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Optically Active (Z)-(R)-(+)-Methyl 2-phenyl-2-(pyrid-4-yl) Vinyl Sulfoxide : Synthesis and Structure

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Abstract . (Z)-(R)-(+)-Methyl 2-phenyl-2-(pyrid-4-yl) vinyl sulfoxide was obtained in high enantiomeric purity by microbiological sulfoxidation of the corresponding sulfide by *Mortierella isabellina*. The (R) absolute configuration of the chiral sulfur of this stereoisomer was determined by X-ray crystallography.

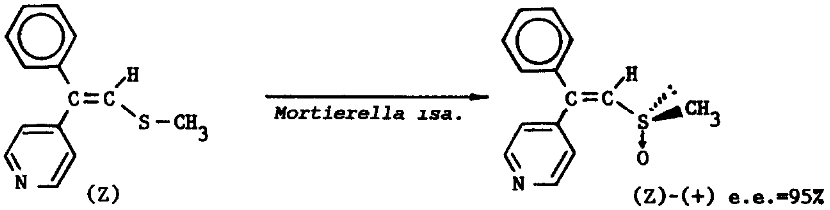
The sulfoxide group occurs in various pharmacologically active agents and pesticides. In particular, certain vinyl sulfoxides have been reported to possess antianoxia properties, probably by inhibition of the enzymes of the respiratory chain such as cytochrome oxidase and succinate dehydrogenase[1,2]. By depressing oxidative processes and stimulating the anaerobic glycolysis, they may enable the organism to tolerate low oxygen supply. Moreover, as oxygen carriers, some of these compounds may have cardiovascular effects.

Besides being in (Z) and (E) diastereomeric forms these vinyl sulfoxides have an asymmetric sulfur atom. Hence the enantioselective synthesis of both (R) and (S) enantiomers has to be made in order to perform pharmacological studies and to establish structure-activity relationships.

Among the vinyl sulfoxides that we have synthesized a stereochemical study was carried out on (Z) diastereomer of methyl 2-phenyl-2-(pyrid-4-yl) vinyl sulfoxide 2, as this derivative was conveniently obtained as a crystalline solide by oxidation with m-chloro perbenzoic acid (m-CPBA) of the corresponding vinyl sulfid 1[3]. The structural determination of this derivative by X-ray diffraction has confirmed the (Z) configuration of the racemate (triclinic, space group $P\bar{1}$)[4].

A potential ressource for obtaining chiral sulfoxides is the use of microorganisms. In a screening experiment we have shown that vinyl sulfides can be asymmetrically oxidized into sulfoxides of (R) and (S) absolute configuration by microbial strains of bacteria, yeasts and fungi[5].

Subsequently, the enantioselective microbiological sulfoxidation of the starting (Z)-vinyl sulfide **1** by *Mortierella isabellina* NRRL 1757 afforded one of the two enantiomers in 45 % chemical yield and an enantiomeric excess (e.e.) of 95 %[6].



1 2

The bioconversion was performed in water, with the resting mycelium of the fungus previously grown for 3 days. The sulfide (c = 1 g/L) was incubated for 24 h at 27°C in a rotary shaker. The work up consisted simply of filtration to remove the mycelium, extraction of the filtrate with ethyl acetate and purification by flash chromatography (20 % MeOH in AcOEt)

The optical purity was established by ^1H NMR, the sharpness of the S-methyl signal allowing accurate measurement of the chemical shift in presence of a chiral reagent, (R)-(-)-N-(3,5-dinitrobenzoyl)-α-phenylethylamine[7]. The radiocrystallographic study of the stereoisomer gave the following results[8].

Crystal Data : $C_{14}H_{13}NOS$, M = 243.33, white crystals from Et_2O, m.p. 137.5 - 138°C, orthorhombic, space group $P2_12_12_1$, a = 5.569 (2), b = 24.685 (9), c = 9.255 (2) Å V = 1272 $Å^3$, Z = 4, Dc = 1.27 $g.cm^{-3}$, Dm = 1.26 $g.cm^{-3}$, F(000) = 512.

Structure determination and refinement : the cell parameters and intensity data were obtained on a fully automated "Enraf-Nonius CAD-4" diffractometer with graphite-monochromated Cu-Kα radiation ($\bar{\lambda}$ = 1.54178 Å). Of the 1297 reflections with $\theta_{max} \leq 65°$ 743 were considered as observed after correction for Lorentz-polarization effects. There was no correction for absorption (μ = 20.48 cm^{-1}). The scattering factors for non-H atoms were taken from International Tables for X-ray Crystallography[9] and for H atoms from Stewart et al.[10]. The structure was solved by direct methods using Multan 80 and Fourier techniques[11]. The non-H atoms were located in the best E-map.

The fractional coordinates were refined by block-diagonal least-squares together with isotropic and then anisotropic thermal parameters. H atoms were derived from difference Fourier synthesis and refined with the other atoms.

Final cycles of refinement with anisotropic thermal parameters for non-H atoms and isotropic for H atoms led to R = 0.042 for 206 parameters, R_w = 0.054, S = 0.826.
A projection of the molecule showing the crystallographic numbering scheme is given in figure 1. The bond lengths, bond angles and selected torsion angles are given in table 1.

