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

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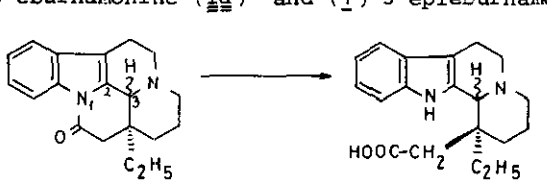
Abstract - Starting from (±)-eburnamonine (1a) and (±)-3-epieburnamonine (1b), compounds 5 and 11 were prepared. The reaction of the mesylate of 5 or 11 with NaCN in DMF led to a mixture of 16 and 17. The structures of the new compounds were elucidated.

In previous articles we have described the synthesis and the strikingly different chemical behaviour of mesylates of 1-ethyl-1-hydroxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo[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, (±)-eburnamonine (1a)[4] and (±)-3-epieburnamonine (1b)[2] were

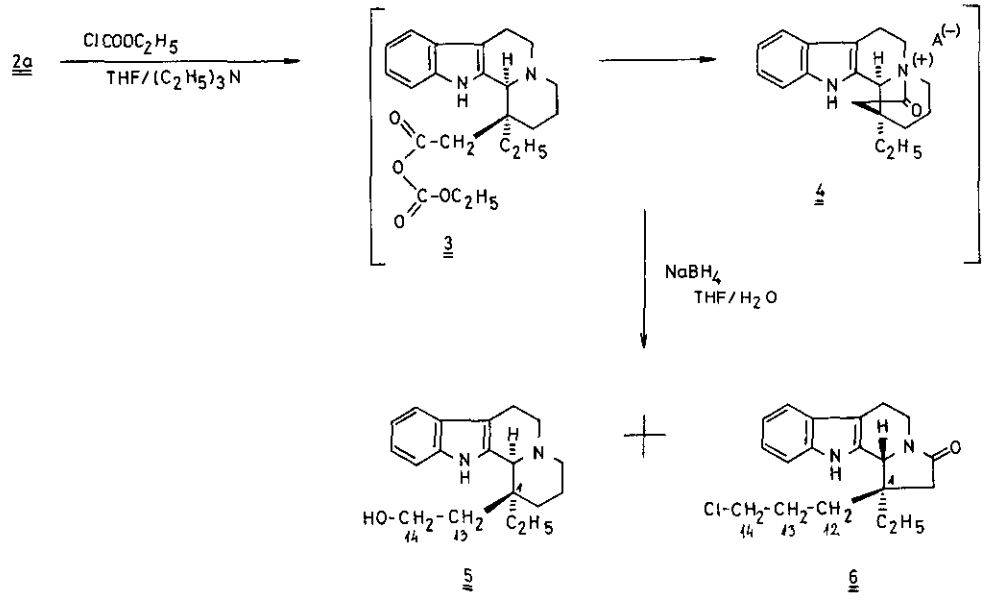


1a 3H-α
b 3H-β

2a 12bH-α
b 12bH-β

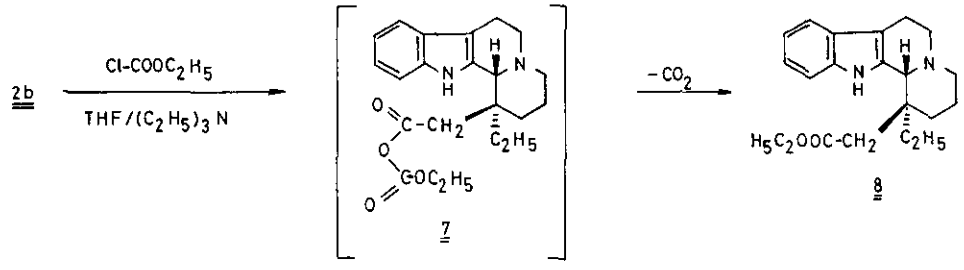
chosen, from which 2a and 2b were prepared.[5,6]

Since reduction of 2a with $LiAlH_4$ failed[6] to afford the hydroxyethyl compound 5, other methods were tried. With $NaBH_4$ in DMSO and in the presence of $MeSO_3H$[7], or with B_2H_6 in THF[8], 1a was recovered. However, the mixed anhydride (3) prepared by reacting 2a with $ClCO_2Et$ in THF in the presence of Et_3N, gave on reduction with $NaBH_4$[9] the expected compound (5) in 37.8 % yield.

