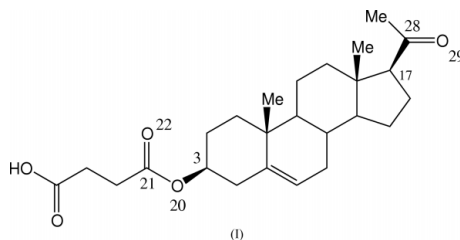


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Key indicators

Single-crystal X-ray study
T = 298 K
Mean $\sigma(\text{C}-\text{C})$ = 0.009 Å
R factor = 0.066
wR factor = 0.191
Data-to-parameter ratio = 7.4For details of how these key indicators were
automatically derived from the article, see
<http://journals.iucr.org/e>.Pregnenolone hemisuccinate: a *P1* structure
with $Z' = 4$ The structure of the title compound, $\text{C}_{25}\text{H}_{36}\text{O}_5$, was refined in
space group *P1*, with $Z' = 4$. The high value for Z' is due to a
degree of free rotation around the ester bond $\text{C}-\text{O}$ at the 3
position of the steroidal *A-D* nucleus.

Comment

As part of our interest in the synthesis of hydrophilic steroid
derivatives, we have studied the monoesterification of pre-
gnenolone (Δ^5 -pregnen-3 β -ol-20-one) using the anhydride of
various dicarboxylic acids, in order to obtain the hemiesters
capable of forming water-soluble salts. Pregnenolone,
progesterone and the vast majority of corticosteroids belong
to the pregnanes, a family considered to be the largest indi-
vidual group of steroids. Furthermore, pregnenolone is a key
intermediate in the biosynthesis of cortisol and related ster-
oids, included in the general metabolism of cholesterol (Voet
& Voet, 1990). Some hemisuccinate derivatives of these
compounds have been studied, although with poor structural
characterization. For example, the powder X-ray diffraction
pattern (Parson, 1966) and the hypnotic properties (Gyermek
et al., 1968) of the hemisuccinate of progesterone have been
described.In the case of pregnenolone, the formation of esters using
the alcoholysis of anhydrides has two possible outcomes, *viz.*
the esterification of the OH group, or of the ketone at C28
after reduction to the corresponding alcohol. In this work, we
explore the first alternative. The title compound, (I), was
prepared starting from pregnenolone, succinic anhydride and
pyridine (see *Experimental*).The asymmetric unit of (I) contains four independent
molecules, with no evidence of pseudo- or non-crystal-
lographic symmetry. Crystals belonging to this class, namely
 $Z' = 4$ in space group *P1*, are not uncommon, with 153
occurrences reported in the Cambridge Structural Database
(CSD, Version 5.24; Allen, 2002). Cholesterol hemimethanol
solvate, for which the structure was recently redetermined
(Shieh & Nordman, 2002), belongs to this class.Each independent molecule (Figs. 1–4) adopts a similar
geometry (Table 1), with the expected all-*trans* *A/B/C/D*
junctions and $\text{C5}=\text{C6}$ bond lengths in the range 1.290 (8)–Received 25 June 2003
Accepted 15 August 2003
Online 23 August 2003Dedicated to the memory of
Professor Francisco Giral.

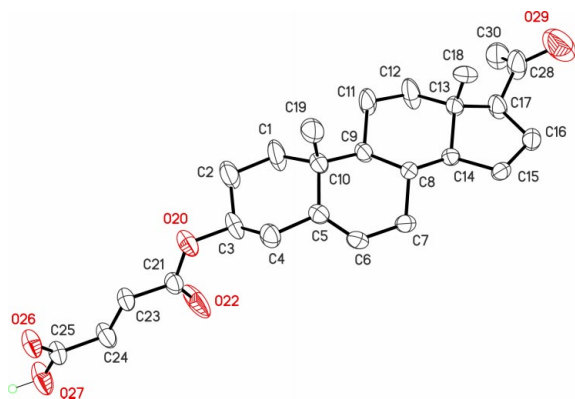


Figure 1
The structure of the first independent molecule in the asymmetric unit of (I), with displacement ellipsoids at the 25% probability level. For clarity, H atoms have been omitted except for the hydroxyl group.

