Competitive Diene and Dienophilic Character of 2,3,4,5,5-Pentachloro-1-azacyclopentadiene in Diels-Alder Reaction with Conjugated Dienes[1]

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Received December 16, 1980

The reaction of the title azadiene 1 with cyclopentadiene via the ene moiety of 1 as the dienophile yielded 5 quantitatively. Chlorination of 5 gave rise to a single dichloro derivative 6. The cycloadduct 7, obtained from reacting cyclopentene with 1, was found to be different from 9, the hydrogenation product of 5, thus eliminating any product which requires 1 behaving as a diene. Also, the use of ^{15}N label in this sequence rules out **5a**, an imine isomer, as a candidate. However, the existence of the diene character of 1 in reaction with a conjugated diene was found upon heating 1 with cyclohexadiene. Two adducts were isolated in a ratio of 4:1. The minor product was assigned structure 12 which is similar to 5 derived from 1. The cyclohexene adduct of 1 was found to be identical with 14, the dihydro derivative of the major adduct from cyclohexadiene. The latter is assigned structure 10, analogous to the regiospecific formation of *endo*-5-substituted-2-azanorbornenes from 1 and olefins such as styrene. In the case of an acyclic diene addend such as *trans*-piperylene, 1 behaves only as a diene, yielding the adduct 16 only. It appears that the steric factor is an important one in deciding the diene or dienophilic reactivity of 1.

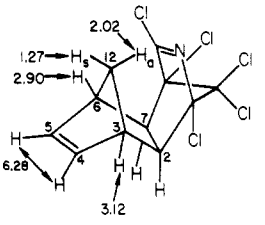
Introduction

The title azadiene 1 has been used as a Diels-Alder diene addend.[1] The cycloadducts are not the expected bridgehead azanorbornenes[1a] but the 2-azabicyclo[2.2.1]hept-2-enes.[1b] It appears that 1 has undergone a chlorine [1,5] sigmatropic shift to form the 2-azadiene **1a** prior to reaction with olefins. Since C=N bonds of Schiff bases and imino chlorides and C=C bonds in conjugation with a carbonyl group have served as excellent dienophiles in Diels-Alder reaction,[2] the imine and ene moieties of the 1-azadiene 1 and 2-azadiene **1a** may compete with their own diene system in a [4 + 2] cycloaddition reaction. Such competition will be manifested in new structures for the polycyclic amine adducts. As part of our continuing program to study the reactivities and properties of α- and β-pyrrolenines (cyclic 1- and 2-azadienes), we have reacted azadiene 1 with cyclopentadiene, cyclohexadiene, and *trans*-piperylene. With cyclopentadiene, 1 behaves only as a dienophile via the ene moiety. With *trans*-piperylene, the mode of cycloaddition is reversed, and the azadiene 1 reacts exclusively as a diene of the rearranged **1a**. The reaction with cyclohexadiene yields both. This paper describes the versatile azadiene-diene system and the comparative diene and dienophilic character of the title azadiene.

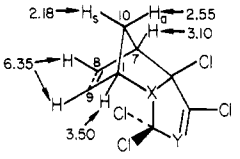
Results and Discussion

Azadiene-Cyclopentadiene Reaction. The first step in the synthesis of the well-known insecticide chlordane involves mixing hexachlorocyclopentadiene (2) with cyclopentadiene to produce chlordene (3).[3] Analogously, when 2,3,4,5,5-pentachloro-1-azacyclopentadiene (1) was mixed with cyclopentadiene monomer at room temperature, the reaction mixture solidified on standing to yield a single adduct quantitatively, which analyzed correctly for $C_9H_6Cl_5N$. Chlordene (3) and the azadiene adduct showed similar IR spectra: 3 (νHC=CH 1600 cm^{-1}, νClC=CCl 1400 cm^{-1}) and adduct (1600, 1450 cm^{-1}). However, the ^1H NMR spectrum of chlordene (3) is enormously more complex and different in chemical shifts from that of the adduct, which appears to fit a norbornene moiety as found in the previously studied azaaldrin.[1] Thus, the vinylic protons of azaaldrin [δ 6.28 (m)] and the adduct [δ 6.35 (m)] are very similar and quite unlike those of chlordene [3, δ 5.70 (m)]. In the case of azaaldrin, the δ 2.02 broadened doublet which is assigned to the bridge proton H_a anti to the vinyl hydrogens was resolved by means of double resonance to decouple the long-range w-shaped coupling mechanism. Thus, the anti bridge proton H_a of the adduct at δ 2.55 was decoupled from the vinyl protons to resolve the broadened doublet at δ 2.55 into a doublet of triplets (J = 13, 1 Hz). The syn bridge proton H_s, lacking the long-range w-shaped broadening effect, remained as a doublet of triplets at δ 2.18 (J = 13, 1 Hz) in the decoupled spectrum. On the other hand, the H_a of azaaldrin at δ 1.27 is a broadened doublet due to the w-shaped couplings with the endo hydrogens at C-2,7. The above assignments as shown in Chart I are therefore compatible with structures 4 and 5. It should be noted that both H_a's in the two aza adducts appear at lower field than the syn protons, the reverse being true for norbornene itself as shown by Marchand and Rose.[4] This may be due to

