THE STRUCTURE OF CALLICHILINE[1]

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Abstract—The *bis*-indoline alkaloid callichiline and five of its derivatives were investigated by the ^{13}C NMR spectral method and their C shifts assigned. This analysis and biogenetic considerations limited the alkaloid to two structures of which one was shown by a single-crystal X-ray crystallographic analysis of the natural base to be the actual structure of the alkaloid. Callichiline crystallizes in the monoclinic system, space group $P2_1$, with $a = 8.776(3)$ Å, $b = 15.443(5)$ Å, $c = 14.145(5)$ Å, $\beta = 90.87(3)°$, and $Z = 2$. Atomic positional and thermal parameters were refined by least-squares calculations to $R = 0.052$ over 2625 reflections measured by diffractometer.

Some time ago it was shown that the African plant *Callichilia subsessilis* Stapf. produces three bis-indoline alkaloids,[4,5] vobtusine, subsessiline and callichiline. Whereas the structures of the first two bases have been established,[6,7] an unambiguous assignment of the configuration of callichiline has yet to be presented. Two studies of the mass spectroscopy of the alkaloid and several of its derivatives[8,9] suggested the natural compound to be made up of 11-demethoxyvandrikine (1) and C(16')–C₁-attached beninine (2) units[8,9] doubly coupled to each other by C(3)–C(2') and C(14)–C₁–C(16') bonds, C(15)–C(2') and C(14)–C₁–C(16') bonds or C(18)–C(2') and C(19)–C₁–C(16') bonds.[9] The lack of completeness of the structure analysis and the biogenetic implausibility of the proposed points of attachment of the alkaloid's two subunits required further work on callichiline. The present communication presents a ^{13}C NMR spectral determination of the alkaloid and some of its derivatives and an X-ray analysis of the natural base.
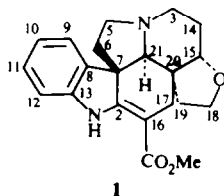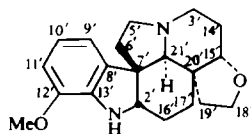
For the preparation of callichiline models for the ^{13}C NMR spectral study the alkaloid was exposed to the following transformations. A reaction with sodium cyanoborohydride in acetic acid at room temperature yielded a dihydro product (3), in which the vinylogous urethane of the vandrikine unit had become saturated. The same reaction at 90° led to a mixture of a *seco*-dihydro compound (4), in which the vandrikine moiety had been converted into an indole system,[10] an isomer (5) and an unidentified substance. Sodium borohydride reduction afforded the same three materials but in a different ratio.[11]

Inspection of the aromatic C resonances of callichiline permitted the ready identification of the 2-alkylideneindoline and indoline units by comparison with the aromatic C shifts of vincadifformine[12] (a demethoxyvandrikine-like base) and 2'-deoxyvobtusine 18'-lactone,[7] respectively. The C(8') and C(13') signals of the indoline unit in the callichiline spectra were 3.8 ppm upfield and 1.3 ppm downfield, respectively, with respect to the signals of like C's in the vobtusine derivative[7] reflecting presumably a difference in $N_{a'}$ substitution. The absence of both $N_{a'}$ and N_a substituents in callichiline was confirmed by the H-count in the sford spectrum revealing 46 of the 48 hydrogens bound to carbons.

The constancy of *ca* a half of the C shifts of the three hydride reduction products, in which the C(2)–C(16) double bond of the vandrikine-like indole alkaloid monomer unit had been removed, identified the carbons of the chemically unchanged monomer base and, by difference, those of the modified residue of each substance. The signals of the latter in the callichiline spectra were identical in multiplicity, albeit not in chemical shift, with those of the 2-alkylideneindoline portion of vobtusine (6).[6] These observations pointed to the possible presence of an 11-demethoxy-14,14-disubstituted vandrikine residue in callichiline as in vobtusine (6).

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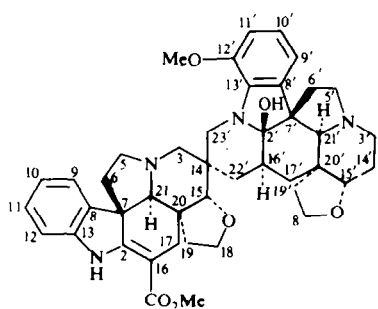
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Conversion of callichiline into its dihydro product **3** (*vide supra*) caused the quaternary carbons 7 and 20 to shift upfield 4.4 and 6.2 ppm, respectively. This shift difference was reminiscent of that between vobtusine (**6**) and its $2\beta,16\beta$-dihydro derivative[7] and pointed to part structure **7** as representing the reduction product **3**. The transformation of the Aspidosperma alkaloid ring system of callichiline into one of the vincadine type in the *seco*-dihydro compounds **4** and **5** and the tagging of the newly generated aminomethylene at C(21) with D[11] led to facile shift assignment of the indoloazacyclononane system of the reduction products. In view of the known relationship between the large ring conformation and the C(16) stereochemistry in vincadine-like compounds as reflected by their C(6) shift[13,14] the major *seco*-dihydro substance could be shown to possess part structure **8a** and its isomer **8b**.[15] The behavior of callichiline on reduction and the ^{13}C NMR spectroscopy of the products were in accord with a 14,14-disubstituted 11-demethoxyvandrikine part structure for the alkaloid.
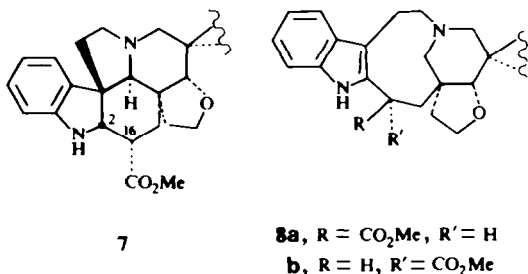

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8a, R = CO₂Me, R′ = H
b, R = H, R′ = CO₂Me

