

**(19S)-19-Methyl-5-androstene-3 $\beta$ ,17 $\beta$ ,19-triol Dihydrate,  
a Steroid Pertinent to the Mechanism of Estrogen Biosynthesis**

BY DOUGLAS C. ROHRER, WILLIAM L. DUAX AND YOSHIO OSAWA

*Medical Foundation of Buffalo, 73 High Street, Buffalo, New York 14203, U.S.A.*

(Received 30 October 1975; accepted 26 February 1976)

(19S)-19-Methyl-5-androstene-3 $\beta$ ,17 $\beta$ ,19-triol dihydrate (C<sub>20</sub>H<sub>32</sub>O<sub>3</sub>·2H<sub>2</sub>O) is orthorhombic, space group  $P2_12_12_1$ ;  $a = 12.522$  (6),  $b = 24.175$  (9),  $c = 6.484$  (4) Å,  $V = 1962.8$  Å<sup>3</sup>;  $Z = 4$ ,  $M = 356.5$ ,  $D_c = 1.206$ ,  $D_m = 1.187$  g cm<sup>-3</sup>. The configuration of C(19) is *S*, rather than *R* as had previously been reported by Wicha & Caspi [*J. Chem. Soc. (C)* (1968), pp. 1740-1746]. The methyl and hydroxyl substituents on C(19) are *trans* and *syn* to C(1) and form torsion angles to C(1) of  $-179.4$  and  $58.1^\circ$  respectively. This places the bulky methyl group over the *B* ring and the hydroxyl over the *A* ring.

### Introduction

The crystal and molecular structure of (19S)-19-methyl-5-androstene-3 $\beta$ ,17 $\beta$ ,19-triol dihydrate was analyzed to determine the configuration of C(19) and to study the conformation of the C(19) substituents. This compound was synthesized by the procedure described by Caspi & Wicha (1966) and isolated as the major product of two resulting isomers (Osawa, Shibata, Rohrer, Weeks & Duax, 1975).

### Experimental

A crystal with dimensions  $0.08 \times 0.24 \times 0.58$  mm was used for measurements of the lattice parameters and intensities. The systematic absences along the axial rows were consistent with the space group  $P2_12_12_1$  ( $D_2^4$ , No. 19) and the cell constants determined by a least-squares refinement procedure using the  $\theta$  values for 15 reflections [ $\lambda(\text{Cu } K\alpha) = 1.54178$  Å] are  $a = 12.522$  (6),  $b = 24.175$  (9) and  $c = 6.484$  (4) Å. Integrated intensities for 2346 independent reflections were measured on an Enraf-Nonius CAD-4 diffractometer to a maximum  $\theta$  of  $75^\circ$  using Ni-filtered Cu  $K\alpha$  radiation. Lorentz and polarization corrections were applied to the intensities. Normalized structure factor amplitudes were computed and the structure solved with the multi-solution direct-methods program *MULTAN* (Germain, Main & Woolfson, 1971).

The atomic parameters for the non-hydrogen atoms were refined first isotropically then anisotropically by a full-matrix least-squares procedure. The hydrogens were located from a difference map and included in the final least-squares calculations, their positional and isotropic thermal parameters ( $B = 3.5$  Å<sup>2</sup>) being held fixed. The quantities  $1/\sigma_F^2$  were used as weights, where  $\sigma_F$  is defined by Stout & Jensen (1968; equation H. 14), and an instability correction of 0.07 was used.  $R = \sum(|F_o| - |F_c|) / \sum|F_o|$  for the 1634 data with  $I > 3.0\sigma(I)$  was 0.069 and the  $R$  value for all 2346 data

was 0.108. The final positional parameters are given in Table 1.\*

### Discussion

The crystallographically observed conformation of (19S)-19-methyl-5-androstene-3 $\beta$ ,17 $\beta$ ,19-triol is shown in Fig. 1. The thermal vibrational ellipsoids in these *ORTEP* (Johnson, 1970) drawings are scaled to a 60%

\* A list of structure factors and the anisotropic thermal parameters for the non-hydrogen atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31728 (13 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

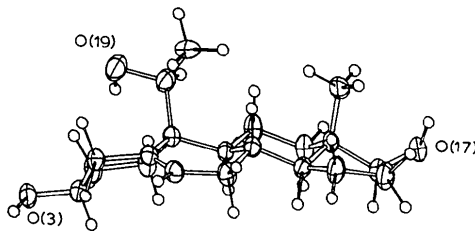
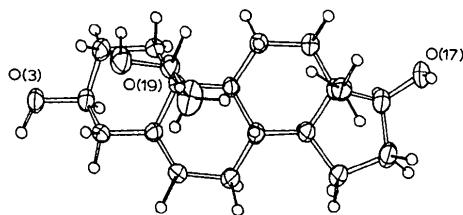


Fig. 1. The observed conformation of (19S)-19-methyl-5-androstene-3 $\beta$ ,17 $\beta$ ,19-triol. The thermal ellipsoids are scaled to a 60% probability level and the hydrogens are shown as circles.



