SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. XLIII[1]. UNEXPECTED REARRANGEMENT OF 3-ACYLINDOLENINES

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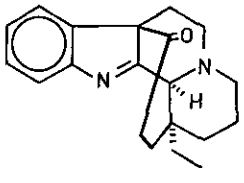
Abstract - The stable 3-acylindolenine derivative (1) was transformed to new heterocyclic compounds (7,9) through unusual rearrangements.

Recently, we reported the synthesis of the 3-acylindolenine derivative 1 *via* intramolecular acylation[2]. Our subsequent studies on the chemical behaviour of this molecule disclosed a remarkable reluctance of the oxo group towards usual carbonyl reactions. Thus, treatment of 1 with $NaBH_3CN$ in CF_3COOH has left the keto function intact and led, rather, to the reduction of the C-N double bond giving product 2 (in addition to minor amounts of 3).



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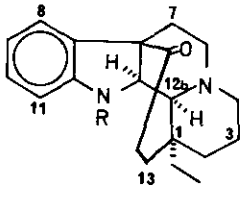
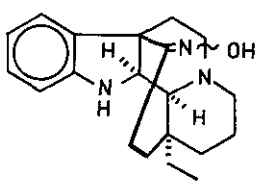


2 R=H

3 R=CH_2CF_3

With the conjugated double bond thus eliminated, much of the regular chemical reactivity of oxo group could be restored: reaction of 2 with hydroxylamine gave

the oxime 4 while the reduction of 2 with $LiAlH_4$ afforded the epimeric alcohols 5 and 6.



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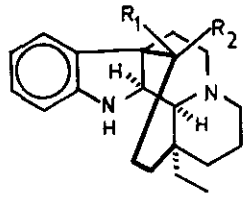
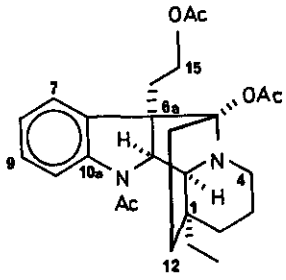


	R_1	R_2
5	HO	H
6	H	OH

Surprisingly, however, acetylation of 2 with $AcOH/Ac_2O$ mixture gave 7, a rearranged triacetyl derivative, in high yield rather than the expected N-acetyl-2. In its turn, when hydrolized with sodium hydroxide in ethanol under reflux, 7 is converted into 8 (40.5 %) and 9 (47.5 %). A closer study of this reaction disclosed that products 8 and 9 are in equilibrium and can be mutualy interconverted. Refluxing of either 8 or 9 in ethanol affords the same product mixture in which the ratio of 8:9 is approx. 2.2:1.



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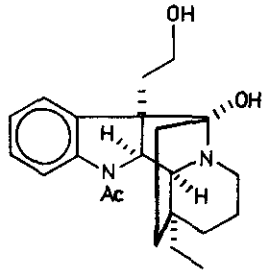

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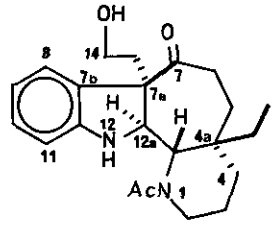
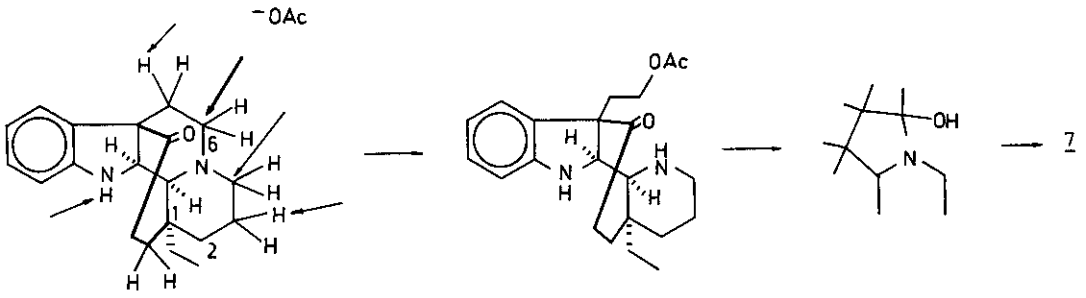


