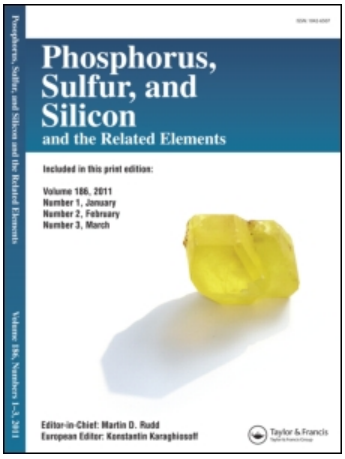

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In Search of new Organophosphorus Pesticides and Insecticides. Part III: Synthesis and Anticholinesterase Studies of 3-(Subs)-Quinoxy/Pyridinoxy/Cyclica Mino-2,3- Dihydro-2-(4-Chlorophenyl)-1*H*-Naphth [1,2-E][1,3,2] Oxazaphosphorine 3-Sulfides

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IN SEARCH OF NEW ORGANOPHOSPHORUS PESTICIDES AND INSECTICIDES. PART III: SYNTHESIS AND ANTICHOLINESTERASE STUDIES OF 3-(SUBS)-QUINOXY/PYRIDINOXY/CYCLICA MINO-2,3- DIHYDRO-2-(4-CHLORO-PHENYL)-1*H*-NAPHTH [1,2-E][1,3,2] OXAZAPHOSPHORINE 3-SULFIDES

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In situ treatment of (cyclic) amino derivatives with the product obtained from the cyclocondensation of 1-p-chloroanilinomethyl naphthol-2 and thiophosphoryl chloride in dry benzene-THF afforded the titled oxazaphosphorine sulfides in good yield. Subsequently, the reaction of pyridinoxy/quinoxythiophosphorodi chloridates and 1-p-chloro anilino methyl naphthol-2 in dry benzene-THF mixture gave the corresponding pyridinoxy/quinoxy oxaza phosphorine 3-sulfides in quantitative yield. All the condensations proceeded smoothly by employing triethylamine to scavenge the liberated hydrogen chloride gas. Anticholinestease studies of these compounds indicated very high degree of inhibition several times higher than the reference standard-methyl parathion.

Keywords: Naphthoxazaphosphorine; Anticholinesterase Agents; Synthesis; New Pesticides

INTRODUCTION

One of the most formidable problems facing the third world today is the population explosion. Current world population is estimated 3500 million

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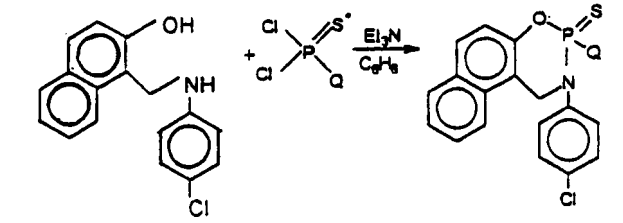
and this is expected to double by the year 2000. A large proportion of the current population has an inadequate supply of food and for many, starvation and malnutrition is an everyday problem[1]. The use of chemical fertilizers and pesticides is a major objective, and if mass starvation is to be avoided chemicals will, of necessity remain essential to agricultural productivity for the foreseeable future. As a consequence, present global awareness following a series of warnings about the indiscriminate use of pesticides has projected the easily degradable organophosphorus pesticides to wide acceptability.[2] Our continuous effort to find new organophosphorus heterocyclic compounds for use as agricultural pesticides and insecticides, having low mammalian toxicity, has led us to the synthesis of yet another series of six membered phosphorus-nitrogen-oxygen heterocyclic oxazaphosphorine sulfides. We had earlier reported[3–6] the synthesis and anticholinesterase evaluation of a series of seven and nine membered ring systems possessing S-S linkage with nitrogen and phosphorus as part of the heterocycle (Parts **I** & **II**).[3–5] Though these compounds registered more potency than the reference standard methyl parathion, metabolic degradation such as oxidation and ring opening gave rise to more toxic products with high mammalian toxicity. The mammalian toxicity factor portrays a serious drawback for any pesticide since life is threatened by the pesticide residue in crops through contamination. Consequently, insects species seem to have developed resistance to the poison by a process of natural selection. These new series of organophosphorines are envisioned to over-ride the above limitations because of their proven effectiveness as systemic fungicides, chemosterilants and nematicides. Among the phosphorus heterocyclic compounds, dioxaphospholines, dioxaphosphorines, dibenzodioxaphosphepins and oxazaphosphorine ring system were reported to be very stable and many of these compounds have been studied for their chemotherapeutic and industrial applications. Dulog and Silvan[7] and later Berlin and Nagabhushanan[8] reported the synthesis of benzodioxaphosphole cyclic system. Naidu and Raju[9] also reported a series of benzooxazaphosphorine 2-oxides. The nitrogen mustard derivative of naphthooxazaphosphorine is also a target compound in our investigation and they are prepared with the idea of testing them as carcinolytic agents.[11,12] Following the report of Sosnovsky,[10] several analogues and related compounds of cyclophosphamide showed high to moderate activity in vivo against Leukemia P-388 at a dose of 55 mg/kg. Our main objective is to increase the efficiency of organophosphorus compounds as

