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### The Structure of Tetrazole Steroid Analogues.

## II.\* The Structure of 3,6-Diaza-*A,B*-bishomocholest-4a-eno[3,4-*d*][6,7-*d*]bistetrazole (HS-650) Monohydrate

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#### Abstract

The crystal structure of a bistetrazolo steroid (HS-650) in the form of its aqueous solvate,  $C_{27}H_{42}N_8 \cdot H_2O$ , has been determined by direct methods. The crystals are orthorhombic,  $P2_12_12_1$ , with  $a = 9.025$  (1),  $b = 12.776$  (1),  $c = 50.253$  (4) Å,  $Z = 8$ ,  $D_m = 1.134$  (3),  $D_x = 1.138$  Mg m<sup>-3</sup>. Anisotropic least-squares refinement by cascade matrices led to the residual value  $R = 0.087$  for a total of 6185 unique reflections [ $R = 0.065$  for 4456 reflections,  $I > 3\sigma(I)$ ]. The fusion of tetrazole groups to rings *A* and *B* of the steroid has produced strains in the rings resulting in an overall *cis* conformation. A computer-graphics picture system was used to show the disorder associated with high thermal parameters, observed in the cholesteryl side chains of both molecules. Solvent water molecules hydrogen-bond with tetrazole groups to form continuous sheets parallel to (001). The two molecules in the asymmetric

unit are related by a pseudo twofold axis approximately parallel to [010] and the crystal packing consequently shows pseudo  $C222_1$  symmetry.

#### Introduction

As part of a study of the synthesis of tetrazolo steroids 3,6-diaza-*A,B*-bishomocholest-4a-eno[3,4-*d*][6,7-*d*]bistetrazole (HS-650) and 4,6-diaza-*A,B*-bishomo-4a-eno[4,3-*d*][6,7-*d*]bistetrazole (HS-649) (Fig. 1) were produced when cholest-4-ene-3,6-dione was treated with excess of hydrazoic acid and boron trifluoride in benzene (Singh, Butani, Malhotra & Paul, 1978). Although tetrazoles are metabolically stable the chemical and structural changes produced by introduction of such groups into steroids may affect the course of drug action. The work described here and in a following paper was undertaken in order to ascertain the chemical structures and to characterize important features of the molecular geometry of these two compounds.

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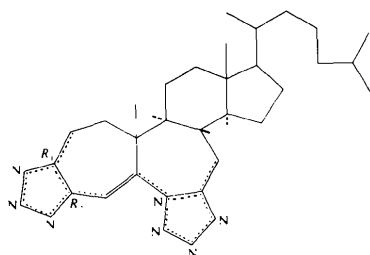


Fig. 1. Structural formula showing delocalization as indicated by the X-ray analysis (HS-650:  $R_1 = N$ ,  $R_2 = C$ ; HS-649:  $R_1 = C$ ,  $R_2 = N$ ).

X-ray analyses of other members of this series have been completed in this laboratory (Husain & Palmer, 1981; Husain, 1981; Palmer & Chattopadhyay, 1982). The tetrazolo steroids HS-650 and HS-649 are both 4-ene and have *cis*-like conformations at the *A*–*B* junction similar to that found in bile acids (Watson, 1980). Ring *A*-homo in both compounds has a distorted sofa or butterfly-like conformation and is quasi enantiomeric to the ring *B*-homo in HS-665 (Husain, Palmer, Singh, Bhardwaj & Paul, 1981).

### Experimental

A solution of HS-650 in a mixture of aqueous ethanol and acetone, evaporated slowly at room temperature, formed a gel which eventually crystallized into lozenge-shaped crystals. Systematic absences observed in precession photographs showed the space group to be  $P2_12_12_1$ . The unit-cell parameters were determined by least-squares refinement of the  $\theta$ ,  $\chi$  and  $\phi$  values of eight reflections measured accurately on a Hilger & Watts Y290 four-circle diffractometer using  $\text{Cu } K\alpha$  radiation (Tickle, 1975). Intensities of 15845 reflections, measured in the  $\omega$ - $2\theta$  scanning mode for  $\theta < 77^\circ$ , produced a set of 6185 unique reflections. Lorentz and polarization factors were applied in the usual way. Semi-empirical absorption corrections were applied ( $\mu_{\text{Cu } K\alpha} = 0.501 \text{ mm}^{-1}$ ,  $\mu_r \approx 2.0$  to  $4.0$ ) using the method of North, Phillips & Mathews (1968) modified by Tickle (1979).

