11a and **11b** were oils that crystallized on long standing. **11b:** ir (Nujol) 1705, 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) τ 1.48 (d, 2 H), 2.47 (d, 1 H), 2.74 (q, 1 H), 6.06 (q, 1 H), 6.44 (m, 2 H), 6.88 (s, 3 H), 6.95 (s, 3 H); mass spectrum M^+ 219. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98. Found: C, 60.55; H, 6.08. **11a:** ir (Nujol) 1705, 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) τ 1.47 (d, d, 1 H), 2.36 (1, d, 1 H), 2.78 (m, 2 H), 6.03 (m, 2 H), 6.35 (q, 1 H), 6.80 (s, 3 H), 7.00 (s, 3 H); mass spectrum M^+ 219. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.19; H, 6.08; N, 19.06.

Reaction of Diazouracil 3 with Methyl Isonicotinate. To 17.40 g (0.12 mol) of methyl isonicotinate was added 1.40 g (8.0 mmol) of diazouracil **3**. The stirred reaction mixture was heated at 130° for 2 hr, allowed to come to room temperature, and added to 50 ml of hot H_2O. This suspension was continuously extracted with $CHCl_3$ for 48 hr. The H_2O suspension was evaporated in vacuo and the resulting residue was treated with excess CH_2N_2 in benzene. The resulting solution was treated with charcoal, evaporated in vacuo, and chromatographed on neutral alumina (grade III) with benzene–acetonitrile (9:1) to give 180 mg of **18b** (8%), 90 mg of **17b** (4%), 50 mg of **8** (5%), and mono-O-methylated products (3%). Compound **18b:** mp 233–234°; ir (Nujol) 1730, 1700, 1655 cm^{-1} (C=O); mass spectrum M^+ 275. Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.72; H, 4.76; N, 14.98.

Reaction of Diazouracil 3 with 4-Methoxypyridine. To 10 ml (0.10 mol) of 4-methoxypyridine was added 1.50 g (9.0 mmol) of diazouracil **3**. The stirred solution was heated at 130–135° for 3 hr. The crude reaction mixture was allowed to cool and added to 35 ml of hot H_2O. This brown slurry was continuously extracted with $CHCl_3$ for 48 hr. The H_2O suspension was evaporated in vacuo and the resulting solid dried in vacuo at 90°C for 1 hr. This residue showed molecular ions at *m/e* 222, 219, and 112. The residue was transferred with a small amount of CH_3OH and methylated with excess CH_2N_2–benzene. After shaking for 1 hr and standing overnight, the reaction mixture was treated with charcoal and chromatographed on neutral alumina (grade III) with benzene–acetonitrile progressing to ethanol to give 170 mg of **8** (13%), 290 mg of **19b** (13%), 140 mg of **20** (7%), 25 mg of **21b** (2%), and mono-O-methylated products (5%). In addition, some *N*-methyl-4-pyridone was also obtained. Compounds **20** and **21b** could be sublimed but **19b** partially (40–50%) rearranged to **20** on sublimation. Compound **19b:** mp 175° dec; ir (Nujol) 1695, 1655 cm^{-1} (C=O); mass spectrum M^+ 247. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.02; H, 5.42; N, 17.15. Compound **20:** mp 257–260°; ir (Nujol) 1685, 1645, 1555 cm^{-1} (C=O); mass spectrum M^+ 247. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.18; H, 5.35; N, 16.91. Compound **21b:** mp 254–256°; ir (Nujol) 1695, 1650 cm^{-1} (C=O); mass spectrum M^+ 278. Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.07; N, 20.14. Found: C, 51.75; H, 5.08; N, 20.18.

Acknowledgment. The authors wish to thank Professor R. A. Abramovitch for interesting discussions.

Registry No.—**1**, 2435-76-9; **2**, 38099-09-1; **3**, 35124-90-4; **11a**, 56817-24-4; **11b**, 56817-25-5; **13a**, 56817-26-6; **13b**, 56817-27-7; **14a**, 56817-28-8; **14b**, 56817-29-9; **17b**, 56817-30-2; **18b**, 56817-31-3; **19b**, 56817-32-4; **20**, 56817-33-5; **21b**, 7033-42-3; pyridine, 110-86-1; methanol, 67-56-1; methyl isonicotinate, 2459-09-8; 4-methoxypyridine, 620-08-6.

References and Notes

(1) T. C. Thurber and L. B. Townsend, *J. Heterocycl. Chem.*, **9**, 629 (1972).
(2) T. C. Thurber and L. B. Townsend, *J. Am. Chem. Soc.*, **95**, 3081 (1973).
(3) T. C. Thurber, R. J. Pigmire, and L. B. Townsend, *J. Heterocycl. Chem.*, **11**, 645 (1974).
(4) S. H. Chang, I. Kim, and B.-S. Hahn, *Daehan Hwahak Hwoejee*, **9**, 75 (1965); *Chem. Abstr.*, **64**, 17588*g* (1965).
(5) F. G. Fischer and E. Fahr, *Justus Liebigs Ann. Chem.*, **651**, 65 (1962).
(6) Some leading references dealing with free-radical and carbene reactions in pyridines are: (a) R. A. Abramovitch, *Intra-Sci. Chem. Rep.*, **3**, 211 (1969); (b) R. A. Abramovitch and J. G. Saha, *Tetrahedron*, **21**, 3297 (1965); (c) R. A. Abramovitch and O. A. Koleoso, *J. Chem. Soc. B*, 1292 (1968); (d) *ibid.*, 779 (1969); (e) R. A. Abramovitch and J. G. Saha, *Adv. Heterocycl. Chem.*, **6**, 229–333 (1966).
(7) Unreported results from the senior authors laboratory.
(8) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Vol. 5, Pergamon Press, Elmsford, N.Y., 1969, p 307.

