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

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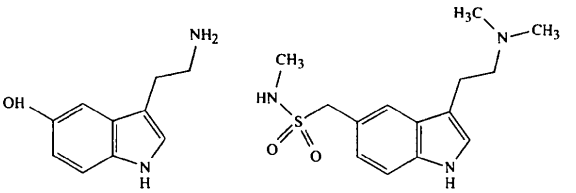
Abstract

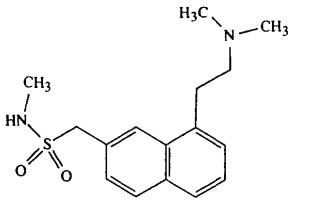
The title molecule, $C_{16}H_{22}N_2O_2S$, is the naphthalenic bioisostere of sumatriptan, a well known agonist of the 5-hydroxytryptamine 5-HT_{1D} receptor. The ethylamine side chain adopts an extended conformation (*ac*,*ap*,*ap*) and its plane is perpendicular to the naphthalene ring plane. This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

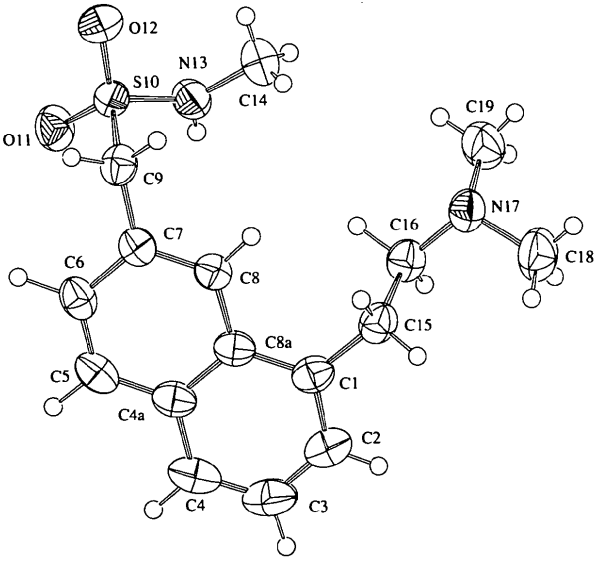


Fig. 1. *PLATON* (Spek, 1990) drawing of the title molecule. The displacement ellipsoids are drawn at the 50% probability level.

plane through the ten atoms is 0.024 (2) Å, with a mean deviation of 0.013 (2) Å. The ethylamine side chain adopts an extended conformation with atoms C11, C12, N13 and C14 in a plane which is approximately perpendicular to the plane of the naphthalene ring system. The torsion angles along the chain, C2—C1—C15—C16 = 101 (1), C1—C15—C16—N17 = 178 (1) and C15—C16—N17—C19 = −171 (1)°, indicate an *ac,ap,ap* conformation (Klyne & Prelog, 1960). This arrangement has been observed for serotonin in the serotonin creatinine sulfate monohydrate complex (Karle, Dragonette & Brenner, 1965) and in bufetonine (Falkenberg, 1972). The *N*-methylsulfamoyl side chain is folded (+*ac*,−*sc*,−*sc* conformation) so that the amino H atom (H13) is above the naphthalenic plane. The dimethylamino N atom is involved in a hydrogen bond with the NH group of a symmetry related molecule: N13···N17^{i} = 3.029 (3), H13···N17^{i} = 2.29 (4) Å and N13—H13···N17^{i} = 158 (1)° [symmetry code: (i) $x, y-1, z$].

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

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

	x	y	z	U_{eq}
C1	0.8657 (2)	0.6603 (5)	1.0409 (2)	0.048 (1)
C2	0.9515 (2)	0.6527 (6)	1.0776 (2)	0.064 (1)
C3	0.9928 (2)	0.4831 (7)	1.1341 (2)	0.071 (1)
C4	0.9497 (2)	0.3165 (7)	1.1563 (2)	0.063 (1)
C4a	0.8601 (2)	0.3133 (5)	1.1205 (2)	0.047 (1)
C5	0.8120 (2)	0.1422 (5)	1.1413 (2)	0.053 (1)
C6	0.7264 (2)	0.1355 (5)	1.1046 (2)	0.049 (1)
C7	0.6841 (2)	0.3050 (4)	1.0458 (1)	0.041 (1)
C8	0.7293 (2)	0.4767 (4)	1.0263 (2)	0.041 (1)
C8a	0.8182 (2)	0.4857 (5)	1.0620 (1)	0.043 (1)
C9	0.5906 (2)	0.2991 (5)	1.0034 (2)	0.045 (1)
S10	0.5558 (1)	0.1057 (1)	0.9183 (1)	0.043 (0)
O11	0.5888 (1)	−0.1199 (3)	0.9464 (1)	0.056 (1)
O12	0.4668 (1)	0.1354 (4)	0.8816 (1)	0.061 (1)
N13	0.5970 (2)	0.1841 (4)	0.8554 (1)	0.052 (1)
C14	0.5684 (3)	0.3878 (7)	0.8045 (2)	0.068 (1)
C15	0.8232 (2)	0.8525 (5)	0.9815 (2)	0.048 (1)
C16	0.7942 (2)	0.7834 (5)	0.8923 (2)	0.049 (1)
N17	0.7505 (1)	0.9714 (4)	0.8369 (1)	0.049 (1)
C18	0.8076 (3)	1.1616 (6)	0.8405 (3)	0.074 (2)
C19	0.7128 (3)	0.8859 (7)	0.7535 (2)	0.073 (2)

