157. The Revised Structure of the Norditerpenoid Alkaloid Peregrine

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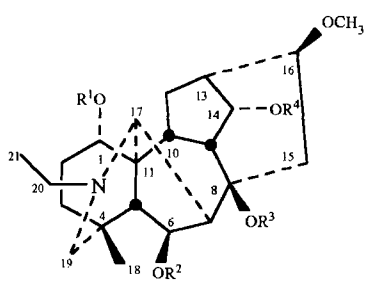
(22.VI.94)

The structure of peregrine (**1**), a norditerpenoid alkaloid isolated from *Delphinium peregrinum* var. *elongatum* BOISS., was revised on the basis of the ^{1}H-COSY, HMQC, HMBC, and ROESY NMR spectra and of the X-ray analysis of its parent alcohol **2**. Some of the ^{13}C-NMR resonances of **1** and the related alkaloids peregrine alcohol (**2**), 14-*O*-acetylperegrine (**3**), bicoloridine (**4**), bicoloridine alcohol (**5**), 6-*O*-acetylbicolorine (**6**), bicolorine (**7**), and 14-*O*-acetylbicolorine (**8**), were also reassigned.

1. Introduction. – While studying the alkaloids of *Delphinium peregrinum* var. *elongatum* BOISS., we isolated a new norditerpenoid alkaloid, peregrine (**1**), the structure of which was determined mainly by ^{1}H- and ^{13}C-NMR spectroscopy [1]. The clue to establish the configuration of the AcO group at C(6) as α was the assignment of the methine C-resonances at 42.4 and 56.4 ppm to C(5) and C(7), respectively, by comparison of the ^{13}C-NMR spectrum of **1** with those of related published norditerpenoid alkaloids [2] [3]. From a SFSD experiment, the 1-H signal at δ 2.72 (*d*, $J = 7.2$ Hz) was attributed to *H*–C(5), owing to its one-bond correlation with the ^{13}C-NMR signal at δ 42.4 (*d*). Since the *H*–C(5) signal was coupled with the 1-H signal at δ 5.22 (*d*, $J = 7.2$ Hz), the latter was



1 $R^1 = CH_3$ $R^2 = Ac$ $R^3 = CH_3$ $R^4 = H$
2 $R^1 = CH_3$ $R^2 = H$ $R^3 = CH_3$ $R^4 = H$
3 $R^1 = CH_3$ $R^2 = Ac$ $R^3 = CH_3$ $R^4 = Ac$
4 $R^1 = H$ $R^2 = Ac$ $R^3 = CH_3$ $R^4 = H$
5 $R^1 = H$ $R^2 = H$ $R^3 = CH_3$ $R^4 = H$
6 $R^1 = H$ $R^2 = Ac$ $R^3 = H$ $R^4 = H$
7 $R^1 = H$ $R^2 = H$ $R^3 = H$ $R^4 = H$
8 $R^1 = H$ $R^2 = H$ $R^3 = H$ $R^4 = Ac$

ascribed to *H*–C(6) in β configuration (α for the AcO group) by reason of the *ca.* 20, 90, and 90° dihedral angles between H_β–C(5) and H_β–C(6), H_β–C(5) and H_α–C(6), and H_β–C(6) and H–C(7), respectively, measured on a *Dreiding* model of the molecule.

Now in the light of new NMR data, and the X-ray analysis of peregrine alcohol (= 6-*O*-deacetylperegrine; **2**), the configuration of the AcO group at C(6) was established as β for peregrine (**1**).

2. Results and Discussion. – HMQC [4], HMBC [5], and ROESY [6] experiments with peregrine (**1**) allowed a more reliable interpretation of its ^{1}H-NMR data.

