A Facile Synthesis and Antimicrobial Activity of 2,10-Dichloro-6-(aryloxy/thiophenoxy)-4,8-dinitrodibenzo[*d,g*][1,3,6,2]-dioxathiaphosphocin- 6-Oxides

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Received August 10, 1999

Novel 6-substituted 2,10-dichloro-4,8-dinitrodibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin-6-oxides **4** were synthesized by reacting 5,5'-dichloro-3,3'-dinitro-2,2'-dihydroxydiphenyl sulfide (**2**) with different aryl phosphorodichloridates, trichloromethylphosphonic dichloride and O-2-chloroethyl phosphoryldichloride (**3**) in the presence of triethylamine at 55-60°. Some of these compounds are prepared by reacting the monochloride, 2,6,10-trichloro-4,8-dinitrodibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin-6-oxide (**5**) *in situ* with substituted phenols and thiols. **5** is prepared by condensing **2** with phosphorus oxychloride. The ^{1}H nmr chemical shifts of the dibenzodioxathiaphosphocin moiety indicates the presence of more than one conformer in solution. However the presence of more than one conformer in each example cannot be entirely eliminated. Interestingly **4d** on oxidation to 12-sulphone by H_2O_2 in acetic acid medium yielded only 12-sulphoxide **6a**. The ir, ^{1}H, ^{13}C, ^{31}P nmr and mass spectral data are discussed. Some of these compounds were screened for antifungal activity against *Curvularia lunata* and *Aspergillus niger* and antibacterial activity on *Bacillus subtilis* and *Klebsiella pneumoniae*. A few of them possess significant activity.

J. Heterocyclic Chem., **37**, 275 (2000).

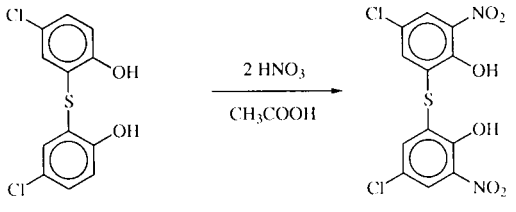
Introduction.

The dibenzo dioxathiaphosphocins are potential antioxidants, stabilizers in oils and polymers [1] and also superior ligands in transition metal-mediated hydroformation reactions [2]. In view of this, the title compounds (**4a-i**) were synthesized by reacting **2** with aryl phosphorodichloridates, trichloromethylphosphonic dichloride, and O-2-chloroethyl phosphoryldichloride in presence of triethylamine. Introduction of substituted phenols/thiols with bulky substituents in **4** was not successful by this method, the preparation and purification of the corresponding phosphorodichloridates was found to be difficult as they were moisture sensitive, thermally unstable and explosive in nature. An alternative approach involving a two-step process has been developed to overcome these difficulties. First, the precursor 2,6,10-trichloro-4,8-dinitrodibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin-6-oxide (**5**) was prepared in standard fashion from **2** and phosphorus oxychloride. In the second step, **5** was reacted with various substituted phenols/thiols in presence of triethylamine.

Results and Discussion.

Reaction of 4-chlorophenol with sulphur dichloride afforded 5,5'-dichloro-2,2'-dihydroxydiphenyl sulphide (**1**) [3]. Nitration of **1** using HNO_3 gave 5,5'-dichloro-3,3'-dinitro- 2,2'-dihydroxydiphenyl sulphide (**2**) (Scheme I).