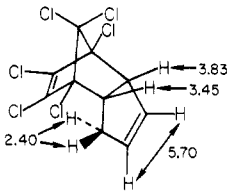
Chart I. ^1H NMR Chemical Shifts and Assignments for Azaaldrin, Chlordene (3), and the Adduct



azaaldrin



4, X = N; Y = CCl
5, X = CCl; Y = N



chlordene, 3

(1) This is Part 6 of the Azadiene Chemistry series. (a) Part 4: C. M. Gladstone, P. H. Daniels, and J. L. Wong, *J. Org. Chem.*, **42**, 1375 (1977). (b) Part 5: P. H. Daniels, J. L. Wong, J. L. Atwood, L. G. Canada, and R. D. Rogers, *ibid.*, **45**, 435 (1980).

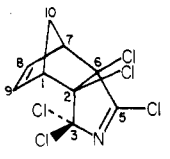
(2) J. Hamer, Ed., "1,4-Cycloaddition Reactions", Academic Press, New York, 1967, p 127.

(3) S. H. Herzfeld, R. E. Lidov, and H. Bluestone, U.S. Patent 2606910 (1953); *Chem. Abstr.*, **47**, 8775*b* (1953).

(4) A. P. Marchand and J. E. Rose, *J. Am. Chem. Soc.*, **90**, 3724 (1968).

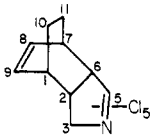
0022-3263/81/1946-3036$01.25/0

Chart II. ^{13}C NMR Chemical Shifts (δ) and Assignments for 5 and 12



5

C-1	52.0
C-2	85.93
C-3	109.33
C-5	166.84
C-6	88.63
C-7	56.58
C-8	136.90
C-9	137.39
C-10	60.15



12

C-1	42.34
C-2	81.18
C-3	113.60
C-5	166.84
C-6	83.07
C-7	44.07
C-8	130.89
C-9	135.87
C-10	25.65
C-11	15.48

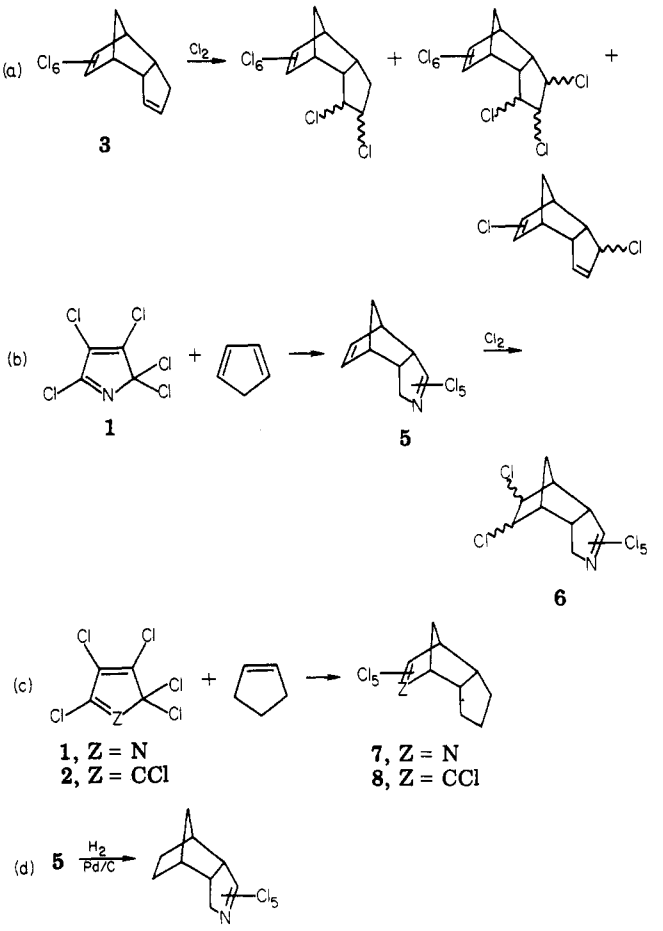
either the neighboring chloro and nitrogen or the dichloro groups deshielding the anti hydrogen while pushing the syn hydrogen into the shielding domain of the vinyl.

