

SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. XXVI¹.
AN UNUSUAL SIDE-CHAIN ELIMINATION FROM INDOLE NUCLEUS

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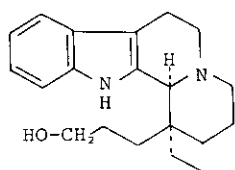
*Abstract - Investigating the Hofmann reaction of quaternary
salt 2 an unusual side-chain elimination from position 3 of
the indole nucleus has been observed.*

With the purpose of SAR studies on alkaloid-like compounds the synthesis of
3-substituted indole derivatives (3-7), containing the indicated azabicyclo[3.3.1]-
nonane moiety at position 2 of the indole nucleus, has been intended.

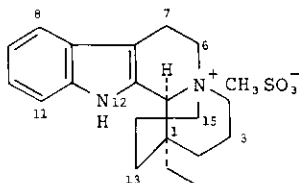
To reach this goal Hofmann elimination of quaternary salt 2 induced by appropriate
nucleophile seemed to be an attractive approach. Though Atta-Ur-Rahman² reported
exclusive C_{12b}-N cleavage in the degradation of a similar quaternary β -carboline
derivative, Kutney³, in the same type reaction, isolated two cyano-substituted
derivatives; the main product (28 %) arose by C₆-N bond opening, the other one
(14 %) by C_{12b}-N fission.

The quaternary salt 2 has been prepared in 71 % yield⁵ from the optically active
[1(S), 12b(S)] alcohol 1⁴ by mesylation.

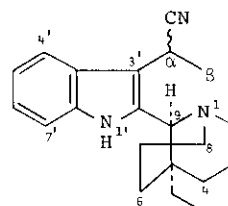
By reacting 2 with NaCN in ethylene glycol at 200 °C the cyano derivatives 3 and
4 have been obtained in 68 % combined yield. The epimers have been separated by
column chromatography on silica gel (Kieselgel 60, 0.063-0.2 mm, Merck; elution with
ethyl acetate - diethylamine 10:1). Compound 3 (epimer A) has been obtained as a
yellow oil in 42 % yield⁶.



1



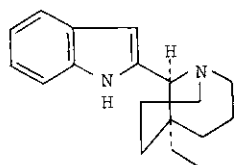
2



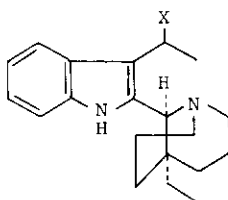
3 epimer A

4 epimer B

Cyanide 4 (epimer B) has been isolated as colourless crystals in 26 % yield⁷. On the other hand, when 2 was reacted with NaOH in the same conditions, to our surprise, compound 8 was isolated in good yield (80 %) ⁸.

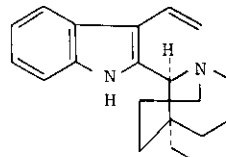


8



5 X = H

7 X = OH



6

By column chromatography (Kieselgel 60, 0.063-0.2 mm, Merck; elution with toluene-diethylamine 10:1) of the mother liquor small amounts of 3'-ethyl (5, brownish oil, yield 3 %) ⁹ and 3'-vinyl (6, dark oil, yield < 1 %) ¹⁰ derivatives could also be isolated.

