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Efficient Synthesis and Crystal Structure of 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

Junmin Huang, Hui Chen, and Ruyu Chen

Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China

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ABSTRACT: *In order to search for novel antitumor and antiviral agents with high activity and low toxicity, some 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 (***2a–e***) have been designed incorporating the proximate carbonyl and phosphoryl groups into the benzoannulated phosphadiamide heterocycle and synthesized in acceptable yields. These compounds contain the proximate carbonyl and phosphoryl groups in the fused heterocycle. Their structures were confirmed by spectroscopic methods and microanalyses. The results from X-ray crystallography analysis of* **2a** *showed that the proximate carbonyl and phosphoryl groups are not coplanar because of their being jointly located in the fused heterocycle, having ring tension, and this then destroys the conjugation between the C=O and the P=O moieties. As a result, the length of the P–C bonds measured as 1.851(3)–1.852(3) Å are 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), C(3), N(2), N(3), and P(1) atoms of the [1,4,2]diazaphosphorino moiety exist preferably in the boat conformation. The coplanar C(1), C(3), N(2), and N(3) atoms, within an average deviation of 0.0102 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 0.7067 and 0.6315 Å, respectively.* © 2002 John Wiley & Sons, Inc. Heteroatom Chem 13:63–71, 2002; DOI 10.1002/hc.1107

INTRODUCTION

Organophosphorus compounds are ubiquitous in nature and they have broad applications in the fields of agriculture and medicine. During the past two decades, α-ketophosphonates and their derivatives have attracted considerable attention because these compounds are endowed with special physical, chemical, and pharmacological properties due to the proximity of the carbonyl and the phosphoryl groups [1–12]. For example, it is well known that phosphonoformic acid (PFA) is effective in AIDS chemotherapy as an antiviral agent with activity against HIV, HSV, and human cytomegalovirus (HCMV) [13,14]. However, its clinical applications are restricted because of its poor penetration across mucosal or cellular membranes and its by-effect on bones

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Correspondence to: Junmin Huang; e-mail: jmhuang@public.tpt.tj.cn.

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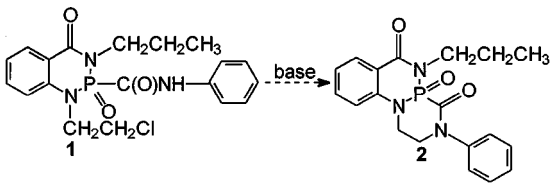
[15,16]. In the study on new pharmaceuticals and agrochemicals, the application of heterocycles is suggested to improve the biological activity. A sizeable number of endogenous compounds that play a key role in regulation of various life processes consist of fused heterocycles. Furthermore, benzoannulated and related analogs of cyclophosphamide possess antitumor activity and have also created an increasingly wide interest in chemistry, medicine, and agricultural science [17–20]. As a part of our ongoing program to develop novel antitumor and antiviral agents with high activity and low toxicity, some 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 have been designed incorporating the proximate carbonyl and phosphoryl groups into the benzoannulated phosphadiamide heterocycle, and they have been synthesized in acceptable yields. These compounds contain the proximate carbonyl and phosphoryl groups in the fused heterocycle.

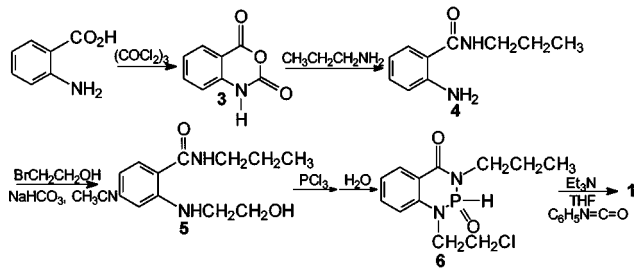
RESULTS AND DISCUSSION

Synthesis of the Title Products

There has been a rapidly growing interest in heterocyclic compounds because of their pharmaceutical importance and extensive application in organic synthesis [21]. Efficient methodologies for forming the bond connecting the carbonyl and the phosphoryl groups are available in the arsenal of the synthetic chemist [1,22]. However, to the best of our knowledge, very few fused heterocycles bearing the proximate carbonyl and phosphoryl groups in the heterocyclic structure have been so far reported. According to the capability of possible cyclization between the amido and chloroethyl groups forming the proximate carbonyl and phosphoryl groups in the fused heterocyclic structure, as shown in Scheme 1, *N*-phenyl 1-(2-chloroethyl)-3-propyl-1,2,3,4-tetrahydro-4-oxo-1,3,2-benzodiazaphosphorin-2-carboxamide 2-oxide (**1**) was prepared by the multistep route outlined in Scheme 2. Preparation of 1-(2-chloroethyl)-3-propyl-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1*H*)-one 2-oxide (**6**) was readily accomplished in a



SCHEME 1

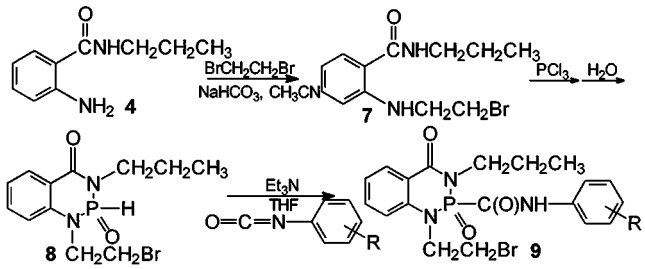


SCHEME 2

four-step sequence starting from the cheap and available *o*-aminobenzoic acid, that formed compound **1** by the addition reaction with phenyl isocyanate with the help of triethylamine in tetrahydrofuran (THF). In order to protect the amino group and activate the carbonyl group of *o*-aminobenzoic acid, we transformed it into the corresponding cyclic anhydride **3** by the action of triphosgene, a safe and stable replacement for phosgene. Then the reaction of the cyclic anhydride **3** with propylamine was carried out under very mild conditions and in good yields to provide *N*-propyl anthranilamide **4**. Subsequently, the phosphorus reagent **6** could be obtained by the reaction of *N*-propyl anthranilamide **4** with 2-bromoethanol, followed by treatment of the intermediate anthranilamide derivative **5** with phosphorus trichloride.