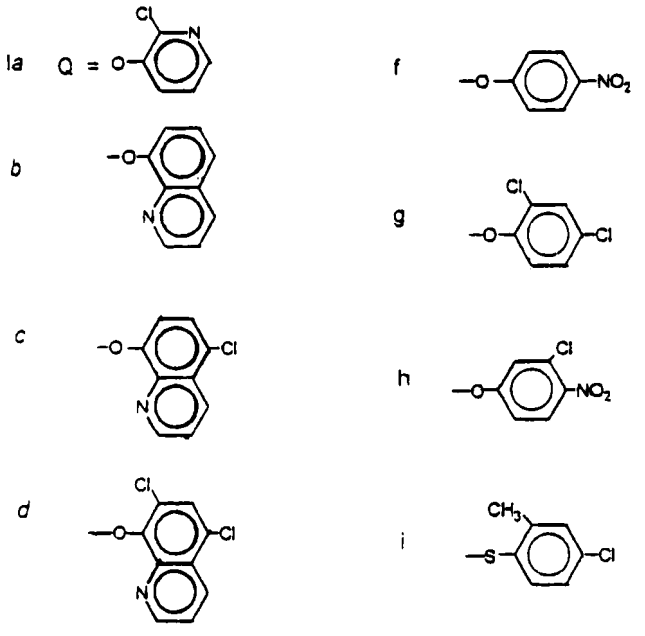
enzyme (acetylcholinesterase) inhibitors, bearing in mind their sizes, shapes and polarity which are very important to the stability of the initial enzyme-substrate complex. Also considering the fact that metabolic processes may either destroy the phosphorus compound or affect its activity generally by oxidation processes as seen in the in vivo conversion of Parathion to the more active Paraoxon[13], and the oxidative demethylation of Dimefox; we were motivated to carefully choose these series of oxazaphosphorine 3-sulfides for synthesis. The intermediate metabolic oxidation products of the titled compounds will be considerably more toxic and at the same time will be more susceptible to hydrolysis to the inactive acids.

