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Structure of 2-Bromo-4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*]-[1,4]diazepine (Brotizolam), $C_{15}H_{10}BrClN_4S$*

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Abstract. $M_r = 393{\cdot}7$, monoclinic, $P2_1/c$, $a = 15{\cdot}749\,(3)$, $b = 12{\cdot}928\,(2)$, $c = 7{\cdot}346\,(5)$ Å, $\beta = 95{\cdot}44\,(3)^\circ$, $U = 1488{\cdot}9$ Å^3, $Z = 4$, $D_x = 1{\cdot}756$ Mg m^{-3}, μ(Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å) $= 2{\cdot}98$ mm^{-1}, $F(000) = 784$, room temperature, $R = 0{\cdot}047$ for 1730 observed reflections. The angle between the mean planes of the phenyl and thieno rings is 71·7 (5)°; the seven-membered ring adopts a boat conformation which is slightly flatter than in 1,4-benzodiazepines which do not have an extra ring fused across the N(1)—C(2) bond [N(1)—C(3) in the present compound]. Bond lengths and angles are normal.

Introduction. Following the success of a number of 5-phenyl-1,4-benzodiazepines as psychotropic agents, many analogous molecules have been synthesized with the aim of producing superior drugs.

Brotizolam (Weber, Bauer, Langbein & Daniel, 1978) incorporates two major modifications of the basic benzodiazepine framework; it has a triazolo ring fused across the N(1)—C(2) bond of the parent system and a thieno ring replaces the usual fused benzene ring. This 'heterodiazepine' is effective as a hypnotic and has an extremely high affinity for the benzodiazepine receptor, binding more strongly than the triazolobenzodiazepines alprazolam (Hester, Duchamp & Chidester, 1971), and estazolam (Meguro & Kuwada, 1970) by factors of *ca* 10 and 60, respectively (Braestrup & Squires, 1978). The structure of brotizolam is now reported as part of a study of structure–activity relationships for this class of compounds.

Experimental. Crystals from aqueous ethanol. Enraf–Nonius CAD-4 diffractometer. Crystal 0·7 × 0·25 × 0·25 mm. Cell dimensions from setting angles of 25 reflections. Graphite-monochromated Mo $K\alpha$ radiation. No absorption correction. 2626 reflections, ω–2θ scans, $\theta_{max} = 25^\circ$, 1730 considered observed [$I > 2{\cdot}5\sigma(I)$], index range h −18 to 18, k 0 to 15, l 0 to 8. Two standard reflections measured every 2 h, no significant variation in intensity. Structure solved by Patterson and Fourier methods. All H atoms located from difference Fourier map. Least-squares refinement, $\sum w(\Delta F)^2$ minimized. H isotropic, non-H anisotropic. Final calculated shifts all $\leq 0{\cdot}2\,\sigma$. $R = 0{\cdot}047$, $wR = 0{\cdot}058$; $w = 1/[\sigma^2(F) + 0{\cdot}002F^2]$. Residual electron density in final difference map within $\pm 0{\cdot}9$ e Å^{-3}. No correction for secondary extinction. Computations were carried out with *SHELX* (Sheldrick, 1978) using complex neutral-atom scattering factors (*International Tables for X-ray Crystallography,* 1974) and *PLUTO* (Motherwell & Clegg, 1978).

Discussion. Final atomic parameters are listed in Table 1;† bond lengths, bond angles and selected torsion angles are in Table 2. The atomic numbering scheme is illustrated in Fig. 1.

Bond lengths and angles for the thieno ring are within the range generally observed for this moiety [see *e.g.* Caughenour & Dennis (1975), Prout & Miao (1982)], other lengths and angles are in agreement with those found in 1,4-benzodiazepines (Hamor & Martin, 1983).

