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SHORT COMMUNICATION

SYNTHESIS, CHARACTERIZATION AND X-RAY STRUCTURE OF AN OXAZINE DERIVATIVE

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ABSTRACT. The 5,6-dihydro-6-methyl-2,3-diphenyl-2H-1,4-oxazine-2-ol compound (**2**) was prepared unambiguously by condensation of 1,2-diphenylethanone with 1-amino-2-propanol in the presence of glacial acetic acid. The product was characterized by FT-IR, ^{1}HNMR, UV-Vis spectroscopy and X-ray crystallography. Quantum chemical calculations are used to the proposed mechanism.

KEY WORDS: 1,2-Diphenylethanone, 1-Amino-2-propanol, Oxazine

INTRODUCTION

The chemistry of oxazine derivative compounds is the subjects of growing interest [1-4]. Many of these compounds are relevant to the biochemistry of enzymes [5] and cytotoxic drugs [6]. Various oxazine compounds have been found to show versatile bioactivities [7]. Oxazines derivatives are an important class of hetrocycles, which has attracted much synthetic interest due to their wide range of biological activities. Considerable attention has been focused on these compounds since the discovery of Efavirenz a trifluromethyl-1,3-oxazin-2-one which is a non-nucleoside reverse transcriptase inhibitor and a selective anti-HIV drug [8]. Several benzoxazinones exhibit diverse pharmacological properties, such as antagonism to progesterone receptor [9], antitummour [10], antiviral [11], antithrombotic [12], antimycobacterial [13], anti-inflammatory [14], antidiabetic and hypolipidaemic [15] effects.

In this work we report the synthesis of 5,6-dihydro-6-methyl-2,3-diphenyl-2H-1,4-oxazine-2-ol methyl-2,3-diphenyl-2H-1,4-oxazine-2-ol (**2**). Characterization was performed using elemental analysis, UV-Vis and ^{1}HNMR spectroscopy. The structure of this oxazine compound was determined by X-ray crystallography, and we propose a detailed reaction mechanism for the formation of **2** from 1,2-diphenylethanone and 1-amino-2-propanol, and the biological activity of this compound can be investigated.

EXPERIMENTAL

Materials and measurements

Chemicals were purchased from the Fluka (Switzerland) and Merck (Germany) Chemical companies and all the reagents were used without further purification.

^{1}HNMR spectra were taken on a Bruker Spectrospin Avance 400 MHz (USA) ultra shield spectrometer in DMSO-d_6 and chemical shifts were reported relative to Me_4Si as internal standard, FT-IR (KBr pellet, 450-4400 cm^{-1}) spectrum was taken with Perkin-Elmer Model RX-I FT-IR spectrometer (England). The electronic spectra were recorded on a Beckman DU-7000 UV-Vis spectrophotometer (USA). Elemental analysis (C, H, and N) data were obtained with an Exeter Analytical CE-440 elemental analyzer (USA). Melting points were taken using an electro thermal IA 9100 apparatus in open capillary tubes (England).

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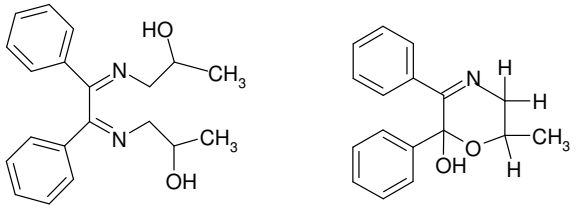
Synthesis

5,6-Dihydro-6-methyl-2,3-diphenyl-2H-1,4-oxazine-2-ol (**2**) (Scheme 1) was prepared by the following procedure (Scheme 2): to a magnetically stirred solution of 1 mmol 1-amino-2-propanol in methanol was added drop wise a solution of 1 mmol of appropriate 1,2-diphenylethanone with some drops of glacial acetic acid in methanol and the reaction mixture was refluxed for 5 h. The purity of the synthesized compound was monitored by TLC using ($CHCl_3$-CH_3OH 2:1) mixture as eluent. In this work, the product (5,6-dihydro-6-methyl-2,3-diphenyl-2H-1,4-oxazine-2-ol (2) (Scheme 1) was prepared as a white powder with high yield. The solid formed was filtered, recrytallized from hot methanol, yielding white crystals. Yield 86 % and m.p. 157 °C. Anal. calc. for $C_{17}H_{17}NO_2$: C, 76.40; H, 6.63; N, 5.243; found: C, 76.2; H, 6.2; N, 5.1%. ^{1}H NMR ($CDCl_3$): δ 2.5 (ab-quartet, 2H, CH_2), 4.2 (m, 1H, CH), 1.2 (d, 3H, CH3), 3.9 (s, 1H, OH), 7.14 - 7.71 (m, 10H, phenyl). FT-IR (KBr, cm^{-1}): 3180 (b, OH), 1641 (s, C=N).