Scheme I



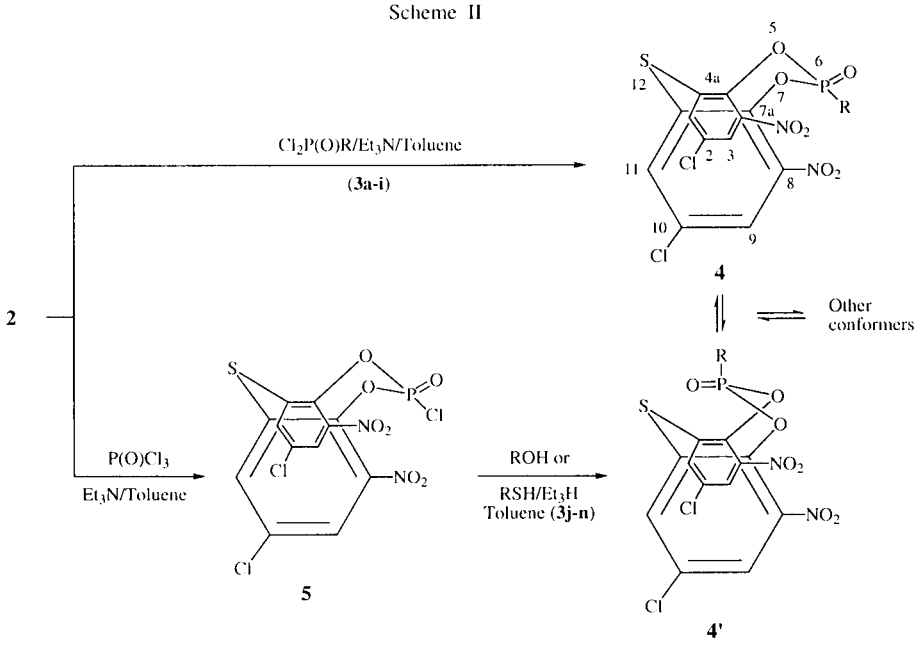
1 **2**

Cyclocondensation of **2** with aryl phosphorodichloridates (**3a-g**) or trichloromethylphosphonic dichloride (**3h**) or O-2-chloroethyl phosphoryldichloride (**3i**) in presence of triethylamine yielded 2,10-dichloro-6-(aryloxy/alkoxy/trichloromethyl)-4,8-dinitrodibenzo[*d,g*][1,3,6,2]-dioxathiaphosphocin-6-oxides (**4** → **4'** etc) which interestingly crystallyzed with one molecule of triethylamine. In an alternative approach, **2** was treated with phosphorus oxychloride/triethylamine in dry toluene at 50-55° to give 2,6,10-trichloro-4,8-dinitrodibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin 6-oxide (**5**). **5**, without further purification, was reacted with a series of substituted phenols/thiophenols to yield **4** → **4'** (Scheme II). The second method is advantageous in that it does not require the use of uncommon phosphorodichloridates which are often difficult to purify. The condensation products (**4**) were isolated by filtration of the triethylamine hydrochloride followed by evaporation of the solvent under reduced pressure. Further purification was carried out by washing with water followed by recrystallization from a suitable solvent.

Attempts to prepare sulphone (**6c**) by oxidising **4d** with hydrogen peroxide (30%) in acetic acid resulted with partial success in the formation of the corresponding sulphoxide (**6a**) only and not the expected sulphone (**6c**). Presence of the sulphoxide function between the two bulky chloronitrophenyl moieties in the rigid heterocyclic system may perhaps stereochemically prevent further oxidation to the sulphone. Another view could be that **6a** may be in equilibrium with its ring-closed isomer **6b** which may electronically prevent further oxidation.

Reaction yields, elemental analyses and ir and ^{31}P data of **4** are given in Table 1. Tables 2, 3 and 4 contain ^{1}H, ^{13}C

Scheme II



Compoud	R	Compoud	R	Compoud	R
4a	C_6H_5O	**4f**	2'-Cl-C_6H_4O	**4k**	2',3',4',6'-Cl_4-C_6HO
4b	2'-H_3C-C_6H_4O	**4g**	4'-Cl-C_6H_4O	**4l**	C_6H_5S
4c	3'-H_3C-C_6H_4O	**4h**	Cl_3C	**4m**	4'-Cl-C_6H_4S
4d	4'-H_3C-C_6H_4O	**4i**	$ClCH_2CH_2O$	**4n**	4'-H_3C-C_6H_4S
4e	2',6'-$(H_3C)_2$-C_6H_3O	**4j**	4'-O_2N-C_6H_4O		