### Structure determination and refinement

The structure was solved by direct methods using the routine *YZARC* (Declercq, Germain & Woolfson, 1979), based on 500 reflections having  $|E| \geq 1.6$ . In addition to the origin-fixing reflections 147 reflections, initially assigned random phases, were used in the tangent-formula expansion, after least-squares refinement. The *E* map corresponding to the solution with

the best figures of merit revealed the positions of 58 non-H atoms, 29 for each molecule, out of a total of 70. The two molecules were designated *A* and *B* respectively, and their atoms numbered accordingly.

The partial structure of HS-650 starting with  $R = 0.42$  was refined by block-diagonal-matrix least squares using the program *LSHELX 76* (Sheldrick, 1976). Refinement of the scale factor, positional and isotropic thermal parameters for two complete passes in two blocks reduced  $R$  to 0.28 using reflections with  $I > 3\sigma(I)$ . A difference electron density map revealed possible side-chain atoms with low density. The electron density was diffuse from C(A23) to C(A27) in molecule *A* and for atoms C(B26) and C(B27) in molecule *B*. Further isotropic refinements including possible side-chain atoms reduced  $R$  to 0.21, and subsequent anisotropic refinement gave  $R = 0.13$ . Some of the side-chain atoms had very high anisotropic thermal parameters and classical studies of difference electron density maps did not fully resolve the nature of the disorder. Using the program *FRODO* (Jones, 1978; Tickle, 1980) on an Evans and Sutherland Picture System II (Computer Graphics), the disordered side-chain atoms were fitted to both the observed and difference electron densities, the latter omitting side-chain atoms from the structure factor calculations.

Adjustments were made in order to produce a model with torsion angles, bond lengths and bond angles close to ideal values, optimally fitting the electron density. Fig. 2(a) and (b) show how it was in fact possible to fit alternative conformations into the diffuse density regions. However, since no definite alternative atomic positions were resolved in the maps, it was not possible to assign coordinates or refine occupancies of alternate sites. The refinement was completed using the best possible single side-chain positions for both molecules, employing cascade-matrix least-squares analysis (Sheldrick, 1979). H atoms were geometrically positioned and refined with isotropic temperature factors. Free

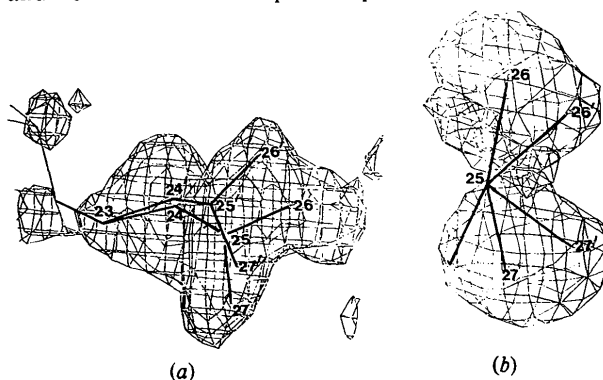


Fig. 2. Difference electron density in the disordered regions. (a) Molecule *A* and (b) molecule *B*. The disordered atoms C(A24) to C(A27) and C(B26), C(B27) were omitted from the structure factor calculations.  $R$  at this stage was 0.087. Contours at the  $0.1 \text{ e } \text{Å}^{-3}$  level are shown.

