Synthesis and Crystal Structure of 10a-oxo-1-Phenylimino-10-propyl-3,4,10,10a-tetrahydro-1*H*-2-thia-4a,10-diaza-10aλ^5-phospha-phenanthren-9-one

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ABSTRACT: *The title novel fused tricyclic phosphoroheterocycle, $C_{19}H_{20}N_3O_2PS$, was synthesized in an excellent yield of 88.5% via the reaction of 1-(2-bromoethyl)-2,3-dihydro-3-propyl-1,3,2-benzodiazaphosphorin-4(1H)-one 2-oxide with phenyl isothiocyanate, which contains the proximate imino and phosphoryl groups in the fused heterocycle. The crystallographic data analysis reveals that the title compound crystallizes into triclinic space group P_1^- with unit cell parameters: $a = 9.159(3)$ Å, $b = 10.463(4)$ Å, $c = 10.698(4)$ Å, $\alpha = 88.090(6)°$, $\beta = 86.921(6)°$, $\gamma = 70.528(6)°$, $V = 965.0(6)$ Å^3 for $Z = 2$ and there is a fused three-ring in the molecule. The structure has been solved by direct methods and refined to $R = 0.0424$ for 2451 observed reflections with $I > 2\sigma(I)$. The proximate imino and phosphoryl groups are not coplanar because both are jointly located in the fused heterocycle, thus having ring tension and this then destroys the conjugation between the C=N and the P=O moieties.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:671–676, 2005; Pub-
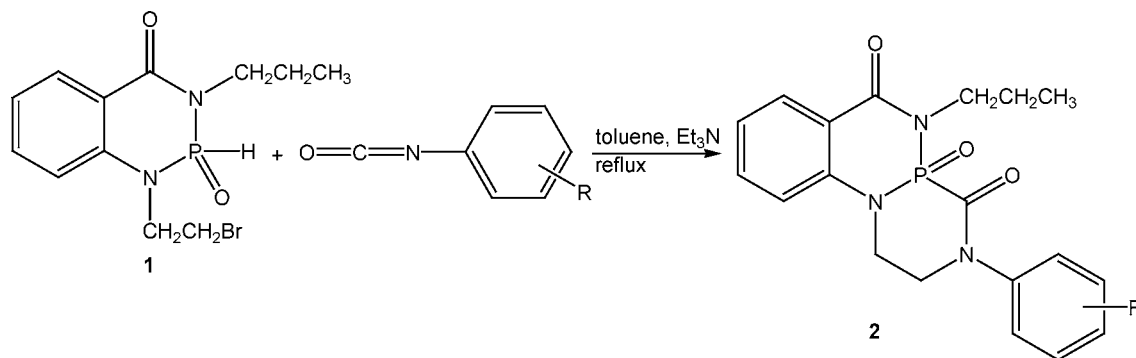
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INTRODUCTION

Organophosphorus compounds are ubiquitous in nature, and they have broad applications in the fields of agriculture and medicine [1–4]. The incorporation of heterocycles is recommended to improve the biological activity, particularly, phospha-heterocycles, such as benzoannulated and related analogs of cyclo-phosphamide possess anitumor activity, and have also created an increasingly wide interest in the chemistry, medicine, and agricultural sciences [5–8]. Studies on the biological activities of phosphoroheterocycles have attracted significant attention in past decades [9]. As a part of the continuous research in our laboratory to develop novel antitumor and antiviral agents with high activity and low toxicity, in the previous work [7,10] we have reported that the fused phosphorus heterocyclic 10a-oxo-2-(substituted)phenyl-10-propyl-3,4,10,10a-tetrahydro-2*H*-2,4a,10-triaza-10aλ^5-phospha-phenanthrene-1,9-dione (**2**) was designed incorporating the proximate carbonyl and phosphoryl

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SCHEME 1

groups into the benzoannulated phosphadiamide heterocycle, and they were synthesized in acceptable yields via the addition and ring-closure reaction of 1-(2-bromoethyl)-2,3-dihydro-3-propyl-1,3,2-benzodiazaphosphorin-4(1H)-one 2-oxide (**1**) with (substituted) phenyl isocyanates, as shown in Scheme 1.