Carbon-13 Fourier Transform Nuclear Magnetic Resonance Spectroscopy of Indolo[2,3-*a*]quinolizidines. Specific Deuteration and Relaxation Methods in Structure Assignments[1]

Gordon W. Gribble,*[2] Randall B. Nelson,[3] Jerry L. Johnson,[4] and George C. Levy[5]

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, General Electric Corporate Research and Development, Schenectady, New York 12301, and Department of Chemistry, Florida State University, Tallahassee, Florida 32306.

Received April 9, 1975

The carbon-13 chemical shifts of the indole alkaloid 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**), confirmed by selective deuteration, and the observed chemical shift differences between trans and cis C/D quinolizidine ring fusion in the 2-*tert*-butyl derivatives (**2** and **3**) are discussed in terms of steric compression and electronic effects. A two-bond deuterium-induced ^{13}C relaxation effect on the signal of nonprotonated carbons is observed and used for chemical shift assignments. The spin-lattice relaxation (T_1) times of **1** are an independent means of assigning chemical shifts, especially for nonprotonated carbons, and the results show that all of the carbons in **1** are relaxed primarily by the dipolar mechanism.

The past five years have seen enormous advances in the application of carbon-13 NMR spectroscopy to the structure elucidation and analysis of organic molecules.[6] Included in this array of compounds are plant indole alkaloids, which have recently been examined[7] by ^{13}C NMR, using the signal assignment techniques[6] of selective and off-resonance decoupling, lanthanide chelation, spectral comparison, and chemical shift considerations.

We wish to report a ^{13}C NMR study of the indole alkaloid 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine[8] (**1**) (*Dracontomelum mangiferum*) using the techniques of carbon deuteration[9] and spin-lattice relaxation times[7b,10] to assign chemical shifts and to study relaxation pathways, and to report a study of the effect of ring conformation on the ^{13}C chemical shifts in the 2-*tert*-butyl derivatives **2** and **3**,[11] which have trans and cis C/D ring fusions, respectively.

The synthetic accessibility[8b] of **1** and its deuterated[8b,12] and alkyl[11] derivatives makes this alkaloid ideal for a ^{13}C NMR study as a simple model for the general class of *Corynanthe-Yohimbe* indole alkaloids.

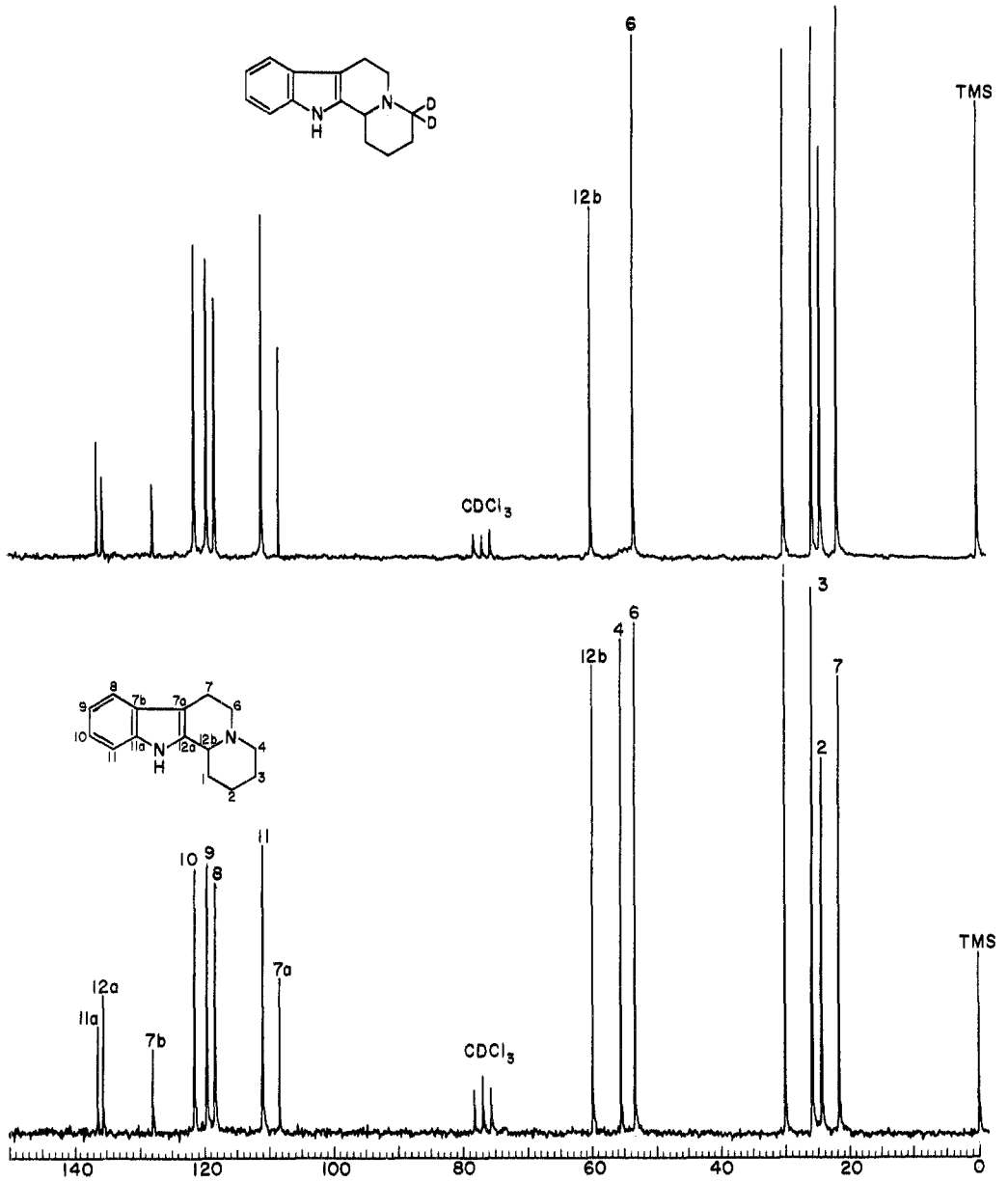
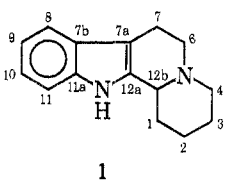
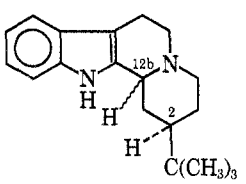


Figure 1. 25.2-MHz ^{13}C FT NMR spectrum of 1 (bottom) and 1-*4*-d_2 (top) in $CDCl_3$.



