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Synthesis of Dinaphtho-dioxaphosphocin-8-oxides, Epoxides and Bisphosphonates

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ABSTRACT

Preparation of 8-substituted-16*H*-dinaphtho [2,1-d:1′,2′-g] [1,3,2] dioxaphosphocin 8-oxides (5a–g) **with an eight-membered phosphorus heterocyclic system** (2) **and their epoxides and bisphosphonates was accomplished by reacting 8-bromo-dinaphthophosphocin** (2) **with different mono and bis Grignard reagents** (3a–g **and** 6) **followed by oxidation with H_2O_2. Their structures were confirmed by elemental and spectral (^1H, ^{13}C and ^{31}P NMR) data analysis. Some of these compounds are found to possess moderate antimicrobial activity.**

KEYWORDS

Dioxaphosphocin 8-oxides, dioxaphosphocin bisphosphonates, antimicrobial activity.

1. Introduction

The organophosphate moiety is an important pharmacophore in agricultural and pharmaceutical chemistry.[1] Phosphocin/phosphepin and their related derivatives have an organophosphate functional group and represent an important class of pesticides, antibiotics, herbicides and antiviral agents.[2] Some of them are well known for their environmentally friendly pesticidal activities since they degrade hydrolytically and enzymatically to non-toxic residues.[3] In our continuous quest to prepare some bioactive eco-friendly pesticides, we synthesized some dinaphthophosphocin 8-oxides, and their epoxide and bisphosphonate derivatives following our reported synthetic strategy.[4]

2. Results

Preparation of 8-substituted-16*H*-dinaphtho [2,1-d:1′,2′-g] [1,3,2] dioxaphosphocin 8-oxides (**5a–g**), was accomplished in three steps. Cyclization of equimolar quantities of bis (2-hydroxy-1-naphthyl) methane (**1**) with phosphorus tribromide in the presence of triethylamine in toluene formed the corresponding 8-bromo-dinaphthophosphocin (**2**). Subsequent reaction of **2** with different mono and bis Grignard reagents (**3a–g** and **6**) formed the corresponding P-alkylated (**4a–g**) and C-bis phosphorylated (**7** and **8**) products which on oxidation with H_2O_2 and a catalytic amount of hexachloroacetone (HCA) in dichloromethane afforded the corresponding dinaphtho-dioxaphosphocin 8-oxides (**5a–g**) and 8-methylene/ethene bisdinaphtho-dioxaphosphocin 8-oxides (**9** and **10**). The 8-ethene/propene derivatives **5f** and **5g**, on oxidation with the same reagent under similar conditions, gave two oxidation products, **5f′** and **5g′**, one with both P(III) and C=C of the side chain oxidized to the corresponding phosphoryl (P=O) and epoxide. In the other case P(III) is only oxidized to P=O, retaining the side chain C=C functional group (**5f** and **5g**). The progress of the reaction was monitored by thin layer chromatography (TLC). Separation and purification of the intermediate (**2**) failed since it is unstable and moisture-sensitive. It was treated with Grignard reagents and the formation of the expected products was used to deduce and confirm its structure.

Characteristic IR absorption bands for P-$C_{aliphatic}$ and P=O stretching vibrations were observed in the regions 749–759 and 1225–1236 cm^{-1}, respectively[5] (see Table 1).

The chemical shifts of the naphthyl protons of these compounds (**5a–g**, **5f′**, **5g′**, **9** and **10**) were observed in the region δ 7.08–8.34 ppm. The bridged methylene protons of dioxaphosphocin 8-oxides (**5a–g′**) resonated as two distinct doublets in the regions δ 5.12–5.24 ppm and δ 4.74–4.94 ppm ($^2J_{H,H}$ = 16.0–16.4 Hz), indicating their non-equivalence and geminal coupling. Study of the signal pattern showed that it is similar to those of previously reported and related dioxaphosphocins.[6] The protons of the P-$C_{aliphatic}$ moiety of the side chain exhibited signals in the expected range (see Table 2).

