THE REVISED STRUCTURE OF PANICULINE

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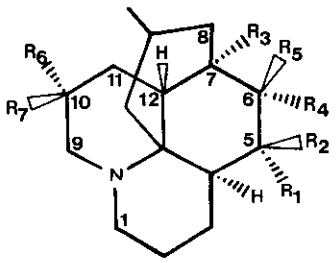
Abstract - The original structure of paniculine has been revised based upon additional physical data.

The study of Lycopodium confertum has led to the isolation of paniculine and deacetylpaniculine as the major components present in the alkaloids mixture. Paniculine, 1, had been previously isolated from L.paniculatum as a minor component and its structure was proposed on the basis of physical data and some chemical transformations[1,2]. A detailed study of the ^{1}H(400 MHz) and ^{13}C-NMR (100 MHz) of paniculine and of other closely related alkaloids necessitates modifying the structure to 1b, i.e. 10α-hydroxyacetyldihydrolycopodine.



1 R_2=OAc; R_3=OH; R_1=R_4=R_5=R_6=R_7=H

1b R_2=OAc; R_6=OH; R_1=R_3=R_4=R_5=R_7=H

1c R_2=R_6=OH; R_1=R_3=R_4=R_5=R_7=H

1d R_2+R_1=O; R_6=OH; R_3=R_4=R_5=R_7=H

2 R_2=OAc; R_1=R_3=R_4=R_5=R_6=R_7=H

3 R_2=OH; R_4=OH; R_1=R_3=R_5=R_6=R_7=H

Examination of the ^{1}H-NMR spectrum of acetyldihydrolycopodine, 2, particularly in the region 2.5-3.8 ppm, revealed with precision the environment around the nitrogen atom: the lowest field signals (δ 3.43 and 3.16) were assigned to axial protons on the basis of the observed coupling constants (two large J_{gem} and J_{aa} values and a small J_{ae} (see Table 1). The different J_{gem} values observed (13.5 vs. 11.6Hz) can be correlated to the different orientations of these axial protons with respect to the nitrogen lone electron pair[3]. On the basis of this observation, the signal at δ 3.43 is tentatively assigned to H-1 axial. Extensive double irradiation experiments established the absorptions of the corresponding equatorial protons, H-1 and H-9, at δ2.50 and 2.55 respectively[4].

Table 1 ^{1}H-NMR data for 1b, 2 and 3[4]

	1b	2	3
H-1 ax	3.42	3.43	3.42
	(ddd,13.5,13.5,4.8)	(ddd,13.5,13.5,3.5)	(ddd,14.0,14.0,3.5)
H-1 eq	2.49	2.50	2.51
	(dd,13.5,5.9)	(dd,13.5,4.9)	(m)
H-9 ax	2.95	3.16	3.18
	(dd,10.8,10.8)	(ddd,11.6,11.6,3.0)	(ddd,12.4,12.4,3.0)
H-9 eq	2.75	2.55	2.51
	(ddd,10.8,5.2,1.8)	(dd,11.6,3.0)	(m)
H-10 ax	3.80	1.7	1.55
	(dddd,10.8,10.8,5.2,5.2)	-	-
H-5 eq	5.07	5.08	3.83
	(dd,6.0,6.0)	(dd,6.5,6.5)	(bd,6.0)
H-6 ax	2.09	2.08	-
	(ddd,16.4,6.0,6.0)	(ddd,16.2,6.5,6.5)	-
H-6 eq	1.52	1.48	3.72
	(d)	(d,16.2)	(s)

In $CDCl_3$, ppm from TMS (J values in Hz). Spectra were determined on a Bruker WH-400 spectrometer (400 MHz).

Table 2 ^{13}C-NMR data for 1b, 2,3 and 1d[4,7]

Compound	C-1	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12
1b	47.0	70.2	31.2	35.0	41.8	54.7	68.5	34.4	43.5
2	47.0	70.4	31.3	35.0	41.9	47.2	26.4	24.8	45.4
3	47.4	75.0	78.7	44.2	40.4	47.3	27.0	26.8	45.0
1d	46.6	212.7	43.0	36.7	42.6	55.0	68.1	34.8	43.3

In $CDCl_3$, ppm from TMS. Spectra were determined on a Bruker WH-400 spectrometer (100 MHz).

