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The synthesis and characterisation of cyclazines and related N-bridged annulenes

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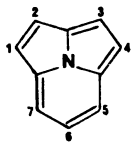
Abstract - The chemistry of [3.3.3]cyclazines (pyrido-[2,1,6-*de*]quinolizines) is reviewed and an improved synthesis of these compounds is presented. It is shown that the cyclazine concept may be extended to higher bridged annulenes by incorporating two, independently linked, internal nitrogen atoms. The synthesis and properties of two such doubly N-bridged annulene systems, pyrazino[2,1,6-*cd*:5,4,3-*c'd'*]dipyrrolizine (a [14]-annulene derivative) and pyrazino[2,1,6-*cd*:5,4,3-*c'd'*]-di-indolizine (a [16]annulene derivative) are described.

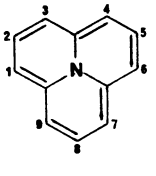
INTRODUCTION

The name 'cyclazine' was originally proposed by Boekelheide (ref 1) in 1958 to denote "the general case of a conjugated unsaturated cycle held planar by three covalent bonds to an internal nitrogen atom". Such compounds, which clearly fall within the general category of bridged annulenes, are exemplified in formulae 1-4. The names used here are based on our recent suggestions (ref 2) for modification of the originally proposed system of nomenclature: (i) to facilitate pronunciation the three numerals, indicating the numbers of atoms in the annulene ring that lie between the points of attachment to the central nitrogen, are placed in front of the word cyclazine (rather than in the middle of it), and (ii) these numerals are listed in increasing (rather than decreasing) order so that their sequence starts at the same point and proceeds in the same direction as the IUPAC numbering sequence of the peripheral annulene cycle.



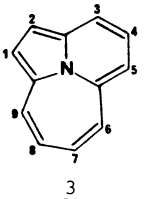
1

[2.2.3]Cyclazine



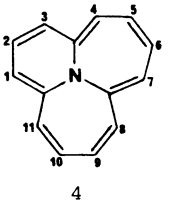
2

[3.3.3]Cyclazine



3

[2.3.4]Cyclazine



4

[3.4.4]Cyclazine

The purpose of this lecture is to outline selected aspects of cyclazine chemistry with which my research group in the University of Edinburgh has been associated and to describe, in particular, some of the more recent developments in our work.

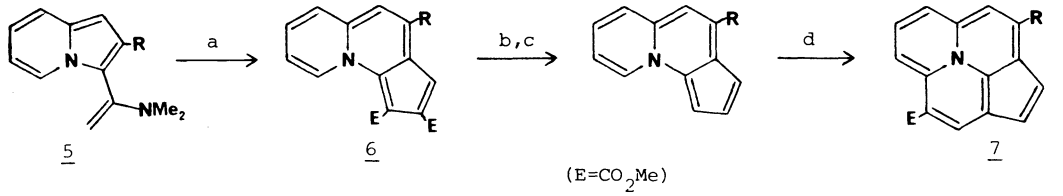
[3.3.3]CYCLAZINES

Experimental studies related to a synthesis of [3.3.3]cyclazine were first described in 1954 by Boekelheide and Gall (ref 3) who referred to the compound as 'tricyclazine' at that time. Four subsequent reports by various authors (ref 4) described unsuccessful approaches to the compound but it was not until 15 years later that we had the good fortune to find a viable route. With the benefit of hindsight, based on a knowledge of the high reactivity of [3.3.3]cyclazine, it is clear that the earlier approaches to its synthesis had little chance of success and that responsibility must

rest, at least partially, with the early MO studies (refs 1b and 5) which had predicted that [3.3.3]cyclazine would be a stable compound of high resonance energy.

The opportunity to synthesise compounds containing a [3.3.3]cyclazine substructure was first presented to us when we discovered, rather by chance, that 3-(1-dimethylaminovinyl)indolizines 5 were converted into cyclopenta[*c*]quinolizines 6 by reaction with dimethyl acetylenedicarboxylate (DMAD) in boiling toluene (ref 6). Decarboxylation of these compounds and further reaction with acetylenic esters in boiling nitrobenzene gave tetracyclic products 7 which could be hydrolysed and decarboxylated by conventional methods (Scheme 1). The resulting cyclopenta[*cd*][3.3.3]-cyclazines were green air-stable compounds, judged to be aromatic on the basis of their ^{1}H n.m.r. spectra (ref 7).

