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The Synthesis of 1,3,6-Triazacycl[3.3.3]azines *

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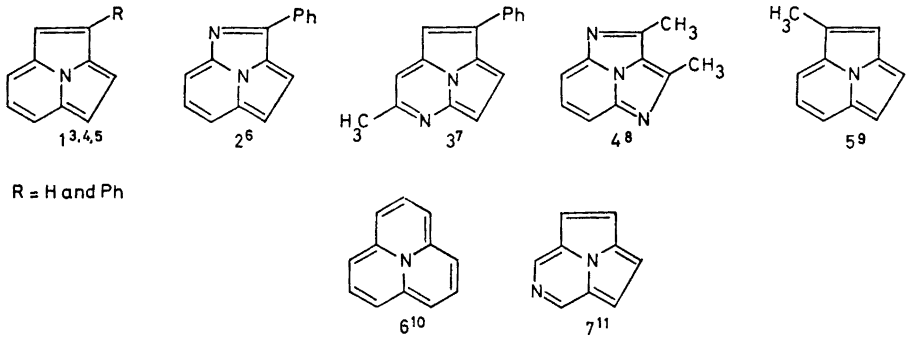
The syntheses of seven members of the 1,3,6-triazacycl[3.3.3]azine system, *8a–g*, structural proofs, spectral properties, and the results of simple HMO calculations are described.

For some time compounds belonging to the cyclazine family have attracted considerable attention [1,2] and to date the members *1–7* have been synthesized.



Cyclazines contain a completely conjugated perimeter of sp^2-hybridized carbon atoms held largely planar by a centrally-lying sp^2-hybridized nitrogen atom.[3,12,13] These molecules were "desired in order to obtain experimental evidence regarding current theories and methods of calculating resonance energies of aromatic molecules".[1] Various properties of cycl[3.2.2]azine, *1* (R=H), such as π-electron structure from Hückel MO calculations,[3,12] electron spectrum and basicity,[13,14] NMR spectra of the parent compound,

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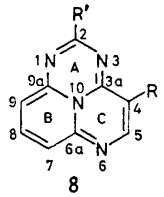
the dideuterated derivative and their conjugate acids,[15] ESR spectrum of the anion,[16,17] and electrophilic substitution reactions [3,18] have been studied. An X-ray structural determination of cycl[3.2.2]azine has been reported which indicates that the molecule is almost completely planar.[19]

Substitution of a nitrogen atom on the periphery in a nonangular position for a carbon atom leads to an azacyclazine, and 2-phenyl-1-azacycl[3.2.2]azine, *2*, was the first compound of this type to be synthesized.[6] The azacyclazines were prepared to obtain compounds which could be converted to quaternary salts, more suitable for pharmacological testing than the insoluble carbocyclic parent compounds.[6] We hoped that the introduction of nitrogen atoms in peripheral positions would generate a ring system more easily prepared than that of the carbocyclic cycl[3.3.3]azine.

This communication reports the preparation of the following seven 1,3,6-triazacycl[3.3.3]azines,* *8a–g*, including the parent compound, structural proofs, a discussion of spectral properties, and the results of simple molecular orbital calculations. From these findings it is evident that the compounds, which represent a new type of azacyclazines, possess aromatic properties. In a separate paper [21] their mass spectra are discussed.



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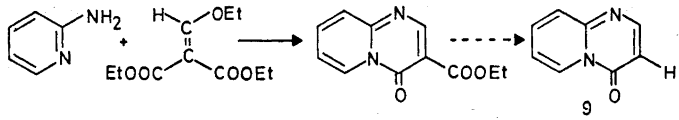
	R	R′
8a	H	H
8b	CN	H
8c	CN	CH_3
8d	COOEt	H
8e	COOEt	CH_3
8f	H	CH_3
8g	COOMe	H

The route utilized for the synthesis of the 1,3,6-triazacycl[3.3.3]azine system is based on the observation by Lappin [22] and by Adams and Pachter [23] that 2-aminopyridine reacts with ethoxymethylene malonic ester to form 4H-pyrido-[1,2a]pyrimidine-4-one, *9*.



9

When 2,6-diaminopyridine, *10*, was condensed with ethoxymethylene-malononitrile, *11*, or ethyl ethoxymethylenecyanoacetate, *12*, (*cf.* Chart 1) compounds *13* and *14*, respectively, resulted. These, on acylation, gave *15*, *16*, *17*, or *18*, which after cyclodehydration yielded the desired cyclazine. The starting materials are commercially available and, moreover, both *11*

* Gibson and Leaver have referred to the cycl[3.3.3]azines as 9b-azaphenalenes.[20] In the present case, the 1,3,6-triazacycl[3.3.3]azines should thus be called 1,3,6,9b-tetraazaphenalenes. We have chosen to retain the established cyclazine nomenclature (Ref. 5 in Ref. 3) since this enables comparisons with other cyclazine systems (*e.g.* cycl[3.2.2]azine, which is not a phenalene) to be made directly.