1



2 (12bα-H; cis)
3 (12bβ-H; trans)

Results and Discussion

Chemical Shifts. 1 and Deuterated Derivatives. The fully proton-decoupled pulse and Fourier transform ^{13}C spectrum of 1 is shown in Figure 1 and the chemical shifts of 1 and the deuterated derivatives 1-*1*-d_2, 1-*3*-d_2, 1-*4*-d_2, 1-*6*-d_2, 1-*7*-d_2, 1-*12b*-d_1, and 1-*9*-d_1 are tabulated in Table I.[13,14]

The methylene (C-1, C-2, C-3, C-4, C-6, C-7) and methine (C-12b) carbons corresponding to the seven well-separated upfield signals (Figure 1) can be unambiguously assigned in the order of increasing chemical shift, C-7 < C-2 < C-3 < C-1 < C-6 < C-4 < C-12b because complete replacement of hydrogen by deuterium on a carbon atom causes that ^{13}C signal to disappear. This follows from the increased spin-lattice relaxation time (T_1) of the deuterated carbon,[9a] which under typical short pulse intervals of 0.4–0.8 sec leads to saturation of the signal. One also expects increased complexity and decreased intensity from ^{13}C–D splitting and a decreased nuclear Overhauser effect.

The chemical shifts of the nondeuterated carbons are unchanged except for the carbons adjacent to the deuterated ones which show a uniform upfield shift of −0.1 to −0.2 ppm. This agrees with the reported second-atom deuterium shifts in deuteriobenzenes.[9d,15] For example, in 1-*7*-d_2 the signal for C-6 is shifted upfield (−0.11 ppm) while that for C-4 remains essentially unchanged (+0.03). In 1-*4*-d_2 the signal for C-3 is shifted upfield by −0.20 ppm. In 1-*3*-d_2 both C-2 (−0.16 ppm) and C-4 (−0.09 ppm) are more shielded than nonflanking carbons. It is interesting to note that in 1-*1*-d_2 not only are the two flanking carbons, C-2 (−0.21 ppm) and C-12b (−0.08 ppm), shifted upfield, but so is C-12a (−0.15 ppm), which represents a large third-atom deuterium shift.

The unusual feature of the seven-signal aliphatic portion

Table I
^{13}C Chemical Shifts of 1 and Deuterated Derivatives[a]

Carbon	1	1-1-d_2	1-3-d_2	1-4-d_2	1-6-d_2	1-7-d_2	1-12b-d_1	1-9-d_1
1	29.96	b	29.95	29.96	29.82	29.94	29.75	30.11
2	24.31	24.10	24.15	24.29	24.24	24.31	24.24	24.44
3	25.74	25.69	b	25.54	25.66	25.73	25.68	25.87
4	55.75	55.75	55.65	b	55.62	55.77	55.53	55.75
6	53.51	53.57	53.57	53.46	b	53.40	53.35	53.53
7	21.62	21.61	21.63	21.66	21.35	b	21.55	21.77
12b	60.27	60.19	60.28	60.22	60.11	60.26	b	60.27
8	118.06	118.00	118.11	118.08	117.94	118.09	118.10	117.97
9	119.31	119.39	119.35	119.31	119.16	119.29	119.38	b
10	121.20	121.19	121.24	121.19	121.04	121.19	121.28	121.15
11	110.75	110.80	110.75	110.79	110.72	110.74	110.94	110.76
7a	108.11	108.12	108.12	108.11	107.91	c	108.00	108.28
7b	127.59	127.56	127.55	127.63	127.47	127.54	127.32	127.86
11a	136.08	136.14	136.07	136.18	136.05	136.03	135.89	136.41
12a	135.24	135.09	135.20	135.33	135.23	135.23	135.33	135.44

[a] In $CDCl_3$ solution (except 1-12b-d_1, which was in $CDCl_2CDCl_2$). Chemical shifts downfield from Me_4Si in parts per million, ±0.03–0.05 ppm. [b] A low-intensity multiplet could sometimes barely be discerned. [c] The signal is very weak (see text).

of the ^{13}C spectrum of 1 is the high field position of C-7, appearing at higher field than what one might predict for a benzylic-type methylene carbon. This pronounced shielding, which is also seen in the ^{13}C spectra of 3-methylindole[16] and *o*-alkylanilines,[17,18] probably reflects the increased electron density at the (enamine) carbon C-7a in 1, and the cyclohexene-like half-chair conformation of ring C (vide infra).