Experimental

Crystal data

$C_{16}H_{22}N_2O_2S$
M_r = 306.43
Monoclinic
$P2_1/c$
a = 17.154 (2) Å
b = 5.748 (1) Å
c = 17.657 (2) Å
β = 111.96 (1)°
V = 1614.6 (4) Å^3
Z = 4
D_x = 1.26 Mg m^{-3}
Cu $K\alpha$ radiation
λ = 1.5418 Å
Cell parameters from 30 reflections
θ = 12–25°
μ = 1.78 mm^{-1}
T = 291 K
Parallelepiped
0.48 × 0.10 × 0.03 mm
Colourless
Crystal source: slow evaporation from toluene

Data collection

Huber four-circle (Rigaku RU200 generator) diffractometer
$\theta/2\theta$ scans
Absorption correction: none
2912 measured reflections
2912 independent reflections
2096 observed reflections [$I > 2.5\sigma(I)$]
θ_{max} = 67.5°
$h = -20 \rightarrow 19$
$k = 0 \rightarrow 6$
$l = 0 \rightarrow 19$
1 standard reflection monitored every 50 reflections
intensity decay: 4%

Refinement

Refinement on F
R = 0.042
wR = 0.050
S = 0.90
2096 reflections
257 parameters
H atoms refined isotropically
$w = 1/[\sigma^2(F) + 0.00406F^2]$
$(\Delta/\sigma)_{max}$ = 0.10
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.32 e Å^{-3}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

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

C2—C1	1.370 (4)	C8a—C1	1.427 (4)
C15—C1	1.510 (4)	C3—C2	1.385 (5)
C4—C3	1.356 (5)	C4a—C4	1.426 (4)
C5—C4a	1.417 (4)	C8a—C4a	1.418 (4)
C6—C5	1.366 (4)	C7—C6	1.411 (4)
C8—C7	1.375 (4)	C9—C7	1.496 (3)
C8a—C8	1.417 (3)	S10—C9	1.782 (3)
O11—S10	1.427 (2)	O12—S10	1.427 (2)
N13—S10	1.590 (2)	C14—N13	1.445 (4)
C16—C15	1.517 (4)	N17—C16	1.462 (3)
C18—N17	1.454 (4)	C19—N17	1.454 (4)
C8a—C1—C2	118.1 (3)	C3—C2—C1	122.2 (3)
C15—C1—C8a	121.4 (2)	C4a—C4—C3	119.6 (3)
C4—C3—C2	121.3 (3)	C8a—C4a—C4	118.9 (3)
C5—C4a—C4	122.0 (3)	C6—C5—C4a	121.6 (3)
C8a—C4a—C5	119.2 (2)	C8—C7—C6	119.8 (2)
C7—C6—C5	119.6 (3)	C9—C7—C8	119.3 (2)
C9—C7—C6	120.8 (2)	C4a—C8a—C1	119.9 (2)
C8a—C8—C7	121.9 (2)	C8—C8a—C4a	117.8 (2)
C8—C8a—C1	122.3 (2)	O11—S10—C9	108.0 (1)
S10—C9—C7	113.3 (2)	O12—S10—O11	119.0 (1)
O12—S10—C9	105.8 (1)	N13—S10—O11	106.1 (1)
N13—S10—C9	108.4 (1)	C14—N13—S10	121.8 (2)
N13—S10—O12	109.1 (1)	N17—C16—C15	112.8 (2)
C16—C15—C1	114.5 (2)	C19—N17—C16	110.5 (2)
C18—N17—C16	111.0 (3)	C19—N17—C18	109.6 (3)
C15—C1—C2	120.4 (3)		

Data collection, cell refinement and data reduction: local programs. Structure solution: *SHELXS*86 (Sheldrick, 1985). Structure refinement: *SHELX*76 (Sheldrick, 1976). Molecular graphics: *PLATON* (Spek, 1990).

