Synthesis and bioactivity of some new 2-substituted-3,4-dihydro-1-(9*H*- carbazol-4-yloxy)methyl-3-[2-(2-methoxyphenoxy)ethyl]-1,3,2 λ^5-oxazaphosphole 2-oxides, sulfides and selenides

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Abstract

Novel 2-substituted-3,4-dihydro-1-(9*H*-carbazol-4-yloxy)methyl-3-[2-(2-methoxyphenoxy) ethyl]-1,3,2λ^5-oxazaphosphole 2-oxides (**3a-e**) were synthesized by condensation of 1-(9*H*-carbazol-4-yloxy)-3-[2-(2-methoxy phenoxy)ethylamino]propan-2-ol (**1**) (carvedilol) with dichlorides of aryl phosphorodichloridates / *N,N*-bis(2-chloroethyl)phosphoramidic dichloride (**2a-e)** in the presence of triethylamine at 40 to 45 °C. The other title compounds (**6a-c, and 6d-f**) were prepared in two steps. In the first step, dichlorophenylphosphine/ethyl phosphorodichloridite was reacted with **1** in the presence of Et_3N to give the corresponding P(III) intermediates (**5a,b**) in N_2 atmosphere. In the second step, **5a,b** were treated with H_2O_2, S or Se to convert them to the corresponding P(V) state (**6a-c, 6d-f**). Compounds **3a-e, 6a-f** were screened for antifungal and antibacterial activity. Most of these compounds exhibited moderate activity.

Keywords: 1-(9*H*-Carbazol-4-yloxy)-3-[2-(2-methoxy phenoxy)ethyl amino] propan-2-ol; aryl phosphorodichloridates, triethylamine, oxazaphosphole 2-oxides, sulfides, selenides

Introduction

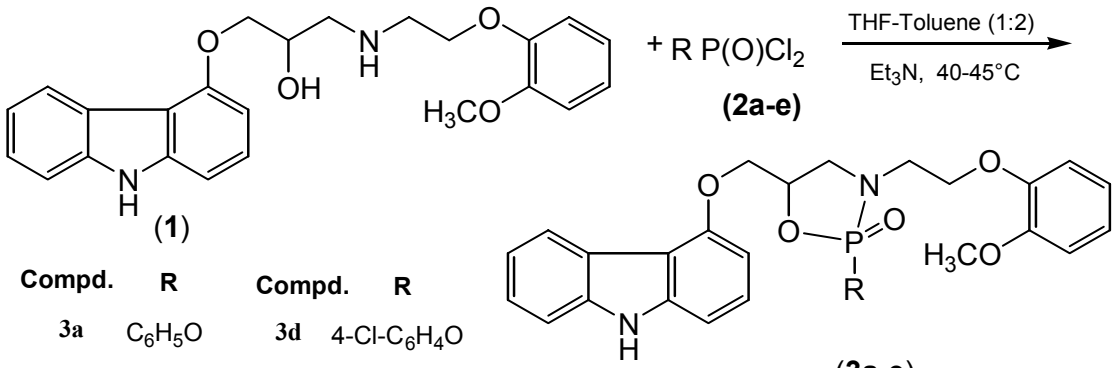
Organophosphorus compounds are ubiquitous in nature and find applications in the field of agriculture, medicine and industry.[1,2] Some organophosphorus compounds are important pesticides,[3] bactericides,[4,5] and antibiotics.[4] Synthesis of new multi-ring phosphorus heterocycles for applications in medicine and industry has attracted the attention of researchers in recent years. Phosphorus analogues of α-pyrones act as HIV protease inhibitors.[6] A number of research groups has become interested in organophosphorus heterocyclic compounds since they are finding extensive use as pesticides in agriculture, as stabilizers in polymers and as lubricant oil additives.

Carvedilol is a non-selective beta blocker indicated for the treatment of mild to moderate congestive heart failure (CHF). It is used in the management of CHF, and as an adjunct to conventional treatments (ACE inhibitors and diuretics). The use of carvedilol provides additional morbidity and mortality benefits in CHF. We have successfully phosphorylated carvedilol and introduced bio-active moieties at phosphorus.

Herein we report the synthesis of some novel oxazaphosphole 2-oxide derivatives (**3a-e**), and some oxides, sulfides and selenides (**6a-f**). and their antimicrobial activity.

