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NEW PHENOLIC ISOCULARINE AND BENZYLISOQUINOLINE ALKALOIDS AND THEIR BIOGENETIC RELATIONSHIP

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Abstract: The first three phenolic isocularines and the first diphenolic 7,8,3',4'-tetraoxygenated tetrahydrobenzylisoquinoline were isolated from Sarcocapnos crassifolia.A pathway for the biogenesis of cularine is considered.

Continuing with our search for new sources of cularine and cancentrine-type cularine (isocularine) alkaloids[1], we have now found in Sarcocapnos crassifolia the first three examples of phenolic isocularine alkaloids, namely sarcocapnidine 1, claviculine 2 and oxosarcocapnidine 3, and the first natural diphenolic 7,8,3', 4'-tetraoxygenated tetrahydrobenzyl-isoquinoline, crassifoline 4. Their structures have been established on the basis of spectroscopic data, as well as some chemical transformations and synthesis.

Crassifoline 4 was isolated as an oil, $[\alpha]_D$=+20.6 (c=1.6 g/l. MeOH)[2]. Its phenolic nature was inferred from the bathochromic shift of its UV spectrum in basic media and the presence of a broad band at 3440 cm^{-1} in its IR spectrum. The PMR reveals the presence of two O-methyl singlets, five aromatic protons, and a methine quartet centered at δ4.14 characteristic of an 8-oxygenated 1,2,3,4 tetrahydroisoquinoline system[3]. The mass spectrum showed, in addition to a molecular ion at m/e 329 (M^+,0.1%), a base peak at m/e 192 characteristic of the tetrahydroisoquinoline moiety. Finally, structure 4 for crassifoline was established by direct comparison of the alkaloid with a synthetic sample[4].

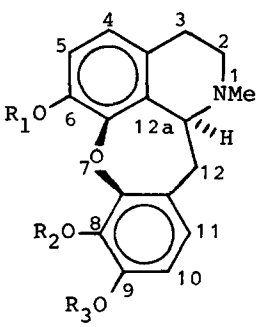
Sarcocapnidine 1 was isolated as a white, crystalline, optically active substance, mp 126-127ºC (EtOH), $[\alpha]_D$=+385.4 (c=0.0696 g/l). Its molecular formula[2], $C_{19}H_{21}NO_4$, was obtained by elemental analysis and confirmed by MS (M^+,base peak; f: 327,1456; c: 327,1470). The bathochromic shift of its UV spectrum in basic media together with the broad signal in its IR at 3460 cm^{-1} revealed its phenolic nature. The PMR spectrum showed a methine proton centered at δ4.48 as a doublet of doublets (dd, J_{AX}=11.8 Hz, J_{BX}=4.8 Hz) characteristic of the cularine skeleton, and four aromatic protons, two of which accidentally coincided as a singlet at δ6.57 and the remaining two as an AB quartet at δ_A6.73 and δ_B6.91 ppm J_{AB}=8.5 Hz.

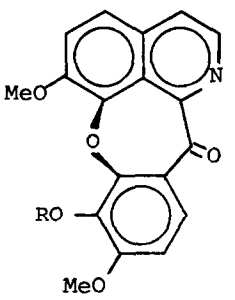
Treatment of sarcocapnidine with diazomethane yielded sarcocapnine[1] 5,which proved that sarcocapnidine was a cancentrine-type cularine alkaloid. Since

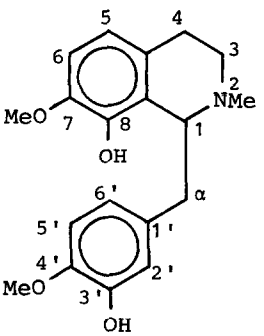
sarcocapnidine gave a positive Gibb's test[5], the phenolic function must be located at the C-8 position. This was confirmed by the ^{13}C NMR shifts[6] observed in passing from phenol to phenoxide[7], which established the presence of a free methine in para position to the phenolic function ($\Delta\delta$=-6.38 ppm). Structure 1 for sarcocapnidine was also supported by its synthesis from crassifoline 4 by phenolic oxidative coupling, which gave a mixture of sarcocapnidine 1 (6% yield) and O-demethylcularine 6 (3% yield)[8].

