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# NOYAINE, THE FIRST C-RING SECOCULARINE ALKALOID

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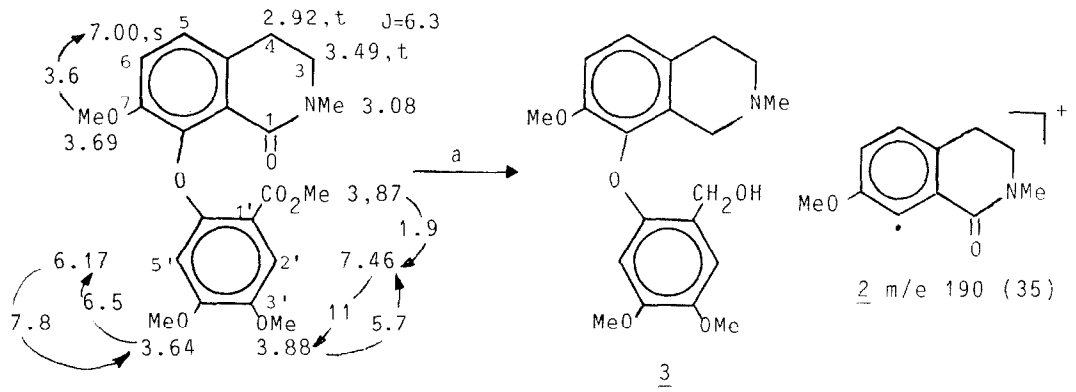
Summary: We describe the isolation and structure determination of noyaine (1), which has been obtained from Corydalis claviculata (L.)DC. Its structure was confirmed by synthesis from cularine (4) and also by total synthesis.

Continuing with our study of alkaloids from Corydalis claviculata (L.)DC[1]. (Fumariaceae) we wish to report here the isolation of a new alkaloid, noyaine (1), whose structure was confirmed by synthesis from cularine (4), its probable biogenetic precursor, and also by total synthesis.

Noyaine (1) was obtained as an amorphous, colourless substance. Its UV spectrum, with absorption bands at $\lambda_{max}^{EtOH}$ (log $\varepsilon$ ): 220(4.20), 254(3.98) and 312(3.73) nm remained unchanged upon addition of acid or base. The PMR spectrum, indicated around expression 1, showed as the most striking features two triplets at $\delta$ 2.92(2H) and 3.49(2H)(J=6.3 Hz) and a singlet at $\delta$ 3.08(3H, NMe), which are characteristic of the isoquinol-1-one system.[2] Further proof of the presence of such a system was obtained from the IR spectrum, which showed an absorption peak at 1660 $cm^{-1}$ characteristic of the carbonyl group of a $\delta$-lactame. The CMR spectrum, with two singlets at $\delta$ 165.99 and 161.99, revealed the presence of two carbonyl groups in the molecule. There were also four quartets at $\delta$ 56.75, 56.39, 55.79 and 51.56 corresponding to four methoxyl groups, the last of them appearing at an unusually high field for a typical aromatic methoxyl group. This feature and the presence of a second carbonyl group established a carboxymethyl group as a benzene ring substituent. In addition, the aromatic region of the spectrum exhibited five singlets due to quaternary oxygenated carbons (155.02, 153.25, 152.27, 144.10 and 143.00), three singlets due to quaternary non-oxygenated carbons (132.33, 124.45 and 110.32) and four doublets due to methine carbons (123.57, 116.30, 114.09 and 99.78), and the aliphatic part exhibited two triplets due to the methylene groups (48.22 and 28.63) and one quartet at 34.92 for the N-methyl group.

Further proof for the structure was obtained from the MS spectrum, which showed the molecular ion at m/e 401(100). This corresponds to the molecular formula $C_{21}H_{23}NO_7$, which was confirmed by high resolution MS, (found: 401.1460, calculated: 401.1475). Other significant peaks were observed at m/e 386(40), 342(10) and 190(35), the latter due to the upper part of the molecule (2).

