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Synthesis and Antimicrobialactivity of 2-Alkylcarbamato-2,3-Dihydro-5-Propylthio-1*H*-1,3,2-Benzodiazaphosphole 2-Oxides

D. Srinivasulu, C. Devendranath Reddy, and B. Sankar Reddy

Department of Chemistry, Sri Venkateswara University, Tirupati, 517 502, India

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ABSTRACT: *Novel 2-alkylcarbamato/thiocarbamato-2,3-dihydro-5-propylthio-1H-1,3,2-benzodiazaphosphole 2-oxides (**4a–J**) were synthesized by cyclization of 4-propylthio-1,2-phenylenediamine (**3**) with the corresponding dichlorophosphoryl carbamates/thiocarbamates (**2a–J**) that were obtained by the addition of alcohols/thiols to isocyanatophosphoryl dichloride (**1**). The structures of the title compounds were confirmed by the ^{1}H, ^{13}C, ^{31}P NMR, and mass spectral studies. Some of these products were found to possess significant antimicrobial activity.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:336–340, 2000

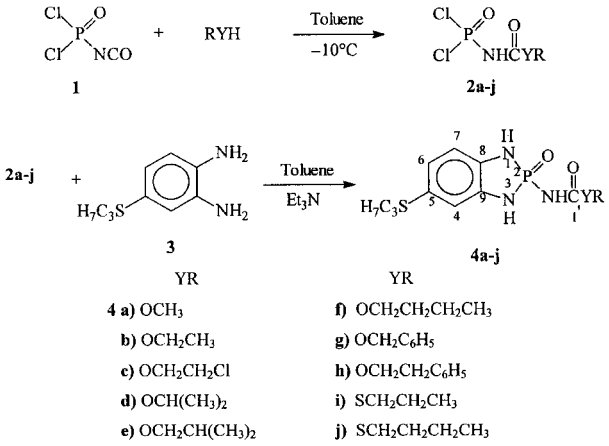
INTRODUCTION

Most of the phosphorus carbamates have acquired much importance recently because these compounds have been investigated for their antitumor [1] and pesticidal [2] properties. Some bendazoles [3] have anthelmintic activity that depends to some extent on the nature of substituents. Benzodiazaphospholes that are analogous to bendazoles are expected to possess a broad spectrum of biological activity with less toxicity. Some phosphorus heterocyclic esters are known [4–6] to be insecticides and bactericides. Industrially, they have also been found to be useful as lubricating oil additives, antioxidants, and polymer stabilizers [7]. In view of these possible applications, the relatively rare class of organophosphorus carbamate heterocycles (**4a–j**) were synthesized and characterized by NMR (^{1}H, ^{13}C, and ^{31}P) and mass spectral analyses and tested for antimicrobial activity.

Correspondence to: C. Devendranath Reddy.

RESULTS AND DISCUSSION

Synthesis of 2-alkylcarbamato/thiocarbamato-2,3-dihydro-5-propylthio-1*H*-1,3,2-benzodiazaphosphole 2-oxides (**4a–j**) is accomplished through a two-step process (Scheme 1): (1) the addition of isocyanatophosphoryl dichloride (**1**) [1] to various alcohols/thiols at $-10°C$ under an inert atmosphere and anhydrous conditions in dry toluene to afford the corresponding dichlorophosphoryl carbamates/thiocarbamates (**2a–j**); (2) condensation of **2a–j** *in situ*



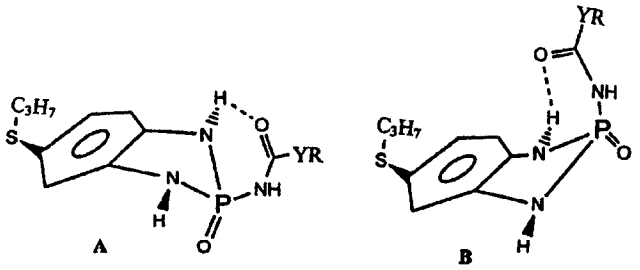
SCHEME 1

with 4-propylthio-1,2-phenylenediamine (**3**) [8] in the presence of triethylamine at 40–50°C.

