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Structure and Conformation of Aconitine

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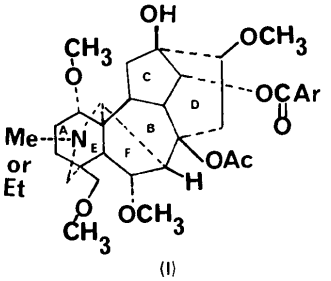
Abstract. $C_{34}H_{47}NO_{11}$, $M_r = 645{\cdot}75$, orthorhombic, $P2_12_12_1$, $a = 15{\cdot}601\ (5)$, $b = 17{\cdot}069\ (6)$, $c = 12{\cdot}248\ (4)$ Å, $V = 3261{\cdot}6$ Å^3, $Z = 4$, $D_c = 1{\cdot}31$ Mg m^{-3}; μ(Mo $K\alpha$) $= 0{\cdot}104$ mm^{-1}; $R = 0{\cdot}072$ for 2322 observed reflections. The *A* ring in this diterpenoid alkaloid is in a chair form and the substitution pattern is 1α-OCH_3, 3α-OH, 6α-OCH_3, 8β-$OCOCH_3$, 14α-$OCOC_6H_5$, 15α-OH, 16β-OCH_3, *N*-ethyl.

Introduction. Aconitine (I) is one of a number of natural products which have profound effects on sodium channels. These substances produce a depolarization of excitable membranes by increasing the permeability of the membrane to sodium ions and have demonstrated competitive binding in neuroblastoma cells. Such pharmacological data have led Catterall (1980) and others (Matsutani, Seyama, Narahashi & Iwara, 1981) to suggest a common receptor for these compounds which mediates the 'open' state of the sodium channel. As part of an investigation of the steric requirements for binding to the sodium-channel receptor the structures of aconitine and other sodium-channel neurotoxins are being determined. Assignment of the skeleton of aconitine, the most accessible and important alkaloid of the *Aconitum* class, has been based on the X-ray crystallographic analysis of demethanolaconinone by Przybylska (1961). This structure determination will corroborate the configuration found earlier and will determine the conformation of ring *A* which was unavailable in the derivative structure.



(I)

Crystals were obtained from a commerical sample (K and K Laboratories, New York) by vapor diffusion of ether into a methanol solution of aconitine. Preliminary photographic examination established the systematic absences as $h00$: $h = 2n + 1$, $0k0$: $k = 2n + 1$, and $00l$: $l = 2n + 1$ and the space group as $P2_12_12_1$. Unit-cell dimensions and the orientation parameters of the crystal were determined by least-squares refinement of the angular coordinates of 12 centered reflections on a Picker FACS-1 diffractometer using Mo $K\alpha$ radiation ($\lambda = 0{\cdot}71069$ Å) and a graphite monochromator. Data were collected in the $\theta/2\theta$ scan mode with a scan width of $\Delta 2\theta = (1{\cdot}5 + 0{\cdot}692 \tan\theta)°$; backgrounds were measured for 20s at either end of the scan. Of the 2419 unique reflections measured in the range $3° < 2\theta < 40°$, 2322 had $I > 3\sigma(I)$ where $\sigma(I) = T + S^2B + (0{\cdot}02I^2)$, T is the peak count, B is the background count and S is the scale factor required to scale the background counting time to the time interval of the scan. The intensities of three reflections were monitored after every 50 reflections during the data collection; there was no significant decrease in intensity during the experiment. Lorentz and polarization corrections were applied and E values were calculated by using a K curve. Phase angles for 500 E values were determined using *MULTAN* 78 (Main, Lessinger, Woolfson, Germain & Declercq, 1978); the resulting E map revealed all 46 non-H atoms. After least-squares refinement of the non-H atoms with isotropic thermal parameters, a series of difference Fourier syntheses with $(\sin\theta/\lambda)_{max} = 0{\cdot}3$ Å^{-1} revealed the positions of all 47 H atoms. These atoms were included in the model but their parameters were not refined. All non-H atoms were refined anisotropically with unit weights to a final residual, $\sum||F_o| - |F_c||/\sum|F_o|$, of 0·072 for the 2400 reflections included in the refinement; reflections with $I < 3\sigma(I)$ were given a weight of 0·0 if $F_o \geq F_c$. The standard deviation of an observation of unit weight is 0·68. Scattering factors are those of Cromer & Mann (1968). Programs are from the XRAY 76 system (Stewart, 1976). Final positional parameters for the non-H atoms are given in Table 1;* the numbering

