This was distilled at 15 mm pressure through the same column to give, after a forerun (diglyme), 5.8 g of product boiling at 90–100° (most at 98–100°), $[\alpha]^{20}D$ −69.7° (*c* 0.025, $CHCl_3$).

**(1*R*,2*R*)-2-Methylcyclopropylcarbonyl Chloride.** A solution of 5.8 g (0.058 mol) of the above acid and 6 ml (9.7 g, 0.080 mol) of $SOCl_2$ in 19 ml of $C_6H_6$ was refluxed for 6 hr, and then the more volatile components were distilled through a 12-in. Vigreux column until the pot temperature reached 100°. Continuation at 70 mm pressure gave, after a forerun, 5.5 g (80%) of product boiling at 66.0–67.0°. A sample was treated with MeOH to give the methyl ester: bp 71.0° (90 mm); $[\alpha]^{20}D$ −90.3° (*c* 0.0301, MeOH); $\theta_{max}$ (227.5 nm) +114° (methanol). Another small sample was hydrolyzed to the acid and extracted with chloroform; assuming complete conversion and recovery, $[\alpha]^{20}D$ −88° (lit.[12] −77.4°).

**(1*R*,2*R*)-α,α,2-Trimethylcyclopropanemethanol.** To the Grignard formed from 2.4 g (0.100 mol) of Mg and 15.7 g (0.110 mol) of MeI in 65 ml of $Et_2O$, over $N_2$, was added with stirring 5.4 g (0.045 mol) of (1*R*,2*R*)-2-methylcyclopropylcarbonyl chloride in 30 ml of $Et_2O$. Stirring was continued at room temperature for 20 hr and then gentle refluxing for another 6 hr. Saturated $NH_4Cl$ solution (75 ml) was added; the layers were separated and the organic solution was dried over $MgSO_4$. The ether was removed by distillation through a Vigreux column, and then the pressure was reduced to give 1.9 g (37%) of product: bp 79–81° (100 mm); $[\alpha]^{21}D$ −33.5° (*c* 0.0254, MeOH); nmr ($CCl_4$) δ 1.3 (s, 1), 1.15 (s, 6), 1.1–0.4 (complex 6–7); mass spectrum base peak at *m/e* 72, strong peaks at 59, 70, 81, 96, 99, weak parent peak; ir (neat film) strong OH, CH, other peaks at 1470, 1380, 1240, 1160, 1080, 1040, 960, 940, 910, 890, 860, 810 $cm^{-1}$. A higher boiling fraction (119–120° (100 mm) could be redistilled 72–74° (17 mm)) developed a violet color on standing in air and reacted with bromine: ir (neat film) 2900–3000, 1450, 1380, 1290 (weak), 1250 (weak), 1200, 1150, 1080, 840 $cm^{-1}$; mass spectrum base peak *m/e* 55, weak parent ion 224, strong peaks at 97, 83, 81, 69, 67, 53; nmr see Table I.

**(1*S*,2*R*)-Dimethyl(2-methylcyclopropyl)carbenium Ion.** Following the published procedure,[7] 26 mg (0.23 mmol) of (1*R*,2*R*)-α,α,2-trimethylcyclopropanemethanol was dissolved in 0.5 ml of 95% ethanol and added dropwise to 12 ml of 90% $FSO_3H$–10% $SbF_5$ (by weight) at −78° with vigorous stirring. After the mixture was stirred for an additional 10 min, a small sample was transferred *via* a prechilled syringe into a jacketed silica cell (0.2-mm path length) cooled with nitrogen. To minimize fogging, the cell was mounted in a plastic box with silica windows and the chamber of the spectropolarimeter purged continuously with dry nitrogen. Temperature was monitored by means of an iron–constantan thermocouple taped to the cell between the fill-ports.

**Acknowledgment.** These studies were carried out while the author was associated with the research group of Professor Carl Djerassi, whose encouragement and advice is deeply appreciated. He would also like to thank Edward Bunnenberg and Günter Barth for helpful advice, Ruth Records for obtaining the CD spectra, and Thomas Gibson for drawing his attention to ref 20 and 21. Thanks are also due Kenneth B. Wiberg and Herman Richey for graciously transmitting copies of their chapters in Vol. III of ref 2b prior to publication.

# Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. XIX. *Aspidosperma* Alkaloids[1]

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**Abstract:** The natural abundance $^{13}C$ nmr spectra of the *Aspidosperma* alkaloids tabersonine and vincadifformine, of the structurally related, new bases vandrikidine, vandrikine, and hazuntinine, of the indole–indoline alkaloid vincaleukoblastine (VLB) and leurosine, and of the indoline alkaloid vindoline and suitable models have been recorded. Chemical shift assignments have been made for all carbons of the alkaloids except some of the carbomethoxyvelbanamine portions of the indole–indoline alkaloids. The data have been used for the structure determination of the new indole bases and for ascertaining the presence of an epoxide linkage in leurosine. Anomalous, hence potentially misleading single frequency off-resonance data are described. A structurally diagnostic, endocyclic homoallyl shielding effect is portrayed by the use of a variety of models.

