Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

3-Bromomethyl-3-ethyl-3,4,6,7,8,8a-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]-oxazine-1,4-dione

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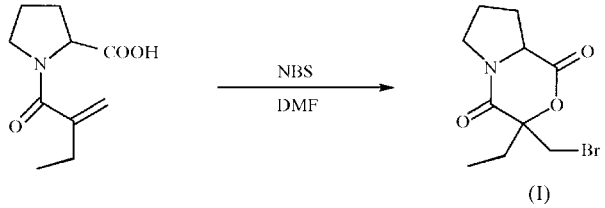
Received 18 February 2004
Accepted 10 May 2004
Online 22 June 2004

In the title compound, $C_{10}H_{14}BrNO_3$, the six-membered lactone ring is in a boat conformation, with the two carbonyl groups *cis* to one another across the boat basal plane. C—H···O hydrogen bonds and weak C—H···Br interactions stabilize the crystal structure.

Comment

The analogues (*S*)- or (*R*)-1,4-dioxotetrahydropyrrolo[2,1-*c*]-[1,4]oxazine, prepared from α,β-unsaturated acids with (*S*)- or (*R*)-proline *via* a highly asymmetric bromolactonization reaction, are useful as versatile synthetic building blocks for many active products (Kirkovsky *et al.*, 2000; Jew *et al.*, 2000; Corey, 1987). In the course of our studies of the asymmetric synthesis of camptothecin analogues with anticancer activities, crystals of the title compound, (I), a key chiral building block for the preparation of these types of compounds, have been obtained from the asymmetric bromolactonization of (*S*)-*N*-ethylacryloylproline with *N*-bromosuccinimide in an anhydrous dimethylformamide solution.



(I)

The bond lengths and angles in (I) have normal values (Table 1) and compare with those obtained from MM2 calculations (CambridgeSoft, 2001), except that the C4—N5 bond length [1.316 (4) Å] is shorter than the theoretical value (1.359 Å). The chiral centre at atom C3 (*S*) is characterized by the Br1—C10—C3—O2 [−65.8 (3)°] and O2—C3—C11—C12 [62.4 (4)°] torsion angles, thus confirming reported experimental results (Jew *et al.*, 1979*a*,*b*,*c*; Hayashi *et al.*, 1981). The configuration of (I) is the same as that of closely related 3-bromomethyl-3-methyl-1,4-dioxo-3,4,6,7,8,8a-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine [compound 23 of Crout *et al.* (1991)]. To further confirm the *S* configuration preference in the asymmetric bromolactonization reaction of α,β-unsaturated acids with (*S*)-proline, the energies of *S* and *R* configuration products of the title bromolactone, (I), and compound 23 were calculated using the *HYPERCHEM* program (Hypercube, 1998) at the semi-empirical AM1 computational level. An r.m.s. gradient of 0.05 kcal mol^{-1} Å^{-1} for the forces acting on each atom was employed as the convergence criterion. The final energies of (*S*)-bromolactones (−2866.84

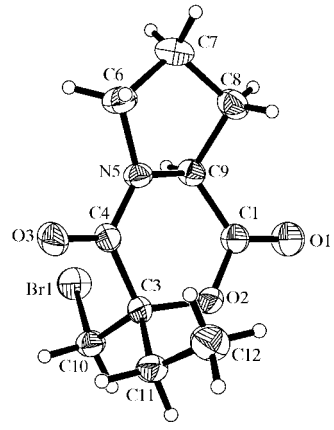


Figure 1
A view of the molecular structure of (I), with the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

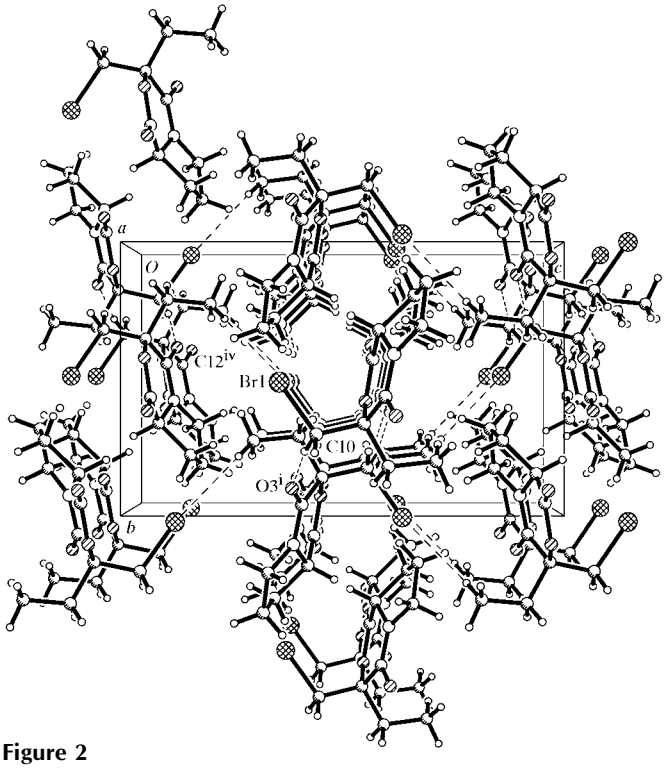


Figure 2
The molecular packing of (I). The stronger intramolecular contacts (Table 2) are shown as dashed lines. [Symmetry codes: (i) $x-\frac{1}{2}$, $\frac{3}{2}-y$, $1-z$; (iv) $\frac{3}{2}-x$, $1-y$, $z-\frac{1}{2}$.]

