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(−)-(1*R*,5*R*,9*R*)-2-Ethoxyethyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan Hydrobromide*†

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Abstract. $C_{18}H_{28}NO_2^+.Br^-$, $M_r = 370{\cdot}336$, orthorhombic, $P2_12_12_1$, $a = 8{\cdot}0069\,(2)$, $b = 11{\cdot}6213\,(3)$, $c = 19{\cdot}7450\,(6)$ Å (refinement on θ only), $V = 1837{\cdot}28\,(9)$ Å^3, $Z = 4$, $D_m = 1{\cdot}33\,(2)$, $D_x = 1{\cdot}335$ Mg m^{-3}, $\lambda(\text{Cu }K\alpha) = 1{\cdot}54178$ Å, $\mu(\text{Cu }K\alpha) = 2{\cdot}38$ mm^{-1}, $F(000) = 776$, 291 K, final $R = 0{\cdot}034$ for 3055 observed reflections. The *N*-side-chain torsion angles starting from the asymmetric carbon towards the terminal methyl group are about at the global energy minimum in the four-dimensional torsional space: (−)-synclinal, (+)-synclinal, antiperiplanar and antiperiplanar respectively. An intramolecular (C—)H···O hydrogen bond is present.

Introduction. On the basis of *in vivo* pharmacological studies in mice the title compound was classified as a morphine-like agonist (Merz & Stockhaus, 1979). In spite of a large structural resemblance it lacks the kappa opioid properties of its (2″*S*)-*N*-tetrahydrofurfuryl analogue, of which it might be considered an opened ring counterpart. Only a moderate partial agonism has been observed in the rabbit vas deferens bioassay (Verlinde & De Ranter, 1988). The main purpose of this study is to gain further insight into the factors determining the conformation of the *N*-side chain, which is believed to be essential for opioid kappa activity (De Ranter, Verlinde, Blaton & Peeters, 1984).

Experimental. Crystals obtained at room temperature from an equimolar ethyl acetate–methanol solution. Density measured by flotation in *n*-heptane/CCl_4, ~0·5 × 0·2 × 0·2 mm, Hilger & Watts computer-controlled four-circle diffractometer, Ni-filtered Cu $K\alpha$ radiation, $\omega/2\theta$ scan technique ($2\theta_{\max} = 140°$, $0 \le h \le 8$, $0 \le k \le 14$, $-23 \le l \le 24$), cell dimensions by least-squares refinement of the θ values of 24 reflections with $44 < 2\theta < 50°$, space group $P2_12_12_1$ from systematic absences $h00$ for h odd, $0k0$ for k odd, $00l$ for l odd respectively. Four standard reflections (600, 060, 0010, $34\bar{3}$) monitored after each 50 reflections did not reveal a significant change in intensity. 3304 independent reflections measured (Friedel's law not obeyed), 3055 observed reflections [with $I > 3\sigma(I)$], Lorentz–polarization corrections, absorption corrections by the method of North, Phillips & Mathews (1968) with values between 0·997 and 0·818, scattering factors from Cromer & Mann (1968), and Stewart, Davidson & Simpson (1965) (for H), anomalous-dispersion correction for Br (*International Tables for X-ray Crystallography*, 1974).

The position of the Br was revealed through a Patterson synthesis at 0·25 0·225 0·215. Expansion of the model either by Fourier methods or by direct methods on the difference structure proved to be very hard. However, it was then realized that the Br atom is on a pseudo special position: it creates an inversion centre at 0 $\frac{1}{4}$ 0 yielding the space group *Pmcn*. Therefore the extra symmetry was destroyed and a Br at 0·22 0·225 0·215 served as input for *DIRDIF* (Beurskens *et al.*, 1981). The resulting *E* map now revealed the complete molecule. At this stage we again went through our earlier *DIRDIF* trials with the Br on the pseudo special position as an enantiomorph fixation procedure is present in the program to anticipate these troublesome cases. Indeed, in the maps a partial structure could now be recognized. Refinement with *XRAY76* (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976) by block-diagonal least squares on *F*, first with isotropic temperature factors and then

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* *Chemical Abstracts* name: (−)-(2*R*,6*R*,11*R*)-3-ethoxyethyl-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocin-8-ol hydrobromide.

