262. ^{13}C-NMR. Spectroscopy of Naturally Occurring Substances. XLV. Iboga Alkaloids[1])

by **Ernest Wenkert**[2]), **David W. Cochran, Hugo E. Gottlieb** and **Edward W. Hagaman**

Department of Chemistry, Indiana University, Bloomington, Indiana 47401, U.S.A.

and **Raimundo Braz Filho**[3]), **Francisco José de Abreu Matos** and **Maria Iracema Lacerda Machado Madruga**

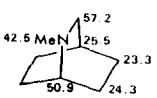
Departamento de Química Orgânica e Inorgânica, Centro de Ciências, Universidade Federal do Ceará, 60.000 Fortaleza, Brazil

(29. III. 76)

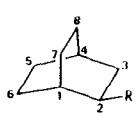
Summary. The carbon shifts of the Iboga-type alkaloids catharanthine, voacangine, coronaridine, ibogaine, dihydrocatharanthine and epiibogamine were recorded and correlated with the conformation of the natural bases. A ^{13}C-NMR. analysis of heyneanine determined its C(19) configuration and a similar study of epiheyneanine proved its structure.

In connection with problems of structure determination and synthesis of indole alkaloids of the Iboga type it became of importance to apply ^{13}C-NMR. spectroscopy thereto. As a consequence the following study of a select group of such natural products was undertaken and isoquinuclidine (**1**), its N-methyl derivative (**2**), some monosubstituted bicyclo[2.2.2]octanes (**3**) and two bicyclo[2.2.2]octenes (**4**) used as models. The carbon shifts of the first two models are depicted on formulas **1**[4]) and **2** and those of bicycles **3**[5]) and **4**[6]) listed in Table 1.

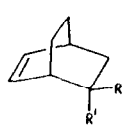
1



2



3a, R = Me
b, R = Et
c, R = CH_2OH
d, R = CH(OH)Me
e, R = CHO
f, R = CO_2H
g, R = CO_2Et
h, R = Ac



4a, R = CHO
R' = H
4b R = H
R' = CHO

[1]) For part XLIV see [1].

[2]) Present address: Department of Chemistry, Rice University, Houston, Texas 77001, U.S.A.

[3]) Present address: Departamento de Química, Universidade Federal Rural do Rio de Janeiro, Brazil.

[4]) The nitrogen perturbs appreciably the vicinal methylene shifts of isoquinuclidine (**1**) (*cf.* the 26.1 ppm methylene shift of bicyclo[2.2.2]octane [2]).

[5]) The total of the γ-effects on C(1) and C(3) is 7.7 ppm greater for the hydroxy group of **3c** than the methyl group of **3b**, relative to **3a**. The comparable magnitude of the γ-effect of the two groups as a result of fixed gauche, non-bonded interactions [3] [4] and the shielding of γ-carbons by hydroxy groups *trans* anti-periplanar to them within rigid six-membered rings [5] suggest that the excess shielding by the hydroxy group of **3c** is an acyclic equivalent of the latter phenomenon. This result indicates that caution must be exercised in the assessment of shielding contributions to γ carbon atoms from oxygen in all staggered, acyclic conformations.

[6]) The introduction of a double bond into the strained bicyclo[2.2.2]octane skeleton leads to stronger deshielding of the allylic carbons and a decrease of the endocyclic homoallyl effect relative to the shift differences of cyclohexenes and cyclohexanes [2] [6] (*cf.* also the **6b** → **5a** change).

Table 1. *Carbon Shifts of 2-substituted bicyclo[2.2.2]octanes*[a])