Results and Discussion

The novel phosphorus heterocyclic compounds (**3a-e**), (Scheme 1) were prepared in a one-pot synthetic route, starting from carvedilol (**1**) with various phenyl phosphoro- dichloridates[7,8] (**2**) in equimolar quantities in the presence of triethylamine in dry tetrahydrofuran and toluene (1:3) at 40-45 °C. The synthesis of a few of the other title compounds such as oxide, sulfide and selenide derivatives (**6a-f**) was accomplished through a two-step route involving (**1**) with dichlorophenylphosphine and ethyl dichlorophosphite (**4a,b**) in the presence of triethylamine in dry tetrahydrofuran and toluene under N_2 to form the corresponding trivalent phosphorus intermediates **(5a,b)**. These were further converted into the corresponding oxides, sulfides and selenides by reaction with hydrogen peroxide, sulfur and selenium respectively at 45-50 °C to produce the title compounds **6a-f** (Scheme 2). Products were obtained by filtration of triethylamine hydrochloride, evaporation of the filtrate, washing the residue with water and recrystallization of the solid products from methanol. Thin layer chromatography was employed to monitor reaction progress and determine the purity of the products. All the title compounds are readily soluble in polar solvents and melt in the range of 60-110 °C.

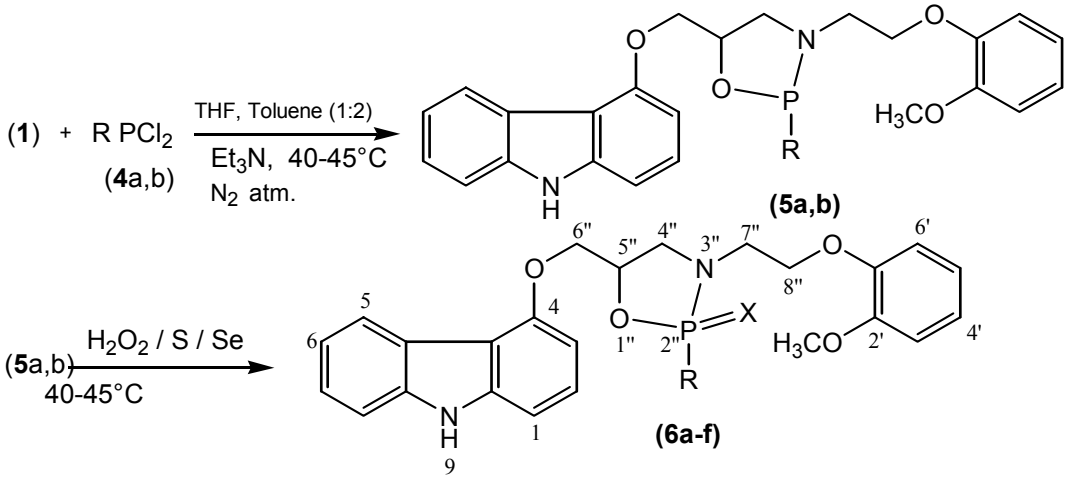


Compd.	R	Compd.	R
3a	C_6H_5O	3d	4-Cl-C_6H_4O
3b	NO_2-C_6H_4O	3e	$(ClCH_2CH_2)_2N$
3c	2-Cl-C_6H_4O		

Scheme 1

Appearance of characteristic IR bands[9,10] for NH (3410-3357 cm^{-1}), P=O (1236-1306 cm^{-1}) and P-O-C (982-907, 1200-1170 cm^{-1}), in **3a-e, 6a-f** confirm the presence of these functional groups.

Aromatic protons resonated as multiplets at δ 8.27-6.50. The NH proton of the carbazole moiety gave a signal in the range of δ 11.20-11.26. The C-4 methylene protons gave multiplets at δ 4.62-4.42 indicating their non-equivalence due to their existence in axial and equatorial positions in the rigid ring conformation. The chemical shifts of protons present in the substituents were in the expected regions.



Compd.	R	X	Compd.	R	X
6a	C_6H_5	O	**6d**	CH_3CH_2O	O
6b	C_6H_5	S	**6e**	CH_3CH_2O	S
6c	C_6H_5	Se	**6f**	CH_3CH_2O	Se

Scheme 2

^{13}C NMR chemical shifts of **1, 3a, 3c, 3e, and 6d** were interpreted on the basis of additivity rules,[11] the intensity of the signals and coupling with phosphorus. The endocyclic oxygen bonded to C-5'', gave signals at δ 68.5-75.3.[11,12] The methylene carbon C-4'' which is in the heterocyclic ring resonate in the region 41.0 to 50.9 ppm (OCH_3) carbon signals are observed in the region 55.0-58.0 ppm respectively.

