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trans-Myristic Acid 3-*tert*-Butoxycarbonylamino-2-oxopiperidin-5-yl Ester,† a New Anthelmintic Compound

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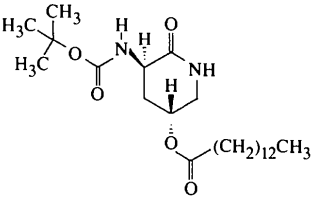
Abstract

The title compound, $C_{24}H_{44}N_2O_5$, is a 3-amino-5-hydroxy-piperidin-2-one derivative. Single-crystal X-ray diffraction was performed to determine the relative stereochemistry at the chiral centres. The substituents of the 2-piperidone ring have a *trans* configuration. The molecule crystallized in a monoclinic cell with a long *c* axis [47.742 (5) Å]; the space group is $P2_1/c$. The crystal structure is stabilized by hydrogen bonds along the *b*-axis direction.

Comment

As part of a general program of synthesis of new anthelmintic compounds, a series of 3-amino-5-hydroxy-piperidin-2-one derivatives has been synthesized. These compounds are structural analogues of secondary marine metabolites, which exhibit promising *in vitro* and *in vivo* anthelmintic activity (Crews & Hunter, 1993). Synthesis of the title compound, (I), involves a spontaneous lactone–lactam interconversion (Bols & Lundt, 1991; Chida, Tobe, Murai, Yamazaki & Ogawa, 1994), giving the racemic product. The ^{1}H NMR data were not sufficient to give the relative stereochemistry of the substituents at C2 and C4; thus, X-ray diffraction was used to determine the molecular structure and obtain the relative configurations.



(I)

The molecule contains a 2-piperidone ring substituted at C2 and C4. The substituents are a *tert*-butoxycarbonylamino group at C2 and a myristate group at C4. These substituents are *trans* with respect to each other, as is shown in Fig. 1; this configuration was expected, based on the synthesis. The 2-piperidone ring has a distorted half-chair conformation as in the 2-piperidone ring of (3*S*)-3-*tert*-butoxycarbonylamino-2-piperidone, (II) (Valle, Crisma, Toniolo, Yu & Johnson, 1989). The puckering parameters q_1, φ_2 and q_2 (Cremer & Pople, 1975) have values of 0.277 (2) Å, 282.7 (5)° and −0.341 (2) Å, respectively, for (I), and 0.331 (8) Å, −86.9 (15)° and −0.381 Å for (II) (Valle *et al.*, 1989). The presence of the substituent at C4 increases distortion from the symmetrical conformation of the ring, but comparison of torsion angles of the rings in (I) and (II) shows that they have similar conformations (see Table 3).

The N2 atom is equatorial to the ring, while O4 is axial, and in this conformation, the two substituents avoid overcrowding on one side of the ring. The hydrocarbon chain of myristic acid is planar, the maximum deviation from the least-squares plane being 0.04 (2) Å for C24. The *tert*-butoxycarbonylamino group is in its usual extended (*trans-trans*) arrangement, as in (II)

† Alternative name: 5-(*tert*-butoxycarbonylamino)-6-oxopiperidin-3-yl tetradecanoate.

