Tetrahedron Vol 39, No. 22, pp 3737 to 3747, 1983
Printed in Great Britain

0040-4020/83 $3.00 + .00
Pergamon Press Ltd

SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS—XVI[1]

NEW ROUTE TO THE STEREOSELECTIVE SYNTHESIS OF (+)-VINCAMINE, (−)-VINCAMONE AND (+)-APOVINCAMINIC ACID ESTERS

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(*Received in USA 7 January* 1983)

Abstract—A stereoselective method has been elaborated for the synthesis of oxime esters, (−)-**4a, b**, from which, as common intermediates, (+)-apovincaminic acid esters (**3a, b**), (+)-vincamine (**1**) and (−)-vincamone (**2**) can be prepared.

(+)-Vincamine (**1**), isolated from *Vinca minor*, and (−)-vincamone (**2**) have significant cerebral vasodilatory effects. Since the first vincamine synthesis published by Kuehne,[2a] several papers have dealt with the synthesis of these derivatives.[2b–d] A semisynthetic derivative of (+)-vincamine, the (+)-apovincaminic acid ethyl ester (Cavinton®) also has a valuable therapeutic effect.[1,3a–c]

The stereoselective total synthesis of (+)-vincamine, which can also be performed on an industrial scale, was published some years ago.[4a] Relying on the experience of these investigations, we sought a stereoselective synthesis of a common intermediate of type **4** which can be used for the preparation of the above compounds of biological value (**1**, **2** and **3**).[4b]

The basic principle of our synthesis design was that alkylation in position 1 of the tetracyclic derivative **6** or **7**, which we had carried out by means of several electrophilic olefins,[1] should be realized with a bulky electrophilic olefin, thus ensuring the stereoselective hydrogenation of the molecule in the desired direction. The side chain introduced in this step should also facilitate the formation of the *E*-ring. Diethyl methylenemalonate, with strong electrophilic character, appeared to meet all of the above requirements.[5a,b]

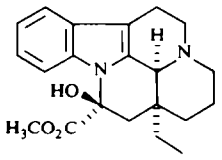
First, enamine **6**[6] was reacted with 4 equivalents of diethyl methylenemalonate in dichloromethane solution. The red oil remaining after the removal of solvent could not be crystallized even after converting it into salt form, and it consumed only 20–25% of the calculated amount of H_2 when hydrogenated in ethanol solution in the presence of Pd–C catalyst. From the complex mixture of partially hydrogenated derivatives, compounds **9a–d** and **10a** could be isolated in crystalline form, either as a base or a salt, after low pressure column chromatography and then preparative layer chromatography. In all these compounds the quinolizidine ring exists in the *trans* conformation, as shown by the intense Bohlmann bands appearing in the IR spectra of their chloroform solutions in the 2800–2700 cm^{-1} region and by the NMR signals of their 12b protons appearing below $\delta = 3.80$ ppm. The *cis* relationship of the 12b proton in esters **9a–d** with respect to the C_1-Et group is shown by the chemical shifts of the indole NH ($\delta = 7.82$–8.01 ppm) and of the Me protons of the Et group ($\delta = 0.98$–1.38 ppm). In the NMR spectrum of the *trans* derivative **10a** the indole NH signal is at $\delta = 9.52$ ppm, and the Me protons appear at $\delta = 0.70$ ppm.[4a] The ^1H NMR spectra also show that, at C_1 of the *trans* ester **10a**, one methylene malonic ester is connected whereas in the *cis* derivatives **9a–d**, one to four methylene malonic ester molecules are connected respectively as a result of Michael-type reactions.[7]

The given structures of **9a–d** *cis* and **10a** *trans* esters are also supported by their mass spectra. The *m/e* values of the molecular ions of all derivatives are 426, since under the conditions of measurement methylene malonic ester units are cleaved from products **9b–d** in a retro-Michael reaction; and following the further fragmentation the *m/e* 127 and 99 ions are detected with intensities proportional to the number of methylene malonic ester units.

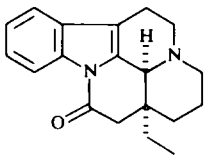
The structures of esters **9a–d** and **10a** also have been established by chemical methods.

By heating the *cis* esters **9a–d** in benzene in the presence of KOBu^t, they can be converted into the same substance, the *cis* lactam ester **11**. By following the reaction on TLC it can be observed that compounds **9b–d** yield ester **9a** in the first step, which closes later to lactam ester **11**. Consequently, molecules containing several methylene malonic ester units may be forced into *retro*-Michael reactions by means of bases (e.g. aqueous alcoholic KOH). Lactam ester **11** can be converted into *cis* lactam **13** of known structure,[1,8] by heating in dilute aqueous sulfuric acid, via hydrolysis and subsequent decarboxylation. The base-catalysed cyclization of *trans* ester **10a** yields *trans lactam ester* **12**, from which, by heating in aqueous sulfuric acid, *trans* lactam **14**, of known structure,[8] can be prepared.

It has been shown that the alkylation of enamine



1



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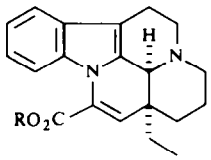

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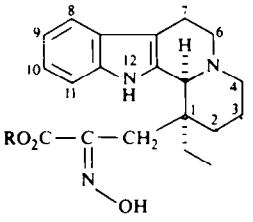

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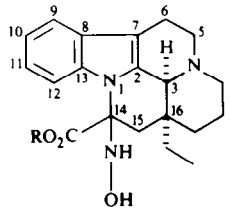
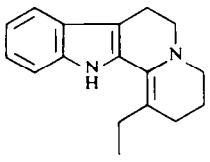
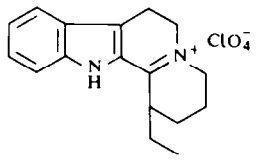


5

3-5	R
a	CH_3
b	C_2H_5
c	H



6



7

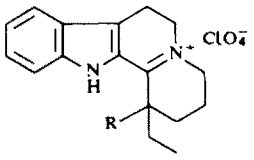
6 with diethyl methylene malonate can be carried out in low yields only, and the processing of the mixture is complicated owing to the formation of several products by Michael reaction.

It was observed by Buzás *et al.*[9] that the good electrophile acrolein is able to alkylate iminium salt **7** in the presence of triethylamine or very small amounts of KOBu^t. We have found that reacting iminium perchlorate **7** in methylene chloride, in the presence of very small amounts of KOBu^t, with 1.5 equivalents of diethyl methylene malonate, gave the adduct **8a** in a yield of *ca* 90–94%. The product can be isolated and identified in crystalline form. Hydrogenation of iminium salt **8a** in the presence of 10% Pd–C catalyst in DMF solvent, is highly stereoselective due to the presence of the bulky group in position 1, and the *cis* ester **9a** can be isolated in a yield of 85%. *Trans* derivative **10a** was obtained only in a yield of 3%. By hydrogenating iminium salt **8a** with sodium borohydride, the ratio of *trans* ester **10a** can be increased (28% yield).

After achieving the highly stereoselective synthesis of *cis* ester **9a** successfully, our investigations were continued toward the formation of the *E* ring. Diester **9a**, owing to its active hydrogen in position 2′, was considered, according to literature sources,[10] applicable for transformation into the corresponding α-hydroxyimino ester by means of isonitrosation with alkyl nitrites. However, the acid or base catalysed isonitrosation of diester **9a** with alkyl nitrites did not yield the desired products.

On the basis of the investigations of Onischenko,[11] it could be assumed that the monoadduct hemiester (**15a**), obtained by hydrolysis from diester **9a**, will be applicable for the preparation of α-hydroxyimino esters of type **4**, owing to its active hydrogen and its readiness to decarboxylate. The selective hydrolysis of diester **9a** with 1.1 to 1.3 equivalents of aqueous ethanolic potassium hydroxide at room temperature, yielded hemiester **15a** in a yield of 75–80%. One should note that on alkaline treatment the above discussed *retro*-Michael reaction takes place, too, which enables adducts **9b–d**, eventually formed, to convert into hemiester **15a** as well.

