Tetrahedron. Vol. 27, pp. 331 to 335 Pergamon Press 1971. Printed in Great Britain

THE CRYSTAL STRUCTURE AND MOLECULAR CONFORMATION OF 2,2,6β-TRICHLOROTESTOSTERONE ACETATE

W. L. DUAX, Y. OSAWA*, A. COOPER†, and D. A. NORTON
The Medical Foundation of Buffalo, Buffalo, New York 14203

(*Received in USA* 26 *August* 1970; *Received in the UK for publication* 7 *September* 1970)

Abstract—Crystals of 2,2,6β-trichlorotestosterone acetate ($C_{21}H_{27}O_3Cl_3$) are monoclinic, space group $P2_1$, with unit cell dimensions $a = 9{\cdot}757$ Å, $b = 14{\cdot}100$ Å, $c = 7{\cdot}786$ Å, $\beta = 90{\cdot}77°$. The structure was solved by X-ray diffraction methods from the 3-dimensional Patterson and Fourier syntheses and was refined by block-diagonal least-squares to a final R of 0·09. The A-ring of the steroid molecule is found to be in the typical half-chair conformation in contrast to the half-boat conformation previously predicted from the interpretation of CD, ORD and NMR measurements.

FROM the interpretation of ORD, CD, and NMR, the A-ring of 2,2,6β-trichlorotestosterone acetate (Fig 1) was predicted to have the half-boat or "nonsteroidal" half-chair conformation.[1,2] Since the conformations of A rings containing the 4-en-3-one system in a number of steroids determined by X-ray analysis have been found to be half-chair,[3,4] and since the boat form is generally energetically less favourable, the structural investigation of 2,2,6β-trichlorotestosterone acetate was undertaken.

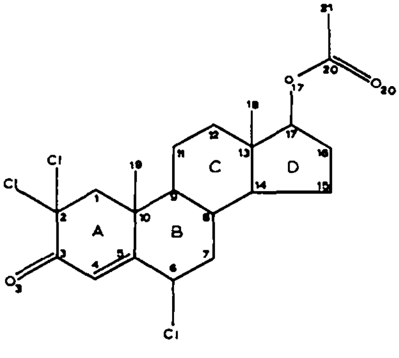

FIG 1. 2,2,6β-trichlorotestosterone acetate. Molecular skeleton and number of the atoms.

RESULTS AND DISCUSSION

The A-ring of the steroid molecule was determined to be in the normal half-chair conformation for steroids containing the 4-en-3-one system, in conflict with the interpretation of the CD and the ORD measurements by Kondo *et al.*[1] Furthermore, there is no case in the literature in which a 4-en-3-one steroid having a 2α substituent has been

---

* Faculty Research Awardee, PRA-72, of the American Cancer Society.

† Present Address: Hospital Data Science, Inc., 516 Fifth Avenue, Suite 1006, New York, New York 10036.

shown through x-ray analysis to be in the half-boat conformation. While it is still possible that the conformation of the A-ring of 2,2,6β-trichlorotestosterone acetate in solution is half-boat, this conflict is noteworthy in that these ORD and CD predictions for the α,β-unsaturated ketone were dependent upon the Cotton effect of the $n \rightarrow \pi^*$ transition band in which the octant rule[5] is in general no longer applicable in its original form,[6] and in that the 6β-axial chlorine atom probably influences the Cotton effect of a 4-en-3-one through its electronic factor.[7]

