

SYNTHESIS OF 2-SUBSTITUTED-2,3-DIHYDRO-3-(2-NITROPHENYL)-1H-NAPHTH[1,2-*e*][1,3,2]OXAZAPHOSPHORINE 2-OXIDES

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Abstract: Several 2-aryloxy/chloroethoxy-2,3-dihydro-3-(2-nitrophenyl)-1H-naphth[1,2-*e*][1,3,2]oxazaphosphorine 2-oxides (3a-i) were synthesised from reactions of equimolar quantities of 1-(2-nitroanilinomethyl)-2-naphthol (1) with various aryl phosphorodichloridates (2a-h) and O-2-chloroethyl phosphoryl dichloride (2i) at 50-60°C in toluene-tetrahydrofuran (3:1) mixture in the presence of triethylamine. IR, ¹H, ¹³C, ³¹P NMR and mass spectra were recorded and analysed.

Introduction

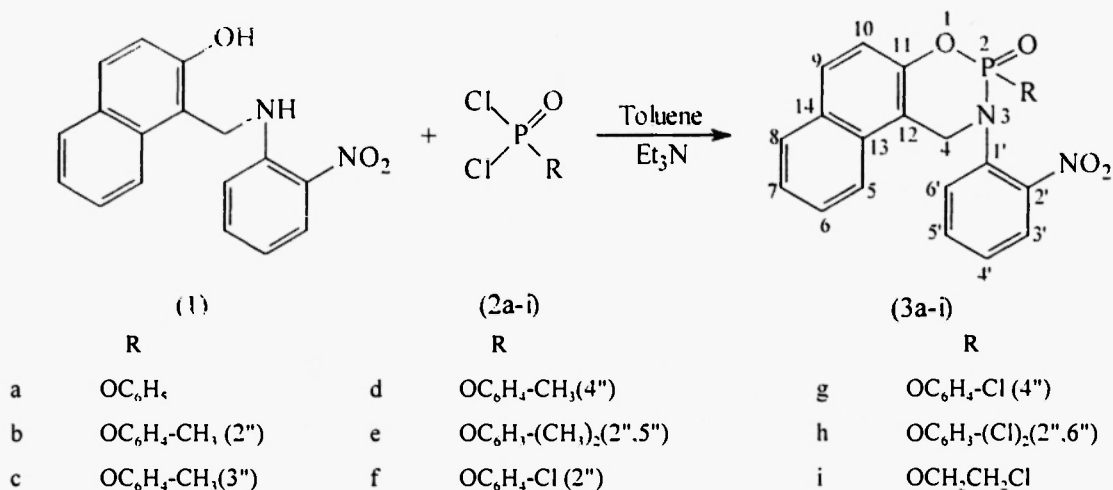
Naphthoxazaphosphorine 2-oxides exhibited good anticholinesterase activity *in vitro*¹. In view of the various applications associated with organophosphorus heterocycles²⁻⁴ 2-aryloxy/chloroethoxy-2,3-dihydro-3-(2-nitrophenyl)-1H-naphth[1,2-*e*][1,3,2]oxazaphosphorine 2-oxides (3a-i), a rare class of heterocycles have been synthesised, expecting them to possess broad spectrum of biological activity with less toxicity. The products were characterised by elemental, IR, NMR (¹H, ¹³C, ³¹P) and mass spectral data.

Results and Discussion

When equimolar quantities of 1-(2-nitroanilinomethyl)-2-naphthol (1) were condensed with aryl phosphorodichloridates (2a-h) and O-2-chloroethyl phosphoryl dichloride (2i), members of 3 were obtained (Scheme 1). Two equivalents of triethylamine served as the base with dry toluene - tetrahydrofuran (3:1) mixture as the solvent at 50-60°C. Members of 3 were obtained by filtering off the triethylamine hydrochloride and removing the solvent under reduced pressure. On washing the residue with water followed by 2-propanol and recrystallisation from ethanol afforded pure products. Physical and spectral data of the compounds are found in tables 1-4.

IR Spectra⁵ of 3a-i (Table 1) showed bands (in cm⁻¹) at 1500-1525 and 1319-1368 (N-O), 1251-1275 (P=O), 1125-1177 and 950-979 (P-O-C_{arom}) 730 -759 (P-N) and 1038-1060 (N-C).

