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Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. 56. Strychnos Alkaloids[1]

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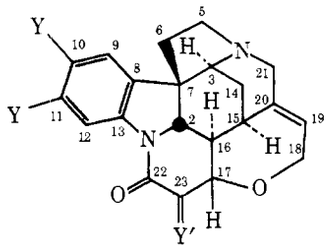
Received June 13, 1977

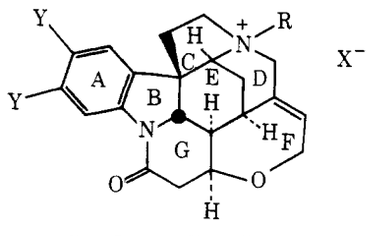
An exhaustive ^1H and ^{13}C NMR analysis of the Strychnos alkaloids strychnine, brucine, Wieland Gumlich aldehyde, diaboline, hemitoxiferin-I, 10-methoxy-*O*-demethyltsilanine, toxiferine-I, and strychnospermine and their derivatives is presented. The data have been used for the solution of a variety of configurational and conformational problems.

The naturally abundant Strychnos alkaloids are characterized by an azabicyclo[3.3.1]nonane system fused to an indoline unit. They vary in structural complexity from the pentacyclic alkaloid tubifolidine (**14** minus the 16β-methyl group) to heptacyclic strychnine (**1a**) and "dimeric" substances such as toxiferine-I (**12**). The present communication presents a composite study of the ^{13}C NMR spectroscopy of the Strychnos and related alkaloids.[3]

The study was initiated by the analysis of the spectra of strychnine (**1a**), its hydrochloride (**2a**), methiodide (**2b**), *N*-oxide (**2c**), and 23-oximino derivative (**1b**), as well as of brucine (**1c**) and its hydrochloride (**2d**).[6] The aromatic carbon resonances of compounds **1** and **2** can be assigned by comparison with indoline shifts of Aspidosperma bases.[7] The aromatic methines can be differentiated from the olefinic ones by the larger residual coupling in the single-frequency off-resonance decoupled (sford) spectra (the decoupler frequency being set at the high-field end of the spectrum and therefore close to the olefinic proton resonances) and the splitting caused by the meta hydrogens ($^3J_{CH}$).[8] Most upfield carbon signals are assigned on the basis of their multiplicities and chemical-shift theory.[9] Being an allylic carbon, C(15) shows larger residual coupling than C(16) and reveals long-range coupling with olefinic H(19). C(18) couples with the same hydrogen. The distinction between the aminomethylenes C(5) and C(21) is founded on the exhibition of second-order coupling by the former but not the latter and unequal residual coupling of the latter to each of its own hydrogens. For further differentiation of the aminomethylenes as well as the methylenes at highest field, C(6) and C(14), individual carbons and their attached hydrogens were related by way of Birdsall plots, a series of sford experiments at various decoupling frequencies.[10] All carbon shifts of compounds **1** and **2** are presented in Table I.

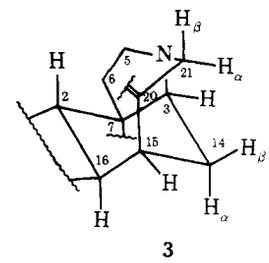


1a, Y = H; Y′ = H_2
b, Y = H; Y′ = NOH
c, Y = OMe; Y′ = H_2



2a, R = Y = H; X = Cl
b, R = Me; X = I; Y = H
c, R = O^-; Y = H
d, R = H; X = Cl; Y = OMe

The above study necessitated a ^1H NMR spectral investigation of the Strychnos alkaloid systems, especially in order to ascertain the conformation of strychnine (**1a**) and its relatives. Even though an analysis of a 250-MHz ^1H NMR spectrum of the alkaloid has been reported,[11] the new measurements (Tables II and III) require a reversal of shift assignment within each pair of geminal hydrogens at C(5), C(14), and C(21). The small vicinal couplings, ca. 2–5 Hz, between the hydrogens of C(3), C(14), C(15), and C(16) and the large H(2)–H(16) coupling, 10.5 Hz, confirm the equatoriality of H(3) and H(15) and the axiality of H(2) and H(16) within a chair conformation of ring E (**3**). It has been shown that H(18α) is coupled with H(15) and H(19) with the low-field hydrogen at C(21).[11] Further double irradiation experiments



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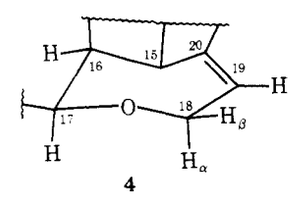

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Table I. Carbon Shifts of Compounds 1 and 2 [a]

	1a[b]	1b[b,c]	1c[b,d]	2a[e]	2b[e,f]	2c[e]	2d[e,g]
C(2)	59.9[h]	58.7	59.8[h]	58.4	58.0	58.1	58.8
C(3)	59.8[h]	59.4	59.3[h]	60.6	73.8	82.1	60.3
C(5)	50.1	49.3	49.6	50.0	61.3	67.5	49.9
C(6)	42.6	42.6	41.9	40.3	38.4	38.7	39.9
C(7)	51.7	51.4	51.4	51.2	52.4	52.6	51.4
C(8)	132.4	132.1	122.9	129.3	129.1	130.6	120.3
C(9)	121.9	121.7	105.1	122.3	123.4	122.8	107.0
C(10)	123.8	124.7	145.6	123.9	123.4	124.2	146.0
C(11)	128.1	128.3	148.5	128.9	129.1	129.0	149.2
C(12)	115.8	115.5	100.5	115.0	115.0	115.2	100.7
C(13)	141.8	141.4	135.3	141.5	141.3	141.5	135.4
C(14)	26.7	26.3	26.3	24.3	24.0	24.5	24.3
C(15)	31.4	31.5	31.1	29.6	28.6	29.5	29.6
C(16)	48.0	45.2	47.7	46.1	46.0	46.8	46.3
C(17)	77.3	75.0	77.1	75.7	75.4	76.1	76.0
C(18)	64.3	65.5	64.0	63.1	63.1[h]	63.5	63.1
C(19)	126.8	128.0	126.7	134.3	135.1	132.9	134.3
C(20)	140.2	138.5	139.8	132.7	132.5	135.6	132.7
C(21)	52.4	52.3	52.1	50.9	63.4[h]	70.3	51.1
C(22)	168.8	159.6	168.2	168.5	168.6	168.9	168.2
C(23)	42.2	148.3	41.8	41.0	40.8	41.5	41.0