The ^{13}C NMR chemical shifts in the region δ 145.8–148.0 ppm are assigned to C-2 and C-2′ (see Table 3). The downfield shifts of their signals may be due to their attachment to the oxygens. In almost all compounds, this signal appeared as a doublet due to coupling with phosphorus ($^2J_{POC\text{-}2\&C\text{-}2'}$ = 8.7–10.8 Hz). The upfield signal in the region δ 119.8–121.8 ppm was assigned to C-3 and C-3′. This upfield shift of their resonance signals may be attributed to the *ortho* effect of the oxygens.

As expected, the C-1 and C-1′ signals appeared upfield in the region δ 121.0–122.8 ppm. A careful analysis of the spectral data showed that the presence of 4-phosphoryl oxide does not significantly affect the chemical shifts of the carbons of the dioxaphosphocin heterocyclic moiety when compared with the chemical shifts of 2,2′-dihydroxy binaphthyl.[7]

Only three carbons, C-1′, C-2′ and C-3′ of the side chain alkyl groups in (**5a–g**, **9** and **10**) experienced coupling with phosphorus (see Fig. 1), with $J_{P\text{-}C\text{-}1'}$ = 14.0 Hz, $^2J_{P\text{-}C\text{-}2'}$ = 4.7 Hz and $^3J_{P\text{-}C\text{-}3'}$ = 17.1 Hz. The carbons beyond C-3′ such as C-4′ did not show any coupling with phosphorus. The significance of this high-low-high coupling profile is yet to be understood in P-alkyl side chain systems. Perhaps this may arise, at least in part, from γ-type interactions as was suggested before.[5]

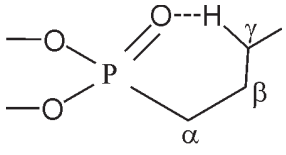

Figure 1 8-alkyl-dinaphtho-dioxaphosphocinphosphonate 8-oxide.