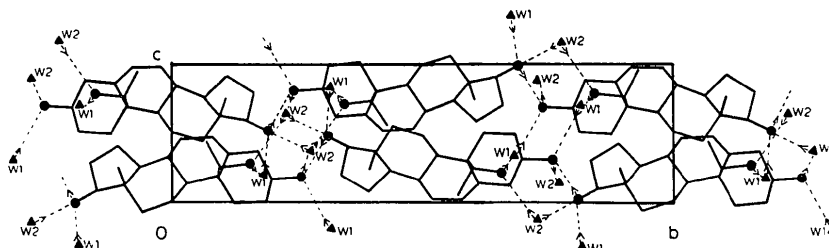


Fig. 3. Projection of the structure down the  $a$  axis. The circles represent the hydroxyl oxygens and the triangles the water oxygens.

Table 2. *Hydrogen-bond distances (Å) and angles (°)*

	O...O	H...O	O-H...O	Symmetry operator
O(3)—H...O(W2)	2.750	1.82	143	$\frac{1}{2}-x, 2-y, \frac{1}{2}+z$
O(17)—H...O(3)	2.878	2.06	164	$-x, \frac{1}{2}+y, -\frac{1}{2}-z$
O(19)—H...O(W1)	2.716	1.91	173	$-x, -\frac{1}{2}+y, -\frac{1}{2}-z$
O(W1)—H <sub>A</sub> ...O(17)	2.841	1.92	156	$\frac{1}{2}+x, \frac{3}{2}-y, -1-z$
O(W1)—H <sub>B</sub> ...O(3)	2.878	1.94	146	$\frac{1}{2}-x, 2-y, \frac{1}{2}+z$
O(W2)—H <sub>A</sub> ...O(17)	2.988	2.37	116	$x, y, z$
O(W2)—H <sub>B</sub> ...O(19)	2.838	1.96	165	$-x, \frac{1}{2}+y, -\frac{1}{2}-z$

has only two hydrogen bonds, while all of the remaining oxygens are involved in three hydrogen bonds. A list of the hydrogen bonds is given in Table 2. There are no unusual non-bonded contacts.

In a proposed reaction mechanism for the stereospecific methyl lithium reaction of 3 $\beta$ ,17 $\beta$ -diacetoxy-5-androsten-19-al to the corresponding 19-hydroxy-19-methyl derivative, the newly formed asymmetric center at C(19) was assigned an *R* configuration (Caspi & Wicha, 1966; Wicha & Caspi, 1968, 1969). This assignment was based on the following: (1) a C(1) eclipsed conformation of the C(19) aldehyde in the starting material was preferred; (2) the methyl lithium approached C(19) from between the *A* and *C* rings, rather than from over the *B* ring; (3) the methyl substituent was locked into the position between the *A* and *C* rings for steric reasons; (4) the formation of a hemiketal derivative across the *A* ring between C(19) and C(3) through the C(19) hydroxyl indicated that the hydroxyl must be located over the *A* ring. The proposed mechanism and the resulting configurational assignment of C(19) have been the source of conflicting reports (Skinner & Akhtar, 1969; Osawa, 1972; Osawa, Shibata, Rohrer, Weeks & Duax, 1975). The crystallographic results from this structure determination clearly show that the configurational assignment of C(19) as *R* is incorrect. The conformation of the hydroxyl over the *A* ring (Fig. 4) explains how the hemiketal derivative can be formed across the *A* ring. Furthermore, the location of the C(19) methyl substituent over the *B* ring in this structure suggests that the methyl lithium approaches C(19) from over the *B* ring rather than from between the *A* and *C* rings. The steric availability of this direction of approach is also indicated by the conformation of the (19*R*) isomer, where

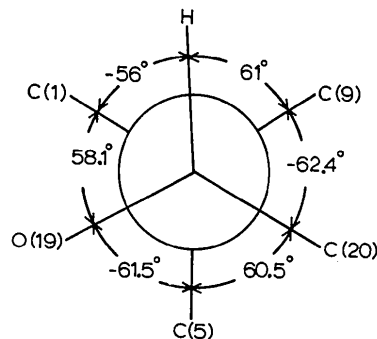


Fig. 4. A Newman projection viewed from C(19) to C(10) showing the conformation of the C(19) substituents.

the methyl substituent is also located over the *B* ring. These results support our earlier proposals regarding this reaction, the similar tritiated sodium borohydride reduction of C(19) aldehydes and the mechanism of estrogen biosynthesis (Osawa, 1972; Osawa, Shibata, Rohrer, Weeks & Duax, 1975).

The authors wish to express their gratitude to Miss M. Tugac for her assistance in the preparation of the illustrations and to Dr K. Shibata for the synthesis of this compound. This work has been supported by Grant No. CA-10906 awarded by the National Cancer Institute, and Grant No. HD-04945 awarded by the National Institute of Child Health and Human Development of DHEW.

#### References

- ALTONA, C., GEISE, H. J. & ROMERS, C. (1968). *Tetrahedron*, **24**, 13-32.

