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(−)-5-Ethyl-2'-hydroxy-2-isobutyl-9,9-dimethyl-6,7-benzomorphan Hydrobromide*

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Abstract. $C_{20}H_{32}NO^{+}.Br^{-}$, $M_r = 382.39$, orthorhombic, $P2_12_12_1$, $a = 11.482$ (1), $b = 11.532$ (1), $c = 14.560$ (1) Å, $V = 1928$ Å^3, $Z = 4$, $D_m = 1.31$ (by flotation), $D_c = 1.32$ Mg m^{-3}, $F(000) = 808$, $\mu(Cu\ K\alpha) = 3.21$ mm^{-1}. The structure was solved by a Patterson method and refined to $R = 0.037$ for 1713 independent reflections. Hydrogen bonds between Br, O and N atoms link the molecules into chains parallel to the b axis.

Introduction. In the 6,7-benzomorphan series this compound acts mainly as an antagonist of narcotic analgesics, itself showing only weak analgesic activity (private communication from ACF Chemiefarma NV). As the side chain on the nitrogen has always been considered of great pharmacological importance, the conformation of the isobutyl group is worth investigating.

For prismatic crystals of the title compound the space group was determined from photographs as $P2_12_12_1$ from the orthorhombic symmetry and the systematic absences for $h00$, $0k0$ and $00l$ with h, k and l odd respectively. The cell parameters were obtained from a least-squares calculation of the setting angles of 30 reflections, measured on a Nonius CAD-4 automatic diffractometer using Cu $K\alpha$ radiation ($\lambda = 1.54178$ Å) and a θ–2θ scan. 1897 independent

reflections were collected, of which 182 were rejected for their low intensities $[I < 3\sigma(I)]$. They were corrected for Lorentz and polarization factors but not for absorption. The positions of the non-hydrogen atoms of the molecule were obtained from a Patterson synthesis followed by a superposition map (minimum

Table 1. *Atomic coordinates for the non-hydrogen atoms with e.s.d.'s in parentheses*

	x	y	z
Br	0.3909 (1)	0.0554 (0)	0.1421 (0)
O(2')	0.2264 (4)	0.2717 (3)	0.0909 (3)
C(1)	0.2318 (4)	0.7642 (4)	0.3068 (3)
N	0.3397 (4)	0.8226 (3)	0.2666 (3)
C(3)	0.3871 (5)	0.7532 (4)	0.1880 (3)
C(4)	0.2932 (4)	0.7382 (4)	0.1162 (3)
C(5)	0.1770 (4)	0.6857 (4)	0.1525 (4)
C(6)	0.2055 (4)	0.5620 (4)	0.1868 (3)
C(7)	0.2478 (4)	0.5446 (4)	0.2750 (3)
C(8)	0.2609 (5)	0.6428 (4)	0.3437 (4)
C(9)	0.1347 (4)	0.7613 (4)	0.2356 (3)
C(10)	0.0934 (6)	0.6861 (4)	0.0693 (4)
C(11)	−0.0264 (5)	0.6312 (6)	0.0792 (4)
C(12)	0.0986 (6)	0.8856 (4)	0.2079 (4)
C(13)	0.0284 (5)	0.7080 (5)	0.2853 (4)
C(14)	0.4353 (4)	0.8500 (4)	0.3355 (4)
C(15)	0.3972 (6)	0.9109 (4)	0.4208 (4)
C(16)	0.3327 (6)	1.0262 (5)	0.4022 (4)
C(17)	0.5044 (6)	0.9310 (7)	0.4796 (4)
C(1')	0.1985 (5)	0.4685 (4)	0.1269 (4)
C(2')	0.2332 (4)	0.3578 (4)	0.1551 (4)
C(3')	0.2715 (5)	0.3400 (4)	0.2438 (4)
C(4')	0.2789 (4)	0.4338 (4)	0.3032 (3)

