Acta Cryst. (1989). B45, 396–404

A Comparison of the Crystal Structures of Some Quaternary Trimethylammonium Salts Related to Dopamine and Noradrenaline with those of the Corresponding Amines: a Comment on their Nicotine-like Biological Activities

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(*Received* 14 *December* 1988; *accepted* 27 *February* 1989)

Abstract

The crystal structures of seven substituted phenethylammonium salts and one (phenylpropyl)-ammonium salt have been determined. (I) Trimethyl(phenethyl)ammonium iodide, $C_{11}H_{18}N^+.I^-$, M_r = 291·2, orthorhombic, $P2_12_12_1$ (No. 19), a = 6·040 (2), b = 7·689 (2), c = 26·528 (9) Å, V = 1232 (1) Å^3, Z = 4, D_x = 1·56 g cm^{-3}, Mo $K\alpha$ radiation (λ = 0·71073 Å), μ = 25·33 cm^{-1}, $F(000)$ = 576, T = 298 K, R (wR) = 0·0302 (0·0305) for 1991 reflections with $I > 3\sigma(I)$. (II) (*p*-Hydroxyphenethyl)trimethylammonium iodide, $C_{11}H_{18}NO^+.I^-$, M_r = 307·2, triclinic, $P\bar{1}$ (No. 2), a = 9·619 (1), b = 9·926 (1), c = 14·179 (2) Å, α = 95·24 (1), β = 97·50 (1), γ = 98·97 (1)°, V = 1317·2 (3) Å^3, Z = 4, D_x = 1·55 g cm^{-3}, Mo $K\alpha$ radiation (λ = 0·71073 Å), μ = 23·79 cm^{-1}, $F(000)$ = 608, T = 298 K, R (wR) = 0·0351 (0·0373) for 4320 reflections with $I > 3\sigma(I)$. (III) (*m*-Hydroxyphenethyl)trimethylammonium iodide hemihydrate, $C_{11}H_{18}NO^+.I^-.\frac{1}{2}H_2O$, M_r = 316·2, monoclinic, $P2_1/n$ (non-standard, No. 14), a = 8·048 (2), b = 9·782 (3), c = 17·447 (7) Å, β = 90·15 (1)°, V = 1374 (2) Å^3, Z = 4, D_x = 1·53 g cm^{-3}, Mo $K\alpha$ radiation (λ = 0·71073 Å), μ = 22·86 cm^{-1}, $F(000)$ = 628, T = 298 K, R (wR) = 0·0719 (0·0655) for 1006 reflections with $I > 1\sigma(I)$. (IV) (3,4-Dihydroxyphenethyl)-trimethylammonium iodide (coryneine iodide), $C_{11}H_{18}NO_2^+.I^-$, M_r = 323·2, monoclinic, $P2_1/a$ (non-standard, No. 14), a = 13·144 (5), b = 15·676 (7), c = 6·832 (2) Å, β = 103·50 (3)°, V = 1369 (1) Å^3, Z = 4, D_x = 1·57 g cm^{-3}, Mo $K\alpha$ radiation (λ = 0·71073 Å), μ = 22·98 cm^{-1}, $F(000)$ = 640, T = 298 K, R (wR) = 0·0306 (0·0325) for 1880 reflections with $I > 3\sigma(I)$. (V) 2-Hydroxy-2-phenylethylamine hydroiodide, $C_8H_{12}NO^+.I^-$, M_r = 265·1, monoclinic, $P2_1/a$ (non-standard, No. 14), a = 10·377 (5), b = 7·934 (4), c = 11·957 (6) Å, β = 90·76 (4)°, V = 984 (1) Å^3, Z = 4, D_x = 1·79 g cm^{-3}, Mo $K\alpha$ radiation (λ = 0·71073 Å), μ = 31·69 cm^{-1}, $F(000)$ = 512, T = 298 K, R (wR) = 0·1022 (0·1128) for 2116 reflections with $I > 3\sigma(I)$. (VI*A*) (2-Hydroxy-2-phenylethyl)trimethylammonium iodide, $C_{11}H_{18}NO^+.I^-$, M_r = 307·2, monoclinic, $P2_1/n$ (non-standard, No. 14), a = 5·945 (3), b = 13·540 (6), c = 16·182 (6) Å, β = 99·42 (3)°, V = 1285 (1) Å^3, Z = 4, D_x = 1·59 g cm^{-3}, Mo $K\alpha$ radiation (λ = 0·71073 Å), μ = 24·39 cm^{-1}, $F(000)$ = 608, T = 298 K, R (wR) = 0·0200 (0·0215) for 1801 reflections with $I > 3\sigma(I)$. (VI*B*) (2-Hydroxy-2-phenylethyl)trimethylammonium iodide, $C_{11}H_{18}NO^+.I^-$, M_r = 307·2, orthorhombic, $P2_12_12_1$ (No. 19), a = 5·919 (2), b = 13·775 (9), c = 15·866 (8) Å, V = 1294 (1) Å^3, Z = 4, D_x = 1·58 g cm^{-3}, Mo $K\alpha$ radiation (λ = 0·71073 Å), μ = 24·22 cm^{-1}, $F(000)$ = 608, T = 298 K, R (wR) = 0·0346 (0·0309) for 1207 reflections with $I > 3\sigma(I)$. (VII) [(3,4-Dihydroxyphenyl)-2-hydroxyethyl]trimethylammonium chloride, $C_{11}H_{18}NO_3^+.Cl^-$, M_r = 247·8, monoclinic, $P2_1$ (No. 4), a = 6·660 (1), b = 15·617 (2), c = 6·079 (1) Å, β = 102·83 (1)°, V = 616·4 (2) Å^3, Z = 2, D_x = 1·33 g cm^{-3}, Mo $K\alpha$ radiation (λ = 0·71073 Å), μ = 3·00 cm^{-1}, $F(000)$ = 264, T = 298 K, R (wR) = 0·0459 (0·0486) for 1822 reflections with $I > 3\sigma(I)$. (VIII) (3,4-Dihydroxyphenacyl)trimethylammonium chloride methanol solvate, $C_{11}H_{16}NO_3^+.Cl^-.CH_3OH$, M_r = 277·8, monoclinic, $P2_1/n$ (non-standard, No. 14), a = 7·735 (1), b = 13·836 (3), c = 13·599 (2) Å, β = 101·77 (1)°, V = 1424·8 (4) Å^3, Z = 4, D_x = 1·29 g cm^{-3}, Mo $K\alpha$ radiation (λ = 0·71073 Å), μ = 2·71 cm^{-1}, $F(000)$ = 592, T = 298 K, R (wR) = 0·0459 (0·0437) for 1075 reflections with $I > 3\sigma(I)$. (IX) (*m*-Hydroxyphenylpropyl)trimethylammonium iodide, $C_{12}H_{20}NO^+.I^-$, M_r = 321·2, monoclinic, $P2_1/a$ (non-standard, No. 14), a = 11·788 (7), b = 7·722 (4), c = 15·266 (12) Å, β = 96·24 (5)°, V = 1381 (2) Å^3, Z = 4, D_x = 1·54 g cm^{-3}, Mo $K\alpha$ radiation (λ = 0·71073 Å), μ = 22·71 cm^{-1}, $F(000)$ = 640, T = 298 K, R (wR) = 0·0638 (0·0644) for 2214 reflections with $I > 3\sigma(I)$. Synthetic and analytical details have been described for (I), (II), (III) and (IX) [Barlow, Thompson & Scott (1969). *Br. J. Pharmacol.* **37**, 555–584], (IV) [Barlow, Bowman, Ison & McQueen (1974). *Br. J. Pharmacol.* **51**, 585–597], (V), (VII) and (VIII) [Armstrong & Barlow (1976). *Br. J. Pharmacol.* **57**, 501–516], and (VI) [Barlow & González (1986). *Arch. Farmacol. Toxicol.* **12**, 87–98]. The crystal