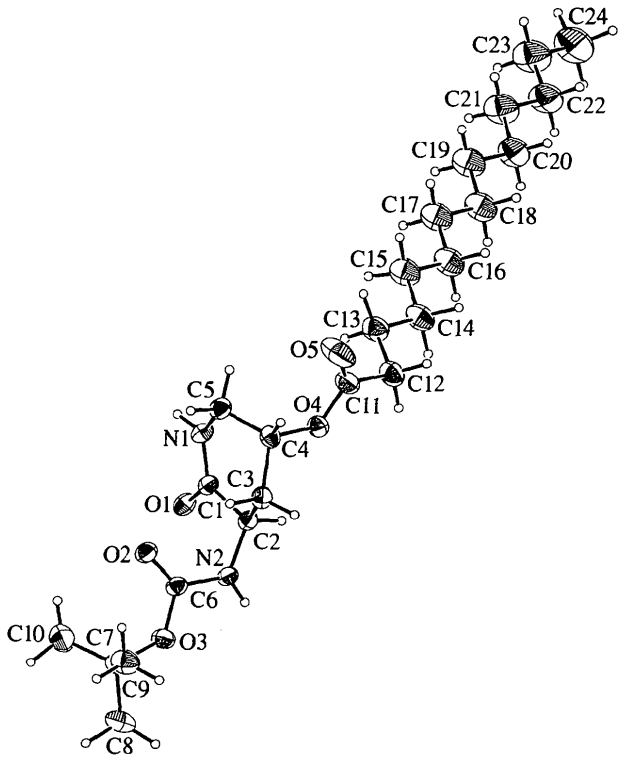


Fig. 1. A *ZORTEP* (Zsolnai, 1994*a*) drawing of (I) showing the atom-numbering scheme and conformation. Note that the molecule is as long as possible. Displacement ellipsoids are drawn at the 50% probability level and H atoms are drawn as spheres of arbitrary radii.

(Valle *et al.*, 1989). The groups are spatially extended in opposite directions, making the molecule as long as possible, 23.845 (9) Å (C8···C24) from end to end. There is a short intramolecular contact between O5 and H4 (bonded to C4) whose geometry is described in Table 2.

The molecule has two different segments clearly distinguished by properties and affinities. A polar head formed by the 2-piperidone ring and the *tert*-butoxycarboxylamino substituent, and the non-polar hydrocarbon chain of myristic acid. Both segments have high affinity for groups of similar polarity, which greatly affects packing. The extended conformation separates the non-polar and polar regions of the molecule in order to increase the polar and hydrophobic interactions with symmetry equivalent molecules in the crystal.

Molecules of (I) are linked by hydrogen bonds between N1—H1N···O2 and N2—H2N···O1. This linkage produces infinite chains along the *b*-axis direction. These chains are formed by alternate centrosymmetrically related molecules with two equivalent hydrogen bonds in each direction (see Table 2). Fig. 2 shows the hydrogen bonding among molecules of the same chain. Fig. 3 shows the packing of the molecules in the unit cell. The crystals grow as needles with the *b* axis parallel to the long dimension. Analysis of the packing demonstrates that the intermolecular hydrogen bonds in the structure are oriented in a direction approximately parallel to the *b* axis and suggests that these interactions can account for the observed crystal habit. In addition,

