

SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. XXV¹.

A NEW APPROACH TO (\pm)-TETRAHYDROSECODIN-17-OL, (\pm)-TETRAHYDROSECODINE,
 (\pm)-VINCADIFFORMINE, (\pm)- ψ -VINCADIFFORMINE AND (\pm)-MINOVINE

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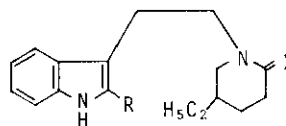
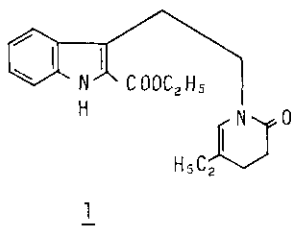
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Abstract - Starting from 1 the syntheses of the title compounds were
 achieved using Polonovski reaction of 7 as the key step.

In Kuehne's studies on the biomimetic alkaloid syntheses the biogenetically
 proposed secodine intermediate 8 plays an important role².

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 1³ as starting material. The envisaged
 intermediate 4 (tetrahydrosecodin-17-ol) could serve as a source for producing
 dihydrosecodine (5) and tetrahydrosecodine (6a).



2a: R=COOC₂H₅, X=O

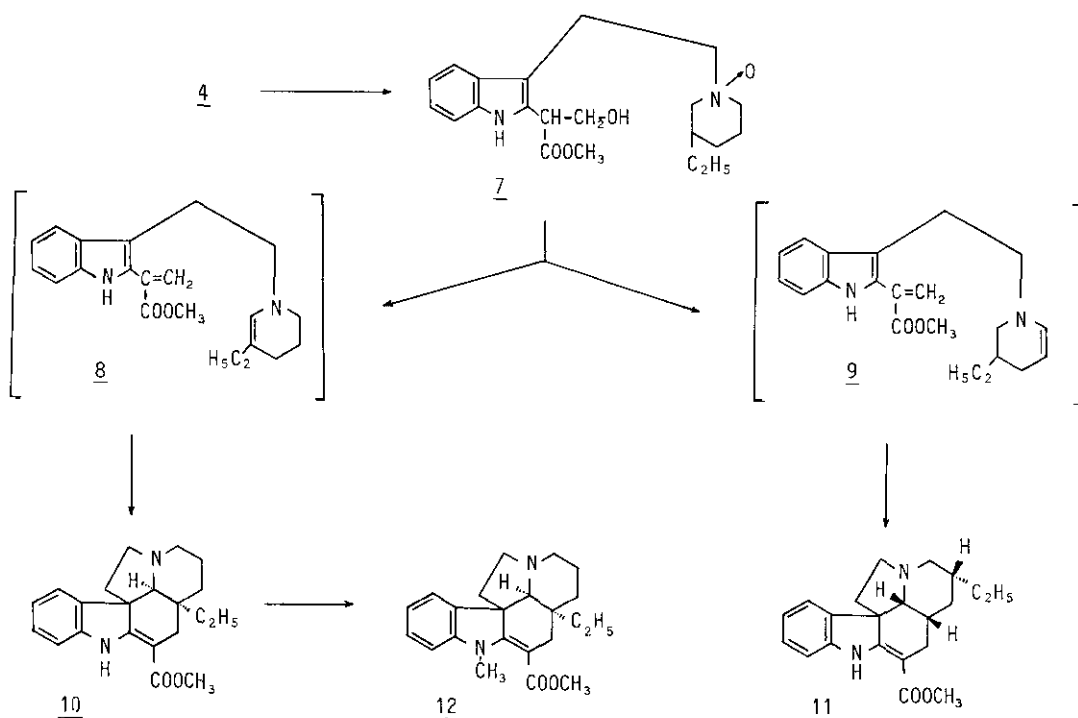
b: R=CH₂OH, X=H₂

c: R=CH₂OCO \emptyset , X=H₂

d: R=CH₂CN, X=H₂

e: R=CH₂COOCH₃, X=H₂

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/CH₂Cl₂, -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 separation¹³ [Al₂O₃150 PF₂₅₄₊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 literature¹⁵⁻¹⁹.



