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(±)-2-Aza-3,9-dioxotricyclo[4.4.4.0^{1,6}]-tetradecane: dimeric and catemeric hydrogen bonding in two polymorphs of a propellanoid keto lactam

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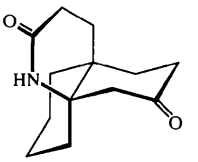
Abstract

The title compound, $C_{13}H_{19}NO_2$, is the cyclized ring-chain tautomer of the corresponding angularly substituted $\Delta^{1(9)}$-2-octalone and exists in two crystalline polymorphs, (I) and (II), displaying fundamentally different intermolecular hydrogen-bonding patterns, neither of which involves the ketone. In (I), amide groups are paired by hydrogen bonding in non-centrosymmetric dimers (space group *C*2/*c*). In (II), hydrogen bonding proceeds from the NH of each molecule to the amide C=O of a screw-related neighbor, generating parallel, centrosymmetrically related, counterdirectional chains passing through the cell in the *b* direction (space group $P2_1/c$). Several intermolecular C=O···H—C close contacts were found for both (I) and (II).

Comment

Our interest in the solid-state hydrogen-bonding modes of keto carboxylic acids (Thompson *et al.*, 1992; Coté *et al.*, 1996; Lalancette *et al.*, 1998) has led us to synthesize several $\Delta^{1(9)}$-2-octalones with angular substituents (Lalancette *et al.*, 1991). One such synthesis, intended to provide 4a-(2-carboxyethyl)-2-oxo-(3*H*)-2,3,4,4a,5,6,7,8-octahydronaphthalene (Becker & Birnbaum, 1980; Mayer *et al.*, 1984), also yielded the title compound, (I), which evidently arose by cyclization of the corresponding bicyclic enone carboxamide. Numerous such propellanoid compounds have been prepared since the mid-1960s (Altman *et al.*, 1966; Thompson, 1966, 1967). It is noteworthy that the analogous lactone is reportedly not formed from the corresponding keto carboxylic acid (Mayer *et al.*, 1984; Onan *et al.*, 1984), but it is not yet clear whether the ring-chain equilibria for this acid *versus* its amide are really dramatically different or whether an unfavorable equilibrium is merely displaced by selective precipitation of the highly crystalline lactam (I). Many of the issues and factors governing the five principal solid-state hydrogen-bonding modes known for keto acids also arise in keto amides (Berkovitch-Yellin & Leiserowitz, 1980), and we have examined the solid-state structure of the title compound, which is additionally of interest because it crystallizes in two polymorphs, (I) and (II), with fundamentally different intermolecular hydrogen-bonding patterns.



(I)

Fig. 1 shows the asymmetric unit for both (I) and (II), with its numbering. All bond lengths and angles for (I) and (II) are essentially identical, with an r.m.s. deviation of only 0.05 Å for the superimposed structures. As expected, the lactam ring is flattened to a half-chair around the amide function, while the two remaining rings adopt chair conformations. Of the two 'all-chair' conformations available, the one adopted has the N atom equatorial to the ketone ring. In semi-empirical (*AM*1) molecular-modeling studies (Dewar *et al.*, 1985; Wavefunction, 1995), the enthalpy advantage found for this conformer was so slight (0.4 kcal mol^{-1}) (1 cal = 4.184 J) that the actual choice of conformers might easily be dominated by packing forces.

Fig. 2 is a partial packing diagram for (I), with extracellular molecules, illustrating the packing of the non-centrosymmetric dimers paired by N—H···O=C hydrogen bonding involving only the amide [N···O = 3.004 (4) Å]. The two halves of each dimer are of identical handedness, related by twofold axes that occur at special positions $a = 0$, $c = \frac{1}{4}$ and $\frac{3}{4}$ and at $a = \frac{1}{2}$, $c = \frac{1}{4}$ and $\frac{3}{4}$. The dimer units themselves are centrosymmetrically arrayed around $\frac{1}{2},\frac{1}{2},\frac{1}{2}$ and $0,\frac{1}{2},\frac{1}{2}$. For (I), three intermolecular C=O···H—C close contacts were found: between O1 and H5*B* (2.53 Å), and juxtaposing O2 with H11*A* (2.64 Å) and H7*A* (2.68 Å). Such contacts presumably represent polar attractions contributing materially to the packing forces (Jönsson, 1972; Leiserowitz, 1976; Berkovitch-Yellin & Leiserowitz, 1982).

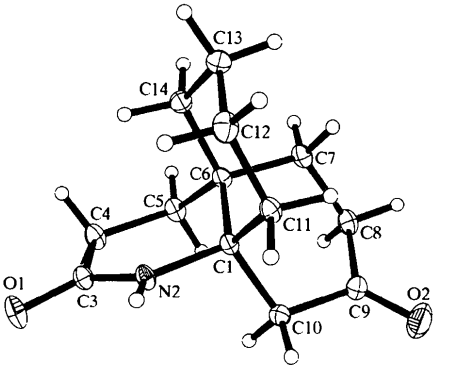


Fig. 1. The asymmetric unit for both (I) and (II) with its numbering. Ellipsoids are set at the 20% probability level.