RESULTS AND DISCUSSION

3-subs-quinoxy/2-chloro-3-pyridinoxy-2,3-dihydro-2-(4-chlorophenyl)-1*H*-naphth [1,2-e][1,3,2]oxazaphosphorine 3-sulfides (Ia-i) were synthesized by treating equimolar quantities of 1-p-chloroanilinomethylnaphthol-2 (**A**) with various aryloxy/quinoxy-aminothiophosphorodichloridates (**B**) in the presence of triethylamine in refluxing benzene-solution (scheme 1). The corresponding **cyclicamino/thiophenyl-2,3-dihydro-2-(4-chlorophenyl)-1*H*-naphth[1,2-e] [1,3,2] oxazaphosphorine 3-sulfides (IIa-g)** were synthesized in two steps. First, the reaction of equimolar quantities 1-p-chloroanilinomethylnaphthol-2 (**A**) with thio phosphoryl chloride (**C**) in the presence of triethylamine afforded the intermediate monochloridate 2,3-dihydro-2-(4-chlorophenyl)-3-chloro-1*H*-naphth[1,2-*e*][1,3,2] oxazaphosphorine 3-sulfides (**D**); and second **D** was reacted *in situ* with a number of cyclic/acyclic amines and thiols to give **IIa-g** in good yields (scheme 2). The intermediate monochloridate route was adopted since cyclic/acyclic thiophosphoramidic dichloride (**E**) could not be obtained in the pure form by treating the amine with the thiophosphoryl chloride. The crude thiophosphoramidic dichlorides (**E**) extensively decomposed when purification was attempted under reduced pressure. They are also highly toxic and moisture sensitive. All these cyclocondensations proceeded smoothly in benzene-THF (1:1) mixture and the course of each reaction was monitored by TLC. Triethylamine was employed during these cyclizations so as to convert the liberated hydrogen

