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A Key Intermediate in the Synthesis of (+)-Hernandulcin

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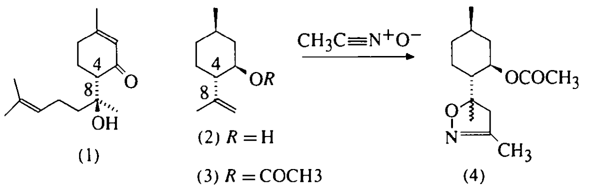
Abstract

(5*R*)-3,5-Dimethyl-5-[(1′*R*,2′*R*,4′*R*)-2′-acetoxy-4′-methylcyclohexyl]-Δ^2-isoxazoline ($C_{14}H_{23}NO_3$) is a key intermediate in the reaction pathway aiming at the synthesis of (+)-hernandulcin. The five-membered heterocycle ring is in a twist conformation and the cyclohexane ring is in a chair conformation. The molecular packing involves C—H···O intermolecular contacts.

Comment

The naturally occurring bisabolane sesquiterpene (+)-hernandulcin, (1), isolated from the central american herb *Lippia dulcis*, has been shown to be *ca* 1000 times sweeter than sucrose while being non-mutagenic and non-toxic (Compadre, Raouf, de Compadre, Pezzuto & Kinghorn, 1987). The relative and absolute configurations of (+)-(4*S*,8*S*)-hernandulcin, (1), were proposed as shown in the scheme, based on its synthesis from (*R*)-(−)-limonene (Mori & Kato, 1986).



Our synthetic endeavours towards natural (+)-hernandulcin, (1), are based upon stereoselective cycloaddition reactions of suitable nitrile oxides and (−)-isopulegol, (2), and derivatives. The absolute configuration of (2) is the same as (+)-hernandulcin at C4, and thus the synthetic strategy depends upon the correct diastereoselection at C8 in the cycloaddition reaction. The cycloaddition reaction was carried out on isopulegyl acetate, (3), with acetonitrile oxide, using conditions developed recently in our laboratory, and led in good yield to the cycloadduct isoxazoline, (4), which could be crystallized. The definition of the new stereogenic centre at C8, created in the cycloaddition reaction, is not amenable to the usual spectroscopic methods, including high-field NMR. In order to determine unambiguously its configuration, which will be of aid in the prediction of the steric course of subsequent reactions, a crystal-structure determination of (4) was undertaken.

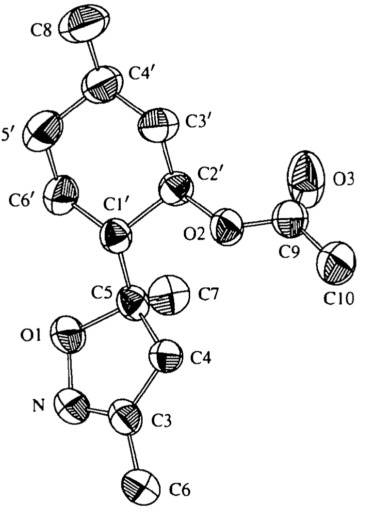


Fig. 1. Projection of $C_{14}H_{23}NO_3$ showing the atom labelling. 50% probability displacement ellipsoids are shown for non-H atoms.

The coplanar relationship between the two rings, which are joined by one single bond, forces the quaternary methyl group into an orthogonal axis. The isoxazoline ring is in a twist conformation and the six-membered carbocycle ring is in a chair conformation, as shown by the Cremer & Pople (1975) puckering parameters of q_2 = 0.258 (4) Å, Φ_2 = 51 (1)° and Q = 0.579 (5) Å, θ = 175.5 (5), Φ = 187 (7)°, respectively. The molecular packing involves intermolecular C—H···O interactions: C4···N^{i} =

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3.477 (6), H′4···N^{i} = 2.61 (4) Å, C4—H′4···N^{i} = 142 (3)°; C6···O1^{i} = 3.437 (6), H′6···O1^{i} = 2.51 (5) Å, C6—H′6···O1^{i} = 171 (4)°; C10···O3^{ii} = 3.393 (8), H10···O3^{ii} = 2.52 (5) Å, C10—H10···O3^{ii} = 151 (4)° [symmetry codes: (i) $\frac{3}{2} - x, \frac{1}{2} + y, 2 - z$; (ii) $x - \frac{1}{2}, \frac{1}{2} - y, z$].

Experimental

Crystals of the title compound were obtained from hexane solution by slow evaporation at 277 K.