 DOI: 10.1107/S010827010401131X

and −2587.61 a.u.) were slightly lower than those of (*R*)-bromolactones (−2864.90 and −2586.73 a.u.) for (I) and compound 23, respectively. Thus, qualitatively, there is an energy advantage in the *S* configuration bromolactone.

The lactone ring of (I) adopts a boat conformation (Fig. 1). Atoms O1 and O3 of the two carbonyl groups lie 0.118 (6) and 0.140 (5) Å, respectively, from the boat basal plane, which indicates that the two carbonyl groups have a *cis* orientation. Atoms C9 and C3 lie 0.295 (5) and 0.193 (5) Å, respectively, from the boat plane (N5/C4/O2/C1). The pyrrolidine ring is in an envelope conformation, the flap atom C8 lying 0.559 (6) Å from the C7/C6/N5/C9 plane.

The packing structure of (I) involves weak C10—H10*B*···O3 and very weak C10—H10*A*···O2 hydrogen bonds (Table 2). These are responsible for the formation of dimer aggregates, which are additionally stabilized by weak C12—H12*C*···Br1 interactions (Fig. 2).

Experimental

To a stirred solution of (*S*)-*N*-ethylacryloylproline (20 mmol, 3.94 g) in anhydrous dimethylformamide (40 ml) was added *N*-bromosuccinimide (40 mmol, 7.12 g) in portions under argon at room temperature. The reaction mixture was stirred for 24 h and then evaporated to dryness under reduced pressure. The residue was diluted with water (60 ml) and extracted with ethyl acetate (20 ml × 3). The combined organic phase was washed with saturated $NaHCO_3$ solution (30 ml), water (30 ml) and brine (30 ml), and then dried over $MgSO_4$ before being evaporated to dryness. The residue was crystallized from ethyl acetate to give (I) in 76% yield (m.p. 377.7–379.2 K). Single crystals of (I) suitable for X-ray diffraction were grown from a solution in methanol by slow evaporation. ^{1}H NMR ($CDCl_3$, TMS, internal reference): δ 4.51 (*dd*, 1H, NCHCO), 3.89, 3.61 (*d*, 2H, CH_2Br), 3.73, 3.60 (*m*, 2H, CH_2N), 1.82–2.50 (*m*, 6H, 3 × CH_2), 0.93 (*t*, 3H, CH_3).

Crystal data

$C_{10}H_{14}BrNO_3$
M_r = 276.13
Orthorhombic, $P2_12_12_1$
a = 8.897 (3) Å
b = 9.003 (3) Å
c = 14.577 (5) Å
V = 1167.6 (7) Å^3
Z = 4
D_x = 1.571 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 1022 reflections
θ = 2.7–25.5°
μ = 3.51 mm^{-1}
T = 293 (2) K
Block, colourless
0.20 × 0.10 × 0.08 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.541, T_{max} = 0.767
4889 measured reflections
2055 independent reflections
1769 reflections with $I > 2\sigma(I)$
R_{int} = 0.024
θ_{max} = 25.0°
$h = -10 \rightarrow 10$
$k = -9 \rightarrow 10$
$l = -13 \rightarrow 17$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.030
$wR(F^2)$ = 0.069
S = 1.03
2055 reflections
137 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0392P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.30 e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter = 0.020 (11), 847 Friedel pairs

Table 1
Selected geometric parameters (Å, °).

Br1—C10	1.943 (3)	C4—N5	1.316 (4)
C1—O2	1.336 (4)	C6—N5	1.462 (4)
C3—O2	1.454 (4)	C9—N5	1.453 (4)
O2—C3—C4	113.4 (2)	C9—C8—C7	102.7 (3)
C10—C3—C4	111.7 (2)	N5—C9—C1	112.9 (2)
O2—C3—C11	105.8 (2)	C3—C10—Br1	113.4 (2)
Br1—C10—C3—O2	−65.8 (3)	O2—C3—C11—C12	62.4 (4)

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

D—H···A	D—H	H···A	D···A	D—H···A
C10—H10*B*···O3^{i}	0.97	2.25	3.206 (4)	169
C12—H12*C*···Br1^{ii}	0.96	3.03	3.627 (4)	122
C10—H10*A*···O2^{iii}	0.97	2.60	3.560 (4)	173

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

H atoms were positioned from a difference Fourier map and then treated as riding, with C—H distances of 0.97 (CH_2) and 0.96 Å (CH_3), and U_{iso}(H) values of 1.2 (CH_2) or 1.5 (CH_3) times U_{eq}(C).

Data collection: *SMART* (Bruker, 1997); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1997) and *SHELXTL* (Bruker, 1998); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

The authors thank Professor Lin-Hong Weng and Dr Zhen-Xia Chen for their help with the X-ray crystallographic analysis.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA1049). Services for accessing these data are described at the back of the journal.

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