Synthesis and Antimicrobial Activity of Novel 2-Alkyl/Arylcarbamato-6-(1,1-dimethylethyl)-3-cyclohexyl-3,4-dihydro-2*H*-1,3,2-benzoxazaphosphorine-2-Oxides

Y. Hari Babu, P. Vasu Govardhana Reddy, C. Suresh Reddy*,
C. Devendranath Reddy and P. Uma Maheswari Devi^

*Department of Chemistry, Sri Venkateswara University, Tirupati - 517 502, India
^Department of Microbiology, Sri Padmavathi Mahila Viswavidyalayam, Tirupati, India
Received March 21, 2002

Novel 2-alkyl/arylcarbamato-6-(1,1-dimethylethyl)-3-cyclohexyl-3,4-dihydro-2*H*-1,3,2-benzoxazaphosphorine-2-oxides (**IV**) have been synthesized from reactions of 2-cyclohexylaminomethyl-4-*t*-butylphenol **I** [8c] with various dichlorophosphinyl carbamates (**III**) [8a-b] in dry toluene in the presence of triethylamine at 40-50 °C. All the title compounds (**IVa-j**) at reflux temperature are degraded to 2-amino-6-(1,1-dimethylethyl)-3-cyclohexyl-3,4-dihydro-2*H*-1,3,2-benzoxazaphosphorine-2-oxide (**IVk**) exclusively. The structures are determined by ir, nmr and mass spectral studies. They were screened for antifungal activity against *Penicillium notatum*, *Aspergillus niger* and *Helminthosporium* sps, and antibacterial activity on *Escherchia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. A few of them possess significant activity.

J. Heterocyclic Chem., **39**, 1039 (2002).

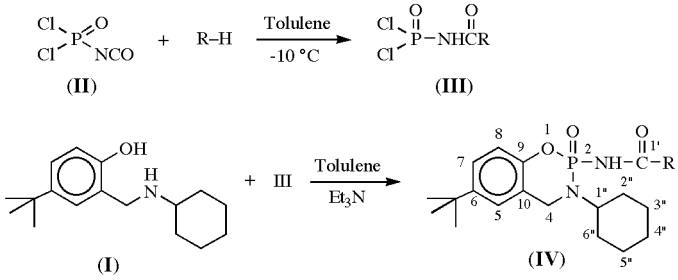
Introduction.

Large number of cyclophosphamide and its benzannulated derivatives are found to possess significant antitumour activity [1-6]. Certain carbamate derivatives are highly anticholinergic and poison animals and insects effectively. They exhibit direct effect on acetylcholine receptors because of their pronounced structural resemblance to acetylcholine [7]. In view of the possible biological and industrial potential for applications of substituted carbamate heterocycles, the title compounds (**IVa-j**) were synthesized.

Results and Discussion.

The synthetic route (Scheme-1) involves the addition of isocyanatophosphonic dichloride (**II**) [8a] to various alcohols/thiols at -10 °C under inert, anhydrous

Scheme 1

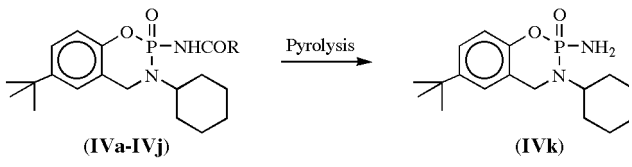


Compd.	R	Compd.	R
IVa	OCH_3	**IVf**	$OCH_2CH(CH_3)_2$
IVb	OCH_2CH_3	**IVg**	OC_6H_{11}
IVc	OCH_2CH_2Cl	**IVh**	$OCH_2C_6H_5$
IVd	$OCH(CH_3)_2$	**IVi**	$OCH_2CH_2C_6H_5$
IVe	$OCH_2CH_2CH_2CH_3$	**IVj**	$SCH_2CH_2CH_3$

Conditions, in dry toluene to afford the corresponding dichlorophosphinyl carbamates (**IIIa-j**) [8b]. Cyclocondensation of **IIIa-j** *in situ* with 2-cyclohexylaminomethyl-4-*t*-butylphenol (**I**) [8c] in the presence of triethylamine at 40-50 °C, yielded the title compounds (**IVa-j**). Thin layer chromatography was employed to follow the progress of the reaction. Filtration of insoluble triethylamine hydrochloride followed by evaporation of the solvent from the filtrate afforded crude compounds (**IV**) which on recrystallization from ethanol gave analytically pure samples. Primary and secondary alcohols reacted readily with isocyanatophosphonic dichloride, but *t*-butyl alcohol failed to react under the same conditions.

