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SECOCULARINES: A NEW GROUP OF ISOQUINOLINE RELATED ALKALOIDS PRESENT IN THE FUMARIACEAE

J.M.Boente, L.Castedo*, D.Domínguez, A.Fariña, A.Rodriguez de Lera and M.C.Villaverde

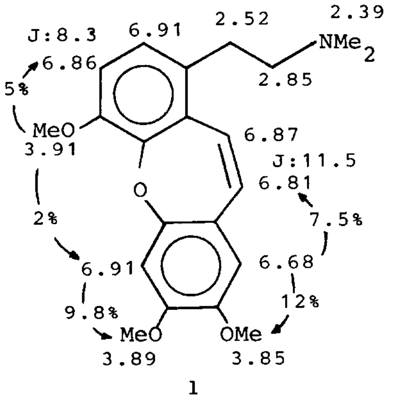
Departamento de Química Orgánica de la Facultad de Química e Instituto de Productos Naturales Orgánicos(Sección Alcaloides)del C.S.I.C.,Santiago(SPAIN)

Abstract: The isolation and structure of secocularine and secocularidine, the first two members of a new group of isoquinoline related alkaloids, the secocularines, is reported.

Our current studies on the chemical components of the Fumariaceae *Sarcocapnos crassifolia* (Desf.)D.C. and *Corydalis claviculata* (L.)D.C.[1] have led us to the isolation of the first two members of a new group of alkaloids which we have named secocularines.They may be included among the isoquinolines since they are probably biogenetically derived from cularines by an *in vivo* Hofmann degradation[2].

Secocularine(1)was obtained from *S.crassifolia* growing in Southern Spain as an amorphous substance.Its UV exhibited characteristic absorptions at λ_{max}(EtOH)(log ε):220(4.32), 235sh(4.25), 296sh(3.78) and 320(3.88)nm. The MS with a base peak at m/e 58($CH_2{=}\overset{+}{N}Me_2$)[2] and the molecular ion at m/e 355(6%), confirmed the molecular formula $C_{21}H_{25}NO_4$ established by elemental analysis of its perchlorate.The pmr(250 MHz,$CDCl_3$) showed a singlet at δ2.39(6H) and two multiplets centered at 2.52(2H) and 2.85(2H) ppm which indicated the presence of a $-CH_2CH_2NMe_2$ side chain; in addition, three singlets due to methoxyl groups at 3.85,3.89 and 3.91, two singlets at 6.88 (1H) and 6.91(1H), and two AB_q at (δ_A=6.81, δ_B=6.87, J=11.5Hz,2H) and (δ_A=6.86, δ_B=6.91,J=8.3 Hz, 2H) were also observed. All the above data suggest structure(1)for secocularine.This assignment was finally confirmed by direct comparison (tlc,MS,UV,pmr) with synthetic secocularine(1),obtained by Hofmann degradation of cularine methiodide[3].The assignment of all resonances in the pmr spectrum of secocularine was achieved on the basis of an NMR NOE difference study(NOEDS)[4] and the results are summarized in structure(1).

A second alkaloid,named secocularidine,(4a) was isolated from *C.claviculata* as colorless prisms,mp 189-90°(MeOH)[5]. Its UV was very close to that of secocularine (1), but exhibited a bathochromic shift upon addition of a base,suggestive of a phenolic secocularine structure. Methylation of secocularidine with diazomethane gave secocularine(1)(tlc,pmr,MS), thus establishing its oxygenated substitution pattern.The phenolic group of secocularidine was initially tentatively considered



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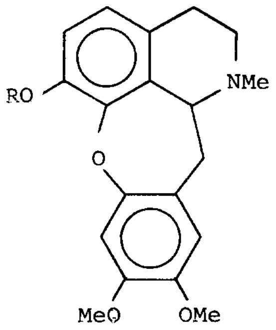
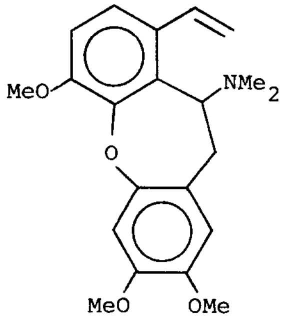


2a R=Me

2b R=H



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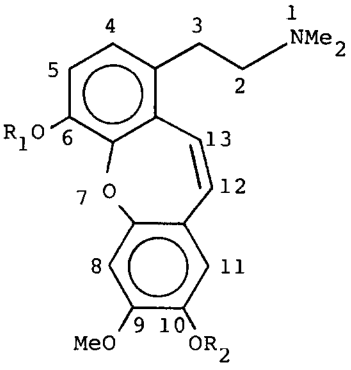

4a R_1=H, R_2=Me

4b R_1=Me, R_2=H

as located on the lower ring of the secocularine skeleton. To check this posibility we prepared the secocularine derivative 4b from 10-O-demethylcularine methiodide[1c]. Direct comparison of the data of synthetic 4b[6] with those of secocularidine clearly showed that the two compounds are not identical, thus ruling out position C-10 for the hydroxy group of secocularidine. Since we had a large supply of cularidine 2b we next carried out the preparation of compound 4a by Hofmann elimination of the methiodide of 2b. The main degradation product was, unexpectedly, identical (tlc, IR, NMR) to natural secocularidine, thus unequivocally establishing structure 4a for the alkaloid.

