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The Crystal and Molecular Structure of Ajmaline and *N*-*n*-Propyl-21-*epi*-isoajmalinium Bromide

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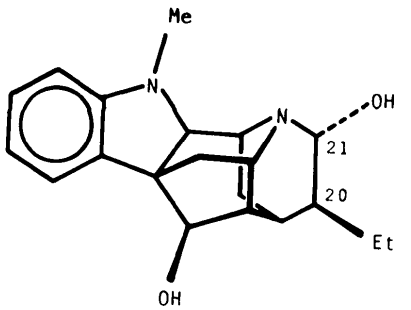
Ajmaline free base, crystallized from an aprotic solvent, and what was originally thought to be *N*-*n*-propylisoajmalinium bromide were subjected to crystal structure analysis. The free base crystallized from dichloromethane with two molecules each of the alkaloid and the solvent per asymmetric unit (space group $P2_12_12_1$); the symmetry-independent ajmaline molecules are intermolecularly hydrogen-bonded to form pseudo-dimers which display a largely hydrophobic surface and are thus suitable species for lipid solubility. The bromide was found to display unexpected stereochemistry in its quinuclidinium moiety. The C(20) ethyl and C(21) hydroxyl substituents were found to be in a *cis* configuration and thus the analysis demonstrated the existence of the *N*-*n*-propyl-21-*epi*-isoajmalinium ion. The analyses reveal the presence of considerable strain in the quinuclidine moieties and the probable presence of modest double-bond character in the C(21)—O(2) bond. The crystallographic data are: for the free base a = 10·938 (2), b = 14·445 (3), c = 25·117 (4) Å; for the bromide, space group $P2_1$, a = 9·642 (3), b = 11·206 (4), c = 9·971 (4) Å, β = 102·64 (2)°, Z = 2 (*t ca* −120°C for both). The respective R values are 0·076 (8463 data) and 0·047 (3372 data).

Introduction

The alkaloid ajmaline (I), isolated from the roots of *Rauwolfia serpentina* (Siddiqui & Siddiqui, 1931), may be regarded as the parent of a family of antiarrhythmic drugs. Its chemical structure (Mukherjee, Robinson & Schlittler, 1949; Anet, Chakravarti, Robinson & Schlittler, 1954; Robinson, 1955; Finch, Hobson, Robinson & Schlittler, 1955; Woodward, 1956) and stereochemistry (Bartlett *et al.*, 1962) are known. Ajmaline can be converted into another natural product, isoajmaline (20-*epi*-21-*epi*-ajmaline) (Taylor, 1965; Shamma & Walker, 1963), simply by heating above its melting point (Anet *et al.*, 1954); the two stereoisomers display similar antiarrhythmic activity. The conversion of ajmaline in ethanolic alkali occurs *via* a ring-opened amino aldehyde intermediate (*chano*-ajmaline).



(I)

Petter (1974) has characterized some of the physical properties of ajmaline, isoajmaline and 17-acetylajmaline. By determining the pK_a of each (the tertiary N atom of the quinuclidine system serves as a Brönsted base; the pK_a values reported are 8·32, 8·17, and 6·25 respectively) and their distribution coefficients between water and *cis*-9-octadecen-1-ol as a function of *p*H, he has demonstrated the probable importance of the deprotonated form for their solubility in lipophilic media. In an effort to characterize the microspecies presented by ajmaline under lipophilic conditions, we have carried out a crystal structure analysis of its free base crystallized from an aprotic solvent, dichloromethane.

We have also used crystal structure analysis to investigate another aspect of ajmaline chemistry. The *N*-alkylated derivative, *N*-*n*-propylajmalinium bitartrate, has been found to be a considerably more effective antiarrhythmic agent than the parent alkaloid (Diederich & Boykson, 1973; Femmer & Grünheid, 1976). In view of the greater lipophilicity of isoajmaline compared to ajmaline (Petter, 1974), the characterization of *N*-*n*-propylisoajmalinium salts was also of interest. Such characterization has raised questions concerning the stereochemistry of the cation (Muxfeldt, 1974). We have carried out an analysis of what was originally thought to be *N*-*n*-propylisoajmalinium bromide and have thereby established the existence of the *N*-*n*-propyl-21-*epi*-isoajmalinium cation. We report the results of these analyses and our interpretation of their significance.

