# Structure of 4-(2-chloro-4,5-dimethoxybenzylidene)-2-methyl-5-oxazolone. X-ray and NMR study

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The azlactone of 6-chloroveratraldehyde 3 (4-(2-chloro-4,5-dimethoxybenzylidene)-2-methyl-5-oxazolone) was synthesized from 6-chloroveratraldehyde 2 and its structure investigated using X-ray crystallographic and nuclear magnetic resonance methods. Compound 3 crystallized in the  $P2_1/c$  (#14) space group (Z = 4) with cell dimensions a = 9.148(2), b = 22.938(2), c = 6.707(1) Å, and  $\beta = 111.50(2)^\circ$ . The X-ray study shows that azlactone 3 exists as the Z-isomer and crystallizes as a planar structure, i.e., both the phenyl and azlactone ring systems, as well as the functional groups attached to them, lie in the same plane. The <sup>1</sup>H and <sup>13</sup>C NMR spectral values also support the formation of the Z-isomer only, during the synthesis of 4-(2chloro-4,5-dimethoxybenzylidene)-2-methyl-5-oxazolone.

KEY WORDS: X-ray; NMR; Z-isomer; azlactone; veratraldehyde.

## Introduction

Our research involves the medicinal chemistry of certain derivatives synthesized from aromatic azlactones. We recently reported on the structures of phenyl-pyruvic acids (enol form) and enolic acetate derivatives obtained from aromatic azlactones.<sup>1,2</sup> A direct route for the synthesis of these novel enol acetates (2-acetoxy-3-phenylpropenoic acids) was also developed.<sup>3</sup> Due to the importance of isomerism in biological activity, our studies also focused on the geometric preference of these compounds, which were reported recently to exist in the Z-configuration.<sup>1-3</sup> These findings prompted us to investigate the structures of the parent azlactones used to synthesize the enols of phenylpyru-

vic acids. This paper reports on the synthesis and the NMR and X-ray studies of the structure of one of these parent azlactones, namely 4-(2-chloro-4,5-dimethoxy-benzylidene)-2-methyl-5-oxazolone **3**.

# Experimental

#### **Synthesis**

The synthesis of 3 involved the ring chlorination of veratraldehyde 1, yielding 6-chloroveratraldehyde  $2^4$  (2-chloro-4,5-dimethoxybenzaldehyde), which was converted to the corresponding azlactone 3 (Scheme 1). The structure of 3 was investigated by NMR spectroscopy and X-ray crystallography.

## Synthesis of 6-chloroveratraldehyde 2

Veratraldehyde (50 g; 0.30 mol) was dissolved in chloroform (75 ml) and chlorine slowly passed into this well-stirred solution which was kept at about 40°C. After 1 h, the mixture was cooled and nitrogen bubbled through to remove excess chlorine and hydrochloric

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acid. The mixture was cooled in ice, the product filtered off and washed with ethanol. The process was repeated with the filtrate, which yielded more of the product. The two fractions were combined and dried (27.8 g; 0.14 mol). Recrystallization from ethanol gave colorless needles of 2, m.p. 149–151°C.

## Synthesis of 4-(2-chloro-4,5dimethoxybenzylidene)-2-methyl-5-oxazolone 3

A mixture of 6-chloroveratraldehyde (20 g; 0.1 mol), N-acetylglycine (11.7 g; 0.1 mol), anhydrous sodium acetate (16.4 g; 0.2 mol) and acetic anhydride (60 ml) was stirred for 2 h at  $105-110^{\circ}$ C. A mixture (320 ml) of equal volumes of water and ethanol was added and stirred for 30 min. The crystals that formed were filtered off, washed with the water/ethanol mixture and dried (21.0 g; 0.075 mol). Treatment with activated charcoal and crystallization in chloroform gave yellow crystals of 3, m.p. 239-241^{\circ}C.

# X-ray analysis

Yellow prisms of 3 ( $C_{13}H_{12}CINO_4$ ) were obtained from chloroform. All diffraction measurements were performed at room temperature and data collected with an Enraf-Nonius CAD-4 diffractometer using graphite monochromated Cu-K $\alpha$  radiation. The crystal data and a summary of intensity data collection are listed in Table 1. A total of 2386 unique reflections were measured. Lorentz-polarization and empirical absorption corrections were applied to the data. The structure was solved by direct methods using MOLEN<sup>5</sup> and refined anisotropically. It was determined that the azlactone **3** crystallized as a single conformer in the space group  $P2_1/c$  with Z = 4. The refined atomic coordinates are given in Table 2 and the molecular structure with the atomic numbering, shown in Fig. 1.

