A FACILE SYNTHESIS, SPECTRAL (IR, ^1H, ^{13}C & ^{31}P NMR) CHARACTERISTICS AND ANTIMICROBIAL ACTIVITY OF 6-ARYLOXY/ ARYLTHIO/ALKYLAMINO DIBENZO [d,*f*][1,3,2]-DIOXAPHOSPHEPIN 6-SULFIDES

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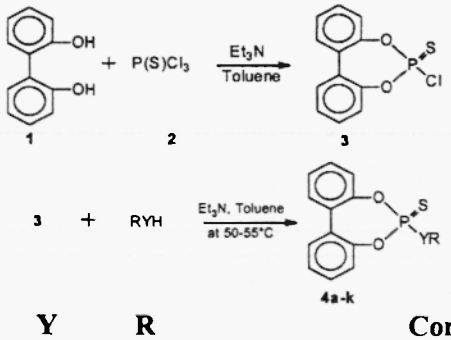
Abstract : A series of 6-aryloxy/arylthio/alkylamino dibenzo[d,f][1,3,2]-dioxaphosphepin 6-sulfides (4) were synthesized with a two step process with moderate yields starting from 2,2N-dihydroxybiphenyl (1) and thiophosphoryl chloride (2). Initially, the intermediate 6-cnloro dibenzo[d,f][1,3,2]-dioxaphosphepin 6-sulfide (3) was obtained which on subsequent reaction with substituted phenols/thiophenols/ alkylamines in the presence of triethylamine at 50-55°C in dry toluene afforded members of 4. Their chemical structures were confirmed by elemental, IR and ^1H, ^{13}C, ^{31}P NMR spectral data analysis. The compounds were screened for antifungal activity against *Curvularia lunata* and *Aspergillus niger* and for antibacterial activity against *Bacillus subtilis* and *Escherichia coli*. Some of them possessed significant activity.

Introduction

Most of the organophosphorus esters are potential pesticides[1]. Dibenzodioxaphosphocins and dioxathiaphosphocins have been used as antioxidants[2-3] and superior ligands[4]. In our endeavour to develop high potency pesticides and antimicrobial compounds, a series of 6-aryloxy/arylthio/ alkyl-amino dibenzo[*d,f*][1,3,2]-dioxaphosphepin 6-sulfides (4a-k) were synthesized in a two-step process. First, the intermediate 6-chloro dibenzo[*d,f*] [1,3,2]-dioxaphosphepin 6-sulfide (3) was prepared from 2,2N-dihydroxy-biphenyl (1) and thiophosphorylchloride (2). In the second step, 3 was reacted with various substituted phenols/thiophenols/alkylamines in the presence of triethylamine in dry toluene medium. Their structures were established by elemental, IR and ^1H, ^{13}C & ^{31}P NMR spectral data analysis. These compounds were tested for their bio-activity and some of them possessed significant antimicrobial activity.

Results and Discussion

The synthesis of 6-chloro dibenzo[*d,f*][1,3,2]-dioxaphosphepin 6-sulfide (3) was achieved by reacting 2,2N-dihydroxybiphenyl (1) with thiophosphoryl chloride (2) in the presence of triethylamine in dry toluene at 40-45°C (Scheme 1). The intermediate monochloride 3 was reacted in the same vessel *in situ* and under the same conditions with various substituted phenols/ thio-phenols/alkylamines at 50-55°C to afford compounds 4a-k.



Compd.	Y	R	Compd.	Y	R
4a	O	C_6H_4-Cl(2N)	4g	O	C_6H_4-NO_2(4N)
4b	O	C_6H_4-Cl(3N)	4h	S	C_6H_5
4c	O	C_6H_3-Cl_2(2N,4N)	4i	S	C_6H_4-Cl(4N)
4d	O	C_6H-Cl_4(2N,3N,4N,6N)	4j	N	$(CH_2CH_2CH_2CH_3)_2$
4e	O	C_6H_4-CH_3(4N)	4k	NH	C_6H_{11}
4f	O	C_6H_4-$C(CH_3)_3$(4N)			

SCHEME 1

Their synthetic and IR data of 4a-k were given in Table 1. All members of 4 exhibited characteristic IR absorptions in the regions 751-778 cm^{-1} for (P=S) and 937-949 & 1189-1193 cm^{-1} for (P-O-$C_{aromatic}$) in 4a-g[5-7].

Table 2 contains the ^{1}H NMR chemical shifts for 4a-k and ^{31}P NMR data for some of the compounds. The proton NMR spectra showed complex multiplets at δ 7.18-8.31 for aromatic protons of dibenzodioxaphosphepin system in 4a-k and 6-aryloxy/arylthio moieties in 4a-i[8,9]. The distinction of the signals for the protons of dibenzodioxaphosphepin moiety and 6-aryloxy/arylthio moiety could not be made due to their identical environment. The other alkyl proton signals in 4j & 4k are observed in the expected region (Table 2). In 4k, the broad signal was observed at δ 4.02 due to NH proton of cyclohexylamine moiety. The methyl and *tert*-butyl protons of the phenoxy moieties in 4e and 4f resonated at δ 2.34 and δ 1.33 respectively as singlets.

