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(+)-4-HYDROXYSARCOCAPNINE: STRUCTURE AND STEREOCHEMICAL CONSIDERATIONS

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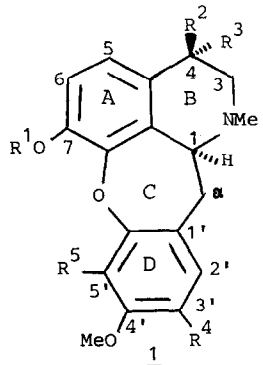
Summary: (+)-4-Hydroxysarcocapnine obtained from *Sarcocapnos enneaphylla* (L.) DC. has been shown by spectral studies and synthesis to possess the new 4-hydroxyisocularine structure (1a). Straightforward assignment of the configuration of a 4-hydroxycularine by NMR is also discussed.

Our current studies on the alkaloids of the *Fumariaceae*[1], have led us to the isolation from *Sarcocapnos enneaphylla* (L.) DC of the first 4-hydroxyisocularine, (+)-4-hydroxysarcocapnine 1a. This alkaloid and the recently described 4-hydroxycularine, (+)-limousamine 1c[2], are the only known cularine alkaloids bearing a hydroxyl group at C-4.

Structure 1a for (+)-4-hydroxysarcocapnine [mp 145-146°C(EtOH), $[\alpha]_D$+314° (c 0.11, $CHCl_3$)], was established on the basis of spectroscopic and chemical evidence. Its UV showed absorptions at λ_{max}^{EtOH} (log ε): 218(4.26), 230(sh,4.09) and 282(3.46). The IR spectrum in CCl_4 exhibited a broad band at 3511 cm^{-1}, which did not change upon dilution and was therefore attributed to an intramolecularly hydrogen bonded OH. The molecular formula $C_{20}H_{23}O_5N$, obtained by elemental analysis, was confirmed by MS, in which molecular ion appeared at m/e 357(86%). Important fragments were also observed at 342(49%), 324(49%), 314(26%), 192(100%) and 190(43%). The pmr (250MHz, $CDCl_3$, δ) of 1a exhibited the characteristic cularine ABX system of protons at C_α and C_1[3], which now appeared at 4.17(H_1, dd, $J_{1-\alpha\underline{\alpha}}$: 2.9, $J_{1-\alpha\underline{\beta}}$: 11.3), 3.34($H_{\alpha\underline{\alpha}}$, dd, $J_{\alpha\underline{\alpha}-\alpha\underline{\beta}}$: 16.1) and 2.91($H_{\alpha\underline{\beta}}$, dd). In addition, the presence of three methoxyl groups at 4.05(C_5,) and 3.86(C_4, and C_7), one N-Me at 2.62 and two pairs of ortho coupled aromatic protons (6.60 and 6.74, J: 8.6, H_3, and H_2,; 6.83 and 7.14, J: 8.4, H_6 and H_5) clearly suggested an isocularine substitution pattern.[4] The hydroxyl group was placed at C_4 on the basis of the observation of a second ABX system: 4.58(H_4, dd after exchange with D_2O, $J_{4-3\underline{\alpha}}$: 2.3, $J_{4-3\underline{\beta}}$: 3.9), 3.01($H_{3\underline{\beta}}$, dd, $J_{3\underline{\alpha}-3\underline{\beta}}$: 11.6) and 2.80($H_{3\underline{\alpha}}$, dd). All the above assignments were based on decoupling and NOEDS experiments (Fig. II)[5].