All of the alkyl/arylcarbamato compounds (**IVa-j**) are readily soluble in polar organic solvents and melt within the 120-172 °C range. Interestingly on reflux in toluene, they suffered thermal degradation to give only one product, 2-amino-6-(1,1-dimethylethyl)-3-cyclohexyl-3,4-dihydro-2*H*-1,3,2-benzoxazaphosphorine-2-oxide (**IVk**) (Scheme 2).

Scheme 2



Reaction yields, elemental analysis, ir [9] and ^{31}P nmr data are given in Table 1. ^{1}H, ^{13}C nmr and mass spectral data for some members of **IV** are presented in Tables 2, 3 and 4 respectively. Their proton nmr spectra (Table 2) exhibited signals in the δ 6.72-7.36 range accounting for the aromatic protons of benzoxazaphosphorine and phenethyl moieties in **III**. In compounds **IVa-j** the 4(H) protons resonated as two multiplets at δ 3.49-4.27 and δ 3.78-4.41 respectively. This indicates that the methylene

Table 1

Physical, IR and ^{31}P NMR Spectral Data of 2-Alkyl/arylcarbamato-6-(1,1-dimethylethyl)-3-cyclohexyl-3,4-dihydro-2*H*-1,3,2-benzoxazaphosphorine-2-oxides (**IVa-j**)

Compd.	m.p (°C)	Yield [a] (%)	Molecular Formula	Elemental Analysis Found/(Calcd) C	H	N	IR (cm^{-1}) P-NH	C=O	P=O	^{31}P NMR
IVa	158-160	75.7	$C_{19}H_{29}O_4N_2P$	59.81 (60.0)	7.60 (7.63)	7.42 (7.36)	3075	1727	1270	-1.11
IVb	160-162	65.9	$C_{20}H_{31}O_4N_2P$	60.67 (60.9)	7.71 (7.86)	7.12 (7.08)	3083	1720	1269	-1.37
IVc	129-130	76.5	$C_{20}H_{30}O_4N_2PCl$	56.34 (56.0)	6.70 (7.0)	6.42 (6.53)	3170	1763	1261	-1.99
IVd	120-121	60.7	$C_{21}H_{33}O_4N_2P$	61.93 (61.7)	8.24 (8.0)	6.71 (6.86)	3182	1722	1260	-1.66
IVe	128-129	57.8	$C_{22}H_{35}O_4N_2P$	62.35 (62.5)	8.03 (8.2)	6.61 (6.63)	3085	1725	1260	-1.56
IVf	123-125	75.8	$C_{22}H_{35}O_4N_2P$	62.24 (62.5)	8.36 (8.2)	6.58 (6.63)	3155	1728	1272	-1.47
IVg	120-122	66.9	$C_{24}H_{37}O_4N_2P$	64.01 (64.2)	8.12 (8.2)	6.12 (6.25)	3195	1724	1260	-1.34
IVh	131.33	59.6	$C_{25}H_{33}O_4N_2P$	65.33 (65.7)	7.01 (7.2)	6.21 (6.41)	3095	1719	1262	-1.00
IVi	140-141	51	$C_{26}H_{35}O_4N_2P$	66.52 (66.3)	7.56 (7.4)	5.78 (5.95)	3167	1720	1263	-1.23
IVj	170-172	58.2	$C_{21}H_{33}O_3N_2PS$	57.31 (57.2)	7.40 (7.5)	6.20 (6.36)	3171	1718	1298	-2.09

[a] Recrystallized from ethanol.

protons at C-4 are magnetically non-equivalent due to their axial and equatorial orientations in the six-membered chair conformation of the benzoxazaphosphorine ring [10] (Figure 1).