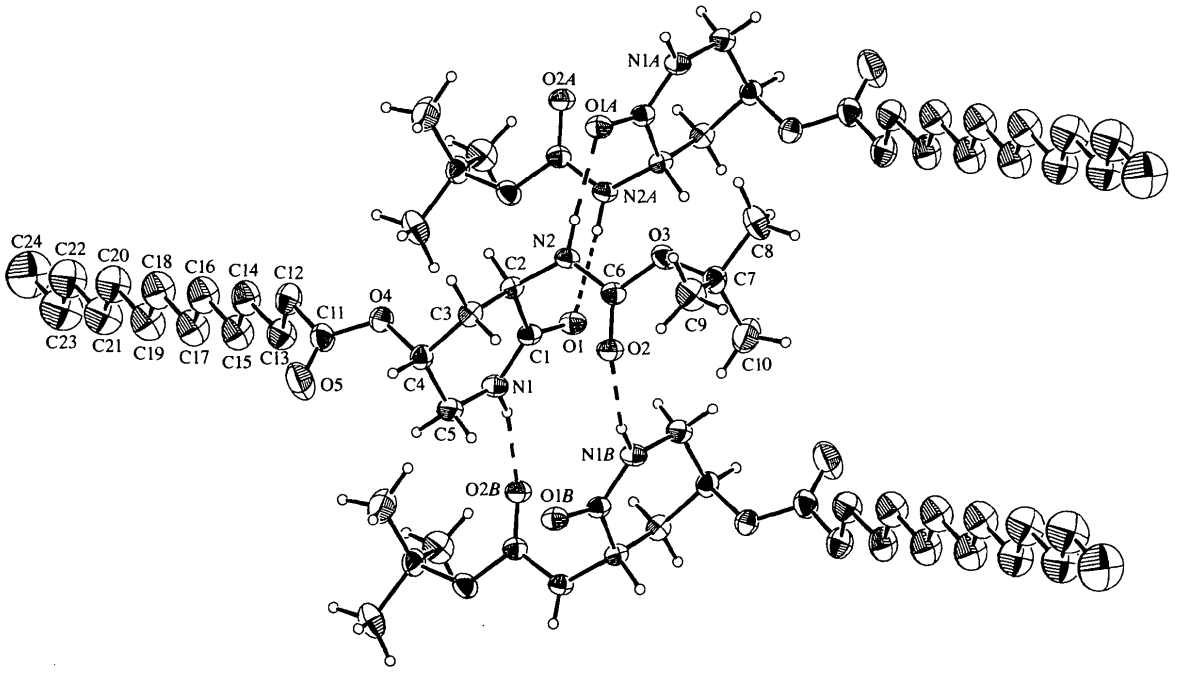


Fig. 2. A *ZORTEP* (Zsolnai, 1994*a*) drawing of a chain of molecules of (I). Dashed lines represent hydrogen bonds. Myristate chains are parallel to enhance interactions with other equivalent chains. Some H atoms have been omitted for clarity.

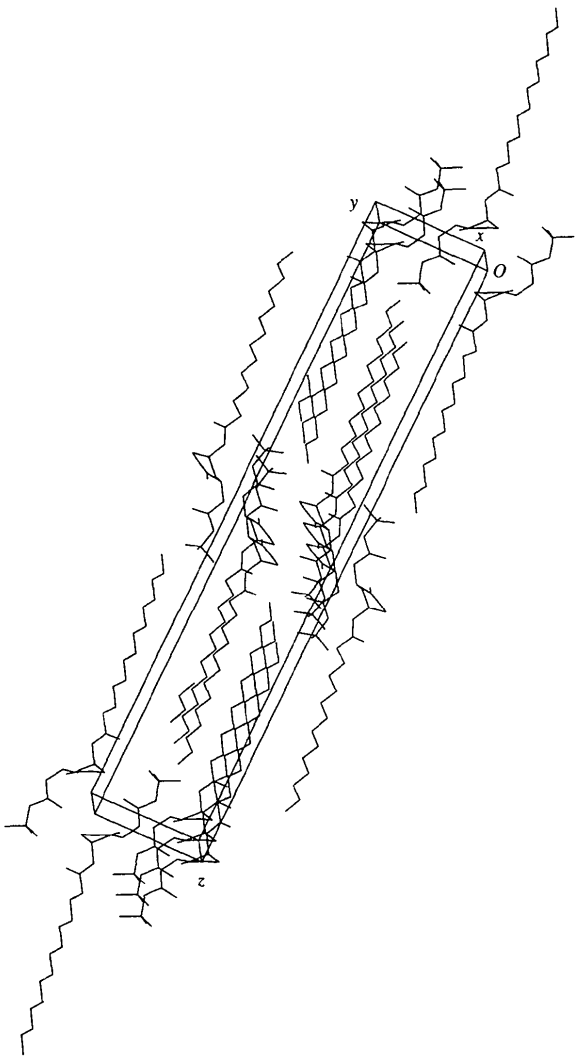


Fig. 3. A *ZORTEP* (Zsolnai, 1994*a*) drawing of the unit cell and packing. H atoms have been excluded for clarity.

the hydrocarbon chains, as expected, extend in the direction of the long *c* axis of the unit cell, with the packing interactions between the non-polar chains occurring along the crystallographic *a* axis.

Experimental

The title compound was synthesized by adding hydroxybenzothiazole to a stirred solution of (5-hydroxy-2-oxopiperidin-3-yl)carbamic acid *tert*-butyl ester (Gordon *et al.*, 1997) and myristic acid in dry DMF; this was allowed to react for 3 h under an atmosphere of nitrogen. The mixture was diluted with water and extracted with AcOEt. The product was obtained by evaporation *in vacuo* of the organic layer (Gordon *et al.*, 1997) and was recrystallized by vapour diffusion (ethyl acetate/hexane) at room temperature.

