Zoanthamide (3): mp 278–280 °C; $[\alpha]_D$ +133° (*c* 0.83, $CHCl_3$); IR ($CHCl_3$) 1770, 1715, 1670, 1660, 1640 cm^{-1}; UV (CH_3CN) 235 nm (ε 23 900); ^1H NMR ($CDCl_3$) see Table I; ^{13}C NMR ($CDCl_3$) see Table II; HRMS, obsd *m/z* 523.2549, $C_{30}H_{37}NO_7$ requires 523.2570.

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Synthesis of Vinca Alkaloids and Related Compounds. 21.[1] Preparation of (±)-Eburnamonine, (±)-3-Epieburnamonine, and (±)-*C*-Norquebrachamine from a Common Intermediate

György Kalaus,† Numan Malkieh,† Ildikó Katona,† Mária Kajtár-Peredy,‡ Tibor Koritsánszky,‡ Alajos Kálmán, Lajos Szabó,† and Csaba Szántay*†

Department of Organic Chemistry, Technical University, Budapest Gellért tér 4, H-1521, Budapest, Hungary, and Central Research Institute for Chemistry, Hungarian Academy of Sciences, Budapest, Pusztaszeri út 59-67, H-1525, Budapest, Hungary

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The pentacyclic indole derivatives (±)-eburnamonine (**8b**) and (±)-3-epieburnamonine (**17b**) and the tetracyclic (±)-*C*-norquebrachamine (**10**) have been synthesized from the easily available common intermediate **2a**. In the course of the syntheses some unexpected transformations were observed. Structure elucidations of new products were performed partly by X-ray analysis.

In the synthesis of therapeutically important Vinca alkaloids, the enamine **1**,[2] serving as key intermediate, was made to react with paraformaldehyde.[3] If the reaction is effected in the melt, a product of structure **3** was isolated in addition to the hydroxymethyl derivative **2a** (Scheme I). The latter, which contains the C1 ethyl and the C12 hydrogen in the trans relationship, is formed with high stereoselectivity. At the boiling point of dichloromethane, pure **2a** is obtained in high yield.

Derivatives with the eburnane skeleton[4] can be prepared through the aldehyde obtained by oxidation of **2a**. In the present work, however, another approach was realized.

The natural compounds are mostly derived from the 1-ethyl, 12b-H cis epimers; therefore, the possibility that compounds of type **2** might be epimerized to the cis isomers was investigated. **2a** was converted with phosphoryl chloride to the chloride **2e**, which was oxidized in glacial acetic acid with $Na_2Cr_2O_7$.[5] The resulting iminium salt **4e** was reduced catalytically (H_2/Pd/C) or with $NaBH_4$. In the first case the **2e**:**5e** ratio was 1.6:1 and in the second 5:1. Thus, when the reducing agent is hydride ion, the trans epimer strongly predominates in the reaction mixture.

Because it was assumed on the basis of our earlier experiences[2b] that an increase in the bulk of the C1 substituent would favor the formation of the cis epimer, the acetyl **2b** and benzoyl **2c** derivatives were oxidized to the iminium salts **4b,c**. In fact, reduction of the latter compounds gave a higher proportion of the cis epimers **5b,c** than saturation of **4e**. As **2b,c** are hydrolyzed considerably more easily in alkaline medium than **5b,c**, separation of the two isomers becomes facile.

The results are summarized in Table I. Further hydrolysis of the esters **5b,c** yields the alcohol **5a**, and from this the derivative **5d** could be obtained by mesylation.

As we have previously shown,[6] the (−)-nitrile **5f** can be converted into (−)-eburnamonine in very good yield. Consequently the preparation of the nitrile from **5e** by a simple displacement reaction was attempted (Me_2SO at 100 °C, sodium cyanide for 1 h). However, the expected

Scheme I

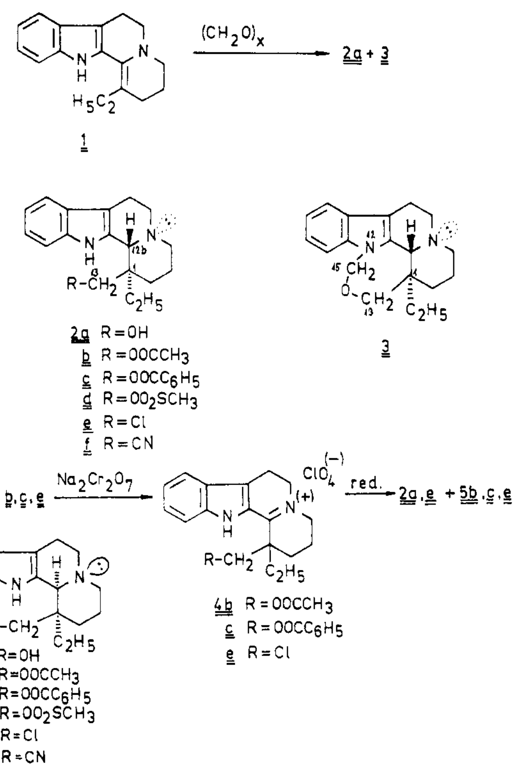


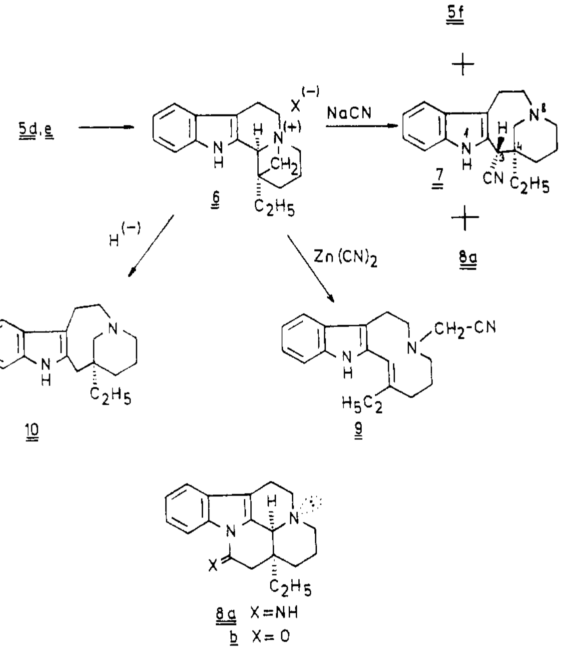
Table I. Reduction of Esters 4b and 4c

starting material	reacn conditions	product ratio[a] 2a, %	5b or 5c, %
4b	$NaBH_4$ (ethanol), 0 °C	44.8	53.4
	Pd/C/H_2, room temp	32.4	38.3
4c	$NaBH_4$ (ethanol), 0 °C	13.8	65.2
	Pd/C/H_2, room temp	16.6[b]	33.8

[a] After selective hydrolysis. [b] Unchanged starting material was also contained in the reaction mixture.

† Technical University.
‡ Hungarian Academy of Sciences.

Scheme II



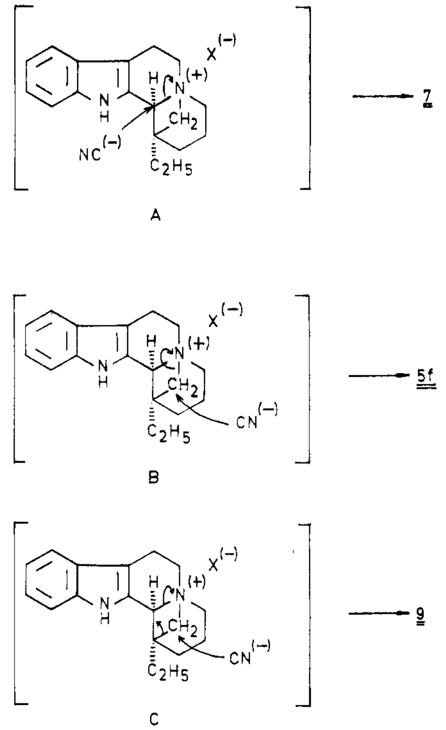
5f could be isolated only in 12.4% yield, a nitrile **7** being formed as the main product (41.4%) (Scheme II). The structure of **7**, was unequivocally proved by X-ray analysis (see later).

The nitrile **7** is presumably formed through the quaternary salt (X = Cl). This presumed intermediate was conveniently prepared from the mesylate **5d** and converted to the salt **6** (X = CH_3SO_3), which on reaction with sodium cyanide in Me_2SO gave **7** as the main product (44.5%) besides the nitrile **5f** (7.4%) and the imino derivative **8a** (10.4%).

From **5f** its tautomer (**8a**) was also prepared in alkaline methanol, which can be converted into (±)-eburnamonine (**8b**)[7] with aqueous hydrochloric acid.

If the displacement reaction was carried out in methanol instead of Me_2SO, a very small quantity of a substance **9**, containing a ten-membered ring, could also be isolated in

Scheme III



addition to the products mentioned above (**5f**, 1.1%; **7**, 72.4%; **8a**, 10.4%).

The constitution of **9** followed from its NMR spectra. ^{1}H and ^{13}C NMR data attested to the presence of an unchanged indole moiety. The ^{13}C resonance at 115.75 ppm is readily assignable to the nitrile group. Partial structure CH=C(Et) within the ten-membered ring was evidenced by the ^{1}H signal at 6.25 ppm, which exhibited only allylic couplings, by the ethyl group resonances, and by the olefinic carbon signals. All remaining ^{13}C signals were attributable to methylene carbons, three of which are adjacent to a nitrogen atom. The occurrence of a two-proton singlet at 3.33 ppm and a carbon signal at 43.33 ppm, giving rise to a "sharp" triplet in the off-resonance decoupled spectrum, suggested the presence of an "isolated" methylene group. Its carbon chemical shift value is in accordance with the NCH_2CN fragment.

Use of zinc cyanide instead of sodium cyanide gave compound **9** as the sole product (71.6%).

A possible explanation of the different behavior of sodium cyanide and zinc cyanide is the following. Sodium cyanide forms an ion pair, the small anionic part of which readily attacks the most strongly electrophilic site of the molecule, namely, C12b (Scheme III, process A) and, to a lesser extent, the bridge carbon atom (process B). On the other hand, owing to steric reasons, for zinc cyanide, which has considerably more covalent character, only the second strongest electrophilic site, the carbon atom of the bridge methylene, is accessible; thus this is the site of attack. However, it is not quite clear, why process C predominates over process B when zinc cyanide is used.