[a] In ppm downfield from Me_4Si. [b] In $CDCl_3$, $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [c] Methanol was added to improve the solubility. [d] δ(OMe) = 55.7 and 56.0 ppm. [e] In Me_2SO-d_6, $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.5$ ppm. [f] δ(NMe) = 54.4 ppm. [g] δ(OMe) = 55.8 and 56.2 ppm. [h] Values within any vertical column may be interchanged.

Table II. Proton Chemical Shifts [a]

	1a[b,c]	2c[d,e]	5c[f]	8a[g]	11[d]	12[h]	13a	13b[i]	14	15[j]
H(2)	3.85	4.0	4.30	3.3	3.95	6.1	3.80	3.72	3.32	4.00
H(3)	3.92	4.25	3.94	3.4[k]	3.55	4.3[k]	3.34	3.31	3.40	3.47
H(5α)	3.19	3.45	3.30	3.0[k]	2.9[k]	4.3[k]	3.16	3.18	3.14	3.15
H(5β)	2.86	3.8[k]	2.8[k]	3.0[k]	2.9[k]	4.3[k]	2.85	2.84	2.84	2.87
H(6α)	1.87	2.4	1.7[k,l]	1.8[k]	1.7[k]	3.1[l]	1.85	1.80	1.79	1.97
H(6β)	1.87	2.0	1.98[l]	2.5	2.4	3.3[l]	2.53	2.51	2.48	2.47
H(9)	7.15	7.5	7.09	7.05	7.4	7.95	7.03	6.90	6.99	*n*
H(10)	7.08	7.15	7.09	6.8	7.1	7.45	6.76	6.29	6.70	*n*
H(11)	7.23	7.3	7.26	7.1	7.2	7.75	7.04		6.99	*n*
H(12)	8.09	7.95	8.00	6.7	7.55	7.1	6.62	6.19	6.57	*n*
H(14α)	1.43	1.5	1.55	1.7	1.7	2.3	1.64	1.65	1.64	1.68
H(14β)	2.34	2.6	2.26	1.95	2.0	2.6	1.93	1.99	1.98	2.17
H(15)	3.13	3.25	2.8[k]	2.9[k]	2.7	*n*	1.97	1.77	1.74	2.08
H(16)	1.25	1.4	1.87	1.9[k]	2.25		1.75	1.80	1.5[k]	1.5[k]
H(17α)	4.27	4.35	5.80	3.45[l]		*o*	3.84	3.59	1.15	3.93
H(17β)				3.5[l]	5.2	*o*	3.56	3.89	1.15	
H(18α)	4.05	4.1[k]	4.05	4.0[m]	3.95	4.8	1.31	1.13	0.95	3.57
H(18β)	4.13	4.1[k]	4.30	4.1[m]	3.95	4.8	1.31	1.13	0.95	4.00
H(19)	5.88	6.3	5.85	5.75	5.6	6.4	3.69 (β)	3.54 (α)	1.5[k]	1.4[k]
H(20)							1.35	1.35	*n*	2.3[k]
H(21α)	3.69	3.9[k]	3.73	3.4[k]	3.45	4.9	3.03	3.03	3.09	2.3[k]
H(21β)	2.71	3.9[k]	2.72	3.1[k]	2.95	4.1	2.49	2.32	2.15	2.3[k]

[a] δ values for $CDCl_3$ solutions are at 220 MHz unless stated otherwise. [b] Reinterpreted 250-MHz data of ref 11. [c] δ (H-23α) = 3.11, δ(H-23β) = 2.66 ppm. [d] At 100 MHz in Me_2SO-d_6. [e] At 40 °C, δ(H-23α) = 3.0, δ(H-23β) = 2.6 ppm. [f] δ ($NCOCH_3$) = 2.37, $\delta(OCOCH_3)$ = 2.06 ppm. [g] At 100 MHz in 1:1 $CDCl_3$–CD_3OD. [h] At 100 MHz in D_2O, δ(NMe) = 3.65 ppm. [i] δ(OMe) = 3.75 ppm. [j] δ(H-23α) = 3.02, δ(H-23β) = 2.63 ppm. [k] Approximate shift. [l,m] Signals within a vertical column may be reversed. [n] Unmeasured shift. [o] δ(H-17) = 7.05 ppm.

now establish that H(19) is coupled with H(15). Since this implies that H(15), H(18α), and the deshielded H(21) are well out of the plane of the C(19)–C(20) double bond,[12] the data are in consonance with ring D and F boat and chair conformations (**3** and **4**), respectively, and require the assignment of the low-field H(14) and H(21) multiplets to those hydrogens occupying flagpole positions on the boat ring D, i.e., H(14β) and H(21α), respectively. The chair conformation of the tetrahydrooxepin ring F is supported by the observation of H(15)–H(18α) coupling and by the low magnitude of the H(15)–H(16) and H(16)–H(17) coupling constants.

