Structure of β(±)-3-(1-Allyl-2,3-dimethyl-3-piperidyl)phenol Hydrobromide*

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Abstract. $C_{16}H_{24}NO^+.Br^-$, $M_r = 326.29$, orthorhombic, *Pcab*, $a = 13.812$ (2), $b = 19.841$ (3), $c = 11.995$ (2) Å, $V = 3287.16$ Å^3, $Z = 8$, $D_m = 1.318$, $D_x = 1.318$ Mg m^{-3}, $\lambda(Cu\,K\alpha_1) = 1.54056$ Å, $\mu = 3.358$ mm^{-1}, $F(000) = 1360$, $T = 297$ K, $R = 0.046$ for 2342 observed reflexions. In the solid state, this narcotic antagonist has the piperidine ring in the chair form with the 1-allyl, 2-methyl and 3-aryl all equatorial, while the 3-methyl is axial. The molecular structure is basically the same as that of the α isomer, except for the conformation of the 3-methyl and the orientations, in the solid state, of the aryl and allyl groups. Intermolecular hydrogen bonds, N–H⋯Br⋯H–O, link the molecules into zigzag chains parallel to **a**.

Introduction. The original purpose in undertaking structural analyses by X-ray diffraction of the α and β isomers of the title compound (I) was to check the stereochemistry in the solid state, and to determine absolute configurations for comparison with related chiral centres of (−)-morphine. For the α(−)-1-allyl-2,3-dimethyl-3-arylpiperidine hydrobromide, these objectives were accomplished and reported (Ahmed, 1984), but the crystal sample of the β isomeric form used for the present study was found to be a racemate β(±). Consequently, the stereochemical assignment was determined but not the absolute configuration. The β(+) enantiomorph is known to be a more active narcotic antagonist than the corresponding β(−).

(I)
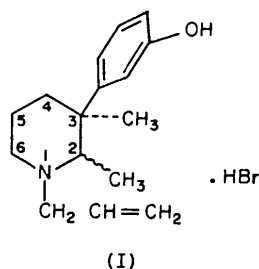
Experimental. Crystals obtained from mixture of ethanol and ether; density by flotation in aqueous KI

solution. Nearly spherical crystal $0.27 \times 0.33 \times 0.37$ mm; Enraf–Nonius CAD-4 diffractometer; Ni-filtered Cu radiation. Cell parameters from least-squares fit of θ values of 20 reflexions with $34 \leq \theta \leq 52°$. *hkl* intensity data to $\theta = 75°$, $h = 0$ to 17, $k = 0$ to 24, $l = 0$ to 14; ω–2θ scans, $\Delta\omega = (1.0 + 0.14 \tan\theta)°$ plus 50% for backgrounds. Three standard reflexions every hour, max. variation $\pm 5\%$ from mean. 3380 independent reflexions measured, 2342 observed with $I \geq 3.0\sigma(I)$. Corrections for scale variation and Lorentz and polarization effects, absorption ignored because crystal faces not well defined; estimated absorption correction 2.48 to 3.46. Non-centro-symmetric space group $Pca2_1$ with two independent molecules in asymmetric unit assumed, structure derived by heavy-atom method, H atoms located from difference map. Then realized that the two molecules were related so space group changed to *Pcab* with one molecule in asymmetric unit. Block-diagonal least-squares refinement of atomic parameters (including H with isotropic thermal parameters) minimized $\sum w(|F_o| - |F_c|)^2$, $w = \{1 + [(|F_o| - 20)/30]^2\}^{-1}$, convergence at $R = 0.046$ for observed reflexions, $wR = 0.061$, $S = 1.46$, mean $(\Delta/\sigma) = 0.05$, max. $(\Delta/\sigma) = 0.21$ (0.51 for H). Residual electron density in final difference map -0.62 to 0.42 e Å^{-3}, most of largest perturbations near Br. Scattering-factor curves from *International Tables for X-ray Crystallography* (1974) and Stewart, Davidson & Simpson (1965) for H. Computations with *NRC* system (Ahmed, Hall, Pippy & Huber, 1973) and *ORTEP* (Johnson, 1971). The refined atomic parameters are listed in Table 1.†

