Synthesis of *Vinca* Alkaloids and Related Compounds. Part 18.[1] Stereochemical Investigations on Some Intermediates leading to (+)-Vincamine

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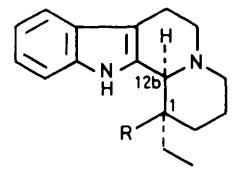
The C-2′ absolute configurations of hydroxy esters (**1**) and (**2**) have been determined by *X*-ray analysis. The absolute configurations at C-15 of several compounds with the E-homoeburnane skeleton [(**3**)—(**6**)] and the relative configurations at C-14 and -15 of compound (**8**) have been elucidated. The dominant conformation of compounds (**3**)—(**7**) have been established on the basis of ^{13}C n.m.r. and c.d. spectroscopic results. A new method has been elaborated for the preparation of oxime (**10**), a compound of importance in the synthesis of *Vinca* alkaloids.

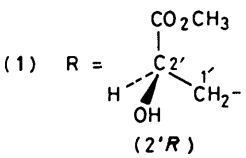
We assumed that the intermediates in the syntheses of racemic and (+)-vincamine reported by us[2] and of racemic vincamine reported by Gibson and Saxton[3] are the C-2′ epimeric hydroxy esters (**1**) and (**2**). This assumption was supported by the fact that both epimers could be oxidized into vincamine, but the racemic (**1**) prepared by us had a *ca.* 30 °C higher m.p. than racemic (**2**). In order to clarify this problem and to determine the C-14 and -15 configurations of related compounds with the E-homoeburnane skeleton the absolute configuration at C-2′ of (1*S*,12b*S*)-(**1**) hydroxy ester was determined by *X*-ray analysis.

X-Ray Analysis of the Molecular Structure of (−)-(**1**).—The final relative atomic co-ordinates† with their e.s.d.s are given in Tables 1 and 2. The geometry of the molecular (Figure 1) does not exhibit any unusual feature worthy of mention. Ring C adopts a twisted envelope E_6 (sofa) form (puckering parameters[4] $O = 0.53$ Å, $\psi = 229.2°$, $\theta = 123.7°$) between the planar indole moiety and the slightly flattened chair ($O = 0.60$ Å, $\psi = 204.2°$, $\theta = 164.7°$) ring D. The latter exhibits the sharpest pucker (the relevant torsion angles are given in Table 3) at the *trans* C/D junction. The ring system bears two substituents at C(1). The ethyl group is linked α-equatorially. Its terminal 16-methyl group is synclinal[5] (+sc) with C(2) of ring D across the C(1)–C(15) bond. The second side-chain, a β-substituted methyl 2-hydroxypropionate involving a novel chiral centre C(2′), is protruding from the mean plane of the fused ring system. Since the chirality of C(12b) is known to be *S* the chiral centres of molecule (**1**) can be fixed accordingly (Figure 1). Following the CIP system[6] the non-hydrogen substituents of C(2′), O(1), C(13), and C(1′) are ranked in a clockwise direction. Consequently, the absolute configuration of C(2′) is *R*.

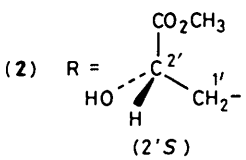
The ester methyl group is situated at the top of a zig-zag chain at a distance of 6.35 Å from the least-squares plane of the rings A—D ($0.3994X + 0.6166Y - 0.6784Z - 4.3362 = 0$). The second farthest atom ($\Delta = 5.01$ Å) O(2) is the acceptor of an intramolecular hydrogen bond attached to the O(1)-H moiety (O···O = 2.70, H···O = 2.47 Å, ∢OH···O = 92.3°). O(1) is simultaneously the acceptor of an intermolecular hydrogen bond between the N(12)-H group of the symmetry equivalent molecule (N···O = 2.19, H···O = 1.98 Å, ∢NH···O = 154.7°).

Since hydroxy ester (**1**) with the (1*S*,12b*S*,2′*R*) configuration could not be epimerized at C-2′ in the presence of either base or acid, another route had to be found for the preparation of epimer (**2**) with the (1*S*,12b*S*,2′*S*) configuration. In the base-catalysed cyclization of hydroxy ester (**1**), hydroxylactam (**3**) is obtained as the main product (70%) in addition to a small amount (7%) of the stereoisomer (**4**).[2] These compounds can be separated by crystallization or t.l.c. The physical data of optically active hydroxylactams (**3**) and (**4**) which were not reported earlier are in this paper.

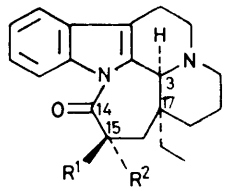




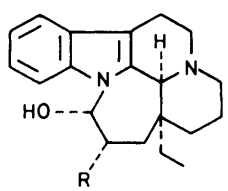
(1) R = 2′*R*



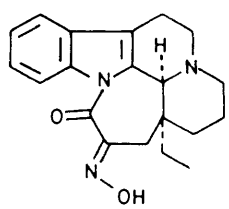
(2) R = 2′*S*



(**3**) R^1 = OH, R^2 = H
(**4**) R^1 = H, R^2 = OH
(**5**) R^1 = H, R^2 = Cl
(**6**) R^1 = Cl, R^2 = H
(**7**) R^1 = H, R^2 = H



(**8**) R = OH
(**9**) R = H



(**10**)

† Bond distances and angles together with U_{ij} values and structure factors are deposited in Supplementary Publication No. SUP 56023 (31 pp.). For details of Supplementary Publications see Instructions for Authors in *J. Chem. Soc., Perkin Trans. 2*, 1984, Issue 1.

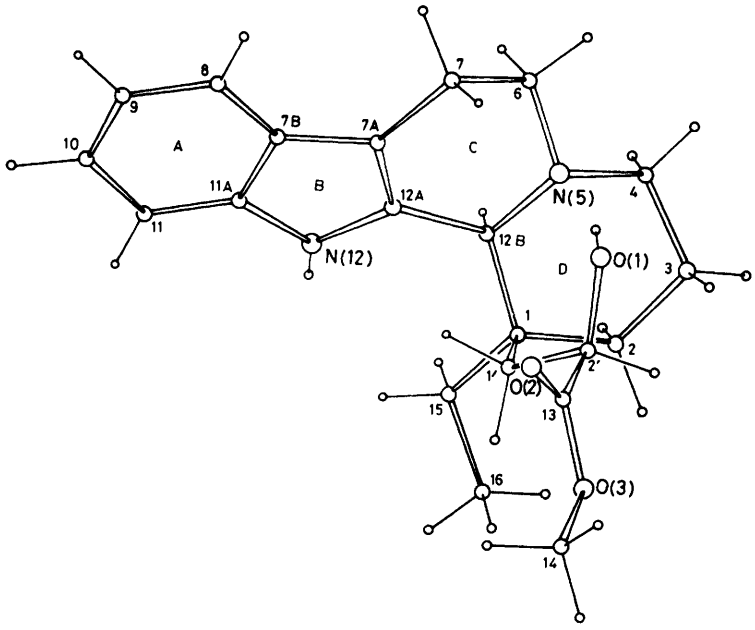


Figure 1. A perspective view of the molecule showing the main plane of the fused ring system. The bare numbers are for carbon unless indicated otherwise. The hydrogen atoms are shown but not labelled

