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Synthesis of *Vinca* Alkaloids and Related Compounds, LXII[1]

SYNTHESIS OF DESMETHOXY "DECARBOMETHOXY APOCUANZINE"

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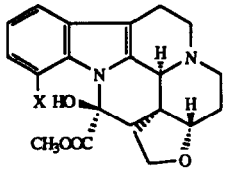
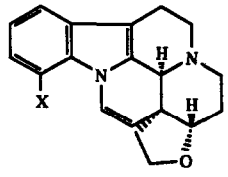
Abstract: Starting from the intermediate product (5) of the desmethoxy cuanzine synthesis, (±)-desmethoxy "decarbomethoxy apocuanzine" (4) was synthesized.

Among other alkaloids, cuanzine (1) and a side-alkaloid, decarbomethoxy apocuanzine (3), were isolated[2] from the root bark of *Voacanga chalotiana* collected in Angola. According to the established structures[3-5], they are relatives, and both of them contain the eburnane skeleton in which an additional tetrahydrofuran ring is formed. Cuanzine (1) and its 12-desmethoxy analogue (2) have been recently synthesized by different teams[6-8].



1 X = OCH_3
2 X = H

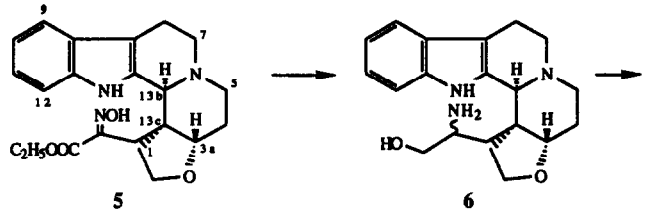


3 X = OCH_3
4 X = H

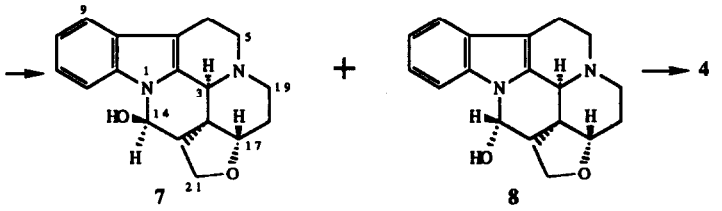
Starting from the intermediate product 5 of our desmethoxy cuanzine synthesis[8], we prepared the amino-alcohol 6 by reduction with lithium aluminium hydride. According to NMR investigations, 6 is an epimeric mixture at the -C^*HNH_2- carbon. The 7 and 8 epimers were formed by periodate oxidation from 6, presumably through an intermediate aldehyde or via its iminium derivative. Unequivocal evidence for the relative configuration at C-14 in 8 was readi-

†Dedicated to Professor Gábor Fodor on the occasion of his 75th birthday.

ly available from selective ^1H-{^1H} NOE difference experiments, which demonstrate the spatial proximity of the protons on the 14 and 17 carbon atoms in this epimer. It follows that the hydroxyl group has α space orientation in **8**; consequently, **7** is the 14β-hydroxy-epimer. From the epimeric mixture of compound **7** and **8**, the desmethoxy decarbomethoxy apocuanzine (**4**) was prepared by water elimination carried out by heating with acetic anhydride. The structure of **4** was verified by IR and NMR spectroscopy.



5 **6**



7 **8**

Consequently, the synthesis of the bare ring skeleton of cuanzine type alkaloids was accomplished. Our experiments for the preparation of some derivatives of **4** including the synthesis of decarbomethoxy apocuanzine itself (**3**) are currently in progress.

EXPERIMENTAL

Infrared spectra were recorded on a Nicolet 7199 Fourier transform spectrometer and the frequencies (cm^{-1}) of significant peaks are reported. The NMR spectra were run, where it is not indicated, in deuteriochloroform solutions at ambient temperature, using Varian XL-100 and XL-400 instruments for conventional and 2D experiments. Chemical shifts are in ppm relative to internal TMS. 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. Thin layer chromatography was carried out on silica gel layer (Macherey-Nagel, Polygram SIL G/UV_{254}) and column chromatography also on silica gel (Merck, Geduran SI 60, 0.063-0.200 mm). Mps are uncorrected.