Table 1. Refined positional parameters ( $\times 10^4$ ) with e.s.d.'s in parentheses and equivalent isotropic thermal parameters ( $\times 10^3$ ) for non-H atoms

$$U_{eq} = (U_{11}U_{22}U_{33})^{1/3}.$$

Molecule A	x	y	z	$U_{eq} (\text{\AA}^2)$	Molecule B	x	y	z	$U_{eq} (\text{\AA}^2)$
C(A1)	4197 (4)	-4208 (3)	4419 (1)	60	C(B1)	620 (4)	-4119 (3)	616 (1)	58
C(A2)	4946 (5)	-3515 (4)	4619 (1)	67	C(B2)	-104 (5)	-3384 (4)	419 (1)	66
C(A4)	2740 (5)	-3617 (3)	4930 (1)	59	C(B4)	1990 (5)	-3597 (3)	90 (1)	59
C(A4a)	1515 (4)	-3686 (3)	4751 (1)	54	C(B4a)	3241 (5)	-3698 (3)	264 (1)	55
C(A5)	1527 (4)	-3736 (3)	4484 (1)	51	C(B5)	3313 (4)	-3755 (3)	531 (1)	49
C(A7)	-498 (4)	-3098 (4)	4189 (1)	62	C(B7)	5442 (4)	-3201 (3)	805 (1)	58
C(A7a)	291 (5)	-2172 (4)	4088 (1)	68	C(B7a)	4752 (5)	-2224 (4)	911 (1)	67
C(A8)	1743 (4)	-2410 (3)	3940 (1)	54	C(B8)	3308 (4)	-2389 (3)	1069 (1)	53
C(A9)	3016 (4)	-2756 (3)	4129 (1)	54	C(B9)	1947 (4)	-2722 (3)	894 (1)	51
C(A10)	2768 (4)	-3823 (3)	4279 (1)	51	C(B10)	2098 (4)	-3787 (3)	742 (1)	50
C(A11)	4486 (5)	-2812 (4)	3971 (1)	68	C(B11)	536 (5)	-2716 (4)	1068 (1)	67
C(A12)	4883 (6)	-1804 (4)	3818 (1)	75	C(B12)	245 (5)	-1668 (4)	1212 (1)	74
C(A13)	3639 (5)	-1516 (3)	3626 (1)	66	C(B13)	1561 (5)	-1380 (3)	1390 (1)	59
C(A14)	2239 (5)	-1395 (3)	3797 (1)	65	C(B14)	2938 (5)	-1349 (4)	1209 (1)	61
C(A15)	1077 (7)	-878 (5)	3618 (1)	98	C(B15)	4131 (6)	-833 (5)	1385 (1)	93
C(A16)	2095 (9)	-113 (5)	3448 (1)	107	C(B16)	3236 (7)	-7 (5)	1540 (1)	104
C(A17)	3720 (7)	-399 (4)	3508 (1)	77	C(B17)	1588 (6)	-222 (3)	1495 (1)	69
C(A18)	3427 (6)	-2315 (4)	3404 (1)	77	C(B18)	1731 (6)	-2150 (4)	1624 (1)	72
C(A19)	2350 (5)	-4734 (3)	4089 (1)	67	C(B19)	2494 (5)	-4702 (3)	933 (1)	60
C(A20)	4757 (9)	-186 (5)	3266 (1)	93	C(B20)	626 (7)	84 (4)	1739 (1)	79
C(A21)	6325 (9)	463 (7)	3315 (1)	121	C(B21)	-992 (7)	-181 (5)	1711 (1)	95
C(A22)	4635 (12)	992 (5)	3184 (1)	124	C(B22)	803 (9)	1245 (4)	1793 (1)	88
C(A23)	5425 (12)	1302 (8)	2929 (1)	167	C(B23)	142 (10)	1665 (5)	2057 (1)	105
C(A24)	4861 (15)	912 (15)	2699 (2)	236	C(B24)	516 (10)	2774 (5)	2103 (1)	118
C(A25)	5502 (18)	1200 (17)	2437 (2)	250	C(B25)	-280 (18)	3258 (7)	2350 (2)	172
C(A26)	5232 (21)	2392 (14)	2372 (2)	282	C(B26)	129 (25)	4394 (10)	2370 (2)	311
C(A27)	5082 (20)	588 (15)	2217 (2)	294	C(B27)	29 (22)	2719 (9)	2595 (2)	233
N(A4')	4208 (4)	-3561 (3)	4875 (1)	61	N(B4')	563 (4)	-3472 (3)	156 (1)	61
N(A3')	4953 (5)	-3499 (3)	5103 (1)	78	N(B3')	-244 (5)	-3390 (3)	-68 (1)	75
N(A2')	3975 (6)	-3505 (3)	5295 (1)	83	N(B2')	702 (5)	-3423 (3)	-263 (1)	83
N(A1')	2587 (5)	-3576 (3)	5192 (1)	71	N(B1')	2104 (5)	-3571 (3)	-174 (1)	76
N(A4'')	59 (3)	-3761 (3)	4369 (1)	59	N(B4'')	4782 (3)	-3834 (2)	633 (1)	53
N(A3'')	-949 (4)	-4520 (4)	4422 (1)	79	N(B3'')	5725 (4)	-4627 (3)	572 (1)	68
N(A2'')	-2074 (4)	-4300 (5)	4274 (1)	84	N(B2'')	6927 (4)	-4447 (4)	706 (1)	78
N(A1'')	-1851 (4)	-3428 (5)	4128 (1)	81	N(B1'')	6794 (4)	-3588 (4)	854 (1)	72
O(A1)	3387 (6)	-1257 (4)	4849 (1)	120	O(B1)	1428 (6)	-1223 (4)	149 (1)	128

