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Syntheses of 2-(substituted phenoxy)-2,3-dihydro-1*H*-naphtho-(1,8-*de*)-1,3,2-diazaphosphorine 2-oxides

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Abstract. A series of diazaphosphorine 2-oxides were prepared by condensing 1,8-diaminonaphthalene with different aryloxyphosphorodichloridates and their structures confirmed by IR and NMR spectra. These compounds produced behavioural abnormalities leading to death in cockroaches due to their action on the nervous system.

Keywords. Naphtho-(1,8-*de*)-1,3,2-diazaphosphorine 2-oxides; infrared; nuclear magnetic resonance; toxicity.

1. Introduction

2-Amino-ethyl phosphonic acid derivatives are held in reserve as reagents for the emergency regeneration of adenosine triphosphate on which all life activity depends (Emsley and Hall 1976). Due to the structural similarity of heterocyclic phosphates and their derivatives with purines, they are expected to function as anti-metabolites in cancer chemotherapy (Timmis and Lister 1966). Imidazole derivatives of organophosphorus compounds are effective fungicides (Tolkmith *et al* 1967). In view of the widespread use of organophosphorus compounds in agriculture, medicine and industry (Van Wazer 1961), a series of 2-(substituted phenoxy)-2,3-dihydro-1*H*-naphtho-(1,8-*de*)-1,3,2-diazaphosphorine 2-oxides have been synthesised and their spectral and biological properties are evaluated.

2. Results and discussion

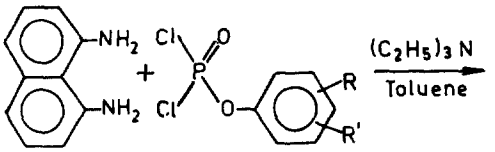
Different diazaphosphorine 2-oxide compounds are prepared by condensing equimolar quantities of 1,8-diaminonaphthalene with substituted aryloxyphosphorodichloridates in toluene in the presence of triethylamine. Diamine and dichloridate are mixed at room temperature and gradually brought to the reflux temperature with stirring in about two hours. The cyclised product is isolated by filtering the reaction mixture and washing the residue with water to remove triethylamine hydrochloride (table 1).

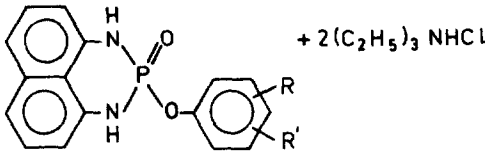
*For correspondence.

Table 1. Synthesis of diazaphosphorine 2-oxides.

