ENNEAPHYLLINE, SARCOPHILLINE AND NORSARCOCAPNIDINE, NEW PHENOLIC CULARINES FROM SARCOCAPNOS PLANTS

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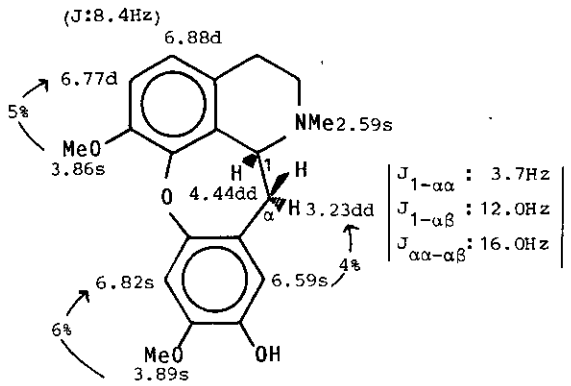
Abstract - Three new phenolic cularines have been isolated from Sarcocapnos species. Their structures have been elucidated by spectroscopic studies, chemical correlations and total synthesis.

Our current research on the alkaloids of the Fumariaceae Sarcocapnos crassifolia[1] (Desf.)DC and Sarcocapnos enneaphylla[2] (L.)DC has led us to the isolation of three new phenolic cularine alkaloids, enneaphylline 1, sarcophylline 2 and norsarcocapnidine 3 this last being the first example of an N-norisocularine alkaloid.

Enneaphylline 1 (from S.crassifolia and S.enneaphylla) was obtained as colorless prims of mp: 205-207°C (EtOH), $|\alpha|_D^{25}$:+256° (c:0.8, EtOH). Its UV spectrum exhibited bands at λ_{max}(EtOH)(log ε): 226(4.04) and 284(3.85) nm. Its phenolic nature was deduced from a strong bathochromic shift to λ_{max}(EtOH, NaOH)(log ε): 223(4.33), 284(3.66) and 303(3.71) nm observed on addition of base, and from the IR spectrum (KBr), which displayed one broad band at 3440 (OH) cm^{-1}. Its molecular formula, $C_{19}H_{21}NO_4$, was established by high resolution MS, which showed the molecular ion at m/z (%)=327.1465 (100) (calculated 327.1470) together with fragments at m/z (%)=312 (64) and 174 (39).

The pmr spectrum, with NOEDS[3], suggested the cularine type structure 1. This was finally confirmed by direct comparison (tlc, MS, UV, pmr) with synthetic enneaphylline, which was obtained from the mixture of sarcocapnidine 5 and enneaphylline 1 produced by phenolic oxidative coupling[4] of crassifoline 4[5] (also present in the same plant). This constitutes the first evidence of the co-occurrence in the



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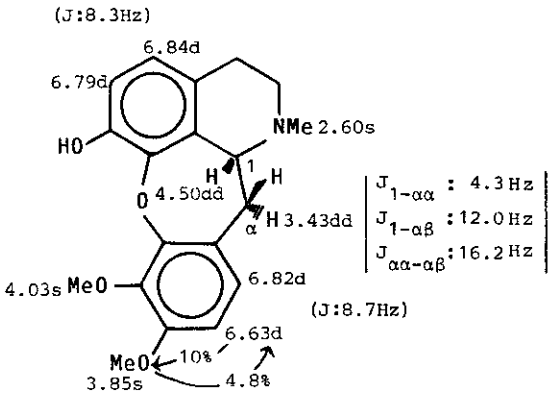

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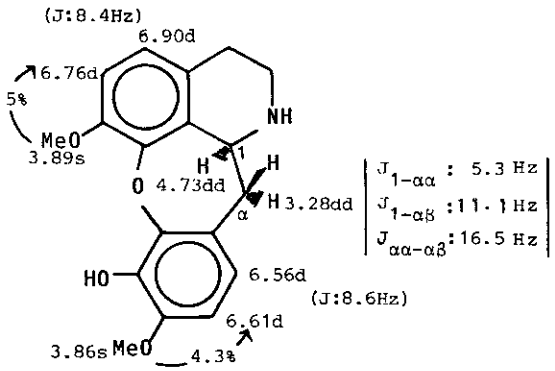

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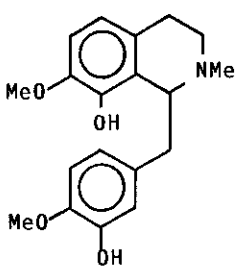

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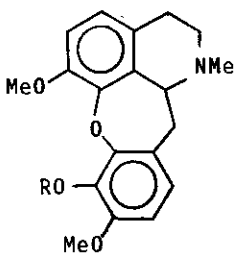


