SYNTHESIS OF STEREOISOMERIC VINCAMINES*

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Dedicated to the memory of Dr Karel Bláha

The synthesis of (±)-vincamine (*I*), (±)-16-epi-vincamine (*XVIII*) and (±)-16-epi-21-epi-vincamine (*XVII*) from 1-ethyl-2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizine (*IV*) and 2-chloroacrylonitrile is described. It is characterized by a novel method of oxidation of the key intermediates, (±)-deoxyvincamine (*II*) and (±)-16-epi-21-epi-deoxyvincamine (*XIII*) with oxodiperoxymolybdenum (pyridine) (hexamethylphosphoric triamide). The deoxy derivatives *II* and *XIII* were prepared by direct or stepwise acid or alkaline hydrolysis of stereoisomeric (±)-eburnane-16-carbonitriles *IX*–*XII*, obtained by reduction of the primary imonium salt *V*, and subsequent esterification. In some cases, the hydrolysis is accompanied by epimerization at $C_{(16)}$.

Since the discovery of cerebrovasodilator properties[1,2] of (+)-vincamine (*I*) and many of its derivatives (especially esters of apovincaminic acid[3–6]) a great number of its partial as well as total syntheses have been described[7–12]. The method developed by the Szantay's group[13,14] and the semi-synthetic approach of LeMen and co-workers[15–17] are the most important practical approaches, the latter particularly in connection with the biomimetic synthesis of the key intermediate, (±)-vincadifformine[18,19]. Surprisingly, only one synthesis[20] used direct introduction of the $C_{(16)}$-hydroxyl group into the stereoisomeric deoxyvincamines *II* and *III*. Our present communication describes the preparation of, and mutual relations between, the stereoisomeric deoxyvincamines and a novel method of their oxidation to give the isomeric vincamines.

About ten years ago a short synthesis of 16-substituted eburnane skeleton was described[21,22] which was based on the addition-elimination reaction of 2-chloroacrylonitrile with the well-known[23] Wenkert's enamine *IV*. The reaction product *V* was converted into the 21-epimeric eburnan-16-ones *VI* and *VII* (ref.[21]) on the one hand and into 16-epi-21-epi-deoxyvincaminic acid (*VIII*) on the other[22]. We, too, started from the same synthons. Analysis of ^{1}H NMR spectra has proven that

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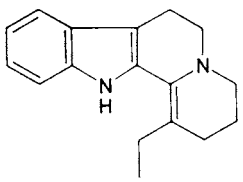
already the primary pentacyclic immonium salt[21] *V* is a mixture of 16-epimers. Its reduction with zinc powder in dilute acetic acid at room temperature afforded quantitatively a noncrystalline mixture of nitriles *IX*–*XII* which were separated into the pure components by column chromatography on silica gel and fractional crystallization. We have confirmed that the mentioned reaction affords slightly more[21] *cis*-isomers *IX* and *X* than *trans*-isomers *XI* and *XII*, whereas the reduction with sodium borohydride leads stereospecifically to a mixture of *trans*-isomers from which we isolated the isomer *XI*, in addition to the nitrile *XII* isolated by Szantay and collaborators[22].

The stereochemistry of the individual eburnane-16-carbonitriles *IX*–*XII* and the chemically related derivatives has been derived from analysis of their infrared and ^{1}H NMR spectra. Our stereochemical assignments are based on the ^{1}H and ^{13}C NMR results of the Italian authors[24] who elucidated the conformation of stereoisomeric (±) vincamines and assigned conformation *A* to the pair of *cis*-epimers and conformation *B* to the two *trans*-isomers. Whereas the *trans* or *cis* annelation of the C/D rings was detected by the presence or absence of the *trans*-bands[25–28] in the infrared spectra, the stereochemistry of the D/E fusion was derived from ^{1}H NMR data. As the result of different shielding by the lone electron pair of the $N_{(4)}$ nitrogen atom the signal of proton at $C_{(21)}$ is shifted downfield in the *trans*-series (singlet at about 3·00 ppm; conformation *B*) as compared with the *cis*-series (singlet at about 3·75 ppm; conformation *A*). Finally, the pseudoequatorial or pseudoaxial character of the proton at $C_{(16)}$ was decided from the coupling constants, particularly from the vicinal constant $J_{ax,ax}$ (8–12 Hz) which is substantially greater than the constants $J_{ax,eq}$ and $J_{eq,eq}$ (maximum 5 Hz). Therefore the doublets of doublets with one of the coupling constants greater than 8 Hz should correspond to a pseudoequatorial proton at $C_{(16)}$.