Comparison of the spectra of callichiline and its N-oxide (**9**)[16] identified conclusively the N_b-attached C centers, i.e. the aminocarbons in the vandrikine part of the alkaloid. A similar comparison of the spectra of callichiline N_b-oxide (**9**) and the di-N-oxide (**10**)[17] revealed the aminocarbons of the second alkaloid monomer unit. The downfield shifts of carbons 3′, 5′ and 21′ (11.8, 16.3 and 7.3 ppm, respectively) of the dioxide with respect to the monooxide compared favorably with the $\Delta\delta$ values of like carbons (10.2, 15.0 and 8.6 ppm, respectively) of vobtusine N_b-oxide vs vobtusine (**6**).[7]

The tetrahydrofuran moiety of the second isomer unit and its immediate environment appeared to be structurally traditional in view of the similarity of the oxymethylene (65.5 ppm) and oxymethine (78.6 ppm) signals with those of vandrikine (64.7 and 79.8 ppm,

respectively).[12] Further insight into this part of callichiline's complex structure came from a Yb(DPM)₃ shift study of vobtusine (**6**) and callichiline. In the absence of any strong coordination site in the two substances only the CO oxygen of the urethane vinylogue and the ether O of the tetrahydrofurans competed for complexation with the lanthanide shift agent. The ease of ether coordination differed markedly in the two portions of each alkaloid (the complexation ratios being 10:1 and 6:1 in vobtusine and callichiline, respectively) presumably due to the *steric interference of the C(14) substituents with the* tetrahydrofuran coordination in the vandrikine-like parts of the compounds. The Yb(DPM)₃ $\Delta\delta$ values[18] confirmed certain shift assignments in both alkaloid monomer units of callichiline and in conjunction with the N-oxide spectral results identified fragment **11** in the non-vandrikine-like portion of the alkaloid.
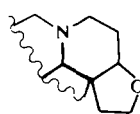

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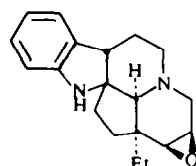
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Consideration of all spectral data, including assignment of the remaining non-protonated C resonances of 61.4 and 84.8 ppm to C(7′) and C(2′), respectively, led to two possible structures for callichiline—a C(16′)–C₁-attached beninine fragment united to 11-demethoxyvandrikine by way of C(14)–C(2′) and C(14)–C(22′) bonds (**13**) or a C(16′)–C₁-attached andragine-like (**12**)[19] unit joined to 11-demethoxyvandrikine via C(14)–C(7′) and C(14)–C(22′) bonds (**14**). Differentiation between these structures was left to an X-ray crystallographic analysis of the alkaloid.
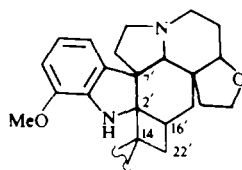
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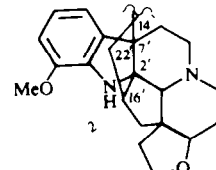
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A single-crystal X-ray analysis established that callichiline has the structure and relative stereochemistry represented by (**15**). A view of the solid-state conformation is provided in Fig. 1 which also gives the atom numbering scheme, one of the C atoms in one of the tetrahydrofuran rings being disordered over two positions, C(18) and C(18″). Fractional atomic coordinates are in Table 2, interatomic distances and angles are in Table 3, and torsion angles are in Table 4.[20]

Although the mean lengths of chemically equivalent bonds in **15** do not depart significantly from expected values,[21] there are some individual distances which merit comment. Apparent shortening of the C(18)–C(19) [C(18″)–C(19)] and C(18′)–C(19′) bonds may be ascribed to lack of conformation rigidity in
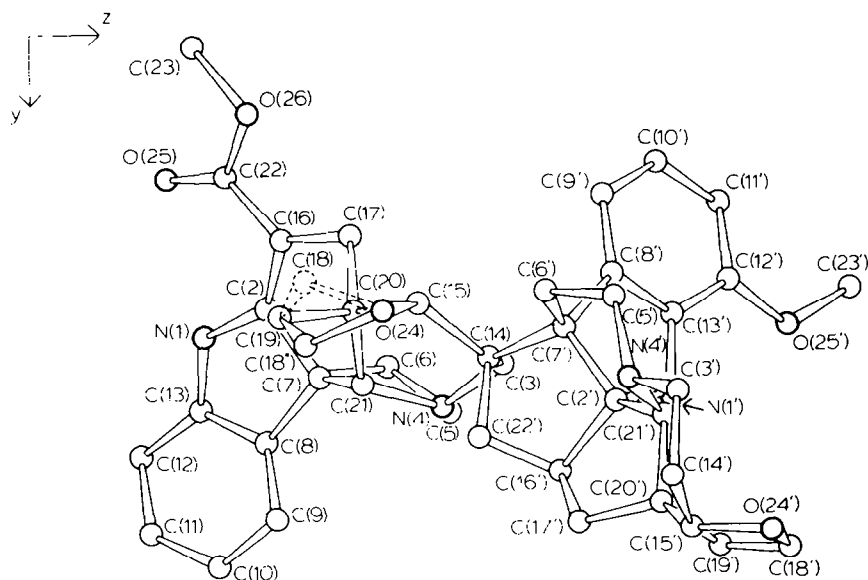
Fig. 1. Atom numbering scheme and solid-state conformation of callichiline (15); one of the carbon atoms in one of the tetrahydrofuran rings is disordered over two sites, C(18) and C(18″).

the tetrahydrofuran rings. Bond lengthening due to steric strain at a number of tetrasubstituted C centers is evident, e.g. the longest bond, C(14)–C(7′) at 1.586(6) Å, involving the spiro C center. The short H(1)...O(25) distance of 2.26 Å indicates the presence of an intramolecular N—H...O hydrogen bond similar to that found in dibromovobtusine.[6] There are no abnormally short intermolecular separations, all of the shorter distances corresponding to normal van der Waals' type interactions.

