^{13}C Nmr Assignments of Selected Octahydroindolizines

Philip E. Sonnet

Federal Research, Science and Education Administration, USDA, Laramie, WY 82071

Daniel A. Netzel

Laramie Energy Technology Center, Laramie, WY 82071

and

Robert Mendoza

University of Wyoming, Laramie, WY 82071

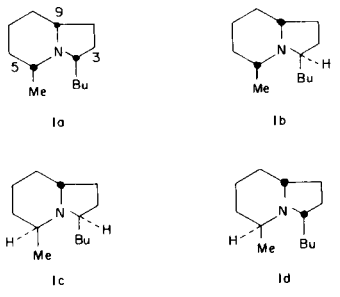
Received November 6, 1978

Several octahydroindolizines including the four geometrical isomers of 3-butyl-5-methyloctahydroindolizine, which is an attractant of Pharaoh's and [*Monomorium pharaonis*(L.)], have been examined by ^1H and ^{13}C nmr spectroscopy. The conformations of these compounds are discussed.

J. Heterocyclic Chem., **16**, 1041 (1979).

In 1973 Ritter and co-workers (1) isolated an attractant from the Pharaoh ant, *Monomorium pharanois* (L.), an insect that is not readily controlled by applications of conventional insecticide. The structure **1**, 3-butyl-5-methyloctahydroindolizine, was assigned to this pheromone (see Scheme 1). A combination of infrared, ^1H nmr and mass spectral data was correlated in an effort to assign the geometrical configuration of **1** (2). An unambiguous synthesis of the four racemates of **1** (3) aided in the assignment of **1a**, (5*Z*,9*Z*)-3-butyl-5-methyloctahydroindolizine, as the attractant (4). This compound which was found in conjunction with the two related pyrrolidines was maned Monomorine 1. More recently, (6*E*,10*Z*)-3,4,7,11-tetramethyl-6,10-tridecadienal, faranal, has been identified as the trail pheromone of the Pharaoh ant (5).

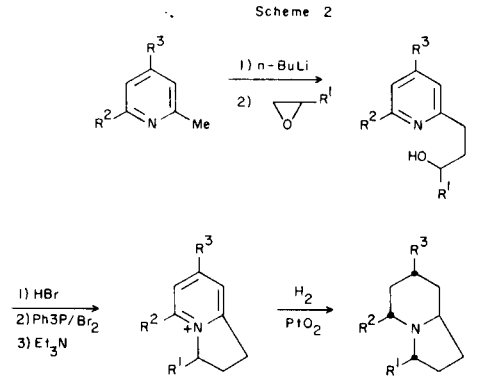
Scheme 1



Pearce, Gore, and Silverstein (6) have shown the potential utility of ^{13}C nmr techniques for structure assignment in insect pheromones. As they pointed out, this technique will find greater use in pheromone investigations as the sensitivities of nmr spectrometers are increased thereby meeting the challenge imposed by the limited quantities of pheromone available (generally microgram quantities). We felt that ^{13}C assignments for the octahydroindolizines **1a-d** would benefit subsequent studies of the natural products of the ants. In addition, this particular heterocyclic ring system has not yet been investigated spectroscopically to any great extent (see reference 3b and references therein). ^{13}C nmr data have been reported only for the parent compound (7).

Several octahydroindolizines, **2, 3** and**4**, having the stereochemical configuration of **1a** were synthesized by the route described previously (Scheme 2) (3). The ^1H nmr data were obtained for these compounds in trifluoracetic acid (TFA) and reported in Table 1. Also included in this table are the quivalent ^1H nmr data for (7*Z*,9*Z*)-5,7-dimethyoctahydroindolizine, compound **5** (**8**), and **1a-d**, which we had reported previously (3). Each of the new octahydroindolizines, **2-4**, was uniform by gas chromatography and yielded a ^{13}C spectrum (*vide infra*) which indicated that a single racemate had been synthesized. Also, each compound **2-4** and each of the set of isomers **1a-d** was found to be essentially conformationally pure as evidenced by unchanging ^1H nmr spectra down to -40°. Finally, the ^{13}C nmr spectrum of **1a** only exhibited

Scheme 2



2 R^1=Me, R^2=R^3=H

3 R^1=R^3=Me, R^2=H

4 R^1=R^2=Me, R^3=H

0022-152X/79/051041-07$02.25

Table 1

^{1}Nmr Spectral Data of the Octahydroindolizines in Trifluoroacetic Acid (a)

