THE CHEMISTRY OF ANTIAROMATIC AZACYCL[3.3.3]AZINES

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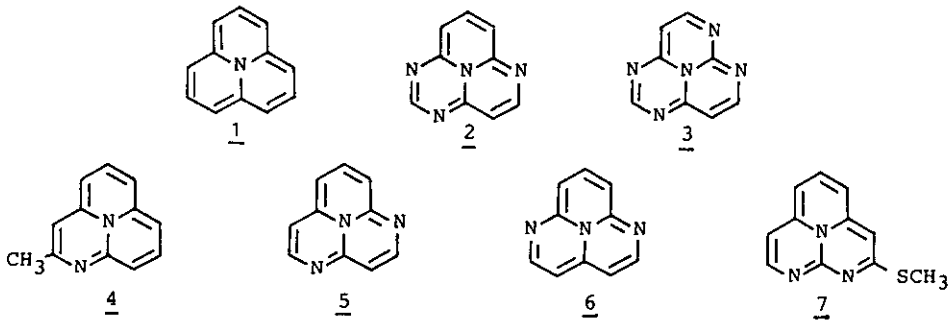
Abstract - The syntheses and reactions of antiaromatic azacycl[3.3.3]azines are reviewed.



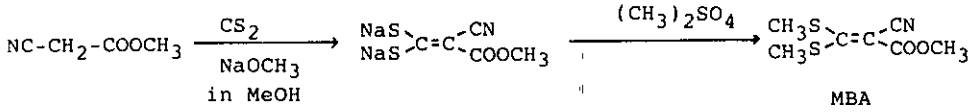
Scheme I

The first synthesis of cycl[3.3.3]azine (1) was achieved by Farquhar and Leaver in 1969 after considerable efforts by several groups for around a decade.[1] Contrary to theoretical predictions, it was revealed that 1 is a highly reactive compound susceptible to both oxidation and reduction and its ^{1}H-nmr spectrum displays a strong paratropic shift. These features were regarded as evidence for antiaromatic character of this nitrogen-bridged peripheral 12 π electron system.[2] A little later, Ceder and his co-workers synthesized triaza- and tetraaza-cycl[3.3.3]azines (2 and 3) and found that their proton signals in ^{1}H-nmr spectra appeared in the relatively low field (δ: 4.8-7.3), which fact suggested that 2 and 3 had aromatic character.[3]

These finding prompted us to undertake the synthetic study of monoaza- and diazacycl[3.3.3]azines in order to clarify the correlation of the number of peripheral nitrogen atom with aromatic or antiaromatic character. The present paper deals with the successful synthesis of some derivatives of 2-methyl-1-aza- (4), 1,4-diaza- (5), 1,6-diaza- (6) and 2-methylthio-1,9-diaza-cycl-

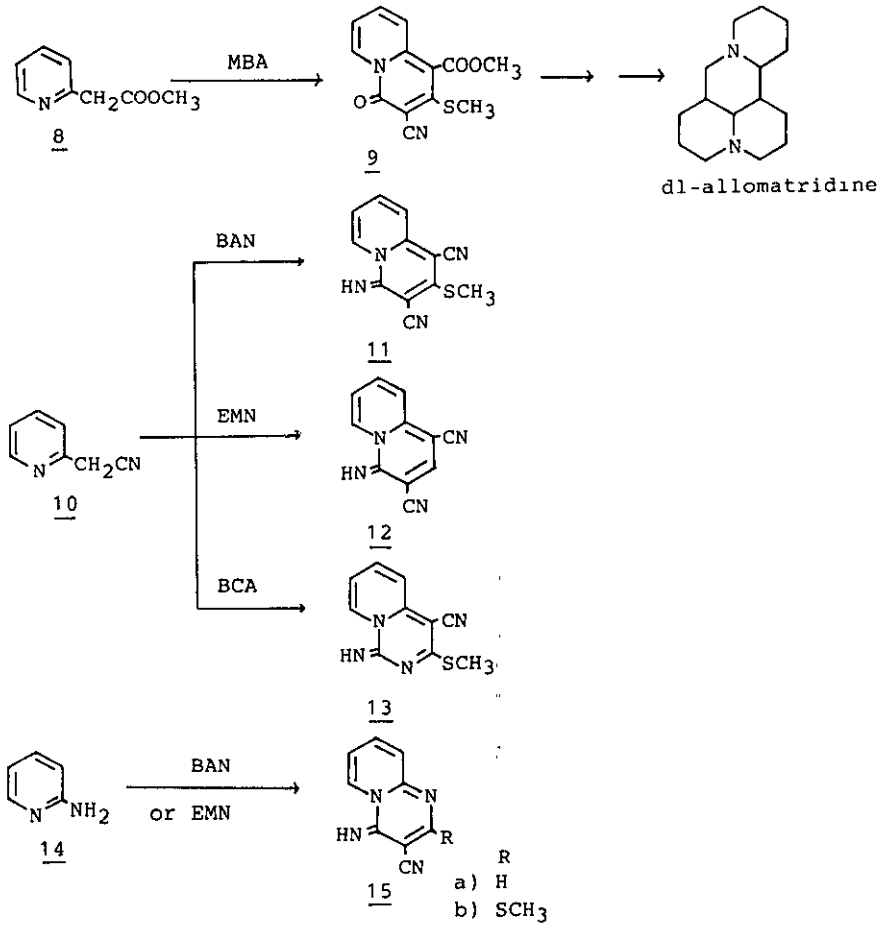
[3.3.3]azine (7), their conversions into the respective parent bases, 4, 5, 6, and 7, and the ^{1}H-nmr spectral examinations of these parent bases and their hydrobromides.[4] Some interesting reactions observed during the course of these studies will be also described. (Scheme I)

