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Synthesis and Antibacterial Activity of 2-Alkylcarbamato/Trichloromethyl/Chloroethoxy/Aryloxy-1,2,3,4-Tetrahydro-1,3,2-Benzodiazaphosphorine 2-Oxides

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ABSTRACT: *Several 2-trichloromethyl/2-chloroethoxy/2-aryloxy-1,2,3,4-tetrahydro-1,3,2-benzodiazaphosphorine 2-oxides (**4a–d**), and 2-alkyl/alkenyl/alkynylcarbamato 2-oxides (**7a-f**) have been synthesized from reactions of equimolar quantities of 2-aminobenzylamine (**2**) with various aryl or alkyl phosphorodichloridates (**3b–d**), trichloromethylphosphonic dichloride (**3a**) and dichlorophosphinyl carbamates (**6a–f**) at 40–50°C in dry toluene in the presence of triethylamine. IR, ^{1}H, ^{13}C, ^{31}P NMR and mass spectral analyses were collected and analyzed and supported all structures. The title compounds were screened for antibacterial activity against Bacillus subtilis and Escherichia coli. Several of the agents exhibited significant activity in the assays.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:323–328, 2000

INTRODUCTION

Organophosphorus compounds are ubiquitous in nature and they have multifaceted applications. Benzoannulated and related analogs [1–3] of cyclophosphamide [4] possess antitumour activity against lymphoid leukemia in mice. Phosphorus carbamates form an important class of compounds having antitumour [5], pesticidal [6], and bactericidal properties [7–9]. In view of this, the title compounds **4a–d** and **7a–f** were synthesized and characterized by elemental, IR, NMR (^{1}H, ^{13}C and ^{31}P), and mass spectral analyses and tested for their antibacterial activity.

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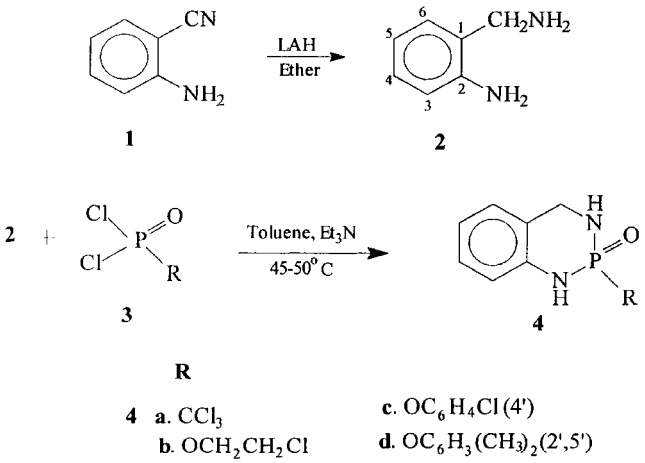
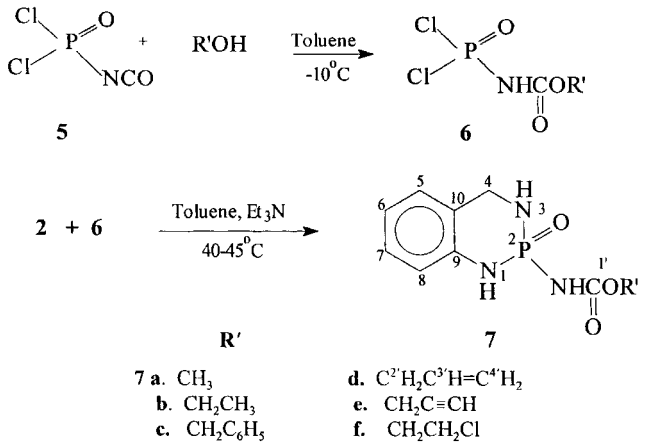
RESULTS AND DISCUSSION

Syntheses of 2-trichloromethyl/chloroethoxy/aryloxy-1,2,3,4-tetrahydro-1,3,2-benzodiazaphosphorine 2-oxides (**4a–d**) were accomplished by the condensation of equimolar quantities of 2-aminobenzylamine (**2**) [10–12] with trichloromethylphosphonic dichloride (**3a**), *O*-2-chloroethyl phosphoryl dichloride (**3b**), and aryl phosphorodichloridates (**3c,d**) in dry toluene in the presence of triethylamine at 45–50°C (Scheme 1). Purification of members of **4** was achieved by filtering off the triethylamine hydrochloride, evaporating the filtrate, washing the residue with water, and recrystallizing the solid products from suitable solvents.

