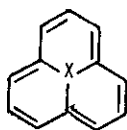


SYNTHESIS OF AZAPHENALENES

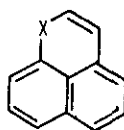
Shieu-Jeing Lee and James M. Cook*

Department of Chemistry, University of Wisconsin-Milwaukee,
Milwaukee, Wisconsin 53201Abstract - The syntheses and properties of the tricyclic azaphenalenenes are reviewed.

Azaphenalenenes are tricyclic molecules which contain a completely conjugated perimeter of sp^2 -hybridized carbon atoms and/or sp^2 -hybridized nitrogen atoms held largely planar by a centrally-lying sp^2 -hybridized atom¹⁻³ ($X = C$ or N). The basic molecular skeletons of the simplest azaphenalenenes are depicted below. Boekelheide⁴ has proposed that this class of



X = N



heterocycles be termed cycl-[3.3.3]-azines, when the nitrogen atom is contained in the center portion of the structure. The designation [3.3.3] refers to the number of atoms on the periphery of the cycle between points of bonding to the internal nitrogen atom. Azaphenalenenes, in general, were initially prepared to determine their biological activity, principally as the corresponding quaternary salts which are more suitable for testing than their carbocyclic parent compounds.⁵

The 9b-azaphenalene (1), cycl-[3.3.3]-azine, has been studied, in a theoretical sense, by several investigators^{2,4} who have predicted that the resonance energy of 1 will be greater than that of the stable and well-studied azatricycle, cycl-[2.2.3]-azine (2). The azine (2) was prepared previously in order to evaluate current theories and methods for calculating resonance energies of aromatic molecules.⁵

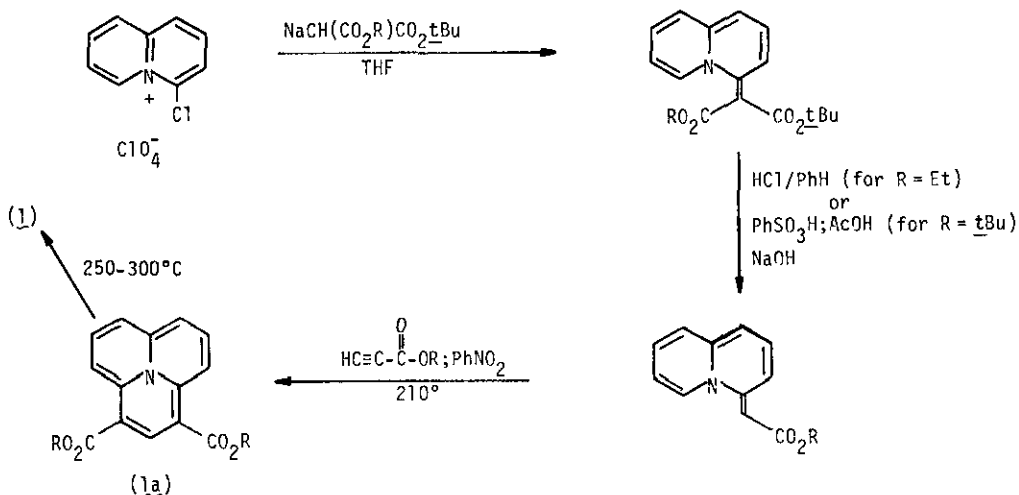
Leaver and coworkers⁶ reported the synthesis of cyc1-[3.3.3]-azine (1) from 4-chloroquinolinium perchlorate via the route illustrated below (Scheme I):



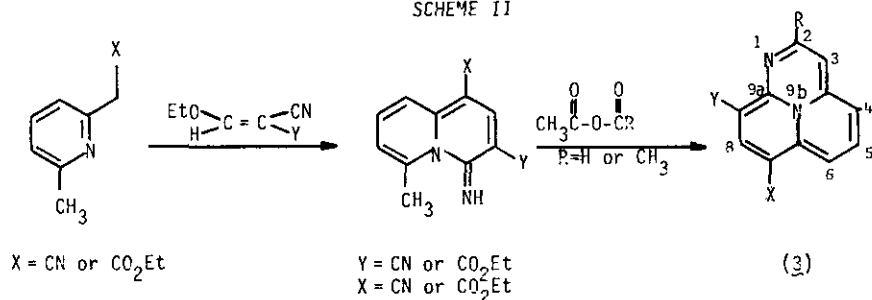
The NMR spectrum of compound (1) contained a triplet centered at $\delta 3.65$ (protons 2,5,8) and a doublet centered at $\delta 2.07$ (protons 1,3,4,6,7,9); these δ -values are among the highest yet reported for protons so joined to a trigonal carbon. This high degree of shielding is regarded as evidence of a paramagnetic ring-current⁷ in the peripheral non-aromatic system of 12 π -electrons. Despite the lack of aromatic character, according to the foregoing criteria, the diester (1a; R=Et) does undergo substitution reactions with certain electrophilic reagents, most notably tetranitromethane, N,N-dimethylformamide/phosphoryl chloride, and acetyl chloride. These reactions were regarded as analogous to those known to occur for a typical enamine and not regarded as electrophilic aromatic substitution.

In 1976, Ceder and coworkers⁸ reported that the reaction between 6-substituted 2-methylpyridines and a variety of reagents led to 1,9b-diazaphenalene (3) and 1,9,9b-triazaphenalene (4) derivatives, as shown in Schemes II and III, respectively.

SCHEME I

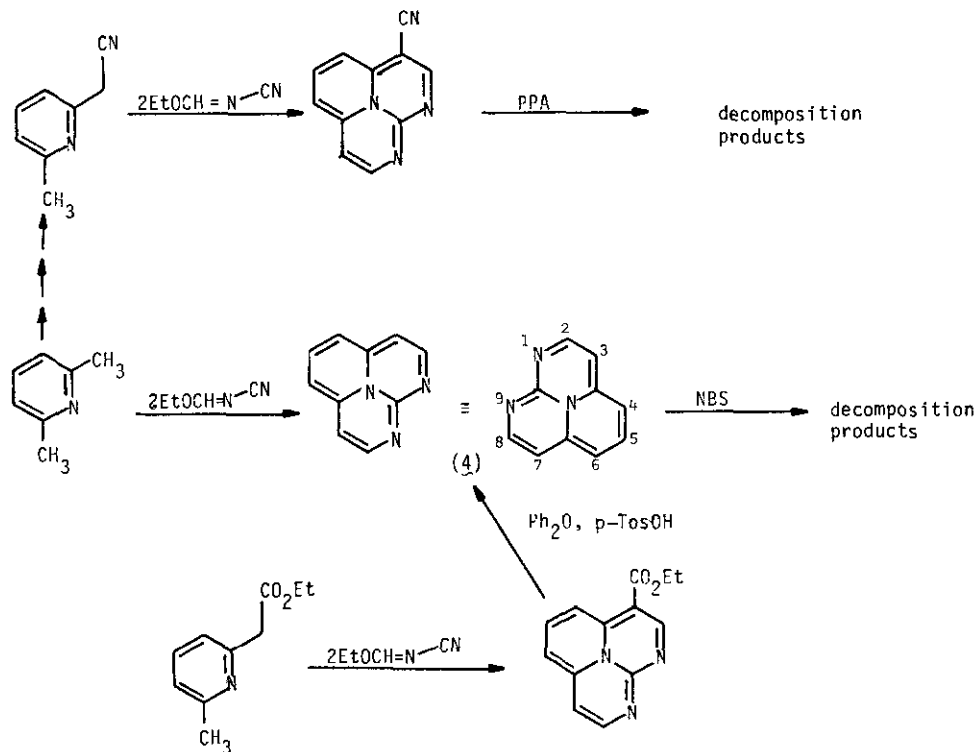


SCHEME II

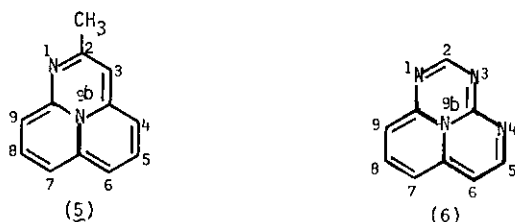


Attempts to remove the cyano group from 3-cyano-1,9-diazacycl-[3.3.3]-azine with polyphosphoric acid to provide the parent **4** were unsuccessful. Decarboxylation of the corresponding 3-carbomethoxy derivative in diphenyl ether which contained traces of *p*-toluenesulfonic acid, on the other hand, gave the parent diazacyclazine **4** as a blue-green crystalline solid, rather insoluble in non-polar solvents and fairly unstable both in air and in solution.