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Experimental

Samples of ajmaline free base and *N*-*n*-propyl-21-*epi*-isoajmalinium bromide were obtained, through the courtesy of the late Professor Hans Muxfeldt, from Giulini-Pharma, Hannover, BRD. Single crystals of the free base and the salt were obtained by evaporation, at *ca* 8 °C, of dichloromethane and methanol solutions respectively. Space groups were determined from precession photographs. Lattice parameters (Table 1) were determined by least-squares calculations (Stewart, Kruger, Ammon, Dickinson & Hall, 1972) from 2θ values of automatically centered reflections from the cooled crystal (*ca* −120 °C) used for intensity-data collection.

Intensities were measured for crystals maintained at *ca* −120 °C (Syntex LT-1 low-temperature device) with a Syntex $P\bar{1}$ autodiffractometer operating in an ω-scan mode. The scan rate varied from 2·0 to 24·0° min^{-1}; the scan range was 0·75° and background intensity was measured on each side of the reflection center ($\Delta\omega$ = 1·0°) for one-half the total scan time. Three reference reflections displayed neither systematic nor significant deviations in their intensities during the data collection. Intensities were classified as observed when $I \geq 2\sigma(I)$. They were corrected for Lorentz and polarization effects, and those of the bromide for absorption also.

Initial models for the free base and for the bromide were obtained by direct methods and the heavy-atom technique respectively. H atoms were either located from difference maps (free base) or calculated from geometrical considerations (most of those in the bromide). Refinement was by block-diagonal least-squares calculations in which individual blocks contained the variables associated with one non-hydrogen atom (coordinates and anisotropic temperature factors) and those of any H atoms bonded to it (coordinates and isotropic temperature factors); a single scale factor was refined for each model. Reflections classified as unobserved for which the calculated intensity was

Table 1. *Crystal data for ajmaline free base and N-n-propyl-21-epi-isoajmalinium bromide*

	Ajmaline	*N*-*n*-Propyl-21-*epi*-isoajmalinium bromide
Crystal size (mm)	0·20 × 0·29 × 0·35	0·30 × 0·30 × 0·30
Space group	$P2_12_12_1$	$P2_1$
Z	8	2
a	10·938 (2) Å	9·642 (3) Å
b	14·445 (3)	11·206 (4)
c	25·117 (4)	9·971 (4)
β		102·64 (2)°
Number of contributing 2θ values	48	30
$2\theta_{min}$–$2\theta_{max}$	34·6–41·4°	31–42°
Formula per asymmetric unit	$C_{42}H_{56}Cl_4N_4O_4$	$C_{20}H_{33}BrN_2O_2$
D_x (t = −120 °C)	1·36 g cm^{-3}	1·42 g cm^{-3}
μ	3·5 cm^{-1}	21 cm^{-1}
Number of unique data	9557	4337
Number of observed data	6455	3108
Data-set resolution $(\sin\theta/\lambda)_{max}$ Mo $K\alpha$	0·807 Å^{-1}	0·904 Å^{-1}

Table 2. *Fractional atomic coordinates (with estimated standard deviations) for the non-hydrogen atoms*

