

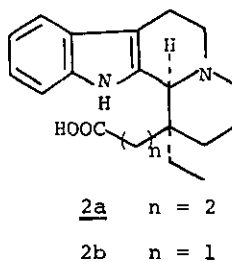
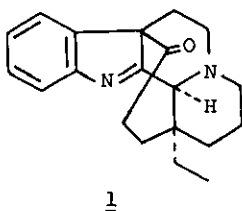
SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. XXVIII¹.NOVEL TYPE REARRANGEMENT OF AN INDOL[2,3-a]QUINOLIZIDINE
INTO INDOLIZINO[8,7-b]INDOLE

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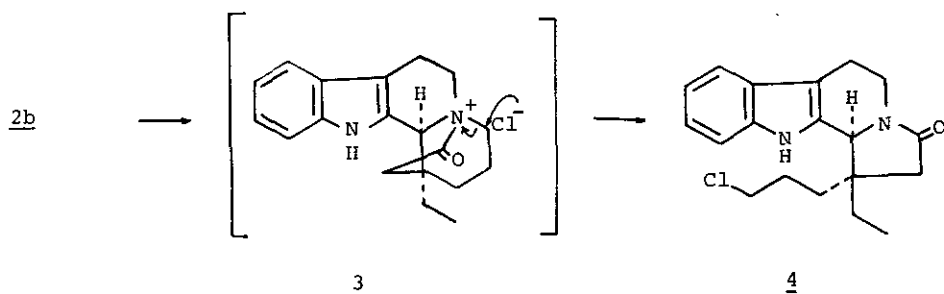
Abstract - Internal acylation of indolo[2,3-a]quinolizidine derivatives may lead either to 3-acylindolenines or to indolizino[8,7-b]indole derivatives depending on the structural properties of the starting materials.

In our previous communication¹ we reported the formation of a 3-acylindolenine derivative (1) by reacting carboxylic acid 2a with ethyl chloroformate in THF in the presence of N-methylmorpholine at 0 → 25 °C.

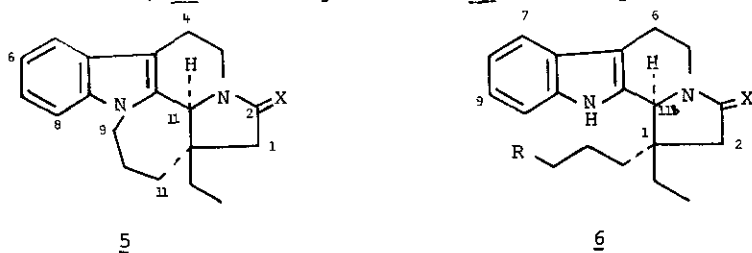


Investigating the scope and limitations of this unusual acylation, the levorotatory acid 2b, prepared first by Bartlett and Taylor² and containing a one methylene group shorter side chain than 2a, has been reacted under the same conditions. Instead of the expected 3-acylindolenine type compound, only rearranged lactam 4 has been obtained in 64 % yield. Lactam 4 is supposed to be formed via an intramolecular acylation leading to intermediate 3 followed by nucleophilic cleavage of the C₄-N bond. Analogous intermolecular N-acylation of a tertiary

nitrogen followed by C-N cleavage in pyrrolidine ring has already been observed by Martin et al.³ and Calverley⁴.



In addition to spectroscopic structure elucidation of 4⁵, a few chemical transformations have been carried out starting from this compound. On refluxing 4 (4h) with 96 % ethanol, 5a in 62 % yield⁶ and 6a in 34 % yield⁷ have been formed.