On reduction of the quaternary salt **6** with hydride ion ($NaBH_4$/ethanol or Na/NH_3), *C*-norquebrachamine (**10**) was formed exclusively. The trans epimer **2e** of **5e** reacted quite differently with sodium cyanide in Me_2SO. The reaction was considerably slower, heating at 100 °C for about 4 days being needed for disappearance of the starting material, and even then a well-defined derivative could be isolated only in poor yield (24.9%).

Structure **13b** was inferred from NMR spectral observations. While the chemical shift values of the aromatic

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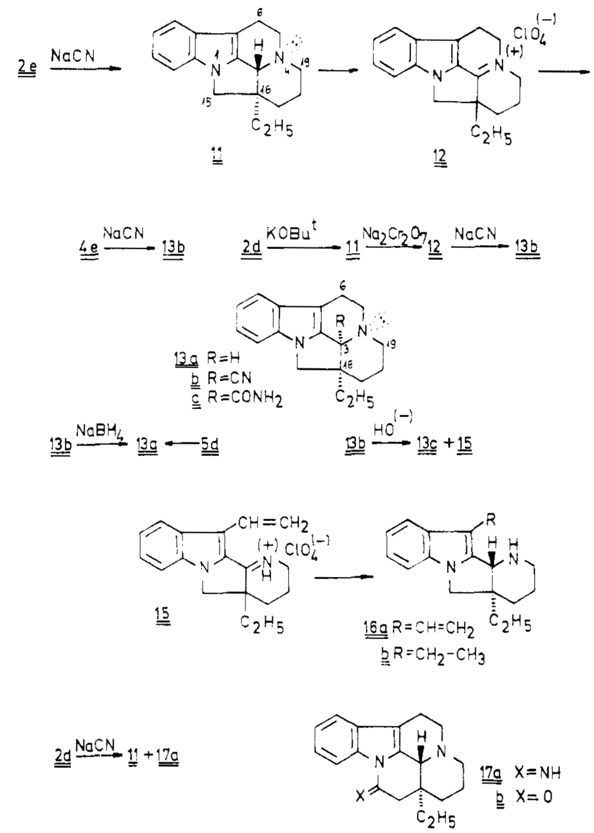
Scheme IV



carbon resonances indicated that the product contained an unchanged indole moiety, the indole NH signal was missing from its ^1H NMR spectrum. This observation combined with ^1H and ^{13}C NMR evidence for an "isolated" methylene group (3.66 and 4.00 ppm, J_{gem} = 11 Hz, in the proton spectrum and the signal at 56.64 ppm in the carbon spectrum) was indicative of an intramolecular ring closure involving C16 of the side chain and the indole nitrogen atom. ^{13}C NMR disclosed the presence of a nitrile group in the product. The position of this substituent followed from the replacement of the C3 methine signal of **2e** by a quaternary carbon resonance (61.47 ppm) in the spectrum of **13b**. The chemical shift values of the C- and D-ring methylene carbon atoms and, in particular, those of C19 and C6 (45.90 and 16.58 ppm, respectively) are characteristic of a cis–cis C/D/E ring junction[8] which defines the steric arrangement of the substituent groups at C16 and C3.

The probable way of formation of the substance is that either before or after ring closure at the indole nitrogen intermediate 11 is oxidized during the long time of heating in Me_2SO to iminium compound **12** which is converted by attack of cyanide ion into the pseudocyanide **13b** (Scheme IV).

To investigate the two possibilities, first the immonium perchlorate **4e** was treated in Me_2SO at 100 °C with excess sodium cyanide. After 2 h **13b** was isolated in 34.5% yield. Second, the mesylate **2d** was converted with KO-*t*-Bu/Me_2SO to noreburnane 11. Oxidation of the latter gave the iminium salt **12**, which rapidly reacted even at room temperature with sodium cyanide to give after 90 min the expected product **13b** in 72% yield.

We conclude that when the reaction is performed in a single operation, ring closure is the primary process followed by oxidation but that the alternative reaction sequence proceeds simultaneously cannot be excluded.

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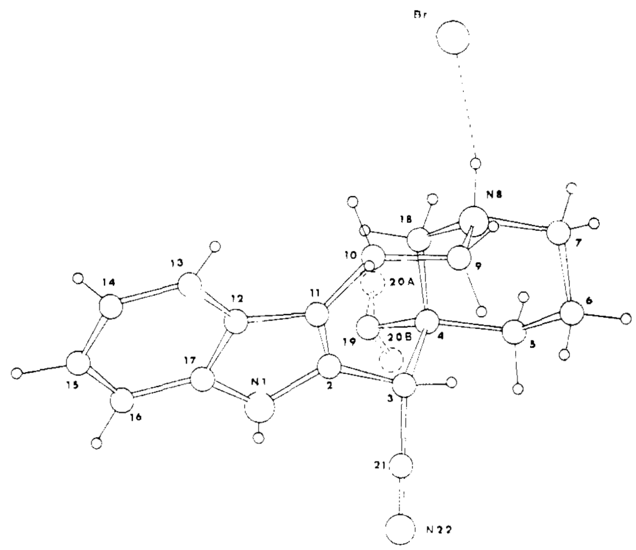

Figure 1. Perspective view of the molecular structure of **7** showing atomic numbering. The bare numbers are for carbon atoms unless indicated otherwise. The H atoms except those belonging to the conformationally disordered 4-ethyl moiety are shown but not labeled. The hydrogen bond formed between Br^- and the protonated N8 atom is also shown. The disordered C20 carbon atoms are given with dotted lines.

The pseudocyanide **13b** was converted by $NaBH_4$, with retention of the stereochemistry at C3, into *E*-noreburnane **13a**. It should be mentioned here that the cis isomer mesyloxy derivative **5d** similarly gave **13a** on treatment with base (KO-*t*-Bu/Me_2SO).

Refluxing of pseudocyanide **13b** with alcoholic alkali gave partly **13c** and partly the seco derivative **15**, formed by an elimination reaction, as the isolable products, the latter in the form of its perchlorate.

Compound **15** can be reduced stepwise, with $NaBH_4$ to the vinyl derivative **16a**, and then the carbon–carbon double bond of the latter can be catalytically saturated to obtain **16b**.

When mesylate **2d** was reacted in methanol with sodium cyanide, the imino compound **17a** was isolated (50.7%), in addition to a small amount (7.5%) of 11. Thus under the given conditions **2f**, presumably formed as an intermediate, very rapidly undergoes ring closure. Treatment of **17a** with aqueous hydrochloric acid yielded (±)-3-epieburnamonine (**17b**).[7]

Crystal Structure of 7. A perspective view of the molecular structure of **7** depicted in Figure 1 shows a distorted eight-membered heteroring fused to a coplanar aromatic indole moiety at the C2–C11 = 1.361 (3) Å) double bond and sharing three atoms—among other the protonated N8 atom—with a piperidine ring.

The positionally disordered C20 atom of the 4-ethyl moiety is represented by dotted lines without its disordered H atoms. Nor are the disordered H positions belonging to C(19) shown. The ethyl group is bound equatorially to the six-membered ring (C19–C4–C5–C6 = 171.1 (4)°). One of its disordered methyl group (C20b) is almost eclipsed (synperiplanar) with C5 (ω_1 = 17.0 (7)°) while the other (C20a) is antiperiplanar with C3 (ω_2 = −176.3 (7)°) across the C4–C19 bond. The nitrile group (C21–N22 = 1.140 (4) Å) bound to C3 also exhibits equatorial orientation (C21–C3–C4–C18 = 172.2 (4)°) relative to the eight-membered ring. The latter due to the great number of the substituted atoms (five out of eight) and the C2–C11 double bond exhibits a rather distorted shape which considerably differs from the canonical forms described by

Hendrickson.[9] It possesses only one mirror plane bisecting the C11 and C18 atoms [the lowest asymmetry parameter[10] ΔC_2(C11) = 4.7° and the corresponding asymmetry factor[11] fC_2(C11) = 4.9 × 10^{-2} Å]. The piperidine ring assumes almost perfect chair conformation to which C3 and C9 are linked axially.

The protonated N8 sitting in the center of the ternary ammonium base at the top of a distorted pyramid formed by three weakened N^+–C(sp^3) single bonds (mean bond length, 1.511 (3) Å) maintains a hydrogen bond with Br^- anion with the parameters given below. A somewhat weaker hydrogen bond is also formed with Br^- donated by the N1–H1 group of the indole moiety.

	N···Br, Å	H···Br, Å	∠NH···Br, deg
N1–H1···Br[x, y, z]	3.505	2.86	139.5
N8–H8···Br[1 − x, y − 1/2, 1/2 − z]	3.185	2.22	165.4

Experimental Section

General. All melting points are uncorrected. Thin-layer chromatography separations were carried out on silica gel (Kieselgel 60 $PF_{254+366}$) developed by C_6H_6–MeOH (10:1.4) eluted by CH_2Cl_2–MeOH (10:1). The organic layers were dried over $MgSO_4$.