However, the title compound **2** could not be detected when the compound **1** was treated with lithium diisopropylamide in THF. Under the presumably more forcing conditions of the use of sodium hydride in THF, no reaction occurred to provide compound **2** even after 12 h at the reflux temperature.

In order to achieve the cyclization reaction to provide the title compounds, we examined the use of the 2-bromoethyl group in place of the chloroethyl group in compound **1**. The *N*-(substituted)phenyl 1-(2-bromoethyl)-3-propyl-1,2,3,4-tetrahydro-4-oxo-1,3,2-benzodiazaphosphorin-2-carboxamide 2-oxides (**9a–d**) were prepared as with use of the synthetic method for compound **1**, as shown in Scheme 3. We have previously reported that the reaction of the



SCHEME 3

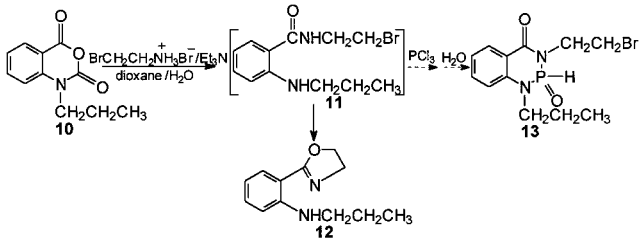
cyclic anhydride **10** with 2-bromoethylamine (generated from its hydrobromide salt) in place of propylamine provided oxazoline **12** by cyclization of the expected intermediate anthranilamide derivative **11** [23,24]. Thus, unfortunately, as the analog of 1-(2-bromo-ethyl)-3-propyl-2,3-dihydo-1,3,2-benzodiazaphosphorin-4(1*H*)-one 2-oxide (**8**) and **6**, 1-propyl-3-(2-bromoethyl)-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1*H*)-one 2-oxide (**13**) could not be obtained as outlined in Scheme 4.

The title compounds, 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 (**2a–e**), were eventually prepared by two methods, as shown in Schemes 5 and 6, respectively. The first involved the intramolecular cyclization reaction by treatment of compound **9** with sodium hydride at the reflux temperature in THF (method 1). The second method was to reflux the mixture of the phosphorus reagent **8** containing a P—H bond with the (substituted)phenyl isocyanate in the presence of triethylamine. This involved an addition reaction to form the amido functionality and the bromoethyl group in the same molecule and subsequent intramolecular cyclization involving the two groups in a one-pot procedure (method 2).

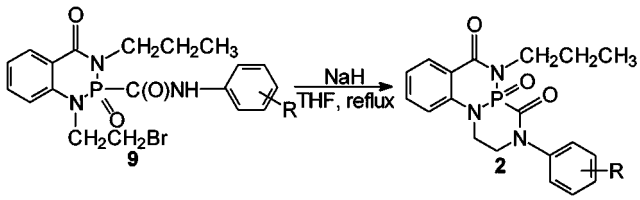
The Structures of the Products

The structures of all the title compounds were confirmed by ^{1}H NMR, ^{31}P NMR spectroscopy and elemental analyses. Their physical constants are listed in Table 1, and data of the ^{1}H NMR, ^{31}P NMR spectra are listed in Table 2.

The crystal data, data collection and refinement parameter for the title compound **2a** are listed in Table 3. Data were collected with a SMART CCD 1000 area detector, graphite monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å) being used. 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 the full-matrix least-squares procedures using the SHELXL-97 package.



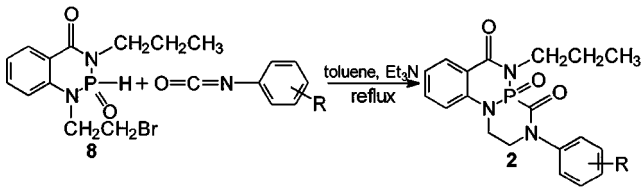
SCHEME 4



SCHEME 5

The crystal structure of 2-propyl-5-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-oxide (**2a**) 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 nonhydrogen atoms were refined anisotropically. Hydrogen atoms were located from difference maps and then added geometrically, refined isotropically with a riding model. The fractional coordinates of nonhydrogen atoms and equivalent isotropic thermal parameters are given in Table 4, and selected bond lengths and angles are listed in Table 5.

For compound **2a**, a Newman projection of the P—C bond and the torsion angle between P=O and C=O groups are given in Fig. 3, indicating that the proximate carbonyl and phosphoryl groups are not coplanar because of their being jointly located in the fused heterocycle with ring tension, which then destroys the conjugation between the C=O and the P=O moieties. As a result, the length of the P—C bond measures 1.851(3) and 1.852(3) Å and is the same as that of a P—C bond not involved in conjugation (1.80–1.85 Å). The bond lengths of N(2)—C(4) and N(1)—C(10) [1.402(3) and 1.392(4) Å, respectively] are shorter than that of a normal C—N bond (1.47 Å) [25] that is close to the value of N(1)—C(17) bond (1.485(4) Å) or N(2)—C(3) bond (1.480(4) Å); furthermore, the length of C(9)—C(10) (1.470(5) Å) is also shorter than the normal single bonds of C(17)—C(18) and C(18)—C(19) [1.502(5), and 1.502(6) Å, respectively], which reveal that the atoms of N(2), C(4), C(5), C(6), C(7), C(8), C(9), and C(10)



