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OXOCOMPOSTELLINE AND OXOCULARINE, STRUCTURE AND SYNTHESIS

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Summary: Structures (1) and (2) were deduced for these two new oxocularine alkaloids from spectral data and synthesis. The latter was achieved by a novel approach based on intramolecular cyclization between a phenoxide and an intermediate benzyne.

We have recently described[1] the isolation and structure of sarcocapnine and oxosarcocapnine, the first two cancentrine-type cularine alkaloids to have been isolated, from Sarcocapnos enneaphylla(D.C.). We wish to report here the isolation and synthesis of two new oxocularine alkaloids from Fumariaceae plants

Oxocompostelline 1 (from *Sarcocapnos enneaphylla*) was obtained as yellow crystals from ethanol, mp 259ºC, $\{\alpha\}_D^{25}=0$. Its IR spectrum (BrK) displayed a carbonyl conjugated absorption band at 1670 cm^{-1}, and no signals were apparent at frequencies higher than 3000 cm^{-1}. Its UV spectrum exhibited λ_{max} (EtOH) (log ε) 208(4.67), 254(4.41), 292(sh) and 397(3.61) nm; on addition of acid a bathochromic shift was observed, λ_{max} (EtOH-HCl) (log ε) 208(4.67), 261(4.34), 410(3.47) and 460(3.23) nm. Its molecular formula was established by elemental analysis and confirmed by mass spectrometry which showed m/e (%) 321(M^+,72), 306(5), 293(5) and 278(100). The PMR (80 MHz, $CDCl_3$,δ) of 1 exhibited signals at 4.08(s,3H,-OC$\underline{H}_3$), 5.99(s,2H,-OC$\underline{H}_2$O-), 6.90(s,1H,Ar$\underline{H}$), 7.11(s,1H,Ar$\underline{H}$) and two AB quartets, at δ_A=7.53, δ_B=7.71, J_{AB}=9 Hz and at $\delta_{A'}$=7.69, $\delta_{B'}$=8.63, $J_{A'B'}$=5.7 Hz. These data suggest that oxocompostelline possesses structure 1.

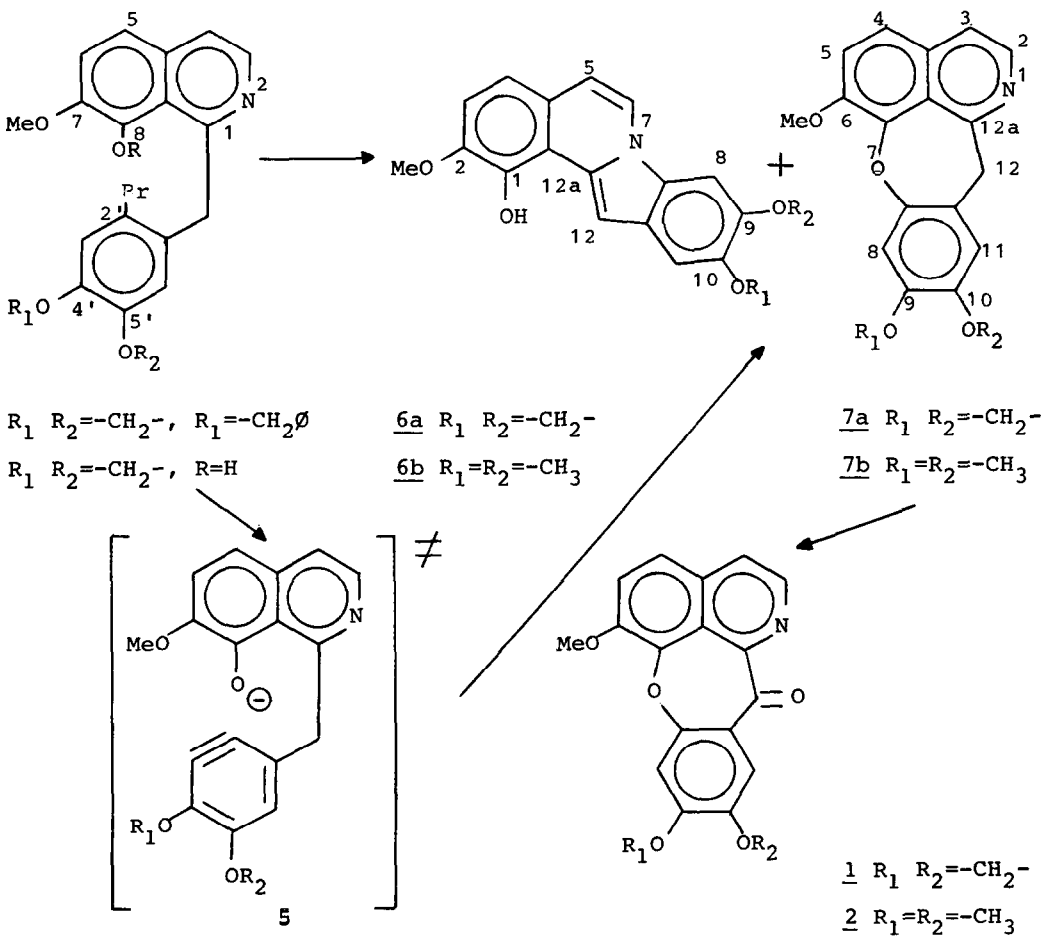
Oxocularine 2 (from *Corydalis claviculata*) was also obtained as yellow crystals from ethanol, mp 198-199ºC[2] (lit.[3] 194-195ºC), $\{\alpha\}_D^{25}=0$. This compound has already been obtained synthetically by oxidation of appropriate precursors[3].