1α-Ethyl-1β-(hydroxymethyl)-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine (2a) and 1α-Ethyl-1β,12-(methanoxymethano)-1,2,3,4,6,7,12,12bβ-octahydroindolo-[2,3-*a*]quinolizine (3). To a suspension of 1 perchlorate (90.0 g, 255.1 mmol) in CH_2Cl_2 (450 mL) and H_2O (750 mL) was added 2 M NaOH (180 mL). The mixture was stirred for 10 min, then (a) the organic layer was separated, dried, and evaporated to 100 mL, and then paraformaldehyde (18.0 g, 601.2 mmol) was added to it. The solvent was removed in vacuo, and the residue was heated at 160–170 °C for 4 h. The residual substance was crystallized from MeOH to afford **2a** [49.5 g, 68.2%, mp 233–235 °C (lit.[3] mp 235–236 °C)]. The mother liquor was concentrated and then separated by column chromatography [350 g of Kieselgel 60 (0.0063–0.02); eluent, C_6H_6–MeOH (100:1)]. The faster running fraction was evaporated and crystallized from EtOH to give **3** (5.9 g, 7.8%) as white crystals, mp 145–147 °C (EtOH). Anal. Calcd (found) for $C_{19}H_{24}N_2O$: C, 76.99 (76.87); H, 8.16 (8.42); N, 9.45 (9.67). IR (KBr) 2800–2710 cm^{-1} (Bohlmann); MS, *m/z* (relative intensity) 296 (100), 295 (72), 266 (39), 237 (17), 197 (9), 169 (12), 168 (10); ^1H NMR ($CDCl_3$) δ 0.72 (3 H, t, *J* = 7 Hz, CH_2CH_3), 3.30 (1 H, dd, J_{AB} = 13 Hz, 13-H_A), 3.31 (1 H, 12b-H), 4.00 (1 H, d, 13-H_B), 5.02 (1 H, d, J_{AB} = 11.3 Hz, 15-H_A), 5.87 (1 H, d, 15-H_B), 6.95–7.5 (4 H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 6.92 ($C1CH_2CH_3$), 19.23 ($C1CH_2CH_3$), 21.52 (C3), 22.01 (C7), 28.69 (C2), 41.50 (C1), 53.44 (C6), 56.33 (C4), 69.57 (C12b), 77.17 (C15), 80.38 (C13), 108.52 (C11), 111.68 (C7a), 117.99 (C8), 119.12 (C9), 121.32 (C10), 126.31 (C7b), 135.36 (C12a), 135.54 (C11a).

(b) The organanic layer was separated and dried, and paraformaldehyde (18.0 g, 601.2 mmol) was added to it. The reaction mixture was stirred at reflux for 3 h, then filtered, and evaporated to dryness in vacuo. The residue was crystallized from MeOH to yield **2a** (61.7 g, 85.1%).

Preparation of 2e. The alcohol **2a** (18.0 g, 63.3 mmol) was dissolved in $POCl_3$ (180 mL) and then stirred at reflux for 3.5 h under argon. The solvent was removed under reduced pressure, and the remaining oil was dissolved in MeOH (90 mL), treated with 40% NaOH to pH 10, and then extracted with CH_2Cl_2 (320 mL). The organic layer was dried and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (400 mL), mixed with Kieselgel 60 (0.0065–0.02) (90 g), and allowed to stand for 4 h. The filtrate was evaporated, and the residue was treated with *i*-PrOH to give **2e** (12.50 g, 65.2%), mp 111–113 °C. Anal. Calcd (found) for $C_{18}H_{23}ClN_2$: C, 71.38 (71.58); H, 7.65 (7.86); N, 9.25 (9.17). IR (KBr) 3480 cm^{-1} (indole NH); MS, *m/z* (relative intensity) 302 (12), 267 (100), 197 (5), 169 (7); ^1H NMR (py-d_5) δ 0.60 (3 H, t, *J* = 7.7 Hz, CH_2CH_3), 3.73 (1 H, t, 12b-H), 3.79 (1 H, d, *J* = 11.7 Hz, 13-H_A), 4.21 (1 H, d, 13-H_B), 9.59 (1 H, br, s, NH); ^{13}C NMR (py-d_5) δ 7.41 ($C1CH_2CH_3$), 22.21 (C7)*, 22.56 (C3)*, 24.50 ($C1CH_2CH_3$), 31.35 (C2), 41.74 (C1), 53.81 (C13), 54.36 (C6), 56.39 (C4), 65.49 (C12b), 111.74 (C11), 112.24 (C7a), 118.06 (C8), 119.44 (C9), 121.58 (C10), 127.79 (C7b), 133.36 (C12a), 137.78 (C11a) [* may be interchanged].

Oxidation of 2e. To a solution of **2e** (8.0 g, 26.4 mmol) in hot AcOH (60 mL) was added $Na_2Cr_2O_7 \cdot 2H_2O$ (5.60 g, 18.8 mmol) in AcOH (12 mL). The reaction mixture was allowed to stand at room temperature for 12 h and heated on a water bath for 3 h to complete the reaction. After the mixture was cooled, 70% $HClO_4$ (2.96%) was added to the warm solution, and the yellow crystals were collected by filtration and washed with water to afford **4e** (6.6 g, 62.3%), mp 227–229 °C (MeOH). Anal. Calcd (found) for $C_{18}H_{22}Cl_2N_2O_4$: C, 53.87 (53.90); H, 5.52 (5.46); N, 6.98 (6.76). IR (KBr) 3260 (indole NH), 1622 cm^{-1} (C=N^+).

Reduction of 4e. (a) The compound **4e** (1.00 g, 2.49 mmol) was dissolved in MeOH (100 mL) and cooled to 0 °C, and then $NaBH_4$ (1.00 g, 26.4 mmol) was added in small portions. The solution was stirred at 0 °C for 30 min and at room temperature for 1 h, then acidified with AcOH, and evaporated in vacuo. The residue was treated with water (120 mL), CH_2Cl_2 (100 mL), and 40% NaOH to pH 10. The organic layer was dried, evaporated, and fractionated by TLC to afford **5e** (0.05 g, 6.6%), mp 133–135 °C (*i*-PrOH) (lit.[14] mp 134–136 °C). Anal. Calcd (found) for $C_{18}H_{23}ClN_2$: C, 71.38 (71.17); H, 7.65 (7.47); N, 9.25 (8.78). IR (KBr) 3420 cm^{-1} (indole NH); MS, *m/z* (relative intensity) 304 (3.5), 303 (2.7), 302 (10), 268 (21), 267 (100), 266 (8), 265 (6), 170 (8), 169 (12), 168 (5), 156 (5); ^1H NMR (py-d_5) δ 1.02 (3 H, t, *J* = 7.5 Hz, CH_2CH_3), 2.02 (2 H, q, CH_2CH_3), 3.47 (1 H, dd, J_{gem} = 11.2 Hz, $J_{long\ range}$ = 0.9 Hz, 13-H_A), 3.54 (1 H, t, 12b-H), 4.36 (1 H, d, 13-H_B), 9.96 (1 H, br s, NH); ^{13}C NMR (py-d_5) δ 8.45 ($C1CH_2CH_3$), 22.31 (C3), 22.56 (C7), 30.15 ($C1CH_2CH_3$), 30.90 (C2), 41.44 (C1), 51.82 (C13), 54.16 (C6), 56.89 (C4), 65.98 (C12b), 111.93 (C11), 112.13 (C7a), 118.14 (C8), 119.39 (C9), 121.68 (C10), 127.59 (C7b), 132.66 (C12a), 137.8 (C11a). **2e** (0.24 g, 31.8%) was also obtained.

(b) A solution of **4e** (2.00 g, 5.0 mmol) in MeOH (170 mL) was hydrogenated over 10% Pd/C (2.0 g) at room temperature and in atmospheric pressure for 3 h and then the catalyst removed by filtration. The filtrate was evaporated under reduced pressure, treated with 40% NaOH to pH 10, and extracted with CH_2Cl_2 (100 mL). The organic layer was dried and evaporated, and the residual oil was separated by TLC to afford **5e** (0.28 g, 18.4%) and **2e** (0.44 g, 29.0%).

Acylation of 2a. (a) To a solution of **2a** (2.50 g, 8.79 mmol) in pyridine (15 mL) was added Ac_2O (15 mL). The reaction mixture was allowed to stand at room temperature for 3 days, and then the solvent was removed in vacuo. The remaining oil was treated with 5% $NaHCO_3$ to give **2b** (1.87 g, 65.0%) mp 107–109 °C (MeOH–H_2O). Anal. Calcd (found) for $C_{20}H_{26}N_2O_2$: C, 73.58 (73.53); H, 8.04 (8.09); N, 8.57 (8.87). IR (KBr) 3370 (indole NH), 1710 cm^{-1} (C=O); MS, *m/z* (relative intensity) 327 (5), 326 (24), 325 (9), 268 (21), 267 (100), 197 (5), 170 (7), 55 (6). ^1H NMR ($CDCl_3$) δ 0.69 (3 H, t, *J* = 7.5 Hz, CH_2CH_3), 2.18 (3 H, s, $COCH_3$), 3.45 (1 H, t, 12b-H), 4.06 (1 H, d, *J* = 12.2 Hz, 13-H_A), 4.74 (1 H, d, 13-H_B), 8.61 (1 H, br s, NH); ^{13}C NMR ($CDCl_3$) δ 7.34 ($C1CH_2CH_3$), 21.05 ($COCH_3$), 21.95 ($C1CH_2CH_3$)*, 22.04 (C3)*, 22.24 (C7)*, 30.97 (C2), 40.84 (C1), 53.93 (C6), 56.62 (C4), 65.58 (C12b), 70.07 (C13), 110.92 (C11), 112.18 (C7a), 117.82 (C8), 119.26 (C9), 121.41 (C10), 127.14 (C7b), 132.89 (C12a), 136.50 (C11a), 171.48 ($COCH_3$) [* may be interchanged].

(b) To a solution of **2a** (30.0 g, 105.5 mmol) in pyridine (180 mL) was added benzoyl chloride (18.0 mL 156.1 mmol). The reaction mixture was allowed to stand at room temperature for 1 h and then poured into 5% $NaHCO_3$ (350 mL). The precipitate was collected by filtration and washed with water and EtOH to afford **2c** (39.3 g, 95.9%) as a white powder, mp 156–157 °C. Anal. Calcd (found) for $C_{25}H_{28}N_2O_2$: C, 77.28 (77.17); H, 7.26 (7.04); N, 7.21 (7.42). IR (KBr) 3400 (indole NH), 1702 cm^{-1} (C=O); MS, *m/z* (relative intensity) 388 (18), 267 (100), 197 (11), 169 (27), 105 (62), 77 (59), 55 (18), 51 (21); ^1H NMR ($CDCl_3$) δ 0.74 (3 H,

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t, J = 7.4 Hz, CH_2CH_3), 1.26 (1 H, dq, J_{AB} = 14.8 Hz, $CH_AH_BCH_3$), 2.14 (1 H, dq, $CH_AH_BCH_3$), 3.55 (1 H, 12b-H), 4.32 (1 H, d, J_{AB} = 12 Hz, 13-H_A), 4.92 (1 H, d, 13-H_B), 6.95–7.7 (7 H, m, Ar), 8.10 (2 H, m, C2'H + C6'H), 8.71 (1 H, br s, NH); ^{13}C NMR ($CDCl_3$) δ 7.41 ($C1CH_2CH_3$), 21.96 (C3 + $C1CH_2CH_3$), 22.19 (C7), 31.09 (C2), 41.12 (C1), 53.87 (C6), 56.64 (C4), 65.96 (C12b), 70.50 (C13), 111.02 (C11), 112.11 (C7a), 117.78 (C8), 119.22 (C9), 121.38 (C10), 127.05 (C7b), 128.67 (C3' + C5'), 129.72 (C2' + C6'), 132.85 (C12a), 133.48 (C4'), 136.46 (C11a), 166.96 (PhCOO).

