
Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and torsion angles have been deposited with the IUCr (Reference: TA1075). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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1,7-Dimethyl-5-phenyl-2-(3-thenoylaminomethyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-4-ium Chloride

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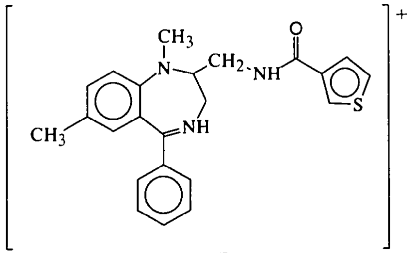
Abstract

The seven-membered ring of $C_{23}H_{24}N_3OS^+.Cl^-$ has a conformation halfway between a distorted boat and a distorted sofa. The 3-thenoylaminomethyl moiety is in an extended conformation. This conformation is stabilized by two hydrogen bonds with the chloride anion, one from the protonated basic N atom of the heptadiene ring and another from the amidic N atom. The thienyl ring shows 180° rotational disorder.

Comment

The title compound, (I), belongs to a series of 2-acylaminomethylbenzodiazepine derivatives with opioid activity. This single-crystal structure analysis is part of a structure–activity study on κ-opioid agonists related to tifluadom. Fig. 1 shows the molecule. Bond lengths and angles show small deviations from values found in other compounds of the series (Blaton, Peeters, Meurisse & De Ranter, 1996, and references therein). The puckering parameters [sequence N1, C2, C3, N4, C5, C5a, C9a: q_2 = 0.678 (3), q_3 = 0.299 (3) Å, φ_2 = −36.0 (2), φ_3 = −142.8 (5)°] and asymmetry parameters [$\Delta C_s(C_3)$ = 0.071 (1)] indicate a conformation halfway between a distorted boat and a distorted sofa. The 3-thenoylaminomethyl side chain has the extended conformation and substitutes the diazepine ring axially at position 2. This side chain is stabilized by two N—H···Cl hydrogen bonds [N4···Cl = 3.052 (2), H4···Cl = 2.28 Å, N4—H4···Cl = 150.4°; N12···Cl = 3.213 (2), H12···Cl = 2.40, N12—H12···Cl = 158°].



(I).

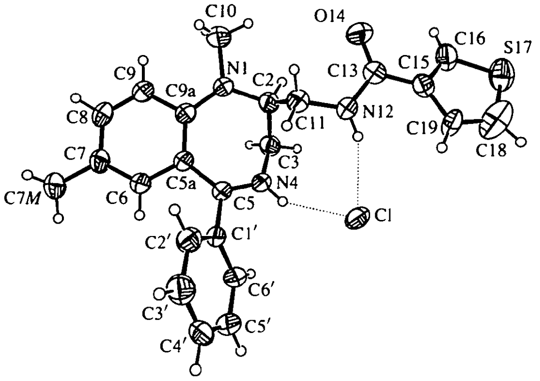


Fig. 1. Perspective view of the title compound with the thienyl ring in the *A* conformation showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 40% probability level.

Experimental

Crystals of the title compound were obtained by slow evaporation at room temperature from a solution in methanol/amyl acetate.

Crystal data

$C_{23}H_{24}N_3OS^+.Cl^-$
M_r = 425.96
Monoclinic
$P2_1/n$
a = 10.319 (2) Å
b = 8.933 (2) Å
c = 23.976 (2) Å
β = 94.92 (2)°

Cu $K\alpha$ radiation
λ = 1.54184 Å
Cell parameters from 24 reflections
θ = 15–23°
μ = 2.560 mm^{-1}
T = 293 K
Prism

$V = 2201.8\,(7)$ Å^3
$Z = 4$
$D_x = 1.285$ Mg m^{-3}
$D_m = 1.280$ Mg m^{-3}
D_m measured by flotation in chloroform/*n*-heptane
0.40 × 0.30 × 0.15 mm
Orange

