

Crystal and molecular structure of analgesics, I. Ciramadol hydrobromide, C₁₅H₂₃O₂N · HBr¹

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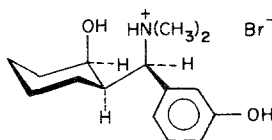
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Introduction

The structural formula of the title compound is



The synthesis, relative stereochemistry, and preliminary biological activity of ciramadol hydrochloride, a potent benzylamine analgesic, have been reported (Yardley et al., 1978).

In view of the continued clinical interest in ciramadol (Staquet, 1980), an X-ray crystallographic study was performed both as a check on the relative configurations of the three adjacent chiral centers and to determine the absolute configuration. The actual determinations were made on a hydrobromide salt prepared specifically for this project. In addition, this compound offers the opportunity of observing the N⁺-H ··· Br⁻ hydrogen bond, which has been a subject of interest recently in these laboratories. It was also expected that the infrequently observed O-H ··· Br⁻ hydrogen bond would be present.

¹Systematic name: (-)-(1R*, 2R*)-2-[(R*)-α-(Dimethylamino)-m-hydroxybenzyl]cyclohexanol hydrobromide.

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Experimental

A crystal, $0.55 \times 0.3 \times 0.3$ mm, was mounted, after preliminary photographic work, on a Syntex $P2_1$ automatic diffractometer. The data set was collected with graphite monochromated Cu $K\alpha$ radiation using the θ - 2θ scan technique over a dispersion-corrected base width of 2° ; the scan speed was variable over the range 2.02 – 29.30° per minute. Frequent measurement of the intensities of standard reflections showed no decay with time. Structure amplitudes were obtained in the usual way; absorption corrections were not made. Crystal data and details of the data collection are given in Table 1.

Structure Solution and Refinement

The structure was solved using Patterson superposition and Fourier procedures. The positions of the bromide ions were obtained from a sharpened $P(uvw)$ function. Four-fold superposition of these positions revealed most of the remaining atoms (except hydrogen). The missing atoms were located in a subsequent electron density function phased with the atoms already found. The structure was then refined by full-matrix least squares (Gantzel et al., 1969; Carrell, 1976). The nonhydrogen atoms, after initial isotropic refinement, were then refined anisotropically. A difference map at this stage revealed 23 of the 24 hydrogen atoms. The missing hydrogen atom, which is bonded to O(6), was not included in subsequent calculations. The weights, w , for $|F_{hkl}|$ were $\sigma^{-2}(F)$, with $w = 0$ for reflections below the threshold values. The least-squares function minimized was $\sum w(|F_o| - |F_c|)^2$. The scattering factors for carbon, nitrogen, oxygen, and bromide were those

Table 1. Crystal data and data collection

Formula	$C_{15}H_{24}O_2N^+Br^-$
M_x	330.28
Lattice constants	$a = 11.256(2)$ Å $b = 16.591(2)$ $c = 8.500(2)$
Space group	$P2_12_12_1$
Z	4
D_x	1.38 g cm $^{-3}$
$(\sin \theta / \lambda)_{\max}$	0.61 Å $^{-1}$
Number of unique reflections	1715
Threshold	$I_o = 2.33 \sigma(I)$
Number of reflections below threshold	57
$\sigma(I)$	counting statistics
$\sigma(F)$	$\sigma(F) = (F/2) \{[\sigma^2(I)/F^2] + \delta^2\}^{1/2}$, where δ (instrumental uncertainty) = 0.034

of Cromer and Mann (1968) and for hydrogen those of Stewart et al. (1965). Anomalous scattering factors for bromide were those of Cromer and Liberman (1970). Reflections 031 and 102, with $\Delta F/\sigma(F)$ of 42.9 and 13.0, respectively, appeared to be suffering from extinction and were assigned $w = 0$. The final R value for observed data was 4.4%. The final refined positional and thermal parameters, with their estimated standard deviations, are listed in Tables 2 and 3.

