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(+)-3-Oxo-23,24-dinor-5α-cholan-22-oic Acid: Hydrogen-Bonding Patterns in a Steroidal Keto Acid and its Monohydrate

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Abstract

The X-ray crystal structures of the title steroidal keto acid in both its anhydrous, $C_{22}H_{34}O_3$, (I), and monohydrate, $C_{22}H_{34}O_3 \cdot H_2O$, (II), forms have been determined. Neither hydrogen-bonding pattern involves the ketone. Compound (I) forms infinite carboxyl-to-carboxyl hydrogen-bonding chains. This is the first observed case of a keto carboxylic acid forming such an acid-to-acid catemer. In (II), each carboxyl is hydrogen bonded to three water molecules and each water forms hydrogen bonds with carboxyl groups from three steroid molecules, creating a network of connected ten-membered hydrogen-bonding rings.

Comment

For keto carboxylic acids, the most common of the four previously known solid-state hydrogen-bonding patterns is acid dimerization (both centrosymmetric and noncentrosymmetric), with no ketone involvement. The others, in order of diminishing prevalence, are carboxyl-to-ketone catemers, intramolecular hydrogen bonds and carboxyl-to-ketone dimers, of which only two instances are known. Several additional patterns are known for hydrates. Numerous examples of these patterns have been referenced and discussed previously (Thompson *et al.*, 1992; Coté *et al.*, 1996).

The crystalline states of acetic (Jones & Templeton, 1958) and formic acids (Nahringbauer, 1978; Jong & Chen, 1994) involve catemers created by repeating intermolecular O—H···O=C hydrogen bonds (acid-to-acid catemer), a pattern uncommon among functionally unelaborated carboxylic acids, which typically form hydrogen-bonding dimers (Leiserowitz, 1976). Having recently published the case of a 3-oxo-17-carboxysteroid which forms carboxyl-to-ketone catemers (Brunskill *et al.*, 1997), we now report the hydrogen-bonding behavior of the title compound, a steroidal keto acid present as a single enantiomer and existing in both anhydrous, (I), and monohydrate, (II), forms. The anhydrous form, (I), presents an instance of catemeric hydrogen bonding which involves only the carboxyl function, a hydrogen-bonding mode known in unelaborated acids (see above), but not previously observed in keto acids. The hydrogen-bonding pattern of the monohydrate, (II), involves insertion of water into the acid-to-acid catemer structure observed for (I), with minimal changes to overall packing. Catemer formation is uncommon in carboxylic acids, but is expected to occur more frequently in monoenantiomeric species (von Sydow, 1958; Abrahamsson, 1959; Lin *et al.*, 1974), where centrosymmetry is excluded and absence of an antipode lessens the number of possible packing arrangements (Leiserowitz, 1976).
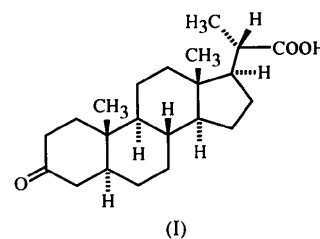

(I)

Fig. 1 shows the title compound with its steroid numbering and with the water of hydration which is present in (II). Because each water is also hydrogen bonded to the carboxyl C=O group of two other molecules, the choice of which of those relationships to show for (II) is arbitrary. Among the few conformational options present, the substituents at C20, which have the *S* configuration, are staggered with respect to those at C17, and the carboxyl group is turned, with its carbonyl toward the top (β) face of the molecule, so that the carboxyl plane coincides approximately with the C20—H20 bond [torsion angle H20*A*—C20—C22—O2 4.4(7)°]. The asymmetric units of (I) and (II) differ very slightly in the torsion angles around these sites. In (I), the C16—C17—C20—C21 torsion angle is 178.4(6)° and the C17—C20—C22—O2 torsion

angle is $-112.6\,(7)°$, producing a carboxyl (C20, C22, O2, O3) versus molecular plane (C2, C4, C6, C8, C11) dihedral angle of $78.9\,(3)°$. In (II), these angles are $172.1\,(2)$, $-108.7\,(3)$ and $81.3°$, respectively. No disorder was detected in the three methyl groups in either structure, which all adopt staggered arrangements relative to the other substituents at their points of attachment, C10, C13 and C20.

