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A TOTAL SYNTHESIS OF (±)-VINCAMINE†

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Abstract—(±)-Homoeburnamenine (3), previously prepared in connection with the total synthesis of (±)-eburnamine (1), has been converted into (±)-vincamine (2).

At the time that our synthesis of (±)-eburnamine (1)‡ was completed[1] only one total synthesis[2] of (±)-vincamine (2) had been reported. In view of the reported pharmacological properties of vincamine[3] and its possible clinical use, and the fact that the yield in the penultimate stage of the published synthesis was extremely low an alternative synthesis seemed desirable, and an obvious route from our synthetic intermediate, homoeburnamenine (3), suggested itself. Thus, oxidation of dihydroxyhomoeburnamenine (4) under appropriate conditions should afford the dioxo compound (5) which on reaction with sodium methoxide should give vincamine directly, either by methanolysis of the N_a–CO bond followed by cyclisation, or by a benzil–benzilic ester type of transformation following nucleophilic attack by methoxide ion at either CO group. In the event the oxidation of dihydroxyhomoeburnamenine proved to be a complex reaction from which the dioxo compound 5 was never obtained, and vincamine was eventually prepared by a stepwise process.

Our first attempts to form the dioxo system at positions 16 and 17' were performed using dihydroxyhomoeburnamenine lactams (**6a** and **6b**)[1] as models. Since eburnamine glycol (7) is reported[4] to be oxidised to 17-hydroxyeburnamonine (8) by brief treatment with Sarett's reagent, the use of this oxidant was investigated; however, with **6a** serious loss of material was encountered and no useful product could be isolated. The use of the pyridine-sulphur trioxide complex in DMSO and triethylamine[5] on **6a** led to a multiplicity of products and again no useful product was obtained.

Since the glycol-amides (**6a** and **6b**) are formally carbinolamines they may be susceptible to oxidation by cupric salts. However, with cupric acetate and ammonium nitrate in aqueous acetic acid **6b** was unaffected at room temperature, and at 100° was slowly converted into a product of higher R_f value which was also the product obtained when **6b** was treated under the same conditions with acetic acid alone. That this product was almost certainly the ketone (**9b**) obtained by acid-catalysed dehydration of **6b** was established by the isolation of the analogous ketone (**9a**) by similar treatment of the glycol-amide (**6a**). In **9a** the ketone CO absorption was observed at 1724 cm^{-1} and the C-17' methylene group resonated as an AB system of two doublets centred on τ 5.82 and 5.02, with J = 19.5 Hz.

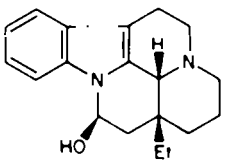
Following these initial experiments we turned our attention to the oxidation of dihydroxyhomoeburnamenine (4), which was prepared in almost quantitative yield by the osmium tetroxide hydroxylation of homoeburnamenine (3). Although this material appeared to be homogeneous (TLC analysis) only a poor yield (~36%) of crystalline material could be isolated, and it was therefore concluded that hydroxylation proceeds on either face of the homoeburnamenine double bond to give a mixture of diastereoisomeric *cis*-glycols. This was supported by the NMR spectrum of the mixture, which exhibited two broad singlets at τ 3.87 and 4.37; since these signals together accounted for one proton, they were interpreted as the C-17' proton resonances of the two stereoisomers. Unfortunately, the glycol (4) could not be obtained by reduction (LAH) of the lactam (**6a**) owing to the formation of an insoluble aluminate complex with the glycol function.

