Nuclear Magnetic Resonance Spectral Analysis of the Ergot Alkaloids[1]

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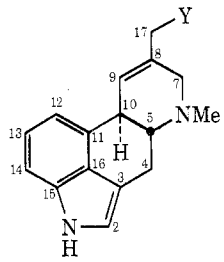
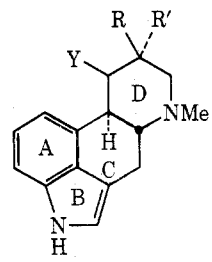
A full analysis of the pmr chemical shifts and coupling characteristics of the ergot alkaloids agroclavine, elymoclavine (and its acetate), festuclavine, and fumigaclavine B is described and some earlier assignments relating to their stereochemistry are revised. The ^{13}C nmr spectra of the ergoline bases methyl lysergate, its dihydro product, ergonovine, ergonovinine, ergotamine, ergotaminine, ergokryptinine, agroclavine, elymoclavine acetate, and festuclavine, their derivatives and models were recorded and their chemical shifts assigned. The cmr analysis confirms the stereochemistry of the alkaloids and the pmr signal assignment in the case of elymoclavine acetate. Pmr and cmr analyses of fumigaclavine B establish the stereochemistry of this rare alkaloid.

The hallucinogenic activity of some lysergic acid derivatives[3] and the antitumor activity of various ergolines[4] have reawakened recently interest in the structure[5-7] and biosynthesis[8] of the ergot alkaloids. The complete absence of available ^{13}C nmr spectral data on this alkaloid family and the disagreement between ^{1}H nmr spectral data on some clavine members of the group[7] with their established stereochemistry[9,10] necessitated a general nmr study of the ergot alkaloid system. As a consequence the complete pmr analysis of four clavines—agroclavine (**1a**), elymoclavine (**1b**) (and its acetate **1c**), festuclavine (**2a**), and fumigaclavine B (**2c**)—and cmr analysis of selected members of the clavine and lysergic acid types of ergot alkaloids were undertaken.



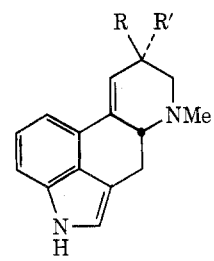
1a, Y = H
b, Y = OH
c, Y = OAc



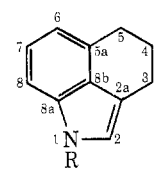
2a, R = Me; R′ = Y = H
b, R = CO_2Me; R′ = Y = H
c, R = H; R′ = Me; Y = OH

Proton magnetic resonance spectra at 220 MHz were run on deuteriopyridine solutions of agroclavine (**1a**) and elymoclavine acetate (**1c**) and on a deuteriochloroform solution of elymoclavine (**1b**). The interrelationship of the hydrogens of rings C and D was established by analysis of the spin-spin coupling characteristics deduced from the spectral fine structure, intensity distribution and width of the complex, but nearly first-order multiplets. The identification of the C-5 and C-7 hydrogens was confirmed by the observation of an expected deshielding effect exerted by the neighboring positive nitrogen on the addition of trifluoroacetic acid to the solution of agroclavine (**1a**).[11] The chemical shifts and coupling constants of the three compounds are listed in Table I. The coupling constant for the hydrogens at the bridgehead carbons 5 and 10 proved to be 9.5 Hz, consistent with their being cis and nearly eclipsed or trans with a dihedral angle of somewhat less than 180°. Since the constraint of the indole ring upon ring C does not tolerate an eclipsed, cis arrangement, the coupling data prove a trans C/D stereochemistry. This result is in agreement with stereostructure 1 for clavines on the basis of chemical interconversions.[9,12,13] While it is in contradistinction to stereochemical arguments based on an earlier pmr study of agroclavine (**1a**) and elymoclavine (**1b**),[7] the previous analysis involved incorrect chemical shift assignment of the 4α, 4β, and 5 hydrogens.

