Facile Synthesis, Spectral Characterization and Antimicrobial Activity of 6-Substituted-2,4,8,10-Tetra-*t*-Butyl Dibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin 6-Oxides

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Several novel 2,4,8,10-tetra-*t*-butyl-6-substituted dibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin 6-oxides were synthesized in high yield by cyclocondensation of 2,2'-thiobis(2,4-di-*t*-butylphenol) with phosphorus oxychloride in the presence of triethylamine and a catalytic amount of dimethylaminopyridine (DMAP) in dry toluene followed by *in situ* reaction with different bulky phenols/thiophenols under the same reaction conditions. The structures of the synthesized compounds were confirmed by analytical, IR, multinuclear NMR studies. Their antibacterial and antifungal activities were evaluated against *Staphylococcus aureus, Escherichia coli, Aspergillus niger* and *Fusarium oxysporium,* respectively. Some of them showed moderate activity against these microorganisms.

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Introduction.

Synthesis of dibenzodioxathiaphosphocins and their analogues is drawing much attention as they find use as antioxidants, polymer, oil stabilizers and antibiotics [1-5]. Our continuous endeavour to develop biologically active phosphorus heterocyclic compounds [6] led to an efficient synthesis of interesting types of such classes of compounds in a two-step process, one pot procedure starting from 2,2'-thiobis(2,4-di-*t*-butylphenol) (**1**) and phosphorus oxychloride followed by reaction with different bulky phenols/thiophenols by using DMAP as a catalyst.

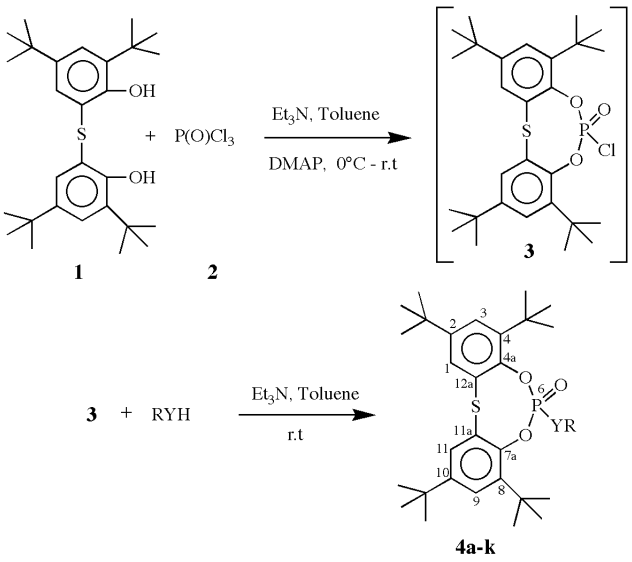
Results and Discussion.

In the first step, the eight membered ring monochloride (**3**) was prepared by cyclocondensation of 2,2'-thiobis(2,4-di-*t*-butylphenol) (**1**) with phosphorus oxychloride (**2**) in the presence of triethylamine in anhydrous toluene at room temperature by using catalytic amount of DMAP (Chart 1). Progress of the reaction was monitored by TLC analysis (ethyl acetate-hexane, 1:3). In the second step, the monochloride **3** was further reacted *in situ* with different bulky phenols/thiophenols under the same reaction conditions affording the title compounds **4**. We have already showed (**6**) that this procedure is more advantageous than the alternate one starting with phosphorodichloridate reagents.

All these reactions occurred at room temperature. Triethylamine was used in these reactions as a base to scavenge the liberated hydrogen chloride by forming its salts and the formed triethylammonium chloride was separated from the reaction mixture by filtration. In these reactions DMAP acts as a catalyst.

Product yields, elemental analysis, ir and ^{31}P nmr data of **4a-k** are given in Table 1. ^{1}H and ^{13}C nmr spectral data are provided in Table 2, 3 and 4. Compounds **4a-k** showed infrared absorption bands [7,8] in the regions 1214-1315 cm^{-1} for P=O. Bands at 919-971 and 1183-1226 cm^{-1} for P-O and O-C in P-O-$C_{aromatics}$ respectively were present in **4a-g**.

