attracting substituent causes a bathochromic shift, increasing \( \lambda \). (At the '*' positions the reverse would be true.)

5,6-dichloro- substitution of course produces no noticeable colour change in the azulene since the effects cancel out.
Several nucleophiles were successfully substituted in the 6-position of 5,6-dichloroazulene, including morpholine (via nitrogen), benzyl mercaptan (via sulphur), and benzyl alcohol (via oxygen), all of which caused an increase in the redness of the compound. Good yields were obtained with morpholine, benzyl mercaptan, and benzyl alcohol. A small yield of substitution product was obtained with sodium ethoxide.

Substitution was not achieved with nucleophiles such as thiourea, guanidine, phenylhydrazine, sodium cyanide, copper cyanide, or diethyl sodiomalonate.

The reaction of 3,4-dichlorothiophene dioxide with 6,6-di(methylthio)fulvene (31) might be expected to produce 4-methylthio-6,7-dichloroazulene (32).

6,6-Di(methylthio)fulvene was prepared from cyclopentadiene, carbon disulphide, and methyl iodide (Expt. A.8), and treated with 3,4-dichlorothiophene-1,1-dioxide (Expt. A.9), but no azulene was obtained, and $^1$H nmr spectroscopy showed, by the loss of methyl absorption, that decomposition of the fulvene had occurred.
Similarly, starting with 6-dimethylamino-6-azafulvene (34) and 3,4-dichlorothiophene a route to 6,7-dichloro-4-aza-azulene (33) seemed possible.

The azafulvene was prepared from sodio cyclopentadiene and a dimethylnitrosamine / dimethylsulphate complex (Expt. A.10) and treated with 3,4-dichlorothiophene-1,1-dioxide, firstly with benzene as solvent (Expt. A.11(i)) which produced only decomposition material, and then without solvent (Expt. A.11(ii)). The second approach did indeed produce evidence in the mass spectrum for a protonated form of the aza-azulene, but in very small yield, so that no characterisation was possible.

In connection with this type of approach to the azulene ring system there appeared in 1975 a paper by some Japanese workers which claimed that the reaction of 6-dimethylaminofulvene with 3,6-diphenyltetrazine proceeded with the loss of nitrogen to give 4,7-diphenyl-5,6-diaza-azulene (37).
The literature report described this compound as yellow in colour, whereas it would be expected to be blue or some shade of purple. Attempts were therefore made to repeat the work of Sasaki et al. under a variety of conditions (Expt. A.12) but with no success, the mass spectrum of the reaction mixture indicating no addition products at all.

This fulvene-tetrazine reaction was pursued further with 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (38) (Expt. A.13). Owing to the electron-withdrawing nature of the pyridyl groups, this tetrazine would be expected to be more reactive towards 6-dimethylaminofulvene than the diphenyl compound, but no evidence of aza-azulene (38a) was found.

Subsequent to our work, the reaction of 6-dialkylaminofulvenes with 3,6-diphenyl-1,2,4,5-tetrazine has been studied by Bachmann and Neunhoeffer who reported a variety of products depending on reaction conditions, one of those obtained being the 5-alkylaminomethylene-1,4-diphenyl-5H-cyclopenta[d]pyridazine (35), which may be hydrolysed to the 1,4-diphenyl-2H-cyclopenta[d]pyridazine-5-carboxaldehyde (36).
Similarly, Friedrichsen and Von Wallis have reported the reaction of fulvenes with 3,6-dimethoxycarbonyl 1,2,4,5-tetrazine to give 4a,5-dihydro-2H-cyclopenta[d]pyridazines (41), which may be converted to the 2H-cyclopenta[d]pyridazine type pseudoazulene (41a) via the following scheme:
PART B : APPROACHES TO THE SYNTHESIS OF
PYRROLO[1,2-\(\alpha\)]PYRROLES (PYRROLIZINES), A PYRAZINO-
[2,1,6-\(\text{cd}; 5',4',3'-\text{c'd'}\)]DIPYRROLIZINE, AND
PYRROLO[1,2-\(\alpha\)]AZEPINES.

Huisgen and his co-workers\textsuperscript{29} have shown that
N-substituted pyrroles may be synthesised by
cycloaddition of activated acetylenes to mesoionic
oxazolium-5-oxides\textsuperscript{(43)} which are generated \textit{in situ}
by the action of acetic anhydride on N-acyl-
\(\alpha\)-aminoacids. The initial cycloadduct (44) loses
carbon dioxide spontaneously to form the pyrrole:-

\[
\begin{align*}
&\text{CO}_2\text{H} \\
&\text{R} \\
&\text{N} \\
&\text{R}' \\
&\text{R''} \\
&\text{Ac}_2\text{O} \\
&\text{R} \\
&\text{N} \\
&\text{R'} \\
&\text{R''} \\
&\text{MeO}_2\text{C}\cdot\text{C}==\text{C}\cdot\text{CO}_2\text{Me}
\end{align*}
\]
Application of this procedure to proline (N-acetyl derivative formed in situ) gave the dihydropyrrolizine (40b) and the reaction was further extended by Pizzorno and Albonico who used N-formyl-proline (39; R = H) and ethyl propiolate to obtain the dihydropyrrolizine (40a).

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; 5,4,3-c'd] dipyrrolizine (54), a hypothetical compound that possesses the peripheral π-system of [14]annulene.
A direct adaptation (route a) of the Huisgen procedure would require, as starting material, the dioxopiperazine (53) but it is also possible to envisage a route (route b) starting with the bispyrrolidone (55).

In order to test the relative merits of these two routes it was appropriate to compare the efficiency of pyrrolidone-N-acetic acid (42) as a starting material in the dihydropyrrolizine synthesis with that of the isomeric N-formylproline (39) which is known\(^\text{30}\) to give good yields of the compound (40).
It was apparent, moreover, that the route from the pyrrolidone, if successful, ought to be readily capable of extension to other bicyclic systems containing bridgehead nitrogen atoms. Thus by starting with caprolactam in place of pyrrolidone, the tetrahydro-pyrrolo[1,2-a]azepine (45) would be obtained and this route would be preferable to the alternative type (a) approach since the seven-membered cyclic amino-acid required for the latter is not readily available.

This type (b) approach has been used in the synthesis of pyrrolo[1,2-a]indolones (57) from isatin-N-acetic acids (56).

Pyrrolidone-N-acetic acid was prepared from pyrrolidone and ethyl bromoacetate (Expts. B.4 & B.5) in good yield and reacted with dimethyl acetylene-dicarboxylate in acetic anhydride (Expt. B.6) to give dimethyl 5,6-dihydro-3H-pyrrolizine-1,2-dicarboxylate.
(40) in 25% yield. The product prepared thus was identical with an authentic sample, but the reaction was less clean than the preparation from N-formylproline and the yield was considerably lower. In view of this result, the proposed bis-pyrrolidone route (b) to the pyrazinodipyrrolizline (54) was not investigated since it seemed likely to be less satisfactory than route (a).

The dioxopiperazine (53) should be obtainable by self-condensation of diethyl pyrrolidine-2,5-dicarboxylate (51) followed by ester hydrolysis.

According to the procedure of Cignarella and Nathansohn,\textsuperscript{32} the required diester (51) was easily prepared from \(\alpha,\alpha'-\) dibromo-adipic ester and benzylamine (Expt. B.9) followed by hydrogenolysis of the N-benzyl derivative. A direct preparation of pyrrolidine-2,5-dicarboxylic acid was attempted by reaction of 2,5-dibromo-adipic acid with ammonia but without success. (Expt. B.10).
As shown by Ingold\textsuperscript{33}, it was possible to separate the \textit{meso}-isomer from the mixture of stereoisomeric dibromoadipic esters by crystallisation.

The crystalline \textit{meso}-ester gave rise to a pyrrolidine which was predominantly the \textit{cis}-isomer (ratio 5:1) while the remaining oily mixture gave a pyrrolidone which was a mixture (ca. 60:40 by $^1$H nmr) of \textit{trans}- and \textit{cis}-isomers.

The mixture of stereoisomeric esters was converted to 100\% \textit{trans}-isomer (Expt. B.9) by treatment with sodium ethoxide\textsuperscript{34}, prior to hydrogenation to remove the benzyl group (Expt. B.11). Examination of models suggested that the \textit{trans}-isomer should give some steric advantage during the approach of a second pyrrolidine molecule in the condensation step.

Condensation was effected by prolonged heating at 220°C (Expt. B.12) followed by separation on alumina which yielded the dioxopiperazine (52) in 20\% yield.

De-esterification was attempted by the method of Fieser and Fieser\textsuperscript{35} using anhydrous lithium iodide, a method used for the demethylation of methyl esters, but this was unsuccessful. Hydrolysis was eventually effected, quantitatively, by the stoichiometric addition of aqueous sodium hydroxide (Expt. B.13).

Final treatment of the di-acid (53) with dimethyl acetylenedicarboxylate gave a product that did indeed show the anticipated pyrazino[2,1,6-cd; 5,4,3-c'd']dipyrrolizine (54) (Expt. B.14) in the mass spectrum but the yield was too small for characterisation.
Despite the poor yield of dihydropyrrolizine (40) obtained from pyrrolidone-N-acetic acid, it was thought worthwhile to try this method as an approach to the pyrrolo[1,2-a]azepine (45). \(\epsilon\)-Caprolactam-N-acetic acid was readily obtained but it reacted with dimethyl acetylenedicarboxylate in acetic anhydride even less efficiently than the corresponding pyrrolidone; the required product (45) was identifiable by mass spectrometry but the yield was insufficient for characterisation.

Two other possible approaches to the pyrrolo-[1,2-a]azepine system were also investigated and, although they are unrelated to the reactions already discussed in this section, it seems appropriate to consider them here. Both approaches were based on pyrrole-2-carbaldehyde as starting material.

The reaction of the aldehyde with 4-chloropent-3-en-2-one was investigated first as a possible route to the pyrroloazepinone (46).
4-Chloro-pent-3-en-2-one (47) was prepared from acetylacetone and oxalyl chloride by the method of Clark and Heathcock\(^3b\) (Expt. B.1). A mixture of two stereoisomers was produced and this was expected to yield a mixture of stereoisomeric intermediates (48), only one of which \([\text{the Z-isomer-(48a)}]\) would be suitable for cyclisation. A product was indeed obtained in the presence of base (Expt. B.2) which, from \(^1\text{H} \text{nmr}\) and mass spectral data appeared to contain both of the open-chain intermediates (48). However cyclisation was not obtained under more vigorous conditions.

The second possible route from pyrrole-2-aldehyde to the pyrrolo[1,2-\(a\)]azepine system was based partly on Schweizer's 3\(H\)-pyrrolizine synthesis\(^37\) (scheme x) which involves a Michael addition to vinyltriphenylphosphonium bromide followed by an intramolecular Wittig reaction, and partly on Fuchs' cyclohexadiene synthesis\(^38\) (scheme y) which involves a similar sequence of reactions starting with an enolate anion and butadienyltriphenylphosphonium bromide.
By combining appropriate features of these two schemes, it is possible to envisage a route (scheme z) to 5H-pyrrolo[1,2-a]azepine (49) starting with pyrrole-2-aldehyde and butadienyltriphenylphosphonium bromide.

\[
\begin{align*}
\text{CHO} & \\
\text{HPPh}_3 & \\
\text{NaH} & \\
\text{CHO} & + \\
\text{HPPh}_3 & \\
\rightarrow & \\
\text{CH} & \\
\text{CH} & \\
\text{PPH}_3 & \\
\text{PPH}_3 & \\
\end{align*}
\]

Scheme z

Treatment of azepine (49) with trityl fluoroborate might be expected to aromatise the ring-system to the azonia-azulene, which by analogy with previously reported\textsuperscript{39} representatives of this ring-system, ought to be blue. The initial reaction, in dry ether (Expt. B.3), produced an orange oily product which, however, did not produce a blue product on treatment with trityl fluoroborate and was not further characterised.
Indolizine itself has the structure (58):

Its 2-substituted derivatives are easily prepared via the Tschitschibabin synthesis\(^3\) from a 2-alkylpyridine and an \(\alpha\)-halogenoketone:

\[
\begin{align*}
R - \text{CH}_2 R'' &+ \text{CO} \text{CH} X R' \rightarrow \text{R.T.} \\
& \rightarrow \text{salt} \\
& \rightarrow \text{NabCO}_3 \\
& - \text{H}_2 \text{O} \\
& - \text{HX}
\end{align*}
\]

The indolizine studied here was mainly 1-methyl-2-phenyl indolizine prepared from 2-ethylpyridine and \(\alpha\)-bromo-acetophenone (Expt. C 1).