In Fig 2, all important intramolecular distances and angles are given. The average standard deviations for these dimensions are 0·1 Å and 0·02 Å for distances to hydrogen and to non-hydrogen atoms respectively and 1, 5, and 10° for angles of the types C–C–C, C–C–H, and H–C–H. While C—C bond lengths in the C- and D-rings are within one standard deviation of the expected values, those in the A- and B-rings are often more than two standard deviations from the expected values and these distortions could be attributed to the presence of the Cl atoms. The C(20)—O(20) bond distance of 1·13 Å is shortened due to the thermal motion of the O(20) atom which is considerably greater in the *y*- and *z*- directions than that of the C(20) atom (the bond lying nearly parallel to the *a* direction). The interatomic distances between the 2β-Cl atom and the 19-Me H atoms, H(19)A and H(19)C, are 2·7 and 2·6 Å, respectively, which is about 0·4 Å less than the sum of the van der Waals radii of H and Cl. The interatomic distance from the 6β-Cl to the nearest Me hydrogen, H(19)B, is 3·0 Å. This closer approach to the 19-Me hydrogen atoms to the 2β-Cl atom than to the 6β-Cl atom also contradicts the interpretation of the NMR shifts by Kondo *et al.*,[2] who proposed the half-boat conformation of the A-ring.

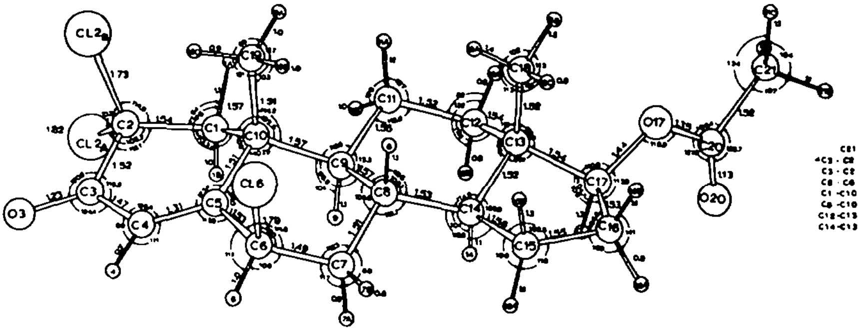

FIG 2. Summary of interatomic bond distances and angles observed in 2,2,6β-trichlorotestosterone acetate.

Atoms C(21), C(20), O(20), and O(17) are planar within 0·001 Å and C(17) is only 0·055 Å out of this plane which makes an angle of 90·0° with the least squares plane through atoms C(14)—C(17) of the D-ring. As expected, the conjugated 4-en-3-one system (including C(2), C(6), and C(10)) is planar to within ± 0·04 Å. Distances of the Cl atoms from this plane are Cl(2α) = 1·08 Å, Cl(2β) = 1·61 Å, Cl(6) = 1·7 Å.

In Fig 3, a projection of the entire molecule parallel to the least-squares plane through atoms C(5) to C(17) is shown, and oxygen atom O(3) is 1·3 Å below this least squares plane.

The torsional angles for the steroid nucleus are given in Table 1. The B- and C-rings of the steroid have the normal chair conformation. The D-ring is a distorted β-envelope and can be described by the parameters $\Delta = 23{\cdot}5$ and $\phi m = 46{\cdot}9$.[8]

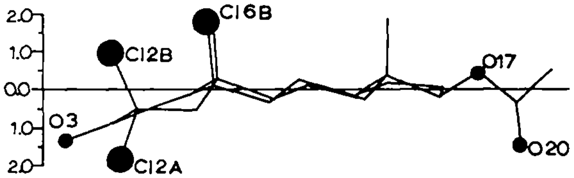

FIG 3. Projection of the molecule parallel to the least squares plane through atoms C(5)—C(17). The scale shows the departures (in Å units) of the atoms from the plane.