Table 1. Final fractional co-ordinates ($\times 10^4$) for non-hydrogen atoms. E.s.d.s are given in parentheses

	x	*y*	*z*	B_{eq}(Å^2)
C(1)	−2 622(2)	−1 114(1)	1 987(1)	2.8(1)
C(2)	−4 142(2)	−501(4)	2 016(1)	3.5(1)
C(3)	−4 166(2)	1 051(4)	2 719(2)	3.8(1)
C(4)	−3 089(2)	799(4)	3 711(1)	3.6(1)
N(5)	−1 677(2)	434(2)	3 571(1)	2.8(1)
C(6)	−567(2)	582(3)	4 496(1)	3.4(1)
C(7)	889(2)	599(3)	4 301(1)	3.5(1)
C(7A)	983(2)	−1 059(3)	3 723(1)	2.8(1)
C(7B)	2 185(2)	−2 165(3)	3 710(1)	2.9(1)
C(8)	3 658(2)	−1 970(4)	4 099(1)	3.6(1)
C(9)	4 527(2)	−3 357(5)	3 969(2)	4.5(1)
C(10)	3 962(3)	−4 925(5)	3 453(2)	4.8(1)
C(11)	2 510(2)	−5 156(4)	3 048(2)	4.1(1)
C(11A)	1 638(2)	−3 747(3)	3 189(1)	3.0(1)
N(12)	176(2)	−3 607(3)	2 885(1)	3.0(1)
C(12A)	−205(2)	−1 976(3)	3 206(1)	2.6(1)
C(12B)	−1 708(2)	−1 342(3)	3 065(1)	2.6(1)
C(1′)	−1 890(2)	124(3)	1 395(1)	3.0(1)
C(2′)	−2 023(2)	2 201(3)	1 418(1)	3.0(1)
C(13)	−1 347(2)	2 984(3)	672(1)	3.5(1)
C(14)	−1 721(3)	3 461(8)	−1 021(2)	6.6(1)
C(15)	−2 782(2)	−2 996(3)	1 484(2)	3.8(1)
C(16)	−3 957(3)	−3 161(4)	524(2)	5.7(1)
O(1)	−1 328(2)	2 986(2)	2 327(1)	4.2(1)
O(2)	−192(2)	3 652(5)	841(1)	6.5(1)
O(3)	−2 237(2)	2 850(4)	−220(1)	4.5(1)

$B_{eq} = 4/3^* (B^*G)$ where *G* is the direct metric tensor.

Table 2. Fractional co-ordinates ($\times 10^3$) for hydrogen atoms

	x	*y*	*z*	B_{iso}(Å^2)
HN	−55	−457	271	4.0
H(2a)	−473	−13	129	3.6
H(2b)	−464	−167	225	3.6
H(3a)	−392	231	239	4.3
H(3b)	−524	117	280	4.3
H(4a)	−306	197	416	4.1
H(4b)	−343	−37	408	4.1
H(6a)	−72	180	489	3.7
H(6b)	−62	−58	497	3.7
H(7a)	100	182	390	3.6
H(7b)	175	62	499	3.6
H(8)	410	−78	448	3.8
H(9)	564	−323	428	4.6
H(10)	469	−596	338	5.3
H(11)	208	−635	263	4.7
H(12)	−222	−244	338	3.0
H(1a′)	−75	−20	165	3.1
H(1b′)	−226	−32	63	3.1
H(2′)	−316	251	127	3.3
H(14a)	−251	332	−172	6.2
H(14b)	−77	275	−105	6.2
H(14c)	−144	493	−94	6.2
H(15a)	−177	−334	136	3.7
H(15b)	−301	−400	199	3.7
H(16a)	−398	−451	20	5.1
H(16b)	−374	−220	−2	5.1
H(16c)	−498	−285	60	5.1
HO	79	412	240	4.0

We have found that the hydroxylactams (**3**) and (**4**) could not be epimerized by thermal treatment, *e.g.* by refluxing in toluene or chlorobenzene, but in the presence of a strong base (*e.g.* KOBu^t) epimerization of C-15 takes place and the equilibrium is shifted (7.7:1) toward the thermodynamically more stable form (**3**). When hydroxylactam (**3**) was allowed to stand at room temperature in methanol, in the presence of $NaOCH_3$, hydroxy ester (**1**) was recovered in unchanged optical purity. Under similar conditions, through the ring opening of epimer (**4**), a new compound was obtained, the t.l.c. characteristics and m.s. and n.m.r. spectra of which suggested that the hydroxy ester (**2**) described by Gibson and Saxton was obtained ($[\alpha]_D^{22}$ −115°). The resulting compound could be oxidized into (+)-vincamine with Ag_2CO_3–Celite.

These investigations proved that the epimeric hydroxy ester (**2**) is of configuration (1*S*,12b*S*,2′*S*), and hydroxylactam (**3**) of configuration (15*R*) whereas its epimer (**4**) is 15*S*. From this the

Table 3. Relevant torsion angles (°) with their e.s.d.s in parentheses

C(4)–C(3)–C(2)–C(1)	−44.6(3)
C(4)–N(5)–C(12B)–C(1)	70.9(2)
N(5)–C(4)–C(3)–C(2)	51.2(3)
N(5)–C(12B)–C(1)–C(2)	−58.9(2)
C(7A)–C(7)–C(6)–N(5)	−55.1(2)
C(7A)–C(12A)–C(12B)–N(5)	0.4(3)
N(12)–C(12A)–C(12B)–C(1)	−61.5(3)
C(12A)–C(7A)–C(7)–C(6)	20.4(3)
C(12A)–C(12B)–N(5)–C(6)	−37.5(2)
C(12B)–C(1)–C(2)–C(3)	47.6(3)
C(12B)–N(5)–C(4)–C(3)	−65.6(3)
C(12B)–N(5)–C(6)–C(7)	67.9(3)
C(12B)–C(12A)–C(7A)–C(7)	7.0(3)
C(1′)–C(1)–C(2)–C(3)	−78.0(3)
C(1′)–C(1)–C(12B)–N(5)	68.5(2)
C(2′)–C(1′)–C(1)–C(2)	38.8(3)
C(2′)–C(1′)–C(1)–C(12B)	−84.2(3)
C(13)–C(2′)–C(1′)–C(1)	−173.0(3)
C(14)–O(3)–C(13)–C(2′)	−177.1(5)
C(15)–C(1)–C(2)–C(3)	163.9(3)
C(15)–C(1)–C(12B)–N(5)	−174.6(2)
C(15)–C(1)–C(1′)–C(2′)	157.6(2)
C(16)–C(15)–C(1)–C(2)	48.4(3)
O(1)–C(2′)–C(1′)–C(1)	68.0(2)
O(2)–C(13)–C(2′)–C(1′)	−101.4(4)
O(2)–C(13)–C(2′)–O(1)	21.8(4)
O(2)–C(13)–O(3)–C(14)	3.7(5)
O(3)–C(13)–C(2′)–C(1′)	79.4(3)
O(3)–C(13)–C(2′)–O(1)	−157.4(3)