Oxidation of the glycol (4) was limited by the necessity to use non-acidic conditions in view of the ease of the acid-catalysed dehydration of this type of system. As with the lactam (**6a**) Sarett's reagent gave no useful product, neither could the desired product be obtained by use of 1-chlorobenzotriazole,[6] silver carbonate on celite,[7] or pyridine-chromium trioxide in dichloromethane.[8] Oxidation with the pyridine-sulphur trioxide complex in DMSO and triethylamine was then investigated in some detail. With rigorously dried reagents no oxidation was observed, neither was oxidation observed in the presence of one equivalent of water; however, with the addition of 1% water to substrate oxidation of 4 proceeded with reproducible results, and preparative plate chromatography of the product led to the isolation of three compounds, two of which were identified as the two epimers of the desired compound (**10**). The third product, obtained in insufficient amount for secure identification, is tentatively regarded as the product **11** of dehydration of **10**; it was only obtained when the pyridine–sulphur trioxide complex was added directly to the reaction mixture, i.e. without prior solution in DMSO, and is presumed to arise by intramolecular elimination of sulphuric acid from the bisulphate ester of **10**.

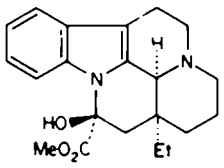
The epimers (**10**) are formally acyloins and should therefore be susceptible to oxidation by cupric acetate. As expected, both epimers were converted by means of cupric acetate in methanol into the same product, which melted at 198–201.5°; unexpectedly, however, this product exhibited M$^+$, 294, and gave IR, UV, and mass

†Preliminary communication: K. H. Gibson and J. E. Saxton, *Chem. Comm.* 1490 (1969).

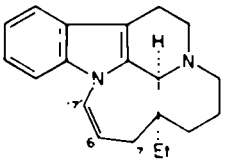
‡The configurations shown are those of the naturally-occurring alkaloids; all synthetic compounds reported here are racemic, but only one enantiomer is illustrated.



(–) – Eburnamine 1



(+) – Vincamine 2



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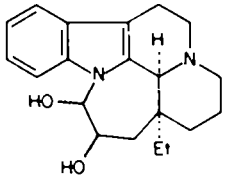

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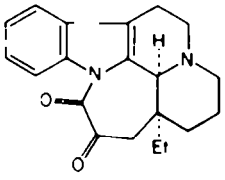

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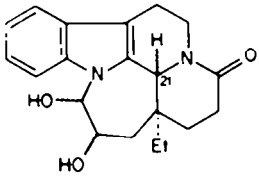
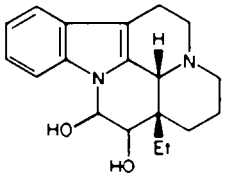


6a: α–H at C–21
6b: β–H at C–21



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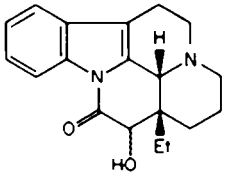

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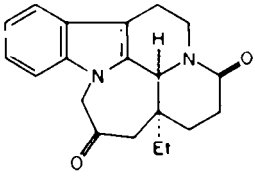
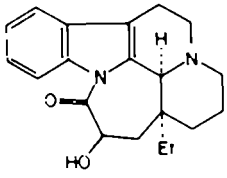


9a: α–H at C–21
9b: β–H at C–21



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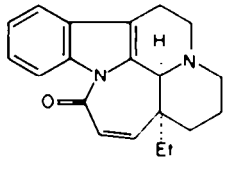
ammoniacal silver nitrate.[11] Alternatively, the fragmentation may be analogous to the base-induced decomposition of formic acid esters to carbon monoxide and alkoxide ion (13 → 15 → 12). The third possibility involves fragmentation of the mixed anhydride (16), itself obtained by attack of acetate on the dioxo compound (5) followed by a benzilic acid type of rearrangement, and is formally analogous to the acid-catalysed decarbonylation of α-hydroxy acids.

The attempts at the preparation of the dioxo compound 5 having proved abortive, a stepwise route to vincamine was then developed. Alkaline hydrolysis of the epimers (10) afforded a mixture of hydroxy acids which were esterified by means of diazomethane to give the methyl esters (17), m.p. 194–196°,[12] together with a compound, m.p. 145–150°, which is probably (+)-methyl eburnamoninate, although an authentic specimen was not available for direct comparison.