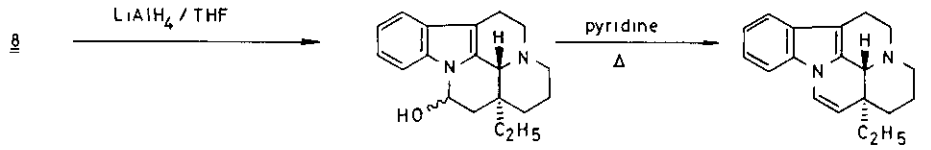


As a by-product the indoloindolizine derivative (6)[10] was isolated. When the salt ($Et_3N \cdot HCl$), precipitated in the first step, was filtered off, the percentage of 5 increased from 37.8 % to 59.9 %.

Performing the same reaction sequence starting from the 3β-epimer 2b, the mixed anhydride (7) formed in the first step was unstable and gave rise by elimination of CO_2 to the ester 8[11] in 79.7 % yield.

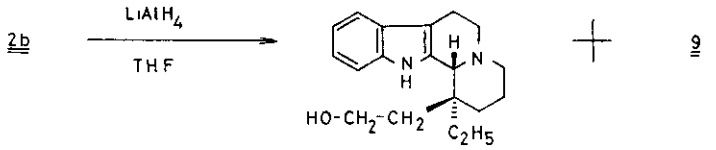


Reduction of 8 with $LiAlH_4$ resulted in the formation of a mixture of (±)-3-epi-eburnamine and (±)-3-epiisoeburnamine (9),[12] which were converted by refluxing in pyridine to (±)-3-epieburnamenine (10).[13]



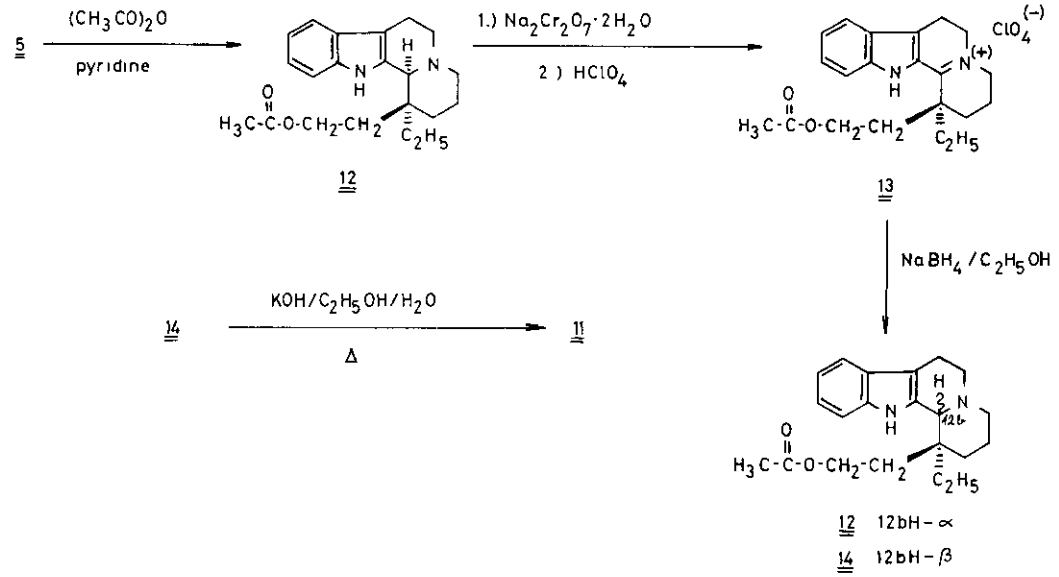
9 10

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

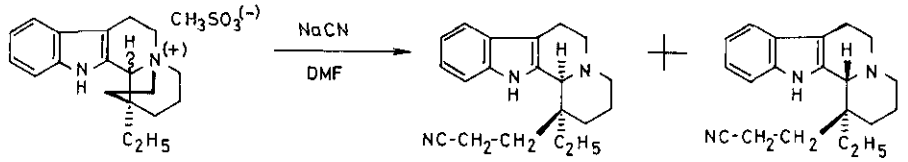


11

An alternative route to 11 involves acylation of 5 in pyridine with Ac_2O followed by oxidation of 12 in AcOH with $Na_2Cr_2O_7 \cdot 2H_2O$.[14] The isolated iminium salt (13) was reduced[15] in EtOH with $NaBH_4$ to give a mixture of two epimeric acetates 12 and 14 (ratio = 1:1.5, yield = 77.3 %). After separation, hydrolysis of the latter gave rise to 11.



