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N-Methyl- and *N*-Ethylbenzhydrylamine Hydrochloride

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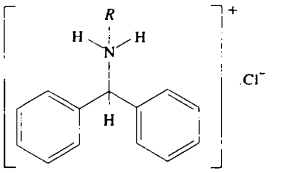
Abstract

The title compounds, MBH ($C_{14}H_{16}N^+.Cl^-$) and EBH ($C_{15}H_{18}N^+.Cl^-$), respectively, act as inhibitors of smooth-muscle spasms. Both compounds crystallize in enantiomorphous space groups, but EBH presents two crystallographically inequivalent enantiomers. In both cases, the molecular conformation can be classified as deformed helical C_s. Both compounds form infinite chains along **b** through two types of N—H···Cl bond.

Comment

Benzhydrylamine derivatives inhibit smooth-muscle spasms (Bruno Blanch, 1990), often exhibiting greater biological activity than their parent compounds. In their presence, histamine becomes a partial agonist and, given that the antispasmodic effect has been proved to be of the non-competitive type (Grand *et al.*, 1984), either their receptor is different from that of histamine or they act on another site of the same receptor (Goeta, 1995).

In order to understand the interaction between drug and receptor (and thereby gain insight into the reasons for the drug's biological activity), it is necessary to know the three-dimensional structure of the drug molecule. If the structure of the receptor is not known directly, analysis of the structural features of a series of related drug molecules may cast light on its possible structure and improve the understanding of the mechanism of the drug–receptor interaction. The structures of benzhydrylamine hydrochloride (BH) (Goeta, Punte & Rivero, 1993) and 4,4′-dichloro-*N*,*N*-diethylbenzhydrylamine hydrochloride (DDBH) (Castelleto *et al.*, 1993) are already known; we report herein the structures of the *N*-methyl- (MBH) and *N*-ethyl- (EBH) hydrochloride derivatives. Both compounds are more active than BH and DDBH, and EBH exhibits greater activity than MBH.



MBH: R = CH_3
EBH: R = CH_2CH_3

Intramolecular bond distances and angles for both compounds studied are within expected ranges. In both compounds, the phenyl rings are planar within experimental error. Molecular geometries and atomic labelling are shown in Figs. 1 and 2, while the molecular parameters that are believed to be important for changes in activity are described in the following paragraphs.

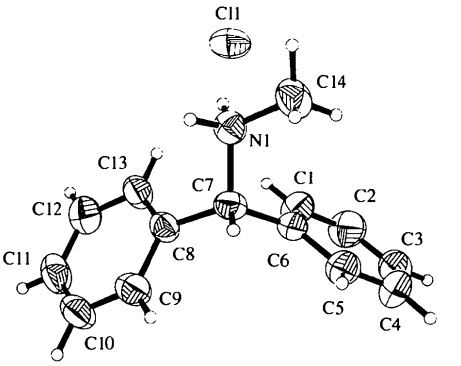


Fig. 1. The molecular structure of MBH showing 50% probability displacement ellipsoids for non-H atoms. H atoms are drawn as small spheres of arbitrary radii.

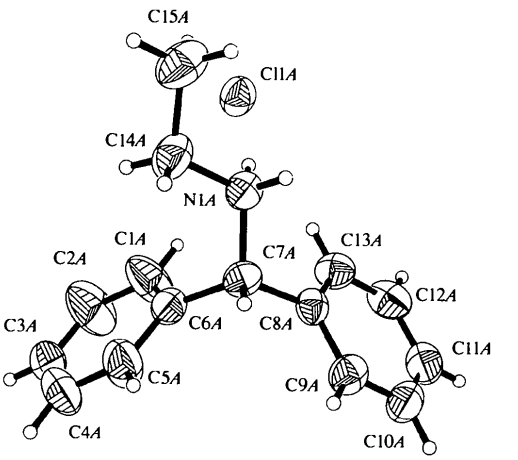


Fig. 2. The molecular structure of EBH (molecule *A*) showing 50% probability displacement ellipsoids for non-H atoms. H atoms are drawn as small spheres of arbitrary radii.