Inspection of the 220-MHz pmr spectra of deuteriochloroform solutions of festuclavine (**2a**) and fumigaclavine B (**2c**) and analysis by the above procedure yielded shift and coupling data for these ergot alkaloids (Table I). The coupling patterns indicate the natural bases to possess trans C/D configurations. Festuclavine (**2a**) exhibits an equatorial C-8 methyl group in accord with chemical findings,[12b,14] while fumigaclavine B (**2c**) shows its 8-methyl and 9-hydroxy functions to be axially oriented. Fumigaclavine B (**2c**) had been considered to possess a H-5/H-8 cis configuration,[15] *i.e.*, an equatorial 8-methyl orientation, on the basis of its base-induced dehydration leading to lysergine (**3a**). However, this experiment does not prove the configuration of the *C*-methyl group in **2c**, since the powerful base needed to execute the dehydration can be expected also to epimerize the C-8 hydrogen of the product and lysergine (**3a**) would be predicted to be more stable than isolysergine (**3b**). This argument is buttressed strongly by the observation of the base-catalyzed isomerization of agroclavine (**1a**) into a mixture of lysergines affording preponderantly lysergine (**3a**).[13]



3a, R = Me; R′ = H
b, R = H; R′ = Me
c, R = CO_2Me; R′ = H
d, R = $CONHCH(CH_3)CH_2OH$; R′ = H
e, R = H; R′ = $CONHCH(CH_3)CH_2OH$
f, R = CO⊣; R′ = H
g, R = H; R′ = CO⊣



4a, R = H
b, R = Me

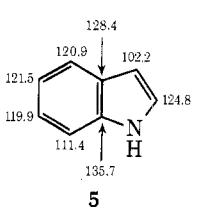
The analysis of the ergot alkaloid family by the natural abundance ^{13}C nmr spectral method was initiated by an inspection of the proton-decoupled and single-frequency off-resonance decoupled cmr spectra of the tricyclic models **4a**[16] and **4b**, prepared from **4a** by treatment with sodium hydride and methyl iodide. Assignment of the carbon shifts of the two compounds relies heavily on a comparison with the reported δ values for indole (**5**) and its 3- and 4-methyl derivatives, **6** and **7**, respectively.[17] Carbons 2, 8, and 8a are apparent from the expected shift pertur-

Table I
^{1}H Chemical Shifts and Coupling Constants

	1a[a]		1b		1c[b]		2a		2c	
	δ	J	δ	J	δ	J	δ	J	δ	J
4α	2.78	dd 15, 12	2.89	dd 15, 12	2.74	dd 15, 12	2.68	dd 15, 11.5	2.58	dd 11, 11
4β	3.31	dd 15, 4	3.37	dd 15, 4	3.27	dd 15, 4	3.39	dd 15, 4.5	3.29	dd 11, 2
5	2.52	ddd 12, 9.5, 4	2.68	ddd 12, 9.5, 4	2.53	ddd 12, 9.5, 4	2.10	ddd 11.5, 9.5, 4.5	2.66	ddd 11, 11, 2
7α	3.24	d 17	3.65	d 17	3.37	d 17	2.95	d[c] 11	3.38	d 12
7β	2.93	dd[c] 17, 4	3.08	dd[c] 17, 4	2.95	dd[c] 17, 4	1.87	t 11	2.82	dd 12, 4
8							2.01	ddd 12, 11, 6.5	2.15	m
9α	6.18	s[c]	6.80	s[c]	6.47	s[c]	2.63	dd[c] 12, 3.5	4.51	s[c] $W_{1/2}$ 6
9β							1.08	q 12		
10	3.74	dd[c] 9.5, 4	4.00	dd[c] 9.5, 4	3.76	dd[c] 9.5, 4	2.97	ddd 12, 9.5, 3.5	2.58	d 11
17	1.77	s	4.45	s	4.66 4.46	AB 12	0.99	d 6.5	1.25	d 7
NMe	2.49	s	2.45	s	2.48	s	2.45	s	2.39	s

[a] Signals of the 4β, 5, 7α, 7β, and NMe hydrogens in $CDCl_3$ with added trifluoroacetic acid appear at 3.19, 2.68, 3.33, 3.13, and 2.56 ppm, respectively, all other signals remaining virtually unchanged. [b] Acetate methyl hydrogens at 2.04 ppm. [c] Broad signal.

bation of N-methylation.[17] Carbons 2a and 5a are deshielded each by *ca.* 10 ppm with respect to C-3 and C-5 of indole (**5**) in analogy with the *ca.* 9 ppm Δδ value for methylation of these indole carbons. While the C-7 shift is close to that of the equivalent center in indole (**5**) and 4-methylindole (**7**), C-6 is shielded anomalously by 7 ppm in comparison to C-5 of **7**. This strong abnormality, also encountered by C-2 (Δδ 4.4 ppm with **6**) and to a smaller extent by most of the aromatic carbons, is due to the strain imposed on the indole nucleus by the trimethylene bridge, an effect reminiscent of the 9-ppm shielding experienced by the ortho methines C-2 and C-7 on conversion of 1,8-dimethylnaphthalene into the strained acenaphthene.[18] Carbon 8b is the only remaining aromatic center, while C-4 is the highest field methylene in view of its feeling the least number of β effects among the three methylenes. Differentiation of the benzylic methylenes relies tentatively on the expected perturbation of their shifts upon imposition of another ring on C-4 and C-5 in the creation of the ergot alkaloid system (*vide infra*). All δ values of tricycles **4a** and **4b** are depicted on formulas **8** and **9**, respectively.