The final stage in the preparation of vincamine involved oxidation of the hydroxy-ester (17) by means of pyridine–sulphur trioxide complex in DMSO–NEt, con-



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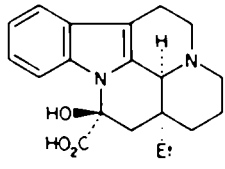

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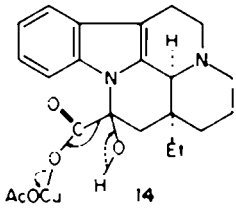

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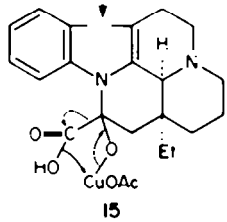

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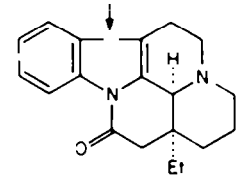

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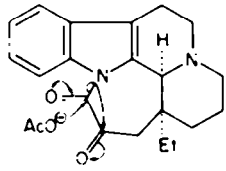

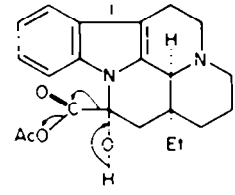

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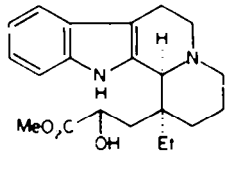

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spectra identical with those reported[9] for (±)-eburnamonine (12)[10] m.p. 201–202°.

The degradation of 10 to eburnamonine by this mild reagent seems at first surprising, but can be explained in three ways, all of which depend for the initial stage on oxidation to the desired dioxo compound (5). One possibility is that water present in the reaction mixture results in formation of vincaminic acid (13), which is then oxidatively cleaved by the cupric acetate (13 → 14 → 12); this is directly analogous to the formation of eburnamonine by the oxidation of vincaminic acid with

taining a trace of water. Chromatography of the product afforded (±)-vincamine (**2**), m.p. 228–229°, identical with authentic (+)-vincamine by TLC comparison in three different solvent systems, and by comparison of IR and mass spectra.[13]

EXPERIMENTAL

M.ps were measured on a Kofler hot-stage apparatus. IR spectra were recorded on a Unicam SP 200 spectrophotometer, or on a Perkin–Elmer P.E. 125 instrument: UV spectra were recorded on a Unicam SP 800 or SP 800A spectrophotometer (95% ethanol as solvent). NMR spectra were measured on Varian A60 or A60A instruments, with tetramethylsilane as internal standard, and mass spectra were recorded on an A.E.I. MS 902 spectrometer.

1,2,3,4,6,7,12,12*bβ* - *Octahydro* - 1 - *ethyl* - 4 - *oxo* - 1,12 - (*β* - *oxo*) - *trimethyleneindolo*[2,3-*a*]*quinolizine* (**9a**). A soln of **6a** (28 mg) in glacial AcOH (2.5 ml) was heated at 85–90° for 12 hr in a dry N_2 atmosphere. Most of the AcOH was evaporated under reduced pressure and the residue was partitioned between $CHCl_3$ (10 ml) and aqueous $NaHCO_3$ (10 ml). The aqueous soln was extracted with further portions of $CHCl_3$ (2 × 5 ml) and the combined extracts were dried (Na_2SO_4) and evaporated. The residue (35.5 mg) was chromatographed on a preparative plate (20 cm × 20 cm × 1 mm; 1:1 Kieselgel G:Kieselgel HF_{254}) with benzene-5% EtOH as eluent (two runs). The relevant portion of Kieselgel was extracted with MeOH. After evaporation of the MeOH the residue was extracted into $CHCl_3$ and evaporation of the $CHCl_3$ yielded an amber gum (24.6 mg 92.3%); $\nu_{max.}$ (in $CHCl_3$) 1724 (ketone), 1632 (δ-lactam) cm^{-1}, $\lambda_{max.}$ (ε) 227 (28,400), 276 (6550), 283 (6100), λ_{sh} 292 nm (4730), τ (in $CDCl_3$) 8.96 (3 H, t, J = 7 Hz, CH_2CH_3), 6.8–8.8 (11 H, m), 5.82 (1 H, d, J = 19.5 Hz, $N_aCHH'CO$), 5.4 (1 H, s, $C_{12}H$), 5.02 (1 H, d, J = 19.5 Hz, $N_aCHH'CO$), 4.9 (1 H, m, C_1HH'), 2.3–2.95 (4 H, m, aromatic protons), m/e 322.168 (100; $C_{20}H_{22}N_2O_2$ requires: 322.168), 305 (25), 293(71), 279 (11), 276 (12), 265 (32), 251 (14), 183 (43).