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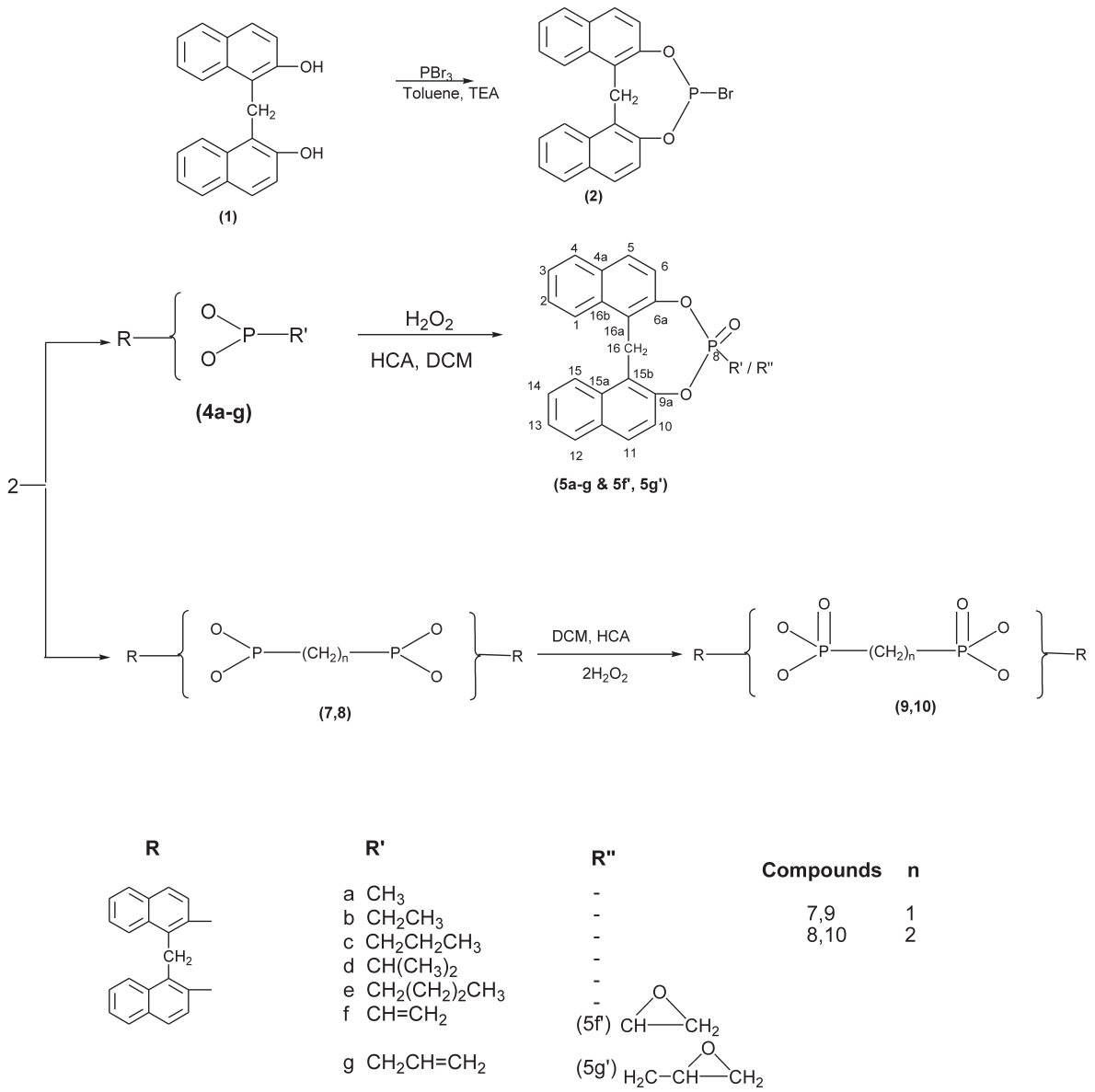

Scheme 1

^{31}P NMR chemical shifts of P(III) derivatives (**4a–g**, **7** and **8**) appeared downfield at δ 118.6 –127.5 ppm, compared with those of their corresponding P(V) derivatives[8] (**5a–g**, **5f′**, **5g′**, **9** and **10**) (δ 19.8–39.2 ppm) (see Table 4).

3. Antimicrobial Activity

The compounds **5a–g, 5f′** and **5g′** were screened for their antibacterial activity against the growth of *Staphylococcus aureus* and *Escherichia coli* and for their antifungal activity against the growth of *Aspergillus niger* and *Helminthosporium oryzae* at concentrations 200 μg disc^{-1} and 400 μg disc^{-1} [9] (see Table 5 and 6). They showed low antibacterial and antifungal activities against the growth of both bacteria and fungi compared with those of the reference compounds.

4. Experimental

4.1. Synthesis of 8-Ethyl-16*H*-dinaphtho [2,1-d:1′,2′-g] [1,3,2] dioxaphosphocin-8-oxide (5b).

To a cooled (0 °C) and stirred solution of bis (2-hydroxy-1-naphthyl) methane (**2**) (1.5 g, 0.05 mol) and triethylamine (1.01 g, 0.01 mol) in 25 mL of dry toluene under N_2 gas, a solution of phosphorus tribromide (1.35 g, 0.05 mol) in 10 mL of dry toluene was added over a period of 20 min. After completion of the addition, the temperature of the reaction mixture was raised to room temperature and stirred for one hour to form the intermediate phosphorobromodite (**5**). The progress of the reaction was monitored by TLC analysis using ethyl acetate and hexane (2:8) as mobile phase and silica gel (mesh 60–120) as adsorbent. The reaction mixture was filtered under nitrogen atmosphere to remove triethylamine hydrobromide.