Discussion. An *ORTEP* drawing showing the molecular stereochemistry of the β isomer is presented in Fig. 1. It corresponds to the molecule listed in Table 1 and the same enantiomorph as the α(−).HBr isomer already determined (Ahmed, 1984). However, it should be noted that the two opposite enantiomorphs are present in the crystal structure, and consequently the absolute

configurations of the β(+) and β(−) molecules have not been determined. As expected, the piperidine ring has the chair conformation with the substituents 1-allyl, 2-methyl and 3-aryl equatorial and the 3-methyl axial. Thus the α and β isomers differ mainly in the configuration of the 2-methyl substituent. In addition, the two isomers in the solid state have widely differing orientations for the aryl and allyl groups as shown by the first three torsion angles in Table 2. These differences have resulted in small variations of 1 to 6° in the torsion angles of the piperidine ring as shown in Table 2; the three largest differences, of 3·2–6·0 (6)°, involve C(2), whose methyl substituent has a different configuration in the two isomers.

Space-filling (Fisher–Hirschfelder–Taylor) models of the two isomers show clearly that a change in the configuration of the 2-methyl substituent requires some conformational changes in the 1-allyl and 3-aryl substituents. Recent conformational-energy calculations by Froimowitz (1986) performed with Allinger & Yuh's (1980) *Molecular Mechanics II (MM2)* program, without access to the present crystallographic results, have shown that minimum energies for the α and β isomers correspond to an equatorial aryl group with C(2)—C(3)—C(9)—C(14) = −64 and −179° for the two isomers respectively. The calculations agree very well with the crystallographic results reported here and by Ahmed (1984), where both molecules are shown to have an equatorial 3-aryl substituent with C(2)—C(3)—C(9)—C(14) = −62·3 (4) and −178·1 (4)°, as listed in Table 2 for the α and β isomers respectively.

Table 1. *Fractional coordinates* ($\times 10^4$, Br $\times 10^5$, H $\times 10^3$) *and equivalent isotropic temperature factors* (Å^2) *for space group Pcab* [*No.* 61, *equivalent positions are* $\pm(x, y, z; -x, \frac{1}{2}-y, \frac{1}{2}+z; \frac{1}{2}-x, \frac{1}{2}+y, -z; \frac{1}{2}+x, -y, \frac{1}{2}-z)$]

$$B_{eq} = \tfrac{8}{3}\pi^2 \textstyle\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j.$$

	x	y	z	B_{eq}/B
Br	35391 (3)	72254 (2)	91687 (4)	4·8
O	7183 (2)	3936 (1)	6900 (3)	5·2
N(1)	4940 (2)	7271 (1)	6940 (3)	3·5
C(2)	5768 (3)	6756 (2)	6793 (4)	3·9
C(3)	5353 (3)	6042 (2)	6579 (4)	3·9
C(4)	4621 (3)	6070 (2)	5622 (4)	4·8
C(5)	3820 (4)	6565 (2)	5821 (5)	5·3
C(6)	4238 (3)	7273 (2)	6017 (4)	4·6
C(7)	6462 (4)	6774 (3)	7767 (5)	6·1
C(8)	4871 (4)	5773 (2)	7642 (4)	5·4
C(9)	6211 (3)	5590 (2)	6220 (3)	3·6
C(10)	6400 (3)	4973 (2)	6743 (3)	3·8
C(11)	7090 (3)	4533 (2)	6328 (4)	3·8
C(12)	7635 (3)	4690 (2)	5408 (4)	4·7
C(13)	7452 (4)	5304 (2)	4888 (5)	5·6
C(14)	6772 (4)	5752 (2)	5291 (4)	4·7
C(15)	5361 (4)	7972 (2)	7115 (5)	5·3
C(16)	4588 (5)	8502 (2)	7135 (6)	7·3
C(17)	4498 (7)	8972 (3)	6415 (8)	10·3
H(O)	748 (4)	373 (2)	669 (4)	3·4 (11)
H(N)	460 (2)	717 (2)	747 (3)	0·5 (7)

Table 2. *Comparison of the torsion angles* (°) *in the* α *and* β *isomers*

The values for the β isomer are for the enantiomorph listed in Table 1.

