CHAPTER 2

SYNTHESIS AND SPECTRAL PROPERTIES OF SOME 2-ALKYLAMIDO-6-CHLORO SALIGENIN CYCLIC PHOSPHORAMIDOTHIONATES

MATERIALS AND METHODS

All melting points were are recorded in open capillary tubes in sulfuric acid bath and are uncorrected.

2.1. PURIFICATION OF SOLVENTS AND CHEMICALS

Organic solvents and chemicals used during the work were of standard commercial grade of high quality (BM, BDH, SM, Fluka, Aldrich and Sigma quality. Organic solvents and other chemicals were purified and dried according to Vogel(1). Silica gel (60-120 mesh) was used for column chromatography.

2.2. SPECTROSCOPIC METHODS

Infrared spectra were scanned on Beckmann IR-20 spectrophotometer and Pye Unicam sp 3 300 S in nujol mull and in liquid film. Ultraviolet spectra were recorded on Shimadzu UV-240 U.V. Visible recording spectrophotometer (Graphicord) in 1-octanol. Mass spectra (EI positive) were recorded on a Jeol JMS -D 300 mass spectrometer at 70 ev. PMR spectra were taken on Varian EM 360-L and Varian CFT-20 spectrometers. ^{13}C and ^{31}P spectra were recorded on Bruker WM-400 spectrometer at 100 and 162 MHz respectively. Chemical shifts in parts per million for ^{1}H NMR spectra were referenced to Me_4Si and for ^{31}P spectra were referenced to H_3PO_4. Solvents used for NMR spectra were chloroform-d and Acetone-d_6.

2.3. PREPARATION OF THIOPHOSPHORYL CHLORIDE ($PSCl_3$)

Thiophosphoryl chloride was prepared according to Moeller et al(2).

2.4. PREPARATION OF 5-CHLORO SALIGENIN (2-HYDROXY-5-CHLORO BENZYL ALCOHOL)

2-hydroxy-5-chloro benzyl alcohol as one of the starting materials for the synthesis of 6-chloro saligenin cyclic phosphoramidothionates was prepared in the following manner :

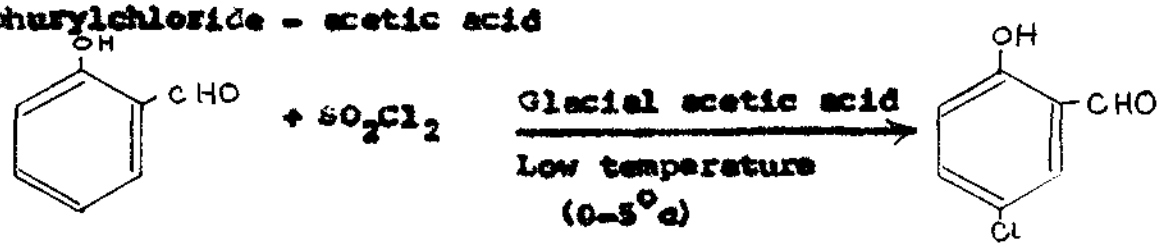
Preparation of the alcohol was done in two stages,

(i) Chlorination of salicylaldehyde to 2-hydroxy-5-chlorobenzaldehyde, and

(ii) reduction of the said aldehyde to alcohol.

(i) Chlorination of Salicylaldehyde :

Chlorination of salicylaldehyde was done by sulphurylchloride - acetic acid

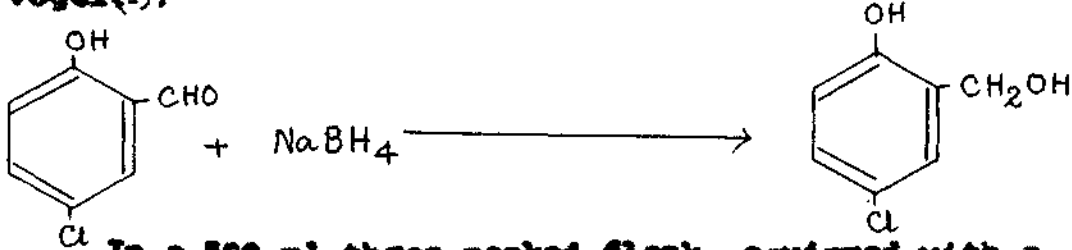


12.2 g (0.1 mol) salicylaldehyde and 13.5 g (0.1 mol) liquid sulphuryl chloride were dissolved in about five times

glacial acetic acid respectively in two separate conical flasks. The sulfuryl chloride solution was added slowly to salicylaldehyde solution with constant stirring to ensure thorough mixing. The temperature of the reaction mixture was kept at 0° to 5°C. After complete addition of sulfuryl chloride the reaction mixture was allowed to stand for half an hour at room temperature. The reaction mixture was poured in cold water (ordinary). The precipitate was filtered with suction on a Buchner funel and was washed thoroughly with cold water and was pressed as dry as possible with a wide glass stopper and then dried. The product thus obtained was recrystallised from methanol. The yield of pure 2-hydroxy-5-chloro benzaldehyde (colourless crystals, m.p. 100°c) was 12.8 g (83% yield).

(ii) Reduction of 2-hydroxy-5-chloro-benzaldehyde :

The reduction was done by sodium borohydride according to vogel(4).



In a 500 ml three-necked flask, equipped with a mechanical stirrer, a thermometer and a dropping funnel was placed a solution of 20.1 g (0.1 mol) 2-hydroxy-5-chloro benzaldehyde in 100 ml methanol and, whilst stirring, a solution of sodium borohydride (1.40g, 0.037 mol sodium borohydride in

2 ml of 2N-sodium hydroxide diluted with 18 ml of water) was added at a rate of 8.5 ml per minute with occasional cooling to keep the reaction mixture at 18-25°c. The reaction mixture was stirred for an additional period of 30 minutes.

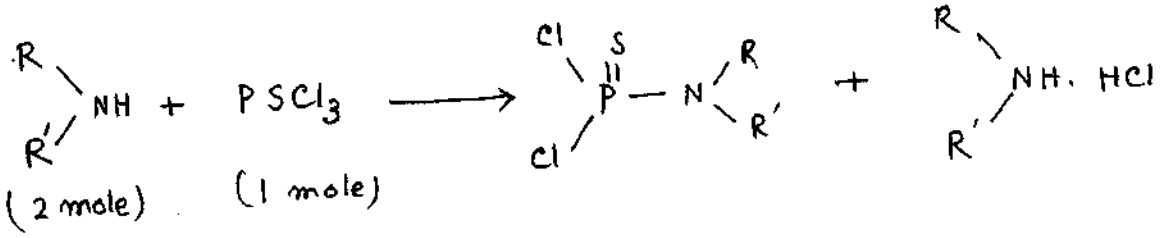
The methanol was removed by distillation on a steam bath. The residue was diluted with 100 ml water and then acidified with 50 ml dilute sulphuric acid. The mixture was extracted with ether, the upper layer of the extract was washed with water to remove excess acid and dried with a little anhydrous magnesium sulphate. Ether was removed by flash distillation. The product thus obtained was recrystallized from chloroform and dried in vacuum. The yield of pure 2-hydroxy-5-chloro benzyl alcohol (colourless crystal, m.p. 89°c) was 83%.

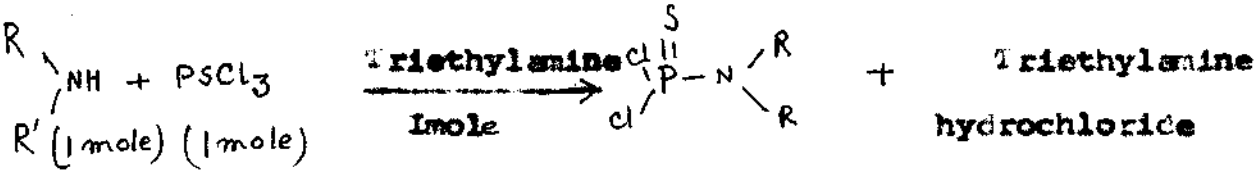
UV. (Fig.2.1) λ_{max}^{EtoH} = 285 nm (ϵ , 3032)

IR (Fig. 2.2) 3420 and 3140 cm^{-1} (OH vibration),

1425 cm^{-1} (OH deformation str. Vib.), 1610 cm^{-1} (c=c str.) 1480 cm^{-1} (CH_2 scissering), 1080 cm^{-1} (C-O str. of primary alcohol,
1210 cm^{-1} (C-O str. of phenol), 895 cm^{-1} (the cone H-atom wagging of the phenyl ring) and 810 cm^{-1} (bending of 2H adjacent of the ring).

2.5. Preparation of alkylamidophosphorodichloridothionate





One mole of thiophosphoryl chloride and two moles of amine (or one mole of amine and one mole of triethyl amine) were allowed to react at -5° to 5°c in benzene or chloroform. The amine solution was added dropwise very slowly with constant vigorous stirring. After an additional stirring period, the solid particles (if present) were filtered off the reaction mixture and washed repeatedly with benzene or chloroform. Excess amine was removed by washing the benzene or chloroform phase with cold 2% hydrochloric acid, then with cold saturated sodium chloride solution. The benzene or chloroform phase was then dried with anhydrous sodium sulphate and filtered, evaporation <u>in vacuo</u> gave the desired alkylamidophosphorodichloridothionate.

The different alkylamidophosphorodichloridothionates were prepared as follows :

2.5.1. <u>N, N-diisobutylamidophosphorodichloridothionate</u>

A solution of 17.60 ml (0.1 mol) of diisobutylamine

and in 20 ml of benzene was added dropwise to a solution of 5.2 ml (0.05 mol) of thiophosphorylchloride in 50 ml benzene at -5° to 5°c. The mixture was stirred for 3 h and then at room temperature for an additional 16h, the solid particles were filtered off and the solution was washed two times with cold 2% hydrochloric acid saturated with sodium chloride and dried over sodium sulphate. The solution was filtered and the solvent rotoevaporated in vacuo to afford a 9.60 g yellowish liquid.

