NEW CULARINE-RELATED ALKALOIDS FROM SARCOCAPNOS BAETICA SUBSP. INTEGRIFOLIA

Luis Castedo,* Susana López, and Carmen Villaverde

Departamento de Química Orgánica de la Facultad de Química y Sección de Alcaloides del CSIC
Universidad de Santiago de Compostela, Spain

Abstract - We report the isolation of four new cularine-related alkaloids from Sarcocapnos baetica (Boiss.& Reuter) Nyman subsp. integrifolia (Boiss) Cuatrec.: (+)-4-hydroxysarcocapnidine (1), 3,4-dioxosarcocapnidine (2), (+)-sarcocapnidine N-oxide (3) and (+)-N-methylcularine (4).

We have recently reported the isolation of the first examples of three new groups of cularine-related alkaloids from plants of the genera Sarcocapnos and Corydalis (Fumariaceae). These were the 4-hydroxyisocularines,[1] the 3,4-dioxocularines[2,3] and the seco and norsecocularines.[3,4,5]

In this paper, we describe the isolation, from aerial parts of Sarcocapnos baetica (Boiss.&Reuter) Nyman subsp. integrifolia (Boiss.) Cuatrec., of four new compounds belonging or biogenetically related to these groups: (+)-4- hydroxysarcocapnidine (1), 3,4-dioxosarcocapnidine (2), (+)-sarcocapnidine N-oxide (3) and (+)-N-methylcularine (4).

(+)-4-Hydroxysarcocapnidine was isolated as an amorphous solid, $[\alpha]_D$ +157.0° (c: 0.13, $CHCl_3$). Its uv spectrum showed absorptions at λmax (EtOH)(log ε)nm 218sh (3.49), 235(3.65), 272sh (3.33) and 280 (3.34), and suffered bathochromic shift in basic media to λmax (EtOH/NaOH)(log ε)nm 218sh (3.57), 236 (3.59), 250sh (3.69) and 288(3.73). Its molecular formula, $C_{19}H_{21}NO_5$, was established by high resolution ms (calcd: 343.1413, found: 343.1412)(100); important fragments were observed at m/z(%) 328$[M-15]^+$(40), 300$[M-43]^+$(14), 190(24) and 174(25). The pmr (250 MHz, $CDCl_3$, δ)(Figure 1) exhibited the characteristic cularine ABX system of C_1 and C_α protons at δ 4.36, 3.51 and 2.82 ($J_{1\text{-}\alpha\alpha}$= 4.2, $J_{1\text{-}\alpha\beta}$= 11.6 and $J_{\alpha\alpha\text{-}\alpha\beta}$= 16.6 Hz); in addition, the presence of signals due to two methoxy groups, one N-methyl group and two pairs of ortho coupled aromatic protons clearly suggested a phenolic isocularine structure. An aliphatic hydroxy group was located at C_4 on the basis of the observation of a second ABX system at δ 4.60 (broad signal, 1H, H_4), 3.03(dd, $J_{4\text{-}3\beta}$= 4.2 and $J_{3\alpha\text{-}3\beta}$= 11.6 Hz, 1H, $H_{3\beta}$) and 2.83(dd, $J_{4\text{-}3\alpha}$= 2.1 and $J_{3\alpha\text{-}3\beta}$=11.6 Hz, 1H, $H_{3\alpha}$).[1]

Structure 1 of (+)-4-hydroxysarcocapnidine was definitively confirmed by an nOe difference study (Figure 1). Syn stereochemistry for this alkaloid was established by simply comparing its H_1 chemical shift (δ 4.36) with that of the parent cularine , (+)-sarcocapnidine (δ 4.60).[1]

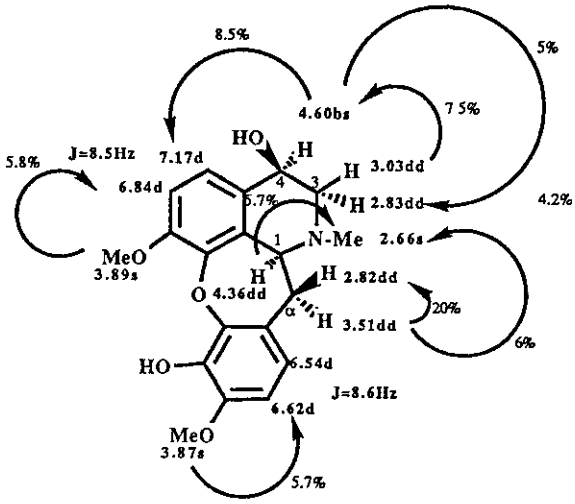
3,4-Dioxosarcocapnidine (2) is a very minor component of S. baetica subsp. integrifolia. It was isolated as an orange, optically inactive, amorphous solid. Its uv spectrum, which showed bands at λmax(EtOH)(log ε)nm 240(3.18), 325(3.02) and 430(2.73) and suffered change upon addition of base to λmax (EtOH/NaOH)(log ε)nm 240(3.21), 335(3.00) and 450(2.65), is

