ЖУРНАЛ СТРУКТУРНОЙ ХИМИИ

2011. Том 52, № 5 *Сентябрь – октябрь* *С. 1015 – 1018*

UDC 548.737:546.18

CRYSTAL AND MOLECULAR STRUCTURES OF 2-(4-CHLOROPHENYL)-5,7-DIMETHOXYQUINOLIN-4-YL PHENYL BIS(2-CHLOROETHYL) PHOSPHORAMIDATE

© 2011 **J.W. Yuan[1], L.B. Qu[1,2]*, X.L. Chen[2], Z.B. Qu[2], Y.C. Li[1]**

[1]*Chemistry and Chemical Engineering School, Henan University of Technology, Henan Province, Zhengzhou, P. R. China*

[2]*Department of Chemistry, Zhengzhou University, Key Laboratory of Organic Chemistry and Chemical Biology, Henan Province, Zhengzhou, P. R. China*

Received January, 29, 2010

2-(4-Chlorophenyl)-5,7-dimethoxyquinolin-4-yl phenyl bis(2-chloroethyl)phosphoramidate is synthesized and characterized by NMR, IR and single crystal X-ray crystallography. The crystal is triclinic, $P\bar{1}$ space group, with $a = 9.5188(19)$, $b = 12.856(3)$, $c = 13.250(3)$ Å, $V = 1412.0(5)$ Å^3, and $Z = 2$ (at 291(2) K). The crystal packing arrangement indicates that the molecule is stacked through π…π aromatic stacking interactions.

K e y w o r d s: crystal and molecular structure, X-ray crystallography, 2-phenyl-4-quinolone, phosphoramidate.

INTRODUCTION

In the latest years, considerable attention has been paid to the development of programs to purposefully synthesize biologically active 2-phenyl-4-quinolones and related derivatives [1, 2]. These compounds can be used as potential antimitotic [3], antibacterial [4], and anti-platelet agents [5] and cardiovascular protectors [6]. Moreover, phosphoramidates, as an important component, have often been introduced to modify a wide variety of structurally diverse natural and biologically active compounds, such as glycolipids and nucleic acids [7, 8]. The corresponding derivatives are sometimes used as prodrugs to increase the water solubility and bio-availability of the agent [9]. Importantly, they have also been found considerable biological interest as anticancer agents [10]. In the previous paper, the correlated phosporamidate derivatives of 2-phenyl-4-quinolones was reported by our group [11, 12]. It is known that the biological activity of a compound is related to the geometry of its molecules and also the non-covalent bond interactions. The fine structure of one representative of 2-phenyl-4-quinolone derivatives series, 2-(4-chlorophenyl)-5,7-dimethoxyquinolin-4-yl phenyl bis(2-chloroethyl)phosphoramidate containing a phosphoramide mustard substituent, was shown in Fig. 1. It was obtained in a high yield by the reaction of 2-phenyl-4-quinolone with phosphoramidochloridate under mild conditions. The structure of the title compound was analyzed based on the X-ray crystallographic data for a deeper understanding of the structure of phosphoramidate derivatives of 2-phenyl-4-quinolones.