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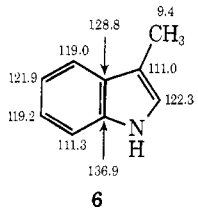

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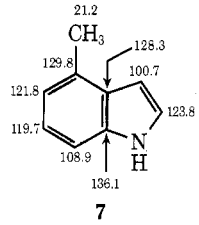

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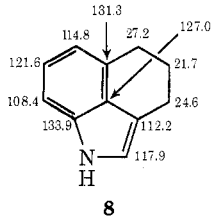

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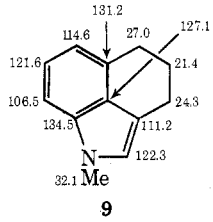

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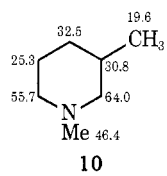
With the chemical shifts of the model **4a** (**8**) in hand and with the recognition of all nonaromatic carbons of agroclavine (**1a**) and elymoclavine acetate (**1c**) being environmentally unique, the cmr analysis of these clavines is easy and dependent on the application of simple chemical-shift theory.[19] Carbon 12 of these compounds feels the shielding peri effect on the imposition of a new ring onto model **8** (Table II).[20]

The carbon shift analysis of festuclavine (**2a**) and methyl 9,10-dihydrolysergate (**2b**) is facilitated by the determination of the C-4 resonance of the clavines **1a** and **1c** (*vide supra*), since the δ values of C-4 and the aromatic carbons would be expected to remain unchanged for compounds of identical C/D ring juncture. Application of standard shift theory[19] elucidates all chemical shifts of the environmentally unique, ring D carbons of festucalvine (**2a**) and methyl 9,10-dihydrolysergate (**2b**) except C-8 and C-10. Differentiation of this carbon pair relies on the shift constancy of C-10 in the two alkaloids (Table II).

While the cmr data discussed thus far are consistent only for a common configuration of the C/D ring juncture among compounds **1a**, **1c**, **2a**, and **2b**, the relative stereochemistry of the bridgeheads required further elaboration. The following interpretation of stereochemically significant features of the ring D carbon shifts of festuclavine (**2a**) and comparison with the shifts of 1,3-dimethylpiperidine (**10**)[21] proves a C-5/C-10 trans stereochemistry for the four substances. On the assumption of festuclavine (**2a**) having its ring D in a chair conformation and of 1,3-dimethylpiperidine (**10**) being in a similar conformational constraint with its methyl groups preponderantly equatorially oriented, the alkaloid can be assessed to have an equatorial methyl group and C-7 and C-8 unencumbered by nonbonded interactions with ring C carbons. This limits festuclavine (**2a**) to the conformational representation **11**.



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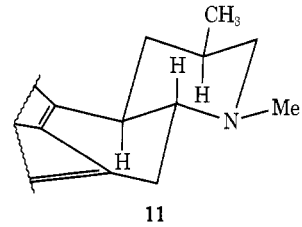

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The chemical shift assignment of all carbons of fumigaclavine B (**2c**) except of its nonaromatic methines follows previous arguments, while the shift analysis of these methines is interwoven intimately with the stereochemistry of their substituents. The identity of the C-4 methylene shift with that of all clavines **1** and **2** is suggestive of a C/D trans configuration.[22] The C-7 signal in the spectrum of **2c** being 8 ppm upfield of that in the festuclavine (**2a**) spectrum is compatible only with the summation of a