Upon completion of the $^{13}C$ nmr spectral analysis of the yohimboid and ajmalicinoid indole alkaloids,[4] a similar study of the structurally more complex *Aspidosperma* alkaloids was undertaken. The investigation was initiated by an inspection of the spectra of tabersonine (**1**) and vincadifformine (**2**), two compounds whose structures are representative of the basic ring skeleton of a large number of these natural substances.

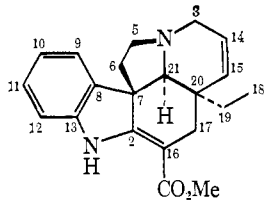
The natural abundance $^{13}C$ nmr spectra of 0.2–1.0 *M* chloroform or deuteriochloroform solutions of the above compounds and others (*vide infra*) were recorded on a Fourier transform spectrometer operating at

(1) For the preceding paper, see E. Wenkert, J. S. Bindra, C.-J. Chang, D. W. Cochran, and F. M. Schell, manuscript submitted for publication.

(2) (a) Indiana University; (b) Eli Lilly and Company; (c) Institut de Chimie des Substances Naturelles; (d) U. E. R. de Chimie Thérapeutique; (e) Faculté des Sciences Pharmaceutiques et Biologiques.

(3) (a) U. S. Public Health Service predoctoral fellowship recipient, 1967–1971; (b) U. S. Public Health Service predoctoral fellowship recipient, 1969–1972.

(4) D. W. Cochran, Ph.D. Dissertation, Indiana University, 1971.

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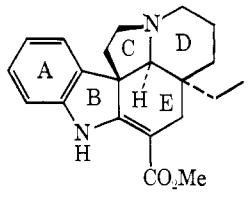


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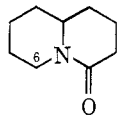
15.08 MHz.[5] Three types of spectra were run: proton-resonance decoupled spectra for the determination of $^{13}C$ chemical shift values, noise off-resonance decoupled spectra for the detection of nonprotonated carbon sites,[6] and single-frequency off-resonance decoupled spectra for the differentiation of carbon species. While the 1:1 signal–carbon relationship permitted a facile analysis of the first two types of spectra, interpretation of the residual coupling in the third form of spectra proved difficult in view of overlapping signals, and a heretofore unobserved and at times misleading effect associated with methylenes substituted by magnetically nonequivalent hydrogens.

The anomaly, *i.e.*, methylenes showing residual coupling other than triplets, was exhibited especially by the spectrum of vindoline (*vide infra*). While the $n + 1$ rule of spin–spin coupling prescribes a symmetrical three-line pattern for methylene groups with magnetically alike hydrogens, the shape of the multiplet of nonequivalently diprotonated carbon centers depends on the single frequency position with respect to the proton chemical shifts. A doublet should arise from the chosen frequency residing between the two proton signals so as to yield identity of the reduced coupling constants, a combination of doublet and singlet from the frequency superposing one of the proton signals thereby eliminating one carbon–hydrogen coupling and a four-line pattern from the frequency being removed a considerable, unequal distance from the proton resonances. Excellent examples illustrating this frustrating, although, once recognized, diagnostically useful effect were the single-frequency off-resonance decoupled spectra of chloroform solutions of 4-quinolizidone (**3**). While the substance possesses seven



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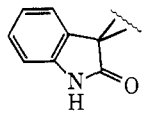

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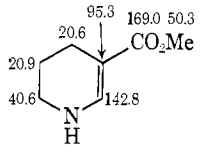


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methylenes, spectra based on single frequencies chosen arbitrarily both upfield and downfield of its pmr spectral range exhibit six triplets and one downfield pair of doublets. The latter signal, 41.4 ppm, represents the amidomethylene group, C(6) in **3**, whose hydrogens are known to be magnetically nonequivalent (pmr $\delta$ 2.28 and 4.63 ppm).[7] *Thus, great caution needs to be exercised in interpreting single-frequency off-resonance decoupled spectra of structurally complex natural products of especially unknown constitution.*

The chemical shifts of the aromatic carbons of tabersonine (**1**) and vincadifformine (**2**) were assigned by comparison with the benzene carbon shifts of oxindole alkaloids. Since the C(2) carbomethoxyalkylidene substituent makes **1** and **2** oxindole vinylogs, previously analyzed oxindole bases of part structure **4** can serve as good models for the present analysis. As Table I indicates, the aryl carbon $\delta$ values of **1** and **2** are very similar to those of rhyncophylline (**4a**),[1] isorhyncophylline (**4b**),[1] and gelsemine (**4c**).[8]

Table I. $^{13}C$ Chemical Shifts[a]

| | 1 | 2 | 4a | 4b | 4c |
|---|---|---|---|---|---|
| C(8) | 137.8 | 138.0 | 134.1 | 134.2 | 132.1 |
| C(9) | 121.4 | 121.0 | 122.8 | 125.2 | 128.0[b] |
| C(10) | 120.5 | 120.5 | 122.4 | 122.1 | 121.7 |
| C(11) | 127.6 | 127.4 | 127.8 | 127.4 | 128.3[b] |
| C(12) | 109.2 | 109.3 | 109.7 | 109.6 | 109.0 |
| C(13) | 143.1 | 143.4 | 141.5 | 140.7 | 140.6 |

[a] For description of the data, see Table II. [b] These values may be interchanged.