(*a*) Ajmaline free base

	10^4x	10^4y	10^4z
N(1,*A*)	3822 (4)	5254 (3)	1732 (1)
C(2,*A*)	3846 (4)	5212 (3)	1143 (2)
C(3,*A*)	2980 (4)	4554 (3)	858 (2)
N(4,*A*)	1692 (3)	4920 (3)	850 (1)
C(5,*A*)	1718 (4)	5903 (3)	669 (2)
C(6,*A*)	2308 (4)	6487 (3)	1096 (2)
C(7,*A*)	3665 (4)	6248 (3)	1002 (2)
C(8,*A*)	4494 (4)	6682 (3)	1416 (2)
C(9,*A*)	5109 (5)	7501 (3)	1432 (2)
C(10,*A*)	5798 (5)	7716 (3)	1898 (2)
C(11,*A*)	5785 (5)	7110 (4)	2323 (2)
C(12,*A*)	5145 (5)	6275 (4)	2313 (2)
C(13,*A*)	4501 (4)	6059 (3)	1849 (2)
C(14,*A*)	3440 (4)	4399 (3)	283 (2)
C(15,*A*)	2688 (4)	5026 (3)	−88 (2)
C(16,*A*)	2564 (4)	5998 (3)	175 (2)
C(17,*A*)	3783 (4)	6406 (3)	400 (2)
C(18,*A*)	824 (6)	5071 (4)	−1064 (2)
C(19,*A*)	488 (4)	5084 (3)	−476 (2)
C(20,*A*)	1416 (4)	4572 (3)	−129 (2)
C(21,*A*)	959 (4)	4399 (3)	451 (2)
C(22,*A*)	4131 (6)	4423 (4)	2020 (2)
O(1,*A*)	3866 (4)	7390 (3)	318 (1)
O(2,*A*)	970 (3)	3445 (2)	556 (1)
N(1,*B*)	1670 (4)	1302 (3)	1166 (1)
C(22,*B*)	2973 (5)	1485 (4)	1146 (2)
C(2,*B*)	1078 (4)	1543 (3)	1678 (2)
C(3,*B*)	1014 (4)	2570 (3)	1839 (2)
N(4,*B*)	28 (3)	3068 (2)	1555 (1)
C(5,*B*)	−1138 (4)	2515 (3)	1593 (2)
C(6,*B*)	−1010 (4)	1644 (3)	1263 (2)
C(7,*B*)	−182 (4)	1064 (3)	1626 (1)
C(8,*B*)	195 (5)	183 (3)	1347 (2)
C(9,*B*)	−346 (6)	−671 (4)	1289 (2)
C(10,*B*)	180 (6)	−1337 (4)	963 (2)
C(11,*B*)	1229 (6)	−1134 (3)	686 (2)
C(12,*B*)	1793 (5)	−273 (4)	727 (2)
C(13,*B*)	1270 (5)	391 (3)	1064 (2)
C(14,*B*)	819 (4)	2647 (3)	2448 (2)
C(15,*B*)	−548 (4)	2800 (3)	2541 (2)
C(16,*B*)	−1291 (4)	2152 (3)	2177 (2)
C(17,*B*)	−850 (4)	1119 (3)	2167 (2)
O(1,*B*)	−1851 (4)	487 (3)	2185 (1)
C(18,*B*)	−2800 (5)	3901 (4)	2923 (2)
C(19,*B*)	−2149 (5)	4116 (3)	2400 (2)
C(20,*B*)	−798 (4)	3821 (3)	2385 (2)
C(21,*B*)	−219 (4)	3970 (3)	1822 (2)
O(2,*B*)	870 (3)	4489 (2)	1868 (1)
C(*S*1)	6482 (5)	3256 (4)	234 (2)
Cl(1,*S*1)	8094 (1)	3308 (1)	300 (0)
Cl(2,*S*1)	5779 (1)	2952 (1)	842 (1)
C(*S*2)	7512 (5)	5858 (5)	1237 (2)
Cl(1,*S*2)	8996 (1)	6220 (1)	1392 (1)
Cl(2,*S*2)	7199 (2)	5959 (2)	557 (1)

Table 2 (*cont.*)

(*b*) *N*-*n*-Propyl-21-*epi*-isoajmalinium bromide

	10^4x	10^4y	10^4z
Br	7455 (0)	−5000	9386 (0)
N(1)	6247 (3)	309 (3)	5243 (3)
C(2)	6349 (4)	605 (4)	6710 (4)
C(3)	6155 (5)	−390 (4)	7706 (5)
N(4)	7517 (4)	−1107 (3)	8238 (4)
C(5)	8750 (5)	−230 (4)	8616 (5)
C(6)	8989 (5)	405 (4)	7342 (5)
C(7)	7756 (4)	1309 (4)	7089 (4)
C(8)	7640 (4)	2009 (4)	5779 (5)
C(9)	8262 (5)	3060 (4)	5490 (6)
C(10)	7967 (6)	3479 (5)	4136 (6)
C(11)	7068 (6)	2855 (5)	3102 (6)
C(12)	6434 (5)	1782 (5)	3371 (5)
C(13)	6746 (5)	1364 (4)	4725 (5)
C(14)	5757 (7)	182 (5)	9004 (6)
C(15)	7095 (9)	338 (5)	10116 (5)
C(16)	8312 (7)	773 (5)	9491 (5)
C(17)	7937 (5)	1877 (4)	8516 (5)
C(18)	7537 (10)	−2401 (9)	12615 (7)
C(19)	6914 (8)	−1304 (7)	11903 (7)
C(20)	7642 (8)	−896 (6)	10767 (6)
C(21)	7435 (6)	−1796 (5)	9583 (5)
C(22)	4871 (5)	−157 (5)	4507 (5)
C(23)	7701 (5)	−2010 (4)	7162 (5)
C(24)	9162 (5)	−2592 (5)	7416 (5)
C(25)	9183 (6)	−3595 (5)	6399 (6)
O(1)	9113 (4)	2683 (4)	8758 (4)
O(2)	6162 (4)	−2436 (3)	9314 (4)

greater than the cut-off value also contributed to the refinement. Weights were obtained from $\sigma^2(F) = \sigma^2(F_o) + 0{\cdot}0125|F_o| + 0{\cdot}001|F_o|^2$. For the free base, 8463 reflections contributed to the refinement of 711 variables to give $R = 0{\cdot}076$ and $R_w = 0{\cdot}075$; a 50 sin θ term was added to the aforementioned weighting scheme. For the bromide, 3372 data contributed to the refinement of 384 variables to give $R = 0{\cdot}047$* and $R_w = 0{\cdot}059$. The coordinates for the non-hydrogen atoms are presented in Table 2.

