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Structure and Absolute Configuration of (–)-3-(1-Cyclopropylmethyl-3-isobutyl-3-pyrrolidinyl)phenol Hydrobromide, $C_{18}H_{28}NO^+.Br^-$*

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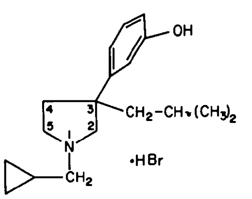
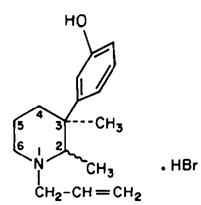
Abstract. $M_r = 354\cdot34$, orthorhombic, $P2_12_12_1$, $a = 14\cdot551$ (1), $b = 16\cdot013$ (1), $c = 7\cdot797$ (1) Å, $V = 1816\cdot7$ Å^3, $Z = 4$, $D_m = 1\cdot294$, $D_x = 1\cdot295$ Mg m^{-3}, λ(Cu $K\alpha_1$) = 1·54056 Å, $\mu = 3\cdot076$ mm^{-1}, $F(000) = 744$, $T = 296$ K, $R = 0\cdot025$ for 2021 reflexions with $I \geq 2\cdot0\sigma(I)$. In the solid state, the five-membered pyrrolidine ring has the envelope conformation with the 3-isobutyl axial. The 1-cyclopropylmethyl and the 3-aryl are both equatorial and *cis* to each other. The absolute configuration of this laevo antipode, which is pharmacologically active as a narcotic antagonist, has been determined as 3*S*. The dextro antipode is known to be inactive. Each Br is involved in two N—H···Br···H′—O′ hydrogen bonds which bridge the molecules into zigzag chains parallel to *z*.

Introduction. The laevo antipode of the title compound (I) is an active narcotic antagonist of fentanyl in rats, while its dextro antipode is inactive. The present X-ray study of the molecular stereochemistry and its absolute configuration has been undertaken for comparison with the related active antipode α(–)-3-(1-allyl-2,3-dimethyl-3-piperidyl)phenol hydrobromide (II), whose crystal structure has been reported (Ahmed, 1984), and eventually also with the morphine group.



(I)



(II)

Experimental. Crystal density by flotation in aqueous KI solution. Prismatic crystal 0·17 × 0·20 × 0·56 mm mounted along the prism length (*z* axis). Enraf–Nonius CAD-4 diffractometer, Ni-filtered Cu radiation. Cell parameters by least squares utilizing 24 reflexions with $78° < 2\theta < 144°$. Intensities measured for the *hkl* octant in a right-handed system of axes to $2\theta = 150°$, $h \leq 18$, $k \leq 20$, $l \leq 9$, ω–2θ scans with $\Delta\omega = 1\cdot5 \times (0\cdot8 + 0\cdot14\tan\theta)°$, horizontal aperture width $(3\cdot0 + 0\cdot4\tan\theta)$ mm, ω scan speed 0·6 to 3·35° min^{-1}. Three standard reflexions measured every 1 h of exposure time varied only within ±1%. 2143 independent reflexions, 2021 with $I \geq 2\cdot0\sigma(I)$ considered observed. Intensity data corrected for scale, Lorentz and polarization, and for absorption by the Gaussian integration method; transmission factors 1·582–2·405. Structure determination by the heavy-atom method: Br from a sharpened Patterson map; lighter atoms from a Fourier map; H atoms from a difference map. Refinement by block-diagonal least squares 9 × 9 per atom (4 × 4 for H), but the H atoms in the methyl groups were not refined.

The absolute configuration was based on the measured intensities of the ten Friedel pairs of reflexions with significant differences in their $|F_c(hkl)|$ and $|F_c(\overline{hkl})|$, Table 1. Further refinement of the correct model converged at $R = 0\cdot025$ and $wR = 0\cdot029$ for the 2021 observed reflexions, $S = 0\cdot54$, mean and max. Δ/σ 0·1 and 0·5 (max. 0·3 for the non-hydrogen atoms), residual electron density within $\pm 0\cdot23$ e Å^{-3}. Two very strong reflexions (012 and 120) showing extinction effect were excluded in the last two cycles. $\sum w(|F_o| - |F_c|)^2$ minimized with $w^{-1} = 1 + [(|F_o| - 15)/30]^2$. Scattering-factor curves including f' and f'' for Br from *International Tables for X-ray Crystallography* (1974), and from Stewart, Davidson & Simpson (1965) for H. Computations with the *NRC* programs (Ahmed, Hall, Pippy & Huber, 1973) and *ORTEP* (Johnson, 1971).

