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Synthesis of Vinca Alkaloids and Related Compounds LX[1]. A Simple Transformation of Apovincamine into Vincamine**

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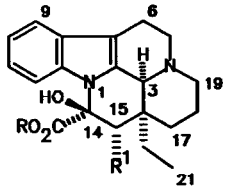
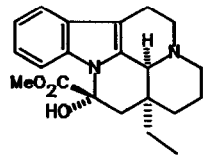
Abstract: *The 15α-chloro-vincamine derivative* **2** *was prepared and proved to be key intermediate of a two-step transformation of apovincamine into vincamine. The structure of* **2** *was established via detailed NMR and X-ray investigations.*

The transformation of (+)-vincamine (**1**) or (-)-epivincamine (**5**) into (+)-apovincamine (**3**) can be achieved in a straightforward way via various methods[2]. The reverse process, however, requires more delicacy, and up until now only three such methods have been published[3], all of them more or less tedious in practice.



	R	R^1
1	Me	H
2	Me	Cl
6	Et	Cl



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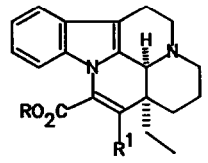


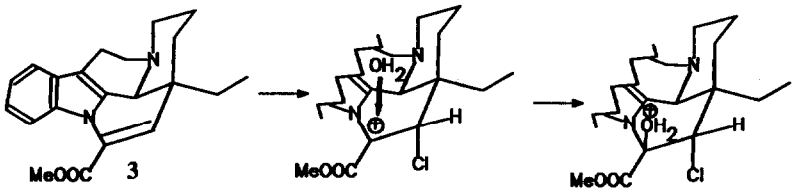
	R	R^1
3	Me	H
4	Me	Cl
7	Et	H

Since apovincaminic acid esters are easily available through total synthesis[4], their efficient conversion into (+)-vincamine is a goal of considerable attraction. Here we describe a convenient, two-step method for the transformation of **3** into **1**, involving addition of the elements of HOCl and subsequent catalytic reduction.

Lewin and Poisson[3b] reported that when attempting hypohalogenide addition onto **3** in aqueous solution, they obtained a mixture of different products which was not studied further. We have found, however, that when (+)-apovincamine (**3**) was dissolved in concentrated hydrochloric acid and treated with aqueous solution of sodium nitrite, the crystalline HCl salt of the 15α-chloro derivative **2** had formed after 15-20 min. in 76 % yield with no other isomers being isolable or detectable.

** *We dedicate this paper to Professor Gábor Fodor on the occasion of his 75th birthday.*

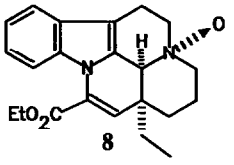
The very high regio- and stereoselectivity of the reaction is remarkable. Assuming an HOCl addition one would rationalize this selectivity by following the usual pattern of the generally accepted mechanism:



Accordingly, in the first step the chloro cation attacks at C(15) and after formation of a carbocation, in the second step a molecule of water attacks the quasi-planar cation from the β face. Selective formation of the vincamine-type configuration at C(14) may be attributed to an anomeric effect[5]. Finally, deprotonation gives rise to **2**. However, some experimental observations seem to contradict this reaction sequence.

From the foregoing mechanism one may conclude that using HOCl as reactant instead of the HCl + $NaNO_2$ system would be appropriate, and should afford the same result (**3** → **2**). However, when HOCl was applied as a reaction partner in acidic medium, or a combination of hydrochloric acid and an oxidizing agent (e.g. H_2O_2) was used, no halohydrin **2** could be isolated, only polyhalogenated products were detected. Consequently it is quite possible that a different reaction sequence is involved when the HCl + $NaNO_2$ system is applied.

Investigating further the said transformation, another, unique procedure for obtaining 15α-chloro-vincamines was found. When the N-oxide (**8**)[6] was reacted with thionyl chloride in benzene for 24 h at room temperature, **6** was obtained in 30 % yield after work up. The presence of the N-oxide function proved to be imperative for this process. It is worthy of note that **8** is stable in cc. hydrochloric acid. Taking account of the above experimental results, it is clear that further studies of the reaction sequence are required for putting forward a plausible mechanism with regard to the highly selective chlorohydrine formation. The investigation of the reaction conditions relating to the formation of the 15α-chloro-vincamines will be further pursued.



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It is noted that (+)-vincamine (**1**) also gave the chloro derivative **2** (80 %) when **1** was reacted according to the above procedure (HCl + $NaNO_2$). With this route the first step probably involves dehydration of **1** into **3**. This assumption is substantiated by the fact that under the same reaction conditions 14-epivincamine (**5**) also converted into **2**. Upon carrying out the above reaction without sodium nitrite, only dehydration (**1** → **3**) occurred.