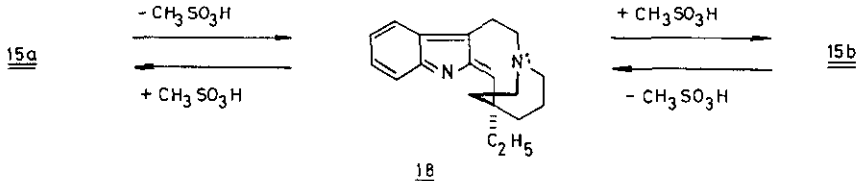
The mesylates (15a,b) derived from 5 and 11 were prepared, and then each of the pure stereoisomeric salts were allowed to react with NaCN in DMF.



15a 12bH-α
b 12bH-β

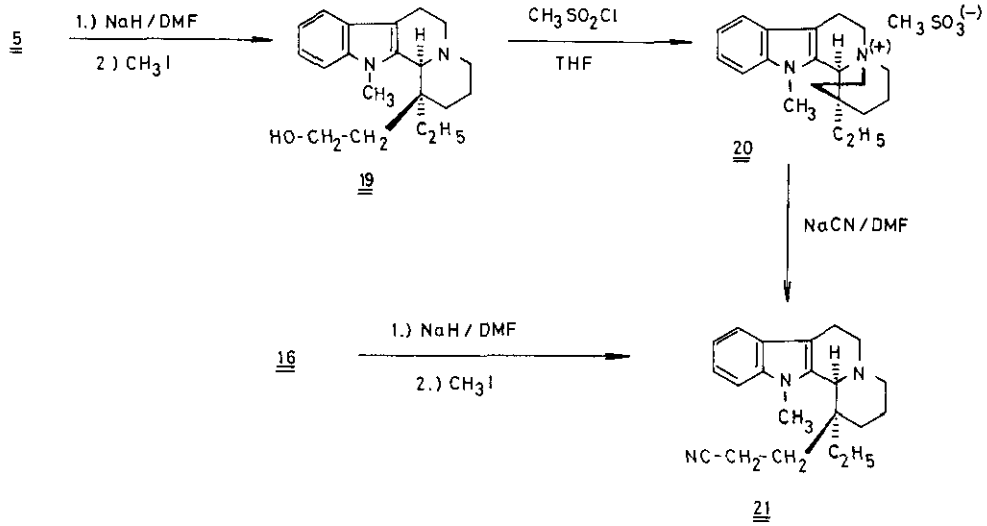
16 17

A mixture of epimers 16 and 17[16] 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]



18

To support our assumption we prepared the N_{ind} - methyl derivative (19), from which the mesylate salt 20 was preapred. Reaction of the latter with NaCN in DMF afforded - as expected - a single product (21), i.e., no epimerisation occurred.



19 20 21

Compound 21 was also prepared by the selective methylation of 16. No reaction of 15 with $Zn(CN)_2$ (*cf.*[2]) was observed.

We can conclude from the above investigations that the mesylates (i.e. the quaternary salts 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 ^1H- and ^{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_4Si. 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 $PF_{254+366}$) developed with C_6H_6-MeOH 10:1.4 and eluted with CH_2Cl_2-MeOH (10:1). The organic layers were dried over $MgSO_4$.

1β-Carboxymethyl-1α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]quinolizine (2a). To a solution of 1a (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 2a (3.07 g, 96.4 %) as white powder, mp 203-206 °C (decomp.)

1β-Carboxymethyl-1α-ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizine (2b). To a solution of 1b (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 2b (0.98 g, 92.4 %), mp 148-151 °C (decomp.)