Table II
^{13}C Nmr Chemical Shifts of Clavine and Lysergic Acid Systems

	1a[a]	1c[b]	2a[b,c]	2b[d]	2c[a]	3c[b]	3d[d]	3e[d]	3f-12[d]	3g-13[d]	3g-14[d]
C-2	118.3	117.9	117.7	118.4	117.9	118.2	119.1	119.0	119.4	119.7	119.4
C-3	111.2	111.3	110.5	109.9	110.6	110.2	108.9	108.9	108.8	109.0	108.2
C-4	26.4	26.4	26.6	26.4	26.6	26.9	26.8	26.9	26.6	26.9	26.7
C-5	63.6	63.4	66.7	66.4	60.7	62.6	62.6	62.0	62.4	61.7	61.9
C-7	60.2	56.8	65.0	58.3	56.9	54.6	55.5	54.0	55.1	53.0	53.7
C-8	131.9	130.9[e]	30.2	39.3	35.8	41.8	42.8	~42.2	42.5	41.8	~42.2
C-9	119.4	124.8	36.2	30.3	68.1	117.6	120.1	119.0	118.3	118.1	117.6
C-10	40.8	40.5	40.4	40.7	41.4	136.0	135.0	136.1	136.0	137.1	136.7
C-11	131.9	131.3[e]	132.7[e]	132.0	130.8	127.6	127.4	127.6	127.1	127.9	126.7
C-12	112.0	112.2	112.0	112.0	112.9	112.0	111.0	111.0	111.0	111.4	111.5
C-13	122.0	122.6	122.0	122.0	122.0	122.9	122.4	122.1	122.2	122.4	122.2
C-14	108.4	108.7	108.3	108.7	108.0	109.4	109.0	109.8	110.2	110.3	110.2
C-15	134.0	133.4	133.1	133.2	134.0	133.7	133.7	133.7	133.8	133.8	133.6
C-16	126.6	126.1	125.9	125.8	122.9	125.9	125.8	125.7	125.9	126.1	125.8
C-17	19.9	66.2	19.3	173.6	16.5	172.4	171.2	172.1	174.3	175.3	175.8
NMe	40.2	40.5	42.7	42.4	42.9	43.4	43.4	43.6	43.4	42.5	42.6
Me		20.6		51.5		51.9	17.4	17.2			
C=O		170.7									
NCH							46.4	46.2			
OCH_2							64.4	64.3			

[a] In pyridine-d_5 solution. [b] In $CDCl_3$ solution. [c] δ(pyridine-d_5) = $\delta(CDCl_3) \pm 0.3$ ppm except for C-13 and C-16, which are 120.8 and 121.7 ppm, respectively. [d] In DMSO-d_6 solution. [e] Signals in any one column may be reversed.

Table III
^1H–^{13}C Chemical Shift Correlation of Elymoclavine Acetate (1c)

	$\delta(^{13}C)$	Calcd $\delta(^1H)$[a]	Exptl $\delta(^1H)$[b]
Ac Me	20.6	2.04[b]	2.04
C-4	26.4	2.99	3.01[c]
NMe	40.5	2.49	2.48
C-10	40.5	3.69	3.76
C-7	56.8	3.22	3.16[d]
C-5	63.4	2.50	2.53
C-17	66.2	4.56	4.56[e]

[a] Each value is ± 0.05 ppm. [b] From Table I. [c] The average of 3.27 and 2.74 ppm. [d] The average of 3.37 and 2.95 ppm. [e] Center of gravity of AB pair of doublets.

γ effect of 5 ppm by an axial 9-hydroxy group and a reduced β effect of 3 ppm by the reorientation of the 8-methyl group from an equatorial into an axial conformation. The presence of an axial hydroxy function in fumigaclavine B (**2c**) is in consonance with the abnormally high-field resonance of C-5 ($\Delta\delta$ 5.9 ppm with C-5 of **2a**). Identification of the latter leads to the immediate shift designation for C-9 in view of this oxymethine being expected to exhibit a low-field signal. The cancellation of a γ effect by an axial β effect on C-10 produces nearly the same chemical shift for this methine in festuclavine (**2a**) and fumigaclavine B (**2c**). Finally, C-8 is allotted its shift by being the remaining methine. All these arguments support strongly stereostructure **2c** for fumigaclavine-B.

While both the ^1H and ^{13}C nmr spectra of the clavines 1 and 2 now showed the substances to belong to the C/D trans series, the recent misinterpretation of the pmr spectra of **1a** and **1b**[7] necessitated careful checking of the above ^1H nmr results. As a consequence a cmr method of analysis was used to determine the chemical shifts of the nonaromatic hydrogens of elymoclavine acetate (**1c**) and their relationship to specific carbon shifts.[23] This method is based on a graphical technique[23] involving the plotting of residual splitting observed in a series of single-frequency, off-resonance, decoupled cmr spectra spanning the pmr spectral region of interest against the decoupling frequency. The pairs, trios, and quartets of resultant straight lines corresponding to methine, methylene, and methyl resonances, respectively, intersecting at the locus at which the residual splitting constant and concomitantly the distance between the frequencies of a specific hydrogen and the applied radiation equal zero yield the δ values of hydrogens bound to specific carbons.[24] While the technique leads to the same information obtainable by specific hydrogen decoupling experiments, it has the advantage of defining all hydrogen resonances without prior knowledge of the pmr spectrum and otherwise time-consuming optimization of carbon signals.

