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Oxyacanthine

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Abstract

The crystal structure of the title compound (IUPAC name: 6,6′,7-trimethoxy-2,2′-dimethyloxyacanthan-12′-ol), $C_{37}H_{40}N_2O_6$, consists of helical chains, the principal intrachain interaction being hydrogen bonding between the hydroxyl group and one of the amine N atoms. The molecular structure is analysed in detail and results are compared with those reported previously for structurally

related tetrandrine. One heterocycle of the molecule assumes a half-boat conformation while the other exists in a conformation intermediate between a half-boat and a half-chair. By analogy with tetrandrine, one amine N atom is predicted to have unrestricted access to its lone pair, whereas the other should display reduced reactivity in reactions dependent on accessibility to a lone pair.

Comment

Oxyacanthine, (I), is a representative member of a subgroup of bisbenzyltetrahydroisoquinoline (BBTI) alkaloids in which the two benzyltetrahydroisoquinoline units are linked by two ether bridges in a head-to-head, tail-to-tail fashion. Interest in BBTI alkaloids stems from their widespread occurrence and their broad spectrum of biological activities, vasodilatory (and hence antihypertensive) activity being one of the most important. For structurally related tetrandrine, (II), which differs from (I) in the mode of ether linkage in the benzyl portion of the molecule and in the configuration at one of the two chiral C atoms, it has been reported (King *et al.*, 1988) that its vasodilator effect results from direct interaction at the diltiazem binding site on voltage-operated Ca^{2+} channels. In another study, some oxyacanthine subgroup alkaloids (*e.g.* aromoline, cepharanthine) have also been reported to relax vascular smooth muscle (Kamiya, Sugimoto & Yamada, 1993) and the mechanism of this activity is likely to be similar to that of tetrandrine. Consequently, the conformational rigidity of (I) and (II), imposed by two ether bridges, makes these molecules useful probes for modelling of the diltiazem binding site. Since accurate structural and conformational information is indispensable for performing such studies and since (II) is the only head-to-head BBTI alkaloid so far studied by X-ray crystallography (Gilmore, Bryan & Kupchan, 1976), we report herein on the crystal structure of (I).
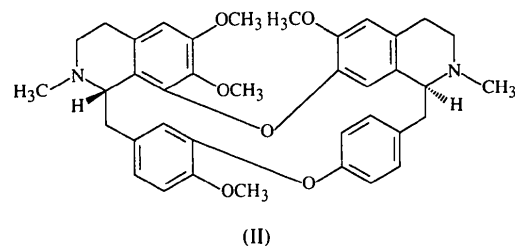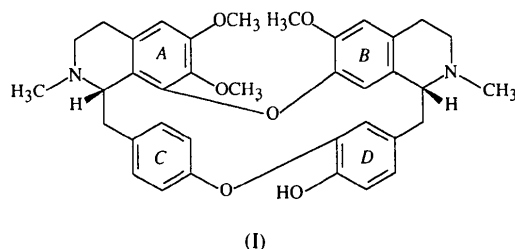

(I)

(II)

Fig. 1 shows an *ORTEP*II (Johnson, 1971) drawing of the molecular structure with the atomic numbering scheme.
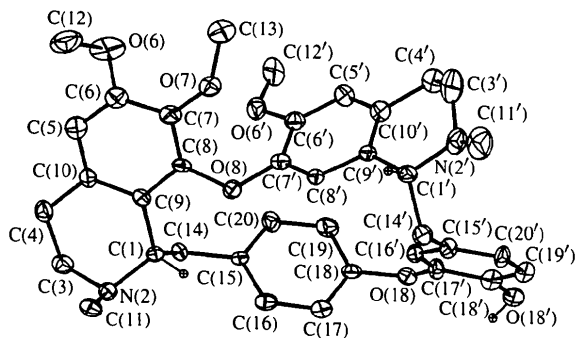

Fig. 1. A perspective view of the title molecule (in correct absolute configuration) with atom numbering. Displacement ellipsoids are drawn at the 40% probability level. Only the hydroxyl H and the H atoms bonded to the chiral C atoms are shown for clarity. The alternative position for the disordered methoxy group at C(6) is not shown.

