291. ^{13}C-NMR. Spectroscopy of Naturally Occuring Substances. XLII. Conformational Analysis of Quebrachamine-like Indole Alkaloids and Related Substances[1])

by **Ernest Wenkert, Edward W. Hagaman, Nicole Kunesch,** and **Nai-yi Wang**
Department of Chemistry, Rice Universtity, Houston, Texas 77001, U.S.A.

and **Béla Zsadon**
Department of Chemical Technology, Eötvös Loránd University, Muzeum krt. 6–8, 1088 Budapest, Hungary

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Summary. The ^{13}C shifts of 16α- and 16β-substituted derivatives of quebrachamine, 14,15-dehydroquebrachamine, cleavamine, 15,20α-dihydrocleavamine and 15,20β-dihydrocleavamine are determined and correlated with possible conformations of these tetracycles. The method of analysis of the C(16) configuration of these compounds, which emanated from this study, is used for the determination of the configuration of the site of coupling of vindoline and cleavamine β-chloroindolenine.

Introduction. – Ever since the structure determination of quebrachamine (**1a**) [2] and the medicinally important indole-indoline alkaloids vincaleukoblastine and vincristine [3] it has become clear that nature produces the unusual indoloazacyclononane system, biogenetically related to the *Aspidosperma* & *Iboga* bases [4]. No systematic study of the spatial configuration of the medium-sized heterocycle has been reported, although the ring conformation in vincaminorine and vincaminoreine [5] as well as in carbomethoxydihydrocleavamines derived from catharanthine [6] has been determined by the ^{1}H-NMR. analysis of a key, centrally located hydrogen atom and X-ray analyses of salts have shown the ring orientation in cleavamine (**3a**) [7], vincristine [3] and related, synthetic 'dimers' [8] in the solid state. Since the solution conformation of the medium-sized cycle and of the piperidine ring fused to it can be expected to exert much influence on the chemistry and biology of the natural and synthetic indole bases incorporating these rings, it was felt highly desirable to undertake a ^{13}C-NMR. study of a select group of such substances in view of the high sensitivity of this spectral method of analysis to configuration and in order to evaluate the factors inducing conformational change. The compounds chosen for the study consisted of five quebrachamine-like alkaloids—(+)-quebrachamine (**1a**), 16α-carbomethoxy-(+)-quebrachamine (≡(+)-epivincadine [9]) (**1b**), 16β-carbomethoxy-(+)-quebrachamine (≡(+)-vincadine [9]) (**1c**), 16α-carbomethoxy-14,15-dehydro-(+)-quebrachamine (≡(+)-6,7-dehydroepivincadine [9]) (**2a**) and 16β-carbomethoxy-14,15-dehydro-(+)-quebrachamine (≡(+)-6,7-dehydrovincadine [9]) (**2b**)—16β-hydroxymethyl-(+)-quebrachamine (**1d**), six cleavamine-like compounds—cleavamine (**3a**) [6], 16α-carbomethoxycleavamine (≡18β-carbomethoxycleavamine [6])

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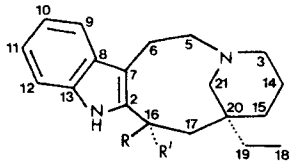
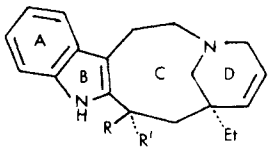
[1]) For part XLI see [1].

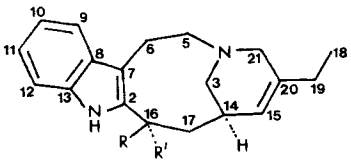
(**3b**), 16β-hydroxymethylcleavamine (**3c**), 16α-methoxycleavamine (**3d**), 16β-carbomethoxycleavamine (≡18α-carbomethoxycleavamine [6]) (**3e**), 16β-methoxycleavamine (**3f**)—and eight dihydrocleavamine-like substances—15,20α-dihydrocleavamine (≡4β-dihydrocleavamine [6]) (**4a**), 16β-hydroxymethyl-15,20α-dihydrocleavamine (**4b**), 16α-carbomethoxy-15,20α-dihydrocleavamine (≡18β-carbomethoxy-4β-dihydrocleavamine [6]), (**4c**), 15,20β-dihydrocleavamine (≡4α-dihydrocleavamine [6]) (**4d**), 16α-carbomethoxy-15,20β-dihydrocleavamine (≡18β-carbomethoxy-4α-dihydrocleavamine [6]) (**4e**), 16β-carbomethoxy-15,20β-dihydrocleavamine (≡18α-carbomethoxy-4α-dihydrocleavamine [6]) (**4f**), velbanamine (**4g**) [10], *enantio*-16β-carbomethoxyvelbanamine (*enantio*-**4h**) [11][2]).



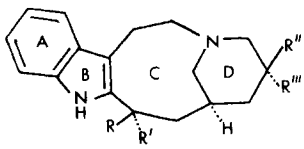
1a, R = R′ = H
b, R = H, R′ = CO_2Me
c, R = CO_2Me, R′ = H
d, R = CH_2OH, R′ = H



2a, R = H, R′ = CO_2Me
b, R = CO_2Me, R′ = H



3a, R = R′ = H
b, R = H, R′ = CO_2Me
c, R = CH_2OH, R′ = H
d, R = H, R′ = OMe
e, R = CO_2Me, R′ = H
f, R = OMe, R′ = H
g, R = H, R′ = CH_2OH



