Pergamon

Tetrahedron Vol. 51, No. 33, pp. 9103-9118, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00508-0

Synthesis of Vinca Alkaloids and Related Compounds LXXVII[1]. Dimers of Criocerine

István Moldvai[a], Csaba Szántay Jr.[b]*, Gábor Tárkányi[b] and Csaba Szántay[a]*

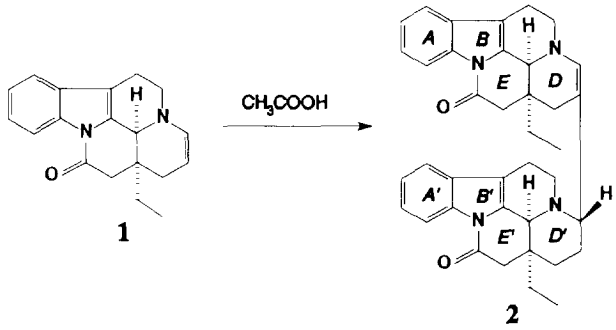
[a]Central Research Institute for Chemistry of the Hungarian Academy of Sciences, H-1525 Budapest, POB. 17, Hungary

[b]Chemical Works of Gedeon Richter, Spectroscopic Research Department, H-1475 Budapest, POB. 27, Hungary

Abstract: Criocerine analogues of type **3**, when dissolved in acetic acid, form the novel dimeric compounds of type **6** whose structures were thoroughly investigated by NMR spectroscopic methods.

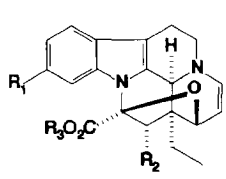
Previously we reported that 18,19-dehydro-vincamone **1**, when treated with acetic acid, gives the dimeric compound **2**.[2]

We have been interested in exploring this reaction with other eburnane derivatives bearing an enamine

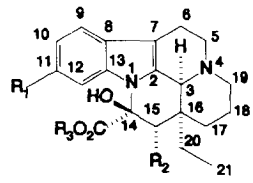


1 **2**

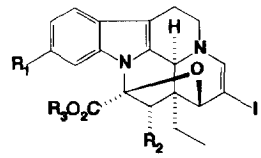
function in ring *D*. One candidate that suggested itself for this process was (-)-criocerine **3a**, whose efficient preparation from (+)-vincamine **4a** has also been described recently.[3a,b]



3a-e



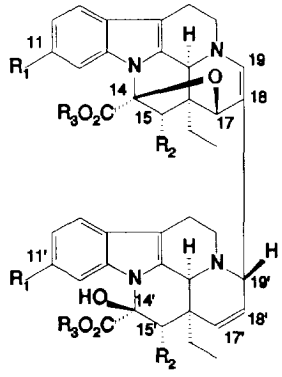
4a-e



5a-e

	R_1	R_2	R_3
a	H	H	Me
b	NO_2	H	Me
c	Br	H	Me
d	H	Cl	Me
e	H	Cl	Et

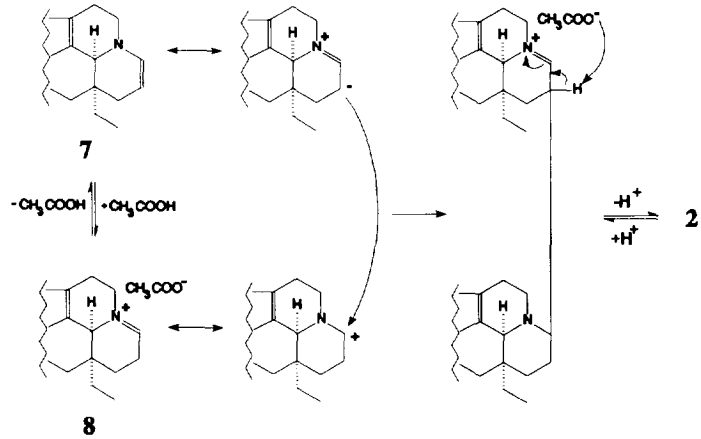
In examining the reaction of **3a** with acids, **3a** was dissolved in acetic acid at room temperature. On working up the reaction mixture after 24 h with concentrated aqueous ammonium hydroxide solution, the novel dimer derivative **6a** was obtained in 86 % yield.



6a-e

A few criocerine analogues were also prepared. Vincamine derivatives **4b**[4], **4c**[5] and **4d-e**[6] were transformed into iodo-compounds **5b-e** with the aid of iodine in a straightforward way, then the iodo-derivatives were reduced into **3b-e** in good yields. The reduction was selective for the halogen derivatives **5c-5e**, and the iodo-enamine function could be reduced without injury to the aromatic bromo- or aliphatic chloro-group. The other substituted criocerine-analogues **3b-e** gave the dimers **6b-e** in good yields (**6b**: 67%, **6c**: 75%, **6d**: 83%, **6e**: 80%). Neither the presence of the substituents in ring *A* and ring *E*, nor the ester group has any significant influence on the dimerization reaction.

It is interesting to compare the mechanisms leading to the different dimers **2** and **6**. Earlier we proposed[2] that the formation of **2** involves an enamine (**7**) ⇄ iminium salt (**8**) equilibrium in the presence of acetic acid.

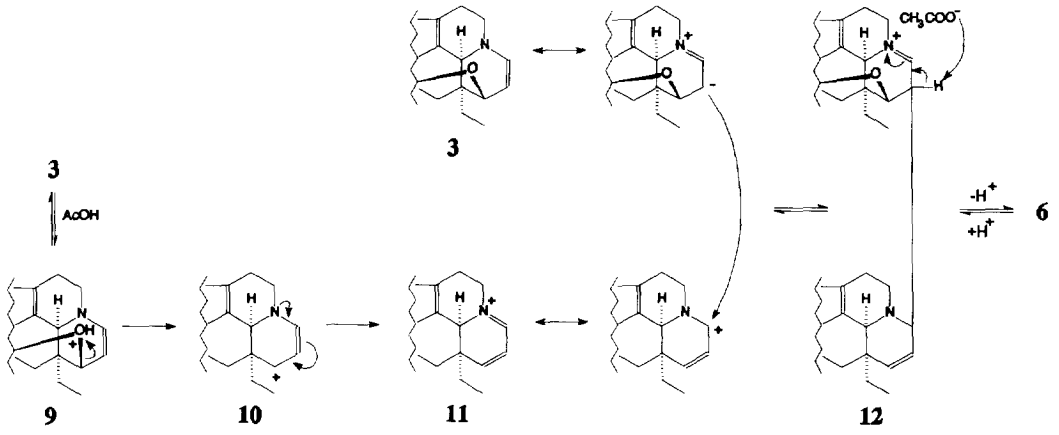


7

8

2

The dimerization process giving rise to **6** can be rationalized in analogy to that leading to **2**, but it is likely that in the initial step the protonation facilitates cleavage of the tetrahydrofuranyl ring. The resulting carbocation **10** rearranges into the more stable "ene-iminium" **11**. In the dimerization step the electrophilic **11** and the nucleophilic enamine-type **3** react to give the dimeric iminium **12** which is then stabilized by deprotonation forming the end product **6**.

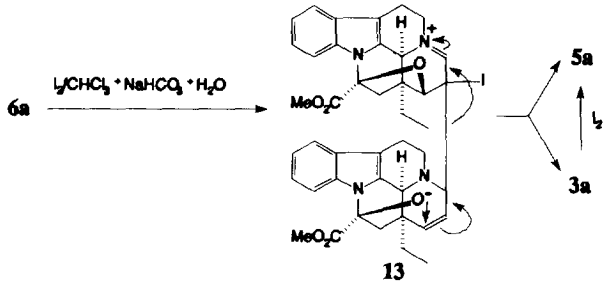


Regarding this hypothesis it is noted that the tetrahydrofuranyl ring in the criocerine-like unit of the dimer end-product **6** remains intact in the acidic reaction mixture. According to one possible explanation the transformation **9**→**10** is not a separate step but synchronized by the attack of **3**.

