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Steroids and Related Studies. LIV. The Structure of 17a-Methyl-3β-pyrrolidinyl-17a-aza-*D*-homo-5α-androstane (HS691)

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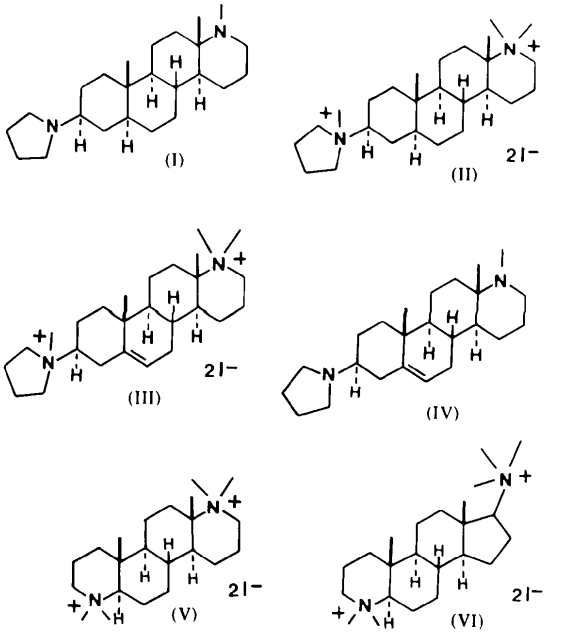
Abstract

The crystal structure of 17a-methyl-3β-pyrrolidinyl-17a-aza-*D*-homo-5α-androstane (HS691), $C_{24}H_{42}N_2$, comprising two independent molecules in space group $P1$, has been determined using direct methods, successive electron density syntheses and least-squares analysis. The structure was refined by block-diagonal least squares to $R_o = 0{\cdot}054$, $R_w = 0{\cdot}062$ for 2271 observed reflections and $R_o = 0{\cdot}075$, $R_w = 0{\cdot}089$ for a total of 3290 reflections measured on a four-circle diffractometer in the $\omega/2\theta$ scanning mode. The two independent molecules in $P1$, $a = 7{\cdot}228\,(1)$, $b = 10{\cdot}276\,(2)$, $c = 15{\cdot}095\,(3)$ Å, $\alpha = 98{\cdot}377\,(8)$, $\beta = 84{\cdot}690\,(9)$, $\gamma = 99{\cdot}409\,(12)°$, are related by a pseudo twofold axis. The two molecules have very similar geometry, the major differences being in the puckering of the pyrrolidine rings and their orientations with respect to the modified steroid skeleton. The methyl carbon atom C(20) on N(17a) is equatorial in both molecules.

Introduction

The title compound, hereinafter designated as HS691 (I), is the neutral base of dihydrochandonium iodide, HS692 (II), the saturated congener of the potent synthetic competitive neuromuscular blocking agent chandonium iodide, HS310 (III) (Singh, Paul & Parashar, 1973; Singh & Paul, 1974; Palmer, Kalam, Singh & Paul, 1980). HS692 (II) is itself active as a neuromuscular blocker but with only about half the potency of HS310 (III) (Teerapong *et al.*, 1979). In view of the striking chemical similarity of (II) and (III), which differ only at the 5,6 bond [double bond (Δ) in HS310 (III)], this difference in biological activity is quite remarkable. This effect clearly demonstrates the extreme sensitivity of the acetylcholine receptor binding sites to the precise geometry of competitive blockers, and emphasizes the need for accurate measurement of molecular geometry in parallel with pharmacological appraisal of proposed new drugs. The analysis described in the present paper is part of a programme of work designed to elucidate structure/activity relationships of steroidal neuromuscular blockers. Crystal structures previously published in this series include HS309 (IV) (Mazid, Palmer, Singh & Paul, 1977), HS310 (III), HS342 (V) and HS469 (VI) (Palmer, Kalam Singh & Paul, 1980) and stercuronium (Husain, Palmer & Tickle, 1979; Husain, 1981; Husain & Palmer, 1981). The crystal structure of the steroid derivative pancuronium is also known (Savage, Cameron, Ferguson, Hannaway & Mackay, 1971).