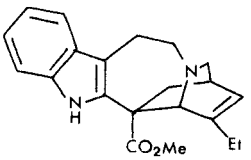
4a, R = R′ = R‴ = H, R″ = Et
b, R = CH_2OH, R′ = R‴ = H, R″ = Et
c, R = R‴ = H, R′ = CO_2Me, R″ = Et
d, R = R′ = R″ = H, R‴ = Et
e, R = R″ = H, R′ = CO_2Me, R‴ = Et
f, R = CO_2Me, R′ = R″ = H, R‴ = Et
g, R = R′ = H, R″ = OH, R‴ = Et
h, R = CO_2Me, R′ = H, R″ = OH, R‴ = Et

While the quebrachamine-like substances **1** and **2** were on hand, the cleavamine-like substances **3** and **4a–f** had to be prepared from catharanthine (**5**). Reduction of the latter by sodium borohydride in acetic acid has been reported to yield 16α-carbomethoxycleavamine (**3b**) [6], but repetition of this reaction has shown it to be more complex. Both borohydride and cyanoborohydride reductions yielded **3b** accompanied by 16β-carbomethoxycleavamine (**3e**), its 15,20β-dihydro derivative (**4f**) and pseudocatharanthine[3]). Reduction by formic acid in formamide [13] produced **3b**

[2] For sake of clarity of the present and future presentations all compounds are named to represent their absolute configuration and their carbon atoms designated by the biogenetic numbering system. The heretofore used empirical names are placed in parenthesis.

[3] The conversion of catharanthine into pseudocatharanthine in hot acetic acid has been noted before [12].

and **4f**. Lithium aluminum hydride reduction of the two epimeric esters led to the carbinols **3c** and **3g**. Cleavamine (**3a**) was prepared by the reported procedure of hydrolysis and decarboxylation of 16α-carbomethoxycleavamine (**3b**) [6]. Methanolysis of the β-chloroindolenine **6**, derived from treatment of cleavamine (**3a**) with *t*-butyl hypochlorite [14], yielded two methyl ethers, **3d** and **3f**, in analogy with previous experience in the 15,20α-dihydrocleavamine (**4a**) series [14].



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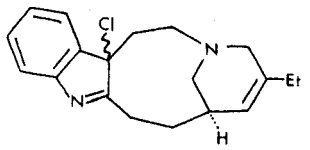

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The dihydrocleavamines (**4a** and **4d**) and their 16α-carbomethoxy derivatives (**4c** and **4e**, respectively) were prepared by reported procedures [6] [15]. Velbanamine (**4g**) came from the degradation of vincaleukoblastine [10] [12][4]), while *enantio*-16β-carbomethoxyvelbanamine (**4h**) was the product of reduction of pandoline [11]. 16β-Hydroxymethyl-15,20α-dihydrocleavamine (**4b**) was prepared by the platinum-catalysed hydrogenation of the alcohol **3c**.

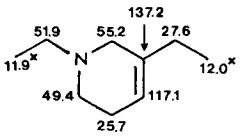
Shift assignment. – On the assumption of the C(16) substituent being a major factor in the conformational behavior of the nine-membered ring of the quebrachamoid and cleavamoid compounds the ^{13}C-NMR. spectra of substances of like C(16) configuration were correlated for the initial analysis. 16β-Carbomethoxycleavamine (**3e**), the quebrachamine equivalent **2b**, the 15,20β-dihydrocleavamine ester **4f** and vincadine (**1c**) were chosen as representative of the 16β-substituted series of compounds. The signals of the carbomethoxy and methyl groups of the four esters and those of the olefinic carbons of **3e** are recognized by their characteristic field positions and SFORD. (single-frequency off-resonance decoupled) multiplicities. As in the olefinic carbon shift analysis of tabersonine, an *Aspidosperma* alkaloid relative of **2b** [16], the allyl substituents next to C(15) cause a net deshielding of the latter with respect to its olefinic neighbor. Finally, the quebrachamoid alkaloids **2b** and **1c** contain only one non-aromatic methine and quaternary center each.

The non-aromatic methines of **3e** can be differentiated by the difference of their residual, one-bond coupling constants in SFORD. spectra in view of the strong shift dissimilarity of the methine protons [17] [18]. The same argument identifies C(16) of **4f**, while the C(14) and C(20) shifts of this substance are coincidentally nearly identical. The three aminomethylene signals of the four esters are expectedly downfield of those of the remaining methylenes. The aminomethylenes within the six-membered heterocycle display characteristic shift modifications as a function of the substitution site of the ethyl group. Thus the one-carbon bridge of the azabicyclo [6.3.1]dodecanes is shielded by 6.1 ppm in **4f** with respect to **1c**, while the amino-

[4]) The authors are indebted to Dr. *N. Neuss* for a sample of **4g**.

methylene of the three-carbon bridge is deshielded by 6.3 ppm in **4f** *vs.* **1c**. C(5) is insensitive to the location of the ethyl group.

C(6) differs from the other C,C-methylenes[5]) by being allylic and thus possessing characteristic, residual, one-bond coupling properties. This feature is so distinctive as to allow easy recognition of C(6) not only in the four substances under present consideration but also in other 16-substituted substances of structures **1**, **2**, **3** and **4**. The methylene of the ethyl group of olefinic ester **3e** is identified by comparison with the previously reported model piperidine **7** [19], thus obtaining the C(17) shift by default. Similarly, the ethyl methylene of **4f** is based on model **8**, while the C(15) and C(17) shifts are virtually the same. The C(19) shift of **2b** and the C(14), C(15) and C(19) shifts of **1c** may be allocated directly from the shifts of the same carbon atoms in tabersonine and vincadifformine, respectively (*vide infra*) [16], completing the shift assignment of all non-aromatic carbon atoms of the four esters.



