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Synthesis and Antimicrobial Activity of 8-Alkylcarbamato-16*H*-Dinaphtho [2,1-*d*:1′,2′-*g*] 1,3,2-Dioxaphosphocin 8-Oxides

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ABSTRACT: *A new family of phosphorus heterocycles, namely 8-alkylcarbamato-16H-dinaphtho-[2,1-d: 1′,2′-g] 1,3,2-dioxaphosphocin 8-oxides (***4a–j***) has been obtained by reaction of bis(2-hydroxy-1-naphthyl)methane (***3***) with a series of dichlorophosphosphinyl carbamates (***2a–j***) in dry toluene in the presence of triethylamine at 40–45°C. The intermediates* **2a–j** *were obtained by the addition of alcohols/thiol to isocyanatophosphonic dichloride (***1***) at −10°C in dry toluene. The structures of the title compounds were confirmed by the elemental analyses, IR,* ^{1}H, ^{13}C, *and* ^{31}P *NMR spectra. The FAB mass spectrum of one member of the family is discussed. These compounds were found to possess good antimicrobial activity.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:16–20, 2001

INTRODUCTION

Certain carbamates have structural resemblance to acetylcholine, and they possess high affinity for the enzyme cholinesterase [1]. Substituted phosphinyl carbamates [2] gained much importance due to their potential activity against several forms of tumors. Some esters of dibenzodioxaphosphocin are used as pesticides and additives [3–5] in polymer and oil industries. The title compounds (**4a–j**) were synthesized with the idea of exploring their possible use in the above areas, and they were characterized by elemental, IR, NMR (^{1}H, ^{13}C, and ^{31}P), and mass spectral analyses and tested for their antimicrobial activity.

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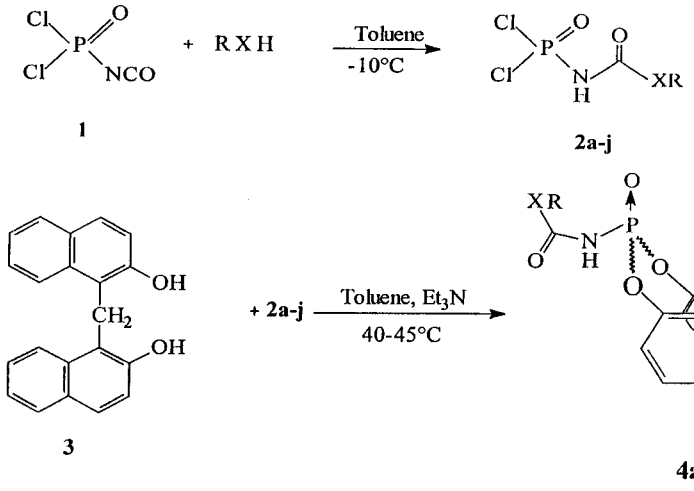
RESULTS AND DISCUSSION

The synthetic route (Scheme 1) involves the addition reaction of isocyanatophosphonic dichloride (**1**) to various alcohols/thiol at −10°C under inert, anhydrous conditions in dry toluene to afford the corresponding dichlorophosphinyl carbamates [2,6] (**2a–j**). Cyclocondensation of **2a–j** in situ with bis(2-hydroxy-1-naphthyl)methane (**3**) in the presence of triethylamine at 40–45°C yielded the title compounds **4a–j**. In the present study, thin-layer chromatography was employed to follow the reaction. The primary and secondary alcohols reacted readily with isocyanatophosphonic dichloride (**1**) to give their respective carbamates (**2**), but tertiary alcohols (*t*-butyl alcohol) did not react to form the expected corresponding carbamates (**2**), obviously due to steric factors.

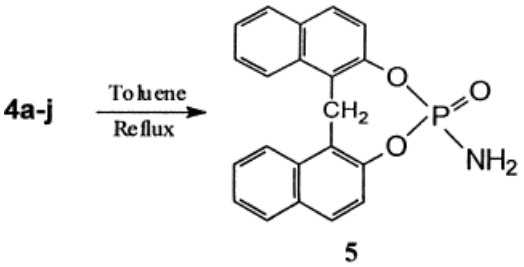
If the reaction was run at higher temperature, pyrolysis of the resultant products (**4a–j**) occurred with the formation of only one product, 8-amino-16*H*-dinaphtho [2,1-*d*:1′,2′*g*] 1,3,2-dioxaphosphocin 8-oxide (**5**).

Reaction yields, elemental analyses, and IR [7] and ^{31}P NMR data are given in Table 1. Tables 2 and 3 contain ^{1}H and ^{13}C NMR data for compounds **4**.