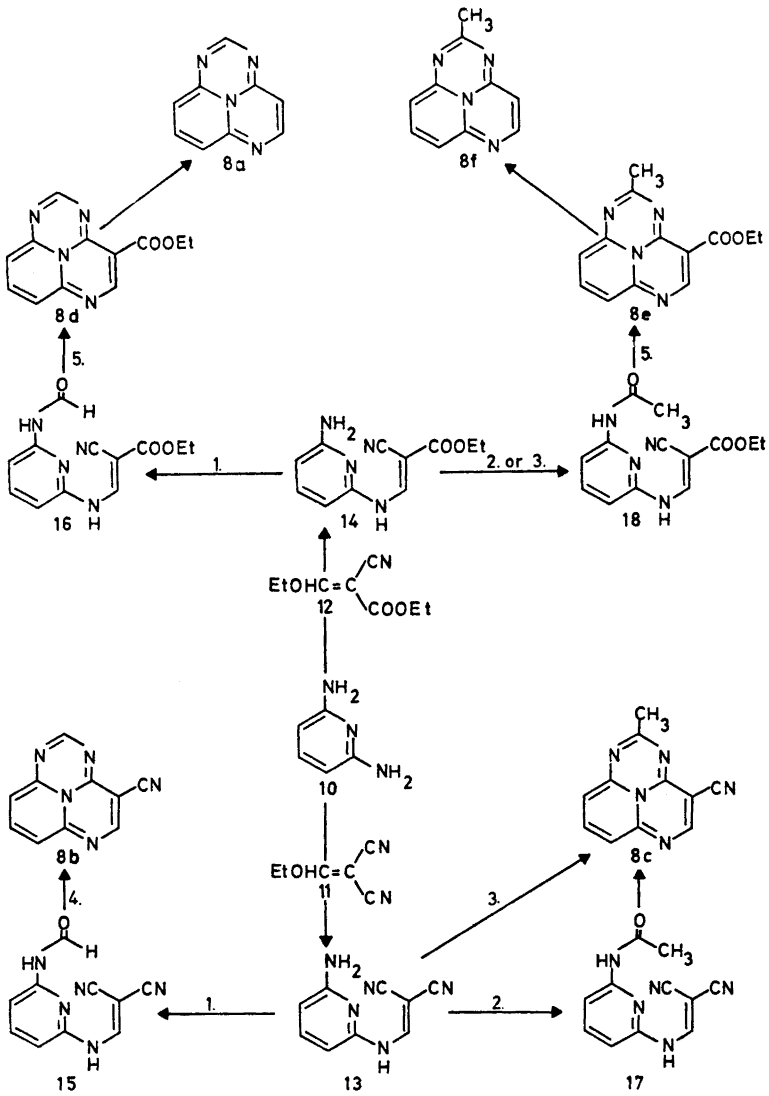
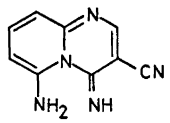


Chart 1. Reagents: 1. acetic-formic anhydride in pyridine at room temperature. 2. acetic anhydride in pyridine at room temperature. 3. acetic anhydride in glacial acetic acid at reflux. 4. reflux in toluene over anhydrous $MgSO_4$. 5. reflux in diphenyl ether or biphenyl-diphenyl ether.

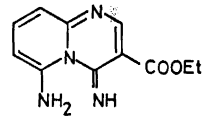
and *12* can be easily prepared.[24,25] The four triazacyclazines *8b*, *8c*, *8d*, and *8e* were obtained by varying the acylating agent.

The condensation products *13* and *14* were prepared by refluxing 2,6-diaminopyridine with *11* and *12*, respectively, in benzene. The proposed

structures were supported by mass (*13*: $M^+ = 185$ and *14*: $M^+ = 232$) and nuclear magnetic resonance (NMR) spectra. The resonance spectrum of *13* showed the presence of NH_2 protons at $\delta = 6.10$, a singlet at $\delta = 8.60$, and three protons in the aromatic region, a one-proton triplet at $\delta = 7.38$, and a group centered at $\delta = 6.30$, corresponding to two protons. In the spectrum of *14* a similar pattern is found in the aromatic region with a one-proton triplet at $\delta = 7.35$ and a two-proton group centered at $\delta = 6.38$. Typical ethyl ester absorption is observed at $\delta = 1.08$ and 4.20, as well as NH_2 absorption at $\delta = 6.10$, a singlet at $\delta = 8.98$, and broad NH absorption at $\delta = 10.72$. The structures of the condensation products are of type *13* and *14*, rather than *13a* and *14a*. This is based on the observation that the infrared spectrum of the product derived from 2,6-diaminopyridine and *11* contains two cyano bands at 2225 and 2235 cm^{-1}, while one cyano band at 2230 cm^{-1} is present in the condensation product obtained from 2,6-diaminopyridine and *12*. Formylation of *13* and *14* with acetic–formic anhydride [26] gave *15* and *16*, respectively, and



13a



14a

acetylation of *13* and *14*, using acetic anhydride in pyridine, yielded *17* and *18*, respectively. The infrared spectra of the acylated compounds *15* and *17* again displayed two cyano bands at 2210 and 2230 cm^{-1}, whereas the spectra of *16* and *18* exhibited one cyano band at 2230 cm^{-1} and a conjugated carbonyl band at 1685 cm^{-1}. The NMR spectrum of *17*, reproduced with assignments in

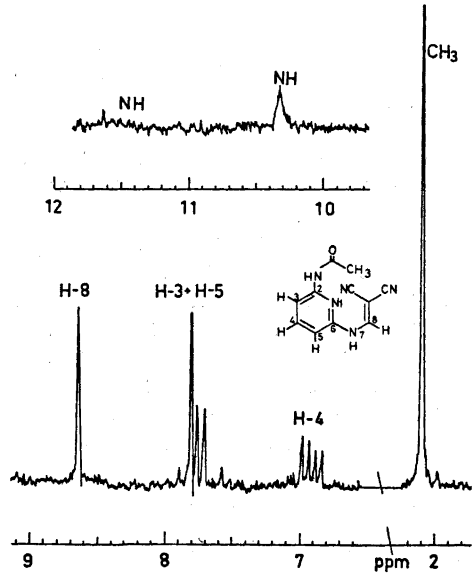


Fig. 1. NMR spectrum of *17*.

Fig. 1, is in complete agreement with the proposed structure, and the spectrum of *18* is very similar to that of *17*, showing in addition to the protons observed above, a typical ethyl ester pattern. The mass spectra of *17* and *18* displayed the expected molecular ions at $m/e = 227$ and 274, respectively, while in the spectra of *15* and *16*, the molecular ion peak was missing and the fragment at highest mass corresponded to M – CHO.