† Structural Studies of Substituted 6,7-Benzomorphan Compounds. IX. Part VIII: Verlinde, Blaton, De Ranter & Peeters (1984).

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anisotropically; full-matrix least squares finally executed. H positions from ΔF synthesis included in refinement with fixed isotropic temperature factors of the atoms to whom they are attached; final $R = 0.034$, $wR = 0.051$ and $S = 0.12$, $w = (10.0 + |F_o| + 0.05|F_o|^2)^{-1}$; $(\Delta/\sigma)_{\rm ave} = 0.06$, $(\Delta/\sigma)_{\rm max} = 0.35$, $-0.99 \leq$ final $\Delta\rho$ excursions ≤ 0.49 e Å^{-3} (the minimum is near the Br).

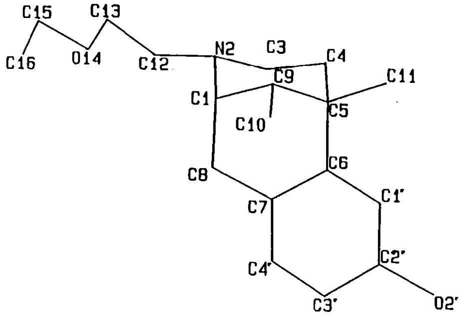

Fig. 1. Atomic numbering scheme.

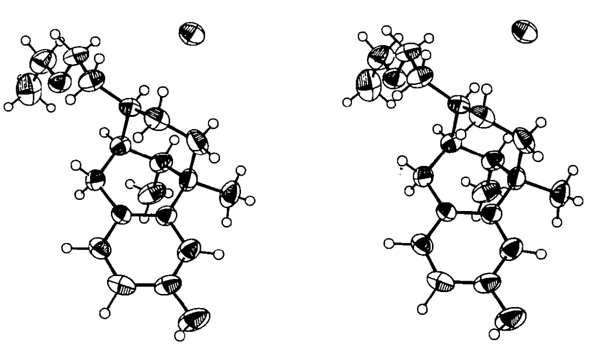

Fig. 2. Stereoscopic view of the title compound with 50% probability anisotropic displacement ellipsoids for the non-hydrogen atoms.

Table 1. *Atomic coordinates and equivalent isotropic thermal parameters with e.s.d.'s of the refined parameters in parentheses*

$$B_{\rm eq} = \tfrac{4}{3}\textstyle\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$B_{\rm eq}$(Å^2)
Br	−0·25756 (6)	0·26672 (3)	0·78522 (2)	5·33 (1)
C(1′)	−0·3774 (4)	−0·3211 (3)	0·8719 (2)	4·44 (9)
C(2′)	−0·3126 (5)	−0·4307 (3)	0·8731 (2)	4·29 (9)
O(2′)	−0·4240 (4)	−0·5201 (2)	0·8669 (1)	6·22 (9)
C(3′)	−0·1396 (5)	−0·4486 (3)	0·8800 (1)	4·26 (9)
C(4′)	−0·0389 (4)	−0·3519 (3)	0·8858 (1)	3·84 (8)
C(1)	−0·0586 (4)	−0·0211 (2)	0·8935 (1)	3·30 (7)
N(2)	−0·0612 (3)	0·0299 (2)	0·8227 (1)	3·37 (6)
C(3)	−0·1618 (4)	−0·0440 (2)	0·7756 (1)	4·09 (8)
C(4)	−0·3375 (5)	−0·0599 (3)	0·8024 (2)	4·81 (10)
C(5)	−0·3445 (4)	−0·1035 (2)	0·8767 (1)	3·83 (8)
C(6)	−0·2752 (4)	−0·2245 (2)	0·8791 (1)	3·49 (7)
C(7)	−0·1013 (3)	−0·2406 (2)	0·8858 (1)	3·30 (7)
C(8)	0·0189 (4)	−0·1411 (3)	0·8950 (1)	3·78 (8)
C(9)	−0·2395 (5)	−0·0220 (2)	0·9201 (1)	3·87 (7)
C(10)	−0·2385 (6)	−0·0514 (3)	0·9956 (1)	5·35 (10)
C(11)	−0·5284 (5)	−0·0994 (3)	0·9003 (3)	6·02 (14)
C(12)	0·1083 (5)	0·0583 (3)	0·7945 (1)	4·52 (9)
C(13)	0·1862 (5)	0·1648 (3)	0·8246 (1)	4·72 (9)
O(14)	0·2318 (3)	0·1469 (1)	0·8928 (1)	4·43 (6)
C(15)	0·3200 (6)	0·2411 (3)	0·9219 (2)	6·17 (13)
C(16)	0·3618 (7)	0·2161 (5)	0·9921 (3)	7·58 (17)