The chloro compound **2** can be conveniently transformed into the appropriate dehalogenated derivative (**1**) by hydrogenolysis (H_2, Pd/C, r.t., in MeOH) in 75-85 % yield and without the formation of the C-14 epimer **5**.

Although the stereoelectronic requirements for water elimination in **2** are clearly not ideal, its treatment with acid (p-$MeSO_3H$, benzene, reflux, 2h) afforded the unsaturated chloro derivative (**4**) in 85 % yield. The easy dehydration of **2** into **4** could be thought of as being indicative of an antiperiplanar arrangement for C(14)-OH and H-15, as opposed to the found *cis* relationship between them. This observation added special significance to the unambiguous verification of the stereostructure of **2** as detailed below.

When starting from **2**, many unusual reactions have been observed which will be presented in a subsequent paper.

Structure determinations.

NMR spectroscopy. The structures of compounds **2** and **4** were first deduced from detailed ^{1}H and ^{13}C NMR studies. ^{1}H and ^{13}C chemical shifts are collected in Table 1 and Table 2, respectively. For the sake of completeness and comparison, we have also included the relevant ^{1}H data for **1**, **3**, and **5** in Table 1 and the ^{13}C assignments for compounds **1** and **3** in Table 2. For each of these compounds the assignments presented here were secured by the concerted use of 2D ^{1}H-^{1}H and ^{13}C-^{1}H correlation experiments and homonuclear 1D NOE measurements (see also the $^{13}C\{^{1}H\}$ NOEs for **2** in Table 2). It is noted that ^{13}C assignments for **1** and **5** were reported earlier[7], and for **7** and **8** ^{13}C chemical shifts are given in ref. 6. Elaborate NMR data for various indole compounds containing the eburnane skeleton have been published before[8]. However, our computer-aided literature search failed to locate any detailed high-field ^{1}H NMR assignments, such as given in Table 1, for the known compounds **1**, **3** and **2**.[9] Some of the most informative $^{1}H\{^{1}H\}$ NOEs for compounds **1** - **4** are listed in Table 3.

For the 15α-chloro derivative **2** several pieces of evidence readily establish the configuration at C(15): Most importantly, irradiation of H-15 gave an NOE into H_e-17, while no NOE connection was detected between H-15 and H-3, which assignes a β position to H-15 (see Fig. 2 for a perspective view of **2**). As compared to vincamine (**1**), in **2** C(3) is shifted upfield by δ -2.8 ppm as a result of a C(15)α-Cl $\leftrightarrow$ C(3)H γ_{gauche} steric interaction. Futhermore, the C(15)α-Cl exerts a γ_{gauche} upfield shift of -4.4 ppm on C(20) and a γ_{anti} effect on C(17) ($\Delta\delta$ = -1.3 ppm). It should be noted, however, that the $\delta_{C(3)}$ and $\delta_{C(17)}$ values may also be affected by γ-steric interactions with the C(21)H_3 group. For this reason, the

Table 1. ^{1}H Chemical Shifts for Compounds **1** - **5**.

	1	**2**	**3**	**4**	**5**
Proton					
H-3	3.91(s)[d]	4.18(s)[d]	4.12(s)[d]	4.40(s)[d]	3.78(s)[d]
H_a-5	3.31-3.38(m)[a]	3.29-3.41(m)[a]	3.22(ddd)	3.17(ddd)	3.17(ddd)
H_e-5	3.31-3.38(m)[a]	3.29-3.41(m)[a]	3.33(ddd)	3.28(ddd)	3.26(ddd)
Hα-6	2.44-2.64(m)[b]	2.56-2.68(m)[b]	2.47(dddd)	2.43(dddd)	2.45-2.60(m)[a]
Hβ-6	2.98(m)	2.99(m)	3.00(dddd)	2.91(dddd)	2.96(dddd)
H-9	7.48(m)	7.50(m)	7.45(m)	7.38(m)	7.46(m)
H-10,11	7.06-7.15(m)[c]	7.12-7.19(m)	7.08-7.19(m)	7.04-7.12(m)	7.07-7.15(m)
H-12	7.06-7.15(m)[c]	7.03(m)	7.22(m)	6.91(m)	7.30(m)
H-15	2.22(d)[Hα-15]	-	6.13(s)	-	1.98(d)[Hα-15]
	2.11(d)[Hβ-15]	4.30(s)[Hβ-15]		7.38(m)	2.57(d)[Hβ-15]
H_a-17	1.68(m)	1.68(m)	0.99(td)	1.19(td)	1.17-1.35(m)[b]
H_e-17	1.47(m)	1.56(m)	1.49(ddd)	1.65(m)	1.17-1.35(m)[b]
H_a-18	1.72(m)	1.80(m)	1.69(ddddd)	1.72(m)	1.67(m)
H_e-18	1.38(m)	1.37(m)	1.38(ddddd)	1.41(m)	1.17-1.35(m)[b]
H_a-19	2.44-2.64(m)[b]	2.44(m)	2.57-2.64(m)[a]	2.50-2.66(m)[a]	2.45-2.60(m)[a]
H_e-19	2.44-2.64(m)[b]	2.56-2.68(m)[b]	2.57-2.64(m)[a]	2.50-2.66(m)[a]	2.45-2.60(m)[a]
H_x-20	1.45(dq)	1.84(dq)	1.80-2.00(m)[b]	2.26(dq)	1.38(dq)
H_y-20	2.24(dq)	2.48(dq)	1.80-2.00(m)[b]	1.68(dq)	2.12(dq)
H_3-21	0.90(t)	0.93(t)	1.00(t)	0.98(t)	0.87(t)
OMe	3.82(s)	3.85(s)	3.93(s)	3.96(s)	3.71(s)
OH	4.66(s)	4.56(s)	-	-	4.40(s)