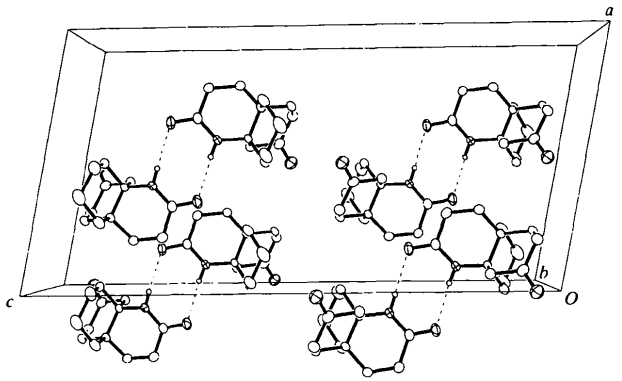


Fig. 2. A partial packing diagram for (I), with extracellular molecules, illustrating the non-centrosymmetric dimers formed by amide pairing of molecules related by a twofold axis. Ellipsoids are set at the 20% probability level.

Fig. 3 illustrates the packing for (II), which involves helical hydrogen-bonding catemers proceeding from the amide NH of each molecule to the amide C=O of a neighbor, screw-related in **b** [N···O = 3.007 (2) Å]; the ketone is not involved in the hydrogen bonding. Centrosymmetrically related pairs of parallel single-strand helices pass counterdirectionally along the *bc* faces of each chosen cell at $\frac{1}{4}$ and $\frac{3}{4}$ in **c**. Five intermolecular C=O···H—C close contacts were found for (II), joining O1 with H4*A* (2.52 Å) and H11*B* (2.69 Å), and joining O2 with H8*B* (2.61 Å), with H5*A* (2.66 Å) and with H13*B* (2.68 Å). Despite virtually identical asymmetric units for (I) and (II), their crystal densities differ significantly [D_x = 1.229 for (I) *versus* 1.275 Mg m^{-3} for (II)]. The 3.6% greater density for (II) corresponds to more efficient packing and is consistent with the greater number of C=O···H—C close contacts observed.

The two hydrogen-bonding patterns found for (I) and (II) are analogs of the dimeric and catemeric hydrogen-bonding modes known for simple carboxylic acids (Leiserowitz, 1976). Acids also containing a keto function most frequently dimerize without participation of the ketone, analogous to keto amide (I). The formation of amide catemers without ketone participation, seen in (II), corresponds to a far rarer hydrogen-bonding arrangement in keto acids, the acid-to-acid catemer mode, for which we know of only three cases (Haneishi *et al.*, 1974; Nishizawa *et al.*, 1989; Lalancette *et al.*, 1998). The absence of ketone involvement in the hydrogen bonding of both (I) and (II) is consistent with a much greater negative-charge density expected for an amide O atom than a ketone O atom. The normal order of carbonyl basicity is amide >> acid > ester > ketone, with a gap of *ca* 5 pK_a units separating amides from acids, and far smaller differences (1–1.5 pK_a units) among the last three.

The solid-state (KBr) infrared spectrum of (II) has multiple C=O absorptions, at 1720 and 1710 cm^{-1} (ketone) and 1691, 1671, 1664 and 1659 cm^{-1} (amide). The dimeric polymorph (I) has its KBr peaks at 1712.5 and 1659.5 cm^{-1}. In $CHCl_3$ solution, the absorptions appear at 1723, 1710, 1664 and 1637 cm^{-1}.

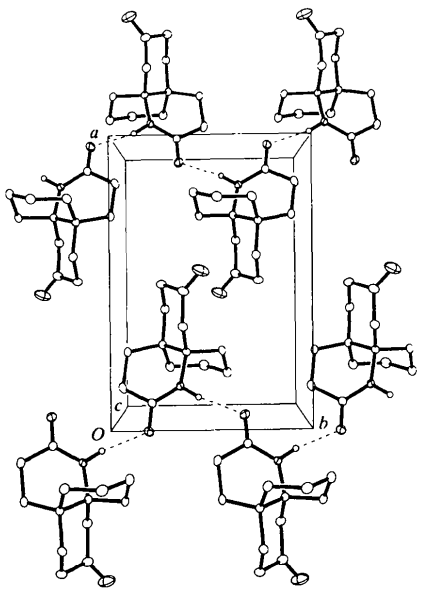


Fig. 3. A partial packing diagram for (II), with extracellular molecules, illustrating the catemers created by hydrogen-bonding proceeding from the NH of each molecule to the amide C=O of a screw-related neighbor. The parallel, centrosymmetrically related chains pass counterdirectionally through the cell in the *b* direction. Ellipsoids are set at the 20% probability level.