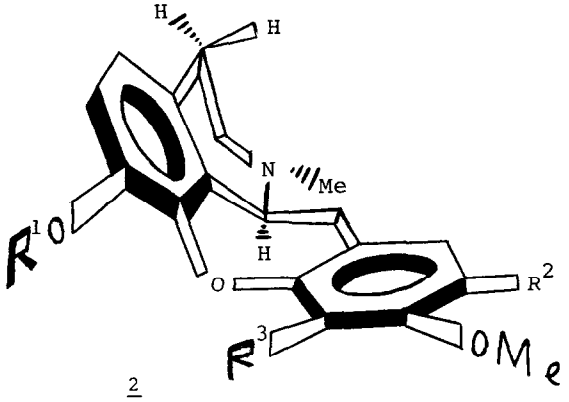
Comparison of the pmr data of the C_α-protons of 1a with those of sarcocapnine 2a[6] and cularine 2b[3] shows that both 1a and 2a have the twist-boat conformation established for ring C in cularine 2b[3,7], with the oxygen atom close to H-1 as depicted in molecular structure 2. Dreiding model analysis reveals that its ring B can have either a half-chair conformation or a distorted form, the two being easily interconverted by simply rotating the N-C_3-C_4 bonds, without ring C being involved. The observed coupling constants between H_4 and the neighbouring protons at C_3 in (+)-4-hydroxysarcocapnine reveal that H_4 must be quasi-equatorial, thus establishing a quasi-axial position for the hydroxyl group. Accordingly, distorted form A or half-chair conformation B is expected depending on whether the compound has *syn* (H_1 and H_4 on the same side) or *anti* stereochemistry (Fig. I). The fact that (+)-4-hydroxysarcocapnine shows a 2.4% NOE between H_1 and $H_{3\alpha}$ (Fig. I) indicates that it would have the *syn* stereochemistry shown in A, and structure 1a was therefore assigned to it.

In order to confirm the above configuration at C_4, we have carried out the synthesis of both epimers by means of the oxidation of a suitable precursor at the benzylic position. Treatment of phenolic tetrahydrobenzylisoquinoline 3a with lead tetraacetate[8] afforded in 83% yield both C_4



1

a, R^1=Me, R^2=OH, R^3=R^4=H, R^5=OMe
b, R^1=Me, R^3=OH, R^2=R^4=H, R^5=OMe
c, R^1=H, R^2=OH, R^3=R^5=H, R^4=OMe
d, R^1=H, R^3=OH, R^2=R^5=H, R^4=OMe
e, R^1=Me, R^2=OH, R^3=R^5=H, R^4=OMe
f, R^1=Me, R^3=OH, R^2=R^5=H, R^4=OMe
g, R^1=Ac, R^2=OH, R^3=R^5=H, R^4=OMe
h, R^1=Ac, R^3=OH, R^2=R^5=H, R^4=OMe
i, R^1=Me, R^2=OAc, R^3=R^4=H, R^5=OMe
j, R^1=Me, R^3=OAc, R^2=R^4=H, R^5=OMe



2

a, R^1=Me, R^2=H, R^3=OMe
b, R^1=Me, R^2=OMe, R^3=H
c, R^1=H, R^2=OMe, R^3=H

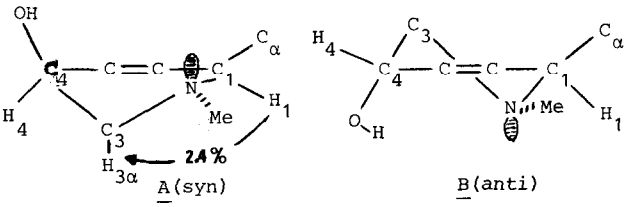


Fig.I :Ring B conformations in 4-hydroxycularines

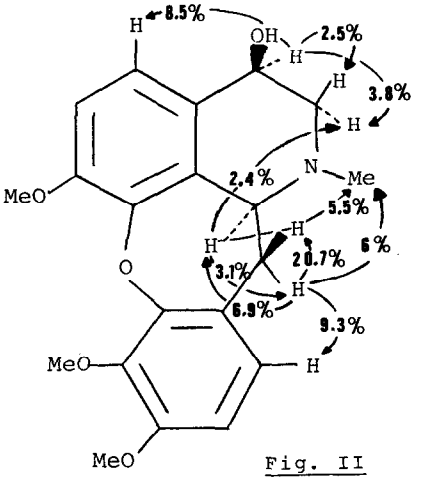
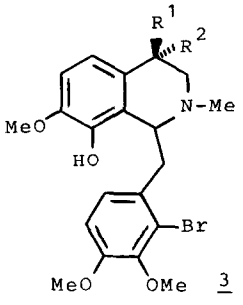