Computer programs used also included the CRYSDNET series (Bernstein et al., 1974), and the graphics programs VIEW (Carrell, 1976) and DOCK (Badler et al., 1979).

Discussion

Stereochemistry

A view of the molecule in the plane of the benzene ring is shown in Fig. 1. The cyclohexane ring is in the expected chair conformation, with the hydroxyl substituent axial and *cis* to the bond to the central carbon atom. Figure 1 also shows the correct absolute configuration of ciramadol hydrobromide, which is $(-)-(1R,2R)$ -2-[(*R*)- α -(dimethylamino)-*m*-hydroxybenzyl]cyclohexanol hydrobromide. The positional parameters of Table 2 were used in the preparation of Fig. 1, and in the calculation of the data of Table 4, which demonstrates that the absolute configuration has been correctly determined.

Bond distances and angles

The molecular geometry is shown in Fig. 2 and 3. There are no surprises: the average observed C–C bond distance in the benzene ring is 1.385 Å, r.m.s. 0.010 Å, as compared with the average σ_{C-C} from the least squares of 0.005 Å; the corresponding values for the cyclohexyl ring are 1.520 Å, 0.015 Å, and 0.008 Å.

The 20 C–H bond distances vary from 0.78 Å to 1.17 Å, e.s.d., 0.09 Å, compared with σ_{C-H} of 0.05 Å from the least squares.

The ten bond angles of the benzene ring, internal and external, expected to be 120° for sp^2 hybridization, average to 120.0°, e.s.d. 1.5°; the ten bond angles of the cyclohexane ring, expected value 109.5°, average to 110.8°, e.s.d. 2.1°. The covalent quantities are thus in pleasing agreement with the expected values.

Molecular packing and hydrogen bonding

A stereo view of one unit cell is shown in Fig. 4. There are no abnormally short intermolecular nonbonded distances. The structure is held together by a network of O–H \cdots Br⁻ and N⁺–H \cdots Br⁻ hydrogen bonds.

Table 2. Positional and thermal parameters for the nonhydrogen atoms^a

Atom	x	y	z	B ₁₁	B ₂₂	B ₃₃	B ₁₂	B ₁₃	B ₂₃
Br	0.87394(4)	0.90680(3)	0.43229(7)	2.35(2)	7.22(2)	7.09(3)	-0.30(2)	0.29(2)	3.09(3)
O(C(6))	-0.3779(3)	0.6718(2)	0.4575(4)	2.7(1)	3.3(1)	7.0(2)	0.3(1)	0.8(1)	-1.3(1)
O(C(15))	0.0651(6)	0.6170(2)	-0.0220(4)	15.4(4)	8.0(2)	2.8(1)	-5.7(3)	1.2(2)	-0.9(1)
N	0.0927(3)	0.5792(2)	0.4766(3)	2.2(1)	3.1(1)	2.60(9)	-0.22(7)	0.0(1)	0.4(1)
C(1)	0.0556(4)	0.6349(3)	0.6036(5)	3.7(2)	5.6(2)	2.5(1)	-0.5(2)	0.1(1)	-0.7(1)
C(2)	0.0851(5)	0.4925(3)	0.5285(6)	4.4(2)	3.6(1)	5.5(2)	-0.1(2)	-0.4(2)	1.8(2)
C(3)	0.0307(3)	0.5915(2)	0.3191(4)	2.4(1)	2.5(1)	2.4(1)	0.0(1)	0.1(1)	-0.7(1)
C(4)	-0.1015(3)	0.5756(2)	0.3316(4)	2.2(2)	2.5(1)	2.5(1)	-0.2(1)	0.2(1)	0.2(1)
C(5)	-0.1821(3)	0.6327(2)	0.3905(4)	2.4(2)	2.5(1)	3.3(1)	-0.1(1)	0.2(1)	-0.2(1)
C(6)	-0.3071(3)	0.6145(2)	0.3972(5)	2.6(2)	2.6(1)	3.1(1)	0.1(1)	0.2(1)	0.0(1)
C(7)	-0.3443(4)	0.5407(2)	0.3476(5)	2.6(2)	3.4(1)	3.8(1)	-0.3(1)	-0.9(1)	0.3(1)
C(8)	-0.2658(4)	0.4853(2)	0.2879(7)	3.0(2)	3.3(1)	6.5(3)	-0.7(2)	-0.1(2)	-1.8(2)
C(9)	-0.1446(4)	0.5018(2)	0.2815(5)	2.9(2)	3.0(1)	4.6(2)	0.2(1)	0.0(2)	-1.3(1)
C(10)	0.0662(3)	0.6732(2)	0.2438(4)	2.4(2)	3.1(1)	2.5(1)	0.0(1)	0.3(1)	0.3(1)
C(11)	0.1950(4)	0.6916(2)	0.2416(5)	2.8(2)	3.4(1)	4.3(2)	-0.4(1)	0.4(1)	0.9(1)
C(12)	0.2179(4)	0.7735(3)	0.1635(6)	3.9(2)	4.0(1)	5.2(2)	-1.5(2)	0.2(2)	1.3(2)
C(13)	0.1656(6)	0.7784(3)	-0.0009(7)	5.6(2)	6.0(2)	4.5(2)	-1.5(2)	0.7(2)	2.4(2)
C(14)	0.0367(6)	0.7576(4)	0.0025(8)	6.2(3)	8.4(3)	4.9(2)	-1.8(3)	-1.1(3)	3.7(3)
C(15)	0.0111(5)	0.6763(4)	0.0767(6)	5.1(2)	8.6(3)	4.1(2)	-3.3(3)	-1.6(2)	2.7(2)