The structure of hemiester **15a** could be established in two ways. Its thermal decarboxylation led to ester



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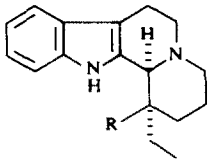

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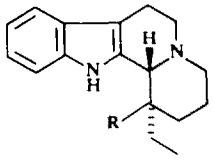
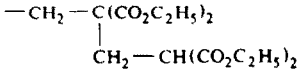


10

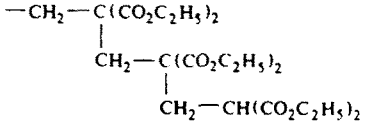
8 – 10 R

a $-CH_2-CH(CO_2C_2H_5)_2$

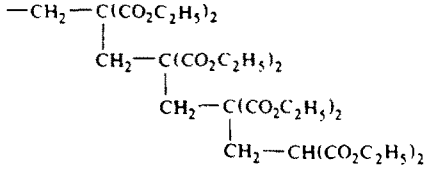
b

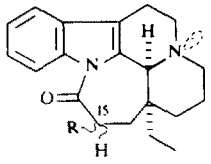


c

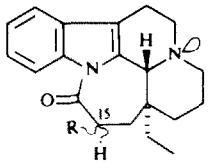


d

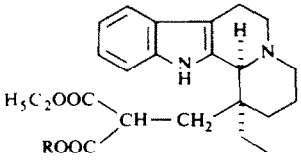




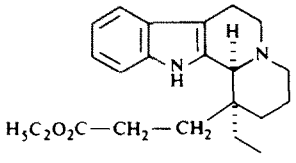
11 R $CO_2C_2H_5$
13 H



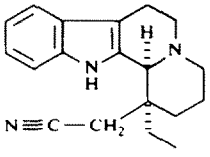
12 R $CO_2C_2H_5$
14 H



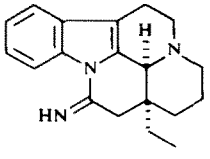
15	R
a	H
b	CH_3



16



17



18

16 of already known structure.[1] By methylating the carboxy group with diazomethane a mixed ester (**15b**) was obtained. In the ^{1}H NMR spectrum of this ester, a quartet appeared at $\delta = 4.08$ ppm (OCH_2CH_3) and the OMe protons absorbed at $\delta = 3.62$ ppm; furthermore, the doubling of these signals owing to the presence of diastereomers, establishes the structures of compounds **15b** and **15a**.

From hemiester **15a** α-hydroxyiminioester **4b** could be prepared under very simple reaction conditions (sodium nitrite treatment in aqueous acetic acid at room temperature) in a yield of 70–72%. The product could be resolved with D-dibenzoyl tartaric acid in good yield (44%). The laevorotatory ethyl ester (−)-**4b** obtained after resolution can be converted into methyl ester (−)-**4a** by boiling in methanol in the presence of a catalytic amount of sodium methoxide.[12]

Structure elucidation of oxime esters (−)-**4a,b**

As known, the tautomeric equilibrium of α-oxoesters corresponding to oxime esters **4a, b** is shifted completely in favour of the cyclic eburnan form (e.g. **1**), and open α-oxoesters cannot be isolated at all.[4a] Therefore, it was of interest to investigate the tautomeric equilibria of the corresponding α-oxime esters (**4a,b**⇌**5a,b**). It is worth mentioning, that in some reactions compounds **4a,b** manifest themselves in their cyclic form **5a,b**, and in protic medium the α-oxime ester **4a** could be almost completely converted into the cyclic hydroxyaminoester **5a**, as will be shown later.

It is interesting to note that in the IR spectra of bases **4a,b**, in addition to the band characteristic of the CO group of conjugated esters (1706 and 1710 cm^{-1}), no ν C=N band of the oxime could be observed, either in crystalline form or in $CHCl_3$ solution. On the other hand, in the IR spectra of their hydrochloride salts, strong bands assigned to ν C=N vibration could be observed at 1620 cm^{-1}.

In the ^{1}H NMR spectra of (−)-**4a, b** derivatives recorded in $CDCl_3$, indole NH protons, exchangeable by D_2O, can be observed at $\delta = 7.87$ and 7.94 ppm, indicating the open oxime ester tautomeric form. The broad OH absorptions at 10.18 and 10.70 ppm indicate the *E*-geometry of oximes. The dominant character of the open oxime form **4a, b** is established unambigously by the 152.20 and 152.44 ppm lines of the ^{13}C NMR spectra of the compounds which can be assigned to the sp^2 C atoms adjacent to the oxime group.

The steric structures of compounds **4** and their salts were determined by X-ray diffraction.

Suitable single crystals could be prepared from both the base (−)-**4b** (B) and its hydrochloride (BH). In interpreting the results of X-ray diffraction, we use the atom numbering of the tautomeric form **5**, having the eburnan skeleton.

The results of X-ray diffraction investigations

Figure 1 shows a perspective view of the molecular structure computed from the final atomic coordinates of the *protonated base* (**BH**) listed with their e.s.d.'s

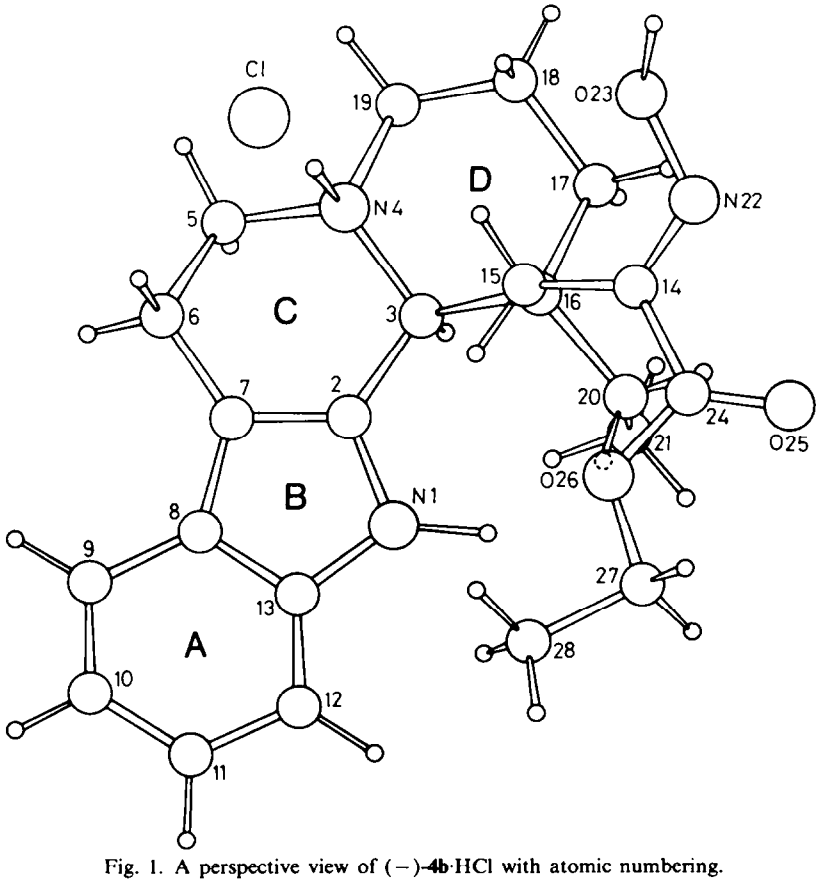


Fig. 1. A perspective view of (−)-**4b**·HCl with atomic numbering.

