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X-ray Structure Investigations of Potential β-Blockers. III

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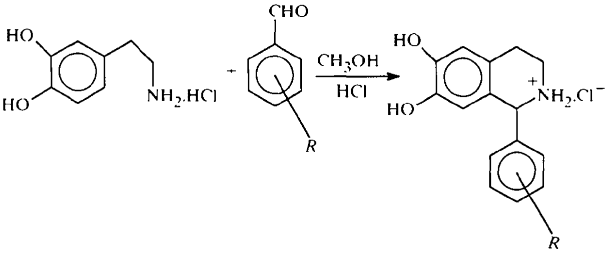
Abstract

X-ray studies of 6,7-dihydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinolinium chloride hydrate ($C_{15}H_{16}NO_2^+.Cl^-.H_2O$), 6,7-dihydroxy-1-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolinium chloride ($C_{16}H_{18}NO_3^+.Cl^-$) and 6,7-dihydroxy-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinolinium chloride ($C_{15}H_{15}N_2O_4^+.Cl^-$) show that the saturated parts of the rings have deformed half-chair conformations, with equatorially attached phenyl rings. All three structures are ionic, and hydrogen bonds are observed.

Comment

This paper is a continuation of the structural work on saturated isoquinoline derivatives reported by Olszak (Olszak *et al.*, 1994, 1996). Tetrahydroisoquinolines are known to exhibit β-adrenomimetic activity (Brzezińska, 1994). A group of 1-aryl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline [where 1-aryl is phenyl in (I), 2-methoxyphenyl in (II) and 4-nitrophenyl in (III)] derivatives was synthesized at the Institute of Chemistry and Technology of Drugs, University of Medicine, Łódź, in order to determine the role of the hydrophobic group at C1 on the activity of these structures as β-adrenoreceptors (Brzezińska *et al.*, 1996).



(I) R=H
(II) R=2-OCH$_3$
(III) R=4-NO$_2$

The title structures, (I).H_2O, (II) and (III), are shown in perspective views with the atomic numbering schemes in Figs. 1–3. Selected bond lengths, bond angles and details of the hydrogen-bonding geometry are listed in Tables 1–6.

The title structures differ slightly from each other in the substituents on the phenyl group (see Scheme). The saturated parts of the molecules have either half-chair, (I), or deformed half-chair tending towards twisted-boat conformations, (II) and (III). The Cremer & Pople (1975) puckering parameters for the N1–C1–C9–C8–C3–C2 atom sequence are: Q = 0.504 (2), 0.498 (3), 0.563 (2) Å; φ_2 = 165.2 (4), 142.4 (4), 156.4 (3)°; θ_2 = 131.3 (3), 129.1 (3), 128.9 (2)° for (I), (II) and (III), respectively. There are pseudo-twofold axes passing through the midpoints of the N1—C2 and C8—C9 bonds [asymmetry parameters (Nardelli, 1983*a*): Δ_2 =

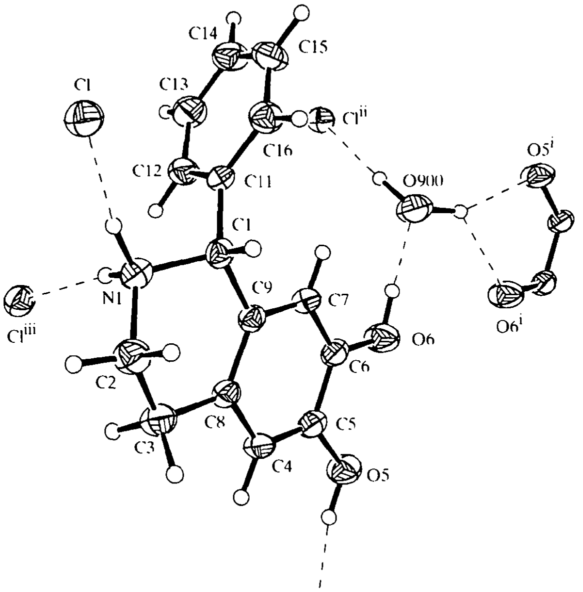


Fig. 1. Plot of (I), showing the atomic numbering scheme. Displacement ellipsoids are shown at 40% probability. Symmetry codes are as given in Table 2.

0.057 (1), 0.028 (1), 0.0294 (9) for (I), (II) and (III), respectively].

The phenyl rings and the aromatic parts of the saturated isoquinoline moieties are planar, and make angles of 77.72 (7), 80.96 (9) and 89.50 (6)° for (I), (II) and (III), respectively. Saturation of the isoquinoline moieties does not influence the aromatic parts of the molecules. The phenyl rings are equatorial with torsion angles of C2—N1—C1—C11 −178.1 (2), 171.2 (2), −177.2 (2)°; C11—C1—C9—C8 −149.8 (2), −133.8 (3), −142.4 (2)°, for (I), (II) and (III), respectively.