Structure **4** is based on the imine moiety of **1** reacting as a dienophile while **5** is derived from the ene of **1**. Both structures are shown in the endo configuration in agreement with the endo rule for the Diels–Alder reaction and our previous observations.[1] The structure is further elucidated by examining the ^{13}C NMR spectrum of the adduct. In Chart II are shown the assignments of the carbon resonance of the adduct in terms of structure **5**. It is apparent that the low-field signal of δ 166.84 (ClC=N) cannot be accommodated by **4**.

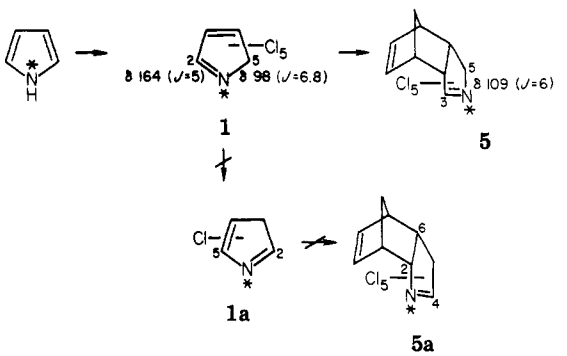
Furthermore, Scheme I summarizes some pertinent structural assignments and chemical evidences in support of **5**. It has been reported that chlorination of chlordene (**3**) yielded a complex mixture of products (mono-, di-, and trichlorinated as well as stereoisomers) as indicated by column chromatography[5a] and gas chromatography.[5b] The azadiene adduct yielded only a single dichloro derivative **6**, which analyzed correctly for $C_9H_6Cl_7N$. This chlorination product was found to be homogeneous by GLC and HPLC. Upon reaction of **1** with cyclopentene, a single adduct **7** was obtained: ^1H NMR δ 3.36 (m, 2 H), 1.80 (m, 6 H). A similar spectrum was observed for the similarly prepared carbon analogue **8**: δ 3.40 (m, 2 H), 1.76 (m, 6 H). However, hydrogenation of **5** yielded **9**, whose proton spectrum [δ 2.56 (s, 1 H), 2.75 (s, 1 H), 2.95 (s, 1 H), 1.70 (m, 5 H)] does not match that of **7**, hence eliminating the structure which requires **1** behaving as a diene.

However, the possibility exists that the 1-azadiene **1** rearranges to 2-azadiene **1a** even at room temperature prior to reacting with cyclopentadiene. Thus, ^{15}N label was introduced into this reaction sequence to examine the formation of the isomeric cycloadduct **5a**. Scheme II shows the results of this isotope study. When a pyrrole mixture, ^{14}N–^{15}N (6:4), was treated with sulfuryl chloride in the usual manner,[1] the pentachloro derivative **1** was isolated, exhibiting the same properties as the unlabeled one. Two distinguishing features were noticed in the otherwise identical ^{13}C NMR spectrum: the C-2 signal at δ 163.9 was significantly broadened (J_{C-N} = 5 Hz, estimated at half-width) and the C-5 signal at δ 98.3 was split into a distinct doublet (J_{C-N} = 6.8 Hz). The cyclopentadiene adduct of the above showed a proton-decoupled ^{13}C NMR spectrum which is singularly compatible with structure **5**. The lowest

Scheme I



Scheme II



field resonance at δ 166.8, assigned to C-3, appeared as a doublet (J_{C-N} = 4.9 Hz), and the signal at δ 109.2, assigned to the *gem*-dichloro carbon[1b] C-5, was the remaining doublet (J_{C-N} = 6 Hz). If structure **5a** were correct, the singlets in the region of δ 86–89 for CCl, assignable to C-2,6 in **5a**, would become a doublet. Furthermore, the ^1H NMR spectrum of the ^{15}N-labeled adduct was found to be superimposable with that of the regular adduct, attesting to the separation of the nitrogen from all hydrogens by more than three bonds as in **5**.

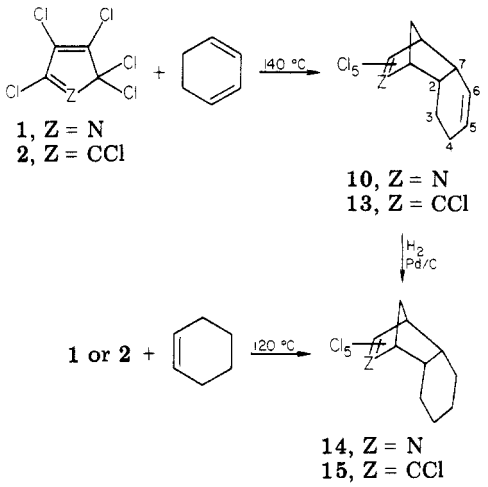
Azadiene Behaving as Diene and Dienophile in Reaction with Cyclohexadiene. Since pentachloro-1-azacyclopentadiene (**1**) behaves as a diene in reactions with olefins such as norbornadiene, styrene, etc.,[1] its dienophilic reactivity with cyclopentadiene is unique. In order to test the competitiveness of the diene vs. dienophilic character of **1**, it was allowed to react with other conjugated dienes.