[a,b,c] Like superscripts denote overlapping signals. [d] Broadened by long-range couplings to H_2-6 (homoallylic) and H_e-17,19 ('W').

Table 2. ^{13}C Chemical Shifts for Compounds 1 - 4.

Carbon	1	2	3	4
C(2)	131.4	129.9	130.9	128.6[a]
C(3)	59.1	56.3	55.6	53.0
C(5)	50.9	50.8	51.3	51.8
C(6)	16.8	16.8	16.2	16.2
C(7)	105.9	106.7	108.6	108.8
C(8)	129.0	129.0	129.0	128.7[a]
C(9)	118.4	118.6	118.1	118.6
C(10)	120.2	120.6	120.1	120.7
C(11)	121.6	121.8	121.8	122.5
C(12)	110.3	111.6	112.3	109.8
C(13)	134.1	134.8	133.9	133.1[a]
C(14)	81.9	86.3	128.0	124.2
C(15)	44.4	66.9	128.2	126.3
C(16)	35.0	40.6	37.6	43.2
C(17)	25.1	23.8	28.5	31.0
C(18)	20.8	20.8	20.2	20.8
C(19)	44.5	44.5	44.8	44.9
C(20)	28.9	24.5	27.2	24.9
C(21)	7.6	6.5	8.6	9.4
C=O	174.4	172.5	163.8	163.5
OMe	54.4	53.8	52.4	53.3

[a] Assignments confirmed via selective $^{13}C\{^1H\}$ measurements by irradiating H-3, H-9 and H-12, respectively.

interpretation of these ^{13}C shift differences between **1** and **2** as being indicative of the α position of the C(15)-Cl in **2** is justifiable only upon assuming that the rotameric population distribution about the C(16)-C(20) bond of the C(16)-Et group is not perturbed significantly when going from **1** to **2**. (This issue will be taken up in more detail below). The one point where our NMR investigations fell short of giving unambiguous information was the determination of the configuration of C(14) in **2**, wherefore an X-ray study of **2** was undertaken (see below).

Several chemical shift differences in Tables 1 and 2 stand out as being worth reflecting on. In **4**, as a result of the introduction of the Cl atom, C(20), C(3) and C(17) are shifted -2.3, -2.6 and +2.5 ppm, respectively, from their values in **3**. While the effect on C(20) clearly stems from the Cl ⇔ C(20)H_2 γ-interaction, the shifts on C(17) and C(3) are somewhat

Table 3. Some of the ^1H-^1H NOE Connectivities for Compounds 1 - 4.

Compound	*irr. H.*	*Observed Enhancement* H_x-20	H_y-20	H_3-21	H_c-17	H-3	other
1[c]	H-3	3.5%	0.7%	1.4%	-	*	H_α-15(3.7%);H_a-5(4.6%)
	H_3-21	3.2%[a]	2.8%[b]	*	3.2%[a]	1%	H_β-15(1.6%);H_α-15(2.8%)[b]
2	H-3	5.9%	~1%	-	-	*	H_a-5(4.6%)
	H_3-21	2.7%	2.4%	*	2.0%	-	H-15(4.6%)
	H-15	-	-	5.4%	2.5%	-	OH(4.1%)
3	H-3	3.8%[a]	3.8%[a]	3.7%	-	*	H_a-5(4.3%)
	H_3-21 (+Ha-17)	3.9%[b]	3.9%[b]	*	5.1%	2.4%	H-15(3.4%)
4	H-3	1.8%	-	9.3%	-	*	H_a-5(4.6%)
	H_3-21	5.0%	5.0%	*	-	5.8%	

[a,b] For each compound like superscripts depict overlapping signals that both contribute to the measured enhancement. [c] For **5** analogous enhancements were of the same intensity as for **1** within experimental error.