TABLE 1. TORSIONAL ANGLES IN THE RINGS[a, b]

Ring A		Ring B		Ring C		Ring D	
Bond	ϕ(A–B)	Bond	ϕ(A–B)	Bond	ϕ(A–B)	Bond	ϕ(A–B)
C(1)—C(2)	−51·9	C(5)—C(6)	−45·6	C(8)—C(9)	−47·3	C(13)—C(14)	45·9
C(2)—C(3)	29·5	C(6)—C(7)	50·9	C(9)—C(11)	47·6	C(14)—C(15)	−31·9
C(3)—C(4)	−8·3	C(7)—C(8)	−60·9	C(11)—C(12)	−54·0	C(15)—C(16)	4·7
C(4)—C(5)	9·0	C(8)—C(9)	62·2	C(12)—C(13)	59·2	C(16)—C(17)	23·7
C(5)—C(10)	−29·0	C(9)—C(10)	−53·3	C(13)—C(14)	−62·9	C(13)—C(17)	−42·3
C(1)—C(10)	49·8	C(5)—C(10)	46·2	C(8)—C(14)	57·2		

[a] The sign convention for torsional angles is that of W. Klyne and V. Prelog, *Experimentia*, **16**, 521 (1960).

[b] ϕ(A–B) is the torsional angle about the A—B bond, in which the other two atoms required to define the angle are those attached to either end of the bond and are in the ring in question.

TABLE 2. EXPERIMENTAL DATA

Formula	$C_{21}H_{27}O_3Cl_3$
Molecular weight	433·59
Melting point	211–212°C
a	9·757 ± 0·003 Å
b	14·100 ± 0·004 Å
c	7·786 ± 0·001 Å
β	90·77 ± 0·02°
ρ x-ray	1·34 g. cm^{-3}
ρ measured	1·30 g. cm^{-3}
Space group	$P2_1$
z	2
Linear absorption coefficient, μ	39·4 cm^{-1}
Crystal size (approx. sphere)	0·12 to 0·16 mm dia.
Reflections measured	2399
Reflections above background	1294

TABLE 3. POSITIONAL PARAMETERS OF THE NON-HYDROGEN ATOMS, AT THE END OF THE LEAST-SQUARES REFINEMENT

	X/A	Y/B	Z/C
C(1)	0·7825 (13)	0·6239 (9)	0·2454 (17)
C(2)	0·7602 (14)	0·5189 (9)	0·2904 (19)
C(3)	0·7977 (17)	0·4973 (10)	0·4766 (20)
C(4)	0·7797 (15)	0·5769 (10)	0·5969 (17)
C(5)	0·7505 (12)	0·6644 (9)	0·5532 (15)
C(6)	0·7420 (13)	0·7376 (10)	0·6990 (13)
C(7)	0·8029 (15)	0·8301 (9)	0·6489 (15)
C(8)	0·7468 (12)	0·8657 (9)	0·4786 (14)
C(9)	0·7820 (12)	0·7918 (8)	0·3353 (12)
C(10)	0·7113 (13)	0·6937 (8)	0·3730 (14)
C(11)	0·7511 (16)	0·8283 (10)	0·1507 (15)
C(12)	0·8065 (16)	0·9279 (9)	0·1194 (16)
C(13)	0·7564 (15)	0·9991 (9)	0·2540 (15)
C(14)	0·8061 (13)	0·9620 (11)	0·4280 (14)
C(15)	0·7903 (15)	1·0473 (9)	0·5532 (16)
C(16)	0·8161 (14)	1·1335 (10)	0·4353 (18)
C(17)	0·8320 (15)	1·0947 (10)	0·2531 (17)
C(18)	0·6018 (13)	1·0136 (9)	0·2436 (17)
C(19)	0·5578 (15)	0·6942 (10)	0·3493 (15)
C(20)	0·8646 (13)	1·2055 (8)	0·0277 (15)
C(21)	0·7809 (18)	1·2602 (12)	−0·1048 (18)
O(3)	0·8293 (16)	0·4163 (8)	0·5199 (15)
O(17)	0·7738 (9)	1·1557 (8)	0·1220 (12)
O(20)	0·9796 (9)	1·2062 (8)	0·0440 (14)
Cl(2A)	0·8817 (5)	0·4539 (3)	0·1602 (6)
Cl(2B)	0·5979 (4)	0·4758 (3)	0·2435 (7)
Cl(6B)	0·5683 (3)	0·7500 (−)	0·7663 (4)

EXPERIMENTAL

Crystals of 2,2,6β-trichlorotestosterone acetate, which had been grown from acetone, were somewhat unstable and decomposed over a period of months. Unit cell constants (Table 2) were determined from a least-squares fit to 24 measurements of three dimensional vectors of $2\theta > 60°$.

