(−)-(1R,5R,9R)-2'-Hydroxy-2-(3-methoxypropyl)-5,9-dimethyl-6,7-benzomorphan Hydrobromide Monohydrate*†

By C. L. Verlinde, N. M. Blaton, O. M. Peeters and C. J. De Ranter‡

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

Abstract. $C_{18}H_{28}NO_2^+.Br^-.H_2O$, $M_r = 388\cdot344$, monoclinic, $P2_1$, $a = 10\cdot929$ (5), $b = 8\cdot110$ (3), $c = 10\cdot675$ (3) Å, $\beta = 96\cdot50(3)°$, $V = 940\cdot1$ (6)Å^3, $Z = 2$, $D_m = 1\cdot35$ (2), $D_x = 1\cdot372$ Mg m^{-3}, λ(Mo $K\alpha$) = $0\cdot71069$ Å, μ(Mo $K\alpha$) = $2\cdot18$ mm^{-1}, $F(000) = 408$, 291 K, final $R = 0\cdot034$ for 3040 observed reflections. The N-side-chain torsion angles starting from C(1) towards C(16) are at a local energy minimum in the four-dimensional torsional space: antiperiplanar, antiperiplanar, (−)-synclinal and antiperiplanar respectively. An intramolecular (C−)H⋯O hydrogen bond is present. The crystal packing is essentially determined by the water molecule.

Introduction. The structure of the title compound was determined as part of a structure–activity study on 6,7-benzomorphans. On the basis of *in vivo* pharmacological studies in mice it was classified as a morphine-like agonist (Merz & Stockhaus, 1979). The main purpose of this study lies in the determination of the N-side-chain conformation which is believed to be essential for opioid activity.

Experimental. Crystals obtained at room temperature from an equimolar ethyl acetate–methanol solution. Density measured by flotation in benzene/CCl$_4$, ~1·5 × 0·7 × 0·5 mm, Syntex $P2_1$ computer-controlled four-circle diffractometer, graphite-monochromated Mo$K\alpha$ radiation, ω-scan technique ($2\theta_{max} = 50°$, $0 \leq h \leq 12$, $-9 \leq k \leq 9$, $-12 \leq l \leq 12$), cell dimensions by least-squares refinement of the setting angles of 24 reflections with $26 < 2\theta < 30°$, space group $P2_1$ from systematic absences 0k0 for k odd. Three standard reflections (0$\overline{2}$0, 001, $\overline{3}$01) monitored after each 50 reflections decreased slowly to 89% of their initial intensity. 3307 independent reflections measured

(Friedel's law not obeyed), 3040 observed reflections [$I > 2\sigma(I)$]. Lorentz–polarization corrections, absorption corrections by the method of North, Phillips & Mathews (1968), 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 and served as input for *DIRDIF* (Beurskens *et al.*, 1981). The resulting E map showed the complete molecule, including the water molecule. Refinement with *XRAY76* (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976) by block-diagonal least squares on F, first with isotropic temperature factors and then anisotropically; full-matrix least squares finally executed. H positions from ΔF synthesis included in refinement with fixed isotropic temperature factors of the atoms to which they are attached increased by 10%; final $R = 0\cdot034$, $wR = 0\cdot046$ and $S = 0\cdot09$, $w = (25\cdot0 + |F_o| + 0\cdot10|F_o|^2)^{-1}$; $(\Delta/\sigma)_{ave} = 0\cdot10$, $(\Delta/\sigma)_{max} = 1\cdot46$ [for H(14B), the worst defined atom in the ΔF map], $-0\cdot81 \leq$ final $\Delta\rho$ excursions $\leq 0\cdot86$ e Å^{-3} (both near Br).

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. An *ORTEP* view (Johnson, 1965) is shown in Fig. 2. Bond lengths and angles are as expected. The fused-ring system is also normal: a flat aromatic ring connected to a six-membered half-boat ring, and a piperidine ring in the chair conformation perpendicular to it. Following the N-side chain from C(1) to C(16) an antiperiplanar [−162·4 (4)]/antiperiplanar [179·3 (4)]/(−)-synclinal [−63·1 (5)]/antiperiplanar [−177·5 (4)°] conformation is adopted. Empirical potential-energy calculations