The corresponding values of the bond lengths and angles (Table 2) in the two benzyltetrahydroisoquinoline residues agree quite well with each other with the exception of the N(2')—C(3') bond length, which is significantly shorter than the N(2)—C(3) bond distance. This may be caused by large thermal motion of the C(3) atom, its value of U_{eq} being much larger than those of the neighbouring atoms (Table 1).

From the biological point of view the most important structural features are torsion angles around rotatable bonds which define the spatial relationship between groups potentially participating in the drug–receptor interaction, *i.e.* aromatic rings, amine N atoms and/or the N-lone pair directions. Such conformational degrees of freedom in (I) are rotations about the bonds of the ether and methylene bridges, and puckering of the partially saturated rings.

For the ether bridge connecting rings C and D, the values of the torsion angles about the ether bonds (Table 2) fall within the ranges defining the so-called skew conformation, in which one ring is more or less coplanar with the C—O—C plane of the ether and the other ring is more or less perpendicular to this plane (van der Heijden, Griffith, Chandler & Robertson, 1975). However, the conformation of the other ether bridge, involving rings A and B, belongs to the 'twist' category. As to the methylene bridges, the torsion angles around the C(1')—C(14') bond have approximately staggered values (Table 2), whereas the bonds on C(1) almost eclipse those on C(14), as shown by the torsion angles N(2)—C(1)—C(14)—C(15) = 132.1 (4) and C(9)—C(1)—C(14)—C(15) = 100.9 (5)°, *i.e.* the conformation of the 'unprimed' benzyltetrahydroisoquinoline residue is considerably strained with respect

to the low-energy conformations [N(2)—C(1)—C(14)—C(15) = 180 or −60°].

Mutual orientation of the benzene rings can also be defined by the dihedral angles between the mean planes of these rings: A/B = 75.0 (1), A/C = 63.7 (1), A/D = 46.9 (1), B/C = 32.1 (1), B/D = 62.1 (1), C/D = 69.8 (1)°. The benzene rings themselves show significant deviations from planarity, as illustrated by the χ^2 values (using *CRYSRULER*; Rizzoli, Sangermano, Calestani & Andreetti, 1987) of 62, 103, 80 and 194 for rings A, B, C and D, respectively.

While the prevailing conformation of cyclohexene is half chair (Cox, Mkandawire & Mallinson, 1981) and this conformation was also found for both non-aromatic rings in tetrandine, the ring C1', N2', C3', C4', C10', C9' in (I) adopts a 3'α-half-boat conformation, as shown by its endocyclic torsion angles (Table 2) or by the puckering parameters (Cremer & Pople, 1975) Q = 0.497 (6) Å, φ = 57.6 (6) and θ = 120.1 (5)°. Deviation from ideal C_s(HB) symmetry can be measured by the asymmetry parameter ΔC_s(C3') = 0.009 (2)° (Nardelli, 1983). The other heterocyclic ring is characterized by the puckering parameters Q = 0.518 (4) Å, φ = −106.4 (6) and θ = 127.0 (4)° (calculated for the sequence C1, N2, C3, C4, C10, C9), which correspond to a conformation which is almost precisely midway between the N2α-half-boat and N2α,3β-half-chair conformation; the asymmetry parameters are ΔC_s(N2) = 0.065 (2) and ΔC_2(N2,C3) = 0.067 (2)°.

