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Radical-Ion Chemistry of Natural Indolenines: 19,20-Dehydrotubifoline

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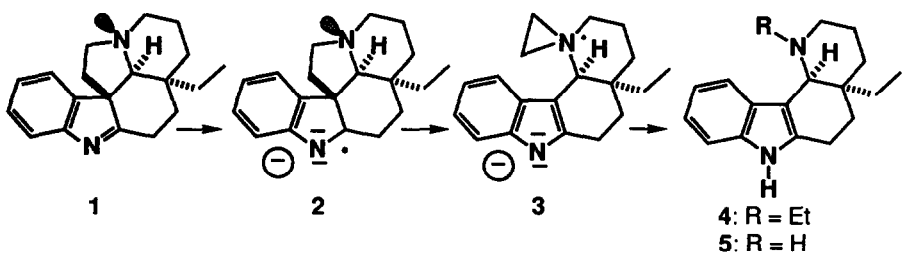
Abstract: *19,20-dehydrotubifoline was reductively rearranged with Na in boiling dioxane to 15-methyldeplancheine 11.*

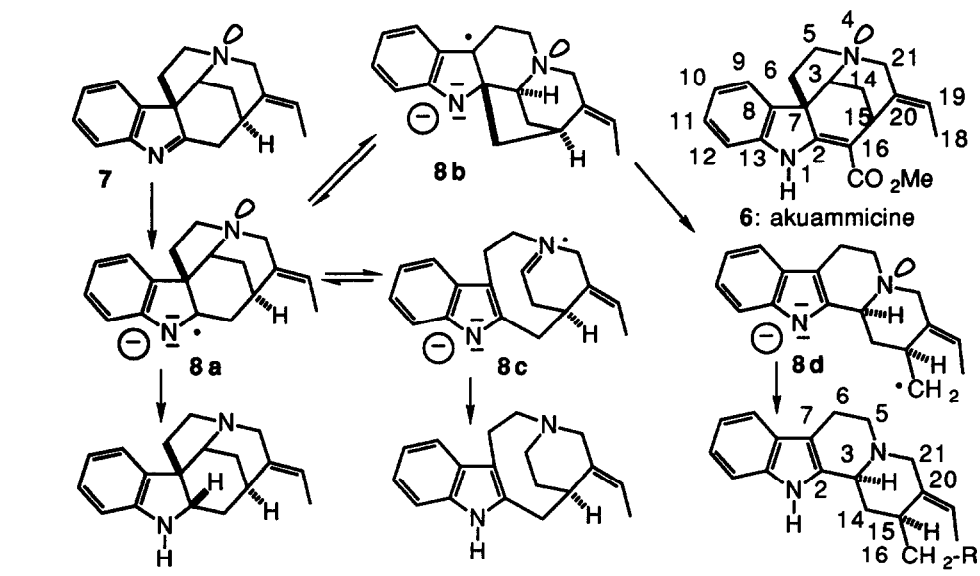
In the course of our synthesis of tuboxenine[1] we met a novel fragmentation of indolenine **1** to indoles **4** and **5**, that was induced by formation of the radical-anion **2** upon treatment with sodium in boiling tetrahydrofurane. The intermediate aziridinyl radical **3** is thought to account for the reaction.



The transformation appeared to give a possible entry into the small class of iridoid indole alkaloids lacking the ethanamine bridge of tryptamine[2]. For that purpose, 19,20-dehydrotubifoline **7** (Scheme) was prepared[3] from akuammicine **6** and further refluxed in tetrahydrofurane in the presence of sodium. The (reduced) indoline **9**[3] was then isolated (14%) as the sole transformation product, along with some unreacted **7** (30%). Raising the temperature upon using dioxane as the solvent[4] resulted in a more complex reaction that yielded indoles **10**[3] (28%) and **11**[5] (27%) along with indoline **9**[3] (12%).

The structure of **11** (15-methyldeplancheine) was assessed[5] upon its UV, and ^{1}H and ^{13}C NMR spectra, which disclosed a new methyl group (δ_C 19.94 ppm; δ_H 1.13 ppm, J= 7.2 Hz). The quaternary aromatic carbons C-2 and C-7 were clearly differenciated at 133.61 and 107.25 ppm respectively; the relationships of C-14 and C-5 with C-2, C-7, and with some aliphatic carbons in the molecule were deduced from HMBC NMR experiments[6]: the 14-protons coupled with C-3 and C-15 (^{2}J), and with C-2, C-16 and C-20 (^{3}J), while the 5-protons coupled with C-6 (^{2}J), and with C-3, C-7 and C-21 (^{3}J).