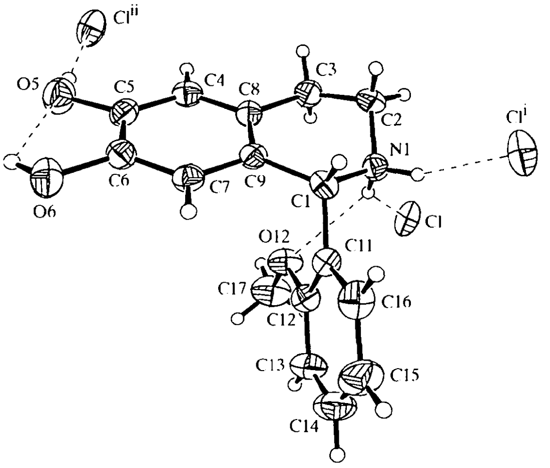


Fig. 2. Plot of (II), showing the atomic numbering scheme. Displacement ellipsoids are shown at 40% probability. Symmetry codes are as given in Table 4.

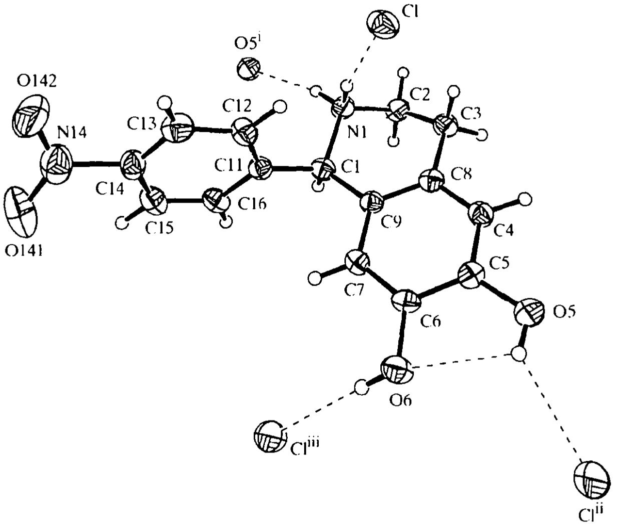


Fig. 3. Plot of (III), showing the atomic numbering scheme. Displacement ellipsoids are shown at 40% probability. Symmetry codes are as given in Table 6.

The molecules within all three structures are linked by an intermolecular net of hydrogen bonds (see Tables 2, 4 and 6). A comparison of bond lengths and angles with those of similar compounds studied previously (Olszak *et al.*, 1994, 1996) does not reveal any significant differences. All three structures are found to be ionic, with the proton of the hydrochloric acid added to the N atom of the isoquinoline moiety.

Experimental

The three structures were synthesized using the Picket–Spengler reaction of 3-hydroxytyramine with the appropriate aldehydes (Brzezińska *et al.*, 1996).

Compound (I)

Crystal data

$C_{15}H_{16}NO_2^+.Cl^-.H_2O$
$M_r = 295.75$
Monoclinic
$P2_1/n$
$a = 9.118\,(1)$ Å
$b = 9.149\,(2)$ Å
$c = 17.633\,(1)$ Å
$\beta = 95.17\,(1)°$
$V = 1464.9\,(4)$ Å^3
$Z = 4$
$D_x = 1.341$ Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 25 reflections
$\theta = 22.87–36.56°$
$\mu = 2.372$ mm^{-1}
$T = 293\,(2)$ K
Prism
0.2 × 0.1 × 0.1 mm
Colourless

Data collection

Rigaku AFC-5*S* diffractometer
ω scan
Absorption correction: empirical ψ-scan correction (North *et al.*, 1968)
$T_{min} = 0.668$, $T_{max} = 0.789$
8388 measured reflections
2180 independent reflections

1289 reflections with $I > 2\sigma(I)$
$R_{int} = 0.062$
$\theta_{max} = 60.08°$
$h = -10 \rightarrow 10$
$k = -10 \rightarrow 10$
$l = -19 \rightarrow 19$
3 standard reflections every 150 reflections intensity decay: <2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.027$
$wR(F^2) = 0.057$
$S = 0.788$
2180 reflections
252 parameters
H-atom treatment: see below
$w = 1/[\sigma^2(F_o^2) + (0.0230P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.032$

$\Delta\rho_{max} = 0.141$ e Å^{-3}
$\Delta\rho_{min} = -0.209$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0041 (2)
Scattering factors from *International Tables for Crystallography* (Vol. C)

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

N1—C2	1.503 (2)	C3—C8	1.512 (3)
N1—C1	1.506 (3)	C3—C2	1.511 (3)
C1—C11	1.506 (2)	C9—C8	1.388 (2)
C1—C9	1.522 (3)		