The co-occurrence of alkaloids 1 and 4 in the same natural source and the above biogenetically patterned synthesis of 1 from 4 points to the direct oxidative coupling of a 7,8,3',4' tetraoxygenated tetrahydrobenzylisoquinoline as being the most probable among the routes proposed for cularine biogenesis[4,8,9].

Claviculine 2 was obtained as crystals, mp 112-113ºC (EtOH) $[\alpha]_D$=+443 (c= 0.41 g/l, MeOH), and analysed[2] as $C_{18}H_{19}NO_4$ (M^+, base peak, f: 313,1323; c: 313,1309). Its phenolic nature was deduced from its UV (bathochromic shift in basic media) and IR (3420 cm^{-1}) spectra. The PMR spectrum showed a cularine-like C_{12a} methine proton centered at δ4.43 (dd,J_{AX}=11.8 Hz,J_{BX}=4.4 Hz) together with a methoxyl singlet at δ3.79 ppm. In addition, its methylation with CH_2N_2 gave sarcocapnine 5, suggesting a diphenolic isocularine skeleton for the alkaloid. The ^{13}C NMR shifts[6] of claviculine vs its phenolate allowed us to locate the two phenolic groups at C8 ($\Delta\delta$=-8 ppm for a methine para-carbon) and C_6 or C_9 ($\Delta\delta$= -6.81 ppm for a quaternary para-carbon). Of the two possible structures 2 and 7 fitting in with the above structure, 7 was discarded due to the likely instability of its catechol function.







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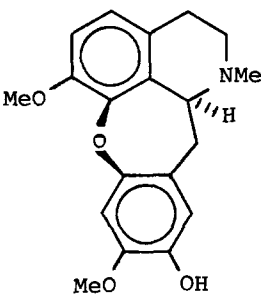

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1 R_1=R_3=Me, R_2=H

2 R_1=R_2=H, R_3=Me

5 R_1=R_2=R_3=Me

7 R_1=Me, R_2=R_3=H

3 R=H

8 R=Me

9 R=-CH_2OMe

Oxosarcocapnidine 3 was isolated as yellow crystals[2], mp 231-232ºC (MeOH), $|\alpha|_D$=0. It was found to contain a phenolic function (bathochromic shift on addition of base and ν_{max} at 3400 cm^{-1}) and a conjugated carbonyl(1670 cm^{-1}). The

PMR showed two methoxyl singlets and three aromatic AB quartets, thus suggesting an isocularine skeleton. This was confirmed by methylation of oxosarcocapnidine with CH_2N_2 to oxosarcocapnine[1] 8. Furthermore, the phenolic function was located at the C8 position on the basis of its partial synthesis from sarcocapnidine 1. Thus, Fremy's salt oxidation[10] of the O-methoxy-methyl protected sarcocapnidine 9 followed by acid deprotection gave 3 in 58% yield.

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2 All new compounds gave correct elemental analyses and the following spectroscopic data:

Crassifoline 4:NMR($CDCl_3$),δ 2.37(s,3H,NMe),2.43-3.16(m,6H,3x-CH_2),3.84 and 3.86(ss 6H,2x-OMe), 4.14(q,1H,J_{AX}=8 Hz and J_{BX}=3.7 Hz,H-1), 4.86(broad s,2H,-OH, disappears with D_2O), 6.57(d,1H,J=9 Hz,H_6), 6.74(d,1H,J=9 Hz,H_5), 6.75-6.90 (m,3H,H_2,,H_5, and H_6,) ppm. MS m/e(%): 329(M^+,0.1), 193(12.5), 192(100), 177(12.5), 138(97) and 123(97).