- CASPI, E. & WICHA, J. (1966). *Chem. Commun.* **7**, 209–210.  
 GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* **A22**, 368–376.  
 JOHNSON, C. K. (1970). *ORTEP*. Oak Ridge National Laboratory Report ORNL-3794.  
 OSAWA, Y. (1972). *Endocrinology*. Proc. Fourth Int. Congr. of Endocrinology, Washington, edited by R. O. SCOW, pp. 814–819. Amsterdam: Excerpta Medica.  
 OSAWA, Y., SHIBATA, K., ROHRER, D., WEEKS, C. & DUAX, W. L. (1975). *J. Amer. Chem. Soc.* **97**, 4400–4402.  
 ROHRER, D. C., WEEKS, C. M., OSAWA, Y. & DUAX, W. L. (1976). *J. Med. Chem.* **19**, 410–414.  
 SKINNER, S. J. M. & AKHTAR, M. (1969). *Biochem. J.* **114**, 75–81.  
 STOUT, G. H. & JENSEN, L. H. (1968). *X-ray Structure Determination*. New York: Macmillan.  
 WICHA, J. & CASPI, E. (1968). *J. Chem. Soc. (C)*, pp. 1740–1746.  
 WICHA, J. & CASPI, E. (1969). *J. Chem. Soc. (C)*, pp. 947–951.

*Acta Cryst.* (1976). **B32**, 2413

## Configuration de l'Ion Ruthénate: Structure Cristalline du Dihydroxotrioxoruthénate(VI) de Baryum, Ba[RuO<sub>3</sub>(OH)<sub>2</sub>]

PAR G. NOWOGROCKI

*U.E.R. Sciences exactes et naturelles, Université de Picardie, 33 rue Saint Leu, 80039 Amiens Cédex, France*

ET F. ABRAHAM, J. TRÉHOUX ET D. THOMAS

*Laboratoire de Cristallographie, U.E.R. de Chimie, Université des Sciences et Techniques de Lille, B.P. 36, 59650 Villeneuve d'Ascq, France*

(Reçu le 25 février 1976, accepté le 16 mars 1976)

The structure of so-called barium ruthenate monohydrate has been determined from three-dimensional diffractometer data by Fourier and full-matrix least-squares methods. Crystal data show evidence of a hexagonal subcell:  $a = 5.787$ ,  $c = 8.491$  Å,  $Z = 2$ , space group  $P6_3/mmc$ . In this subcell, refinement to  $R_1 = 0.033$  indicates partial occupancy of the O atom sites which can be explained by steric considerations. Refinement of the actual structure was carried out in a rhombohedral cell (hexagonal parameters  $a' = a/\sqrt{3} = 10.023$ ,  $c' = 3c = 25.471$  Å,  $Z = 18$ , space group  $R\bar{3}c$ ) to  $R_1 = 0.023$ . The dihydroxotrioxoruthenate(VI) ions have a trigonal-bipyramid configuration with three short Ru–O bonds (1.755 Å) and two longer Ru–OH bonds (2.02 Å). They form six layers of  $[\text{RuO}_3(\text{OH})_2]^{2-}$  ions, stacked perpendicularly to the  $c'$  axis and separated by  $\text{Ba}^{2+}$  ions. Stacking defects in the succession of the layers lead to a statistical hexagonal symmetry.

### Introduction

Lors d'une étude antérieure, les caractéristiques cristallographiques du ruthénate de baryum monohydraté BaRuO<sub>4</sub>·H<sub>2</sub>O ont été précisées (Nowogrocki, Thomas & Tridot, 1967): la maille de symétrie hexagonale ( $a = 5,79$ ,  $c = 8,46$  Å) contient deux unités formulaires. L'exploitation de mesures d'intensité sur film permet de déterminer sans difficulté la position des atomes métalliques mais celle des atomes d'oxygène ne put être menée à bien. Un examen plus attentif des enregistrements photographiques révèle la présence d'un petit nombre de réflexions, de faible intensité, incompatibles avec la maille annoncée. Dans les diagrammes de cristal tournant autour de  $c$ , elles sont disposées sur des strates intermédiaires, nécessitant la multiplication du paramètre suivant  $c$  par trois. L'exploration de ces strates par la méthode de Weissenberg conduit à définir une maille  $H'$  qui se déduit de la précédente ( $H$ ) à l'aide des relations:  $\mathbf{a}' = \mathbf{a} - \mathbf{b}$  et  $\mathbf{c}' = 3\mathbf{c}$ . Les para-

Tableau 1. *Données cristallographiques de BaRuO<sub>4</sub>·H<sub>2</sub>O*

	$H$	$H'$
Système cristallin	Hexagonal	Rhomboédrique
Paramètres	$a = 5,787$ Å $c = 8,491$	$a' = 10,023$ Å $c' = 25,471$ (axes hexagonaux)
Groupe spatial	$P6_3/mmc$	$R\bar{3}c$
$D_m$	4,25 g cm <sup>-3</sup>	
$D_c$	4,32	
$Z$	2	18

mètres ont été précisés lors des mesures d'intensité sur monocristal et sont rassemblés dans le Tableau 1.

L'étude structurale a donc été reprise sur ces nouvelles bases.

### Partie expérimentale

Le monocristal choisi, préparé selon la technique décrite précédemment (Nowogrocki *et al.*, 1967), se