Acta Cryst. (1994). C**50**, 1350–1352

2-(4-Cyanobenzoylaminomethyl)-1-methyl-5-(3-thienyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-4-ium *p*-Toluenesulfonate

O. M. Peeters, N. M. Blaton, R. L. Meurisse and C. J. De Ranter

Laboratorium voor Analytische Chemie en Medicinale Fysicochemie, Faculteit Farmaceutische Wetenschappen, Katholieke Universiteit Leuven, Van Evenstraat 4, B-3000 Leuven, Belgium

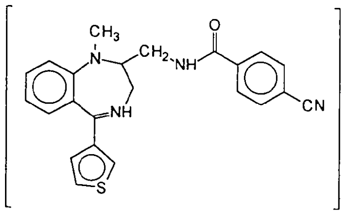
(*Received* 21 *January* 1994; *accepted* 28 *February* 1994)

Abstract

The observed global conformation of the title compound, $C_{23}H_{21}N_4OS^+.C_7H_7O_3S^-$, is common for 2-acylaminomethyl derivatives of benzodiazepine. This conformation is stabilized by two hydrogen bonds from the *p*-toluenesulfonate anion, one from the protonated basic N atom of the heptadiene ring and another from the amidic N atom in the side chain. The thienyl ring exhibits 180° rotational disorder.

Comment

The title compound (I) belongs to a series of 2-acylaminomethylbenzodiazepine derivatives with opioid activity. As part of a structure–activity study of κ-opioid agonists related to tifluadom, this crystal structure determination was undertaken.



(I)

A view of the molecule is given in Fig. 1. Another combination of the potentially disordered parts is shown in Fig. 2. Bond lengths and angles do not show any unexpected features in comparison with other compounds of the series (Meurisse, Blaton, De Ranter & Peeters, 1992, and references therein). The puckering parameters [q_2 = 0.831 (4), q_3 = 0.225 (4) Å, φ_2 = 157.9 (3), φ_3 = 55 (1)°] and asymmetry parameters [ΔC_s(C3) = 0.034 (2)] indicate a conformation approximately midway between boat and sofa (Boessenkool & Boeyens, 1980). The 2-substituent is positioned axially on the diazepine ring with the cyanophenyl ring nearly parallel to the benzo moiety [dihedral angle 27.4 (2)°]. The thienyl ring approaches perpendicularity with the benzo group [dihedral angle 44.9 (4)° for ring *A*, 55.2 (4)° for ring *B*] to a lesser extent than analogous substituents in other derivatives of the series (58–70°). Both orientations of the disordered toluenesulfonate anion form hydrogen bonds with N4 and N12. In the *A* orientation, bonds are formed with two O atoms [N4···O9''*A* = 2.675 (6), H4···O9''*A* = 1.66 Å, N4—H4···O9''*A* = 155°; N12···O8''*A* = 2.879 (7), H12···O8''*A* = 1.86 Å, N12—H12···O8''*A* = 150°]. In orientation *B*, a bond is formed with only one O atom [N4···O10''*B* = 2.78 (1), H4···O10''*B* = 1.95 Å, N4—H4···O10''*B* = 132°; N12···O10''*B* = 2.596 (9), H12···O10''*B* = 1.71 Å, N12—H12···O10''*B* = 132°].

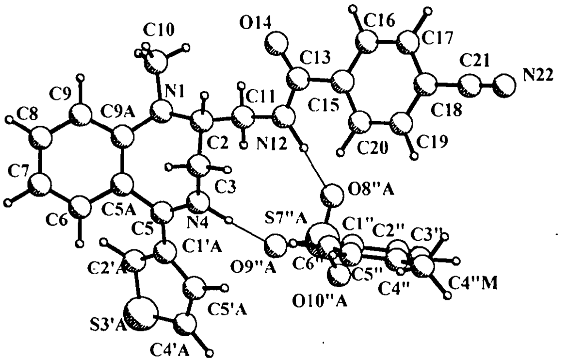


Fig. 1. *PLUTO* (Motherwell & Clegg, 1978) drawing of the molecule with *A* disordered parts.

