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An Efficient Synthesis and Crystal Structure of Novel 1-Oxo-2-propyl-4-(substituted)-phenylimino-1,2,3,4,5,6,7,8-octahydro-[1,4,3]thiazaphosphorino[4,3-*a*][1,3,2]-benzodiazaphosphorine 3-Oxides

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ABSTRACT: *A series of 1-oxo-2-propyl-4-(substituted)phenylimino-1,2,3,4,5,6,7,8-octahydro-[1,4,3]thiazaphosphorino[4,3-a][1,3,2]benzodiazaphosphorine 3-oxides (***5a–g***) has been synthesized in excellent yields via the reaction of 1-(2-bromoethyl)-2,3-dihydro-3-propyl-1,3,2-benzodiazaphosphorin-4(1H)-one 2-oxide with (substituted) phenyl isothiocyanates, which contain the proximate imino and phosphoryl groups in the fused heterocycle. The structures of all of the new compounds were confirmed by spectroscopic methods and microanalyses. The results from X-ray crystallography analysis of* **5a** *showed that the proximate imino and phosphoryl groups are not coplanar due to their being 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. As a result, the length of the P—C bond, measured as 1.8285(18) Å, is just the same as that of a P—C bond not involved in conjugation (1.80–1.85 Å). Also, the C(1), C(2), S(1), C(3), P(1), and N(2) atoms of the [1,4,3]thiazaphosphorino moiety exist preferably in the boat conformation. The coplanar C(1), N(2), C(3), and S(1) atoms, within an average deviation of 0.0564 Å, form the ground floor of the boat conformation, whereas, the P(1) and C(2) atoms are on the same side of the coplanar structure with the distance of 0.7729 Å and 0.7621 Å, respectively. On the other hand, around the C=N double bond, the P(1)—C(3) bond and the N(1)—C(11) bond are in a trans relationship because of the repulsive action of the n-propyl group in the 2-position of the title compound.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:599–610, 2002; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10041

INTRODUCTION

Organophosphorus compounds are ubiquitous in nature and they have broad applications in the fields of agriculture and medicine [1–4]. There has been a considerably growing interest in heterocyclic compounds because of their pharmaceutical importance and extensive application in organic synthesis, and the application of heterocycles is suggested to enhance the biological activity and/or offer other

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This manuscript is dedicated to Professor William E. McEwen, the Founding Editor and Editor-in-Chief for the past 13 years of HETEROATOM CHEMISTRY, on the occasion of his 80th birthday.

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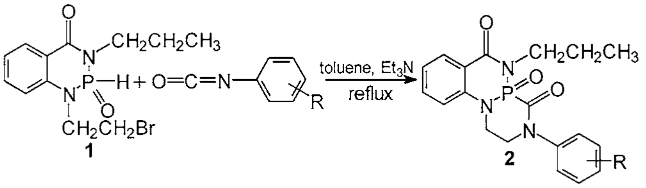
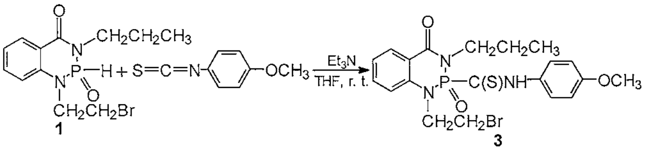
diverse properties [5–10]. A sizeable number of endogenous compounds that play a key role in the regulation of various life processes consist of fused heterocycles. Furthermore, benzoannulated and related analogs of cyclophosphamide possess antitumor activity, and have also created an increasingly wide interest in the chemistry, medicine, and agricultural sciences [11–13]. As a part of ongoing studies in our laboratory to develop novel antitumor and antiviral agents with high activity and low toxicity, in the previous work [14], we have reported that the fused phosphorus heterocyclic 2-propyl-5-(substituted)phenyl-1,4-dioxo-1,2,3,4,5,6,7,8-octahydro-[1,4,2]diazaphosphorino[1,2-*a*][1,3,2]-benzodiazaphosphorine 3-oxides (**2**) were designed incorporating the proximate carbonyl and phosphoryl 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(1*H*)-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 (substituted) phenyl isothiocyanates. At room temperature, *N*-*p*-methoxyphenyl-1-(2-bromoethyl)-3-propyl-1,2,3,4-tetrahydro-4-oxo-1,3,2-benzodiazaphosphorin-2-thiocarboxamide 2-oxide (**3**) could be prepared by the reaction of **1** with *p*-methoxyphenyl isothiocyanate in the presence of triethylamine (Scheme 2). According to the capability of possible cyclization between the thiocarboxamide and the bromoethyl groups forming the proximate thiono and phosphoryl groups in the fused heterocyclic structure of **4**, as shown in Scheme 3, treatment of **3** with sodium hydride at the reflux temperature in THF produced only the fused phosphorus heterocyclic **5a** due to the selectivity of S-alkylation in the cyclization step, as outlined in Scheme 4, in which **4** could not be formed because of $k_2 \gg k_1$. Under the milder conditions of the use of triethylamine in benzene at the reflux temperature (Scheme 5), the condensed 1,3,2-benzodiazaphosphorine (**5a**) was still the only product of the ring closure of **3**.



SCHEME 1



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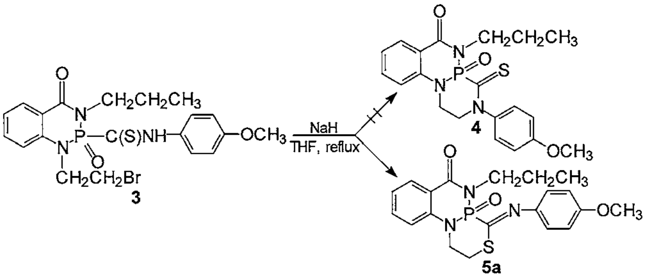

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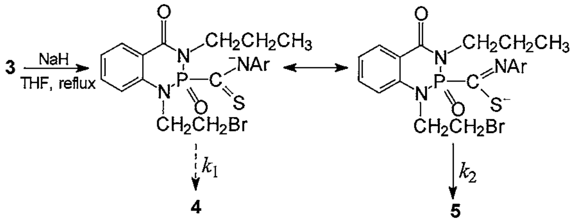

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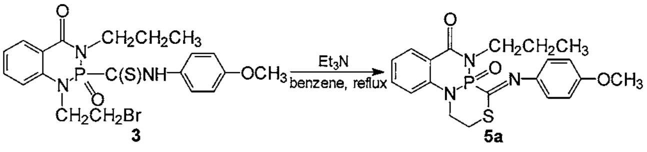

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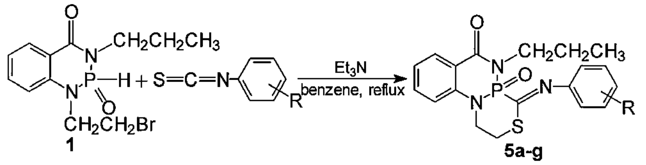

SCHEME 6

On the other hand, the second method of preparation of **5** (Scheme 6) was to reflux a mixture of the phosphorus reagent **1**, containing a P—H bond, with the (substituted) phenyl isothiocyanate in the presence of triethylamine. A series of condensed 1,3,2-benzodiazaphosphorines (**5a–g**) was prepared, which involved an addition reaction to form the thiocarboxamide functionality and the bromoethyl group in the same intermediate that subsequently

TABLE 1 Experimental Data of Compounds **5a–g**

					Found/Calcd (%)		
No	*R*	*Yield (%)*	*mp (°C)*	*Molecular Formula*	*C*	*H*	*N*
5a	*p*-CH_3O	82.5[a] (81.8)[b] (73.5)[c]	188–190	$C_{20}H_{22}N_3O_3PS$ (415.45)	57.72 (57.82)	5.24 (5.34)	10.28 (10.11)
5b	*o*-CH_3O	80.6	185–187	$C_{20}H_{22}N_3O_3PS$ (415.45)	57.81 (57.82)	5.26 (5.34)	9.92 (10.11)
5c	H	88.5	160–162	$C_{19}H_{20}N_3O_2PS$ (385.43)	59.18 (59.21)	5.27 (5.23)	10.77 (10.90)
5d	*p*-CH_3	90.4	138–140	$C_{20}H_{22}N_3O_2PS$ (399.45)	60.26 (60.14)	5.57 (5.55)	10.69 (10.52)
5e	*p*-Cl	86.5	177–179	$C_{19}H_{19}ClN_3O_2PS$ (419.87)	54.39 (54.35)	4.69 (4.56)	9.93 (10.01)
5f	*m*-Cl	87.2	118–120	$C_{19}H_{19}ClN_3O_2PS$ (419.87)	54.60 (54.35)	4.65 (4.56)	9.98 (10.01)
5g	*o*-Br	85.0	157–159	$C_{19}H_{19}BrN_3O_2PS$ (464.32)	49.13 (49.15)	4.32 (4.12)	8.95 (9.05)

[a] Yield determined by isolation based on **5** in Scheme 6.
[b] Total Yield of **5a** in Scheme 5 and 2.
[c] Total Yield of **5a** in Scheme 3 and 2.

underwent intramolecular cyclization via the selectivity of S-alkylation involving the two groups, all of this taking place in a one-pot procedure.