The final ring closure – dehydration of the intermediates to the respective cyclazines was accomplished in a variety of ways:

(i) sublimation at *ca.* 180° (*15*→*8b*);

(ii) refluxing in toluene containing anhydrous magnesium sulfate for *ca.* 24 h (*15*→*8b* and *17*→*8c*);

(iii) treatment with thionyl chloride or phosphorus oxychloride in pyridine (*15*→*8b*);

(iv) refluxing in *o*-dichlorobenzene for 48 h (*15*→*8b*);

(v) refluxing in biphenyl – diphenyl ether, b.p. 254°, or in diphenyl ether, b.p. 259°, for *ca.* 20 min (*16*→*8d* and *18*→*8e*).

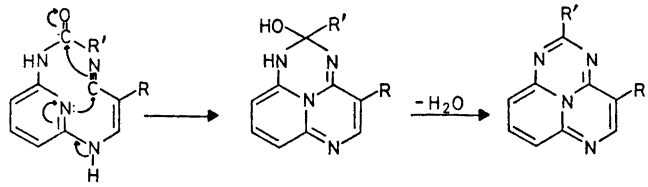
Of the methods used to effect ring closure, refluxing in high-boiling solvents proved to be the most satisfactory and general.[27]

In an attempt to improve the acetylation step, we refluxed *13* with acetic anhydride in glacial acetic acid. Instead of the acetylated product *17*, the cyclazine *8c* was formed directly after a reaction period of *ca.* 30 min. This reaction is synthetically extremely important and made this particular member of the azacyclazine group easily available. Based on this knowledge, it was expected that under the same conditions, *14* would produce the cyclazine *8e* directly. This was not the case, however, but after a short period (*ca.* 30 min) of reflux, a quantitative yield of *18* was obtained.

Our ultimate synthetic goal was to obtain the unsubstituted parent system, *8a*, and the original plan was to hydrolyze the cyano compound, *8b*, or the ethyl ester, *8d*, to 4-carboxy-1,3,6-triazacycl[3.3.3]azine, which could then be decarboxylated to yield *8a*. After ring closure – dehydration of *16* in a mixture of biphenyl and diphenyl ether for longer periods (*cf.* Experimental section), we unexpectedly observed two blue bands on the thin layer chromatograms. One was the normal product *8d* and the other, slower-moving, and less stable one, was proven to be the parent compound, 1,3,6-triazacycl[3.3.3]azine, *8a*. Likewise, when *18* was subjected to the same procedure, two blue products, *8e* and *8f*, were isolated. Refluxing of *16* and *18* in diphenyl ether alone did not yield *8a* or *8f*, but only *8d* and *8e*, respectively. This suggests that biphenyl, or an impurity in this compound, hydrolyzed the ester to a carboxylic acid which was decarboxylated at the high reflux temperature (254°). We also wish to report an additional observation for which we can offer no rational explanation. As a third product from some of the ring closure reactions, which gave mainly the ethyl ester *8e*, traces of the methyl ester *8g* were found. Analytical data (vapor phase chromatography and NMR spectra) indicated the absence of detectable amounts of *methyl* ethoxymethylenecyanoacetate in *12*, and refluxing of *8e* with methanol did not result in any ester exchange. The solvent in which the preparative thin layer chromatographic (TLC) separations were performed did contain methanol (EtOAc – MeOH, 9:1), but pure *8e* isolated

by preparative TLC did not yield any *8g* on repeated chromatography in that solvent mixture.

The ring closure step may be initiated by an electron pair from the pyridine system as indicated in the following proposal.



The cyclazines *8a–g* are dark-blue, crystalline compounds. The two members which are substituted at the 4-position with a cyano group are characterized by fairly high melting points, *ca.* 270°, and very low solubility in organic solvents. The carbethoxy analogs, on the other hand, have lower melting points, *ca.* 150°, and are relatively soluble in nonpolar organic solvents. The chromatographic R_F-values are unusually low, and, to obtain a resonable rate of mobility, the developing solvents must be quite polar (*e.g.* ethyl acetate – ethanol). All the compounds are stable to heat, air, and light.

Since the 1,3,6-triazacycl[3.3.3]azine system is a new one, and no comparisons can be made with known compounds of similar structure, a detailed structural proof is necessary. In the following sections we wish to report structural proofs for the seven cyclazines using spectral properties, propose that these compounds possess aromatic character, and briefly mention the results of simple HMO calculations.

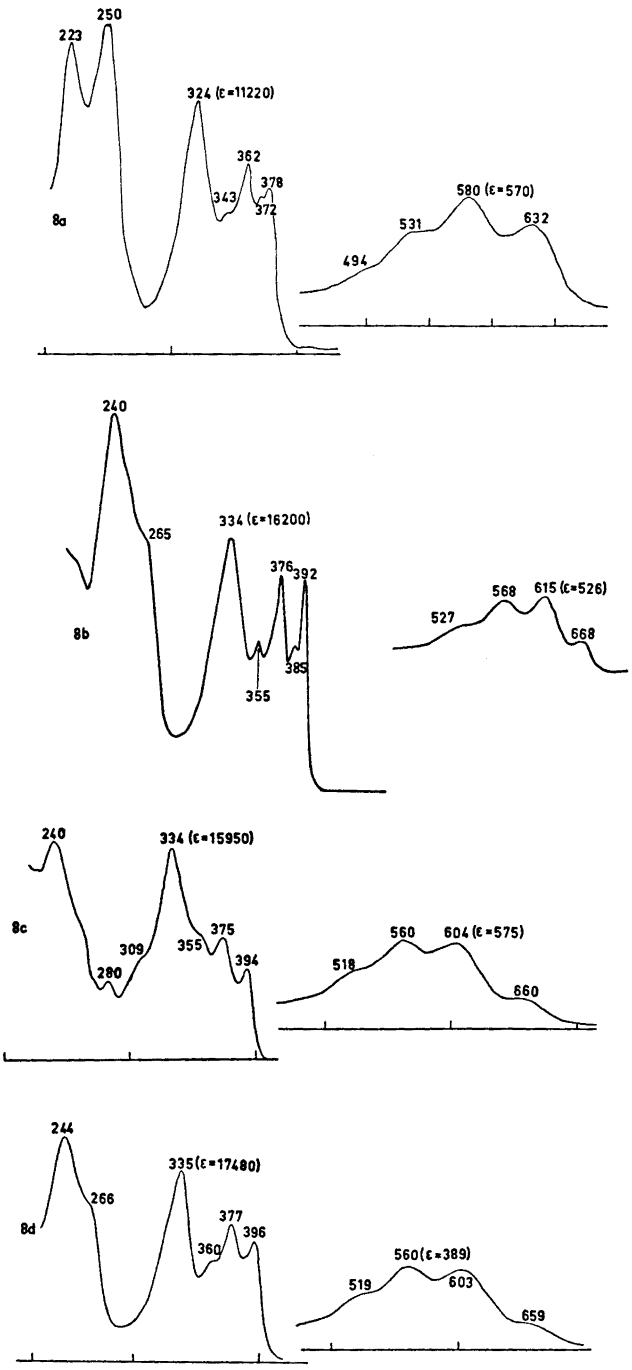
The molecular compositions of *8a–g* are summarized in Table 1 and they are based on exact masses obtained by high-resolution mass spectrometry.