Discussion. The refined atomic parameters are presented in Table 2.† Fig. 1(*a*) presents the molecular structure in the solid state, drawn in the absolute configuration determined using the atomic parameters from Table 2. The five-membered pyrrolidine ring has the envelope conformation with the 3-isobutyl axial

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† Lists of structure factors, anisotropic thermal parameters, H parameters, and some mean-plane calculations have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39384 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Intensity ratios of Friedel pairs with a significant dispersion effect*

hkl	Observed*	Calculated†
111	1·20	1·17
122	1·17	1·13
131	0·94	0·94
132	0·77	0·84
211	1·44	1·15
221	0·93	0·93
312	1·07	1·06
321	1·12	1·10
331	1·06	1·05
411	0·89	0·90

* $[I(hkl) + I(h\bar{k}\bar{l}) + I(\bar{h}k\bar{l}) + I(\bar{h}\bar{k}l)]/[I(\bar{h}\bar{k}\bar{l}) + I(\bar{h}kl) + I(h\bar{k}l) + I(hk\bar{l})]$.

† $[F_c(hkl)/F_c(\bar{h}\bar{k}\bar{l})]^2$.

Table 2. *Fractional coordinates* (×10⁴; Br ×10⁵; H ×10³) *and equivalent isotropic temperature factors* (Å²)

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

	x	y	z	B_{eq}/B
Br	59134 (2)	62612 (2)	82973 (4)	4·5
O	921 (2)	4397 (1)	5151 (3)	4·4
N(1)	5027 (1)	6202 (1)	4476 (3)	3·3
C(2)	4118 (2)	5753 (2)	4464 (3)	3·0
C(3)	3405 (2)	6437 (2)	4755 (3)	2·9
C(4)	3804 (2)	7134 (2)	3630 (4)	3·7
C(5)	4834 (2)	7090 (2)	3896 (5)	4·4
C(6)	5778 (2)	5803 (2)	3451 (4)	4·1
C(7)	5991 (2)	4931 (2)	3985 (4)	4·6
C(8)	5519 (3)	4203 (2)	3170 (6)	5·7
C(9)	6488 (3)	4397 (3)	2717 (6)	6·6
C(10)	3392 (2)	6684 (2)	6677 (4)	3·5
C(11)	2725 (2)	7381 (2)	7211 (4)	4·2
C(12)	3200 (4)	8086 (3)	8055 (11)	11·5
C(13)	2020 (4)	7048 (4)	8440 (8)	9·4
C(14)	2446 (2)	6146 (2)	4239 (3)	2·9
C(15)	2106 (2)	5392 (2)	4860 (4)	3·1
C(16)	1221 (2)	5138 (2)	4468 (3)	3·3
C(17)	661 (2)	5622 (2)	3433 (4)	3·9
C(18)	993 (2)	6374 (2)	2812 (4)	3·9
C(19)	1882 (2)	6635 (2)	3202 (4)	3·5
H(O)	30 (3)	417 (3)	455 (6)	8·6 (12)
H(N)	520 (2)	624 (2)	555 (4)	4·5 (7)

while the 1-cyclopropylmethyl and the 3-aryl are both equatorial. The absolute configuration of this active laevo antipode is 3*S*, the priority sequence C(2) > C(14) > C(4) > C(10) being assumed. For comparison, Fig. 1(*b*) shows a similar view of the active agonist α(−)-3-(1-allyl-2,3-dimethyl-3-piperidyl)phenol HBr (Ahmed, 1984) which also has the absolute configuration 3*S*. There is remarkable similarity between these two active antipodes, especially in the environment of H(N) and in the orientations of the aromatic rings. One notable difference is the change in the position of OH relative to the rest of the molecule: it is substituted on position 3 of the phenyl ring in one molecule and on position 5 in the other. Space-filling models of these two molecules show that the orientation of the phenyl ring on the pyrrolidine ring is nearly fixed by the axial H atoms on C(2) and C(4), while the phenyl on the piperidine ring has freedom for partial rotation, but insufficient to bring OH to the position shown in Fig. 1(*a*). This may signify that the position of OH on the phenyl ring is not a deciding factor in the activity of these compounds. A stereochemical correlation of the more active antipodal forms of opiate antagonists based on compounds (I) and (II) has been published elsewhere (Ahmed, Iorio & Casy, 1983).