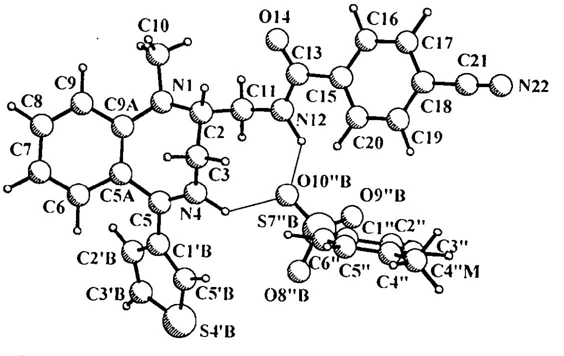


Fig. 2. *PLUTO* (Motherwell & Clegg, 1978) drawing of the molecule with *B* disordered parts.

Experimental

Crystal data

$C_{23}H_{21}N_4OS^+.C_7H_7O_3S^-$
M_r = 572.69
Monoclinic
$P2_1/n$
a = 7.727 (4) Å
b = 33.04 (2) Å
c = 11.264 (6) Å
β = 101.57 (3)°

Cu $K\alpha$ radiation
λ = 1.54184 Å
Cell parameters from 24 reflections
θ = 20–25°
μ = 2.021 mm^{-1}
T = 293 K
Irregular

$V = 2817.\ (2)$ Å^3
$Z = 4$
$D_x = 1.350$ Mg m^{-3}
$D_m = 1.36$ Mg m^{-3}
D_m measured by flotation in *n*-heptane/CCl$_4$

0.32 × 0.19 × 0.19 mm
Dark orange
Crystal source: methanol/amyl acetate solution

Data collection

Stoe Stadi-4 four-circle diffractometer
ω–2θ scans
Absorption correction: empirical (*EMPIR*; Stoe & Cie, 1988*b*)
$T_{\min} = 0.403$, $T_{\max} = 0.529$
9138 measured reflections
4655 independent reflections

2888 observed reflections $[I > 3.0\sigma(I)]$
$R_{\rm int} = 0.0157$
$\theta_{\max} = 64.01°$
$h = -8 \rightarrow 8$
$k = 0 \rightarrow 38$
$l = -13 \rightarrow 13$
4 standard reflections
frequency: 60 min
intensity variation: <3%

Refinement

Refinement on F
$R = 0.0580$
$wR = 0.0843$
$S = 3.09$
2888 reflections
412 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F) + 0.00040F^2]$

$(\Delta/\sigma)_{\max} = 0.428$
$\Delta\rho_{\max} = 0.45$ e Å^{-3}
$\Delta\rho_{\min} = -0.31$ e Å^{-3}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Tables 2.2B and 2.3.1)