Table 1

Physical IR and ^{31}P NMR Spectral Data of 2,10-Dichloro-6-(aryloxy/thiophenoxy)-4,8-dinitrodibenzo[*d*,*g*][1,3,6,2]dioxathiaphosphocin-6-Oxides **4**

Compound	Yield (%)	Mp (°C)	Molecular Formula	Elemental Analysis Calcd./Found			IR (cm^{-1})			^{31}P NMR Data [c]
				C	H	N	P=O	$ArNO_2$		ppm
4a	58 [a]	198-199	$C_{18}H_9Cl_2N_2O_8PS \cdot Et_3N$	46.76 47.02	3.92 4.15	6.82 6.95	1255	1535	1345	-5.1, -11.6
4b	56 [a]	175-177	$C_{19}H_{11}Cl_2N_2O_8PS \cdot Et_3N$	47.63 47.87	4.16 4.32	6.67 6.51	1250	1534	1351	-3.12, -10.11
4c	56 [a]	136-138	$C_{19}H_{11}Cl_2N_2O_8PS \cdot Et_3N$	47.63 —	4.16 —	6.67 —	1243	1530	1351	-11.55, -11.69
4d	57 [a]	196-197	$C_{19}H_{11}Cl_2N_2O_8PS \cdot Et_3N$	47.63 47.79	4.16 4.42	6.67 6.72	1250	1535	1345	-10.74
4e	55 [a]	180-182	$C_{20}H_{13}Cl_2N_2O_8PS \cdot Et_3N$	48.46 48.68	4.38 4.22	6.52 6.61	1246	1534	1351	-9.65
4f	51 [a]	155-156	$C_{18}H_8Cl_3N_2O_8PS \cdot Et_3N$	44.29 43.96	3.56 3.92	6.46 6.47	1255	1535	1345	-10.83, -14.05
4g	53 [a]	169-170	$C_{18}H_8Cl_3N_2O_8PS \cdot Et_3N$	44.29 —	3.56 —	6.46 —	1255	1535	1345	-11.81
4h	58 [a]	154-156	$C_{13}H_4Cl_5N_2O_7PS \cdot Et_3N$	35.56 35.91	2.98 3.22	6.55 6.62	1290	1530	1345	[d]
4i	52 [a]	214-216	$C_{14}H_8Cl_3N_2O_8PS \cdot Et_3N$	39.85 —	3.85 —	6.97 —	1265	1534	1345	[d]
4j	48 [b]	199-201	$C_{18}H_8Cl_2N_3O_{10}PS \cdot Et_3N$	43.58 43.82	3.50 3.78	8.47 8.25	1265	—	—	-12.58, -14.86
4k	42 [b]	210 (dec)	$C_{18}H_5Cl_6N_2O_8PS \cdot Et_3N$	38.22 38.48	2.67 3.02	5.57 5.72	1240	1534	1356	-11.83, -14.84
4l	40 [a]	90-92	$C_{18}H_9Cl_2N_2O_7PS_2 \cdot Et_3N$	45.58 45.29	3.82 3.58	6.64 6.71	1238	1539	1354	-10.02, -11.06
4m	36 [b]	85-87	$C_{18}H_8Cl_3N_2O_7PS_2 \cdot Et_3N$	43.22 —	3.48 —	6.30 —	1238	1540	1355	-10.05, -14.83
4n	35 [a]	234-236	$C_{19}H_{11}Cl_2N_2O_7PS_2 \cdot Et_3N$	46.45 —	4.05 —	6.50 —	1235	1540	1355	-14.86

[a] Recrystallized from ethyl acetate, reported yields are after one recrystallization. [b] Recrystallized from methanol. [c] Chemical shifts in ppm from 85% phosphoric acid. [d] ^{31}P nmr spectrum not recorded for **4h** and **4i**; Et_3N = Triethylamine.