In the ^{1}H-COSY spectrum of **1** (*Table 1*), the 1-H signal at δ 1.46 (*s*) gave a W coupling with the signal at 3.16 (*s*, 1 H), which in turn showed a one-bond connectivity with the methine C-resonance at 64.7 ppm for C(17) in the HMQC spectrum (*Table 2*). Moreover, in the HMBC experiment (*Table 2*) the 1-H *s* at δ 1.46 gave three-bond correlations with the resonances at δ 64.7 (*d*), 25.9 (*q*), and 57.6 (*t*), corresponding to C(17), C(18), and C(19), respectively. This information allows us to assign the *s* at δ 1.46 to H–C(5) unambiguously. On the other hand, the

Table 1. *Scalar and Spatial Correlation of the Protons of Peregrine* (**1**)

Proton	COSY	ROESY
H_β–C(2) H–C(10)	H–C(9), H_α–C(3), H_β–C(3)	H_β–C(3), H–C(5), H_β–C(14), CH_3O–C(1)
H_α–C(3)	H_β–C(3), H_β–C(2)	H_β–C(3), CH_3(18)
H_β–C(3)	H_α–C(3), H_β–C(2)	H_α–C(3), H–C(5)
H–C(5)	H–C(17) (W)	H–C(10), H_β–C(3), H_α–C(6), CH_3(18)
H_α–C(6)	H–C(7)	H–C(5), H–C(7), CH_3(18)
H–C(7)	H_α–C(6)	H_α–C(6), CH_2(20), CH_3O–C(8)
H–C(9)	H–C(14), H–C(10)	H–C(10), H_β–C(14)
H_α–C(12)	H_β–C(12)	H_β–C(12), H–C(17), CH_3O–C(16)
H_β–C(12)	H_α–C(12), H–C(13)	H_α–C(12), H–C(13), H_β–C(14)
H–C(13)	H_β–C(12), H_β–C(14)	H_β–C(12), H_β–C(14), CH_3O–C(16)
H_β– C(14)	H–C(9), H–C(13)	H–C(10), H–C(9), H_β–C(12), H–C(13)
H–C(17)	H–C(5) (W)	H–C(7), H_α–C(12), CH_2(20)
CH_3(18)		H_α–C(3), H_β–C(3), H–C(5), H_α–C(6)
CH_2(20)	CH_3(21)	H–C(7), H–C(17), CH_3(21)
CH_3(21)	CH_2(20)	H–C(17), $CH_2(19)_\alpha$, CH_2(20)
CH_3O–C(1)		H_α–C(12), H_β–C(12)
CH_3O–C(8)		H–C(7)
CH_3O–C(16)		H–C(13)

Table 2. *^1H, HMQC, and HMBC NMR Data of Peregrine* (**1**)[a])

Proton		Correlated C-atom	
		HMQC	HMBC
H_β–C(12) H–C(10)	1.97 (*m*)	26.5 (*t*) 46.2 (*d*)	C(8), C(9), C(11), C(12), C(17)
H_α–C(3)	1.58 (br. *d*, J = 15)	37.1 (*t*)	
H_β–C(3)	1.20 (*m*)	37.1 (*t*)	C(19)
H–C(5)	1.46 (*s*)	56.4 (*d*)	C(4), C(6), C(7), C(18), C(19)
H_α–C(6)	5.22 (*d*, J = 7.2)	73.4 (*d*)	C(7), C(8), C(11), CO
H–C(7)	2.71 (*d*, J = 7.2)	42.4 (*d*)	C(5), C(8), C(9), C(11), C(17)
H–C(9)	3.04 (*t*, J = 5.8)	44.6 (*d*)	C(8), C(10), C(12), C(13), C(14), C(15)
H_α–C(12)	2.23 (*dd*, J = 14.5, 5.5)	28.6 (*t*)	C(10), C(11), C(14), C(16)
H_β–C(12)	1.85 (*m*)	28.6 (*t*)	C(10), C(16)
H–C(13)	2.33 (br. *t*, J = 6.1)	38.6 (*d*)	C(9), C(10), C(14), C(15), C(16)
H_β– C(14)	3.97 (*dt*, J = 5.6, 5.2)	75.5 (*d*)	C(8), C(16)
H–C(17)	3.16 (*s*)	64.7 (*d*)	C(5), C(6), C(11), C(19)
CH_3(18)	0.82 (*s*)	25.9 (*q*)	C(3), C(4), C(5), C(19)
$CH_2(19)_\alpha$	2.60 (*d*, J = 11.9)	57.6 (*t*)	
CH_2(20)	2.46 (*m*)	49.3 (*t*)	C(17), C(19), C(21)
CH_3(21)	1.04 (*t*, J = 7.1)	13.6 (*q*)	C(20)
CH_3O–C(1)	3.25 (*s*)	56.0 (*q*)	C(1)
CH_3O–C(8)	3.07 (*s*)	48.3 (*q*)	C(8)
CH_3O–C(16)	3.34 (*s*)	56.4 (*q*)	C(16)
Ac	2.04 (*s*)	21.7 (*q*)	CO

