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3-(Diphenylmethoxy)-8-methyl-8-azoniabicyclo[3.2.1]octane Methanesulphonate Monohydrate (Benztropine Methanesulphonate Monohydrate)

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Abstract. $C_{21}H_{26}NO^+.CH_3SO_3^-.H_2O$; $M_r = 421{\cdot}56$, monoclinic, $P2_1/c$, $a = 16{\cdot}220\ (5)$, $b = 10{\cdot}948\ (4)$, $c = 12{\cdot}770\ (4)$ Å, $\beta = 99{\cdot}00\ (3)°$, $U = 2240$ Å^3, $Z = 4$, $D_x = 1{\cdot}250$ g cm^{-3}, μ(Cu $K\alpha$) = 14·5 cm^{-1}. The structure was refined to $R = 0{\cdot}049$ for 2379 unique reflexions.

Introduction. Benztropine, a potent anticholinergic drug, is also of interest as one of the first drugs shown potently to inhibit the uptake of the neurotransmitter dopamine back into the nerve terminal (Coyle & Snyder, 1969; Horn, Coyle & Snyder, 1971). This uptake is thought to be the main mechanism for the termination of the synaptic actions of dopamine and also of noradrenaline (Horn, 1976). Although the crystal and molecular structures of several inhibitors of noradrenaline uptake have been previously reported by us, *e.g.* imipramine (Post, Kennard & Horn, 1975), *N*,*N*-dimethylspiro[5*H*-dibenzo[*a*,*d*]cycloheptene-5,1′-cyclohexan]-4′-amine (Rodgers, Kennard, Sheldrick & Horn, 1976) and chlorimipramine (Post & Horn,

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Table 1. *Atomic coordinates* ($\times 10^4$)

Overall isotropic temperature factor for H atoms: 0·089 (2) Å^2.

	x	*y*	*z*		*x*	*y*	*z*
S(1)	142 (1)	4146 (1)	2166 (1)	C(25)	4057 (2)	−294 (3)	3780 (3)
O(11)	948 (1)	4416 (2)	1868 (2)	C(26)	3854 (2)	471 (3)	4564 (3)
O(12)	137 (2)	4391 (3)	3274 (2)	C(8)	1200 (2)	6271 (3)	5027 (3)
O(13)	−148 (2)	2958 (3)	1844 (3)	H(11)	903	4185	6144
C(9)	−555 (3)	5209 (5)	1500 (3)	H(21)	1440	2213	5969
H(91)	−585	5146	650	H(22)	903	2705	4733
H(92)	−383	6127	1756	H(31)	2068	1768	4308
H(93)	−1157	4987	1710	H(41)	3082	3523	4014
O(*W*1)	1561 (2)	6803 (3)	2236 (3)	H(42)	2035	3603	3385
C(1)	1440 (2)	4139 (3)	5741 (2)	H(51)	2575	5528	4131
C(2)	1453 (2)	2839 (3)	5318 (3)	H(61)	3387	4443	5862
C(3)	2223 (2)	2559 (3)	4805 (2)	H(62)	2987	5932	5943
C(4)	2442 (2)	3627 (3)	4139 (2)	H(71)	2081	5229	7026
C(5)	2351 (2)	4867 (3)	4647 (3)	H(72)	2489	3743	6956
C(6)	2826 (2)	4989 (3)	5767 (3)	H(1)	1065	4777	4207
C(7)	2223 (2)	4516 (3)	6498 (3)	H(101)	2390	780	6145
N(8)	1456 (1)	4983 (2)	4815 (2)	H(121)	4040	2864	6882
O(1)	2937 (1)	2303 (2)	5591 (2)	H(131)	5122	2672	8459
C(10)	2986 (2)	1067 (3)	5953 (2)	H(141)	5337	702	9400
C(11)	3643 (2)	1001 (3)	6927 (2)	H(151)	4486	−1076	8749
C(12)	4134 (2)	2000 (3)	7291 (2)	H(161)	3396	−893	7188
C(13)	4743 (2)	1892 (4)	8178 (3)	H(221)	2207	−1051	5209
C(14)	4866 (2)	784 (4)	8706 (3)	H(231)	2575	−2406	3792
C(15)	4385 (2)	−211 (4)	8343 (3)	H(241)	3753	−1920	2906
C(16)	3774 (2)	−109 (3)	7462 (3)	H(251)	4578	−79	3380
C(21)	3190 (2)	211 (3)	5096 (2)	H(261)	4219	1286	4767
C(22)	2730 (2)	−826 (3)	4814 (3)	H(81)	1211	6799	4314
C(23)	2938 (3)	−1594 (3)	4014 (3)	H(82)	1625	6671	5672
C(24)	3595 (3)	−1321 (3)	3516 (3)	H(83)	576	6271	5221

