SYNTHESIS OF HETEROCYCLIC COMPOUNDS

A THESIS

SUBMITTED TO THE

UNIVERSITY OF BOMBAY

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

BY

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1983

Dedicated To
My Parents

STATEMENT REQUIRED TO BE SUBMITTED
UNDER RULE 0.413 OF THE UNIVERSITY
OF BOMBAY

No part of this work has been submitted for a degree or diploma or other academic award. The literature concerning the problem investigated has been surveyed and all the necessary references are given. The experimental work has been carried out entirely by me. In accordance with the usual practice, due acknowledgement has been made wherever the work presented is based on the results of other workers.

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Professor B. D. Tilak,
Research Guide.

C O N T E N T S

GENERAL REMARKS

Infrared spectra were recorded on Perkin-Elmer Infracord 137 spectrophotometer and Pye Unicam SP-3.300 spectrophotometer in nujol mulls. The absorption values are recorded in cm^{-1}.

Nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer, using $CDCl_3$ as solvent and TMS as an internal standard. The chemical shifts (δ) are reported in parts per million (ppm). Coupling constants (J) are in Hertz (Hz). The following abbreviations are used : s-singlet; d-doublet; t-triplet; q-quartet; m-multiplet.

All mass spectra were recorded on AEI-MS-30 mass spectrometer at 70 eV. The samples were introduced through direct inlet probe and were volatalised at minimum source temperature. The source temperature was between 150-200^{o}C for most of the samples.

Spectral charts, wherever necessary, have been reduced to standard size and attached at the end of the discussion. The actual values are given in the discussion.

Temperatures are in ^{o}C. Melting points are uncorrected.

The figure underlined are structure numbers and the figures in superscript are literature references.

CHAPTER I : PART - A

SYNTHESIS OF 2-CHLORO-3,6-DIARYL-3,4-DIHYDRO-1,3,2-OXAZAPHOSPHORIN-2-OXIDES.

INTRODUCTION

Phosphorus, a universal constituent of protoplasm, is required for growth, health and reproduction in all forms of plants and animals, e.g. as nucleic acids, nucleotide enzymes, metabolic intermediates and phosphatides. It shares this important position in life processes with other elements such as nitrogen, oxygen, hydrogen, carbon and sulfur.

The expansion of all branches of phosphorus chemistry has been enormous. Organic phosphorus compounds are used in various fields such as animal foodstuffs, dental materials, detergents, electrical materials, fertilisers, flame retardants, food additives, glass technology, luminescent phosphorus, matches, medicines, metal treatment, nerve gases, oil additives, pesticides, pigments, plastics, refractories, smoke generators, surfactants and water treatment.

Organic phosphorus compounds are enjoying relatively rapid growth and a great deal of research effort is being expended on them throughout the world. In the fields of biocides, petroleum additives and flotation agents there are a number of patents and the rate at which patents are being granted is increasing.

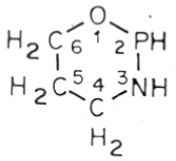
The research in the chemistry of organophosphorus compounds was first undertaken by Lassaigne in 1820 in order to prepare phosphate esters. The chemistry of organophosphorus compounds was developed extensively by Michaelis in Germany during the late 19th century and the beginning of this century. His work laid the foundation of organophosphorus chemistry, especially the chemistry of compounds containing P-N bond. Overlapping the later stages of work of Michaelis, a Russian chemist, A. E. Arbuzov; conducted extensive research especially on the trivalent phosphorus compounds. However, commercial utilization of organophosphorus compounds was only initiated in 1920s. Further significant progress came only around World War II and in the wake of great post-war developments in plastics (polyvinylchloride in particular). The quest for higher compression, higher horsepower automobile engines provided an outlet for organic phosphorus compounds as gasoline additives and oil additives. Increasing attention to industrial safety has opened the door to the use of phosphate ester-based fluids as lubricants for turbines and gas-compressors. Whereas phosphate ester based fluids and alkyl diaryl phosphates had low toxicity which led to their use in food-wrap plastic films, organophosphorus pesticides developed in 1937 by Gerhard Schrader in Germany were highly effective in control of several insect

pests. In addition to insecticidal and acaricidal activity, organophosphorus compounds showed a wide spectrum of biological activity. Some compounds were useful as nematocides, some as antihelmentic agents and some show inhibitory activity against cholinesterases.

