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SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS XXVII[1]
FORMATION OF A STABLE 3-ACYLINDOLENINE

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Abstract: A stable 3-acylindolenine derivative (2) has been prepared via intramolecular electrophilic acylation. The reactivity of 2 has been studied.

Recently Y.Ban and co-workers[2] described a previously unknown reactive species; different 3-acylindolenines formed by photorearrangement of 1-acyl-indoles. They assumed 3-acylindolenines to be hardly generated by any other method[2b]. The photoisomerisation process was used as a general entry to the total synthesis of different kinds of indole alkaloids.

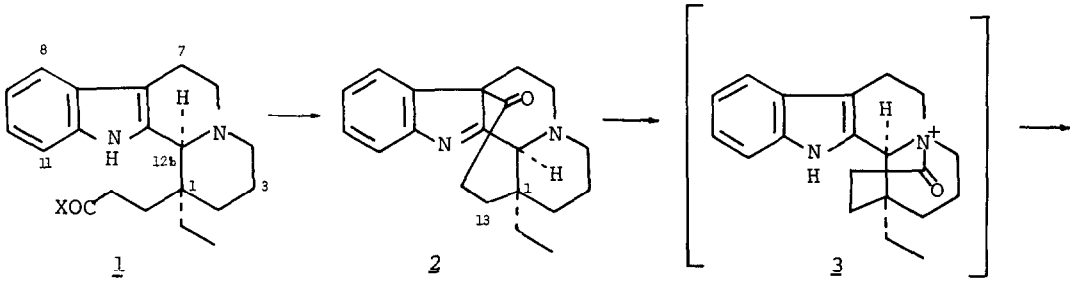
We wish to report here that 3-acylindolenine type compounds can also be generated via an electrophilic substitution reaction.

Electrophilic substitutions constitute by far the largest and most important group of indole reactions. Most of the results can be explained by the supposition that N_1, C_2, C_3 system of indole behaves as an enamine triad[3], and therefore a competitive acylation at N_1 and C_3 is, in principle, possible.

When our starting compound, the levorotatory acid 1a[4] was treated with phosphoryl chloride at room temperature, intramolecular acylation at indole nitrogen took place and a lactam was formed[4]. The same lactam was obtained by boiling a toluene solution of the methyl ester 1b[4] using NaH suspension as base.

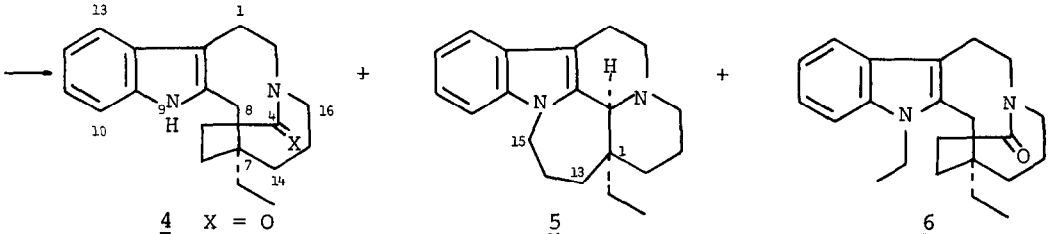
However, when 1a was reacted with ethyl chloroformate in THF in the presence of N-methyl-morpholine (0° 30 min, thereafter stirred overnight at r.t.), stable crystalline ketone (2) could be isolated after treatment of the evaporation residue with acetone. [2: yield 54 %; mp 168-169 $^{\circ}$C (acetone); $[\alpha]_D^{25}=-122^{\circ}$ (c=1.0; CH_2Cl_2); MS m/e(%): 308 (M^+,100), 307 (45), 280 (18), 279 (25), 266 (18), 252 (20), 197 (27), 184 (38), 169 (36), 124 (29); UV (EtOH):

λ_{max}=217 (lgε=4.22), 226 (lgε=4.20), 261 [nm] (lgε=3.87); IR(KBr): 2786, 2773, 2738 (Bohlmann bands), 1710 (CO), 1586 (C=N), 795[cm^{-1}] (CH, 4H, adjacent H atoms on aromatic ring); ^{1}H-NMR[5]: δ = 0.94 (3H, t, J=7.5 Hz, $-CH_2-\underline{C}H_3$), 3.09 (1H, s, C12b-H), 7.1-7.75 (4H, m, aromatic); ^{13}C-NMR: δ = 7.3 ($-CH_2-\underline{C}H_3$), 21.3 (C3), 27.8 (C13), 28.8 ($-\underline{C}H_2-CH_3$), 30.4 (C14), 33.9 (C2), 37.2 (C7), 40.5 (C1), 50.1 (C6), 54.6 (C4), 68.3 (C7a), 73.1 (C12b), 120.7 (C11), 122.8* (C8), 125.9* (C9), 128.7* (C10), 138.3 (C7b), 156.8 (C11a), 185.0 (C12a), 204.6 (C15); $C_{20}H_{24}N_2O$ (308.41) Calc.: C 77.88, H 7.84, N 9.08; Found: C 78.10, H 7.94, N 9.07]. In this reaction, presumably a mixed anhydride has been formed which acylated the C_3 position of the indole-enamine system.