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and bond distances involving H atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36867 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Fractional coordinates* ($\times 10^4$) *and* U_{eq} ($\times 10^3$) *for the non-*H *atoms in aconitine*

$U_{eq} = \frac{1}{3}$ trace $\tilde{U}$ where $\tilde{U}$ is the diagonalized U_{ij} matrix.

	x	y	z	U_{eq}(Å^2)
N	4694 (4)	4309 (3)	7050 (5)	55 (4)
C(1)	6511 (4)	4698 (4)	7579 (5)	46 (4)
C(2)	6518 (4)	4392 (4)	6429 (6)	51 (4)
C(3)	6238 (5)	4988 (5)	5613 (6)	57 (4)
C(4)	5372 (5)	5377 (5)	5911 (5)	54 (5)
C(5)	5464 (4)	5798 (4)	7031 (5)	46 (4)
C(6)	4599 (4)	6110 (4)	7487 (5)	46 (4)
C(7)	4259 (4)	5457 (4)	8263 (6)	43 (4)
C(8)	4337 (4)	5760 (4)	9427 (6)	44 (6)
C(9)	5233 (4)	6100 (4)	9595 (5)	40 (4)
C(10)	5939 (4)	5578 (4)	9066 (5)	42 (4)
C(11)	5729 (4)	5183 (4)	7922 (5)	43 (4)
C(12)	6173 (5)	5002 (5)	10012 (6)	54 (4)
C(13)	5663 (4)	5251 (4)	11003 (6)	50 (4)
C(14)	5510 (4)	6110 (4)	10773 (5)	47 (4)
C(15)	4058 (4)	5164 (4)	10360 (6)	48 (4)
C(16)	4794 (5)	4803 (4)	11048 (6)	52 (4)
C(17)	4874 (4)	4756 (4)	8044 (5)	42 (4)
C(19)	4654 (5)	4768 (5)	6028 (6)	61 (4)
C(20)	3958 (6)	3783 (5)	7176 (8)	74 (6)
C(21)	4062 (8)	3079 (7)	6708 (16)	172 (13)
C(22)	7466 (5)	3768 (5)	8433 (6)	67 (5)
C(23)	5161 (5)	5950 (5)	4994 (6)	61 (5)
C(24)	5610 (7)	7170 (6)	4296 (8)	101 (7)
C(25)	3804 (12)	7086 (7)	6580 (11)	193 (14)
C(26)	2935 (5)	6416 (5)	9505 (7)	67 (5)
C(27)	2553 (6)	7228 (6)	9525 (10)	108 (8)
C(28)	4687 (5)	7177 (4)	11535 (6)	56 (4)
C(29)	3968 (5)	7343 (4)	12282 (6)	53 (4)
C(30)	3554 (5)	6761 (4)	12842 (6)	55 (4)
C(31)	2877 (5)	6936 (5)	13546 (7)	63 (5)
C(32)	2630 (5)	7718 (6)	13661 (7)	75 (6)
C(33)	3050 (6)	8301 (5)	13110 (8)	78 (6)
C(34)	3707 (6)	8114 (4)	12407 (6)	66 (5)
C(35)	3965 (6)	4188 (6)	12439 (8)	92 (7)
O(C1)	6599 (3)	4029 (3)	8293 (4)	54 (3)
O(C3)	6221 (4)	4657 (4)	4529 (4)	82 (4)
O(C23)	5754 (4)	6593 (3)	5061 (5)	77 (4)
O(C6)	3954 (4)	6294 (3)	6684 (4)	74 (3)
O(C8)	3791 (3)	6465 (3)	9534 (4)	50 (3)
O(C26)	2535 (3)	5820 (3)	9468 (5)	74 (4)
O(C15)	3564 (3)	4545 (3)	9971 (4)	62 (3)
O(C14)	4868 (3)	6397 (2)	11522 (4)	50 (2)
O(C28)	5081 (4)	7647 (3)	11013 (5)	88 (5)
O(C16)	4541 (3)	4790 (3)	12178 (4)	64 (3)
O(C13)	6148 (3)	5100 (3)	11966 (4)	62 (3)

scheme is that of Pelletier & Keith (1970) for C_{19} diterpenoid alkaloids.

