Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

Ethyl 4-(2-bromomethyl-5,5-dimethyl-1,3-dioxan-2-yl)-5-methylisoxazole-3-carboxylate

Brendan Twamley,[a]* Monika Szabon-Watola,[b] Shikha Sharma[b] and Nicholas R. Natale[b]‡

[a]University Research Office, University of Idaho, Moscow, ID 83844-3010, USA, and [b]Department of Chemistry, University of Idaho, Moscow, ID 83844-2343, USA

‡ Current address: Center For Structural and Functional Neuroscience, Department of Biomedical and Pharmaceutical Sciences, University of Montana, Missoula, MT 59812, USA.

Correspondence e-mail: btwamley@uidaho.edu

Key indicators

Single-crystal X-ray study
T = 90 K
Mean σ(C–C) = 0.005 Å
R factor = 0.033
wR factor = 0.092
Data-to-parameter ratio = 14.9

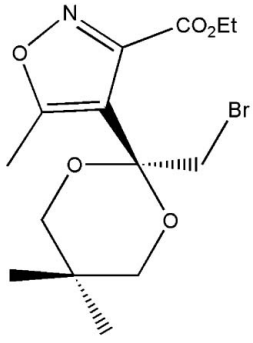
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 22 March 2007
Accepted 27 March 2007

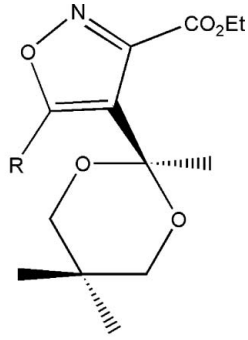
In the structure of the title compound, $C_{14}H_{20}BrNO_5$, at 90 (2) K, the isoxazole is an axial substituent of the chair conformation dimethyldioxanyl ring. There is an antiparallel arrangement of the isoxazole rings with an oxygen to ring centroid distance of 3.402 (6) Å.

Comment

Isoxazole containing drugs, such as valdecoxcib (Zhang *et al.*, 2003), oxacillin (Murai *et al.*, 1981) and isoxicam (Sircar *et al.*, 1985), are known to metabolize by hydroxylation at the 5-methyl position. We sought a route to the 5-hydroxylmethylene analog (III) from acetal (II). We examined bromination of (II) to (IV) followed by nucleophilic displacement with water, which is more effective than our previous efforts to produce (III) (Zhou & Natale, 1998), but is complicated by the presence of a by-product which was difficult to separate chromatographically at the bromide stage. Compound (I) is the by-product produced during the bromination of (II).



(I)



(II) R = CH_3
(III) R = CH_2OH
(IV) R = CH_2Br

The molecular stucture of the title compound, (I), is shown in Fig. 1. The six-membered dioxane ring adopts a similar chair conformation to the acetal monomer (II) (Zhou *et al.*, 2000), the dimer (Burkhart *et al.*, 2001) and the methylisoindolyl-isoxazole-substituted monomer (Nelson *et al.*, 2004). In (I), and in all related compounds, the isoxazole adopts an axial position on the dioxane ring. A comparison of the torsion angles is shown in Table 1. Significant intermolecular interactions have been discounted for the arrangement of the isoxazole to the dioxane ring (*e.g.* hydrogen bonding, *etc.*; Zhou *et al.*, 2000); however, the packing arrangement of all monomers show similarities – an antiparallel arrangement of the isoxazoles (for distances and angles see Table 1). The

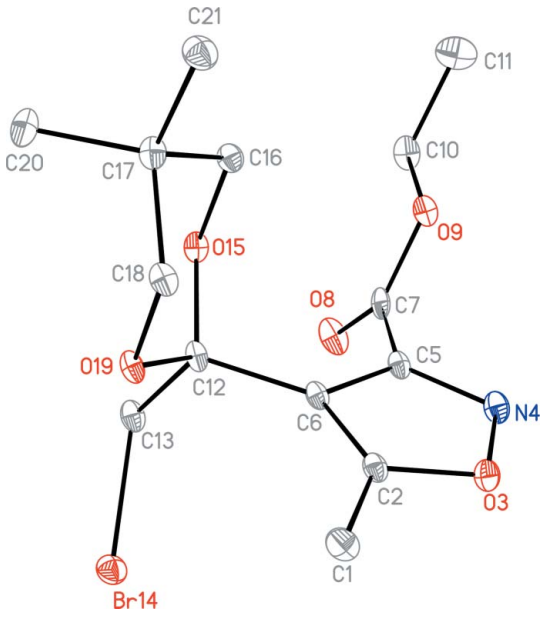


Figure 1
A displacement ellipsoid plot (30%) of the molecular structure of (I). H atoms have been omitted for clarity.