The calculated ^1H δ values depicted in Table III were acquired by assigning to the known hydrogen resonance of the unambiguous acetate methyl group the measured decoupling frequency at the time of total collapse of the fine structure of the carbon signal at 20.6 ppm into a singlet and then adding to this frequency the measured difference (in hertz) of its value and that of the frequency of the locus of multiplet collapse of each nonaromatic carbon signal. The ^1H shift data of Table III are based on the experimental results shown in Figure 1. The nonequivalent, methylene carbon signals of C-4 and C-7 require special treatment. Were narrow line width associated with their residual splitting multiplets, their one-bond ^1H–^{13}C coupling could be expected to be reflected solely by the diagonal and parallel, dashed, vertical lines in their plot in Figure 1. Since in practice not all long-range ^1H–^{13}C couplings are eliminated in the single-frequency, off-resonance, decoupled cmr spectra and the signals display bandwidths of several hertz, the central components of the reduced splittings cannot be analyzed individually. However, the individual hydrogen resonances can be determined in view of their being equidistant from the frequency representing the confluence of the diagonal lines in Figure 1. The magnitude of the bandwidths of the C-4 and C-7 signals is described by the size of the separation of the dashed, vertical lines in their plots and the center of the broad signals by the solid vertical lines.

A large number of ergot alkaloids are based structurally on the lysergic acid system (**3**). An analysis of the cmr spectra of five natural products, ergonovine (**3d**), ergonovinine (**3e**), ergotamine (**3f-12**), ergotaminine (**3g-13**), and ergokryptinine (**3g-14**), was undertaken and modeled after the chemical shift assignment of methyl lysergate (**3c**). The latter was easy in view of the uniqueness of each nonaromatic carbon center. All chemical shifts of the model and the alkaloids are listed in Table II. Expectedly, conjugation of the ring D double bond with the indole nucleus

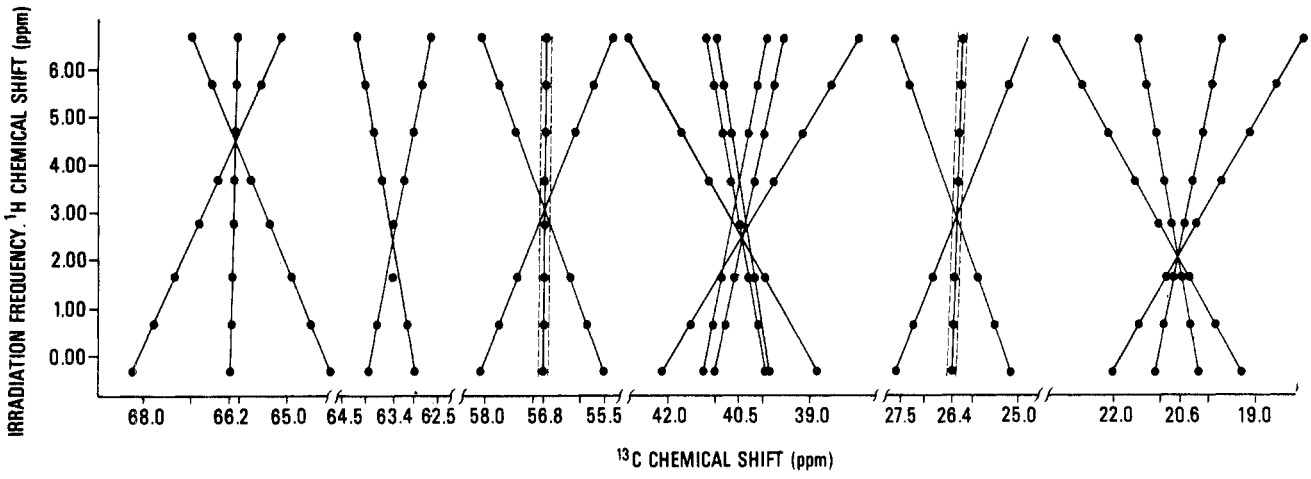
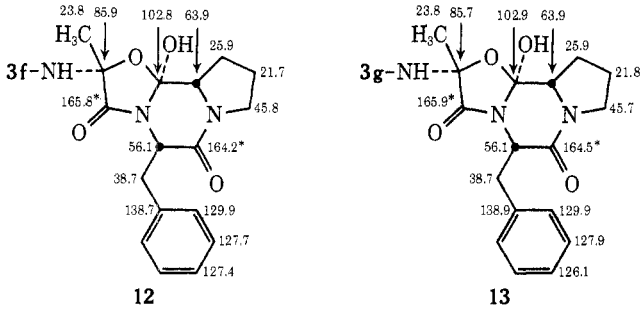
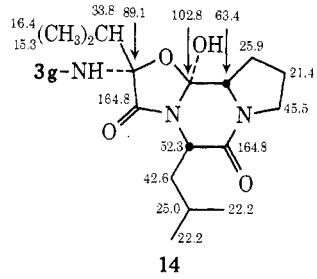


