SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. XLV.[1] A NEW HETEROCYCLIC RING SYSTEM

Zsuzsanna Kardos-Balogh, Ferenc Sóti, Mária Incze, Mária Kajtár-Peredy, and Csaba Szántay*

Central Research Institute for Chemistry of the Hungarian Academy of Sciences, H-1525 Budapest, POB 17, Hungary

Abstract - The indole derivative 1 rearranges under acidic conditions to a new heterocyclic ring system (2). On reacting the latter with LAH a second rearrangement takes place, and compound 3 is formed.

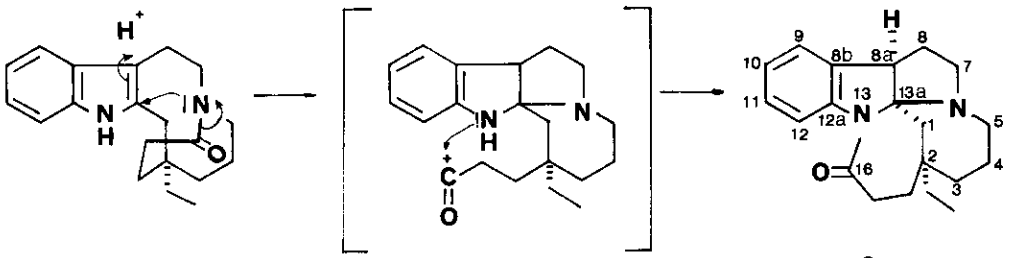
In a previous article we described[2] the synthesis of lactam 1. An attempted reduction of the amide function with $NaBH_3CN$ in CF_3COOH gave rise to the rearranged product 2. Since 2 has the same oxidation level as the starting compound, we omitted the reducing agent, and found that in the same solvent the same product was formed, however at lower rate. When sodium acetate was added to the CF_3COOH the reaction accelerated up again. No product was detectable in acetic acid either in presence or absence of sodium acetate. (see Table).

Table

Transformation of 1 to 2.

Solvent		Reaction time (h)	Yield (%)
CF_3COOH	+ -	16	41
	+ $NaBH_3CN$	4	39
	+ NaOAc	4	59
CH_3COOH	+ -	16	-
	+ NaOAc	16	-

On the basis of the above results we propose that the reaction proceeds through the following sequence. In the first step protonation takes place at C-13b accompanied by rearrangement leading to an acylium cation. The latter attacks the indole nitrogen forming a new lactam ring thereby the end-product[3].



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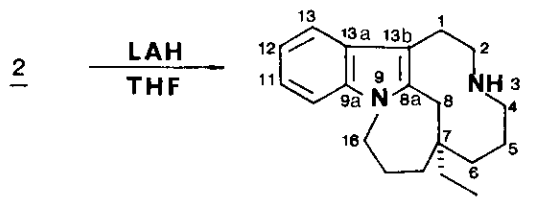
The first step needs a strong acid (CF_3COOH). Both BH_3CN^- and CH_3COO^- anions (the latter from sodium acetate) stabilize by solvation the positively charged intermediates thus lowering their energies and accelerating their formations.



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On treatment of 2 with LAH in THF, in addition to the reduction of the lactam function, a ten-membered ring was formed and the indole ring system was recovered. Reconstruction of the aromatic system is likely the driving force of the latter rearrangement.

EXPERIMENTAL

Infrared spectra were recorded on a Nicolet 7199 Fourier transform spectrophotometer 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 ^1H-{^1H}NOE measurements were performed in the difference mode. Mutual ^1H - ^1H couplings are given only once, at their first occurrence 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).

(-)-(2R:8aS:13aR)-2-Ethyl-2,13-(16-oxo-propano)-2,3,4,5,7,8,8a,13-octahydro-1H-azecino[1,2:1,8a]pyrrolo[2,3-b]indole (2)