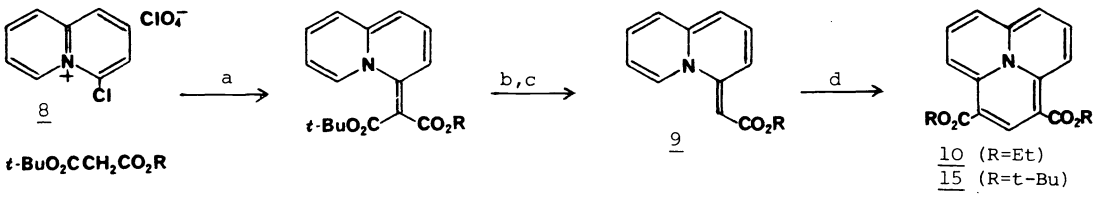
Scheme 1



Reagents: a, DMAD,PhMe, heat; b, aq.HCl, heat; c, aq.NaOH; d, HC≡CE,$PhNO_2$,heat

Recognition of this reaction as a formal cycloaddition of the acetylenic ester to a 4-methylene-4*H*-quinolizine moeity, followed by dehydrogenation, led naturally to a synthesis of [3.3.3]cyclazines lacking the fused five-membered ring (ref 8). The methylenequinolizines 9 required for this purpose were stabilised by an electron-withdrawing substituent on the exocyclic carbon atom and were obtained by reaction of 4-chloro-quinolizinylium perchlorate 8 (ref 9) with the sodium derivatives of alkyl t-butyl malonates, followed by selective removal of the t-butoxycarbonyl group. Reaction of 9 with alkyl propiolates proceeded smoothly, in boiling nitrobenzene, to give dialkyl [3.3.3]cyclazine-1,3-dicarboxylates, *eg* 10 (Scheme 2).

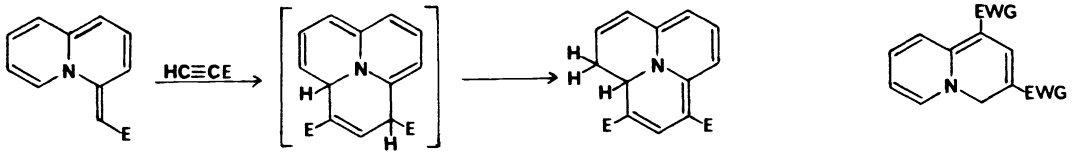
Scheme 2



Reagents: a, NaH,THF; b, HCl,PhH; c, aq.NaOH; d, HC≡C.CO_2R,$PhNO_2$, heat

This was essentially a three-stage synthesis from the quinolizinylium salt 8 and gave a 47% overall yield of the diethyl ester 10. One of the intermediates 9 required careful handling as it was somewhat air-sensitive. By conducting the final stage of the reaction for a shorter time, we were able to show that a 3a,4-dihydrocyclazine 11 was formed as a stable intermediate which could be isolated as a deep purple solid. Clearly, it could not be the first intermediate of the reaction sequence and must have been formed, by H-migration, from an earlier intermediate (as, *eg*, in Scheme 3). The stability of 11 appears to be associated with the presence of a 4*H*-quinolizine substructure bearing electron-withdrawing groups in its 1- and 3-positions [formula 12]. This type of structure is found repeatedly in the chemistry of [3.3.3]cyclazines and its stability has been commented upon in other contexts (refs 10 and 11).

Scheme 3

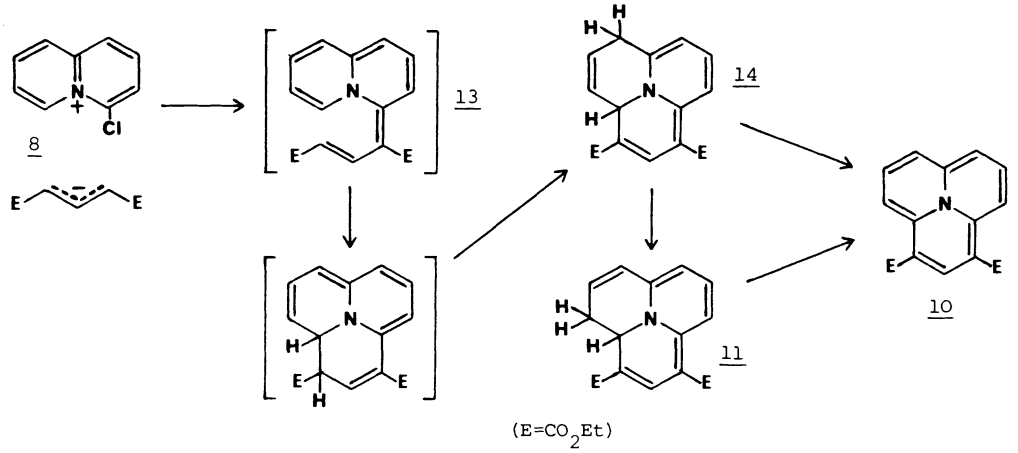


11 12

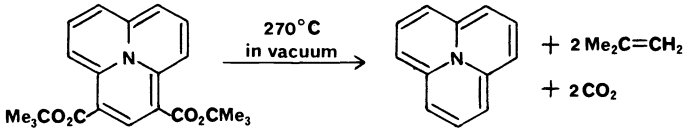
(E=CO_2Et)