	3a[b])	**3b**[c])	**3c**[d])	**3d**[c])	**3d'**[c]) [e])	**3e**[f])	**3f**[g])	**3g**[g])	**3h**[c])	**4a**[f]) [h])	**4b**[f]) [h])
C(1)	30.2	28.0	24.5[i])	24.2	25.8	25.2	27.2	27.3	26.3	29.9	30.4
C(2)	30.2	37.9	38.2	43.8	43.8	49.2	41.5	41.6	49.5	49.8	50.5
C(3)	35.6	34.1	29.9	30.4	30.6	24.7	27.7	27.9	25.9	25.0[i])	26.4
C(4)	25.0	24.8	24.1[i])	23.7	24.0	23.5	23.5	23.5	23.4	29.0	29.0
C(5)	26.1[i])	26.1[i])	25.8[i])	25.7[i])	25.6[i])	26.0[i])	26.0[i])	26.0[i])	25.9[i])	135.0[j])	24.8[i])
C(6)	25.0[i])	25.4[i])	25.2[i])	24.8[i])	24.1[i])	25.0[i])	24.8[i])	24.9[i])	24.5[i])	133.0[j])	24.5[i])
C(7)	20.3	20.7	20.4	20.3	20.6	21.6	21.6	21.6	21.0	20.8	130.3[j])
C(8)	27.4[i])	27.5[i])	26.7[i])	26.4[i])	27.1[i])	25.0[i])	25.0[i])	25.0[i])	24.6[i])	24.5[i])	135.5[j])
α-C	21.0	28.7	65.6	69.2	71.2	204.1	182.2	175.8[k])	209.4	203.3	202.9
β-C		12.1		20.8	21.8				27.7		

[a]) The δ values are in ppm downfield from TMS; δ(TMS) = $\delta(CDCl_3)$ + 76.9 ppm. [b]) Ref. [7]. [c]) Ref. [8]. [d]) Ref. [9]. [e]) The minor isomer **3d** from the reaction of **3e** with methyllithium. [f]) Ref. [10]. [g]) Ref. [11]. [h]) Carbon atoms numbered as in compounds **3** for sake of convenience. [i]–[j]) Signals within any vertical column may be reversed. [k]) Ester δ(Me) = 14.1 and $\delta(CH_2)$ = 59.9 ppm.

Table 2. Carbon Shifts of Iboga Alkaloids[a])

	5a	**5a**[b])	**5b**[c])	**6a**[d])	**6b**	**6c**[e])	**6d**	**6e**	**7a**[b])	**7b**
C(2)	136.0	138.6	139.1	137.3	136.5[f])	143.0	136.5[f])	135.9[f])	135.6[f])	141.9
C(3)	52.9	53.2	52.6	53.0	53.1	54.1	52.1[g])	52.0[g])	56.1	54.5
C(5)	49.3	49.4	47.6	51.5	51.5	49.8	51.1[g])	50.9[g])	53.5	49.3
C(6)	21.0	20.9	19.5	22.0	22.2	20.5	21.3	21.6	17.9	20.0
C(7)	110.2	110.0	109.4	109.7	110.3	108.8	110.7	109.6	108.8	109.7
C(8)	128.4	128.5	128.1	128.7	128.8	129.8	129.5	128.4	126.5	129.3
C(9)	117.7	117.8	118.1	100.4	118.3	100.4	119.3	118.3	117.8	117.5
C(10)	118.9	118.7	119.0	153.6	119.0	153.7	119.3	120.3	118.6	118.8
C(11)	121.3	121.9	121.7	111.4	121.8	110.9	123.2	122.1	121.4	120.6
C(12)	110.2	111.3	110.2	110.9	110.3	110.5	111.4	110.4	111.3	110.2
C(13)	134.7	135.4	134.7	130.5	135.6[f])	129.8	136.3[f])	135.6[f])	135.1[f])	134.2
C(14)	30.4	30.4	29.3	27.2	27.2	26.3	26.7	26.0	24.4	26.1
C(15)	123.4	123.2	121.6	31.9	32.0	31.9	22.9	28.6	28.2	31.4
C(16)	55.0	55.6	46.0	55.0	55.1	41.2[f])	56.8	54.1	47.1	33.7
C(17)	38.0	37.4	35.8	36.2	36.3	34.0	36.8	36.5	34.4	34.7
C(18)	10.5	11.2	10.2	11.5	11.6	11.8	20.2	22.1	12.0	11.9
C(19)	25.9	26.2	26.1	26.6	26.6	27.7	72.3	70.7	25.6	28.2
C(20)	148.5	148.1	149.0	38.9	38.9	41.8[f])	39.5	40.2	37.1	41.6
C(21)	61.5	62.9	63.0	57.2	57.2	57.3	59.7	54.7	55.4	57.0
C=O	173.6	172.7		175.4	175.9		175.7	174.8	171.7	
OMe	52.0	52.6		52.2	52.4		52.8	52.6	52.7	