* The anisotropic temperature factors, fractional coordinates and isotropic temperature factors for the H atoms, observed and calculated structure factors, bond angles between non-hydrogen atoms, dihedral angles and a stereoscopic packing diagram (for *N*-*n*-propyl-21-*epi*-isoajmalinium bromide) have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32951 (86 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Results and discussion

The analysis for ajmaline has confirmed its chemical structure and relative stereochemistry; no attempt was made to check its absolute configuration. The symmetry-independent ajmaline free base molecules are shown (Johnson, 1971) in Fig. 1; the atom labelling scheme is also given. The projection displays the interaction between the hydrophilic portion of the quinuclidine moieties of the two molecules. There is reciprocal hydrogen bonding between the quinuclidine tertiary N atom of one molecule and the C(21) hydroxyl group of the second. The distances N(*A*)···O(*B*), 2·780, and N(*B*)···O(*A*), 2·766 Å, are indicative of fairly strong hydrogen bonding. The second ajmaline hydroxyl group, that at C(17) of molecule *B*, serves as the donor in a weak hydrogen bond with the C(21) hydroxyl group of a symmetry-related molecule, O(1,*B*)···O(2,*B*′) = 2·983 Å; the hydroxyl group at C(17) of molecule *A* is not involved in hydrogen bonding. Thus the two symmetry-independent ajmaline molecules form a pseudo-dimer, displaying approximate C_2 symmetry, with a hydrophilic core and a generally hydrophobic surface.

Since the crystal packing (Fig. 2) is governed largely by hydrophobic forces, it may be viewed as a model for the lipid solubility of the free base. While the dichloromethane molecules are too small to be representative of lipid molecules, they also pack in pairs in an almost purely hydrophobic environment. Thus they serve primarily a space-filling role but their presence demonstrates the suitability of the pseudo-dimer as a lipid-soluble entity. It is also noteworthy that 17-acetylajmaline, in which the single hydrogen-bond donor on the surface of the dimer has been replaced by an acetyl group, displays far greater lipophilicity than either ajmaline or isoajmaline (Petter, 1974).

The asymmetric unit of *N*-*n*-propyl-21-*epi*-isoajmalinium bromide is shown in Fig. 3 which

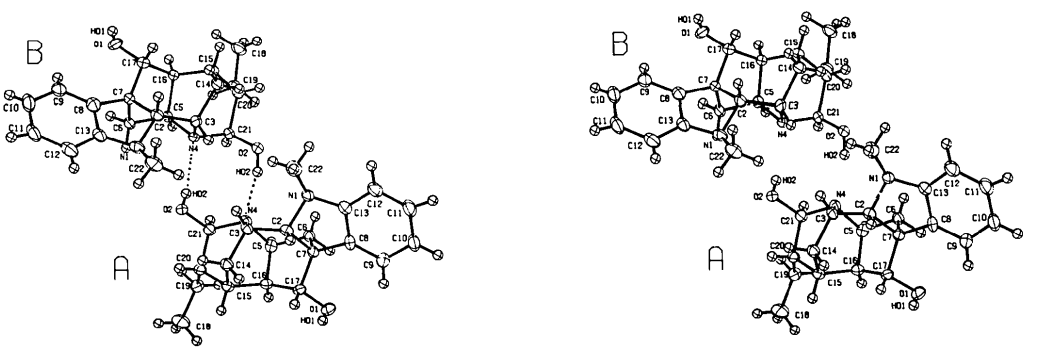


Fig. 1. Stereoscopic projection of the two symmetry-independent ajmaline free base molecules displaying the pseudo-dimeric nature of the crystal packing unit. The dotted lines represent hydrogen bonds in the interior of the pseudo-dimers. The thermal ellipsoids of the non-hydrogen atoms represent the 65% probability level; H atoms are depicted with arbitrary isotropic temperature factors ($B = 0{\cdot}5$ Å^2).