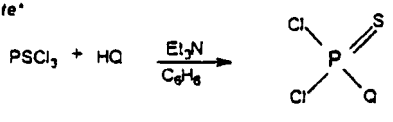


A B I



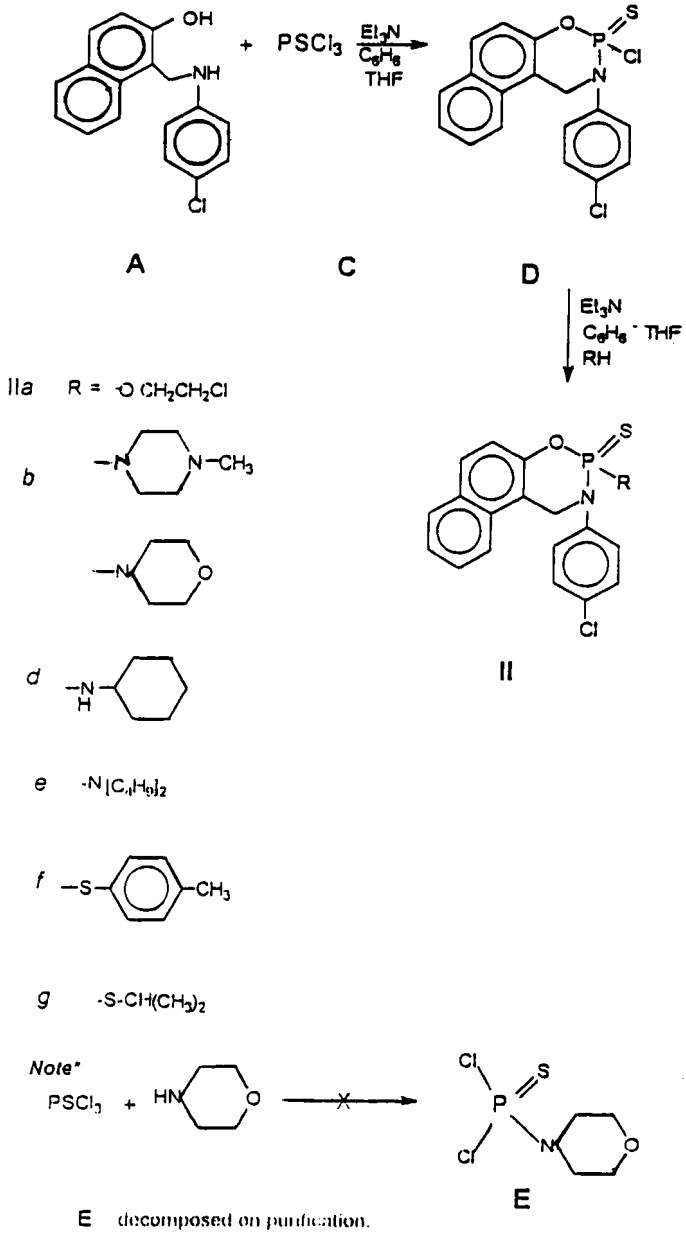
e $-N(CH_2CH_2Cl)_2$

Note



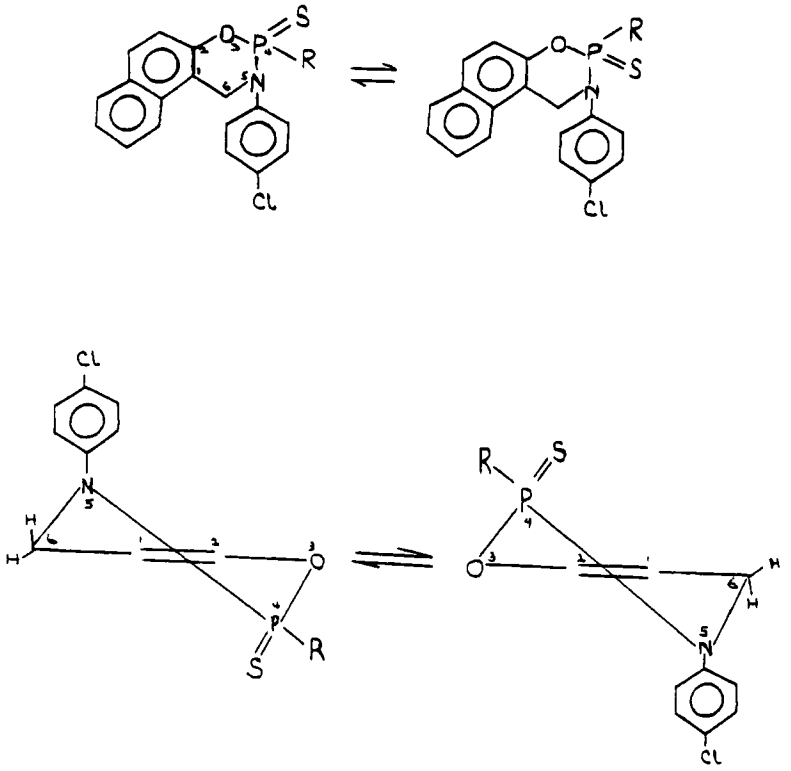
C B

SCHEME I



SCHEME 2

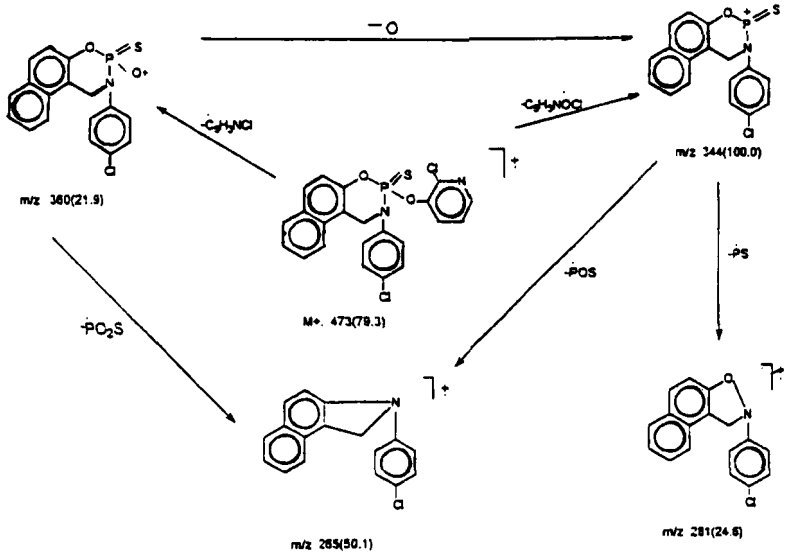
chloride to triethylamine hydrochloride. The reaction between the dichloridates (**B**) and amino-hydroxy groups in **A** is presumed to be a nucleophilic substitution at the pentavalent phosphorus of the dichloridate (or thiophosphoryl chloride) by the hydroxylamino groups.[14] The yields of all the titled compounds were fairly good (62–89%) and their physical constants are given in Table I. It was interesting to observe that chlorosubstitution at positions 5 and 7 of the quinoline ring of the dichloridate showed a quantitative effect on the rate of cyclization. The rate of cyclization of the unsubstituted quinoline was much slower than the substituted. The structures of compounds **Ia-i** and **IIa-g** were supported[15–19] by their IR, NMR(^{1}H & ^{31}P) and mass spectra (Tables II and III). In the IR spectra, they exhibited bands in the region 812–730 (P=S), 1240–1220, 980–955 (P-O-$C_{aromatic}$), 1090–1065, 740–680 (P-N-$C_{aliphatic}$), and 1100–1075, 745–660 cm^{-1} (P-N-$C_{aromatic}$). In the mass spectra, the molecular ions are significant in all spectra (Table III), hence the stability of the exocyclic P-N bond to the electron impact process in the spectra oxazaphosphorines has been pointed out by Edmundson[20] and they may have contributed to the greater molecular ion abundance. The pattern of fragmentation of **Ia** is giving in scheme 4. ^{31}P NMR spectra recorded for compounds **Ia, Ie, Ih, Ii, IIb, IId** and **IIf** showed clearly resolved (doublets in each case) signals in their chemical shifts. This doublets measuring equal in height and intensity may be attributed to the partially distorted tetrahedral geometry of the naphtha [1,2-e][1,3,2]oxazaphosphorine 3-sulfide ring system. Since the electronic configuration of phosphorus is $(1S^2)(2S^2)(2P^6)(3S^2)(3P^3)$, suitable quinquevalent compounds $R_3P{=}O$ are known to be resolvable