9

The constitution and stereochemistry of the new products as portrayed in 7-9 were inferred from high field ^1H (400 MHz) and ^{13}C (100.6 MHz) nmr spectra. The assignment of the resonances in terms of proton and carbon chemical shifts, δ_H, δ_C ^{13}C-multiplicities and interproton couplings, J_{HH}, was performed by means of standard one- and two-dimensional (1D, 2D) FT nmr techniques and the fully assigned spectral parameters are collected in the Experimental. First, proton-proton chemical shift correlation (COSY) experiment[3] was run to establish ^1H-^1H connectivities within the molecular framework and, then, these pieces of informa-

tion, combined with results of carbon-proton chemical shift correlation experiment (mediated by one-bond C-H couplings)[3] served as the starting point for the determination of the carbon-carbon connectivities. Carbon-carbon sequences involving quaternary ^{13}C atoms were inferred from a series of carbon-proton chemical shift correlation experiments in which the relevant time periods were systematically varied such as to obtain observable proton-to-carbon magnetization transfer for the expected range (1.5 to 7 Hz) of multiple bond $^{n}J_{CH}$ (n=2,3,4) couplings[3]. Examination of the collected spectral parameters shows that these are best accommodated within the proposed formulas 7, 8 and 9. The most relevant stereochemical feature of 7 and 8 follows from the value of $^{3}J_{11a,11b}$ (6.7 Hz) which suggests that these protons assume a *gauche* steric disposition. The stereochemistry thus inferred has received further support by the occurrence of sizable four-bond ^{1}H-^{1}H couplings between H_{12eq} and H_{11b} (1.7 Hz), as well as between H_{12ax} and H_{2ax} (2.3 Hz). Formation of 9 gives rise to major variations in the stereochemistry of the molecule. This is clearly reflected by the 9.9 Hz assumed by the vicinal coupling $^{3}J_{12a,12b}$ in 9, a value characteristic of protons in *trans* relative orientation. Corroborative evidence for the resulting stereochemistry as shown in 9 was readily available from selective ^{1}H-{^{1}H} NOE experiments. Preirradiation of the resonance due to H-12a resulted in signal enhancements of resonances due to H-5_{α}, H-13B, H-2_{α}, H-4_{α} and H-14A, while performing the same experiment with the preirradiation frequency set at the resonance of H-12b gave rise to enhanced signal intensities for protons N-COC$\underline{H}_3$ and C$\underline{H}_A$H$_B$CH$_3$. It can be seen that the spatial proximities reflected by the observed NOE effects are best accounted for by the stereochemistry portrayed in 9. Thus two unexpected rearrangements (2 ⟶ 7 and 8 ⟶ 9) were observed. In the first case (2 ⟶ 7) the rearrangement presumably starts by the attack of an acetate anion at C_6, the latter site being in α-position to the protonated nitrogen. In principle, the attack could also occur at the proton of the C_7-H bond causing a Hoffmann type elimination[4], or at several other electrophilic centers of the molecule. Position C_6 is apparently favoured owing to the through-space neighbouring group effect of the sterically close keto-function[5]. The ring opening is followed by the formation of the aminocarbinol function and subsequent O-acetylation. Again, the last step is rather surprising since under the given conditions pseudobasic aminocarbinols usually afford the corresponding iminium salt[6]. In our case, however, formation of the bridge-head double bond is unfavoured

as Bredt's rule points out.



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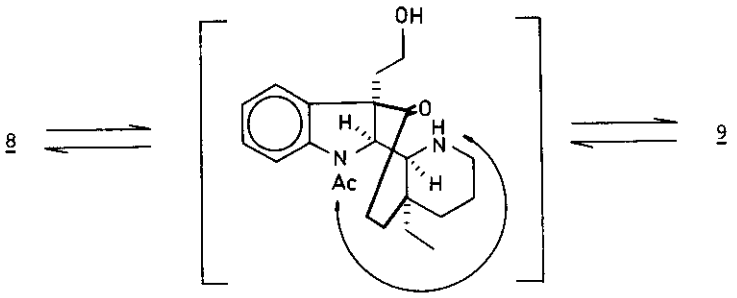
Compound 7 can in principle also be formed through an elimination-addition mechanism.



10

The second rearrangement, 8 ⇌ 9, can be rationalized by assuming the formation of 10, an intermediate ketone, which is in equilibrium with both 8 and 9. The ready conversion of 8 ⇌ 10 is the consequence of the destabilization of the amino-carbinol function by deacetylation, while transition 10 ⇌ 9 is governed by the facile transacetylation of the two, sterically proximate amino groups.

EXPERIMENTAL

Infrared spectra were recorded on a Nicolet 7199 Fourier transform spectrometer and the frequencies (cm^{-1}) of significant peaks are reported. All nmr spectra were run on deuteriochloroform solutions at ambient temperature using a Varian Associates model XL-100 for low-field and model XL-400 instrument for high field conventional and 2D experiments. Selective $^{1}H\text{-}\{^{1}H\}$NOE measurements were performed in the difference

mode. Mutual ^1H - ^1H couplings are given only once, at their first occurence in the Experimental. Mass spectra were recorded on an AEI MS-902 mass spectrometer (70 eV, ion source temp. 200 °C, direct inlet). The purification of the compounds was carried out by column chromatography on silica gel (Merck Kieselgel 60, 0.063 - 0.2 mm).