Similarly to tetrandine, the C(11) methyl group occupies a pseudoaxial position on N(2) with the lone pair equatorial, whereas C(11') is in a pseudo-equatorial position at N(2') with the lone pair oriented axially. It was reported for tetrandine (Gilmore, Bryan & Kupchan, 1976) that, compared with N(2'), the N(2) atom has reduced reactivity towards electrophilic reagents owing to sterically hindered access to the lone pair on N(2). In the present structure, (I), as a result of a different type of ether linkage in the benzyl portion and different chirality of the C(1') atom, the lone pair of N(2) points out from the molecular surface (and hence is sterically unhindered), but the lone pair on N(2') is directed towards the phenyl ring D and approximately parallel to its plane. Consequently, in (I) we predict that the N(2') atom will display reduced reactivity in processes which depend the approach of an electrophile along the lone-pair axis (including *e.g.* hydrogen bonding).

As shown in Table 2, the methoxy substituent at C(6') lies close to the plane of the phenyl ring, whereas that bonded to C(7) has an out-of-plane conformation. The disordered methoxy group at C(6) oscillates between an in-plane and an out-of-plane conformation [torsion angles C(5)—C(6)—O(6)—C(12) = 8 (2) and C(5)—C(6)—O(106)—C(112) = 82 (3)°].

The crystal packing is dominated by a hydrogen bond O(18')—H···N(2) ($-\frac{1}{2} + x$, $-\frac{1}{2} - y$, $1 - z$) [O···N =

2.793 (4), O—H = 0.94, H···N = 1.97 Å, O—H···N = 150°], which links the molecules into spirals parallel to the *a* axis. The spirals are packed *via* van der Waals interactions.

Experimental

Oxyacanthine, (I), was isolated from the root of *Mahonia aquifolium* (Košťálová, Hrochová & Tomko, 1986) and finally recrystallized from ethanol.

Crystal data

$C_{37}H_{40}N_2O_6$	Mo $K\alpha$ radiation
$M_r = 608.73$	$\lambda = 0.71073$ Å
Orthorhombic	Cell parameters from 25
$P2_12_12_1$	reflections
$a = 10.749$ (6) Å	$\theta = 7-18°$
$b = 13.068$ (5) Å	$\mu = 0.080$ mm^{-1}
$c = 22.643$ (9) Å	$T = 293$ K
$V = 3181$ (1) Å^3	Prism
$Z = 4$	$0.40 \times 0.30 \times 0.25$ mm
$D_x = 1.271$ Mg m^{-3}	Colourless
$D_m = 1.26$ (1) Mg m^{-3}	
D_m measured by pycno-	
metry and flotation in	
CHBr$_3$/hexane	

Data collection

Syntex $P2_1$ diffractometer	$\theta_{max} = 25°$
$\theta/2\theta$ scans	$h = 0 \rightarrow 13$
Absorption correction:	$k = 0 \rightarrow 17$
none	$l = 0 \rightarrow 29$
3353 measured reflections	2 standard reflections
3038 independent reflections	monitored every 100
1833 observed reflections	reflections
$[I > 2\sigma(I)]$	intensity decay: none
$R_{int} = 0.034$	

Refinement

Refinement on F^2	$(\Delta/\sigma)_{max} = -0.119$
$R(F) = 0.053$	$\Delta\rho_{max} = 0.386$ e Å^{-3}
$wR(F^2) = 0.1077$	$\Delta\rho_{min} = -0.178$ e Å^{-3}
$S = 1.228$	Extinction correction: none
1833 reflections	Atomic scattering factors
482 parameters	from *International Tables*
H-atom treatment: see text	*for X-ray Crystallography*
$w = 1/[\sigma^2(F_o^2) + (0.0739P)^2]$	(1974, Vol. IV)
where $P = (F_o^2 + 2F_c^2)/3$	

