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Synthesis of 2-Substituted-5,5-Dimethyl-1,3,2-Dioxaphosphorinane-2-Oxides

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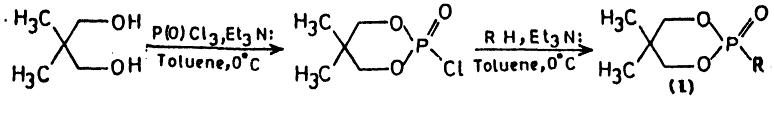
The equimolar reaction of 2,2,-dimethyl-1,3-propanediol with phosphorus oxychloride afforded the monochloride, 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide which was subsequently reacted with various thiols and amines to yield a series of 2-thiophenyl/thioalkyl/alkylamino-5,5-dimethyl-1,3,2-dioxaphos phorinane-2-oxides. Their structures were confirmed by elemental analyse, IR, ^{1}H, ^{31}P NMR and mass spectra.

INTRODUCTION

Promising anticancer activity of cyclophosphamide[1] and derivatives of cyclophosphamide[2] prompted the studies on six membered organophosphorus compounds. In continuation of our work[3] a series of 2-thiophenyl/thioalkyl/alkylamino-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxides I(a–h) were synthesised and their ^{1}IR, ^{1}H, ^{31}P NMR and mass spectral charateristics were studied.

RESULTS AND DISCUSSION

Synthesis of the title compounds I(a–h) was accomplished by the equimolar reaction of 2,2-dimethyl-1,3-propanediol and phosphorus oxychloride to get the monochloride, which *in situ* reacted with thiols and amines in presence of triethylamine in toluene.



	R		R
Ia	C_6H_5S	e	$C_5H_{10}N$
b	C_3H_7S	f	C_4H_8NO
c	C_4H_9S	g	C_3H_6NS
d	C_4H_4N	h	$C_5H_{11}N_2$

All these compounds gave moderate yields (44–53%) with melting points ranging from 95–166°C (Table-1). The IR spectra of these compounds exhibited characteristic bands at 1310–1275 ν(P═O)[4], 1160–1085 (P—O—C aliph)[5]

TABLE-1
PHYSICAL, IR AND ^{31}P NMR DATA OF Ia–h*

Compd. No.	R	m.p. (°C)	Yield† (%)	Mol. formula	IR spectra (cm^{-1})				^{31}P signal
					ν(P=O)	P—X—$C_{aromatic}$		P—O—$C_{aliphatic}$	
						ν(P—X)	ν(X—C)		
Ia	C_6H_5S	94–95	48	$C_{11}H_{15}O_3PS$	1300	620(P—S)	535(S—C)	1100	+56.10
Ib	C_3H_7S	160–162	44	$C_8H_{17}O_3PS$	1310	610	540	1090	–2.33
Ic	C_4H_9S	154–156	47	$C_9H_{19}O_3PS$	1304	625	525	1085	–3.79
Id	Pyrrolidinyl	114–116	50	$C_9H_{14}NO_3P$	1300	780(P—N)	1020(N—C)	1160	+6.11
Ie	Piperidinyl	128–130	48	$C_{10}H_{16}NO_3P$	1310	785	1010	1160	+6.03
If	Morpholinyl	158–160	52	$C_9H_{18}NO_4P$	1300	730	1050	1145	+5.19
Ig	Thioazolidinyl	165–167	53	$C_8H_{16}NO_3PS$	1300	790	1015	1085	+3.24
Ih	N-Methylpiperazinyl	170–172	51	$C_{10}H_{21}N_2O_3P$	1275	735	1025	1100	+4.23

*All compounds gave satisfactory elemental analysis C ± 0.3, H ± 0.1

†Yields are reported after recrystallisation.

1025–1010 ν(N—C), 790–735 ν(P—N)[6], 625–610 ν(P—S) and 540–525 cm^{-1} ν(S—C)[7].

In ^1H NMR spectra 4 and 6 methylene protons of these compounds resonated as three distinct doublets in the region δ 3.73–4.48 exhibiting the AA′ BB′ pattern of splitting. However, it is interesting to note that the two upfield signals account for one proton each and the downfield signal accounts for two protons. The 5,5-dimethyl protons resonated separately at δ 0.88–0.92 and 1.12–1.33 indicating their non-equivalence. The thio and amino groups gave signals in the expected range[8] (Table-2).