[a]) The δ values are in ppm downfield from TMS; δ(TMS) = $\delta(CDCl_3)$ + 76.9 ppm. [b]) In the DMSO; δ(TMS) = δ(the DMSO) + 77.4 ppm. [c]) $\delta(CH_2)$ =

(6a) and

causing

C(11) re

-1] [13]

The

catharan

lenes. C

carbome

in sford

by their

the moc

aminom

tion and

Com

the $\Delta\delta$(

by the

preferre

of a γ-h

change

hydroge

7-C(20)

C(20). T

of only

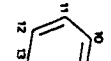
group.

C(16) ar

γ-effect

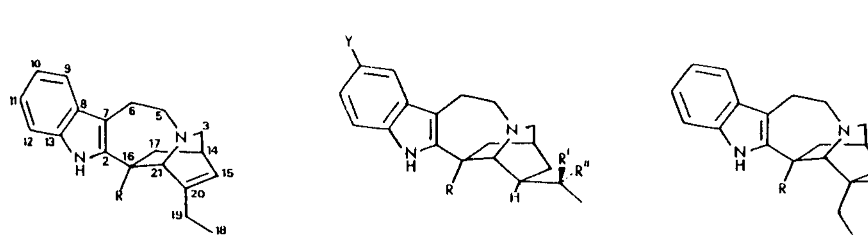
assignm

20-epim



C(19)	25.9	26.2	26.1	26.6	26.6	27.7	72.3	70.7	25.6	28.2
C(20)	148.5	148.1	149.0	38.9	38.9	41.8f)	39.5	40.2	37.1	41.6
C(21)	61.5	62.9	63.0	57.2	57.2	57.3	59.7	54.7	55.4	57.0
C=O	173.6	172.7		175.4	175.9		175.7	174.8	171.7	
OMe	52.0	52.6		52.2	52.4		52.8	52.6	52.7	

The chemical shifts of all indole carbon atoms of the Iboga alkaloids catharanthine (**5a**), coronaridine (**6b**), heyneanine (**6d**), dihydrocatharanthine (**7a**), and epiibogamine (**7b**) as well as the alkaloid model **5b** fit those previously assigned to natural, α,β-disubstituted indole bases [12]. The 10-methoxy group of voacangine



5a, R = CO_2Me
b, R = CH_2OH

6a, R = CO_2Me, R′ = R″ = H, Y = OMe
b, R = CO_2Me, R′ = R″ = Y = H
c, R = R′ = R″ = H, Y = OMe
d, R = CO_2Me, R′ = Y = H, R″ = OH
e, R = CO_2Me, R′ = OH, R″ = Y = H

7a, R = CO_2Me
b, R = H

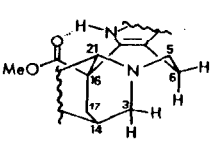
(**6a**) and ibogaine (**6c**) induces unequal shift perturbations on its *ortho* centers, causing the C(11) and C(12) shifts to become similar. However, in the coupled spectra C(11) reveals a doublet of doublets ($^1J_{CH}$ and $^3J_{CH}$) and C(12) a doublet ($^1J_{CH}$) [11] [13].

The great dissimilarity of the environment of the non-aromatic carbon atoms of catharanthine (**5a**) allows their direct signal assignment except for the five methylenes. C(17) is recognizable by its shift change in the alcohol **5b** as well as by the carbomethoxy-induced, strong non-equivalence of its hydrogens (doublet of doublets in sford spectra; same observation for **6a** and **6b**), while C(6) and C(19) are identified by their coupling characteristics and by shift comparison with coronaridine (**6b**) and the models, leaving C(15) determined for **6a** and **6b**. The shift assignment for the aminomethylenes of all the Iboga bases is associated intimately with their conformation and will be discussed below.

