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Steroids and Related Studies. XXXIX. The Crystal Structure and Stereochemistry of 17a-Methyl-3β-pyrrolidinyl-17a-aza-D-homo-5-androstene (HS-309)

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The crystal and molecular structure of 17a-methyl-3β-pyrrolidinyl-17a-aza-D-homo-5-androstene (HS-309), $C_{24}H_{40}N_2$, has been determined by direct methods. The compound crystallizes in space group $P2_1$ with a = 15·454 (4), b = 10·165 (3), c = 6·772 (2) Å, β = 91·41 (1)°. The structure was refined by full-matrix least-squares calculations to R = 0·053 for 1724 observed reflexions. The molecule has two tertiary N atoms with a N···N separation of 10·14 Å. All rings of the steroid skeleton are *trans*-connected with *A*, *C* and *D* in the chair conformation and *B* in a half-chair conformation. The pyrrolidine ring has a conformation between an envelope and a half-chair. Excluding methyl groups the r.m.s. displacement of all the atoms from the least-squares plane through the molecule is 0·31 Å.

Introduction

Since the discovery of the neuromuscular blocking activity of the bisquaternary steroidal alkaloid malouetine (I) (Quévauviller & Lainé, 1960; Khuong Huu-Lainé & Pinto-Scognamiglio, 1964), many compounds have been prepared employing the almost rigid steroid nucleus to support one or two quaternary ammonium substituents (Martin-Smith, 1971; Buckett, 1972). Several such compounds have been tested (Mushin & Mapleson, 1964; Baird & Reid, 1967; Feldman & Tyrell, 1970; Marshall, Paul & Singh, 1973*a*,*b*; Gandiha, Marshall, Paul & Singh, 1974; Gandiha, Marshall, Paul, Rodger, Scott & Singh, 1975), and one, pancuronium (II) (Buckett, Marjoribanks, Marwick & Morton, 1968; Buckett, Hewett

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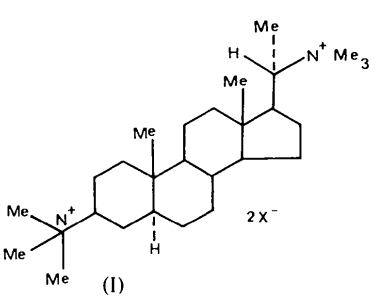

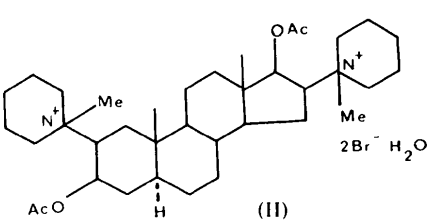

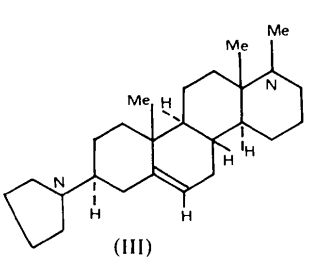

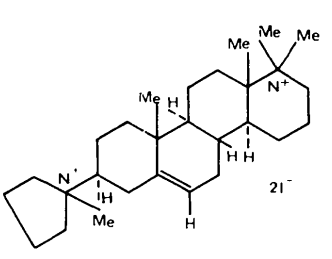

& Savage, 1967, 1973), is currently in widespread clinical use as a muscle relaxant.

The synthetic aza steroid HS-309 (III), the subject of the present X-ray analysis, may be converted into the dimethiodide HS-310 (IV), also known as chandonium iodide (Singh & Paul, 1974), a potent non-depolarizing neuromuscular blocking agent (Gandiha *et al.*, 1974, 1975). HS-310 is one of a series of bisquaternary aza steroids synthesized by Singh and co-workers (Singh, Paul & Parashar, 1973; Singh & Paul, 1974) to investigate the importance of the $N^+\cdots N^+$ inter-onium separation and stereochemical conformation on neuromuscular blocking activity. The correlation of $N^+\cdots N^+$ distances and neuromuscular blocking activity has been discussed by several authors (for example, Lonsdale & Milledge, 1965; Pauling & Petcher, 1973) and is still the subject of some controversy. As a neutral base, HS-309 has no quaternary N atoms and therefore may not exhibit neuromuscular blocking activity.

The present study is the first (Mazid, 1975) of a series of structure analyses of the synthetic compounds of Singh *et al.*, undertaken in order to provide quantitative details of their stereochemistry and ultimate correlation of structure and activity. The crystal structure of HS-310 has also been determined (Kalam, 1976) and found to have a very similar conformation to that of HS-309, thus establishing the rigidity of the steroidal skeleton and the likelihood of its preservation *in vivo*, a factor which is of great importance to an understanding of the biological activity.

Experimental

HS-309 was crystallized from acetone, in the form of platey needles, *c* being the needle axis. Preliminary cell parameters were derived from Weissenberg and precession photographs, and the space group was determined to be $P2_1$ with $Z = 2$. Accurate cell parameters were determined by least-squares calculations from 20 θ values measured on a Hilger & Watts Y290 computer-controlled four-circle diffractometer, using Cu $K\alpha_1$ radiation. Intensities for $\theta < 77°$ were measured on the same instrument employing the ω–2θ step scanning mode, with a scan width of 1·0° in 100 steps, and scan rate of 1 s per step. The background was counted for 10 s on either side of the extreme position for each reflexion. Reference reflexions were measured periodically. 2345 independent intensities were measured of which 1724 were classified as observed with $I_o(hkl) > 3\sigma I_o(hkl)$. The discrepancy between symmetry-equivalent intensities, measured by $\Sigma \Delta I/\Sigma I$ where $\Delta I = |I(hkl) - I(\bar{h}k\bar{l})|$ and $I = [I(hkl) + I(\bar{h}k\bar{l})]/2$, was 3·0%. Lorentz and polarization factors were applied but no absorption correction [μ(Cu $K\alpha$) = 4·74 cm^{-1}] was made. Crystal data are given in Table 1.

