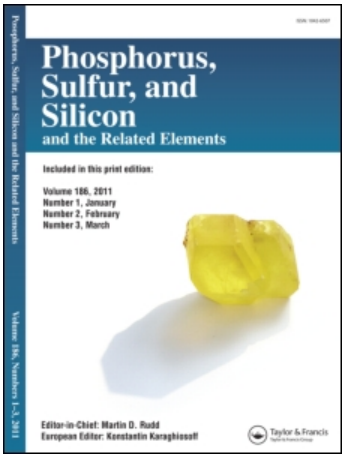

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-SUBSTITUTED-2,3-DIHYDRO-5-THIOPHENOXY-1*H*-1,3,2-BENZODIAZAPHOSPHOLE 2-OXIDES

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-SUBSTITUTED-2,3-DIHYDRO-5-THIOPHENOXY-1*H*-1,3,2-BENZODIAZAPHOSPHOLE 2-OXIDES

L. NAGAPRASADA RAO[a], C. NAGARAJU[a], C. DEVENDRANATH REDDY[a*], T.S. AUSCHWITZ[b], CHAD W. BROWN[b], JOZEF KLUCIK[b], MATTHEW R. HICKEY[b], CYNTHIA A. WAKEFIELD[b] and K. DARRELL BERLIN[b]

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Several 2-aryloxy-2,3-dihydro-5-thiophenoxy-1*H*-1,3,2-benzodiazaphosphole 2-oxides **3a-c**, trichloromethyl-2,3-dihydro-5-thiophenoxy-1*H*-1,3,2-benzodiazaphosphole 2-oxide (**3d**), and 2-chloroethoxy-2,3-dihydro-5-thiophenoxy-1*H*-1,3,2-benzodiazaphosphole 2-oxide (**3e**), and 2-alkylcarbamato-2,3-dihydro-5-thiophenoxy-1*H*-1,3,2-benzodiazaphosphole 2-oxides **6**have been synthesized from reactions of equimolar quantities of 4-thiophenoxy-1,2-phenylenediamine (**1**) with various aryl or alkyl phosphorodichloridates **2a-c,e**, trichloromethylphosphonc dichloride (**2d**), and dichlorophosphinyl carbamates **5a-e** at 50–65 °C in dry toluene in the presence of triethylamine. Substituted ureas of the type RR'P(O)NHC(O)NHR" **8a,b** were obtained via a reaction of **1** with chlorides **7a,b** of arylcarbamidophosphoric acids. Oxidation of a few of the title compounds with H_2O_2 in acetic acid gave the corresponding sulfones **9a-d**. IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and mass spectral analyses, were collected and analyzed and supported all structures. Some compounds were screened for antifungal activity against *Curvularia lunata* and *Aspergillus niger* and for antibacterial activity against *Bacillus subtilis* and *Klebsiella pneumoniae*. Several of the agents exhibited significant activity in the assays.

Keywords: 2-Substituted-2,3-dihydro-5-thiophenoxy-1*H*-1,3,2-benzodiazaphosphole 2-oxides; NMR analysis; mass spectral analysis; antifungal activity; antimicrobial activity

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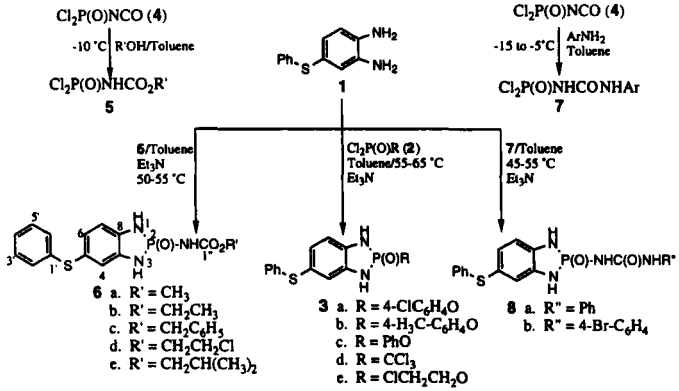
INTRODUCTION

A variety of organophosphorus compounds containing diazaphosphole rings and certain phosphorus carbamates were investigated many years ago and demonstrated to some degree useful insecticidal, bacteriacidal, antiviral, antitumor, and anticarcinogenic activity[1–6] which appeared partially dependent upon the nature and location of substituents on the aromatic ring. Some benzimidazole carbamates have antihelmintic activity dependent to some extent on the substituents.[7] We report herein the synthesis of selected benzodiazaphospholes, as cited in the title, which are a relatively rare class of heterocycles. The products were purified, characterized by elemental, NMR (^1H, ^{13}C, and ^{31}P), and mass spectral analyses, and, in some cases, were tested for antimicrobial activity.