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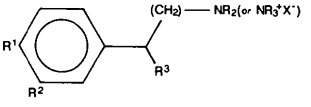
0108-7681/89/040396-09$03.00

conformation of the quaternary trimethylammonium compounds is not markedly different from that of the corresponding amines and is not likely to explain why the quaternary salts are active at nicotine-sensitive acetylcholine receptors rather than at α- and β-adrenergic receptors.

Introduction

Catecholamines such as dopamine, noradrenaline and adrenaline are transmitter substances in the sympathetic branch of the peripheral and central nervous systems. Their trimethylammonium salts, however, to varying degrees, activate nicotine-sensitive acetylcholine receptors. The quaternary derivative of dopamine, coryneine, for instance, is particularly active (Barlow, Thompson & Scott, 1969; Barlow, Bowman, Ison & McQueen, 1974). This paper describes an X-ray crystallographic study of a series of quaternary trimethylammonium compounds and a comparison of their structures with the analogous amines whose crystal structures have been determined as zwitterions or ammonium salts. The compounds are trimethyl(phenethyl)ammonium iodide (I), (*p*-hydroxyphenethyl)trimethylammonium iodide [(II), hordenine methiodide], (*m*-hydroxyphenethyl)trimethylammonium iodide [(III), leptodactyline iodide], (3,4-dihydroxyphenethyl)trimethylammonium iodide [(IV), coryneine iodide], 2-hydroxy-2-phenylethylamine hydroiodide (V), (2-hydroxy-2-phenylethyl)trimethylammonium iodide [(VI*A*) and (VI*B*)], [(3,4-dihydroxyphenyl)-2-hydroxyethyl]trimethylammonium chloride [(VII), the quaternary trimethylammonium analogue of noradrenaline and adrenaline], (3,4-dihydroxyphenacyl)trimethylammonium chloride [(VIII), the quaternary trimethylammonium analogue of adrenalone] and (*m*-hydroxyphenylpropyl)trimethylammonium iodide (IX). The structural formulae for these nine compounds (together with those for noradrenaline, adrenaline and adrenalone, and three other catecholamines) are given in the scheme below.



Compound	*p*-R^1	*m*-R^2	β-R^3	NR_2 or $NR_3^+ X^-$
(I)	H	H	H	$-N(Me)_3^+ I^-$
Tyramine	OH	H	H	$-NH_2$
(II)	OH	H	H	$-N(Me)_3^+ I^-$
(III)	H	OH	H	$-N(Me)_3^+ I^-$
Dopamine	OH	OH	H	$-NH_2$
(IV)	OH	OH	H	$-N(Me)_3^+ I^-$
(V)	H	H	OH	$-NH_3^+ I^-$
(VI)	H	H	OH	$-N(Me)_3^+ I^-$
Noradrenaline	OH	OH	OH	$-NH_2$
Adrenaline	OH	OH	OH	−NHMe
Isoproterenol	OH	OH	OH	$-NHCHMe_2$
(VII)	OH	OH	OH	$-N(Me)_3^+ Cl^-$
Adrenalone	OH	OH	=O	−NHMe
(VIII)	OH	OH	=O	$-N(Me)_3^+ Cl^-$
(IX)	H	OH	H	$-CH_2N(Me)_3^+ I^-$

With the exception of (V) and (IX) the compounds are all (β-phenylethyl)trimethylammonium iodides or chlorides. They may be hydroxy-substituted at either the *meta*- and/or *para*-phenyl positions. The β-C atom is either unsubstituted, bears a hydroxyl group or is a keto-C atom. Compound (V) is an ammonium salt while (IX) is a (γ-phenylpropyl)amine salt.

Of these, the leptodactyline (III), the (*m*-hydroxyphenylpropyl)trimethylammonium (IX) and the coryneine (IV) iodides can have marked nicotine-like activity. The quaternary trimethylammonium derivative of adrenalone, (VIII), is also active, whereas that of noradrenaline and, hence, adrenaline, (VII), is only weakly active (Fig. 1).

The crystal structures were determined to assess the effect of trimethyl substitution at the N atom on the molecular conformation and to see if such a marked change in biological specificity could be explained by a conformational change. The conformation of the phenethylamines is determined by the two torsion angles which fix the position of the N atom relative to the phenyl ring. These determine the distance between the N atom and substituents attached to the ring and to the β-C atom, parameters commonly discussed in the case of the catecholamines. The symmetrical position with the N atom and the side chain lying in a vertical plane and the ring lying in a horizontal plane (*e.g.* Fig. 2*a*) is not always found for the amines. The expectation is that the bulk associated with a trimethylated quaternary N atom should force the side chain to be both fully extended and in a plane perpendicular to the phenyl ring. Deviations from this conformation in the crystal could arise either from steric interactions

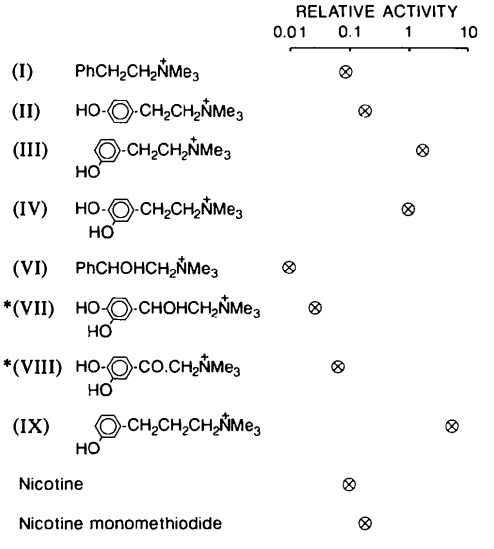


Fig. 1. Relative activities on the *rectus abdominis* muscle in the frog (*Rana pipiens*) (Barlow, Thompson & Scott, 1969). Asterisks denote that results for compounds (VII) and (VIII) were obtained from tests for nicotine-like activity on guinea-pig ileum, relative to compound (IV) (Barlow, 1987).

between substituents on the β-C atom and *ortho*-phenyl H atoms, which seems unlikely unless the β substituent is large, or, more likely, from intermolecular and crystal-packing effects.