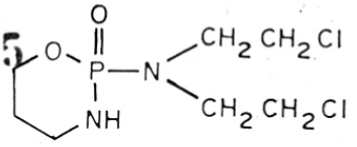
In 1958, N. Brock and H. Williams first synthesised tetrahydro derivative of the, as yet unknown, oxazaphosphorin ring system[1] viz. tetrahydro-2H-1,3,2-oxazaphosphorin. A number of substituted derivatives of tetrahydro-2H-1,3,2-oxazaphosphorin were synthesised, which led to the discovery of cyclophosphamide 2[Endoxan^{R}] a well-known commercial anticancer drug.

Various ring systems with two oxygen and one phosphorus atoms have been described in literature (Chart 1). These are 1,3,2-dioxaphospholidines (five membered rings) and 1,3,2-dioxaphosphorins (six membered rings), azaphosphocines (eight membered rings). Likewise, various ring systems with phosphorus, oxygen and nitrogen have also been reported such as

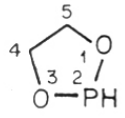
1,3,2-oxazaphospholidine (five membered ring),
1,3,2-oxazaphosphorine (six membered ring),
1,3,2-oxazaphosphepine (seven membered ring),
1,3,2-oxazaphosphocine (eight membered ring),
1,3,2-oxazaphosphonine (nine membered ring).



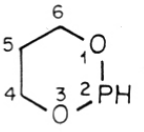
TETRAHYDRO-2H-1,3,2-OXAZAPHOSPHORINE



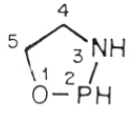
CYCLOPHOSPHAMIDE



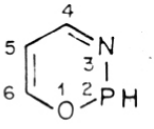
1,3,2-DIOXAPHOSPHOLINE



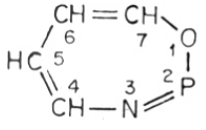
1,3,2-DIOXAPHOSPHORINE



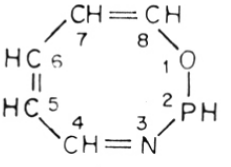
1,3,2-OXAZAPHOSPHOLIDINE



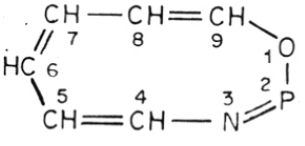
2H-1,3,2-OXAZAPHOSPHORINE



1,3,2-OXAZAPHOSPHEPINE



2H-1,3,2-OXAZAPHOSPHOCINE



1,3,2-OXAZAPHOSPHONINE

CHART - 1 .

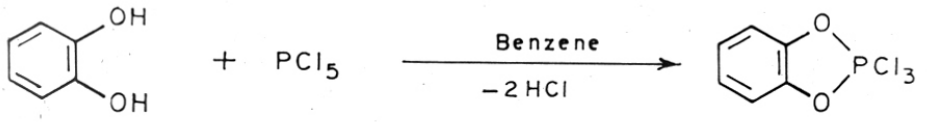
Though the various ring systems have been described in the literature, only their tetrahydro derivatives have been reported.

Anschütz et al[3] refluxed catechol 1 with phosphorus pentachloride in benzene for three hours to obtain 2,2,2-trichlorobenzo-1,3,2-dioxaphospholidin 2 (Chart 2).

2-Chloro-2-oxo-1,3,2-dioxaphosphorin[4] 4 was obtained by the interaction of 1,3-propanediol 3 with phosphorus oxychloride in benzene at 25° under pressure (Chart 3).

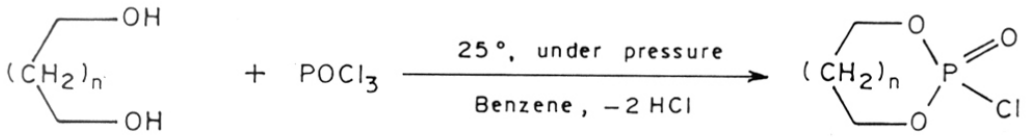
The reaction of salicylic acid with PCl_3[5,6], PCl_5[7], and $POCl_3$[8] has received widespread attention and the various products formed have been extensively studied. Salicylic acid 5 on refluxing with PCl_3 in toluene yields 2-chloro-4-oxo-benzo-1,3,2-dioxaphosphorin 6. On oxidation with dry oxygen 6 gets converted to 2-chloro-2,4-dioxobenzo-1,3,2-dioxaphosphorin 8. On refluxing 5 with PCl_5 in toluene 2,2,2-trichloro-4-oxobenzo-1,3,2-dioxaphosphorin 7 is obtained. Partial hydrolysis of 7 by treatment with pyridine-water-ether mixture gives 8. The chlorination of 6 in CCl_4 gives the addition product 7 (Chart 4).

