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Short Note

4,4-Bis(hydroxymethyl)-2-phenyl-2-oxazoline

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Abstract: The title compound, 4,4-bis(hydroxymethyl)-2-phenyl-2-oxazoline **2**, a well-known substance, was resynthesized in high yields through a conventional method. The structure of compound **2** was characterized for the first time by a single-crystal X-ray structure determination. The compound was further established through NMR spectroscopy (1D and 2D). In the molecular packing, two molecules of 4,4-bis(hydroxymethyl)-2-phenyl-2-oxazoline interact through H-Bonds to define "dimers" in which phenyl groups interact especially using $\pi \ldots \pi$ contact.

Keywords: 2-oxazoline; amino acids precursors; X-ray crystallography; 2D NMR

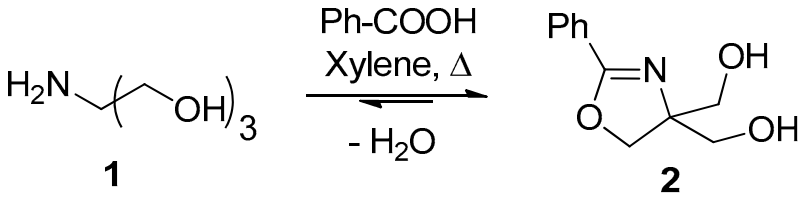
1. Introduction

Oxazolines are heterocyclic compounds found in many bioactive natural products and drugs [1–3], including anti-inflammatory, anti-HIV, and antitumor agents [4,5]. The oxazoline ring has low reactivity towards nucleophiles, radicals, oxidizing agents, and acids, and is used in applications requiring high chemical resistance [6,7]; they are also widely used as linkers in asymmetric catalysis [8], monomeric building blocks [9,10], and ligands in cross-coupling reactions [11,12]. Continuing our investigations in the use of oxazoline in heterocyclic chemistry [13–17] we describe in this short note our results concerning the resynthesis of 4,4-bis(hydroxymethyl)-2-phenyl-2-oxazoline (CAS No. [62203-32-1]) [18–24], an oxazolinic precursor of biheterocyclic amino acids. Herein, the spectroscopic characterization and the first X-ray crystal structure determination of the title compound **2**, are described.

2. Results and Discussion

2.1. Synthesis

Compound **2** was resynthesized using Billman's method [18]. It was obtained in an 85% yield from condensation of a commercial product 2-amino-2-(hydroxymethyl)propane-1,3-diol **1** (CAS No. [77-86-1]) and benzoic acid in reflux of xylene using as material dean-stark to immediately remove the water formed (Scheme 1).



Scheme 1. Synthesis strategy of compound **2**.

A single crystal of the title compound was obtained by recrystallization from ether/hexane and its structure was established on the basis of NMR spectroscopy (Figure 1) and X-ray diffraction. The definite assignment of the chemical shifts of protons and carbons are shown in Table 1.