a/ To a solution of 1 (700 mg, 2.254 mmol) in CF_3COOH (25 ml) $NaBH_3CN$ (500 mg, 7.958 mmol) was added in small portions, then the reaction mixture was refluxed for 4 h. The solvent was removed in *vacuo*, the residue was dissolved in $CHCl_3$ (50 ml) and washed with 10 % $NaHCO_3$ solution (5x50 ml) and water (3x50 ml). The organic layer was dried over $MgSO_4$ and evaporated in *vacuo*. The residue was purified by column chromatography (n-hexane-diethylamine 10:1 v/v) to give 2 (271 mg, 38.7 %), mp 110-113 °C (cyclohexane); $[\alpha]_D^{25}$ -79.5 ° (c=1.0, ethanol); ms (m/z, %) 310 (M^+, 95), 309 (10), 281 (100), 267 (11), 253 (30), 240 (16); ir (KBr), (ν, cm^{-1}) 1655 (CO, amide); ^1H-nmr (400 MHz, δ, ppm) 0.81 (3H, t, J = 7.4 Hz, $CH_2\underline{CH}_3$), 1.20 (2H, q, $\underline{CH}_2CH_3$), 1.32 (1H, dddd, J_{gem} = 14.0 Hz, $J_{3\alpha,4\beta}$ = 13.6 Hz, $J_{3\alpha,4\alpha}$ = 5.6 Hz, $J_{3\alpha,14\alpha}$ = 2.3 Hz, C3-H_α), 1.66 (1H,ddd, J_{gem} = 12.3 Hz, $J_{7\beta,8\beta}$ = 5.0 Hz, $J_{7\alpha,8\beta}$ ~ 1 Hz, C8-H_β), 1.68 (1H, m, C3-H_β), 1.71 (1H, dddd, J_{gem} = 14.5 Hz, $J_{14\alpha,15\beta}$ = 13.5 Hz, $J_{14\alpha,15\alpha}$= 2.2 Hz, C14-H_α), 1.77 (1H, dddd, $J_{14\beta,15\alpha}$ = 6.5 Hz, $J_{14\beta,15\beta}$= 2.8 Hz, $J_{1A,14\beta}$= 1 Hz, C14-H_β), 1.81 (1H, dddd, J_{gem} = 14.2 Hz, $J_{3\beta4\alpha}$ = 2.8 Hz, $J_{4\alpha,5\beta}$= 5.5 Hz, C4-H_α), 1.98 (1H, d, J_{gem} = 15.0 Hz, C1- H_A), 2.00 (1H, dd, $J_{1B,3\beta}$ = 1.8 Hz, C1-H_B), 2.29 (1H, br ddd, $J_{4\beta5\alpha}$ = 11.5 Hz, C4-H_β), 2.33 (1H, dddd, $J_{7\beta,8\alpha}$ = 13.3 Hz, $J_{7\alpha,8\alpha}$ = 6.4 Hz, $J_{8\alpha,8a}$= 9.5 Hz, C8-H_α), 2.40 (1H, ddd, J_{gem} = 13.5 Hz, C15-H_α), 2.79 (1H, dddd, J_{gem} = 13.0 Hz, $J_{4\beta,5\beta}$ ~ 1 Hz, $J_{3\beta,5\beta}$ ~ 1 Hz, C5-H_β), 2.86 (1H, ddd, J_{gem} = 12.4 Hz, C7-H_α), 2.99

(1H, ddd, C7-H_β), 3.04 (1H, dd, C5-H_α), 3.47 (1H, br d, C8a-H), 4.45 (1H, ddd, C15-H_β), 7.01 (1H, ddd, $J_{9,10}$ = 7.45 Hz, $J_{10,11}$ = 7.35 Hz, $J_{10,12}$ = 1.1 Hz, C10-H), 7.13 (1H, ddd, $J_{9,11}$ = 1.5 Hz, $J_{9,12}$ = 0.6 Hz, C9-H), 7.18 (1H, ddd, $J_{11,12}$ = 8.2 Hz, C11-H), 8.24 (1H, ddd, C12-H); ^{13}C-nmr (100.6 MHz, δ, ppm) 7.8 ($CH_2\underline{C}H_3$), 28.5 (C4), 33.6 (C14), 33.7 (C8), 35.4 (C15), 38.6 (C2), 41.0 ($\underline{C}H_2CH_3$), 41.6 (C3), 46.6 (C1), 53.8 (C5), 55.9 (C8a), 57.1 (C7), 94.8 (C13a), 116.7 (C12), 123.5 (C10), 124.5 (C9), 127.8 (C11), 132.1 (C8b), 143.0 (C12a), 175.0 (C16); Calcd. for $C_{20}H_{26}N_2O$ (310.43) C, 77.38; H, 8.44; N, 9.03; Found C, 77.52; H, 8.28; N, 9.11.

b/ A solution of 1 (700 mg, 2.254 mmol) in CF_3COOH (25 ml) was refluxed for 16 h. The solvent was evaporated in *vacuo*. The residue was dissolved in $CHCl_3$ (50 ml) washed with 10 % $NaHCO_3$ solution (5x50 ml) and water (3x50 ml). The organic layer was dried over $MgSO_4$ and evaporated in *vacuo*. The residue was purified by column chromatography to give 2 (287 mg, 41.0 %), mp: 111-113 °C (cyclohexane).