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

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

	Occupancy	x	y	z	$U_{\rm eq}$
N1	1.00	0.3796 (5)	0.1741 (1)	0.3288 (3)	0.059 (1)
C2	1.00	0.2987 (6)	0.1458 (1)	0.2338 (4)	0.057 (2)
C3	1.00	0.1546 (6)	0.1655 (1)	0.1400 (4)	0.057 (2)
N4	1.00	0.2307 (5)	0.1966 (1)	0.0724 (3)	0.054 (1)
C5	1.00	0.2734 (5)	0.2323 (1)	0.1171 (4)	0.048 (1)
C5*A*	1.00	0.2696 (6)	0.2412 (1)	0.2434 (4)	0.045 (1)
C6	1.00	0.2137 (6)	0.2810 (1)	0.2684 (4)	0.055 (2)
C7	1.00	0.2102 (7)	0.2939 (2)	0.3831 (4)	0.065 (2)
C8	1.00	0.2676 (7)	0.2668 (2)	0.4785 (4)	0.069 (2)
C9	1.00	0.3206 (6)	0.2282 (2)	0.4591 (4)	0.059 (2)
C9*A*	1.00	0.3205 (6)	0.2134 (1)	0.3417 (4)	0.050 (2)
C10	1.00	0.4631 (8)	0.1530 (2)	0.4408 (5)	0.085 (3)
C11	1.00	0.4365 (7)	0.1257 (2)	0.1775 (5)	0.074 (2)
N12	1.00	0.3702 (6)	0.0912 (1)	0.1025 (4)	0.073 (2)
C13	1.00	0.3501 (8)	0.0548 (2)	0.1510 (5)	0.076 (2)
O14	1.00	0.3775 (7)	0.0492 (1)	0.2596 (4)	0.109 (2)
C15	1.00	0.2925 (7)	0.0205 (1)	0.0637 (4)	0.066 (2)
C16	1.00	0.3344 (8)	−0.0188 (2)	0.1016 (5)	0.074 (2)
C17	1.00	0.2871 (8)	−0.0508 (2)	0.0247 (6)	0.078 (2)
C18	1.00	0.1943 (7)	−0.0439 (2)	−0.0937 (5)	0.069 (2)
C19	1.00	0.1495 (8)	−0.0051 (2)	−0.1321 (5)	0.076 (2)
C20	1.00	0.1950 (8)	0.0269 (2)	−0.0536 (5)	0.072 (2)
C21	1.00	0.1470 (8)	−0.0780 (2)	−0.1767 (6)	0.084 (3)
N22	1.00	0.1118 (8)	−0.1050 (2)	−0.2398 (6)	0.109 (3)
C1'*A*	0.5	0.343 (3)	0.2619 (3)	0.038 (1)	0.043 (7)
C2'*A*	0.5	0.429 (2)	0.2967 (3)	0.0791 (6)	0.057 (6)
S3'*A*	0.5	0.4468 (4)	0.3284 (1)	−0.0368 (3)	0.063 (1)
C4'*A*	0.5	0.339 (2)	0.2954 (4)	−0.1417 (6)	0.083 (8)
C5'*A*	0.5	0.291 (3)	0.2611 (4)	−0.089 (1)	0.056 (7)
C1'*B*	0.5	0.298 (3)	0.2632 (4)	0.034 (1)	0.037 (5)
C2'*B*	0.5	0.414 (3)	0.2960 (5)	0.0689 (5)	0.053 (9)
C3'*B*	0.5	0.441 (2)	0.3184 (4)	−0.0275 (6)	0.18 (2)
S4'*B*	0.5	0.3250 (7)	0.2997 (1)	−0.1606 (4)	0.065 (2)
C5'*B*	0.5	0.240 (3)	0.2616 (3)	−0.089 (1)	0.046 (5)
C1''	1.00	0.1189 (7)	0.1077 (1)	−0.2942 (4)	0.026 (2)
C2''	1.00	0.1461 (8)	0.0817 (2)	−0.3831 (5)	0.075 (2)
C3''	1.00	0.001 (1)	0.0587 (2)	−0.4453 (6)	0.107 (3)
C4''	1.00	−0.166 (1)	0.0620 (2)	−0.4173 (8)	0.108 (3)
C4''*M*	1.00	−0.316 (1)	0.0355 (3)	−0.486 (1)	0.166 (5)
C5''	1.00	−0.1902 (9)	0.0884 (2)	−0.3271 (7)	0.101 (3)
C6''	1.00	−0.0486 (9)	0.1108 (2)	−0.2664 (5)	0.079 (2)
S7''*A*	0.67	0.2812 (4)	0.13844 (8)	−0.2197 (2)	0.059 (1)
O8''*A*	0.67	0.4032 (6)	0.1123 (1)	−0.1399 (4)	0.075 (2)
O9''*A*	0.67	0.2006 (6)	0.1683 (1)	−0.1534 (4)	0.079 (2)
O10''*A*	0.67	0.3608 (8)	0.1566 (2)	−0.3133 (4)	0.092 (3)
S7''*B*	0.33	0.3110 (8)	0.1374 (2)	−0.2145 (5)	0.054 (3)
O8''*B*	0.33	0.282 (1)	0.1773 (2)	−0.2686 (9)	0.092 (5)
O9''*B*	0.33	0.473 (1)	0.1189 (3)	−0.235 (1)	0.097 (6)
O10''*B*	0.33	0.300 (2)	0.1374 (4)	−0.0874 (6)	0.114 (6)

