SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. XXIII[1] TRANSPOSITION OF FUNCTIONALITY ON THE INDOLO-QUINOLIZIDINE SKELETON

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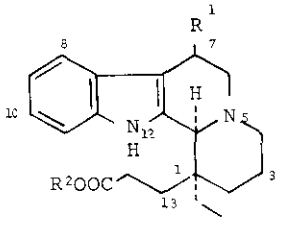
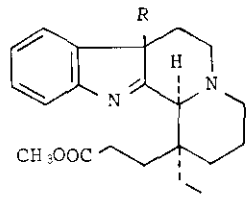
Abstract - Bromination and subsequent reactions with nucleophiles of a substituted indolo[2,3-a]quinolizidine derivative yielded instead of the expected indolenine derivatives 7-substituted indolo[2,3-a]quinolizidines.

Aiming at the synthesis of biologically active derivatives we intended to prepare C-7a substituted indolo[2,3-a]quinolizidine derivatives of type 6.



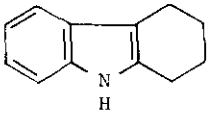


1 R^1 = H, R^2 = CH_3
2 R^1 = OCH_3, R^2 = CH_3
3 R^1 = OC_2H_5, R^2 = C_2H_5
4 R^1 = NH-CH_2-C_6H_5, R^2 = CH_3

5 R = Br
6 R = OCH_3

Searching for appropriate reactions in the literature it was found that treatment of tetrahydrocarbazole (7) with tert-butyl hypochlorite yielded a solution of the chloroindolenine 8 which gave with sodium methoxide in methanol methoxyindolenine 10 as main product[2]. Bromination and subsequent hydrolysis of 7 followed the same substitution pattern[3] yielding 11 through intermediate 9.

Bromination of 2,3-dimethylindole (12) gave rise to 3-bromo-2,3-dimethyl-indolenine (14) in good yield[4].



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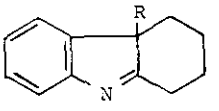
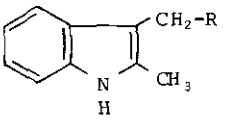
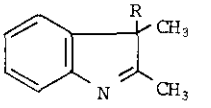


8 R = Cl
9 R = Br
10 R = OCH_3
11 R = OH



12 R = H
13 R = OH



14 R = Br
15 R = OH

An anomalous substitution was reported by Plant and Tomlinson[5], who claimed that with 2,3-dimethylindole (12) the bromination-hydrolysis sequence gave instead of 3-hydroxyindolenine (15), 3-hydroxymethyl-2-methylindole (13). A reinvestigation by Dmitrienko et al.[4] questioned the validity of structure 13 and proved that substitution had occurred also in this case at position C-3 leading to compound 15, which stabilized as a dimer.

Taking into account all these results we were surprised to find that events took another course in our hands when the same reaction sequence was applied to the indolo[2,3-a]quinolizidine derivative 1. Although bromination furnished the indolenine derivative 5, further treatment of 5 by sodium methoxide in methanol[2] yielded, instead of the expected indolenine derivative 6, compound 2, containing the methoxy group at C-7. Under acidic conditions[4] no reaction took place. With other nucleophiles ($C_2H_5O^-$, $C_6H_5-CH_2-NH_2$) again C-7 substituted derivatives (3 and 4) were obtained i.e. transposition of functionality on the indolo-quinolizidine skeleton was observed.

The new derivatives (2,3,4, and 5) are unstable but can be stored in a refrigerator for a few days.

The spectroscopic data are in accord with the structures of the new compounds (see Experimental). Proton and carbon-13 NMR spectra disclosed that products 2 and 3 were formed as inseparable mixtures of C-7 epimers with a net predominance (approx 70%) of the isomer containing the C-7-OR function in β orientation (2a and 3a). A still higher predominance (>95%) of this configuration has been found

for product 4.

It follows from the above studies that in our case the previously proposed reaction mechanism[4] cannot be valid. The most plausible process in an HX elimination from positions C-7 and C-7a, followed by 1,4-addition.

EXPERIMENTAL

Infrared spectra were recorded on a Nicolet 7199 Fourier transform spectrometer and the frequencies (cm^{-1}) of significant peaks are reported. ^{1}H and ^{13}C NMR spectra were recorded at 100 and 25 MHz, respectively, using a Varian XL-100 FT instrument. Deuterochloroform was used as the solvent, chemical shifts are in ppm relative to internal TMS. Mass spectra were recorded on an AEI MS-902 mass spectrometer (70eV, ion source temp. 200 ^{o}C, direct insertion).

The purification of compounds was carried out by column chromatography on silica gel (Merck Kieselgel 60, 0,063-0,2 mm).