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}
C(1)	0.3549 (3)	0.0333 (3)	0.4856 (2)	0.042 (1)
N(2)	0.4169 (3)	0.0413 (2)	0.4277 (1)	0.048 (1)
C(3)	0.5522 (4)	0.0544 (3)	0.4377 (2)	0.062 (1)
C(4)	0.5817 (4)	0.1537 (4)	0.4699 (2)	0.061 (1)
C(5)	0.5093 (4)	0.2669 (4)	0.5519 (2)	0.069 (1)
C(6)	0.4253 (5)	0.2950 (3)	0.5940 (2)	0.066 (1)
C(7)	0.3213 (4)	0.2361 (3)	0.6048 (2)	0.051 (1)
C(8)	0.3015 (3)	0.1507 (3)	0.5700 (2)	0.043 (1)
C(9)	0.3834 (4)	0.1227 (3)	0.5255 (2)	0.044 (1)
C(10)	0.4914 (4)	0.1804 (3)	0.5172 (2)	0.054 (1)
C(11)	0.3684 (6)	0.1251 (4)	0.3915 (2)	0.060 (1)
O(6)	0.4146 (7)	0.3855 (10)	0.6273 (6)	0.075 (3)
O(106)	0.4763 (12)	0.3735 (15)	0.6282 (8)	0.075 (4)
C(12)	0.494 (3)	0.467 (2)	0.6121 (15)	0.142 (11)
C(112)	0.459 (5)	0.466 (2)	0.598 (2)	0.124 (14)
C(13)	0.2702 (5)	0.2697 (4)	0.7052 (2)	0.080 (2)
C(14)	0.3842 (3)	−0.0705 (3)	0.5138 (2)	0.050 (1)
C(15)	0.2752 (3)	−0.1284 (2)	0.5382 (2)	0.042 (1)
C(16)	0.1704 (4)	−0.1476 (3)	0.5044 (2)	0.053 (1)
C(17)	0.0725 (4)	−0.2028 (3)	0.5258 (2)	0.056 (1)
C(18)	0.0747 (4)	−0.2378 (3)	0.5824 (2)	0.052 (1)
C(19)	0.1777 (4)	−0.2226 (3)	0.6165 (2)	0.062 (1)
C(20)	0.2782 (4)	−0.1687 (3)	0.5937 (2)	0.055 (1)
O(7)	0.2318 (3)	0.2670 (2)	0.6444 (1)	0.062 (1)
O(8)	0.1943 (2)	0.0930 (2)	0.5718 (1)	0.050 (1)
O(18)	−0.0219 (3)	−0.2930 (2)	0.6067 (1)	0.060
C(1')	−0.2229 (4)	0.0958 (3)	0.6523 (2)	0.058 (1)
N(2')	−0.2971 (3)	0.0876 (3)	0.7057 (2)	0.076 (1)
C(3')	−0.2341 (6)	0.1093 (5)	0.7580 (3)	0.112 (2)
C(4')	−0.1221 (5)	0.0418 (5)	0.7679 (2)	0.070 (1)
C(5')	0.0872 (5)	0.0304 (3)	0.7208 (2)	0.062 (1)
C(6')	0.1692 (4)	0.0435 (3)	0.6745 (2)	0.058 (1)
C(7')	0.1221 (4)	0.0808 (3)	0.6217 (2)	0.048 (1)
C(8')	−0.0023 (4)	0.0980 (3)	0.6155 (2)	0.045 (1)
C(9')	−0.0850 (4)	0.0811 (3)	0.6617 (2)	0.046 (1)
C(10')	−0.0376 (4)	0.0499 (3)	0.7153 (2)	0.057 (1)
C(11')	−0.4073 (6)	0.1467 (6)	0.7027 (3)	0.133 (2)
C(12')	0.3390 (5)	−0.0236 (5)	0.7287 (2)	0.091 (2)
C(14')	−0.2744 (4)	0.0211 (3)	0.6062 (2)	0.059 (1)
C(15')	−0.2602 (4)	−0.0900 (3)	0.6190 (2)	0.051 (1)
C(16')	−0.1458 (4)	−0.1382 (3)	0.6086 (2)	0.052 (1)
C(17')	−0.1313 (4)	−0.2405 (3)	0.6166 (2)	0.051 (1)
C(18')	−0.2296 (4)	−0.3009 (3)	0.6350 (2)	0.051 (1)
C(19')	−0.3404 (5)	−0.2543 (3)	0.6478 (2)	0.059 (1)
C(20')	−0.3552 (4)	−0.1498 (4)	0.6396 (2)	0.058 (1)
O(6')	0.2940 (3)	0.0259 (2)	0.6763 (1)	0.065 (1)
O(18')	−0.2192 (3)	−0.4042 (2)	0.6414 (1)	0.062 (1)