The bond lengths and valence angles for (I) are listed in Table 3; the C—H lengths are 0·86 (3) – 1·16 (2) Å. The three bonds in the cyclopropyl group, and the adjoining C(6)—C(7) bond, have a mean length of only 1·491 (4) Å, indicating some hybridization and conjugation effect as discussed by Allen (1981). The other bond lengths are in the ranges commonly observed, except that C(11)—C(12) is shortened to 1·478 (7) Å due to the high thermal motion of C(12). The endocyclic valence angles in the pyrrolidine ring range from 100·4 (2)° at C(3) to 106·4 (2)° at N(1) (mean 104·4°), similar to the corresponding values of 100·8 (2) – 107·9 (2)° (mean 103·6°) in 2,5-bis-(hydroxymethyl)-3,4-pyrrolidinediol (Lamotte-Brasseur, Dupont & Dideberg, 1977). The C(3)—C(10)—C(11) angle of 117·1 (3)° is indicative of some distortion from a tetrahedral arrangement at C(10), and the C—C—OH angles of 117·7 (3) and 121·5 (3)° at C(16) show some distortion from a trigonal arrangement. Similar C—C—OH angles of 117·8 (4) and 121·5 (4)° were observed in compound (II).

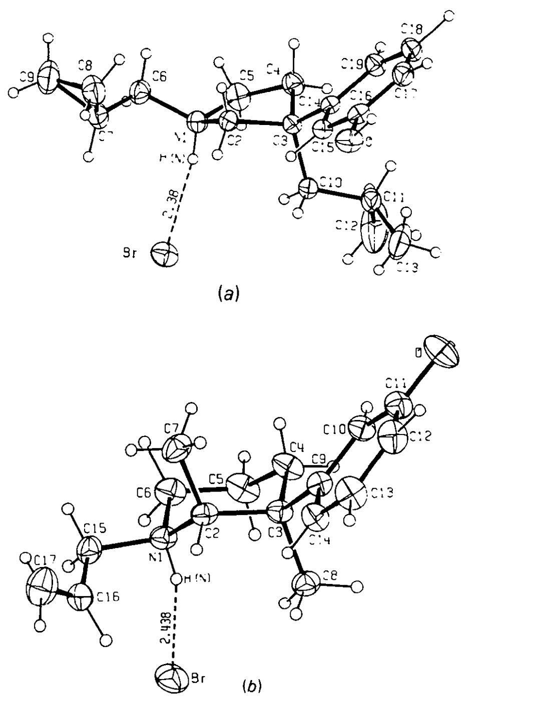

Fig. 1. Molecular structures in the solid state drawn in the absolute configurations determined for the active antagonists: (*a*) the (−)-pyrrolidine compound (I) and (*b*) the α(−)-piperidine compound (II). The thermal ellipsoids are at 30% probability for both, and the H atoms are shown by small circles.

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

O–C(16)	1·372 (4)	C(2)–C(3)–C(10)	109·6 (2)
N(1)–C(2)	1·505 (3)	C(2)–C(3)–C(14)	111·3 (2)
N(1)–C(5)	1·518 (4)	C(4)–C(3)–C(10)	111·8 (2)
N(1)–C(6)	1·497 (4)	C(4)–C(3)–C(14)	114·7 (2)
C(2)–C(3)	1·526 (4)	C(10)–C(3)–C(14)	108·8 (2)
C(3)–C(4)	1·534 (4)	C(3)–C(4)–C(5)	105·2 (2)
C(3)–C(10)	1·550 (4)	N(1)–C(5)–C(4)	105·5 (2)
C(3)–C(14)	1·525 (4)	N(1)–C(6)–C(7)	113·7 (2)
C(4)–C(5)	1·515 (4)	C(6)–C(7)–C(8)	121·1 (3)
C(6)–C(7)	1·490 (5)	C(6)–C(7)–C(9)	116·9 (3)
C(7)–C(8)	1·495 (5)	C(8)–C(7)–C(9)	59·7 (3)
C(7)–C(9)	1·494 (6)	C(7)–C(8)–C(9)	60·1 (3)
C(8)–C(9)	1·486 (6)	C(7)–C(9)–C(8)	60·2 (3)
C(10)–C(11)	1·537 (4)	C(3)–C(10)–C(11)	117·1 (3)
C(11)–C(12)	1·478 (7)	C(10)–C(11)–C(12)	112·3 (3)
C(11)–C(13)	1·502 (7)	C(10)–C(11)–C(13)	110·3 (3)
C(14)–C(15)	1·392 (4)	C(12)–C(11)–C(13)	107·9 (4)
C(14)–C(19)	1·393 (4)	C(3)–C(14)–C(15)	119·9 (3)
C(15)–C(16)	1·385 (4)	C(3)–C(14)–C(19)	121·4 (3)
C(16)–C(17)	1·384 (4)	C(15)–C(14)–C(19)	118·7 (3)
C(17)–C(18)	1·385 (5)	C(14)–C(15)–C(16)	120·6 (3)
C(18)–C(19)	1·393 (4)	O–C(16)–C(15)	117·7 (3)
C(2)–N(1)–C(5)	106·4 (2)	O–C(16)–C(17)	121·5 (3)
C(2)–N(1)–C(6)	115·7 (2)	C(15)–C(16)–C(17)	120·8 (3)
C(5)–N(1)–C(6)	112·1 (2)	C(16)–C(17)–C(18)	119·0 (3)
N(1)–C(2)–C(3)	104·7 (2)	C(17)–C(18)–C(19)	120·6 (3)
C(2)–C(3)–C(4)	100·4 (2)	C(14)–C(19)–C(18)	120·3 (3)

