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9α-Fluoro-16α-methyl-3,11-dioxoandrosta-1,4-diene-17β-carboxylic acid: catemeric hydrogen bonding and acetic acid solvation in a steroidal keto acid related to dexamethasone

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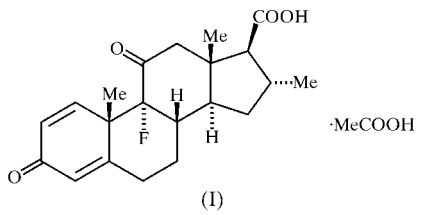
The title keto acid crystallizes as a solvate, $C_{21}H_{25}FO_4\cdot C_2H_4O_2$, with two molecules each of steroid and acetic acid per asymmetric unit. The former are approximately parallel, with opposite end-to-end orientation, and form translational carboxyl-to-ketone hydrogen-bonding catemers [O···O = 2.679 (6) and 2.650 (5) Å, and O—H···O = 165 and 162°] that involve the 3-ketone group and follow the *a* axis. The acetic acid molecules are paired by hydrogen bonding, and neither they nor the F atom nor the 11-ketone group play any overt role in the hydrogen-bonding scheme of the steroid. Intermolecular C—H···O=C close contacts involving three different neighboring molecules exist to the 11-ketone group, the steroidal carboxyl group and one of the acetic acid molecules.

Comment

In keto carboxylic acids, centrosymmetric acid pairing that excludes the ketone group dominates the hydrogen-bonding modes. However, in chiral non-racemates, that prevalence yields to non-centrosymmetric patterns and, particularly when



(I)

significant conformational restrictions are present, the incidence of acid-to-ketone catemers rises dramatically (Brunskill *et al.*, 1997). In our study of these hydrogen-bonding modes we have therefore often sought keto acids with terpenoid origins as subject materials, and we now report the crystal structure and hydrogen-bonding behavior of the title steroid, (I). Compound (I) is related to a synthetic anti-inflammatory glucocorticoid and is the ninth in our series of steroidal keto acid structures.

Fig. 1 shows the asymmetric unit. The upper molecule, (I), which is oriented approximately parallel to (I′), has identical but unprimed numbering. (I′) differs from (I) only by rotation of the acid about the C17—C20 bond, the only significant conformational option present. The carboxyl group in both (I) and (I′) is turned so that the C16—C17 bond lies near the plane of the carboxyl group, with the C=O bond turned toward C16. In (I), the C16—C17—C20—O3 torsion angle is −12.6 (9)°, while in (I′) it is −2.5 (9)°. The dihedral angle between the carboxyl (C17/C20/O3/O4) and ketone planes (C2/C3/C4/O1) is 14.2 (4)° for (I) and 9.8 (4)° for (I′). In both (I) and (I′), the three methyl groups are all staggered relative to the C atoms to which they are attached (C10, C13 and C16), without discernible disorder. The *A* ring is highly planar (Thompson *et al.*, 1999), with none of its six C atoms deviating from the average plane by more than 0.032 (4) Å in either (I) or (I′).

Complete or partial averaging of C—O bond lengths and C—C—O angles by disorder is frequent in carboxyl dimers (Leiserowitz, 1976) but cannot occur in catemeric hydrogen bonding, whose geometry precludes the disordering processes. In (I), these bond lengths are 1.195 (7) and 1.335 (8) Å, with angles of 126.8 (7) and 111.4 (6)°; for (I′), the lengths are 1.208 (7) and 1.333 (7) Å, and the angles are 125.3 (6) and 112.9 (5)°. Our own survey of 56 keto acid structures that are

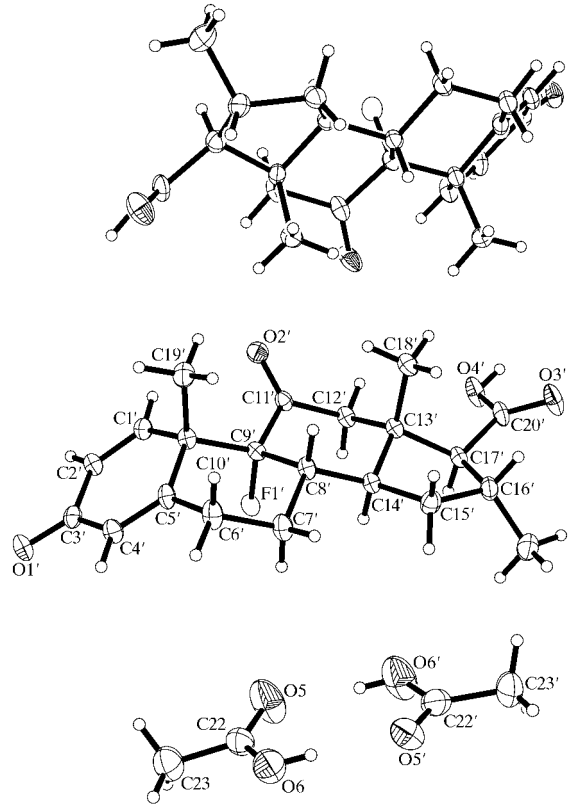


Figure 1
A view of the title compound, with the steroidal numbering shown for molecule (I′); molecule (I) has identical but unprimed numbering. Displacement ellipsoids are shown at the 20% probability level.