	X
a	O
b	H ₂

	X	R
a	O	OC ₂ H ₅
b	H ₂	H
c	O	CN

When reduced with LAH in THF (reflux, 2h) 4 furnished 5b (yield 12 %)⁸ and 6b (yield 78 %)⁹. 5b could also be obtained as a result of reduction of 5a (yield 89 %) under the same conditions. On refluxing 4 with KCN in ethanol (50 h), the cyano derivative (6c) has been isolated in 86 % yield¹⁰. All these transformations are in accord with the depicted structure of 4. The above rearrangement (2 $\rightarrow$ 4) indicates that, in addition to the terminal atoms of the N₁, C₂, C₃ indole-enamine system, the basic nitrogen of the piperidine ring can take part as nucleophile in the intramolecular acylation process of indolo[2,3-a]quinolizidine-1-aliphatic acids. Further investigations to decide whether what kind of structural or stereochemical factors influence the actual nucleophilic attack are in progress.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

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3. S.F.Martin, C.-Y.Tu, M.Kimura, and S.H.Simonsen, *J. Org. Chem.*, **47**, 3634 (1982)
4. M.J.Calverley, *J. Chem. Res. (S)*, 1983, 190; *J. Chem. Res. (M)*, 1983, 1848
5. Compound **4**: mp 174-176 °C (ethanol); $[\alpha]_D^{25}$ -107° (c=1.0, ethanol); MS m/z (%) 330 (M⁺, 100), 329 (26), 301 (19), 253 (24), 237 (11), 171 (47), 170 (74), 169 (76), 143 (21); IR (KBr) 3300 cm⁻¹ (indole NH, bonded), 1669 cm⁻¹ (lactam CO), 650 cm⁻¹ (CCl); ¹H-NMR¹¹ δ (ppm) 0.68 (3H, t, J=7.2 Hz, -CH₂-CH₃), 1.31 (2H, q, -CH₂-CH₃), 1.6-2.2 (4H, m, C₁₂-H₂+C₁₃-H₂), 2.36 (1H, d, J_{gem}=16 Hz, C₂-H_A), 2.46 (1H, d, C₂-H_B), 2.6-3.1 (3H, m, C₆-H₂+C_{5a}-H), 3.67 (2H, m, C₁₄-H₂), 4.56 (1H, m, C_{5b}-H), 4.80 (1H, s, C_{11b}-H), 7.0-7.6 (4H, m, aromatic), 8.17 (1H, broad s, indole NH); ¹³C-NMR¹¹ δ (ppm) 8.3 (-CH₂-CH₃), 21.0 (C₆), 27.5 (-CH₂-CH₃), 28.4 (C₁₃), 35.0 (C₁₂), 37.7 (C₅), 41.2 (C₂), 44.4 (C₁), 45.3 (C₁₄), 62.5 (C_{11b}), 110.5 (C_{6a}), 111.1 (C₁₀), 118.3⁺ (C₇), 119.8⁺ (C₈), 122.2⁺ (C₉), 126.8 (C_{6b}), 129.8 (C_{11a}), 136.7 (C_{10a}), 172.4 (C₃); Calc. for C₁₉H₂₃ClN₂O (330.85) C, 68.97; H, 7.01; Cl, 10.72; N, 8.47. Found C, 69.12; H, 6.97; Cl, 10.76; N, 8.51.
6. Compound **5a**: mp 134-136 °C (ethanol); $[\alpha]_D^{25}$ -240° (c=1.0, ethanol); MS m/z (%) 294 (M⁺, 77), 293 (49), 265 (100), 264 (11), 263 (11), 237 (9); IR (KBr) 1694 cm⁻¹ (lactam CO); ¹H-NMR δ (ppm) 0.7-1.4 (5H, m, -CH₂-CH₃), 1.6-2.4 (4H, m, C₁₁-H₂+C₁₀-H₂), 2.41 (1H, d, J_{AB}=15.2 Hz, C₁-H_A), 2.54 (1H, d, C₁-H_B), 2.8-3.3 (3H, m, C₄-H₂+C_{3a}-H), 3.97 (1H, m, C₉-H_A), 4.45-4.8 (2H, m, C_{3b}-H+C₉-H_B), 4.83 (1H, t, J ~ 1.5 Hz, C_{11b}-H), 7.1-7.7 (4H, m, aromatic); ¹³C-NMR δ (ppm) 7.1 (-CH₂-CH₃), 20.9 (-CH₂-CH₃), 21.0 (C₄), 24.8 (C₁₀), 34.3 (C₁₁), 37.0 (C₃), 43.4 (C₁), 44.5 (C_{11a}), 62.9 (C_{11b}), 106.7 (C_{4a}), 108.7 (C₈), 118.4^x (C₅), 119.0^x (C₆), 121.3^x (C₇), 126.3 (C_{4b}), 132.6 (C_{11a}), 136.5 (C_{8a}), 172.9 (C₂); Calc. for C₁₉H₂₂N₂O (294.39) C, 77.51; H, 7.53; N, 9.52. Found C, 77.50; H, 7.58;

N, 9.60.