(-)-(1S:7aR:12aS:12bS)-1-Ethyl-15-oxo-1,2,3,4,6,7,7a,12,12a,12b-decahydro-1,7a-propanoindolo[2,3-a]quinolizin 2

(-)-(1S:7aR:12aS:12bS)-1-Ethyl-15-oxo-12-(2,2,2-trifluoro-ethyl)-1,2,3,4,6,7,7a,12,12a,12b-decahydro-1,7a-propanoindolo[2,3-a]quinolizin 3.

A solution of 1 (10.0 g, 0.0324 mol) in CF_3COOH (100 ml) was cooled to -10 °C, and $NaBH_3CN$ (5.0 g, 0.0798 mol) was added in small portions in argon atmosphere. The reaction mixture was stirred at -10 ° for 1 h and at room temperature overnight, then poured onto ice (500 g). The organic layer was separated and the aqueous phase was extracted with $CHCl_3$ (2 x 300 ml). The combined extracts were neutralized by 5 % $NaHCO_3$, then dried over $MgSO_4$ and evaporated in *vacuo*, the residue was dissolved in EtOH to afford 2 (5.45 g, 54 %); mp 237-238 °C (ethanol); $[\alpha]_D^{25}$-557.4° (c = 1.0, $CHCl_3$); ms (m/z, %) 310 (M^+, 8.5), 254 (11), 180 (89), 144 (11), 143 (14), 124 (100); ir (KBr), (ν, cm^{-1}) 3350 (NH, indoline), 2805, 2748 (Bohlmann bands), 1686 (CO), 1603, 762 (aromatics); ^1H-nmr (δ, ppm) 0.92 (3H, t, J = 7.5 Hz, $CH_2\underline{CH}_3$), 1.93 (2H, q, $\underline{CH}_2CH_3$), 2.55 (1H, d, $J_{12a,12b}$ = 8.0 Hz, C12b-H), 1.1-2.9 (12H, m, C2-H_2 + C3-H_2 + C4-H_2 + C7-H_2 + C13-H_2 + C14-H_2), 3.0-3.5 (2H, m, C6-H_2), 3.93 (1H, br d, NH), 4.16 (1H, dd, $J_{12a,NH}$ = 4.0 Hz, C12a-H), 6.6 - 7.2 (4H, m, aromatics); ^{13}C-nmr (δ, ppm) 7.9 ($CH_2\underline{C}H_3$), 21.2 (C3), 29.3 ($\underline{C}H_2CH_3$), 29.7 (C13), 31.8 (C7), 34.9 (C2), 37.8 (C14), 40.0 (C1), 47.7 (C6), 56.1 (C4), 57.4 (C7a), 65.5 (C12a), 69.0 (C12b), 110.9 (C11), 119.6 (C9), 124.2 (C8), 128.3 (C10), 129.6 (C7b), 152.3 (C11a), 208.8 (C15); Calc. for $C_{20}H_{26}N_2O$ (310.43) C, 77.38; H, 8.44; N, 9.03. Found C, 77.42; H, 8.40; N, 9.05. The mother liquor was concentrated and subjected to column chromatography (EtOAc-Et_2NH 9:1 v/v, R_f 0.4) to give 3 (2.3 g, 18 %); mp 138-140 °C (ethanol); $[\alpha]_D^{25}$- 443.4 ° (c = 1.0, $CHCl_3$); ms (m/z, %) 392 (M^+, 7), 336 (10), 226 (7), 225 (7), 180 (100), 124 (71); ir (KBr), (ν, cm^{-1}) 2799, 2741 (Bohlmann bands), 1700 (CO, amide), 1602 (aromatics), 1262, 1147, 1130 (CF_3), 752 (aromatics); ^1H-nmr (δ, ppm) 0.87 (3H, t, J = 7.4 Hz, $CH_2\underline{CH}_3$), 2.74 (1H, d,