relative configuration of C-14 and -15 in the *cis*-diol[3] (**8**) was elucidated. When the β-hydroxylactam (**3**) was heated with phosphoryl chloride in chlorobenzene, in a kinetically controlled S_N2 reaction, the α-chlorolactam (**5**) was first formed which, during the completion of the reaction, was partly epimerized to β-chlorolactam (**6**). By crystallizing the mixture (total yield 90%) from MeOH, α-chlorolactam (**5**) can be obtained (76%), and the β-chlorolactam (**6**) can be isolated by preparative layer chromatography of the mother liquor (6%). In neutral or acidic media, (**5**) is relatively stable; however, on heating in the presence of a base, *e.g.* triethylamine, in EtOH it is converted into the thermodynamically more stable β-chlorolactam (**6**).

Under similar conditions, when α-hydroxylactam (**4**) is treated with phosphoryl chloride, the thermodynamically more stable β-chlorolactam (**6**) is obtained as the main product.

The significance of chlorolactams (**5**) and (**6**) being obtained in excellent yields is supported by our observation that either alone or as a mixture, both can be converted under very mild conditions, in aqueous acetic acid with $NaNO_2$ at room temperature, into the (*E*)-isomer of oxime (**10**) in 68% yield, which, according to the literature,[7,8] could be prepared previously only by the α-isonitrosation of lactam (**7**) with alkyl nitrites in the presence of bases (*e.g.* KOBu^t). Oxime (**10**) can be used for the direct synthesis of (+)-vincamine and (+)-apovincaminic esters.[8]

Compounds (**3**)—(**6**) of known absolute configuration showed characteristic ^{13}C n.m.r. and c.d. spectra which appeared to be suitable for investigating the conformational properties of the substituent of C-15 and of the seven-membered E ring. ^{13}C N.m.r. data of compounds (**3**)—(**6**) are summarized in Table 4. The chemical shift of the quaternary C(17) atom can be assigned unambiguously in all four compounds. The nearly identical values of the four shifts, *i.e.* the absence of the γ-gauche effect of the C-15 substituents, indicates that they are quasi-equatorial in the four compounds [(**3**)—(**6**)].

Table 4. ^{13}C Chemical shifts of compounds (**3**)—(**6**)

Carbon atom	Compounds (3)	(4)	(5)	(6)
2	132.71	131.84	131.89(s)	131.84(s)
3	62.07	65.38	62.69(d)	61.46(d)
5	51.22	51.45	51.07(t)	51.16(t)
6	17.23	17.55	17.61(t)	17.23(t)
7	118.91	120.11	118.76(s)	118.79(s)
8	130.20	129.76	129.70(s)	129.85(s)
9	117.79	117.82	117.74(d)	117.74(d)
10	125.05*	125.31*	125.14(d)*	125.17(d)*
11	124.20*	123.97*	125.00(d)*	124.05(d)*
12	117.36	116.62	116.74(d)	117.39(d)
13	135.90	137.04	136.55(s)	136.31(s)
14	174.60	175.30	169.70(s)	167.38(s)
15	66.28	68.04	59.09(d)	56.22(d)
16	42.47	40.78	41.33(t)	45.05(t)
17	36.56	37.56	38.41(s)	38.06(s)
18	32.26	30.45	30.36(t)	32.11(t)
19	21.03	20.89	20.89(t)	20.89(t)
20	45.72	45.46	44.52(t)	45.43(t)
21	28.93	26.47	29.87(t)	29.37(t)
22	7.66	7.25	7.25(q)	7.66(q)

* Assignments may be interchanged.

The C(6), C(20), C(5), and C(19) chemical shifts are nearly the same, and correspond to C/D *cis* ring anellation.[9] Consequently, between the epimeric pairs [(**3**) and (**4**)] and [(**5**) and (**6**)] the only difference which may occur is the conformation of ring E.

The chemical shifts due to C(18) in the β-substituted compounds (**3**) and (**6**) are δ 32.26 and 32.11 p.p.m., and in the α-isomers (**4**) and (**5**) δ 30.45 and 30.36 p.p.m., respectively. The reason for the difference is that in the α-isomers (**4**) and (**5**) and C(15) atom is in the γ-gauche position with respect to C(18) if the C(15) substituents are quasi-equatorial. Due to the γ-gauche effect a shift in the same direction could be expected to occur for the C(15) atom. However, the experimental data show an opposite shift. The reason is that in compounds (**4**) and (**5**) the C-15 substituent is almost coplanar with the C=O group, whereas it is not coplanar in (**3**) and (**6**). It is known[10] that *e.g.* with α-halogenated cyclohexanones the nearly coplanar position of the halogen and the carbonyl group causes a *ca.* 3.5 p.p.m. increase in the chemical shift of the α-carbon atom.

The decrease in the chemical shift of C(3) in the β-isomers [δ 62.07 for (**3**) and 61.46 p.p.m. for (**6**)] with respect to the α-isomers [δ 65.38 for (**4**) and 62.69 p.p.m. for (**5**)] can be interpreted with the γ-gauche interaction. On the basis of these data it is highly probable that the dominant conformation of β-isomers (**3**) and (**6**) can be described by formula (A) and that of α-isomers (**4**) and (**5**) by formula (B) (Figure 2).

Circular Dichroism.—In order to obtain further information on the stereochemistry of the compounds studied, their chiroptical properties were also investigated. The c.d. data and, in most instances, u.v. spectra recorded in ethanol for (**1**)—(**9**), are in the Experimental section. Since some compounds were available only in the form of their hydrochloride salts, all spectral data used for comparison refer to the latter. Compared with the c.d. spectra of free bases, those of the hydrochlorides contain all bands in the same sign pattern, but with somewhat different absolute and relative intensities and shifted 5—10 nm hypsochromically.