Dihydroxyhomoeburnamenine (**4**). Homoeburnamenine (115 mg)[3] was dissolved in dry pyridine (0.5 ml) and a soln of osmium tetroxide (100 mg) in dry pyridine (1 ml) was added. The mixture was stirred at ambient temp. for 22 hr under N_2. A soln of sodium metabisulphite (190 mg) in pyridine (2 ml) and water (3 ml) was added and stirring was continued for a further 2 hr. The soln was extracted with $CHCl_3$ (4 × 6 ml) and the combined extracts were washed with brine and then dried (Na_2SO_4). Evaporation of the solvent and trituration of the residue with benzene gave a pale-yellow crystalline material (143.6 mg), shrinkage *ca.* 115°, then m.p. 152–160°, which was virtually a single spot on TLC analysis. Recrystallisation from benzene gave *dihydroxyhomoeburnamenine* (46.7 mg 36.5%), m.p. 158–164° (dec); $\nu_{max.}$ (KCl disc) 3360 (broad; OH), no *trans*-bands, 1010–1062 (complex bands; C–OH) cm^{-1}, $\lambda_{max.}$ (ε) 224 (28,400), 284 (7330), 292 (6170), λ_{sh} 278 nm (7000) (in EtOH), τ (in $CDCl_3$) 9.08 (3 H, t J = 7 Hz, CH_2CH_3), 6.6–8.9 (15 H, m), 5.7–6.25 (2 H, m, $C_{16}HOH$), 3.87 and 4.37 (1 H, two bs's, C_{17}-H[isomers]), 2.4–3.0 (5 H, m, aromatic protons and C_{17}-OH), *m/e* 326.198 (100; $C_{20}H_{26}N_2O_2$ requires: 326.199), 308 (42), 297 (19), 295 (17), 291 (18), 279 (53), 267 (47), 238 (28), 237 (19). (Found: C, 73.8; H, 7.7; N, 8.5. $C_{20}H_{26}N_2O_2$ requires: C, 73.6; H, 8.0; N, 8.6%).

Oxidation of dihydroxyhomoeburnamenine (**4**)

(A) A soln of pyridine–sulphur trioxide complex (380 mg) in DMSO (2.0 ml anhyd and 0.28 ml containing 0.01% water; 1% water to substrate) was added to a vigorously stirred mixture of **4** (48.9 mg), DMSO (1.0 ml, anhyd), and triethylamine (3 ml). The mixture was stirred at room temp. under dry N_2 for 16 hr, at the end of which time some starting material was still present (TLC analysis). More pyridine-sulphur trioxide complex (200 mg) was added, and the mixture stirred for a further 18 hr, then partitioned between ether–ethylene chloride (2:1, 30 ml) and brine (30 ml). The organic layer was washed with further portions of brine (2 × 15 ml) and then dried ($MgSO_4$). After evaporation of the solvent the residue was chromatographed on a preparative plate (20 cm × 20 cm × 1 mm; 1:1 Kieselgel G:Kieselgel HF_{254}, double run using EtOAc–1% 0.88 ammonia as eluent). Methanolic extraction of the relevant portions of adsorbent, followed by evaporation of the solvent, extraction of the residue with $CHCl_3$ and evaporation of the $CHCl_3$ led to the isolation of three products.