## Spectroscopic analysis

NMR analysis of **3** was performed at 200 MHz (<sup>1</sup>H) and 50 MHz (<sup>13</sup>C) on a Bruker AC-200 spectrometer, with CDCl<sub>3</sub> as solvent and TMS as internal standard. The melting points (uncorrected) were determined on an Electrothermal melting point apparatus.

# **Results and discussion**

#### X-ray analysis

The five atoms forming the heterocyclic azlactone ring, all lie in the same plane (C13-N17-C16-O15  $= 0.1(4)^{\circ}$  and C16-O15-C14-C13  $= -0.0(5)^{\circ}$ ). Co-planarity also exists between the azlactone ring and the aromatic ring (C2-C12-C13-C14 = $-180.0(4)^{\circ}$ ). The carbonyl group (C14-O18) in the azlactone ring is orientated trans with respect to the aromatic ring, which means that this azlactone exists in the Z-configuration. This carbonyl group forms the acid moiety when the azlactone undergoes hydrolysis, and the identical trans orientation was also recently observed for the acid moieties of the conformers of enol ester derivatives<sup>1-3</sup> which were obtained from these azlactones. The two methoxy groups of 3 are both orientated co-planar with the aromatic ring  $(C6-C5-O10-C11 = 0.3(5)^{\circ} \text{ and } C5-C4-O8-C9$ =  $179.7(3)^{\circ}$ ), with their methyl groups directing away from each other. Therefore, except for the methyl protons, all the atoms in this conformation of 3 lie in the same plane, with the ortho-chloro atom and the

Concerion and Struct	are kermement of 3
Cmpd	
Color, shane	Yellow prisms
Formula weight	M = 281.7
Symmetry	Monoclinic
Space group	
The group	721/C
Temp.	
cell constants	$(25 \text{ reflections with } 11^\circ < 0$ $< 33^\circ)$
a, Ą	9.148(2)
<i>b</i> , A	22.938(2)
<i>c</i> , Å	6.707(1)
β°,	111.50(2)
Cell volume, Å <sup>3</sup>	1309.5(3)
Formula units/unit cell	4
$D_{\rm calc}$ , g.cm <sup>-3</sup>	1.429
$\mu_{cake}$ cm <sup>-1</sup>	27.1
F(000)	584
Diffractometer/scan	ω-2θ
Radiation, graphite	$C_{\rm u}K_{\rm cl}, \lambda = 1.54184$ Å
monochromator	
Max. crystal dimensions, mm	$0.5 \times 0.12 \times 0.06$
Scan width	$2.2 + 0.15 \tan \theta$
Standard reflections	-2-22, 0-100
Decay of standards	-1%
Total number of reflections	2386
measured	
20 range, deg	[4-130]
Range of h, k, l	0/7, 0/26, -10/10
Reflections observed $[F_o \ge 3\sigma(F_o)]$	691
Corrections applied	Lorentz-polarization, empirical ( $\psi$ scan) absorption
Computer programs	MOLEN
Source of structure factors used	International Tables for X- ray Crystallography
Structure solution	Direct methods
Treatment of hydrogen atoms	Theoret. positions or $\Delta F$ synthesis, refined isotropically
No. of parameters varied	220
Weighting scheme	$w = 1/\sigma(F)^2$
R	$\sum   F_0  -  F_0 /\sum  F_0  = 0.042$
<i>R</i>	0.042
Largest feature final diff.	3.2(4)
map, e. $Å^{-3}$	

Table 1. Crystal Data and Summary of Intensity Data Collection and Structure Refinement of 3

benzylic proton (on C12) on the same side of this planar structure.