The singlet integrating for 9H in the region δ 1.17-1.25 is assigned to the *t*-butyl protons. The multiplates, in the δ 1.41-2.41 region, are attributed to the cyclohexyl protons. The exocyclic P-NH-CO proton of **IVb-j** is observed in the down field region as a broad signal at δ 8.90-9.94. But the same proton in **IVa** resonated as a doublet at δ 9.26 (*J* = 9.6 Hz). The NH proton signals were confirmed by D_2O exchange experiments. 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 [11]. They are also not experiencing any coupling with the phosphorus atom.

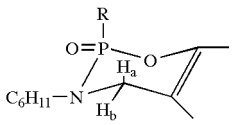


Figure 1

The proton-decoupled ^{13}C nmr chemical shifts of **IVa-j** are given in Table 3. The oxygen-bearing carbon C(9) resonated as a doublets in the downfield region at δ 147.1-153.6 (^2J = 7.6-7.8 Hz) [12]. The doublet in the upfield region at δ 116.6 - 18.1 (^{3}J = 7.2 - 7.8 Hz) is assigned to C(8). Another doublet at δ 123.9-124.6 (*J* = 7.0-7.3 Hz) is ascribed to C(10). The chemical shifts at δ 122.8-124.0, 145.8-147.2 and 125.2-128.7 are attributed to C(5), C(6) and C(7) respectively. The C(4) resonating at δ 42.7-44.6. The low intense signal at δ 34.0-34.6 and δ 31.1-31.8 are for C(11) and C(12) respectively. The signal at δ 55.1-55.8 is assigned to C(1") for all compounds, except IVh, where it resonates as a doublet with ^2J = 4.4 Hz. C(4"), C(2") and C(6"), C(3") and C(5") of cyclohexyl moiety exhibited signals in the expected range [13] which are given in Table 3.

The carbonyl carbon C(1') of the carbamate function resonated in the range of 146.3-159.0 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 [11]. The resonances of other carbon atoms of the carbamate moiety appeared in the expected regions (Table 3). ^{31}P nmr signals [14] of these compounds (**IVa-j**) appeared in the range -1.00 to -2.09 ppm (Table 1).

The EI mass spectra for **IVa-j** (Table 4) is rationalized in the Scheme 3. Appearance of M^+ at the appropriate molecular weights, $[M-(R\text{-}OH)]^{+\cdot}$ at m/z 348, $[M-(NHCOOR)]^+$ at m/z 305, $[M-(COOR)+H]^+$ at m/z 322 and $[M-(C_6H_{11})]^+$ at m/z 325 with the benzoxazaphosphorine-2-oxide moiety conclusively establishes their proposed structures [15,16] and these ions may be used as diagnostic daughter ions of these compounds for their monitoring in

Table 2

^{1}H NMR Chemical Shift (*J* in Hz) Data [a] of 2-Alkyl/arylcarbamato-6-(1,1-dimethyl-ethyl)-3-cyclohexyl-3,4-dihydro-2*H*-1,3,2-benzoxazaphosphorine-2-oxides (**IVa-j**) [b]