1977), this is the first such determination carried out on a potent inhibitor of dopamine uptake.

Small, colourless, irregularly-shaped crystals were obtained from water. Intensities were measured on a Syntex $P2_1$ diffractometer with graphite-monochromated Cu $K\alpha$ radiation, and a crystal 0·35 × 0·2 × 0·07 mm. Accurate cell dimensions were obtained by a least-squares procedure from 15 strong reflexions. Systematic absences $h0l$, l odd and $0k0$, k odd fixed the space group as $P2_1/c$. 3379 reflexions were measured in the range $0 < 2\theta < 116°$; after application of Lp corrections, merging equivalent reflexions gave 2380 unique reflexions with $F > 4\sigma(F)$.

Table 2. *Bond lengths* (Å)

S(1)–O(11)	1·448 (4)	S(1)–O(12)	1·442 (3)
S(1)–O(13)	1·422 (4)	S(1)–C(9)	1·747 (6)
C(1)–C(2)	1·524 (6)	C(1)–C(7)	1·526 (6)
C(1)–N(8)	1·504 (6)	C(2)–C(3)	1·530 (6)
C(3)–C(4)	1·520 (6)	C(3)–O(1)	1·437 (4)
C(4)–C(5)	1·522 (6)	C(5)–C(6)	1·520 (6)
C(5)–N(8)	1·506 (6)	C(6)–C(7)	1·542 (7)
C(10)–O(1)	1·428 (4)	C(10)–C(11)	1·507 (6)
C(10)–C(21)	1·516 (6)	C(11)–C(12)	1·389 (5)
C(11)–C(16)	1·395 (5)	C(12)–C(13)	1·386 (5)
C(13)–C(14)	1·386 (6)	C(14)–C(15)	1·377 (6)
C(15)–C(16)	1·381 (6)	C(21)–C(22)	1·375 (5)
C(21)–C(26)	1·390 (6)	C(22)–C(23)	1·405 (7)
C(23)–C(24)	1·356 (7)	C(24)–C(25)	1·364 (6)
C(25)–C(26)	1·384 (6)	C(8)–N(8)	1·507 (6)

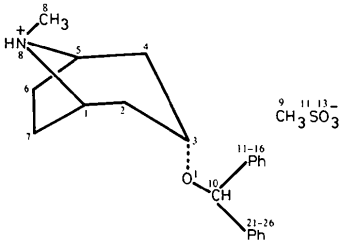

Fig. 1. The title compound, showing the non-H atom numbering scheme.

Multisolution Σ_2 sign expansion with the program *SHELX* located all non-hydrogen atoms. Isotropic least-squares refinement proceeded to $R = 0·13$, and anisotropic refinement to $R = 0·09$. All H atoms except those of water were located from difference syntheses. In the final stages of refinement C—H and N—H distances were fixed at 1·08 and 0·95 Å respectively, and H—C—H angles at 109·5°; H atoms were allotted an overall isotropic temperature factor and one reflexion clearly in error was omitted. To allow for extinction, a parameter x was included in the refinement, where F_c was multiplied by $[1 - xF^2/\sin\theta]$; x refined to $7(1) \times 10^{-7}$. The final $R' = \Sigma w^{1/2}\Delta/\Sigma w^{1/2}|F_o|$ was 0·0542, with an R of 0·0494; the weighting scheme was $w = 1/[\sigma^2(F) + 0·001F^2]$. A final difference map showed no peaks >0·28 e Å^{-3}. Final atomic coordinates are given in Table 1, with derived bond lengths and angles in Tables 2 and 3.*