Figure 1. ^{1}H–^{13}C chemical shift correlation for elymoclavine acetate (**1c**).

modifies the C-11 and C-14 shifts.[19] As the $\Delta\delta$(C-7) for methyl lysergate (**3c**) and its dihydro derivative (**2b**) indicates, the introduction of a double bond into the piperidine nucleus shields the homoallyl carbon (*i.e.*, C-7).[25] While a difference of the chemical shift of C-8 for the quasi-equatorial (**3d, 3f-12**) and quasi-axial C-8 carboxamido compounds (**3e, 3g-13, 3g-14**) is noticeable, it is minimal and hence of little stereochemically diagnostic value. However the $\Delta\delta$(C-7) is sterically more revealing.

Application of chemical shift theory and recourse to carbon shift data of peptides[26] allow the assignment of the aminopropanol carbons of ergonovine (**3d**) and ergonovinine (**3e**) (Table II) as well as the environmentally diverse carbons of the peptide portions of ergotamine (**3f-12**), ergotaminine (**3g-13**), and ergokryptinine (**3g-14**). The shifts of the latter are designated on formulas **12**, **13**, and **14**, respectively.





Experimental Section

The pmr spectra were recorded on a Varian HR-220 spectrometer at 16°. The pmr δ values in Tables I and III are in parts per million downfield from TMS (used as internal standard). The J values in Table I are in hertz. The cmr spectra were obtained on a Varian DP-60 spectrometer operating in the Fourier transform mode at 15.08 MHz and 25–40° and on a Varian XL-100-15 Fourier transform spectrometer at 33°. The cmr δ values of Tables II and III and on formulas **5–10** and **12–14** are in parts per million downfield from TMS [δ(TMS) = δ($CDCl_3$) + 76.9 = δ(pyridine-d_5 C-4) + 134.6 = δ(DMSO-d_6) + 39.5 ppm], those of formulas **5–7** having been converted from the CS_2 scale [δ(TMS) = δ(CS_2) + 192.4 ppm].[17] Starred δ values within any one formula may be reversed.

1-Methyl-1,3,4,5-tetrahydrobenz[*cd*]indole (9). A 50% dispersion of sodium hydride in mineral oil, 435 mg, was added to a stirring solution of 1.45 g of **8** in 25 ml of dry dimethylformamide under nitrogen and the mixture was stirred while being cooled in ice for 15 min. A solution of 1.30 g of methyl iodide in 25 ml of dimethylformamide was added and the stirring mixture was allowed to warm to room temperature during 20 min. Cold water was added and the mixture was extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated. Vacuum distillation of the product yielded **9**, bp 169–172° (8 Torr).

Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 83.99; H, 7.78; N, 8.27.

Registry No.—**1a**, 548-42-5; **1b**, 548-43-6; **1c**, 5080-45-5; **2a**, 569-26-6; **2b**, 35470-53-2; **2c**, 6879-93-2; **3c**, 4579-64-0; **3d**, 60-79-7; **3e**, 479-00-5; **3f-12**, 113-15-5; **3g-13**, 639-81-6; **3g-14**, 511-10-4; **8**, 826-67-5; **9**, 50921-47-6.