Scheme 1



Compd.	YR	Compd	YR
4a.	OC_6H_5	**4g.**	OC_6H_4-F(2')
4b.	OC_6H_4-CH_3(4')	**4h.**	SC_6H_4-Br(2')
4c.	OC_6H_3-$(CH_3)_2$(2'&6')	**4i.**	SC_6H_4-Br(3')
4d.	OC_6H_4-Cl(2')	**4j.**	SC_6H_4-Cl(4')
4e.	OC_6H_3-Cl_2(2'&4')	**4k.**	SC_6H_4-CH_3(4')
4f.	OC_6H-Cl_4(2',3',4'&6')		

^{1}H NMR spectra (Table 2) of dibenzodioxathiaphosphocin moiety exhibited two sets of signals at δ 7.51-7.60 and 7.30-7.44 for H(1&11) and H(3 & 9), respectively [6,8,9]. Some of these compounds showed coupling constants (J = 1.9-2.4 Hz) due to meta-coupling to each other. The protons of the 6-aryloxy/arylthio moieties gave the signals at δ 6.62-7.34; the signals due to aliphatic methyl protons for **4b, 4c** and **4k** appeared as singlets at δ 2.34, 2.22 and 3.09, respectively.

^{13}C nmr chemical shifts of dibenzodioxathiaphosphocin moieties were interpreted based on additivity rules, computed chemical shifts of **1**, carbon couplings with phosphorus and intensity of signals. The oxygen bearing C(4a) and C(7a) resonated as doublets in the down field region δ 149.8-151.9 ($^2J_{POC(4a,7a)}$ = 9.2-9.5 Hz) [6,8]. The chemical shifts of the bridged C(11a) and C(12a) appeared as low intensity signals at δ 119.8-124.8 ($^3J_{POCC(11a,12a)}$ = 2.6-5.8 Hz) [8,9]. The bulky *t*-butyl group attached to C(4) & C(8) and C(2) & C(10) showed signals in the regions δ 140.2-141.0 ($^3J_{POCC(4,8)}$ = 5.3-7.2 Hz) as doublets and δ 130.6-131.5 as singlets, respectively [9]. The doublet for C(4) & C(8) is due to interaction with phosphorus atom of the heterocyclic ring. ^{13}C nmr chemical shifts of C(4a & 7a) and C(11a & 12a) appeared downfield by 4-6 ppm when compared with the chemical shifts of **1**. This might be due to the deshielding effect of heterocyclic ring with P=O system [9]. The *t*-butyl carbons [-*C*-$(CH_3)_3$] attached to C(2 & 10)

Table 1

Physical, IR and ^{31}P NMR Data of 6-Substituted-2,4,8,10-tetra-*t*-butyldibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin 6-Oxides (**4a-k**)

Compd.	Mp (°C)	Yield (%)	Mol. Formula (Mol. weight)	Elemental Analysis (%) Calcd. (Found)		IR (cm^{-1}) (KBr)			^{31}P NMR [c] (ppm) (85% H_3PO_4)
				C	H	P=O	P-O-$C_{aromatic}$ P-O	O-C	
4a	168-170	92[a]	$C_{34}H_{45}O_4PS$ (580.77)	70.32 (70.10	7.81 7.69)	1310	971	1200	-17.56
4b	178-180	94[a]	$C_{35}H_{47}O_4PS$ (594.79)	70.68 (70.45	7.96 7.82)	1309	964	1199	-17.40
4c	260-261	91[b]	$C_{36}H_{49}O_4PS$ (608.82)	71.02 (70.85	8.11 8.03)	1309	963	1198	-9.99
4d	266-268	90[a]	$C_{34}H_{44}ClO_4PS$ (615.21)	66.38 (66.09	7.21 7.13)	1315	947	1217	-
4e	208-210	91[a]	$C_{34}H_{43}Cl_2O_4PS$ (649.66)	62.86 (62.91	6.67 6.57)	1214	967	1183	-
4f	201-203	89[a]	$C_{34}H_{41}Cl_4O_4PS$ (718.55)	56.83 (56.65	5.75 5.68)	1257	920	1212	-11.18
4g	242-243	92[b]	$C_{34}H_{44}FO_4PS$ (598.76)	68.20 (67.93	7.41 7.29)	1275	919	1226	-17.33
4h	220-222	90[b]	$C_{34}H_{44}BrO_3PS_2$ (675.73)	60.43 (60.15	6.56 6.46)	1266	639(P-S)	510 (S-C)	-10.75
4i	214-215	91[b]	$C_{34}H_{44}BrO_3PS_2$ (675.73)	60.43 (60.24	6.56 6.50)	1273	648(P-S)	516 (S-C)	-10.78
4j	184-186	90[a]	$C_{34}H_{44}ClO_3PS_2$ (631.28)	64.69 (64.47	7.02 6.91)	1253	653 (P-S)	566 (S-C)	-17.62
4k	220-222	89[a]	$C_{35}H_{47}O_4PS_2$ (626.86)	67.06 (67.12	7.56 7.44)	1275	646 (P-S)	515 (S-C)	-9.65