SYNTHESES OF MONOAZA- AND DIAZA-CYCL[3.3.3]AZINE DERIVATIVES



Scheme II

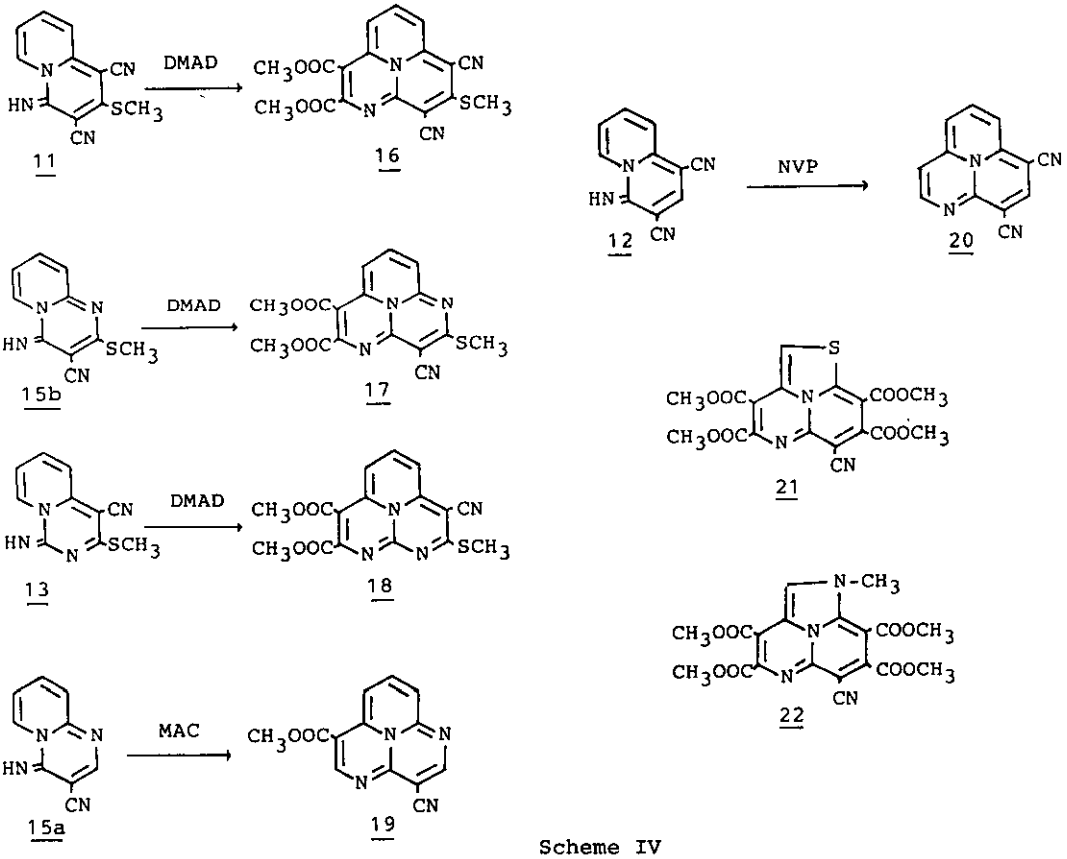
Kobayashi and co-workers including us carried out the extensive studies of the reaction of heteroaromatic active methylenes with various ketene dithioacetals and their analogues, and obtained many interesting results.[5] Ketene dithioacetals appropriately functionalized (cyano, methoxycarbonyl, sulfonyl, nitro, acyl, etc.) are versatile reagents which have been extensively utilized in



Scheme III

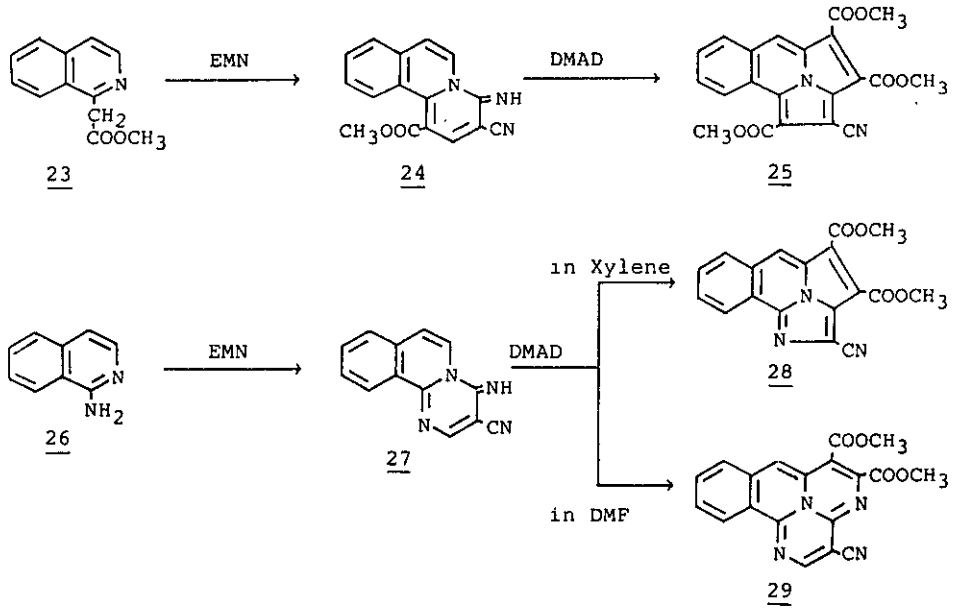
heterocyclic synthesis. One of these, methyl 2,2-bis-(methylthio)-1-cyanoacrylate (MBA), is also an extremely interesting synthon and is used as a three carbon fragment for the synthesis of heterocyclic compounds having cyano or ester groups. This ketene dithioacetal, MBA is easily prepared by the condensation of methyl cyanoacetate with carbon disulfide in methanol in presence of sodium methoxide, followed by methylation with dimethyl sulfate.[6] (Scheme II)