Experimental

Compound (VI) was determined in two crystalline modifications, (VI*A*) and (VI*B*). For all ten structure determinations diffraction intensity data were collected on Nicolet four-circle automated diffractometers by $\theta/2\theta$ variable-speed scans [except for (IX) where Wyckoff ω scans were used]. Table 1 gives the data-collection parameters and Table 2 gives details of data reduction, structure solution and refinement.* Structure solution was usually by heavy-atom and difference Fourier methods, although direct methods were used for the chlorides [(VII) and (VIII)] and *DIRDIF* (Beurskens *et al.*, 1984) was used to complete the solution of (V). No extinction corrections were applied. Absorption corrections, where applied, were analytical by Gaussian integration between measured crystal faces. Structures were refined by blocked-cascade least squares on a Data General Desktop minicomputer with the *SHELXTL* (Sheldrick, 1981) package, or, in the case of (III), by full-matrix least squares on a Digital MicroVAX II computer with the *SHELXTL-Plus* (Sheldrick, 1988, for Nicolet Instrument Corporation) package. Unless stated explicitly below, the following procedure was adopted for the structure refinements. All non-H atoms were refined with anisotropic thermal parameters. The phenyl rings were refined as regular hexagons (C—C 1·395 Å). Non-hydroxyl H atoms were incorporated at geometrically idealized positions (C—H 0·96 Å, fixed U_{iso} of $1{\cdot}2U_{eq}$ of C) and refined by a riding model. Hydroxyl H atoms were located from difference Fourier maps (usually low-angle, $\sin\theta/\lambda < 0{\cdot}25$). Any large positive peaks (> 1 e Å^{-3}) in the final ΔF maps were only found close to iodine. The function minimized during refinement was $\sum w(F_o - |F_c|)^2$, where $w^{-1} = [\sigma^2(F) + gF^2]$ and values of g are given in Table 2. Atomic scattering factors and corrections for anomalous dispersion were taken from *International Tables for X-ray Crystallography* (1974).

Structure refinement

The structure refinement details of compounds (I) to (VI) and compound (VIII) are as follows: Compound (I), phenyl was freely refined. Compound (II), which has two molecules per asymmetric unit, phenyls also were freely refined. Compound (III), iodine lies close to the mirror plane at $x = 0{\cdot}5$; the rest of the structure from ΔF map together with 'ghost' image. High correlations were found during least-squares refinement, and poor molecular geometry. NC_4 end of the molecule was fixed as tetrahedral. All non-H atoms except iodine were isotropically refined. Hydroxyl and water H atoms were not located. Damped full-matrix least-squares refinement. Compound (IV), phenyl was freely refined. Compound (V), we were unable to solve the structure from data collected from one of many thin plates. The thicker crystal used here was probably a monoclinic twin (as unit-cell-determining reflections if not carefully scrutinized on the diffractometer gave poor orthorhombic cell parameters in the least-squares

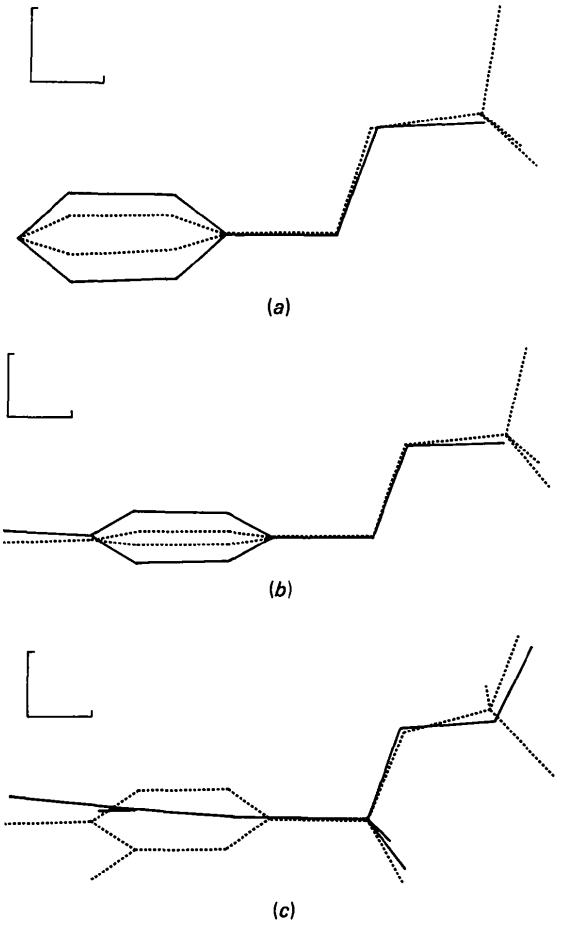


Fig. 2. Superposition of the central C1—C7 bond with the N atom in the plane of the paper for (*a*) phenethylamine (PEAHCL; solid) and trimethyl(phenethyl)ammonium iodide [(I); dashed], (*b*) tyramine (TYRAMH; solid) and hordenine methiodide [(II); dashed] and (*c*) adrenaline (ADRENL; solid) and adrenaline trimethylammonium chloride [(VII); dashed].

* A table summarizing the crystal data for the nine compounds, and lists of structure factors, bond lengths and interbond angles, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51665 (216 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Data-collection parameters for compounds* (I)–(IX)

	(I)	(II)	(III)	(IV)	(V)	(VI*A*)	(VI*B*)	(VII)	(VIII)	(IX)
Crystal habit	Plate	Hexagonal tablet	Tablet	Tablet	Plate	Hexagonal plate	Needle	Triangular prism	Needle	Plate
Crystal size (mm)	0·7 × 0·3 × 0·06	0·4 × 0·4 × 0·1	0·25 × 0·25 × 0·25	0·5 × 0·3 × 0·1	0·45 × 0·40 × 0·10	0·5 × 0·4 × 0·15	0·1 × 0·1 × 0·25	0·75 × 0·5 × 0·4	0·5 × 0·6 × 0·2	1·0 × 0·35 × 0·05
Diffractometer	$P2_1$	*R3m/V*	$P2_1$	*R3m/V*	$P2_1$	*R3m/V*	*R3m/V*	$P2_1$	$P2_1$	*P3m*
Unit-cell determination										
No. of reflections	15	25	15	15	9	20	20	15	15	22
2θ range (°)	16–25	24–26	6–19	24–26	26–34	15–20	13–22	23–27	23–27	20–23
Scan range 2θ (°)	2·9–65·0	2·9–55·0	2·9–50·0	2·9–50·0	2·9–60·0	2·9–50·0	2·9–65·0	2·9–60·0	2·9–40·0	2·9–65·0
Range of *hkl*	0/10, 0/12, 0/41	−12/12, 0/12, −18/18	0/10, 0/12, −21/21	−16/16, 0/19, 0/8	0/14, 0/11, −16/16	0/7, 0/16, −19/19	0/10, 0/21, 0/24	0/10, 0/22, −9/9	0/9, 0/15, −14/14	0/15, 0/10, −19/19
Scan type	$\theta/2\theta$	$\theta/2\theta$	$\theta/2\theta$	$\theta/2\theta$	$\theta/2\theta$	$\theta/2\theta$	$\theta/2\theta$	$\theta/2\theta$	$\theta/2\theta$	Wyckoff ω
Scan speeds 2θ (° min^{-1})										
min.	2·00	2·00	2·00	2·00	1·50	2·00	4·18	2·00	2·55	1·50
max.	29·30	29·30	29·30	29·30	29·30	29·30	29·30	29·30	29·30	29·30
No. of standard reflections	2	3	2	2	3	3	2	3	3	2
Frequency of standards	100	100	200	100	100	100	100	97	50	100
Variation/decay (%)	2	3	1	3	4	2	3	1	61	3
Data collected	2671	6727	2760	2465	3207	2451	2301	2363	1531	5529