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

N1—C2	1.462 (5)	C21—N22	1.139 (8)
N1—C9*A*	1.395 (5)	C1'*A*—C2'*A*	1.36 (1)
N1—C10	1.471 (6)	C1'*A*—C5'*A*	1.41 (1)
C2—C3	1.520 (6)	C2'*A*—S3'*A*	1.700 (9)
C2—C11	1.500 (7)	S3'*A*—C4'*A*	1.70 (1)
C3—N4	1.469 (6)	C4'*A*—C5'*A*	1.36 (1)
N4—C5	1.299 (5)	C1'*B*—C2'*B*	1.41 (2)
C5—C5*A*	1.459 (5)	C1'*B*—C5'*B*	1.36 (1)
C5—C1'*A*	1.49 (1)	C2'*B*—C3'*B*	1.36 (1)
C5—C1'*B*	1.43 (1)	C3'*B*—S4'*B*	1.700 (9)
C5*A*—C6	1.429 (6)	S4'*B*—C5'*B*	1.70 (1)
C5*A*—C9*A*	1.430 (5)	C1''—C2''	1.367 (7)
C6—C7	1.365 (6)	C1''—C6''	1.395 (9)
C7—C8	1.399 (6)	C1''—S7''*A*	1.698 (5)
C8—C9	1.373 (7)	C1''—S7''*B*	1.853 (7)
C9—C9*A*	1.409 (6)	C2''—C3''	1.418 (9)
C11—N12	1.450 (6)	C3''—C4''	1.39 (1)
N12—C13	1.342 (7)	C4''—C4''*M*	1.53 (1)
C13—O14	1.213 (7)	C4''—C5''	1.38 (1)
C13—C15	1.508 (7)	C5''—C6''	1.382 (8)
C15—C16	1.382 (7)	S7''*A*—O8''*A*	1.450 (4)
C15—C20	1.400 (6)	S7''*A*—O9''*A*	1.452 (5)
C16—C17	1.371 (7)	S7''*A*—O10''*A*	1.452 (5)
C17—C18	1.400 (7)	S7''*B*—O8''*B*	1.450 (9)
C18—C19	1.377 (7)	S7''*B*—O9''*B*	1.45 (1)
C18—C21	1.462 (8)	S7''*B*—O10''*B*	1.452 (8)
C19—C20	1.377 (7)		
C9*A*—N1—C10	116.6 (4)	C5—C1'*A*—C5'*A*	122 (1)
C2—N1—C10	112.1 (4)	C5—C1'*A*—C2'*A*	124 (1)
C2—N1—C9*A*	124.8 (4)	C2'*A*—C1'*A*—C5'*A*	112 (1)
N1—C2—C11	110.9 (4)	C1'*A*—C2'*A*—S3'*A*	111.7 (7)
N1—C2—C3	112.4 (4)	C2'*A*—S3'*A*—C4'*A*	92.0 (5)
C3—C2—C11	112.3 (4)	S3'*A*—C4'*A*—C5'*A*	111.7 (7)
C2—C3—N4	110.3 (4)	C1'*A*—C5'*A*—C4'*A*	112 (1)
C3—N4—C5	122.1 (4)	C5—C1'*B*—C5'*B*	125 (1)
N4—C5—C1'*B*	116.8 (6)	C5—C1'*B*—C2'*B*	121.6 (8)
N4—C5—C1'*A*	117.2 (6)	C2'*B*—C1'*B*—C5'*B*	112 (1)
N4—C5—C5*A*	120.5 (4)	C1'*B*—C2'*B*—C3'*B*	112.3 (8)
C5*A*—C5—C1'*B*	122.1 (6)	C2'*B*—C3'*B*—S4'*B*	111.7 (7)
C5*A*—C5—C1'*A*	122.0 (6)	C3'*B*—S4'*B*—C5'*B*	92.0 (6)
C5—C5*A*—C9*A*	124.7 (4)	C1'*B*—C5'*B*—S4'*B*	112 (1)
C5—C5*A*—C6	116.3 (4)	C6''—C1''—S7''*B*	122.8 (4)
C6—C5*A*—C9*A*	119.0 (4)	C6''—C1''—S7''*A*	118.2 (4)
C5*A*—C6—C7	122.5 (4)	C2''—C1''—S7''*B*	117.4 (5)
C6—C7—C8	117.7 (5)	C2''—C1''—S7''*A*	122.0 (4)
C7—C8—C9	122.0 (4)	C2''—C1''—C6''	119.7 (5)
C8—C9—C9*A*	121.8 (4)	C1''—C2''—C3''	118.6 (6)
C5*A*—C9*A*—C9	116.9 (4)	C2''—C3''—C4''	121.4 (6)
N1—C9*A*—C9	118.8 (4)	C3''—C4''—C5''	118.9 (7)
N1—C9*A*—C5*A*	124.2 (4)	C3''—C4''—C4''*M*	118.9 (7)
C2—C11—N12	113.4 (4)	C4''*M*—C4''—C5''	122.2 (8)
C11—N12—C13	121.5 (5)	C4''—C5''—C6''	119.4 (7)
N12—C13—C15	116.8 (5)	C1''—C6''—C5''	121.9 (6)
N12—C13—O14	122.4 (5)	C1''—S7''*A*—O10''*A*	105.5 (3)
O14—C13—C15	120.8 (5)	C1''—S7''*A*—O9''*A*	108.1 (3)
C13—C15—C20	122.2 (5)	C1''—S7''*A*—O8''*A*	105.9 (3)
C13—C15—C16	118.9 (5)	O9''*A*—S7''*A*—O10''*A*	112.4 (3)
C16—C15—C20	118.8 (5)	O8''*A*—S7''*A*—O10''*A*	112.3 (4)

