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THE STRUCTURE OF CUANZINE

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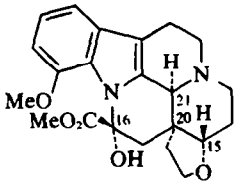
Abstract—The structure of cuanzine has been determined to be **1** by an investigation of its IR, UV, MS, ^{1}H- and ^{13}C-NMR spectra.

The benzene extract of the root bark of *Voacanga chalotiana* collected in Angola has been reported to contain a complex mixture of alkaloids,[1] largely consisting of a new base which we proposed to designate cuanzine. The present communication is concerned with the elucidation of structure **1** for this new compound. In the process, high resolution mass spectrometry, high field proton magnetic resonance and ^{13}C-NMR spectroscopy were employed.



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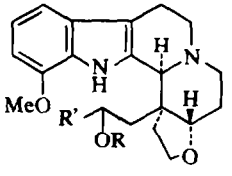
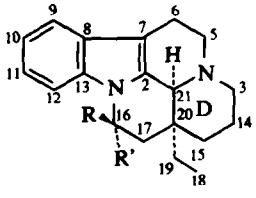
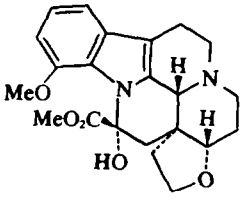


3: R = H; R′ = CO_2Me
4a: R = H; R′ = CH_2OH
4b: R = Ac; R′ = CH_2OAc



5: R = OH; R′ = CO_2Me
7: R = CO_2Me; R′ = OH



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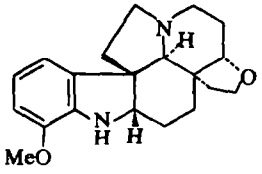

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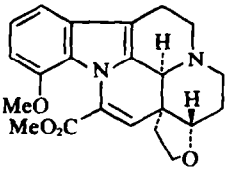

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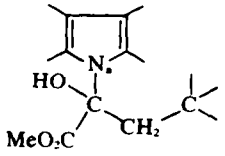
The molecular ion peak at *m/e* 398·1842 proves cuanzine to possess the molecular formula $C_{22}H_{26}N_2O_5$ (calc. for $C_{22}H_{26}N_2O_5$ 398·1842), while the UV absorption at 226, 270 and 292 nm (lg ϵ 4·65, 3·98 and 3·75) shows that this alkaloid contains a methoxyindole chromophore. The ^{1}H-NMR spectrum in benzene-d_6 (100 MHz) furnishes corroborative evidence for the nature of the substituent in the indole moiety by revealing an 1,2,3-hydrogen substitution pattern at δ 6·44 (dd, J_{ortho} 7, J_{meta} 2 Hz), 7·05 (t, J_{ortho} 7 Hz) and 7·19 (dd, J_{ortho} 7, J_{meta} 2 Hz), and a singlet at δ 3·40 for a methoxy group. The presence of a carbomethoxy and of a hydroxyl group is secured by IR absorptions ($CHCl_3$) at 1746 and 3530 cm^{-1}, ^{1}H-NMR signals at δ 3·33 (3H, s) and 4·88 (1H, bs), the last signal disappearing upon deuteronation, and by the MS peaks at *m/e* 339 and 380 due respectively to the loss of CO_2Me and H_2O. No acetyl derivative is obtained from cuanzine even under forced conditions.

The spectroscopic properties of the two products obtained by $NaBH_4$ reduction of cuanzine in THF suggest that the N atom of the indole moiety is substituted as indicated in the partial formula **2**.



2

The product (**3**), which forms first, $C_{22}H_{28}N_2O_5$ (M^+ = 400·1994; calc. for $C_{22}H_{28}N_2O_5$ 400·1998) derives from the reduction of the C-N_a linkage shown in partial structure **2**; in fact, in its ^{1}H-NMR spectrum (100 MHz, benzene − d_6) **3** exhibits the presence of an indole NH group as broad singlet at δ 8·04 and three protons assignable to a

HO—CH_X—CH_AH_B— grouping (δ_A 1·64, δ_B 2·26, δ_X 4·24, J_{AB} 15, J_{AX} 10, J_{BX} 3 Hz). Irradiation of the X part of this ABX system causes the double doublets at δ 2·26 and 1·64 to become an AB system, thus confirming the above structural assignment.

