

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

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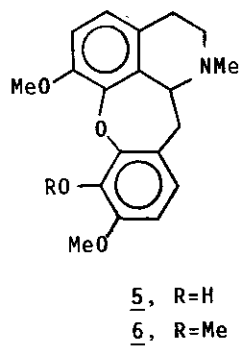
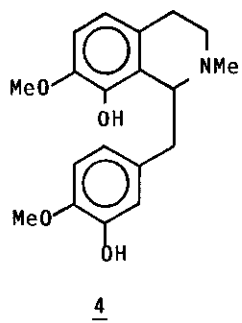
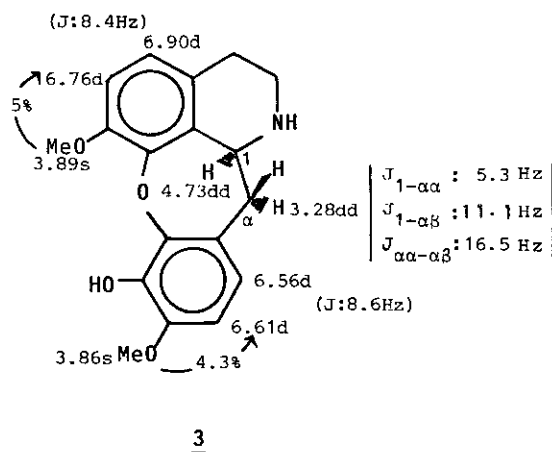
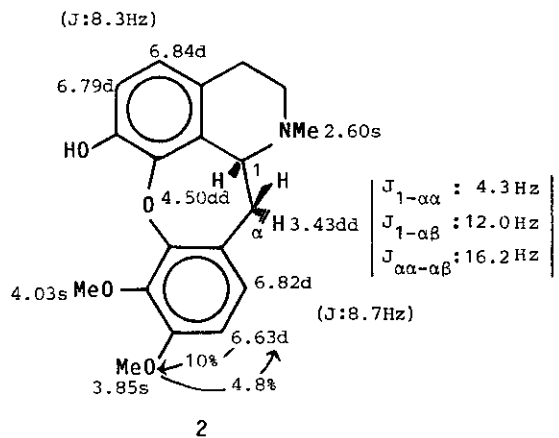
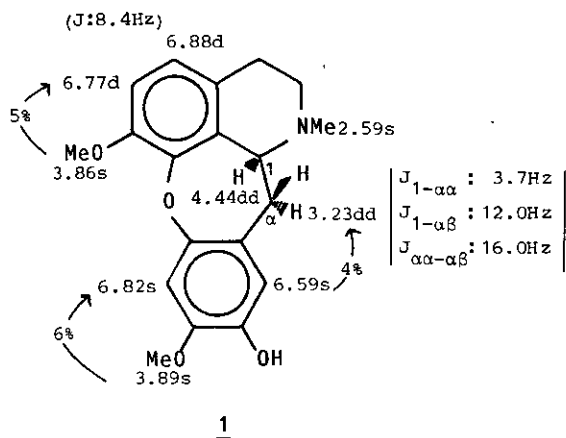
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Abstract - Three new phenolic cularines have been isolated from
Sarcocapnos species. Their structures have been elucidated by
 spectroscopic studies, chemical correlations and total synthesis.

Our current research on the alkaloids of the Fumariaceae Sarcocapnos crassifolia¹
 (Desf.)DC and Sarcocapnos enneaphylla² (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
 prisms of mp: 205-207°C (EtOH), $[\alpha]_D^{25}$: +256° (c:0.8, EtOH). Its UV spectrum ex-
 hibited 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 mole-
 cular formula, $\text{C}_{19}\text{H}_{21}\text{NO}_4$, 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 NOEDS³, suggested the cularine type structure 1. This was
 finally confirmed by direct comparison (tlc, MS, UV, pmr) with synthetic enneaphy-
 lline, which was obtained from the mixture of sarcocapnidine 5 and enneaphylline
1 produced by phenolic oxidative coupling⁴ of crassifoline 4⁵ (also present in
 the same plant). This constitutes the first evidence of the co-occurrence in the

