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cis-(±)-5-[2-(Dimethylamino)ethyl]-3-hydroxy-2-(4-methoxyphenyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-4-one

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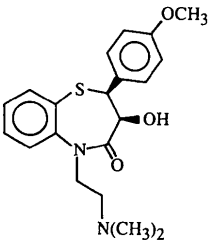
Abstract

The title compound, $C_{20}H_{24}N_2O_3S$, is a drug intermediate of diltiazem. The molecule is stabilized by covalent bonding and weak hydrogen bonding, and the crystal packing is stabilized by hydrogen bonding. The seven-membered ring is distorted showing a twist-boat conformation. The methoxyphenyl and hydroxy groups are *cis* oriented with respect to one another, with the phenyl ring in an axial position. Intermolecular hydrogen bonding produces dimers in the crystal.

Comment

The title compound, (I), and the diltiazem-related compound (II) (Kumaradhas, Nirmala & Ravikumar, 1995) are drug intermediates of diltiazem, (III) (Kojic-Prodic, Ruzic-Toros & Sunjic, 1984). Diltiazem belongs to the family of drugs commonly called calcium antagonists and is useful in the treatment of cardiac and coronary diseases (Mitchell, Schroeder & Mason, 1982; Parisi, Strauss, Melntyre & Sasahara, 1982). The pharmacological action and conformation of compound (I) are unknown, so the structure and conformation have been studied by X-ray analysis.



(I)

The bond lengths C(2)—S(7) [1.771 (3) Å] and S(7)—C(8) [1.833 (3) Å] are unequal, one of them being affected by conjugation with the adjacent π-electron system. The carbonyl bonds fall into three categories: (i) C_{sp^3}—O single bonds [C(17)—O(18) 1.418 (3) and C(16)—O(15) 1.429 (3) Å]; (ii) C_{sp^2}—O single bonds [C(12)—O(15) 1.382 (3) Å]; (iii) C=O double bond [C(19)=O(20) 1.226 (3) Å]. The bond attached to the aromatic ring [N(21)—C(3) 1.430 (3) Å] is different in length to both N(24)—C(25) [1.455 (4) Å] and N(24)—C(26) [1.445 (4) Å].

The methoxyphenyl and hydroxy groups are *cis* oriented with respect to one another [torsion angle C(9)—C(8)—C(17)—O(18) −48.9 (8)°] (Fig. 1). The methoxyphenyl group occupies an axial position in the molecule. The carbonyl O(20) atom and the aminoethyl group are in pseudo-axial positions.

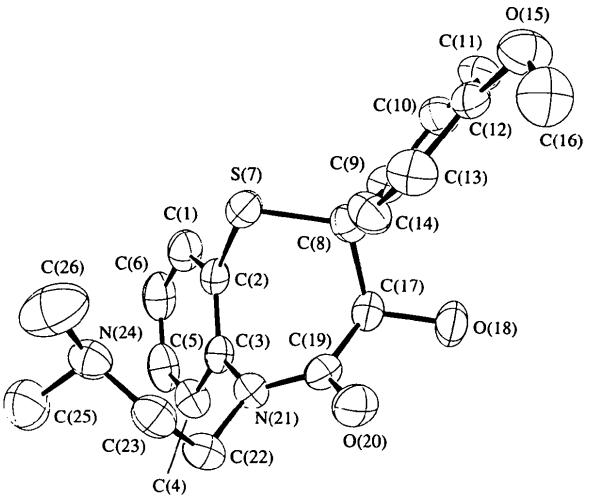


Fig. 1. The molecular structure of (I) showing 50% probability displacement ellipsoids. H atoms have been omitted for clarity.

The torsion angles of the title compound (Table 3) are very close to those found in both compounds (II) and (III), and show a twist-boat conformation. The conformation of the seven-membered ring is determined using the least-squares plane passing through atoms S(7), C(8) and C(17), and shows atoms C(2) and C(3) lying above this plane and atoms C(19) and N(21) lying below.

The crystal packing is stabilized by hydrogen bonds involving the hydroxy groups of neighbouring molecules forming dimers in the crystal; O(18)—H(18) 0.82 (3), H(18)···O(15^i) 2.25 (3), O(18)···O(15^i) 2.984 (12) Å and O(18)—H(18)···O(15^i) 149.9 (14)° [symmetry code: (i) $1-x, y, \frac{1}{2}-z$].