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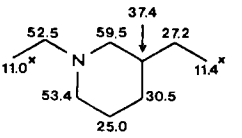

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The shift designation for 15,20β-dihydrocleavamine (**4d**) and quebrachamine (**1a**) rests on that for esters **4f** and **1c**, respectively, and the known perturbations accompanying the removal of the carbomethoxy group. Thus, for example, in quebrachamine only C(16) and C(17) are affected by the loss of the ester unit, thereby substantiating the previous methylene shift allocations for **1c**. The replacement of the carbomethoxy group of **1c** by a hydroxymethyl group (**1c** → **1d**) again causes only insignificant shift changes at all centers except C(16) and C(17). This behavior is observed also for compounds **3c** and **3f** with respect to **3e**. The introduction of a 20β-hydroxy group into **4d** and **4f**, *i.e.* **4d** → **4g** and **4f** → **4h**, respectively, leads to shift alteration in the vicinity of the oxycarbon atom in consonance with the $\Delta\delta$ values for models **8** and 1,3-diethyl-3-piperidinol [19]. The 16β-substituted derivatives of structure types **1**, **2**, **3** and **4** discussed thus far, **1c**, **1d**, **2b**, **3c**, **3e**, **3f**, **4f** and **4h**, as well as three 16-unsubstituted compounds, **1a**, **4d** and **4g**, have as common characteristic a C(6) shift of 22.0 $\pm$ 0.7 ppm[6]). All δ values of these substances are listed in Table 1.

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[5]) For ease of description and differentiation of carbon substituents in ^{13}C-NMR. analysis and in analogy with common, organochemical usage of the terms C-, N- and O-methyl for the portrayal of methyl groups bonded to carbon, nitrogen and oxygen atoms, respectively, it is proposed to identify methylene and methine groups in similar fashion. Thus the elements other than hydrogen attached to these groups are designated by individual capital letters alphabetically arrayed preceding the name; *e.g.*: C,O-methylene or C,C,N-methine refer to a methylene flanked by a carbon and a oxygen atom and a methine bonded to a nitrogen and two carbon atoms, respectively.

[6]) The C(6) shift of 15,20β-dihydrocleavamine (**4d**) lies slightly outside this range, a fact to be discussed forthwith (*vide infra*).

Table 1. *^{13}C-Shifts of 16β-Substituted and Related Unsubstituted Quebrachamines and Cleavamines*[a])

	1a	**1c**	**1d**	**2b**	**3c**	**3e**	**3f**	**4d**	**4g**	**4h**	**4f**	**4b**[b])
C(2)	139.7	135.2[c])	141.2	135.1[c])	138.1	138.4	[e])	139.4	138.5	[e])	135.0	139.0
C(3)	54.9	55.0	55.1	54.4	47.6	47.0	47.3	51.7	50.6	50.9	50.6	48.4
C(5)	53.2	52.7	53.0	51.5	51.7	51.2	51.3	53.2	52.3	52.0	52.5	52.8
C(6)	21.7	21.8	22.0	21.3	22.2	21.7	21.7	24.1[c])	22.7	22.4	22.1	21.5
C(7)	108.3	109.4	109.1	109.1	109.1	109.5	109.0	108.7	108.0	109.2	109.5	108.2
C(8)	128.6	127.7	127.8	127.6	128.1	127.9	128.4	128.8	127.4	127.7	127.8	127.6
C(9)	117.1	117.4	117.2	117.3	117.3	117.5	117.5	117.3	116.8	117.5	117.4	116.7
C(10)	118.4	118.5	118.4	118.5	118.5	118.6	118.5	118.5	118.4	119.0	118.6	117.5
C(11)	119.9	120.6	120.1	120.6	120.4	120.9	120.8	120.1	120.4	121.4	120.7	119.3
C(12)	109.9	110.5	110.3	110.4	110.3	110.6	110.4	109.8	110.8	111.1	110.5	110.2
C(13)	134.5	134.9[c])	134.8	134.7[c])	134.8	135.0	[e])	134.7	135.2	134.0	135.0	135.2
C(14)	22.6	22.3	22.5	124.6	34.0	34.1	33.4	33.8	30.1	30.5	32.8[c])	35.3[c])
C(15)	33.4	33.9	34.1	135.4	124.7	124.0	124.4	37.6	40.4	39.5	36.7[d])	36.0
C(16)	22.4	37.8	33.7	38.1	36.6[c])	39.3	75.8	23.3[c])	22.7	39.3	39.0	38.5
C(17)	34.7	38.6	35.8	44.1	36.2[c])	39.1	41.8	31.9	31.5	36.1	36.3[d])	34.1
C(18)	7.8	7.4	7.6	8.3	12.3	12.3	12.3	11.4	6.9	6.9	11.3	12.2
C(19)	32.0	30.6	31.0	29.3	27.3	27.3	27.3	27.5	32.3	32.6	27.3	28.0
C(20)	36.9	37.9	37.6	40.9	[e])	138.4	138.2	32.9	71.6	71.2	33.1[c])	32.6[c])
C(21)	56.6	56.7	56.8	51.5	57.1	57.5	57.5	61.2	65.8	66.1	61.3	56.3
C=O		176.2		175.6		175.8				175.2	176.1	
OMe		52.0		52.0		52.2	57.4			52.2	52.1	
OCH_2			67.4		66.6							65.2

[a]) The δ values are in ppm downfield from TMS: δ(TMS) = δ($CDCl_3$) + 76.9 ppm.
[b]) In DMSO-d_6; δ(TMS) = δ(DMSO-d_6) + 39.5 ppm.
[c])[d]) Signals in any vertical column may be interchanged.
[e]) Non-protonated-carbon-atom signal undetected because of small sample size.