In the numerous reports concerning the utility of ketene dithioacetals of the synthesis of heterocycles, for example, we succeeded that the reaction of methyl pyridine-2-acetate (8) with MBA gave easily 4-oxoquinolizine derivative (9), in good yield, and then using 9 as a starting material, the total synthesis of dl-allomatridine was carried out in the convenient method.[5b] Furthermore we found that 4-iminoquinolizine derivatives (11, 12) were obtained easily by the reaction of pyridine-2-acetonitrile (10) with 2,2-bis(methylthio)-1-cyanoacrylonitrile (BAN) or ethoxymethylenemalononitrile (EMN).[7] This type of cyclization is usefully applied to preparation of various 4-iminoquinolizine analogous (13, 15).[8] (Scheme III)



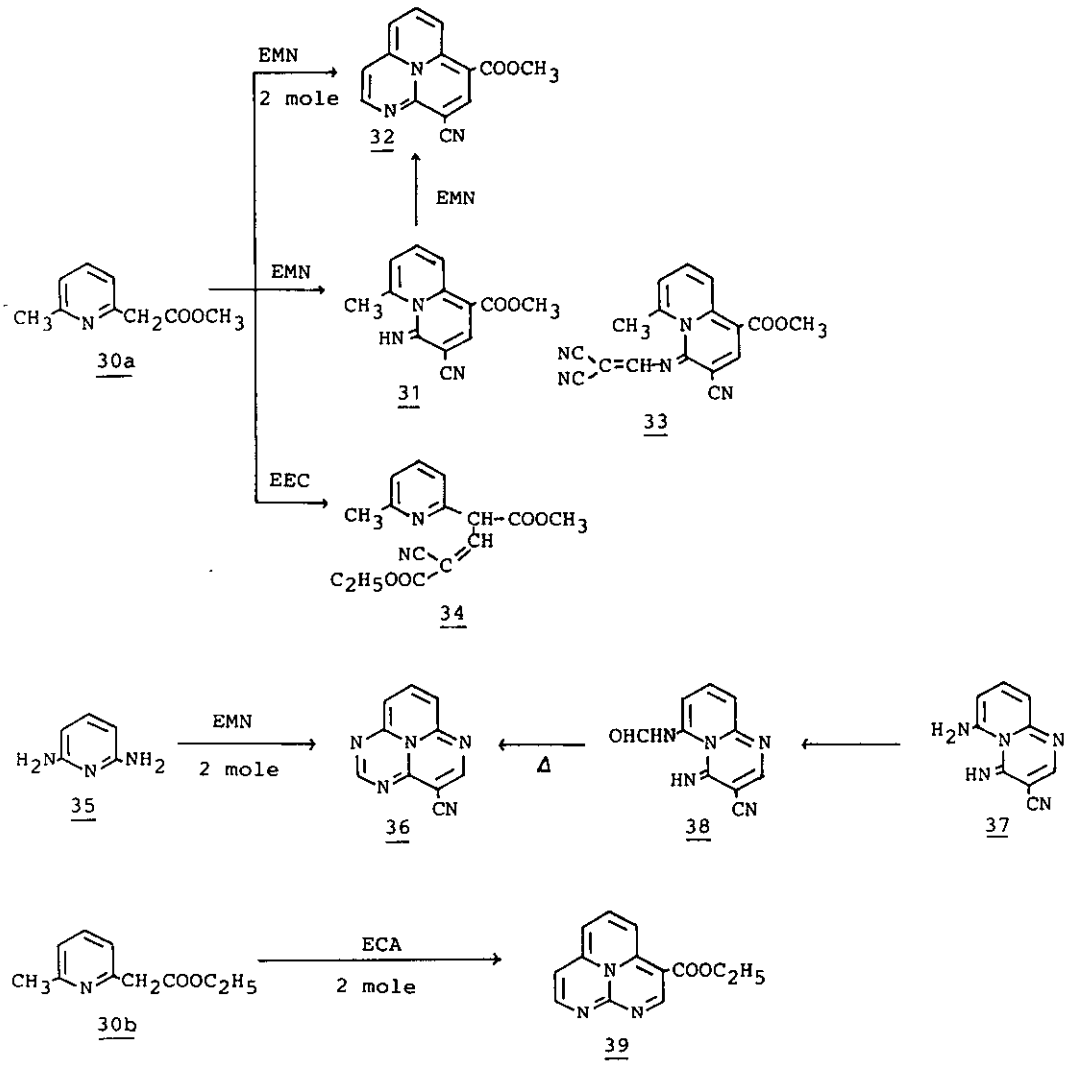
Scheme IV

In the course of the study of the reactivity of 11, we found that 11 undergoes the Diels-Alder reaction with dimethyl acetylenedicarboxylate (DMAD) to give 1-azacycl[3.3.3]azine derivative (16), a new nitrogen-bridged 12 annulene heterocyclic ring system. This type of cycloaddition is generally applicable to preparation of a wide range of 12 π cyclazine systems. Thus, we successfully prepared diazacycl[3.3.3]azine (17, 18, 19) from the reaction of the appropriate iminoderivatives of pyrido-pyrimidines (15b, 13, 15a) with DMAD or methyl acetylenecarboxylate (MAC).[4d,7,8] Matsumoto reported the synthesis of 5-azacycl[3.2.3]azines (21, 22) by this reaction.[1b] Similarly, the reaction of 12 with the so-called "masked acetylene", N-vinylpyrrolidone (NVP), afforded 7,9-dicyano-1-azacycl[3.3.3]azine (20).[9] (Scheme IV)