The shifts of the vinylogous amide unit (C(2), C(16), and the carbomethoxy carbons) are based on the shifts of the model methyl 1,4,5,6-tetrahydronicotinate (**5**).[4,9] Carbons 18 and 21 are identified from the off-resonance data, since they are the only C-methyl and saturated methine groups, respectively. The quaternary sites C(7) and C(20), whose signals were determined in a direct manner by the noise off-resonance decoupling technique,[6] are distinguished from each other by the shift of the former being invariant in the spectra of alkaloids **1** and **2**, while that of the latter reflects the presence or absence of the ring D double bond. A similar distinction can be made between the aminomethylenes C(3) and C(5), characterized by the lowest field methylene signals. The effect of the introduction of a double bond into a piperidine ring on the allylic carbons appears to be variable. It can cause an upfield shift of up to several ppm, as noted from a comparison of the $\delta$ values of *N*-methylpiperidine (**6**)[1,4,10,11] and 1,2-dimethylpiperidine (**7**)[1,4,11,12] with those of 1-methyl-3-piperideine (**8**),[4] 1,2-dimethyl-3-piperideine (**9**),[4] and 1,2-dimethyl-4-piperideine (**10**).[4]

The neopentyl carbon center at C(6) is the lowest field methylene except for the aminomethylenes throughout the *Aspidosperma* alkaloid series (*vide infra*). It remains constant at 44–46 ppm, at least 10 ppm downfield of any other diprotonated neopentyl site. The olefinic methines of tabersonine (**1**) are distinguished

(5) The nmr instrument consisted of a Varian Associates DP-60 magnet working at 14 kG with an external $^{19}F$ lock, a white-noise generator and adjustable, home-built crystal oscillator for proton decoupling, a Fabri-Tek 1074 time-averaging computer, and Digital Electronics Corp. PDP-8/I computer for signal averaging and Fourier transformation of the free induction decay. The samples were spun in 13-mm o.d. tubes and the solvent signal was used as internal standard.

(6) E. Wenkert, A. O. Clouse, D. W. Cochran, and D. Doddrell, *J. Amer. Chem. Soc.*, **91**, 6879 (1969).

(7) F. Bohlmann and D. Schuhmann, *Tetrahedron Lett.*, 2435 (1965).

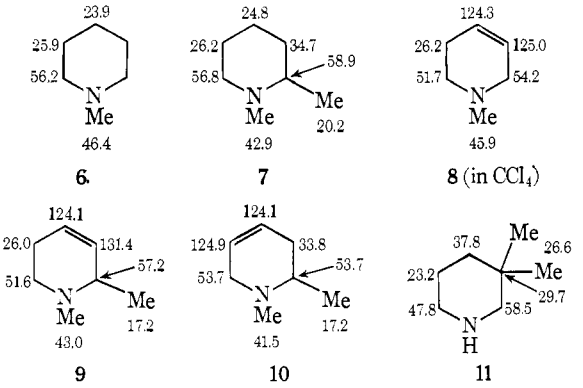
(8) E. Wenkert, C.-J. Chang, A. O. Clouse, and D. W. Cochran, *Chem. Commun.*, 961 (1970); E. Wenkert, C.-J. Chang, D. W. Cochran, and R. Pellicciari, *Experientia*, **28**, 377 (1972).

(9) All $\delta$ values denoted on the formulas are in ppm downfield from TMS. Unless otherwise indicated, the chemical shifts are from spectra in chloroform solution; $\delta^{TMS} = \delta^{CHCl_3} + 77.2$ ppm. The $\delta$ values from spectra in carbon tetrachloride solution are based on $\delta^{TMS} = \delta^{CCl_4} + 95.9$ ppm.

(10) W. O. Crain, W. C. Wildman, and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 990 (1971); I. Morishima, K. Okada, T. Yonezawa, and K. Goto, *ibid.*, **93**, 3922 (1971).

(11) G. Ellis and R. G. Jones, *J. Chem. Soc., Perkin Trans. 2*, 437 (1972).

(12) A. J. Jones and M. M. A. Hassan, *J. Org. Chem.*, **37**, 2332 (1972).



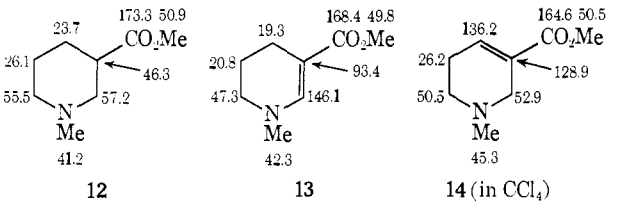

from each other by strong $\beta$ effects[13] of the C(20) substituents deshielding C(15), a relationship observed also in model **9**. Carbon 14 of vincadifformine (**2**) is expected to resonate at high field in view of a $\gamma$ effect[13] resulting from the 1,3-diaxial steric involvement of C(17), a phenomenon related to the shielding of C(5) in 3,3-dimethylpiperidine (**11**)[14] by the axial methyl group. The C(15) shift of vincadifformine (**2**) can be extrapolated approximately from that of C(4) in model **11** plus a $\gamma$ effect[15] exerted by C(18). If it be assumed that the **1** → **2** change enhances the $\gamma$ effect[13] by C(14) on C(17) by the introduction of nonbonded hydrogen–hydrogen interactions, the C(17) shift in vincadifformine (**2**) must be upfield from that of tabersonine (**1**). While this fixes the $\delta$ values of C(17) and C(19) in **2**, their differentiation in **1** is difficult at best and must be considered tentative at this time. The chemical shifts of all nonaromatic carbons of the two alkaloids are listed in Table II.

