O(8) atoms; the methanol is near to the O(4) and O(12) atoms. Both guest molecules have distances larger than 3·6 Å (without considering hydrogens) from the surrounding atoms.

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Structure of 8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 3,5-Dichlorobenzoate Methylsulfate Monohydrate (MDL 72222), an Antagonist at Neuronal 5-HT Receptors

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Abstract. $C_{15}H_{18}Cl_2NO_2^+.CH_3SO_3^-.H_2O$, $M_r = 428{\cdot}33$, triclinic, $P\bar{1}$, $a = 7{\cdot}457\ (2)$, $b = 8{\cdot}389\ (1)$, $c = 15{\cdot}916\ (3)$ Å, $\alpha = 79{\cdot}59\ (1)$, $\beta = 85{\cdot}63\ (2)$, $\gamma = 87{\cdot}16\ (2)°$, $V = 975{\cdot}8\ (2)$ Å^3, $Z = 2$, $D_x = 1{\cdot}46$ g cm^{-3}, $\bar{\lambda}$(Cu $K\alpha$) = 1·54178 Å, $\mu = 42{\cdot}32$ cm^{-1}, $F(000) = 448$, room temperature, $R = 0{\cdot}041$ for 2419 independent observed reflections. The cation can be described in terms of the tropane group and an approximately planar dichlorobenzoate group. This conformation is compared with those of some structurally related antichlolinergic agents.

Introduction. Among a series of substituted benzoic acid esters of tropine (Fozard & Gittos, 1983), the title compound named MDL 72222 exerts potent and selective blocking actions at certain excitatory 5-hydroxytryptamine receptors on mammalian peripheral neurones (Fozard, 1984). As it is related to atropine and to potent anticholinergics, we decided to investigate its structure and to compare it with models of anticholinergics.

Experimental. White crystal 0·15 × 0·12 × 0·10 mm (from ethanol). Density not determined. Unit-cell parameters and intensity data obtained on an Enraf–Nonius CAD-4 diffractometer with graphite-monochromated Cu $K\alpha$ radiation in ω/θ scan mode ($0 < \theta < 65°$). Cell dimensions refined by least-squares fitting of θ values of 25 reflections. No appreciable drop in intensity of two standard reflections (003 and 00$\bar{3}$)

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checked every 5400 s. 3320 independent reflections collected in $\pm h,k,\pm l$ range −8,0,−18 to 8,9,18; 2419 with $I \geq 3\sigma(I)$ used in subsequent calculations. Intensities corrected for Lorentz and polarization effects but not for absorption. Scattering factors for non-H atoms from *International Tables for X-ray Crystallography* (1974) (Cl and S corrected for anomalous dispersion) and for H from Stewart, Davidson & Simpson (1965). The Wilson statistical test showed a centrosymmetric intensity distribution. Structure solved with *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) and standard Fourier techniques. H atoms located by ΔF synthesis. Block-diagonal-matrix least-squares refinement on F of observed reflections; $w = 1$ if $|F_o| < P$, $P = [F_o^2(\max)/10]^{1/2}$, $w = (P/F_o)^2$ if $|F_o| > P$; anisotropic thermal parameters for all non-H atoms and isotropic ones for H. Final $R = 0{\cdot}041$, $wR = 0{\cdot}052$, $S = 0{\cdot}829$ (2419 reflections, 327 parameters). In final cycle mean and max. Δ/σ 0·1 and 0·5. Residual electron density within $\pm 0{\cdot}3$ e Å^{-3}. Calculations carried out on a Mini 6-92 CII-Honeywell-Bull computer (programs *CRISTA, CRISAF, CRISEC, UTIL,* Laboratory of Crystallography, University of Bordeaux I, Talence).*

Discussion. The atomic parameters are given in Table 1 with the numbering scheme shown in Fig. 1. Bond distances and angles, close to expected values, are listed in Table 2. A view of the crystal structure is shown in Fig. 2.

The phenyl group C(1) to C(6) is planar to well within the limits of experimental error (plane I). The ester grouping, C(1), C(7), O(8), O(9), C(10) is also essentially planar (plane II). The dihedral angle between these two planes is only 7 (1)° [C(2)—C(1)—C(7)—O(8) = −7 (1)° with the sign convention defined by Klyne & Prelog (1960)] so that the phenyl ring and the ester group are almost coplanar.