[a] Recrystalized from IPA; [b] Recrystalized from IPA + DCM. [c] ^{31}P NMR spectra not recorded for **4d** and **4e** [d] The minus symbol (-) indicates appearance of signal upfield.

Table 2

^{1}H NMR Spectral Data[a,b] of 6-Substituted-2,4,8,10-tetra-*t*-butyldibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin 6-Oxides (**4a-k**)

Comp.	H(1,11)	H(3,9)	$C(CH_3)_3$ (2,10)	$C(CH_3)_3$ (4,8)	2'	3'	4'	5'	6'	Ar-CH_3
4a	7.52 (d, 2.1)	7.40 (d, 2.2)	1.37	1.42	6.98-7.28 (5H, m, OAr-H)				-	
4b	7.57 (d, 2.3)	7.41	1.31	1.39	7.15 (d, 8.3)	7.28 (d, 8.2)	-	7.28 (d, 8.2)	7.15 (d, 8.3)	2.34 (3H, s, 4'-CH_3)
4c	7.55	7.35	1.28	1.46	-	6.94 (d, 7.5)	6.72	6.94 (d, 7.5)	-	2.22 [6H, s, 2' & 6'$(CH_3)_2$]
4d	7.51 (d, 2.5)	7.37 (d, 2.9)	1.24	1.30	7.05-7.34(4H, m, OAr-H)				-	
4e	7.51 (d, 1.9)	7.32 (d, 2.0)	1.24	1.30	7.18-7.28 (3H, m, OAr-H)				-	
4f	7.52	7.30 (d, 1.7)	1.28	1.46	-	-	-	7.27		-
4g	7.60	7.44	1.33	1.40	7.16- 7.28 (4H, m, OAr-H)				-	
4h	7.51 (d, 2.4)	7.33 (d, 2.0)	1.28	1.47	7.18-7.29 (4H, m, OAr-H)				-	
4i	7.51 (d, 2.4)	7.33	1.28	1.47	7.08-7.30 (4H, m, OAr-H)				-	
4j	7.59	7.42	1.31	1.38	7.3 (d, 9.0)	7.37	-	7.37	7.30 (d, 9.0)	-
4k	7.54 (d, 2.2)	7.34	1.28	1.46	6.92 (d, 7.0)	7.27	-	7.27	6.92 (d, 7.0)	3.09 (3H, s, 4'-CH_3)

[a] Data in parenthesis are coupling constants J_{H-H} (in Hz); [b] Measured in deuteriochloroform.

and C(4 & 8) exhibited signals at δ 34.4-34.7 and 35.3-35.4, respectively. The signals at δ 30.1-30.7 and 31.3-31.4 were ascribed for methyl carbons of *t*-butyl group [-C-(CH_3)$_3$] attached to C (2 & 10) and C(4 & 8), respectively [9]. The chemical shifts for the remaining carbons in dibenzodioxathiaphosphocin ring and phenoxy/thiophenoxy moieties were observed in the expected region (Table 3, 4). ^{31}P nmr signals for **4a-k** appeared in the region -17.62 to -9.65 ppm [10] (Table 1).

Antimicrobial Activity.