Protonation of strychnine (**1a** → **2a**) introduces small but significant shift perturbations throughout the carbon framework. The olefinic carbons become greatly polarized, C(19) being deshielded and C(20) shielded each by 7.5 ppm.[13] The carbon shifts of the methiodide (**2b**) are nearly identical with those of the hydrochloride (**2a**) except for large β effects (11–14 ppm) on carbons 3, 5, and 21. The *N*-oxide (**2c**) shows a similar shift pattern, the β shifts being even larger (17–22 ppm) and the double bond less polarized than in **2a** or **2b**.

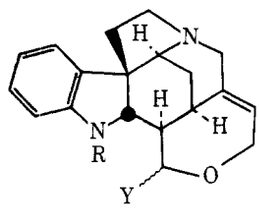
The hexacyclic Wieland Gumlich aldehyde derivatives, substances **5** and **6**, contain an anomeric center at C(17). Thus the 17-hydroxy compounds can equilibrate and present two sets of carbon signals in their ^{13}C NMR spectra. The carbon-

Table III. ^{1}H–^{1}H Coupling Constants of Nonaromatic Hydrogens [a]

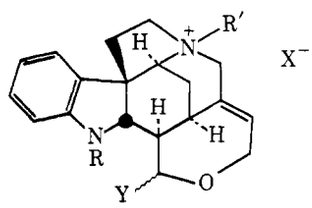
$^3J_{HH}$	1a[b]	2c[c]	5c	8a[d]	11[c]	12[e]	13a	13b	14	15
2–16	10.5	11	10	*f*	13		8.5	8.5	10	11
16–17α	3.1	3	<2	*f*			2.5	2.5	7	4
16–17β				*f*	12		<1	<1	7	
15–16	3.1	3	<2	*f*	3		*f*	*f*	<1	*f*
15–20							*f*	*f*	*f*	*f*
20–21α							5	6	5	*f*
20–21β							12	12	12	*f*
19–20							<1	2.5	*f*	*f*
18α–19	5.7	6.5[g]	5.5	7[g]	6[g]	6.5	6.5	6.5	7	12.5, 3
18β–19	6.9	8[g]	5	7[g]	6[g]	6.5	6.5	6.5	7	6, <1
3–14α	1.8	<1	<2	3	2	3.5[g]	3.5	3.5	3	3
14α–15	2.0	<2	<2	3	3	3.5[g]	3.5	3.5	3	3
14β–15	4.6	4[g]	4.5	4	4	3.5[g]	3.5	3.5	3	3
3–14β	4.1	3	4.5	4	4	3.5[g]	3.5	3.5	3	3
5α–6β	*f*	<1	<1	*f*	*f*	*f*	8.5	8.5	8.5	9
5β–6β	*f*	5.5	6.5	*f*	*f*	*f*	8.5	8.5	8.5	9.5
5β–6α	*f*	14	12.5	*f*	*f*	*f*	2.5	2.5	3	3
5α–6α	*f*	7	7	*f*	*f*	*f*	10	10	10	9
17–23α	8.4	8.5								8
17–23β	3.3	3								5
$^2J_{HH}$										
5–5	*f*	11.5	11	11	*f*	*f*	*f*	11	12	12
6–6	*f*	13	13	13	*f*	*f*	13.5	13.5	13.5	13.5
14–14	14.4	14.5	14	14	13	14	13.5	13.5	13.5	13.5
17–17				*f*			11	11		
18–18	14.2	*f*	14	12.5	*f*	*f*				12.5
19–19										*f*
21–21	14.8	14.5	15	*f*	*f*	*f*	12	12	12	14
23–23	17.4	17.5								16

[a] J values in Hz. [b] Reinterpreted 250-MHz data of ref 11. Other coupling constants for 1 are $^4J_{15-19}$ = 2.5, $^4J_{19-21\alpha}$ = 1.2, $^5J_{15-18\alpha}$ = 2.5, and $^4J_{5\alpha-21\alpha}$ = 1.7 Hz. [c] At 100 MHz in Me_2SO-d_6. [d] At 100 MHz in 1:1 $CDCl_3$–CD_3OD. [e] At 100 MHz in D_2O. [f] Unmeasured coupling constant. [g] Approximate coupling constant.

shift analyses of Wieland Gumlich aldehyde (**5a–b**), its N_a, O-diacetyl derivative (**5c**), and diaboline (N_a-acetyl Wieland Gumlich aldehyde, **5d–e**), as well as of Wieland Gumlich aldehyde N_b-methiodide (**6a–b**), hemitoxiferin-I (Wieland Gumlich aldehyde N_b-methochloride, **6c–d**), and diaboline hydrochloride (**6e–f**), follow closely from the arguments presented for compounds **1** and **2**. The absence of a N_a-acyl substituent, e.g., as in **5a–b**, causes shielding of the ring A



5a, R = H; Y = β-OH
b, R = H; Y = α-OH
c, R = Ac; Y = β-OAc
d, R = Ac; Y = α-OH
e, R = Ac; Y = β-OH



6a, R = H; R′ = Me; X = I; Y = β-OH
b, R = H; R′ = Me; X = I; Y = α-OH
c, R = H; R′ = Me; X = Cl; Y = β-OH
d, R = H; R′ = Me; X = Cl; Y = α-OH
e, R = Ac; R′ = H; X = Cl; Y = α-OH
f, R = Ac; R′ = H; X = Cl; Y = β-OH

carbons ortho and para to N_a, as expected from model data.[9] Aminomethine C(3) is distinguished from C(2) by its shift invariance through the series of compounds. The good correlation of the residual couplings from the sford spectra of **5c** with the actual hydrogen shifts (cf. Tables II and III) confirms the signal assignment presented in Table IV.