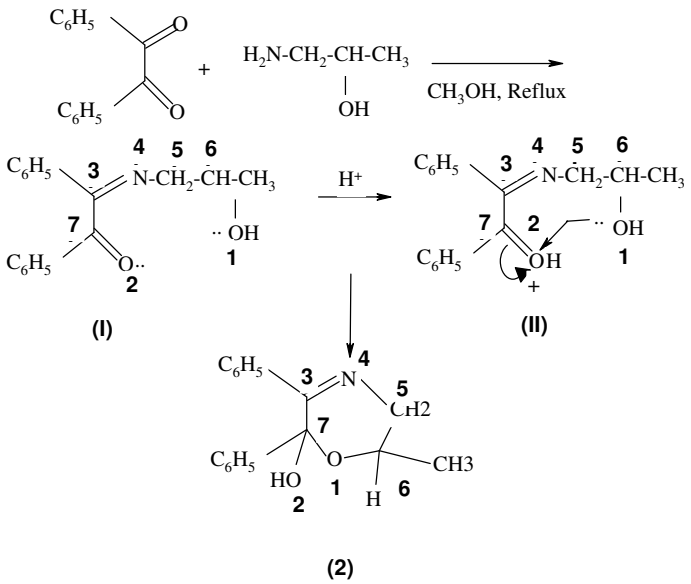
1 **2**

Scheme 1. Structure of the a,a'-[(1,2-diphenyl-1,2-ethanediylidene)bis(nitrilo-methylene)]bis-ethanol (**1**) and 5,6-dihydro-6-methyl-2,3-diphenyl-2H-1,4-oxazine-2-ol (**2**).

The theoretical calculations have been used for investigating of the electronic properties of compounds **I**, **II** and **2** and then the X-ray data and theoretical calculated data were compared. All semi-empirical calculations were performed using Austin Model 1 (AM1) [16] at high precision as implemented in MOPAC 6.0 program. MOPAC 6.0 was used exclusively for the work presented herein [17], and the geometries of all molecules were previously optimized. Some important bond lengths, bond angles, torsion angles and heat of formation for compound **I**, **II** and 2 are given in Table 1.

Table 1. Selected geometric parameters (bond lengths in Å, bond angles in °) and heat of formations ΔH_F (kcal/mol) by X-ray crystallography and AM1 semi-empirical calculations for compounds **I**, **II** and **2**.

	I	**II**	**2**	X-ray data
O1-C2	-	-	1.428	1.420
O1-C6	1.418	1.426	1.428	1.448
C3-N4	1.289	1.279	1.291	1.283
C5-C6	1.546	1.540	1.535	1.514
C2-O2	1.237	1.317	1.413	1.406
C2-O1-C6	-	-	116.55	112.68
C3-N4-C5	122.64	128.49	120.76	119.43
N4-C3-C2	125.54	126.27	123.26	123.73
ΔH_F	-13.887	145.284	-17.559	-



Scheme 2. Schematic representation of the preparation of 5,6-dihydro-6-methyl-2,3-diphenyl-2H-1,4-oxazine-2-ol (**2**).

*X-ray diffraction data of 5,6-dihydro-6-methyl-2,3-diphenyl-2H-1,4-oxazine-2-ol (**2**)*