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The bridge angles of 113.2 (3) in MBH, 112.8 (2) in molecule *A* of EBH and 113.0 (3)° in molecule *B* of EBH, show good agreement with the corresponding angle in diphenylmethane (DPM) [112.5 (6)°; Barnes *et al.*, 1981]. The dihedral angles subtended between the least-squares planes of the two phenyl rings and the central plane defined by the three C atoms that form the bridge, Φ_1 and Φ_2, are 56.6 (3) and 83.3 (2)°, respectively, for MBH. For molecule *A* of EBH, Φ_1 = 70.3 (3) and Φ_2 = 83.4 (2)°; for molecule *B*, Φ_1 = 54.3 (3) and Φ_2 = 85.3 (2)°. The angles between the phenyl rings, Φ_{12}, are 72.5 (1), 74.4 (1) and 74.3 (1)° for MBH, molecule *A* of EBH and molecule *B* of EBH, respectively.

Comparison of these values with the corresponding angles in BH, Φ_1 = 57.8 (3), Φ_2 = 68.3 (2) and Φ_{12} = 97.7 (2)°, reveals that substitution at the N atom of BH changes its helical C_2 conformation into a deformed helical C_s conformation in MBH and EBH. The classification of Barnes *et al.* (1981) for the basic conformations of diphenylmethane has been adopted. The same deformed helical C_s conformation has been observed by Castelleto *et al.* (1993) in DDBH. The proximity to 90° of one of the angles between the phenyl mean planes and the bridge plane in MBH, EBH and DDBH assigns their conformations as 'perpendicular distorted'.

Examination of the packing in MBH shows that the N atom participates in two hydrogen bonds with Cl^- ions as acceptors, the N···Cl distances being 3.091 (4) and 3.070 (3) Å. These intermolecular contacts are responsible for the formation of infinite chains along **b**. The packing of EBH also involves infinite chains along **b**. In this case, the crystallographically distinct molecules *A* and *B* form non-interacting chains. The N···Cl contact distances within chains of molecule *A* are 3.164 (3) and 3.122 (3) Å; those within chains of molecule *B* are 3.139 (3) and 3.121 (3) Å.

Many non-classic antihistamines which act upon the H1 histamine receptor site are known to be chiral. Both MBH and EBH crystallize in enantiomorphous space groups (although this does not determine that the molecules are chiral). The chirality of MBH and EBH molecules might imply some kind of stereoselectivity in the receptor site and could explain their greater activity. We have measured the optical activity of MBH in solution, trying to rationalize the increments on going from BH to MBH and EBH. The lack of optical activity shown by MBH (Castelleto *et al.*, 1992) allows us to discard its action on a stereoselective site.

The conformational differences, observed crystallographically, between benzhydrylamine hydrochloride and its more active derivatives (MBH, EBH and DDBH), would indicate that the receptor site needs the drug to present a deformed helical C_s conformation. However, neither this assumption nor the geometrical differences between the derivatives explains the differences in their activities. Variations in the degree of hydrophobicity (Castelleto *et al.*, 1992) indicating deeper or easier membrane penetration and measured by the partitioning coefficient (Fuyita, Iwasa & Hansch, 1964) might explain the observed differences. Further research is in progress to investigate these proposals.

Experimental

N-Methylbenzhydrylamine hydrochloride was prepared by first adding a 33% solution of *N*-methylamine (69 m*M*) to cold stirred formic acid (140 m*M*) over a period of 0.5 h. The solution was then slowly heated to 373 K and water distilled off. Benzophenone (17 m*M*) was added to the hot mixture and the temperature raised to 453–458 K for 6 h. After cooling, the mixture was poured into water (50 ml) and the solid product was collected, washed and dried. Methanol (8 ml) and 6 *N* HCl (14 ml) were added and the reaction mixture stirred at 348–353 K for 24 h. After standing at 273 K for 2 h, a white precipitate appeared, which was separated by filtration, dried and recrystallized from methanol (yield 90%). *N*-Ethylbenzhydrylamine hydrochloride was prepared by the same procedure starting from *N*-ethylamine (yield 56%).

MBH

Crystal data

$C_{14}H_{16}N^+.Cl^-$
M_r = 233.73
Orthorhombic
$P2_12_12_1$
a = 8.967 (1) Å
b = 9.160 (2) Å
c = 15.710 (7) Å
V = 1290.4 (7) Å^3
Z = 4
D_x = 1.20 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 22 reflections
θ = 5–8°
μ = 0.269 mm^{-1}
T = 295 (2) K
Triangular prism
0.35 × 0.30 × 0.25 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: none
1319 measured reflections
1319 independent reflections
986 reflections with $F > 4\sigma(F)$
θ_{max} = 25.0°
h = 0 → 10
k = 0 → 10
l = 0 → 18
1 standard reflection
frequency: 30 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.100
S = 1.081
1319 reflections
166 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0406P)^2 + 0.2396P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute configuration: Flack (1983)
Flack parameter = 0.03 (15)