Scheme V

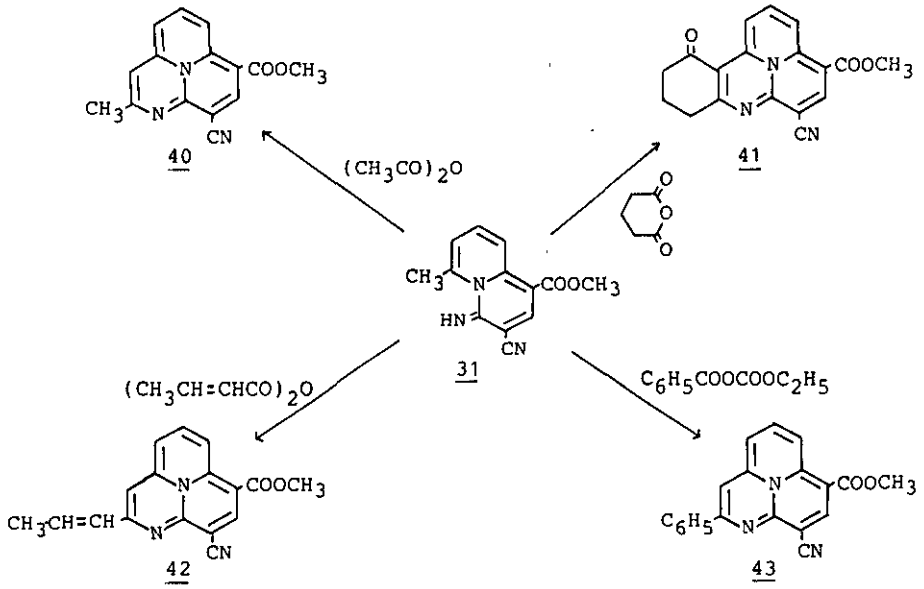
Nevertheless, an attempted reaction of 4-iminobenzoquinolizine (24) with DMAD resulted in the formation of an unexpected benzo(g)cycl[3.2.2]azine (25) accompanied by double construction. While the reaction of 4-iminopyrimido[2,1-a]isoquinoline (27) with DMAD in xylene gave also 1-azabenzo(h)cycl[3.2.2]azine (28) by the same course, the normal Diels-Alder adduct, 1,4-diazabenzo(j)cycl-[3.3.3]azine (29) was produced in the reaction in dimethylformamide (DMF). The mechanism of formation of 25 and 28 is very much interesting, but it is not elucidated.[10] (Scheme V)

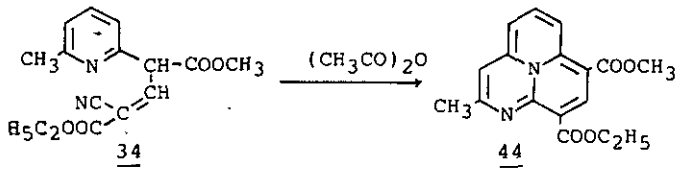


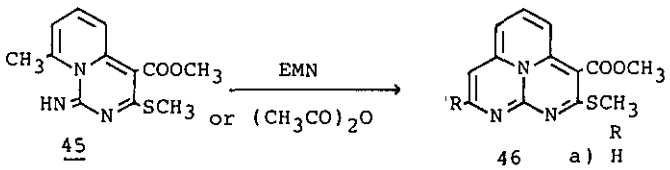
Scheme VI

As an extension of the study on the reaction of 4-iminoquinolizine derivative, we prepared 6-methyl-4-iminoquinolizine derivative (31) by the reaction of methyl 6-methylpyridine-2-acetate (30a) with EMN. During the course of this experiment, we happened to find that 31 readily undergoes a novel ring closure reaction.[4b,11] Thus, treatment with another mole of EMN gave 1-azacycl[3.3.3]-azine derivative (32) through 4-(2,2-dicyanovinyl)imino-6-methylquinolizine derivative (33), and 32 was also obtained directly by the reaction with two molar equivalents of EMN. Such a ring closure is apparently the other promising approach to the synthesis of azacyclazine systems. For example, 4-cyano-1,3,6-triazacycl[3.3.3]azine (36), which had been prepared through a rather trouble-

some route by Ceder et al., was much more advantageously synthesized by the reaction of 2,6-diaminopyridine (35) with two mole EMN. Ceder et al.[12] applied this type of reaction to the preparation of ethyl 1,9-diazacycl[3.3.3]azine carboxylate (39). In the case of the reaction of 30a with ethyl ethoxymethylenecyanoacetate (EEC), a simple condensation product (34) instead of a quinolizine derivative was obtained.[11b] (Scheme VI)







