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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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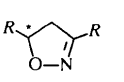
Abstract

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.

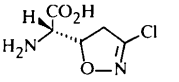
Comment

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).

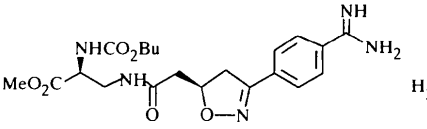
The absolute configuration of the 2-isoxazoline stereocentre is of paramount importance for biological activity. For instance, 5*S* stereochemistry was found to be required in activicin for high potency *in vivo*, while for XR229, the 5*R* configuration was found essential. For dihydromuscimol, it was 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).



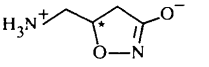
2-Isoxazolines



Activicin (AT-125)
Antitumor agent

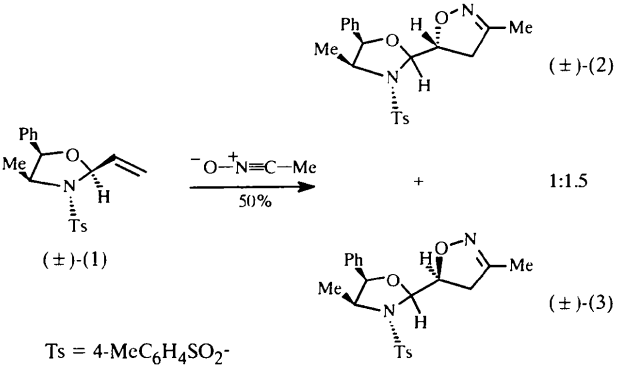


XR229
Antithrombotic agent



(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

and angles are listed in Table 1. The oxazolidine ring is bonded through C2 to C5′ of the 2-isoxazoline moiety. The configuration of the molecule is quite interesting. All the substituents on the three C atoms in the oxazolidine ring are located on the same side of the five-membered ring, while the toluene-4-sulfonate group is located on the opposite side. In NMR spectroscopy, a strong nuclear Overhauser effect (NOE) has been observed between the methyl protons on C41 and one of the H atoms on C4′, and a weaker one between the same methyl protons and H5′ (Soucy *et al.*, 1998). The results of the crystal structure determination have confirmed the spatial arrangement observed in solution.

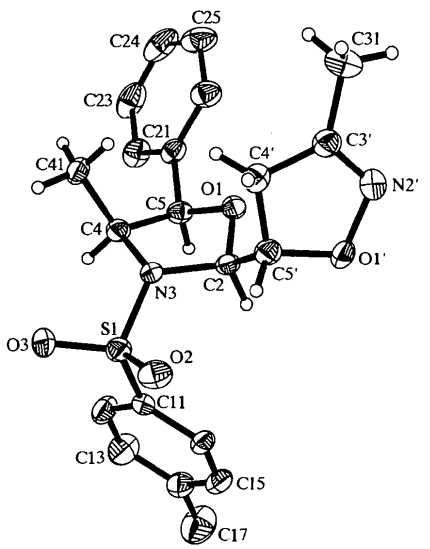


Fig. 1. View of the title compound, with ellipsoids at the 30% probability level.

The bond distances and angles around the S atom are normal. The O—S—O angle [120.95 (9)°] is larger than the other angles [average 107.07 (9)°], as expected because of the double bonds. The other bond distances also seem normal. The N2′=C3′ double bond is clearly shorter [1.262 (3) Å] than the other single bonds. The internal angles of the oxazolidine ring are all very similar and vary between 100.45 (14) and 108.23 (13)°. These angles are slightly smaller than the tetrahedral value because of the slight strain inside the five-membered ring. In the 2-isoxazoline ring, the angles are again reduced because of the strain inside the five-membered cycle. Four angles are similar [100.8 (2)–109.16 (14)°], but the angle at C3′ is larger [115.7 (2)°] because of its sp^2 hybridization. The N2′ atom also has the same hybridization, but its angle is reduced to 108.0 (2)° because of the presence of the lone pair of electrons. Selected torsion angles, especially those around C2 and C5′, are listed in Table 1, showing the conformation of the two rings.

The oxazolidine cycle clearly has an envelope conformation, with coplanarity of the four atoms C2, C4, C5 and N3 [mean deviation from the best plane is 0.051 Å and the O1 atom is 0.561 (2) Å out of the plane]. The conformation of the 2-isoxazoline ring is also of the envelope type, although the deviation of the fifth atom [C5′ 0.189 (3) Å] from the best calculated place (mean deviation = 0.001 Å) is smaller.

These results have clearly shown the relative stereochemistry of all the chiral centres. The oxazolidine ring has the 2*S**,4*S**,5*R** configuration, while the 2-isoxazoline ring has the 5′*S** configuration. From inspection of the 2-isoxazolinyl moiety, one can assume that if the reactive conformer resembled the one obtained in the solid state, the cycloaddition should occur on the alkene face opposite the *N*-tosyl group of (1). The low level of asymmetric induction can be attributed to free rotation around the C2—C5′ bond, which could give access to the *re* or *si* face of the alkene. Enlightened by these findings, we have decided to focus our efforts on the use of more conformationally rigid auxiliaries in an attempt to impede the rotation of the alkene function.

Experimental

Compound (3) was prepared as described previously (Soucy *et al.*, 1998) and single crystals were obtained by recrystallization from diethyl ether.