The remaining six aliphatic ^{13}C chemical shifts are consistent with those reported for simple piperidines.[7h,19] The downfield position of C-1 relative to C-3 is due to the β effect[20] of C-12a. Carbon 6 is found to be more shielded than C-4. This is probably due in part to the half-chair conformation of ring C, which introduces eclipsing[26,27] between C-6 protons and C-7 protons. This effect is analogous to the shielding observed[21] (−4.3 ppm) for the methylene carbons in *cis*-1,4-di-*tert*-butylcyclohexane, which exists in a twist–boat conformation with eclipsed methylene groups. Likewise, C-4 in cyclohexene (−4.7 ppm) and cyclopentane (−1.3 ppm) (eclipsed hydrogens) is shielded relative to cyclohexane (staggered hydrogens).[22]

The four protonated aromatic carbons in 1 are assigned in the order of increasing chemical shift, C-11 < C-8 < C-9 < C-10, based partially on the assignments reported[16] for indole and methyl-substituted indoles, and on the disappearance of the signal at 119 ppm in 1-9-d_1. Our assignments for C-9 and C-10 differ from those normally reported for these carbons in indoles[16] and indole alkaloids.[7] We believe that the original assignments[16] for C-5 and C-6 in indoles are incorrect and should be reversed.[23]

The four signals with reduced intensity are assigned to the four nonprotonated carbons in the order of increasing chemical shift: C-7a < C-7b < C-12a < C-11a. The low-field peaks at 135.24 and 136.08 ppm are assigned to the carbons adjacent to the indole nitrogen, C-12a and C-11a, with the lower field signal assigned to the benzene carbon C-11a.[24] This also follows from the shifts observed in pyrroles[25] and indoles.[7a] The distinction between the C-12a and C-11a assignment is confirmed by the results with 2 and 3 and relaxation measurements (vide infra).

The remaining two nonprotonated carbons C-7a and C-7b are assigned to the signals at 108.11 and 127.59 ppm, respectively. The increased electron density in the π orbital on C-7a, due to the enamine character of the indole double bond, accounts for the pronounced shielding of C-7a. An olefinic analogue such as the α carbon in α-methylstyrene absorbs at 142.4 ppm.[26]

A striking feature in the spectrum of 1-7-d_2 is the greatly reduced signal for C-7a. We ascribe this to the fact that C-7a is primarily relaxed by the C-7 protons (vide infra) and substitution of deuterium at C-7 leads to a relative saturation of the C-7a signal. The signal for C-7 itself is eliminated by the effect of the directly bonded deuteriums.

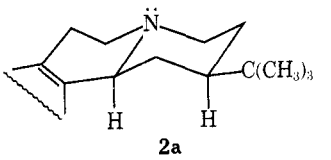
Table II
^{13}C Chemical Shifts of 1, 2, and 3[a]

Carbon	1	2	3	δ (2 → 3)
1	29.96	31.05	28.72	−2.33
2	24.31	46.65	41.03	−5.62
3	25.74	26.72	26.42	−0.30
4	55.75	56.09	50.82	−5.27
6	53.51	53.11	45.83	−7.28
7	21.62	21.76	16.78	−4.98
12b	60.27	60.31	54.30	−6.01
8	118.06	118.14	118.07	−0.07
9	119.31	119.38	119.53	+0.15
10	121.20	121.27	121.52	+0.25
11	110.75	110.79	111.09	+0.30
7a	108.11	108.06	107.61	−0.45
7b	127.59	127.58	127.74	+0.16
11a	136.08	136.12	135.90	−0.22
12a	135.24	135.29	132.85	−2.44
2α		32.4	32.0	−0.4
2β		27.5	27.3	−0.2

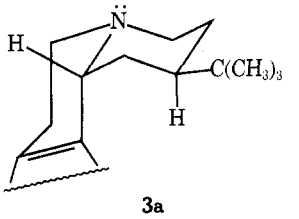
[a] See Table I.

An independent method for identifying nonprotonated carbons is to use two pulse intervals as shown in Figure 2 for 1-6-d_2. The short pulse interval effectively suppresses the four nonprotonated carbons C-7a, C-7b, C-11a, C-12a, as well as the $CDCl_3$ and Me_4Si lines (long T_1's) and the CD_2 multiplet. The long pulse interval increases the intensity of the lines of the nonprotonated carbons to the point where they nearly match the intensity of the protonated carbons. The integral trace in Figure 2 shows this clearly.

Chemical Shifts. 2-*tert*-Butyl Derivatives. The ^{13}C chemical shifts of the *cis*- and *trans*-2-*tert*-butyl derivatives of 1 (**2** and **3**) are tabulated in Table II and the spectra shown in Figure 3. The dominant conformations are **2a** (≥95%) and **3a** (>99.9%).[11] The *tert*-butyl holding group