Reduction of 2a via Its Anhydride 3. To a suspension of 2a (2.00 g, 6.40 mmol) in THF (200 ml) were added Et_3N (2.0 ml, 14.3 mmol) and $ClCO_2Et$ (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 $NaBH_4$ (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 % $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried and evaporated. The remaining oil was crystallized from MeOH to yield 5 (0.82 g, 42.9 %) as white powder, mp 176-179 °C. Ms, m/z (relative intensity) 298(89), 297(100), 283(14), 267(52), 197(49), 185(18), 170(67), 115(10); ^{1}H nmr ($CDCl_3$) δ 1.10 (3H,t,J=7.5 Hz, $CH_2\underline{CH_3}$), 3.33(1H,br s,C12b-H), 3.43 (1H, ddd, J_{gem}=11.5 Hz, C14-$\underline{H}_A\underline{H}_B$), 3.70(1H,ddd, J_{vic}=10.5 +4.0 Hz, C14-$H_A\underline{H}_B$), 5.6 (1H, br s,OH), 6.95-7.5(4H,m,Ar), 7.8 (1H,br s, NH); ^{13}C nmr ($CDCl_3$) δ 8.31 ($CH_2\underline{CH_3}$), 21.54(C7), 22.94(C3), 32.64*(C2), 34.94*($\underline{CH_2}CH_3$), 38.39(C13), 40.73(C1), 54.11(C6), 56.49(C4), 58.75(C14), 67.42(C12b), 110.71(C11), 111.96(C7a), 118.08(C8), 119.38 (C9), 121.63(C10), 126.94(C7b), 132.63(C12a), 136.38(C11a)/* may be interchanged/. Elemental analysis data $C_{19}H_{26}N_2O$ (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 5 (0.32 g, 17.0 %), and 6 (0.35 g, 16.5 %) mp 202-203 °C (MeOH). Ir(KBr) 3200 (indole NH), 1675 cm^{-1} (amide C=O); ms, m/z (relative intensity) 332(36), 330 (100), 303(6), 301(16), 253(17), 171(32), 170(55), 169(52), 143(16), 115(10); ^{1}H nmr ($CDCl_3$) δ 0.68(3H,t,J=7.2 Hz, $CH_2\underline{CH_3}$), 1.31(2H,q, $\underline{CH_2}CH_3$), 2.36 (1H,d,J_{AB}= 16 Hz, C2-$\underline{H}_A\underline{H}_B$), 2.46 (1H,d,C2-$H_A\underline{H}_B$), 2.6-3.1 (3H,m,C6-$H_2$+C5-$\underline{H}_A\underline{H}_B$), 3.67 (2H,m, C14-$H_2$), 4.54 (1H,m,C5-$H_A\underline{H}_B$), 4.79 (1H,br s, C11b-H), 7.0-7.6 (4H,m,Ar), 8.11 (1H, br s), (NH); ^{13}C nmr ($CDCl_3$) δ 8.30 ($CH_2\underline{CH_3}$), 21.03(C6), 27.52 ($\underline{CH_2}CH_3$), 28.37(C13), 34.96(C12), 37.68(C5), 41.21(C2), 44.40(C1), 45.34(C14), 62.52(C11b), 110.50(C6a), 111.10(C10), 118.27(C7), 119.79(C8), 122.22(C9), 126.76(C6b), 129.82(C11a), 136.69 (C10a), 172.38(C3). Elemental analysis data $C_{19}H_{23}ClN_2O$ (330.84) Calc.: C 68.97, H 7.01, N 8.47 Found: C 69.02, H 7.13, N 8.28.

1β-(Ethoxycarbonyl)methyl-1α-ethyl-1,2,3,4,6,7,12,12bβ-octahydro[2,3-a]quinolizine (8). To a solution of 2b (0.92 g, 2.94 mmol) in THF (100 ml) were added Et_3N (2.0 ml, 14.3 mmol) and $ClCO_2Et$ (1.0 ml, 10.5 mmol). The reaction mixture was stirred at room temperature for 30 min. The precipitate was filtered, and the filtrate was evaporated *in vacuo*. The residue was crystallized from MeOH to give 8 (0.80 g, 79.7 %) as white crystals, mp 134-135 °C. Ir(KBr) 3280 (indole NH), 1695 cm^{-1} (C=O), ms, m/z (relative intensity) 340(76), 339(100), 338(33), 325(12), 311(10), 295(11), 267(36), 197(44), 170(45), 169(31). ^{1}H Nmr ($CDCl_3$) δ 0.66(3H,t, J=7.5 Hz, $CH_2\underline{CH_3}$), 1.33 (3H,t,J=7.0 Hz, $CO_2CH_2\underline{CH_3}$), 3.34 (1H,br s,C12b-H), 4.27 (2H,q,$CO_2\underline{CH_2}CH_3$), 6.95-7.5(4H,m,Ar), 9.51(1H,br s, NH); ^{13}C nmr ($CDCl_3$) δ 7.15