Table 2

^{1}H NMR Chemical shift (J in Hz) Data [a] of 2,10-Dichloro-6-(aryloxy/thiophenoxy)-4,8-dinitrodibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin-6-Oxides **4**

Compound	H(3,9) & H(1, 11)	Ar-H	O-Ar-CH_3
4a [b]	7.46 - 8.05 (m, 4H)	6.95 - 7.35 (m, 5H)	
4b [c]	7.56 - 8.55 (m, 4H)	7.00 - 7.45 (m, 4H)	2.18 (s, 3H)
4c [c]	7.52 - 8.12 (m, 4H)	6.84 - 7.25 (m, 4H)	2.24 (s, 3H)
4d [c]	7.53 - 8.13 (m, 4H)	6.98 - 7.08 (m, 4H)	2.25 (s, 3H)
4e [c]	7.17 - 8.10 (m, 4H)	6.85 - 6.97 (m, 3H)	2.37 (s, 6H)
4f [c]	7.55 - 8.12 (m, 4H)	6.94 - 7.67 (m, 4H)	
4g [b]	7.35 - 8.07 (m, 4H)	7.29 - 7.32 (d, 2H, 8.8)	
		7.07 - 7.10 (d, 2H, 8.8)	
4h [c]	7.45 - 8.12 (m, 4H)	—	
4i [b]	7.25 - 8.05 (m, 4H)	3.67 - 3.78 (m, 2H, CH_2Cl)	
		4.25 - 4.35 (m, 2H, OCH_2)	
4j [b]	7.38 - 8.23 (m, 4H)	7.27 - 7.31 (d, 2H, 8.6)	
		8.16 - 8.19 (d, 2H, 8.6)	
4k [b]	7.40 - 8.23 (m, 4H)	7.88 (s, 1H)	
4l [b]	7.44 - 8.07 (m, 4H)	7.08 - 7.34 (m, 5H)	
4m [b]	7.37 - 8.20 (m, 4H)	7.12 - 7.30 (m, 4H)	
4n [b]	7.52 - 8.24 (m, 4H)	7.02 - 7.15 (m, 4H)	2.38 (s, 3H)

[a] Chemical shifts in δ and J (Hz) given in parentheses. [b] Recorded in dimethyl sulfoxide-d_6. [c] Recorded in Deuteriochloroform.

Table 3

^{13}C NMR Chemical shift data [a,d] of 2,10-Dichloro-4,8-dinitrodibenzo[*d,g*][1,3,6,2] dioxathiaphosphocin-6-Oxides **4**

Compound	C(1/11)	C(2/10)	C(3/9)	C(4/8)	C(4a/7a)	C(11a/12a)
4a [b]	136.6	126.7	124.5	137.6	150.2	123.1
4b [c]	135.1	128.2	126.4	139.9	150.7	125.0
4c [c]	135.3	129.2	125.5	139.8	152.7	124.8
4d [c]	135.3	129.9	125.8	139.8	152.7	124.8
4e [c]	134.1	126.7	124.4	141.2	152.8	124.3
4f [c]	135.1	127.7	125.8	140.1	152.2	124.5
4g [b]	137.2	128.5	126.3	140.3	151.8	124.8
4j [b]	136.8	—	126.7	137.8	150.8	124.6
4n [b]	135.5	127.5	126.7	139.6	149.8	123.5

[a] Chemical shifts in ppm. [b] Recorded in dimethyl sulfoxide-d_6. [c] Recorded in Deuteriochloroform. [d] **4h, 4i, 4k-m** gave unresolved spectra due to poor solubility.

nmr data for **4**. The ir spectra of **4a-4n** [4,5] exhibited characteristic bands in the regions 1235-1290 cm^{-1} for (P=O), 1530-1540 and 1345-1356 cm^{-1} for (Ar-NO_2), 1155-1210 and 945-970 cm^{-1} for (P-O-C_{aro}).

The ^{1}H nmr spectra of dibenzodioxathiaphosphocin moiety in **4** showed six *meta* coupled (J ≈ 2.5 Hz) doublets in the range of 7.17-8.55 ppm, which suggest that at least three conformers are present in solution for the dibenzodioxathiaphosphocin moiety. Out of the six signals, four are more intense. The aryloxy/arylthio moieties of **4** showed signals in the region δ 6.84-8.19. Conformations of a boat-chair, boat-boat, twist-boat and boat-boat systems with distorted (or) distended features or a tub-like topology have been considered [6, 9b, 9c, 6b, 6c] for the dibenzodioxaphosphocin system. In the present case, a suitable crystal of **4** for X-ray diffraction studies, to determine the stereochemistry of the conformer in the solid state, could not be grown.