Table 1.

Cyclazine	Mol. formula	M^+ calc.	M^+ found	ΔM
8a	$C_9H_6N_4$	170.0592	170.0589	0.0003
8b	$C_{10}H_5N_5$	195.0545	195.0549	0.0004
8c	$C_{11}H_7N_5$	209.0701	209.0723	0.0022
8d	$C_{12}H_{10}N_4O_2$	242.0804	242.0799	0.0005
8e	$C_{13}H_{12}N_4O_2$	256.0960	256.0960	0.0000
8f	$C_{10}H_8N_4$	184.0749	184.0747	0.0002
8g	$C_{11}H_8N_4O_2$	228.0647	228.0638	0.0009

The mass spectrometrical fragmentation patterns of the azacyclazines are in complete agreement with the proposed structures. A large number of doubly charged ions are also present in the spectra. This is very typical of, in particular, N-heterocyclic systems possessing aromatic character.* A more detailed analysis of the mass spectra of *8a–g* is presented in an accompanying communication.[21]

* For a discussion of doubly charged ions in nitrogen heterocyclic aromatic systems *cf.* Ref. 21 and references therein.


250
223
324 (ε=11220)
362
378
343
372
8a
580 (ε=570)
531
632
494
240
265
334 (ε=16200)
376
392
8b
568
615 (ε=526)
527
668
385
355
240
334 (ε=15950)
8c
309
355
375
394
280
560
604 (ε=575)
518
660
244
335(ε=17480)
266
377
8d
396
360
560(ε=389)
519
603
659

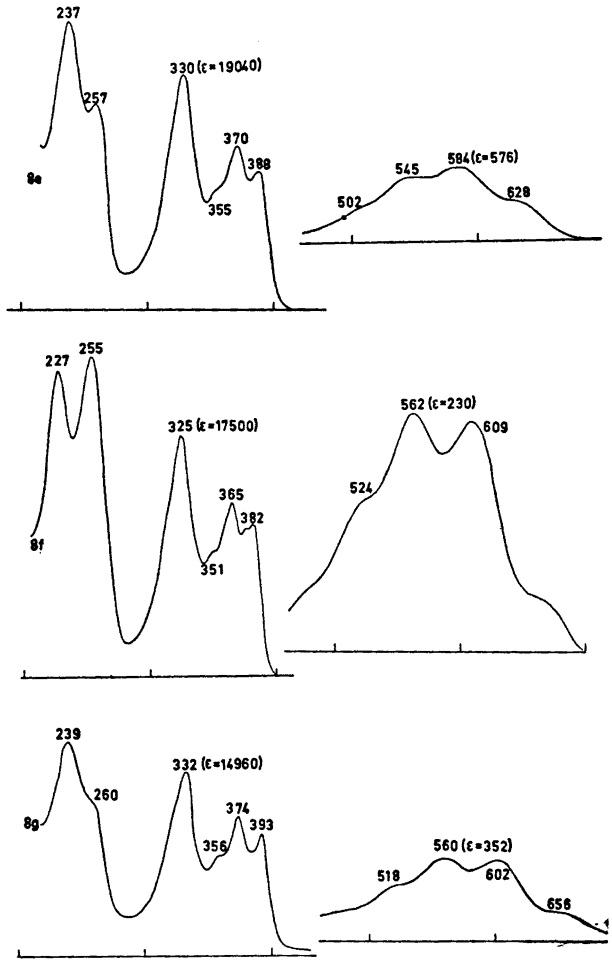


Fig. 2. UV spectra of *8a – g*.

The infrared spectra of all seven azacyclazines lack NH absorption. Only one cyano band at 2215 cm^{-1} is found in the spectra of *8b* and *8c*, respectively. In the spectra of *8d*, *8e*, and *8g*, a conjugated carbonyl absorption at 1719 cm^{-1} is present. These results are in complete accord with the proposed structures. Compounds *8a – g* all contain the same chromophore, and very similar electronic spectra would therefore be anticipated. The ultraviolet and visible spectra for *8a – g* are reproduced in Fig. 2. The long-wavelength absorption, λ_{max} = 500 – 670 nm, responsible for the blue color of the compounds, is of low intensity, $\varepsilon = 500$, and displays in all cases four bands, separated by *ca.* 45 nm. The region between 220 – 400 nm is also very similar in all the spectra. In both regions small intensity and wavelength differences exist in the different

spectra. The most characteristic feature of these spectra, however, is the fine structure, or presence of seven distinct bands between 240 and 375 nm, which is often observed in the spectra of aromatic systems.