All arguments used heretofore in connection with the distribution of δ values to the 16β-substituted compounds could be applied to the shift assignment of the 16α derivatives **1b**, **2a**, **3b**, **3d** and **4e** as well as cleavamine (**3a**), leading to the shifts presented in Table 2. The C(16) substitution of the latter by either carbomethoxy or methoxy groups, *i.e.* **3a** → **3b** or **3a** → **3d**, respectively, perturb the C(16) and C(17) shifts, while leaving all other non-aromatic carbon shifts unaffected. The C(17) shift designation for epivincadine (**1b**), and hence for its dehydro derivative **2a**, was confirmed by correlation of the C(17) and H(17) shifts [18] [20]. As in the case of the 16β-substituted substances the 16α compounds are characterized by a constant C(6) signal, which, however, appears at lower field (26.2 ± 0.3 ppm).

Three dihydrocleavamines, **4a**, **4b** and **4c**, are the sole representatives of the 20β-ethyl configuration. Whereas their C(6) shifts identify **4b** and both **4a** and **4c** as compounds belonging to the 16β and 16α series, respectively, their piperidine carbon atoms reveal δ values which cannot be accommodated by calculation on the basis of the presence of a piperidine chair and an axial ethyl group, preventing an unambiguous assignment of the piperidine methines.

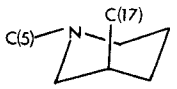
The indole ^{13}C shifts are based on those reported by *Parker & Roberts* [21] as corrected by *Gribble et al.* [22]. Thus all ring A unsubstituted indole alkaloids reported previously require C(10) and C(11) shift inversions [23].

Table 2. *^{13}C-Shifts of 16α-Substituted and Related Unsubstituted Quebrachamines and Cleavamines*[a])

	1b	2a	3a	3b	3d	4e	4c	4a
C(2)	133.7	134.4	139.2	134.2	[d])	133.7	133.8	138.4
C(3)	53.8[b])	52.0	53.5[b])	52.8[b])	53.1[b])	55.8	51.2[b])	51.4[b])
C(5)	54.0[b])	53.7	53.8[b])	53.2[b])	53.9[b])	54.1	51.8[b])	52.2[b])
C(6)	26.2	26.0	26.1	26.0	26.1	26.5	26.4	26.0
C(7)	111.5	111.5	109.5	110.9	112.2	111.4	111.8	109.6
C(8)	127.6	127.8	128.5	127.5	[d])	127.6	127.6	128.3
C(9)	117.9	118.0	117.6	117.7	118.1	118.0	118.1	117.6
C(10)	118.7	118.7	118.5	118.5	118.6	118.7	118.8	118.6
C(11)	121.4	121.3	120.3	121.0	121.4	121.2	121.4	120.5
C(12)	110.6	110.5	109.8	110.3	110.4	110.5	110.5	109.8
C(13)	135.7	135.7	135.2	135.5	[d])	135.6	135.7	[d])
C(14)	23.6	127.0	35.3	34.3	34.4	31.1	34.8[c])	35.0[c])
C(15)	37.3	132.9	122.3	121.5	122.0	39.0[b])	31.0	31.2
C(16)	40.9	39.1	22.4	38.3	72.8	42.0	37.5	21.3
C(17)	42.8	43.4	34.1	37.5	41.5	40.3[b])	38.5	33.7
C(18)	7.3	7.7	12.6	12.3	12.6	11.4	11.7	11.7
C(19)	35.6	33.1	27.6	27.4	27.5	27.7	28.6	28.7
C(20)	35.6	39.5	140.4	140.8	141.9	36.1	32.1[c])	32.8[c])
C(21)	60.8	58.6	55.1	54.9	54.9	60.6	58.9	58.7
C=O	175.6	175.6		175.3		175.4	175.3	
OMe	51.9	51.8		51.8	55.7	52.0	52.0	

[a]) The δ values are in ppm downfield from TMS: δ(TMS) = $\delta(CDCl_3)$ +76.9 ppm.
[b])[c]) Signals in any vertical column may be interchanged.
[d]) Non-protonated carbon atom signal undetected because of small sample size.

Conformational analysis. – As the above chemical shift discussion illustrates, all compounds **1**, **2**, **3** and **4** fit into two azacyclononane ^{13}C shift patterns, largely dictated by the C(16) substituent orientation, which must have a conformational basis. While, in principle, there are four different, conformational modes of attachment of the nine-membered ring to the piperidine moiety, the form keeping both C(5) and C(17) equatorially disposed to the six-membered cycle is precluded because of severe strain. Furthermore, the C(5) and C(17) diaxially oriented piperidine arrangement is energetically unfavorable, thus suggesting structures **9** and **10** as the most probable conformers[7]).



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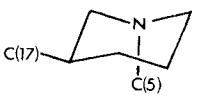

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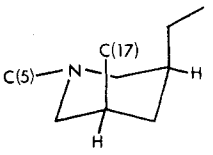
A choice between **9** and **10** can be made by inspection of the piperidine aminomethylene groups in the SFORD. spectra. In general, one-bond carbon/hydrogen multiplets of N-alkylpiperidines appear as approximate triplets of 1:2:1 line inten-

[7]) The structure of vincristine methiodide [3], a N_b-quaternized, C(16) disubstituted velbanamine (**4g**) in which C(5) and C(17) are held diaxially toward the piperidine unit, reveals that the unfavorable conformation plays an important role at least in the transition state of the N_b-methylation.

sity, in the case of the geminal hydrogen atoms exhibiting a shift difference of *ca.* 0.5 ppm or less, or as doublets of doublets for greater $\Delta\delta$ values [24]. The latter multiplet shape reflects the presence of axial aminomethylene hydrogen atoms *trans*-diaxially disposed to the nitrogen electron pair, a structural relationship resulting in strong shielding of the hydrogen [18] [25]. All substances in Table 1 except **4b** reveal four-line multiples for the aminomethylene which constitutes the one-carbon bridge of the azabicyclo[6.3.1]dodecane ring system, thereby revealing themselves as conformers **9**, while only one compound, **4e**, in Table 2 exhibits the same multiplet, albeit for the aminomethylene of the three-carbon bridge. This coupling behavior is sufficient to assign conformer **9** to **4e**. The same choice of conformation can be made for **1b**, **2a**, **3a**, **3b** and **3d** on the basis of their strongly deshielded H–C(16) NMR. signal. The low-field position of the latter, contrasted with the H–C(16) shift of the C(16)-epimers [5] [6] can be interpreted only in terms of a molecular geometry encompassing an axial N_b electron pair.