	α	β
C(2)—N(1)—C(15)—C(16)	−53·9 (5)	173·6 (4)
N(1)—C(15)—C(16)—C(17)	130·0 (5)	−115·2 (7)
C(8)—C(3)—C(9)—C(14)	−62·3 (4)	−178·1 (4)
Piperidine ring		
N(1)—C(2)—C(3)—C(4)	55·2 (4)	51·9 (4)
C(2)—C(3)—C(4)—C(5)	−54·3 (4)	−56·1 (5)
C(3)—C(4)—C(5)—C(6)	54·7 (5)	57·4 (5)
C(4)—C(5)—C(6)—N(1)	−54·8 (5)	−55·7 (5)
C(5)—C(6)—N(1)—C(2)	59·1 (4)	55·0 (4)
C(6)—N(1)—C(2)—C(3)	−59·7 (4)	−53·7 (4)
Mean absolute value	56·3 (24)	55·0 (19)

Table 3. *Bond lengths* (Å) *and valence angles* (°)

N(1)—C(2)	1·544 (5)	N(1)—C(2)—C(7)	111·5 (4)
N(1)—C(6)	1·472 (6)	C(3)—C(2)—C(7)	112·6 (4)
N(1)—C(15)	1·522 (5)	C(2)—C(3)—C(4)	109·6 (3)
C(2)—C(3)	1·550 (6)	C(2)—C(3)—C(8)	109·9 (4)
C(2)—C(7)	1·512 (7)	C(2)—C(3)—C(9)	107·0 (3)
C(3)—C(4)	1·531 (6)	C(4)—C(3)—C(8)	110·4 (4)
C(3)—C(8)	1·534 (7)	C(4)—C(3)—C(9)	108·6 (3)
C(3)—C(9)	1·547 (6)	C(8)—C(3)—C(9)	111·2 (4)
C(4)—C(5)	1·499 (6)	C(3)—C(4)—C(5)	113·1 (4)
C(5)—C(6)	1·537 (6)	C(4)—C(5)—C(6)	110·3 (4)
C(9)—C(10)	1·400 (6)	C(5)—C(6)—N(1)	111·1 (4)
C(9)—C(14)	1·395 (6)	C(3)—C(9)—C(10)	121·7 (3)
C(10)—C(11)	1·385 (6)	C(3)—C(9)—C(14)	121·0 (4)
C(11)—C(12)	1·372 (7)	C(10)—C(9)—C(14)	117·1 (4)
C(11)—O	1·375 (5)	C(9)—C(10)—C(11)	121·2 (4)
C(12)—C(13)	1·392 (6)	C(10)—C(11)—C(12)	121·6 (4)
C(13)—C(14)	1·381 (7)	C(10)—C(11)—O	115·3 (4)
C(15)—C(16)	1·499 (7)	C(12)—C(11)—O	123·1 (4)
C(16)—C(17)	1·277 (10)	C(11)—C(12)—C(13)	117·4 (4)
C(2)—N(1)—C(6)	113·8 (3)	C(12)—C(13)—C(14)	122·0 (5)
C(2)—N(1)—C(15)	109·7 (3)	C(13)—C(14)—C(9)	120·6 (4)
C(6)—N(1)—C(15)	110·7 (3)	N(1)—C(15)—C(16)	111·8 (4)
N(1)—C(2)—C(3)	110·5 (3)	C(15)—C(16)—C(17)	124·8 (6)

Hydrogen bonds

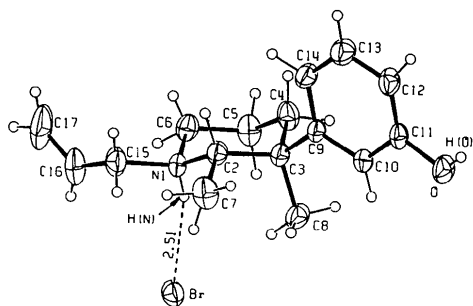| D—H···A	D—H	H···A	D···A	D—H···A
N(1)—H(N)···Br	0·82 (3)	2·51 (3)	3·301 (3)	163 (3)
O′—H(O′)···Br	0·63 (5)	2·61 (5)	3·234 (3)	173 (5)

Fig. 1. Molecular structure of the β isomer showing its stereochemistry and atom numbering. The thermal ellipsoids are at 30% probability. The drawing corresponds to the molecule listed in Table 1. The opposite enantiomorph is also present in the crystal structure.

