This research was supported by NSERC Canada, the A. P. Sloan Foundation, the Merck Frosst Centre for Therapeutic Research, Eli Lilly Grantee Program, Bio-Mega and the University of Toronto.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry, including bond distances and angles involving H atoms, and torsion angles have been deposited with the IUCr (Reference: FG1032). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Fortesyl 2-Phenylpropionate. An Example of a Novel Hydrocarbon Skeleton Containing Three Fused Five-Membered Rings

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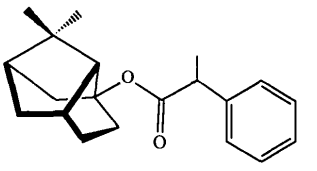
Abstract

The title compound is 8,8-dimethyltricyclo[4.2.1.$0^{3,7}$]-nonan-6-yl 2-phenylpropionate, $C_{20}H_{26}O_2$. Fortesol (8,8-dimethyltricyclo[4,2,1,$0^{3,7}$]nonan-6-ol), derived by acid-catalysed rearrangement of nopyl tosylate, is chiral and forms diastereoisomeric esters with enantiomeric carboxylic and phosphonic acids.

Comment

Fortesol was prepared by Giddings, Jones-Parry, Owen & Whittaker (1986) after solvolysis of the tosylate of a known terpenoid, nopol, in acetic acid. The title compound, (I), was prepared recently by Fortes, Johnstone, Lewis & Whittaker (1994) by reacting chiral fortesol† with racemic 2-phenylpropionyl chloride. The X-ray spectrum of one of the diastereoisomers of the resulting fortesyl 2-phenylpropionate has revealed that the structure previously reported for fortesol by Giddings, Jones-Parry, Owen & Whittaker (1986) was completely erroneous. Fortesol has three fused five-membered rings rather than the previously suggested structure with one six-membered and two four-membered rings.



(I)

Although there are many fused multi-ring hydrocarbons, particularly among terpenes and their derivatives, it is believed that the newly discovered structure of the hydrocarbon skeleton of fortesol is unique. A similar system having a six-membered and two five-membered fused rings has been described by Corey & Glass (1967). The mechanism of rearrangement of nopyl tosylate in acetic acid to give fortesyl acetate has been discussed elsewhere (Fortes, Johnstone, Lewis & Whittaker, 1994).

† The IUPAC name assigned to fortesol in the paper by Fortes, Johnstone, Lewis & Whittaker (1994) was incorrect with respect to the numbering system.

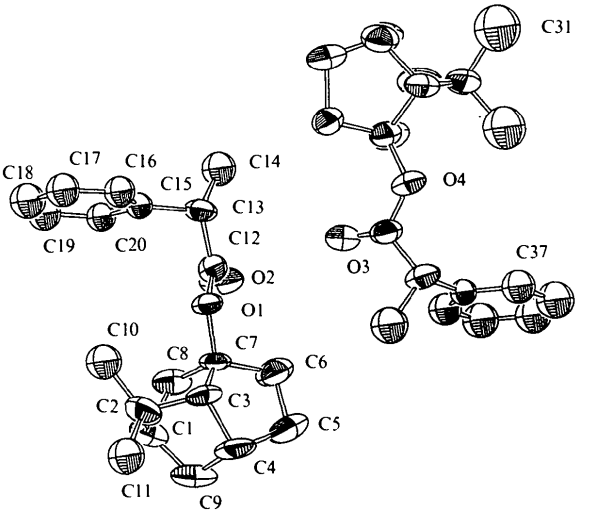


Fig. 1. Two identical molecules of fortesyl 2-phenylpropionate in the unit cell (with 50% probability ellipsoids and H atoms omitted for clarity).

Experimental

Fortesol and 2-phenylpropionyl chloride (molar ratio 1:1) were mixed in diethyl ether with 4-dimethylaminopyridine (1 mol ratio) and left to stand for 16 h at room temperature to give a diastereoisomeric mixture of fortesyl 2-phenylpropionate esters. These were crystallised three times from petroleum ether (b.p. 333–353 K) to give one pure diastereoisomer, which was submitted for X-ray analysis.

Crystal data

$C_{20}H_{26}O_2$
$M_r = 298.42$
Triclinic
$P\bar{1}$
$a = 10.568\ (4)$ Å
$b = 10.622\ (6)$ Å
$c = 8.545\ (4)$ Å
$\alpha = 106.39\ (4)°$
$\beta = 107.50\ (3)°$
$\gamma = 83.38\ (4)°$
$V = 877.1\ (7)$ Å^3
$Z = 2$
$D_x = 1.130$ Mg m^{-3}
Mo $K\alpha$ radiation
$\lambda = 0.71069$ Å
Cell parameters from 17 reflections
$\theta = 7.81–13.06°$
$\mu = 0.0662$ mm^{-1}
$T = 297$ K
Plate
0.30 × 0.30 × 0.10 mm
White

