SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. XXVIII[1]. NOVEL TYPE REARRANGEMENT OF AN INDOLO[2,3-a]QUINOLIZIDINE INTO INDOLIZINO[8,7-b]INDOLE

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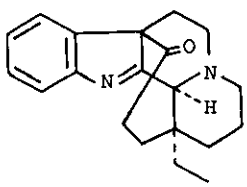
Abstract - Internal acylation of indolo[2,3-a]quinolizidine derivatives may lead either to 3-acylindolenines or to indolizino[8,7-b]indole derivatives depending on the structural properties of the starting materials.

In our previous communication[1] 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.



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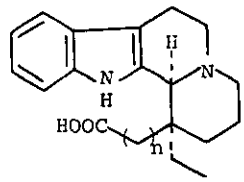
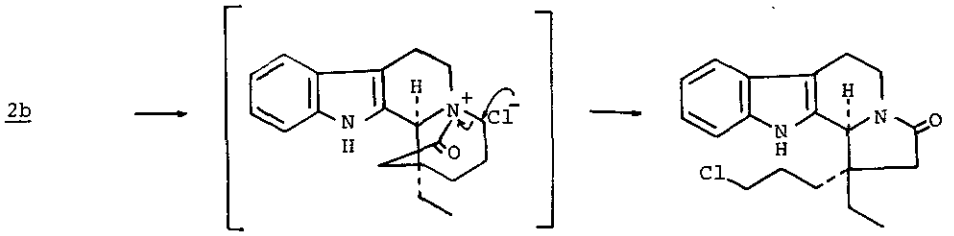


2a n = 2

2b n = 1

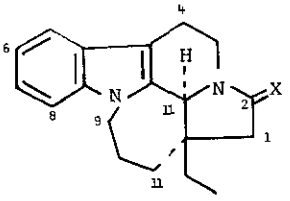
Investigating the scope and limitations of this unusual acylation, the levorotatory acid 2b, prepared first by Bartlett and Taylor[2] and containing a one methylene group shorter side chain than 2a, has been reacted under the same conditions. Instead of the expected 3-acylindolenine type compound, only 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 C_4-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 Calverley[4].



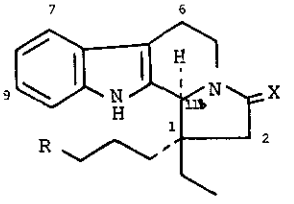
2b → [3] → 4

In addition to spectroscopic structure elucidation of 4[5], a few chemical transformations have been carried out starting from this compound. On refluxing 4 (4h) with 96 % ethanol, 5a in 62 % yield[6] and 6a in 34 % yield[7] have been formed.