7. Compound 6a: mp 159-161 °C (toluene); $[\alpha]_D^{25}$ -101° (c=1.0, ethanol); MS m/z (%) 340 (M^+ , 100), 339 (14), 311 (33), 265 (13), 253 (35), 171 (16); IR (KBr) 3325 cm^{-1} (indole NH, bonded), 1670 cm^{-1} (lactam CO), 1110 cm^{-1} (C-O-C); $^1\text{H-NMR}$ δ (ppm) 0.62 (3H, t, $J=7.2$ Hz, $-\text{CH}_2-\text{CH}_3$), 1.18 (2H, q, $-\text{CH}_2-\text{CH}_3$), 1.21 (3H, t, $J=7.0$ Hz, $-\text{O}-\text{CH}_2-\text{CH}_3$), 1.55-1.85 (4H, m, $\text{C}_{12}-\text{H}_2+\text{C}_{13}-\text{H}_2$), 2.29 (1H, d, $J_{AB}=16$ Hz, C_2-H_A), 2.35 (1H, d, C_2-H_B), 2.55-3.00 (3H, m, $\text{C}_6-\text{H}_2+\text{C}_{5a}-\text{H}$), 3.50 (2H, m, $\text{C}_{14}-\text{H}_2$), 3.54 (2H, q, $-\text{O}-\text{CH}_2-\text{CH}_3$), 4.46 (1H, m, $\text{C}_{5\beta}-\text{H}$), 4.79 (1H, broad s, $\text{C}_{11b}-\text{H}$), 6.95-7.50 (4H, m, aromatic), 8.33 (1H, broad s, indole NH); $^{13}\text{C-NMR}$ δ (ppm) 8.2 ($-\text{CH}_2-\text{CH}_3$), 15.3 ($-\text{O}-\text{CH}_2-\text{CH}_3$), 21.1 (C_6), 25.1 (C_{13}), 27.0 ($-\text{CH}_2-\text{CH}_3$), 33.3 (C_{12}), 37.6 (C_5), 41.1 (C_2), 44.8 (C_1), 62.2 (C_{11b}), 66.5 ($-\text{O}-\text{CH}_2-\text{CH}_3$), 70.7 (C_{14}), 110.0 (C_{6a}), 111.1 (C_{10}), 118.1^x (C_7), 119.5^x (C_8), 121.9^x (C_9), 126.8 (C_{6b}), 130.2 (C_{11a}), 136.7 (C_{10a}), 172.6 (C_3); Calc. for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2$ (340.45) C, 74.08; H, 8.29; N, 8.23. Found C, 73.99; H, 8.32; N, 8.26.
8. Compound 5b: mp 115-118 °C (n-hexane); $[\alpha]_D^{25}$ -30° (c=1.0, ethanol); MS m/z (%) 280 (M^+ , 65), 279 (100), 251 (18), 250 (8), 249 (13); IR (KBr) no indole NH and CO signals; $^1\text{H-NMR}$ δ (ppm) 0.74 (3H, t, $J=7.2$ Hz, $-\text{CH}_2-\text{CH}_3$), 1.23 (2H, q, $-\text{CH}_2-\text{CH}_3$), 1.25-1.60 (2H, m, $\text{C}_{10}-\text{H}_2$), 1.75-2.35 (4H, m, $\text{C}_1-\text{H}_2+\text{C}_{11}-\text{H}_2$), 2.7-3.3 (6H, m, $\text{C}_2-\text{H}_2+\text{C}_3-\text{H}_2+\text{C}_4-\text{H}_2$), 3.55 (1H, broad s, $\text{C}_{11b}-\text{H}$), 3.65 (1H, ddd, $J_{AB}=13.8$ Hz, C_9-H_A), 4.49 (1H, ddd, C_9-H_B), 6.95-7.55 (4H, m, aromatic); $^{13}\text{C-NMR}$ δ (ppm) 7.5 ($-\text{CH}_2-\text{CH}_3$), 22.5 (C_4), 22.9 ($-\text{CH}_2-\text{CH}_3$), 24.9 (C_{10}), 34.5 (C_1), 35.9 (C_{11}), 45.6 (C_9), 46.5 (C_{11a}), 49.9 (C_3), 52.1 (C_2), 68.1 (C_{11b}), 108.1 (C_{4a}), 108.7 (C_8), 118.1^x (C_5), 118.6^x (C_6), 120.4^x (C_7), 127.0 (C_{4b}), 136.5 (C_{11c}), 137.0 (C_{8a}); Calc. for $\text{C}_{19}\text{H}_{24}\text{N}_2$ (280.40) C, 81.38; H, 8.63; N, 9.99. Found C, 81.62; H, 8.61; N, 9.97.
9. Compound 6b: mp 143-144 °C (n-hexane); $[\alpha]_D^{25}$ -24° (c=1.0, ethanol); MS m/z (%) 282 (M^+ , 22), 281 (12), 184 (100), 156 (11); IR (KBr) 3430 cm^{-1} (indole NH), 2775 cm^{-1} (Bohlmann band); $^1\text{H-NMR}$ δ (ppm) 0.91 (3H, t, $J=7.2$ Hz, $-\text{CH}_2-\text{CH}_3$), 1.16 (3H, m, $\text{C}_{14}-\text{H}_3$), 1.3-2.2 (8H, m, $\text{C}_2-\text{H}_2+\text{C}_{12}-\text{H}_2+\text{C}_{13}-\text{H}_2+\text{CH}_2-\text{CH}_3$), 2.6-3.5 (6H, m, $\text{C}_3-\text{H}_2+\text{C}_5-\text{H}_2+\text{C}_6-\text{H}_2$), 3.70 (1H, t, $J \sim 1.5$ Hz, $\text{C}_{11b}-\text{H}$), 7.1-7.7 (4H, m, aromatic), 7.78 (1H, broad s, indole NH); $^{13}\text{C-NMR}$ δ (ppm) 8.8 ($-\text{CH}_2-\text{CH}_3$), 15.1 (C_{14}), 18.7 (C_{13}), 20.8 (C_6), 28.5 ($-\text{CH}_2-\text{CH}_3$), 34.6 (C_2), 41.3 (C_{12}), 47.5 (C_1), 48.7 (C_5), 51.3 (C_3), 67.6 (C_{11b}), 110.3 (C_{6a}), 110.6 (C_{10}), 118.0^x (C_7), 119.2^x (C_8), 121.2^x (C_9), 127.3 (C_{6b}), 133.8 (C_{11a}), 135.9