However, Froimowitz's search also shows a second fairly stable rotamer for the β isomer, only 2·51 kJ mol^{-1} higher than the most stable one, corresponding to C(2)–C(3)–C(9)–C(14) = –138°, but this rotamer is not found in the crystal structure.

The bond lengths and valence angles are listed in Table 3. Although most are comparable to those of the α isomer, three bond lengths have significant deviations of 0·30 (9) – 0·034 (9) Å, possibly due to low estimates for the standard deviations. Among corresponding valence angles in the two structures, the largest deviations occur in the two exocyclic angles at C(11) [6·2 (6) and 5·3 (6)°], two of the exocyclic angles at C(3) [3·9 (5) and 3·1 (4)°] and C(2)–N(1)–C(15) [4·0 (4)°]. It is quite plausible that these angular changes are caused by the differences in the configuration of the C(2) substituent, and the hydrogen-bonding environments in the two crystal structures.

Each Br forms two hydrogen bonds, N(1)–H(N)··· Br···H(O)–O, to link the molecules into zigzag chains parallel to the a axis. The geometry of these bonds is given in Table 3.

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X-ray Structure Analysis of 1,4-Dioxane, Phase I at 279 K and Phase II at 153 K

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Abstract. Two crystalline phases of 1,4-dioxane, $C_4H_8O_2$, $M_r = 88\cdot105$, were investigated. Phase I exists in the temperature region from 278 to 285 K, phase II from below 133 to 278 K. Both phases monoclinic, $P2_1/n$, $Z = 2$, $F(000) = 96$. Dioxane I at 279 K: $a = 4\cdot584$ (7), $b = 9\cdot183$ (13), $c = 5\cdot818$ (10) Å, $\beta = 99\cdot63$ (14)°, $V_c = 241\cdot5$ (14) Å^3. Dioxane II at 153 K: $a = 5\cdot736$ (12), $b = 6\cdot507$ (13), $c = 6\cdot144$ (13) Å, $\beta = 100\cdot21$ (18)°, $V_c = 225\cdot7$ (18) Å^3. $D_x = 1\cdot211$ (7) (I), $D_x = 1\cdot296$ (10) g cm^{-3} (II), room-temperature density of liquid $D_m = 1\cdot034$ g cm^{-3}. Mo Kα, $\lambda = 0\cdot71069$ Å, $\mu = 1\cdot798$ cm^{-1} for I, 1·924 cm^{-1} for II. $R = 0\cdot060$ and 0·039 with 500 and 627 observed reflections. In both cases the molecule has its center on a crystallographic inversion center, and the ring geometry is that of a nearly ideal chair. The endocyclic C–O bond lengths range between 1·423 (3) and 1·432 (2) Å. They compare well with those of other dioxane and carbohydrate structures where the anomeric effect does not occur.

Introduction. In the course of the series of X-ray investigations on small cyclic ethers, we have previously reported the structures of non-substituted four- and five-membered rings, *i.e.* oxetane (Luger & Buschmann, 1984) and tetrahydrofuran (Luger & Buschmann, 1983). Our interest was directed towards tetrahydropyran and dioxane as the corresponding six-membered rings. Tetrahydropyran has two plastic crystalline phases with different cubic lattices below the melting point [phase I between 213 and 224 K, cubic, *Fm3m*, $a = 8\cdot34$ (2) Å, $Z = 4$; phase II between 163 and 213 K, cubic, *P43n*, $a = 10\cdot42$ (5) Å, $Z = 8$, see also Fig. 1] and a third non-plastic phase below 163 K for which only crystalline powder has been obtained up to now.

Dioxane has its melting point at 285 K and a transition point between ordinary crystalline phases at 278 K. This was discovered by a differential thermoanalysis run between 133 and 293 K on a Mettler thermoanalyzer TA1 (Fig. 1). The crystal and