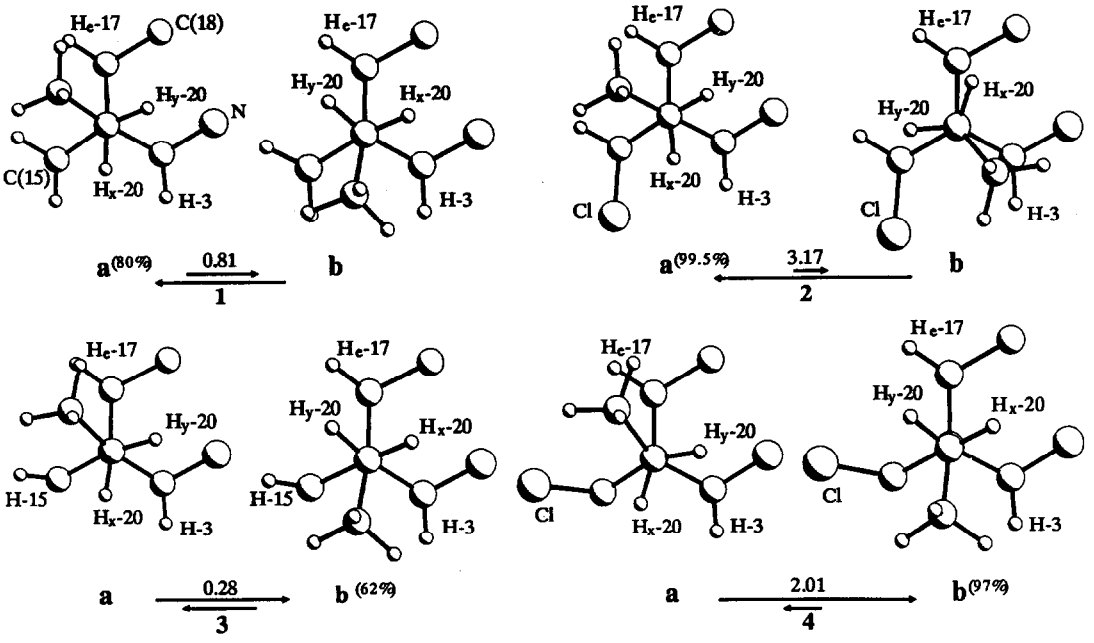

Fig 1. MM2 energy-minimized representations, as generated by the PLUTO program, of the two most likely staggered rotamers of the C(16)-ethyl group in compounds **1-4**. The calculated energy differences (in kcal/mole above the arrows) between the two rotameric forms, together with the approximate percentages of the main conformations at 24°C, are also shown.

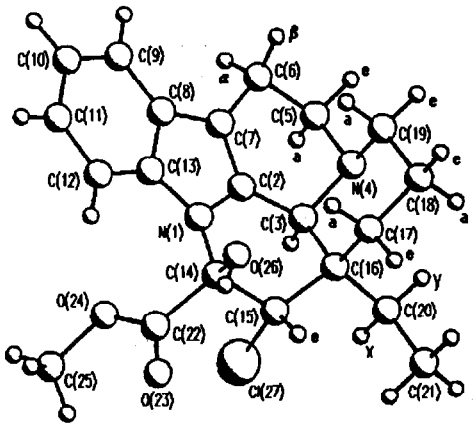

Fig 2. An X-ray determined perspective view of compound **2** showing the atomic labelling.

inconsistent with those expected from the γ-shift increments for Cl[10]. Therefore, with reference to the remarks made on the C(20)-Et group above, we attribute these shift differences between **4** and **3** as being at least partly due to a substantial difference in the conformational equilibrium about the C(16)-C(20) bond. Indeed, this observation prompted us to take a closer look at this aspect of the structures of compounds **1** - **4** by evaluating the relevant NOE contacts (Table 3) in these molecules.

In general, the intensity of the H-3--H_3-21 NOE connection provides the most sensitive and reliable information on the conformational characteristics of the C(16)-Et group. In addition, the enhancements observed on the H_2-20 protons upon irradiating H-3, together with those measured on H_e-17 upon

