Synthesis of *N*-(Substituted aryl/cyclohexyl)-*N*'-[5-bromo-5-nitro-2-oxido-1,3,2-dioxaphosphorinane-2-yl]ureas

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N-(Substituted aryl/cyclohexyl)-*N'*-[5-bromo-5-nitro-2-oxido-1,3,2-dioxaphosphorinane-2-yl]ureas RR′P(O)NHC(O)NHR″ (**5**) were synthesized by the reactions of 2-bromo-2-nitro-1,3-propanediol (**4**) with chlorides of aryl/cyclohexyl carbamidophosphoric acids (**3**) in the presence of triethylamine at room temperature. Their ir, ^{1}H, ^{13}C and ^{31}P nmr spectral data are discussed.

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Introduction.

Organophosphorus carbamates demonstrate insecticidal, bactericidal, antiviral, antitumour and anti carcinogenic activity [1-8]. In view of their remarkable bioactivity, some rare classes of organophosphorus urea derivatives, of the type RR′P(O)NHC(O)NHR″ (**5**) were synthesized.

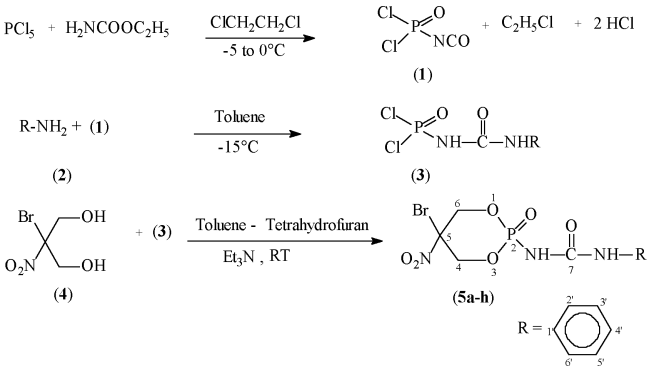
Results and Discussion.

Addition of equivalent amounts of isocyanatophosphonic dichloride (**1**) [2-3] to various amines (**2**) at -15 °C in dry toluene led to the formation of corresponding chlorides of aryl/cyclohexyl carbamidophosphoric acids (**3**) [9]. The powerful electron withdrawing effect of two chlorine atoms markedly enhances the electrophilic character of carbonyl carbon of **1** and facilitates rapid nucleophilic addition of the aryl amines even at low temperatures. Aromatic amines with electron donating substitutents in the ring added to **1** more effectively when compared to the aliphatic amines as indicated by their yields. Surprisingly addition of diphenylamine to **1** is unsuccessful due to steric reasons. These addition reactions between **1** and **2** took place in non-polar solvents at –15 °C. The reaction products separated from the reaction mixture immediately as crystalline compounds, after completion of the addition of amines to **1**. Further purification of carbamidophosphoric acids (**3**) could not be made due to their insolubility in many organic solvents and air sensitivity. Hence they were reacted directly with a solution of 2-bromo-2-nitro-1,3-propanediol (**4**) in tetrahydrofuran in the presence of two equivalents of triethylamine to afford **5a-h**.

Product yields, elemental analyses, ir and ^{31}P nmr data of **5a-h** are given in Table 1. Tables 2 and 3 contain their ^{1}H and ^{13}C nmr data. Compounds **5a-h** exhibited characteristic bands in ir spectra [10] for P=O (1235-1264 cm^{-1}), NO_2 (1538-1564 cm^{-1}), C-Br (548-598 cm^{-1}), C=O (1613-1677 cm^{-1}) and P-NH (3267-3341 cm^{-1}).

The ^{1}H nmr spectra (400 MHz) [11] of **5a-h** (Table 2) exhibited multiplets in the range of δ 4.03-4.80 accounting for the 4 and 6 methylene protons of the dioxaphosphorinane. The aromatic protons resonated as multiplets at δ 6.82-7.95. The signal of phosphoryl amidic proton of P(O)-N*H*-C=O appeared in extreme downfield at δ 9.17-10.05 when compared to the carbamidic C(O)N*H*R proton resonance signal which occurred at δ 7.90-9.42. The NH proton signals were confirmed by D_2O exchange experiments.

