

(–)-3,6-Dioxo-5 β -cholanolic acid: hydrogen bonding in the hemihydrate of a steroidal diketo acid

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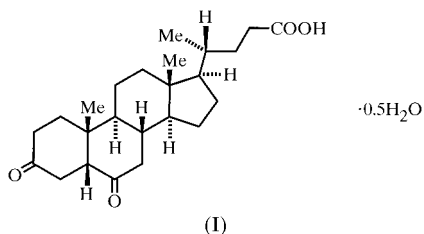
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The hemihydrate of the title diketo acid, $C_{24}H_{36}O_4 \cdot 0.5H_2O$, forms hydrogen-bonded carboxyl dimers related by a C_2 axis at crystallographic sites on the a and b edges of the chosen cell [$O \cdots O = 2.643(7)$ and $2.716(7)$ Å]. The ketone ends of the molecules approach each other at sites near $(\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$, $(\frac{1}{2}, 0, \frac{1}{2})$, $(0, 0, \frac{1}{2})$ and $(0, \frac{1}{2}, \frac{1}{2})$ in an interleaved arrangement incorporating partial-occupancy water hydrogen bonded to the B -ring ketone.

Comment

The carbonyl basicities of carboxylic acids and ketones are sufficiently similar that the two may compete as hydrogen-bond acceptors. Keto acids thus display several solid-state hydrogen-bonding modes not seen in functionally unelaborated acids. Our continuing study of the crystallography of keto acids explores the molecular characteristics that control their five known hydrogen-bonding modes. The most common of these is acid dimerization without ketone involvement, but carboxyl-to-ketone catemers constitute a sizable minority of cases. The remaining types, intramolecular hydrogen bonds, acid-to-acid catemers and carboxyl-to-ketone dimers, are all comparatively rare. In addition, about a dozen hydrates are known, having more complex hydrogen-bonding patterns (Lalancette *et al.*, 1990, 1997, 1998).



We have investigated the hydrogen-bonding motif of the title diketo acid and we describe here the structure of its hemihydrate, (I). Compound (I) (Fig. 1), present as a single enantiomer, is the sixth in a series of steroidal keto acids we have examined. Because of the rigidity of the polycyclic

structure, the major conformational options all lie in the branched chain attached at C17. Here, the substituents at C20 (which has the R configuration) are staggered with respect to those at C17, with the methyl (C21) *anti* to C16 [torsion angle $C16-C17-C20-C21$ is $-177.0(4)^\circ$]. The remainder of this chain extends generally away from the ring system, as shown, with the carboxyl turned so that the $O3-C24-C23-C22$ torsion angle is $-63.8(7)^\circ$. At the remote end of the molecule, the *cis* juncture between the two ketone rings (A and B) forces the A ring to lie at an angle to the plane of the remaining rings, creating a molecule with an angled L-shape. A partial water of hydration is found at an $O \cdots O$ distance of $2.891(8)$ Å relative to the B -ring ketone ($O2$), but we were unable to find any electron density attributable to H atoms attached to this water, at least in part because its oxygen has an occupancy of only 50%. We have therefore chosen to model the presumed hydrogen bond (shown it as a 'ghost' species in Fig. 1) to $O2$ using a water $O-H$ distance of 0.80 Å, an $H \cdots O2$ distance of 2.15 Å and an $O-H \cdots O$ angle of 153° .

Distances to the species next nearest to the water O atom are so large that they are assumed to have little bearing on the position of the second water H atom [$3.34(2)$ Å to another (partial) water and $3.55(1)$ Å to $O1$ in an adjacent molecule]. Thus, lacking a hydrogen-bonding partner, this hydrogen may well be disordered. Consequently, we have no information on the position of the remaining unfound water hydrogen and have not attempted to show it in our asymmetric unit. There are, however, two intermolecular $C-H \cdots O$ close contacts to this water oxygen (2.67 Å to $H4B$ and 2.71 Å to $H2A$), which are close enough to exclude any water hydrogen from extending in those directions. These distances lie within the range we often employ (*ca.* 2.7 Å) for non-bonded $H \cdots O$ packing interactions (Steiner, 1997). Using compiled data for a large number of $C-H \cdots O$ contacts, Steiner & Desiraju (1998) find 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.

