Nuclear Magnetic Resonance Spectra of Bridgehead Diazabicyclo[3.3.1]nonanes and -[3.2.1]octanes and Adamantanes. Effects of Alkyl Substitution

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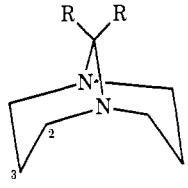
Abstract: The nmr spectra of the title compounds are presented and discussed. The *R*-value criterion for conformation of the bicyclic materials indicates substantial flattening of the hexahydropyrimidine rings, ψ (nmr) being under 50° for both bicyclo[3.3.1]nonyl and -[3.2.1]octyl systems. The effect of alkyl substitution upon chemical shift is discussed.

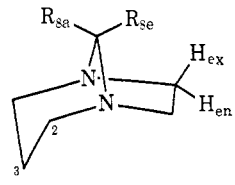
The fact that axial and equatorial hydrogens of six-membered rings have, in general, different nmr chemical shifts has allowed a great deal of conformational analysis work to be done on such systems.[1] The effects of heteroatomic ring substitution have received particular study, and one useful result of this work has been the observation of a large upfield shift of an axial hydrogen which is antiparallel to an adjacent axial lone pair, such as that of nitrogen.[2] We wish to report nmr studies of several compounds containing hexahydropyrimidine rings which are constrained by bicyclic structures to have both nitrogen lone pairs equatorial. We suggest that these compounds are of particular interest because they show detectable effects of magnetic anisotropy of the nitrogen atoms, which have not been pointed out previously.

Results

The bridgehead diazabicyclic compounds **1–5** were prepared by condensation of bishomopiperazine or homopiperazine with the appropriate carbonyl compound. We did not observe any of the more strained



1, R = H
2, R, R = $(CH_2)_5$

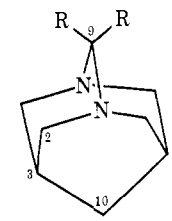


3, R = H
4, R, R = $(CH_2)_5$
5, R_{8a} = H; R_{8e} = CH_3

axial C_8-methyl isomer of **5** from the condensation of homopiperazine with acetaldehyde. The hexahydropyrimidine rings of **1–5** are all expected to exist in flattened chair conformations by analogy with the parent hydrocarbons. Both X-ray structure determinations[3,4] on derivatives of bicyclo[3.3.1]nonane and calculations[5,6] on the hydrocarbon show it to exist in a flattened chair,chair conformation, and calculations[5] on bicyclo[3.2.1]octane predict it to also be in a flattened chair conformation. The nmr spectra of **1–5** (Tables I and II) bear out this expectation, since the similarity of observed *J* values for the entire set shows they are in the same gross conformation, and compounds **2** and **4** are constrained to chair conformations by the pentamethylene substituents. For compound **3**, benzene-d_6 solvent was required to separate the H_{8e} and H_{2a} signals and allow measurements of the couplings. The long-range couplings reported were verified by decoupling. The five bond J_{8e-3e} is geometrically similar to cases reported in the literature;[7,8] J_{8e-2e} and J_{8a-en} have the familiar "W-plan" geometry.

The nmr spectrum of **5** was consistent with the H_{8a},-Me_{8e} isomer drawn, since saturation of the C_6–C_7 hydrogens sharpened the H_8 signal, and saturation of H_{3e} had no effect. The J_{2e-3e} coupling was unusually small in this series, and only resolved for **3** and **5**, although broadening was observed for the other compounds.

We also investigated the bispidine–formaldehyde and -cyclohexanone adducts **6** and **7** to use in chemical shift



6, R = H
7, R, R = $(CH_2-)_5$

comparisons. The spectral data are summarized in Table III. There was too much substitution to use couplings to assign chemical shifts to H_{2a} and H_{2e} of **7**, but the assignment given is the only one consistent with compounds **1–5**.