Discussion. The structure of aconitine presented in Fig. 1 established unequivocally the earlier assignment from X-ray (Przybylska, 1961; Birnbaum, 1972) and chemical (Bachelor, Brown & Büchi, 1960) work of 1α-OCH_3, 3α-OH, 6α-OCH_3, 8β-$OCOCH_3$, 14α-$OCOC_6H_5$, 15α-OH, 16β-OCH_3, *N*-ethyl, where an α designates a substituent on the same side of the molecule as the N bridge and a β designates a substituent on the other side. The bond lengths and bond angles for the non-H atoms are given in Tables 2 and 3 respectively.

The conformation of aconitine is: ring *A* in chair form, as shown in the inset in Fig. 1; ring *B*: a chair form; ring *C*: an envelope with C(14) at the flap; ring *E*: a chair form; ring *F*: a half chair; and ring *D*: a boat with the end at C(15) flattened. The chair form for ring *A* has been found only when no opportunity for formation of a hydrogen bond with the N atom exists either due to a lack of an H-atom donor (Kerr & Codding, 1982) or due to hydrogen-bond formation with a counter ion (Birnbaum, 1972). In aconitine the only H-atom donor to the unprotonated N atom is the hydroxyl group on C(3); however, the N···O(C3) distance is 3·945 (8) Å. Jesaconitine perchlorate (Pelletier, De Camp, Finer-Moore & Ichinohe, 1979) has

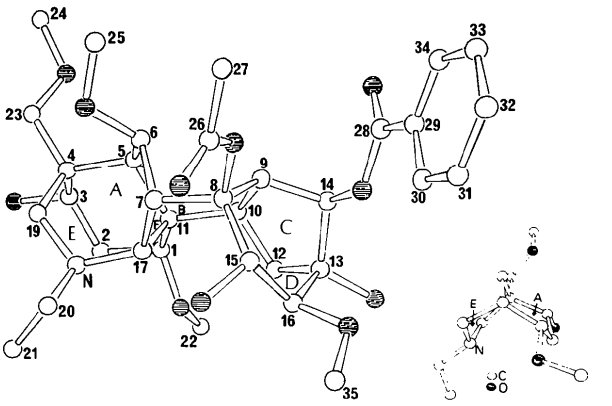

Fig. 1. Perspective drawing of aconitine showing the atomic-labeling scheme. The O atoms are labeled according to the C atom that connects the O atom to the skeleton. The insert shows the chair–chair junction of rings *A* and *E*; no intramolecular hydrogen bonds are present in these rings.

Table 2. *Bond distances* (Å) *for the non-*H *atoms in aconitine*

The e.s.d.'s are in parentheses.

N–C(17)	1·464 (9)	C(12)–C(13)	1·512 (10)
N–C(19)	1·478 (10)	C(13)–C(14)	1·511 (10)
N–C(20)	1·466 (10)	C(13)–C(16)	1·557 (10)
C(1)–O(C1)	1·443 (8)	C(13)–O(C13)	1·426 (8)
C(1)–C(2)	1·503 (10)	C(14)–O(C14)	1·444 (8)
C(1)–C(11)	1·534 (9)	C(15)–C(16)	1·553 (10)
C(2)–C(3)	1·492 (10)	C(15)–O(C15)	1·391 (8)
C(3)–O(C3)	1·443 (9)	C(16)–O(C16)	1·440 (9)
C(3)–C(4)	1·550 (11)	C(20)–C(21)	1·341 (16)
C(4)–C(5)	1·555 (10)	C(22)–O(C1)	1·435 (9)
C(4)–C(19)	1·535 (11)	C(23)–O(C23)	1·438 (10)
C(4)–C(23)	1·525 (11)	C(24)–O(C23)	1·377 (12)
C(5)–C(6)	1·555 (10)	C(25)–O(C6)	1·378 (14)
C(5)–C(11)	1·569 (9)	C(26)–O(C8)	1·338 (9)
C(6)–C(7)	1·557 (9)	C(26)–O(C26)	1·195 (10)
C(6)–O(C6)	1·441 (9)	C(26)–C(27)	1·509 (13)
C(7)–C(8)	1·521 (10)	C(28)–O(C14)	1·361 (8)
C(7)–C(17)	1·556 (9)	C(28)–O(C28)	1·195 (10)
C(8)–C(9)	1·527 (9)	C(28)–C(29)	1·476 (11)
C(8)–C(15)	1·590 (10)	C(29)–C(30)	1·369 (10)
C(8)–O(C8)	1·480 (8)	C(29)–C(34)	1·386 (10)
C(9)–C(10)	1·558 (9)	C(30)–C(31)	1·396 (11)
C(9)–C(14)	1·507 (9)	C(31)–C(32)	1·396 (12)
C(10)–C(11)	1·588 (9)	C(32)–C(33)	1·368 (13)
C(10)–C(12)	1·563 (10)	C(33)–C(34)	1·376 (13)
C(11)–C(17)	1·528 (9)	C(35)–O(C16)	1·402 (11)