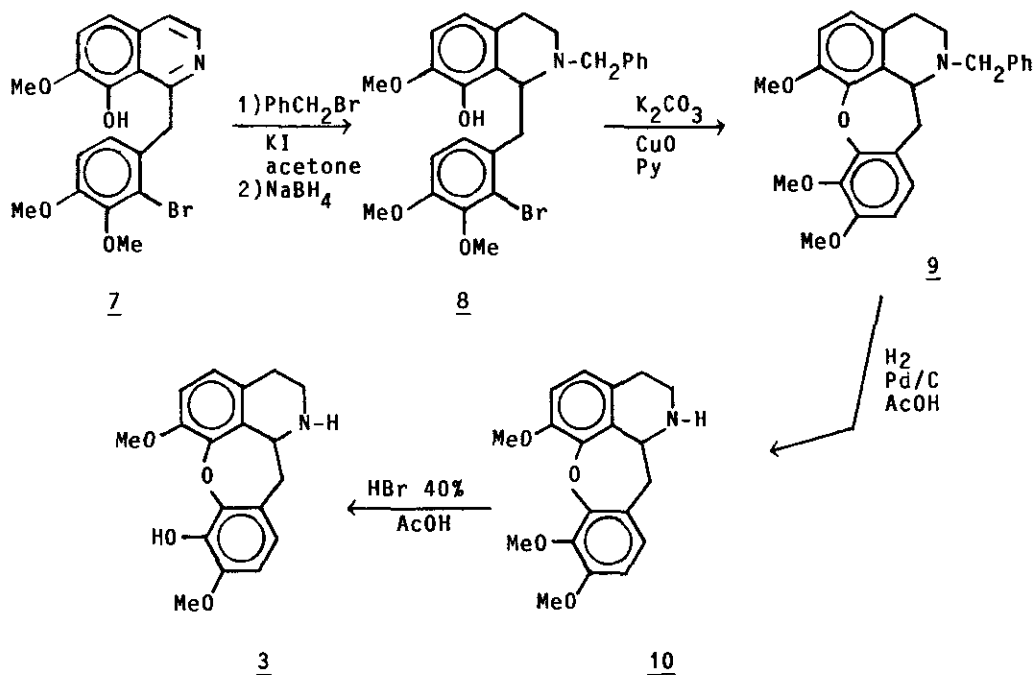


same natural source, of the isomeric cularines 1 and 5 and their putative biogenetic precursor 4.

Sarcophylline 2 was obtained from S. crassifolia and S. enneaphylla as an amorphous substance, $[\alpha]_D^{25} : +200^\circ$ (c: 1.65, CHCl_3). The bathochromic shift of its UV spectrum in basic media $\lambda_{\text{max}}(\text{EtOH})(\log \epsilon)$: 219(4.01), 282(3.36); $\lambda_{\text{max}}(\text{EtOH}/\text{OH}^-)(\log \epsilon)$: 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 $\text{C}_{19}\text{H}_{21}\text{NO}_4$ 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 spectrum³, 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 6⁶. All the pmr assignments were confirmed by NOEDS experiments³.

Norsarcocapnidine 3 was obtained from Sarcocapnos crassifolia as an amorphous solid, $[\alpha]_D^{25} : +347.5^\circ$ (c: 0.8, EtOH). Its phenolic nature was deduced from its UV spectrum $\lambda_{\text{max}}(\text{EtOH})(\log \epsilon)$: 225(4.16), 278(3.52) nm; $\lambda_{\text{max}}(\text{EtOH}/\text{OH}^-)(\log \epsilon)$: 227(4.30), 284(3.73) and 293 sh (3.69) nm and IR spectrum (CHCl_3) (3450 cm^{-1}). The molecular formula $\text{C}_{18}\text{H}_{19}\text{NO}_4$ 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 oxidation⁷ 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 cularines⁸, 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-nortetrahydrobenzylisoquinolines⁹, we decided to protect the nitrogen with the easily removable benzyl group. N-benylation (BrCH_2Ph , KI, acetone) of 7 followed by NaBH_4 reduction of the crude product afforded the N-benzyltetrahydro-



benzylisoquinoline **8** (72% yield), whose reaction with cupric oxide and potassium carbonate in dry pyridine gave the N-benzylated curarine **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-demethylation¹¹ of **10** (HBr , AcOH) then afforded N-norsarcocapnidine **3** (70% yield), which was identical (tlc, UV, MS, pmr) with the natural product.

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