Experimental

Cyclohexanone-2-propionitrile (Stork *et al.*, 1963) was subjected to Robinson annulation (Becker & Birnbaum, 1980) with equimolar quantities of methyl vinyl ketone and NaOMe in cold MeOH, yielding 10-(2-cyanoethyl)-$\Delta^{1(9)}$-octal-2-one as the major crystalline distillable product, accompanied by 2% of (I). After purification, crystals of (I), m.p. 462 K, were obtained from acetone–methyl acetate, while benzene–ethyl acetate provided (II), whose m.p. appears to be about 437 K, but which also apparently undergoes transformation to (I) under heating in the capillary.

Polymorph (I)

Crystal data

$C_{13}H_{19}NO_2$
M_r = 221.29
Monoclinic
$C2/c$
a = 11.966 (3) Å
b = 8.602 (1) Å
c = 23.688 (3) Å
β = 101.09 (1)°
V = 2392.7 (7) Å^3
Z = 8
D_x = 1.229 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 31 reflections
θ = 2.91–12.38°
μ = 0.082 mm^{-1}
T = 293 (2) K
Rectangular prism
0.80 × 0.30 × 0.20 mm
Pale yellow

Data collection

Siemens *P*4 diffractometer
$2\theta/\theta$ scans
Absorption correction: numerical (*XPREP*; Sheldrick, 1997)
T_{min} = 0.971, T_{max} = 0.982
2809 measured reflections
2115 independent reflections
1038 reflections with $I > 2\sigma(I)$
R_{int} = 0.051
θ_{max} = 25°
$h = -14 \rightarrow 14$
$k = -1 \rightarrow 10$
$l = -1 \rightarrow 28$
3 standard reflections
every 97 reflections
intensity variation: <1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.065
$wR(F^2)$ = 0.162
S = 1.01
2115 reflections
149 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0526P)^2 + 1.1209P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.184 e Å^{-3}
$\Delta\rho_{min}$ = −0.142 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected bond lengths (Å) for (I)*

O1—C3	1.240 (4)	C1—N2	1.474 (4)
O2—C9	1.216 (4)	N2—C3	1.325 (4)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2···O1^{i}	0.86	2.19	3.004 (4)	156
C5—H5*B*···O1^{ii}	0.97	2.53	3.453 (5)	158
C7—H7*A*···O2^{iii}	0.97	2.68	3.562 (5)	152
C11—H11*A*···O2^{iii}	0.97	2.64	3.575 (4)	161

Symmetry codes: (i) $2 - x, y, \frac{1}{2} - z$; (ii) $\frac{3}{2} - x, y - \frac{1}{2}, \frac{1}{2} - z$; (iii) $2 - x, -y, 1 - z$.

Polymorph (II)

Crystal data

$C_{13}H_{19}NO_2$
M_r = 221.29
Monoclinic
$P2_1/c$
a = 11.135 (2) Å
b = 7.626 (2) Å
c = 13.580 (2) Å
β = 90.62 (1)°
V = 1153.1 (4) Å^3
Z = 4
D_x = 1.275 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 32 reflections
θ = 6.18–12.17°
μ = 0.085 mm^{-1}
T = 293 (2) K
Rectangular prism
0.92 × 0.32 × 0.12 mm
Colorless

Data collection

Siemens *P*4 diffractometer
$2\theta/\theta$ scans
Absorption correction: numerical (*XPREP*; Sheldrick, 1997)
T_{min} = 0.969, T_{max} = 0.991
3507 measured reflections
2653 independent reflections
1712 reflections with $I > 2\sigma(I)$
R_{int} = 0.033
θ_{max} = 27.50°
$h = -14 \rightarrow 14$
$k = -1 \rightarrow 9$
$l = -1 \rightarrow 17$
3 standard reflections
every 97 reflections
intensity variation: <1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.060
$wR(F^2)$ = 0.151
S = 1.03
2653 reflections
149 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0483P)^2 + 0.6911P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.503 e Å^{-3}
$\Delta\rho_{min}$ = −0.215 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 3. *Selected bond lengths (Å) for (II)*

O1—C3	1.237 (3)	C1—N2	1.479 (2)
O2—C9	1.200 (3)	N2—C3	1.341 (3)

Table 4. *Hydrogen-bonding geometry (Å, °) for (II)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2···O1^{i}	0.86	2.16	3.007 (2)	171
C4—H4*A*···O1^{ii}	0.97	2.52	3.423 (3)	156
C11—H11*B*···O1^{i}	0.97	2.69	3.446 (3)	135
C5—H5*A*···O2^{iii}	0.97	2.66	3.625 (3)	179
C8—H8*B*···O2^{iii}	0.97	2.61	3.393 (3)	138
C13—H13*B*···O2^{iv}	0.97	2.68	3.632 (3)	169

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

The crystals used in the determination of both (I) and (II), although large, were well within the size permitted by the normal focus tube.