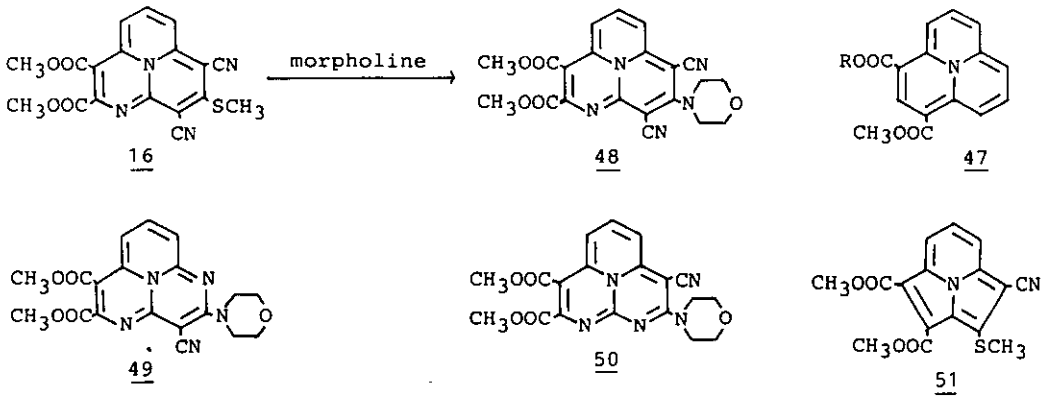
Scheme VII

Further, 31 reacted with an excess of hot acetic anhydride giving the corresponding 2-methyl-1-azacyclazine derivative (40). Syntheses of 1-azacycl-[3.3.3]azine derivatives such as 41 and 42 were also effected by the reaction of 31 with glutaric anhydride and crotonic anhydride.[4b] We recently succeeded in the synthesis of 2-phenyl-1-azacycl[3.3.3]azine (43) by applying the mixed

anhydride prepared from benzoic acid and ethyl chloroformate to 31.[9] Compound 34 was also transformed into 2-methyl-1-azacyclazine derivative (44) by means of hot acetic anhydride.[11b] In a similar manner, 1,9-diazacycl[3.3.3]azine derivatives (46a,b) could be obtained from the corresponding 4-iminopyrido[1,2-c]pyrimidine (45).[13] (Scheme VII)

REACTIONS OF AZACYCLAZINE

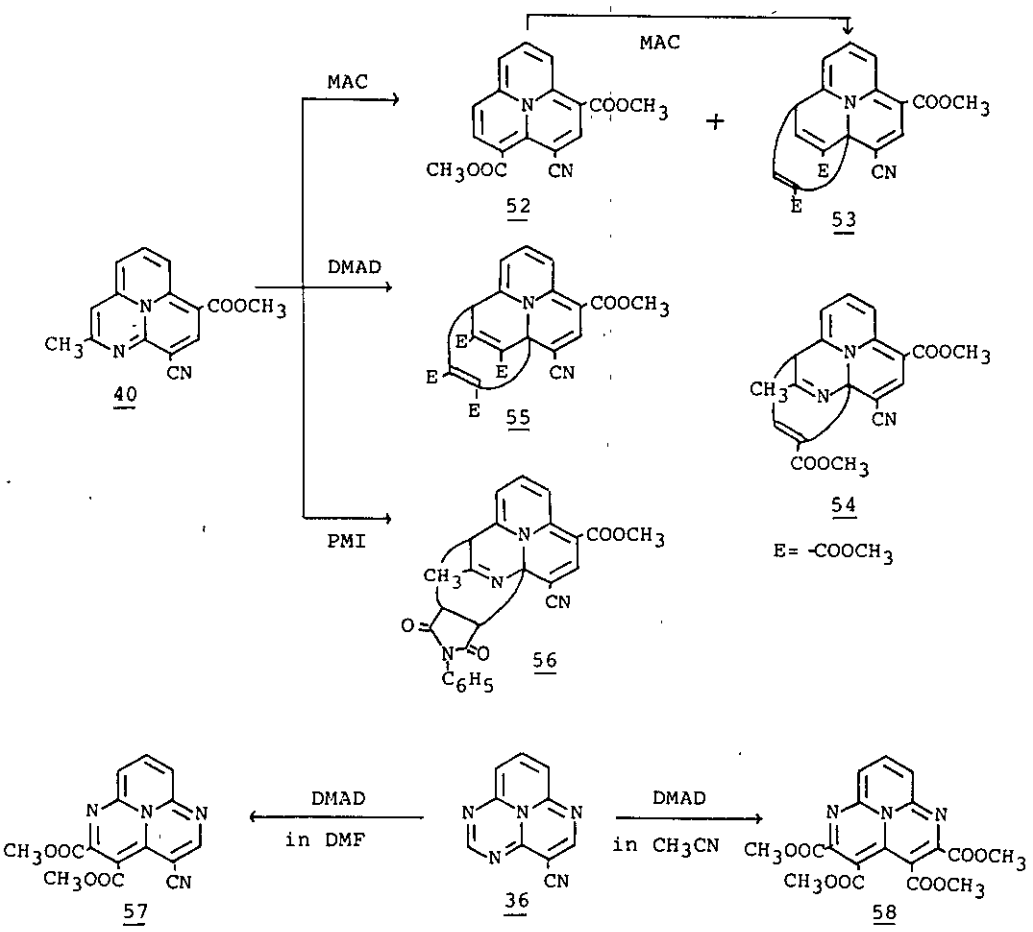
Farquhar and Leaver[1c] have described that while cycl[3.3.3]azine derivative (47) is rather stable owing to effect of its electron-attracting groups, it is highly susceptible to bromination, nitration and the Diels-Alder reaction. The above-mentioned monoaza- and diazacyclazine derivatives are also appreciably stable, however there are noticed some characteristic reactivities. The 7-methylthio group of 1-azacycl[3.3.3]azine derivative (16) readily reacted with nucleophiles such as amines and active methylenes. For example, 16 reacted easily with morpholine in ethanol to give the displacement product (48).[7] Quite similarly, morpholino derivatives (49, 50) were obtained from the corresponding methylthio derivatives of 1,4-diaza- and 1,9-diazacycl[3.3.3]azines (17, 18).[8] On the contrary, the cycl[3.3.3]azine derivative 51 did not react with morpholine, no displacement product being formed.[14] These observations suggest that the nitrogen-bridged peripheral 12 π electron systems of 16, 17 and 18 have antiaromatic character and reversely the nitrogen-bridged peripheral 10 π electron system of 51 has aromatic character. (Scheme VIII)