Table 1. *Crystal data for* HS-309

$C_{24}H_{40}N_2$, $M_r = 356·7$	$Z = 2$
Monoclinic	$F(000) = 396$
$a = 15·454$ (4) Å	$D_m = 1·06$ g cm^{-3}
$b = 10·165$ (3)	$D_c = 1·11$
$c = 6·772$ (2)	λ(Cu $K\alpha_1$) = 1·5405 Å
$\beta = 91·41$ (1)°	μ(Cu $K\alpha$) = 4·74 cm^{-1}
Systematic absences: $0k0$, $k = 2n + 1$	Crystal size: 0·10 × 0·25 × 0·30 mm
Space group: $P2_1$	ω axis: *c*
$V = 1063·5$ Å^3	

Structure determination and refinement

The structure was determined by direct methods using the tangent formula (Karle & Hauptman, 1956) as implemented by Germain, Main & Woolfson (1971) in the program *MULTAN*. *E* values were calculated by the *K*-curve method, and the 216 reflexions with $|E| > 1·60$ were used to generate 32 phase sets. Several of the phase sets had similar values of the three figures of merit, RESID, ABSFOM and PSIZERO. The phase set with the lowest RESID (21·61), fourth highest ABSFOM (1·072) and eleventh smallest PSIZERO (2259) was selected for calculation of an *E* map. The 26 highest peaks in this map revealed the positions of all the non-H atoms in the asymmetric unit. The *R* index for this trial structure, calculated with isotropic temperature factors $\overline{U_C^2} = 0·04$ Å^2 and $\overline{U_N^2} = 0·03$ Å^2, was 0·31.

Refinement of the structure was undertaken in a full-matrix least-squares analysis, using a modified version of Cruickshank & Smith's *SFLS* program. Isotropic refinement of the non-H parameters converged at $R_{obs} = 0·112$ for the 1724 observed reflexions, with a further reduction to 0·094 with anisotropic temperature factors. A difference electron-density map revealed all 40

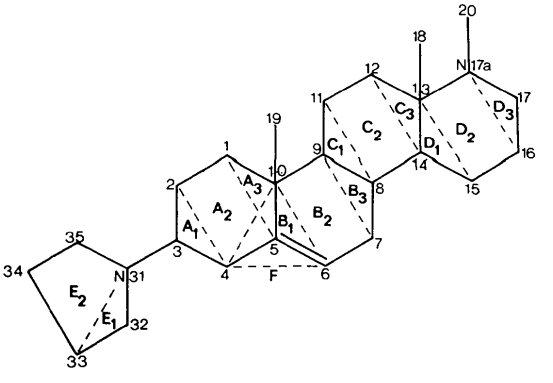

Fig. 1. Numbering scheme for non-H atoms. [H atoms are numbered according to the heavy atoms to which they are attached, *e.g.*, H(11) and H(12) to atom C(1).] The numbering scheme for least-squares planes is also shown.

Table 2. *Atomic parameters*

(*a*) Non-hydrogen atoms (e.s.d.'s in parentheses)

	x	*y*	*z*		*x*	*y*	*z*
C(1)	0·3500 (3)	0·4893 (8)	0·1179 (6)	C(14)	0·1580 (3)	0·6639 (7)	0·6562 (6)
C(2)	0·4396 (3)	0·4503 (7)	0·0505 (6)	C(15)	0·1543 (3)	0·7111 (7)	0·8704 (6)
C(3)	0·5089 (3)	0·5473 (7)	0·1235 (6)	C(16)	0·0671 (3)	0·7783*	0·9049 (8)
C(4)	0·5045 (3)	0·5574 (7)	0·3501 (6)	C(17)	−0·0071 (3)	0·6917 (10)	0·8392 (8)
C(5)	0·4146 (2)	0·5854 (7)	0·4218 (6)	N(17a)	0·0015 (2)	0·6452 (7)	0·6375 (6)
C(6)	0·4020 (3)	0·6826 (7)	0·5496 (6)	C(18)	0·0882 (3)	0·4415 (8)	0·7277 (8)
C(7)	0·3175 (3)	0·7175 (7)	0·6392 (6)	C(19)	0·3512 (3)	0·3627 (7)	0·4397 (7)
C(8)	0·2485 (3)	0·6097 (7)	0·6056 (5)	C(20)	−0·0776 (3)	0·5765 (9)	0·5752 (10)
C(9)	0·2526 (2)	0·5618 (7)	0·3913 (5)	N(31)	0·5954 (2)	0·5052 (7)	0·0680 (5)
C(10)	0·3415 (2)	0·5004 (8)	0·3456 (6)	C(32)	0·6638 (3)	0·5955 (8)	0·1320 (8)
C(11)	0·1759 (3)	0·4741 (7)	0·3365 (6)	C(33)	0·7401 (3)	0·5644 (9)	−0·0028 (9)
C(12)	0·0891 (3)	0·5366 (8)	0·3872 (7)	C(34)	0·7025 (4)	0·4904 (8)	−0·1744 (9)
C(13)	0·0830 (3)	0·5693 (7)	0·6058 (6)	C(35)	0·6044 (3)	0·4956 (8)	−0·1477 (7)

(*b*) Positional and isotropic thermal parameters for the 40 H atoms located in the structure determination. $\bar{U}^2_{iso}$ is the isotropic temperature factor in the expression $B_{iso} = 8\pi^2 U^2_{iso}$. (H atoms are numbered according to the heavy atoms to which they are attached.)