¹H NMR Spectra⁶ of 3a-i (Table 2) exhibited doublets due to coupling with phosphorus for H (4) in the range of δ 4.40-4.65. The protons of aromatic moieties showed multiplets in the range of δ 6.50-8.25. The signals due to methyl protons of the 2-aryloxy moieties resonated as singlets in the region 1.95-2.10 ppm. In 3i, the chloroethoxy proton signals appeared as triplets at δ 4.30 and 3.80, respectively.



The interpretation of ¹³C NMR chemical shifts is based on the low intensity signal of the non-protonated aromatic carbons and calculated values. The data are discussed in terms of i) naphth[1,2-e][1,3,2]oxazaphosphorine 2-oxide. ii) *N*-phenyl moiety and iii) 2-aryloxy/chloroethoxy moiety.

Naphth[1,2-e][1,3,2]oxazaphosphorine 2-oxide

The low intensity chemical shifts at δ 145.6-147.5 ($J=6.9$ -8.1 Hz) were assigned to oxygen bearing carbon (C-11) of naphthoxazaphosphorine 2-oxide. The quaternary carbons C-12, C-13 and C-14 showed low intensity signals at δ 120.1-121.9 ($J=6.9$ -8.0 Hz), 132.2-132.5 and 131.3-131.6, respectively. The high intensity singlet signals in the region 130.9-131.1, 125.4-126.0, 128.7-130.0, 127.5-127.9, 126.3-127.0 and 118.1-120.4 ppm were attributed to C-5, C-6, C-7, C-8, C-9 and C-10, respectively. The bridged methylene (C-4) carbon resonated in the region 37.0-38.0 ppm and did not exhibit coupling with phosphorus⁷.

N-Phenyl moiety

The nitrogen bearing carbon (C-1') exhibited a singlet in the region 143.5-144.8 ppm. The nitro group bearing carbon (C-2') resonated resolved as low intensity singlet at δ 131.3-132.0. The other protonated carbons C-3', C-4', C-5' and C-6' showed signals in the region 122.5-123.9, 114.7-115.8, 135.2-136.9 and 112.4-114.7 ppm, respectively with high intensity.

2-Aryloxy/chloroethoxy moiety

The low intensity downfield signal in the region 147.2-147.5 ppm was assigned to C-1'' of the aryloxy moiety.

The other carbons of aryloxy moiety, C-2'', C-3'', C-4'', C-5'' and C-6'' gave signals in the expected regions⁷. In 3i, the chloroethoxy carbons chemical shifts appeared at 67.0 ($J=5.7$ Hz) (C-1'') and 43.8 ppm (C-2'') ($J=8.1$ Hz) respectively.

Phosphorus resonance signals in the compounds 3a-h were observed at δ -18.46 to -20.63, whereas in 3i the signal was appeared at δ 13.93. These values are in good agreement with the reported values of similar compounds⁷.

El mass spectra for the compounds 3a&d and CI mass spectra for the compounds 3g&i were recorded (Table 4). The compounds 3a & 3d did not show M^+ due to their instability at 70 eV. However, the compounds 3g and 3i showed ($M^+ + H$) and $[(M^+ + H) + 2]$ confirming the presence of a chlorine atom in the molecules.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. IR Spectra were run as KBr pellets using a Perkin Elmer 285 double beam spectrometer (ν_{max} in cm^{-1}). The ^1H , ^{13}C , ^{31}P NMR spectra were recorded in CDCl_3 or $\text{DMSO}-d_6$ using varian Gemini FT 300 MHz instrument and chemical shifts were referenced to TMS (^1H and ^{13}C) and 85% H_3PO_4 (^{31}P). Mass spectra were recorded on a Auto Spec Q instrument at University of Kuwait, Kuwait. Microanalytical data were obtained from Central Drug Research Institute, Lucknow, India. Compound 1 was prepared according to literature procedure³ and characterised by ^1H , ^{13}C and mass spectra.

Synthesis of 2-(2'',5''-dimethylphenoxy)-2,3-dihydro-3-(2-nitrophenyl)-1*H*-naphth[1,2-*e*][1,3,2]oxazaphosphorine 3-oxide (3e): General Procedure

A solution of 2,5-dimethylphenyl phosphorodichloridate (2e, 2.4 g, 0.01 mole) in 20 ml of dry toluene was added dropwise to the cooled (0°C) and stirred solution of 1-(2-nitroanilinomethyl)-2-naphthol (1, 2.94 g, 0.01 mole) and triethylamine (2.02g, 0.02 mole) in 30 ml of dry toluene and 10 ml of tetrahydrofuran for twenty minutes. After completion of the addition, the temperature of the reaction mixture was slowly raised to room temperature and stirred for two hours. The reaction mixture was heated to $50-60^\circ\text{C}$ for three hours with stirring. The completion of the reaction was monitored by TLC analysis. The solid triethylamine hydrochloride was filtered off and the filtrate was evaporated under reduced pressure. The gummy residue was washed with water, dried and treated with 2-propanol. A white amorphous solid obtained was recrystallized from ethanol to afford 3e, yield 2.07 g (45%), mp $202-204^\circ\text{C}$. Physical and spectral data of 3a-i are given in tables 1-4.