C2—N1—C1	111.15 (17)	C7—C9—C8	119.9 (2)
N1—C1—C11	111.11 (16)	C7—C9—C1	118.43 (19)
N1—C1—C9	109.42 (18)	C8—C9—C1	121.64 (19)
C11—C1—C9	114.12 (17)	C9—C8—C4	118.3 (2)
C8—C3—C2	113.8 (2)	C9—C8—C3	121.82 (19)
N1—C2—C3	110.4 (2)	C4—C8—C3	119.89 (19)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H101···Cl	1.09 (2)	2.12 (2)	3.206 (2)	172 (2)
O6—H600···O900	0.94 (2)	1.70 (2)	2.644 (2)	178 (2)
O900—H901···O6^i	1.03 (2)	2.10 (2)	2.847 (2)	128 (1)
O900—H901···O5^i	1.03 (2)	2.22 (2)	3.186 (2)	155 (1)
O900—H902···Cl^{ii}	1.04 (2)	2.17 (1)	3.206 (2)	176 (1)
N1—H102···Cl^{iii}	0.93 (2)	2.28 (2)	3.189 (2)	165 (2)
O5—H500···Cl^{iv}	0.94 (2)	2.21 (2)	3.126 (2)	168 (2)

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

Compound (II)

Crystal data

$C_{16}H_{18}NO_3^+.Cl^-$
$M_r = 307.76$
Monoclinic
$P2_1/a$
$a = 7.846$ (2) Å
$b = 19.956$ (4) Å
$c = 9.751$ (1) Å
$\beta = 94.60$ (1)°
$V = 1521.8$ (5) Å^3
$Z = 4$
$D_x = 1.343$ Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 25 reflections
$\theta = 23.23$–31.19°
$\mu = 2.306$ mm^{-1}
$T = 293$ (2) K
Prism
0.2 × 0.15 × 0.1 mm
Colourless

Data collection

Rigaku *AFC*-5*S* diffractometer
ω scan
Absorption correction: empirical ψ-scan correction (North *et al.*, 1968)
$T_{\min} = 0.575$, $T_{\max} = 0.794$
2025 measured reflections
1840 independent reflections

1012 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.025$
$\theta_{\max} = 60.06°$
$h = 0 \rightarrow 6$
$k = 0 \rightarrow 22$
$l = -10 \rightarrow 10$
3 standard reflections every 100 reflections intensity decay: <2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.033$
$wR(F^2) = 0.062$
$S = 0.751$
1840 reflections
193 parameters
H-atom treatment: see below
$w = 1/[\sigma^2(F_o^2) + (0.0178P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} = 0.093$

$\Delta\rho_{\max} = 0.140$ e Å^{-3}
$\Delta\rho_{\min} = -0.157$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0043 (2)
Scattering factors from *International Tables for Crystallography* (Vol. C)

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

N1—C2	1.493 (3)	C2—C3	1.500 (3)
N1—C1	1.503 (3)	C3—C8	1.517 (3)
C1—C11	1.514 (3)	C8—C9	1.386 (3)
C1—C9	1.517 (3)		
C2—N1—C1	113.7 (2)	C9—C8—C4	119.3 (3)
N1—C1—C11	107.7 (2)	C9—C8—C3	121.4 (3)
N1—C1—C9	110.7 (2)	C4—C8—C3	119.4 (3)
C11—C1—C9	115.3 (2)	C8—C9—C7	119.6 (2)
N1—C2—C3	108.9 (2)	C8—C9—C1	122.5 (3)
C2—C3—C8	112.1 (2)	C7—C9—C1	117.8 (3)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H102···Cl	0.90	2.46	3.224 (2)	143
N1—H102···O12	0.90	2.34	2.926 (3)	123
O6—H600···O5	0.82	2.25	2.697 (3)	115
N1—H101···Cl^i	0.90	2.19	3.041 (2)	158
O5—H500···Cl^{ii}	0.82	2.26	3.076 (2)	174

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

Compound (III)

Crystal data

$C_{15}H_{15}N_2O_4^+.Cl^-$
$M_r = 322.74$
Orthorhombic
Pbca
$a = 15.1362$ (8) Å
$b = 15.8851$ (7) Å
$c = 11.861$ (1) Å
$V = 2851.8$ (3) Å^3
$Z = 8$
$D_x = 1.503$ Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 25 reflections
$\theta = 22.84$–29.61°
$\mu = 2.570$ mm^{-1}
$T = 293$ (2) K
Sphere
0.15 mm (radius)
Colourless

Data collection

Rigaku *AFC*-5*S* diffractometer
ω scan
Absorption correction: calculated (Nardelli, 1993)
$T_{\min} = 0.567$, $T_{\max} = 0.590$
15 728 measured reflections
2114 independent reflections