Crystal data

$C_{24}H_{44}N_2O_5$
M_r = 440.61
Monoclinic
$P2_1/c$
a = 6.6176 (9) Å
b = 8.3800 (5) Å
c = 47.7420 (5) Å
β = 90.497 (10)°
V = 2647.5 (16) Å^3
Z = 4
D_x = 1.105 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.7107 Å
Cell parameters from 25 reflections
θ = 3.185–5.820°
μ = 0.076 mm^{-1}
T = 293 (2) K
Needle
2.10 × 0.35 × 0.10 mm
Colourless

Data collection

Rigaku AFC-7*S* diffractometer
ω scans
Absorption correction:
ψ scans (Molecular Structure Corporation, 1993)
T_{min} = 0.934, T_{max} = 1.000
7487 measured reflections
6075 independent reflections
2814 reflections with $I > 2\sigma(I)$
R_{int} = 0.027
θ_{max} = 27.52°
$h = 0 \rightarrow 8$
$k = -1 \rightarrow 10$
$l = -62 \rightarrow 62$
3 standard reflections
every 197 reflections
intensity decay: 0.3%

Refinement

Refinement on F^2
$R(F)$ = 0.047
$wR(F^2)$ = 0.176
S = 1.044
6075 reflections
375 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0804P)^2 + 0.1065P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.172 e Å^{-3}
$\Delta\rho_{min}$ = −0.187 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

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

O1—C1	1.235 (2)	O4—C11	1.333 (3)
C1—N1	1.332 (2)	C11—O5	1.195 (3)
C1—C2	1.530 (3)	C11—C12	1.497 (3)
C2—N2	1.454 (2)	C12—C13	1.520 (4)
C2—C3	1.521 (3)	C13—C14	1.512 (4)
C3—C4	1.507 (3)	C14—C15	1.507 (4)
C4—O4	1.468 (2)	C15—C16	1.505 (4)
C4—C5	1.502 (3)	C16—C17	1.508 (4)
C5—N1	1.454 (3)	C17—C18	1.503 (4)
N2—C6	1.341 (2)	C18—C19	1.496 (4)
C6—O2	1.223 (2)	C19—C20	1.502 (4)
C6—O3	1.348 (2)	C20—C21	1.484 (4)
O3—C7	1.468 (2)	C21—C22	1.505 (4)
C7—C9	1.507 (4)	C22—C23	1.487 (5)
C7—C10	1.515 (4)	C23—C24	1.460 (5)
C7—C8	1.519 (4)		
O1—C1—N1	122.2 (2)	O3—C7—C8	101.2 (2)
O1—C1—C2	120.1 (2)	C9—C7—C8	111.0 (2)
N1—C1—C2	117.6 (2)	C10—C7—C8	111.3 (2)
N2—C2—C3	111.89 (15)	C11—O4—C4	117.4 (2)
N2—C2—C1	110.1 (2)	O5—C11—O4	123.4 (2)
C3—C2—C1	114.5 (2)	O5—C11—C12	124.2 (2)
C4—C3—C2	112.2 (2)	O4—C11—C12	112.3 (2)
O4—C4—C5	109.5 (2)	C11—C12—C13	111.3 (2)
O4—C4—C3	107.1 (2)	C14—C13—C12	113.4 (2)
C5—C4—C3	111.0 (2)	C15—C14—C13	114.7 (3)
N1—C5—C4	111.7 (2)	C16—C15—C14	114.3 (3)
C1—N1—C5	126.7 (2)	C15—C16—C17	115.9 (3)
C6—N2—C2	120.3 (2)	C18—C17—C16	115.5 (3)
O2—C6—N2	124.8 (2)	C19—C18—C17	116.1 (3)
O2—C6—O3	125.4 (2)	C18—C19—C20	115.8 (3)