Despite the absence of ring G, the δ values of the ring C, D, and E carbons of compounds **5** are similar to those of strychnine (**1a**), indicating maintenance of the ring conformations. Nevertheless, some conformational relaxation occurs, as revealed by the ca. 4-ppm shielding of C(6). The identity of the ring D conformation in **1a** and **5c** is reflected by the similarity of certain regions of their ^{1}H NMR spectra, e.g., the nonequivalence of the geminal hydrogens of C(14) and C(21) as well as allylic and homoallylic coupling of H(21α) and H(18α), respectively (vide supra) (cf. Tables II and III).

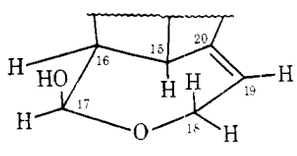
The carbon shifts of N_a,O-diacetyl Wieland Gumlich aldehyde (**5c**)[14] are similar to those of strychnine (**1a**) and thus consistent with the presence of an equatorial 17β-acetoxy group within ring F in the chair form, as proposed earlier on the basis of ^{1}H NMR and molecular rotation measurements.[15] Since the ^{13}C NMR data of **5c** are correlatable readily with those of the major components of the anomer mixtures of Wieland Gumlich aldehyde (**5a–b**) and its N_b-metho salts **6a–b** and **6c–d**, the preponderant anomers **5a**, **6a**, and **6c**, respectively, possess an equatorial 17β-hydroxy group. The ca. 7-ppm shielding of C(17) and ca. 3-ppm shielding of C(15) and C(18) of the minor anomers point to an axial 17α-hydroxy group within ring F still in the chair form. The pattern of conformation, however, differs in the cases of diaboline (**5d–e**) and its hydrochloride (**6e–f**). One pair of anomers reveals shifts consistent with an axial 17α-hydroxy structure within conformation **4** (**5d** and **6e**), whereas the other pair exhibits anomalous shifts, e.g., the hemiacetal carbon being shielded

Table IV. Carbon Shifts of Compounds 5 and 6 [a]

	5a [b]	5b [b]	5c [b,c]	5d [d]	5e [d]	6a [e,f]	6b [e,f]	6c [g,h]	6d [g,h]	6e [i]	6f [i]
C(2)	60.5	62.3	63.5	65.4	66.0	61.2	62.0	61.3	62.6	63.6	64.8
C(3)	58.8	58.4	58.6	59.4	59.4	75.5	75.3	75.7	75.5	61.6	61.6
C(5)	50.4	50.4	51.4	51.9	51.9	63.9	63.9	64.1	64.1	52.7	53.5
C(6)	37.9	38.3	38.1	39.0	38.8	36.5	36.5	36.4	36.4	36.4	36.0
C(7)	53.5	53.5	53.5	*j*	54.4	56.1	56.4	56.3	56.6	49.0	*j*
C(8)	130.8	130.1	133.9	137.0	135.6	128.7	128.7	129.1	129.0	132.6	*j*
C(9)	121.2	120.9	121.1	123.4	122.7	123.7	123.7	123.9	123.9	122.9	122.3
C(10)	118.7	118.4	124.1	126.2	126.2	121.3	121.0	121.7	121.6	125.8	126.2
C(11)	127.4	127.8	127.8	128.6	128.6	131.0	131.0	131.1	131.1	129.3	129.3
C(12)	110.6	109.7	118.5	118.8	120.3	112.8	112.5	113.2	113.0	118.6	120.0
C(13)	149.4	149.3	142.1	142.3	142.3	150.5	150.5	150.5	150.5	140.7	140.9
C(14)	25.6	24.4	25.4	25.6	25.8	25.0	24.4	25.1	24.4	22.9	22.9
C(15)	31.3	27.6	33.2	29.4	29.4	30.5	27.6	30.7	27.7	27.6	27.6
C(16)	46.0	50.5	44.7	50.8	47.9	46.9	50.6	47.0	51.2	48.3	46.9
C(17)	104.6	97.6	102.1	97.0	94.0	103.9	96.8	104.3	97.8	95.6	93.1
C(18)	61.6	59.6	64.3	59.4	55.9	62.7	59.2	63.1	60.4	58.4	55.6
C(19)	126.0	124.6	124.8	127.7	127.7	135.8	135.3	135.9	135.3	134.2	134.2
C(20)	139.4	138.7	141.8	139.9	143.0	133.9	133.7	134.1	133.2	131.6	*j*
C(21)	52.7	52.3	53.5	53.2	53.2	65.6	65.6	65.8	65.8	52.7	53.5
C=O			169.8	172.2	172.2					172.8	173.6
Me			23.9	23.2	23.2					22.5	22.5

[a] In ppm downfield from Me_4Si. [b] In 5:1 $CDCl_3$–MeOH, $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [c] δ(OAc) = 168.5, 20.8 ppm., [d] In 1:2:1 MeOH-d_4–MeOH–NH_3 (concd), $\delta(Me_4Si) = \delta$(MeOH) + 49.5 ppm. [e] In 1:1 Me_2SO-d_6–D_2O, $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.5$ ppm. [f] δ(NMe) = 55.6 ppm. [g] In 1:1 D_2O–H_2O; the 150.5-ppm peak was taken as reference. [h] δ(NMe) = 55.8 ppm. [i] In 1:1 D_2O–H_2O, dioxane as internal reference, $\delta(Me_4Si) = \delta(C_4H_8O_2) + 66.6$ ppm. [j] Signal not observed.