The Grignard reagent[10] (**3b**) was cooled to 15 °C, and the phosphorobromodite (**2**) was added over 15 min under nitrogen. After the addition, the reaction mixture was brought to room temperature and stirred for 90 min. The progress of the reaction was monitored by TLC (ethyl acetate:hexane 2:8) analysis. After completion of the reaction the mixture was cooled to 5 °C. It was then hydrolysed by slow addition of saturated aqueous NH_4Cl solution with cooling. The solvent was removed under vacuum and the residue was extracted with ethyl acetate. The extract was washed with brine solution and dried over anhydrous $MgSO_4$ and then evaporated using a rotavaporator. The crude product (**5b**) obtained was dissolved in dichloromethane (30 mL) and three drops of HCA were added as a

Table 1 Analytical and infrared spectral data of compounds **5a–g**, **5f′**, **5g′**, **9** and **10**.

Compound	M.p./°C	Yield [a]/%	Molecular formula	Elemental analysis Found (Calcd)/%		$\bar{\nu}$/cm^{-1}	
				C	H	P=O	P-$C_{aliphatic}$
5a	127–128	79	$C_{22}H_{17}O_3P$	73.12 (73.32)	4.62 (4.75)	1228	759
5b	139–140	82	$C_{23}H_{19}O_3P$	73.66 (73.79)	5.02 (5.11)	1230	758
5c	148–149	85	$C_{24}H_{21}O_3P$	74.11 (74.24)	5.36 (5.44)	1226	758
5d	218.–219	89	$C_{24}H_{21}O_3P$	74.16 (74.24)	5.31 (5.44)	1225	757
5e	167–168	84	$C_{25}H_{23}O_3P$	74.51 (74.60)	5.61 (5.76)	1228	755
5f	162–163	56	$C_{23}H_{17}O_3P$	74.06 (74.19)	4.52 (4.60)	1226	749
5g	182–184	60	$C_{24}H_{19}O_3P$	74.51 (74.60)	4.83 (4.95)	1225	749
5f′	120–121	81	$C_{23}H_{17}O_4P$	71.02 (71.14)	4.33 (4.41)	1227	758
5g′	140–141	89	$C_{24}H_{19}O_4P$	71.50 (71.64)	4.60 (4.75)	1232	750
9	156–157	78	$C_{44}H_{32}O_6P_2$	73.15 (73.29)	4.17 (4.29)	1236	752
10	142–143	73	$C_{44}H_{30}O_6P_2$	73.41 (73.54)	4.40 (4.48)	1231	756

[a] After one crystallization.

catalyst and hydrogen peroxide (30 % H_2O_2, 0.2 mL, 0.05 mol) was added dropwise at 0–5 °C. The reaction mixture was brought to room temperature and kept with stirring for two hours until the completion of the oxidation reaction was observed using TLC analysis (ethyl acetate and hexane (2:8) as mobile solvent and silica gel (mesh 60–120) as adsorbent). The reaction mixture was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$ and the solvent was evaporated in a rotavaporator. The resulting crude product was recrystallized from 2-propanol to yield 1.54 g (82 %) of **5b**, m.p. 139–140 °C.

Synthesis of other compounds **5a** and **5c–g** was accomplished using the same procedure.

Table 2 ^{1}H NMR spectral data [a,b] of compounds **5a–g**, **5g′**, **9** and **10**.

