SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS XXXV \(^1\).
PREPARATION OF 1-ETHYL-1-HYDROXYETHYL-OCTAHYDROINDOL[2,3-a]QUINOLIZINE DERIVATIVES AND REACTIONS OF THEIR MESYLATES WITH CYANIDE ION

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Abstract - Starting from \((\pm)\)-eburnamonine (1\(a\)) and \((\pm)\)-3-epieburnamonine (1\(b\)), compounds 5 and 11 were prepared. The reaction of the mesylate of 5 or 11 with NaCN in DMF led to a mixture of 16 and 17. The structures of the new compounds were elucidated.

In previous articles we have described the synthesis and the strikingly different chemical behaviour of mesylates of 1-ethyl-1-hydroxyethyl-1,2,3,4,6,7,12,12b-octahydroindol[2,3-a]quinolizine epimers\(^2\) and the homologue containing two more methylene groups in the side chain\(^3\). In order to study the scope and limitations of the side chain length dependent reactions, the homologous derivatives 5 and 11 with a C\(_2\) side chain were prepared and their reactions were investigated. As starting compounds, \((\pm)\)-eburnamonine (1\(a\))\(^4\) and \((\pm)\)-3-epieburnamonine (1\(b\))\(^2\) were

\[ 1a \quad 3H - \alpha \]
\[ 1b \quad 3H - \beta \]
\[ 2a \quad 12bH - \alpha \]
\[ 2b \quad 12bH - \beta \]
chosen, from which $2_a$ and $2_b$ were prepared.\textsuperscript{5,6}

Since reduction of $2_a$ with LiAlH$_4$ failed\textsuperscript{6} to afford the hydroxyethyl compound $5$, other methods were tried. With NaBH$_4$ in DMF and in the presence of MeSO$_3$H\textsuperscript{7}, or with B$_2$H$_6$ in THF\textsuperscript{8}, $2_a$ was recovered. However, the mixed anhydride ($3$) prepared by reacting $2_a$ with ClCO$_2$Et in THF in the presence of Et$_3$N, gave on reduction with NaBH$_4$\textsuperscript{9} the expected compound ($5$) in 37.8 \% yield.

As a by-product the indoloindolizine derivative ($6$)\textsuperscript{10} was isolated. When the salt (Et$_3$N-HCl), precipitated in the first step, was filtered off, the percentage of $5$ increased from 37.8 \% to 59.9 \%.

Performing the same reaction sequence starting from the 3β-epimer $2_b$, the mixed anhydride ($7$) formed in the first step was unstable and gave rise by elimination of CO$_2$ to the ester $8$\textsuperscript{11} in 79.7 \% yield.
Reduction of $8$ with LiAlH$_4$ resulted in the formation of a mixture of (+)-3-epi-
epiburnamine and (+)-3-epiisoeburnamine ($9$),$^{12}$ which were converted by refluxing in
pyridine to (+)-3-epiburnamenine ($10$).$^{13}$

When the carboxylic acid ($2b$) was reduced, the desired compound ($11$) was obtained
predominantly but accompanied with small amount of $9$.

An alternative route to $11$ involves acylation of $5$ in pyridine with Ac$_2$O followed
by oxidation of $12$ in AcOH with Na$_2$Cr$_2$O$_7$·2H$_2$O.$^{14}$ The isolated iminium salt ($13$)
was reduced$^{15}$ in EtOH with NaBH$_4$ to give a mixture of two epimeric acetates $12b$ and
$14$ (ratio = 1:1.5, yield = 77.3%). After separation, hydrolysis of the latter gave rise to $11$. 

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The mesylates (15a, b) derived from 5 and 11 were prepared, and then each of the pure stereoisomeric salts were allowed to react with NaCN in DMF.

A mixture of epimers 16 and 17 was formed in both cases. It seems that under the conditions applied the mesylate salts interconverted presumably via a seco intermediate (18). 17, 18, 19

To support our assumption we prepared the Nind−methyl derivative (19), from which the mesylate salt 20 was prepared. Reaction of the latter with NaCN in DMF afforded—as expected—a single product (21), i.e., no epimerisation occurred.
Compound 2\textsuperscript{18} was also prepared by the selective methylation of 1\textsubscript{16}. No reaction of 1\textsubscript{15} with Zn(CN),\textsubscript{2} (cf.\textsuperscript{2}) was observed.