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

C(1)—N(2)	1.475 (6)	C(18)—O(18)	1.378 (7)
C(1)—C(9)	1.508 (7)	O(8)—C(7')	1.380 (6)
C(1)—C(14)	1.532 (7)	O(18)—C(17')	1.380 (6)
N(2)—C(11)	1.464 (7)	C(1')—N(2')	1.453 (7)
N(2)—C(3)	1.482 (5)	C(1')—C(9')	1.510 (6)
C(3)—C(4)	1.522 (8)	C(1')—C(14')	1.532 (8)
C(4)—C(10)	1.487 (8)	N(2')—C(3')	1.392 (8)
C(6)—O(106)	1.40 (2)	N(2')—C(11')	1.416 (8)
C(6)—O(6)	1.407 (14)	C(3')—C(4')	1.509 (10)
C(7)—O(7)	1.374 (7)	C(4')—C(10')	1.501 (8)
C(8)—O(8)	1.377 (6)	C(6')—O(6')	1.361 (5)
C(9)—C(10)	1.397 (7)	C(9')—C(10')	1.379 (7)
O(6)—C(12)	1.41 (3)	C(12')—O(6')	1.436 (7)
O(106)—C(112)	1.40 (4)	C(14')—C(15')	1.489 (6)
C(13)—O(7)	1.439 (5)	C(18')—O(18')	1.362 (5)
C(14)—C(15)	1.500 (7)		
N(2)—C(1)—C(9)	112.7 (4)	C(8)—O(8)—C(7')	123.9 (4)
N(2)—C(1)—C(14)	109.9 (4)	C(18)—O(18)—C(17')	116.5 (3)
C(9)—C(1)—C(14)	113.3 (9)	N(2')—C(1')—C(9')	114.3 (5)
C(11)—N(2)—C(1)	113.0 (4)	N(2')—C(1')—C(14')	108.8 (4)
C(11)—N(2)—C(3)	110.4 (5)	C(3')—N(2')—C(11')	109.7 (6)
C(1)—N(2)—C(3)	108.4 (4)	C(3')—N(2')—C(1')	115.2 (4)
N(2)—C(3)—C(4)	112.1 (5)	C(11')—N(2')—C(1')	112.3 (5)
C(10)—C(4)—C(3)	114.2 (5)	N(2')—C(3')—C(4')	113.3 (6)
C(10)—C(9)—C(1)	120.4 (5)	C(10')—C(4')—C(3')	108.9 (5)
C(9)—C(10)—C(4)	120.8 (4)	C(10')—C(9')—C(1')	121.6 (5)
C(6)—O(6)—C(12)	117.2 (13)	C(9')—C(10')—C(4')	119.7 (4)
C(15)—C(14)—C(1)	116.1 (4)	C(15')—C(14')—C(1')	116.8 (4)
C(7)—O(7)—C(13)	115.5 (4)	C(6')—O(6')—C(12')	115.6 (5)
C(9)—C(1)—N(2)—C(3)		55.0 (5)	
C(1)—N(2)—C(3)—C(4)		−63.6 (5)	
N(2)—C(3)—C(4)—C(10)		39.0 (6)	
N(2)—C(1)—C(9)—C(10)		−23.7 (5)	
C(1)—C(9)—C(10)—C(4)		−1.3 (5)	
C(3)—C(4)—C(10)—C(9)		−6.3 (6)	
C(5)—C(6)—O(6)—C(12)		8 (2)	
C(5)—C(6)—O(106)—C(112)		82 (3)	