$J_{12a,12b}$ = 6.7 Hz, C12b-H), 1.0-3.5 (16H, m, C2-H_2 + C3-H_2 + C4-H_2 + C6-H_2 + + C7-H_2 + C13-H_2 + C14-H_2 + $C\underline{H}_2CH_3$), 3.88 (1H, dq, J_{gem} = 16.2 Hz, $J_{H,F}$ = 9.2 hz, $NC\underline{H}_A\underline{H}_BCF_3$), 4.05 (1H, dq, $J_{H,F}$ = 10.0 Hz, $NCH_A\underline{H}_BCF_3$), 4.06 (1H, d, C12a-H), 6.65-7.25 (4H, m, aromatics); ^{13}C-nmr (δ, ppm) 7.5 ($CH_2\underline{C}H_3$), 20.5 (C3), 26.8 ($\underline{C}H_2CH_3$), 28.9 (C13), 32.9 (C7), 35.3 (C2), 37.1 (C14), 40.6 (C1), 47.7 (C6), 49.8 ($^2J_{C,F}$ = 30.2 Hz, $N\underline{C}H_2CF_3$), 56.3 (C4), 57.5 (C7a), 69.2 (C12b), 69.4 (C12a), 110.5 ($^5J_{C,F}$ = 1.9 Hz, C11), 121.3 (C9), 124.9 (C8), 125.5 ($^1J_{C,F}$ = 287 Hz, $NCH_2\underline{C}F_3$), 128.7 (C10), 129.4 (C7b), 151.6 (C11a), 209.1 (C15); Calc. for $C_{22}H_{27}F_3N_2O$ (392.46) C, 67.32; H, 6.94; F, 14.52; N, 7.14. Found C, 67.41; H, 6.92; F, 14.70; N, 7.15.

(-)-(1S:7aR:12aS:12bS)-1-Ethyl-15-(hydroxyimino)-1,2,3,4,6,7,7a,12,12a,12b-decahydro-1,7a-propanoindolo[2,3-a]quinolizine 4

A solution of 2 (8.0 g, 0.0258 mol) and $NH_2OH.HCl$ (9.0 g, 0.129 mol) in anhydrous pyridine (70 ml) was refluxed for 24 h then the solvent was removed in *vacuo*. The residue was dissolved in a mixture of $CHCl_3$ (200 ml) and water (100 ml), then treated with saturated Na_2CO_3 solution. The organic layer was separated, the aqueous phase was extracted with $CHCl_3$ (2x100 ml). The combined extracts were dried over $MgSO_4$ and evaporated in *vacuo*. The residue was purified by column chromatography (toluene-Et_2NH 10:1 v/v) to give 4 (3.2 g, 38 %). Light yellow oil; $[\alpha]_D^{25}$-382.3 ° (c = 1.0, $CHCl_3$); ms (m/z, %) 325 (M^+, 22), 308 (22), 307 (30), 306 (22), 267 (100), 195 (69); ir ($CHCl_3$) (ν, cm^{-1}) 3587, 3260 (OH), 3389 (NH), 1607 (aromatics), 935 (NO), 751 (aromatics); ^{1}H-nmr (δ, ppm) 0.89 (3H, t, J = 7.5 Hz, $CH_2C\underline{H}_3$), 1.0-3.4 (17H, m, C2-H_2 + C3-H_2 + C4-H_2 + C6-H_2 + C7-H_2 + C13-H_2 + C14-H_2 + + C12b-H), 3.76 (1H, br s, NH), 4.05 (1H, br d, J = 7.2 Hz, C12a-H), 5.5 (1H, br, N-OH), 6.6-7.2 (4H, m, aromatics); ^{13}C-nmr (δ, ppm) 7.8 ($CH_2\underline{C}H_3$), 20.0 (C3), 20.2 (C14), 30.1^x ($\underline{C}H_2CH_3$), 30.2^x (C13), 34.1 (C7), 35.7 (C2), 39.4 (C1), 47.8 (C6), 50.5 (C7a), 55.9 (C4), 67.5 (C12b), 68.4 (C12a), 110.7 (C11), 120.4 (C9), 124.3 (C8), 127.6 (C10), 134.0 (C7b), 150.7 (C11a), 165.6 (C15); Calc. for $C_{20}H_{27}N_3O$ (325.45) C, 73.81; H, 8.36; N, 12.91. Found C, 73.64; H, 8.27; N, 12.95.

(-)-(1S:7aR:12aS:12bS)-1-Ethyl-15α-hydroxy-1,2,3,4,6,7,7a,12,12a,12b-decahydro-1,7a-propanoindolo[2,3-a]quinolizine 5

(-)-(1S:7aR:12aS:12bS)-1-Ethyl-15β-hydroxy-1,2,3,4,6,7,7a,12,12a,12b-decahydro-1,7a-propanoindolo[2,3-a]quinolizine 6.