Table 1. Atomic coordinates ($\times 10^4$) of (−)-**4b**·HCl(BH). E.s.d's are given in parentheses.

	x/a	y/b	z/c	B_{eq}
Cl	-4640(4)	-1480(2)	-1116(1)	4.3(4)
N(1)	-3974(9)	-4434(5)	-3103(4)	2.6(10)
C(2)	-3291(11)	-3928(7)	-2525(5)	2.4(10)
C(3)	-3278(11)	-4280(7)	-1751(5)	2.5(10)
N(4)	-2761(9)	-3385(5)	-1281(4)	3.1(10)
C(5)	-1335(11)	-2883(7)	-1569(5)	3.6(10)
C(6)	-1731(13)	-2430(8)	-2311(6)	4.4(10)
C(7)	-2572(13)	-3103(7)	-2785(5)	2.9(10)
C(8)	-2792(11)	-3083(7)	-3552(5)	2.8(10)
C(9)	-2223(12)	-2421(8)	-4110(6)	4.0(10)
C(10)	-2705(13)	-2608(8)	-4812(6)	4.2(10)
C(11)	-3593(13)	-3426(9)	-4980(5)	4.6(10)
C(12)	-4148(12)	-4078(8)	-4450(5)	3.7(10)
C(13)	-3643(11)	-3885(6)	-3740(5)	2.8(10)
C(14)	-7686(11)	-4392(7)	-1348(5)	2.7(10)
C(15)	-6153(11)	-3972(7)	-1517(5)	2.3(10)
C(16)	-4776(11)	-4718(6)	-1425(5)	2.6(10)
C(17)	-4511(12)	-5000(7)	- 608(5)	3.1(10)
C(18)	-3937(13)	-4121(8)	- 164(5)	4.1(10)
C(19)	-2446(12)	-3693(5)	- 494(5)	3.2(10)
C(20)	-5192(12)	-5717(7)	-1830(5)	3.7(10)
C(21)	-3853(14)	-6445(8)	-1931(6)	4.8(10)
N(22)	-8429(10)	-4352(6)	- 739(4)	3.8(10)
O(23)	-7585(9)	-3845(5)	- 194(3)	4.4(10)
C(24)	-8652(11)	-4853(7)	-1909(6)	3.4(10)
O(25)	-9735(8)	-5414(5)	-1810(4)	4.7(10)
O(26)	-8281(9)	-4521(5)	-2578(4)	4.6(10)
C(27)	-9265(13)	-4806(8)	-3203(5)	4.9(10)
C(28)	-8761(17)	-4115(9)	-3808(6)	6.6(10)

B_{eq}=4/3*TRACE(B*G)

in Tables 1 and 3, the corresponding atomic coordinates for B are listed in Tables 2 and 4. In the salt lattice N^4 is protonated, in the neighbourhood of which Cl^- ion is situated at a distance of 3.09 Å forming a Cl...HN H-bond (Cl...H = 1.98 Å, NH...Cl = 172°). In both structures Cl4–N22 distance (1.29(1) Å for BH and 1.24(3) Å for B) indicates localized double bonds. The sum of the bond angles around Cl4 is 359.8 and 359.7°, respectively. The conspicuous difference between the conformation of B and BH is the different amount of rotation about the Cl4–C15 bond (the torsion angles[13]: Cl6–C15–Cl4–N22 = 95.1 (1.9) for BH and −89.6 (4.5)° for B, while Cl6–C15–Cl4–C24 = −90.9 (1.7) for BH and 97.0(4.4)° for B, respectively). This may presumably be attributed to the different H-bonding of the molecule in the crystal lattices. In BH the =N–OH moiety (N22–O23–H23) acts as donor towards Cl^- in another H-bond (Cl...O = 3.03, Cl...H = 1.98 Å, NH...Cl = 133°). The N1–H1 group also forms a weak interaction with Cl^- anion. In the packing of B, the orientation of the side chain is in favour of forming an intermolecular H-bond between N1–H1 and O25 atoms (N...O = 3.08, H...O = 2.19 Å, NH...O = 147°). The O23...N4 bridgehead distance of 2.74 Å suggests the presence of another intermolecular H-bond. Nevertheless, this packing-induced difference in the surroundings of molecules B and BH has no practical effect on the puckering of the non-planar C and D rings as shown by the *puckering parameters*[14] and *asymmetry factors*.[15]

		Ring C		Ring D	
		B	BH	B	BH
Puckering parameters	Q	0.55 Å	0.51 Å	0.63 Å	0.61 Å
	φ	332°	327°	(238°)	(295°)
	Θ	135°	132°	5°	3°
Asymmetry factors	fC_2	0.9 pm	1.1 pm	(through N4–C5)	
	fC_s	15.2	16.4	(through C2)	
		(half chair)			(chair)

Table 2. Atomic coordinates ($\times 10^4$) of (−)-**4b**(B). E.s.d's are given in parentheses.

	x/a	y/b	z/c	B_{eq}
N(1)	5825(18)	9714(14)	980(12)	5.7(10)
C(2)	4798(19)	9225(16)	1368(11)	3.2(10)
C(3)	4777(19)	8016(19)	1638(13)	4.3(10)
C(4)	3547(17)	7766(16)	1813(10)	4.7(9)
C(5)	2932(28)	8590(22)	2418(16)	7.6(10)
C(6)	2779(21)	9736(19)	1943(13)	4.2(10)
C(7)	3965(20)	9952(19)	1534(15)	5.1(10)
C(8)	4342(19)	10972(17)	1231(12)	3.5(10)
C(9)	3838(23)	12061(19)	1233(13)	5.3(10)
C(10)	4481(24)	12879(17)	837(14)	5.4(10)
C(11)	5729(25)	12669(21)	501(15)	6.3(10)
C(12)	6193(29)	11658(17)	523(13)	5.8(10)
C(13)	5530(19)	10850(16)	856(13)	3.4(10)
C(14)	5101(28)	6500(18)	-364(13)	5.3(10)
C(15)	4777(22)	7328(17)	236(10)	3.6(10)
C(16)	5402(22)	7256(17)	1032(13)	4.8(10)
C(17)	5173(32)	5991(17)	1430(14)	8.4(10)
C(18)	3823(22)	5765(21)	1655(17)	7.1(10)
C(19)	3425(34)	6722(19)	2232(13)	7.8(10)
C(20)	6892(20)	7313(18)	938(13)	4.3(10)
C(21)	7477(23)	7630(20)	1666(13)	5.2(10)
N(22)	5954(18)	6636(15)	-824(10)	4.9(10)
O(23)	6680(14)	7576(11)	-801(8)	4.8(8)
C(24)	4376(20)	5537(18)	-506(14)	4.5(10)
O(25)	3403(15)	5434(13)	-296(9)	4.9(8)
O(26)	4899(16)	4786(13)	-931(9)	6.1(8)
C(27)	4200(21)	3849(18)	-1170(13)	4.6(10)
C(28)	5102(3)	3203(25)	-1611(18)	10.0(10)
O(29)	3853(13)	245(12)	-976(7)	4.5(7)
O(30)	5856(15)	452(11)	-1989(8)	5.7(8)

B_{eq}=4/3*TRACE(B*G)

The transformation of oxime esters (−)-**4a, b** *into* (+)-*apovincaminic acid esters and* (+)-*vincamine*

After establishing the structures of derivatives (−)-**4a, b** unambiguously, investigations were carried out to convert these compounds into the pharmaceutically important (+)-apovincaminic acid esters and (+)-vincamine.

By heating the oxime esters (−)-**4a, b** for 0.5–1.0 hr in methanol or ethanol containing conc sulfuric acid, apovincamine (+)-**3a** and cavinton (+)-**3b** were obtained in yields of 72–82%.

When this reaction was carried out at room temperature for 120 hr, the cyclic hydroxyaminoester **5a** could be isolated in a yield of 72–75%. The structure of the cyclic form, **5a**, was determined by spectroscopic methods. Heating the cyclic form, **5a**, in the same mixture of methanol and conc sulfuric acid, gave (+)-apovincamine (**3a**) in a yield of 85%. All this substantiates the assumption that the cyclic form is the intermediate in this reaction.

Oxime ester (−)-**4a** was suitable material for the simultaneous preparation of vincamine (+)-**1** and apovincamine (+)-**3a**. Derivative (−)-**4a** was heated on a steam bath for 2 hr in dilute aqueous sulfuric acid in the presence of acetic acid to aid dissolution, whereupon the mixture contained (+)-vincamine, (−)-epivincamine and the starting compound, (−)-**4a**. The mixture of bases extracted from the aqueous solution by methylene chloride after basification with aqueous NH_4OH, was epimerized in NaOMe/MeOH, whereupon (+)-vincamine could be separated in crystalline form (38%), and oxime ester (−)-**4a**, containing an acidic hydrogen, remained in the methanolic alkaline solution. By adding methanol containing conc sulfuric acid to this solution and heating the mixture on a steam bath, apovincamine (+)-**3a** could be obtained in a way discussed above in a yield of 33%. If desired, the proportion of (+)-vincamine can be increased significantly (to 67–75%) by carrying out this reaction in the presence of sodium pyrosulfite.[16]

Transformation of oxime ester (−)-**4b** *into* (−)-*vincamone*

Oxime ester (−)-**4b** is also useful for the preparation of pharmaceutically important (−)-vincamone. This compound was converted with NaOH in aqueous ethanol into oxime carboxylic acid, (−)-**4c**, in a yield of 73%, which on heating in decalin, forms *cis* nitrile **17** upon water elimination, in a yield of *ca* 73%. This latter derivative proved to be identical with the compound isolated by French authors[17] after the