Experimental

Methyl (2*S*,3*S*)-3-(4-methoxyphenyl)glycidate was ring-opened thermally with 2-aminothiophenol and the resulting product was hydrolyzed and cyclized. The cyclized product was then treated with 2-chloroethyldimethylamine hydrochloride in the presence of base to produce the title compound. Recrystallization was from acetone at room temperature. The density D_m was measured by flotation in a xylene/CCl_4 mixture.

Crystal data

$C_{20}H_{24}N_2O_3S$
M_r = 372.47
Orthorhombic
Pbcn
a = 11.447 (1) Å
b = 12.989 (1) Å
c = 24.881 (1) Å
V = 3699.2 (5) Å^3
Z = 8
D_x = 1.338 Mg m^{-3}
D_m = 1.337 Mg m^{-3}

Mo $K\alpha$ radiation
λ = 0.7093 Å
Cell parameters from 25 reflections
θ = 5–11°
μ = 0.198 mm^{-1}
T = 294 K
Rectangular block
0.27 × 0.22 × 0.17 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
3252 measured reflections
3252 independent reflections
1847 observed reflections [$I > 2\sigma(I)$]

θ_{max} = 24.9°
$h = 0 \rightarrow 13$
$k = 0 \rightarrow 15$
$l = 0 \rightarrow 29$
2 standard reflections
frequency: 60 min
intensity decay: <2%

Refinement

Refinement on F^2
$R(F)$ = 0.0486
$wR(F^2)$ = 0.1087
S = 1.205
3252 reflections
235 parameters
H atoms refined as riding

$w = 1/[\sigma^2(F_o^2) + (0.0691P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.061
$\Delta\rho_{max}$ = 0.257 e Å^{-3}
$\Delta\rho_{min}$ = −0.239 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *SHELXL*93 (Sheldrick, 1993)

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)	0.0025 (3)	0.5470 (2)	0.4393 (1)	0.054 (8)
C(2)	0.0425 (2)	0.4615 (2)	0.4116 (1)	0.039 (6)
C(3)	−0.0381 (2)	0.3955 (2)	0.3876 (1)	0.036 (6)
C(4)	−0.1568 (2)	0.4162 (2)	0.3917 (1)	0.045 (7)
C(5)	−0.1949 (3)	0.5007 (2)	0.4201 (1)	0.056 (8)
C(6)	−0.1154 (3)	0.5653 (2)	0.4443 (1)	0.060 (9)
S(7)	0.1938 (6)	0.4329 (6)	0.4121 (3)	0.050 (2)
C(8)	0.2337 (2)	0.4452 (2)	0.3410 (1)	0.042 (7)
C(9)	0.3495 (2)	0.3912 (2)	0.3335 (1)	0.039 (7)
C(10)	0.3641 (2)	0.2861 (2)	0.3410 (1)	0.046 (7)
C(11)	0.4706 (2)	0.2389 (2)	0.3321 (1)	0.046 (7)
C(12)	0.5657 (2)	0.2972 (2)	0.3167 (1)	0.038 (6)
C(13)	0.5544 (2)	0.4027 (2)	0.3117 (1)	0.045 (7)
C(14)	0.4470 (2)	0.4481 (2)	0.3193 (1)	0.042 (7)
O(15)	0.6745 (2)	0.2569 (2)	0.3048 (8)	0.052 (5)
C(16)	0.6815 (3)	0.1495 (2)	0.2929 (1)	0.056 (8)
C(17)	0.1311 (2)	0.4104 (2)	0.3040 (9)	0.039 (6)
O(18)	0.1693 (2)	0.4078 (2)	0.2498 (7)	0.052 (5)
C(19)	0.0810 (2)	0.3063 (2)	0.3203 (1)	0.039 (6)
O(20)	0.1123 (2)	0.2274 (2)	0.2975 (7)	0.052 (5)
N(21)	−0.0014 (2)	0.3049 (2)	0.3597 (9)	0.036 (5)
C(22)	−0.0502 (2)	0.2050 (2)	0.3754 (1)	0.045 (7)
C(23)	0.0240 (2)	0.1503 (2)	0.4167 (1)	0.049 (7)
N(24)	0.0276 (2)	0.2004 (2)	0.4692 (1)	0.049 (6)
C(25)	−0.0836 (3)	0.1892 (3)	0.4969 (1)	0.080 (1)
C(26)	0.1206 (4)	0.1558 (3)	0.5008 (2)	0.093 (1)