Herein, we wish to report our further investigation on the reaction of **1** with phenyl isothiocyanate. Treatment of the phosphorus reagent **1**, containing a $P-H$ bond, with phenyl isothiocyanate in refluxing benzene for 8 h in the presence of triethylamine readily led to the formation of 10a-oxo-1-phenylimino-10-propyl-3,4,10,10a-tetrahydro-1H-2-thia-4a,10-diaza-10aλ^5-phospha-phenanthren-9-one (**3**) in 88.5% yield (Scheme 2). The structure of **3** was characterized by spectroscopic methods and microanalyses, and was further confirmed by the X-ray diffraction analysis.

EXPERIMENTAL

Melting point was determined using a YANACO MP-500 apparatus and are uncorrected. The ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a BRUKER AM-400 spectrometer operating at 400.030 MHz for ^{1}H and 100.599 MHz for ^{13}C. Tetramethylsilane (TMS) was used as an internal standard for ^{1}H and ^{13}C NMR, and 85% phosphoric acid (H$_3$PO$_4$) was used as an external standard for ^{31}P NMR spectroscopy. The nuclei that are deshielded relative to their respective standards are assigned a positive chemical shift. Coupling constants, J, are given in hertz. Mass spectra were recorded on a Hewlett-Packard 5988 instrument. Elemental analyses were carried out on a Yana MT-3 instrument. Column chromatography was performed using silica gel H (10–40 μm, Haiyang Chemical Factory of Qingdao). 1-(2-Bromoethyl)-3-propyl-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-one 2-oxide **1** was prepared according to the reported methods [7,10].

Preparation of 10a-oxo-1-phenylimino-10-propyl-3,4,10,10a-tetrahydro-1H-2-thia-4a, 10-diaza-10aλ^5-phospha-phenanthren-9-one **3**

A mixture of **1** (0.99 g, 3 mmol), phenyl isothiocyanate (0.36 g, 3 mmol), triethylamine (0.61 g, 6 mmol, distilled from calcium hydride), and 30 mL of dry benzene was heated at reflux for 8 h, and then the produced triethylamine hydrobromide was filtered off. The solvent from the filtrate was removed under reduced pressure, and the residue was
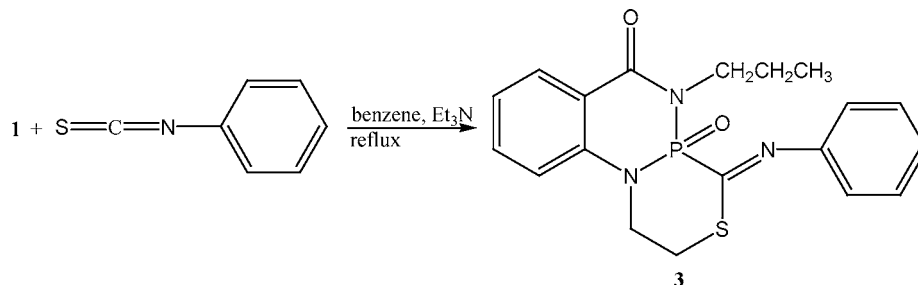
SCHEME 2