From a study of the canonical forms of the indolizine structure it can be seen that the 1 and 3 positions will have a higher electron density than the others:
Coulson et al. have made a study of the electron densities of all ring positions in the indolizine model which suggests that the order of preference for electrophilic substitution at a ring carbon is likely to be

$$3 > 1 > 5 > 2 > 7 > 6 > 8$$

In the Boekelheide synthesis of cycl[3,2,2]azines, indolizine behaves as a conjugated tetraene, undergoing cycloaddition at the 3- and 5- positions with dimethyl acetylenedicarboxylate.

J.E. Roff studied the possibility of an analogous cycloaddition reaction involving the addition of diphenylcyclopropenone to 1-methyl-2-phenyl indolizine (Expt. C.3) and obtained a 60% yield of a yellow crystalline compound which analysed for a 1:1 adduct. Although formulae (59) or (60) were consistent with the analytical data, neither was acceptable since the $^1$H nmr spectrum of this yellow compound (m.p. 158°C)
showed a doublet at 88.6, which could be attributed to the indolizine 5-proton, and the ratio of aromatic to methyl protons suggested that no hydrogen had been lost.

This led to a consideration of an acyl-indolizine structure (61). However this structure was readily discounted since the compound, unlike known 3-acyl-indolizines, was not hydrolysed to the parent indolizine (and α-phenylcinnamic acid) by boiling with hydrochloric acid (Expt. C 6).

Instead, a second yellow crystalline compound, m.p. 214-217°C was obtained, but this proved to be merely the hydrochloride since it was reconverted into the original adduct by treatment with sodium hydroxide.

The formation of the adduct from 1-methyl-2-phenylindolizine was accompanied by an upfield shift
of the $^1\text{H}$ methyl resonance from $\delta 2.3$ to $\delta 1.9$ and this suggested that the original C-1 of the indolizine was no longer part of an aromatic ring.

Accordingly, the structure next considered was the ring expanded product (62) which might have been produced by the following reaction sequence:

![Scheme 1](image-url)
However treatment of this structure with base such as aqueous NaOH or methanolic sodium methoxide would be expected to cleave the ring at the N-CO bond to give the open-chain acid or ester shown in (63). Experiment C.8 shows that this did not occur.

Additionally, it was observed that whereas 1,2-dimethylindolizine (Expts. C.2/C.4) gave an analogous yellow crystalline product in a 40% yield, indolizines such as 2-methylindolizine (Expt. C.6), 2-phenylindolizine (Expt. C.7), and 2-phenyl-5-methyl indolizine (Expt. C.5), which do not have a substituent in the 1-position, gave no such product under the same conditions.

On the basis of this evidence a structure was proposed of the form (64) which could be formed by the mechanism shown in scheme 1, but with an alternative cyclisation mode in the ketene intermediate (62a).

The product (64; R=H) from a 1-unsubstituted indolizine would exist as the phenol tautomer (65), which would probably be colourless, and strongly chelated on alumina via the N and OH centres.

The experiments with 2-methyl- and 2-phenyl-indolizines were repeated but instead of using a chromatographic work-up the products were extracted into
alkaline solution which was carefully titrated to pH 7, at which point a pale yellow precipitate was formed which could be filtered off. (Expts. C. 6/C. 7). Mass spectrometry showed the expected parent ion peaks but yields were low (<15%) and no further confirmation of structure was possible.

Confirmation of the cyclohexa-2,4-dienone structure (64) as correct was obtained via $^{13}$C nmr and, to a lesser extent, UV spectra. The $^{13}$C nmr spectrum of the product from 1-methyl-2-phenylindolizine showed a quaternary carbon atom at $\delta$ 59.9, and that of the product from 1,2-dimethylindolizine showed a corresponding signal at $\delta$ 60.2. To confirm the presence of a pyridine nitrogen in the non-crystalline product from 1,2-dimethylindolizine, the crude product was treated with methyl iodide (Expt. C.8) to produce the N-methiodide (66).

The $^{13}$C spectrum of this product showed a new peak due to the N-methyl group at $\delta$ 46.29, which is characteristic for CH$_3$ carbons of this type.
\[ \lambda_{\text{max}} \text{ (EtOH)} \quad \varepsilon \]

\begin{align*}
255 & \quad 14,260 \\
360 & \quad 6,000 \\
243 & \quad 16,680 \\
282 \text{ (sh.)} & \quad 6,580 \\
345 & \quad 5,700 \\
230 & \quad 21,870 \\
285 \text{ (sh.)} & \quad 5,620 \\
237 & \quad 23,800 \\
295 \text{ (sh.)} & \quad 4,660 \\
349 & \quad 3,850 \\
252 & \quad 9,120 \\
372 & \quad 7,760
\end{align*}

**Table 1**
Comparison of the UV spectra with those of known compounds containing a similar structure is shown in table 1, and the agreement is sufficiently close to confirm the suggested dienone structure for the adducts.

UV photolysis of this structure would be expected to cleave the ring between the carbonyl carbon and the quaternary carbon to give an open chain derivative such as (67). Photolysis in aqueous dioxan gave no evidence of the production of the acid (67a), but photolysis in methanol (Expt. C.11) gave a product that showed mass spectroscopic evidence of the production of the ester (67b). Since no pure specimen could be isolated, the structure of this photolysis product remains unconfirmed.

An interesting analogue of the cyclohexadienone ring system would be the unknown cyclohexadienethione system (68).

An attempt was made to prepare this via diphenylcyclopropenethione (Expt. C.12), under conditions
similar to those used for diphenylcyclopropenone, but this was unsuccessful, the major product appearing to be the cyclohexadienone, which had presumably been formed by oxidation of the thione.

The Boekelheide preparation of cycl[3,2,2]azines mentioned earlier involves the cycloaddition of an electrophilic acetylene across the 3 and 5 positions of an indolizine. It also seemed possible that there might be an alternative route to the cyclazine ring system from indolizines via a two step process involving electrocyclic ring closure of the 10π system present in a 3-vinylindolizine:

![Diagram of the reaction]

The vinylindolizine system chosen for an initial study was that derived from the reaction of 1-methyl-2-phenylindolizine with phenylethynyltriphenylphosphonium bromide, as outlined in the following scheme.
The initially formed bromide (70; X = Br) was converted into the perchlorate (70; X = ClO₄) for ease of handling.
Treatment of this perchlorate with sodium hydroxide (Expt. C.17) and separation of the products on alumina gave a greenish oil whose mass spectrum showed a peak at m/z 309, corresponding to the vinylindolizine (71), but this did not appear to be a major component of the oil and no pure product could be isolated.

However treatment of (70) with 1 molar equivalent of diazabicycloundecene (DBU) (Expt. C.18) in acetonitrile gave an oily product, vacuum sublimation of which yielded a trace of greenish oil which was fluorescent in the UV, a characteristic of cyclazine systems. The mass spectrum showed a peak at m/z 307, corresponding to C\textsubscript{23}H\textsubscript{17}N, the formula for cyclazine (72).

The mass spectrum also showed strong peaks at m/z 287 and 288, corresponding to triphenylphosphine oxide, but no peak at m/z 262 (triphenylphosphine).

Repetition of this experiment on a larger scale (0.5 g of perchlorate) failed to give an isolable yield.
of the cyclazine and the experiment was not pursued further.

Heating of the perchlorate (70) did not cause cyclisation, the starting material remaining unchanged up to its melting point (206°C) and decomposing (in sulpholane) at temperatures above this. (Expt. C.17)

Similarly photolysis (Expt. C.16) gave no products other than dark chromatographically immobile material which increased with the length of irradiation.

A second variation of this approach to the system of cyclazines via 3-vinylindolizines was then considered, starting from 3-N,N-dimethylaminomethylene-1-methyl-2-phenylindolizinium perchlorate (73) (Expt. C.19) which is simply prepared from 1-methyl-2-phenylindolizine and a Me₂NCHO/POCl₃ complex.

\[
\text{R} \quad \xrightarrow{\text{Me₂NCHO/POCl₃}} \quad \text{R'}
\]

\[
\overset{\text{NMe₂}}{\text{C}} \quad \overset{\text{ClO₄}^-}{\text{O}}
\]

This compound was known⁴⁷ to undergo reaction with reactive methyl and methylene compounds in the presence of base. For example, when nitromethane is used, the product is the 3-2'-nitrovinylindolizine (74). (Expt. C.24) An interesting fulvene system (75) is produced by reaction with cyclopentadiene.

The 6-(1-methyl-2-phenylindolizin-3-yl)fulvene (75) was prepared (Expt. C.19) in a 78% yield. However
subsequent attempts to convert this compound into a cyclazine system of the form (76) via cyclodehydrogenation were not successful owing to the compound's instability to the presence of a wide range of oxidising agents (Expt. C.20) including palladium charcoal, nitrobenzene, chloranil, and ferric chloride.
Because of this it was decided to attempt the preparation of a more stable formylated or acylated fulvene. The 2-formylfulvene (75b) was approached by treatment of (75) with DMF/POCl₃ and the 2-acylfulvene (75c) by treatment with acetic anhydride. Both reactions however appeared to give a complex mixture of products which were not identified.

Attention was then turned to the possibility of reaction of the dimethylaminomethyleneindolizinium salt (73) with tetrachlorocyclopentadiene to produce the tetrachloro-fulvene (77) which might be expected to be more stable and which could undergo cyclisation with loss of HCl.

![Chemical Structure](image)

Tetrachlorocyclopentadiene was prepared from hexachlorocyclopentadiene by the method of Roedig and Hörnig and reacted with the indolizinium perchlorate in acetonitrile with triethylamine as the base (Expt. C.21). A dark purple crystalline solid was obtained in 50% yield, 45% of the indolizinium perchlorate being recovered, but no tetrachlorocyclopentadiene.

Thermolysis of this tetrachlorofulvene (Expt. C.22) in sulpholane at ~100°C showed no cyclised product on work-up, much dark decomposition material being present.
UV photolysis on the other hand produced little dark material (Expt. C.23), the purple colour of the solution fading completely after 6 to 7 hours of irradiation. TLC in ether showed a brownish spot, \( R_f \approx 0.7 \), which was sensitive to UV light at 336 nm. The yield however was very small. On evaporation of the ethanol from the photolysis solution large amounts of HCl vapour were observed.

Investigation was then extended to other 3-substituted indolizines prepared in a similar way from the dimethylaminomethyleneindolizinium perchlorate.

A solution of the perchlorate in nitromethane was heated (Expt. C.24) in the presence of triethylamine and 3-(2-nitrovinyl)-1-methyl-2-phenylindolizine (74) was recovered in 80% yield after alumina chromatography.

It was hoped that thermolysis or photolysis of compound (74) would cause cyclodehydrogenation to give the cyclazine (78) or that HNO\(_2\) would be lost to form the cyclazine (79).
Heating in sulpholane (Expt. C.25) to 165°C caused no change in the starting material, and heating to reflux temperature (285°C) produced only decomposition material. The experiment was monitored by TLC.

UV irradiation (Expt. C.26) in ethanol caused a gradual loss of the red colour of the starting material, and the appearance of a pale yellow spot in the TLC which had a greater Rf than starting material and was fluorescent in UV light. This fraction was separated on alumina but the UV spectrum was not similar to that of a reference cyclazine (2,3-diphenylcycl[3,2,2]azine) though it is possible that any relevant absorbance may have been obscured by the presence of other UV absorbing substances.