Recently, we have developed a simplified and improved synthesis of the cyclazine diester 10 from 4-chloroquinolizinylium perchlorate 8 by reaction with the lithium derivative of diethyl glutaconate (Scheme 4). The first observable products of this reaction were two dihydrocyclazines, the hitherto unknown 3a,6-dihydro-compound 14 and the 3a,4-dihydro-compound 11, identical with the intermediate obtained in our first [3.3.3]cyclazine synthesis. These compounds are believed to be formed from an initial quinolizinylideneglutaconate 13 by electrocyclisation followed by hydrogen (prototropic?) migration to generate relatively stable 4*H*-quinolizine substructures bearing the ester groups in their 1- and 3-positions. The orange-red 3a,6-dihydrocyclazine 14, which appeared to be the main initial product, was rather labile, being converted partially into the purple 3a,4-isomer 11 and partially into the fully unsaturated cyclazine 10 as the reaction proceeded. Efficient conversion of these dihydro-compounds into the cyclazine was possible neither with boiling nitrobenzene, which had been used successfully in our previous synthesis, nor with high potential quinones (*eg* DDQ, *o*-chloranil) since these reacted with the cyclazine product. A number of other reagents were tried, unsuccessfully, but finally a smooth dehydrogenation was achieved with phenanthrene-9,-10-quinone. This route to the cyclazine 10 shows a clear advantage over our previous route in giving an improved overall yield (50-60%) in essentially one operational step, no isolation of intermediates being necessary.

Scheme 4



Because of the instability of [3.3.3]cyclazines in protic media, it is not possible to convert the diester 10 into the parent compound 2 by conventional procedures of hydrolysis and decarboxylation. Instead, we obtained the parent cyclazine, from its di-t-butoxycarbonyl derivative 15 by thermolysis in a sealed, evacuated tube. Thereafter, because of its sensitivity to oxygen, the cyclazine was handled entirely under nitrogen.



For an understanding of the chemical and physical properties of [3.3.3]cyclazine, it is useful to compare the compound with the isoelectronic phenalenyl anion. Like all odd-alternant hydrocarbons, the phenalenyl system has a non-bonding molecular orbital (NBMO) (Fig 1) which may be doubly occupied, singly-occupied, or unoccupied so that the system can exist as an anion, a free-radical, or a cation, all of which have considerable stability. The corresponding species formed by replacing the central C atom by N are [3.3.3]cyclazine, its radical-cation, and its dication. We have been able to observe all these species, the two cations being obtained sequentially by oxidation of the parent cyclazine with chlorine or bromine (ref 8). The ease with which chemical oxidation occurs is reflected in the unusually low first IP of 5.9 eV, measured by UVPE spectroscopy (ref 12).

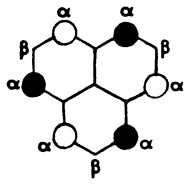


Fig. 1. NBMO of phenalenyl.

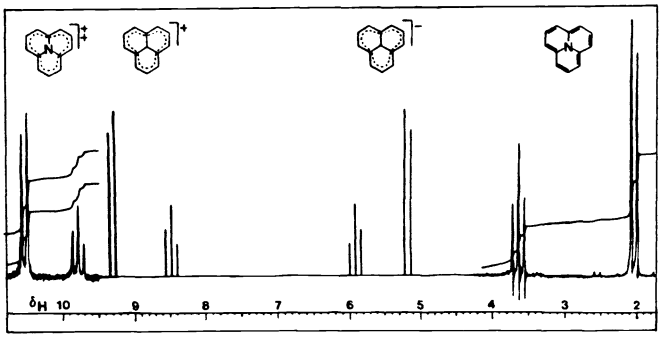


Fig. 2. ^{1}H n.m.r. spectra of [3.3.3]cyclazine and its dication compared with those of phenalenyl anion and cation reconstructed from literature data (ref. 13).