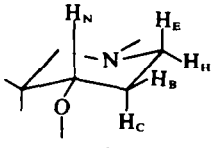
Further reduction of **3** transforms the carbomethoxy group into a primary alcoholic function: the diol formed (**4a**), $C_{21}H_{28}N_2O_4$, $M^+ = 372$, shows in fact no carbonyl absorbance in the IR spectrum. Acetylation of **4a** affords a diacetate (**4b**), $C_{25}H_{32}N_2O_6$, $M^+ = 456$, the ^{1}H-NMR spectrum of which (benzene – d_6, 100 MHz) contains two —OCOMe groups at δ 1·43 and 1·72, a complex multiplet at δ 5·35 for a —CHOAc proton and a separate signal for only one proton of a —CH_2OAc grouping at δ 3·98 as a double doublet ($J_1 = 11$, $J_2 = 4$ Hz).

The chemical and spectroscopic evidence for the presence in cuanzine of grouping **2** allows to deduce that the new base possesses a vincamine-like structure, the remaining O atom of cuanzine having to be engaged in the formation of an ethereal linkage between the C atom at C-18 and one of the C atoms of the D-ring of the vincamine skeleton (**5**). In fact, the ^{1}H-NMR spectrum of cuanzine (300 MHz, Fig 1) shows the lack of any signal attributable to an aliphatic methyl group and the presence of a clear AB system for the two geminal protons at C-17 (H_I and H_D) at δ 2·82 and 1·93 (J 15 Hz), this latter signal being slightly broadened due to a long range coupling effect.* Furthermore, the double doublet at δ 4·72 (H_N, J_1 10, J_2 7 Hz), may just be assigned to an oxymethynic proton.

Extensive double resonance experiments at 100 MHz allow to deduce that this signal is coupled with the 10-lines pattern centered at δ 1·55 (H_B) and with the the 12-lines pattern centered at δ 1·72 (H_C). Although in the 100 MHz spectrum the two aforementioned signals appear rather deformed and partially superimposed, it is clearly visible that the irradiation at δ 4·72 causes the signal of H_B to become a doublet of triplet ($J_1 = 13$, $J_2 = 3·5$ Hz), whereas the one of H_C changes into a ddd pattern (J_1 13, J_2 12, J_3 5 Hz).

*We retain for cuanzine the same numbering system used for vincamine.

The residue multiplicity of the signals at δ 1·55 and 1·72 suggests that the protons H_B and H_C are adjacent to two further methylene protons (H_E and H_H). In fact, irradiation on sweeping the zone between δ 1·50–1·75 causes, in addition to the decoupling of the signal at δ 4·72, a remarkable simplification of the complex signals at δ 2·10–2·40 and δ 2·65–2·80, indicating that H_E and H_H resonate in these areas, respectively. These results, the value of the chemical shifts and of the coupling constants indicate that the protons H_N, H_B and H_C, H_E and H_H are linked respectively to the C atoms at the C-15, C-14 and C-3 positions and possess the relative orientation depicted in partial formula **6**.



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Further analysis of the ^{1}H-NMR spectrum shows a complex signal centered at δ 3·80 due to the oxymethylene protons H_K and H_L at C-18. The irradiation of this multiplet collapses the 8-lines system at δ 1·13 due to H_A into a doublet (J 11·5 Hz), while the zone between δ 2·65–2·80, in which H_G resonates, is remarkably simplified. The irradiation of the latter zone, in which H_H also resonates, causes, beside the simplification of the multiplet centered at δ 3·80 (H_K and H_L), and the decoupling of the H_C and H_B signals, the disappearance of two long-range coupling effects. The doublet slightly broadened for H_D at δ 1·93 becomes a sharp doublet, while the large singlet at δ 4·05 ($W_{1/2}$ *ca* 3·5 Hz) due to the proton H_M becomes narrower ($W_{1/2}$ *ca* 2 Hz). A simplification of this latter signal occurs also by irradiation of the H_J protons at C-5 resonating at δ 3·10–3·00.