## Spectroscopic analysis

The <sup>1</sup>H NMR data of 3 appear in Table 3. The NMR spectrum of 3 exhibits only singlets. Of signifi-

Atom	x	у	Z	$B(Å^2)$
CI	0.4048(3)	0.1814(1)	0.7027(5)	3.29(7)
C2	0.2928(3)	0.2258(1)	0.6463(5)	2.84(6)
C3	0.1342(3)	0.2079(1)	0.5674(5)	2.96(6)
C4	0.0923(3)	0.1505(1)	0.5468(5)	3.07(7)
C5	0.2093(4)	0.1066(1)	0.6057(5)	3.13(7)
C6	0.3648(3)	0.1226(1)	0.6828(5)	3.46(7)
C17	0.6046(1)	0.1979(0)	0.8025(2)	5.58(2)
08	-0.0574(2)	0.1302(1)	0.4720(4)	4.28(6)
C9	-0.1784(4)	0.1730(2)	0.4122(9)	6.1(1)
010	0.1561(2)	0.0512(1)	0.5784(4)	4.28(6)
CII	0.2715(4)	0.0054(1)	0.6356(7)	5.2(1)
CI2	0.3380(3)	0.2865(1)	0.6689(5)	3.27(7)
CI3	0.2482(3)	0.3342(1)	0.6246(5)	3.25(7)
C14	0.3162(4)	0.3935(1)	0.6584(6)	3.93(8)
015	0.1878(3)	0.4305(1)	0.5945(4)	4.34(6)
C16	0.0569(4)	0.3945(1)	0.5293(6)	4.01(8)
N17	0.0833(3)	0.3400(1)	0.5423(4)	3.49(6)
018	0.4473(3)	0.4115(1)	0.7248(5)	5.58(7)
C19	-0.0976(5)	0.4254(2)	0.4515(9)	6.2(1)

" Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as:  $4/3(a^2\beta_{1,1} +$  $b^{2}\beta_{2,2} + c^{2}\beta_{3,3} + ab\cos\gamma\beta_{1,2} + ac\cos\beta\beta_{1,3} + bc\cos\alpha\beta_{2,3}$ ).



Hydrogen Atom	РРМ
H-3(Ar)	8.45(s) <sup>4</sup>
H-6(Ar)	7.56(s)
Ar-CH=C	6.91(s)
$CH_3 - O(C - 4)$	3.95(s)
$CH_3 - O(C - 5)$	3.93(s)
$CH_3 - C = N$	2.40(s)

Table 3. <sup>1</sup>H NM Data of 3

"s, Singlet.

Table 4.	<sup>13</sup> C	NMR	Data	of	3
Table 4.	C	TATALLE	Data	UI.	9

Carbon Atom	PPM
Carbon Atom $CH=C-C=O$ $CH_3-C=N$ $C-5(Ar)$ $C-4(Ar)$ $Ar-CH=C$ $C-1(Ar)$ $Ar-CH=C$ $C-2(Ar)$ $C-3(Ar)$	PPM 167.7(s)" 165.8(s) 147.8(s) 151.9(s) 131.6(s) 130.1(s) 126.4(d) 123.5(s) 114.2(d)
C-6(Ar) $CH_{2}-O(C-4)$	112.2(d) 56.2(a)
$CH_3 = O(C-4)$ $CH_3 = O(C-5)$	56.2(q) 56.1(q)
$CH_3 - C = N$	15.8(q)

"s, Singlet; d, doublet; q, quartet.

cance is the absorption of the benzylic proton (Ar-CH=C) which appears at  $\delta = 6.91$ . Only one signal for the benzylic proton is observed, indicating the presence of only one geometrical isomer, namely

the Z-isomer, as the E-isomer has been reported to absorb further downfield ( $\sim 7.5$  ppm).<sup>6,7</sup> The value at  $\delta = 6.91$  is in agreement with values between 6.93 and 7.02 ppm reported for the benzylic proton of similar azlactones (Z-isomers).<sup>6</sup> The two singlets at  $\delta = 3.93$ and  $\delta = 3.95$  were assigned to the methyl protons of the two methoxy groups, and the signal at  $\delta = 2.40$ , to the methyl protons on the azlactone ring. The integration of three protons for each of these singlets supports CH<sub>3</sub>-hybridization. The  $^{13}$ C NMR data of 3 appear in Table 4. The chemical shift values of the C=O and C=N carbon atoms of the azlactone ring are very close to each other and absorb far downfield. The signal at  $\delta = 167.7$  was assigned to the carbonyl carbon and the one at  $\delta = 165.8$  to the C=N carbon.<sup>8</sup> The benzylic carbon atom (Ar-CH=C) absorbs at  $\delta = 126.4$ , which further supports the presence of the Z-isomer, as the E-isomer of similar azlactones is reported to absorb further downfield ( $\sim$ 140 ppm).<sup>9</sup>

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