($CH_2\underline{CH}_3$), 14.35($CO_2CH_2\underline{CH}_3$), 22.48(C3+C7), 24.95($\underline{CH}_2CH_3$), 32.79(C2), 41.41(C1), 43.09 (C13), 53.54(C6), 56.61(C4), 61.10($CO_2\underline{CH}_2CH_3$), 66.91(C12b), 111.14(C11), 112.34 (C7a), 117.37(C8), 119.03(C9), 121.14(C10), 127.35(C7b), 133.65(C12a), 136.76 (C11a), 174.38($\underline{C}OOC_2H_5$). Elemental analysis data $C_{21}H_{28}N_2O_2$ (340.45) Calc.: C 74.08, H 8.29, N 8.23 Found: C 74.17, H 8.37, N 8.38.

Eburnamenine (3β, 16α)(10). To a suspension of $LiAlH_4$ (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 9 (0.34 g, 78.1 %) mp 227-229 °C (MeOH). Ms, m/z (relative intensity) 296(73), 295(100), 268(21), 249(5). 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 9 (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); ^{1}H nmr ($CDCl_3$) δ 0.70(3H,t, J=7.5 Hz, $CH_2\underline{CH}_3$), 5.16 (1H,d,J=7.6 Hz, C15-H), 6.90 (1H,d, C14-H), 6.95-7.5(4H,m,Ar); ^{13}C nmr ($CDCl_3$) δ 8.07($CH_2\underline{CH}_3$), 21.47(C6), 21.74(C18), 23.47 ($\underline{CH}_2CH_3$), 30.58(C17), 37.74(C16), 53.55(C5), 55.62(C19), 65.84(C3), 107.05 (C7), 108.63(C12), 117.79(C15), 118.46(C9), 119.87(C10), 120.15(C14), 121.18(C11), 128.32(C8), 132.62(C2), 134.37(C13). Elemental analysis data $C_{19}H_{22}N_2$ (278.39) Calc.: C 81.97, H 7.97, N 10.06 Found: C 82.03, H 8.07, N 10.19.

Reduction of 2b. To a suspension of 2b (2.00 g, 6.40 mmol) in THF (100 ml) was added $LiAlH_4$ (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 CH_2Cl_2 (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(39), 237(8), 197(32), 185(16), 170(38), 169(27); ^{1}H nmr ($CDCl_3$) δ 0.65 (3H,t,J=7.5 Hz, $CH_2\underline{CH}_3$), 3.47(1H,br s, C12b-H), 4.00(2H,m,C14-H_2), 6.95-7.5(4H,m,Ar), 9.12(1H,br s, indole NH); ^{13}C nmr ($CDCl_3$+DMSO-d_6, 3:1) δ 7.25($CH_2\underline{CH}_3$), 22.34(C3+C7), 25.46($\underline{CH}_2CH_3$), 32.31(C2), 39.37(C1), 39.78(C13), 53.81(C6), 56.68(C4), 57.08(C14), 66.54(C12b), 110.83(C7a),

111.01(C11), 117.27(C8), 118.46(C9), 120.49(C10), 127.04(C7b), 134.89(C12a), 136.37(C11a). Elemental analysis data $C_{19}H_{26}N_2O$ (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 9 (0.48 g, 25.3 %) and 11 (0.25 g, 13.1 %, total yield= 0.82 g, 42.9 %).

1β-(2-Acetyloxyethyl)-1α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]quinolizine (12). To a solution of 5 (1.01 g, 3.38 mmol) in pyridine (10 ml) was added Ac_2O (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 12 (0.89 g, 77.2 %) as white crystals, mp 128-131 °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). ^1H Nmr ($CDCl_3$) δ 1.17(3H,t,J=7.5 Hz, $CH_2\underline{CH_3}$), 1.93(3H,s,$COCH_3$), 3.32(1H,br s, C12b-H), 4.02(2H,m,C14-H_2), 7.0-7.5(4H,m,Ar), 7.8(1H,br s, NH); ^{13}C nmr ($CDCl_3$) δ 8.11($CH_2\underline{CH_3}$) 20.90($CO\underline{CH_3}$), 22.04*(C3), 22.30*(C7), 31.62($\underline{CH_2}CH_3$), 32.05+(C13), 32.80+(C2), 39.44(C1), 54.04(C6), 56.73(C4), 61.34(C14), 66.70(C12b), 110.83(C11), 112.07(C7a), 117.86(C8), 119.32(C9), 121.50(C10), 126.99(C7b), 133.34(C12a), 136.28(C11a), 170.86($\underline{C}OCH_3$)/*,+ may be interchanged/. Elemental analysis data $C_{21}H_{28}N_2O_2$ (340.45) Calc.: C 74.08, H 8.29, N 8.23 Found: C 74.11, H 8.11, N 8.37.