Discussion

Conformations of 1–5. The measurement of couplings at C_2 and C_3 for **1–5** allows application of the *R*-

(1) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965.
(2) (a) J. B. Lambert and R. G. Keske, *Tetrahedron Lett.*, 2023 (1969); (b) J. B. Lambert, R. G. Keske, R. E. Carhart, and A. P. Jovanovich, *J. Amer. Chem. Soc.*, **89**, 3761 (1967); (c) F. G. Riddell and O. A. R. Williams, *Tetrahedron Lett.*, 2073 (1971); (d) E. L. Eliel, L. D. Kopp, J. E. Dennis, and S. A. Evans, Jr., *ibid.*, 3409 (1971).
(3) W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965).
(4) M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964).
(5) G. J. Gleicher and P. R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 582 (1967).
(6) N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. Catledge, *ibid.*, **90**, 1199 (1968).
(7) K. Tori and M. Ohtsuru, *Chem. Commun.*, 856 (1966).
(8) A. H. Hartmann and E. L. Eliel, *J. Amer. Chem. Soc.*, **93**, 2572 (1971).

Table I. Nmr Chemical Shifts for Bicyclic Hexahydropyrimidines (τ, $CDCl_3$)

Signal	Multiplicity	1	2	3	4	5
H_{2a}	t of d	6.58	6.27	Obscured	6.96	6.83
H_{2e}	d of d	6.86	7.10	Obscured	7.38	7.30
H_{3a}	Multiplet	7.84	7.90	8.12	Obscured	8.16
H_{3e}	Various	8.70[a]	8.70 (m)	8.90[b]	8.97[b]	8.96[c]
H_a(bridge)	Various	6.06 (s)		5.98[a]		5.89 (q)
H_e(bridge)	Various			6.73[d]		8.96 (Me)
Others	Multiplet		7.9–8.6 (10 H)	6.75–7.42 (4 H)	6.80–7.15 (4 H) 7.8–8.7 (10 H)	7.01 (4 H)

[a] d of br t. [b] d of t of q. [c] d of t of t. [d] d of q.

Table II. Nmr Coupling Constants for Bicyclic Hexahydropyrimidine (Hz)

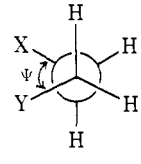
	1	2	3[a]	4	5[b]
Solvent	$CDCl_3$	$CDCl_3$	C_6D_6	CCl_4	$(CD_3)_2CO$
J_{2a-2e}	14	14.5	13	14	13
J_{3a-3e}	13	13.5	14	14	14
J_{2a-3a}	13.5	14	13	13.5	13
J_{2a-3e}	5.5	6.5	4.5	6	5
J_{2e-3a}	6.5	8.0	6.5	7	6.5
J_{2e-3e}	Unres[c]	Unres	1.5	Unres	1.2

[a] $J_{3a-3e} = 10.5$, $J_{3e-2e} = J_{3e-3c} = 1.5$, $J_{3a-en} = 1.0$. [b] $J_{3e-Me} = 6.5$. [c] Unresolved.

Table III. Nmr Data for 1,3-Diazaadamantanes (τ, CCl_4)

	6	7
H_{2a}	6.77 (br s, $W_{1/2}$ 4.5)	6.30 (d, J = 14)
H_{2e}		7.10 (d, J = 14)
H_g	6.02 (s)	
H_3	8.16 (m)	Obscured
H_{10}	8.68 (m)	8.60–8.70 (m)
Others		7.85–8.10 (m, 6 H) 8.40–8.55 (m, 6 H)

value criterion for conformation of the six-membered rings. As recently discussed by Lambert,[9] the value of $R = (J_{aa} + J_{ee})/(J_{ae} + J_{ea})$ for a $-CH_2CH_2-$ segment of a six-membered ring seems to be a remarkably good guide to conformation, and Buys showed[10] that R can be related to Ψ, the internal dihedral (torsional) angle (shown in **8**). For cyclohexane-shaped chairs, R



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values fall in the range 1.9–2.2, and lower R values indicate flattening of the ring, leading to lower Ψ values. Lambert's review includes an impressive series of Ψ values derived from R and compared with X-ray Ψ values; the agreement is good over the entire range from R = 3.9 (Ψ(nmr) = 66°, Ψ(X-ray) = 69°) for 1,4-dithiocyclohexane to R = 1.12 (Ψ(nmr) = 47°, Ψ(X-ray) = 47°) for 1,4-cyclohexandedione dioxime, which is in a twist-boat conformation. The R and Ψ values determined for **1–5** (shown in Table IV) are noteworthy in that all fall below the lowest published chair cyclohexane ring values (R = 1.42, Ψ(nmr) = 51° for 1,4-dimethylenecyclohexane).