The piperidinium ring C(10), C(11), C(12), N(13), C(14), C(15) is in a chair-like conformation flattened at C(10). Atoms C(10) and N(13) are displaced by −0·440 (3) and 0·889 (3) Å on opposite sides of the plane containing C(11), C(12), C(14), C(15) (plane III). The ring flattening is also evidenced by the values of torsion angles C(14)—C(15)—C(10)—C(11) (36°) and C(15)—C(10)—C(11)—C(12) (−35°) compared with C(15)—C(14)—N(13)—C(12) (76°) and C(14)—N(13)—C(12)—C(11) (−75°). The ester oxygen atom, O(9), is substituted axially and the *N*-methyl group equatorially. The dihedral angles between planes I–III and planes II–III are 76 (1) and 80 (1)° (Fig. 1).

The five-membered ring C(12), N(13), C(14), C(17), C(16) is in an envelope conformation, the N atom being displaced by 0·681 (3) Å from the mean plane through

Table 1. *Atomic coordinates* (×10⁴) *and equivalent isotropic temperature factors*

$$B_{\rm eq} = \tfrac{4}{3}\sum_i \sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$B_{\rm eq}$(Å^2)
C(1)	3185 (4)	10575 (3)	−755 (2)	2·9 (1)
C(2)	2793 (4)	8944 (3)	−546 (2)	3·2 (2)
C(3)	2028 (4)	8350 (3)	262 (2)	3·2 (2)
C(4)	1640 (4)	9321 (4)	875 (2)	3·2 (2)
C(5)	2066 (4)	10943 (4)	639 (2)	3·0 (1)
C(6)	2801 (4)	11594 (3)	−156 (2)	2·9 (1)
C(7)	4053 (4)	11160 (3)	−1622 (2)	3·1 (2)
O(8)	4579 (3)	10283 (3)	−2110 (1)	4·1 (1)
O(9)	4189 (3)	12772 (2)	−1781 (1)	3·1 (1)
C(10)	5269 (4)	13443 (3)	−2566 (2)	3·0 (1)
C(11)	4195 (4)	13589 (4)	−3350 (2)	3·2 (2)
C(12)	3027 (5)	15156 (4)	−3523 (2)	3·5 (2)
N(13)	4268 (4)	16546 (3)	−3585 (2)	3·3 (1)
C(14)	4597 (4)	16483 (4)	−2658 (2)	3·2 (2)
C(15)	5916 (4)	15061 (4)	−2419 (2)	3·2 (2)
C(16)	1677 (5)	15391 (4)	−2774 (3)	4·4 (2)
C(17)	2729 (5)	16272 (4)	−2204 (2)	4·2 (2)
C(18)	3461 (6)	18144 (4)	−3998 (3)	5·6 (2)
Cl(19)	1493 (1)	6320 (1)	507 (1)	4·8 (0)
Cl(20)	1608 (1)	12202 (1)	1391 (1)	4·4 (0)
S(21)	427 (1)	8251 (1)	3798 (0)	3·3 (0)
O(22)	293 (4)	8013 (4)	2944 (2)	6·3 (2)
O(23)	1476 (4)	6948 (3)	4305 (2)	6·0 (2)
O(24)	−1276 (3)	8561 (3)	4250 (2)	4·2 (1)
C(25)	1689 (5)	9996 (4)	3731 (2)	4·2 (2)
O(26)	2480 (4)	3760 (3)	4420 (2)	6·6 (2)

Table 2. *Bond distances* (Å) *and angles* (°)