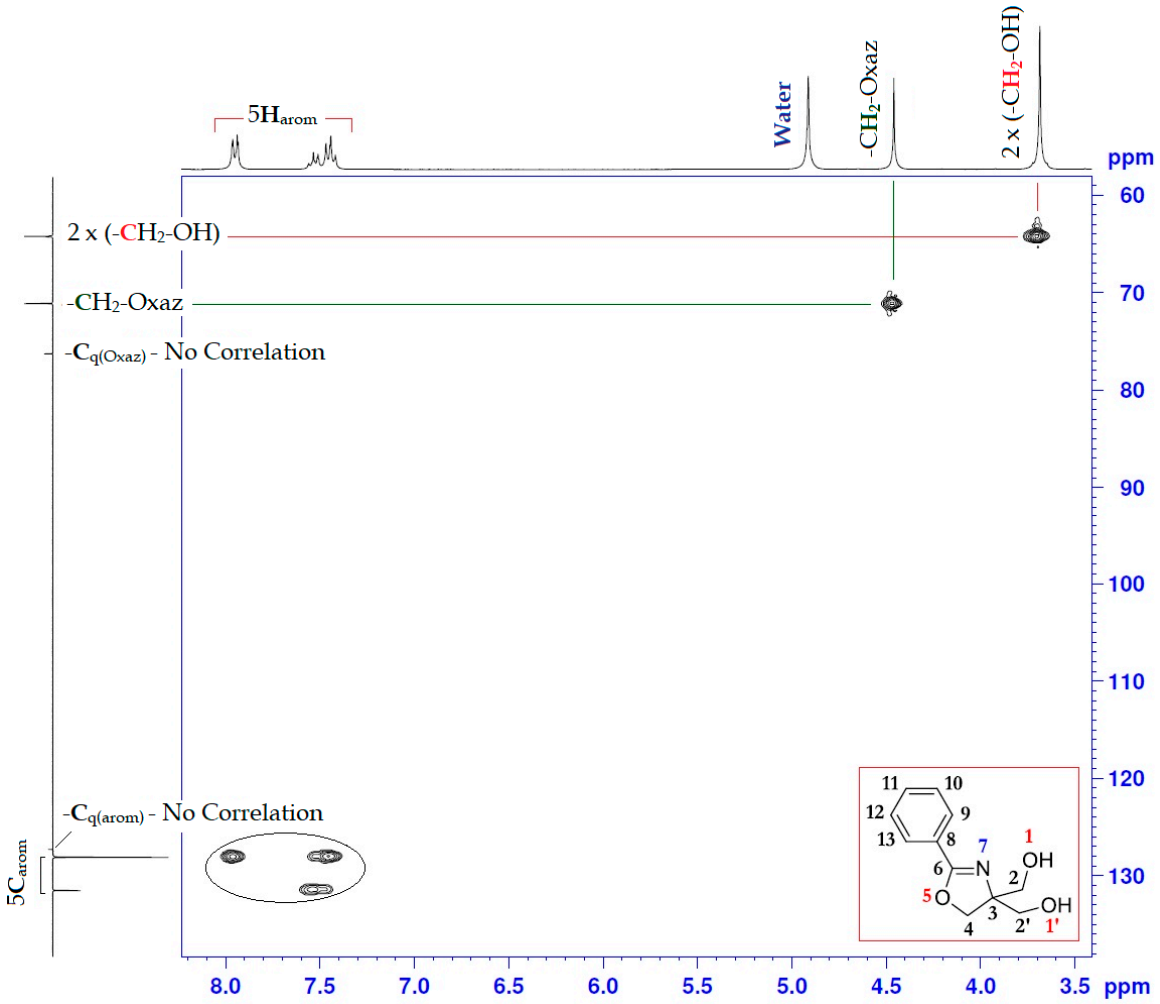


Figure 1. ^{1}H-^{13}C Heteronuclear 2D spectrum (in CD_3OD) of compound **2**.

Table 1. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectral data for compound **2** in acetone-d_6, including the obtained results by homonuclear 2D shift-correlated and heteronuclear 2D shift-correlated. Chemical shifts δ in ppm.

Position	δ_H	δ_C	Correlation ^{1}H-^{13}C
1 and **1′**	3.8 (2H, e)	-	-
2 and **2′**	3.7 (4H, s)	64.20	$2H^2$-C^2; $2H^{2'}$-$C^{2'}$
3	-	76.25	-
4	4.45 (2H, s)	71.09	$2H^4$-C^4
6	-	165.51	-
8–13	7.15–8.23 (5H, m)	127.25–131.46	$5H_{arom}$-$5C_{arom}$

We first produced the ^{1}H-NMR spectrum of the product **2** in methanol CD_3OD but we noted the absence of the signals of the protons of the two alcohol functions, and after we produced the same spectrum, but this time in the hot acetone, hence, the appearance of a signal widened to 3.8 ppm corresponding to the two alcoholic protons.

2.2. *X-ray Structure Determination of* **2**

In the absence of X-ray crystallographic data determination for compound **2**, a crystallographic study was performed. The X-ray diffraction analysis revealed that compound **2** crystallizes in the monoclinic space group C2/c with four molecules per unit cell. The asymmetric unit contains one molecule 4,4-bis(hydroxymethyl)-2-phenyl-2-oxazoline (Figure 2). All C-C, C=C, C-N, C=N, and C-O bond lengths are in the normal range and are comparable to those in related compounds [17,25–27]. In the oxazoline ring, the C7–N1 and C10–N1 bond lengths are 1.269 Å and 1.480 Å, respectively. The lower value of 1.269 Å clearly indicates a double bond character in C7–N1. In addition, the conjugation of the electronic clouds of the C7–N1 bond and the aromatic ring make the H bonds stronger on the benzene ring side than on the ethylenic one, O3...H5-C5: 2.470 Å, O2...C9-H9B: 2.618 Å. In the phenyl group, all the angles C-C-C or C-C-H are around 120° and is a completely planar molecule. The five-membered oxazoline ring adopts an envelope conformation in the compound and makes a dihedral angle of 3.89(6)° with its phenyl substituent.