	x	*y*	*z*	$\bar{U}^2_{iso}$ (×10⁴)		*x*	*y*	*z*	$\bar{U}^2_{iso}$ (×10⁴)
H(11)	0·335	0·583	0·070	483	H(162)	0·062	0·804	1·054	622
H(12)	0·307	0·425	0·054	483	H(171)	−0·008	0·605	0·937	811
H(21)	0·456	0·352	0·105	608	H(172)	−0·066	0·738	0·857	811
H(22)	0·441	0·442	−0·105	608	H(181)	0·055	0·383	0·625	889
H(3)	0·496	0·638	0·063	419	H(182)	0·055	0·446	0·862	889
H(41)	0·548	0·625	0·404	502	H(183)	0·151	0·405	0·751	889
H(42)	0·526	0·462	0·412	502	H(191)	0·415	0·339	0·460	831
H(6)	0·449	0·733	0·601	486	H(192)	0·318	0·293	0·342	831
H(71)	0·292	0·802	0·574	508	H(193)	0·326	0·362	0·579	831
H(72)	0·323	0·731	0·790	508	H(201)	−0·134	0·618	0·630	915
H(8)	0·262	0·528	0·704	403	H(202)	−0·065	0·481	0·628	915
H(9)	0·239	0·639	0·306	415	H(203)	−0·075	0·579	0·425	915
H(111)	0·181	0·383	0·423	579	H(321)	0·645	0·692	0·117	622
H(112)	0·177	0·445	0·190	579	H(322)	0·682	0·577	0·282	622
H(121)	0·040	0·465	0·348	586	H(331)	0·772	0·646	−0·054	816
H(122)	0·078	0·613	0·283	586	H(332)	0·789	0·500	0·069	816
H(14)	0·145	0·733	0·572	503	H(341)	0·726	0·390	−0·176	814
H(151)	0·161	0·626	0·969	544	H(342)	0·719	0·533	−0·308	814
H(152)	0·207	0·772	0·903	544	H(351)	0·581	0·572	−0·235	639
H(161)	0·064	0·865	0·819	622	H(352)	0·569	0·410	−0·215	639

* Kept constant to define the origin along **b**.

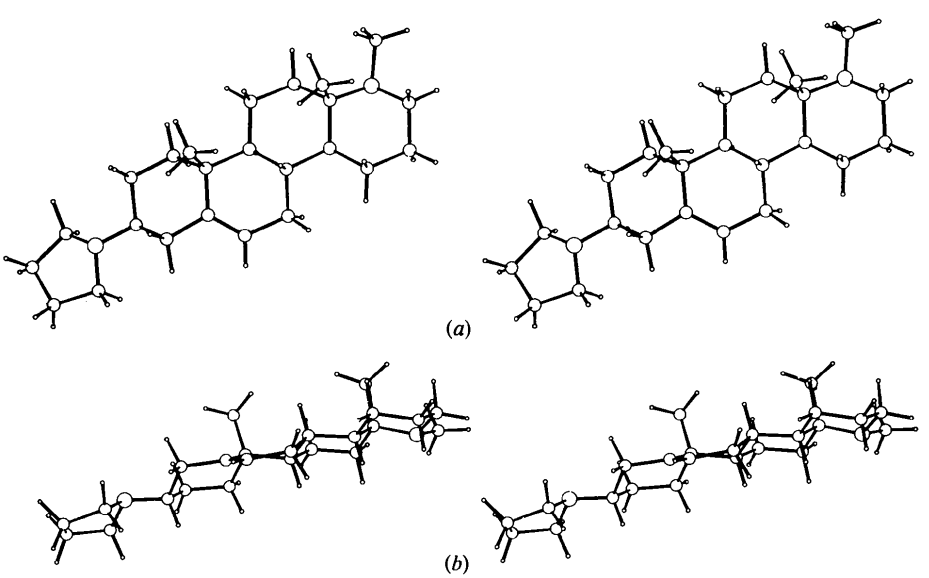

Fig. 2. Stereoviews of the molecule (*a*) viewed perpendicular to the plane of atoms C(4), C(6) and C(10), and (*b*) viewed approximately parallel to the plane of the steroid skeleton along a direction defined by the mid-points of bonds C(6)–C(7) and C(9)–C(10).

Table 3. *Bond lengths and angles*

(*a*) Bond lengths (Å) for non-hydrogen atoms with e.s.d.'s in parentheses

Ring *A*		Ring *B*	
C(1)–C(2)	1·521 (6)	C(5)–C(6)	1·330 (5)
C(2)–C(3)	1·529 (6)	C(6)–C(7)	1·496 (6)
C(3)–C(4)	1·541 (5)	C(7)–C(8)	1·543 (6)
C(4)–C(5)	1·510 (6)	C(8)–C(9)	1·533 (5)
C(5)–C(10)	1·503 (5)	C(9)–C(10)	1·550 (5)
C(10)–C(1)	1·554 (5)	C(10)–C(19)	1·544 (6)
Ring *C*		**Ring *D***	
C(9)–C(11)	1·520 (6)	C(14)–C(15)	1·530 (6)
C(11)–C(12)	1·532 (7)	C(15)–C(16)	1·533 (6)
C(12)–C(13)	1·522 (6)	C(16)–C(17)	1·505 (8)
C(13)–C(18)	1·540 (7)	C(17)–N(17a)	1·455 (7)
C(13)–C(14)	1·537 (6)	N(17a)–C(13)	1·498 (6)
C(14)–C(8)	1·550 (5)	C(17a)–C(20)	1·461 (7)
Pyrrolidine ring			
N(31)–C(3)	1·462 (5)	C(32)–C(33)	1·542 (7)
N(31)–C(32)	1·457 (6)	C(33)–C(34)	1·492 (9)
N(31)–C(35)	1·474 (6)	C(35)–C(34)	1·532 (7)