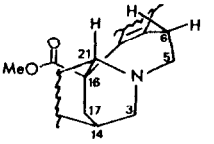
Comparison of the $\Delta\delta$(C(20)) value for voacangine (**6a**) and ibogaine (**6c**) with the $\Delta\delta$(C(7)) value for the **3g** bicyclo[2.2.2]octane pair reveals the γ-effect exerted by the carbomethoxy group to be weaker in the alkaloids than in the models. The preferred rotamer population of the ester function of the models, involving exposure of a γ-hydrogen to the face of the π-cloud, leads to a strong γ-effect [12], whereas the change of the ester conformation in voacangine (**6a**) and coronaridine (**6b**) due to a hydrogen bond between the carbonyl oxygen and the indole nitrogen decreases the at C(20) γ-effect and forces the methoxy group into a non-bonded δ-interaction with C(20). The **6b** → **6d** change, as the **3b** → **3d** model alteration, modifies the shifts of only carbon atoms within non-bonded interacting distance from the new hydroxy group. The C(20) inversion of ibogaine (**6c**) into epiibogamine (**7b**) merely shields C(16) and leaves the C(19) shift invariant as a consequence of the replacement of the γ-effect exerted by N_b in **6c** [12] by one of equal magnitude by C(16) in **7b**. The shift assignment of dihydrocatharanthine (**7a**) follows the same arguments as for its 20-epimer (*vide supra*), while the general shift pattern of **7a** is in sharp contrast

with that of the other Iboga bases and suggests that dihydrocatharanthine (**7a**) is conformationally unique (*vide infra*).

The Iboga alkaloid skeleton possesses a limited amount of conformational flexibility, *e.g.* the isoquinuclidine appearing in two slightly staggered twist forms and the tetrahydroazepine assuming two different conformations. The seven-membered ring of form **8** places C(6) and C(3) into a non-bonded interaction of the azabutane-*gauche* type, leading to γ-effects between them, whereas form **9** forces C(6) into an eclipsed azabutane interaction with C(21). Comparison of the aminomethylene shift of N-methylisoquinuclidine (**2**) with the shifts of the as yet unassigned aminomethylene groups of **5**, **6** and **7b** shows that C(3) must feel a γ-effect from C(6) in all these substances. The aminomethylene shifts can be designated readily for the alkaloids, whose C(3) and C(5) resonances vary greatly from each other, on the basis of a *ca.* 5 ppm optimum shift for a methylene-methylene *gauche* interaction. These arguments support conformation **8** (without specifying an exact isoquinuclidine twist boat form) for catharanthine (**5a**), voacangine (**6a**), coronaridine (**6b**) and heyneanine (**6d**).



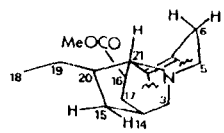
8



9

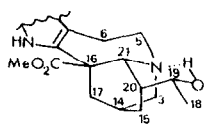
Whereas the seven-membered ring chair form, incorporated in structure **8**, might be expected to be the favored conformation for the Iboga alkaloid skeleton, the tetrahydroazepine boat form **9** permits greater conformational flexibility within the isoquinuclidine nucleus. The latter is needed in dihydrocatharanthine (**7a**) in which especially an eclipsed form of the isoquinuclidine moiety maximizes the energetically unfavorable, non-bonded interaction between the axial ethyl and carbomethoxy sidechains. The tetrahydroazepine ring inversion into an isoquinuclidine twist boat form of **9** is indicated by the extra shielding of C(6) of dihydrocatharanthine (**7a**) in which this center is exposed to a γ-effect from C(21) within an eclipsed azabutane conformation [14]. The conformational change removes the γ-effect between C(3) and C(6) as shown by the aminomethylene resonances, C(3) now appearing at a field position nearly identical with that of N-methylisoquinuclidine (**2**), while adding a γ-effect between C(6) and C(21). Its magnitude is low in view of the loss of an acyclic γ-effect from C(18), which, as the strong shielding of C(15) in **7a** shows, is oriented preponderantly toward C(15) in dihydrocatharanthine (**7a**). The mild shielding of C(17) in **7a** *vs.* **6b** may be due in part to a γ-effect from N_a which in the tetrahydroazepine boat (**9**) is not involved in hydrogen bonding with the carbomethoxy group. Thus conformation **10** represents dihydrocatharanthine (**7a**). The intermediacy of the shifts of C(3) and C(6) of ibogaine (**6c**) and epiibogamine (**7b**) suggests that these alkaloids may be a mixture of the conformations depicted in **8** and **9**. The carbon shifts of all the alkaloids are listed in Table 2.