Table 2. *Bond lengths* (Å) *and bond angles* (°)

C(1′)—C(2′)	1·375 (5)	C(4)—C(5)	1·552 (5)
C(1′)—C(6)	1·396 (4)	C(5)—C(6)	1·512 (4)
C(2′)—O(2′)	1·375 (4)	C(5)—C(9)	1·530 (4)
C(2′)—C(3′)	1·407 (5)	C(5)—C(11)	1·546 (5)
C(3′)—C(4′)	1·387 (5)	C(6)—C(7)	1·411 (4)
C(4′)—C(7)	1·387 (4)	C(7)—C(8)	1·516 (4)
C(1)—N(2)	1·518 (3)	C(9)—C(10)	1·529 (4)
C(1)—C(8)	1·527 (5)	C(12)—C(13)	1·507 (5)
C(1)—C(9)	1·541 (5)	C(13)—O(14)	1·410 (4)
N(2)—C(3)	1·502 (4)	O(14)—C(15)	1·424 (5)
N(2)—C(12)	1·505 (4)	C(15)—C(16)	1·456 (7)
C(3)—C(4)	1·515 (5)		

C(2′)—C(1′)—C(6)	121·5 (3)	C(6)—C(5)—C(9)	110·9 (2)
C(1′)—C(2′)—O(2′)	117·0 (3)	C(6)—C(5)—C(11)	111·6 (3)
C(1′)—C(2′)—C(3′)	120·6 (3)	C(9)—C(5)—C(11)	109·6 (3)
O(2′)—C(2′)—C(3′)	122·4 (3)	C(1′)—C(6)—C(5)	122·0 (3)
C(2′)—C(3′)—C(4′)	117·4 (3)	C(1′)—C(6)—C(7)	118·7 (3)
C(3′)—C(4′)—C(7)	123·1 (3)	C(5)—C(6)—C(7)	119·2 (2)
N(2)—C(1)—C(8)	112·4 (2)	C(4′)—C(7)—C(6)	118·6 (3)
N(2)—C(1)—C(9)	107·7 (2)	C(4′)—C(7)—C(8)	118·8 (3)
C(8)—C(1)—C(9)	111·7 (2)	C(6)—C(7)—C(8)	122·5 (2)
C(1)—N(2)—C(3)	110·7 (2)	C(1)—C(8)—C(7)	115·8 (2)
C(1)—N(2)—C(12)	114·5 (2)	C(1)—C(9)—C(5)	109·2 (2)
C(3)—N(2)—C(12)	112·3 (2)	C(1)—C(9)—C(10)	109·3 (3)
N(2)—C(3)—C(4)	110·6 (2)	C(5)—C(9)—C(10)	114·3 (2)
C(3)—C(4)—C(5)	113·8 (3)	N(2)—C(12)—C(13)	114·1 (3)
C(4)—C(5)—C(6)	108·7 (2)	C(12)—C(13)—O(14)	111·3 (2)
C(4)—C(5)—C(9)	107·9 (2)	C(13)—O(14)—C(15)	113·6 (2)
C(4)—C(5)—C(11)	108·0 (3)	O(14)—C(15)—C(16)	110·2 (3)

Discussion. The atomic numbering scheme is given in Fig. 1 and parameters are listed in Table 1.* Bond lengths and angles are given in Table 2. *ORTEP* stereopairs (Johnson, 1965) are shown in Fig. 2. The typical benzomorphan nucleus is present: a planar aromatic ring, perpendicular to it a piperidine in the chair conformation, and an interconnecting six-membered ring which is midway between the half-chair and the half-boat. The absolute configuration of the three asymmetric carbon atoms was confirmed through comparison of the 105 most significant Bijvoet pairs. These were retained according to a selection procedure by Beurskens, Noordik & Beurskens (1980) with $N = 2$ and $N' = 6$. The Bijvoet coefficient proved to be exactly one ($s < 0.0001$). Bond lengths are fairly normal except for C(15)—C(16) which is badly affected by the large anisotropic displacement of both atoms involved. Repulsion between H(2′) and the phenyl ring opens up the C(3′)—C(2′)—O(2′) valence angle by some 2°. Considering the four torsion angles in the *N*-side chain