The reactivity of other carbanions towards this dimethylaminomethyleindolizinum perchlorate was also investigated.

Malononitrile gave a 40% yield of product (80) on being refluxed with the indolizinum salt in acetonitrile in the presence of triethylamine (Expt. C.27).

Warming the salt in ethyl cyanoacetate after the addition of a few drops of triethylamine produced orange crystals of compound (81) in 70% yield (Expt. C.28), the product crystallising from the solution on cooling.
The conjugated system present in compound (81) is analogous to that in the quinolizinyldenecyanoacetate (82) which is known to cyclise thermally (\(\sim 210^\circ C\)) to the cycl[3,3,2]azin-l-one (83).

It seemed worthwhile, therefore, to investigate the possibility of an analogous cyclisation of product (81), though it was recognised that either or both of the two stereo-isomeric forms shown below might be present and that only one of these isomers could undergo a cyclisation to give the cycl[3,2,2]azin-5-one (84).
A small quantity of the indolizine was heated in 1,2,4-trichlorobenzene (Expt. C.29) to 210°C but the starting material was recovered in near-quantitative yield. Nmr examination of compound (81) reveals only one vinyl proton, the lowfield chemical shift of which suggests that it is cis- to the CO₂Et group. (ie. The product is probably (81a), the isomer unfavourable for cyclisation.)

Analogous to the above reaction with ethyl cyanoacetate is the reaction of cyanoacetamide with the dimethylaminomethyleneindolizinium perchlorate (Expt. C.30), from which product (85) was obtained in 32% yield.

![Chemical Structure](image)

85

To summarise, it does not appear that the cyclazine or cyclazinone type of ring system will be prepared via cyclisation of 3-sustituents on to the indolizine 5-position. It should be noted that the reverse procedure, cyclisation of 5-substituents on to the 3-position, has previously been established by Boekelheide et al.⁵⁰

In view of the readiness with which indolizines react with diphenylcyclopropenone, it seemed worthwhile to investigate their reactivity towards other annulenones. It was already known⁵¹ that tetraphenylcyclopentadienone (tetracyclone) does not react with indolizines but the tetrachloro-compound, which is known only transiently in...
the monomeric form, is much more reactive and is readily available from 2,3,4,4,5-pentachlorocyclopentenone by dehydrochlorination (cf. section A).

Treatment of an ethereal solution of 1-methyl-2-phenylindolizine containing one molar equivalent of DBU with a solution of the pentachlorocyclopentenone produced an immediate deep blue colour, and hydrogen chloride was evolved on work-up. A 55% yield of a deeply coloured crystalline compound was obtained which gave a molecular ion in the mass spectrum corresponding to \( \text{C}_{20} \text{H}_{12} \text{NOC}_{13} \). Structure (86), or the isomer with the indolizine linked to a \( \beta \)-carbon of the dienone seems the most likely possibility, and such a compound would be expected to be deeply coloured by analogy with tetraphenycyclopentadienone and other monomeric arylcyclopentadienones.

![Structure Figure](image)

2-Methyl- and 2-phenyl- indolizine reacted in a similar way with the pentachlorocompound and DBU.

An additional point of interest which was noted only with 2-methylindolizine (Expt. C.32) was the formation of a deep purple-violet colour on combination of the two reactants in the absence of base. This
colour was unstable to air or water, turning to the deep blue colour, which was immediately obtainable by the addition of a drop of DBU.

Owing to difficulties in recrystallisation, none of these highly coloured compounds was obtained pure and satisfactory analytical results are lacking.
EXPERIMENTAL PROCEDURE AND RESULTS
'6% Deactivated alumina', unless otherwise stated, refers to chromatographic alumina (Laporte Industries Ltd.) which had been deactivated by shaking with water (6g. per 100g. alumina).

Unless otherwise stated, solutions were dried over anhydrous magnesium sulphate or anhydrous calcium chloride.

Melting point determinations were carried out on a glass microscope slide on a hot-plate and are uncorrected.

Analyses were by Mr. Grunbaum of the Chemistry Department.

Infrared spectra were recorded on a Perkin-Elmer 157-G spectrophotometer.

N.m.r. data were obtained on a Varian EM 360 60 Mhz nuclear magnetic resonance spectrometer using tetramethyl silane as internal standard.
A. THE SYNTHESIS OF AZULENES AND PSEUDOAZULENES FROM 6-N,N-DIMETHYLAMINO FULVENE

A.1 Reaction of 6-dimethylamino-2(N,N-dimethylformimmonium) fulvene perchlorate with aniline

The fulvene perchlorate was prepared as outlined by Jessep. The fulvene perchlorate (1.0 g., 3.62 mmol.) was dissolved in methyl cyanide (100 ml.) and aniline (0.337 g., 3.62 mmol.) in methyl cyanide (30 ml.) was added dropwise under reflux. The solution was refluxed for 2 hrs and the solvent removed under vacuum. The residual brown oil was extracted with light petroleum (b.p. 60-80°C) which, on evaporation yielded orange-red needles (0.3 g., 40%).

C_{19}H_{16}N_{2} requires M 272

found M^+ 272

$^1$H nmr also indicated the disubstituted product (12).

The experiment was repeated as above with a two molar ratio of aniline. Extraction of the residue from the reaction with light petroleum yielded on evaporation orange-brown crystals (0.4 g., 50%) identical with the product from the preceding experiment. Recrystallisation from methanol gave orange platelets of 6-phenylamino-2-(N-phenyliminomethyl) fulvene (12).
m.p. 98-100°C

$^1$H n.m.r. $\delta$ 6.3-7.5 (multiplet, 17 H)
$\delta$ 8.27 (doublet, 2 H)

Analysis for C$_{19}$H$_{16}$N$_2$ requires: C = 83.8%; H = 5.9%; N = 10.3%.

found : C = 83.5%; H = 5.8%; N = 10.2%.

The same product was obtained when the iminium salt (5) was treated with one equivalent of aniline in refluxing ethanol.

A.2 Reaction of 6-dimethylamino-2-([N,N-dimethylformimmonium] fulvene perchlorate with cyanoacetamide.

The fulvene perchlorate (1.0 g., 3.62 mmoles) was dissolved in acetonitrile (100 ml.) together with cyanoacetamide (0.357 g., 3.62 mmoles), and triethylamine (0.439 g., 3.62 mmoles). The solution was refluxed for 2 hours, cooled, and an equal volume of water added.

Extraction with methylene chloride ($2 \times 75$ ml.), drying of the extract over anhydrous magnesium sulphate, and evaporation yielded a red oil which was crystallised from methanol to yield dark orange prisms (0.4 g.).

m.p. 180-182°C.

$^1$H n.m.r. suggested the product to be the open chain compound (6) rather than the cyclised product (7).

$\delta$ 3.55 & 3.75 (singlets, each 3 H); $\delta$ 6.9 (rounded, 2 H);
$\delta$ 6.85 (singlet, 1 H); $\delta$ 7.35 (doublet, 1 H); $\delta$ 7.78, 8.00, 8.18, 8.55 (singlets, each 1 H).
Mass spectrometry gave $\text{M}^+ 215$, corresponding to $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}$ (6), but a good analysis could not be obtained.

**A.3 Preparation of 3,4-dichlorotetrahydrothiophene-1,1-dioxide (14) and its further chlorination to 3,3,4,4-tetrachlorotetrahydrothiophene-1,1-dioxide (15).**

The dichloro compound (14) was prepared from butadiene sulphone and sulphuryl chloride as outlined by Jordan and Kipnis.

The dichloro-compound (10 g.), recrystallised from methanol, was dissolved in carbon tetrachloride (350 ml.) and an excess of chlorine (26 g., weighed as solid chlorine) was passed through in a nitrogen stream over a period of five hours while heating at around 40°C and illuminating the solution with a 500W projector lamp. (cf. Bluestone et al. 59). On concentration of the solution a white crystalline mass was recovered. (7.95 g., mp. 94-98°C). $^1\text{H}$ n.m.r. spectra of this substance indicated that chlorination was only partially complete.

The products recovered above were redissolved in carbon tetrachloride (180 ml.), fresh dichloro compound added (1.0 g.), and the solution was irradiated in a photochemical reactor for 5 hours while an excess of gaseous chlorine was bubbled through in a stream of nitrogen. Crystallisation from the cooled solution yielded white crystals (8.1 g.), mp. 172°C. (lit. 59 mp. 174-7°C).

$^1\text{H}$ n.m.r. indicated that the product was pure
3,3,4,4-tetrachlorotetrahydrothiophene-1,1-dioxide. $^1$H n.m.r., δ 4.27 (singlet).

### A.4 Preparation of 3,4-dichlorothiophene-1,1-dioxide (16).

3,4-Dichlorothiophene-1,1-dioxide (16) was prepared by dehydrochlorination of 3,3,4,4-tetrachlorotetrahydrothiophene-1,1-dioxide with ammonia in methanol as outlined by Bluestone et al.\(^{59}\) Pale orange needles (80%). m.p. 112-113°C (lit. m.p. 112-113°C) $^1$H n.m.r. δ 6.73 (singlet).

![Structure of 3,4-dichlorothiophene-1,1-dioxide (16)](structure.png)

### A.5 Preparation of 5,6-dichloroazulene (17)

3,4-Dichlorothiophene-1,1-dioxide (0.75 g., 4.05 mmoles) was dissolved in benzene (25 ml.) and freshly recrystallised 6-dimethylaminofulvene (0.49 g., 4.05 mmoles) was added at room temperature in benzene (25 ml.). The solution turned dark blue within half a minute, and on refluxing for 1 hour became greenish-black. Chromatography on alumina, eluting with benzene, yielded 5,6-dichloroazulene (46%). m.p. 57-58°C from light petroleum bp. 60-80°C. $^1$H n.m.r. δ 7.18-7.50 (multiplet, 3 H); δ 7.99 (triplet, 1 H); δ 8.06 (doublet, 1 H); δ 8.55 (singlet, 1 H). C_{10}H_{6}Cl_{2} requires: C = 60.9%; H = 3.1%. found : C = 60.7%; H = 3.5%.
Nucleophilic Substitution of 5,6-dichloroazulene.

(a) with sodium ethoxide in ethanol.

(i) The dichloroazulene (0.1 g.) in ethanol was treated with an ethanolic solution of sodium ethoxide (0.013 g. sodium, 1:1 molar ratio) and the mixture was refluxed for 4 hours. The reaction was monitored by TLC but no products appeared. On acidification with dilute aqueous HCl, extraction into ether, and evaporation, the residue was identified by n.m.r. spectroscopy as unreacted 5,6-dichloroazulene.

(ii) The dichloroazulene (0.1 g.) was dissolved in dimethylformamide (10 ml.) and a 3 molar excess of sodium ethoxide in dry dimethylformamide (25 ml.) was added. The mixture was refluxed for 2 hours, poured into water, neutralised with dilute HCl, and extracted into ether (2 x 25 ml.). The resulting dark residue was chromatographed on alumina, eluting with a 50/50 mixture of benzene/ether, and a pale purple fraction was recovered which on evaporation gave a purple-brown oil. A crystalline purple sublimate was recovered from this oil. Mass spectrometry showed M⁺ 208/206, corresponding to C₁₂H₁₁OCl, which is 5-chloro-6-ethoxy azulene (21).

¹H n.m.r. δ 1.53 (triplet, 3 H); δ 4.25 (quartet, 2 H); δ 6.65-7.30 (multiplet, 4 H); δ 8.17 (doublet, 1 H); δ 8.53 (singlet, 1 H).

The yield was not sufficient to allow elemental analysis.

(iii) 5,6-Dichloroazulene (0.1 g.) was dissolved in sulpholane (25 ml.) and sodium ethoxide (prepared from 0.04 g. sodium; 3 molar excess) was added. After heating
for 2 hours at 120-140 °C only decomposition material was recovered together with a small amount of unchanged dichloroazulene.

(b): with benzyl alcohol.