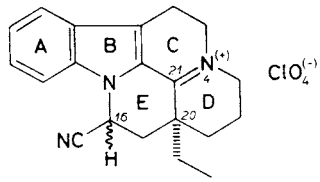
The conversion of the obtained individual nitriles *IX*–*XII* into the methyl esters of deoxyvincaminic acids met with some complications. In the *trans*-series (*B*), boiling of the cyano-equatorial isomer *XI* with concentrated hydrochloric acid afforded smoothly the corresponding deoxyvincaminic acid[22] *VIII* which was esterified with diazomethane to give (±)-16-epi-21-epi-deoxyvincamine[22] (*XIII*). On the other hand, under the same conditions the isomer *XII* with pseudoaxial cyano group could not be hydrolysed at all and was quantitatively recovered from the reaction mixture. On boiling with dilute sulfuric acid, *XII* afforded only the hydration product, 21-epi-eburnane-16α-carboxamide (*XIV*) which resisted further acid hydrolysis. Hydrolysis of *XII* with dilute sodium hydroxide in aqueous ethanol was accompanied by complete epimerization at $C_{(16)}$ and, after esterification with diazomethane, the ester *XIII* was obtained in an 80% yield. The ester with pseudoaxial methoxycarbonyl function could not be prepared in this way.

Even more complex was the situation in the *cis*-series (*A*). Hydrolysis of the isomer with pseudoaxial cyano group *IX* by boiling with concentrated hydrochloric acid,

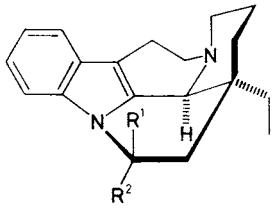
followed by esterification with diazomethane, led to a mixture of the epimeric (±)-deoxyvincamine (*II*) with the amide *XV* of retained configuration (which, however, could be converted into the ester *II* in 80% yield by alkaline hydrolysis and esterification). The mechanism of epimerization at $C_{(16)}$ under conditions of acid hydrolysis is not clear. The epimeric nitrile *X* with the pseudoequatorial cyano group could not be hydrolysed at all (similarly to the nitrile *XII*) and only after prolonged boiling with very concentrated ethanolic sodium hydroxide it was converted into (±)-eburnane-16α-carboxamide (*XVI*) of retained configuration.



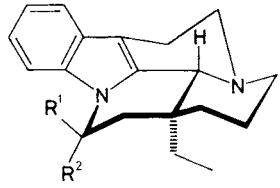
IV



V



A



B

I, R^1= OH ; R^2= $COOCH_3$
II, R^1= H ; R^2= $COOCH_3$
III, R^1= $COOCH_3$; R^2= H
VI, R^1 + R^2= O
IX, R^1= CN ; R^2= H
X, R^1= H ; R^2= CN
XV, R^1= $CONH_2$; R^2= H
XVI, R^1= H ; R^2= $CONH_2$
XVIII, R^1= $COOCH_3$; R^2= OH

VII, R^1 + R^2= O
VIII, R^1= COOH ; R^2= H
XI, R^1= CN ; R^2= H
XII, R^1= H ; R^2= CN
XIII, R^1= $COOCH_3$; R^2= H
XIV, R^1= H ; R^2= $CONH_2$
XVII, R^1= $COOCH_3$; R^2= OH

It seems that the amide *XVI* is the most stable compound of the whole system, probably for steric reasons. It arises by alkaline hydrolysis not only of (±)-eburnane-16β-carbonitrile (*IX*) but also of (±)-eburnane-16β-carboxamide (*XV*). Thus, also in the *cis* (*A*) series the methyl ester of pseudoaxial deoxyvincaminic acid could not be prepared in this way. In both the *cis* (*A*) and the *trans* (*B*) series, these esters are accessible by hydrogenation of the corresponding α,β-unsaturated esters[29].

