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(*S*)-1,10-Dimethoxy-2,9-dihydroxyaporphinium Chloride (Boldine Hydrochloride), $C_{19}H_{22}NO_4^+.Cl^-$

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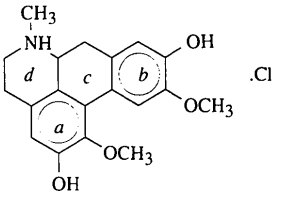
Abstract

Boldine (5,6,6a,7-tetrahydro-1,10-dimethoxy-6-methyl-4*H*-dibenzo[*de*,*g*]quinoline-2,9-diol) is an aporphine alkaloid noted for its antioxidant properties. A salient feature of the molecule is the non-planarity of the biphenyl system, which exhibits a dihedral angle of 151.1 (8)° between the least-squares planes of the two benzenoid rings and torsion angles of 25.7 (3), −150.6 (2), −155.9 (2) and 27.8 (3)° about the biphenyl bond. Methoxy C atom C13 lies only 0.195 (4) Å above the mean plane of the ring to which it is attached, with torsion angles about the C10—O2 bond of 168.6 (2) and −11.3 (4)°. Methoxy C atom C14 is displaced −1.101 (3) Å from the corresponding ring plane, with torsion angles about the C1—O3 bond of 102.3 (2) and −79.7 (3)°. All intramolecular bonds and angles are within the expected range.

Comment

Boldine is the major alkaloidal constituent of the Chilean boldo tree *Peumus boldus Mol.* (*Monimiaceae*), and has attracted attention recently due to its potent antioxidant activity (Speisky & Cassels, 1994) attributed to the presence of two phenol groups and a highly conjugated biphenyl system incorporating a benzylamine functionality (Cassels *et al.*, 1995). As this alkaloid acts as a chain-breaking antioxidant, which affords a highly stabilized free radical after reacting with species such as HOz, the degree of conjugation between the two aromatic rings, associated with the planarity of the biphenyl moiety, is a key factor in its antioxidant activity.



The molecular structure of this alkaloid exhibits the common substituted aporphine skeleton, with two aromatic rings, (*a*) and (*b*), and two rings, (*c*) and (*d*), with near half-chair conformation. The interplanar angle between the aromatic rings is 151.1 (8)°. A fairly large number of aporphine (5,6,6a,7-tetrahydro-6-methyl-4*H*-dibenzo[*de*,*g*]quinoline) structures have been studied by X-ray crystallography (Ashida, Pepinsky & Okaya, 1963; Giesecke, 1973; Brown & Hall, 1977; Roques, Declercq & Germain, 1978; Roques, Djakouré & Rossi, 1978; Zabel, Watson, Urzúa & Cassels, 1979; Fonseca & García-Blanco, 1984; Wei, Basu, Einstein & Hingerty, 1984; Touré, Germain & Djakouré, 1985; Ribár, Mészáros, Engel, Gasic & Kanyó, 1991; Ribár, Mészáros, Gasic, Kanyó & Engel, 1991; Ribár, Lazar, Gasic, Kanyó & Engel, 1992).

The twist angles of the biphenyl system have been evaluated by some of these authors, following Klyne & Prelog's (1960) convention, as the average of the torsion angles C1—C11b—C11a—C11 and C11c—C11b—C11a—C7a. The calculated twist angles for a few related compounds are listed in Table 3. The variation of this parameter has been discussed by Brown & Hall (1977) for a very small data set. Several years earlier, Shamma (1972) pointed out that the 1,2,9,10-tetraoxygenated aporphines have specific rotations of +119° or less at 589 nm, while in the 1,2,10,11-tetraoxygenated series the corresponding values are +139° or more, and that this difference could be explained on the basis of a greater twist angle in those compounds in which steric compression between C1 and C11 substituents leads to greater steric strain. Now that X-ray structural data are available for a considerably larger number of aporphines and derivatives, it can be seen that this interpretation is generally valid. Boldine and cataline, both bearing a methoxy group at C1 and an H atom at C11, show similar twist angles of 26.8 (3) and 27.9 (1)°, respectively, considerably larger than that of 20.9 (6)° of isoboldine, which has a less bulky hydroxy group at C1, but smaller than that of 31.8 (3)° of isocorydine, which has a methoxy group at C1 and a hydroxy group at C11.