Since the LCAO coefficients for the NBMO of phenalenyl are non-zero only at the six equivalent α-positions, the charges in the two phenalenyl ions and the spin-density in the radical are largely concentrated at these positions. The effect in the ions can be seen in their ^{1}H n.m.r. spectra (Fig 2), the α-protons (doublet) being less shielded in the cation and more shielded in the anion, relative to the β-protons (triplet). The same effect is seen in comparing the spectrum of the cyclazine dication with that of the neutral cyclazine. The effect of replacing a carbon atom by nitrogen is to increase the positive charge by one unit and it is not surprising, therefore, that the spectrum of the cyclazine dication is shifted, as a whole, to higher frequency relative to that of the phenalenyl cation. The corresponding change from phenalenyl anion to neutral cyclazine results, however, in a shift of the spectrum to lower frequency. This apparently anomalous result may be explained in the following way: if the cyclazine were to retain the electron distribution of the phenalenyl anion, it would exist as a zwitterion; to avoid this energetically unfavourable charge separation, the non-bonding electrons of the cyclazine tend to reside largely in a lone-pair orbital, leaving a peripheral conjugated system containing 12 π-electrons; this [12]annulene perimeter sustains a paramagnetic ring current and the protons are unusually strongly shielded (δ 2.1 and 3.6).

This observation of strong paratropism in [3.3.3]cyclazine implies the existence of a low-lying excited electronic state and correlates well with the unusually low energy of the first electronic transition which occurs in the near infrared at 1290 nm (93 kJ mol^{-1}) (ref 14). MO calculations (refs 12, 14a, and 15) show that the formal degeneracy of the non-bonding orbitals of [12]annulene is lifted by interaction with the central nitrogen but only to a small extent, the resulting frontier orbitals of [3.3.3]-cyclazine being close in energy but well separated spatially (refs 14a and 16a) (Fig 3).

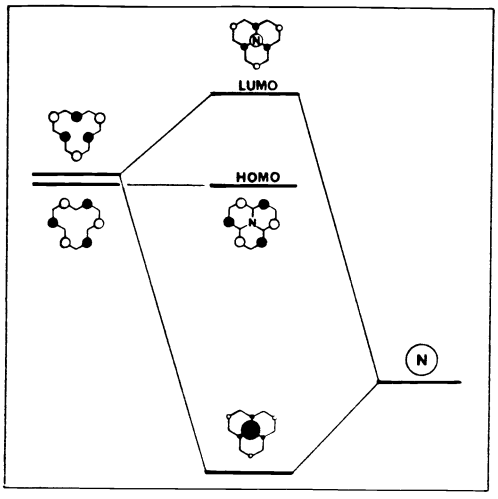


Fig. 3. Correlation of frontier orbitals of [3.3.3]cyclazine with NBMOs of [12]annulene.

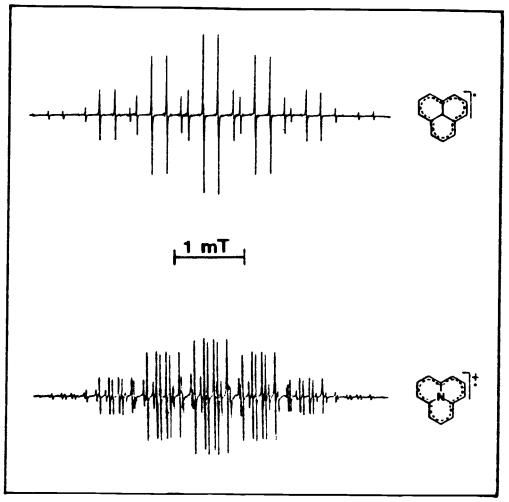


Fig. 4. E.s.r. spectra of phenalenyl radical and [3.3.3]cyclazine radical-cation.

In the cyclazine radical-cation, the unpaired electron retains approximately the same distribution as in the phenalenyl radical (ref 16b). The e.s.r. spectra of these two species (Fig 4) both show a large septet splitting ($a_{\alpha H}$) and a small quartet splitting ($a_{\beta H}$), the hyperfine coupling constants being almost equal for the two species. In addition, however, each line in the cyclazine radical-cation spectrum shows a small triplet splitting due to the nitrogen atom (ref 16a).

In view of the high π-electron density at the α-positions, it is to be expected that [3.3.3]cyclazines will be stabilised by electron-withdrawing (EW) substituents or ring nitrogen atoms at those positions. In practice, it is found that at least two such substituents are required for stability to oxygen, and the success of our synthetic routes is dependent on the presence of EW groups which appear in the 1-and 3-positions of the cyclazine products. Other workers (ref 17) have prepared numerous stable α-polyaza-derivatives of [3.3.3]cyclazine and this work has culminated recently in a synthesis of 1,3,4,6,7,9-hexa-aza[3.3.3]cyclazine (ref 18), a system previously known only in substituted form. Less obviously predictable is the stabilisation afforded by *peri*-fusion of [3.3.3]-cyclazine to a five-membered ring: the cyclopenta[*cd*][3.3.3]cyclazines (Fig 5) are air-stable and diatropic, the 1,2-bond apparently being an essential part of the ring current pathway. We have suggested (ref 7) that these characteristics are due to an incipient charge separation which, taken to completion, would convert the molecular perimeter into a [13]annulenyl anion [formula 16].