Compound	Yield (%)[a]	Reaction time (min)	M.P.(°C)	Molecular formula	Found (calcd)[(%)]		NMR spectra[b]			
					C	H	J_{H-P}	N–H	Naphthyl	Aromatic
1	61	300	238–240	$C_{16}H_{13}N_2O_2P \cdot \frac{1}{2} H_2O$	62·5 (62·7)	4·4 (4·6)	24	8·2 (*d*, 2H)	6·7–7·1 (*m*, 6H)	7·2–7·5 (*m*, 5H)
2	65	330	235–236	$C_{17}H_{15}N_2O_2P$	65·7 (65·8)	4·9 (4·8)	24	8·21 (*d*, 2H)	6·6–7·0	7·1–7·5 (*m*, 5H)
3	65	330	230–231	$C_{17}H_{15}N_2O_2P$	65·5 (65·8)	5·1 (4·8)	24	8·15 (*d*, 2H)	6·6–7·1 (*m*, 6H)	7·3–7·6 (*m*, 4H)
4	74	340	253–255	$C_{17}H_{15}N_2O_2P$	65·7 (65·8)	4·6 (4·8)	24	8·18 (*d*, 2H)	6·6–7·0 (*m*, 6H)	7·2–7·5 (*m*, 4H)
5	75	320	185–186	$C_{18}H_{17}N_2O_2P \cdot \frac{1}{2} H_2O$	64·5 (64·8)	5·3 (5·1)	24	8·22 (*d*, 2H)	6·6–7·2 (*m*, 6H)	7·3–7·5 (*m*, 3H)
6	72	315	240–242	$C_{18}H_{17}N_2O_2P \cdot \frac{1}{2} H_2O$	64·4 (64·8)	5·5 (5·1)	—	—	—	—
7	72	300	206–207	$C_{18}H_{17}N_2O_2P \cdot \frac{1}{2} H_2O$	64·5 (64·8)	5·4 (5·1)	24	8·2 (*d*, 2H)	6·6–7·2 (*m*, 6H)	7·3–7·6 (*m*, 3H)
8	71	315	210–211	$C_{18}H_{17}N_2O_2P \cdot \frac{1}{2} H_2O$	64·6 (64·8)	5·0 (5·1)	24	8·2 (*d*, 2H)	6·7–7·2 (*m*, 6H)	7·2–7·5 (*m*, 3H)
9	70	350	235–236	$C_{16}H_{12}N_2O_2PCl \cdot H_2O$	55·1 (55·2)	3·9 (4·1)	24	8·21 (*d*, 2H)	6·6–7·0 (*m*, 6H)	7·0–7·5 (*m*, 4H)
10	85	340	208–210	$C_{16}H_{12}N_2O_2PCl \cdot H_2O$	55·1 (55·2)	4·0 (4·3)	24	8·2 (*d*, 2H)	6·8–7·1 (*m*, 6H)	7·2–7·6 (*m*, 4H)
11	87	360	205–206	$C_{16}H_{11}N_2O_2PCl_2$	52·6 (52·7)	3·1 (3·1)	—	—	—	—

[a]Products obtained after crystallising once; [b]δ values in ppm, J in Hz.





Compound no.	R	R′
1	H	H
2	2-CH_3	H
3	3-CH_3	H
4	4-CH_3	H
5	3-CH_3	5-CH_3
6	3-CH_3	4-CH_3
7	2-CH_3	3-CH_3
8	2-CH_3	6-CH_3
9	2-Cl	H
10	4-Cl	H
11	2-Cl	4-Cl

The reaction between 1,8-diaminonaphthalene and aryloxyphosphorodichloridates leading to naphthodiazaphosphorine is a nucleophilic substitution of the amino groups of the diamine at the phosphorus atom of the dichloridate. Similar nucleophilic substitution leading to cyclisation was reported earlier by refluxing the diamine in a current of dry nitrogen. But this procedure requires a long time for completion of the reaction and the yields of the products are poor. It has been found that the condensation of the diamine with dichloridate proceeds smoothly in the presence of triethylamine in toluene and the yields of the cyclised products are also high. This may be due to the fact that the base acts as a driving force in effecting the nucleophilic substitution by scavenging the hydrogen chloride as and when it is formed. A study of the yields and the reaction times indicates that various substituents like methyl groups or chlorine atoms present in the aryloxy moiety of the dichloridate have very little effect on the rate of the reaction and the yields.

2.1 *IR spectra*

P=O stretching frequencies of all these compounds are observed at the lower wavelength region 1220–1200 cm^{-1} showing that the oxygen of the P=O group is

involved in hydrogen bonding with the hydrogen of the amidic (−NH) group (Bellamy and Beecher 1952). The P−N−C group gives two bands, 760–740 cm^{-1} and 970–940 cm^{-1} for P−N and N−C stretching respectively (Holmstedt and Larsson 1951; Burgada *et al* 1963). Three characteristic bands at 3200–3160 cm^{-1} (N−H stretching), 1390–1360 cm^{-1} (N−H vibration) and 1070–1050 cm^{-1} (N−H rocking) are observed for the (P)−N−H group (Chittenden and Thomas 1966; Nyquist 1964; Freid and Steger 1966). A very intense band appears at 1070–980 cm^{-1} due to (P)−O−C stretching. A strong absorption band at 810–740 cm^{-1} is attributed to the P−O−(C) stretching mode (Thomas and Chittenden 1964) and a third band with variable intensity arises from the deformation vibration of the (P−O−C) group at 1170–1120 cm^{-1}.

