

5-Ethyl-2'-hydroxy-2-[(1-hydroxycyclopropyl)methyl]-9,9-dimethyl-6,7-benzomorphan Hydrochloride (Bremazocine),* C₂₀H₂₉NO₂.HCl†

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(Received 9 April 1984; accepted 30 May 1984)

Abstract. $M_r = 351.92$, monoclinic, $P2_1/n$, $a = 15.326$ (3), $b = 11.285$ (3), $c = 11.381$ (2) Å, $\beta = 108.17$ (2)°, $V = 1870$ (1) Å³, $Z = 4$, $D_m = 1.24$, $D_x = 1.250$ Mg m⁻³, $\lambda(\text{Mo } K\alpha) = 0.71069$ Å, $\mu(\text{Mo } K\alpha) = 0.220$ mm⁻¹, $F(000) = 760$, room temperature, final $R = 0.053$ for 1747 observed reflections. The (1-hydroxycyclopropyl)methyl side chain adopts a similar conformation to that in ketazocine, while the alcohol oxygen position and lone-pair orientation are those predicted for opiate kappa-agonist activity, as was suggested by the structure of (1*R*,5*R*,9*R*,13*S*)-*N*-(tetrahydrofurfuryl)normetazocine. The results of intramolecular potential-energy calculations are reported.

Introduction. Since bremazocine is classified as a putative opiate kappa-agonist (Römer, Büscher, Hill, Maurer, Petcher, Welle, Bakel & Akkerman, 1980) and possesses an alcohol oxygen instead of an ether or keto oxygen found in other benzomorphan kappa-agonists (Merz & Stockhaus, 1979; Martin, Eades, Thompson, Huppler & Gilbert, 1976), its structure was determined. Moreover, information on the orientation of the oxygen lone pairs seemed worthwhile for comparison with (1*R*,5*R*,9*R*,13*S*)-*N*-(tetrahydrofurfuryl)normetazocine (Peeters, De Ranter & Blaton, 1982), which displays the same action profile.

Experimental. Crystals obtained at room temperature from an equimolar ethyl acetate-methanol solution. Density measured by flotation in *n*-heptane/CCl₄, crystal $\sim 0.4 \times 0.3 \times 0.2$ mm, Syntex $P2_1$ computer-controlled diffractometer, graphite-monochromated Mo $K\alpha$ radiation, ω -scan technique ($2\theta_{\text{max}} = 46^\circ$, $0 \leq h \leq 16$, $-12 \leq k \leq 12$, $-12 \leq l \leq 11$), cell dimensions by least-squares refinement of the setting angles of 24 reflections with $15^\circ < 2\theta < 23^\circ$, space group $P2_1/n$ from systematic absences $0k0$, $h0l$ for k and $h+l$ odd respectively. Three standard reflections ($4\bar{1}0$, $10\bar{1}$, 021)

monitored after every 50 reflections showed 6% intensity fluctuation throughout data collection; 2611 independent reflections measured, 1747 observed reflections with $I > 2\sigma(I)$, Lorentz-polarization corrections, no absorption correction, scattering factors from Cromer & Mann (1968), and Stewart, Davidson & Simpson (1965) (for H), scattering factor for Cl corrected for anomalous dispersion (*International Tables for X-ray Crystallography*, 1974). The position of the chloride obtained from a sharpened Patterson synthesis served as input for *DIRDIF* (Beurskens, Bosman, Doesburg, Gould, van den Hark, Prick, Noordik, Beurskens & Parthasarathi, 1981). The resulting E map showed all non-hydrogen atoms present in the asymmetric unit. 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 performed; H positions from ΔF synthesis included in refinement with fixed positions and overall temperature factors; final $R = 0.053$, $R_w = 0.061$ and $S = 1.36$, $w = (50.0 + |F_o|)^{-1}$; $(\Delta/\sigma)_{\text{ave}} = 0.03$, $(\Delta/\sigma)_{\text{max}} = 0.31$, final $\Delta\rho$ excursions ≤ 10.38 e Å⁻³ (rejection ratio = 0.3).

Discussion. The atomic-numbering scheme is given in Fig. 1 and parameters are listed in Table 1. § Bond lengths and angles are given in Tables 2 and 3. An *ORTEP* (Johnson, 1965) stereoview of the molecule is shown in Fig. 2. Compared with previously determined benzomorphan compounds, the structure does not reveal any outstanding features. It should be remarked, however, that the typical C(5)–C(10)–C(11) bond angle, in the vicinity of 120°, for 5-ethyl-9,9-dimethyl-6,7-benzomorphan is also present here [118.8 (4)°]. Intramolecular potential-energy calculations using the program *EENY* (Motherwell, 1974), and empirical

* *Chemical Abstracts* name: 6-ethyl-1,2,3,4,5,6-hexahydro-3-[(1-hydroxycyclopropyl)methyl]-11,11-dimethyl-2,6-methano-3-benzazocin-8-ol hydrochloride.

