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Stereochemistry of Anticholinergic Agents. XVI.* Structure of *endo*-2-Phenylpropionic Acid 8-Methyl-8-azabicyclo[3.2.1]oct-3-yl Ester (Hydratropyltropine) Hydrochloride Dihydrate, $C_{17}H_{24}NO_2^+.Cl^-.2H_2O$†

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Abstract. $M_r = 345{\cdot}9$, monoclinic, $P2_1/c$, $a = 8{\cdot}104\ (7)$, $b = 19{\cdot}647\ (6)$, $c = 12{\cdot}173\ (6)$ Å, $\beta = 105{\cdot}82\ (5)°$, $U = 1864{\cdot}8$ Å^3, $Z = 4$, $D_x = 1{\cdot}232$ Mg m^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}182$ mm^{-1}, $F(000) = 744$, room temperature, $R = 0{\cdot}0637$ for 1202 observed reflections. The phenyl ring is oriented at an angle of 83 (1)° to the plane of the ester group and forms, with the tropane ring system, the extremities of a claw-like arrangement, typical of anticholinergic agents. The N···centre-of-phenyl-ring distance is 6·08 (1) Å.

Introduction. The title compound differs from the potent anticholinergic alkaloid atropine in that the 2-hydroxmethyl group of atropine has been reduced to methyl. This simple chemical modification results in a 200-fold decrease in anticholinergic activity as measured by the effect on salivation in dogs (Barlow, 1964). The crystal structure of atropine (hyoscyamine) hydrobromide has been determined (Kussäther & Haase, 1972). The structure analysis of the title compound was undertaken to determine whether there might be a geometrical basis for the difference in anticholinergic activity between the two compounds.

Experimental. Crystals from aqueous ethanol, Enraf–Nonius CAD-4 diffractometer, crystal 0·4 × 0·2 × 0·2 mm, cell dimensions from setting angles of 25 reflections, graphite-monochromated Mo $K\alpha$ radiation, no absorption corrections, 3252 unique reflections scanned, ω–2θ mode, $2 < \theta < 25°$, 1202 used in analysis [$I > 3{\cdot}5\sigma(I)$], index range $h \pm 9$, $k\ 0/21$, $l\ 0/13$; three standard reflections measured every 2 h, no significant variation with time; structure solved by direct methods with *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978); H atoms mostly located from difference map, remainder in calculated positions, not refined but included in calculations with $U_{iso} = 0{\cdot}05$ Å^2; non-hydrogen atoms refined anisotropically; full-matrix least squares, F magnitudes, $R = 0{\cdot}064$, $wR = 0{\cdot}082$, $w = 1/[\sigma^2(F) + 0{\cdot}0006\,F^2]$; max. Δ/σ in final least-squares cycle 0·06; residual electron density in final difference map within $\pm 0{\cdot}3$ e Å^{-3}; no correction for secondary extinction; atomic scattering factors from *International Tables for X-ray Crystallography* (1974); computations carried out with *SHELX* (Sheldrick, 1978).

Discussion. Final atomic parameters are listed in Table 1;‡ bond lengths and selected torsion angles are in Table 2. The geometry of the cation is illustrated in Fig. 1.

The tropane ring system adopts a conformation typical of 3α-substituted derivatives, with the piperidinium ring C(1)–(5),N in a chair-like shape, which is, however, significantly flattened at C(3). C(1), C(2), C(4), C(5) are coplanar to within ±0·003 Å, N and C(3) being displaced by 0·88 (1) and 0·49 (1) Å on opposite sides of this plane. This distortion is also evident from the values of the ring torsion angles (Table 2). The ring flattening at C(3) has been attributed to repulsive interactions between the axial substituent and the ethylene bridge (Hamor & Kings, 1980). The five-membered ring C(1),C(5)–(7),N is in the envelope conformation, the nitrogen atom being displaced by 0·71 (1) Å from the mean plane through the other four atoms.