saturating H_3-21, are also good indicators in this regard. (Such comparisons among these molecules are reasonable on account of the relaxationally similar environments of the protons involved). The most important staggered rotamers about the C(16)-C(20) bond are illustrated in Fig. 1. The third rotameric form in which C(21)H_3 intersects C(17) and C(3) may be safely ignored due to the severe N(4)-lone-pair ⇔ C(21)H_3 and H_a-18 ⇔ C(21)H_3 steric strains associated with this conformation for each of these compounds. This assumption is experimentally supported by the lack of NOE connection between the H_a-18 and the C(21)H_3 protons for each of these compounds, and MM2 molecular mechanics calculations[11] which assign an insignificant population to the third rotameric form. The diastereotopic H_2-20 protons are distinguished as H_x-20 and H_y-20 as depicted in Fig. 1 and Fig. 2. H_x-20 and H_y-20 were identified and assigned in a straightforward way from the NOE results shown in Table 3. These NOE connectivities indicate that when going from **3** into **4**, the dipolar interaction between H-3 and the H_3-21 protons increases significantly, while the H-3--H_y-20 NOE connection is practically lost in **4**. (It should be pointed out that although the information content of the experiment when H_3-21 was irradiated in **3** is limited by the simultaneous saturation of the overlapping H_a-17 signal, clearly the source of the observed enhancement on H-3 can only be H_3-21). All this indicates that while **3** may be characterized by a conformational equilibrium in which both the **'a'** and **'b'** rotamers (Fig. 1) are significantly populated, in **4** the equilibrium is shifted considerably toward the **'b'** form. In fact the absence of NOE into H_c-17 when irradiating the H_3-21 protons suggests a predominant **'b'** rotamer for **4**. (Indeed, model studies show that upon the introduction of the C(15)-chlorine atom the **'a'** rotamer in **4** becomes markedly more congested than **'b'**). In light of these results the observed ^{13}C shift differences between **3** and **4** are are easily understood: The C(17) ⇔ C(21)H_3 γ_{gauche} interaction that is associated with the contribution of the **'a'** rotamer in **3** is absent in **4**, and C(17) is therefore shifted downfield (+2.5 ppm) in **4**. On the other hand, for the same reason C(3) becomes sterically more compressed in **4**, which explains the upfield shift of -2.6 ppm on this carbon.

In the case of vincamine (**1**) the NOE results reflect the presence of an **'a'⇔'b'** equilibrium in which both rotamers contribute, but **'a'** is clearly preferred (cf. NOE data on **3**). On the other hand **2** possesses a virtually homogeneous **'a'** conformation, as indicated by the vanishing of the H_3-21--H-3 NOE contact and the simultaneous increase of the H-3--H_x-20 dipolar interaction. Clearly, this shift toward the **'a'** rotamer is the result of the Cl ⇔ C(21)H_3 steric compression in the **'b'** form of the chloro compound **2** (Fig. 1). Following a similar argument as for the apovincamine compounds **3** and **4**, this ethyl conformational effect alone would be expected to move C(3) slightly downfield upon the Cl substitution of H_α-15 in vincamine (**1** → **2**). However, as was pointed out above, in **2** C(3) is shifted -2.8 ppm upfield, which is probably a result of the combined Cl γ_{gauche} shielding and the ethyl conformational deshielding effect. This upfield shift of C(3) also suggests that in vincamine (**1**) the contribution of the **'a'** conformer is relatively minor.

In conclusion, relative to the two "parent" compounds **1** and **3**, respectively, the Cl subtitution on C(15) shifts the **'a'⇔'b'** equilibrium in the opposite sense: in **2** toward **'a'**, and in **4** toward **'b'**. These conclusions were also verified, and were in good agreement, with MM2 calculations the results of which are depicted in Fig. 1. During the structural elucidation of analogously substituted vincamine derivatives, one must therefore be careful not to ignore the possible effects that these conformational changes may bring about on the relevant ^1H and ^{13}C chemical shifts.

Some further shift differences among these compounds also merit a few brief comments: Compared to **1**, in 14-epivincamine (**5**) H_α-15 is shifted -0.24 ppm upfield and H_β-15 +0.46 ppm downfield. These shifts are in good agreement with the shift increments for axially and equatorially oriented OH in cyclohexane derivatives[12]. It is further noted that in the apovincamine compounds (**3**, **4**) H_a-17 moves significantly upfield from its value in **1** and **2**. Clearly, this is partly due to the loss of the OH ⇔ H_a-17 van der Waals interaction present in **1** and **2** (Fig. 2), and partly to the anisotropic shielding effect of the C(14)=C(15) bond. The former contribution may be demonstrated by the similar loss of the OH ⇔ H_a-17 interaction in the 14-epi compound **5**, where H_a-17 also shows an upfield shift relative to **1**.