* Lists of structure factors, anisotropic thermal parameters and torsion angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33701 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

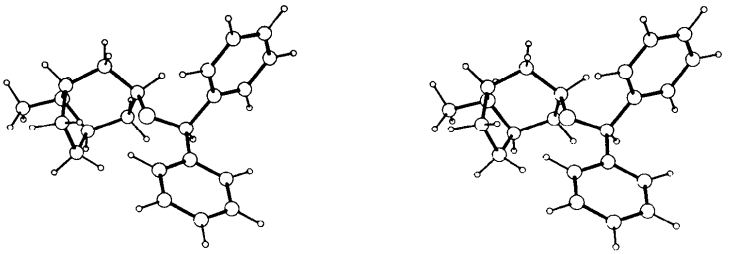

Fig. 2. Stereoview of the benztropine cation.

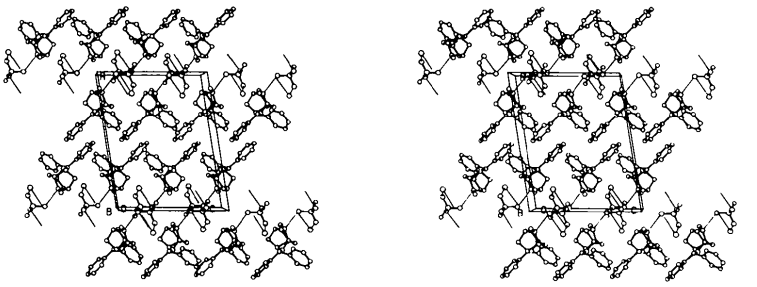

Fig. 3. Stereo packing diagram down b; H bonds are shown by narrow lines. H atoms are omitted.

Table 3. *Bond angles* (°)

O(11)–S(1)–O(12)	111·4 (3)	O(11)–S(1)–O(13)	112·4 (3)
O(12)–S(1)–O(13)	113·7 (3)	O(11)–S(1)–C(9)	106·1 (3)
O(12)–S(1)–C(9)	104·6 (3)	O(13)–S(1)–C(9)	108·0 (3)
C(2)–C(1)–C(7)	114·9 (3)	C(2)–C(1)–N(8)	107·0 (3)
C(7)–C(1)–N(8)	102·6 (3)	C(1)–C(2)–C(3)	113·3 (3)
C(2)–C(3)–C(4)	111·3 (3)	C(2)–C(3)–O(1)	111·3 (3)
C(4)–C(3)–O(1)	107·9 (3)	C(3)–C(4)–C(5)	113·6 (4)
C(4)–C(5)–C(6)	114·3 (3)	C(4)–C(5)–N(8)	107·2 (3)
C(6)–C(5)–N(8)	102·5 (4)	C(5)–C(6)–C(7)	105·3 (3)
C(1)–C(7)–C(6)	104·5 (3)	C(1)–N(8)–C(5)	101·3 (3)
C(1)–N(8)–C(8)	113·3 (3)	C(5)–N(8)–C(8)	113·7 (3)
C(3)–O(1)–C(10)	114·1 (3)	O(1)–C(10)–C(11)	107·9 (3)
O(1)–C(10)–C(21)	111·1 (3)	C(11)–C(10)–C(21)	111·1 (3)
C(10)–C(11)–C(12)	122·2 (4)	C(10)–C(11)–C(16)	118·6 (4)
C(12)–C(11)–C(16)	119·1 (4)	C(11)–C(12)–C(13)	120·3 (4)
C(12)–C(13)–C(14)	120·1 (4)	C(13)–C(14)–C(15)	119·8 (4)
C(14)–C(15)–C(16)	120·4 (4)	C(11)–C(16)–C(15)	120·2 (4)
C(10)–C(21)–C(22)	121·9 (4)	C(10)–C(21)–C(26)	120·0 (4)
C(22)–C(21)–C(26)	118·2 (4)	C(21)–C(22)–C(23)	120·1 (5)
C(22)–C(23)–C(24)	120·4 (5)	C(23)–C(24)–C(25)	120·5 (5)
C(24)–C(25)–C(26)	119·6 (5)	C(21)–C(26)–C(25)	121·3 (4)

