SYNTHESIS AND CHARACTERIZATION OF 2-ALKYLCARBAMATO -1,2,3,4 - TETRAHYDRO-1,3,2-BENZODIAZAPHOSPHORINE 2-OXIDES

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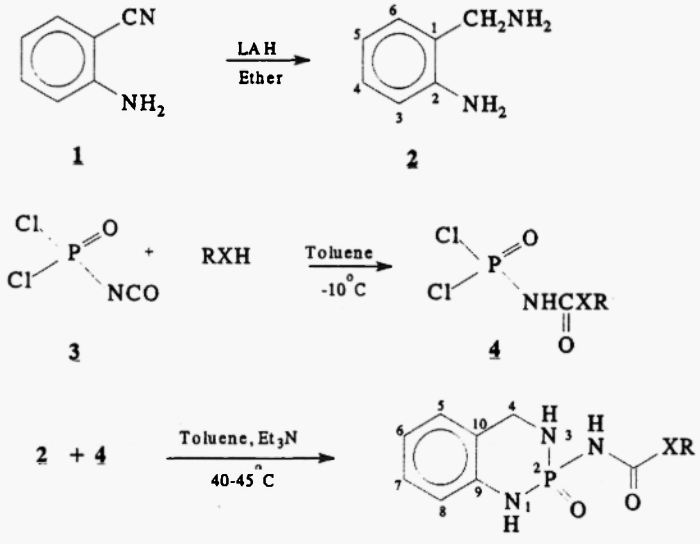
Abstract: Novel 2- alkylcarbamato-1,2,3,4-tetrahydro-1,3,2-benzodiazaphosphorine 2-oxides (**5a-h**) have been synthesized from reaction of equimolar quantities of 2- aminobenzylamine **2** with various dichlorophosphinyl carbamates **4** in dry toluene in the presence of triethylamine at 40-45°C. The title compounds (**5a-h**) at reflux temperature gave only 2- amino-1,2,3,4 - tetrahydro-1,3,2-benzodiazaphosphorine 2-oxide **6**. The structures are characterized by IR, ^{1}H,^{13}C,^{31}P NMR and mass spectral studies.

Introduction

Certain carbamate derivatives are highly anti cholinergic and poison insects and other animals. They exhibit direct effect on acetylcholine receptors because of their pronounced structural resemblance to acetylcholine (1). The benzoannulated and related analogs (2) of cyclophosphamide (3) possess antitumour activity. In view of the various possible applications of substituted carbamate heterocycles, the title compounds **5a-h** were synthesized and characterized by elemental, IR, NMR, and mass spectral analyses.

Results and Discussion

The synthetic route (Scheme 1) involves addition of isocyanatophosphonic dichloride (**3**) (4) with various alcohols/thiols at -10°C under inert, anhydrous conditions in dry toluene to afford the corresponding dichlorophosphinyl

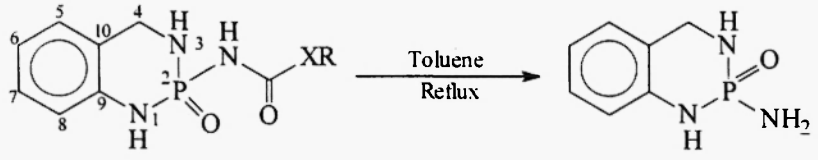


	XR				
5a.	$OCH(CH_3)_2$	**5d.**	$OCH_2CH_2OC_2H_5$	**5g.**	$S(CH_2)_2CH_3$
5b.	$O(CH_2)_3CH_3$	**5e.**	OC_6H_{11}	**5h.**	$S(CH_2)_3CH_3$
5c.	$OCH_2CH(CH_3)_2$	**5f.**	$O(CH_2)_2C_6H_5$		

Scheme 1

carbamates (**4a-h**). Cyclocondensation of **4a-h** *in situ* with 2-aminobenzylamine (**2**) in the presence of triethylamine at 40-45°C yielded the title compounds **5a-h**. In the present study, thin layer chromatography was employed to follow the reaction. Workup consisted of filtration of insoluble triethylamine hydrochloride followed by evaporation of the solvent. Recrystallization of the solid products from a suitable solvent afforded compounds **5**. Interestingly, primary and secondary alcohols reacted readily with **3**, but *t*-butyl alcohol failed under the same conditions.