Transformation of 10 into (+)-minovine (12) was carried out both according to the method described in the literature¹, and by methylation of 10 with methyl iodide [Na/NH₃, 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: $^1\text{H-NMR}$ (CDCl_3): δ 0.83+0.90 (3H,t, $\text{C}_{18}\text{-H}_3$), 1.2 (2H,m, $\text{C}_{19}\text{-H}_2$), 3.74 (3H,s, $\text{C}_{23}\text{-H}_3$), 3.95-4.35 (3H,m, $\text{C}_{16}\text{-H}+\text{C}_{17}\text{-H}_2$), 4.56 (1H,br s, $\text{C}_{17}\text{-OH}$), 7.0-7.6 (4H,m,aromatic H), 8.79 (1H,br s, $\text{N}_1\text{-H}$) ppm. $^{13}\text{C-NMR}$ (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}) ppm¹².
MS: m/z (%) 358 (4.9), 126 (100), 59 (32.3), 43 (65.8).
8. Compound 5: $^1\text{H-NMR}$ (CDCl_3): δ 0.90 (3H,t, $\text{C}_{18}\text{-H}_3$), 3.85 (3H,s, $\text{C}_{23}\text{-H}_3$), 6.15 (1H,d,J=1Hz, $\text{C}_{17}\text{-H}_A$), 6.53 (1H,d,J=1Hz, $\text{C}_{17}\text{-H}_B$), 9.3 (1H,br s, $\text{N}_1\text{-H}$) ppm. MS: m/z (%) 340 (18.1), 168 (6.3), 126 (100), 58 (35.0), 55 (20.7).
9. Compound 6a: $^1\text{H-NMR}$ (CDCl_3): δ 0.92 (3H,t, $\text{C}_{18}\text{-H}_3$), 1.25 (2H,m, $\text{C}_{19}\text{-H}_2$), 1.56 (3H,d,J=7.4Hz, $\text{C}_{17}\text{-H}_3$), 3.72 (3H,s, $\text{C}_{23}\text{-H}_3$), 4.10 (1H,q, $\text{C}_{16}\text{-H}$), 6.95-7.65 (4H,m,aromatic H), 8.39 (1H,br s, $\text{N}_1\text{-H}$) ppm. $^{13}\text{C-NMR}$ (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}) ppm¹². MS: m/z (%) 342 (56.2), 170 (8.0), 156 (14.8), 126 (100), 58 (43).
10. Compound 6b: $^1\text{H-NMR}$ (CDCl_3): δ 0.92 (3H,t, $\text{C}_{18}\text{-H}_3$), 1.25 (2H,m, $\text{C}_{19}\text{-H}_2$), 1.58 (3H,d,J=7.4Hz, $\text{C}_{17}\text{-H}_3$), 3.67^x (3H,s, $\text{C}_{23}\text{-H}_3$), 3.69^x (3H,s, $\text{N}_1\text{-CH}_3$), 4.20 (1H,

- q, C₁₆-H), 7.0-7.7 (4H, m, aromatic H) ppm¹². ¹³C-NMR (CDCl₃): δ 11.4 (C₁₈), 16.9 (C₁₇), 21.9 (C₆), 25.3 (C₁₄), 27.4 (C₁₉), 30.3 (N₁-CH₃), 30.6 (C₁₅), 36.3 (C₁₆), 37.7 (C₂₀), 52.3 (C₂₃), 54.3 (C₃), 60.0 (C₅), 60.2 (C₂₁), 108.9 (C₁₂), 110.5 (C₇), 118.6^x (C₉), 119.2^x (C₁₁), 121.6 (C₁₀), 127.5 (C₈), 134.8 (C₂), 137.2 (C₁₃), 173.7 (C₂₂) ppm¹². MS: m/z (%) 356 (63.5), 230 (9.8), 171 (16.3), 170 (22.0), 126 (100).
11. Compound 7: ¹H-NMR (CDCl₃): δ 0.85 + 0.92 (3H, t, C₁₈-H₃), 1.2 (2H, m, C₁₉-H₂), 3.67 (3H, s, C₂₃-H₃), 3.9-4.5 (3H, m, C₁₆-H + C₁₇-H₂), 6.95-7.6 (4H, m, aromatic H), 9.02 (1H, br s, N₁-H) ppm. ¹³C-NMR (CDCl₃): δ 10.8; 10.9 (C₁₈), 17.5 (C₆), 20.3 (C₁₄), 26.2 (C₁₉), 28.4 (C₁₅), 32.5 (C₂₀), 46.0 (C₁₆), 52.2 (C₂₃), 63.5 (C₁₇), 63.5; 64.3 (C₃), 68.8; 69.4 (C₂₁), 70.9 (C₅), 108.2; 108.3 (C₇), 111.4 (C₁₂), 117.8^x (C₉), 119.4^x (C₁₁), 121.9 (C₁₀), 127.6 (C₈), 131.0 (C₂), 135.9 (C₁₃), 172.7 (C₂₂) ppm¹². 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. ¹H- and ¹³C-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-O1 SG-2 (70 eV, ion source temp. 150 °C, direct insertion) mass spectrometer. Mps are uncorrected.
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