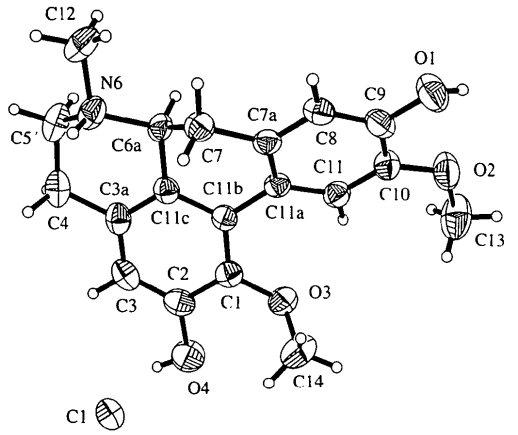


Fig. 1. Structure of of boldine hydrochloride with atom labelling, showing 50% probability displacement ellipsoids. H atoms are drawn as small circles of arbitrary radii.

Experimental

The title compound was recrystallized in 2-propanol/ether.

Crystal data

$C_{19}H_{22}NO_4^+.Cl^-$
$M_r = 363.8$
Orthorhombic
$P2_12_12_1$
$a = 7.556\,(2)$ Å
$b = 11.587\,(2)$ Å
$c = 20.255\,(4)$ Å
$V = 1773.5\,(9)$ Å^3
$Z = 4$
$D_x = 1.363$ Mg m^{-3}
Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 30 reflections
$\theta = 10$–$30°$
$\mu = 0.239$ mm^{-1}
$T = 298$ K
Parallelepiped
$0.70 \times 0.44 \times 0.28$ mm
Colourless

Data collection

Siemens *R3m/V* four-circle diffractometer
$\theta/2\theta$ scans
Absorption correction: none
5023 measured reflections
4887 independent reflections
2818 observed reflections $[I > 2\sigma(I)]$
$R_{int} = 0.0154$
$\theta_{max} = 35.0°$
$h = -7 \rightarrow 12$
$k = -11 \rightarrow 18$
$l = -17 \rightarrow 32$
2 standard reflections monitored every every 100 reflections
reflections
intensity decay: none

Refinement

Refinement on F
$R = 0.0409$
$wR = 0.0466$
$S = 1.19$
2818 reflections
249 parameters
Only H-atom U's refined
$w = 1/[\sigma^2(F) + 0.0006F^2]$
$(\Delta/\sigma)_{max} = 0.057$
$\Delta\rho_{max} = 0.43$ e Å^{-3}
$\Delta\rho_{min} = -0.19$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8. and 6.1.1.4)
Absolute configuration: Rogers (1981) parameter = 1.22 (16)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
Cl	0.3574 (1)	0.3645 (1)	0.1444 (1)	0.054 (1)
N6	−0.5508 (3)	0.0906 (2)	0.3042 (1)	0.045 (1)
O1	−0.6056 (3)	0.4487 (2)	0.5962 (1)	0.057 (1)
O2	−0.4115 (3)	0.6177 (2)	0.5389 (1)	0.058 (1)
O3	−0.0265 (2)	0.4796 (1)	0.3706 (1)	0.045 (1)
O4	0.1496 (2)	0.3894 (2)	0.2691 (1)	0.062 (1)
C1	−0.1039 (3)	0.3898 (2)	0.3359 (1)	0.037 (1)
C2	−0.0151 (3)	0.3466 (2)	0.2804 (1)	0.043 (1)
C3	−0.0945 (3)	0.2650 (2)	0.2411 (1)	0.045 (1)
C3a	−0.2616 (3)	0.2218 (2)	0.2571 (1)	0.040 (1)
C4	−0.3460 (4)	0.1345 (2)	0.2119 (1)	0.052 (1)
C5	−0.5337 (4)	0.1036 (2)	0.2311 (1)	0.054 (1)
C6a	−0.5176 (3)	0.2043 (2)	0.3383 (1)	0.037 (1)
C7	−0.5100 (3)	0.1866 (2)	0.4125 (1)	0.040 (1)
C7a	−0.4752 (3)	0.3012 (2)	0.4453 (1)	0.035 (1)
C8	−0.5550 (3)	0.3263 (2)	0.5056 (1)	0.039 (1)
C9	−0.5289 (3)	0.4313 (2)	0.5357 (1)	0.042 (1)
C10	−0.4240 (3)	0.5147 (2)	0.5050 (1)	0.040 (1)
C11	−0.3423 (3)	0.4905 (2)	0.4455 (1)	0.038 (1)
C11a	−0.3634 (3)	0.3811 (2)	0.4154 (1)	0.032 (1)
C11b	−0.2689 (3)	0.3456 (2)	0.3543 (1)	0.032 (1)
C11c	−0.3451 (3)	0.2575 (2)	0.3145 (1)	0.035 (1)
C12	−0.7294 (4)	0.0431 (3)	0.3207 (2)	0.065 (1)
C13	−0.2832 (5)	0.6980 (3)	0.5177 (2)	0.075 (1)
C14	0.1114 (4)	0.4463 (3)	0.4148 (1)	0.058 (1)