SCHEME III

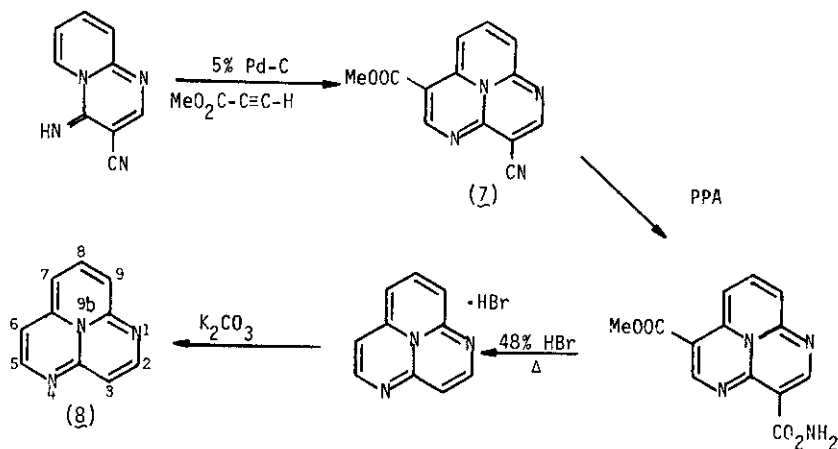


The parent 1,9,9b-triazaphenalene [(4), also called 1,9-diazacyl-[3.3.3]-azine], prepared by Ceder and coworkers, was the first isomer of the seven possibilities in the diazacyl-[3.3.3]-azine group to be synthesized. With respect to aromaticity, the chemical shifts for the protons (δ 4.3-6.2) in the NMR spectrum are between those for the "corresponding" protons in 2-methyl-1-azacyl-[3.3.3]-azine [(5), δ 3.75-5.6]⁹ and 1,3,4-triazacyl-[3.3.3]-azine [(6), δ 5.3-6.9]. This order indicates that the degree of aromaticity increases with the number of peripheral N-atoms in the azaphenalenes; treatment of (4), however, with N-bromosuccinimide (NBS) effected decomposition of the compound and no brominated products were isolated.

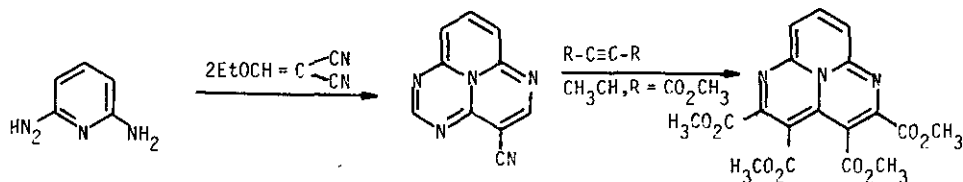


In 1978, Kuya and coworkers^{10a} reported the synthesis of 1,4,9b-triazaphenalene derivative (7) by a route which employed palladium on carbon (Pd/C) as the reagent for one of the key reactions in the pathway, as illustrated in Scheme IV. Furthermore, degradation of (7) generated the parent compound [(8), Scheme IV]. Comparison of the chemical shifts in the NMR spectrum of [(8), δ 4.55-6.34] to those of cycl-[3.3.3]-azines indicated that (8) may well be antiaromatic.

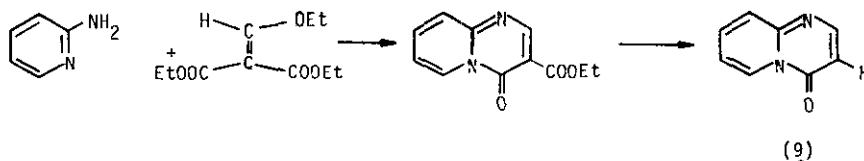
SCHEME IV



In a somewhat similar study Awaya et al. have prepared the cycl-[3.3.3]-azine derivative 4-cyano-1,3,6-triazacycl-[3.3.3]-azine by reaction of 2,6-diaminopyridine with ethoxymethylene malonitrile, moreover, this blue-colored needle-like solid^{10b} was converted into tetramethyl 1,6-diazacycl-[3.3.3]-azine-2,3,4,5-tetracarboxylate^{10c} on heating with dimethyl acetylenedicarboxylate in acetonitrile (see below).



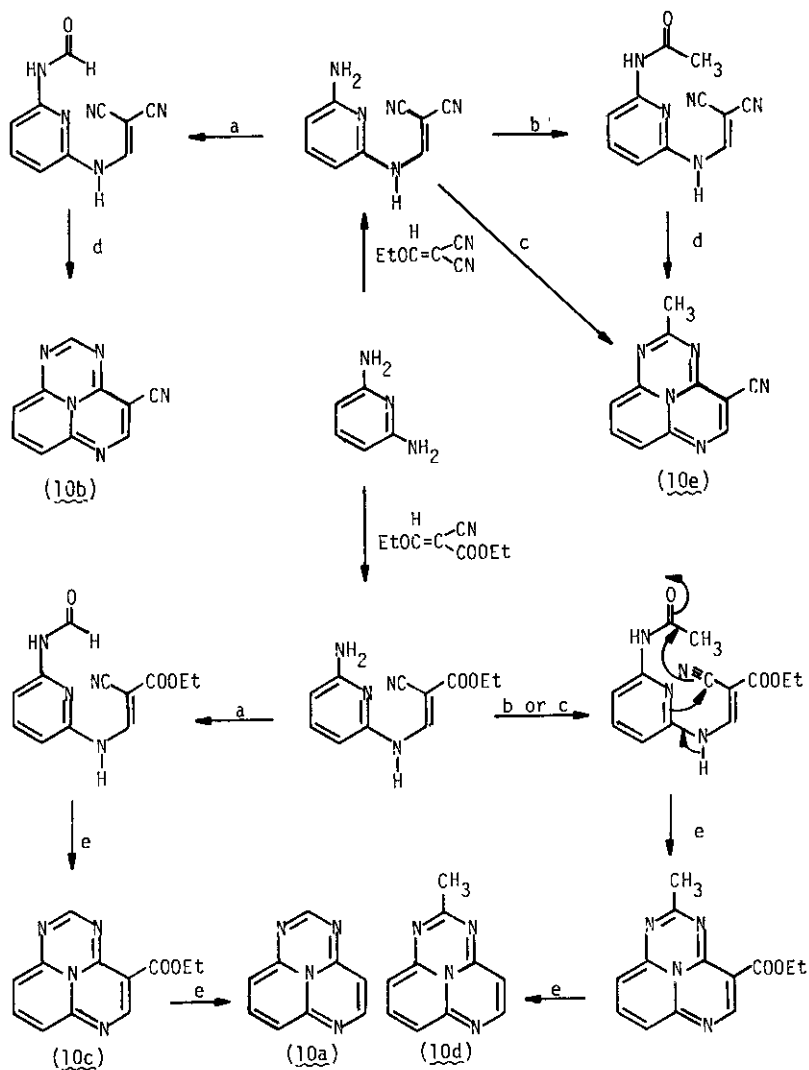
The related 1,3,6,9b-tetraazaphenalene [(10a), 1,3,6-triazacycl-[3.3.3]-azine] and its derivatives have been synthesized, and their properties were thoroughly studied by Ceder and coworkers¹³⁻¹⁷. The route chosen for the preparation of the 1,3,6,9b-tetraazaphenalene system was based on the observation by Lapper,¹¹ Adams and Pachter¹² that 2-aminopyridine reacts with ethoxymethylenemalonic ester to form 4H-pyrido(1,2-a)-pyrimidin-4-one (9) as shown below:



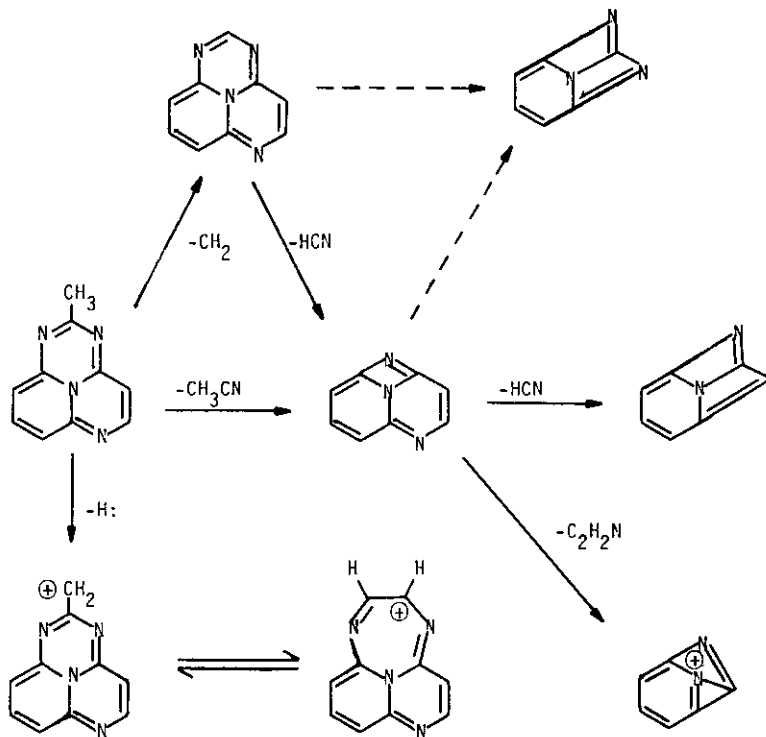
Ceder and coworkers¹³ synthesized the desired tetraaza derivatives (10a-10e) in similar fashion, as shown in Scheme V.

The tetraazaphenalenes (10a-10e) underwent fragmentation in the mass spectrometer via loss of hydrogen cyanide from the parent ion;¹⁴ a pathway common to N-containing heterocyclic systems. If a C-methyl group was placed adjacent to a heterocyclic nitrogen atom, these molecules then lost the units of acetonitrile. The proposed Scheme for these transformations was in complete accord with the reported structures, as illustrated after Scheme V.

SCHEME V



- a = Acetic-formic anhydride in pyridine at room temperature
 b = Acetic anhydride in pyridine at room temperature
 c = Acetic anhydride in glacial acetic acid at reflux
 d = Reflux in toluene over anhydrous magnesium sulfate
 e = Reflux in diphenyl ether or biphenyl-diphenyl ether

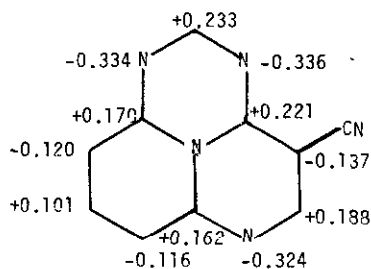
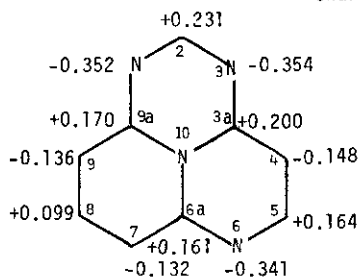


Hückel molecular orbital calculations¹³ have been carried out on the systems (10a) and (10b), the values for the charge densities and free valences predict both electrophilic substitution and radical attack will occur at the same positions; C-4 (preferred), C-7 and C-9 in the parent system (10a) and at C-7 and C-9 in the case of the 4-substituted compound. The bond orders obtained indicated that these systems show little tendency for alternation, which suggests a lack of alternate single and double bonds.¹³ The charge-density values for the central nitrogen atom, N-10, of the compounds studied indicated a delocalization of electrons from the central nitrogen atom. This, together with the bond-order values obtained for the bonds between the peripheral positions and the central nitrogen atom (3a-10, 6a-10, and 9a-10), which indicate rather strong bonding, support the assumption that the 1,3,6-triazacycl-[3.3.3]-azine system is aromatic.

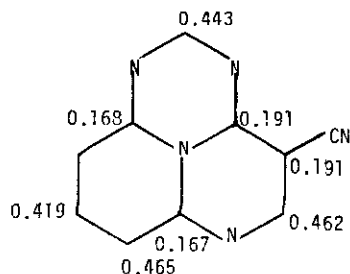
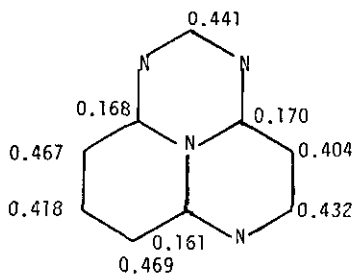
The experimental data are in agreement with the predictions based on calculations for Ceder and coworkers^{15,16} have shown that electrophilic bromination of (10a) with N-bromosuccinimide, under mild conditions, occurs preferentially (80%) in position-4. Treatment of 10c with more of

the electrophile, or 10e under similar conditions, then gave bromination at carbon atoms -7 and -9, as illustrated in Schemes VI and VII, respectively. Likewise, bromination ¹⁷ of (10e) under photochemical conditions, known to favor the bromine atom, gave a similar result.

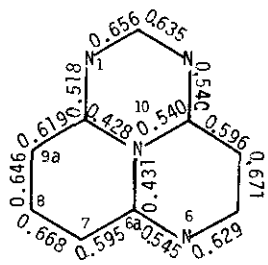
Charge densities



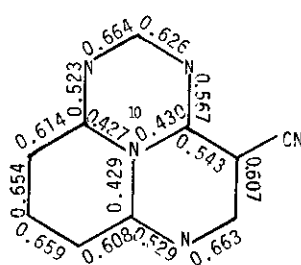
Free valences



Bond Orders



10a

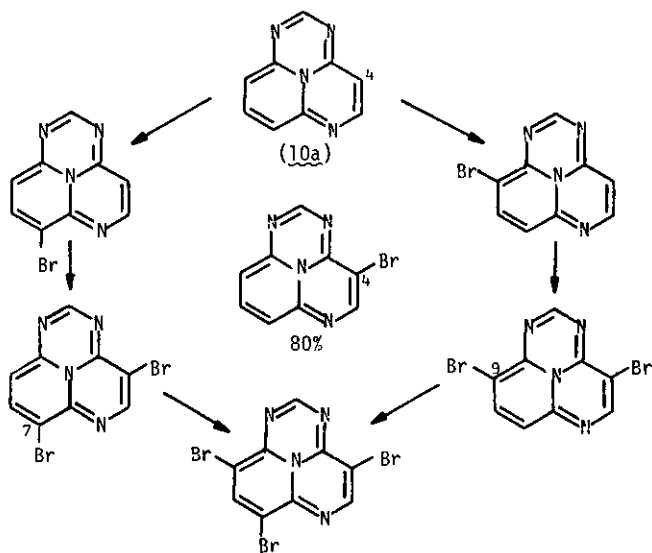


10b

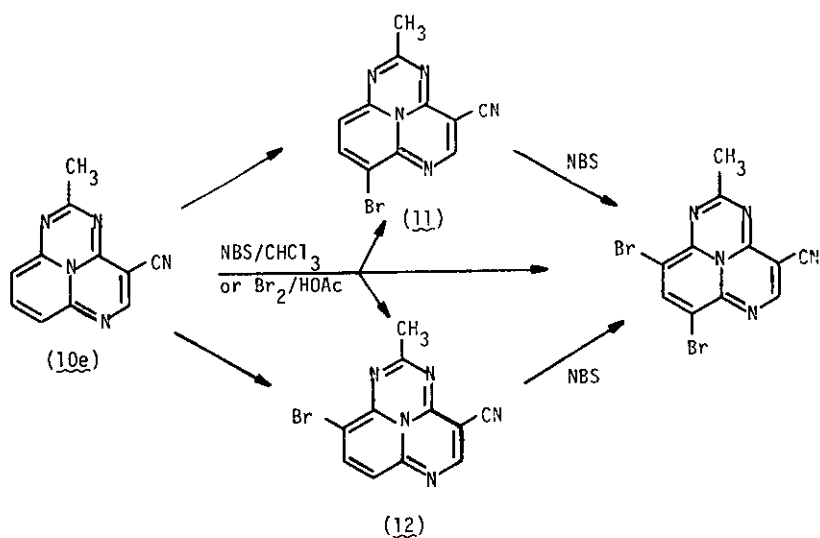
Determination of the position of bromination in the two monobromo isomers (11) and (12) was accomplished using NMR spectroscopy for protons adjacent to an amino group in an aminopyridine undergo a downfield shift ^{17b} upon acylation of the amino group due to the diamagnetic anisotropy of the carbonyl group.