^{31}P NMR chemical shifts[13,14] of the compounds (**3a-e**), **6a** and **6d**, appeared in the region –3.2 to 21.69 ppm. Whereas in **6b, 6c, 6e and 6f** signals appeared in the down field region 62.36-96.28 ppm due to the replacement of oxygen by sulfur and selenium at phosphorus atom obviously increasing the deshielding of phosphorus.

The mass spectral data of the representative compounds (**3a, 3d** and **6d**) exhibited $[M+2]^+$, $M^{+\cdot}$ and ions with substituted benzoxazaphosphole moieties at appropriate *m/z* values.

Table 1. Antibacterial activity of (**3a-e**), (**6a-f**) Zone of inhibition (mm)

Compd	*Staphylococcus aureus*		*Echerichia coli*	
	250 µg/disc	500 µg/disc	250 µg/disc	500 µg/disc
3a	14	18	10	15
3b	14	19	12	18
3c	13	15	14	17
3d	10	14	11	16
3e	15	19	6	11
6a	11	17	12	16
6b	13	18	12	16
6c	15	20	13	19
6d	12	18	14	19
6e	13	18	12	15
6f	12	15	11	14

Table 2. Physical, analytical IR and ^{31}P NMR data of compounds **3a-e, 6a-f**

Compnd	Molecular Formula	M.P. °C	Yield[a] (%)	Elemental Analysis Found (Calcd.)			IR λmax cm^{-1}				^{31}P NMR
				C	H	N	NH	P=O	P-O	O-C	
3a	$C_{30}H_{29}N_2O_6P$	102-104	70	66.06 (66.17	5.29 5.36	5.20 5.14)	3404	1253	935	1178	-4.19
3b	$C_{30}H_{28}N_3O_8P$	98-100	75	61.20 (61.12	4.74 4.78	7.06 7.12)	3392	1276	964	1183	7.04
3c	$C_{30}H_{28}N_2O_6ClP$	100-102	65	62.14 (62.23	4.82 4.87	4.79 4.83)	3357	1278	960	1192	13.13
3d	$C_{30}H_{28}N_2O_6ClP$	78-80	58	62.13 (62.23	4.81 4.87	4.78 4.83)	3399	1236	965	1200	14.25
3e	$C_{28}H_{32}N_2O_6Cl_2P$	120-122	58	56.68 (56.77	5.39 5.44	7.14 7.09)	3388	1250	936	-	17.68
6a	$C_{30}H_{29}N_2O_5P$	103-105	53	68.26 (68.17	5.47 5.53	5.24 5.30)	3378	1245	958	1170	21.69
6b	$C_{30}H_{29}N_2O_4PS$	78-80	67	66.28 (66.16	5.31 5.36	5.08 5.14)	3389	680 (P=S)	955	1180	79.63
6c	$C_{30}H_{29}N_2O_4PSe$	105-107	60	68.40 (68.31	5.50 5.54	5.26 5.31)	3394	680 (P=Se)	982	1172	96.28
6d	$C_{26}H_{29}N_2O_5P$	106-108	70	59.20 (59.08	5.47 5.53	5.24 5.29)	3365	1255	975	1182	20.12

6e	$C_{26}H_{29}N_2O_5PS$	100-102	69	61.02 (60.92	5.64 5.70	5.39 5.46)	3410	777 (P=S)	926	1183	62.36
6f	$C_{26}H_{29}N_2O_4PSe$	100-104	63	55.71 (55.82	5.16 5.22	4.95 5.00)	3405	687 (P=Se)	907	1190	84.68