Compound No.	3-CH_3	5-CH_3	7-CH_3	H_A; H_E	H_A:H_E (b)
2	1.44			2.8-3.6; 3.7-4.0 (c)	3:1
3	1.45		1.05	2.7-3.5; 3.6-3.9 (c)	3:1
4	1.54	1.48		3.0-3.8	-(c)
5		1.41	1.04	2.9-3.4; 3.7-4.0	3:1 (e)
1a		1.49		2.9-3.9	-(d,f)
1b		1.40		3.0-3.7; 3.7-4.2	2:1 (f)
1c		1.46		3.1-3.6; 3.6-4.2	1:2 (f)
1d		1.36		3.0-3.8; 3.8-4.3	2:1 (f)

(a) Protons on the carbons bonded to the protonated nitrogen are shifted downfield in differing amounts. Thus axial hydrogens (H_A) appear as an envelope at 3.0-3.5 ppm, and equatorial hydrogens (H_E) appear as a discrete envelope at 3.5-4.0 ppm. (b) Intensity ratio. In a strict sense, protons on the 5-membered ring can only be approximated as axial or equatorial. (c) The lone equatorial proton appears as a broadened doublet that is coupled to a geminal proton (J = 12 Hz). (d) The protons on carbons attached to nitrogen are broadened and only partially separated. (e) Reference (8). (f) Reference (3).

slight shifting of the signals down to -40°. In order to enhance the clarity of the discussion, we here describe the ^{1}H nmr and infrared data first and the ^{13}C data second. Conformational assignments were made by using the ^{1}H nmr and infrared data, since these are more readily interpreted. The ^{13}C chemical shift assignments were then made on the basis of these conformational assignments, by employing a combination of analogy, deuteration, spin-lattice relaxation (T_1) measurements, and by comparing the ^{1}H-decoupled with ^{1}H-coupled spectra.

Compound **5**, (7*Z*,9*Z*)-5,7-dimethyloctahydroindolizine was described by Luning and Lundin (8) as a *trans*-fused system with both methyl groups in equatorial positions (see Scheme 3). The assignment rested upon the relative strengths of the Bohlmann bands in the infrared spectra (2800 cm^{-1}) of the four racemates of the 5,7-dimethyl compound. These bands refer to the amount of α-hydrogen *trans*-biaxially oriented to the nitrogen lone pair (9), and this criterion of structure had been shown applicable to this heterocyclic system (10). In addition, the ^{1}H nmr spectrum of **5** in TFA showed the presence of three axial and one equatorial proton on carbons adjacent to nitrogen (11) (see Table 1). The proton shifts of the methyl groups (C-5, 1.41 ppm; C-7, 1.04 ppm) are therefore indicative of equatorially bound methyls at these positions in the *trans*-fused conformation. Compound **3** in TFA showed three axial to one equatorial α-hydrogen, and the shift of the C-7 methyl was 1.05 ppm, which is just the value expected for equatorial methyl at C-7. The conformation of **3** is therefore the same as **5**, and the shift of the C-3 methyl of **3** (1.45 ppm) is therefore regarded as typical of a methyl group at that position (pseudoequatorial) for this conformation. The C-3 methyl of compound **2** also absorbed at 1.44 ppm, and this compound too is regarded as *trans*-fused with the C-3 methyl bound to C-3 in the same sense as **3**. However, **4**, in which methyls at C-3 and C-5 would be eclipsed in a *trans*-fused 6-ring chair arrangement, exhibited an unresolved ^{1}H nmr resonance for the α-hydrogens; both methyls were shifted to lower field (C-3, 1.54 ppm; C-5, 1.48 ppm); and the Bohlmann bands were somewhat diminished. The presence of the Bohlmann bands ruled out *cis* fusion of the rings (9). A *trans*-fused boat arrangement is an alternative assignment of the spectral data. In this conformation the eclipsed methyls are less hindered sterically than the *trans*-fused chair arrange-

