Synthesis of 3-(Substituted)-2,4,8,15-tetroxa-3-phosphadispiro[5.2.5]hexadecane-3-oxides

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Novel 3-(substituted)-2,4,8,15-tetroxa-3-phosphadispiro[5.2.5]hexadecane-3-oxides (**3-12**) have been synthesized by cyclization of 1,5-dioxaspiro[5.5]undecande-3,3-dimethanol (**1**) with various substituted aryl phosphorus dichloridates (**2**) in dry toluene-THF in the presence of triethylamine at 40-60 °C. Their molecular structures were determined by ir, nmr and mass spectral studies and were screened for antifungal activity against *Curvularia lunata* and *Aspergillus niger*, and antibacterial activity on *Staphylococcus aureus* and *Escherichia coli*. Most of them possess significant activity.

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Introduction.

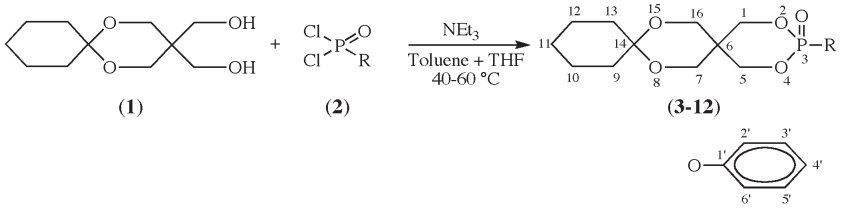
Our research interest has been focused on the development of new synthetic methodology centered around biologically active phosphorus heterocycles [1] because functionalized phosphorus heterocycles and their derivatives are bioactive substances of great interest [2,3]. Cyclophosphamide and 1,3,2-dioxaphosphorinane 2–oxides are potential anticancer agents [4-6]. In addition cyclic phosphonate derivatives have been employed as anti-hypertensive agents [7], biocatalysts [8] and antibodies that catalyze the enantioselective aminolysis of lactones [9]. P(V)-Six membered heterocycles play a central role in the regulation of cell physiology [10]. Industrially they are good flame retardants [11], and stabilizers in alkyl resins and vinyl plastics [13]. They are excellent synthetic precursors as well [12]. In view of their multifaceted applications, synthesis of some phosphadispiro hexadecane 3-oxides have been accomplished.

Results and Discussion.

Cyclization of 1,5-dioxaspiro[5.5]undecande-3,3-dimethanol (**1**) [14] with various substituted arylphosphorodichloridates (**2**) [15] was accomplished by the condensation of their equimolar quantities in dry toluene - tetrahydrofuran mixture (3:1) in the presence of triethylamine at 40-60 °C (Scheme 1). The progress of the reaction was monitored by thin layer chromatographic (TLC) analysis of the reaction mixture at different time intervals. Solid triethylamine hydrochloride was removed by filtration. The reaction products (**3-12**) were isolated from the filtrate by removing the solvent in a rotary evaporator and recrystallizing the residue after washing with water. Reaction yields, elemental analysis, ir [16] and ^{31}P nmr data are given in Table 1. ^{1}H, ^{13}C nmr and mass spectral data (**3, 4, 5** and **11**) for these compounds (**3-12**) are presented in Tables 2, 3, and 4, respectively.

The aromatic protons of the aryloxy moiety exhibited chemical shifts in the δ 6.6-7.8 range [17]. In compounds **3-12** the $H_a(1)$, $H_a(5)$ and $H_e(1)$, $H_e(5)$ protons resonated as two multiplets at δ 3.33-3.64 and δ 3.89-4.12 respectively [18-20]. This indicates that the methylene protons at C_1 and C_5 are magnetically non-equivalent due to their equatorial and axial orientations in the six-membered chair conformation of the dioxaphosphorinane ring (Figure 1).