(±)-13cβ-(2-Amino-3-hydroxypropyl)-1,2,3aβ,4,5,7,8,13,13bα,13c-decahydro-furo[3,2-a]indolo[3,2-h]quinolizine **(6)**

To a stirred suspension of $LiAlH_4$ (0.38 g, 10 mmole) in dry tetrahydrofuran (40 ml) ethyl (±)-3-{1,2,3aβ,4,5,7,8,13,13bα,13c-decahydrofuro[3,2-*a*]indolo[3,2-*h*]quinolizin-13cβ-yl}-2-hydroxy-imino-propionate (**5**, 0.397 g, 1.0 mmole) was slowly added and then the suspension was boiled for

3 hours. The excess hydride was carefully decomposed at ice cooling by succesively adding water (0.5 ml), 15 % aqueous NaOH solution (0.5 ml), and again water (1.5 ml). After 30 minutes of stirring it was filtered and washed thoroughly with tetrahydrofuran (5x5 ml). The combined extracts were dried ($MgSO_4$) and evaporated to yield **6** (0.296 g, 87 %) as a light yellow foam which was pure enough for the next step. According to NMR examinations, it was an epimeric mixture in the ratio of about 7:3. ^{13}C-NMR (δ, ppm): 21.38 (C8), 26.72 + 25.46 (C4), 38.10 + 34.95 (C1), 39.50 + 33.36 (C13c-$\underline{C}H_2$), 46.29 + 45.14 (C13c), 49.93 + 50.29 (CH-NH_2), 51.09 + 50.69 (C5), 54.45 (C7), 64.23 + 65.15 (C13b), 65.60 + 66.07 (C2), 67.81 + 68.44 (CH_2OH), 81.18 + 79.92 (C3a), 111.13 (C12), 111.46 + 111.68 (C8a), 117.90 (C9), 119.53 + 119.33 (C10), 121.74 + 121.51 (C11), 127.05 + 127.18 (C8b), 133.25 + 133.40 (C13a), 136.72 + 136.89 (C12a).

***14-Epimers of (±)-17α,21-Epoxy-14,15-dihydro-14-hydroxy-3α,16α-eburnamenine* (7 and 8)**

To a solution of compound **6** (0.205 g, 0.6 mmole) in dichloromethane (5 ml) an aqueous solution (5 ml) of sodium periodate (0.141 g, 0.66 mmole) was added and stirred for 20 minutes at room temperature. After separation the aqueous phase was extracted with dichloromethane (2x5 ml), the combined extracts were dried ($MgSO_4$), and evaporated. From the residue (0.191 g) the pure epimers **7** and **8** were separated by column chromatography on SiO_2 (25 g, toluene-diethylamine 9-1 v/v, R_f 14β > R_f 14α).

Compound **7**, the 14β-epimer (0.049 g, 26 %), was a light yellow slowly solidifying oil; IR (KBr, ν, cm^{-1}): 3375 (OH, H-bounded), 1045 (C-O), 742 (o-disubstd. A-ring); ^{1}H-NMR ($CDCl_3$ + DMSO-d_6, δ, ppm): 1.4-2.1 (4H, m, C18-H_2 + C20-H_A + C15-H_A), 2.3-3.4 (9H, m, C5-H_2 + C6-H_2 + C19-H_2 + C15-H_B + C20-H_B + OH), 3.9-4.1 (2H, m, C21-H_2), 4.25 (1H, br s, C3-H), 4.56 (1H dd, $J_{17,18}$ = 8.5 and 8.0 Hz, C17-H), 6.01 (1H, dd, $J_{14,15}$ = 4.0 and 1.5 Hz, C14-H), 7.0-7.55 (4H, m, aromatic protons); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, δ, ppm): 17.17 (C6), 28.11 (C18), 34.52 (C20), 39.40 (C15), 42.65 (C19), 42.89 (C16), 50.98 (C5), 56.37 (C3), 63.85 (C21), 73.67 (C14), 74.99 (C17), 104.56 (C8a), 110.96 (C12), 117.99 (C9), 119.71 (C10), 120,77 (C11), 128.48 (C8), 131.23 (C2), 135.47 (C13).