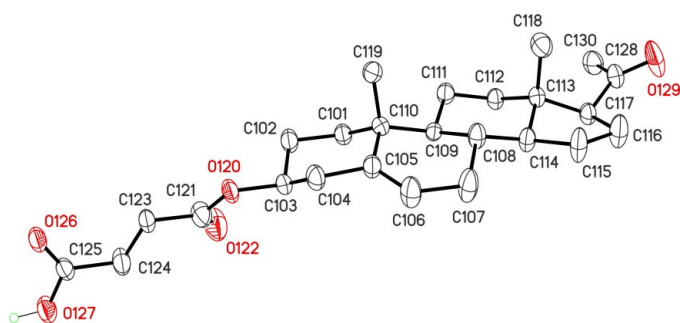


Figure 2
The structure of the second independent molecule in the asymmetric unit of (I), with displacement ellipsoids at the 25% probability level. For clarity, H atoms have been omitted except for the hydroxyl group. The numbering scheme is based on that adopted for the first independent molecule, with all atoms numbers shifted by 100.

1.327 (7) Å (Table 1). The geometry of the *A–D* system is identical to that observed for two pregnenolone derivatives characterized previously by X-ray analysis (Kolb *et al.*, 1987). The four molecules in the asymmetric unit are almost parallel to one another, stacking along the *b* axis. Intermolecular contacts are limited to classical double hydrogen bonds (Moulton & Zaworotko, 2001) involving free carboxylic acid groups (Table 2), forming two independent discrete dimers in the unit cell (Fig. 5). All four molecules have the same absolute configurations for the chiral centers, *e.g.* 3*S*, 8*R*, 9*S*, 10*R*, 13*S*, 14*S* and 17*S* for the C1-containing molecule. This unique handedness precludes the possibility of a centrosymmetric structure, making the space group assignment unambiguous.

It is noteworthy that the X-ray structure of pregnenolone was previously reported in space group $P2_1$ with $Z' = 1$ (CSD refcode PREGOL). One reason that (I) crystallizes with $Z' = 4$ can be found in the succinic moiety. A least-squares fit (Sheldrick, 1998) of the four independent molecules, using all non-H atoms, clearly indicates that substantial deviations are observed for the carbonyl atoms O22, O122, O222 and O322. For instance, comparing the C1-molecule with the others, the r.m.s. deviations are 0.388, 0.317 and 0.324 Å for the C101-, C201- and C301-molecules, respectively, while the deviations

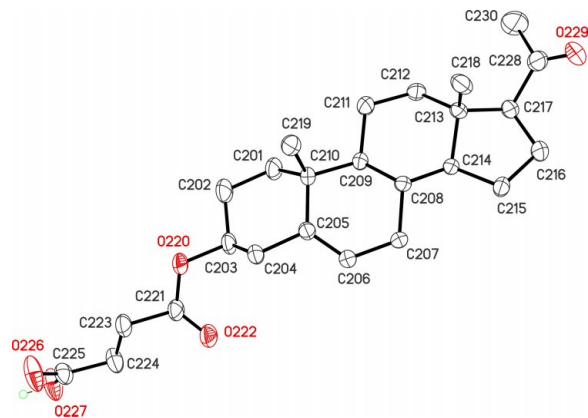


Figure 3
The structure of the third independent molecule in the asymmetric unit of (I), with displacement ellipsoids at the 25% probability level. For clarity, H atoms have been omitted except for the hydroxyl group. The numbering scheme is based on that adopted for the first independent molecule, with all atoms numbers shifted by 200.