(*b*) Bond angles (°) for the non-hydrogen atoms with e.s.d.'s in parentheses

Ring *A*		Ring *B*	
C(10)–C(1)–C(2)	114·6 (4)	C(4)–C(5)–C(6)	119·9 (4)
C(1)–C(2)–C(3)	111·7 (4)	C(10)–C(5)–C(6)	122·0 (4)
C(2)–C(3)–C(4)	108·5 (3)	C(5)–C(6)–C(7)	125·6 (4)
N(31)–C(3)–C(4)	109·8 (3)	C(6)–C(7)–C(8)	112·3 (3)
N(31)–C(3)–C(2)	111·5 (4)	C(7)–C(8)–C(9)	108·7 (3)
C(3)–C(4)–C(5)	113·3 (3)	C(8)–C(9)–C(10)	111·9 (3)
C(4)–C(5)–C(10)	118·0 (3)	C(9)–C(10)–C(5)	111·3 (3)
C(5)–C(10)–C(1)	107·5 (3)	C(9)–C(10)–C(19)	111·1 (3)
C(19)–C(10)–C(1)	109·6 (3)	C(19)–C(10)–C(5)	108·4 (3)
C(1)–C(10)–C(9)	109·9 (3)		
Ring *C*		**Ring *D***	
C(14)–C(8)–C(9)	112·3 (3)	C(8)–C(14)–C(15)	112·1 (3)
C(14)–C(8)–C(7)	109·8 (3)	C(13)–C(14)–C(15)	111·2 (3)
C(8)–C(9)–C(11)	111·6 (3)	C(14)–C(15)–C(16)	109·7 (4)
C(10)–C(9)–C(11)	113·9 (3)	C(15)–C(16)–C(17)	111·2 (4)
C(9)–C(11)–C(12)	112·5 (4)	C(16)–C(17)–N(17a)	112·3 (4)
C(11)–C(12)–C(13)	112·6 (4)	C(17)–N(17a)–C(13)	113·5 (4)
C(12)–C(13)–C(14)	106·8 (3)	C(17)–N(17a)–C(20)	109·3 (4)
C(12)–C(13)–C(18)	109·5 (4)	C(13)–N(17a)–C(20)	114·4 (5)
C(14)–C(13)–C(18)	112·3 (3)	N(17a)–C(13)–C(14)	106·1 (4)
C(13)–C(14)–C(8)	114·0 (3)	N(17a)–C(13)–C(18)	113·0 (4)
		N(17a)–C(13)–C(12)	108·9 (4)
Pyrrolidine ring			
C(3)–N(31)–C(35)	112·6 (3)	C(3)–N(31)–C(32)	113·6 (3)
C(32)–N(31)–C(35)	104·6 (4)	N(31)–C(32)–C(33)	104·8 (4)
C(32)–C(33)–C(34)	106·0 (4)	C(33)–C(34)–C(35)	104·9 (4)
C(34)–C(35)–N(31)	103·8 (4)		

(*c*) Bond lengths (Å) involving H atoms

C(1)–H(11)	1·03	C(6)–H(6)	0·94
C(1)–H(12)	1·03	C(7)–H(71)	1·04
C(2)–H(21)	1·09	C(7)–H(72)	1·03
C(2)–H(22)	1·06	C(8)–H(8)	1·08
C(3)–H(3)	1·03	C(9)–H(9)	0·99
C(4)–H(41)	1·02		
C(4)–H(42)	1·10		
C(11)–H(111)	1·09		
C(11)–H(112)	1·04		
C(12)–H(121)	1·07		
C(12)–H(122)	1·06		
C(14)–H(14)	0·92		
C(20)–H(201)	1·04		
C(20)–H(202)	1·06		
C(20)–H(203)	1·02		
C(32)–H(321)	1·03		
C(32)–H(322)	1·07		
C(33)–H(331)	1·03		
C(33)–H(332)	1·10		
C(34)–H(341)	1·08		
C(15)–H(151)	1·09		
C(15)–H(152)	1·04		
C(16)–H(161)	1·05		
C(16)–H(162)	1·05		
C(17)–H(171)	1·10		
C(17)–H(172)	1·04		
C(19)–H(191)	1·02		
C(19)–H(192)	1·09		
C(19)–H(193)	1·03		
C(18)–H(181)	1·04		
C(18)–H(182)	1·05		
C(18)–H(183)	1·05		
C(34)–H(342)	1·04		
C(35)–H(351)	1·03		
C(35)–H(352)	1·10		

(*d*) Bond angles (°) involving hydrogen atoms

C(2)–C(1)–H(11)	110	C(7)–C(8)–H(8)	110
C(2)–C(1)–H(12)	107	C(9)–C(8)–H(8)	110
C(10)–C(1)–H(11)	103	C(14)–C(8)–H(8)	107
C(10)–C(1)–H(12)	113		
H(11)–C(1)–H(12)	109	C(8)–C(9)–H(9)	107
		C(10)–C(9)–H(9)	112
C(3)–C(2)–H(21)	109	C(11)–C(9)–H(9)	100
C(3)–C(2)–H(22)	110		
C(1)–C(2)–H(21)	110	C(9)–C(11)–H(111)	109
C(1)–C(2)–H(22)	111	C(9)–C(11)–H(112)	112
C(21)–C(2) H(22)	105	C(12)–C(11)–H(111)	107
		C(12)–C(11)–H(112)	111
N(31)–C(3)–H(3)	109	H(111)–C(11)–H(112)	106
C(2)–C(3)–H(3)	109		
C(4)–C(3)–H(3)	110	C(11)–C(12)–H(121)	107
		C(11)–C(12)–H(122)	107
C(3)–C(4)–H(41)	111	C(13) C(12)–H(121)	109
C(3)–C(4)–H(42)	107	C(13)–C(12)–H(122)	118
C(5)–C(4)–H(41)	111	H(121)–C(12)–H(122)	103
C(5)–C(4)–H(42)	108		
H(41)–C(4)–H(42)	106	C(8)–C(14)–H(14)	109
		C(15)–C(14)–H(14)	109
C(5)–C(6)–H(6)	121	C(13)–C(14)–H(14)	101
C(7)–C(6)–H(6)	113		
		C(14)–C(15)–H(151)	109
C(6)–C(7)–H(71)	110	C(14)–C(15)–H(152)	110
C(6)–C(7)–H(72)	112	C(16)–C(15)–H(151)	109
C(8)–C(7)–H(71)	106	C(16)–C(15)–H(152)	113
C(8)–C(7)–H(72)	107	H(151)–C(15)–H(152)	106
H(71)–C(7)–H(72)	110		
C(15)–C(16)–H(161)	108	H(181)–C(18)–H(182)	111
C(15)–C(16)–H(162)	111	H(181)–C(18)–H(183)	110
C(17)–C(16)–H(161)	108	H(182)–C(18)–H(183)	110
C(17)–C(16)–H(162)	111		
H(161)–C(16)–H(161)	109	N(31)–C(32)–H(321)	112
		N(31)–C(32)–H(322)	110
C(16)–C(17)–H(171)	108	C(33)–C(32)–H(321)	110
C(16)–C(17)–H(172)	112	C(33)–C(32)–H(332)	110
N(17a)–C(17)–H(171)	108	H(321)–C(32)–H(322)	109
N(17a)–C(17)–H(172)	111		
H(171)–C(17)–H(172)	106	C(32)–C(33)–H(331)	114
		C(32)–C(33)–H(332)	113
N(17a)–C(20)–H(201)	114	C(34)–C(33)–H(331)	109
N(17a)–C(20)–H(202)	101	C(34)–C(33)–H(332)	107
N(17a)–C(20)–H(203)	103	H(331)–C(33)–H(332)	107
H(201)–C(20)–H(202)	114		
H(201)–C(20)–H(203)	114	C(33)–C(34)–H(341)	111