The final step of the synthesis of stereoisomeric vincamines required an introduction of hydroxyl into position 16 in the intermediates *II* and *XIII*. According to Najer and Pascal[20], this group can be introduced by air-oxidation in a strongly alkaline medium under formation of vincamine and its 16-epimer. We failed to reproduce this experiment even using elemental oxygen. We tried therefore to utilize the method of Vedejs and collaborators[30] who introduced hydroxyl into the α-position to the carbonyl group in lactones and esters with oxodiperoxymolybdenum (pyridine) (hexamethylphosphoric triamide), MoO_5.Py.HMPA (ref.[31]). In our experiments we generated carbanion in the activated position 16 of the corresponding deoxyvincamine by treatment with lithium diisopropylamide. This carbanion was then oxidized in situ with the mentioned complex in tetrahydrofuran. Whereas with (±)-16-epi-21-epi-deoxyvincamine (*XIII*) the oxidation led almost stereospecifically to (±)-16-epi-21-epi-vincamine (*XVII*), the reaction of (±)-deoxyvincamine (*II*) afforded only a mixture of (±)-vincamine (*I*) and (±)-16-epi-vincamine (*XVIII*) in which the epi-isomer predominated in the ratio 1 : 9. Thus, in both cases the hydroxyl approaches the molecule from the bottom, less hindered, side.

The described synthesis represents the way to three of the four theoretically possible stereoisomeric racemic vincamines in practical yields from the easily accessible deoxyvincamines.

EXPERIMENTAL

Melting points were determined on a micro melting point apparatus Boetius (G.D.R.). Infrared spectra were recorded on a UR-10 spectrometer (Zeiss, Jena G.D.R.); wavenumbers are given in cm^{-1}. The ultraviolet spectra were measured in methanol on spectrophotometer Specord UV-VIS (Zeiss, Jena G.D.R.) and are expressed in the form λ_{max} (log ε); λ are given in nm and ε in $l\,mol^{-1}\,cm^{-1}$. ^{1}H NMR spectra were taken on a Tesla BS-487 (80 MHz) instrument with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. Mass spectra were recorded on an AEI MS 902 instrument (70 eV, direct inlet).

Immonium Perchlorate *V*

To a stirred solution of enamine *IV* (2·5 g) in dichloromethane (75 ml), 2-chloroacrylonitrile (1·75 g; 2 equivalents) was added dropwise at 10°C under nitrogen. After standing at room temperature for 16 h the mixture was evaporated to dryness in vacuo. The oily residue was dissolved in methanol and acidified with 70% aqueous perchloric acid. The product was filtered off and crystallized from methanol to yield 3·4 g of *V* (78%), m.p. 258–263°C. ^{1}H NMR (CD_3SOCD_3): 6·18 d, 1 H (—CH_{eq}—CN, J = 6·0); 5·93 dd, 1 H (—CH_{ax}—CN, J = 11·0; J' = 5·5). For $C_{20}H_{22}ClN_3O_4.CH_3OH$ (435·9) calculated: 57·85% C, 6·01% H, 9·64% N; found: 57·98% C, 5·74% H, 10·22% N.

Nitriles *XI* and *XII*

To an ice-cooled methanolic (100 ml) solution of the oily addition product (prepared from 2·5 g of *IV* as described above) sodium borohydride (3 g) was added portionwise. After 15 minutes

stirring at room temperature the reaction mixture was treated with 15% acetic acid, freed from methanol by distillation in vacuo, made alkaline with NH_4OH and extracted with chloroform. The extract was evaporated to dryness in vacuo to yield crude product (2·53 g) which on recrystallization from methanol gave *XI* (0·42 g); m.p. 227–229°C. UV spectrum: 273 (3·98), 280 (3·97), 289 (3·77). IR spectrum (KBr pellet): 2 820, 2 760 (*trans* bands); 2 250 (CN); 1 635 (aromatic vibrations). ^{1}H NMR (CF_3COOH): 7·10–7·70 m, 4 H (aromatic H); 5·50 d, 1 H (—CH—CN, J = 7·0); 4·43 d, 1 H (12bH); 1·10 deformed t, 3 H (—CH_2CH_3). For $C_{20}H_{23}N_3$ (305·4) calculated: 78·65% C, 7·59% H, 13·76% N; found: 78·99% C, 7·74% H, 13·76% N. The mother liquor on evaporation and crystallization of the residue from methanol yielded *XII* (0·52 g), m.p. 166–168°C. UV spectrum: 274 (3·98); 280 (3·96); 290 (3·78). IR spectrum (KBr pellet): 2 810, 2 750 (*trans* bands); 2 250 (CN); 1 630 (aromatic vibrations). ^{1}H NMR (CF_3COOH): 7·10–7·70 m, 4 H (aromatic H); 5·15 m, 1 H (—CH—CN); 4·48 d, 1 H (12bH, J = 8·0); 1·00 deformed t, 3 H (—CH_2CH_3). ^{1}H NMR ($CDCl_3$): 7·00–7·60 m, 4 H (aromatic H); 4·75 dd, 1 H (—CH—CN, J = 10·0; J' = 6·0); 2·90 bs, 1 H (12bH); 0·63 deformed t,3 H (—CH_2CH_3).