RESULTS AND DISCUSSION

All of the new compounds were characterized by spectral data and elemental analyses, and, in the case of **5a**, the molecular structure was confirmed by X-ray analysis. The physical constants of the title compounds (**5a–g**) are listed in Table 1, and data of the ^{1}H NMR, ^{31}P NMR, IR, and MS spectra are listed in Tables 2 and 3.

The crystal data, data collection, and refinement parameter for the structure of **5a** are listed in Table 4. Data were collected with an Enraf-Nonius

TABLE 2 ^{1}H NMR (200 MHz, $CDCl_3$, TMS) and ^{31}P NMR (80.96 MHz, $CDCl_3$, 85% H_3PO_4) Data of Compounds **5a–g**

No	δ_P *(ppm)*	δ_H *(ppm), J (Hz)*
5a	−4.15830 (single)	0.95 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.3$); 1.82 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$); 3.22 (dbr, 1H, $1/2 \times SC\mathbf{H}_2CH_2N$, $^2J_{HH} = 15.4$); 3.77 (s, 3H, $OC\mathbf{H}_3$); 3.75–3.90 (m, 2H, $1/2 \times SCH_2C\mathbf{H}_2N + 1/2 \times NC\mathbf{H}_2CH_2CH_3$); 4.13–4.25 (m, 1H, $1/2 \times NC\mathbf{H}_2CH_2CH_3$); 4.32–4.50 (m, 2H, $1/2 \times SC\mathbf{H}_2CH_2N + 1/2 \times SCH_2C\mathbf{H}_2N$); 6.83–8.27 (m, 8H, $2 \times C_6\mathbf{H}_4$)
5b	−4.54432 (single)	0.95 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.83 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$); 3.24 (dbr, 1H, $1/2 \times SC\mathbf{H}_2CH_2N$, $^2J_{HH} = 15.5$); 3.72 (s, 3H, $OC\mathbf{H}_3$); 3.75–3.92 (m, 2H, $1/2 \times SCH_2C\mathbf{H}_2N + 1/2 \times NC\mathbf{H}_2CH_2CH_3$); 4.10–4.25 (m, 1H, $1/2 \times NC\mathbf{H}_2CH_2CH_3$); 4.30–4.48 (m, 2H, $1/2 \times SC\mathbf{H}_2CH_2N + 1/2 \times SCH_2C\mathbf{H}_2N$); 6.82–8.28 (m, 8H, $2 \times C_6\mathbf{H}_4$)
5c	−4.54268 (single)	0.95 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.3$); 1.82 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$); 3.22 (dbr, 1H, $1/2 \times SC\mathbf{H}_2CH_2N$, $^2J_{HH} = 15.2$); 3.77–3.90 (m, 2H, $1/2 \times SCH_2C\mathbf{H}_2N + 1/2 \times NC\mathbf{H}_2CH_2CH_3$); 4.12–4.23 (m, 1H, $1/2 \times NC\mathbf{H}_2CH_2CH_3$); 4.35–4.49 (m, 2H, $1/2 \times SC\mathbf{H}_2CH_2N + 1/2 \times SCH_2C\mathbf{H}_2N$); 6.89–8.28 (m, 9H, $C_6\mathbf{H}_5 + C_6\mathbf{H}_4$)
5d	−4.41490 (single)	0.95 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.3$); 1.82 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$); 2.30 (s, 3H, $C_6H_4C\mathbf{H}_3$); 3.25 (dbr, 1H, $1/2 \times SC\mathbf{H}_2CH_2N$, $^2J_{HH} = 15.4$); 3.72–3.90 (m, 2H, $1/2 \times SCH_2C\mathbf{H}_2N + 1/2 \times NC\mathbf{H}_2CH_2CH_3$); 4.13–4.28 (m, 1H, $1/2 \times NC\mathbf{H}_2CH_2CH_3$); 4.34–4.50 (m, 2H, $1/2 \times SC\mathbf{H}_2CH_2N + 1/2 \times SCH_2C\mathbf{H}_2N$); 6.82–8.26 (m, 8H, $2 \times C_6\mathbf{H}_4$)
5e	−4.70622 (single)	0.94 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.3$); 1.81 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$); 3.22 (dbr, 1H, $1/2 \times SC\mathbf{H}_2CH_2N$, $^2J_{HH} = 15.6$); 3.72–3.90 (m, 2H, $1/2 \times SCH_2C\mathbf{H}_2N + 1/2 \times NC\mathbf{H}_2CH_2CH_3$); 4.10–4.28 (m, 1H, $1/2 \times NC\mathbf{H}_2CH_2CH_3$); 4.32–4.50 (m, 2H, $1/2 \times SC\mathbf{H}_2CH_2N + 1/2 \times SCH_2C\mathbf{H}_2N$); 6.83–8.26 (m, 8H, $2 \times C_6\mathbf{H}_4$)
5f	−4.76903 (single)	0.95 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.3$); 1.82 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$); 3.26 (dbr, 1H, $1/2 \times SC\mathbf{H}_2CH_2N$, $^2J_{HH} = 15.5$); 3.75–3.92 (m, 2H, $1/2 \times SCH_2C\mathbf{H}_2N + 1/2 \times NC\mathbf{H}_2CH_2CH_3$); 4.10–4.29 (m, 1H, $1/2 \times NC\mathbf{H}_2CH_2CH_3$); 4.32–4.50 (m, 2H, $1/2 \times SC\mathbf{H}_2CH_2N + 1/2 \times SCH_2C\mathbf{H}_2N$); 6.82–8.27 (m, 8H, $2 \times C_6\mathbf{H}_4$)
5g	−4.63475 (single)	0.96 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.3$); 1.84 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$); 3.24 (dbr, 1H, $1/2 \times SC\mathbf{H}_2CH_2N$, $^2J_{HH} = 15.4$); 3.73–3.95 (m, 2H, $1/2 \times SCH_2C\mathbf{H}_2N + 1/2 \times NC\mathbf{H}_2CH_2CH_3$); 4.08–4.29 (m, 1H, $1/2 \times NC\mathbf{H}_2CH_2CH_3$); 4.31–4.53 (m, 2H, $1/2 \times SC\mathbf{H}_2CH_2N + 1/2 \times SCH_2C\mathbf{H}_2N$); 6.80–8.23 (m, 8H, $2 \times C_6\mathbf{H}_4$)