Table 2. *Fractional coordinates and isotropic thermal parameters for the hydrogen atoms*

	x	y	z	U ($Å^2 \times 10^3$)
H(1)	0·2223	0·8164	0·3631	29
H(2)	0·3250	0·9000	0·2500	31
H(3,1)	0·4019	0·6783	0·2165	35
H(3,2)	0·4500	0·7875	0·1538	35
H(4,1)	0·3293	0·6833	0·0703	33
H(4,2)	0·2500	0·8125	0·0769	33
H(8,1)	0·2206	0·6245	0·4051	31
H(8,2)	0·3250	0·6454	0·3665	31
H(10,1)	0·1361	0·6479	0·0186	42
H(10,2)	0·0875	0·7625	0·0673	42
H(11,1)	−0·0500	0·5875	0·0096	56
H(11,2)	−0·0272	0·5674	0·1313	56
H(11,3)	−0·0901	0·6942	0·0947	56
H(12,1)	0·1428	0·9337	0·1641	42
H(12,2)	0·1094	0·9344	0·2599	42
H(12,3)	0·0500	0·8750	0·1538	42
H(13,1)	0·0171	0·7307	0·3540	42
H(13,2)	−0·0483	0·7387	0·2501	42
H(13,3)	0·0309	0·6184	0·2801	42
H(14,1)	0·4750	0·7625	0·3269	40
H(14,2)	0·5000	0·9000	0·3077	40
H(15)	0·3447	0·8448	0·4484	46
H(16,1)	0·2500	1·0097	0·3651	57
H(16,2)	0·3832	1·0704	0·3553	57
H(16,3)	0·3142	1·0475	0·4584	57
H(17,1)	0·5500	0·8625	0·4904	64
H(17,2)	0·5591	0·9894	0·4459	64
H(17,3)	0·4811	0·9627	0·5441	64
H(1′)	0·1695	0·4788	0·0567	34
H(2′)	0·2250	0·2045	0·1382	50
H(3′)	0·3035	0·2509	0·2597	42
H(4′)	0·3115	0·4184	0·3667	38

Fig. 1. Atomic numbering of the molecule with bond lengths (Å) and e.s.d.'s in parentheses.

Table 3. *Bond angles* (°) *with e.s.d.'s in parentheses*

N—C(1)—C(8)	111·1 (4)	C(1)—C(8)—C(7)	115·3 (4)
N—C(1)—C(9)	110·0 (4)	C(1)—C(9)—C(5)	108·0 (4)
C(8)—C(1)—C(9)	112·2 (4)	C(1)—C(9)—C(12)	110·7 (4)
C(1)—N—C(3)	110·5 (4)	C(1)—C(9)—C(13)	105·6 (4)
C(1)—N—C(14)	115·1 (4)	C(5)—C(9)—C(12)	113·3 (4)
C(3)—N—C(14)	110·6 (4)	C(5)—C(9)—C(13)	112·6 (4)
N—C(3)—C(4)	109·3 (4)	C(12)—C(9)—C(13)	106·3 (4)
C(3)—C(4)—C(5)	114·8 (4)	C(5)—C(10)—C(11)	119·1 (4)
C(4)—C(5)—C(6)	106·7 (4)	N—C(14)—C(15)	115·8 (4)
C(4)—C(5)—C(9)	108·2 (4)	C(14)—C(15)—C(16)	113·5 (4)
C(4)—C(5)—C(10)	105·4 (4)	C(14)—C(15)—C(17)	107·7 (5)
C(6)—C(5)—C(9)	109·2 (4)	C(16)—C(15)—C(17)	110·9 (5)
C(6)—C(5)—C(10)	112·8 (4)	C(6)—C(1′)—C(2′)	120·5 (5)
C(9)—C(5)—C(10)	114·2 (4)	O(2′)—C(2′)—C(1′)	116·5 (4)
C(5)—C(6)—C(7)	120·4 (4)	O(2′)—C(2′)—C(3′)	123·4 (4)
C(5)—C(6)—C(1′)	120·0 (4)	C(1′)—C(2′)—C(3′)	120·1 (5)
C(7)—C(6)—C(1′)	119·3 (4)	C(2′)—C(3′)—C(4′)	119·2 (5)
C(6)—C(7)—C(8)	122·5 (4)	C(7)—C(4′)—C(3′)	121·1 (5)
C(6)—C(7)—C(4′)	119·8 (4)		
C(8)—C(7)—C(4′)	117·8 (4)		

function). Subsequent isotropic and anisotropic refinements by block-diagonal least squares using the XRAY program system (Stewart, Kruger, Ammon, Dickinson & Hall, 1976) lowered the R value to 0·060. A difference synthesis at this stage gave the coordinates of the H atoms, which were given the isotropic thermal parameters of their adjacent atoms and, although not refined, were included in the subsequent calculations. The final refinements, after elimination of two reflections suffering from extinction, yielded an R value of 0·037 for 1713 contributing reflections. The atomic coordinates of the non-hydrogen atoms are given in Table 1;* the positional parameters of the H atoms with their isotropic temperature factors are given in Table 2.