$LiAlH_4$ (1.0 g, 0.0264 mol) was suspended in THF (100 ml) in argon atmosphere. A solution of 2 (1.0 g, 0.0032 mol) in THF (25 ml) was added dropwise at reflux temperature within 30 min. The reaction mixture was refluxed for one more hour, then cooled and the excess $LiAlH_4$ was decomposed with water (1 ml), 15 % NaOH (1 ml) and water (3 ml). The precipitated solids were filtrated and washed with $CHCl_3$ (50 ml). The combined filtrates and washings were dried over $MgSO_4$ and evaporated in *vacuo*. The residue was separated by column chromatography (cyclohexane-EtOAc 1:1 v/v). The fraction with higher retention factor (R_f 0.38) was evaporated and crystallized from EtOH to give 5 (0.54 g, 53.6 %); mp 123-126 °C (ethanol); $[\alpha]_D^{25}$ -165.1 ° (c = 1.0, $CHCl_3$); ms (m/z, %), 312 (M^+, 32), 311 (5), 255 (12), 182 (100); ir ($CHCl_3$), (ν, cm^{-1}) 3570 (OH), 3382 (NH), 1024 (C-OH); ^{1}H-nmr (δ, ppm) 0.87 (3H, t, J = 7.5 Hz, $CH_2\underline{CH}_3$), 1.78 (2H, q, $\underline{CH}_2CH_3$), 2.49 (1H, d, $J_{12a,12b}$ = 8.0 Hz, C12b-H), 1.0-2.9 (14H, m, C2-H_2 + C3-H_2 + C4-H_2 + C6-H_2 + + C7-H_2 + C13-H_2 + C14-H_2), 3.5 (2H, br, OH + NH), 4.02 (1H, d, C12a-H), 4.45 (1H, dd, J = 9.6 Hz, 1 Hz, C15-H), 6.6-7.2 (4H, m, aromatics); ^{13}C-nmr (δ, ppm) 8.2 ($CH_2\underline{C}H_3$), 22.2 (C3), 30.6 (C13), 31.6 ($\underline{C}H_2CH_3$), 32.0 (C7), 34.5 (C14), 35.3 (C2), 39.5 (C1), 48.3 (C6), 50.4 (C7a), 56.3 (C4), 66.6 (C12a), 68.9 (C12b), 79.7 (C15), 110.5 (C11), 119.1 (C9), 126.2 (C8), 127.9 (C10), 132.1 (C7b), 152.6 (C11a); Calc. for $C_{20}H_{28}N_2O$ (312.44) C, 76.88; H, 9.03; N, 8.97. Found C, 77.24; H, 8.76; N, 8.96.

The fraction with lower retention factor (R_f 0.22) was evaporated and crystallized from EtOH to give 6 (0.28 g, 27.8 %); mp 206-209 °C (ethanol); $[\alpha]_D^{25}$ -138.1 ° (c = 1.0, $CHCl_3$); ms (m/z, %) 312 (M^+, 17), 311 (15), 182 (100); ir ($CHCl_3$), (ν, cm^{-1}) 3392 (NH), 3170 (OH), 1090 (C-OH); ^{1}H-nmr (δ, ppm) 0.89 (3H, t, J = 7.4 Hz, $CH_2\underline{CH}_3$), 1.80 and 1.90 (2H, dq, $\underline{CH}_A\underline{H}_BCH_3$), 2.51 (1H, d, $J_{12a,12b}$ = 8.0 Hz, C12b-H), 1.0-3.2 (14H, m, C2-H_2 + C3-H_2 + C4-H_2 + C6-H_2 + C7-H_2 + C13-H_2 + C14-H_2), 3.5 (1H, br, NH), 3.55 (1H, br d, J = 6.8 Hz, C15-H), 3.92 (1H, d, C12a-H), 6.25 (1H, br, C15-OH), 6.0-7.15 (4H, m, aromatics); ^{13}C-nmr (δ, ppm) 8.2 ($CH_2\underline{C}H_3$), 22.3 (C3), 26.4 (C13), 27.4 (C7), 31.2 ($\underline{C}H_2CH_3$), 31.3 (C14), 35.0 (C2), 40.7 (C1), 47.9 (C6), 51.4 (C7a), 55.6 (C4), 66.4 (C12a), 69.6 (C12b), 74.8 (C15), 110.4 (C11), 120.0

(C9), 123.5 (C8), 127.3 (C10), 137.2 (C7b), 150.7 (C11a); Calc. for $C_{20}H_{28}N_2O$ (312.44) C, 76.88; H, 9.03; N, 8.97. Found C, 76.77; H, 8.87; N, 8.91.