For both compounds, data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS* (Siemens, 1996); data reduction: *XSCANS* (Siemens, 1996); program(s) used to solve structures: *SHELXTL*97 (Sheldrick, 1997); program(s) used to refine structures: *SHELXTL*97; molecular graphics: *SHELXTL*97; software used to prepare material for publication: *SHELXTL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1543). Services for accessing these data are described at the back of the journal.

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(2*S**,4*S**,5*R**)-4-Methyl-2-[(5*S**)-3-methyl-4,5-dihydroisoxazol-5-yl]-5-phenyl-3-(toluene-4-sulfonyl)oxazolidine

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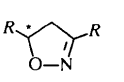
Abstract

The title compound, $C_{21}H_{24}N_2O_4S$, containing 2-isoxazoline and oxazolidine moieties, was studied in order to determine its relative configuration, which could not be determined unambiguously by NMR techniques. The results have shown that the substituents on the three C atoms of the oxazolidine cycle are all on the same side of the ring, while the aromatic group of the toluene-4-sulfonate substituent on the N atom is located on the opposite side. The 2-isoxazoline ring was found to have the 5′*S** configuration.

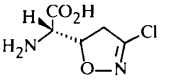
Comment

Chiral 2-isoxazolines are an important class of compounds that include the antitumor agent activicin (AT-125; Mzengeza & Whitney, 1988), the antithrombotic agent XR229 (Wityak *et al.*, 1997) and the neurotransmitter inhibitor agent dihydromuscimol (De Amici *et al.*, 1990).

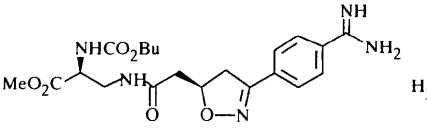
The absolute configuration of the 2-isoxazoline stereocentre is of paramount importance for biological activity. For instance, 5*S* stereochemistry was found to be required in activicin for high potency *in vivo*, while for XR229, the 5*R* configuration was found essential. For dihydromuscimol, it was demonstrated that inhibitory effects on the neurotransmitter GABA–uptake system reside exclusively in the 5*R*-enantiomer, whereas GABA–mimetic activity is due to the 5*S* species (GABA is γ-aminobutyric acid). In addition, 2-isoxazolines are very versatile intermediates and have been used for the synthesis of a wide variety of natural products (Torsell, 1988).



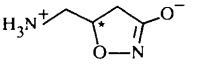
2-Isoxazolines



Activicin (AT-125)
Antitumor agent

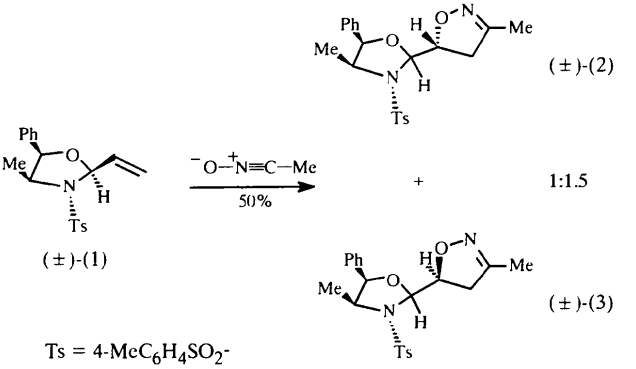


XR229
Antithrombotic agent



(5*RS*)-Dihydromuscimol

At the start of a program aimed at the asymmetric synthesis of 2-isoxazolines, we chose (±)-norephedrine to be our auxiliary, mainly based on the results reported for other highly asymmetric processes (Abdallah *et al.*, 1982). Racemic compounds were chosen for initial studies due to their lower toxicity and the lower cost of starting materials. However, we came across a problem with the characterization of the mixture of diastereomers obtained from the 1,3-dipolar cycloaddition of acetonitrile oxide onto 2-vinyloxazolidine, (1) (Soucy *et al.*, 1998). Indeed, due to free rotation around the C2—C5′ σ-bond, it was not possible to determine unambiguously by NMR techniques the stereochemistry at the C5′ stereocentre for each of the isomers (2) and (3). Thus, it became important to try to obtain crystals suitable for X-ray diffraction studies. Fortunately, we were able to crystallize compound (3), the major isomer obtained in the reaction shown below.



Ts = 4-MeC$_6$H$_4$SO$_2$-

The crystal belongs to the centrosymmetric $P2_1/c$ space group. Therefore, the unit cell contains two enantiomeric forms. A labelled diagram of the molecule is shown in Fig. 1. A few selected bond distances