Interestingly, all of the alkylcarbamato compounds (**5a-h**) on reflux in toluene suffered thermal degradation to only one product, 2-amino-1,2,3,4-tetrahydro-1,3,2-benzodiazaphos- phorine 2-oxide(**6**).



5a-h **6**

Reaction yields, elemental analysis, IR (5) and ^{31}P NMR data are given in Table 1. Appropriate ^{1}H ^{13}C NMR and mass spectral data for some members of **5** are presented in Tables 2,3 and 4 respectively. The proton NMR spectra (Table 2) exhibited signals in the range of δ 6.72-7.30 accounting for the aromatic protons of benzodiazaphosphorine and phenethyl moieties in **5**. In compounds **5a-f** the 4(H) protons resonated as two multiplets at δ 3.83-4.06 and δ 4.24-4.43 respectively. This indicates that the two methylene protons at C-4 are magnetically non-equivalent due to their orientation in axial and equatorial positions in the six-membered chair conformation of the benzodiazaphosphorine ring (Figure 1). The proton signal of the exocyclic P-NH-CO is observed in the downfield as doublet at δ 8.65-8.84 (J = 6.0-8.7 Hz) when compared to other two endocyclic NH protons. The NH signals were confirmed by a D_2O exchange experiment. It is of interest to observe that the protons of the carbamate function resonated downfield when compared to those of the corresponding protons in the free alcohols (6) and phosphorus coupling is limited to P-NH only and is not extended to other protons of carbamate side chain.

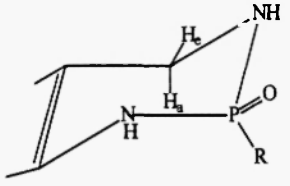


Figure 1

The ^{13}C NMR chemical shifts of **5a-f** are given in Table 3. The nitrogen - bearing carbon C(9) resonated as a singlet in the downfield region at δ 141.3 -141.5. The doublet in the upfield region at δ 116.8 - 116.9 [^{3}J=9.1 Hz] is assigned to C (8). The doublet at δ 124.2-124.4 [^{3}J=6.8-7.0 Hz] is ascribed to C (10). The chemical shifts at δ 125.7-125.8, 119.7-119.8 and 127.1-127.2 are attributed to C(5), C(6) and C (7) respectively. The C(4) absorbed at δ 43.2. The carbonyl carbon C(1') of the carbamate function resonated in the range of 153.8-154.5 ppm. The C-2' chemical shifts of the carbamate function appears downfield (~10 ppm) when compared to the signals of the corresponding carbon chemical shifts in the respective free alcohols (6). The remaining carbons of the carbamate function resonated in the expected regions. ^{31}P NMR signals (7) of these compounds (**5a-h**) appeared in the range 2.44-3.28 ppm (Table 1).

Mass spectral analyses were conducted on a few representative compounds (Table 4) and were confirmatory for the molecular ions for **5b**, **5e** and **5f** (8). Interestingly in **5b**, **5e** loss of n-butanol and cyclohexanol respectively was observed with the formation of 2-isocyanato-1,2,3,4-tetrahydro-1,3,2-benzodiazaphoshorine 2-oxide as the base peak at m/z 209. But in **5f** the base peak is observed at m/z 91 (100) due to tropylium cation. $(M-ROH)^+$, $[(M-COOR)+H]^+$ and $(M-NHCOOR)^+$ are observed uniformally as common ions in **5b**, **5e** and **5f**.

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. The ^1H, ^{13}C, and ^{31}P NMR spectra were taken on Varian Gemini 300 MHz NMR spectrometer operating at 299.9 MHz (^1H), 75.5 MHz (^{13}C) and 121.5 MHz (^{31}P). Compounds were dissolved in DMSO-d_6, and chemical shifts were referenced to TMS (^1H and ^{13}C) and 85% H_3PO_4 (^{31}P). Mass spectral data (EI) were collected on a AUTO SPEC-Q instrument at 70 eV.

Synthesis of 2-phenethylcarbamato-1,2,3,4-tetrahydro-1,3,2-benzodiazaphosphorine 2 -oxide 5f

A general procedure for members of **5** is illustrated with that for **5f**. A solution of phenethyl alcohol (1.22 g, 0.01 mol) in dry toluene (20 mL) was added dropwise (20 minutes) to a cold (-10°C) solution of **3** (1.60 g, 0.01 mol) in dry toluene (20 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 **2** (1.22g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) in dry toluene (40 mL). When the addition was complete, the mixture was stirred for 2 hours and then warmed slowly to 40-45°C. After 4 hours of stirring at 40-45°C, triethylamine hydrochloride was filtered 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 methanol, yielding 2.02 g (61%) of **5f**, mp 202-203°C. Physical and spectral data of **5a-h** are provided in Tables 1- 4.