TABLE 3 IR and MS Data of Compounds **5a–g**

	IR (ν_{max}, cm^{-1})			
No	*C=O*	*C=N*	*P=O*	*MS (m/z, %)*
5a	1662.4	1597.5	1336.7	415 (36), 386 (1), 372 (1), 355 (2), 282 (5), 254 (23), 253 (16), 240 (100), 194 (5), 193 (8), 180 (19), 165 (26), 137 (10), 133 (8), 132 (19), 107 (9), 104 (9), 90 (20), 77 (28), 64 (9), 51 (6), 47 (11), 43 (24)
5b	1660.8	1600.4	1336.5	415 (34), 386 (1), 372 (1), 355 (2), 282 (9), 254 (21), 253 (17), 240 (100), 194 (7), 193 (9), 180 (21), 165 (28), 137 (15), 133 (9), 132 (15), 107 (8), 104 (9), 90 (20), 77 (27), 64 (9), 51 (7), 47 (12), 43 (27)
5c	1667.4	1602.5	1338.3	385 (38), 356 (2), 342 (1), 325 (3), 282 (6), 254 (22), 253 (14), 240 (76), 194 (4), 193 (7), 180 (15), 165 (20), 137 (13), 132 (21), 104 (17), 103 (13), 90 (17), 77 (100), 64 (8), 51 (48), 47 (26), 43 (54)
5d	1664.5	1596.2	1335.5	399 (39), 370 (3), 356 (2), 339 (3), 282 (8), 254 (20), 253 (16), 240 (87), 194 (6), 193 (8), 180 (17), 165 (25), 137 (12), 132 (24), 104 (15), 117 (9), 91 (100), 90 (19), 77 (32), 65 (57), 64 (7), 51 (10), 47 (26), 43 (42), 39 (18)
5e	1669.2	1604.4	1338.8	421 (37), 419 (12), 392 (3), 390 (1), 378 (2), 376 (1), 361 (3), 359 (1), 282 (7), 254 (24), 253 (18), 240 (100), 194 (6), 193 (9), 180 (18), 165 (25), 137 (12), 132 (20), 104 (11), 139 (12), 137 (4), 113 (10), 111(3), 90 (18), 77 (31), 64 (7), 51 (8), 47 (14), 43 (29)
5f	1670.5	1603.8	1337.9	421 (36), 419 (13), 392 (3), 390 (1), 378 (3), 376 (1), 361 (3), 359 (1), 282 (8), 254 (25), 253 (17), 240 (100), 194 (8), 193 (7), 180 (20), 165 (28), 137 (17), 132 (22), 104 (13), 139 (11), 137 (4), 113 (9), 111(3), 90 (17), 77 (29), 64 (8), 51 (9), 47 (15), 43 (31)
5g	1670.2	1605.6	1339.4	465 (33), 463 (32), 436 (2), 434 (2), 422 (1), 420 (1), 405 (2), 403 (2), 384 (6), 282 (8), 254 (25), 253 (20), 240 (100), 194 (9), 193 (7), 183 (11), 181 (10), 180 (24), 165 (21), 157 (9), 155 (8), 137 (15), 132 (26), 104 (14), 90 (16), 77 (28), 64 (8), 51 (8), 47 (12), 43 (29)

TABLE 4 Crystallographic Data

Empirical formula	$C_{20}H_{22}N_3O_3PS$
Color	Colorless
Crystal size (mm^3)	$0.50 \times 0.42 \times 0.40$
Crystal system	Monoclinic
Space group	$P2(1)/n$
Unit-cell dimensions	$a = 13.273(3)$, $b = 10.628(2)$, $c = 14.048(3)$ Å, $\beta = 95.50(3)^\circ$
Volume (Å^3)	1972.6(7)
Z	4
Formula weight	415.44
Density (calc.) (mg m^{-3})	1.399
Absorption coefficient (mm^{-1})	0.272
$F(000)$	1352
Diffractometer/scan	Enraf-Nonius CAD4
Radiation/wavelength (Å)	Mo Kα (graphite mono chrom.)/0.71073
Temperature (K)	293 ± 2
θ range for data collection (deg.)	2.02–24.97
Scan type	$\omega - 2\theta$
Index ranges	$-15 \leq h \leq 15$, $0 \leq k \leq 12$, $0 \leq l \leq 16$
Reflections measured	3605
Independent/observed reflections	3456 ($R_{int} = 0.0326$)
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3456/0/254
Weight	$1/[\sigma^2(F_0{}^2) + (0.0816P)^2 + 0.4285P]$ $P = (F_0{}^2 + 2Fc^2)/3$
Goodness of fit on F^2	1.003
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0348$, $wR_2 = 0.1074$
R indices (all data)	$R_1 = 0.0449$, $wR_2 = 0.1120$
Largest diff. peak and hole (e Å^{-3})	0.311/−0.278

CAD4 diffractometer, using graphite monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods using the SHELXS-97 package and refined on F^2 using the data $[I > 2\sigma(I)]$ by full-matrix least-squares procedures using the SHELXL-97 package.

The crystal structure of **5a**, 1-oxo-2-propyl-4-*p*-methoxyphenylimino-1,2,3,4,5,6,7,8-octahydro-[1,4,3]thiazaphosphorino[4,3-*a*][1,3,2]benzodiazaphosphorine 3-oxide 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. All of the non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located from difference maps and added geometrically, and then refined isotropically with a riding model. The fractional coordinates of non-hydrogen atoms and equivalent isotropic thermal parameters are given in Table 5, and the bond lengths and angles are listed in Tables 6 and 7, respectively. The other details of the X-ray analysis are collected in Tables 8–11.

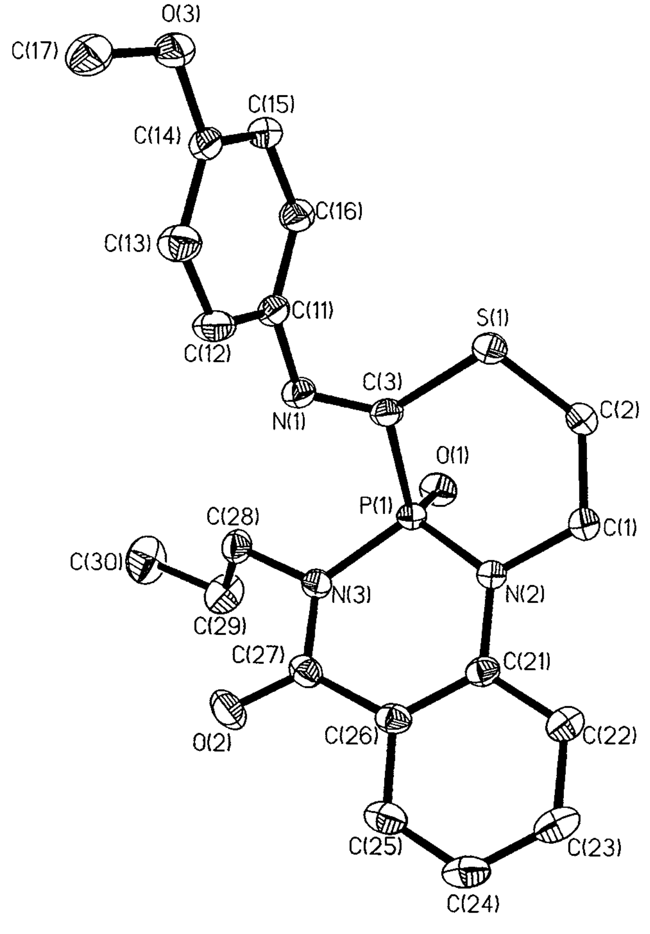

FIGURE 1 Ball and stick representation of compound **5a** showing the crystallographic numbering scheme.