assuming the tetrahedral configuration. However the phosphorus atom is in a stale of oscillation, with an oscillating frequency much slower than that of nitrogen. Increasing the weight of the groups further slows down the oscillation in phosphorus compounds thereby conforming it to stable stereoisomers. The double signals clearly observed in the ^{31}P NMR chemical shifts of compounds **Ia, Ie, Ih, Ii, IIb, IId** and **IIf** may be due to the assymetric quinquevalent phosphorus or to a rigid pluckering of the molecular framework. Obviously, because the six-membered ring is fused with unsaturated naphtho-ring, the compound assumes a semi-chair conformation with the almost planar nitrogen atom. The assymetric disposition of the naphtho-ring in respect to exocyclic substituents on the phosphorus atom causes the stereoisomerism, hence the compounds exist as two stereoisomers. (scheme 3).



SCHEME 3

Anticholinesterase activity

All the compounds synthesized **Ia-i** and **IIa-g** were screened in vitro for their anticholinesterase activity by the colorimetric technique,[22–24] employing healthy sheep liver as the source of the enzyme, α-napththyl acetate as substrate and fast blue B (a diazonium salt) as the colouring agent. The degree of cholinesterase inhibition caused by these compounds was compared to the inhibitory effect at the same concentration (5, 10, and 20 ppm) of a standard commercial pesticide – methyl parathion (technical grade 80%). Compounds **Ia, c, d, h** and **IIb** with chloropyridinoxy and 2-chloroethoxy moiety attracted to the phosphorus showed high degree of inhibition, 5 times greater than the reference standard. Compounds **Ib, f, g,**



SCHEME 4

and **IIf** showed moderate inhibition, while the rest of the compounds showed little or no degree of inhibition. Further toxicology protocol (exhaustive *in vivo* screening) of the oxazaphosphorine 3-sulfides may be explored in view of the fact that the enzyme oxidase in the living system converts thiophsphoryl (P=S) to the corresponding phosphoryl (P=O) function.[13] This conversion is essential for pesticidal activity.