Interestingly, all primary and secondary alcohols/thiols reacted readily with isocyanatophosphoryl dichloride (**1**) to give their respective carbamates/thiocarbamates (**2a–j**), but tertiary alcohols/thiols failed to form the corresponding expected carbamates/thiocarbamates (**2**) under the same conditions, obviously due to steric factors. Attempts to convert **4a–j** to the respective urea derivatives by heating with various amines were unsuccessful [9]. Physical and IR data δ 4a–j are given in Table 1.

^{1}H NMR spectra (Table 2) showed doublets for H(6) at δ 6.55–6.69 (J = 7.8–8.1 Hz) in **4c–e**. Compound **4f** exhibited a doublet of doublets for H(6) at δ 6.64 (J = 8.3, 1.5 Hz). Compounds **4c–e** and **4f** showed doublets for H(7) at δ 6.73–7.01 (J = 7.8–8.3 Hz). A singlet was observed for H(4) at δ 6.68–6.81 in **4c–e**, while, in **4f**, a doublet was found for H(4) at δ 6.83 (J = 1.5 Hz).

It is interesting to observe the appearance of two doublets in **4d** and **4e** for the endocyclic H(1) and H(3) at δ 8.60–8.64 (J = 8.2–11.6 Hz) and at δ 8.66–8.68 (J = 8.4–11.6 Hz), respectively, while the exocyclic proton of PNHC = O group also appeared as a doublet at further downfield δ 8.99–9.15 (J = 9.2–9.6 Hz). All signals due to NH were confirmed by D_2O exchange. The presence of the two doublets for PNH protons indicates their nonequivalence. An alternative explanation might be that two conformers may exist as shown subsequently and which involve some intramolecular H-bonding as illustrated [14].



Locked conformations **A** and **B** would make the protons on nitrogen nonequivalent on the assumption that the interconversion barrier between **A** and **B** was of sufficient magnitude. The presence of two distinct ^{31}P NMR signals provide support for the assumption that two conformers **A** and **B** exist. Further, the N–P bond of N–P = O in the cyclic system may have some double bond character, and this consequently makes the system rigid, with a sufficient energy barrier to prevent interconversion. It is of interest to note that phosphorus coupling occurs only with the NH group of the carbamate moiety in the side chain and does not extend beyond this group. The signals for the protons of the carbamate group

TABLE 1 Physical and IR Data of Compounds **4**

				Analysis Found (Required) (%)			*IR (cm^{-1})*		
Compound	*m.p. (°C)*	*Yield (%)*	*Mol. Formula*	*C*	*H*	*N*	*P=O*	*C=O*	*P–NH–(Ar)*
4a	144–145 (d)	54[b]	$C_{11}H_{16}N_3O_3PS$	43.65 (43.82)	5.22 (5.35)	13.78 (13.95)	1289	1708	3316
4b	140–141 (d)	51[c]	$C_{12}H_{18}N_3O_3PS$	48.55 (48.68)	5.64 (5.75)	13.17 (13.33)	1290	1715	3330
4c	131–132 (d)	53[a]	$C_{12}H_{17}ClN_3O_3PS$	41.33 (41.18)	4.99 (4.90)	12.15 (12.01)	1290	1704	3308
4d	129 (d)	56[c]	$C_{13}H_{20}N_3O_3PS$	47.21 (47.38)	6.04 (6.12)	12.58 (12.76)	1285	1713	3360
4e	173–174	58[c]	$C_{14}H_{22}N_3O_3PS$	48.75 (48.94)	6.52 (6.46)	12.12 (12.24)	1321	1736	3302
4f	168–169	55[c]	$C_{14}H_{22}N_3O_3PS$	48.89 (48.94)	6.37 (6.46)	12.18 (12.24)	1287	1703	3302
4g	132–133	42[a]	$C_{17}H_{20}N_3O_3PS$	54.01 (54.08)	5.19 (5.34)	11.21 (11.13)	1285	1730	3360
4h	139–140	44[b]	$C_{18}H_{22}N_3O_3PS$	55.37 (55.21)	5.74 (5.66)	10.62 (10.74)	1289	1723	3335
4i	177–178 (d)	49[c]	$C_{13}H_{20}N_3O_2PS_2$	45.02 (45.18)	5.92 (5.83)	12.10 (12.17)	1285	1720	3340
4j	155–156	51[c]	$C_{14}H_{22}N_3O_2PS_2$	46.57 (46.75)	6.12 (6.17)	11.51 (11.69)	1290	1730	3368