Table 1. Carbon shifts of callichiline and its derivatives[a]

	15	7	9	10	8a	8b		15	7	9	10	8a	8b
C(2)	166.5	65.0	165.0	165.4	128.1	133.2	C(2′)	84.8	85.7	83.7	83.0	84.3	84.2
C(3)	54.5	55.0	71.3	71.6	53.5[b]	67.5	C(3′)	49.9[b]	49.8[b]	49.6[b]	61.4	49.7[b]	49.8[b]
C(5)	51.8	52.3	64.9	65.2	46.8[b]	53.5	C(5′)	50.4[b]	50.2[b]	50.0[b]	66.3	50.3[b]	50.9[b]
C(6)	43.4	41.9	40.4[b]	40.1[b]	19.9	25.1	C(6′)	31.1	31.4	30.1	24.8	30.9	31.0
C(7)	57.3	53.1	55.6	56.3	113.0	112.0	C(7′)	61.4	61.0	61.9	60.2	61.3	62.5
C(8)	136.2	134.6	133.1	133.4	127.9	127.3	C(8′)	131.8	132.2	129.3	130.0	131.1	133.4
C(9)	121.4	118.5	122.2	122.5	117.8	117.9	C(9′)	115.6	116.0	114.1	114.5	114.8	115.5
C(10)	120.8	122.6	121.4	121.7	119.0	118.7	C(10′)	118.8	118.2	118.6	119.6	119.0	119.1
C(11)	127.6	127.6	128.2	128.3	121.8	121.4	C(11′)	109.0	109.0	109.0	109.1	109.5	109.4
C(12)	109.7	108.4	110.0	110.5	110.3	110.4	C(12′)	144.1	143.8	143.9	144.3	143.9	144.0
C(13)	143.1	150.4	142.2	142.2	135.3	135.7	C(13′)	139.2	138.9	138.7	137.8	138.6	139.0
C(14)	58.6	58.6	56.4	57.3	58.5	58.5	C(14′)	27.3	27.2	27.0	25.9	27.2	27.3
C(15)	83.1	86.1	83.7	84.0	85.0	82.4	C(15′)	78.6	78.5	78.1	78.8	78.4	78.5
C(16)	94.4	40.7	92.9	92.9	44.0	38.6	C(16′)	48.6	48.1	47.3	49.2	48.6	49.2
C(17)	34.2	31.4	33.2	33.6	36.7	41.8	C(17′)	41.1	41.3	42.0	44.0	40.6	40.6
C(18)	65.6	66.3	65.3	65.4	66.3	64.8	C(18′)	65.5	65.4	65.6	66.0	65.4	65.5
C(19)	38.5	41.5	36.4[b]	34.8[b]	38.4	46.0	C(19′)	37.8	37.7	37.3	39.3	37.5	37.8
C(20)	49.5	43.7	47.0	47.4	46.8	47.7	C(20′)	56.0	55.9	56.1	56.7	55.7	55.9
C(21)	66.5	71.2	82.2	82.7	46.8	62.9	C(21′)	77.6	77.2	76.7	84.0	77.1	77.5
C=O	168.0	175.2	167.2	167.5	172.1	175.0	C(22′)	38.1	40.7	39.9	42.0	37.1	39.5
OMe	50.7	51.7	51.0	51.1	52.3	52.3	OMe′	55.1	55.0	54.8	54.9	54.9	55.1

[a]In ppm downfield from TMS; δ(TMS) = δ(CDCl₃) + 76.9 ppm.   [b]Signals in any vertical column may be reversed.

Table 2. Fractional atomic coordinates ($\times 10^4$; $\times 10^3$ for hydrogen atoms[a]), isotropic thermal parameters and bond lengths involving hydrogen atoms, with standard deviations in parentheses

Atom	x	y	z	Atom	x	y	z	U	$d(\overset{\circ}{A})$
N(1)	-2835(5)	2048(4)	650(3)	H(1)	-303(7)	173(4)	29(4)	7(2)	0.72(6)
C(2)	-1979(5)	1792(4)	1428(3)	H(3A)	-31(5)	178(3)	439(3)	3(1)	1.07(4)
C(3)	146(4)	2417(3)	4316(3)	H(3B)	-1(4)	275(3)	487(3)	7(2)	0.94(4)
N(4)	-612(3)	2892(3)	3573(2)	H(5A)	-251(7)	364(4)	352(4)	7(2)	1.09(7)
C(5)	-2267(5)	2961(5)	3668(4)	H(5B)	-263(6)	277(4)	436(3)	5(2)	1.08(5)
C(6)	-2954(5)	2448(5)	2897(3)	H(6A)	-404(6)	273(4)	273(3)	5(2)	1.07(5)
C(7)	-1820(5)	2558(4)	2072(3)	H(6B)	-285(6)	169(3)	305(3)	5(2)	1.19(5)
C(8)	-2311(6)	3289(4)	1410(4)	H(9)	-163(7)	445(4)	211(4)	9(2)	1.06(6)
C(9)	-2228(9)	4171(5)	1530(5)	H(10)	-288(13)	544(8)	84(7)	19(5)	1.15(13)
C(10)	-2812(12)	4702(6)	811(6)	H(11)	-374(8)	479(5)	-54(5)	10(3)	1.07(7)
C(11)	-3421(12)	4323(7)	-11(6)	H(12)	-372(11)	311(7)	-84(7)	15(4)	1.15(10)
C(12)	-3506(10)	3442(6)	-127(5)	H(15)	190(5)	109(3)	351(3)	3(1)	1.05(5)
C(13)	-2927(6)	2935(5)	600(4)	H(17A)	45(4)	49(2)	241(3)	2(1)	0.99(4)
C(14)	1871(4)	2346(3)	4145(3)	H(17B)	-80(6)	90(4)	297(4)	7(2)	0.90(6)
C(15)	2012(4)	1733(3)	3283(3)	H(18A)[b]	410(-)	170(-)	145(-)	6(-)	1.04(-)
C(16)	-1334(5)	1028(4)	1616(3)	H(18B)[b]	317(-)	82(-)	188(-)	6(-)	1.04(-)
C(17)	-240(6)	992(3)	2452(3)	H(18"A)[b]	316(-)	289(-)	193(-)	6(-)	1.07(-)
C(18)	3240(9)	1490(7)	1897(6)	H(18"B)[b]	403(-)	202(-)	142(-)	6(-)	1.06(-)
C(18")	3165(11)	2197(10)	1896(7)	H(19A)[b]	184(-)	253(-)	137(-)	6(-)	1.05(-)
C(19)	1713(5)	1886(4)	1584(3)	H(19B)[b]	121(-)	152(-)	103(-)	6(-)	1.06(-)
C(20)	747(4)	1826(3)	2498(3)	H(19C)[b]	118(-)	230(-)	110(-)	6(-)	1.04(-)
C(21)	-252(4)	2647(3)	2588(3)	H(19D)[b]	181(-)	127(-)	128(-)	6(-)	1.05(-)
C(22)	-1513(6)	303(4)	955(4)	H(21)	32(4)	315(2)	224(3)	1(1)	1.06(4)
C(23)	-888(13)	-1144(6)	569(7)	H(1')	169(7)	303(4)	690(4)	7(2)	0.89(6)
O(24)	3451(3)	1821(3)	2837(2)	H(3'A)	785(5)	246(3)	626(3)	3(1)	0.89(4)
O(25)	-2279(5)	339(3)	236(3)	H(3'B)	675(5)	262(3)	709(3)	3(1)	0.95(4)
O(26)	-776(5)	-411(3)	1227(3)	H(5'A)	499(5)	139(3)	622(3)	3(1)	0.94(4)
N(1')	1547(4)	2758(-)	6353(2)	H(5'B)	640(5)	135(3)	564(3)	4(1)	1.03(5)
C(2')	2850(4)	2836(3)	5700(3)	H(6'A)	411(5)	98(3)	467(3)	3(1)	1.00(5)
C(3')	7021(5)	2735(4)	6455(3)	H(6'B)	472(5)	190(3)	431(3)	4(1)	0.98(4)
N(4')	5667(4)	2579(3)	5865(3)	H(9')	186(5)	17(3)	499(3)	4(1)	1.05(5)
C(5')	5381(5)	1664(3)	5684(4)	H(10')	19(5)	-46(3)	608(3)	5(2)	0.99(5)
C(6')	4284(5)	1601(3)	4846(3)	H(11')	-61(6)	25(4)	740(4)	6(2)	0.95(6)
C(7')	2718(5)	2003(3)	5069(3)	H(14'A)	833(6)	378(4)	683(4)	6(2)	1.00(5)
C(8')	1751(5)	1405(3)	5657(3)	H(14'B)	783(6)	382(3)	575(3)	5(2)	0.98(5)
C(9')	1403(6)	530(4)	5549(4)	H(15')	626(6)	490(3)	633(3)	5(2)	1.06(5)
C(10')	446(7)	155(4)	6203(4)	H(16')	196(4)	395(3)	516(3)	2(1)	0.87(4)
C(11')	-91(6)	613(4)	6963(4)	H(17'A)	485(4)	406(2)	479(2)	1(1)	0.92(4)
C(12')	278(6)	1477(3)	7082(4)	H(17'B)	391(6)	479(3)	511(3)	4(2)	0.95(5)
C(13')	1179(5)	1863(3)	6400(3)	H(18'A)	394(9)	405(5)	835(5)	12(3)	1.11(8)
C(14')	7452(6)	3682(4)	6382(4)	H(18'B)	452(9)	508(5)	809(5)	10(3)	0.97(8)
C(15')	6144(5)	4263(4)	6616(3)	H(19'A)	242(7)	428(4)	706(4)	8(2)	0.97(8)