We can conclude from the above investigations that the mesylates (i.e. the quaternary salts 1\textsubscript{15}) described in this paper gave, in contrast to their higher homologues, a mixture of the epimer nitriles.

**EXPERIMENTAL**

**General.** The ir spectra were measured with a SPECTROMOM 2000 spectrophotometer. The \textsuperscript{1}H- and \textsuperscript{13}C-nmr spectra were recorded on a VARIAN XL-100 Fourier transform spectrometer operating at 100.1 and 25.16 MHz, respectively. Chemical shifts (in ppm) are relative to internal Me\textsubscript{4}Si. Mass spectra were determined using a JEOL-JMS-01-SG-2 instrument. All melting points are uncorrected. Thin-layer chromatography separations were carried out on silica gel (Kieselgel 60 PF\textsubscript{254}+366) developed with C\textsubscript{6}H\textsubscript{6}-MeOH 10:1.4 and eluted with CH\textsubscript{2}Cl\textsubscript{2}-MeOH (10:1). The organic layers were dried over MgSO\textsubscript{4}.

\textit{18-Carboxymethyl-1α-ethyl-1,2,3,4,6,7,12,12β-octahydroindolo[2,3-a]quinolizine (2\textsubscript{a})}. To a solution of 1\textsubscript{18} (3.00 g, 10.19 mmol) in EtOH (150 ml) was added KOH (3.0 g, 54 mmol) in water (30 ml). The reaction mixture was refluxed for 6 h, and then evaporated in vacuo. The residue was diluted with water (20 ml), and acidified with AcOH to pH 6. The precipitate was collected by filtrations and washed with cold water to afford 2\textsubscript{a} (3.07 g, 96.4 %) as white powder, mp 203-206 °C (decomp.)

\textit{18-Carboxymethyl-1α-ethyl-1,2,3,4,6,7,12,12β-octahydroindolo[2,3-a]quinolizine (2\textsubscript{b})}. To a solution of 1\textsubscript{18} (1.00 g, 3.40 mmol) in EtOH (70 ml) was added KOH (1.0 g, 18 mmol) in water (10 ml). The reaction mixture was refluxed for 3.5 h, and then evaporated in vacuo. The residue was dissolved in water (10 ml) and acidified with AcOH to pH 6. The precipitate was collected by suction and washed with cold water to afford 2\textsubscript{b} (0.98 g, 92.4 %), mp 148-151 °C (decomp.)

