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(+)-3-Oxo-5α-cholan-24-oic acid: catemeric hydrogen bonding in a steroidal keto acid

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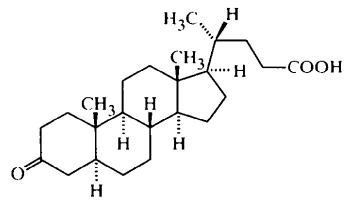
Abstract

The title keto acid ($C_{24}H_{38}O_3$) forms translational carboxyl-to-ketone hydrogen-bonding catemers, which follow no crystallographic axis [O···O = 2.712 (3) Å]. The cell contains two screw-related molecules having opposite end-to-end orientation, each of which participates in a separate hydrogen-bonding chain.

Comment

In the crystal structures of keto carboxylic acids, the commonest of the five known solid-state motifs is acid dimerization, in which the ketone is not involved (Coté *et al.*, 1996). In order of diminishing prevalence, the others are carboxyl-to-ketone chains (catemers) (Barcon *et al.*, 1998), intramolecular hydrogen bonds (Thompson *et al.*, 1996), carboxyl-to-ketone dimers (four cases known) (Kosela *et al.*, 1995), and acid-to-acid catemers (three cases known) (Lalancette *et al.*, 1998); several cases exist of hydrates with more complex hydrogen-bonding patterns (Lalancette *et al.*, 1997, 1998).

We have investigated the hydrogen-bonding motif of the steroidal keto acid (I), present as a single enantiomer. Fig. 1 shows the asymmetric unit with its steroid numbering. The significant 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 C24 *anti* to C16 [torsion angle C16—C17—C20—C24 = 176.6 (2)°]. The remainder of this chain (C20, C21, C22, C23, O2, O3) extends away from the ring system, as shown. The carboxyl group is oriented so that the carboxyl plane coincides approximately with the C21—C22 bond and its carbonyl group is nearly eclipsed with C21 [torsion angle O2—C23—C22—C21 = −5.4 (4)°].



(I)

While complete or partial averaging of carboxyl C—O bond lengths and C—C—O angles by disorder is frequent in dimers (Leiserowitz, 1976), the geometry of catemers precludes disordering processes. Acids engaged in catemeric hydrogen bonding are highly

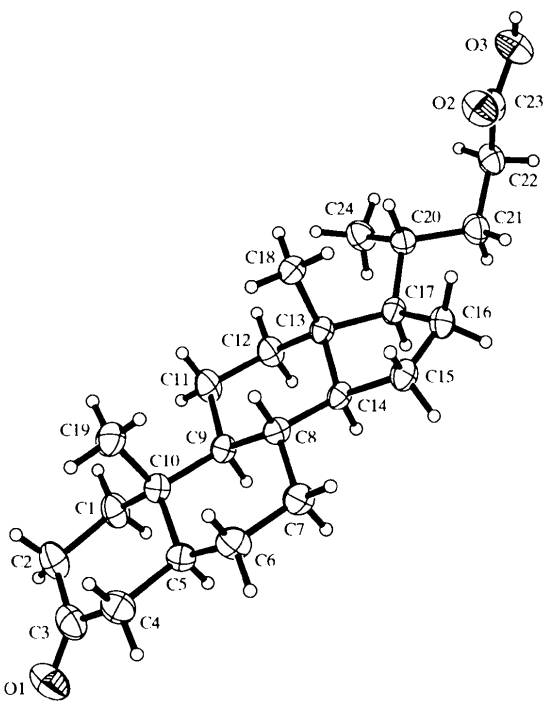


Fig. 1. *ORTEP*II (Johnson, 1976) plot of (I) with its steroidal numbering. Ellipsoids are set at the 30% probability level.

ordered and (I) shows no significant averaging. The bond lengths are 1.196 (3) for C=O and 1.332 (3) Å for C—O, with angles of 126.8 (2) for C—C=O and 111.1 (2)° for C—C—O. Our own survey of 56 keto acid structures that are not acid dimers gives average values of 1.20 (1) and 1.32 (2) Å, and 124 (1) and 113 (2)° for these lengths and angles. Values cited as typical for highly ordered dimeric carboxyls are 1.21 and 1.31 Å, and 123 and 112°, respectively (Borthwick, 1980).