^aEstimated standard deviations with respect to the last digit reported are in parentheses. The anisotropic temperature factor expression is $T = \exp[-\frac{1}{2}(h^2 a^{*2} B_{11} + k^2 b^{*2} B_{22} + l^2 c^{*2} B_{33} + 2hka^*b^*B_{12} + 2hla^*c^*B_{13} + 2klb^*c^*B_{23})]$.

Table 3. Positional and thermal parameters for the hydrogen atoms^a

Atom	x	y	z	B	Atom	x	y	z	B
H(OC(15))	0.063(9)	0.558(6)	0.13(10)	10(2)	H(C9)	-0.093(5)	0.461(3)	0.225(3)	4(1)
H(N)	0.179(7)	0.590(4)	0.441(8)	8(2)	H(C(10))	0.022(5)	0.719(3)	0.296(6)	5(1)
H(1C)	0.061(4)	0.687(2)	0.552(5)	3(1)	H(1C(11))	0.241(6)	0.697(3)	0.364(8)	6(1)
H(2C(1))	-0.019(6)	0.615(3)	0.645(8)	6(2)	H(2C(11))	0.233(4)	0.653(3)	0.180(6)	4(1)
H(3C(1))	0.093(6)	-0.379(3)	0.707(7)	6(1)	H(1C(12))	0.161(4)	0.822(3)	0.230(5)	3(1)
H(1C(2))	0.117(4)	0.463(3)	0.450(5)	4(1)	H(2C(12))	0.306(6)	0.788(3)	0.180(7)	5(1)
H(3C(2))	-0.008(5)	0.482(3)	0.569(7)	6(1)	H(1C(13))	0.143(6)	0.836(4)	-0.020(8)	7(2)
H(2C(2))	0.129(6)	0.496(4)	0.633(8)	8(2)	H(2C(13))	0.211(5)	0.742(3)	-0.063(6)	4(1)
H(C(3))	0.068(3)	0.554(2)	0.267(4)	2(1)	H(1C(14))	0.001(4)	0.784(2)	0.059(5)	3(1)
H(C(5))	-0.149(4)	0.684(3)	0.428(5)	4(1)	H(2C(14))	-0.029(8)	0.767(4)	-0.066(10)	8(2)
H(C(7))	-0.426(4)	0.531(2)	0.351(5)	3(1)	H(C(15))	0.069(6)	0.670(4)	0.098(8)	7(2)
H(C(8))	-0.283(6)	0.425(3)	0.263(7)	6(1)					

^aEstimated standard deviations as in Table 2. The isotropic temperature factor expression is: $T = \exp(-B \sin^2 \theta / \lambda^2)$.