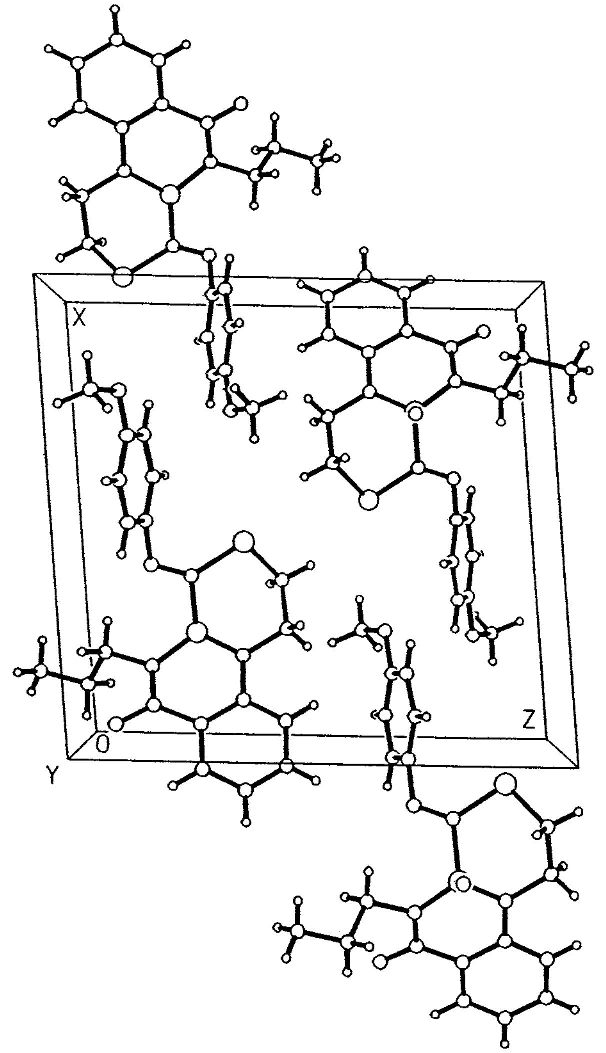

FIGURE 2 ORTEP drawing of compound **5a**.

For compound **5a**, a Newman projection of the P—C bond and the torsion angle between P=O and C=N groups [Table 8, torsion angle of O(1)—P(1)—C(3)—N(1) being 107.23(16)°] are given in Fig. 3, indicating that the proximate *p*-methoxyphenylimino and phosphoryl groups are not coplanar due to their being jointly located in the fused 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(3) bond is measured as 1.8285(18) Å and is just the same as that of a P—C bond not involved in conjugation (1.80–1.85 Å) [15]. The fact that the bond lengths, P(1)—N(2) of 1.6579(15) Å and P(1)—N(3) of 1.6626(15) Å, are shorter than the normal bond length of P—N (1.76 Å) but close to the bond length of P=N (1.64 Å) indicates that there is dπ—pπ bonding in the P—N bonds [15].

TABLE 5 Atomic Coordinates (10^4) and Equivalent Isotropic Displacement Coefficients ($10^3 \times Å^2$)

Atom	*x*	*y*	*z*	$U_{eq}{}^a$
S(1)	479(1)	1924(1)	1361(1)	47(1)
P(1)	2458(1)	1107(1)	2462(1)	30(1)
O(1)	2374(1)	−262(1)	2434(1)	44(1)
O(2)	4373(1)	2932(1)	4144(1)	55(1)
O(3)	−2613(1)	4976(1)	3527(1)	48(1)
N(1)	993(1)	2365(2)	3245(1)	38(1)
N(2)	2916(1)	1802(1)	1539(1)	33(1)
N(3)	3179(1)	1667(1)	3400(1)	33(1)
C(1)	2331(1)	1656(2)	592(1)	41(1)
C(2)	1298(1)	1058(2)	634(1)	43(1)
C(3)	1221(1)	1861(2)	2473(1)	34(1)
C(11)	62(1)	3026(2)	3273(1)	36(1)
C(12)	110(1)	4268(2)	3564(2)	46(1)
C(13)	−767(2)	4959(2)	3645(2)	47(1)
C(14)	−1702(1)	4389(2)	3453(1)	36(1)
C(15)	−1754(1)	3134(2)	3180(1)	40(1)
C(16)	−878(1)	2459(2)	3084(1)	40(1)
C(17)	−2589(2)	6162(2)	3998(2)	53(1)
C(21)	3831(1)	2475(2)	1582(1)	33(1)
C(22)	4247(2)	2816(2)	739(2)	44(1)
C(23)	5148(2)	3486(2)	780(2)	53(1)
C(24)	5648(2)	3826(2)	1645(2)	54(1)
C(25)	5244(2)	3498(2)	2475(2)	47(1)
C(26)	4342(1)	2822(2)	2462(1)	36(1)
C(27)	3976(1)	2511(2)	3393(1)	37(1)
C(28)	2916(1)	1210(2)	4345(1)	41(1)
C(29)	3658(2)	268(2)	4789(2)	56(1)
C(30)	3407(2)	−141(3)	5767(2)	72(1)

$^a U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$.

As shown in Table 11, the first plane is defined by C(21), C(22), C(23), C(24), C(25), and C(26) atoms within an average deviation of 0.0009 Å, the second plane is defined by C(1), N(2), C(3), and S(1) atoms within an average deviation of 0.0564 Å, and the third plane is defined by C(11), C(12), C(13), C(14), C(15), and C(16) atoms within an average deviation of 0.0064 Å. In the [1,3,2]diazaphosphorino moiety, the atoms of C(27) and N(2) are coplanar to the first plane with the distance of 0.0048 and −0.0705 Å, respectively; also, N(3) and P(1) atoms are far from the coplanar structure and on the same side of the first plane, with the distances of 0.2316 Å and 0.2840 Å, respectively. The C(1), C(2), S(1), C(3), P(1), and N(2) atoms of the [1,4,3]thiazaphosphorino moiety in **5a** prefer the boat conformation. The coplanar C(1), N(2), C(3), and S(1) atoms form the ground floor of the boat conformation, whereas the P(1) and C(2) atoms are on the same side of the coplanar structure with the distances of 0.7729 Å and 0.7621 Å, respectively.

The plane defined by C(1), N(2), C(3), and S(1) atoms of the [1,4,3]thiazaphosphorino moiety forms a 33.58° dihedral angle with one phenyl plane of the [4,3-*a*][1,3,2]benzodiazaphosphorine, and a 70.70° dihedral angle with the other phenyl plane in **5a**. The dihedral angle formed by these two phenyl planes is 76.74°.

From Fig. 1, it can be seen that the P(1)—C(3) bond and the N(1)—C(11) bond are in a trans relationship because of the repulsive action of the *n*-propyl group in the 2-position of the title compound. The IR spectra of compounds **5** show normal stretching absorption bands, indicating the existence of groups amide carbonyl C=O (1660.8–1670.5 cm^{-1}), P=O (1335.5–1339.4 cm^{-1}), and C=N (1596.2–1605.6 cm^{-1}). The MS (70 eV, EI) spectra of **5** record the existence of molecular ion peaks, indicating that the heterocycle skeletons are of some stability.

In the ^{1}H NMR spectra of the title compounds (**5**), for example of **5c** (R = H), the six methylene protons in the PNC**H**$_2$C**H**$_2$S moiety and PNC**H**$_2$CH$_2$CH$_3$ group resonate at δ 3.22 (dbr, 1H, $^2J_{HH} = 15.2$), δ 3.77–3.90 (m, 2H), δ 4.12–4.23 (m, 1H), and δ 4.35–4.49 (m, 2H), as shown in Fig. 4. The signal of δ 3.22 (dbr, 1H, $^2J_{HH} = 15.2$) is contributed from one of the two methylene protons in PNCH$_2$C**H**$_2$S. The NMR experimental method of double resonance was used to

TABLE 6 Bond Lengths (Å)

Bond	*Distance*	*Bond*	*Distance*	*Bond*	*Distance*
S(1)—C(3)	1.7660(19)	S(1)—C(2)	1.813(2)	P(1)—O(1)	1.4596(14)
P(1)—N(2)	1.6579(15)	P(1)—N(3)	1.6626(15)	P(1)—C(3)	1.8285(18)
O(2)—C(27)	1.218(2)	O(3)—C(14)	1.374(2)	O(3)—C(17)	1.422(3)
N(1)—C(3)	1.271(2)	N(1)—C(11)	1.425(2)	N(2)—C(21)	1.406(2)
N(2)—C(1)	1.483(2)	N(3)—C(27)	1.388(2)	N(3)—C(28)	1.486(2)
C(1)—C(2)	1.516(3)	C(11)—C(12)	1.382(3)	C(11)—C(16)	1.388(3)
C(12)—C(13)	1.390(3)	C(13)—C(14)	1.384(3)	C(14)—C(15)	1.388(3)
C(15)—C(16)	1.384(3)	C(21)—C(22)	1.401(3)	C(21)—C(26)	1.402(3)
C(22)—C(23)	1.388(3)	C(23)—C(24)	1.376(3)	C(24)—C(25)	1.373(3)
C(25)—C(26)	1.395(3)	C(26)—C(27)	1.476(3)	C(28)—C(29)	1.497(3)
C(29)—C(30)	1.508(3)				

