SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. XXV[1]. A NEW APPROACH TO (±)-TETRAHYDROSECODIN-17-OL, (±)-TETRAHYDROSECODINE, (±)-VINCADIFFORMINE, (±)-ψ-VINCADIFFORMINE AND (±)-MINOVINE

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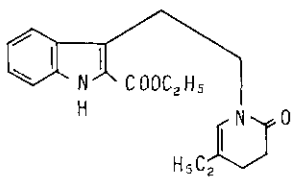
Abstract - Starting from 1 the syntheses of the title compounds were achieved using Polonovski reaction of 7 as the key step.

In Kuehne's studies on the biomimetic alkaloid syntheses the biogenetically proposed secodine intermediate 8 plays an important role[2].
Our aim was to synthesize vincadifformine (10), ψ-vincadifformine (11) and minovine (12) through the key intermediates 8 and 9 by utilizing our previously described, easily accessible compound 1[3] as starting material. The envisaged intermediate 4 (tetrahydrosecodin-17-ol) could serve as a source for producing dihydrosecodine (5) and tetrahydrosecodine (6a).



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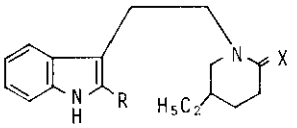
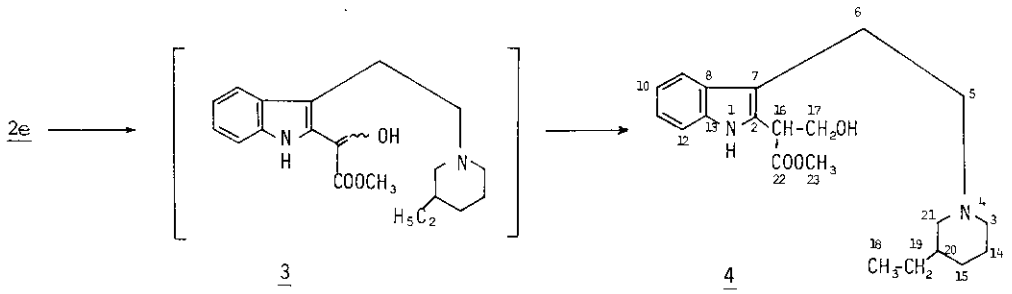


2a: R=$COOC_2H_5$, X=O
b: R=CH_2OH, X=H_2
c: R=$CH_2OCO\phi$, X=H_2
d: R=CH_2CN, X=H_2
e: R=CH_2COOCH_3, X=H_2

At the outset 1 was reduced catalytically [Pd/C, methanol, RT, 90 %, mp 127-128 °C from benzene-hexane] to 2a, which upon further reduction [LAH/THF, 70 °C/5 h, 89.7 %, mp 154-155 °C from benzene-hexane] provided 2b. Using the method described by Kutney[4], 2b was transformed to 2e by the following steps.

Benzoylation [benzoyl chloride/pyridine, 70 °C/2h] of 2b gave 2c [90 %, mp 132-134 °C from acetonitrile], which was reacted with KCN in abs. DMSO [75 °C/1h] furnishing 2d [65.2 %, mp 127-129 °C from acetonitrile]. When treated with methanol/HCl in the presence of trace of water [RT/24h] 2d gave rise to 2e. $HClO_4$ [94.4 %, mp 52-53 °C from methanol-ether].

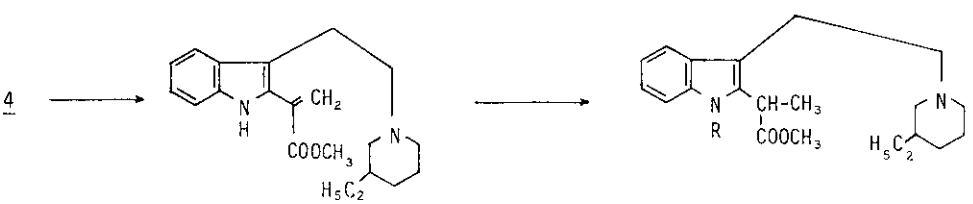
For continuation of the synthetic sequence the ester 2e was formylated in benzene with methyl formate in the presence of sodium hydride[4,5] [35 °C/2h] and the obtained enol 3 was immediately reduced [$NaBH_4$/methanol, -20 °C, 44.9 %] to the diastereomers of 16,17,15,20-tetrahydrosecodin-17-ol[6] (4)[7].



3 4

Water elimination from the latter compound [$(CH_3CO)_2O$/pyridine, RT/1h, 60.4 % or: toluene/Δ/7h, 40 %] yielded 15,20-dihydrosecodine[6] (5)[8]. Catalytic reduction (Pd/C methanol, RT, 98.3 %) of 5 furnished a mixture (6a)[9] of racemic 16,17,15,20-tetrahydro-secodine[6] and its diastereomer.

Attempted chemoselective methylation [Na/NH_3, CH_3I] of 2e to 6a was unsuccessful, instead the dimethylated product[10] was obtained (6b, 34,5 %, mp 183-185 °C from methanol).