even more than C(17) of any of the aforementioned 17-epimeric alcohols. The data are explicable most easily on the basis of a 17β-hydroxy configuration within a ring F boat form (7) for the anomers **5e** and **6f**, leading to C(18) being shielded



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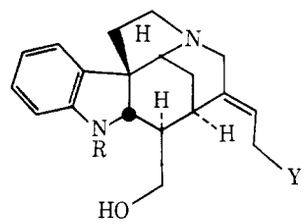


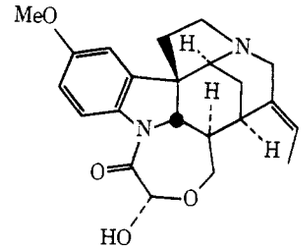
8a, R = H; Y = OH
b, R = Ac; Y = OH
c, R = Y = H
d, R = Ac; Y = H

by the 17β-hydroxy group and the C(15) shift remaining invariant in view of the loss of a γ effect from the hydroxy group being balanced by one from the ring oxygen. The unusual behavior of diaboline (**5d–e**) vis-à-vis the other Wieland Gumlich aldehyde derivatives may reflect the absence of the stabilizing hydrogen bond between the hydroxy group and N_a in **5e**, a small energy difference between chair and boat forms of ring F, and preference of the hemiacetal hydroxy function for axiality in ring compounds, i.e., the equivalent of the "anomeric effect" in the carbohydrate field.[16,17]

The shift assignments for the retuline-like substances **8a–c** and 16-isoretuline (**8d**)[18] parallel those for substances **5–6**. Among the aminomethines the C(3) shift remains unperturbed, whereas the δ value for C(2) shows large variation. Larger residual coupling in the sford spectra distinguished C(18) from the other methylenes of **8a** and **8b**. The differentiation of the aminomethylenes is based on C(5) being expected to show relatively little shift change with respect to compounds **5–6**. The identity of the C(5) and C(21) shifts was confirmed by Birdsall plots on diol **8a**.[10] All shifts of substances 8 are listed in Table V.

A comparison between the shifts of compounds 8 with those of Wieland Gumlich aldehyde (**5a–b**) shows widespread differences, suggestive of conformation changes. The large deshielding of C(2) is most prominent but not explicable fully by assumed modification of the γ effect exerted by the C(17) oxygen. The simultaneous deshielding of C(14) and C(21) points to a change of ring D to that of a chair form, thereby gaining a δ effect for C(2) and C(21) and losing a γ effect by the latter and C(14). This conclusion is corroborated by the ^{1}H NMR evidence. The olefinic hydrogen of diol **8a** exhibits a well-defined triplet due to vicinal coupling with the hydroxymethyl hydrogens. Thus in contrast to $J_{H(19)\text{-}H(15)} = 2.5$ Hz for strychnine (**1a**), H(19) is relatively free from allylic coupling with H(15) and H(21). Inspection of a model of **8a** shows this to be consistent with a flattened ring D chair. The partial ring D inversion back to that common in bicyclo[3.3.1]nonane systems[19–21] relieves nonbonded interactions between the C(16) and C(20) side chains. The low-field hydrogens of the C(14) and C(21) methylenes are 0.3–0.5 ppm more shielded in the diol (**8a**) than in strychnine (**1a**) or in the Wieland Gumlich aldehyde system (cf. **5c**), wherein they occupy flagpole positions. In view of the change of the hydrogen orientation relative to the double bond and N_b, the shift nonequivalence of the C(14) and C(21) hydrogen pairs is less than 0.25 ppm compared to 0.7–1.0 ppm in **1a** and **5c**. This fact is reflected in the splitting pattern of the sford spectra of compounds **8**, i.e., triplets instead of doublets of doublets.

The alkaloid 10-methoxy-*O*-demethyltsilanine (**9**)[22] is similar to compounds **8**, but contains an additional seven-membered ring G. The lack of shielding of C(2) relative to compounds 8 precludes ring G being in the boat form since in this event the ring oxygen should affect C(2) as it shields C(15) of the diaboline isomer **5e**. This fact, the ca. 10-ppm de-



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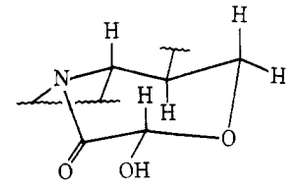

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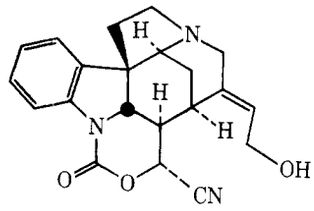
Table V. Carbon Shifts of Compounds 8, 9, 11, and 12 [a]