16 48 47

49 50 51

Scheme VIII

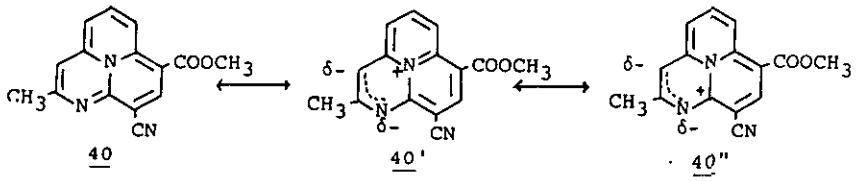


Scheme IX

We will now describe novel behavior in the reaction of 40 with dienophiles.[4e,15] Treatment of 40 with one molar equivalent of MAC in hot DMF afforded a deaza compound, dimethyl 3-cyanocycl[3.3.3]azine-1,4-dicarboxylate (52). The reaction of 40 with two molar equivalents of MAC gave the Diels-Alder adduct of 52, 1,3a-ethenocycl[3.3.3]azine derivative (53), which was also formed from 52 and MAC. On the other hand, treatment of 40 with DMAD in DMF afforded only 55 resulting from the reaction with two moles of DMAD, and the reaction with N-phenylmaleimide (PMI) gave rise to the Diels-Alder adduct (56). The formation of 52 from 40 and MAC can be rationalized by the initial formation of the Diels-Alder adduct (54) and subsequent extrusion of an acetonitrile molecule by the retro Diels-Alder process. This is not new and convenient route for the synthesis of 52, which had been previously obtained by a troublesome

course by Farquhar and Leaver,[1c] but is also promising for the ring transformation of 1-azalogous of cycl[3.3.3]azines to the corresponding 1-deazacycl-azines. Thus we succeeded in the conversion of a 1,3,6-triazacycl[3.3.3]azine 36 to 1,6-diazacycl[3.3.3]azines, 57 and 58, by the reaction with DMAD in DMF and that in acetonitrile.[16] (Scheme IX)

In the course of our studies,[11b] we observed that the ^{1}H-nmr signals of the protons of stable 1-azacycl[3.3.3]azine derivatives (40) appear at a lower magnetic field than that of the unstable free base 4. Since these protons are affected by the electron-attracting groups, the effect can not be due to the diatropicity of 40 but is the result of partial polarization of charge in the azacyclazine nucleus, as represented by formulas 40' and 40" in Scheme X. The resonance contribution of such polarized structure must, nevertheless, be relatively small since the proton chemical shifts showed no evidence of the aromaticity which would be associated with quinolizinium system in fully polarized structures (40', 40"). As pointed out by Farquhar and Leaver, the lack of aromatic character in the stable 1-azacycl[3.3.3]azine (40) is reflected in the ease with which addition reactions occur. Especially, we think that a partial polarized structure of 40' may be an important contribution in the addition reactions of 40 with dienophiles.[4e]

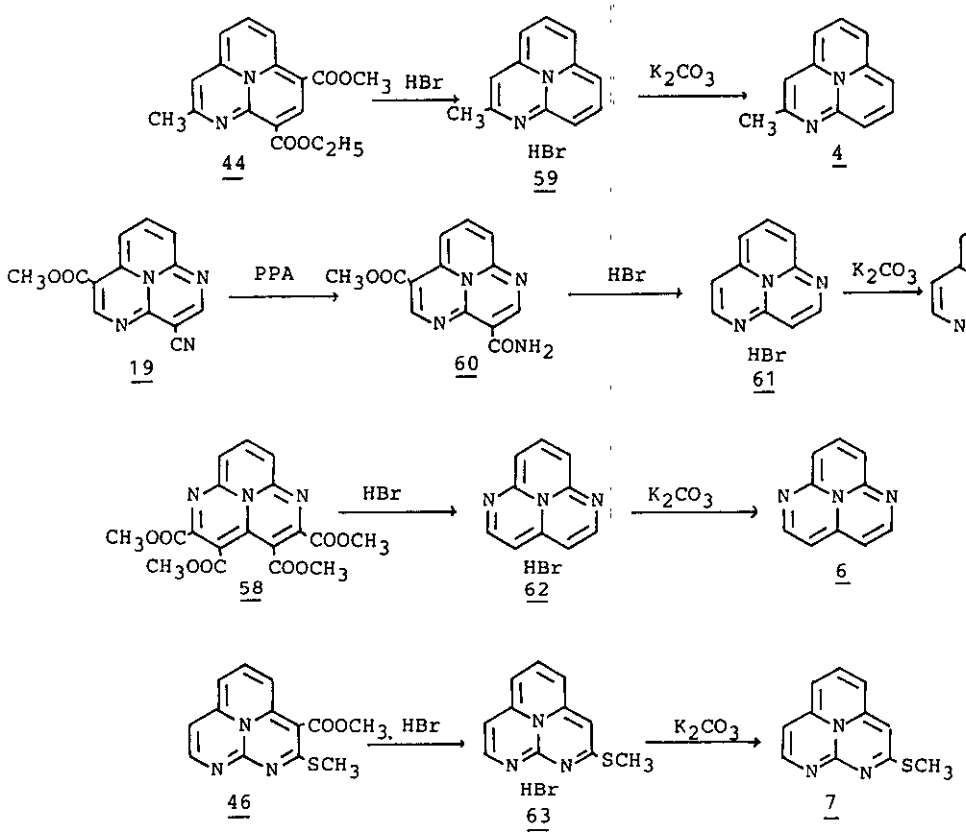


40 40' 40"