characteristic of a highly conjugated phenolic system. Its pmr ($CDCl_3$, 250MHz, δ)(Figure 1) suggested a phenolic 3,4-dioxoisocularine structure, exhibiting signals due to five aromatic protons, two methoxy groups and one highly deshielded N-methyl group; no more signals were observed in the aliphatic region of the spectrum. In addition to the molecular ion at m/z(%) 353.0895 (calcd: 353.0894) (53), which established the molecular formula $C_{19}H_{15}NO_6$, the mass spectrum also showed significant peaks at m/z (%) 325$[M-28]^+$(42) and 310 $[M-43]^+$(100) due to correlative losses of carbonyl and methyl fragments. The structure of 3,4-dioxosarcocapnidine (2) was finally confirmed by a pmr nOe difference study (Figure 1).

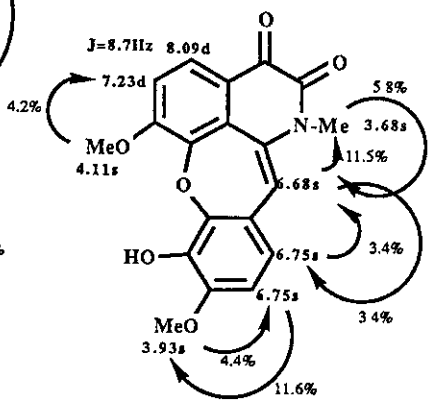
In view of the evidence previously reported for the biogenetic transformation of 4-hydroxyaporphines into 4,5-dioxoaporphines,[6] 3,4-dioxocularines can be considered as probably derived biogenetically from 4-hydroxycularines by further oxidation. The co-occurrence of 4-hydroxyisocularines and their related 3,4-dioxoisocularines sn Sarcocapnos enneaphylla[1,2] and S. baetica subsp. integrifolia supports this hypothesis.

(+)-Sarcocapnidine N-oxide (3) was isolated as a white, optically active $[\alpha]_D$ +430°(c: 0.20, MeOH) amorphous powder. Its phenolic nature was deduced from a bathochromic shift observed in its uv spectrum on addition of base: λmax(EtOH)(log ε) 217 sh(3.35), 240(3.65) and 281(3.60) nm; λmax(log ε)(EtOH/NaOH) 221 sh(3.40), 246(3.71), 283(3.69) and 294 sh(3.66) nm. Its molecular formula, $C_{19}H_{21}NO_5$, was established by high resolution ms, which showed the molecular ion at m/z(%) 343.1411 (calcd: 343.1413)(9). In addition, the mass spectrum showed characteristic fragments of an N-oxide at m/z(%) 327$[M-16]^+$(16), 284$[M-59]^+$(100) and 60$[CH_2{=}NMeOH]^+$ (58). The pmr ($CDCl_3$, 250MHz, δ)(Figure 1) was also very significant, exhibiting signals due to four aromatic protons, which appear as two pairs of doublets, two methoxy groups and a highly deshielded N-methyl group (δ 3.13). It also showed the characteristic ABX cularine system at downfield δ 4.64, 3.93 and 3.52 ($J_{1\text{-}\alpha\alpha}$=3.6, $J_{1\text{-}\alpha\beta}$=10.5 and $J_{\alpha\alpha\text{-}\alpha\beta}$=13.5 Hz). All the pmr assignments and the location of the phenolic group at $C_{5'}$ were confirmed by nOe (Figure 1) and decoupling experiments. Structure 3 of (+)-sarcocapnidine N-oxide was finally confirmed by direct comparison (tlc and pmr) with a synthetic mixture of the two diasteroisomeric sarcocapnidine N-oxides.[7]