† Structural Studies of Substituted 6,7-Benzomorphan Compounds. VIII. Part VII: Verlinde & De Ranter (1983).

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§ Lists of structure factors, anisotropic thermal parameters, H-atom coordinates, distances and angles involving H atoms, torsion angles and mean-plane calculations have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39556 (22 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

constants from Giglio (1969) reveal that this is mainly due to the steric influence of the C(13) methyl group which repels the C(11) methyl group. This is shown in Fig. 3 where the total intramolecular energy as well as the close-contact energy between these two methyl groups are presented as a function of the bond angle C(5)–C(10)–C(11). The crystal conformation corresponds to a minimum in the energy map (Fig. 4) for varying the C(5)–C(10)–C(11) bond angle *versus* the C(6)–C(5)–C(10)–C(11) torsion angle. The torsion angles reveal that the N side chain adopts a similar conformation to those in gemazocine and ketazocine (Gelders, De Ranter & Schenk, 1979; Verlinde & De Ranter, 1983). The N side chain was also explored in a conformational-energy study. The energy map for varying C(1)–N(2)–C(14)–C(15) and N(2)–C(14)–C(15)–O(15) angles sets the crystal conformation in a region of minimum energy. The map (Fig. 5) is quite similar to that for (1*R*,5*R*,9*R*,13*S*)-*N*-(tetrahydrofurfuryl)normetazocine (Peeters, De Ranter & Blaton, 1982), where the present conformation was one of the predicted minima. In that paper, this conformation was suggested to be responsible for a supplementary binding site, giving rise to the opiate kappa-agonist action profile.

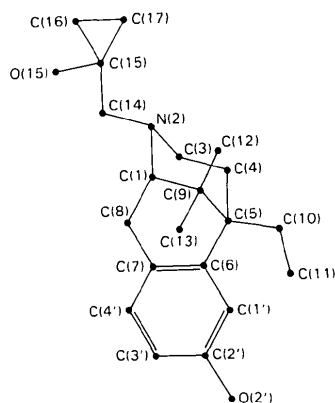


Fig. 1. Atomic-numbering scheme.

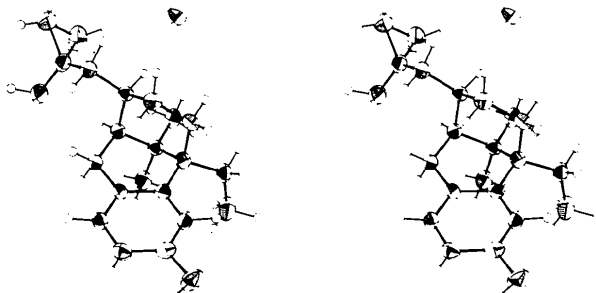


Fig. 2. Stereoscopic view of breamazocine. HCl with 50% probability thermal ellipsoids for the non-hydrogen atoms.

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

$$B_{eq} = \frac{4}{3} \sum_i \sum_j \beta_{ij} \mathbf{a}_i \cdot \mathbf{a}_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq} (Å ²)
Cl	8497 (1)	-2794 (1)	-1057 (1)	3.70 (3)
C(1')	8759 (2)	3102 (4)	948 (4)	2.64 (13)
C(2')	8467 (3)	4207 (4)	472 (4)	2.68 (13)
O(2')	9102 (2)	5116 (2)	755 (3)	3.91 (11)
C(3')	7568 (3)	4387 (4)	-247 (4)	2.82 (14)
C(4')	6983 (2)	3436 (4)	-521 (4)	2.59 (13)
C(1)	6953 (2)	68 (3)	-30 (4)	2.29 (12)
N(2)	7339 (2)	-500 (3)	-973 (3)	2.24 (10)
C(3)	8135 (3)	198 (4)	-1120 (4)	2.61 (13)
C(4)	8862 (2)	341 (4)	121 (4)	2.50 (13)
C(5)	8505 (2)	882 (4)	1148 (4)	2.38 (12)
C(6)	8166 (2)	2133 (3)	707 (3)	2.28 (12)
C(7)	7253 (2)	2294 (4)	-70 (4)	2.45 (12)
C(8)	6570 (2)	1297 (4)	-437 (4)	2.63 (13)
C(9)	7688 (2)	96 (4)	1258 (4)	2.44 (13)
C(10)	9356 (3)	886 (4)	2335 (4)	3.23 (14)
C(11)	9274 (3)	1469 (5)	3499 (5)	4.54 (18)
C(12)	7972 (3)	-1176 (4)	1699 (4)	3.29 (15)
C(13)	7204 (3)	607 (4)	2147 (4)	3.32 (15)
C(14)	6645 (3)	-755 (4)	-2215 (4)	2.61 (13)
C(15)	5822 (3)	-1427 (4)	-2137 (4)	2.86 (13)
O(15)	5146 (2)	-747 (3)	-1850 (3)	4.18 (11)
C(16)	5501 (3)	-2442 (4)	-3007 (5)	4.13 (17)
C(17)	5943 (3)	-2665 (5)	-1658 (5)	4.72 (18)