With respect to the carbamates, a condensation involving equivalent amounts isocyanatophosphonic dichloride (**5**) and various alcohols at −10°C in dry toluene (Scheme 2) led to the corresponding dichlorophosphinyl carbamates **6a–f**. The reaction mixtures were then added to **2** under similar conditions utilized previously for the generation of **4** and gave **7a–f**. Purification of **7a–f** was like that for **4**, namely, via recrystallization from 2-propanol or 2-propanol-methanol (3:1). Interestingly, all primary,



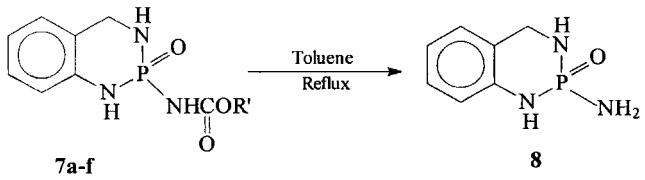
SCHEME 1



SCHEME 2

secondary, alkenyl, and alkynyl alcohols reacted readily with **5**, but *t*-butyl alcohol failed under the same conditions.

Compounds **7a–f** on reflux in toluene gave **8**, indicating their thermal instability at this reflux temperature. Interestingly, all of the alkylcarbamato compounds (**7a–f**) on reflux in toluene gave only one product (**8**).



Reaction yields, elemental analyses, and IR data [13–16] are given in Table 1. Tables 2–5 contain ^{1}H, ^{13}C, ^{31}P NMR, and mass spectral data for compounds **4** and **7**.

^{1}H NMR spectra (Tables 2 and 3) exhibited signals in the range of δ 6.59–7.36 accounting for the aromatic protons of benzodiazaphosphorine, benzyl, and phenoxy moieties in **4** and **7**. The 4(H) protons resonated as a multiplet at δ 4.03–4.47 in **4a, 4b, 4d,** and **7b**, but, in **7a** and **7c–f**, their signal appeared as two multiplets at δ 3.83–4.0 and δ 4.25–4.38, respectively. This indicates that the two methylene protons at C-4 are magnetically nonequivalent due to their orientation at axial and equatorial positions in the six-membered chair conformation of the benzodiazaphosphorine ring (Figure 1). The proton signal of the exocyclic P-NH-CO is observed as a doublet in the region δ 8.74–9.04 (J = 8.0–9.2 Hz). It is of interest to note that phosphorus coupling is limited to P-NH protons only and is not extended to the other protons of the carbamate moiety in **7a–f**. It is also observed that the signals for the protons of the carbamate function appear slightly downfield when compared to the signals of the corresponding protons in the free alcohols [17].^{13}C NMR chemical shifts of compounds of **4** and **7** are given in Table 4. The nitrogen-bearing carbon C(9) resonates as a doublet in the downfield region at δ 139.7–146.9 [^{2}J = 7.0–9.1 Hz]. The doublet in the upfield region at δ 116.5–117.4 [^{3}J = 9.1–9.9 Hz] is assigned to C(8). The chemical shifts at δ 125.7–127.0, 119.7–121.9, and 127.2–129.6 are attributed to C(5), C(6), C(7), respectively. The doublet at δ 121.8–125.2 [^{3}J = 6.8–7.6 Hz] is ascribed to C(10). C(4) resonates at δ 40.3–44.6. The carbonyl carbon C(1′) of the carbamate function resonates in the range of 153.6–154.8 ppm. The C-2′ chemical shifts of the carbamate function appear downfield (~10 ppm) in the compounds (**7a–f**) when compared to the signals of the corresponding carbon chemical shifts in the respective free alcohols [17]. The remaining carbons of the carbamate function resonate in the expected regions.