As illustrated in Scheme VIII, acylation of the 5-bromo derivative (13) would provide a system in which such a shift for H-3 would occur; whereas in (14) the free amino group lacks an adjacent proton, therefore, no such shift would be expected.

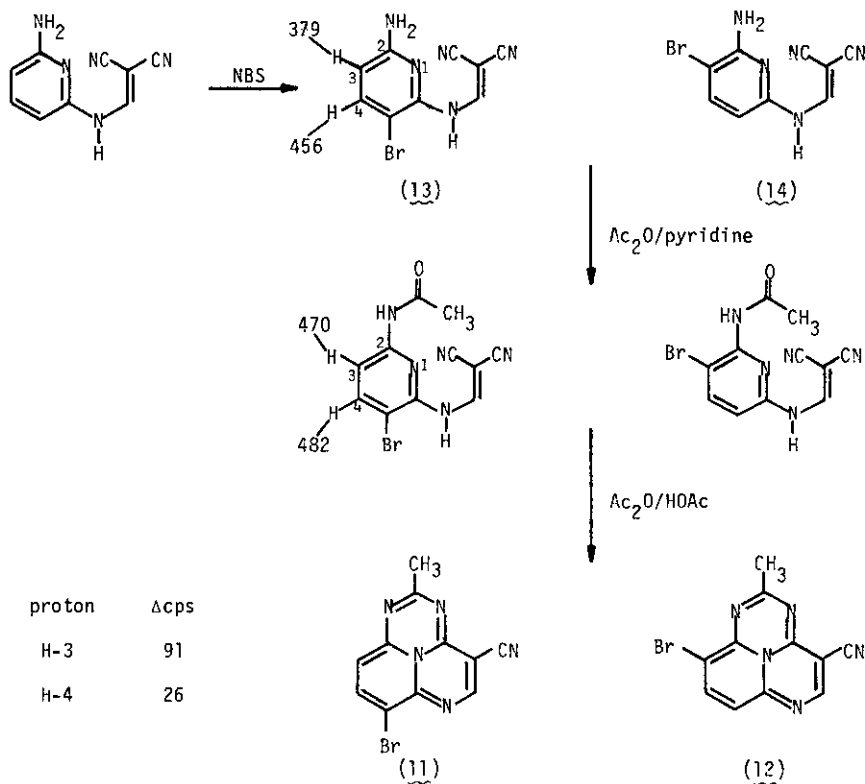
SCHEME VI



SCHEME VII



SCHEME VIII



The 1,3,6-triazacycl-[3.3.3]-azine 10a is stable both in the solid state and in solution, and the compound is easily soluble in chloroform, acetic and trifluoroacetic acids. The NMR spectra of 10a (in CDCl_3 and CF_3COOH) contained an ABX-multiplet (H-7, H-8, and H-9), an AX quartet (H-4 and H-5), and a one proton singlet (H-2). The coupling constants and chemical-shift values show good correlation with the calculated charge-density values on the adjacent carbon atoms and are listed in Table 1.

In 1977, Ceder and coworkers¹⁹ completed the synthesis of another tetraazaphenalene derivative, 1,3,4,9b-tetraazaphenalene (15) by condensation of 2-amino-6-methylpyridine with two moles of N-cyanoformamide (Scheme IX).

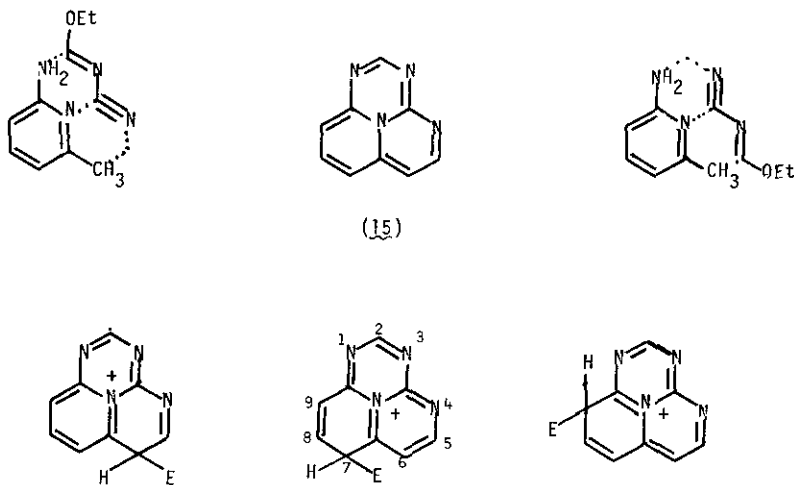
Table I. Charge density values, ^{13}C NMR chemical shifts, and coupling constants (in Hz) for 10a.

	H-4	H-9	H-7	H-8	H-5	H-2
Charge-density values	-0.148	-0.136	-0.132	+0.099	+0.164	+0.231
δCDCl_3	4.86	5.29 ^a	5.75 ^a	6.68	6.99	6.50
$\delta\text{CF}_3\text{COOH}$	6.16	6.75	7.13	7.88	8.04	7.40
Multiplicity	doublet	multiplet	multiplet	triplet	doublet	singlet
Coupling constants (CDCl_3)		$J_{4-5}=5.2$	$J_{7-8}=7.6$	$J_{8-9}=8.5$	$J_{7-9}=1.3$	

^a The assignment of chemical-shift values to H-7 and H-9 are based on results of lanthanide shift-reagent studies on 2-methyl-1,3,6-triazacycl-[3.3.3]-azine.¹⁹

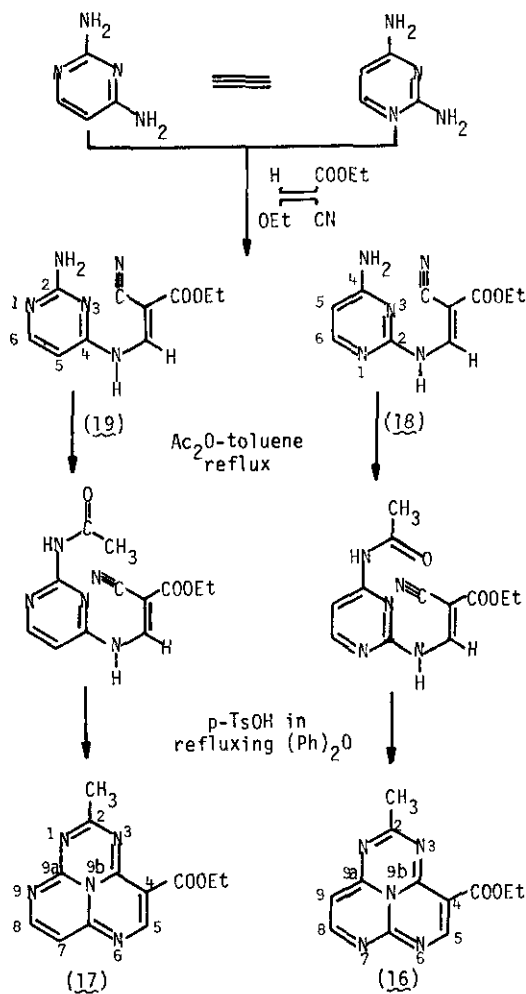
The proton chemical shift values in the NMR spectrum of (15) are in the same region (6.5.3-6.9) as those of the isomeric 1,3,6-triazacycl-[3.3.3]-azine (6.4.9-6.5),¹⁵ which indicate that (15) possesses a similar degree of aromatic character. Electrophilic substitution in (15) occurred at positions -6, -7 and -9, as expected, on the basis of the resonance structures outlined below:

SCHEME IX



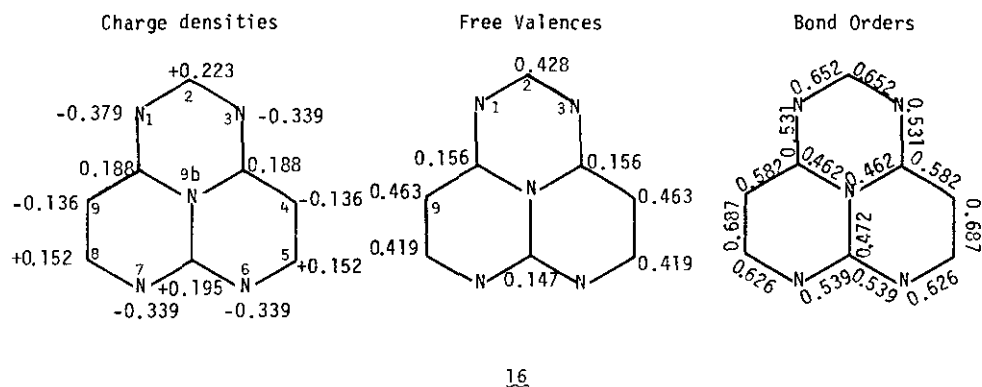
When (15) was treated with N-bromosuccinimide (NBS), a mixture of three monobromo isomers and two dibromo derivatives were isolated; however, no tribromo derivatives were found. This was rationalized by Ceder²⁰ in terms of steric arguments, the peri relationship of bromine atoms in the 6- and 7-positions in (15) would be expected to cause bond and angle deformation of the ring system, and therefore, may prohibit orbital overlap of the pi bonds.

In 1972, attempts were made to prepare an azaphenalene which contained five nitrogen atoms aligned in a symmetrical arrangement. This would provide a suitable substrate for electron spin resonance studies^{21,22} if the molecule contained no substituents. Ceder and Witte,²³ however, have succeeded only in preparing (16), which can be considered a 1,3,6,7,9b-pentaazaphenalene derivative. The general approach utilized for the synthesis of (10a) was employed for preparation of (16). The condensation could and did occur either at the 2- or 4- amino group, consequently the isomeric system 1,3,4,7,9b-pentaazaphenalene (17) was also formed (Scheme X).



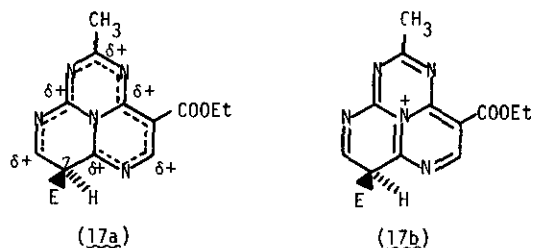
It was not possible to distinguish directly between the two condensation products (18) and (19) using nuclear magnetic resonance spectroscopy or any other conventional spectroscopic technique. It was apparent, however, that in the spectrum of the monocondensation products (18) or (19), the chemical shift of H-5, was located at higher field than H-6 since H-6 was adjacent to N-1 in the pyrimidine ring. This was drastically altered on acylation of the remaining free amino group, while the corresponding change in chemical shift of H-6 was only about one-half as large. This type of simple correlation was again employed to confirm the structures of (16) and (17) since acylation of 18 led to a large downfield shift ($\Delta 99$ cps) for H-5, while a similar shift (< 26 cps) was not observed on acylation of 19. Conversion of 18 and 19 into 16 and 17, respectively, therefore, unambiguously confirmed the structures of these two pentazaphenalenes.

Examination of the mass spectrum of (16) indicated that the molecule underwent fragmentation in a manner entirely analogous to that of the corresponding 1,3,6,9b-tetraazaphenalene derivative previously discussed. Simple Hückel molecular orbital calculations were also carried out on (16); charge densities, free valences and bond orders are as shown below.

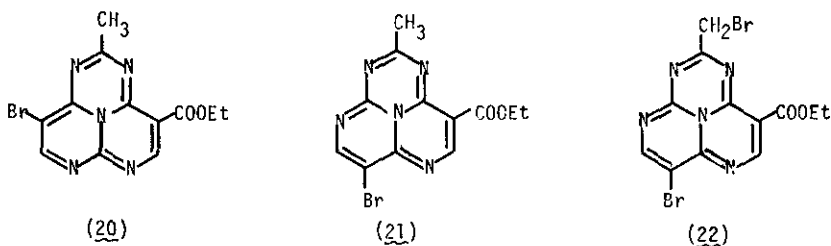


The highest electron density on carbon was found at position -9 of (16) as was the case with (10a) and its derivatives.¹³ In order to verify these theoretical predictions, Ceder and Rosen²⁴ treated (16) with NBS which resulted in a 60% yield of the desired 9-bromo derivative (20). The conditions, however, necessary to monobrominate (16) were somewhat more vigorous than those needed to produce the 7- or 9-bromo derivatives of (10a). Efforts to brominate (16) by treatment with bromine in glacial acetic acid were unsuccessful since (16) was unstable in the medium. Attempts to decarboxylate (16), analogous to the method employed to prepare (10a) in order to obtain the symmetrical system, failed because (16) was also unstable under these conditions. The observations reported above indicate that the 1,3,6,7,9b-pentazaphenalene system (16) was less susceptible to electrophilic substitution and, in some respects, chemically more unstable than the corresponding 1,3,6,9b-(10a-10d) systems.

From an argument employing resonance structures, one can predict that an electrophile (E⁺) should attack at position -7 in (17). For the intermediate resulting from substitution at this position one can draw six resonance forms with the positive charge on carbon as represented by (17a), as well as three structures with the charge on the central nitrogen atom. The latter set, represented by (17b), are the only ones in which all carbon and nitrogen atoms possess full octets.



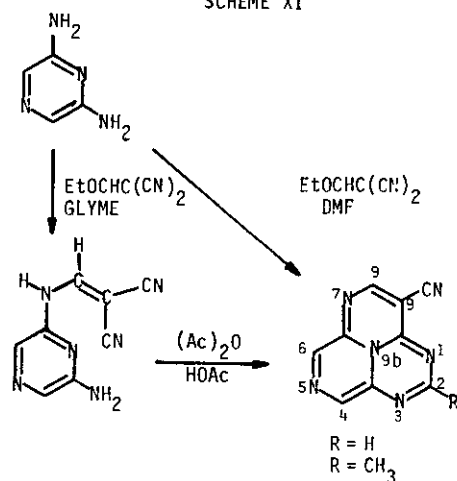
In order to study this hypothesis, experimentally, (17) was treated with NBS and this provided high yields of the 7-bromo derivative (21) as predicted.



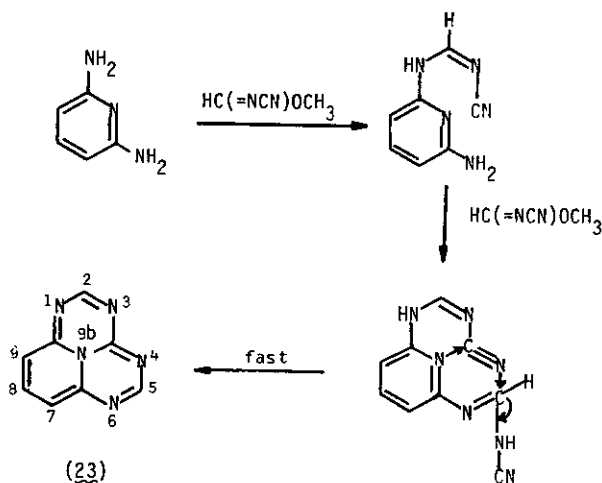
Interestingly the monobromo compound (21) was found to be much more stable than the corresponding 9-bromo derivative [(20), from (16)]. The greater stability of system (17) was also demonstrated on treatment with bromine in glacial acetic acid after which the dibromo compound (22) was isolated; however, in this medium (16) was completely destroyed.