Table 2. Bond lengths (Å)

C(1')–C(2')	1.377 (6)	C(5)–C(6)	1.533 (6)
C(1')–C(6)	1.394 (6)	C(5)–C(9)	1.570 (6)
C(2')–O(2')	1.381 (5)	C(5)–C(10)	1.558 (5)
C(2')–C(3')	1.381 (6)	C(6)–C(7)	1.415 (5)
C(3')–C(4')	1.370 (6)	C(7)–C(8)	1.504 (6)
C(4')–C(7)	1.402 (6)	C(9)–C(12)	1.538 (6)
C(1)–N(2)	1.520 (6)	C(9)–C(13)	1.542 (7)
C(1)–C(8)	1.521 (6)	C(10)–C(11)	1.520 (8)
C(1)–C(9)	1.546 (5)	C(14)–C(15)	1.498 (7)
N(2)–C(3)	1.505 (6)	C(15)–O(15)	1.408 (6)
N(2)–C(14)	1.508 (4)	C(15)–C(16)	1.493 (7)
C(3)–C(4)	1.511 (5)	C(15)–C(17)	1.489 (7)
C(4)–C(5)	1.561 (7)	C(16)–C(17)	1.493 (8)

Table 3. Bond angles (°)

C(2')–C(1')–C(6)	121.4 (3)	C(5)–C(6)–C(7)	119.4 (3)
C(1')–C(2')–O(2')	117.5 (3)	C(4')–C(7)–C(6)	118.0 (3)
C(1')–C(2')–C(3')	120.6 (4)	C(4')–C(7)–C(8)	119.0 (3)
O(2')–C(2')–C(3')	121.9 (3)	C(6)–C(7)–C(8)	123.0 (3)
C(2')–C(3')–C(4')	118.7 (4)	C(1)–C(8)–C(7)	115.3 (3)
C(3')–C(4')–C(7)	122.6 (3)	C(1)–C(9)–C(5)	107.4 (3)
N(2)–C(1)–C(8)	111.6 (3)	C(1)–C(9)–C(12)	109.8 (3)
N(2)–C(1)–C(9)	110.4 (3)	C(1)–C(9)–C(13)	105.8 (3)
C(8)–C(1)–C(9)	111.6 (3)	C(5)–C(9)–C(12)	113.8 (3)
C(1)–N(2)–C(3)	111.4 (3)	C(5)–C(9)–C(13)	113.6 (3)
C(1)–N(2)–C(14)	115.3 (3)	C(12)–C(9)–C(13)	106.2 (4)
C(3)–N(2)–C(14)	110.7 (3)	C(5)–C(10)–C(11)	118.8 (4)
N(2)–C(3)–C(4)	109.8 (3)	N(2)–C(14)–C(15)	113.6 (3)
C(3)–C(4)–C(5)	114.4 (3)	C(14)–C(15)–O(15)	115.6 (3)
C(4)–C(5)–C(6)	106.1 (3)	C(14)–C(15)–C(16)	117.3 (4)
C(4)–C(5)–C(9)	108.2 (3)	C(14)–C(15)–C(17)	119.0 (4)
C(4)–C(5)–C(10)	104.8 (3)	O(15)–C(15)–C(16)	117.2 (3)
C(6)–C(5)–C(9)	110.4 (3)	O(15)–C(15)–C(17)	116.3 (4)
C(6)–C(5)–C(10)	112.8 (3)	C(16)–C(15)–C(17)	60.1 (3)
C(9)–C(5)–C(10)	113.9 (3)	C(15)–C(16)–C(17)	59.8 (3)
C(1')–C(6)–C(5)	121.6 (3)	C(15)–C(17)–C(16)	60.1 (3)
C(1')–C(6)–C(7)	118.7 (3)		

