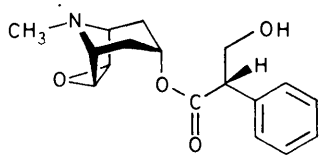
Solid-state Stereochemistry of Anhydrous (−)-Scopolamine Hydrobromide

Robert Glaser *
Department of Chemistry, Ben Gurion University of the Negev, Beersheva 84105, Israel
Jean-Pierre Charland
Chemistry Division, National Research Council, Ottawa K1A OR6, Canada
André Michel
Département de Chimie Structurale, Université de Sherbrooke, Sherbrooke, Québec J1K 2RI, Canada

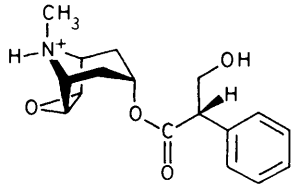
The solid-state structure of anhydrous (N*r*,C_α-*S*)-(−)-scopolamine hydrobromide [(−)-hyoscine], an acetylcholine antagonist, has been determined by single crystal *X*-ray diffraction analysis. (−)-Scopolamine hydrobromide [anhydrous form] gives crystals belonging to the orthorhombic $P2_12_12_1$ space group, and at 298 K: a = 7.348(1), b = 10.482(1), c = 22.867(1) Å, V = 1 761.26(1) Å^3, Z = 4, $R(F)$ = 0.053, and $R_w(F)$ = 0.049. The (*S*)-absolute configuration was determined from the effects of anomalous dispersion of the bromide atom. The *N*-methyl group exists in an axial configuration similar to that previously described for the hemihydrate. However, in the anhydrous form the tropate residue exhibits a different conformation from that noted for the hemihydrate. The tropate ester moiety in (N*r*,C_α-*S*)-(−)-scopolamine hydrobromide [anhydrous form] and (N*s*,C_α-*S*)-*N*-butylhyoscinium bromide both exhibit very similar crystalline-state conformations, while that in the hemihydrate form is reasonably similar to (N*s*,C_α-*S*)-(−)-hyoscyamine hydrobromide [(−)-atropine].

(−)-Scopolamine [(−)-hyoscine[1] (**1**)] is an antimuscarinic (or atropinic) drug that inhibits the action of acetylcholine on structures innervated by postganglionic parasympathetic nerves.[2] (−)-Hyoscine is a tropane alkaloid natural product isolated from the belladonna plant *hyoscyamus niger* (henbane) and consists of the (C_α-*S*)-(−)-tropic acid[3] ester of the 3-*endo*-substituted amino alcohol, scopine.[2] N.m.r. spectroscopy has recently shown that scopolamine free base (**1**) exists pre-

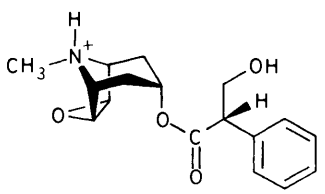


(**1**)

dominantly as the equatorial *N*-CH_3 diastereoisomer at the fast exchange limit (FEL) for isomer interconversion in $CDCl_3$ solution.[4] The ^{1}H and ^{13}C n.m.r. spectral parameters were also measured for the two *N*-CH_3 (N*r* or *s*,C_α-*S*)-diastereomers of (−)-scopolamine hydrobromide (**2a**, **e**) at the slow exchange limit (SEL) for interconversion in various solvents.[4]

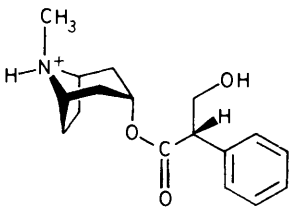


(**2a**)

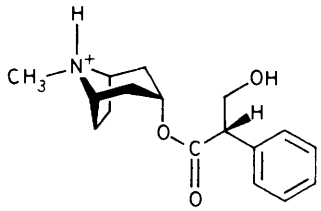


(**2e**)

Scopolamine hydrobromide (**2**) undergoes a diastereoisomerization reaction in solution at the labile stereogenic[5] nitrogen which interconverts the two protonated *N*-CH_3 species *via* a prototropic shift/nitrogen inversion mechanism.[4] Considerable confusion existed in the literature regarding the *N*-CH_3



(**3a**)



(**3e**)

chemical shift for the single species of scopolamine hydrobromide reported in D_2O [reported as 53.42,[6] 34.31,[7] or 25.72[8] ppm]. On the other hand, ^{13}C n.m.r. SEL spectral parameters were reported for each of the pair of protonated *N*-CH_3 (N*r* or *s*,C_α-*S*)-diastereoisomers of atropine salts (**3a**, **e**) in D_2O,[4,8] acidic methanol,[9] and CD_2Cl_2[4] solutions [*e.g.* ratio (**3a**):(**3e**) *ca.* 1:7 in D_2O[4] and *ca.* 1:18 in CD_2Cl_2[4]].

