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Synthesis and Characterization of 6-Alkylcarbamato-2,10-dichlorodibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin 6-Oxides

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ABSTRACT

Novel 6-alkylcarbamato/thiocarbamato-2,10-dichlorodibenzo[d,g][1,3,6,2]dioxathiaphosphocin 6-oxides were synthesized by cyclization of 5,5′-dichloro-2,2′-dihydroxydiphenyl sulfide with the corresponding dichlorophosphinyl carbamates/thiocarbamates that were obtained by the addition of alcohols/thiols to dichloroisocyanatophosphine oxide and were characterized by IR, ^1H, ^{13}C, ^{31}P NMR, and mass spectral studies. A ^{13}C NMR analysis revealed $^2J_{POC}$ and $^3J_{POCC}$ couplings. © *1996 John Wiley & Sons, Inc.*

INTRODUCTION

Phosphorus carbamates form important classes of antitumor agents [1] and pesticides [2]. Some phosphorus heterocyclic esters were reported [3–5] to possess insecticidal and bactericidal properties. Industrially, they were found to be useful as lubricating oil additives, antioxidants, and polymer stabilizers [6]. In view of these possible applications of organophosphorus carbamate heterocycles, the title compounds **4a–j** were synthesized and characterized by elemental, IR, NMR, and mass spectral analyses.

RESULTS AND DISCUSSION

The synthetic route (Scheme 1) involves the addition reaction of dichloroisocyanatophosphine oxide (**1**) [1] with various alcohols/thiols at −10°C under inert, anhydrous conditions in dry toluene to afford the corresponding dichlorophosphinyl carbamates/thiocarbamates (**2a–j**). Cyclization of **2a–j** *in situ* with 5,5′-dichloro-2,2′-dihydroxydiphenyl sulfide (**3**) in the presence of triethylamine at 0°C yielded compounds **4a–j**. The yields are in the range of 36–48% for the two-step conversion of the dichloroisocyanatophosphine oxide to the final products (Table 1).

The primary and secondary alcohols/thiols reacted readily with dichloroisocyanatophosphine oxide (**1**) to give their respective carbamates/thiocarbamates (**2**), but tertiary alcohols/thiols (*t*-butyl alcohol/*t*-butyl thiol) did not react to form the expected corresponding carbamates/thiocarbamates (**2**), obviously due to steric factors. Attempts to convert **4** to the corresponding (X = NH) urea derivatives by heating with various amines were unsuccessful, but the reactions led to pyrolysis of the formed products (**4a–j**) [7].

The IR spectra of **4a–j** exhibited characteristic bands [8–11] in the regions 3250–3320 (P–NH), 1710–1760 (COXR), 1260–1270 (P=O), 1220–1240 and 970–995 (P–O–C_{aro}), and 640–670 (Ar–S–Ar) cm^{-1}. Physical and ^{31}P NMR data of compounds **4a–j** are given in Table 1.

Only three sets of signals for the six protons of the dibenzodioxathiaphosphocin moiety were observed in their ^1H NMR spectra (Table 2). This shows

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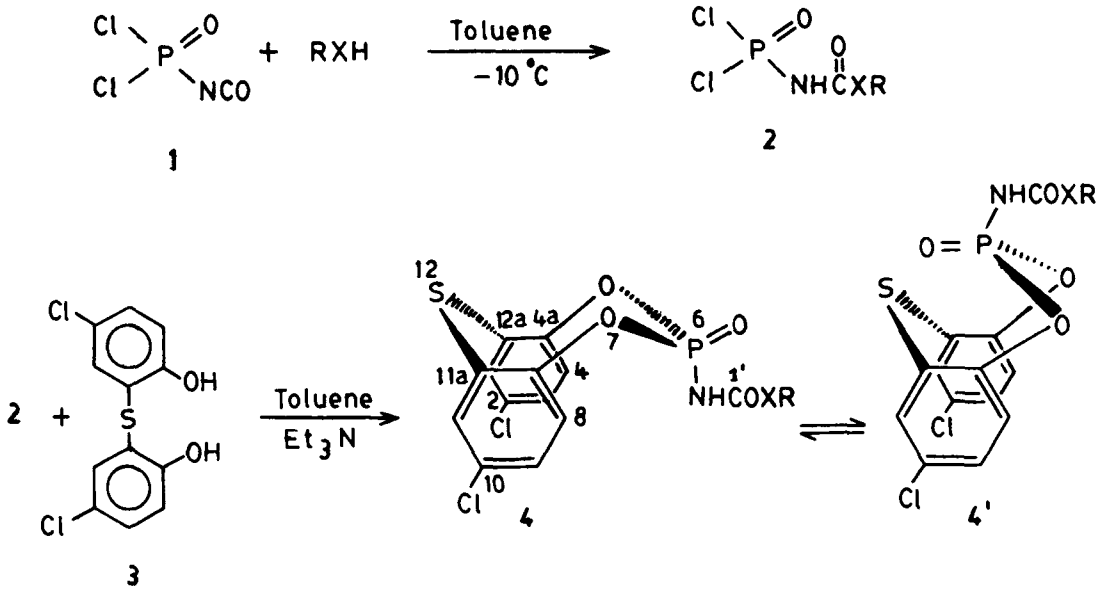