SCHEME 6

TABLE 1 Experimental Data of Compounds **9a–d** and **2a–e**

					Found/Calcd. (%)[a]		
No.	*R*	*Yield (%)*	*mp (°C)*	*Molecular Formula*	*C*	*H*	*N*
9a	H	93.5	189–191	$C_{19}H_{21}BrN_3O_3P$	50.70 (50.68)	5.01 (4.70)	9.50 (9.33)
9b	4-Cl	92.6	180–182	$C_{19}H_{20}BrClN_3O_3P$	46.95 (47.08)	4.12 (4.16)	8.56 (8.67)
9c	4-CH_3	93.8	186–187	$C_{20}H_{23}BrN_3O_3P$	51.70 (51.74)	5.06 (4.99)	9.22 (9.05)
9d	4-NO_2	94.2	195 dec.	$C_{19}H_{20}BrN_4O_5P$	46.15 (46.08)	4.02 (4.07)	11.24 (11.31)
2a	H	62.5[b] (70.4)[c]	152–154	$C_{19}H_{20}N_3O_3P$	61.52 (61.79)	5.35 (5.46)	11.16 (11.38)
2b	4-Cl	61.0[b] (68.6)[c]	169–171	$C_{19}H_{19}ClN_3O_3P$	56.38 (56.52)	5.02 (4.74)	10.17 (10.41)
2c	4-CH_3	67.2[b] (71.4)[c]	159–161	$C_{20}H_{22}N_3O_3P$	62.42 (62.66)	5.99 (5.78)	10.87 (10.96)
2d	4-NO_2	56.0[b]	182–184	$C_{19}H_{19}N_4O_5P$	54.92 (55.08)	4.90 (4.62)	13.27 (13.52)
2e	2-Cl	(65.8)[c]	175–177	$C_{19}H_{29}ClN_3O_3P$	56.47 (56.52)	4.82 (4.74)	10.18 (10.41)

[a]Values within parentheses represent the calculated values.
[b]Yield determined by isolation based on Compound **2** in method 1.
[c]Yield in parentheses determined by isolation based on Compound **2** in method 2.

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 **9a–d** and **2a–e**

No.	δ_P	δ_H
9a	4.12	0.93 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.73 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$); 3.39–4.02 (m, 4H, $NC\mathbf{H}_2CH_2CH_3$ + $PNC\mathbf{H}_2CH_2Br$); 4.12 (m, 2H, $PNCH_2C\mathbf{H}_2Br$); 6.92–8.38 (m, 9H, $C_6\mathbf{H}_5 + C_6\mathbf{H}_4$); 9.04 (br, 1H, C(O)N**H**)
9b	4.02	0.92 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.74 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$); 3.40–4.05 (m, 4H, $NC\mathbf{H}_2CH_2CH_3$ + $PNC\mathbf{H}_2CH_2Br$); 4.15 (m, 2H, $PNCH_2C\mathbf{H}_2Br$); 6.95–8.35 (m, 8H, $2 \times C_6\mathbf{H}_4$); 9.50 (br, 1H, C(O)N**H**)
9c	4.23	0.92 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.73 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$); 2.31 (s, 3H, $C\mathbf{H}_3C_6H_4$); 3.38–4.02 (m, 4H, $NC\mathbf{H}_2CH_2CH_3 + PNC\mathbf{H}_2CH_2Br$); 4.10 (m, 2H, $PNCH_2C\mathbf{H}_2Br$); 6.94–8.32 (m, 8H, $2 \times C_6\mathbf{H}_4$); 9.04 (br, 1H, C(O)N**H**)
9d	3.61	0.93 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.75 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$); 3.42–4.04 (m, 4H, $NC\mathbf{H}_2CH_2CH_3$ + $PNC\mathbf{H}_2CH_2Br$); 4.14 (m, 2H, $PNCH_2C\mathbf{H}_2Br$); 6.90–8.35 (m, 8H, $2 \times C_6\mathbf{H}_4$); 9.56 (br, 1H, C(O)N**H**)
2a	−7.74	0.95 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.88 (m, 2H, $PNCH_2C\mathbf{H}_2CH_3$); 3.60–4.15 (m, 5H, $PNC\mathbf{H}_2$ CH_2 CH_3 + $PNC\mathbf{H}_2CH_2N + 1/2 \times PNCH_2C\mathbf{H}_2N$); 4.96 (m, 1H, $1/2 \times PNCH_2C\mathbf{H}_2N$); 6.92–8.35 (m, 9H, $C_6\mathbf{H}_5 + C_6\mathbf{H}_4$)
2b	−7.89	0.95 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.90 (m, 2H, $PNCH_2C\mathbf{H}_2CH_3$); 3.62–4.14 (m, 5H, $PNC\mathbf{H}_2CH_2$ $CH_3 + PNC\mathbf{H}_2CH_2N + 1/2 \times PNCH_2C\mathbf{H}_2N$); 4.98 (m, 1H, 1/2 $\times PNCH_2C\mathbf{H}_2N$); 6.90–8.34 (m, 8H, $2 \times C_6\mathbf{H}_4$)
2c	−7.65	0.96 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.90 (m, 2H, $PNCH_2C\mathbf{H}_2CH_3$); 2.32 (s, 3H, $C\mathbf{H}_3C_6H_4$); 3.60–4.12 (m, 5H, $PNC\mathbf{H}_2CH_2CH_3 + PNC\mathbf{H}_2CH_2N + 1/2 \times PNCH_2\mathbf{H}_2N$); 4.95 (m, 1H, $1/2 \times PNCH_2C\mathbf{H}_2N$); 6.94–8.35 (m, 8H, $2 \times C_6\mathbf{H}_4$)
2d	−8.28	0.97 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.92 (m, 2H, $PNCH_2C\mathbf{H}_2CH_3$); 3.60–4.16 (m, 5H, $PNC\mathbf{H}_2CH_2$ $CH_3 + PNC\mathbf{H}_2CH_2N + 1/2 \times PNCH_2C\mathbf{H}_2N$); 5.05 (m, 1H, $1/2 \times PNCH_2C\mathbf{H}_2N$); 6.94–8.38 (m, 8H, $2 \times C_6\mathbf{H}_4$)
2e	−7.96	0.96 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.94 (m, 2H, $PNCH_2C\mathbf{H}_2CH_3$); 3.61–4.12 (m, 5H, $PNC\mathbf{H}_2CH_2$ $CH_3 +$ $PNC\mathbf{H}_2CH_2N + 1/2 \times PNCH_2C\mathbf{H}_2N$); 4.92 (m, 1H, 1/2 $\times$ $PNCH_2C\mathbf{H}_2N$); 6.92–8.30 (m, 8H, $2 \times C_6\mathbf{H}_4$)

