Synthesis and Antimicrobial activity of *N*-(substituted)-*N*'-[1,2,4,8,10,11-hexachloro-6-oxido-12*H*-dibenzo(*d*,*g*)(1,3,2)-dioxaphosphocin-6-yl]ureas

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Substituted dibenzo dioxaphosphocin-6-yl ureas were synthesized by reacting hexachlorophene (4) with different carbamidophosphoric acid dichlorides (3) in the presence of triethylamine in dry toluene at 45-50 °C. Their IR, ^{1}H, ^{13}C and ^{31}P NMR spectral data is discussed. These compounds were found to possess good antimicrobial activity.

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Introduction.

Organophosphorus compounds being ubiquitous in nature have found multifaceted applications. Phosphorous heterocycles substituted with carbamate moieties are an important as antitumour agents [1], pesticides [2], and bactericides [3,4]. Substituted phosphoryl ureas of the type RR'P(O)NHCONR"R'" possessed pesticidal activity [5-7]. In view of this, several *N*-(substituted)-*N*'-[1,2,4,8,10,11-hexachloro-6-oxido-12*H*-dibenzo(*d*,*g*)(1,3,2)dixoaphosphocin-6-yl] ureas have been synthesised, expecting them to possess broad spectrum of biological activity and were characterised by elemental, IR, NMR (^{1}H, ^{13}C and ^{31}P) analyses.

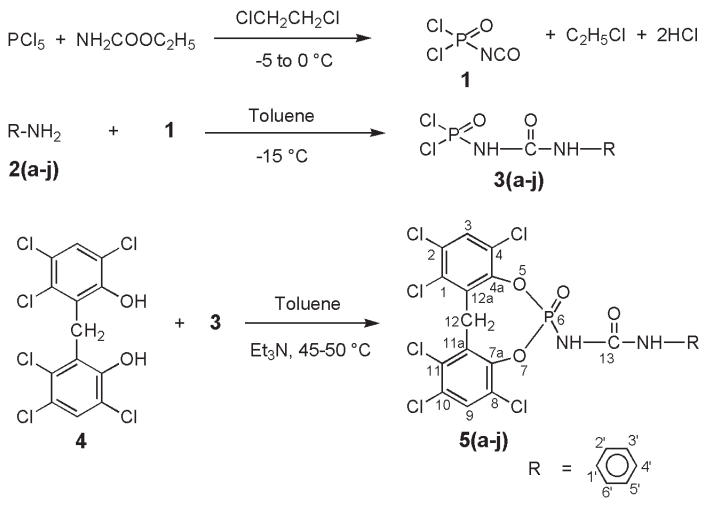
Results and Discussion.

The synthetic route (Scheme-I) involves the addition of dichloroisocyanato phosphine oxide [1,8] (**1**) with various amines (**2a-j**) at -15 °C under inert anhydrous conditions in dry toluene to afford the corresponding carbamidophosphoric acid dichlorides [9,10] (**3a-j**). After the addition of amines to **1** was completed, the products separated from the reaction mixture immediately as crystalline compounds. Further purification of carbamidophosphoric acid dichlorides (**3a-j**) could not be accomplished due to their insolubility in many organic solvents and air sensitivity. Hence they were reacted directly *in situ* with a solution of hexachlorophene (**4**) in toluene in the presence of two equivalents of triethylamine to yield the compounds **5a-j** and their structures agree with the IR [11,12] and NMR (^{1}H [13], ^{13}C [14,15] and ^{31}P [16]) data (Table 1,2 and 3).

Antimicrobial Activity.

The compounds **5a-j** (Table 4) were screened for their antifungal activity against *Aspergillus niger* and

Scheme I



Compd.	R	Compd.	R
5a	C_6H_5	**5f**	$C_{10}H_7$(1')
5b	C_6H_4-Cl(4')	**5g**	C_6H_3-$(OCH_3)_2$(3',4')
5c	C_6H_4-Br(4')	**5h**	C_6H_4-CH_2Cl(2')
5d	C_6H_4-CH_3(4')	**5i**	C_6H_{11}
5e	C_6H_3-$(CH_3)_2$(2',4')	**5j**	C_4H_8O