[a]) Chemical shifts in ppm rel. to $SiMe_4$ (= 0 ppm); coupling constants J in Hz. C-Multiplicities were established by DEPT data.

s at δ 1.46 correlated with the methine C-resonance at 56.4 ppm in the HMQC spectrum, so this signal was readily attributed to C(5).

The 1-H *d* (J = 7.2 Hz) at δ 2.71 was assigned to *H*–C(7) on account of its three-bond connectivities with the C-resonances at δ 56.4 (*d*) and 48.2 (*s*), ascribed to C(5) and C(11), respectively, and the NOE's with CH_2(20) and CH_3O–C(8) in the ROESY spectrum (*Table 1*). Since the *H*–C(7) signal at δ 2.71 gave a one-bond correlation with the C-resonance at δ 42.4 (*d*) in the HMQC experiment, this signal was assigned to C(7).

The ^{1}H-COSY spectrum of **1** showed that the 1-H *d* at δ 5.22 (J = 7.2 Hz) was coupled with *H*–C(7). Furthermore, that signal gave a one-bond connectivity with the methine C-resonance at δ 73.4 in the HMQC spectrum and three-bond correlations with the C-resonances at δ 79.1 (*s*, C(8)), 48.2 (*s*, C(11)), and 170.2 (*s*, CO) in the HMBC spectrum. Consequently, the signal at δ 5.22 was assigned to *H*–C(6).

In essence, the NMR signals at δ 1.46 (*s*, 1 H) and 56.4 (*d*), 5.22 (*d*, J = 7.2 Hz, 1 H) and 73.4 (*d*), and 2.71 (*d*, J = 7.2 Hz, 1 H) and 42.4 (*d*) belong to CH(5), CH(6), and CH(7), respectively. Considering the J(*H*–C(6), *H*–C(7)) of 7.2 Hz, *H*–C(6) must be in α configuration, in agreement with the 10 and 110° dihedral angles for H–C(7) and H_α–C(6), and H–C(7) and H_β–C(6), respectively, observed in a *Dreiding* molecular model of **1**. In addition, the ROESY spectrum (*Table 1*) showed spatial correlation between the angular CH_3 group and the corresponding signal for *H*–C(6), which corroborated the α configuration (β for the AcO group) established for *H*–C(6).

The ^{1}H-COSY, HMQC, HMBC, and ROESY NMR spectra of peregrine (**1**) allowed us to reassign certain of its previously published ^{13}C-NMR data (*Table 3*) [1], and the comparison of spectra from compound to compound, taking into account known substituent effects, also permitted some already published C-resonances to be reassigned for

Table 3. *^{13}C-NMR Assignments for Peregrine* (**1**), *Peregrine Alcohol* (**2**), *14-O-Acetylperegrine* (**3**), *Bicoloridine* (**4**), *Bicoloridine Alcohol* (**5**), *6-O-Acetylbicolorine* (**6**), *Bicolorine* (**7**), *and 14-O-Acetylbicolorine* (**8**)[a])