The ^{31}P NMR signals of these compounds varied with the substituents ranging from δ +56.10 to −3.79 (Table-2). This clearly indicated the effect of the substituent group on the phosphorus signal (Table-1). Mass spectra of some of these compounds were recorded. They exhibited molecular ion peaks which followed expected fragmentation pathways[8].

TABLE-2

^1H NMR CHEMICAL SHIFTS OF I(a–h)

Compd. No.	4 and 6-CH_2			$5,5(CH_3)_2$	R—H
	$H_{AA'}$	H_B	$H_{B'}$		
Ia	4.25 (10.8)	4.06 (10.7)	396 (11.3)	1.33, 0.92	7.36–7.55 (m, 5H, ArH)
Ib	4.48 (10.7)	4.07 (10.5)	3.95 (9.6)	1.32, 0.90	3.93–3.98 (m, 2H, CH_2) 1.06–1.30 (m, 2H, CH_2) 0.86–0.91 (m, 3H, CH_3)
Ic	4.47 (10.7)	4.04 (11.6)	3.97 (11.1)	1.32, 0.90	3. 83–3.93 (m, 2H, CH_2) 1.06–1.25 (m, 4H, CH_2) 0.89–0.93 (m, 3H, CH_3)
Id	4.48 (10.8)	4.80 (10 .8)	3.73 (11. 1)	1.22, 0.88	3.16–.33 (m, 4H, 2′ and 5′-CH_2) 1.32–1.37 (m, 4H, 3′ and 4′-CH_2)
Ie	4.47 (10.4)	3.81 (11.1)	3.74 (11.1)	1.21, 0.88	3.14–3.20 (m, 4H, 2′ and 6′-CH_2) 1.54–1.57 (m, 4H, 3′ and 5′-CH_2) 1.21–1.34 (m, 2H, 4′-CH_3)
If	4.33 (10.7)	3.83 (11.2)	3.76 (11.2)	1.21, 0.86	3.65–3.68 (m, 4H, 3′ and 5′-CH_2) 3.20–1.34 (m, 4H, 2′ and 6′-CH_2)
Ig	4.47 (10.4)	4.03 (11.1)	3.91 (11.5)	1.32, 0.90	4.31–4.39 (m, 2H, 2′-CH_2) 3.78–3.89 (m, 2H, 5′-CH_2) 3.58–3.61 (m, 2H, 3′-CH_2)
Ih	4.20 (11.2)	3.80 (10.7)	3.74 (10.8)	1.12, 0.90	3.57–3.60 (m, 4H, 2′ and 6′-CH_2) 2.70–3.85 (m, 4H, 3′ and 5′-CH_2) 0.95 (s, 3H, -NCH_3)

EXPERIMENTAL

Melting points were taken in an open capillary tube and are uncorrected. RSIC–CDRI, Lucknow has experimented on the elemental analyses. Infrared spectra (ν_{max} in cm^{-1}) in KBr pellets were recorded on a Perkin-Elmer model 781 spectrophotometer. NMR spectra were recorfed on Varian XLAA 300 MHz NMR spectrometer, for ^1H NMR spectra in $CDCl_3$ using TMS as internal standard and for ^{31}P NMR spectra in $CDCl_3$ using 85% H_3PO_4 as external standard. The EI mass spectra were recorded on DS-505 using ionisation potential of 70 eV and a direct inlet system.

2(4′-Morpholinyl)-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide (If)

A solution of 2,2-dimethyl-1,3-propanediol (0.01 mol) and triethylamine (0.02 mol) in dry toluene (50 mL) was stirred (0°C) and phosphorus oxychloride (0.01 mol) in dry toluene (20 mL) was added to it. The reaction mixture was warmed (40°C) and reaction was continued for 4 h to get the monochloride, 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide. The reaction mixture was cooled to 0°C and a solution of morpholine (0.01 mol) and triethylamine (0.01 mol) in dry toluene (30 mL) was added to it. The reaction was stirred for another 4 h (40°C) to completion. The solid triethylamine hydrochloride was separated by filtration and the filtrate was evaporated to give crude which was washed with water, dried and recrystallised from the mixture ethylacetate-hexane (1:1) as white crystalline solid 1.22 g (52%) of If m.p 158–159°C

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