Scheme X

SYNTHESES OF PARENT AZACYCLAZINES

In order to obtain the respective parent bases of the above mentioned monoaza- and diaza-cycl[3.3.3]azine derivatives, we examined various conditions for removal of their methoxycarbonyl and cyano groups, and succeeded in isolation of 2-methyl-1-aza- (4), 1,4-diaza- (5), 1,6-diaza- (6), and 2-methylthio-1,9-diaza-cycl[3.3.3]azine (7) as an unstable compound in each case. Thus, heating in polyphosphoric acid (PPA) was effective for the conversion of a cyano group, and methoxycarbonyl and amide groups could be easily removed upon treatment with 48% hydrobromic acid under reflux to give hydrobromides (59, 61, 62, 63), which were in turn converted to the respective free bases (4, 5, 6, 7) as shown in Scheme XI.[4]



Scheme XI

Cyclic conjugated systems with 4n π electrons, which did not fit Huckel's 4n+2 rule for aromaticity, were generally classified as "pseudoaromatic". However, both theory and experiment suggest that for at least some members of the 4n series, cyclic delocarization of π electrons leads to strong destabilization of the compound, in contrast to the stabilization characteristic of aromaticity. For this reason, Breslow[17] proposed the term "antiaromatic" to describe such systems. Antiaromaticity is explained by quantum mechanical calculation at various levels of sophistication. In practice, however, the experimental evidence for antiaromaticity in cyclic conjugated compounds with 4n π electrons is very difficult and has been successful so far in only a few cases. At present, the simple and convenient method of the evidence for antiaromaticity is the measurement of ^{1}H-nmr spectra in which 4n π annulenes have a paramagnetic ring current detectable. Actually, Sondheimer[18] reported that the ^{1}H-nmr spectra of the antiaromatic 4n systems are typical of paratropic systems, consisting of

inner proton bands at low fields, and outer proton bands at high field. Unfortunately, our azacycl[3.3.3]azine series could not appear at inner proton bands in the ^{1}H-nmr spectra, and then the ^{1}H-nmr spectral data for azacyclazines (4, 5, 6, 7) and their hydrobromide salts (59, 61, 62, 63) are given in Table I and Figure 1.[4] With increasing a number of nitrogen atom in the periphery of the typical antiaromatic cyclazine; cycl[3.3.3]azine (1), the ^{1}H-nmr bands showed at the progressively lower fields, but that of the typical aromatic cyclazine; cycl[3.2.2]azine (51), showed at the lower fields than 7 ppm. Clearly, the signals of the all ring protons of azacyclazines (4, 5, 6, 7) appears between δ : 3.7-6.4 in the comparatively high magnetic fields. The results established that we did not regard this low degree of deshielding as evidence of an aromatic property in new [12]annulene heterocyclic ring systems, azacyclazines (4, 5, 6, 7). Thus, they are examples of [12]heteromonocyclic systems which, on the

Table I. ^{1}H-nmr spectral data of Azacyclazines(4,5,6,7) and Their hydrobromides(42,44,45,46)[a)]

No	C-3	C-4 or C-6		C-5	C-7 or C-9		C-8
59[b)]	4.64	5.50	6.17	6.70	5.50	6.26	6.94
4[c)]	3.71	3.84	4.28	5.64	4.24	4.54	5.40

No	C-2 or C-5		C-3 or C-6		C-7 or C-9		C-8
61[b)]	6.61	7.05	5.30	5.85	6.13	6.21	7.28
5[c)]	5.90	6.34	4.55	4.61	4.63	5.25	6.15

No	C-2 and C-6	C-3 and C-4	C-7 and C-9	C-8
62[b)]	6.95	5.25	5.92	7.20
6[c)]	6.10	3.90	4.78	6.05

No	C-3	C-4 or C-6		C-5	C-7	C-8
63[b)]	6.22	6.13	6.53	7.15	5.44	6.35
7[c)]	4.62	4.82	4.95	6.10	4.65	6.34

a) The number in each entry is the chemical shift value(δ) observed in ppm relative to tetramethylsilane. b) The solvent used was DMSO-d_6. c) The solvent used was $CDCl_3$.