The solubilities of the cyano derivatives in solvents normally used for NMR spectra were too low to obtain signals of sufficient intensity. Therefore, *8b*, *8c*, and *8e* were dissolved in arsenic trichloride, containing tetramethylsilane as the internal reference. The 2-methyl derivative, *8f*, reacted immediately with the solvent, yielding a precipitate which made impossible all attempts to obtain a spectrum, and unfortunately, *8a* and *8d* were available in insufficient quantities. The spectra of *8b*, *8c*, and *8e* with assignments are reproduced in Figs. 3, 4, and 5. The aromatic region in these spectra is of an ABC or, approximately,

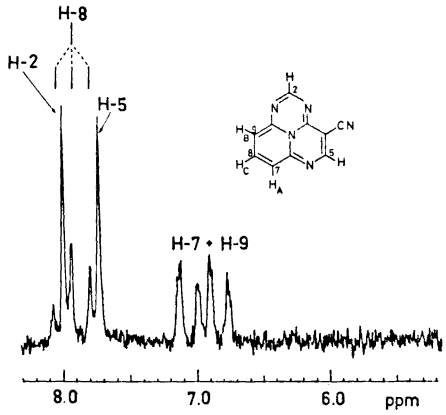


Fig. 3. NMR spectrum of *8b*.

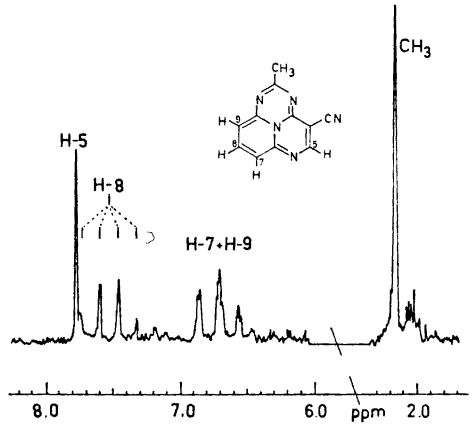


Fig. 4. NMR spectrum of *8c*.

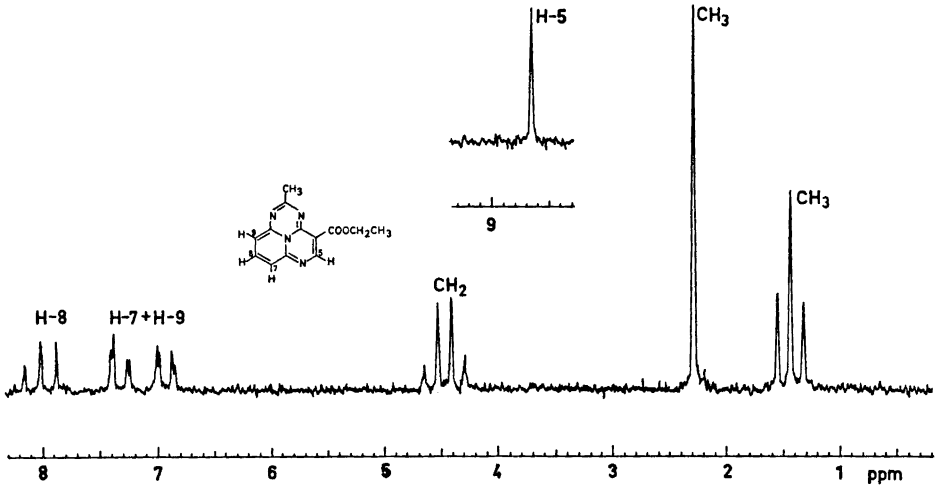


Fig. 5. NMR spectrum of *8e*.

an ABX type. In the spectrum of *8c*, the signal from H-8 gives rise to a quartet, while the same proton in the spectra of *8b* and *8e* appears as a triplet. Expansion of the aromatic region in the spectrum of *8e* shows, however, that the H-8 signal is a quartet. After expansion of this region in the spectrum of *8b*, the triplet remains unchanged, indicating that the coupling constants J_{AC} and J_{BC} are the same. The AB part of these spectra appears as two quartets, well-separated in *8e*, and overlapping in *8b* and *8c*. In all these spectra the H-5 signal is a singlet. A one-proton singlet due to H-2 is found at $\delta = 8.03$ in the spectrum of *8b*, while the CH_3 group in the same position in *8c* and *8e*, gives rise to a three-proton singlet at $\delta = 2.15$ and 2.25, respectively. A typical CH_3-CH_2-O pattern is observed in the spectrum of *8e*. The NMR spectra of *8b*, *8c*, and *8e* are thus in complete agreement with the proposed structures and provide final and conclusive structure proof. Even though it was not possible to record the NMR spectra of *8a*, *8d*, *8f*, and *8g*, the similarity of the chromophores in the ultraviolet and visible spectra and the detailed correspondence of the fragmentation patterns in the mass spectra of all azacyclazines,[21] leave no doubt about the correctness of these structures.

HMO calculations of the ω-type have been carried out on the systems *8a*, *8b*, and *8d*. Adjustments were made in the Coulomb integrals, using $\alpha_x = \alpha + h_x\beta$, and in the resonance integrals with $\beta_{xy} = k_{xy}\beta$, according to Table 2.[28]

Table 2. Parameters used in the MO calculations.

Element	Bond	h_x	k_{xy}
C	C_4-C_{11}[a]	$h_C = 0.0$	$k_{C-C} = 0.8$
N	C–N	$h_{\dot{N}} = 0.5$	$k_{C-\dot{N}} = 1.0$
	C–N	$h_{\ddot{N}} = 1.5$	$k_{C-\ddot{N}} = 0.8$
O	C=O	$h_{\dot{O}} = 1.0$	$k_{C=\dot{O}} = 1.0$
	C–O	$h_{\ddot{O}} = 2.0$	$k_{C-\ddot{O}} = 0.8$

[a] In compound *8b*, atoms 11 and 12 refer to the cyano substitutent, C(11)≡N(12), and in *8d*, atoms 11, 12 and 13 refer to the ester group, C(11)(=O(12))–O(13).

The value used for ω was 1.4. The resonance energies have been calculated by comparing the energies of the completely delocalized and the completely localized systems. These values, given in Table 3, are in good agreement with that of 4.1618 β obtained for cycl[3.3.3]azine, *6* (R = H), with the same program and using the above parameters (*cf.* also Ref. 3, p. 1463). The values for the charge densities (Table 4) and free valences (Table 5) predict both electrophilic substitution and radical attack at the same positions, C-4, C-7, and C-9, in

Table 3. Resonance energies.