Table 4. *Selected structural parameters for tricyclic antidepressants, benztropine and dopamine*

For references, see text.

	Benzene-ring centroid(s) to N atom (Å)		Dihedral angle between benzene rings (°)
Imipramine HCl*	7·22	6·25	130
	6·08	6·54	123
Chlorimipramine HCl	6·10	6·55	123
N,N-Dimethylspiro-[5*H*-dibenzo[*a,d*]-cycloheptene-5,1′-cyclohexan]-4′-amine	5·53	7·23	120
Benztropine methanesulphonate	6·91	7·07	97
Dopamine HCl	5·14		–

* Two independent molecules.

The chemical structure of the benztropine cation and the atomic labelling scheme for its non-H atoms are given in Fig. 1. H atoms are numbered such that H(*mn*) is the *n*th H on C(*m*); H(1) is the acidic H atom. Diagrams of the structure are given in Figs. 2 and 3.

Discussion. The main difference between benztropine and the tricyclic antidepressants that we have previously studied is that, although the latter drugs are potent inhibitors of noradrenaline uptake, they have only weak effects on dopamine uptake, whereas benztropine is a strong inhibitor of the latter process. In Table 4 are shown benzene-ring centroid to N atom distances, and dihedral angles between benzene rings, for various tricyclic antidepressants, benztropine and dopamine. Some similarities in these structural parameters can be seen; it is however difficult, from these limited data, to suggest what structural or conformational parameters might be associated with the observed pharmacological differences. The problem is further complicated by the fact that, although the tricyclic antidepressants are known to interact competitively with the noradrenaline-uptake site (Horn, 1976), benztropine interacts non-competitively with the dopamine transport system (Horn *et al.*, 1971). This implies that benztropine and dopamine may not necessarily be acting at the same site on the membrane, and thus that a structural comparison of the two molecules may not be meaningful. Structure determinations of other related dopamine-uptake inhibitors are needed to obtain a better understanding of the reason why benztropine can potently inhibit dopamine uptake, whereas the tricyclic antidepressants are much less effective.

The N atom is protonated, as would be expected in a methanesulphonate salt. The following H bonding contacts are observed (Å); N(8)···O(12), 2·75 [with H(1)···O(12), 1·82; second atom at x,y,z]; O(W1)···O(11), 2·81 (second atom at x,y,z); and O(W1)···O(13), 3·02 (second atom at $-x, \frac{1}{2}+y, \frac{1}{2}-z$). There are no other unusually short non-bonded contacts.

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References

COYLE, J. T. & SNYDER, S. H. (1969). *Science*, **166**, 899–901.

HORN, A. S. (1976). *Postgrad. Med. J. Suppl.* 3, **52**, 25–30.

HORN, A. S., COYLE, J. T. & SNYDER, S. H. (1971). *Mol. Pharmacol.* **7**, 66–80.

POST, M. L. & HORN, A. S. (1977). *Acta Cryst.* B**33**, 2590–2592.

POST, M. L., KENNARD, O. & HORN, A. S. (1975). *Acta Cryst.* B**31**, 1008–1013.

RODGERS, J. R., KENNARD, O., SHELDRICK, G. M. & HORN, A. S. (1976). *Acta Cryst.* B**32**, 1293–1295.