Additional quantity of *XI* (0·38 g) and *XII* (0·46 g) was obtained from mother liquors by column chromatography on neutral Al_2O_3 (130 g, activity II, benzene and benzene–2% chloroform). Overall yield of *XI* and *XII* was 0·80 g (26·5%) and 0·98 g (32·3%), respectively.

Nitriles *IX*, *X*, *XI* and *XII*

To a cooled, vigorously stirred solution of the oily adduct (prepared from 2-chloroacrylonitrile (3·5 ml) and *IV* (10·5 g) as described above) in a mixture of acetic acid–water (1 : 2) was added portionwise zinc dust (60 g). The suspension was stirred for 15 h at room temperature, then filtered and the filtrate was evaporated to dryness in vacuo. The residue was diluted with water and the product was extracted with dichloromethane. The organic layer was successively washed with 10% aqueous sodium hydroxide and water and after drying ($MgSO_4$) evaporated to dryness in vacuo to afford an oily (12·4 g, quantitative) mixture of *XI*, *XII*, *IX* and *X* with R_F values (TLC, silica gel, benzene–acetone (6 : 2), 0·1% NH_4OH) 0·8, 0·9, 0·5 and 0·4, respectively.

The oil was chromatographed on a column of silica gel (600 g); dichloromethane eluted a mixture of *XI* and *XII* (3·9 g, 30·7%), and dichloromethane with 3% methanol a mixture of *IX* and *X* (5·2 g, 41%). The separation of individual isomers was achieved by recrystallization of corresponding mixtures from methanol. Nitriles *XI* (1·54 g, 12·1%) and *XII* (1·05 g, 8·3%) were identical in all respects with those described above. Nitrile *IX* (1·15 g, 9·1%), m.p. 144–147°C. ^{1}H NMR ($CDCl_3$): 7·00–7·60 m, 4 H (aromatic); 4·83 dd, 1 H (—CH—CN, J = 10·6; J' = 6·4); 3·71 bs, 1 H (12bH); 0·92 t, 3 H (—CH_2CH_3, J = 7·0). For $C_{20}H_{23}N_3$ (305·4) calculated: 78·65% C, 7·59% H, 13·76% N; found: 79·01% C, 7·66% H, 13·80% N. Nitrile *X* (2·48 g, 19·5%), m.p. 164–166°C. ^{1}H NMR ($CDCl_3$): 7·00–7·62 m, 4 H (aromatic H); 5·09 dd, 1 H (—CH—CN, J = 6·5; J' = 2·0); 3·85 bs, 1 H (12bH); 0·92 t, 3 H (—CH_2CH_3, J = 7·0). For $C_{20}H_{23}N_3$ (305·4) calculated: 78·65% C, 7·59% H, 13·76% N; found: 78·08% C, 7·59% H, 13·76% N.

16-epi-21-epi-Deoxyvincaminic Acid (*VIII*)

A solution of nitrile *XI* (0·5 g) in conc. hydrochloric acid (10 ml) was refluxed for 2 h and then evaporated to dryness in vacuo. The residue was neutralized with saturated aqueous solution of sodium hydrogen carbonate and the precipitate formed was filtered off, washed with water, dried and crystallized from methanol yielding *VIII* (0·4 g, 75·4%), m.p. 184–187°C. IR spectrum (KBr pellet): 1 615 (COO^-); 1 480 (subst. aromatic ring). ^{1}H NMR (CD_3SOCD_3): 7·20 m, 1 H (aromatic H); c. 6·90 m, 3 H (aromatic H); 4·50 dd, 1 H (—CHCOOH, J = 10·8; J' = 4·0); c. 2·90 bs, 1 H (12b H); 0·65 deformed t, 3 H (—CH_2CH_3). Mass spectrum: 324 (M^+). For

$C_{20}H_{24}N_2O_2.CH_3OH$ (356·5) calculated: 70·76% C, 7·92% H, 7·86% N; found: 69·82% C, 8·15% H, 8·19% N.