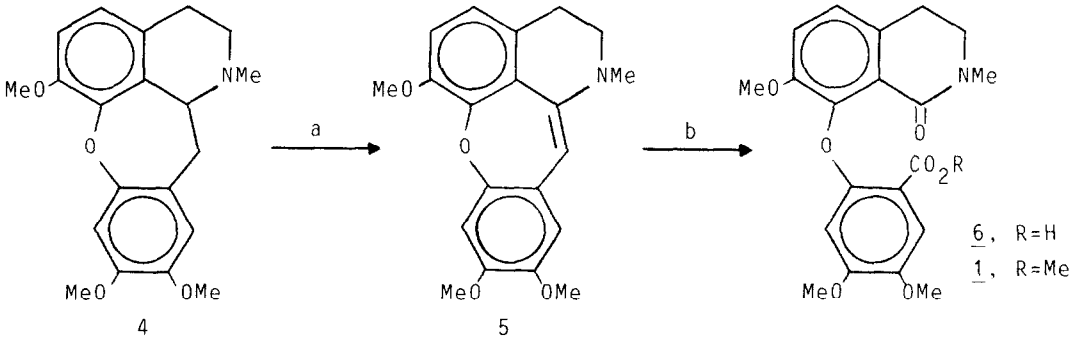



1 (PMR and nOes) — 3

a. $LiAlH_4$, THF, 4.5h reflux, 78%

As expected, treatment of noyaine (1) with $LiAlH_4$ led to the tetrahydroisoquinoline (3), whose spectroscopic data[3] clearly showed the reduction of the δ-lactame and esther functions.

In order to confirm structure 1 for noyaine, synthesis of this compound was planned using cularine (4) as the starting material, (Scheme I), and 1,α-dehydrocularine (5) as an intermediate to be transformed into noyaine by oxidative cleavage of its $C_1$-$C_\alpha$ double bond. The synthesis of 5 was carried out by photochemical oxidation of cularine (4) in the presence of benzophenone using the same conditions as previously developed in our laboratory for the synthesis of 6a,7-dehydroaporphines from the corresponding aporphines[4], (10:1 molar ratio of benzophenone/cularine, pyridine-water 1:1 v/v, 450 w Hanovia lamp, 4h). Under these conditions we were able to obtain 5 as a slightly yellow compound[5,6]. This was the first synthesis of a dehydrocularine, a class of cularine derivatives which, so far, have not been isolated from nature. Treatment of dehydrocularine 5 with $O_2$ (triplet) allowed us to obtain a 23% yield of the carboxy-isoquinol-1-one 6[7], which was easily

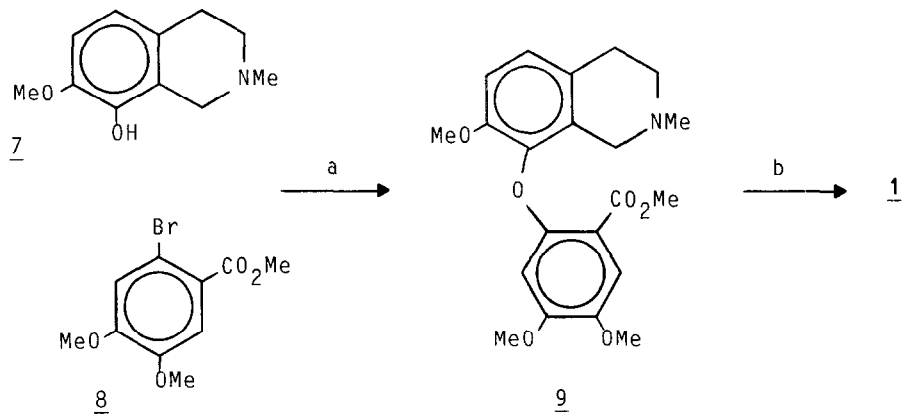



4 — 5

6, R=H
1, R=Me

a. hν, $Ph_2CO$, $Py/H_2O$, 4h, 33%; b. $O_2$, t-BuOH, Δ, 4 days, 23%;
c. $CH_2N_2$, $MeOH/Et_2O$, 100%

**Scheme I**




a. CuO, Py, anh. $K_2CO_3$, 160ºC, 3h, 57%; b. $KMnO_4$, acetone, 20%.

**Scheme II**

transformed into noyaine by methylation with diazomethane.

Finally, we also carried out a total synthesis of noyaine (1) based on the Ullmann condensation reaction[8] of the phenolic 1,2,3,4-tetrahydroisoquinoline[9] 7 and the methyl bromobenzoate [10] 8 (Scheme II). Treatment of a mixture of these compounds with CuO powder in the presence of anhydrous $K_2CO_3$ and pyridine led to the 1,2,3,4-tetrahydroisoquinoline [6,11] 9 in 57% yield. Oxidation of 9 with $KMnO_4$/acetone yielded, among other oxidation products, noyaine (1), in 20% yield.