The ^{13}C NMR data (Table 3) of 4 was interpreted based on additivity rules, C-P couplings and signal intensities. The oxygen-bearing C(4a) and C(7a) resonated in the downfield at δ 138.1-150.0[10]. The doublet at δ 120.5-123.1 [$^{3}J_{(POCC-4,8)}$ = 2.0-6.0 Hz] was attributed to C(4) and C(8). Their signal appeared as a doublet due to their long range coupling with phosphorus[11]. Chemical shifts of the bridged C(12) and C(13) appeared at δ 128.3-130.2 [$^{3}J_{(POCC-12,13)}$ = 2.0-3.2 Hz][11]. The doublets observed in the region δ 126.9-129.3 [^{5}J = 2.0-4.6 Hz] and δ 128.8-132.0 [$^{4}J_{(POCCC-1,11)}$ = 1.6-3.1 Hz] were attributed to C(2), C(10) and C(1), C(11), respectively[12].

The carbon chemical shifts of the 6-aryloxy (4a-g), arylthio (4h-i) and alkylamino (4j-k) groups were presented in Table 4. In 4a-i, the low intensity signal at δ 148.1-151.8 was assigned to C(1N) which was attached to an oxygen atom[10]. The C(2N) and C(6N) signals occurred in the region δ 121.7-130.4 [$^{3}J_{(POCC-2N,6N)}$ = 2.3-7.6 Hz]. C(3N) and C(5N) chemical shifts were observed as doublets in the region δ 127.2-131.5 [$^{4}J_{(POCCC-3N,5N)}$ = 1.6-3.6 Hz]. The resonance signal at δ 124.9-127.7 was ascribed to C(4N). In 4j the signals observed at δ 47.2, 27.4, 19.5 and 13.2 are due to alkyl C(1N)-(4N), respectively[13]. Similarly, in 4k the low intensity signal at δ 50.9 ascribed for C(1N). The doublets observed at δ36.1 [$^{3}J_{(PNCC-2N,6N)}$ = 4.5 Hz] and δ 25.4 [$^{4}J_{(PNCCC-3N,5N)}$ = 19.5 Hz)] for C(2N) & C(6N) and C(3N) & C(5N) respectively. The upfield low intensity signal ascribed for C(4N)[13].

The ^{31}P NMR peaks (Table 2) were observed in the range of 55.14-68.72 ppm with respect to 85% phosphoric acid. In 4f & 4k, the two resonance signals in ^{31}P NMR spectrum may be due to the presence of two conformers[14].

Antimicrobial Activity

All the dibenzodioxaphosphepin 6-sulfides were tested for their antifungal activity at two different concentrations (500 and 1000 ppm) following Benson technique[15] against *Aspergillus niger* and *Curvularia lunata* (Table 5). Their antibacterial activity was evaluated on *Bacillus subtilis* and *Escherichia coli* by the method of Vincent and Vincent[16]. Some of the compounds exhibits moderate toxicity against both the fungi and bacteria.

Experimental

Melting points were determined in the open capillary tubes on a Mel-temp apparatus and were uncorrected. Microanalyses were performed by the Central Drug Research Institute, Lucknow, India. Their IR spectra (ν_{max} in cm^{-1}) were recorded as KBr pellets on a Perkin-Elmer 1000 unit. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer operating at 400 MHz for H-1 and 100 MHz for C-13. ^{31}P NMR spectra were recorded on a amx 400 spectrometer operating at 161.98 MHz. All NMR data were taken in deuteriochloroform and were referenced to tetramethylsilane (^{1}H and ^{13}C) or 85% phosphoric acid (^{31}P).

6-(2N,4N-dichlorophenoxy)dibenzo[d,f][1,3,2]-dioxaphosphepin 6-sulfide (4a)

A solution of thiophosphoryl chloride (0.51 g, 0.003 mol) in dry toluene (20 mL) was added dropwise over a period of twenty minutes to a cooled (0°C) and stirred solution of 2,2N-dihydroxybiphenyl (1, 0.56 g, 0.003 mol) and triethylamine (0.61 g, 0.006 mol) in dry toluene (25 mL). After the addition, the temperature of the reaction mixture was slowly raised to room temperature and was maintained there for 2 hours. Stirring was continued for another 3 hours at 40-45°C. Formation of the intermediate, 6-chloro dibenzo[*d,f*][1,3,2]-dioxaphosphepin 6-sulfide (3) was monitored by thin layer chromatography (TLC) analyses.