The c.d. spectra of epimers (**1**) and (**2**) are practically identical (Figure 3). This is not unexpected, since the chiral centre C-2′ which is enantiomeric in the two epimeric molecules is located

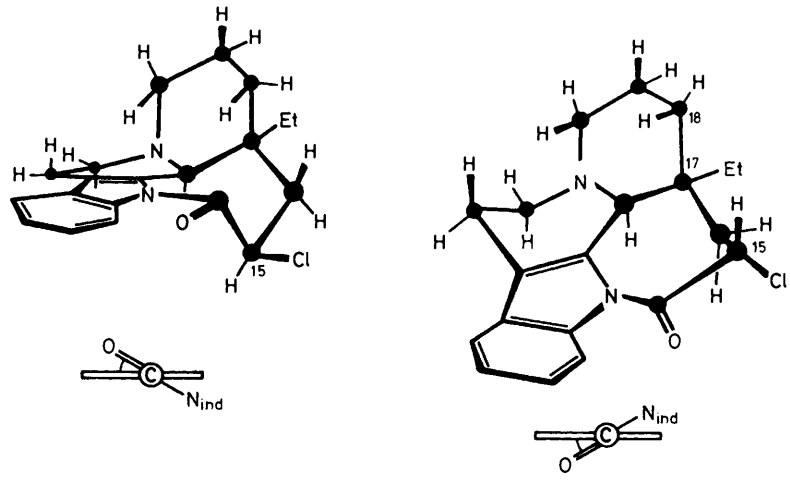


Figure 2. Dominant conformations of [(**3**), (**6**)] A and [(**4**), (**5**)] B

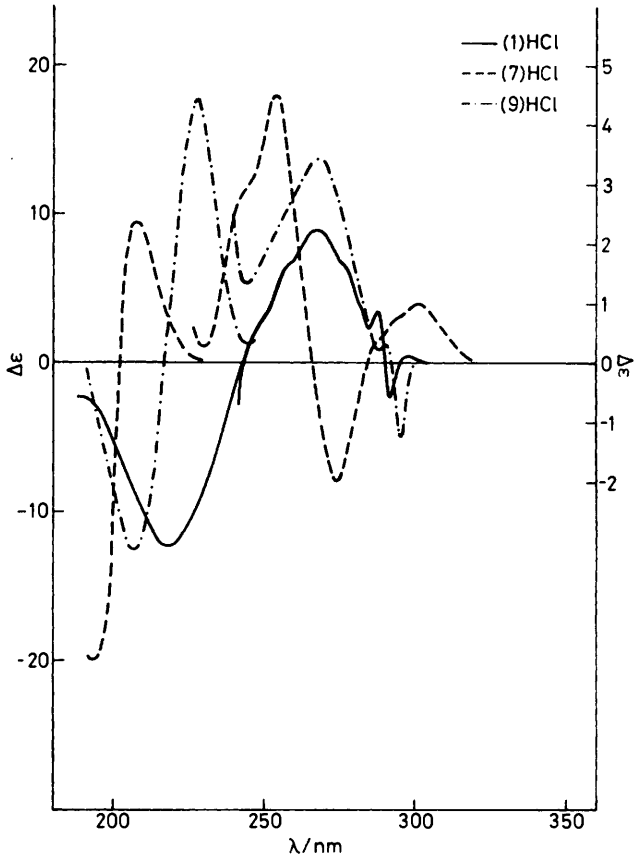


Figure 3. C.d. spectra of (**1**), (**7**), and (**9**) hydrochlorides in ethanol

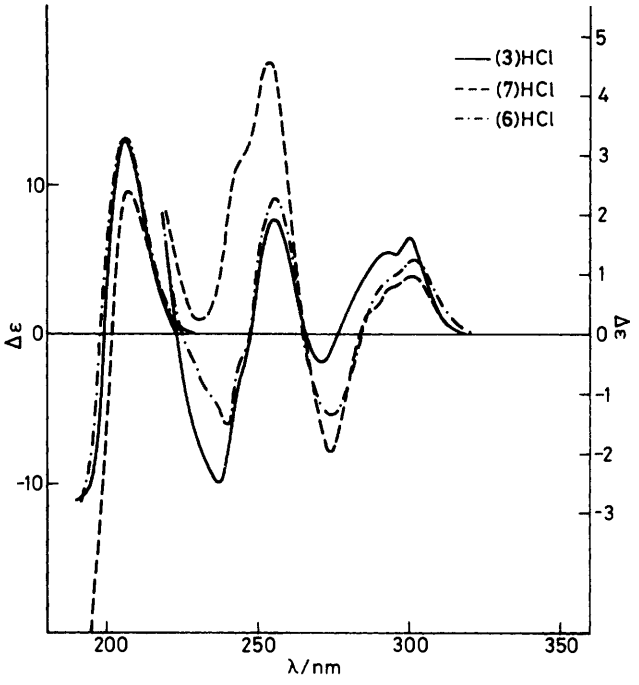


Figure 4. C.d. spectra of (**3**), (**6**), and (**7**) hydrochlorides in ethanol

so far from the chromophoric indole ring that it can hardly influence the chiroptical properties which are due mostly to the latter.

The 15β-substituted derivatives (**3**) and (**6**) show c.d. spectra similar to each other (Figure 4), but significantly different from those of the 15α-epimers (**4**) and (**5**) which, for their part, are also similar (Figure 5). These results are in agreement with the conclusions drawn from ^{13}C n.m.r. studies suggesting inverted conformations for the seven-membered ring of the 15β- and the 15α-epimers. The 15-unsubstituted lactam (**7**) resembles in its c.d. spectrum the thermodynamically more stable 15β-epimers, and differs from the 15α-ones. This indicates that the major conformation of (**7**) is of type A (Figure 2).

On the basis of the known absolute geometries of the molecules, an interpretation of the chiroptical properties may also be attempted. Most of the bands in the c.d. spectra of the compounds studied can be assigned to the indole chromophore present in the molecules. The lowest energy electronic transitions of indole are due to excitations of the aromatic π-electron system, and are usually labelled, following Platt's notation for aromatic hydrocarbons,[12] as ^1L_b, ^1L_a, ^1B_b, and ^1B_a in the sequence of increasing energy. The corresponding

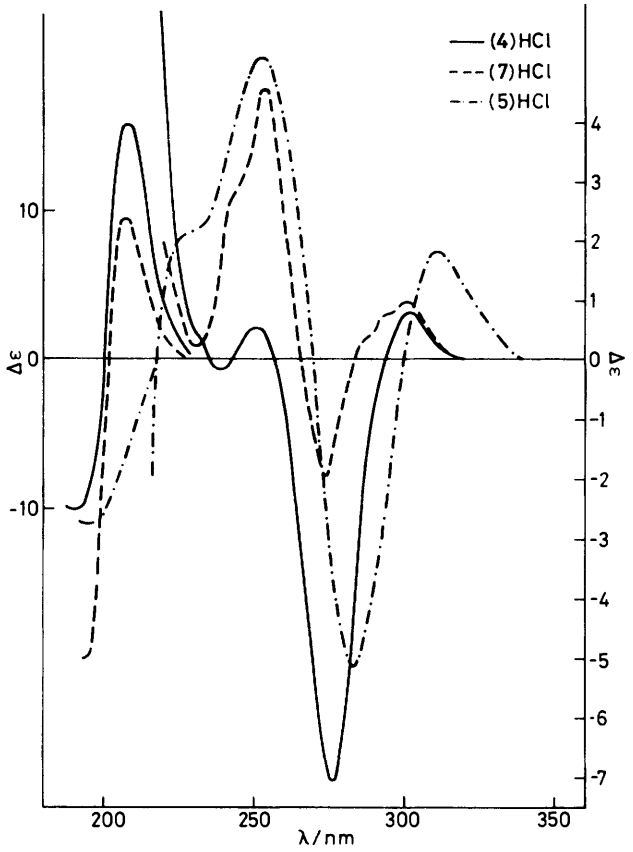


Figure 5. C.d. spectra of (**4**), (**5**), and (**7**) hydrochlorides in ethanol

absorption bands in the u.v. spectrum of indole can be found at *ca.* 290, 270, 220, and 200 nm, respectively.