C(1)—C(2)	1·389 (5)	O(9)—C(10)	1·471 (4)
C(1)—C(6)	1·397 (5)	C(10)—C(11)	1·517 (5)
C(1)—C(7)	1·487 (5)	C(10)—C(15)	1·525 (5)
C(2)—C(3)	1·383 (5)	C(11)—C(12)	1·534 (5)
C(3)—C(4)	1·385 (5)	C(12)—N(13)	1·508 (5)
C(3)—Cl(19)	1·736 (4)	C(12)—C(16)	1·534 (5)
C(4)—C(5)	1·391 (5)	N(13)—C(14)	1·505 (4)
C(5)—C(6)	1·370 (5)	N(13)—C(18)	1·501 (6)
C(5)—Cl(20)	1·738 (3)	C(14)—C(15)	1·521 (5)
C(7)—O(8)	1·196 (4)	C(14)—C(17)	1·522 (5)
C(7)—O(9)	1·338 (4)	C(16)—C(17)	1·547 (6)
S(21)—O(22)	1·421 (3)	S(21)—O(24)	1·448 (3)
S(21)—O(23)	1·466 (3)	S(21)—C(25)	1·762 (4)
C(2)—C(1)—C(6)	120·1 (3)	O(9)—C(10)—C(11)	111·3 (3)
C(2)—C(1)—C(7)	117·5 (3)	O(9)—C(10)—C(15)	105·9 (3)
C(6)—C(1)—C(7)	122·4 (3)	C(11)—C(10)—C(15)	113·5 (3)
C(1)—C(2)—C(3)	119·0 (3)	C(10)—C(11)—C(12)	113·8 (3)
C(2)—C(3)—C(4)	122·5 (3)	C(11)—C(12)—N(13)	106·8 (3)
C(2)—C(3)—Cl(19)	118·5 (3)	C(11)—C(12)—C(16)	113·8 (3)
C(4)—C(3)—Cl(19)	118·9 (3)	N(13)—C(12)—C(16)	103·2 (3)
C(3)—C(4)—C(5)	116·5 (3)	C(12)—N(13)—C(14)	101·3 (2)
C(4)—C(5)—C(6)	123·2 (3)	C(12)—N(13)—C(18)	113·3 (3)
C(4)—C(5)—Cl(20)	118·0 (2)	C(14)—N(13)—C(18)	113·1 (3)
C(6)—C(5)—Cl(20)	118·8 (2)	N(13)—C(14)—C(15)	106·3 (3)
C(1)—C(6)—C(5)	118·6 (3)	N(13)—C(14)—C(17)	103·6 (3)
C(1)—C(7)—O(8)	123·6 (3)	C(15)—C(14)—C(17)	114·7 (3)
C(1)—C(7)—O(9)	111·9 (3)	C(10)—C(15)—C(14)	114·0 (3)
O(8)—C(7)—O(9)	124·5 (3)	C(12)—C(16)—C(17)	104·7 (3)
C(7)—O(9)—C(10)	115·9 (2)	C(14)—C(17)—C(16)	105·0 (3)
O(22)—S(21)—O(23)	112·8 (2)	O(23)—S(21)—O(24)	110·9 (2)
O(22)—S(21)—O(24)	114·6 (2)	O(23)—S(21)—C(25)	104·8 (2)
O(22)—S(21)—C(25)	106·4 (2)	O(24)—S(21)—C(25)	106·5 (2)

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* Lists of structure amplitudes, anisotropic thermal parameters, H-atom coordinates and least-squares-planes data have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44510 (26 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

the four C atoms (plane IV). The dihedral angles between planes I–IV and planes II–IV are 55 (1) and 57 (1)° while that between planes III–IV is 66 (1)° (Figs. 1 and 3*a*).

The tropine system has an approximate mirror plane of symmetry passing through the N atom, O(9), C(10) and C(18) (plane V). The deviations of the 'symmetrical' atoms from plane V are for the couple C(11)–C(15) −1·269 (3) and 1·271 (3) Å, for the couple C(12)–C(14) −1·204 (4) and 1·122 (3) Å and for the couple C(16)–C(17) −0·906 (4) and 0·638 (4) Å. The angle between the ester plane (plane II) and this pseudo-mirror plane is 41 (1)° (Figs. 3*a* and 3*b*).

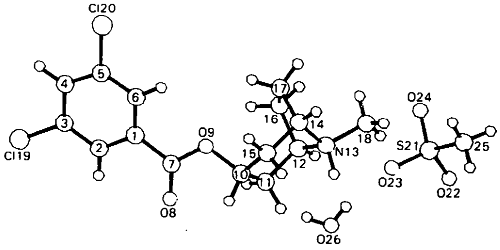


Fig. 1. Projection on the phenyl plane showing the numbering of atoms.