[a] Recrystallized from methanol

Table 3. ^{1}H NMR of **3a-e, 6a-f**

Compd	Ar-H	-CH_2- (4")	CH (5")	-CH_2- (6")	-NCH_2CH_2O-	-OCH_3/ Ar-NH	Other H
1	7.52-6.51 (m, 11H)	4.30-4.14 (m, 2H)	3.96-3.52 (m, 1H)	3.01-2.76 (m, 2H)	4.63 (t, 2H,CH_2O) 2.66 (t, 2H, NCH_2)	3.72 (s, 3H) 11.21 (s, Ar-NH)	5.17 (s, 1H, OH), 2.01 (brs, 1H, NH)
3a	8.23-6.65 (m, 16H)	4.19-4.00 (m, 2H)	3.33-3.30 (m, 1H)	2.94-2.90 (m, 2H)	3.85 (t, 2H,CH_2O) 2.84 (t, 2H, NCH_2)	3.70 (s, 3H) 11.26 (s, Ar-NH)	-
3b	8.20-6.56 (m, 15H)	4.29-4.15 (m, 2H)	3.92-3.51 (m, 1H)	3.10-2.96 (m, 2H)	3.78 (t, 2H,CH_2O) 2.77 (t, 2H, NCH_2)	3.71 (s, 3H) 11.23 (s, Ar-NH)	-
3c	8.16-6.54 (m, 15H)	4.30-4.20 (m, 2H)	3.98-3.59 (m, 1H)	3.11-2.97 (m, 2H)	4.56 (t, 2H,CH_2O) 2.79 (t, 2H, NCH_2)	3.72 (s, 3H) 11.25 (s, Ar-NH)	-
3d	8.15-6.53 (m, 15H)	4.27-4.15 (m, 2H)	3.93-3.53 (m, 1H)	3.12-2.91 (m, 2H)	4.63 (t, 2H,CH_2O) 2.82 (t, 2H, NCH_2)	3.76 (s, 3H) 11.21 (s, Ar-NH)	-
3e	8.27-6.58 (m, 11H)	4.29-4.26 (m, 2H)	3.92-3.59 (m, 1H)	3.09-2.95 (m, 2H)	4.64 (t, 2H,CH_2O) 2.81 (t, 2H, NCH_2)	3.70 (s, 3H) 11.30 (s, Ar-NH)	3.49-3.40 (m, 4H, NCH_2), 3.30-3.27 (m, 4H, CH_2Cl)
6a	8.22-6.50 (m, 12H)	4.26-4.19 (m, 2H)	3.90-3.61 (m, 1H)	3.07-2.92 (m, 2H)	4.61 (t, 2H,CH_2O) 2.86 (t, 2H, NCH_2)	3.71 (s, 3H) 11.25 (s, Ar-NH)	-

6b	8.02-6.54 (m, 16H)	4.28-4.08 (m, 2H)	3.92-3.02 (m, 1H)	3.12-2.98 (m, 2H)	4.63 (t, 2H,CH_2O) 2.81 (t, 2H, NCH_2)	3.76 (s, 3H) 11.20 (s, Ar-NH)	-
6c	8.12-6.52 (m, 16H)	4.26.17 (m, 2H)	3.95-3.62 (m, 1H)	3.01-2.76 (m, 2H)	4.62 (t, 2H,CH_2O) 2.82 (t, 2H, NCH_2)	3.73 (s, 3H) 11.21 (s, Ar-NH)	-
6d	8.23-6.51 (m, 11H)	4.34-4.20 (m, 2H)	3.90-3.59 (m, 1H)	3.10-2.96 (m, 2H)	4.63 (t, 2H,CH_2O) 2.80 (t, 2H, NCH_2)	3.73 (s, 3H) 11.08 (s, Ar-NH)	3.53-3.32 (m, 2H, CH_2) 1.50 (t, 3H, CH_3)
6e	8.23-6.59 (m, 11H)	4.32-4.13 (m, 2H)	3.92-3.56 (m, 1H)	3.05-2.95 (m, 2H)	4.61 (t, 2H,CH_2O) 2.75 (t, 2H, NCH_2)	3.72 (s, 3H) 11.23 (s, Ar-NH)	3.50-3.10 (m, 2H, CH_2) 1.48 (t, 3H, CH_3)
6f	8.21-6.57 (m, 11H)	4.31-4.10 (m, 2H)	3.94-3.53 (m, 1H)	3.02-2.92 (m, 2H)	4.60 (t, 2H,CH_2O) 2.76 (t, 2H, NCH_2)	3.76 (s, 3H) 11.32 (s, Ar-NH)	3.47-3.10 (m, 2H, CH_2) 1.42 (t, 3H, CH_3)