Table 2. *Contd*

Atom	x	y	z	Atom	x	y	z	U	d(Å)
C(16')	2719(5)	3624(3)	5012(3)	H(19'B)	347(8)	511(4)	674(5)	9(2)	1.03(7)
C(17')	4125(5)	4200(3)	5230(3)	H(21')	430(5)	284(3)	698(3)	3(1)	1.01(4)
C(18')	4468(8)	4501(7)	7843(5)	H(22'A)	362(5)	314(3)	365(3)	3(1)	1.05(4)
C(19')	3539(6)	4472(3)	6972(4)	H(22'B)	196(5)	360(3)	358(3)	3(1)	1.01(4)
C(20')	4555(5)	3975(3)	6258(3)	H(23'A)	-115(6)	199(4)	895(4)	6(2)	0.85(6)
C(21')	4343(5)	2992(3)	6285(3)	H(23'B)	-39(9)	104(6)	868(5)	12(3)	0.98(8)
C(22')	2609(5)	3244(3)	4022(3)	H(23'C)	-212(9)	121(6)	829(5)	12(3)	1.25(8)
C(23')	-932(9)	1587(6)	8563(5)						
O(24')	6002(4)	4301(3)	7618(3)						
O(25')	-154(4)	1992(4)	7815(2)						

[a] Hydrogen atoms bear the same labels as the atoms to which they are bonded

[b] These hydrogen atoms were included at their calculated positions with 50% occupancy, but were not refined

Table 3. Interatomic distances (Å) and angles (°), with standard deviations in parentheses

(a) Bond Lengths

N(1)-C(2)	1.381(6)	C(15)-O(24)	1.426(5)	C(5')-C(6')	1.519(7)
N(1)-C(13)	1.375(9)	C(16)-C(17)	1.514(7)	C(6')-C(7')	1.545(6)
C(2)-C(7)	1.499(7)	C(16)-C(22)	1.465(8)	C(7')-C(8')	1.512(6)
C(2)-C(16)	1.334(8)	C(17)-C(20)	1.553(7)	C(8')-C(9')	1.394(7)
C(3)-N(4)	1.436(5)	C(18)-C(19)	1.533(10)	C(8')-C(13')	1.369(6)
C(3)-C(14)	1.540(6)	C(18)-O(24)	1.433(10)	C(9')-C(10')	1.386(8)
N(4)-C(5)	1.465(6)	C(18")-C(19)	1.425(12)	C(10')-C(11')	1.376(8)
N(4)-C(21)	1.482(5)	C(18")-O(24)	1.471(12)	C(11')-C(12')	1.382(8)
C(5)-C(6)	1.470(8)	C(19)-C(20)	1.559(6)	C(12')-C(13')	1.390(7)
C(6)-C(7)	1.554(7)	C(20)-C(21)	1.548(6)	C(12')-O(25')	1.365(6)
C(7)-C(8)	1.524(8)	C(22)-O(25)	1.212(7)	C(14')-C(15')	1.498(7)
C(7)-C(21)	1.554(6)	C(22)-O(26)	1.331(7)	C(15')-C(20')	1.543(6)
C(8)-C(9)	1.374(10)	C(23)-O(26)	1.469(10)	C(15')-O(24')	1.427(6)
C(8)-C(13)	1.373(8)	N(1')-C(2')	1.486(5)	C(16')-C(17')	1.548(6)
C(9)-C(10)	1.398(11)	N(1')-C(13')	1.420(5)	C(16')-C(22')	1.519(6)
C(10)-C(11)	1.401(13)	C(2')-C(7')	1.569(6)	C(17')-C(20')	1.536(7)
C(11)-C(12)	1.372(14)	C(2')-C(16')	1.561(6)	C(18')-C(19')	1.468(8)
C(12)-C(13)	1.384(10)	C(2')-C(21')	1.558(6)	C(18')-O(24')	1.421(8)
C(14)-C(15)	1.550(6)	C(3')-N(4')	1.462(6)	C(19')-C(20')	1.559(7)
C(14)-C(7')	1.585(6)	C(3')-C(14')	1.514(8)	C(20')-C(21')	1.529(6)
C(14)-C(22')	1.541(6)	N(4')-C(5')	1.457(6)	C(23')-O(25')	1.414(8)
C(15)-C(20)	1.564(6)	N(4')-C(21')	1.460(6)		