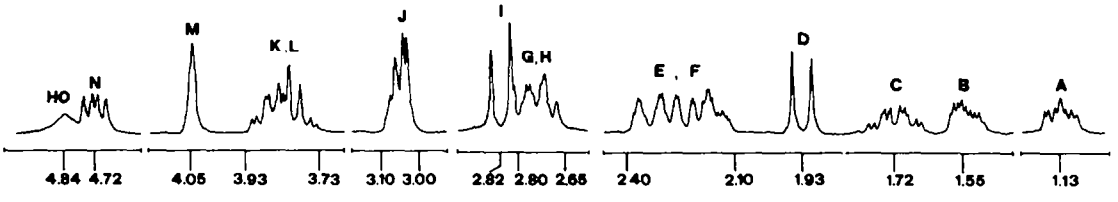
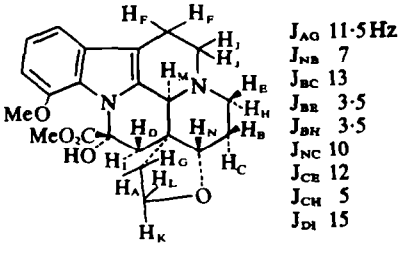


Fig 1.



The two remaining protons to be considered (H_F) give rise to a complex signal in the same zone where proton H_E resonates (δ 2·40–2·10). In order to confirm the above structural assignments and to determine the exact position of the methoxy group on the indole moiety, a study of the ^{13}C-NMR spectrum of cuanzine was performed in comparison with those of vincamine (5) and 16-epivincamine (7). ^{1}H-decoupled and wide-band off resonance decoupled spectra were recorded on a FT spectrometer operating at 25·2 MHz for cuanzine and vincamine, and at 22·3 MHz for 16-epivincamine.

Analysis of the chemical shifts allows to deduce the assignments summarized in Table 1. The chemical shifts of the aromatic carbon atoms of vincamine and epivincamine are in agreement with those reported in literature for other indole alkaloids.[2] The determination of the specific location of the methoxy group results from the application of the methoxy substituent parameters[3] (α, +31·4; *o*, −14·4; *m*, +1·0; *p*, −7·7 ppm) to the aromatic chemical shifts of **5** and **7**. The calculation leads to the assignment of the methoxy group of cuanzine at the C-12 position.

Table 1. The spectra were taken in $CDCl_3$. All shifts are in ppm downfield from TMS.

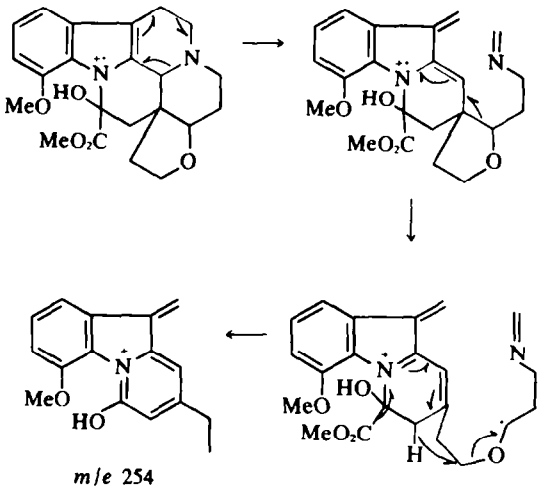
Carbon	5	7	1
2	131·4	131·7	131·7
3	44·5	44·6	42·5
5	50·9	50·9	50·9
6	16·9	16·6	17·4
7	103·9	106·1	103·2
8	128·9	128·6	130·7
9	118·4	118·1	111·9
10	121·5	121·4	120·8
11	120·1	120·2	106·0
12	110·2	112·4	145·6
13	134·1	135·6	123·8
14	20·8	20·7	27·8
15	25·2	24·2	74·4
16	81·9	82·9	83·6
17	44·3	47·0	42·5
18	7·6	7·5	63·8
19	28·8	28·9	34·4
20	35·1	36·3	43·3
21	59·1	58·7	56·5
C=O	174·3	172·4	173·0
OMe	54·1	53·2	54·9
Ar—OMe	—	—	53·1

The high-field region of the ^{13}C-NMR spectrum of cuanzine reveals the absence of any methyl group, the presence of an oxymethyne and an oxymethylene C atom, and a modification of nearly all the chemical shifts, in particular those of C atoms belonging to ring D. The localization at C-15 of the substituting oxygen is indicated by the characteristic downfield shifts (*ca* 7 ppm) of the C atoms C-14 and C-20, and the upfield shifts (*ca* 2 ppm) of the C atoms C-3 and C-21, which are dislocated respectively in position α and β to the ethereal function.