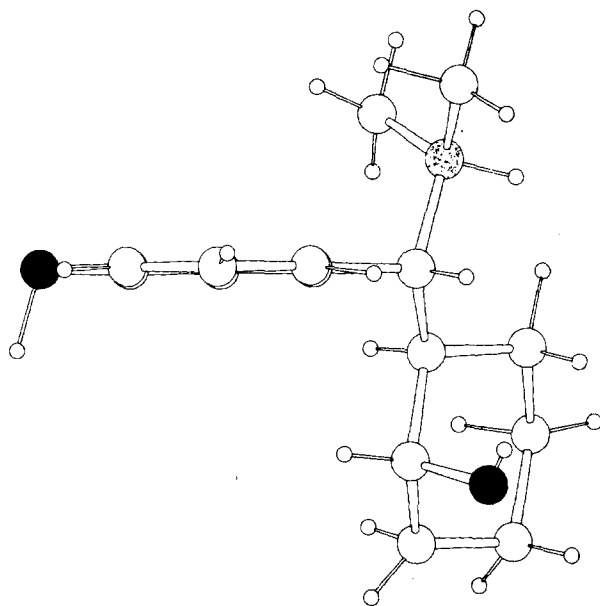


Fig. 1. The molecule as viewed with the plane of the benzene ring edge-on. Large open circles, carbon; small open circles, hydrogen; filled circles, oxygen; stippled circle, nitrogen.

Table 4. Absolute configuration data^a

hkl	RI_{obs}	RI_{calc}	hkl	RI_{obs}	RI_{calc}
521	+0.09	+0.07	182	+0.08	+0.05
511	+0.08	+0.07	171	+0.08	+0.06
342	-0.08	-0.09	162	-0.09	-0.09
272	-0.12	-0.12	161	+0.10	+0.09
262	+0.15	+0.14	142	+0.07	+0.07
212	+0.12	+0.12	114	+0.15	+0.12

^a $RI = (I_+ + I_-)/(I_+ - I_-)$, where I_+ is intensity of (hkl) , and I_- of $(\bar{h}\bar{k}\bar{l})$. For Br^- and $\text{Cu } K\alpha$, $\Delta f'' = 0.8$ and $\Delta f''' = +0.128$. The table includes all reflections with $|RI_{\text{obs}}| > 0.06$.

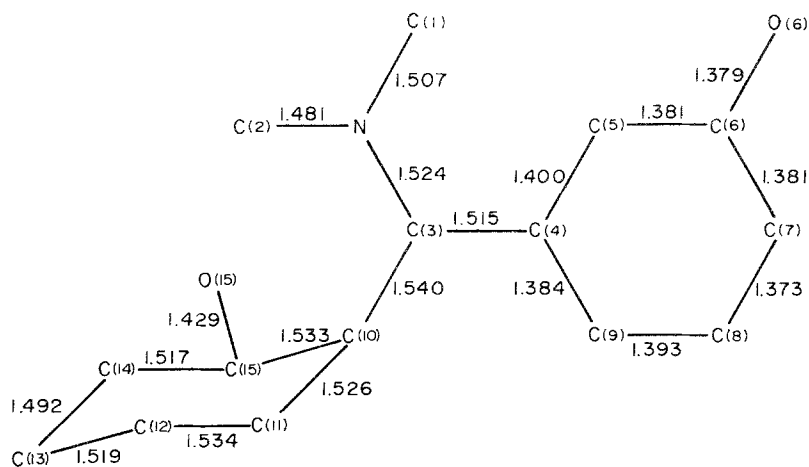


Fig. 2. Covalent bond distances. The standard errors are in the range 0.005–0.007 Å.