Dimer **6a** was also prepared in another way starting directly from the iodo-derivative **5a**. Dissolving **5a** in acetic acid and allowing it to react with tin dust at reflux temperature for 5 min, dimer **6a** was obtained in 83 % yield. With this procedure probably **3a** first is formed, which then immediately dimerizes into **6a**.

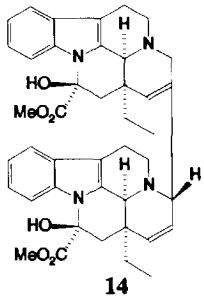
We attempted to re-cyclise the vincamine-like part of **6a** into an oxygen bridge using a procedure already successfully applied for the "monomer".[3a,b] However, iodo-criocerine **5a** was obtained in 84% yield instead of the expected dimer with two tetrahydrofuranyl-rings. We assume that, in the first step, the enamine unit of **6a** is iodinated forming iminium **13**. The C(18)-C(19)' bond then opens up to form **5a** and **3a**. Finally, **3a** transforms into the iodinated product **5a**.

On investigating other reactions of **6a**, new dimer derivatives were obtained by reduction. When **6a** was allowed to react with $NaBH_3CN$ in the presence of CF_3CO_2H in a mixture of THF and MeOH for 5 min. at

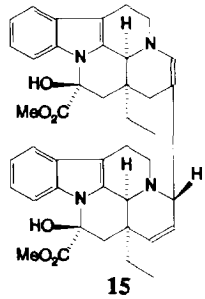


room temperetaure, dimer **14** was obtained (77%). On the other hand, hydrogenation of **6a** in the presence of palladium catalyst in DMF for 3 h at room temperature gave dimer **15** selectively in 70% yield.

The formation of **14** can be rationalized by the usual pattern of the generally accepted mechanism for the reduction of enamines[7], but the site of the selective protonation in the first step is unusual. In the initial step the tetrahydrofuranyl-ring of **6a** is protonated to form oxonium ion **16**. During regeneration of the hydroxyl group, carbocation **17** is formed which then rearranges into the conjugated iminium **18**. Finally **18** is reduced in the customary way yielding the end-product **14**.

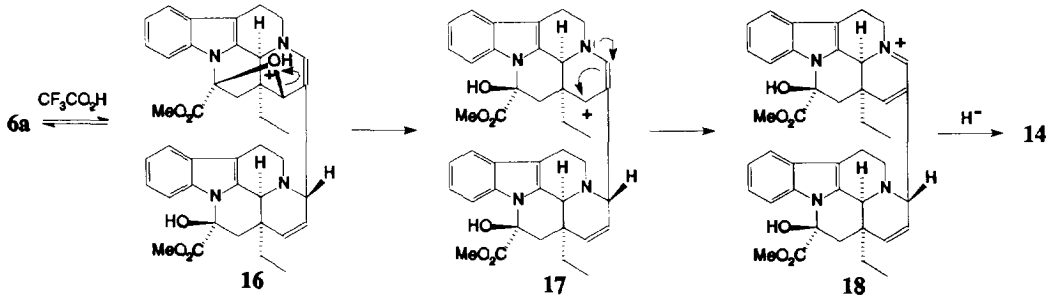


14



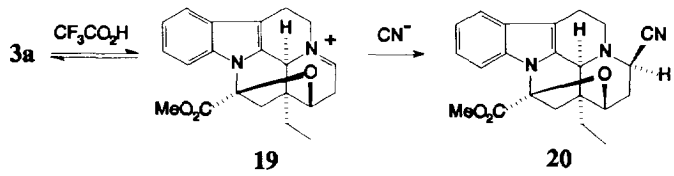
15

In the case of the catalytic hydrogenation leading to **15**, only the carbon-oxygen bond of **6a** participates in the reduction; the double bond C(17)'=C(18)' and the enamine part C(18)-C(19) remain intact. In the absence of acid the isomerization of the double bond does not occur in **6a**.



16 **17** **18**

To obtain further insight into these processes **3a** was allowed to react with cyanide ion in trifluoroacetic acid. In this case no dimerization occurred and the "monomer" aminonitrile **20** was isolated in 14% yield.



19 **20**

Structure elucidation

All the above structures were verified by high-field NMR measurements. The main NMR spectroscopic properties of the starting materials **1-4** had been reported earlier,[2,4,5,6] and those of compounds **6**, **14**, **15** and **20** are discussed below. ^1H and ^{13}C NMR data for compounds **6a**, **6d**, **14**, **15** and **20** are collected in Tables 1 and 2. For all other dimeric compounds NMR characterization is given in the experimental section.

Compound 6a. The structure of **6a** was fully resolved by one and two-dimensional NMR methods (COSY, HETCOR, $^1H\{^1H\}$ NOE difference). In the ^{13}C spectrum the quaternary carbons at δ 91.3 (typical value for C(14) in criocerine analogues[3]) and δ 82.1 (typical value for C(14) in vincamine analogues[6]) immediately suggest that one of the units in dimer **6a** has retained the criocerine-like structure of **3a**, and in the other unit cleavage of the O—C(17') has led to a vincamine-like (**4a**) structure; this accords with the appearance of an OH signal at δ 3.60 in the ^1H spectrum. The presence of the ring-*D* enamine moiety in the *criocerine unit* is evident from the singlet due to H-19 in the ^1H spectrum as well as the downfield shift of C(6) to δ 21.3, since the ensuing flattening of ring *D* eliminates the C(6)-C(19) γ_{gauche} interaction which is present in the vincamine half [$\delta_{C(6)}$=16.7]. The location of H-19 was corroborated by its strong NOE connection to the H_2-5 protons. All the remaining protons could then be readily identified in the criocerine unit by following the scalar H-H coupling network (COSY) and measured NOE connectivities. (In geminal pairs the α and β protons were distinguished on the basis of their coupling patterns and NOE connections). Assignment of the proton-bearing carbons follows in a straightforward way from the 2D C-H correlation experiment (HETCOR). Since H-17 can be unambiguously identified in the ^1H and ^{13}C spectra, it is clear that ring *D* is substituted on C(18). This is also indicated by the coupling pattern of H-19 ($J < 2$Hz) and the negligible NOE between H-17 and H-19. In the *vincamine half*, all the ^1H spin systems and carbon signals are readily identified in the same manner; these are, with the exception of ring *D'* possessing a double bond, characteristic of the vincamine-like structure.[6] Ring *D'* is substituted at C(19'), i.e. on a carbon next to N(4) as indicated by the δ 55.7 ppm chemical shift of the C(19') methine carbon as well as the H-19'—H_2-5' NOE connection. The location of the double bond is verified by the H-19'—H-18' and H-17'—H_2-15', H_3-21' NOEs. It follows that the fusion of the two indole units occurred at C(18)-C(19)'. Steric considerations suggest that H-19' in the vincamine half must be axially (i.e. β) oriented. Experimentally this is indicated by the presence of an NOE between H-19' and H_β-6'. Further, in **6a** the values $^1J_{C(3')H}$=139 Hz, $^1J_{C(19')H}$=131 Hz were measured. Since the direct CH coupling $^1J_{CH}$ in a -N-CH- moiety is generally 6-8 Hz smaller in an antiperiplanar arrangement of the N lone pair and the C-H bond than in a synclinal orientation,[8] these values accord with the fact that in ring *D'* H-3' is equatorial, H-19' is axial and the N lone pair is axial.

Our NOE results gave no indication of the existence of any predominant or preferential conformation about the C(18)-C(19)' bond at room temperature.