TABLE 7 Bond Angles (deg)

Angle	*(deg)*	*Angle*	*(deg)*
C(3)—S(1)—C(2)	99.52(9)	O(1)—P(1)—N(2)	117.13(8)
O(1)—P(1)—N(3)	114.57(8)	N(2)—P(1)—N(3)	103.52(8)
O(1)—P(1)—C(3)	111.76(8)	N(2)—P(1)—C(3)	101.99(8)
N(3)—P(1)—C(3)	106.58(8)	C(14)—O(3)—C(17)	117.22(15)
C(3)—N(1)—C(11)	120.61(15)	C(21)—N(2)—C(1)	117.90(14)
C(21)—N(2)—P(1)	125.00(12)	C(1)—N(2)—P(1)	117.05(12)
C(27)—N(3)—C(28)	117.52(15)	C(27)—N(3)—P(1)	127.41(12)
C(28)—N(3)—P(1)	115.06(12)	N(2)—C(1)—C(2)	114.04(15)
C(1)—C(2)—S(1)	113.70(14)	N(1)—C(3)—S(1)	125.45(14)
N(1)—C(3)—P(1)	118.61(14)	S(1)—C(3)—P(1)	115.75(10)
C(12)—C(11)—C(16)	119.04(17)	C(12)—C(11)—N(1)	117.65(16)
C(16)—C(11)—N(1)	123.17(17)	C(11)—C(12)—C(13)	120.95(18)
C(14)—C(13)—C(12)	119.67(19)	O(3)—C(14)—C(13)	124.47(18)
O(3)—C(14)—C(15)	115.86(16)	C(13)—C(14)—C(15)	119.66(17)
C(16)—C(15)—C(14)	120.30(17)	C(15)—C(16)—C(11)	120.37(18)
C(22)—C(21)—C(26)	118.75(17)	C(22)—C(21)—N(2)	120.28(17)
C(26)—C(21)—N(2)	120.96(16)	C(23)—C(22)—C(21)	120.3(2)
C(24)—C(23)—C(22)	120.8(2)	C(25)—C(24)—C(23)	119.23(19)
C(24)—C(25)—C(26)	121.6(2)	C(25)—C(26)—C(21)	119.26(18)
C(25)—C(26)—C(27)	117.37(17)	C(21)—C(26)—C(27)	123.38(16)
O(2)—C(27)—N(3)	119.90(18)	O(2)—C(27)—C(26)	122.21(18)
N(3)—C(27)—C(26)	117.84(15)	N(3)—C(28)—C(29)	112.88(15)
C(28)—C(29)—C(30)	112.20(18)		

TABLE 8 Torsion Angles (deg)

Torsion Angle	*(deg)*	*Torsion Angle*	*(deg)*
O(1)—P(1)—N(2)—C(21)	−115.18(14)	N(3)—P(1)—N(2)—C(21)	11.95(16)
C(3)—P(1)—N(2)—C(21)	122.51(15)	O(1)—P(1)—N(2)—C(1)	62.27(15)
N(3)—P(1)—N(2)—C(1)	−170.60(12)	C(3)—P(1)—N(2)—C(1)	−60.05(14)
O(1)—P(1)—N(3)—C(27)	128.31(15)	N(2)—P(1)—N(3)—C(27)	−0.41(17)
C(3)—P(1)—N(3)—C(27)	−107.54(16)	O(1)—P(1)—N(3)—C(28)	−52.46(14)
N(2)—P(1)—N(3)—C(28)	178.82(12)	C(3)—P(1)—N(3)—C(28)	71.69(13)
C(21)—N(2)—C(1)—C(2)	−172.96(16)	P(1)—N(2)—C(1)—C(2)	9.4(2)
N(2)—C(1)—C(2)—S(1)	58.9(2)	C(3)—S(1)—C(2)—C(1)	−60.41(16)
C(11)—N(1)—C(3)—S(1)	1.5(3)	C(11)—N(1)—C(3)—P(1)	176.39(13)
C(2)—S(1)—C(3)—N(1)	178.46(17)	C(2)—S(1)—C(3)—P(1)	3.48(12)
O(1)—P(1)—C(3)—N(1)	107.23(16)	N(2)—P(1)—C(3)—N(1)	−126.85(15)
N(3)—P(1)—C(3)—N(1)	−18.64(17)	O(1)—P(1)—C(3)—S(1)	−77.43(12)
N(2)—P(1)—C(3)—S(1)	48.49(11)	N(3)—P(1)—C(3)—S(1)	156.71(10)
C(3)—N(1)—C(11)—C(12)	−122.6(2)	C(3)—N(1)—C(11)—C(16)	61.8(3)
C(16)—C(11)—C(12)—C(13)	−1.7(3)	N(1)—C(11)—C(12)—C(13)	−177.51(18)
C(11)—C(12)—C(13)—C(14)	1.5(3)	C(17)—O(3)—C(14)—C(13)	−12.2(3)
C(17)—O(3)—C(14)—C(15)	166.76(18)	C(12)—C(13)—C(14)—O(3)	178.79(18)
C(12)—C(13)—C(14)—C(15)	−0.1(3)	O(3)—C(14)—C(15)—C(16)	179.96(17)
C(13)—C(14)—C(15)—C(16)	−1.0(3)	C(14)—C(15)—C(16)—C(11)	0.8(3)
C(12)—C(11)—C(16)—C(15)	0.5(3)	N(1)—C(11)—C(16)—C(15)	176.09(17)
C(1)—N(2)—C(21)—C(22)	−9.9(2)	P(1)—N(2)—C(21)—C(22)	167.54(14)
C(1)—N(2)—C(21)—C(26)	169.79(16)	P(1)—N(2)—C(21)—C(26)	−12.8(2)
C(26)—C(21)—C(22)—C(23)	−0.1(3)	N(2)—C(21)—C(22)—C(23)	179.61(18)
C(21)—C(22)—C(23)—C(24)	0.1(3)	C(22)—C(23)—C(24)—C(25)	−0.2(3)
C(23)—C(24)—C(25)—C(26)	0.3(3)	C(24)—C(25)—C(26)—C(21)	−0.3(3)
C(24)—C(25)—C(26)—C(27)	179.68(19)	C(22)—C(21)—C(26)—C(25)	0.2(3)
N(2)—C(21)—C(26)—C(25)	−179.51(16)	C(22)—C(21)—C(26)—C(27)	−179.82(16)
N(2)—C(21)—C(26)—C(27)	0.5(3)	C(28)—N(3)—C(27)—O(2)	−6.3(3)
P(1)—N(3)—C(27)—O(2)	172.88(14)	C(28)—N(3)—C(27)—C(26)	170.98(15)
P(1)—N(3)—C(27)—C(26)	−9.8(2)	C(25)—C(26)—C(27)—O(2)	7.8(3)
C(21)—C(26)—C(27)—O(2)	−172.23(18)	C(25)—C(26)—C(27)—N(3)	−169.47(16)
C(21)—C(26)—C(27)—N(3)	10.5(3)	C(27)—N(3)—C(28)—C(29)	−74.6(2)
P(1)—N(3)—C(28)—C(29)	106.09(18)	N(3)—C(28)—C(29)—C(30)	177.3(2)