Fig. 2 illustrates the packing of (I) in the cell, with extracellular molecules included to show the two hydrogen-bonding chains. When hydrogen-bonding catemers occur, their component molecules are often screw-related, with the helices following a cell axis. In (I), neither of these is the case: the catemers are translational and aligned with no crystallographic axis. The hydrogen-bonding links advance in stepwise fashion, so that each involves translationally related molecules one cell apart in both **a** and **c** (an infinite chain structure with base vector 1,0,−1). The O···O distance for the hydrogen bond is 2.712 (3) Å. The intermolecular O—H···O distance and angle are 1.98 (3) Å and 155 (1)°. For each hydrogen bond, the dihedral angle between the plane of the ketone (C2—C3—C4—O1) and that of the carboxyl group (C22—C23—O2—O3) involved is 53.1 (1)°.

Each cell contains a screw-related pair of molecules (Z = 2 in $P2_1$), whose long axes have the same orientation. Each cell thus holds members of two separate, parallel translational hydrogen-bonding catemers, which are counterdirectional and screw-related to each other. Some aspects of this packing resemble the catemeric hydrogen bonding recently reported for (+)-3-oxo-4-androsten-17β-carboxylic acid (Brunskill *et al.*, 1997), with each structure containing infinite catemers with translationally related components. However, in the latter case, the catemeric chains diverge due to the orientation of the molecules relative to the *b* axis.

The class of keto carboxylic acids including steroids and steroid-like triterpenoids shows a significant diminution in the prevalence of the common acid–acid dimer hydrogen-bonding motif. Of 14 examples (including two recently published by this group and the present example) there are six screw-related catemers, three translational catemers, two acid-to-acid catemers, one acid-to-ketone dimer and two acid-to-acid dimers. Thus, in this sampling the acid-to-acid dimer motif is present less than 15% of the time, significantly below the level of occurrence for all keto acids, where the acid-to-acid dimer motif occurs *ca* 50% of the time. The molecular characteristics that most probably account for this are (i) the predominance of single antipodes, (ii) the limited conformational flexibility afforded by fused-ring systems and (iii) the much higher (C + H):O ratio. The first point relates to the loss of the close-packing advantages afforded by inversion and glide symmetries (Kitaigorodsky, 1973). The remaining close-packing symmetry operation, the 2_1 screw axis, does not facilitate dimer formation since it cannot place the molecules in the required 'head-to-head' orientation. Dimers can be produced by a twofold rotation axis but this symmetry operation is not favorable for closest packing in a primitive setting (Kitaigorodsky, 1973). Thus dimer formation is largely dependent on the molecule adopting two crystallographically independent conformations, *i.e.* two molecules in the asymmetric unit. Adoption of such conformations is seen in both the acid-to-ketone dimer and the acid-to-acid dimers [TEVGIK (Kosela *et al.*, 1995), GIKVAX (Rodriguez & Lechat, 1988), ZASKUS (Jain *et al.*, 1995); the refcodes given here are from the Cambridge Structural Database (1998)]. In addition, the structural rigidity imposed by fused-ring systems (ii) may often diminish the conformational options that permit formation of such non-centrosymmetric dimer motifs. The third point relates to the possibility that dispersion forces rather than hydrogen-bonding requirements may dominate the packing. A comparison of (I) to the packing of non-acid keto steroids with similar carbon skeletons [CHENON (Nassimbeni, Russell *et al.*, 1977), CHOENO (Sheldrick *et al.*, 1976), CLBUST (Nassimbeni, Orpen *et al.*, 1977), LAVDAN (Decanniere *et al.*, 1993), TOXEL (Galdecki *et al.*, 1996) and ZZZMAY01 (Ribar *et al.*, 1991)] shows similarities, despite the absence of the carboxyl group, which