Compound	Resonance energy
8a	4.3726 β
8b	4.4441 β
8d	5.0655 β

Table 4. Charge densities.

Compound	1	2	3	3a	4	5	6	6a
8a	−0.352	+0.231	−0.354	+0.200	−0.148	+0.164	−0.341	+0.161
8b	−0.334	+0.233	−0.336	+0.221	−0.137	+0.188	−0.324	+0.162
8d	−0.330	+0.234	−0.336	+0.229	−0.146	+0.200	−0.322	+0.164
Compound	7	8	9	9a	10	11	12	13
8a	−0.132	+0.099	−0.136	+0.170	+0.438			
8b	−0.116	+0.101	−0.120	+0.171	+0.439	+0.196	−0.342	
8d	−0.113	+0.102	−0.116	+0.172	+0.439	+0.339	−0.618	+0.101

Table 5. Free valences.

Compound	2	3a	4	5	6a	7	8	9	9a	11
8a	0.441	0.170	0.464	0.432	0.161	0.469	0.418	0.467	0.168	
8b	0.443	0.191	0.172	0.462	0.167	0.465	0.419	0.464	0.168	0.461
8d	0.443	0.189	0.171	0.461	0.167	0.463	0.419	0.463	0.168	0.244

Table 6. Bond orders.

Compound	1−2	1−9a	2−3	3−3a	3a−4	3a−10	4−5	5−6	6−6a
8a	0.656	0.518	0.635	0.540	0.596	0.425	0.671	0.629	0.545
8b	0.664	0.523	0.626	0.567	0.543	0.430	0.607	0.663	0.529
8d	0.666	0.524	0.624	0.573	0.540	0.430	0.600	0.670	0.525
Compound	6a−7	6a−10	7−8	8−9	9−9a	9a−10	4−11	11−12	11−13
8a	0.595	0.431	0.668	0.646	0.619	0.428			
8b	0.608	0.429	0.659	0.654	0.614	0.427	0.410	0.862	
8d	0.612	0.428	0.657	0.657	0.612	0.427	0.421	0.702	0.365

the unsubstituted system, and at C-7 and C-9 in the 4-substituted one.* In the 4-substituted compounds, radical substitution is also favored at C-5, while in the unsubstituted compound attack at C-2 is favored over that at C-5. The

* *Cf.* the accompanying communication, Ref. 29.

bond orders (Table 6) obtained, show that these systems have little tendency for alternation, suggesting a lack of alternate single and double bonds. The charge-density values for the central nitrogen atom, N-10, in all three compounds studied, show 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 (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.

EXPERIMENTAL

General. MO calculations were carried out with a program which incorporated the ω-technique of Streitwieser on an IBM Model 360 – 65 digital computer. The program, Hückel II (Author: Dr. S. Weckherlin), was obtained through the courtesy of the "Deutsches Rechenzentrum", Darmstadt. Ultraviolet (UV) and visible spectra were measured in ethanol with a Cary Model 15 spectrophotometer. Infrared (IR) spectra were determined in KBr with a Beckman IR 9 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Model A-60 spectrometer, with tetramethylsilane as internal reference. Mass spectra (MS) were recorded with an LKB 900 mass spectrometer, and the exact mass measurements were obtained with a GEC – AEI 902 instrument. Thin layer chromatography (TLC) was performed on Silica Gel GF_{254} (Merck) according to Stahl and the spots were visualized with short-wave ultraviolet light and with iodine vapor. Microanalyses were carried out at the Microanalytical Laboratory, University of Copenhagen, Copenhagen.

Condensation of 2,6-diaminopyridine with ethoxymethylenemalononitrile to 13. A mixture of 4.5 g (41.2 mmol) of 2,6-diaminopyridine, recrystallized from benzene, and 5.1 g (41.2 mmol) of ethoxymethylenemalononitrile was refluxed in 250 ml of benzene for 24 h. A white crystalline solid separated out upon cooling and was collected by filtration. A crude yield of 7 g (92 %) of *13*, m.p. 208 – 210°, was obtained. Thin layer chromatography (EtOAc – MeOH, 9:1) showed the presence of only one major product ($R_F = 0.76$), plus traces of starting material ($R_F = 0.0$). IR: 3330 – 3420 (NH), 2220 and 2235 (CN) cm^{-1}. UV: λ_{max} at 240, 281, and 349 nm. NMR (DMSO-d_6): singlet at 8.60 (1H), triplet at 7.38 (1H), multiplet at 6.25 (2H), and NH absorption at 6.10 (2H) ppm. MS: $M^+ = 185$.

Formylation of 13 to 15. A mixture of 0.70 ml (7.4 mmol) of acetic anhydride and 0.30 ml (7.9 mmol) of formic acid was allowed to stand at 50° for 2 h, after which time 1 g (5.4 mmol) of *13*, dissolved in 10 ml of anhydrous ether, was added. The solution was stirred at room temperature and after 24 h the progress of the reaction was continuously followed by TLC (EtOAc – MeOH, 9:1, $R_F = 0.68$). After 16 additional hours of stirring, the reaction mixture was filtered and 1 g (87 %) of a yellow solid, m.p. 230 – 235°, was collected. This product, *15*, displayed extreme insolubility and therefore recrystallization was not attempted. The yield of *15* could be improved by replacing ether with pyridine in the formylation step. IR: 3200 – 3490 (NH), 2220 and 2235 (CN), and 1685 (C=O) cm^{-1}. UV: λ_{max} at 251, 273, 280, and 335 nm.