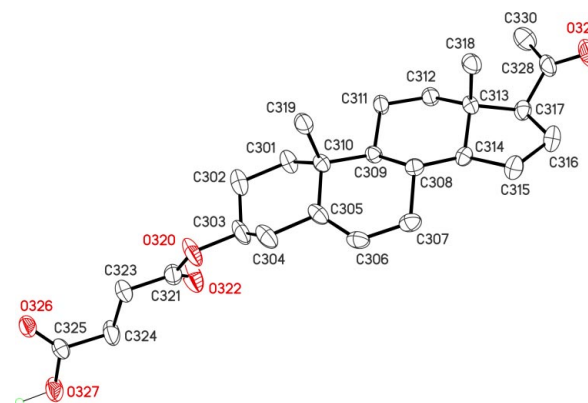
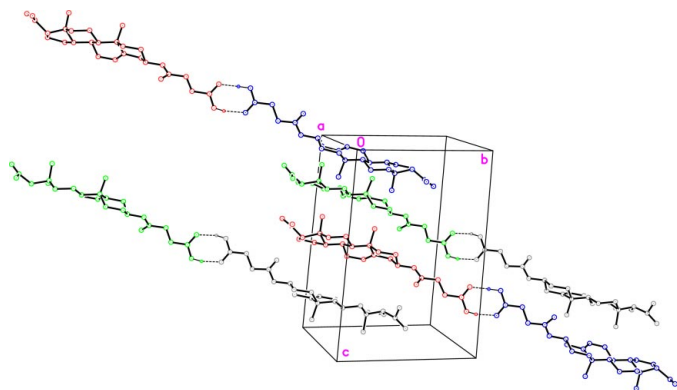


Figure 4
The structure of the fourth independent molecule in the asymmetric unit of (I), with displacement ellipsoids at the 25% probability level. For clarity, H atoms have been omitted except for the hydroxyl group. The numbering scheme is based on that adopted for the first independent molecule, with all atoms numbers shifted by 300.

from O22 are 1.245, 0.982 and 1.122 Å for O122, O222 and O322, respectively. These deviations are a consequence of the rotational freedom around the O20–C21 σ bond, whereas the *A–D* steroidal nucleus is unaffected by the flexibility of the lateral chain at C3 (Fig. 6). This is very probably valid for any steroid derivative, for which five- and six-membered rings are built-up essentially of Csp^3 atoms, giving a rigid core.

Crystal structures with $Z' > 1$ can pose problems as the molecules in these crystals are generally not very densely packed, giving poorly diffracting samples (Lehmler *et al.*, 2002). This phenomenon is also associated with low melting point compounds, sometimes close to room temperature (McCourt *et al.*, 1996). However, these structures are of interest, because large Z' values do not appear accidentally. They may be related to packing conflicts (Kitaigorodskii, 1973), non-crystallographic symmetry induced by intermolecular contacts, cocrystallization phenomenon, *etc.* The limiting case, $Z' \rightarrow \infty$, can be considered as a frontier between the crystalline and glassy states (Lehmler *et al.*, 2002). Based


Figure 5

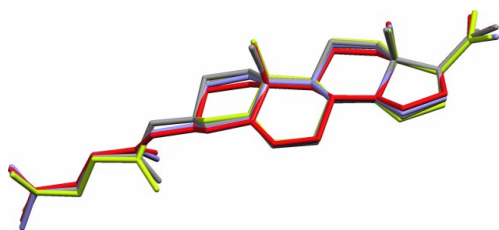
The crystal packing of structure (I). Eight molecules are displayed and intermolecular hydrogen bonds are represented with dotted lines. The four molecules within the unit cell constitute the asymmetric unit and the color codes are as follows: grey = C1-containing molecule; red = C101-containing molecule; green = C201-containing molecule; blue = C301-containing molecule. Symmetry codes for symmetry related molecules: grey = $x, y + 2, z$; red = $x, y - 2, z - 1$; green = $x, y - 2, z$; blue = $x, y + 2, z + 1$.

on the same concept, soft matter, including nematic phases, would be characterized by $Z \rightarrow \infty$.