N2—C6—O3	109.8 (2)	C21—C20—C19	115.8 (3)
C6—O3—C7	121.1 (2)	C20—C21—C22	116.4 (3)
O3—C7—C9	109.0 (2)	C23—C22—C21	115.5 (3)
O3—C7—C10	111.4 (2)	C24—C23—C22	116.9 (4)
C9—C7—C10	112.4 (2)		
O1—C1—C2—N2	−37.3 (2)	C1—C2—N2—C6	−54.5 (2)
N1—C1—C2—N2	146.1 (2)	C2—N2—C6—O3	169.5 (2)
O1—C1—C2—C3	−164.4 (2)	N2—C6—O3—C7	165.0 (2)
N1—C1—C2—C3	19.0 (2)	C6—O3—C7—C8	−177.0 (2)
N2—C2—C3—C4	−166.7 (2)	C3—C4—O4—C11	−151.9 (2)
C1—C2—C3—C4	−40.6 (2)	C4—O4—C11—C12	−174.6 (2)
C2—C3—C4—O4	−63.4 (2)	O4—C11—C12—C13	102.9 (3)
C2—C3—C4—C5	56.1 (2)	C11—C12—C13—C14	178.2 (2)
O4—C4—C5—N1	69.4 (2)	C13—C14—C15—C16	−178.4 (3)
C3—C4—C5—N1	−48.7 (2)	C15—C16—C17—C18	180.0 (3)
O1—C1—N1—C5	169.4 (2)	C17—C18—C19—C20	179.5 (3)
C2—C1—N1—C5	−14.0 (3)	C19—C20—C21—C22	179.5 (3)
C4—C5—N1—C1	29.3 (3)	C21—C22—C23—C24	−178.6 (4)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C4—H4···O5	1.00 (2)	2.684 (3)	2.30 (2)	101.6 (13)
N1—H1N···O2^{i}	0.88 (2)	2.980 (3)	2.12 (2)	165 (2)
N2—H2N···O1^{ii}	0.86 (2)	2.910 (3)	2.06 (3)	175.4 (18)

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

Table 3. *Torsion angles (°) in the 2-piperidone rings of (I) and (II)*

	(I)	(II)
C4—C5—N1—C1	29.3 (3)	−26.8 (14)
C2—C1—N1—C5	−14.0 (3)	12.4 (14)
C1—C2—C3—C4	−40.6 (2)	48.1 (10)
N1—C1—C2—C3	19.0 (2)	−23.3 (12)
C2—C3—C4—C5	56.1 (2)	−62.9 (10)
C3—C4—C5—N1	−48.7 (2)	51.1 (11)

The structure was solved by direct methods. Most H atoms were located at difference Fourier maps except those bonded to the final atoms of the myristate chain (C16–C24). Those bonded to the C2, C3, C4, C5, N1 and N2 atoms were freely refined. H atoms of the *tert*-butyl group were all refined with the same C—H distance and U_{iso} value which converged to 0.99 (2) Å and 0.114 (4) Å^2, respectively. All H atoms belonging to the linear carbon chain were refined with $U_{iso} = 1.2U_{eq}$ of the parent atom and equal C—H distances [0.939 (16) Å], except for those bonded to C24 which were refined with $U_{iso} = 1.5U_{eq}$ of C24 and a C—H distance equal to that of the *tert*-butyl group.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1993). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *MSC/AFC Diffractometer Control Software*. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ZORTEP* (Zsolnai, 1994*a*) and *XPMA* (Zsolnai, 1994*b*). Software used to prepare material for publication: *PLATON*93 (Spek, 1993).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1028). Services for accessing these data are described at the back of the journal.

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(1*R*,2*R*)-(−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine:† a Salen Ligand of Jacobsen's Catalyst

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Abstract

In the title compound, $C_{36}H_{54}N_2O_2$, two salicylideneimine moieties are situated nearly perpendicular to each other so that one of them has to be rotated for complexation. There are O—H···N intramolecular hydrogen bonds in both salicylideneimine moieties.

Comment

Cationic manganese(III) complexes of the salen ligand [*N*,*N*′-ethylenebis(salicylideneaminato)] are effective catalysts for the epoxidation of various olefins

† Alternative systematic name: 4,4′,6,6′-tetra-*tert*-butyl-2,2′-[1,2-cyclohexanediylbis(nitrilomethylidyne)]diphenol.