The seven-membered ring is in a cycloheptatriene-like boat conformation. The bow and stern angles of 56·8 (6) and 29·2 (6)° compare with values of 54 and 31° in estazolam (Kamiya, Wada & Nishikawa, 1973) and 53 and 36°, respectively, in alprazolam (Hester *et al.,* 1971), slightly flatter than commonly found in 1,4-benzodiazepines not having an extra ring fused across the N(1)—C(2) bond [N(1)—C(3) in the present compound] (bow angles 58–64°, stern angles 32–40°) (Hamor & Martin, 1983).

The phenyl, triazolo and thieno rings are each planar to within the limits of experimental error. The angle between the thieno and phenyl rings is 71·7 (5)°, slightly smaller than in 2′-chloro-substituted 1,4-benzodiazepines (range 73–86°). An interesting difference, however, is that the Cl atom 'points' towards the same

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† Lists of structure factors, anisotropic thermal parameters, H-atom parameters and the results of mean-plane calculations have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39809 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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side of the molecule as C(4) (see Fig. 1), whereas in all other crystal structures of 5-phenyl-1,4-benzodiazepines, any 2′-substituent has been found to lie on the opposite side of the molecule relative to this atom (Hamor & Martin, 1983).

All intermolecular contact distances correspond to normal van der Waals interactions.

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Table 1. *Fractional atomic coordinates* (×10⁴) *with e.s.d.'s in parentheses and equivalent isotropic temperature factors* (Å² ×10³)

$U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33} + 2U_{13}\cos\beta)$.

	x	y	z	U_{eq}
Br	1518 (1)	−1312 (1)	−1499 (1)	49
Cl	730 (1)	−5540 (1)	−3246 (2)	50
S(9)	3287 (1)	−2298 (1)	−1871 (2)	31
N(1)	4211 (3)	−4078 (3)	−2085 (6)	24
N(2)	5552 (3)	−4536 (4)	−1795 (7)	36
N(3)	5094 (3)	−5286 (4)	−2860 (6)	34
N(5)	2984 (3)	−5929 (4)	−2714 (6)	31
C(1)	5031 (4)	−3842 (4)	−1347 (7)	31
C(3)	4301 (3)	−4987 (4)	−3040 (7)	28
C(4)	3553 (4)	−5486 (5)	−4022 (8)	33
C(6)	2596 (3)	−5309 (4)	−1765 (7)	28
C(7)	1996 (4)	−3464 (5)	−1568 (8)	34
C(8)	2224 (3)	−2456 (4)	−1618 (8)	31
C(10)	3413 (3)	−3631 (4)	−1892 (7)	27
C(11)	2682 (3)	−4152 (4)	−1742 (7)	27
C(12)	5248 (4)	−2920 (5)	−172 (9)	39
C(1′)	1993 (4)	−5750 (4)	−502 (8)	30
C(2′)	1132 (4)	−5871 (4)	−1024 (8)	32
C(3′)	580 (4)	−6277 (5)	107 (10)	44
C(4′)	890 (4)	−6573 (5)	1886 (10)	46
C(5′)	1750 (5)	−6468 (5)	2421 (10)	49
C(6′)	2295 (4)	−6060 (5)	1243 (9)	39

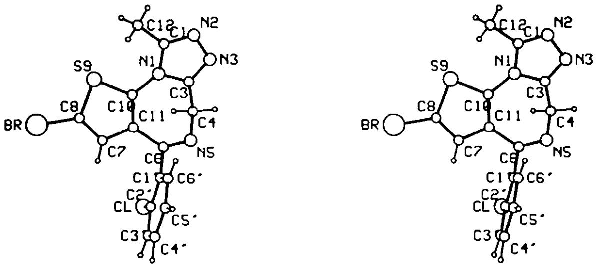

Fig. 1. Stereoscopic view of the molecule in a direction perpendicular to the mean plane of the thieno ring.