EXPERIMENTAL SECTION

All melting points are unconected and were recorded on a Mel-Temp apparatus, Laboratory devices, Cambridge, Massachusetts USA. The elemental analysis was performed at the Regional Sophisticated Instrumentation Centre, Central Drug Research Institute (RSIC-CDRI) Lucknow, India. IR spectra was recorded as KBr disc or nujol mulls on a Perkin Elmer PE 781 spectrophotometer. ^{1}H NMR was recorded in $CDCl_3$ on a Varian EM-390 and FX100 MHz (Jeol Ltd) using TMS as internal standard. ^{31}P NMR was recorded on a Brucker WM-250 spectrometer at 101.2 MHz, and Brucker WM-300 instrument operating at 121.4 MHz

using 85% H_3PO_4as external standard. Mass spectra was determined on a Jeol JMS-D300 with JMA-2000 data processing unit at 70ev and trap current of 100 μA at RSIC- CDRI, Lucknow. 1-p-chloroanilinomethylnaphthol-2, thiophosphoryl chloride and phenoxy/pyridinoxy/quinoxythiophosphorodichloridates were prepared as described in literature.[25–28]

TABLE I Physical characteristics data of compounds **Ia-i** and **IIa-g**

Compounds	*m.p. °C*	*Yield %*	*Mol. Formula*	*Found (%) (Calc)*	
				C	*H*
Ia	92 94	77	$C_{22}H_{15}N_2O_2P_SCl_2$	55.3	3.2 (5.8 3.1)
Ib	169–170	80	$C_{22}H_{18}N_2O_2PSCl$	63.3	4.0 (63. 3.6)
Ic	143–145	62	$C_{26}H_{17}N_2O_2PSCl_2$	60.4	3.7 (60.0 3.2)
Id	150–152	89	$C_{26}H_{16}N_2O_2PSCl_3$	56.0	3.3 (55.7 2.8)
Ie	45–47	73	$C_{21}H_{20}N_2OPSCl2$	56.2	4.3 (56.0 4.4)
If	140–142	66	$C_{23}H_{16}N_2O_4PSCl$	57.9	3.4 (57.5 3.3)
Ig	109–111	79	$C_{23}H_{15}NO_2PSCl_3$	54.1	2.9 (54.1 2.9)
Ih	177–179	85	$C_{23}H_{15}N_2O_4PSCl_2$	53.3	2.6 (53.1 2.8)
Ii	88–90	71	$C_{24}H_{16}NOPS2Cl_2$	57.8	3.6 (57.6 3.2)
IIa	41–43	66	$C_{22}H_{23}N_3OPSCl$	59.9	5.2 (60.0 5.2)
IIb	158–160	69	$C_{19}H_{16}NO_2PSCl_2$	54.2	4.0 (54.2 3.8)
IIc	160–162	78	$C_{21}H_{20}N_2O_2PSCl$	58.5	4.7 (58.6 4.7)
IId	130–132	87	$C_{23}H_{23}N_2OPSCl$	62.9	5.3 (62.7 5.2)
IIe	137–139	82	$C_{25}H_{30}N_2OPSCl$	63.7	6.6 (63.8 6.4)
IIf	94–96	64	$C_{23}H_{19}NOPS_2Cl$	60.1	4.1 (60.0 4.1)
IIg	76–78	75	$C_{20}H_{19}NOPS_2Cl$	57.1	4.5 (57.1 4.5)

3-(4-Nitro-3-chlorophenoxy)-2,3-dihydro-2-(4-chlorophenyl)-1H-naphth[1,2-e] [1,3,2]oxazaphosphorine 3-sulfides (Ih; Table I)

4-Nitro-3-chlorophenylthiophosphorodichloridate (3.0g, 0.01 mol) in dry benzene-THF (25 ml) was added dropwise to a cold (10–15°) and stirred solution of 1-p-chloroanilinomethylnaphthol-2 (2.8g, 0.01 mol) and triethylamine (2.05g, 0.02 mol) in dry benzene-THF (50ml). The reaction mixture was stirred at room temperature for 3 hr and refluxed for an addi-

tional 7 hr. The progress of the reaction was monitored by TLC. Triethylamine hydrochloride that separated out was filtered off and the filterate concentrated in a rotaevaporator. The gummy residue obtained was washed with distilled water, light petroleum (60–80°) and propan-2-ol. The residue was crystallized from propan-2-ol to afford **Ih** as pale yellow crystals, yield 4.4g (85%). This typical procedure was used for the preparation of other series of compounds (**Ia-i**).