Oxidation of 12. To a solution of 12 (0.89 g, 2.61 mmol) in AcOH (5 ml) was added $Na_2Cr_2O_7 \cdot 2H_2O$ (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 which were collected by suction and washed with water and EtOH to afford 13 (0.50 g, 43.6 %) mp 160-162 °C (EtOH). Anal. Calcd (found) for $C_{21}H_{27}ClN_2O_6$: 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=$\overset{+}{N}$=).

Reduction of 13. To a suspension of $NaBH_4$ (0.50 g, 13.2 mmol) in EtOH (70 ml) was added 13 (0.50 g, 1.14 mmol) in small portions at 0 °C. The reaction mixture was stirred for 2 h, then acidified with 1M HCl and evaporated in vacuo. The residue was treated with saturated Na_2CO_3, and extracted with CH_2Cl_2. The organic layer was dried, evaporated, and separated by tlc to afford 12 (0.12 g, 30.9 %), and 14 (0.18 g, 46.4 %) mp 180 °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 ($CDCl_3$) δ 0.67(3H,t J=7.5 Hz, $CH_2\underline{CH}_3$), 2.15(3H,s,$COCH_3$), 3.30 (1H br s, C12b-H), 4.12 (1H,ddd,ΣJ=12.2+11.0+5.6 Hz, C14-$\underline{H}_A\underline{H}_B$), 4.80 (1H,ddd,ΣJ=12.2+10.6+5.2 Hz,C14-$\underline{H}_A\underline{H}_B$), 6.95-7.5(4H,m,Ar), 9.64 (1H,br s, NH); ^{13}C nmr ($CDCl_3$) δ 7.00($CH_2\underline{CH}_3$), 21.09($CO\underline{CH}_3$), 22.24(C3+C7), 25.27 ($\underline{CH}_2CH_3$), 32.35(C2), 36.04(C13), 39.30(C1), 54.01(C6), 56.89(C4), 62.34(C14), 66.74(C12b), 111.21(C11), 111.51(C7a), 117.54(C8), 118.87(C9), 121.11(C10), 126.66 (C7b), 132.69(C12a), 136.79(C11a), 172.84($\underline{C}OCH_3$).

1α-Ethyl-1β-(2-hydroxyethyl)-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizine (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 %).

1β-(2-Cyanoethyl)-1α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]quinolizine (16) and 1β-(2-cyanoethyl)-1α-ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]-quinolizine (17). (a) A solution of 5 (0.33 g, 1.11 mmol) in pyridine (6 ml) was cooled to 0 °C, and $MeSO_2Cl$ (0.3 ml, 3.9 mmol) 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_2Cl_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.[16] mp 166-169 °C/; ir(KBr) 3380 (indole NH), 2300 cm^{-1} (CN); ^{1}H nmr ($CDCl_3$) δ 1.15 (3H,t,J=7.5 Hz,$CH_2\underline{CH}_3$), 3.32(1H,br s, C12b-H), 6.95-7.5(4H,m,Ar), 7.70(1H,br s, NH); ^{13}C nmr ($CDCl_3$) δ 7.89($CH_2\underline{CH}_3$), 11.51(C14), 21.99(C3+C7), 29.16(C13), 30.28 ($\underline{CH}_2CH_3$), 32.95(C2), 39.54(C1), 53.86(C6), 56.81(C4), 66.15(C12b), 110.82(C11), 112.10(C7a), 117.96(C8), 119.50(C9), 120.68(CN), 121.72(C10), 126.74(C7b), 132.75 (C12a), 136.08(C11a); and 17 (0.05 g, 14.7 %) mp 228-229 °C (MeOH) /lit.[16] mp 228-229 °C/; ir(KBr) 3350 (indole NH), 2300 cm^{-1} (CN). ^{1}H Nmr ($CDCl_3$) δ 0.67 (3H,t,J=7.5 Hz,$CH_2\underline{CH}_3$), 3.24 (1H,br s, C12b-H), 6.95-7.5(4H,m,Ar), 7.70(1H,br s, NH); ^{13}C nmr ($CDCl_3$+DMSO-d_6,3:1) δ 7.65($CH_2\underline{CH}_3$), 12.34(C14), 21.92(C3), 22.07(C7), 24.86($\underline{CH}_2CH_3$), 32.74(C2), 33.71(C13), 39.49(C1), 53.97(C6), 56.54(C4), 67.23(C12b),