(-)-6α-Acetoxy-6aα-(2-acetoxyethyl)-11-acetyl-1,2,3,4,6,6a,11aα,11bα-octahydro-1β,6β-ethanoindolizino[1,2-b]indole (7)

A solution of 2 (1.0 g, 3.22 mmol) in Ac_2O (10 ml) and AcOH (1 ml) was refluxed for 3 h, then poured onto ice (50 g). The aqueous mixture was extracted with $CHCl_3$ (3 x 50 ml), the combined extracts were neutralized by 5 % $NaHCO_3$, then washed with water, dried over $MgSO_4$ evaporated in *vacuo*. The residue was crystallized from EtOH to give 7 (1.3 g, 88.8 %); mp 223-225 °C (ethanol); $[\alpha]_D^{25}$ -18° (c=1.0, $CHCl_3$); ms (m/z, %) 454 (M^+,19), 411 (18), 209 (28), 167 (100), 152 (20), 139 (11), 138 (21); ir (KBr), (ν, cm^{-1}) 1738 (two CO, esters), 1671 (CO, amide), 1596 (aromatics), 1248 (two COC, esters), 763 (aromatics); ^{1}H-nmr (δ, ppm) 0.46 (1H, dddd, J_{gem} = 15.0 Hz, $J_{12A,13A}$ = 11.7 Hz, $J_{12A,13B}$ = 8.2 Hz, $J_{12A,2\alpha}$ = 2.3 Hz, C12-H_A), 0.68 (3H, t, J = 7.5 Hz, $CH_2\underline{CH_3}$), 1.17 (1H, dq, J_{gem} = 13.5 Hz, $C\underline{H_A}H_BCH_3$), 1.22 (1H, dddd, $J_{12B,13A}$ = 8.5 Hz, $J_{12B,13B}$ ~ 1 Hz, $J_{12B,11b}$ = 1.7 Hz, C12-H_B), 1.30 (1H, dq, $CH_A\underline{H_B}CH_3$), 1.37 (1H, dddd, J_{gem} = 13 Hz, $J_{2\alpha,3\alpha}$ = 5.8 Hz, $J_{2\alpha,3\beta}$ = 13 Hz, C2-Hα), 1.45 (1H, m, C3-H_A), 1.73 (1H, m, C2-H_β), 1.78 (1H, m, C13-H_A), 1.83 (1H,m, C3-H_B), 1.88 (3H, s, $OCOCH_3$), 1.98 (1H, dt, J_{gem} = 13.9 Hz, J_{vic} = 6.9 Hz, C14-H_A), 2.12 (1H, dt, C14-H_B), 2.20 (3H, s, $OCOCH_3$), 2.39 (3H, s, $NCOCH_3$), 2.68 (1H, ddd, J_{gem}= = 14 Hz, C13-H_B), 2.94 (1H, ddd, J_{gem} = 15.0 Hz, $J_{4\alpha,3\alpha}$ = 5.8 Hz, $J_{4\alpha,3\beta}$ = 13.2 Hz, C4-Hα), 3.36 (1H, ddd, J_{vic} = 6.3 and ~ 1 Hz, C4-Hβ), 3.39 (1H, dd, $J_{11a,11b}$ = = 6.7 Hz, C11b-H), 3.81 (1H, dt, J_{gem} = 11.6 Hz, J_{vic} = 6.9 Hz, C15-H_A), 3.82 (1H, dt, C15-H_B), 4.73 (1H, d, C11a-H), 7.11 (1H, dd, $J_{7,8}$ = 7.7 Hz, $J_{8,9}$ = 7.4 Hz, C8-H), 7.28 (1H, ddd, $J_{9,10}$ = 8.0 Hz, $J_{7,9}$ = 1.0 Hz, C9-H), 7.92 (1H, dd, C7-H), 8.14 (1H, d, C10-H); ^{13}C-nmr (δ, ppm) 7.2 ($CH_2\underline{CH_3}$), 20.8 ($OCO\underline{CH_3}$), 22.0 (C3), 22.1 ($OCO\underline{CH_3}$), 24.3 ($NCO\underline{CH_3}$), 28.6 (C12), 29.8 (C13), 30.8 ($\underline{CH_2}CH_3$), 32.2 (C1), 36.1 (C2), 36.8 (C14), 42.6 (C4), 59.8 (C6a), 60.8 (C15), 65.2 (C11b), 69.0 (C11a), 100.5 (C6), 116.8 (C10), 124.3 (C8), 126.9 (C7), 128.7 (C9), 131.9 (C6b), 144.6 (C10a), 168.8 ($O\underline{C}OCH_3$), 169.4 ($N\underline{C}OCH_3$), 170.6 ($O\underline{C}OCH_3$); (Products 7 and 8 were shown by nmr spectra to occur as ca. 60:40 mixtures of rotational isomers due to the restricted rotation of the N-acetyl group. The data reported here refer to the major component in which the carbonyl oxygen is pointing toward the aromatic ring.) Calc. for $C_{26}H_{34}N_2O_5$ (454.55) C, 68.70; H, 7.54; N, 6.16. Found C, 68.55; H, 7.52;

N, 6.15.