In **6a** H-17 gave an NOE into only one of the H-20 signals (δ 1.47, ~3 %), while H-3 gave an NOE at only the other H-20 signal (δ 1.68, ~3 %). This is consistent with a) a conformational equilibrium about the C(16)-C(20) bond in which only conformers I and/or II contribute significantly with no appreciable population of III; b) the predominant presence of III with practically no contribution from I and II. However, H_3-21 gave significant NOEs into H-17, H-3, H_α-15 and H_β-15 and thus the latter option can be rejected. It also follows that I and II both contribute with comparable weights in the equilibrium. III does not participate appreciably probably because its steric energy is increased by the interaction of H_3-21 with the bulky C(18) substituent (i.e. the vincamine unit). From this the assignment of H_x-20 and H_y-20 is clear: the H-17—H_y-20 and H-3—H_x-20

Table 1. ^{1}H Chemical Shifts for Compounds **6a**, **6d**, **14** and **15**.

	6a	**6d**	**14**	**15**
Proton				
H-3	4.36(s)[a]	4.42(s)[a]	4.03(s)[a]	4.02(s)[a]
H_α-5	3.45(m)	3.49(m)	3.34-3.48(m)	3.35(m)
H_β-5	3.62(ddd)	3.66(dt)	3.34-3.48(m)	3.57(dd)
H_α-6	2.58-2.89(m)	2.63-2.81(m)	2.56(m)	2.67(m)
H_β-6	2.58-2.89(m)	2.63-2.81(m)	3.10(m)	2.82(m)
H-9	7.36(m)	7.34-7.41(m)	7.45(m)	7.48(m)
H-10,11	6.92-7.12(m)	6.90-7.21(m)	6.97-7.12(m)	7.01-7.16(m)
H-12	6.99(m)	6.90-7.21(m)	6.97-7.12(m)	7.01-7.16(m)
H_α-15	2.74(d)	-	2.37(d)	2.39(d)
H_β-15	2.37(d)	4.49(s)	2.29(d)	2.19(d)
H-17	4.04(d)[c]	4.14(d)[c]	5.74(s)	1.59(dd) [H_α-17] 2.32(dd) [H_β-19]
H-18	-	-	-	
H-19	5.99(s)[c]	6.06(s)[c]	2.82(dd) [H_α-19] 3.27(dd) [H_β-19]	5.76(d) -
H_x-20	1.68(dq)	1.53-1.85(m)	1.98(dq)[c]	1.44(dq)
H_y-20	1.47(dq)	1.53-1.85(m)	1.65(dq)[c]	1.73(dq)
H-21	1.04(t)	1.04(t)	0.95(t)	0.91(t)
OMe	4.00(s)	4.04(s)	3.83(s)[b]	3.83(s)
OH	-	-	3.90 (br s)	4.57(br s)
H-3'	4.00(s)[a]	4.14(s)[a]	4.03(s)[a]	3.94(s)[a]
H_α-5'	2.58-2.89(m)	2.63-2.81(m)	2.90(m)	2.67(m)
H_β-5'	2.58-2.89(m)	2.85(m)	3.10(m)	2.94(dd)
H_α-6'	2.58-2.89(m)	2.32(m)	2.38(m)	2.35(m)
H_β-6'	2.58-2.89(m)	2.63-2.81(m)	2.87(m)	2.85 (m)
H-9'	7.36(m)	7.34-7.41(m)	7.39(m)	7.42(m)
H-10,11'	6.92-7.12(m)	6.90-7.21(m)	6.97-7.12(m)	7.01-7.16(m)
H-12'	6.94(m)	6.90-7.21(m)	6.97-7.12(m)	7.01-7.16(m)
H_α-15'	2.25(d)	-	2.25(s)	2.26(s)
H_β-15'	2.22(d)	4.45(s)	2.25(s)	2.26(s)
H-17'	5.36(dd)	5.39(dd)	5.50(dd)	5.71(dd)
H-18'	4.92(dd)	4.90(dd)	4.90(dd)	5.24(dd)
H-19'	3.20(t)	3.12(t)	3.29(t)	3.26(t)
H_x-20'	1.87(dq)[c]	1.96-2.12(m)	1.89(dq)[d]	1.90(dq)[c]
H_y-20'	1.55(dq)[c]	1.96-2.12(m)	1.57(dq)[d]	1.52(dq)[c]
H-21'	0.93(t)	0.92(t)	0.94(t)	0.93(t)
OMe'	3.81(s)	3.87(s)	3.81(s)[b]	3.79(s)
OH	3.60(s)	3.09(br s)	3.71 (br s)	3.87(br s)

[a] Broadened by long-range couplings. [b,c,d] Like superscripts denote interchangeable assignments. [e] Small coupling (~ 1 Hz) between H-17 and H-19.

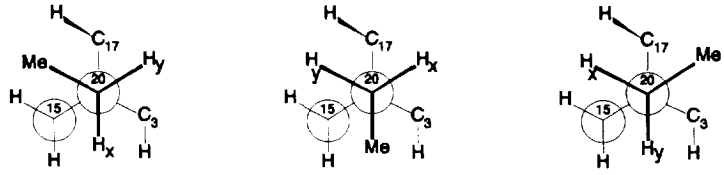
Table 2. ^{13}C Chemical Shifts for Compounds **6a**, **6d**, **14** and **15**.

Carbon	6a	6d	14	15
C(2)	132.1[a]	134.7[a]	131.4[i]	132.8[i]
C(3)	55.1	54.7	57.8	57.1
C(5)	49.7	49.8	49.5	49.6
C(6)	21.3	21.2	16.6	20.4
C(7)	111.7	110.8	106.1[a]	106.6[a]
C(8)	129.1[b]	131.4[b]	129.0[b]	129.0[b]
C(9)	118.0[g]	118.1[g]	118.2	118.3[c]
C(10)	120.2[f]	121.4[f]	120.1[c]	120.1
C(11)	121.5[h]	122.7[h]	121.6	121.4[d]
C(12)	110.5	112.2	110.4	110.4[e]
C(13)	136.3[c]	137.6[c]	137.1	134.0[b]
C(14)	91.3	90.9	82.0	82.2
C(15)	45.1	62.8	43.7	43.6
C(16)	44.2	45.4	37.0[i,j]	34.7[i]
C(17)	79.7	74.9	126.4	24.0
C(18)	112.3[k]	112.1	137.2[j]	111.8[k]
C(19)	135.3	136.3	44.0	129.7
C(20)	24.8	22.8	34.7	29.7
C(21)	9.2	7.5	8.6	7.7
C=O	169.3[e]	167.2[e]	172.7[d]	173.0[g]
OMe	53.1[d]	53.4[d]	53.9	54.2[h]
C(2)'	134.0[a]	134.9[a]	132.0[l]	132.4[l]
C(3)'	58.3	56.1	58.1	57.8
C(5)'	46.3	46.3	46.7	46.0
C(6)'	16.7	16.7	16.3	16.6
C(7)'	106.6	107.6	106.5[a]	106.7[a]
C(8)'	131.3[b]	129.3[b]	129.1[b]	129.2[b]
C(9)'	118.2[g]	118.2[g]	118.2	118.4[c]
C(10)'	121.0[f]	120.6[f]	120.2[c]	120.1
C(11)'	122.4[h]	121.6[h]	121.6	121.6[d]
C(12)'	111.7	112.5	110.4	110.8[e]
C(13)'	138.0[c]	138.3[c]	137.1	134.4[f]
C(14)'	82.2	86.5	82.0	82.2
C(15)'	44.0	65.3	43.7	43.6
C(16)'	36.5	41.2	36.6[l]	36.6[l]
C(17)'	126.7	123.8	128.2	129.1
C(18)'	131.5	132.2	128.8	130.8
C(19)'	55.7	56.0	57.0	56.7
C(20)'	35.1	32.7	35.0	34.7
C(21)'	8.8	7.4	8.6	8.6
C=O'	172.6[e]	169.0[e]	173.1[d]	174.2[g]
OMe'	53.1[d]	53.4[d]	53.9	53.9[h]

[a,b,c,d,e,f,g,h] Like supersripts denote interchangeable assignments. [i,j,k,l] Assignment confirmed by selective $^{13}C\{^1H\}$ NOE difference measurements by irradiating H-3 (i), H-17 (j), H-19 (k) or H-3' (l).