[a]Recrystallized from ethanol.
[b]Recrystallized from ethanol + methanol.
[c]Triturated with 2-propanol.

TABLE 2 ^{1}H NMR Data of Compounds **4**[a,b] (δ from TMS)

Compound	*H(4), H(6), and H(7)*	*R-H*	*H(1) and H(3)*	*-NHCO-*	*H(12), H(11), and H(10)*	^{31}*P NMR (85% H_3PO_4)*
4a	6.57–7.10 (m, 3H, 4, 6, and 7-H)	3.48 (s, 3H, OCH_3)	8.32 (d, 8.4 Hz)	8.60 (d, 9.1 Hz)	0.93 (t, 3H, 12-H) 1.51 (sext, 2H, 11-H) 2.75 (t, 2H, 10-H)	−0.09
4b	6.77–7.10 (m, 3H, 4, 6, and 7-H)	3.93 (m, 2H, OCH_2) 1.13 (m, 3H, CH_3)	8.27 (d, 8.3 Hz)	8.62 (s)	0.93 (t, 3H, 12-H) 1.50 (sext, 2H, 11-H) 2.75 (t, 2H, 10-H)	0.94
4c	6.81 (s, 1H, 4-H) 6.55 (d, 7.9, 1H, 6-H) 6.93 (d, 7.9, 1H, 7-H)	4.15 (m, 2H, OCH_2) 3.76 (m, 2H, CH_2Cl)	8.42 (d, 8.2 Hz)	8.80 (s)	0.93 (t, 3H, 12-H) 1.53 (sext, 2H, 12-H) 2.76 (t, 2H, 10-H)	0.57 1.26
4d	6.70 (s, 1H, 4-H) 6.61 (d, 8.1, 1H, 6-H) 6.75 (d, 8.1, 1H, 7-H)	4.60 (m, 1H, OCH) 0.81 (d, 6.8, 6H, $2CH_3$)	8.60 (d, 8.2 Hz), 8.66 (d, 8.4 Hz)	8.99 (d, 9.6 Hz)	0.93 (t, 3H, 12-H) 1.52 (sext, 2H, 11-H) 2.73 (t, 2H, 10-H)	17.37 17.53
4e	6.68 (s, 1H, 4-H) 6.69 (d, 7.8, 1H, 6-H) 6.73 (d, 7.8, 1H, 7-H)	3.57 (d, 6.4, 2H, OCH_2) 1.44 (m, 1H, CH) 0.69 (d, 6.8, 6H, $2CH_3$)	8.64 (d, 11.6 Hz), 8.68 (d, 11.6 Hz)	9.15 (d, 9.2 Hz)	0.93 (t, 3H, 12-H) 1.51 (m, 2H, 11-H) 2.73 (t, 2H, 10-H)	12.73 12.87
4f	6.83 (d, 1.5, 1H, 4-H) 6.64 (dd, 8.3, 1.5, 1H, 6-H) 7.01 (d, 8.3, 1H, 7-H)	3.88 (t, 2H, OCH_2) 1.46 (m, 2H, CH_2) 1.25 (m, 2H, CH_2) 0.84 (t, 3H, CH_3)	8.25 (d, 8.4 Hz)	8.40 (d, 9.3 Hz)	0.93 (t, 3H, 12-H) 1.52 (m, 2H, 11-H) 2.76 (t, 2H, 10-H)	−3.15 −3.65
4g	6.45–6.80 (m, 3H, 4, 6, and 7-H)	4.99 (s, 2H, OCH_2) 7.30–7.37 (m, 5H, C_6H_5)	8.35 (d, 8.3 Hz)	8.75 (s)	0.92 (t, 3H, 12-H) 1.50 (sext, 2H, 11-H) 2.72 (t, 2H, 10-H)	4.28 23.95
4h	6.73–6.82 (m, 3H, 4, 6, and 7-H)	4.07 (t, 2H, OCH_2) 2.80 (t, 2H, CH_2) 7.08–7.29 (m, 5H, C_6H_5)	8.37 (d, 8.4 Hz)	8.53 (s)	0.91 (t, 3H, 12H) 1.50 (sext, 2H, 11-H) 2.74 (t, 3H, 10-H)	−2.93 −3.48
4i	6.79–7.36 (m, 3H, 4, 6, and 7-H)	2.44 (t, 2H, SCH_2) 1.58 (m, 2H, CH_2) 1.21 (t, 3H, CH_3)	—	—	0.93 (t, 3H, 12H) 1.53 (m, 2H, 11-H) 2.76 (t, 2H, 10-H)	−11.33 −24.31
4j	6.59–6.91 (m, 3H, 4, 6, and 7-H)	2.83 (t, 2H, SCH_2) 1.61–1.69 (m, 4H, $2CH_2$) 1.15 (t, 3H, CH_3)	—	—	0.93 (t, 3H, 12-H) 1.53 (m, 2H, 11-H) 2.75 (t, 2H, 10-H)	−13.86 −13.98