Scheme 3

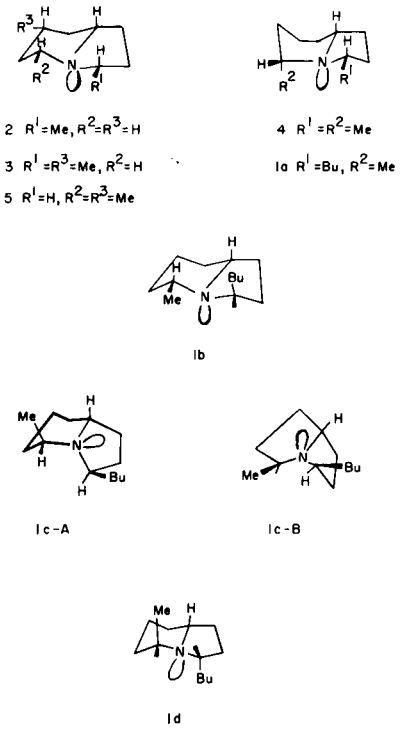


Table 2

^{13}C Nmr Shifts (a) for Octahydroindolizines

Compound No.	Ring Carbons								CH_3			Butyl Carbons			
Compound (b)	C-1	C-2	C-3	C-5	C-6	C-7	C-8	C-9	3	5	7	$-CH_2$	$-CH_2$	$-CH_2$	$-CH_3$
Octahydroindolizine X (c,d)	30.1	20.3	53.9	52.7	25.1	24.2	30.7	64.1							
1a (5*Z*, 9*Z*)-3-Butyl-5-methyl X	31.8	29.7	61.8[e]	59.7	36.4	25.3	30.9	67.6		22.9		39.8	28.7	23.2	14.3
1b (5*E*,9*E*)-3-Butyl-5-methyl X	33.0	26.8	56.6[e]	51.8	35.3	24.9	30.6	58.9		20.9		25.2	29.6	23.3	14.3
1c (5*Z*,9*E*)-3-Butyl-5-methyl X	26.6	19.6	55.0	48.4	36.4	27.6	29.1	59.4		20.6		29.1	28.9	23.5	14.4
1d (5*E*,9*Z*)-3-Butyl-5-methyl X	33.2	32.0	55.4	47.2	33.1	19.8	30.1	58.7		7.4		28.44	28.36	23.5	14.3
2 (9*Z*)-3-Methyl X	29.2	31.6	59.9	50.9	25.7	24.7	30.7	65.3	18.8						
3 (7*Z*,9*Z*)-3,7-Dimethyl X	28.8	31.2	59.9	50.4	34.2	30.8	39.9	65.4	18.5		22.0				
4 (5*Z*,9*Z*)-3,5-Dimethyl X	30.0	32.1	60.0	58.3	36.0	25.0	31.2	67.6	25.5	22.9					

(a) Ppm from TMS. (b) *Z* and *E* refer to the *cis* and *trans* hydrogen relative to the alkyl on C-3. (c) X = octahydroindolizine. (d) E. Wenkert, J. S. Bindra, C. Chang, D. W. Cochran and F. M. Schnell, *Acc. Chem. Res.*, 7, 46 (1974). (e) Conformed by deuteration.

ment, the C-5 hydrogen becomes skewed relative to the nitrogen lone pair, and the C-5 methyl is now axial. The data for **1a** (3) was quite reasonably very similar to that for **4**. Thus placement of alkyl groups on carbons 3 and 5 , as in the pheromone **1a**, appears to alter the piperidine ring from chair to boat.

The proton nmr spectra and Bohlmann band intensities of **1b-1d** were described earlier (3) and the ^{1}H nmr data are presented in Table 1. In compound **1b** the C-5 methyl group was equatorial (1.40 ppm), and the ratio of axial to equatorial α-hydrogen was 2:1. These data permitted assignment of the *trans*-fused 6-ring chair conformation as had been determined for **2, 3,** and **5** with the butyl group on C-3 assuming a pseudoaxial position *trans* to the nitrogen lone pair. A discussion of the ^{1}H and ^{13}C nmr data for **1c** and **1d** is deferred until later.

The ^{13}C spectrum of octahydroindolizine has been recorded and the signals have been assigned (7). The methine carbons of the substituted octahydroindolizines were routinely assigned to the lowest field signals in the spectra (Table 2). Methyl carbons were distinguished from methylene carbons by comparing the proton decoupled to coupled spectra. In addition, it was possible to distinguish those methylene carbons of a butyl chain from ring methylene carbons by spin-lattice relaxation times for the set of isomers **1a-d** (see Table 3). For carbons bearing the same numbers of protons and relaxing primarily by dipole-dipole interaction, the relaxation time is related to the motions within a molecule. Because of segmented motion the relaxation time of the chain methylene carbons are normally longer than the relaxation times of the ring carbons in the same molecule. This difference formed the basis for distinguishing between the two types of methylene carbons.

