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(−)-3,7-Dioxo-5β-cholanic acid: dual hydrogen-bonding modes in a diketonic bile-acid derivative

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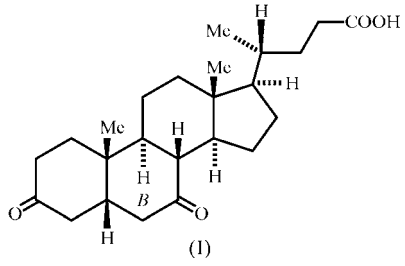
The asymmetric unit of the title compound, $C_{24}H_{36}O_4$, contains three molecules, all differing in their side-chain conformations and all linked by hydrogen bonding confined entirely within a three-molecule block. One connection is of the acid-to-ketone type [O···O = 2.7055 (19) Å and O—H···O = 180°] and the other involves carboxyl pairing [O···O = 2.6485 (18) and 2.6598 (18) Å, and O—H···O = 168 and 174°]. Numerous intermolecular C—H···O close contacts connect neighbouring molecules.

Comment

For our study of hydrogen-bonding modes in crystalline keto acids, steroid compounds are of special value as molecularly rigid single enantiomers with the potential for multiple ketone receptors. The title compound, (I), supplements our previous reports on steroidal diketo acids related to the bile acids (Thompson *et al.*, 2001; Newman *et al.*, 2002; Lalancette & Thompson, 2003). The natural bile acids all have *cis AB* ring junctions, a carboxyl group in the C17 side chain and oxygenation at the 3-position; most are oxygenated at the 6-, 7- and/or 12-positions as well. Various combinations of these acids are present in substantial quantities in vertebrate bile, where they function as surfactants, and they are isolatable directly from gall bladders. Although the ring oxygenation typically involves hydroxyl groups, a few natural bile acids contain ketone functions as well (Fieser & Fieser, 1959). Compound (I) is not known to occur naturally, but was produced by oxidation of a known natural source (see *Experimental*).



(I)

Fig. 1 shows the asymmetric unit of (I), consisting of three molecules, designated (I*A*), (I*B*) and (I*C*), which have significant conformational differences only at the extremity of the five-carbon acid chain attached at C17. Superimposition of truncated molecules lacking the carboxyl (C24) and stripped of all H atoms shows negligible differences, with r.m.s. deviations averaging less than 0.1 Å.

All three molecules have an *anti* conformational arrangement about the C20—C22 bond, but only (I*C*) also has an *anti* conformation about C22—C23, the torsion angle of which (C20—C22—C23—C24) is −174.27 (16)°. The two remaining molecules have similar *gauche* arrangements about C22—C23, with the above torsion angle being 80.2 (2)° for (I*A*) and 67.2 (2)° for (I*B*). However, these two molecules differ in the conformations of their carboxyl groups; the torsion angle O3—C24—C23—C22 is 129.8 (2)° for (I*A*) and −0.3 (3)° for (I*B*).

Values typical of C—O bond lengths and C—C—O angles in highly ordered dimeric carboxyl groups are 1.21 and 1.31 Å, and 123 and 112°, respectively (Borthwick, 1980). Full or partial averaging of these bond lengths and angles by disorder is common in dimeric acids but is invariably absent in other hydrogen-bonding modes, which cannot support the underlying averaging mechanisms. All the carboxyl groups in (I) show negligible disordering (Table 1).

Fig. 1 also illustrates the entire hydrogen-bonding scheme, which consists of molecules (I*A*), (I*B*) and (I*C*), with no hydrogen bonding beyond the three molecules shown. This leaves the two C3 ketone functions at the remote ends of this

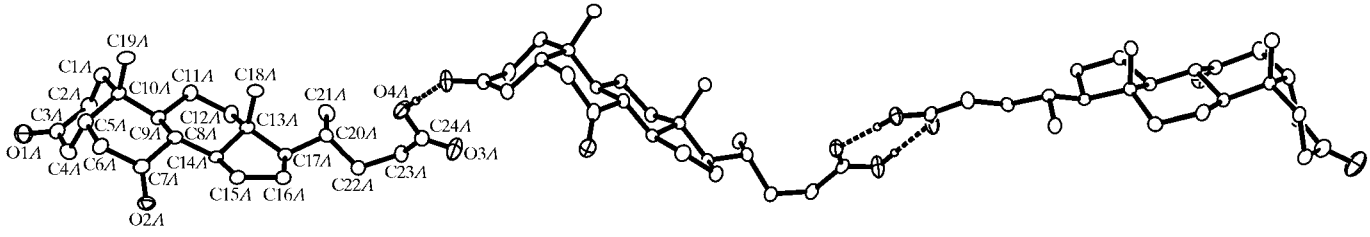


Figure 1
The asymmetric unit of (I); the three identically numbered molecules differ significantly only in their side-chain conformations. The hydrogen-bonding mode connecting (I*A*) and (I*B*) differs from that between (I*B*) and (I*C*). For clarity, all carbon-bound H atoms have been removed. Displacement ellipsoids are set at the 50% probability level.