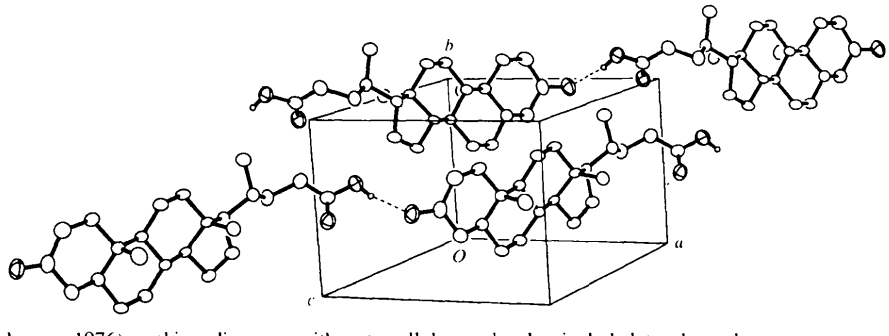


Fig. 2. *ORTEP*II (Johnson, 1976) packing diagram, with extracellular molecules included to show the two separate parallel translational catemers, which are counterdirectional and screw-related. All non-carboxyl-H atoms have been removed for clarity. Ellipsoids are set at the 30% probability level.

include space group, molecular orientation and β angle of the cell.

Experimental

Compound (I) was purchased as the (+)-enantiomer, of known absolute configuration (Fieser & Fieser, 1959), from Steraloids Inc., Newport, RI, USA. Crystals, m.p. 462 K, were obtained from acetic acid.

The solid-state (KBr) spectra of catemers typically display carbonyl absorption shifts due to removal of hydrogen bonding from carboxyl C=O and addition of hydrogen bonding to ketone C=O. In (I), these bands are seen at 1742 and 1708 cm^{-1}, respectively, but in $CHCl_3$ solution, where dimers predominate, they coalesce to a single peak at 1712 cm^{-1}.

Although the chosen crystal was large (0.85 × 0.70 × 0.60 mm), it was well within the focal spot of the normal focus tube and the 1 mm diameter collimator.

Crystal data

$C_{24}H_{38}O_3$
M_r = 374.54
Monoclinic
$P2_1$
a = 10.458 (2) Å
b = 7.619 (2) Å
c = 13.280 (2) Å
β = 91.94 (1)°
V = 1057.5 (4) $Å^3$
Z = 2
D_x = 1.176 Mg m^{-3}
D_m = 1.175 (3) Mg m^{-3}
D_m measured by flotation in cyclohexane/ CCl_4

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 30 reflections
θ = 5.98–18.79°
μ = 0.075 mm^{-1}
T = 293 (2) K
Rectangular prism
0.85 × 0.70 × 0.60 mm
Colorless

Data collection

Siemens $P4$ diffractometer
$2\theta/\theta$ scans
Absorption correction: face-indexed, numerical (Sheldrick, 1994)
T_{min} = 0.950, T_{max} = 0.972
4695 measured reflections
4153 independent reflections
3202 reflections with $I > 2\sigma(I)$

R_{int} = 0.030
θ_{max} = 26°
$h = -12 \rightarrow 12$
$k = -9 \rightarrow 9$
$l = 0 \rightarrow 16$
3 standard reflections
every 97 reflections
intensity decay: −1.1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.122
S = 1.07
4151 reflections
255 parameters
H atoms: see text
$w = 1/[\sigma^2(F_o^2) + (0.045P)^2 + 0.094P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = −0.001
$\Delta\rho_{max}$ = 0.118 e $Å^{-3}$
$\Delta\rho_{min}$ = −0.119 e $Å^{-3}$

Extinction correction: *SHELXTL/PC* (Sheldrick, 1994)
Extinction coefficient: refined to 0.0
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = 1.0 (16) using 1910 Friedel pairs

Table 1. *Selected geometric parameters (Å, °)*

O1—C3	1.204 (3)	O3—C23	1.332 (3)
O2—C23	1.196 (3)		
O2—C23—C22	126.8 (2)	O3—C23—C22	111.1 (2)

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H3···O1^i	0.78 (3)	1.98 (3)	2.712 (3)	155 (1)

Symmetry code: (i) $1 + x, y, z - 1$.

All non-carboxyl-H atoms were found in electron-density difference maps but were replaced in calculated positions and allowed to refine as riding models on their appropriate C atoms. Torsion angles for the methyl rotors were allowed to refine. Displacement factors for the methine- and methylene-H atoms were refined as two groups and displacement factors for H atoms of each methyl group were refined as individual groups. The carboxyl-H atom was found in an electron density difference map but was replaced in a calculated position and the O—H distance allowed to refine with its displacement factor also free to refine.