Table 2. *Molecular dimensions*

(*a*) Bond lengths (Å)

N(1)–C(1)	1·386 (7)	C(7)–C(8)	1·353 (8)
N(1)–C(3)	1·383 (7)	C(7)–C(11)	1·415 (8)
N(1)–C(10)	1·403 (7)	C(8)–Br	1·858 (5)
C(1)–N(2)	1·279 (7)	C(8)–S(9)	1·714 (6)
C(1)–C(12)	1·492 (9)	S(9)–C(10)	1·736 (5)
N(2)–N(3)	1·402 (7)	C(10)–C(11)	1·347 (8)
N(3)–C(3)	1·302 (7)	C(1′)–C(2′)	1·383 (8)
C(3)–C(4)	1·470 (8)	C(2′)–Cl	1·747 (6)
C(4)–N(5)	1·489 (7)	C(2′)–C(3′)	1·363 (8)
N(5)–C(6)	1·258 (7)	C(3′)–C(4′)	1·404 (10)
C(6)–C(11)	1·501 (7)	C(4′)–C(5′)	1·380 (10)
C(6)–C(1′)	1·502 (8)	C(5′)–C(6′)	1·380 (9)
		C(6′)–C(1′)	1·384 (8)

(*b*) Bond angles (°)

C(1)–N(1)–C(3)	104·5 (4)	S(9)–C(8)–C(7)	112·5 (4)
C(1)–N(1)–C(10)	132·8 (5)	C(8)–S(9)–C(10)	89·8 (3)
C(3)–N(1)–C(10)	122·4 (4)	S(9)–C(10)–N(1)	120·9 (4)
N(1)–C(1)–N(2)	109·9 (5)	S(9)–C(10)–C(11)	113·4 (4)
N(1)–C(1)–C(12)	123·8 (5)	N(1)–C(10)–C(11)	125·7 (5)
N(2)–C(1)–C(12)	126·2 (5)	C(6)–C(11)–C(7)	123·9 (5)
C(1)–N(2)–N(3)	108·7 (4)	C(6)–C(11)–C(10)	125·0 (5)
N(2)–N(3)–C(3)	106·8 (4)	C(7)–C(11)–C(10)	111·1 (5)
N(1)–C(3)–N(3)	110·1 (5)	C(6)–C(1′)–C(2′)	122·2 (5)
N(1)–C(3)–C(4)	120·4 (4)	C(6)–C(1′)–C(6′)	120·0 (5)
N(3)–C(3)–C(4)	129·5 (5)	C(2′)–C(1′)–C(6′)	117·7 (5)
C(3)–C(4)–N(5)	110·8 (5)	Cl–C(2′)–C(1′)	119·3 (4)
C(4)–N(5)–C(6)	117·7 (5)	Cl–C(2′)–C(3′)	117·9 (5)
N(5)–C(6)–C(11)	126·4 (5)	C(1′)–C(2′)–C(3′)	122·7 (6)
N(5)–C(6)–C(1′)	118·0 (5)	C(2′)–C(3′)–C(4′)	119·1 (6)
C(11)–C(6)–C(1′)	115·7 (5)	C(3′)–C(4′)–C(5′)	119·0 (6)
C(8)–C(7)–C(11)	113·3 (5)	C(4′)–C(5′)–C(6′)	120·7 (7)
Br–C(8)–S(9)	120·4 (3)	C(1′)–C(6′)–C(5′)	120·8 (6)
Br–C(8)–C(7)	127·1 (4)		

(*c*) Selected torsion angles (°); e.s.d.'s *ca* 0·6°

C(10)–N(1)–C(3)–C(4)	4·8	N(5)–C(6)–C(11)–C(10)	−36·5
N(1)–C(3)–C(4)–N(5)	−70·0	C(6)–C(11)–C(10)–N(1)	−0·3
C(3)–C(4)–N(5)–C(6)	68·1	C(11)–C(10)–N(1)–C(3)	34·0
C(4)–N(5)–C(6)–C(11)	−3·3	N(5)–C(6)–C(1′)–C(2′)	−92·9
		C(11)–C(6)–C(1′)–C(2′)	87·7

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