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## 21-Acetoxy-16 $\alpha$ -propionoxy-11 $\beta$ ,17 $\alpha$ -dihydroypregna-1,4-diene-3,20-dione Monohydrate

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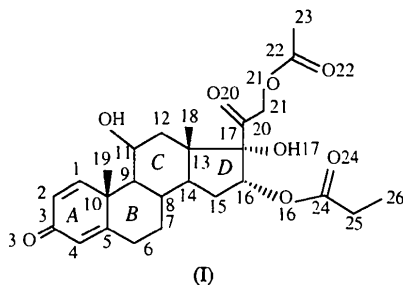
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### Abstract

The title steroid derivative, 21-acetoxy-11 $\beta$ ,17 $\alpha$ -dihydroxy-3,20-dioxopregna-1,4-dienyl 16 $\alpha$ -propionate monohydrate, C<sub>26</sub>H<sub>34</sub>O<sub>8</sub>·H<sub>2</sub>O, crystallizes in the *P6*<sub>1</sub> space group. The hydrogen-bonded steroid molecules, related by a hexagonal screw axis, form a cylindrical tunnel containing a disordered water chain.

### Comment

The title compound, (I), a diester of 16 $\alpha$ -hydroxy-prednisolone, was prepared by Infarm Co. Ltd as part of a research program based on the synthesis of new corticoid derivatives.



A view of (I) is shown in Fig. 1. The bond lengths and valency angles (Table 2) are within the ranges of mean values for steroid structures (Duax & Norton, 1975). In the propionate moiety, the C24—C25 and C25—C26 bond lengths are probably affected by the thermal vibrations of the terminal C25 and C26 atoms.

The O3 atom deviates from the plane of ring A [planar within 0.014(3) Å] by 0.032(9) Å. The plane of ring A and the mean plane through atoms C5—C17 make a dihedral angle of 42.6(2)° with one another. The distance of atom O3 from the C5—C17 plane is 2.540(7) Å.

Rings B and C both have chair conformations. The asymmetry parameters (Duax & Norton, 1975) for ring

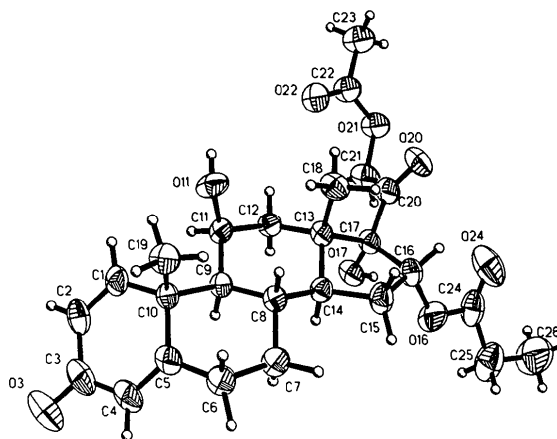


Fig. 1. A perspective drawing of the title molecule. Non-H atoms are shown as 50% probability displacement ellipsoids.

B are  $\Delta C_3(10) = 2.4(5)$ ,  $\Delta C_2(9,10) = 2.6(6)$  and  $\Delta C_2(8,9) = 9.8(3)^\circ$ , and for ring C are  $\Delta C_2(9,11) = 0.9(5)$ ,  $\Delta C_3(11) = 3.4(4)$  and  $\Delta C_3(8) = 6.7(4)^\circ$ .

Ring D adopts a slightly deformed half-chair conformation. The C13 and C14 atoms lie on opposite sides of the C15—C17 plane at respective distances of 0.49(1) and 0.29(1) Å. The asymmetry parameter  $\Delta C_2(16)$  is 3.3(5)° and the pseudo-rotation parameters  $\Delta$  and  $\varphi$  (Altona, Geize & Romers, 1968) are 8.3(1) and 49.0(2)°, respectively. The ring-junction configurations are quasi-*cis* for A/B and *trans* for both B/C and C/D.