Data collection: *XSCANS* (Fait, 1991). Cell refinement: *XSCANS* (Siemens, 1996). Data reduction: *XSCANS*. Program(s) used to solve structure: *SHELXTL/PC* (Sheldrick, 1994). Program(s) used to refine structure: *SHELXTL/PC*. Molecular graphics: *SHELXTL/PC*. Software used to prepare material for publication: *SHELXTL/PC*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1512). Services for accessing these data are described at the back of the journal.

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A β-turn retro-enantiomeric analogue of achatin-I, H–D-Asp-[γCONH]-D-Ala–L-Phe–Gly–OH

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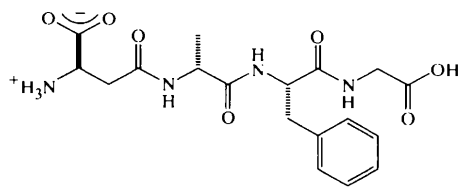
Abstract

A retro-enantiomeric analogue of achatin-I, β-D-aspartyl-D-alanyl-L-phenylalanylglycine, H–D-Asp-[γCO-NH]-D-Ala–L-Phe–Gly–OH ($C_{18}H_{24}N_4O_7$), was crystallized from an aqueous dimethylformamide solution. The γ-amide bond at the D-Asp[1] residue imparts β-amino acid characteristics on this residue. The peptide adopts a β-turn conformation and its loop shape is similar to that of achatin-I.

Comment

By reversing sequences using enantiomeric amino acids, we are using retro-enantiomeric (RE) methods to synthesize new peptides that mimic the conformation of the parent molecule (Doi *et al.*, 1995). This technique has now been applied to achatin-I (H–Gly–D-Phe–Ala–Asp–OH). Achatin-I was isolated from the ganglia of an African giant snail and is the first example of an endogenous neuropeptide having a D-amino acid (Kamatani *et al.*, 1989). The crystal structure determination of achatin-I has shown the molecule to have a β-turn conformation in the solid state (Kamatani *et al.*, 1990).

In the chemical syntheses of RE analogues of achatin-I, an additional approach was explored through the linkage of a γ-amide bond at the D-Asp[1] residue. RE-modified achatin-I (H–D-Asp–D-Ala–Phe–Gly–OH) and [γCONH]-RE-achatin-I (H–D-Asp-[γCONH]-D-Ala–Phe–Gly–OH; γ-REACH) were tested for crystallization and crystals of the latter peptide were obtained from an aqueous dimethylformamide solution.



γ-REACH

When the two carboxy groups are compared (D-Asp[1] and Gly[4]), the ionized states seem to be different. At the D-Asp[1] residue, the C1—O1 and C1—O1*T* bond distances are 1.242 (5) and 1.217 (5) Å, respectively, suggesting that the D-Asp[1] residue has an ionized carboxylate group and is a zwitterion. In contrast, significant differences are observed in the C4—O4 and C4—O4*T* bond lengths [1.211 (4) and 1.314 (4) Å, respectively] and the C-terminus of Gly[4] is assumed to be in the unionized carboxyl form.

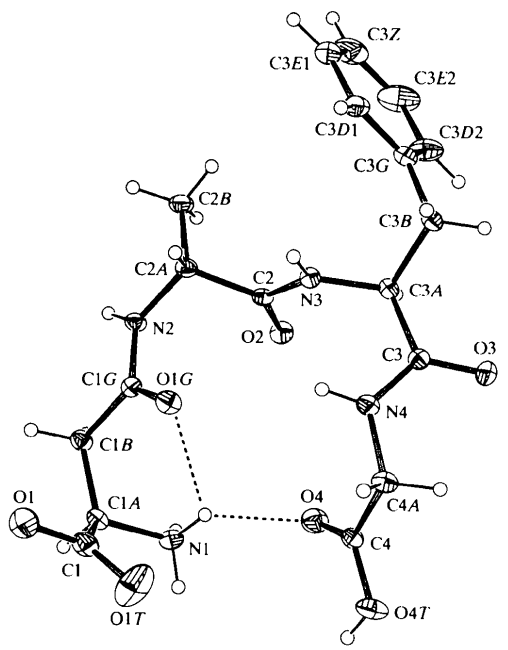


Fig. 1. A view of the title compound with displacement ellipsoids drawn at the 50% probability level.