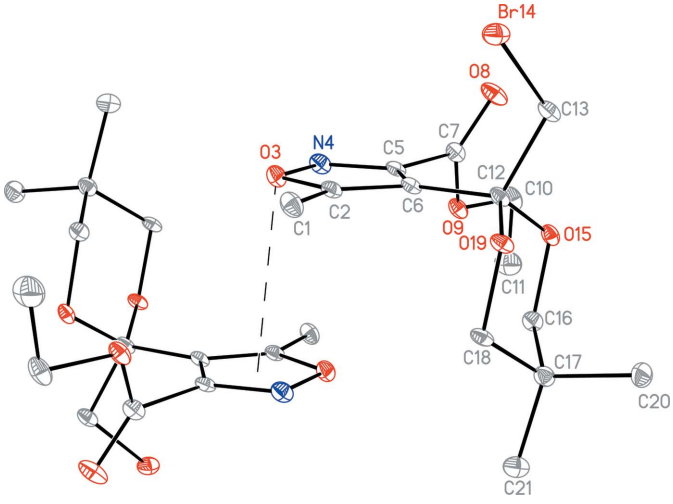


Figure 2
A side-on displacement ellipsoid plot (30%) of the isoxazole arrangement in (I). The dashed line indicates the interaction given in Table 1 between O3 and the isoxazole centroid. H atoms have been omitted for clarity.

antiparallel isoxazole arrangement is shown in Fig. 2. The packing in (I) also leads to a short intermolecular contact between Br14 and Br14^{i} [symmetry code: (i) $2-x, -y, 1-z$] of 3.3538 (5) Å, displayed in Fig. 3. The isoxazole antiparallel arrangement is also seen in the dimer (Burkhart *et al.*, 2001); however, there are significant distortions to this geometry compared with the monomers.

Experimental

Recrystallized *N*-bromosuccinimide (1.38 g, 7.77 mmol, 1.1 equivalents) was added to a stirred solution of (II), ethyl 4-[1-(1,3-dioxanyl)]-ethyl-5-methyl-3-isoxazolylcarboxylate (2 g, 7.07 mmol), in CCl_4 (20 ml) at room temperature. The reaction mixture was stirred for

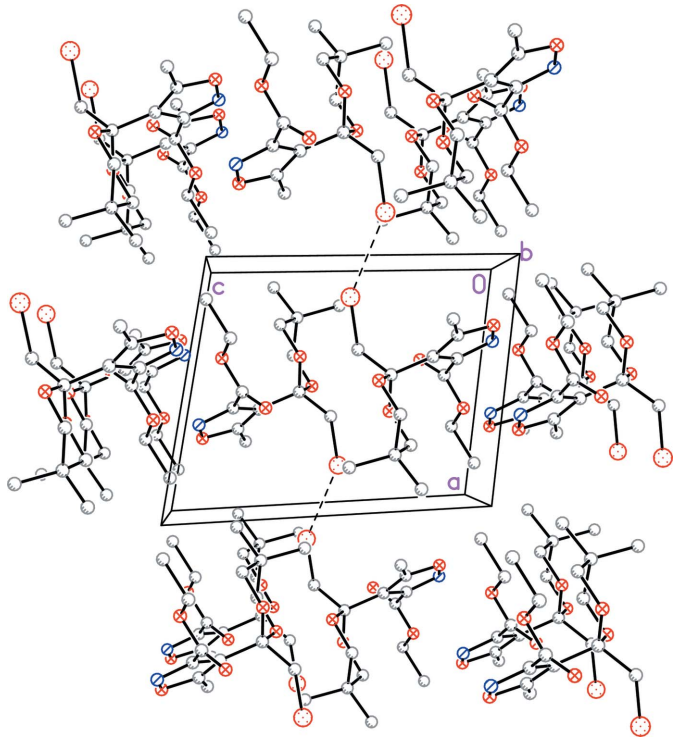


Figure 3
A packing diagram of (I) showing the complete arragengement of antiparallel isoxazoles as well as intermolecular Br···Br interactions (indicated by dashed lines). H atoms have been omitted for clarity.