TABLE 3 Crystallographic Data for Compound **2a**

Empirical formula	$C_{19}H_{20}N_3O_3P$
CCDC deposit no.	000903b
Color	Colorless
Crystal size (mm)	$0.10 \times 0.15 \times 0.20$
Crystal system	Monoclinic
Space group	P2(1)/c
Unit-cell dimensions (Å)	$a = 9.7585(9)$, $b = 21.4319(19)$, $c = 17.7900(16)$ $\beta = 100.823(2)^\circ$
Volume (Å^3)	3654.5(6)
Z	8
Formula weight	369.35
Density (calcd.) (mg m^{-3})	1.343
Absorption coefficient (mm^{-1})	0.175
F(000)	1552
Diffractometer scan	SMART CCD 1000
Radiation/wavelength (Å)	Mo K_α (graphite mono chrom.)/0.71073
Temperature (K)	298 ± 2
θ range for data collection (deg)	2.23–25.03
Scan type	$\omega - \pi$
Index ranges	$-11 \le h \le 8$, $-25 \le k \le 24$, $-17 \le l \le 21$
Reflections measured	15024
Independent/observed reflections	6410 (Rint = 0.0309) ($[I \ge 2\sigma(I)]$)
Absorption correction	SADABS
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6410/0/469
Weight	$1/[\sigma^2(F_0^2) + (0.0984P)^2 + 0.7604P]$ $P = (F_0^2 + 2Fc^2)/3$
Goodness-of-fit on F^2	1.026
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0534$, $wR2 = 0.1455$
R indices (all data)	$R1 = 0.0776$, $wR2 = 0.1657$
Largest diff. peak and hole (e Å^3)	$0.844/-0.473$

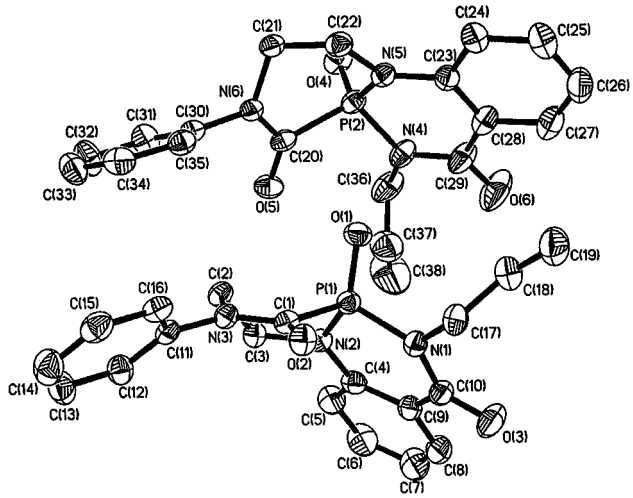


FIGURE 1 Ball-and-stick representation of compound **2a** showing the crystallographic numbering scheme.

form a delocalized π system. The bond lengths, P(1)—N(1) of 1.660(2) Å and P(1)—N(2) of 1.654(2) Å, or P(2)—N(4) of 1.655(3) Å and P(2)—N(5) of 1.653(2) 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), which indicate that there is dπ—pπ bonding in the P—N bonds.

The plane defined by N(2), C(4), C(5), C(6), C(7), C(8), C(9), and C(10) atoms is coplanar within an average deviation of 0.0053 Å, as shown in Table 6. Also, P(1) and N(1) atoms are at the same side of the coplanar structure with the distance of 0.2744 and 0.1482 Å, respectively. The plane defined by N(2), P(1), and N(1) atoms forms a 11.88° dihedral angle with the former plane. The C(1), C(2), C(3), N(2), N(3), and P(1) atoms of the [1,4,2]diazaphosphorino moiety in 2-propyl-5-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-oxide prefer the boat conformation. The coplanar C(1), C(3), N(2), and N(3) atoms, within an average deviation of 0.0102 Å, form the ground floor of the boat conformation. Also, P(1) and C(2) atoms are at the same side of the coplanar structure with the distance of 0.7067 and 0.6315 Å respectively (Table 6).

In the ^{1}H NMR spectra of the title compounds **2a–e**, the two methylene protons in the $PNCH_2C\mathbf{H}_2N$ moiety of the [1,4,2]diazaphosphorino group resonate as two multiplets at $\delta = 3.60$–4.16 and $\delta =$

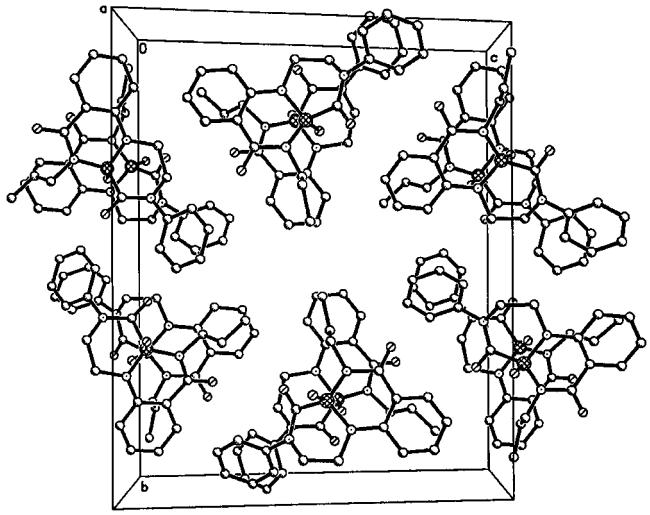


FIGURE 2 ORTEP drawing of compound **2a**.