2.5.2. N,N-Dipropylamidophosphorodichloridothionate

A solution of 13.70 ml (0.1 mol) of dipropylamine in 20 ml of benzene was added dropwise to a stirred solution of 5.2 ml (0.05 mol) of thiophosphoryl chloride in 50 ml of benzene at -5° to 5°c. After working up the reaction mixture as in 2.5.1, a yellowish liquid (8.18g) was thus obtained.

2.5.3. N,N-Dibutylamidophosphorodichloridothionate

A solution of 8.50 ml (0.05 mol) of dibutylamine and 5.90 ml (0.05 mol) of triethylamine in 20 ml of benzene was added dropwise to a stirred solution of 5.20 ml (0.05 mol) of thiophosphoryl chloride at -5 to 5°c for 3h. After working up the reaction mixture as in 2.5.1, a colourless liquid (9.0 g) was thus obtained.

2.5.4. 2,6-Dimethylmorpholinophosphorodichloridothionate

A solution of 11.51 ml (0.05 mol) of 2,6 dimethylmorpholine and 5.90 ml (0.05 mol) of triethylamine in 20 ml of benzene was added dropwise to a stirred solution of 5.20 ml (0.05 mol) of thiophosphoryl chloride at -5° to 5°c for 1h. After working up the reaction mixture as in 2.5.1. a yellowish liquid (10.1 g) was thus obtained.

2.5.5. 2-Ethylpiperidinophosphorodichloridothionate

A solution of 6.90 ml (0.05 mol) of 2-ethylpiperidine and 3.90 ml (0.05 mol) of triethylamine in 20 ml of benzene was added dropwise to a stirred solution of 5.20 ml (0.05 mol) of thiophosphorylchloride at -5 to 5°c for 3h. After working up the reaction mixture as in 2.5.1. a reddish liquid (7.50g) was thus obtained.

2.5.6. 4-Benzylpiperidinophosphorodichloridothionate

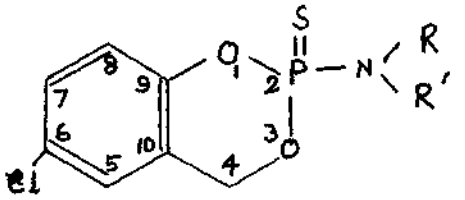
A solution of 8.90 ml (0.05 mol) of 4-benzylpiperidine and 5.90 ml (0.05 mol) of triethylamine in 20 ml of benzene was added dropwise to a stirred solution of 5.20 ml(0.05 mol) of thiophosphoryl chloride at -5° to 5°c for 3 h. After working up as in 2.5.1. a colourless liquid (10.45g) was thus obtained.

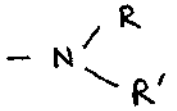
2.5.7. Hexamethylenimidophosphorodichloridothionate

A solution of 6.90 ml (0.05 mol) of hexamethylenimine

and 5.90 ml (0.05 mol) of triethylamine in 20 ml of benzene was added dropwise to a stirred solution of 5.20 ml (0.05 mol) of thiophosphoryl chloride in 50 ml of benzene at -5° to 5°c for 3 h. After working up the reaction mixture as in 2.5.1, a yellowish liquid (7.30 g) was thus obtained.

2.6. Preparation of some alkylamido-6-chloro-4H-1, 3, 2-benzodioxaphosphorin 2-Sulphides



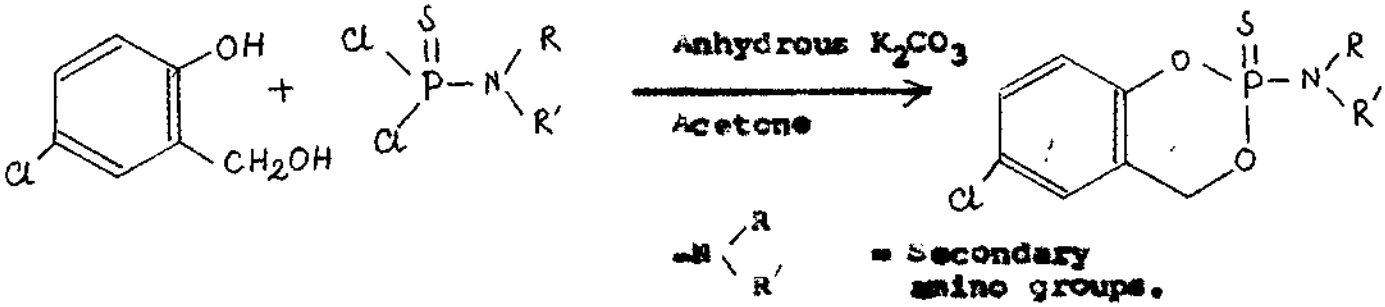


= Secondary amino group

General Procedure

2-alkylamido-6-chloro-4H, 1, 3, 2-benzodioxaphosphorin 2-sulphides were prepared by adding a solution of 1 mol of 2-hydroxy 5-chlorobenzyl alcohol in dry acetone to 1 mol of 2-alkylamidophosphorodichloridothionate at a low temperature. 2 mol of anhydrous potassium carbonate was then added in instalments with constant stirring. The temperature of the reaction mixture was kept below 5°C during the addition of potassium carbonate. The reaction was completed by stirring at the temperature 5°-27°C for an additional time of 12-16 h. After the filtration of solid particles the solvent was removed under reduced pressure at room temperature. In some cases the crude product was directly recrystallized from methanol to give pure compound, while in other cases an additional chloroform extraction was necessary prior to recrystallization. In the later case, the crude product was extracted with chloroform and washed with ice-cooled 1% HCl and then with cold water repeatedly.

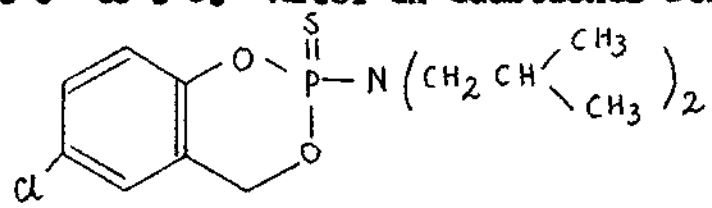
It was then dried with anhydrous sodium sulphate and chloroform was removed under reduced pressure. The pure compound were then obtained by recrystallisation from methanol. In other cases the crude product was purified by column chromatography over silica gel (60-120 mesh).



The different phosphoramidothionates were prepared as follows :

2.6.1. 2-N,N-Diisobutylamido-6-chloro-4H-1,3,2-benzodioxaphosphorin 2-sulphide (CL-6).

This compound (CL-6) was prepared by condensation of equimolar quantities of 1.59g (0.01 mol) of 2-hydroxy-5-chloro benzyl alcohol and 2.5 ml (0.01 mol) of N, N diisobutylamidophosphorodichloridothionate in presence of 2.76g (0.02 mol) of anhydrous potassium carbonate in 50 ml of acetone as solvent; potassium carbonate was added by instalments to the stirred solution at 0° to 5°C. After an additional stirring for 16h at



the room temperature, the solids were filtered off and the solvent was removed under reduced pressure. The crude product was washed with methenol saturated with n-heptane and then was recrystallised from methanol. 2.7g product CL-6 (white crystal) was obtained.

Yield, 78%; Mol.Formula, $C_{15}H_{23}O_2$ MeCl; Mol.wt. 347.70; M.P., 91°; R_f 0.91 (benzene-acetone, 8:2)

Anal.Calcd for : C, 51.76 ; H, 6.61; N, 4.02; Found for : C, 51.76; H, 6.58; N, 4.00.

UV (Fig.2-3) : $\lambda_{max}^{1\text{-octanol}}$ 279 (ϵ, 1316). IR (Fig.2-4) : 1010 cm^{-1}(S), P-O-C alkyl; 1240 cm^{-1}(S) and 915 cm^{-1}(S), P-O-C aryl; 815 cm^{-1}(S), P = S(I); 650 cm^{-1}(S), P-S(II); 1050 cm^{-1}(S), Ar-Cl; 735 cm^{-1}(m), P-N(Str).

Mass (Fig.2-5) :

m/z	349 $(M+2)^+$	347 (M^+)	314	304
% R I	6.79	16.83	22.23	Base peak

248	219	187	174	140	112	77
95.88	20.0	25.0	10.0	12.5	6.25	17.5

^{1}HNMR (Acetone-d_6/TMS ppm (Fig. 2-6) : δ 0.73-0.90 (d, 12 H, CH_3 gr.), 1.20-2.20 (m, 2H, CH), 2.73-3.70 (m, 4H, $-N(CH_2-)_2$), 4.83-5.66 (m, 2H, $-CH_2-O-P$), 6.80-7.30 (3H, aromatic).