Preparation of 2-amino-1,2,3,4-tetrahydro-1,3,2-benzodiazaphosphorine 2-oxide 6

A solution of **5f** (0.82 g, 0.0025 mol) in 30 mL of dry toluene and few drops of dimethyl formamide was pyrolised vigorously for 1 hour. Cooled the solution immediately and filtered the separated solid product. It was washed with water and recrystallized from 2-propanol-methanol (3 :1) to afford pure compound **6**, yield 0.34 g (75 %), mp 200-201°C (Found : C, 45.69; H, 5.66; $C_7H_{10}N_3OP$ requires C, 45.91; H, 5.50 %); ν_{max} (KBr)/cm^{-1} 1178 (P=O); ^1H-NMR δ 3.80 - 3.93 (m, 2H, 4-H), 6.46 - 6.62 (m, 2H, 5,6-H), 6.79 (s, 1H, 7-H), 6.97 (s, 1H, 8-H), 7.39 (s, 1H, 1-H), 4.12 (s, 1H, 3-H), 8.01 (s, 2H, NH_2); ^{31}P- NMR (85% H_3PO_4) 3.92 ppm.

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Table 1: Physical, IR and ^{31}P NMR data of compounds 5.

Compd	m.p (°C)	Yield (%)	Molecular formula	Found (Calcd) %		IR (cm^{-1})		^{31}P NMR[c]
				C	H	P=O	C=O	
5a	249-250	65[a]	$C_{11}H_{16}N_3O_3P$	48.89 (49.07)	6.08 (5.99)	1225	1735	+ 2.44
5b	220-221	54[a]	$C_{12}H_{18}N_3O_3P$	51.06 (50.88)	6.22 (6.40)	1220	1740	+ 2.71
5c	205-206	63[a]	$C_{12}H_{18}N_3O_3P$	- (50.88)	- (6.40)	1220	1738	+ 2.75
5d	198-199	60[a]	$C_{12}H_{18}N_3O_4P$	48.31 (48.16)	6.15 (6.06)	1222	1730	+ 2.60
5e	207-208	56[a]	$C_{14}H_{20}N_3O_3P$	54.18 (54.36)	6.69 (6.52)	1220	1735	+ 2.48
5f	202-203	61[a]	$C_{16}H_{18}N_3O_3P$	57.86 (58.01)	5.29 (5.48)	1225	1730	+ 2.75
5g	192-193	52[b]	$C_{11}H_{16}N_3O_2PS$	- (46.31)	- (5.65)	1230	1730	+ 3.27
5h	236-238	48[b]	$C_{12}H_{18}N_3O_2PS$	48.34 (48.15)	5.95 (6.06)	1225	1734	+ 3.28

a. Recrystallized from methanol b. Triturated with ethanol
c. ^{31}P Chemical shifts were expressed in δ, from 85% H_3PO_4 as external standard.

Table 2: ^1H and ^{31}P NMR data of compounds 5[a]