**Table II.** $^{13}$C Chemical Shifts[a]

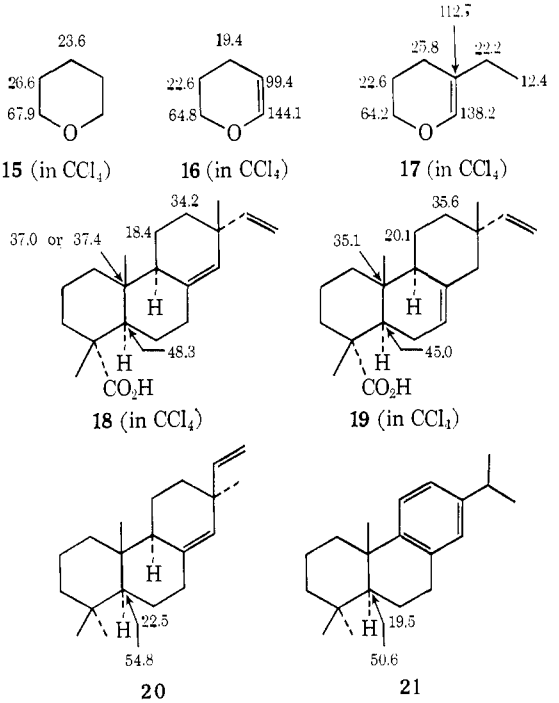
| | 1[b] | 2[b] | 23[c] | 24[c] | 26[c] |
|---|---|---|---|---|---|
| C(2) | 166.7 | 167.8 | 167.4 | 167.4 | 166.0 |
| C(3) | 50.3[d] | 51.7 | 49.9 | 45.7 | 49.2 |
| C(5) | 50.8[d] | 50.7 | 50.8 | 51.2 | 51.4 |
| C(6) | 44.3 | 45.3 | 44.2 | 45.1 | 43.6 |
| C(7) | 55.0 | 55.5 | 54.8 | 54.2 | 54.8 |
| C(14) | 124.8 | 22.2 | 127.6 | 27.4[f] | 51.8 |
| C(15) | 132.9 | 32.9 | 129.6 | 79.8 | 57.0 |
| C(16) | 92.2 | 92.8 | 90.8 | 93.9 | 90.7 |
| C(17) | 26.7[e] | 25.6 | 28.1 | 26.6[f] | 23.3 |
| C(18) | 7.3 | 7.3 | 17.7 | 64.7 | 7.0 |
| C(19) | 28.4[e] | 29.3 | 67.9 | 34.6 | 26.3 |
| C(20) | 41.2 | 38.2 | 46.0 | 46.4 | 36.8 |
| C(21) | 69.9 | 72.7 | 66.3 | 68.7 | 70.8 |
| C=O | 168.8 | 169.2 | 168.3 | 168.5 | 168.8 |
| OMe | 50.8 | 50.9 | 50.8 | 50.8 | 50.7 |

[a] In parts per million downfield from TMS. [b] In chloroform solution; $\delta^{TMS} = \delta^{CHCl_3} + 77.2$ ppm. [c] In deuteriochloroform solution; $\delta^{TMS} = \delta^{CDCl_3} + 76.9$ ppm. [d,e,f] Values may be interchanged.

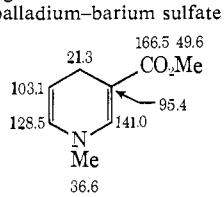
Inspection of a broad spectrum of $^{13}$C chemical shift data on alkaloids[1,4] has led to the conclusion that the incorporation of a double bond in a piperidine nucleus results in shielding of the homoallyl carbons. This *endocyclic homoallyl effect* is exhibited by C(21) in tabersonine (**1**), C(6) in **8** and **9**, C(2) in **10**, C(5) and C(6) in **13**,[16] and C(6) in arecoline (**14**).[1] It is observed




also in six-membered oxygen heterocycles (the C(5) and C(6) shifts of dihydropyrans **16** and **17**) and carbocycles (shift differences of 4.2 ppm for C(4) and C(5) of cyclohexene, of 3.5 and 3.1 ppm for C(4) and C(5) of 1-methylcyclohexene, respectively, of C(5), C(10), C(11), and C(12) in isopimaric (**18**) and sandaracopimaric (**19**) acids,[13b] and of C(5) and C(6) in pimaric (**20**) and dehydroabietic (**21**) acids).[13b]




Recently there were isolated three new *Aspidosperma* alkaloids, vandrikidine, vandrikine and hazuntinine.[17] Since a preliminary, variegated spectral analysis showed them to be structurally of the tabersonine–vincadif-




i (in $CCl_4$)

(13) (a) D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, **89**, 6612 (1967); (b) E. Wenkert and B. L. Buckwalter, *ibid.*, **94**, 4367 (1972).

(14) The authors are indebted to Professor E. Eliel for a gift of this substance.

(15) D. M. Grant and E. G. Paul, *J. Amer. Chem. Soc.*, **86**, 2984 (1964).