* E-mail: qulingbo@zzu.edu.cn

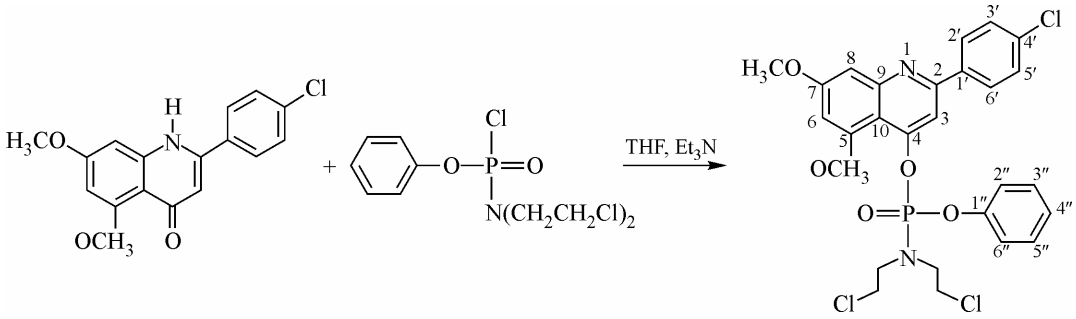

Fig. 1. Synthesis of the title compound

EXPERIMENTAL

Synthesis. 2-(4-Chlorophenyl)-5,7-dimethoxy-4-quinolone (0.5 g, 1.6 mmol) and phenyl bis(2-chloroethyl) phosphoramidochloridate (0.54 g, 1.7 mmol) was dissolved in tetrahydrofuran (40 ml) and stirred at room temperature for 20 min. A mixed solution of dry triethylamine (0.25 ml, 1.7 mmol) and tetrahydrofuran (5 ml) was added dropwise to the stirred solution. The reaction mixture was allowed to stand for 1 h before heating for 10 h to reflux. The solution was filtered, evaporated to dryness, and the residue was purified by column chromatography on silica gel (cyclohexane: ethyl acetate, 3:1). A 0.6 g colorless crystal was obtained, yield: 65 %. m.p. 106—107 °C. Found, %: C 54.28, H 4.29, N 4.72. $C_{27}H_{26}Cl_3N_2O_5P$. Calculated, %: C 54.43, H 4.40, N 4.70.

NMR spectra were measured on a Bruker Avance 400 MHz spectrometer. ^{1}H and ^{13}C chemical shifts were determined relative to internal TMS. ^{31}P chemical shifts were determined relative to 85 % H_3PO_4 as the external standard. Infrared (IR) spectra in KBr pellets were recorded on a Shimadazu IR-408 spectrometer. ^{1}H NMR ($CDCl_3$) δ: 7.89 (s, 1H, 3-H), 6.55 (d, $^4J_{H—H}$ = 1.4 Hz, 1H, 6-H), 7.10 (d, $^4J_{H—H}$ = 1.4 Hz, 1H, 8-H), 8.04 (d, $^3J_{H—H}$ = 8.5 Hz, 2H, 2′6′-H), 7.44 (d, $^3J_{H—H}$ = 8.5 Hz, 2H, 3′5′-H), 3.94 (s, 6H, 5, 7-OCH_3), 7.25 (d, $^3J_{H—H}$ = 8.2 Hz, 2H, 2″6″-H), 7.33 (d, $^3J_{H—H}$ = 8.0 Hz, 2H, 3″5″-H), 7.17 (t, $^3J_{H—H}$ = 7.6 Hz, 1H, 4″-H), 3.70—3.59 (m, 8H, NCH_2 CH_2Cl). ^{13}C NMR ($CDCl_3$) δ: 157.3 (2-C), 106.6 (d, $^3J_{C—P}$ = 2.7 Hz, 3-C), 155.2 (d, $^2J_{C—P}$ = 6.7 Hz, 4-C), 156.4 (5-C), 99.7 (6-C), 161.6 (7-C), 100.9 (8-C), 153.6 (9-C), 108.2 (d, $^3J_{C—P}$ = 6.8 Hz, 10-C), 137.0 (1′-C), 128.7 (2′6′-C), 128.9 (3′5′-C), 135.8 (4′-C), 55.7 (5-OCH_3), 56.0 (7-OCH_3), 150.4 (d, $^2J_{C—P}$ = 7.2 Hz, 1″-C), 120.2 (d, $^3J_{C—P}$ = 5.0 Hz, 2″6″-C), 129.9 (3″5″-C), 125.5 (4″-C), 49.4 (d, $^2J_{C—P}$ = 4.4 Hz, NCH_2), 41.7 (CH_2Cl). ^{31}P NMR ($CDCl_3$) δ: –0.70. IR(KBr), ν(cm^{-1}): 2962, 2935, 2835 (CH_3, CH_2), 1590 (C=N), 1210 (P=O), 1036 (P—O).

Single crystal X-ray diffraction. Crystals of X-ray quality were obtained by slow crystallization of the material from methanol at room temperature with subsequent drying in air.

The X-ray diffraction analysis of the title compound (0.20×0.18×0.16 mm) was carried out at 291(2) K on an R-Axis-IV diffractometer with a graphite monochromatic MoK_α radiation (λ = = 0.71073 Å) in oscillation scan mode. The unit cell dimensions were obtained with the least-squares refinements, and the structure was solved by direct methods using the SHELXS-97 program [13] and refined by the full matrix least squares fitting on F^2 with anisotropic thermal parameters for all non-hydrogen atoms using SHELXL-97 [14]. Hydrogen atoms were generated geometrically. Molecular illustrations were prepared using the XP package.

The crystal is colorless and triclinic; $C_{27}H_{26}Cl_3N_2O_5P$; M = 595.82; a = 9.5188(19) Å, b = = 12.856(3) Å, c = 13.250(3) Å; α = 110.90(3)°, β = 100.55(3)°, γ = 103.08(3)°; V = 1412.0(5) Å^3, d_x = = 1.401 g/cm^3, Z = 2, $P\bar{1}$ space group. The scan angle is 1.72 < θ < 25.00°. A total of 4471 reflections were measured, 4471 being independent (R_{int} = 0.0000). Absorption correction was introduced semi-empirically from equivalents. Final values of divergence factors are R = 0.0587 and R_w = 0.1509. GOOF = 1.075, extinction coefficient 0.019(2). Coordinates of atoms and structural parameters of the crystal have been deposited with the Cambridge Crystal Structure Database (CCDC 680149).