Compound	*t*-butyl-H	Cyclohexyl-H	Methylene-H	Ar-H	-NH-	OR-H
IVa	1.17 (s, 9H)	1.41-1.66 (m, 11H)	4.13-4.19 (m, H_b) 4.28-4.32 (m, H_a)	6.72-7.36 (m, 3H)	9.26 (d, *J*=9.6 Hz)	3.46 (s, 3H, OCH_3)
IVb	1.25 (s, 9H)	1.55-1.83 (m, 11H)	4.27-4.32 (m, H_b) 4.41-4.44 (m, H_a)	6.95-7.32 (m, 3H)	9.2 (brs, 1H)	4.03 (q, 2H, OCH_2) 1.14 (t, 3H, CH_3)
IVc	1.20 (s, 9H)	1.46-1.67 (m, 11H)	4.14-4.19 (m, H_b) 4.25-4.29 (m, H_a)	6.81-7.24 (m, 3H)	9.18 (brs, 1H)	4.64 (t, 2H, OCH_2) 4.14 (t, 2H, CH_2Cl)
IVd	1.18 (s, 9H)	1.46-2.1 (m, 11H)	3.95-4.19 (m, H_b) 4.25-4.30 (m, H_a)	6.74-7.18 (m, 3H)	9.16 (brs, 1H)	4.64 (m, 1H, OCH) 1.02 (d, 6H, $2CH_3$)
IVe	1.21 (s, 9H)	1.53-1.71 (m, 11H)	3.78 (brs, 2H)	6.8-7.6 (m, 3H)	9.66 (brs, 1H)	3.85 (m, 2H, OCH_2) 1.93 (m, 2H, CH_2) 1.15 (m, 2H, CH_2) 0.86 (brs, 3H, CH_3)
IVf	1.22 (s, 9H)	1.42-1.69 (m, 11H)	3.96-4.21 (m, H_b) 4.21-4.30 (m, H_a)	6.79-7.23 (m, 3H)	9.20 (brs, 1H)	3.61 (d, 2H, OCH_2) 1.66-1.69 (m, 1H, CH) 0.85 (d, 6H, $2CH_3$)
IVg	1.23 (s, 9H)	1.43-1.73 (m, 11H)	4.01-4.13 (m, H_b) 4.20-4.29 (m, H_a)	6.87-7.24 (m, 3H)	9.48 (brs, 1H)	4.87 (s, 1H, CH) 1.21-1.60 (m, 10H, C_6H_{10})
IVh	1.23 (s, 9H)	1.44-1.76 (m, 11H)	3.40-3.49 (m, H_b) 3.95-4.05 (m, H_a)	6.9-7.3 (m, 8H)	9.55 (brs, 1H)	5.06 (s, OCH_2)
IVi	1.21 (s, 9H)	1.41-1.72 (m, 11H)	3.92-3.96 (m, H_b) 3.98-4.02 (m, H_a)	6.8-7.2 (m, 8H)	9.03 (brs, 1H)	4.8 (t, 2H, OCH_2) 2.78 (t, 2H, CH_2)
IVj	1.25 (s, 9H)	1.42-1.77 (m, 11H)	4.00-4.10 (m, H_b) 4.15-4.26 (m, H_a)	7.0-7.2 (m, 3H)	9.78 (brs, 1H)	2.65 (m, 2H,SCH_2) 1.52-1.59 (m, 2H, CH_2) 0.94 (t, 3H,CH_3)

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

Table 3

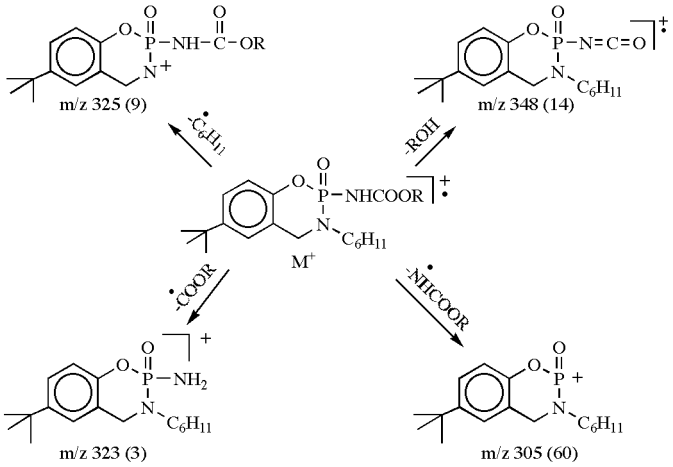
^{13}C NMR Chemical Shift Data [a] of Compounds 2-Alkyl/arylcarbamato-6-(1,1-dimethylethyl)-3-cyclohexyl-3,4-dihydro-2*H*-1,3,2-benzoxazaphosphorine-2-oxides (**IVa-j**) [b]