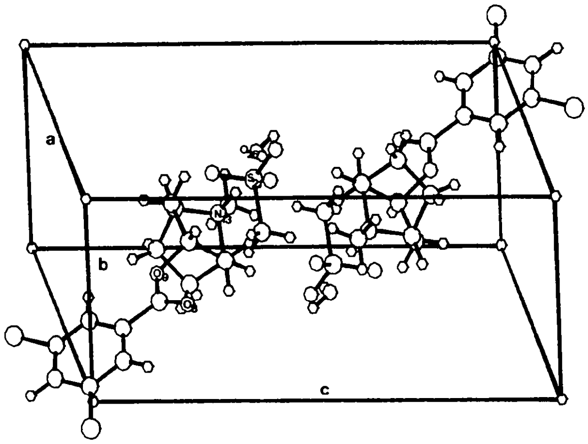
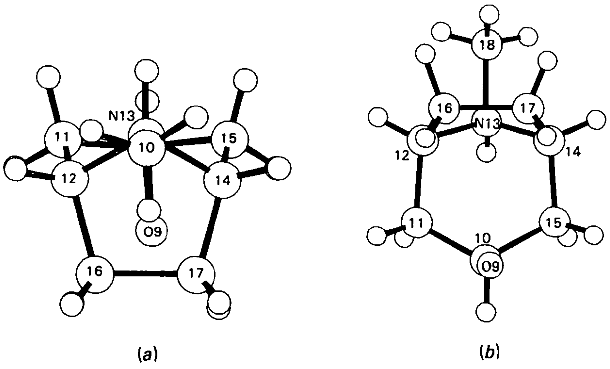


Fig. 2. Contents of a unit cell.



(*a*) (*b*)

Fig. 3. (*a*) Projection of the tropine system on the mean plane C(12)–C(14)–C(16)–C(17). (*b*) Projection of the tropine system on the mean plane C(11)–C(12)–C(14)–C(15).

The orientation of the planar ester group relative to the tropine system is defined by the two torsion angles C(7)–O(9)–C(10)–C(11) = 81 (1) and C(7)–O(9)–C(10)–C(15) = −156 (1)°.

Assuming that the cationic head and the phenyl ring are involved in the binding of this molecule to 5-HT receptors we have calculated the distance between N(13) and Φ_1, the centre of the phenyl ring, as 7·3 Å. The deviation of N(13) from plane I is −1·446 (3) Å so that the angle between the line N(13)–Φ_1 and plane I is 11·3°.

We have compared MDL 72222 with anticholinergic agents such as scopolamine *N*-oxide (Huber, Fodor & Mandava, 1971), *N*-butylhyoscíamine (Léger, Gadret & Carpy, 1978) and *O*-benzoyltropine (a weak agent) (Hamor, 1976). The conformation of the tropine system is very close in the four compounds; however, the *N*-methyl group is axial in scopolamine and hyosciamine and equatorial in *O*-benzoyltropine and MDL 72222. The nitrogen to centre-of-phenyl-ring distances are also comparable, in the range 7·1–7·7 Å. However, the deviation of N from the plane of the phenyl ring is much higher in scopolamine and hyosciamine (−5·436 and −3·994 Å) than in *O*-benzoyltropine and MDL 72222 (−1·480 and −1·446 Å). Finally, the orientation of the phenyl ring relative to the plane of the ester group differs also between the two sub-groups of molecules, being 78 and 69° in scopolamine and hyosciamine and only 6 and 7° in *O*-benzoyltropine and MDL 72222.

The organic cations are hydrogen bonded with water molecules N(13)···O(26) $(1-x,\ 2-y,\ -z)$ = 2·699 (4) Å, N(13)–H(113) = 1·03 (4) Å, H(113)···O(26) = 1·68 Å, N(13)–H(113)···O(26) = 170 (3)°. At the same time the hydrogen-bond network links a methanesulfonate and a water molecule, O(24)···O(26) $(-x,\ 1-y,\ 1-z)$ = 2·733 (4), O(24)···H(126) = 1·92 (4) Å, O(24)···H(126)–O(26) = 168 (4)°.

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