(-)-6α-Hydroxy-6aα-(2-hydroxyethyl)-11-acetyl-1,2,3,4,6,6a,11aα,11bα-octahydro-1β,6β-ethanoindolizino[1,2-b]indole 8

(-)-1-Acetyl-4aβ-ethyl-7aα-(2-hydroxyethyl)-1,2,3,4,4a,5,6,7,7a,12,12aα,12bβ-dodecahydropyrido[3,2':6,7]cyclohept[1,2-b]indole 9

A solution of 7 (8.0 g, 0.0176 mol) and NaOH (16.0 g, 0.4 mol) in 96 % EtOH (700 ml) was refluxed for 2.5 h. The solvent was removed in *vacuo*, the residue was diluted with water (500 ml) and extracted with $CHCl_3$ (3x200 ml). The organic layer was dried over $MgSO_4$ and evaporated in *vacuo*. The residue was separated by column chromatography on Al_2O_3 (CH_2Cl_2:EtOH 10:1 v/v). The fraction with lower retention factor (R_f 0.66) was evaporated and crystallized from ethanol to give 8 (2.6 g, 40.5 %); mp 207-209 °C (ethanol); $[\alpha]_D^{25}$-96.4 ° (c = 1.0, $CHCl_3$); ms (m/z, %) 370 (M^+, 57), 167 (48), 162 (13), 161 (14), 152 (38), 139 (30), 138 (51), 130 (36), 111 (100); ir ($CHCl_3$), (ν, cm^{-1}) 3400 (OH), 3170 (OH), 1656 (CO, amide), 1394 (OH), 1189 (C-O), 1064 (C-O), 600 (OH); ^{1}H-nmr (δ, ppm) 0.57 (1H, m, C12-H_A), 0.72 (3H, t, J = 7.5 Hz, $CH_2\underline{CH_3}$), 1.22 (1H, m, C12-H_B), 1.25 (1H, dq, $\underline{CH_AH_B}CH_3$), 1.33 (1H, m, C2-H_α), 1.42 (1H, dq, $\underline{CH_AH_B}CH_3$), 1.43 (1H, m, C3-H_A), 1.54 (1H, ddd, J_{gem} = = 15 Hz, $J_{14A,15A}$ = 2.0 Hz, $J_{14A,15B}$ = 2.7 Hz, C14-H_A), 1.68 (1H, ddd, J_{gem} = = 14.5 Hz, J_{vic} = 8.2 and ~ 1 Hz, C13-H_A), 1.76 (1H, ddd, J_{gem} = 13 Hz, $J_{2\beta 3\alpha}$ = = 1 Hz, $J_{2\beta 3\beta}$ = 5.5 Hz, C2-H_β), 1.81 (1H, m, C13-H_B), 1.87 (1H, m, C3-H_B), 2.38 (3H, s, $NCOCH_3$), 2.53 (1H, ddd, $J_{14B,15A}$ = 5.0 Hz, $J_{14B,15B}$ = 11.6 Hz, C14-H_B), 2.82 (1H, ddd, J_{gem} = 14.8 Hz, $J_{3\alpha,4\alpha}$ = 5.2 Hz, $J_{3\beta,4\alpha}$ = 12.8 Hz, C4-H_α), 3.38 (1H, dd, $J_{11a,11b}$ = 7.0 Hz, $J_{11b,12B}$ = 1.4 Hz, C11b-H), 3.39 (1H, ddd, $J_{3\alpha,4\beta}$ = = 1 Hz, $J_{3\beta,4\beta}$ = 6.2 Hz, C4-H_β), 3.68 (1H, ddd, J_{gem} = 12.4 Hz, C15-H_A), 3.84 (1H, ddd, C15-H_B), 4.80 (1H, d, C11a-H), 4.55 and 5.3 (1H + 1H, br lines, 2xOH), 7.07 (1H, dd, $J_{7,8}$ = 7.5 Hz, $J_{8,9}$ = 7.0 Hz, C8-H), 7.20 (1H, dd, $J_{7,9}$ = 1 Hz, C7-H), 7.25 (1H, ddd, $J_{9,10}$ = 8.0 Hz, C9-H), 8.12 (1H, d, C10-H); ^{13}C-nmr (δ, ppm) 7.30 ($CH_2\underline{CH_3}$), 21.5 (C3), 24.4 ($NCO\underline{CH_3}$), 27.9 (C12), 31.3 (C13 + $\underline{CH_2}CH_3$), 32.2 (C1), 35.6 (C2), 38.5 (C14), 41.1 (C4), 57.7 (C15), 59.0 (C6a), 65.2 (C11b), 65.7 (C11a), 91.2 (C6), 117.3 (C10), 124.0 (C8), 124.1 (C7), 128.2 (C9), 135.3 (C6b), 143.2 (C10a), 169.7 ($N\underline{C}OCH_3$); Calc. for $C_{22}H_{30}N_2O_3$ (370.48) C,71.32; H, 8.16; N, 7.56. Found C, 71.42; H, 8.23; N, 7.49.