References and Notes

(1) Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. XXI. For paper XX see N. Neuss, H. E. Boaz, J. L. Occolowitz, E. Wenkert, F. M. Schell, P. Potier, C. Kan, M. M. Plat, and M. Plat, *Helv. Chim. Acta*. **56**, 2660 (1973).
(2) (a) Eli Lilly and Co.; (b) Purdue University; (c) Indiana University.
(3) A. Hofmann in A. Burger, "Drugs Affecting the Central Nervous System," Vol. 2, Marcel Dekker, New York, N. Y., 1968, p 169.
(4) H. G. Floss, J. M. Cassady, and J. E. Robbers, *J. Pharm. Sci.*, **62**, 699 (1973).
(5) R. W. Baker, C. Chothia, P. Pauling, and H. P. Weber, *Mol. Pharmacol.*, **9**, 23 (1973).
(6) K. Bailey and A. A. Grey, *Can. J. Chem.*, **50**, 3876 (1972).
(7) R. G. Mrtek, H. L. Crespi, G. Norman, M. I. Blake, and J. J. Katz, *Phytochemistry*. **7**, 1535 (1968).
(8) H. G. Floss, *Abh. Deut. Akad. Wiss. Berlin*. 395 (1972).
(9) A. Stoll and A. Hofmann in R. H. F. Manske, "The Alkaloids," Vol. VIII, Academic Press, New York, N. Y., 1965, p 725.
(10) A. Hofmann, "Die Mutterkornalkaloide," F. Enke Verlag, Stuttgart, Germany, 1964.
(11) J. C. N. Ma and E. W. Warnhoff, *Can. J. Chem.*, **43**, 1849 (1965).
(12) (a) S. Yamatodani and M. Abe, *Bull. Agr. Chem. Soc. Jap.*, **19**, 94 (1955); (b) *ibid.*, **20**, 95 (1956); (c) *ibid.*, **21**, 200 (1957).
(13) E. Schreier, *Helv. Chim. Acta*. **41**, 1984 (1958).
(14) S. Yamatodani and M. Abe, *J. Agr. Chem. Soc. Jap.*, **28**, 44, 501 (1954).
(15) J. F. Spilsbury and S. Wilkinson, *J. Chem. Soc.*, 2085 (1961).
(16) A. B. A. Jansen, J. M. Johnson, and J. R. Surtees, *J. Chem. Soc.*, 5573 (1964).
(17) R. G. Parker and J. D. Roberts, *J. Org. Chem.*, **35**, 996 (1970).
(18) A. J. Jones, T. D. Alger, D. M. Grant, and W. M. Litchman, *J. Amer. Chem. Soc.*, **92**, 2386 (1970).
(19) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N. Y., 1972; G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N. Y., 1972.
(20) Comparison of the δ values of agroclavine (**1a**) with those of elymoclavine acetate (**1c**) (Table II) shows that the effect of the introduction of an acetoxy group at C-17 is expectedly shielding on C-7 and surprisingly deshielding on C-9. The latter phenomenon is a consequence of the allyl acetate effect (E. Wenkert and E. W. Hagaman, unpublished observations) first referred to in the prostaglandin field [G. Lukacs, F. Piriou, S. D. Gero, D. A. van Dorp, E. W. Hagaman, and E. Wenkert, *Tetrahedron Lett.*, 515 (1973)].
(21) D. W. Cochran, Ph.D. Dissertation, Indiana University, 1971.

(22) A cis ring juncture would be expected to shield C-4 by a decreased β effect of N_b in one conformation or an added γ effect from C-7 in another conformation.
(23) *Cf.* B. Birdsall, N. J. M. Birdsall, and J. Feeney, *J. Chem. Soc., Chem. Commun.*, 316 (1972).
(24) The scheme is founded on the theoretical analysis $J_R = J_{CH}\Delta f/\gamma^{H_2}/2\pi$ (J_R = residual splitting constant, J_{CH} = natural ^{13}C–^1H coupling constant, Δf = distance of ^1H frequency from applied radiation frequency in hertz, $\gamma^{H_2}/2\pi$ = decoupling field strength): R. R. Ernst, *J. Chem. Phys.*, **45**, 3845 (1966); K. G. R. Pachler, *J. Magn. Resonance*, **7**, 442 (1972).
(25) E. Wenkert, D. W. Cochran, E. W. Hagaman, F. M. Schell, N. Neuss, A. S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, *J. Amer. Chem. Soc.*, **95**, 4990 (1973).
(26) F. R. N. Gurd, P. J. Lawson, D. W. Cochran, and E. Wenkert, *J. Biol. Chem.*, **246**, 3725 (1971); M. Christl and J. D. Roberts, *J. Amer. Chem. Soc.*, **94**, 4565 (1972).

Nuclear Magnetic Resonance Spectroscopy. Carbon-13 Chemical Shifts of Chlorinated Organic Compounds[1a]

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The ^{13}C chemical shifts of a variety of perchlorocarbons, their hydrogen-substituted derivatives, and chlorocarbon ketones have been determined and assigned to specific carbons by high-resolution nuclear magnetic resonance spectroscopy. The assignment of ^{13}C resonances for these substances was often aided by ^{13}C–^1H couplings and Overhauser enhancements observed in the carbon spectra of the hydrogen-substituted derivatives. Correlations between ^{13}C chemical shifts and structure were found for simple molecules and these correlations appear to provide the possibility of reasonable structural assignments for complex perchlorocarbons.