6 h, during which time the mixture turned red and then faded to amber. The mixture was filtered to remove the succinimide and the solvent evaporated under reduced pressure. The resulting residue was purified by careful silica gel chromatography. The by-product, (I), eluted first (Rf = 0.44, SiO_2/CH_2Cl_2), followed closely by the desired product (IV) (60% yield, Rf = 0.42, SiO_2/CH_2Cl_2). The by-product was purified by recrystallization from hexane which gave (I) as colorless needles in 22% yield; m.p. 395–396 K. MS (FAB) *m/z* (% Rel. Int.): 364 (94, ^{81}Br *M*+), 362 (95, ^{79}Br *M*+), 282 (22, *M*-HBr), 278 (98, ^{81}Br), 276 (100, ^{79}Br), 268 (37, *M*-HBrCH_2+).

Crystal data

$C_{14}H_{20}BrNO_5$
M_r = 362.22
Triclinic, $P\overline{1}$
a = 8.9698 (5) Å
b = 9.3913 (5) Å
c = 11.1474 (6) Å
α = 68.299 (3)°
β = 72.618 (3)°
γ = 68.573 (3)°
V = 797.51 (8) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 2.60 mm^{-1}
T = 90 (2) K
0.26 × 0.17 × 0.06 mm

Data collection

Bruker–Siemens SMART APEX diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2006)
T_{min} = 0.552, T_{max} = 0.860
13695 measured reflections
2891 independent reflections
2712 reflections with $I > 2\sigma(I)$
R_{int} = 0.024

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.033
$wR(F^2)$ = 0.092
S = 1.11
2891 reflections
194 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.72 e Å^{-3}
$\Delta\rho_{min}$ = −0.45 e Å^{-3}

Table 1
Geometrical parameter comparison (Å, °).

Torsion angle	O3···Cg^{ii}	C6···O3···Cg^{ii}	Reference
19.5 (4)	3.402 (6)	95.3 (3)	This work
22.2	3.383	95.3	Nelson *et al.* (2004)
28.2	–	–	Burkhart *et al.* (2001)
−33.0	–	–	Burkhart *et al.* (2001)
−26.4	3.309	96.6	Zhou *et al.* (2000)

Torsion angle defined by C2—C6—C12—O19 in (I). *Cg* is the centroid of C2, O3, N4, C5 and C6. Symmetry code of antiparallel molecule: (ii) $1-x, -y, 2-z$.

H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms with C—H distances 0.98 Å for methylene groups with $U_{iso}(H) = 1.2U_{eq}(C)$ and 0.99 Å for methyl groups with $U_{iso}(H) = 1.5U_{eq}(C)$.

Data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT-Plus* (Bruker, 2006); data reduction: *SAINT-Plus*; program(s) used to solve structure: *XS* in *SHELXTL* (Bruker, 2003); program(s) used to refine structure: *XL* in *SHELXTL*; molecular graphics: *XP* in *SHELXTL*; software used to prepare material for publication: *publCIF* (Westrip, 2007).

The diffraction facility was established at the University of Idaho with the assistance of the NSF-EPSCoR program and the M. J. Murdock Charitable Trust, Vancouver, WA. NRN thanks NINDS for NS 038444.

References

Bruker (2003). *XS*, *XL* and *XP* in *SHELXTL*. Version 6.14. Bruker AXS Inc., Madison, Wisconsin, USA.
Bruker (2006). *APEX2* (Version 2.1-RC12), *SAINT-Plus* (Version 7.23a) and *SADABS* (Version 2004/1) in the *APEX2 Software Suite* (Version 2.1-RC12). Bruker AXS Inc., Madison, Wisconsin, USA.
Burkhart, D. J., Zhou, P., Blumenfeld, A., Twamley, B. & Natale, N. R. (2001). *Tetrahedron*, **57**, 8039–8046.
Murai, Y., Nakagawa, T., Yamaoka, K. & Uno, T. (1981). *Chem. Pharm. Bull.* **29**, 3290–3297.
Nelson, J., Twamley, B. & Natale, N. R. (2004). *Acta Cryst.* E**60**, o2255–o2257.
Sircar, J. C., Capiris, T., Bobovski, T. P. & Schwender, C. F. (1985). *J. Org. Chem.* **50**, 5723–5727.
Westrip, S. P. (2007). *publCIF*. In preparation.
Zhang, J. Y., Yuan, J. J., Wang, Y., Bible, R. H. Jr & Breau, A. P. (2003). *Drug Metab. Dispos.* **31**, 491–501.
Zhou, P. & Natale, N. R. (1998). *Tetrahedron Lett.* **39**, 8249–8252.
Zhou, P.-W., Fisher, J. D., Staples, R. J., Vij, A. & Natale, N. R. (2000). *Acta Cryst.* C**56**, 1146–1147.