Oxidation of 2b. To a solution of **2b** (2.0 g, 6.12 mmol) in hot AcOH (18 mL) was added $Na_2Cr_2O_7 \cdot 2H_2O$ (0.90 g, 3.12 mmol) in AcOH (2.5 mL). The reaction mixture was allowed to stand at room temperature for 12 h and heated for an additional 4 h on a water bath to complete the reaction. The warm solution was treated with 70% $HClO_4$ (0.7 mL); during cooling and scraping yellow crystals precipitated, which were collected by suction and washed with water to afford **4b** (1.25 g, 48.1%), mp 198–200 °C. Anal. Calcd (found) for $C_{20}H_{25}ClN_2O_6$: C, 56.53 (56.62); H, 5.94 (5.74); N, 6.59 (6.55). IR (KBr) 3340 (indole NH), 1734 (C=O), 1618 cm^{-1} (C=N^+).

Oxidation of 2c. A solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (10.0 g, 33.6 mmol) in AcOH (20 mL) was added to a solution of **2c** (20.0 g, 51.5 mmol) in hot AcOH (100 mL). The reaction mixture was allowed to stand at room temperature for 1.5 h and then treated with 70% $HClO_4$ (8.0 mL). After cooling, the yellow crystals were collected by filtration and washed with water and EtOH to give **4c** (16.3 g, 65.0%), mp 209–212 °C (EtOH). Anal. Calcd (found) for $C_{25}H_{27}ClN_2O_6$: C, 61.65 (61.74); H, 5.58 (5.83); N, 5.75 (5.53). IR (KBr) 3380 (indole NH), 1715 (C=O), 1617 cm^{-1} (C=N^+).

Reduction of 4b. (a) To a solution of **4b** (1.00 g, 2.35 mmol) in EtOH (30 mL) was added $NaBH_4$ (0.45 g, 11.9 mmol) in small portions at 0 °C, and then the reaction mixture was stirred for 1 h. The temperature was raised to 45 °C, and the solution was stirred for an additional 25 min, then poured into water (70 mL), and extracted with CH_2Cl_2. The organic layer was dried and evaporated, and the residue was separated by TLC to afford **5b** (0.41 g, 53.4%), mp 100–101 °C (*n*-hexane). Anal. Calcd (found) for $C_{20}H_{26}N_2O_2$: C, 73.58 (73.39); H, 8.04 (8.00); N, 8.57 (8.21). IR (KBr) 3400 (indole NH), 1710 cm^{-1} (C=O); MS, *m/z* (relative intensity) 327 (7), 326 (30), 325 (12), 267 (100), 197 (5), 170 (6), 169 (7); ^1H NMR ($CDCl_3$) δ 1.14 (3 H, t, J = 7.5 Hz, CH_2CH_3), 1.60 (3 H, s, $COCH_3$), 1.9 (2 H, q, CH_2CH_3), 3.39 (1 H, t, 12b-H), 4.29 (2 H, s, 13-H_2), 7.81 (1 H, br s, NH); ^{13}C NMR ($CDCl_3$) δ 7.92 ($C1CH_2CH_3$), 20.38 ($COCH_3$), 21.92 (C7), 22.08 (C3), 29.37 ($C1CH_2CH_3$), 31.21 (C2), 40.70 (C1), 53.97 (C6), 56.79 (C4), 65.35 (C12b), 66.79 (C13), 110.54 (C11), 111.46 (C7a), 117.80 (C8), 119.18 (C9), 121.39 (C10), 126.82 (C7b), 132.91 (C12a), 136.14 (C11a), 170.81 ($COCH_3$). **2a** (0.30 g, 44.8%) was also obtained.

(b) A solution of **4b** (1.00 g, 2.36 mmol) in acetone (80 mL) was added to 10% Pd/C (1.0 g), which was previously prehydrogenated in acetone (10 mL). The mixture was hydrogenated at room temperature and at atmospheric pressure. The catalyst was removed by filtration, the filtrate was evaporated, and then the remaining oil was basified with saturated solution of Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was dried and evaporated, and the residual oil was partially hydrolyzed with NaOH (20 mg) in EtOH (20 mL) at 45 °C for 5 min. The solution was extracted with CH_2Cl_2, and the organic layer was dried, then evaporated, and separated by TLC to give **5b** (0.30 g, 38.8%) and **2a** (0.19 g, 32.4%).

Reduction of 4c. (a) A suspension of **4c** (1.00 g, 2.05 mmol) in EtOH (20 mL) was cooled to 0 °C, and then $NaBH_4$ (0.45 g, 11.9 mmol) was added in small portions. The reaction mixture was stirred at 0–5 °C for 20 min and at 50–55 °C for an additional 2 h, then poured into water (100 mL), and extracted with CH_2Cl_2. The organic layer was dried and evaporated, and the residue was fractionated by TLC, to afford **5c** (0.24 g, 12.4%), mp 147–149 °C (EtOH). Anal. Calcd (found) for $C_{25}H_{28}N_2O_2$: C, 77.28 (77.35); H, 7.26 (7.00); N, 7.21 (7.50). IR (KBr) 3470 (indole NH), 1705 cm^{-1} (C=O); MS, *m/z* (relative intensity) 388 (14), 267 (100), 197 (11), 169 (28), 105 (28), 77 (33), 55 (19), 51 (12). ^1H NMR ($CDCl_3$) δ 1.15 (3 H, t, J = 7.4 Hz, CH_2CH_3), 3.45 (1 H, 12b-H), 4.53 (1 H, d, J_{AB} = 11.2 Hz, 13-H_A), 4.64 (1 H, d, 13-H_B), 6.95–7.6 (9 H, m, Ar), 7.88 (1 H, br s, NH). **2a** (0.08 g, 13.8%) was also obtained.

(b) A solution of **4c** (1.00 g, 2.05 mmol) in acetone (75 mL) was added to 10% Pd/C (0.5 g), which was previously prehydrogenated in acetone (10 mL). The mixture was hydrogenated at room temperature and at atmospheric pressure (consumption, 42 mL of H_2, 0.85 equiv). The catalyst was removed by filtration, and the filtrate was evaporated and partially hydrolyzed with NaOH (40 mg) in EtOH (20 mL) at 45 °C for 5 min. The solution was poured into water and extracted with CH_2Cl_2. The organic layer was dried, evaporated, and separated by TLC to give **5c** (0.27 g, 33.8%) and **2a** (0.10 g, 16.6%).

1α-Ethyl-1β-(hydroxymethyl)-1,2,3,4,6,7,12,12α-octahydroindolo[2,3-*a*]quinolizine (5a).[4a] (a) To a solution of **5b** (0.25 g, 0.76 mmol) in MeOH (15 mL) was added $NaOCH_3$ (0.01 g, 0.19 mmol). The reaction mixture was refluxed for 1.5 h and then poured into water (25 mL). The precipitate was collected by suction and washed with water to afford **5a** (0.14 g, 65.0%) as white crystals, mp 227–228 °C (MeOH). Anal. Calcd (found) for $C_{18}H_{24}N_2O$: C, 76.01 (76.22); H, 8.50 (8.30); N, 9.85 (10.01). IR (KBr) 3300 cm^{-1} (indole NH); MS, *m/z* (relative intensity) 285 (17), 284 (77), 283 (100), 267 (56), 197 (42), 184 (10), 170 (49), 169 (43), 168 (10), 156 (13), 144 (11), 143 (13), 55 (9); ^1H NMR (py-d_5) δ 0.97 (3 H, t, J = 7.5 Hz, CH_2CH_3), 1.91 (2 H, q, CH_2CH_3), 3.59 (1 H, br s, 12b-H), 3.74 (1 H, d, J_{gem} = 10.8 Hz, 13-H_A), 4.02 (1 H, d, 13-H_B), 10.05 (1 H, br s, NH); ^{13}C NMR (py-d_5) δ 8.59 ($C1CH_2CH_3$), 22.31 (C7), 23.24 (C3), 29.91 ($C1CH_2CH_3$), 32.24 (C2), 41.09 (C1), 54.37 (C6), 56.39 (C4), 67.33 (C12b), 68.12 (C13), 111.24 (C7a), 111.84 (C11), 118.15 (C8), 119.29 (C9), 121.53 (C10), 127.68 (C7b), 133.76 (C12a), 137.77 (C11a).

(b) To a solution of **5c** (1.19 g, 3.06 mmol) in EtOH (10 mL) was added a solution of KOH (0.80 g, 14.3 mmol) in EtOH (10 mL). The reaction mixture was refluxed for 30 min and then diluted with water (50 mL). The precipitate was collected by filtration and washed with water to afford **5a** (0.80 g, 91.8%).

Mesylation of 5a. A solution of **5a** (2.00 g, 7.03 mmol) in pyridine (28 mL) was cooled to 0 °C; CH_3SO_2Cl (2.0 mL, 25.8 mmol) was added. The reaction mixture was stirred at 0–5 °C for 2 h, and then the solvent was distilled in vacuo (0.5 mbar). The residue was treated with ice–water (30 mL) and concentrated NH_4OH (3 mL). The solid was collected by filtration and washed with water to afford **5d** (2.48 g, 97.3%), mp 180 °C dec. IR (KBr) 3450 (indole NH), 1345, 1170 cm^{-1} (SO_2); MS, *m/z* (relative intensity) 362 (7), 267 (100), 197 (10), 169 (14); ^1H NMR ($CDCl_3$) δ 1.18 (3 H, t, J = 7.5 Hz, CH_2CH_3), 1.95 (2 H, q, CH_2CH_3), 2.59 (3 H, s, CH_3SO_2O), 3.43 (1 H, 12b-H), 4.20 (1 H, d, J_{AB} = 10 Hz, 13-H_A), 4.58 (1 H, d, 13-H_B), 6.95–7.55 (4 H, Ar), 7.87 (1 H, br s, NH).