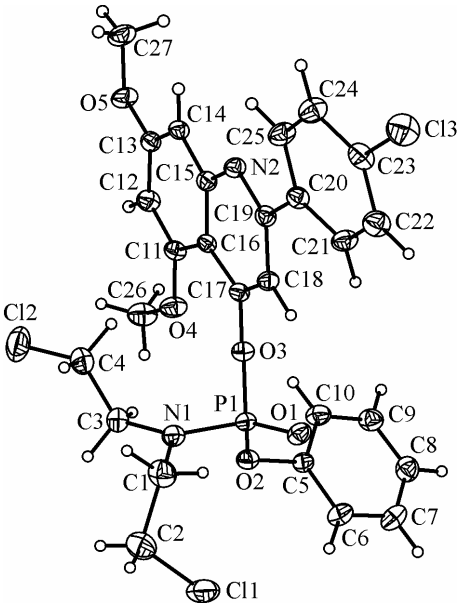

Fig. 2. View of the molecule of the title compound. Thermal ellipsoids are drawn at the 30 % probability level

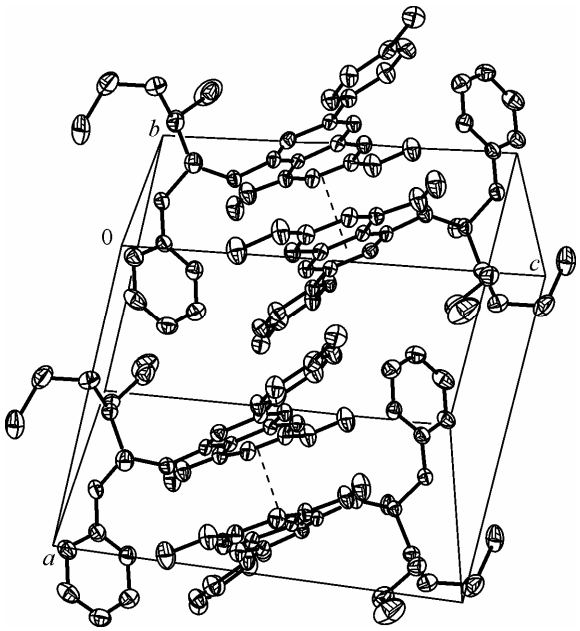

Fig. 3. Crystal packing of the title compound. Thermal ellipsoids are drawn at the 30 % probability level

RESULTS AND DISCUSSION

The X-ray structural study revealed the specific features and geometry of the title compound that was isolated as well-shaped crystals. An overall view of the molecule is shown in Fig. 2. The P=O bond length (1.455(3) Å) in the crystal structure is close to the normal P=O bond length found in $P(O)Cl_3$ (1.45 Å) [15, 16] and is shorter than those of P(1)—O(2) (1.585(2) Å) and P(1)—O(3) (1.598(2) Å). The P—N bond length (1.629(3) Å) is shorter than the typical P—N bond length found in $NaHPO_3NH_2$ (1.77 Å) [17].

The environment of the amine N(1) atom of the compound is approximately trigonal planar, since the C(1)—N(1)—C(3), C(1)—N(1)—P(1), and C(3)—N(1)—P(1) angles have the values of 118.0(3)°, 120.6(3)°, and 121.0(2)° respectively with average 119.9°, which indicates sp^2 hybridization for the nitrogen atoms (deviation from the ideal value of 120° can be caused by electronic and/or steric effects). The C(18)—C(19)—C(20)—C(21) torsion angle is 12.5(5)°, which shows that the plane of the quinoline ring is not coplanar with the 4-chlorophenyl group. Furthermore, the C(16)—C(15)—N(2)—C(19) torsion angle has a value of 1.3(5)°, which indicates that the quinoline ring is not absolutely planar.

In the crystal packing, as shown in Fig. 3, the adjacent molecules consisting of two enantiomers with a phosphorus atom as a stereogenic center are stacked through π…π aromatic stacking interactions with a face-to-face distance of 3.40 Å and a 0° angle between the quinoline rings. Interestingly, the conjugated molecular planes are arranged in a head-to-tail fashion due to a strong ′push-pull′ electron system. No intramolecular and intermolecular hydrogen bonds were observed in the crystal structure. Intermolecular π…π stacking interactions also make a considerable contribution to the supramolecular organization of the crystal structure.

This work was supported by the Chinese National Science Foundation (No. 20472076) and the Henan Academic Foundation of Science and Technology (No. 0512001400).

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