NOEs originate from conformers II and I, respectively. [No attempt was made to quantify this equilibrium since it is affected by the many other conformational degrees of freedom of the overall system, most notably the rotamers about the C(18)-C(19') bond]. In regard to this equilibrium we did not exploit very small (~ 1 %) NOEs observed on H-17 or H-3 since these protons have a tendency to show long-range NOEs due to their isolated nature; therefore such enhancements may reflect either long-range NOEs or the contribution of a minor conformation.

In the vincamine unit NOEs indicated measurable contributions of all the pertinent conformations analogous to I, II and III, thus making the assignment of H_x-20' and H_y-20' ambiguous.



Compound ***6d***. The NMR features of **6d** could be analyzed in exact analogy to **6a**. Verification of the configuration of C(15) as well as the effects of the Cl substitution on the ethyl conformation in **4d** were discussed before,[6] and the NMR data showed direct analogy in terms of chemical shifts and NOE interactions for both units of **6d**. Accordingly, the dominant conformation about the C(16)-C(20) bond is I.

Compounds ***14*** *and* ***15***. For both **14** and **15** the spectral characteristics of the C(19')-substituted "southern" units accord with the vincamine half of **6a**. In both compounds the appearance of an additional OH signal and the upfield shift of C(14) to ~ δ 82 indicate that in the "northern" units the tetrahydrofuranyl rings opened up to give vincamine-like structures. Both compounds contain a double bond in ring *D* as indicated by the relevant olefinic CH and aliphatic CH_2 ^1H and ^{13}C signals, both showing mutual allylic J-couplings in the ^1H spectra. In **14** the pertinent CH_2 carbon [C(19)] resonates at δ 44.0 [i.e. it is in the vicinity of N(4)] which suggests that the double bond is located between C(17) and C(18). In **15** the analogous resonance is δ 24.0 [C(17)], in accord with the depicted location of the ring *D* double bond. As compared to **15**, in **14** C(6) is shifted upfield due to the C(6)⇔C(19) γ_{gauche} interaction which is absent in **15**. These structures were also corroborated by the observed NOEs from H-17 into H_β-15 and H_3-21 in **14**, and the H-19—H_2-5 NOE connection. It may be noted that C(18) in **14** is shifted 25.4 ppm downfield of its value in **15**, which is typical difference for conjugated and non-conjugated alkenes.[9]

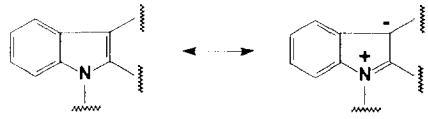
With regard to the rotameric equilibrium about the C(16)-C(20) bond in **15**, the following NOEs were observed: H-3 → H_x-20 (δ 1.44), H_3-21; H_α-15 → H_x-20, H_3-21; H_α-17 → H_y-20 (δ 1.73), H_3-21; H_β-15 → H_y-20, H_3-21; H_3-21 → H_α-17, H_α-15, H_β-15, H-3. By following an analogous reasoning to that discussed above, these results indicate a III⇄II equilibrium, in similarity to vincamine.[6] Further, these NOEs also provide distinction between the assignments of the diastereotopic H_2-17 and H_2-20 protons, respectively.

Similarly to **6a**, in the vicamine unit of **14** all rotamers about the C(16')-C(20') bond contribute measurably to the I⇄II⇄III equilibrium. As expected, the situation was measured to be analogous in both units of **14**.

In all of the dimers **6a**, **6d**, **14** and **15** the H_2-5' protons are ca. 0.5-0.8 ppm upfield of the H_2-5 protons as well as their values in criocerine[3] and vincamine[6]. This effect is probably due to inter-unit van der Waals interactions involving mainly H-17 and H-19.

In vincamine (**4a**) $\delta_{C(20)}$=28.9 ppm,[6] but the introduction of the double bond in ring *D*' deprives C(20') of its γ_{gauche} steric effect with C(18'), thus shifting C(20') downfield in all dimeric compounds. [Note that C(20) also shows this effect in **14**, but, as expected, not in **15**]. Also, as compared to vincamine, in the criocerine half the C(17)-O gives an additional γ-upfield effect on C(20) in **6a** and **6d**. These opposite shifts account for the 10 ppm difference between $\delta_{C(20)}$ and $\delta_{C(20')}$ in the latter compounds.

It may be interesting to note that in all of the above criocerine-like structures $\delta_{C(7)}$ is shifted 4-5 ppm downfield of its value in the vincamine-like units (Table 2). This effect may be rationalized as follows. The relatively low chemical shift of C(7) in indole compounds (typically ca. 106 ppm in vincamine analogues) is due to the relatively high contribution of the charged mesomeric form[10] shown below. In criocerines the tetrahydrofuranyl ring forces C(14) away from the indole plane; this causes the indole nitrogen to depart from its ideal planar arrangement, and its diminished delocalization reduces the contribution of the pertinent charged mesomer, which in turn moves C(7) downfield to ca. 110 ppm.



EXPERIMENTAL

Mp-s are uncorrected. Optical rotations were recorded in chloroform at 25±2 °C. IR spectra were taken on a Nicolet 205 FT-IR spectrometer using KBr pellets. Mass spectra were run on an AEI-MS-902 (70 eV; direct insertion) and on a Kratos MS-902 mass spectrometers. 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 δ_{TMS}=0.00 ppm. The COSY, HETCOR and NOE experiments were recorded by using the standard spectrometer software package. NOEs were measured in non-degassed samples with 4 s preirradiation 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[11] was employed, using 8 s preirradiation times and a 3 Hz line-broadening before Fourier transformation.

Synthesis

The 18-iodo-criocerine analogues **5b-5e** were prepared according to our earlier procedure with iodine[3a] starting from vincamine derivatives **4b-4e**.

(-)-11-Nitro-18-iodo-18,19-dehydro-14,17-epoxy-14,15-dihydroeburnamenine-14α-carboxylic acid methyl ester (3α,14β,16α,17β) ***5b***. Yield 83.4 %, mp 191-197 °C (from isopropanol), $[\alpha]_D$=-182.8 (c=0.5; CH_2Cl_2).

IR: 1750, 1600, 1500 cm^{-1}.

^1H NMR ($CDCl_3$), δ: 1.06 (3H, t, H_3-21); 1.55 (1H, dq, H_y-20); 1.80 (1H, dq, H_x-20); 2.52 (1H, d, H_β-15); 2.72 (1H, m, H_α-6); 2.80 (1H, m, H_β-6); 2.89 (1H, d, H_α-15); 3.43 (1H, m, H_α-5); 3.70 (1H, dd, H_β-5); 4.15 (3H, s, OCH_3); 4.37 (1H, s, H-17); 4.45 (1H, s, H-3); 6.35 (1H, s, H-19); 7.38 (1H, d, H-9); 7.95 (1H, d, H-12); 8.01 (1H, dd, H-10).

(-)-11-Bromo-18-iodo-18,19-dehydro-14,17-epoxy-14,15-dihydroeburnamenine-14α-carboxylic acid methyl ester (3α,14β,16α,17β) ***5c***. Yield 71.4 %, mp 205-212 °C (from ether), $[\alpha]_D$=-99.1 (c=0.2; CH_2Cl_2).

IR: 1742, 1600 cm^{-1}.

FAB-MS (DMSO; NOBA; *m/z*): 555.7 (MH^+); 427.7 (M-I); 327.7; 281.7; 251.1; 207.6; 91.4.