	8a [b]	8a [c]	8b [b,d]	8c [c]	8d [e,f]	9 [e,g]	11 [c,h]	12 [i,j]
C(2)	69.5	69.3	68.3	70.0	70.2	72.5	65.0	70.5
C(3)	61.4	61.4	60.9	61.5	61.6	61.5	60.5	77.2
C(5)	53.1	53.5	53.3	53.5	53.8	53.3	53.0	60.8
C(6)	42.2	43.4	41.4	43.3	42.4	45.0	44.3	38.7
C(7)	52.8	53.0	51.8	52.8	52.3	51.8	50.7	53.6
C(8)	132.3	133.4	138.2	133.5	137.2	137.2	134.2	133.9
C(9)	121.1	121.5	122.1	119.0	122.3	107.3	122.9	124.0
C(10)	118.7	117.1	125.0	117.1	125.0	157.1	124.6	121.3
C(11)	127.4	127.2	127.4	127.1	127.3	112.3	128.1	130.4
C(12)	109.5	108.3	117.0	108.3	117.2	117.0	113.6	109.0
C(13)	148.6	150.0	140.0	150.0	140.4	133.3	139.8	145.6
C(14)	27.4	28.1	27.5	28.0	28.4	27.6	28.3	21.5
C(15)	28.3	28.5	29.9	28.0	31.5	28.8	26.8	30.0
C(16)	48.4	49.1	47.3	49.2	47.3	45.2	46.3	113.4
C(17)	64.0	63.5	62.5	64.0	64.7	74.2	69.0	132.9
C(18)	56.5	56.5	56.7	12.5	12.8	12.6	56.2	57.5
C(19)	125.3	126.0	125.2	121.4	120.2	121.0	128.4	130.4
C(20)	137.4	137.1	138.2	136.2	135.2	132.8	132.8	134.4
C(21)	57.0	57.5	57.9	57.6	58.8	57.1	55.8	65.2

[a] In ppm downfield from Me_4Si. [b] In 7:1 $CDCl_3$–MeOH, $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [c] In Me_2SO-d_6, $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.5$ ppm. [d] δ(NAc) = 170.0, 22.8 ppm. [e] In $CDCl_3$. [f] δ(NAc) = 170.5, 23.0 ppm. [g] δ(OMe) = 55.3, δ(NCOCHOH) = 166.5, 92.0 ppm. [h] $\delta(NCO_2)$ = 149.1, δ(CN) = 116.3 ppm. [i] In 1:5 D_2O–MeOH, $\delta(Me_4Si) = \delta$(MeOH) + 49.5 ppm. [j] δ(NMe) = 48.5 ppm.

shielding of C(17), and the β effect of ether formation[9] without an added γ effect indicate the presence of an equatorial and hence α-hydroxy group (cf. **10**). The stereochemistry of this functionality had been unknown heretofore. The chemical shifts of the alkaloid (**9**) are presented in Table V.

Carbon-13 NMR analysis proved useful for the elucidation of the structure of a $C_{21}H_{21}O_3N_3$ byproduct of the degradation of 23-oximinostrychnine (**1b**) to Wieland Gumlich aldehyde (**5a–b**).[23] The compound reveals carbon shifts characteristic of the retuline-like substances **8**. Small upfield shifts relative to **8a** are noted at carbons 2, 7, 15, and 16, as well as deshielding of C(17), and indicate structure changes near carbons 2 and 16. The signals at 149.0 and 116.3 ppm, in conjunction with the infrared absorption bands of 1740 and 2160 cm^{-1}, suggest the presence of carbamate and nitrile functions, respectively. On the basis of these facts and the chemical origin of the substance, structure **11** (as yet without C(17) stereochemical detail) can be proposed for the compound. A high-resolution mass spectrum reveals peaks with *m/e* 363 (M^+), 345 ($M - H_2O$), and 332 ($M - CH_2OH$), characteristic



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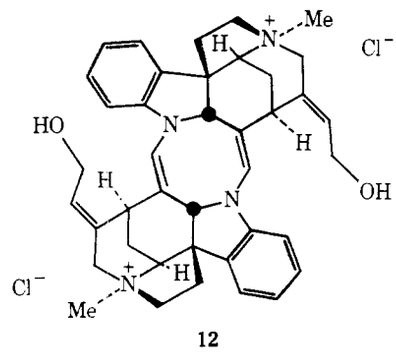


12

of the presence of a ring linking N_a and C(16).[24] The ^1H NMR spectrum shows an olefinic hydrogen without significant allylic coupling, in accord with the presence of a hydroxyethylidene side chain attached to a flattened ring D chair (cf. Tables II and III). The vicinal coupling of 12 Hz exhibited in the 5.15-ppm H(17) signal indicates the C(17) stereochemistry as depicted in formula **11**. All carbon shifts of the hexacycle are listed in Table V.

The symmetrical, "dimeric" alkaloid toxiferine-I (**12**) has features in common with the retuline-like compounds **8**, permitting its shift assignment to be based on the latter. The olefinic methine shifts are designated from Birdsall plots.[10] An interesting facet of the ^{13}C NMR spectrum is the very high-field position of the C(14) signal. This must be due to a γ effect from the N_b-methyl group (even on consideration of the solvent shifts[6]) and is in sharp contrast to the C(14) shift of the N_b-metho salts **2b** and **6a–d** whose ring D is in the boat form. The γ effect is reciprocated, the methyl group being shielded strongly relative to the substances possessing a ring D boat.

All the alkaloids examined thus far possess a C(19)–C(20) double bond. Its saturation makes the allocation of the carbon signals more difficult than heretofore. Hence much use is made of correlations with the hydrogen resonances presented in Table II. Moreover, the latter show that the 19,20-dihydro compounds of the present study fall into two groups. 3-Deoxyisostrychnosplendine (**13a**),[25] deacetylstrychnospermine (**13b**),[25] and 16β-methyltubilfolidine (**14**)[26] are characterized by large chemical-shift nonequivalence of the geminal C(21) hydrogens. Contrastingly, these hydrogens in dihydrostrychnine (**15**) are shielded nearly equally. The carbon shifts of compounds **13–15** are illustrated in Table VI.