The structure of oxocompostelline 1 was confirmed by total synthesis based on a novel cyclization in the key step which leads to the cularine skeleton. This cyclization consists in a phenoxide ion attack upon an intermediate benzyne generated by the action of dimsyl sodium[4] on an aromatic 6'-bromo-benzylisoquinoline. Treatment of 2-benzoyl-8-benzyloxy-1,2-dihidro-7-methoxy isoquinoline 1-carbonitrile[5] with 2-bromo-4,5-methylenedioxy-benzyl chloride[6] in phase transfer conditions[7] and subsequent basic hydrolysis[5] gave compound 3 in 90% yield.

Debenzylation of 3 by acid treatment yielded phenolic compound 4, which was dehydrohalogenated by reaction with dimsyl sodium[4] (DMSO,40ºC,3 h), giving rise to the intermediate benzyne 5, which is of a type known to be attacked by nitrogen[8] and oxygen[9] nucleophiles. In the present case it was impossible for us to avoid N-attack. The final yield was thus 65% pyrrocoline[10] 6a (generated by N-attack) together with 20% of the desired O-attack generated cularine[10] 7a. Oxidation of 7a is effected quickly and efficiently by several oxidation agents (air, Fremy's salt, etc.) giving rise to a product (1) identical to the compound isolated from nature.

In a similar fashion, the same synthetic scheme was used to synthesize oxocularine 2, obtaining in the cyclization step 50% of pyrrocoline 6b[10] and 25% of cularine 7b[11].

The new synthetic approach described here offers the advantage over other methods of allowing the preparation of N-norcularines, cularines and oxocularines from a common intermediate, the tetradehydronorcularine 7.



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2 Complementary spectroscopic data for oxocularine 2:
High resolution mass spectrum for $C_{19}H_{15}NO_5$: c:337,0950; f:337,0934.
MS: m/e(%): 337(M^+,100), 322(8), 309(12), 294(83).
PMR (80 MHz, $CDCl_3$, δ): 3.89(s,3H,-OC$\underline{H}_3$), 3.89(s,3H,-OC$\underline{H}_3$), 4.13(s,3H,-OC$\underline{H}_3$), 6.94(s,1H,Ar$\underline{H}$), 7.24(s,1H,Ar$\underline{H}$), 7.58(d,1H,J_{AB}=9 Hz), 7.75(d,1H,J_{AB}=9 Hz), 7.74(d,1H,$J_{A'B'}$=5.4 Hz), 8.68(d,1H,$J_{A'B'}$=5.4 Hz).