- No such type of proton present
[a]Chemical shift in δ
Recorded in DMSO-d_6

Table 4. ^{13}C chemical shifts of **1, 3a, 3c, 3e** and **6d**

Compd	Chemical shifts in ppm
1	100.4 (C-1), 122.6 (C-2), 112.5 (C-3), 154.8 (C-4), 149.3 (C-4a), 103.6 (C-4b), 121.6 (C-5), 122.2 (C-6), 120.9 (C-7), 111.6 (C-8), 126.2 (C-8a), 138.8 (C-9a), 140.8 (C-1') 114.0 (C-2'), 120.6 (C-3'), 122.3 (C-4'), 111.6 (C-5'), 148.1 (C-6'), 70.4 (O<u>C</u>H_2), 68.4 (OCH_2-<u>C</u>H-OH), 48.4 (CH-<u>C</u>H_2-NH), 52.4 (HN<u>C</u>H_2-CH_2O), 65.4 (HN<u>C</u>H_2-<u>C</u>H_2O), 55.5 (O<u>C</u>H_3).
3a	100.3 (C-1), 123.7 (C-2), 115.4 (C-3), 149.6 (C-4), 147.7(C-4a), 104.4 (C-4b), 119.9 (C-5), 122.4 (C-6), 123.1 (C-7), 111.5 (C-8), 126.3 (C-8a), 139.0 (C-9a), 145.0 (C-1'), 112.4 (C-2'), 118.7 (C-3'), 121.5 (C-4'), 110.4 (C-5'), 147.1 (C-6'), 154.5 (C-1'"), 120.7 (C-2'"& C-6'"), 129.4 (C-3'"& C-5'"), 124.5 (C-4'"), 68.6 (C-6", O<u>C</u>H_2), 69.7 (C-5", <u>C</u>H), 46.3 (C-4", <u>C</u>H_2), 45.5 (C-7" N<u>C</u>H_2), 65.4

(C-8", $\underline{C}H_2O$), 55.4 ($O\underline{C}H_3$).

3c 100.3 (C-1), 123.4 (C-2), 112.4 (C-3), 149.4 (C-4), 141.2 (C-4a), 104.3 (C-4b), 119.8 (C-5), 122.4 (C-6), 120.7 (C-7), 111.5 (C-8), 126.4 (C-8a), 138.9 (C-9a), 141.2 (C-1'), 115.3 (C-2'), 121.5 (C-3'), 122.4 (C-4'), 114.2 (C-5'), 147.1 (C-6'), 154.3 (C-1'"), 124.5 (C-2'"), 130.3 (C-3'"), 122.8 (C-4'"), 128.2 (C-5'"), 118.6 (C-6'"), 69.8 (C-6", $O\underline{C}H_2$), 75.1 (C-5", $\underline{C}H$), 45.3 (C-4", $\underline{C}H_2$), 43.9 (C-7", $N\underline{C}H_2$), 65.9 (C-8", $\underline{C}H_2O$), 58.0 ($O\underline{C}H_3$).

3e 100.3 (C-1), 121.5 (C-2), 114.6 (C-3), 154.3 (C-4), 149.3 C-4a), 104.3 (C-4b), 118.6 (C-5), 122.2 (C-6), 119.7 (C-7), 110.2 (C-8), 127.2 (C-8a), 138.9 (C-9a), 142.1 (C-1') 115.4 (C-2'), 120.7 (C-3'), 121.6 (C-4'), 113.4 (C-5'), 148.5 (C-6'), 69.7 (C-6", $O\underline{C}H_2$), 74.3 (C-5", $\underline{C}H$), 46.1 (C-4", $\underline{C}H_2$), 43.8 (C-7", $N\underline{C}H_2$), 67.6 (C-8", $\underline{C}H_2O$), 55.4 ($O\underline{C}H_3$), 47.6 ($N\underline{C}H_2CH_2Cl$), 42.2 ($NCH_2\underline{C}H_2Cl$).

6d 101.6 (C-1), 122.0 (C-2), 111.4 (C-3), 155.1 (C-4), 141.9 (C-4a), 105.4 (C-4b), 119.9 (C-5), 122.1 (C-6), 121.8 (C-7), 112.4 (C-8), 127.6 (C-8a), 139.7 (C-9a), 141.9 (C-1'), 115.1 (C-2'), 118.0 (C-3'), 121.4 (C-4'), 114.4 (C-5'), 147.7 (C-6'), 70.6 (C-6", $O\underline{C}H_2$), 75.3 (C-5", $\underline{C}H$), 47.5 (C-4", $\underline{C}H_2$), 44.7 (C-7", $N\underline{C}H_2$), 66.1 (C-8", CH_2O), 56.3 ($O\underline{C}H_3$), 65.9 ($O\underline{C}H_2CH_3$), 16.6 ($OCH_2\underline{C}H_3$).