The dramatic shift differences of many carbon centers in coronaridine (**6b**) and dihydrocatharanthine (**7a**) allow a ready recognition of the C(20) configuration of

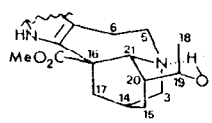


10

the Iboga alkaloids. Thus the shift correspondence of heyneanine (**6d**) and coronaridine (**6b**) at all sites removed from oxy-C(19) confirms the previously assigned *exo* configuration[7]) of the hydroxyethyl sidechain [15]–[16]. The heretofore unknown C(19) configuration of heyneanine (**6d**)[8]) can be determined by comparison of the relevant carbon shifts of the alkaloid with those of coronaridine (**6b**) and models **3b**, **3d** and **3d'** (see Table 1). As the shift changes for C(1) and C(3) in the **3b** → **3d** and **3b** → **3d'** conversions demonstrate, both carbon atoms are shielded in both diastereomeric alcohols. Whereas the same phenomenon might be expected for C(21) and C(15) of heyneanine (**6d**) with respect to coronaridine (**6b**), C(15) is shielded excessively and C(21) surprisingly is deshielded. This fact points to a hydrogen bond between N_b and the hydroxy substituent. The presence of the new ring places the oxygen into a *gauche*-butane relationship with C(15), thereby accounting for part of the shielding of the latter, and removes it from any non-bonded interaction with C(21). The deshielding of the latter by 2.5 ppm must imply the removal of the acyclic γ-effect of the methyl group in coronaridine (**6b**), in analogy with the $\Delta\delta$(C(1)) value of 2.2 ppm for the **3b** → **3a** change, thereby orienting the methyl function of hey-



11



12

neanine (**6d**) toward C(15) and accounting for the remainder of the shielding of the latter. These arguments lead to the relative configuration for heyneanine depicted in **6d** and conformation **11**.

Recently there was isolated an indole alkaloid [18] whose mass-spectral and ^{1}H-NMR. analysis suggested it to be a heyneanine isomer [19][8]). In view of the above data it seemed reasonable that a ^{13}C-NMR. analysis of this new *Peschiera affinis* (MUELL. ARG.) MIERS constituent, named epiheyneanine, would furnish its relative configuration. The ^{13}C-NMR. spectra of the natural base reveal a shift pattern nearly identical with that of heyneanine (**6d**) except for the C(15) and C(21) shifts (see Table 2). This behavior can be interpreted only on the basis of epiheyneanine being

[7]) The *exo* configuration on the isoquinuclidine nucleus is defined as a sidechain orientation toward the aminomethylene bridge. Thus, for example, in voacangine (**6a**) C(2) is *exo* and the ester function *endo*.

[8]) Some time after completion of this work the relative configuration of heyneanine and epiheyneanine was reported in [17].

19-isoheyneanine (**6e**). The deshielding of C(15) by 5.7 ppm and shielding of C(21) by 5.0 ppm corroborates this point and shows epiheyneanine (**6e**) to possess conformation **12**[9]).

The financial support of this work by the *U.S. Public Health Service* and gifts of samples by Drs. *David R. Battiste* (Rice University) (**1**, **2**), *N. Neuss* (Eli Lilly and Co.) (**5a**), *N. Wang* (Rice University) (**5b**), *L. Dorfman* (Ciba-Geigy Corp., Summit) (**6a**, **6b**, **6c**, **7a**, **7b**) and *B. S. Joshi* (Ciba-Geigy Corp., Bombay) (**6d**) are acknowledged gratefully.