Glaser *et al.*[4] have recently shown that scopolamine hydrobromide in D_2O gave a dynamic ^{13}C n.m.r. spectrum at 295 K showing decidedly broadened signals (especially for *N*-CH_3). However, two drops of trifluoroacetic acid (TFA) added to the 3 cm^3 ^{13}C n.m.r. sample (*ca.* 0.15 mol dm^{-3}) dramatically sharpened all spectral lines and now enabled the SEL observation of two species [ratio (**2a**):(**2e**) *ca.* 18:1]. This behaviour was in accord with the known higher acidity for protonated scopolamine cations (pK_a = 7.55) *vis-á-vis* that for protonated atropine cations (pK_a = 9.25),[10] and this was most likely the reason behind the confusion in the ^{13}C n.m.r. data[6–8] in the literature.[4] In addition, both ^{1}H and ^{13}C n.m.r. spectroscopy showed that the diastereoisomeric ratio was now reversed in CD_2Cl_2 solution [ratio (**2a**):(**2e**) *ca.* 1:18].[4] Stereochemical assignments for *N*-CH_3 stereochemistry in solution-state (**2a**, **e**) species were confirmed by solid-state CP-MAS ^{13}C n.m.r. spectra of crystalline equatorial *N*-CH_3 (N*r*,C_α-*S*)-atropine hydrobromide[11,12]/sulphate[4] and axial *N*-CH_3 (N*r*,C_α-*S*)-scopolamine hydrobromide.[13] Crystalline (*S*)-scopolamine hydrobromide[13] has been reported as the hemihydrate (**2**)·0.5H_2O, but no co-ordinates were presented

Table 1. Crystallographic details for (N*r*,C$_\alpha$-*S*)-(−)-scopolamine hydrobromide [anhydrous form] (**2**)-anh.

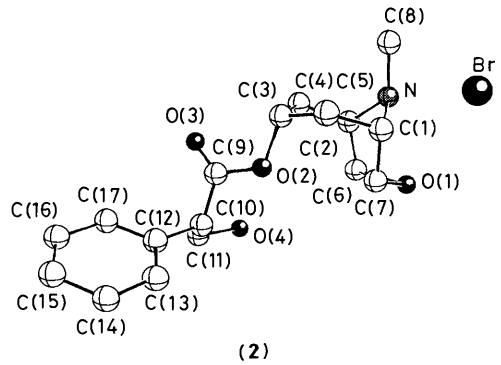
Formula	$C_{17}H_{21}NO_4$·HBr
M	384.27
Space group	$P2_12_12_1$
a/Å	7.348(1)
b/Å	10.482(1)
c/Å	22.867(1)
V/Å^3	1 761.26(1)
Z	4
D_c/g cm^{-3}	1.449
Linear abs coeff, cm^{-1}	23.3
T/K	298
Crystal size/mm^3	0.20 × 0.15 × 0.10
Radiation	graphite-monochromated Mo–K_α (λ = 0.709 30 Å)
Collection range	$+h, +k, +l$ ($0 \leq h \leq 8$, $(0 \leq k \leq 11$, $0 \leq l \leq 27$)
2θ limits	$1.0° \leq 2\theta \leq 49.8°$
Scan type	$\omega - 2\theta$
Scan width/°	0.80 + 0.35 tan θ
Scan speed/deg min^{-1}	4
Background time/scan time	0.33
Unique data	2 223
Unique data with $F_o^2 \geq 2.5\sigma(F_o^2)$	1 318
No. of variables	298
R(*F*)	0.053
$R_w(F)$	0.049
Weighting factor, *w*	σ_F^{-2}
Goodness of fit[a]	1.175

[a] Goodness of fit = SQRT[$(\Sigma_i w_i(|F_{obs}|_i - |F_{calc}|_i)\}^2)$/(no. of reflections − no. of parameters)].

nor were any to be found in the Cambridge Crystallographic Data Base. The desire to obtain co-ordinates for stereochemical augmentation provided the impetus to undertake a new single crystal *X*-ray diffraction analysis of this compound. In the course of this study, a new anhydrous form was observed. This paper describes the crystal and molecular structure of anhydrous (N*r*,C$_\alpha$-*S*)(−)-scopolamine hydrobromide (**2a**).

Results and Discussion

The Solid-state Molecular Geometry of Anhydrous Scopolamine Hydrobromide.—Anhydrous crystals of (−)-scopolamine hydrobromide (**2**) belonging to the orthorhombic space group



(**2**)

† For details of the CCDC deposition scheme, see 'Instructions for Authors (1989)' in the January issue of *J. Chem. Soc., Perkin Trans. 2*, 1989.

Table 2. Atomic parameters for anhydrous (N*r*,C$_\alpha$-*S*)-(−)-scopolamine hydrobromide (**2**)-anh, e.s.d.s refer to the last digit printed.[a]

Atom	*x*	*y*	*z*
Br	0.368 30(14)	0.434 27(10)	0.459 10(4)
O(1)	0.536 2(9)	0.536 5(6)	0.603 40(24)
O(2)*	1.071 2(8)	0.633 0(5)	0.636 80(23)
O(3)*	1.263 8(10)	0.785 7(6)	0.606 70(24)
O(4)*	0.906 8(10)	0.930 9(8)	0.667 0(3)
N	0.754 1(10)	0.465 1(6)	0.523 4(3)
C(1)	0.813 5(13)	0.414 5(8)	0.583 3(3)
C(2)	1.019 7(13)	0.434 7(9)	0.590 2(3)
C(3)	1.084 4(11)	0.572 1(9)	0.580 6(3)
C(4)	0.971 1(13)	0.645 6(8)	0.533 1(3)
C(5)	0.769 5(13)	0.608 5(8)	0.534 1(4)
C(6)	0.687 0(14)	0.620 9(9)	0.591 5(4)
C(7)	0.715 1(14)	0.500 9(9)	0.624 9(3)
C(8)	0.841 8(12)	0.410 9(8)	0.471 5(3)
C(9)*	1.171 7(12)	0.740 8(7)	0.644 7(4)
C(10)*	1.145 7(15)	0.706 1(8)	0.702 4(3)
C(11)*	1.074 4(15)	0.933 8(10)	0.695 8(4)
C(12)*	1.307 8(13)	0.780 9(8)	0.742 1(4)
C(13)*	1.304 9(14)	0.705 8(8)	0.789 2(4)
C(14)*	1.446 5(16)	0.689 3(10)	0.826 2(4)
C(15)*	1.608 4(17)	0752 7(10)	0.813 8(5)
C(16)*	1.613 4(16)	0.834 5(11)	0.767 4(4)
C(17)*	1.467 8(16)	0.844 5(10)	0.730 6(4)