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Experimental

The synthesis and crystallization of HS691 have been described by Singh, Bhardwaj, Ahuja & Paul (1979). The triclinic crystals have poor morphology but produce a good X-ray diffraction pattern. D_m determined by flotation in aqueous KCl solution is 1·088 (5) Mg m^{-3}. Trial cell dimensions were obtained from precession photographs and refined prior to data collection using 12 θ, χ, φ values [λ(Cu $K\alpha$) = 1·54178 Å] measured on a Hilger & Watts computer-controlled four-circle diffractometer (Tickle, 1975). The unit-cell parameters were later refined again using 26 high-θ values giving the values shown in the *Abstract*; $Z = 2$ independent molecules per unit cell, $D_c = 1·095$ Mg m^{-3}. Since the synthesis of HS691 was carried out under stereospecific conditions (Singh *et al.*, 1979) the crystals could not belong to the centrosymmetric space group $P\bar{1}$. A search for higher-symmetry cells was undertaken, however, using the program *XCELL* (Rodgers, 1979) but this procedure failed to detect anything other than a triclinic cell. Intensities were measured in the ω/θ step-scanning mode with 0·02° steps and scan width calculated as $a + b \tan\theta$ where a = 0·60° and b = 0·142. Four reflections monitored during the data collection at intervals of 50 measurements showed no significant fluctuations in intensity. In the range $\theta \leq 65°$ a total of 5435 reflections were measured which resulted in a unique data set of 3555 reflections after scaling and merging equivalents, of which 2271 with $I_o \geq 3\sigma(I_o)$ were classified as observed. The usual Lp factors were applied and semi-empirical absorption corrections were made using a modification of the North, Phillips & Mathews (1968) method (Kopfmann & Huber, 1968; Tickle, 1979; Husain, Palmer, Singh, Bhardwaj & Paul, 1981). μ(Cu $K\alpha$) = 0·400 mm^{-1} and μr = 0·15–0·30 for the crystal used for collection of intensities.

Structure determination and refinement

The structure was solved partially by direct methods and completed by calculation of successive difference electron density syntheses and least-squares refinement. Numerous attempts to solve the structure employing various facilities of the program *MULTAN* 78 (Declercq, Germain & Woolfson, 1979) were initially unsuccessful. Using the routine *TANG* in the program suite *SHELX* 76 (Sheldrick, 1978) six E maps were produced, one of which yielded a 22-atom fragment. This was expanded to 42 atoms by a process of alternate difference electron density synthesis and isotropic full-matrix least-squares analysis. Sites developing extremely high or low temperature factors were deleted. The most promising molecular fragment was then employed for the calculation of modified E values based on molecular scattering factors in *MULTAN* (Rodgers, 1980). The E value distribution thus produced was more centric than that previously calculated. One of the new *MULTAN* 78 phase sets gave a 31-atom model which was subsequently developed employing the above difference synthesis/least-squares analysis technique until all 52 non-hydrogen atoms had been located. Full-matrix isotropic least-squares refinement converged to R_o = 0·140 and anisotropic block-diagonal least-squares refinement to R_o = 0·109 for 2271 observed reflections. Most of the H positions were located on a difference map. Computations to this point were undertaken on the University of London CDC 6600 and 7600 computers. The analysis was then transferred to the Cambridge University IBM 370/165 computer employing a local version of the *SHELX* program incorporating a cascade least-squares procedure (Sheldrick, 1979). H atoms were included in calculated positions riding geometrically on the C atoms; C—H distances were constrained to 1·08 Å and H—C—H angles to 109·5°. Individual isotropic temperature factors were refined for each H atom. Weights were calculated for the final least-squares cycle* as $w = [\sigma^2(|F|) + 0·005808|F|^2]^{-1}$.

Results and discussion

The atom-numbering scheme is shown in Fig. 1. Atoms in molecule 2 will be denoted by primes. H atoms are

* Lists of structure factors, anisotropic temperature factors and coordinates of H atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36241 (25 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