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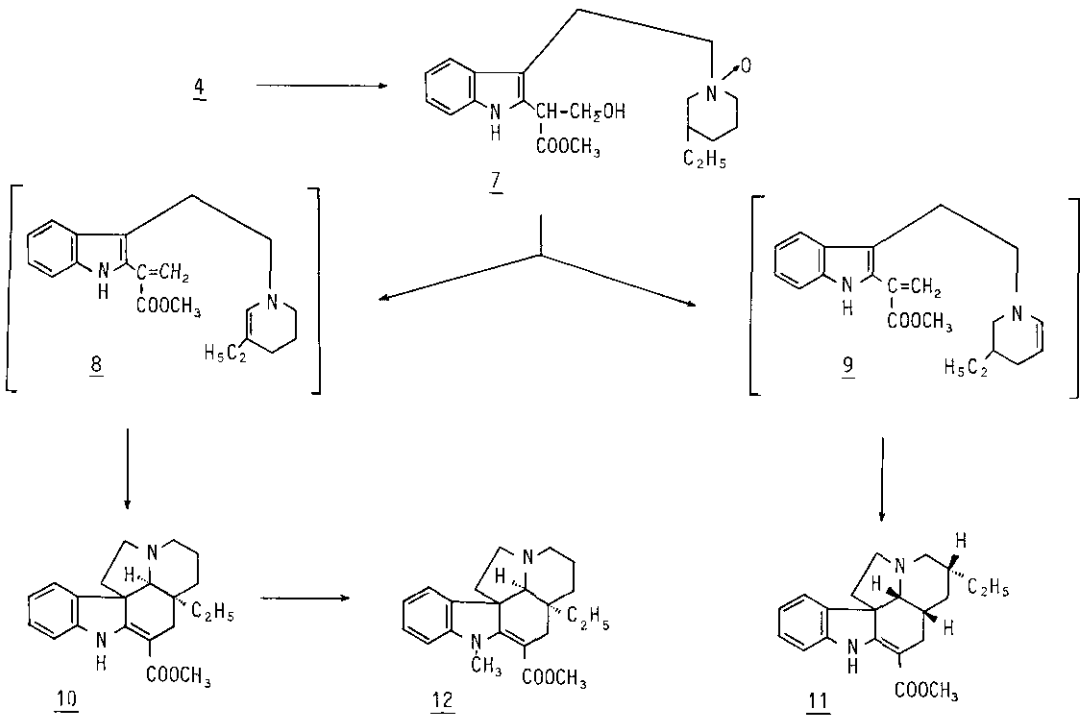
6a: R=H

b: R=CH_3

A synthesis of the key secodine intermediate 8 and its isomer 9 could now be projected through transformation of 4 into its N-oxide [7, m-CPBA/CH_2Cl_2,-15 °C, 50 min, 50.1 %] and subsequent treatment of 7 with acetic anhydride [in pyridine, RT/1h]. As a result of the latter reaction 8 and its isomer 9 were formed and were immediately cyclized into a 2:1 mixture of (±)-vincadifformine 10 and (±)-ψ-vincadifformine 11 (12,3 %). After flash chromatographic separation[13] [$Al_2O_3$150 $PF_{254+366}$/TypT/, eluting with benzene-hexane 1:1] 10 was crystallized from acetone-water [mp 123-125 °C, lit.[14-15] 124-125 °C] and proved to be identical with the product, obtained on hydrogenation of tabersonine, while 11 was isolated as an oil. All their spectroscopic data were in accord with those reported in the literature[15-19].



Transformation of 10 into (±)-minovine (12) was carried out both according to the method described in the literature[1], and by methylation of 10 with methyl iodide [Na/NH_3, oil, 20 %].

The spectroscopic data were again identical with those reported.

The above synthetic sequence further demonstrates that the postulated biogenetic secodine intermediate 8 and its isomer 9 indeed undergo the biogenetically proposed cyclizations.