[a] Symmetry equivalents [−0.500 + *x*, 1.500 − *y*, 1.000 − *z*] of atoms marked with an asterisk (*) were used in the intermolecular tropate ester residue depicted in Figure 3.

$P2_12_12_1$ were obtained by vapour diffusion of acetone into either absolute or 95% ethanol solutions of the salt. The crystal data are provided in Table 1. The atomic parameters *x*, *y*, and *z* are listed in Table 2. The numbering scheme is shown in structure (**2**). Intramolecular distances and angles are given in Table 3, and selected torsion angles are presented in Table 4. Tables of thermal parameters and hydrogen atom co-ordinates have been deposited at the Cambridge Crystallographic Data Centre.†

The (C$_\alpha$-*S*)-absolute configuration of crystalline anhydrous (−)-(**2**) was determined from the effects of anomalous dispersion by the bromine atom.[14] The (C$_\alpha$-*S*)-absolute configuration of (−)-tropic acid had previously been chemically correlated with D-(−)-alanine,[3] while anomalous dispersion had been used to determine (C$_\alpha$-*S*)-stereochemistry for the major *N*-oxide diastereoisomer produced by oxidation of (−)-scopolamine free base (**1**).[15] While the molecular geometry of the tropate residue in solid-state anhydrous scopolamine HBr is different from that of the hemihydrate,[13] in both cases the *N*-CH_3 group was axially disposed relative to the piperidine ring and thus the (N*r*,C$_\alpha$-*S*)-descriptor will be used for the solid-state species (**2a**). In the solid-state 6,7-deoxy analogue, (N*s*,C$_\alpha$-*S*)-hyoscyamine hydrobromide[11,12] [(−)-enantiomer of atropine hydrobromide], the *N*-CH_3 group is equatorially oriented. Equatorial *N*-CH_3 orientation seems usually to be the rule in tropane alkaloid crystal structures such as (N*s*)-tropine hydrobromide,[16] (N*s*)-pseudotropine free base,[17] (N*s*)-*O*-benzoyltropine hydrochloride,[18] (N*s*)-*O*-benzoylpseudotropine hydrochloride,[19] (N*s*)-benztropine mesylate,[20] (3*r*,N*s*)-3-bromotropane hydrobromide[21] and the ecognine (1*R*,2*R*,3*RS*,5*S*,8*S*)-(−)-cocaine hydrochloride.[22] The equatorial disposition of the *N*-CH_3 group is likely the result of unfavourable *cis*-1,3-diaxial non-bonded interactions between CH_3 protons and piperidine-ring axial protons in these structures[11,12,16–22] containing the labile stereogenic nitrogen. The axial *N*-CH_3 group was noted also in the kinetic reaction products (N*s*,C$_\alpha$-*S*)-*N*-butylhyoscinium bromide[23] (**4**) and (N*s*,C$_\alpha$-*S*)-scopolamine *N*-oxide

Table 3. Non-hydrogen intramolecular and selected intermolecular bond distances and angles for anhydrous (N*r*,C$_{\alpha}$-*S*)-(−)-scopolamine hydrobromide (**2**)-anh; e.s.d.s refer to the last digit printed.

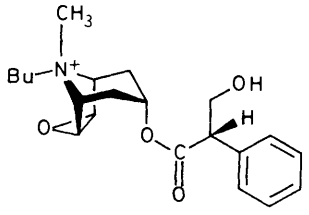
(*a*) Distances/Å

O(1)–C(6)	1.111(12)	C(4)–C(5)	1.532(13)
O(1)–C(7)	1.452(12)	C(5)–C(6)	1.452(13)
O(2)–C(3)	1.438(9)	C(6)–C(7)	1.486(13)
O(2)–C(9)	1.362(10)	C(9)–C(10)	1.454(11)
O(3)–C(9)	1.198(11)	C(10)–C(11)	1.543(14)
O(4)–C(11)	1.397(13)	C(10)–C(12)	1.506(13)
N–C(1)	1.532(10)	C(12)–C(13)	1.334(13)
N–C(5)	1.527(11)	C(12)–C(17)	1.377(15)
N–C(8)	1.465(10)	C(13)–C(14)	1.352(15)
C(1)–C(2)	1.538(13)	C(14)–C(15)	1.392(17)
C(1)–C(7)	1.499(12)	C(15)–C(16)	1.365(15)
C(2)–C(3)	1.532(13)	C(16)–C(17)	1.365(15)
C(3)–C(4)	1.578(11)		
Br · · · O(4)*	3.223(7)	O(4)*–H(4)*	1.21(9)
Br · · · H(4)*	2.03(9)	Br · · · H(N)	2.31(7)
Br · · · N	3.209(7)	O(1) · · · H(N)	2.06(7)
N–H(N)	1.14(8)		