4 Perchlorate:mp 228-230ºC(EtOH); λ_{max}(EtOH)(log ε):214(4.23), 232 sh(4.19), 282(3.82); λ_{max}(EtOH/OH^-)(log ε):226(4.51), 246(4.18), 296(3.95).

Sarcocapnidine 1 λ_{max}(EtOH)(log ε):238(3.8) and 281(3.5); λ_{max}(EtOH/OH^-) (log ε):250(3.73) and 294(3.62).NMR($CDCl_3$) δ:2.59(s,3H,NMe), 2.74-3.5(m,6H, 3xCH_2), 4.48(dd,J_{AX}=12 Hz,J_{BX}=4.6 Hz,H_{12a}), 3.87(s,6H,2x-OCH_3), 6.57(s,2H, H_{10} and H_{11}), 6.74(d,1H,J_{AB}=8.5 Hz,H_5) and 6.91(d,1H,J_{AB}=8.5 Hz,H_4) ppm. MS m/e(%):327.1456($C_{19}H_{21}NO_4$,100%), 312(51), 310(29), 296(20), 284(24), 281(36), 174(40) and 148(14). ^{13}C NMR(DMSO-d_6-dioxane as internal standard) (only non oxygenated aromatic carbons) δ(multiplicity):109.08(d), 111.12(d), 120.69(d), 121.00(s), 125.57(d), 127.32(s) and 132.10(s) ppm. ^{13}C NMR(DMSO-d_6-dioxane-NaOD) δ(multiplicity):109.05(d), 110.92(d), 114.31(d), 120.92(s), 125.03(d), 126.66(s) and 133.00(s) ppm.

Claviculine 2:λ_{max}(EtOH)(log ε):218(4.59) and 276(4.10) nm. λ_{max}(EtOH/OH^-) (log ε):240(5.66) and 292(4.55) nm. NMR($CDCl_3$) δ:2.58(s,3H,NMe), 2.76-3.51 (m,6H,3x-CH_2-), 3.79(s,3H,-OMe), 4.47(dd,1H,J_{AX}=11.7 Hz,J_{BX}=4.5 Hz,H_{12a}), 5.03(broad s,2H,-OH,disappears with D_2O), 6.53(s,2H,ArH), 6.77(s,2H,ArH). MS m/e(%):313.1323(M^+,100), 298(43), 296(34), 270(13), 161(9), 148(11) and 132(16). ^{13}C NMR(DMSO-d_6-D_2O)(only non oxygenated aromatic carbons), δ(multiplicity):109.48(d), 115.33(d), 121.62(d), 121.97(s), 126.34(d), 126.50(s) and 131.87(s) ppm. ^{13}C NMR(DMSO-d_6-NaOD) δ (multiplicity):109.50 (d), 117.85(d), 113.62(d), 123.04(s), 125.15(d), 119.69(s) and 131.04(s)ppm.

Oxosarcocapnidine 3: λ_{max}(EtOH)(log ε):252(4.26), 342(3.34) and 396(3.59)nm. λ_{max}(EtOH/OH^-)(log ε):243(4.26), 340(3.34) and 400(3.57) nm. λ_{max}(EtOH/H^+)

(log ε):217(4.28), 265(4.05) and 458(3.55) nm. NMR($CDCl_3$) δ:3.95(s,3H,-OMe), 4.98(s,3H,-OMe), 6.80(d,1H,J=8.7 Hz,H_{11}), 7.32(d,1H,J=8.7 Hz,H_{10}), 7.61(d,1H, J=9 Hz,H_5), 7.78(d,1H,J=5.5 Hz,H_3), 7.82(d,1H,J=9 Hz,H_4) and 8.74(d,1H,J=5.5 Hz,H_2). MS m/e(%):323(M ,100), 308(8), 306(14), 295(13), 280(50), 265(11), 237(16) and 209(11).

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