(5) (a) R. B. March, *J. Econ. Entomol.*, **45**, 452 (1952); (b) K. H. Buchel, A. E. Ginsberg, and R. Fischer, *Chem. Ber.*, **99**, 416 (1966).

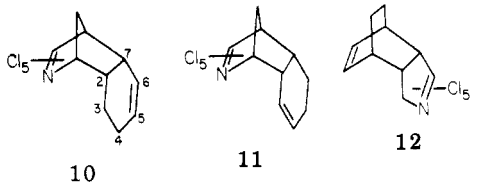
Table I. ^{1}H NMR Spectral Data of Piperylene Adducts (δ_{Me_4Si} 0)

	16		17		
H	δ	J, Hz	δ	J, Hz	Δδ(N–CCl)
5 exo	3.28	$J_{5x,6e} = -3.88$	3.29	$J_{5x,6e} = 4.0$	−0.01
6 endo	2.08	$J_{6e,6x} = -12.6$	1.85	$J_{6e,6x} = -12.5$	0.23
6 exo	2.79	$J_{6x,5x} = 8.47$	2.67	$J_{6x,5x} = 8.5$	0.12
8	5.10	$J_{8,5x} = 7.92$	5.00	$J_{8,5x} = 8.5$	0.10
9	5.75	$J_{9,8} = 14.8$	5.67	$J_{9,8} = 15.5$	0.08
10	1.72	$J_{10,9} = 6.16$	1.69	$J_{10,9} = 6.0$	0.03

Scheme III

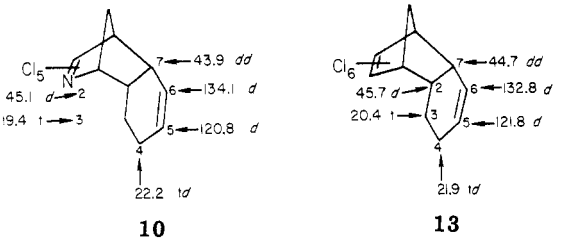


With cyclohexadiene, the three likely Diels–Alder products are **10**–**12**. When **1** was allowed to react with cyclo-

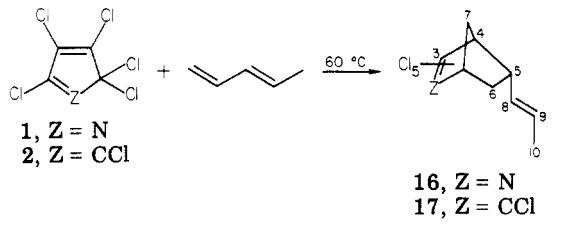


hexadiene in toluene between 80 and 140 °C for 24 h, two adducts were isolated in a ratio of 4:1. The minor adduct was assigned structure **12** on account of the close similarity of its ^{13}C NMR spectrum to that of the cyclopentadiene adduct **5**. The chemical shift assignments based on **12** are also shown in Chart II for comparison. A clue to the identity of the major product came from the carbocyclic diene **2** yielding a similar product with cyclohexadiene. Both of these adducts were reduced cleanly to the dihydro derivatives which were found to be identical with the cycloadducts of cyclohexene with **1** and **2**. These observations are shown in Scheme III. In reference to the carbocyclic series, the cyclohexadiene adduct is **13** and the dihydro derivative is **15**. The azadiene adduct of cyclohexene must be **14**; hence the major adduct of **1** is either **10** or **11**. Structure **11** is not the expected product based on our previous observations[1] on regiospecific formation of *endo*-5-substituted-2-azanorbornenes from **1** and monosubstituted olefins such as styrene. The structural assignment of **10** is further based on the ^{13}C NMR analysis as shown in Chart III. The gated decoupled spectrum of known[6] **13** reveals fine splittings for the resonances at δ 21.9 and 44.7. These long-range couplings can be attributed to the adjacent 5,6-vinyl hydrogens, thus placing C-4 and C-7 at δ 21.9 and 44.7, respectively. In turn, this allows the placement of C-2 and C-3 at δ 45.7 and 20.4, respectively. The olefinic carbons are assigned on the basis of the most highly substituted carbon appearing at lowest field.[7] Analogously, C-4 and C-7 in **10** show similar fine splittings and thus their assignments are made as shown.