TABLE 9 Anisotropic Displacement Parameters ($10^3 \times Å^2$)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S(1)	29(1)	74(1)	38(1)	−1(1)	−2(1)	8(1)
P(1)	24(1)	34(1)	31(1)	−1(1)	3(1)	1(1)
O(1)	43(1)	35(1)	52(1)	0(1)	2(1)	−2(1)
O(2)	57(1)	61(1)	44(1)	−9(1)	−10(1)	−13(1)
O(3)	32(1)	56(1)	56(1)	−10(1)	2(1)	9(1)
N(1)	30(1)	45(1)	38(1)	0(1)	5(1)	5(1)
N(2)	28(1)	40(1)	30(1)	−2(1)	3(1)	−1(1)
N(3)	28(1)	40(1)	31(1)	−2(1)	1(1)	3(1)
C(1)	35(1)	58(1)	31(1)	−3(1)	2(1)	−2(1)
C(2)	35(1)	59(1)	35(1)	−8(1)	−1(1)	−3(1)
C(3)	25(1)	40(1)	36(1)	2(1)	4(1)	1(1)
C(11)	30(1)	46(1)	32(1)	0(1)	5(1)	4(1)
C(12)	30(1)	48(1)	61(1)	−6(1)	7(1)	−4(1)
C(13)	39(1)	40(1)	63(1)	−7(1)	6(1)	0(1)
C(14)	31(1)	46(1)	33(1)	−1(1)	5(1)	6(1)
C(15)	30(1)	49(1)	41(1)	−6(1)	5(1)	−4(1)
C(16)	34(1)	41(1)	44(1)	−6(1)	6(1)	1(1)
C(17)	45(1)	50(1)	64(1)	−4(1)	6(1)	16(1)
C(21)	29(1)	31(1)	41(1)	−1(1)	7(1)	2(1)
C(22)	41(1)	47(1)	44(1)	3(1)	11(1)	−1(1)
C(23)	44(1)	53(1)	65(1)	9(1)	20(1)	−4(1)
C(24)	38(1)	47(1)	78(2)	−1(1)	14(1)	−10(1)
C(25)	35(1)	42(1)	63(1)	−8(1)	0(1)	−4(1)
C(26)	28(1)	33(1)	45(1)	−3(1)	2(1)	3(1)
C(27)	33(1)	38(1)	40(1)	−5(1)	−4(1)	3(1)
C(28)	39(1)	51(1)	31(1)	0(1)	3(1)	7(1)
C(29)	56(1)	59(1)	53(1)	17(1)	9(1)	18(1)
C(30)	89(2)	74(2)	51(1)	19(1)	4(1)	16(2)

The anisotropic displacement factor exponent takes the form: $-2\pi^2[(ha^*)^2U_{11} + \cdots + 2hka^*b^*U_{12}]$.

TABLE 10 Hydrogen Coordinates (10^4) and Isotropic Displacement Parameters ($10^3 \times Å^2$)

Atom	*x*	*y*	*z*	U_{eq}
H(1A)	2719	1156	191	80
H(1B)	2235	2471	303	80
H(2A)	966	975	−1	80
H(2B)	1398	228	895	80
H(12A)	760	4655	3708	80
H(13A)	−728	5825	3839	80
H(15A)	−2403	2735	3059	80
H(16A)	−918	1597	2880	80
H(17A)	−3265	6482	4000	80
H(17B)	−2296	6057	4645	80
H(17C)	−2189	6744	3672	80
H(22A)	3907	2578	131	80
H(23A)	5428	3707	198	80
H(24A)	6269	4291	1666	80
H(25A)	5585	3748	3079	80
H(28A)	2254	835	4272	80
H(28B)	2895	1912	4772	80
H(29A)	4324	629	4842	80
H(29B)	3659	−452	4376	80
H(30A)	3893	−746	6030	80
H(30B)	3415	580	6180	80
H(30C)	2745	−511	5711	80

TABLE 11 The Least-Squares Planes

Atom	*Distance (Å)*
Plane equation: $6.8030\,x - 9.1218\,y - 0.3338\,z = 0.2964^a$	
C21	−0.0001
C22	−0.0001
C23	−0.0005
C24	0.0013
C25	−0.0016
C26	0.0010
C27	0.0048
N3	0.2316
P1	0.2840
N2	−0.0080
O2	−0.1336
C1	−0.2410
Plane equation: $0.6321\,x + 10.6035\,y - 0.7409\,z = 1.9194^b$	
C1	−0.0604
N2	0.0619
C3	−0.0520
S1	0.0505
P1	−0.7729
C2	−0.7621
C21	0.8295
N3	−0.2023
O1	−2.2278
N1	0.4104
Plane equation: $-0.9485\,x - 2.9910\,y + 13.4771\,z = 3.5067^c$	
C11	−0.0067
C12	0.0100
C13	−0.0045
C14	−0.0044
C15	0.0077
C16	−0.0022
N1	0.0647
O3	0.0059
C17	0.2840
C3	−0.8465

[a] An average deviation of 0.0009 Å for the fitted atoms C21, C22, C23, C24, C25, C26.

[b] An average deviation of 0.0564 Å for the fitted atoms C1, N2, C3, S1. The plane defined by C1, N2, C3, and S1 atoms forms a 33.58° dihedral angle with the former plane.

[c] An average deviation of 0.0064 Å for the fitted atoms C11, C12, C13, C14, C15, C16. The plane defined by C11, C12, C13, C14, C15, and C16 atoms forms a 76.74° dihedral angle with the first plane. The plane defined by C11, C12, C13, C14, C15, and C16 atoms forms a 70.70° dihedral angle with the second plane.

analyze the signals of the other five protons. The experimental result of $NC\mathbf{H}_2CH_2C\mathbf{H}_3\{NCH_2C\mathbf{H}_2CH_3\}$ is outlined in Fig. 5, and we can deduce that the two methylene protons in the $PNC\mathbf{H}_2CH_2CH_3$ group resonate at δ 3.77–3.90 and 4.12–4.23 (t, 1H, $^2J_{HH} \approx {}^3J_{PH} \approx 16.5$). Treatment of the proton that resonates at δ 3.22 (dbr, 1H, $^2J_{HH} = 15.2$) using the same double resonance method produced the result outlined in Fig. 6, and we can also deduce that the two methylene protons in the $PNCH_2C\mathbf{H}_2S$ moiety resonate at δ 3.22 and 4.35–4.49. Therefore, the NMR signals of these

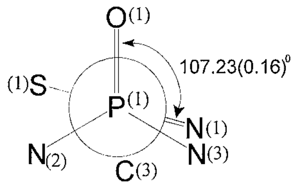

FIGURE 3 Newman projection of the P(1)–C(3) bond for the compound **5a**.

six methylene protons can be expressed as δ 3.22 (dbr, 1H, $1/2 \times SC\mathbf{H}_2CH_2N$, $^2J_{HH} = 15.2$); 3.77–3.90 (m, 2H, $1/2 \times SCH_2C\mathbf{H}_2N + 1/2 \times PNC\mathbf{H}_2CH_2CH_3$); 4.12–4.23 (m, 1H, $1/2 \times PNC\mathbf{H}_2CH_2CH_3$); 4.35–4.49 (m, 2H, $1/2 \times SC\mathbf{H}_2CH_2N + 1/2 \times SCH_2C\mathbf{H}_2N$).

The two methylene protons in the $PNCH_2C\mathbf{H}_2S$ moiety of **5** resonate as two multiplets at δ 3.22–3.26 and δ 4.30–4.53, respectively, which can be explained by the anisotropic effect of the adjacent P=O group. This assumption was verified by X-ray crystallographic analysis of the title compound **5a**, as shown in Fig. 7, in which this phenomenon has also been reported in the literatures [14,16].

EXPERIMENTAL

Instruments

Melting points were determined with a model YANACO MP-500 apparatus and are uncorrected. IR spectra were recorded on a SHIMADZU-435 spectrometer, and band positions are reported in wave numbers (cm^{-1}). The ^1H and ^{31}P NMR spectra were recorded on a BRUKER AC-P200 instrument. Tetramethylsilane (TMS) was used as an internal standard for ^1H NMR spectroscopy, and 85% phosphoric acid (H_3PO_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 Hz. 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).

Compound **1**, 1-(2-bromoethyl)-2,3-dihydro-3-propyl-1,3,2-benzodiazaphosphorin-4 (1*H*)-one 2-oxide, was prepared according to the previous work [14]. (Substituted) phenyl isothiocyanates were prepared according to the literature method [17].