Table 3. Atomic coordinates ($\times 10^3$) for hydrogen atoms of (−)-**4b**·HCl(BH). E.s.d's are given in parentheses.

	x/a	y/b	z/c	B_{iso}
HN(1)	-486(1)	-500(1)	-297(1)	3.6
HO(23)	-856(1)	-332(1)	- 18(1)	5.3
H(5A)	-101(1)	-237(1)	-120(1)	4.4
H(5B)	- 50(1)	-337(1)	-162(1)	4.4
H(6A)	- 74(1)	-219(1)	-254(1)	5.3
H(6B)	-239(1)	-181(1)	-221(1)	5.3
H(9)	-157(1)	-184(1)	-400(1)	4.8
H(10)	-241(1)	-214(1)	-522(1)	5.6
H(11)	-393(1)	-354(1)	-553(1)	5.0
H(12)	-488(1)	-465(1)	-459(1)	4.8
H(15A)	-614(1)	-373(1)	-205(1)	3.6
H(15B)	-595(1)	-338(1)	-120(1)	3.6
H(17A)	-553(1)	-522(1)	- 39(1)	4.0
H(17B)	-377(1)	-556(1)	- 56(1)	4.0
H(18A)	-473(1)	-361(1)	- 16(1)	4.5
H(18B)	-369(1)	-434(1)	34(1)	4.5
H(19A)	-160(1)	-417(1)	- 48(1)	4.1
H(19B)	-213(1)	-309(1)	- 21(1)	4.1
H(20A)	-559(1)	-554(1)	-233(1)	4.4
H(20B)	-602(1)	-604(1)	-155(1)	4.4
H(21A)	-421(1)	-705(1)	-219(1)	5.4
H(21B)	-342(1)	-664(1)	-144(1)	5.4
H(21C)	-299(1)	-614(1)	-222(1)	5.4
H(27A)	-915(1)	-550(1)	-335(1)	5.2
H(27B)	-1040(1)	-469(1)	-309(1)	5.2
H(28A)	-933(1)	-420(1)	-427(5)	6.0
H(28B)	-761(1)	-422(1)	-391(1)	6.0
H(28C)	-886(1)	-340(1)	-364(1)	6.0
HN(4)	-342(1)	-270(1)	-117(1)	4.0
H(3)	-255(1)	-487(1)	-173(1)	4.0

Table 4. Atomic coordinates ($\times 10^3$) of (−)-**4b**(B). E.s.d's are given in parentheses.

	x/a	y/b	z/c	B_{iso}
H(15A)	391(1)	721(1)	33(1)	4
H(15B)	473(1)	807(1)	000(1)	4
H(9)	301(1)	1219(1)	143(1)	4
H(10)	411(1)	1367(1)	81(1)	4
H(11)	610(1)	1333(1)	25(1)	4
H(12)	700(1)	1151(1)	30(1)	4
HN(1)	659(1)	936(1)	80(1)	4
H(5A)	212(1)	830(1)	262(1)	4
H(5B)	357(1)	872(1)	289(1)	4
H(6A)	208(1)	964(1)	157(1)	4
H(6B)	258(1)	1038(1)	232(1)	4
H(20A)	722(1)	654(1)	76(1)	4
H(20B)	711(1)	790(1)	51(1)	4
H(21A)	847(1)	765(1)	158(1)	4
H(21B)	728(1)	703(1)	210(1)	4
H(21C)	718(1)	842(1)	184(1)	4
H(27A)	389(1)	340(1)	- 68(1)	4
H(27B)	346(1)	408(1)	-151(1)	4
H(28A)	470(1)	248(1)	-182(1)	4
H(28B)	588(1)	301(1)	-125(1)	4
H(28C)	543(1)	370(1)	-209(1)	4
H(3)	528(1)	789(1)	212(1)	5.3

Beckmann rearrangement of 16-oximinoaspidospermidine.

Cis nitrile **17** can also be regarded as the tautomeric form of imino derivative **18**, and indeed, in a base catalyzed reaction, it can be converted nearly quantitatively into imino derivative **18**, which was prepared by Warnant *et al.*[18] in an independent way.

From compound **18**, (−)-vincamone can be prepared easily by means of acidic hydrolysis.[18]

EXPERIMENTAL

IR spectra were recorded on Spektromom 2000 and UR-10 Infrared Spectrometers. NMR spectra were recorded at 60 MHz on a Perkin–Elmer R-12 Spectrometer, and at 100 MHz on a Varian XL 100–15 (Fourier transform) instrument in $CDCl_3$ soln with TMS as internal reference. Chemical shifts are expressed in units of δ (ppm downfield from TMS) and coupling constants (J) are given in Hertz (Hz). Mass spectra were taken on an AEI-MS-902 (70 eV, direct insertion) mass spectrometer. Mps are uncorrected.

(±) - 1 - *Ethyl* - 1 - (2′,2′ - *diethoxycarbonylethyl*) - 1,2,3,4,6,7 - *hexahydro* - 12*H* - *indolo*[2,3-*a*]*quinolizin* - 5 - *iumperchlorate* (**8a**)

To a suspension of **7** iminium-perchlorate[6] (10.00 g, 28.4 mmole) in dry CH_2Cl_2 (75 ml), freshly distilled diethyl methylenemalonate (7.36 g, 42.7 mmole), and then KOBu^t (150 mg, 1.34 mmole) in dry CH_2Cl_2 (10 ml), were added with stirring. The stirring was continued at room temp for 24 hr. A few drops of AcOH were added and the solvent was evaporated under reduced pressure. The residue was triturated with ether (2 × 10 ml) and the oil was crystallized from EtOH, to give **8a** (14.0 g, 94%) as yellow crystals, m.p. 155–156° (EtOH). (Found: C, 56.97; H, 6.50; N, 5.52. Calc for $C_{25}H_{33}N_2O_8$ (524.98): C, 57.20; H, 6.34; N, 5.34.) IR(KBr): 3300 (indole NH), 1730, 1720 (ester CO), 1610, 1590 cm^{-1} (C=N).

Alkylation of enamine **6** *with diethyl methylenemalonate*

Iminium-perchlorate **7** (5.00 g, 14.2 mmole) in CH_2Cl_2 (44 ml) was shaken with 2% NaOH aq for 2 min. After separation the organic layer was dried (K_2CO_3) and freshly distilled diethyl methylenemalonate (9.7 g, 56.3 mmole) was added dropwise to the stirred soln. The reaction was allowed to stand for 24 hr at room temp under an Ar atmosphere. The soln was evaporated to dryness *in vacuo* and the red oil obtained was triturated with petroleum ether (3 × 40 ml). The residue (11 g) was dissolved in EtOH (150 ml), treated with HCl/EtOH to pH 7–7.5 and hydrogenated over 10% Pd/C (2 g). When the H_2 consumption ceased (25% of the calculated amount) the catalyst was filtered off and the solvent was removed *in vacuo*. The residue was treated with 5% Na_2CO_3 aq (50 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness to afford a complex mixture (4.5 g), which was separated by low-pressure column chromatography on Silica gel (KG-60PF$_{254+366}$) eluting with benzene:MeOH (6:1).

The faster running fraction (80 mg oil) was crystallized from EtOH (2 ml) to give **10a** (42 mg, 0.7%) as white crystals. M.p. 132–133° (EtOH). (Found: C, 70.85; H, 8.27; N, 6.61. Calc for $C_{25}H_{34}N_2O_4$ (426.55): C, 70.40; H, 8.03; N, 6.57). IR (KBr): 3270 (indole NH), 2800–2700 (Bohlmann bands), 1730, 1700 cm^{-1} (ester CO). MS *m/e* (%): 426 (M^+, 13), 425 (7.1), 411 (0.8), 397 (0.8), 381 (4.2), 353 (1.8), 335 (0.5), 307 (0.6), 267 (100), 237 (5.2), 197 (6), 170 (7.6), 169 (9.1). ^{1}H NMR ($CDCl_3$, δ): 9.52 (1H, s, indole NH), 7.50–7.05 (4H, m, aromatic), 4.32, 4.30 (4H, q, J_1 = 7.3 Hz, OCH_2–CH_3), 3.82 (1H, d, d, J_1 = 7.4 Hz, J_2 = 4 Hz, 2′-H), 3.39 (1H, s, 12b-H), 1.36 (6H, t, d, J = 7.3 Hz, OCH_2–CH_3), 0.70 ppm (3H, t, J = 7.7 Hz, CH_2CH_3).