5

	X
a	O
b	H_2



6

	X	R
a	O	OC_2H_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 % yield[10]. All these transformations are in accord with the depicted structure of 4. The above rearrangement (2 → 4) indicates that, in addition to the terminal atoms of the N_1, C_2, C_3 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); ^{1}H-NMR[11] δ (ppm) 0.68 (3H, t, J=7.2 Hz, $-CH_2-\underline{CH}_3$), 1.31 (2H, q, $-\underline{CH}_2-CH_3$), 1.6-2.2 (4H, m, $C_{12}-H_2+C_{13}-H_2$), 2.36 (1H, d, J_{gem}=16 Hz, C_2-H_A), 2.46 (1H, d, C_2-H_B), 2.6-3.1 (3H, m, $C_6-H_2+C_{5\alpha}-H$), 3.67 (2H, m, $C_{14}-H_2$), 4.56 (1H, m, $C_{5\beta}-H$), 4.80 (1H, s, $C_{11b}-H$), 7.0-7.6 (4H, m, aromatic), 8.17 (1H, broad s, indole NH); ^{13}C-NMR[11] δ (ppm) 8.3 ($-CH_2-\underline{CH}_3$), 21.0 (C_6), 27.5 ($-\underline{CH}_2-CH_3$), 28.4 (C_{13}), 35.0 (C_{12}), 37.7 (C_5), 41.2 (C_2), 44.4 (C_1), 45.3 (C_{14}), 62.5 (C_{11b}), 110.5 (C_{6a}), 111.1 (C_{10}), 118.3$^+$ (C_7), 119.8$^+$ (C_8), 122.2$^+$ (C_9), 126.8 (C_{6b}), 129.8 (C_{11a}), 136.7 (C_{10a}), 172.4 (C_3); Calc. for $C_{19}H_{23}ClN_2O$ (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); ^{1}H-NMR δ (ppm) 0.7-1.4 (5H, m, $-CH_2-CH_3$), 1.6-2.4 (4H, m, $C_{11}-H_2+C_{10}-H_2$), 2.41 (1H, d, J_{AB}=15.2 Hz, C_1-H_A), 2.54 (1H, d, C_1-H_B), 2.8-3.3 (3H, m, $C_4-H_2+C_{3\alpha}-H$), 3.97 (1H, m, C_9-H_A), 4.45-4.8 (2H, m, $C_{3\beta}-H+C_9-H_B$), 4.83 (1H, t, J ~ 1.5 Hz, $C_{11b}-H$), 7.1-7.7 (4H, m, aromatic); ^{13}C-NMR δ (ppm) 7.1 ($-CH_2-\underline{CH}_3$), 20.9 ($-\underline{CH}_2-CH_3$), 21.0 (C_4), 24.8 (C_{10}), 34.3 (C_{11}), 37.0 (C_3), 43.4 (C_1), 44.5 (C_{11a}), 62.9 (C_{11b}), 106.7 (C_{4a}), 108.7 (C_8), 118.4^x (C_5), 119.0^x (C_6), 121.3^x (C_7), 126.3 (C_{4b}), 132.6 (C_{11a}), 136.5 (C_{8a}), 172.9 (C_2); Calc. for $C_{19}H_{22}N_2O$ (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}H-NMR δ (ppm) 0.62 (3H, t, J=7.2 Hz, $-CH_2-CH_3$), 1.18 (2H, q, $-CH_2-CH_3$), 1.21 (3H, t, J=7.0 Hz, $-O-CH_2-CH_3$), 1.55-1.85 (4H, m, $C_{12}-H_2+C_{13}-H_2$), 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, $C_6-H_2+C_{5\alpha}-H$), 3.50 (2H, m, $C_{14}-H_2$), 3.54 (2H, q, $-O-CH_2-CH_3$), 4.46 (1H, m, $C_{5\beta}-H$), 4.79 (1H, broad s, $C_{11b}-H$), 6.95-7.50 (4H, m, aromatic), 8.33 (1H, broad s, indole NH); ^{13}C-NMR δ (ppm) 8.2 ($-CH_2-CH_3$), 15.3 ($-O-CH_2-CH_3$), 21.1 (C_6), 25.1 (C_{13}), 27.0 ($-CH_2-CH_3$), 33.3 (C_{12}), 37.6 (C_5), 41.1 (C_2), 44.8 (C_1), 62.2 (C_{11b}), 66.5 ($-O-CH_2-CH_3$), 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 $C_{21}H_{28}N_2O_2$ (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}*H-NMR* δ (*ppm*) 0.74 (3H, t, J=7.2 Hz, $-CH_2-CH_3$), 1.23 (2H, q, $-CH_2-CH_3$), 1.25-1.60 (2H, m, $C_{10}-H_2$), 1.75-2.35 (4H, m, $C_1-H_2+C_{11}-H_2$), 2.7-3.3 (6H, m, $C_2-H_2+C_3-H_2+C_4-H_2$), 3.55 (1H, broad s, $C_{11b}-H$), 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}C-NMR δ (ppm) 7.5 ($-CH_2-CH_3$), 22.5 (C_4), 22.9 ($-CH_2-CH_3$), 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 $C_{19}H_{24}N_2$ (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}H-NMR δ (ppm) 0.91 (3H, t, J=7.2 Hz, $-CH_2-CH_3$), 1.16 (3H, m, $C_{14}-H_3$), 1.3-2.2 (8H, m, $C_2-H_2+C_{12}-H_2+C_{13}-H_2+CH_2-CH_3$), 2.6-3.5 (6H, m, $C_3-H_2+C_5-H_2+C_6-H_2$), 3.70 (1H, t, J ~ 1.5 Hz, $C_{11b}-H$), 7.1-7.7 (4H, m, aromatic), 7.78 (1H, broad s, indole NH); ^{13}C-NMR δ (ppm) 8.8 ($-CH_2-CH_3$), 15.1 (C_{14}), 18.7 (C_{13}), 20.8 (C_6), 28.5 ($-CH_2-CH_3$), 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 $C_{19}H_{26}N_2$ (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); ^{1}H-NMR δ (ppm) 0.68 (3H, t, J=7.2 Hz, $-CH_2-CH_3$), 1.32 (2H, q, $-CH_2-CH_3$), 1.6-2.1 (4H, m, $C_{12}-H_2+C_{13}-H_2$), 2.36 (1H, d, J_{AB}=16Hz, C_2-H_A), 2.43 (1H, d, C_2-H_B), 2.25-2.7 (2H, m, $C_{14}-H_2$), 2.7-3.1 (3H, m, $C_6-H_2+C_{5\alpha}-H$), 4.55 (1H, m, $C_{5\beta}-H$), 4.79 (1H, broad s, $C_{11b}-H$), 7.0 - 7.6 (4H, m, aromatic), 8.4 (1H, broad s, indole NH); Calc. for $C_{20}H_{23}N_3O$ (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 $CDCl_3$. The chemical shift values signed with identical symbols are interchangeable.

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