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17-Oxo-17a-oxa-17a-homo-5α-androstan-3α,4β-diyl diacetate

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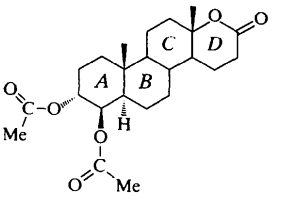
Abstract

The title compound, $C_{23}H_{34}O_6$, a ring *D* lactone, has two acetoxy groups in positions 3α and 4β. All ring junctions are *trans* which results in a planar molecule. The two acetoxy groups have different behaviour, one of them being disordered and exhibiting double-bond delocalization. The ordered acetoxy group is involved in two weak intramolecular C—H···O bonds.

Comment

The title compound, (I), is the diacetate form of the 3α,4β-dihydroxy-17a-oxa-17a-homo-5α-androstan-17-one, a key intermediate for the synthesis of a previously prepared potential aromatase inhibitor 4-hydroxy-17a-oxa-17a-homoandrost-4-ene-3,17-dione (Tavares da Silva *et al.*, 1997). It was prepared in order to study the conformation and molecular interactions of steroids related with aromatase inhibition (Paixão *et al.*, 1998).



(I)

The X-ray analysis gives ring bond lengths and angles in good agreement with expected values (Paixão *et al.*, 1998). The two acetoxy groups are in positions 3α and 4β. The 4β acetoxy group has bond lengths and valence angles within normal values and its constituent atoms (O4, C41, C42, O41) are highly coplanar [sum of the valence angles about C41 is 360.0 (7)°] as expected from the double bond between C41 and O41. In the 3α acetoxy group, the O3—C31 bond length approaches the value of a delocalized double bond similar to that of carboxylate anions. Furthermore, the structure refinement shows that this group is disordered over two positions in such a way that the 50.3 (8)% occupied site appears to have a normal C31—O31*B* double bond and the 49.7 (8)% occupied site appears to have a longer C31—O31*A* bond relative to the characteristic lengths in a *gem*-diol (*International Tables for Crystallography*, 1995, Vol. C). Both disordered components have a small distortion from the expected coplanarity of an acetoxy group [sums of valence angles around C31 are 346.7 (7) and 348.4 (7)°].

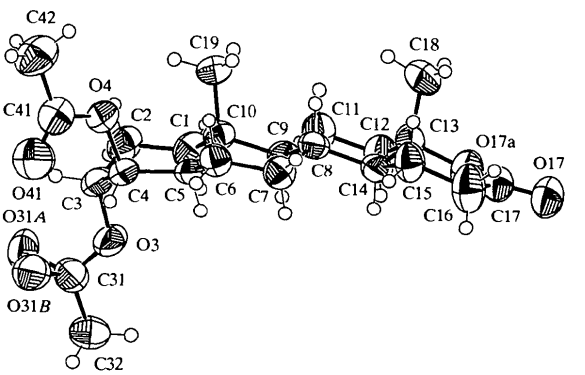


Fig. 1. *ORTEP*II (Johnson, 1976) plot of the title compound. Displacement ellipsoids are drawn at the 50% probability level.

The distance between terminal-O atoms O31*A* and O17 is 12.424 (6) Å. The pseudo-torsion angle C19—C10—C13—C18 is −4.0 (3)°. All ring junctions are *trans*. Rings *A*, *B* and *C* have slightly flattened chair conformations [average torsion angles 52 (4), 56 (5) and 56 (2)°, respectively]. The six-membered ring *D* characteristic of a γ-lactone has a 14α-sofa conformation [ΔC_s(14) = 4.5 (3), ΔC_2(13,14) = 15.8 (4) and ΔC_2(15,16) = 41.0 (4)°; Duax & Norton, 1975].

There are no classical hydrogen bonds in this compound and cohesion of the structure is mainly due to van der Waals interactions. However, two short contacts that may correspond to weak C—H···O intramolecular interactions involving the well ordered 4β-acetoxy group should be noted [C4—H4···O41 2.677 (4) Å and C19—H19*B*···O4 3.087 (4)°]. No such intramolecular interactions exist for the 3α-acetoxy group and this may well explain why this group is disordered.

It should be stated that because none of the atoms is a strong enough anomalous scatterer at the Mo $K\alpha$ wavelength, the absolute configuration was not determined by the X-ray data, and the assumed chirality of the molecule is that determined from the route of synthesis.