O—H$\cdots$O angle is $163\,(1)°$. For both (I) and (II), the Bernstein–Etter graph-set analysis is useful in describing the hydrogen-bonding patterns (Bernstein et al., 1995; Etter et al., 1990; Etter, 1990). For (I), the hydrogen-bonding pattern is a chain with a simple first-order motif: $N_1 = C(4)$.
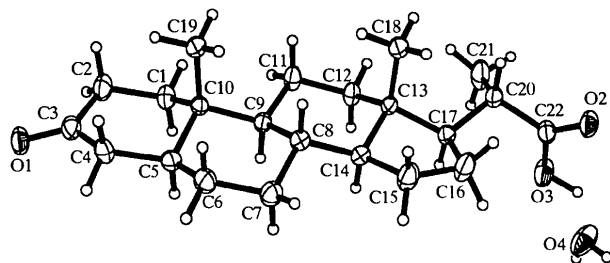

Fig. 1. A view of the title compound with its steroidal numbering; ellipsoids are set at the 30% probability level. The slight differences in distances and angles between (I) and its hydrated form, (II), are described in the Comment. The water associated with (II) is shown, arbitrarily, in one of its three possible positions relative to the carboxyl.
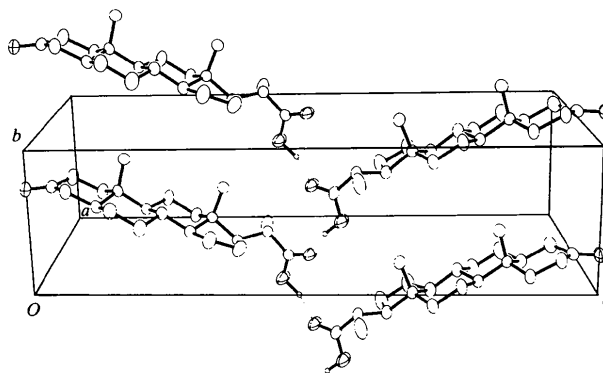

Fig. 2. A partial packing diagram showing the hydrogen-bonding pattern for (I), with all carbon-bound H atoms removed for clarity. Ellipsoids are set at the 30% probability level.

Complete or partial averaging of carboxyl C—O bond lengths and C—C—O angles by disorder is frequent in hydrogen-bonding dimers (Leiserowitz, 1976). However, acid-to-ketone catemers, acid-to-acid catemers, hydrates, and other hydrogen-bonding structures whose geometry precludes the usual carboxyl disordering processes, are typically found to be highly ordered, as is the case here. Our survey of 28 acid-to-ketone catemers gives average values of 1.197 and 1.320 Å, and 124.5 and 112.8° for these C—O lengths and C—C—O angles, respectively, while values cited as typical for ordered dimeric carboxyls are 1.21 and 1.31 Å, and 123 and 112° (Borthwick, 1980). In (I), these bond lengths and angles are $1.192\,(6)$ and $1.297\,(7)$ Å, and $126.5\,(6)$ and $113.4\,(5)°$, while in (II), they are $1.216\,(3)$ and $1.309\,(3)$ Å, and $124.0\,(2)$ and $113.8\,(2)°$, respectively.

Fig. 2 shows the packing arrangement for (I). The intermolecular hydrogen bonding occurs halfway along the c cell dimension, where the carboxyl groups meet, yielding a polar hydrophilic environment. The acid-to-acid hydrogen bonding in (I) is not dimeric but catemeric, involving a pseudo-2_1-screw axis parallel to b. Catemeric arrangements in acid-to-acid hydrogen bonding are scarce, and this is the only reported instance of an occurrence in a keto acid. Adjacent carboxyl groups involved in a hydrogen bond in (I) do not lie in the same plane and are turned relative to each other to produce a carboxyl–carboxyl (C20, C22, O2, O3 versus C20′, C22′, O2′, O3′) dihedral angle of $9.0\,(4)°$. The hydrogen-bond length [O$\cdots$O] is $2.607\,(6)$ Å and the

