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RING-OPENED INDOLE ALKALOIDAL ARTEFACTS FROM *LEUCONOTIS* SPECIES AND THE FACILE RING RECLOSURE OF LEUCONOLAM

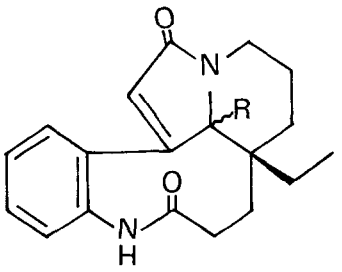
S.H. Goh and Abdul Razak Mohd Ali

Department of Chemistry, University of Malaya,

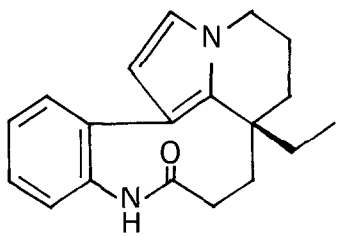
Kuala Lumpur, Malaysia.

SUMMARY: *Leuconotis eugenifolia* and *L. griffithii* provide ring-opened indole alkaloids leuconolam, epileuconolam, rhazinilam, and 5,21-dihydrorhazinilam. Facile ring reclosures of leuconolam by acid and base furnished novel diazaspiroleuconolam derivatives and a pentacyclic (Melodinus-type) alkaloid respectively.

In our continuing studies on ring-opened alkaloids, we have found that *Leuconotis eugenifolia* (Apocynaceae) provided the previously reported leuconolam (**1a**)[1,2] and rhazinilam (**2**)[3,4] as well as two new ring-opened indole alkaloids 5,21-dihydrorhazinilam (**3**) and epileuconolam (**1b**). Epileuconolam (**1b**) is likely an artefact since it was readily obtained together with leuconolam methyl ether (**1c**) by extraction of the crude plant material with 10% aqueous H_2SO_4/MeOH but not under neutral or basic conditions. All compounds were appropriately characterised by their spectral data.



1a, R = β-OH
1b, R = α-OH
1c, R = OMe



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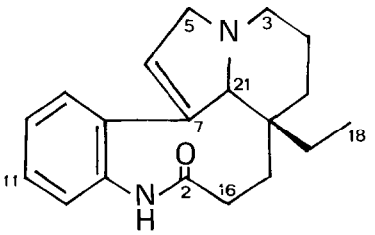

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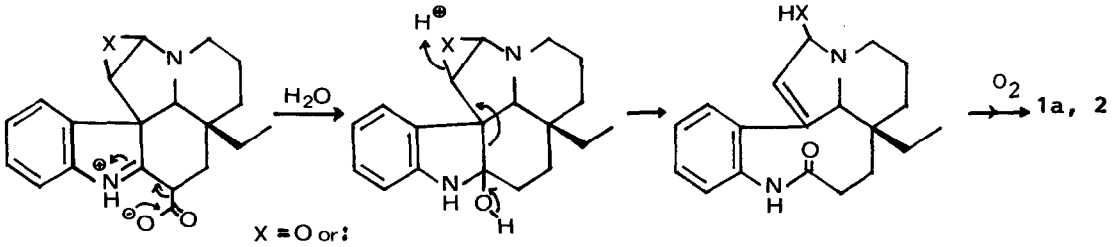
5,21-Dihydrorhazinilam (**3**) showed the following spectral characteristics:- $\delta(CDCl_3$, 90 MHz): 8.1 (1H, s, exchangeable with D_2O, NH), 7.20-7.28 (4H, m, ArH), 5.62 (1H, m, =CH), 3.73 (1H, m, NCH<u>H</u>), 3.3 (1H, br s, 21-CH), 1.2-3.1 13H, m, CH_2) and 0.58 (3H, t, CH_3); CMR $\delta(CDCl_3)$: 179.1 (C-2), 136.2, 138.7 & 141.0 (C-7, 8, 13), 130.2 (C-6), 126.6, 127.2, 127.9 & 129.2 (C-9, 10, 11, 12), 75.9 (C-21), 50.3 & 58.1 (C-3,5), 41.2 (C-20), 21.1, 26.3, 27.4, 29.2 & 37.2 (C-14, 15, 16, 17, 19), 6.8 (C-18); λ_{max}(EtOH): 213 (18,200), 227 (4,500) and 261 nm (2,670); EI-MS m/z: 296.182 (60%, M^+; calcd for $C_{19}H_{24}N_2O$, 296.1888), 279 (6), 265 (100), 253 (6), 240 (32), 237 (62), 209 (52) and 171 (25). The compound on prolonged exposure to air gave the known compound rhazinilam (**2**); in fact, all dihydrorhazinilam (**3**) fractions were observed to contain traces of rhazinilam even after careful TLC separations, indicating that the dihydro-compound (**3**) is a precursor of rhazinilam.