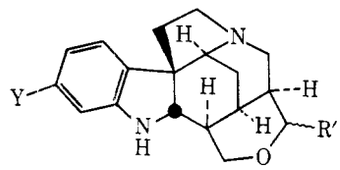
The published 220-MHz ^1H NMR spectra of **13a** and **13b** provide evidence for a cis fusion of rings D and F, both in the chair form.[25] Ring D of **14** is similarly in the chair conformation. In each of these compounds H(20α) is anti ($^3J_{HH}$ = 12 Hz) to the more shielded H(21) and gauche ($^3J_{HH}$ = 5–6 Hz) to the less shielded C(21) hydrogen. The high-field H(21) thus occupies an axial position on a chair piperidine and is shielded strongly (δ = 2.2–2.5 ppm), being anti to the nitrogen lone-electron pair. A chair ring F is evident also from the ^{13}C NMR data. The axial α-methyl group of **13a** is gauche to C(15) and C(17), these carbons being shielded in **13a** relative to **13c**.

Table VI. Carbon Shifts of Compounds 13–15 [a]

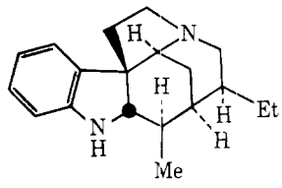
	13a	13c	13d[b,c]	13d[c,d]	13d[c,e]	14	15[f]
C(2)	68.2	68.4	69.2	70.3	70.0	75.0	67.6
C(3)	61.3	61.5	60.7	60.0	60.8	62.3	62.5
C(5)	54.5	54.8	54.2	54.2	54.5	54.0	53.7
C(6)	44.0	44.0	42.4	41.6	42.5	43.3	46.4
C(7)	53.3	*g*	50.7	51.9	51.8	54.0	51.4
C(8)	134.1	134.1	130.9	128.5	129.8	133.8	134.9
C(9)	121.9	121.9	122.3	121.4	121.8	121.7	121.7
C(10)	119.2	119.2	107.9	110.7	109.8	118.5	124.2
C(11)	127.6	127.6	158.5	158.7	159.1	127.2	127.9
C(12)	109.6	109.6	104.4	104.8	105.0	109.0	115.5
C(13)	149.3	149.3	141.6	141.9	142.3	149.0	140.6
C(14)	27.2	27.4	26.3	26.2	26.7	32.1	31.3
C(15)	23.7	30.7	30.8	31.3	31.8	34.9	30.1
C(16)	43.2	43.0	40.6	40.4	41.2	43.0[h]	53.3
C(17)	63.0	71.5	71.0	69.8	70.7	19.3	76.4
C(18)	16.1	17.6	17.8	17.5	17.5	13.0	68.4
C(19)	71.8	76.1	75.6	76.4	76.2	27.2	32.6
C(20)	37.2	37.2	37.1	37.0	37.7	43.5[h]	34.9
C(21)	53.5	48.8	48.5	49.3	49.3	55.9	57.8
C=O			169.1	168.9	168.7		
Me			23.8	23.4	23.2		

[a] In ppm downfield from Me_4Si, $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Major rotamer at −26 °C. [c] δ(OMe) = 55.4 ppm. [d] Minor rotamer at −26 °C. [e] At 55 °C. [f] δ(C-22) = 169.3, δ(C-23) = 41.1 ppm. [g] Signal masked. [h] Signals may be interchanged.

Similarly, the equatorial β-methyl group of **13c** is gauche to C(21), the latter being shielded in **13c** relative to **13a.** All other shifts for these two 19-epimers are practically identical.



13a, R = Y = H; R′ = α-Me
b, R = H; R′ = β-Me; Y = OMe
c, R = Y = H; R′ = β-Me
d, R = Ac; R′ = β-Me; Y = OMe



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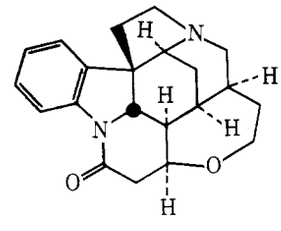
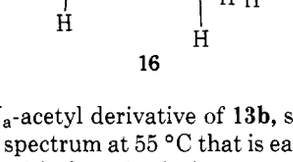


15

In the absence of an ether bridge and the removal of the gauche interaction between the oxygen and C(2) and C(21) in 16β-methyltubifolidine (**14**),[26] these carbons are deshielded strongly in **14** relative to **13c,** whereas C(15) is deshielded less strongly. Such comparisons with **13c** but not with **13a** being possible indicate that the preferred rotamer for the ethyl side chain of **14** is the one whose methyl group is gauche to C(21) and anti to C(15). The interaction of the ether oxygen with the positions gauche to it are observed also in the ^1H NMR spectra, wherein H(2) and H(21β) of **13a** and **13b** are deshielded by 0.2–0.5 ppm relative to **14.** The ^1H and ^{13}C NMR data of dihydrostrychnine (**15**) establish the conformation of its seven-membered ring F as in formula **16.** This arrangement is indicated by the vicinal coupling between H(16) and H(17) and between the C(18) and C(19) hydrogens (see Table III). The gauche relationship between the ether oxygen and C(2) is shown by the similarity of this carbon's shifts in **15** and compounds **13,** wherein such interaction exists. The nearly equivalent C(15) shifts of **15** and **13c** favor a chair conformation for the seven-membered ring, which also excludes a nonbonded interaction between carbons 18 and 21. The chemical shift of the latter is similar to that of C(21) of **14,** wherein a gauche interaction with C(18) does exist (vide supra). Other anomalies include C(14) being less shielded in **15** than in **13,** the C(21) hydrogens being equivalent (vide supra), and H(14β) being deshielded. All these facts are explicable on the assumption of a lessening of the 1,3-diaxial interaction between C(2) and C(21) and the flattening of ring D to form a intermediate between a chair and a boat. A ring D chair would be disfavored since it involves eclipsing of the C(19) and C(20) substituents.