(16) The close C(4) and C(5) shifts of **13** [E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, *J. Org. Chem.*, **33**, 747 (1968)] were differentiated by the diminution of the C(4) signal in a cmr spectrum of 4-deuterio-**13**, prepared by the dithionite reduction of methyl nicotinate methiodide in deuterium oxide [D. Mauzerall and F. H. Westheimer, *J. Amer. Chem. Soc.*, 77, 2261 (1955)] and hydrogenation of the resultant monodeuterio derivative of product i over palladium–barium sulfate [*cf.* K. G. Dave, R. B. Dunlap, M. K. Jain, E. H. Cordes, and E. Wenkert, *J. Biol. Chem.*, **243**, 1073 (1968)]. As the $\Delta\delta$ of C(6) in **12** and **13** indicates, the magnitude of the effect may vary with the polarity of the double bond and with the extra trigonality introduced into the ring system.

(17) P. Potier and C. Kan, unpublished observations.

formine type,[17] the challenging determination of their configuration by cmr spectroscopy was undertaken.

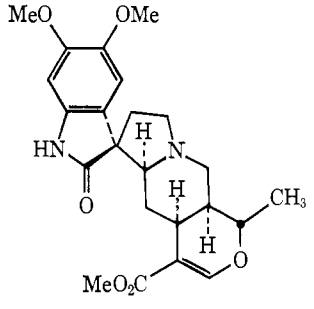
The cmr spectra of vandrikidine and vandrikine, isomeric $C_{22}H_{26}O_4N_2$ bases, reveal a highly modified aromatic region from that of tabersonine (**1**) (*cf.* Table I) and the presence of an extra methyl signal in the region characteristic of aromatic methoxy groups, 55–57 ppm. Since these facts imply a methoxylated ring A and require determination of the specific site of the methoxyl group, methoxy substituent parameters ($\alpha$, +30.2, o, −15.5, m, 0, p, −8.9 ppm[18]) are applied to the aromatic shift data of tabersonine. This calculation leads to a pattern compatible only with the placement of the methoxy group at C(11) of the alkaloids. The 11-methoxy alkaloid vindoline and its dihydro derivative possess similar benzene carbon shifts despite a difference in their $N_a$ substitution pattern. The $\delta$ values of the aromatic carbons of the four compounds are listed in Table III.

**Table III.** $^{13}C$ Chemical Shifts[a]

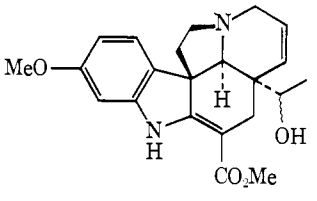
| | 23 | 24 | 27 | 28 | 26 | 22 |
|---|---|---|---|---|---|---|
| C(8) | 130.4 | 130.5 | 124.9 | 125.2 | 128.7 | 123.7 |
| C(9) | 122.0 | 121.5 | 122.4 | 122.7 | 103.5 | 108.2 |
| C(10) | 105.2 | 104.8 | 104.5 | 104.1 | 149.3 | 148.3 |
| C(11) | 159.9 | 159.8 | 161.1 | 160.6 | 143.5 | 144.9 |
| C(12) | 96.6 | 96.5 | 95.6 | 95.6 | 95.3 | 97.1 |
| C(13) | 144.0 | 144.1 | 153.6 | 154.0 | 137.0 | 134.7 |
| OMe | 55.3 | 55.2 | 55.1 | 55.0 | 55.9, 55.9 | 56.8, 56.3 |

[a] For description of the data see Tables II and IV.

Hazuntinine, a $C_{23}H_{28}O_5N_2$ base, is a ring A dimethoxy base[17] whose aromatic carbon shifts are similar to those of the oxindole alkaloid carapanaubine (**22**). This fact and a substituent parameter calculation indicate the methoxy groups to be positioned at C(10) and C(11). In view of $N_a$ of hazuntinine being part of a vinylogous amide unit and hence the alkaloid being an oxindole vinylog carapanaubine is as good a model for the analysis of the aromatic cmr region (*cf.* Table III) as the oxindole bases gelsemine, rhyncophylline, and isorhyncophylline (**4** each) were for tabersonine (**1**) and vincadifformine (**2**) (*vide supra*).



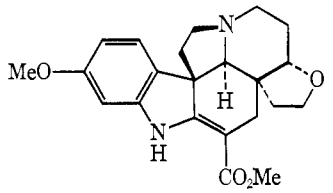

**22**



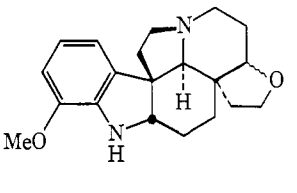

**23**

The nonaromatic $^{13}C$ shifts of vandrikidine (Table II) reveal the alkaloid to be tabersonine-like. The vinylogous amide unit and ring D double bond are present, but one methylene group is replaced by an oxymethine moiety. Furthermore, only carbons 14–21 appear to be perturbed by the presence of the extra oxygen function, which has been shown from non-cmr data[17] to be a hydroxyl group. The latter must reside at C(19) in view of the shielding of C(15) and C(21)[19] and the 10.4 ppm downfield shift of the C-methyl group, C(18), from its position in tabersonine (**1**), a change reminiscent of the 9.7 ppm deshielding $\beta$ effect of hydroxyl groups in acyclic compounds.[20] The similarity of the remaining carbon shifts to those in **1** reflects the same relative stereochemistry. As a consequence, structure **23** can be assigned to vandrikidine.