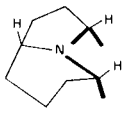
Most of the ^{13}C chemical shift assignments for **2** were made on the basis of no significant difference expected from the parent heterocyclic other than those due to substituent shifts induced by the pseudoequatorial 3-methyl carbon. An α-effect of +5.6 ppm has been found for equatorial methyl in cyclohexane and piperidine rings (12), and the α-effect of a methyl on cyclopentane was found to be +9.3 ppm (13). The assignment of the 59.9 ppm signal of **2** to C-3 constitutes an α-effect of +6.0 ppm (59.9 ppm for **2** as compared with 53.9 ppm for C-3 of octahydroindolizine). Neither of the other two low field signals would be reasonable for C-3 in view of the magnitude and sign of the expected substituent effect. Only the signals at 31.6 ppm and 29.2 ppm deviate significantly in magnitude from the shifts of the parent heterocyclic. The choice of 31.6 ppm for the C-2 signal was based upon the resulting magnitude of the β- and γ-effects, +11.3 ppm and -0.9 ppm, respectively. The β-effects for methyl substituted pyrrolidine (14) and methylcyclopentane (13) were found to be +9.1 ppm and +9.5 ppm, respectively; the γ-effects were found to be +0.1 ppm in both compounds. The reverse assignment of 31.6 ppm for C-1 and 29.2 ppm for C-2 would give values for the β- and γ-effects of +8.9 ppm and +1.5 ppm, respectively. The unlikely high positive value noted for the γ-effect led us instead to assign 31.6 ppm to C-2. The γ-effects from the assignments to **2** were, therefore, C-1 (-0.9 ppm), C-5 (-1.8 ppm), and C-9 (+1.2 ppm). The substituent parameters derived from **2** and other compounds are in Table 4. The methyl carbon signal at 18.8 ppm was typical of a *C*-methylpyrrolidine (14).

Carbons 3,5, and 9 were expected to give essentially the same signals in **3** as in **2**, and the assignments were made accordingly. Similarly, C-1 and C-2 were rationalized as for **2**. The α- and β-effects values due to the C-7 methyl carbon of **3** were +6.4 ppm and +8.9 ppm, respectively, which is consistent with 4-methylpiperidine (15). The assignments made gave an α-effect of +6.1 ppm (comparison with **2**), a β-effect of +8.5 ppm for C-6 and +9.2 ppm for C-8. The C-3 methyl carbon signal was assigned to the value at 18.5 ppm, which is consistent with our earlier spectral interpretation. Thus the conformation of **3** is the same as for **2**. The signal for the C-7 methyl carbon was

assigned the value of 22.0 ppm based on carbon-hydrogen coupling pattern and this value is close to the 23.4 ppm value for an equatorial 4-methyl carbon on a piperidine ring (15).

Assignments for the shifts of the C-1, 2, 3, 7, 8 and 9 carbons of **4** were made on the basis of analogy with the assignments previously made. Substitution at C-5 by the methyl group shifted the C-5 signal 7.4 ppm downfield from that of **2** which, like **4** has a 3-methyl group. Carbon 6 was likewise shifted downfield by 10.3 ppm. The corresponding α-effect on C-3 in 2-methylpiperidine versus piperidine was found to be +7.6 ppm (15a) or +8.2 ppm (15b). The difference in the β-effects (2.7 ppm, or 2.1 ppm) was taken to be further evidence (*vide supra*) that the C-5 methyl carbon of **4** was not equatorially oriented on a chair piperidine ring. Furthermore, the C-3 methyl carbon was dramatically shifted downfield in **4** by 6.7 ppm (7.0 ppm) from its shift in the spectrum of **2** (3). The C-5 methyl signal appeared at 22.9 ppm, 2 ppm lower field than in **1b** and **1c**. The methyl carbon signal of 2-methylpiperidine resonates at 23.5 ppm. The downfield shifts of the methyl carbon signals of **4** can be ascribed to a *syn*-axial interaction (16) (Figure 1). Such **d**-effects are large when the carbons are in an eclipsed configuration; an extreme example of this effect is the 7 ppm downfield shift of the methyl carbons of 1,8-dimethylnaphthalene relative to 1-methylnaphthalene (17). One cannot estimate the effect experienced by the C-5 methyl carbon in **4** because the exact conformation of the molecule is presumably altered by the presence of the C-3 methyl carbon. Clearly, however, the presence of substituents in a *cis* relationship on C-3 and C-5 entailed severe steric interaction and produced unique displacement of the spectral features of the compound, which can be quite useful diagnostically. The key spectral features were identical in infrared, ^{1}H nmr, and ^{13}C nmr for the synthesized natural product, **1a**, and compound **4**.

Figure 1



Compound 4

Thus the relative substituted configurations were assumed to be the same. All of the ^{13}C signals of **1a** excepting that of C-1, 3, and 5 could be assigned within 0.5 ppm of those of **4**.