Data collection

AFC-6S diffractometer
$\omega/2\theta$ scans
Absorption correction: empirical, ψ scan
$T_{min} = 0.86$, $T_{max} = 1.00$
3097 measured reflections
3907 independent reflections
2912 observed reflections [$I > 2.5\sigma(I)$]
$R_{int} = 0.023$
$\theta_{max} = 25°$
$h = 0 \rightarrow 13$
$k = -13 \rightarrow 13$
$l = -10 \rightarrow 10$
3 standard reflections monitored every 150 reflections
intensity decay: 2.70%

Refinement

Refinement on F
$R = 0.0712$
$wR = 0.0680$
$S = 2.245$
1795 reflections
304 parameters
H-atom parameters not refined
Weighting scheme based on measured e.s.d.'s
$(\Delta/\sigma)_{max} = 0.0214$
$\Delta\rho_{max} = 0.315$ e Å^{-3}
$\Delta\rho_{min} = -0.225$ e Å^{-3}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

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

U_{iso} for phenyl and methyl C atoms (with e.s.d.'s in parentheses); $U_{eq} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$ for other atoms (e.s.d.'s not given).

	x	y	z	U_{eq}
O1	0.5809	0.6865	0.0846	0.0520
O2	0.7136 (9)	0.7936 (7)	0.3344 (10)	0.0766
C1	0.7747 (10)	0.3972 (10)	0.012 (1)	0.0693
C2	0.661 (1)	0.413 (1)	−0.142 (1)	0.0750
C3	0.5620 (10)	0.4487 (8)	−0.036 (1)	0.0559
C4	0.579 (1)	0.3374 (9)	0.053 (2)	0.0841
C5	0.543 (1)	0.401 (1)	0.218 (2)	0.1061
C6	0.579 (1)	0.545 (1)	0.266 (1)	0.0850
C7	0.6254 (10)	0.5582 (8)	0.120 (1)	0.0526
C8	0.7721 (10)	0.5335 (9)	0.140 (1)	0.0604
C9	0.726 (1)	0.2970 (10)	0.073 (2)	0.0897
C10	0.674 (1)	0.521 (1)	−0.224 (1)	0.075 (3)
C11	0.628 (1)	0.284 (1)	−0.287 (1)	0.082 (3)
C12	0.631 (1)	0.7938 (9)	0.204 (1)	0.0545
C13	0.578 (1)	0.9158 (9)	0.140 (1)	0.0603
C14	0.6083 (10)	1.037 (1)	0.286 (1)	0.070 (3)
C15	0.6402 (9)	0.9182 (8)	0.003 (1)	0.042 (2)
C16	0.5623 (10)	0.9200 (9)	−0.159 (1)	0.058 (2)
C17	0.620 (1)	0.915 (1)	−0.288 (1)	0.067 (3)
C18	0.752 (1)	0.914 (1)	−0.252 (1)	0.076 (3)
C19	0.8330 (10)	0.9147 (10)	−0.095 (1)	0.066 (3)
C20	0.7734 (10)	0.9146 (9)	0.031 (1)	0.050 (2)
O3	0.2920 (9)	0.8240 (7)	0.257 (1)	0.0896
O4	0.1083 (7)	0.9335 (6)	0.3042 (9)	0.0585
C21	0.1613 (9)	1.0612 (9)	0.333 (1)	0.0539
C22	0.195 (1)	1.0766 (9)	0.178 (1)	0.0712
C23	0.152 (1)	1.223 (1)	0.174 (2)	0.1024
C24	0.113 (1)	1.282 (1)	0.335 (2)	0.0829
C25	0.225 (1)	1.3250 (10)	0.493 (2)	0.0999
C26	0.229 (1)	1.227 (1)	0.597 (1)	0.0867
C27	0.277 (1)	1.0961 (10)	0.500 (1)	0.0657
C28	0.0571 (10)	1.1658 (9)	0.371 (1)	0.0606
C29	0.084 (1)	1.2040 (10)	0.562 (2)	0.0954
C30	0.058 (1)	1.100 (1)	0.637 (2)	0.112 (4)
C31	0.004 (1)	1.329 (1)	0.630 (2)	0.131 (5)
C32	0.181 (1)	0.8253 (9)	0.274 (1)	0.0648
C33	0.115 (1)	0.7091 (10)	0.279 (1)	0.0662
C34	0.152 (1)	0.582 (1)	0.162 (1)	0.082 (3)
C35	0.1515 (9)	0.7015 (8)	0.463 (1)	0.043 (2)
C36	0.053 (1)	0.7107 (10)	0.539 (1)	0.069 (3)
C37	0.093 (1)	0.706 (1)	0.715 (2)	0.087 (3)
C38	0.224 (1)	0.697 (1)	0.796 (1)	0.077 (3)
C39	0.316 (1)	0.689 (1)	0.720 (1)	0.077 (3)
C40	0.280 (1)	0.6900 (10)	0.553 (1)	0.066 (3)