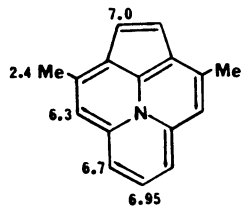
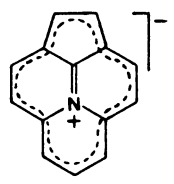


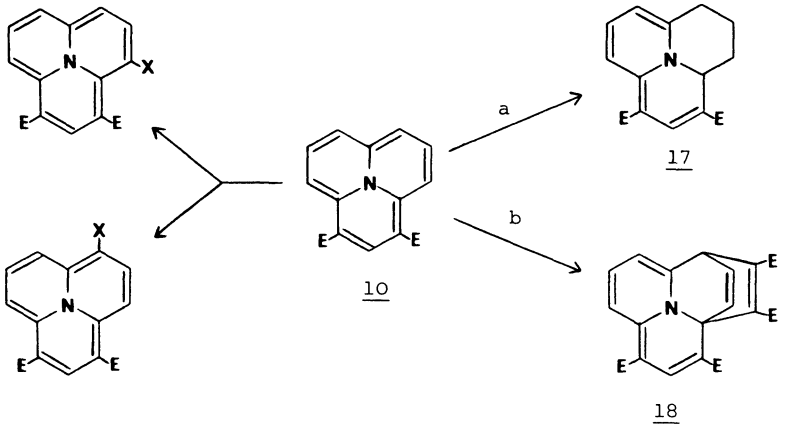
Fig. 5. ^{1}H chemical shifts of 3,9-dimethylcyclopenta-[cd][3.3.3]cyclazine



16

The chemical reactions of the parent [3.3.3]cyclazine, other than electron-transfer oxidation, have received little attention since they give rise either to uncharacterisable polymeric materials or to complex mixtures of products. A more rewarding subject for investigation is the 1,3-diester 10 which undergoes electrophilic substitution in the 4-and 6-positions, catalytic hydrogenation (1 atm) to the tetrahydro-compound 17, and cycloaddition with DMAD to form the adduct 18 (Scheme 5). Compounds 17 and 18 contain a 1,3-di(alkoxycarbonyl)-4*H*-quinolizine substructure and provide a further illustration of the way in which the stability of this type of residual conjugation influences the chemistry of [3.3.3]cyclazines.

Scheme 5

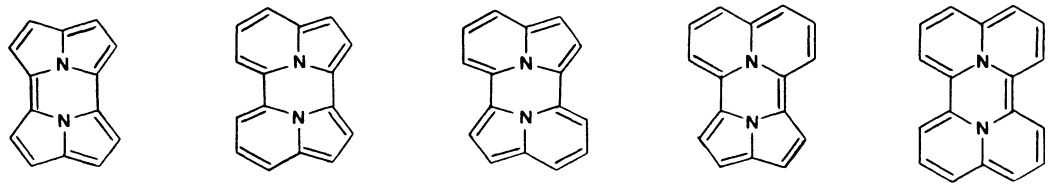


(E=CO_2R; X=COR, NO_2 etc)

Reagents: a, H_2,Pd-C,1 atm.; b, DMAD

DOUBLY N-BRIDGED ANNULENES

Of the three uncharged cyclazines originally proposed by Boekelheide (ref 1b), [2.2.3]cyclazine and [3.3.3]cyclazine are now known and only [3.4.4]cyclazine remains to be synthesised. This last compound, because of its seven-membered component rings, presents a much more difficult synthetic problem. It seemed possible, however, that the cyclazine concept might be more easily extended to higher bridged annulene systems by joining two internal nitrogen atoms, each by three covalent bonds, to the annulene perimeter. The possibilities, restricted to molecules containing only five- and six-membered rings, are shown in formulae 19-23. To date, we have synthesised two of these doubly N-bridged annulene systems, 19 (ref 19) and 21 (ref 11), the first of which is a [14]- and the second a [16]-annulene derivative.