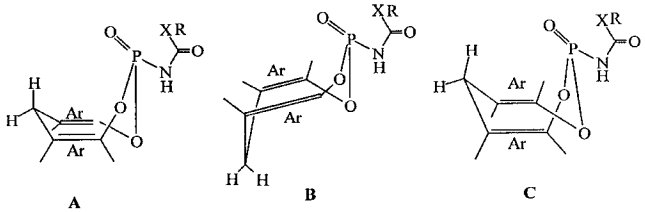
	XR		XR
4a.	OCH_3	**4f.**	$OCH_2CH(CH_3)_2$
b.	OCH_2CH_3	**g.**	OC_6H_{11}
c.	OCH_2CH_2Cl	**h.**	$OCH_2C_6H_5$
d.	$OCH(CH_3)_2$	**i.**	$OCH_2CH_2C_6H_5$
e.	$OCH_2(CH_2)_2CH_3$	**j.**	$SCH_2CH_2CH_3$

SCHEME 1



SCHEME 2

The proton NMR spectra of **4** showed only six signals in the region δ 7.22–8.32 (Table 2). This suggests a symmetrical arrangement about the central dioxaphosphocin ring. Although the data correlated reasonably well with that reported [8] for similar protons in naphthoxazin and certain dinaphthocrown ethers, the corresponding protons in **4** were more downfield. This suggests a deshielding influence by a nearby group that could possibly arise from the phosphoryl function. The bridging methylene protons appear as two distinct doublets in the region δ 4.78–4.83 and 5.19–5.25 ($^2J_{H\text{-}H}$ = 16.2–16.5 Hz), indicative of the nonequivalence of the two protons. A search of the literature did not reveal any type of study on the class of compounds represented by **4**. However, investigations [9] have been recorded on a few dioxaphosphocins in which a long range, $^5J_{H\text{-}P}$ = 2.9 Hz, was reported between one of the methylene protons and phosphorus. It was suggested that the lone electron pair on phosphorus was directed toward one of the protons as illustrated with conformation **A**. No such coupling was observed in the H-1 spectra of **4**. An examination of space-filling models suggests two possible strain-free conformations (**B** and **C**) for the dioxaphosphocin 8-oxide ring system in **4**. In conformer **B**, there is a rigid chair, and in conformer **C**, a boat system exists with the P=O and CH_2 far apart. Actually, the models imply that the bulky naphthyl groups may force the CH_2 and P=O groups to be far removed from each other to minimize nonbonded interactions.



The ^{13}C NMR chemical shifts of compounds **4b** and **4d** are given in Table 3. The ^{13}C NMR signals of the dinaphthodioxaphosphocin moiety resonated at the expected regions based on the reported values of the model compound, dinaphtho crown ether [8,10]. The C-2′ in the carbamate function resonated down-

TABLE 1 Physical and IR and ^{31}P NMR Spectral Data of Compounds **4a–j**

				Elemental Analyses		*IR (cm^{-1})*			
Compound	*m.p. (°C)*	*Yield[a] (%)*	*Mol. Formula*	*Foun C*	*(Calcd) H*	*P=O*	*C=O*	*P–NH*	*^{31}P NMR[b] (ppm)*
4a	284–286	56	$C_{23}H_{18}NO_5P$	65.75 (65.87)	4.48 (4.32)	1207	1744	3383	−7.96
4b	286–288	55	$C_{24}H_{20}NO_5P$	66.36 (66.51)	4.59 (4.65)	1217	1712	3305	−8.65, −10.47
4c	264–266	51	$C_{24}H_{19}ClNO_5P$	— (61.61)	— (4.09)	1259	1724	3382	−10.29
4d	282–284	50	$C_{25}H_{22}NO_5P$	66.98 (67.11)	4.76 (4.95)	1213	1718	3375	−10.01
4e	272–274	52	$C_{26}H_{24}NO_5P$	67.49 (67.67)	5.12 (5.24)	1220	1715	3375	—
4f	266–268	51	$C_{26}H_{24}NO_5P$	67.82 (67.67)	5.15 (5.24)	1264	1732	3295	—
4g	262–264	50	$C_{28}H_{26}NO_5P$	69.09 (68.98)	5.25 (5.37)	1220	1740	3365	—
4h	216–218	58	$C_{29}H_{22}NO_5P$	— (70.30)	— (4.47)	1207	1727	3393	−13.08
4i	230–232	56	$C_{30}H_{24}NO_5P$	70.91 (70.72)	4.59 (4.74)	1211	1734	3369	−12.97
4j	264–266	50	$C_{25}H_{22}NO_4PS$	64.72 (64.50)	5.12 (5.19)	1225	1725	3345	−16.95

[a]Triturated with isopropanol.
[b]^{31}P Chemical shifts were expressed δ, from 85% H_3PO_4 as external standard. **4e, 4f, 4g** ^{31}P NMR not recorded.