displays the *cis* configuration of the ethyl and hydroxyl groups of the quinuclidinium moiety. As might be expected, the conformations of the free base and cation are very similar. With the exception of that portion of the molecule directly affected by the differences in stereochemistry in the two derivatives, all equivalent dihedral angles in the three independent molecular moieties differ by less than 9·0°. The only conformational differences between the free base and the cation that lie outside this range are assignable to steric interactions between the *cis*-quinuclidinium substituents (Fig. 4). The free base, in which the bulky substituents are *trans*, has the C(20)–C(21) bond in an approximately eclipsed conformation; the average C(15)-C(20)C(21)N(4) dihedral angle is 15·8°, whereas accommodation of the bulky substituents in the *cis* configuration requires an opening of this angle to 28·0° in the cation. Appropriate changes of similar magnitude are observed for the dihedral angle C(14)C(15)C(20)-C(21) which changes from an average of 50·9° in the free base to 39·8° in the cation. The steric interaction between the hydroxyl and ethylene groups is further reflected in the C(20)C(21)O(2) angle which opens up from an average of 109·7° in the free base to 116·5° in the cation; the C(19)C(20)C(21) angle is essentially unchanged, 112·7 and 111·8° respectively.

We have carried out model calculations which we believe demonstrate that formation of an *N-n*-propyl-isoajmalinium cation is, if not precluded, then at least improbable because of steric hindrance. Maintaining the observed conformation but replacing the hydroxyl group, with the observed C–O distance and idealized exocyclic bond angles (the endocyclic angle is 108·2°), in the normal configuration for isoajmaline, results in a non-bonded contact distance between the O atom and C_β of the propylium group, C(24), of only 2·65 Å. We then rotated the propylium group 120° about the N(4)–C(23) bond in a counterclockwise direction looking down this bond (Fig. 3). This provides the only sensible alternative orientation of the propyl chain and clearly that most suitable for the 21 epimer. The non-bonded contact distance between C(24) and the hydroxyl O atom is increased to 3·30 Å, a value that is still much shorter than the sum of the van der Waals

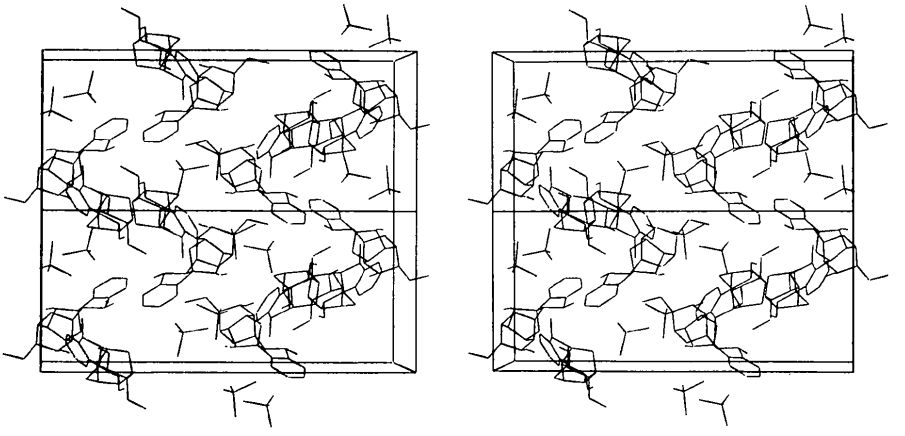


Fig. 2. Stereoscopic packing diagram displaying two unit cells of ajmaline free base projected on the *xz* plane (*x* vertical).

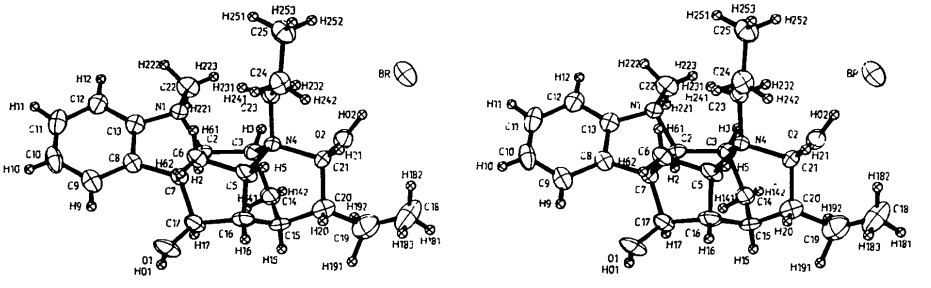
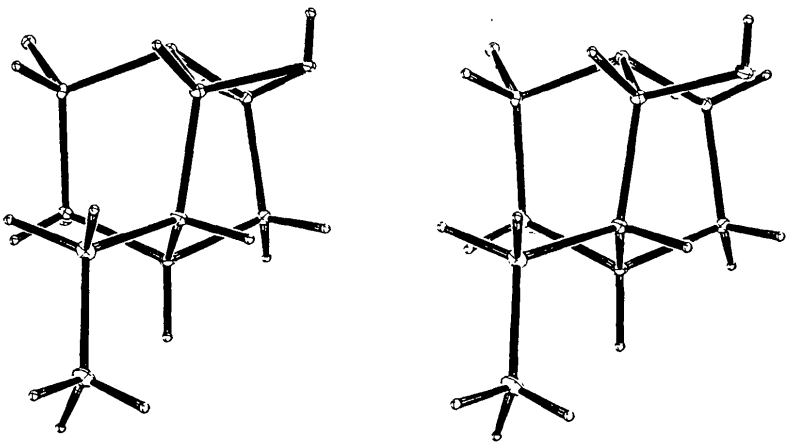