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2. A similar situation is found in the phenanthrene alkaloids: M. Shamma, "The isoquinoline alkaloids", Academic Press, N.Y., 1972; M. Shamma and J. L. Moniot, "Isoquinoline Alkaloids Research 1972-1977", Plenum Press, N.Y., 1978.

3. This reaction, first carried out by R. H. F. Manske in his work on the structure of cularine (2a) (J. Am. Chem. Soc. 72, 55 (1950)), gave elimination material of unknown composition. Our experiments, using sodium ethoxide in refluxing ethanol for 3.5 hours, gave in 83% yield a mixture of olefins (1) and (3) in the ratio 6:1 which were separated by PTLC.
Secocularine 1 crystalized from ethanol as the perchlorate, mp 194-196°, which analyzed for $C_{21}H_{25}NO_4.HClO_4$.The free base showed: IR ν_{max}^{BrK} 1604, 1562 and 1510 cm^{-1}; MS m/e(%): 355(M^+, 6%), 297(2%), 165(1%), 152(1%), 139(1%) and 58($CH_2=\overset{+}{N}Me_2$, 100%).
Styrene 3: UV λ_{max}^{EtOH} 284 nm. ^{1}HNMR (250 MHz, Cl_3CD) δ 2.29(s, 6H, NMe_2), 2.96(dd, J=15.4 and 3.9 Hz, 1H), 3.40(dd, J=15.4 and 7.3 Hz, 1H), 3.82 (s, 3H, OMe), 3.86(s, 3H, OMe), 3.90(broad s, 4H, OMe + 1H), 5.17(dd, J=10.9 and 1.40 Hz, 1H), 5.42(dd, J=17.3 and 1.4, 1H), 6.59(s, 1H), 6.81(d, J=8.5, 1H), 6.81(s, 1H), 7.08(dd, J=17.3 and 10.9, 1H), 7.17 (d, J=8.5, 1H).

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5. *Secocularidine* 4a: UV λ_{max}^{EtOH} (log ε): 216(3.88), 236sh(3.83), 296sh(3.41), 320(3.51); $\lambda_{max}^{EtOH/^-OH}$(log ε): 216(4.13) and 330(3.57). IR ν_{max}^{KBr}: 1604, 1565 and 1512 cm^{-1}; ^{1}HNMR (250 MHz, Cl_3CD): 2.32(s, 6H, NMe_2), 2.44(m, 2H, H_3), 2.84(m, 2H, H_2), 3.86(s, 3H, OMe), 3.89(s, 3H, OMe), 6.67(s, 1H), 6.68(s, 1H), 6.72(d, J=11.4 Hz, 1H), 6.82(d, J=11.4 Hz, 1H), 6.85 (d, J=8.2 Hz, 1H), 6.89(d, J=8.2 Hz, 1H). MS m/e(%): 341(M^+, 2%), 284 (1%), 283(1%), 165(1%), 152(2%), 139(2%), 115(2%) and 58($CH_2=\overset{+}{N}Me_2$).

6. 10-*O-demethylsecocularine* 4b: UV λ_{max}^{EtOH} (log ε): 226(3.95), 298sh(3.45) and 320(3.50); $\lambda_{max}^{EtOH/^{-}OH}$: 220(4.19), 274(3.91), 302(3.65) and 350(3.42). MS m/e(%): 341(0.6), 287(0.6), 283(0.4), 165(0.4), 152(0.5), 139(0.6), 115(0.5), 59(3), 58(100, $CH_2=\overset{+}{N}Me_2$). ^{1}H-NMR(250 MHz, $CDCl_3$), δ 2.32(s, 6H, NMe_2), 2.45(m, 2H, H_3), 2.80(m, 2H, H_2), 3.90(s, 6H, 2xOMe), 6.67(s, 1H, H_{11}), 6.72(d, J=11.5, H_{12}), 6.81(d, J=11.5, 1H, H_{13}), 6.84(d, J=8.4, 1H, H_5), 6.89(d, J=8.4, 1H, H_4) and 6.89(s, 1H, H_8) (assignments are based on the observation of NOE at δ 6.89(3.8%) and δ 6.84(2.5%) upon irradiation of the methoxyl signals at δ 3.90).

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