X-Ray structure determination of **2**. The crystals of **2** are orthorhombic (M_w = 388.90), space group $P2_12_12_1$ (no.19), a = 8.516(2), b = 4.029(1), c = 6.215(2) Å, V = 1937.3(5) Å^{-3}, Z = 4, D_{calc} = 1.33 g/cm^3, *F(000)* = 824. Intensities were measured from a crystal of 0.23 x 0.15 x 0.20 mm^3 with an Enraf-Nonius CAD-4 diffractometer at room temperature (296±1 K) using graphite monochromatized MoKα radiation (λ = 0.71069 Å) $\omega/s\theta$ scan mode, $2<\theta<25°$ (h: 0→10, k: 0→16, l: 0→19 and their Friedel pairs), scan width (θ): (0.51 + 0.35tanθ). the structure was solved with a direct methods program MULTAN11/82[13] and full-matrix refinement (program CRYSTALS[14]) with anisotropic temperature factors for the non-H atoms and fixed isotropic temperature factor (U = 0.07 Å^2) for the hydroxilic H(25); the rest of the H atoms were treated as riding atoms (H-atom positions calculated to their idealized positions with C-H distance 1.02 Å with fixed U = 0.07 Å^2) using 2480 (Friedel pairs included) reflections (3390 unique reflections, R_{int} = 0.0204) with $I > 3\sigma I$ (from counting statistics) and 248 parameters converged to R = 0.0322 and R_w = 0.0316. The Tukey and Prince weighting scheme was used with six parameters (11.795, -17.816, 14.076, -6.630, 3.038 and -0.448 with the maximum weight of 10000). Scattering factors including anomalous scattering were taken from ref. 15. In the course of isotropic refinement of the positional parameters, an empirical absorption correction (μ = 0.22 cm^{-1}) was calculated with the DIFABS program[16]; minimum and maximum absorption corrections were 0.845 and 1.238. The largest parameter shift/error in the final cycle of refinement was < 0.01; maximum peak height in the final $\Delta\rho$ map was 0.26 e/Å^3. The absolute configuration was determined by refining Flack's enantiopole parameter[17], *x*, using the

Table 4. Fractional Coordinates with E.S.D.-s in Parentheses (x 10^4) and Isotropic Temperature Factors (x10^5) for compound **2** {U_{iso} = [U(11) x U(22) x U(33)]$^{1/3}$}.

Atom	x/a	y/b	z/c	U_{iso}(Å^2)	Atom	x/a	y/b	z/c	U_{iso}(Å^2)
Cl(27)	-8600.4(7)	-1965.7(5)	-2584.8(4)	461	C(25)	-10417(4)	-85(3)	-4141(2)	713
O(23)	-8795(2)	416(1)	-2820(1)	515	H(25)	-3914(37)	-4334(21)	-2369(21)	700
O(24)	-8844(2)	-429(1)	-3978(1)	490	H(1)	-6082	-3041	-3074	700
O(26)	-5574(2)	154(1)	-2832(1)	354	H(2)	-4410	-4057	-3949	700
N(1)	-5871(2)	-1046(1)	-3788(1)	297	H(3)	-2492	-4016	-3751	700
N(4)	-3720(2)	-3161(1)	-2989(1)	313	H(4)	-3494	-3252	-5056	700
C(2)	-5109(3)	-1919(2)	-3738(1)	279	H(5)	-2058	-2722	-4530	700
C(3)	-5171(3)	-2575(2)	-3011(1)	276	H(6)	-3110	-1462	-6030	700
C(5)	-3492(4)	-3621(2)	-3805(1)	375	H(7)	-3804	49	-6610	700
C(6)	-3209(4)	-2923(2)	-4515(2)	426	H(8)	-5335	1158	-5853	700
C(7)	-4231(3)	-2074(2)	-4421(1)	329	H(9)	-6497	739	-4537	700
C(8)	-4403(3)	-1245(2)	-4932(1)	330	H(10)	-6744	-882	-1871	700
C(9)	-3796(4)	-1002(2)	-5702(2)	416	H(11)	-4093	-1147	-1408	700
C(10)	-4183(4)	-127(2)	-6033(2)	472	H(12)	-3762	-954	-2406	700
C(11)	-5144(4)	501(2)	-5602(2)	467	H(13)	-2746	-2641	-1496	700
C(12)	-5774(3)	280(2)	-4843(2)	405	H(14)	-1574	-1749	-1780	700
C(13)	-5407(3)	-612(2)	-4518(1)	316	H(15)	-2091	-2102	-3206	700
C(14)	-6587(3)	-577(2)	-3087(1)	306	H(16)	-1402	-3060	-2718	700
C(15)	-6821(3)	-1310(2)	-2378(2)	319	H(17)	-5039	-3208	-1469	700
C(16)	-5462(3)	-2014(2)	-2203(1)	299	H(18)	-6927	-3041	-1697	700
C(17)	-3963(3)	-1464(2)	-1970(2)	383	H(19)	-6506	-2824	-266	700
C(18)	-2548(3)	-2133(2)	-1934(2)	456	H(20)	-5202	-1969	-462	700
C(19)	-2325(3)	-2599(2)	-2764(2)	373	H(21)	-7089	-1803	-690	700
C(20)	-5916(3)	-2715(2)	-1513(2)	428	H(22)	-10840	-356	-4680	700
C(21)	-6204(5)	-2292(3)	-664(2)	637	H(23)	-11152	-264	-3669	700
C(22)	-8203(3)	-140(2)	-3285(2)	368	H(24)	-10347	640	-4184	700

CRYSTALS program and a value of -0.02(7) was obtained indicating the correct enantiomer. The molecular geometry obtained corresponds with the known (+)-vincamine. Positional parameters with e.s.d.'s and equivalent isotropic temperature factors are given in Table 4. A view of the molecule (program PLUTO[18]) with the labelling scheme is presented in Fig. 2.