The chemical shifts of the C atoms C-16, C-5 and C-6 are in practise unaffected, while the carbon C-17 suffers both the presence of the ethereal oxygen in β and the steric tension due to the presence of the tetrahydrofurane ring.

The mass spectrum of cuanzine (Fig 2) is also compatible with structure **1** for this alkaloid.

The most abundant fragment ions, in addition to the mentioned M—H_2O and M—CO_2Me, correspond to the loss of 87 (M—CO_2Me—CO) and 102 (M—$CH_2C(OH)CO_2Me$) mass units, on the analogy with the behaviour of vincamine.[4] In comparison with the fragmentation pattern exhibited by vincamine, the fragments derived from the elimination of the ethyl group at C-20 are obviously missing. However, cuanzine shows the presence of an intense ion at *m/e* 254, which is formed presumably through the mechanism illustrated in Scheme 1.



SCHEME 1

The most noteworthy peaks in the spectra of the derivatives **3**, **4a** and **4b** occur at *m/e* 311 ($C_{19}H_{23}N_2O_2$), 227 ($C_{14}H_{15}N_2O$), 215 ($C_{13}H_{15}N_2O$), 214 ($C_{13}H_{14}N_2O$), 200 ($C_{12}H_{12}N_2O$), 199 ($C_{12}H_{11}N_2O$), 186 ($C_{12}H_{12}N_2O$). The production of these ions may be conveniently visualized (Scheme 2) as being triggered by homolysis of the allylically labilized C_{21}—C_{20} bond to give the intermediate ion **8**. Further cleavage of the C_{16}—C_{17} linkage leads to the peak at *m/e* 311 (path *a*), while expulsion of an additional H atom and of the portion of molecule including the tetrahydrofurane ring offers a route to the ion at *m/e* 227 (path *b*). From the same intermediate **8** ions at *m/e* 215, 214, 200, 199 and 186 are produced through obvious decompositions.

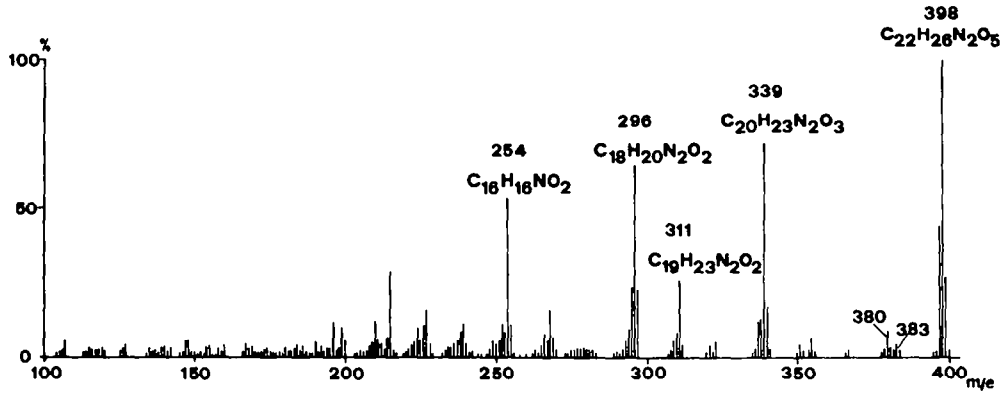
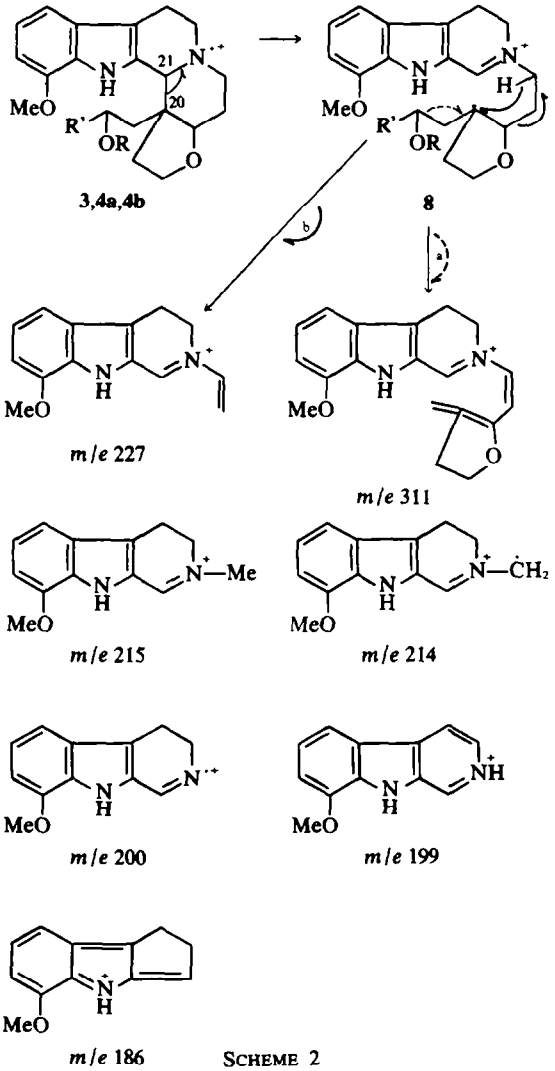


