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Absolute Configuration of (I) (–)-(3*S*,4*R*)- and (II) (–)-(3*S*,4*S*)-3-Methyl-4-phenyl-4-piperidinecarboxylic Acid Hydrobromide†

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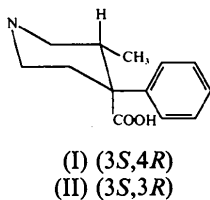
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Abstract

An X-ray diffraction study of the title compounds (4-carboxy-3-methyl-4-phenylpiperidinium bromide, $C_{13}H_{18}NO_2^+ \cdot Br^-$) showed that the absolute configurations of (I) and (II) are (3*S*,4*R*) and (3*S*,4*S*), respectively. In both structures the phenyl group is equatorial and the carboxyl group is axial. In (I) the methyl group is in an axial position while in (II) it is in an equatorial position.

Comment

The benzyl ester of 3-methyl-4-phenyl-4-piperidinecarboxylic acid is an intermediate in the synthesis of 1-[4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenyl-4-piperidinecarboxylic acid (Levocabastine, Janssen Research Foundation internal code R50547), the prototype of a chemical series of compounds with specific H_1 -antihistaminic activity. The geometry of the four possible racemates of the latter compound could be derived from the NMR spectra of their benzyl esters (Stokbroeckx *et al.*, 1986). In order to confirm the geometries of the piperidine moieties and obtain their absolute configurations, X-ray structure determinations of the title compounds were undertaken.



The absolute configuration of (I), determined from an *R*-factor ratio test (Hamilton, 1965), is (3*S*,4*R*), and that of (II), obtained from the calculation of the Bijvoet coefficient (Beurskens, Noordik & Beurskens, 1980), is (3*S*,4*S*). The main difference between the two compounds

can be seen in Figs. 1 and 2 by superimposing the piperidiny rings. In (I) the methyl is in an axial position and at the backside of the ring, while in (II) the methyl group is equatorial and in front of the ring. Each piperidiny ring is in a slightly distorted chair conformation [(I) θ_2 4.9 (7)°, Q_1 0.569 (6) Å; (II) θ_2 174.0 (4)°, Q_1 0.567 (3) Å] and each phenyl ring is planar [χ^2 (I) 5.63, (II) 6.62]. In (I), with the methyl group axial, the phenyl ring is nearly coplanar with the mean plane of the piperidiny ring, while in (II), with the methyl group equatorial, the phenyl ring is approximately perpendicular to this plane. Both structures are stabilized by a nearly identical network of hydrogen bonds between N, O and Br atoms, forming endless chains in the *b* direction.

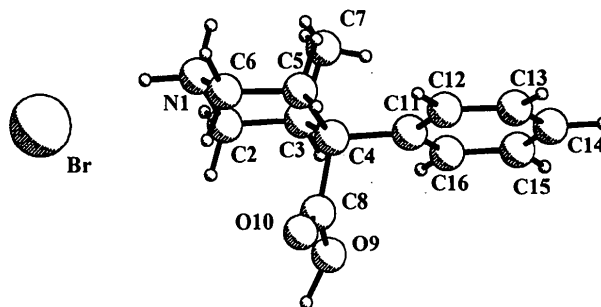


Fig. 1. PLUTO diagram of molecule (I) showing the atomic numbering scheme.

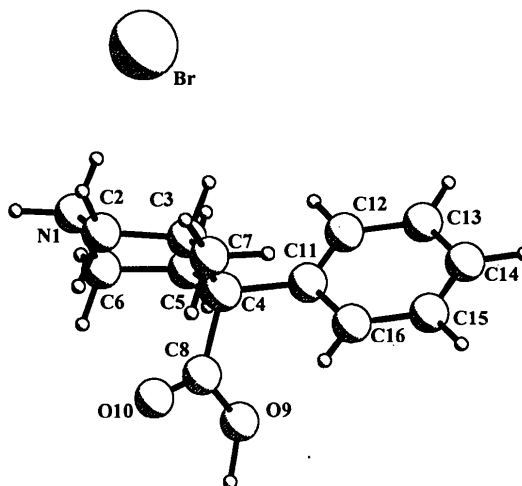


Fig. 2. PLUTO diagram of molecule (II) showing the atomic numbering scheme.