Table 3. *Bond angles* (°) *in aconitine*

C(11)–C(1)–C(2)	116·8 (6)	C(10)–C(11)–C(17)	107·2 (5)
C(11)–C(1)–O(C1)	109·7 (5)	C(5)–C(11)–C(17)	99·0 (5)
C(2)–C(1)–O(C1)	107·0 (5)	C(10)–C(12)–C(13)	107·2 (6)
C(1)–C(2)–C(3)	112·9 (6)	C(12)–C(13)–C(14)	101·9 (6)
C(2)–C(3)–C(4)	112·9 (6)	C(12)–C(13)–C(16)	110·4 (6)
C(2)–C(3)–O(C3)	110·8 (6)	C(12)–C(13)–O(C13)	109·5 (6)
C(4)–C(3)–O(C3)	111.6 (6)	C(14)–C(13)–C(16)	110·3 (6)
C(3)–C(4)–C(5)	109·0 (6)	C(14)–C(13)–O(C13)	114·4 (6)
C(3)–C(4)–C(23)	106·8 (6)	C(16)–C(13)–O(C13)	110·1 (6)
C(3)–C(4)–C(19)	111·6 (6)	C(9)–C(14)–C(13)	102·3 (5)
C(5)–C(4)–C(23)	111·9 (6)	C(9)–C(14)–O(C14)	114·4 (5)
C(5)–C(4)–C(19)	107·4 (6)	O(C14)–C(14)–C(13)	108·6 (5)
C(23)–C(4)–C(19)	110·2 (6)	C(8)–C(15)–C(16)	116·2 (5)
C(11)–C(5)–C(6)	102·0 (5)	C(8)–C(15)–O(C15)	113·1 (6)
C(11)–C(5)–C(4)	109·2 (6)	C(16)–C(15)–O(C15)	107·1 (5)
C(6)–C(5)–C(4)	113·2 (6)	C(13)–C(16)–C(15)	115·4 (6)
C(7)–C(6)–O(C6)	109·6 (5)	C(13)–C(16)–O (C16)	106·2 (6)
C(7)–C(6)–C(5)	105·6 (5)	C(15)–C(16)–O(C16)	109·0 (6)
O(C6)–C(6)–C(5)	115·8 (5)	C(7)–C(17)–N	115·2 (5)
C(8)–C(7)–C(17)	111·9 (5)	C(7)–C(17)–C(11)	100·8 (5)
C(6)–C(7)–C(8)	107·6 (5)	C(11)–C(17)–N	109·6 (5)
C(6)–C(7)–C(17)	103·6 (5)	C(4)–C(19)–N	114·0 (6)
C(7)–C(8)–C(9)	109·2 (5)	C(17)–N–C(19)	115·9 (5)
C(7)–C(8)–C(15)	115·7 (5)	C(17)–N–C(20)	112·5 (6)
C(7)–C(8)–O(C8)	108·2 (5)	C(19)–N–C(20)	112·3 (6)
C(9)–C(8)–C(15)	113·4 (5)	N–C(20)–C(21)	114·1 (9)
C(9)–C(8)–O(C8)	101·9 (5)	C(4)–C(23)–O(C23)	108·0 (6)
C(15)–C(8)–O(C8)	107·4 (5)	C(23)–O(C23)–C(24)	113·8 (6)
C(10)–C(9)–C(14)	101·6 (5)	C(1)–O(C1)–C(22)	114·0 (5)
C(8)–C(9)–C(14)	113·3 (5)	C(6)–O(C6)–C(25)	113·3 (8)
C(8)–C(9)–C(10)	111·9 (5)	C(8)–O(C8)–C(26)	121·4 (6)
C(9)–C(10)–C(11)	117·6 (5)	O(C26)–C(26)–C(27)	125·2 (8)
C(9)–C(10)–C(12)	102·5 (5)	O(C8)–C(26)–C(27)	109·7 (7)
C(11)–C(10)–C(12)	115·8 (5)	O(C8)–C(26)–O(C26)	125·1 (8)
C(1)–C(11)–C(5)	112·4 (5)	C(16)–O(C16)–C(35)	113·9 (6)
C(1)–C(11)–C(10)	107·9 (5)	C(14)–O(C14)–C(28)	118·8 (5)
C(1)–C(11)–C(17)	117·6 (5)	O(C14)–C(28)–O(C28)	123·0 (7)
C(5)–C(11)–C(10)	112·6 (5)	O(C14)–C(28)–C(29)	110·6 (6)
O(C28)–C(28)–C(29)	126·4 (7)	C(30)–C(31)–C(32)	118·4 (7)
C(28)–C(29)–C(34)	118·3 (7)	C(31)–C(32)–C(33)	120·9 (8)
C(28)–C(29)–C(30)	112·0 (6)	C(32)–C(33)–C(34)	119·8 (8)
C(30)–C(29)–C(34)	119·7 (7)	C(33)–C(34)–C(29)	120·5 (8)
C(29)–C(30)–C(31)	120·7 (7)	C(29)–C(28)–O(C28)	126·4 (7)