Reduction of 2\textsubscript{a} via Its Anhydride 3. To a suspension of 2\textsubscript{a} (2.00 g, 6.40 mmol) in THF (200 ml) were added Et\textsubscript{3}N (2.0 ml, 14.3 mmol) and ClCO\textsubscript{2}Et (2.0 ml, 20.9 mmol). The reaction mixture was stirred at room temperature for 24 h. After that, the solid part was filtered and the filtrate was dropped into a suspension of NaBH\textsubscript{4} (4.0 g, 105.6 mmol) in water (40 ml) at 0-5 °C. The solution was stirred for an
additional 80 min, then acidified with AcOH to pH 6 and concentrated in vacuo. The residue was treated with 5% NaHCO₃ and extracted with CH₂Cl₂. The organic layer was dried and evaporated. The remaining oil was crystallized from MeOH to yield 8 (0.82 g, 42.9%) as white powder, mp 176-179 ºC. Ms, m/z (relative intensity) 298(89), 297(100), 283(14), 267(52), 197(49), 185(18), 170(67), 115(10); ¹H nmr (CDCl₃) δ 1.10 (3H,t, J=7.5 Hz, CH₂CH₃), 3.33 (1H, br s, Cl₂b-H), 3.43 (1H, ddd, J=11.5 Hz, Cl₁₄-H), 3.70 (1H, ddd, J=10.5 +4.0 Hz, Cl₁₄-H), 5.6 (1H, br s, OH), 6.95-7.5 (4H, m, Ar), 7.8 (1H, br s, NH); ¹³C nmr (CDCl₃) δ 8.31 (CH₃), 21.54 (C₇), 22.94 (C₃), 32.64 (C₂), 34.94 (CH₂CH₃), 38.39 (Cl₁₃), 40.73 (C₁), 54.11 (C₆), 56.49 (C₄), 58.75 (Cl₁₄), 110.71 (C₁₁), 111.96 (C₇α), 118.08 (C₈), 119.38 (C₉), 121.63 (C₁₀), 126.94 (C₇β), 132.63 (C₁₂α), 136.38 (C₁₁α)/* may be interchanged/. Elemental analysis data C₉H₆N₂O₂ (298.42) Calc.: C 76.46, H 8.78, N 9.39 Found: C 76.53, H 8.71, N 9.45. The mother liquor was concentrated and separated by tlc, to afford 8 (0.32 g, 17.0%), and 6 (0.35 g, 16.5%) mp 202-203 ºC (MeOH).
(CH₂CH₃), 14.35(CO₂CH₂CH₃), 22.48(C₃H₇), 24.95(CH₂CH₃), 32.79(CH₃), 41.41(Cl), 43.09(C₃H₇), 53.54(C₆), 61.10(CO₂CH₂CH₃), 66.91(C₁₂H₇), 111.14(C₁₁), 112.34(C₇H₇), 117.37(C₈), 119.03(C₉), 121.14(C₁₀), 127.35(C₇H₇), 133.65(C₁₂), 136.76(C₁₃), 174.38(COOC₂H₅).

Elemental analysis data C₂₁H₂₈N₂O₂ (340.45): Calc.: C 74.08, H 8.29, N 8.23; Found: C 74.17, H 8.37, N 8.38.

Eburnamenine (38, 16a)(10). To a suspension of LiAlH₄ (0.50 g, 13.2 mmol) in boiling THF (25 ml) was dropped a solution of 8 (0.50 g, 1.47 mmol) in THF (25 ml). The reaction mixture was stirred at reflux for an additional 30 min, and then decomposed with 10% NaOH (5 ml) and water (5 ml). After cooling, the organic layer was separated, dried and evaporated in vacuo. The remaining oil was purified by tlc to afford 2 (0.34 g, 78.1%) mp 227-229°C (MeOH). Ms, m/z (relative intensity) 296(73), 295(100), 268(21), 249(56).

A solution of 9 (0.34 g, 1.15 mmol) in pyridine (34 ml) was refluxed for 14 h, then evaporated in vacuo. The remaining oil was separated by tlc to give 2 (0.15 g, 47.0%) and 10 (0.08 g, 25.1%) as white crystals, mp 113-115°C (MeOH); ms, m/z (relative intensity) 278(74), 277(53), 263(12), 250(61), 249(100), 248(70), 219(10), 206(12), 193(10); ¹H nmr (CDCl₃) δ 0.70(3H, t, J=7.5 Hz, CH₂CH₃), 5.16(1H, d, J=7.6 Hz, C₁₅-H), 6.90(1H, d, C₁₄-H), 6.95-7.5(4H, m, Ar); ¹³C nmr (CDCl₃) δ 8.07(CH₂CH₃), 21.47(C₆), 21.74(C₁₈), 23.47(CH₂CH₃), 30.58(C₁₇), 37.74(C₁₆), 53.55(C₅), 55.62(C₁₉), 65.84(C₃), 107.05(C₇), 108.63(C₁₂), 117.79(C₁₅), 121.18(C₁₁), 128.32(C₈), 132.62(C₂), 134.37(C₁₃). Elemental analysis data C₁₉H₂₄N₂ (278.39): Calc.: C 81.97, H 7.97, N 10.06; Found: C 82.03, H 8.07, N 10.19.