refinement of the side-chain atoms resulted in apparent shortening of the bonds accompanied by high thermal parameters associated with the diffuse electron density. Weights were calculated during the final least-squares cycle as  $w = [\sigma^2(|F| + 0.00437|F|^2)]^{-1}$ . A parameter was included in order to account for secondary extinction; its final value was 0.00168.

**Results and discussion**

The final atomic coordinates of the non-H atoms of molecules A and B of HS-650, and their isotropic temperature factors are given in Table 1.\* The H atoms

\* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, deviations of atoms from least-squares planes and dihedral angles between them, and selected intermolecular contact distances and an accompanying diagram have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36981 (33 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. Torsion angles ( $^\circ$ ) at ring junctions of molecules A and B of HS-650

E.s.d.'s are 0.5-0.7 $^\circ$ .

Ring junction	Atoms involved	Molecule A	Molecule B
A-B	C(1)-C(10)-C(5)-N(4'')	-158.6	-158.2
	C(9)-C(10)-C(5)-C(4a)	-106.1	-105.5
B-C	C(10)-C(9)-C(8)-C(14)	-176.0	-178.1
	C(11)-C(9)-C(8)-C(7a)	-171.2	-172.4
C-D	C(12)-C(13)-C(14)-C(15)	167.9	168.3
	C(17)-C(13)-C(14)-C(8)	176.9	178.9
A-T1	C(2)-N(4')-C(4)-N(1')	-176.1	-176.0
	N(3')-N(4')-C(4)-C(4a)	-180.0	178.7
B-T2	C(5)-N(4'')-C(7)-N(1'')	177.1	177.3
	N(3'')-N(4'')-C(7)-C(7a)	-180.0	178.2

are numbered according to the C atoms to which they are bonded. Intramolecular bond lengths are shown in Fig. 3 and bond angles are in Fig. 4. Molecules A and B are related by a pseudo twofold axis approximately





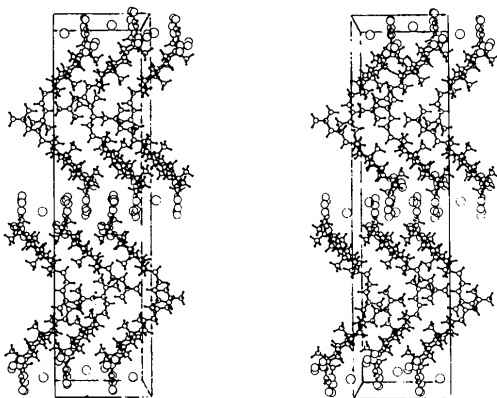


Fig. 6. The crystal packing as viewed along [100].