Experimental

To prepare the title compound, 3α,4β-dihydroxy-17a-oxa-17a-homo-5α-androstan-17-one (100 mg, 0.32 mmol) was dissolved in dry pyridine (4.3 ml) and acetic anhydride (0.76 ml) was added. After 115 h of stirring at room temperature, the solution was diluted with dichloromethane (100 ml) and the organic phase washed with 10% aqueous hydrochloric acid (3 × 100 ml), 10% sodium hydrogencarbonate (2 × 100 ml) and water (2 × 100 ml), and then dried and evaporated to dryness to give the pure title compound (110.75 mg). ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 0.97 (3H, *s*, 19-H$_3$), 1.30 (3H, *s*, 18-H$_3$), 2.06 (3H, *s*, $COCH_3$), 2.09 (3H, *s*, $COCH_3$), 2.60 (1H, *ddd*, $J_{16\beta,16\alpha}$ = 19.0, $J_{16\beta,15\beta}$ = 9.0, $J_{16\beta,15\alpha}$ = 9.0 Hz, 16β-H), 2.71 (1H, *ddd*, $J_{16\alpha,16\beta}$ = 19.0, $J_{16\alpha,15\beta}$ = 8.5, $J_{16\alpha,15\alpha}$ = 2.5 Hz, 16α-H), 4.85 (2H, *m*, 3-H and 4-H); ^{1}C NMR (75.6 MHz, $CDCl_3$; Me_4Si): δ 13.4, 19.7, 20.0, 21.0, 21.1, 21.2, 22.1, 24.2, 28.5, 30.4, 31.8, 35.5, 37.6, 39.0, 43.3, 46.2, 53.6, 69.3, 72.8, 83.2, 169.7, 169.8, 171.5. Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of the steroid in methanol.

Crystal data

$C_{23}H_{34}O_6$
M_r = 406.50
Orthorhombic
$C222_1$
a = 14.752 (5) Å
b = 23.919 (8) Å
c = 12.505 (6) Å
V = 4412 (3) Å^3
Z = 8
D_x = 1.224 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.70930 Å
Cell parameters from 25 reflections
θ = 7.72–10.75°
μ = 0.087 mm^{-1}
T = 293 (2) K
Block
0.49 × 0.37 × 0.20 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
Profile data from ω–2θ scans
Absorption correction: none
8237 measured reflections
3886 independent reflections
1753 reflections with $I > 2\sigma(I)$
R_{int} = 0.077
θ_{max} = 24.93°
$h = 0 \rightarrow 17$
$k = -28 \rightarrow 28$
$l = -14 \rightarrow 14$
3 standard reflections
frequency: 180 min
intensity decay: 2.3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.033
$wR(F^2)$ = 0.090
S = 0.927
3886 reflections
277 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0436P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.147 e Å^{-3}
$\Delta\rho_{min}$ = −0.143 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.00147 (17)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected bond lengths (Å)*

O4—C41	1.338 (4)	C31—O31*A*	1.398 (6)
O3—C31	1.246 (3)	C31—O31*B*	1.213 (5)
O41—C41	1.204 (4)	C31—C32	1.474 (4)
C41—C42	1.483 (5)		

The H atoms of the organic moiety were placed at calculated positions and refined as riding using *SHELXL97* (Sheldrick, 1997) defaults. During the refinement, it was found that the O31 atom of the 3α-acetoxy group had an unusually anisotropic displacement ellipsoid, which was elongated in a direction perpendicular to the O3/C31/C32 plane. Considering this feature a sign of a possible disorder of the O31 atom, it was split in two sites with refinable occupancy, constrained to add up to unity. The refined occupancy converged to 0.497 (8)/0.503 (8), with a significant decrease in the R factor compared with the refinement with the atom position unsplit. Examination of the crystal structure with *PLATON* (Spek, 1995) showed that there are no voids in the crystal lattice with large enough volume to be occupied by a solvent molecule. All calculations were performed on a Pentium 150 MHz PC running LINUX.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software* (Enraf–Nonius, 1989). Data reduction: *SDP-Plus* (Frenz, 1985). Program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL97*. Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *SHELXL97*.