Table 2. *Selected geometric parameters (Å, °)*

N6—C5	1.493 (3)	C3a—C11c	1.386 (3)
N6—C6a	1.508 (3)	C4—C5	1.513 (4)
N6—C12	1.496 (4)	C6a—C7	1.518 (3)
O1—C9	1.370 (3)	C6a—C11c	1.520 (3)
O2—C10	1.379 (3)	C7—C7a	1.508 (3)
O2—C13	1.411 (4)	C7a—C8	1.392 (3)
O3—C1	1.385 (3)	C7a—C11a	1.393 (3)
O3—C14	1.428 (3)	C8—C9	1.375 (3)
O4—C2	1.359 (3)	C9—C10	1.396 (3)
C1—C2	1.401 (3)	C10—C11	1.383 (3)
C1—C11b	1.398 (3)	C11—C11a	1.416 (3)
C2—C3	1.375 (3)	C11a—C11b	1.486 (3)
C3—C3a	1.397 (3)	C11b—C11c	1.422 (3)
C3a—C4	1.507 (3)		
C5—N6—C6a	110.6 (2)	C7—C6a—C11c	109.6 (2)
C5—N6—C12	109.7 (2)	C6a—C7—C7a	109.0 (2)
C6a—N6—C12	111.6 (2)	C7—C7a—C11a	119.9 (2)
C10—O2—C13	117.8 (2)	O1—C9—C8	117.8 (2)
C1—O3—C14	115.1 (2)	O1—C9—C10	122.5 (2)
O3—C1—C2	118.2 (2)	O2—C10—C9	114.6 (2)
O3—C1—C11b	121.1 (2)	O2—C10—C11	125.3 (2)
O4—C2—C1	116.3 (2)	C7a—C11a—C11	118.4 (2)
O4—C2—C3	123.5 (2)	C7a—C11a—C11b	118.0 (2)
C4—C3a—C11c	121.2 (2)	C1—C11b—C11c	118.2 (2)
C3a—C4—C5	113.5 (2)	C11a—C11b—C11c	118.4 (2)
N6—C5—C4	111.1 (2)	C3a—C11c—C6a	122.3 (2)
N6—C6a—C7	110.0 (2)	C6a—C11c—C11b	117.3 (2)
N6—C6a—C11c	110.6 (2)		

