Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Ethyl 5-methyl-4-(2,5,5-trimethyl-1,3-dioxan-2-yl)isoxazole-3-carboxylate

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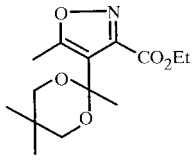
Received 26 January 2000
Accepted 14 June 2000

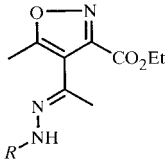
The title compound, $C_{14}H_{21}NO_5$, possesses an isoxazolyl group in the axial position of the 1,3-dioxanyl ring. The two rings are rotated about the bond joining them such that the two C(methyl)—C(dioxanyl)—C—C torsion angles are 92.1 (2) and −84.1 (2)°. In this conformation, neither the methyl nor ethoxycarbonyl substituents on the isoxazole are presented towards the dioxanyl chair.

Comment

In our work to synthesize ligands of the AMPA [(*RS*)-2-amino-3-(3-carboxyl-5-methyl-4-isoxazolyl)propionic acid] receptor in the central nervous system for pharmacological study (Krogsgaard-Larsen *et al.*, 1996), our lateral lithiation method applied to ethyl 4-acetyl-5-methyl-3-isoxazolylcarboxylate has been developed with 5,5-dimethyl-1,3-dioxanyl as both a protecting and directing group (Zhou & Natale, 1998). The recent report of the AMPA receptor binding domain (Armstrong *et al.*, 1998), and its detailed interaction with kainate, provides a framework for systematic structure-based design of compounds to treat neurodegenerative disorders, and the title compound, (I), is central to our strategy for defining the structure–activity relationship of AMPA receptor ligands. The X-ray study presented here is a part of this work to understand the function of this 1,3-dioxanyl group in the lateral lithiation process.



(I)



(II) R = $CH_3C_6H_4SO_2$
(III) R = C_6H_5NHCO
(IV) R = 2,4-$(NO_2)_2C_6H_3$

The molecular structure of (I) is shown in Fig. 1. Selected bond lengths and angles are listed in Table 1. The isoxazole group is located at an axial position on the six-membered dioxane group. The torsion angles describing the geometry around the C2—C8 bond are shown at the bottom of Table 1.

The least-squares planes of the isoxazole and the carboxylate groups form a dihedral angle of 62.8 (1)°. Table 2 shows the twist for related isoxazolyl compounds (II)–(IV). The relative twist of the isoxazole to the ester moiety is approximately *gauche*, and differs from that found in the other three 5-methylisoxazolyl-2-carboxylate derivatives recently reported, wherein (II) was observed to be *syn*, (III) was *anti*, and (IV) was orthogonal (Burkhart *et al.*, 1999). While we attribute these conformational differences in part to crystal-packing forces, the capability of the isoxazolyl ester to adopt divergent conformations is essential to its chemical and biological function.

The shortest intermolecular interaction is 3.176 (3) Å, so short-range interactions could not effect the conformation observed in the solid state.

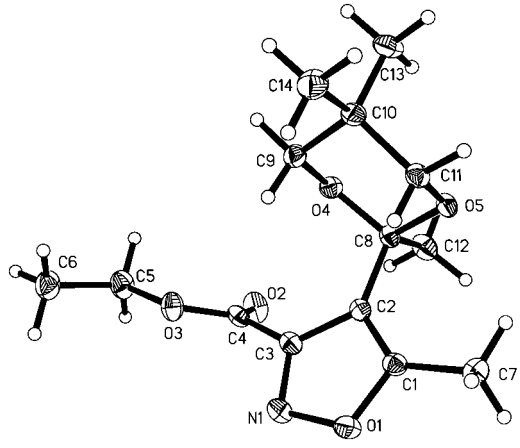


Figure 1
The molecular structure of (I) with the atomic numbering scheme and displacement ellipsoids shown at the 30% probability level.