the least-squares planes through  $A_1$  and  $A_3$  respectively are negligibly small in both molecules of HS-650. Planes  $A_1$  and  $A_3$  form the 'wings', and  $A_2$  the body of the butterfly. The 'head' of the butterfly is C(4a) and the 'tail' is formed by C(1)–C(2). The deviations of C(1) and C(2) from the least-squares plane through ring  $A$ -homo show that the tail of the butterfly is well below its head, atom C(4a). The dihedral angles between the planes  $A_1$ ,  $A_2$  and  $A_2$ ,  $A_3$  show that wing  $A_3$  is more bent ( $36^\circ$ ) than wing  $A_1$  ( $47^\circ$ ) with respect to the body  $A_2$ . The similarity in the details of the conformation of ring  $A$ -homo in both molecules is remarkable. The deviations of atoms N(4'), C(4), C(4a) and C(5) from the least-squares plane through ring  $A$  in both molecules are very small, confirming the effect of delocalization induced by the tetrazole ring  $T_1$  and the double bond at C(4a)=C(5). In ring  $B$ -homo, the dihedral angles between planes  $B_1$  and  $B_2$  are very small,  $2.50$  and  $3.98^\circ$  in molecules  $A$  and  $B$  respectively. The deviations of the atoms in ring  $B$  are within  $0.4$  Å and the conformation could be described as an envelope with atoms C(8), C(9) and C(10) forming the flap. Tetrazole ring  $T_2$ , which is planar, makes dihedral angles of  $29$  and  $28^\circ$  with ring  $B$ -homo, in molecules  $A$  and  $B$  respectively.

The rings  $T_1$ ,  $A$ ,  $B$ ,  $C$  and  $D$  form a curved surface, convex towards the  $\beta$  face of the molecule. This curvature, however, does not seem to influence the C(18)⋯C(19) distance significantly, which is  $4.726$  and  $4.813$  Å in molecules  $A$  and  $B$  respectively as compared to the usual value observed in steroids of around  $4.6$  Å (Duax & Norton, 1975). The pseudo torsion angle [C(19)–C(10)⋯C(13)–C(18)] defining the longitudinal molecular twist is  $5.38$  and  $6.42^\circ$  in molecules  $A$  and  $B$  respectively. The proximity of a water molecule, as shown in Fig. 6, clearly suggests that the  $\alpha$  face of the modified steroid is hydrophilic.

#### The cholesteryl side chain

The average C–C bond distance in the side chain containing atoms C(17) to C(27) is  $1.493$  Å in

molecule  $A$  and  $1.512$  Å in molecule  $B$ . If disordered atoms are omitted, *i.e.* from C(17) to C(23) in molecule  $A$ , the mean C–C bond length is  $1.523$  Å; in molecule  $B$ , the mean C–C bond length of atoms without disorder [C(17) to C(25)] is  $1.527$  Å. The cholesteryl chain in molecule  $B$  is extended, the C(B17)⋯C(B25) distance being  $6.407$  Å, while that in molecule  $A$  is slightly more curled, C(A17)⋯C(A25) =  $5.974$  Å.

#### Molecular packing and H bonding

The molecules pack head to head and tail to tail along the  $c$  axis, as shown in the [100] projection in Fig. 6, with the steroid planes approximately parallel. The mode of packing allows the side chains freedom of movement, especially near the extreme ends.