$C_{37}H_{40}N_2O_6$

N(2)—C(1)—C(14)—C(15)	−132.1 (4)
C(9)—C(1)—C(14)—C(15)	100.9 (5)
C(1)—C(14)—C(15)—C(16)	52.4 (6)
C(6)—C(7)—O(7)—C(13)	−67.2 (6)
C(7)—C(8)—O(8)—C(7')	−30.4 (5)
C(17)—C(18)—O(18)—C(17')	−69.2 (6)
C(9')—C(1')—N(2')—C(3')	25.0 (6)
C(1')—N(2')—C(3')—C(4')	−58.1 (7)
N(2')—C(3')—C(4')—C(10')	55.4 (7)
C(8)—O(8)—C(7')—C(8')	130.0 (4)
C(8)—O(8)—C(7')—C(6')	−56.1 (5)
N(2')—C(1')—C(9')—C(10')	7.7 (6)
C(1')—C(9')—C(10')—C(4')	−7.2 (6)
C(3')—C(4')—C(10')—C(9')	−22.5 (7)
N(2')—C(1')—C(14')—C(15')	−67.5 (6)
C(9')—C(1')—C(14')—C(15')	59.6 (6)
C(1')—C(14')—C(15')—C(16')	−79.6 (6)
C(18)—O(18)—C(17')—C(16')	−5.4 (6)
C(5')—C(6')—O(6')—C(12')	9.0 (6)

The methoxy group at C6 is disordered over two positions, denoted —O6—C12 and —O106—C112, with occupancy factors fixed at 0.6 and 0.4, respectively (based on heights in the $\Delta\rho$ map). The parameters for the H atoms found in the $\Delta\rho$ map were refined. The remainder were placed at calculated positions with the isotropic displacement factors set equal to $1.1 \times U_{eq}$ of the bonded atom.

Data collection: *Syntex P2₁ Software*. Cell refinement: *Syntex P2₁ Software*. Data reduction: *XP21* (Pavelčík, 1987). Program(s) used to solve structure: *MULTAN80* (Main *et al.*, 1980). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *ORTEPII* (Johnson, 1971).

Lists of structure factors, least-squares-planes data, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: KA1162). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Two $P2_1/n$ Monoclinic Phases of Fluorene-4-carboxylic Acid at 296 K

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Abstract

The structures of two phases of fluorene-4-carboxylic acid, $C_{14}H_{10}O_2$, from room-temperature growths have been determined. In the α phase, O—H···O hydrogen bonding occurs *via* cyclic dimers about a center of symmetry; in the β phase, cyclic dimers with O—H···O hydrogen bonds are formed between two crystallographically inequivalent molecules and do not involve a center of symmetry, though centers of symmetry are present in the crystal. The present evidence strongly suggests that the β phase is metastable with respect to the α phase at room temperature, but the regions of stability have not been determined.

Comment

As one of a series of studies of hydrogen bonding in crystalline carboxylic acids, we have previously described the structure of fluorene-1-carboxylic acid (hereafter, F1CA) (Blackburn, Dobson & Gerkin, 1996). Here we report on another fluorene monocarboxylic acid, fluorene-4-carboxylic acid, (I). No previous structural report on this acid has appeared.

(I)
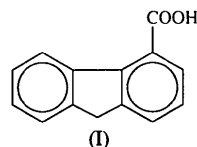
Growths of this acid produced two monoclinic phases, designated α and β, whose structures have been determined. In Fig. 1, an *ORTEPII* (Johnson, 1976) drawing of the α-phase dimer is presented together with our numbering scheme; the two β-phase molecules are shown in Fig. 2.

The hydrogen bonding in the α phase (Fig. 1) is of the cyclic dimer type about a center of inversion; in the β phase it is also of cyclic dimer type (Fig. 2) but is formed by two crystallographically inequivalent molecules, and does not involve a center of inversion. Geometric details of these hydrogen bonds are given in Table 5. All have donor–acceptor distances which are