Discussion. The atomic numbering system commonly accepted for the benzomorphan class is given in Fig. 1, together with the bond lengths of the molecule. For easy comparison the rings are named in the same way

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* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34916 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.
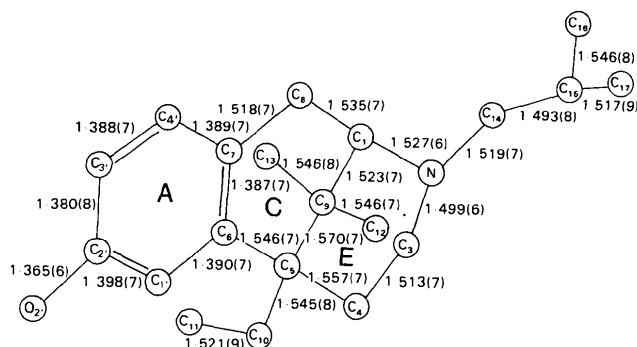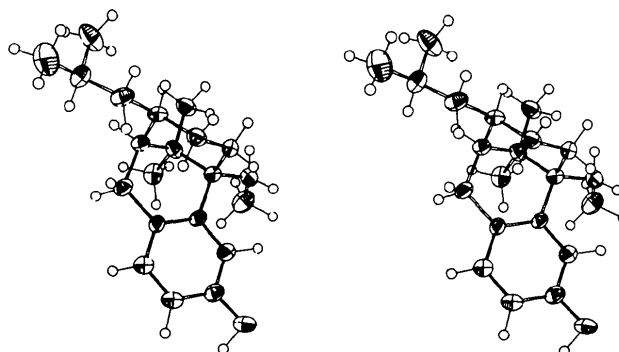

Fig. 2. Stereoscopic view of the protonated molecule with 50% probability thermal ellipsoids for the non-hydrogen atoms.

as in morphine (Gylbert, 1973). Bond angles are in Table 3.

An *ORTEP* stereopair (Johnson, 1965) of the (−)-5-ethyl-2′-hydroxy-2-isobutyl-9,9-dimethyl-6,7-benzomorphan cation is shown in Fig. 2.

The T shape of the fairly rigid morphine-like substances is displayed by the acute angle between planes A and E (86·5°); between the plane through A and C and the mean plane of E the angle is 83·9°. The
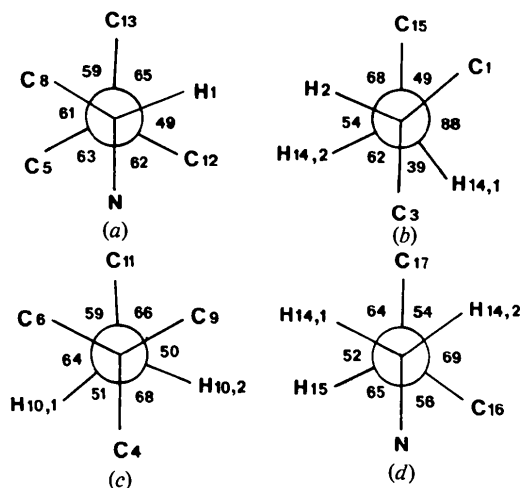
Fig. 3. Selected Newman projections, along (a) C(1)—C(9), (b) N—C(14), (c) C(5)—C(10), and (d) C(14)—C(15).