Another approach to the synthesis of pentaazaphenalenenes was carried out by Shaw and coworkers,^{25,26} and is illustrated in Schemes XI and XII, respectively.

SCHEME XI

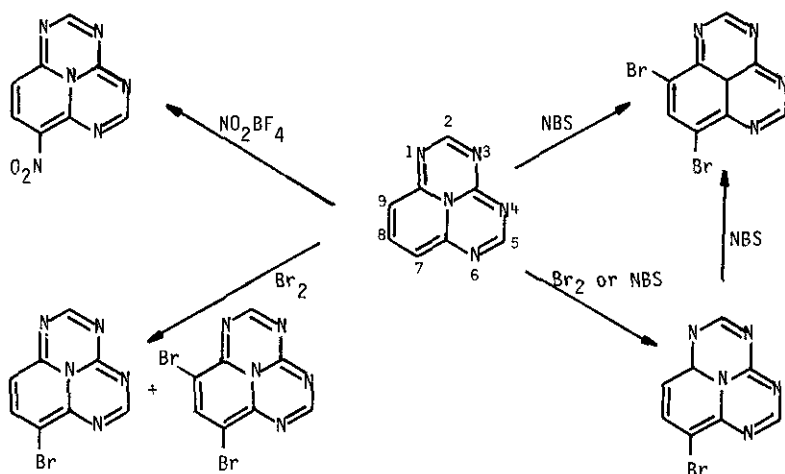


SCHEME XII

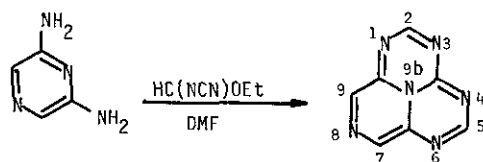


The construction of the parent compound was realized; as illustrated in Scheme XII, and the new heterocycle, 1,3,4,6,9b-pentaazaphenalene (23), does undergo some reactions with electrophiles typical of aromatic molecules (see Scheme XIII).²⁷ A similar approach to the synthesis of 1,3,4,6,8,9b-hexaazaphenalene (24) and 1,3,4,6,7,9b-hexaazaphenalene (25) systems was also reported by Shaw and coworkers,^{25,26,27} as shown in Schemes XIV and XV. However, no further work has been reported as regards the properties of (24) and (25).

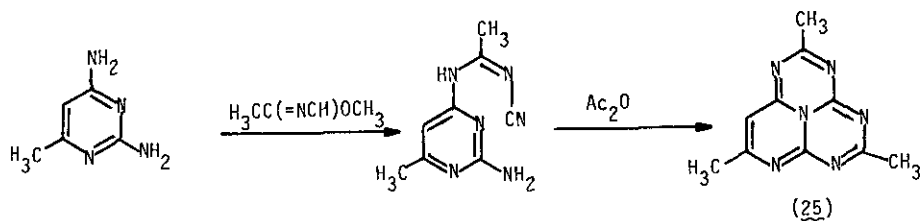
SCHEME XIII



SCHEME XIV

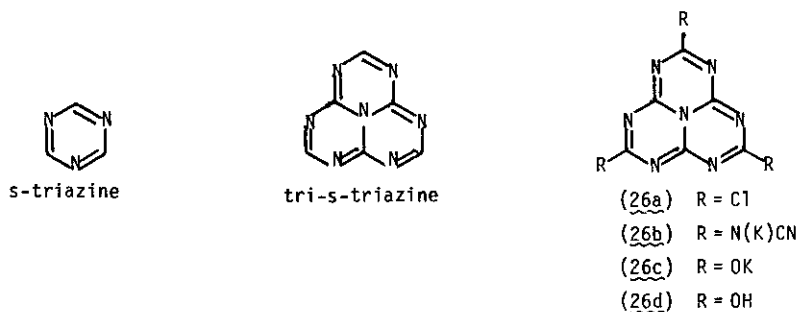


SCHEME XV

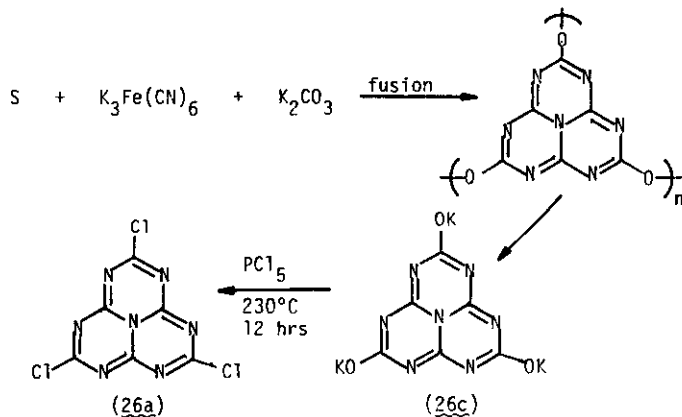


Certain heat-stable, insoluble and chemically inactive compounds, such as melon, melem and melonic acid, all of which contain the nucleus $\text{C}_6\text{N}_7\text{H}_7$, have been known since 1835. Tri-potassium melonate (26b) was first described as an undesirable by-product obtained when sulfur,²⁸ potassium ferricyanide and potassium carbonate were heated to a high temperature during

the preparation of potassium thiocyanate. This area of chemical investigation, however, lay dormant for almost a century until Pauling and Sturdivant²⁹ established the structure of this nucleus by physical methods. It was found to be a coplanar arrangement of three fused-s-triazine rings represented by structure (26).



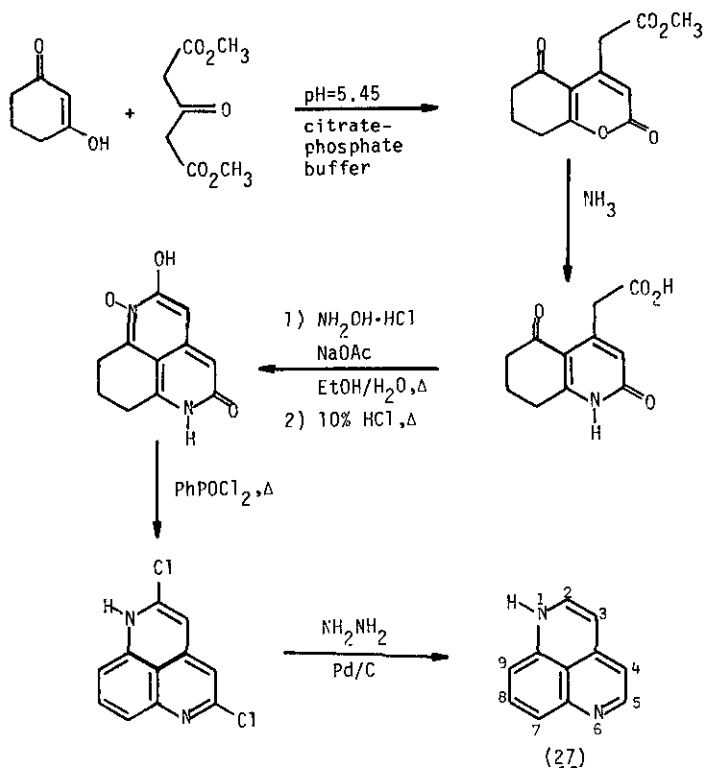
Chemical support for Pauling's hypothesis was realized with the synthesis of cyameluric chloride (26a) from the polymeric melon by way of potassium melonate (26b), potassium cyamelurate (26c) and cyameluric acid (26d) reported by Redemann and Lucas.³⁰



The infrared spectra of the heptaazaphenalene derivatives (26a)-(26d) contained a strong absorption near 6.5μ which has been assigned to a C=N stretching mode. All the compounds of which infrared spectra were recorded did contain sharp and very strong maxima³² in this region, and it is assumed that this characteristic frequency represents the in-plane vibration of the tri-s-triazine system.³¹