2.2 *^1H NMR spectra*

The N−H chemical shifts in all these compounds (table 1) appeared at 8·2 ppm as a doublet contrary to the resonance signal for the NH_2 protons of 1,8-diaminonaphthalene. The coupling of NH protons with the phosphorus atom results in the splitting of the NH proton resonance signal to a doublet (J = 24 Hz). Hydrogen bonding of the NH proton with the P=O group (Williams and Fleming 1973) and the deshielding effect of the diazaphosphorine ring system may be the factors responsible for the extreme downfield shift of its resonance signal. A multiplet in the downfield region at 7–7·6 ppm appeared for the aryloxy protons. A complex six-proton multiplet at 6·6–7·2 ppm is assigned to the protons of the naphthalene moiety of these molecules. Compounds 2 and 3 exhibited the methyl chemical shifts at 2·2 ppm as a singlet. The dimethyl compounds 5 and 8 also showed only one methyl signal at 2·2 ppm since the two methyl groups are indistinguishable. For compound 7, two separate signals appeared at 2·2 and 1·7 ppm due to the C_2 and C_3 methyl groups of the aryloxy moiety.

3. Toxicity evaluation

Different concentrations of test compounds (2, 3, 4 & 10) were prepared in acetone. A known concentration of test compound was sprayed on the surface of the cuticle of cockroaches (*Paramecium americana*) and the effects observed. The mortality in each group was noted after 24 hours.

Observations were made on the behavioural aspects of cockroaches after the topical applications of some of these compounds (2, 3, 4 & 10). The findings revealed that immediately after the application of a lethal dose of the compounds the cockroaches exhibited a decreased response to feed and external stimuli, restlessness and impairment of locomotion leading to paralysis or a lethargic state. All these observed behavioural abnormalities may be due to the direct action of the compounds on the nervous system of the cockroaches. From the LD_{50} values it was observed that chlorine-substituted compounds in the 2-phenoxy group were more toxic than methyl- and dimethyl-substituted compounds. Greater toxicity of compounds 10 and 4 over fenvalirate, a known insecticide, suggests the possibility of their use as insecticides.

4. Experimental

Melting points are determined on mel-temp apparatus, TEMPO Instruments, India, and are uncorrected. The elemental analyses were performed at the Central Drug Research Institute, Lucknow. The infrared spectra were recorded on a Perkin-Elmer infrared spectrometer model 983 in nujol mulls and KBr pellets. The nuclear magnetic resonance spectra were recorded on a 90 MHz FT NMR spectrometer at sweep width 1000 Hz in d_6-acetone, with TMS as the internal standard, at the National Chemical Laboratory, Pune.

4.1 *Starting materials*

1,8-Diaminonaphthalene was procured from the Aldrich Chemical Company, USA, and recrystallised with an ethanol-water mixture (1 : 1) before use.

Phenyl and substituted phenylphosphorodichloridates were prepared according to the reported procedure (Rubstova and Zhilina 1959).

4.2 *2-(Phenoxy)2,3-dihydro-1 H-naphtho-(1,8-de) 1,3,2-diazaphosphorine 2-oxide*

To a stirred solution of (1·58 g, 0·01 mol) of 1,8-diaminonaphthalene and (2·02 g, 0·01 mol) of triethylamine in 50 ml of dry toluene, (2·15 g, 0·01 mol) of phenylphosphorodichloridate in 15 ml of dry toluene was added dropwise over a period of thirty minutes. The reaction mixture was stirred for 3 hours at room temperature and again refluxed for 2 hours and cooled. It was filtered, the residue washed with water to remove triethylamine hydrochloride and the compound was recrystallised from 2-propanol. Compounds 2–11 were prepared similarly.

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