Compound **8**, the 14α-epimer (0.038 g, 20 %) was a light yellow oil; IR (KBr, ν, cm^{-1}): 3390 (br, OH, H-bounded), 1070 (C-O), 742 (o-disubstd. A-ring); ^{1}H-NMR (400 MHz, δ, ppm): 1.48 (1H, dd, J_{gem} = -13.6 Hz, $J_{14,15a}$ = 9.5 Hz, C15-H_a), 1,45-1.6 (2H, m, C18-H_e + C20-H_A), 1.62 (1H, dddd, J_{gem} = -13.5 Hz, $J_{17,18a}$ = 10.3 Hz, $J_{18a,19a}$ = 12.0 Hz, $J_{18a,19e}$ = 4.5 Hz, C18-H_a), 2.33 (1H, ddd, J_{gem} = -12.0 Hz, $J_{18e,19a}$ = 2.8 Hz, C19-H_a), 2.42 (1H, ddd, $J_{18e,19e}$ = 3.0 Hz, C19-H_e), 2.52 (1H, dd, $J_{14,15e}$ = 5.0 Hz, C15-H_e), 2,53 (1H, dddd, J_{gem} = -16,0 Hz, $J_{5α,6α}$ = 4.6 Hz, $J_{5β,6α}$ < 1Hz, $J_{3,6α}$ = 2.0 Hz, C6-$H_α$), 2.65 (1H, m, C20-H_B), 2.87 (1H, dddd, $J_{5α,6β}$ = 11.1 Hz, $J_{5β,6β}$ = 7.0 Hz, $J_{3,6β}$ = 2.4 Hz, C6-$H_β$), 3.20 (1H, ddd, J_{gem} = -13.5 Hz, C5-$H_α$), 3.26 (1H, ddd, C5-$H_β$), 3.47 (1H, dd, $J_{17,18e}$ = 6.3 Hz, C17-H), 3.9-4.0 (2H, m, C21-H_2), 4.05 (1H, dd, C3-H), 5.52 (1H, dd, C14-H), 7,1-7,2 (2H, m, C10-H + C11-H), 7.47 (1H, br d, C9-H), 7.73 (1H, br d, C12-H); ^{13}C-NMR (δ, ppm): 17.23 (C6), 27.86 (C18), 33.76 (C20), 42.06 (C15), 42.24 (C19), 45.03 (C16), 50.53 (C5), 55.96 (C3), 63.97 (C21), 74.69 (C17), 76.15 (C14), 105.39 (C8a), 112.39 (C12), 118.18 (C9), 120.32 (C10), 121,51 (C11), 128.47 (C8), 132.49 (C2), 136.92 (C13).

***(±)-17α,21-Epoxy-3α,16α-eburnamenine [(±)-Desmethoxy "Decarbomethoxy Apocuanzine"]* (4)**

A solution of the epimeric mixture of compounds **7** and **8** (0.075 g, 0.24 mmole) in acetic anhydride (0.5 ml) was stirred at 100 °C for 30 minutes. After cooling it was poured onto crushed ice (10 g), basified with $NaHCO_3$ (1 g), and extracted with dichloromethane (3x3 ml). The combined extracts were dried ($MgSO_4$), and evaporated *in vacuo* to give **4** (0.054 g, 77 %). It was further purified by column chromatography on SiO_2 (10 g, toluene-diethylamine 95-5 v/v) to yield the analytically pure **4** (0.029 g, 41 %); mp: 128-131 °C; IR (KBr, ν, cm^{-1}): 1636 (C=C in E-ring), 1060 (C-O), 735 (o-disubstd. A-ring); ^{1}H-NMR (δ, ppm): 1.6-2.2 (3H, m, C18-H_2 + C20-H_A), 2.4-3.5 (7H, m, C20-H_B + C5-H_2 + C6-H_2 + C19-H_2), 3.62 (1H, dd, J = 9.0 and 8.0 Hz, C17-H), 3.9-4.2 (2H, m, C21-H_2), 4.60 (1H, br dd, C3-H), 5.22 (1H, d, $J_{14,15}$ = 7.8 Hz, C15-H), 6.93 (1H, d, C14-H), 7.0-7.5 (4H, m, aromatic protons).

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