Reaction of 5e with NaCN. To a solution of **5e** (2.0 g, 6.6 mmol) in Me_2SO (28 mL) was added NaCN (0.65 g, 13.2 mmol) at 90 °C, and the reaction mixture was stirred at 100 °C for 1 h. The solution was poured into water (300 mL), and then extracted with CH_2Cl_2. The organic layer was dried, evaporated, and then fractionated by TLC to afford **5f** (0.24 g, 12.4%), mp 190–191 °C (MeOH). Anal. Calcd (found) for $C_{19}H_{23}N_3$: C, 77.77 (77.73); H, 7.90 (7.91); N, 14.32 (14.60). IR (KBr) 3350 (indole NH), 2250 cm^{-1} (CN); MS, *m/z* (relative intensity) 293 (80), 292 (95), 278 (30), 253 (15), 197 (80), 170 (100), 169 (58), 115 (15); ^1H NMR (py-d_5) δ 1.01 (3 H, t, J = 7.5 Hz, CH_2CH_3), 2.13 (1 H, dd, J_{gem} = 17.2 Hz, $J_{long\ range}$ = 0.8 Hz, 13-H_A), 3.16 (1 H, d, 13-H_B), 3.42 (1 H, t, 12b-H), 10.14 (1 H, br s, NH); ^{13}C NMR (py-d_5) δ 8.34 ($C1CH_2CH_3$), 22.26 (C3), 22.56 (C7 + C13), 31.80 ($C1CH_2CH_3$), 32.80 (C2), 39.81 (C1), 53.66 (C6), 56.54 (C4), 65.93 (C12b), 111.85 (C11), 112.59 (C7a), 118.15 (C8), 119.35 (C9), 119.61 (CN), 121.78 (C10), 127.39 (C7b), 132.06 (C12a), 137.83 (C11a). **7** (0.80 g, 41.4%) was also obtained, mp 219–220 °C. Anal. Calcd (found) for $C_{19}H_{23}N_3$: C, 77.77 (77.53); H, 7.90 (7.81); N, 14.32 (14.60). IR (KBr) 3300 (indole NH), 2250 cm^{-1} (CN); MS, *m/z* (relative intensity) 293 (98), 181 (8), 168 (18), 163 (99), 143 (18), 125 (100), 124 (97), 110 (80), 97 (30), 96 (95), 55 (18), 43 (44), 42 (30); ^1H NMR (py-d_5) δ 0.69 (3 H, t, J = 7.5 Hz, 20-H_3), 5.12 (1 H, s, 3-H), 11.67 (1 H, br s, NH); ^{13}C NMR (py-d_5) δ 7.85 (C20), 18.90 (C6), 26.46 (C10), 29.51 (C5), 31.69 (C19), 35.86 (C3), 41.49 (C4), 51.61 (C9), 52.07 (C7), 53.71 (C18), 111.69 (C16), 112.58 (C11), 118.60 (C13), 119.39 (CN), 119.68 (C14), 122.12 (C15), 127.48 (C12), 128.93 (C2), 136.68 (C17).

Starting from **5d** (at 75 °C for 1.25 h), **5f** (45.3%) and **7** (16.5%) were obtained in a different ratio.

Quaternization of 5d. A solution of **5d** (12.4 g, 34.2 mmol) in MeOH or CH_3CN (500 mL) was refluxed for 25 min. The solvent was removed in vacuo, and the residue was triturated with Et_2O to afford **6** ($X = CH_3SO_3$; 12.2 g, 98.4%), mp 155–157 °C; MS, m/z (relative intensity) 254 (11), 157 (21), 144 (15), 125 (5), 124 (6), 110 (100), 96 (10), 79 (11).

Reactions of Quaternary Salt 6. (a) With NaCN in Me_2SO. To a solution of **6** ($X = CH_3SO_3$; 0.50 g, 1.38 mmol) in Me_2SO (20 mL) was added NaCN (0.50 g, 10.2 mmol). The reaction mixture was stirred at 100 °C for 2 h, then quenched in ice–water, and extracted with CH_2Cl_2. The organic layer was dried, evaporated, and separated by TLC to give **5f** (0.03 g, 7.4%) and **8a** (0.10 g, 24.7%), mp 174–176 °C (MeOH). IR (KBr) 1645, 1616 cm^{-1} (C=NH); MS, m/z (relative intensity) 293 (100), 292 (68), 264 (52), 223 (34), 168 (10); ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 7.4 Hz, CH_2CH_3), 2.38 (1 H, d, J_{AB} = 15.6 Hz, 15-H_A), 2.74 (1 H, d, 15-H_B), 3.87 (1 H, 3-H), 7.1–7.5 (3 H, m, Ar), 7.7 (1 H, br s, C14=NH), 8.58 (1 H, m, 12-H); ^{13}C NMR ($CDCl_3$) δ 7.61 (C16CH_2CH_3), 16.68 (C6), 20.66 (C18), 25.99 (C17), 28.09 (C16CH_2CH_3), 37.19 (C16), 44.24 (C19), 45.45 (C15), 50.64 (C5), 58.01 (C3), 109.73 (C7), 116.85 (C12), 117.74 (C9), 122.29 (C10), 123.26 (C11), 129.96 (C8), 131.99 (C2), 134.66 (C13), 160.32 (C14). **7** (0.18 g, 44.5%) was also obtained.

(b) With NaCN in MeOH. To a solution of **6** ($X = CH_3SO_3$; 12.40 g, 34.2 mmol) in MeOH (500 mL) was added NaCN (12.4 g, 253.0 mmol). The reaction mixture was stirred at reflux for 27 h and then concentrated in vacuo to 100 mL. The residue was diluted with water (500 mL) and extracted with CH_2Cl_2. The organic layer was dried and evaporated, and the residue was treated with MeOH to give **7** (7.3 g, 72.7%). The mother liquor was evaporated and then separated by TLC to give **5f** (0.11 g, 1.1%), **8a** (1.04 g, 10.4%), and **9** (0.085 g, 0.8%), mp 212–214 °C (MeOH). IR (KBr) 3450 (indole NH), 2300 cm^{-1} (CN); MS, m/z (relative intensity) 293 (100), 264 (14), 224 (70), 211 (56), 210 (60), 196 (31), 180 (44), 168 (55), 167 (61), 148 (33), 143 (77); ^1H NMR (2:1 $CDCl_3$ + Me_2SO-d_6) δ 1.17 (3 H, t, J = 7.3 Hz, CH_2CH_3), 1.48 (2 H, m, 5-H_2), 2.1 (2 H, m, 6-H_2), 2.22 (2 H, q, CH_2CH_3), 2.4–2.6 (2 H, m, 4-H_2), 2.83 (4 H, s, 1-H_2 + 2-H_2), 3.33 (2 H, s, N3CH_2CN), 6.25 (1 H, br s, 8-H), 6.8–7.6 (4 H, m, Ar), 9.60 (1 H, br s, NH); ^{13}C NMR (2:1 $CDCl_3$ + Me_2SO-d_6) δ 12.59 (C7CH_2CH_3), 22.14 (C5), 22.71 (C1), 27.20 (C7CH_2CH_3), 27.58 (C6), 43.33 (N3CH_2CN), 44.51 (C4), 53.53 (C2), 109.90 (C13b), 110.88 (C10), 115.75 (CN), 116.90 (C8), 117.64 (C13), 118.12 (C12), 120.28 (C11), 127.66 (C13a), 133.92 (C8a), 136.04 (C9a), 150.56 (C7).

(c) With $Zn(CN)_2$ in Me_2SO. To a solution of **6** ($X = CH_3SO_3$; 1.0 g, 2.76 mmol) in Me_2SO (100 mL) was added $Zn(CN)_2$ (1.0 g, 8.5 mmol). The reaction mixture was stirred at 100 °C for 24 h, then poured into ice–water, and extracted with CH_2Cl_2. The organic layer was dried, evaporated, and then treated with MeOH to afford **9** (0.58 g, 71.6%).

(d) With $NaBH_4$ in EtOH. To a solution of **6** ($X = CH_3SO_3$; 0.50 g, 1.38 mmol) in EtOH (15 mL) was added $NaBH_4$ (0.50 g, 13.2 mmol) in small portions. The reaction mixture was stirred at room temperature for 20 min and then refluxed for additional 30 min. The solution was diluted with water (45 mL), and the precipitate was collected by filtration and washed with water and EtOH to afford **10** (0.30 g, 81.0%) as white powder, mp 281–283 °C dec. Anal. Calcd (found) for $C_{18}H_{24}N_2$: C, 80.55 (80.44); H, 9.01 (9.15); N, 10.44 (10.38). MS, m/z (relative intensity) 268 (39), 143 (21), 125 (100), 124 (48), 110 (37), 96 (12); ^1H NMR (5:1 Me_2SO-d_6 + $CDCl_3$) δ 0.7–3.8 (aliphatic), 6.8–7.5 (4 H, m, Ar), 10.15 (1 H, br s, NH); ^{13}C NMR (2:1 Me_2SO-d_6 + TFA) δ 6.72 (C20), 15.01 (C6), 22.60 (C10), 30.81 (C3 + C19), 31.85 (C5), 35.08 (C4), 48.03 (C9)*, 50.75 (C7)*, 52.76 (C18), 106.79 (C11), 110.98 (C16), 117.61 (C13), 118.87 (C14), 121.10 (C15), 128.49 (C12), 131.84 (C2), 135.07 (C17) [* may be interchanged].

(e) With Na in Liquid NH_3. A solution of **6** ($X = CH_3SO_3$; 0.50 g, 1.38 mmol) in EtOH (10 mL) and NH_3 (50 mL) was distilled at −55 °C. Pieces of Na were added to it until the blue color remained for 30 min. The reaction was treated with solid NH_4Cl and allowed to stand at room temperature for 4 h. The residue was treated with water to give **10** (0.15 g, 40.5%).