Table 3 (*cont.*)

H(202)–C(20)–H(203)	110	C(33)–C(34)–H(342)	112
		C(35)–C(34)–H(341)	111
C(10)–C(19)–H(191)	111	C(35)–C(34)–H(342)	111
C(10)–C(19)–H(192)	107	H(341)–C(34)–H(342)	107
C(10)–C(19)–H(193)	111		
H(191)–C(19)–H(192)	112	C(34)–C(35)–H(351)	119
H(191)–C(19)–H(193)	105	C(34)–C(35)–H(352)	114
H(192)–C(19)–H(193)	111	N(31)–C(35)–H(351)	107
		N(31)–C(35)–H(352)	113
C(13)–C(18)–H(181)	96	H(351)–C(35)–H(352)	101
C(13)–C(18)–H(182)	114		
C(13)–C(18)–H(183)	115		

H atoms in stereochemically feasible positions. The H atoms were included in all subsequent structure-factor calculations with assigned isotropic temperature factors corresponding to those of the heavy atoms to which they were bonded. No attempt was made to refine H atom parameters. After several further refinement cycles the analysis was terminated at $R_{obs} = 0{\cdot}053$, $R' = 0{\cdot}069$, $R = 0{\cdot}073$. Relative weights were assigned using the function:

$$w = [1 - \exp(a \sin^2\theta/\lambda^2)][b + |F_o| + c|F_o|^2 + d|F_o|^3]^{-1}$$

where $a = 20{\cdot}0$, $b = 60{\cdot}0$, $c = 5 \times 10^{-6}$, $d = 1 \times 10^{-6}$. With this weighting scheme the mean value of $w(|F_o| - |F_c|)^2$ was approximately constant over ranges of both $|F|_o$ and $\sin\theta/\lambda$ in the final cycle of least squares. The atomic scattering factors of Hanson, Herman, Lea & Skillman (1964) were used throughout.

Final positional and (for H atoms only) thermal parameters are given in Table 2 with the numbering scheme of Fig. 1. Fig. 2 shows stereoviews of the molecule. Bond lengths, bond angles and torsion angles for the non-H atoms are given in Tables 3 and 4.*

Discussion

Most of the bond lengths in HS-309 are close to the expected values. The average C–C single-bond lengths in rings *A*, *B*, *C*, *D* and the pyrrolidine ring are 1·526, 1·533, 1·533, 1·522 and 1·522 Å respectively. The average value of all the C–C single-bond lengths in the molecule is 1·529 Å (expected value 1·541 Å, Kennard, Watson, Allen, Isaacs, Motherwell, Pettersen & Town, 1972). In ring *B* the C(5)=C(6) double-bond length is 1·330 (5) Å. Also in ring *B*, C(6)–C(7) has a value of 1·496 (6) Å, which is lower than the average of the other single C–C bond lengths in the structure by 5σ. In the pyrrolidine ring C(33)–C(34) has a low value, 1·492 (9) Å, less than the average C–C bond length by 4σ. The average of the six C–N bond lengths [three to N(17) in ring *D*, and three to N(31) in the pyrrolidine ring] is 1·468 Å (expected value 1·472 Å, Kennard *et al.*, 1972). C(13)–N(17) in ring *D* is 1·498 (6) Å, which is longer than the average by 5σ.

The presence of the double bond C(5)=C(6) in ring *B* has caused partial flattening of the ring and opened bond angle C(5)–C(6)–C(7) to the unusually large value of 125·6 (4)°. C(6)–C(5)–C(10) has also opened to 122·0 (4)°. The average internal C–C–C

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32771 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 4. *Torsion angles* (°) *in the steroid skeleton and pyrrolidine ring*

Ring *A*		Ring *B*	
C(1)–C(2)–C(3)–C(4)	56	C(5)–C(6)–C(7)–C(8)	13
C(2)–C(3)–C(4)–C(5)	−51	C(6)–C(7)–C(8)–C(9)	−43
C(3)–C(4)–C(5)–C(10)	50	C(7)–C(8)–C(9)–C(10)	62
C(4)–C(5)–C(10)–C(1)	−47	C(8)–C(9)–C(10)–C(5)	−46
C(5)–C(10)–C(1)–C(2)	50	C(9)–C(10)–C(5)–C(6)	14
C(10)–C(1)–C(2)–C(3)	−58	C(10)–C(5)–C(6)–C(7)	2
Ring *C*		Ring *D*	
C(8)–C(14)–C(13)–C(12)	−56	C(15)–C(16)–C(17)–N(17a)	−52
C(14)–C(13)–C(12)–C(11)	59	C(16)–C(17)–N(17a)–C(13)	58
C(13)–C(12)–C(11)–C(9)	−58	C(17)–N(17a)–C(13)–C(14)	−60
C(12)–C(11)–C(9)–C(8)	51	N(17a)–C(13)–C(14)–C(15)	60
C(11)–C(9)–C(8)–C(14)	−48	C(13)–C(14)–C(15)–C(16)	−58
C(9)–C(8)–C(14)–C(13)	52	C(14)–C(15)–C(16)–C(17)	52
Pyrrolidine ring			
N(31)–C(35)–C(34)–C(33)	−29	C(35) -C(34) -C(33) -C(32)	7
C(34)–C(33)–C(32)–N(31)	18	C(33)–C(32)–N(31)–C(35)	−36
C(32)–N(31)–C(35)–C(34)	41	C(2)–C(3)–N(31)–C(35)	61
C(4)–C(3)–N(31)–C(32)	−61	C(2)–C(3)–N(31)–C(32)	−179
C(4)–C(3)–N(31)–C(35)	−179		