Table 3. *Twist angles (°) in the biphenyl system in related compounds*

	Twist angle	Reference
Leucoxine hydrobromide	14.3 (3)	*a*
Isoboldine hydrobromide	20.9 (6)	*a*
N,O-Diacetyllaurelliptine	22.3 (3), 24.0 (3)	*b*
Apomorphine hydrochloride-$(H_2O)_2$	22.8 (3), 24.7 (4)	*c*
Nanteine	23.7 (6)	*d*
Laurelliptine (free base)	24.1 (2)	*e*
N,O-Diacetyl-4-hydroxynornantenine	24.1 (4)	*f*

Boldine hydrochloride	26.8 (3)	*g*
Cataline (free base)	27.9 (1)	*h*
Bulbocapnine methiodide	30.1 (3)	*i*
Isocorydine methiodide	30.6 (6)	*j*
Bulbocapnine (free base)	31.3 (5)	*k*
Isocorydine (free base)	31.8 (3)	*l*

References: (*a*) Brown & Hall (1977); (*b*) Roques, Declerq & Germain (1978); (*c*) Giesecke (1973); (*d*) Ribár, Mészáros, Engel *et al.* (1991); (*e*) Roques, Djakouré & Rossi (1978); (*f*) Zabel *et al.* (1979); (*g*) This work; (*h*) Fonseca & García-Blanco (1984); (*i*) Wei *et al.* (1984); (*j*) Touré *et al.* (1985); (*k*) Ribár, Mészáros, Gasic *et al.* (1991); (*l*) Ribár *et al.* (1992).

Data collection: *P3/P4–PC Diffractometer Program* (Siemens, 1991). Cell refinement: *P3/P4–PC Diffractometer Program*. Data reduction: *XDISK* in *SHELXTL-Plus* (Sheldrick, 1992). Program(s) used to solve structure: *XS* in *SHELXTL-Plus*. Program(s) used to refine structure: *XLS* in *SHELXTL-Plus*. Molecular graphics: *XP* in *SHELXTL-Plus*. Software used to prepare material for publication: *XPUBL* in *SHELXTL-Plus*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry, including contact distances, have been deposited with the IUCr (Reference: PT1029). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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[D-Ala^2,D-Leu^5]-Enkephalin Hydrochloride

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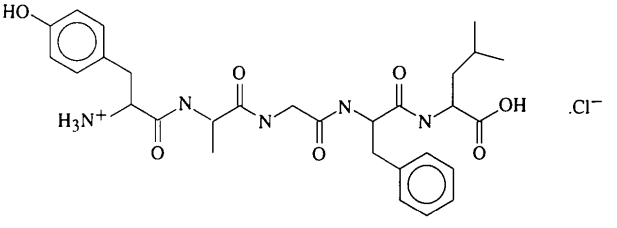
Abstract

The title compound, L-tyrosyl-D-alanyl-glycyl-L-phenylalanyl-D-leucine hydrochloride ($C_{29}H_{40}N_5O_7^+.Cl^-$), co-crystallizes with 2-butanone (C_4H_8O). The structure determination reveals a slightly distorted type I′ β-bend conformation stabilized by one intramolecular hydrogen bond. This conformation is similar to that observed for other [Leu]-enkephalin analogues.

Comment

[D-Ala^2,D-Leu^5]-enkephalin (DADLE) is a linear opioid peptide agonist which has slightly improved δ-receptor selectivity when compared with [Leu]-enkephalin (Schiller, 1991). DADLE is an important opioid peptide often used as a standard in activity studies.



DADLE.HCl

The crystal structure of DADLE is shown in Fig. 1. The bond distances and angles observed in this structure were within accepted limits. Except for the disordered Leu side-chain, the e.s.d.s for the bond lengths ranged from 0.009 to 0.020 Å in the peptide, and from 0.014 to 0.020 Å in the solvent; the e.s.d.s for the bond angles ranged from 0.6 to 1.4° in the peptide, and 1.2 to 1.7° in the solvent. The Leu^5 side-chain is disordered with approximately equal occupancy for the two positions. The respective conformation of the disorder may be described by the χ^1 torsion angles N5—C5*A*—C5*B*—C5*G* of 68.6 (8)° and N5—C5*A*—C5*B*′—C5*G*′ of 159.5 (7)°.