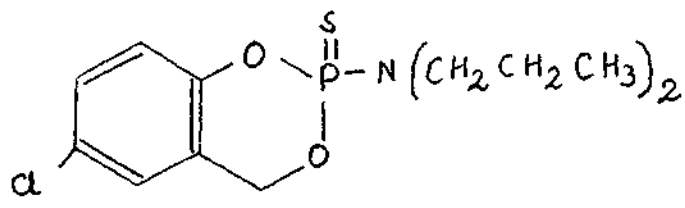
^{31}P NMR ($CDCl_3/H_3PO_4$) ppm (Fig.2-7) δ 69.80 (J, 10.79 Hz)

^{13}C NMR ($CDCl_3$/TMS) ppm (Fig. 2.8) :

^{13}C Atom	δ Values (ppm)	$^{n}J_{AB}$ *	Coupling constant (Magnitude in Hz)
C_3	19.91 19.83	$^{4}J(^{31}P\text{-}N\text{-}C_1\text{-}C_2\text{-}C_3)$	7.32
C_2	25.72	$^{3}J(^{31}P\text{-}N\text{-}C_1\text{-}C_2)$	15.19
C_1	52.71 52.68	$^{2}J(^{31}P\text{-}N\text{-}C_1)$	3.00
C_4	66.35	$^{2}J(^{31}P\text{-}O\text{-}C_4)$	5.33
C_8	120.21	$^{3}J(^{31}P\text{-}O\text{-}C_9\text{-}C_8)$	8.22
C_5	124.97	-	-
C_{10}	122.24 122.14	$^{3}J(^{31}P\text{-}O\text{-}C_9\text{-}C_{10})$	10.81
C_7	128.34	-	-
C_6	128.98	-	-
C_9	149.68 149.61	$^{2}J(^{31}P\text{-}O\text{-}C_9)$	7.34

* $^{n}J_{AB}$ is used to represent a coupling over n bonds between nuclei A and B.

2.62. 2-N,N-Dipropylamido-6-chloro-4H-1,3,2-benzodioxaphosphorin 2-sulphide (CL-7)



A solution of equimolar quantities 1.59g (0.01 mol) of 2-hydroxy-5-chlorobenzyl alcohol and 2.28 ml (0.01 mol) of N,N-dipropylamidophosphorodichloridothionate, in 50 ml of dry acetone in presence of 2.76g (0.02 mol) of anhydrous potassium carbonate at 0° to 5°c. The reaction was carried out in the same manner as that in 2.6.1. After 18h stirring the solid was filtered off and the solvent (acetone) was removed under reduced pressure at room temperature. The crude product was washed with methanol saturated with n-heptane and then the compound was purified by column chromatography using silica gel (60-120 mesh) as absorbent. Elution was carried out with dry, distilled thiophene free benzene and the progress of chromatographic fractionation had been monitored by examining the IR spectra of selected fraction and also by TLC technique (coating material silica gel G, solvent benzene-acetone 9:1). After removal of solvent in vacuo 2.71g of product CL-7 (liquid) was obtained.

Yield, 85%; Mol.Formula, $C_{13}H_{19}O_2NPSCl$; Mol.wt., 319.64; Rf, 0.84 (benzene:acetone 9:1)

Anal.Calcd. for : C, 48.8; H, 5.94; N, 4.37; Found for : C, 48.6; H, 5.8; N, 4.41.

UV(Fig.2.9) : $\lambda_{max.}^{1\text{-octanol}}$ 280 (ε, 1479). IR (Fig.2.10) : 1020 cm^{-1}(s), P-O-C alkyl; 1240-1250 cm^{-1}(s) and 910cm^{-1}(s), P-O-C aryl; 810 cm^{-1}(s), P=S (I); 655 cm^{-1}(s), P=S (II); 1045 cm^{-1}(s), Ar-Cl; 735 cm^{-1}(s), P-N (str.).

Mass (Fig.2.11) : m/e 321$(M+2)^+$ 319(M^+) 290 286

% RI 10.0 23.18 36.24 75.44

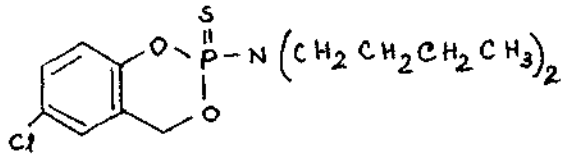
248 219 187 146 140 112 77 43

24.76 12.55 31.25 25.0 25.0 40.0 60.0 Base peak

^1H NMR (Acetone-d_6/TMS) ppm (Fig.2.12) :

0.66-0.88 (m, 6H, CH_3 gr), 1.0-1.9 (m, 4H, $-CH_2-$),
2.43-3.53 (m, 4H, $-N(CH_2)_2$), 4.26-5.7
(m, 2H, $-CH_2-O-P$), 6.23-7.5 (m, 3H, aromatic).

2.6.3. 2-N,N Dibutylamido-6-chloro-4H-1, 3, 2 benzodioxaphosphorin 2-sulphide (CL-10)



A solution of equimolar quantities of 1.59g (0.01 mol) of 2 hydroxy-5-chloro benzyl alcohol and 2-62g (0.01 mol) of N,N dibutylaminocophosphorodichloridothionate in 50 ml of dry acetone in presence of 2.76 g (0.02 mol) of anhydrous potassium carbonate. The reaction and purification were carried out in the same manner as that in 2.6.2. Removal of solvent in vacuo gave 2.6g of colourless liquid product CL-10.

Yield, 75%; Mol.Formula, $C_{15}H_{23}O_2NPSCl$; Mol.wt., 347.70;
Rf, 0.86 (benzene; acetone, 8:2).
Anal.Calcd for : C, 51.76; H, 6.61; N, 4.02. Found for :
C, 51.57; H, 6.50; N, 4.10.

UV (Fig.2.13) : $\lambda_{max}^{1\text{-Octanol}}$ 279 (ϵ, 1620). IR(Fig.2.14) :

1020 cm^{-1}(s), P-O-C alkyl; 1240-1250 cm^{-1}(s) and 910 cm^{-1}(s), P-O-C aryl; 810 cm^{-1}(s), P=S(I); 655 cm^{-1}(s), P=S(II); 1040 cm^{-1}(s), Ar-Cl; 730 cm^{-1}(s), P-N(Str).

Mass (Fig.2.15) : m/e 349(M+2)$^+$ 347(M+) 314 304 262

ARI 6.58 19.05 Base peak 25.20 33.80

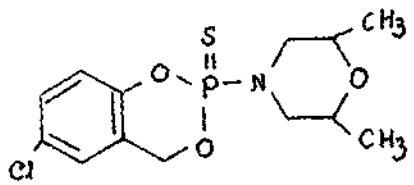
248 219 187 174 140 112 77

24.90 19.17 37.50 37.50 15.0 25.0 87.50

^{1}H NMR (Acetone- d_6/TMS) ppm (Fig.2.16) :

0.80-0.90 (t, 6H, $-CH_3$ gr.), 1.20-2.10 (m, 8H, $-CH_2-$), 2.91-3.40 (m, 4H, $-N(CH_2)_2$), 4.73-5.56 (m, 2H, $-CH_2-O-P$), 6.80-7.46 (m, 3H, aromatic).

2.6.4. 2-(2,6-dimethylmorpholino)-6-chloro-4H-1,3,2-benzodioxaphosphorin 2-sulphide (CL-12)



To a solution of 1.59g (0.01 mol) of 2 hydroxy 5-chlorobenzyl alcohol in 20 ml of acetone cooled in ice-water, was added, slowly with stirring, 2.26g (0.01 mol) of 2,6 dimethylmorpholinodichloridothionate in 30 ml of acetone. After addition was completed, the mixture was kept for 2h at room temperature, the 2.76g (0.02 mol) of anhydrous potassium

carbonate was added in instalments for 3h. The solid was filtered off and after removal of acetone the product was obtained. Recrystallisation from methanol gave 2.35g CL-12 as a white crystal.

Yield, 71%; Mol.Formula, $C_{13}H_{17}O_3NPCl$; Mol.wt., 333.45; M.P., 94°; Rf, 0.84 (benzene:acetone, 8:2).

Anal.Calcd for : C, 46.78; H, 5.0; N, 4.19. Found for : C, 45.0; H, 5.03; N, 4.10.

UV (Fig.2.17) : $\lambda_{max}^{1\text{-Octanol}}$, 279 (ε, 1360). IR(Fig.2.18) : 1020 cm^{-1}(s), P-O-C alkyl; 1240 cm^{-1}-1250 cm^{-1}(s) 910 cm^{-1}(s), P-O-C aryl; 910 cm^{-1}(s), P=O(I); 660 cm^{-1}(s), P=O(II); 1040 cm^{-1}(s), Ar-Cl; 735cm^{-1}(s), P-N(str.).

Mass(Fig.2.19) :

m/e	335(M+2)$^+$	333(H^+)	318	300
%RI	3.60	11.26	92.20	5.53

219	187	160	140	112	77	42
8.20	31.25	11.25	13.25	30.0	33.88	Base peak

^1H NMR (Acetone-d_6 & $CDCl_3$ /TMS) ppm (Fig. 2.20) : δ 1.10-1.27 (d, 6H, $-CH_3$ gr.), 2.06-2.78 (m, 4H, $-N(CH_2)_2$), 3.51-3.80 (m, 2H, -CH-O-C e), 5.10-5.54 (m, 2H, $-CH_2$-O-P), 6.86-7.51 (m, 3H, aromatic).

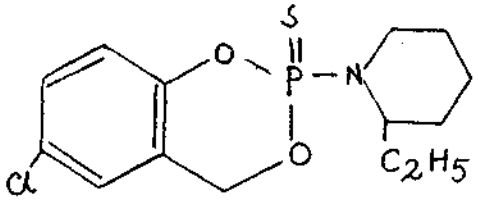
^{31}P NMR ($CDCl_3/H_3PO_4$) ppm (Fig.2.21) : δ 66.0 (J.10.79Hz)

^{13}C NMR($CDCl_3$/TMS) ppm (Fig. 2.22) :

^{13}C Atom	δValues (ppm)	$^{n}J_{AB}$*	Coupling constant (Magnitude in Hz)
C_3	18.56	-	-
C_1	50.30	-	-
C_2	72.01	$^{3}J(^{31}P-N-C_1-C_2)$	3.94
C_4	66.45	$^{2}J(^{31}P-O-C_4)$	5.18
C_8	120.32 120.23	$^{3}J(^{31}P-O-C_9-C_8)$	8.19
C_5	125.03	-	10.86
C_{10}	122.07	-	
C_7	123.78	-	-
C_6	129.26	-	-
C_9	149.41	-	-

*$^{n}J_{AB}$ is used to represent a coupling over n bonds between nuclei A and B.