In compounds (**1**) and (**2**) the signs of the c.d. bands are determined by the absolute conformation (helicity) of the tetrahydropyridine ring (ring C) connected directly to the chromophore and constituting the chiral 'second sphere.' According to an epimerical rule based primarily on the chiroptical properties of stereoisomeric yohimbanes,[13] the (*M*) helicity of ring C which is controlled by the (*S*) configuration of chiral centre C-3, which corresponds to C-12b in compounds (**1**) and (**2**) with an indoloquinolizidine skeleton, induces a positive c.d. in the ^1L_a band of indole. Since the chiral second sphere (ring C) in indoloquinolizidine and the yohimbane skeleton is the same, the above rule also holds for compounds (**1**) and (**2**), the c.d. spectra of which are indeed similar to that of yohimbane.

In molecules of (**9**)* there are two rings (ring C and E) bound directly to the indole chromophore and constituting the chiral second sphere. From the similarity of the c.d. spectrum of (**9**) and of those of (**1**) and (**2**) (and of yohimbane) it can be concluded that the presence of the seven-membered ring E does not significantly alter the chiroptical properties of the indoloquinolizidine moiety. The appearance of an oxo-group in position 14 of (**9**), however, causes a characteristic change in the c.d. spectrum mainly above 230 nm. Lactam (**7**) exhibits a rather weak, positive c.d. band with a maximum at 301 nm and with a definite fine structure, characteristic of the ^1L_b aromatic transitions, on its low wavelength wing. This means that the new band has to be assigned to a transition which is of lower energy than the ^1L_b transition of the indole chromophore. Another characteristic feature of the c.d. spectrum of (**7**) is a negative band at 274 nm.

* Compound (**9**) was prepared according to Buzas *et al.*[11] by LAH reduction of lactam (**7**).

Table 5. Calculated electronic transitions of non-coplanar *N*-formylindole

Type	λ/nm	*f**	O=C-N-C-(benezene) (°)	*R*†
			−10	+3.5
$n\rightarrow\pi^*$	300	0.001	−20	−1.3
			−30	−6.3
$\pi\rightarrow\pi^*$			−10	+1.8
(^1L_b)	285	0.007	−20	+3.0
			−30	+4.0
$\pi\rightarrow\pi^*$			−10	+2.6
(^1L_a)	258	0.15	−20	+4.6
			−30	+5.7
$\pi\rightarrow\pi^*$			−10	−1.0
(^1B_b)	226	0.06	−20	−1.0
			−30	−0.03
$\pi\rightarrow\pi^*$			−10	−0.8
(^1B_a)	219		−20	−0.9
			−30	−2.5

* Oscillator strength. † Reduced rotational strength.

By inspection of the Dreiding model of lactam (**7**) it can be seen that the C=O bond is in neither of the two possible conformations A and B coplanar with the indole ring. The O=C–N–C(benzene) torsion angle is of a small negative value (*ca.* −10°) in conformation A (Figure 2) and of a larger positive one (*ca.* +30°) in conformation B (Figure 3). Within the amide moiety of lactam (**7**) the carbonyl group is bound to the positively polarized nitrogen atom of the aromatic indole system. Both these structural features must entail a weakening on the donor-type conjugation of the nitrogen atom toward the C=O group. Therefore the carbonyl group of lactam (**7**) can be considered to be similar to that of a ketone, and the c.d. band due to its $n\rightarrow\pi^*$ transition can be expected to appear at a higher wavelength (*ca.* 300 nm) than in the case of normal amides. Since the positve band at *ca.* 300 nm can also be found in the c.d. spectra of the other carbonyl-containing derivatives (**3**)—(**6**), we assign it to the $n\rightarrow\pi^*$ transition of the carbonyl chromophore in ring E.

This assumption is supported by the results of a theoretical study performed on a simple model, *N*-formylindole. The geometries used for the calculation are characterized by the *cis* position of the carbonyl oxygen and the benzene moiety of indole, and by three different negative values of the O=C–N–C(benzene) torsion angle. CNDO/S-CI calculations[14] including 36 singly excited configurations were used for the determination of transition energies, dipole strengths, and rotational strengths. The results are summarized in Table 5.

The calculation yields five transitions for *N*-formylindole in the spectral range above 200 nm. The lowest energy one is the $n\rightarrow\pi^*$ transition of the carbonyl chromophore which is followed by the aromatic $\pi\rightarrow\pi^*$ transitions of the indole ring. The rotational strength of the $n\rightarrow\pi^*$ transition changes sign between torsion angles 10 and 20°. This remarkable result can be explained by the symmetry properties of this transition summarized in the well known octant rule for ketones. With an increasing torsion angle a significant part of the indole ring passes from a 'front' octant into a 'rear' octant which causes the sign inversion of the rotational strength. The optical activity induced in the indole chromophore by the non-coplanar formyl group of negative torsion angle is of positive sign for both the

^1L_b and ^1L_a transitions. The absolute values of the calculated rotational strengths increase with increasing torsion angles.

The positive sign of the first c.d. band found in the spectra of the carbonyl compounds (**3**)—(**7**) is in agreement with the results of the calculation. As suggested by the ^{13}C n.m.r. studies, the 15β-substituted derivatives (**3**) and (**6**) adopt conformation A characterized by a small negative value (not exceeding $-10°$) of the O=C–N–C(benzene) torsion angle. For this geometry of the *N*-formylindole moiety, the calculation predicts a positive $n\rightarrow\pi^*$ c.d. band of relatively low intensity, and the same was found experimentally. In compounds (**4**) and (**5**) of 15α-configuration, ring E is of conformation B and, consequently, the sign of the torsion angle is inverted with respect to that in (**3**) and (**6**). However, the absolute value of the *positive* torsion angle is larger than 20° in this conformation, the sign of the $n\rightarrow\pi^*$ rotational strength predicted by calculation is again positive, in agreement with the sign of the experimental c.d. bands. The intensity of this band is highest in the spectrum of (**5**). This, too, is in accord with the calculation. Repulsion between the nearly coplanar C–Cl and C=O bonds in this molecule may somewhat increase the O=C–N–C(benzene) torsion angle and, consequently, the absolute value of the rotational strength as well. The weak, positive $n\rightarrow\pi^*$ band of (**7**), too, corresponds to the presumed A conformation of this molecule.