The dichloroazulene (0.1 g.) was dissolved in benzyl alcohol (25 ml., bp. 205 °C) together with sodium benzyloxide (from 0.07 g. Na; 1 molar equiv.) in 10 ml. benzyl alcohol and the solution was stirred for 2 hours at 110-120 °C to avoid decomposition of the azulene which is rapid at temperatures above ~130 °C. Water (15 ml.) was added, the organic phase was separated, and the alcohol was distilled off under reduced pressure. The purple residue (~5 ml.) was passed through a column of deactivated alumina, eluting with benzene. A deep purple crystalline compound was recovered which was recrystallised from light petroleum to give 6-benzyloxy-5-chloroazulene (0.080 g., 60%).

Purple needles, m.p. 116-117 °C.

C\textsubscript{17}H\textsubscript{13}ClO requires : C = 75.98%; H = 4.84%.
found : C = 75.88%; H = 5.63%.
Mass spectrometry showed a fragment peak at m/z 162 & 164 (C\textsubscript{10}H\textsubscript{7}Cl) possibly due to the rearrangement:

\[
\begin{array}{c}
\text{Cl} \\
\text{OCH}_2\text{Ph}
\end{array}
\xrightarrow{+ 1^+} 
\begin{array}{c}
\text{Cl} \\
\text{H}
\end{array}
+ \text{PhCHO}
\]

\(^1\text{H} \text{n.m.r.} \text{ showed } \delta 5.30 \text{ (singlet, 2 H); } \delta 6.85 \text{ (doublet 1 H); } \delta 7.2-7.8 \text{ (multiplet, 7 H); } \delta 7.67 \text{ (triplet, 1 H); } \delta 8.15 \text{ (doublet, 1 H); } \delta 8.52 \text{ (singlet, 1 H).}

(c) \text{ with benzyl mercaptan.}

Sodium (25 mg.) was dissolved in 2-methoxyethanol (25 ml.) and the solution was treated with an excess of benzyl mercaptan, then heated to 70°C under nitrogen and 5,6-dichloroazulene (0.1 g.) was added dropwise in 2-methoxyethanol (15 ml.). The solution was stirred under nitrogen for 2½ hours, at 60-70°C, during which time the colour changed from blue to mauve. TLC (benzene) showed no original dichloroazulene remaining. The products were partitioned between water and ether and the organic layer yielded a partly crystalline purple residue which was recrystallised from light petroleum, b.p. 60-80°C., to give 6-benzylthio-5-chloroazulene (40%) (17a; R=SCH\textsubscript{2}Ph). Purple prisms, m.p. 123-126°C.

C\textsubscript{17}H\textsubscript{13}ClS requires: C = 71.70; H = 4.57; M\textsuperscript{+} = 284/286. Found: C = 70.82; H = 4.49; M\textsuperscript{+} = 284/286.

\(^1\text{H} \text{n.m.r.} \text{ showed } \delta 4.30 \text{ (singlet, 2 H); } \delta 7.03 \text{ (doublet, 1 H); } \delta 7.20-7.55 \text{ (multiplet, 7 H); } \delta 7.77 \text{ (triplet, 1 H); } \delta 8.05 \text{ (doublet, 1 H); } \delta 8.42 \text{ (singlet, 1 H).}

-55-
(d): with thiourea.

(i) The dichloroazulene (0.1 g.) was first dissolved in 2-methoxyethanol (25 ml., b.p. 125°C) with thiourea (0.04 g., 1 mol. equiv.). After refluxing for 2½ hours and partition between ether and water, only unreacted 5,6-dichloroazulene was recovered, as identified by $^1$H n.m.r. spectroscopy.

(ii) The above experiment was repeated with a 3 molar excess of thiourea in sulpholane (30 ml.) heating to 150°C. On work-up, a small amount of starting material was recovered ($^1$H n.m.r.), most of the product being dark greenish decomposition products.

(e): with morpholine.

The dichloroazulene (0.1 g.) was dissolved in morpholine (25 ml., b.p. 128-130°C) and the solution was refluxed for 2½ hours during which it became dark and opaque. Partition between water and ether gave a purple organic fraction. After drying over anhydrous magnesium sulphate followed by evaporation, a dark purple paste was recovered which was eluted with ether on a column of alumina. A purple crystalline compound was recovered which was recrystallised from light petroleum (b.p. 60-80°C) to yield 5-chloro-6-morpholino azulene (0.08 g.; 65%). m.p. 87-89°C. 

$^1$H n.m.r.: $\delta$ 3.20 (multiplet, 4 H); $\delta$ 3.90 (multiplet, 4 H); $\delta$ 6.83 (doublet, 1 H); $\delta$ 7.25 (multiplet, 2 H); $\delta$ 7.72 (triplet, 1 H); $\delta$ 8.12 (doublet, 1 H); $\delta$ 8.54 (singlet, 1 H).
(f): with guanidine carbonate.

(i) The azulene (0.1 g.) was dissolved in 2-methoxyethanol (25 ml., b.p. 125°C) and guanidine carbonate (0.08 g., 1.5 mol. equiv.) was added. After refluxing for 2½ hours and partition into ether and water the organic extract was shown by $^1$H nmr spectroscopy to contain only unreacted 5,6-dichloroazulene.

(ii) The above experiment was repeated with an excess of guanidine carbonate (0.5 g.) and in the presence of aqueous sodium hydroxide. After acidification only a tarry residue was recovered whose mass spectrum showed little evidence of $^{16}$209/211 (C$_{11}$H$_{10}$N$_3$Cl).

(g): with phenylhydrazine.

The azulene (0.1 g.) was dissolved in 2-methoxyethanol (25 ml.) and refluxed with a large excess (10 ml.) of phenylhydrazine. After work-up the product was a dark reddish-brown oil which could not be characterised.

(h): with malononitrile.

(i) The sodium salt of malononitrile was prepared from sodium ethoxide (0.45 g.) and malononitrile (0.5 g.) in dimethylformamide. On addition of an excess of this sodium salt to a solution of 5,6-dichloroazulene (0.1 g.) in dimethylformamide (25 ml.) there was a rapid colour change from blue to dark orange-red. The solution was heated at 110°C for ½ hour, then partitioned between water and ether. After drying with anhydrous calcium chloride, the organic fraction yielded a trace of dark crystalline material which gave a mass spectrum with $^{16}$226 & 228. (C$_{13}$H$_7$ClN$_2$ requires M$^+$ 226/228.)

(ii) Repetition of the above experiment in ethanol
in the presence of sodium ethoxide yielded sufficient product to obtain an IR spectrum which showed strong C≡N absorption at 2200 cm⁻¹. Mass spectroscopy showed m/e 161 & 163, C¹⁰H₆Cl. (28)

![Chemical structure](image)

(i) : with diethyl malonate.

Reaction of 5,6-dichloroazulene with a 3-fold excess of diethyl sodiomalonate in abs. ethanol produced only unreacted azulene plus some chromatographically immobile decomposition material.

(j) : with sodium cyanide.

The azulene (0.1 g.) was added to a saturated solution of sodium cyanide in 2-methoxyethanol (30 ml.) and the solution was refluxed for 2 hours, during which the colour changed from blue to reddish-purple. After partition between water and ether, the brownish organic residue was passed down a column of deactivated alumina, eluting with light petroleum, but the reddish product appeared to decompose on the alumina and no 5-chloro-6-cyanoazulene was recovered.

(k) : with copper (I) cyanide.

Cuprous cyanide was prepared by the method of Laist. Reaction of this with 5,6-dichloroazulene in acetonitrile gave only a greenish tarry product on work-up which could not be characterised. The same result was obtained with pyridine as solvent.
(1): under acid conditions.

Refluxing 5,6-dichloroazulene (0.1 g.) in ethanol (25 ml.) with the addition of conc. sulphuric acid (10% v/v, 2.5 ml.) for 2½ hours produced no reaction.

A.7 Reaction of 6-(N,N-dimethylamino) fulvene and 2,3,4,4,5-pentachlorocyclopentadienone.

The pentachloro-compound (19) (2 g., 7.8 mmoles) was dissolved in acetonitrile (30 ml.) and added dropwise to a vigorously stirred solution of 6-(N,N-dimethylamino) fulvene (0.97 g., 8 mmoles) in acetonitrile (25 ml.) containing anhydrous sodium ethoxide (1.0 g.). The solution rapidly darkened and became opaque. After stirring for 1 hour benzene (100 ml.) was added to dissolve a tarry residue, together with water (150 ml.). All products were extracted into the organic fraction, which on evaporation yielded an intractable black tar.

The same result was obtained when the experiment was repeated (a) with a 2 molar excess of fulvene and (b) with an excess of fulvene and diazabicycloundecene (DBU) as base.

Subsequent tests on the pentachloro-compound showed that it was unstable to bases such as DBU, triethylamine, or sodium ethoxide, although stable in the presence of 6-(N,N-dimethylamino) fulvene alone.

A.8 Preparation of 6,6-bis(methylthio)fulvene (31).

This was prepared by the method of Gompper and Kutter. The product was purified by short-path distillation. (C.3 mm Hg, -90°C). $^1$H nmr: $\delta$ 2.45 (singlet, 6 H); $\delta$ 6.50 (multiplet, 4 H).
A.9 Reaction of 6,6-bis(methylthio)fulvene with 3,4-dichlorothiophene-1,1-dioxide.

The dichlorothiophene dioxide (0.25 g., 1.35 mmoles) in benzene (20 ml.) was mixed with the fulvene (1.35 mmoles) dissolved in benzene (20 ml.) and the solution stirred at room temperature for 12 hours. TLC (benzene) showed no reaction had occurred.

On being refluxed for 4 hours the solution darkened but TLC showed no blue product (32). Evaporation of the solvent gave a brown paste, the $^1$H nmr spectrum of which showed the presence of the thiophene dioxide, but no Me singlets due to the remaining fulvene, the spectrum being dominated by an unidentifiable mixture of decomposition products.

\[ \text{32} \]

A.10 Preparation of 6-N,N-dimethylamino-6-azafulvene (34).

This was prepared by the method of Hafner et al. 24

The product was distilled under vacuum (5 mm Hg, 60°C) to give a dark yellow orange oil which was pure 6-N,N-dimethylamino-6-azafulvene.

$^1$H nmr: $\delta$ 3.35 (singlet, 6 H); $\delta$ 6.1-6.8 (multiplet, 4 H).

A.11 Reaction of 6-N,N-dimethylamino-6-azafulvene with 3,4-dichlorothiophene-1,1-dioxide.

(i) in benzene. The thiophene dioxide (freshly recrystallised, 0.30 g., 1.64 mmoles) and 6-N,N-dimethylamino-6-azafulvene (0.20 g., 1.64 mmoles) were dissolved in
benzene (25 ml.) and stirred in the dark at room temperature for 12 hours. TLC (silica; benzene) showed no products apart from some dark immobile material. Refluxing the solution for 1 hour produced only an increase in this dark material.

(ii) without solvent. Addition of the thiophene dioxide portionwise to the fulvene, in the above quantities produced effervescence of an acidic gas. The mixture was then heated for 1 hour at 60°C, and the oily product was chromatographed on a column of deactivated alumina in chloroform. A yellow fraction was recovered which gave a brown gum on evaporation whose mass spectrum showed $^m$e 242/244/246, corresponding to $C_{11}H_{12}N_2Cl_2$ (33a), with secondary peaks at $^m$e 198/200/202, $C_9H_6NC_2$ (33b).

A.12 Preparation of 3,6-diphenyl-1,2,4,5-tetrazine and its attempted reaction with 6-(N,N-dimethylamino) fulvene.

The tetrazine (36) was prepared by the method of Müller and Herrdegen. The product was purified on a column of deactivated alumina, eluting with dichloromethane.

6-Dimethylaminofulvene (0.12 g.) and 3,6-diphenyl-1,2,4,5-tetrazine (0.12 g.) were dissolved in benzene (25 ml) and stirred in a closed system in the dark under nitrogen at room temperature for five days. Chromatography on alumina recovered only unreacted fulvene and tetrazine, contrary to the findings of Sasaki et al.

The same result was observed when the reaction
mixture was (i) refluxed for 24 hours and chromatographed on silica or (ii) stirred under argon in the dark.