The slower running fraction was separated by preparative TLC [$Al_2O_3PF_{254+366}$ (Typ T); CH_2Cl_2:benzene 2:1; eluting with CH_2Cl_2:MeOH 25:1; R_f **9a** > **9b** > **9c** > **9d**], to give the following *cis*-esters which were isolated as hydrochloride salts.

Compound **9a**. HCl, 185 mg (2.8%); m.p. 205–207° (EtOH–ether). (Found: C, 64.70; H, 7.92; N, 6.28. Calc for $C_{25}H_{35}N_2O_4Cl$ (463.09): C, 64.85; H, 7.40; N, 6.05). IR(KBr): 3350 (indole NH), 2800–2750 (Bohlmann bands), 1720 cm^{-1} (ester CO). MS *m/e*, (%): 426 (M^+, 15), 425 (12), 411 (1), 381 (8), 365 (0.5), 353 (2), 307 (0.6), 267 (100), 253 (2), 237 (4), 197 (12), 185 (8), 184 (7), 170 (10), 169 (12), 156 (5), 145 (0.6), 144 (5), 143 (3), 127 (1), 124 (3). ^{1}H NMR ($CDCl_3$, δ): 7.82 (1H, s, indole NH), 7.51–7.02 (4H, m, aromatic), 4.10, 4.09 (4H, q, J = 7.3 Hz, OCH_2CH_3), 3.36 (1H, s, 12b-H), 3.32 (1H, d, d, J_1 = 7.3 Hz, J_2 = 6 Hz, 2′-H), 1.18 (6H, t, J = 7.2 Hz, OCH_2–CH_3), 1.13 ppm (3H, t, J = 7 Hz, CH_2CH_3).

Compound **9b**. HCl, 210 mg (2.3%); m.p. 211–212° (EtOH–ether). (Found: C, 62.35; H, 7.39; N, 4.53. Calc. for $C_{33}H_{47}N_2O_8Cl$ (635.18): C, 62.40; H, 7.46; N, 4.41). IR(KBr): 3250 (indole NH), 1740–1715 cm^{-1} (ester CO). IR($CHCl_3$): 3245 (indole NH, 2800–2755 (Bohlmann bands), 1740–1715 cm^{-1} (ester CO). MS *m/e*, (%): 426 (6), 425 (3), 411 (0.3), 397 (0.3), 381 (2), 353 (1), 267 (100), 253 (3), 237 (5), 197 (8), 185 (6), 184 (6), 170 (10), 169 (10), 156 (6), 144 (5), 127 (10), 99 (10). ^{1}H NMR ($CDCl_3$, δ): 7.93 (1H, s, indole NH), 7.54–7.06 (4H, m, aromatic), 4.25–3.91 (8H, m, OCH_2CH_3), 3.35 (1H, s, 12b-H), 3.34 (1H, t, J = 5.5 Hz, 4′-H), 1.29–1.06 ppm (15H, m, OCH_2–CH_3 and CH_2CH_3).

Compound **9c**. HCl, 830 mg (7.3%); m.p. 181–183° (EtOH–ether). (Found: C, 60.62; H, 7.47; N, 3.49. Calc for $C_{41}H_{59}N_2O_{12}Cl$ (807.35): C, 60.99; H, 7.36; N, 3.47.) IR(KBr): 3350 (indole NH), 1740–1715 cm^{-1} (ester CO). IR($CHCl_3$): 3320 (indole NH), 2790–2750 (Bohlmann bands), 1740–1715 cm^{-1} (ester CO). MS *m/e*, (%): 426 (5), 425 (3), 411 (0.3), 381 (2), 365 (0.6), 353 (0.6), 332 (0.3), 307 (0.3), 267 (100), 253 (1), 237 (2), 197 (5), 185 (2), 184 (3), 170 (5), 169 (6), 156 (2), 145 (3), 144 (4), 143 (3), 127 (50), 124 (2), 99 (30). ^{1}H NMR ($CDCl_3$, δ): 7.97 (1H, s, indole NH), 7.52–7.04 (4H, m, aromatic), 4.25–3.86 (12H, m, OCH_2CH_3), 3.70 (1H, t, J = 6 Hz, 6′-H), 3.30 (1H, s, 12b-H), 1.36–1.00 ppm (21H, m, OCH_2–CH_3 and CH_2–CH_3).

Compound **9d**. HCl, 78 mg (0.56%); m.p. 171–174° (EtOH–ether). IR(KBr): 3320 (indole NH), 1760–1730 cm^{-1} (ester CO). IR($CHCl_3$): 3300 (indole NH), 2800–2745 (Bohlmann bands), 1760–1730 cm^{-1} (ester CO). MS *m/e*, (%): 426 (7), 425 (5), 411 (0.5), 397 (1), 381 (3), 353 (1), 307 (0.5), 287 (0.5), 267 (100), 253 (1), 237 (3), 197 (6), 185 (3), 184 (3), 170 (8), 169 (7), 156 (4), 144 (8), 127 (60), 99 (50). ^{1}H NMR($CDCl_3$, δ): 8.01 (1H, s, indole NH), 7.55–7.05 (4H, m, aromatic), 4.27–3.83 (16H, m, OCH_2–CH_3), 3.75 (1H, t, J = 6.5 Hz, 8′-H), 3.30 (1H, s, 12b-H), 1.38–0.98 ppm (27H, m, OCH_2–CH_3 and CH_2–CH_3).

(±) - 1α - *Ethyl* - 1β - (2′,2′ - *diethoxycarbonylethyl*) - 1,2,3,4,6,7,12,12bα - *octahydro* - *indolo*[2,3-*a*]*quinolizine* **9a** *and its* 12*bβ*-*Epimer* **10a**

Iminium-perchlorate **8a** (1.00 g, 1.91 mmole) was hydrogenated over 10% Pd/C (0.4 g) in dry DMF (11 ml). When the H_2 consumption stopped the catalyst was removed by filtration, washed with DMF (10 × 2 ml) and the solvent was evaporated to dryness *in vacuo*. The residue was crystallized from EtOH–ether (2:1) to give the perchlorate salt of **9a** (0.85 g, 84.7%), m.p. 195–197° (EtOH–ether). IR(KBr): 3320 (indole NH), 1720 cm^{-1} (ester CO). After evaporation of the mother liquor the residue was partitioned between CH_2Cl_2 (8 ml) and 5% $NaHCO_3$ aq (10 ml). The organic layer was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by preparative TLC (KG 60PF$_{254+366}$; benzene:MeOH 14:3; eluting with acetone:ether 1:1) and the oil obtained (45 mg) was crystallized

from EtOH (1 ml) to give **10a** (25 mg, 3%), m.p. 131–133° (EtOH).

Preparation of (±) - 14 - *oxo* - 15 - *ethoxycarbonyl* - E - *homo* - *eburnan* (**11**) *by ring closure of* **9a–d**

Compounds **9a–d** (1 mmole) in dry benzene (10–15 ml) were refluxed with KOBu^t (145 mg, 1.3 mmole) under N_2 for 0.5–1 hr. The mixture was acidified with AcOH to pH 6 and evaporated to dryness under reduced pressure. The residue was treated with 5% Na_2CO_3 aq (15 ml) and extracted with CH_2Cl_2 (3 × 5 ml). The combined extracts were dried ($MgSO_4$), evaporated and the residual oil crystallized from EtOH (1 ml) to afford **11** in yields of 75.7, 80.8, 69.5 and 45.0%, respectively, m.p. 143–144° (EtOH). (Found: C, 72.45; H, 7.77; N, 7.35. Calc for $C_{23}H_{28}N_2O_3$ (380.47): C, 72.60; H, 7.42; N, 7.36.) IR(KBr): 1738 (ester CO), 1690 cm^{-1} (lactam CO). MS *m/e*, (%): 380 (M^+, 100), 379 (35), 363 (20), 352 (17), 351 (26), 335 (12), 329 (9.1), 307 (55), 237 (17). ^{1}H NMR ($CDCl_3$, δ): 8.52–7.35 (4H, m, aromatic), 4.31 (2H, q, J = 7.2 Hz, OCH_2CH_3), 4.08 (1H, s, 3-H), 3.75 (1H, d, J = 11 Hz, 15-H), 1.34 (3H, t, J = 7.6 Hz, OCH_2–CH_3), 0.91 ppm (3H, t, J = 8.1 Hz, CH_2–CH_3).