2.6.5. 2-(2-Ethylpiperidino)-6-chloro-4H-1, 3, 2-benzodioxaphosphorin 2-sulphide (CL-14).



1.58g (0.01 mol) of 2-hydroxy 5-chlorobenzyl alcohol and 2.46g (0.01 mol) of 2-ethylpiperidinophosphorodichloridothionate in 50 ml of dry acetone and 2.76g (0.02 mol) of anhydrous potassium carbonate. The reaction mixture was stirred for 12h. Recrystallization from methanol gave a white crystal of 2.50 g of CL-14.

Yield, 76%; Mol. Formula, $C_{13}H_{19}O_2NPSCl$; Mol.wt.331.50; M.P., 110°; Rf, 0.81 (benzene:acetone, 8:2).

Anal.Calcd for : C, 47.05; H, 5.73; N, 4.22.

Found for : C, 47.0; H, 5.60; N, 4.0.

UV (Fig.2-23) : $\lambda_{max}^{1\text{-Octanol}}$, 279(ε, 1198). IR(Fig.2-24) : 1020 cm^{-1}(s), P-O-C alkyl; 1240-1250 cm^{-1}(s) and 910cm^{-1}(s), P-O-C aryl; 810 cm^{-1}(s), P=S(i); 655 cm^{-1}(s), P=S(ii); 1050 cm^{-1}(s), Ar-Cl; 730 cm^{-1}(s), P-N(Str.)

Mass (Fig.2-25) : m/z 333$(M+2)^+$ 331(M^+) 302 298

	MRI	3.31	9.22	Base peak 88.97

187	157	140	112	77
10.0	72.50	10.0	10.0	13.75

^1H NMR ($CDCl_3$/TMS) ppm (Fig.2-26) : δ 0.84-1.02 (t, 3H, CH_3 gr.), 1.13-1.36 (m, 2H, $-CH_2-$), 1.53 (m, 6H, $-CH_2$ at 2,2,3 position of the piperidine ring), 3.10-3.95 (m, 3H, $-N(CH_2)_2$), 4.80-5.75 (m, 2H, $-CH_2-O-P$), 6.84-7.14 (m, 3H, aromatic).

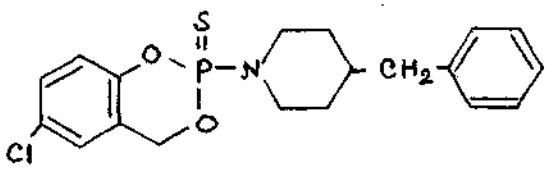
^{31}P NMR($CDCl_3$/H_3PO_4) ppm (Fig.2-27) : δ 66.68 (J, 10.79 Hz)

^{13}C NMR ($CDCl_3$ / TMS) ppm (Fig. 2.28) :

^{13}C Atom	δ Values (ppm)	$^nJ_{AB}$*	Coupling constant (Magnitude in H_z).
C_3^1	10.86		
C_2^1	18.71		
C_3^3	22.67		
C_2^3	26.04		
C_2^2	40.16		
C_1^1	54.09		
C_4	66.47 66.42	$^2J(^{31}P\text{-}O\text{-}C_4)$	5.30
C_8	120.30 120.22	$^3J(^{31}P\text{-}O\text{-}C_9\text{-}C_8)$	8.15
C_5	124.98		
C_{10}	122.37	$^3J(^{31}P\text{-}O\text{-}C_9\text{-}C_{10})$	11.46
C_7	128.39		
C_6	129.03		
C_9	149.99 149.92	$^2J(^{31}P\text{-}O\text{-}C_9)$	6.88

* $^nJ_{AB}$ is used to represent a coupling over n bonds between nuclei A & B.

2.6.6. 2-(4-Benzylpiperidino)-6-chloro-4H-1, 3, 2-benzodioxaphosphorin 2-sulphide (CL-15).



To a stirred solution of 1.59g (0.01 mol) of 2-hydroxy 5-chlorobenzyl alcohol and 3.08 g(0.01 mol) of 4-benzyl piperidinophosphorodichloridothionate was added 2.76g (0.02 mol) of anhydrous potassium carbonate at 0° to 5°c. After 18h the solid was filtered off and the solvent (acetone) was removed under reduced pressure. The combined filtrate was washed with methanol saturated with n-heptane and the residue was purified by column chromatography (silica gel) using benzene-chloroform (9:1) as eluent. On evaporation of solvent a 3.20g colourless high viscous liquid product CL-15 was obtained.

Yield, 81.40%; Mol.Formula, $C_{19}H_{21}O_2NPSCl$; Mol wt. 393.50; Rf, 0.92 (benzene:acetone, 8:2).

Anal. Calcd for : C, 57.94; H, 5.36; N, 3.55. Found for : C, 57.90; H, 5.30; N, 3.41.

UV (Fig. 2-29) : $\lambda_{max}^{1\text{-octenol}}$ 279 (ϵ, 1282). IR(Fig. 2-30) : 1020 cm^{-1}(s), P-O-C alkyl; 1240-1250 cm^{-1} (s) and 900 cm^{-1}(s), P-O-C aryl; 805 cm^{-1}(s), P=S(i); 650 cm^{-1}(s), P=S(ii); 1050 cm^{-1}(s), Ar-Cl; 745 cm^{-1}(s), C-N(str.)

Mass (Fig.2-31) : m/e 393(M^+) 360 302 187 174

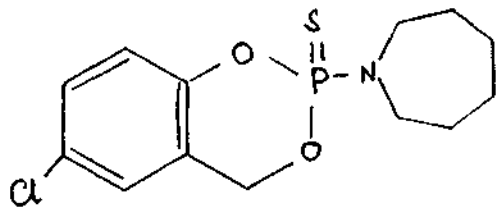
%RI 4.64 24.53 13.70 70.0 70.0

140 112 77 40

12.50 16.25 26.60 Base peak

^1H NMR ($CLCl_3$/TMS) ppm (Fig.2-32) : δ 3.45-3.96 (m, 2H, $-CH_2-$ in the sidechain of piperidine ring), 1.04-1.95 (m, 8H, $-CH_2$ of piperidine ring), 2.68-3.00 (m, 4H, $-N(CH_2)_2$), 4.80-5.75 (m, 2H, $-CH_2-O-P$), 6.84-7.14 (m, 3H, aromatic).

2.6.7. 2-Hexamethyleniмido-6-chloro-4H-1, 3, 2-benzodioxaphosphorin 2-sulphide (CL-17).



To a stirred solution of 1.59g (0.01 mol) of 2-hydroxy 5-chloro benzyl alcohol and 2.32g (0.01 mol) of hexamethyleniмidodichlorideothionate was added 2.76g (0.02 mol) anhydrous potassium carbonate at 0° to 5° for 15h. The reaction was carried in same manner as that in 2.6.1. Evaporation of the solvent followed by recrystallization of the residue from methanol gave 2.8g product CL-17 as a white crystal.

Yield, 89%, Mol.Formula, $C_{13}H_{17}O_2NBCl$;

Mol.wt., 317.45; M.P., 101°; R Rf, 0.89 (benzene: acetone, 8:2).

Anal.Calcd. for : C, 49.14; H, 4.35; N, 4.41.

Found for : C, 49.20; H, 4.3; N, 4.35.

UV(Fig. 2.33) : $\lambda^{1\text{-octanol}}_{max}$ 279 (t, 1384), IR(Fig. 2.34) 1020 cm^{-1}(s)

P-O-C alkyl; 1240 cm^{-1}-1250cm^{-1}(s) and 905 cm^{-1}(s),

P-O-C aryl; 805 cm^{-1}(s), P=O (i); 650 cm^{-1}(s), P=O (ii);

1060 cm^{-1}(s), δ^{730} cm^{-1}(s), P-N (str.)

Mass (Fig. 2.35) :

m/e	319 $(M+2)^+$	317 (M^+)	28.4
%RI	5.61	17.13	Base peak

219	197	143	140	112	77
7.50	40.0	98.0	12.50	17.50	37.50

^1H NMR ($CDCl_3$/TMS) ppm (Fig. 2.36) : 1.65 (m, 8H, hexamethylenimine ring), 3.24-3.48 (m, 4H, $-N(CH_2)_2$), 4.80-5.74 (m, 2H, $-CH_2-O-P$), 6.84-7.15 (m, 3H, aromatic).

^{31}P NMR ($CDCl_3/H_3PO_4$) ppm (Fig. 2.37) : δ 68.03.

^{13}C NMR ($CDCl_3$/TMS) ppm (Fig. 2.38) :

^{13}C Atom	δ values (ppm)	$^nJ_{AB}$*	Coupling constant (Magnitude in Hz).
C_3	26.44	$^4J(^{31}P\text{-}N\text{-}C_1\text{-}C_2\text{-}C_3)$	7.52
C_2	29.98	$^3J(^{31}P\text{-}N\text{-}C_1\text{-}C_2)$	10.96
C_1	48.52	$^2J(^{31}P\text{-}N\text{-}C_1)$	5.08
C_4	66.20	$^2J(^{31}P\text{-}O\text{-}C_4)$	5.50
C_8	120.18 120.10	$^3J(^{31}P\text{-}O\text{-}C_9\text{-}C_8)$	8.23
C_5	124.98		
C_{10}	122.39 122.27	$^3J(^{31}P\text{-}O\text{-}C_9\text{-}C_{10})$	11.35
C_7	128.41		
C_6	129.05		
C_9	149.69 149.61	$^2J(^{31}P\text{-}O\text{-}C_9)$	7.26

* $^nJ_{AB}$ is used to represent a coupling over n bonds between nuclei A and B.