Starting materials were identified by mass spectrometry and n.m.r. spectra.

A.13 Reaction of 3,6-di(2-pyridyl)-1,2,4,5-tetrazine with 6-(N,N-dimethylamino)fulvene.

3,6-Di(2-pyridyl)-1,2,4,5-tetrazine was prepared by the method of Dallacker.

The tetrazine (0.236 g., 1 mmole) and 6-dimethylaminofulvene (freshly recrystallised, 0.121 g., 1 mmole) were dissolved in chloroform (25 ml) and stirred under nitrogen at room temperature for 2 hours. TLC (CHCl₃) showed only starting materials plus some immobile yellowish-brown material. On evaporation of the solvent and chromatography on alumina, eluting with chloroform, only starting material was recovered, with no trace of 4,7-di(2-pyridyl)-5,6-diaza-azulene (38a), which would probably be blue or otherwise highly coloured.
B. APPROACHES TO THE SYNTHESIS OF PYRROLO[1,2-a]AZEPINES, PYRROLO[1,2-a]PYRROLES (PYRROLIZINES) AND A PYRAZINO-[2,1,6-cd : 5,4,3-c'd']DIPYRROLIZINE.

B.1 Preparation of 4-Chloropent-3-en-2-one (47).

The β-chloroenone was prepared by the method of Clark and Heathcock. 36

Acetylacetone (10.0 g, 100 mmoles) in chloroform (30 ml) was treated with oxalyl chloride (25 g, 100 mmoles) and the solution refluxed for 15 minutes. The products were distilled under vacuum (6 mm Hg, 45-50°C). A pale yellow oil (5 g) was recovered which, as shown by its 1H nmr spectrum contained the two isomers (47a) and (47b).

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

\[ 47a \]

\[ 47b \]

δ 2.08 (singlet, 3 H)  δ 2.16 (singlet, 3 H)
2.30 (singlet, 3 H)  2.33 (doublet, 3 H; J = 1Hz)
6.10 (singlet, 1 H)  6.43 (quartet, 1 H; J = 1Hz)

B.2 Reaction of pyrrole-2-aldehyde with 4-chloropent-3-en-2-one.

Pyrrole-2-aldehyde was prepared by the method of Organic Syntheses. 53

Sodium (0.3 g) was dissolved in abs. ethanol (25 ml) and pyrrole-2-aldehyde (1.0 g, 10 mmoles) was dissolved in the solution. 4-Chloropent-3-en-2-one (redistilled, 1.23 g, 10 mmoles) was added dropwise, producing an immediate white precipitate. After stirring
at room temperature for 10 minutes, water was added and the yellow solution was extracted with ether (3x50 ml). On evaporation of the extract an orange-yellow oil (1.5 g) was obtained which was chromatographed on a column of deactivated alumina, eluting with chloroform.

The $^1$H nmr spectrum of the major fraction indicated the presence of N-(1-methyl-3-oxobut-1-enyl)-pyrrole-2-carbaldehyde (48).

The mass spectrum showed $m/e$ 177 ($C_{10}H_{11}NO_2$ requires 177) but some material was also present at higher molecular weight.

\[
\begin{align*}
\text{1H nmr:} & \quad \delta \\
& \quad \{ \begin{array}{ll}
6.92 & \text{multiplet, 1 H} \\
7.13 & \text{multiplet, 1 H} \\
6.30 & \text{multiplet, 1 H} \\
9.42 & \text{singlet, 1 H} \\
2.15 & \text{singlet, 3 H} \\
2.30 & \text{singlet, 3 H} \\
5.45 & \text{singlet, 1 H}
\end{array} \}
\end{align*}
\]

(The presence of $H_f$ at $\delta 5.45$ distinguishes the product from a mixture of starting materials, as the single proton in the $\beta$-chloro-enone lies above $6\delta$ for both isomers.)

B.3 Reaction of pyrrole-2-aldehyde with butadienyltriphenylphosphonium bromide.

(1) Sodium (0.3 g) was dissolved in abs. ethanol (25 ml) and pyrrole-2-aldehyde (1.0 g, 10 mmoles) added with stirring at room temperature, followed by butadienyl-

triphenylphosphonium bromide$^{38}$ (4.0 g, 10 mmoles) portionwise. A red colour was immediately formed.

After 15 minutes the mixture was poured into water and extracted with ether (3x50 ml), and the extract was
backwashed, and dried over anhydrous magnesium sulphate. On evaporation an orange-yellow paste was recovered, the $^1$H nmr spectrum of which was not in agreement with the anticipated compound (49), containing a considerable aldehyde signal and much unidentified absorption at $\delta$5.6-3.

(ii) The above experiment was repeated using sodium hydride in anhydrous ether to generate the sodium pyrrolide, using similar quantities of both reactants. An orange viscous oil was recovered on evaporation of the organic extract. Treatment of the orange oil with trityl fluoborate gave no blue colour due to the formation of an aromatic species (50).

![Chemical structures](images/49_50)

Chromatography of the oil on alumina and a study of the eluate by mass spectroscopy showed only starting material.

**B.4 Preparation of N-ethoxycarbonylmethylpyrrolidin-2-one (44).**

Pyrrolidone (15.0 g, 177 mmoles) was added dropwise to a stirring suspension of sodium hydride (50% dispersion in oil, 8.5 g, 177 mmoles) in sodium dried benzene (100 ml). After all reaction had ceased ethyl bromoacetate (21.7 g, 177 mmoles) was added portionwise, keeping the temperature below 5°C. The solution was then raised to room temperature and stirred for 18 hours. Sodium bromide was filtered off and the filtrate was fractionally distilled under reduced pressure
to give a colourless oil (20 ml) which was
N-ethoxycarbonylmethylpyrrolidin-2-one (14+).

\[ \text{B.5 Hydrolysis of N-ethoxycarbonylmethylpyrrolidin-2-one.} \]

The ethyl ester (11.5 g, 63 mmoles) was treated
with 6% methanolic potassium hydroxide (1 molar equiv.)
in the cold and the solution was heated under reflux for
2.5 hours. After evaporation of the methanol, the residual
white solid potassium salt was redissolved in a little
ethanol and treated with dil. aqueous hydrochloric acid
(1 mole). The free acid was precipitated by the careful
addition of ether, filtered, and washed with a little
ether. The acid (5.5 g; 58%) formed white prisms,
m.p. 142-144°C (lit. m.p. 143°C)
\[ \text{\(1H\ nmr (dmso-d}_6\)}: \delta \text{2.1-2.6 (multiplet, 4 H);} \]
\[ \delta \text{3.50 (triplet, 2 H);} \delta \text{4.00 (singlet, 2 H).} \]

\[ \text{B.6 Reaction of N-carboxymethylpyrrolidin-2-one with} \]
\[ \text{dimethyl acetylenedicarboxylate (DMADC).} \]

The acid (0.5 g, 3.5 mmoles) was dissolved in
freshly distilled acetic anhydride (8 ml) and DMADC
(3.5 g, large excess) was added. The solution was heated
under nitrogen to 120°C for 20 minutes, during which some
darkening occurred. The solution was evaporated under
oil-pump vacuum (0.1 mm Hg, T below 100°C) and the residual
oil was chromatographed on silica (30 g) eluting with chloroform. On evaporation a red oil was recovered (3rd fraction), the nmr spectrum of which corresponded to compound (41). Recrystallisation from ether gave white prisms (25%). m.p. 86-88°C.

An authentic specimen of the same compound was synthesised from N-formylproline by the method of Pizzorno and Albonico, with DMADC instead of ethyl propiolate. m.p. 89-91°C. mixed m.p. 84°C. The IR and nmr spectra of the two compounds were identical.

\[ \text{\textsuperscript{1}H nmr:} \]

\begin{align*}
(a) & \ 2.50 \delta \text{ (multiplet, 2 H)} \\
(b) & \ 3.15 \delta \text{ (triplet, 2 H)} \\
(c) & \ 3.95 \delta \text{ (triplet, 2 H)} \\
(d) & \ 3.80 \delta \text{ (singlet, 6 H)} \\
(e) & \ 7.15 \delta \text{ (singlet, 1 H)}
\end{align*}

B.7 Preparation of N-carboxymethylhexahydroazepin-2-one.

Caprolactam (22.6 g; 200 mmoles) was dissolved in sodium-dried benzene (100 ml) and sodium hydride (50% dispersion in oil, 9.6 g; 200 mmoles) was added with vigorous stirring. After all reaction had ceased, ethyl bromoacetate (33.4 g; 200 mmoles) was added slowly with cooling, and the mixture was stirred at room temperature for 12 hours, then partitioned between water and ether. The organic layer was separated, dried over magnesium sulphate, filtered, and evaporated to give N-ethoxy-carboxymethylhexahydroazepin-2-one (55) (24 g; 130 mmoles). Hydrolysis to the free acid was effected with methanolic potassium hydroxide and treatment of the potassium salt with dil. aqueous hydrochloric acid. Potassium chloride was filtered off and the free acid was precipitated from
the ethanolic filtrate by careful addition of ether.

Yield = 5.1 g. (25% from ester).

m.p. = 145-147°C.

C₈H₁₃NO₃ requires: C = 56.14; H = 7.60; N = 8.18%.

found : C = 55.93; H = 7.63; N = 8.04%.

¹H nmr (CDCl₃): δ 1.75 (broad, 6 H); δ 2.6 (broad, 2 H);
δ 3.4 (broad, 2 H); δ 4.15 (singlet, 2 H); δ 9.60 (singlet, 1 H).

B.8 Reaction of N-carboxymethylhexahydroazepin-2-one with dimethyl acetylenedicarboxylate (DMADC).

The azepin-2-one (0.5 g; 3 mmoles) was dissolved in a mixture of acetic anhydride (8 ml) and DMADC (2.9 g; large excess) and the solution was heated to 120°C under nitrogen for 30 minutes. Effervescence was observed. The solution was evaporated under reduced pressure and the oily residue chromatographed on silica, eluting with chloroform. The second fraction contained an aromatic singlet (δ 7.35) in the ¹H nmr spectrum. Mass spectroscopy of this fraction showed M⁺ 251. (C₁₃H₁₇NO₄ requires M⁺ 251). The yield was insufficient for characterisation.

B.9 Preparation of diethyl pyrrolidine-2,5-dicarboxylate.

(i) The acid chloride of α,α'-dibromo-adipic acid was prepared as described in Organic Syntheses.

The acid chloride (100 g) was stirred and treated slowly, in the cold, with water (10 ml). Much heat was generated and HCl fumes were evolved.

α,α'-Dibromo-adipic acid. m.p. 159-161°C. (lit. 151-153°C) was obtained.

¹H nmr (dmsod₆): δ 2.15 (broad, 4 H); δ 4.32 (triplet, 2 H).
(ii) The acid chloride (150 g; 0.44 moles) was added dropwise to ice-cooled abs. ethanol (500 ml) and the solution was stirred overnight at room temperature. Water (500 ml) was then added and the upper aqueous mixture was decanted and extracted with ether (600 ml). The extract was washed with 2% NaHSO$_3$ (100 ml), 3% Na$_2$CO$_3$ (2 x 75 ml) and finally water (2 x 30 ml), then dried over anhydrous potassium carbonate.

On evaporation, diethyl$\alpha,\alpha'$-dibromoadipate was recovered, the $^1$H nmr spectrum of which showed the presence of meso- and DL-isomers. A portion was recrystallised from benzene to give the pure meso-isomer, m.p. 64-66°C. (lit. 67°C).

(iii) The diethyl ester (mixture of diastereoisomers) (82 g; 0.23 moles) was dissolved in benzene (250 ml) and benzylamine (82 g; 0.88 moles) was added to the refluxing solution. After stirring at reflux for 6 hours, and cooling, a quantitative yield of benzylamine hydrobromide (86 g; 0.46 moles) was filtered off. On evaporation of the filtrate and distillation under oil-pump vacuum to remove residual benzylamine, the $^1$H nmr spectrum of the remaining oil, diethyl N-benzylpyrrolidine-2,5-dicarboxylate (56) suggested that the product contained a slight predominance of the trans-ester.