TABLE 4 Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients (10^3 Å^2) for Compound **2a**

Atom	*x*	*y*	*z*	*U(eq)*[a]
P(1)	4522(1)	3059(1)	9465(1)	41(1)
N(1)	5042(3)	2893(1)	8651(1)	48(1)
N(2)	5091(2)	2459(1)	10023(1)	43(1)
N(3)	5806(2)	3709(1)	10692(1)	41(1)
O(1)	3055(2)	3247(1)	9362(1)	55(1)
O(2)	6219(2)	4059(1)	9535(1)	52(1)
O(3)	6010(3)	2293(1)	7840(1)	82(1)
C(1)	5664(3)	3697(1)	9920(2)	41(1)
C(2)	5011(3)	3242(1)	11048(2)	45(1)
C(3)	5337(3)	2575(1)	10857(2)	47(1)
C(4)	5554(3)	1893(1)	9765(2)	48(1)
C(5)	5765(4)	1378(2)	10249(2)	64(1)
C(6)	6246(5)	821(2)	10003(3)	83(1)
C(7)	6518(5)	759(2)	9280(3)	90(1)
C(8)	6321(4)	1263(2)	8798(2)	72(1)
C(9)	5837(3)	1831(1)	9028(2)	52(1)
C(10)	5656(3)	2342(2)	8466(2)	53(1)
C(11)	6690(3)	4149(1)	11158(1)	42(1)
C(12)	7576(3)	3943(2)	11806(2)	55(1)
C(13)	8448(4)	4374(2)	12252(2)	73(1)
C(14)	8425(4)	4992(2)	12042(2)	72(1)
C(15)	7541(4)	5190(2)	11409(2)	62(1)
C(16)	6661(3)	4776(1)	10960(2)	50(1)
C(17)	4680(4)	3362(2)	8031(2)	59(1)
C(18)	3339(4)	3218(2)	7491(2)	78(1)
C(19)	2981(6)	3695(2)	6866(2)	101(2)
P(2)	−519(1)	2865(1)	9756(1)	46(1)
O(4)	−1727(2)	2702(1)	10095(1)	64(1)
O(5)	1789(2)	2719(1)	10842(1)	60(1)
O(6)	125(5)	1800(2)	8136(2)	129(1)
N(4)	30(3)	2295(1)	9258(2)	60(1)
N(5)	−645(2)	3460(1)	9156(1)	46(1)
N(6)	916(2)	3713(1)	10703(1)	45(1)
C(20)	937(3)	3101(1)	10529(2)	45(1)
C(21)	−304(3)	4080(1)	10345(2)	50(1)
C(22)	−527(3)	4093(1)	9486(2)	50(1)
C(23)	−842(3)	3404(1)	8356(2)	50(1)
C(24)	−1320(4)	3898(2)	7883(2)	66(1)
C(25)	−1496(4)	3841(2)	7095(2)	78(1)
C(26)	−1195(4)	3296(2)	6766(2)	79(1)
C(27)	−740(4)	2803(2)	7221(2)	76(1)
C(28)	−546(4)	2839(2)	8021(2)	61(1)
C(29)	−105(5)	2283(2)	8456(2)	80(1)
C(30)	1919(3)	3996(1)	11306(2)	44(1)
C(31)	2082(4)	3782(2)	12042(2)	62(1)
C(32)	3023(4)	4073(2)	12608(2)	79(1)
C(33)	3779(4)	4578(2)	12442(2)	72(1)
C(34)	3616(3)	4791(2)	11708(2)	61(1)
C(35)	2697(3)	4495(1)	11132(2)	49(1)
C(36)	374(5)	1689(2)	9657(3)	88(1)
C(37)	1762(5)	1492(2)	9667(3)	101(1)
C(38)	1868(9)	773(2)	9853(4)	181(4)

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

4.92–5.05, respectively, which could 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 **2a**, as shown in Fig. 4.

EXPERIMENTAL

Instruments

Melting points were determined with a model YANACO MP-500 apparatus and are uncorrected. The ^{1}H and ^{31}P NMR spectra were recorded on a BRUKER AC-P200 instrument. Tetramethylsilane (TMS) was used as an internal standard for ^{1}H NMR, 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. 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).

*3,1-Benzoxazine-2,4(1H)-dione (**3**)*

To a stirred solution of *o*-aminobenzoic acid (24.69 g, 0.18 mol) in 180 ml of acetonitrile at 50–55°C were added dropwise pyridine (28.48 g, 0.36 mol) and a solution of triphosgene (17.80 g, 0.06 mol) in 100 ml of dichloromethane at the same time. After completion of the addition, the temperature of the reaction mixture was maintained at 50–55°C for an additional 2 h. The solvent was removed under reduced pressure and 200 ml of water was added to the residue. The precipitated solid collected by filtration was washed with water followed by chilled dichloromethane, and dried in a vacuum dryer, yielding 27.72 g (94.4%) of **3**, mp 237–240°C. The intermediate **3** thus obtained was pure enough for further manipulations but could be recrystallized from ethanol/water, mp 242°C dec. (Ref. [26,27], mp 243°C dec.).

*N-Propyl 2-Aminobenzic Amide (**4**)*

To a stirred suspension of **3** (16.31 g, 0.10 mol) in 150 ml of dioxane, propylamine (8.85 g, 0.15 mol) was added dropwise at 40°C over a period of 30 min. Stirring was continued for an additional 1.5 h at 60–70°C, and then the solvent was removed under reduced pressure to yield 17.20 g (96.5%) of **4**, which was used without further purification. An analytical sample was recrystallized from ether, mp 101–102°C. ^{1}H NMR ($CDCl_3$, ppm; *J*, Hz): 0.96 (t, 3H, $NHCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.60 (m, 2H, $NHCH_2C\mathbf{H}_2CH_3$); 3.33 (m, 2H, $NHC\mathbf{H}_2CH_2CH_3$); 5.42 (br, 2H, $N\mathbf{H}_2$); 6.14 (br, 1H, C(O)N**H**); 6.60–7.34 (m, 4H, $C_6\mathbf{H}_4$). Anal. calcd. for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.50; H, 7.82; N, 15.69.