*N-p-methoxyphenyl-1-(2-Bromoethyl)-3-propyl-1,2,3,4-tetrahydro-4-oxo-1,3,2-benzodiazaphosphorin-2-thiocarboxamide 2-Oxide (**3**)*

A mixture of 3.0 mmol of **1**, 3.0 mmol of *p*-methoxyphenyl isothiocyanate, and 6.0 mmol of dry triethylamine in 20 ml of anhydrous THF was stirred at room temperature for 3 h, then the solvent and the triethylamine were removed under reduced pressure to furnish **3**, which was recrystallized from a mixture of ethyl acetate–light petroleum ether (bp 60–90°C) as yellow crystals, 93.5% yield, mp 114–115°C. ^1H NMR ($CDCl_3$, ppm; J, Hz): 0.92 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.72 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$); 3.24 (m, 1H, $1/2 \times PNC\mathbf{H}_2CH_2CH_3$); 3.80 (s, 3H, $OC\mathbf{H}_3$); 3.52–4.24 (m, 5H, $1/2 \times PNC\mathbf{H}_2CH_2CH_3 + PNC\mathbf{H}_2C\mathbf{H}_2Br$); 6.85–8.32 (m, 8H, $2 \times C_6\mathbf{H}_4$); 10.96 (br, 1H, C(S)N**H**).

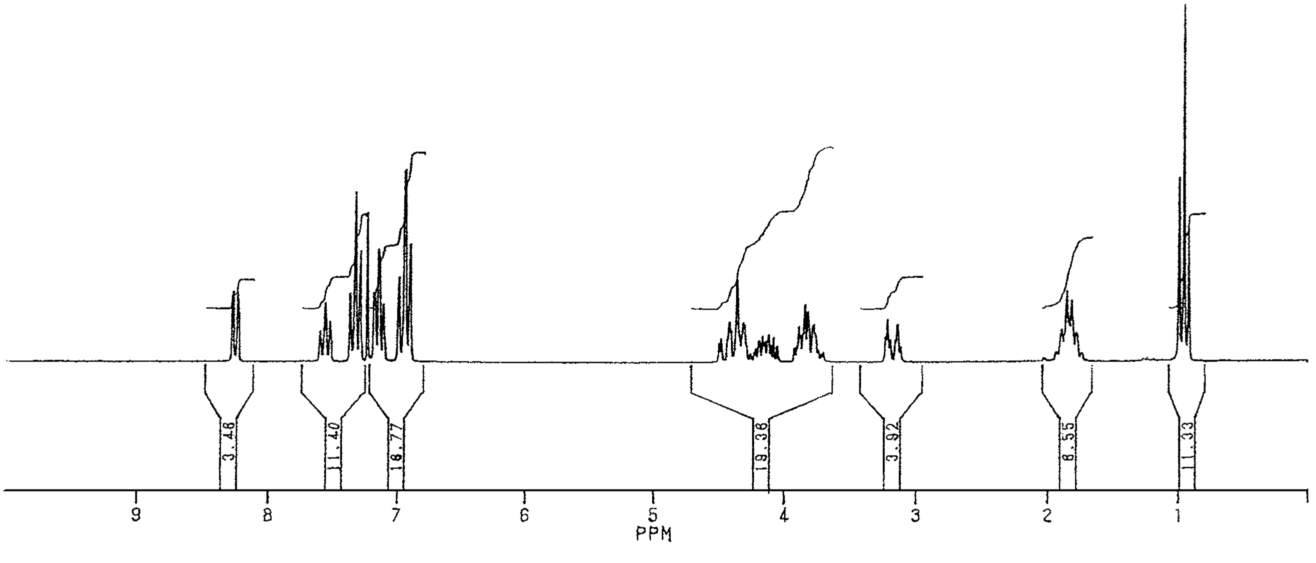

FIGURE 4 ^1H NMR spectrum of compound **5c**.

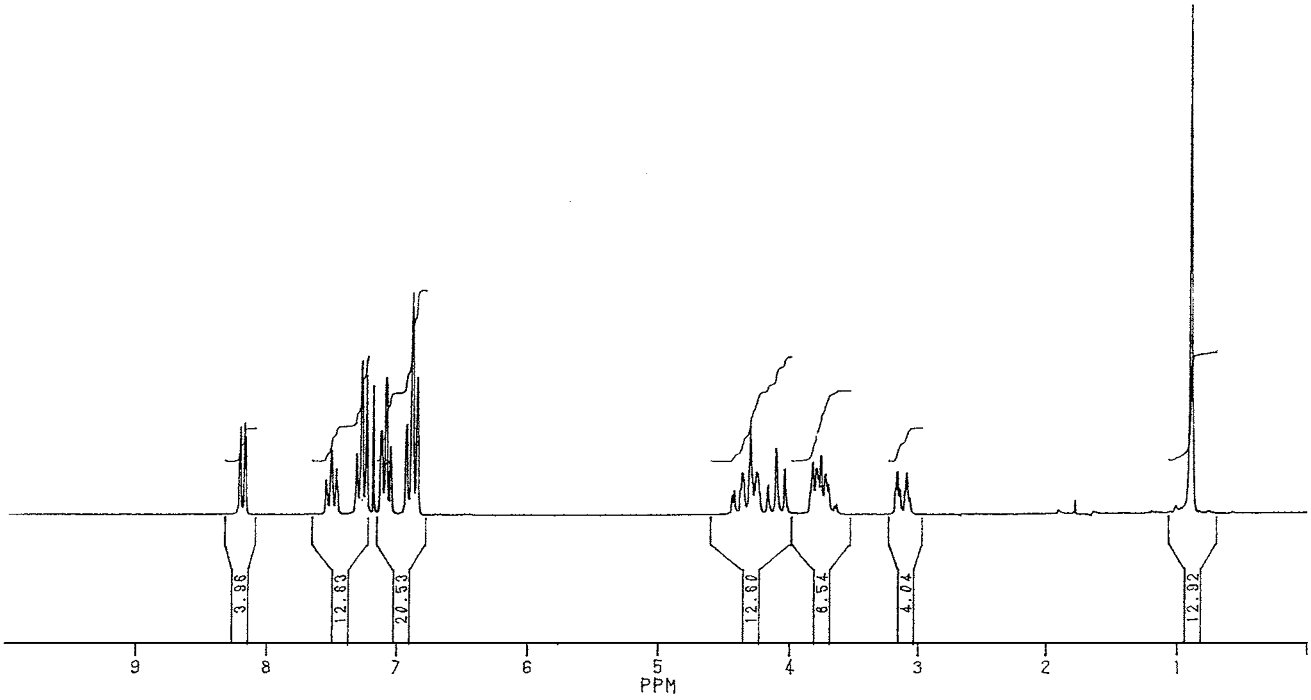

FIGURE 5 ^{1}H NMR spectrum of compound **5c** using the double resonance method.