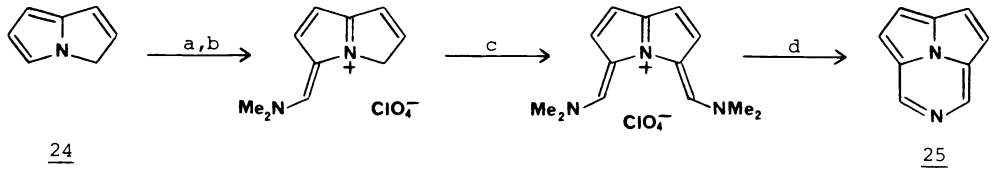


19 PDP 20 21 PDI 22 23

Pyrazino[2,1,6-*cd*: 5,4,3-*c'd'*]dipyrrolizine (PDP)

Our starting point for the synthesis of this compound was 3*H*-pyrrolizine, 24 which is readily available, by the method of Schweizer and Light (ref 20), from pyrrole-2-carbaldehyde and vinyltriphenylphosphonium bromide. Brief attempts to approach the synthesis of PDP by coupling two pyrrolizine molecules failed and a longer route *via* 6-aza[2.2.3]cyclazine 25 was therefore adopted. The synthesis of this compound from 3*H*-pyrrolizine had been the subject of a previous study (ref 2) in our laboratories and is shown in Scheme 6.

Scheme 6

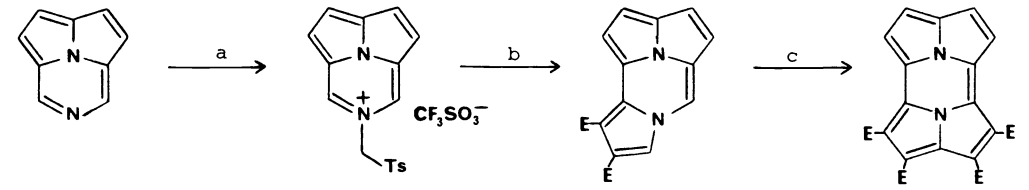


24 25

Reagents: a, $Me_2NCHO,POCl_3$; b, $NaClO_4$; c, Me_2NCHS,Ac_2O; d, NH_3

The azacyclazine 25 was quaternised with tosylmethyl triflate and the resulting salt, 26 was allowed to react with DMAD in the presence of triethylamine. This procedure (Scheme 7), which yielded the previously unknown pyrrolo[2',1';3,4]pyrazino[2,1,6-*cd*]pyrrolizine ring system, was based on the method of Abramovitch and Alexanian (ref 21) for the conversion of 2-unsubstituted pyridines into indolizines; the initial product of 1,3-dipolar cycloaddition to the ylide derived from 26 rearomatises by elimination of *p*-toluenesulphinic acid (thus avoiding the need for dehydrogenation inherent in earlier related procedures), leaving an unsubstituted pyrrolic α-position. Attempted decarboxylation of the diacid obtained from the ester 27 caused much decomposition and gave no more than a trace of the parent pyrrolopyrazinopyrrolizine. This compound, like the isomeric pyrrolopyrimidinopyrrolizine (ref 22) was evidently quite labile and failed to survive the severe conditions required for decarboxylation. Fortunately, the diester 27, despite its EW substituents, was able to react further with DMAD in boiling toluene, in the presence of a palladium-charcoal catalyst. These conditions, which were based on Boekelheide's second synthesis (ref 23) of [2.2.3]cyclazines from indolizines, gave the PDP-tetraester 28, presumably by [12+2]π-cycloaddition followed by dehydrogenation (Scheme 7). Hydrolysis of the ester, and decarboxylation in boiling pyrrolidin-2-one containing copper(I) acetate gave the pyrazinodipyrrolizine as a red solid, stable to air and light. The overall yield from 3*H*-pyrrolizine was 6%.