SCHEME 1

	XR		XR
4 a)	OCH_3	**f)**	OC_6H_{11}
b)	OCH_2CH_3	**g)**	$OCH_2C_6H_5$
c)	OCH_2CH_2Cl	**h)**	$SCH_2CH_2CH_3$
d)	$OCH(CH_3)_2$	**i)**	$SCH(CH_3)_2$
e)	$OCH_2CH(CH_3)_2$	**j)**	$SCH_2CH_2CH_2CH_3$

TABLE 1 Physical, IR, and ^{31}P NMR Data of Compounds **4**

				Analysis		*IR (Cm^{-1})*		
Compd.	*mp °C*	*Yield (%)*	*Mol. Formula*	*Found C*	*(Required) H*	*P=O*	*C=O*	*^{31}P NMR[c]*
4a	184–185	42[a]	$C_{14}H_{10}Cl_2NO_5PS$	41.16 (41.40)	2.30 (2.48)	1265	1740	−8.46
4b	178–179	40[a]	$C_{15}H_{12}Cl_2NO_5PS$	42.46 (42.88)	2.80 (2.88)	1260	1740	−9.52
4c	224–225	44[a]	$C_{15}H_{11}Cl_3NO_5PS$	39.24 (39.63)	2.16 (2.44)	1265	1730	−11.87
4d	172–173	40[a]	$C_{16}H_{14}Cl_2NO_5PS$	43.92 (44.26)	3.04 (3.25)	1270	1720	−9.95
4e	176–177	38[a]	$C_{17}H_{16}Cl_2NO_5PS$	45.13 (45.55)	3.59 (3.60)	1260	1710	−9.48
4f	194–195	36[b]	$C_{19}H_{18}Cl_2NO_5PS$	48.32 (48.12)	3.79 (3.83)	1265	1720	−8.44
4g	234–235	38[b]	$C_{20}H_{14}Cl_2NO_5PS$	49.40 (49.81)	2.86 (2.93)	1270	1730	−9.32
4h	168–169	46[b]	$C_{16}H_{14}Cl_2NO_4PS_2$	42.70 (42.68)	3.04 (3.13)	1260	1760	−17.64
4i	165–166	44[b]	$C_{16}H_{14}Cl_2NO_4PS_2$	42.49 (42.68)	2.96 (3.13)	1265	1750	−18.24
4j	178–179	48[b]	$C_{17}H_{16}Cl_2NO_4PS_2$	43.59 (43.98)	3.12 (3.47)	1260	1760	−18.56

[a]Recrystallized from ethanol.
[b]Washed with 2-propanol.
[c]^{31}P NMR chemical shifts were expressed in δ from 85% H_3PO_4 as external standard.

TABLE 2 ^{1}H NMR Data of Compounds **4** (δ from TMS)[a]