The formation of ring-opened indoles can be postulated as arising from the rearrangement of aspidosperma alkaloids as shown in the scheme below:-



Epileuconolam (**1b**) showed the following spectral characteristics:- $\delta(CDCl_3$, 90 MHz): 8.1-8.2 (1H, m, ArH), 7.0-7.5 (3H, m, ArH), 6.20 (1H, s, =CH), 4.4 (1H, m, NCH<u>H</u>), 1.25-3.79 (11H, m, CH_2) and 0.73 (3H, t, CH_3); CMR $\delta(CDCl_3)$: 175.8 (C-2), 173.2 (C-5), 164.1 (C-7), 148.6 (C-13), 123.4 (C-8), 118.1 (C-6), 115.8, 121.4, 124.2 & 131.4 (C-9, 10, 11, 12), 93.6 (C-21), 44.5 (C-20), 16.8, 26.1, 30.4, 33.0, 34.1, & 37.0 (C-3, 14, 15, 16, 17, 19) and 8.2 (C-18); ν_{max}(KBr & $CHCl_3$): 3400 (broad, s, OH & NH), 1680 (s, CO), 1640 (s, CO), 1600 (m), 1500 (m), 1370 cm^{-1} (m); λ_{max}(EtOH) 203 (13,000), 251 (16,700) and 342 nm (3,540); EI-MS m/z 326.158 (100%, M^+; Calcd for $C_{19}H_{22}N_2O_3$, 326.1630), 308 (68, M-H_2O), 297 (6, M-Et), 279 (6, M-H_2O-Et), 261 (12), 251 (18), 186 (43), 159 (50) and 145 (56). The mass spectral data are almost identical to those of leuconolam (**1a**)[1] and the CMR spectrum also shows

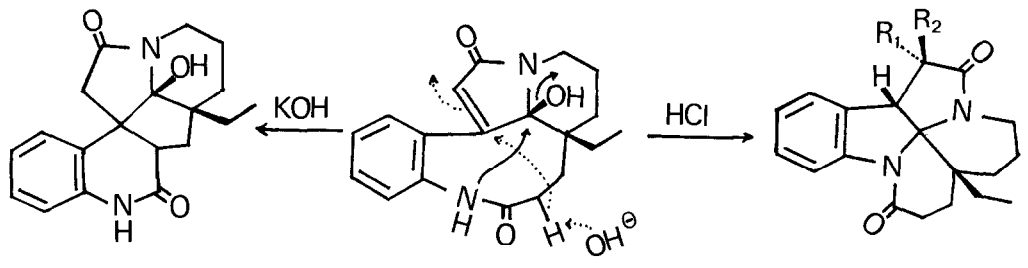
similarities, which support the assignment of epileuconolam as (**1b**), the alpha hydroxy isomer of leuconolam (**1a**).

Reaction of leuconolam (**1a**) with HCl in methanol gave, apart from leuconolam methyl ether (**1c**), two novel cyclisation products, assigned as **4a** and **4b**, in 45% and 30% yields with the beta-chloro isomer (**4a**) predominating. The structures of these compounds were assigned based on their mass and NMR spectral data below:-

β-Chlorodiazaspiroleuconolam (**4a**) had m.p. 210-211, δ($CDCl_3$, 90 MHz): 7.89 - 7.98 (1H, m, ArH), 7.15 - 7.29 (3H, m, ArH), 4.63 (1H, s, 6-CH), 4.18 (1H, s, 7-CH), 1.0 - 1.9 & 2.59 - 2.85 (12H, m, CH_2), and 0.94 (3H, t, CH_3); CMR δ($CDCl_3$) 172.5 (C-2), 166.8 (C-5), 131.5 & 141.4 (C-8,13), 119.6, 124.1, 125.6 & 129.0 (C-9, 10, 11, 12), 92.8 (C-21), 57.6 (C-6), 51.1 (C-7), 37.1 (C-20), 19.2, 27.8, 27.8, 30.4, 30.6 & 36.6 (C-3, 14, 15, 16, 17, 19) and 7.7 (C-18). λ_{max}(EtOH) 205 (26,100), 244 sh (6,630) and 280nm sh (1,460). ν_{max} (KBr) 1710 (s, CO), 1670 (s, CO) and 1600 cm^{-1}(m); EI-MS m/z 344.129 (100 %, M^+; calcd for $C_{19}H_{21}N_2O_2Cl$, 344.1286), 346 (35, M+2), 316 (16), 309 (85), 301 (22), 281 (10), 265 (7), 253 (5), 207 (6), 171 (14), 157 (8) and 128 (14).