The ester group C(3), O(1), C(9), O(2), C(10) adopts the antiperiplanar conformation typical of esters, torsion angle C(10)–C(9)–O(1)–C(3) −178·9 (9)°; the corresponding angle in atropine hydrobromide is −170° (Kussäther & Haase, 1972). The orientation of the ester group relative to the semi-rigid tropane ring system is determined by the conformation about O(1)–C(3). Torsion angles C(9)–O(1)–C(3)–C(4)

* Part XV: Chananont & Hamor (1981).

† Contribution from the Crystallography Unit, Universities of Aston and Birmingham.

‡ Lists of structure factors, anisotropic thermal parameters, H-atom coordinates, bond angles, and details of the hydrogen-bonding geometry have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39981 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Fractional coordinates* ($\times 10^4$) *with e.s.d.'s in parentheses and equivalent isotropic thermal parameters* ($Å^2 \times 10^4$)

$U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33} + 2U_{13}\cos\beta)$.

	x	y	z	U_{eq}
C(1)	−2571 (9)	−224 (4)	−3740 (6)	454
C(2)	−659 (9)	−221 (4)	−3535 (6)	459
C(3)	234 (8)	−811 (4)	−2804 (6)	465
C(4)	−568 (9)	−976 (4)	−1847 (6)	504
C(5)	−2475 (9)	−922 (4)	−2194 (6)	477
C(6)	−3380 (9)	−1340 (4)	−3227 (7)	528
C(7)	−3436 (9)	−876 (4)	−4254 (6)	502
C(8)	−4745 (9)	−9 (4)	−2651 (7)	620
C(9)	1178 (10)	−1459 (5)	−4190 (8)	623
C(10)	868 (11)	−2126 (5)	−4831 (9)	791
C(11)	2190 (12)	−2274 (5)	−5399 (10)	1093
C(12)	−967 (10)	−2164 (4)	−5588 (8)	505
C(13)	−2130 (10)	−2558 (4)	−5269 (7)	516
C(14)	−3819 (12)	−2570 (5)	−5908 (9)	649
C(15)	−4342 (13)	−2187 (6)	−6845 (10)	800
C(16)	−3201 (18)	−1784 (5)	−7205 (8)	813
C(17)	−1511 (15)	−1775 (4)	−6564 (10)	693
N	−2929 (6)	−210 (3)	−2585 (5)	384
O(1)	139 (6)	−1424 (3)	−3478 (5)	552
O(2)	2156 (7)	−1007 (3)	−4270 (5)	687
O*W*(1)	7217 (7)	−4451 (3)	−4366 (5)	724
O*W*(2)	3636 (7)	−862 (3)	−254 (5)	821
Cl	1090 (3)	−1034 (1)	1336 (2)	727

Table 2. *Molecular dimensions*

(*a*) Bond lengths (Å)

C(1)–C(2)	1·501 (10)	O(1)–C(9)	1·365 (9)
C(2)–C(3)	1·519 (10)	C(9)–O(2)	1·212 (10)
C(3)–C(4)	1·516 (10)	C(9)–C(10)	1·511 (11)
C(4)–C(5)	1·491 (9)	C(10)–C(11)	1·454 (10)
C(5)–C(6)	1·514 (10)	C(10)–C(12)	1·523 (11)
C(6)–C(7)	1·538 (11)	C(12)–C(13)	1·356 (10)
C(7)–C(1)	1·512 (10)	C(13)–C(14)	1·378 (11)
C(1)–N	1·511 (8)	C(14)–C(15)	1·335 (13)
C(5)–N	1·491 (9)	C(15)–C(16)	1·377 (13)
N–C(8)	1·505 (8)	C(16)–C(17)	1·379 (13)
O(1)–C(3)	1·447 (8)	C(12)–C(17)	1·380 (12)

(*b*) Intramolecular non-bonded distances (Å); e.s.d.'s are 0·01 Å. The corresponding values for atropine are given in parentheses; e.s.d.'s for these are *ca* 0·05 Å.