Compd.	*H(1,11)*	*H(3,9)*	*H(4,8)*	*-NH-*	*R-H*
4a	7.86 (d, 2.6)	7.59 (dd, 8.5, 2.4)	7.23 (dd, 8.5, 1.5)	5.78 (d, 8.0)	3.78 (s, 3H, OCH_3)
4b	7.39 (d, 2.5)	7.20 (dd, 8.8, 2.4)	6.92 (dd, 8.7, 1.5)	5.80 (d, 7.7)	3.09 (m, 2H, OCH_2) 1.18 (t, 3H, CH_3)
4c	7.93 (d, 2.7)	7.63 (dd, 8.8, 2.5)	7.42 (dd, 8.8, 1.7)	5.68 (d, 7.8)	4.56 (t, 2H, OCH_2) 4.13 (t, 2H, CH_2Cl)
4d	7.48 (d, 2.6)	7.32 (dd, 8.6, 2.6)	7.20 (dd, 8.8, 1.6)	5.74 (d, 7.6)	4.23 (m, 1H, OCH) 1.02 (d, 6H, $2CH_3$)
4e	7.89 (d, 2.7)	7.53 (dd, 8.7, 2.6)	7.25 (dd, 8.6, 1.8)	5.79 (d, 7.8)	3.96 (d, 2H, OCH_2) 1.57–1.64 (m, 1H, CH) 0.83 (d, 6H, $2CH_3$)
4f	7.90 (d, 2.7)	7.61 (dd, 8.7, 2.6)	7.34 (dd, 8.7, 1.5)	5.81 (d, 7.6)	4.66–4.72 (m, 1H, OCH) 1.16–1.90 (m, 10H)
4g	7.82 (d, 2.6)	7.60 (dd, 8.5, 2.4)	7.36 (dd, 8.7, 1.6)	5.78 (d, 7.5)	4.26 (s, 2H, OCH_2) 6.80–7.26 (m, 5H, ArH)
4h	7.94 (d, 2.8)	7.64 (dd, 8.6, 2.5)	7.36 (dd, 8.7, 1.6)	5.86 (d, 7.8)	2.44 (t, 2H, OCH_2) 1.52–1.59 (m, 2H, CH_2) 0.93 (t, 3H, CH_3)
4i	7.90 (d, 2.7)	7.61 (dd, 8.6, 2.5)	7.28 (dd, 8.6, 1.6)	5.84 (d, 7.8)	1.76 (m, 1H, SCH) 1.15 (d, 6H, $2CH_3$)
4j	7.87 (d, 2.6)	7.58 (dd, 8.6, 2.4)	7.29 (dd, 8.6, 1.6)	5.88 (d, 7.8)	2.42 (t, 2H, SCH_2) 1.62–1.68 (m, 4H, $2CH_2$) 1.02 (t, 3H, CH_3)

[a]Data in parentheses are coupling constants $J_{H\text{-}H}$ (in Hz).

the symmetrical disposition of the two substituted benzene rings [12] in the dibenzodioxathiaphosphocin moiety. The doublet of doublets in the region δ 6.92–7.42 (J = 8.5–8.8 and 1.5–1.8 Hz) was assigned to H(4) and H(8). Another doublet of doublets at δ 7.20–7.64 (J = 8.5–8.8 and 2.4–2.6 Hz) was attributed to H(3) and H(9). Both H(1) and H(11) resonated as a doublet at δ 7.39–7.94 (J = 2.5–2.8 Hz). The proton signal for P–NH appeared as a doublet in the region δ 5.68–5.88 (J = 7.5–8.0 Hz). It is of interest to note that the coupling with phosphorus is limited to P–NH only and not extended to the other protons of the carbamate moiety. It is also observed that the signals for the protons of the carbamate function appeared slightly downfield when compared to the signals of the corresponding protons in the free alcohols/thiols [13].

The ^{13}C NMR chemical shifts of compounds **4a–j** are given in Table 3. The oxygen-bearing carbons C(4a) and C(7a) resonated as a doublet in the downfield region δ 150.4–151.1 [$^2J_{POC(4a,7a)}$ = 8.6–9.1 Hz] [14]. The chemical shifts of the bridged carbons C(11a) and C(12a) appeared as low-intensity doublets in the region δ 125.4–127.6 [$^3J_{POCC(11a,12a)}$ = 3.4–4.0 Hz]. The doublet in the region δ 124.0–125.0 [$^3J_{POCC(4,8)}$ = 4.5–5.3 Hz] was ascribed to C(4) and C(8) [15]. The chlorine-substituted carbons C(2) and C(10) gave signals in the region δ 131.4–132.0. Chemical shifts at δ 129.6–130.6 and 134.9–135.2 were suggested for carbons C(3,9) and C(1,11), respectively. The ^{13}C NMR chemical shifts of carbons C(4a,7a) and C(11a,12a) appeared downfield by δ 3–6 when compared with the chemical shifts of **3**. This might be due to the deshielding effect of P = O in the heterocyclic ring. The carbonyl carbon C(1′) in the carbamate function resonated as a doublet in the range δ 152.8–181.2 [$^2J_{PNC}$ = 7.1–10.8 Hz]. The C-2′ chemical shifts of the carbamate function appeared downfield (~δ 10) in all compounds when compared with the signals of the corresponding carbon chemical shifts in the respective free alcohols/thiols [13]. The remaining carbons of the carbamate function resonated in the expected regions.

The ^{31}P NMR signals [16] for the carbamate compounds **4a–g** appeared in the region δ −8.44 to −11.87, whereas the thiocarbamate compounds **4h–j** resonated in the upfield region δ − 17.64 to − 18.56 (Table 1). This may be attributed to the difference in the electrochemical nature of oxygen and sulfur.

Chemical ionization mass spectra of compounds **4a–j** showed $(M + 4)^+$, $(M + 2)^+$, M^+, $(M\text{-}XR)^+$, $(M\text{-}HXR)^+$, $(M\text{-}NHCOXR)^+$, and RXH^+ as characteristic ions. The ion at *m/z* 331 was observed as the base peak in most of the compounds. The other principal ions observed are *m/z* 284, 268, 252, 190, 173, and 142, which are obviously derived from the dibenzodioxathiaphosphocin 6-oxide moiety [17].