The carbonyl O atom of the 17 $\beta$  side chain is oriented above ring D synclinal to the C13—C17 bond; the C13—C17—C20—O20 torsion angle is 83.5(6)°. Two planar fragments (C17, C20, O20, C21 and O21, C22, O22, C23) make a dihedral angle of 82.3(3)° with one another.

The relative orientation of the 16 $\alpha$  side chain with respect to the substituents at C17 is given by the O16—C16—C17—C20, O16—C16—C17—O17 and O16—C16—C17—C13 torsion angles, which have values of  $-104.9(5)$ ,  $19.5(6)$  and  $134.2(4)^\circ$ , respectively. The C16, O16, C24, O24, C25 fragment is planar within 0.038(4) Å.

The most interesting feature of the present study is the molecular arrangement in the hexagonal lattice. A fragment of the crystal packing is shown in Fig. 2. The planar A rings of the steroid molecules form a helical chain around a hexagonal screw axis. The diameter of the hole is 6.7 Å (calculated as the H2...H2 maximum distance on a projection perpendicular to [001]). Inside the hole, another helical chain is created by the water molecules surrounding the 6<sub>1</sub> axis, with distances of 2.97(1) Å between water O atoms. The refinement part of the structure investigation indicated the strong disorder of the water O100 atoms. The nearest approaches of the water O atoms to the steroid atoms are

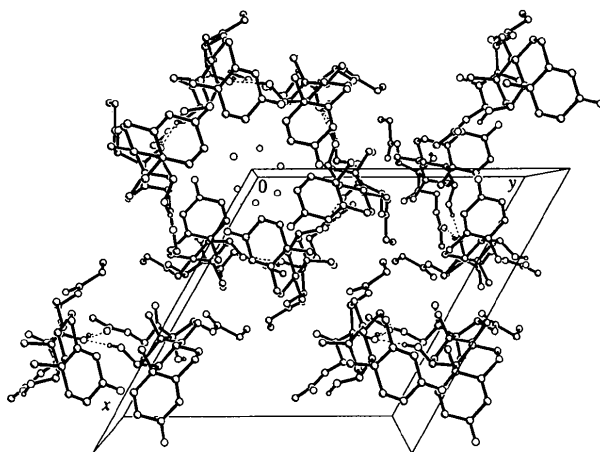


Fig. 2. Packing diagram viewed down the *c* axis. The water O atoms are shown as six circles enclosing the  $6_1$  axis. H atoms, except for H110 and H170, have been omitted for clarity.

O3...O100<sup>i</sup> of 3.15 (3) and H211...O100 of 2.80 (8) Å [symmetry code: (i)  $-x + y, -x, z + \frac{2}{3}$ ].

The hexagonal symmetry of the crystals is stabilized by intermolecular hydrogen bonds. The O17 atom, as both a donor and an acceptor, is hydrogen bonded to the carbonyl O22 atom and the hydroxyl O11—H group of adjacent molecules; H170...O22<sup>ii</sup> 2.03 (9), O17...O22<sup>ii</sup> 2.827 (5) Å and O17—H...O22<sup>ii</sup> 164 (7)°, and H110...O17<sup>iii</sup> 2.11 (7), O11...O17<sup>iii</sup> 2.928 (5) Å and O11—H...O17<sup>iii</sup> 168 (6)° [symmetry codes: (ii)  $y, -x + y, z - \frac{1}{6}$ ; (iii)  $x - y, x, z + \frac{1}{6}$ ].

## Experimental

Crystals of the title compound were obtained by slow evaporation of a 1:1 ethanol/tetrachloromethane solution.