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not acid dimers gives average values of 1.200 (10) and 1.32 (2) Å, and 124.5 (14) and 112.7 (17)°, for these lengths and angles, in agreement with typical values of 1.21 and 1.31 Å, and 123 and 112°, cited for highly ordered dimeric carboxyl groups (Borthwick, 1980). The acetic acid molecules are paired by hydrogen bonding as dimers in which disorder is possible. However, by the usual criterion of averaging or partial averaging in C—O bond lengths and C—C—O angles, one of the acetic acid molecules appears significantly more ordered than the other. In (I), these lengths are 1.201 (9) and 1.270 (10) Å, with angles of 121.2 (9) and 116.3 (8)°, while in (I′), the lengths are 1.238 (9) and 1.268 (11) Å, and the angles are 120.7 (9) and 116.9 (9)°. In the absence of any obvious mechanism by which two coupled halves of such a dimer might display different degrees of disorder, the significance of these differences is not apparent.

Fig. 2 shows one of the two asymmetric units within the cell, with extracellular molecules included to illustrate the counter-directional hydrogen-bonding chains created by the catemeric acid-to-ketone hydrogen bonding among translationally related molecules [O···O = 2.679 (6) and 2.650 (5) Å, and O—H···O = 165 and 162° for (I) and (I′), respectively; Table 1]. The second asymmetric unit (not shown) is screw-related to the first (in *b*) and generates a second pair of catemers that are screw-related to those shown. The net result is two translational chains of molecules oriented in each direction along *a*, including one counter-directional pair of catemers of type (I) and another pair of type (I′).

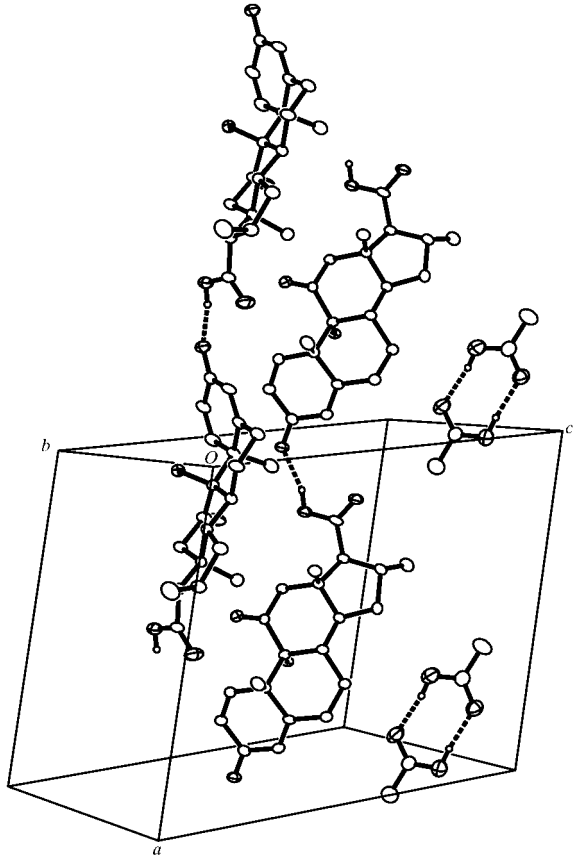

Figure 2
A partial packing diagram, showing the two molecules of the asymmetric unit, with extracellular molecules included to illustrate one of the two sets of counter-directional translational catemers passing through the cell in the *a* direction. All H atoms bound to C atoms have been omitted for clarity. Displacement ellipsoids are shown at the 20% probability level.

Except for the complexity arising here because Z' is 2, this catemeric hydrogen-bonding arrangement closely resembles those found for 3-oxoandrosta-1,4-diene-17β-carboxylic acid (Thompson *et al.*, 1999) and 3,11-dioxoandrost-4-ene-17β-carboxylic acid (Newman *et al.*, 2002), which share important structural features with (I). In both those cases, as in (I), hydrogen bonding extends catemerically from the carboxyl to the 3-ketone group, and the units of the hydrogen-bonded chain are translationally related. Because the catemers in (I) are translational, the intermolecular dihedral angle between the ketone and carboxyl planes for each hydrogen bond is the same as the corresponding intramolecular dihedral angle.

Neither the acetic acid molecule nor the F atom plays any obvious role in the hydrogen-bonding scheme of the steroid. It appears that the acetic acid serves to fill a void left by the stacking and hydrogen bonding of the steroid molecules. This idea is reinforced by the apparent ease with which (I) loses solvent, as evidenced by the odor of acetic acid that accumulates in closed vials of (I). The occupancy of the acetic acid molecules in (I) was 0.969 (6), based on refinement optimization for all atoms in both acetic acid molecules. The observed hydrogen bonding involves only the *A* ring ketone, with the 11-ketone function also playing no part in the hydrogen bonding. We have now examined 3-keto-steroids with additional ketone functionality at either the 6- (*B* ring) or the 11-position (*C* ring) but have yet to observe any involvement of those functions in the hydrogen-bonding schemes.