A table of selected intermolecular contact distances less than  $3.6$  Å for non-H atoms and an accompanying diagram have been deposited. The tetrazole rings  $T_1$  and  $T_2$  of molecules  $A$  and  $B$  are linked by water molecules forming an infinite sheet perpendicular to the  $c$  axis. There is a noticeably close proximity ( $<3.15$  Å) of the water molecules O(A1) and O(B1) with the rings  $T_1$  and  $T_2$ , both at  $x,y,z$  and in symmetry-related positions. The angles N(A4')–O(A1)–N(B3'') =  $128.53$ , N(A3')–O(A1)–N(B3'') =  $112.30$  and N(A4')–O(A1)–N(A3') =  $98.15^\circ$  suggest that there is disordering associated with water molecule O(A1) such that at any one instant only one of three possible N⋯HO bonds is formed. Similarly, the angles at O(B1), N(B4')–O(B1)–N(B3') =  $95.88$ , N(B4')–O(B1)–N(A3'') =  $129.37$ , N(A3'')–O(B1)–N(B3') =  $110.02^\circ$ , suggest probable H bonding of N(B4') and N(B3') or N(B4') and N(A3'') and N(B3') *via* the water molecule O(B1) at any instant. The time-averaged positions of the water molecules O(A1) and O(B1) are shown in Fig. 6. Pseudo  $C$ -centring is generated by the pseudo twofold axis relating the molecules  $A$  and  $B$ .

The  $\chi^2$  test was applied to compare the bond lengths and angles of molecules  $A$  and  $B$  in HS-650. If all the bond lengths in the two molecules are taken,  $\chi^2 = 196.9$  for 40 degrees of freedom, which is highly significant. Exclusion of the bonds in the cholesteryl chain involving atoms C(21) to C(27) gave  $\chi^2 = 94.4$  for 33 degrees of freedom, which is still highly significant at the 0.1% level. The bonds mainly responsible for this lack of correspondence are C(15)–C(16) and C(13)–C(17) in ring  $D$ , and C(5)–N(4'') in ring  $B$ , all of which show differences  $>3\sigma$ .

#### Potential energy and conformation of the cholesteryl side chains

In order to investigate further the nature of the disorder in the cholesteryl side chains of molecules  $A$  and  $B$

calculation of non-bonded potential-energy functions for molecules packed in the crystal environment was undertaken using the program *EENY* (W. D. S. Motherwell). Energy values were calculated for a given set of atoms using empirical atom-pair functions (Giglio, 1969).

For an atom pair separated by a distance  $r$  (Å) the energy is defined as

$$E_r = a \exp(-br)/r^d - c/r^6$$

where  $a$ ,  $b$ ,  $c$  and  $d$  are constants and  $r > 2$  Å. Calculations of  $E_r$  were undertaken as a joint function of  $\tau_4 = C(A22)-C(A23)-C(A24)-C(A25)$ ,  $\tau_5 = C(A23)-C(A24)-C(A25)-C(A26)$  in molecule  $A$  and  $\tau_{10} = C(B23)-C(B24)-C(B25)-C(B26)$  in molecule  $B$ . The various energy maps indicated:

(a)  $\tau_4$  is restricted to the range 140–200° in which  $-210 < E_r < -170$  kJ mol<sup>-1</sup>. The position for  $\tau_4$  derived in the structure analysis is 177.3°, in good agreement with the energy calculation.

(b)  $\tau_{10}$  is restricted to the range 160–240° ( $-210 < E_r < -130$  kJ mol<sup>-1</sup>). The value derived by X-ray analysis,  $-178.0^\circ$ , again lies in the middle of the range predicted.

(c)  $\tau_5$  is completely free to rotate in the range 0 to 360° with  $E_r$  always in the range of  $\tau_4$  and  $\tau_5$ . This result is again in keeping with smeared electron density discussed above.

The energy calculations confirm the existence of a wide range of conformations of the cholesteryl side chains indicated in the electron density, and show  $\tau_5$  to be the least constrained in the crystal structure. Placement of the side-chain atoms by computer graphics was probably achieved optimally. Further confirmation of the results was obtained by using the program *EENY* in refinement mode in which  $E_r$  is minimized by steepest descents, the parameters being again  $\tau_4$ ,  $\tau_5$  and  $\tau_{10}$ . Minimization converged with very little change in energy from that derived from the input parameters,  $\tau_4$  and  $\tau_5$  having changed insignificantly and  $\tau_{10}$  having changed from  $-178$  to  $-175^\circ$ , which is barely significant. It would appear that under con-

ditions of biological activity, the cholesteryl side chains would be far less restricted than in the crystal structure, although of course they would be subject to hindrance from solvent atoms.

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