16

Being the N_a-acetyl derivative of **13b,** strychnospermine (**13d**) reveals a spectrum at 55 °C that is easily interpretable by comparison with that of **13b.** At room temperature, however, some signals begin to broaden, and at −26 °C two sets of signals are apparent. Since the alkaloid contains no epimerizable centers such as Wieland Gumlich aldehyde (**5a–b**) and its derivatives (**5–6**) and since the Δδ values between the two signal sets are too small to imply any significant conformational change, the two groups of signals therefore must reflect the presence of two possible rotamers of the acetyl group.[27] Thus, the rotation barrier of the amide linkage of strychnospermine (**13d**) is higher than that of the acetamides of the Wieland Gumlich aldehyde series, **5c, 5d–e,** and **6e–f.**[28]

Registry No.—**1a,** 57-24-9; **1b,** 24180-59-4; **1c,** 357-57-3; **2a,** 1421-86-9; **2b,** 2131-76-2; **2c,** 7248-28-4; **2d,** 5786-96-9; **5c,** 2871-28-5; **8a,** 900-98-1; **11,** 64754-36-5; **12,** 6696-58-8; **13a,** 22153-1305; **13b,** 6516-44-5; **14,** 34174-79-3; **15,** 15006-14-1; **5a,** 466-85-3; **5b,** 38570-01-3; **5d,** 64783-88-6; **5e,** 509-40-0; **6a,** 64754-37-6; **6b,** 64754-38-7; **6c,** 24180-76-5; **6d,** 64754-39-8; **6e,** 64783-89-7; **6f,** 11032-42-1; **8b,**

13013-60-0; **8c**, 13941-27-0; **8d**, 10388-62-2; **9**, 29028-14-6; **13c**, 22153-12-4; **13d**, 509-45-5.

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(1) Part 55: see E. Wenkert and H. E. Gottlieb, *Heterocycles*, in press.
(2) On leave of absence from the Department of Pharmacy, University of Sydney, Sydney, N.S.W., Australia, fall semester 1975, during which time this study was completed.
(3) The nonprotonated carbon signals of brucine (**1c**) have been assigned by the use of their relaxation times.[4] The carbon-shift assignment of the present study differs in part from that of a recent investigation[5] of strychnine (**1a**), brucine (**1c**), their trifluoroacetic acid salts, and brucine N_b-methiodide.
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(14) Compound **5c**, mp 203–205 °C, is the major product of acetylation of **5a–b**.[16]
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(16) Whereas an alternative explanation might be based on the two diaboline isomers being N_a-acetyl rotamers of the same 17α-hydroxy ring F chair system, this argument fails to account for the absence of such rotamer effect in **5c** and for the large C(18) and C(20) shift difference in the two isomers. The relatively big $\Delta\delta$ value of C(12) may be due to a different amide rotamer population distribution in the two epimers.
(17) The spectrum of diaboline hydrochloride (**6e–f**) nearly shows signal coalescence of the carbon pairs of the epimers at 80 °C.
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Carbon-13 Magnetic Resonance of Cotton Terpenoids: Carbon–Proton Long-Range Couplings

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Received August 19, 1977

The ^{13}C NMR spectra of five sesquiterpenoids and three C_{25} terpenoids found in *Gossypium hirsutum* and *G. Barbadense* cottons have been analyzed. Chemical shift assignments for the aryl and carbonyl carbons were made using long-range carbon–proton couplings and single frequency irradiation before and after deuterium exchange. Large deuterium isotope shifts are observed for the exchange of the hydroxy proton that is syn and strongly hydrogen bonded to the aldehyde function.

Some primitive varieties of cotton are more resistant than cultivated cottons toward the cotton bollworm and tobacco budworm (*Heliothis* spp.).[1] This greater resistance has been correlated with higher concentrations of several terpenoids, such as hemigossypolone (**1a**) and its 7-methyl ether derivative (**1b**), and the C_{25} terpenoids, such as heliocides H_1 (**3a**), B_1 (**3b**), and H_2 (**3c**).[2,3] The structures of hemigossypolone and **3c** were determined by mass, proton, and carbon-13 spectra. Compound **3c** was synthesized from hemigossypolone and its stereochemistry determined by x-ray crystal analysis.[4,5] The structures of **3a** and **3b** were based upon syntheses and carbon-13 spectra.[6–8] The carbon-13 spectra were essential in assigning the structures of several of the heliocides. However, it was not possible to make unambiguous shift assignments for carbons 2, 6, 7, or 8 or to distinguish between the bridgehead carbons 9 and 10 or the carbonyl carbons 1 and 4 with proton-decoupled spectra. It was also important to study the carbon-13 spectra of the sesquiterpenoids hemigossypol (**2a**), methoxyhemigossypol (**2b**) (the biosynthetic precursors of **1a** and **1b**[9]), and gossypol (**2c**) because of their biosynthetic relationship to the heliocides and to assist in the analysis of new, structurally related terpenoids.

One-bond couplings and off-resonance decoupling are of little value in uniquely assigning the aromatic and carbonyl carbons because most are quaternary. Shift assignments based upon additivity relationships also fail because of the many ortho interactions.[10] However, proton-decoupled carbon-13 chemical shifts are useful in the structural analysis of polysubstituted aromatic natural products once shift assignment ambiguities are resolved, and chemical shift changes are correlated with substituent changes.[6,7] This is especially important when the quantity isolated from natural sources precludes the use of coupled spectra as an assignment technique.[6]

0022-3263/78/1943-1105$01.00/0