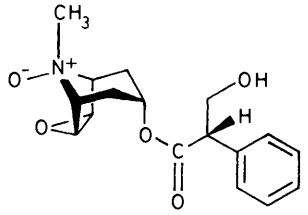
(*b*) Angles/°

C(6)–O(1)–C(7)	61.7(6)	O(1)–C(7)–C(1)	112.1(6)
C(3)–O(2)–C(9)	116.8(6)	O(1)–C(7)–C(6)	58.9(6)
C(1)–N–C(5)	100.2(6)	C(1)–C(7)–C(6)	104.6(6)
C(1)–N–C(8)	117.7(6)	O(2)–C(9)–O(3)	122.4(8)
C(5)–N–C(8)	118.6(7)	O(2)–C(9)–C(10)	112.3(7)
N–C(1)–C(2)	108.9(6)	O(3)–C(9)–C(10)	125.2(8)
N–C(1)–C(7)	102.8(7)	C(9)–C(10)–C(11)	109.2(7)
C(2)–C(1)–C(7)	109.1(7)	C(9)–C(10)–C(12)	113.6(8)
C(1)–C(2)–C(3)	114.9(7)	C(11)–C(10)–C(12)	115.2(7)
O(2)–C(3)–C(2)	105.6(6)	O(4)–C(11)–C(10)	109.0(8)
O(2)–C(3)–C(4)	111.4(7)	C(10)–C(12)–C(13)	122.4(9)
C(2)–C(3)–C(4)	113.3(7)	C(10)–C(12)–C(17)	120.6(8)
C(3)–C(4)–C(5)	112.2(7)	C(13)–C(12)–C(17)	117.0(9)
N–C(5)–C(4)	108.6(7)	C(12)–C(13)–C(14)	124.6(10)
N–C(5)–C(6)	101.7(7)	C(13)–C(14)–C(15)	118.0(9)
C(4)–C(5)–C(6)	113.2(8)	C(14)–C(15)–C(16)	118.8(11)
O(1)–C(6)–C(5)	115.9(8)	C(15)–C(16)–C(17)	120.4(11)
O(1)–C(6)–C(7)	59.4(6)		
Br · · · H(4)*–O(4)*	166(6)	Br · · · H(N)–N	132(4)
O(1) · · · H(N)–N	100(4)	O(1) · · · H(N) · · · Br	114(3)

[a] Asterisk denotes symmetry-equivalent atoms [−0.500 + *x*, 1.500 − *y*, 1.000 − *z*].



(**4**)



(**5**)

hydrobromide[15] (**5**) where the stereogenic nitrogen is no longer labile. Two *N*-oxide diastereoisomers are formed in the oxidation of scopolamine free base [(**5**) is the major product].

Comparison of Molecular Conformations in Anhydrous and Hemihydrate Crystals.—As noted above, the co-ordinates for the hemihydrate were not available, and the molecular geometry was not extensively discussed by Pauling and Petcher.[13] The hemihydrate was described as belonging to space group *P*4/*mmm*, *a* = 11.965(7), *c* = 26.52(2) Å, *Z* = 8, and *R* = 0.09.[13] Non-bonding distances between the nitrogen and the four oxygen atoms [N · · · O(1), O(2), O(3), or O(4)] were noted as: 2.47, 3.88, 5.41, and 8.04[3] Å for (**2**)·0.5H_2O[13] *vs.* 2.54, 3.91, 5.38, and 5.99 Å for the anhydrous form. In addition, they defined dihedral angles from three best planes to describe the conformation of the molecule.[13] Plane *A* was defined as the 'mirror plane' through the scopine moiety which goes through N, C(3), C(8), and O(1) and 'relates' C(1), C(2), C(7) with C(5), C(4), C(6); plane *B* was described as going through the ester group O(2), O(3), C(9), C(10); while plane *C* was the benzene ring.[13]* In the hemihydrate the following dihedral angles were noted: plane *A* with plane *B* 44.5°, plane *A* with plane *C* 79.4°, plane *B* with plane *C* 87.4° for (**2**)·0.5H_2O[13] *vs.* 66.9(8)°, 69.7(3)°, and 63.9(8)° for the anydrous form. Additional stereochemical information on the hemihydrate was provided by Leger *et al.*[23] in their discussion of *N*-butylhyoscinium bromide (**4**) [(2)·0.5H_2O torsion angles C(4)–C(3)–O(2)–C(9), C(3)–O(2)–C(9)–C(10), O(2)–C(9)–C(10)–C(12), and C(9)–C(10)–C(12)–C(13)].† The major difference appears to be torsion angle C(4)–C(3)–O(2)–C(9) in the two crystal forms: −176.9°[23] in (**2**)·0.5H_2O *vs.* −76.6° in (**2**)-anh. Expectedly, the ester C(3)–O(2)–C(9)–C(10) angle is antiperiplanar in both cases: −170.2°[23] in (**2**)·0.5H_2O *vs.* 178.8° in (**2**)-anh. The acyl O(2) in (**2**)-anh appears to eclipse H(10) while there is better staggering in (**2**)·0.5H_2O: O(2)–C(9)–C(10)–C(12) is 77.4°[23] in (**2**)·0.5H_2O *vs.* 108.5° in (**2**)-anh. Finally, the pitch of the phenyl ring *vis-á-vis* C(9) [C(9)–C(10)–C(12)–C(13)]‡ is different in both cases: −36.4°[23] in (**2**)·0.5H_2O *vs.* −111.6° in (**2**)-anh. Clearly, the molecular conformation in the two crystal forms are significantly different.