Within the 2.7 Å range we employ as our standard criterion (Steiner, 1997) three non-bonded intermolecular C—H···O═C packing interactions exist for molecule (I) of the steroid, *viz.* one for the *C* ring ketone (2.66 Å to H7′*B* in a screw-related neighbor) and two for the carboxyl group (2.68 Å to H23*F* and 2.60 Å to H4*A* in different translationally related neighbors). In addition, molecule (I′) has a 2.57 Å contact between O3′ and H4′*A* in a translationally related neighbor. Two close contacts exist for O5′ in acetic acid (2.67 Å to H7*B* and 2.63 Å to H12*B* in neighbors related by a translation and a screw, respectively). Using compiled data for a large number of C—H···O contacts, Steiner & Desiraju (1998) have found significant statistical directionality, even as far out as 3.0 Å, and conclude that these are legitimately viewed as 'weak hydrogen bonds', with a greater contribution to packing forces than simple van der Waals attractions.

The solid-state (KBr) IR spectrum of (I) displays absorptions at 1720 (COOH and 11-ketone) and 1662 cm^{-1} (3-ketone), with an alkene absorption at 1610 cm^{-1}. In $CHCl_3$ solution, these peaks appear at 1723, 1667 and 1630 cm^{-1}.

Experimental

Compound (I), which has not been reported previously, is related to dexamethasone, a synthetic anti-inflammatory glucocorticoid.

(+)-9α-Fluoro-11β,21-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-diene (21-deoxydexamethasone), of known relative and absolute stereochemistry (Dupont *et al.*, 1974; Joly *et al.*, 1974), was purchased from Steraloids Inc. (Newport, RI, USA) and subjected to cleavage by sodium periodate in aqueous dioxane. Jones oxidation of the resulting hydroxy acid yielded (I), which was crystallized from acetic acid (m.p. 563 K, with loss of acetic acid and whitening from lower temperatures).

Crystal data

$C_{21}H_{25}FO_4\cdot C_2H_4O_2$
M_r = 420.46
Monoclinic, $P2_1$
a = 12.823 (3) Å
b = 11.269 (4) Å
c = 15.407 (4) Å
β = 102.860 (15)°
V = 2170.5 (11) Å^3
Z = 4
D_x = 1.287 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 31 reflections
θ = 2.9–10.2°
μ = 0.10 mm^{-1}
T = 296 (2) K
Thin five-sided plate, colorless
0.48 × 0.32 × 0.08 mm

Data collection

Siemens $P4$ diffractometer
$2\theta/\theta$ scans
Absorption correction: analytical (Sheldrick, 1997*b*)
T_{min} = 0.963, T_{max} = 0.993
8416 measured reflections
4036 independent reflections
2608 reflections with $I > 2\sigma(I)$
R_{int} = 0.051
θ_{max} = 25.0°
$h = -15 \rightarrow 15$
$k = -13 \rightarrow 13$
$l = -18 \rightarrow 18$
3 standard reflections every 97 reflections
intensity variation: <4%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.059
$wR(F^2)$ = 0.146
S = 1.06
4036 reflections
542 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0724P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.00
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0061 (17)

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O4—H4B···O1^{i}	0.82	1.88	2.679 (6)	165
O4′—H4′B···O1′^{ii}	0.82	1.86	2.650 (5)	162
O6—H6C···O5′	0.82	1.88	2.701 (8)	174
O6′—H6′C···O5	0.82	1.84	2.657 (10)	172

Symmetry codes: (i) $1 + x, y, z$; (ii) $x - 1, y, z$.

Friedel-related data were averaged. All steroid H atoms for (I) and (I′) were found in electron-density difference maps, but H atoms bound to C atoms were placed in calculated positions (0.97 Å for methylene H atoms, 0.98 Å for methine H atoms, 0.93 Å for vinyl H atoms and 0.96 Å for methyl H atoms) and allowed to refine as riding atoms on their respective C atoms. The displacement parameters of these H atoms were fixed at $1.2U_{eq}$ of their respective C atoms. For each acetic acid molecule, the carboxyl H atom and one methyl H atom were found in electron-density difference maps; the remaining methyl H atoms were generated geometrically. Methyl H atoms were placed 0.96 Å from the methyl C atoms, and carboxyl H atoms were placed 0.82 Å from their respective O atoms. These H atoms were allowed to refine as riding atoms on their respective parent atoms, with displacement parameters fixed at $1.2U_{eq}$(C) for methyl H atoms and $1.5U_{eq}$(O) for carboxyl H atoms. After refinement, the occupancies of the acetic acid molecules were optimized by fixing all previously refined positional and displacement-parameter values, and independently refining the occupancy of the acetic acid atoms as a single group. The absolute configuration was not determined.

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997*a*); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997*a*); molecular graphics: *SHELXP*97 (Sheldrick, 1997*b*); software used to prepare material for publication: *SHELXL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1413). Services for accessing these data are described at the back of the journal.

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