Scheme 1



Compound	R	Compound	R
5a	C_6H_5	**5e**	C_6H_3-$(CH_3)_2$(2′,4′)
5b	C_6H_4-Cl(4′)	**5f**	C_6H_{11}
5c	C_6H_4-Br(4′)	**5g**	C_6H_4-CH_2Cl(2′)
5d	C_6H_4-CH_3(4′)	**5h**	$C_{10}H_8$ (1′)

The ^{13}C nmr chemical shifts were recorded for **5b, 5c, 5d, 5f** and **5h** (Table 3). The C-4 and C-6 carbons resonated at δ 45.9-55.9 and C-5 signal appeared at δ 65.4-66.4. The C=O carbon gave signal at δ 146.1-157.6.

The ^{31}P nmr resonances [12] of these compounds **5a-h** appeared in the range -14.34 to -6.29 ppm (Table 1).

EXPERIMENTAL

The melting points were determined on a Mel. Temp. apparatus and are 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 1430 unit. ^{1}H and ^{13}C nmr spectra were recorded on AMX 400 MHz spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 161.9

Table 1

Physical, IR and ^{31}P NMR Spectral Data of *N*-(Substituted aryl/cyclo-hexyl)-*N'*-[5-bromo-5-nitro-2-oxido-1,3,2-dioxaphosphorinane-2-yl] Ureas

Compounds (**5a-h**)	M.P. (°C)	Yield (%)	Molecular formula	Elemental analysis Found /(Calcd) C	H	N	IR cm^{-1} NO_2	C-Br	P=O	C=O	P-NH	^{31}P NMR
5a	159-161 (d)	52	$C_{10}H_{11}N_3PO_6Br$	31.96 (31.60)	2.47 (2.91)	11.36 (11.05)	1552	565	1238	1632	3276	-6.82
5b	148-150	60	$C_{10}H_{10}N_3PO_6ClBr$	28.62 (28.97)	2.09 (2.43)	9.83 (10.13)	1548	548	1245	1677	3317	-13.54
5c	109-111 (d)	62	$C_{10}H_{10}N_3PO_6Br_2$	25.60 (26.16)	2.76 (2.19)	9.72 (9.15)	1556	578	1249	1658	3314	-7.28
5d	99-101 (d)	61	$C_{11}H_{13}N_3PO_6Br$	33.08 (33.52)	3.86 (3.32)	10.12 (10.66)	1548	569	1248	1613	3267	-6.29
5e	142-144	58	$C_{12}H_{15}N_3PO_6Br$	35.68 (35.31)	3.38 (3.70)	10.52 (10.29)	1538	582	1252	1636	3289	-
5f	214-216	48	$C_{10}H_{17}N_3PO_6Br$	30.52 (31.10)	4.01 (4.43)	10.24 (10.88)	1564	598	1259	1628	3322	-6.47
5g	145-147	56	$C_{11}H_{12}N_3PO_6ClBr$	33.32 (33.61)	3.40 (3.07)	10.41 (10.68)	1556	575	1235	1658	3286	-14.34
5h	150-152	53	$C_{14}H_{13}N_3PO_6Br$	39.52 (39.09)	2.67 (3.04)	10.04 (9.76)	1563	561	1264	1670	3341	-6.99

Compounds triturated with 2-propanol.

Table 2

^1H NMR Chemical shift [a] Data of *N*-(Substituted aryl/cyclohexyl)-*N'*-[5-bromo-5-nitro-2-oxido-1,3,2-dioxaphosphorinane-2-yl] Ureas

Compound	CH_2(4&6)	Ar-H	Cyclohexyl / *CH_2*-Ph	Ar-CH_3	P(O)-N*H*-CO	C(O)-N*H*-R
5a [c]	4.14-4.61 (m, 4H)	6.87 - 7.24 (m, 5H)		—	9.82 (brs)	8.64 (brs)
5b [b]	4.17-4.72 (m, 4H)	6.96-7.41 (m, 4H)		—	9.62 (brs)	9.18 (brs)
5c [b]	4.03-4.44 (m, 4H)	6.90-7.36 (m, 4H)		—	9.99 (brs)	9.42 (brs)
5d [c]	4.09-4.80 (m, 4H)	6.94-7.32 (m, 4H)		2.31 (s, 3H)	10.05 (brs)	9.26 (brs)
5e [b]	4.06-4.52 (m, 4H)	6.82-7.18 (m, 3H)		2.12 (s, 3H) 2.26 (s, 3H)	—	—
5f [b]	4.15-4.78 (m, 4H)	—	1.29-1.91 (m, 11 H)	—	9.81 (brs)	7.90 (brs)
5g [b]	4.41-4.58 (m, 4H)	7.10-7.35 (m, 4H)	4.22 (s, 2H)	—	9.66 (brs)	8.46 (brs)
5h [c]	4.16-4.67 (m, 4H)	7.10-7.95 (m, 8H)		—	9.17 (7.8 Hz)	8.60 (brs)

