THE C(16') CONFIGURATION OF VINCALEUKOBLASTINE-LIKE NATURAL AND SYNTHETIC SUBSTANCES[1]

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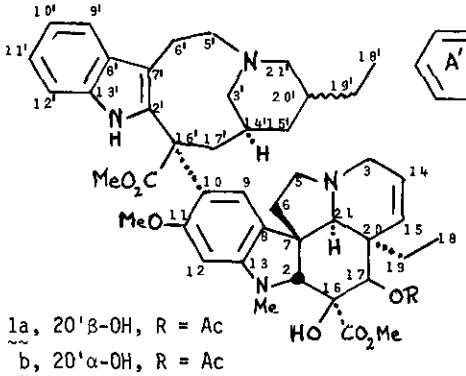
Dedicated to Professor Tetsuji Kametani on the occasion of his retirement from the Chair of Organic Chemistry at the Pharmaceutical Institute of Tohoku University.

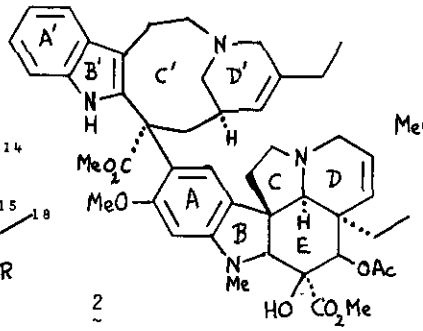
Comparison of the ^{13}C NMR spectra of a vincaleukoblastine derivative and a synthetic C(16') epimer system yields carbon shift parameters diagnostic of the stereochemistry of the site of attachment between the indole and indoline portions of vincaleukoblastine-like substances.

The medicinally important, structurally complex indole-indoline alkaloids vincaleukoblastine (VLB) (1a) and vincristine are members of a large group of natural bases of "dimeric" nature encompassing monomeric alkaloid units of the Aspidosperma and the 16',21'-seco-Iboga types bonded to each other by a C(10)-C(16') linkage.[2] The relative configuration of this bond is of great significance in the structure analysis of new alkaloids and of synthetic products of coupling of two monomeric moieties en route to the "dimeric" alkaloids or their relatives. The complete ^{13}C NMR analysis of vincaleukoblastine (1a), leurosidine (1b) and leurosine (1c)[3] in concert with the spectral data reported in this communication for 15',20'-anhydrodeacetylvincaleukoblastine (1d),[4] 15',20'-anhydro-16'-isovincaleukoblastine (2), vindoline (3a)[6] and deacetylvindoline (3b) reveal a simple, empirical, chemical shift-based diagnosis of the C(16') configuration.[7]

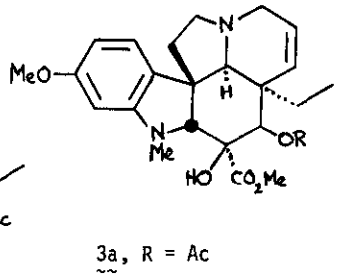
The chemical shift assignment of 1d, 2 and 3b (Table I) follows from the earlier work on 1a-c[3] and 3a.[6] The perturbation of the ring D' carbon shifts due to the introduction of the $\Delta^{15'-20'}$ linkage is in consonance with the δ values of alkyl-3-piperideine[3] and cleavamine[8] models.



1a, 20'β-OH, R = Ac
b, 20'α-OH, R = Ac
c, 15'α,20'α-oxido, R = Ac
d, $\Delta^{15'-20'}$, R = H



2



3a, R = Ac
b, R = H

Table I. Carbon Shifts of 15',20'-Anhydrodeacetyl-VLB, 15',20'-Anhydro-16'-iso-VLB, Vindoline and Deacetylvindoline[a]