The fraction with higher retention factor (R_f 0.79) was evaporated and crystallized

from EtOH to give 9 (3.1 g, 47.5 %); mp 204-206 °C (ethanol); $[\alpha]_D^{25}$ - 193 ° (c = 1.0, $CHCl_3$); ms (m/z, %) 370 (M^+, 12), 161 (100), 153 (27), 130 (66); ir ($CHCl_3$), (ν, cm^{-1}) 3630 (OH), 3538 (OH, bridged) 3390 (NH, indoline), 1702 (CO), 1643 (CO, amide), 1607, 753 (aromatics); ^{1}H-nmr (δ, ppm) 0.78 (3H, t, J = 7.5 Hz, $CH_2\underline{CH}_3$), 1.24 (1H, dq, J_{gem} = 14.3 Hz, $\underline{CH}_A H_B CH_3$), 1.48 (3H, s, $NCOCH_3$), 1.45-1.55 (2H, m, C3-H_2), 1.51 (1H, m, C4-H_α), 1.66 (1H, dqd, $J_{HB,5\alpha}$ = 1.3 Hz, $CH_A\underline{H}_B CH_3$), 1.72 (1H, m, C4-H_β), 1.76 (1H, ddd, J_{gem} = 15.7 Hz, $J_{5\beta,6\alpha}$ = 4.2 Hz, $J_{5\beta,6\beta}$ = 4.2 Hz, C5-H_β), 1.95 (1H, dddd, $J_{5\alpha,6\alpha}$ = 4.3 Hz, $J_{5\alpha,6\beta}$ = 14.1 Hz, C5-H_α), 2.05 (1H, ddd, J_{gem} = 13.9 Hz, $J_{13A,14A}$ = 4.7 Hz, $J_{13A,14B}$ = 6.0 Hz, C13-H_A), 2.28 (1H, ddd, J_{gem} = = 13.2 Hz, $J_{2\alpha,3\alpha}$ = 4.5 Hz, $J_{2\alpha,3\beta}$ = 10.2 Hz, C2-H_α), 2.35 (1H, ddd, $J_{13B,14A}$ = = 7.6 Hz, $J_{13B,14B}$ = 5.1 Hz, C13-H_B), 2.60 (1H, ddd, J_{gem} = 18.0 Hz, C6-H_β), 2.83 (1H, br, OH), 2.86 (1H, ddd, C6-H_α), 3.21 (1H, d, $J_{12a,12b}$ = 9.9 Hz, C12b-H), 3.46 (1H, dddd, J_{gem} = 11.6 Hz, $J_{14A,OH}$ = 2.5 Hz, C14-H_A), 3.59 (1H, dddd, $J_{14B,OH}$ = = 6.0 Hz, C14-H_B), 3.84 (1H, s, NH), 4.34 (1H, d, C12a-H), 4.73 (1H, br dd, J_{vic} = 2.6 Hz, C2-H_β), 6.62 (1H, ddd, $J_{10,11}$ = 7.9 Hz, $J_{9,11}$ = 1.0 Hz, $J_{8,11}$ = 0.6 Hz, C11-H), 6.82 (1H, ddd, $J_{8,9}$ = 7.6 Hz, $J_{9,10}$ = 7.4 Hz, C9-H), 7.09 (1H, ddd, $J_{8,10}$ = = 1.3 Hz, C10-H), 7.40 (1H, ddd, C8-H); ^{13}C-nmr (δ, ppm) 6.9 ($CH_2\underline{C}H_3$), 20.2 (C3), 21.6 ($NCO\underline{C}H_3$), 25.0 ($\underline{C}H_2CH_3$), 27.8 (C5), 29.4 (C4), 36.9 (C6), 38.3 (C2), 38.7 (C4a), 40.5 (C13), 59.5 (C14), 60.9 (C12a), 62.3 (C12b), 65.0 (C7a), 109.5 (C11), 119.5 (C9), 126.5 (C7b), 128.7 (C8), 129.0 (C10), 148.6 (C11a), 172.0 ($N\underline{C}OCH_3$), 210.0 (C7); Calc. for $C_{22}H_{30}N_2O_3$ (370.48) C, 71.32; H, 8.16; N, 7.56. Found C, 71.49; H 8,07; N, 7.61.

Refluxing of either pure 8 or pure 9 in ethanol for 12 hours, after evaporation and chromatographic separation (on Al_2O_3 column, CH_2Cl_2:EtOH 10:1 v/v) affords the same product mixture in which the ratio of 8:9 is approx. 2.2:1.

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