(±) - 14 - *Oxo* - 15 - *ethoxycarbonyl* - 3 - *epi* - E - *homo* - *eburnan* (**12**)

Compound **10a** (980 mg, 2.3 mmole) in dry benzene (20 ml) was refluxed with KOBu^t (335 mg, 2.99 mmole) under N_2 for 0.5 hr. The mixture was acidified with AcOH to pH 6 and evaporated to dryness. The residue was partitioned between CH_2Cl_2 (20 ml) and 5% aq Na_2CO_3 (25 ml). The aqueous layer was extracted further with CH_2Cl_2 (2 × 5 ml), the combined organic extracts were dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residue was crystallized from EtOH (3 ml) to give **12** (720 mg, 82.4%), m.p. 173–175° (EtOH). (Found: C, 72.48; H, 7.42; N, 7.36. Calc. for $C_{23}H_{28}N_2O_3$ (380.47); C, 72.60; H, 7.42; N, 7.36.) IR(KBr): 2750–2700 (Bohlmann bands), 1735 (ester CO), 1680 cm^{-1} (lactam CO). MS *m/e*, (%): 380 (M^+, 100), 379 (38), 363 (14), 352 (11), 351 (16), 335 (11), 323 (5.5), 307 (34), 280 (6.3), 277 (4.8), 266 (8), 265 (6.7), 252 (28), 251 (8.5), 237 (10), 169 (9.7). ^{1}H NMR ($CDCl_3$, δ): 8.56–7.24 (4H, m, aromatic), 4.32 (2H, q, J = 7.6 Hz, OCH_2CH_3), 4.08 (1H, d, d, J_1 = 13.6 Hz, J_2 = 2.7 Hz, 15-H), 3.41 (1H, s, 3-H), 1.35 (3H, t, J = 7.6 Hz, OCH_2CH_3), 0.74 ppm (3H, t, J = 6 Hz, CH_2CH_3).

General method for the preparation of lactams **13** and **14**

Compound **11** or **12** (100 mg, 0.263 mmole) in 10% H_2SO_4 aq (15 ml) containing EtOH (0.3 ml) was heated under reflux for 6–8 hr. The mixture was treated with 25% NH_4OH to pH 8–9 with cooling and extracted with CH_2Cl_2 (3 × 2 ml). The combined extracts were dried ($MgSO_4$), evaporated to dryness, and the residue was crystallized from MeOH (0.5 ml) to afford lactams **13** or **14**.

Cis lactam **13**: 36 mg (44.3%), m.p. 162–163° (MeOH). (lit[8]. m.p. 164°). IR(KBr): 1695 cm^{-1} (lactam CO).

Trans lactam **14**: 26 mg (32.0%), m.p. 138–139° (MeOH). (lit[8].: m.p. 132°). IR(KBr): 2810–2700 (Bohlmann bands), 1690 cm^{-1} (lactam CO).

(±) - 1α - *Ethyl* - 1β - (2′ - *carboxy* - 2′ - *ethoxycarbonylethyl*) - 1,2,3,4,6,7,12,12*bα* - *octahydro* - *indolo*[2,3-*a*]*quinolizine* **15a**

To a soln of **9a** (400 mg, 0.94 mmole) in EtOH (5 ml) a soln of KOH (63 mg, 1.15 mmole) in water (0.6 ml) was added. The mixture was allowed to stand at room temp for 4–5 hr. After evaporation the residue was dissolved in water (2 ml) and extracted with ether (3 ml). The aqueous layer was partially evaporated to remove ether and acidified with AcOH to pH 4–5 with cooling. The ppt was filtered off, washed with water, and dried to afford **15a** (298 mg, 79%) hemiester, m.p. 119–121° (water). IR(KBr): 3300 (indole NH), 1715 (ester CO), 1600 cm^{-1} (carboxylate). MS *m/e*, (%): 354 (M^+-44, 53), 353 (58), 339 (8), 325 (8.3), 309 (12), 281 (2), 267 (100), 197 (35), 185 (20), 171 (40), 170 (43), 169 (37), 44 (100).

(±) - *Ethyl* - (1α - *ethyl* - 1,2,3,4,6,7,12,12*bα* - *octahydroindolo*[2,3-*a*]*quinolizin* - 1β - *yl*)*propionate* (**16**)

Compound **15a** (225 mg, 0.567 mmole) in dry benzene (3 ml) was heated under reflux for 3 hr. The solvent was evaporated under reduced pressure and the residue was crystallized from EtOH (2 ml) to give **16** (140 mg, 69.8%), m.p. 134° (EtOH). (lit.[1]: m.p. 136–138°), identical with an authentic sample).[1]

(±) - 1α - *Ethyl* - 1β - (2′ - *methoxycarbonyl* - 2′ - *ethoxycarbonylethyl*) - *indolo* [2,3-*a*] - 1,2,3,4,6,7,12,12*bα* - *octahydro* - *quinolizine* (**15b**)

To a suspension of **15a** (100 mg, 0.251 mmole) in CH_2Cl_2 (2 ml), an excess of diazomethane in CH_2Cl_2 was added. The mixture was stirred at 0° until the solid dissolved. The solution was evaporated to dryness *in vacuo*. The residue was dissolved in MeOH (0.5 ml), treated with HCl/MeOH to pH 4 and crystallized by adding ether (2 ml) to afford **15b** (72 mg, 63.8%), m.p. 187–189° (ether). (Found: C, 64.33; H, 7.20; N, 6.02. Calc for $C_{24}H_{33}N_2O_4Cl$ (448.98): C, 64.20; H, 7.19; N, 6.24.) IR(KBr): 3350 (indole NH), 1730, 1720 cm^{-1} (ester CO). ^{1}H NMR ($CDCl_3$, δ): 7.80 (1H, s, indole NH), 7.51–6.97 (4H, m, aromatic), 4.18, 4.16 (2H, q, J = 7 Hz, OCH_2–CH_3), 3.63, 3.60 (3H, s, OCH_3), 3.36 (1H, s, 12b-H), 3.34 (1H, d, d, J_1 = 13 Hz, J_2 = 1.5 Hz, 2′-H), 1.27–1.07 ppm (6H, m, OCH_2–CH_3 and CH_2CH_3).

(±) - *Ethyl* - (1,2,3,4,6,7,12,12*bα* - *octahydro* - *indolo*[2,3-*a*]*quinolizin* - 1β - *yl*)*pyruvate oxime* [(±)-**4b**]

To a soln of **15a** (0.75 g, 1.885 mmole) in AcOH (15 ml), a soln of $NaNO_2$ (0.39 g, 5.65 mmole) in water (5 ml) was added. The mixture was allowed to stand at room temp for 1 hr. Upon cooling to 0–5° it was basified with 30% NaOH aq to pH 11 and extracted with CH_2Cl_2 (5 × 30 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to 5 ml and the crystalline product filtered off to give (±)-**4b** (0.52 g, 72%), m.p. 156–158° (CH_2Cl_2). (Found: C, 68.95; H, 7.37; N, 10.85. Calc for $C_{22}H_{29}N_3O_3$ (383.47): C, 68.90; H, 7.62; N, 10.96.) IR(KBr): 3400 (indole NH, OH), 1710 cm^{-1} (ester CO). MS *m/e*, (%): 383 (M^+, 98), 382 (59), 366 (100), 354 (10), 338 (7.7), 310 (31), 292 (29), 278 (8.5). ^{1}H NMR ($CDCl_3$, δ): 10.70 (1H, broad, NOH), 7.94 (1H, s, indole NH), 7.50–6.94 (4H, m, aromatic), 4.04 (2H, q, J = 7 Hz, OCH_2), 3.36 (1H, s, 12b-H), 1.11 (3H, t, J = 7 Hz, OCH_2CH_3), 1.03 ppm (3H, t, J = 6 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$, δ): 165.22 (CO), 152.44 (C=N), 136.42 (C–11a), 132.23 (C–12a), 126.69 (C–7b), 121.57 (C–10), 119.23 (C–9), 117.97 (C–8), 112.06 (C–7a), 110.99 (C–11), 67.39 (C–12b), 61.47 (OCH_2), 56.87 (C–4), 54.54 (C–6), 41.89 (C–1), 33.14 (C–2), 31.35 (CH_2–CH_3), 27.71 (CH_2–C=N), 21.52–21.18 (C–7/C–3), 13.84 (OCH_2–CH_3), 8.25 ppm (CH_2–CH_3).