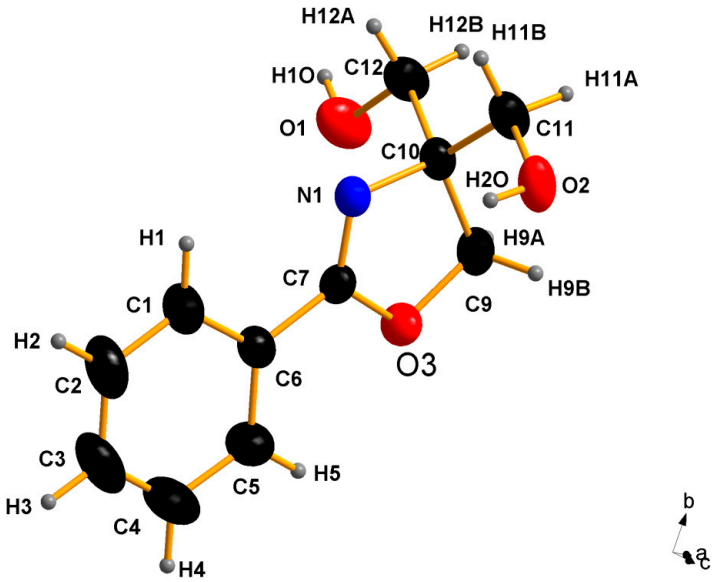


Figure 2. Asymmetric unit in the crystal structure of 4,4-bis(hydroxymethyl)-2-phenyl-2-oxazoline, ellipsoids drawn at 50%.

Within the 3D framework of the title compound, two molecules 4,4-bis(hydroxymethyl)-2 -phenyl-2-oxazoline interact through H-Bonds as depicted on Figure 3 to define "dimers" in which phenyl group interact especially using π … π contact. Two neighbouring such "dimers" use the same interactions to propagate in the 3D. The phenyl groups in neighbouring molecules are set in planes making a dihedral angle of 5.881(66)°.

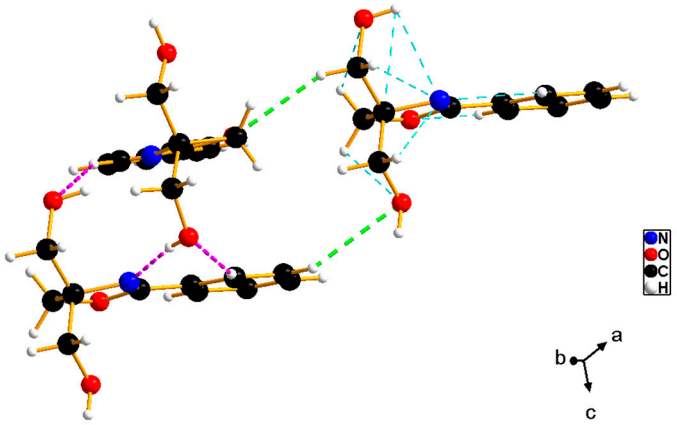


Figure 3. Portion of the 3D structure of compound **2** showing the intra- (cyan), and inter-connections H-Bonds (Pink, between two neighbouring molecules "dimers" and green between two neighbouring "dimers".

The structure of compound **2** is stabilized by several intra- and intermolecular hydrogen bonds (C-H … O, C-H … N, O-H … N, and O-H … C) and π … π interaction between the phenyl rings, as shown in Figure 3. The intramolecular hydrogen bonds C5-H5 … O3 (2.470 Å), C9-H9A … O1 (2.538 Å), C9-H9B … O2 (2.618 Å) and O2-H2O … C10 (2.624 Å) contribute to the stabilization of the molecular configuration. The intermolecular hydrogen bonds, especially O1′-H1′ … N1′ (1.930 Å) and C5′-H5′ … O1′ (2.596 Å), make phenyl groups parallel and offset (Figure 3). The centroid-to-centroid distance of adjacent phenyl rings is 3.310(2) Å. According to the quadrupolar model of stacking of aromatic rings proposed by Hunter & Sanders, this arrangement is the energetically favourable one [28].