At the opposite end of the molecule, the ketone groups protrude from the ab cell face so as to interleave with those from the adjacent cell. These ketone C=O groups overlap and stack with their dipoles opposed in an aligned alternating fashion that maximizes attractive dipolar interactions. Pairs of carbonyls are nearly parallel in this arrangement, with dihedral angles between adjacent ketone planes (C2, C3, C4, O1 versus C2′, C3′, C4′, O1′) of $10.5\,(1)°$. Because these carbonyls are not exactly parallel, the intermolecular C$\cdots$O distance is $3.238\,(8)$ Å at one end of the stacking and $3.402\,(8)$ Å at the other. In order for the ketone carbonyls to adopt this arrangement, the rigid all-trans polycyclic portions of the molecules must stack at an angle relative to the C=O axes, leading to the observed herring-bone-like pattern. Within a given molecule, the dihedral angle between the plane of the ketone (C2, C3, C4, O1) and the general molecular plane (C2, C4, C6, C8, C11) is found to be $19.6\,(1)°$. The observed intermolecular 'herring-bone' (C2, C4, C6, C8, C11 versus C2′, C4′, C6′, C8′, C11′) dihedral angle of $28.9\,(1)°$ thus corresponds closely to $(2 \times 19.6°) - 10.5°$. Adjacent hydrogen-bonded molecules are parallel to the (011) and (01$\bar{1}$) planes, respectively.

Fig. 3 illustrates the packing of (II) in the cell, which involves insertion of water into the hydrogen-bonding pattern of (I), with relatively little disruption of the remaining packing. Each water participates in hydrogen bonds to three carboxyl groups, while each carboxyl is hydrogen bonded to three waters, forming a network of connected ten-membered hydrogen-bonding rings.
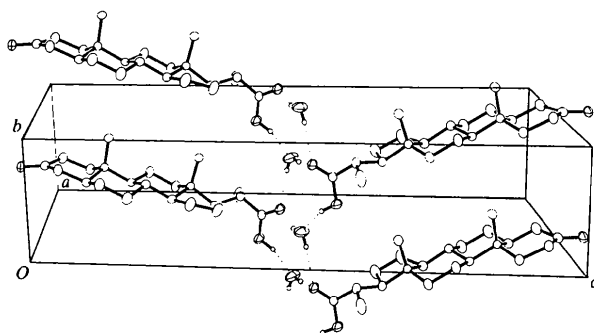
Fig. 3. A partial packing diagram showing the hydrogen-bonding pattern for (II), with all carbon-bound H atoms removed for clarity. Ellipsoids are set at the 30% probability level.

This complex hydrogen-bonding pattern provides three distinct types of intermolecular hydrogen bonds: carboxyl hydrogen-to-water oxygen, plus two different water hydrogen-to-carbonyl oxygen (in the Bernstein–Etter nomenclature, N_1 = DDD). Three higher-order hydrated chain networks are present, each containing two distinct types of these hydrogen bonds: a pseudo-2_1-screw-related C=O···H—O—H···O=C chain described as N_2 = $C(4)$, a pseudo-2_1-screw-related O=C—O—H···O(H)—H···O=C catemer designated N_3 = $C(6)$ and a translational catemer, also O=C—O—H···O(H)—H···O=C, described as N_4 = $C(6)$. The highest-order network, N_5 = $R_4^4(10)$, describes the ring structure, which contains all three of these hydrogen-bond types.

Carboxyl groups of molecules that are related by the pseudo-screw axis are turned relative to each other, producing a carboxyl–carboxyl (C20, C22, O2, O3 versus C20', C22', O2', O3') dihedral angle of 4.4 (2)°. For the stacked overlapping ketone C=O groups in (II), the intermolecular C···O distances are 3.064 (3) and 3.107 (3) Å; the smaller difference compared with (I) reflects a narrower intermolecular ketone–ketone dihedral angle of 4.7 (1)°. Within each molecule, the C2, C3, C4, O1 versus C2, C4, C6, C8, C11 dihedral angle is now 13.7 (1)°, indicating a flattening of the ketone ring, and the intermolecular 'herring-bone' dihedral angle has correspondingly flattened to 23.0 (1)°.