(C_{10a}); Calc. for C₁₉H₂₆N₂ (282.42) C, 80.80; H, 9.28; N, 9.92. Found C, 80.77; H, 9.24; N, 9.95.

10. Compound 6c: mp 199-200 °C (ethanol); $[\alpha]_D^{25}$ -115 ° (c=1.0, ethanol); IR (KBr) 3260 cm⁻¹ (indole NH, bonded), 2240 cm⁻¹ (CN), 1668 cm⁻¹ (lactam CO); ¹H-NMR δ (ppm) 0.68 (3H, t, J=7.2 Hz, -CH₂-CH₃), 1.32 (2H, q, -CH₂-CH₃), 1.6-2.1 (4H, m, C₁₂-H₂+C₁₃-H₂), 2.36 (1H, d, J_{AB}=16Hz, C₂-H_A), 2.43 (1H, d, C₂-H_B), 2.25-2.7 (2H, m, C₁₄-H₂), 2.7-3.1 (3H, m, C₆-H₂+C_{5α}-H), 4.55 (1H, m, C_{5β}-H), 4.79 (1H, broad s, C_{11b}-H), 7.0-7.6 (4H, m, aromatic), 8.4 (1H, broad s, indole NH); Calc. for C₂₀H₂₃N₃O (321.40) C, 74.74; H, 7.21; N, 13.07. Found C, 74.72; H, 7.19; N, 13.04.
11. All NMR spectra have been recorded in CDCl₃. The chemical shift values signed with identical symbols are interchangeable.

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