RESULTS AND DISCUSSION

When equimolar quantities of 4-thiophenoxy-1,2-phenylenediamine (**1**) were condensed with members of **2**, namely, arylphosphorodichloridates, trichloromethylphosphonic dichloride, and *O*-2-chloroethylphosphoryl chloride, members of **3** were obtained (Scheme 1). Two equivalents of triethylamine served as the base with very dry toluene as the solvent and with a temperature ranging between 55–65 °C. Purification of members of **3** was achieved by filtering off the triethylamine hydrochloride, evaporating the filtrate, washing the residue with water, and recrystallizing the solid products from ethanol. Physical and spectral data for the products obtained are found in Tables I-VI.



SCHEME 1

$C_{18}H_{14}ClN_2O_2PS$	137–139[a]	45	55.45	3.51	7.24	1232	3360	–	–	
			(55.61)	(3.63)	(7.21)					
$C_{19}H_{17}N_2O_2PS$	134–136[b]	42	62.12	4.48	7.65	1224	3354	–	–	
			(61.95)	(4.65)	(7.60)					
$C_{18}H_{15}N_2O_2PS$	105–107[b]	40	61.16	4.40	7.89	1220	3362	–	–	
			(61.01)	(4.27)	(7.91)					
$C_{13}H_{10}Cl_3N_2OPS$	254–256[c]	55	41.26	2.86	7.37	1215	3367	–	–	
			(41.13)	(2.66)	(7.38)					
$C_{14}H_{14}ClN_2O_2PS$	162–164[c]	41	49.18	3.96	8.20	1264	3368	–	–	
			(49.35)	(4.14)	(8.22)					
$C_{14}H_{14}N_3O_3PS$	224–226[c]	56	50.38	4.45	12.77	1263	3414	3105	1731	
			(50.15)	(4.21)	(12.54)					
$C_{15}H_{16}N_3O_3PS$	218–220[c]	54	51.83	4.81	12.20	1263	3414	3104	1733	
			(51.58)	(4.62)	(12.03)					
$C_{20}H_{18}N_3O_3PS$	204–206[c]	55	58.62	4.22	10.05	1262	3410	3099	1728	
			(58.39)	(4.41)	(10.21)					
$C_{15}H_{15}ClN_3O_3PS$	192–194[c]	48	46.76	3.85	10.91	1265	3411	3102	1726	

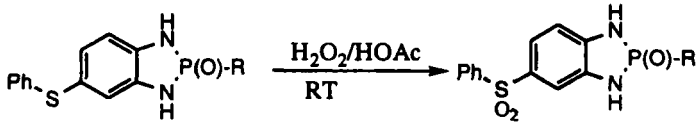
$C_{17}H_{20}N_3O_3PS$	185 (dec)[c]	46	53.92	5.26	11.32	1264	3415	3105	1734	
			(54.10)	(5.34)	(11.13)					
$C_{19}H_{17}N_4O_2PS$	116–118[c]	38	57.68	4.15	14.35	1200	3323	3194	1671	
			(57.57)	(4.32)	(14.13)					
$C_{19}H_{16}BrN_4O_2PS$	198–200[c]	35	48.21	3.47	11.68	1223	–	3210	1664	
			(48.02)	(3.39)	(11.79)					
$C_{14}H_{14}ClN_2O_4PS$	210–212[c]	70	44.96	3.88	7.56	1225	3362	–	–	1154
			(45.11)	(3.79)	(7.51)					
$C_{18}H_{14}ClN_2O_4PS$	156–158[a]	68	51.55	3.19	6.61	1222	3355	–	–	1152
			(51.38)	(3.35)	(6.65)					
$C_{13}H_{10}Cl_3N_2O_3PS$	218–220[c]	70	38.08	2.62	6.80	1210	3363	–	–	1150
			(37.93)	(2.45)	(6.81)					
$C_{14}H_{14}N_3O_5PS$	216–217[a]	65	45.56	3.92	11.40	1260	3410	–	1728	1152
			(45.78)	(3.84)	(11.44)					

hanol.
with 2-propanol.
ethanol.