Tetrahydro-2-methyl-1,3,6,2-dioxaphosphocine-2-oxides and 2-sulfides 10 were synthesised by reaction between



1 2

CHART – 2.



3 4

CHART – 3.

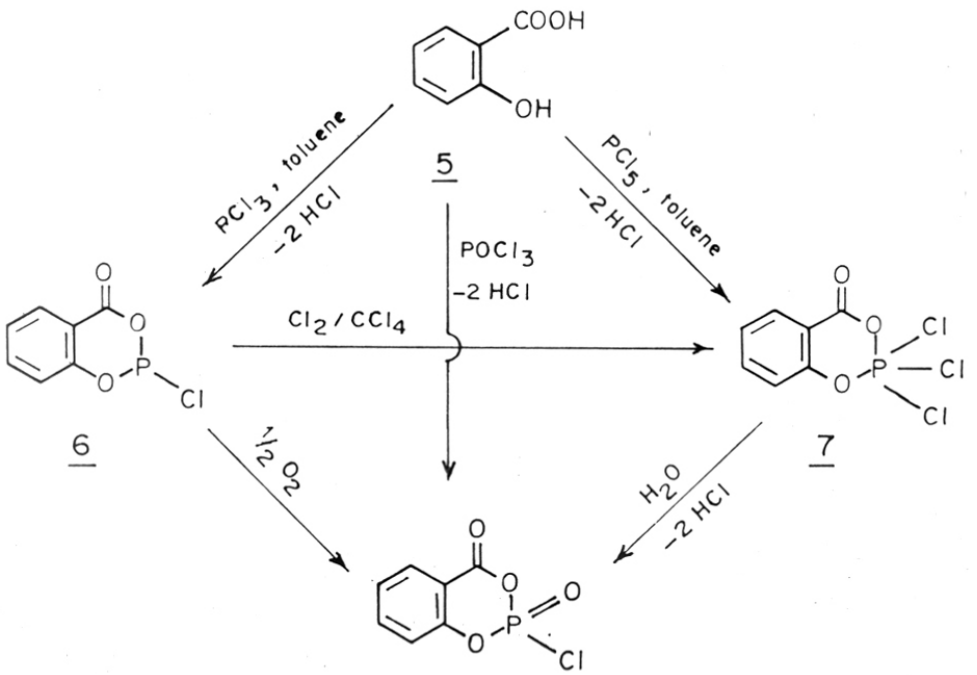


CHART – 4.

equimolar amounts of methyl phosphonic or methyl phosphorothionic dichloride and the appropriate 2,2'-iminobisethanol in presence of triethylamine in dry benzene[9] (Chart 5).

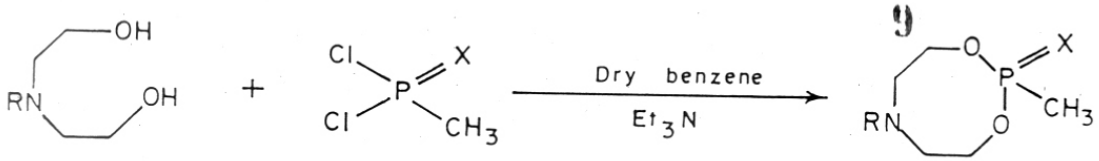
Feldman et al[10] treated d-pseudoephedrine 11 with phosphorus oxychloride at 5-8° in benzene with two moles of triethylamine. After 8 hours they obtained 2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphosphol-2-oxide 12 (Chart 6).

Interaction of 3-amino-1-propanol 13 with phosphorus oxychloride and triethylamine in dry dichloromethane yielded 2-chlorotetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide[11] 14 (Chart 7).

2-Oxo-1,3,2-oxazaphospholanes 15 and 2-oxo-1,3,2-oxazaphosphorinanes[12] 16 were synthesised by interaction of $ROP(O)Cl_2$, $HO(CH_2)_nX$ (X = Cl, Br) and $R'NH_2$ in the presence of NaH as a cyclising agent (Chart 8).