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
C(1)	84.7	85.6	84.2	72.6	72.9	72.5	72.9	72.6
C(2)	26.5	26.5	27.1	29.7	29.6	28.9	29.7	29.4
C(3)	37.1	37.5	37.2	31.6	31.8	31.8	32.2	31.6
C(4)	34.5	34.6	34.2	32.8	32.6	33.1	32.8	32.6
C(5)	56.4	58.9	56.5	52.8	54.8	52.3	54.8	54.6
C(6)	73.4	73.0	73.1	72.3	72.5	72.7	72.0	72.4
C(7)	42.4	45.9	42.0	42.3	45.5	45.1	50.2	50.4
C(8)	79.1	80.9	78.5	79.9	81.8	74.6	76.0	76.2
C(9)	44.6	43.8	41.2	44.4	44.4	48.5	46.1	43.5
C(10)	46.2	46.3	46.0	44.4	43.5	44.3	44.4	44.0
C(11)	48.2	48.3	48.5	48.9	48.9	48.2	48.4	48.7
C(12)	28.6	28.5	28.6	30.6	30.3	29.7	29.7	29.7
C(13)	38.6	37.7	39.1	40.0	39.9	39.3	40.0	36.7
C(14)	75.5	75.2	76.3	75.9	75.8	76.1	76.1	77.3
C(15)	33.0	33.1	35.8	37.8	37.4	43.5	42.4	42.7
C(16)	82.5	82.4	83.6	83.3	83.0	81.9	82.4	82.2
C(17)	64.7	64.3	64.0	65.5	65.1	65.5	64.9	65.0
C(18)	25.9	26.0	26.1	27.3	27.5	27.3	27.4	27.5
C(19)	57.6	58.1	57.5	61.6	62.2	61.3	61.8	61.9
C(20)	49.3	49.6	48.5	48.3	48.6	48.4	48.4	48.4
C(21)	13.6	13.8	13.6	12.9	13.1	13.0	13.0	13.0
CH_3O–C(1)	56.0	56.3	56.0					
CH_3O–C(8)	48.3	48.6	48.0	48.0	48.5			
CH_3O–C(16)	56.4	56.5	56.5	56.4	56.6	56.3	56.3	56.1
CH_3CO	170.2		171.5[b])	170.9		170.8		170.7
CH_3CO	21.7		21.7[b])	21.5		21.7		21.4

[a]) Chemical shifts in ppm rel. to Me_4Si (= 0 ppm); solvent $CDCl_3$.

[b]) The second AcO group showed signals at 171.5 and 21.4 ppm, respectively.

peregrine alcohol [1] (**2**), 14-*O*-acetylperegrine [1] (**3**), bicoloridine [7] (**4**), bicoloridine alcohol [1] (**5**), 6-*O*-acetylbicoloridine [8] (**6**), bicoloridine [7] (**7**), and 14-*O*-acetylbicolorine [9] (**8**; *Table 3*).

To confirm the structure emanated from the NMR data, an X-ray analysis of peregrine alcohol [1] (**2**) was carried out, since we could not obtain suitable crystals from peregrine (**1**) itself. The molecular structure of **2** is illustrated in the *Figure*. The geometry of the molecule is generally as expected for such fused ring systems [10], and the substituents are 1α-MeO, 6β-OH, 8-MeO, 14α-OH, and 16β-MeO.