### Crystal data

C<sub>26</sub>H<sub>34</sub>O<sub>8</sub>·H<sub>2</sub>O

*M<sub>r</sub>* = 492.55

Hexagonal

*P*6<sub>1</sub>

*a* = 17.172 (4) Å

*c* = 14.965 (9) Å

*V* = 3822 (3) Å<sup>3</sup>

*Z* = 6

*D<sub>x</sub>* = 1.284 Mg m<sup>-3</sup>

*D<sub>m</sub>* not measured

Cu *K*α radiation

λ = 1.54178 Å

Cell parameters from 30 reflections

θ = 17.6–24.8°

μ = 0.800 mm<sup>-1</sup>

*T* = 293 (2) K

Transparent needle

0.65 × 0.26 × 0.18 mm

Colorless

### Data collection

Kuma KM-4 four-circle diffractometer

ω/θ scans

Absorption correction: none

2947 measured reflections

2700 independent reflections

1874 observed reflections

[*I* > 2σ(*I*)]

*R*<sub>int</sub> = 0.0277

θ<sub>max</sub> = 80.4°

*h* = -18 → 0

*k* = 0 → 21

*l* = 0 → 15

3 standard reflections

monitored every 100 reflections

intensity decay: <1%

### Refinement

Refinement on *F*<sup>2</sup>

*R*(*F*) = 0.0580

*wR*(*F*<sup>2</sup>) = 0.1678

*S* = 1.005

2698 reflections

421 parameters

*w* = 1/[σ<sup>2</sup>(*F*<sub>o</sub><sup>2</sup>) + (0.1141*P*)<sup>2</sup>]

where *P* = (*F*<sub>o</sub><sup>2</sup> + 2*F*<sub>c</sub><sup>2</sup>)/3

(Δ/σ)<sub>max</sub> = 0.098

Δρ<sub>max</sub> = 0.423 e Å<sup>-3</sup>

Δρ<sub>min</sub> = -0.263 e Å<sup>-3</sup>

Extinction correction:

*SHELXL93*

Extinction coefficient:

0.0023 (5)

Atomic scattering factors

from *International Tables*

for *Crystallography* (1992),

Vol. C, Tables 4.2.6.8 and

6.1.1.4)

Absolute configuration:

Flack (1983) parameter

= -0.2 (4)

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å<sup>2</sup>)

$$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> <sub>eq</sub>
O3	0.2256 (4)	0.0201 (3)	1.5285 (4)	0.084 (2)
O11	0.2204 (3)	0.3372 (3)	1.2684 (3)	0.054 (1)
O16	0.5346 (3)	0.3761 (3)	0.9807 (3)	0.068 (1)
O17	0.3580 (3)	0.2669 (2)	0.9915 (2)	0.043 (1)
O20	0.3757 (3)	0.4741 (3)	0.9331 (3)	0.063 (1)
O21	0.2157 (3)	0.3645 (3)	0.8528 (2)	0.054 (1)
O22	0.1618 (3)	0.3798 (3)	0.9835 (2)	0.055 (1)
O24	0.5338 (4)	0.4358 (3)	0.8516 (3)	0.085 (2)
C1	0.1997 (3)	0.1848 (4)	1.4115 (3)	0.045 (1)
C2	0.1783 (4)	0.1108 (4)	1.4556 (3)	0.053 (1)
C3	0.2472 (5)	0.0919 (4)	1.4891 (4)	0.058 (1)
C4	0.3394 (5)	0.1591 (4)	1.4732 (4)	0.054 (1)
C5	0.3634 (3)	0.2359 (3)	1.4306 (3)	0.042 (1)
C6	0.4596 (3)	0.3049 (4)	1.4127 (4)	0.049 (1)
C7	0.4773 (3)	0.3262 (4)	1.3126 (4)	0.046 (1)
C8	0.4080 (3)	0.3441 (3)	1.2670 (3)	0.035 (1)
C9	0.3123 (3)	0.2689 (3)	1.2884 (3)	0.032 (1)
C10	0.2949 (3)	0.2577 (3)	1.3924 (3)	0.036 (1)
C11	0.2375 (3)	0.2701 (3)	1.2336 (3)	0.036 (1)
C12	0.2577 (3)	0.2805 (3)	1.1337 (3)	0.037 (1)
C13	0.3509 (3)	0.3580 (3)	1.1114 (3)	0.034 (1)
C14	0.4210 (3)	0.3475 (3)	1.1652 (3)	0.036 (1)
C15	0.5099 (3)	0.4192 (4)	1.1246 (4)	0.050 (1)
C16	0.4890 (3)	0.4168 (4)	1.0242 (4)	0.045 (1)
C17	0.3851 (3)	0.3582 (3)	1.0139 (3)	0.036 (1)
C18	0.3568 (4)	0.4492 (3)	1.1294 (4)	0.047 (1)
C19	0.3078 (4)	0.3438 (4)	1.4388 (4)	0.049 (1)
C20	0.3447 (4)	0.3944 (3)	0.9466 (3)	0.044 (1)
C21	0.2607 (5)	0.3250 (4)	0.8994 (4)	0.050 (1)
C22	0.1654 (4)	0.3866 (4)	0.9023 (4)	0.050 (1)
C23	0.1162 (5)	0.4200 (5)	0.8458 (5)	0.062 (2)
C24	0.5569 (4)	0.3940 (4)	0.8955 (4)	0.061 (2)
C25	0.6112 (5)	0.3453 (6)	0.8663 (5)	0.083 (2)
C26	0.6465 (8)	0.3699 (10)	0.7756 (7)	0.122 (4)
O100	0.0663 (11)	0.1072 (13)	0.965 (2)	0.37 (2)