(9) J. B. Lambert, *Accounts Chem. Res.*, **4**, 87 (1971).
(10) H. R. Buys, *Recl. Trav. Chim. Pays-Bas*, **88**, 1003 (1969).

Table IV. Nmr-Derived R and Ψ Values for 1,5-Diazabicyclo[3.3.1]nonane and -[3.2.1]octane Derivatives

Compd	R	Ψ(nmr), deg
1	1.17	48
2	1.00	45
3	1.26	49
4	1.08	47
5	1.24	49

As discussed above, the six-membered rings of the hydrocarbon analogs are shown both by calculation and X-ray to be flattened chairs. The nonbonded ring–ring interaction is relieved mostly by flattening and not much by twisting. The published X-ray data for the bicyclo[3.3.1]nonane derivatives allow calculation of the Ψ values. For the 1-brosylmethyl-5-methyl-9-hydroxy derivative,[3] the four Ψ (X-ray) values fell in the range 43.6–to 45.2, while for the 3-aza hydrobromide,[4] Ψ (X-ray) averaged 43.0° in the cyclohexane ring and 50.2° in the piperidine ring. Our Ψ(nmr) values are in surprisingly good agreement with these figures and extend the known range for Ψ(nmr) values for chair cyclohexane rings downward from 51 to 45°. The effect of placing an axial alkyl group on the hexahydropyrimidine ring (**2** *vs.* **1**, **4** *vs.* **3** and **5**) is indicated to cause even more flattening and lowering of Ψ. Such an effect is qualitatively reasonable, since the axial 1,3 alkyl–H interaction might be expected to force H_{2a} and H_{4a} outward, which would tend to flatten t he ring.

Alkylation Effects on Chemical Shift. The chemical shifts observed for the axial and equatorial hydrogens at C_2 and C_3 of **1–5** are noteworthy because the axial hydrogens appear downfield of the equatorial ones ($\Delta_{ae}(n) = \tau(H_a) - \tau(H_e)$ at carbon $n < 0$). The values observed in carbon tetrachloride are summarized in Table V. The compounds were run in $CDCl_3$ and some

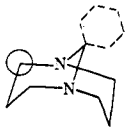
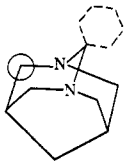
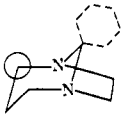
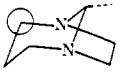
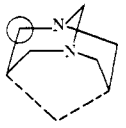
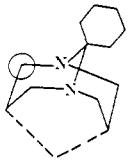
Table V. Δ_{ae} Values for Bicyclic Hexahydropyrimidines (ppm, CCl_4)

Compd	$\Delta_{ae}(2)$	$\Delta_{ae}(3)$
1	−0.21	−0.89
2	−0.85	−0.77
3	−0.31[a]	−0.86[a]
4	−0.91	
5	−0.26	−0.81

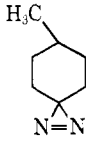
[a] In C_6D_6 solvent.

in C_6D_6 as well, and wherever comparisons could be made, $\Delta_{ae}(n)$ was fairly constant. Differences in Δ_{ae} were less than 0.1 ppm except at position 2 of **5**, where Δ_{ae} was −0.47 in $CDCl_3$.