(b) Bond Angles

|					
C(2)-N(1)-C(13)	110.9(4)	C(17)-C(16)-C(22)	122.1(5)	C(2')-C(7')-C(6')	112.8(3)
N(1)-C(2)-C(7)	107.6(4)	C(16)-C(17)-C(20)	110.5(4)	C(2')-C(7')-C(8')	103.0(3)
N(1)-C(2)-C(16)	129.5(5)	C(19)-C(18)-O(24)	103.0(6)	C(6')-C(7')-C(8')	112.1(4)

(b)   Bond Angles

C(7)-C(2)-C(16)	122.8(4)	C(19)-C(18")-O(24)	106.6(8)	C(7')-C(8')-C(9')	131.0(4)
N(4)-C(3)-C(14)	111.5(3)	C(18)-C(19)-C(20)	102.7(5)	C(7')-C(8')-C(13')	108.8(4)
C(3)-N(4)-C(5)	114.8(4)	C(18")-C(19)-C(20)	105.0(5)	C(9')-C(8')-C(13')	120.2(4)
C(3)-N(4)-C(21)	117.0(3)	C(15)-C(20)-C(17)	110.1(4)	C(8')-C(9')-C(10')	117.8(5)
C(5)-C(4)-C(21)	109.3(3)	C(15)-C(20)-C(19)	101.8(3)	C(9')-C(10')-C(11')	121.7(5)
N(4)-C(5)-C(6)	106.8(4)	C(15)-C(20)-C(21)	114.4(3)	C(10')-C(11')-C(12')	120.5(5)
C(5)-C(6)-C(7)	103.8(4)	C(17)-C(20)-C(19)	109.0(4)	C(11')-C(12')-C(13')	117.7(5)
C(2)-C(7)-C(6)	108.4(4)	C(17)-C(20)-C(21)	111.5(3)	C(11')-C(12')-O(25')	125.9(5)
C(2)-C(7)-C(8)	100.9(4)	C(19)-C(20)-C(21)	109.6(3)	C(13')-C(12')-O(25')	116.3(5)
C(2)-C(7)-C(21)	115.4(4)	N(4)-C(21)-C(7)	105.3(3)	N(1')-C(13')-C(8')	112.3(4)
C(6)-C(7)-C(8)	111.3(4)	N(4)-C(21)-C(20)	114.6(3)	N(1')-C(13')-C(12')	125.6(4)
C(6)-C(7)-C(21)	103.2(3)	C(7)-C(21)-C(20)	112.8(4)	C(8')-C(13')-C(12')	122.0(5)
C(8)-C(7)-C(21)	117.6(4)	C(16)-C(22)-O(25)	123.6(5)	C(3')-C(14')-C(15')	111.7(4)
C(7)-C(8)-C(9)	130.1(5)	C(16)-C(22)-O(26)	113.7(5)	C(14')-C(15')-C(20')	116.5(4)
C(7)-C(8)-C(13)	108.8(6)	O(25)-C(22)-O(26)	122.8(5)	C(14')-C(15')-O(24')	108.9(4)
C(9)-C(8)-C(13)	121.1(6)	C(15)-O(24)-C(18)	105.9(4)	C(20')-C(15')-C(24')	104.2(4)
C(8)-C(9)-C(10)	118.3(7)	C(15)-O(24)-C(18")	107.3(4)	C(2')-C(16')-C(17')	105.8(3)
C(9)-C(10)-C(11)	119.3(3)	C(22)-O(26)-C(23)	115.3(5)	C(2')-C(16')-C(22')	106.1(4)
C(10)-C(11)-C(12)	122.2(8)	C(2')-N(1')-C(13')	106.6(3)	C(17')-C(16')-C(22')	116.4(4)
C(11)-C(12)-C(13)	116.9(7)	N(1')-C(2')-C(7')	103.7(3)	C(16')-C(17')-C(20')	104.0(4)
N(1)-C(13)-C(8)	109.4(5)	N(1')-C(2')-C(16')	113.6(3)	C(19')-C(18')-O(24')	108.8(5)
N(1)-C(13)-C(12)	128.5(6)	N(1')-C(2')-C(21')	109.3(3)	C(18')-C(19')-C(20')	104.1(5)
C(8)-C(13)-C(12)	122.1(7)	C(7')-C(2')-C(16')	106.2(3)	C(15')-C(20')-C(17')	116.9(4)
C(3)-C(14)-C(15)	104.9(3)	C(7')-C(2')-C(21')	118.9(3)	C(15')-C(20')-C(19')	99.7(4)
C(3)-C(14)-C(7')	110.1(3)	C(16')-C(2')-C(21')	105.3(3)	C(15')-C(20')-C(21')	112.8(4)
C(3)-C(14)-C(22')	111.7(3)	N(4')-C(3')-C(14')	108.8(4)	C(17')-C(20')-C(19')	111.5(4)
C(15)-C(14)-C(7')	113.7(3)	C(3')-N(4')-C(5')	113.4(4)	C(17')-C(20')-C(21')	102.7(3)
C(15)-C(14)-C(22')	115.0(3)	C(3')-N(4')-C(21')	109.9(3)	C(19')-C(20')-C(21')	113.7(4)
C(7')-C(14)-C(22')	101.6(3)	C(5')-N(4')-C(21')	111.1(3)	C(2')-C(21')-N(4')	112.6(3)
C(14)-C(15)-C(20)	115.9(3)	N(4')-C(5')-C(6')	107.7(4)	C(2')-C(21')-C(20')	104.0(3)
C(14)-C(15)-O(24)	111.8(3)	C(5')-C(6')-C(7')	111.8(4)	N(4')-C(21')-C(20')	109.0(3)
C(20)-C(15)-O(24)	107.5(3)	C(14)-C(7')-C(2')	103.0(3)	C(14)-C(22')-C(16')	105.4(3)
C(2)-C(16)-C(17)	116.8(5)	C(14)-C(17')-C(6')	111.9(3)	C(15')-O(24')-C(18')	109.2(4)
C(2)-C(16)-C(22)	120.5(4)	C(14)-C(7')-C(8')	113.4(3)	C(12')-O(25')-C(23')	117.0(5)