Scheme 1



Compd.	R	Compd.	R
3	4′-$CH_3C_6H_4O$	**8**	C_6H_5O
4	4′-ClC_6H_4O	**9**	2′-3′-$(CH_3)_2C_6H_3O$
5	4′-H_3CO-C_6H_4O	**10**	2′-4′-$(CH_3)_2C_6H_3O$
6	$C_{10}H_7O$	**11**	2′-$(EtOOC)C_6H_4O$
7	4′-$NO_2C_6H_4O$	**12**	2′-ClC_6H_4O

Table 1

Physical, IR and ^{31}P NMR spectral data of Synthesis of 3-(substituted)-2,4,8,15-tetroxa-3-phosphadispiro[5.2.5]hexadecane-3-oxides (**3-12**).

Compd.	m.p °C	Yield (%)	Molecular formula	Elemental analysis Found (Calcd) C	H	IR (cm^{-1}) P=O	P-O-$C_{aliphatic}$	P-O-$C_{aromatic}$ P-O	O-C	^{31}P NMR
3	190	70	$C_{18}H_{25}O_6P$	58.43 (58.69)	6.76 (6.79)	1317	1160	985	1253	-18, 33
4	179-180	68	$C_{17}H_{22}O_6PCl$	52.34 (52.57)	5.63 (5.67)	1299	1152	926	1208	-11.01, -11.42
5	185	71	$C_{18}H_{25}O_7P$	55.99 (56.25)	6.46 (6.51)	1318	1160	987	1253	-20.67
6	161	58	$C_{21}H_{25}O_6P$	62.08 (62.37)	6.15 (6.18)	1322	1176	990	1267	-17.23
7	194	63	$C_{17}H_{22}O_8NP$	50.88 (51.12)	5.48 (5.51)	1295	1148	983	1252	-16.81
8	174-176	65	$C_{17}H_{23}O_6P$	57.38 (57.62)	6.45 (6.49)	1310	1150	994	1257	-16.52
9	178-179	60	$C_{19}H_{27}O_6P$	59.44 (59.68)	7.03 (7.06)	1320	1147	990	1248	-16.02
10	179-180	63	$C_{19}H_{27}O_6P$	59.42 (59.68)	7.01 (7.06)	1286	1127	983	1251	-15.86
11	172	49	$C_{20}H_{27}O_8P$	59.10 (56.33)	6.30 (6.33)	1316	1160	988	1264	-20.62
12	180-181	64	$C_{17}H_{22}O_6PCl$	52.38 (52.57)	5.63 (5.67)	1308	1145	985	1257	-17.12

Table 2

^1H NMR Chemical Shifts (J in Hz) Data of **3-12** [a]