16-epi-21-epi-Deoxyvincamine (*XIII*)

A) A solution of nitrile *XI* (0·51 g) in dilute hydrochloric acid (15 ml, 2 : 1) was refluxed for 3 h, then evaporated in vacuo and dried in a desiccator over potassium hydroxide. The residue was dissolved in methanol and treated with ethereal solution of diazomethane. The reaction mixture was evaporated in vacuo, the solution was brought to pH 7 by saturated aqueous solution of sodium hydrogen carbonate and the product was extracted with chloroform. After removal of the solvent in vacuo the oily residue was dissolved in benzene (10 ml) and filtered through a column of Al_2O_3 (20 g, neutral). The residue left after evaporation of benzene in vacuo was crystallized from methanol affording the ester *XIII* (0·42 g, 75·2%), m.p. 109—112°C. IR spectrum (KBr pellet): 2 840, 2 760 (*trans* bands); 1 735 (ester); 1 625 (aromatic vibrations); 745 (disubst. benzene ring). ^{1}H NMR ($CDCl_3$): 7·45 m, 1 H (aromatic H); c. 7·05 m, 3 H (aromatic H); 4·68 dd, 1 H (—CH—$COOCH_3$, $J = 11·0$; $J' = 6·0$); 3·81 s, 3 H (—$COOCH_3$); 2·41 dd, 1 H (CHH_{eq}—CH—$COOCH_3$, $J = 14·0$; $J' = 6·0$); 1·58 dd, 1 H (—CHH_{ax}—CH—$COOCH_3$, $J = 14·0$; $J' = 6·0$); 1·75 q, 2 H (—CH_2CH_3, $J = 7·0$); 0·80 t, 3 H (—CH_2CH_3, $J = 7·0$). Mass spectrum *m/z*: 338·1989 (calculated for $C_{21}H_{26}N_2O_2$ 338·1994; M^+).

B) Nitrile *XII* (0·25 g) was dissolved in a mixture of ethanol (5 ml) and 20% aqueous sodium hydroxide (5 ml), the solution was refluxed for 50 h, acidified with concentrated hydrochloric acid and the separated hydrated silicon dioxide was filtered off. The filtrate was evaporated in vacuo and the residue was extracted several times with methanol. The residue obtained after removing the solvent in vacuo was crystallized from methanol affording 0·183 g (80·6%) of ester *XIII* (m.p. 109—111°C, undepressed on admixture with the sample prepared ad *A*), identical (IR and ^{1}H NMR spectra and TLC mobilities) with that prepared above.

21-epi-Eburnane-16α-carboxamide (*XIV*)

A solution of nitrile *XII* (0·5 g) in dilute sulfuric acid (4 ml; 1 : 1) was refluxed for 2 h. The cold solution was neutralized with an aqueous solution of sodium hydrogen carbonate and the resulting precipitate was collected and washed with water. Crystallization of the crude product (0·47 g, 88·8%) gave *XIV*, m.p. 272—275°C (decomp.). IR spectrum (KBr pellet): 3 300, 3 200 (—NH_2), 1 680 (amide), 1 620 (aromatic vibrations), 740 (disubst. benzene ring). Mass spectrum *m/z*: 332 (M^+). For $C_{20}H_{25}N_3O·0·5\ CH_3OH$ (339·4) calculated: 72·53% C, 8·02% H, 12·50% N; found: 72·37% C, 7·97% H, 12·50% N.

16-epi-21-epi-Vincamine (*XVII*)

A solution of lithium diisopropylamide (LDA) (prepared at 0°C from diisopropylamine (0·39 ml 2·2 mmol) in THF (3 ml) and 1·22 ml of 2·3M butyllithium (2·8 mmol) in hexane) was stirred at 0°C for 0·5 h and then a solution of *XIII* (0·20 g, 0·6 mmol) in THF (8 ml) was added dropwise. The stirring at 0°C was continued for 0·5 h and MoO_5.Py.HMPT reagent[31] (0·28 g) was added. After 0·5 h another portion of the oxidation reagent (0·12 g) was added (total 0·9 mmol). The reaction mixture was stirred for additional 2 h at room temperature and decomposed with water (5 ml). The aqueous layer was extracted several times with chloroform and the extracts were combined with the first separated organic layer. After drying ($MgSO_4$) the solvents were removed in vacuo and the semisolid residue was crystallized from methanol yielding *XVII* (0·09 g, 44%), m.p. 209—210°C, identical with an authentic sample. Mass spectrum, *m/z* (relative