Detailed analysis of the endocyclic torsion angles[22] indicates that 5-membered rings B, C, E' and G' all approximate to envelope forms, whereas rings F, B' and F' have conformations intermediate between envelope and half-chair forms. Flattened chair conformations are adopted by 6-membered rings C' and D'. The conformations of rings D and E are characterized by having two relatively small, non-adjacent torsion angles (7.5–12.8°) and both rings lie closer to 1,3-diplanar forms than to half-chair forms.[23]

Formula **15** having been determined for the structure of callichiline, it now is possible to speculate on the origin of the natural base. The following elaboration of a simple Aspidosperma alkaloid system illustrates the most likely biogenetic pathway to the structurally complex natural product.

15
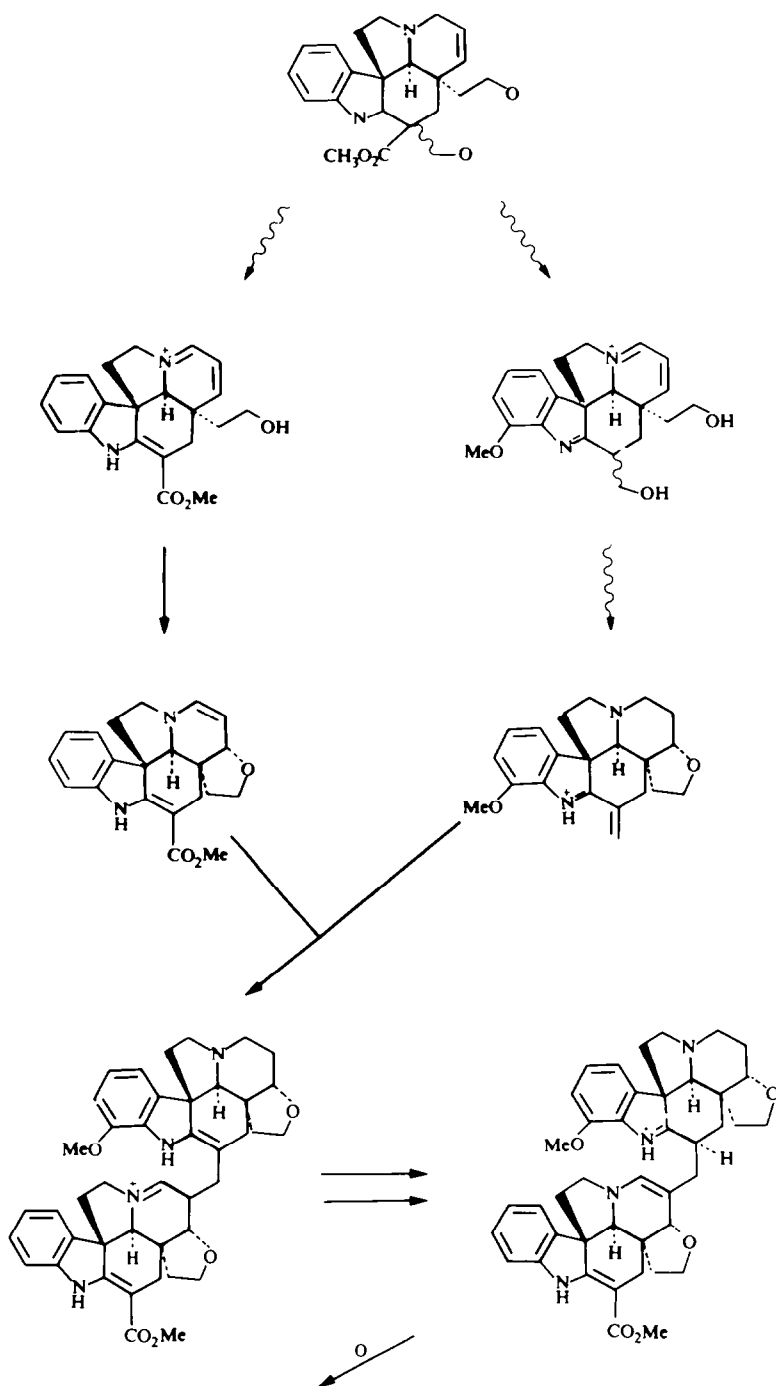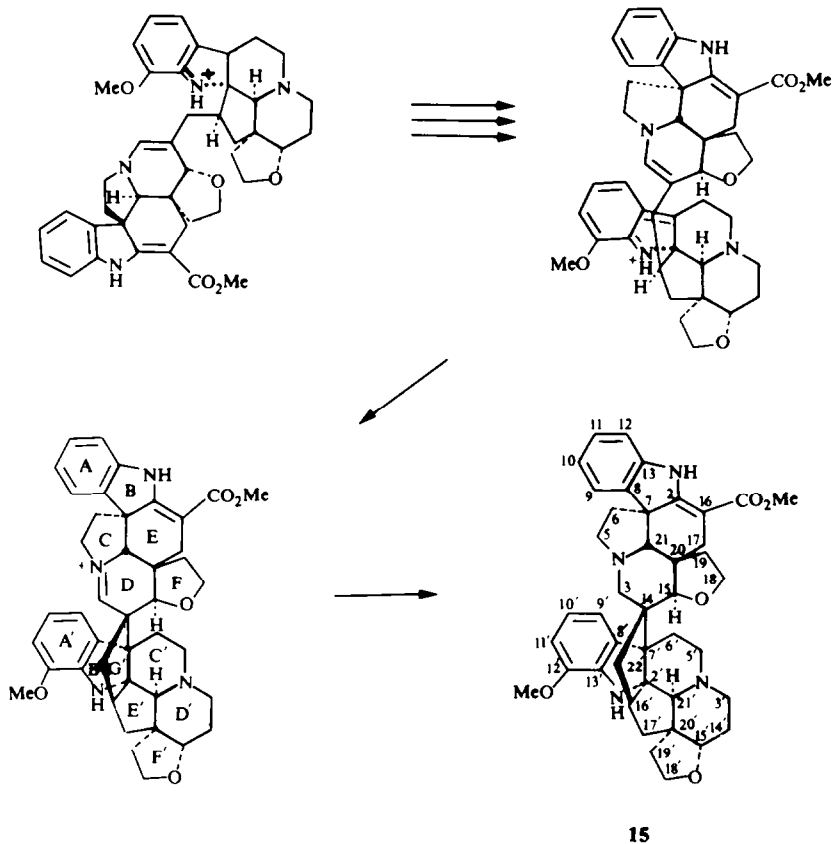
EXPERIMENTAL