chromatographed on a column of silica gel using a mixture of 30% ethyl acetate-light petroleum ether to elute the product, 1.02 g (88.5% yield). Further recrystallization from a mixture of dichloromethane and hexane (2:5, V/V) afforded the title compound as colorless crystals (mp, 160–162°C). ^{1}H NMR (CDCl$_3$ as a solvent, TMS as an internal reference, δ): 0.95 (t, 3H, NCH$_2$CH$_2$**CH$_3$**, $^{3}J_{HH}$ = 7.3); 1.82 (m, 2H, NCH$_2$**CH$_2$**CH$_3$); 3.22 (dt, 1H, 1/2 × SCH$_2$CH$_2$N, $^{2}J_{HH}$ = 15.0, $^{3}J_{HH}$ = 4.0); 3.77–3.90 (m, 2H, 1/2 × SCH$_2$CH$_2$N + 1/2 × NCH$_2$CH$_2$CH$_3$); 4.12–4.23 (m, 1H, 1/2 × NCH$_2$CH$_2$CH$_3$); 4.35–4.49 (m, 2H, 1/2 × SCH$_2$CH$_2$N + 1/2 × SCH$_2$**CH$_2$**N); 6.90–8.30 (m, 9H, C$_6$**H$_5$** + C$_6$**H$_4$**). ^{31}P NMR (CDCl$_3$ as a solvent, 85% H$_3$PO$_4$ as an external reference, δ): –4.54 (single). ^{13}C NMR (CDCl$_3$ as a solvent), δ ppm: 11.686 [s, C(19)]; 22.675 [s, C(18)]; 25.122, 25.221 [d, J_{PC} = 9.96, C(9)]; 46.916 [s, C(17)]; 48.729, 48.752 [d, J_{PC} = 2.31, C(8)]; 113.118, 113.187 [d, J_{PC} = 6.94, C(4)]; 116.659 [s, C(2)]; 120.093 [s, C(12), C(16)]; 122.371 [s, C(6)]; 126.073 [s, C(14)]; 129.407 [s, C(13), C(15)]; 131.258 [s, C(7)]; 135.165 [s, C(5)]; 141.467, 141.490 [d, J_{PC} = 2.31, C(3)]; 148.273, 148.556 [d, J_{PC} = 28.47, C(11)]; 161.227, 163.292 [d, J_{PC} = 207.74, C(10)]; 162.581, 162.603 [d, J_{PC} = 2.21, C(1)]. MS (70 eV, EI, m/z): 385, 22%. Elemental analysis calculated: C 59.21, H 5.23, N 10.90; found: C 59.18, H 5.27, N 10.77.

Crystal Structure Determinations and Refinements

A colorless prismatic-shaped single crystal of **3**, which was cultured by the solvent loss technique in a mixture of dichloromethane and hexane (2:5, V/V), was subjected to the X-ray diffraction analysis. The crystal data, data collection, and refinement parameters for the title compound are listed in Table 1. Data were collected with a Bruker SMART 1000 CCD area-detector diffractometer, using graphite monochromatized Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods using SHELXS-97 package and refined with full-matrix least-squares procedures using SHELXL-97 software. All non-hydrogen atoms of the molecule were obtained from the E-map and refined anisotropically. All the hydrogen atoms were located from a difference Fourier map and placed at calculated position refined with riding model position parameters isotropically. The fractional atomic coordinates of non-hydrogen atoms, and equivalent isotropic displacement parameters are given in Table 2. The bond lengths, bond angles, and the selected torsion angles are listed in Table 3.

TABLE 1 Crystal Data and Structure Refinement

CCDC deposit No.	225112
Empirical formula	C$_{19}$H$_{20}$N$_3$O$_2$PS
Formula weight	385.41
Crystal description	Colorless prismatic
Crystal size (mm)	0.30 × 0.20 × 0.15
Crystal system	Triclinic
Space group	P^{-1}
Unit-cell dimensions	a = 9.159(3) Å
	b = 10.463(4) Å
	c = 10.698(4) Å
	α = 88.090(6)°
	β = 86.921(6)°
	γ = 70.528(6)°
Volume (Å^3)	965.0(6)
Z	2
Density (calc.) (mg m^{-3})	1.326
Diffractometer (scan)	Bruker SMART 1000 CCD area-detector diffractometer
Radiation/wavelength	Mo K$_\alpha$ (graphite mono chrom.)/0.71073 Å
Scan type	φ and ω scans
Absorption coefficient (mm^{-1})	0.269
$F(000)$	404
Temperature (K)	293(2)
θ range for data collection, deg.	2.36–25.02
T_{max}, T_{min}	0.9608, 0.9237
Index ranges	$h = -4 \rightarrow 10$
	$k = -12 \rightarrow 12$
	$l = -12 \rightarrow 12$
Reflections measured	4050
Independent/observed reflections	3400 (R_{int} = 0.0162)
Absorption correction	SADABS
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3400/0/235
Weight	$1/[\sigma^2(F_0^2) + (0.0768P)^2 + 0.0538P]$, where $P = (F_0^2 + 2F_c^2)/3$
Goodness-of-fit on F^2	1.024
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0424, wR2 = 0.1097
R indices (all data)	R1 = 0.0636, wR2 = 0.1296
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e·Å^{-3})	0.202, −0.356