Reduction of 2₉. To a suspension of 2₉ (2.00 g, 6.40 mmol) in THF (100 ml) was added LiAlH₄ (1.8 g, 47.4 mmol). The reaction mixture was stirred at 0-5°C for 3 h, and then treated with AcOEt (3 ml), water (3 ml), and CH₂Cl₂ (50 ml). The organic layer was separated, dried, and evaporated. The remaining oil was crystallized from MeOH to give 11 (0.57 g, 29.8%) as white crystals, mp 184-186°C; ms, m/z (relative intensity) 298(90), 297(100), 283(11), 267(8), 191(32), 185(16), 170(38), 169(27); ¹H nmr (CDCl₃) δ 0.65(3H, t, J=7.5 Hz, CH₂CH₃), 3.47(1H, br s, C₁₂b-H), 4.00(2H, m, C₁₄-H₂), 6.95-7.5(4H, m, Ar), 9.12(1H, br s, indole NH); ¹³C nmr (CDCl₃-d₆, DMSO-d₆, 3:1) δ 7.25(CH₂CH₃), 22.34(C₃H₇), 25.46(CH₂CH₃), 32.31(C₂), 39.37(C₁), 39.78(C₁₃), 53.81(C₆), 56.68(C₄), 57.08(C₁₄), 66.54(C₁₂), 110.83(C₁₃).
 Elemental analysis data

C_{19}H_{18}N_{2}O (298.42) Calc.: C 76.46, H 8.78, N 9.39 Found: C 76.50, H 8.91, N 9.57. The mother liquor was concentrated and separated by tlc to afford \( \text{Ia} \) (0.48 g, 25.3 %) and \( \text{Ib} \) (0.25 g, 13.1 %, total yield = 0.82 g, 42.9 %).

\(-\text{Ia}-(\text{2-Acetylxyethyl})-\text{Ia-ethyl}-1,2,3,4,6,7,12,12\text{ba-Octahydroindolo}[2,3-a]quinolizine}\) (\( \text{Ia} \)). To a solution of \( \text{Ia} \) (1.01 g, 3.38 mmol) in pyridine (10 ml) was added \( \text{Ac}_2\text{O} \) (10 ml). The reaction mixture was allowed to stand at room temperature for 12 h, then the solvent was evaporated in vacuo (0.2 mbar). The remaining oil was treated with cold 5 % NaHCO\(_3\) to afford \( \text{Ia} \) (0.89 g, 77.2 %) as white crystals, mp 128-131 \( ^\circ \text{C} \) (MeOH). Ir (KBr) 3390 (indole NH), 1715 cm\(^{-1}\) (C=O); ms, m/z (relative intensity) 340 (92), 339 (100), 325 (14), 281 (14), 267 (34), 197 (41), 185 (18), 170 (45), 169 (27).

\( ^1\text{H} \) Nmr (CDCl\(_3\)) \& 6.11 (3H, t, J=7.5 Hz, CH\(_2\)CH\(_3\)), 1.93 (3H, s, COCH\(_3\)), 3.32 (1H, br s, Cl\(_{12b}\)-H), 4.02 (2H, m, C\(_{14}\)-H\(_2\)), 7.0-7.5 (4H, m, Ar), 7.8 (1H, br s, NH); \( ^{13}\text{C} \) nmr (CDCl\(_3\)) \& 8.11 (CH\(_2\)CH\(_3\)), 20.90 (COCH\(_3\)), 22.04 (C3), 22.30 (C7), 31.62 (CH\(_2\)CH\(_3\)), 32.05 (C13), 32.80 (C2), 39.44 (Cl), 54.04 (C6), 56.73 (C4), 61.34 (C14), 66.70 (Cl2b), 110.83 (Cl1), 112.07 (C7a), 117.86 (C8), 119.32 (C9), 121.50 (Cl0), 126.99 (C7b), 133.34 (Cl2a), 136.28 (Cl1a), 170.86 (CO\(_{2}\)O) \(^+\), may be interchanged. Elemental analysis data

C\(_{21}\)H\(_{28}\)N\(_2\)O\(_2\) (340.45) Calc.: C 74.08, H 8.29, N 8.23; Found: C 74.11, H 8.11, N 8.37.