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10 All new compounds gave satisfactory elemental analysis.
6a: mp 250-252º(MeOH); IR(BrK): 3340 cm^{-1}; UV λ_{max}(EtOH): 210,235(sh),248(sh), 283(sh),296,306,320 and 360; UV λ_{max}(EtOH-NaOH): 212,250(sh),280(sh),306,320 and 380; MS: m/e(%): 307(M^+,100),292(30),289(29),264(55) and 206(18); PMR(80 MHz,$CDCl_3$,δ): 4.00(s,3H,-OC$\underline{H}_3$),6.00(s,2H,-OC$\underline{H}_2$O-),6.43(s,-O$\underline{H}$),6.56 (d,1H,J=7.5 Hz,$\underline{H}_5$),6.94(d,1H,J=9 Hz,$\underline{H}_3$),7.11(d,1H,J=9Hz,$\underline{H}_4$),7.19(s,2H,$\underline{H}_8$ and $\underline{H}_{11}$)7.54(s,1H,$\underline{H}_{12}$),7.75(d,1H,J=7.5 Hz,$\underline{H}_6$).

7a: mp 154-156º($CHCl_3$-petroleum ether); IR(BrK): 1490,1600 cm^{-1}; UV λ_{max}(EtOH): 215,230,285 and 350 nm; λ_{max}(EtOH-HCl): 218,250,295 and 394 nm; MS:m/e(%): 307(M^+,100),292(20),264(17) and 262(24); PMR(MHz,$CDCl_3$,δ): 4.07(s,3H,-OC$\underline{H}_3$), 4.56(s,2H,-C$\underline{H}_2$-),5.89(s,2H,-OC$\underline{H}_2$O-),6.77(d,1H,J=9 Hz,$\underline{H}_5$),6.94(d,1H,J=9 Hz,$\underline{H}_4$), 7.38(d,1H,J=5.8 Hz,$\underline{H}_3$),7.49(s,2H,$\underline{H}_8$ and $\underline{H}_{11}$) and 8.16(d,J=5.8 Hz,$\underline{H}_2$).

6b: mp 201-203º(MeOH); UV λ_{max}(EtOH):235,246(sh),286(sh),298,307,315 and 356 nm; UV λ_{max}(EtOH-OH^-): 250(sh),309,321 and 374 nm; MS: m/e(%): 323(M^+,100),308(92),

264(27),161.5(30). PMR(80 MHz,$CDCl_3$,): 3.98(s,6H,2x-$OC\underline{H}_3$),4.00(s,3H,-$OC\underline{H}_3$), 6.54(d,1H,J=7.4 Hz,$\underline{H}_5$),6.97(d,1H,J=9 Hz,H_4),7.08(d,1H,J=9 Hz,$\underline{H}_3$),7.21 and 7.25(each s,2H,$\underline{H}_8$ and $\underline{H}_{11}$),7.56(s,1H,$\underline{H}_{12}$) and 7.80(d,J=7.4 Hz,$\underline{H}_6$).

7b: Complementary spectroscopic data:
MS: m/e(%): 323(M^+,100),308(28). PMR(80MHz,$CDCl_3$,δ):3.84(s,3H,-$OC\underline{H}_3$),3.85 (s,3H,-$OC\underline{H}_3$),4.09(s,3H,-$OC\underline{H}_3$),4.60(s,2H,-$C\underline{H}_2$-),6.77(d,1H,J=9Hz,$\underline{H}_5$),6.94(d, 1H,J=9 Hz,$\underline{H}_4$),7.39(d,1H,J=5.8 Hz,$\underline{H}_3$),7.50(s,2H,$\underline{H}_8$ and $\underline{H}_{11}$) and 8.15(d,1H, J=5.8 Hz,$\underline{H}_2$).

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