RESULTS AND DISCUSSION

The crystal structure of **3** is shown in Figs. 1 and 2. Figure 1 is a perspective view of the compound showing the atomic-numbering scheme, and Fig. 2 depicts the molecular packing in the unit cell.

The crystallographic data reveal that the torsion angle, O(1)−P(1)−C(10)−N(3), between P=O and C=N groups is −108.3(2)°, indicating that the proximate imino and phosphoryl groups are not coplanar because both are jointly located in the fused

TABLE 2 Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($\mathring{A}^2$)
$U_{eq} = (1/3) \sum_i \sum_j U^{ij} a^i a^j \, \mathbf{a}_i \mathbf{a}_j$

Atom	x	y	z	U_{eq}
P(1)	0.76400 (7)	0.36698 (6)	0.15932 (6)	0.0398 (2)
S(1)	0.49644 (7)	0.27725 (8)	0.25830 (7)	0.0570 (2)
N(1)	0.9518 (2)	0.3269 (2)	0.18392 (18)	0.0418 (5)
N(2)	0.7593 (2)	0.2718 (2)	0.04036 (18)	0.0412 (5)
N(3)	0.7479 (2)	0.2559 (2)	0.3891 (2)	0.0501 (5)
O(1)	0.68193 (19)	0.51277 (17)	0.14787 (17)	0.0527 (5)
O(2)	1.20796 (19)	0.2180 (2)	0.14432 (18)	0.0600 (5)
C(1)	1.0746 (3)	0.2423 (3)	0.1122 (2)	0.0433 (6)
C(2)	1.0404 (3)	0.1862 (2)	−0.0026 (2)	0.0417 (6)
C(3)	0.8898 (3)	0.1989 (2)	−0.0355 (2)	0.0405 (6)
C(4)	0.8713 (3)	0.1363 (3)	−0.1442 (2)	0.0534 (7)
C(5)	0.9988 (3)	0.0653 (3)	−0.2181 (3)	0.0620 (8)
C(6)	1.1474 (3)	0.0561 (3)	−0.1875 (3)	0.0642 (8)
C(7)	1.1664 (3)	0.1156 (3)	−0.0811 (3)	0.0534 (7)
C(8)	0.6055 (3)	0.2662 (3)	0.0079 (2)	0.0478 (6)
C(9)	0.4755 (3)	0.3410 (3)	0.0986 (2)	0.0507 (7)
C(10)	0.6764 (3)	0.2943 (2)	0.2888 (2)	0.0426 (6)
C(11)	0.6750 (3)	0.2008 (3)	0.4887 (2)	0.0477 (6)
C(12)	0.5529 (3)	0.2814 (3)	0.5616 (3)	0.0639 (8)
C(13)	0.4883 (4)	0.2248 (3)	0.6591 (3)	0.0686 (9)
C(14)	0.5433 (4)	0.0901 (3)	0.6840 (3)	0.0647 (8)
C(15)	0.6668 (4)	0.0087 (3)	0.6133 (3)	0.0689 (8)
C(16)	0.7347 (3)	0.0636 (3)	0.5165 (3)	0.0584 (7)
C(17)	0.9905 (3)	0.3984 (3)	0.2876 (2)	0.0490 (6)
C(18)	1.0396 (4)	0.5181 (3)	0.2440 (3)	0.0620 (8)
C(19)	1.0891 (5)	0.5804 (4)	0.3531 (4)	0.1010 (13)