^1H NMR ($CDCl_3$), δ: 1.03 (3H, t, H_3-21); 1.51 (1H, dq, H_y-20); 1.75 (1H, dq, H_x-20); 2.43 (1H, d, H_β-15); 2.65 (1H, m, H_α-6); 2.75 (1H, m, H_β-6); 2.82 (1H, d, H_α-15); 3.34 (1H, m, H_α-5); 3.63 (1H, dd, H_β-5); 4.05 (3H, s, OMe); 4.31 (1H, s, H-17); 4.33 (1H, s, H-3); 6.31 (1H, s, H-19); 7.10 (1H, dd, H-10); 7.21 (2H, m, H-9, H-12).

^{13}C NMR ($CDCl_3$), δ: 9.1 (C-21); 21.2 (C-6); 24.8 (C-20); 45.5 (C-16); 45.6 (C-15); 49.7 (C-5); 53.2 (C-3); 53.5 (OMe); 62.7 (C-18); 85.3 (C-17); 91.0 (C-14); 111.5 (C-7); 115.3 (C-12); 116.2 (C-11); 119.4 (C-9); 124.4 (C-10); 129.8, 135.6, 138.2 (C-8, C-2, C-13); 142.9 (C-19); 168.3 (C=0).

(+)-15α-Chloro-18-iodo-18,19-dehydro-14,17-epoxy-14,15-dihydroeburnamenine-14α-carboxylic acid methyl ester (3α,14β,16α,17β) ***5d***. Yield 78.4 %, mp 199-201 °C (from isopropanol), $[\alpha]_D$=+10.6 (c=0.5; CH_2Cl_2).

IR: 1760, 1600 cm^{-1}.

FAB-MS (DMSO; NOBA; *m/z*): 511.7 (MH^+); 510.7 (M^+); 475.7 (M-Cl); 451.7 (M-MeCO); 383.7 (M-I), 375.7; 349.8; 299.8; 266.7; 247.6; 231.6; 191.1; 105.4.

^1H NMR ($CDCl_3$), δ: 1.04 (3H, t, H_3-21); 1.72 (1H, dq, H_y-20); 1.85 (1H, dq, H_x-20); 2.68-2.89 (2H, m, H_2-6); 3.47 (1H, m, H_α-5); 3.69 (1H, dd, H_β-5); 4.08 (3H, s, OMe); 4.41 (1H, s, H-17); 4.47 (1H, s, H-3); 4.52 (1H, s, H-15); 6.35 (1H, s, H-19); 7.04 (1H, m, H-12); 7.14 (2H, m, H-10, H-11); 7.39 (1H, m, H-9).

^{13}C NMR ($CDCl_3$), δ: 7.5 (C-21); 21.3 (C-6); 22.7 (C-20); 47.0 (C-16); 50.0 (C-5); 53.2 (C-3); 53.6 (OMe); 61.3 (C-18); 62.7 (C-15); 79.8 (C-17); 90.5 (C-14); 111.9 (C-7); 112.2 (C-12); 118.5 (C-9); 121.5 (C-10); 123.0 (C-11); 131.0, 133.5, 137.9 (C-8, C-2, C-13); 143.8 (C-19); 166.6 (C=0).

(+)-15α-Chloro-18-iodo-18,19-dehydro-14,17-epoxy-14,15-dihydroeburnamenine-14α-carboxylic acid ethyl ester (3α,14β,16α,17β) ***5e***. Yield 85.0 %, mp 201-203 °C (from isopropanol), $[\alpha]_D$= +90.6 (c=0.5; CH_2Cl_2).

IR : 1755, 1605 cm^{-1}.

^{1}H NMR ($CDCl_3$), δ: 1.04 (3H, t, H_3-21); 1.45 (3H, t, $OCH_2C\underline{H}_3$); 1.72 (1H, dq, H_y-20); 1.83 (1H, dq, H_x-20); 2.66-2.88 (2H, m, H_2-6); 3.45 (1H, m, H_α-5); 3.67 (1H, dd, H_β-5); 4.40 (1H, d, H-17); 4.46 (1H, br s, H-3); 4.49 (1H, s, H-15); 4.50, 4.61 (2H, m, $OC\underline{H}_{x,y}CH_3$); 6.33 (1H, s, H-19); 7.06-7.18 (3H, m, H-10, H-11, H-12); 7.39 (1H, m, H-9).

^{13}C NMR ($CDCl_3$), δ: 7.5 (C-21); 14.0 ($OCH_2\underline{C}H_3$); 21.3 (C-6); 22.8 (C-20); 47.0 (C-16); 49.9 (C-5); 53.2 (C-3); 61.5 (C-18); 62.8 (C-15); 63.1 ($O\underline{C}H_2CH_3$); 79.8 (C-17); 90.5 (C-14); 111.8 (C-7); 112.3 (C-12); 118.5 (C-9); 121.4 (C-10); 122.9 (C-11); 131.0, 133.6, 137.9 (C-8, C-2, C-13); 143.8 (C-19); 166.1 (C=0).

Compounds **3b-3e** were prepared by reduction of the iodo-enamine function of **5b-5e** with palladium in formic acid.[3b]

(-)-11-Nitro-18,19-dehydro-14,17-epoxy-14,15-dihydroeburnamenine-14α-carboxylic acid methyl ester (3α,14β,16α,17β) ***3b***. Yield 86.0 %, mp 118-122 °C (precipitated crystals after an aqueous work-up), $[\alpha]_D$=-29.7 (c=0.2; $CHCl_3$).

IR: 1760, 1625, 1595, 1505 cm^{-1}.

^{1}H NMR ($CDCl_3$), δ: 1.06 (3H, t, H_3-21); 1.51 (1H, dq, H_y-20); 1.73 (1H, dq, H_x-20); 2.50 (1H, d, H_β-15); 2.71 (1H, m, H_α-6); 2.73-2.89 (2H, m, H_β-6, H_α-15); 3.45 (1H, m, H_α-5); 3.68 (1H, dd, H_β-5); 4.12 (3H, s, OMe); 4.23 (1H, dd, H-17); 4.39 (1H, s, H-3); 4.65 (1H, dd, H-18); 5.91 (1H, d, H-19); 7.36 (1H, d, H-9); 7.92 (1H, d, H-12); 7.98 (1H, dd, H-10).

^{13}C NMR ($CDCl_3$), δ: 9.1 (C-21); 20.6 (C-6); 24.7 (C-20); 43.8 (C-16); 45.1 (C-15); 49.3 (C-5); 53.7 (OMe); 54.4 (C-3); 77.7 (C-17); 91.3 (C-14); 99.2 (C-18); 108.4 (C-12); 112.0 (C-7); 116.7 (C-10); 118.0 (C-9); 135.6, 135.8 (C-8, C-2); 137.4 (C-19); 142.4 (C-13); 143.3 (C-11); 168.7 (C=0).

(+)-11-Bromo-18,19-dehydro-14,17-epoxy-14,15-dihydroeburnamenine-14α-carboxylic acid methyl ester (3α,14β,16α,17β) ***3c***. Yield 81.6 %, mp 108-111 °C (precipitated crystals after an aqueous work-up), $[\alpha]_D$=+6.4 (c=0.2; $CHCl_3$).

IR: 1720, 1605 cm^{-1}.

FAB-MS (DMSO; NOBA; *m/z*): 429.9 (MH^+); 401.8; 369.9 (M-MeCO); 341.8; 307.9; 289.8; 250.7; 218.8; 167.6; 120.0; 105.5.

^{1}H NMR ($CDCl_3$), δ: 1.03 (3H, t, H_3-21); 1.46 (1H, dq, H_y-20); 1.71 (1H, dq, H_x-20); 2.42 (1H, d, H_α-15); 2.61 (1H, m, H_α-6); 2.68-2.82 (2H, m, H_β-6, H_α-15); 3.40 (1H, m, H_α-5); 3.61 (1H, dd, H_β-5); 4.06 (3H, s, OMe); 4.19 (1H, dd, H-17); 4.28 (1H, s, H-3); 4.63 (1H, dd, H-18); 5.87 (1H, d, H-19); 7.08 (1H, m, H-10); 7.19 (2H, m, H-9, H-12).