the same substitution pattern on ring *A* as aconitine but due to the protonation of the N atom, ring *A* is observed in boat form with short contacts to both the O atoms bound to C(3) and to C(1). At biological pH the N atom in aconitine would be protonated which would permit formation of either an intramolecular hydrogen bond as in jesaconitine (*A* ring in boat form) or a hydrogen bond with the receptor having the *A* ring in a chair form thus exposing the N atom.

Table 4 contains the torsion angles for the various rings in aconitine. Torsion angles have been tabulated for six other C_{19} diterpenoid alkaloids (Codding & Kerr, 1981; Kerr & Codding, 1982); these examinations have established that there is a high degree of structural rigidity in the skeleton. The torsion angles for aconitine follow the trends established earlier except for two rings, *A* and *D*. Ring *A* shows the expected difference in torsion angles arising from the chair *vs* the boat form for this six-membered ring; C(2)–C(3)–C(4)–C(5) is 60·5 (8)° rather than ⟨8·2°⟩ (the average for the six structures analyzed previously) and C(5)–C(11)–C(1)–C(2) is −44·4 (8)° as compared to ⟨6·4°⟩ for the six boat forms.

Ring *D* does not have the flexibility of ring *A* so the differences in torsion angles observed are more subtle and somewhat unexpected. Aconitine is the only diterpenoid alkaloid analyzed which has a substituent on C(15); this substitution pattern permits the formation of an intramolecular hydrogen bond between the carbonyl O of the acetyl group on C(8) and the H atom of the hydroxyl group on C(15) [O(C15)···O(C26) 2·774 (7), H···O(C26) 2·05 Å, ∠O(C26)···H–O(C15) 126°]. Formation of this hydrogen bond and reduction of unfavorable contacts