[a] Chemical shifts in δ and J (Hz) given in parenthesis; [b] Recorded in $CDCl_3$; [c] Recorded in dimethyl sulfoxide-d_6.

MHz for ^{31}P. Compounds were dissolved in $CDCl_3$ and DMSO-d_6. The chemical shifts were referenced to TMS (^1H and ^{13}C) and 85% H_3PO_4 (^{31}P).

2-Bromo-2-nitro-1,3-propanediol (**4**) was procured from Aldrich Chemical Company, inc. USA and was used without further recrystallization.

Preparation of 4-Bromophenyl Carbamidophosphoric Acid Dichloride (**3c**).

A solution of 4-bromo aniline (**2c**, 0.86 g, 50.0 mmol) in dry toluene (25 ml) was added drop wise (20 min) to a cold solution (-15 °C) of isocyanato-phosphonic dichloride (**1**, 0.8 g, 50.0 mmol) in dry toluene (30 ml). After the addition the

Table 3

^{13}C NMR Chemical Shift [a] Data of *N*-(Substituted aryl/cyclohexyl)-*N*'-[5-bromo-5-nitro-2-oxido-1,3,2-dioxaphosphorinane-2-yl] Ureas

Carbon atoms	**5b** [b]	**5c** [b]	**5d** [c]	**5f** [b]	**5h** [c]
C-4 & 6	50.2	49.5	45.9	49.1	55.9
C-5	66.4	65.7	66.2	65.4	65.5
C-7'	154.2	157.6	156.8	152.3	146.1
C-1'	136.1	138.0	136.4	49.1	140.0
C-2'	118.8	119.0	118.6	32.7	118.3
C-3'	129.9	132.1	129.9	25.6	128.6
C-4'	124.3	115.4	131.9	24.9	125.9
C-5'	129.9	132.1	129.9	25.6	124.9
C-6'	118.8	119.0	118.6	32.7	128.4
C-7'					137.0
C-8'					122.0
C-9'					134.0
C-10'					124.9
Methyl carbon			20.1		

[a] Chemical shifts in ppm; [b] Recorded in $CDCl_3$; [c] Recorded in dimethyl sulfoxide-d_6.

temperature of the reaction mixture was maintained between -15 °C to -5 °C for 30-40 minutes. Later, the temperature of the mixture was raised to room temperature, with stirring for 30-40 minutes. 4-Bromophenyl carbamidophosphoric acid dichloride being insoluble in toluene separated out. It was collected by filtration and dried under reduced pressure [9].

Synthesis of *N*-Bromophenyl-*N'*-[5-bromo-5-nitro-2-oxido-1,3,2-dioxaphosphorinane-2-yl]urea (**5c**).

A solution of 4-bromophenyl carbamidophosphoric acid dichloride (**3c**, 0.694 g, 20.0 mmol) in toluene (20 ml) was added to the solution of 2-bromo-2-nitro-1,3-propanediol (**4**, 0.400 g, 20.0 mmol) and triethylamine (0.404 g, 40.0 mmol) in dry tetrahydrofuran (20 ml) at 0 °C. After the addition, the temperature of the reaction mixture was maintained at 0 °C for 1 hour and then stirred at room temperature for 5-6 hours. The progress of the reaction was monitored by TLC in the 1:4 mixture of ethyl acetate and hexane as mobile solvent and silica gel as adsorbent. Triethylamine hydrochloride was separated by filtration and, the solvent from the filtrate was evaporated under reduced pressure. The residue obtained after washing with water was triturated with 2-propanol to afford 0.57 g (62%) of pure 5c, m.p 109-111°C (d). Physical and spectral data of 5c are given in Tables 1-3. Other members of **5** are prepared by the same procedure.

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