$^1$H nmr:

\[
\delta \quad \begin{cases} 
1.18 \\
1.25 \\
1.9 \ (\text{multiplet, } 4 \ \text{H}) \\
3.95 \ (\text{singlet, } 2 \ \text{H}) \\
4.10 \ (\text{quartets, } 4 \ \text{H}) \\
4.07 \ (\text{quartets, } 4 \ \text{H}) \\
7.30 \ (\text{broad, } 5 \ \text{H})
\end{cases}
\]

![Chemical Structure](image-url)
(iv) Using the method of Lowe and Ridley\textsuperscript{34} the mixture of isomers (45 g) obtained in (iii) above was added to a solution of sodium ethoxide in ethanol (Na 3.0 g, abs. ethanol 200 ml) and stirred at room temperature for 84 hours to isomerise cis-ester to trans-ester.

(v) The diethyl meso-\(\alpha,\alpha\)'-dibromoadipate (4 g) prepared in (ii) above was dissolved in benzene (15 ml) and brought to reflux. Benzylamine (4.0 g) was added portionwise and the solution was refluxed with stirring for 6 hours. The benzylamine hydrobromide was filtered off and the benzene evaporated as before to give mainly diethyl N-benzylpyrrolidine-2,5-\textit{cis}-dicarboxylate.

\(\text{\(^1H\)}\text{nmr}\) shows the ratio of cis/trans isomer to be approximately 5:1. (cis-\textit{diethyl} protons upfield from trans-)

B.10 \textbf{Attempted reaction of 2,5-dibromoadipic acid with ammonia.}

A sample (5 g) of the acid (water insoluble) was dissolved in conc. ammonia (s.g. 0.88) and refluxed for 3 hours. The solution was reduced to small volume and made slightly acidic. On cooling, a white crystalline product was filtered off, subliming above 120\textdegree C, which was insoluble in ether, and therefore not starting material. (Possibly 2,5-diamino adipic acid.) There was no trace of pyrrolidine-2,5-dicarboxylic acid. (57)
B.11 Hydrogenation of diethyl N-benzylpyrrolidine-2,5-dicarboxylate.

The N-benzyl compound was dissolved in abs. ethanol (1:5 w/v) and after the addition of palladium charcoal (1g/100ml) it was agitated (4 atm. H₂; 40°C) for several hours in a hydrogenation apparatus, hydrogen uptake being monitored by a pressure gauge. After filtration to remove the charcoal, the solvent ethanol and toluene were evaporated to give a quantitative yield of diethyl pyrrolidine-2,5-dicarboxylate.

B.12 Self condensation of diethyl pyrrolidine-2,5-dicarboxylate.

After an unsuccessful attempt at lower temperature, the diethyl pyrrolidine-2,5-dicarboxylate (0.5 g; 2.33 mmols) was heated under nitrogen at 220°C for 2 hours. The 1H nmr spectrum of the product showed signals that were not present in the spectrum of starting material. After standing for some weeks the oil partially crystallised. The supernatant was decanted and the mass spectrum of the crystalline material gave M⁺ 338 corresponding to (52) C₁₆H₂₂N₂O₆ with a fragment at m/e 265, (338 - CO₂Et). A repetition of the experiment with a larger amount of the ester (2.5 g), heating at 200°C for 48 hours and separation of the resulting oil on alumina (10% deactivated with acetic acid) in ether gave some brown material followed by a white solid, dioxopiperazine (52) (0.4-0.5 g) which was not recrystallised.
B.13 **De-esterification of dioxopiperazine (52) with sodium hydroxide.**

Sodium hydroxide (0.012 g) was dissolved in water (2 ml) and the dioxopiperazine (0.050 g; 0.50 molar equivalent) was added. The water insoluble dioxopiperazine dissolved on shaking as it underwent hydrolysis. After acidification with aqueous dil. hydrochloric acid and extraction into ether to remove unreacted diester, the pH of the aqueous layer was carefully raised to 7. Reduction to small volume under reduced pressure precipitated a white solid which was filtered and dried. Yield 9.5 mg. (23%).

m.p. 136-138°C.


(C₁₂H₁₄N₂O₆ (53) requires M 282).

![Chemical Structure](image)

B.14 **Reaction of dioxopiperazine (53) with dimethyl acetylenedicarboxylate (DMADC).**

The acid (53) prepared in '13' above (20 mg; 0.1 mmoles) and DMADC (20 mg; 0.2 mmoles) were dissolved in acetic anhydride and refluxed for 1 hour. Water was added to convert the acetic anhydride to acetic acid and the mixture was extracted with ether. On evaporation to dryness of both fractions, most product was recovered from the organic layer. The major peak in
the mass spectrum showed at $m/e$ 282, (starting material) with only a small peak at $m/e$ 442, ($C_{22}H_{22}N_8O_8$ requires $M 442$), corresponding to the hexahydropyrazinodipyrrrolizine (54).
C. NEW REACTIONS OF INDOLIZINES.

C.1 Preparation of 1-methyl-2-phenylindolizine.

C.2 Preparation of 1,2-dimethylindolizine.
This was prepared by the method of Tschitshibabin from 2-ethylpyridine and chloroacetone, in 50% yield.

C.3 Reaction of 1-methyl-2-phenylindolizine with diphenylcyclopropenone.
The indolizine (3.1 g; 15 mmoles) and diphenylcyclopropenone (3.1 g; 15 mmoles) were refluxed for 3 hours in sodium dried toluene (40 ml). A further 1 g of diphenylcyclopropenone was added and refluxing was continued for a further 2 hours.

Solvent was removed under vacuum and the residue was redissolved in a little benzene and separated on a column of 6% deactivated alumina, eluting with benzene. Some starting material (indolizine) was isolated first, followed by a yellowish-brown band (major product) which was evaporated to give a brown oil (ca. 4 g) which was further separated on alumina, eluting with chloroform, to give a bright yellow product. Recrystallisation from benzene gave 6-methyl-2,3,5-triphenyl-6-(2-pyridyl)cyclohexa-2,4-dienone (3.8 g; 62%).

Bright yellow crystals, m.p. 155-156°C.
Analysis. Found: C, 85.75%; H, 5.92%; N, 3.56%; M⁺ 413.
C₃₀H₂₃NO requires: C, 85.47%; H, 5.98%; N, 3.99%; M⁺ 413.
The ¹H nmr spectrum showed singlets at 61.80, 61.85, and 66.40, a multiplet from 66.8-7.3 and two doublets at 67.55 and 68.53 with ratios 3 : 3 : 1 : 14 : 1 : 1. /over
The $^{13}$C nmr spectrum showed a quaternary carbon at $\delta$ 59.9.

C.4 Reaction of 1,2-dimethylindolizine with diphenylcyclopropenone.

1,2-Dimethylindolizine (freshly recrystallised ex. MeOH, 1.0 g; 7 mmoles) was dissolved in sodium dried toluene (5 ml) and diphenylcyclopropenone (1.45 g; 7 mmoles) in sodium dried toluene (10 ml) was added dropwise over 45 minutes, with refluxing.

The toluene was removed under vacuum and the residue redissolved in benzene, applied to an alumina column (6% deactivated) and eluted with benzene.

A bright yellow band was eluted as before, but evaporation gave a gum which could not be crystallised from a variety of solvents.

Analysis found : C, 82.7%; H, 5.9%; N, 3.6%; $M^{+}$ 351.

C$_{25}$H$_{21}$NO requires : C, 85.5%; H, 5.9%; N, 4.0%; $M^{+}$ 351.

$^{1}$H nmr spectrum showed singlets at $\delta$ 1.84, $\delta$ 1.90, and $\delta$ 6.52, a multiplet at $\delta$ 6.9-7.85, and a doublet at $\delta$ 8.65 with ratios 3 : 3 : 1 : 13 : 1.

The $^{13}$C nmr spectrum showed a quaternary carbon atom at $\delta$ 60.2 (20% intensity), two methyl carbons at $\delta$ 20.0 (33%) and $\delta$ 23.1 (29%), and seventeen other peaks at $\delta$ 121.9 (48%), $\delta$ 122.0 (45%), $\delta$ 123.4 (35%), $\delta$ 126.5 (41%), $\delta$ 127.2 (85%), $\delta$ 127.7 (100%), $\delta$ 128.7 (85%), $\delta$ 129.7 (12%), $\delta$ 130.9 (71%), $\delta$ 134.6 (17%), $\delta$ 136.4 (35%), $\delta$ 139.6 (16%), $\delta$ 149.1 (36%), $\delta$ 150.5 (18%), $\delta$ 153.4 (21%), $\delta$ 160.7 (15%), and $\delta$ 189.0 (8%).
C.5 **Reaction of 2-phenyl-5-methylindolizine with diphenylcyclopropenone.**

The indolizine (0.5 g) was dissolved in sodium dried toluene (4 ml) and diphenylcyclopropenone (C.5 g) in sodium dried toluene (5 ml) was added dropwise to the refluxing solution during 1 hour. Refluxing was continued for 3 hours.

The toluene was evaporated and the residue was redissolved in benzene. Chromatography on alumina (6% deactivated; elution with benzene) gave a small recovery of starting material but no evidence of an adduct. Any phenol that may have been present was not removed from the column by a more polar solvent. (CHCl₃).

C.6 **Reaction of 2-methylindolizine with diphenylcyclopropenone.**

The experiment was performed as in '5' above using 2-methylindolizine (0.1 g).

No yellow colour was observed in the products. No attempt was made to separate the products by chromatography, but the crude residue from evaporation of the toluene was examined by mass spectrometry. A peak at m/e 337 confirmed the presence of a 1:1 adduct. The residue was dissolved in ether and washed with aqueous sodium hydroxide. Some residue insoluble in the ether and aqueous phases was filtered off and the aqueous fraction was titrated to pH 7 with dil. hydrochloric acid. A cloudiness was observed in the neutral solution, which was then extracted with ether to give a yellow solution.
On drying over calcium chloride and evaporation, a yellow glassy product was recovered. Mass spectrometry again showed a peak at m/e 337 suggesting that the adduct was acidic, as required by the phenolic structure of (65).

\[
\begin{align*}
R &\quad \text{Ph} \\
\text{Ph} &\quad \text{OH}
\end{align*}
\]

\[65 \quad R = \text{Me}\\n69 \quad R = \text{Ph}\]

C.7 Reaction of 2-phenylindolizine with diphenylcyclopropenone.

The indolizine (freshly recrystallised; 0.4 g) was dissolved in boiling toluene (10 ml) and diphenylcyclopropenone (0.4 g) in toluene (10 ml) was added through the condenser. The solution was refluxed for 5 hours, the toluene was evaporated, and the residue partitioned between ether and 2M aqueous sodium hydroxide. The aqueous fraction was separated and treated with dil. hydrochloric acid to pH 7. Extraction with ether, drying, and evaporation of the extract gave a trace (a few mg.) of residue which gave a mass spectrometric peak m/e 399 corresponding to adduct (69). (C_{29}H_{21}NO).

C.8 Reaction of the product from 1,2-dimethylindolizine and diphenylcyclopropenone with methyl iodide.

The yellow compound prepared in '4' above (0.11 g) was dissolved in acetonitrile (7 ml) and methyl iodide (0.2 g) added. The solution was refluxed for
1 hour, and the product was precipitated by the careful addition of ether. Filtration gave yellowish crystals (0.08 g) which were recrystallised from methanol to give 5,6-dimethyl-2,3-diphenyl-6-(2-pyridyl)cyclohexa-2,4-dienone N-methiodide. (0.07 g). (66).

m.p. 133-136°C.

Analysis of the iodide was not satisfactory however, even after further recrystallisation.

Analysis found : C, 61.9%; H, 4.9%; N, 2.7%.

C_{25}H_{24}NOI requires : C, 63.2%; H, 4.9%; N, 2.8%.