Chlorocarbon chemistry is growing in interest and importance,[2] and because the number of techniques for structural analysis of this type of substance is limited, we have investigated the degree to which ^{13}C nmr (cmr) spectra might be useful in this difficult area.

Detection and interpretation of the cmr resonances of chlorocarbons is substantially harder than for hydrocarbons of corresponding structures because of the absence of Overhauser enhancement of the ^{13}C signals associated with proton decoupling and the lack of spin–spin splitting information, as can be obtained for hydrocarbons by off-resonance decoupling. Nonetheless, we have been able to find correlations between ^{13}C chemical shifts and structural features for chlorocarbons and it is possible that cmr spectra may, in the long run, prove nearly as useful in the chlorocarbon area as ^{19}F spectra have been in the study of fluorocarbon structures.

Experimental Section

Chlorocarbons. *cis*- and *trans*-1,2-dichloroethylene, trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane, hexachloroethane, hexachloropropene, 1,1-difluorohexachloropropane, 1,1,1-trifluoropentachloropropane, hexachlorobutadiene, and hexachlorocyclopentadiene were commercial samples. All of the other chlorocarbons used in this study were generously provided by Professor R. West (University of Wisconsin) and Dr. V. Mark (Hooker Research Center).

Cmr Spectra. Cmr spectra were obtained for ^{13}C in natural abundance using a Varian DFS-60 spectrometer[3] operating at 15.08 MHz. For the hydrogen- and fluorine-substituted chlorocarbons, cmr spectra were determined both with and without proton or fluorine noise decoupling.[4] The preferred solvent was chloroform, which provides resonances for a proton field-frequency lock and internal ^{13}C reference. However, dioxane, cyclohexane, benzene, or tetrachloroethylene were sometimes used. Sweep rates of 40 Hz sec^{-1} or less were employed, which allowed the use of a high radiofrequency power level without saturation of the ^{13}C resonances.[5] The chemical shifts were reproducible to ±1.0 ppm. This variation in chemical shift with solvent, while relatively large, is not so large as to vitiate the structural correlations to be described later. Chemical shifts measured relative to internal standard were corrected to carbon disulfide as internal reference by the relation $\delta_C^{CS_2} = \delta_C^{INT} + N$, where N is 165.8 ppm for cyclohexane, 126.2 ppm for dioxane, 115.4 ppm for chloroforms, 64.6 ppm for benzene, and 71.0 ppm for tetrachloroethylene in a 1:1 tetrachloroethylene–dioxane mixture. Coupling constants and line widths are believed accurate to ±3 Hz. All chemical shifts obtained in this study are presented in Tables I–III. If it is desired that the shifts be referenced to tetramethylsilane (TMS), they can be corrected by the relation $\delta_C^{TMS} = 192.8 - \delta_C^{CS_2}$.

Results and Discussion

Assignments. The bulk of the compounds we have investigated are perchloroalkenes and cycloalkenes which are available in considerable profusion.[2] For these compounds, it is easy to distinguish between the resonances of the double-bond carbons, which fall between 50 and 75 ppm, and those of the single-bond carbons, which come between 90 and 120 ppm. It is interesting that the 50–75-ppm range of the alkenic carbon resonances for perchloroalkenes is not substantially different from the 40–80-ppm range of the corresponding resonances of ordinary alkenes,[6] although the alkane carbons of the perchlorocarbons are shifted some 50 ppm downfield relative to hydrocarbons by the substituent effect of the chlorines.

With the start provided by the differences between double-bonded and single-bonded carbons and taking advantage of symmetry or spin–spin splittings where present, it is possible to assign unambiguously the resonances of many of the compounds shown in Table I, which is arranged to highlight the structural features of each compound for future comparisons. The resonances of the more complicated compounds were assigned (where possible) so as to be consistent with the general pattern of correlation of chemical shifts with structures, as will be discussed below.

A. Single-Bonded Carbon Chemical Shifts. The data of Table I show that the chemical shift of a single-bonded carbon is strongly influenced by the nature of the directly bonded atoms. The single-bonded carbons are here classified as trichloromethyl (CCl_3), dichloromethylene (CCl_2), or chloromethine (CCl). Each class is then subdivided according to the number of directly attached double-bonded or single-bonded carbons. The chemical shift of each subgroup falls within a relatively narrow range, as illustrated in Figure 1.

1. The CCl_3 Carbon. Chemical shifts for trichlorometh-