N···O(1)	3·81 (3·74)	N···C(9)	4·95 (4·91)
N···O(2)	5·31 (5·30)	N···C(10)	5·98 (5·93)

N···centre of phenyl ring 6·08 (6·12)

(*c*) Selected torsion angles (°); e.s.d.'s are *ca* 1·2°

C(1)–C(7)–C(6)–C(5)	−0·3
C(7)–C(6)–C(5)–N	29·3
C(6)–C(5)–N–C(1)	−47·1
C(5)–N–C(1)–C(7)	46·7
N–C(1)–C(7)–C(6)	−28·3
C(3)–C(2)–C(1)–N	57·8
C(2)–C(1)–N–C(5)	−74·0
C(1)–N–C(5)–C(4)	75·0
N–C(5)–C(4)–C(3)	−59·4
C(5)–C(4)–C(3)–C(2)	38·9
C(4)–C(3)–C(2)–C(1)	−38·6
C(3)–C(2)–C(1)–C(7)	−55·2
C(2)–C(1)–C(7)–C(6)	87·4
C(3)–C(4)–C(5)–C(6)	54·7
C(4)–C(5)–C(6)–C(7)	−87·5
C(9)–O(1)–C(3)–C(2)	74·7
C(9)–O(1)–C(3)–C(4)	−162·6
C(13)–C(12)–C(10)–C(9)	−104·5
C(17)–C(12)–C(10)–C(9)	71·6
C(12)–C(10)–C(9)–O(1)	63·2
C(10)–C(9)–O(1)–C(3)	−178·9
C(11)–C(10)–C(9)–O(1)	−166·5

and C(9)–O(1)–C(3)–C(2) (Table 2) are quite similar to the corresponding angles in *O*-benzoyltropine hydrochloride, −154·5 and 82·5° (Hamor, 1976) and in atropine hydrobromide, −177 and 74° (Kussäther & Haase, 1972). This orientation apparently results in a favourable interaction between the carbonyl oxygen atom and the equatorial H atoms at C(2) and C(3). The phenyl ring is planar to within ±0·007 Å and is steeply inclined to the plane of the ester group [dihedral angle 83 (1)°]. In atropine hydrobromide the corresponding dihedral angle is 90° and the relevant torsion angles C(12)–C(10)–C(9)–O(1) and C(13)–C(12)–C(10)–C(9) are also similar, with values of 77 and −119° (*cf.* Table 2).

The overall shape of the cation is remarkably similar to that of atropine in the hydrobromide salt [*cf.* Fig. 1 and the stereodiagram in Kussäther & Haase (1972)]. Intramolecular non-bonded distances between the onium nitrogen atom and O(1), C(9), O(2), C(10) and the centre of the phenyl ring, which may be relevant to the binding of the antagonist to the muscarinic receptor, agree very closely with those in atropine, the maximum difference being only 0·07 Å (see Table 2).

The conformation adopted by atropine is typical of potent anticholinergic agents (Meyerhöffer, 1972; Guy & Hamor, 1974; Pauling & Datta, 1980) and the 200-fold reduction in anticholinergic activity brought about by the replacement of OH by H (atropine→title compound) is therefore not due to the cation adopting a conformation that is unsuitable for binding to the muscarinic receptor. It would seem that the hydroxyl group of atropine may be directly involved in the binding.

Bond lengths and angles are generally normal. The methyl C(11) is however involved in a rather short bond with C(10) of 1·454 (10) Å, possibly an artefact of the high thermal motion of C(11) [U_{33} = 0·195 (12) $Å^2$].

In the crystal, cations (*via* the N atom), chloride ions and water molecules are linked by a network of N–H···Cl, O–H···Cl and O–H···O hydrogen bonds. Details have been deposited.