^{31}P NMR signals appear in the range of −4.14 to 8.05 ppm for **4a–d** (Table 2). In the corresponding carbamate series **7a–f** [18], phosphorus signals are observed in the region 0.19 to 0.54 ppm (Table 3). The ^{31}P signal for compound **8** occurs at δ 3.92.

ANTIBACTERIAL ACTIVITY

The compounds **4a–d** and **7a–f** were tested for their antibacterial activity according to the method of Vincent and Vincent [19] on *Bacillus subtilis* (gram +ve) and *Escherichia coli* (gram −ve) with two different concentrations (500 and 1000 ppm). Most of them exhibited significant toxicity (Table 6) against B. subtilis.

TABLE 1 Physical and IR Data of Compounds **4** and **7**

Compound	m.p. (°C)	Yield (%)	Mol. Formula	Found (Required) %			IR (cm^{-1})				
				C	H	N	P=O	P–NH–CO	C=O	P–NH(Ar)	P–NH(CH_2)
4a	245–246	65[a]	$C_8H_8Cl_3N_2OP$	33.37 (33.66)	3.10 (2.82)	9.45 (9.81)	1227	—	—	3220	3169
4b	255 (dec)	45[c]	$c_9H_{12}ClN_2O_2P$	— (43.83)	— (4.90)	— (11.36)	1235	—	—	3360	3190
4c	184—186	46[c]	$C_{13}H_{12}ClN_2O_2P$	52.75 (52.99)	3.95 (4.10)	9.76 (9.51)	1228	—	—	3356	—
4d	201—202	48[a]	$C_{15}H_{17}N_2O_2P$	62.25 (62.49)	6.08 (5.94)	9.66 (9.72)	1230	—	—	—	—
7a	226—228	58[b]	$C_9H_{12}N_3O_3P$	44.55 (44.82)	4.86 (5.02)	17.78 (17.42)	1222	3150	1740	3338	3215
7b	206—208	59[b]	$C_{10}H_{14}N_3O_3P$	46.87 (47.06)	5.78 (5.53)	16.40 (16.47)	1220	3150	1740	3338	3216
7c	214—216	57[a]	$C_{15}H_{16}N_3O_3P$	57.05 (56.78)	5.24 (5.08)	13.02 (13.24)	1224	3176	1730	3333	—
7d	209—210	55[b]	$C_{11}H_{14}N_3O_3P$	49.26 (49.44)	5.07 (5.28)	15.70 (15.72)	1235	3141	1735	3307	3210
7e	212—213	55[b]	$C_{11}H_{12}N_3O_3P$	49.75 (49.82)	4.25 (4.56)	16.15 (15.84)	1238	3140	1738	3305	3210
7f	183—184	52[a]	$C_{10}H_{13}ClN_3O_3P$	41.32 (41.47)	4.78 (4.52)	14.64 (14.51)	1226	3145	1730	3335	3212

[a]Recrystallized from 2-propanol.
[b]Recrystallized from 2-propanol-methanol (3:1).
[c]Triturated with 2-propanol.

EXPERIMENTAL

The melting points were determined on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed at the Central Drug Research Institute, Lucknow, India. IR spectra were recorded as KBr pellets on a Perkin-Elmer 683 unit. ^1H, ^{13}C and ^{31}P NMR spectra were recorded on Varian XL-300 or XL-400 spectrometers operating at 300 or 400 MHz for H-1, 75.46 or 100.57 MHz for C-13, and 161.89 MHz (XL 400) for P-31. NMR spectra of **4**, **7**, and **8** were recorded using DMSO-d_6, with TMS as the reference for ^1H and ^{13}C and 85% H_3PO_4 for ^{31}P NMR. Mass spectra were recorded on a Jeol JMSD-300 instrument at 70eV.