Table 1 : Physical and IR spectral data of 6-aryloxy/arylthio/alkylamino dibenzo [*d,f*][1,3,2]-dioxaphosphepin 6-sulfides (4a-k)

Com-pound	Yield[a] (%)	mp (°C)	Mol. Formula	Elemental Analyses Calcd / Found		IR (Cm^{-1})		
						P=S	P-O-$C_{aromatic}$	
				C	H		P-O	O-C
4a	58	90-92	$C_{18}H_{12}O_3ClPS$	57.69 57.56	3.23 3.12	752	938	1190
4b	60	115-117	$C_{18}H_{12}O_3ClPS$	57.69 57.82	3.23 3.32	759	940	1189
4c	54	98-101	$C_{18}H_{11}O_3Cl_2PS$	52.83 52.70	2.71 2.61	752	937	1190
4d	48	100-102	$C_{18}H_9O_3Cl_4PS$	45.22 45.09	1.90 1.78	752	939	1191
4e	70	96-98	$C_{18}H_{15}O_3PS$	64.40 64.54	4.27 4.35	755	949	1178
4f	68	88-90	$C_{22}H_{21}O_3PS$	66.65 66.53	5.34 5.22	751	937	1193
4g	55	126-128	$C_{18}H_{12}O_5NPS$	56.11 55.98	3.14 3.03	752	940	1191
4h	50	104-106	$C_{18}H_{13}O_2PS_2$	60.66 60.74	3.68 3.77	752	601(P-S)	541(S-C)
4i	45	87-90	$C_{18}H_{12}O_2ClPS_2$	55.32 55.20	3.09 2.98	751	606(P-S)	542(S-C)
4j	70	112-114	$C_{20}H_{26}O_2NPS$	63.98 63.82	6.98 6.88	778	1096(P-N)	712(N-C)
4k	78	93-95	$C_{18}H_{20}O_2NPS$	62.59 62.43	5.84 5.72	774	1093(P-N)	715(N-C)

[a]Recrystallized from isopropanol, reported yields are after one recrystallization

Table 2 : ^1H and ^{31}P NMR chemical shift data[a,b,d] of 6-aryloxy/arylthio/ alkylamino dibenzo[*d,f*][1,3,2]-dioxaphosphepin 6-sulfides (4a-k)

Compound	Aromatic-H & OAr-H	O-Ar-CH_3	^{31}P NMR Data[c] ppm
4a	7.31-7.56 (m, 12H)	-	68.72
4b	7.30-7.60 (m, 12H)	-	64.12
4c	7.32-7.59 (m, 11H)	-	63.60
4d	7.32-7.59 (m, 9H)	-	X
4e	7.18-7.60 (m, 12H)	2.34 (s, 3H)	64.80
4f	7.21-7.59 (m, 12H)	1.33 (s, 9H)	64.39, 55.95
4g	7.34-8.31 (m, 12H)		64.22
4h	7.29-7.58 (m, 13H)		X
4i	7.32-8.02 (m, 12H)		64.50
4j	7.19-7.61 (m, 8H)	2.72 (t, 4H, $N(CH_2)_2$) 1.62-1.72 (m, 4H, $(CH_2)_2$) 1.24-1.35 (m, 4H, $(CH_2)_2$) 0.89 (t, 3H, $(CH_3)_2$)	63.49
4k	7.31-7.59 (m, 8H)	4.02 (brs, 1H, NH) 3.09-3.12 (m, 1H, N-CH) 1.06-1.97 (m, 10H, N-C_6H_{11})	63.23, 55.14

[a]Chemical shifts in δ values
[b]Recorded in Deuteriochloroform
[c]Chemical shifts in ppm from 85% phosphoric acid
[d] ^{31}p NMR not recorded for **4d** & **4h**

Table 3 : ^{13}C NMR chemical shift (J in Hz) data[a,b] of dibenzo [*d,f*][1,3,2]-dioxaphosphepin 6-sulfides (4a-k)

Compound	C(1/11)	C(2/10)	C(3/9)	C(4/8)	C(12/13)	C(4a/7a)
4a	130.2 (3.1)	127.2 (4.6)	130.3	121.8 (6.0)	128.8	148.0
4b	131.7	127.2 (3.0)	138.0	122.1 (2.2)	130.2 (2.4)	147.2
4c	130.0	127.4 (3.8)	130.1 (1.8)	121.7 (3.4)	128.5 (2.3)	145.7 (5.7)
4d	132.0 (1.6)	127.5 (3.3)	132.1 (2.1)	123.1 (2.0)	129.2 (2.4)	150.0
4e	130.2	126.6 (2.3)	135.5	120.6 (4.6)	129.9 (2.0)	148.2 (10.3)
4f	130.1	127.0 (2.3)	130.2 (2.3)	120.5 (5.6)	128.9 (2.3)	X
4g	130.7 (1.7)	127.7 (2.4)	138.2	122.3 (4.6)	129.3 (2.1)	148.5
4h	130.6 (1.9)	127.6 (2.4)	136.5	122.3 (4.5)	129.3 (2.1)	148.5
4i	130.6 (1.9)	129.3 (2.0)	137.6 (4.9)	122.3 (4.6)	130.0 (3.2)	138.1 (4.5)
4j	128.8	126.9 (2.3)	129.8 (7.9)	121.3 (4.6)	128.3 (2.3)	147.6
4k	129.5	127.2 (2.3)	130.1 (7.9)	121.8 (4.6)	128.8 (2.3)	148.2 (6.2)