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* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, least-squares planes data and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51135 (23 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

starting from C(1) towards C(16) its conformation is essentially (–)-synclinal [–75·0 (4)]/(+)-synclinal [69·4 (4)]/antiperiplanar [174·5 (3)]/antiperiplanar [179·8 (4)°]. In order to evaluate the influence of packing effects on this conformation a potential-energy grid search of the four-dimensional torsional space of the isolated molecule was executed. For that purpose use was made of the program *EENY* (Motherwell, 1974) which calculates non-bonded van der Waals interactions, with parameters by Giglio (1969). The crystal coordinates were used except for the H positions which were optimized through *MMP*2 force-field calculations (Allinger & Flanagan, 1983). Only the section with the last two torsion angles antiperiplanar contained low-energy conformations with a global minimum present for the first two torsion angles at –55 and 95° respectively (Fig. 3). A possible cause for the small discrepancy between calculation and crystal structure is the presence of an intramolecular (C–)H···O hydrogen bond [C(1)···O(14) 3·038 (4), H(1)···O(14) 2·23 (4) Å, C(1)–H(1)···O(14) 133 (4)°]. This particular type of hydrogen bond has been crystallographically reviewed by Taylor & Kennard (1982). In their terminology the nearest-neighbour contact is 0·47 Å, and the angle of elevation of the H···O vector above the lone-pair plane of the oxygen atom is 22°. The fact that the (C–)H proton donor is immediately adjacent to a protonated N also complies with their findings. The suggested decrease of electron density at (C–)H through an inductive effect is a phenomenon supported by X-ray photoelectron spectra and CNDO/2 calculations by Sæthre, Carlson, Kaufman & Koski (1975) on morphine and congeners. For these compounds they clearly showed that only about 0·2 positive charge resides on the N while the remainder is delocalized over the neighbouring atoms. Since the observed structure is quite close to the calculated global minimum for the isolated molecule the absence of any serious packing effects on the *N*-side-chain conformation can be inferred. The packing of the crystal (Fig. 4) is essentially achieved by forming endless chains along **b** through hydrogen bonds between the phenol and bromide, and between bromide and piperidinium [N(2)···Br 3·254 (3), H(2)···Br 2·45 (4) Å, N(2)–H(2)···Br 162 (3)°, O(2′)···Br$^{\mathrm{i}}$ 3·242 (3), H(2′)···Br$^{\mathrm{i}}$ 2·49 (5) Å, O(2′)–H(2′)···Br$^{\mathrm{i}}$ 159 (4)°; (i) *x*,*y*–1,*z*].

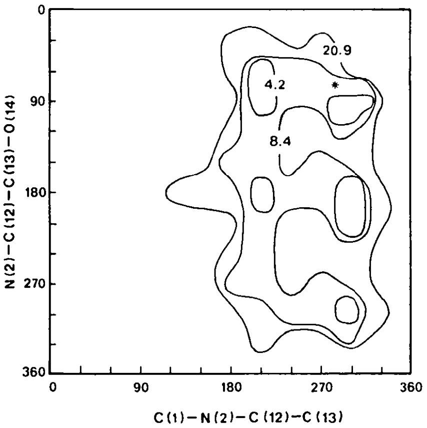

Fig. 3. Map of the intramolecular potential-energy calculations with both C(12)–C(13)–O(14)–C(15) and C(13)–O(14)–C(15)–C(16) antiperiplanar; the contours are in kJ mol^{-1}. The asterisk indicates the conformation adopted in the crystal.

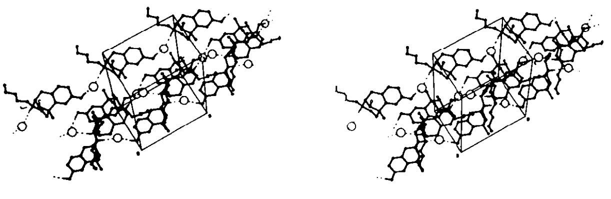

Fig. 4. Stereoscopic view of the crystal packing. Hydrogen bonds are indicated by dashed lines.

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