Table 1. *Selected geometric parameters (Å, °) for MBH*

N1—C14	1.484 (5)	C6—C7	1.522 (5)
N1—C7	1.512 (5)	C7—C8	1.515 (5)
C14—N1—C7	114.0 (3)	N1—C7—C8	110.3 (3)
N1—C7—C6	111.3 (3)	C6—C7—C8	113.2 (3)

Table 2. *Hydrogen-bonding geometry (Å, °) for MBH*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1N···Cl1	0.95 (4)	2.16 (4)	3.091 (4)	166 (3)
N1—H2N···Cl1^{i}	0.94 (4)	2.15 (4)	3.070 (3)	168 (3)

Symmetry code: (i) $-x, \frac{1}{2}+y, \frac{3}{2}-z$.

EBH

Crystal data

$C_{15}H_{18}N^{+}.Cl^{-}$
M_r = 247.75
Monoclinic
$P2_1$
a = 9.615 (2) Å
b = 9.102 (2) Å
c = 15.933 (3) Å
β = 91.13 (3)°
V = 1394.1 (5) Å^3
Z = 4
D_x = 1.180 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 494 reflections
θ = 2.45–20.31°
μ = 0.253 mm^{-1}
T = 295 (2) K
Rectangular prism
0.40 × 0.30 × 0.20 mm
Colourless

Data collection

Siemens SMART CCD diffractometer
ω scans
Absorption correction: multi-scans (*SADABS*; Sheldrick, 1996)
T_{min} = 0.786, T_{max} = 1.000
10 171 measured reflections

6194 independent reflections
3793 reflections with $F > 4\sigma(F)$
R_{int} = 0.035
θ_{max} = 27.47°
$h = -12 \rightarrow 12$
$k = -11 \rightarrow 11$
$l = -19 \rightarrow 20$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.052
$wR(F^2)$ = 0.116
S = 1.033
6188 reflections
326 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0373P)^2 + 0.0613P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.010
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.17 e Å^{-3}

Extinction correction: *SHELXL93* (Sheldrick, 1993)
Extinction coefficient: 0.0157 (16)
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute configuration: Flack (1983)
Flack parameter = 0.01 (6)

Table 3. *Selected geometric parameters (Å, °) for EBH*

N1*A*—C14*A*	1.503 (4)	N1*B*—C14*B*	1.492 (4)
N1*A*—C7*A*	1.510 (4)	N1*B*—C7*B*	1.511 (4)
C6*A*—C7*A*	1.515 (4)	C6*B*—C7*B*	1.518 (4)
C7*A*—C8*A*	1.523 (4)	C7*B*—C8*B*	1.510 (4)
C14*A*—C15*A*	1.511 (5)		
C15*A*—C14*A*—N1*A*	110.5 (3)	C15*B*—C14*B*—N1*B*	110.5 (3)
C14*A*—N1*A*—C7*A*	113.6 (3)	C14*B*—N1*B*—C7*B*	114.6 (3)
N1*A*—C7*A*—C6*A*	112.3 (2)	N1*B*—C7*B*—C6*B*	112.1 (2)
N1*A*—C7*A*—C8*A*	111.6 (2)	N1*B*—C7*B*—C8*B*	111.7 (2)
C6*A*—C7*A*—C8*A*	112.8 (2)	C6*B*—C7*B*—C8*B*	113.0 (3)

Table 4. *Hydrogen-bonding geometry (Å, °) for EBH*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1*A*—H1*A*N···Cl1*A*	0.92 (3)	2.26 (4)	3.164 (3)	168 (3)
N1*A*—H2*A*N···Cl1*A*^{i}	0.87 (4)	2.30 (4)	3.122 (3)	158 (3)
N1*B*—H1*B*N···Cl1*B*	0.91 (3)	2.25 (4)	3.139 (3)	165 (3)
N1*B*—H2*B*N···Cl1*B*^{ii}	0.89 (2)	2.32 (3)	3.121 (3)	149 (3)