The low-field position of H(16) of **4a** and **4c** [6], two 15,20-dihydrocleavamines, show these substances to feel the same anisotropic deshielding of H–C(16) by N_b, possible only in a conformation related, but not equal to **9** in which the N_b lone pair is axial with respect to the piperidine ring. This fact and the observation of the invariance of the C(5) and C(6) shifts of **4a** and **4c** when compared with compounds of and related to the 16α-substitution series (see Table 2) indicate the nine-membered ring conformation of the two substances to be unchanged. Similary, the C(5) and C(6) shifts of **4b**, a 15,20α-dihydrocleavamine of the 16β-substitution series, being the same as other members of the 16β series reveals **4b** also to have a N_b lone pair axial to the piperidine ring. Since calculations of the piperidine carbon shifts of compounds **4a**, **4b** and **4c**, based on a piperidine chair conformation, do not account for the excess shielding of the ring carbons, especially C(3), conformation **11** is precluded. It appears that the piperidine ring of the three substances must be distorted in the direction of some boat conformation, a point in accord with the prediction of need for conformational adjustment of structure **11** in view of the strong non-bonded interaction of C(17) and C(19) therein[8]).



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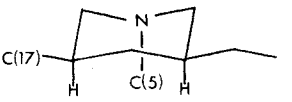
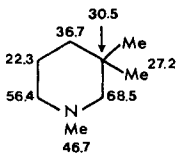


12

Interpretation of the C(6) and C(21) shifts of the C(16)-epimer pair **1b** and **1c** as well as of the C(6) and C(3) shifts of the pair of C(16)-epimers **4e** and **4f** in the light of shift data for 1,3,3-trimethylpiperidine (**13**) and *trans*-1,3,5-trimethylpiperidine (**14**), respectively, permits the determination of the conformation of the nine-mem-

8) Whereas the piperidine ring can remain a chair and the ethyl group assume an equatorial stance in conformation **12**, this is unrealistic in view of the unchanged, low-field position of H—C(16) for **4a** and **4c**.

bered ring in these compounds. C(21) of **1b** is *ca.* 8 ppm upfield of the comparable center of 1,3,3-trimethylpiperidine (**13**), shielding attributable to the acyclic γ-effect of the methyl component of the ethyl group and a γ-effect from a site on the azacyclononane system. The last effect can be due only to C(6) or C(16) of which the latter is excluded in view of the known disposition of H(16) toward N_b. This limits epivincadine (**1b**) to conformation **15a**. This spatial representation is impossible for the C(16)-epimer vincadine (**1c**) in view of the much larger steric requirement of a carbomethoxy group over a hydrogen. Indeed, the conformation is changed in **1c** as shown by a *ca.* 4 ppm extra shielding of C(21) in this compound. This can be interpreted most readily by the addition of a γ-effect from C(16) while the C(6)–C(21) relationship is maintained. Furthermore, the new structural arrangement causes shielding of C(6) and C(16) by *ca.* 4 and 3 ppm, respectively, in view of their mutual interaction. These facts limit **1c** to conformation **16a**. The difference of the latter from conformation **15a** lies in a ring inversion around C(16) comparable to the half inversion of a cyclohexane chair. The shift behavior of C(3), C(6) and C(16) of the dihydrocleavamines parallels that of the vincadines yielding conformations **15b** and **16b** to **4e** and **4f**, respectively.



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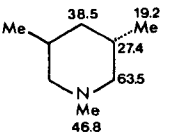

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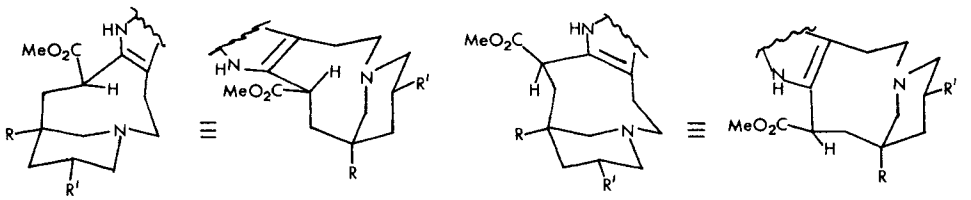
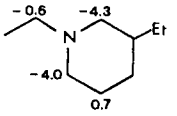


15a, R = Et, R′ = H
b, R = H, R′ = Et

16a, R = Et, R′ = H
b, R = H, R′ = Et

The azacyclononane conformations depicted in formulas **15** and **16** apply also to the piperidine-containing substances **2** and **3** and the 15,20α-dihydrocleavamines **4a**, **4b** and **4c**. Not only do the C(6) and C(16) shifts of compounds **4** remain unaffected by the introduction of a double bond into the piperidine nucleus, but also the conformational weathervane, the C(3) shift, as well as the C(5), C(14) and C(21) shifts of the cleavamines (**3**) show the conformational invariancy as illustrated by the similarity of the $\Delta\delta$ values between models **7** and **8** (see **17**) and, for example, between **3e** and **4f** (see **18**). A similar pattern emerges from a comparison of the vincadines **1b** and **1c** with their dehydro counterparts **2a** and **3a**, although complicated by the difference of rotamer population preference of the ethyl sidechain in **1** and **2**. The H–C(16) resonances [6] of **4e**, **3b** and **4c**—5.47, 5.11 and 5.02 ppm, respectively—

show the conformation **15b** of **4e** to be maintained, albeit with minor alteration, on introduction of a piperidine double bond or inversion of C(20) stereochemistry.