The formation of hydrogen-bonding rings in (II) imparts added structural rigidity in the packing at the hydrogen-bonding sites compared with (I), as indicated by the displacement parameters for the atoms in the acid side chains. In (II), a lower degree of rotational freedom around the bonds C17—C20 and C20—C22 is indicated by the lower C21, O2 and O3 anisotropies compared with (I). Extra rigidity around this site for (II) is also reflected in the rest of the molecule, which overall has lower displacement parameters than in (I).

The KBr IR spectrum of (I) displays its principal C=O absorption at 1713 cm^{-1}, with a shoulder at ca 236

1730 and a smaller peak at ca 1650 cm^{-1}. The KBr spectrum for (II) also has its absorption at 1713 cm^{-1}, but the shoulder has diminished, while the peak to the right, now ca 1660 cm^{-1}, has strengthened. In CHCl$_3$ solution, where dimers predominate, the absorption is at 1707, with a shoulder at 1737–1740 cm^{-1}.

Experimental

Crytals of compound (II) were used as purchased from Steraloids Inc, Wilton, NH, USA. According to the supplier, following a partially aqueous synthetic step, the material crystallized from an acetone–CH$_2$Cl$_2$ solvent mixture. The maximum crystal dimension of 0.88 mm for (II) was large, but well within the focal spot of the normal-focus tube (1 × 1 mm). Crystals of (II) lose water above ca 373 K, as evidenced by whitening and fracturing, and the anhydrous form then melts at 526 K. Crystals of (I) were obtained by such a thermal dehydration of (II), and were then recrystallized from absolute ethanol.

Compound (I)

Crystal data

$C_{22}H_{34}O_3$	Mo $K\alpha$ radiation
M_r = 346.49	λ = 0.71073 Å
Monoclinic	Cell parameters from 28
$C2$	reflections
a = 12.433 (2) Å	θ = 3.24–12.20°
b = 6.629 (1) Å	μ = 0.074 mm^{-1}
c = 24.559 (4) Å	T = 293 (2) K
β = 93.38 (1)°	Columnar
V = 2020.6 (6) Å^3	0.56 × 0.26 × 0.18 mm
Z = 4	Colorless
D_x = 1.143 Mg m^{-3}	
D_m = 1.14 (1) Mg m^{-3}	
D_m measured by flotation in hexane/CCl$_4$	

Data collection

Siemens $P4$ diffractometer	R_{int} = 0.042
$2\theta/\theta$ scans	θ_{max} = 25.05°
Absorption correction:	h = −14 → 14
face-indexed numerical	k = −7 → 7
T_{min} = 0.981, T_{max} = 0.987	l = −29 → 29
4058 measured reflections	3 standard reflections
3575 independent reflections	every 97 reflections
1590 reflections with	intensity decay: 1.4%
$F > 4\sigma(F)$	

Refinement

Refinement on F^2	$\Delta\rho_{max}$ = 0.128 e Å^{-3}
$R[F^2 > 2\sigma(F^2)]$ = 0.073	$\Delta\rho_{min}$ = −0.121 e Å^{-3}
$wR(F^2)$ = 0.156	Extinction correction:
S = 1.05	SHELXL93
3568 reflections	Extinction coefficient:
236 parameters	0.0020 (4)

H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0309P)^2 + 0.5593P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$

Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = -1 (3)

Table 1. *Selected geometric parameters ($\mathring{A}$, °) for (I)*

O1—C3	1.222 (5)	O3—C22	1.297 (7)
O2—C22	1.192 (6)	O3—H3	1.01 (5)
O2—C22—C20	126.5 (6)	O3—C22—C20	113.4 (5)
C16—C17—C20—C21	178.4 (6)	H20A—C20—C22—O2	4.4 (7)
C17—C20—C22—O2	−112.6 (7)		

Table 2. *Hydrogen-bonding geometry ($\mathring{A}$, °) for (I)*

D—H$\cdots$$A$	D—H	H$\cdots$$A$	$D$$\cdots$$A$	D—H$\cdots$$A$
O3—H3$\cdots$O2^i	1.01 (5)	1.62 (5)	2.606 (6)	164 (1)

Symmetry code: (i) $\frac{1}{2} - x, y - \frac{1}{2}, 1 - z$.