Crystal data

$C_{14}H_{23}NO_3$
$M_r = 253.341$
Monoclinic
$P2_1/a$
$a = 10.538\ (1)$ Å
$b = 8.895\ (1)$ Å
$c = 16.031\ (1)$ Å
$\beta = 102.742\ (9)°$
$V = 1465.7\ (2)$ Å^3
$Z = 4$
$D_x = 1.148$ Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 25 reflections
$\theta = 9.00$–$15.79°$
$\mu = 0.080$ mm^{-1}
$T = 293\ (2)$ K
Irregular
0.38 × 0.25 × 0.23 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
2667 measured reflections
2571 independent reflections
1052 observed reflections [$I > 2\sigma(I)$]

$R_{\rm int} = 0.0285$
$\theta_{\rm max} = 24.97°$
$h = -12 \rightarrow 12$
$k = 0 \rightarrow 10$
$l = 0 \rightarrow 19$
3 standard reflections
frequency: 60 min
intensity decay: 1.1%

Refinement

Refinement on F^2
$R(F) = 0.0535$
$wR(F^2) = 0.1048$
$S = 1.154$
2571 reflections
233 parameters
Only coordinates of H atoms refined, one common U
$w = 1/[\sigma^2(F_o^2) + (0.0429P)^2 + 0.8671P]$
where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\rm max} = -0.005$
$\Delta\rho_{\rm max} = 0.177$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.206$ 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)

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

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

	x	y	z	$U_{\rm eq}$
N	0.7309 (4)	−0.3185 (4)	0.9672 (2)	0.0638 (10)
O1	0.7716 (3)	−0.3229 (3)	0.8879 (2)	0.0655 (9)
O2	0.6000 (3)	0.0359 (3)	0.7244 (2)	0.0543 (8)
O3	0.7241 (3)	0.2216 (4)	0.6931 (3)	0.0976 (13)
C3	0.6642 (4)	−0.2009 (5)	0.9692 (3)	0.0526 (11)
C4	0.6462 (4)	−0.1063 (5)	0.8912 (3)	0.0494 (11)
C5	0.7436 (4)	−0.1753 (5)	0.8449 (3)	0.0481 (10)
C6	0.6042 (5)	−0.1701 (6)	1.0437 (3)	0.0650 (14)
C7	0.8706 (5)	−0.0899 (6)	0.8620 (3)	0.0636 (13)
C1′	0.6894 (4)	−0.2130 (5)	0.7503 (2)	0.0464 (10)
C2′	0.6771 (4)	−0.0753 (5)	0.6916 (3)	0.0496 (11)
C3′	0.6108 (5)	−0.1144 (6)	0.6006 (3)	0.0599 (12)
C4′	0.6826 (5)	−0.2373 (6)	0.5634 (3)	0.0692 (14)
C5′	0.7028 (6)	−0.3728 (6)	0.6224 (3)	0.0741 (15)
C6′	0.7680 (5)	−0.3327 (6)	0.7145 (3)	0.0632 (13)
C8	0.6113 (7)	−0.2787 (8)	0.4724 (3)	0.097 (2)
C9	0.6354 (4)	0.1816 (5)	0.7230 (3)	0.0585 (12)
C10	0.5525 (6)	0.2811 (7)	0.7622 (4)	0.080 (2)

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

N—C3	1.265 (5)	C5—C1′	1.535 (5)
N—O1	1.429 (4)	C1′—C2′	1.533 (5)
O1—C5	1.482 (4)	C1′—C6′	1.536 (6)
O2—C9	1.350 (5)	C2′—C3′	1.512 (6)
O2—C2′	1.450 (4)	C3′—C4′	1.524 (6)
O3—C9	1.195 (5)	C4′—C5′	1.518 (7)
C3—C4	1.484 (5)	C4′—C8	1.531 (7)
C3—C6	1.494 (6)	C5′—C6′	1.527 (6)
C4—C5	1.523 (5)	C9—C10	1.477 (7)
C5—C7	1.510 (6)		
C3—N—O1	108.9 (3)	C2′—C1′—C6′	107.7 (3)
N—O1—C5	108.7 (3)	C5—C1′—C6′	114.0 (3)
C9—O2—C2′	118.0 (3)	O2—C2′—C3′	109.3 (3)
N—C3—C4	114.6 (4)	O2—C2′—C1′	107.5 (3)
N—C3—C6	120.5 (4)	C3′—C2′—C1′	111.5 (4)
C4—C3—C6	124.9 (4)	C2′—C3′—C4′	112.2 (4)
C3—C4—C5	102.0 (3)	C5′—C4′—C3′	109.9 (4)
O1—C5—C7	106.5 (3)	C5′—C4′—C8	112.0 (5)
O1—C5—C4	102.5 (3)	C3′—C4′—C8	111.3 (4)
C7—C5—C4	112.0 (4)	C4′—C5′—C6′	112.8 (4)
O1—C5—C1′	105.0 (3)	C5′—C6′—C1′	111.0 (4)
C7—C5—C1′	114.3 (4)	O3—C9—O2	122.4 (4)
C4—C5—C1′	115.2 (3)	O3—C9—C10	125.5 (5)
C2′—C1′—C5	113.2 (3)	O2—C9—C10	112.1 (4)

H atoms were placed at the positions found in difference Fourier maps and refined with an overall isotropic displacement parameter that converged to $U = 0.081\ (3)$ Å^2.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *CAD-4 Software*. Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *ORTEPII* (Johnson, 1976).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: LI1142). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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

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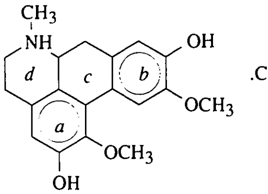
Abstract

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.

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