Compd.	Cyclohexyl-H H(10), H (11) & H(12)	H(9) & H(13)	Equatorial-H H(1) & H(5)	Axial-H H(1)&H(5)	H(7)&H(16)	Aryl moiety-H
3	1.23-1.62 (m, 6H)	1.63-1.93 (m, 4H)	3.52 (s, 2H)	4.06 (s, 2H)	4.44-4.62 (m, 4H)	6.6-7.3 (m, 4H) 2.28 (s,3H, CH_3)
4	1.25-1.70 (m, 6H)	1.70-1.81 (m, 4H)	3.37 (m, 2H)	4.01 (s, 2H)	4.31 (d, $2H_a$) 4.44-4.95 (m, $2H_e$)	7.22 (d, 2H), 7.30 (d, 2H)
5	1.33-1.51 (m, 6H)	1.64-1.92 (m, 4H)	3.47 (m, 2H)	4.04 (s, 2H)	4.41-4.59 (m, 4H)	6.87-7.83 (m, 4H) 3.73 (s, 3H, OCH_3)
6	1.28-1.68 (m, 6H)	1.67-1.90 (m, 4H)	3.57 (s, 2H)	3.98 (s, 2H)	4.37-4.78 (m, 4H)	6.85-7.72 (m, 7H)
7	1.27-1.71 (m, 6H)	1.65-1.93 (m, 4H)	3.42 (m, 2H)	4.11 (m, 2H)	4.46-4.93 (m, 4H)	7.12-7.14 (d, 2H), 8.21-8.29 (d, 2H)
8	1.21-1.59 (m, 6H)	1.60-1.81 (m, 4H)	3.33 (m, 2H)	3.89 (m, 2H)	4.28-4.81 (m, 4H)	6.89-7.27 (m, 5H)
9	1.24-1.63 (m, 6H)	1.67-1.98 (m, 4H)	3.62 (s, 2H)	3.94 (s, 2H)	4.41-4.71 (m, 4H)	6.98-7.10 7.21-7.32 (m, 3H) 2.31 (s, 3H, CH_3) 2.25 (s, 3H, CH_3)
10	1.23-1.64 (m, 6H)	1.65-1.97 (m, 4H)	3.48 (s, 2H)	3.99 (s, 2H)	4.42-4.84 (m, 4H)	6.86-7.08, 7.31-7.38 (m, 3H) 2.32 (s, 3H, CH_3), 2.28 (s, 3H, CH_3)
11	1.26-1.54 (m, 6H)	1.61-1.81 (m, 4H)	3.64 (s, 2H)	3.97 (s, 2H)	4.42-4.61 (m, 4H)	7.35 (d, 2H), 7.54 (d, 2H) 4.56 (q, 2H, OCH_2), 1.19 (t, 3H, CH_3)
12	1.27-1.72 (m, 6H)	1.69-1.83 (m, 4H)	3.52 (m, 2H)	4.12 (m, 2H)	4.38-4.93 (m, 4H)	7.20-7.63 (m, 4H)

[a] Recorded in $CDCl_3$

Table 3

^{13}C NMR chemical shift data [a] of compounds Synthesis of 3-(substituted)-2,4,8,15-tetroxa-3-phosphadispiro[5.2.5]hexadecane-3-oxides (**3-12**)

Compd	C-1	C-5	C-6	C-7	C-9	C-10	C-11	C-12	C-13	C-14	C-16	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	Methyl Carbons
3	72.6	72.6	34.1	60.1	31.9	22	25	22	31.9	98.3	59.4	148.6	120.4	130.8	136.3	130.8	120.4	20
4	72.1	71.8	34.1	60.2	31.9	22	25	22	31.9	98.3	59.5	148.6	121.7	129.9	130.2	129.4	121.5	-
5	73.2	73.2	34.9	61.4	32.2	22.4	25.4	22.4	32.2	99.4	60.5	148.6	115.9	119.8	157.8	119.8	115.9	53.7
7	72.4	72.4	35.1	61.5	32.3	22.6	25.7	22.3	32.3	98.7	60.7	149.5	129.1 (d, J = 4.4)	125.2	145.1	126.3	129.1 (d, 4.4)	-
8	73.2	73.2	34.8	60.0	31.8	22.4	25.3	22.4	31.6	98.0	6.0	149.8 (d, J = 8.2)	119.3 (d, J = 5.0)	128.4	126.1	128.4	119.3 (d, J = 5.0)	-
9	72.5	72.3	34.2	61.3	31.3	22.2	25.1	22.2	31.1	98.7	61.1	147.2	127.5	137.8	126.1	127.6	118.6	12.8 & 20.3 (C-2' & 3')
10	71.9	71.1	33.9	60.1	30.7	22.2	25.2	22.2	30.5	98.4	59.8	146.7 (d, 7.6)	128.3	130.4	134.5	127.1 (d, 4.6)	119.3 (d, 6.7)	17.8 & 20.8 (C-2' & 4')
11	71.7	70.8	34.9	61.4	32.4	22.5	25.6	22.4	32.2	99.2	60.5	151.6	117.5	135.5	119.0	131.2	129.8	168.0 (C=O) 63.3(OCH_3) 14.1 (CH_3)
12	72.7	72.3	34.6	61.7	32.3	22.6	25.8	22.6	32.7	99.1	60.9	148.4 (d, 7.4)	129.1	127.9	126.3	132.5	120.4	-

[a] Data in parentheses are coupling constants, J in Hz; [b] Recorded in $CDCl_3$.