Fig 2.



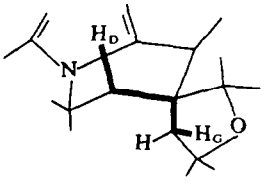
SCHEME 2

As far as the relative stereochemistry of cuanzine, the *cis*-relationship between the C_{21}-H linkage and the lone pair of the nitrogen N_b results from the absence of Bohlmann bands in the IR spectrum and from the already mentioned long-range W coupling between H_M and H_H and between H_M and one of the protons H_J at C-5. Molecular models show in fact that this long-range couplings are possible only for such a stereochemical disposition.

Chromate oxidation of **1** and H_2-Pd reduction inverts the configuration at C-21[5] affording 21-epicuanzine (**9**), which shows strong Bohlmann bands at 2800-2740 cm^{-1} in the IR spectrum and the upfield shift of the C-21 proton at δ 2·95 (100 MHz, benzene-d_6), as a trans quinolizidine system requires.[6]

As concerns the D/E ring fusion, it is in our opinion to attribute to the oxygen substituted ethyl chain at C-20 the same orientation of C_{21}-H (that is cis D/E ring fusion) as, being fixed the equatorial orientation of the C_{15}-O linkage, an opposite configuration at C-20 would induce a higher steric tension. On the other hand we must point out the presence in *V. chalotiana* of beninine (**10**), the skeleton of which must be biogenetically related to that of cuanzine.

As far as the relative configuration at C-16 is concerned, it has to be noticed that ring E of cuanzine should possess the half-chair conformation depicted in partial formula **11**, as suggested by the mentioned broadening of the signal at δ 1·93 (H_D) due to the long-range W coupling effect with



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the H_G proton. Acid treatment of cuanzine quickly eliminates a molecule of water to give apocuanzine (**12**), $C_{22}H_{24}N_2O_{41}$, $M^+ = 380$, unsaturated ester IR absorption at 1730 cm^{-1}, UV maxima (MeOH) at 225, 264 and 322 nm (lg ϵ 4·38, 3·86 and 3·91 respectively). The ^{1}H-NMR spectrum of **12** (100 MHz, benzene-d_6) is characterised by a singlet at δ 6·00 due to the olefinic proton at C-17 and by the strong upfield shift at δ 3·54 of the C-15 proton, which now experiences the shielding zone of the double bond. The easy of dehydration can be readily rationalized if the hydroxyl group at C-16 is placed in an axial position, which means that the stereochemistry at C-16 must be the same of 16-epivincamine.

Evidence for the correctness of these relative stereochemical assignments comes from the comparison of the CD curves of vincamine, 16-epivincamine and cuanzine.*

The shape of the curves in EtOH is the same in the 260–300 nm region (positive Cotton effects); in addition, cuanzine, like 16-epivincamine, shows a strong positive Cotton effect between 230–250 nm, opposite in sign to the one exhibited in this region by vincamine. This also establishes for cuanzine the absolute configuration represented in structure **1**.

EXPERIMENTAL

M.ps are corrected. Proton NMR spectra were determined on Varian XL-100 and HR 300 spectrometers. Carbon-13 NMR spectra were recorded at 25·2 MHz on a Varian XL-100 and at 22·3 MHz on a Bruker WH 90, both the instruments being equipped with Fourier transform. Low-resolution mass spectra were determined on a Varian CH-7 spectrometer; high-resolution mass measurements were obtained on a Varian MAT 311 instrument.