Molecular mechanics calculations were used to compare models of the anhydrous and hemihydrate conformational types. The starting geometry for the anhydrous conformation was obtained from the crystal co-ordinates. The starting structure for the hemihydrate conformational model began with the crystalline anhydrous form geometry which was then modified by changing torsion angles C(4)–C(3)–O(2)–C(9), C(3)–O(2)–C(9)–C(10), O(2)–C(9)–C(10)–C(12), and C(9)–C(10)–C(12)–C(13) to values for (**2**)·0.5H_2O as described by Leger *et al.*[23] Final values for these angles in (**2**)-anh and (**2**)·0.5H_2O conformational models are also listed in Table 4 [calculated model of (**2**)-anh was found to be *ca.* 1.7 kcal higher than the model of (**2**)·0.5H_2O]. The molecular conformation in the (−)-scopolamine hydrobromide anhydrous crystal (*X*-ray) (**2**) *vis-á-vis* that of the hemihydrate model (molecular mechanics calculation) is pictorially compared in Figure 1. The molecular mechanics calculated model of (**2**)·0.5H_2O, depicted in Figure 1, appears to be almost identical with Pauling and Petcher's[13] illustration

* In the case of (**2**)-anh, the equation of best plane *A* through N, O(1), and C(3,8) was: 1.045(21)*X* − 9.061(18)*Y* + 11.02(6)*Z* = 2.35(5). The equation for best plane *B* through O(2,3), and C(9,10) was: 6.27(4)*X* + 4.50(16)*Y* − 6.76(11)*Z* = 5.27(13). The equation for best plane *C* through C(12–17) was: 2.37(3)*X* + 8.02(3)*Y* + 12.73(9)*Z* = 10.967(17).

† The source of values for the four torsion angles C(4)–C(3)–O(2)–C(9), C(3)–O(2)–C(9)–C(10), O(2)–C(9)–C(10)–C(12), and C(9)–C(10)–C(12)–C(13) in (**2**)·0.5H_2O[13] appears to be a private communication, although this is not explicitly noted.[23] In addition, there appears to be a mix-up between the pro-*R* C(2) and the pro-*S* C(4) since Leger *et. al.*[23] compared two different torsion angles in their table, C(4)–C(3)–O(2)–C(9) in (**2**)·0.5H_2O *vs.* C(2)–C(3)–O(2)–C(9) in (**4**). Inspection of the illustration of (**2**)·0.5H_2O conformation provided by Pauling and Petcher[13] clearly shows that the −176.9° value is for C(4)–C(3)–O(2)–C(9) and not for C(2)–C(3)–O(2)–C(9).

‡ Also here, there is an ambiguity as to the atom descriptor for the *ortho* carbon [C(13) *vs.* C(17)] but it is clear that the pitch of the phenyl *vis-á-vis* the ester plane is different.

Table 4. Comparison of selected non-hydrogen torsion angles/° for crystalline-state anhydrous (N*r*,C$_\alpha$-*S*)-(−)-scopolamine hydrobromide (**2**)-anh, (N*r*,C$_\alpha$-*S*)-(−)-scopolamine hydrobromide (**2**)·0.5H$_2$O, (−)-(N*s*,C$_\alpha$-*S*)-(−)-hyoscyamine hydrobromide [(−)-atropine hydrobromide] (**3**), (N*s*,C$_\alpha$-*S*)-*N*-butylhyoscinium bromide [(−)-scopolamine butylbromide] (**4**), and (N*s*,C$_\alpha$-*S*)-(−)-scopolamine *N*-oxide (**5**) together with MMX molecular mechanics models for (**2**)-anh and (**2**)·0.5H$_2$O.

	2-anhydrous		2-hemihydrate				
	X-ray	MMX	*X*-ray[a]	MMX	(**3**)[b]	(**4**)[a]	(**5**)[c]
C(1)–C(2)–C(3)–C(4)	−33.9(5)				−54.0[d]	−31.7	−35.6
C(2)–C(3)–C(4)–C(5)	35.7(5)				55.5[d]	30.6	34.2
C(3)–C(4)–C(5)–N	−58.9(6)				−58.4[d]	−53.4	−54.0
C(4)–C(5)–N–C(1)	75.7(7)				63.2[d]	73.9	72.3
C(5)–N–C(1)–C(2)	−72.4(7)				−66.2	−73.8	−74.0
N–C(1)–C(2)–C(3)	54.2(6)				55.1	55.3	56.7
C(2)–C(3)–O(2)–C(9)	160.0				74.2	164.5	150.2
C(4)–C(3)–O(2)–C(9)	−76.6	−77.2	−176.9	−158.7	−156.3[d]	−69.6	−85.8
C(3)–O(2)–C(9)–C(10)	178.8	176.3	−170.2	174.1	−170.2	−177.8	−176.6
O(2)–C(9)–C(10)–C(12)	108.5(9)	108.7	77.4	72.2	77.3	118.0	81.9
C(9)–C(10)–C(12)–C(13)	−111.6(10)	−108.8	−36.4	79.5	−119.4	−107.9	−129.1
O(4)–C(11)–C(10)–C(12)	−169.3(12)				−168.9	−168.8	−175.3

[a] Data calculated from co-ordinates in ref. 23. [b] Data calculated from co-ordinates in ref. 12. [c] Data calculated from co-ordinates in ref. 15. [d] The position C(4) in (**3**) was calculated by reflection of C(2) through the N–C(3)–C(8) plane for the purpose of this table.