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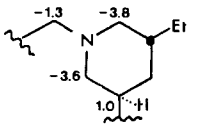

18

In the presence of a C(16)-substituent all compounds **1**, **2**, **3** and **4** adjust their nine-membered ring conformation in a fashion to orient the substituent equatorially. In the absence of a C(16) sidechain the conformation depends on piperidine substitution. Thus cleavamine (**3a**) and its 15,20α-dihydro derivative (**4a**) adopt the conformation of the 16α-substitution series (**15**), quebrachamine (**1a**) and velbanamine (**4g**) that of the 16β-substitution series and 15,20β-dihydrocleavamine (**4d**) that of a variant of the latter series. The conformation of **3a** and **4a** rests on the C(16) hydrogen shifts which reveal the presence of the N_b-induced, anisotropic deshielding of H_β–C(16) observed for all **15**-like substances. The C(16) doublet of doublets in the SFORD. spectra of **3a** yields calculated H_α– and H_β–C(16) shifts of 2.65 and 3.60 ppm [18], respectively, in accord with experimental values of 2.63 and 3.58 ppm, respectively, determined by decoupling of the otherwise unrecognizable upfield proton signal by irradiation of the downfield signal in the ^{1}H-NMR. spectrum. A similar calculation of the H–C(16) shifts of **1a** from its C(16) SFORD. triplet gave a δ value of 2.68 ppm, similar to the H_α–C(16) shift of **3a** and hence characteristic of unperturbed C(16) hydrogen atoms[9]). Whereas, finally, **4d** reveals a C(16) triplet in its SFORD. spectra, thus typing it as a material belonging to the 16β-substitution series (conformation **16**), its anomalous C(3), C(5) and C(6) shifts indicate the presence of some conformer **15**.

The coupling characteristics of H–C(16) of **1b** and **4e** (J = 12, 3 Hz) [29] fit conformations **15a** and **15b**, respectively. Similarly, the H–C(16) J values for **1c** and **4f** (6 resp. 2 Hz) [26] are in agreement with conformers **16a** and **16b**, respectively. Just as the H–C(16) shift can be used for identification of the 16α-substitution series, *i.e.* conformers **15**, the C(21) or C(3) multiplicity can be utilized for recognition of the 16β-substituted derivatives of **1** and **2** or **3** and **4**, respectively, *i.e.* conformers **16**. Without exception the compounds of the 16β series display strong non-equivalence of the hydrogen atoms of the aminomethylene common to both the azacyclonane and piperidine rings by the exhibition of a doublet of doublets in their SFORD. spectra. Conversely, the signal of this aminomethylene appears as a triplet in the SFORD. spectra of substances of the 16α series[10]).

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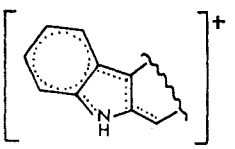
[9]) Since the C(16) triplet, arising from one-bond, carbon-hydrogen coupling, is the consequence of equivalence or mild non-equivalence (*vide supra*) of the C(16) hydrogen atoms, the value of 2.68 ppm represents the average shift for these hydrogen atoms.

[10]) Care must be exercised in the initial identification of the proper aminomethylene in view of the possibility of a doublet of doublets being associated with one of the two remaining aminomethylenes. Thus, for example, C(21) of compound **4e** exhibits such a multiplet.

16'β-(10-Vindolyl-)cleavamine. The medicinal importance of the indole-indoline alkaloids vincristine and vincaleukoblastine, formally a product of the combination of vindoline and carbomethoxyvelbanamine (*e.g.* **4h**), has focused attention on the products of coupling of vindoline with cleavamine and dihydrocleavamine derivatives [1] [8] [27–31]. Whereas the products of synthesis have the vindoline unit attached to C(16) of a cleavamine (**3**) or dihydrocleavamine (**4**) system, the majority are C(16) disubstituted. A few of the 16-monosubstituted 'dimers' had their structures determined by X-ray analysis [8] or by circular dichroism study [30]. In light of the above ^{13}C-NMR. investigation of 16-substituted derivatives of **3** and **4** it was of interest to ascertain whether this method of analysis could be applied successfully to the determination of the C(16) configuration of such 'dimers'. For this reason the product of coupling of vindoline and cleavamine (**3a**) was synthesized. Condensation of vindoline with the indolenine **6** in methanolic hydrogen chloride [29] yielded a coupling product. Since this reaction is a solvolysis, presumably proceeding by way of the cation **19**, the same condensation could be expected to take place on starting with the methyl ethers **3d** or **3f** [29] [32], especially in view of their being side-



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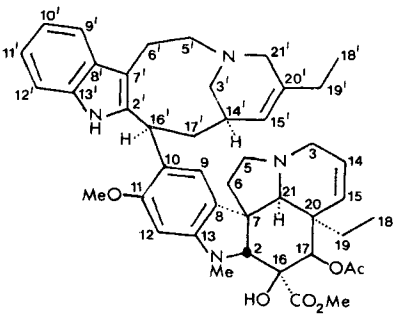

20

Table 3. *^{13}C-Shifts of 16'β(10-Vindolyl-)cleavamine*[a])