Table 2. Selected geometric parameters (Å, °)

O3—C3	1.244 (7)	C8—C9	1.534 (6)
O11—C11	1.422 (6)	C8—C14	1.536 (7)
O16—C24	1.322 (8)	C9—C11	1.533 (6)
O16—C16	1.440 (6)	C9—C10	1.578 (6)
O17—C17	1.434 (5)	C10—C19	1.547 (7)
O20—C20	1.212 (6)	C11—C12	1.525 (7)
O21—C22	1.329 (6)	C12—C13	1.521 (6)
O21—C21	1.437 (6)	C13—C14	1.532 (6)
O22—C22	1.221 (7)	C13—C18	1.541 (6)
O24—C24	1.179 (8)	C13—C17	1.572 (6)
C1—C2	1.312 (8)	C14—C15	1.529 (7)
C1—C10	1.509 (7)	C15—C16	1.541 (8)
C2—C3	1.463 (9)	C16—C17	1.556 (7)
C3—C4	1.438 (9)	C17—C20	1.521 (7)
C4—C5	1.331 (7)	C20—C21	1.511 (8)

C5—C6	1.499 (8)	C22—C23	1.496 (8)
C5—C10	1.514 (7)	C24—C25	1.592 (11)
C6—C7	1.536 (8)	C25—C26	1.459 (12)
C7—C8	1.530 (7)		
C24—O16—C16	119.3 (5)	C12—C13—C18	110.9 (4)
C22—O21—C21	116.4 (4)	C14—C13—C18	111.8 (4)
C2—C1—C10	124.1 (5)	C12—C13—C17	115.8 (4)
C1—C2—C3	121.5 (6)	C14—C13—C17	99.9 (3)
O3—C3—C4	122.5 (6)	C18—C13—C17	109.0 (4)
O3—C3—C2	120.5 (6)	C15—C14—C13	102.9 (4)
C4—C3—C2	117.0 (5)	C15—C14—C8	119.5 (4)
C5—C4—C3	123.0 (6)	C13—C14—C8	114.7 (4)
C4—C5—C6	122.8 (5)	C14—C15—C16	103.9 (4)
C4—C5—C10	122.2 (5)	O16—C16—C15	106.1 (4)
C6—C5—C10	114.9 (4)	O16—C16—C17	111.6 (4)
C5—C6—C7	111.8 (4)	C15—C16—C17	106.9 (4)
C8—C7—C6	113.7 (4)	O17—C17—C20	109.1 (4)
C7—C8—C9	110.6 (4)	O17—C17—C16	111.7 (4)
C7—C8—C14	109.8 (4)	C20—C17—C16	114.2 (4)
C9—C8—C14	108.3 (4)	O17—C17—C13	107.4 (4)
C11—C9—C8	115.4 (4)	C20—C17—C13	111.6 (4)
C11—C9—C10	114.9 (4)	C16—C17—C13	102.5 (4)
C8—C9—C10	111.5 (4)	O20—C20—C21	121.3 (5)
C1—C10—C5	112.1 (4)	O20—C20—C17	122.7 (5)
C1—C10—C19	106.5 (4)	C21—C20—C17	116.0 (4)
C5—C10—C19	108.0 (4)	O21—C21—C20	112.4 (5)
C1—C10—C9	110.4 (4)	O22—C22—O21	122.3 (5)
C5—C10—C9	106.3 (4)	O22—C22—C23	126.1 (5)
C19—C10—C9	113.5 (4)	O21—C22—C23	111.6 (5)
O11—C11—C12	113.0 (4)	O24—C24—O16	122.1 (6)
O11—C11—C9	109.2 (4)	O24—C24—C25	129.1 (6)
C12—C11—C9	112.5 (4)	O16—C24—C25	108.8 (6)
C13—C12—C11	113.4 (4)	C26—C25—C24	111.8 (8)
C12—C13—C14	109.0 (4)		