The authors are indebted to Dr J. C. Prata Pina for his invaluable assistance in the maintenance of the CAD-4 diffractometer and to the Cultural Service of the German Federal Republic Embassy, the Deutscher Akademischer Austauschdienst (DAAD) and the German Agency for Technical Cooperation (GTZ) for the offer of the diffractometer which enabled the experimental work to be carried out. This work was supported by Fundação para a Ciência e a Tecnologia (FCT) and 'Programa PRAXIS XXI'.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1276). Services for accessing these data are described at the back of the journal.

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Racemic 3-(3,4-dimethoxyphenyl)-5a,6,8,9-tetrahydro-1*H*,7*H*-pyrano[4,3-*b*][1]benzopyran-1-one, an active antitumor agent†

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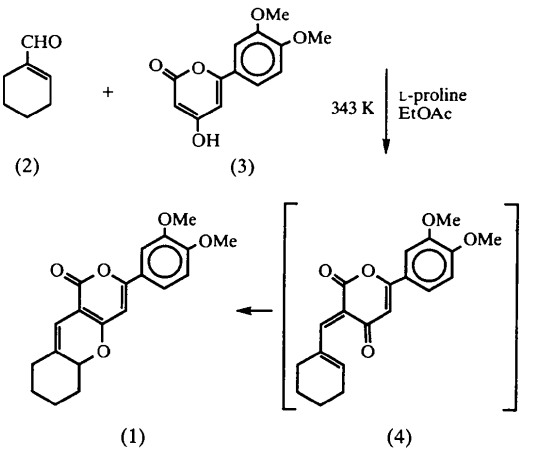
Abstract

The title racemic compound, $C_{20}H_{20}O_5$, an antitumor agent, was obtained from the condensation reaction of 2-cyclohexenecarboxaldehyde and 4-hydroxy-6-(3,4-dimethoxyphenyl)-2-pyrone in the presence of L-proline. The X-ray structure (173 K) shows a linear tricyclic skeleton in which the cyclohexane ring has a chair conformation, with the junction H atom axially oriented on the lone asymmetric C atom. The structure is disordered, such that the two enantiomers lie on the same site. The dimethoxyphenyl ring is virtually coplanar with the 2-pyrone ring, the angle between these two planes being 4.56 (11)°.

† Alternative name: 3-(3,4-dimethoxyphenyl)-5a,6,8,9-tetrahydro-1*H*,5a*H*-pyrano[4,3-*b*]chromen-1-one.

Comment

In search of structurally unique anticancer agents, we have synthesized several compounds of a class of tricyclic pyranopyrones *via* the condensation reactions of cyclohexenecarboxaldehydes and 6-substituted 4-hydroxy-2-pyrones (Hua, Chen, Sin *et al.*, 1997; Hua, Chen, Robinson & Meyers, 1997). During *in vitro* anticancer screening, several tricyclic pyranopyrones have exhibited pronounced activity (Newell *et al.*, 1998). The product from the reaction of 1-cyclohexenecarboxaldehyde, (2), with 4-hydroxy-6-(3,4-dimethoxyphenyl)-2-pyrone, (3), in the presence of L-proline (see reaction scheme) was found to possess exceptional inhibitory activity against DNA, RNA and protein synthesis. Purification of this product through silica gel column chromatography with a gradient mixture of hexane–diethyl ether as eluant afforded an orange product whose absolute structure could not be determined from its elemental and spectral analysis alone. It was necessary to turn to X-ray crystal-structure analysis for unambiguous characterization. The isolated material exhibited zero optical rotation. It was crystallized from diethyl ether as orange single crystals, shown by X-ray diffraction to be racemic 3-(3,4-dimethoxyphenyl)-5a,6,8,9-tetrahydro-1*H*,7*H*-pyrano[4,3-*b*][1]benzopyran-1-one, (1), formed *via* electrocyclization of the intermediate, (4).



The molecular structure of (1) at 173 K, with the atom-numbering scheme (Fig. 1), shows the compound to have the predicted tricyclic linear skeleton with near-coplanarity of the C3-dimethoxyphenyl and pyrone rings, the angle between these two planes being 4.56 (11)°, similar to that in biphenyl (Baudour & Sanquer, 1983). The *meta*-methoxy group (C14-methoxy) is *syn* to the pyrone carbonyl. The structure is disordered, such that both enantiomers of (1) lie on the same site and most of their equivalent atoms are superimposed and occupy the same positions. With the exception of the C7 atoms, the atoms of the cyclohexane rings, which