Oxidation of \( \text{Ia} \). To a solution of \( \text{Ia} \) (0.89 g, 2.61 mmol) in AcOH (5 ml) was added Na\(_2\)Cr\(_2\)O\(_7\)-2H\(_2\)O (0.42 g, 1.41 mmol) in hot AcOH (1.0 ml). The reaction mixture was allowed to stand at room temperature for 4 h, then was treated with 70 % HClO\(_4\) (0.4 ml). After cooling, the yellow crystals that precipitated were collected by suction and washed with water and EtOH to afford \( \text{Ia} \) (0.50 g, 43.6 %) mp 160-162 \( ^\circ \text{C} \) (EtOH). Anal. Calcd (found) for C\(_{21}\)H\(_{27}\)Cl\(_{2}\)N\(_2\)O\(_6\): C, 57.46 (57.70); H, 6.20 (6.32); N, 6.38 (6.49). Ir (KBr) 3350 (indole NH), 1740 (C=O), 1620 cm\(^{-1}\) (C=O).

Reduction of \( \text{Ia} \). To a suspension of NaBH\(_4\) (0.50 g, 13.2 mmol) in EtOH (70 ml) was added \( \text{Ia} \) (0.50 g, 1.14 mmol) in small portions at 0 \( ^\circ \text{C} \). The reaction mixture was stirred for 2 h, then acidified with 1M HCl and evaporated in vacuo. The residue was dried, evaporated, and separated by tlc to afford \( \text{Ic} \) (0.12 g, 30.9 %), and \( \text{Id} \) (0.18 g, 46.4 %) mp 180 \( ^\circ \text{C} \) (decomp.) Ir (KBr) 3300 (indole NH), 1705 cm\(^{-1}\) (C=O); ms, m/z (relative intensity) 339 (100), 325 (13), 281 (13), 267 (33), 197
(40), 185(17), 170(42), 169(25). $^1$H Nmr (CDCl$_3$) $\delta$ 0.67 (3H, t, J=7.5 Hz, CH$_2$CH$_3$), 2.15 (3H, s, COCH$_3$), 3.30 (1H, br s, Cl$_{12b}$-H), 4.12 (1H, ddd, J=12.2+11.0+5.6 Hz, Cl$_{14}$-H$_{A/B}$), 4.80 (1H, ddd, J=12.2+1.0+5.2 Hz, Cl$_{14}$-H$_{A/B}$), 6.95-7.5 (4H, m, Ar), 9.64 (1H, br s, NH); $^{13}$C nmr (CDCl$_3$) $\delta$ 7.00 (CH$_2$CH$_3$), 21.09 (COCH$_3$), 22.24 (C$_3$+C$_7$), 25.27 (CH$_2$CH$_3$), 32.35 (C$_2$), 36.04 (C$_{13}$), 39.30 (C$_1$), 54.01 (C$_6$), 56.89 (C$_4$), 62.34 (C$_{14}$), 66.74 (C$_{12b}$), 111.21 (C$_{11}$), 111.51 (C$_{7a}$), 117.54 (C$_8$), 118.87 (C$_9$), 121.11 (C$_{10}$), 126.66 (C$_{7b}$), 132.69 (C$_{12a}$), 136.79 (C$_{11a}$), 172.84 (COCH$_3$).

$^{13}$-Ethyl-$^{13}$-(2-hydroxyethyl)-1,2,3,4,6,7,12,12ba-octahydroindolo[2,3-alquinolizine (11). To a solution of 14 (120 mg, 0.35 mmol) in boiling EtOH (5 ml) was added a solution of KOH (100 mg, 1.8 mmol) in water (1.0 ml). The reaction mixture was refluxed for 10 min, then diluted with water (10 ml). After cooling, the precipitate was collected by filtration and washed with water to afford 11 (86 mg, 81.8%).

1p-(2-Cyanoethyl)-1a-ethyl-1,2,3,4,6,7,12,12ba-octahydroindolo[2,3-alquinolizine (16) and 1a-(2-cyanoethyl)-1a-ethyl-1,2,3,4,6,7,12,12ba-octahydroindolo[2,3-alquinolizine (17). (a) A solution of 5 (0.33 g, 1.11 mmol) in pyridine (6 ml) was cooled to 0°C, and MeSO$_2$Cl (0.3 ml. 3.9 ml) was added. The reaction mixture was stirred for 30 min, and then the solvent was evaporated at room temperature in vacuo (0.02 mbar). The remaining oil was dissolved in EtOH (15 ml), refluxed for 30 min, and then evaporated to dryness. The residue was dissolved in DMF (30 ml) and NaCN (0.5 g, 10.2 mmol) was added. The reaction mixture was stirred at 140°C for 16 h, and then poured into cold water and extracted with CH$_2$Cl$_2$. The organic layer was dried and evaporated. The residue was separated by tlc / developed with CHCl$_3$-MeOH (10:1)/ to give 16 (0.25 g, 73.5 %) mp 166-169°C (MeOH)/lit. 16a