Com-pound	Carbon Number																	
	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}	C-1'	C-2" & C-6"	C-3" & C-5"	C-4"	C-1'	C-2'	C-3'	C-4' & 8'	C-5' & 7'	C-6
IVa	43.4	123.8	146.4	125.4	117.7 (d, *J* = 7.2 Hz)	148.2 (d, 7.7)	124.5 (d, 7.3)	34.4	32	55.2	31.0	25.9	25.2 (d, 5.2)	155.1	52.5	-	-	-	-
IVb	43.3	123.9	146.3	125.3	117.7 (d, 7.3)	148.1 (d, 7.6)	124.4	34.4	32	55.1	31.5	25.8	25.2	154.5	55.1	14.4	-	-	-
IVc	43.5	124	146.5	125.2	117.7 (d, 7.3)	148.2 (d, 7.6)	124.5	34.4	32	55.6	31.5	25.8	25.2	154.3	63.2	21.8	-	-	-
IVd	43.3	123.9	146.3	125.3	117.7 (d, 7.2)	148.2 (d, 7.7)	124.4 (d, 7.3)	34.4	32	55.1	31.5	25.8	25.2	146.3	61.3	14.4	-	-	-
IVe	43.3	123.6	146.3	125.4	117.8 (d, 7.3)	148.3 (d, 7.6)	123.9	34.3	32	55.3	31.4	25.7	25.3	146.3	68.8	43.4	21.8	-	-
IVf	43.7	123.6	146.5	128.5	117.6 (d, 7.3)	147.6 (d, 7.7)	124.6	34.5	31	55.5	31.1	24.4	24.3	146.4	68.7	44.8	24.1	-	-
IVg	44.6	122.8	146.2	128.7	117.6 (d, 7.2)	153.6 (d, 7.8)	124.6 (d, 7.2)	34.3	31	55.4	31.1	29.7	28.8	159 (d, 5.2)	60.2	48.8	30.3	28.9	-
IVh	44.2	123.5	147.2	125.7	118.1 (d, 7.3)	148.5 (d, 7.8)	124.3 (d, 7.0)	34.3	32	55.8 (d, 4.4)	31.2	25.8	25.2 (d, 4.6)	154.5	67.9	135.8	128.7	127.7	127.3
IVi	42.7	122.9	145.9	125.6	116.8 (d, 7.5)	145.9	124.3	34	32	54.4	31.4	24.9	24.7	152.8	65.3	34.0	136.2	127.8 125 (C_7')	127.4
IVj	43.9	123.6	145.8	125.6	116.7 (d, 7.6)	148.7 (d, 7.7)	124.3	34.6	32	55.5	31.3	25.8	25.0	154.3	29.3	25.0	14.1	-	-

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

bio and eco systems.

Scheme 3



EXPERIMENTAL

The melting points were determined on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed at the Central Drug Research Institute, Lucknow, India. IR spectra were recorded as KBr pellets and Nujol mulls on a Perkin-Elmer 283 unit. The ^{1}H, ^{13}C, and ^{31}P NMR spectra were taken on AMX 400 MHz spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 161.9 MHz for ^{31}P. 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). Mass spectral data (EI) were collected on a JEOL JMSD-300 instrument at 70 eV.

Synthesis of 2-Isopropylcarbamato-6-(1,1,-dimethylethyl)-3-cyclohexyl-3,4-dihydro-2*H*-1,3,2-benzoxazaphosphorine-2-oxide (**IVd**).

A solution of isopropyl alcohol (0.60 g, 0.01 mole) in 20 ml dry toluene is added drop wise during 30 minutes to a cold solution (-10 °C) of dichloro isocyanatophosphine oxide (**II**, 1.6 g, 0.01 mole) in 20 ml of dry toluene. After the addition, the temperature of the reaction mixture is slowly raised to room temperature and stirring is continued for another 2 hours. This reaction mixture is added drop wise to a cold (0 °C) solution of **I** (2.61 g, 0.01 mole) and triethylamine (2.02 g, 0.02 mole) in 30 ml of dry toluene. After the addition, the temperature of the reaction mixture is slowly raised to 40-50 °C and stirring is continued for an additional five hours. The completion of the reaction is monitored by thin layer chromatography (TLC) in the 1:6 mixture of ethyl acetate and *n*-hexane as mobile solvent. The triethylamine hydrochloride is filtered and the solvent from the filtrate is evaporated under reduced pressure. The residue is washed with water followed by chilled 2-propanol and recrystallized from ethanol to afford **IVd**, yield 2.47 g (60.7%), mp: 120-121 °C. Other members of **IV** are prepared by this procedure. Physical and spectral data of **IVa-j** are provided in Tables 1-4.

Preparation of 2-Amino-6-(1,1-dimethylethyl)-3-cyclohexyl-3,4-dihydro-2*H*-1,3,2-benzoxazaphosphorine-2-oxide (**IVk**).