TABLE 5 Selected Bond Lengths and Bond Angles for Compound **2a**

Atoms	*Bond Lengths (Å)*	*Bond Angles (deg)*	*Atoms*	*Bond Lengths (Å)*	*Bond Angles (deg)*	*Atoms*	*Bond Lengths (Å)*	*Bond Angles (deg)*
P(1)—O(1)	1.466	(2)	P(1)—N(2)	1.654	(2)	P(1)—N(1)	1.660	(2)
P(1)—C(1)	1.851	(3)	N(1)—C(10)	1.392	(4)	N(1)—C(17)	1.485	(4)
N(2)—C(4)	1.402	(3)	N(2)—C(3)	1.480	(4)	N(3)—C(1)	1.355	(3)
N(3)—C(11)	1.433	(3)	N(3)—C(2)	1.479	(3)	O(2)—C(1)	1.226	(3)
O(3)—C(10)	1.231	(4)	C(2)—C(3)	1.516	(4)	C(4)—C(5)	1.392	(4)
C(4)—C(9)	1.396	(4)	C(5)—C(6)	1.384	(5)	C(6)—C(7)	1.367	(6)
C(7)—C(8)	1.369	(6)	C(8)—C(9)	1.395	(4)	C(9)—C(10)	1.470	(5)
C(11)—C(12)	1.378	(4)	C(11)—C(16)	1.387	(4)	C(12)—C(13)	1.398	(5)
C(13)—C(14)	1.374	(5)	C(14)—C(15)	1.352	(5)	C(15)—C(16)	1.380	(4)
C(17)—C(18)	1.502	(5)	C(18)—C(19)	1.502	(6)			
P(2)—O(4)	1.465	(2)	P(2)—N(5)	1.653	(2)	P(2)—N(4)	1.655	(3)
P(2)—C(20)	1.852	(3)	O(5)—C(20)	1.223	(3)	O(6)—C(29)	1.223	(4)
N(4)—C(29)	1.408	(5)	N(4)—C(36)	1.488	(4)	N(5)—C(23)	1.406	(4)
N(5)—C(22)	1.474	(4)	N(6)—C(20)	1.349	(4)	N(6)—C(30)	1.442	(4)
N(6)—C(21)	1.470	(4)	C(21)—C(22)	1.503	(4)	C(23)—C(24)	1.379	(5)
C(23)—C(28)	1.403	(4)	C(24)—C(25)	1.384	(5)	C(25)—C(26)	1.364	(6)
C(26)—C(27)	1.354	(6)	C(27)—C(28)	1.403	(5)	C(28)—C(29)	1.442	(5)
C(30)—C(31)	1.368	(4)	C(30)—C(35)	1.379	(4)	C(31)—C(32)	1.378	(5)
C(32)—C(33)	1.373	(5)	C(33)—C(34)	1.365	(5)	C(34)—C(35)	1.383	(4)
C(36)—C(37)	1.416	(6)	C(37)—C(38)	1.577	(7)			
O(1)—P(1)—N(2)	119.94	(12)	O(1)—P(1)—N(1)	113.67	(12)	N(2)—P(1)—N(1)	103.55	(12)
O(1)—P(1)—C(1)	110.15	(12)	N(2)—P(1)—C(1)	101.82	(12)	N(1)—P(1)—C(1)	106.35	(12)
C(10)—N(1)—C(17)	116.8	(2)	C(10)—N(1)—P(1)	127.1	(2)	C(17)—N(1)—P(1)	115.8	(2)
C(4)—N(2)—C(3)	118.2	(2)	C(4)—N(2)—P(1)	124.66	(19)	C(3)—N(2)—P(1)	116.36	(17)
C(1)—N(3)—C(11)	122.3	(2)	C(1)—N(3)—C(2)	117.3	(2)	C(11)—N(3)—C(2)	120.4	(2)
O(2)—C(1)—N(3)	125.6	(3)	O(2)—C(1)—P(1)	121.1	(2)	N(3)—C(1)—P(1)	113.31	(19)
N(3)—C(2)—C(3)	113.1	(2)	N(2)—C(3)—C(2)	112.5	(2)	C(5)—C(4)—C(9)	118.3	(3)
C(5)—C(4)—N(2)	120.2	(3)	C(9)—C(4)—N(2)	121.5	(3)	C(8)—C(9)—C(4)	119.6	(3)
C(8)—C(9)—C(10)	117.1	(3)	C(4)—C(9)—C(10)	123.3	(3)	O(3)—C(10)—N(1)	119.5	(3)
O(3)—C(10)—C(9)	122.3	(3)	N(1)—C(10)—C(9)	118.2	(3)			
O(4)—P(2)—N(5)	118.79	(14)	O(4)—P(2)—N(4)	114.30	(13)	N(5)—P(2)—N(4)	102.48	(13)
O(4)—P(2)—C(20)	108.91	(13)	N(5)—P(2)—C(20)	102.86	(12)	N(4)—P(2)—C(20)	108.56	(14)
C(29)—N(4)—C(36)	115.9	(3)	C(29)—N(4)—P(2)	125.3	(2)	C(36)—N(4)—P(2)	117.1	(2)
C(23)—N(5)—C(22)	117.9	(2)	C(23)—N(5)—P(2)	124.6	(2)	C(22)—N(5)—P(2)	117.53	(19)
C(20)—N(6)—C(30)	122.9	(2)	C(20)—N(6)—C(21)	117.9	(2)	C(30)—N(6)—C(21)	118.6	(2)
O(5)—C(20)—N(6)	125.7	(3)	O(5)—C(20)—P(2)	121.1	(2)	N(6)—C(20)—P(2)	113.2	(2)
N(6)—C(21)—C(22)	113.6	(2)	N(5)—C(22)—C(21)	112.0	(2)	C(24)—C(23)—C(28)	118.5	(3)
C(24)—C(23)—N(5)	121.2	(3)	C(28)—C(23)—N(5)	120.3	(3)	C(27)—C(28)—C(23)	118.7	(3)
C(27)—C(28)—C(29)	118.0	(3)	C(23)—C(28)—C(29)	123.3	(3)	O(6)—C(29)—N(4)	119.9	(4)
O(6)—C(29)—C(28)	120.7	(3)	N(4)—C(29)—C(28)	119.4	(3)			