Cuanzine (**1**). The new alkaloid, isolated as described,[1] showed the following properties: m.p. 196° (from benzene), $[\alpha]_D^{22} - 11°$ (*c* 1, $CHCl_3$), $[\alpha]_D^{22} + 30°$ (*c* 2, pyr); λ_{max}^{MeOH} 226, 270, 292 nm (lg ϵ 4·65, 3·98, 3·75), λ_{min}^{MeOH} 246, 290 nm (lg ϵ 3·61, 3·74), inflexion at 282 nm (lg ϵ 3·87); $\nu_{max}^{CDCl_3}$ 3530, 1746, 1620, 1575 cm^{-1}; ^{1}H-NMR spectrum, Fig 1; mass spectrum, Fig 2; ^{13}C-NMR, Tab. 1. (Found: C, 66·29; H, 6·60; N, 6·99 – $C_{22}H_{26}N_2O_5$ requires: C, 66·32; H, 6·58; N, 7·03).

Sodium borohydride reduction of cuanzine

(a) A soln of cuanzine (80 mg) in anhyd THF (10 ml) was treated at room temp with $NaBH_4$ (50 mg) for 40 min. The solid material was filtered off, the mother liquors evaporated to dryness under reduced pressure and the residue, after addition of 10 ml of water, extracted with AcOEt-benzene 4:1. The organic phase was dried and evaporated to give 75 mg of a solid material which was chromatographed on silica gel (15 g) eluting with $CHCl_3$. 39 mg of **3** were collected, amorphous, λ_{max}^{MeOH} 221,269,281sh, 290 nm (lg ϵ 4·57, 3·92, 3·84, 3·81); γ_{max}^{Nujol} 3600-3180 (broad) 1738, 1628, 1575 cm^{-1}; ^{1}H-NMR (100 MHz, C_6D_6): 8·04 (1H, bs, NH), 7·22 (1H, dd, J_1 7, J_2 2 Hz, C_9–H), 7·09 (1H, t, *J* 7 Hz, C_{10}–H), 6·52 (1H, dd, J_1 7, J_2 2 Hz, C_{11}–H), 4·24 (1H, dd, J_1 10, J_2 3 Hz, C_{16}–H), 3·85-3·60 (3H, m, C_{15}–H and C_{18}-methylene), 3·52 (3H, s, —OMe), 3·36 (1H, bs, C_{21}–H), 3·00 (3H, s, —CO_2Me), 2·26 (1H, dd, J_1 15, J_2 3 Hz, C_{17}–H), 1·64 (1H, dd, J_1 15, J_2 10 Hz, C_{17}–H); MS: 400·1994 ($C_{22}H_{28}N_2O_5$, 27%), 399·1914 ($C_{22}H_{27}N_2O_5$, 13), 311·1752 ($C_{19}H_{23}N_2O_2$, 100), 227·1183 ($C_{14}H_{15}N_2O$, 17), 215·1179 ($C_{13}H_{15}N_2O$, 47), 214·1108 ($C_{13}H_{14}N_2O$, 18), 200·0946 ($C_{12}H_{12}N_2O$, 17), 199·0868 ($C_{12}H_{11}N_2O$, 17), 186·0918 ($C_{12}H_{12}NO$, 27). It yielded a hydrobromide, m.p. 270° (from Me_2CO). (Found: C, 54·82; H, 6·09; N, 5·78; Br, 16·59—$C_{22}H_{29}N_2O_5Br$ requires: C, 54·89; H, 6·03; N, 5·82; Br, 16·63).