Formation of **9**, **10** and **11** from **7** is accounted for by equilibration of the primarily formed radical-anion **8a** with **8b** and **8c**: simple reduction of **8a** and of **8c** yields **9** and **10**, respectively. Further fragmentation of **8b** to **8d** rationalises the formation of **11**, featuring the geissoschizine skeleton. Of interest is the fact that zinc-acetic acid reduction of **7** was earlier shown[7] to give **9** and dihydro-**8b**, while no fragmented **11** was then detected. Only when the 16-methoxycarbonyl appendage was present (*e.g.* in akuammicine **6**) did the reagent promote both rearrangement and fragmentation to **12**.



Scheme

Finally it is thought that the α-orientation of the lone pair of electrons of N-4 in **7** as compared to its β-orientation in **1** is responsible for the reaction following a different course, due to the impossibility for the basic nitrogen to participate in the formation of an aziridinyl radical such as **3**.[8]

References and Notes:

1. Hugel, G.; Cossy, J.; Lévy, J. *Tetrahedron Lett.*, **1987**, *28*, 1773-1776.
2. For example, apparicine, uleine, ellipticine, vallesamine, angustilobine.
3. Smith, G.F.; Wrobel, J.T. *J.Chem.Soc.*, **1960**,.792-795.
4. Compound **7** (70 mg) and sodium (100 mg) were heated in a sealed tube at 100°C for 3 h in dry dioxane (6ml). After filtration and evaporation of the organic layer, tlc separation of the residue gave **11** (20mg, 28%), **9**[3] (9mg, 12%): LRMS, 266, (M^+ 100%), 251, 158, 123, 122, 108, 107; ^{1}H nmr (300MHz ; $CDCl_3$), δ: 1,62 (d, 3H, J= 6.6 Hz, H_3-18), 5.23 (q, 1H, J= 6.6 Hz, H-19) and **10**[3] (19mg, 28%): LRMS, 268 (M^{+2}), 266 (M^+), 144, 143, 138 (100%), 123, 107; ^{1}H nmr (300MHz; $CDCl_3$), δ: 1.80 (d, 3H, J= 6.6 Hz, H_3-18), 5.70 (q, 1H, J= 6.6 Hz, H-19), 8.35 (s, 1H, H-1).
5. **11**: mp 112-15°C (MeOH/ether); $[\alpha]_D$ +11° (c=0.4, MeOH); HRMS, calc.,266.1783, found, 266.1789; LRMS, 266 (100%), 265, 251, 237, 169, 156;uv (MeOH), 224, 272, 284, 290 nm; ^{1}H nmr (300MHz ; $CDCl_3$), δ: 1.13 (d, 3H, J= 7.2 Hz, H_3-16), 1.66 (d, 3H, J= 6.8 Hz, H_3-18), 1.77 (dt, 1H, J= 13.5; 8.5 Hz, H-14), 2.22 (dt, 1H, J= 13.5; 6 Hz, H-14), 2.70 (m, 2H, H-15, H-6), 2.95 (m, 2H, H-5, H-6), 3.10 (d, 1H, J= 11.3 Hz, H-21), 3.18 (m, 1H, H-5), 3.46 (d, 1H, J= 11.3 Hz, H-21), 3.92 (bd, 1H, H-3), 5.47 (q, 1H, J= 6.8 Hz, H-19), 7.10 (m, 2H, H-10, H-11), 7.35 (d, 1H, J= 6.8 Hz, H-12), 7.43 (d, 1H, J= 7.2 Hz, H-9), 8.3 (sl, 1H, N_1-H). ^{13}C nmr, (75 MHz, $CDCl_3$) δ: 13.15 (18), 19.66 (6), 19.94 (16), 32.49 (15), 36.57 (14), 51.14 (5), 56.15 (3), 58.99 (21), 107.29 (7), 110.97 (12), 118.02 (9), 119.34 (10), 120.99 (19), 121.45 (11), 127.17 (8), 133.61 (2), 136.01 (13), 136.54 (20).
6. Heteronuclear Multiple Bond Correlation: Bax, A.; Summers, M.F. *J.Am.Chem.Soc.*, **1986**, *108*, 2093-2094.
7. Hinshaw, W.B.; Lévy, J.; Le Men, J. *Tetrahedron Lett.*, **1971**, 995-998.
8. Thanks are due to Prof. L. Le Men-Olivier and to B. Richard for providing us with akuammicine.

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