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Table 1 : Physical^a and IR (cm⁻¹) data of compounds 3a-i

Compd	Molecular formula	m.p. ^o C	Yield (%)	Found (calcd)%			P=O	N-O		P-O-C _{arom}	
				C	H	N		asym	sym	P-O	O-C
3a	C ₂₁ H ₁₇ N ₂ O ₅ P	140-142	54	63.62 (63.89)	3.86 (3.96)	6.60 (6.48)	1265	1507	1361	965	1177
3b	C ₂₃ H ₁₉ N ₂ O ₅ P	206-208	58	64.75 (64.57)	4.10 (4.29)	6.04 (6.27)	1263	1500	1368	965	1170
3c	C ₂₃ H ₁₉ N ₂ O ₅ P	174-176	56	64.40 (64.57)	4.18 (4.29)	6.22 (6.27)	1265	1522	1361	972	1155
3d	C ₂₃ H ₁₉ N ₂ O ₅ P	194-196	50	64.56 (64.57)	4.26 (4.29)	6.30 (6.27)	1251	1507	1346	957	1160
3e	C ₂₅ H ₂₁ N ₂ O ₅ P	202-204	45	65.16 (65.22)	4.59 (4.60)	6.10 (6.08)	1251	1507	1353	972	1133
3f	C ₂₃ H ₁₆ ClN ₂ O ₅ P	198-200	56	59.20 (59.18)	3.48 (3.45)	5.96 (6.00)	1251	1500	1330	979	1140
3g	C ₂₃ H ₁₆ ClN ₂ O ₅ P	170-172	60	59.12 (59.18)	3.38 (3.45)	6.08 (6.00)	1273	1500	1328	957	1175
3h	C ₂₃ H ₁₅ Cl ₂ N ₂ O ₅ P	212-214	42	54.98 (55.11)	3.10 (3.02)	5.66 (5.59)	1251	1515	1319	950	1135
3i	C ₁₉ H ₁₆ ClN ₂ O ₅ P	176-178	48	54.50 (54.49)	3.80 (3.85)	6.80 (6.69)	1275	1512	1354	950	1125

^aRecrystallised from ethanolTable 2: ¹H and ³¹P NMR Data^{a,b} of compounds 3a-i

Compd.	Ar-H	Methylene-H (4-CH ₂)	R"-CH ₃	NH	³¹ P NMR ^c
1	6.60-8.20 (m, 10H)	4.65-4.90 (m, 2H)		5.85 (br s, 1H, NH)	-
3a	6.62-8.21 (m, 15H)	4.66 (d, 2.6, 2H)			-18.89
3b	6.65-8.23 (m, 14H)	4.65 (d, 2.5, 2H)	2.10 (s, 3H, CH ₃)		-18.55
3c	6.61-8.24 (m, 14H)	4.62 (d, 2.6, 2H)	2.05 (s, 3H, CH ₃)		-18.84
3d	6.50-8.10 (m, 14H)	4.60 (d, 2.5, 2H)	2.10 (s, 3H, CH ₃)		-18.70
3	6.50-8.10 (m, 13H)	4.61 (d, 2.6, 2H)	1.95 (s, 3H, 2"-CH ₃) 2.05 (s, 3H, 5"-CH ₃)		-18.46
3f	6.50-8.10 (m, 14H)	4.62 (d, 2.4, 2H)			-19.13
3g	6.55-8.15 (m, 14H)	4.65 (d, 2.5, 2H)			-18.84
3h	6.55-8.1 (m, 13H)	4.65 (d, 2.4, 2H)			-20.63
3i	6.70-8.25 (m, 10H)	4.4 (d, 2.6, 2H)	4.30 (t, 2H, OCH ₂) 3.80 (t, 2H, CH ₂ Cl)		13.93

^aChemical shifts in δ from TMS, J (Hz) given in parentheses^bRecorded in CDCl₃^cChemical shifts in δ from 85% H₃PO₄