Table 4. *Torsion angles* (°) *for aconitine*

Ring *A*		Ring *B*		Ring *C*	
C(1)–C(2)–C(3)–C(4)	−51·5 (8)	C(7)–C(8)–C(9)–C(10)	−42·1 (7)	C(9)–C(10)–C(12)–C(13)	−3·8 (7)
C(2)–C(3)–C(4)–C(5)	60·5 (8)	C(8)–C(9)–C(10)–C(11)	38·7 (7)	C(10)–C(12)–C(13)–C(14)	−25·3 (7)
C(3)–C(4)–C(5)–C(11)	−59·1 (7)	C(9)–C(10)–C(11)–C(17)	−51·9 (7)	C(12)–C(13)–C(14)–C(9)	46·0 (6)
C(4)–C(5)–C(11)–C(1)	51·6 (7)	C(10)–C(11)–C(17)–C(7)	64·3 (6)	C(13)–C(14)–C(9)–C(10)	−48·7 (6)
C(5)–C(11)–C(1)–C(2)	−44·4 (8)	C(11)–C(17)–C(7)–C(8)	−76·6 (6)	C(14)–C(9)–C(10)–C(12)	31·6 (6)
C(11)–C(1)–C(2)–C(3)	43·8 (8)	C(17)–C(7)–C(8)–C(9)	65·0 (7)		
Ring *D*		Ring *E*		Ring *F*	
C(9)–C(14)–C(13) C(16)	−71·2 (6)	N–C(17)–C(11)–C(5)	69·0 (6)	C(5)–C(6)–C(7)–C(17)	−9·4 (6)
C(14)–C(13)–C(16)–C(15)	27·5 (8)	C(17)–C(11)–C(5)–C(4)	−73·4 (6)	C(6)–C(7)–C(17)–C(11)	38·9 (6)
C(13)–C(16)–C(15)–C(8)	18·7 (9)	C(11)–C(5)–C(4)–C(19)	61·9 (7)	C(7)–C(17)–C(11)–C(5)	−52·8 (6)
C(16)–C(15)–C(8)–C(9)	−19·9 (8)	C(5)–C(4)–C(19)–N	−43·9 (8)	C(17)–C(11)–C(5)–C(6)	46·7 (6)
C(15)–C(8)–C(9)–C(14)	−25·7 (8)	C(4)–C(19)–N–C(17)	43·8 (8)	C(11)–C(5)–C(6)–C(7)	−22·7 (6)
C(8)–C(9)–C(14)–C(13)	71·6 (6)	C(19)–N–C(17)–C(11)	−58·4 (7)		
Side chains					
C(16)–C(15)–C(8)–O(C8)	−131·6 (6)	C(11)–C(5)–C(4)–C(23)	−177·0 (6)		
C(15)–C(8)–O(C8)–C(26)	−56·4 (8)	C(5)–C(4)–C(3)–O(C3)	−174·0 (6)		
C(8)–C(15)–C(16)–O(C16)	138·1 (6)	C(12)–C(13)–C(14)–O(C14)	167·3 (5)		
C(15)–C(16)–O(C16)–C(35)	77·2 (8)	C(5)–C(11)–C(1)–O(C1)	−166·3 (5)		
C(7)–C(8)–C(15)–O(C15)	−17·0 (8)	C(17)–C(7)–C(6)–O(C6)	116·0 (6)		

among the substituents on ring *D* has the net effect of flattening the boat form at C(15) as demonstrated by the smaller torsion angles around C(15) in aconitine: C(13)–C(16)–C(15)–C(8) 18·7 (9) and C(16)–C(15)–C(8)–C(9) −19·9 (8)°. These angles, averaged over the six structures reported in Codding & Kerr (1981) and Kerr & Codding (1982), are 25·4 and 22·8° respectively. Close contacts between C(15) and the axial substituent on C(14), which is an $-OCOC_6H_5$ group in aconitine, may well contribute to the flattening of ring *D*. The torsion angle C(14)–C(13)–C(16)–C(15) is larger in aconitine by *ca* 6°. Acetylation of C(15) or deacetylation of C(8) greatly reduces the toxicity of aconitine (Jacyno, 1981); thus, the positions of these H-bond donors and acceptors are likely important in receptor binding. Another intramolecular hydrogen bond is present between the methoxy O atom on C(16) and the H atom of the hydroxyl group on C(13); O(C16)···O(C13) 2·575 (5), H···O(C16) 1·85 Å, ∠O(C13)–H···O(C16) 136°. No other hydrogen bonds, either intra- or inter-molecular were observed in the structure. The packing of aconitine molecules appears to be determined by van der Waals contacts.

Thus, aconitine and other similar diterpenoids have an inflexible framework with conformational freedom only in the *A* ring and in the free edge of the *D* ring. H-bond formation appears to determine ring conformation and thus the pharmacology of this neurotoxin.

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Antazoline Hydrochloride*†

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Abstract. $C_{17}H_{20}N_3^+.Cl^-$, monoclinic, *I*2/*c*, *a* = 25·819 (5), *b* = 5·917 (3), *c* = 21·549 (4) Å, *β* = 104·30 (3)°, *Z* = 8, D_c = 1·26 Mg m^{-3}, *μ*(Cu *K*α) = 1·98 mm^{-1}. The structure was refined to an *R* factor of 0·041 from 2086 observed reflections. Comparison of the present and previous crystal-structure determinations seems to substantiate the idea that a distance of 6·00–6·40 Å between the amino N and the centre of

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† 4,5-Dihydro-*N*-phenyl-*N*-(phenylmethyl)-1*H*-imidazole-2-methanamine hydrochloride.

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