Resolution of the oxime **4b**

To a soln of racemic **4b** (450 mg, 1.175 mmole) in EtOH (15 ml), a soln of D-dibenzoyl tartaric acid (422 mg), 1.175 mmole) in CH_2Cl_2 (5 ml) was added. After evaporation to dryness *in vacuo* the residue was dissolved in a mixture of CH_2Cl_2 (12 ml) and EtOH (1 ml) and allowed to crystallize at 0° for a fortnight. The crystalline salt of (−)-**4b** [405 mg, 46.5%; $[\alpha]_D^{22} = -47°$, $[\alpha]_{546}^{22} = -65°$ (*c* 0.875, EtOH)] was partitioned between CH_2Cl_2 (5 ml) and 5% Na_2CO_3aq. The organic layer was dried, the solvent was evaporated and the residue was crystallized from EtOH (2 ml) to yield (−)-**4b** (198 mg, 44%). M.p. 172–173° (EtOH). $[\alpha]_D^{25} = -59°$, $[\alpha]_{546}^{25} = -71°$; (*c* 1.00, DMF). (−)-**4b**. HCl: m.p. 248° (dec, EtOH–water). IR(KBr): 3340 (indole NH), 1725 (ester CO), 1620 cm^{-1} (C=N).

Crystal structure determinations on (−)-**4b** *base and its* HCl *salt*

	Base (B)	Salt (BH)
Chemical formula:	$C_{22}H_{29}N_3O_3 \cdot 2H_2O$	$C_{22}H_{29}N_3O_3 \cdot HCl$
MW:	419.53	419.96
Crystal symmetry:	orthorhombic	orthorhombic
Space group:	$P2_12_12_1$	$P2_12_12_1$
a:	10.986(1) Å	8.689(1) Å
b:	12.283(3)	13.695(4)
c:	17.455(6)	18.337(5)
V:	2355.4 Å^3	2182.03 Å^3
Z:	4	4
D_c:	1.183 g. cm^{-3}	1.278 g. cm^{-3}
F(OOO)	904	896
N_{tot}	1726	2198
N_{obs}	1124	966
R_{obs}	0.151	0.070
R_w	0.185	0.069

The symmetry independent reflexions for both compounds were collected on an Enraf–Nonius CAD-4 computer-controlled four-circle diffractometer equipped with graphite monochromator using Mo*Kα* radiation ($\lambda = 0.71073$ Å). Cell constants were determined by least-squares refinements from the setting angles of 25 reflexions for each crystal. No absorption correction was applied in either case. Both crystal structures were solved by direct method using program MULTAN.[19] The non-hydrogen atoms including Cl of the *protonated base* were located in an *E*-map (based on the use of 277 E values greater than 1.5) and in a subsequent Fourier synthesis. The full-matrix least-squares refinement of the positional and anisotropic vibrational parameters of the non-hydrogen atoms resulted in a final conventional R value given above. The fractional coordinates of H atoms were located in a difference Fourier map and were included in the final structure factor calculations with individual isotropic thermal parameters. The E-map computed from the best set of phase combination by ther use of 212 normalized structure factors having $E \geq 1.45$ gave the positions of 26 non-hydrogen atoms of the *base* (R = 0.43). One successive cycle of structure factor and Fourier calculations allowed the location of the missing 2 atoms of the molecule. Because U/4 × 19 Å^3 is about 31, two further non-hydrogen atoms could be expected in the asymmetric unit. Indeed, two subsequent difference map calculations (at R = 0.26 and 0.19) revealed two O atoms which represent two water molecules. The hydrogen positions were generated from assumed geometries. However, no H positions were generated to Cl7, Cl8, Cl9, O23, O29 and O30 atoms. Since it was then apparent from both structural models that the ring closure to Cl4 could not be achieved the refinement was terminated at R = 0.151. Atomic scattering factors were taken from *International Tables for X-ray Crystallography*.[20] All calculations were performed on a PDP-11/34 minicomputer with the Enraf-Nonius SDP-34 system applied with some local modifications. The final fractional coordinates of the non-hydrogen atoms are given in Tables 1 and 2 and those of H atoms in Tables 3 and 4.

Transesterification of (−)-**4b** *to* (−)-**4a**

A soln of (−)-**4b** (1.00 g, 2.61 mmole) in MeOH (20 ml) was heated with $NaOCH_3$ (30 mg, 0.56 mmole) under N_2 for 4 hr. The mixture was acidified with AcOH to pH 6 and evaporated to dryness *in vacuo*. The residue was treated with 25% aq NH_4OH (5 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic extracts were dried ($MgSO_4$), evaporated *in vacuo*, and recrystallized from MeOH (5 ml) to afford (−)-**4a** (0.73 g, 75.8%), m.p. 195° (MeOH). (Found: C, 68.27; H, 7.29; N, 11.28. Calc for $C_{21}H_{27}N_3O_3$ 369.44): C, 68.27; H, 7.36; N, 11.38.) IR(KBr): 3420 (indole NH, OH), 1706 cm^{-1} (ester CO). MS *m/e*, (%): 369 (M$^+$, 100), 368 (42), 352 (40), 340 (4.4), 310 (13), 292 (9.5), 267 (18), 253 (44), 211 (9.5), 197 (35), 184 (30), 170 (40), 169 (35). ^{1}H NMR ($CDCl_3$, δ): 10.18 (1H, broad, NOH), 7.87 (1H, s, indole NH), 7.50–7.03 (4H, m, aromatic), 3.53 (3H, s, OCH_3), 3.37 (1H, s, 12b-H), 1.13 ppm (3H, t, J = 7 Hz, CH_2–CH_3). ^{13}C NMR ($CDCl_3$, δ): 165.84 (CO), 152.20 (C=N), 136.53 (C–11a), 133.10 (C–12a), 126.76 (C–7b), 121.27 (C–10), 119.02 (C–9), 117.66 (C–8), 111.83 (C–7a), 111.18 (C–11), 67.38 (C–12a), 56.93 (C–4), 54.38 (C–6), 52.00 (OCH_3), 41.89 (C–1), 33.02 (CH_2–CH_3), 31.13 (C–2), 27.88 (CH_2–C=N), 21.81–21.67 (C–7/C–3), 8.28 ppm (CH_2–CH_3). $[\alpha]_D^{22} = -61.4°$; $[\alpha]_{546}^{22} = -72.6°$ (*c* 1.02, DMF). (−)-**4a**. HCl: m.p. 247° (dec., MeOH). IR(KBr): 3350 (indole NH, OH), 1738 (ester CO), 1618 cm^{-1} (C=N).

(+)-*Apovincamine* (**3a**)

(A) The methyl ester (−)-**4a** (2.00 g, 5.42 mmole) was heated in a mixture of MeOH (37.5 ml) and conc H_2SO_4 (13.5 ml) on a water bath for 1 hr. The soln was poured into ice-water (80 ml), basified with conc NH_4OH to pH 9, and extracted with CH_2Cl_2 (3 × 20 ml). The combined extracts were dried ($MgSO_4$), filtered, evaporated *in vacuo* and the residue was recrystallized from MeOH (5 ml) to yield 1.32 g (72.5%) of (+)-apovincamine, m.p. 160–162°; (lit[1].: m.p. 160–162°). IR, MS, ^{1}H NMR spectra were identical with those of an authentic sample.[1]

(B) The hydroxyamino ester (−)-**5a** (1.00 g, 2.7 mmole) gave under the same circumstances as described in method A 0.75 g (82%) of (+)-apovincamine.