The ^{13}C nmr chemical shifts of dibenzodioxathiaphosphocin moieties of **4** (Table 3) were interpreted on the basis of a comparison with the ^{13}C nmr data of **2**, additivity rules, C-P couplings, and intensity of signals. The oxygen-bearing carbons C(4a) and C(7a) appeared in the downfield region (δ 149.8-152.8) [7]. The chemical shifts of the bridged carbons C(11a) and C(12a) resonated at δ 123.1-125.0 [8]. The nitro-substituted carbons C(4) and C(8) gave signals at δ 137.6-141.2.

The carbon chemical shifts of the 6-aryloxy (**4a-4g, 4j**) and arylthio (**4n**) groups (Table 4) were assigned by comparison with those of related systems [6f, 9]. The C(1') signal appeared in the region 131.7-152.7, while the C(2') and C(6') signals occurred in the region δ 117.0-130.4. Chemical

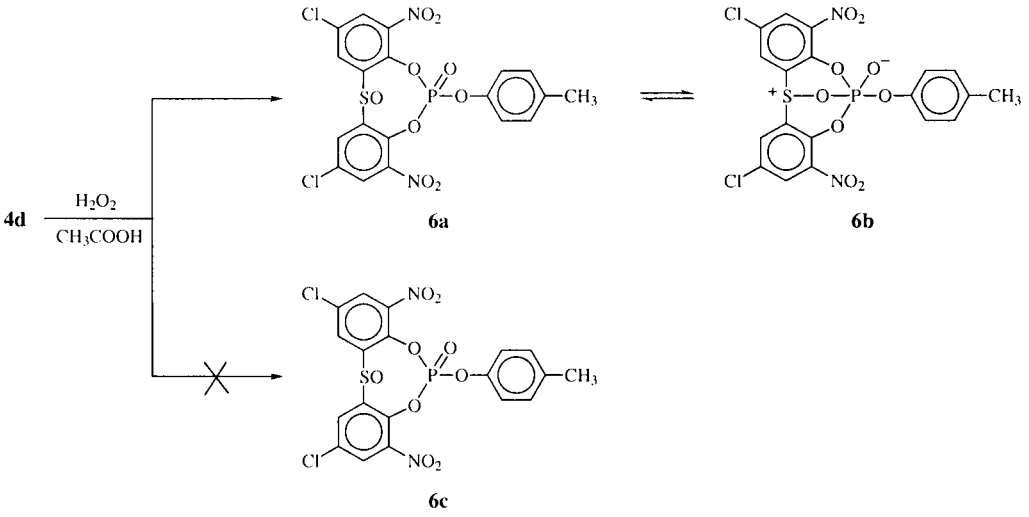


Table 4

^{13}C NMR data [a,d] of 6-aryloxy/thioaryloxy moieties in **4**

Compound	C(1')	C(2')	C(3')	C(4')	C(5')	C(6')	C''(CH_3)
4a [b]	150.2	119.6	129.2	124.5	129.2	119.6	—
4b [c]	150.7	130.4	135.3	124.8	128.2	—	15.7
4c [c]	152.7	119.8	140.7	125.2	130.0	117.0	21.3
	(5.6)	(5.6)	(9.1)			(5.7)	
4d [c]	149.4	120.2	130.4	134.6	130.4	120.2	22.7
4e [c]	144.9	130.1	128.7	124.0	128.7	130.1	17.4
4f [c]	152.2	125.4	130.1	124.8	127.7	121.9	
				(5.7)			
4g [b]	144.5	121.3	134.3	129.2	134.3	122.1	
		(5.7)					
4j [b]	150.8	122.6	124.6	137.8	124.6	122.6	
4n [b]	131.7	127.5	129.2	135.5	127.5	129.2	22.5

[a] Chemical shifts in ppm and J (Hz) given in parentheses. [b] Recorded in dimethyl sulfoxide-d_6. [c] Recorded in Deuteriochloroform. [d] **4h, 4i, 4k-m** gave unresolved spectra due to poor solubility.