20		**20**		**20**		**20**	
C(2)	83.2	C(14)	124.0	C(2')	138.3	C(14')	35.4
C(3)	50.9	C(15)	130.2	C(3')	47.2	C(15')	124.9
C(5)	52.0	C(16)	79.5	C(5')	51.4	C(16')	34.7
C(6)	43.9	C(17)	76.2	C(6')	23.1	C(17')	39.3
C(7)	53.0	C(18)	7.4	C(7')	108.6	C(18')	12.3
C(8)	122.4	C(19)	30.7	C(8')	128.9	C(19')	27.4
C(9)	120.2	C(20)	42.8	C(9')	117.2	C(20')	140.4
C(10)	124.6	C(21)	66.5	C(10')	118.3	C(21')	56.2
C(11)	157.4	C=O	170.4	C(11')	121.6		
C(12)	93.9	OMe	51.9	C(12')	109.9		
C(13)	151.7	Ar OMe	55.7	C(13')	134.5		
		NMe	38.5				
		Ac C=O	171.5				
		Ac Me	20.9				

[a]) The δ values are in ppm downfield from TMS: δ(TMS) = δ($CDCl_3$) +76.9 ppm.

products of the condensation with vindoline in cases of incomplete reaction. When vindoline was treated with a mixture of **3d** and **3f** in methanolic hydrogen chloride, the same coupling product was obtained.

As Table 3 indicates, several ^{13}C-NMR. criteria reveal the vindolylcleavamine to possess structure **20**. Thus the C(3′) and C(6′) shifts show the compound to be 16′β-substituted, an argument substantiated by the general correspondence of the shifts of C(5′) and the ethylpiperidine unit with those of 16β-carbomethoxycleavamine (**3e**). The C(3′) hydrogen atoms are non-equivalent and H–C(16) is benzhydrylic without being deshielded by N_b.

The financial support of this work by the U.S. *Public Health Service* is acknowledged gratefully. *N.K.* is indebted to the *C.N.R.S.* (France) and *N.S.F.* (U.S.A.) for a fellowship during 1975–1976 under their scientific exchange program.

Experimental Part

Melting points were determined on a *Reichert* microhotstage and are uncorrected. IR. and UV. spectra were recorded on *Perkin-Elmer* 167 and *Cary* 17 spectrophotometers, respectively. Mass spectra were obtained on a *CEC* 21-110 spectrometer, while ^{1}H-NMR. spectra were run on deuteriochloroform solutions with TMS as internal standard (δ = 0 ppm) and registered on a *Varian* A-60 spectrometer. The ^{13}C-NMR. spectra were recorded on a *Varian* XL-100-15 spectrometer operating at a ^{13}C RF-frequency of 25.20 MHz in the *Fourier* transform mode. Deuteriochloroform solutions of the substrates (0.04–0.5 M) yielded spectra possessing digital resolution of $\pm$ 0.6 Hz (5000 Hz spectral widths and 8 K data points in the real spectrum). Chemical shifts, referenced to TMS *via* the deuteriochloroform solvent signal, δ(TMS) = δ($CDCl_3$) +76.9 ppm, are reproducible within $\pm$ 0.05 ppm.

Reduction of Catharanthine (**5**). The sodium borohydride reduction of 3.30 g of **5** hydrochloride reported by *Kutney et al.* [6] was followed exactly. The product mixture was chromatographed on 100 g of silica gel. Elution with CH_2Cl_2 yielded 1.05 g of 16α-carbomethoxycleavamine (**3b**), m.p. 121–123° [6], elution with CH_2Cl_2/MeOH 100:1 gave 370 mg of a mixture and elution with CH_2Cl_2/MeOH 50:1 led to the recovery of 574 mg of catharanthine (**5**). Rechromatography of the central fractions on 18 g of silica gel and elution with CH_2Cl_2 yielded 190 mg of 16β-carbomethoxycleavamine (**3e**) as a gum. IR. ($CHCl_3$): 3470 (NH), 1722 cm^{-1} (C=O). ^{1}H-NMR.: 0.85 (*t*, J = 7 Hz, 3, Me), 3.67 (*s*, 3, OMe); 3.94 (*d*, J = 5 Hz, 1, H–C(16)); 5.38 (br. *s*, 1, H–C(15)); 6.8–7.5 (*m*, 4, aromatic Hs). – Accurate mass for $C_{21}H_{26}O_2N_2$: Calc. 338.1994; Found 338.1995. – Elution with CH_2Cl_2/MeOH 500:1 gave 33 mg of 16β-carbomethoxy-15,20β-dihydrocleavamine (**4f**), m.p. 167–169° [6], and 30 mg of amorphous pseudocatharanthine [12] (IR., ^{1}H-NMR. and MS. identical with reported spectra); accurate mass for $C_{21}H_{24}O_2N_2$: Calc. 336.1836; Found 336.1848.

A solution of 278 mg of sodium cyanoborohydride in 3 ml of methanol was added slowly to a solution of 1.10 g of **5** hydrochloride in 10 ml of glacial acetic acid at 90°. After 1 h the reaction was worked up as in the borohydride reduction [6]. Chromatography of the oily residue, 1.1 g, on 60 g of silica gel and elution with CH_2Cl_2 yielded 500 mg of **3b**. Further elution revealed the presence of trace amounts of starting **5** and other products.

A solution of 124 mg of **5** in 5 ml of 90% HCO_2H/$HCONH_2$ 1:1 was stirred at 100° for 5 h. It was diluted with 10 ml of H_2O, neutralized with NH_3 and extracted with CH_2Cl_2. The extract was dried over Na_2CO_3 and the solvent evaporated. The residue, 130 mg consisting of starting **5** and two other products, was separated by preparative TLC. (silica gel, CH_2Cl_2/MeOH 200:1), yielding 21 mg of **3b** and 22 mg of **4f**.