Experimental Compound (I)

Crystal data

$C_{13}H_{18}NO_2^+ \cdot Br^-$
 $M_r = 300.19$

Cu $K\alpha$ radiation
 $\lambda = 1.54184$ Å

† Internal codes of Janssen Research Foundation: R53714 and R63650 for (I) and (II), respectively.

Monoclinic
 $P2_1$
 $a = 6.9898$ (8) Å
 $b = 7.3709$ (8) Å
 $c = 13.410$ (2) Å
 $\beta = 97.46$ (1)°
 $V = 685.1$ (1) Å³
 $Z = 2$
 $D_x = 1.455$ Mg m⁻³

Data collection

Hilger & Watts four-circle diffractometer
 $\omega/2\theta$ scans (speed 1.2° min⁻¹, width 1.2°)
 Absorption correction: empirical (North, Phillips & Mathews, 1968)
 $T_{\min} = 0.719$, $T_{\max} = 0.991$
 1905 measured reflections
 1377 independent reflections

Refinement

Refinement on F
 $R = 0.0383$
 $wR = 0.0549$
 $S = 1.59$
 1320 reflections
 154 parameters
 H-atom parameters not refined
 $w = 1/[\sigma^2(F) + 0.00100F^2]$
 $(\Delta/\sigma)_{\max} = 0.001$
 $\Delta\rho_{\max} = 0.53$ e Å⁻³
 $\Delta\rho_{\min} = -0.49$ e Å⁻³

Cell parameters from 24 reflections
 $\theta = 20-25^\circ$
 $\mu = 4.040$ mm⁻¹
 $T = 293$ K
 Prism
 $0.25 \times 0.25 \times 0.20$ mm
 Colourless

1320 observed reflections
 $[I > 3.0\sigma(I)]$
 $R_{\text{int}} = 0.017$
 $\theta_{\max} = 70^\circ$
 $h = -5 \rightarrow 8$
 $k = 0 \rightarrow 8$
 $l = -16 \rightarrow 16$
 2 standard reflections monitored every 50 reflections
 intensity variation: 1.5%

Extinction correction: Zachariasen (1967) and Larson (1970)
 Extinction coefficient: 0.51 (7)
 Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV Tables 2.2B, 2.3.1)
 Absolute configuration: determined with an R -factor ratio test (Hamilton, 1965)

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²) for compound (I)

$$U_{\text{eq}} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

	x	y	z	U_{eq}
Br	0.96325 (7)	3/4	0.65140 (4)	0.0514 (2)
N1	0.8285 (7)	0.6307 (7)	0.4190 (4)	0.048 (2)
C2	0.7966 (9)	0.8111 (9)	0.3689 (5)	0.051 (2)
C3	0.6967 (8)	0.7892 (7)	0.2611 (4)	0.047 (2)
C4	0.4997 (8)	0.6936 (8)	0.2609 (5)	0.043 (2)
C5	0.5295 (8)	0.5118 (8)	0.3183 (5)	0.047 (2)
C6	0.6413 (9)	0.5318 (9)	0.4218 (5)	0.053 (2)
C7	0.8314 (8)	0.6937 (9)	0.1947 (4)	0.051 (2)
C8	0.3624 (7)	0.8131 (8)	0.3124 (4)	0.045 (2)
O9	0.3649 (7)	0.9839 (7)	0.2842 (4)	0.071 (2)
O10	0.2574 (5)	0.756 (1)	0.3714 (3)	0.059 (1)
C11	0.3927 (8)	0.6660 (9)	0.1530 (5)	0.049 (2)
C12	0.2791 (9)	0.511 (1)	0.1284 (5)	0.057 (2)
C13	0.182 (1)	0.494 (1)	0.0315 (6)	0.073 (3)
C14	0.195 (1)	0.621 (2)	-0.0397 (5)	0.078 (3)
C15	0.303 (1)	0.775 (2)	-0.0171 (6)	0.079 (3)
C16	0.400 (1)	0.796 (1)	0.0801 (6)	0.068 (3)

Table 2. Selected geometric parameters (Å, °) for compound (I)