With respect to the carbamates, a condensation involving equivalent amounts isocyanatophosphonic dichloride (**4**)[2] and various alcohols at −10 °C in dry toluene (Scheme 1) led to the corresponding dichlorophosphinyl carbamates **5a-e**. The reaction mixtures were then added to **1** under similar conditions utilized previously for the generation of **3** and gave **6a-e**. Purification of **6a-e** was like for **3**, namely, via recrystallization from methanol. Interestingly, all primary and secondary alcohols reacted readily with **4**, but *t*-butyl alcohol failed under the same conditions.

Somewhat surprising was the observation that aromatic amines reacted with **4**at −15 °C to −5 °C under nearly identical conditions employed to obtain **6** and gave members of **7** (acid chlorides of arylcarbamidophosphoric acids[8]) which were condensed with **1** to yield crude **8a** and **8b** (Scheme 1). Recrystallization (methanol) of these reaction products gave pure **8a** and **8b**. That the electronegative bromine atom did not sufficiently reduce the nucleophilicity of the nitrogen atom and deter the reaction was somewhat unusual, especially in the formation of **7**. Possibly the powerful electron-withdrawing effect of the two chlorine atoms in **4** sufficiently enhanced the electronic deficit on the carbonyl carbon of **4** to allow attack by the nitrogen atoms of the arylamines even at the cold temperatures employed.

In an effort to ascertain if the sulfur atom was still susceptible to oxidation, representative compounds **3a, 3d**, **3e**, and **6a** were treated with hydrogen peroxide in acetic acid at room temperature (Scheme 2). Good yields of the corresponding sulfones **9a-d** were realized after evaporating the acetic acid from the reaction mixture, washing the solid residue with water, and recrystallizing (methanol) the crude initial reaction products.



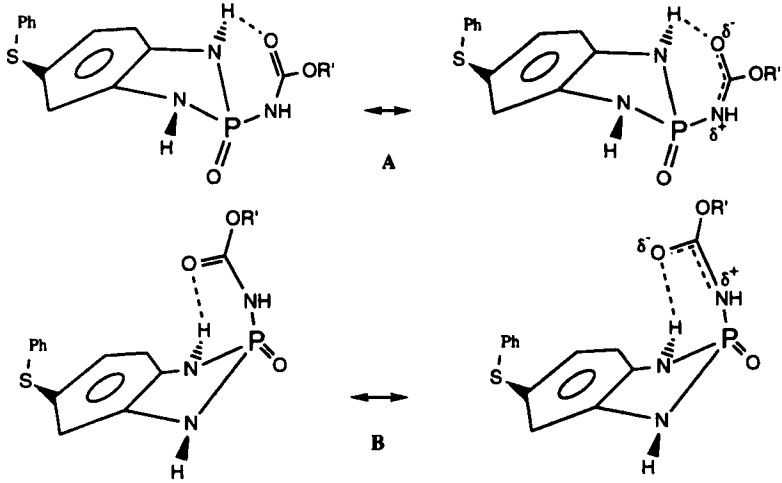
9 a. R = $ClCH_2CH_2O$
b. R = 4-ClC_6H_4O
c. R = CCl_3
d. R = $NHCO_2CH_3$

SCHEME 2

6.97	[dd, 1H, 8.4, 1.9 Hz, H(3)]	-	-	7.20–7.43	8.39	-
7.18	[d, 1H, 1.9 Hz, H(3)]			(m, 5H)	(brs, 4H)	
7.10	[d, 1H, 8.2 Hz, H(6)]					
6.81	[d, 1H, 8.4 Hz, H(6)]	7.16–7.40	–	7.12–7.41	6.08	–2.7
7.14	[s, 1H, H(4)]	(m, 4H)		(m, 5H)	(brs, 2H)	–5.2
7.06	[d, 1H, 8.4 Hz, H(7)]					
6.92	[d, 1H, 8.4 Hz, H(6)]	6.82–7.39	2.20	7.11–7.39	5.73	–2.1
7.09	[s, 1H, H(4)]	(m, 4H)	(s, 3H)	(m, 5H)	(brs, 2H)	–5.0
7.02	[d, 1H, 8.4 Hz, H(7)]					
6.78	[d, 1H, 8.3 Hz, H(6)]	7.05–7.34		7.11–7.55	5.70	–2.4
6.90	[s, 1H, H(4)])	(m, 5H)		(m, 5H)	(brs, 2H)	–5.1
7.05	[d, 1H, 8.3 Hz, H(7)]					
6.95	[d, 1H, 8.2 Hz, H(6)]			7.01–7.48		3.0
7.33	[s, 1H, H(4)]			(m, 5H)		4.7
7.37	[d, 1H, 8.2 Hz, H(7)]					
6.74	[d, 1H, 8.3 Hz, H(6)]		OCH_2CH_2Cl	7.10–7.25	5.64	0.2
7.17	[s, 1H, H(4)]		3.77–4.05	(m, 5H)	(brs, 2H)	
7.27	[d, 1H, 8.3 Hz, H(7)]					