2a



3a

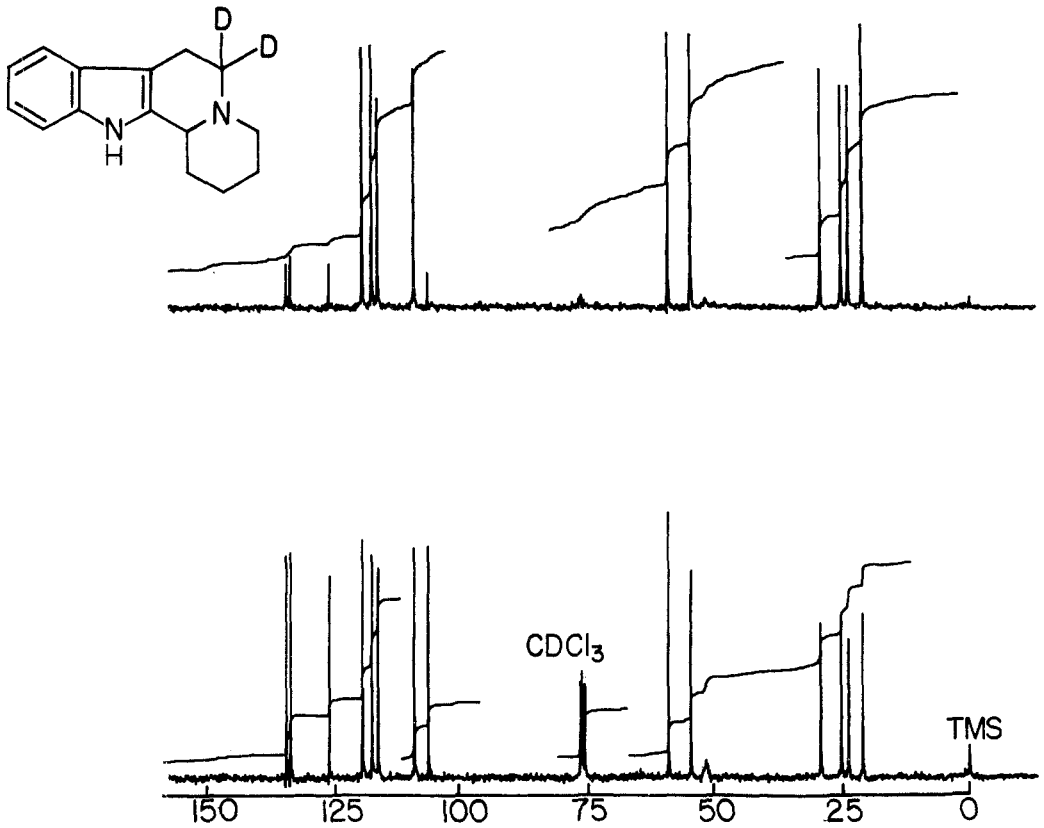


Figure 2. 67.9-MHz ^{13}C FT NMR spectrum of 1-*6-d*$_2$: (top) 300 90° (34 μsec) pulses, repetition time 1 sec; (bottom) 120 90° pulses, repetition time 20 sec. Each spectrum 15 kHz, 16K transform.

allows one to study the effect of C/D ring fusion on ^{13}C chemical shifts without itself perturbing the ^{13}C spectrum, since a *tert*-butyl group largely affects only the directly attached carbon (α effect).[21]

The chemical shifts of the six benzene carbons (C-7b, C-8, C-9, C-10, C-11, C-11a) show virtually no change in **1–3**, and the chemical shifts of the *tert*-butyl group carbons, C-2α and C-2β, are very similar in **2** and **3**.

In general, the other carbons in **1** and **2**, which both have a trans C/D ring fusion,[11] have the same chemical shift (Table II). The only exceptions are C-2 in **2**, which experiences an α effect of the *tert*-butyl group of +22.34 ppm (downfield), and C-1 and C-3, which each experience the β effect of a *tert*-butyl group of +1.09 and +0.97 ppm, respectively. The corresponding α and β effects of the *tert*-butyl group on a cyclohexane ring are +21.2 and +0.5 ppm, respectively.[21]

The remaining carbons in the C and D rings (C-4, C-12b, C-6, C-7, C-7a, C-12a) show little chemical shift differences between **1** and **2**, perhaps indicating the absence of significant ring distortion induced by the *tert*-butyl group.

In contrast, the cis-fused system **3** shows striking chemical shift differences in the ^{13}C spectrum (Table II). The signals for C-3 in **2** and **3** are essentially the same, as expected, since the immediate steric environments of the C-3 protons are the same in each isomer. However, C-4, C-6, C-7, and C-12b are all shifted upfield in the spectrum of **3**: −5.27, −7.28, −4.98, and −6.01 ppm, respectively. A Dreiding model of **3** shows a 1,4-gauche interaction between the C-4 axial proton and the C-7 pseudoaxial proton (~1.7–1.8 Å), leading to shielding of both carbons. By comparison, the reported steric-induced shielding of the 3,5 ring carbons in axial-methyl cyclohexanes (γ_a effect) is −5.4 ppm,[28] and the empirically derived shift is calculated to be −5.24 ppm (r_{HH} = 1.88 Å).[27]

The upfield shift of −2.33 ppm for C-1 in **3** relative to **2** perhaps reflects the difference between an equatorial and an axial effect (−3.7 ppm in methylcyclohexanes),[28] and a steric compression between the equatorial C-1 proton and the N–H (~2.4 Å) in **3**.

The upfield shifts of C-2, C-4, and C-12a (−5.62, −5.27, and −2.44 ppm) in **3** relative to **2** may be partially due to steric compression[27,28] between the axial C-2 and C-4 protons and the indole π orbital on C-12a ($r_{HC} \simeq$ 2.5 Å). This specific shielding of C-12a in **3** provides an independent method for distinguishing it from C-11a and from the other nonprotonated carbons.

It is difficult to rationalize the upfield shifts of C-6 and C-12b (−7.28 and −6.01 ppm, respectively) in terms of steric compression, since no significant interaction appears to be present in **2** or **3** involving these protons. Therefore, the shielding of C-6 and C-12b in **3** relative to **2** may be due in part to a reduction in overlap between the nitrogen lone pair and the antibonding orbital of an adjacent axial C–H bond—an interaction in trans-fused quinolizidines such as **2** that has been suggested to account for both infrared "Bohlmann bands" [11,29a] and the shielding of protons that are trans diaxial to a nitrogen lone pair.[11,29] Thus, in **2** the carbons α to the nitrogen (C-6, C-12b) may actually be *deshielded* relative to **3** which does not have protons on C-6 and C-12b trans diaxial to the nitrogen lone pair.[30]

Relaxation Studies. The spin-lattice relaxation times (T_1) and the nuclear Overhauser effects (NOE) were measured for all of the carbons in **1** and for the unsaturated carbons in 1-*7-d*$_2$ and 1-*12b-d*$_1$ (Table III).