Data collection

Stoe Stadi4 four-circle diffractometer
$2\theta/\omega$ scans
Absorption correction: ψ scans (*EMPIR*; Stoe & Cie, 1992*a*)
$T_{\min} = 0.37$, $T_{\max} = 0.68$
7906 measured reflections
3696 independent reflections
2489 observed reflections [$I > 2.0\sigma(I)$]
$R_{\rm int} = 0.0391$
$\theta_{\max} = 64.54°$
$h = -12 \rightarrow 12$
$k = 0 \rightarrow 10$
$l = -28 \rightarrow 28$
4 standard reflections
frequency: 60 min
intensity decay: 1.4%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.0462$
$wR(F^2) = 0.1247$
$S = 1.121$
3690 reflections
311 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F_o^2) + (0.0384P)^2 + 0.8467P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} = 0.001$
$\Delta\rho_{\max} = 0.29$ e Å^{-3}
$\Delta\rho_{\min} = -0.17$ e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0013 (2)
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. 4, Tables 2.2B and 2.3.1)

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

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

	x	*y*	*z*	$U_{\rm eq}$
Cl	1.38615 (7)	0.0729 (1)	0.21370 (3)	0.0773 (3)
N1	0.8489 (2)	0.0473 (4)	0.21006 (9)	0.067 (1)
C2	0.9667 (3)	0.0200 (4)	0.1814 (1)	0.056 (1)
C3	1.0596 (3)	−0.0887 (4)	0.2126 (1)	0.058 (1)
N4	1.1309 (2)	−0.0167 (3)	0.26000 (9)	0.0516 (8)
C5	1.0769 (2)	0.0304 (3)	0.3039 (1)	0.0461 (8)
C5a	0.9387 (2)	0.0176 (3)	0.3097 (1)	0.0483 (9)
C6	0.9062 (3)	−0.0018 (3)	0.3659 (1)	0.054 (1)
C7	0.7811 (3)	−0.0096 (4)	0.3809 (1)	0.060 (1)
C7*M*	0.7509 (3)	−0.0380 (5)	0.4405 (1)	0.079 (2)
C8	0.6833 (3)	0.0103 (4)	0.3379 (1)	0.066 (1)
C9	0.7080 (3)	0.0275 (4)	0.2833 (1)	0.066 (1)
C9a	0.8362 (2)	0.0279 (4)	0.2660 (1)	0.054 (1)
C10	0.7340 (3)	0.0829 (5)	0.1719 (1)	0.094 (2)
C11	1.0294 (3)	0.1694 (4)	0.1689 (1)	0.060 (1)
N12	1.1330 (2)	0.1548 (3)	0.1319 (1)	0.0599 (9)
C13	1.1076 (3)	0.1624 (4)	0.0762 (1)	0.060 (1)
O14	0.9960 (2)	0.1681 (3)	0.05416 (9)	0.087 (1)
C1′	1.1644 (2)	0.0996 (3)	0.3490 (1)	0.0449 (8)
C2′	1.1272 (3)	0.2305 (4)	0.3739 (1)	0.059 (1)
C3′	1.2066 (3)	0.2954 (4)	0.4159 (1)	0.074 (1)
C4′	1.3222 (3)	0.2308 (5)	0.4343 (1)	0.077 (2)
C5′	1.3611 (3)	0.1006 (5)	0.4098 (1)	0.080 (2)
C6′	1.2822 (3)	0.0350 (4)	0.3664 (1)	0.060 (1)
C15*A*	1.226 (3)	0.163 (6)	0.045 (1)	0.056 (5)
C16*A*	1.208 (2)	0.124 (4)	−0.0099 (8)	0.076 (5)
S17*A*	1.3525 (4)	0.1362 (8)	−0.0413 (2)	0.094 (1)
C18*A*	1.429 (2)	0.197 (4)	0.0185 (9)	0.127 (9)
C19*A*	1.354 (2)	0.206 (3)	0.0611 (8)	0.065 (4)
C15*B*	1.217 (4)	0.17 (1)	0.039 (2)	0.06 (1)
C16*B*	1.338 (3)	0.199 (6)	0.065 (1)	0.09 (1)
S17*B*	1.453 (1)	0.206 (1)	0.0155 (4)	0.101 (2)
C18*B*	1.337 (2)	0.167 (4)	−0.035 (1)	0.13 (1)
C19*B*	1.221 (3)	0.139 (6)	−0.017 (1)	0.082 (9)