Preparation of 2-Aminobenzylamine (**2**) *by Reduction of Anthranilonitrile with Lithium Aluminium Hydride [10,11].*

2-Trichloromethyl-1,2,3,4-tetrahydro-1,3,2-benzodiazaphosphorine 2-oxide (**4a**). The general procedure to obtain members of **4** is illustrated by the synthesis of **4a**. A solution of trichloromethylphosphonic dichloride (**3a**, 2.37 g, 0.01 mol) in 25 mL of dry toluene was added dropwise over a period of 20 minutes to a cold solution (0°C) of 2-aminobenzylamine (**2**, 1.22 g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) in 30 mL of dry toluene. After completion of the addition, the temperature of the reaction mixture was maintained at 0°C for 2 hours, and then the temperature of the reaction mixture was raised slowly to 45–50°C and stirring was continued for 4–5 hours. Progress of the reaction was monitored by TLC analysis. Triethylamine hydrochloride was filtered off, and the solvent, was evaporated from the filtrate under reduced pressure. The residue was washed with water and recrystallized from 2-propanol, yielding 1.86 g (65%) of **4a**, m.p. 245–246°C. Physical and spectral data of **4a–d** are provided in Tables 1–5.

Compounds **4b–d** were synthesized by adopting the same procedure.

2-Propargylcarbamato-1,2,3,4-tetrahydro-1,3,2-benzodiazaphosphorine 2-oxide (**7e**). A solution of propargyl alcohol (0.56 g, 0.01 mol) in 20 mL of dry toluene was added dropwise over a period of 20 minutes to a cold solution (− 10°C) of **5** (1.60 g, 0.01 mol) in 20 mL of dry toluene. After the addition, the temperature of the reaction mixture was raised slowly to room temperature, and stirring was continued for another 2 hours. This reaction mixture was added dropwise to a cold solution (0°C) of **2** (1.22 g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) in 30 mL of dry toluene. After the addition, the temperature

TABLE 2 ^{1}H and ^{31}P NMR Spectral Data of **2**[a] and **4**[a]

	4-H	*5-H*	*6-H*	*7-H*	*8-H*	*R-H*	*1-H*	*3-H*	*^{31}P NMR*[c]
2[b]	3.82 (s, 2H, CH_2)	6.97 (7.2, 3-H)	7.0 (8.0, 8.0, 4-H)	6.63 (7.2, 7.2, 5-H)	6.60 (8.0, 6-H)				
4a	4.26–4.47 (m, 2H)	6.95 (8.0)	6.85 (7.2, 7.6)	7.11 (7.6, 7.6)	7.07 (7.6)		8.74 (6.0)	6.48	8.05 7.99
4b	4.21—4.32 (m, 2H)	6.82—6.89 (m, 2H)		7.10 (7.6, 7.6)	7.01 (7.6)	3.76—4.02 (m, 4H, C_2H_4)	—	—	6.45 −0.20
4c	3.88 (s, 2H)	6.72 (8.0)	6.59 (7.2, 7.2)	7.07 (7.2, 7.2)	7.16 (8.4)	7.12—7.34 (m, 4H, Ar-H)	8.20	—	−4.14
4d	4.03—4.25 (m, 2H)	6.85 (7.6)	6.79 (7.2, 7.2)	7.05 (7.6, 7.6)	7.10 (7.6)	6.80—7.14 (m, 3H, Ar-H) 2.25(s, 3H, CH_3) 2.12(s, 3H, CH_3)	8.32 (5.6)	5.65 (6.8)	5.61

[a]Data in parentheses are coupling constants; *J* in Hz.
[b]Recorded in $CDCl_3$.
[c]^{31}P Chemical shifts were expressed in δ, from 85% H_3PO_4 as external standard.