The multiplets in the region δ 4.28-4.95, are attributed to the H(7) and H(16) protons [14]. The cyclohexyl protons resonated as multiplets at δ 1.21-1.98 [18].

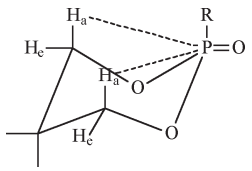


Figure 1

In the proton - decoupled ^{13}C nmr [14,18,21,22] the C-1, C-5 and C-7, C-16 resonated at δ 70.8-73.2 and δ 59.4-61.7 respectively. The signal of C-14 appeared down field at δ 98.0-99.4 while that of C-16 appeared upfield at δ 33.9-35.1. The cyclohexyl carbons exhibited signals in the expected range. The oxygen bearing C-1′ of aryloxy moiety resonated in downfield at δ 146.7-151.6. ^{31}P nmr chemical shifts of these compounds (**3-12**) appeared in the region -11.42 to -20.67 ppm [23].

Presence of ions at appropriate m/z corresponding to the molecular ion of compounds **3**, **4**, **5** and **11** confirm their structures [14,24]. Although the fragmentation pattern is complex, it is possible to glean information on the structure of **3** *via* the presence of major ions at m/z 353 and m/z 325 for the $[M^+-CH_3]$ and $[M^+-C_3H_7]$ respectively. Similarly, **4** had high intensity peak patterns for M^++2, and C_3H_7 fragments at m/z 345 and m/z 43 respectively. In **5**, the major ion at m/z 212 resulted from the $H_2PO_2C_6H_4OCH_3$ fragment. The ion at m/z 353 was attributed to the $[M-C_2H_5COO^{\bullet}]^+$ in **11**.

Antimicrobial Activity.

Compounds **3-12** and standard antifungal Griseofulvin were screened for their antifungal activity against *Curvularia lunata* and *Aspergillus niger*. Agar-cup method [25] was used for screening the activity of these compounds at two different concentrations (250, 500 µg/disc). Their antibacterial activity was evaluated according to disc - diffusion method [26,27] at two different concentrations against *Staphylococcus aureus* and *Escherichia coli* and their activity compared with the standards Penicillin. The title compounds showed significant antifungal and antibacterial activity (Table 5).

EXPERIMENTAL

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 283 unit. The ^1H, ^{13}C and ^{31}P

Table 4

Mass Spectral Data of **3**, **4**, **5** and **11**

Compd.	m/z (relative abundance)
3	367 ($M^{+\cdot}$, 23), 353 (36), 325 (48), 278 (44), 235 (28), 212 (54), 188 (32), 181 (14), 151 (12), 133 (20), 108 (82), 83 (100), 55 (90)
4	388 (($M^{+\cdot}$, 28), (M^{+} +2, 12)), 359 (14), 345 (100), 289 (5), 260 (4), 209 (3),181 (16), 128 (22), 111 (2), 99 (18), 83 (27), 55 (76)
5	384 ($M^{+\cdot}$, 42), 342 (27), 328 (18), 277 (13), 286 (32), 212 (48), 204 (42), 186 (23), 123 (44), 99 (18), 83 (22), 55 (14)
11	426 ($M^{+\cdot}$, 22), 384 (12), 370 (14), 381 (28), 353 (36), 278 (12), 212 (42), 183 (8), 164 (30), 148 (22), 99 (11)

