Carbon-13 Nuclear Magnetic Resonance Analysis of Vobasine-Like Indole Alkaloids[1]

Alain Ahond, Anne-Marie Bui, and Pierre Potier

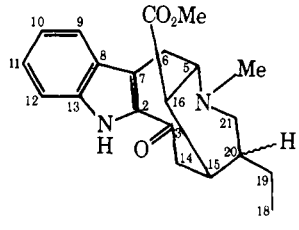
Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, 91190 Gif-sur-Yvette, France

Edward W. Hagaman and Ernest Wenkert*[2]

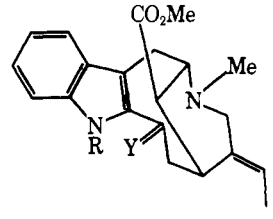
Department of Chemistry, Indiana University, Bloomington, Indiana 47401

Received October 28, 1975

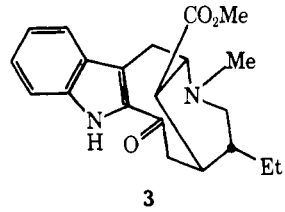
In continuation of a ^{13}C NMR study of indole alkaloids of various structure types[3] an analysis of selected samples of the α-acylindole family was undertaken. Aside from determining the basic carbon shifts of this alkaloid group—dregamine (**1a**), tabernaemontanine (**1b**), vobasine (**2a**), ochropamine (**2b**), and their derivatives 16-epidregamine (**3**), vobasinol (**2c**), and vobasinyl acetate (**2d**)—it was of interest to ascertain by direct analysis the C(20) stereochemistry of **1a** and **1b**[4] and to discover whether the strong anisotropic shielding of the methoxy protons of the alkaloids by the proximate indole ring[5] is reflected by any carbon shift perturbation of the ester function.



1a, 20β-H
b, 20α-H



2a, R = H; Y = O
b, R = Me; Y = O
c, R = H; Y = α-H, β-OH
d, R = H; Y = α-H, β-OAc



3

Inspection of the ^{13}C NMR spectra of the indolic compounds led to the chemical shifts depicted in Table I. The shift assignment is facilitated by the strong dissimilarity of most carbons from each other, when both the field position and multiplicity of their signals is utilized, and limited only to the differentiation of the methylene and nonaromatic methine resonances. The aminomethylene and α-ketomethylene signals are downfield of those of the other methylenes. Epimerization of C(16) with accompanying α-keto deuteration distinguishes C(14) from C(21) in dregamine (**1a**) and its 16 epimer (**3**). The same low-field methylene pair in tabernaemontanine (**1b**) is differentiated by C(21) deuteration of 20,21-didehydrotabernaemontanine.[6] The upfield pair of methylene signals of **1a**, **1b**, and **3** belong to C(6) and C(19) whose hydrogens occupy separate field positions. As a consequence the carbon–hydrogen, one-bond coupling characteristics of these signals in single-frequency, off-resonance decoupled (sford) spectra permit their allocation. The double bond of vobasine (**2a**) and its relatives (**2**) reduces C(6) to being the only upfield methylene, while comparison of vobasine-like compounds of different C(3) oxidation level with each other distinguishes C(14) from C(21) in these substances.

The aminomethine, C(5), possesses the lowest field methine signal of all substances. The next lowest field methine signal, that of C(16), exhibits sharp one-bond coupling components in its sford spectra in contrast to all other methine signals and characteristic of few long-range carbon–hydrogen interactions and no second-order couplings. This criterion is of special significance in the differentiation of C(16) from C(20) of **1b** in view of the shift similarity of these carbon centers. Only one methine remains in vobasine (**2a**) and its relatives (**2**), whose shift serves as a model δ value for C(15) in compounds **1** and **3**. Carbon 15 in **1a** was identified also by the observation of a 3-Hz β-deuterium substitution effect exerted by the three deuteriums in 14,14,16-trideuteriodregamine.

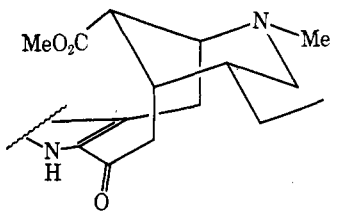
Conversion of the equatorial state of the carbomethoxy group within the piperidine ring of dregamine (**1a**) into the axial form, i.e., into 16-epidregamine (**3**), causes ca. 5 ppm

Table I. Carbon Shifts of α-Acylindole Alkaloids and Their Derivatives[a]