3. Materials and Methods

3.1. General Methods and Physical Measurements

Melting point was determined with an Electrothermal melting point apparatus and was uncorrected. NMR spectra (^{1}H and ^{13}C) were recorded on a Bruker AM 300 spectrometer (operating at 300 MHz for ^{1}H, at 75 MHz for ^{13}C) (Bruker Analytische Messtechnik GmbH, Rheinstetten, Germany). NMR data are listed in ppm and are reported relative to tetra-methylsilane (^{1}H, ^{13}C); residual solvent peaks being used as internal standard. X-ray diffraction data were collected at room temperature with a Bruker APEXII CCD detector diffractometer (CNRST-Rabat).

3.2. Resynthesis of 4,4-Bis(hydroxymethyl)-2-phenyl-2-oxazoline

0.179 mol of 2-amino-2-(hydroxymethyl)propane-1,3-diol and 0.179 mol of benzoic acid in 150 mL of xylene were refluxed for 24 h with azeotropic elimination of the water formed. After evaporation of the 2/3 xylene and cooling, the obtained solid was filtered under vacuum and then recrystallized from an ethanol/water mixture. Single crystals of the title compound were obtained by recrystallization from ether/hexane. Yield = 85% (white solid); m.p. = 140–142 °C. ^{1}H-NMR (300 MHz; Acetone-d_6): 3.7 (4H, 2 × -CH_2–OH, s); 3.81 (2H, 2 × -CH_2–OH, e); 4.45 (2H, -CH_2(Oxaz), s); 7.15–8.23 (5H_{arom}, m). ^{13}C-NMR (75 MHz; CD_3OD): 64.20 (2C, 2 × -CH_2–OH); 71.09 (1C, -CH_2(Oxaz)); 76.25 (1C, -Cq(Oxaz)); 127.25, 128.08, 131.49 (6C_{arom}); 165.51 (1C, CN). The supporting ^{13}C-NMR, ^{1}H-NMR, ^{1}H-^{13}C NMR are presented in the Supplementary Materials file.

3.3. Crystal Data for the 4,4-Bis(hydroxymethyl)-2-phenyl-2-oxazoline

Crystal Data for $C_{11}H_{13}NO_3$ (M = 207 g/mol): monoclinic, space group C2/c (no. 15), a = 15.8302(5) Å, b = 10.1380(3) Å, c = 14.2916(7) Å, β = 114.267(1)°, V = 2090.95(14) Å^3, Z = 4, T = 296 K, λ(MoKα) = 0.71073 Å, Dcalc = 1.317 mg/m^3, 46,455 reflections measured (5° ≤ 2θ ≤ 54.0°), 32,038 unique (Rint = 0.028) which were used in all calculations. The final R1 was 0.059 (I > 2σ(I)) and wR2 was 0.178 (all data).

4. Conclusions

In summary, we obtained the X-ray crystal structure of 4,4-bis(hydroxymethyl)-2-phenyl -2-oxazoline **2**, for the first time and found it to have one independent molecule per asymmetric unit. In the molecular packing, supramolecular dimers are formed; this is mediated by C-H … O, C-H … N, O-H … N, and O-H … C hydrogen bonds.

Supplementary Materials: The following are available online. Figure S1: ^{13}C-NMR spectrum of compound **2**, Figure S2: ^{1}H-NMR spectrum (in acetone-d_6) of compound **2**, Figure S3: ^{1}H-NMR spectrum (in CD_3OD) of compound **2**, Figure S4: Heteronuclear ^{1}H-^{13}C spectrum of compound **2** and crystallographic data for compound **2** in crystallographic information file (CIF) format. CCDC 2015223 also contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the Cambridge Crystallographic Data Centre http://www.ccdc.cam.ac.uk/conts/retrieving.html.

Author Contributions: S.H., S.B. performed the experiments; H.F., A.A., and Y.A. conceived and designed the experiments, analyzed the data and wrote the paper; H.Z. collection of X-ray diffraction data, B.E.B. X-ray structure determination and M.L. X-ray structure description and review. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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