Table 4. *Selected torsion angles (°) with e.s.d.'s in parentheses*

Ring A		Ring E	
C(7)—C(6)—C(1')—C(2')	0·3 (7)	C(9)—C(1)—N—C(3)	−64·0 (5)
C(6)—C(1')—C(2')—C(3')	1·9 (8)	C(1)—N—C(3)—C(4)	57·1 (5)
C(1')—C(2')—C(3')—C(4')	−2·2 (8)	N—C(3)—C(4)—C(5)	−54·2 (5)
C(2')—C(3')—C(4')—C(7)	0·4 (7)	C(3)—C(4)—C(5)—C(9)	54·0 (5)
C(3')—C(4')—C(7)—C(6)	1·8 (8)	C(4)—C(5)—C(9)—C(1)	−56·3 (5)
C(4')—C(7)—C(6)—C(1')	−2·1 (7)	C(5)—C(9)—C(1)—N	62·8 (5)

Ring C		N side chain	
C(8)—C(1)—C(9)—C(5)	−61·4 (5)	C(1)—N—C(14)—C(15)	−49·1 (6)
C(1)—C(9)—C(5)—C(6)	59·4 (5)	C(3)—N—C(14)—C(15)	−175·4 (4)
C(9)—C(5)—C(6)—C(7)	−31·8 (6)	N—C(14)—C(15)—C(16)	−56·4 (6)
C(5)—C(6)—C(7)—C(8)	4·0 (7)	N—C(14)—C(15)—C(17)	−179·5 (4)
C(6)—C(7)—C(8)—C(1)	−3·9 (7)		
C(7)—C(8)—C(1)—C(9)	33·4 (6)		

torsion angles listed in Table 4 confirm the previously reported conformation of the benzomorphan nucleus (Gelders, De Ranter & Schenk, 1979, and references therein), in agreement with the chirality of laevorotatory benzomorphan molecules.

In Fig. 3 Newman projections are given along bonds involving the chiral centres C(1) and C(5), which can be described as (1R), (5R), and along the N side chain. The conformation of the isobutyl group very nearly fits that of the N side chain of the agonist/antagonist NCBME (Gelders, De Ranter & Overbeek, 1979) and the antagonists gemazocine and cyclazocine (Gelders, De Ranter & Schenk, 1979). This conformation may be expected to be that of minimum energy for the given molecule, as it exceeds the calculated energy minimum by only 9·6 kJ mol⁻¹. This small difference can be accounted for by packing forces in the crystal. In the calculations (Motherwell, 1974) only the intramolecular energy has been considered and the empirical constants used are those from Giglio (1969).

Bond lengths (Fig. 1) and bond angles (Table 3) do not show any outstanding features. By analogy with the previously determined benzomorphan compounds of this series, the packing in the crystal is mainly achieved by hydrogen bonds between Br, O and N atoms, values

Table 5. *Hydrogen-bond distances (Å) and angles (°) between donor and acceptor atoms*

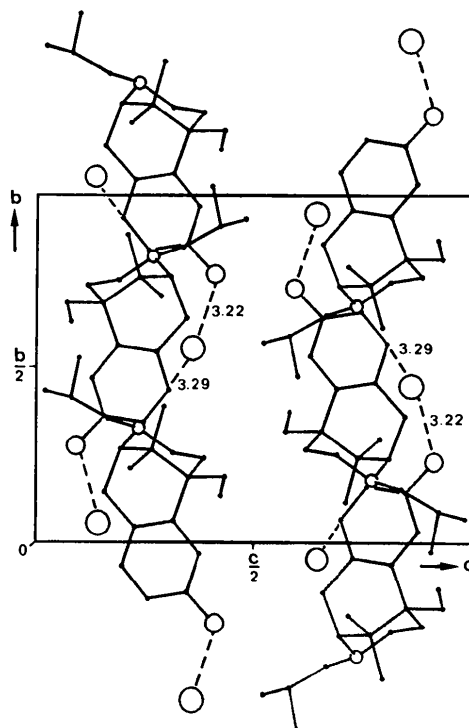| D—H···A	D—H···A	D···A	H···A	D—H
O(2')—H(2')···Br	120·3	3·217 (4)	2·567	1·04
N—H(N)···Br	142·0	3·292 (4)	2·500	0·94

Fig. 4. Projection in the (100) plane of the crystal structure showing the packing and the hydrogen-bond scheme. Large, medium and small circles represent Br, O and N atoms respectively.

for which are given in Table 5. The molecules are linked in endless chains parallel to the b axis (Fig. 4).

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