Chart III. ^{13}C NMR Data (δMe_4Si 0) for the Cyclohexadiene Adducts 10 and 13

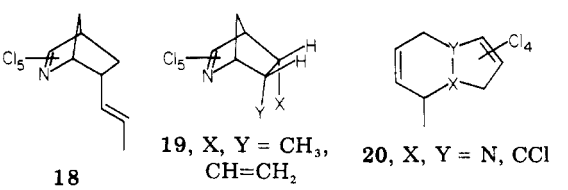


Scheme IV



Azadiene as a Diene in Reaction with *trans*-Piperylene. *trans*-Piperylene was found to react with azadiene **1** as shown in Scheme IV. In this case, only one cycloadduct was produced according to GLC analysis, and it was assigned structure **16** based on ^{1}H NMR data as compiled in Table I.

The carbon analogue **17**, which was prepared by Cárdenas,[6] starting with hexachlorocyclopentadiene (**2**) under similar conditions, was used for spectral comparison. The three protons on C-5,6 and the vinyl hydrogens of **16** form a coupled ABCXY pattern, and the spectrum was analyzed by using the iterative computer program LAOCN 3 executed on a Dec 1080 computer. The chemical shifts and coupling constants thus obtained and those reported by Cárdenas for **17** are shown in Table I. The Δδ(N–CCl) values for H-5$_{exo}$, H-6$_{exo}$, and H-6$_{endo}$ are in agreement with those observed for the series of *endo*-5-substituted-2-azanorbornenes[1b] and hence incompatible with structure **18**, a double bond positional isomer of **16**. The other two conceivable structures are **19** and **20**. Structure **19** may



be derived from reacting the trans-disubstituted double bond in piperylene with **1**. However, various attempts at

(6) C. G. Cárdenas, *J. Org. Chem.*, **36**, 1631 (1971).

(7) L. P. Lindeman and J. Q. Adams, *Anal. Chem.*, **43**, 1245 (1971).

using trans-disubstituted olefins as dienophiles gave no adducts with 1. Structure **20** is an adduct involving piperylene as a diene. Considering the necessary cisoid conformation which is unlikely for *trans*-piperylene, formation of **20** as the cycloadduct is not deemed plausible. Clearly, the ^{1}H NMR spectrum observed for the azadiene adduct is incompatible with either **19** or **20**.

Conclusion. In the Diels–Alder reaction of pentachloroazacyclopentadiene, there can be two starting materials, 1 and **1a**, where 1 behaves as a dienophile but not as a diene, while the opposite is true for **1a**. For cycloadditions analogous to the inverse electron demand on the dienophiles by hexachlorocyclopentadiene (2), reactions of the title azadiene with conjugated dienes most likely involve the LUMO of 1 or **1a** and HOMO of the enes, following the FMO (frontier molecular orbital) control mechanism.[8] The ionization potentials (HOMO energies) for cyclopentadiene, cyclohexadiene, and piperylene (8.55,[9] 8.40,[10] and 8.56 eV,[9] respectively) are very similar, hence the LUMO–HOMO energy gap cannot be the cause for the variation of cycloadducts among the enes. However, cyclopentadiene is a much more reactive diene, undergoing [4 + 2] dimerization spontaneously with half-life of 25 h at 25 °C, whereas both cyclohexadiene and piperylene form dimers under strenuous conditions[11] (200 °C, 24 h). Thus, the efficiency of orbital overlap may be an important factor. It is conceivable that orbital overlap between cyclopentadiene as a diene and the ene portion of azadiene 1 as the dienophile is maximized relative to the reversed arrangement. But, for steric reasons, this arrangement is less favored in comparison with that involving azadiene 1 as diene and one ene portion of cyclohexadiene as dienophile. This steric argument is further intensified in the case of *trans*-piperylene which lacks the cisoid arrangement to compete as a diene. Hence, the sluggishness of 1 in the latter two cases gives way to its conversion to **1a**.[12] The apparently more kinetically active **1a** isomer takes over as the diene addend. It is interesting to note that in each reaction of 1 and **1a**, the nitrogen atom appears to stay as far away as possible from the new bond formation site.

Experimental Section

^{1}H NMR spectra were obtained by using a Varian A-60A spectrometer or a Perkin-Elmer R-12A spectrometer. ^{13}C NMR spectra were obtained on a Bruker WH-90DS spectrometer or a Varian CFT-20 spectrometer, courtesy of the University of Kentucky, Lexington, Kentucky. NMR samples were prepared in $CDCl_3$ containing 1% tetramethylsilane (δMe_4Si 0). IR spectra were run on a Beckman IR-12. UV spectra were obtained with a Cary 14 spectrophotometer. GLC analyses were performed on a Hewlett-Packard 5750B chromatograph with dual flame-ionization detector. All analyses were performed on a 6 ft × 0.125 in. aluminum column packed with 20% SE-30 on Chromosorb W AW DMCS and at 30 mL/min of nitrogen, T_I = 270 °C, T_D = 250 °C, T_C = 200 °C (unless otherwise noted). Melting points are uncorrected. Combustion analyses were performed by either Midwest Microlab, Ltd., Indianapolis, IN, or M-H-W Laboratories, Garden City, MI. ^{15}N-Pyrrole (95%) was purchased from Merck Co.