Concerning the mechanism of transformation 2 $\longrightarrow$ 8, similarly to the formation of 3 and 4, addition of hydroxide anion to vinyl derivative 6 followed by retrohydroxy-alkylation process or oxydation to 3'-acetyl derivative and its acyl fission was originally assumed. Since the 3'-hydroxyalkyl derivative 7 could not even be detected in the reaction mixture, this supposition requires further investigation and confirmation.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. For part XXV. see Gy. Kalaus, M. Kiss, M. Kajtár-Peredy, J. Brlik, L. Szabó, and Cs. Szántay, the preceding paper.
2. Atta-Ur-Rahman, J. A. Beisler, and J. Harley-Mason, *Tetrahedron*, **36**, 1063 (1980).
3. J. P. Kutney, Ka Kong Chan, A. Failli, J. M. Fromson, C. Gletsos, A. Leutwiler, V. R. Nelson, and J. P. de Souza, *Helv. Chim. Acta*, **58**, 1648 (1975).
4. J. Laronze, J. Y. Laronze, J. Lévy, and J. Le Men, *Bull. Soc. Chim. France*, 1195 (1977).
5. Compound **2**: mp 330 °C (decomp.); $[\alpha]_D^{20} +13.4^\circ$ (c= 1.0; H₂O); IR (KBr): 3280 cm⁻¹ (indole NH, bonded), 1215, 1176, 1043, 553 and 526 cm⁻¹ (SO₃); ¹H-NMR (DMSO-d₆+CDCl₃, 3:1): δ (ppm) 1.10 (3H, t, J=7.5 Hz, CH₂-CH₃), 2.48 (3H, s, CH₃SO₃⁻), 4.94 (1H, broad s, C_{12b}-H), 6.95-7.65 (4H, m, aromatic), 9.94 (1H, broad s, indole NH); ¹³C-NMR (DMSO-d₆+CDCl₃, 3:1): δ (ppm) ¹¹ 7.3 (CH₂-CH₃), 17.3 (C₇), 20.3^x (C₁₄), 20.5^x (C₃), 28.4⁺ (C₁₅), 32.1⁺ (CH₂-CH₃), 33.2⁺ (C₂), 36.4 (C₁), 39.4 (CH₃SO₃⁻), 51.2 (C₁₃), 63.1 (C₆), 64.7 (C₄), 69.1 (C_{12b}), 107.4 (C_{7a}), 112.7 (C₁₁), 117.9 (C₈), 119.7 (C₉), 122.6 (C₁₀), 125.4* (C_{12a}), 125.9* (C_{7b}), 137.4 (C_{11a}); Calc. for C₂₁H₃₀N₂O₃S (390.54): C, 64.58; H, 7.74; N, 7.17; S, 8.21. Found: C, 64.65; H, 7.69; N, 7.18; S, 8.20.
6. Compound **3**: $[\alpha]_D^{20} +78^\circ$ (c=1.0; CHCl₃); MS m/e (%): 321 (M⁺, 35), 320 (4), 392 (100), 209 (18), 183 (11), 155 (11), 96 (14); IR (KBr): 3403 cm⁻¹ (indole NH, bonded; 3490 cm⁻¹ in CHCl₃), 2236 cm⁻¹ (CN); ¹H-NMR (CDCl₃): δ (ppm) 0.74 (3H, t, J=7.2 Hz, CH₂-CH₃), 1.1-1.3 (2H, m, CH₂-CH₃), 1.69 (3H, d, J=7.4 Hz, C_β-H₃), 4.10 (1H, s, C₉-H), 4.35 (1H, q, C_α-H), 7.0-7.8 (4H, m, aromatic), 8.25 (1H, broad s, indole NH); ¹³C-NMR (CDCl₃): δ (ppm) ¹¹ 6.6 (CH₂-CH₃), 20.4 (C_β), 22.1^x (C₇), 22.2 (C_α), 24.0^x (C₃), 31.2 (C₅), 31.3 (C₆), 34.5 (CH₂-CH₃), 37.8 (C₄), 46.1 (C₂), 55.0 (C₈), 60.4 (C₉), 109.6