α-Chlorodiazaspiroleuconolam (**4b**) had m.p. 248-249 C; δ ($CDCl_3$, 90MHz) 7.7-7.8 (2H, m, ArH), 7.1-7.3 (2H, m, ArH), 5.07 (1H, d, J 7 Hz, 6-CH), 4.20 (1H, d, J 7 Hz, 7CH), 1.0-1.7 and 2.5-2.7 (12H, m, CH_2) 0.94, t, 3H (CH_3); CMR δ($CDCl_3$): 172.2 (C-2), 166.5 (C-5), 142.5 & 128.7, (C-8, 13), 119.4, 124.5, 128.1 & 128.3 (C-9, 10, 11, 12), 89.9 (C-21), 57.3 (C-6), 47.5 (C-7) , 38.2 (C-20), 19.9, 26.7, 26.7, 27.1, 29.3 & 37.5 (C-3, 14, 15, 16, 17, 19), 7.2 (C-18) ; λ_{max}(EtOH) 205 (27,600), 238 sh (8,310), 278nm sh (2,470); ν_{max}(KBr): 1710 (s, CO), and 1680 (s, CO); E.I.-M.S. m/z: 344.130 (100 %, M^+, calcd for $C_{19}H_{21}N_2O_2Cl$, 344.1286), 346 (35, M+2), 316 (17), 309 (65), 301 (10), 281 (9), 265 (5), 253 (5), 207 (11), 171 (17), 157 (12) and 128 (13).

The isomers **4a** and **4b** had C-6-H to C-7-H coupling constants of <0.2 and 7 Hz respectively as a result of differences in dihedral angles as expected from the structures shown. The structure of **4b** was confirmed by single crystal X-ray crystallography[5]. The mechanism of formation of these diazaspiro-derivatives is shown below as a transannular attack of nitrogen of the incipient carbonium ion centre followed by a non-stereospecific anti-Markownikoff addition of HCl.



5 1a

4a R_1 = H, R_2 = Cl
4b R_1 = Cl, R_2 = H

The reaction of leuconolam (**1a**) with potassium hydroxide in methanol is depicted as an internal Michael addition (shown above) which is interesting in that it yields a pentacyclic (Melodinus-type[6]) alkaloid (5), 5-oxo-14,15,18,19-tetrahydro-21-hydroxy-meloscine, in 80% yield. This facile reaction therefore also provides an alternative pathway in the biogenesis of Melodinus alkaloids. **5** had HMR δ($CDCl_3$, 90 MHz): 9.16 (1H, br s, exchangeable with D_2O, NH), 7.36-7.45 (1H, m, ArH), 7.09-7.27 (2H, m, ArH), 6.67-7.02 (1H, m, ArH), 4.04-4.18 (1H, m, NCHH), 1.68 (1H, s, OH, exchangeable with D_2O), 1.6-2.95 (12H, m, CH_2), 0.72 (3H, t, CH_3); CMR δ($CDCl_3$): 171.1 (C-2), 170.9 (C-5), 121.9 & 135.9 (C-8,13), 116.1, 123.6, 128.7 & 129.1 (C-9, 10, 11, 12), 100.8 (C-21), 51.6 (C-3), 50.6 (C-7),49.7 (C-16), 46.6 (C-20), 19.5, 26.2, 27.8, 32.4 & 37.1 (C-6, 14, 15, 17, 19) and 7.3 (C-18). λ_{max} (EtOH) 212 (30,000), 251 (9,720), 258 (8,420), 284 (2,620) and 293nm (2,180); ν_{max} (KBr): 3480 (s), 3365 (s), 1700 (br s) and 1590 cm^{-1}(s); E.I.-M.S. m/z: 326.167 (45%, M^+, calcd for $C_{19}H_{22}N_2O_3$, 326.1630), 309 (8), 297 (4), 279 (6), 255 (7), 242 (7), 228 (13), 186 (100), 167 (30), 160 (11) and 159 (79).

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5. $C_{19}H_{21}N_2O_2Cl$ forms colourless monoclinic crystals with the space group $P2_1$, a = 9.903, b = 7.513, c = 11.399 A.

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