For the higher energy c.d. bands of compounds (**3**)—(**7**), the results of the calculation cannot be applied directly, because the signs and magnitudes of the transitions of the indole chromophore are determined not only by the chirally disposed carbonyl group, but by the chiral ring C as well. Since the conformation of the latter and, therefore, its contribution to the optical activity is identical in the carbonyl compounds (**3**)—(**7**) on the one hand, and in compound (**9**) with no oxo function, on the other, it is the difference between the c.d. spectra of these two groups of compounds which can be ascribed to the effect of the chiral *N*-formylindole moiety. However, the interpretation is, even in this restricted form, extremely simplified, since the effects due to complex interactions of the different parts of the molecules are not taken into consideration. Simple additivity of the chiroptical effects can by no means be assumed.

In the c.d. spectra of compounds (**3**)—(**7**) a negative band (of different intensities in the single compounds) can be found at *ca.* 275 nm. This has to be assigned most probably to the ^1L_a transition of the indole chromophore. (The ^1L_b transition overlaps with the low wavelength part of the $n\rightarrow\pi^*$ band.) The corresponding band in the c.d. spectrum of (**9**) is positive; therefore the difference which may be attributed to the *N*-formylindole moiety in the carbonyl derivatives is in all compounds negative. In the case of the 15α-epimers (**4**) and (**5**), this sign agrees with the calculated one, for (**7**) unsubstituted at the 15-position and for its 15β-substituted derivatives (**3**) and (**6**); however, the calculation predicts a positive c.d. in this transition. This contradiction cannot be explained at the moment. Nevertheless, there is a correlation between theory and experiment, if the intensities of this band in the c.d. spectra of the five carbonyl compounds are compared. The 15α-epimers (**4**) and (**5**) of conformation B, which, according to the calculation, must give negative c.d. in the ^1L_a band, exhibit a much stronger negative maximum in their c.d. spectra than does unsubstituted (**7**), the major conformation of which is A. At the same time, in the spectra of the 15β-epimers (**3**) and (**6**) with a fixed A conformation the negative 275 nm band is even weaker than the corresponding band of (**7**).

The bands found below 260 nm in the c.d. spectra of compounds (**3**)—(**7**) cannot be safely assigned on the basis of the experimental and theoretical information available. The higher wavelength component of the B type band pair is in all cases positive and the one of lower wavelength is negative, as in the c.d. spectrum of yohimbine. As our calculations indicate, the rotational strengths due to these transitions are hardly affected by the carbonyl group and their signs are therefore determined by the chiral conformation of ring C which is the same in all molecules.

Experimental

I.r. spectra were recorded on a Spectromom 2000 i.r. spectrometer. ^1H and ^{13}C n.m.r. spectra were recorded at 100 and 25 MHz, respectively, on a JEOL FX-100 Fourier Transform instrument in $CDCl_3$ solution with Me_4Si as internal reference. Mass spectra were taken with an AEI-MS-902 (70 eV; direct insertion) mass spectrometer. M.p.s are uncorrected. The c.d. spectra were measured with Roussel-Jouan dichrograph Mark III (Jobin-Yvon) at room temperature in cells of 1 mm length, and at 1 mM concentration.

The hydroxy ester (1*S*,12b*S*,2′*R*)-(**1**) was prepared by the method described in the literature;[2] δ_C 8.54 ($CH_2\underline{C}H_3$), 21.18 (C-7), 22.73 (C-3), 31.88* ($\underline{C}H_2CH_3$), 35.60* (C-2), 40.61† (C-1′), 40.78† (C-1), 52.07 (OCH_3), 53.91 (C-6), 56.25 (C-4), 67.28‡ (C-2′), 68.68‡ (C-12b), 110.72 (C-7a), 112.27 (C-11), 118.23 (C-8), 119.46 (C-9), 121.83 (C-10), 126.66 (C-7b), 131.40 (C-12a), 136.11 (C-11a), and 174.95 p.p.m. (CO). (**1**)-Hydrochloride had m.p. 245 °C (from MeOH); c.d. (EtOH) 297 (+0.11), 294.5 (0), 291.5 (−0.57), 290 (0), 287.5 (+0.87), 284.5 min. (+0.57), 281.5 sh. (+0.95), 276.5 sh. (1.61), 267 (+2.24), 258 sh (+1.65), 250 sh. (+0.76), 243 (0), 218 (−12.3), and 190! (−2.2).

Crystal Structure Determination of (1S,12*b*S,2′R)-(**1**).—*Crystal data.* $C_{21}H_{28}N_2O_3$, MW = 356.47, monoclinic, a = 9.795(1), b = 7.387(3), c = 14.265(1) Å, β = 106.00(2)°, U = 992.2(11) Å^3, D_c = 1.193 g cm^{-3}, Z = 2, $F(000)$ = 384, space group $P2_1$. Intensities of 2 276 independent reflections were collected by an ω–2θ scan in the range $2\theta \leqslant 155°$ on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated Cu-K_α (λ = 1.5418 Å) radiation. Cell constants were determined by least squares from the setting angles of 25 reflections. After data reduction 2 216 reflections with $F - 1.7\sigma(F) > 0$ were taken as observed. No absorption (μ = 6.5 cm^{-1}) correction was applied. The phase problem was solved by direct methods with the MULTAN program[15] by the use of 320 normalized structure factors having $E \geqslant 1.37$. The E map computed from the phase set with the best consistency revealed 25 of the 26 non-hydrogen atoms. The missing C(1) atom was located in a subsequent Fourier calculation (R = 0.25). Full-matrix least-squares refinement of the positional and anisotropic vibrational parameters of non-hydrogen atoms resulted in a final R of 0.044 (R_w = 0.069, R_{tot} = 0.049). The hydrogen atom positions (except of HN) were generated from assumed geometries and checked then in a difference electron density map in which the co-ordinates of HN could also be determined. The hydrogen positions were not refined, however. In a final difference map the highest visible peak was *ca.* 0.2 e Å^{-3}. Scattering factors were taken from ref. 16. All calculations were performed on a PDP 11/34 (64K) computer with an Enraf-Nonius SDP-34 system.

(3S,15R,17S)-14-*Oxo*-15β-*hydroxy*-E-*homoeburnane* (**3**) *and* (3S,15S,17S)-14-*Oxo*-15α-*hydroxy*-E-*homoeburnane* (**4**).—The cyclization of (1*S*,12b*S*,2′*R*) hydroxy ester (**1**) was carried out according to the literature[2] to yield (**3**) as a colourless oil (70%); $[\alpha]_D^{22}$ +69.4° (*c* 1.18 in $CHCl_3$); δ_H 0.95 (3 H, t, J 7 Hz, CH_2CH_3), 3.90 (1 H, br s, OH), 3.98 (1 H, br, 3-H), 4.33 (1 H, q, J

*†‡ Assignments may be interchanged.