Regarding the biogenesis of noyaine (1), this compound might be formed *in vivo* from oxidation cleavage of the $C_1$-$C_\alpha$ bond of cularine (4), a process that might take place during the catabolic degradation of 4, the major alkaloid in C. claviculata (L.) DC.

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2. B.D.Krane and M. Shamma, J. Nat. Products, 45, 377 (1982).
3. PMR (250 MHz, $CDCl_3$, $\delta$ ): 6.97 and 6.80 ($AB_q$, J=8.4 Hz, 2H, H-5 and H-6), 6.91 (s, 1H, ArH), 6.10 (s, 1H, ArH), 4.77 (s, 2H, $CH_2OH$), 3.85, 3.66 and 3.64 (3s, 9H, 3xOMe), 3.55 (s, 2H, H-1), 2.93 (t, J=5.7 Hz, 2H, H-4), 2.67 (t, J=5.7 Hz, 2H, H-3) and 2.42 (s, 3H, NMe); MS, m/e (%): 359 ($M^+$, 13), 358 (21), 341 (26), 328 (100), 326 (90), 191 (85), 190 (62), 176 (28), 174(36); IR (film) $\nu_{max}$: 1190, 1280, 1510, 2800-3000, 3400 $cm^{-1}$.

4. L.Castedo, T.Iglesias, A.Puga, J.M.Saá, and R.Suau, Heterocycles, 15, 915 (1981).
5. Dehydrocularine (5), mp 148-150ºC($Et_2O$); UV $\lambda_{max}^{EtOH}$ (log ε ): 228 (3.56), 280 (2.98) and 362 (2.89) nm, $\lambda_{max}^{EtOH/HCl}$(log ε ): 216 (3.37), 242 sh (3.09), 262 (2.87) and 386 (2.57) nm; IR (KBr) $\nu_{max}$: 1120, 1260, 1500, 1560, 1610, 2800-3000 $cm^{-1}$; PMR (80 MHz, $CDCl_3$, δ ): 6.89 (s, 1H, ArH), 6.85 (s, 2H, H-5 and H-6), 6.57 (s, 1H, ArH), 5.53 (s, 1H, H-α ), 3.91, 3.86 and 3.81 (3s, 9H, 3xOMe), 3.34 (t, J=6Hz, 2H, H-3), 3.10 (s, 3H, NMe) and 2.75 (t, J=6Hz, 2H, H-4); MS m/e (%): 339 ($M^+$, 100), 324 (83), 296 (17), 281 (17), 238 (17), 139 (20).
6. Satisfactory elemental analysis was obtained for this compound.
7. Carboxy-isoquinol-1-one 6, PMR (250 MHz, $CDCl_3$, δ ): 7.44 (s, 1H, H-2'), 7.17 and 7.13 ($AB_q$, J= 8.5 Hz, 2H, H-5 and H-6), 5.92 (s, 1H, H-5'), 3.88, 3.83 and 3.65 (3s, 9H, 3xOMe), 3.54 (m, 2H, H-3), 3.09 (s, 3H, NMe) and 2.99 (m, 2H, H-4); MS m/e (%): 387 ($M^+$, 28), 343 (15), 328 (31), 207 (100), 178 (31), 164 (34), 142 (34).
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10. T.Zincke, and B.Francke, Liebigs Ann., 293, 120 (1920).
11. Tetrahydroisoquinoline 9, mp 220-222ºC (as hydrochloride); PMR (250 MHz, $CDCl_3$, δ): 7.45 (s, 1H, H-2'), 6.10 (s, 1H, H-5'), 6.97 and 6.82 ($AB_q$, J= 8.4 Hz, 2H, H-5 and H-6), 3.90, 3.89, 3.70 and 3.64 (4s, 12H, 4xOMe), 3.51 (bs, 2H, H-1), 2.90 (t, J=6 Hz, 2H, H-4), 2.63 (t, J=6 Hz, 2H, H-3) and 2.41 (s, 3H, NMe); MS m/e (%): 387 ($M^+$, 1.5), 386 (5), 372(5), 328(8), 313 (4), 177 (14), 176 (100), 174 (11).

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