SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. XXVI[1]. AN UNUSUAL SIDE-CHAIN ELIMINATION FROM INDOLE NUCLEUS

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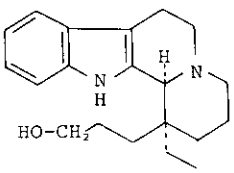
Abstract - Investigating the Hofmann reaction of quaternary salt 2 an unusual side-chain elimination from position 3 of the indole nucleus has been observed.

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-Rahman[2] reported exclusive C_{12b}-N cleavage in the degradation of a similar quaternary β-carboline derivative, Kutney[3], in the same type reaction, isolated two cyano-substituted derivatives; the main product (28 %) arose by C_6-N bond opening, the other one (14 %) by C_{12b}-N fission.

The quaternary salt 2 has been prepared in 71 % yield[5] from the optically active [1(S), 12b(S)] alcohol 1[4] 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 % yield[6].



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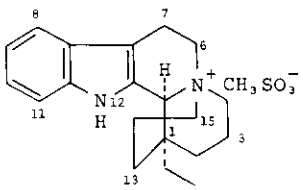

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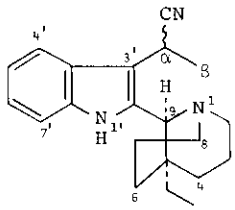
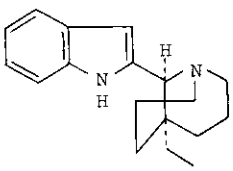


3 epimer A

4 epimer B

Cyanide 4 (epimer B) has been isolated as colourless crystals in 26 % yield[7]. 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].



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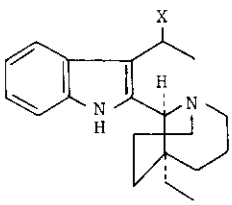
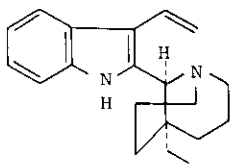


5 X = H

7 X = OH



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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 ⟶ 8, similarly to the formation of 3 and 4, addition of hydroxide anion to vinyl derivative 6 followed by retrohydroxyalkylation 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° (c= 1.0; H_2O); IR (KBr): 3280 cm^{-1} (indole NH, bonded), 1215, 1176, 1043, 553 and 526 cm^{-1} (SO_3); ^{1}H-NMR (DMSO-d_6+$CDCl_3$, 3:1): δ (ppm) 1.10 (3H, t, J=7.5 Hz, CH_2-CH_3), 2.48 (3H, s, $CH_3SO_3^-$), 4.94 (1H, broad s, C_{12b}-H), 6.95-7.65 (4H, m, aromatic), 9.94 (1H, broad s, indole NH); ^{13}C-NMR (DMSO-d_6+$CDCl_3$, 3:1): δ (ppm)[11] 7.3 (CH_2-CH_3), 17.3 (C_7), 20.3[x] (C_{14}), 20.5[x] (C_3), 28.4[+] (C_{15}), 32.1[+] (CH_2-CH_3), 33.2[+] (C_2), 36.4 (C_1), 39.4 ($CH_3SO_3^-$), 51.2 (C_{13}), 63.1 (C_6), 64.7 (C_4), 69.1 (C_{12b}), 107.4 (C_{7a}), 112.7 (C_{11}), 117.9 (C_8), 119.7 (C_9), 122.6 (C_{10}), 125.4[*] (C_{12a}), 125.9[*] (C_{7b}), 137.4 (C_{11a}); Calc. for $C_{21}H_{30}N_2O_3S$ (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° (c=1.0; $CHCl_3$); 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 $CHCl_3$), 2236 cm^{-1} (CN); ^{1}H-NMR ($CDCl_3$): δ (ppm) 0.74 (3H, t, J=7.2 Hz, CH_2-CH_3), 1.1-1.3 (2H, m, CH_2-CH_3), 1.69 (3H, d, J=7.4 Hz, C_β-H_3), 4.10 (1H, s, C_9-H), 4.35 (1H, q, C_α-H), 7.0-7.8 (4H, m, aromatic), 8.25 (1H, broad s, indole NH); ^{13}C-NMR ($CDCl_3$): δ (ppm)[11] 6.6 (CH_2-CH_3), 20.4 (C_β), 22.1[x] (C_7), 22.2 (C_α), 24.0[x] (C_3), 31.2 (C_5), 31.3 (C_6), 34.5 (CH_2-CH_3), 37.8 (C_4), 46.1 (C_2), 55.0 (C_8), 60.4 (C_9), 109.6