Table 5

Antimicrobial activity of 2,10-dichloro-6-substituted-4,8-dinitrodibenzo-[*d,g*][1,3,6,2]dioxathiaphosphocin-6-oxides

	Zone of inhibition (mm)					
	Fungi				Bacteria	
Compound	*Curvularia lunata*		*Aspergillus niger*		*Bacillus subtilis*	*Klebsiella pneumoniae*
	500	1000	500	1000	1000	1000
4a	—	—	7	10	—	9
4b	8	11	—	—	5	—
4c	—	—	—	—	—	—
4d	11	14	—	—	6	—
4e	—	—	—	—	—	—
4f	—	—	—	—	—	—
4h	—	—		—	—	—
4j	7	11	—	—	6	—
4k	—	—	6	11	—	13
4l	8	10	12	15	8	12

Concentration in ppm; "—" indicates no activity.

shifts for the C(3'), C(4') and C(5') were observed at δ 124.6-140.7, 124.0-137.8, and 124.6-134.3 respectively, depending on the nature of substituents at various positions. The observed upfield shift of about 4 ppm for the methyl group attached to C(2') (**4b** and **4e**) was attributed to its γ-interaction with the exocyclic oxygen [9b, 10].

The ^{31}P nmr signals appeared in the range of -3.12 to -14.86 ppm from 85% phosphoric acid. Only one ^{31}P signal was observed in **4d, 4e, 4g** and **4n**, but in other members of **4**, two distinct signals appeared with varying intensities (≈60:30) [11] suggesting their existence in two distinct conformations.

Antimicrobial Activity.

Some of the title compounds (**4a-f, 4h** and **4j-l**) were tested for their antifungal activity against *Aspergillus niger* and *Curvularia lunata*. The Benson H. J. [12a] technique was followed for testing the compounds at two different concentrations (500 and 1000 ppm). Their antibacterial activity was evaluated according to the method of Vincent and Vincent [12b] on *Bacillus subtilis* and *Klebsiella pneumoniae*. Few of them exhibited significant toxicity against either the fungi or bacteria.

EXPERIMENTAL

The 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. ^1H and ^{13}C nmr spectra were recorded on a Varian XL-300 spectrometer operating at 300 MHz for H-1 and 75.46 MHz for C-13. ^{31}P nmr were recorded on a Varian XL-400 spectrometer operating at 161.89 MHz. All nmr data were taken in deuteriochloroform or dimethyl-d_6 sulfoxide solutions and were referenced to tetramethylsilane (^1H and ^{13}C) or 85% phosphoric acid (^{31}P). Mass spectra were recorded on a AUTO SPEC Q instrument using a solid probe at 70 eV.

5,5'-Dichloro-3,3'-dinitro-2,2'-dihydroxydiphenyl Sulphide (**2**).

Nitric acid 7 ml (0.1 mole) was added over a period of 15-20 minutes to a stirred solution of 5,5'-dichloro-2,2'-dihydroxydiphenyl sulphide (**1**, 14.35 g, 0.05 mole) in acetic acid (125 ml) at 14-15°. After the addition, the reaction was continued at room temperature for 2-3 hours. After completion of the reaction, the solid 5,5'-dichloro-3,3'-dinitro-2,2'-dihydroxydiphenyl sulphide was filtered; washed with water, dried and recrystallised from ethyl acetate to yield 14.5 g (75%) of **2**, mp 188-189°; ir (potassium bromide): ν 1520, 1315 (Ar-NO_2) cm^{-1}, 3210 (Ar-OH) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 8.01 (d, J = 2.7 Hz, 2H, 4 & 4'-H), 7.48 (d, J = 2.6 Hz, 2H, 6 & 6'-H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 123.1 (s, 2C, C-1 & 1'), 150.2 (s, 2C, C-2 & 2'), 137.6 (s, 2C, C-3 & 3'), 124.5 (s, 2C, C-4 & 4'), 126.6 (s, 2C, C-5 & 5'), 136.6 (s, 2C, C-6 & 6'); ms: m/z (%) 380 (30, M+4), 378 (85, M+2), 376 (100, M^+), 358 (20), 328 (14), 314 (22), 282 (19), 254 (21), 226 (20), 192 (23), 173 (26).