EXPERIMENTAL

Mp-s are uncorrected. Optical rotations were recorded in chloroform or methanol at 25 ± 2 °C. IR spectra were taken on a Specord IR 75 spectrometer using KBr pellets. Mass spectra were run on an AEI-MS-902 (70 eV; direct insertion) mass spectrometer. NMR measurements were carried out on a Varian VXR-300 instrument (300 MHz for ^1H and 75 MHz for ^{13}C) at 24 °C in $CDCl_3$. Chemical shifts are given relative to $\delta_{TMS}=0.00$ ppm. The COSY (COSY-90, magnitude mode), HETCOR and NOE experiments were recorded by using the standard spectrometer software package. The HETCOR experiments were run with ^1H decoupling in the F_1 dimension. NOEs were measured in non-degassed samples with 4 s pre-irradiation times. FIDs were exponentially multiplied prior to Fourier transformation (LB = 1 Hz). For the selective $^{13}C\{^1H\}$ NOE measurements the pulse-sequence described by Sanchez-Ferrando[19] was employed, using 8 s pre-irradiation times and a 3 Hz exponential line-broadening before Fourier transformation.

Synthesis

(+)-15α-Chloro-vincamine (2.HCl and 2). A/ from **3**: To a solution of (+)-apovincamine (**3**; 6.7 g; 20 mM) in concentrated hydrochloric acid (70 ml), a solution of sodium nitrite (3.6 g; 50 mM) in water (20 ml) was added dropwise (10-15 min) at 10-15°C, and the mixture was stirred for 15-20 min., then diluted with iced water (80 ml) and the precipitate filtered off and washed with water (3 x 15 ml). The crude product was treated in hot acetone (50 ml), filtered off, washed with acetone (2 x 15 ml) and dried to give **2**.HCl (6.42 g; 75.9 %), mp 214-220 °C.

2.HCl (6.4 g) was dissolved in a mixture of methanol / water (85 ml / 20 ml), the hot solution was cleared with active carbon, filtered and the pH of the filtrate was adjusted to 8 by using concentrated aqueous ammonium hydroxide solution (5 ml). The filtrate was kept in refridgerator overnight. The obtained crystals were filtered off, washed with water (2 x 10 ml), dried to yield **2** (5.6 g; 72.3 %), mp 190-192 °C, $[\alpha]_D=+115.2°$ (c=0.2; $CHCl_3$).

IR: 3450, 1720 cm^{-1}

MS (m/e, %): 391 (8); 390 (37); 389 (32); 388 (100, M^+); 387 (25); 373 (7, M-15); 354 (26), 353 (77, M-35); 352 (43); 351 (14); 341 (5, M-47); 336 (6); 335 (13, M-53); 329 (12, M-59); 324 (6); 232 (24); 320 (6); 318 (14, M-70); 307 (9, M-81); 300 (6, M-88); 295 (7); 294 (18, M-94); 293 (16); 282 (12, M-106); 266 (16); 265 (35, M-123); 264 (21); 263 (14); 253 (24); 252 (48, M-136); 251 (20); 237 (10); 236 (7); 225 (8); 224 (40); 209 (8); 195 (5); 194 (9); 180 (13); 168 (8); 167 (8); 153 (9); 147 (7); 133 (6); 132 (10).

B/ from **1**: To a solution of (-)-vincamine (**1**; 28.3g; 80 mM) in concentrated HCl (340 ml), a solution of sodium nitrite (14 g; 0.2 M) in water (980 ml) was added dropwise (10-15 min) at 10-15 °C, and the mixture was stirred for 15-20 min. The mixture was diluted with iced water (300 ml) and the precipitate was filtered off and washed with water (3 x 50 ml). The crude product was treated in hot acetone (200 ml), filtered off, washed with acetone (2 x 50 ml) and dried to give **2**.HCl (27 g; 79.8 %).