- (C₃), 111.3 (C₇), 118.1 (C₄), 119.8⁺ (C₅), 121.9⁺ (C₆), 122.2 (CN), 125.4 (C_{3a}), 135.0 (C₂), 135.2 (C_{7a}); Calc. for C₂₁H₂₇N₃ (321.45): C, 78.46; H, 8.47; N, 13.07. Found: C, 78.52; H, 8.47; N, 13.09.
7. Compound 4: mp 92-94 °C; [α]_D²⁰ +4.5° (c=1.0; DMF); MS m/e (%): 321 (M⁺, 32), 320 (4), 292 (100), 209 (20), 183 (12), 155 (13), 96 (18); IR (KBr): 3405 and 3320 cm⁻¹ (indole NH, different bonded forms; 3495 cm⁻¹ in CHCl₃), 2236 cm⁻¹ (CN); ¹H-NMR (CDCl₃): δ (ppm) 0.75 (3H, t, J=7 Hz, CH₂-CH₃), 1.20 (2H, m, CH₂-CH₃), 1.70 (3H, d, J=7.4 Hz, C_β-H₃), 3.98 (1H, s, C₉-H), 4.25 (1H, q, C_α-H), 7.0-7.9 (4H, m, aromatic), 8.24 (1H, broad s, indole NH); ¹³C-NMR (CDCl₃): δ (ppm)¹¹ 6.7 (CH₂-CH₃), 20.1 (C_β), 22.1^x (C₇), 22.4 (C_α), 24.0^x (C₃), 31.2 (C₅), 31.6 (C₆), 34.6 (CH₂-CH₃), 37.6 (C₄), 46.2 (C₂), 55.1 (C₈), 60.4 (C₉), 109.9 (C₃), 111.3 (C₇), 118.7 (C₄), 119.9⁺ (C₅), 122.0⁺ (C₆), 122.2 (CN), 125.2 (C_{3a}), 134.9 (C₂), 135.2 (C_{7a}); Calc. for C₂₁H₂₇N₃ (321.45): C, 78.46; H, 8.47; N, 13.07. Found: C, 78.49; H, 8.46; N, 13.10.
8. Compound 8: mp 65-67 °C; [α]_D²⁰ +79.2° (c=1.0; CHCl₃); MS m/e (%): 268 (M⁺, 44), 267 (7), 239 (100), 156 (52), 143 (19), 130 (31), 96 (17); IR (CHCl₃): 3450, 3435, 3430 and 3400 cm⁻¹ (indole NH, different bonded forms), 1295 cm⁻¹ (CN); ¹H-NMR (CDCl₃): δ (ppm) 0.84 (3H, t, J=7.5 Hz, CH₂-CH₃), 3.88 (1H, broad s, C₉-H), 6.53 (1H, s, C₃-H), 6.9-7.6 (4H, m, aromatic), 8.93 (1H, broad s, indole NH); ¹³C-NMR (CDCl₃): δ (ppm)¹¹ 6.9 (CH₂-CH₃), 23.1^x (C₇), 24.2^x (C₃), 31.3 (C₆), 31.5 (C₅), 34.4 (CH₂-CH₃), 36.4 (C₄), 46.0 (C₂), 54.8 (C₈), 62.5 (C₉), 101.7 (C₃), 110.6 (C₇), 119.1⁺ (C₆), 119.9⁺ (C₄), 121.2 (C₅), 128.6 (C_{3a}), 135.1 (C₂), 137.1 (C_{7a}); Calc. for C₁₈H₂₄N₂ (268.39): C, 80.55; H, 9.01; N, 10.44. Found: C, 80.54; H, 9.05; N, 10.45.
9. Compound 5: ¹H-NMR (CDCl₃): δ (ppm) 0.68 (3H, t, J=7 Hz, C₅-CH₂-CH₃), 1.04 (2H, m, C₅-CH₂-CH₃), 1.27 (3H, t, J=7.5 Hz, C_β-H₃), 1.4-2.4 (8H, m, C₃-H₂+C₄-H₂+C₆-H₂+C₇-H₂), 2.80 (2H, q, C_α-H₂), 2.55-3.50 (4H, m, C₂-H₂+C₈-H₂), 4.01 (1H, broad s, C₉-H), 6.95-7.7 (4H, m, aromatic), 8.0 (1H, broad s, indole NH); ¹³C-NMR (CDCl₃): δ (ppm)¹¹ 6.5 (C₅-CH₂-CH₃), 15.7 (C_β), 17.8 (C_α), 22.0^x (C₇), 24.2^x (C₃), 31.2 (C₅), 31.3 (C₆), 34.5 (C₅-CH₂-CH₃), 37.6 (C₄), 46.5 (C₂), 55.9 (C₈), 60.4 (C₉), 110.5 (C₇), 117.5 (C₃), 118.8⁺ (C₄), 118.9⁺ (C₅), 121.4⁺ (C₆), 127.6 (C_{3a}), 133.5 (C₂), 135.3 (C_{7a}).
10. Compound 6: ¹H-NMR (CDCl₃): δ (ppm) 4.13 (1H, broad s, C₉-H), 5.31 (1H, dd, J_{gem}: 2.2 Hz, J_{cis}: 11.6 Hz, C_β-H_A), 5.68 (1H, dd, J_{trans}: 17.8 Hz, C_β-H_B).
11. The chemical shift values signed with identical symbols are interchangeable.

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