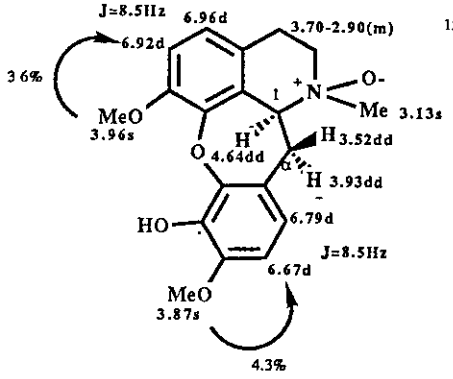
From S. baetica subsp. integrifolia, two amorphous solids were isolated which had a very similar pmr and ms but different Rf values (in neutral Al_2O_3, 95%CH_2Cl_2-5%MeOH). Given that their spectral data suggested a quaternary cularine salt structure, we considered the possibility of the different Rf values being due to two different anions. This was confirmed by the transformation of both salts into the iodide when treated with KI.[8] The spectroscopic data given are those of the quaternary cularine iodide, which was obtained as an optically active $[\alpha]_D$ +200° (c: 0.42, MeOH), amorphous solid. Its uv spectra in neutral, acidic and basic media were characteristic of a non-phenolic cularine-type compound, with λmax(EtOH)(logε)nm 235(3.20) and 285(3.20). The molecular formula, $C_{21}H_{26}NO_4$, was established by high resolution ms, which showed a very small molecular ion at m/z(%) 356.1851 (calcd: 356.1854)(1.3) and characteristic fragments at m/z(%) 355 $[M-1]^+$(5.6), 341$[M-15]^+$(34), 326 $[M-30]^+$(100) and 58$[CH_2{=}NMe_2]^+$ (62). The pmr spectrum (250MHz, $CDCl_3$, δ) (Figure 1) showed signals due to four aromatic protons, which appear as a pair of doublets and two singlets; a very highly deshielded ABX cularine system, due to H_1 and H_α protons, centred at δ 5.28, 3.80 and 3.47 ($J_{1\text{-}\alpha\alpha}$= 3.5, $J_{1\text{-}\alpha\beta}$= 12.6, and $J_{\alpha\alpha\text{-}\alpha\beta}$=15.1Hz); three methoxy groups, and two highly deshielded N-methyl groups. These data suggested the structure of (+)-cularine methiodide (4) for this compound, which proved to be identical (tlc, pmr, ms) to cularine methiodide obtained by N-methylation (MeI, MeOH) of (+)-cularine. All assignments of its pmr spectrum data were based on nOe (Figure 1) and decoupling experiments.



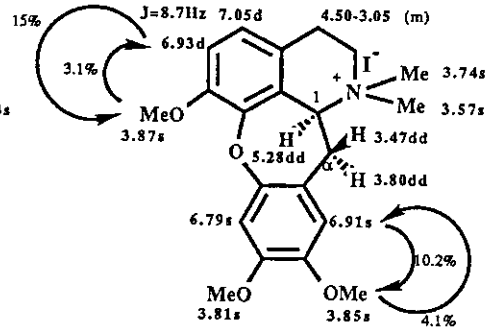
(+)-4-hidroxysarcocapnidine (1)



3,4-dioxosarcocapnidine (2)

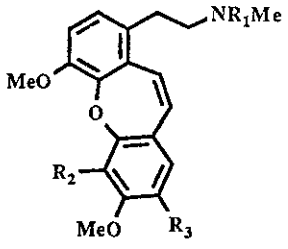


(+)-sarcocapnidine N-oxide (3)



(+)-cularine methiodide (4)

Figure 1



(5) $R_1=R_3=H$, $R_2=OH$
(6) $R_1=Me$, $R_2=H$, $R_3=OMe$

Figure 2

(+)-Sarcocapnidine N-oxide (3) and (+)-cularine methiodide (4) have previously been described as synthetic compounds which have been used as intermediates in the partial synthesis of norsecosarcocapnidine (5)[7] and secocularine (6),[4] (Figure 2) respectively. Alkaloids 5 and 6 may therefore be derived biogenetically from 3 and 4, respectively, by means of "in vivo" degradation. It is noteworthy, however, that although we have isolated from Sarcocapnos baetica subsp. integrifolia the first examples of a cularine N-oxide and a quaternary cularine salt, no secocularine or norsecocularine-type alkaloids have been isolated from the plant. This fact led us to consider that the latter compounds could not be formed during the extraction and manipulation of their respective proposed precursors.[4,7]

ACKNOWLEDGEMENTS.

We thank the CAICYT (Spain) for its financial support. Susana López thanks the Ministerio de Educación y Ciencia (Spain) for an FPI grant.

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Received, 7th June, 1988