1.7 and 11.9 Hz, 15-H), 7.30 (3 H, m, Ph), 8.50 (1 H, m, 12-H), m.p. of (**3**)·HCl 250—252 °C (from MeOH); c.d. (in EtOH) 300 (+1.62), 292 (+1.35), 277 (0), 271 (−0.47), 265.5 (0), 255 (+1.94), 247 (0), 245 sh. (−0.69), 237 (−2.51), 223 (0), 206 (+13.0), 199 (0), and 190! (−11.0) and the α-hydroxylactam (**4**) (7.3%), m.p. 141—142 °C (from MeOH) (Found: C, 77.6; H, 7.4; N, 8.4. Calc. for $C_{20}H_{24}N_2O_2$: C, 77.74; H, 7.4; N, 8.6%), $[\alpha]_D^{22}$ −28.7° (*c* 1.0 in $CHCl_3$); $\nu_{max.}$ 3 400 (OH) and 1 660 cm^{-1} (amide CO); δ_H 0.89 (3 H, t, *J* 7.2 Hz, CH_2CH_3), 4.07 (1 H, br s, 3-H), 4.53 (1 H, dd, *J* 3.2 and 12 Hz, 15-H), 7.5 (3 H, m, Ph), and 8.4 (1 H, m, 12-H); *m/z* 324 (M^+, 100%), 296 (21), and 267 (66).

(**4**)-Hydrochloride had m.p. 235—237 °C (from MeOH); c.d. (in EtOH) 302 (+0.81), 294 (0), 276.5 (−7.02), 258 (0), 250 (+0.56), 244 (0), 240 (−0.18), 235 (0), 230 sh. (+0.53), 208 (+15.9), 200 (0), and 190! (—10.3).

(1S,12*b*S,2′S)-1α-*Ethyl*-1β-(2-*hydroxy*-2-*methoxycarbonylethyl*)-1,2,3,4,6,7,12,12*b*α-*octahydroindolo*[2,3-a]*quinolizine* (**2**) *Hydrochloride*.—To a solution of hydroxylactam (**4**) (0.12 g, 0.37 mmol) in methanol (1.6 ml) and methylene dichloride (0.5 ml), KOBu^t (15 mg) was added and allowed to stand at room temperature for 24 h. The excess of base was decomposed with acetic acid, and the solution was evaporated to dryness. The residue was suspended in 5% aqueous sodium carbonate, and extracted with methylene dichloride. The organic layer was dried, filtered, and evaporated. The residual oil was dissolved in methanol (1 ml), acidified with HCl–MeOH and the crystalline salt filtered off, washed with cold methanol to yield (**2**)-hydrochloride (0.10 g, 68.8%), m.p. 235 °C (from MeOH) (Found: C, 64.3; H, 7.5; N, 7.2. Calc. for $C_{21}H_{29}ClN_2O_3$: C, 64.2; H, 7.4; N, 7.1%); c.d. (in EtOH) 296 (+0.21), 294 (0), 291.5 (−0.23), 290.5 (0), 287.5 (+1.09), 284.5 min. (+0.76), 277 sh. (+1.70), 267.5 (2.26), 250 sh. (+0.65), 243.5 (0), 220.5 (−10.9), 193 min. (−2.4), and 190! (−4.0); optical rotation of the free base (**2**), $[\alpha]_D^{22}$ −115° (*c* 0.98 in $CHCl_3$); $\nu_{max.}$ 3 280 (NH, OH) and 1 740 cm^{-1} (ester CO); δ_H 1.17 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.40 (1 H, br, 12b-H), 3.69 (3 H, s, OCH_3), 4.14 (1 H, dd, *J* 2.5 and 9 Hz, 2′-H), 7.0—7.5 (5 H, m, Ph and OH), and 7.91 (1 H, br s, NH); δ_C 8.22 (CH_2CH_3), 21.56 (C-7), 21.85 (C-3), 32.44* (CH_2CH_3), 33.81* (C-2), 39.14† (C-1′), 40.25† (C-1), 52.39 (OCH_3), 54.09 (C-6), 56.63 (C-4), 66.40‡ (C-2′), 68.27‡ (C-12b), 110.77 (C-7a), 111.89 (C-11), 111.94 (C-8), 119.40 (C-9), 121.69 (C-10), 126.60 (C-7b), 132.60 (C-12a), 135.93 (C-11a), and 176.09 p.p.m. (CO); *m/z* 356 (M^+, 56%), 355 (25), 297 (5.6), 267 (100), and 169 (22); t.l.c. [silica gel, benzene–MeOH (14:3)] R_F (**2**) > (**1**).

(3S,15S,17S)-14-*Oxo*-15α-*chloro*-E-*homoeburnane* (**5**) *and* (3S,15R,17S)-14-*Oxo*-15β-*chloro*-E-*homoeburnane* (**6**).—(A) 15α-Hydroxylactam (**3**) (4.2 g, 13 mmol) was boiled with phosphoryl chloride (4.2 g) in chlorobenzene (100 ml) for 3 h under stirring. After cooling at 0 °C the solution was mixed with ice–water (100 g) and basified with 5% aqueous sodium carbonate. The organic layer was separated, and the water phase extracted with methylene dichloride (2 × 50 ml). The combined organic layer was dried, filtered, and evaporated to dryness under reduced pressure. The residue (3.8 g) was recrystallized from methanol to give (**5**) (3.2 g), m.p. 155 °C (from MeOH) (Found: C, 73.3; H, 6.5; N, 8.05. Calc. for $C_{20}H_{23}ClN_2O$: C, 73.55; H, 6.8; N, 8.2%); $[\alpha]_D^{22}$ 0° (*c* 1.0 in $CHCl_3$); $\lambda_{max.}$(EtOH) 307 (ε 4 600 dm^3 mol^{-1} cm^{-1}), 267 (11 200), 258 (14 000), 254 (14 000), 221 sh (14 000), and 202 nm (28 900); $\nu_{max.}$ 1 695 cm^{-1} (amide CO); δ_H 0.92 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.17 (1 H, m, J_{AB} 15.9, J_{BX} 2.8 Hz, 16-H_B), 2.44 (1 H, m, J_{AB} 15.9, J_{AX} 7.8 Hz, 16-H_A), 4.46 (1 H, br s, 3-H), 4.91 (1 H, m, J_{AX} 7.8, J_{BX} 2.8 Hz, 15-H_X), 7.3 (3 H, m, Ph), and 8.37 (1 H, m, 12-H); c.d. (in EtOH) 313 (+2.06), 300 (0), 285 (−4.43), 270 (0), 254 (+5.09), 232 sh. (2.02), 221 (0), 205 sh. (−3.0), and 190! (−11.4); *m/z* 342 (M^+, 100%), 279 (26), 252 (37), 251 (21), 250 (16), 249 (48), 237 (13), 223 (13), 194 (16), 180 (27), and 169 (27). (**5**)-Hydrochloride had m.p. 202—203 °C (from acetone); $\lambda_{max.}$(EtOH) 303 (ε 6 450 dm^3 mol^{-1} cm^{-1}) 294 (6 050), 278 sh. (6 800), 264.5 sh. (10 300), 252 (16 600), 248 (16 700), and 200! nm (34 000); c.d. (EtOH) 311 (+1.82), 300 (0), 283 (−5.13), 270 (0), 252.5 (+5.08), 277 sh. (+2.13), 218 (0), and 195! (−11.0)