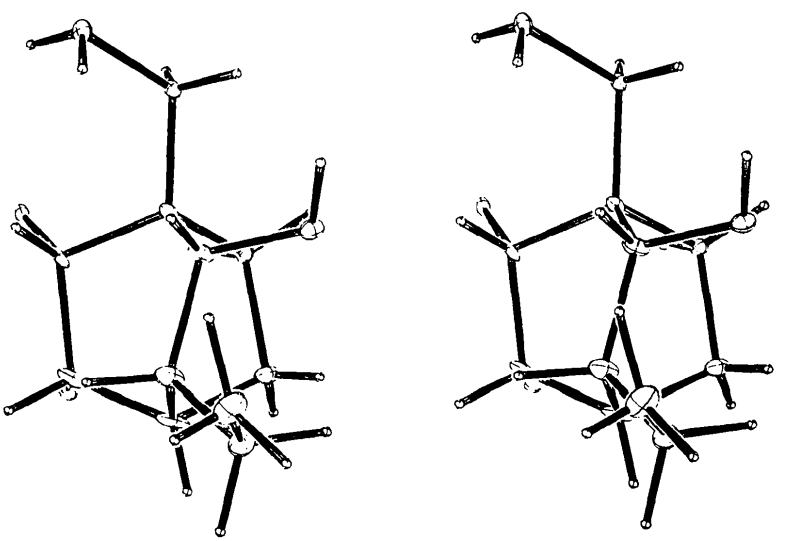
Fig. 3. Stereoscopic projection of the asymmetric unit of *N-n*-propyl-21-*epi*-isoajmalinium bromide. Thermal ellipsoid representations are as described in Fig. 1. H(O2) of the hydroxyl group at C(21) is hydrogen-bonded to the Br^- ion (O···Br, 3·126 Å) as is that of the C(17) hydroxyl group of a symmetry-related molecule (O···Br, 3·182 Å).

radii for O and methylene C atoms (Pauling, 1960), 3·40 Å. The observed C(24)···O(2) distance is 3·79 Å.

In our model calculations, the conformation, *i.e.* the dihedral angle set of the quinuclidinium system, of the observed *cis* form was maintained. It remains a possibility that a conformational change in the opposite sense from that described in the comparison of the observed cation with the free base would provide a suitable spatial arrangement for the normal isoajmaline configuration. There is, however, some indication from the different observed conformations that the relationship between the propyl and the hydroxyl groups would not be greatly influenced by such a change. In particular, the dihedral angles that display the greatest differences in the free base and the cation involve bonds to C(20) in the quinuclidine system. The changes in the intraring dihedral angle about N(4)–C(21) are approximately 8° and thus fall at the upper end of the range of conformational deviations, as reflected by dihedral



(*a*)



(*b*)

Fig. 4. The conformation and configuration of the quinuclidine moieties (*a*) of the free base and (*b*) of the *N*-*n*-propyl-21-*epi*-isoajmalinium ion displayed in stereoscopic projection. The end methyl group of the propyl group has been deleted.

angles, observed in other portions of the molecule. Considerable strain is indicated by the bonding geometry of the quinuclidine cage system. It therefore seems probable that if the *trans* configuration were accessible to the *N*-*n*-propylisoajmalinium ion it would have been adopted.