The intensities were measured on a General Electric single crystal orienter by the stationary-crystal stationary-counter method using CuKα radiation monochromatized by balanced nickel and cobalt filters and by electronic pulse height discrimination. Periodic measurement of "standard" reflections did not indicate a perceptible systematic decomposition of the crystal over the period of data collection, even though the crystals took on a yellowish cast. Lorentz and polarization corrections were applied to the data and the structure was solved by routine application of the heavy atom method.[9]

The scattering factors used in the refinement were taken from *International Tables for X-ray Crystallography* (1962). In order to define the origin, the y-parameter of Cl atom Cl(6) was held constant during refinement and three cycles of block diagonal least-squares refinement of the positional and isotropic thermal parameters of the nonhydrogen atoms yielded an R value (defined as $\Sigma|F_o - F_c|/\Sigma|F_o|$) of 0·18. Further refinement using anisotropic thermal parameters and a weighing scheme in which

$$\sqrt{w} = 1{\cdot}0 \text{ for } |F_o| < 12{\cdot}0 \text{ and}$$

$$\sqrt{w} = 12{\cdot}0/|F_o| \text{ for } |F_o| > 12{\cdot}0,$$

converged with $R = 0{\cdot}10$ for the 1294 observed spectra and $R = 0{\cdot}14$ for all spectra.

A three dimensional Fourier difference synthesis was then computed and the positions of the 27 H atoms were located. Two further cycles of refinement holding the H atom positional and thermal parameters constant resulted in negligible parameter shifts and reduction of R to 0·088. Refinement was terminated at this point with the minimization function, $\Sigma w(|F_o| - |F_c|)^2/(m-n)$ at 1·3. Table 3 lists the final atomic coordinates for the nonhydrogen atoms.*

Acknowledgement—Crystals used in this determination were generously supplied by Dr. K. Yasuda of the Teikoku Hormone Manufacturing Company, Kawasaki, Japan.

The authors are grateful to Mrs. C. Devine, Miss P. Strong, and Mr. D. Maracle for their assistance in the preparation of the data and illustrations. The work was supported in part by U.S. Publie Health Service Grant No. CA 10906-02 from the National Cancer Institute.

REFERENCES

[1] Y. Kondo, K. Kondo, T. Takemoto, K. Yasuda and G. Snatzke, *Tetrahedron* **21**, 1191 (1965)

[2] Y. Kondo, T. Takemoto and K. Yasuda, *Chem. Pharm. Bull* **12**, 976 (1964)

[3] A. Cooper, E. M. Gopalakrishna and D. A. Norton, *Acta Cryst.* **B24**, 935–41 (1968)

[4] A. Cooper, C. T. Lu and D. A. Norton, *J. Chem. Soc.* B. 1228 (1968)

[5] W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Am. Chem. Soc.* **83**, 4013 (1961)

[6] C. Djerassi, R. Records, E. Bunnenberg, K. Mislow and A. Moscowitz, *Ibid.* **84**, 870 (1962)

[7] P. Crabbe, *Optical Rotary Dispersion and Circular Dichroism in Organic Chemistry* p. 219. Holden Day, San Francisco (1965)

[8] C. Altona, H. J. Geise and C. Romers *Tetrahedron* **24**, 13 (1968)

[9] See for example H. Lipson and W. Cochran, *The Determination of Crystal Structures, The Crystalline State*. Vol. III. Bell, London (1953)

---

* Material supplementary to this article (hydrogen atom positional parameters, nonhydrogen atom thermal parameters, obsrved and calculated structure amplitudes) is available from the authors upon request.