Crystal data

$C_{21}H_{24}N_2O_4S$
M_r = 400.48
Monoclinic
$P2_1/c$
a = 9.919 (7) Å
b = 19.331 (7) Å
c = 11.080 (8) Å
β = 96.53 (6)°
V = 2111 (2) Å^3
Z = 4
D_x = 1.260 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 23 reflections
θ = 3.69–8.53°
μ = 0.181 mm^{-1}
T = 293 (2) K
Hexagonal plate
0.54 × 0.42 × 0.12 mm
Colourless

Data collection

Siemens *P*4 diffractometer
$2\theta/\omega$ scans
Absorption correction: none
5916 measured reflections
5619 independent reflections
2300 reflections with $I > 2\sigma(I)$
R_{int} = 0.037
θ_{max} = 29°
$h = 0 \rightarrow 13$
$k = 0 \rightarrow 26$
$l = -15 \rightarrow 15$
3 standard reflections
every 97 reflections
intensity decay: 6.3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.066
$wR(F^2)$ = 0.098
$w = 1/[\sigma^2(F_o^2) + (0.001P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$

S = 1.037
5619 reflections
253 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

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

S1—O3	1.4250 (14)	N2′—C3′	1.262 (3)
S1—O2	1.439 (2)	N3—C2	1.482 (2)
S1—N3	1.628 (2)	N3—C4	1.497 (2)
S1—C11	1.759 (2)	C2—C5′	1.518 (3)
O1—C2	1.402 (2)	C3′—C4′	1.478 (3)
O1—C5	1.427 (2)	C4—C5	1.538 (3)
O1′—N2′	1.428 (2)	C4′—C5′	1.514 (3)
O1′—C5′	1.444 (2)		
O3—S1—O2	120.95 (9)	O1—C2—C5′	110.08 (15)
O3—S1—N3	106.73 (9)	N3—C2—C5′	113.20 (15)
O2—S1—N3	105.49 (9)	N2′—C3′—C4′	115.7 (2)
O3—S1—C11	108.08 (9)	N2′—C3′—C31	120.4 (2)
O2—S1—C11	106.84 (10)	C4′—C3′—C31	123.9 (2)
N3—S1—C11	108.21 (9)	N3—C4—C41	110.2 (2)
C2—O1—C5	105.87 (13)	N3—C4—C5	100.45 (14)
N2′—O1′—C5′	109.16 (14)	C3′—C4′—C5′	100.8 (2)
C3′—N2′—O1′	108.0 (2)	O1—C5—C4	103.08 (14)
C2—N3—C4	108.23 (13)	O1′—C5′—C4′	104.9 (2)
C2—N3—S1	119.65 (11)	O1′—C5′—C2	107.54 (15)
C4—N3—S1	119.92 (12)	C4′—C5′—C2	114.9 (2)
O1—C2—N3	104.14 (13)		

C5′—O1′—N2′—C3′	8.2 (2)
C5—O1—C2—N3	−37.0 (2)
C5—O1—C2—C5′	−158.67 (15)
C4—N3—C2—O1	15.1 (2)
C4—N3—C2—C5′	134.7 (2)
O1′—N2′—C3′—C4′	−0.3 (2)
C2—N3—C4—C41	−112.3 (2)
C2—N3—C4—C5	10.4 (2)
N2′—C3′—C4′—C5′	−7.1 (2)
C2—O1—C5—C4	44.2 (2)
N3—C4—C5—O1	−32.0 (2)
C41—C4—C5—O1	86.6 (2)
N2′—O1′—C5′—C4′	−12.2 (2)
N2′—O1′—C5′—C2	110.5 (2)
C3′—C4′—C5′—O1′	11.1 (2)
C3′—C4′—C5′—C2	−106.8 (2)
O1—C2—C5′—O1′	−71.5 (2)
N3—C2—C5′—O1′	172.37 (13)
O1—C2—C5′—C4′	44.8 (2)
N3—C2—C5′—C4′	−71.3 (2)

The H atoms were introduced at calculated positions (C—H distances 0.93–0.98 Å, depending on atom type) and treated as riding atoms, with displacement parameters 1.2 times the U_{eq} value of the parent atom.

Data collection: *XSCANS* (Siemens, 1996). Cell refinement: *XSCANS*. Data reduction: *SHELXTL* (Sheldrick, 1995). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *SHELXTL*. Software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1188). Services for accessing these data are described at the back of the journal.

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2,3,4,5,6,7-Hexahydro-9,10-dimethoxy-1,2-benzothiazonin-3-one 1,1-dioxide

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Abstract

The amide group in the nine-membered ring of the title compound, $C_{13}H_{17}NO_5S$, has the *trans* conformation. The molecules are linked into infinite one-dimensional chains by bifurcated intermolecular N—H···O hydrogen bonds involving the amide O atom and one of the sulfonyl O atoms of the same neighbouring molecule. The compound was prepared by the Friedel–Crafts acylation of 1,2-dimethoxybenzene and glutaric acid anhydride, followed by reduction of the aryl ketone, esterification, chlorosulfonation, treatment with ammonia, saponification and cyclization of the corresponding 5-(2-sulfamoylphenyl)butanoic acid.

Comment

For several years, we have been studying ring enlargement reactions of NH acidic heterocycles using 3-amino-2*H*-azirines, (I), as reagents (Heimgartner, 1991). For a successful reaction, the pK_a value of the heterocycle has to be below 8 as the first reaction step