Compound (II)

Crystal data

$C_{22}H_{34}O_3.H_2O$
$M_r = 364.51$
Monoclinic
$C2$
$a = 12.696$ (3) $\mathring{A}$
$b = 6.168$ (2) $\mathring{A}$
$c = 26.784$ (7) $\mathring{A}$
$\beta = 101.26$ (2)°
$V = 2057.1$ (10) $\mathring{A}^3$
$Z = 4$
$D_x = 1.177$ Mg m^{-3}
$D_m = 1.18$ (1) Mg m^{-3}
D_m measured by flotation in hexane/CCl$_4$

Mo $K\alpha$ radiation
$\lambda = 0.71073$ $\mathring{A}$
Cell parameters from 28 reflections
$\theta = 10.07–16.74°$
$\mu = 0.079$ mm^{-1}
$T = 293$ (2) K
Plate
$0.88 \times 0.50 \times 0.14$ mm
Colorless

Data collection

Siemens P4 diffractometer
$2\theta/\theta$ scans
Absorption correction: face-indexed numerical
$T_{min} = 0.958$, $T_{max} = 0.967$
7240 measured reflections
3624 independent reflections
2910 reflections with $F > 4\sigma(F)$

$R_{int} = 0.047$
$\theta_{max} = 25.00°$
$h = -16 \rightarrow 16$
$k = -8 \rightarrow 8$
$l = -34 \rightarrow 34$
3 standard reflections every 97 reflections
intensity decay: 0.4%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.044$
$wR(F^2) = 0.131$
$S = 1.05$
3598 reflections
252 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0608P)^2 + 0.0737P]$
where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} = -0.001$
$\Delta\rho_{max} = 0.199$ e $\mathring{A}^{-3}$
$\Delta\rho_{min} = -0.146$ e $\mathring{A}^{-3}$
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = -1 (1)

Table 3. *Selected geometric parameters ($\mathring{A}$, °) for (II)*

O1—C3	1.218 (2)	O3—C22	1.309 (3)
O2—C22	1.216 (3)		
O2—C22—C20	124.0 (2)	O3—C22—C20	113.8 (2)
C16—C17—C20—C21	172.1 (2)	C17—C20—C22—O2	−108.7 (3)

Table 4. *Hydrogen-bonding geometry ($\mathring{A}$, °) for (II)*

D—H$\cdots$$A$	D—H	H$\cdots$$A$	$D$$\cdots$$A$	D—H$\cdots$$A$
O3—H3$\cdots$O4	0.94 (3)	1.69 (3)	2.603 (3)	163 (1)
O4—HW2$\cdots$O2^i	0.78 (4)	2.13 (4)	2.879 (3)	161 (4)
O4—HW1$\cdots$O2^{ii}	0.76 (5)	2.09 (5)	2.830 (3)	166 (4)

Symmetry codes: (i) $\frac{1}{2} - x, y - \frac{1}{2}, 1 - z$; (ii) $x, y - 1, z$.

For both (I) and (II), H-atom treatment for the organic portion was the same. All non-carboxyl H atoms were visible in electron-density difference maps, placed in calculated positions and allowed to refine as riding atoms on their appropriate C atoms. The carboxyl H atom was visible in an electron-density difference map, placed in a calculated position and the O—H distance allowed to refine. Its displacement parameter was fixed at 0.08 $\mathring{A}^2$. Methine and methylene H-atom displacement parameters were refined as separate groups. The displacement parameters for the H atoms for each of the three methyl rotors were refined as individual groups. Water H atoms in (II) were found in an electron-density difference map and their positional and displacement parameters were allowed to refine.

For both compounds, data collection: *XSCANS* (Fait, 1991); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structures: *SHELXTL/PC* (Sheldrick, 1994); program(s) used to refine structures: *SHELXTL/PC*; molecular graphics: *SHELXTL/PC*; software used to prepare material for publication: *SHELXTL/PC*.

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