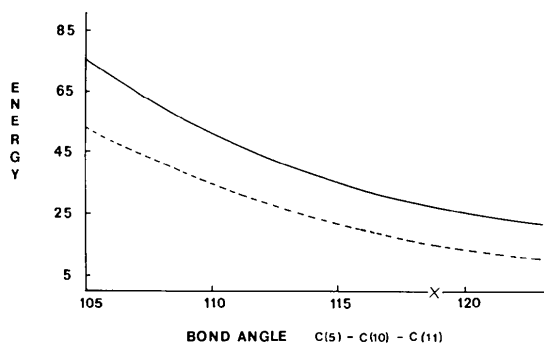


Fig. 3. Bond angle *versus* total intramolecular potential energy (full line) and close-contact energy between methyl(11) and methyl(13) (dashed line); energy in kJ mol^{-1} . The cross indicates the crystal bond angle.

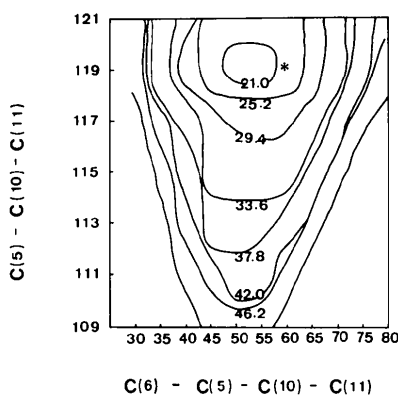


Fig. 4. Map of the intramolecular potential-energy calculations; the contours are in kJ mol^{-1} . The asterisk indicates the conformation adopted in the crystal.

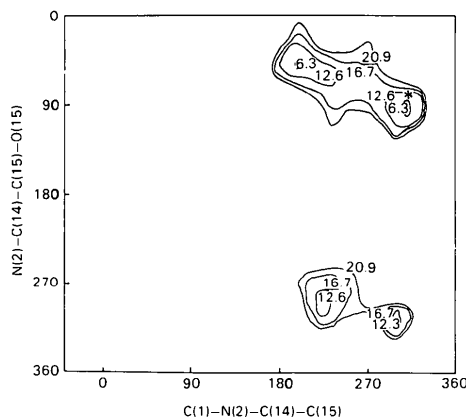


Fig. 5. Map of the intramolecular potential-energy calculations; the contours are in kJ mol^{-1} . The asterisk indicates the conformation adopted in the crystal.

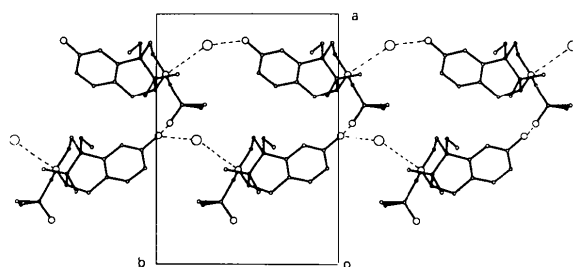


Fig. 6. A view of the crystal structure along *c* showing the packing. Hydrogen bonds are indicated by dashed lines.

The packing of the molecules in the crystal (Fig. 6) is essentially achieved by hydrogen bonds between the chloride ion and the phenolic O of one molecule and the N atom of a neighbouring molecule. The phenolic O is also bonded to the alcoholic O of a third molecule. Endless chains are thus formed parallel to *a* and the diagonal of *b* and *c* $\{N(2)\cdots Cl\ 3.157(4)$, $H(2)\cdots Cl\ 2.23(4)$ Å, $\angle N(2)-H(2)\cdots Cl\ 141(2)^\circ$; $O(2')\cdots Cl^i\ 3.079(4)$, $H(2')\cdots Cl^i\ 2.09(4)$ Å, $\angle O(2')-H(2')\cdots Cl^i\ 173(4)^\circ$; $O(15)\cdots O(2'')^i\ 2.788(5)$, $H(15)\cdots O(2'')^i\ 1.73(4)$ Å, $\angle O(15)-H(15)\cdots O(2'')^i\ 165(4)^\circ$ [symmetry operations: (i) $x, y+1, z$; (ii) $x-\frac{1}{2}, -y+\frac{1}{2}, z-\frac{1}{2}$].

The authors thank ACF CHEMIEFARMA NV-Maarssen for providing the title compound.

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