heterocycle having ring tension, and this then destroys the conjugation between the C=N and the P=O moieties. As a result, the length of the P(1)–C(10) bond is measured as 1.833(2) $\mathring{A}$ and is just the same as that of a *P─C* bond not involved in conjugation
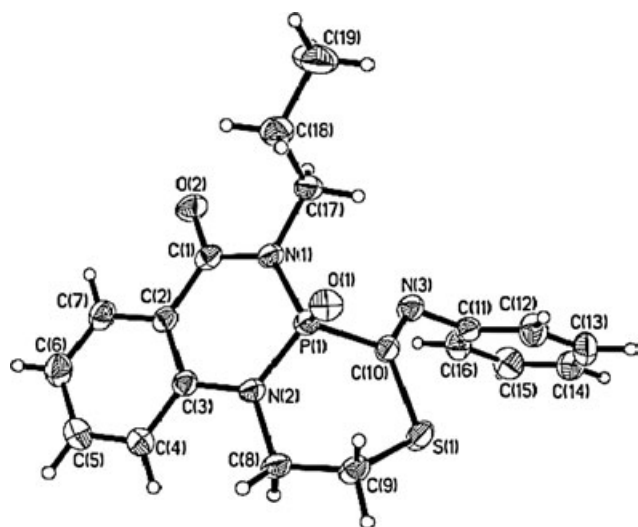
FIGURE 1 View of the molecule **3**, showing the atom-numbering scheme.

(1.80–1.85 $\mathring{A}$) [11]. The plane defined by N(2), C(8), S(1), and C(10) atoms displays a coplanar configuration with a mean deviation to the least square plane of 0.0246 $\mathring{A}$. The N(2), C(8), C(9), S(1), C(10), and P(1) atoms of the thiazaphosphorino moiety in the title compound prefer the boat conformation. The coplanar N(2), C(8), S(1), and C(10) atoms form the ground floor of the boat conformation, whereas the P(1) and C(9) atoms are on the same side of the coplanar structure with the distances of 0.7849 $\mathring{A}$ and 0.7362 $\mathring{A}$, respectively. The torsion angle of C(11)–N(3)=C(10)–P(1) is 179.39(18)°, showing that the phenyl group on N(3) position is far away from the N(1) propyl group to avoid steric conflicts.

The EI-MS spectrum of **3** shows the existence of strong molecular ion peak, indicating that the heterocyclic skeletons have some stability. From the two-dimensional (2D) H-C COSY (Fig. 3), it can be seen that the two methylene protons in the PNCH_2CH_2CH_3 group resonate at 3.77–3.90 and 4.12–4.23 ppm. The signal of 3.22 (dt, 1H, $^2J_{HH} = 15.0$, $^3J_{HH} = 4.0$) is contributed from one of the two methylene protons in PNCH_2CH_2S, and another proton signal is at 4.35–4.49, which can be explained by the anisotropic effect of the adjacent P=O group. This assumption was verified by the X-ray

TABLE 3   Geometrical Details

Bond lengths (Å)			
P(1)–O(1)	1.4629 (18)	P(1)–N(2)	1.653 (2)
P(1)–N(1)	1.663 (2)	P(1)–C(10)	1.833 (2)
S(1)–C(10)	1.764 (3)	S(1)–C(9)	1.810 (3)
N(1)–C(1)	1.388 (3)	N(2)–C(3)	1.414 (3)
N(1)–C(17)	1.480 (3)	C(2)–C(7)	1.397 (3)
C(3)–C(4)	1.398 (4)	C(4)–C(5)	1.380 (4)
C(5)–C(6)	1.388 (4)	C(6)–C(7)	1.362 (4)
C(11)–C(12)	1.375 (4)	C(11)–C(16)	1.383 (4)
C(12)–C(13)	1.383 (4)	C(13)–C(14)	1.352 (4)
C(15)–C(16)	1.386 (4)	C(17)–C(18)	1.518 (4)
C(18)–C(19)	1.516 (4)	N(3)–C(10)	1.270 (3)
N(2)–C(8)	1.489 (3)	O(2)–C(1)	1.228 (3)
N(3)–C(11)	1.433 (3)	C(2)–C(3)	1.403 (3)
C(1)–C(2)	1.470 (4)	C(14)–C(15)	1.373 (4)
C(8)–C(9)	1.509 (3)		