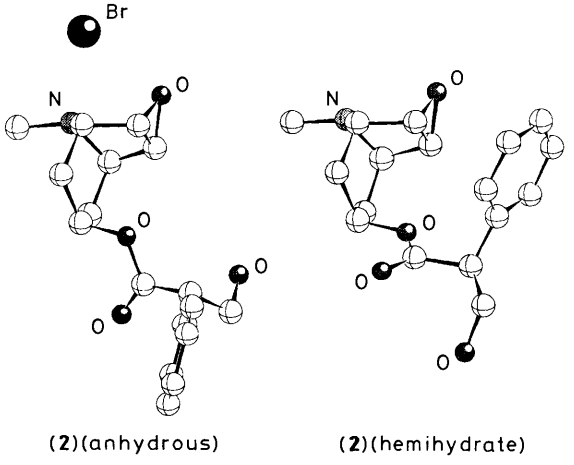


Figure 1. Comparison of crystalline-state molecular geometry of anhydrous (N*r*,C$_\alpha$-*S*)-(−)-scopolamine hydrobromide (**2**)-anh with the molecular mechanics hemihydrate model for (**2**)·0.5H$_2$O [starting structure for the hemihydrate model began with the crystalline anhydrous form geometry which was then modified by changing torsion angles C(4)–C(3)–O(2)–C(9), C(3)–O(2)–C(9)–C(10), O(2)–C(9)–C(10)–C(12), and C(9)–C(10)–C(12)–C(13) to values for (**2**)·0.5H$_2$O as described by Leger *et al.*[23]].

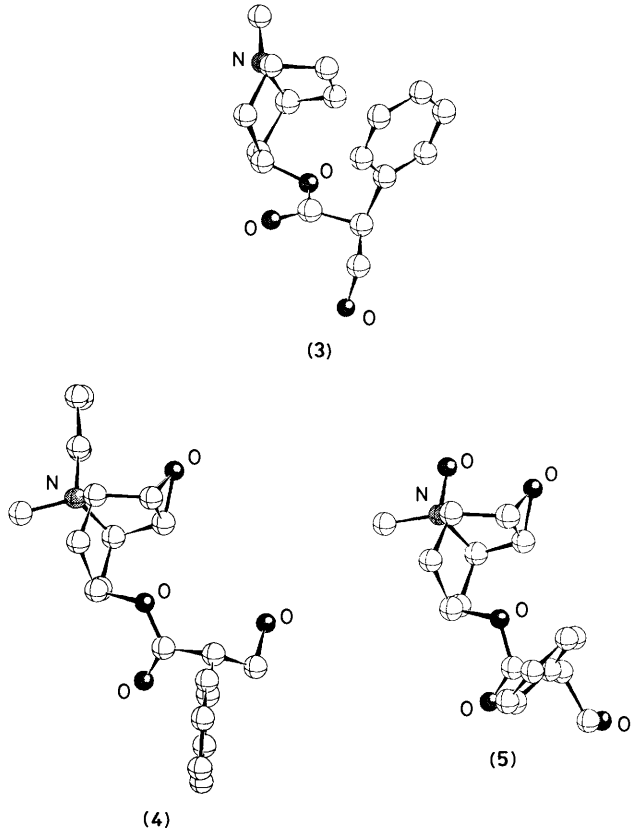


Figure 2. Comparison of crystalline-state molecular geometries of (N*s*,C$_\alpha$-*S*)-(−)-hyoscyamine hydrobromide[12] [(−)-atropine hydrobromide] (**3**), (N*s*,C$_\alpha$-*S*)-*N*-butylhyoscinium bromide [(−)-scopolamine butyl bromide][23] (**4**), and (N*s*,C$_\alpha$-*S*)-(−)-scopolamine *N*-oxide[15] (**5**).

* Original co-ordinates are for (N*r*,C$_\alpha$-*R*)-hyoscyamine hydrobromide (**3**),[12] and thus all signs have been changed to give the (N*s*,C$_\alpha$-*S*)-(−)-enantiomer. In ref. 12 there are errors in co-ordinates for C(4,15,16,17) [their atoms C(2,13,14,15)]. The position of C(4) in (**3**) was calculated by reflection of C(2) through the N–C(3)–C(8) plane for the purpose of Table 4. The positions of phenyl ring C(15–17) in (**3**) were calculated from phenyl ring C(12–14) positions *via* reflection by the plane containing the C(11)–C(12) bond and perpendicular to the C(12)–C(13)–C(14) plane. A direct comparison of the two reported structures for (**3**)[11,12] was not done since co-ordinates were available from only one article.[12] However, the solid-state structures of both atropine hydrobromide molecules appear to be almost identical as shown by rotation of the Kussäther *et al.*[12] structure into an orientation similar to that depicted by Pauling and Petcher.[11]

† Original c = 9.244 Å; the unit cell length for (**4**) is in error. Correct value is listed as c = 11.856 Å according to the Cambridge Crystallographic Data Base.

of the molecule projected down (100) in the hemihydrate crystal.