The cmr spectrum of the nonaromatic portion of vandrikine (Table II), the vandrikidine (**23**) isomer whose extra oxygen function is an ether[17] instead of a hydroxyl group, shows the alkaloid to be vincadifformine-like. A vinylogous amide unit is present and the ring D double bond missing. The C-methyl group is absent, oxymethylene and oxymethine shifts are exhibited, and all ring D shifts are modified. The presence of an axial, C(15), oxygen substituent is indicated by C(3) and C(21) experiencing shifts of 5.0 and 4.0 ppm, respectively, corresponding to $\gamma$ effects, by C(14) and C(20) suffering characteristic $\beta$ effects, 5.2 and 8.2 ppm, respectively, and by the disappearance of the C(15) methylene of vincadifformine (**2**). If it be assumed that the missing C-methyl group is an oxymethylene and therefore C(15) and C(18) are bound to each other by an ether linkage, a *cis*-tetrahydrofuran unit is created for which all chemical shifts are accounted. As a result, the relative configuration **24**, similar to the structure of beninine (**25**),[21] can be assigned to vandrikine.




**24**




**25**

The nonaromatic part of the cmr spectrum of hazuntinine (Table II), whose extra oxygen is known to be part of an ether subunit, reveals the presence of a vinylogous amide moiety and a C–Me group, the absence of the ring D double bond, and the replacement of two vincadifformine (**2**) methylenes by oxymethines. The signals of the latter appear at extraordinarily high field, a behavior characteristic of epoxide carbons.[22] Centers C(14) and C(15) must be the points of attachment of the oxide, since carbons 3, 5, and 6 appear as methylene groups. Comparison of the cmr spectrum of hazuntinine with that of tabersonine (**1**) indicates that the introduction of an epoxide unit leads to shielding of C(17), *i.e.*, a $\gamma$ effect, but little perturbation of C(19) and C(21). This suggests that the oxide is oriented cis to C(17) and trans to the ethyl side chain and structure **26** can be assigned to hazuntinine.[23]

(18) P. C. Lauterbur, *J. Amer. Chem. Soc.*, **83**, 1846 (1961); K. S. Dhami and J. B. Stothers, *Can. J. Chem.*, **44**, 2855 (1966).

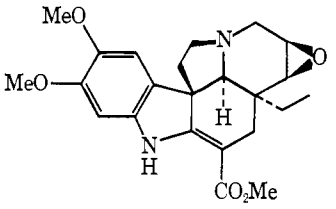
(19) Carbons 15 and 21 experience full $\gamma$ effects, while conversely C(17) is deshielded or nearly unperturbed. These facts are a consequence of specific, but not readily interpretable rotamer population preferences in the side chains of vandrikidine and tabersonine.

(20) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Amer. Chem. Soc.*, **92**, 1338 (1970).

(21) A. A. Gorman, V. Agwada, M. Hesse, U. Renner, and H. Schmid, *Helv. Chim. Acta*, **49**, 2072 (1966).

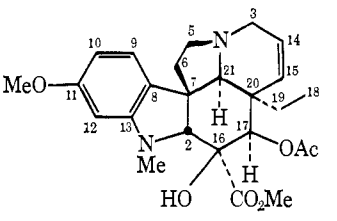
(22) The oxymethine shift of cyclohexene oxide is 51.3 ppm.

(23) While the assignment of the gross structure is on firm ground, that of the stereochemistry of the epoxide is only tentative at this time in view of the cmr arguments neglecting presently unknown, dipolar effects of epoxides on neighboring carbons.

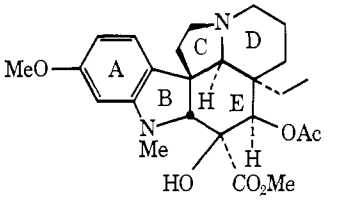


26

The experience gained from the $^{13}C$ nmr analyses of the natural bases **1**, **2**, **23**, **24**, and **26** was of immense value in the cmr spectral dissection of the *Aspidosperma* alkaloid vindoline (**27**) and its dihydro derivative (**28**).



27



28

The aromatic carbon shifts of the two substances follow from the analysis of corresponding carbon centers in vandrikidine (**23**) and vandrikine (**24**) (Table III), while the shifts of the acetate and carbomethoxy carbons and of the $N_a$- and C-methyl groups are based on chemical shift theory.[24] Since the substitution patterns of vindoline (**27**) and tabersonine (**1**) differ only in ring E, the $\delta$ values of carbons 3, 5, 6, and 14 of the two alkaloids are similar and only the C(15) shifts differ in view of the added $\gamma$ effect of the 17$\beta$-acetate unit in **27**. A close relationship exists also between the chemical shifts of carbons 3, 5, 6, 14, and 15 of dihydrovindoline (**28**) and vincadifformine (**2**). The sole, remaining methylene signal in the spectra of **27** and **28** is that of C(19). The hydroxyl group makes C(16) the farthest downfield, nonprotonated, saturated carbon site, while the constancy of chemical shift of C(7) and shift variability of C(20) depending on the C(14)–C(15) environment differentiate the quaternary carbons in the two substances.