111.41(C11), 111.70(C7a), 117.49(C8), 118.92(C9), 120.86(CN), 121.08(C10), 126.87 (C7b), 133.08(C12a), 136.91(C11a). Elemental analysis data $C_{20}H_{25}N_3$ (307.42) Calc.: C 78.13, H 8.20, N 13.67 Found: C 78.36, H 8.39, N 13.38. (b) To a solution of 11 (220 mg, 0.74 mmol) in pyridine (5 ml) was added $MeSO_2Cl$ (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 CH_2Cl_2. The organic layer was dried and evaporated. The residue was separated by tlc /developed with $CHCl_3$-MeOH (10:1)/ to afford 16 (18 mg, 7.9 %) and 17 (38 mg, 16.7 %).

1α-Ethyl-1β-(2-hydroxyethyl)-12-methyl-1,2,3,4,6,7,12,12bα-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 Et_2O. The reaction mixture was stirred at room temperature for 15 min. After dropping CH_3I (0.2 ml, 3,8 mmol), the stirring was continued for 1 h. The solution was poured into ice-water, and then extracted with CH_2Cl_2. 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); ^{1}H nmr ($CDCl_3$) δ 0.92 (3H,t,J=7.2 Hz, $CH_2\underline{CH_3}$), 1.1-2.2(8H,m, $\underline{CH_2}CH_3$+C2-H_2+C3-H_2+C13-H_2), 2.42(1H,br s, OH), 2.5-3.4(6H,m,C4-H_2+C6-H_2+C7-H_2), 3.40(1H,br s,C12b-H), 3.54(3H,s,NCH_3), 3.5-3.7(2H,m,C14-H_2), 7.0-7.55(4H,m,Ar); ^{13}C nmr ($CDCl_3$) δ 8.21($CH_2\underline{CH_3}$), 22.74(C7), 33.08($\underline{CH_2}CH_3$), 34.39(C13), 34.50(NCH_3), 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(C11a). Elemental analysis data $C_{20}H_{28}N_2O$ (312.44) Calc.: C 76.88, H 9.03, N 8.97 Found: C 76.97, H 9.11, N 9.12.

1β-(2-Cyanoethyl)-1α-ethyl-12-methyl-1,2,3,4,6,7,12,12bα-octahidroindolo[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 Et_3N (0.3 ml) was added $MeSO_2Cl$ (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 h, then poured into water and

extracted with CH_2Cl_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). ^1H Nmr ($CDCl_3$) δ 0.93(3H,t,J=7.4Hz,$CH_2\underline{CH_3}$), 1.15-2.15(10H,m,C2-H_2+C3-H_2+$\underline{CH_2}CH_3$+CH_2CH_2CN), 2.4-3.3(6H,m,C4-H_2+C6-H_2+C7-H_2), 3.42(1H,br s,C12b-H), 3.54 (3H,s,NCH_3), 7.0-7.55(4H,m,Ar); ^{13}C nmr ($CDCl_3$) δ 8.04($CH_2\underline{CH_3}$), 11.47(C14), 21.99(C3), 23.42(C7), 28.18(C13), 29.27(C2), 34.10(NCH_3), 37.12($\underline{CH_2}CH_3$), 42.49(C1), 52.05(C6), 56.45(C4), 66.04(C12b), 110.02(C11), 114.24(C7a), 118.24(C8), 119.74(C9) 120.89(CN), 121.81(C10), 127.38(C7b), 136.62(C12a), 140.54(C11a). 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 16 (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_2O. The reaction mixture was stirred at room temperature for 15 min, then CH_3I (0.15 ml, 2.8 mmol) was added, and stirring was continued for 1 h. The solution was poured into ice-conc. NH_4OH, and the precipitate was collected by suction to afford 21 (0.18 g, 59.4 %).

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