Acetylation of 13 to 17 and to 8c. (a) In pyridine. To a solution of 1 g (5.4 mmol) of *13* in 12 ml of pyridine, 0.70 ml (7.4 mmol) of freshly distilled acetic anhydride was added. The temperature was not allowed to rise above 15° during the addition. The clear solution was allowed to stand at room temperature for 3.5 days, during which time a slight precipitate formed. It was removed by filtration and the remaining solution was poured into 25 ml of water. The thick, white precipitate formed was washed with water and dried over P_2O_5 in a vacuum desiccator. A crude yield of 0.7 g (57 %) of *17*, m.p. 233 – 234°, was obtained. The product was purified by sublimation at 200°/1 torr. IR: 3250 – 3400 (NH), 2220 and 2230 (CN), and 1685 (C=O) cm^{-1}. UV: λ_{max} at 232, 272, 280, and 334 nm. NMR (DMSO-d_6): singlet at 2.10 (3H), quartet at 6.88 (1H), triplet at 7.75 (2H), singlet at 8.65 (1H), and broad NH absorption at 10.33 (1H) and 11.50 (1H) ppm (*cf.* Fig. 1). MS: $M^+ = 227$.

(b) In acetic acid. To a solution of 7 g (38 mmol) of *13* in 70 ml of glacial acetic acid 3.9 ml (42 mmol) of acetic anhydride was added. The mixture was refluxed for 30 min, after which time the solution had turned deep-blue. Upon cooling, a dark-blue solid precipitated. It was collected, and the remaining solution was evaporated to dryness *in vacuo*. The blue solid thus obtained was combined with the precipitate and was purified by column chromatography on 30 g of alumina, activity I. Benzene – ether (1:1) eluted 5.5 g (70 %) of *8c* with m.p. 268 – 270°. IR: 2220 cm^{-1} (CN). The UV and NMR ($AsCl_3$) spectra are reproduced above. MS: $M^+ = 209.0723$. (Found: C 62.9; H 3.4; N 33.5. Calc. for $C_{11}H_7N_5$: C 63.1; H 3.4; N 33.5.)

Ring closure of 15 to 8b. (a) When *15* was heated at 180°/1 torr in a sublimation tube, dark-blue crystals of *8b*, m.p. 264 – 266°, sublimed. (b) A suspension of 100 mg of *15* in 80 ml of toluene was refluxed for 24 h in a Soxhlet extraction apparatus using anhydrous $MgSO_4$ to remove the water formed during the cyclodehydration reaction. The blue toluene solution obtained was evaporated to dryness on a rotatory evaporator yielding *ca.* 30 mg of *8b*. The blue solid was purified by column chromatography on alumina, activity III, with benzene as the eluent. M.p. 264 – 267°. (c) A suspension of 500 mg of *15* in 50 ml of *o*-dichlorobenzene was refluxed for 48 h. The solution was deep-blue and evaporation to dryness yielded a blue solid, *8b*, which was purified by sublimation at 180°/1 torr. M.p. 269 – 270°. (d) To a solution of 200 mg (0.93 mmol) of *15* in 8 ml of distilled pyridine was added 0.08 ml (1.1 mmol) of freshly distilled thionyl chloride and the mixture was kept at 90° for 12 h. The excess of pyridine was removed *in vacuo* leaving a dark tar, which was triturated with benzene yielding a blue solution. After evaporation of the benzene, 14 mg of a blue-green solid, *8b*, was obtained and was purified by column chromatography on 4 g of alumina, activity III, with benzene as the eluent. Yield: 4.4 mg (2.4 %), m.p. 263 – 264°. The procedure can be scaled-up without complications. (e) To a solution of 100 mg (0.46 mmol) of *15* in 6 ml of distilled pyridine was added 0.04 ml (0.31 mmol) of phosphorus oxychloride and the mixture was kept at 90° for 7 h. The work-up procedure was the same as described above under (d). Yield: 1.6 mg (2 %), m.p. 264 – 265°. Thin layer chromatography (EtOAc) of the blue products obtained according to procedures (a) – (e), showed the presence of only one and the same product, *8b*, $R_F = 0.21$. IR: 2210 cm^{-1} (CN). The UV and NMR spectra are reproduced above. MS: $M^+ = 195.0549$.

Ring closure of 17 to 8c. A suspension of 500 mg of *17* in 350 ml of toluene was refluxed in a Soxhlet apparatus for 7 days using anhydrous $MgSO_4$ to remove the water formed. The unreacted solid was removed by filtration and the deep-blue toluene solution was evaporated to dryness *in vacuo* yielding 140 mg of *8c*. The same procedure was repeated with the unreacted starting material and an additional 75 mg of *8c* was obtained. The total crude yield was 215 mg (47 %), m.p. 265 – 266°. The product was purified by column chromatography, as described under acetylation of *13*, part (b).

Condensation of 2,6-diaminopyridine with ethyl ethoxymethylenecyanoacetate to 14. A solution of 11.0 g (101 mmol) of recrystallized 2,6-diaminopyridine and 16.9 g (101 mmol) of ethyl ethoxymethylenecyanoacetate in 1 l of benzene was refluxed for 16 h. Upon cooling, a white crystalline solid, *14*, precipitated. It was collected and the remaining solution was evaporated to dryness *in vacuo*. The white solid thus obtained was combined with the first crystalline precipitate giving a crude yield of 23.4 g (95 %), m.p. 166 – 168°. Thin layer chromatography (EtOAc) showed the presence of only one major product ($R_F = 0.65$), plus traces of starting material ($R_F = 0.08$). The condensation product, *14*, was used without further purification. IR: 3330 – 3350 (NH), 2230 (CN), and 1710 (C=O) cm^{-1}. UV: λ_{max} at 250, 273, 282, and 335 nm. NMR (DMSO-d_6): triplet at 1.08 (3H), quartet at 4.20 (2H), amino NH at 6.10 (2H), multiplet at 6.38 (2H), triplet at 7.35 (1H), broad NH absorption at 10.72 (1H), and broad singlet at 8.98 (1H) ppm. MS: $M^+ = 232$.