Inspection of the selected torsion angles listed in Table 4 for (**2**)-anh, (**2**)·0.5H$_2$O,[13,23] (N*s*,C$_\alpha$-*S*)-(−)-hyoscyamine hydrobromide[12,*] [(−)-atropine] (**3**), (N*s*,C$_\alpha$-*S*)-*N*-butylhyoscinium bromide[23,†] (**4**), and (N*s*,C$_\alpha$-*S*)-scopolamine *N*-oxide hydro-

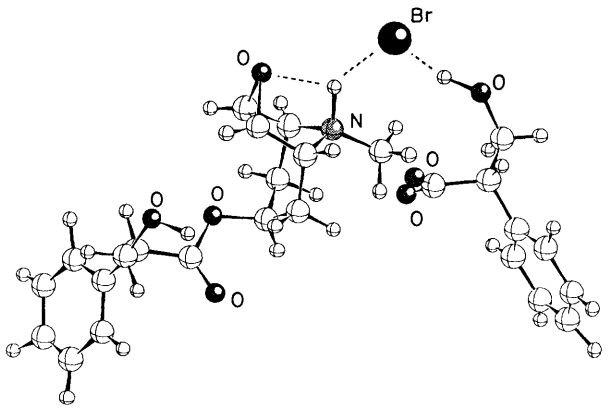


Figure 3. Intramolecular three-centre and intermolecular hydrogen-bonding in crystalline anhydrous (−)-scopolamine hydrobromide (**2**)-anh.

bromide[15] (**5**) shows that anhydrous scopolamine hydrobromide (**2**) and (**4**) have very similar conformations, while (**2**)·0.5H_2O is reasonably similar to (**3**) [with the exception of the pitch of the phenyl ring *vis-á-vis* C(9)]. The crystalline-state conformation of (**5**) appears to be intermediate between that of (**2**)-anh, (**4**), and that of (**2**)·0.5H_2O, (**3**) (see Figures 1 and 2).

All three single crystal *X*-ray diffraction structures of scopolamine (**2**)-anh and its derivatives (**4**) and (**5**) have a piperidine-ring chair markedly flattened at C(3), as shown by the reduced ±(30–36)° C(1)–C(2)–C(3)–C(4) and C(2)–C(3)–C(4)–C(5) torsion angles. This appears to be due to non-bonded interactions between ethano-bridge protons and O(2) rather than involving the axial *N*-CH_3, since similar angles are found for equatorial *N*-CH_3 tropanes, *e.g.* ±(36–37)° for corresponding torsion angles in *O*-benzoyltropine hydrochloride.[18] While the degree of flattening at C(3) in equatorial *N*-CH_3 (**3**) appears to be less, it is noted that these torsion angles involve estimated co-ordinates for C(4). Alkaloids (**2**) and (**3**) both exhibit flattening at C(3) in the solution state as evidenced by similar vicinal coupling of axial methylene protons H(21,41) to H(3) [$^3J_{21-3}$ and $^3J_{3-41}$ 4–5 Hz] and similar coupling between equatorial protons H(22,42) to H(3) [$^3J_{21-3}$ and $^3J_{3-41}$ < 1 Hz].[4]

The position of the N*H* atom in the crystal permits the attainment of a three-centre intramolecular hydrogen-bond, while the bromide anion also undergoes intermolecular hydrogen-bonding (see Figure 3). Hydrogen-bonding distances and angles are presented in Tables 3 and 4, respectively.

Experimental

(−)-Scopolamine hydrobromide (lot no. 12995-A) was purchased from K&K Labs Division of ICN Biomedicals, Inc. Dissolution in absolute ethanol followed by vapour diffusion of acetone yielded clear, colourless, crystalline prisms, belonging to the orthorhombic system $P2_12_12_1$. Melting point 202–204 °C (uncorrected) [lit.,[1] 195 °C (anhydrous)] was determined on a Reychert 'Thermopan' microscope; $[\alpha]_D^{25}$ −24° (*c* = 5, H_2O) [lit.,[1] $[\alpha]_D^{25}$ −24–26° (*c* = 5)].

Intensity data were collected at 298 K on an Enraf–Nonius CAD-4 automatic diffractometer. Table 1 provides crystallographic and data collection details. The NRCVAX programs[24,25] were used for centring, indexing, and data collection. The unit-cell dimensions were obtained by a least-squares fit of 24 centred reflections in the range 30° ≤ 2θ ≤ 45°. Reflections were measured with a constant scan speed of 4° min^{-1}. During data collection, the intensities of three standard reflections were monitored after every 100 reflections. No decay was observed.

The structure was solved by direct methods and refined by full-matrix least squares using the NRCVAX programs.[24,25] No absorption correction was applied. Hydrogen positions were located in a difference Fourier map. The final refinement included anisotropic thermal parameters for the non-hydrogen atoms, and isotropic thermal parameters for the hydrogen atoms. At convergence the final discrepancy indices on *F* were $R(F) = 0.053$ and $R_w = 0.049$ for the 1 318 reflections with $F_0^2 \geq 2.5\sigma(F_0^2)$ and 298 variables.* The residual positive and negative electron density in the final map was +0.57 and −0.66 e $Å^{-3}$, respectively, while the mean and maximum shift/esd was 0.05 and 0.174, respectively. The (*S*)-absolute configuration has been determined from the effects of anomalous dispersion from the bromine atom on twenty Friedel pairs of reflections.[14] The ETA[26] parameter for the (*S*)-enantiomer model was refined to be +0.96(5).