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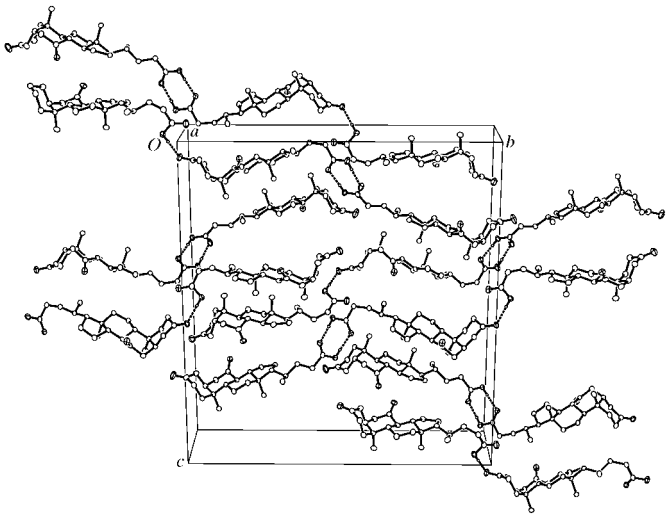

Figure 2
A partial packing diagram for (I), with extra molecules included to illustrate the three-molecule hydrogen-bonded block and its isolation from other hydrogen bonding. For clarity, all C-bound H atoms have been omitted. Displacement ellipsoids are drawn at the 50% probability level. Dashed lines indicate hydrogen bonds.

block without hydrogen-bonding partners, as is the case for all the *B*-ring ketones at C7.

Fig. 2 shows the packing of the cell with the chosen asymmetric unit and includes extra molecules to illustrate the three-molecule hydrogen-bonded block and its isolation from other hydrogen bonding. Within the 2.7 Å range we use as a standard for non-bonded H···O packing interactions (Steiner, 1997), a dozen intermolecular C—H···O close contacts exist (Table 2).

We characterize the geometry of hydrogen bonding to carbonyl groups using a combination of H···O═C angle and H···O═C—C torsion angle. These describe the approach of the acid H atom to the receptor O atom in terms of its deviation from, respectively, C═O axiality (ideal = 120°) and planarity with the carbonyl (ideal = 0°). In the acid-to-ketone connection in (I), these two angles are 124.3 and 40.2°, respectively.

The solid-state (KBr) IR spectrum of (I) has a broad C═O absorption centred at 1703 cm^{-1}, which is shifted to 1711 cm^{-1} in $CHCl_3$ solution. In addition, the KBr spectrum contains a much smaller peak at 1653 cm^{-1}, absent in $CHCl_3$ and probably due to the single ketone (of the six in the asymmetric unit) whose position is shifted by hydrogen bonding.

Experimental

3α-Hydroxy-7-oxo-5β-cholanic acid (7-ketolithocholic acid, isolatable from the bile of guinea pig and nutria), purchased from TCI America, Portland, Oregon, USA, was dissolved in acetone and subjected to Jones oxidation, yielding 92% of (I). Refrigerating an acetonitrile solution produced the crystal used (m.p. 433 K). Compound (I) may also be obtained by oxidation of either 'ursodeoxycholic' or 'chenodeoxycholic' acid, the latter being one of the two principal steroidal acids in human bile. The sign of rotation for (I) is well established (Kagan & Jacques, 1957) and the absolute stereochemistry, consistent with our experimental Flack (1983) parameter, corresponds to that of other steroids and bile acids (Fieser & Fieser, 1959; Klyne & Buckingham, 1978).