The saturated methine signals differ significantly in the spectra of **27** and **28** only by one of them changing position by 5.3 ppm. This movement must be associated with C(21) in view of the endocyclic, homoallyl effect (*vide supra*) and the expected imperviousness of C(2) and C(17).[25] The latter two carbons can be distinguished from each other by the difference of their residual coupling to their own protons in single-frequency off-resonance decoupled spectra of vindoline (**27**). This method of analysis[26] is made especially effective by the sharp difference of the 2$\beta$- and 17$\alpha$-hydrogen shifts, 3.75 and 5.43 ppm, respectively.[27] Proton decoupling at a frequency in the pmr spectra range of $-1$ to 0 ppm ($\delta$ scale) causes the 83.2- and 76.2-ppm cmr signals to display residual carbon–hydrogen coupling of 45 and 59 Hz, respectively, while the decoupling frequency being in the 8–9 ppm pmr range leads to residual splitting of 46 and 34 Hz, respectively. Thus the 83.2-ppm carbon shift is related to the 3.75-ppm hydrogen shift and the 76.2-ppm cmr signal to the 5.43-ppm pmr signal. All $^{13}C$ chemical shifts of the nonaromatic portions of vindoline (**27**) and dihydrovindoline (**28**) are listed in Table IV.

**Table IV.** $^{13}C$ Chemical Shifts[a]

| | **27**[b] | **28**[b] | **29a**[c] | **30**[c] |
|---|---|---|---|---|
| C(2) | 83.2 | 83.5 | 83.1 | 82.7 |
| C(3) | 50.9 | 52.4 | 50.0 | 49.7 |
| C(5) | 51.9 | 51.4 | 50.0 | 49.7 |
| C(6) | 43.9 | 43.4 | 44.3 | 43.8 |
| C(7) | 52.6 | 52.4 | 52.8 | 52.6 |
| C(14) | 123.9 | 22.4 | 124.1 | 123.8 |
| C(15) | 130.2 | 33.0 | 129.7 | 129.4 |
| C(16) | 79.5 | 78.3 | 79.3 | 78.9 |
| C(17) | 76.2 | 75.6 | 76.4 | 75.8 |
| C(18) | 7.5 | 7.8 | 8.1 | 7.9 |
| C(19) | 30.6 | 29.9 | 30.5 | 30.5 |
| C(20) | 42.8 | 40.0 | 42.3 | 42.1 |
| C(21) | 67.0 | 72.3 | 65.4 | 65.1 |
| Ester C=O | 170.4 | 170.0 | 170.2 | 169.9 |
| Ac C=O | 171.7 | 172.3 | 171.2 | 170.8 |
| OMe | 51.9 | 52.0 | 51.8 | 51.6 |
| NMe | 38.0 | 37.7 | 38.0 | 37.6 |
| CMe | 20.8 | 20.7 | 20.7 | 20.4 |

[a] In parts per million downfield from TMS. [b] In deuteriochloroform solution; $\delta^{TMS} = \delta^{CDCl_3} + 76.9$ ppm. [c] In chloroform solution; $\delta^{TMS} = \delta^{CHCl_3} + 77.2$ ppm.

The complete cmr analysis of vindoline (**27**) provides the background for the challenging task of describing the biomedically important, structurally highly complex alkaloid vincaleukoblastine (VLB) (**29a**) and leurosine, the related, indole–indoline base of still uncertain constitution. Since both compounds contain C(10)-substituted vindoline units,[27,28,29] the nonaromatic segments of this portion of their molecular architecture have essentially the same chemical shifts as vindoline (**27**) (Table IV). The $\delta$ values of the vindolinic, aromatic carbons fit those calculated[24] for the model 10-*tert*-butylvindoline except for a slightly upfield C(8) position (Table V). The aromatic carbon shifts of the carbomethoxyvelbanamine part of VLB (**29a**) and of the related fragment of leurosine are based on those of velbanamine (**29b**), whose indole carbon shifts are derived from those of the yohimboid and

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

(25) Contrastingly, C(17) suffers a 1.1 ppm upfield shift in the change of tabersonine (1) into vincadifformine (2). This is a consequence of the 14$\beta$-17$\beta$ hydrogen–hydrogen repulsion in the latter, which is absent in the 17$\beta$-acetoxy compounds: D. M. Grant and B. V. Cheney, *J. Amer. Chem. Soc.*, **89**, 5315 (1967).

(26) It is based on the mathematical relationship derived by R. R. Ernst [*J. Chem. Phys.*, **45**, 3845 (1966)]; [*cf.* also K. G. R. Pachler, *J. Magn. Resonance*, 7, 442 (1972)] and previously has been put to quantitative use: *inter alia* B. Birdsall, N. J. M. Birdsall, and J. Feeney, *J. Chem. Soc., Chem. Commun.*, 316 (1972).

(27) M. Gorman, N. Neuss, and K. Biemann, *J. Amer. Chem. Soc.*, **84**, 1058 (1962).