mp 166-169°C; ir(KBr) 3380 (indole NH), 2300 cm$^{-1}$ (CN); $^1$H nmr (CDCl$_3$) $\delta$ 0.67 (3H, t, J=7.5 Hz, CH$_2$CH$_3$), 3.32 (1H, br s, C$_{12b}$-H), 6.95-7.5 (4H, m, Ar), 7.70 (1H, br s, NH); $^{13}$C nmr (CDCl$_3$) $\delta$ 7.65 (CH$_2$CH$_3$), 12.34 (C$_{14}$), 21.99 (C$_{3}$+C$_7$), 29.16 (C$_{1}$), 30.28 (CH$_2$CH$_3$), 39.54 (C$_{13}$), 53.86 (C$_6$), 56.81 (C$_4$), 66.15 (C$_{12b}$), 110.82 (C$_{11}$), 112.10 (C$_{7a}$), 117.96 (C$_8$), 119.50 (C$_9$), 120.68 (C$_{10}$), 121.72 (C$_{12a}$), 136.40 (C$_{11a}$), and 172.84 (COCH$_3$).

mp 166-169°C; ir(KBr) 3380 (indole NH), 2300 cm$^{-1}$ (CN); $^1$H nmr (CDCl$_3$) $\delta$ 0.67 (3H, t, J=7.5 Hz, CH$_2$CH$_3$), 3.32 (1H, br s, C$_{12b}$-H), 6.95-7.5 (4H, m, Ar), 7.70 (1H, br s, NH); $^{13}$C nmr (CDCl$_3$+DMSO-d$_6$, 3:1) $\delta$ 7.65 (CH$_2$CH$_3$), 13.14 (C$_{14}$), 21.92 (C$_{3}$), 22.07 (C$_{7}$), 24.86 (CH$_2$CH$_3$), 32.74 (C$_2$), 33.71 (C$_{13}$), 39.49 (C$_1$), 53.97 (C$_6$), 56.54 (C$_4$), 67.23 (C$_{12b}$), 74.25 (C$_{12a}$), 136.40 (C$_{11a}$), and 172.84 (COCH$_3$).
111.41(Cll), 111.70(C7a), 117.49(C8), 118.92(C9), 120.86(CN), 121.08(C10), 126.87(C7b), 133.08(C12a), 136.91(Clla).


(b) To a solution of 11 (220 mg, 0.74 mmol) in pyridine (5 ml) was added MeSO2Cl (0.2 ml, 2.6 mmol) at 0-5 °C. The reaction mixture was stirred at room temperature for 25 min, then evaporated in vacuo (0.02 mbar). The remaining oil was refluxed in EtOH (15 ml) for 30 min, and then evaporated. The residue was dissolved in DMF (30 ml), NaCN (0.5 g, 1.02 mmol) was added, and the reaction mixture was stirred at 130 °C for 16 h. The solution was poured into cold water and extracted with CH2Cl2. The organic layer was dried and evaporated. The residue was separated by tlc (developed with CHCl3-MeOH 10:1) to afford 16 (18 mg, 7.9 %) and 17 (38 mg, 16.7 %).