In conclusion, we have found that for the pregnenolone derivative reported here, a $Z' > 1$ structure was obtained because of the contrast between a rigid core and a lateral chain with a high degree of rotational freedom. Obviously, this should be considered as an *a posteriori* explanation as it is almost impossible to predict the Z' value that will be observed in the crystalline state.

Experimental

In a round-bottomed flask, pregnenolone (1 g, 3.16 mmol) was dissolved in pyridine (20 ml) and succinic anhydride (3.6 g, 36 mmol) was added under a nitrogen atmosphere with magnetic stirring. The reaction was stirred at 373 K for 2.5 h. After cooling to room temperature, the mixture was poured over 100 ml of distilled water and the pH adjusted to 3 with dilute HCl (1:3). The white solid that formed was filtered off, washed repeatedly with distilled water and dried at 333 K under vacuum to obtain 1.19 g of (I) as white microcrystals (yield 90%, m.p. 452–454 K). Analysis found: C 71.9, H 8.6,


Figure 6

Best least-squares fit between the four independent molecules in (I). Atomic positions for the fitted molecules were computed using all non-H atoms by means of XP (Sheldrick, 1998) and plotted with *MERCURY* (CCDC, 2002). Color codes are identical to those used in Fig. 5: grey = C1-molecule, red = C101-molecule, green = C201-molecule, blue = C301-molecule. Note the large deviations observed for O22, O122, O222 and O322 on the succinic moiety.

O 19.1%; calculated for $C_{25}H_{36}O_5$: C 72.1, H 8.7, O 19.2%. Spectroscopic data are in agreement with the X-ray structure. IR (CsI pellets) $\nu_{(C=O)}$ 1734, 1704 cm^{-1} , $\nu_{(C-O)}$ 1322, 1090 cm^{-1} ; FAB⁺ m/z 417 [M^+ , 13%]; ^{13}C NMR displacement for C3, pregnenolone: $\delta = 71.65$ p.p.m., (I): $\delta = 74.41$ p.p.m.

Crystal data

$C_{25}H_{36}O_5$
 $M_r = 416.54$
 Triclinic, $P1$
 $a = 11.4692$ (10) Å
 $b = 11.8174$ (12) Å
 $c = 17.6837$ (14) Å
 $\alpha = 96.925$ (9)°
 $\beta = 104.907$ (6)°
 $\gamma = 95.201$ (8)°
 $V = 2280.7$ (4) Å³

$Z = 4$
 $D_x = 1.213$ Mg m⁻³
 Mo $K\alpha$ radiation
 Cell parameters from 50 reflections
 $\theta = 2.4$ – 12.0°
 $\mu = 0.08$ mm⁻¹
 $T = 298$ (1) K
 Irregular rod, colourless
 0.5 × 0.3 × 0.3 mm

Data collection

Bruker P4 diffractometer
 $2\theta/\omega$ scans
 9296 measured reflections
 7990 independent reflections
 5778 reflections with $I > 2\sigma(I)$
 $R_{int} = 0.031$
 $\theta_{max} = 25^\circ$

$h = -1 \rightarrow 13$
 $k = -13 \rightarrow 13$
 $l = -21 \rightarrow 20$
 2 standard reflections
 every 98 reflections
 intensity decay: 0.5%

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.066$
 $wR(F^2) = 0.191$
 $S = 1.26$
 7990 reflections
 1082 parameters
 H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.1P)^2]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{max} < 0.001$
 $\Delta\rho_{max} = 0.96$ e Å⁻³
 $\Delta\rho_{min} = -0.22$ e Å⁻³
 Extinction correction: *SHELXL12-Plus*
 Extinction coefficient: 0.0083 (17)

Table 1

Selected geometric parameters (Å, °).