*N-Propyl 2-(2-Hydroxyethyl)aminobenzoic Amide (**5**) and N-Propyl 2-(2-Bromoethyl) amino benzoic Amide (**7**)*

A mixture of **4** (8.91 g, 0.05 mol), 0.1 mol of 2-bromoethanol or 1,2-dibromoethane, sodium bicarbonate (8.4 g, 0.1 mol) and 50 ml of acetonitrile was refluxed for 6–8 h, until the spot of **4** disappeared on silica gel TLC monitoring, developed with a solvent mixture of ethyl acetate/petroleum ether (1:1). The liquid was collected by filtration followed by washing with ethyl acetate, and then the solvent of the filtrate was removed under reduced pressure and the residue was chromatographed on a column of silica gel using a mixture of ethyl acetate/light petroleum (bp 60–90°C) to elute the intermediate **5** or **7**.

5: 75.5% yield, mp 77–78°C. ^{1}H NMR ($CDCl_3$, ppm; J, Hz): 0.93 (t, 3H, $NHCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.60 (m, 2H, $NHCH_2C\mathbf{H}_2CH_3$); 3.30–3.58 (m, 2H, $NHC\mathbf{H}_2CH_2CH_3 + NHC\mathbf{H}_2CH_2OH$); 3.94 (m, 2H, $NHCH_2C\mathbf{H}_2OH$); 4.24 (br, 1H, $NHCH_2CH_2O\mathbf{H}$); 6.25 (br, 1H, $C(O)N\mathbf{H}CH_2CH_2CH_3$); 6.65–7.35 (m, 4H, $C_6\mathbf{H}_4$); 7.82 (br, 1H, $N\mathbf{H}CH_2CH_2OH$). Anal. calcd. for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.72; H, 8.05; N, 12.51.

7: 62.8% yield, mp 51–53°C. ^{1}H NMR ($CDCl_3$, ppm; J, Hz): 0.95 (t, 3H, $NHCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.61 (m, 2H, $NHCH_2C\mathbf{H}_2CH_3$); 3.35 (m, 2H,

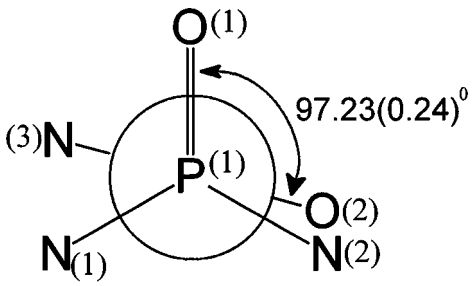


FIGURE 3 Newman projection of the P—C bond for the compound **2a**.

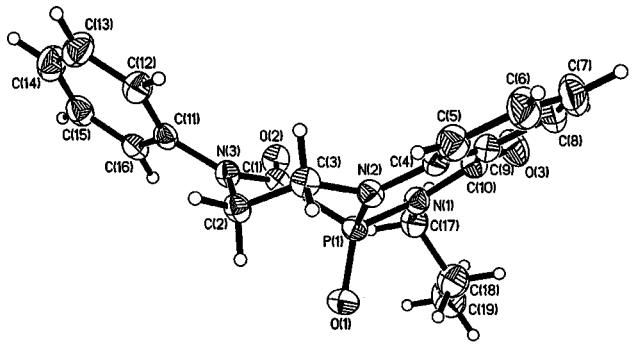


FIGURE 4 The preferred boat conformation of compound **2a** and the relative locations between C_7—H and the P=O bond.

NHC**H**$_2$CH$_2$CH$_3$); 3.58–3.92 (m, 4H, NHC**H**$_2$C**H**$_2$Br); 6.24 (br, 1H, C(O)N**H**CH$_2$CH$_2$CH$_3$); 6.62–7.38 (m, 4H, C$_6$**H**$_4$); 7.65 (br, 1H, N**H**CH$_2$CH$_2$Br). Anal. calcd. for $C_{12}H_{17}BrN_2O$: C, 50.54; H, 6.01; N, 9.82. Found: C, 50.49; H, 5.86; N, 9.65.

*1-(2-Chloroethyl)-3-propyl-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-one 2-Oxide (**6**) and 1-(2-Bromoethyl)-3-propyl-2,3-dihydro-1,3,-2-benzodiazaphosphorin-4(1H)-one 2-Oxide (**8**)*

A mixture of 0.04 mol of **5** and 0.085 mol of phosphorus trichloride in 250 ml of dry benzene was refluxed for 18 h. The solvent was removed under reduced pressure and cold dilute sodium bicarbonate was added. The mixture, extracted into dichloromethane, was washed with brine and dried over Na_2SO_4. The solvent, collected by filtration followed by washing with ethyl acetate, was removed under reduced pressure and the resulting oil was purified by flash chromatography [silica gel 60; ethyl acetate/light petroleum (bp 60–90°C), 1:1] to give 7.86 g (68.5%) of **6**: mp 94–96°C. ^{1}H NMR ($CDCl_3$, ppm; J, Hz): 0.97 (t, 3H, NCH$_2$CH$_2$C**H**$_3$, $^3J_{HH} = 7.4$); 1.75 (m, 2H, NCH$_2$C**H**$_2$CH$_3$); 3.50–3.86 (m, 4H, NC**H**$_2$CH$_2$CH$_3$ + NC**H**$_2$CH$_2$Cl); 4.32 (m, 2H, NCH$_2$C**H**$_2$Cl); 6.86–8.30 (m, 4H, C$_6$**H**$_4$); 7.82 (d, 1H, P(O)**H**, $^1J_{PH} = 642.5$). ^{31}P NMR ($CDCl_3$, ppm): 5.89. Anal. calcd. for $C_{12}H_{16}ClN_2O_2P$: C, 50.27; H, 5.62; N, 9.77. Found: C, 50.15; H, 5.58; N, 9.56.