1a-Ethyl-1a-(2-hydroxyethyl)-12-methyl-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]-quinolizine [19]. To a solution of 5 (0.50 g, 1.67 mmol) in DMF (20 ml) was added 50 % NaH (0.30 g, 6.2 mmol) which was previously washed with Et2O. The reaction mixture was stirred at room temperature for 15 min. After dropping CH3I (0.2 ml, 3.8 mmol), the stirring was continued for 1 h. The solution was poured into ice-water, and then extracted with CH2Cl2. The organic layer was dried and evaporated. The remaining oil was purified by tlc to give 19 (0.29 g, 55.4 %) as oil. Ms, m/z (relative intensity) 321(83), 311(100), 297(15), 281(65), 211(45), 184(93), 183 (38), 55(17); 1H nmr (CDCl3) δ 0.92 (3H, t, J=7.2 Hz, CH2CH3), 1.1-2.2(8H,m, CH2CH3+C2H2+C3H2+C13-H2), 2.42(1H,brs, OH), 2.5-3.4(6H,m,C4-H2+C6-H2+C7-H2), 3.40(1H,brs,C12b-H), 3.54(3H,s,NCH3), 3.5-3.7(2H,m,C14-H2), 7.0-7.55(4H,m,Ar); 13C nmr (CDCl3) δ 8.21(CH2CH3), 22.74(C7), 33.08(CH2CH3), 34.39(C13), 34.50(NCH3), 34.61(C2), 43.46(C1), 51.85(C6), 56.32(C4), 58.52(C14), 67.73(C12b), 110.00(C11), 114.49(C7a), 117.99(C8), 119.45(C9), 121.57(C10), 127.62(C7b), 136.71(C12a), 140.89(C12a). Elemental analysis data C20H28N2O (312.44) Calc.: C 76.88, H 9.03, N 8.97 Found: C 76.97, H 9.11, N 9.12.

1a-(2-Cyanoethyl)-1a-ethyl-12-methyl-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]-quinolizine [21]. (a) To a solution of 19 (0.29 g, 0.93 mmol) in a mixture of THF (15 ml) and Et3N (0.3 ml) was added MeSO2Cl (0.3 ml, 3.9 mmol). The reaction mixture was stirred at room temperature for 15 min, then filtrated and evaporated. The residue was dissolved in DMF (20 ml), and NaCN (0.4 g, 6.8 mmol) was added. The reaction mixture was stirred at reflux for 15 min, then poured into water and
extracted with CH$_2$Cl$_2$. The organic layer was dried and evaporated. The residue was purified by tlc to give 21 (0.13 g, 43.6 %) mp 110-111 °C (MeOH). Ir(KBr) 2240 cm$^{-1}$ (CN); ms, m/z (relative intensity) 321(22), 282(22), 281(100), 211(10), 184(11).

$^1$H Nmr (CDCl$_3$) δ 0.93(3H, t, J=7.4Hz,CH$_2$CH$_3$), 1.15-2.15(10H, m,C$_2$-H$_2$+C$_3$-H$_2$+CH$_2$CH$_3$+CH$_2$CH$_2$CN), 2.4-3.3(6H, m,C$_4$-H$_2$+C$_6$-H$_2$+C$_7$-H$_2$), 3.42(1H, br s,Cl$_2$b-H), 3.54 (3H,s,NCH$_3$), 7.0-7.55(4H, m,Ar); $^{13}$C nmr (CDCl$_3$) δ 8.04(CH$_2$CH$_3$), 11.47(C14), 21.99(C3), 23.42(C7), 28.18(C13), 29.27(C2), 34.10(NCH$_3$), 37.12(CH$_2$CH$_3$), 42.49(C1), 52.05(C6), 56.45(C4), 66.04(Cl$_2$b), 110.02(C11), 114.24(C7a), 118.24(C8), 119.74(C9), 120.89(CN), 121.81(C10), 127.38(C7b), 136.62(Cl$_2$a), 140.54(Cl$_2$a). Elemental analysis data C$_{21}$H$_{27}$N$_3$ (321.45) Calc.: C 78.46, H 8.47, N 13.07 Found: C 78.29, H 8.51, N 13.33. (b) To a solution of 6 (0.29 g, 0.94 mmol) in DMF (10 ml) wad added 50% NaH (0.3 g, 6.2 mmol), which was previously washed with Et$_2$O. The reaction mixture was stirred at room temperature for 15 min, then CH$_3$I (0.15 ml, 2.8 mmol) was added, and stirring was continued for 1 h. The solution was poured into ice-conc. NH$_4$OH, and the precipitate was collected by suction to afford 21 (0.18 g, 59.4 %).

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