The structure of the title compound was solved by direct methods in the *P*<sub>6</sub><sub>1</sub> and *P*<sub>6</sub><sub>5</sub> space groups. Each of the *E* maps revealed all the non-H atoms of the steroid molecule and a low additional peak for the second molecule. Initial isotropic and anisotropic refinement cycles for only the steroid molecule gave a high final *R* value of 0.071, a peak of 1.17 e Å<sup>-3</sup> near the *b*<sub>1</sub> axis on the difference map, large e.s.d.'s for the positional parameters and significant differences between observed and calculated structure factors for a few reflections with small indices. All parameters were corrected after the setting of the peak by the O atom, with a site occupancy factor of 1, before isotropic refinement. As the presence of water molecules in the ratio 1:1 was confirmed by elemental analysis of the crystal, the water O atoms must be strongly disordered. The calculated percentage content of carbon is 65.8% for the unsolvated compound and 63.4% for the monohydrate compound, while the amount of carbon found was 63.6 (3)%. A similar problem with the hexagonal molecular arrangement has been discussed for the structure of avarol (Puliti, De Rosa & Mattia, 1994). The water H atoms could not be located from the difference maps. The alkyl H atoms at the C23, C25 and C26 atoms were fixed geometrically with riding models and *U* = 1.2*U*<sub>eq</sub>(C). All other H atoms were located from the difference Fourier map and refined isotropically. The absolute structure was assigned to agree with the known configuration of the main steroid skeleton in the *P*<sub>6</sub><sub>1</sub> space group. Parallel refinement of the unsuitable enantiomer in the *P*<sub>6</sub><sub>5</sub> space group gave the same *R* = 0.058 and *wR* = 0.1477 values as for the *P*<sub>6</sub><sub>1</sub> group.

Data collection: *Kuma KM-4 Software* (Kuma, 1991). Cell refinement: *Kuma KM-4 Software*. Data reduction: *Kuma KM-4 Software*. Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990*a*). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics:

*SHELXTL/PC* (Sheldrick, 1990*b*). Software used to prepare material for publication: *SHELXL93*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and torsion angles have been deposited with the IUCr (Reference: KA1173). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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## (*R*<sub>S</sub>)-4-*p*-Toluenesulfinylcyclohexa-1,4-diene-carboxylic Acid Ethyl Ester

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## Abstract

The structure determination of C<sub>16</sub>H<sub>18</sub>O<sub>3</sub>S by single-crystal X-ray diffraction revealed the *para* regiochemistry of the title compound.

## Comment

In connection with our interest in using chiral sulfoxides in asymmetric synthesis, we have studied both the reactivity and selectivity of enantiopure sulfinyl heterodiene