Scheme 7

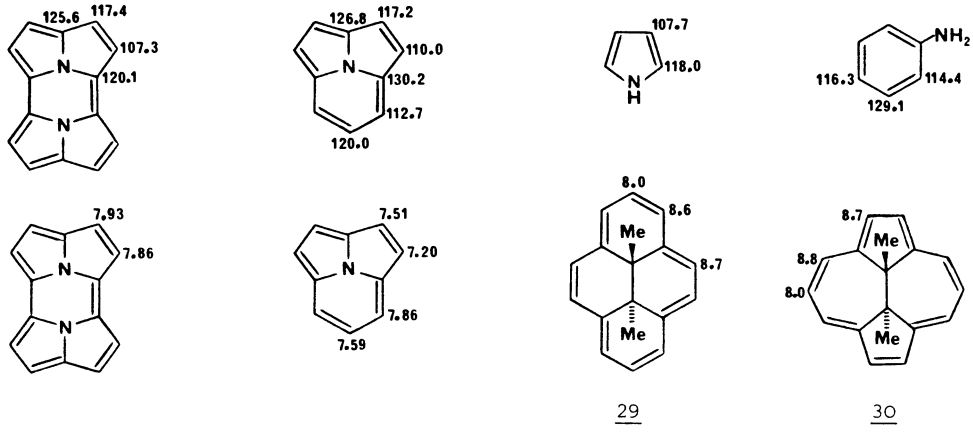


25 26 27 28

Reagents; a, $CF_3SO_2OCH_2Ts$; b, DMAD,Et_3N; c, DMAD,Pd-C, heat

The ^{13}C and ^{1}H n.m.r. data for PDP are shown in Fig 6 together with the data for some related compounds. The low values of the ^{13}C chemical shifts are seen to be typical of an electron-rich aromatic compound, matching particularly closely those in the pyrrolizine moeity of [2.2.3]cyclazine, and providing evidence of strong electron-release from the nitrogen atoms to the non-quaternary carbon atoms. In attempting to assess the diatropicity of PDP, it is necessary to examine the ^{1}H chemical shifts and first to make allowance for the shielding effect of the nitrogen atoms. Since each proton in PDP is vicinal to a nitrogen atom, this shielding effect may be taken as roughly equal to the average shielding of a benzenoid proton by an *ortho*-amino-substituent (*ie* -0.7 p.p.m.). We may thus estimate a 'corrected' ^{1}H chemical shift for PDP of 7.9 + 0.7 = 8.6 p.p.m. which is free from the effect of enhanced π-electron density. Since the effect of ring current on ^{1}H chemical shift increases with increasing ring size, we must then choose a reference compound with the same size of conjugated ring (*ie* a [14]annulene derivative) which is as nearly planar as possible. These requirements are best fulfilled in the dihydropyrene 29 (ref 24) and the dihydroazupyrene 30 (ref 25) which show ^{1}H chemical shift

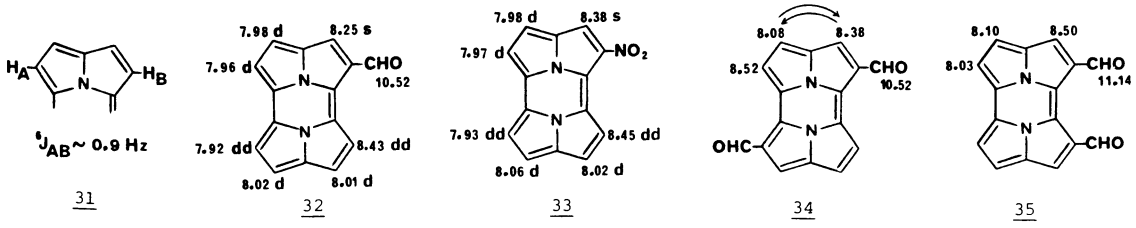
ranges of 8.0-8.7 and 8.0-8.8 p.p.m., respectively. Correspondence of the average shift (8.55 p.p.m.) for 29 and 30 with the 'corrected' value for PDP is close and, although the effects of differing geometries are difficult to assess, we may conclude that the three bridged [14]annulenes 29, 30 and 19 (PDP) sustain peripheral diamagnetic ring currents of similar magnitude.



29 30

Fig. 6. ^{13}C and ^{1}H chemical shifts (δ/p.p.m.) of pyrazino[2,1,6-cd:5,4,3-c'd']dipyrrolizine and selected reference compounds.

We have carried out two studies of electrophilic substitution in PDP: the Vilsmeier reaction with an excess of N,N-dimethylformamide-phosphoryl chloride gave a good yield of two dialdehydes together with a trace of a monoaldehyde, and nitration with copper(II) nitrate in acetic anhydride gave a low yield of a mononitro-derivative, much of the starting material being lost through oxidation. In assigning structures to these products, we have made use of a feature, observed (ref 26) many times in the ^{1}H n.m.r. spectra of pyrrolizine derivatives, namely an unusually large six-bond coupling (*ca* 0.9 Hz) between dissimilar protons H_A and H_B in diametrically opposing positions (formula 31). In the monoformyl and mononitro-derivatives of PDP, the non-vicinally coupled proton (next to CHO or NO_2) did not show this long-range coupling and was therefore in the 2-position,



31 32 33 34 35

Fig. 7. ^{1}H n.m.r. data for substituted pyrazinodipyrrolizines. An arrow A ⌒ B indicates that irradiation of proton A causes a nuclear Overhauser enhancement (2-5%) of the signal due to proton B.

