

Synthesis, infrared and mass spectral studies of substituted 2-cyclohexyl-2,3-dihydro-1H-1,3,2-benzodiazaphosphole 2-oxides

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Abstract. A series of the title compounds have been prepared and the structures assigned to them were confirmed by IR and mass spectra. The existence of hydrogen bonding between the amidic hydrogens and the phosphoryl oxygen in these compounds is indicated by the IR spectra. The benzodiazaphosphole ring system appears to be quite stable under electron impact. An interesting type of McLafferty rearrangement occurred in many of these molecules resulting in the formation of ions of benzodiazaphosphinous acid along with the ejection of cyclo-hexane moiety from the molecular ion. Cleavage of P-N bonds of the molecular ions leading to the formation of the *o*-phenylene diamine cations is observed.

Keywords. Benzodiazaphosphole 2-oxides; infrared; mass spectral study.

1. Introduction

Organophosphorus compounds structurally relating to purine and 8-azaguanine have been synthesized and shown to possess promising antitumour activity (Arnold *et al* 1958; Takamizawa *et al* 1970). The nitrogen mustard derivative of the benzodiazaphosphole ring was first prepared by Friedman (1963) which was found to possess antitumour activity (Hsu *et al* 1964). Zimmer and Sill (1964) prepared a pyridine analogue of this compound which is an effective anticancer agent giving complete regression in walker 256 tumours in rats. Even the phosphoric acid derivatives not containing the nitrogen mustard group have been shown to be effective anti-cancer agents (Perroneous *et al* 1952; Crossley *et al* 1953). Several organophosphate esters like malathion and ekatin are dreadful organophosphorus poisons finding widespread use as agrochemicals particularly as powerful insecticides (Heath 1961; Khorana 1961). The present paper describes the synthesis, IR and mass spectral studies of a series of 2-cyclohexyl benzo-diazaphosphole 2-oxides, (2-8) naphthodiazaphosphorine 2-oxide (9) and diazaphospholopyridine 2-oxide (10).

2. Results and discussion

The title compounds (2-10, table 1) are prepared by reacting equimolar quantities of cyclohexyl phosphonicdichloride (1) with different substituted *o*-diamines in refluxing inert solvent like bromobenzene or *o*-dichlorobenzene in nitrogen atmosphere. The progress of the condensation was followed by collecting the evolved hydrogen chloride

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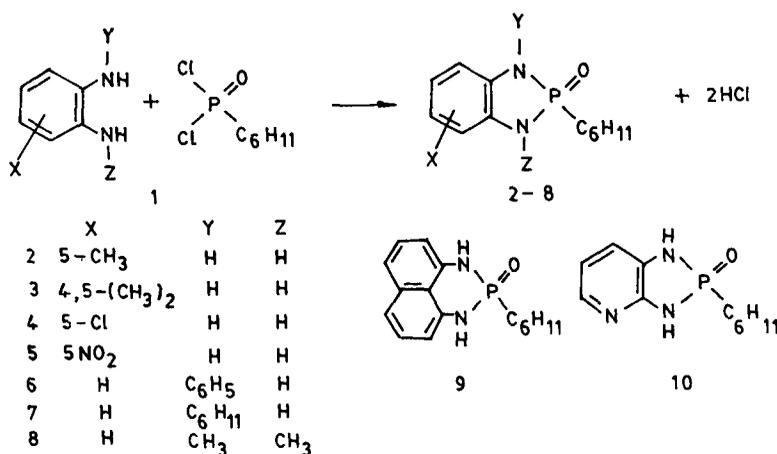
Table 1. Synthesis of benzodiazaphosphole 2-oxides