(C_3,), 111.3 (C_7,), 118.1 (C_4,), 119.8$^+$ (C_5,), 121.9$^+$ (C_6,), 122.2 (CN), 125.4 (C_{3a},), 135.0 (C_2,), 135.2 (C_{7a},); Calc. for $C_{21}H_{27}N_3$ (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; $[\alpha]_D^{20}$ +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 $CHCl_3$), 2236 cm^{-1} (CN); ^{1}H-NMR ($CDCl_3$): δ (ppm) 0.75 (3H, t, J=7 Hz, CH_2-C<u>H</u>$_3$), 1.20 (2H, m, C<u>H</u>$_2$-CH_3), 1.70 (3H, d, J=7.4 Hz, C_β-H_3), 3.98 (1H, s, C_9-H), 4.25 (1H, q, C_α-H), 7.0-7.9 (4H, m, aromatic), 8.24 (1H, broad s, indole NH); ^{13}C-NMR ($CDCl_3$): δ (ppm)[11] 6.7 (CH_2-<u>C</u>H$_3$), 20.1 (C_β), 22.1[x] (C_7), 22.4 (C_α), 24.0[x] (C_3), 31.2 (C_5), 31.6 (C_6), 34.6 (<u>C</u>H$_2$-CH_3), 37.6 (C_4), 46.2 (C_2), 55.1 (C_8), 60.4 (C_9), 109.9 (C_3,), 111.3 (C_7,), 118.7 (C_4,), 119.9$^+$ (C_5,), 122.0$^+$ (C_6,), 122.2 (CN), 125.2 (C_{3a},), 134.9 (C_2,), 135.2 (C_{7a},); Calc. for $C_{21}H_{27}N_3$ (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; $[\alpha]_D^{20}$ +79.2 ° (c=1.0; $CHCl_3$); MS m/e (%): 268 (M^+, 44), 267 (7), 239 (100), 156 (52), 143 (19), 130 (31), 96 (17); IR ($CHCl_3$): 3450, 3435, 3430 and 3400 cm^{-1} (indole NH, different bonded forms), 1295 cm^{-1} (CN); ^{1}H-NMR ($CDCl_3$): δ (ppm) 0.84 (3H, t, J=7.5 Hz, CH_2-C<u>H</u>$_3$), 3.88 (1H, broad s, C_9-H), 6.53 (1H, s, C_3,-H), 6.9-7.6 (4H, m, aromatic), 8.93 (1H, broad s, indole NH); ^{13}C-NMR ($CDCl_3$): δ (ppm)[11] 6.9 (CH_2-<u>C</u>H$_3$), 23.1[x] (C_7), 24.2[x] (C_3), 31.3 (C_6), 31.5 (C_5), 34.4 (<u>C</u>H$_2$-CH_3), 36.4 (C_4), 46.0 (C_2), 54.8 (C_8), 62.5 (C_9), 101.7 (C_3,), 110.6 (C_7,), 119.1$^+$ (C_6,), 119.9$^+$ (C_4,), 121.2 (C_5,), 128.6 (C_{3A},), 135.1 (C_2,), 137.1 (C_{7a},); Calc. for $C_{18}H_{24}N_2$ (268.39): C, 80.55; H, 9.01; N, 10.44. Found: C, 80.54; H, 9.05; N, 10.45.

9. Compound 5: ^{1}H-NMR ($CDCl_3$): δ (ppm) 0.68 (3H, t, J=7 Hz, C_5-CH_2-C<u>H</u>$_3$), 1.04 (2H, m, C_5-C<u>H</u>$_2$-CH_3), 1.27 (3H, t, J=7.5 Hz, C_β-H_3), 1.4-2.4 (8H, m, C_3-H_2+C_4-H_2+C_6-H_2+C_7-H_2), 2.80 (2H, q, C_α-H_2), 2.55-3.50 (4H, m, C_2-H_2+C_8-H_2), 4.01 (1H, broad s, C_9-H), 6.95-7.7 (4H, m, aromatic), 8.0 (1H, broad s, indole NH); ^{13}C-NMR ($CDCl_3$): δ (ppm)[11] 6.5 (C_5-CH_2-<u>C</u>H$_3$), 15.7 (C_β), 17.8 (C_α), 22.0[x] (C_7), 24.2[x] (C_3), 31.2 (C_5), 31.3 (C_6), 34.5 (C_5-<u>C</u>H$_2$-CH_3), 37.6 (C_4), 46.5 (C_2), 55.9 (C_8), 60.4 (C_9), 110.5 (C_7,), 117.5 (C_3,), 118.8$^+$ (C_4,), 118.9$^+$ (C_5,), 121,4$^+$ (C_6,), 127.6 (C_{3a},), 133.5 (C_2,), 135.3 (C_{7a},).

10. Compound 6: ^{1}H-NMR ($CDCl_3$): δ (ppm) 4.13 (1H, broad s, C_9-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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