C/ from **3** without isolation of **2**: To a solution of **3** (6.72 g; 20 mM) in concentrated HCl (70 ml), a solution of sodium nitrite (3.6 g; 52 mM) in water (20 ml) was added according to the above procedure. After 15 min. chloroform (250 ml) and broken ice (200 g) were added. The mixture was alkalized to pH 8 by adding concentrated aqueous ammonium hydroxide solution (70 ml). The organic layer was separated, the aqueous phase was extracted with chloroform (2 x 100 ml), and the combined organic phase was washed with water (3 x 100 ml) and dried (Na_2SO_4). The filtrate was evaporated *in vacuo* and the residue (5.6 g; 72.3 %) was crystallized from methanol to give **2**.

(+)-15α-Chloro-vincaminic acid ethyl ester (**6**). The treatment of **7** (20 g; 57 mM) according to procedure "A" [HCl (140 ml), sodium nitrite (10 g / water (40 ml))] afforded **6**.HCl (14.4 g; 57.4 %), mp 204-207 °C (from ethanol).

After basification **6**.HCl yielded **6** (12.8 g; 55 %), mp 194-196 °C, $[\alpha]_D = +101.7°$ (c =0.2; $CHCl_3$).

IR: 3440, 1715 cm^{-1}.

MS (m/e, %): 404 (35), 403 (29), 402 (100 M^+), 401 (19, M-1), 384 (1.7, M-18), 373 (9, M-29), 367 (74, M-Cl), 355 (6, M-47), 349 (17, 367-18), 337 (7), 332 (9, M-70), 329 (19, M-73), 321 (9), 293 (11), 280 (7), 265 (18), 264 (16), 263 (12), 253 (22), 252 (53), 251 (12), 237 (12), 224 (24), 223 (7), 222 (6), 209 (7), 180 (9).

^1H NMR ($CDCl_3$), δ: 0.92 (3H, t, H_3-21); 1.25 (3H, t, OCH_2CH_3); 1.37 (1H, m, H_e-18); 1.55 (1H, m, H_e-17); 1.68 (1H, m, H_a-17); 1.80 (1H, m, H_a-18); 1.84 (1H, dq, H_x-20); 2.44 (1H, m, H_a-19); 2.48 (1H, dq, H_y-20); 2.56-2.68 (2H, m, H_α-6, H_e-19); 2.99, (1H, m, H_β-6); 3.29-3.41 (2H, m, H_2-5); 4.15 (1H, s, H-3); 4.29 (1H, s, H-15); 4.29-4.45 (2H, m, OCH_2CH_3); 4.48 (1H, s, OH); 7.05 (1H, m, H-12); 7.09-7.18 (2H, m, H-10, H-11); 7.49 (1H, m, H-9).

Reaction of apovincaminic acid ethyl ester N-oxide (**8**) *with thionyl chloride*. **8** (1.08 g; 3 mM) was dissolved in benzene (30 ml) at room temp. and thionyl chloride (0.4 ml; 6 mM) was added and the mixture was stirred for 24 h. The mixture was evaporated to dryness *in vacuo* and the residue dissolved in a mixture of ethyl acetate / water (60 ml / 15 ml) and alkalized to pH 8 by adding aqueous ammonium hydroxide solution (1 ml). The organic layer was separated and washed with water (2 x 10 ml), dried (Na_2SO_4), filtered and the filtrate was evaporated in reduced pressure. The residue (0.96 g) was chromatographed on silica (30 g; eluent: chloroform, 200 ml; chloroform / methanol 9 / 1, 200 ml). The solvent was evaporated under reduced pressure and the residue was crystallized from acetone to give **6** (0.35 g; 29.6 %).

(-)-15-Chloro-apovincamine (**4**). A mixture containing **2** (0.77 g; 2 mM) and p-toloene sulphonic acid monohydrate (0.95 g; 5 mM) in benzene (30 ml) was refluxed using a water-separating device for 2 h and then cooled. After adding 10 ml of water, the pH was adjusted to 8 by using concentrated aqueous ammonium hydroxide solution (1 ml). After extraction the organic phase was washed with water (2 x 10 ml), dried (Na_2SO_4), filtered and the filtrate was evaporated under reduced pressure. The residue was crystallized from methanol (5 ml) to afford **4** (0.62 g; 84.9 %), mp 162-166 °C, $[\alpha]_D = -27.4°$ (c =0.2; $CHCl_3$).

IR: 3480, 1710 cm^{-1}.

Catalytic reduction of **2**. **2** (0.38 g; 1 mM) was dissolved in a mixture of methanol / triethylamine (20 ml / 2 ml) and potassium carbonate (0.5 g) and 10 % Pd/C catalyst (about 50 mg) was added and the mixture was hydrogenated according to the above procedure. After 6 h the catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in a mixture of chloroform / water (30 ml / 10 ml). After extraction the organic phase was washed with water 2 x 5 ml), dried (Na_2SO_4), filtered and the filtrate was evaporated under reduced pressure. The residue (0.3 g; 84.7 %) was crystallized from acetone to give **1**. This substance was identical in all respects examined with the natural compound.

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