Compound	Ar-H	H_a	H_b	R_1	R_2	R_3	R_4
5a	7.49–8.23 (m, 12H)	5.24 (d, 16.1)	4.75 (d, 16.1)	4.74 (d, 16.4)	1.13	–	–
5b	7.12–8.28 (m, 12H)	5.23 (d, 16.2)	4.73 (d, 16.2)	1.81 (m, 2H)	1.20 (m, 3H)	–	–
5c	7.09–8.18 (m, 12H)	5.12 (d, 16.1)	4.74 (d, 16.1)	2.25–2.40 (m, 2H)	1.30–1.50 (m, 5H)		
5d	7.23–8.32 (m, 12H)	5.19 (d, 16.1)	4.94 (d, 16.1)	2.43–2.54 (m, 1H)	1.48–1.57 (m, 6H)		
5e	7.23–8.34 (m, 12H)	5.16 (d, 16.1)	4.93 (d, 16.1)	2.18–2.24 (m, 2H)	1.48–1.57 (m, 6H)	1.19–1.21 (m, 2H)	0.92–0.94 (m, 3H)
5f	7.30–8.30 (m, 12H)	5.21 (d, 16.0)	4.74 (d, 16.0)	5.82–5.94 (m, 1H)	5.20–5.33 (m, 2H)		
5g	7.22–8.28 (m,12H)	5.15 (d, 16.1)	4.82 (d, 16.1)	3.06–3.11 (m, 2H)	6.02–5.90 (m, 2H)	5.39–5.40 (m, 2H)	
5g′	7.08–8.21 (m, 12H)	5.16 (d, 16.2)	4.83 (d, 16.2)	3.03–3.12 (m, 2H)	4.10–4.30 (m, 1H)	4.30–4.50 (m, 2H)	
9	7.21–8.30 (m, 12H)	5.20 (d, 16.1)	4.78 (d, 16.2)	1.28 (m, 2H)			
10	7.22–8.28 (m, 12H)	5.21 (d, 16.2)	4.74 (d, 16.2)	1.82 (m, 2H)	1.89 (m, 2H)		

[a] Chemical shifts in ppm from TMS and coupling constants in Hz given in brackets.
[b] Recorded in deuterochloroform.

Table 3 ^{13}C NMR spectral data [a,b] of compounds **5a–g**, **9** and **10**.

Compounds	C(1/15)	C(2/14)	C(3/13)	C(4/12)	C(5/11)	C(6/10)	C(6a/16a)	6(15a/16b)	C(15/16B)	C(4a/11a)	C16	C′	C2′	C3′	C4′
5a	127.3	125.8	125.4	129.4	129.1	120.4 (4.8)	148.6 (13.0)	124.4	132.2	132.6	24.1	13.8 (136.0)			
5b	128.9	125.4	124.3	129.3	129.0	120.4 (4.6)	148.5 (12.2)	123.3	132.2	132.4	24.0	27.6 (139.4)	14.5 (7.1)		
5c	128.8	125.1	124.0	128.9	128.8	120.1 (4.4)	148.7	123.4	132.0	132.6	24.2	28.4 (140.2)	26.1 (4.7)	16.15 (15.6)	
5d	128.8	125.0	124.0	128.95	128.8	120.1 (4.3)	148.8 (11.3)	123.4	132.7	131.5	24.2	26.8 (140.7)	16.0 (4.7)		
5e	126.8	125.0	125.2	129.0	127.8	120.5 (4.6)	148.7 (13.0)	121.4	132.3	133.	24.1	34.6 (138.2)	30.4 (4.7)	22.6 (14.7)	12.9
5f	127.0	125.4	124.8	129.5	129.4	120.9	149.1	–	132.0	133.0	24.0	123.4	116.2	–	–
5g	126.9	125.6	125.3	129.0	128.8	(3.6) 120.3	(13.2) 148.7 (12.2)		–	132.0	130.0	(131.8) 24.2	(4.6) 36.5 (132.8)	134.2	
9	127.9	125.4	124.6	129.1	128.8	120.3 (4.6)	148.5 (12.2)	–		132.4	132.7	24.1	15.2 (140)		
10	128.6	125.0	126.3	129.3	128.9	120.1 (4.4)	148.8 (12.6)	121.2	132.3	132.6	24.0	26.8 (148.2)	27.1 (148.1)		

[a] Chemical shifts in ppm from TMS and coupling constants in Hz given in brackets.
[b] Recorded in deuterochloroform.

Table 4 ^{31}P NMR chemical shifts (ppm) of compounds **4a–g, 5a–g** and **7–10**.