The butyl carbons were assigned on the basis of T_1 measurements, as mentioned previously. Butylcyclopentane has been examined by ^{13}C nmr (18) and our methylene carbon assignments were parallel to those. Moreover, the α- and β-effects of a butyl group are slightly different from a methyl substituent: a butyl substituent gave an α-effect of +14.8 ppm for butylcyclopentane; a methyl substituent gave an α-effect of +9.3 ppm in methylcyclopentane (18); the β-effects were +7.2 ppm and +9.3 ppm for the butyl and methyl substituent in cyclopentane, respectively. Thus, the replacement of butyl for methyl (**4** — **1a**) should cause an additional upfield shift of C-3 (we observed -1.8 ppm) and a downfield shift of C-2 (our assignment gave +2.4 ppm). Carbon-5 was also shifted downfield in **1a** by 1.4 ppm relative to **4**. The α-methylene carbon of the butyl group of **1a** was assigned to the signal at 39.8 ppm. This value was well downfield of the analogous signals of **1b-d** and it was indicative of a *syn*-axial effect resulting from the near eclipsing of this carbon with the C-5 methyl carbon.

It was convenient to deuterate **1a** at C-3. This was accomplished by reducing an iminium salt with lithium aluminum deuteride producing both **1a** and **1b** 3-D (Scheme 4). In general, the replacement of H with D on carbon increases the relaxation time of that carbon atom, but because of the usual pulse time employed for ^{13}C nmr, the carbon signal becomes saturated and the signal intensity sharply decreases. The deuterium quadrupole moment and spin coupling further reduce signal intensity. A more thorough analysis of the value of deuteration to ^{13}C nmr spectral interpretation has been described (19). The ^{13}C spectra of the deuterated compound confirmed our C-3 assignments for compounds **1a** and **1b** (that is to say the C-3 signals disappeared) and thereby substantiated our general assignment of C-3 to a lower field than C-5 i the other compounds described.

Compound **1b** had been shown by ^{1}H nmr to exist *trans*-fused with the C-5 methyl group oriented equatorially in a

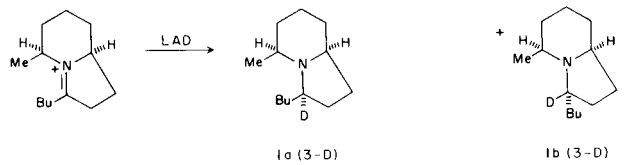
Table 3

^{13}C Spin-Lattice Relaxation Times (sec) for 3-Butyl-5-methyloctahydroindolizines

Compound (a)	Ring Carbons									butyl Carbons			
(**1a-1d**)	C-1	C-2	C-3	C-5	C-6	C-7	C-8	C-9	5-CH_3	α-CH_2	β-CH_2	γ-CH_2	δ-CH_3
(5*Z*,9*Z*)-3-Butyl-5-methyl X (b)	1.80	1.78	3.43	3.34	1.79	1.67	1.85	3.23	1.44	2.05	2.61	3.23	3.50
(5*E*,9*E*)-3-Butyl-5-methyl X	1.32	1.38	2.17	2.17	1.25	1.49	1.36	2.40	1.46	1.07	1.97	2.54	3.11
(5*Z*,9*E*)-3-Butyl-5-methyl X	1.44	1.40	2.37	2.22	1.59	1.39	1.61	2.60	2.12	1.61	2.01	2.49	3.30
(5*E*,9*Z*)-3-Butyl-5-methyl X	1.66	1.75	3.17	2.83	1.90	1.57	1.70	3.17	3.14	2.04	2.38	3.07	3.67

(a) Z and E refer to the *cis* and *trans* hydrogen relative to the alkyl on C-3. (b) X = octahydroindolizines.

Scheme 4



1a (3-D) 1b (3-D)

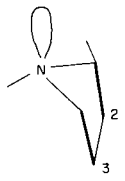
(a) This reduction (described with lithium aluminum hydride in reference 3) gave a ratio of 7:3 (**1a**:**1b**), and the ^{13}C nmr spectrum of the product mixture was examined.

chair conformation. The ^{13}C signal for the C-5 methyl carbon was assigned the value of 20.9 ppm. From this value one might estimate the *syn*-axial effect of **1a** to be about 2 ppm. The methine carbons for **1b** were all shifted upfield [C-3 assigned by deuteration as described for **1a**; C-5 (-7.9 ppm), and C-9 (-8.7 ppm)]. Since the only difference between **1b** and, for example, **2** and **3** was the position of the substituent at C-3, the axial conformation of the butyl group was evidently responsible for these changes. Consistent with the configuration of the axial butyl group was the 25.2 ppm assignment for the α-methylene carbon signal. A nitrogen lone pair *trans* oriented to a β-substituent can exert a marked shielding on that group (20). In **1b** the nitrogen lone pair is, in fact, in an axial position relative to the butyl group. The combination of lone pair-induced shielding and the reduction or absence of steric hindrance resulting from the *syn*-axial-induced deshielding noted in **1a** could produce a net upfield shift of the butyl α-methylene carbon signal of -14.6 ppm.

