HETEROCYCLES, Vol 27, No 8, 1988

STRUCTURE AND STEREOCHEMISTRY OF THALICSILINE, A NEW ANTIINFLAMMATORY C_{20}-DITERPENOID ALKALOID FROM <u>THALICTRUM SESSILE</u>.

Yang-Chang Wu,*[a] Tian-Shung Wu,[b] Masatake Niwa,[c] Sheng-Teh Lu,[d]
Yoshimasa Hirata,[c] Donald R. McPhail,[e] Andrew T. McPhail,*[e] and
Kuo-Hsiung Lee*[a]

a. Natural Products Laboratory, Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27514, U.S.A.

b. Department of Applied Chemistry, Providence College of Arts and Science, Taichung 40211, Taiwan, R.O.C.

c. Faculty of Pharmacy, Meijo University, Tempaku, Nagoya 468, Japan

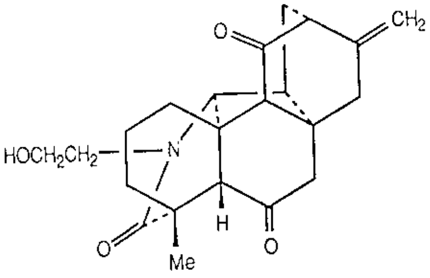
d. School of Pharmacy, Kaohsiung Medical College, Kaohsiung 80731, Taiwan, R.O.C.

e. Department of Chemistry, Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706, U.S.A.

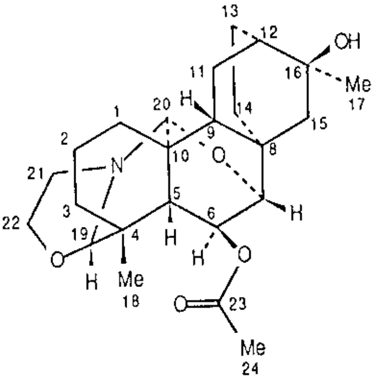
<u>Abstract</u> - Antiinflammatory thalicsiline, the first ajaconine-type alkaloid bearing an oxygen function at C_6, has been isolated from <u>Thalictrum sessile</u>, and its structure and stereochemistry have been established by spectral data and a single-crystal <u>X</u>-ray analysis.

We reported recently on the isolation of thalicsessine (1), a spiradine-type C_{20}-diterpenoid alkaloid from the roots of <u>Thalictrum sessile</u> Hayata.[1] Further investigations on bioactive compounds with novel structures from this same plant have now resulted in the isolation of a new ajaconine-type[2] C_{20}-diterpenoid alkaloid, thalicsiline (2), which was characterized on the basis of spectral data in conjunction with a single-crystal <u>X</u>-ray analysis. Thalicsiline demonstrated significant antiinflammatory activity in rats.[3]

Thalicsiline (2) [$C_{24}H_{35}NO_5$, m/z 417.2481 ($\underline{M}^+$), mp 183-186 °C, $[\alpha]_D^{20}$-11.4° (<u>c</u> 0.1, MeOH) was isolated in 0.00021% yield and showed ir bands (Nujol) at 3540 (OH), 1720 and 1240 (acetyl), and 1100 cm^{-1} (ether). The presence of an ajaconine-type [C(7)- C(20) carbinolamine ether linkage] skeleton in 2 was indicated by comparison of the ^{13}C nmr chemical shift values[4] with literature data.[5,6] The ^1H nmr spectrum (400 MHz, $CDCl_3$) of 2 is in accord with the assigned structure. Presence of an oxazolidine ring system was revealed by a five-proton multiplet pattern between