Crystal data

$C_{24}H_{36}O_4$
M_r = 388.53
Orthorhombic, $P2_12_12_1$
a = 7.61770 (10) Å
b = 27.6911 (4) Å
c = 29.9256 (4) Å
V = 6312.58 (15) Å^3
Z = 12
D_x = 1.226 Mg m^{-3}
Cu $K\alpha$ radiation
μ = 0.65 mm^{-1}
T = 100 (2) K
Block, colourless
0.22 × 0.13 × 0.12 mm

Data collection

Bruker SMART CCD APEX-II area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Blessing, 1995)
T_{min} = 0.871, T_{max} = 0.927
27061 measured reflections
10459 independent reflections
9648 reflections with $I > 2\sigma(I)$
R_{int} = 0.022
θ_{max} = 69.6°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.091
S = 1.07
10459 reflections
758 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0471P)^2 + 1.0308P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.01
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.00006 (2)
Absolute structure: Flack (1983), with 3935 Friedel pairs
Flack parameter: 0.14 (13)

Table 1
Selected geometric parameters (Å, °).

O3*C*—C24*C*	1.216 (2)	O4*B*—C24*B*	1.317 (2)
O3*B*—C24*B*	1.215 (2)	O4*C*—C24*C*	1.319 (2)
O3*A*—C24*A*	1.209 (2)	O4*A*—C24*A*	1.326 (2)
O3*B*—C24*B*—C23*B*	123.81 (16)	O4*C*—C24*C*—C23*C*	111.82 (15)
O4*B*—C24*B*—C23*B*	113.57 (15)	O3*A*—C24*A*—C23*A*	124.21 (18)
O3*C*—C24*C*—C23*C*	124.73 (16)	O4*A*—C24*A*—C23*A*	113.66 (16)

Table 2
Close-contact and hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C1*A*—H1*AA*···O1*B*^{i}	0.99	2.69	3.145 (2)	108
C4*A*—H4*AA*···O2*C*^{ii}	0.99	2.57	3.369 (2)	137
C6*A*—H6*AA*···O4*A*^{iii}	0.99	2.62	3.345 (2)	130
C11*A*—H11*F*···O2*A*^{iv}	0.99	2.67	3.495 (2)	141
C16*A*—H16*E*···O3*C*^{ii}	0.99	2.60	3.459 (2)	145
C22*A*—H22*E*···O3*C*^{ii}	0.99	2.67	3.527 (3)	145
C1*C*—H1*CA*···O4*C*^{v}	0.99	2.65	3.070 (2)	106
C2*C*—H2*CA*···O4*C*^{v}	0.99	2.65	3.297 (2)	123
C11*B*—H11*D*···O2*B*^{iv}	0.99	2.58	3.095 (2)	113
C19*B*—H19*D*···O1*C*^{vi}	0.98	2.54	3.434 (2)	152
C6*C*—H6*CB*···O4*C*^{vii}	0.99	2.66	3.223 (2)	117
C14*C*—H14*A*···O2*A*^{viii}	1.00	2.64	3.593 (2)	161
O4*A*—H4*AC*···O1*B*	0.84	1.87	2.7055 (19)	180
O4*B*—H4*BC*···O3*C*	0.84	1.81	2.6485 (19)	178
O4*C*—H4*CC*···O3*B*	0.84	1.82	2.6598 (18)	178

Symmetry codes: (i) $x-\frac{1}{2}, -y-\frac{1}{2}, -z$; (ii) $x+\frac{1}{2}, -y+\frac{1}{2}, -z$; (iii) $x+\frac{1}{2}, -y-\frac{1}{2}, -z$; (iv) $x-1, y, z$; (v) $-x+1, y+\frac{1}{2}, -z+\frac{1}{2}$; (vi) $x, y-1, z$; (vii) $-x, y+\frac{1}{2}, -z+\frac{1}{2}$; (viii) $x-\frac{1}{2}, -y+\frac{1}{2}, -z$.

All H atoms were found in electron-density difference maps but were placed in calculated positions and allowed to refine as riding on their respective C or O atoms. The O—H distances were fixed at 0.84 Å. For methyl, methylene and methine H atoms, C—H distances were fixed at 0.98, 0.99 and 1.00 Å, respectively. U_{iso}(H) values were set at $1.5U_{eq}$(parent) for H atoms on O and methyl C atoms, and at $1.2U_{eq}$(parent) for all others.

Data collection: *SMART* (Bruker, 2000); cell refinement: *SMART*; data reduction: *SAINT-Plus* (Bruker, 2000); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 2000); software used to prepare material for publication: *SHELXTL*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3014). Services for accessing these data are described at the back of the journal.

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