The $^{13}$C nmr spectrum showed a quaternary carbon atom at $\delta$60.2 (48% intensity), two methyl carbons at $\delta$26.1 (20%) and $\delta$21.0 (40%), and an N-methyl carbon at $\delta$46.3 (28%). Nineteen other peaks were present at $\delta$126.0 (37%), $\delta$127.1 (42%), $\delta$127.3 (19%), $\delta$127.7 (55%), $\delta$127.8 (100%), $\delta$128.2 (97%), $\delta$128.6 (91%), $\delta$128.9 (45%), $\delta$129.1 (43%), $\delta$130.6 (88%), $\delta$131.3 (29%), $\delta$132.8 (29%), $\delta$137.9 (34%), $\delta$145.9 (28%), $\delta$149.2 (38%), $\delta$149.5 (32%), $\delta$151.6 (35%), $\delta$156.6 (25%), and $\delta$192.9 (28%).

C.9 Reaction of 6-methyl-2,3,5-triphenyl-6-(2-pyridyl)-cyclohexa-2,4-dienone (64) with concentrated hydrochloric acid.

The yellow compound obtained in '3' above (0.2 g) was refluxed in conc. hydrochloric acid (5 ml) for 2½ hours. An insoluble solid remained on cooling. The hydrochloric acid supernatant was decanted from the glassy product and the solid dried under vacuum.
The $^1$H nmr spectrum showed the methyl singlets to have moved downfield from $\delta 1.85$ to $\delta 2.35$.

The decanted hydrochloric acid was neutralised and extracted with ether, giving only a trace recovery of starting material.

A small sample (ca. 0.05 g) of the solid product obtained was refluxed in 2M sodium hydroxide (5 ml) for 2 hours. The non-crystalline starting material was thus converted to a crystalline bright yellow precipitate which was filtered off, washed with water, and dried under vacuum. The $^1$H nmr and IR spectra were identical with those of the original compound (64).

C.10 **Reaction of product from 1-methyl-2-phenylindolizine and diphenylcyclopropenone with sodium methoxide in methanol.**

The adduct (0.2 g) was dissolved in a solution of sodium methoxide in methanol (0.05 g Na in 9 ml MeOH) and the solution was refluxed for $2\frac{1}{2}$-3 hours. On cooling and addition of water, a fine yellow precipitate was obtained. Filtration and drying gave a quantitative recovery of starting material as shown by nmr spectroscopy.

C.11 **Photolysis of the product obtained from 1-methyl-2-phenylindolizine and diphenylcyclopropenone.**

The 6-methyl-2,3,5-triphenyl-6-(2-pyridyl)-cyclohexa-2,4-dienone (0.5 g) was dissolved in methanol (150 ml) and irradiated in a Hanovia photochemical reactor (100W medium pressure mercury arc) for 4 hours which caused darkening of the yellow solution. On
evaporation of the methanol to small volume, TLC showed a UV fluorescent spot with $R_f$ less than that of starting material. Separation on alumina (deactivated 5% w/v with acetic acid) gave a fraction, the mass spectrum of which corresponded to $C_{31}H_{27}NO_2$, $M^+ 445$, which agrees with the ring-opened methyl ester (67b). The yield was too small for characterisation.

![67b](image)

C.12 Reaction of 1-methyl-2-phenylindolizine with diphenylcyclopropenthione.

Diphenylcyclopropenthione was prepared from diphenylcyclopropenone by the method of Lown and Maloney. $\nu_{\max} 1350 \text{ cm}^{-1} (C=S)$.

The indolizine (0.103 g; 0.50 mmoles) was dissolved in sodium dried toluene (3 ml) and flushed with nitrogen before being brought to reflux. Diphenylcyclopropennethione (0.111 g; 0.50 mmoles) in sodium dried toluene (2 ml) was added dropwise over 30 minutes and the solution was refluxed under nitrogen for a further 2 hours. Chromatography on deactivated alumina gave a bright yellow product which proved by mass spectrometry to be not the thione (68) but the ketone (64).
C.13 Reaction of 1-methyl-2-phenylindolizine with phenoylethylntriphenylphosphonium bromide.

The indolizine (2 g) and phenoylethylntriphenylphosphonium bromide (1 molar equiv.) (87) were refluxed for 2 hours in methyl cyanide (50 ml), cooled, and the solvent removed under vacuum. A dark red oil was recovered which was washed well with ether. It solidified to an orange amorphous mass, 2-(1-methyl-2-phenylindolizin-3-yl)-2-phenylethenyl triphenylphosphonium bromide. A solution of the bromide, in methanol, was treated with perchloric acid followed by ether to give the perchlorate (53%), yellow needles, m.p. 206°C, identical with a specimen prepared by G.R. Birchall.

C.14 Reaction of [2-(1-methyl-2-phenylindolizin-3-yl)-2-phenylethenyl]triphenylphosphonium bromide (70) with sodium hydroxide.

A portion of the orange solid prepared in C.13 above (0.1 g) was dissolved in 2N sodium hydroxide (20 ml). A few drops of methanol were required to complete dissolution and the solution was stirred at room temperature for ½ hour. Ether was added and the organic layer separated and washed three times with water to remove any methanol. The organic fraction was dried over magnesium sulphate and evaporated to give a solid non-crystalline orange residue. (Starting material is insoluble in ether.) The ¹H nmr spectrum did not correspond to compound (71), no vinyl protons being apparent.
Reaction of [2-(1-methyl-2-phenylindolizin-3yl)-2-phenylethenyl]triphenylphosphonium perchlorate with sodium hydroxide.

The perchlorate (0.1 g) was dissolved in aqueous sodium hydroxide (2N), stirred briefly and extracted with ether. TLC showed a bright UV fluorescent spot. On evaporation of the ether and separation of the residue on a column of 6% deactivated alumina, eluting with toluene, a greenish oil was obtained which gave a peak in the mass spectrum with $M_e$ 309 corresponding to $C_{23}H_{19}N$ (71), together with many other peaks of unknown origin.


The perchlorate (0.1 g) was dissolved in abs. ethanol (150 ml) and irradiated in a Hanovia photochemical reactor (100W medium pressure mercury arc) for 2½ hours under nitrogen. Monitoring by TLC showed only a loss of starting material with time, and an increase in dark immobile material.

Thermolysis of [2-(1-methyl-2-phenylindolizin-3yl)-2-phenylethenyl]triphenylphosphonium perchlorate.

The perchlorate (0.1 g) was dissolved in sulpholane.
(5 ml) and heated at 210°C for 2 hours. Dilution with water and extraction with ether gave a pale yellow organic fraction which on drying and evaporation gave no discernible residue. The aqueous layer was precipitated with methanol and the green solid recovered was identified as starting material.

Refluxing of the sulphonylamine solution (b.p. 285°C) indicated that the perchlorate decomposes at a higher temperature.


(i) with sodium ethoxide. The perchlorate (0.1 g) was treated with an excess of sodium ethoxide in absolute ethanol. On extraction into ether after addition of water a greenish oil was recovered, attempted sublimation of which produced only a black tar.

(ii) with diazabicyclo(5,4,0)undec-5-ene (DBU). The perchlorate (70) (0.1 g) was dissolved in acetonitrile (5 ml) and DBU (0.023 g; 1 mol. equiv.) was added. Immediately the solution changed from green to orange-brown. TLC in ether showed no mobile products, so the solution was heated on a steam bath for 1 hour. On evaporation of the solvent and sublimation of the residue on to a cold finger, a yellowish oil was recovered which fluoresced under UV light. Mass spectrometry showed a large M⁺ 307, corresponding to C_{23}H_{17}N, (72) or an isomer.
Also strong peaks showed at 287 and 288 (Ph₃PO) with no peak at 262 (Ph₃P).

Repetition on a larger scale however (0.5 g indolizine) still gave no isolable yield of cyclazine (72).

C.19 Preparation of 6-(1-methyl-2-phenylindolizin-3-yl) fulvene (75).

3-N,N-Dimethylaminomethylene-1-methyl-2-phenylindolizinium perchlorate (73) was prepared from 1-methyl-2-phenyl indolizine and a dimethylformamide/POCl₃ complex. (Vilsmeier reaction). Recrystallisation from methanol gave yellow needles, $\nu_{\text{max}} 1100 \text{ cm}^{-1}$ (ClO₄⁻). The indolizinium perchlorate (1.0 g) was dissolved in acetonitrile (30 ml) and cyclopentadiene (0.35 g) and triethylamine (4 drops) were added. The solution was refluxed for 1 hour, then separated on alumina eluting with 1:1 toluene-ether. A prominent red band was eluted and this yielded the fulvene (0.5 g; 78%), reddish platelets, m.p. 135-137°C, identical with a specimen prepared by S.V. Heath.

Further elution yielded a small amount (35 mg; 2%) of an unidentified dark crystalline compound, which gave a deep purple solution in chloroform or methanol. Analysis found: C, 63.83%; H, 6.93%; N, 4.52%.

C.20 Attempted cyclodehydrogenation of 6-(1-methyl-2-phenyl indolizin-3-yl) fulvene with oxidising agents.

Portions of the indolizine were tested for possible cyclodehydrogenation

(i) with ferric chloride in boiling methanol
(ii) with chloranil in boiling methanol
(iii) with boiling nitrobenzene
(iv) with palladium charcoal in boiling 1,2,4-trichlorobenzene.

All the above tests resulted in decomposition giving only dark products immobile by TLC, apart from (iv), where some starting material remained.

C.21 Reaction of 3-(N,N-dimethylaminomethylene)-1-methyl-2-phenylindolizinium perchlorate with tetrachlorocyclopentadiene.

Tetrachlorocyclopentadiene was prepared by the method of Roedig and Hörnig from hexachlorocyclopentadiene with zinc and acetic acid, and recrystallised from acetone. The indolizinium perchlorate (73) (1.0 g) and tetrachlorocyclopentadiene (0.56 g; 1 molar equivalent) were dissolved in acetonitrile (20 ml) and 1 drop of triethylamine was added. An immediate colour change was observed from green to purple. The solution was heated briefly to reflux before removal of the solvent. Separation of the residue on a column of alumina, eluting with ether, yielded 6-(1-methyl-2-phenyl indolizin-3-yl) tetrachlorofulvene (77). Purple crystals, m.p. 65-66°C. Yield = 55%

Analysis found : C, 58.26%; H, 3.34%; N, 3.48%.
C_{20}H_{13}Cl_{4}N requires : C, 59.86%; H, 3.09%; N, 3.32%.

C.22 Attempted thermolysis of 6-(1-methyl-2-phenyl indolizin-3-yl) tetrachlorofulvene.

The tetrachlorofulvene (77) (0.1 g) was dissolved in sulpholane (3 ml) and the solution heated to 100°C, at which point the purple solution turned black. The sulpholane was partitioned between water and ether. TLC of the ether
fraction showed only one purple spot due to starting material with no indication of the dehydrochlorination product (89). Much dark material remained in the aqueous fraction.

C.23 **Photolysis of 6-(1-methyl-2-phenylindolizin-3-yl)-tetrachlorofulvene.**

The tetrachlorofulvene (77) (0.1 g) was dissolved in absolute ethanol (150 ml) and irradiated in a Hanovia photochemical reactor (100W medium pressure mercury arc) for 4 hours. The purple colour of the solution had then faded. After partial evaporation of the ethanol, TLC in chloroform showed a yellow-brown spot with $R_f \sim 0.7$ which was fluorescent under UV light.

On evaporation of the ethanol to dryness, hydrogen chloride fumes were evolved. Separation on a column of deactivated alumina, eluting with ether, yielded a few milligrams of a yellowish oil which was fluorescent under ultraviolet light. The product was not further characterised.

C.24 **Reaction of 3-(N,N-dimethylaminomethylene)-1-methyl-2-phenylindolizinium perchlorate with nitromethane.**

The indolizinium perchlorate (73) (0.5 g) was dissolved in nitromethane (5 ml) and refluxed for 1 hour after the addition of 2 drops of triethylamine. The solution rapidly turned from green to dark red. The nitromethane was removed under vacuum and the residue passed down a column of deactivated alumina, eluting with a 1:1 mixture of ether/toluene.