^{13}C NMR ($CDCl_3$), δ: 9.1 (C-21); 20.8 (C-6); 24.7 (C-20); 43.6 (C-16); 45.3 (C-15); 49.5 (C-5); 53.4 (OMe); 54.1 (C-3); 77.4 (C-17); 91.2 (C-14); 99.1 (C-18); 111.5 (C-7); 115.0 (C-12); 115.9 (C-11); 119.4 (C-9); 124.2 (C-10); 130.0, 136.6, 138.1 (C-8, C-2, C-13); 137.4 (C-19); 168.7 (C=0).

(+)-15α-Chloro-18,19-dehydro-14,17-epoxy-14,15-dihydroeburnamenine-14α-carboxylic acid methyl ester (3α,14β,16α,17β) ***3d***. Yield 79.2 %, mp 144-146 °C, $[\alpha]_D$=+14.2 (c=0.5; CH_2Cl_2).

IR: 1760, 1640, 1620 cm^{-1}.

FAB-MS (DMSO, NOBA; *m/z*): 385.8 (MH^+); 349.9 (M-Cl); 325.8 (M-MeCO); 266.8; 249.7; 231.7, 219.7; 207.6; 172.1; 147.4; 105.5.

^{1}H NMR ($CDCl_3$), δ: 1.05 (3H, t, H_3-21); 1.65-1.85 (2H, m, $H_{x,y}$-20); 2.65-2.90 (2H, m, H_2-6); 3.52 (1H, m, H_α-5); 3.68 (1H, dd, H_β-5); 4.09 (3H, s, OMe); 4.31 (1H, dd, H-17); 4.41 (1H, s, H-3); 4.55 (1H, s, H-15); 4.61 (1H, dd, H-18); 5.93 (1H, d, H-19); 7.01 (1H, m, H-12); 7.11 (2H, m, H-10, H-11); 7.39 (1H, m, H-9).

^{13}C NMR ($CDCl_3$), δ: 7.3 (C-21); 21.0 (C-6); 22.6 (C-20); 45.2 (C-16); 49.8 (C-5); 53.5 (OMe); 54.1 (C-3); 62.7 (C-15); 72.1 (C-17); 90.6 (C-14); 98.3 (C-18); 111.9 (C-7, C-12); 118.5 (C-9); 121.5 (C-10); 122.8 (C-11); 131.3, 134.5, 137.9 (C-8, C-2, C-13); 138.4 (C-19); 167.1 (C=0).

(+)-15α-Chloro-18,19-dehydro-14,17-epoxy-14,15-dihydroeburnamenine-14α-carboxylic acid ethyl ester (3α,14β,16α,17β) ***3e***. Yield 72.1 %, mp 140-141 °C, $[\alpha]_D$=+90.6 (c=0.5; CH_2Cl_2).

IR: 1760, 1640, 1620 cm^{-1}.

^{1}H NMR ($CDCl_3$), δ: 1.04 (3H, t, H_3-21); 1.45 (3H, t, $OCH_2C\underline{H}_3$); 1.75 (2H, m, $H_{x,y}$-20); 2.70 (1H, m, H_α-6); 2.82 (1H, m, H_β-6); 3.52 (1H, m, H_α-5); 3.67 (1H, dd, H_β-5); 4.31 (1H, dd, H-17); 4.41 (1H, s, H-3); 4.49, 4.65 (2H, m, $OC\underline{H}_{x,y}CH_3$); 4.53 (1H, s, H-15); 4.61 (1H, dd, H-18); 5.92 (1H, d, H-19); 7.10 (3H, m, H-10, H-11, H-12); 7.39 (1H, m, H-9).

^{13}C NMR ($CDCl_3$), δ: 7.3 (C-21); 14.0 ($OCH_2\underline{C}H_3$); 20.9 (C-6); 22.6 (C-20); 45.1 (C-16); 49.7 (C-5); 54.1 (C-3); 62.7 (C-15); 63.0 ($O\underline{C}H_2CH_3$); 72.0 (C-17); 90.5 (C-14); 98.4 (C-18); 111.8 (C-7); 112.0 (C-12); 118.5 (C-9); 121.4 (C-10); 122.7 (C-11); 131.2, 134.5, 137.8 (C-2, C- 8, C-13); 138.3 (C-19); 166.6 (C=0).

(-)-19'α(18,19-Dehydro-14α-carbomethoxy-14,17-epoxy-14,15-dihydroeburnamenine (3α,14β,16α,17β)-18-yl)17',18'-dehydro-14'β-hydroxy-14',15'-dihydro-eburnamenine (3'α,16'α)-14'α-carboxylic acid methyl ester ***6a***.

A/ (-)-Criocerine **1a** (3.51 g; 10 mM) was dissolved in acetic acid (14 ml) at room temperature and the reaction mixture was stirred for 24 h, then cooled with an ice-bath. To the mixture a cold concentrated aqueous ammonium hydroxide solution (30 ml) was added and the precipitated crystals were filtered off, washed with cold water (100 ml) and dried to give **6a** (3.01 g; 86.0 %). Mp 185-187 °C (219-221 °C; recryst. from methanol), $[\alpha]_D$=-99.1 (c=0.2; $CHCl_3$).

IR: 1760, 1740, 1645, 1620 cm^{-1}.

FAB-MS (DMSO, NOBA; *m/z*): 701 (MH^+); 641 (M+H-60); 531 (M+H-170); 171, 136.

B/ To a suspension of (-)-18-iodo-criocerine (**5a**, 476 mg, 1.0 mM) in acetic acid (6 ml), tin dust (0.5 g) was added and the mixture was heated at reflux for 5 min. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in a mixture of chloroform (100 ml) and concentrated aqueous ammonium hydroxide solution (20 ml). The organic layer was separated and washed with water (3x20 ml), dried (Na_2SO_4), filtered, and the filtrate was evaporated in reduced pressure. The residue (290 mg; 83.0 %) was crystallized from isopropanol to give **6a**.

Dimers **6b-6e** were prepared according to the above procedure by following route A.

(-)-19'α(11-Nitro-18,19-dehydro-14α-carbomethoxy-14,17-epoxy-14,15-dihydroeburnamenine (3α,14β,16α,17β)-18-yl) 11'-nitro-17',18'-dehydro-14'β-hydroxy-14',15'-dihydro-eburnamenine (3'α,16'α)-14'α-carboxylic acid methyl ester ***6b***. Yield 67.3 %. mp 300 °C (decomp.), $[\alpha]_D$=-246.8 (c=0.2; $CHCl_3$).

IR: 1760, 1740, 1640, 1620, 1505, 1500 cm^{-1}.

^1H NMR ($CDCl_3$), δ: 0.94 (3H, t, H_3-21'); 1.06 (3H, t, H_3-21); 1.49 (1H, dq, H_y-20); 1.57 (1H, dq, H_y-20'); 1.70 (1H, dq, H_x-20); 1.89 (1H, dq, H_x-20'); 2.27 (3H, m, H_α-6', H_2-15'); 2.46 (1H, d, H_β-15); 2.62-2.85 (6H, m, H_2-5', H_2-6, H_β-6', H_α-15); 3.14 (1H, t, H-19'); 3.48 (1H, m, H_α-5); 3.69 (1H, dd, H_β-5); 3.85 (3H, s, OMe'); 3.98 (1H, s, H-3'); 4.09 (4H, s, OMe, H-17); 4.39 (1H, s, H-3); 4.96 (1H, dd, H-18'); 5.45 (1H, dd, H-17'); 6.00 (1H, s, H-19); 7.36-7.42 (2H, m, H-9, H-9'); 7.92-8.07 (4H, m, H-10, H-10', H-12, H-12').