IR analysis of **3a-e** (Table I) showed bands at 3360–3368 cm^{-1} (PN-H), 1215–1264 cm^{-1} (P=O), 1265–1300 cm^{-1} and 905–925 cm^{-1} (PNC-Ar), and 1230–1254 cm^{-1} and 938–947 cm^{-1} (POC-Ar).[9–12]In **6a-e**, bands appeared at 3410–3415 cm^{-1} (PN-H), 3099–3105 cm^{-1} (PN-HC=O), 1725–1735 cm^{-1}(C=O), and 1260–1265 cm^{-1} (P=O).[9–12] In **8a** and **8b**, bands were visible at 1671 and 1664 cm^{-1} (C=O) and at 1200 and 1223 cm^{-1} (P=O), respectively. In **9a-d**, absorption was observed in the ranges of 1210–1260 cm^{-1} (P=O) and at 1310–1320 cm^{-1} as well as at 1150–1154 cm^{-1} (SO_2).

Proton NMR spectra were rather simple for some systems. The data are recorded in Tables II-IV, while carbon-13 NMR spectra are given in Table V for the most of the products cited herein. For members of **3**, doublets appeared for H(6) in the range of δ 6.74–6.95 (J = 8.2–8.4 Hz) while doublets for H(7) occurred at δ 7.02–7.37 (J = 8.2–8.4 Hz). A singlet for H(4) was at δ 6.9–7.3. Proton signals for the phenyl ring attached to the sulfur atom in **3** were a complex multiplet at δ 7.0–7.55. The aryloxy moieties of **3a-c** exhibited multiplets in the range of δ 6.82–7.40 while the protons on the chloroethyl group in **3e** also appeared as a multiplet at δ 3.77–4.05. The broad signals for protons on nitrogen were seen at δ 5.64–6.08 and confirmed by a D_2O exchange experiment.



Quite surprising was the appearance of two doublets in **6** for the endocyclic PNH protons at δ 8.88–8.93 (J = 17.7–17.9 Hz) and at δ 8.76–8.80

(J = 17.7–18.4 Hz) while the exocyclic proton in the PNHC=O group was also a doublet but much further downfield at δ 9.22–9.42 (J = 8.8–9.9 Hz). All signals were confirmed by D_2O exchange. The presence of the two doublets for PNH protons indicates the protons are nonequivalent. One would not expect the N-P bond rotational barrier to be significant, but it is conceivable that sufficient double bond character could exist in the N-P and/or N-C bond of the N-P=O and N-C=O groups. This situation might induce nonequivalence in the nearby PNH groups but it is not intuitively obvious. An alternative explanation might be that two conformers may exist as shown below and which involve some intramolecular H-bonding as illustrated. Locked conformations **A** and **B** would make the protons on nitrogen nonequivalent, assuming the interconversion barrier between **A** and **B** was of sufficient magnitude. This interaction could also influence the coupling of P to the proton on HNC=O which is a considerably smaller coupling than that between P and the ring proton on HN. The double bond character in the N-C bond of the NC=O group might also deshield the proton. Stabilization and preservation of the two conformers could be aided also via H-bonding and/or dipole-dipole interactions of the conformers with DMSO as the solvent. In addition, the striking appearance of two ^{31}P NMR signals lends credence to the supposition that at least two conformers exist. Unfortunately, the literature is void of any determination of the double bond character of N-P bonds in N-P=O-containing cyclic systems. It would seem more defensible if such a bonding were present in the above molecules since **A** and **B** almost appear like enantiomers except for the fact that the P=O group points towards the aryl ring in **A** and away from the ring in **B**. Some double bond character in the N-P bond might "lock" the systems with an energy barrier sufficient to retard interconversion. It was also noted that phosphorus coupling did not extend past the NH group in the carbamate portion. Moreover, the protons in the carbamate group of the compounds appeared slightly downfield when compared to signals of the corresponding protons in the free alcohols.[13] Presumably, the presence of the C=O group induces the additional small downfield shifts. Signals for the aryl protons of the thiophenoxy group occurred at δ 6.66–7.34. The above tentative hypotheses deserve additional evaluation in other related systems.