TABLE 2 ^{1}H NMR Data of Compounds **4** (δ from TMS)

		CH_2 (bridged)			
Compound	*Ar–H*	*H_a*	*H_b*	*NH*	*R–H*
4a	7.27–8.29 (m, 12H)	5.25 (16.4)	4.80 (16.5)	7.05 (brs, 1H)	3.81 (s, 3H, OCH_3)
4b	7.32–8.30 (m, 12H)	5.19 (16.5)	4.78 (16.4)	7.01 (brs, 1H)	4.24 (q, 2H, OCH_2) 1.35 (t, 3H, CH_3)
4c	7.32–8.32 (m, 12H)	5.22 (16.4)	4.79 (16.3)	—	4.92 (t, 2H, OCH_2) 4.35 (t, 2H, CH_2Cl)
4d	7.22–8.28 (m, 12H)	5.23 (16.3)	4.80 (16.4)	—	5.02–5.08 (m, 1H, OCH) 1.28 (d, 6H, $2CH_3$)
4e	7.30–8.27 (m, 12H)	5.20 (16.3)	4.82 (16.2)	6.85 (brs, 1H)	4.48 (t, 2H, OCH_2) 1.29–1.82 (m, 4H, $2CH_2$) 0.93 (t, 3H, CH_3)
4f	7.28–8.27 (m, 12H)	5.21 (16.2)	4.80 (16.3)	7.02 (brs, 1H)	3.24 (d, 2H, OCH_2) 1.62–1.67 (m, 1H, CH) 0.85 (s, 6H, $2CH_3$)
4g	7.28–8.27 (m, 12H)	5.21 (16.2)	4.83 (16.2)	7.05 (brs, 1H)	5.01 (s, 1H, CH) 1.20–1.59 (m, 10H)
4h	7.34–8.28 (m, 12H)	5.20 (16.3)	4.81 (16.4)	6.80 (brs, 1H)	5.25 (s, 2H, OCH_2) 7.18–7.36 (m, 5H, Ar-H)
4i	7.22–8.28 (m, 12H)	5.23 (16.3)	4.80 (16.4)	—	4.41 (t, 2H, OCH_2) 2.95 (t, 2H, CH_2) 7.15–7.23 (m, 5H, Ar-H)
4j	7.30–8.29 (m, 12H)	5.19 (16.4)	4.79 (16.3)	6.90 (brs, 1H)	2.64 (t, 2H, SCH_2) 1.55–1.63 (m, 2H, CH_2) 0.98 (t, 3H, CH_3)

Note: Data in parentheses are coupling constants, *J* in Hz.

TABLE 3 ^{13}C NMR Chemical Shifts of 8-Ethyl/Isopropylcarbamato-16*H*-dinaphtho-[2,1-*d*: 1′, 2′-*g*] 1,3,2-Dioxaphosphocin 8-Oxides (**4b, 4d**)

4b	δ 127.0 (s, 2C, C-1,15), 125.3 (s, 2C, C-2,14), 123.2 (s, 2C, C-3,13), 129.1 (s, 2C, C-4,12), 129.1 (s, 2C, C-5,11), 120.4 (s, 2C, C-6,10), 149.2 (s, 2C, C-6a,9a), 131.6 (s, 2C, C-15b,16a), 132.6 (s, 2C, C-4a,11a), 23.6 (s, 1C, $\underline{C}H_2$), 161.5 (s, 1C, $\underline{C}=O$), 56.8 (s, 1C, $O\underline{C}H_2$), 15.4 (s, 1C, $\underline{C}H_3$)
4d	δ 127.2 (s, 2C, C-1,15), 125.2 (s, 2C, C-2,14), 123.4 (s, 2C, C-3,13), 128.9 (s, 2C, C-4,12), 128.9 (s, 2C, C-5,11), 1204. (s, 2C, C-6,10), 149.0 (s, 2C, C6a,9a), 131.5 (s, 2C, C-15b,16a), 132.2 (s, 2C, C-4a,11a), 23.6 (s, 1C, $\underline{C}H_2$), 160.0 (s, 1C, $\underline{C}=O$), 58.0 (s, 1C, $O\underline{C}H$), 21.8 (s, 2C, $2\underline{C}H_3$).

field (δ 10–15) when compared to the signals in the corresponding free alcohols [11]. The remaining carbon signals in **4b** and **4d** occurred in the expected region. The ^{13}C NMR chemical shifts for the other members of **4** were not assignable due to poor solubility of the compounds and high signal density from unresolved patterns.