c/ To a solution of 1 (700 mg, 2.254 mmol) in CF_3COOH (25 ml) NaOAc (500 mg, 9.254 mmol), was added then the reaction mixture was refluxed for 4 h. The solvent was evaporated in *vacuo*. The residue was dissolved in $CHCl_3$ (50 ml) and washed with 10 % $NaHCO_3$ solution (5x50 ml) and water (3x50 ml). The organic layer was dried over $MgSO_4$ and evaporated in *vacuo*. The residue was purified by column chromatography to give 2 (410 mg, 58.6 %), mp 111-113 °C (cyclohexane).

d/ A solution of 1 (700 mg, 2.254 mmol) in CH_3COOH (25 ml) was refluxed for 16 h. After the usual work-up the unchanged 1 was obtained.

e/ To a solution of 1 (700 mg, 2.254 mmol) in CH_3COOH (25 ml) NaOAc (500 mg, 9.254 mmol) was added. The reaction mixture was refluxed for 16 h. After the usual work-up the unchanged 1 was obtained.

(-)-(7R)-7-Ethyl-7,9-propano-2,3,4,5,6,7,8,9-octahydro-1H-azecino[5,4-b]indole (3)

LAH (1.0 g, 0.0264 mol) was suspended in THF (40 ml) in argon atmosphere. A solution of 2 (1.0 g, 0.00322 mol) in THF (40 ml) was added dropwise at room temperature within 1 h. The reaction mixture was refluxed for 4 h, then cooled and the excess LAH was decomposed with water (1 ml), 15 % NaOH solution (1 ml) then water (3 ml). The precipitated solids were filtrated, washed with $CHCl_3$ (50 ml). The combined filtrates and washings were dried over $MgSO_4$ and evaporated in *vacuo*.

The residue was purified by column chromatography (n-hexane-diethylamine 10:1 v/v) to give 3 (810 mg, 84.3 %); mp 159-160 °C (cyclohexane); $[\alpha]_D^{25}$= -11 ° (c = 1.0; $CHCl_3$); ms (m/z, %) (296, M^+), 267 (25), 226 (76), 210 (10); ir ($CHCl_3$, ν, cm^{-1}) 3425 (NH, vw); ^{1}H-nmr (100 MHz, δ, ppm) 0.91 (3H, t, J = 7.2 Hz, $CH_2C\underline{H}_3$), 0.7-2.1 (11H, m, C6-H_2 + C5-H_2 + C14-H_2 + C15-H_2 + $C\underline{H}_2CH_3$ + NH), 2.4-3.5 (8H, m, C8-H_2 + + C4-H_2 + C2-H_2 + C1-H_2), 3.76 (1H, m, C16-H_A), 4.46 (1H, m, C16-H_B), 6.9-7.6 (4H, m, aromatics); ^{13}C-nmr (25.2 MHz, δ, ppm) 8.0 ($CH_2\underline{C}H_3$), 24.4 (C1), 24.5^X (C15), 25.0^X (C5), 26.8 ($\underline{C}H_2CH_3$), 33.2 ° (C14), 35.4 (C8), 37.4 (C7), 42.6° (C6), 44.2 (C16), 45.7$^+$ (C2), 46.6 (C4), 108.3 (C10), 108.6 (C13b), 118.4 (C13), 118.5 (C12), 120.8 (C11), 126.9 (C13a), 135.9 (C8a), 137.5 (C9a); Calcd.for $C_{20}H_{28}N_2$ (296.44) C, 81.02; H, 9.52; N, 9.45. Found C, 80.83; H, 9.65; N, 9.53.

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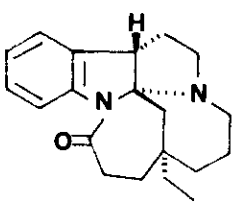
REFERENCES AND NOTES

1. For part XLIV. see M. Incze, F. Sóti, Zs. Kardos-Balogh, M. Kajtár-Peredy, and Cs. Szántay, Arch. Pharm. in press.
2. Zs. Kardos-Balogh, F. Sóti, M. Incze, M. Kajtár-Peredy, and Cs. Szántay, Tetrahedron Letters, 1985, 26, 5593.
3. Isomer 2a was neither isolated nor detected by NMR.



2a

4. The chemical shift values signed with identical symbols are interchangeable.

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