1.63-1.93 [m, 4H, H(9) and H(13)], 2.28 (s, 3H, CH_3), 3.52 [s, 2H, H(1) and $H(5)_{equatorial}$], 4.06 [s, 2H, H(1) & $H(5)_{axial}$], 4.44-4.62 [m, 4H, H(7) and H(16)], 6.63-7.35 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$) δ: 20 (C-7′), 22 (C-10 and 12), 25 (C-11), 31.9 (C-9 and 13), 34.1 (C-6), 59.4 (C-16), 60.1 (C-7), 72.6 (C-1 and 5), 98.3 (C-14), 120.4 (C-2′ and 6′), 130.8 (C-3′ and 5′), 136.3 (C-4′), 148.6 (C-1′); ^{31}P NMR ($CDCl_3$) δ: -18.33 ppm; MS m/z (%): 367 (M^{+}-1, 23), 353 (36), 325 (48), 278 (44), 235 (28), 212 (54), 188 (32), 181 (14), 151 (12), 133 (20), 108 (82), 83 (100).

Anal. Calcd. for $C_{18}H_{27}O_6P$: C, 58.37, H, 7.29. Found: C, 58.08; H, 7.26.

Table 5

Antimicrobial Activity of **3-12**

Compd.	Zone of inhibition (mm)							
	Bacteria				Fungi			
	Staphylococcus aures		*Escherichia coli*		*Curvularia lunata*		*Aspergillus niger*	
	250 µg/disc	500 µg/disc	250 µg/disc	500 µg/disc	250 µg/disc	500 µg/disc	250 µg/disc	500 µg/disc
3	2	3	2	5	8	15	7	12
4	6	12	6	11	16	21	14	21
5	4	7	3	8	9	14	7	13
6	2	3	2	4	10	18	11	18
7	8	11	7	12	22	24	19	23
8	1	3	2	3	7	12	9	15
9	3	5	2	6	10	15	8	13
10	5	10	5	9	13	18	13	21
11	7	12	6	11	11	17	9	19
12	6	11	7	13	15	21	12	19
Penicillin	24		20					
Griseofulvin					28		28	

NMR spectra were taken on a AMX-400 MHz spectrometer operating at 400 MHz for ^1H, 100 MHz for ^{13}C and 161.9 MHz for ^{31}P in DMSO-d_6 and $CDCl_3$, and chemical shifts were referenced to TMS (^1H and ^{13}C) and 85% H_3PO_4 (^{31}P). Mass spectral data were recorded on GC-MS instrument at 70 eV, with a direct inlet system.

Synthesis of 3-(4-Methylphenoxy)-2,4,8,15-tetroxa-3-phosphadispiro[5.2.5]hexadecane 3-Oxide (**3**).

A solution of 4-methylphenylphosphorodichloridate (1.13 g, 0.005 mol) in dry toluene-THF (3:1) (20 mL) was added to a stirred solution of 1,5-dioxaspiro[5.5]undecande-3,3-dimethanol (1.08 g, 0.005 mol) and triethylamine (1.01 g, 0.01 mol) in dry toluene-THF (3:1) (50 mL) at room temperature over a period of thirty minutes. After the addition, the temperature was slowly increased to 40-60 °C and heating was continued for about five hours with stirring. Progress of the reaction was followed by TLC. Triethylamine hydrochloride was separated from the reaction mixture by filtration and the solvent was removed from the filtrate in a rotary evaporator. The residue after washing with water to remove the residual triethylamine hydrochloride was dried and recrystallized from a mixture of hexane and ethyl acetate (5:2) to yield the title compound (**3**) (1.29 g, 70%) mp 190 °C. IR (KBr) cm^{-1}: 1317 (P=O), 1160 (P-O-$C_{aliphatic}$), 985 and 1253 (P-O-$C_{aromatic}$); ^1H NMR ($CDCl_3$) δ: 1.23-1.62 [m, 6H, H(10), H(11) & H(12)],

Compounds **4-12** were prepared by this procedure and their synthetic and analytical, ir, ^1H, ^{13}C, ^{31}P NMR and mass spectral data are given in Tables 1, 2, 3 and 4 respectively.

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