Table 1

Physical, IR and ^{31}P NMR Data of Compounds **5**

Product	M.P (°C)	Yield[a] (%)	Molecular formula (Molecular mass)	Elemental Analysis Found (Calcd) %			IR (cm^{-1})			^{31}P NMR[b]
				C	H	N	C=O	P=O	P-NH	
5a	205-207	59	$C_{20}H_{11}N_2PO_4Cl_6$ (587.01)	40.92 (40.78)	1.89 (1.88)	4.77 (4.78)	1684	1257	3288	-8.19, -13.40
5b	98-101	62	$C_{20}H_{10}N_2PO_4Cl_7$ (621.45)	38.65 (38.59)	1.62 (1.60)	4.50 (4.48)	1681	1250	3241	-8.18, -12.83
5c	112-113	59	$C_{20}H_{10}N_2PO_4Cl_6Br$ (665.91)	36.07 (36.13)	1.51 (1.52)	4.20 (4.19)	1675	1241	3226	-8.37, 13.38
5d	149-151	60	$C_{21}H_{13}N_2PO_4Cl_6$ (601.04)	41.96 (41.88)	2.18 (2.19)	4.66 (4.67)	1660	1286	3282	-7.82, -12.36
5e	98-100	52	$C_{22}H_{15}N_2PO_4Cl_6$ (615.06)	42.96 (42.79)	2.46 (2.48)	4.55 (4.56)	1674	1250	3310	-8.15, -13.46
5f	77-79	56	$C_{24}H_{13}N_2PO_4Cl_6$ (637.07)	45.25 (45.13)	2.05 (2.08)	4.39 (4.38)	1663	1244	3241	-7.11, -13.13
5g	72-74	53	$C_{22}H_{15}N_2PO_6Cl_6$ (647.06)	40.84 (40.73)	2.34 (2.35)	4.33 (4.35)	1670	1245	3310	-8.16, -13.44
5h	127-129	61	$C_{21}H_{12}N_2PO_4Cl_7$ (635.48)	39.69 (39.56)	1.90 (1.88)	4.41 (4.39)	1665	1242	3379	-7.83, -12.63
5i	101-102	51	$C_{20}H_{17}N_2PO_4Cl_6$ (593.06)	40.50 (40.39)	2.89 (2.88)	4.72 (4.71)	1683	1249	3295	-7.68, -12.61
5j	128-130	52	$C_{18}H_{13}N_2PO_5Cl_6$ (581.00)	37.21 (37.12)	2.25 (2.26)	4.82 (4.84)	1670	1251	3399	-9.30, -12.73

[a] Recrystallized from iso propyl alcohol; [b] ^{31}P chemical shifts were expressed in δ, from 85% H_3PO_4 as external standard.

Table 2

^1H NMR Data [a,b] of Compounds **5**

Compd.	3-H & 9H	$12CH_2$	R-H	P(=O)-NH	C(=O)-NH
5a	7.36	4.20	6.58-7.03 (m, 5H)	9.35 (s, 1H)	5.25 (brs, 1H)
5b	7.33	4.39	7.03-7.28 (m, 4H)	9.40 (s, 1H)	6.20 (s, 1H)
5c	7.29	4.35	7.19-7.25 (m, 4H)	9.45 (s, 1H)	6.24 (brs, 1H)
5d	7.28	4.33	7.02-7.20 (m, 4H) 2.27 (s, 3H, CH_3)	9.25 (brs, 1H)	5.94 (brs, 1H)
5e	7.23	4.38	6.70-7.13 (m, 3H) 2.26 (s, 3H, 2'-CH_3) 2.38 (s, 3H, 4'-CH_3)	9.10 (brs, 1H)	5.90 (brs, 1H)
5f	7.23	4.33	7.30-7.88 (m, 8H)	9.80 (s, 1H)	5.80 (brs, 1H)
5g	7.32	4.38	6.69-7.01 (m, 3H) 3.78 (s, 3H, 3'OCH_3) 3.80 (s, 3H, 4'OCH_3)	9.18 (s, 1H)	5.30 (brs, 1H)
5h	7.29	4.31	7.11-7.17 (m, 4H) -CH_2 4.37 (s, 2H)	9.35 (s, 1H)	5.40 (brs, 1H)
5i	7.32	4.31	1.29-1.81 (m, 11H)	9.80 (s, 1H)	6.90 (brs, 1H)
5j	7.31	4.37	3.68-3.80 (m, 8H)	9.78 (s, 1H)	-

[a] Chemical shifts (δ); [b] Recorded in $CDCl_3$.

Helminthosporium oryzae by comparing with standard fungicide Bavestein. Disc diffusion method [17] was followed for screening the compounds at three different concentrations (25, 50, 100 ppm). Their antibacterial activity was evaluated according the disc diffusion method [18,19] at three different concentrations against *Escherichia colia* and *Staphylococcus aureus* by comparing with standards Streptomycin. The title compounds showed greater antifungal activity than antibacterial activity.

Compounds **5a-d, 5j** were more effective against *Staphylococcus aureus* and the compound **5a-d** were effective against *Escherichia coli.* However all these compounds exhibited better antifungal activity against *Aspergillus niger* and *Helminthosporium oryzae.*

EXPERIMENTAL

Melting points were taken on Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by the Central Drug Research Institute, Lucknow, India. IR spectra were recorded as KBr pellets on a Perkin - Elmer 1430 unit. ^1H NMR and ^{13}C NMR spectra were recorded on AMX 400 MHz spectrometer operating at 400 MHz for ^1H, 100 MHz for ^{13}C and 161.9 MHz for ^{31}P. Compounds were dissolved in $CDCl_3$. The chemical shifts are referenced to TMS (^1H and ^{13}C) and 85% H_3PO_4 (^{31}P).

Hexachlorophene (**4**) was procured from Aldrich chemical company, inc. USA and was used without further recrystallization.

Preparation of 4-Chlorophenylcarbamidophosphoric Acid

Table 3
^{13}C NMR spectral data of compounds **5**[a] .