Table VI. Nmr Chemical Shift Increments at C_2 upon Alkylation

Compd. compared		Alkylation position (relative to C_2)	Solvent	$\Delta\tau(H_{2a})$	$\Delta\tau(H_{2e})$	$\Delta(\Delta_{ae}(2))$
2 *vs.* **1**		$\beta_a + \beta_e$	CCl_4 $CDCl_3$	−0.30 −0.31	+0.34 +0.24	−0.64 −0.55
7 *vs.* **6**		$\beta_a + \beta_e$	$CDCl_3$	−0.47	+0.33	−0.80
4 *vs.* **3**		$\beta_a + \beta_a$	C_6D_6	+0.33	+0.87	−0.54
5 *vs.* **3**		β_e	C_6D_6	+0.68	+0.52	+0.16
6 *vs.* **1**		α_a	CCl_4	0.06	−0.15	+0.21
7 *vs.* **2**		α_a	CCl_4 $CDCl_3$	−0.11 −0.06	−0.16 −0.14	+0.05 +0.08

The occurrence of negative Δ_{ae} values is not unprecedented. Both spiroazirene- and spirocyclopropane-substituted six-membered rings such as those of **9**[11] and **10**[12] gave negative $\Delta_{ae}(2)$ values. In both cases the



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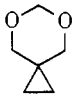

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origin of the negative Δ_{ae} value was attributed to anisotropic effects of the three-membered ring.

In compounds **1**–**5**, the unusual bis-diaxial substitution of the hexahydropyrimidine ring is a prime candidate for causing shifts of the axial and equatorial hydrogens. Effects of alkylation upon chemical shifts in six-membered rings have been the subject of several studies.[2,13] We have compared alkylation effects in compounds **1**–**7**. As expected from previous work, $\Delta_{ae}(3)$ of both **1** and **3** are insensitive to alkylation at the bridging carbon (substitution γ to C_3), although the absolute chemical shifts are quite different in benzene-d_6. Significant changes in Δ_{ae} are observed upon alkylation in the β and α positions, however. In Table VI we make pairwise comparisons of the effect of alkyl substitution on both chemical shifts and Δ_{ae} in the solvents studied. Thus, the first line of Table VI compares the chemical shifts at position 2 for compound **2** with those for compound **1** and indicates that the H_{2a} signal of **2** occurs 0.30 ppm downfield from that of **1**, while the H_{2e} signal of **2** appears 0.34 ppm upfield from that of **1**, causing a −0.64-ppm increment in $\Delta_{ae}(2)$. It is apparent from the first three comparisons in Table VI that β_a,β_e substitution causes a large decrease in the observed $\Delta_{ae}(2)$ value (−0.54 to −0.80 ppm) as a result of about equal upfield shifts of the H_{2e} and downfield shifts of the H_{2a} signals (in C_6D_6, this is superimposed upon an upfield shift of all of the H_{2a}, H_{2e}, H_{3a}, and H_{3e} signals upon alkylation). In comparing the shifts at C_2 of **5** with **3**, the change is a single β_e alkylation, and here $\Delta(\Delta_{ae}(2))$ is +0.16, opposite in sign to that observed when both β_a and β_e are alkylated. We interpret this as showing that an axial β substituent is much more important than an equatorial one in its influence on chemical shift, in qualitative agreement

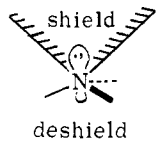
(11) J. J. Uebel and J. C. Martin, *J. Amer. Chem. Soc.*, **86**, 4618 (1964).
(12) J. E. Anderson, *Org. Magn. Resonance*, **3**, 475 (1971).
(13) (a) E. L. Eliel, M. H. Gianni, Th. H. Williams, and J. B. Stothers, *Tetrahedron Lett.*, 741 (1962); (b) H. Booth, *Tetrahedron*, **22**, 615 (1966).

with previous work, and that it both deshields H_a and shields H_e substantially.

The rest of Table VI considers the effect of α_a alkylation on the C_2 chemical shifts by comparing adamantyl to bicyclo[3.3.1]nonyl derivatives. Admittedly, a fairly substantial geometrical change has taken place upon introducing the methylene group, for the C_3–C_6 distance decreased by about 15% from 2.96 to 2.52 Å.[5] Even so, our data suggest a considerably less important chemical shift increment for α than for β substitution, as might be expected if steric hindrance were a very important factor in causing the shift differences.