[a]Recorded in DMSO-d_6.
[b]Values in parentheses are coupling constants; *J* in Hz.

appeared slightly downfield when compared to those of the corresponding protons in the free alcohols/thiols [15]. The presence of the C=O group is responsible for these additional small downfield shifts.

The ^{13}C NMR chemical shifts were recorded for some of the title compounds, namely for **4a–h** (Table 3). Chemical shifts at δ 122.4–122.9 and 123.5–124.8 were assigned to C(5) and C(6), respectively. The upfield doublets at δ 109.6–112.2 and 112.5–119.8 [$^{3}J_{PNCC(4,7)}$ = 12.0–12.4 Hz] were ascribed for C(4) and C(7), respectively. The nitrogen-bearing ring carbons, C(8) and C(9), resonate as a doublet in the downfield region δ 131.4–132.1 and 132.2–133.3 ppm [$^{2}J_{PNC(8,9)}$ = 13.1–13.7 Hz], respectively. The signal for C(1′) in **4a–h** occurred at δ 153.4–155.2 ppm, while the C(2′) chemical shifts of the carbamate function appeared downfield (~10 ppm) compared to the corresponding signals in the respective free alcohols/thiols [15] due to the presence of the C=O group. The remaining carbons of the carbamate function resonated in the expected regions.

The ^{31}P NMR signals [16,17] for the carbamate

TABLE 3 ^{13}C NMR Data of Compounds **4**[a] (δ from TMS)[b]