The methanolic mother liquor was separated by preparative t.l.c. [silica gel, benzene–MeOH (14:3)], R_F (**5**) > (**6**), followed by elution with methylene dichloride–MeOH (8:2) to yield a further 0.2 g of (**5**) (total yield 3.4 g, 76%), and 0.27 g (6%) of (**6**), m.p. 142 °C (from MeOH); $[\alpha]_D^{22}$ +63.3° (*c* 1.0 in $CHCl_3$) (Found: C, 73.4; H, 6.65; N, 8.2. Calc. for $C_{20}H_{23}ClN_2O$: C, 73.55; H, 6.8; N, 8.2); $\nu_{max.}$ 1 720 cm^{-1} (amide CO); δ_H 0.96 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.05 (1 H, m, J_{AB} 15.1, J_{BX} 1.6 Hz, 16-H_B), 2.45 (1 H, m, J_{AB} 15.1, J_{AX} 11.3 Hz, 16-H_A), 4.06 (1 H, br s, 3-H), 4.72 (1 H, m, J_{AX} 11.3, J_{BX} 1.6 Hz, 15-H_X), 7.3 (3 H, m, Ph), and 8.48 (1 H, m, 12-H); *m/z* 342 (M^+, 71%), 308 (100), 307 (64), 280, (22), 252 (45), 249 (34), 223 (18), and 169 (20); c.d. (EtOH) 304 (+2.78), 295 sh. (2.17), 280 sh. (0.53), 273.5 min. (+0.10), 261.5 (+0.97), 256 (0), 252.5 sh. (−1.02), 244.5 (−1.58), 236.5 sh. (−0.91), 231.5 (0), 211.5 (+12.6), 202 (0), and 190! (−9.5).

(**6**)-Hydrochloride had m.p. 229 °C (from MeOH); c.d. (EtOH) 301 (+1.25), 295 sh. (+0.98), 284 (0), 257 (−1.36), 265 (0), 255.5 (+2.29), 247.5 (0), 246.5 sh. (−0.20), 240 (−1.51), 232 sh. (−0.84), 228 sh. (−0.34), 225 (0), 205.5 (+13.4), 197.5 (0), and 190! (−8.0).

(B) 15α-Hydroxylactam (**4**) (0.50 g, 1.5 mmol) was treated with phosphoryl chloride in the same conditions as written in (A). After work-up, the residue was crystallized from methanol to yield the 15β-chlorolactam (**6**) (0.31 g, 60%).

(C) *Base-catalysed epimerization of lactam* (**5**). A solution of 15α-chlorolactam (**5**) (0.10 g, 0.29 mmol) in ethanol (2 ml) was boiled with triethylamine (50 mg) for 6 h. After evaporation to dryness *in vacuo*, the residue was recrystallized from methanol to give the 15β-chlorolactam (**6**) (90 mg, 90%).

Oxidation of Hydroxy Ester (1S,12*b*S,2′S)-(**2**).—To a hot solution of compound (**2**) (0.40 g, 1.12 mmol) in dry toluene (16 ml) Fétizon reagent (2.0 g) was added. The mixture was refluxed and stirred under nitrogen for 6 h. Thereafter the reagent was removed by filtration, washed with hot toluene, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in methanol (2 ml) containing $NaOCH_3$ (46 mg), and refluxed under nitrogen for 1 h. After cooling to 0 °C, the crystalline product was separated by filtration and washed with cold MeOH to yield (+)-vincamine (0.25 g, 62%), identical in every respect with an authentic sample.[2]

(3S,17S)-14-*Oxo*-15-*hydroxyimino*-E-*homoeburnane* (E)-(**10**).—To the solution of 15-chlorolactams (**5**) or (**6**) (0.20 g, 0.58 mmol) in acetic acid (4 ml) and water (1 ml) a solution of sodium nitrite (1.2 g) in water (4 ml) was added dropwise under stirring. The solution was allowed to stand at room temperature for 24 h, basified with aqueous NH_4OH (pH 9), and extracted with methylene dichloride (3 × 5 ml). The extracts were filtered and evaporated to dryness. The residue (0.19 g) was recrystallized from ether to give oxime (**10**) (0.13 g, 68%), identical in every respect with an authentic sample.[7,8]

Lactam (**7**) was synthesized by our method,[8] $\lambda_{max.}$(EtOH) 301 (ε 4 450 dm^3 mol^{-1} cm^{-1}), 292 (4 800), 276 sh. (10 000), 269 (11 100), 242 (17 000), and 200! nm (34 000); c.d. (EtOH) 302.5 (+2.49), 296 sh. (+2.0), 284.5 sh. (+1.13), 273.5 min. (+0.11), 258 (+2.74), 248 (+2.00), 242 (+1.41), 233 min. (+0.89), 212 (+11.76), 204.5 (0), and 195! (−20.7).

(**7**)-Hydrochloride had m.p. 258 °C (from ethyl acetate);

*†‡ Assignments may be interchanged.

$\lambda_{max.}$(EtOH) 299 (ε 5 400 dm^3 mol^{-1} cm^{-1}), 291 (5 400), 270 (11 000), 264 (12 000), 239 (18 700), and 200! nm (35 000); c.d. (EtOH) 301 (+0.98), 294 sh. (+0.77), 288 sh. (+0.41), 284 (0), 274 (−1.99), 266 (0), 254 (+4.53), 244 sh. (+2.95), 230 min. (+0.23), 207 (+9.47), 202 (0), and 194! (−20.0).

The optically active compound (**9**) was prepared by the method of Buzas *et al.*,[11] m.p. 134 °C (from light petroleum); $[\alpha]_{546}^{25}$ +78° (*c* 1.0 in $CHCl_3$); $\lambda_{max.}$(EtOH) 293 (ε 6 800 dm^3 mol^{-1} cm^{-1}), 285 (8 020), 276 (7 460), and 230 nm (32 800); c.d. (EtOH) 324 (−0.08), 313.5 (0), 299 (+1.07), 295 min. (+0.77), 290 sh. (+1.41), 256.5 min. (1.39), 233 (+22.3), 220.5 (0), 206 (−8.6), and 190! (−7.0).

(**9**)-Hydrochloride had $\lambda_{max.}$(EtOH) 293 (ε 4 650 dm^3 mol^{-1} cm^{-1}), 282 (7 260), 271 (8 270), and 223 nm (35 400); c.d. (EtOH) 295 (−1.25), 292 (0), 290 (+0.30), 287 min. (+0.22), 268 (+3.44), 244 min. (+1.33), 228 (+17.7), 217.5 (0), 207 (−12.6), and 190 (0).

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