Compound	P(III) compounds **4a–g, 7, 8**	Compound	P(V) compounds **5a–g, 9, 10**
4a	120.6	**5a**	32.6
4b	123.2	**5b**	30.0
4c	118.6	**5c**	29.2
4d	124.6	**5d**	31.9
4e	120.8	**5e**	39.2
4f	123.8	**5f**	28.6
4g	130.0	**5g**	19.8
7	123.6	**9**	23.8
8	127.5	**10**	30.1

4.2. Synthesis of 8-Methylene bis (16*H*-dinaphtho[2,1-d:1′2′-g] [1,3,2] dioxaphosphocin-8-oxide (9).

The Grignard reagent (**6**) solution in 30 mL of tetrahydrofuran was cooled to 15 °C and the solution of **2** in toluene (20 mL) was added over 15 min under nitrogen atmosphere. After the addition, the reaction mixture was brought to room temperature and stirred for 90 min. The reaction was monitored by TLC using ethyl acetate and hexane (2:8) as mobile solvent and silica gel (mesh 60–120) as adsorbent. After completion of the reaction, the mixture was cooled to 5 °C. It was hydrolysed by the addition of saturated aqueous NH_4Cl solution. Tetrahydrofuran was removed under vacuum and the residue was extracted with ethyl acetate. The extract was washed with brine solution and dried over anhydrous $MgSO_4$ and rotavaporated. The resulting crude products (**7** and **8**) were dissolved in dichloromethane (30 mL) and hydrogen peroxide (30 % H_2O_2, 0.4 mL, 0.01 mol) containing three drops of HCA as catalyst was added dropwise at 0–5 °C. The mixture was brought to room temperature and kept for two hours. Progress of the reaction was monitored by TLC using ethyl acetate and hexane (2:8) as mobile solvent and silica gel (mesh 60–120) as adsorbent. The reaction mixture was washed with saturated NaCl solution and dried over anhydrous $MgSO_4$. The solvent was rotavaporated. The resulting crude product was recrystallized from 2-propanol to yield 0.5 g (78 %) of **9**, m.p. 156–157 °C.

The compounds **5a, 5b, 5e, 5f** and **5f′** show significant activity against *Staphylococcus aureus* and **5a, 5f** and **5f′** are active against *Escherichia coli* (see Table 5). Compounds **5a, 5d, 5f, 5g, 5f′** and **5g′** are active against *Aspergillus niger* and compounds **5a,**

Table 5 Antibacterial activity of compounds **5a–g, 5f′** and **5g′**.

Compound	Zone of inhibition/mm			
	Staphylococcus aureus		*Escherichia coli*	
	200 μg disc^{-1}	400 μg disc^{-1}	200 μg disc^{-1}	400 μg disc^{-1}
5a	14	19	13	20
5b	13	18	11	15
5c	10	16	9	15
5d	5	11	6	12
5e	13	19	6	12
5f	14	20	13	18
5g	12	18	11	17
5f′	15	22	13	21
5g′	14	20	11	19
Penicillin [a]	22		21	

[a] Standard antibacterial compound.

Table 6 Antifungal activity of compounds **5a–g**, **5f′** and **5g′**.

Compound	Zone of inhibition/mm			
	Aspergillus niger		*Helminthosporium oryzae*	
	200 μg disc^{-1}	400 μg disc^{-1}	200 μg disc^{-1}	400 μg disc^{-1}
5a	16	22	18	23
5b	14	23	16	22
5c	13	21	14	20
5d	18	24	17	23
5e	13	22	13	21
5f	17	25	16	23
5g	16	23	15	22
5f′	17	26	14	22
5g′	16	24	14	21
Griseofulvin [a]	28		28	

[a] Standard antifungal compound.

5b, 5d and **5f** are active against *Helminhosporium oryzae* (see Table 6). From the above, compounds **5a** and **5f** show 60 % inhibition effectiveness in all bacteria and fungi when compared with those of the reference compounds.

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