(3α,16α)-14-Imino-14,15-dihydroeburnamenine (8a). To a solution of **5f** (0.10 g, 0.34 mmol) in MeOH (20 mL) was added NaOH (0.10 g). The reaction mixture was refluxed for 2 h, then poured onto saturated solution of NaCl, and extracted with CH_2Cl_2. The organic layer was dried and evaporated, and the residue was treated with cold MeOH to afford **8a** (0.09 g, 90.0%).

(±)-Eburnamonine (8b). HCl (2 M; 0.4 mL) was added to a solution of **8a** (0.04 g, 0.14 mmol) in MeOH (10 mL). The reaction mixture was refluxed for 40 min, then quenched in an aqueous solution of $NaHCO_3$ (pH 8), and extracted with CH_2Cl_2. The organic layer was dried, and evaporated, and the residue was treated with cold MeOH to afford **8b** (0.03 g, 74.7%), mp 204–206 °C (lit.[2a] mp 201–202 °C). IR (KBr) 1700 cm^{-1} (CO); MS, m/z (relative intensity) 294 (100), 293 (74), 265 (35), 237 (30), 224 (28), 180 (14), 168 (14), 167 (17), 147 (8); ^1H NMR ($CDCl_3$) δ 0.91 (3 H, t, J = 7.5 Hz, CH_2CH_3), 3.94 (1 H, t, 3-H), 7.1–7.5 (3 H, m, Ar), 8.4 (1 H, m, 12-H); ^{13}C NMR ($CDCl_3$) δ 7.58 (C16CH_2CH_3), 16.54 (C6), 20.69 (C18), 27.04 (C17), 28.31 (C16CH_2CH_3), 38.31 (C16), 44.38 (C19), 50.63 (C5), 57.53 (C3), 112.35 (C7), 116.22 (C12), 117.99 (C9), 123.75 (C10), 124.19 (C11), 130.19 (C8), 132.18 (C2), 134.27 (C13), 167.36 (C14).

Preparation of 13b. (a) NaCN (0.19 g, 3.88 mmol) was added to a solution of **2e** (1.00 g, 3.30 mmol) in Me_2SO (14 mL). The reaction mixture was stirred at 100 °C and under argon for 4 days, then quenched in water, and extracted with CH_2Cl_2 (150 mL). The organic layer was dried and evaporated, and the remaining oil was treated with MeOH to afford **13b** (0.24 g, 24.9%) as white crystals, mp 158–160 °C (EtOH). Anal. Calcd (found) for $C_{19}H_{21}N_3$: C, 78.31 (78.21); H, 7.26 (7.53), N, 14.42 (14.80). IR (KBr) 2220 cm^{-1} (CN); MS, m/z (relative intensity) 291 (55), 264 (65), 263 (100), 235 (31), 221 (41), 205 (11), 193 (11); ^1H NMR (py-d_5) δ −0.01 (1 H, ddd, $\sum J$ = 13 + 13 + 3.5 Hz, 17-H_B), 0.89 (3 H, t, J = 7.5 Hz, CH_2CH_3), 3.66 (1 H, d, J = 11.0 Hz, 15-H_A), 4.00 (1 H, d, 15-H_B); ^{13}C NMR ($CDCl_3$) δ 9.65 (C16CH_2CH_3), 16.58 (C6), 19.98 (C18), 26.37 (C16CH_2CH_3), 27.67 (C17), 45.90 (C19), 49.48 (C5), 56.64 (C15), 58.51 (C16), 61.47 (C3) 105.28 (C7), 110.61 (C12), 118.58 (CN), 119.69 (C9), 119.90 (C10), 122.22 (C11), 129.82 (C8), 138.02 (C2)*, 138.22 (C13)* [* may be interchanged].

(b) A solution of **4e** (2.0 g, 4.98 mmol) in Me_2SO (20 mL) was heated to 90 °C, and then NaCN (0.49 g, 10.0 mmol) was added to it in small portions. The reaction mixture was stirred at 100 °C under argon for 2 h. The solution was poured into water (250 mL) and extracted with CH_2Cl_2 (50 mL). The organic layer was dried and evaporated, and the residue was treated with MeOH to afford **13b** (0.50 g, 34.5%).

(c) NaCN (2.0 g, 40.8 mmol) was added to a solution of **12** (2.00 g, 5.48 mmol) in Me_2SO (100 mL). The reaction mixture was stirred at room temperature for 1.5 h and then poured into ice–water. The precipitate was collected by filtration and washed with water and with EtOH to afford **13b** (1.15 g, 72.0%).

Mesylation of 2a. To a cold solution of **2a** (2.0 g, 7.03 mmol) in pyridine (28 mL) was added CH_3SO_2Cl (2.0 mL, 25.8 mmol). The reaction mixture was stirred at 0–5 °C for 1 h, and then the solvent was removed in vacuo (0.5 mbar). The remaining oil was treated with ice–water (40 mL) and concentrated NH_4OH (4 mL). The resulting solid was collected by filtration and washed with water to afford **2d** (2.0 g, 78.5%). IR (KBr) 3370 (indole NH), 1340, 1150 cm^{-1} (SO_2); MS, m/z (relative intensity) 362 (33), 267 (100), 266 (97), 237 (8), 197 (18), 184 (17), 169 (19); ^1H NMR ($CDCl_3$) δ 0.69 (3 H, t, J = 7.6 Hz, CH_2CH_3), 1.16 (1 H, dq, J_{AB} = 14.8 Hz, $CH_AH_BCH_3$), 2.17 (1 H, dq, $CH_AH_BCH_3$), 3.15 (3 H, s, OSO_2CH_3), 3.59 (1 H, 12b-H), 4.14 (1 H, d, J_{AB} = 10 Hz, 13-H_A), 4.78 (1 H, d, 13-H_B), 6.95–7.55 (4 H, m, Ar), 8.54 (1 H, br s, NH); ^{13}C NMR ($CDCl_3$) δ 7.23 (C1CH_2CH_3), 21.78 (C1CH_2CH_3)*, 21.99 (C3)*, 22.21 (C7), 30.40 (C2), 37.39 (SO_2CH_3), 40.93 (C1), 53.43 (C6), 56.20 (C4), 64.33 (C12b), 74.44 (C13), 111.15 (C11), 112.46 (C7a), 117.70 (C8), 119.25 (C9), 121.44 (C10), 126.91 (C7b), 132.31 (C12a), 136.76 (C11a) [* may be interchanged].

Reactions of 2d. (a) KO-t-Bu (1.2 g, 10.7 mmol) was added to a solution of **2d** (2.55 g, 7.03 mmol) in Me_2SO (50 mL). The reaction mixture was stirred at room temperature for 70 min and then poured into cold water. The precipitate was collected by filtration, washed with water and EtOH to afford **11** (1.58 g, 84.3%), mp 86–88 °C (EtOH). Anal. Calcd (found) for $C_{18}H_{22}N_2$: C, 81.15 (80.98); H, 8.32 (8.42); N, 10.51 (10.70). MS, m/z (relative intensity) 266 (100), 265 (52), 237 (13), 197 (20), 196 (24), 169 (16), 168 (19), 115 (10); ^1H NMR ($CDCl_3$) δ −0.61 (1 H, dq, $J_{AB} \sim$ 15 Hz, $J_{vic} \sim$ 7.5 Hz, $CH_AH_BCH_3$), 0.62 (3 H, dd, $\sum J$ = 15 Hz, CH_2CH_3), 1.65 (1 H, dqd, $J_{vic} \sim$ 7.5 Hz, $CH_AH_BCH_3$), 3.19 (1 H, 3-H), 3.78 (1 H, dd, $J_{\alpha,\beta}$ = 10.8 Hz, $J_{\beta,16\text{-}CH_B}$ = 1.9 Hz, 15-H_β), 3.88 (1 H, d, 15-H_α), 6.95–7.5 (4 H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 7.77 (C16CH_2CH_3), 20.99 (C16CH_2CH_3), 22.77 (C18), 24.65 (C6), 30.19

(C17), 51.26 (C5), 54.03 (C19), 56.26 (C15), 57.39 (C16), 67.95 (C3), 106.05 (C7), 110.76 (C12), 119.07 (C9), 119.55 (C10), 120.50 (C11), 131.47 (C8), 142.62 (C2), 147.72 (C13).

(b) NaCN (2.0 g, 40.8 mmol) was added to a solution of **2d** (2.55 g, 7.03 mmol) in MeOH (100 mL). The reaction mixture was stirred at reflux for 54 h, then quenched in a saturated solution of NaCl (150 mL), and extracted with CH_2Cl_2. The organic layer was dried and evaporated, and the remaining oil was fractionated by TLC to afford **11** (0.14 g, 7.5%) and **17a** (1.05 g, 50.7%), mp 146–148 °C (MeOH). IR (KBr) 1660, 1624 cm^{-1} (=NH); MS, m/z (relative intensity) 293 (100), 292 (96), 264 (21), 262 (10), 223 (3), 169 (4); ^1H NMR ($CDCl_3$) δ 0.6–1.3 (5 H, m, CH_2CH_3), 7.1–7.5 (3 H, m, Ar), 7.75 (1 H, br s, C14=NH), 8.57 (1 H, m, 12-H); ^{13}C NMR ($CDCl_3$) δ 7.33 (C16CH_2CH_3), 20.09 (C16CH_2CH_3), 21.19 (C6), 21.52 (C18), 31.44 (C17), 38.08 (C16), 45.23 (C15), 52.43 (C5), 55.49 (C19), 66.31 (C3), 110.44 (C7), 116.93 (C12), 117.81 (C9), 122.31 (C10), 123.13 (C11), 129.78 (C8), 133.19 (C2), 135.70 (C13), 160.60 (C14).

Oxidation of 11. A warm solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (1.50 g, 5.03 mmol) in AcOH (3 mL) was added to **11** (1.50 g, 5.63 mmol) in AcOH (10 mL). The reaction mixture was allowed to stand at room temperature for 30 min and then 70% $HClO_4$ (0.75 mL) was added and the mixture allowed to stand in a refrigerator overnight. The yellow crystals were filtered and washed with water and MeOH to give **12** (1.19 g, 57.7%), mp 203–204 °C (MeOH). Anal. Calcd (found) for $C_{18}H_{21}ClN_2O_4$: C, 59.26 (59.10); H, 5.80 (5.88); N, 7.68 (8.00). IR (KBr) 1620 cm^{-1} ($C=N^+$).