2,3,3,5,6-Pentachloro-4-azatricyclo[5.2.1.0^{2,6}]deca-4,8-diene (5). To 5 g (21 mmol) of 2,3,4,5,5-pentachloro-1-azacyclopentadiene (1) was added 1.37 g (1 equiv) of freshly distilled cyclopentadiene monomer, and the reaction mixture stirred for 17 h at 22–24 °C. Another 0.69 g (0.5 equiv) of cyclopentadiene was added and stirring continued for another 24 h. The solid, red-green mass showed quantitative reaction via GLC analysis. Dicyclopentadiene was removed in vacuo and the residue chromatographed on 150 g of silica gel eluted with hexane. The eluent was evaporated, and the pale yellow residue recrystallized from aqueous ethanol to yield 5.83 g (90.0%) of white, crystalline **5**: mp 173–74.5 °C; ^{1}H NMR δ 6.35 (m, 2 H), 3.5 (m, 1 H), 3.1 (m, 1 H), 2.55 (d, J = 13 Hz, 1 H), 2.18 (dt, J = 13, 1 Hz, 1 H).

Anal. Calcd for $C_9H_6Cl_5N$: C, 35.35; H, 1.96; N, 4.58. Found: C, 35.36; H, 1.94; N, 4.46.

1,7,8,10,10-Pentachloro-2-azatricyclo[5.2.1.0^{2,6}]dec-8-ene (7). To 1 g (4.2 mmol) of 1 was added 0.355 g (1.25 equiv) of cyclopentene. The reaction mixture was heated at 60 °C for 54 h in a sealed tube. GLC analysis showed 91% reaction. After evaporation in vacuo the dark brown reaction product was column chromatographed on 25 g of silica gel and eluted with hexane. The eluent was evaporated, and the off-white solid was recrystallized from aqueous ethanol and sublimed at 60 °C (10 torr) to yield 1.01 g (78.2%) of white, crystalline **7**: mp 80–81 °C; NMR as described in text.

Anal. Calcd for $C_9H_8Cl_5N$: C, 35.12; H, 2.60; N, 4.55. Found: C, 35.09; H, 2.70; N, 4.50.

2,3,3,5,6-Pentachloro-4-azatricyclo[5.2.1.0^{2,6}]dec-4-ene (9). **5** (250 mg, 0.8 mmol) was dissolved in 20 mL of ethyl acetate and 5 mg of 5% Pd/C was added. This mixture was hydrogenated at 15 psig in a Parr pressure reactor for 5 min. The solution was filtered and the solvent evaporated. The off-white residue was recrystallized from aqueous ethanol and sublimed at 60 °C (0.5 torr) to yield 238 mg (94.6%) of white, crystalline **9**: mp 194–195 °C; NMR as described in text.

Anal. Calcd for $C_9H_8Cl_5N$: C, 35.12; H, 2.60; N, 4.55. Found: C, 35.45; H, 2.77; N, 4.33.

1,8,9,11,11-Pentachloro-10-azatricyclo[6.2.1.0^{2,7}]undeca-5,9-diene (10) and 2,3,3,5,6-Pentachloro-4-azatricyclo[5.2.2.0^{2,6}]undeca-4,8-diene (12). To 2 g (8.3 mmol) of 1 was added 0.960 g (1.25 equiv) of cyclohexadiene. The mixture was heated at 80–140 °C for 24 h. The green-black residue was column chromatographed on 55 g of silica gel and eluted with hexane and chloroform–hexane (4:6). The first 15 hexane fractions were combined and evaporated, and the pink, solid residue was recrystallized from aqueous ethanol and sublimed at 55 °C (0.2 torr) to yield 1.56 g (58%) of white, crystalline **10**: mp 56–58 °C; ^{1}H NMR δ 6.10 (m, 1 H), 5.82 (m, 1 H), 3.20 (m, 2 H), 1.95 (m, 4 H).

Anal. Calcd for $C_{10}H_8Cl_5N$: C, 37.56; H, 2.50; N, 4.38. Found: C, 37.54; H, 2.48; N, 4.31.

Fractions 16–20 obtained from chloroform–hexane as eluent were combined and evaporated, and the residue was recrystallized from aqueous ethanol to yield 0.38 g (14%) of white, crystalline **12**; ^{1}H NMR δ 6.40 (m, 2 H), 3.48 (m, 1 H), 3.14 (m, 1 H), 2.24 (m, 2 H), 1.35 (m, 2 H).