Bond angles (deg.)			
O(1)–P(1)–N(2)	117.38 (10)	O(1)–P(1)–N(1)	114.08 (10)
N(2)–P(1)–N(1)	103.99 (10)	O(1)–P(1)–C(10)	110.10 (11)
N(2)–P(1)–C(10)	102.52 (11)	N(1)–P(1)–C(10)	107.76 (11)
C(10)–S(1)–C(9)	100.06 (12)	C(1)–N(1)–C(17)	117.20 (19)
C(1)–N(1)–P(1)	126.94 (17)	N(17)–N(1)–P(1)	115.66 (16)
C(3)–N(2)–C(8)	117.51 (19)	C(3)–N(2)–P(1)	124.84 (16)
C(8)–N(2)–P(1)	117.61 (16)	C(10)–N(3)–C(11)	118.4 (2)
O(2)–C(1)–N(1)	119.7 (2)	O(2)–C(1)–C(2)	121.8 (2)
N(1)–C(1)–C(2)	118.4 (2)	C(7)–C(2)–C(3)	119.2 (2)
C(7)–C(2)–C(1)	117.2 (2)	C(3)–C(2)–C(1)	123.6 (2)
C(4)–C(3)–C(2)	118.7 (2)	C(4)–C(3)–N(2)	120.5 (2)
C(2)–C(3)–N(2)	120.8 (2)	C(5)–C(4)–C(3)	120.3 (3)
C(4)–C(5)–C(6)	121.0 (3)	C(7)–C(6)–C(5)	119.0 (3)
C(6)–C(7)–C(2)	121.8 (3)	N(2)–C(8)–C(9)	113.3 (2)
C(8)–C(9)–S(1)	114.80 (17)	N(3)–C(10)–S(1)	125.00 (19)
N(3)–C(10)–P(1)	120.01 (19)	S(1)–C(10)–P(1)	114.93 (14)
C(12)–C(11)–C(16)	119.1 (2)	C(12)–C(11)–N(3)	121.9 (2)
C(16)–C(11)–N(3)	118.9 (2)	C(11)–C(12)–C(13)	120.1 (3)
C(14)–C(13)–C(12)	120.9 (3)	C(13)–C(14)–C(15)	119.6 (3)
C(14)–C(15)–C(16)	120.4 (3)	C(11)–C(16)–C(15)	119.7 (3)
N(1)–C(17)–C(18)	113.4 (2)	C(19)–C(18)–C(17)	110.8 (3)

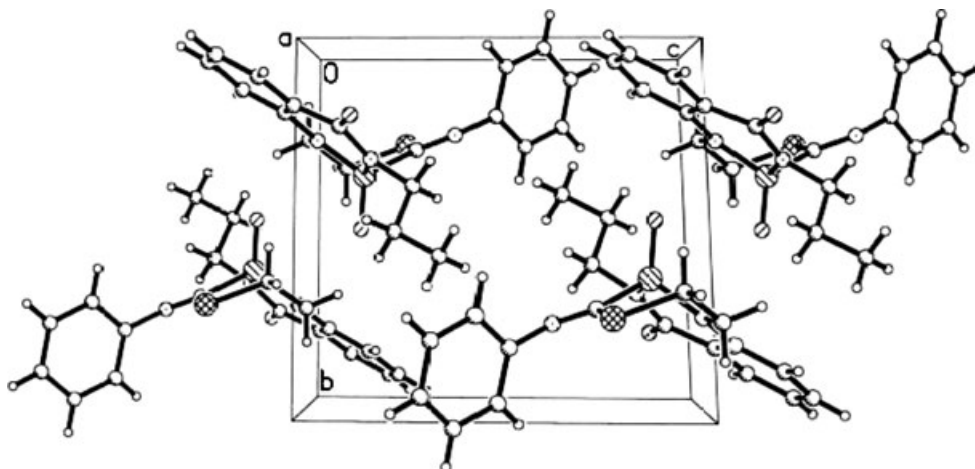| Torsion angles (deg.)			
O(1)–P(1)–C(10)–N(3)	−108.3 (2)	N(2)–P(1)–C(10)–N(3)	126.0 (2)
N(1)–P(1)–C(10)–N(3)	16.7 (2)	O(1)–P(1)–C(10)–S(1)	74.29 (16)
C(11)–N(3)–C(10)–S(1)	−3.5 (4)	C(11)–N(3)–C(10)–P(1)	179.39 (18)