Preparation of 13a. (a) $NaBH_4$ (0.80 g, 21.2 mmol) was added to a solution of **13b** (0.48 g, 1.64 mmol) in MeOH (40 mL). The reaction mixture was stirred at reflux for 20 h, then acidified with AcOH (pH 5), and evaporated to dryness. The residue was dissolved in CH_2Cl_2 (80 mL) and alkalized with 40% NaOH to pH 10. The organic layer was separated, dried, and evaporated to give **13a** (0.41 g, 93.8%, oil), which was isolated as **13a**·HCl, mp 283–286 °C. Anal. Calcd (found) for $C_{18}H_{23}ClN_2$: C, 71.38 (71.48); H, 7.65 (7.72); N, 9.25 (9.11). Or it may have been purified by TLC (9:1) C_6H_6–MeOH to give **13a** as white crystals, mp 98–99 °C (CH_3CN). MS, m/z (relative intensity) 266 (100), 265 (6), 237 (10), 198 (16), 197 (17), 196 (82), 194 (48), 180 (10), 168 (10), 44 (31); ^1H NMR ($CDCl_3$) δ 0.46 (1 H, ddd, J_{gem} = 13.5 Hz, 17-H_β), 1.04 (3 H, t, J = 7.5 Hz, CH_2CH_3), 1.66 (1 H, ddd, 17-H_α), 1.94 (2 H, q, CH_2CH_3), 2.03 (1 H, m, 19-H_β), 2.45 (1 H, m, J_{gem} = 15.3 Hz, 6-H_α), 2.54 (1 H, m, 19-H_α), 2.93 (1 H, ddd, 6-H_β), 3.3 (2 H, m, 5-H_2), 3.57 (1 H, d, J = 10.5 Hz, 15-H_A), 4.06 (1 H, d, 15-H_B), 4.22 (1 H, t, J = 3.8 Hz, 3-H); ^{13}C NMR ($CDCl_3$) δ 9.63 (C16CH_2CH_3), 17.20 (C6), 21.42 (C18), 28.37 (C16CH_2CH_3), 30.05 (C17), 45.71 (C19), 51.27 (C5), 54.82 (C16), 57.21 (C15), 59.57 (C3), 102.36 (C7), 109.98 (C12), 118.84 (C9), 119.04 (C10), 120.51 (C11), 130.88 (C8), 137.54 (C2), 144.10 (C13).

(b) To a solution of **5d** (0.50 g, 1.38 mmol) in Me_2SO (25 mL) was added KO-t-Bu (0.30 g, 2.68 mmol). The reaction mixture was stirred at room temperature for 15 min, then poured into cold water, and extracted with CH_2Cl_2. The organic layer was dried, evaporated, and purified by TLC to afford **13a** (0.30 g, 88.0%).

Reaction of 13b with NaOH. NaOH (4.80 g, 120 mmol) in water (20 mL) was added to a suspension of **13b** (3.50 g, 12.0 mmol) in EtOH (20 mL). The reaction mixture was stirred at reflux for 48 h, then poured into water (400 mL), and extracted with CH_2Cl_2. The organic layer was dried and evaporated, and the residue was fractionated by TLC to afford **15**, which was isolated as perchlorate salt (1.50 g, 33.9%), mp 220–222 °C dec. Anal. Calcd (found) for $C_{18}H_{21}ClN_2O_4$: C, 59.25 (59.42); H, 5.85 (5.58); N, 7.68 (7.30). IR (KBr) 1685 ($C=N^+$), 1620 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.97 (3 H, t, J = 7.2 Hz, CH_2CH_3), 3.98 (1 H, d, J = 10.4 Hz, 15-H_A), 4.10 (2 H, t, 19-H_2), 4.46 (1 H, d, 15-H_B), 5.78 (1 H, dd, J_{gem} = 0.9 Hz, J_{cis} = 11.2 Hz, 5-H_A), 6.00 (1 H, dd, J_{trans} = 17.4 Hz, 5-H_B), 7.27 (1 H, dd, 6-H); ^{13}C NMR (1:1 $CDCl_3$ + Me_2SO-d_6) δ 8.31 (C16CH_2CH_3), 15.91 (C18), 23.98 (C16CH_2CH_3), 29.31 (C17), 43.34 (C19), 51.71 (C16), 52.21 (C15), 111.98 (C12), 118.89 (C5), 122.93 + 123.24 + 127.64 (C9 + C10 + C11), 127.42 (C6), 129.57 (C2), 136.88 (C13), 175.63 (C3). **13c** (0.72 g, 19.4%) was also obtained as white crystals, mp 237–238 °C (MeOH). Anal. Calcd (found) for $C_{19}H_{23}N_3O$: C, 73.75 (73.75); H, 7.49 (7.22); N, 13.58 (13.76). IR (KBr) 1675 cm^{-1} (amide CO); MS, m/z (relative intensity) 309 (0.3), 265 (100), 264 (6), 263 (10), 235 (6), 132 (6); ^1H NMR ($CDCl_3$) δ 0.16 (1 H, ddd, J_{gem} = 13 Hz, 17-H_β), 0.91 (3 H, t, J = 7.3 Hz, CH_2CH_3), 2.08 (1 H, m, J_{gem} = 10.3 Hz, 19-H_β), 2.44 (1 H, m, J_{gem} = 15.5 Hz, 6-H_α), 2.65 (1 H, m, 19-H_α), 2.92 (1 H, m, 6-H_β), 3.56 (1 H, d, J = 10.0 Hz, 15-H_A), 4.32 (1 H, d, 15-H_B), 6.0 and 7.5 (2 H, br s, $CONH_2$); ^{13}C NMR ($CDCl_3$) δ 9.50 (C16CH_2CH_3), 17.11 (C6), 20.34 (C18), 24.29 (C16CH_2CH_3), 28.66 (C17), 46.80 (C19), 49.87 (C5), 56.77 (C15), 58.27 (C16), 69.10 (C3), 103.82 (C7), 110.34 (C12), 118.90 (C9), 119.15 (C10), 120.92 (C11), 130.32 (C8), 138.71 (C2), 143.13 (C13), 175.55 ($CONH_2$).

Stepwise Reduction of 15. To a solution of **15** (0.50 g, 1.37 mmol) in MeOH (50 mL) at 0 °C was added $NaBH_4$ (1.0 g, 26.0 mmol) in small portions. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for an additional 1 h, then poured into water, and extracted with CH_2Cl_2 (150 mL). The organic layer was dried and evaporated, and the remaining oil was treated with MeOH to afford **16a** (0.25 g, 71.2%), mp 121–122 °C. Anal. Calcd (found) for $C_{18}H_{22}N_2$: C, 81.15 (81.09); H, 8.32 (8.40); N, 10.51 (10.62). IR (KBr) 1620 cm^{-1} (C=C); MS, m/z (relative intensity) 266 (97), 265 (49), 251 (40), 237 (100), 223 (13), 209 (12); ^1H NMR ($CDCl_3$) δ 0.78 (3 H, m, CH_2CH_3), 1.83 (1 H, s, NH), 3.37 (1 H, dd, J_{gem} = 10.0 Hz, $J_{long\ range}$ = 1.8 Hz, 15-H_A), 3.98 (1 H, d, 15-H_B), 4.14 (1 H, br s, 3-H), 5.12 (1 H, ddd, J_{gem} = 1.9 Hz, J_{cis} = 11.4 Hz, $J_{long\ range}$ = 0.5 Hz, 5-H_A), 5.66 (1 H, ddd, J_{trans} = 17.7 Hz, $J_{long\ range}$ = 0.5 Hz, 5-H_B), 7.00 (1 H, ddd, $J_{long\ range}$ < 0.5 Hz, 6-H); ^{13}C NMR ($CDCl_3$) δ 7.92 (C16CH_2CH_3), 19.43 (C18)*, 20.89 (C16CH_2CH_3)*, 29.88 (C17), 47.14 (C19), 50.34 (C16), 51.26 (C15), 66.96 (C3), 108.08 (C7), 108.97 (C12), 109.80 (C5), 119.57 (C9), 120.68 (C10), 121.38 (C11), 128.93 (C6), 129.46 (C8), 134.6 (C2), 141.87 (C13) [* may be interchanged].

To a prehydrogenated suspension of 10% Pd/C (0.14 g) in MeOH (2 mL) was added a solution of **16a** (0.17 g, 0.64 mmol) in MeOH (14 mL). The mixture was hydrogenated at room temperature and at atmospheric pressure for 30 min, and then the catalyst was removed by filtration. The filtrate was evaporated to yield **16b** (0.12 g, 70.2%), mp 78–81 °C (CH_3CN). Anal. Calcd (found) for $C_{18}H_{25}ClN_2$: C, 70.91 (70.75); H, 8.26 (8.14); N, 9.19 (9.17). MS, m/z (relative intensity) 270 (1.3), 269 (15), 268 (71), 267 (46), 240 (18), 239 (100), 237 (15), 225 (16), 210 (16), 182 (17); ^1H NMR ($CDCl_3$) δ 0.78 (3 H, m, CH_2CH_3), 1.26 (3 H, t, J = 7.5 Hz, 5-H_3), 1.96 (1 H, br s, NH), 2.78 (2 H, q, 6-H_2), 3.36 (1 H, dd, J_{gem} = 10 Hz, $J_{long\ range}$ = 2 Hz, 15-H_A), 3.96 (1 H, d, 15-H_B), 4.12 (1 H, s, 3-H); ^{13}C NMR ($CDCl_3$) δ 7.93 (C16CH_2CH_3), 16.68 (C5), 17.16 (C6), 19.37 (C18)*, 20.92 (C16CH_2CH_3)*, 29.92 (C17), 47.25 (C19), 50.40 (C16), 51.03 (C15), 66.54 (C3), 108.60 (C12), 110.02 (C7), 118.04 (C9), 118.96 (C11), 120.56 (C10), 131.14 (C8), 133.83 (C2), 138.46 (C13) [* may be interchanged].