bond angles in rings *A*, *B*, *C* and *D* are 112·3, 115·3, 111·6 and 110·7° respectively, with a wide variation in individual values, depending on environment. In particular there is a tendency for the internal, and external, bond angles around the quaternary C atoms C(10) and C(13) to be small, with average values 109·6° around C(10) and 109·4° around C(13). Bond angles in the pyrrolidine ring are close to the expected values, the geometry of this ring being similar to that in hydroxyproline (Donohue & Trueblood, 1952). The three C—N—C bond angles to N(17) in ring *D* show a spread of values from 109·4 to 114·4°.

Table 5. *Asymmetry parameters* (°)

Ring *A*		Conformation
$\Delta C_s^1 = 6{\cdot}9$	$\Delta C_2^{2,3} = 4{\cdot}8$	3α,10β chair
$\Delta C_s^2 = 2{\cdot}7$	$\Delta C_2^{3,4} = 9{\cdot}0$	
$\Delta C_s^3 = 5{\cdot}6$	$\Delta C_2^{1,2} = 5{\cdot}1$	
Ring *B*		
$\Delta C_s^5 = 23{\cdot}0$	$\Delta C_2^{6,7} = 44{\cdot}3$	8β,9α half-chair
$\Delta C_s^6 = 19{\cdot}9$	$\Delta C_2^{7,8} = 48{\cdot}6$	
$\Delta C_s^7 = 42{\cdot}6$	$\Delta C_2^{5,6} = 2{\cdot}3$	
Ring *C*		
$\Delta C_s^8 = 4{\cdot}0$	$\Delta C_2^{9,11} = 8{\cdot}7$	9α,13β chair
$\Delta C_s^9 = 4{\cdot}2$	$\Delta C_2^{8,14} = 8{\cdot}0$	
$\Delta C_s^{11} = 7{\cdot}9$	$\Delta C_2^{8,9} = 1{\cdot}9$	
Ring *D*		
$\Delta C_s^{13} = 0{\cdot}4$	$\Delta C_2^{14,15} = 7{\cdot}9$	14α,17β chair
$\Delta C_s^{14} = 6{\cdot}0$	$\Delta C_2^{13,17} = 2{\cdot}7$	
$\Delta C_s^{15} = 5{\cdot}6$	$\Delta C_2^{13,14} = 4{\cdot}7$	
Ring *E*		
$\Delta C_s^{N31} = 8{\cdot}3$	$\Delta C_2^{33} = 9{\cdot}4$	Distorted envelope–half-chair
$\Delta C_s^{35} = 22{\cdot}4$	$\Delta C_2^{34} = 29{\cdot}8$	(Pseudo-rotation phase angle
$\Delta C_s^{32} = 27{\cdot}2$		$\Delta = -16{\cdot}8$)

Bond distances and angles involving H atoms are given in Table 3. The average C—H distance is 1·04 Å and average C—C—H and H—C—H angles are both 109·0°.

Conformational features of the molecule may be described in terms of (i) torsion angles (Table 4), (ii) asymmetry parameters (Table 5), and (iii) least-squares planes (Tables 6, 7 and 8).

The pseudo torsion angle C(19)—C(10)···C(13)—C(18) (Duax & Norton, 1975) giving a quantitative measure of the twist about the length of the molecule has a value of +6·0° in HS-309. Conformation and symmetry in the six-membered rings *A*, *B*, *C* and *D* depart, as is to be expected, from the ideal. Following Duax & Norton (1975) the magnitude of the asymmetry parameters ΔC_s and ΔC_2, Table 5, have been calculated to indicate the deviation (about bond directions and bond-angle bisectors) from mirror and twofold symmetry. (A true *m* plane corresponds to $\Delta C_s = 0$, and a twofold axis to $\Delta C_2 = 0°$.) Rings *A*, *C* and *D* have low values for all values of both ΔC_s and ΔC_2, showing good approximation to the ideal chair conformation. The average dihedral angles in these

Table 6. *Coefficients p, q, r, s in the equation* ($pX' + qY' + rZ' = s$) *of the least-squares planes in* HS-309

The equations are defined with respect to orthogonal axes X' (a^*), Z' (c), Y' expressed in Å.

Plane	*p*	*q*	*r*	*s* (Å)	R.m.s. displacement (Å)
Entire molecule excluding methyls	0·185	0·822	0·538	5·757	0·306
Steroid skeleton excluding methyls	0·143	0·818	0·558	5·689	0·280
A	0·220	0·909	0·354	6·374	0·217
A_1	0·656	0·750	0·079	8·660	
A_2	0·044	−0·880	−0·472	−4·669	0·028
A_3	0·574	0·812	0·108	7·386	
B	0·184	0·702	0·688	5·926	0·203
B_1	0·159	0·635	0·756	5·729	
B_2	0·026	0·668	0·744	5·071	0·100
B_3	0·667	0·697	0·262	6·374	
C	0·121	0·830	0·544	5·744	0·227
C_1	0·521	0·803	0·291	6·347	
C_2	0·146	−0·749	−0·647	−5·015	0·018
C_3	0·590	0·779	0·212	5·028	
D	0·036	0·794	0·607	5·725	0·237
D_1	0·569	0·775	0·278	5·248	
D_2	0·247	−0·685	−0·686	−5·447	0·024
D_3	0·498	0·804	0·326	4·316	
E	0·236	0·888	0·399	6·486	0·167
E_1	0·338	0·679	0·652	6·675	
E_2	0·223	0·937	0·268	6·720	0·137
F	0·155	0·634	0·758	5·711	0·001