Experimental

The title compound (I) was prepared by acid catalytic azeotropic distillation from ethyl 4-acetyl-5-methyl-3-isoxazolylcarboxylate reacted with neopentyl glycol. The product was obtained by Kugelrohr distillation: 366 K/0.05 mmHg, recrystallized with hexane, m.p. 353–355 K, yield 96%. ^{1}H NMR ($CDCl_3$): 0.66 (*s*, 3H), 1.21 (*s*, 3H), 1.38 (*t*, J = 7.20 Hz, 3H), 1.65 (*s*, 3H), 2.47 (*s*, 3H), 3.36 (*q*, 4H), 4.39 p.p.m. (*q*, J = 7.20 Hz, 2H); ^{13}C NMR ($CDCl_3$): 11.6, 14.0, 21.8, 22.5, 29.7, 29.8, 62.4, 71.8, 96.2, 114.0, 156.4, 161.6, 167.6 p.p.m. Calculated for $C_{14}H_{21}NO_5$: C 59.35, H 7.39, N 4.94%. Found: C 59.35, H 7.40, N 4.90%.

Crystal data

$C_{14}H_{21}NO_5$
M_r = 283.32
Triclinic, $P\overline{1}$
a = 8.571 (8) Å
b = 9.5382 (9) Å
c = 10.3449 (9) Å
α = 105.7991 (10)°
β = 94.1123 (11)°
γ = 112.6952 (13)°
V = 735.72 (12) Å^3
Z = 2
D_x = 1.279 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 74 reflections
θ = 2.09–27.02°
μ = 0.097 mm^{-1}
T = 193 (2) K
Block, colorless
0.40 × 0.20 × 0.20 mm

Data collection

SMART CCD area-detector diffractometer	$R_{int} = 0.035$
φ and ω scans	$\theta_{max} = 25.4^\circ$
3851 measured reflections	$h = -10 \rightarrow 9$
2688 independent reflections	$k = -10 \rightarrow 12$
2392 reflections with $I > 2\sigma(I)$	$l = -12 \rightarrow 10$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0451P)^2 + 0.4327P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.047$	$(\Delta/\sigma)_{max} = 0.005$
$wR(F^2) = 0.120$	$\Delta\rho_{max} = 0.30$ e Å^{-3}
$S = 1.058$	$\Delta\rho_{min} = -0.30$ e Å^{-3}
2688 reflections	Extinction correction: *SHELXTL* (Bruker, 1997*b*)
182 parameters	Extinction coefficient: 0.017 (4)
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °).

O1—C1	1.359 (2)	O4—C9	1.438 (2)
O1—N1	1.410 (2)	O5—C8	1.418 (2)
O2—C4	1.201 (2)	O5—C11	1.436 (2)
O3—C4	1.331 (2)	N1—C3	1.309 (2)
O3—C5	1.462 (2)	C2—C3	1.425 (2)
O4—C8	1.422 (2)	C2—C8	1.520 (2)
C1—C2—C8—O5	−26.4 (2)	C3—C2—C8—C12	−84.1 (2)
C3—C2—C8—O4	33.4 (2)	C2—C8—O4—C9	70.9 (2)
C1—C2—C8—C12	92.1 (2)	C2—C8—O5—C11	−69.3 (2)

Table 2
Comparison of the torsion angles (°) for the isoxazolyl compounds (I)–(IV).

Compound	C2—C3—C4—O3
(I)	62.8 (1)
(II)	175.8 (2)
(III)	−1.6 (3)
(IV)	108.2 (3)

H atoms were treated as riding, with C—H distances 0.98 Å and U_{iso} values 1.2 × U_{eq} of the attached atom.

Data collection: *SMART* (Bruker, 1997*a*); cell refinement: *SMART*; data reduction: *SHELXTL* (Bruker, 1997*b*); 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*.

This work was supported through funding received from the NSF-Idaho EPSCoR project under NSF Cooperative Agreement number OSR-9350539. The single-crystal CCD X-ray facility at the University of Idaho was established with the assistance of NSF-EPSCoR program under NSF OSR-9350539 and the M. J. Murdock Charitable Trust, Vancouver, WA, USA.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1265). Services for accessing these data are described at the back of the journal.

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