N1—C2	1.494 (8)	C8—O9	1.315 (8)
N1—C6	1.502 (8)	C8—O10	1.222 (7)
C2—C3	1.530 (8)	C11—C12	1.406 (9)
C3—C4	1.547 (7)	C11—C16	1.37 (1)
C3—C7	1.547 (8)	C12—C13	1.392 (9)
C4—C5	1.546 (8)	C13—C14	1.35 (1)
C4—C8	1.532 (8)	C14—C15	1.38 (1)
C4—C11	1.554 (8)	C15—C16	1.40 (1)
C5—C6	1.509 (8)		
C2—N1—C6	111.3 (5)	N1—C6—C5	111.9 (5)
N1—C2—C3	110.7 (5)	C4—C8—O10	123.9 (6)
C2—C3—C7	110.8 (5)	C4—C8—O9	112.8 (5)
C2—C3—C4	110.3 (5)	O9—C8—O10	123.3 (6)
C4—C3—C7	113.6 (5)	C4—C11—C16	120.8 (6)
C3—C4—C11	112.5 (5)	C4—C11—C12	121.0 (5)
C3—C4—C8	110.3 (4)	C12—C11—C16	118.1 (6)
C3—C4—C5	109.4 (4)	C11—C12—C13	119.0 (7)
C8—C4—C11	103.9 (4)	C12—C13—C14	122.0 (8)
C5—C4—C11	111.6 (5)	C13—C14—C15	120.1 (7)
C5—C4—C8	109.0 (5)	C14—C15—C16	118.9 (9)
C4—C5—C6	113.2 (5)	C11—C16—C15	121.8 (7)

Table 3. Hydrogen-bonding geometry (Å, °) for compound (I)

D	H	A	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
N1	H1B	Br	1.037	2.260	3.257 (5)	160.8
N1	H1A	Br ⁱ	1.057	2.423	3.352 (5)	146.0
O9	H9	Br ⁱⁱ	1.034	2.371	3.220 (5)	138.7

Symmetry codes: (i) $2 - x, -\frac{1}{2} + y, 1 - z$; (ii) $1 - x, \frac{1}{2} + y, 1 - z$.

Compound (II)

Crystal data

$C_{13}H_{18}NO_2 \cdot Br^-$
 $M_r = 300.19$
 Orthorhombic
 $P2_12_12_1$
 $a = 9.711$ (2) Å
 $b = 9.928$ (2) Å
 $c = 13.765$ (2) Å
 $V = 1327.1$ (4) Å³
 $Z = 4$
 $D_x = 1.502$ Mg m⁻³
 $D_m = 1.50$ Mg m⁻³
 D_m measured by flotation in n -heptane/bromoform

Cu $K\alpha$ radiation
 $\lambda = 1.54184$ Å

Cell parameters from 24 reflections
 $\theta = 20-25^\circ$
 $\mu = 4.171$ mm⁻¹
 $T = 293$ K
 Prism
 $0.25 \times 0.20 \times 0.20$ mm
 Colourless

Data collection

Hilger & Watts four-circle diffractometer
 $\omega/2\theta$ scans (speed 1.2° min⁻¹, width 1.2°)
 Absorption correction: empirical (North, Phillips & Mathews, 1968)
 $T_{\min} = 0.792$, $T_{\max} = 1.000$
 2702 measured reflections
 2469 independent reflections

2266 observed reflections
 $[I > 3.0\sigma(I)]$
 $R_{\text{int}} = 0.015$
 $\theta_{\max} = 70^\circ$
 $h = 0 \rightarrow 11$
 $k = -12 \rightarrow 12$
 $l = 0 \rightarrow 16$
 2 standard reflections monitored every 50 reflections
 intensity variation: 1.6%

Refinement

Refinement on F

R = 0.0293

wR = 0.0369

S = 1.67

2266 reflections

155 parameters

H-atom parameters not refined

 $w = 1/[\sigma^2(F) + 0.00020F^2]$ $(\Delta/\sigma)_{\max} = 0.012$ $\Delta\rho_{\max} = 0.36 \text{ e } \text{\AA}^{-3}$ $\Delta\rho_{\min} = -0.34 \text{ e } \text{\AA}^{-3}$

Extinction correction:

Zachariasen (1967) and
Larson (1970)

Extinction coefficient:

0.58 (5)

Atomic scattering factors
from *International Tables*
for X-ray Crystallogra-
phy (1974, Vol. IV Tables
2.2B, 2.3.1)Absolute configuration: the
Bijvoet coefficient was
between 0.934 (1) and
exactly 1 for 371 and 72
selected Bijvoet pairs,
respectivelyTable 6. Hydrogen-bonding geometry (Å, °) for
compound (II)

D	H	A	D—H	H...A	D...A	D—H...A
N1	H1A	Br	1.070	2.200	3.269 (3)	176.9
N1	H1B	Br ^j	1.037	2.400	3.339 (3)	150.1
O9	H9	Br ⁱ	1.161	2.268	3.201 (2)	135.5

Symmetry codes: (i) $\frac{1}{2} + x, \frac{1}{2} - y, -z$; (ii) $x, 1 + y, z$.