The T_1 values for all of the protonated carbons in **1** are found to be less than 1 sec. The NOE's are found to be close to the maximum theoretical value (η = 1.988), and therefore the dominant mechanism for the relaxation of the protonated carbons is clearly the ^{13}C–^1H dipolar–dipolar mechanism.[31] The methylene carbon T_1's are all approximately 0.3 sec, about twice as fast as the methine carbon

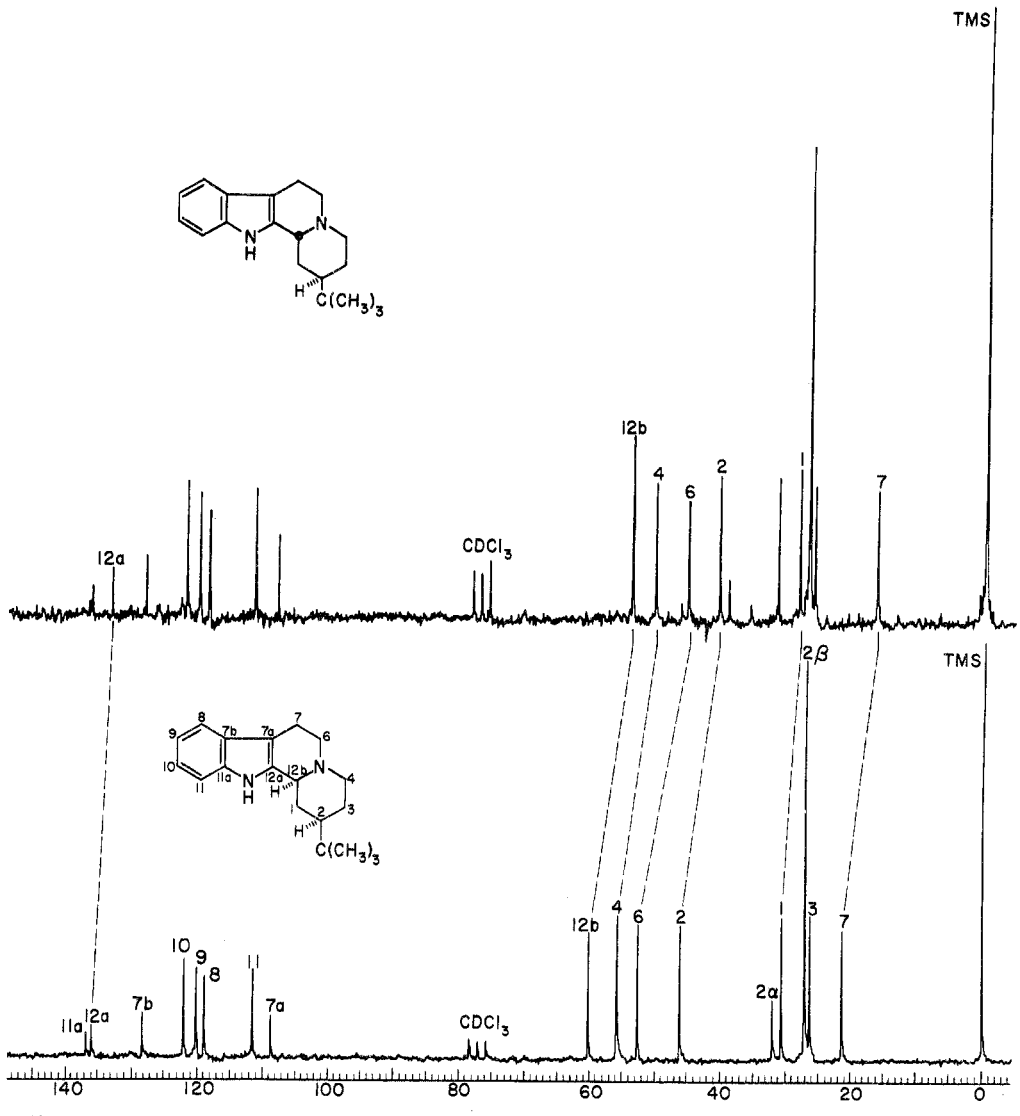


Figure 3. 25.2-MHz ^{13}C FT NMR spectrum of **2** (bottom) and **3** (top) in $CDCl_3$.

Table III
Spin-Lattice Relaxation Times for 1, 1-7-d_2 and 1-12b-d_1 [a]

	1				1-7-d_2	1-12b-d_1
Carbon	T_1	NOE (η)	T_1^{DD}	T_1^{DD} (calcd)	T_1	T_1
1	0.31					
2	0.32					
3	0.31					
4	0.28					
6	0.30					
7	0.31					
12b	0.67					
8	0.60	2.0			0.77[b]	0.75[b]
9	0.52	2.0			0.77[b]	0.75[b]
10	0.54	2.0			0.77[b]	0.75[b]
11	0.60	1.8			0.77[b]	0.75[b]
7a	7.7	1.8	8.5	12	~22	9.9
7b	10.2	1.7	11.9	25	~22	12.1
11a	7.0	1.5	9.3	18	14.6	9.7
12a	5.7	1.6	7.6	11	12.2	11.2

[a] All T_1's in sec (±10–15%), determined at 25.2 MHz and 38°C. [b] T_1's ±10–20%.

T_1's (Table III), indicating that the molecule is undergoing largely isotropic molecular motion.[31,32]

The NOE's for the four nonprotonated carbons indicate that those carbons are also largely relaxed by the dipolar mechanism involving nearby protons. This is also the case in other large molecules such as cholesteryl chloride,[32] mescaline,[31] and codeine,[7b] where overall molecular motion is slow. The T_1^{DD} contribution to the T_1^{obsd} can be calculated[31] from eq 1, where η is the observed NOE. These values are shown in Table III.

$$T_1^{DD} = T_1^{obsd} \frac{1.988}{\eta} \quad (1)$$

The longer T_1's for the protonated carbons in 1-7-d_2 and 1-12b-d_1 result from solution viscosity effects. The two specifically deuterated samples were run at significantly lower concentrations; the lower viscosities of the solutions resulted in more rapid molecular tumbling. The ratios 0.77/0.56 and 0.75/0.56 (≈1.4) correspond to the differentials for molecular tumbling.

The large increase in T_1 for the nonprotonated carbons in 1-7-d_2 (e.g., 22 sec for C-7a and C-7b, Table III) clearly implicates the protons on C-7 as those responsible in part for relaxing C-7a, C-7b, C-11a, and C-12a by the dipolar mechanism. As would be predicted, the closest nonprotonated carbon to C-7, C-7a, is affected more than the other carbons and, in fact, its signal disappears completely with normal pulse intervals (vide supra). Likewise, the T_1 values for 1-12b-d_1 indicate that the C-12b proton relaxes C-12a more than C-7a and that C-7b and C-11a are not appreciably relaxed by this proton.