A mixture of 0.05 mol of **7** and 0.051 mol of phosphorus trichloride in 250 ml of dry benzene was refluxed for 5 h. Ethyl acetate was added to the reaction mixture and it was washed with cold dilute sodium bicarbonate followed by brine, then dried over Na_2SO_4. The solvent, collected by filtration followed by washing with ethyl acetate, was removed under reduced pressure and the residual oil was purified by flash chromatography [silica gel 60; ethyl acetate/light petroleum (bp 60–90°C), 1:1] to give 10.56 g (63.8%) of **8**: mp 82–84°C. ^{1}H NMR ($CDCl_3$, ppm; J, Hz): 0.96 (t, 3H, NCH$_2$CH$_2$C**H**$_3$, $^3J_{HH} = 7.4$); 1.77 (m, 2H, NCH$_2$C**H**$_2$CH$_3$); 3.55–3.80 (m, 4H, NC**H**$_2$CH$_2$CH$_3$ + NC**H**$_2$CH$_2$Br); 4.15 (m, 2H, NCH$_2$C**H**$_2$Br); 6.90–8.32 (m, 4H, C$_6$**H**$_4$); 7.86 (d, 1H, P(O)**H**, $^1J_{PH} = 645.9$). ^{31}P NMR ($CDCl_3$, ppm): 5.95. Anal. calcd. for $C_{12}H_{16}BrN_2O_2P$: C, 43.52; H, 4.87; N, 8.46. Found: C, 43.68; H, 5.05; N, 8.66.

TABLE 6 The Least-Squares Planes

Atoms	*Distance (10^3 Å)*
Plane equation:	8.7655 (0.0044) x + 6.1840 (0.0197) y + 2.7922 (0.0185) z = 8.7728 (0.0156)
N(2)	9.4
C(4)	− 6.8
C(5)	− 5.6
C(6)	2.2
C(7)	1.2
C(8)	5.6
C(9)	− 3.3
C(10)	− 2.6
P(1)	− 274.4
N(1)	− 148.2
Plane equation:	9.5215 (0.0026) x − 4.4115 (0.0200) y − 1.9512 (0.0323) z = 1.8166 (0.0328)
C(3)	10.2
N(2)	− 9.3
C(1)	10.2
N(3)	− 11.1
C(2)	− 631.5
P(1)	− 706.7

*N-Phenyl 1-(2-Chloroethyl)-3-propyl-1,2,3,4-tetrahydro-4-oxo-1,3,2-benzodiazaphosphorin-2-carboxamide 2-Oxide (**1**) and N-(Substituted) phenyl 1-(2-Bromoethyl)-3-propyl-1,2,3,4-tetrahydro-4-oxo-1,3,2-benzodiazaphosphorin-2-carboxamide 2-Oxides (**9a–d**)*

A mixture of 3.0 mmol of **6**, 3.0 mmol of phenyl isocyanate, and 12.0 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 **1**, which was recrystallized from a mixture of ethyl acetate-light petroleum (bp 60–90°C) as colorless crystals, 94.6% yield, mp 186–187°C. ^{1}H NMR ($CDCl_3$, ppm; *J*, Hz): 0.94 (t, 3H, $NCH_2CH_2C\mathbf{H}_3$, $^3J_{HH} = 7.4$); 1.72 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$); 3.48–4.02 (m, 4H, $NC\mathbf{H}_2CH_2CH_3 + NC\mathbf{H}_2CH_2Cl$); 4.41 (m, 2H, $PNCH_2C\mathbf{H}_2Cl$); 6.90–8.35 (m, 9H, $C_6\mathbf{H}_5 + C_6\mathbf{H}_4$); 9.26 (br, 1H, C(O)N**H**). ^{31}P NMR ($CDCl_3$, ppm): 4.09. Anal. calcd. for $C_{19}H_{21}ClN_3O_3P$: C, 56.23; H, 5.22; N, 10.35. Found: C, 56.18; H, 5.15; N, 10.32.

Compounds **9a–d** were synthesized by adopting the same procedure, and the corresponding physical and chemical data are provided in Tables 1 and 2.

*The Title Compounds, 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 (**2a–e**)*

Method 1, as Shown in Scheme 5. General Procedure: In each case, 3.0 mmol of *N*-(substituted)phenyl 1-(2-bromoethyl)-3-propyl-1,2,3,4-tetrahydro- 4-oxo-1,3,2-benzodiazaphosphorin-2-carboxamide 2-oxide 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 2 h, and then the mixture was heated at reflux for an additional 4 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, yielding compound **2a–d**, which was recrystallized from a mixture of ethyl acetate/light petroleum (bp 60–90°C) and obtained as colorless crystals. The corresponding physical and chemical data are listed in Tables 1 and 2.

Method 2, as shown in Scheme 6. General Procedure: In each case, a mixture of 1-(2-bromoethyl)-3-propyl-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1*H*)-one 2-oxide (0.99 g, 3 mmol), (substituted) phenyl isocyanate (3 mmol), triethylamine (0.61 g, 6 mmol, distilled from calcium hydride), and 30 ml dry toluene 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 40% ethyl acetate/light petroleum (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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