TABLE 3 ^{1}H and ^{31}P NMR Spectral Data of **7**[a] and **8**

	H(4)	*H(5), H(6)*	*H(7)*	*H(8)*	*R-H*	*H(1)*	*H(3)*	*-NHCO*	*^{31}P NMR*[b]
7a	3.85–3.97 (m, 1H) 4.25–4.34 (m, 1H)	6.73–6.78 (m, 2H)	7.05 (7.6, 7.6)	6.99 (7.2)	3.55 (s, 3H, OCH_3)	7.93 (5.2)	5.30 (5.2)	8.83 (8.4)	0.54
7b	4.25–4.32 (m, 2H)	6.74–6.77 (m, 2H)	7.04 (7.2, 7.2)	6.99 (7.2)	3.93 (q, 2H, OCH_2) 1.03(t, 3H, CH_3)	7.93	5.29 (5.6)	8.74	0.37
7c	3.85–3.97 (m, 1H) 4.26–4.33 (m, 1H)	6.74–6.78 (m, 2H)	7.05 (7.6, 7.6)	6.98 (7.2)	5.02 (s, 2H, OCH_2) 7.05–7.36 (m, 5H, Ar-H)	7.98 (5.6)	5.35 (5.2)	8.95 (9.2)	0.38
7d	3.85–3.96 (m, 1H) 4.26–4.31 (m, 1H)	6.60–6.70 (m, 2H)	7.03 (7.2, 7.2)	6.98 (7.2)	4.44 (d, 4.0, 2H, OCH_2) 5.77–5.81 (m, 1H, CH) 5.28 (J_{trans} = 18 Hz) 5.15 (J_{cis} = 10 Hz) (CH_2)	7.94	—	8.88	0.44
7e	3.83–4.0 (m, 1H) 4.28–4.38 (m, 1H)	6.74–6.77 (m, 2H)	7.05 (7.2, 8.1)	6.99 (7.5)	4.60 (s, 2H, OCH_2) 3.51 (s, 1H, CH)	7.98 (6.0)	5.38 (6.3)	9.04 (9.0)	0.44
7f	3.87–3.98 (m, 1H) 4.30–4.33 (m, 1H)	6.75–6.78 (m, 2H)	7.05 (7.2, 7.2)	7.0 (7.2)	4.17 (s, 2H, OCH_2) 3.66 (s, 2H, CH_2Cl)	7.97	5.35	8.97 (8.0)	0.19
8	3.80–3.93 (m, 2H)	6.46–6.62 (m, 2H)	6.79	6.97		7.39	4.12	8.01 (NH_2)	3.92

[a]Data in parentheses are coupling constants; *J* in Hz.
[b]^{31}P Chemical shifts were expressed in δ, from 85% H_3PO_4 as external standard.

of the reaction mixture was maintained for 2 hours at 0°C, and then raised to 40–45°C with stirring for an additional 5 hours. Progress of the reaction was monitored by TLC analysis. The precipitated triethylamine hydrochloride was filtered off, and the solvent was evaporated from the filtrate under reduced pressure. The residue obtained was washed with water followed by chilled 2-propanol and recrystallized from 2-propanol-methanol (3:1), yielding 1.45 g (55%) of **7e,** m.p. 212–213°C. Physical and spectral data of **7a–f** are provided in Tables 1–5.

Compounds **7a–d** and **7f** were synthesized by adopting the same procedure.