3-(2-nitrovinyl)-1-methyl-2-phenyl indolizine (74)
(80%) m.p. 201-202°C (from toluene) was obtained. Analysis found: C, 73.85%; H, 5.04%; N, 9.81%.

C₇H₁₄N₂O₂ requires: C, 74.10%; H, 5.03%; N, 10.06%.

'H nmr showed: δ 2.25 (singlet, 3 H); δ 7.4 (doublet, 1 H); δ 8.3 (doublet, 1 H); δ 6.9-7.6 (multiplet, 9 H).


The nitrovinylindolizine (74) (0.1 g) was dissolved in sulpholane (3 ml) and heated briefly to reflux (285°C). TLC showed only black immobile material. No starting material remained.

C.26 Photolysis of 3-(2-nitrovinyl)-1-methyl-2-phenylindolizine.

The nitrovinylindolizine (74) (0.1 g) was dissolved in absolute ethanol (150 ml) and irradiated for several hours in a Hanovia photochemical reactor (100W medium pressure mercury arc) after addition of a crystal of iodine, any reaction being followed by TLC in benzene. After a while there was a gradual appearance of a yellow spot (fluorescent in UV) in the TLC with Rf greater than that of starting material.
Separation on deactivated alumina eluting with toluene gave a few milligrams of a yellow oily product whose UV spectrum was not consistent with that of 2,3-diphenylcycl[3,2,2]azine, although the relevant absorption may have been obscured by those of other products.

C.27 Reaction of 1-(N,N-dimeth71aminomethylene)-1-methyl-2-phenylindolizinium perchlorate with malononitrile.

The indolizinium perchlorate (73) (0.5 g) was dissolved in acetonitrile (20 ml) with malononitrile (1.6 g; 10 molar excess). The solution was flushed with nitrogen and three drops of triethylamine were added, which produced a rapid colour change from green to red. After refluxing for 1 hour the solvent was removed under vacuum, the residue taken up in a little chloroform and chromatographed on deactivated alumina, eluting with toluene/ether (1:1).

Reddish-brown crystals were recovered which were recrystallised from toluene to give 1-(1-methyl-2-phenyl indolizin-3-yl)-2,2-dicyanoethene (80), (40%), m.p. 147-149°C

Analysis found : C, 79.92%; H, 4.67%; N, 13.76%.
C_{13}H_{13}N_{3} requires : C, 80.56%; H, 4.58%; N, 14.87%.

C.28 Reaction of 3-(N,N-dimethylaminomethylene)-1-methyl-2-phenylindolizinium perchlorate with ethyl cyanoacetate.

The indolizinium perchlorate (73) (0.7 g) was dissolved in ethyl cyanoacetate (10 ml) with warming and, after addition of three drops of triethylamine, heated briefly to 120°C then allowed to cool.
Orange crystals of l-(l-methyl-2-phenylindolizin-3-yl)-2-cyano-2-ethoxycarbonylethene (81) precipitated and were filtered and washed with a little ether. Orange needles m.p. 141-143°C.

IR C≡N stretch 2195 cm⁻¹ (ethyl cyanoacetate C≡N 2280 cm⁻¹)
Yield 0.45 g (70%).
Analysis found : C, 76.22%; H, 5.33%; N, 8.44%.
C₂₁H₁₈N₂O₂ requires : C, 76.36%; H, 5.45%; N, 8.48%.

¹H nmr showed : δ 1.30 (triplet, 3 H); δ 2.23 (singlet, 3 H);
δ 4.28 (quartet, 2 H); δ 6.9-7.65 (multiplet, 9 H);
δ 8.15 (singlet, 1 H); δ 8.45 (doublet, 1 H).

C.29 Thermolysis of l-(l-methyl-2-phenylindolizin-3-yl)-2-cyano-2-ethoxycarbonylethene.

The indolizine (81) (0.1 g) was dissolved in 1,2,4-trichlorobenzene (5 ml) and heated to reflux (210°C) for 1 hour. TLC in methanol showed no new product. After removal of the solvent under vacuum the residue was identified by IR spectroscopy as starting material.

C.30 Reaction of 3-(N,N-dimethylaminomethylene)-l-methyl-2-phenylindolizinium perchlorate with cyanoacetamide.

The indolizinium perchlorate (73) (0.8 g) and cyanoacetamide (2 molar equiv.) were dissolved together in acetonitrile (15 ml) and three drops of triethylamine were added. There was a rapid colour change from green to red. The solution was then refluxed for 1 hour. After evaporation of solvent the residue was
well triturated with ether and reddish-purple crystals were filtered from the washings and washed again with a little cold methanol.

l-(1-methyl-2-phenylindolizin-3yl)-2-cyano-2-aminocarbonyl-ethene (85) (0.2 g; 32%). Reddish purple prisms m.p. 159-161°C.

Found : C, 75.58%; H, 4.97%; N, 13.92%; M+ 301.

\[ \text{C}_{19}\text{H}_{15}\text{N}_{3}\text{O} \] requires : C, 75.75%; H, 4.98%; N, 13.95%; M+ 301.

\[ \delta \] 2.25 (singlet, 3 H); 5.85 (singlet, broad, 2 H); 6.9-7.7 (multiplet, 9 H); 8.3 (singlet, 1 H).

C31 Reaction of 1-methyl-2-phenyl indolizine with 2,3,4,5-pentachlorocyclopentenone in the presence of base.

The indolizine (0.2 g) and DBU (0.145 g) were dissolved in anhydrous ether (10 ml) and the cyclopentenone (0.25 g; 1 mol. equiv.), in ether, was added dropwise. Immediately a deep blue colour was formed. The ether layer was decanted from a dark tarry deposit and evaporated. White fumes of HCl were observed on evaporation to dryness. Dark crystals (0.25 g) were recovered which gave a deep blue solution in ether, chloroform or methanol. In the \( ^1\text{H} \) nmr spectrum the methyl singlet was unmoved from that of 1-methyl-2-phenyl indolizine. IR spectroscopy showed a C=O absorption at 1700 cm\(^{-1}\). Mass spectrometry showed M+ 387 (main peak in isotopic cluster) corresponding to \( \text{C}_{20}\text{H}_{12}\text{NOCl}_3 \), which may be represented by structure (86b). Owing to difficulties in recrystallisation a satisfactory analytical sample was not obtained.

Found : C, 69.22%; H, 3.9%; N, 4.1%.

\[ \text{C}_{20}\text{H}_{12}\text{NOCl}_3 \] requires : C, 61.77%; H, 3.1%; N, 3.6%.
Reaction of 2-methylindolizine with 2,3,4,4,5-pentachlorocyclopenten-2-one.

The indolizine (0.4 g) was dissolved in dichloromethane (25 ml) and the cyclopentenone (0.75 g; 1 mol. equiv.) was added with stirring. Immediately a deep purple colour was formed which was unstable to exposure to air.

DBU (0.45 g; 1 mol. ratio) was then added in dichloromethane (5 ml). Immediately a deep blue colour was formed. The solvent was removed under vacuum and the dark residue chromatographed on a column of alumina eluting with ether. It proved difficult to separate the blue fraction from a more mobile yellowish-brown band which probably contained unreacted 1-methylindolizine. The experiment was repeated with a slight excess of the pentachloro-compound and a much cleaner blue product was recovered from the column, eluting with ether. On evaporation, a dark amorphous non-crystalline solid (0.2 g) was recovered. The mass spectrum showed little evidence of $M^+$ corresponding to $C_{14}H_8Cl_3NO$ (86c), although decomposition of the product may have occurred on standing. Crystallisation of the solid was not achieved from a variety of solvents.

Found : C, 57.4%; H, 2.6%; N, 4.6%.

$C_{14}H_8Cl_3NO$ requires : C, 53.4%; H, 2.5%; N, 4.5%.

\[
\begin{align*}
&86 \quad a : R = H, \quad R' = \text{Ph} \\
&b : \quad \text{Me,} \quad \text{Ph} \\
&c : \quad H, \quad \text{Me}
\end{align*}
\]
C.33  Reaction of 2-phenylindolizine with 2,3,4,4,5-pentachlorocyclopenten-2-one.

The indolizine (0.3 g) was dissolved in acetonitrile (25 ml), with warming, and the chlorocompound (1 mol. equiv.) was added dropwise, in acetonitrile (5 ml) with the solution at reflux. An immediate dark blue colour was produced. The solvent was evaporated, and the residue was taken up in a little chloroform and chromatographed on a column of 10% deactivated alumina, eluting with an ether/chloroform (1:1) mixture. A dark non-crystalline solid (0.45 g) was recovered on evaporation. Mass spectrometry gave $M^+$ 372/374/376/378 corresponding to $C_{19}H_{10}NOCl_3$. Compound (86a) requires $C_{19}H_{10}NOCl_3$.

Recrystallisation was effected from toluene.

Found : C, 55.4%; H, 2.2%; N, 2.6%.

($C_{19}H_{10}NOCl_3$ requires : C, 59.61%; H, 2.75%; N, 3.85%).
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A NEW AND CONVENIENT SYNTHESIS OF AZULENES FROM 6-N,N-DIMETHYLAMINOFULVENE AND THIOPHENE 1,1-DIOXIDES.

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The cycloaddition reactions of fulvenes with dienes, * heterodiene s* and 1,3-dipoles* have been studied recently by several groups of workers and it has been recognised that the fulvenes may function either as 2π-or as 6π-addends. 6-N,N-Dimethylaminofulvene (1) shows a particularly marked propensity for [6+4]cycloaddition and this periselectivity has been rationalised by Houk and his coworkers using the Frontier MO method. When the 4π-addend is a 5-alkoxycarbonyl-2-pyri dine, such cycloadditions to the fulvene (1) are followed by spontaneous loss of dimethylamine and carbon dioxide, thus providing a convenient synthesis of azulenes, albeit in low yield. We now report an improved route to azulenes based on similar principles but utilising thiophene 1,1-dioxides (2) as the 4π-components. The reactions are believed to take the course outlined in the Scheme though there is no direct evidence for the intermediate cycloadducts (3).

\[
\begin{align*}
\text{Cycloaddition} & : \\
\text{1} + \text{2} & \rightarrow \text{3} \\
\text{3} & \rightarrow \text{4}
\end{align*}
\]

Formation of azulene (4a), as shown by the appearance of a blue colour and by t.l.c., commenced at room temperature when the fulvene (1) was added, under nitrogen, to a solution of thiophene 1,1-dioxide \(^6\) (2a) (approx. 1 equiv.) in tetrahydrofuran. The reaction was completed by raising the temperature slowly to reflux and, after 3 hr., azulene (33%) was isolated by chromatography on alumina in pentane. A similar reaction with 3,4-dichloro-
thiophene 1,1-dioxide \(^7\) (2b) proceeded more rapidly and gave 5,6-dichloroazulene (4b) (46%), blue plates, m. p. 58-59\(^\circ\) C (CDCl\(_3\)) \(7.30-7.35\) (H-1 and H-3), \(7.41\) (d, H-7), \(7.88\) (t, H-2, \(J_1,2\) 3.7\(\text{Hz}\)), \(8.03\) (d, H-8, \(J_7,8\) 11\(\text{Hz}\)), \(8.52\) (s, H-4).

Despite the moderate yields, we believe that this reaction provides a highly convenient route to azulene; the fulvene (1) is obtainable \(^8\) in one stage from cyclopentadiene, and a solution of thiophene dioxide (2a) is easily prepared from the commercially available 2,5-dihydrocompound by addition of bromine and dehydrobromination \(^6b\) with powdered sodium hydroxide in tetrahydrofuran. Work-up of the reaction mixture is straightforward since no chromatographically mobile products other than azulene are formed. The hitherto unknown 5,6-dichloroazulene (4b) is a useful source of other azulenes with uncommon substitution patterns since the chlorine at C-6 is susceptible to nucleophilic displacement (e.g., by secondary amines and by thiolate anions).

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*Professor K. N. Houk has kindly informed us that similar observations, which are shortly to be published, have been made independently in his laboratory.