(±)-3-Epieburnamonine (17b). HCl (1 M; 2 mL) was added to a solution of **17a** (0.28 g, 0.95 mmol), and the reaction mixture was refluxed for 1 h. The solution was evaporated, and the residue was treated with 5% $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried and evaporated to afford **17b** (0.26 g, 92.5%), mp 138–139 °C (MeOH) (lit.[7] mp 138–139 °C). Anal. Calcd (found) for $C_{19}H_{22}N_2O$: C, 77.51 (77.55); H, 7.53 (7.43); N, 9.52 (9.48). IR (KBr) 1708, 1655 cm^{-1} (amide CO); MS, m/z (relative intensity) 294 (87), 293 (100), 265 (11), 237 (17); ^1H NMR ($CDCl_3$) δ 0.6–1.4 (5 H, m, CH_2CH_3), 2.31 (1 H, dd, J = 16.8 + 1.8 Hz, 15-H_β), 2.76 (1 H, d, 15-H_α), 2.95 (1 H, 3-H), 7.15–7.5 (3 H, m, Ar), 8.33 (1 H, m, 12-H); ^{13}C NMR ($CDCl_3$) δ 7.30 (C16CH_2CH_3), 20.65 (C16CH_2CH_3), 21.20 (C6), 21.49 (C18), 31.71 (C17), 39.26 (C16), 44.08 (C15), 52.07 (C5), 55.26 (C19), 65.57 (C3), 112.74 (C7), 116.16 (C12), 118.07 (C9), 123.70 (C10), 123.94 (C11), 129.89 (C8), 133.31 (C2), 135.06 (C13), 167.46 (C14).

X-ray Analysis of 7. Compound **7** ($C_{19}H_{24}N_3 \cdot HBr$ with $^1/_2$ CH_3OH) crystallizes in the centrosymmetric monoclinic space group $P2_1/c$ derived from the systematic absences (in $h0l$, $l = 2n + 1$, in $0k0$, $k = 2n + 1$). The size of the crystal selected for X-ray measurements was about 0.1 × 0.15 × 0.25 mm^3. The precise cell dimensions, a = 7.831 (1) Å, b = 13.685 (1) Å, c = 20.139 (1) Å, β = 123.01 (1)°, V = 1809.8 (7) $Å^3$ (Z = 4, D_c = 1.432 Mg m^{-3}), and $F(000)$ = 812, were determined by least-squares refinement on diffractometer angles for 25 automatically centered reflections. The reflection intensities were collected on a computer-controlled Enraf-Nonius CAD-4 diffractometer using graphite monochromated Cu Kα radiation (λ = 1.5418 Å) with $\omega/2\theta$ scan in the range 1.5° < θ < 78.0° [scan width 0.4 + (0.14 tan θ)]. The scan rate for each reflection was determined by a rapid prescan at 10°

Table II. Fractional Atomic Coordinates of the Non-Hydrogen Atoms of 7 with Standard Deviations in Parentheses[a]

	x	y	z	B_{eq}
Br	0.01648 (5)	1.15188 (3)	0.15281 (2)	2.55 (1)
O23	0.5000 (0)	1.0000 (0)	0.0000 (0)	15.7 (3)
N1	0.2719 (3)	0.9999 (2)	0.3199 (1)	2.35 (5)
N8	0.5292 (3)	0.6887 (2)	0.3003 (1)	2.19 (6)
N22	−0.1974 (5)	0.8905 (3)	0.1955 (2)	4.68 (8)
C2	0.3238 (4)	0.9019 (2)	0.3241 (1)	1.99 (6)
C3	0.1771 (4)	0.8292 (2)	0.2627 (1)	2.19 (6)
C4	0.2348 (4)	0.7981 (2)	0.2024 (1)	2.31 (6)
C5	0.1173 (5)	0.7044 (3)	0.1576 (1)	2.85 (8)
C6	0.1836 (5)	0.6146 (3)	0.2114 (2)	2.33 (7)
C7	0.4113 (5)	0.5984 (2)	0.2552 (2)	2.44 (8)
C9	0.5427 (4)	0.6984 (2)	0.3776 (2)	2.43 (7)
C10	0.6370 (5)	0.7936 (2)	0.4210 (1)	3.07 (7)
C11	0.5122 (4)	0.8861 (2)	0.3897 (1)	2.23 (6)
C12	0.5842 (4)	0.9788 (2)	0.4285 (1)	2.05 (7)
C13	0.7627 (5)	1.0090 (3)	0.4986 (1)	3.05 (8)
C14	0.7823 (5)	1.1063 (3)	0.5211 (2)	3.5 (1)
C15	0.6297 (6)	1.1733 (3)	0.4750 (2)	2.51 (9)
C16	0.4529 (5)	1.1456 (2)	0.4052 (2)	2.28 (8)
C17	0.4319 (4)	1.0487 (2)	0.3838 (1)	1.96 (6)
C18	0.4618 (4)	0.7754 (2)	0.2464 (1)	2.10 (7)
C19	0.1934 (7)	0.8858 (3)	0.1466 (2)	4.4 (1)
C20A	0.220 (1)	0.8801 (6)	0.0834 (4)	4.3 (1)
C20B	0.032 (1)	0.8845 (9)	0.0719 (6)	6.6 (2)
C21	−0.0343 (5)	0.8651 (2)	0.2231 (2)	3.01 (7)
C24	0.310 (2)	0.999 (1)	0.0023 (7)	8.8 (3)

[a] The given isotropic temperature parameters (B_{eq}) are one-third of the trace of the orthogonalized anisotropic B_{ij} tensor

min^{-1} in θ at which point any reflection with $I < \sigma(I)$ was coded as unobserved. Three standard reflections were monitored every hour and showed no significant (~1.8%) deviation. 3813 reflections were thus recorded, of which—after correction for Lorentz and polarization effects—3377 with $I > 0.3\sigma(I)$ were taken as observed. Although $\mu = 31.5$ cm^{-1}, no absorption correction was applied. The structure was solved by the MULTAN[12] program. The full-matrix least-squares refinement minimized $\sum w(\Delta F)^2$. 213 parameters were refined. In the course of the isotropic refinement (about $R = 0.15$) a difference Fourier synthesis revealed a conformational disorder around the terminal C20 atom of the 4-ethyl moiety; moreover, an additional methanol molecule was observed in a partly special position. Its oxygen atom is fixed in a center of symmetry at (0.5,1.0,0) while the methyl group occupies randomly (with 50–50% of probability) either of two center of symmetry related positions. Consequently, a half molecule of CH_3OH per each molecule of 7 had to be taken into account. The occupancy factors of the methanol C24 atom were fixed to 0.5 while those of C20 were allowed to vary. However, both remained in the vicinity of 0.5. The hydrogen positions were generated from assumed geometries and were only taken into account in the structure factor calculations with individual isotropic temperature factors (B_i of the corresponding heavy atom increased by 1 Å^2). No location of the randomly distributed H atoms belonging to the positionally disordered methanol molecule were attempted. The refinement was terminated at $R = 0.043$, $R_w = 0.068$, $S = 3.52$, $w = [\sigma^2(F_0) + 0.25(pF_0)^2]^{-1}$, where $p = 0.01$. Scattering factors were taken from ref 13. All calculations were performed on a PDP 11/34 minicomputer with the Enraf-Nonius SDP program package. The final positional and isotropic temperature factors of the non-hydrogen atoms are given in Table II.

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Registry No. 1·$HClO_4$, 55390-29-9; (±)-**2a**, 64361-56-4; (±)-**2b**, 58451-77-7; (±)-**2c**, 97805-31-7; (±)-**2d**, 97720-67-7; (±)-**2e**, 56897-79-1; (±)-**3**, 97805-30-6; (±)-**4b**, 97720-56-4; (±)-**4c**, 97720-58-6; (±)-**4e**, 97720-54-2; (±)-**5a**, 58451-76-6; (±)-**5b**, 58451-77-7; (±)-**5c**, 58451-79-9; (±)-**5d**, 97720-59-7; (±)-**5e**, 56897-78-0; (±)-**5f**, 63038-13-1; (±)-**6** (X = CH_3SO_3), 97720-61-1; (±)-**7**, 97720-62-2; (±)-**8a**, 97805-35-1; (±)-**8b**, 2580-88-3; **9**, 97731-53-8; (±)-**10**, 97720-63-3; (±)-**11**, 97748-88-4; (±)-**12**, 97720-66-6; (±)-**13a**, 97731-48-1; (±)-**13b**, 97720-64-4; (±)-**13c**, 97720-70-2; (±)-**15**, 97720-69-9; (±)-**16a**, 97720-71-3; (±)-**16b**, 97720-72-4; (±)-**17a**, 97748-89-5; (±)-**17b**, 60384-17-0.

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Synthetic Studies Directed toward Cembranolides. Synthesis of the Basic Nucleus of Crassin Acetate

William G. Dauben,* R. Kent Saugier, and Ilona Fleischhauer[1]

Department of Chemistry, University of California, Berkeley, California 94720

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A stereospecific synthesis of the basic crassin acetate nucleus, *erythro*-1-(hydroxymethyl)-14-hydroxy-4,8,12-trimethylcyclotetradeca-(*E*,*E*,*E*)-3,7,11-triene, has been achieved. Stereospecific syntheses of the two precursors to this ring system, (*E*,*E*)-3,7-dimethyl-9-(phenylthio)nona-3,7-dienal and (*E*)-2,8-bis(trimethylsiloxy)-2,7-dimethyloct-6-en-3-one, have been developed. These moieties were combined via an aldol condensation to yield *erythro*-9-hydroxy-10-[1-oxo-2-methyl-2-(trimethylsiloxy)propyl]-1-(phenylthio)-14-(trimethylsiloxy)-3,7,13-trimethyltetradeca-(*E*,*E*,*E*)-2,6,12-triene which, in a series of reactions, was cyclized to the titled 14-membered ring system.

In contrast to the mono- and sesquiterpenes, previous to 1962, the natural diterpene series contained no head-to-tail monocycles corresponding to the monoterpenes limonene and terpinolene and the sesquiterpenes germacrene and humulene. In 1962, research in this laboratory provided the first example of such an analogous monocyclic structure derived from the diterpene geranylgeraniol, cembrene (1), a naturally occurring 14-carbon ring compound isolated from pine trees.[2] In the subsequent years

(1) Recipient of Feodor-Lynen Fellowship, Alexander von Humboldt Stiftung, 1983–1984.

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