Returning to the Δ_{ae} values for **1**–**5**, it seems quite clear from Table VI that the effect of the two β_a alkyl groups on $\Delta_{ae}(3)$ will be to give a negative value of nearly the magnitude observed, since $\Delta_{ae}(3)$ would be expected to be in the range of +0.4–+0.6 (as it is for cyclohexane,[14] *N*-methylpiperidine (C_4),[20] and protonated *N*-methylpiperidine (C_2)[26]) if the alkyl effects are not taken into account. The smaller negative $\Delta_{ae}(2)$ values observed for **1** and **3** do *not* seem explainable on the basis of double α_a alkylation. In fact, the measured α_a effect indicates a tendency to make $\Delta_{ae}(2)$ more positive.

We suggest that anisotropic effects of the nitrogens are at least partially responsible for the negative $\Delta_{ae}(2)$ values observed. The lone pair on nitrogen ought to create "shielding" and "deshielding" zones, just as



olefinic and ketonic π electrons do, and, by analogy, one ought to expect shielding on the side of the lone pair and deshielding on the back side. Compounds like those studied here are ideal for observation of such an effect because of the fact that the nitrogens cannot invert, which obviously would exchange shielding and deshielding areas, and average out such effects. We suggest, then, that H_{2a} is relatively deshielded by its proximity to the back side of N_5, whereas H_{2e} feels a much smaller effect because of its greater distance from N_5 (and, indeed, should be shielded relatively to H_{2a} by the N_1 lone pair) and that this is a major factor in causing negative Δ_{ae} values at C_2.

Another case where nitrogen back-side deshielding effects seem to be readily detectable is in causing the large chemical shift differences observed in frozen conformations of hexahydrotetrazane derivatives.[15]

Experimental Sections

The preparation of the compounds used has been described previously[16] except for **5**.

8(e)-Methyl-1,5-diazabicyclo[3.2.1]octane (5) was prepared by stirring a cooled solution of homopiperazine and acetaldehyde for 12 hr, followed by azeotropic removal of water with toluene. After distillation of the solvent, the residue was distilled [bp (12 mm) 67–70°] and purified by vpc (XF-1150) at 95°. Exact mass, calcd for $C_7H_{14}N_2$, 112.1016; found, 112.1022.

Nmr spectra were run on Varian HA-100 or XL-100 equipment, locked on internal TMS when $CDCl_3$ or CCl_4 was the solvent. For decoupling studies, deuterium locked with deuterioacetone as solvent was employed to allow more decoupling power on the XL-100.

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(14) F. A. Bovey, F. P. Hood, III, E. W. Anderson, and R. L. Kornegay, *J. Chem. Phys.*, 41, 2041 (1964).

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(16) S. F. Nelsen and P. J. Hintz, *ibid.*, 94, 7114 (1972).

Electrochemical Oxidation of Tetraalkylhydrazines. Effects of Hydrazine and Hydrazine Radical Cation Geometry

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Contribution from the Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706. *Received February 8, 1972*

Abstract: A series of 25 tetraalkylhydrazines were studied by cyclic voltammetry at a gold electrode in acetonitrile (0.1 *M* in sodium perchlorate) and found to give chemically reversible one-electron oxidations with no evidence for radical cation decay, even at scan rates of about 0.01 V/sec. The observed $E_{1/2}$ values were spread over an 850-mV range from −0.28 to +0.56 V (*vs.* sce). The results are discussed in terms of inductive effects and conformational effects in the hydrazine and the hydrazinium radical cations. Nitrogen and ring inversion are apparently rapid compared to electron transfer for these compounds. Irreversible oxidation potentials for four hydrazines which give radical cations that decompose rapidly, even at scan rates up to 100 V/sec, are presented, and reasons for the lesser stability are discussed.

The discovery that the radical cation of tetramethylhydrazine (**1**) was stable enough at room temperature to give an esr spectrum which persists for several minutes[1] encouraged us to study the hydrazine–hydrazinium radical couple $I \rightleftharpoons I^{\cdot+}$. This was expected to be

(1) S. F. Nelsen, *J. Amer. Chem. Soc.*, 88, 5666 (1966).