The minimized energy geometry of the molecular mechanics calculated model compounds were determined by the MMX88 program,[27] and were performed on a Micro VAX-II computer under MicroVMS V4.5. MMX88[27] is an enhanced version of Allinger's[28] MM2 program with MMP1 π-subroutines[29] incorporated for localized π-electron systems. Structure (**2**) and those in Figures 1–3 were drawn with the BALL AND STICK 2.0 program.[30]

* The final discrepancy index $R(F)$ is defined as: $R(F) = (\Sigma_i||F_{obs}|_i - |F_{calc}|_i|)/(\Sigma_i|F_{obs}|_i)$; the weighted value R_w is defined as: $R_w(F) = \mathrm{SQRT}[(\Sigma_i\{w_i(|F_{obs}|_i - |F_{calc}|_i|)\}^2)/(\Sigma_i\{w_i(|F_{obs}|_i)\}^2)]$, and the particular weighting factor w_i used is given in Table 1.

References

1 'The Merck Index,' ed. M. Windholz, Merck, Rahway, 1983, 10th edn., p. 1209, and references therein.
2 N. Weiner, in 'The Pharmacological Basis of Therapeutics,' eds. L. S. Goodman, A. Gilman, T. W. Rall, and F. Murad, Macmillan, New York, 1985, 7th edn., pp. 130–144.
3 G. Fodor and G. Cserpreghy, *J. Chem. Soc.*, 1961, 3222.
4 R. Glaser, Q.-J. Peng, and A. S. Perlin, *J. Org. Chem.*, 1988, **53**, 2172.
5 K. Mislow and J. Seigel, *J. Am. Chem. Soc.*, 1984, **106**, 3319.
6 L. Simeral and G. E. Maciel, *Org. Magn. Reson.*, 1974, **6**, 226.
7 H. W. Avdovitch and G. A. Neville, *Can. J. Spectrosc.*, 1983, **28**, 1.
8 J. Feeney, R. Foster, and E. A. Piper, *J. Chem. Soc., Perkin Trans. 2*, 1977, 2016.
9 K. H. Pook, W. Schulz, and R. Banholzer, *Leibigs Ann. Chem.*, 1975, 1499.
10 D. W. Newton and R. B. Kluza, in 'Principles of Medicinal Chemistry,' ed. W. O. Foye, Lea and Febiger, Philadelphia, 1981, 2nd edn., pp. 901–908.
11 P. J. Pauling and T. J. Petcher, *Nature (London)*, 1970, **228**, 673.
12 E. von Kussäther and J. Hasse, *Acta Crystallogr., Sect. B*, 1972, **28**, 2896.
13 P. J. Pauling and T. J. Petcher, *J. Chem. Soc., Chem. Commun.*, 1969, 1001.
14 J. M. Bijvoet, A. F. Peerdeman, and A. J. Van Bommel, *Nature (London)*, 1951, **168**, 271.
15 C. S. Huber, G. Fodor, and N. Mandava, *Can. J. Chem.*, 1971, **49**, 3258.
16 J. W. Viser, J. Manassen, and J. D. De Vries, *Acta Crystallogr.*, 1954, **7**, 288.
17 H. Schenk, C. H. MacGillavry, S. Skolnik, and J. Laan, *Acta Crystallogr.*, 1967, **23**, 423.
18 T. J. Hamor, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1359.
19 P. Chananont and T. J. Hamor, *J. Chem. Res.*, 1978, (*S*) 414; (*M*) 5064.
20 P. G. Jones, O. Kennard, and A. S. Horn, *Acta Crystallogr., Sect. B*, 1978, **34**, 3125.
21 T. J. Hamor and N. Kings, *Acta Crystallogr., Sect. B*, 1980, **36**, 3153.
22 E. J. Gabe and W. H. Barnes, *Acta Crystallogr.*, 1963, **16**, 796.
23 J. M. Leger, M. Gadret, and A. Carpy, *Acta Crystallogr., Sect B*, 1978, **34**, 3705.
24 Program 'The NRCVAX Crystal Structure System in Crystallographic Computing' (ref. 25).

25 E. J. Gabe, F. L. Lee, and Y. LePage, in 'Data Collection, Structure Determination, Proteins, and Data Bases,' vol. 3, eds. G. M. Sheldrick, C. Kruger, and R. Goddard, Clarendon Press, Oxford, 1985; pp. 167–174.
26 D. Rogers, *Acta Crystallogr., Sect. A*, 1981, **37**, 734.
27 Program MMX88, Serena Software Inc., P.O.B. 3076, Bloomington, Indiana 47402-3076, USA.
28 N. L. Allinger, *J. Am. Chem. Soc.*, 1977, **99**, 8127.
29 N. L. Allinger and J. **T.** Sprague, *J. Am. Chem. Soc.*, 1973, **95**, 3893.
30 N. Müller and A. Falk, 'BALL AND STICK 2.0 Molecular Graphics Program for Apple Macintosh Computers,' Johannes Kepler University, Linz, Austria, 1988.

Received 7th February 1989; *Paper* 9/00577C