We have measured the distances from the four nonproto-

nated carbons to nearby protons (≤4.0 Å) using Dreiding models and have calculated[31-33] (eq 2) the T_1^{DD}'s using $\tau_c = 7.8 \times 10^{-11}$ sec (calculated using the average T_1 from the 11 protonated carbons and $r = 1.09$ Å). These calculated T_1^{DD}'s (Table III) are in only fair agreement with T_1^{DD}, as might be expected from the sensitivity of T_1^{DD} to the internuclear distance and to τ_c, but the parallel nature of the two sets of values (C-7b > C-11a > C-7a > C-12a) is informative. Thus, one can immediately distinguish C-11a and C-12a, which have very similar chemical shifts, from the different relaxation times due to their local environment (C-11a has two protons within 3 Å whereas C-12a has six protons within 3 Å).

$$\frac{1}{T_1^{DD}} = \frac{h^2}{2\pi}\gamma_H^2\gamma_C^2 \sum_i r_{CH_i}^{-6}\tau_c \qquad (2)$$

These results show that (1) deuterium substitution, when synthetically convenient, is a powerful tool for assigning ^{13}C chemical shifts to directly bonded carbons as well as to adjacent carbons (two-bond deuterium isotope effect[15]), (2) the striking chemical shift differences between trans and cis C/D ring fusion (**2** and **3**) allows ^{13}C NMR to be used as a method for establishing the stereochemistry of unknown indole or quinolizidine alkaloids, and (3) spin-lattice relaxation times, coupled with deuterium substitution, are a powerful probe for chemical shift assignments, especially for nonprotonated carbons, for which other techniques (e.g., the various proton decoupling methods) are not generally useful.

Experimental Section

Compounds. The syntheses of **1**, **1**-*3*-d_2, **1**-*4*-d_2, **1**-*6*-d_2, **1**-*7*-d_2, **1**-*12b*-d_1, **2**, and **3** have been described.[8b,11,12]

1,1-Dideuterio-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**-*1*-d_2) was prepared from *N*-[2-(3-indolyl)ethyl]-2-piperidone[34] by a seqence involving K_2CO_3-catalyzed deuterium exchange,[12] $POCl_3$ cyclization,[34] and $NaBH_4$ reduction.[8b,11,12]

9-Deuterio-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**-*9*-d_1) was prepared from 5-bromoindole by a sequence involving *n*-butyllithium–D_2O (5-deuterioindole), oxalyl chloride–ammonia–$LiAlH_4$ (5-deuteriotryptamine), and glutaraldehyde–$NaBH_4$.[8b]

NMR Spectra. Carbon-13 Fourier transform spectra (0.1–0.5 *M* $CDCl_3$ with added Me_4Si as an internal chemical shift reference) were run on a Varian XL-100-15 NMR spectrometer at 25.2 MHz, except for **1**-*6*-d_2 and **1**-*9*-d_1, which were run on a Bruker HX-270 spectrometer at 67.9 MHz. In general, 8K free induction decays (FID's) were acquired over spectral widths of 5 kHz. Some spectra were obtained with short (≤1 sec) pulse intervals while other spectra were acquired using pulse intervals of 4–10 sec; in both cases the H_1 pulse widths used were <90°.

Spin-Lattice Relaxation Measurements. Carbon-13 T_1's were determined by the inversion-recovery pulse sequence as modified by Freeman and Hill.[35] T_1 measurements were separately performed on the aliphatic and unsaturated carbon regions, because the available H_1 field was not large enough to allow T_1 measurements over 4–5 kHz. T_1's were determined from semilogarithmic plots in the usual way.[31,35] No sample degassing was used since ^{13}C T_1's <10 seç are not significantly affected by 0.2 atm of O_2. T_1's reported in this study of 10–20 sec include minor contributions from dissolved air.

Acknowledgments. We wish to thank Mr. Joseph D. Cargioli and Dr. Gordon L. Nelson, who participated in part of this work, and Professor Robert Ditchfield for stimulating discussions and unpublished calculations. G.W.G., R.B.N., and J.L.J. are grateful to Merck Sharp and Dohme, Eli Lilly, and the National Institutes of Health (CA-14237) for their support of this work and our research program.

Registry No.—**1**, 4802-79-3; **1**-*1*-d_2, 56817-44-8; **1**-*3*-d_2, 51263-49-1; **1**-*4*-d_2, 51263-50-4; **1**-*6*-d_2, 51263-51-5; **1**-*7*-d_2, 51263-52-6; **1**-*9*-d_1, 56817-45-9; **1**-*12b*-d_1, 34388-09-5; **2**, 40587-68-6; **3**, 40587-69-7; *N*-[2-(3-indolyl)ethyl]-2-piperidone, 38199-31-4; 5-bromoindole, 10075-50-0.