The structures were solved by combined Patterson and direct methods techniques. Refinement was by full-matrix least squares. H atoms were calculated at geometrical positions except for those of the methyl and hydroxyl groups. Data were collected with Hilger & Watts Y290 software. Cell refinement was by PARAM in the XRAY76 program package (Stewart *et al.*, 1976); the structure was solved using DIRDIF (Beurskens *et al.*, 1981) and refined with NRCVAX (Gabe, Le Page, Charland, Lee & White, 1989); molecular graphics were produced using PLUTO (Motherwell & Clegg, 1978) and PARST (Nardelli, 1983) was used to prepare the material for publication.

Table 4. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²) for compound (II)
$$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

	x	y	z	U _{eq}
Br	0.29446 (4)	0.68254 (3)	0.01793 (3)	0.0451 (1)
N1	0.4831 (3)	0.9550 (3)	0.0095 (3)	0.049 (1)
C2	0.5029 (4)	0.9985 (4)	0.1140 (4)	0.050 (1)
C3	0.3668 (4)	1.0338 (4)	0.1620 (3)	0.042 (1)
C4	0.2778 (4)	1.1363 (3)	0.1026 (3)	0.031 (1)
C5	0.2700 (3)	1.0847 (3)	-0.0042 (3)	0.036 (1)
C6	0.4114 (4)	1.0587 (4)	-0.0482 (3)	0.044 (1)
C7	0.3965 (5)	1.0752 (5)	0.2678 (4)	0.064 (2)
C8	0.3433 (4)	1.2759 (3)	0.0983 (3)	0.036 (1)
O9	0.2593 (3)	1.3669 (2)	0.0586 (2)	0.051 (1)
O10	0.4593 (3)	1.3025 (3)	0.1204 (2)	0.059 (1)
C11	0.1347 (4)	1.1471 (3)	0.1486 (3)	0.033 (1)
C12	0.0248 (4)	1.0700 (3)	0.1164 (3)	0.037 (1)
C13	-0.1027 (4)	1.0768 (4)	0.1635 (3)	0.045 (1)
C14	-0.1223 (4)	1.1602 (4)	0.2415 (3)	0.049 (1)
C15	-0.0142 (5)	1.2388 (4)	0.2734 (3)	0.052 (1)
C16	0.1130 (4)	1.2331 (4)	0.2282 (3)	0.042 (1)

Table 5. Selected geometric parameters (Å, °) for
compound (II)

N1—C2	1.513 (6)	C8—O9	1.335 (4)
N1—C6	1.474 (5)	C8—O10	1.196 (4)
C2—C3	1.519 (5)	C11—C12	1.386 (4)
C3—C4	1.566 (5)	C11—C16	1.405 (5)
C3—C7	1.541 (6)	C12—C13	1.400 (5)
C4—C5	1.559 (4)	C13—C14	1.370 (5)
C4—C8	1.526 (4)	C14—C15	1.380 (6)
C4—C11	1.531 (4)	C15—C16	1.384 (6)
C5—C6	1.523 (5)		
C2—N1—C6	111.9 (3)	N1—C6—C5	109.3 (3)
N1—C2—C3	111.7 (3)	C4—C8—O10	125.7 (3)
C2—C3—C7	108.1 (3)	C4—C8—O9	112.1 (3)
C2—C3—C4	113.8 (3)	O9—C8—O10	122.0 (3)
C4—C3—C7	115.1 (3)	C4—C11—C16	120.1 (3)
C3—C4—C11	109.3 (3)	C4—C11—C12	121.9 (3)
C3—C4—C8	112.4 (3)	C12—C11—C16	118.0 (3)
C3—C4—C5	107.8 (3)	C11—C12—C13	120.5 (3)
C8—C4—C11	109.3 (3)	C12—C13—C14	121.0 (4)
C5—C4—C11	111.6 (3)	C13—C14—C15	119.1 (4)
C5—C4—C8	106.4 (3)	C14—C15—C16	120.9 (4)
C4—C5—C6	112.7 (3)	C11—C16—C15	120.6 (4)

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71782 (31 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: NA1065]

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