16,17' - *Dihydro* - 16,17 - *dehydro* - 17' - *oxohomoeburnamenine* (**11**) (4.9 mg, 10.7%) was obtained as an amber gum; $\nu_{max.}$ (in $CHCl_3$), 1700 cm^{-1}, qualitative UV spectrum showed a distorted indole chromophore ($\lambda_{max.}$ 233, 275 nm), *m/e* 306 (44), 294 (23), 293 (18), 277 (100), 265 (9), 252 (11), 248 (14), 236 (79).

The higher R_f isomer of 16 - *hydroxy* - 17' - *oxodihydrohomoeburnamenine* (**10**) (8.9 mg, (18,3%) was obtained as an amber gum; $\nu_{max.}$ (in $CHCl_3$) 1700, 1617 cm^{-1}, *m/e* 324 (100; M$^+$), 295 (82; M$^+$–Et), 294 (73, M$^+$–CH_2O or M$^+$–Et–1), 293 (55, M$^+$–CH_2OH), 277 (18, M$^+$–H_2O–Et), 267 (82, M$^+$–CO–Et), 265 (41, M$^+$–CH_2O–Et), 252 (41, M$^+$–CH_2CHOH·CO), 237 (32, M$^+$–CHOH·CO–Et), 224 (32, M$^+$–CH_2CHOH CO–CH_2CH_2).

The lower R_f isomer of 16 - *hydroxy* - 17' - *oxodihydrohomoeburnamenine* (**10**) (12.6 mg, 26%) was also obtained as an amber gum; $\nu_{max.}$ (in $CHCl_3$) 1700, 1617 cm^{-1}, *m/e* 324 (50), 295 (100), 294 (35), 293 (30), 267 (30), 265 (25), 252 (35), 237 (25), 224 (25).

To each product was added twice its weight of copper acetate and 2, 2.5 and 5 ml of MeOH respectively. The solns were refluxed for 4 hr and then the MeOH was evaporated *in vacuo*. The residues were examined by TLC analysis which showed that **11** was unaffected by the treatment but the two isomers of **10** had been converted to the same compound. Compound **11** was isolated by preparative plate chromatography (EtOAc–1% 0.88 ammonia) and the IR spectrum of the product (3.0 mg) was the same as that of the starting material. The combined product from the two isomers of **10** was isolated (10.1 mg) by preparative plate chromatography (EtOAc–1% 0.88 ammonia) and then recrystallised from EtOH to give eburnamonine (4.3 mg) as colourless prisms, m.p. 198–201.5° (lit.[10] m.p. 201–202°), identical in IR spectrum (KCl disc), UV spectrum (in EtOH), and mass spectrum to the published data.[9]

(B) When the oxidative procedure was repeated with dropwise addition of the pyridine-sulphur trioxide complex in wet DMSO soln over 1 hr, the isolated products were eburnamonine (10.7 mg, 24.2%), high R_f **10** (6.3 mg, 13%), and low R_f **10** (12.5 mg, 25.7%).