Table 2. *Structure solution and refinement details for compounds* (I)–(IX)

	(I)	(II)	(III)	(IV)	(V)	(VI*A*)	(VI*B*)	(VII)	(VIII)	(IX)
Independent data	2594	6097	1799	2293	2442	2088	2196	2139	1317	4994
R_{int}	0·009	0·009	0·008	0·019	0·013	0·013	0·016	0·005	0·019	0·009
Solution method	Heavy/*ΔF*	Heavy/*ΔF*	Heavy/*ΔF*	Heavy/*ΔF*	Heavy/*DIRDIF*	Heavy/*ΔF*	Heavy/*ΔF*	Direct/*ΔF*	Direct/*ΔF*	Heavy/*ΔF*
Program	*SHELX*	*SHELX*	*SHELX-Plus*	*SHELX*	*SHELX*	*SHELX*	*SHELX*	*SHELX*	*SHELX*	*SHELX*
Refinement method*	Bcls	Bcls	Fmls	Bcls	Bcls	Bcls	Bcls	Bcls	Bcls	Bcls
Absorption correction	Anal.	Anal.	None	Anal.	Anal.	Anal.	Anal.	None	None	None
No. of grid points (anal.)	192	168	—	192	304	432	48	—	—	—
transmission min.	0·499	0·44	—	0·484	0·3897	0·409	0·674	—	—	—
coefficients max.	0·854	0·79	—	0·723	0·7493	0·692	0·989	—	—	—
Refined data	1991	4320	1006	1880	2116	1801	1207	1822	1075	2214
$I > n\sigma(I)$: n	3	3	1	3	3	3	3	3	3	3
R	0·0302	0·0351	0·0719	0·0306	0·1022	0·0200	0·0346	0·0459	0·0459	0·0638
wR†	0·0305	0·0373	0·0655	0·0325	0·1128	0·0215	0·0309	0·0486	0·0437	0·0644
g value	0·0003	0·0004	0·00025	0·0003	0·006	0·0001	0·0003	0·0012	0·00003	0·0008
S	1·234	1·345	2·738	1·400	4·947	1·483	1·176	1·421	3·884	1·823
Data:parameter ratio	16	16	16	13	23	14	10	14	7	17
Max. Δ/σ	0·006	0·04	0·06	0·04	0·055	0·005	0·006	0·002	0·02	0·007
Max. $\Delta\rho$ (e Å^{-3})										
positive	0·84	1·07	0·92	0·86	5·22	0·48	0·57	0·41	0·24	3·13
negative	0·65	0·95	0·92	0·43	1·92	0·37	0·49	0·27	0·27	1·05
H atoms										
location	*a*	*b*	*c*	*b*	*b*	*b*	*b*	*d*	*d*	*b*
refinement	*e*	*f*	*e*	*f*	*f*	*f*	*g*	*f*	*f*	*f*

Notes: (*a*) geometric; (*b*) OH by *ΔF* synthesis, geometric; (*c*) OH/H_2O not located, geometric; (*d*) all by *ΔF* synthesis; (*e*) riding; (*f*) OH fixed, riding; (*g*) OH refined, riding.

* Bcls = blocked-cascade least squares, Fmls = full-matrix least squares.
† $w^{-1} = [\sigma^2(F) + gF^2]$.

cell refinement). Monoclinic data were solved for I (on glide plane at approximately $x = 0, y = 0{\cdot}25, z = 0{\cdot}11$) from Patterson synthesis then *DIRDIF* was used for remaining non-H atoms. Damped, then free, blocked-cascade least-squares refinement. $-NH_3^+$ was treated as a terminal methyl for the placement of H atoms. Compound (VI*A*), phenyl freely refined. Compound (VI*B*), hydroxyl position was refined with fixed U_{iso}. Compound (VIII), there was severe crystal decay during data collection (intensity of standard reflections decreased by 61%), probably as a result of solvent loss.

Results

Table 3 lists the non-H-atom coordinates and equivalent isotropic thermal parameters for compounds (I)–(IX). Table 4 defines and lists the values of the torsion angles which determine the conformation of the side chain, and gives the intramolecular distances from the N atom to the phenyl-ring centroid (N.RNG) and to the *meta*- and *para*-hydroxyl O atoms (N.*m*-O and N.*p*-O, respectively). In addition to the results for compounds (I)–(VIII) determined in this paper, Table 4

includes results for the analogous amines and/or ammonium compounds for comparison. Coordinates for published structures were retrieved from Version 3·20 of the *Cambridge Structural Database* (Allen *et al.*, 1979) and derived structural parameters for these structures were calculated using the program *GEOM*78 (Murray-Rust & Motherwell, 1978). Compounds retrieved and used for comparison in this and other tables are referred to by their unique CSD reference code.

Table 3. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters* (Å $\times 10^3$)

Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
Compound (I)				
N	5159 (6)	5095 (5)	1707 (1)	38 (1)
C(6)	256 (9)	4565 (8)	319 (2)	61 (2)
C(5)	−288 (11)	4173 (10)	−174 (3)	81 (3)
C(4)	1107 (12)	4631 (8)	−560 (2)	71 (2)
C(3)	3056 (12)	5469 (8)	−452 (2)	68 (2)
C(2)	3571 (9)	5912 (7)	36 (2)	53 (1)
C(1)	2152 (8)	5498 (7)	428 (2)	45 (1)
C(7)	2717 (9)	6019 (8)	970 (2)	58 (2)
C(8)	4248 (7)	4690 (7)	1185 (2)	43 (1)
C(9)	6686 (8)	3616 (7)	1836 (2)	52 (2)
C(10)	3359 (8)	5199 (7)	2096 (2)	48 (1)
C(11)	6463 (9)	6760 (7)	1716 (2)	51 (1)
I	1220 (1)	277 (1)	1802 (1)	44 (1)
Compound (II)				
I(1)	1681 (1)	2287 (1)	4175 (1)	63 (1)
C(1)	2925 (5)	971 (4)	8580 (3)	46 (1)
C(2)	4317 (5)	1069 (4)	8421 (3)	50 (1)
C(3)	4680 (5)	1126 (5)	7506 (3)	54 (2)
C(4)	3640 (4)	1101 (4)	6737 (3)	45 (1)
O(4)	4049 (4)	1147 (4)	5854 (2)	64 (1)
C(5)	2228 (5)	1032 (4)	6884 (3)	50 (1)
C(6)	1887 (5)	960 (4)	7796 (3)	51 (1)
C(7)	2555 (6)	890 (4)	9579 (3)	58 (2)
C(8)	2663 (5)	2310 (4)	10088 (3)	45 (1)
N(1)	2386 (4)	2355 (3)	11125 (2)	44 (1)
C(9)	987 (5)	1523 (5)	11213 (3)	56 (2)
C(10)	3518 (5)	1809 (6)	11729 (3)	67 (2)
C(11)	2355 (9)	3801 (5)	11466 (4)	91 (3)
I(1′)	8546 (1)	2516 (1)	−1040 (1)	51 (1)
C(1′)	6824 (4)	3498 (4)	3261 (3)	46 (1)
C(2′)	7302 (5)	2661 (4)	2585 (3)	50 (1)
C(3′)	7409 (5)	3016 (4)	1677 (3)	51 (1)
C(4′)	7049 (5)	4241 (4)	1434 (3)	52 (1)
O(4′)	7083 (5)	4624 (4)	533 (2)	79 (2)
C(5′)	6600 (6)	5114 (5)	2101 (3)	60 (2)
C(6′)	6490 (5)	4736 (5)	3004 (3)	57 (2)
C(7′)	6694 (5)	3060 (5)	4243 (3)	57 (2)
C(8′)	8088 (4)	3582 (4)	4896 (3)	45 (1)
N(1′)	8172 (4)	3189 (3)	5907 (2)	44 (1)
C(9′)	7032 (5)	3671 (5)	6388 (3)	52 (2)
C(10′)	9594 (5)	3858 (5)	6439 (3)	59 (2)
C(11′)	8057 (6)	1650 (4)	5900 (3)	59 (2)
Compound (III)				U_{iso}
I(1)	5200 (1)	4925 (3)	6724 (1)	78 (1)*
C(2)	7641 (9)	2520 (7)	5145 (4)	64 (2)
C(3)	8896	3290	4803	77 (3)
C(4)	10557	2939	4919	58 (2)
C(5)	10964	1817	5376	47 (2)
C(6)	9709	1047	5718	48 (2)
C(1)	8047	1399	5602	49 (2)
O(5)	12594 (12)	1451 (10)	5509 (6)	65 (2)
C(7)	6687 (17)	609 (15)	5995 (8)	64 (2)
C(8)	6347 (14)	1190 (12)	6772 (6)	46 (2)
N(1)	4804 (14)	731 (13)	7174 (7)	53 (2)
C(9)	4715 (16)	1393 (14)	7939 (7)	66 (2)
C(10)	3299 (14)	1153 (13)	6740 (7)	64 (2)
C(11)	4840 (18)	−776 (13)	7269 (9)	51 (3)
O(1′)	14829 (25)	3141 (13)	4956 (15)	54 (2)

	x	y	z	U_{eq}
Compound (IV)				
I	3776 (1)	11512 (1)	11027 (1)	58 (1)
C(1)	437 (3)	8962 (3)	3584 (7)	47 (1)
C(6)	937 (3)	9137 (3)	5558 (7)	50 (2)
C(5)	1714 (3)	9748 (3)	6016 (6)	41 (1)
O(5)	2178 (3)	9908 (2)	7984 (4)	65 (1)
C(4)	1998 (3)	10192 (2)	4467 (6)	38 (1)
O(4)	2756 (2)	10808 (2)	5042 (4)	55 (1)
C(3)	1523 (3)	10007 (3)	2497 (6)	47 (1)
C(2)	748 (3)	9384 (3)	2065 (7)	50 (1)
C(7)	−471 (4)	8336 (3)	3088 (9)	63 (2)
C(8)	−106 (3)	7427 (3)	3348 (7)	44 (1)
N	−988 (3)	6775 (2)	2908 (6)	48 (1)
C(9)	−1736 (4)	6928 (4)	4208 (10)	81 (3)
C(10)	−491 (4)	5919 (3)	3347 (9)	72 (2)
C(11)	−1540 (4)	6789 (4)	758 (8)	74 (2)
Compound (V)				
I(1)	44 (1)	2559 (1)	1130 (1)	45 (1)
C(2)	4580 (7)	2048 (9)	−3834 (5)	43 (3)
C(3)	4734	2282	−4981	50 (4)
C(4)	3993	3482	−5549	58 (4)
C(5)	3098	4449	−4971	53 (4)
C(6)	2944	4214	−3824	44 (3)
C(1)	3684	3014	−3256	39 (3)
C(7)	3450 (12)	2624 (12)	−2037 (11)	44 (3)
O(7)	2893 (11)	3970 (12)	−1460 (8)	68 (4)
C(8)	2562 (12)	1114 (14)	−1941 (9)	42 (3)
N(1)	2383 (10)	647 (13)	−709 (7)	49 (3)
Compound (VI*A*)				
I	7989 (1)	−1470 (1)	8718 (1)	46 (1)
C(1)	2893 (5)	4268 (2)	8493 (2)	40 (1)
C(2)	1241 (6)	4689 (3)	8895 (2)	58 (1)
C(3)	1396 (7)	5684 (3)	9124 (2)	69 (1)
C(4)	3208 (8)	6248 (3)	8959 (2)	64 (1)
C(5)	4865 (7)	5838 (2)	8570 (2)	60 (1)
C(6)	4704 (6)	4845 (2)	8333 (2)	49 (1)
C(7)	2819 (5)	3176 (2)	8251 (2)	44 (1)
O(7)	578 (4)	2779 (2)	8127 (2)	64 (1)
C(8)	4252 (5)	2621 (2)	8972 (2)	38 (1)
N	4823 (4)	1548 (2)	8830 (1)	36 (1)
C(9)	6610 (6)	1242 (2)	9565 (2)	52 (1)
C(10)	5796 (7)	1403 (2)	8042 (2)	53 (1)
C(11)	2781 (5)	887 (2)	8807 (2)	51 (1)
Compound (VI*B*)				
I	14437 (1)	−933 (1)	6335 (1)	56 (1)
C(2)	11742 (7)	−1961 (3)	8984 (3)	51 (3)
C(3)	11858	−2923	9254	62 (3)
C(4)	10103	−3564	9069	55 (3)
C(5)	8232	−3243	8612	54 (3)
C(6)	8117	−2281	8341	46 (2)
C(1)	9872	−1640	8527	39 (2)
C(7)	9683 (14)	−582 (4)	8253 (4)	39 (2)
O(7)	11815 (10)	−123 (4)	8160 (3)	60 (2)
C(8)	8381 (13)	−53 (4)	8935 (4)	40 (2)
N(1)	7753 (9)	1013 (4)	8786 (3)	36 (2)
C(9)	6017 (15)	1285 (6)	9442 (5)	53 (3)
C(10)	9750 (14)	1666 (5)	8880 (4)	50 (3)
C(11)	6724 (16)	1164 (5)	7926 (4)	52 (3)

* U_{eq} not U_{iso}.