C15—C16—C17	120.9 (5)	O8″A—S7″A—O9″A	112.2 (3)
C16—C17—C18	119.8 (5)	C1″—S7″B—O10″B	106.2 (6)
C17—C18—C21	119.9 (5)	C1″—S7″B—O9″B	109.5 (5)
C17—C18—C19	119.9 (5)	C1″—S7″B—O8″B	103.7 (6)
C19—C18—C21	120.2 (5)	O9″B—S7″B—O10″B	112.4 (7)
C18—C19—C20	119.9 (5)	O8″B—S7″B—O10″B	112.2 (6)
C15—C20—C19	120.6 (5)	O8″B—S7″B—O9″B	112.2 (7)
C18—C21—N22	178.8 (7)		

C9A—N1—C2—C11	133.5 (5)	N4—C5—C5A—C9A	37.4 (7)
C9A—N1—C2—C3	6.9 (6)	C5—C5A—C9A—N1	−0.4 (7)
N1—C2—C11—N12	167.1 (4)	C2—C11—N12—C13	−80.2 (6)
N1—C2—C3—N4	65.8 (5)	C11—N12—C13—O14	3.8 (9)
C2—C3—N4—C5	−78.6 (5)	C11—N12—C13—C15	−175.8 (5)
C3—N4—C5—C5A	8.4 (7)	N12—C13—C15—C16	155.0 (5)
N4—C5—C1′A—C2′A	−164 (1)	N12—C13—C15—C20	−26.2 (8)

Data were collected with a variable scan speed of 0.6–2.4° $\min^{-1}$ and a scan width of 1.4° in steps of 0.02° with extra steps for α_1–α_2 dispersion. The structure was solved by direct methods and refined by full-matrix least-squares techniques. Difference Fourier maps showed an 180° rotational disorder of the thienyl ring and a 60° rotational disorder of the sulfonate group. These disordered positions were modelled as idealized rigid groups. In the first instance, the complementary occupancy, positional and rotational parameters were refined, while keeping the isotropic displacement parameters fixed, then the positional, rotational and individual anisotropic parameters were refined with fixed population parameters. H-atom positions were calculated, except those of the methyl groups which were obtained from a difference Fourier synthesis. Data collection and cell refinement: *DIF*4 (Stoe & Cie, 1988*a*). Data reduction: *REDU*4 (Stoe & Cie, 1992*a*). Program(s) used to solve structure: *MULTAN*80 (Main *et al.*, 1980). Program(s) used to refine structure: *NRCVAX* (Gabe, Le Page, Charland, Lee & White, 1989). Molecular graphics: *PLUTO* (Motherwell & Clegg, 1978). Software used to prepare material for publication: *PARST* (Nardelli, 1983).