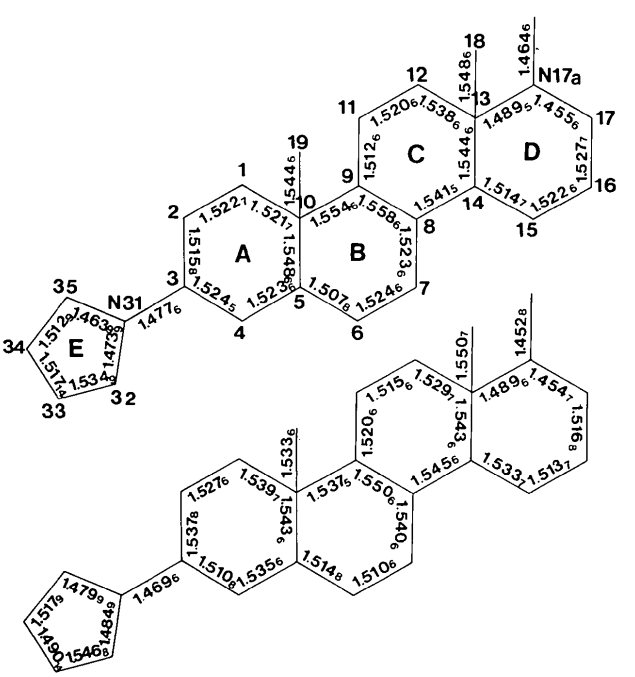

Fig. 1. Bond lengths (Å) with e.s.d.'s subscripted (0·005–0·014 Å).

numbered according to the corresponding C-atom numbers. Fractional coordinates are listed in Table 1. Bond lengths and angles are shown in Figs. 1 and 2 and principal torsion angles in Fig. 3. Computer drawings of the two molecules and of the molecular packing are shown in Figs. 4 and 5 respectively. With the exception

Table 1. *Refined positional parameters* ($\times 10^4$) *for non-*H *atoms with e.s.d.'s in parentheses*

$$U_{iso} = (U_{11}U_{22}U_{33})^{1/3} \times 10^4.$$

	x	y	z	U_{iso} (Å^2)
Molecule 1				
C(1)	11732 (7)	2702 (5)	−3251 (3)	682
C(2)	12022 (8)	2049 (5)	−4214 (3)	784
C(3)	10184 (7)	1575 (5)	−4653 (3)	678
C(4)	9009 (7)	2699 (5)	−4541 (3)	686
C(5)	8736 (6)	3330 (5)	−3571 (3)	633
C(6)	7447 (7)	4367 (6)	−3445 (3)	752
C(7)	7025 (6)	4868 (5)	−2458 (3)	647
C(8)	8803 (6)	5383 (4)	−1967 (3)	563
C(9)	10150 (5)	4320 (4)	−2130 (4)	556
C(10)	10623 (6)	3860 (4)	−3141 (3)	577
C(11)	11862 (6)	4772 (5)	−1595 (3)	597
C(12)	11365 (6)	5161 (4)	−602 (3)	594
C(13)	10113 (6)	6260 (4)	−424 (3)	536
C(14)	8348 (6)	5760 (4)	−954 (3)	552
C(15)	6924 (7)	6710 (5)	−747 (3)	685
C(16)	6405 (7)	6919 (5)	258 (3)	709
C(17)	8154 (6)	7341 (5)	788 (3)	635
N(17a)	9483 (5)	6404 (3)	548 (2)	554
C(18)	11240 (7)	7563 (4)	−714 (3)	662
C(19)	11765 (7)	5021 (5)	−3596 (3)	680
C(20)	11008 (7)	6765 (5)	1154 (3)	692
N(31)	10525 (7)	1079 (4)	−5612 (3)	763
C(35)	11695 (12)	22 (6)	−5786 (4)	986
C(34)	11477 (13)	−547 (8)	−6759 (4)	1175
C(33)	9522 (14)	−305 (7)	−6911 (4)	1101
C(32)	8784 (11)	491 (6)	−6049 (4)	991
Molecule 2				
C(1′)	4033 (6)	2360 (4)	−202 (3)	630
C(2′)	3765 (7)	1263 (5)	−1000 (3)	743
C(3′)	5632 (8)	838 (4)	−1415 (3)	675
C(4′)	6741 (7)	522 (4)	−694 (3)	698
C(5′)	6996 (6)	1651 (4)	92 (3)	618
C(6′)	8238 (7)	1387 (5)	781 (3)	745
C(7′)	8647 (6)	2579 (5)	1487 (3)	678
C(8′)	6838 (6)	3042 (4)	1955 (3)	579
C(9′)	5530 (6)	3245 (4)	1245 (3)	539
C(10′)	5109 (6)	2011 (4)	543 (3)	560
C(11′)	3809 (6)	3800 (5)	1701 (3)	670
C(12′)	4269 (7)	5058 (5)	2352 (3)	680
C(13′)	5540 (6)	4885 (4)	3069 (3)	623
C(14′)	7301 (6)	4351 (4)	2595 (3)	628
C(15′)	8724 (7)	4274 (5)	3271 (3)	773
C(16′)	9236 (8)	5624 (6)	3814 (4)	832
C(17′)	7513 (8)	6210 (6)	4229 (3)	783
N(17′a)	6192 (6)	6223 (4)	3561 (3)	723
C(18′)	4412 (8)	3944 (5)	3709 (3)	785
C(19′)	3925 (7)	854 (4)	970 (3)	683
C(20′)	4713 (9)	6963 (7)	3968 (5)	1047
N(31′)	5303 (7)	−305 (4)	−2119 (3)	755
C(35′)	4277 (12)	−28 (6)	−2858 (4)	1054
C(34′)	4607 (14)	−1129 (7)	−3614 (5)	1240
C(33′)	6316 (13)	−1640 (7)	−3413 (4)	1138
C(32′)	7064 (11)	−705 (5)	−2583 (4)	911