Table 3 (*cont.*)

	x	*y*	*z*	U_{eq}
Compound (VII)				
Cl(1)	7717 (1)	480	5827 (1)	52 (1)
C(2)	2075 (2)	2372 (1)	−2064 (2)	46 (1)
C(3)	3871	1909	−2040	46 (1)
C(4)	5405	1861	−65	37 (1)
C(5)	5144	2275	1885	34 (1)
C(6)	3347	2738	1860	37 (1)
C(1)	1813	2786	−115	39 (1)
O(4)	7204 (3)	1429 (2)	86 (4)	51 (1)
O(5)	6666 (3)	2244 (1)	3820 (3)	45 (1)
C(7)	−193 (4)	3267 (2)	−159 (5)	43 (1)
O(7)	−664 (3)	3311 (2)	1970 (4)	56 (1)
C(8)	−21 (3)	4185 (2)	−949 (4)	39 (1)
N(1)	−2059 (3)	4607 (1)	−2025 (3)	35 (1)
C(9)	−3630 (5)	4547 (3)	−655 (8)	74 (1)
C(10)	−1639 (5)	5539 (2)	−2290 (7)	63 (1)
C(11)	−2850 (7)	4252 (4)	−4296 (7)	93 (2)
Compound (VIII)				
Cl(1)	2685 (2)	3040 (1)	672 (1)	55 (1)
C(2)	2859 (4)	−1381 (1)	595 (2)	42 (2)
C(3)	2594	−1280	1574	47 (2)
C(4)	2123	−384	1910	37 (2)
C(5)	1918	411	1267	35 (2)
C(6)	2184	311	288	39 (2)
C(1)	2654	−585	−48	35 (2)
O(4)	1863 (4)	−235 (2)	2851 (2)	51 (1)
O(5)	1412 (4)	1258 (2)	1631 (2)	48 (1)
C(7)	2821 (5)	−649 (3)	−1110 (3)	39 (2)
O(7)	2750 (4)	63 (2)	−1642 (2)	61 (1)
C(8)	3070 (6)	−1649 (3)	−1503 (2)	42 (2)
N(1)	2933 (5)	−1741 (2)	−2626 (2)	38 (1)
C(9)	1195 (6)	−1385 (3)	−3193 (3)	54 (2)
C(10)	4395 (6)	−1216 (3)	−2974 (3)	58 (2)
C(11)	3062 (7)	−2793 (3)	−2847 (3)	63 (2)
C(12)	−2235 (8)	4152 (4)	195 (4)	103 (3)
O(12)	−1167 (5)	3646 (3)	946 (3)	113 (2)
Compound (IX)				
I	−378 (1)	2513 (1)	1070 (1)	50 (1)
C(2)	2009 (4)	3934 (7)	4948 (3)	69 (3)
C(3)	2248	3777	4076	69 (4)
C(4)	1526	2810	3477	57 (3)
C(5)	567	2000	3751	59 (3)
C(6)	329	2158	4622	56 (3)
C(1)	1050	3125	5221	52 (2)
O(5)	−120 (7)	1004 (10)	3200 (4)	99 (3)
C(7)	746 (8)	3342 (15)	6164 (5)	67 (3)
C(8)	1775 (8)	3106 (13)	6864 (5)	56 (3)
C(9)	1361 (7)	2892 (10)	7752 (5)	51 (3)
C(10)	1688 (7)	2577 (12)	9340 (5)	53 (2)
C(11)	3077 (7)	4176 (11)	8581 (5)	53 (3)
C(12)	2946 (8)	1057 (11)	8430 (7)	62 (3)
N(1)	2287 (5)	2672 (8)	8511 (4)	39 (2)

Discussion

All structures in Table 4 have the side chain in the approximately fully extended *trans* conformation (TOR2, torsion angle 1—7—8—9) leading to similarity among the N-atom-to-phenyl-centroid distances (N.RNG) with values from 5·088 to 5·237 Å and in the N-atom-to-*para*-O-atom distances (N.*p*-O) having values from 7·719 to 7·938 Å. Variations in the angle TOR1 (2—1—7—8) (and hence TOR3, the improper torsion angle 2—1—7—9) which corresponds to rotation of the phenyl group about the C1—C7 bond (Table 4) necessarily cause variations in the N-atom-to-*meta*-O-atom distances (N.*m*-O from 6·607 to 7·409 Å) and change the appearance of the molecules when viewed edge-on (Fig. 2).

The orientation of the side chain with respect to the phenyl ring is depicted schematically in Fig. 3 (where the plane of the phenyl ring is drawn as a horizontal line and the projections of TOR1 and TOR3 are drawn). Comparison of PEAHCL and TYRAMC with their corresponding trimethylammonium iodides [(I) and (II), respectively] shows the expected effect of trimethyl substitution, namely, to make the side chain more perpendicular to the phenyl-ring plane. The position for neutral tyramine (TYRAMH) is intermediate (Table 4).

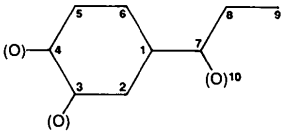
With leptodactyline (III) and the phenylpropyl compound (IX) the *m*-hydroxyl group and the N atom are *anti* [TOR3 of 105° in (III) and TOR4 of 128° in (IX)] while with coryneine (IV) and dopamine (DOPAMN01) these groups are *syn* (TOR3 of 76 and 84°, respectively). It is interesting to note that in 5-hydroxydopamine, HDOPAC, (which has two *meta*-hydroxyl groups) the angles TOR1 (59°) and, hence, TOR3 (49·7°) are at the minimum of the range observed for the non-keto-type compounds. When HDOPAC is trimethylated at the ring hydroxyls to give mescaline (MESCAL) the side chain adopts a more nearly perpendicular orientation with respect to the phenyl ring (TOR1 and TOR3 are 88·5 and 92·5°, respectively). While this might be expected for mescaline on grounds of steric interaction, the conformation of 5-hydroxydopamine is not that expected and is possibly a result of crystal-packing forces.