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

O1—C12	1.334 (9)	C3—C4	1.54 (1)
O1—C7	1.473 (8)	C3—C7	1.53 (1)
O2—C12	1.191 (9)	C4—C5	1.52 (1)
C1—C2	1.53 (1)	C4—C9	1.53 (1)
C1—C8	1.55 (1)	C5—C6	1.53 (1)
C1—C9	1.51 (1)	C6—C7	1.52 (1)
C2—C3	1.53 (1)	C7—C8	1.51 (1)
C2—C10	1.54 (1)	C12—C13	1.53 (1)
C2—C11	1.57 (1)	C13—C14	1.51 (1)
C1—C2—C3	91.9 (7)	O1—C7—C3	109.3 (6)
C2—C1—C9	103.5 (8)	C7—O1—C12	117.7 (6)
C4—C3—C7	98.2 (7)	C10—C2—C11	106.9 (8)
C4—C5—C6	105.5 (8)	O1—C7—C8	111.2 (6)
C5—C4—C9	115.3 (9)		

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN PROCESS* (Molecular Structure Corporation, 1985). Program(s) used to refine structure: *TEXSAN LS*. Molecular graphics: *PLUTO* (Motherwell & Clegg, 1978). Software used to prepare material for publication: *TEXSAN FINISH*.

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Lists of structure factors, anisotropic displacement parameters and H-atom coordinates have been deposited with the IUCr (Reference: HU1137). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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N,*N*-Dimethyl-2-[7-(methylaminosulfonylmethyl)-1-naphthyl]ethylamine, the Naphthalenic Bioisostere of Sumatriptan

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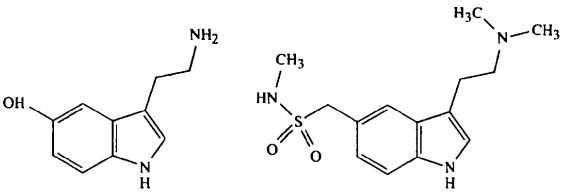
Abstract

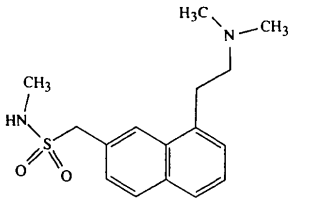
The title molecule, $C_{16}H_{22}N_2O_2S$, is the naphthalenic bioisostere of sumatriptan, a well known agonist of the 5-hydroxytryptamine 5-HT_{1D} receptor. The ethylamine side chain adopts an extended conformation (*ac*,*ap*,*ap*) and its plane is perpendicular to the naphthalene ring plane. This is very similar to that already observed in some analogous indole derivatives.

Comment

The involvement of serotonin, (1) (5-hydroxytryptamine, 5-HT), in the etiology and treatment of migraine has been the subject of intensive investigations. This was prompted by the discovery that sumatriptan, (2) [5-(methylaminosulfonylmethyl)-*N*,*N*-dimethyltryptamine], and other agonists of the 5-HT_{1D} receptor subtype possess clinical efficacy as novel antimigraine agents.



5-HT (1) Sumatriptan (2)



Naphthalenic bioisostere (3)

A simple comparison of the 5-HT_{1D} agonists (1) and (2) would suggest that the key groups required for binding and efficacy are a basic amine group, an indole ring (the NH group of which may participate in hydrogen bonding) and a substituent at the 5 position which is capable of participating in hydrogen bonding as a receptor and/or donor.

With the purpose of identifying a novel series of 5-HT_{1D} agonists for use in migraine therapy, our initial strategy was to study bioisosteric replacement of the indole nucleus of the 5-HT_{1D} agonist sumatriptan and to search for 5-HT_{1D} selectivity in the title compound, (3). In the present study, we discuss the conformation of (3), the naphthalenic bioisostere of (2).

The naphthalenic nucleus is planar within experimental error; the maximum deviation from the mean

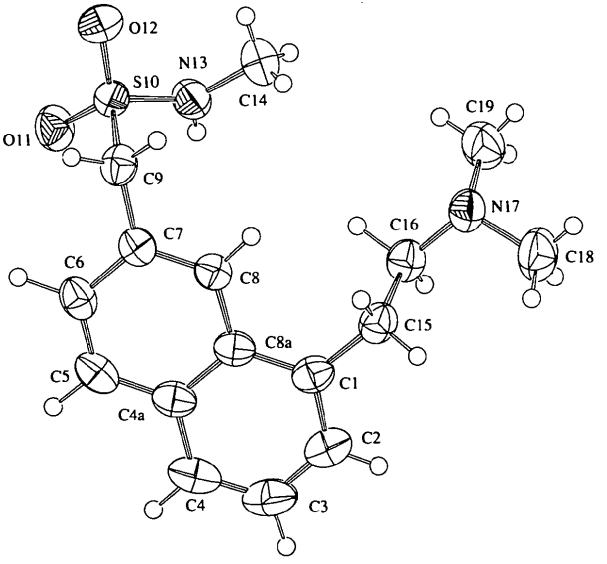


Fig. 1. *PLATON* (Spek, 1990) drawing of the title molecule. The displacement ellipsoids are drawn at the 50% probability level.