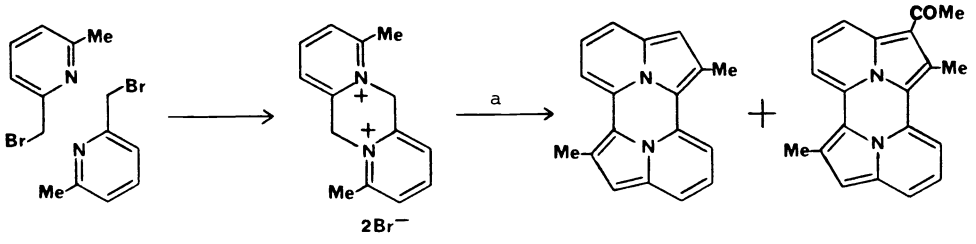
showing that substitution had occurred in the 1-position (formulae 32 and 33). Assignments of the remaining resonances are shown in Fig 7, the deshielding of H-8 by the substituent being a critical key to interpretation. The major dialdehyde was identified as the 1,5-isomer 34, based on the deshielding of H-4 and H-8 and on the small NOE effects, as shown, which serve to eliminate the otherwise possible 1,4-dialdehyde structure. The minor dialdehyde was identified as the 1,8-isomer 35 since the formyl groups deshielded each other but did not deshield any of the non-vicinal nuclear protons.

To summarise the foregoing, all the evidence accumulated to date - the stability, diatropicity, and chemical behaviour of the pyrazinodipyrrolizine 19 - serve to characterise it as a compound of well-developed aromatic character showing many similarities to its [10]annulene relative, [2.2.3]cyclazine.

Pyrazino[2,1,6-*cd*: 5,4,3-*c'd'*]di-indolizine (PDI)

This system was obtained as the 1,6-dimethyl and 2-acetyl-1,6-dimethyl derivatives 37 and 38 by reaction of the self-quaternisation product 36 of 2-bromomethyl-6-methylpyridine with acetic anhydride in the presence of triethylamine (Scheme 8). The reaction was based on the method of Kröck and Krőhnke (ref 27) for the synthesis of indolizines from N-benzyl-2-methylpyridinium salts, and gave a 14% yield of 1,6-dimethyl-PDI, 37 as a brown solid, somewhat unstable in air but considerably less sensitive than [3.3.3]cyclazine. Attempted electrophilic substitutions in this compound gave no products other than black, amorphous material.

Scheme 8

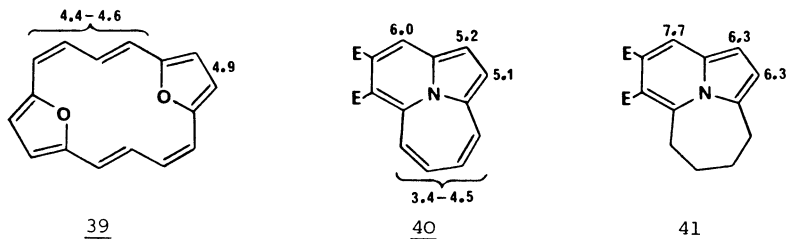


Reagents: a, Ac_2O,Et_3N, heat 36 37 38

Although the molecule of PDI possesses a [16]annulene perimeter, and is therefore potentially antiaromatic, it contains two potentially aromatic substructures in the form of indolizine nuclei. It is of interest, therefore, to compare the n.m.r. spectra of 1,6-dimethyl-PDI with those of related indolizines (Fig 8). We note first that there is no evidence, from the ^{13}C spectra, that the carbon π-electron densities of 37 are increased relative to those of indolizine (ref 28). It is significant, therefore, that the methine protons and also the methyl protons of 37 are appreciably more shielded (by 0.6-1.2 p.p.m. and 0.4 p.p.m., respectively) than their counterparts in 2-methylindolizine (ref 29). This shielding effect may be attributed to the 4n π-electron perimeter of PDI, the paratropicity of which counteracts the diatropicity of the individual indolizine nuclei. There is thus a sharp contrast between PDP (δ_H 7.9) and PDI (average δ_H 5.5). The best available [16]annulene derivative for comparison with PDI appears to be the doubly O-bridged compound 39 (ref 30) which, unlike [16]annulene itself, is conformationally non-mobile and probably almost planar; here the average δ_H (outer protons) is 4.7, showing that PDI fails to exhibit the full shielding effect of its perimeter π-system.

The same effect of superimposing a diatropic substructure upon a paratropic perimeter has been observed (ref 31) in the [2.3.4]cyclazine 40, wherein the 'indolizine' protons are more shielded than their counterparts in the fully diatropic tetrahydro-derivative 41 but less shielded than the 'azepine' protons of 40 which are free from the influence of the diatropic substructure.

37



39 40 41

Fig. 8. ^{13}C and ^{1}H chemical shifts (δ/p.p.m.) of 1,6-dimethyl-pyrazino[2,1,6-cd:5,4,3-c'd']di-indolizine and selected reference compounds.

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