Hydrogen bonding

D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
N(1)–H(N)···Br	0·88 (3)	2·38 (3)	3·248 (2)	170 (3)
O–H(O)···Br′*	1·08 (4)	2·13 (4)	3·213 (3)	178 (4)

*Br′ at $\frac{1}{2}-x$, $1-y$, $z-\frac{1}{2}$.

In the pyrrolidine ring, the smallest torsion angle C(2)–N(1)–C(5)–C(4) is 2·1 (3)°, indicating near planarity for these four atoms, which deviate by a maximum of ±0·012 (3) Å from the mean plane through them. C(3) is −0·632 (2) Å from this plane. The pyrrolidine ring has the envelope conformation with the apex at C(3) [puckering parameters $q_2 = 0{\cdot}410$ Å and $\varphi_2 = 74{\cdot}8°$ (Cremer & Pople, 1975)]. The phenyl ring is planar with $\chi^2 = 5{\cdot}9$, and the O atom deviates from this plane by −0·028 (2) Å. The mean plane through the pyrrolidine ring makes dihedral angles of 56·7 (4)° with the cyclopropyl ring and 26·9 (4)° with the phenyl ring.

Molecules at (*x*,*y*,*z*) and ($\frac{1}{2}-x, 1-y, \frac{1}{2}+z$) are interlinked through Br by two N–H(N)···Br···H(O)′–O′ hydrogen bonds into zigzag chains parallel to *z*. The geometry of these bonds is included in Table 3; angle H(N)···Br···H(O)′ is 93 (1)°. All other intermolecular distances are normal van der Waals interactions.

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References

AHMED, F. R. (1984). *Acta Cryst.* C**40**, 1021–1023.
AHMED, F. R., HALL, S. R., PIPPY, M. E. & HUBER, C. P. (1973). The NRC System of Programs for the IBM/360. Accession Nos. 133–147 in *J. Appl. Cryst.* **6**, 309–346.
AHMED, F. R., IORIO, M. A. & CASY, A. F. (1983). *J. Pharm. Pharmacol.* **35**, 766–767.
ALLEN, F. H. (1981). *Acta Cryst.* B**37**, 890–900.
CREMER, D. & POPLE, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press.
JOHNSON, C. K. (1971). *ORTEP*II. Report ORNL-3794, 2nd rev. Oak Ridge National Laboratory, Tennessee.
LAMOTTE-BRASSEUR, J., DUPONT, L. & DIDEBERG, O. (1977). *Acta Cryst.* B**33**, 409–412.
STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

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Structure of (4βH,6βH,11αH)-3β,10β-Epoxy-8β-isobutyryloxy-1-oxogermacr-2-en-6,12-olide (Tetrahydrozexbrevin), $C_{19}H_{26}O_6$, a Sesquiterpenoid Lactone*

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Abstract. $M_r = 350{\cdot}4$, orthorhombic, $P2_12_12_1$, $a = 9{\cdot}060$ (3), $b = 14{\cdot}080$ (3), $c = 14{\cdot}628$ (4) Å, $V = 1866$ (3) Å^3, $D_x = 1{\cdot}25$ Mg m^{-3}, $Z = 4$, $F(000) = 752$, $T = 293$ K, graphite-monochromated Cu *Kα* radiation, $\lambda = 1{\cdot}5418$ Å, $\mu = 0{\cdot}723$ mm^{-1}, final $R = 0{\cdot}063$ for 1208 observed reflections. The cyclodecene ring adopts a chair–boat conformation with the C(4) and C(10) methyl groups oriented *anti* and is quasi-*trans* fused to the γ-lactone ring. The conformation of the 3(2*H*)-furanone ring is a flattened envelope with O(6) as the flap. Bond lengths are normal; bond angles indicate some strain in the molecule.

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