Fig. II



3

a, R^1=R^2=H
b, R^1=OAc, R^2=H
c, R^1=H, R^2=OAc

acetoxyl epimers(3b and 3c)in the ratio 1/9.When this mixture was subjected to Ullmann cyclization[9],followed by basic hydrolysis,it furnished in 92% yield 4-hydroxysarcocapnine 1a and its C_4 epimer 1b[10],in the same ratio (1/9).The coupling constants between the protons at C_3 and C_4 in the pmr spectrum of 1b[10] show that, as in 1a, H_4 is also quasi-equatorial.4-Epihydroxysarcocapnine 1b must therefore have the conformation and stereochemistry shown in B. The fact that the hydroxyl group is quasi-axial in both epimers was further supported by O-acetylation[11],which shifted H_4 to lower field by an almost equal amount in both(+1.37 and +1.33 ppm in 1a and 1b, respectively)[12].

Final confirmation of the relative configurations of the two epimers came from a comparative pmr study of lanthanide-induced shifts.According to the proposed ring B conformations,complexation of the lanthanide reagent via the quasi-axial OH should induce a

TABLE 1. Pmr data for epimeric 4-hydroxycularines. ΔH_1: δH_1 (anti)-δH_1 (syn)

Compound	H_1 (J in Hz)	ΔH_1	H_4 (J in Hz)[a]
1a (syn)	4.17 dd (11.3, 2.9)	0.43	4.58 dd[b] (3.9, 2.3)
1b (anti)	4.60 dd (12.6, 3.1)		4.57 "t"[c] (3.3, 2.8)
1c (syn)	4.08 dd (11.3, 3.0)	0.36	4.59 dd (3.8, 2.5)
1d (anti)	4.44 dd (12.0, 3.2)		4.55 "t"[c] (J_{app}=2.6)
1e (syn)	4.31 dd (11.6, 3.5)	0.30	4.61[d]
1f (anti)	4.61 dd (11.6, 3.6)		4.52 "t"[c] (J_{app}=2.6)
1g (syn)	4.21 dd (11.3, 3.2)	0.37	4.61[d]
1h (anti)	4.58[d]		4.58[d]

a.- Coupling constants, where indicated, were measured on signals due to protons at C_3.
b.- Broad multiplet before interchange with D_2O. c.-Apparent triplet.d.-Overlapped with signal from the epimer.

TABLE 2. A pmr comparison of the H_1 resonance in cularines and their epimeric 4-hydroxyderivatives. ΔH_1: δH_1 (hydroxycularine)-δH_1 (cularine)

Compound	δH_1	4-hydroxycularine	ΔH_1
sarcocapnine 2a	4.33	syn, 1a	-0.16
		anti, 1b	+0.27
cularine 2b	4.44	syn, 1e	-0.13
		anti, 1f	+0.17
cularidine 2c	4.26	syn, 1c	-0.18
		anti, 1d	+0.18

larger shift in H_1 in the epimer with anti stereochemistry.Sequencial addition of known amounts of Eu(fod)$_3$,did in fact produced very different slopes for H_1 in 4-hydroxysarcocapnine 1a(m:1.7) and its epimer 1b(m:11), proving that the natural compound, which is the less affected, has syn stereochemistry.

It is interesting to note that H_4 in 1b appears at virtually the same chemical shift as in 1a(Table 1),thus ruling out the possibility of making configurational assignments on the basis of differences between the chemical shifts of the carbinyl hydrogen,which is a valid procedure in the aporphine and berberine series[2].The above observation can be explained as a consequence of the different conformations of ring B in 4-hydroxysarcocapnine 1a(syn,A) and its C_4-epimer 1b(anti,B),in both of which H_4 adopts a quasi-equatorial position. However, a clear cut difference between the chemical shifts of H_1 is observed, which is attributable to the fact that H_1 is affected differently by the nitrogen lone pair in the two epimers. In order to establish whether the above feature might be of general diagnostic value for configurational assignments in 4-hydroxycularines, we have studied the recently described limousamine 1c[2] and its epimer 1d, which we have obtained by synthesis[13]. Their pmr spectra showed similar coupling constants and ΔH_1 values to those found for 1a and 1b (Table 1), thus indicating that 1c and 1d also have conformations A and B. Limousamine, which shows H_1 at higher field, must therefore have the syn stereochemistry 1c.