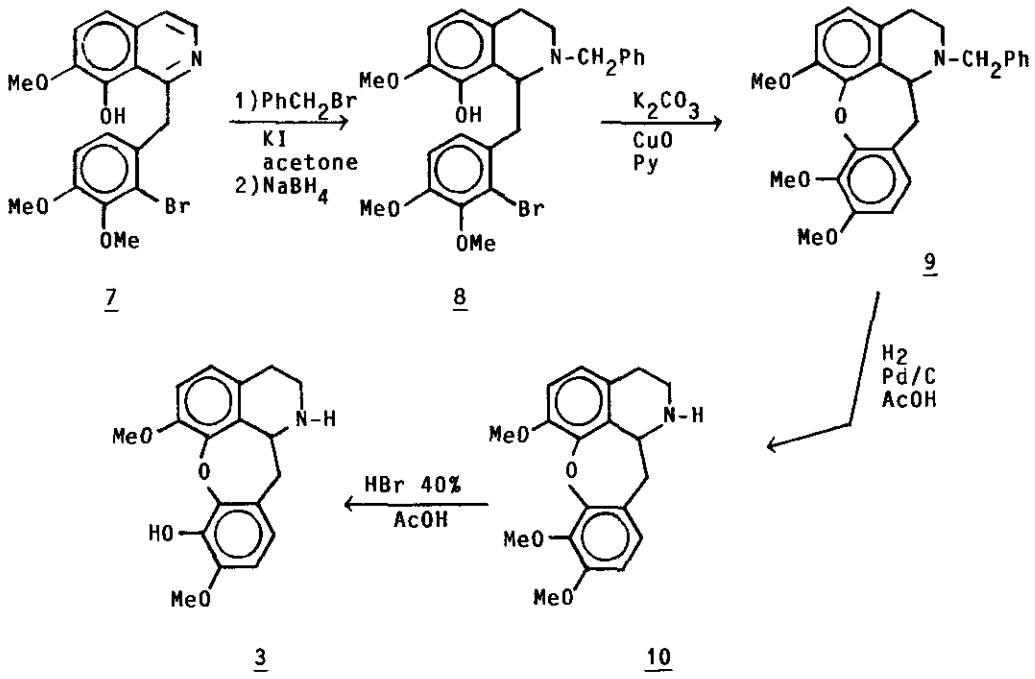
5, R=H
6, R=Me

same natural source, of the isomeric cularines 1 and 5 and their putative biogenetic precursor 4.

Sarcophylline 2 was obtained from S.crassifolia and S.enneaphylla as an amorphous substance, $[\alpha]_D^{25}$:+200° (c: 1.65, $CHCl_3$). The bathochromic shift of its UV spectrum in basic media λ_{max}(EtOH)(log ε): 219(4.01), 282(3.36); λ_{max}(EtOH/OH^-)(log ε): 222(4.10), 285(3.36) and 293(3.40) nm, together with a broad signal in its IR spectrum ($CHCl_3$) at 3400 cm^{-1}, revealed its phenolic nature. The molecular formula $C_{19}H_{21}NO_4$ was established by high resolution MS, which showed the molecular ion at m/z(%): 327.1470 (100) (calculated: 327.1470) and the most important fragments at 312(56), 294(53) and 162(66), and thus permitted the phenolic group to be assigned to the C_7 position. The isocularine skeleton was deduced from its pmr spectrum[3], which exhibited two methoxyl singlets and two aromatic AB quartets, and was confirmed by O-methylation with diazomethane, which gave a product identical to authentic sarcocapnine 6[6]. All the pmr assignments were confirmed by NOEDS experiments[3].

Norsarcocapnidine 3 was obtained from Sarcocapnos crassifolia as an amorphous solid, $[\alpha]_D^{25}$:+347.5°(c: 0.8, EtOH). Its phenolic nature was deduced from its UV spectrum λ_{max}(EtOH)(log ε): 225(4.16), 278(3.52) nm; λ_{max}(EtOH/OH^-)(log ε): 227(4.30), 284(3.73) and 293 sh (3.69) nm and IR spectrum ($CHCl_3$) (3450 cm^{-1}). The molecular formula $C_{18}H_{19}NO_4$ was established by high resolution MS, which showed the molecular ion at m/z(%): 313.1314 (100) (calculated: 313.1318) and fragments at m/z(%): 312(35.5), 298(21) and 160(16). Its pmr data suggested the norisocularine type structure 3. The assignments of the chemical shifts for the -OMe groups and aromatic protons were established by NOEDS and COSY experiments. The substitution pattern was confirmed by partial synthesis from the parent sarcocapnidine 5 by means of Fremy's salt oxidation[7] of its O-methoxymethyl protected derivative followed by Zn-HCl reduction.

The structure of norsarcocapnidine 3 was finally confirmed by total synthesis based on our recently developed approach to cularines[8], which in this case starts from the benzylisoquinoline intermediate 7 and constructs the cularine diaryl ether linkage by Ullmann condensation. As the Ullmann reaction gives a very low yield with N-nortetrahydrobenzylisoquinolines[9], we decided to protect the nitrogen with the easily removable benzyl group. N-benzylation ($BrCH_2Ph$, KI, acetone) of 7 followed by $NaBH_4$ reduction of the crude product afforded the N-benzyltetrahydro-



7 8 9 10 3

benzylisoquinoline 8 (72% yield), whose reaction with cupric oxide and potassium carbonate in dry pyridine gave the N-benzylated cularine 9 (94% yield). N-debenzylation of 9 (H_2, Pd/C-AcOH)[10] led to the previously described N-norsarcocapnine 10[6] (76% yield). Selective O-demethylation[11] of 10 (HBr, AcOH) then afforded N-norsarcocapnidine 3 (70% yield), which was identical (tlc, UV, MS, pmr) with the natural product.

ACKNOWLEDGEMENTS

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