2.7.1. DISCUSSION ON SYNTHESIS

Some chloro saligenin cyclic phosphoramidothionates such as CL-6, CL-7, CL-10, CL-12, CL-14, CL-15 and CL-17 have been synthesized. Of them compound CL-6, CL-12, CL-14 and CL-17 are solid and have been recrystallized from methanol; CL-7, CL-10 and CL-15 are colourless liquid and have been purified by column Chromatography in a pure form. All these compounds have been prepared in good yields. The per cent yield and melting point of these compounds are given in the table below:

Compound	Amido group	Yield(%)	M.P.(^{o}C)
CL-6	Diisobutylamido	78.0	91
CL-7	Dipropylamido	85.0	Liquid
CL-10	Dibutylamido	75.0	Liquid
CL-12	2,6 Dimethylmorpholino	71.0	94
CL-14	2-Ethylpiperidino	76.0	110
CL-15	4-Benzylpiperidino	81.4	Liquid
CL-17	Hexamethylenimido	89.0	101

2.7.2. DISCUSSION ON IR SPECTRA

The IR spectra of the 6-chloro saligenin cyclic phosphoramidothionates have been analysed according to Thomas (3), Bellamy (4), Colthup et al (5) and Das (6). The

Common IR bands for all compounds are summarized below :

1000-1020 cm^{-1}(S), P-O-C (alkyl);

1235-1260 cm^{-1}(S) and

880-915 cm^{-1}(S), P-O-C (aryl);

800-830 cm^{-1}, P = S (i);

630-670cm^{-1}, P = S (ii);

The thionogroup is characterized by two IR absorption bands with frequencies in the normal ranges given by Thomas (3), as both are not observed in amidophosphates; of these two, the lower frequency band is assigned to P=S(ii) bond stretching vibration frequency. The origin of the higher frequency band P=S (i) is uncertain, but whatever its origin, its diagnostic value is beyond doubt. In the nitro-saligenin cyclic alkoxy/ phenoxy compounds, Das et al (7) have observed the two bands in the region : 650-775 cm^{-1}, P = S (ii); and 780-820 cm^{-1}, P=S(i). It may be concluded that in these compounds the frequency of band I is only slightly affected by substitution (alkylamido, alkoxy or phenoxy group to the phosphorus atom) and that of band II is affected to a greater extent. From the above data it can be observed that neither of the two bands shows any systematic shifts which reflects changes in the inductive properties of the substituents, and this is not unexpected if they do indeed arise from mixed modes. It has also been observed that P=S(i) band is of medium intensity while the intensity of the P=S(ii) band is variable. This has also been reported by Thomas (3).

The P–O–C (alkyl) group is characterized by a strong absorption band whose frequency lies between 1000–1020 cm^{-1} while the band due to P–O–C (aryl) group is found in this region; 1235–1260 cm^{-1}; this band is always accompanied by a second absorption band which has been attributed to either the sym. str. of the P–O–C (aromatic) system or a to a separate P–O str. which is not so coupled. Thomas (3) strongly favours the latter explanation which is supported by the persistence of this band in both P–O–P and P–O–H compounds, and by the fact that in the latter the frequency is a linear function of the π- values (where, π is "phosphorus induction constant" for the substituent groups, p 34 ref 3) of the substituents. This band lies between 880–910 cm^{-1} for all compounds; the frequency range quoted is that of the strongest band in this region.

2.7.3. DISCUSSION ON MASS SPECTRA

The fragmentation process of PMS compounds upon electron impact involves the loss of SH from the molecular ion. Jorg, Houriet and Spitell (9) have discussed the spectra of several phosphorothioates and S–alkyl phosphorothioates. Cooks and Gerrard (8) have studied the effects of amino–, chloro–, and alkoxyl substituents on the fragmentation of PMS Compounds. The mass spectra of the chloro saligenin cyclic phosphoramidothionates have been analysed according to Cooks and Gerrard(8) Jörg et al (9) Lamico et al (10,11), Gillis and Occoclowits (12), Ljerassi, Budziekiewicz

and Williams(13) and Shannon(14).

6-chloro saligenin cyclic phosphoramidothionates containing one chlorine atom create a dramatic effect in the mass spectrum because of the (3:1) abundance of the two isotopes (^{35}Cl and ^{37}Cl) the relative intensities of the lines separated by two units, is 3:1.

All compounds show parent molecular ion peaks (M^+). Fragmentation by the loss of '$_5H$' radical is important.

CL-6 The mass spectrum of compound CL-6 exhibits the fragmentation m/z 304 as the base peak by the loss of C_3H_7 from the molecular ion $\frac{m}{z}$ 347. The ion $\frac{m}{z}$314 (% RI 22.23) is formed by the direct elimination of $_5H$ from the molecular ion. The ion m/z 248 (% RI 95.88) resulting from the loss of C_6H_8 molecule from the base peak is obtained. The other major ions are m/z 219 (% RI 20.0), m/z 187 (% RI 25.00), m/z 174 (% RI 10.0), m/z 140 (% RI 12.5), m/z 112 (% RI 6.25) and m/z 77 (% 17.5). (Scheme 1).

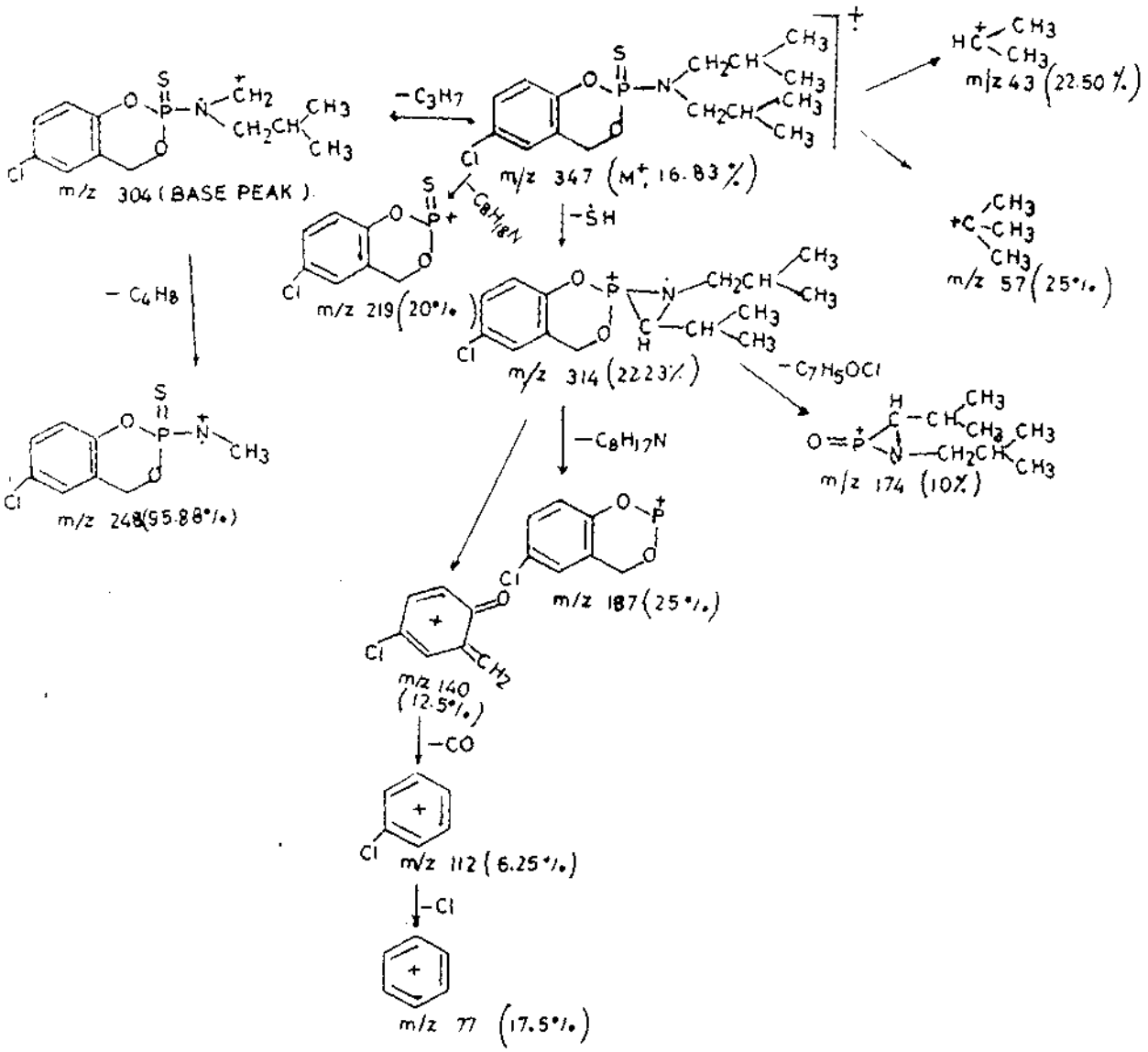
CL-7 For the spectrum of compound CL-7 the molecular ion is m/z 319 (% RI 23.18). The fragmentation m/z 286 (% RI 75.44) is formed by the direct elimination of $_5H$ from the molecular ion. The ion m/z 43 is the base peak. The other major ions are m/z 248 (% RI 24.76), m/z 187 (% RI 31.25), m/z 140 (% RI 25.0); m/z 112 (% RI 40.0), and m/z 77 (% RI 60.0). (Scheme 2).

CL-10 For Compound CL-10, molecular ion peak is m/z 347 (% RI 19.05). The commonest fragmentation involves the loss of SH from the molecular ion which gives rise to the base peak m/z 314. The other major peaks are at m/z 304 (% RI 25.20), m/z 262 (% RI 33.80), m/z 248 (% RI 24.80), m/z 219 (% RI 19.17), m/z 187 (% RI 37.50), m/z 174 (% RI 35.8), m/z 112 (% RI 25.0), and m/z 77 (% RI 87.50). (Scheme-3).