C3—O20	1.463 (7)	C203—O220	1.465 (6)
C5—C6	1.299 (9)	C205—C206	1.327 (7)
O20—C21	1.316 (8)	O220—C221	1.332 (7)
C21—O22	1.150 (8)	C221—O222	1.190 (7)
C21—C23	1.470 (8)	C221—C223	1.509 (7)
C23—C24	1.498 (8)	C223—C224	1.454 (9)
C24—C25	1.462 (8)	C224—C225	1.488 (8)
C25—O26	1.197 (7)	C225—O226	1.193 (7)
C25—O27	1.282 (7)	C225—O227	1.275 (7)
C28—O29	1.356 (14)	C228—O229	1.164 (10)
C103—O120	1.464 (6)	C303—O320	1.470 (6)
C105—C106	1.290 (8)	C305—C306	1.322 (8)
O120—C121	1.281 (8)	O320—C321	1.281 (7)
C121—O122	1.233 (9)	C321—O322	1.210 (7)
C121—C123	1.478 (8)	C321—C323	1.464 (8)
C123—C124	1.472 (9)	C323—C324	1.476 (8)
C124—C125	1.492 (8)	C324—C325	1.486 (8)
C125—O126	1.201 (7)	C325—O326	1.197 (7)
C125—O127	1.299 (7)	C325—O327	1.307 (7)
C128—O129	1.203 (7)	C328—O329	1.208 (7)
C21—O20—C3	117.4 (5)	C221—O220—C203	117.3 (4)
O20—C21—C23	112.9 (5)	O220—C221—C223	111.0 (5)
O27—C25—C24	113.6 (5)	O227—C225—C224	114.9 (5)
C121—O120—C103	118.8 (5)	C321—O320—C303	120.1 (5)
O120—C121—C123	115.3 (6)	O320—C321—C323	115.3 (5)
O127—C125—C124	113.4 (5)	O327—C325—C324	113.4 (5)

Table 2

Hydrogen-bonding geometry (Å, °).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
O27—H27 ⁱ ···O226 ⁱ	0.89	1.77	2.635 (7)	164
O127—H127 ⁱⁱ ···O326 ⁱⁱ	0.87	1.83	2.689 (6)	167
O227—H227 ⁱⁱⁱ ···O26 ⁱⁱⁱ	0.94	1.77	2.683 (6)	165
O327—H327 ^{iv} ···O126 ^{iv}	1.04	1.67	2.707 (5)	174

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

Due to the poor data-to-parameters ratio, non-H atoms were refined anisotropically, with atoms closer than 1.7 Å restrained, with an effective standard uncertainty of 0.04 Å², to have the same U_{ij} components. H atoms bonded to sp^3 - or sp^2 -hybridized C atoms were placed at idealized positions. H atoms of the hydroxyl groups were found in difference maps. In order to avoid H···H bumping involving H30C belonging to the C30 methyl of the acetyl group in the first independent molecule, this methyl was first allowed to rotate about the C28—C30 bond, but afterwards its torsion geometry was fixed. In the final cycles, all H atoms were constrained to ride on their parent atoms, with $U_{iso}(H) = xU_{eq}(\text{parent})$, where constrained distances (Å) and x parameters are: aromatic C—H 0.93 and $x = 1.2$, methine C—H 0.98 and $x = 1.2$, methylene C—H 0.97 and $x = 1.2$, methyl C—H 0.98 and $x = 1.5$, and hydroxyl O—H distance found from difference maps and $x = 1.5$. The highest residual peak observed in the final difference map is located in the vicinity of the C28/O29/C30 acetyl group, at 1.67 Å from C28. Its quite large value is attributable to the fact that this group displays large thermal motions. The U_{eq} parameter for O29, for example, is the largest observed for the overall asymmetric unit, $U_{eq} = 0.224 (5) \text{ \AA}^2$.

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXTL-Plus* (Sheldrick, 1998); program(s) used to refine structure: *SHELXTL-Plus*; molecular graphics: *SHELXTL-Plus* and *MERCURY* 1.1.2 (CCDC, 2002); software used to prepare material for publication: *SHELXTL-Plus*.

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