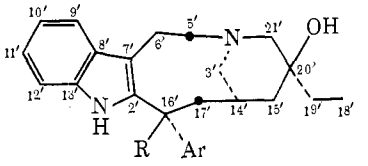
(28) M. Gorman, N. Neuss, and G. H. Svoboda, *ibid.*, **81**, 4745 (1959); N. Neuss, M. Gorman, H. E. Boaz, and N. J. Cone, *ibid.*, **84**, 1509 (1962); N. Neuss, M. Gorman, W. Hargrove, N. J. Cone, K. Biemann, G. Büchi, and R. E. Manning, *ibid.*, **86**, 1440 (1964); J. W. Montcrief and W. N. Lipscomb, *ibid.*, **87**, 4963 (1965).

(29) N. Neuss, M. Gorman, N. J. Cone, and L. L. Huckstep, *Tetrahedron Lett.*, 783 (1968).

Table V. $^{13}C$ Chemical Shifts[a]

| | 29a | 29b | 30 |
|---|---|---|---|
| C(8) | 122.4 | | 122.7 |
| C(9) | 123.3 | | 122.7 |
| C(10) | 120.8 | | 120.1 |
| C(11) | 157.6 | | 157.2 |
| C(12) | 93.8 | | 93.6 |
| C(13) | 152.2 | | 152.3 |
| OMe | 55.3 | | 55.2 |
| C(2′) | 130.9 | 138.5 | 130.4 |
| C(7′) | 116.9 | 108.0 | 116.3 |
| C(8′) | 129.1 | 127.4 | 128.6 |
| C(9′) | 118.4 | 116.8 | 117.7 |
| C(10′) | 121.7 | 120.5 | 121.7 |
| C(11′) | 118.4 | 118.4 | 118.4 |
| C(12′) | 110.0 | 110.8 | 109.8 |
| C(13′) | 134.6 | 135.2 | 134.2 |

[a] For description of the data see Table IV; **29b** in deuteriochloroform solution.

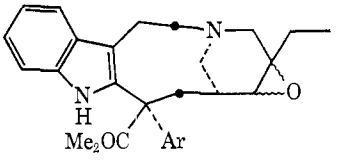


**29a**, R = $CO_2Me$, Ar = 10-vindolinyl
**b**, R = Ar = H

ajmalicinoid alkaloids[4] (Table V). Expectedly, the C(16′) substituents of the indole–indoline bases affect their C(2′) and C(7′) shifts.

The analysis of the nonaromatic carbons of the indolic halves of the indole–indoline alkaloids is exceedingly difficult especially because of the great complexity of the single-frequency off-resonance decoupled spectra. However, three sets of signals are easily decipherable, the VLB (**29a**) and leurosine ester carbonyls at 174.6 and 173.5 ppm, ester methoxyls at 51.9 and 51.6 ppm, and C-methyls at 6.7 and 8.1 ppm, respectively. Further, the all-important noise off-resonance decoupled spectra (*vide supra*)[6] yield the nonprotonated, saturated carbon shifts of 55.3 and 68.8 ppm for VLB (**29a**) and of 54.7 and 59.8 ppm for leurosine. The common $\delta$ value of 55 ppm can be assigned to C(16′), whose substitution pattern has been considered to be the same in the two bases,[27–29] leaving the other signal to be assigned to C(20′). The chemical shifts of C(18′) and C(20′) of velbanamine (**29b**) are 6.9 and 71.6 ppm, respectively, while those of the corresponding carbons of the simpler model 1-ethylcyclohexanol are 6.7 and 70.8 ppm, respectively.[30,31]

Leurosine is known to differ from vincaleukoblastine (**29a**) by its incorporation of an ether unit in place of a hydroxyl group.[29] The ether has been considered to be a 15′,20′-epoxide[32] especially on the basis of the highly complicated, difficulty interpretable, high resolution mass spectrum. The cmr data now shed further light on the ether moiety of leurosine. The high-field position of the nonvindolinic C-methyl group of the alkaloid shows it to suffer three $\gamma$ effects as C(18′) of **29a** and **29b** and supports the presence of a 20′-oxygenated ethylpiperidine unit by biogenetic analogy with the congener vincaleukoblastine (**29a**). The 1.4 ppm diminution of the $\gamma$ effects on C(18′) in leurosine is in agreement with the replacement of a 20′-hydroxy group by a C(20′) ether linkage. Furthermore, the striking dissimilarity of the C(20′) shifts of leurosine and vincaleukoblastine (**29a**), C(20′) of the former being 9 ppm to higher field, can be justified only by the oxygen of leurosine being incorporated in a small, strained ring.[22] Neither the chemistry nor the pmr spectrum of the alkaloid[29,32] favors an oxetane structure, while an epoxide unit is supported by the methyl and nonprotonated carbon shifts of the model 1-ethylcyclohexene oxide, 8.0 and 59.8 ppm, respectively. Hence, the structure of leurosine is depicted by formula **30**.[33]



30, Ar = 10-vindolyl

(30) The prime symbols applied to the carbons of **29b** are used only for the convenience of portraying the structural similarity of velbanamine and one-half of the indole–indoline alkaloids.

(31) The dissimilarity of the C(20′) shifts of VLB (**29a**) and velbanamine (**29b**) reflects probably a modification of the conformation of the nine-membered ring of **29b** by the C(16′) substituents of **29a**.

(32) D. J. Abraham and N. R. Farnsworth, *J. Pharm. Sci.*, **58**, 694 (1969).

(33) Chemical evidence of this structure will be presented elsewhere.