All proton NMR signals for **9a-d** in the aryl rings were downfield (Table IV) compared to the counterparts in **3** and **6**. These chemical shifts are reasonable in view of the much stronger electron-withdrawing affect of the very electronegative sulfonyl group in **9a-d**.

TABLE III H-1 and P-31 NMR Chemical Shifts and J Values for **6a-e** and **8a,b** (from TMS and 85% H_3PO_4)

COMPD	*H (4, 6, 7) (J in Hz)*	*S-C_6H_5*	*P-NH*	*NH-C=O*	*R-H*	*^{31}P (NMR)*
6a	6.89 [d, 1H, 8.4 Hz, H(6)]	6.72–7.26	8.76	9.35	3.45	13.25
	7.18 [s, 1H, 4(H)]	(m, 5H)	(d, 17.7 Hz)	(d, 9.9 Hz)	(s, 3H, OCH_3)	13.42
	7.27 [d, 1H, 8.4 Hz, H(7)]		8.88			
			(d, 17.7 Hz)			
6b	6.88 [d, 1H, 8.3 Hz, H(6)]	6.73–7.30	8.76	9.22	0.85–0.9	13.21
	7.13 [s, 1H, H(4)]	(m, 5H)	(d, 17.7 Hz)	(d, 9.6 Hz)	(t, 3H, CH_3)	
	7.26 [d, 1H, 8.3 Hz, H(7)]		8.90		3.82–3.89	
			(d, 17.7 Hz)		(2, 2H, OCH_2)	
6c	6.86 [d, 1H, 8.2 Hz, H(6)]	6.72–7.34	8.80	9.41	4.94	12.92
	7.14 [s, 1H, H(4)]	(m, 5H)	(d, 18.0 Hz)	(d, 9.5 Hz)	(s, 2H, OCH_2)	13.06
	7.26 [d, 1H, 8.2 Hz, H(7)]		8.93		7.05–7.36	
			(d, 17.7 Hz)		(m, 5H, C_6H_5)	
6d	6.86 [d, 1H, 8.1 Hz, H(6)]	6.71–7.24	8.78	9.42	4.09	12.84
	7.12 [s, 1H, H(4)]	(m, 5H)	(d, 18.4 Hz)	(d, 8.8 Hz)	(s, 2H, OCH_2)	13.01
	7.26 [d, 1H, 8.1 Hz, H(7)]		8.90		3.52	
			(d, 17.9 Hz)		(s, 2H, CH_2Cl)	

COMPD	*H (4, 6, 7) (J in Hz)*	*S-C_6H_5*	*P-NH*	*NH-C=O*	*R-H*	*^{31}P (NMR)*
6e	6.68 [d, 1H, 8.3 Hz, H(6)]	6.66–7.30			3.66–3.75	ND
	7.11 [s, 1H, H(4)]	(m, 5H)			(d, 2H, OCH_2)	
	7.26 [d, 1H, 8.3 Hz, H(7)]				1.8 (m, 1H)	
					0.83 (d, 6H)	
8a	6.67 [dd, 1H, 8.2 Hz, 1.9, H(6)]			9.39	6.83–7.67	ND
				(NHCO)	[m, 10H, ArH]	
	7.24 [d, 1H, 1.9 Hz, H(4)]			8.72		
	7.14 [d, 1H, 8.2 Hz, H(7)]			(CONH)		
8b	6.51–7.30 [m, 3H. Ar-H]				6.66–7.61	ND
					[m, 10H, ArH]	

ND = Not determined.