[atoms C(4), C(5), C(6) and C(10)]

Table 7. *Deviations* (Å) *of individual atoms from one or more of the least-squares planes*

	Entire molecule	Steroid skeleton	*A*	*B*	*C*	*D*	*E*	A_2	B_2	C_2	D_2	E_2	*F*
C(1)	−0·135	−0·301	−0·232					0·028					
C(2)	0·183	−0·052	0·261					−0·028					
C(3)	−0·178	−0·443	−0·234										
C(4)	0·552	0·319	0·201					0·028					0·001
C(5)	0·342	0·178	−0·179	0·064				−0·029					−0·002
C(6)	−0·038	−0·172		−0·066					−0·103				0·001
C(7)	−0·227	−0·294		−0·116					0·102				
C(8)	0·369	0·337		0·319	0·193					0·018			
C(9)	−0·002	−0·066		−0·328	−0·186				−0·098				
C(10)	0·580	0·449	0·184	0·127					0·099				0·001
C(11)	0·329	0·302			0·224					−0·017			
C(12)	−0·239	−0·199			−0·261					0·018			
C(13)	0·269	0·342			0·259	0·265					−0·024		
C(14)	−0·139	−0·104			−0·229	−0·267				−0·018			
C(15)	0·238	0·306				0·232					0·023		
C(16)	−0·429	−0·297				−0·196					−0·024		
C(17)	−0·142	0·026				0·208							
N(17a)	−0·466	−0·332				−0·243					0·025		
C(18)	1·794	1·874			1·794	1·798							
C(19)	2·099	1·968	1·713	1·572									
C(20)	−0·328	−0·155				0·029							
N(31)	0·200	0·130	0·304				0·243					0·104	
C(32)	−0·139						−0·161					−0·411	
C(33)	−0·169						0·027					−0·104	
C(34)	−0·277						0·105					0·164	
C(35)	−0·482						−0·214					0·165	

three rings are all less than 60° however, indicating a degree of flattening. Ring *B* has a dominant twofold axis perpendicular to the double bond C(5)=C(6) with $\Delta C_2^{5,6} = 2{\cdot}3°$, consistent with a half-chair conformation. All the other asymmetry parameters for ring *B* are large, indicating lack of symmetry. The pyrrolidine ring shows both approximate mirror and twofold symmetry ($\Delta C_s^{N31} = 8{\cdot}3°$ and $\Delta C_2^{33} = 9{\cdot}4°$). Its conformation therefore lies between envelope and half-chair. This is confirmed by the value of the pseudorotation phase angle Δ (Altona, Geise & Romers, 1968) which is +16·8° (for an envelope conformation $\Delta = 36°$, while for a half-chair, $\Delta = 0°$, Altona *et al.*, 1968).

Table 8. *Dihedral angles of various sub-portions of* HS-309

Plane 1	Plane 2	Dihedral angles (°)
Plane *A*	Plane *B*	23
Plane *B*	Plane *C*	12
Plane *C*	Plane *D*	6
Plane A_1	Plane A_2	132
Plane A_2	Plane A_3	138
Plane A_3	Plane B_1	47
Plane B_1	Plane B_2	8
Plane B_2	Plane B_3	47
Plane B_3	Plane C_1	11
Plane C_1	Plane C_2	136
Plane C_2	Plane C_3	129
Plane C_3	Plane D_1	4
Plane D_1	Plane D_2	126
Plane D_2	Plane D_3	131
Plane E_1	Plane E_2	28

The steroidal skeleton shows a high degree of planarity and no significant tendency to be convex towards the protruding methyl groups on C(10) and C(13). Least-squares planes have been calculated for various portions of the molecule (Fig. 1). The equations and r.m.s. displacements for these planes are given in Table 6. A selection of distances to these planes from various atoms is given in Table 7. Dihedral angles are in Table 8. The r.m.s. displacement of atoms from the steroid skeleton is 0·280 Å. As expected, atoms C(4), C(5), C(6) and C(10) constituting plane *F* are planar within experimental error (r.m.s. displacement 0·001 Å). Other features of the molecular geometry are confirmed from the least-squares-planes calculations, but on the whole are better summarized in terms of torsion angles and asymmetry parameters.

The ring-junction configurations are all *trans*, the absolute endocyclic torsion angles being: $A/B\ T_1 = 46{\cdot}9 + 14{\cdot}2 = 61{\cdot}1$, $B/C\ T_2 = 61{\cdot}5 + 47{\cdot}8 = 109{\cdot}3$, and $C/D\ T_3 = 56{\cdot}1 + 60{\cdot}0 = 116{\cdot}1°$.

C(20) of the methyl substituent on N(17) has a deviation of 0·03 Å from plane *D* (Table 6) and thus has an equatorial conformation. C(18) of the methyl substituent on C(13) and C(19) of the methyl substituent on C(10) both have a β-axial orientation. N(31) of the pyrrolidine ring is equatorial with respect to ring *A*.

The molecular packing is illustrated in Fig. 3. The molecular planes are orientated approximately parallel to (111). All the intermolecular contacts correspond to van der Waals distances (Table 9).