Anal. Calcd. for $C_{12}H_6Cl_2N_2O_6S$: C, 38.21; H, 1.60; N, 7.43. Found: C, 37.89; H, 1.94; N, 7.15.

2,10-Dichloro-6-(2',6'-dimethylphenoxy)-4,8-dinitrodibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin-6-oxide (**4e**).

A solution of 2,6-dimethylphenyl phosphorodichloridate (**3e**, 2.39 g, 0.01 mole) in dry toluene (25 ml) was added dropwise over a period of 15 minutes to a stirred solution of **2** (3.77 g, 0.01 mole) and triethylamine (2.02 g, 0.02 mole) in dry toluene (60 ml). After completion of the addition, the temperature was slowly raised to 55-60° and stirring was continued for an additional 6-7 hours. Progress of the reaction was monitored by tlc analysis. Triethylamine hydrochloride was then filtered from the mixture, and solvent was evaporated under reduced pressure. The residue was washed with water and then recrystallized from ethyl acetate to give 2.98 g of pure **4e** in 55% yield, mp 180-182°. Physical and spectral data of **4e** are given in Tables 1-4. **4a-4i** were prepared by this procedure.

2,10-Dichloro-6-(2',3',4',6'-tetrachlorophenoxy)-4,8-dinitrodibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin-6-oxide (**4k**).

The typical procedure using phosphorus oxychloride is illustrated in the preparation of **4k**. To a stirred solution of **2** (3.77 g, 0.01 mole) and triethylamine (2.02 g, 0.02 mole) in dry toluene (60 ml) at 0-5° was added dropwise phosphorus oxychloride

(1.53 g, 0.01 mole) in dry toluene (25 ml) over a period of 15 minutes. After raising the temperature to 50-55°, the reaction mixture was stirred for 5 hours, tlc analysis (silica gel) was used to monitor the formation of the monochloride **5**. To the same reaction vessel was added dropwise a solution of 2,3,4,6-tetrachlorophenol (2.32 g, 0.01 mole) and triethylamine (1.01 g, 0.01 mole) in dry toluene (25 ml). The temperature of this new mixture was raised to 55-65°, and stirred for another 4 hours. Filtration of triethylamine hydrochloride left a solution which was evaporated to a solid residue. After being washed with water, the residue was recrystallized from methanol to afford 2.74 g (42%) of **4k**, mp 210° (dec). Physical and spectral data for **4k** are given in Tables 1-3. **4j-4n** were prepared by this procedure.

Oxidation of 2,10-Dichloro-6-(4'-methylphenoxy)-4,8-dinitrodibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin-6-oxide.

Compound **4d** (1.32 g, 0.0025 mole) was dissolved in 30-40 ml of acetic acid. Hydrogen peroxide (30%) was added to the solution at 15°. After the addition, the temperature of the reaction mixture was allowed to rise slowly to room temperature and stirring was continued for 2-3 hours. Purification of this product was achieved by removing acetic acid under reduced pressure followed by washing the crude solid with water. The crude product was recrystallized from ethyl acetate to give pure 0.88 g of sulphoxide (**6a**) instead of sulphone (**6c**) in 65% yield, mp 246-248°; ir (potassium bromide): ν 1245 (P=O), 1083 (S=O), 1515, 1315 (Ar-NO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.10-8.56 (m, 4H, 1,11 & 3,9 - H), 7.1 (s, 4H, Ar-H), 2.35 (s, 3H, CH_3); ms: m/z (%) 544 (3.2, $M^{+\cdot}$) 543 (5, $M^{+\cdot}$ - H), 525 (8), 508 (4), 463 (7), 442 (24), 431 (38), 368 (27), 240 (54), 199 (72), 103 (100).

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