Compounds **4a-k** were screened for antibacterial activity [11] against the growth of *Staphylococcus aureus* (Gram +) and *Escherichia coli* (Gram -) at concentrations 250, 500 and 1000 ppm (Table 5). Most of these compounds exhibited significant and comparable antibacterial activity at all concentrations against both organisms. Penicillin was used as reference compound for comparing the antibacterial activity.

Table 3

^{13}C-NMR Spectral Data [a,b] of Dibenzodioxathiaphosphocin Moieties of **4**

Compd.	C(1,11)	C(2,10)	C(3,9)	C(4,8)	C(4a,7a)	C(11a,12a)	t-C(CH$_3$)$_3$ (2,10)	t-C(CH$_3$)$_3$ (2,10)	t-C(CH$_3$)$_3$ (4,8)	t-C(CH$_3$)$_3$ (4,8)
4a	129.6	131.0	126.4	140.3 (d, 7.1)	149.8 (d, 9.2)	124.8	34.4	30.3	35.4	31.3
4b	131.0	131.5	126.4	140.4 (d, 6.9)	149.9 (d, 9.3)	124.4 (d, 3.5)	34.7	30.2	35.4	31.3
4c	128.3	130.7	125.8	140.2	151.7 (d, 9.4)	123.3	34.4	30.6	35.4	31.4
4f	130.0	130.6	122.7	140.8 (d, 5.3)	151.7 (d, 9.4)	123.1	34.4	30.4	35.4	31.4
4g	126.5	130.9	124.4	140.4 (d, 7.2)	149.9 (d, 9.3)	121.9 (d, 2.6)	34.7	30.1	35.3	31.4
4h	127.5	130.6	125.4	140.7 (d, 5.4)	151.8 (d, 9.5)	119.8	34.4	30.6	35.4	31.4
4i	-	130.6	125.4	140.6 (d, 5.3)	151.7 (d, 9.4)	-	34.4	30.6	35.4	31.4
4j	129.6	131.0	126.5	140.2 (d, 7.0)	149.8 (d, 9.4)	121.3 (d, 5.8)	34.7	30.2	35.3	31.3
4k	127.8	130.8	125.0	141.0 (d, 5.3)	151.9 (d, 9.3)	120.2	34.4	30.7	35.4	31.4

[a] Data in parenthesis are coupling constants J_{P-C} (in Hz); [b] Measured in $CDCl_3$; [c] ^{13}C-NMR not recorded for **4d & 4e**.

Table 4

^{13}C-NMR Spectral Data [a,b] of 6-Aryloxy/Arylthio Moieties of **4**

Compd.	C(1')	C(2')	C(3')	C(4')	C(5')	C(6')	Ar-CH$_3$
4a	147.9	120.0 (d, 5.5)	129.2	124.2	129.2	120.0 (d, 5.5)	-
4b	148.2 (d, 7.5)	120.0 (d, 2.9)	130.3	135.3	130.3	120.0 (d, 2.9)	20.7 (4'-CH$_3$)
4c	141.0 (d, 5.4)	125.6	119.7	123.4	119.7	125.6	16.0 (2'& 6'-CH$_3$)
4f	149.6	127.9	125.5	140.1	120.8	125.6 (d, 3.3)	-
4g	148.0 (d, 7.0)	125.5 (d, 3.4)	124.1	124.3	-	117.0	-
4h	145.3	125.6	124.4	123.7	-	120.2	-
4i	145.2	125.5 (d, 3.2)	-	-	-	-	-
4j	148.1	124.2 (d, 3.5)	-	130.1	-	124.2 (d, 3.5)	-
4k	145.3	121.9	124.5	125.7 (d, 6.2)	124.5	124.7	39.9 (4'-CH$_3$)

[a] Measured in deuteriochloroform; [b] ^{13}C NMR not recorded for **4d & 4e**.

Similarly, their antifungal activity [12] was tested against the growth of *Aspergillus niger* and *Fusarium oxysporium* at the same concentrations (Table 5). Compounds **4a-f, 4h** and **4j** showed moderate activity against the both fungi at all concentrations. Some of them did not show any activity at the specified concentrations. Griseofulvin is used as standard to compare their antifungal activity. It is observed that halogen substituted compounds exhibited more antibacterial and antifungal activity.