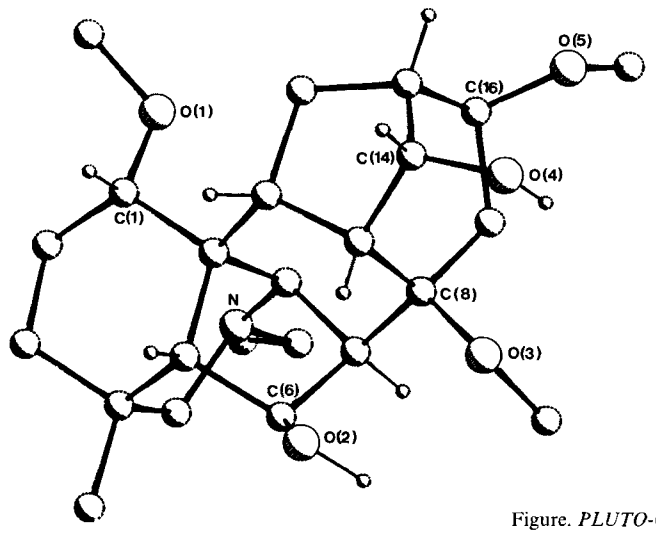


Figure. *PLUTO-Generated view of* **2**

Table 4 presents the *Cremer-Pople* ring parameters [11] for rings A through F. Ring A is in a chair conformation, and rings B and C are slightly distorted chairs. Ring D is close to a 1,2-diplanar (envelope) conformation, with the C(15)–C(16) end flattened. The C(9)–C(8)–C(15)–C(16) and C(8)–C(15)–C(16)–C(13) dihedral angles are −10.2(1.2)° and 9.8(1.2)°, respectively. The ring-puckering coordinates for the five-membered rings E and F indicate an envelope conformation (C_s symmetry) for E, with the apex at C(14), and a slightly distorted twist conformation (C_2 symmetry) for F.

Table 4. Cremer-Pople *Ring-Puckering Parameters*

Ring[a])	q_2	ϕ_2	θ_2	q_3
A	0.1746	114.2	162.5	−0.5548
B	0.2696	50.4	115.5	−0.5909
C	0.2376	143.6	158.4	−0.5996
D	0.5954	120.1	62.1	0.3146
E	0.4758	53.0		
F	0.5358	167.1		

[a]) Ring A: C(5), C(11), C(1), C(2), C(3), C(4); ring B: N, C(19), C(4), C(5), C(11), C(17); ring C: C(7), C(8), C(9), C(10), C(11), C(17); ring D: C(8), C(9), C(14), C(13), C(16), C(15); ring E: C(9), C(14), C(13), C(12), C(10); ring F: C(17), C(7), C(6), C(5), C(11).

There are only two intermolecular nonbonding distances less than 3.2 Å involving O-atoms, and these occur between O(2)···O(5) (2.93(1) Å through $x+1/2,-y-1/2,-z+1$ operation) and O(4)···O(2) (3.16(10) Å through $x-1/2,-y-1/2,-z+1$ operation). The first falls within the range of a weak H-bond interaction, with the O(2)–H···O(5) distance and angle being 2.09(1) Å and 140.2(4)°.

We thank the *Spanish CICYT* for financial support through the SEUI grant PB91-0131.

Experimental Part

NMR Spectra. The spectra were recorded on a *Bruker-AMX-400* spectrometer using $CDCl_3$ as solvent and $SiMe_4$ and solvent as internal standard. The DEPT and 2D-NMR experiments ^{1}H-COSY, HMQC, HMBC ($J = 7$ Hz), and ROESY (spin lock 700 ms) were carried out with standard pulse sequences furnishes in the *Bruker* manual.

X-Ray Diffraction Measurements of **2**. *Crystal Data:* Orthorhombic space group $P2_12_12_1$ with cell dimensions $a = 12.701(1)$ Å, $b = 12.097(1)$ Å, $c = 14.458(1)$ Å; $V = 221.5(2)$ Å^3, $Z = 4$, $\rho_c = 1.260$ gcm^{-3}, $F(000) = 920$. Intensity data were collected using monochromatic CuK_α radiation ($\lambda = 1.5418$ Å) at r.t. on a *Siemens-Stoe-AED* computer-controlled four-circle diffractomcter. From 1791 unique measured reflections ($3° \leq \Theta \leq 120°$), 1688 with $I > 3\sigma(I)$ were considered as observed. The structure was solved by direct methods [12]. H-Atoms were observed from difference electron density *Fourier* synthesis, with the expection of some of the Me protons that were calculated on the basis of configurational plausibility [13]. Full-matrix anisotropic refinement [14] for the non-H-atoms with the H-atoms added as fixed isotropic contribution converged to a final discrepancy index of $R = 0.072$ (unit weight) for 69 atoms and 271 parameters. The final $(\Delta/\sigma)_{max}$ was $0.24 \cdot 10^{-2}$ and the largest peak in a final difference map was 0.4 eÅ^3. Scattering factors were taken from [15].

Lists of observed and calculated structure factors, crystal data, fractional atomic coordinates, anisotropic thermal parameters, and interatomic distances and angles were deposited at the *Cambridge Crystallographic Data Center*.

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