TABLE IV H-1 and P-31 NMR Chemical Shifts and J Values for Members of **9**(from TMS or 85% H_3PO_4)

COMPD	*H(4, 6, 7) (J in Hz)*	*S-C_6H_5*	*P-NH*	*R-H*	*^{31}P (NMR)*
9a	7.96–8.14 (m, 3H)	7.63–8.48		3.8–4.1 (m, 4H)	11.97
		(m, 5H)		OCH_2CH_2Cl	
9b	7.02 [d, 1H, 8.2 Hz, H(6)]	7.68–8.49	4.42	7.18–7.4	–5.26
	7.71 [s, 1H, H(4)]	(m, 5H)		(m, 4H, ArH)	–8.78
	7.66 [d, 1H, 8.2 Hz, H(7)]				
9c	7.39 [s, 1H, H(6)]	7.87–8.38	4.53		4.67
	7.64 [s, 1H, H(4)]	(m, 5H)			10.90
	7.80 [d, 1H, 8.3 Hz, H(7)]				
9d	7.9–8.5	7.73–8.6		3.4	14.21
	(m, 3H)	(m, 5H)		(s, 3H, CH_3)	29.36

The ^{13}C NMR chemical shifts were recorded for some examples of the title compounds, namely for **3a, 3b, 6a-e**, and **8a** (Table V). Patterns for C(4) and C(7) were doublets at 110.1–116.6 ppm ($^3J_{PC}$ = 12.6–13.8 Hz), and 114.5–117.9 ppm ($^3J_{PC}$= 12.6–13.8 Hz), respectively. Shifts at 120.1–121.8 ppm and 125.4–126.2 ppm were assigned to C(5) and C(6), respectively. In the case of C(1′), C(2′,6′), C(4′), and C(3′,5′), the order of shifts was 126.3–126.8, 127.4–127.7, 125.7–126.5, and 129.1–129.6. The nitrogen-bearing ring carbons C(8) and C(9) were downfield at 133.5–134.1 and 138.2–139.5, respectively. The signal for the carbonyl carbon [C(1″)] in **6a-e** occurred at 153.9–156.6 ppm while the C(2″) shifts were downfield (~10 ppm) compared to the corresponding signals in the respective free alcohols,[13] a situation which is again likely due to the presence of the C=O group. Remaining signals appeared in the regions expected. The ^{13}C NMR chemical shifts for the other members of **3** and **9**were not assignable due to poor solubility of the compounds and high signal density from unresolved patterns.

Phosphorus-31 NMR signals were detected in the ranges of –5.25 to 4.76 ppm for **3a-e**, 12.84 to 13.42 ppm for **6a-e**, and –8.78 to 29.36 ppm for **9a-d** (85% H_3PO_4).[14–16]In view of the lack of established model systems in the literature, the use of such data for diagnostic purposes is limited at this time.

TABLE V C-13 NMR Chemical Shifts for **1, 3a, 3b, 6a-e**, and **8a**(PPM Values fr

COMPD	*1*	*3a*	*3b*	*6a*	*6b*	*6c*
Carbon Atom				*Chemical Shifts (Coupling Constants)*		
C(1′)	127.9			126.5	126.6	126.8
C(2′,6′)	129.1	127.7	127.4	127.4	127.5	127.5
C(4′)	126.9	125.9	125.7	125.8	125.8	125.8
C(3′,5′)	129.7	129.2	129.1	129.3	129.3	129.2
C(4)	136.7			110.2	110.1	110.2
	C(1)			(12.6)	(12.6)	(13.8)
C(5)	136.7	121.8	121.7	120.3	120.4	120.4
	C(2)					
C(6)	121.6	125.6	125.7	125.5	125.5	125.4
	C(3)					
C(7)	125.0			114.5	114.6	114.6
	C(4)			(13.8)	(12.6)	(12.6)
C(8)	129.7	133.5	133.6	134.1	134.1	133.9
	C(5)					
C(9)	121.6	138.2	138.5	139.0	139.0	138.9

PD	1	3a	3b	6a	6b	6c	6d	6e	8
Atom	Chemical Shifts (Coupling Constants)								
	C(6)								
			20.2						
		148.5	146.4	154.5	154.0	153.9	153.8	154.2	15
		122.5	120.8	52.1	60.8	66.2	64.9	63.6	13
		129.0	129.5		13.7	136.2	42.3	30.2	127
									12
		132.1	134.4			128.5		18.8	(3″, 4 6″,
		129.0	129.5			127.9			
		122.5	120.8			128.1			
″)						127.9			
″)						128.5			

onstants (J_{PC}) are in parentheses in Hz.