O
CH2
HOCH2CH2
N
O
H
O
Me

1


13
12
OH
16
Me
17
11
20
H
1
9
14
15
2
10
8
21
N
O
3
5
H
22
19
4
6
O
H
H
H
Me
18
O
23
Me
24

2

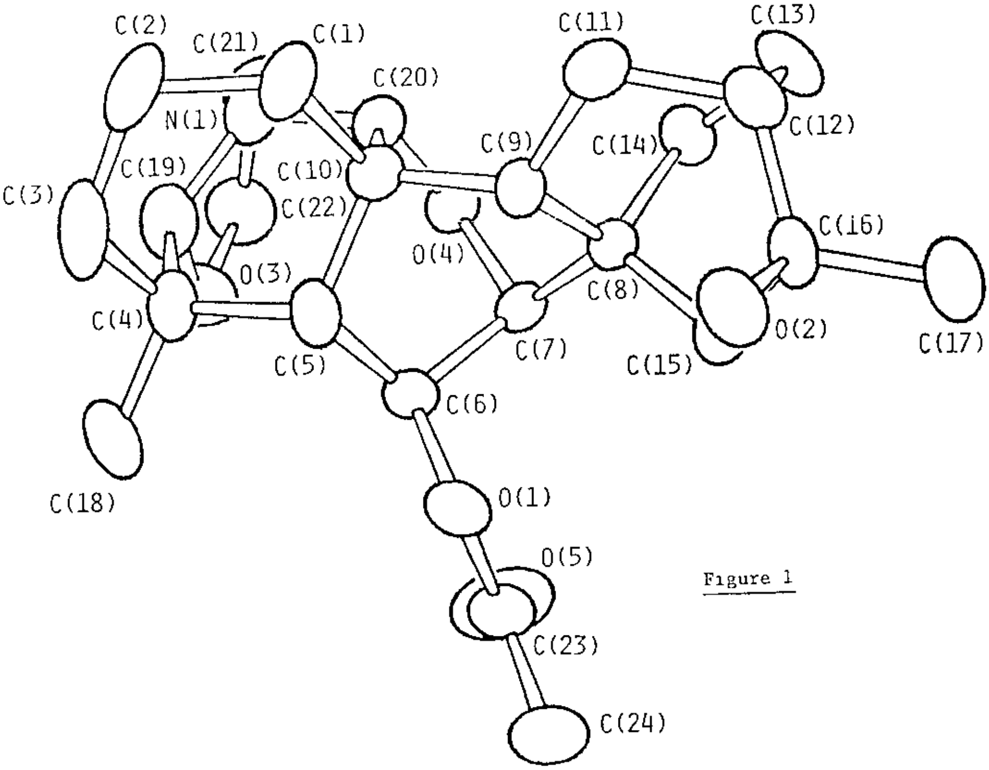

C(2)
C(21)
C(1)
C(20)
C(11)
C(13)
N(1)
C(12)
C(14)
C(19)
C(9)
C(3)
C(10)
C(22)
C(16)
O(4)
O(3)
C(8)
C(4)
C(5)
C(7)
C(15)
O(2)
C(17)
C(6)
C(18)
O(1)
O(5)
C(23)
C(24)

Figure 1

δ3.00 and 4.10, in which the proton at C(19) occurs as a distinct epimeric pair of signals at δ4.11 [(S)] and 3.86 [(R)] in a ratio of ca. 1:3, a phenomenon which is also common in the spirasine series.[7] Other epimeric pairs, a doublet of doublets (J = 2.40 Hz) at δ 5.32 and 5.67 as well as singlets at δ2.05 and 2.06, in approximately the same ratio of 1:3 for each, were assigned to H-C(6) and MeCOO-C(6), respectively. The rest of the characteristic pairs of signals (all ca. 1:3) was assigned as follows: δ 4.82 and 4.58 [H-C(20)], 1.31 and 1.30 [Me-C(16)], and 0.94 and 1.11 [Me-C(4)].

The complete structure and relative stereochemistry of 2 were defined unequivocally by a single-crystal X-ray analysis. Crystal data. $C_{24}H_{35}NO_5$ **(2)**, M = 417.55, monoclinic, space group $P2_1$, a = 10.000(3), b = 12.983(2), c = 8.879(2) Å, β = 107.86(2)°, U = 1097.2 $Å^3$, Z = 2, D_c = 1.264 g cm^{-3}, μ(Cu-Kα radiation, λ = 1.5418 Å) = 6.7 cm^{-1}. Intensity data ($+h$, $+k$, $\pm \ell$; 2051 independent forms) from a crystal of dimensions 0.12 x 0.14 x 0.05 mm were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu-Kα radiation, incident-beam graphite monochromator; ω-2θ scans, θ_{max} = 67°). The crystal structure was solved by direct methods (MULTAN11/82). Hydrogen atoms were located in a difference Fourier synthesis. Full-matrix least-squares refinement (Enral-Nonius SDP) of non-hydrogen atom positional and anisotropic thermal parameters, with hydrogen atoms included at their calculated positions, converged at R = 0.042 [R_w = 0.055, $w = 1/\sigma^2(|F_o|)$] over 1284 reflections with $I > 3.0\sigma(I)$.[8] A view of the solid-state conformation is provided in Figure 1. In the crystals, molecules of 2 related by unit-translation along c are associated by an O-H . . . O hydrogen bond [O(26) . . . O(29) 2.924(5) Å].

ACKNOWLEDGEMENT

The investigation was supported in part by a grant from the National Cancer Institute CA 17625 (K.H. Lee).

REFERENCES AND NOTES

1. Y.C. Wu, T.S. Wu, M. Niwa, S.T. Lu, and Y. Hirata, Heterocycles, 1987, **26**, 943.
2. D. Dvornik and O.E. Edwards, Tetrahedron, 1961, 14, 54.
3. In vivo activity was assayed by Dr. I.H. Hall, Division of Medicinal Chemistry and Natural Products, according to a literature method (I.H. Hall, K.H. Lee, and H.C. Sykes, Planta Medica, 1987, 53, 153). Thalicsiline **(2)** showed a 42% reduction of the carrageenan-induced inflammation in Sprague Dawley rats at 20 mg/kg x 2.

4. ^{13}C Nmr (δ) data (25.0 MHz; $CDCl_3$) for **2**: C(1) 40.54, C(2) 22.70, C(3) 47.21, C(4) 35.16, C(5) 52.18, C(6) 70.79, C(7) 70.91, C(8) 36.27, C(9) 42.53, C(10) 35.28, C(11) 29.02, C(12) 38.26, C(13) 26.68, C(14) 23.52, C(15) 20.24, C(16) 73.83, C(17) 30.19, C(18) 22.58, C(19) 94.60, C(20) 85.59, C(21) 51.01, C(22) 63.30, C(23) 169.72, C(24) 21.41.

5. S.W. Pelletier, R.S. Sawhney, and N.V. Mody, Heterocycles, 1978, **9**, 1241.

6. N.V. Mody and S.W. Pelletier, Tetrahedron, 1978, **34**, 2421.

7. F. Sun, X.T. Liang, D.Yu, C.F. Xu, and J. Clardy, Tetrahedron Letters, 1986, **27**, 275.

8. Atomic coordinates, thermal parameters, bond lengths and angles have been deposited with the Cambridge Crystallographic Data Center.

Received, 14th March, 1988