(b) $NaBH_4$ (110 mg) was added in five portions over a period of 12 h to a soln of cuanzine (160 mg) in THF (10 ml). After evaporation to dryness and addition of water, three extraction with AcOEt-benzene 4:1 were carried out. The organic layer was evaporated and the residue chromatographed with $CHCl_3$ (silica gel, 30 g) to give 51 mg of pure **4a**, amorphous, λ_{max}^{MeOH} 222,269,280sh, 290 nm (lg ϵ 4·54,3·89,3·83,3·78); $\nu_{max}^{CHCl_3}$ 3580,3490,1628, 1575 cm^{-1}; MS: 372 (M^+, 73%), 371 (59), 341 (28), 311 (45), 227 (69), 215 (100), 214 (60), 200 (59), 199 (38), 186 (38). Its hydrochloride melts at 251–252° (from MeOH). (Found: C, 61·64; H, 7·18; N, 6·79; Cl, 8·63—$C_{21}H_{29}N_2O_4Cl$ requires: C, 61·69; H, 7·10; N, 6·85; Cl, 8·70.) Acetylation of **4a** under standard conditions (Ac_2O, pyr) yielded **4b**, amorphous, λ_{max}^{MeOH} 228,268,280sh, 289 nm (lg ϵ 4·31,3·97,3·80,3·58); $\nu_{max}^{CHCl_3}$ 3500,1740,1628,1578; NMR (100 MHz, C_6D_6): 7·84 (1H, bs, NH), 7·21 (1H, dd, J_1 7, J_2 2 Hz, C_9–H), 7·07 (1H, t, *J* 7 Hz, C_{10}–H), 6·50 (1H, dd, J_1 7, J_2 2 Hz, C_{11}–H), 5·35 (1H, m, C_{16}–H), 3·98 (1H, dd, J_1 11, J_2 4 Hz, CHOAc), 3·51 (3H, s, —OMe), 1·72 (3H, s, —OCOMe), 1·43 (3H, s, —OCOMe); MS: 456 (M^+, 69%), 455 (60), 311 (49), 227 (80), 215 (100), 214 (51), 200 (49), 199 (29), 186 (26).

21-Epicuanzine (**9**). **1** (100 mg), dissolved into 5 ml of glacial AcOH, was treated overnight with a soln containing 250 mg of $K_2Cr_2O_7$ in 10 ml of 50% aq acetic acid. Dilution with saturated $KClO_4$ aq gave a ppt which was filtered off, suspended in MeOH (15 ml) and hydrogenated at atmospheric pressure using 30 mg of Pd-C. The mixture was filtered, evaporated and the residue chromatographed (15 g of silica gel, $CHCl_3$–MeOH 99:1) to yield 38 mg of pure **9**, amorphous, λ_{max}^{MeOH} 226,270,281sh, 292 nm (lg ϵ 4·61, 3·97, 3·86, 3·75); ν_{max}^{KBr} 3480, 2795, 2740, 1750, 1622, 1610, 1572 cm^{-1}; NMR (100 MHz, C_6D_6): 7·17 (1H, dd, J_1 7, J_2 2 Hz, C_9–H), 7·02 (1H, t, *J* 7 Hz, C_{10}–H), 6·40 (1H, dd, J_1 7, J_2 2 Hz, C_{11}–H), 5·30 (1H, bs, –OH), 4·2–3·8 (2H, m, C_{18}-methylene), 3·55 (1H, dd, J_1 8, J_2 6 Hz, C_{15}–H), 3·30 (3H, s, –OMe), 3·28 (3H, s, –OMe), 2·95 (1H, bs, C_{21}–H), 2·83 (1H, d, *J* 15 Hz, C_{17}–αH), 2·43 (1H, bd, *J* 15 Hz, C_{17}–β H); MS: 398 (M^+, 100%), 383 (10), 380 (13), 339 (78), 311 (14), 296 (86), 268 (39). Its hydrochloride crystallizes from MeOH, m.p. 114°. (Found: C, 59·67; H, 6·29; N, 6·39; Cl, 8·09–$C_{22}H_{27}N_2O_5Cl$ requires: C, 60·76; H, 6·21; N, 6·44; Cl, 8·17).

Apocuanzine (**12**). 100 mg of **1** were treated for 1 h at 50° with 20 ml of MeOH saturated with gaseous HCl. Neutralization with dil NaOH and extraction with AcOEt yielded 74 mg of **12**, m.p. 230° (from isopropyl ether), λ_{max}^{MeOH} 225, 264, 322 nm (lg ϵ 4·38, 3·86, 3·91); ν_{max}^{KBr} 1730, 1630, 1610, 1572 cm^{-1}; NMR (100 MHz, C_6D_6): 7·19 (1H, dd, J_1 7, J_2 2dd, J_1 7, J_2 2, C_{11}–H), 6·00 (1H, s, C_{17}–H), 3·99 (1H, bs, C_{21}–H), 3·9-3·7 (2H, m, C_{18}–methylene), 3·54 (1H, C_{15}–H), 3·52 (3H, s, –OMe), 3·42 (3H, s, –OMe). (Found: C, 69·41; H, 6·39; N, 7·31–$C_{22}H_{24}N_2O_4$ requires: C, 69·46; H, 6·36; N, 7·36).

*A full discussion of the CD curves of the vincamine alkaloid group will be published elsewhere.

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