Table 3: ^{13}C NMR Spectral data^a of 3a-i

Carbon atoms	Compd.									
	1	3a	3b	3c	3d	3e	3f	3g	3h	3i
C-4	38.5	38.0	38.0	38.0	37.0	37.0	37.0	37.0	37.0	37.8
C-5	130.4	131.0	131.1	131.0	131.0	131.0	131.0	131.0	131.0	130.9
C-6	123.7	125.8	125.8	126.0	125.7	125.7	125.7	125.8	125.7	125.4
C-7	128.8	128.9	128.9	128.9	129.2	130.0	129.7	128.9	130.0	128.7
C-8	127.4	127.9	127.9	127.9	127.9	127.9	127.9	127.9	127.8	127.5
C-9	126.9	126.7	126.7	126.7	126.9	126.9	126.9	127.0	126.9	126.3
C-10	117.9	119.1	119.2	119.2	118.5	118.3	118.2	118.1	118.1	120.4
C-11	152.1	146.6	146.8	146.8	145.7	145.8	145.6	145.6	145.9	147.5
						(8.1)		(8.1)	(6.9)	(6.9)
C-12	116.0	121.6	121.6	-	120.5	120.6	120.3	120.1	120.3	121.9
						(6.9)		(4.6)	(8.0)	(6.8)
C-13	-	132.5	132.5	132.5	-	-	-	-	-	132.2
C-14	130.4	131.6	131.6	-	131.5	131.5	131.5	131.5	131.5	131.3
C-1'	-	144.5	144.6	144.6	143.6	143.6	143.5	143.5	143.6	144.9
C-2'	-	132.0	132.0	132.0	131.5	131.5	131.5	131.5	131.5	131.3
C-3'	122.2	123.5	123.5	123.5	122.5	122.5	122.5	122.5	122.5	123.9
C-4'	114.4	115.7	115.7	115.7	114.7	114.7	114.7	114.8	114.7	115.8
C-5'	136.4	136.2	136.2	136.2	135.2	136.4	135.2	135.3	135.2	136.9
C-6'	114.0	113.5	113.5	113.5	112.5	112.5	112.6	112.4	112.6	114.7
C-1''	-	-	-	-	-	147.5	-	147.2	-	67.0
										(5.7)
C-2''	-	119.8	131.1	-	118.2	125.5	130.1	120.6	130.6	43.8
		(6.9)						(6.9)		(8.1)
C-3''	-	129.9	131.6	136.2	130.2	130.6	127.9	130.1	128.1	
C-4''	-	126.0	126.0	126.0	125.0	125.0	125.6	130.7	125.0	
C-5''	-	129.9	127.2	130.3	130.0	135.2	125.0	130.1	128.1	
C-6''	-	119.8	119.6	115.7	118.1	119.2	120.7	120.6	130.6	
		(6.9)						(6.9)		
C-1'''			16.1	21.1	19.7	14.7				
C-2'''						19.7				

^a Chemical shifts in ppm from TMS, *J* (Hz) given in parentheses

Table 4: Mass spectral data of compounds 3a, 3d, 3g & 3i

Compd.	m/z (relative abundance)
1 EI MS	294 [9.0, (M ⁺)], 164 (6.3), 156 (51.4), 144 (43.2), 138 (45.0), 128 (100), 115 (22.3), 102 (17.9), 92 (9.0).
3a EI MS	398 (81.0), 259 (36.0), 164 (36.0), 156 (45.9), 138 (58.61), 128 (100), 119 (49.5), 108 (41.4), 94 (70.3)
3d EI MS	412 (79.3), 260 (40.5), 156 (52.2), 138 (55.0), 128 (64.0), 119 (56.8), 108 (100), 91 (62.2).
3g CI MS	469 [2.0, (M ⁺ +H)+2], 467 [4.8, (M ⁺ +H)], 433 (6.0), 309 (2.0), 294 (4.0), 261 (8.0), 157 (100), 139 (66.0), 128 (50.0).
3i CI MS	421 [5.8, (M ⁺ +H)+2], 419 [1.8, (M ⁺ +H)], 401 (20.0), 382 (3.5), 367 (5.0), 339 (2.0), 303 (4.0), 299 (18.0), 277 (5.5), 263 (100), 235 (8.0), 231 (5.0), 189 (3.0), 173 (5.5), 157 (25.0), 139 (78.0), 128 (13.0).

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