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3-Oxo-5β-24-norcholanic acid: acid-to-acid hydrogen-bonding catemers employing the rare *anti* carboxyl conformation in the aggregation of a steroid keto acid

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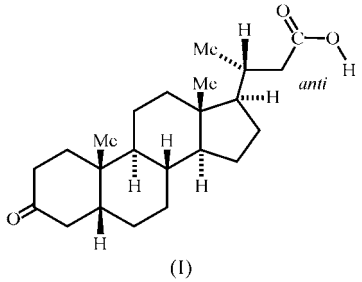
The title ketocarboxylic acid [systematic name: (5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*,20*R*)-3-oxo-24-norcholanic acid], $C_{23}H_{36}O_3$, forms acid-to-acid hydrogen-bonding chains [O$\cdots$O = 2.620 (2) Å and O—H$\cdots$O = 163 (3)°] in which all carboxyl groups adopt the rare *anti* conformation, while the ketone group does not participate in the hydrogen bonding. The occurrence and energetics of this conformation are discussed. One intermolecular C—H$\cdots$O close contact exists, which plays a role in stabilizing the hydrogen-bonding arrangement.

Comment

Our study of factors affecting the choice of hydrogen-bonding mode in ketocarboxylic acids frequently employs chiral non-racemates, whose absence of centrosymmetry favors the ordinarily less common hydrogen-bonding modes by discouraging formation of carboxyl dimers. Within this category, steroids are among the most readily available subject materials. We report here the structure of the title compound, (I), which is a 24-norcholanic acid.



(I)

Fig. 1 shows the title compound with its steroid numbering. The few significant conformational options all lie in the C17 side chain. The substituents on the C17—C20 and C20—C22 bonds are optimally staggered, and the carboxyl group is turned so that its plane coincides approximately with the C20—C22 bond [O2=C23—C22—C20 = −7.4 (3)°]. The disordering of carboxyl C—O bond lengths and C—C—O angles often seen in dimers may also be possible in acid-to-acid catemers (see below) when their geometry permits the underlying averaging processes involved (Kuduva *et al.*, 1999; Das & Desiraju, 2006). However, in (I), these distances and angles all lie within the normal range for highly ordered carboxyl groups (Table 1). What is unusual in (I) is the seldom encountered *anti* arrangement of H and C=O in the carboxyl group, sometimes also called the *antiplanar*, *transoid* or *E* conformation. This is normal in internally hydrogen-bonded carboxyl groups (Coté *et al.*, 1996), but is exceedingly rare in acid-to-acid catemers (Kuduva *et al.*, 1999), which themselves are uncommon, and, of course, it never occurs in carboxyl dimers, which are necessarily *cisoid*. This exceptional arrangement does not appear to be due to any obvious feature of the geometry of (I), whose structure and stereochemistry resemble those of the other 5β steroids we have reported (Thompson *et al.*, 2001; Kikolski, Davison *et al.*, 2006; Kikolski, Lalancette *et al.*, 2006).

Fig. 2 shows the packing of (I). All hydrogen bonding occurs in an acid-to-acid catemer arrangement, whose screw-related components advance in the [100] direction along the *ab* face, while a second chain proceeds counterdirectionally a half-cell away in *c*. These two catemers interleave at their remote ends, with their ketone dipoles opposing to utilize attractive dipolar interactions. The ketone carbonyl groups, which have no part in the hydrogen bonding, are not fully parallel; thus, the intermolecular C$\cdots$O stacking distance is 4.409 (3) Å at one end and 4.962 (3) Å at the other end, yielding a dihedral angle of 29.26 (5)° between adjacent ketone planes, *viz*. C2/C3/C4/O1 *versus* C2′/C3′/C4′/O1′($-x+1$, $y+\frac{1}{2}$, $-z+\frac{3}{2}$).

We characterize the geometry of hydrogen bonding to carbonyl groups using a combination of H$\cdots$O=C angle and H$\cdots$O=C—C or H$\cdots$O=C—C—O 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 group (ideal = 0°). In practice, experimental values for these two quantities cluster strongly around their theoretically ideal angles, so that deviation from them may be used as a rough index of strain in the hydrogen-bonding arrangement. In (I), the angles in question are H3$\cdots$O2—C23, whose value is 128.7 (10)°, and H3$\cdots$O2—C23—O3, whose value is 16.6 (12)°. In the two other known instances of *anti–anti* acid-to-acid catemerization (see below), the corresponding angles are 120.9 and 10.5°, respectively (Bryan & White, 1982), and 117.6 and 0.0° (Wiechert *et al.*, 1997).

Within the 2.6 Å range surveyed for nonbonded intermolecular C—H$\cdots$O packing interactions, only one close contact exists (see Table 2). However, this contact involves donation toward atom O3 from a methylene H atom (H22*A*) directly adjacent to the carboxyl group that is donating its acid H atom to atom O2 in the *anti* hydrogen bond (Fig. 2). This creates a ladder-like set of connections that clearly plays a significant role in stabilizing the hydrogen bonding, although it

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is not clear why it would function less well in the tautomeric *syn–syn* arrangement (see below).