A solution of **IVd** (4.08 g, 0.01 mole) in 30 ml of dry toluene was pyrolised vigorously for 1 hour, the solution was cooled immediately and solid product is collected by filtration. The solid was washed with water and recrystallized from 2-propanol-methanol (3:1) to afford pure compound **IVk**, yield 2.01 g (62.5%), mp 130-132 °C; ν_{max} (nujol) cm^{-1}: 1261 (P=O), 3179 (P-NH), ^{1}H NMR: 4.06 (d, H_a J = 7.9 Hz, CH_2), 3.89 (d, H_b, J = 20 Hz, CH_2), 7.0-7.35. (m, 3H, Ar-H), 9.5 (d, 2H, J = 9.8 Hz, NH_2); ^{31}P NMR: -1.01.

Anal. Calcd. for $C_{17}H_{27}O_2N_2P$: C, 63.35; H, 8.38; N, 8.69. Found: C, 63.19; H, 8.34; N, 8.66.

Table 4

Mass Spectral Data of Important Ions of **IVd**, **IVh** and **IVj**

Compound	m/z (Relative Abundance)
IVd	408 (25, M^+), 348 (14), 325 (9), 322 (3), 305 (60), 279 (15), 265 (34), 243 (18), 239 (49), 228 (18), 147 (21) 91 (76), 79 (90).
IVh	456 (9, M^+), 348 (25), 325 (7), 305 (80), 323 (14), 280 (41), 279 (15) 265 (37), 243 (29), 239 (28), 228 (36), 108 (57), 91 (70), 79 (92).
IVj	440 (3, M^+), 348 (11), 323 (8), 305 (40), 280 (42), 279 (14), 261 (38), 243 (16), 228 (14), 163 (60), 108 (51), 91 (67), 56 (78).

Antimicrobial Activity.

The compounds **IVa-j** and **IVk** (Table 5) were screened for their antinfungal activity against *Penicillium*, *Helmenthosporium* and *Aspergillus niger* by comparing with standard antibiotics Griseofulvin-30, 25 and Nystatin-31 mm respectively. Agar-well method [17] was followed for screening the compounds at three different concentrations (60, 80, 100 μg/disc). Their antibacterial activity was evaluated according the disc-diffusion method [18,19] at three different concentrations against *Escherchia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* by comparing with standards Tetracyclin-13 mm, Gentamycin-14 mm and Vancomcyin-12 mm respectively. The title compounds showed more antifungal activity when compared with antibacterial activity.

The compounds **IVb-d, IVg, IVh, IVj** and **IVk** were more effective against *S. aureus* and the compound **IVh**, **IVi** and **IVj** were effective against *E. coli* and the compounds **IVe, IVf, IVg, IVh, IVi** and **IVj** showed more antibacterial activity against *Pseudomonas aeruginosa*. However all these compounds exhibited more antifungal activity against *Penicillium notatum, Aspergillus niger* and *Helminthosporium* sps.

Table 5

Antimicrobial Activity of 2-Alkyl/Arylcarbamato-6-(1,1-dimethylethyl)-3-cyclohexyl-3,4-dihydro-2*H*-1,3,2-benzoxazaphosphorine-2-oxides

Compound	Concentration µg/disc	Zone of Inhibition (mm) [b] Fungi *Penicillium*	*Helmentho-sporium*	*Aspergillus niger*	Bacteria *Staphylococcus aureus*	*Escherchia coli*	*Pseudomonas aeruginosa*
IVa	60	1	5	3	-	-	-
	80	2	7	5	-	-	-
	100	4	9	7	-	-	-
IVb	60	-	2	5	3	-	-
	80	4	4	7	6	-	-
	100	6	6	10	8	-	-
IVc	60	9	2	3	2	-	-
	80	11	7	4	4	-	-
	100	15	10	7	6	-	-
IVd	60	4	5	5	1	-	-
	80	6	7	6	3	-	-
	100	10	11	9	5	-	-
IVe	60	7	5	7	0	-	2
	80	10	6	9	-	-	3
	100	12	8	13	7	-	6
IVf	60	-	1	6	-	-	-
	80	3	2	9	-	-	-
	100	5	4	10	-	-	5
IVg	60	-	4	3	3	-	-
	80	7	6	4	8	-	-
	100	10	10	6	15	-	1
IVh	60	6	3	3	2	-	4
	80	10	5	5	4	-	6
	100	12	7	7	6	7	10
IVi	60	10	4	3	-	-	-
	80	11	6	6	-	4	2
	100	12	8	7	-	6	3
IVj	60	-	1	5	1	-	-
	80	10	3	7	2	3	-
	100	12	4	9	5	6	-
IVk	60	6	4	4	-	-	3
	80	10	6	6	-	-	6
	100	14	9	8	-	-	8
[a] standards		30	25	31	12	13	14