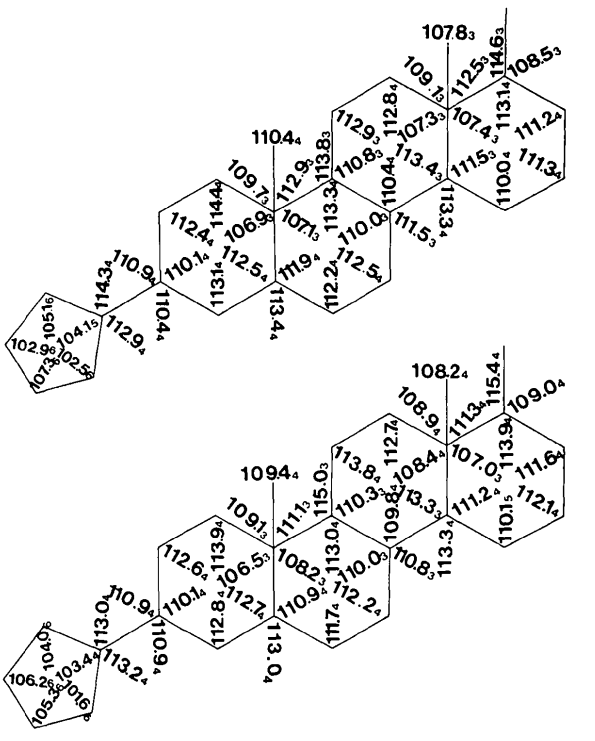

Fig. 2. Bond angles (°) with e.s.d.'s subscripted (0·3–0·6°).

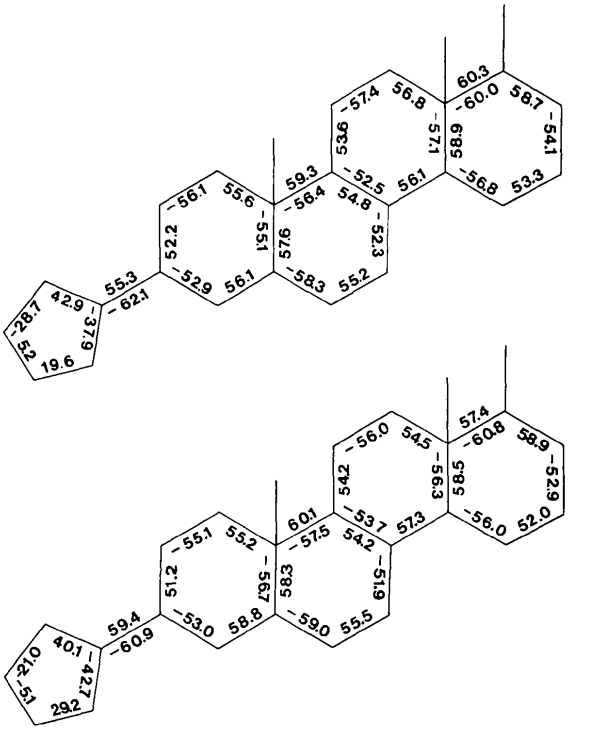

Fig. 3. Torsion angles (e.s.d.'s are 0·5 to 0·7°). Angles not shown (molecule 1, molecule 2): C(35)–N(31)–C(3)–C(2) 55·3, 59·4; C(35)–N(31)–C(3)–C(4) 177·8, −178·3; C(32)–N(31)–C(3)–C(4) −62·1, −60·9; C(32)–N(32)–C(3)–C(2) 175·4, 176·8; C(19)–C(10)–C(9)–C(11) 59·3, 60·3; C(18)–C(13)–N(17a)–C(20) 60·1, 57·4.