The rarity of acid-to-acid catemers, of either *syn* or *anti* carboxyl conformation, diminishes significantly when dimerization is suppressed by precluding centrosymmetric modes. Even so, (I) is only the third instance we have found of any such catemer in a keto acid (Lalancette *et al.*, 1998; Zinczuk *et al.*, 2004). Although our H-atom placement in (I) is dictated by its ordered C—O bond lengths, an extended tautomeric H-atom shift along the chain can be envisioned for (I) that, with appropriate resizing of the C—O bonds, would yield an alternative all-*syn* catemer. However, unless some C atoms are shifted as well, the result appears to produce geometrically unfavorable C—O—H angles, and we have found no evidence for such an alternative species or for any disorder created by such a process, either static or dynamic. We attempted to force such a *syn* conformation on our asymmetric unit, but the refinement could not be improved beyond $R[F^2 > 2\sigma(F^2)] = 0.08$.

Historically, Leiserowitz (1976), working from a very modest 25 000 or so X-ray structures (CCDC, 2000), concluded that only carboxyl groups involved in intramolecular hydrogen bonding display the *antiplanar* conformation. This remains nearly correct, despite the present availability of a vastly expanded structural database. The first 'exception', an acid-to-amide catemer, appears to have been that of Fujinaga & James (1980). Since then, additional examples have gradually accumulated, but the percentage of non-intramolecular *antiplanar* carboxyl structures remains minute. Desiraju and his collaborators (Desiraju *et al.*, 1990; Goud & Desiraju, 1993; Das *et al.*, 2003, 2005; Das & Desiraju, 2006) have published several examples of alternating *syn–anti* catemer formations in phenylpropiolic acids and cubanecarboxylic acids. Among these papers, Kuduva *et al.* (1999) reported that their search of the 181 309 entries in the 1998 Cambridge Structural Database found a total of 73 acid-to-acid catemers, of which four were combined *syn–anti* arrangements and only two represented all-*anti* species. Our own search of the 390 081 entries in the current database (Version 5.28, update of November, 2006; Allen, 2002) has found a total of 153 acid-to-acid catemers, of which the number of *anti–anti* instances remains at only two (Bryan & White, 1982; Wiechert *et al.*, 1997).

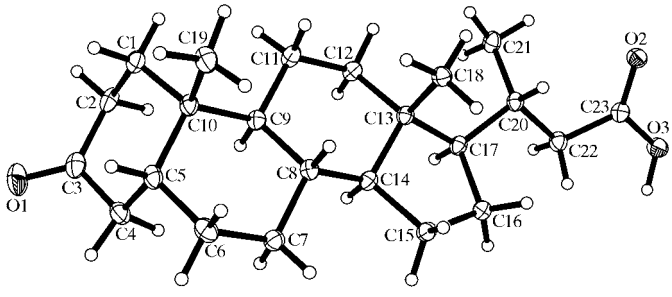

Figure 1
The title compound with its steroid numbering. Displacement ellipsoids are drawn at the 30% probability level.

Because some all-*anti* and all-*syn* catemers are tautomerically related, as described above, and yet the *anti* species is so rarely observed, the clear inference is that *anti* conformations are energetically disfavored. While much interest has therefore focused on the energy difference involved, experimental data seem to be derived entirely from formic acid, and computational results have seldom extended much further. For the most part, $\Delta G_{syn/anti}$ values found for vapor-phase formic acid lie in the 8.5–16.5 kJ mol^{-1} range (Miyazawa & Pitzer, 1959; Lide, 1964, 1966; Hocking, 1976); however, Pawar *et al.* (2007) have recently reported a $\Delta G_{syn/anti}$ for formic acid of *ca* 3.8 kJ mol^{-1} in a solution that permitted hydrogen bonding but suppressed dimerization. The computational values for $\Delta G_{syn/anti}$ generally fall in the range 19–26.5 kJ mol^{-1} (Radom *et al.*, 1972; Allinger & Chang, 1977; Peterson & Csizmadia, 1979; Wiberg & Laidig, 1987), and the few values calculated for acetic and propionic acids are higher than the formic acid values by a few kJ mol^{-1}. The range of values estimated by Gandour (1981) from kinetic data in enzyme models (*ca* 6–23 kJ mol^{-1}) may seem unhelpfully broad, but these represent a variety of acids larger and more complex than formic acid. The applicability of any of these estimates to the crystalline state is unclear.