Methyl 3-(7a-Bromo-1α-ethyl-1,2,3,4,6,7,7a,12b)-octahydroindolo[2,3-a]-quinolizin-1β-yl)-propionate 5

Methyl 3-(1α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]quinolizin-1β-yl)-propionate 1 (5.1 g, 15.0 mmol) was dissolved in methylene chloride (100 ml) containing triethylamine (5 ml). The solution was cooled to 0^{o}C and a solution of bromine (1.15 ml, 1.5 equivalent) in methylene chloride (20 ml) was added dropwise with stirring. After 10 min, water was added and the mixture was extracted with methylene chloride. The dried ($MgSO_4$) organic phase was evaporated to dryness in vacuo at room temperature. The residue was purified by column chromatography on silica gel with elution by 10 % v/v 2-butanone:toluene gave a yellow oil (4.0 g, 63.7 %). MS m/e (%): 418 (M^+, 0.1), 417 (0.1), 387 (0.5), 345 (0.7), 339 (100). IR (neat): 1573 (νC=N), 550 (νC-Br). ^{1}H-NMR: δ (ppm) = 0.85 (3H, t, J=7.5 Hz, Cl-$CH_2\underline{CH_3}$), 3.64 (3H, s, $COOCH_3$), 3.93 (1H, broad s, C12b-H), 7.15-7.7 (4H, m, aromatic). ^{13}C-NMR: δ (ppm) = 7.30 (Cl-CH_2-$\underline{C}H_3$), 21.55 (C3), 26.18 (C13), 28.22 (C2), 28.43 (C14), 28.80 (Cl-$\underline{C}H_2CH_3$), 37.43 (C1), 39.16 (C7), 49.74 (C4), 51.10 (C6), 51.25 ($COO\underline{C}H_3$), 62.45 (C12b), 64.10 (C7a), 121.78+122.68+126.46+129.65 (C8,C9,C10 and C11), 140.59 (C7b), 152.21 (C11a), 174.70 ($\underline{C}OOCH_3$), 176.96 (C12a). $C_{21}H_{27}BrN_2O_2$ (419.36) Calc.: C 60.14; H 6.49; Br 19.05; N 6.68; Found: C 60.12; H 6.51; Br 19.10; N 6.71.

Methyl 3-(1α-Ethyl-7-methoxy-1,2,3,4,6,7,12,12bα-octahydro indolo[2,3-a]-quinolizin-1β-yl)-propionate 2

Bromoindolenine 5 (2.36 g, 5.6 mmol) was dissolved in dry methanol (40 ml) with stirring in a nitrogen atmosphere. The solution was refluxed for 20 minutes in the presence of sodium methoxide (1.5 g, 28 mmol). Removal of solvent the residue was purified by column chromatography on silica gel with elution by 10 % v/v diethylamine:cyclohexane gave a yellow oil (0.67 g, 32.0 %). MS m/e (%): 370 (M^+, 7), 355 (8), 339 (50), 297 (28), 273 (7), 265 (100). IR (neat): 3430 (indole νNH), 2815 ($\nu_s CH_3$), 1080 (ν_{as} C-O-C). ^{1}H-NMR: 2a: δ (ppm)= 1.15 (3H, t, J=7.5 Hz, Cl-$CH_2\underline{CH_3}$), 3.24 (1H, s, C12b-H), 3.51 (3H, s, C7-OCH_3), 3.55 (3H, s, $COOCH_3$), 4.54 (1H, m, Δν=6Hz, C7-H_α), 7.05-7.7 (4H, m, aromatic), 8.0 (1H, broad s, indole NH). 2b: δ (ppm) = 1.15 (3H, t, J=7.5Hz, Cl-$CH_2\underline{CH_3}$), 3.24 (1H, s, C12b-H), 3.53 (3H, s, C7-OCH_3), 3.56 (3H, s, $COOCH_3$), 4.91 (1H, ddd, J=9.3, 5.5, 2.1 Hz, C7-H_β), 7.05-7.8 (4H, m, aromatic), 7.87 (1H, broad s, indole NH). ^{13}C-NMR: 2a: δ (ppm) = 7.96 (Cl-$CH_2\underline{CH_3}$), 21.76 (C3), 28.47^x (C13), 28.76^x (C14), 30.80 (Cl-$\underline{C}H_2CH_3$), 32.86 (C2), 39.33 (C1), 51.35 ($COO\underline{C}H_3$), 56.17 (C7-$O\underline{C}H_3$), 56.54 (C4), 59.28 (C6), 66.24 (C12b), 69.69 (C7), 110.52 (C7a), 110.98 (C11), 118.30 (C8), 120.05$^+$ (C10), 121.83$^+$ (C9), 127.35 (C7b), 136.06 (C12a), 136.88 (C11a), 174.59 ($\underline{C}OOCH_3$). 2b: δ (ppm) = 7.96 (Cl-$CH_2\underline{CH_3}$), 21.76 (C3), 28.47^x (C12), 28.57^x (C14), 31.06 (Cl-$\underline{C}H_2CH_3$), 32.08 (C2), 39.09 (C1), 51.35 ($COO\underline{C}H_3$), 55.87 (C7-$O\underline{C}H_3$), 56.54 (C4), 58.51 (C6), 65.65 (C12b), 73.36 (C7), 110.77 (C11), 119.70 (C8), 120.17$^+$ (C10), 121.61$^+$ (C9), 127.35 (C7b), 134.05 (C12a), 136.2 (C11a), 174.56 ($\underline{C}OOCH_3$). $C_{22}H_{30}N_2O_3$ (370.48) Calc.: C 71.32; H 8.16; N 7.56; Found: C 71,28; H 8.16; N 7.59.