1384 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.047$
$\theta_{\max} = 60.09°$
$h = -16 \rightarrow 16$
$k = -17 \rightarrow 17$
$l = -13 \rightarrow 13$
3 standard reflections every 200 reflections intensity decay: 2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.032$
$wR(F^2) = 0.084$
$S = 0.914$
2114 reflections
259 parameters
H-atom treatment: see below
$w = 1/[\sigma^2(F_o^2) + (0.0530P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} = 0.010$

$\Delta\rho_{\max} = 0.291$ e Å^{-3}
$\Delta\rho_{\min} = -0.243$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0012 (1)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 5. *Selected geometric parameters (Å, °) for (III)*

N1—C2	1.507 (3)	C8—C9	1.392 (3)
N1—C1	1.515 (3)	C9—C1	1.511 (3)
C2—C3	1.508 (3)	C1—C11	1.514 (3)
C3—C8	1.511 (3)		
C2—N1—C1	109.57 (18)	C8—C9—C7	119.5 (2)
N1—C2—C3	107.09 (19)	C8—C9—C1	121.37 (19)
C2—C3—C8	112.5 (2)	C7—C9—C1	119.09 (19)
C4—C8—C9	118.9 (2)	C9—C1—C11	115.73 (18)
C4—C8—C3	119.23 (19)	C9—C1—N1	109.05 (18)
C9—C8—C3	121.9 (2)	C11—C1—N1	108.56 (17)

Table 6. *Hydrogen-bonding geometry (Å, °) for (III)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H102···Cl	0.98 (3)	2.51 (3)	3.481 (2)	168 (2)
O5—H500···O6	0.82	2.30	2.731 (2)	114
N1—H101···O5^{i}	0.96 (3)	1.97 (3)	2.898 (3)	163 (3)
O5—H500···Cl^{ii}	0.82	2.37	3.000 (2)	134
O6—H600···Cl^{iii}	0.82	2.31	3.129 (2)	178

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

For (I), the water H atom parameters were found from $\Delta\rho$ maps, and refined with constraints ($U_{iso} = 1.3U_{eq}$ of the parent O atom). The other H atoms had all parameters refined. For (II), H atoms were constrained to ride on the parent atoms using the *AFIX* option in *SHELXL*97 (Sheldrick, 1997). For (III), an idealized geometry was applied to the hydroxy H atoms and all parameters were refined for the other H atoms.

For all compounds, data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1989*a*); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *TEXSAN* (Molecular Structure Corporation, 1989*b*); program(s) used to solve structures: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structures: *SHELXL*97; molecular graphics: *ORTEX* (McArdle, 1995); software used to prepare material for publication: *PARST* (Nardelli, 1983*b*).

The author is grateful to Dr E. Brzezińska from the Institute of Chemistry and Technology of Drugs, University of Medicine, Łódź, Poland, for supplying him with the crystals.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1324). Services for accessing these data are described at the back of the journal.

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2*H*-1-Benzopyrans. III. 4-Hydroxy-3-methoxycarbonyl-2-dimethoxyphosphoryl-2*H*-1-benzopyran†

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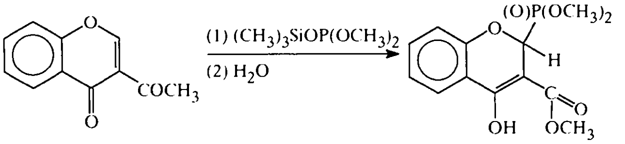
(Received 22 July 1997; accepted 6 April 1998)

Abstract

The title compound, $C_{13}H_{15}O_7P$, consists of two condensed rings, namely, a pyranoid ring with an axially attached partially disordered dimethoxyphosphoryl group and a benzene ring. The conformation of the pyranoid ring is halfway between half-boat and half-chair, and the fusion of the rings does not exert significant influence on the planarity of the benzene ring.

Comment

This paper is a continuation of structural investigations on benzopyran derivatives (Olszak *et al.*, 1994, 1997). Since the 2*H*-1-benzopyran derivatives are known to exhibit spasmolytic effects (Kostka *et al.*, 1994), the title compound, (I), is expected to be pharmacologically active.



(I)

In (I), fusion with the pyranoid ring has no significant influence on the planarity of the benzene ring. The skeleton of the pyranoid ring itself shows a pseudo-twofold axis running through the midpoints of the C1—O1 and C3—C9 bonds [Δ_2(C1—O1) = 0.036 (1); Nardelli, 1983*a*]. Examination of the puckering parameters (Cremer & Pople, 1975) indicates an approximate half-chair conformation of the ring [Q_T = 0.323 (2) Å, Φ_2 = −137.5 (5)° and θ_2 = 116.9 (4)°, for the O1—C1—C2—C3—C9—C8 sequence].

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† Alternative name: methyl 2-dimethoxyphosphoryl-4-hydroxy-2*H*-1-benzopyran-3-carboxylate.

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