Preparation of 2-amino-1,2,3,4-tetrahydro-1,3,2-benzodiazaphosphorine 2-oxide (**8**). A solution of **7d** (0.67 g, 0.0025 mol) in 40 mL of dry toluene containing a few drops of dimethylformamide was

TABLE 4 ^{13}C NMR Spectral Data of **4**[a] and **7**[a]

Carbon Atom	**4a**	**4c**	**4d**	**7a**	**7b**	**7c**	**7d**	**7e**	**7f**
C-4	44.6	40.3	43.6	43.1	43.2	43.2	43.2	43.2	43.2
C-5	126.6	127.0	126.2	125.7	125.7	125.8	125.8	125.8	125.8
C-6	121.1	121.9	121.0	119.7	119.7	119.7	119.7	119.8	119.8
C-7	127.6	129.6	127.6	127.2	127.2	127.2	127.2	127.2	127.2
C-8	117.4	116.5	116.8	116.8	116.9	116.8	116.9	116.9	116.9
	(9.1)	(9.1)	(9.9)	(9.1)	(9.8)	(9.9)	(9.1)	(9.1)	(9.1)
C-9	139.7	146.9	140.8	141.3	141.4	141.2	141.3	141.1	141.3
	(7.6)	(7.6)	(9.1)	(9.1)	(7.6)	(9.1)	(7.6)	(7.0)	(7.2)
C-10	121.8	125.2	122.8	124.4	124.4	124.2	124.3	124.3	124.3
	(6.8)	(7.2)	(7.6)	(7.2)	(6.8)	(7.6)	(7.2)	(6.9)	(6.9)
C-1′	99.0	151.7	149.3	154.8	154.3	154.3	154.0	153.6	154.0
			(7.0)						
C-2′		122.0	125.9	51.8	60.4	65.8	64.8	77.5	64.5
C-3′		129.2	130.6		14.2	136.5	132.9	78.8	42.5
C-4′		130.4	124.6			127.7	117.4	52.0	
C-5′		129.2	136.0			128.3			
C-6′		122.0	119.9			127.9			
C-7′			15.7 (2″, CH_3)			128.3			
			20.6 (5″, CH_3)						
C-8′						127.7			

[a]Data in parentheses are coupling constants; J_{pc} in Hz.

TABLE 5 Mass Spectral Data (% of Important Ions) of **4a** and **7c** [20]

4a	284 [3.5, $M^{+\cdot}$], 249 [2, ($M^{+\cdot}$ − Cl)], 202 [3, ($M^{+\cdot}$ − CCl_2)], 167 [100, ($M^{+\cdot}$ − CCl_3)], 149 [19, ($M^{+\cdot}$ − CCl_3) − H_2O], 122 [5, ($M^{+\cdot}$ − P(O)CCl_3) + 2H].
7c	317 [3, $M^{+\cdot}$], 209 [4, $M^{+\cdot}$ − C_7H_8O)] 167 [8, ($M^{+\cdot}$ − $C_8H_8NO_2$)], 149 [32, ($M^{+\cdot}$ − $C_8H_8NO_2$) − H_2O], 122 [8, ($M^{+\cdot}$ − P(O) $C_8H_8NO_2$) + 2H].

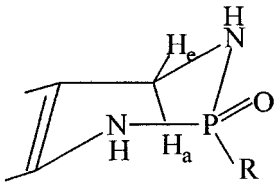


FIGURE 1

pyrolized vigorously for 3 hours. The solution was cooled immediately, and the separated solid product **8** was filtered off and washed with water and recrystallized from 2-propanol-methanol (3:1) to afford pure compound **8**; Yield 1.31 g (72%), m.p. 200–201°C; Anal. Calcd for $C_7H_{10}N_3OP$ (183.1493); C, 45.91; H, 5.50; N, 22.94: Found: C, 45.69; H, 5.66; N, 22.79.

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TABLE 6 Antibacterial Activity of 2-Substituted-1,2,3,4-Tetrahydro-1,3,2-Benzodiazaphosphorine 2-Oxides (**4** and **7**)[a]

	Zone of Inhibition (*mm*)			
	Bacillus subtilis		*Escherichia coli*	
Compound	*500*	*1000*	*500*	*1000*
4a	—	—	—	6
4c	—	—	—	12
4d	11	14	6	8
7a	22	25	—	—
7b	14	16	—	—
7c	12	14	2	—
7d	9	16	8	—
7e	—	2	—	—
7f	16	12	—	8

[a]Concentration in ppm; —, indicates no activity.

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