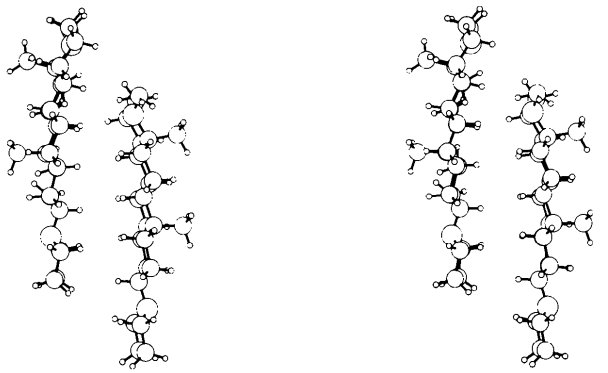

Fig. 4. Steroview of the two molecules showing how they pack α face to α face. The length of the molecules is approximately parallel to [011].

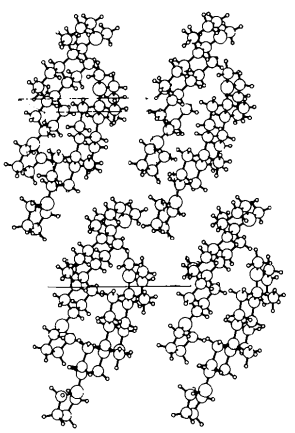

Fig. 5. Molecular packing viewed down x_o.

of the pyrrolidine rings E and E', there is a high degree of correspondence in the molecular geometry of the two molecules.

Modified steroid skeleton

Corresponding bond lengths in the two molecules are very similar. The average ring C–C bond length in molecule 1 is 1·527 Å and 1·528 Å in molecule 2, with no significant differences. The average C–N bond length is 1·471 Å in both molecules compared to an expected value of 1·451 Å (average value of 150 values extracted from the Cambridge Data Base; Kennard, Watson & Allen, 1980) with no significant deviations from these values in either molecule. The average of the 23 C–C–C bond angles in the modified steroid skeleton is 111·10°; 8 of the angles are at least 3σ greater than this value [112·2 (4) to 114·4 (3)°] and 5 are at least 8σ less [106·5 (3) to 108·3 (3)°] in each molecule. All the large bond angles have either central CH or CH_2 substituents, while the small bond angles have either central C(10) or C(13), both bearing CH_3 groups. The average values of the bond angles in these three categories are 112·3° (central CH_2), 111·4° (central CH) and 107·9° (central C bearing CH_3 substituent). The data for the aza steroid HS309 (IV) (Mazid, Palmer, Singh & Paul, 1977) were inspected and found to show a similar effect with average bond angles in the three categories of 112·2° (central CH_2), 111·2° (central CH) and 107·9° (central C bearing CH_3). The linear correlation coefficient calculated for bond angles in HS691 molecule 1 against molecule 2 (steroid skeleton) has a very high value of 0·95. For HS691 against HS309 (excluding bond angles influenced by the Δ5,6 bond in HS309) the corresponding value is 0·85, also indicating a high correlation.

In both molecules of HS691 the four rings of the steroid skeleton are *trans*-connected and all exhibit highly symmetrical chair conformations with small asymmetry parameters ΔC_s and ΔC_2 (Duax & Norton, 1975) (average of 48 values = 3·2°). The absolute torsion angles in the N-bearing modified D rings of the two molecules are slightly larger than in the other rings of the steroid skeletons. A similar effect occurs in HS309 (Mazid *et al.*, 1977). The linear correlation coefficient for torsion angles in molecule 1 of HS691 *versus* molecule 2 (steroid skeletons) has a high value of 0·88. The largest individual difference in torsion angles between the two molecules is 2·7° for C(3)–C(4)–C(5)–C(10) in ring A (about 4σ).