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

C(1)—C(6)	1.376 (4)	C(11)—C(12)	1.380 (4)
C(1)—C(2)	1.385 (4)	C(12)—C(13)	1.382 (4)
C(2)—C(3)	1.394 (4)	C(12)—O(15)	1.382 (3)
C(2)—S(7)	1.771 (3)	C(13)—C(14)	1.377 (4)
C(3)—C(4)	1.390 (3)	O(15)—C(16)	1.429 (3)
C(3)—N(21)	1.430 (3)	C(17)—O(18)	1.418 (3)
C(4)—C(5)	1.375 (4)	C(17)—C(19)	1.525 (4)
C(5)—C(6)	1.376 (4)	C(19)—O(20)	1.226 (3)
S(7)—C(8)	1.833 (3)	C(19)—N(21)	1.359 (3)
C(8)—C(9)	1.511 (4)	N(21)—C(22)	1.465 (3)
C(8)—C(17)	1.559 (4)	C(22)—C(23)	1.509 (4)
C(9)—C(14)	1.384 (4)	C(23)—N(24)	1.461 (4)
C(9)—C(10)	1.388 (4)	N(24)—C(26)	1.445 (4)
C(10)—C(11)	1.383 (4)	N(24)—C(25)	1.455 (4)
C(6)—C(1)—C(2)	120.5 (3)	C(11)—C(12)—O(15)	124.2 (3)
C(1)—C(2)—C(3)	119.1 (3)	C(13)—C(12)—O(15)	116.1 (2)
C(10)—C(2)—S(7)	119.3 (2)	C(14)—C(13)—C(12)	119.8 (3)
C(3)—C(2)—S(7)	121.4 (2)	C(13)—C(14)—C(9)	121.7 (3)
C(4)—C(3)—C(2)	119.8 (2)	C(12)—O(15)—C(16)	117.7 (2)
C(4)—C(3)—N(21)	118.9 (2)	O(18)—C(17)—C(19)	110.4 (2)
C(2)—C(3)—N(21)	121.3 (2)	O(18)—C(17)—C(8)	109.7 (2)
C(5)—C(4)—C(3)	120.2 (3)	C(19)—C(17)—C(8)	112.5 (2)
C(4)—C(5)—C(6)	120.1 (3)	O(20)—C(19)—N(21)	121.7 (3)
C(5)—C(6)—C(1)	120.2 (3)	O(20)—C(19)—C(17)	120.5 (2)
C(2)—S(7)—C(8)	102.7 (1)	N(21)—C(19)—C(17)	117.7 (2)
C(9)—C(8)—C(17)	116.9 (2)	C(19)—N(21)—C(3)	122.9 (2)
C(9)—C(8)—S(7)	107.4 (2)	C(19)—N(21)—C(22)	118.0 (2)
C(14)—C(9)—C(10)	117.6 (3)	C(3)—N(21)—C(22)	119.1 (2)
C(14)—C(9)—C(8)	119.4 (2)	N(21)—C(22)—C(23)	112.6 (2)
C(10)—C(9)—C(8)	123.0 (2)	N(24)—C(23)—C(22)	114.5 (2)
C(11)—C(10)—C(9)	121.4 (3)	C(26)—N(24)—C(25)	110.3 (3)
C(12)—C(11)—C(10)	119.8 (3)	C(26)—N(24)—C(23)	109.2 (3)
C(11)—C(12)—C(13)	119.7 (3)	C(25)—N(24)—C(23)	110.8 (2)

Table 3. *Comparision of torsion angles (°) of the seven-membered ring of (I) with similar rings in compounds (II) and (III), showing the twist-boat conformation*

	(I)[a]	(II)[b]	(III)[c]
C(2)—S(7)—C(8)—C(17)	−33.8 (2)	−32.8 (2)	−42.0 (4)
S(7)—C(8)—C(17)—C(19)	−49.1 (3)	−48.9 (2)	−42.1 (5)
C(8)—C(17)—C(19)—N(21)	84.6 (3)	86.9 (3)	90.6 (5)
C(17)—C(19)—N(21)—C(3)	−3.1 (3)	−8.8 (4)	−13.3 (7)
C(19)—N(21)—C(3)—C(2)	−51.9 (3)	−44.3 (4)	−48.0 (6)
N(21)—C(3)—C(2)—S(7)	−3.8 (3)	−6.1 (4)	0.6 (8)
C(3)—C(2)—S(7)—C(8)	68.3 (2)	66.4 (3)	69.4 (5)

References: (*a*) present compound; (*b*) Kumaradhas, Nirmala & Ravikumar (1995); (*c*) Kojic-Prodic, Ruzic-Toros & Sunjic (1984).