Com- pound	Diamine	Yield (%) ^a	Reaction time in min. ^b	M.P. (°C)	Molecular formula	IR spectra (cm ⁻¹)					
						P=O	P-NH	P-N _{phenyl}	P-N-C _{aromatic}	P-N	
2	3,4-Diaminotoluene	70 ^d	180	273-75 ^c	C ₁₃ H ₁₉ N ₂ OP	1178	3150	1280	910		
3	4,5-Dimethyl- <i>o</i> -phenylenediamine	77 ^d	150	195-98 ^f	C ₁₄ H ₂₁ N ₂ OP · H ₂ O	1140	3160	1300	900		
4	4-Chloro- <i>o</i> -phenylenediamine	71 ^d	160	176-78 ^g	C ₁₂ H ₁₆ N ₂ OCIP · H ₂ O	1140	3150	1285	945		
5	4-Nitro- <i>o</i> -phenylenediamine	34 ^c	130	213-14 ^h	C ₁₂ H ₁₆ N ₃ O ₃ P · 2H ₂ O	1125	3245	1280	920		
6	<i>N</i> -phenyl- <i>o</i> -phenylenediamine	73 ^c	140	209-11 ⁱ	C ₁₈ H ₂₁ N ₂ OP	1200	3150	1278	920		
7	<i>N</i> -cyclohexyl- <i>o</i> -phenylenediamine	76 ^d	190	210-12 ^j	C ₁₈ H ₂₇ N ₂ OP	1210	3150	1278	938		
8	<i>N,N'</i> -dimethyl- <i>o</i> -phenylenediamine	39 ^c	180	110-12 ^k	C ₁₄ H ₂₁ N ₂ OP	1250	—	1290	945		
9	1,8-diamino-naphthalene	95 ^c	110	325-28 ^l	C ₁₆ H ₁₉ N ₂ OP	1175	3145	1268	958		
10	2,3-Diamino-pyridine	88 ^c	1440	233-35 ^m	C ₁₆ H ₁₉ N ₂ OP	1160	3125	1300	960		

All products gave satisfactory microanalyses: C, ± 0.3; H, ± 0.1; N, ± 0.7.

(a) Product isolated after one crystallization, (b) The times recorded were only approximate as the reagents were mixed at 50-100° and then heated to reflux. Condensations were carried out in refluxing. (c) Bromobenzene and (d) *o*-Dichlorobenzene. Compounds recrystallised from (e) methanol (f) 2-propanol-methanol (g) 2-propanol (h) dilute methanol-chlorobenzene (i) benzene-ether (j) dilute methanol (k) cyclohexane-petroleum ether (60-80°) (l) 2-propanol-cyclohexane and (m) methanol-acetone.

in water and titrating it with standard sodium hydroxide solution. The reflux of the reaction mixture was stopped when evolution of hydrogen chloride ceased. The solvent was removed under reduced pressure and the residual viscous semisolids were purified by recrystallization.



The cyclization of 2,3-diaminopyridine with **1** was not successful with this procedure. However, it was accomplished by refluxing 2,3-diaminopyridine with **1** in the presence of triethyl amine in bromobenzene. All these compounds are crystalline solids possessing high melting points and are readily soluble in polar solvents.

The condensation of cyclohexyl phosphonic dichloride (**1**) with *o*-diamine forming benzodiazaphosphole is presumed to be a nucleophilic displacement reaction by the amino groups of *o*-diamine on the phosphorus atom of the phosphonic dichloride. The influence of a substituent either in the benzene ring or on the nitrogens of the *o*-diamines cannot be given in a quantitative relationship without further studies but some general observations may be made regarding the effect of a substituent in the condensation reaction. Basing on yields and reaction time, the presence of substituents like methyl, dimethyl at 4-position of *o*-diamine has little effect on the rate of condensation. Thermal instability in refluxing solvents and poor yields of **5** is due to the strong electron withdrawing effect of the nitro group. But N- and N,N'-disubstitution in *o*-diamine enhances the rate of cyclization and improves the yields indicating that N-substitution facilitates the formation of benzodiazaphosphole. This also suggests that steric factors are less important than polar effects in this nucleophilic substitution reaction.

Cyclization of 1,8-diaminonaphthalene with phosphonic dichloride (**1**) is almost quantitative showing that the formation of six-membered naphthodiazaphosphorine is more favourable than the analogous five-membered benzodiazaphosphole. Reaction of **1** with *o*-diamines requires high boiling solvent and longer reflux time than 4-chloro-3-methyl phenyl and 4-nitrophenyl phosphorodichloridates (Naidu and Reddy 1973). This may be due to the presence of electronegative atom like oxygen between phosphorus and aryl carbon atom and strong electron withdrawing substituents like nitro group and chlorine in the aromatic ring of the phenylphosphorodichloridate which renders the phosphorus atom of the dichloridate more electrophilic.