TABLE II NMR (^{1}H & ^{31}P) data of Oxazaphosphorine

Compounds	*^{1}H NMR ($CDCl_3$)*			*^{31}P NMR*
	Methyl-H	*Methylene-H*	*Aromatic-H*	
Ia	–	4.52–5.28 (m, 2H)	6.78–7.90 (m, 13H)	57.662 58. 710
Id	–	4.88–5.49 (m, 2H)	6.95–7.85 (m, 14H)	–
Ie	–	4.90–5.55 (m, 2H)	6.40–7.60 (m, 10H)	64.112 65.825
Ih	–	4.86–5.38 (m, 2H)	6.77–7.88 (m, 13H)	71.208 72.562
Ii	2.9 (s, 3H)	4.90–5.65 (m, 2H)	6.99 7.95 (m, 13H)	60.448 61.52
IIa	2.3 (s, 3H)	4.30–5.20 (br-m, 2H)	6.80–7.90 (m, 10H)	–
IIb	–	3.80 (s, 4H) 4.68 1.99 (m, 2h)	6.72–7.98 (m, 10H)	52.003 53.128
IId	–	2.90–3.00 (s, 10H) 4.80–5.10 (m, 2H)	6.68–7.91 (m, 10H)	46.444 47.912
IIf	2.5 (s, 3H)	4.87–5.23 (m, 10H)	6.87–7.82 (m, 10H)	59.281 61.018
IIg	2.7–2.9 (d, J=3.1, 6H)	4.92–5.46 (m, 2H) 5.45–5.51 (m, H)	6.92–7.74 (m, 10H)	–

(-) ^{31}P NMR not recorded

2,3-Dihydro-2-(4-chlorophenyl)-3-(N-methylpiperazinyl)-1H-naphth[1,2-e] [1,3,2] oxazaphosphorine 3-sulfide (IIa, Table I)

A mixture of 1-p-chloroanilinomethylnaphthol-2 (2.8g, 0.01 mol) and triethylamine (3.08g, 0.03 mol) in dry benzene-THF (50 ml) was stirred at 5–10 for 45 min. Thiophosphoryl chloride (1.68g, 0.01mol) in dry ben-

zene-THF (20 ml) was then added dropwise to the above stirred solution. After stirring at the same temperature for 4 hr, the mixture was gradually brought to refluxing, then refluxed for 3 hr, cooled to 5° and N-methylpiperazine (1.0g, 0.01 mol) in dry benzene-THF (20 ml) added to it dropwise. The progress of the reaction was followed by TLC using benzene-ethylacetate (4:1) as mobile phase. The reaction mixture was stirred at room temperature for an additional 3 hr. Triethylamine hydrochloride that separated out was filtered off and the filterate concentrated in a rotaevaporator. The residue obtained was washed with water, light petroleum (60–80) and was run through a chromatographic column of silica gel and eluting with a mixture of benzene-ethylacetate (3:1) to afford **IIa** as colorless granules yield 2.9g (66%) melting at 41–43°. Other members of the series (**IIa-g**) were prepared by adopting a general procedure as described for the preparation of **IIa**.

TABLE III Important fragments of naphtha[1,2-e][1,3,2]oxazaphosphorine sulfides

Compounds	*M+*	*m/z (relative intensity)*
Ia	473(79.3)	360(21.9), 344(100.0), 281(24.6), 265(50.1)
Id	557(62.8)	360(72.6), 344(100.0), 281(13.8), 265(37.0)
Ie	450(33.4)	360(28.7), 344(100.0), 281(13.8), 265(14.0)
Ii	500(29.3)	360(40.6), 344(100.0), 281(13.8), 265(14.0)
Ih	517(44.0)	360(19.2), 344(100.0), 281(26.8), 265(4.0)
IIa	443(26.3)	360(50.0), 344(100.0), 281(62.0), 265(21.9)
IIb	424(19.7)	360(77.4), 344(62.8), 281(100.0), 265(25.6)

Acknowledgements

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