Table 1. Bond lengths (Å), bond angles (°) and torsion angles (°) with e.s.d.'s in parentheses

C(1)-C(2)	1.408(8)	C(1)-C(6)	1.401(8)
C(1)-C(7)	1.501(8)	C(2)-C(3)	1.383(9)
C(3)-C(4)	1.390(1)	C(4)-C(5)	1.370(1)
C(5)-C(6)	1.406(9)	C(7)-C(8)	1.458(8)
C(7)-C(14)	1.350(8)	C(8)-C(9)	1.401(9)
C(8)-C(13)	1.400(8)	C(9)-C(10)	1.380(1)
C(10)-N(11)	1.340(9)	N(11)-C(12)	1.354(9)
C(12)-C(13)	1.373(9)	C(14)-S(15)	1.777(6)
S(15)-O(16)	1.495(6)	S(15)-C(17)	1 800(1)

C(1)-C(2)-C(5)	118 5(5)	C(2)-C(1)-C(7)	121.1(5)
C(6)-C(1)-C(7)	120.4(5)	C(1)-C(2)-C(3)	119.7(6)
C(2)-C(3)-C(4)	121 3(6)	C(3)-C(4)-C(5)	119 9(6)
C(4)-C(5)-C(6)	119 7(6)	C(1)-C(6)-C(5)	120.7(6)
C(1)-C(7)-C(8)	116.8(5)	C(1)-C(7)-C(14)	119 2(5)
C(3)-C(7)-C(14)	123.9(5)	C(7)-C(3)-C(9)	121 5(5)
C(7)-C(8)-C(13)	121 5(5)	C(9)-C(8)-C(13)	117 0(5)
C(3)-C(9)-C(10)	118 1(6)	C(9)-C(10)-N(11)	125.9(7)
C(10)-N(11)-C(12)	115 2(6)	N(11)-C(12)-C(13)	123 5(6)
C(3)-C(13)-C(12)	120 2(6)	C(7)-C(14)-S(15)	123 0(5)
C(14)-S(15)-O(16)	104 8(3)	C(14)-S(15)-C(17)	96.8(4)
O(16)-S(15)-C(17)	106 8(4)		

C(2)-C(1)-C(7)-C(14)	29 7(6)
C(13)-C(8)-C(7)-C(14)	129 2(6)
C(1)-C(7)-C(14)-S(15)	171 3(4)
C(7)-C(14)-S(15)-O(16)	123 6(5)
C(7)-C(14)-S(15)-C(17)	127 1(5)

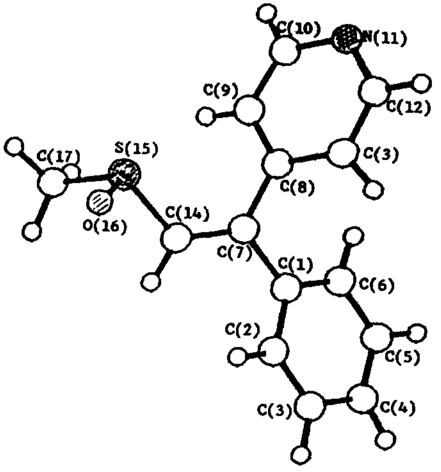


Fig. 1. Perspective view of the title compound with numbering scheme.

The X-ray crystal diffraction study of the title compound showed the (Z)-(R) configuration of this stereoisomer. The absolute configuration of the chiral sulfur is (R).

The bond lengths measured for the stereoisomer are similar to those measured in the racemate[4] except for the S(15)-C(17) bond, which is greater for (Z)-(R) : [1.800(1) Å instead of 1.778(4)Å]. The torsion angle [C(7), C(14), S(15), O(16)] is 123.6(5)° which rules out any delocalization of the π electrons of the sulfinyl group S(15)-O(16) and C(7)-C(14) bonds. Similarly, the angles between the plane of the vinyl group and those containing the phenyl and the pyridyl rings are respectively 34.5(8)° and 51.1(6)°, which also prevents any conjugation. The angle between the phenyl and pyridyl rings is 72.6(3)°. Crystal cohesion is ensured by a dense three-dimensional network of van der Waals interactions[12].

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12. Van der Waals contacts (< 3.7 Å) N(11) ..C(3)^{i} 3.447(9) , N(11)...C(4)^{i} 3.658(9) ; C(6)...C(3)^{ii} 3.618(9) ; C(9) ..O(16)^{ii} 3.368(9) ; C(10...C(13)^{ii} 3.654(9) ; C(17)...C(2)^{iii} 3.640(1) ; O(16)...C(2)^{iv} 3.288(9) ; N(11)...C(12)^{v} 3.610(9) ; C(6)...C(4)^{vi} 3.651(9). Symmetry code · (i) 1+x, y, 1+z ; (ii) 1+x, y, z ; (iii) 3/2-x, 1-y, 1/2+z ; (iv) 1/2-x, 1-y, 1/2+z ; (v) 1/2+x, 1/2-y, 1-z ; (vi) 1/2+x, 1/2-y, -z.