1,8,9,11,11-Pentachloro-10-azatricyclo[6.2.1.0^{2,7}]undec-9-ene (14). A. To 150 mg (0.47 mmol) of **10** in 6 mL of ethyl acetate was added 5 mg of 5% Pd/C and the mixture was hydrogenated at 20 psig for 3 h in a Parr pressure reactor. After filtration and evaporation of the solvent the residue was recrystallized from aqueous ethanol and sublimed at 60 °C (0.2 torr) to yield 141 mg (93%) of crystalline **14**: mp 116–117 °C; ^{1}H NMR δ 2.72 (m, 2 H), 1.55 (m, 8 H).

B. To 2 g (8.3 mmol) of 1 was added 0.823 g (1.2 equiv) of freshly distilled cyclohexene, and the mixture was heated in a sealed tube at 110 °C for 36 h. After being heated, the black reaction mixture was suspended in hexane, filtered, and column chromatographed on 45 g of silica gel in hexane. The eluent was evaporated, and the pale orange residue recrystallized from aqueous ethanol and sublimed at 70 °C (0.3 torr) to yield 0.57 g (58.6%) of white, crystalline **14**, mp 116–117 °C.

Anal. Calcd for $C_{10}H_{10}Cl_5N$: C, 37.32; H, 3.11; N, 4.35. Found: C, 37.26; H, 3.06; N, 4.35.

***endo*-5-(*trans*-1-Propenyl)-3,4,7,7-pentachloro-2-azabicyclo[2.2.1]hept-2-ene (16).** To 1.5 g (5.5 mmol) of 1 was added 0.448 g (1.2 equiv) of *trans*-1,3-pentadiene (*trans*-piperylene). The reaction mixture was heated at 60 °C in a sealed tube for 48 h. The dark brown reaction mixture was column chromatographed on 30 g of silica gel and eluted with hexane. The eluent was

(8) K. N. Houk, *Acct. Chem. Res.*, 8, 361 (1975).
(9) M. J. S. Dewar and S. D. Worley, *J. Chem. Phys.*, 50, 654 (1969).
(10) D. A. Demeo and M. A. El-Sayed, *J. Chem. Phys.*, 52, 2622 (1970).
(11) D. Valentine, N. J. Turro, Jr., and G. S. Hammond, *J. Am. Chem. Soc.*, 86, 5202 (1964).
(12) A similar conversion was reported by M. E. Jung and J. J. Shapiro, *J. Am. Chem. Soc.*, 102, 7862–7866 (1980).

evaporated, and the off-white residue recrystallized from aqueous ethanol and sublimed at 60 °C (10 torr) to yield 1.47 g (81%) of white, crystalline **16**: mp 38–40 °C; ^{1}H NMR as shown in Table I.

Anal. Calcd for $C_9H_8Cl_5N$: C, 35.12; H, 2.60; N, 4.55. Found: C, 35.09; H, 2.70; N, 4.91.

Acknowledgment. This investigation was supported in part by NIH Grant GM 19212 for which we are grateful. The National Science Foundation Research Instrument Grant CHE 76-05683 for the purchase of the Bruker WH-90DS FT-NMR spectrometer is gratefully acknowledged. We also thank Dr. J. T. Joseph for the operation of the spectrometer.

Registry No. 1, 57802-40-1; 5, 65392-20-3; 7, 77630-22-9; 9, 77630-23-0; 10, 77630-24-1; 12, 77630-25-2; 14, 77647-94-0; 16, 77630-26-3; cyclopentadiene, 542-92-7; cyclopentene, 142-29-0; cyclohexadiene, 592-57-4; cyclohexene, 110-83-8; *trans*-piperylene, 2004-70-8.

Steric and Conformational Effects in Nicotine Chemistry[1]

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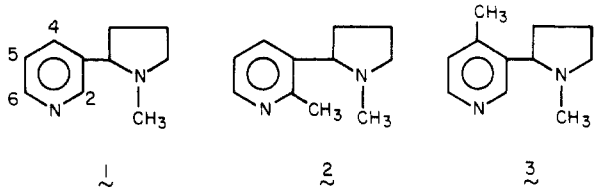
Received October 8, 1980

The stereoselectivity of iodomethylation of nicotine and seven nicotine analogues having pyridine alkyl groups was determined by using ^{13}C NMR. Alkylation at the pyridine (N) and at the pyrrolidine (N′) nitrogens was observed. Two modes of N′-iodomethylation occur, cis and trans to the pyridine ring. N′-Iodomethylation occurs regioselectively cis to the pyridine ring for all compounds examined. The N/N′ and N'_{cis}/N'_{trans} ratios for the nicotinoids were evaluated with regard to (1) the orientation of the *N′*-methyl group in the free base, (2) conformational properties of the pyridine ring with respect to the pyrrolidine ring, and (3) steric hindrance and buttressing effects on the pyridine nitrogen. The Curtin–Hammett principle and the Winstein–Holness equation are used to analyze these reactions.