Such ΔG values have been accepted in varying degrees and sometimes cited as though they might represent carboxylic acids other than those actually employed in the experiments or calculations performed. Such a notion is easily dispelled by considering cases like bicyclo[2.2.2]octane-1-carboxylic acid, where any *anti* conformation must be impossibly hindered. What seems clear is that a range of $\Delta G_{syn/anti}$ values exists, with formic acid at or near one end, since the substituent sterically opposed to acid-H in its *anti* conformer is the least demanding one possible. Values of $\Delta G_{syn/anti}$ probably corre-

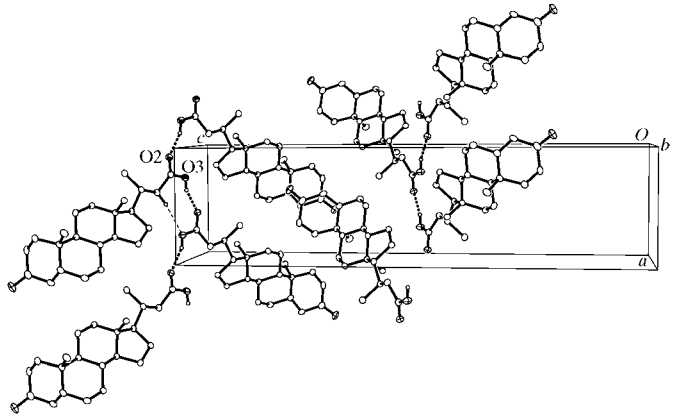

Figure 2
A partial packing diagram with extra molecules included to illustrate the hydrogen-bonding pattern for (I). On the left, one molecule has its carboxyl O atoms numbered to aid in visualizing the hydrogen-bonding scheme. All carbon-bound H atoms have been omitted for clarity, except for one instance, on the left, of the C22-bound H atom involved in the intermolecular C—H···O close contact to O3, indicated by a dashed connection. Displacement ellipsoids are drawn at the 30% probability level.

late generally with steric bulk and the degree of substitution at the acid's Cα atom [*cf.* Newman's 'rule of six' (Newman, 1950, 1956)], and bond polarities may well also play a part. What we may presumably take as proven is that, when instances of *anti* carboxyl hydrogen bonding appear, whatever ΔG disadvantage there is to an *anti* conformation is better than no hydrogen bond at all, although what maximum this places on $\Delta G_{syn/anti}$ is rather difficult to estimate, given the widely varying values offered in the literature for O—H···O bond strength.

Experimental

(+)-3-Hydroxy-5β-Δ^{11}-24-norcholenic acid, of known rotation and absolute configuration (Fieser & Fieser, 1959), was purchased from Steraloids Inc., Newport, Rhode Island, USA, and converted to (I) by catalytic hydrogenation of the C11═C12 double bond, followed by Jones oxidation (Bowden *et al.*, 1946; Bladon *et al.*, 1951; Bowers *et al.*, 1953; Djerassi *et al.*, 1956) to the ketone. Crystals of (I) were obtained from acetic acid (m.p. 457 K). The KBr IR spectrum of (I) displays a single absorption for both C═O groups at 1711 cm^{-1}, essentially unchanged at 1706 cm^{-1} in $CHCl_3$ solution, where dimers predominate.

Crystal data

$C_{23}H_{36}O_3$
M_r = 360.52
Orthorhombic, $P2_12_12_1$
a = 7.47160 (11) Å
b = 8.72260 (12) Å
c = 30.2407 (5) Å
V = 1970.84 (5) Å^3
Z = 4
Cu $K\alpha$ radiation
μ = 0.61 mm^{-1}
T = 100 (2) K
0.31 × 0.04 × 0.04 mm

Data collection

Bruker SMART CCD APEXII area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2001)
T_{min} = 0.834, T_{max} = 0.976
13991 measured reflections
3567 independent reflections
2976 reflections with $I > 2\sigma(I)$
R_{int} = 0.062

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.101
S = 1.04
3567 reflections
243 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O2—C23	1.215 (3)	O3—C23	1.320 (2)
O2—C23—C22	124.41 (17)	O3—C23—C22	116.74 (19)

Table 2
Hydrogen-bond and close-contact geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3···O2^{i}	0.95 (3)	1.69 (3)	2.620 (2)	163 (3)
C22—H22A···O3^{i}	0.99	2.52	3.354 (3)	142

Symmetry code: (i) $x+\frac{1}{2}, -y+\frac{3}{2}, -z+2$.

All H atoms were found in electron-density difference maps. The O-bound H atom was allowed to refine fully. The methyl H atoms were placed in ideally staggered positions, with C—H distances of 0.98 Å [U_{iso}(H) = 1.5U_{eq}(C)]. The methylene and methine H atoms were placed in geometrically idealized positions and constrained to ride on their parent C atoms, with C—H distances of 0.99 and 1.00 Å, respectively [U_{iso}(H) = 1.2U_{eq}(C)].

Data collection: *APEX2* (Bruker, 2006); cell refinement: *APEX2*; data reduction: *SAINT* (Bruker, 2005); program(s) used to solve structure: *SHELXTL* (Sheldrick, 2004); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA3075). Services for accessing these data are described at the back of the journal.

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