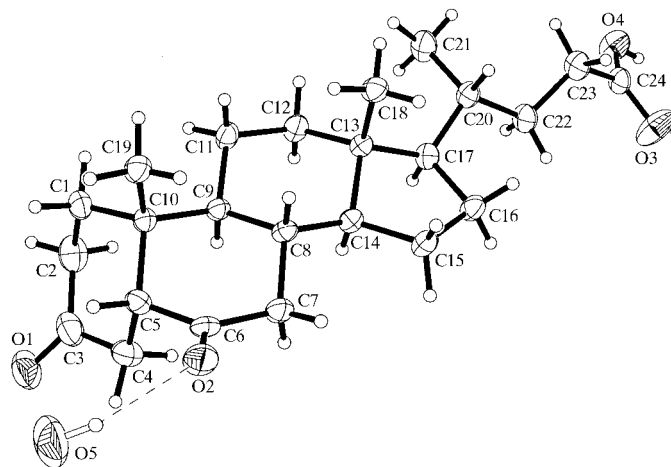


Figure 1
Compound (I) with its steroidal numbering. Half-H atoms are shown for the disordered carboxyl group and a 'ghost' H atom is shown for the partial water of hydration to illustrate its hydrogen-bonding relationship to $O2$. Displacement ellipsoids are drawn at the 20% probability level.

No disorder was detected in the three methyl groups, which all adopt staggered arrangements. However, as is frequently found in carboxyl dimers (Leiserowitz, 1976), essentially complete averaging of carboxyl C—O bond lengths and C—O angles by disorder is observed here. By contrast, values cited as typical for highly ordered dimeric carboxyls are 1.21 and 1.31 Å, and 123 and 112° (Borthwick, 1980). Consistent with this disorder, the partial carboxyl H atoms were found at appropriate positions in electron-density difference maps, and were refined with occupancies set at 50% each.

Fig. 2 illustrates the hydrogen-bond pairing of carboxyl groups at crystallographic sites along the *a* and *b* edges of the chosen cell. The participating molecules are related by a *C*₂ axis. The intermolecular O...O distances for the dimer are 2.643 (7) and 2.716 (7) Å for O4...O4' and O3...O3', respectively, and the O—H...O angles are both 165°. At sites ($\frac{1}{2}, \frac{1}{2}, \frac{1}{2}$), ($\frac{1}{2}, 0, \frac{1}{2}$), (0, 0, $\frac{1}{2}$) and (0, $\frac{1}{2}, \frac{1}{2}$), the bent ketone ends of the molecules approach each other in an arrangement which includes the partial waters of hydration hydrogen bonded to the *B*-ring ketone, as described above. Each water is hydrogen bonded only to its *B*-ring ketone and does not serve to bridge adjacent molecules. At this end of the molecule, the *A*-ring C=O groups overlap and stack with their dipoles opposed in an aligned alternating fashion that presumably maximizes attractive dipolar interactions (Lalancette *et al.*, 1998). In addition to the intermolecular close C—H...O contacts involving water described above, such close contacts were also found between O1 and H5A (2.67 Å), and between O2 and H1B (2.65 Å) in adjacent molecules.

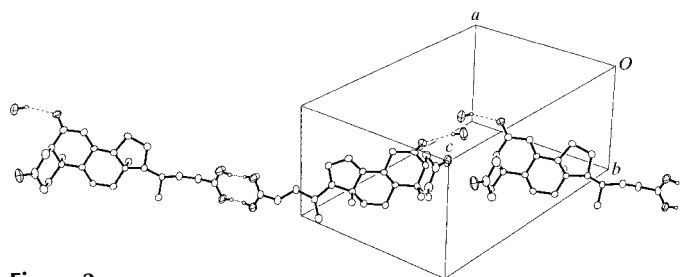


Figure 2

A partial packing diagram, with extracellular molecules to illustrate one of the carboxyl dimers and the packing of the hydrated end of the molecule. All carbon-bound H atoms have been removed for clarity and displacement ellipsoids are drawn at the 20% probability level.