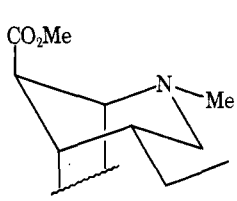
	1a	1b	3	2a	2b[b]	2c[c]	2d[c,d]
C(2)	133.8	133.7	135.0	133.8	133.3	135.4	133.7
C(3)	190.7	190.5	192.5	189.9	190.7	66.8	68.3
C(5)	56.5	56.7	55.4	57.0	57.0	59.4	60.8
C(6)	20.1	18.4	19.4	20.2	21.0	19.6	18.3
C(7)	120.1	120.5	121.1	119.9	120.7	107.3	108.7
C(8)	128.8	128.3	128.3	128.0	126.6	128.7	128.2
C(9)	120.5[e]	120.5[e]	120.8[e]	120.3[e]	120.2[e]	117.6	117.6
C(10)	120.0[e]	119.9[e]	120.5[e]	119.9[e]	119.8[e]	118.6	118.9
C(11)	126.3	126.3	126.9	126.2	125.8	121.4	121.2
C(12)	111.8	111.7	112.4	111.8	109.5	110.0	110.6
C(13)	136.4	136.4	136.7	136.4[f]	138.7	136.7[e]	136.2
C(14)	39.1	45.4	38.9	42.8	45.4	35.5	36.0
C(15)	30.5	31.7	29.5	30.5	30.6	29.2	30.1
C(16)	48.8	43.3	44.3	46.2	46.5	47.1	44.5
C(18)	11.3	12.6	11.4	12.0	12.1	12.2	12.3
C(19)	23.3	25.3	23.5	120.0[e]	119.8	118.6	120.9
C(20)	43.2	42.4	38.0	135.8[f]	135.7	136.5[e]	134.9
C(21)	48.5	46.4	48.6	51.5	51.8	53.9	53.9
C=O	170.9	171.6	173.9	170.9	170.9	174.3	170.0
OMe	50.1	50.1	51.8	50.1	49.8	50.3	49.8
NMe	42.3	42.9	42.6	42.2	42.2	42.1	42.0

[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] $\delta(N_a\text{-Me}) = 32.8$ ppm. [c] The indole carbon resonances are based on those of R. G. Parker and J. D. Roberts [*J. Org. Chem.*, **35**, 996 (1970)] as corrected by G. W. Gribble, R. B. Nelson, J. L. Johnson, and G. C. Levy, *J. Org. Chem.*, **40**, 3720 (1975). [d] The acetyl δ(Me) and δ(CO) values are 21.0 and 169.4 ppm, respectively. [e,f] Signals bearing the same superscript within any vertical column may be reversed.

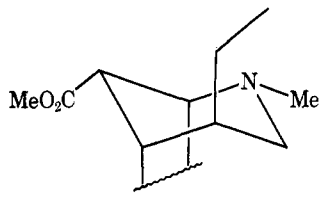
shielding on C(20). This γ effect is possible only in the presence of an axial H(20) and constrains the ethyl group to an equatorial orientation, as illustrated in partial structures **4** and **5**, respectively. As a consequence, tabernaemontanine (**1b**) must possess an axial ethyl function (**6**). This is confirmed by the loss and gain of γ effects in **1b** relative to **1a** at C(14) and C(16), respectively. Furthermore, the chemical shift of the methyl component of the ethyl group reflects the conformation of the two-carbon side chain.[7]



4



5



6

While the shifts of the carbomethoxy group of 16-epidregamine (**3, 5**) are characteristic of methyl cyclohexanecarboxylates,[3b,8] the carbonyl and methoxy groups of compounds **1, 2a,** and **2b** are shielded anomalously by 2.7 ± 0.4 and 1.8 ± 0.2 ppm, respectively. These shift perturbations reflect the close proximity of the carbomethoxy group in substances **1** and **2** to the α-acylindole moiety and are diagnostic of the C(16) stereochemistry. The indole α carbon and neighboring keto carbon respond likewise by being shielded by 1.2 ± 0.1 and 2.0 ± 0.1 ppm, respectively. Since strong anisotropic shielding (0.89 ppm) of the methoxy hydrogens of vobasine (**2a**), relative to 16-isovobasine, by the indole ring was observed some time ago,[5] the shift perturbation of the methoxy carbon may be due to the same effect. Anisotropic shielding of carbon centers has been predicted to be comparable in magnitude to such shielding observed in ^{1}H NMR spectroscopy[9] and therefore has been difficult to isolate as a unique contribution to the chemical shift.[10]

The methyl ester carbonyl shift of vobasinyl acetate (**2d**) is similar to that of the 3-keto systems **1, 2a,** and **2b,** while that of vobasinol (**2c**) is downfield 4.3 ppm owing to hydrogen bonding with the 3β-hydroxy group.[8]

Conjugation of a carbonyl group with the indole ring through its α carbon causes shift alteration throughout the aromatic system. The strong deshielding of the customarily high-field indole β carbon[3,11] is especially characteristic of the α-acyl attachment.