1 2 3

a X = OH
b X = OCH_3
c X = OC_2H_5
d X = $N(C_2H_5)_2$



4 X = O
7 X = H_2

5 6

Catalytic hydrogenation (Pd/C) of ketone (2) in acetic acid-acetic anhydride (5:1) solution provided three products (4-6). The major component (4) could be separated by simple crystallization after work-up. [4: yield 31 %; mp 254-256 °C (ethanol); $[\alpha]_D^{25}$=-86° (c=1.0, CH_2Cl_2); MS m/e (%): 310

(M^+, 50), 309 (3), 281 (8), 157 (100), 156 (45), 154 (30), 144 (18), 143 (15); IR (KBr): 3230 (indole NH, bonded), 1610 [cm^{-1}] (lactam CO); IR ($CHCl_3$): 3475 (indole NH, free), 1624 [cm^{-1}](lactam CO); ^{1}H-NMR: δ = 0.0-0.5 (1H, m, C15-H_A), 1.06 (3H, t, H=7.2 Hz, -CH_2-$\underline{C}H_3$), 2.70 (1H, d, J=16 Hz, C8-H_A), 3.06 (1H, d, C8-H_B), 3.4-3.9 (2H, m, C16-H_2), 4.49 (1H, ddd, J=12.4+4.2+2.2 Hz, C2β-H), 7.0-7.6 (4H, m, aromatic), 8.0 (1H, broad s, indole NH); ^{13}C-NMR: δ = 9.1 (-CH_2-$\underline{C}H_3$), 19.7 (C1), 25.8 (C15), 31.2 (C5), 32.2 (C8), 36.9 (C14), 38.1 (C7), 41.5* (-$\underline{C}H_2$-CH_3), 43.1* (C6), 54.2 (C2), 54.3 (C16), 110.8 (C10), 112.0 (C13b), 117.7+ (C13), 119.3+ (C12), 121.2+ (C11), 127.5 (C13a), 135.7 (C8a), 136.2 (C9a), 174.3 (C4); $C_{20}H_{26}N_2O$ (310.43) Calc.: C 77.37, H 8.44, N 9.03; Found: C 77.43, H 8.30, N 8.84]. Compound 4 could be formed as a result of a C-N acyl migration (3) accompanied by hydrogenolytic fission at the C(12b) - N bond. The structure of 4 is also supported by its chemical reaction; e.g. LAH reduction of 4 gave amine 7. [7: yield 88%, yellow oil; MS m/e (%): 296 (M^+,94), 295 (14), 294 (14), 267 (14), 239 (5), 226 (14), 152 (100), 144 (16), 143 (20), 124 (16), 110 (18), 84 (18), 70 (48), 58 (13), 44 (14); IR(KBr): 3480 (indole NH, free), 3425 [cm^{-1}] (indole NH, bonded), no carbonyl band; ^{1}H-NMR: δ = 1.08 (3H, t, J=7 Hz -CH_2-$\underline{C}H_3$), 1.1-1.8 (10H, m, C14-H_2+C15-H_2+C6-H_2+C5-H_2+-$\underline{C}H_2$-CH_3), 2.78 (4H, s, C1-H_2+C2-H_2), 2.93 (2H, s, C8-H_2), 6.95-7.55 (4H, m, aromatic), 7.7 (1H, broad s, indole NH); ^{13}C-NMR: δ = 9.4 (-CH_2-$\underline{C}H_3$), 25.7 (C1), 27.2 (C5+C15), 33.7 (C8), 36.2 (C6+C14), 39.5 (C7), 45.4 (-$\underline{C}H_2CH_3$), 55.2 (C4+C16), 59.8 (C2), 110.0 (C10), 111.1 (C13b), 117.4* (C13), 120.4* (C11), 128.3 (C13a), 135.3 (C8a), 137.2 (C9a); $C_{20}H_{28}N_2$ (296.44) Calc.: C 81.03, H 9.52, N 9.45; Found: C 81.06, H 9.50, N 9.49].

