Tetrahedron Letters,Vol.27,No.34,pp 4077-4078,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

CLAVIZEPINE, THE FIRST DIBENZOPYRANAZEPINE ALKALOID

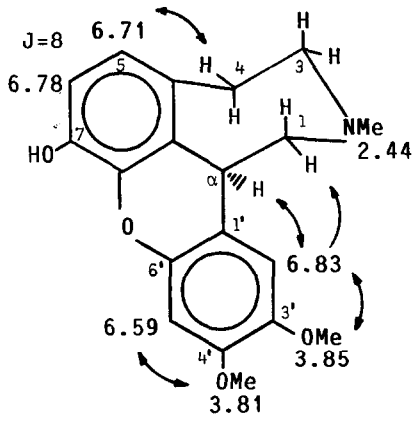
J.M.Boente, L.Castedo, D.Domínguez and M.C.Ferro
Departamento de Química Orgánica, Facultad de Química y
Sección de Alcaloides del CSIC, Santiago de Compostela, Spain

Summary: We report the isolation and structure determination of the first naturally occurring dibenzopyranazepine alkaloid, clavizepine, which has been isolated from Corydalis claviculata (L.) DC[1].

Clavizepine (1) is an optically active compound ($[\alpha]_D$=-40° (0.05, $CHCl_3$)) obtained as colorless crystals of m.p. 234-235º (MeOH). Its UV spectrum exhibited absorption bands at λ_{max}^{MeOH}(log ε): 207(4.40), 250(3.44) and 295(3.62), which upon addition of base suffered a bathochromic shift to $\lambda_{max}^{MeOH/NaOH}$(log ε) 209(4.61), 262(3.83) and 306(3.81), showing the compound's phenolic nature.

Its PMR showed the presence of two tetrasubstituted benzene rings (one of them with two ortho protons and the other with two para protons), two methoxyl groups and one -NMe group. The aliphatic part of the spectrum also exhibited five multiplets which integrated for seven protons. The CMR confirmed the presence of twelve aromatic carbons, and in addition exhibited seven resonances in the aliphatic region, three of them corresponding to methylene groups and one to a methine, as deduced from "off resonance" and INEPT experiments. The mass spectrum showed the molecular ion at m/e 327(73) with other significant peaks at 284(61), 283(100), 271(24), 270(30) and 269(39). The molecular formula $C_{19}H_{21}NO_4$ deduced from the above data was confirmed by high resolution MS (f: 327.1457, c: 327.1470). Since three of the oxygen atoms are involved in the two methoxyl and one hydroxyl groups, the fourth should link the two aromatic rings, thus establishing a diarylether moiety in the clavizepine structure. The aliphatic part of the molecule was elucidated by means of double resonance studies and homonuclear COSY, which revealed the presence of two isolated spin systems, -CH-CH_2- and -CH_2-CH_2-. The connection of these two fragments to the diarylether moiety established above gives clavizepine a |1| benzopyrano |2,3,4-j,k| |3| benzazepine structure. The location of substituents was inferred from NOEDS studies (arrows in Fig. 1). As expected, upon treatment with diazomethane clavizepine (1) yielded O-methylclavizepine[2]. Further proof for structure 1 was obtained by direct (through-one-bond) and long range ^1H-^{13}C correlation studies, which also allowed us to assign all of its resonances (Table I).

From a biogenetic point of view this novel type of alkaloid might be considered as the result of a rearrangement of a cularine system leading to an expansion of the nitrogen-containing ring with concomitant contraction of the oxepine ring.



1

$H_{\alpha\alpha}$: 4.41, d, J: 9.3 Hz
$H_{1\beta}$: 2.28, dd, J: 12.3 and 9.3 Hz
$H_{1\alpha}$: 3.11, d, J: 12.3 Hz[a]
$H_{3\beta}$: 2.12, t, $J_{3\beta-3\alpha}=J_{3\beta-4\alpha}$: 11.8 Hz
$H_{3\alpha}$: 3.20, m
$H_{4\beta}$: 2.69, dd, J: 14.8 and 6 Hz
$H_{4\alpha}$: 3.20, m
(a)Chemical shift and J determined by 2D-JRES.

Fig.1. PMR data and n.O.e.

Table I

CMR data of clavizepine

Carbon	(ppm)	Correlation[b]	Carbon	(ppm)	Correlation[b]
C_α	36.9	$\underline{H}_\alpha$, $H_{2'}$	$C_{1'}$	122.7	$H_{5'}$, $H_{\alpha\alpha}$
C_1	67.6	$\underline{H}_{1\alpha}$, $\underline{H}_{1\beta}$	$C_{2'}$	111.7	$\underline{H}_{2'}$, $H_{\alpha\alpha}$
C_3	57.2	$\underline{H}_{3\alpha}$, $\underline{H}_{3\beta}$	$C_{3'}$	145.7	$H_{5'}$,$C_{3'}$-OMe
C_4	34.8	$\underline{H}_{4\alpha}$, $\underline{H}_{4\beta}$	$C_{4'}$	149.0	$H_{2'}$,$C_{4'}$-OMe
C_{4a}	132.9	(c)	$C_{5'}$	99.9	$\underline{H}_{5'}$
C_5	122.7	$\underline{H}_5$	$C_{6'}$	144.1	$H_{2'}$
C_6	113.2	$\underline{H}_6$	N-Me	47.0	N-Me
C_7	142.7	H_5	$C_{3'}$-OMe	56.4	$C_{3'}$-OMe
C_{7a}	137.9	H_6	$C_{4'}$-OMe	55.9	$C_{4'}$-OMe
C_{7b}	123.1	(c)			

(b)The underlined hydrogens are the protons which correlate through one bond.
(c)These carbons are not observed in the F_2 dimension. Their assigments are interchangeable.

ACKNOWLEDGMENTS:We thank the Comisiôn Asesora (Spain) for its financial support.

REFERENCES

1. For our previous work on the alkaloids of this plant see: J.M.Boente, L.Castedo, D.Domínguez, A.Fariña, A.R. de Lera and M.C.Villaverde, Tetrahedron Lett., 889, (1984) and references therein.
2. O-methylclavizepine. ^{1}H-NMR(250 MHz, $CDCl_3$): 6.78 and 6.72(AB_q,J=8 Hz, H-5 and H-6), 6.78(s,1H,ArH), 6.71(s,1H,ArH), 4.38(d,J=9.6Hz,1H,$H_{\alpha\alpha}$), 3.92(s, 3H,OMe), 3.86(s,6H,2xOMe), 3.07-3.25(m,3H,$H_{1\alpha}$,$H_{3\alpha}$, and $H_{4\alpha}$), 2.73(dd,J_g= 15 Hz,J_t=6 Hz,1H,$H_{4\beta}$), 2.44(dd,J_g=12.6 Hz,J_t=9.8 Hz,1H,$H_{1\beta}$), 2.41(s,3H, NMe), 2.09(t,J=10.6 Hz,1H,$H_{3\beta}$); MS m/e(%): 341(M^+,83), 326(12), 298(57), 297(100), 285(37), 284(25), 283(53), 269(33).

(Received in UK 5 June 1986)