[a]Chemical shifts in ppm and coupling constants J (Hz) given in parenthesis.
[b]Recorded in Deteriochloroform

Table 4 : ^{13}C NMR chemical shift (J in Hz) data[a,b] of 6-aryloxy/arylthio/alkylamino moieties in 4a-k

Compound	C(1N)	C(2N)	C(3N)	C(4N)	C(5N)	C(6N)	C-CH_3
4a	148.2	-	130.1	125.8	130.1	122.2	
4b	151.8	122.8 (4.0)	130.5 (3.6)	124.9	-	122.8 (4.0)	
4c	148.1 (12.6)	130.4	131.5 (2.4)	126.8 (2.3)	127.9	123.4 (3.5)	
4d	150.2	123.8 (4.6)	130.8 (1.7)	125.2	-	123.8 (4.6)	
4e	148.4 (6.8)	121.7 (3.4)	128.9 (1.9)	X	128.9 (1.9)	121.7 (3.4)	20.8
4f	148.2 (13.7)	121.9 (4.6)	127.2 (2.3)	126.7	127.2 (2.3)	121.9 (4.6)	34.5 (4N-t-C) 31.3 (4N-C-$(CH_3)_3$
4g	148.7	124.4	130.5 (1.7)	126.3	130.5 (1.7)	124.4	
4h	148.7	123.7 (3.2)	130.5 (1.6)	126.5	130.5 (1.6)	123.7 (3.2)	
4i	148.6 (13.5)	126.9 (7.6)	130.5 (1.6)	127.7 (2.7)	130.5 (1.6)	126.9 (7.6)	
4j	47.2	27.4	19.5	13.2			
4k	50.9	36.1 (4.5)	25.4 (19.5)	24.4	25.4 (19.5)	36.1 (4.5)	

[a]Chemical shifts in ppm and coupling constants, J (Hz) given in parenthesis.
[b]Recorded in Deuterochloroform

Table 5 : Antimicrobial activity of 6-substituted dibenzo[*d,f*][1,3,2]-dioxaphosphepin 6-sulfides (4a-k)

Compound	Zone of inhibition (mm)							
	Fungi				Bacteria			
	Curvularia lunata		*Aspergillus niger*		*Bacillus subtilis*		*Escherichia coli*	
	500	1000	500	1000	500	1000	500	1000
4a	6	12	8	12	4	7	5	9
4b	6	10	7	10	4	6	7	12
4c	8	15	12	20	7	10	6	11
4d	10	17	11	18	5	9	6	12
4e	X	X	X	X	X	X	X	X
4f	X	X	X	X	X	X	X	X
4g	11	19	8	14	8	15	11	18
4h	X	X	X	X	X	X	X	X
4i	6	11	7	10	6	10	6	11
4j	8	13	7	10	9	16	6	10
4k	11	19	9	17	8	15	7	13

concentration in ppm ; "X" indicates no activity

To a cooled (0°C) solution of 3 was added dropwise a solution of 2,4-dichlorophenol (0.49 g, 0.003 mol) and triethylamine (0.3 g, 0.003 mol) in dry toluene (20 mL). After the addition, the reaction mixture was stirred at room temperature for 2 hours, and then at 50-55°C for another 5 hours. Progress of the reaction was monitored by TLC. Solid triethylamine hydrochloride formed was filtered off and the solvent was evaporated under reduced pressure. The residue was washed with water followed by 40% 2-propanol. Recrystallization of the solid product from 2-propanol to afforded 0.66 g (54%) of 4c, m.p. 98-101°C. Physical and Spectral data of 4c are given in Tables 1-4. Other members of 4 were prepared by this procedure.

Acknowledgements

The authors express their thanks to Professor C. Devendranath Reddy, Department of Chemistry, Sri Venkateswara University, Tirupati for fruitful discussions, Central Drug Research Institute, Lucknow, India for elemental analyses and Indian Institute of Science, Bangalore for spectral recording. One of the author (KAK) is thankful to CSIR for awarding Senior Research Fellowship.

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Received on September 13, 2002