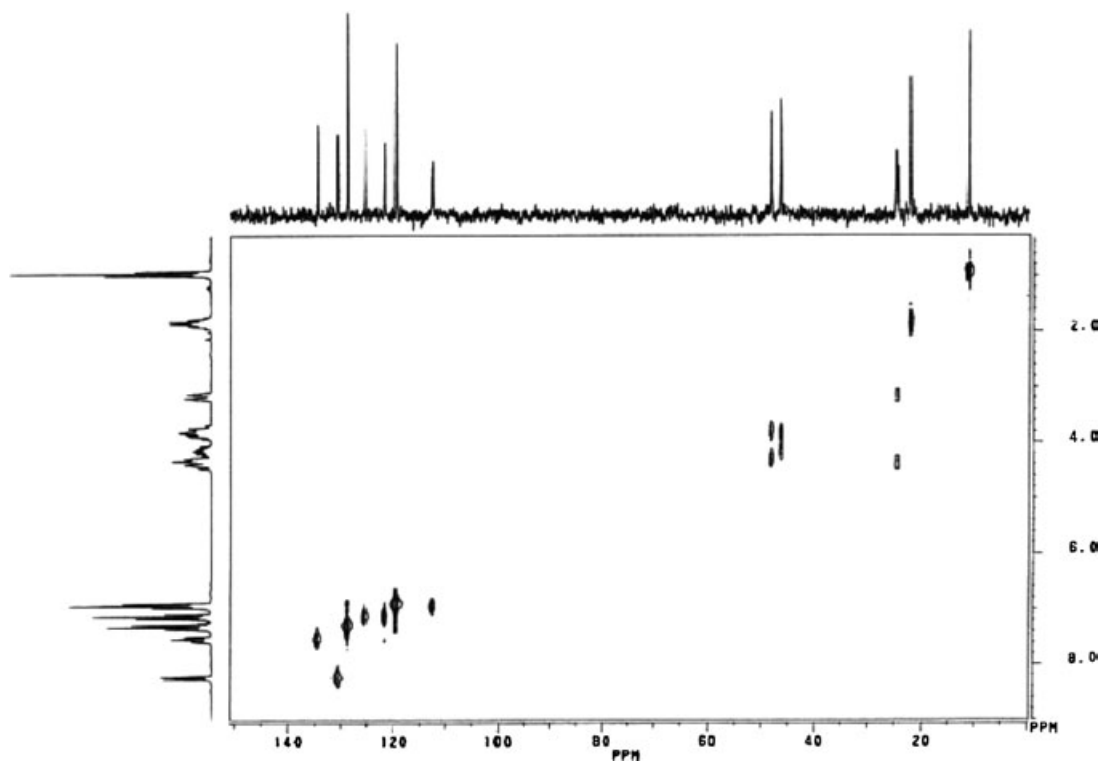**FIGURE 2**   A packing diagram of the title compound **3**.

FIGURE 3 2D H-C COSY spectrum of **3**.

crystallographic analysis of this compound **3** as shown in Fig. 1, in which this phenomenon has also been reported in the literature [12,13].

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