Carbons	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**
C(4)	110.7 (12.3)	111.4 (12.0)	110.7 (12.2)	109.6 (12.4)	109.6 (12.2)	112.0 (12.1)	110.2 (12.2)	112.2 (12.0)
C(5)	122.7	122.4	122.5	122.7	122.5	122.9	122.8	122.6
C(6)	124.6	124.7	124.5	124.8	123.5	124.2	124.4	124.6
C(7)	119.0 (12.3)	119.0 (12.0)	119.6 (12.2)	118.4 (12.4)	112.5 (12.2)	119.8 (12.1)	119.2 (12.2)	119.4 (12.0)
C(8)	131.6 (13.6)	131.3 (13.7)	131.7 (13.1)	131.4 (13.3)	132.1 (13.7)	131.4 (13.4)	131.5 (13.2)	131.6 (13.5)
C(9)	132.4 (13.6)	132.7 (13.7)	132.4 (13.1)	132.5 (13.3)	133.3 (13.7)	132.2 (13.4)	132.3 (13.2)	132.5 (13.5)
C(10)	36.0	36.0	35.8	36.1	37.1	35.8	36.3	35.9
C(11)	22.0	22.0	22.1	22.0	22.1	22.0	22.0	22.0
C(12)	13.0	13.1	13.1	13.0	13.0	13.1	13.0	13.1
C(1′)	155.0	154.3	154.0	154.2	153.4	154.5	155.2	154.3
C(2′)	51.5	60.0	64.1	67.3	70.7	63.8	65.4	64.8
C(3′)		14.4	42.5	21.7	27.1	30.5	134.7	34.6
C(4′)					18.7	18.5	128.6	138.0
C(5′)						13.6	127.8	128.9
C(6′)							127.6	128.3
C(7′)							127.8	126.3
C(8′)							128.6	128.3
C(9′)								128.9

[a]Not recorded for **4i** and **4j**.
[b]Data in parentheses are coupling constants; $J_{p\text{-}c}$ (in Hz).

TABLE 4 Mass Spectral Data (% of important ions) of Compounds **4e** and **4f**

Compound	*m/z Values*
4e	345 [1, $(M + 2)^+$], 343 (5, $M^{+\cdot}$), 270 [29, $(M\text{-}\dot{O}CH_2CH(CH_3)_2^+)$], 269 [100, $(M\text{-}HOCH_2CH(CH_3)_2^{+\cdot})$], 227 [84, $(M\text{-}NHCOOCH_2CH(CH_3)_2^+)$], 226 [55, $(M\text{-}NH_2COOCH_2CH(CH_3)_2^{+\cdot})$], 244 (59), 209 (4), 202 (26), 184 (46), 166 (20), 153 (15), 137 (25), 124 (9), 105 (30).
4f	345 [1, $(M + 2)^+$], 343 (4, $M^{+\cdot}$), 270 [4, $(M\text{-}\dot{O}CH_2CH_2CH_2CH_3)^+$], 269 [3, $(M\text{-}HOCH_2CH_2CH_2CH_3)^{+\cdot}$], 227 [5, $(M\text{-}NHCOOCH_2CH_2CH_2CH_3)^+$], 226 [5, $(M\text{-}NH_2COOCH_2CH_2CH_2CH_3)^{+\cdot}$], 300 (33), 286 (13), 275 (6), 257 (9), 244 (41), 235 (8), 222 (15), 208 (96), 182 (34), 166 (100), 135 (44), 122 (22), 105 (32), 98 (30).

TABLE 5 Antibacterial and Antifungal Activities of Compounds **4**[a]

	Zone of inhibition							
	B. subtilis		*K. pneumoniae*		*A. niger*		*C. lunata*	
Compound	*250 ppm*	*500 ppm*	*250 ppm*	*500 ppm*	*250 ppm*	*500 ppm*	*250 ppm*	*500 ppm*
4a	—	+	—	+	—	+	—	+
4b	+	++	+	+	+	+	—	+
4c	—	+	+	+	+	+	—	++
4e	—	++	++	+	—	—	+	+
4f	—	+	—	+	+	+	+	+
4h	+	+	++	+	—	—	—	—
4i	—	+	++	+	—	+	—	—

[a](−) = Inactive; (+) = weakly active; (++) = moderately active.

compounds **4a–h** appeared in the range δ −3.65 to +17.53, whereas the thiocarbamate compounds **4i** and **4j** resonate in the upfield region δ −11.33 and −24.31, and −13.86 and −13.98, respectively (Table 2). This may be attributed to the difference in the electrochemical nature of oxygen and sulfur.