CL-12 For the Compound CL-12, the molecular ion is m/z 333 (% RI 11.26). The base peak at m/z 42 ($C_2H_2O^+$) is formed from the molecular ion $C_{15}H_{15}O_3$ NRS. The peak at m/z 300 (% RI 5.53) formed by the loss of SH from the molecular ion is very weak. The other major peaks are m/z 318 (% RI 92.20), m/z 319 (% RI 8.20), m/z 187 (% RI 31.25), m/z 160 (% RI 11.25), m/z 140 (% RI 13.25), m/z 112 (% RI 30.0) and m/z 77 (% RI 33.88). (Scheme 4).

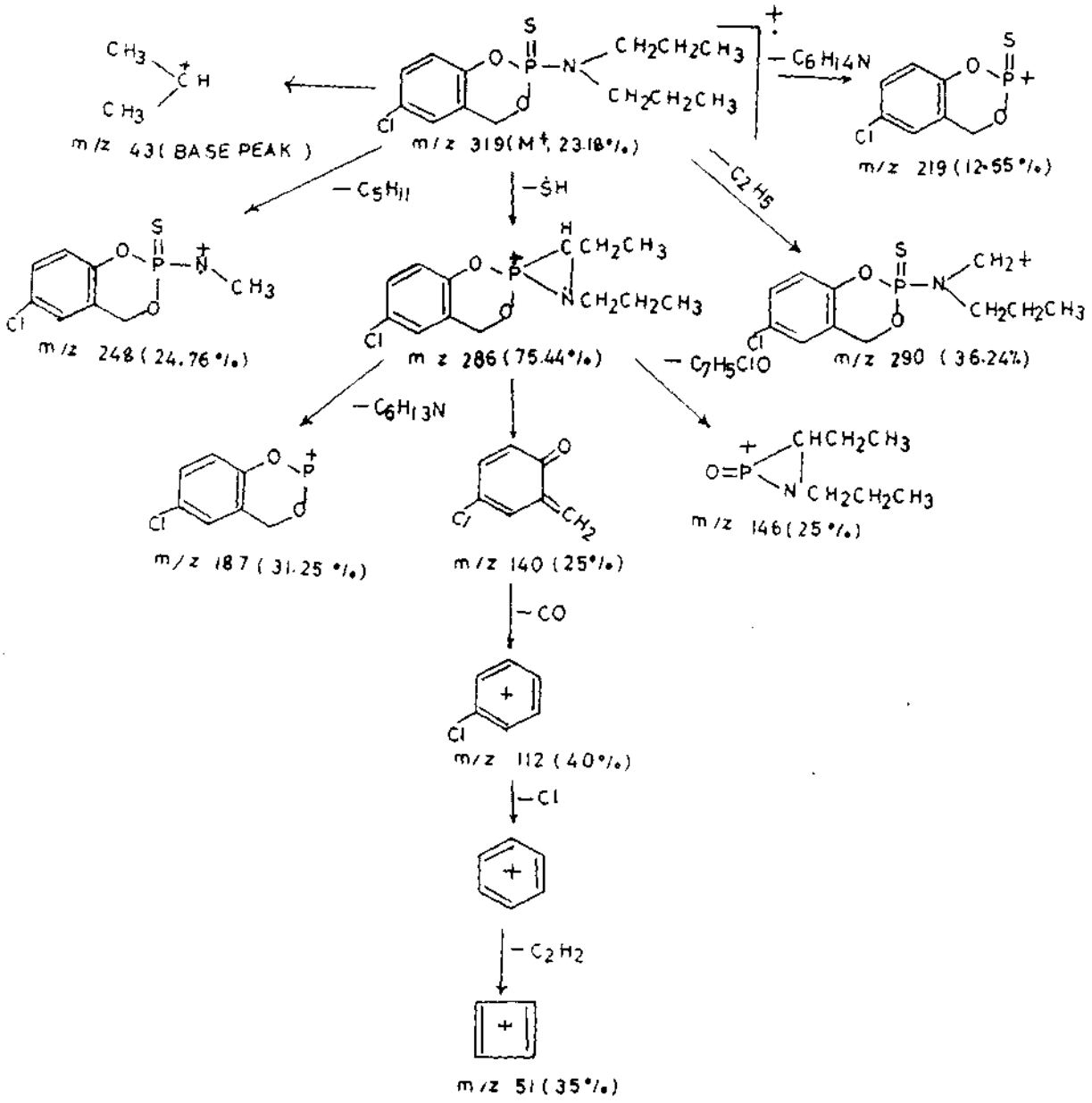
CL-14 For the spectrum of compound CL-14 the molecular ion is at m/z 331 (% RI 9.22). Ethyl group attached to the 2-position of piperidino ring ruptures predominately at the substituent point, which is expelled as a radical to give a base peak at m/z 302. The loss of SH from the molecular ion m/z 331 yields m/z 298 (% RI 88.87). The other major ions are m/z 157 (% RI 72.50), m/z 187 (% RI 10.0), m/z 140 (% RI 10.0), m/z 112 (% RI 10.0) and m/z 77 (% RI 13.75). (Scheme 5).