The effect of trimethyl substitution on the β-hydroxy compounds would appear to be minimal, comparing compound (V) on the one hand with (VI*A*) and (VI*B*) on the other (Fig. 3), but causes a twist away from perpendicular in the case of adrenaline [ADRENL *vs* (VII)]. The *meta*- and β-hydroxyl groups are *syn* in NADRHC, compound (VII), and the second molecule of ISOPROT20 [the improper *m*-O···C—C—O(H) torsion angles defined by atoms 11—1—7—10 (Table 4) lie in the range 24·9 to 44·1°], while they are *anti* in ADRENL (neutral), NADREN (neutral) and the first molecule of ISOPROT20 [*m*-O···C—C—O(H) torsion angles in the range 143·8 to 163·2°].

In the ketones, trimethyl substitution has little effect with the side chain lying close to the plane of the phenyl ring and the *meta*-hydroxyl and the keto group mutually *cisoid*; the torsion angle CC—C=O (Table 4) is −4·075 and 8·08° for ADRENC and (VIII), respectively. The keto group and N atom are also *cisoid* (O=C—CN in Table 4).

The phenylpropyl compound (IX) has a near fully extended side chain (TOR2 of −165·8° and TOR3 of −179·1°) with an N.RNG distance of 6·34 Å and an N.*m*—O distance of 8·39 Å. The side chain is not perpendicular to the phenyl-ring plane, the N-atom being *anti* to the *meta*-hydroxyl group (TOR1 is 136·1° and the improper TOR4 is 128·3°). The

Table 4. *Derived structural parameters (° and Å) for phenethylamines*



TOR1 is the angle 2–1–7–8. TOR2 is the angle 1–7–8–9. TOR3 is the improper torsion angle 2–1–7–9 [TOR4 in (IX) is the analogous torsion angle 2–1–7–N^+]. O=C–CN is the torsion angle 10–7–8–9 in the ketones. CC–C=O is the torsion angle 2–1–7–10 in the ketones.

	TOR1	TOR2	TOR3	N.RNG	N.*m*–O	N.*p*–O	O=C–CN	CC–C=O
Unsubstituted phenethylamines								
Phenethylamine hydrochloride (PEAHCL)[a]	111·903	171·273	119·942	5·154	—	—		
Phenethylamine TMA* iodide (I)	95·181	174·357	100·000	5·165	—	—		
p-HO-substituted phenethylamines								
Tyramine hydrochloride (TYRAMC)[b]	−71·136	−179·426	−71·690	5·164	—	7·822		
Tyramine hydrochloride (TYRAMC11)[c]	−69·124	−176·199	−72·808	5·134	—	7·801		
Tyramine hemihydrate (TYRAMH)[d] mol. 1	−97·489	−177·563	−99·689	5·164	—	7·835		
mol. 2	83·967	−175·183	79·401	5·174	—	7·861		
Hordenine methiodide (II) mol. 1	87·186	−177·000	84·485	5·190	—	7·870		
mol. 2	89·940	−177·711	88·030	5·169	—	7·846		
m-HO-substituted phenethylamines								
Leptodactyline iodide (III)	93·755	165·430	104·969	5·169	6·985	—		
m- and *p*-HO-disubstituted phenethylamines								
Coryneine bromide (BEFPIL)[e]	77·185	179·857	77·316	5·200	6·894	7·890		
Coryneine iodide (IV)	−76·608	178·880	−75·533	5·215	6·832	7·930		
Dopamine hydrochloride (DOPAMN)[f]	79·212	174·191	85·005	5·142	6·825	7·831		
Dopamine hydrochloride (DOPAMN01)[g]	77·568	173·223	84·135	5·096	6·771	7·750		
5-Hydroxydopamine hydrochloride (HDOPAC)[h]	59·119	−170·424	49·678	5·153	6·607	7·884		
	−123·846	−170·424	−133·287	5·153	7·288	7·884		
Mescaline hydrochloride (MESCAL)[i]	−88·809	176·000	−84·880	5·109	6·879	7·796		
	88·530	176·000	92·459	5·109	6·963	7·796		
Unsubstituted (2-hydroxyphenethyl)amines								
(2-Hydroxyphenethyl)amine hydrogen iodide (V)	−79·416	176·667	−76·080	5·121	—	—		
(2-Hydroxyphenethyl)amine TMA iodide (VI*A*)	−92·827	−169·182	−101·023	5·136	—	—		
(2-Hydroxyphenethyl)amine TMA iodide (VI*B*)	−92·536	−174·594	−96·699	5·152	—	—		
m- and *p*-HO-substituted (2-hydroxyphenethyl)amines								
Adrenaline (ADRENL)[j]	−96·395	171·560	−88·804	5·088	6·847	7·719		
Isoproterenol (ISPROT20)[k] mol. 1	−77·239	174·565	−71·902	5·108	6·638	7·777		
mol. 2	−75·838	176·972	−72·514	5·141	6·839	7·874		
Noradrenaline (NADREN)[l]	−90·432	167·479	−77·744	5·170	6·837	7·891		
Noradrenaline hydrochloride (NADRHC)[m]	81·503	176·126	85·048	5·097	6·852	7·793		
Adrenaline TMA chloride (VII)	93·937	154·736	114·028	5·136	7·131	7·799		
m- and *p*-HO-substituted ketones								
Adrenalone hydrochloride (ADRENC)[n]	175·435	−171·242	164·943	5·161	7·257	7·876	8·292	−4·075
Arenalone TMA chloride (VIII)	−171·483	170·042	−161·764	5·237	7·409	7·938	−9·523	8·080

References: (*a*) Tsoucaris, 1961; (*b*) Tamura, Wakahara, Fujiwara & Tomita, 1974; (*c*) Podder, Dattagupta, Sacha & Saenger, 1979; (*d*) Andersen, 1977; (*e*) Hamor & Jones, 1982; (*f*) Bergin & Carlstrom, 1968; (*g*) Giesecke, 1980; (*h*) Andersen, Mostad & Rømming, 1972; (*i*) Tsoucaris, de Rango, Tsoucaris, Zelwer, Parthasarathy & Cole, 1973; (*j*) Andersen, 1975*a*; (*k*) Mathew & Palenik, 1971; (*l*) Andersen, 1975*b*; (*m*) Carlstrom & Bergin, 1967; (*n*) Bergin, 1971.

* TMA = trimethylammonium.

conformation of both the phenethylamine (III) and the (phenylpropyl)amine (IX) trimethylammmonium quaternaries shows some similarity to that of nicotine monohydrogen iodide (Barlow, Howard & Johnson, 1986). In nicotine monohydrogen iodide the torsion angle relating the pyrrolidine N atom *via* the ring-joining bond, to the plane of the pyridine ring (119°), is intermediate between the improper torsion angle TOR3 in compound (III) (105°) and TOR4 in compound (IX) (136°). This similarity can be envisaged by the superposition of nicotine monohydrogen iodide and compound (IX), depicted in Fig. 4, where the smaller angle (16°) is found between the planes of the six-membered rings. As it would appear to be the monoprotonated form of nicotine which is acting at the neuromuscular junction (Barlow & Hamilton, 1962) this conformational similarity may begin to explain the enhanced activity of compounds (III) and (IX) relative to nicotine (Fig. 1). However, compound (IV) which has TOR3 = 76° and also shows enhanced activity is conformationally less like nicotine monohydrogen iodide than either (III) or (IX).