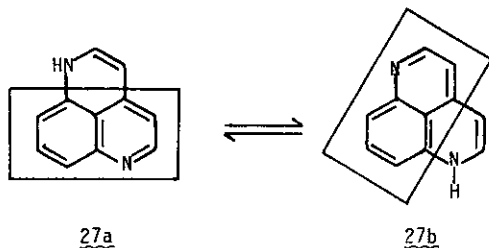
All of the above azaphenalenenes, however, contain an internal nitrogen and have generally been synthesized from pyridine or pyrimidine derivatives. Recently, a new heterocycle, 1,6-diazaphenalene (27),³³ has been synthesized from cyclohexane-1,3-dione in relatively straightforward fashion (Scheme XVI). This compound contains no internal nitrogen atom, and is of special significance because of the similarity in its chemical and physical properties to those (properties) of imidazole.³⁴ The proton transfer from (27a) to (27b) has been shown to be more rapid than the NMR time scale,³⁵ which results in a much simplified NMR spectrum analogous to the behavior observed for imidazole.³⁶ The pKa of (27) as measured by a potentiometric

SCHEME XVI



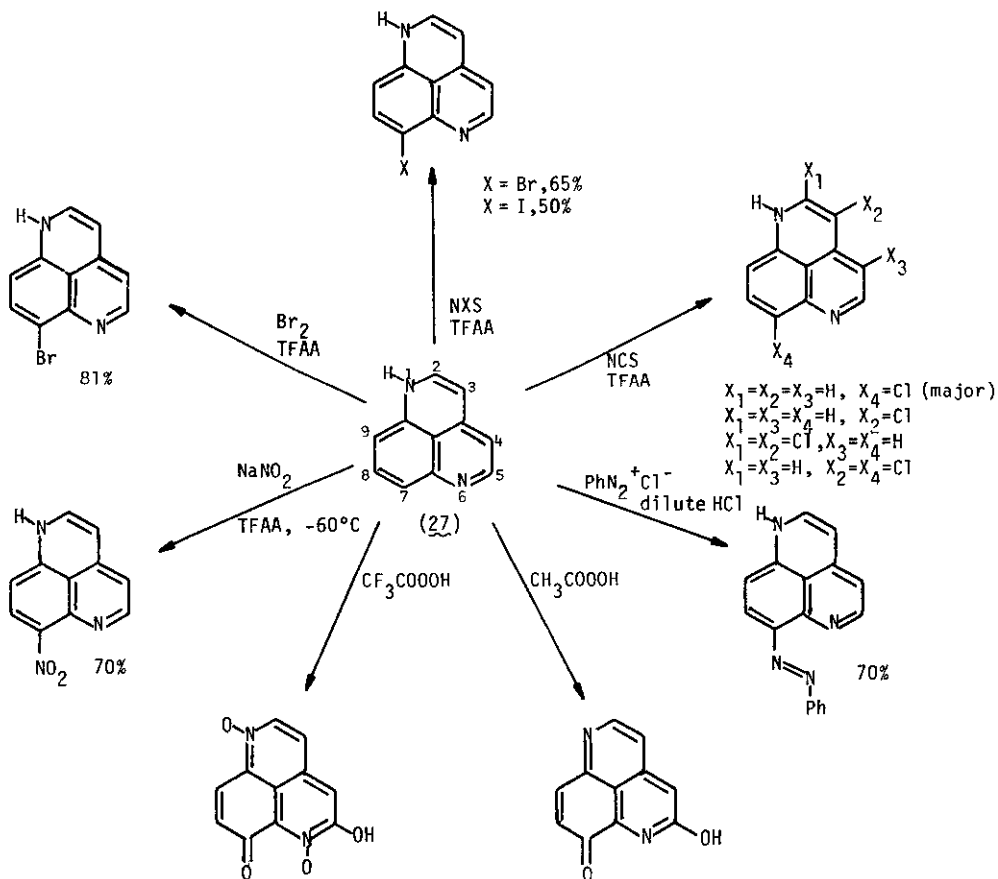
titration³⁵ was found to be 6.56, while the value for imidazole was 6.95 in the same solvent, moreover, some substituted 1,6-diazaphenalenenes have been shown to form acyldiazaphenalenenes which are very unstable,³⁷ analogous to the stability, or lack thereof, of acylimidazoles.³⁸

Examination of the two tautomers of (27) indicated that 1,6-diazaphenalene itself is not aromatic in terms of the Hückel rule^{32b}; however, the two quinoline portions (square) of the heterocycle are aromatic and equal in energy. The proton NMR data [(27), δ 5.97-7.42]³⁵



does suggest that 27 possesses aromatic character and that tautomers (27a) and (27b) are degenerate in energy and therefore identical. Although the similarities in the properties of (27)

SCHEME XVII



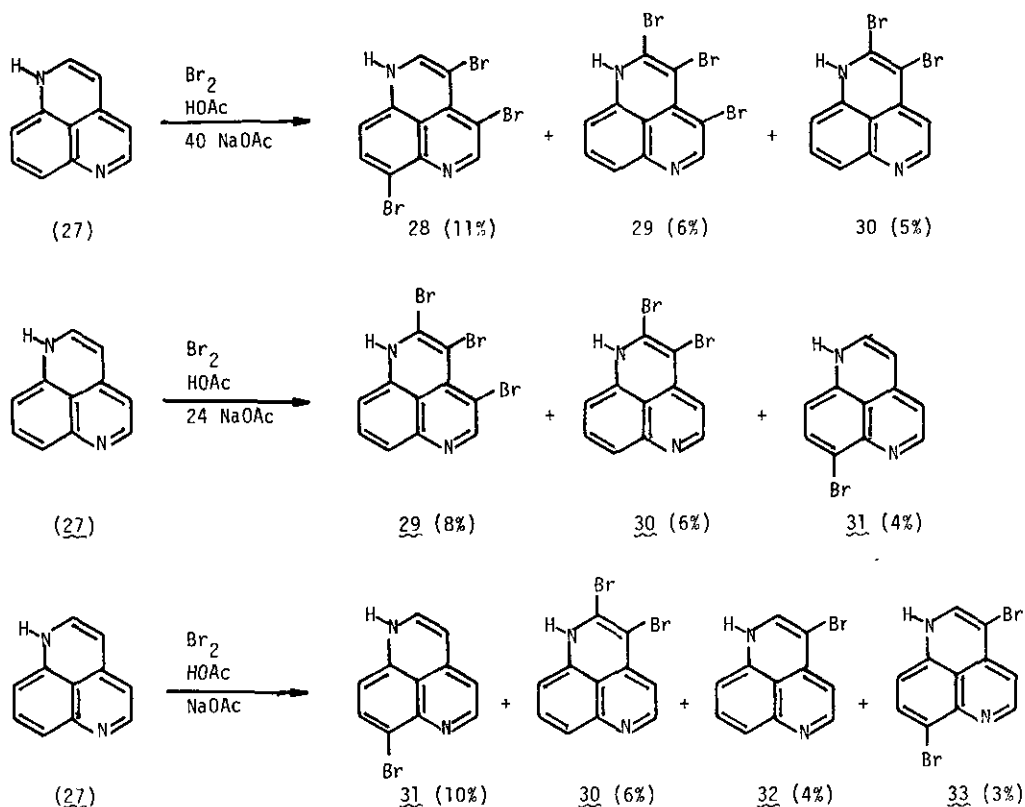
and imidazole are, perhaps, fortuitous, they have prompted a study of the chemical behavior of this molecule toward electrophilic reagents.³⁹