PRINCIPAL MODES OF FRAGMENTATION OF COMPOUND CL-6



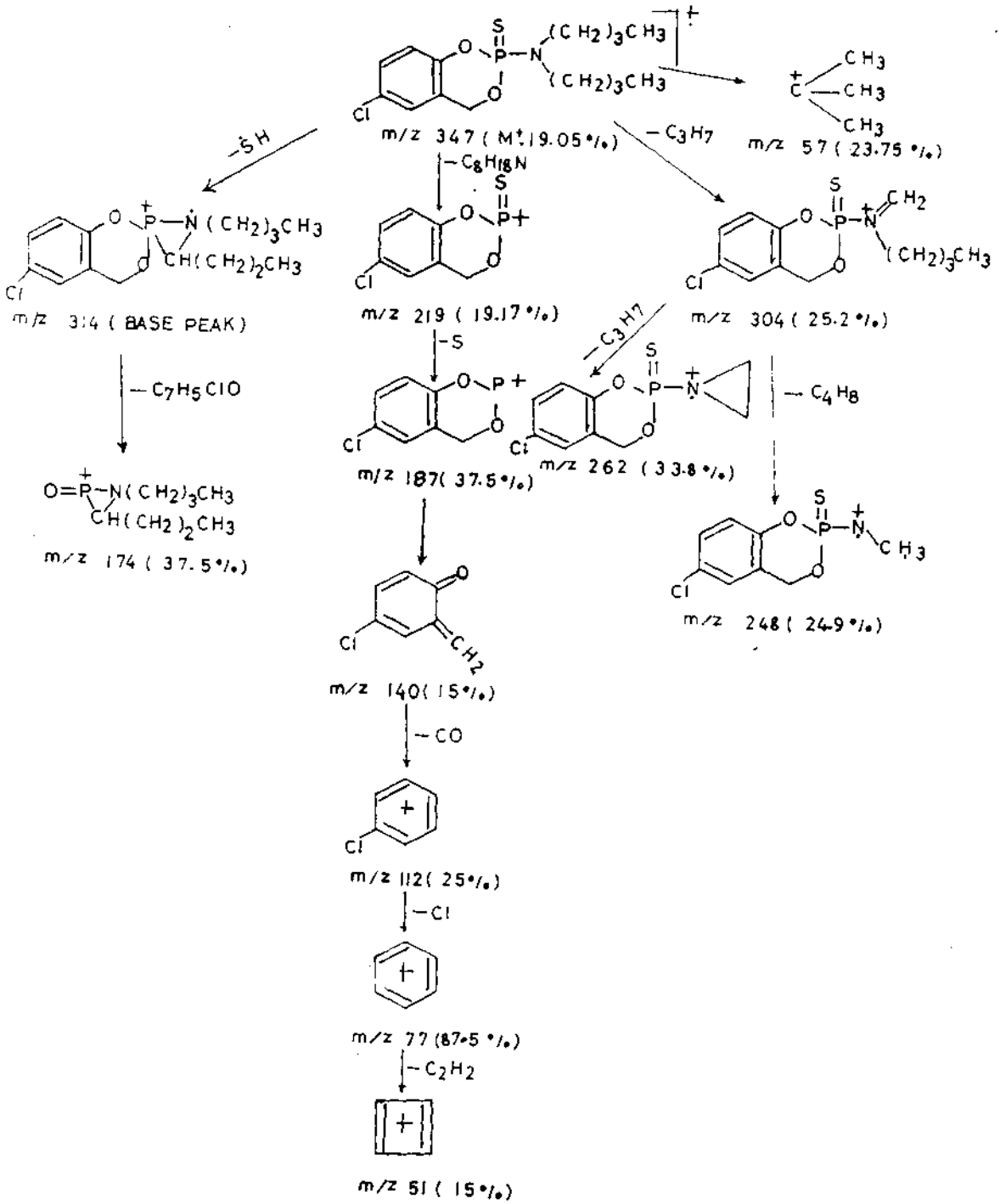
SCHEME – 1

PRINCIPAL MODES OF FRAGMENTATION OF COMPOUND CL-7



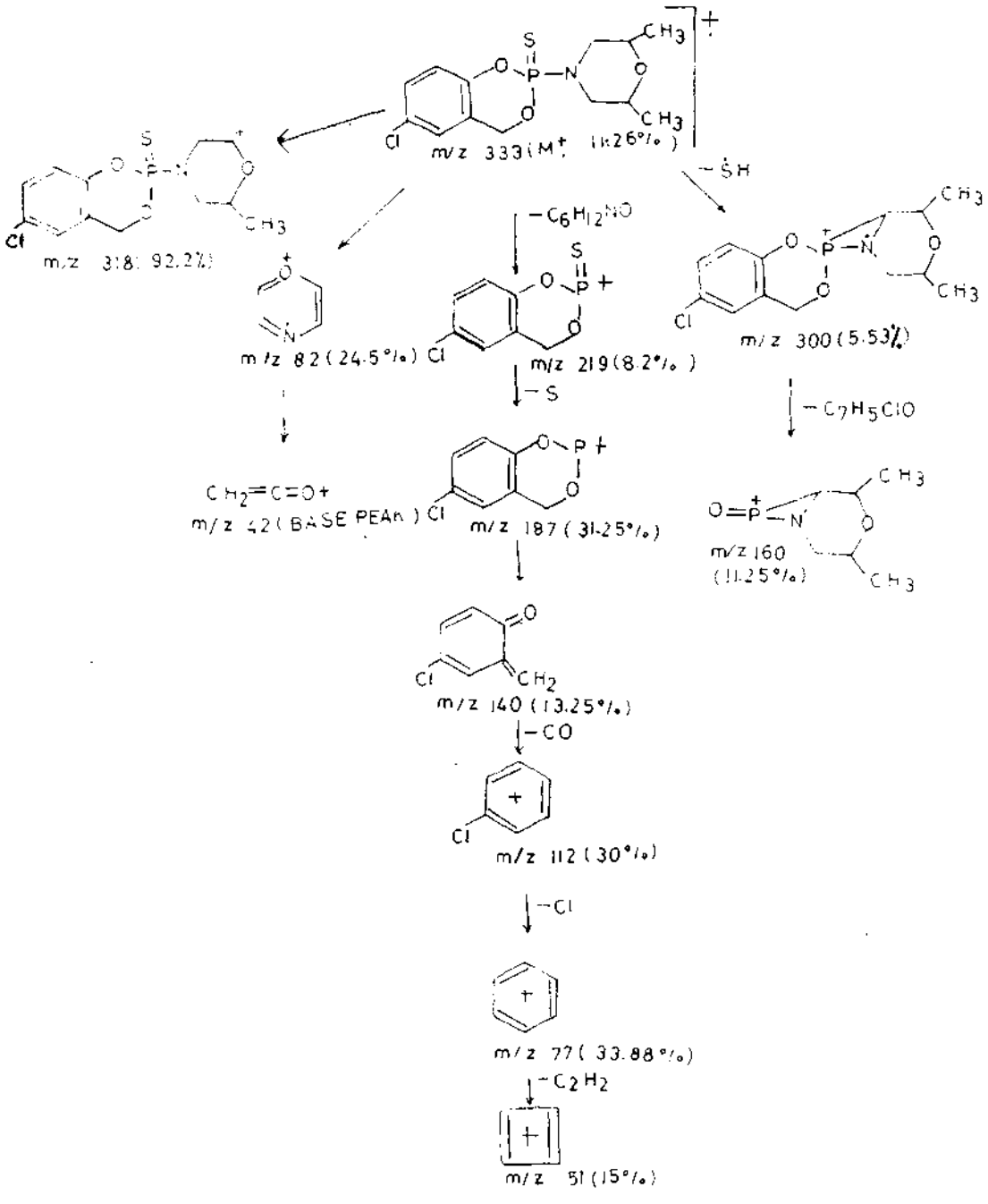
SCHEME - 2

PRINCIPAL MODES OF FRAGMENTATION OF COMPOUND CL-10



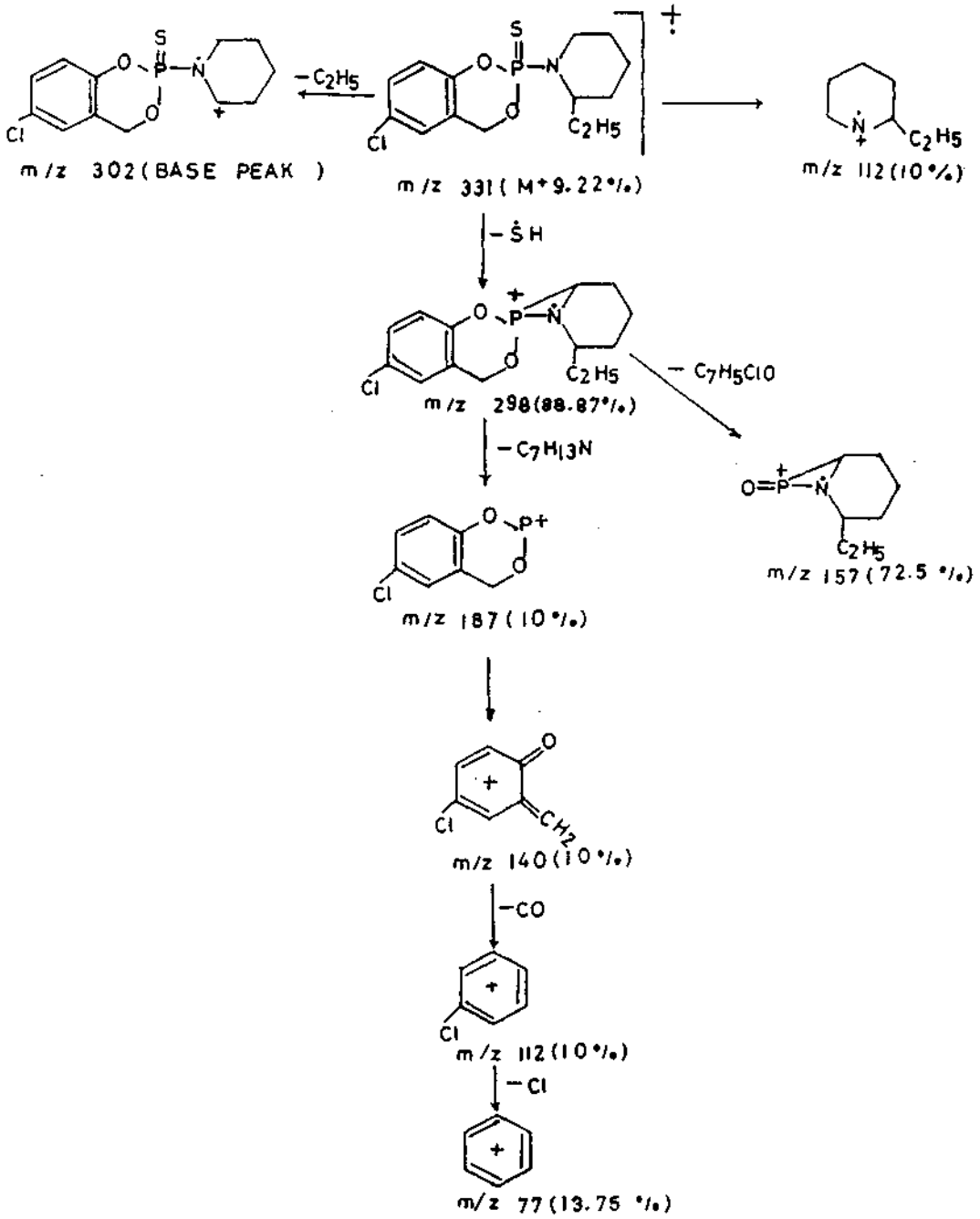
SCHEME - 3

PRINCIPAL MODES OF FRAGMENTATION OF COMPOUND CL-12



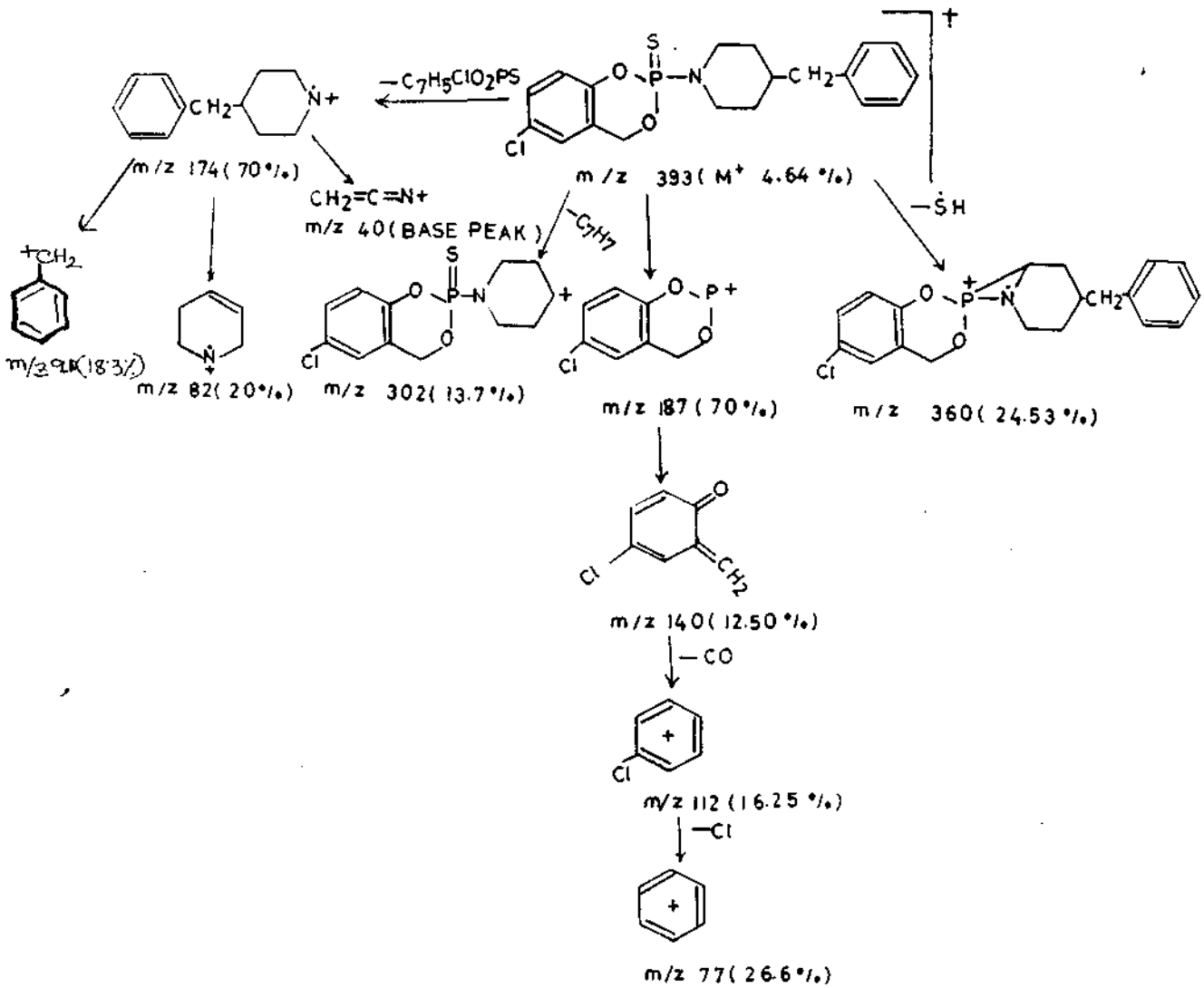
SCHEME-4

PRINCIPAL MODES OF FRAGMENTATION OF COMPOUND CL-14



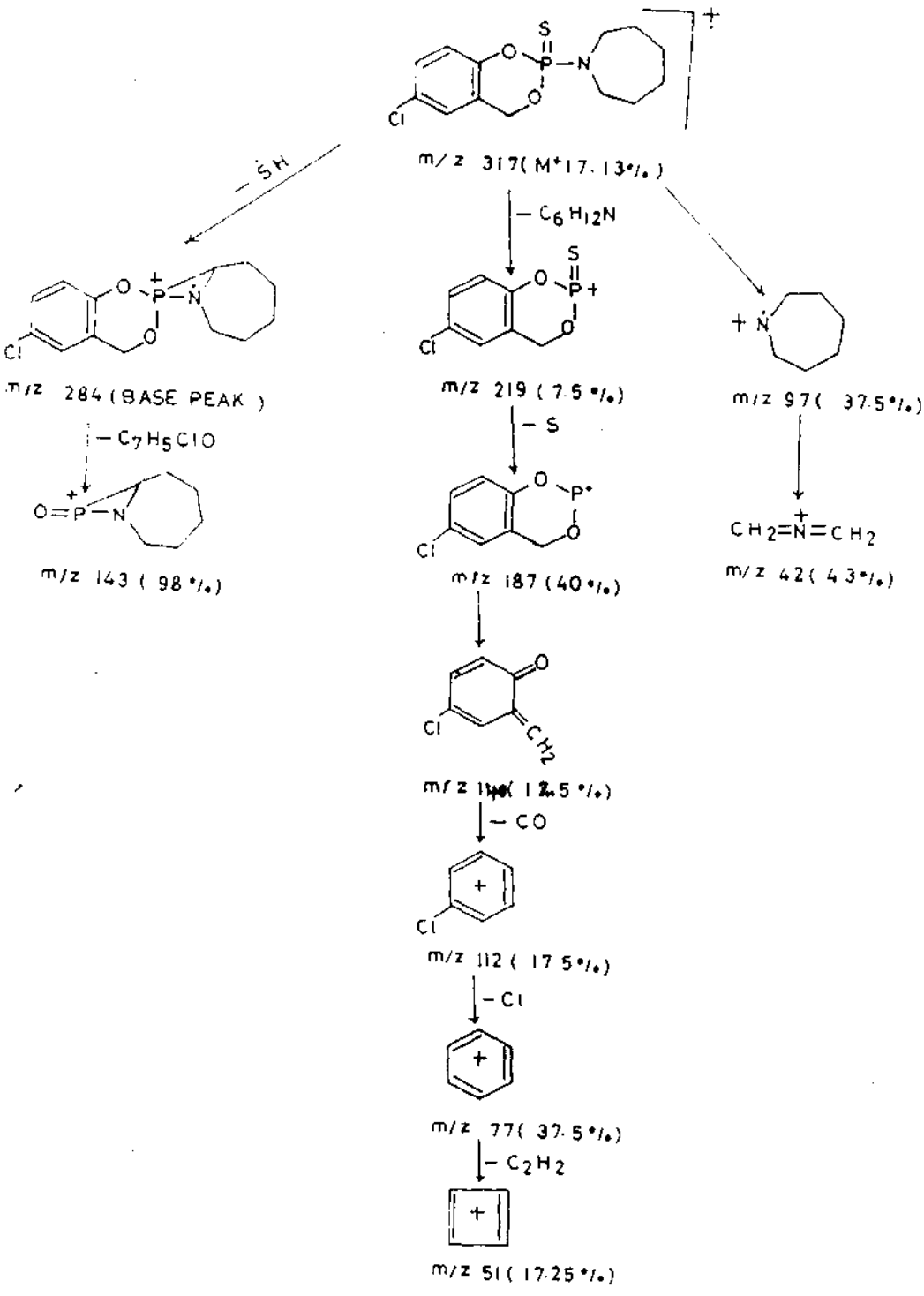
SCHEME-5

PRINCIPAL MODES OF FRAGMENTATION OF COMPOUND CL- 15



SCHEME- 6

PRINCIPAL MODES OF FRAGMENTATION OF COMPOUND CL-17



SCHEME - 7

CL-15 For the spectrum of compound CL-15, the molecular ion is m/z 393 (% RI 4.64). Common fragment is the loss of SH from the molecular ion to yield the ion m/z 360 (% RI 24.53). The base peak at m/z 40 ($C_2H_2N^+$) is formed from the ions at m/z 174. The other important peaks are at m/z 302 (% RI 13.70), m/z 187 (% RI 70.0), m/z 140 (% RI 12.50), m/z 112 (% RI 16.28), m/z 91 (% RI 18.3) and m/z 77 (% RI 26.6) (Scheme 6).

CL-17 For the spectrum of Compound CL-17 the base peak is at m/z 284 formed by the direct expulsion of SH from the molecular ion m/z 317 (% RI 17.13). The other major ions are m/z 187 (% RI 40.0), m/z 143 (% RI 98.0), m/z 140 (% RI 12.50), m/z 112 (% RI 17.5), m/z 97 (% RI 37.50) and m/z 77 (% RI 37.50) (Scheme 7).

2.7.4. DISCUSSION ON NMR SPECTRA

For the proton noise decoupled ^{13}C spectra of CL-6, CL-12, CL-14 and CL-17 at 100 MHz the saturated carbons 2 and 3 bonds from the phosphorus show splitting due to ^{13}C - ^{31}P spin coupling. The coupling to the CH_2 Carbon (C_4) in the dioxaphosphorin ring changes from 5.18 Hz in CL-12, 5.30 Hz in CL-14, 5.33 Hz in CL-6 and 5.50 Hz in CL-17. This probably means that the conformation is almost the same and this is in accord with the small difference in ^{13}C chemical shifts, 66.45 ppm, 66.47 ppm, 66.35 ppm and 66.20 ppm respectively.