Consideration of the spectral data of **1c** and **1d** has been deferred to this point because unambiguous ^{13}C assignment was not possible. Compounds having substituent geometry like that of **1c** and **1d** were not readily available by synthesis, so we proceed by describing the ^{1}H nmr data making ^{13}C assignments where possible. Contrary to our initial report (3), a further purified sample of **1c** showed only a single C-5 methyl (^{1}H nmr:1.46 ppm). The ratio of axial to equatorial α-hydrogen was 1:2 and the Bohlman bands were very weak. A *trans*-fused system for **1c** would produce the same eclipsed situation for methyl and butyl substituents noted in **1a**; however, the ^{13}C nmr data could not be rationalized for this conformation. Compound **1c** was therefore considered to be *cis*-fused, and **1c-A** of the two possible chair conformations (see Scheme 3) placed the C-5 methyl axially and was sterically more crowded than **1c-B**. In addition, structure **1c-B** placed the 5-methyl equatorially; hence **1c-B** was the better alternative.

The ^{13}C nmr spectral analysis of **1c** was as follows: methyl carbon and methine carbon assignments were made as before; the assignment of the 14.4 ppm and the 20.6 ppm signals to the butyl methyl and C-5 methyl carbons, respectively, was unequivocal. In the absence of other qualifying data, the assignments of the methine carbon signals were based upon the the near geometric similarity of the methyl and butyl group to **1b**. The butyl methylene carbons were distinguished by their slower relaxation times from the ring carbons. Because the butyl shifts were not expected to change materially, relative shifts of the butyl carbons would remain the same; and assignments were made on that basis. The configuration of **1c** (**1c-B**) was such that the nitrogen lone pair would be almost *trans* to the C-9:C-1 and C-3:C-2 bonds (Figure 2) and, thus, would inflict a shielding effect on the C-1 and

Figure 2

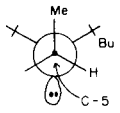


1c-B

C-2 carbons (20). The high field methylene carbon signal, 19.6 ppm, was therefore tentatively assigned to C-2; this assignment constituted an upfield shift of -7.2 ppm from **1b** for that carbon. A similar effect on C-1 would be expected; hence the 26.6 ppm signal was assigned tentatively to that carbon although the 27.6 ppm signal assigned to C-7 cannot be readily ruled out. The C-6 and C-8 carbons were then assigned with little change from **1a** and **1b**.

The ^{1}H nmr data for **1d** indicated a very shielded C-5 methyl group (1.36 ppm). A possible conformation was a *trans*-fused chair arrangement (Scheme 3) that placed the C-5 methyl group axially and *trans* to the nitrogen lone pair. The ratio of axial to equatorial α-hydrogen should be 2:1 and considerable Bohlmann absoprtion should occur. This was indeed the case. The ^{13}C nmr data supported this conformational assignment of the C-5 methyl carbon which resonated at 7.4 ppm. This strong upfield shift (13-15 ppm compared with its isomers **1a-c**) was the result of the positioning of the C-5:C-5 methyl carbon bond *trans*

Figure 3



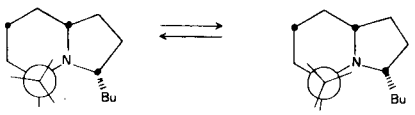
1d Sighted Down the C-5:N Bond

to the nitrogen lone pair (Figure 3). The butyl carbons were assigned as for **1c**; the distinction between the α- and β-methylene carbons (28.44 ppm and 28.36 ppm) could be made on the basis of T_1 measurements. The β-methylene carbon should have greater segmented motion and, therefore, a longer relaxation time (2.38 to 2.04 seconds in our experiments). The methine carbons were distinguish-

able from other carbons, as previously, by their downfield shifts and relaxation times longer than those of the ring methylene carbons. However, again insufficient qualifying data existed for complete assignment of either the methines or ring methylene carbons though tentative assignments are given based upon analogy to **1b**. The signal at 19.8 ppm was assigned to C-7 and represented an upfield shift of -4.4 ppm relative to C-7 of the parent compound, **1**. The γ-shift of an axial methyl group on a chair cyclohexane ring was reported as -5.4 ppm (21).