Alcohols **3c** *and* **3g**. A mixture of 320 mg of ester **3e** and 12 ml of dry ether was added dropwise to a suspension of 54 mg of $LiAlH_4$ in 8 ml of ether and the mixture stirred for 0.5 h. Water, 1 ml, was added slowly and the mixture poured onto ice water. After acidification with 10% H_2SO_4-solution and stirring the solution was made basic with ammonia and extracted with CH_2Cl_2.

The extract was dried, the solvent evaporated, and the solid residue, 290 mg, chromatographed on silica gel and eluted with $CHCl_3$/MeOH 9:1. Evaporation of the solvent and crystallization of the residue from ether/methanol gave alcohol **3c**. – IR. ($CHCl_3$): 3480 (NH), 3450 cm^{-1} (OH). – ^{1}H-NMR.: 0.87 (*t*, J = 7 Hz, 3, Me); 4.08 (*m*, 2, OCH_2); 5,40 (br. *s*, 1, H–C(15)); 6.8–7.5 (*m*, 4, aromatic H's).

$C_{20}H_{26}N_2O$ (310.20) Calc. C 77.33 H 8.44 N 9.02% Found C 77.08 H 8.61 N 8.90%

The same treatment of 80 mg of ester **3b** with 13 mg of $LiAlH_4$ yielded 73 mg of amorphous alcohol **3c** [33]. – IR. ($CHCl_3$): 3490 (NH), 3460 cm^{-1} (OH). – ^{1}H-NMR.: 1.03 (*t*, J = 7 Hz, 3, Me); 3.63 (*m*, 2, OCH_2); 4.20 (*m*, 1, H—C(16)); 5.21 (br. *s*, 1, H—C(15)); 6.8–7.5 (*m*, 4, aromatic H's). – Accurate mass for $C_{20}H_{26}ON_2$: Calc. 310.2045; Found 310.2056.

16-Methoxycleavamines **3d** *and* **3f**. A solution of 120 mg of cleavamine chloroindolenine **6** in 4 ml of anhydrous methanol was treated under nitrogen with 80 ml of anhydrous HCl gas and the pink solution stirred at room temp. for 2 h. It was basified with ammonia and extracted exhaustively with CH_2Cl_2. The extract was dried over Na_2SO_4 and the solvent evaporated. The residual viscous liquid was separated into two components by preparative TLC. on silica gel on development with C_6H_6/$CHCl_3$/MeOH 40:20:1. The first fraction yielded 12 mg of the 16β-methoxy isomer **3f**: m.p. 138–140°. – IR. ($CHCl_3$): 3482 cm^{-1} (NH). – ^{1}H-NMR.: 1.06 (*t*, J = 7 Hz, 3, Me); 3.03 (*s*, 3, OMe); 5.30 (br. s, 1, H—C(15); 6.9–7.5 (*m*, 4, aromatic H's).

$C_{20}H_{26}N_2O$ (310.20) Calc. C 77.33 H 8.44 N 9.02% Found C 77.44 H 8.34 N 8.83%

The second fraction gave 25 mg of 16α-methoxycleavamine (**3d**); m.p. 53–55°. – IR. ($CHCl_3$): 3490 cm^{-1}. – ^{1}H-NMR.: 0.85 (*t*, J = 7 Hz, 3, Me); 3.23 (*s*, 3. OMe); 4.50 (*m*, 1, H—C(16); 5.33 (br. s, 1, H—C(15)); 6.9–7.5 (*m*, 4, aromatic H's). – Accurate mass for $C_{20}H_{26}N_2O$: Calc. 310.2045; Found 310.2048.

Hydrogenation of Cleavamines **3a** *and* **3c**. In view of the recovery of more than 95% starting material on repetition of the platinum-catalysed hydrogenation of **3a** in EtOAc [15] the following alternate procedure was used. A mixture of 50 mg of **3a** and 10 mg of 10% Pd/C in 2 ml of abs. ethanol was hydrogenated at room temp. and atmospheric pressure for 5 h. It was filtered and the solvent of the filtrate evaporated. Chromatography of the resultant residue on silica gel and elution with EtOAc/C_6H_6 1:1 gave 30 mg of **4a**, identical in all respects with the previously reported substance [15].

A mixture of 20 mg of alcohol **3c** and 10 mg of PtO_2 in 2 ml of EtOH was hydrogenated at room temp. and atmospheric pressure for 0.5 h. It was filtered and the catalyst washed exhaustively with hot EtOH. The combined solutions were evaporated and the residue separated on preparative TLC. (silica gel G, $CHCl_3$/MeOH 9:1). This yielded 17 mg of alcohol **4b**; m.p. 210–215°. – Accurate mass for $C_{20}H_{28}N_2O$: Calc. 312.2202; Found 312.2197.

16'β-(10-Vindolyl-)cleavamine (**20**). A solution of 30 mg of cleavamine chloroindolenine **6** and 38 mg of vindoline in 1 ml of MeOH was injected with 20 ml of anhydrous HCl gas at atmospheric pressure and room temp. and stirred under nitrogen at room temp. for 12 h (*cf.* [1] [8] [29]). It was evaporated and the residue dissolved in 5 ml of H_2O, made basic with NH_3 and extracted with CH_2Cl_2. The solvent was evaporated and the residue separated by preparative TLC. (silica gel G, C_6H_6/$CHCl_3$/MeOH 20:20:1), leading to 15 mg of recovered vindoline and 38 mg of amorphous **20**. – Accurate mass for $C_{44}H_{54}N_4O_6$: Calc. 734.4043; Found 734.4031.

A similar reaction with 60 mg of vindoline and 48 mg of a mixture of ethers **3d** and **3f** (60 ml HCl gas in 2 ml DME, for 10 min), followed by the above work-up,led to the recovery of 35 mg of vindoline and the formation of 40 mg of **20**.

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