^{13}C NMR ($CDCl_3$), δ: 8.7 (C-21'); 9.1 (C-21); 16.3 (C-6'); 20.8 (C-6); 24.6 (C-20); 34.8 (C-20'); 36.5 (C-16'); 43.8, 44.0 (C-16, C-15'); 44.9 (C-15); 45.8 (C-5'); 49.3 (C-5); 53.6 (OMe); 54.4 (OMe'); 55.0 (C-3); 56.0 (C-19'); 58.3 (C-3'); 79.7 (C-17); 82.2 (C-14'); 91.6 (C-14); 107.2, 108.7 (C-12, C-12'); 107.5 (C-7'); 111.8, 112.1 (C-7, C-18); 116.0, 116.7 (C-10, C-10'); 117.6, 117.7 (C-9, C-9'); 127.4 (C-17'); 130.3 (C-18'); 132.5, 133.8 (C-8, C-8'); 135.3 (C-19); 135.9, 136.2 (C-2, C-2'); 139.2, 142.5, 142.8, 143.3 (C-11', C-13, C-13', C-11); 168.4, 172.2 (C=O, C=O').

(-)-19'α(11-Bromo-18,19-dehydro-14α-carbomethoxy-14,17-epoxy-14,15-dihydroeburnamenine (3α,14β,16α,17β)-18-yl)11'-bromo-17',18'-dehydro-14'β-hydroxy-14',15'-dihydro-eburnamenine(3'α,16'α)-14'α-carboxylic acid methyl ester ***6c***. Yield 74.8 %, mp 300 °C (decomp.), $[\alpha]_D$=-150.2 (c=0.2; $CHCl_3$).

IR: 1760, 1740, 1640, 1620 cm^{-1}.

FAB-MS (DMSO, NOBA; *m/z*): 857.3 (MH^+); 829.4; 611.4; 609.4 (MH-248), 504.1; 431.8; 401.1; 339.2; 286.3; 249.4; 205.3; 180.5.

^1H NMR ($CDCl_3$), δ: 0.94 (3H, t, H_3-21'); 1.02 (3H, t, H_3-21); 1.45 (1H, dq, H_y-20); 1.56 (1H, dq, H_y-20'); 1.67 (1H, dq, H_x-20); 1.88 (1H, dq, H_x-20'); 2.22 (3H, m, H_α-6', H_2-15'); 2.36 (1H, d, H_β-15); 2.59-2.81 (6H, m, H_2-5', H_2-6, H_β-6', H_α-15); 3.14 (1H, t, H-19'); 3.40 (1H, m, H_α-5); 3.62 (1H, dd, H_α-5); 3.74 (1H, br, OH); 3.83 (3H, s, OMe'); 3.96 (1H, s, H-3'); 4.01 (3H, s, OMe); 4.02 (1H, d, H-17); 4.30 (1H, s, H-3); 4.95 (1H, dd, H-18'); 5.40 (1H, dd, H-17'); 5.96 (1H, s, H-19); 7.09-7.24 (6H, m, H-9, H-9', H-10, H-10', H-12, H-12').

^{13}C NMR ($CDCl_3$), δ: 8.8 (C-21'); 9.1 (C-21); 16.5 (C-6'); 21.1 (C-6); 24.7 (C-20); 35.0 (C-20'); 36.5 (C-16'); 43.9 (C-16); 44.0 (C-15'); 45.1 (C-15); 46.1 (C-5'); 49.5 (C-5); 53.3 (OMe); 54.1 (OMe'); 54.9 (C-3); 55.9 (C-19'); 58.2 (C-3'); 79.7 (C-17); 82.1 (C-14'); 91.5 (C-14); 106.6 (C-7'); 111.6 (C-7); 112.1 (C-18); 113.5 (C-12); 114,9 (C-11); 115.3 (C-12'); 115.8 (C-11'); 119.0, 119.3 (C-9, C-9'); 123.4, 124.2 (C-10, C-10'); 127.0 (C-17'); 128.0, 130.1 (C-8, C-8'); 131.1 (C-18'); 133.0, 134.7 (C-2, C-2'); 135.3 (C-19); 137.0, 138.7 (C-13, C-13'); 168.9, 172.4 (C=O, C=O').

(-)-19'α(15α-Chloro-18,19-dehydro-14α-carbomethoxy-14,17-epoxy-14,15-dihydroeburnamenine (3α,14β,16α,17β)-18-yl)15'α-chloro-17',18'-dehydro-14'β-hydroxy-14',15'-dihydro-eburnamenine(3'α,16'α)-14'α-carboxylic acid methyl ester ***6d***. Yield 82.9 %, mp 300 °C (decomp.), $[\alpha]_D$=-8.6 (c=0.4; $CHCl_3$).

IR: 1760, 1740, 1640, 1620 cm^{-1}.

FAB-MS (DMSO; NOBA; *m/z*): 769.6 (MH^+); 733.6 (M-Cl); 735.2; 709.5 (M-MeCO); 563.5; 385.7; 307.5; 266.7; 232.3; 180.5; 154.4; 105.4; 79.4.

(-)-19'α(15α-Chloro-18,19-dehydro-14α-carboethoxy-14,17-epoxy-14,15-dihydroeburnamenine (3α,14β,16α,17β)-18-yl]15'α-chloro-17',18'-dehydro-14'β-hydroxy-14',15'-dihydro-eburnamenine(3'α,16'α)-14'α-carboxylic acid ethyl ester **6e**. Yield 79.8 %, mp 166-171 °C (decomp.), $[\alpha]_D$=-41.1 (c=0.2; $CHCl_3$).

IR: 1760, 1640, 1620 cm^{-1}.

^1H NMR ($CDCl_3$), δ: 0.92 (3H, t, H_3-21'); 1.03 (3H, t, H_3-21); 1.29 (3H, t, $OCH_2C\underline{H}_3$'); 1.43 (3H, t, $OCH_2C\underline{H}_3$); 1.72 (2H, m, $H_{x,y}$-20); 2.05 (2H, m, $H_{x,y}$-20'); 2.32 (1H, m, H_α-6'); 2.61-2.87 (5H, m, H_2-5', H_2-6, H_β-6'); 3.12 (1H, t, H-19'); 3.49 (1H, m, H_α-5); 3.66 (1H, dt, H_β-5); 4.13 (2H, s, H-3', H-17); 4.30-4.62 (7H, m, H-3, H-15, H-15', $OC\underline{H}_2CH_3$', $OC\underline{H}_2CH_3$); 4.89 (1H, dd, H-18'); 5.40 (1H, dd, H-17'); 6.03 (1H, s, H-19); 7.02-7.18 (6H, m, H-10, H-10', H-11, H-11', H-12, H-12'); 7.33-7.41 (2H, m, H-9, H-9').

^{13}C NMR ($CDCl_3$), δ: 7.5, 7.6 (C-21, C-21'); 13.9, 14.0 ($OCH_2\underline{C}H_3$, $OCH_2\underline{C}H_3$'); 16.7 (C-6'); 21.2 (C-6); 22.8 (C-20); 32.6 (C-20'); 41.2 (C-16'); 45.4 (C-16); 46.2 (C-5'); 49.8 (C-5); 54.7 (C-3); 56.0, 56.1 (C-3', C-19'); 62.8 (C-15); 62.9 ($O\underline{C}H_2CH_3$); 63.1 ($O\underline{C}H_2CH_3$'); 65.2 (C-15'); 74.7 (C-17); 86.4 (C-14'); 90.9 (C-14); 107.5 (C-7'); 110.9 (C-7); 112.0 (C-18); 112.3, 112.7 (C-12, C-12'); 118.1 (C-9, C-9'); 120.5, 121.3, 121.4, 122.6 (C-10, C-10', C-11, C-11'); 124.1 (C-17'); 129.3, 130.9, 131.3, 134.7, 134.9, 138.3 (C-8, C-8', C-2, C-2', C-13, C-13'); 132.0 (C-18'); 136.2 (C-19); 166.7, 168.4 (C=O, C=O');

Reaction of dimer **6a** *with iodine*. Dimer **6a** (350 mg, 0.5 mM) was dissolved in a mixture of chloroform (10 ml) and saturated aqueous $NaHCO_3$ solution (5 ml) and iodine (0.5 g, 2 mM) was added and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was treated with 10 % $Na_2S_2O_3$ solution, washed with water and dried (Na_2SO_4). The filtrate was evaporated and the residue was crystallized from methanol to give **5a** (395 mg, 84 %).