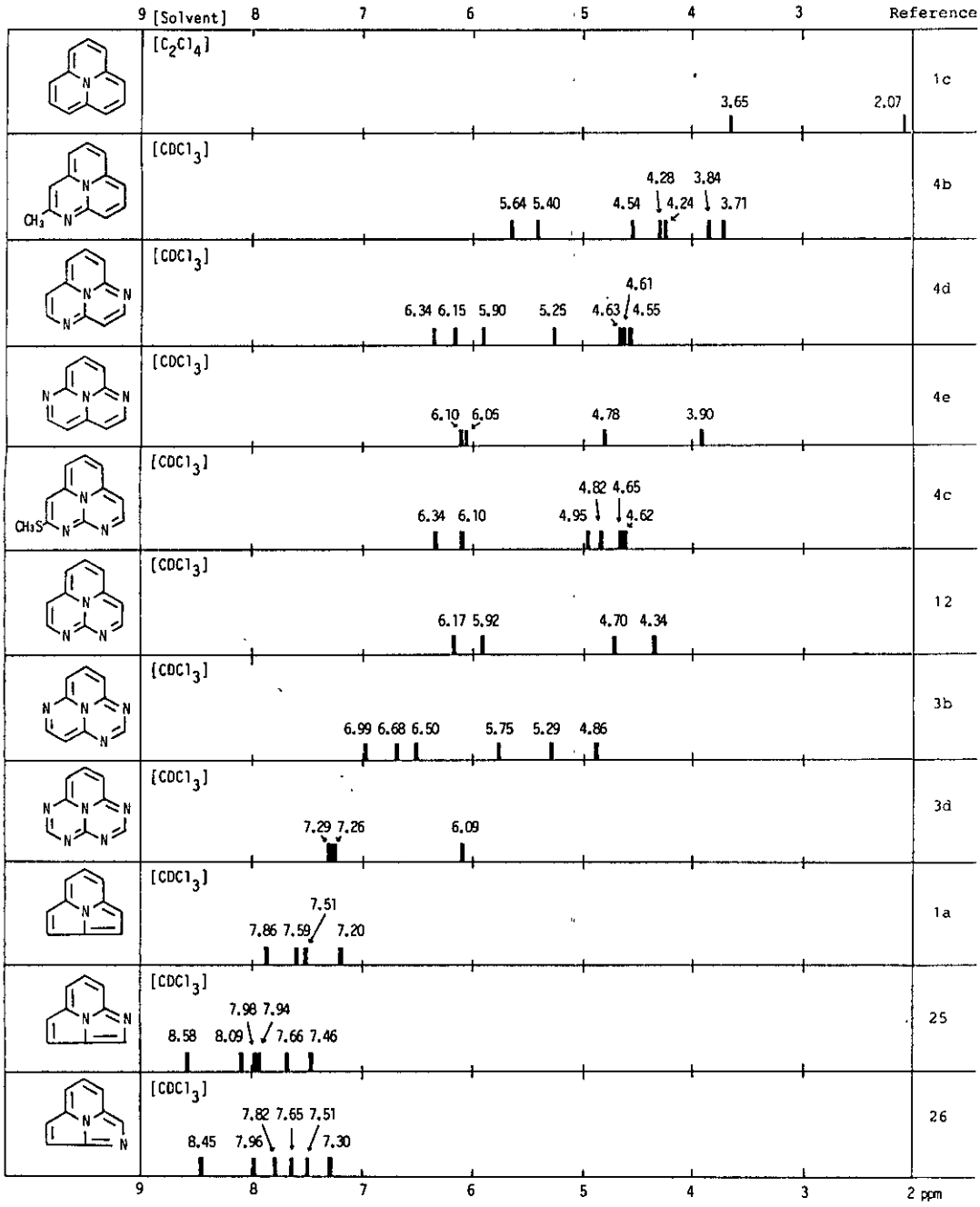


Fig. 1 ^{1}H-nmr spectral data of Cyclazine derivatives with Tetramethylsilane as internal standard.

basis of Dewar's and Breslow's concepts, may be antiaromatic. This antiaromaticity should be reflected in the existence of a paramagnetic ring current in them, when they are placed in a magnetic field. The C-3 protons in azacyclazines, for example, become more shielded by 0.9-1.6 ppm in going from hydrobromides (59, 61, 62, 63) to unstable free bases (4, 5, 6, 7). This large shielding effect can be interpreted as being the result of either one or a combination of the following two factors : an increase in the electron density at the carbon atom, and/or the presence of a paramagnetic ring current. An increase in the electron densities caused by the central nitrogen atom would not be expected to be very significant in view of the properties of diazacyclopent[fg]acenaphthylene,[19] and especially in view of the quantum chemical calculations (SCF-MO method) done by Dewar[2] and Trost[20] who have shown that there is a very small, if any, contribution to the periphery by the central nitrogen atom in cycl[3.3.3]azine (1) and by the central carbon atoms in pyracyclene. The major factor of the shielding effects in the azacyclazines (4, 5, 6, 7) is, in all probability, due to their ability to maintain a paramagnetic ring current. Finally, we suggest that comparison of the ^{1}H-nmr spectra of new cyclazines to the date in Figure 1, may provide a simple measure of the qualitative degree of aromaticity inherent in such molecules.

CONCLUDING REMARKS

In the course of our studies on the syntheses of azacyclazine systems, we found that these azacyclazines (4, 5, 6, 7) were antiaromatic, when they were placed into a magnetic field. At present, we are in view of the quantum chemical calculations in these strange azacyclazines. There are several aspects[21] of cyclazine chemistry in which only little progress has been made so far. Especially, the disadvantage is the lack of physical measurement of such as ESR, ENDOR, photoelectron spectra and X-ray analysis in these azacyclazine fields. However, the most urgent need in these fields, is to elucidate the effects of peripheral nitrogen atom in azacyclazines containing from antiaromatic azacyclazines (4, 5, 6, 7) to aromatic polyazacyclazines (2, 3).

In addition, we succeeded in the syntheses of other cyclazine systems such as 2,3,5-triphenyl-4H-cycl[3.3.2]azin-4-one,[22] [2.2.2.2](1,4)cycl[3.2.2]azinophane[23] and cyclazinophane.[24] Furthermore, we are in the process of preparing other cyclazines with the hope of expanding understanding of these interesting compounds.

ACKNOWLEDGMENT

It's a pleasure to acknowledge the contribution of all our workers, mentioned in the references. Thanks are also due to Professor M. Hamana for encouragement and stimulating discussions.

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