intensity): 354 (64; M^+); 353 (63; M − 1); 295 (18; M − $COOCH_3$); 294 (12; M − $HCOOCH_3$); 293 (27; M − H − $HCOOCH_3$); 266 (11), 265 (18); 253 (29); 252 (100); 251 (39); 237 (35); 223 (15); 209 (17); 169 (17); 168 (15); 147 (16); 119 (16); 115 (17); 110 (15). For $C_{21}H_{26}N_2O_3$ (354·4) calculated: 71·16% C, 7·39% H, 7·90% N; found: 70·74% C, 7·43% H, 7·92% N.

Deoxyvincamine (*II*)

A) From eburnane-16β-carbonitrile (IX). A solution of *IX* (4 g) in concentrated hydrochloric acid (80 ml) was refluxed for 8 h, then evaporated in vacuo and dried over potassium hydroxide in a desiccator. The residue was dissolved in methanol (30 ml) and esterified with ethereal diazomethane by standard procedure. After evaporation in vacuo a crude product (4·4 g) was obtained. According to TLC (silica gel, benzene–acetone (2 : 1) with 0·1% NH_4OH) the product consisted of two compounds having R_F values 0·5 and 0·2. The mixture was treated with concentrated aqueous solution of $NaHCO_3$, extracted with chloroform and after removing the latter in vacuo subjected to column chromatography (silica gel, 200 g). Elution with chloroform containing 1% methanol afforded the product with R_F 0·5 which on crystallization from methanol yielded pure *II* (1·82 g, 41%), m.p. 161–163°C. IR spectrum ($CHCl_3$): 1 758 (ester); 740 (1,2-disubst. benzene ring). ^{1}H NMR ($CDCl_3$): 7·45 m, 1 H (aromatic H); c. 7·10 m, 3 H (aromatic H); 4·68 dd, 1 H (—CH—$COOCH_3$, J = 12·0; J' = 6·0); 3·90 bs, 1 H (12bH); 3·72 s, 3 H (—$COOCH_3$); 0·90 t, 3 H (—CH_2CH_3, J = 7·0). For $C_{21}H_{26}N_2O_2$ (338·4) calculated: 74·52% C, 7·74% H, 8·28% N; found: 74·23% C, 7·93% H, 8·12% N. The mixture of chloroform with 3% methanol brought from the column solid material (R_F 0·2) which on crystallization from ethanol gave pure *XV* (1·2 g, 27%), m.p. 121–124°C, R_F 0·55 (TLC, Kieselgel GF 254 plates, chloroform–acetone (1 : 2) with 0·5% ethanol and 0·1% NH_4OH). IR spectrum ($CHCl_3$): 3 510, 3 400 (NH_2); 1 680 (—$CONH_2$); 1 610, 1 580 (aromatic vibrations). ^{1}H NMR ($CDCl_3$): 8·50 bm, 1 H (aromatic H); 7·00–7·30 m, 3 H (aromatic H); 5·85 and 5·15 2 × bs, 2 × 1 H (—$CONH_2$); 4·84 bd, 1 H (—CH_{eq}—$CONH_2$, J = 7·5); 3·85 bs, 1 H (12bH); 0·91 t, 3 H (—CH_2CH_3, J = = 7·0). Mass spectrum, *m/z*: 323 (M^+). For $C_{20}H_{25}N_3O.C_2H_5OH$ (369·5) calculated: 71·51% C, 8·46% H, 11·38% N; found: 71·25% C, 8·55% H, 11·39% N.

B) From eburnane-16β-carboxamide (XV). A solution of *XV* (0·12 g) in ethanol (5 ml) and 20% aqueous sodium hydroxide (10 ml) was heated under reflux for 48°C when evolution of NH_3 gas ceased. The solution was acidified to pH 4 by diluted hydrochloric acid, filtered to remove separated hydrated silicon dioxide and the filtrate was evaporated to dryness in vacuo. The crystalline residue was extracted several times with methanol, the extracts were evaporated to a small volume (20 ml) and esterified with ethereal diazomethane by standard method. Usual work-up of the reaction mixture and crystallization of the crude product from methanol afforded *II* (0·1 g, 80%), m.p. 160–162°C, identical in all respects with the sample described ad *A*).