From the reaction mixture of hydrogenation of 2 two minor products 5 and 6 could be isolated by column chromatography (Merck Kieselgel 60, 0.063-0.2 mm; petroleum ether-diethylamine (10:1)). [5: yield 7.7 %, yellow oil; MS m/e (%): 294 (M^+, 100), 293 (90), 265 (50), 224 (15); IR(KBr): no indole NH and CO signals; ^{1}H-NMR: δ = 0.87 (3H, t, H=7.5 Hz, -CH_2-$\underline{C}H_3$), 3.95 (1H, broad s, C12b-H), 4.50 (1H, m, C15-H_B), 6.95-7.5 (4H, m, aromatic); ^{13}C-NMR: δ = 7.5 (-CH_2-$\underline{C}H_3$), 17.6 (C7), 21.0 (C3), 23.4 (C14), 27.1 (C2), 31.0 (-$\underline{C}H_2$-CH_3), 39.2 (C1), 39.3 (C13), 44.6 (C4), 47.6 (C15), 52.1 (C6), 64.2 (C12b), 109.3 (C11), 109.5 (C7a), 117.7* (C8), 118.9* (C9), 121.0* (C10), 127.1 (C7b), 136.0 (C12a), 136.8 (C11a); $C_{20}H_{26}N_2$ (294.43) Calc.: C 81.58, H 8.90, N 9.52; Found: C 82.17, H 8.79, N 9.49]. [6: yield 2.5 %, mp 190-192 °C; MS m/e (%): 338 (M^+, 20), 185 (100), 184 (30), 172 (20), 170 (10), 143 (10); IR (KBr): 1640[cm^{-1}](lactam CO); IR ($CHCl_3$): 1624 [cm^{-1}](lactam CO); ^{1}H-NMR: δ = 1.01 (3H, t, J=7 Hz, C7-CH_2-$\underline{C}H_3$), 1.33 (3H, t, J=7.0 Hz, N-CH_2-$\underline{C}H_3$), 2.90 (1H, d, J_{AB} = 16 Hz, C8-H_A), 2.95 (1H, d, C8-H_B), 3.3-4.0 (2H, m, C16-H_2), 4.22 (2H, q, N-$\underline{C}H_2$-CH_3), 4.49 (1H, ddd, J = 12.4+4.0+2.2 Hz, C2β-H), 7.0-7.6 (4H, m, aromatic); ^{13}C-NMR: δ = 8.7 (C7-CH_2-$\underline{C}H_3$), 15.0 (N-CH_2-$\underline{C}H_3$), 20.4 (C1), 26.2 (C15), 31.1 (C8), 31.4 (C5), 38.2 (C14), 38.3 (C7), 39.2 (N-$\underline{C}H_2$-CH_3), 42.2* (C7-$\underline{C}H_2$-CH_3), 42.6* (C6), 54.0+

(C2), 54.1^{+} (C16), 109.5 (C10), 113.1 (C13b), 117.8* (C13), 119.0* (C12), 121.1* (C11), 127.9 (C13a), 136.4 (C8a), 138.1 (C9a), 173.9 (C4); $C_{22}H_{30}N_2O$ (338.48) Calc.: C 78.06, H 8.93, N 8.28; Found: C 77.85, H 8.95, N 8.30].

Compound 2 is actually a moderately active acylating agent. With orthoformates or sodium alcoholates it gives the corresponding esters (1b[4], 1c[4]). It easily acylates nitrogen containing bases as well. In this way diethylamide (1d) has been prepared. [1d: yield 44.0 %, mp 222-227°C; $[\alpha]_D^{25}$ =-124 ° (C=1.5; $CHCl_3$); ^{1}H-NMR: δ = 1.09 (3H, t, J=7 Hz, Cl-CH_2-CH_3), 0.73 + 0.99 (6H, t, J = 7 Hz, N-CH_2-CH_3), 2.9-3.3 (4H, m, N-CH_2 - CH_3), 3.34 (1H, s, C12b-H), 7.0-7.48 (4H, m, aromatic), 8.1 (1H, broad s, indole NH); $C_{24}H_{35}N_3O$ (381.54) Calc.: C 75.54, H 9.25, N 11.01; Found: C 75.81, H 9.01, N 11.10].

Additionally 2 could be hydrolized to 1a in aqueous acid or base.

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References and Notes

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5. All NMR spectra have been recorded in $CDCl_3$.

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