Ethyl 3-(7-Ethoxy-1α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]-quinolizin-1β-yl)-propionate 3

Bromoindolenine 5 (2.36 g, 5.6 mmol) was dissolved in dry ethanol (30 ml) with stirring in a nitrogen atmosphere. A solution of sodium (0.64 g, 28 mmol) in anhydrous ethanol (10 ml) was added and the mixture was refluxed for 30 min. After evaporation the residue was purified by column chromatography on silica gel with elution by 10 % v/v diethylamine:cyclohexane gave a yellow oil (0.63 g, 28.0 %). MS m/e (%): 398 (M^+,12), 383 (5), 369 (3), 353 (100), 328 (2), 311 (80), 265 (20). IR (KBr): 3436 (indole νNH), 2970 and 2870 (ν_{as} CH_3 and $\nu_s CH_3$), 1080 (ν_{as} C-O-C). ^{1}H-NMR: 3a: δ (ppm) = 1.15 (3H, t, J=7.5 Hz, Cl-$CH_2\underline{CH_3}$), 1.15 (3H, t, J=7Hz,

C7-$OCH_2\underline{C}H_3$), 1.20 (3H, t, J=7Hz, $COOCH_2\underline{C}H_3$), 3.23 (1H, s, C12b-H), 3.70 and 3.73 (2H, q, J=7Hz, C7-$OC\underline{H}_2CH_3$), 4.02 (2H, q, J=7Hz, $COOC\underline{H}_2CH_3$), 4.65 (1H, m, $\Delta\nu$=6Hz, C7-H_α), 7.0-7.7 (4H, m, aromatic), 7.97 (1H, broad s, indole NH). 3b: δ (ppm) = 1.15 (3H, t, J=7.5Hz, Cl-$CH_2\underline{C}H_3$), 1.16 (3H, t, J=7Hz, C7-$OCH_2\underline{C}H_3$), 1.20 (3H, t, J=7Hz, $COOCH_2\underline{C}H_3$), 3.23 (1H, s, C12b-H), 3.75 (2H, q, J=7Hz, C7-$OC\underline{H}_2CH_3$), 4.03 (2H, q, J=7Hz, $COOC\underline{H}_2CH_3$), 4.99 (1H, ddd, J=9.3, 5.5, 2.1 Hz, C7-H_β), 7.0-7.8 (4H, m, aromatic), 7.86 (1H, broad s, indole NH). $C_{24}H_{34}N_2O_3$ (398.53) Calc.: C 72.32; H. 8.60; N 7.03; Found: C 72.35; H 8.62; N 7.10.

Methyl 3-(7-Benzylamino-1α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]-quinolizin-1β-yl)-propionate 4

Bromoindolenine 5 (7.0 g, 16.7 mmol) was dissolved in dry methanol (200 ml) with stirring in a nitrogen atmosphere. To the above solution benzylamine (17.98 g, 167 mmol) was added and refluxed for 8 h. The solvent was evaporated in vacuo, the residue was separated by column chromatography. The eluent was ethyl acetate:n-hexane:diethylamine = 5:5:0.1.The crude product was a yellow oil (2.0 g, 27.5 %). MS m/e (%): 445 (M^+, 2.5), 416 (6), 375 (8), 372 (5), 358 (5), 340 (25), 339 (27), 338 (25), 337 (10), 265 (87), 168 (67), 107 (67), 106 (100), 79 (97). IR (neat): 3440 (indole νNH), 3280 (benzylamino νNH). ^{1}H-NMR: δ (ppm) = 1.15 (3H, t, J=7.5 Hz, Cl-$CH_2\underline{C}H_3$), 2.92 (1H, s, C7-NH-), 3.29 (1H, s, C12b-H), 3.49 (3H, s, $COOCH_3$), 3.91 (1H, m, C7-H_α), 3.98 (2H, s, -NH-$C\underline{H}_2$-Ph), 6.95-7.6 (9H, m, aromatic), 7.88 (1H, broad s, indole NH). ^{13}C-NMR: δ (ppm) = 7.94 (Cl-CH_2-$\underline{C}H_3$), 21.88 (C3), 28.53^x (C13), 28.80^x (C14), 30.45 (Cl-$\underline{C}H_2$-CH_3), 32.69 (C2), 39.27 (C1), 49.12 (NH-$\underline{C}H_2$-Ph), 51.38 ($COO\underline{C}H_3$), 51.78 (C7), 56.70 (C4), 59.21 (C6), 66.70 (C12b), 110.78 (C11), 114.88 (C7a), 118.49 (C8), 119.83$^+$ (C10), 121.71$^+$ (C9), 126.64 (C4'), 127.48 (C7b), 128.32 (C2'+C6'+C3'+C5'), 134.53 (C12a), 136.01 (C11a), 141.28 (C1'), 174.36 ($\underline{C}OOCH_3$). $C_{28}H_{35}N_3O_2$ (445.58) Calc.: C 75.47; H 7.92; N 9.43; Found: C 75.51; H 7.95; N 9.47.

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