(±)-*Vincamine* (**2**). Dihydroxyeburnamenine **4** (135 mg) was dissolved in dry DMSO (1 ml) and dry triethylamine (5 ml) was added. The 2-phase mixture was stirred vigorously under N_2 while a soln of pyridine-sulphur trioxide complex (1.03 g) in dry DMSO (5 ml) containing wet DMSO (0.75 ml; 0.01% H_2O) was added dropwise during 5 min. The mixture was stirred at room temp. under N_2 for 18 hr, and then diluted with 2:1 Et_2O:CH_2Cl_2 (150 ml). The resulting soln was extracted with brine (4 × 100 ml), dried (Na_2SO_4), and the solvent evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ and applied to a preparative plate (1:1 Kieselgel G:Kieselgel HF_{254}; 20 cm × 20 cm × 1 mm) which was then developed twice with 50:49:1 EtOAc:$CHCl_3$:0.88 NH_3. After detection under short wave UV (λ 254 nm) the two lower bands (two isomers of **10**) were removed from the plate and extracted with EtOH. After evaporation of the EtOH the residue was extracted with $CHCl_3$. Evaporation of the $CHCl_3$ gave a mixture of the two isomers of **10** (108.7 mg; 85% from homoeburnamenine), which were dissolved in MeOH (8 ml) and 5N NaOH (1.2 ml) was added. The resulting soln was refluxed for 12 hr and then partially evaporated *in vacuo*. The residue was dissolved in water (25 ml) and the aqueous soln extracted with CH_2Cl_2 (2 × 15 ml). The pH was adjusted to 5–6 by addition of 2N AcOH and the soln again extracted with CH_2Cl_2 (3 × 15 ml). These last extracts were dried (Na_2SO_4) and then evaporated. The residue was dissolved in 1:1 CH_2Cl_2:MeOH (6 ml) and an excess of ethereal diazomethane was added. The soln was left at room temp. for 1 hr and the excess of diazomethane then destroyed by addition of glacial AcOH. The solvent was evaporated and the residue was chromatographed on a preparative plate which was developed in 40:58:2 EtOAc:$CHCl_3$:0.88 NH_3. Two bands were visible on exposure at 254 nm and the material in these bands was separately extracted with EtOH, the EtOH was evaporated, and the residues were then separately extracted into $CHCl_3$. The compound of *lower* R_f value was obtained on evaporation of the

$CHCl_3$ as a microcrystalline solid (7.2 mg), m.p. 194–196°, and is the *hydroxy-ester* (**17**): Found: *m/e* 356.20782; $C_{21}H_{28}N_2O_3$ requires: 356.20998.

The compound of higher R_f value crystallised on trituration with ether to give pale yellow needles (7.7 mg) m.p. 127–140°, raised to 145–150° on recrystallisation from cyclohexane, and is probably methyl eburnamoninate.

The hydroxyester **17** (26.7 mg) (combined material from separate preparations) was dissolved in dry DMSO (1 ml), dry triethylamine (3 ml) was added, then a solution of pyridine-sulphur trioxide complex (188 mg) in dry DMSO (1 ml) containing wet DMSO (0.13 ml; 0.01% H_2O) was added dropwise during 5 min. The soln was stirred under N_2 for 16 hr, then diluted with 2:1 ether:CH_2Cl_2 (25 ml) and the resulting soln extracted with brine (2 × 25 ml), dried (Na_2SO_4), and evaporated. The residue was run on a preparative plate (1:1 Kieselgel G:Kieselgel HF_{254}; 20 cm × 20 cm × 1 mm) which was then developed twice with 25:74:1 EtOAc:$CHCl_3$:0.88 NH_3. The portion of Kieselgel containing the desired product (band of intermediate R_f) was extracted with EtOH, the EtOH was evaporated, and the residue extracted with $CHCl_3$. Evaporation of the $CHCl_3$ gave (±)-vincamine (2.3 mg), identical with authentic vincamine by TLC comparison in 4:95:1 MeOH:$CHCl_3$:0.88 NH_3 (R_f 0.75), 10:89:1 EtOH:C_6H_6:0.88 NH_3 (R_f 0.51), 40:59:1 EtOH:$CHCl_3$:NH_3 (R_f 0.13). Recrystallisation from MeOH gave (+)-vincamine, m.p. 228–229° (lit.[14] m.p. 235-236°C) (Found: *m/e* 354.19259; $C_{21}H_{26}N_2O_2$ requires: 354.19433), identical with authentic vincamine by comparison of IR and mass spectra.

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[12]Subsequently Cs. Szántay, L. Szabó and Gy. Kalaus (*Tetrahedron Letters* 191 (1973)) synthesised the same hydroxyester, for which they reported m.p. 234°. Unfortunately, it has not proved possible to compare directly the two samples, but it is tentatively suggested by Prof. Szántay (*loc. cit.*) that they differ in the stereochemistry at C-16.

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