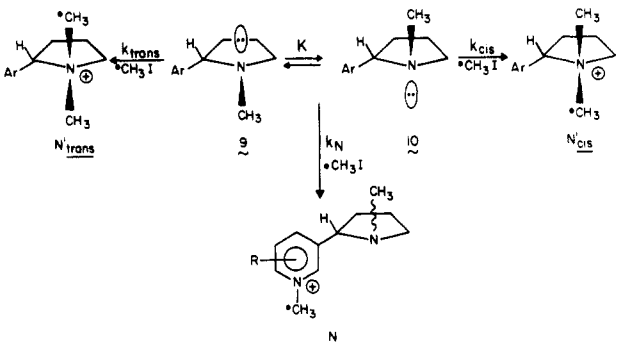
Recently, we and others have observed that 2-methylnicotine (**2**) and 4-methylnicotine (**3**) were both significantly less active than nicotine (**1**) in a variety of pharmacological tests, while 6-methylnicotine retained full nicotinic activity.[1,2,3a,b] The pyridine methyl groups in **2** and **3** are likely not only to alter the reactivity of their respective pyridine nitrogen atoms but also to affect the compounds' ground-state conformational profile. As part of our studies on the pharmacology of nicotine and related compounds, we have prepared[4] a large number of pyridine substituted nicotinoids (**2–8**). We now report results on the iodomethylation of these nicotinoids aimed at evaluating the effect of structure and conformation on nitrogen reactivity in these heterocycles.



Results and Discussion

Each compound was alkylated with 0.7–0.8 equiv of $^{13}CH_3I$ at 0.1–0.6 M in acetonitrile-d_3 6–15 times. Long pulse delays and small pulse flip angles were used in obtaining ^{13}C NMR spectra of the alkylation products in order to minimize the effect of differences in ^{13}C relaxation times (see Experimental Section for complete details).[5] Figures 1 and 2 show ^{13}C and ^{1}H NMR spectra of the total reaction mixture from the alkylation of nicotine with $^{13}CH_3I$. Figure 1 shows three resonances, the relative ratios of which relate directly to the relative rates of the three modes of nicotine alkylation: N (pyridine), N'_{cis} (pyrrolidine attack cis to the pyridine ring), and N'_{trans} (pyrrolidine attack trans to the pyridine ring) (cf. Scheme I). In all cases, the pyridine quaternary methyl carbon appears as a broad singlet while the pyrrolidine quaternary methyl carbons appear as triplets because of ^{14}N coupling of the more symmetrical quaternary nitrogen of the dimethylpyrrolidinium iodide.

Scheme I



A definitive assignment of these methyl resonances was made on the basis of a series of nuclear Overhauser enhancement (NOE) experiments. Table I indicates the results of one such experiment. For example, irradiation of the N'_{cis}-methyl protons of purified *N′*-methylnicotinium iodide in acetonitrile at δ 2.94 results in enhancements of the H_2 and H_4 pyridine protons as well as a small en-

(1) For the previous paper in this series, see: Seeman, J. I.; Dwyer, W. R. Jr.; Osdene, T. S.; Sanders, E. B.; Secor, H. V., submitted for publication.

(2) Sanders, E. B.; Secor, H. V.; Seeman, J. I. U.S. Patent 4 155 909, 1979; U.S. Patent 4 220 781, 1980.

(3) (a) Haglid, F. *Acta Chem. Scand.* **1967**, *21*, 329. (b) Haglid, F. *Acta Pharm. Suec.* **1967**, *4*, 117. (c) Leete, E.; Leete, S. A. S. *J. Org. Chem.* **1978**, *43*, 2122.

(4) (a) Seeman, J. I. *Synthesis*, **1977**, 498. (b) Sanders, E. B.; Secor, H. V.; Seeman, J. I. *J. Org. Chem.* **1978**, *43*, 324. (c) Seeman, J. I.; Secor, H. V.; Whidby, J. F.; Bassfield, R. L. *Tetrahedron Lett.* **1978**, 1901. (d) Sanders, E. B.; Secor, H. V.; Seeman, J. I. *J. Org. Chem.* **1976**, *41*, 2658.

(5) Crowley, P. J.; Robinson, M. J. T.; Ward, M. G. *Tetrahedron*, **1977**, *33*, 915.

0022-3263/81/1946-3040$01.25/0