Compd	H (4)	H (5,6,7,8) Ar-H	R-H	H (1)	H (3)	NHCO
2[b]	3.82 (s, 2H, CH_2)	6.97 (d, 7.2, 3-H)	7.0 (dd, 8.0, 8.0, 4-H)	6.63 (dd, 7.2, 7.2, 5-H)	6.60 (d, 8.0, 6-H)	
5a	3.91-4.06 (m, 1H) 4.28-4.37 (m, 1H)	6.80 - 7.12 (m, 4H)	4.70 - 4.78 (m, 1H, OCH) 0.98 (d, 6H, $2CH_3$)	7.98 (d, 5.1)	5.33 (d, 5.4)	8.70
5b	3.85-3.94 (m, 1H) 4.25-4.33 (m, 1H)	6.73 - 7.05 (m, 4H)	3.88 (t, 2H, OCH_2) 1.19-1.40 (m, 4H, $2CH_2$) 0.81 (t, 3H, CH_3)	7.93 (d, 4.2)	5.29 (d, 5.1)	8.74 (d, 6.0)
5c	3.83-3.99 (m, 1H) 4.24 - 4.34 (m, 1H)	6.73 - 7.05 (m, 4H)	3.68 (d, 6.6, 2H, OCH_2) 1.67- 1.76 (m, 1H, CH) 0.81 (d, 6.3, 6H, $2CH_3$)	7.93 (d, 5.4)	5.29 (d, 6.3)	8.76 (d, 8.4)
5d	3.90 - 4.01 (m, 1H) 4.30 - 4.35 (m, 1H)	6.72 - 7.03 (m, 4H)	4.01 - 4.05 (m, 4H, OCH_2 & CH_2) 3.37 (q,2H, OCH_2) 1.06 (t, 3H, CH_3)	7.91	5.27	8.84 (d, 8.7)
5e	3.89-3.97 (m, 1H) 4.28 - 4.43 (m, 1H)	6.74 - 7.03 (m, 4H)	4.43 (s, 1H, OCH) 1.16 - 1.69 (m, 10H)	7.91 (d, 5.6)	5.26 (d, 5.6)	8.65 (d, 8.4)
5f	3.86 - 3.98 (m, 1H) 4.24 - 4.32 (m, 1H)	6.75 - 7.06 (m, 4H)	4.10 (t, 2H, OCH_2) 2.76 (t, 2H, CH_2Ar) 7.08 - 7.30 (m, 5H, Ar-H)	7.93 (d, 5.2)	5.26 (d, 5.9)	8.80 (d, 8.6)
5g	4.05 - 4.32 (m, 2H)	6.73 - 7.03 (m, 4H)	2.48 (t, 2H, SCH_2) 1.59 -1.65 (m, 2H, CH_2) 0.94 (t, 3H, CH_3)	7.95	5.31	8.75
5h	4.02 - 4.24 (m, 2H)	6.81 - 7.09 (m, 4H)	2.43 (t, 2H, SCH_2) 1.42 -1.57 (m, 4H, $2CH_2$) 1.12 (t, 3H, CH_3)	7.93	5.28	8.78

a. Data in parentheses are coupling constants, *J* in Hz.
b. Recorded in $CDCl_3$

Table 3 : ^{13}C NMR spectral data of 5

Carbon atom	5a	5b	5c	5d	5e	5f
C-4	43.2	43.2	43.2	43.2	43.2	43.2
C-5	125.8	125.8	125.8	125.8	125.7	125.8
C-6	119.7	119.8	119.7	119.7	119.7	119.8
C-7	127.2	127.2	127.2	127.1	127.1	127.2
C-8	116.9 (9.1)	116.9 (9.1)	116.9 (9.1)	116.8 (9.1)	116.9 (9.1)	116.9 (9.1)
C-9	141.5	141.4	141.4	141.3	141.5	141.4
C-10	124.3 (6.8)	124.4 (6.8)	124.3 (6.8)	124.2 (7.0)	124.3 (6.8)	124.4 (6.8)
C-1'	153.9	154.4	154.5	154.3	153.8	154.3
C-2'	67.8	64.2	70.4	63.9	72.7	65.1
C-3'	21.6	30.4	27.4	65.5	31.2	34.5
C-4'		18.5	18.8	67.7	23.4	137.9
C-5'		13.6		15.1	24.9	128.3
C-6'					23.4	128.9
C-7'					31.2	126.4
C-8'						128.9
C-9'						128.3

a. Data in parentheses are coupling constants, *J* in Hz
b. **5g**, **5h** not recorded.

Table 4 : Mass spectral data of 5b, 5e and 5f.

Compd	m/z (relative abundance)
5b.	283 (21, M^+), 227 (4), 209 (100), 208 (91), 184 (26) 183 (32), 167 (42), 165 (85), 149 (20), 120 (90), 119 (30), 118 (32), 104 (18), 93 (33), 91 (20).
5e	309 (20, M^+), 227 (60), 209 (100), 208 (95), 183 (53), 167 (45), 165 (80), 149 (31), 120 (95), 119 (40), 118 (40), 104 (26), 93 (45).
5f	331 (7.5, M^+), 288 (13), 252 (44), 226 (5), 209 (65), 208 (83), 183 (46), 167 (22), 165 (58), 149 (26), 147 (50), 122 (50), 120 (38.5), 119 (41), 118 (39), 104 (83), 91 (100), 77 (51).

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