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

N1—C2	1.467 (4)	C13—C15*A*	1.48 (3)
N1—C9a	1.370 (4)	C13—C15*B*	1.49 (5)
N1—C10	1.469 (4)	C1′—C2′	1.382 (4)
C2—C3	1.516 (4)	C1′—C6′	1.378 (4)
C2—C11	1.525 (5)	C2′—C3′	1.371 (4)
C3—N4	1.451 (3)	C3′—C4′	1.364 (5)
N4—C5	1.301 (3)	C4′—C5′	1.378 (6)
C5—C5a	1.449 (3)	C5′—C6′	1.394 (4)
C5—C1′	1.483 (3)	C15*A*—C16*A*	1.36 (4)
C5a—C6	1.426 (4)	C15*A*—C19*A*	1.40 (4)
C5a—C9a	1.426 (3)	C16*A*—S17*A*	1.73 (2)
C6—C7	1.372 (4)	S17*A*—C18*A*	1.67 (2)
C7—C7*M*	1.510 (4)	C18*A*—C19*A*	1.34 (3)
C7—C8	1.392 (4)	C15*B*—C16*B*	1.37 (5)
C8—C9	1.363 (5)	C15*B*—C19*B*	1.39 (6)
C9—C9a	1.420 (4)	C16*B*—S17*B*	1.75 (3)
C11—N12	1.451 (4)	S17*B*—C18*B*	1.67 (3)
N12—C13	1.342 (4)	C18*B*—C19*B*	1.32 (4)
C13—O14	1.226 (4)		
C9a—N1—C10	119.8 (2)	N12—C13—O14	121.8 (3)
C2—N1—C10	113.6 (2)	O14—C13—C15*A*	124 (1)
C2—N1—C9a	126.2 (2)	N12—C13—C15*B*	120 (2)
N1—C2—C11	109.2 (3)	O14—C13—C15*B*	119 (2)
N1—C2—C3	112.9 (2)	C5—C1′—C6′	120.8 (3)
C3—C2—C11	113.4 (2)	C5—C1′—C2′	119.6 (2)
C2—C3—N4	111.0 (2)	C2′—C1′—C6′	119.6 (3)
C3—N4—C5	123.6 (2)	C1′—C2′—C3′	120.3 (3)
N4—C5—C1′	116.7 (2)	C2′—C3′—C4′	120.7 (3)
N4—C5—C5a	123.0 (2)	C3′—C4′—C5′	119.8 (3)
C5a—C5—C1′	120.3 (2)	C4′—C5′—C6′	120.1 (3)
C5—C5a—C9a	126.7 (2)	C1′—C6′—C5′	119.5 (3)
C5—C5a—C6	114.4 (2)	C13—C15*A*—C19*A*	132 (3)
C6—C5a—C9a	118.8 (2)	C13—C15*A*—C16*A*	116 (2)
C5a—C6—C7	123.9 (3)	C16*A*—C15*A*—C19*A*	112 (3)
C6—C7—C8	115.9 (3)	C15*A*—C16*A*—S17*A*	111 (2)
C6—C7—C7*M*	122.2 (3)	C16*A*—S17*A*—C18*A*	91 (1)
C7*M*—C7—C8	121.9 (3)	S17*A*—C18*A*—C19*A*	114 (2)
C7—C8—C9	122.9 (3)	C15*A*—C19*A*—C18*A*	112 (2)
C8—C9—C9a	122.4 (3)	C13—C15*B*—C19*B*	131 (3)
C5a—C9a—C9	115.9 (2)	C13—C15*B*—C16*B*	117 (4)
N1—C9a—C9	117.1 (2)	C16*B*—C15*B*—C19*B*	112 (3)
N1—C9a—C5a	126.9 (2)	C15*B*—C16*B*—S17*B*	111 (3)
C2—C11—N12	112.9 (3)	C16*B*—S17*B*—C18*B*	90 (1)
C11—N12—C13	120.8 (3)	S17*B*—C18*B*—C19*B*	115 (2)
N12—C13—C15*A*	114 (1)	C15*B*—C19*B*—C18*B*	113 (3)
C2—N1—C9a—C5a	18.3 (5)	N4—C5—C1′—C6′	−44.4 (4)
C9a—N1—C2—C11	−104.2 (3)	N4—C5—C5a—C9a	−34.0 (4)
C9a—N1—C2—C3	23.0 (4)	C5—C5a—C9a—N1	2.1 (5)
N1—C2—C11—N12	−169.7 (2)	C2—C11—N12—C13	89.4 (3)
N1—C2—C3—N4	−76.8 (3)	C11—N12—C13—O14	−6.8 (5)
C2—C3—N4—C5	67.1 (3)	C11—N12—C13—C15*A*	173 (2)
C3—N4—C5—C5a	−0.9 (4)	C11—N12—C13—C15*B*	172 (3)