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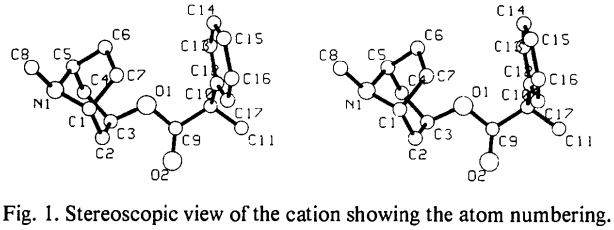

Fig. 1. Stereoscopic view of the cation showing the atom numbering.

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Structure of 1-[(3-Methyl-4-isothiazolyl)methyl]guanidinium Hemisulfate, CG-8345-GO, $C_6H_{10}N_4S.\frac{1}{2}H_2SO_4$

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Abstract. Noradrenaline depletor. $M_r = 219{\cdot}28$, monoclinic, $P2_1/c$, $a = 8{\cdot}653$ (1), $b = 7{\cdot}473$ (2), $c = 32{\cdot}042$ (5) Å, $\beta = 92{\cdot}36$ (1)°, $V = 2070{\cdot}1$ (4) Å^3, $Z = 8$ (two independent molecules), $D_x = 1{\cdot}41$ g cm^{-3}, Cu $K\bar{\alpha}$, $\lambda = 1{\cdot}54178$ Å, $\mu = 34{\cdot}7$ cm^{-1}, $F(000) = 920$, room temperature, $R = 0{\cdot}059$ for 2136 reflections. The two independent molecules exhibit two different conformations in which the position of the guanidine group relative to the ring differs. The two conformations are compared with a model of the α-adrenoceptor ligand. The protonation occurs on double-bonded N(2), which makes the terminal N(1), N(3) equivalent. The molecules are held together by strong hydrogen bonds, which involve the solvate ions.

Introduction. The title compound attracted attention because of its potent depleting action on myocardial noradrenaline. It also blocks selectively the adrenergic transmission to the heart. Its mechanism of action, very similar to that of guanethidine, has been recently elucidated (Kaul & Grewal, 1981).

It seemed interesting to compare the solid-state conformation of CG-8345-GO with those of dihydroimidazole or guanidine α-adrenoceptor ligands (Carpy, Léger, Leclerc, Decker, Rouot & Wermuth, 1982).

Experimental. Small white prisms (from methanol), 0·30 × 0·18 × 0·10 mm, Enraf–Nonius CAD-4 diffractometer with graphite monochromator, 20 reflections ($6 < \theta < 14°$) used to refine orientation matrix, systematic absences: $h0l$ for l odd, $0k0$ for k odd, 3074 ($\pm h,k,l$) independent with $\theta < 60°$, h −10 to +10, k 0 to +8, l 0 to +37, 2136 with $I \geq 3\sigma(I)$, Lp correction, absorption ignored; two check reflections (122, 014) every 5400 s showed no unusual variation (all within $\pm 3\sigma$); direct methods, *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980), anisotropic diagonal matrix, refinement on F using observed reflections, $w = 1$ if $|F_o| < P$, $P = (F^2_{o\max}/10)^{1/2}$, $w = (P/F_o)^2$ if $|F_o| > P$, H from ΔF synthesis – isotropic, $R = 0{\cdot}059$, $wR = 0{\cdot}076$, $S = 1{\cdot}19$ (2136 reflections, 332 parameters), max. $\Delta\rho$ excursion $\pm 0{\cdot}5$ e Å^{-3} in final ΔF map; in final cycle mean and max. $\Delta/\sigma = 0$ and 0·1; H-atom form factors from Stewart, Davidson & Simpson (1965), all other form factors from *International Tables for X-ray Crystallography* (1974), S corrected for anomalous dispersion; Mini 6, CII computer.

Discussion. Table 1 gives the atomic coordinates and Table 2 the bond distances and angles.* Diagrams of the two independent molecules with the atom numbering are shown in Fig. 1.

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and mean planes of atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39967 (25 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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