Experimental Section

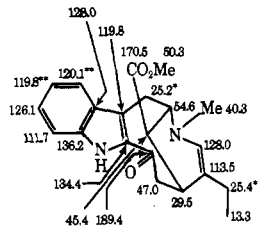
The ^{13}C NMR spectra were recorded on Bruker HX90E and Varian XL-100-15 spectrometers operating at 22.6 and 25.2 MHz in the Fourier transform mode, respectively. The shifts indicated on formula i are from a deuteriochloroform solution [$\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm] and the stars thereon represent interchangeable signals.

Acknowledgment. The authors express their sincere thanks to Aline and Henri-Philippe Husson for the preparation of 21-deuteriotabernaemontanine, Abbas Shafiee for the deuterated derivatives of **1a** and **3**, Pierre Mangeney and Yves Langlois for a sample of i, and Jean-Pierre Cosson and B. C. Das for a sample of **2b**.

Registry No.—**1a,** 2299-26-5; **1b,** 2134-98-7; **2a,** 2134-83-0; **2b,** 2134-97-6; **2c,** 7168-77-6; **2d,** 58324-78-0; **3,** 52389-31-8.

References and Notes

(1) (a) Etudes en Série Indolique. VII. For the previous paper see A. Husson, Y. Langlois, C. Riche, H.-P. Husson, and P. Potier, *Tetrahedron*, **29**, 3095 (1973). (b) Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. XL. For the previous publication see E. Wenkert and E. W. Hagaman, *J. Org. Chem.*, **41**, 701 (1976).
(2) Address correspondence to Department of Chemistry, Rice University, Houston, Texas 77001.
(3) (a) M. C. Koch, M. M. Plat, N. Préaux, H. E. Gottlieb, E. W. Hagaman, F. M. Schell, and E. Wenkert, *J. Org. Chem.*, **40**, 2836 (1975); (b) E. Wenkert, C.-J. Chang, H. P. S. Chawla, D. W. Cochran, E. W. Hagaman, J. C. King, and K. Orito, *J. Am. Chem. Soc.*, in press; and preceding papers.
(4) The recent conversion of tabernaemontanine (**1b**) into ervatamine and the latter's x-ray analysis[1a] indicated the necessity of the revision of the alkaloid's heretofore accepted stereostructure [U. Renner, D. A. Prins, A. L. Burlingame, and K. Biemann, *Helv. Chim. Acta*, **46**, 2186 (1963)].
(5) M. P. Cava, S. K. Talapatra, J. A. Weisbach, B. Douglas, and G. O. Dudek, *Tetrahedron Lett.*, 53 (1963).
(6) The carbon shifts of this substance are delineated on formula i.



i

(7) The ca. 1 ppm difference of C(18) shifts has been shown earlier to be diagnostic of the C(20) stereochemistry in corynantheoid alkaloids.[3a]
(8) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(9) J. A. Pople, *Discuss. Faraday Soc.*, **34**, 7 (1962).
(10) Cf., inter alia, H. Günther, H. Schmickler, H. Königshofen, K. Recker, and E. Vogel, *Angew. Chem., Int. Ed. Engl.*, **12**, 243 (1973); R. H. Levin and J. D. Roberts, *Tetrahedron Lett.*, 135 (1973).
(11) Cf. R. J. Sundberg and F. X. Smith, *J. Org. Chem.*, **40**, 2613 (1975).

A Convenient Method for Estimation of Alkyllithium Concentrations

William G. Kofron* and Leona M. Baclawski

Department of Chemistry, The University of Akron, Akron, Ohio 44325

Received September 30, 1975

Alkyllithium reagents have become increasingly important in organic synthesis. Commercial alkyllithium reagents are usually accompanied with a lot analysis, but often even freshly obtained solutions have obviously deteriorated, being dark colored and cloudy, and most alkyllithium solutions deteriorate after the container is opened. For use in metalation reactions and alkylations, an excess or a deficiency of alkyllithium is often detrimental, especially where dilithio intermediates are formed.[1] Thus analysis of an alkyllithium reagent is often desirable.

The standard procedure for such an analysis requires a double titration—total alkali, which includes the alkyllithium and such species as alkoxides formed by reaction of the reagent with air, from which is subtracted that portion which does not react rapidly with certain halides. The method is said not to be useful for certain alkyllithium reagents.[2]

Since the organolithium compound is so often used for metalation, we offer a convenient method of analysis which is based on the reaction for which the reagent is intended, namely carbon lithiation, and which produces a color at the end point and is thus independent of indicator. A similar acid–indicator system has been proposed; however, solvent plays a critical role, and there is some difference from the values determined by the double titration procedure.[3]

We noticed in the metalation of certain pyridine esters that the red dianion color was not observed until the butyllithium