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7. Compound 4: ^{1}H-NMR ($CDCl_3$): δ 0.83+0.90 (3H,t,C_{18}-H_3), 1.2 (2H,m,C_{19}-H_2), 3.74 (3H,s,C_{23}-H_3), 3.95-4.35 (3H,m,C_{16}-H+C_{17}-H_2), 4.56 (1H,br s,C_{17}-OH), 7.0-7.6 (4H,m,aromatic H), 8.79 (1H,br s, N_1-H) ppm. ^{13}C-NMR ($CDCl_3$): δ 11.0; 11.1 (C_{18}), 20.9 (C_6), 24.1; 24.2 (C_{14}), 27.1; 27.2 (C_{19}), 29.8 (C_{15}), 36.5; 36.6 (C_{20}), 45.7 (C_{16}), 52.4 (C_{23}), 53.7; 54.4 (C_3), 59.1 (C_5), 58.9; 60.1 (C_{21}), 63.7 (C_{17}), 110.9; 111.0 (C_7), 111.3 (C_{12}), 118.2^{x} (C_9), 119.4^{x} (C_{11}), 122.0 (C_{10}), 127.6 (C_8), 129.8; 129.9 (C_2), 135.9 (C_{13}), 172.8 (C_{22}) ppm[12]. MS: m/z (%) 358 (4.9), 126 (100), 59 (32.3), 43 (65.8).
8. Compound 5: ^{1}H-NMR ($CDCl_3$): δ 0.90 (3H,t,C_{18}-H_3), 3.85 (3H,s,C_{23}-H_3), 6.15 (1H,d,J=1Hz,C_{17}-H_A), 6.53 (1H,d,J=1Hz,C_{17}-H_B), 9.3 (1H,br s, N_1-H) ppm. MS: m/z (%) 340 (18.1), 168 (6.3), 126 (100), 58 (35.0), 55 (20.7).
9. Compound 6a: ^{1}H-NMR ($CDCl_3$): δ 0.92 (3H,t,C_{18}-H_3), 1.25 (2H,m,C_{19}-H_2), 1.56 (3H,d,J=7.4Hz,C_{17}-H_3), 3.72 (3H,s,C_{23}-H_3), 4.10 (1H,q,C_{16}-H), 6.95-7.65 (4H,m,aromatic H), 8.39 (1H,br s, N_1-H) ppm. ^{13}C-NMR ($CDCl_3$): δ 11.4 (C_{18}), 19.0 (C_{17}), 21.8 (C_6), 25.5 (C_{14}), 27.5 (C_{19}), 30.8 (C_{15}), 36.9 (C_{16}), 37.9 (C_{20}), 52.3 (C_{23}), 54.4; 54.5 (C_3), 60.1 (C_5), 60.4; 60.5 (C_{21}), 110.7 (C_7), 110.9 (C_{12}), 118.6^{x} (C_9), 119.3^{x} (C_{11}), 121.8 (C_{10}), 128.1 (C_8), 132.6 (C_2), 135.7 (C_{13}), 174.7 (C_{22}) ppm[12]. MS: m/z (%) 342 (56.2), 170 (8.0), 156 (14.8), 126 (100), 58 (43).
10. Compound 6b: ^{1}H-NMR ($CDCl_3$): δ 0.92 (3H,t, C_{18}-H_3), 1.25 (2H,m,C_{19}-H_2), 1.58 (3H,d,J=7.4Hz,C_{17}-H_3), 3.67^{x} (3H,s,C_{23}-H_3), 3.69^{x} (3H,s,N_1-CH_3), 4.20 (1H,

q,C_{16}-H), 7.0-7.7 (4H,m,aromatic H) ppm[12]. ^{13}C-NMR ($CDCl_3$): δ 11.4 (C_{18}), 16.9 (C_{17}), 21.9 (C_6), 25.3 (C_{14}), 27.4 (C_{19}), 30.3 (N_1-CH_3), 30.6 (C_{15}), 36.3 (C_{16}), 37.7 (C_{20}), 52.3 (C_{23}), 54.3 (C_3), 60.0 (C_5), 60.2 (C_{21}), 108.9 (C_{12}), 110.5 (C_7), 118.6^X (C_9), 119.2^X (C_{11}), 121.6 (C_{10}), 127.5 (C_8), 134.8 (C_2), 137.2 (C_{13}), 173.7 (C_{22}) ppm[12]. *MS*: m/z (%) 356 (63.5), 230 (9.8), 171 (16.3), 170 (22.0), 126 (100).

11. Compound 7: ^{1}H-NMR ($CDCl_3$): δ 0.85 + 0.92 (3H,t,C_{18}-H_3), 1.2 (2H,m,C_{19}-H_2), 3.67 (3H,s,C_{23}-H_3), 3.9-4.5 (3H,m,C_{16}-H+C_{17}-H_2), 6.95-7.6 (4H,m,aromatic H), 9.02 (1H,br s, N_1-H) ppm. ^{13}C-NMR ($CDCl_3$): δ 10.8; 10.9 (C_{18}), 17.5 (C_6), 20.3 (C_{14}), 26.2 (C_{19}), 28.4 (C_{15}), 32.5 (C_{20}), 46.0 (C_{16}), 52.2 (C_{23}), 63.5 (C_{17}), 63.5; 64.3 (C_3), 68.8; 69.4 (C_{21}), 70.9 (C_5), 108.2; 108.3 (C_7), 111.4 (C_{12}), 117.8^X (C_9), 119.4^X (C_{11}), 121.9 (C_{10}), 127.6 (C_8), 131.0 (C_2), 135.9 (C_{13}), 172.7 (C_{22}) ppm[12]. MS: m/z (%) 340 (33.7), 338 (9.3), 227 (35.9), 225 (10.6), 195 (11.1), 156 (27.0), 126 (100), 124 (11.7), 112 (28.4).
12. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian XL-100-15 NMR spectrometer at 100.1 and 25.16 MHz respectively. Chemical shifts were measured relative to internal TMS, the values signed with X may be interchanged. Mass spectra were taken on a JEOL-JMS-01 SG-2 (70 eV, ion source temp. 150 °C, direct insertion) mass spectrometer. Mps are uncorrected.
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