The authors thank Dr H. Zeugner, Kali-Chemie Pharma GmbH, Hannover, for providing the title compound.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: NA1089). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Boessenkool, I. K. & Boeyens, J. C. A. (1980). *J. Cryst. Mol. Struct.* **10**, 11–18.

Gabe, E. J., Le Page, Y., Charland, J.-P., Lee, F. L. & White, P. S. (1989). *J. Appl. Cryst.* **22**, 384–387.

Main, P., Fiske, S. J., Hull, S. E., Lessinger, L., Germain, G., Declercq, J.-P. & Woolfson, M. M. (1980). *MULTAN*80. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

Meurisse, R. L., Blaton, N. M., Peeters, O. M. & De Ranter, C. J. (1992). *Acta Cryst.* C**48**, 508–512.

Motherwell, W. D. S. & Clegg, W. (1978). *PLUTO. Program for Plotting Molecular and Crystal Structures.* Univ. of Cambridge, England.

Nardelli, M. (1983). *Comput. Chem.* **7**, 95–98.

Stoe & Cie (1988*a*). *DIF*4. *Diffractometer Control Program.* Version 6.2. Stoe & Cie, Darmstadt, Germany.

Stoe & Cie (1988*b*). *EMPIR. Empirical Absorption Correction Program.* Version 1.2. Stoe & Cie, Darmstadt, Germany.

Stoe & Cie (1992). *REDU*4. *Data Reduction Program.* Version 7.03. Stoe & Cie, Darmstadt, Germany.

Acta Cryst. (1994). C**50**, 1352–1354

5-(2,4-Dichlorophenyl)-2-[(3-furoyl)aminomethyl]-8-methoxy-1-methyl-2,3-dihydro-1*H*-1,4-benzodiazepin-4-ium *p*-Toluenesulfonate

O. M. Peeters, N. M. Blaton, R. L. Meurisse and C. J. De Ranter

Laboratorium voor Analytische Chemie en Medicinale Fysicochemie, Faculteit Farmaceutische Wetenschappen, Katholieke Universiteit Leuven, Van Evenstraat 4, B-3000 Leuven, Belgium

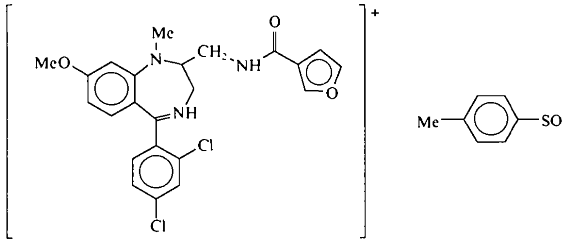
(*Received* 21 *January* 1994; *accepted* 28 *February* 1994)

Abstract

The seven-membered ring of the title compound, $C_{23}H_{22}Cl_2N_3O_3^+.C_7H_7O_3S^-$, adopts a conformation halfway between a distorted boat and a distorted sofa. The 3-furoylaminomethyl moiety is in an extended conformation with the furan ring nearly parallel to the benzo part of the benzodiazepine ring. Two intermolecular hydrogen bonds to the *p*-toluenesulfonate anion stabilize the observed conformation.

Comment

The structure of the title compound (I) was determined as part of a structure–activity study of benzodiazepine derivatives with opioid activity.



(I)

Bond lengths and angles are in the same range as in other protonated 2-acylaminomethylbenzodiazepines (Meurisse, Blaton, Peeters & De Ranter, 1992, and references therein). The global conformation is practically the same in all these compounds. The seven-

Acta Crystallographica Section C
ISSN 0108-2701 ©1994