Recorded in DMSO-d_6

Table 5. FAB mass spectral data of **3a, 3d and 6d**

Compd	m/z (%)
3a	545 [(12.3) $M^{+\bullet}$ +1], 544 [(100), $M^{+\bullet}$], 529 (1.4), 469 (2.7), 407 (52.7), 391 (13.8), 331 (16.6), 307 (22.2), 222 (33.3), 206 (27.7), 154 (91.4), 136 (66.6), 107 (19.4).
3d	581 [(2.7), $M^{+\bullet}$ +2], 580 [(5), $M^{+\bullet}$ +1], 579 [(8.3), $M^{+\bullet}$], 567 (5.5), 559 (62.5), 487 (88.7), 331 (61.1), 222 (83.3), 206 (41.6), 136 (66.6), 102 (100), 91 (11.1).
6d	497 [(94.7), $M^{+\bullet}$ +1], 496 [(16), $M^{+\bullet}$], 407 (100), 373 (16.6), 314 (13.8), 183 (80.5), 180 (47.2), 154 (33.3), 136 (25), 91 (8.3).

Experimental Section

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 discs on a Nicolet 380 FT-IR Spectrometer. ^{1}H, ^{13}C and ^{31}P-NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 161.9 MHz for ^{31}P. The compounds were dissolved in DMSO-d_6, and chemical shifts were referenced to TMS (^{1}H and ^{13}C) and 85% H_3PO_4 (^{31}P). FAB-Mass spectra were recorded on Jeol SX 102/DA-6000 mass spectrometer/Data system using argon/xenon (6 kV, 10 mA) as the FAB gas. Carvedilol was procured from Aurobindo Pharma Ltd, Hyderabad, India and was used without purification.

Synthetic Procedures

Phenyl phosphorodichloridates (**2a-d)** [7,8] and *N,N*-bis (2-chloroethyl)phosphoramidic dichloride (**2e**) [7] were prepared using the reported procedure.

Synthesis of 2-(phenoxy)-3,4-dihydro-1-(9*H*-carbazol-4-yloxy)methyl-3-[2-(2-metho-xy phenoxy)ethyl]-1,3,2λ^5-oxazaphosphole 2-oxide (3a)

Compounds (**3a**) were prepared in a one-pot procedure. Phenyl phosphorodichloridate (**2a)** (0.01 mol) in dry toluene (10 mL) was added dropwise to a stirred solution of (**1)** (0.01 mol) and triethylamine (0.02 mol) in 20 mL of dry toluene and 10 mL of THF at 0 °C during 20 min. After the completion of the addition, the reaction temperature was slowly raised to 40-45 °C and was maintained at this temperature for 6 h with stirring. The progress of the reaction was monitored by TLC using ethyl acetate and hexane (3:1) and silica gel. On separation of the triethylamine hydrochloride by filtration, evaporation of the filtrate, a solid residue was obtained. It was washed with water and recrystallized from methanol to yield compound **(3a)** yield (70%), m.p. 102-104 ^{o}C.

Synthesis of compounds (6a-f)

The syntheses of compounds (**6a-c**) were accomplished through a two-step route. Dichlorophenyl phosphine (**4a)** (0.01 mol) in dry toluene (10 mL) was added dropwise to a stirred solution of (**1)** (0.01 mol) and triethylamine (0.02 mol) in 20 mL of dry THF and 20 mL of dry toluene at 0 °C during 20 min under N_2. After completion of the addition, the reaction temperature was slowly raised to 55-60 °C and was maintained at this temperature for 6 h with stirring. The completion of the reaction was monitored by TLC. After completion of the reaction the solid triethylamine hydrochloride was removed by filtration. The filtratrate containsed trivalent phosphorus intermediate (**5a**), which was further converted without isolation into the corresponding oxide, sulfide, and selinide by reaction with hydrogen peroxide, sulfur or selenium at 5 ^{o}C. After completion of the addition, the temperature was raised to 50-60 ^{o}C and maintained for 3 h. After completion of the reaction and on evaporation of the filtrate in a rota-

evaporator, a solid residue was obtained. It was washed with water and recrystallised from methanol to yield the title compounds (**6a-c).** The compounds (**6d-f**) were prepared by reacting ethyl dichlorophosphite (**4b**) with (**1**) adopting the above procedure.

Antimicrobial Activity

Compounds **3a-e, 6a-f** were screened for their antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* (10^6 cells/mL) by the disc-diffusion method[15,16] in nutrient agar medium at two concentrations (250, 500 µg/disc) in dimethylformamide (DMF). These solutions were added to each filter paper disc and DMF was used as the control. The plates were incubated at 35 °C and examined for zone of inhibition around each disc after 24 h. The results were compared with the activity of the standard antibiotic Penicillin (250 µg/disc). The compounds showed moderate activity against bacteria.

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