It was instructive to compare the T_1 values of the methyl carbons of **1a-d** (Table 3). Although the relaxation times of the butyl methyl carbons remained fairly constant, ranging from 3.11 to 3.67 seconds in our experiments, T_1 values for the C-5 methyl carbons of **1a-c** were 1.44 to 2.12 seconds and for **1d** was 3.14 seconds. A methyl group attached to a carbon chain has considerable rotational freedom and, therefore, a slower relaxation rate (longer T_1). The shorter relaxation time of the C-5 methyl carbons was caused by their somewhat slower rotation related to their proximity to the the ring system. However, the C-5 methyl carbon of **1d** exhibited a markedly longer T_1. Rotational rates can be high despite elevated potential energy barriers if the potential wells are themselves of high energy. A classic example of such a situation was reported for the methyl carbons of 9-methylanthracene (T_1 = 14.0 sec) and 1-methylnaphthalene (T_1 = 5.8 sec) (22). The longer relaxation (*i.e.*, faster rotation) of the methyl carbon of the anthracene indicated comparably unfavorable interactions for all rotameric conformations. The C-5 methyl protons of **1d** (Figure 4) could interact sterically with the axial hydrogens on C-3, 7, and 9 or with the C-5 H in each of its rotameric conformations. Thus the rotation was faster for this methyl group than for **1a-c**, and the relaxation time of the carbon was greater.

Figure 4



1d Sighted Down the C-5 Methyl: C-5 Bond

EXPERIMENTAL

Proton decoupled ^{13}C nmr data were obtained on a Varian CFT-20 (23) equipped with a single sideband crystal filter. A pulse width of 14μs was used to collect between 100 and 500 transients of 8K data points. A sensitivity factor of -0.4s was used to enhance the signal-to-noise ratio further. Spectra were obtained at an equilibrium temperature of 44°. Samples dissolved in deuteriochloroform (and containing TMS for reference) were placed in 5 mm nmr tubes and each sample tube was then coaxially mounted in an 8 mm nmr tube. Deuterium oxide was used to obtain a deuterium lock and was contained in the annular space between the 5 and 10 mm nmr tubes.

Table 4

Substituent Parameters for Octahydroindolizines (a)

3-Me (*cis*) (b)	5-Me (*cis*) (b)	7-Me (*cis*) (b)
α, C-3, +6.0	c	α, C-7, +6.6
β, C-2, +11.3	β, C-6, +10.9	β, C-6, +9.1
γ, C-1, - 0.9	γ, C-7, + 0.8	β, C-7, +9.2
γ, C-5, - 1.8		γ, C-5, -0.5
γ, C-9, + 1.2		γ, C-9, +0.1

(a) These data would be strictly applicable only in the *trans*-fused system with the piperidine ring in a chair conformation. (b) The *cis* assignment is based on the relationship of the methyl substituent to the site of attachment of the pyrrolidine ring to C-9. (c) Only those sites unaffected by substitution at C-3 were examined.

Relaxation times were measured by using the (180°-τ-90°-T) pulse sequence and calculated from an exponential least-squares regression fit of the data (23). No effort was made to de-gas the samples since any dissolved oxygen would have negligible effect on the short relaxation times found.

Proton nmr spectra were obtained in carbon tetrachloride or trifluoroacetic acid solution by using a Varian HA-100-A spectrometer (24). Infrared data were obtained for 1% carbon tetrachloride solutions with a Beckmann Acculab-3 instrument (24). A Fisher-Johns hot stage instrument (24) was employed to measure melting points, and gas chromatographic data were obtained with a Hewlett-Packard 5730A instrument (24) employing a 20 inch × 0.125 inch column of 10% UCW-982 on 80-100 WAW-DMCS. Combustion analyses were obtained from the analytical section of the Laramie Energy Technology Center, Laramie, Wyoming.

Synthesis of the Octahydroindolizines.

The synthesis and characterization of compounds **1a-1d** have been described (3). The details of the preparation of compounds **2, 3,** and **4** were essentially the same as for **1a**. Thus, **2** was synthesized by alkylating the anion of 2-methylpyridine in THF with propylene oxide (Scheme 2). The resulting 2(3-hydroxybutyl)pyridine was converted to its hydrobromide, and then to the corresponding secondary bromide with triphenylphosphine dibromide; the free base was heated under reflux in acetone to produce 3-methyl-1,2-dihydroindolizinium bromide. The dihydroindolizinium salts were isolated as iodides and were obtained in 40-50% yields. Thus, from 2-methylpyridine was obtained 3-methyl-1,2-dihydroindolizinium iodide, m.p. 149-151° (methanol-ether). From 2,6-dimethylpyridine was obtained the 3,5-dimethyl derivative, m.p. 175° dec., and from 2,4-dimethylpyridine was obtained the 3,7-dimethyl analog, m.p. 151-153° (methanol-ether). ^1H nmr data for these iodides (DMSO-d_6) were in accord with the assigned structures. Reduction in ethanol with platinum oxide at 42 psi produced the hydriiodides of **2, 3,** and **4** in quantitative yield.

Compound **2**.

This compound has m.p. 250° dec.