Although the individual differences in the molecular geometry parameters for the two molecules of HS691 discussed above are close to the limits of significance, the correspondence in fine detail does appear to be real in view of the high correlation coefficients. This applies also to bond lengths, the correlation coefficient for which is 0·65, lower than that for either bond angles or torsion angles but still quite a high value. Comparison of the two molecules of HS691 in such detail is only possible because of their co-existence in the crystalline state. Errors which would normally arise when different analyses are compared are thus eliminated. The statistical analyses have been confirmed by calculation of χ^2 tests for bond lengths and angles (Husain, 1981).

Pyrrolidine rings

There are no significant differences in bond lengths in the pyrrolidine rings E comprising atoms N(31), C(32), C(33), C(34) and C(35) in the two molecules of HS691. The largest differences in bond angles are for C(33)–C(34)–C(35), which is 102·9 (6)° in molecule 1 and 106·2 (6)° in molecule 2, and C(32)–C(33)–C(34), which is 107·3 (6)° in molecule 1 and 105·3 (6)° in molecule 2. Differences in the conformations of the two pyrrolidine rings are quite marked (Fig. 3). Ring E of molecule 1 has approximate mirror symmetry about N(31) and twofold symmetry about C(33), while in molecule 2 only the pseudo m-plane is present. Asymmetry parameters are as follows: ΔC_s^{N31} = 7·3° for molecule 1 and 6·1° for molecule 2; ΔC_2^{C33} = 12·1° in molecule 1 and 28·6° in molecule 2. The conformation of ring E in molecule 1 is similar to that

in HS309 for which $\Delta C_s^{N31} = 8{\cdot}4°$ and $\Delta C_s^{C33} = 9{\cdot}3°$ (e.s.d.'s for asymmetry parameters are 0·6–0·8°). The above conformational differences in HS691 are associated with changes of 10·3 and 9·6° in the torsion angles C(32)–C(33)–C(34)–C(35) and C(34)–C(33)–C(32)–N(31) respectively. Other torsion angles in the pyrrolidine rings also show significant changes (e.s.d.'s in torsion angles are 0·5–0·7°). The ring-*E* puckering may alternatively be described in terms of the displacements of atoms C(32), C(33) and C(3) from the exact plane through atoms C(32)–N(31)–C(35). In molecule 1 these displacements are −0·998 (18), −0·931 (18) and 1·109 (18) Å; −0·943 (18), −1·022 (18) and 1·133 (18) Å in molecule 2. Thus both molecules C(32) and C(33) are *exo* with respect to C(3), but their displacements from the reference plane differ by 0·055 Å for C(32) and 0·091 Å for C(33) (about 3σ and 5σ respectively).

The overall molecular conformations may be described in terms of the dihedral angles between the pairs of planes *A–B*, *B–C*, *C–D*, *A–E* and *ABCD–E*. For this purpose the least-squares planes were calculated by including all atoms in each group in spite of their non-planarity. These results (Table 2) are therefore to be regarded as qualitative. The table also includes the corresponding data for HS309 and HS310 for comparison. Both molecules of HS691 are seen to be typically *β*-convex. Large differences in the dihedral angles (denoted by * in the table) all involve ring *B* which is able to flex slightly in HS309 and HS310 due to the *Δ*5,6 bond. The steroid skeletons of molecules 1 and 2 of HS691 are evidently very similar to each other in general topology.

Table 2. *Dihedral angles* (°)

Plane 1	Plane 2	HS691 (molecule 1)	HS691 (molecule 2)	HS309	HS310
ABCD (modified steroid skeleton)	*A*	9·5	10·0	13·6	14·2
ABCD	*B*	3·0	3·6	*169·7	*10·9
ABCD	*C*	1·4	1·7	1·7	2·3
ABCD	*D*	9·3	10·0	6·9	4·4
A	*B*	7·8	7·8	*157·2	*24·9
B	*C*	4·4	5·2	*168·4	*13·2
C	*D*	8·5	8·5	6·4	6·5
A	*E*	6·5	3·4	2·8	13·7

* Indicates highly variable regions.

Table 3. *Selected intermolecular distances* (Å)

A prime denotes an atom in molecule 2.