Cyclic phosphoric acid esters having pesticidal properties have been synthesised[13] by the reaction of o-hydroxybenzyl alcohols and o-hydroxybenzyl amines with $POCl_3$, $PhP(O)Cl_2$, $PhOP(O)Cl_2$ and $EtOP(O)Cl_2$. These reactions yield compounds 17, 18, 19 and 20 (Chart 9).

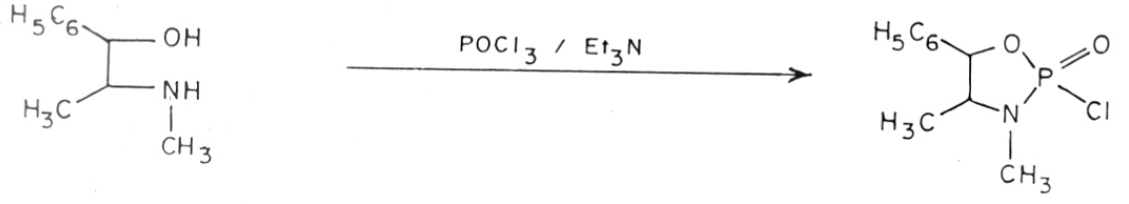
A number of higher membered cyclic N',O-alkylene-N,N-bis(β-chloroethyl)diamidophosphates[14],



9 Where X = (O) or (S) 10

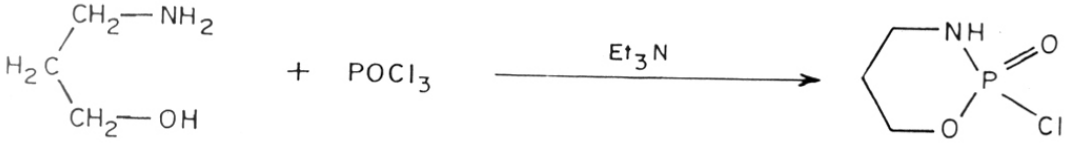
R = alkyl or aryl

CHART – 5



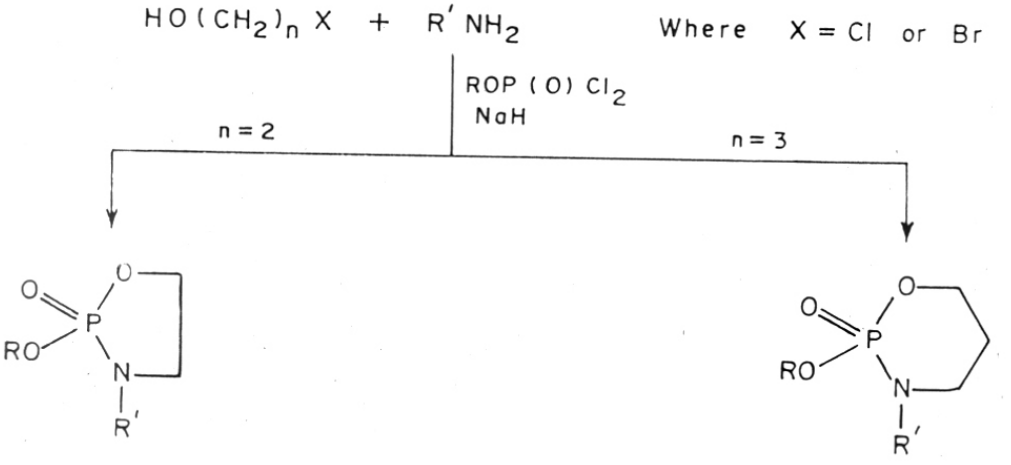
11 12

CHART – 6



13 14

CHART – 7



15 16

CHART – 8

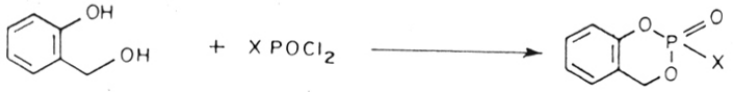
$(ClCH_2CH_2)_2NP(O)N(CH_2)_nO$ (n = 1-6) 22 were prepared by treating dichloro-N,N-bis(β-chloroethyl)amidophosphate with $H_2N(CH_2)_nOH$ 21 in presence of equimolar amounts of triethylamine in dioxane (Chart 10).