Anal. Calcd. for $C_9H_{16}IN$: C, 40.46; H, 6.79; N, 5.24. Found: C, 40.88; H, 6.72; N, 5.27.

Compound **3**.

This compound had m.p. 184-186° (methanol).

Anal. Calcd. for $C_{10}H_{20}IN$: C, 42.71; H, 7.17; N, 4.98. Found: C, 43.15; H, 7.32; N, 4.99.

Compound **4**.

This compound had m.p. 190° dec.

Anal. Calcd. for $C_{10}H_{20}IN$: C, 42.71; H, 7.17; N, 4.98. Found: C, 43.19; H, 7.42; N, 4.99.

The free bases were distilled *via* short path under reduced pressure and checked for purity by gas chromatography.

Acknowledgment.

The work upon which this report is based was done under a cooperative agreement between the Department of Energy, Laramie Energy Technology Center, and the University of Wyoming; and a cooperative agreement between Federal Research, Science and Education Administration, USDA, and the University of Wyoming.

REFERENCES AND NOTES

(1) F. J. Ritter, I. E. M. Rotgans, E. Talman, P. E. J. Verwiel and F. Stein, *Experientia*, **29**, 530 (1973).

(2) E. Talman, F. J. Ritter and P. E. J. Verwiel, *Proc. Instum. Symp. Mass Spectrom., Biochem. Med., Milan*, 1973.

(3a) J. E. Oliver and P. E. Sonnet, *J. Org. Chem.*, **39**, 2662 (1974); (b) P. E. Sonnet and J. E. Oliver, *J. Heterocyclic Chem.*, **12**, 289 (1975).

(4) F. J. Ritter and C. J. Persoons, *Neth. J. Zool.*, **25**, 261 (1975).

(5) F. J. Ritter, I. E. M. Bruggemann-Rotgans, P. E. J. Verwiel, C. J. Persoons and E. Talman, *Tetrahedron Letters*, 2617 (1977).

(6) G. T. Pearce, W. E. Gore and R. M. Silverstein, *J. Magn, Reson.*, **27**, 497 (1977).

(7a) E. Wenkert, J. S. Bindra, C. Chang, D. W. Cochran and F. M. Schell, *Acc. Chem. Res.*, **7**, 46 (1974); (b) Octahydroindolizine is *trans*-fused at room temperature, G = -2.4 kcal./mole; H. S. Aaron and C. P. Ferguson, *Tetrahedron Letters*, 6191 (1968).

(8) B. Luning and C. Lundin, *Acta. Chem. Scand.*, **21**, 2136 (1967).

(9) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

(10) A. E. Theobald and R. G. Lingard, *Spectrochim. Acta, Part A*, **24**, 1245 (1968).

(11a) H. Hamlow, S. Okuda and N. Nakagawa, *Tetrahedron Letters*, 2553 (1964); (b) F. Bohlmann, D. Schumann and H. Schulz, *ibid.*, 173 (1965).

(12) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N. Y., 1972, pp. 65, 272.

(13) M. Christl, H. J. Reich and J. D. Roberts, *J. Am. Chem. Soc.*, **93**, 3463 (1971).

(14) D. G. Hawthorne, S. R. Johns and R. I. Willing, *Aust. J. Chem.*, **29**, 315 (1976).

(15a) G. Ellis and R. G. Jones, *J. Chem. Soc., Perkin Trans II*, 437 (1972); (b) Reference 12, p. 272.

(16) S. H. Grover, J. P. Guthrie, J. B. Stothers and C. T. Tan, *J. Magn. Reson.*, **10**, 227 (1973).

(17) A. J. Jones, P. D. Gardner, D. M. Grant, W. M. Litchman and V. Boekelheide, *J. Am. Chem. Soc.*, **92**, 2386 (1970).

(18) J. Q. Adams and L. P. Lindeman, "Abstracts of Division of Petroleum Chemistry, 163rd National American Chemical Society Meeting, Boston, April 9-14 (1972).

(19) G. W. Gribble, R. B. Nelson, J. L. Johnson and G. C. Levy, *J. Org. Chem.*, **40**, 3720 (1975).

(20) G. J. Jordan and D. R. Crist, *Org. Magn. Reson.*, **9**, 322 (1977), and references therein.

(21) Reference 12, p 65.

(22) G. C. Levy, *Acc. Chem. Res.*, **6**, 161 (1973).

(23) D. A. Netzel, Ph.D. Thesis [Northwestern University, Evanston, Il, (1975)]. Computer program written by Dr. W. W. Conover of the University of Chicago.

(24) Mention of proprietary product does not constitute an endorsement by the U.S. Department of Agriculture, the U.S. Department of Energy, or the University of Wyoming.