(−) - 14 - *Hydroxyamino* - 14 - *methoxycarbonyl* - *eburnan* [(−) - **5a**]

The oxime ester (−)-**4a** (4.00 g, 10.8 mmole) was allowed to stand in a mixture of MeOH (75 ml) and conc H_2SO_4 (27 ml) at room temp for 120 hr. The soln was poured into ice-water (300 ml), basified with conc NH_4OH to pH 9, and extracted with CH_2Cl_2 (3 × 50 ml). The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. The residue was crystallized from MeOH (50 ml) to give 2.90 g (72.5%) as white crystals, m.p. 198°. IR(KBr): 3450 (broad), 3120 (NH, OH), 1758 cm^{-1} (ester CO). MS *m/e*, (%): 369 (M$^+$, 77.0), 352 (88.5), 337 (100.0), 310 (10.5), 308 (27.3). ^{1}H NMR($CDCl_3$, δ): 7.60–7.00 (4H, m, aromatic), 5.50 (1H, broad, NH), 3.78 (1H, s, 3-H), 3.68 (3H, s, OCH_3), 0.89 ppm (3-H, t, J = 7.2 Hz, CH_2–CH_3). ^{13}C NMR($CDCl_3$, δ): 171.16 (CO), 135.84 (C–13), 132.91 (C–2), 128.78 (C–8), 120.92 (C–10), 119.82 (C–11), 117.91 (C–9), 105.73 (C–7), 78.27 (C–14), 58.93 (C–3), 52.64 (OCH_3), 50.94 (C–5), 44.43 (C–19), 39.40 (C–15), 35.31 (C–16), 24.73 (C–17), 28.80 (CH_2–CH_3), 20.94 (C–18), 16.85 (C–6), 7.52 ppm (CH_2–CH_3). $[\alpha]_D^{25} = -34°$ (*c* 1.00, CH_2Cl_2).

(+)-*Apovincaminic acid ethylester, Cavinton*^{R} (**3b**)

The ethyl ester (−)-**4b** (2.00 g, 5.22 mmole) was heated in a mixture of EtOH (45 ml) and conc H_2SO_4 (16 ml) on a water bath for 30 min. The mixture was poured into ice-water (80 ml), treated with conc NH_4OH to pH 9, and extracted with CH_2Cl_2 (3 × 20 ml). The organic layer was dried ($MgSO_4$), filtered, evaporated to dryness *in vacuo*, and the residue was recrystallized from EtOH (5 ml) to give pure Cavinton (1.50 g, 83%), which was identical in all respects with an authentic sample,[1] m.p. 148–152° (lit.[1]: 148–152°).

(+)-*Vincamine* (**1**) *and* (+)-*apovincamine* (**3a**)

To a soln of oxime (−)-**4a** (0.88 g, 2.38 mmole) in AcOH (3.2 ml) 5% aq H_2SO_4 (32 ml) was added and heated on a water bath for 2 hr. The mixture was then basified with conc NH_4OH to pH 9 with ice cooling and extracted with CH_2Cl_2 (3 × 15 ml). The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. The residual oil was dissolved in MeOH (3.00 ml) containing NaOMe (180 mg) and allowed to stand at room temp for 2 hr. The crystalline product was filtered off and washed with cold MeOH to give 0.32 g (38%) of (+)-vincamine, identical with authentic sample, m.p. 234–235° (lit.[1,4a]: m.p. 234–235°).

The methanolic mother liquor was treated with AcOH to pH 6 and evaporated to dryness under reduced pressure. The residue was partitionated between 5% Na_2CO_3 aq (5 ml) and CH_2Cl_2 (10 ml). The organic phase was dried, evaporated, the residue reacted with conc H_2SO_4/MeOH, and worked up according to the preparation mentioned above, to give 0.28 g (35%) of (+)-apovincamine, identical in all respects with an authentic sample.

(−)-(1,2,3,4,6,7,12,12*bα* - *Octahydro* - *indolo*[2,3-*a*]*quinolizin* - 1*β* - *yl*) - *pyruvic acid oxime* [(−)-**4c**]

A soln of 2.00 g (5.22 mmole) oxime (−)-**4b** ester in a mixture of EtOH (10 ml) and water (0.4 ml) was refluxed with NaOH (0.48 g) for 1.5 hr. The solvent was removed *in vacuo* and the residue was dissolved in water (10 ml), acidified with AcOH (pH 6), the crystalline product filtered off, and washed with water to yield (−)-**4c** (1.35 g, 73%), m.p. 110–115° (dec.) (Found: C, 67.26; H, 7.08; N, 12.02. Calc for $C_{20}H_{25}N_3O_3$ (355.42): C, 67.58; H, 7.09; N, 11.82). IR(KBr): 3250 (broad, NH, OH), 1630 (C–N), 1580 cm^{-1} (broad, carboxylate CO). $[\alpha]_{546}^{22} = -16.6°$ (*c* 0.90, MeOH).

(−) - 1*β* - *Cyanomethyl* - 1*α* - *ethyl* - 1,2,3,4,6,7,12,12*bα* - *octahydro* - *indolo*[2,3-*a*]*quinolizine* [(−)-**17**]

A soln of (−)-**4c** (0.30 g, 0.84 mmole) in decalin (6 ml) was heated under stirring at 180° for 2 hr. After cooling, petroleum ether (4 ml) was added to the soln, the crystals were filtered off and washed with petroleum ether to give (−)-**17** (0.18 g, 73%), m.p. 203–204° (MeOH), (lit.[17]: m.p. 202–203°). IR(KBr): 3400 (indole NH), 2750, 2780, (Bohlmann bands), 2280 cm^{-1} (C≡N). MS *m/e*, (%): 293 (M$^+$, 100), 292 (88.9), 278 (10.9), 253 (8.3), 198 (10.9), 197 (34.5), 170 (34.5), 169 (5.1). ^{1}H NMR ($CDCl_3$, *δ*): 7.72 (1H, s, indole NH), 7.52–6.80 (4H, m, aromatic), 3.38 (1H, s, 12b-H), 1.21 ppm (3H, t, $J = 7.3$ Hz, CH_2–CH_3). $[\alpha]_D^{20} = -96.4°$; $[\alpha]_{546}^{22} = -109.1°$ (*c* 1.026, CH_2Cl_2).

(−)-14-*Imino-eburnan* (**18**)

A soln of (−)-**17** nitrile (0.50 g, 1.7 mmole) in MeOH (5 ml) was refluxed with NaOMe (0.18 g, 3.4 mmole) for 2 hr. After cooling, the pH of the soln was adjusted with AcOH to 6, and it was evaporated to dryness *in vacuo*. The residue was treated with 5% Na_2CO_3 aq, and extracted with CH_2Cl_2 (3 × 3 ml). The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated to yield imine **18** (0.49 g, 98%), m.p. 164–165° (MeOH). (Lit.[18]: m.p. 161°). IR(KBr): 3250 (=NH), 1628 cm^{-1} (C=N). MS *m/e* (%): 293 (M$^+$, 100), 292 (49), 265 (10), 264 (29), 237 (7.3), 224 (6.9), 223 (19), 221 (5.5), 168 (6.0), 167 (5.6). ^{1}H NMR ($CDCl_3$, *δ*): 8.6–8.45 (1H, m, 12-H), 7.68 (1H, s, =NH), 7.35–7.10 (3H, m, aromatic), 3.71 (1H, s, 3-H), 0.88 ppm (3H, t, $J = 7.3$ Hz, CH_3–CH_2). $[\alpha]_D^{25} = -99°$; $[\alpha]_{546}^{25} = -114.5°$ (*c* 1.03, $CHCl_3$) (lit.[18]: $[\alpha]_D = -92°$ *c*. 0.5, $CHCl_3$).

(−)-*Vincamone* (**2**)

The compound **18** (0.60 g, 2.04 mmole) was heated in a mixture of water (2.4 ml) and conc HCl (0.6 ml) at 80° for 30 min. The soln was then basified with 10% NaOH aq with ice cooling to pH 8 and extracted with CH_2Cl_2 (3 × 10 ml). The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. The residue (0.60 g) was recrystallized from MeOH to give **2** (0.45 g, 90%) identical in every respect with the authentic sample, m.p. 175 (lit.[18]: m.p. 175). IR(KBr): 1695 (lactam CO), 1618 cm^{-1} (aromatic). $[\alpha]_D^{25} = -97.6°$; $[\alpha]_{546}^{25} = -113.4$ (*c* 1.014, $CHCl_3$).

Acknowledgements—We thank Dr. László Párkányi and Dr. Pál Kolonits for their valuable help. The financial support of the Richter Gedeon Pharmaceutical Company and Hungarian Academy of Sciences is gratefully acknowledged.

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