---

Table 1. *Atomic coordinates* $(\times 10^4,$ Br $\times 10^5)$ *and equivalent isotropic thermal parameters with e.s.d.'s of the refined parameters in parentheses*

$$B_{eq} = \tfrac{4}{3}\Sigma_i\Sigma_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$B_{eq}(\text{Å}^2)$
Br	72889 (4)	150946*	68420 (4)	4·18 (1)
C(1')	8999 (3)	9098 (4)	2443 (3)	2·54 (7)
C(2')	8805 (3)	7593 (4)	1871 (3)	2·52 (8)
O(2')	9603 (2)	7075 (3)	1043 (2)	3·72 (7)
C(3')	7813 (3)	6624 (4)	2128 (3)	2·88 (8)
C(4')	7042 (3)	7200 (4)	2981 (3)	3·01 (9)
C(1)	6542 (3)	11020 (4)	4974 (3)	2·42 (8)
N(2)	7344 (2)	11032 (3)	6234 (2)	2·46 (7)
C(3)	8613 (3)	10404 (4)	6099 (3)	2·69 (9)
C(4)	9192 (3)	11366 (4)	5109 (3)	2·84 (8)
C(5)	8385 (3)	11437 (3)	3825 (3)	2·32 (7)
C(6)	8206 (2)	9707 (3)	3263 (2)	1·91 (6)
C(7)	7234 (2)	8726 (4)	3559 (3)	2·24 (7)
C(8)	6312 (3)	9302 (4)	4423 (3)	2·82 (8)
C(9)	7127 (3)	12150 (4)	4061 (3)	2·51 (8)
C(10)	6228 (4)	12411 (5)	2869 (3)	3·43 (9)
C(11)	9022 (3)	12586 (4)	2960 (4)	3·3 (1)
C(12)	6754 (2)	10097 (7)	7235 (2)	3·10 (7)
C(13)	7308 (4)	10508 (7)	8549 (4)	4·6 (1)
C(14)	6658 (4)	9539 (6)	9488 (4)	4·5 (1)
O(15)	5423 (2)	10041 (5)	9369 (2)	4·15 (6)
C(16)	4735 (5)	9266 (8)	10239 (4)	5·0 (1)
O(17)	8733 (3)	4481 (4)	−287 (3)	4·22 (8)

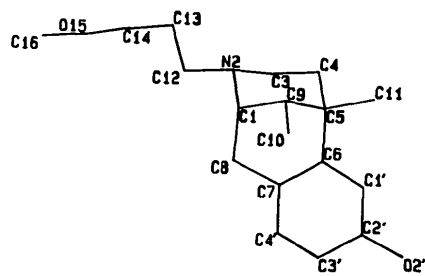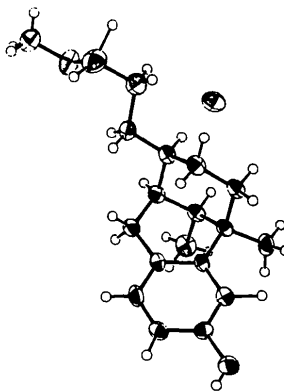* Parameter kept fixed for origin definition.

Fig. 1. Atomic numbering scheme.

Fig. 2. A view of the title compound with 50% probability anisotropic displacement ellipsoids for the non-hydrogen atoms.
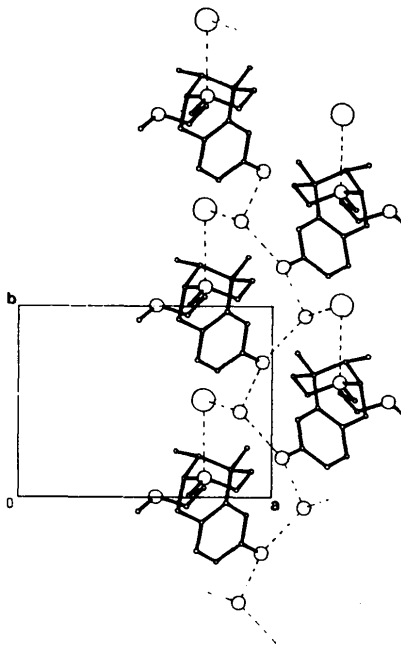
Table 2. *Bond lengths* (Å) *and bond angles* (°)

C(1')—C(2')	1·371 (5)	C(4)—C(5)	1·546 (4)
C(1')—C(6)	1·391 (4)	C(5)—C(6)	1·529 (4)
C(2')—O(2')	1·376 (4)	C(5)—C(9)	1·538 (4)
C(2')—C(3')	1·391 (5)	C(5)—C(11)	1·533 (5)
C(3')—C(4')	1·389 (5)	C(6)—C(7)	1·391 (4)
C(4')—C(7)	1·388 (4)	C(7)—C(8)	1·515 (5)
C(1)—N(2)	1·520 (4)	C(9)—C(10)	1·531 (5)
C(1)—C(8)	1·522 (5)	C(12)—C(13)	1·501 (5)
C(1)—C(9)	1·529 (5)	C(13)—C(14)	1·513 (7)
N(2)—C(3)	1·500 (4)	C(14)—O(15)	1·402 (5)
N(2)—C(12)	1·513 (5)	O(15)—C(16)	1·407 (6)
C(3)—C(4)	1·509 (5)		

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

with the program *EENY* (Motherwell, 1974) and constants by Giglio (1969) indicated this conformation as one of the lowest energy ones in the four-dimensional torsional space.