2.1 IR spectra

The characteristic infrared absorption bands associated with the major functional groups of these compounds are presented in table 1. All the compounds have shown P=O and P-NH stretching vibrations in the regions 1140–1200 and 3125–3245 cm^{-1} showing that the oxygen atom of the phosphoryl group is involved in the hydrogen bonding with the amidic hydrogen atom (Bellamy 1958; Colthup *et al* 1964). Two characteristic bands for P-N-C_(aromatic) group, one at 1318–1268 cm^{-1} for phenyl-N and another at 900–966 cm^{-1} for P-N appeared for all the compounds (Colthup *et al* 1964).

2.2 Mass spectra

The mass spectra of these compounds (table 2) are studied to confirm their structures and to understand their behaviour under electron impact. As a typical example, the fragmentation pattern of 2 is presented in scheme 1.

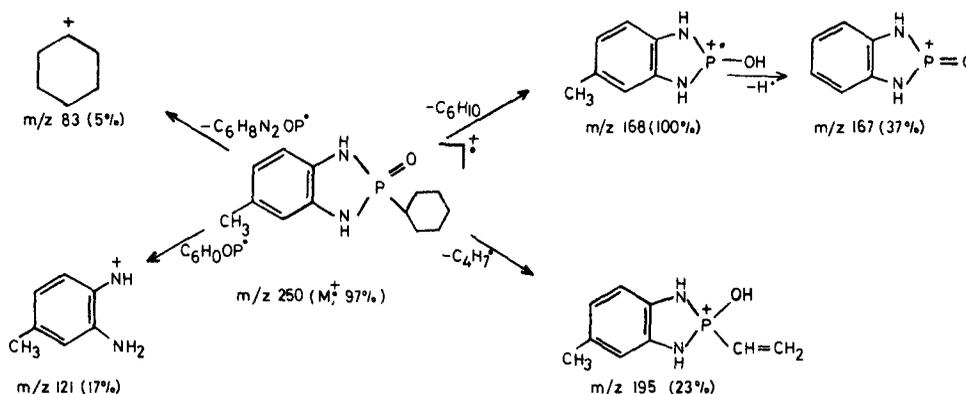
The molecular ion (I) appears with very high intensity (97%) at m/z 250. Cleavage of the P-C bond with simultaneous migration of the β -hydrogen of the cyclohexane moiety to the phosphoryl oxygen results in the formation of the benzodiazaphosphinous acid ion (II) at m/z 168 with the elimination of cyclohexane (Goff *et al* 1977). This ion which forms the base peak of the spectrum subsequently loses hydrogen radical forming the benzodiazaphosphole 2-oxide ion (III) at m/z 167 (35%).

The ion at m/z 195 (23%) is presumed to be derived from the M^+ ion by the McLafferty rearrangement (McLafferty 1959) of the γ -hydrogen in the cyclohexane moiety to the phosphoryl oxygen atom.

Decomposition of the molecular ion with the cleavage of P-N bonds leads to the formation of the ions at m/z 132 (9%), 122 (6%) and 121 (17%). These protonated species of 2-diamines might have formed by the double hydrogen rearrangement during the fission of P-N bonds. The ions at m/z 105, 104 and 94 are derived from 4-methyl *o*-phenylenediamine moiety by the step wise loss of H, $-\text{NH}_2$ and HCN which are characteristic of *o*-diamines (Henrick *et al* 1974).

Table 2. Mass spectral data

Compound	m/z (% relative abundance)
2	250 (M^+ , 97), 195 (23), 182 (11), 181 (11), 168 (100), 167 (35), 151 (22), 150 (20), 149 (15), 121 (17), 119 (16), 94 (11), 83 (5), 55 (26)
3	264 (M^+ , 50), 209 (8), 182 (37), 181 (14), 164 (10), 137 (10), 136 (100), 135 (53), 121 (63), 120 (11), 119 (12), 118 (13), 108 (22), 93 (15), 91 (10), 83 (5)
4	270 (M^+ , 18.9), 215 (5), 202 (3), 188 (9), 187 (5), 177 (10), 144 (32), 143 (12), 142 (100), 141 (19), 97 (13), 83 (5), 80 (18), 78 (10)
5	154 (3), 110 (17), 97 (33), 84 (59), 83 (38), 82 (21), 81 (10), 80 (15), 68 (100), 66 (11)
6	312 (M^+ , 31), 258 (7), 230 (53), 229 (13), 213 (15), 183 (13), 182 (31), 181 (36), 119 (11), 111 (13), 109 (11), 105 (15), 99 (11), 97 (22), 95 (16), 85 (31), 83 (27), 81 (24), 77 (33), 71 (56), 69 (38), 57 (100)
7	318 (M^+ , 60), 294 (24), 241 (15), 240 (100), 239 (14), 181 (23), 168 (15), 154 (75), 153 (46), 137 (18), 83 (6), 81 (30), 67 (12)
8	264 (M^+ , 100), 209 (5), 182 (8), 181 (87), 180 (41), 164 (28), 134 (10), 133 (12), 132 (30), 118 (17)
9	286 (M^+ , 100), 232 (18), 204 (73), 203 (73), 187 (14), 186 (56), 168 (10), 155 (15), 130 (10), 107 (10), 83 (6), 77 (11)
10	237 (M^+ , 33.7), 182 (15), 155 (46.7), 138 (21), 109 (100), 82 (14), 81 (9.3)