The HS-309 molecule is neutral, neither of the N atoms being protonated, and therefore may not exhibit neuromuscular blocking activity. The distance N(17)···N(31) in HS-309 is 10·14 Å, while in the potent neuromuscular blocking agent HS-310 (the dimethiodide of HS-309) the $N^+\cdots N^+$ distance is 10·28 Å (Kalam, 1976). Examples of the $N^+\cdots N^+$ distances found in other non-depolarizing neuromuscular blocking agents are 8·97 Å in (+)-tubocurarine dichloride (Codding & James, 1973), 10·66 Å in (+)-tubocurarine dibromide (Reynolds & Palmer, 1976), 10·60 and 10·75 Å respectively in the two independent molecules in *O,O*-trimethyl-(+)-tubocurarine diiodide (TMTC) (Sobell, Sakore, Tavale, Canepa, Pauling & Petcher, 1972) and 11·08 Å in pancuronium bromide (Savage, Cameron, Ferguson, Hannaway & Mackay, 1971). A great deal of emphasis has been placed on the importance of the $N^+\cdots N^+$ distance in neuromuscular blocking agents (see, for example, Pauling & Petcher, 1973) and this is undoubt-

Table 9. *Selection of short intermolecular contact distances* (Å)

H(121)···H(151^{i})	2·20	C(6)···H(42^{ii})	3·06
H(152)···H(332^{ii})	2·33	C(16)···H(121^{iv})	3·10
H(42)···H(6^{iii})	2·36	C(4)···C(19^{ii})	4·057
H(6)···H(191^{ii})	2·41	C(7)···N(31^{ii})	2·762
H(41)···H(191^{ii})	2·42	C(11)···C(16^{i})	4·036
H(341)···H(152^{iii})	2·42	C(12)···C(151^{i})	4·048
C(151)···H(121^{iv})	3·03	C(12)···C(16^{i})	4·016
C(19)···H(41^{iii})	3·05	C(15)···C(33^{ii})	4·034
C(15)···H(332^{ii})	3·09	C(19)···C(32^{iii})	3·983

Symmetry code

None x,y,z (iii) $1-x, \frac{1}{2}+y, 1-z$

(i) $-x, \frac{1}{2}+y, 1-z$ (iv) $-x, \frac{1}{2}-y, 1-z$

(ii) $1-x, \frac{1}{2}-y, 1-z$

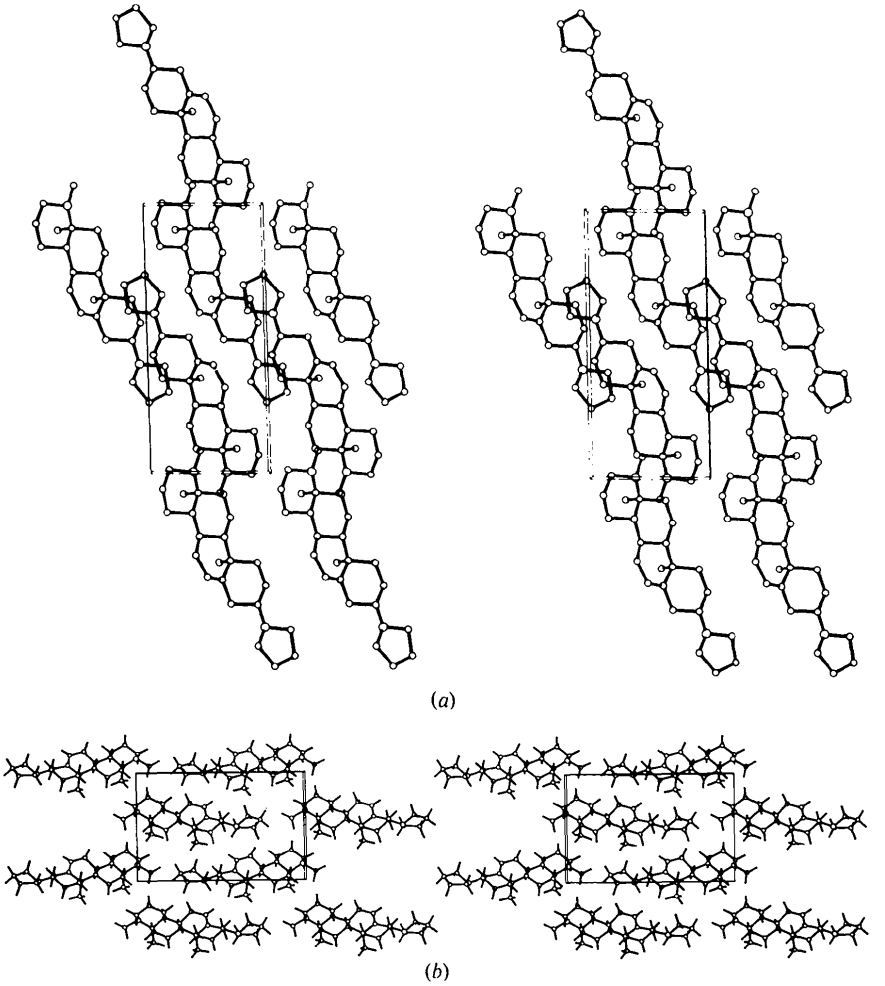

Fig. 3. Stereoviews illustrating the molecular packing as seen along (*a*) the *b* axis, and (*b*) the *c* axis.

edly one factor in determining the potency of the compound. It is now known (Reynolds, Palmer, Gorinsky & Gorinsky, 1975) that the tubocurarine molecule is not rigid but exhibits different conformations in the dibromide and dichloride crystal structures. The conformation of the methylated derivative of (+)-tubocurarine, TMTC, is similar to that in the dibromide indicating that methylation of the two free hydroxyl groups and quaternization of the tertiary N atom does not necessarily cause significant changes in the overall conformation. Increased potency of the methylated derivative (see, for example, Barlow, 1968) is most probably due to quaternization of the tertiary N atom.

The molecular conformation of HS-309 in the crystal is very similar to that of HS-310 (Kalam, 1976), the N atoms being on opposite faces of the molecule in both cases. On this evidence it is reasonable to assume that this conformation would be preserved *in vivo*. HS-310 is 4–5 times more active than tubocurarine in the cat (Gandiha, Marshall, Paul & Singh, 1974). This is probably at least partly due to the rigid conformation of the molecule as opposed to the molecular flexibility and the associated variability of the $N^+ \cdots N^+$ separation in tubocurarine. This information may eventually lead to a better understanding of the nature of the biological receptor site.

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