Electron impact mass spectra of carbamate derivatives **4a–d, 4g–j** did not show any $(M + 2)^{+\cdot}$ and $M^{+\cdot}$ ions due to their instability under electron-impact conditions. However, compounds **4e** and **4f** with isobutanol and *n*-butanol side chains showed $(M + 2)^{+\cdot}$, and $M^{+\cdot}$ peaks (Table 4) in the ratio of 1:22, confirming the presence of the sulfur atom. The $M^{+\cdot}$ ion further degraded and characteristic daughter ions $(M\text{-}YR)^+$, $(M\text{-}HYR)^{+\cdot}$, $(M\text{-}NHCOYR)^+$ and $(M\text{-}NH_2COYR)^{+\cdot}$ were formed.

ANTIMICROBIAL ACTIVITY

The antimicrobial activities of some of these compounds were screened against *Bacillus subtilis* (gram +ve), *Klebsiella pneumoniae* (gram −ve) and fungi *Aspergillus niger* and *Curvularia lunata* by using the paper disc method, with DMF as a solvent at concentrations of 250 and 500 ppm. The culture media was nutrient agar, penicilline was tested as a reference compound for bacteria, potato-dextrose-agar (PDA) was the culture media, and Griseofulvin was the standard for fungi. The zones of inhibition formed were represented by (−), (+) and (++) depending upon the diameter and clarity. Results of antimicrobial screening indicated that most of the compounds show weak to moderate activity against both bacteria and fungi (Table 5).

EXPERIMENTAL

All melting points were determined on a Mel-Temp apparatus and were uncorrected. Elemental analyses were performed by the Central Drug Research Institute, Lucknow, India. All IR spectra were recorded as KBr pellets on a Perkin-Elmer 1483 unit. The ^1H and ^{13}C NMR spectra were taken on Varian Gemini 300 and 400 MHz NMR spectrometers operating at 300 and 400 MHz, respectively, for ^1H, 75 MHz and for ^{13}C, 101 MHz, respectively. The ^{31}P NMR spectra were taken on a Varian Gemini 400 MHz NMR spectrometer operating at 162 MHz. All spectra were recorded using DMSO-d_6 with TMS as the reference for ^1H and ^{13}C and 85%; H_3PO_4 for ^{31}P NMR. Mass spectra (EI) were recorded on a AUTO SPEC Q instrument using solid probe at 70 eV.

2-Isobutylcarbamato-2,3-dihydro-5-propylthio-1H-1,3,2-benzodiazaphosphole 2-oxide (**4e**)

A solution of isobutyl alcohol (0.37 g, 0.005 mol) in 10 mL of dry toluene was added dropwise over a period of 20 minutes to a cold solution (−10°C) of **1** (0.8 g, 0.005 mol) in 15 mL of dry toluene. After the addition, the reaction mixture was slowly warmed to room temperature and stirring was continued for another 2 hours. This reaction mixture was added dropwise *in situ* to a cold solution (0°C) of **3** (0.91 g, 0.005 mol) and triethylamine (1.01 g, 0.01 mol) in 15 mL of dry toluene. After completion of the addition, the temperature of the reaction mixture was allowed to rise to room temperature and stirring was continued for an additional 7 hours at 40–50°C. Progress of the reaction was monitored by TLC analysis. The condensed product, which is insoluble in toluene, was separated by filtration. The solid was washed with water to remove triethylamine hydrochloride and dried. Trituration of the crude product with warm 2-propanol afforded an analytically pure compound, 0.99 g (58%) of **4e**, m.p. 173–174°C. Anal. Calcd for $C_{14}H_{22}N_3O_3PS$ (343.2259): C, 48.94; H, 6.46; N, 12.24. Found: C, 48.75; H, 6.52; N, 12.12.

Compounds **4a–d** and **4f–j** were synthesized by adopting the same procedure.

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