All non-H atoms were found by direct methods and their parameters were refined successfully with a full-matrix least-squares procedure. The H atoms were positioned geometrically and refined using a riding model.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *NRCVAX DATRD2* (Gabe, Le Page, White & Lee, 1987). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Geometrical calculations: *PARST* (Nardelli, 1983). Molecular graphics: *ORTEP*II (Johnson, 1976) in *NRCVAX*. Software used to prepare material for publication: *SHELXL*93.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and torsion angles have been deposited with the IUCr (Reference: BK1153). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Product of a Novel Carbocyclic Enlargement in Aqueous Media: 9β-*tert*-Butoxy-4-(*E*)-ethylidene-8β-methyl-5-oxobicyclo-[6.3.0]undecan-2β-carboxylic Acid Methyl Ester

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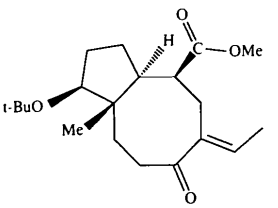
Abstract

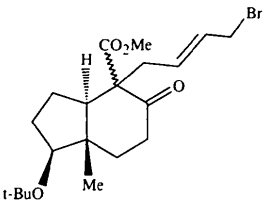
The title compound, $C_{20}H_{32}O_4$, is the major diastereomer obtained by the two-carbon ring expansion of a precursor containing fused five- and six-membered rings. It is shown to have the methyl, *tert*-butoxy and carboxymethyl substituents in mutually *cis* dispositions.

Comment

The formation of carbocycles having medium-to-large ring sizes is of great significance since such species constitute the structural core of many biologically important natural products (Devon & Scott, 1972). As ring-expansion methodologies allow one to avoid the unfavourable entropic factors associated with other routes to medium- and large-ring carbocycles (Dowd & Zhang, 1993; Hesse, 1991; Roxburgh, 1993; Stach & Hesse, 1988), development of efficient procedures of this type is an area of continuing interest. We have recently reported an efficient and general procedure for the two-atom carbocyclic enlargement in aqueous media which is effective for both simple and fused ring systems (Li, Chen, Lu, Haberman & Mague, 1996). In order to define unequivocally the stereochemistry of the major product (1) obtained from the ring-expansion of (2), the structure of (1) was determined.



(1)



(2)

The results demonstrate that the ester functionality is disposed *cis* to the methyl group attached to the ring junction (C2) as well as to the *tert*-butoxy group on C11 of the five-membered ring. The C4–C7, C12, O4 unit is planar within experimental error with C13 0.034 (4) Å out of this plane while the distances and angles associated with it compare favorably with those in related molecules (Ivie, Watson & Dominguez, 1974; Theocharis, Nakanishi & Jones, 1981). All other geometric parameters appear normal. The *trans* ring fusion in (2) is maintained in (1) and there are no unusual intermolecular contacts.

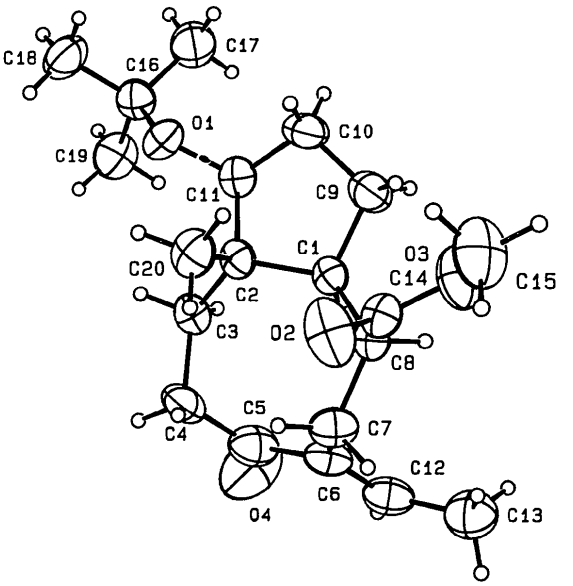


Fig. 1. A perspective view of (1). Displacement ellipsoids are drawn at the 50% probability level except for H atoms which for clarity are arbitrarily small.