Mass spectral analyses were conducted on a few representative compounds (Table VI) and were confirmatory for the molecular ions for **3d, 6e**, and **9b**. Although the fragmentation patterns were many, it was possible to glean information with respect to **3d** via a major ion [*m/z* 216] for the $P(O)CCl_3$ group, and the presence of $[M^+ + 2]$ and $[M^+ + 4]$ fragments were easily identified. Similarly, **6e** had high intensity patterns for fragments arising from the $C_5H_{10}NO_3P$ fragment [*m/z* 216] and from the loss of water. In the case of **9b**, the major ion [*m/z* 278] resulted from the $PhSO_2$ fragment, and, in addition, there was a fragment [*m/z* 127] visible from the $4\text{-}ClC_6H_4O$ group.

ANTIMICROBIAL ACTIVITY

Phosphoramides **3a-e** and **6a-e** were screened for antifungal activity on *Aspergillus niger* and *Curvulara lunata*. A literature technique[17] was followed for testing the compounds at concentrations of 500 ppm and 1000 ppm. As can be seen in Table VII, most of the agents exhibited significant toxicity against both fungi. Antibacterial activity was assessed using a known procedure[18]on *Bacillus subtilis* and *Klebsiella pneumoniae* (Table VII). Agents **3a, 3d, 3e, 6b**, and **6d** displayed strong action against the above bacteria.

CONCLUSIONS

Simple methodology has been developed to obtain several members of the title compounds the structures of which are supported by elemental and a variety of spectral analyses. The advantages of the technology is that the reactions can be performed smoothly, and the products are relatively easy to isolate and purify. Moreover, the type of rare phosphorus heterocycle described has potential utility in the area of antifungal and antibacterial agents.

TABLE VI Mass Spectral *m/z* Values[19,20] (% of Important Ions) for **3d, 6e**, and **9b**

COMPD	*m/z Values*
3d	378 [28,27,9; M^+, $(M^+ + 2)$, $(M^+ + 4)$], 343 [11; $(M^+ - Cl)$], 296 [12; $(M^+ - CCl_2)$], 278 [11; $(M^+ - CCl_2) - H_2O$], 261 [100; $(M^+ - CCl_3)$], 243 [16; $(M^+ - CCl_3) - H_2O$], 216 [32; $(M^+ - O{=}PCCl_3) + 2$ H], 215 [12], 199 [7; $(M^+ - O{=}PCCl_3) - NH_3$], 188 [12], 152 [16].
6e	376 [9; M^+], 358 [4; $(M^+ - H_2O)$], 303 [3.2; $(M^+ - C_4H_{10}O)$], 277 [2.5; $(M^+ - O{=}CC_4H_8O)$], 216 [100; $(M^+ - C_5H_{10}NO_3P) + 2$ H], 199 [10; $(216 - NH_3)$].
9b	420 [5, M^+], 279 [19, $(M^+ - SO_2C_6H_5)$], 278 [100, $(M^+ - SO_2C_6H_5) - H$)], 185 [10], 153 [8, $(M^+ - SO_2C_6H_5) - OC_6H_4Cl$], 141 [3, $SO_2C_6H_5$], 127 [56, OC_6H_4Cl], 125 [68, C_6H_5SO].

TABLE VII Antimicrobial Activity of 2-Substituted-2,3-dihydro-5-thiophenoxy-1*H*-1,3,2-benzodiazaphosphole 2-Oxides **3a-e** and **6a-e**

COMPD	*Zone of inhibition (mm)*					
	Fungi				*Bacteria*	
	Curvularia lunata		*Aspergillus niger*		*Bacillus subtilis*	*Klebsiella pneumoniae*
	500[a]	*1000*[a]	*500*[a]	*1000*[a]	*1000*[a]	*1000*[a]
3a	7	12	6	11	9	10
3b	–[b]	–	–	–	–	–
3c	–	–	–	–	–	–
3d	12	18	14	20	12	15
3e	16	22	13	16	15	17
6a	–	–	–	–	–	–
6b	11	15	8	13	10	12
6c	–	–	–	–	–	–
6d	11	16	9	15	12	14
6e	–	–	–	–	–	–

a. Concentration in ppm.
b. The "__" indicates no activity at the concentrations specified.

EXPERIMENTAL

General

All melting points were determined on a Mel-Temp apparatus and were uncorrected. Elemental analyses were performed by the Central Drug Research Institute, Lucknow, India. All IR spectra were recorded as KBr pellets on a Perkin-Elmer 1430 unit. The ^{1}H, ^{13}C, and ^{31}P NMR spectra were taken on Varian Gemini 300 MHz NMR spectrometer operating at 299.9 MHz (^{1}H), 75.5 MHz (^{13}C), and 121.7 MHz (^{31}P). Compounds were dissolved in DMSO-d_6, and chemical shifts were referenced to TMS (^{1}H and ^{13}C) and 85% H_3PO_4 (^{31}P). Mass spectra data (EI) were collected on a JEOL JMSD-300 instrument at 70 eV with a direct inlet system.