References and Notes

(1) Part of this work has appeared in preliminary form: G. W. Gribble, R. B. Nelson, G. C. Levy, and G. L. Nelson, *Chem. Commun.*, 703 (1972); 148 (1973).
(2) Recipient of a Public Health Service Research Career Development Award (1K04-GM-23756) from the National Institute of General Medical Sciences, 1971–1976; Dartmouth College.
(3) NDEA Predoctoral Fellow, 1971–1973; Dartmouth College.
(4) Goodyear Predoctoral Fellow, 1975–1976; Dartmouth College.
(5) General Electric; Florida State University.
(6) (a) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972; (b) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972; (c) F. W. Wehrli, "Nuclear Magnetic Resonance Spectroscopy of Nuclei Other Than Protons:", T. Axenrod and G. A. Webb, Ed., Wiley-Interscience, New York, N.Y., 1974, Chapter 12; (d) G. A. Gray, *CRC Crit. Rev. Biochem.*, 247 (1973).
(7) (a) R. H. Levin, J.-Y. Lallemand, and J. D. Roberts, *J. Org. Chem.*, **38**, 1983 (1973); (b) F. W. Wehrli, *Chem. Commun.*, 379 (1973); (c) N. Neuss, H. E. Boaz, J. L. Occolowitz, E. Wenkert, F. M. Schell, P. Potier, C. Ran, M. M. Plat, and M. Plat, *Helv. Chim. Acta*, **56**, 2660 (1973); (d) A. Cave, J. Bruneton, A. Ahond, A.-M. Bui, H.-P. Husson, C. Kan, G. Lukacs, and P. Potier, *Tetrahedron Lett.*, 5081 (1973); (e) J. LeMen, G. Lukacs, L. LeMen-Olivier, J. Levy, and M.-J. Hoizey, *ibid.*, 483 (1974); (f) G. Lukacs, M. DeBellefon, L. LeMen-Olivier, J. Levy, and J. LeMen, *ibid.*, 487 (1974); (g) N. K. Hart, S. R. Johns, J/ A. Lamberton, and R. E. Summons, *Aust. J. Chem.*, **27**, 639 (1974); (h) E. Wenkert, J. S. Bindra, C-J. Chang, D. W. Cochran, and F. M. Schell, *Acc. Chem. Res.*, **7**, 46 (1974), and references cited therein; (i) N. J. Bach et al., *J. Org. Chem.*, **39**, 1272 (1974).
(8) (a) S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Chem. Commun.*, 421 (1966); *Aust. J. Chem.*, **19**, 1951 (1966); (b) G. W. Gribble, *J. Org. Chem.*, **37**, 1833 (1972), and references cited therein.
(9) (a) H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961); (b) F. J. Weigert and J. D. Roberts, *J. Am. Chem. Soc.*, **89**, 2967 (1967); (c) H. J. Koch and A. S. Perlin, *Carbohydr. Res.*, **15**, 403 (1970); (d) W. Kitching, M. Bullpitt, D. Doddrell, and W. Adcock, *Org. Magn. Reson.*, **6**, 289 (1974).
(10) For a recent example, see R. E. Echols and G. C. Levy, *J. Org. Chem.*, **39**, 1321 (1974).
(11) G. W. Gribble and R. B. Nelson, *J. Org. Chem.*, **38**, 2831 (1973).
(12) G. W. Gribble and R. B. Nelson, *J. Org. Chem.*, **39**, 1845 (1974).
(13) Our values for **1** agree to within +0.1 to +0.3 ppm of those recently reported by Wenkert.[7h]
(14) In our preliminary report[1] the assignments for C-2, C-3, and C-7 in **1** were reversed, and illustrate the potential dangers of relying solely on model compounds for chemical shift assignments.
(15) (a) R. A. Bell, C. L. Chan, and B. G. Sayer, *Chem. Commun.*, 67 (1972); (b) D. Lauer, E. L. Motell, D. D. Traficante, and G. E. Maciel, *J. Am. Chem. Soc.*, **94**, 5335 (1972); (c) R. H. Martin, J. Moriau, and N. Defay, *Tetrahedron*, **30**, 179 (1974).
(16) R. G. Parker and J. D. Roberts, *J. Org. Chem.*, **35**, 996 (1970).
(17) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley-Interscience, New York, N.Y., 1972, No. 303, 305.
(18) P. C. Lauterbur, *J. Chem. Phys.*, **38**, 1415 (1963).
(19) A. J. Jones and M. M. A. Hassan, *J. Org. Chem.*, **37**, 2332 (1972).
(20) D. M. Grant and E. G. Paul, *J. Am. Chem. Soc.*, **86**, 2984 (1964).
(21) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Am. Chem. Soc.*, **92**, 1338 (1970).
(22) Reference 6b, pp 60, 80–84.
(23) For example, 5-deuterioindole shows collapse of the peak at 120 ppm, previously assigned[16] to C-6: J. L. Johnson and G. W. Gribble, unpublished results.
(24) Benzene is deshielded by +1.5 ppm relative to C-1 in cyclohexene.[6a,b]
(25) T. F. Page, Jr., T. Alger, and D. M. Grant, *J. Am. Chem. Soc.*, **87**, 5333 (1965).
(26) K. S. Dhami and J. B. Stothers, *Can. J. Chem.*, **43**, 510 (1965).
(27) D. M. Grant and B. V. Cheney, *J. Am. Chem. Soc.*, **89**, 5315 (1967).
(28) D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **89**, 6612 (1967).
(29) (a) T. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.*, **71**, 109 (1971); (b) M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brosse, *J. Am. Chem. Soc.*, **86**, 3364 (1964); (c) E. Wenkert, B. Wickberg, and C. L. Leicht, *ibid.*, **83**, 5037 (1961); (d) J. B. Lambert, D. S. Bailey, and B. F. Michel, *ibid.*, **94**, 3812 (1972).
(30) (a) However, calculations on methylamine show that there is little or no effect on the carbon chemical shift as a function of lone pair orientation (R. Ditchfield, unpublished calculations). (b) A similar hyperconjugative type interaction has been invoked to explain *shielding* of the γ carbon in piperidines and other heterocycles: E. L. Eliel et al., *J. Am. Chem. Soc.*, **97**, 322 (1975). We thank Professor Eliel for a preprint of this work.
(31) G. C. Levy, *Acc. Chem. Res.*, **6**, 161 (1973), and references cited therein.
(32) A. Allerhand, D. Doddrell, and R. Komoroski, *J. Chem. Phys.*, **55**, 189 (1971).
(33) A. Allerhand and R. A. Komoroski, *J. Am. Chem. Soc.*, **95**, 8228 (1973).
(34) J. Martel and G. Costerousse, German Offen. 2,200,259; *Chem. Abstr.*, **77**, 152432v (1972).
(35) R. Freeman and H. D. W. Hill, *J. Chem. Phys.*, **54**, 3367 (1971).