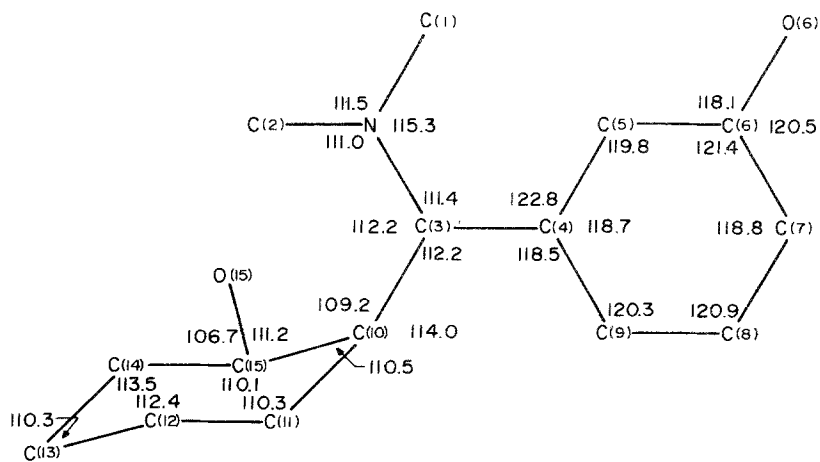


Fig. 3. Covalent bond angles. The standard errors are in the range 0.2–0.4°.

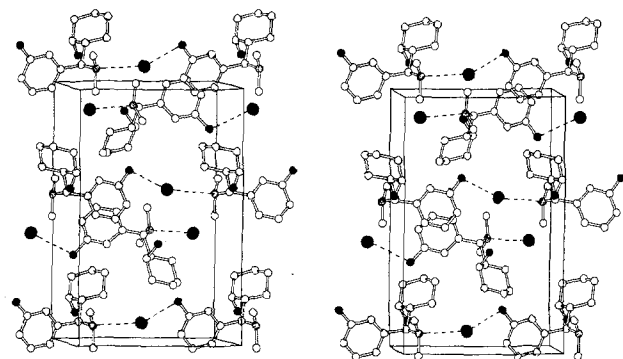


Fig. 4. Stereo view of one unit cell. Hydrogen bonds are shown as dashed lines.

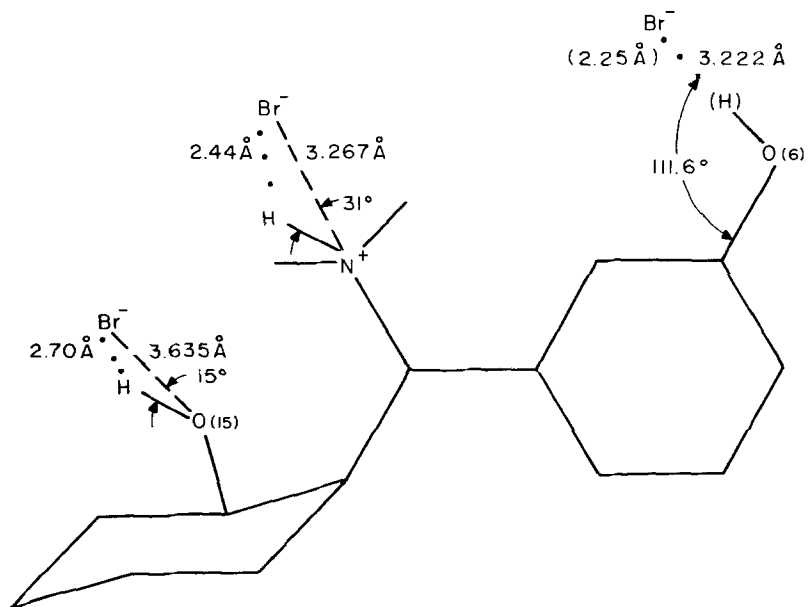


Fig. 5. Details of the hydrogen bonding scheme. (The two methyl groups on the nitrogen atom are not shown.)

The details of the hydrogen bonding scheme are shown in Fig. 5. Although, for unknown reasons, H(O(6)) did not appear in the difference map, its position can be inferred, with a fair degree of confidence, as shown in Fig. 5.

Acknowledgments

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