A number of reactions have been carried out on (27) and a brief survey of these are illustrated in Scheme XVII. For the present discussion attention is directed toward the reaction of (27) with bromine in neutral and acidic media which provides a qualitative means by which to study the difference in the reactivity of (27) vs. the protonated form (27H)⁺. The reactions



were carried out in acetic acid -- sodium acetate solution with one equivalent of bromine.³⁹ Because significant amounts of di- and tri-substituted diazaphenalenenes were formed in this process, yields were low due to recovery of unreacted (27); however, the relative amounts of the isomer present are quite representative. When a large excess of sodium acetate was employed (40/1) the major product was the 3,4,7-tribromo derivative (28) followed by the 2,3,4-tribromo diazaphenylene (29) and the 2,3 dibromo compound (28)^{39b}. Upon reducing the amount of sodium acetate (1:1), the 7-bromo isomer (31) became the major product, accompanied by small amounts of other isomers (see Scheme XVIII). Furthermore when the bromination was carried out in trifluoroacetic acid (only 27H⁺ present)^{39b} an 81% yield of the 7-bromo derivative (31) was realized. Apparently the neutral species reacts with electrophiles preferentially at the 3- and 7- positions while the protonated form reacts selectively at position -7. This pattern of reactivity is in good agreement with theoretical calculations carried out in the neutral, anionic and protonated forms of (27)⁴⁰. The total charge densities obtained for these compounds are given in Table 1. The HOMO and LUMO electron densities are given in Table 2, and the calculated bond orders are listed in Figure 1. The total charge densities in the neutral molecule (27) predict a reactivity to electrophilic substitution in the order of positions 3 > 4 > 9 > 7.⁴⁰ For the protonated form (27H)⁺ the Wheland model of the transition state⁴¹ was utilized to calculate π localization energies (π bonding between the atom undergoing substitution and the rest of the molecule is cut off). The resulting localization energies indicate that the lowest energy sigma complex is reached for substitution at the 2- position, followed by

SCHEME XVIII



substitution at positions-7(9),-8 and-3(5) in that order.⁴⁰ Since electrophilic attack at the 2- position of $(27\text{H})^+$ is electrostatically unlikely, the finding that substitution at position -7(9) is favored over the other possibilities is in complete agreement with the experimental observations. The localization energies relative to substitution at position -7 are given below.⁴⁰

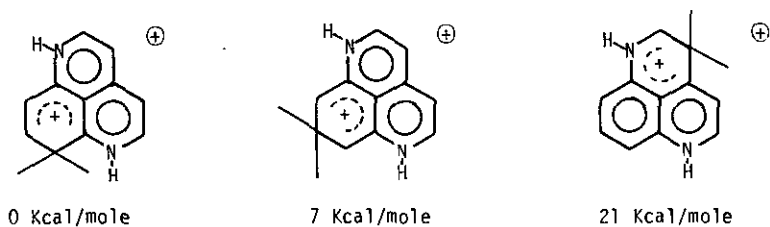


Table 1. Total electron densities for 1,6-diazaphenalene (27), conjugate acid (27H)⁺, anion (27)⁻, 3-chloro-1,6-diazaphenalene 34, and 2,3-dichloro-1,6-diazaphenalene 35.

Atom	<u>27</u>	<u>27H</u> ⁺	<u>27</u> ⁻	<u>34</u>	<u>35</u>
N1	5.1252	5.0544	5.3671	5.1218	5.1382
C2	3.8233	3.7933	3.8235	3.8593	3.7987
C3	4.1101	4.0883	4.1562	4.0286	4.0589
C4	4.0784	4.0883	4.1562	4.0719	4.0755
C5	3.8245	3.7933	3.8235	3.8259	3.8241
N6	5.2547	5.0544	5.3671	5.2605	5.2633
C7	4.0671	4.0671	4.1498	4.0670	4.0659
C8	3.9340	3.8929	3.9285	3.9336	3.9340
C9	4.0766	4.0671	4.1498	4.0754	4.0744

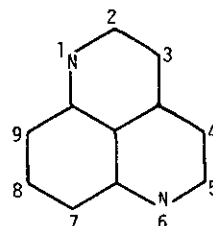


Table 2. Calculated densities and virtual densities of frontier electrons for electrophilic (HOMO) and nucleophilic (LUMO) reactions on 1,6-diazaphenalene (27), conjugate acid (27H)⁺, anion (27)⁻, 3-chloro-1,6-diazaphenalene (34), and 2,3-dichloro-1,6-diazaphenalene (35).

Atom	<u>27</u>		<u>27H</u> ⁺		<u>27</u> ⁻		<u>34</u>		<u>35</u>	
	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO
N1	.384	.170	.348	.239	.361	.334	.399	.169	.342	.163
C2	.078	.212	.024	.382	.001	.244	.120	.215	.117	.208
C3	.266	.001	.273	.002	.314	.021	.273	.002	.313	.000
C4	.242	.088	.273	.002	.314	.021	.215	.094	.221	.090
C5	.017	.213	.024	.382	.001	.244	.012	.211	.001	.211
N6	.326	.328	.348	.239	.361	.334	.277	.335	.282	.326
C7	.277	.163	.300	.003	.323	.028	.241	.156	.219	.165
C8	.023	.116	.000	.088	.000	.157	.016	.111	.014	.133
C9	.238	.041	.300	.003	.323	.028	.217	.041	.200	.044

The ability to predict that (27H)⁺ will react with electrophiles preferentially at the 7- position was employed to design and execute a number of experiments (see Scheme XVII). In all cases in which electrophilic substitution has been performed in acidic media, reaction occurred predominantly at the 7- position. These results correlate well with theoretical predictions and advantage can be taken of this phenomenon to prepare other substituted 1,6-diazaphenalenes.

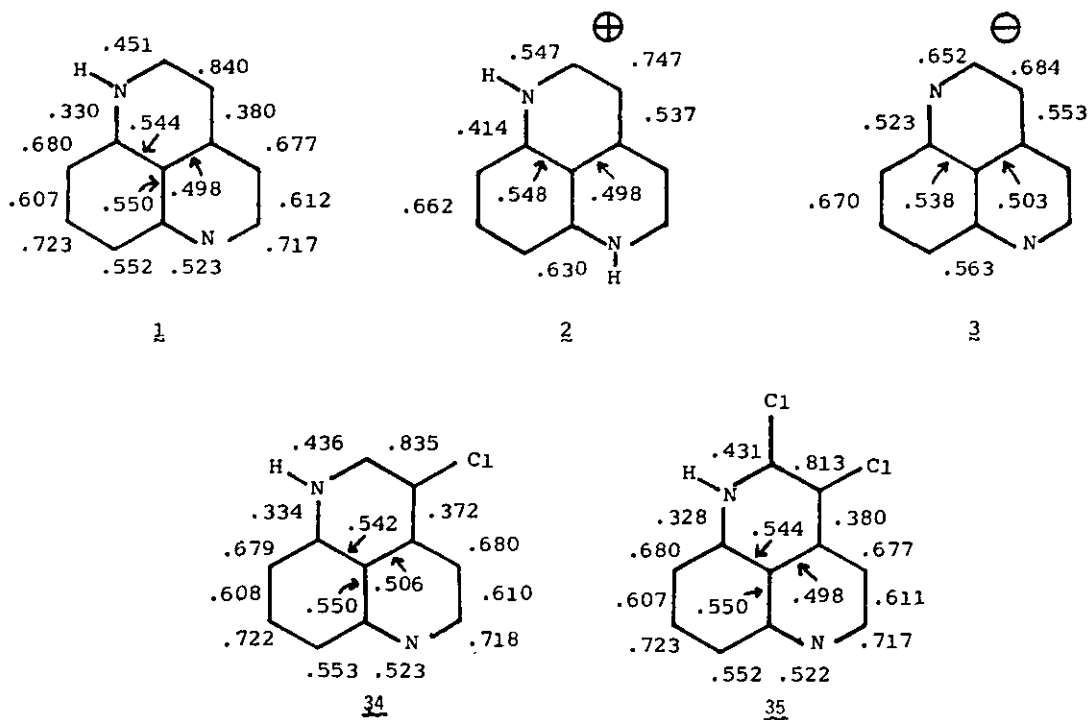


Fig. 1. Calculated bond orders (π) for 1,6-diazaphenalene (27), the cation (27H⁺), and anion (27⁻), 3-chloro-1,6-diazaphenalene 34, and 2,3-dichloro-1,6-diazaphenalene 35.

Finally, the proton chemical shifts for a number of azaphenalenes have been recently compared to aromatic cyclazines in order to examine the question of aromaticity.^{4,5,42} In this vein, certainly, 1,6-diazaphenalene (27) possesses some aromatic character, as proposed earlier, and compounds such as 1 lie at the other extreme (paramagnetic ring-current).⁷ Other azaphenalenes demonstrate aromatic or antiaromatic character to varying degrees and it is suggested that comparison of the proton NMR spectra of new azaphenalenes to the data reported by Kurata et al.⁴² may provide a simple measure of the qualitative degree of aromaticity inherent in such molecules.

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