	Distance (Å)	Contact between rings	Symmetry code for second molecule *x y z*
C(1)···C(34′)	3·730 (8)	*A*···*E*′	1 0 0
C(2)···C(34′)	3·794 (8)	*A*···*E*′	1 0 0
C(12)···C(1′)	3·863 (8)	*C*···*A*′	1 0 0
C(20)···C(12′)	3·873 (8)	*D*···*C*′	1 0 0
C(15)···C(4′)	3·924 (8)	*D*···*A*′	0 1 0
N(31)···C(18′)	3·909 (8)	*E*···*C*′	1 0 $\bar{1}$
C(4)···C(15′)	3·916 (8)	*A*···*D*′	0 0 $\bar{1}$
C(20)···C(33)	3·875 (8)	*D*···*E*′	0 1 1
C(20′)···C(33′)	3·889 (8)	*D*′···*E*′	0 1 1

The methyl carbon atom C(29) on N(17a) is equatorial in both molecules of HS691, slightly less so in molecule 1 [deviation from the ring-*D* least-squares plane = 0·047 (20) Å] than in molecule 2 [deviation = 0·003 (20) Å]. The longitudinal twist about the length of the molecule, defined as the pseudo torsion angle C(19)–C(10)···C(13)–C(18), is −0·8 (8)° in molecule 1 and 0·8 (8)° in molecule 2, a marginal but not significant difference.

All intermolecular contacts are very weak van der Waals contacts (Table 3). The two independent molecules have their lengths and *a* faces approximately parallel and are related by a local pseudo twofold axis approximately parallel to [011] and the length of the molecules. As can be seen in Fig. 4 the molecules pack *a* face to *a* face. There are four contacts between molecule 1, and molecule 2 generated by translation along **a**.

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4,5-Diamino-1-methyl-3-(methylthio)pyridazinium Iodide

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Abstract

The structure of the title compound, $C_6H_{11}N_4S^+.I^-$, $M_r = 298{\cdot}15$, has been determined from three-dimensional X-ray diffractometer data. The material crystallizes in the monoclinic space group $P2_1/n$ with four formula units in a cell of dimensions $a = 7{\cdot}549$ (2), $b = 9{\cdot}605$ (2), $c = 14{\cdot}568$ (2) Å, and $\beta = 89{\cdot}11$ (2)°; D_o (flotation in tetrahydrofuran/tribromomethane) = 1·86, $D_c = 1{\cdot}875$ Mg m^{-3}; μ(Mo $K\alpha$) = 3·214 mm^{-1}. The structure was solved by Patterson and difference Fourier methods and refined by least-squares techniques to a final R value (on F) of 0·038 based on 2035 independent data and 120 variables. The pyridazine cation is planar, with apparently more aromatic character than has been observed in other pyridazine derivatives. The net residual electronic charges as calculated by the CNDO/2 approximation suggest that the positive charge is delocalized over the entire ring, as expected for a pseudo-aromatic system.

Introduction

An area of intense recent activity has been the synthesis of nucleic acid base analogues which are designed to react differently in a biological system from their natural counterparts. Changes in the ring structures of the nucleic acid bases were among the first modifications to be made; the report of antineoplastic activity of 8-azaguanine (Kidder & Dewey, 1949; Law, 1950) helped to stimulate this area of research. Among the derivatives with significant biological activities are 5-aza- (anticancer agents and inhibitors of orotidylic acid pyrophosphorylase), 6-aza- (antiviral agents and inhibitors of orotidylic acid decarboxylase), and 3-deazapyrimidine nucleosides (antiviral agents and inhibitors of cytidine 5′-triphosphate synthetase) in addition to the 8-aza- and 3-deazapurine nucleosides (antiviral agents, anticancer agents, and inhibitors of hypoxanthine–guanine phosphoribosyltransferase and inosine 5′-monophosphate dehydrogenase) (Sidwell & Witkowski, 1979; Montgomery, Johnston & Shealy, 1979). Efforts are continuing in this vein to synthesize new compounds which are more active and more selective for the abnormal tissue.

The synthesis of these derivatives is often not straightforward and the composition and structure of the final product is not always known with certainty. For example, according to established trends, methylation of a 3-substituted pyridazine will result in different products depending on the nature of the substituent (Duffin & Kendall, 1959). An electron-withdrawing group, such as methylthio, deactivates the adjacent ring nitrogen, N(2), and promotes methylation at N(1), while a nonwithdrawing group or an electron-donating group, such as methyl, activates N(2). This is in fact what is observed, but the effects of substituents at the other positions on the course of methylation are not known for sure. In order to clear up a number of ambiguities of this sort, we undertook the X-ray crystal structure determination of the dimethylation product of 4,5-diaminopyridazine-3-thione.

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