As Table 1 shows, 7-O-methyl and 7-O-acetyllimousamine[15] (1e and 1g) also gave consistent ΔH_1 values, further proving that the configuration at C_4 in 4-hydroxycularines can easily be established on the basis of the chemical shift of H_1, which resonates at δ4.08-4.31 in the syn series and further downfield (δ4.44-4.60)in their epimers. It is noteworthy that the H_1 chemical shift of cularine is roughly half way between the values obtained in its syn and anti 4-hydroxyderivatives (Table 2). This makes possible straightforward assignment of the configuration of a 4-hydroxycularine by simply comparing its H_1 chemical shift with that of parent cularine. If the hydroxyl group is at the β-face(syn stereochemistry) the H_1 resonance

would appear upfield, while the contrary effect should be observed in the anti series.

As the data in Table 1 clearly reveal, the chemical shift of H_4 is not significantly affected by the stereochemistry or type of subtitution of the cularine nucleus. Therefore, it cannot be used for configurational diagnosis as previously suggested[2]. However, minor differences between the coupling constants of H_4 with neighbouring protons at C_3 can be observed, their values being much closer in the anti derivatives. This causes the signal of H_4 to appear as a broad triplet. On the other hand, the syn derivatives exhibit this signal as doublet of doublets. This can be explained as a consequence of very small differences between dihedral angles of H_4 with protons at C_3 in the syn and anti derivatives. This fact further confirms that epimers at C_4 in 4-hydroxycularines have different ring-B conformations, H_4 being quasi-equatorial in both.

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11. 4-O-Acetylsarcocapnine (1i): pmr (250MHz, $CDCl_3$, δ): 7.15 and 6.84 (ABq, J: 8.5, H_5 and H_6), 6.77 and 6.61 (ABq, J: 8.6, H_2' and H_3'), 5.95 (broad t, H_4), 4.28, 3.30 and 3.10 (ABX, H_1, $H_{\alpha\alpha}$ and $H_{\alpha\beta}$ respectively, $J_{1-\alpha\alpha}$ 3.3, $J_{1-\alpha\beta}$: 11.6, $J_{\alpha\alpha-\alpha\beta}$: 15.8), 3.09 (dd, $H_{3\beta}$, $J_{3\beta-4}$: 5, $J_{3\beta-3\alpha}$: 12.7), 2.99 (dd, $H_{3\alpha}$, $J_{3\alpha-4}$: 4.1), 4.04 (s, OMe at C_5'), 3.88 (s, OMe at C_7), 3.86 (s, OMe at C_4'), 2.60 (s, N-Me) and 2.12 (s, OAc).
4-Epi-O-acetylsarcocapnine (1j): pmr (250MHz, $CDCl_3$, δ): 7.17 and 6.85 (ABq, J: 8.6, H_5 and H_6), 6.76 and 6.61 (ABq, J: 8.7, H_2' and H_3'), 5.90 (broad t, H_4), 4.69, 3.22 and 2.95 (ABX, H_1, $H_{\alpha\alpha}$ and $H_{\alpha\beta}$ respectively, $J_{1-\alpha\alpha}$: 3.1, $J_{1-\alpha\beta}$: 12.3, $J_{\alpha\alpha-\alpha\beta}$: 15.5), 3.24 (dd, $H_{3\alpha}$, $J_{3\alpha-4}$: 3.5, $J_{3\alpha-3\beta}$: 13.5), 2.89 (dd, $H_{3\beta}$, $J_{3\beta-4}$: 2.9), 4.05 (s, OMe at C_5'), 3.87 (s, OMe at C_7), 3.85 (s, OMe at C_4'), 2.64 (s, N-Me) and 2.13 (s, OAc).
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13. Treatment of cularidine 2c with lead tetraacetate followed by Ac_2O/H_2SO_4, as described by Umezawa[14], gave an epimeric mixture of 4,7-diacetoxy-limousamine, which upon acid hydrolysis (acetone, 3N HCl, 80°, 6 h) produced a 2/3 mixture of limousamine 1c and its C_4 epimer 1d.
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