The structure was solved by direct methods and refined by full-matrix least-squares methods. Difference Fourier maps showed a 180° rotational disorder of the thienyl ring about the bond connecting the ring to the carboxamide moiety. The ring was modelled by two superimposed thiophene rings and refined as two parts with the same distances restraints. The sum of the occupation parameters was constrained to 1. The occupation parameter of part *A* refined to 0.609 (7). H atoms were included at calculated positions and refined using a riding model.

Data collection: *DIF*4 (Stoe & Cie, 1988). Cell refinement: *DIF*4. Data reduction: *REDU*4 (Stoe & Cie, 1992*b*). Program(s) used to solve structure: *MULTAN*80 (Main *et al.*, 1980). Program(s) used to refine structure: *SHELXL*93

(Sheldrick, 1993). Molecular graphics: *ORTEX*2.1 (McArdle, 1994). Software used to prepare material for publication: *PARST* (Nardelli, 1983).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: NA1255). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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(−)-(*R*)-*N*-[(3,4-Dihydro-2*H*-1-benzopyran-2-yl)methyl]-*N*′-(1,4,5,6-tetrahydro-2-pyrimidyl)-1,3-propanediaminium Dibromide†

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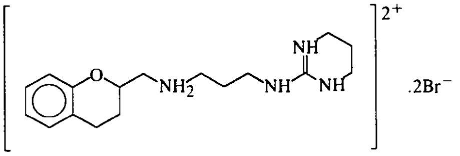
Abstract

The crystal structure and absolute configuration of the (−)-enantiomer of the title compound, $C_{17}H_{28}N_4O^{2+}.2Br^-$, have been determined. The absolute configuration is *R*. The bridging chain between the ring moieties is folded with a −*sc*/*ap*/*sc*/*sc*/*ap*/−*sc* conformation. N—H···Br hydrogen bonds form endless chains in the **b** direction.

Comment

Alniditan (R91274), the hydrochloride form of the title compound, (I), interacts primarily with 5-HT$_{1D}$-serotonergic binding sites and at slightly higher concentrations with the closely related 5-HT$_{1A}$-serotonergic binding sites. Intravenous and subcutaneous injection of alniditan in patients experiencing moderate to severe migraine pain resulted in a significantly higher response rate than placebo, and this response rate increased with increasing doses.



(I)

The crystal structure determination of the title compound was undertaken to obtain the absolute configuration of alniditan. Compared to the values given by Allen *et al.* (1987) the bond lengths are normal. The bond angles do not show unexpected features. The double protonation occurs at the basic N atoms N12 and N18 (or N22). This agrees with the less basic properties of N16 through delocalization of its lone pair. The dihydropyran ring adopts a half-chair conformation with a pseudo twofold axis intersecting the C2—C3 bond. The tetrahydropyrimidine ring has an envelope conformation with the flap at C20. The bridging chain between the ring moieties is folded and has a −*sc*/*ap*/*sc*/*sc*/*ap*/−*sc* conformation. The *gauche* conformation between O1 and N12 is stabilized by an intramolecular hydrogen bond. The packing of the molecules results mainly from N—H···Br intermolecular hydrogen bonds which form endless chains in the **b** direction.

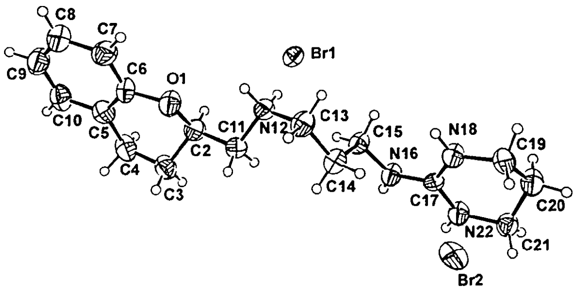


Fig. 1. Perspective view of the title compound with atomic numbering scheme. Displacement ellipsoids are drawn at the 40% probability level.

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† Internal code of the Janssen Research Foundation: R96692.