	3b	1d	2	3a[b]		1d	2
C(2)	82.7	82.5	82.8	83.2	C(2')	130.7	134.3[c]
C(3)	50.7[c]	49.7	50.7	50.9	C(3')	45.9	46.9
C(5)	50.9[c]	50.2	50.7	51.9	C(5')	52.1[c]	53.4[d]
C(6)	44.1	44.5	43.6	43.9	C(6')	25.9	27.7
C(7)	52.7	53.0	52.6[e]	52.6	C(7')	117.1	111.1
C(8)	124.6	122.7	123.9	124.9	C(8')	129.1	128.2
C(9)	122.4	123.6	119.6	122.4	C(9')	118.1	117.8
C(10)	103.9	120.9	126.0	104.5	C(10')	122.0	121.1
C(11)	160.6	157.6	156.0	161.1	C(11')	118.6	118.1
C(12)	95.4	93.7	94.3	95.6	C(12')	110.2	110.2
C(13)	153.2	152.4	151.6	153.6	C(13')	134.6	134.6[c]
C(14)	123.3	123.9	124.3[f]	123.9	C(14')	32.9	34.4
C(15)	130.2	129.8	130.3	130.2	C(15')	123.6	124.2[f]
C(16)	80.4	80.5	79.7	79.5	C(16')	55.3	53.1[e]
C(17)	73.6	73.9	76.3	76.2	C(17')	34.2	38.6
C(18)	7.5	8.5	7.4	7.5	C(18')	12.2	12.5
C(19)	32.2	32.7	30.6	30.6	C(19')	27.6	27.5
C(20)	42.4	42.3	42.7	42.8	C(20')	139.8	140.9
C(21)	67.5	66.2	65.6	67.0	C(21')	54.2[c]	54.2[d]
C=O	172.8	172.8	170.5	170.4	C=O	174.4	175.0
OMe	52.0	52.1	52.0	51.9	OMe	52.1	52.0
Ar OMe	55.0	55.6	55.9	55.1			
NMe	38.3	38.4	38.3	38.0			
Ac C=O			171.3	171.7			
Ac Me			21.0	20.8			

[a] In parts per million downfield from TMS: δ(TMS) = δ($CDC\ell_3$) + 76.9 ppm. [b] From reference 6. [c,d,e,f] δ values with like superscripts may be reversed.

The ^{13}C NMR spectra of substances of VLB-like C(16') configuration (1a-d) show that the resonances of the azacyclononane ring carbons C(3'), C(5'), C(6') and C(17') display 3-6 ppm variations reflecting changes in the conformational disposition of the large ring induced by the piperidine ring substituents. In contrast the resonances of the indole and indoline moieties are insensitive to these changes.

Comparison of the C(16')-epimers 1d and 2 reveal dramatic shift differences for C(16') and its aromatic neighbors C(9), C(10), C(11), C(2') and C(7'). In view of the above observations these differences reflect the C(16') stereochemistry.[9,10] Thus the shift pattern shown in Table II may be a useful criterion for the determination of the stereochemistry of the quaternary, natural or synthetic coupling site.

Table II. Carbon Shift Differences

	1a[a]	1b[a]	1c[a]	1d[a]	2[a]	$\Delta\delta$[b]
C(9)	123.1	123.4	123.4	123.6	119.6	-3.7 ± 0.3
C(10)	120.4	120.4	120.4	120.9	126.0	5.3 ± 0.3
C(11)	157.8	157.6	157.6	157.6	156.0	-1.7 ± 0.1
C(2')	130.9	130.7	130.7	130.7	134.3[c]	3.5 ± 0.1
C(7')	115.9	116.7	116.7	117.1	111.1	-5.4 ± 0.6
C(16')	55.3	55.4	55.3	55.3	53.1[d]	-2.2 ± 0.1

[a] In parts per million downfield from TMS: $\delta(TMS) = \delta(CDCl_3) + 76.9$ ppm. [b] $\Delta\delta = \delta(2) - [\delta(1a) + \delta(1b) + \delta(1c) + \delta(1d)]/4$. [c] Alternatively this shift is 134.6 ppm. [d] Alternatively this shift is 52.6 ppm.

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9. In contrast to the ring A carbons the ring B' centers are minimally affected by ring C' conformational changes and hence show larger shift fluctuations.

10. The correct identification of the sole methine indicative of C(16') stereochemistry, i.e. C(9) [as well as the stereochemically insensitive C(12)] follows from its coupling characteristics. It is differentiated from olefinic methines and from ring A' methines by the magnitude of residual one-bond coupling and the absence of three-bond coupling in SFORD spectra, respectively.

11. The ^{13}C NMR spectra were recorded on a Varian XL-100-15 spectrometer operating at 25.2 MHz in the Fourier transform mode. Deuteriochloroform solutions of the substrates (0.05-0.50 M) were spun in 12 mm. o.d. tubes at 30° C. Chemical shifts reported on the TMS scale ($\delta^{TMS} = \delta^{CDCl_3} + 76.9$ ppm) possess digital resolution of ±0.6 Hz (5000 Hz spectral widths and 8 K data points in the real spectrum).

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