[a] Griseofulvin (30 µg/disc) for *Penicillium* and *Helminthosporium*, Nystatin (25 µg/disc) for *Aspergillus niger*, Vancomycin (10 µg / disc) for *Staphylococcus aureus*, Tetracyclin (15 µg/disc) for *Escherichia coli* and Gentamycin (10 µg/disc) for *Pseudomonas aerugionsa*; [b] diameter of filter paper is 16 mm, compounds **4a-d** tested in 20% ethanol, **4e-k** tested in 30% of ethanol;"-" indicates no activity.

Acknowledgements.

The authors express their thanks to Dr. C. Nagaraju and Dr. M. Venugopal for helpful discussions and the Directors of SIF, IISC Bangalore and CDRI, Lucknow, for the analytical and spectral data.

REFERENCES AND NOTES

[1] Chugai Pharmaceutical Co., Japan Patent, 26819 (1965); *Chem Abstr.*, **64,** 9737 (1966).

[2] H. Arnold, F. Bourseaux and N. Brock, Arzenimittel Forsch, **11,** 143 (1961).

[3] O. M. Friedmon, Z. B. Papanastassiou and R. S. Levi, *J. Mednl. Chem.*, **6,** 82 (1963).

[4] H. Zimmer and A. Sill, *Progr Drug Res.*, **5**, 150 (1964).

[5] H. Arnold and F. Bourseaux, *Angew. Chem.*, **70**, 539 (1958).

[6a] S. M. Ludeman, G. Zon and W. Egan, *J. Med. Chem.*, **22,** 151 (1979); [b] P. B. Farmer and P. J. Cox, *J. Med. Chem.*, **18,** 1106 (1975).

[7] Robert White Stevens, Pesticides in the Environment Marcel Dekker, Inc, New York, Vol. **1**, 1971.

[8a] Z. B. Papanastasiou and T. J. Bardos, *J. Med. Chem.*, **5,** 1000 (1962); [b] L. Nagaprasada Rao, C. Devendranath Reddy and C. Naga Raju, Heterocyclic Communications, **6,** 431 (2000); [c] W. J. Burkie, *J. Am. Chem. Soc.*, **71,** 609 (1949).

[9] L. C. Thomas; The interpretation of the infrared spectra of organophosphorus compounds. Heydon. London. 1974.

[10] R. M. Silverstein, G. C. Bassler and T. C. Morril, Spectrometric Identification of organic compounds, (John Wiley & Sons, New York), 208, 1981.

[11] R. M. Silverstein and F. X. Webster, Spectrometric

Identification of Organic Compounds, 6th Edition, Wiley, New York, 1998.

[12] Van Wazer, Determination of organic structures by physical methods, (Academic Press, New York) Vol. **4**, Chapter 7, 1971.

[13] G. C. Levy and G. L. Nelson, Carbon-13 NMR for Organic Chemists, (Wiley - Interscience, New York, London), 53 (1971).

[14] L. D. Quin and J. G. Verkade, Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis, VCH Publishers, Inc., New York, 1994.

[15] J. H. Beynon, R. A. Saunders and A. E. Williams, The Mass Spectral Study of Organic Molecules, Elsevier, New York, 1968.

[16] M. S. R. Naidu and C. N. Raju, *Indian Journal of Chemistry*, **27B,** 88 (1988).

[17] F. Kavangh, Analytical Microbiology, New York, Academic Press, 290 (1963).

[18] K. R. Cruickshan, Medical Microbiology, A guide to Diagnosis and Control of Infection. IIed. Edinburgh and London: E & S. Livingston Ltd., 888 (1968).

[19] A. W. Beuer, M. M. Kirby, J. C. Sherries and A. Truck, *Am. J. Clin. Pathol.*, **45,** 493 (1969).