These characteristics are shown again in the ^{1}H-NMR spectrum of deacetyllycoclavine, 3, an alkaloid possessing an identical environment around the nitrogen atom as in 2. These unusual assignments (axial protons on methylene carbons next to nitrogen normally absorb ca. 0.5 ppm higher field than the equatorial ones) are probably associated to γ_{HH}- type interactions between H-1 axial and C-14 and γ_{2HH} interactions between H-9 axial and C-4 and C-2[5]. The revised structure of paniculine is in complete agreement with this new information. Thus, placement of an equatorial hydroxyl group at C-10 accounts for the multiplet at δ 3.80 (half-width 35 Hz) assigned to the axial H-10, together with the concomitant simplification of the resonance of the axial H-9 (a triplet at δ 2.95), wheras the axial H-1 remained unaltered[6]. Examination of the ^{13}C-NMR spectra of paniculine and derivatives confirmed the new structure proposed for this alkaloid and also showed a good correlation with that of 2,3 and other lycopodium alkaloids of this type[7]. The presence of the secondary hydroxyl group was indicated by the signal at δ 68.5 (d) and its assignment to C-10 followed from the expected shifts of C-9 (7.5 ppm), C-11 (9.6) and C-12 (-1.7). The signals corresponding to C-2, C-3 and C-4 in paniculine remained unaltered when compared to the values assigned to these carbons in 2,3, 1d and in other lycopodium alkaloids of this type[7]. This information, taken together with the ^{1}H-NMR data, supports the assignment of the secondary hydroxyl group at C-10, not C-2.

The secondary nature of the hydroxyl group present in paniculine was previously discarded in favor of a tertiary one on account of a) lack of an apreciable signal for its geminal proton when the spectrum was run at 60 MHz and b) the inertness of paniculine to undergo oxidation under conditions normally employed to convert secondary alcohols into the corresponding ketones. New attemps to carry out this transformation following a variety of procedures as reported in the literature have been unsuccesful[8]. Deacetylpaniculine, 1c, on the other hand, was readily transformed into a product with the properties of a hydroxy-ketone, whose structure has now been shown to correspond to 1d (Table 2), which demonstrates the differences in reactivities between the secondary OH groups located at C-10 and C-5.

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4.- H-9 eq in 1b appeared in a zone well separated from other signals; hence, its multiplet is better resolved than in either 2 or 3, where it is partially overlapped by the H-1 eq multiplet. Full details of the ^{1}H and ^{13}C-NMR spectra of paniculine and derivatives will be published separately.

5.- The nomenclature is that of Dalling and Grant (D.K. Dalling, D.M. Grant and E.G. E.G.Paul, J. Am. Chem. Soc., 1973, 95, 2718). For a discussion of these effects in terms of ^{1}H-NMR see H.Booth, Tetrahedron, 1966, 22, 615.

6.- The signal of H-10 was shifted to δ 5.46 after treatment of paniculine with trifluoroacetic anhydride.

7.- ^{13}C-NMR signals were assigned using SFORD techniques, by specific proton decoupling and by comparison with literature data (T.T. Nakashima. P.P. Singer. L.M. Brown and W.A. Ayer, Can. J. Chem., 1975, 53, 1936).

8.- Besides Sarett's and Jones reagents, other oxidation reagents tried on paniculine were (yield of recovered starting materials): CrO_3.2py complex (72%), b) DMSO/$(CF_3CO)_2O$, (27%), c) RuO_4/CCl_4 and d) t-BuOK/Ph_2CO/C_6H_6 (18%). Systems b and c also gave, respectively, a 49% and 61% yield of a product tentatively identified as 9-oxo-paniculine and d gave a 38% yield of 10α-hydroxylycopodine, 1d. Oxidation of deacetylpaniculine (1c) gave as the main product 10α-hydroxylycopodine, 1d, (74% by Jones and 64% by system d).

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