Experimental

Compound (I) was purchased as the (–)-enantiomer from Steraloids Inc., Newport, RI, USA. Crystals of the hydrate, obtained from acetone, lose water at a temperature-dependent rate, giving the anhydrous form (m.p. 440 K).

Crystal data

$C_{24}H_{36}O_4 \cdot 0.5H_2O$
 $M_r = 397.56$
 Monoclinic, *C*₂
 $a = 13.144$ (3) Å
 $b = 7.750$ (2) Å
 $c = 22.415$ (5) Å
 $\beta = 100.87$ (1)°
 $V = 2242.4$ (9) Å³
 $Z = 4$

$D_x = 1.178$ Mg m⁻³
 Mo *K*α radiation
 Cell parameters from 35 reflections
 $\theta = 5.3$ – 13.2 °
 $\mu = 0.08$ mm⁻¹
 $T = 293$ (2) K
 Parallelepiped, colorless
 $0.65 \times 0.60 \times 0.10$ mm

Data collection

Siemens *P4* diffractometer
 $2\theta/\theta$ scans
 4412 measured reflections
 2127 independent reflections
 1191 reflections with $I > 2\sigma(I)$
 $R_{int} = 0.050$
 $\theta_{max} = 25.0$ °

$h = -15 \rightarrow 15$
 $k = -9 \rightarrow 9$
 $l = -26 \rightarrow 26$
 3 standard reflections
 every 97 reflections
 intensity decay: variation <1%

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.050$
 $wR(F^2) = 0.109$
 $S = 1.02$
 2127 reflections
 265 parameters

H atoms constrained
 $w = 1/[\sigma^2(F_o^2) + (0.0385P)^2]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{max} < 0.001$
 $\Delta\rho_{max} = 0.11$ e Å⁻³
 $\Delta\rho_{min} = -0.13$ e Å⁻³

Table 1

Selected geometric parameters (Å, °).

O3—C24	1.230 (6)	O4—C24	1.246 (6)
O3—C24—C23	120.7 (5)	O4—C24—C23	117.4 (5)

Table 2

Hydrogen-bonding geometry (Å, °).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
O4—H4...O4 ⁱ	0.82	1.84	2.643 (7)	165
O3—H3...O3 ⁱ	0.82	1.92	2.716 (7)	165
O5—HO5A...O2	0.80	2.15	2.891 (8)	153
C4—H4B...O5 ⁱⁱ	0.97	2.67	3.600 (12)	160
C2—H2A...O5 ⁱⁱⁱ	0.97	2.71	3.670 (12)	171
C5—H5A...O1 ⁱⁱ	0.98	2.67	3.574 (7)	154
C1—H1B...O2 ^{iv}	0.97	2.65	3.576 (7)	160

Symmetry codes: (i) $-x, y, -z$; (ii) $2-x, y, 1-z$; (iii) $2-x, 1+y, 1-z$; (iv) $x, 1+y, z$.

All C-bonded H atoms were refined as riding [$C-H = 0.96$ – 0.98 Å and $U_{iso} = 1.2U_{eq}(C)$], as were the 50% occupancy carboxyl group H atoms. The occupancy of the water O atom was fixed at 50%; an H atom (also 50% occupancy) was placed 0.85 Å from this atom in the direction of O2. The second water H atom was not found.

Data collection cell refinement and data reduction: *XSCANS* (Siemens, 1996); structure solution: *SHELXS97* (Sheldrick, 1997); structure refinement: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXL97*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1302). Services for accessing these data are described at the back of the journal.

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