Several short contact distances are found in the crystal. One of these is an intramolecular (C—)H···O

Fig. 3. A view of the crystal along c showing the packing. Hydrogen bonds are indicated by dashed lines.

hydrogen bond [C(12)···O(15) 2·839 (4), H(12)···O(15) 2·60 (4) Å, C(12)—H(12*A*)···O(15) 97 (2)°] which is compatible with the description of Taylor & Kennard (1982): a nearest-neighbour contact of 0·41 Å, and the immediate adjacency of a positively charged N to the proton donor. This provides a reasonable explanation as to why the C(12)—C(13)—C(14)—O(15) torsion angle is (−)-synclinal instead of antiperiplanar.

The packing of the crystal (Fig. 3) is essentially due to the presence of the water molecule. This molecule serves twice as a proton donor [O(17)···Br^i 3·322 (4), H(17*B*)···Br^i 2·38 (5) Å, O(17)—H(17*B*)···Br^i 174 (4)°; O(17)···O(2′)^{ii} 2·846 (5), H(17*A*)···O(2′)^{ii} 2·20 (6) Å, O(17)—H(17*A*)···O(2′)^{ii} 172 (6)°; (i) *x*, *y*−1, *z*−1; (ii) −*x*+2, *y*−½, −*z*] and once as acceptor [O(2′)···O(17) 2·653 (5), H(2′)···O(17) 1·92 (5) Å, O(2′)—H(2′)···O(17) 171 (6)°]. A hydrogen bond between piperidinium and bromide is also present [N(2)···Br 3·359 (3), H(2)···Br 2·45 (5) Å, N(2)—H(2)···Br 169 (3)°].

References

BEURSKENS, P. T., BOSMAN, W. P., DOESBURG, H. M., GOULD, R. O., VAN DEN HARK, TH. E. M., PRICK, P. A. J., NOORDIK, J. H., BEURSKENS, G. & PARTHASARATHI, V. (1981). *DIRDIF*. Tech. Rep. 1981/2. Crystallography Laboratory, Toernooiveld, 6525 ED Nijmegen, The Netherlands.

CROMER, D. T. & MANN, J. B. (1968). *Acta Cryst.* A24, 321–324.

GIGLIO, E. (1969). *Nature (London)*, 222, 339–341.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

JOHNSON, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, USA.

MERZ, H. & STOCKHAUS, K. (1979). *J. Med. Chem.* 22, 1475–1483.

MOTHERWELL, S. (1974). *EENY*. Potential-energy calculation program, version of June 1974. Univ. of Cambridge, England.

NORTH, A. C. T., PHILLIPS, D. C. & MATHEWS, F. (1968). *Acta Cryst.* A24, 351–359.

STEWART, J. M., MACHIN, P. A., DICKINSON, C. W., AMMON, H. L., HECK, H. & FLACK, H. (1976). The *XRAY*76 system. Tech. Rep. TR-446. Computer Science Center, Univ. of Maryland, College Park, Maryland, USA.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* 42, 3175–3187.

TAYLOR, R. & KENNARD, O. (1982). *J. Am. Chem. Soc.* 99, 5063–5070.

VERLINDE, C. L., BLATON, N. M., PEETERS, O. M. & DE RANTER, C. J. (1988). *Acta Cryst.* In the press.

(−)-(1*R*,5*R*,9*R*,2″*R*)-2′-Hydroxy-5,9-dimethyl-2-[2-(tetrahydro-2-furyl)ethyl]-6,7-benzomorphan Hydrobromide*†

BY C. L. VERLINDE, N. M. BLATON, O. M. PEETERS AND C. J. DE RANTER‡

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

Abstract. $C_{20}H_{30}NO_2^+.Br^-$, $M_r = 396·37$, orthorhombic, $P2_12_12_1$, $a = 12·210 (7)$, $b = 17·219 (12)$, $c = 9·417 (5)$ Å, $V = 1980 (2)$ Å^3, $Z = 4$, $D_m = 1·33 (2)$, $D_x = 1·330$ Mg m^{-3}, $\lambda(Mo\ K\alpha) = 0·71069$ Å, $\mu(Mo\ K\alpha) = 2·21$ mm^{-1}, $F(000) = 832$, 291 K, final $R = 0·061$ for 1598 observed reflections. The N-sidechain torsion angles starting from C(1) towards O(15) are approximately at the global energy minimum in the three-dimensional torsional space: (−)-synclinal, antiperiplanar and (−)-synclinal respectively.

Introduction. Both the title compound and its 3″*S* diastereoisomer have been classified as morphine-like opioid analgesics on the basis of *in vivo* pharmacological tests in mice, and they are about equipotent (Merz & Stockhaus, 1979). In contrast, their counterparts with a methylene instead of an ethylene bridge between N and tetrahydrofuryl (Peeters, De Ranter & Blaton, 1982) display a marked stereoselectivity, with the 2″*S* form being roughly 300 times more potent than the 2″*R* form. The present structure determination together with that of its diastereoisomer should provide some insight into the observed abolition of stereoselectivity.