Concluding remarks

It is difficult to come to any firm conclusion about the relationships between conformation and biological activity when dealing with agonists. Because they produce a response from the tissue, their activity depends upon ability to activate receptors (efficacy) as well as ability to become bound to them (affinity). Some ideas may be obtained, however, by considering the relative activities of enantiomers. With catecholamines acting at adrenergic receptors there is a marked difference between the activity of (−)- and (+)-enantiomers, suggesting that there are interactions of at least three groups in the drug with groups in the receptor. The interacting groups in the catecholamines appear to be the amino group, the *meta*-phenolic group and the *β*-hydroxyl group.

With actions at nicotinic receptors there is also some degree of stereospecificity. Natural (−)-nicotine is more active than (+)-nicotine, though the degree of stereospecificity is not as large as that found for the catecholamines at adrenergic receptors and is different for different types of nicotinic receptor (Barlow & Hamilton, 1965). A charged N atom appears to be important for nicotine-like activity (Barlow & Hamilton, 1962) but it is not easy to identify two other groups which might be involved in a three-point interaction at the receptor site. One such group might be a *meta*-phenolic group but its position relative to the N atom varies considerably from one compound to another and even compounds without it, such as phenethyltrimethylammonium salts, are not inactive.

The structures of the compounds determined here suggest that instead of a three-point interaction between drug and nicotinic receptor, the interaction might involve one point (the charged N atom) and a region of planarity in the molecule (the aromatic ring) without specifying particular groups in the plane. Although such small molecules would be expected to be conformationally quite flexible in solution, an energetic preference for one conformer may make it easier for some molecules to interact rather than others. The favourable disposition of a charged N atom relative to an aromatic ring has been encountered in the structure of the conformationally restricted alkaloid (−)-cytisine (Barlow & Johnson, 1988) which shows nicotine-like biological activity (Dale & Laidlaw, 1912; Barlow & McLeod, 1969).

We thank the Medical Research Council for support, and Mr Phil Darby for producing the illustrations.

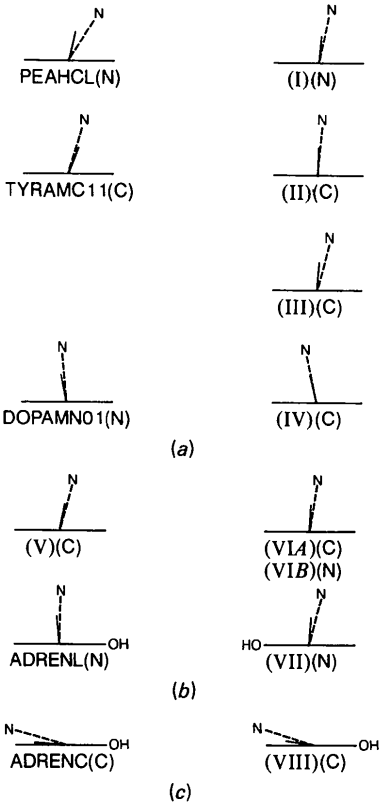


Fig. 3. Schematic representation of the molecular conformations of (*a*) phenethylamines, (*b*) (2-hydroxyphenethyl)amines and (*c*) (*β*-ketophenethyl)amines, viewed from the *p*-phenyl C atom. The plane of the phenyl ring is represented by a horizontal line with the projection of TOR1 (solid) and of TOR3 (dashed) shown. Quaternary trimethyl compounds are depicted on the right-hand side. (C) = centrosymmetric, (N) = non-centrosymmetric, crystal structure.

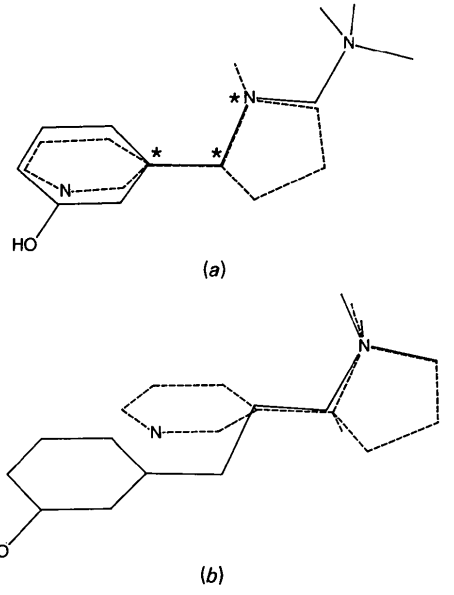


Fig. 4. (*a*) Crystallographic fitting of the starred atoms of nicotine monohydrogen iodide (dashed) and compound (IX) (solid); (*b*) as (*a*) but with the nicotine-monohydrogen-iodide cation translated in the plane to bring the quaternary N atoms into coincidence.

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Structural Phase Transition in 1-Chloroadamantane ($C_{10}H_{15}Cl$)

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(*Received* 20 *September* 1988; *accepted* 27 *February* 1989)

Abstract

The structures of the high-temperature plastic disordered (I) and low-temperature ordered (III) phases of 1-chloroadamantane ($C_{10}H_{15}Cl$, $M_r = 170{\cdot}5$, symmetry C_{3v}) were investigated by X-ray diffraction analysis [$\lambda(\text{Mo } K\bar{\alpha}) = 0{\cdot}7107$ Å, $\mu = 0{\cdot}27$ cm^{-1}, $F(000) = 157$]. Phase I crystallizes in the cubic space group $Fm3m$ and was studied at two temperatures [$a = 9{\cdot}970$ (10) Å at 295 K and $9{\cdot}864$ (10) Å at 257 K, $Z = 4$, $D_x(295\text{ K}) = 1{\cdot}14$ g cm^{-3}, D_m not measured]. The structural analysis confirms the assumptions made in interpreting the dynamical disorder observed by NMR, IQNS and dielectric relaxation measurements. The molecule undergoes a tumbling movement of its C_3 axis between the fourfold crystallographic axes, and a fast uniaxial rotation about the C_3 molecular axis. Steric hindrance analysis showed that ferro- or antiferroelectric local configurations are favoured. Phase III crystallizes in the monoclinic space group $P2_1/c$ [$a = 10{\cdot}018$ (10), $b = 6{\cdot}823$ (7), $c = 13{\cdot}147$ (13) Å, $\beta = 90{\cdot}04$ (4)°, $V = 898{\cdot}7$ Å^3, $Z = 4$, $D_x = 1{\cdot}26$ g cm^{-3}, D_m not measured, $T = 210$ K, $R = 0{\cdot}034$ for 1036 observed reflections]. The procedure for obtaining and selecting good crystals at $T < T_t$ (T_t = transition temperature) is briefly described. In phase III, the molecule takes only one equilibrium position in a lattice site. The threefold axis is fixed and

0108-7681/89/040404-08$03.00