M.ps were recorded on a Reichert micro hotstage and.are uncorrected. IR spectra were observed on a Perkin–Elmer 257 spectrophotometer and ^{13}C NMR spectra of $CDCl_3$ solns were recorded on a Varian XL-100-15 spectrometer operating at 25.2 MHz in the Fourier transform mode.

Hydride reductions of callichiline (15). A soln of 400 mg of 15 and 150 mg $NaBH_4$ in 10 ml glacial AcOH was stirred at room temp for 1 hr and then poured into 100 ml water and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated. Thick-layer chromatography of the residue, 420 mg, on Merck HF_{254} silica gel and development with 12:1 CH_2Cl_2–MeOH yielded 207 mg of amorphous 7. Exact mass: m/e 690.3797 (Calc for $C_{42}H_{50}O_5N_4$: m/e 690.3781).

Sodium cyanoborohydride, 100 mg, was added in portions to a soln of 15 (500 mg) in 15 ml glacial AcOH being heated at 90° and the mixture stirred at this temp for 1.5 hr. Work-up as above and addition of ether to the crude product, 550 mg, caused the precipitation of 80 mg crystalline **8a**. Thick-layer chromatography of the ether filtrate on Merck HF_{254} silica gel and development with 12:1 $CHCl_3$–MeOH led to the following substances, in increasing order of mobility: 150 mg of *seco*-**8a** (combined ppt and TLC eluate crystallized from ether) [m.p. 190–195°; IR (KBr) NH 3400 (m), C=O 1730 (s), C=C 1650 (m), 1580 (m) cm⁻¹. Exact mass: m/e 690.3797 (Calc for $C_{42}H_{50}O_5N_4$: m/e 690.3781)], 75 mg of amorphous *seco*-**8b** [IR (film) NH 3380 (m), C=O 1725 (s), C=C 1610 (m), 1580 (m) cm⁻¹. Exact mass: m/e 690.3776 (Calc for $C_{42}H_{50}O_5N_4$: m/e 690.3781)] and 125 mg of a crystalline substance of unknown constitution (crystallized from acetone) [m.p. 184–188°; IR (KBr) NH 3390 (w), 3260 (w), C=O 1665 (s), C=C 1618 (s), 1605 (s) cm⁻¹].

$NaBH_4$, 550 mg, was added in portions to a soln of 250 mg of 15 in 10 ml glacial AcOH at 95° and the mixture stirred at this temp for 1.5 hr. Work-up as above gave 260 mg of crude product, whose crystallization from ether

yielded 116 mg of **8a**. Thick-layer chromatography of the filtrate on Merck HF_{254} silica gel and development with 1.5:1 cyclohexane–acetone gave 102 mg of isomer **8b** and 10 mg of the compound of unknown structure.

Crystal data: Callichiline (15), $C_{42}H_{48}N_4O_5$, mol wt 688.87; monoclinic, $a = 8.776(3)$ Å, $b = 15.443(5)$ Å, $c = 14.145(5)$ Å, $\beta = 90.87(3)°$, $U = 1917$ Å³, $Z = 2$, $d_{calc} = 1.193$ g cm⁻³, $F(000) = 736$; CuKα radiation, $\lambda = 1.5418$ Å; absorption coefficient for CuKα radiation, $\mu = 6.4$ cm⁻¹; space group $P2_1(C_2^2)$ from the systematic absences, $0k0$ when $k \neq 2n$, and 15 is chiral.

Crystallographic measurements. A crystal of dimensions *ca* $0.06 \times 0.20 \times 1.00$ mm, elongated along *c*, was mounted on the end of a glass fiber. Preliminary unit cell dimensions and space group information were obtained from oscillation and Weissenberg photographs taken with CuKα radiation and precession photographs taken with MoKα ($\lambda = 0.7107$ Å) radiation. Intensities for all unique reflections with $\theta \leq 67°$ were measured on an Enraf–Nonius CAD-3 automated diffractometer (Ni-filtered CuKα radiation) by the $\theta - 2\theta$ scanning procedure as described previously.[24] A total of 2625 intensities for which $I \geq 2.0\sigma(I)$, where $\sigma^2(I) = $ scan count + total background count, were employed in the structure analysis following correction for the usual Lorentz and polarization effects. Refined unit cell parameters were derived by least-squares treatment of the diffractometer setting angles for 40 reflections widely separated in reciprocal space.