There are at least three classes of molecular entities which play important roles in the chemistry and/or biological activity of the ajmaline alkaloids: the free base, the amino aldehyde and the cationic species. We have referred to the role of the amino aldehyde (Anet *et al.*, 1954) in the interconversion of ajmaline to the thermodynamically more stable isoajmaline (Kuhnert-Brandstätter & Heindl, 1976) and have also pointed out the greater antiarrhythmic activity of *N*-*n*-propyl-ajmalinium bitartrate relative to the parent alkaloid. There is also evidence (Petter & Engelmann, 1974) that the cation is the antiarrhythmic active species. Two of the three classes, a free base and a cationic species, are represented in the structures we have determined. It therefore seems appropriate to look more closely at their bonding geometry (Table 3). Except for the example cited above, bond angles of the three molecular entities are normal.

Table 3. *Bond distances (with estimated standard deviations) between non-hydrogen atoms* (Å)

	Ajmaline free base		*N*-*n*-Propyl-21-*epi*-iso-ajmalinium bromide
	Molecule *A*	Molecule *B*	
N(1)–C(2)	1·482 (6)	1·482 (6)	1·482 (6)
N(1)–C(13)	1·411 (6)	1·411 (6)	1·416 (6)
N(1)–C(22)	1·441 (7)	1·451 (7)	1·465 (6)
C(2)–C(3)	1·521 (6)	1·539 (6)	1·532 (7)
C(2)–C(7)	1·550 (6)	1·548 (6)	1·543 (6)
C(3)–N(4)	1·506 (6)	1·478 (6)	1·532 (6)
C(3)–C(14)	1·545 (6)	1·549 (6)	1·565 (8)
N(4)–C(5)	1·492 (6)	1·508 (6)	1·525 (6)
N(4)–C(21)	1·488 (6)	1·491 (5)	1·565 (7)
N(4)–C(23)	–	–	1·513 (6)
C(5)–C(6)	1·510 (7)	1·514 (6)	1·517 (7)
C(5)–C(16)	1·552 (7)	1·565 (6)	1·538 (8)
C(6)–C(7)	1·542 (7)	1·534 (6)	1·541 (6)
C(7)–C(8)	1·514 (6)	1·511 (6)	1·507 (6)
C(7)–C(17)	1·536 (6)	1·544 (6)	1·533 (7)
C(8)–C(9)	1·362 (7)	1·376 (7)	1·381 (7)
C(8)–C(13)	1·412 (7)	1·405 (7)	1·405 (6)
C(9)–C(10)	1·428 (7)	1·388 (8)	1·398 (8)
C(10)–C(11)	1·380 (7)	1·374 (9)	1·383 (8)
C(11)–C(12)	1·395 (8)	1·392 (8)	1·402 (8)
C(12)–C(13)	1·397 (7)	1·401 (7)	1·398 (7)
C(14)–C(15)	1·539 (6)	1·529 (7)	1·516 (9)
C(15)–C(16)	1·557 (7)	1·540 (6)	1·525 (11)
C(15)–C(20)	1·541 (7)	1·551 (6)	1·569 (9)
C(16)–C(17)	1·563 (6)	1·568 (6)	1·565 (8)
C(17)–O(1)	1·438 (6)	1·426 (6)	1·429 (7)
C(18)–C(19)	1·521 (7)	1·525 (7)	1·481 (12)
C(19)–C(20)	1·528 (7)	1·538 (7)	1·526 (11)
C(20)–C(21)	1·560 (6)	1·564 (6)	1·533 (8)
C(21)–O(2)	1·404 (6)	1·412 (6)	1·396 (7)
C(23)–C(24)	–	–	1·523 (7)
C(24)–C(25)	–	–	1·517 (8)

Table 3 shows the similarity of the bond distances in the two symmetry-independent free base molecules; most are equal to within two estimated standard deviations. As expected, the significant differences in bond distances between the free base and the cation are associated with the quinuclidine moiety. Furthermore, both the free base and the cation display bond distances in this portion of the molecule significantly different from the expected values for C–C and C–N single bonds (Kennard *et al.*, 1972). We feel that these deviations are atypical of quinuclidine and are thus an attribute of the fused-ring structure of the ajmaline alkaloids.