Preparation of 2-(4'-Chlorophenoxy)-2,3-dihydro-5-thiophenoxy-1*H*-1,3,2-benzodiazaphosphole 2-Oxide (3a)

The general procedure to obtain members of **3** is illustrated for the preparation of **3a**. A solution of 4-chlorophenyl phosphorodichloridate (**2a**, 2.46 g, 0.01 mol) in dry toluene (25 mL) was added dropwise (20 min) to a stirred solution of 4-thiophenoxy-1,2-phenylenediamine (**1**, 2.16 g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) in dry toluene (60 mL) at room temperature. After the addition was complete, the temperature was slowly raised to 55–65 °C and was then maintained for 6–7 h with stirring. After cooling to room temperature, the triethylamine hydrochloride was filtered off, and the filtrate was evaporated (reduced pressure). The gummy residue was washed with water, dried, and treated with 2-propanol. A white solid formed and was recrystallized (ethanol) to yield **3a** (1.75 g, 45%), mp 137–139 °C. Physical and spectral data for **3a-e** are in Tables I-VI.

Preparation of Methyl Carbamato-2,3-dihydro-5-thiophenoxy-1*H*-1,3,2-benzodiazaphosphole 2-Oxide (6a)

A general procedure for members of **6** is illustrated with that for **6a**. A solution of methanol (0.32 g, 0.01 mol) in dry toluene (20 mL) was added dropwise (20 min) to a cold (-10 °C) solution of **4**[2] (1.60 g, 0.01 mol) in

dry toluene (20 mL). After the addition was complete, the mixture was allowed to warm slowly to room temperature, and stirring was continued for 2 h. The new reaction mixture was then added dropwise to a cold (0 °C) solution of **1** (2.16 g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) in dry toluene (50 mL). When the addition was complete, the mixture was stirred and allowed to warm slowly to 50–55 °C. After 6 h of stirring in the temperature range specified, the triethylamine hydrochloride was filtered off, and the solvent was evaporated (reduced pressure). After washing the solid (water) and after recrystallization (methanol), pure **6a** (1.9 g, 56%) was obtained, mp 224–226 °C. Physical and spectral data on members of **6** are in Tables I-VI.

Preparation of 2-Phenylcarbamido-2,3-dihydro-5-thiophenoxy-1*H*-1,3,2-benzodiazaphosphole 2-Oxide (8a)

A general procedure of the member of **8** is illustrated with that for **8a**. A solution of aniline (0.46 g, 0.005 mol) in dry toluene (25 mL) was added dropwise (0.25 h) to a cold (-15 °C) solution of **4** (0.80 g, 0.005 mol) in dry toluene (30 mL). When the addition was complete, the temperature of the mixture was maintained between −15 °C and −5 °C for 1 h after which time the mixture was allowed to rise to room temperature, with stirring being continued for 30–40 min. This new mixture was added dropwise to a cold (0 °C) solution of **1** (1.08 g, 0.005 mol) and triethylamine (1.01 g, 0.01 mol) in dry toluene (40 mL). After the addition was complete, the mixture was heated with stirring to 45–55 °C for 5–6 h. Triethylamine hydrochloride was filtered off, and the solvent was evaporated (reduced pressure). The residue was washed with water, dried, and treated with 2-propanol. The solid which formed was recrystallized (methanol) to give give pure **8a** (0.75 g, 38%), mp 116–118 °C. Physical and spectral properties of members of **8** are in Tables I-V.

Oxidation of 3a, 3d, 3e, and 6a-General Procedure

A general procedure for this oxidation is illustrated with **3a**. To a solution of sulfide **3a** (0.97 g, 0.0025 mol) in acetic acid (30–40 mL) was added dropwise hydrogen peroxide (30%, 1 mL) at 15 °C. When the addition was complete (0.25 h), the mixture was allowed warm to room temperature slowly, and the resulting mixture was stirred for 2–3 h. Acetic acid was

removed (reduced pressure), and the residual solid was washed with water and recrystallized (ethanol) to give pure **9b** (0.72 g, 68%), mp 156–158 °C. Physical and spectral properties of members of **9** are in Tables I, IV, and VI.

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