Crystallographic structure analysis. The structure was solved by direct methods by use of the MULTAN76[25] suite of programs involving the 400 largest $|E|$-values. The starting set comprised 3 origin-defining reflections, 1 reflection for which the phase was determined by Σ_1 relationships, and 8 general reflections for which phases were allowed to vary. An *E*-map, derived by use of a set of phases which gave one of the highest combined figures-of-merit, allowed approximate positions to be assigned to 47 non-H atoms. Positions

for the remaining 4 non-H atoms in the asymmetric crystal unit were obtained from an F_0 Fourier synthesis phased by these 47 atoms ($R = 0.25$).[26] Full-matrix least-squares adjustment of positional and isotropic thermal parameters reduced R to 0.131. During these iterations the temperature factor for C(18) became significantly larger than those for its neighboring atoms. Thus its contribution was excluded from the next round of structure-factor calculations. Evaluation of a difference Fourier synthesis revealed two maxima of approximately equal magnitude, separated by ca 1 Å, and both in physically acceptable positions for the missing C atom. Accordingly, this atom was included at both sites, C(18) and C(18″), with 50% occupancy in all further structure-factor calculations. H atoms, save those on C(23) which could not be placed unambiguously, were included at their calculated positions in the next series of least-squares calculations. Positional and isotropic thermal parameters for the H atoms were varied in addition to the positional and anisotropic thermal parameters of the non-H atoms during the later least-squares iterations. The refinement converged at $R = 0.052$.

Final atomic positional parameters are in Table 2. Anisotropic thermal parameters (Table 5) and a listing of observed and calculated structure amplitudes are available as supplementary material.[20]

Atomic scattering factors used in all structure-factor calculations were those for C, N and O from Ref. 27, and for H from Ref. 28. In the least-squares iterations, $\Sigma w \Delta^2$ ($\Delta = \|F_0| - |F_c\|$) was minimized with weights, w, assigned according to the scheme $w^{1/2} = 1$ when $|F_0| \leqslant 15.0$, and $w^{1/2} = 15.0/|F_0|$ when $|F_0| > 15.0$; the y-coordinate of N(1′) was held constant throughout to define the origin in this direction.

Supplementary material available. Tables of torsion angles (Table 4), anisotropic thermal parameters (Table 5), and a listing of observed and calculated structure amplitudes (Table 6) have been deposited with the British Lending Library.

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[14] The δ(C-6) values are 22 and 26 ppm for 16β- and 16α-substituted compounds, respectively.

[15] The minor deviation of the C(6) signal positions from the expected δ values[14] indicated that the C(14) substituents of **4** and **5** influence the conformation of their large ring.

[16] A reaction between 70 mg (0.10 mmol) of callichiline and 25 mg of 85% (0.12 mmol) *m*-chloroperbenzoic acid in 2 ml $CHCl_3$ at room temp for 48 hr, followed by the usual work-up, yielded 40 mg of amorphous N_b-oxide, i.e. the product of oxidation in the vandrikine-like portion of callichiline [IR ($CHCl_3$) NH 3340 (m), C=O 1675 (s), C=C 1610 (s) cm⁻¹].

[17] The dioxide was prepared by the oxidation of the monooxide with *m*-chloroperbenzoic acid in $CHCl_3$ at room temp for 48 hr. It decomposed in $CHCl_3$ solution with time.

[18] Vobtusine: C(2) 15, C(16) 22, C(17) 11, C(15) 4, C(18) 3, C-O 58, OMe 25, C(14′) 15, C(15′) 29, C(18′) 29, C(19′) 12, C(20′) 13 ppm. Callichiline: C(2) 12, C(16) 16, C(17) 8, C(15) 3, C(18) 3, C=O 42, OMe 13, C(14′) 9, C(15′) 19, C(18′) 19, C(19′) 8, C(20′) 9 ppm.

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[20] See paragraph at the end of the paper regarding supplementary material.

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[22] Endocyclic torsion angles, $\omega_{ij}(°)$, about the bonds between atoms i and j follow: $\omega_{1,2}$ 15, $\omega_{2,7}$ −15, $\omega_{7,8}$ 11, $\omega_{8,13}$ −2, $\omega_{13,1}$ −8 in ring B; $\omega_{4,5}$ 22, $\omega_{5,6}$ −33, $\omega_{6,7}$ 32, $\omega_{7,21}$ −19, $\omega_{21,4}$ −1 in ring C; $\omega_{3,4}$ 48, $\omega_{4,21}$ 8, $\omega_{21,20}$ −38, $\omega_{20,15}$ 13, $\omega_{15,14}$ 37, $\omega_{14,3}$ −69 in ring D; $\omega_{2,16}$ −8, $\omega_{16,17}$ −39, $\omega_{17,20}$ 59, $\omega_{20,21}$ −32, $\omega_{21,7}$ −12, $\omega_{7,2}$ 36 in ring E; $\omega_{15,20}$ 5, $\omega_{20,19}$ 20, $\omega_{19,18}$ −40, $\omega_{18,24}$ 44, $\omega_{24,15}$ −31 involving C(18), and $\omega_{15,20}$ 5, $\omega_{20,19}$ −24, $\omega_{19,18''}$ 35, $\omega_{18'',24}$ −32, $\omega_{24,15}$ 15 involving C(18″) in ring F; $\omega_{1',2'}$ 24, $\omega_{2',7'}$ −20, $\omega_{7',8'}$ 10, $\omega_{8',13'}$ 5, $\omega_{13',1'}$ −19 in ring B′; $\omega_{2',7'}$ −20, $\omega_{7',6'}$ 37, $\omega_{6',5'}$ −64, $\omega_{5',4'}$ 73, $\omega_{4',21'}$ −53, $\omega_{21',2'}$ 27 in ring C′; $\omega_{7',4'}$ −70, $\omega_{4',21'}$ 66, $\omega_{21',20'}$ −48, $\omega_{20',15'}$ 36, $\omega_{15',14'}$ −39, $\omega_{14',3'}$ 54 in ring D′; $\omega_{2',16'}$ 0, $\omega_{16',17'}$ −25, $\omega_{17',20'}$ 41, $\omega_{20',21'}$ −41, $\omega_{21',2'}$ 26 in ring E′; $\omega_{15',20'}$ 37, $\omega_{20',19'}$ −32, $\omega_{19',18'}$ 16, $\omega_{18',24'}$ 8, $\omega_{24',15'}$ −29 in ring F′; $\omega_{2',7'}$ −22, $\omega_{7',14}$ −39, $\omega_{14,22'}$ −42, $\omega_{22',16'}$ 28, $\omega_{16',2'}$ −3 in ring G′.

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