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

EBH is pseudosymmetrically orthorhombic (space group $Pna2_1$), but with β = 91.18 (3)°. Attempts to refine the structure in that space group showed 54 major systematic absences violations and 377 inconsistent equivalents (R_{int} = 0.15) despite achieving a conventional R of 0.05. The data were recollected using another crystal; this was found to be monoclinic, space group $P2_1$, with β = 91.13 (3)°. The second data set is of better quality than the first; accordingly, the structural results for EBH are based on the second data set. H atoms were allowed to ride on their parent C atoms with U_{iso}(H) = xU_{eq}(C); for methyl H atoms, x = 1.5, while for others, x = 1.2. Idealized tertiary C—H distances were fixed at 0.98 Å. The idealized CH_3 groups were allowed to rotate about their X—C bond; C—H distances in this case were fixed at 0.96 Å. H atoms bonded to N atoms were located from difference Fourier maps. Coordinates and isotropic displacement parameters of these H atoms were refined, but the distance N1*B*—H2*B*N in EBH was restrained to be 0.85 (3) Å .

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989) for MBH; *SMART* (Siemens, 1996*a*) for EBH. Cell refinement: *CAD-4 Software* for MBH; *SMART* for EBH. Data reduction: *MolEN* (Fair, 1990) for MBH; *SAINT* (Siemens, 1996*b*) for EBH. Program(s) used to solve structures: *SHELXS86* (Sheldrick, 1990) for MBH; *SHELXTL* (Siemens, 1995) for EBH. Program(s) used to refine structures: *SHELXL93* (Sheldrick, 1993) for MBH; *SHELXTL* for EBH. For both compounds, molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1158). Services for accessing these data are described at the back of the journal.

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endo-1,4,4-Tribromo-3-methyltricyclo-[5.2.1.$0^{2,6}$]dec-8-ene-5,10-dione 10-Ethylene Acetal

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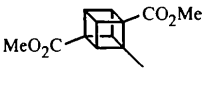
Abstract

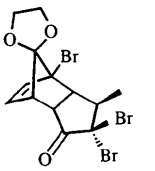
The molecular geometry of the title compound, $C_{13}H_{13}Br_3O_3$, is similar to that observed for the 3-chloro- analogue, *endo*-1,4,4-tribromo-3-methyltricyclo[5.2.1.$0^{2,6}$]dec-8-ene-5,10-dione 10-ethylene acetal.

Comment

We have recently described the preparation of dimethyl 2-methylcubane-1,4-dicarboxylate, (I) (Lowe *et al.*, 1994), through an indirect approach, which featured the *gem*-dibromoketone (II). The structure of (II) was originally assigned on the basis of NOE difference measurements and the X-ray structural analysis reported here was performed to confirm the assignment.



(I)



(II)

The molecular geometry is similar to that observed for the 3-chloro- analogue, *endo*-1,4,4-tribromo-3-chlorotricyclo[5.2.1.$0^{2,6}$]dec-8-ene-5,10-dione 10-ethylene ketal (Gable, Parker & Tsanaktsidis, 1994).

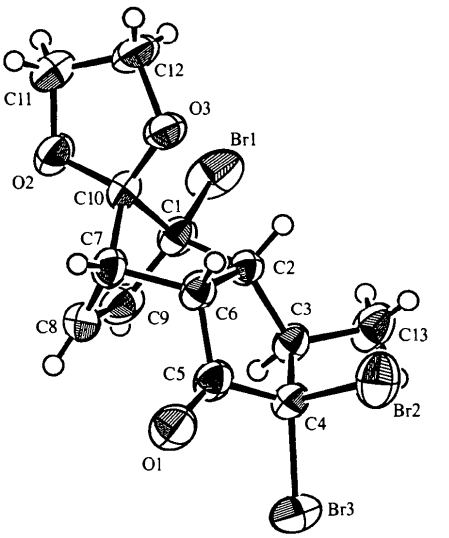


Fig. 1. *ORTEP*II (Johnson, 1976) drawing of (II). Displacement ellipsoids are drawn at the 50% probability level. H atoms are given arbitrary radii of 0.1 Å.

Experimental

Compound (II) was prepared as described by Lowe *et al.* (1994) and crystals were obtained by slow evaporation from diethyl ether.

Crystal data

$C_{13}H_{13}Br_3O_3$
M_r = 456.96
Triclinic
$P\bar{1}$
a = 6.6161 (13) Å
b = 9.633 (2) Å
c = 12.692 (3) Å
α = 98.27 (2)°
β = 104.84 (2)°
γ = 106.74 (2)°
V = 727.8 (3) Å^3
Z = 2
D_x = 2.085 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 11.3–21.2°
μ = 8.314 mm^{-1}
T = 293 (1) K
Block
0.40 × 0.37 × 0.37 mm
Colourless

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