Carbon Atom	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**	**5j**
C(1,11)	134.4	133.9	133.9	133.8	133.9	133.9	132.7	133.2	133.9	134.1
C(2,10)	131.5	132.4	131.1	131.7	131.0	130.8	131.0	131.9	132.0	131.1
C(3, 9)	128.5	128.7	128.9	128.0	128.8	128.8	127.8	128.0	128.8	128.8
C(4, 8)	125.9	125.5	125.5	125.7	125.5	125.8	124.1	127.5	125.8	125.5
C(4a, 7a)	146.9	146.8	146.6	150.8	147.9	146.8	146.8	146.7	146.7	146.6
C(11a, 12a)	129.5	129.1	129.1	129.3	128.8	129.0	129.1	129.1	129.5	129.1
C(12)	30.8	29.6	30.1	30.4	29.5	29.2	29.4	30.3	29.7	29.9
C(13)	153.0	153.7	154.3	156.3	156.1	155.2	150.5	155.5	157.4	153.0
C(1')	146.9	146.7	150.7	135.7	147.0	113.7	132.0	136.0	52.1	
C(2')	119.1	116.7	116.8	119.8	124.6	129.0	131.0	133.5	32.3	43.6
C(3')	127.8	129.1	132.3	130.7	131.1	121.8	141.2	127.5	26.6	63.8
C(4')	119.0	124.6	115.6	127.5	127.6	128.5	105.2	127.0	25.3	
C(5')	128.4	129.1	131.1	130.7	124.6	128.3	124.0	127.0	25.5	63.8
C(6')	117.4	116.7	116.8	119.8	114.8	127.7	111.7	130.3	31.1	42.9
C(7')						119.59				
C(8')						149.8				
C(9')						132.1				
C(10')						128.7				
C'-CH_3				20.8	24.2 (C-4') 21.8 (C-2')					
C'-OCH_3							56.7 (C-4') 56.2 (C-3')			

[a] Recorded in $CDCl_3$.

Table 4

Antifungal and Antibacterial Activities of Compounds **5** in Terms of Zone of Inhibition (mm).

Compd.	Fungi						Bacteria					
	Aspergillus niger			*Helminthosporium oryzae*			*Escherichia coli*			*Staphylococcus aureus*		
	100	50	25	100	50	25	100	50	25	100	50	25
5a	-	-	-	10	6	-	12	7	4	10	8	5
5b	14	9	6	14	9	4	12	8	3	10	8	5
5c	10	6	-	15	15	-	16	12	8	12	9	5
5d	12	10	8	28	15	13	15	12	7	18	14	9
5e	8	5	3	14	11	9	-	-	-	10	8	-
5f	-	-	-	9	-	-	10	5	-	-	-	-
5g	13	11	9	15	12	8	12	8	-	10	7	-
5h	16	11	9	15	10	6	8	5	-	-	-	-
5i	15	11	9	12	6	-	-	-	-	-	-	-
5j	13	10	8	12	5	3	8	4	-	12	10	6
Bavistin	8	5	-	12	9	-						
Streptomycin							10	6	-	9	5	-

Concentrations expressed in ppm; '-' indicates no activity.

Dichloride (**3b**).

A solution of 4-chloro aniline (**2b**, 0.51 g, 4.0 mmol) in dry toluene (25 ml) was added dropwise (20 min) to a cold solution (-15 °C) of isocyanatophosphonic dichloride (**1**, 0.64 g, 4.0 mmol) in dry toluene (30 ml). After the addition the temperature of the reaction mixture was maintained between -15 °C to -5 °C for 30-40 minutes. Later the reaction mixture was brought to room temperature and stirred for 30-40 minutes. 4-Chlorophenyl-carbamidophosphoric acid dichloride being insoluble in toluene separated out. Without isolation and further purification, (**3b**) was used for cyclisation reactions. Other carbamidophosphoric acid dichlorides, **3a-j** were prepared following this procedure.

Synthesis of *N*-Chlorophenyl-*N*'-[1,2,4,8,10,11-hexachloro-6-oxido-12*H*-dibenzo[*d*,*g*]-1,3,2-dioxaphosphocin-6-yl]urea (**5b**).

A solution of 4-chlorophenyl carbamidophosphoric acid dichloride (**2b**, 0.575 g, 2.0 mmol) in toluene (20 ml) was added

to the solution of hexachlorophene (**4**, 0.81 g, 2.0 mmol) and triethylamine (0.404 g, 4.0 mmol) in dry toluene (20 ml) at 0 °C. After the addition, the reaction mixture was maintained at 0 °C for one hour and then stirred at room temperature for further one hour after which the temperature of the reaction mixture was raised slowly to 45-50 °C, with stirring for an additional five hours. The reaction progress was monitored by TLC in the 1:2 mixture of ethyl acetate and hexane as a 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 isopropyl alcohol to afford 0.76 g (62%) of analytically a pure material of **5b**, m.p 98-101 °C. Physical and spectral data of **5b** are given in Tables 1-3.

Other members of **5** are prepared by adopting the same procedure.

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