The ^{31}P NMR signals (Table 1) for most of the 8-alkylcarbamato compounds **4a–i** appeared in the region δ −7.96 to −13.08, whereas in **4j**, the signal resonated upfield at δ −16.95. The replacement of oxygen with sulfur in the carbamate function obviously increased the shielding of phosphorus. In compound **5**, the ^{31}P NMR signal resonated at δ +6.37.

The electron impact mass spectrum of compound **4b** did not show a molecular ion peak. However, its fast atom bombardment mass spectrum exhibited the molecular ion at *m/z* 434 (M^{+}* +1) with an intensity of 10%. The molecular ion degraded into various daughter ions in a stepwise manner. The major ions (M^{+}* − C_2H_2), [(M^{+}* − OC_2H_5) − H_2], (M^{+}* − C_2H_4 and CO_2) and (M^{+}* − $NH_2COOC_2H_5$) appeared as characteristic ions at *m/z* 407 (35), 386 (10), 361 (21), and 344 (42), respectively [12].

Antibacterial activity of the title compounds was evaluated by following the method of Vincent and Vincent [13], and their antifungal activity was screened by the Horsfall and Rich [14] procedure.

All compounds exhibited moderate activity against gram-positive bacteria, *Bacillus subtilis* and *Staphylococcus aureus* at 250 ppm. They also exhibited significant activity against *Curvularia lunata* and *Aspergillus niger* (60–95%) fungal species.

EXPERIMENTAL

The melting points were determined on a Mel-Temp apparatus and were uncorrected. Elemental analyses were performed at the Central Drug Research Institute, Lucknow, India. IR spectra were recorded as KBr pellets on a Perkin-Elmer 683 unit. All NMR spectra were recorded on a Varian AMX 400 MHz spectrometer with data acquisition at 400 MHz (^{1}H), 100 MHz (^{13}C), and 161.3 MHz (^{31}P). All spectra were recorded using $CDCl_3$ as solvent with TMS as the reference compound for ^{1}H and ^{13}C, and 85% H_3PO_4 for ^{31}P NMR. Mass spectra were recorded on a JEOL SX 102/DA/600 instrument using Argon 6 kV, 10 mA.

*8-Isopropylcarbamato-16H-dinaphtho[2,1-d:1',2'-g] 1,3,2-dioxaphosphocin 8-oxide (***4d***)*

A general procedure for members of **4** is illustrated with that for **4d**. A solution of 2-propanol (0.60 g, 0.01 mol) in dry toluene (20 mL) was added dropwise (20 min) to a cold (−10°C) solution of **1** (1.60 g, 0.01 mol) in dry toluene (25 mL). After the addition was complete, the mixture was allowed to warm slowly to room temperature, and stirring was continued for 2 hours. The new reaction mixture was then added dropwise to a cold (0°C) solution of **3** (3.0 g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) in dry toluene (50 mL). When the addition was complete, the mixture was stirred and allowed to warm slowly to 40–45°C. After 5 hours of stirring in the temperature range specified, the triethylamine hydrochloride was filtered off, and the solvent was evaporated from the filtrate under reduced pressure. The residue obtained was washed with water followed by chilled 2-propanol and recrystallized from ethanol, yielding 2.23 g (50%) of **4d**, m.p. 282–284°C. Physical and spectral data of **4a–j** are provided in Tables 1–3.

*Preparation of 8-amino-16H-dinaphtho [2,1-d:1',2'-g] 1,3,2-dioxaphosphocin 8-oxide (***5***)*

A solution of **4d** (0.9 g, 0.002 mol) in 30 mL of dry toluene and a few drops of dimethylformamide was pyrolized vigorously for 30 min. The solution was cooled immediately, and the solid product **5** was filtered off, washed with water, and recrystallized from ethanol to afford pure compound **5**; yield 0.59 g (82%), m.p. 238–240°C. IR ν_{max} (KBr):1222 (P=O), 3224 (P-NH_2)[15] cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 7.25–8.27 (m, 12H, naphthyl-H), 5.21 (d, J = 16.1 Hz H_a), 4.83 (d, J = 15.9 Hz, H_b), 5.02 (s, 2H, NH_2). ^{31}P NMR (85% H_3PO_4): +6.37 ppm.

Analogous results were obtained for other members of **4**.

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