The white single crystals of compound (**2**) obtained by slow evaporation of a solution of (**2**) in methanol at room temperature. All the measurements were performed using graphite-monochromatized Mo K_α radiation at 95 K: $C_{17}H_{17}NO_2$, M_r 267.32, orthorhombic, space group *Pna2₁*, a = 11.5013(12) Å, b = 13.526(2) Å, c = 8.8258(9) Å, V = 1373.0(3) Å^3, Z = 4, d_{calc} = 1.293 g cm^{-3}, μ = 0.085 mm^{-1}. A total of 2297 reflections were collected (θ_{max} = 27.5°), from which 1680 were unique (R_{int} = 0.0181), with 1605 having I > 2σ (I). The structure was solved by direct methods (SHELXS-97) [18] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97) [19]. The non-hydrogen atoms were refined with anisotropic displacement parameters without any constraints. The H atom H6 of the tertiary C-H group was refined with all X-C-H angles equal at a C-H distance of 1.00 Å. The H atoms of the CH_2 group C5 were refined with common isotropic displacement parameters for the H atoms and idealized geometry with approximately tetrahedral angles and C-H distances of 0.99 Å. The H atoms of the methyl group C61 were refined with common isotropic displacement parameters for the H atoms and idealized geometry with tetrahedral angles, enabling rotation around the X-C bond, and C-H distances of 0.98 Å. The H atoms of the phenyl rings were put at the external bisector of the C-C-C angle at a C-H distance of 0.95 Å and common isotropic displacement parameters were refined for the H atoms of the same phenyl group. The H atom H2 of the OH group was refined with a tetrahedral C-O-H angle, enabling rotation around the C-O bond, an O-H distance of 0.84 Å, and with an individual isotropic displacement parameter. Due to the absence of heavier elements the absolute structure of the chiral molecules could not be determined reliably. For 189 parameters final R indices of R1 = 0.0327 and wR^2 = 0.0782 (GOF = 1.085) were obtained. The largest peak in a difference Fourier map was 0.217 eÅ^{-3}. Stereoscopic ORTEP [20] plot of (**2**) is shown in Figure 2.

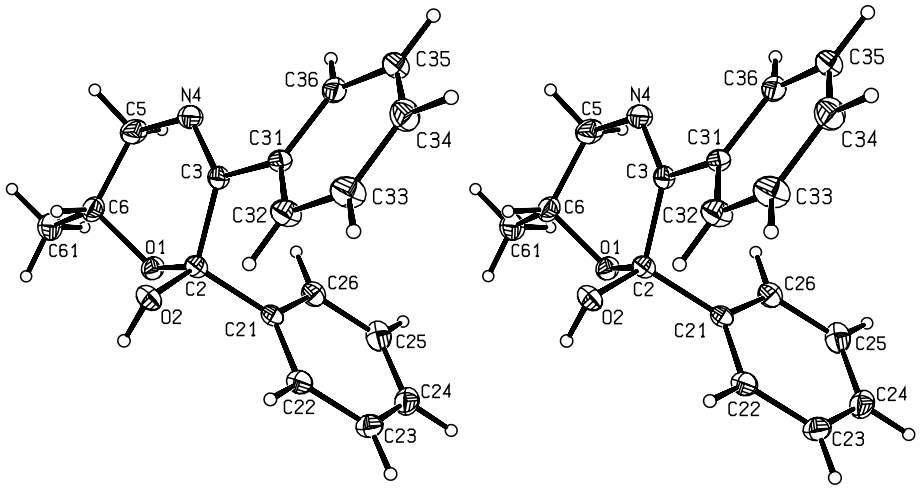


Figure 1. Stereoscopic ORTEP [20] plot of (**2**) showing the atomic numbering scheme. The probability ellipsoids are drawn at the 50% probability level.

RESULTS AND DISCUSSION

The crystal structure analysis of (**2**) confirmed the compound as 5,6-dihydro-6-methyl-2,3-diphenyl-2H-1,4-oxazine-2-ol(2) instead of a,a'-[(1,2-diphenyl-1,2-ethanediylidene)bis(nitrilo-methylene)]bis-ethanol (**1**). O-H…N hydrogen bonds forming chains parallels to the crystallographic an axis. All spectroscopic data for 5,6-dihydro-6-methyl-2,3-diphenyl-2H-1,4-oxazine-2-ol (**2**) are in agreement with the X-ray crystallographic data. Scheme **2** shows the proposed mechanism for the reaction between 1,2-diphenylethanone with 1-amino-2-propanol in the presence of some drops of glacial acetic acid. First **I** is formed by the reaction of C=O group with amine group and gives an imine (**1**). In the presence of H^+ ion the initially imine converted to **II** intermediate, followed by a cyclisation reaction gives compound **2**. Table 1 shows structure **II** in Scheme **2** is an intermediate structure and it has an unstable structure (heat of formation =145.284 kcal/mol) and compound **2** is very stable (heat of formation= -17.559 kcal/mol), and the AM1 optimized geometries of compound **2** are in agreement with the crystallographic data.

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SUPPLEMENTARY MATERIAL

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 662454. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44 1223336033; e-mail: deposit@ccdc.cam.ac.uk or (http://www.ccdc.cam.ac.uk). Supplementary data associated with this article can be found in the online version.

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