BT and JPD thank the FNRS Belgium and the FDS (UCL) for financial support.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry, including bond distances and angles involving H atoms, have been deposited with the IUCr (Reference: PA1134). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Bis(2-imidazolyl)aminomethane Tris(hydrochloride)

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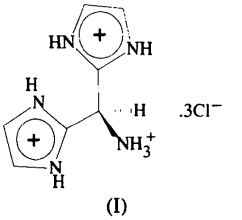
Abstract

Crystals of bis(2-imidazolyl)methylammonium trichloride, $C_7H_{12}N_5^{3+}.3Cl^-$, are composed of units comprised of the $C_7H_{12}N_5^{3+}$ cation and three chloride anions linked by a two-dimensional network of hydrogen bonds. The two imidazole rings form an angle of 67.1 (2)° with one another. One of the chloride ions forms an intramolecular hydrogen bond between the ammonium residue and one of the imidazole rings.

Comment

Imidazole derivates are of special importance in biological systems. The imidazole group has many functions such as protein carrier or nucleophilic agent; it is also a structural ligand at the active-site center of many enzymes. It forms part of some hormones and other biomolecules like histamine. This wide biological distribution has attracted the attention of researchers from many different fields, their aim being to understand and mimic the biological activity of these imidazole derivatives. Of special interest are the attempts to mimic the properties of metallo-enzymes and to relate these properties to the structural shape of simple coordination compounds (Bouwman, Driessen & Reedijk, 1990). To gain a better understanding of the relationship between the structure of the active site and its activity, more data is needed about imidazole compounds coordinated to metal ions, as well as free ligands. The aim of the present study was to determine the molecular structure of bis(2-imidazolyl)aminomethane tris(hydrochloride) (I) [hereafter referred to as $(H_3bima)Cl_3$], which is necessary for comparative studies of coordination compounds containing this and analogous ligands (Koolhaas, Driessen, van Koningsbruggen, Reedijk & Spek, 1993; Tran *et al.*, 1994; Armstrong, Youinou, Palermo & Holm, 1984).



(I)

The molecular structure of the title compound is shown in Fig. 1. The imidazole rings are planar, the largest deviation from the least-squares plane being 0.006 (2) Å for atom N11. The dimensions of both imidazole rings are essentially the same. The angle between the least-squares planes of the imidazole rings is 67.1 (2)°, whereas in the copper complex $[Cu_6(tidah)Cl_{10}(H_2O)]$ [tidah is the anionic form of 1,1,6,6-tetrakis(2-imidazolyl)-2,5-diazahexane], reported previously by Koolhaas, Driessen, van Koningsbruggen, Reedijk & Spek (1993), this angle is 40 (2)°. Crystals of $(H_3bima)Cl_3$ are comprised of units of the $C_7H_{12}N_5^{3+}$ cation interconnected by seven hydrogen bonds with the three neighboring chloride anions. This hydrogen-bond system forms a polymeric two-dimensional network along the crystallographic planes (100) and (010) (Fig. 2). Only the Cl1 and Cl2 chloride anions are involved in this polymeric structure, whereas Cl3 forms an intramolecular bond between the ammo-

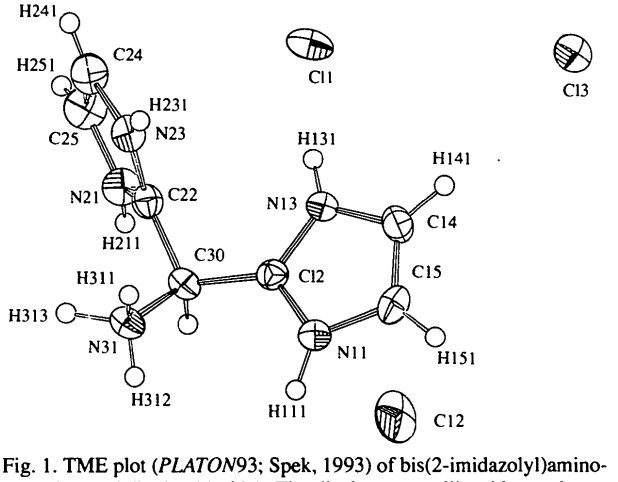


Fig. 1. TME plot (*PLATON*93; Spek, 1993) of bis(2-imidazolyl)aminomethane tris(hydrochloride). The displacement ellipsoids are drawn at the 50% probability level and H atoms are represented as small circles of arbitrary size.