EXPERIMENTAL

All reactions were carried out under anhydrous conditions in nitrogen atmosphere. Melting points were determined on Mel-Temp apparatus using open capillary tubes and are uncorrected. The ir spectra (ν_{max} cm^{-1}) were measured with a SHIMADZU-435/Perkin Elmer 1000 FT IR. All nmr spectra were taken on a BRUKER AC 300 spectrometer operating at 300 MHz for ^{1}H, 75.45 MHz for ^{13}C and 121.7 MHz for ^{31}P nmr. Chemical shifts are expressed in δ/ppm downfield from an internal standard tetramethyl silane (TMS) signal for ^{1}H and ^{13}C and 85% phosphoric acid as an external standard for ^{31}P nmr spectra. Microanalyses were performed at the Central Drug Research Institute (CDRI), Lucknow, India. Routine monitoring of TLC was carried out using pre-coated Kieselgel 60 F_{254} plates (E-Merck).

General Procedure for the Members of **4**.

6-(4'-Methylphenoxy)-2,4,8,10-tetra-*t*-butyldibenzo[*d,g*][1,3,6,2]-dioxathiaphosphocin 6-Oxide (**4b**).

To a cold (0 °C) and stirred solution of 2,2'-thiobis(2,4-di-*t*-butylphenol) (**1**, 2.06 g, 0.01 mole) and triethylamine (2.02 g, 0.02 mole) in dry toluene (40 ml) in the presence of catalytic amount (0.012 g) of DMAP was added dropwise in 20 min. to a solution of phosphorus oxychloride (**2**, 1.53 g, 0.01 mole) in the same solvent (20 ml). After completion of the addition, the reaction mixture was stirred at room temperature. Progress of the reaction was monitored by tlc (ethyl acetate:hexane, 1:3 v/v). When the monochloride **3** formation was completed as indicated

Table 5

Antibacterial and Antifungal Activity of **4a-k**

Compd.	Concentration (ppm)	Zone of inhibition (mm)			
		Bacteria		Fungi	
		Staphylococcus aureus	*Escherichia coli*	*Aspergillus niger*	*Fusarium oxysporium*
4a	250	7	9	-	-
	500	8	11	-	-
	1000	10	13	-	-
4b	250	8	7	-	-
	500	9	10	-	-
	1000	12	13	-	-
4c	250	6	8	-	-
	500	7	10	-	-
	1000	9	13	-	-
4d	250	7	9	6	7
	500	8	12	8	8
	1000	10	14	10	12
4e	250	8	11	8	7
	500	10	13	9	8
	1000	13	15	11	12
4f	250	11	12	8	7
	500	12	14	10	9
	1000	15	17	13	14
4g	250	8	7	-	-
	500	10	8	-	-
	1000	11	9	-	-
4h	250	7	9	6	7
	500	10	10	7	8
	1000	13	12	10	9
4i	250	9	7	-	-
	500	10	9	-	-
	1000	13	11	-	-
4j	250	7	7	-	7
	500	8	9	-	8
	1000	10	10	-	9
4k	250	6	7	-	-
	500	7	8	-	-
	1000	9	10	-	-
	Penicillin	24	28	-	-
	Griseofulvin	-	-	32	34

- Indicates no activity.

by tlc (30 min.) the reaction mixture was filtered to separate triethylamine hydrochloride. The filtrate was cooled to 0 °C and a solution of 4-methylphenol (1.08 g, 0.01 mole) and triethylamine (1.01 g, 0.01 mole) in dry toluene (25 ml) were added to it. After an additional hour of stirring at room temperature, on completion of the reaction as indicated by tlc analyses the reaction mixture was filtered and the solvent was roto-evaporated. The residue after washing with water followed by chilled 2-propanol was recrystallized from 2-propanol to obtain pure **4b**, 2.61 g, (94%), mp 178-180 °C. The physical and spectral data for **4a-k** are given in Tables 1-4. Other members of the compounds were prepared by adopting this procedure.

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