(+)-19'α(17,18-Dehydro-14α-carbomethoxy-14β-hydroxy-14,15-dihydroeburnamenine(3α,16α)-18-yl) 17',18'-dehydro-14'β-hydroxy-14',15'-dihydro-eburnamenine (3'α,16'α)-14'α-carboxylic acid methyl ester **14**. To a solution of dimer **6a** (700 mg, 1.0 mM) in a mixture of THF (30 ml), MeOH (5.0 ml) and trifluoroacetic acid (0.5 ml) at room temperature, sodium cyanoborohydride (1.6 g, 25.4 mM) was added portionwise and the mixture was stirred for 5 min. The reaction mixture was diluted with ethyl acetate (200 ml), water (60 ml) and concentrated aqueous ammonium hydroxide solution (5.0 ml). After extraction, the organic layer was separated and washed with water (2 x 20 ml), dried (Na_2SO_4), filtered and the filtrate was evaporated in reduced pressure. The residue (680 mg) was crystallized from a mixture of diisopropylether and hexane to give a crude **14** (610 mg) which was chromatographed on silica (eluent: cyclohexane + ethyl acetate, 1/1). The solvent was evaporated under reduced pressure and the residue was crystallized from hexane to give pure **14** (539 mg, 77.0 %), mp 219-222 °C, $[\alpha]_D$= + 79.7 (c=0.2;$CHCl_3$).

IR: 1700 cm^{-1}.

MS (*m/z*): 702 (M^+).

(+)-19'α(18,19-Dehydro-14α-carbomethoxy-14β-hydroxy-14,15-dihydroeburnamenine(3α,16α)-18-yl) 17',18'-dehydro-14'β-hydroxy-14',15'-dihydro-eburnamenine (3'α,16'α)-14'α-carboxylic acid methyl ester **15**. Dimer **6a** (700 mg, 1.0 mM) was dissolved in DMF (10 ml) and 10 % Pd/C catalyst (about 100 mg) was added and the mixture was hydrogenated for 3 h. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was chromatographed on silica (eluent: cyclohexane+ethyl acetate 7/3). The solvent was

evaporated under reduced pressure and the residue was crystallized from hexane to give **15** (493 mg, 70.0 %), mp 228-231 °C, $[\alpha]_D$=-119.4 (c=0.2; $CHCl_3$).

IR : 1740, 1665, 1620 cm^{-1}.

MS (*m/z*): 702 (M^+).

Cyanide trapping of criocerine **3a**. To a solution of **3a** (700 mg, 2.0 mM) in dry methylene chloride (10 ml) at 0 °C, trifluoroacetic anhydride (0.8 ml, 5.6 mM) was added and the reaction mixture was stirred for 5 min. To the reaction mixture potassium cyanide (1.0 g, 15.2 mM) in water (2.0 ml) was added and stirred overnight. The mixture was diluted with methylene chloride (40 ml), water (10 ml) and concentrated aqueous ammonium hydroxide solution (3.0 ml). After extraction, the organic layer was separated and washed with water (2x10 ml), dried (Na_2SO_4), filtered and the filtrate was evaporated in reduced pressure. The residue was chromatographed on silica (eluent: ciklohexane+ethyl acetate, 6/4). The solvent was evaporated under reduced pressure and the residue was crystallized from methanol to give **20** (106 mg, 14.0 %), mp 147-149 °C, $[\alpha]_D$= - 19.1 (c=0.5; $CHCl_3$).

IR: 2230, 1700 cm^{-1}.

^1H NMR ($CDCl_3$), δ: 1.05 (3H, t, H_3-21); 1.55 (1H, dq, H_y-20); 1.91 (1H, dq, H_x-20); 2.05-2.23 (2H, m, H_2-18); 2.41 (1H, d, H_β-15); 2.68 (1H, m, H_α-6); 2.83 (1H, d, H_α-15); 3.25-3.53 (3H, m, H_2-5, H_β-6); 3.73 (1H, dd, H-19); 4.07 (4H, s, OMe, H-17); 4.21 (1H, s, H-3); 6.99 (1H, m, H-12); 7.12-7.20 (2H, m, H-10, H-11); 7.47 (1H, m, H-9).

^{13}C NMR ($CDCl_3$), δ: 9.4 (C-21); 19.3 (C-6); 24.7 (C-20); 29.5 (C-18); 42.3 (C-19); 43.9 (C-16); 46.3 (C-15); 49.7 (C-5); 53.4 (C-3); 53.4 (OMe); 79.1 (C-17); 90.6 (C-14); 110.7 (C-12); 113.2 (C-7); 119.3 (C-9); 119.8 (CN); 121.0 (C-10); 122.9 (C-11); 130.5 (C-8); 133.5 (C-2); 137.1 (C-13); 168.3 (C=0).

ACKNOWLEDGEMENTS

The authors wish to thank the late *Dr. J. Tamás* and *Dr. M. Mák* for the mass spectra, *Dr. V. Lakshmi* (Central Drug Research Institute, Lucknow, India) for the preparation of some intermediates and *Dr. H.R. Hendriks* (European Organization for Research and Treatment of Cancer; New Drug Development Office; Free University Hospital, Amsterdam, The Netherlands) for the biological examinations of some dimer derivatives on the antitumor tests. Special thanks are due to *Ms. K. Welker*, *Ms. É. Papp* and *Ms. M. Melegh* for technical assistance.

REFERENCES

1. For part LXXVI see: Kalaus, Gy.; Vágó, I.; Greiner, I.; Kajtár-Peredy, M.; Brlik, J.; Szabó, L.; Szántay, Cs. submitted for publication.
2. Moldvai, I.; Szántay, Cs. Jr.; Tóth, G.; Vedres, A.; Kálmán, A.; Szántay, Cs. *Recl. Trav. Chim. Pays Bas*, **1988**, *107*, 335-342.
3. a) Moldvai, I.; Szántay, Cs. Jr.; Szántay, Cs. *Synthetic Comm.*, **1991**, *21*, 965-967. b) Moldvai, I.; Szántay, Cs. Jr.; Szántay, Cs. *Synthetic Comm.*, **1992**, *22*, 509-512.
4. Sarlet, P.; Hannart, J. *Bull. Soc. Chim. Belg.*, **1979**, *88*, 93-98.
5. Belg. 823.409 (*Chem. Abstr.* 1976, **84**, 5229).
6. Moldvai, I.; Szántay, Cs. Jr.; Rissanen, K.; Szántay, Cs. *Tetrahedron*, **1992**, *48*, 4999-5008.
7. Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.*, **1971**, *93*, 2897-2904.
8. Tourwé, D.; Van Binst, G. *Heterocycles*, **1978**, *9*, 507-533.
9. Kalinowski, H.-O.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; Wiley: New York. 1988; pp. 290-297.
10. Remers, W. A. Indoles. Part I. In *Indoles*; Houlihan, W. J. Ed.; John Wiley and Sons, Inc.: New York, 1972; p. 55.
11. Sanchez-Ferrando, F.; Magn. Reson. Chem., **1985**, *23*, 185-191.

(*Received in UK* 22 *May* 1995; *revised* 20 *June* 1995; *accepted* 23 *June* 1995)