The CH_2's next to the nitrogen coupled have J values of

3.0 Hz in CL-6 and 5.08 Hz in CL-17. The CH_2's β to the next nitrogen have J values of 15.19 Hz in CL-6, 3.94 Hz in CL-12 and 10.96 Hz in CL-17 respectively. These large differences account for the differences in the Ring bond angles. Das (15) reported that in compound ML-15, the plot expansion of the aliphatic region of ^{13}C spectrum (Fig. 2.39) reveals the doubling of lines due to the spin of the ^{31}P nucleus and the plot expansion of aromatic regions of the ^{13}C spectrum of ML-15 (Fig.240), four of the ring carbon show measurable coupling to ^{31}P nucleus. The coupling are :

Carbon	Coupling constants (Hz)
C_8	8.19
C_{10}	12.38
C_9	7.30
C_7	0.93

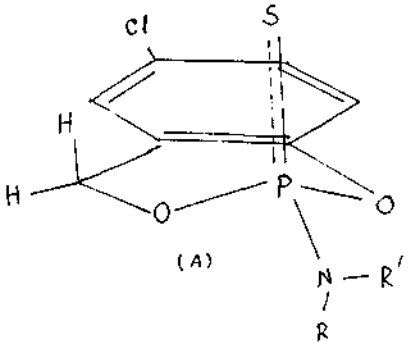
For the aromatic region of ^{13}C spectrum of CL-6, CL-12, CL-14 and CL-17 the chemical shift values and coupling constants are in close agreement with that of ML-15. The carbon γ to the ring nitrogen in CL-6 and CL-17 are coupled to the phosphorus with 7.32 Hz and 7.52 Hz respectively.

The ^{31}P NMR at 162 MHz of CL-6, CL-12, CL-14 and CL-17 give a sharp ^{31}P resonance lines and have the chemical shift values for the phosphorus are 69.80 ppm, 66.0 ppm, 66.68 ppm and 68.03 ppm respectively. Das (15) showed that the selective

decoupling (Fig. 2.4) for EL-16) of the proton adjacent to the nitrogen narrowed otherwise broad line and also showed that the ^{31}P is strongly coupled to proton H_A and H_B (attached to C_4).

The ^1H NMR spectra of CL-6 to CL-17 have signals at $\delta \tau$ 4.75-5.75 ppm for the $-CH_2-$ group protons in the dioxaphosphorin ring and for all the compounds the signal is a eight line multiplet. The other ^1H NMR data of each compound have been assigned.

^{13}C, ^{31}P and ^1H NMR spectral data of the compounds are in general accord with the structure (A). Further studies including X-ray crystal structure determination are in progress.



(A)