Acetylation of 14 to 18. (a) In pyridine. Equivalent amounts of *14* (250 mg, 1.1 mmol) and freshly distilled acetic anhydride (0.10 ml, 1.1 mmol) in 3 ml of anhydrous pyridine were stirred together at room temperature for 3 days. The reaction mixture was then poured into water and the yellow precipitate formed was collected by filtration and dried over P_2O_5. Thin layer chromatography showed that the material was a mixture of starting material, *14* ($R_F = 0.65$), and the acetylated product, *18* ($R_F = 0.69$), and an NMR spectrum indicated that the two compounds were present in a 1:1 ratio. The material was therefore redissolved in pyridine, acetic anhydride was added and the

reaction was allowed to proceed for an additional 5 days. The reaction mixture was worked-up as described above, yielding a white precipitate which was shown by TLC to consist primarily of *18*. Yield: 226 mg (76 %), m.p. 215 – 216°.

(b) In acetic acid. To 500 mg (2.2 mmol) of *14* in 5 ml of glacial acetic acid was added 0.22 ml (2.4 mmol) of acetic anhydride. After the reaction mixture was refluxed for 30 min, the dark, homogeneous liquid was poured into water. A white solid precipitated immediately from the wine-red solution. The precipitate was collected by filtration and dried, yielding 300 mg (51 %) of *18*, m.p. 210 – 212°. Thin layer chromatography showed that this product ($R_F = 0.69$) was identical with that obtained from acetylation in pyridine solution. This reaction was scaled-up without complications. IR: 3280 (NH), 2230 (CN), and 1700 (C=O) cm^{-1}. UV: λ_{max} at 225, 264, 283, and 350 nm. NMR (DMSO-d_6): triplet at 1.25 (3H), singlet at 2.10 (3H), quartet at 4.21 (2H), quartet at 6.98 (1H), triplet at 7.77 (2H), singlet at 10.40 (1H), and broad NH absorption at 9.00 (1H) and 10.87 (1H) ppm. MS: $M^+ = 274$.

Ring closure of 18 to 8e and to 8f. (a) In diphenyl ether. To 1.5 g of diphenyl ether, 100 mg of *18* was added and the suspension was refluxed (b.p. 259°) for 10 min, rapidly cooled, and then diluted with 7.5 ml of hexane. The solution turned deep-blue and a brown solid precipitated which was filtered off and discarded. The blue solution was passed over a short column of alumina, activity I, (10 × 130 mm), the blue solid adsorbed on the alumina and the diphenyl ether was washed out with hexane. The blue product, *8e*, was eluted with benzene and further purified by preparative TLC (EtOAc, $R_F = 0.36$), m.p. 156 – 157°. IR: 1718 cm^{-1} (C=O). The UV and NMR ($AsCl_3$) spectra are reproduced above. MS: $M^+ = 256.0960$.

(b) In biphenyl – diphenyl ether. To a mixture of 7.5 g of biphenyl and 7.5 g of diphenyl ether, 1 g of *18* was added. The reaction mixture was refluxed (b.p. 254°) for 10 min, rapidly cooled, and then diluted with 75 ml of hexane. The solution became very light-blue and a brown precipitate formed which was collected by filtration. The blue solution was treated as described above, and a fresh mixture of biphenyl – diphenyl ether was added to the brown solid and reflux was continued for three additional hours. The reaction mixture was worked up as described above. Analytical TLC (EtOAc – MeOH, 9:1) showed the presence of two blue components ($R_F = 0.36$ and 0.14). These two products were separated by preparative TLC. The faster moving component, $R_F = 0.36$, was identical with *8e*, described under (a). The other product was the decarboxylated compound, *8f*, m.p. 189 – 190°. Its UV spectrum is described above. MS: $M^+ = 184.0747$.

Formylation of 14 to 16. A mixture of 7.0 ml (74.1 mmol) of acetic anhydride and 3 ml (79.5 mmol) of formic acid was allowed to stand at room temperature for 2 h and was then cooled to 0°. 10 g (43.3 mmol) of *14*, dissolved in 100 ml of pyridine, was added and the temperature was kept under 20° during the addition. The solution was stirred at room temperature and the progress of the reaction was continuously followed by TLC (EtOAc, R_F for *16* = 0.58). After 7 days the solution was evaporated to dryness under vacuum and a yellow-white solid, *16*, was isolated and purified by column chromatography on 150 g of alumina, activity I. Yield: 4.5 g (40 %), m.p. 204 – 209°.

Ring closure of 16 to 8d, 8a, and 8g. (a) In biphenyl – diphenyl ether. To a mixture of 15 g of biphenyl and 15 g of diphenyl ether, 2 g (7.7 mmol) of *16* was added. The reaction mixture was refluxed for 4.5 h, rapidly cooled, and then diluted with 150 ml of hexane, yielding a blue solution. It was passed over a short column of alumina, the blue solid adsorbed, and the biphenyl – diphenyl ether washed out with hexane. The blue band was eluted with benzene and purified by preparative TLC (EtOAc – MeOH, 9:1). Three blue components were isolated, 100 mg (5.4 %) of *8d*, with $R_F = 0.33$ and m.p. 138 – 142°, 10 mg (0.6 %) of *8g*, with $R_F = 0.29$ and m.p. 186 – 188°, and 10 mg (0.8 %) of *8a*, with $R_F = 0.21$ and m.p. 179 – 182°. IR: for *8d*, 1720 cm^{-1} (C=O), and for *8g*, 1720 cm^{-1} (C=O). The UV spectra for *8a*, *8d*, and *8g* are reproduced above. MS: M^+ for *8a* = 170.0589 ± 0.0012, M^+ for *8d* = 242.0799 ± 0.0012, and M^+ for *8g* = 228.0638 ± 0.0012.

(b) In diphenyl ether. To 1.5 g of diphenyl ether, 100 mg (0.38 mmol) of *16* was added and the suspension was refluxed for 4 h, rapidly cooled and diluted with 7.5 ml of hexane. The resulting blue solution was passed over a short column of alumina, the blue solid adsorbed, and the diphenyl ether washed out with hexane. The blue product, *8d*, was eluted with benzene and purified by preparative TLC (EtOAc – MeOH, 9:1, $R_F = 0.33$). Yield: 10 mg (11 %), m.p. 139 – 142°. Spectral data for this compound are given above.

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