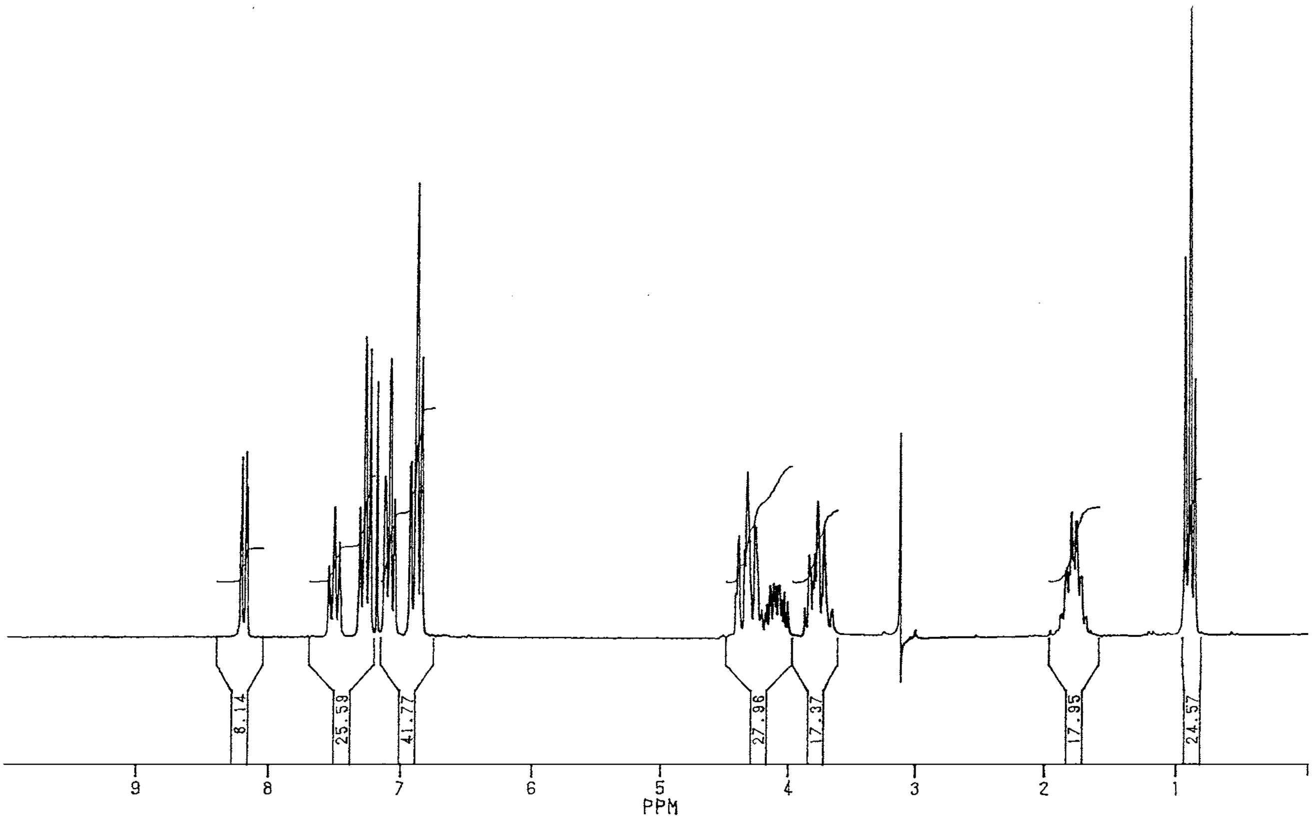

FIGURE 6 ^{1}H NMR spectrum of compound **5c** using the double resonance method.

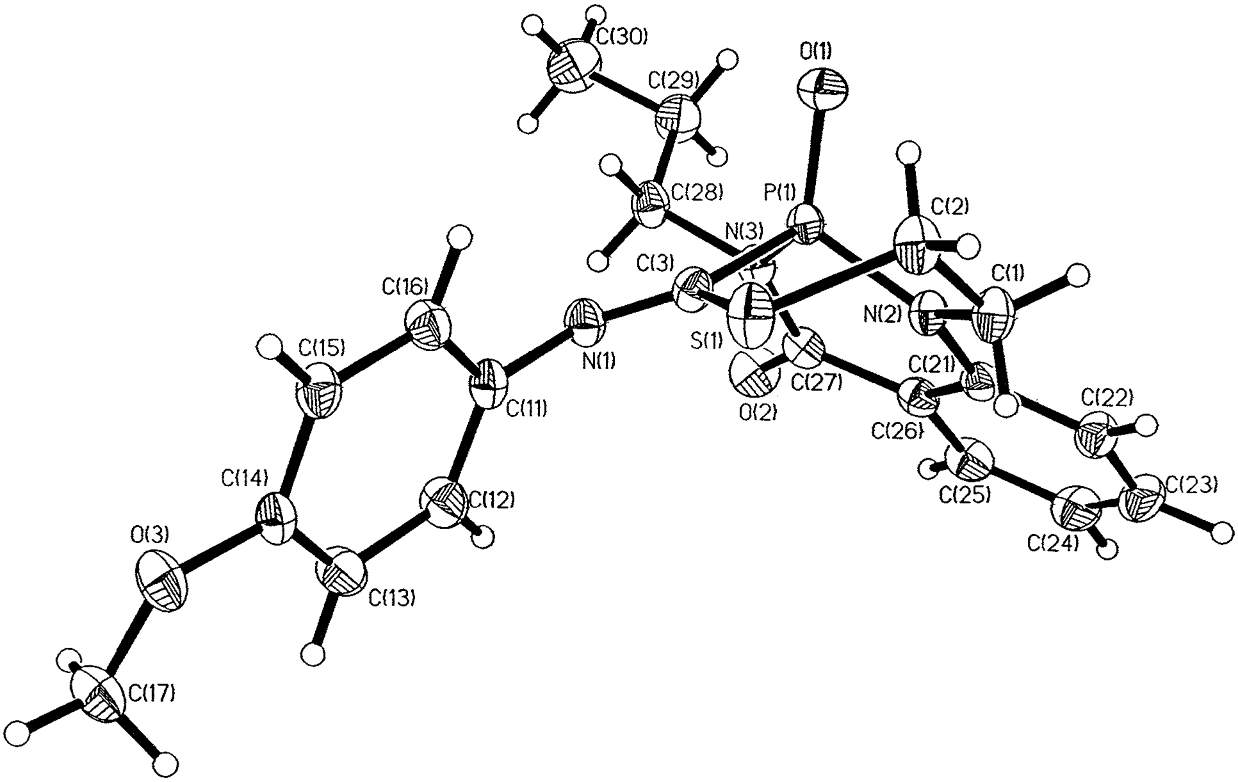

FIGURE 7 The preferred boat conformation of compound **5a** and the relative locations at the C(2)–H and the P(1)=O(1) bonds.

Anal. calcd. for $C_{20}H_{23}BrN_3O_3PS$: C, 48.40; H, 4.67; N, 8.47. Found: C, 48.62; H, 4.90; N, 8.26.

*1-Oxo-2-propyl-4-p-methoxyphenylimino-1,2,3,4,5,6,7,8-octahydro-[1,4,3]thiazaphosphorino-[4,3-a][1,3,2]benzodiazaphosphorine 3-Oxide (***5a***)*

As shown in Scheme 3, 3.0 mmol of **3** was allowed to react with 3.2 mmol of sodium hydride (80% in mineral oil, pentane washed) in 20 ml of anhydrous THF at room temperature for 0.5 h, and then the mixture was heated at reflux for an additional 3 h. Progress of the reaction was monitored by TLC analysis. The mixture was filtered, and after removal of the solvent from the filtrate under reduced pressure, a large amount of water was added to the residue, causing precipitation of compound **5a**, which was recrystallized from a mixture of ethyl acetate–light petroleum ether (bp 60–90°C) and obtained as colorless crystals, 78.6% yield.

As shown in Scheme 5, A mixture of **3** (1.49 g, 3 mmol), triethylamine (0.61 g, 6 mmol, distilled from calcium hydride), and dry benzene (30 ml) 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 chromatographed on a column of silica gel using a mixture of 40% ethyl acetate–light petroleum ether (bp 60–90°C) to elute the product, 87.5% yield.

The physical and chemical data of **5a** are given in Tables 1 and 2. The single crystals of **5a** suitable for X-ray analysis were obtained by recrystallization from the mixture solvent of ethyl acetate and petroleum ether (bp 90–120°C).

*General Procedure for the Preparation of 1-Oxo-2-propyl-4-(substituted)phenylimino-1,2,3,4,5,6,7,8-octahydro-[1,4,3]thiazaphosphorino[4,3-a]-[1,3,2]benzodiazaphosphorine 3-Oxides (***5a–g***)*

As shown in Scheme 6, a mixture of **1** (0.99 g, 3 mmol), (substituted) phenyl isothiocyanate (3 mmol), triethylamine (0.61 g, 6 mmol, distilled from calcium hydride), and dry benzene (30 ml) was heated at reflux for 8–10 h, and then the produced triethylamine hydrobromide was filtered off. The solvent from the filtrate was removed under reduced pressure and the residue was chromatographed on a column of silica gel using a mixture of 30% ethyl acetate–light petroleum ether (bp 60–90°C) to elute the product. The physical and chemical data are also given in Tables 1 and 2.

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