All the compounds show molecular ion with varying intensity except 5. The molecular ions in **8** and **10** themselves appear as base peaks. The nitrosubstituent in **5** has completely deactivated the diazaphosphole ring leading to the extensive decomposition of the molecule. Presence of methyl groups on both the nitrogens in **8** has stabilized the benzodiazaphosphole ring system. Stability of **10** may be attributed to the presence of six membered naphthodiazaphosphorine ring system.

For **3**, **4** and **9** the diamino radical cations derived from their molecular ions appear as base peaks while the ions at m/z 68 ($C_5H_6^+$) and 57 ($CH_3-(CH_2)_3^+$) obtained by the cleavage of cyclohexane moiety in the molecules form the base peaks for **5** and **6**.

The spectra of all the compounds, except **5** showed the ions for $(M-C_6H_{11})^+$ and $(M-C_6H_{10})^+$. Peaks corresponding to the ion species derived from substituted *o*-diamine and cyclohexane moieties appeared in all these molecules.

3. Experimental

All melting points are uncorrected and were determined on a Mel-Temp apparatus. The infrared spectra were recorded on a Perkin-Elmer model 700 infrared spectrophotometer, mass spectra were determined by using a Varian Mat CH7 spectrometer with electron energy 70 eV and trap current 100 μ A. The elemental analysis was performed by Dr R D McDonald of the Australian Microanalytical Service.

3.1 Starting materials

Substituted *o*-diamines were obtained either commercially or synthesized by conventional methods.

3.2 Cyclohexyl phosphonicdichloride (1)

Oxygen was bubbled through the stirred solution of phosphorus trichloride (410 g, 3 mole) in dry cyclohexane (63 g, 0.75 mole) at room temperature until the exothermic reaction was complete (15 hr). The solution was fractionally distilled and the major fraction (56 g, 36%) distilling at 160–165°C/56 mm was collected. The material solidified on standing in a vacuum desiccator (Clayton and Jensen 1948), m.p. 36–37°C.

3.3 2-Cyclohexyl-2,3-dihydro-5-methyl-1H-1,3,2-benzodiazaphosphole 2-oxide (2)

A solution of cyclohexyl phosphonic dichloride in *o*-dichlorobenzene (5.03 g, 0.025 mol in 25 ml) was added dropwise to a stirred solution of 3,4-diaminotoluene (3.05 g, 0.025 mole in 25 ml). The mixture was refluxed with stirring under a slow stream of nitrogen until the evolution of hydrogen chloride was complete (180 min). *o*-Dichlorobenzene was recovered under reduced pressure and the residue on treatment with methanol gave 4.4 g (70%) of the compound, m.p. 260–68°. On recrystallization of this material four times in methanol an analytical sample of 2 as white crystalline plates, m.p. 273–275°, was obtained.

All the compounds reported (3–8) were prepared with this general procedure.

3.4 2-Cyclohexyl-2,3-dihydro-1H-1,3,2-diazaphospholo (4,5-*b*)pyridine 2-oxide (9)

A solution of cyclohexyl phosphonic dichloride in bromobenzene (5.03 g, 0.025 mole in 25 ml) was added dropwise to a hot solution of 2,3-diaminopyridine (2.7 g, 0.025 mole) and triethylamine (5.5 g, 0.05 mole) in bromobenzene (50 ml). The mixture was refluxed with stirring for 24 hr under nitrogen atmosphere. The solvent was removed on a flash evaporator and the residue on washing with water and trituration with methanol and acetone mixture (4:1) afforded an analytical sample as yellow granules, 5.2 g (88%) m.p. 233–35°C.

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