Eburnane-16α-carboxamide (*XVI*)

A) From eburnane-16β-carbonitrile (IX). To a solution of *IX* (0·07 g) in ethanol (8 ml) 20% aqueous sodium hydroxide (1 ml) was added and the mixture was heated under reflux for 4·5 h. Ethanol was removed in vacuo, the mixture was neutralized with dilute hydrochloric acid, the precipitate formed was filtered off, washed with water and dried (0·058 g). Purification by filtration through a column of silica gel (5 g) in chloroform–methanol mixture (97 : 3) followed by crystallization from methanol yielded *XVI* (0·045 g, 60%), m.p. 219–222°C. R_F 0·45 (TLC, Kieselgel GF 254, chloroform–acetone (1 : 2) with 0·5% EtOH and 0·1% NH_4OH). IR spectrum ($CHCl_3$): 3 510, 3 400 (—NH_2); 1 680 (—$CONH_2$); 1 610, 1 580 (aromatic vibrations). ^{1}H NMR ($CDCl_3$): 7·48 bm, 1 H (aromatic H); 7·00–7·30 m, 3 H (aromatic H); 6·20 and 5·98 2× bs, 2×1 H

(—$CONH_2$); 4·45 dd, 1 H (—CH_{ax}—$CONH_2$, J = 12·0; J' = 5·5); 3·88 bs, 1 H (12bH); 0·88 t, 3 H (—CH_2CH_3, J = 7·0). Mass spectrum, *m/z*: 323·1992 (calculated for $C_{20}H_{25}N_3O$ 323·1998; M^+).

B) From eburnane-16β-carboxamide (XV). To a solution of *XV* (0·02 g) in ethanol (3 ml) 20% aqueous sodium hydroxide (0·5 ml) was added and the mixture was refluxed for 3·5 h. Ethanol was removed in vacuo and the product was extracted with dichloromethane. The combined extracts were dried ($MgSO_4$), evaporated in vacuo and the residue was crystallized from methanol affording *XVI* (0·015 g, 75%) identical in all respects with that described under *A*).

C) From eburnane-16-carbonitriles IX and X. An ethanolic solution of *IX* or *X* (0·018 g) was refluxed with solid sodium hydroxide (5 mg) for 8 h. The residue left after removing of ethanol in vacuo was diluted with water (1 ml) and the product was extracted with dichloromethane. The extract was dried over anhydrous $MgSO_4$ and evaporated to dryness in vacuo yielding in both experiments *XVI* (0·014 g, 73% and 0·016 g, 84%, respectively) identical in all respects with the sample described under *A*).

Vincamine (*I*) and 16-epi-Vincamine (*XVIII*)

To a stirred solution of diisopropylamine (0·3 ml, 2·1 mmol) in THF (3 ml) a 1·6M solution of butyllithium (1·4 ml, 2·25 mmol) in hexane was added dropwise under nitrogen. After stirring at 0°C for 0·5 h a solution of *II* 0·2 g, 0·6 mmol) in THF (8 ml) was added dropwise and the stirring at 0°C was continued for 0·5 h. Then MoO_5.Py.HMPT reagent[31] (0·28 g) was added in one portion and the mixture was stirred for 0·25 h at 0°C and for another 0·25 h at 20°C. The dirty-green solution was again cooled to 0°C and a new portion (0·12 g) of the oxidation reagent (total 0·9 mmol) was added while the stirring was continued for 2 h at 20°C. The solution was decomposed with water (5 ml), the aqueous layer was separated and extracted several times with chloroform. The extracts were combined with the upper organic layer, dried over anhydrous $MgSO_4$, evaporated in vacuo and the viscous oily product was chromatographed on a column of silica gel (40 g). Chloroform with 2—3% methanol eluted in early fractions crystals which on crystallization from methanol afforded *I* (11 mg, 5·2%), m.p. 216—220°C. From the post-vincamine fractions *XVIII* was gained (0·083 g, 39·7%), m.p. 206—209°C (ref.[29] 203—204°C). Both *I* and *XVIII* were identical in their m.p., IR spectra, TLC and GLC mobilities with the respective authentic samples of vincamine and its 6-epimer.

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