Experimental Part

The ^{13}C-NMR. spectra were recorded on *Varian* DP-60 and XL-100-15 NMR. spectrometers operating at 15.1 and 25.2 MHz, respectively, in the *Fourier* transform mode. The shifts on formulas **1** and **2** are in ppm downfield from TMS; δ(TMS) = δ($CDCl_3$) + 76.9 ppm.

REFERENCES

[1] *E. Wenkert, H. E. Gottlieb, O. R. Gottlieb, M. O. da S. Pereira & M. D. Formiga,* Phytochemistry, in press.
[2] *J. B. Stothers, J. R. Swenson & C. T. Tan,* Canad. J. Chemistry *53*, 581 (1975).
[3] *J. D. Roberts, F. J. Weigert, J. I. Kroschwitz & H. J. Reich,* J. Amer. chem. Soc. *92*, 1338 (1970).
[4] *G. E. Maciel, H. C. Dorn, R. L. Greene, W. A. Kleschick, M. R. Peterson, Jr. & G. H. Wahl, Jr.* Org. magn. Res. *6*, 178 (1974).
[5] *E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell & D. W. Cochran,* J. Amer. chem. Soc. *97*, 322 (1975).
[6] *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 & Y. Rolland,* J. Amer. chem. Soc. *95*, 4990 (1973).
[7] *B. A. Kazanskii & P. I. Svirskaya,* Žur. obšč. Chim. *29*, 2584 (1959).
[8] *B. A. Kazanskii & P. I. Zakezhenskaya,* Doklady Akad. Nauk. S.S.S.R. *72*, 57 (1950).
[9] *N. A. Belikova, Y. F. Plate & A. A. Bobyleva,* Ž. organ. Chim. *2*, 77 (1966).
[10] *O. Diels & K. Alder,* Liebigs Ann. Chem. *478*, 137 (1930).
[11] *R. Seka & O. Tramposch,* Ber. deutsch. chem. Ges. *75*, 1379 (1942).
[12] *E. Wenkert, C.-J. Chang, H. P. S. Chawla, D. W. Cochran, E. W. Hagaman, J. C. King & K. Orito,* J. Amer. chem. Soc. *98*, 3645 (1976).
[13] *E. Wenkert, B. L. Buckwalter, I. R. Burfitt, M. J. Gašić, H. E. Gottlieb, E. W. Hagaman, F. M. Schell & P. M. Wovkulich,* 'Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances,' in *G. C. Levy,* 'Topics in Carbon-13 NMR Spectroscopy,' vol. 2, Wiley-Interscience, New York, N.Y. 1976.
[14] *D. K. Dalling & D. M. Grant,* J. Amer. chem. Soc. *96*, 1827 (1974).
[15] *T. R. Govindachari, B. S. Joshi, A. K. Saksena, S. S. Sathe & N. Viswanathan,* Tetrahedron Letters *1965*, 3873.
[16] *S. M. Kupchan, J. M. Cassady & S. A. Telang,* Tetrahedron Letters *1966*, 1251.
[17] *M. de Bellefon, M.-M. Debray, L. Le Men-Olivier & J. Le Men,* Phytochemistry *14*, 1649 (1975).
[18] *M. C. Fonteles, D. Jerram, F. J. A. Matos & R. P. Uhlquist,* Planta Medica *25*, 175 (1974).
[19] *F. J. A. Matos, R. Braz Fo., O. R. Gottlieb, F. W. L. Machado & M. I. L. M. Madruga,* Phytochemistry *15*, 572 (1976).

[9]) *Note added in Proof*: In a recent ^{13}C-NMR study of some Iboga alkaloids *Ahond et al.* (*A. Ahond*, private communication) have reported chemical shifts for dihydrocatharanthine (**7a**) in $CDCl_3$ which the above investigation indicates to reflect conformation **8** for this compound. While catharanthine (**5a**) shows no conformational difference in $CDCl_3$ *vs.* d_6-DMSO (*cf.* Table 2), the conformation of the more crowded dihydrocatharanthine thus must be solvent dependent.