Unfortunately, it was not possible to grow a suit-

TABLE 3 ^{13}C NMR Data of Compounds[a] **4** (δ from TMS)[b]

Carbon Number	***4a***	***4b***	***4c***	***4d***	***4e***	***4f***	***4h***	***4i***	***4j***
C(1,11)	135.0	134.9	135.0	135.0	135.1	134.9	135.2	135.0	134.9
C(2,10)	131.8	131.6	131.8	131.4	131.5	131.7	132.0	131.9	131.7
C(3,9)	130.6	130.4	130.5	130.1	129.6	130.4	130.5	130.1	129.9
C(4,8)	124.1	124.1	124.0	124.7	125.0	124.0	124.0	124.1	124.5
	(d, 5.0)	(d, 5.2)	(d, 5.3)	(d, 5.2)	(d, 5.1)	(d, 4.5)	(d, 4.6)	(d, 4.8)	(d, 5.1)
C(4a,7a)	150.8	150.6	150.9	151.0	151.1	150.9	150.4	150.9	150.8
	(d, 8.8)	(d, 8.6)	(d, 9.0)	(d, 8.9)	(d, 8.9)	(d, 8.7)	(d, 9.0)	(d, 9.1)	(d, 8.9)
C(11a,12a)	125.9	126.1	125.4	125.9	127.6	126.2	126.2	126.5	126.9
	(d, 3.4)	(d, 3.6)	(d, 3.7)	(d, 3.5)	(d, 3.4)	(d, 3.4)	(d, 3.6)	(d, 3.9)	(d, 4.0)
C(1′)	158.4	157.6	155.2	176.4	181.2	152.8	156.3	154.7	158.9
	(d, 9.6)	(d, 9.4)	(d, 10.8)	(d, 10.1)	(d, 8.6)	(d, 7.1)	(d, 8.1)	(d, 8.6)	(d, 8.8)
C(2′)	45.5	52.2	64.7	57.4	67.7	74.6	25.7	27.3	22.3
			(d, 10.1)						
C(3′)	—	18.3	44.8	26.4	30.5	31.1	28.8	26.8	37.2
			(d, 4.2)						
C(4′)	—	—	—	—	19.1	23.2	12.7	—	21.2
C(5′)	—	—	—	—	—	24.7	—	—	13.5

[a]Not recorded for **4g**.
[b]Data in parentheses are coupling constants $J_{P\text{-}C}$ (in Hz).

able crystal of **4** for X-ray diffraction studies to determine the conformer in the solid state. Space-filling models imply that a boat–chair (BC) conformation **4** is more likely, but a boat–boat (BB) conformation **4′** may also be possible for the eight-membered dibenzodioxathiaphosphocin ring, as illustrated in Scheme 1. Undoubtedly, an equilibrium exists between several forms in solution [18,19].

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. Elemental analyses were performed at the Central Drug Research Institute, Lucknow, India. Infrared spectra were recorded as KBr pellets on a Perkin-Elmer 137 spectrophotometer. All NMR spectra were recorded on a Varian XLAA-300 MHz spectrometer with data acquisition at 299.94 MHz (^1H), 75.43 MHz (^{13}C), and 121.48 MHz (^{31}P). All spectra 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 D-300 instrument at 70 eV.

2,10-Dichloro-6-ethylcarbamatodibenzo[d,g][1,3,6,2]dioxathiaphosphocin 6-Oxide (**4b**)

A solution of ethanol (0.46 g, 0.01 mol) in 20 mL of dry toluene was added dropwise over a 30-minute time period to a cold solution (−10°C) of **1** (1.60 g, 0.01 mol) in 20 mL of dry toluene. After the addition, the temperature of the reaction mixture was allowed to rise slowly to room temperature, and stirring was continued for another 2 hours. This reaction mixture was added dropwise *in situ* to a cold solution (0°C) of **3** (2.87 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 allowed to rise slowly to 40–45°C, and stirring was continued for an additional 5 hours. The precipitated triethylamine hydrochloride was filtered off, and the solvent from the filtrate was evaporated under reduced pressure. The residue was washed with water, followed by 2-propanol, and recrystallized from ethanol, yielding 1.68 g (40%) of **4b**, mp 178–179°C; anal. calcd for $C_{15}H_{12}Cl_2NO_5PS$ (420.2033): C, 42.88; H, 2.88. Found: C, 42.56; H, 2.80.

Compounds **4a** and **4c–j** were synthesized by adopting the aforementioned procedure.

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