Three analyses of monosubstituted quinuclidine derivatives which are of particular interest for comparison have been reported: quinuclidinyl di-α,α'-thienylglycollate (Meyerhöffer, 1970), quinuclidinyl benzilate hydrobromide (Meyerhöffer & Carlström, 1969) and (*R*)-(–)-3-acetoxyquinuclidinium methiodide (Baker & Pauling, 1972). Of the three, the thienylglycollate is highly suitable for comparison with ajmaline free base. It was hoped that the hydrobromide and the methiodide would serve as suitable models for comparison with the cation. Unfortunately, the accuracy of the bond distances in the hydrobromide is suspect because of systematic errors in the refined model; *e.g.* dispersion corrections for the Br^- ion were neglected. The precision in the individual bond distances in the methiodide structure suffers from the heavy I^- ion but all bond distances appear reasonable and chemically equivalent bonds are of equal length within experimental error. We therefore draw upon the thienylglycollate and the methiodide derivatives for comparison and also take note of the C–C distances in bicyclo[2.2.2]octane-1,4-dicarboxylic acid (Ermer & Dunitz, 1969), a derivative of the homocyclic analogue of quinuclidine. Appropriately averaged bond distances for the reference structures are presented in Table 4, while average bond distances for the quinuclidine moiety of the free base and those of the cation are displayed in Fig. 5. The C–N distances in Table 4 are in good agreement with the average values found for the tertiary N atom in tetracycline derivatives: protonated dimethylamine group (Stezowski, 1976, 1977), $\langle C-N \rangle$ = 1·500 Å, and non-protonated dimethylamine group (Von Dreele & Hughes, 1971; Stezowski, 1976, 1977; Prewo & Stezowski, 1977), $\langle C-N \rangle$ = 1·468 Å.

Several bond distances in ajmaline free base and in *N*-*n*-propyl-21-*epi*-isoajmalinium bromide are signifi-

Table 4. *Reference bond distances for quinuclidine and quinuclidinium systems* (Å)

	Free base	Methiodide	Homocyclic
$N-C_\alpha$	1·471	1·51	–
$C_\alpha-C_\beta$	1·542	1·52	1·544
$C_\beta-C_\gamma$	1·522	1·53	1·541

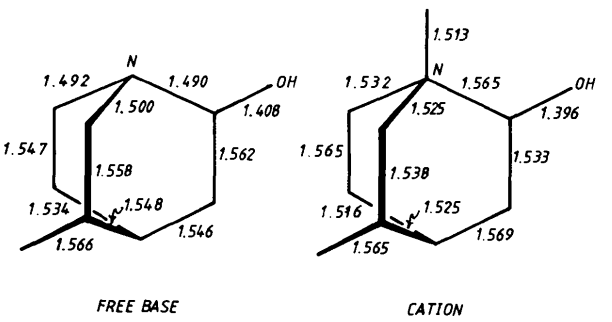


Fig. 5. Bond distances in the quinuclidine moieties (averaged for ajmaline free base).

cantly longer than the reference values. The C–N distances in the free base are all significantly longer than expected and in fact approach the mean value in the protonated dimethylamine group of the tetracyclines. Similarly, the intraring C–N distances in the cation are longer than expected; in contrast, the C–N bond to the propyl group is approximately the expected length. Several C–C bonds in the free base and the cation are longer than normal. In the free base, two quinuclidine intraring C_α–C_β bonds are significantly elongated. All three ajmaline molecular moieties display long C_β–C distances to the hydroxylated C(17); thus the strain extends beyond the internal structure of the quinuclidine cage. The cation also displays two long C–C bonds within the quinuclidine cage: a C_α–C_β and a C_β–C_γ bond. The systematic nature of the deviations from expected bond lengths indicates that there is considerable strain associated with the quinuclidine cage. That the strain may be attributed to the complex fused-ring structure is further supported by the intra-quinuclidine dihedral angles about the C(3)–C(14) and C(5)–C(16) bonds. These bonds have N(4)$C_\alpha C_\beta$C(15) dihedral angles, averaged over the three molecules, of 25·2 and 22·2° respectively (maximum deviation from the average = 1·8°), whereas the monosubstituted quinuclidine structures have a maximum comparable dihedral angle of 13·8° (Baker & Pauling, 1972).

The C–O distance in the quinuclidine hydroxyl group in all three molecular entities is significantly shorter than that for the analogous group at C(17). The respective average values, with their associated maximum deviations, are 1·404 (8) and 1·431 (7) Å; the latter agrees well with the average C–O distance in analogous groups in tetracycline derivatives (Von Dreele & Hughes, 1971; Stezowski, 1976, 1977; Prewo & Stezowski, 1977), 1·432 Å, and with the expected value for a paraffinic hydroxyl group (Kennard *et al.*, 1972), 1·43 Å. The shortened C–O distance probably indicates modest double-bond character in the C(21)–O(2) bond. This observation, in conjunction with the unusually long C(21)–N(4) distance, 1·565 (7) Å, displayed by the cation, supports assumptions that a ring opened species, *e.g.* an *N*-*n*-propyl-*chano*-ajmaline derivative, plays a role in the chemistry of the ajmaline alkaloids. The stereochemistry of the observed cation is almost certainly achieved *via* such an intermediate.

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