A mixture of 2-piperidylcarbinol 23, anhydrous Et_3N and dioxane when added dropwise to a solution of $Et_3NP(O)Cl_2$ in dioxane and kept for 48 hours at room temperature, yielded[15] 24 (Chart 11). Compound 25 was similarly prepared.

Petitcolas et al[16] heated 3,2-$HOC_{10}H_6CONHPh$ 26 in benzene with $Cl_3CCCl{:}NPOCl_2$ to obtain hygroscopic 1-oxa-2-phospha-3-aza-4-(N-trichloroacetylanilino)-2-oxo-2-chloro-1,2-dihydroanthracene 27 (Chart 12). Petitcolas et al[17] have synthesised compounds 29 and 30 by refluxing the precursor 28 with $POCl_3$ and $PhO\text{-}P(O)Cl_2$ respectively (Chart 13).

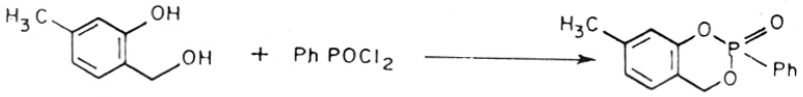
Compound 32, useful as an anticancer drug, was prepared[18] by stirring o-(2-carboxyethyl)-N-bis(2-chloroethyl)phosphorodiamidate 31 in dioxane with dicyclohexyl carbodiimide (DCC) for five hours (Chart 14).

2-[Bis(2-chloroethyl)amino]tetrahydro-4H-1,3,2-oxazaphosphorine-4-one[19] 32 was prepared by cyclisation of $H_2NCO(CH_2)_2OP(O)ClN(CH_2CH_2Cl)_2$ with NaH (Chart 15).

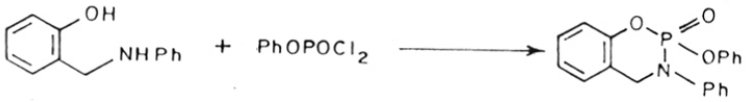


Where
X = OEt ,
= Ph

17



18



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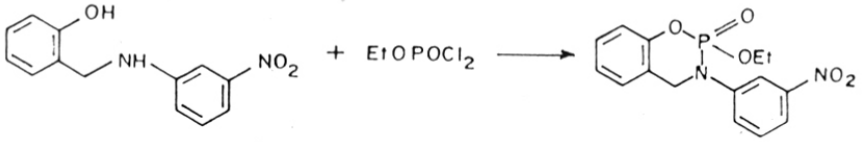

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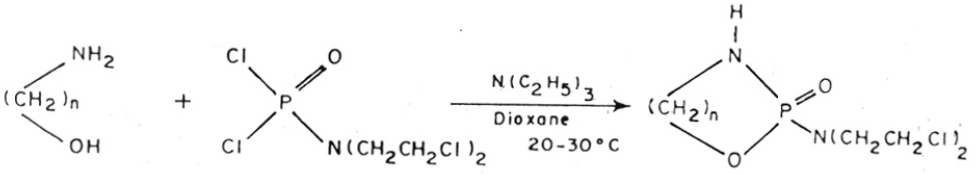
CHART – 9

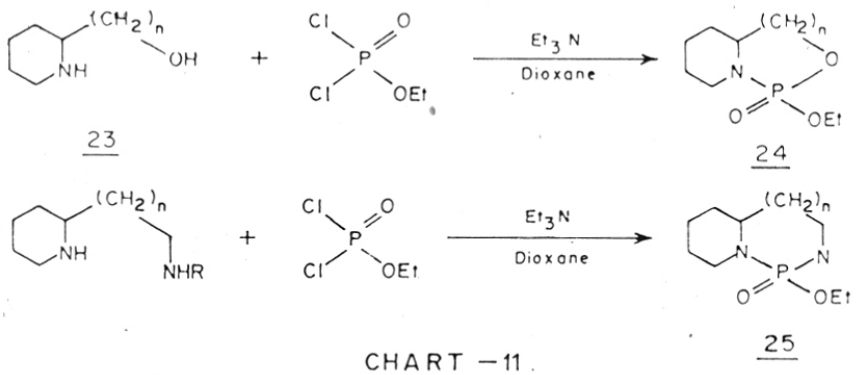


21

n = 2 – 6

22

CHART – 10



23 24 25

CHART – 11

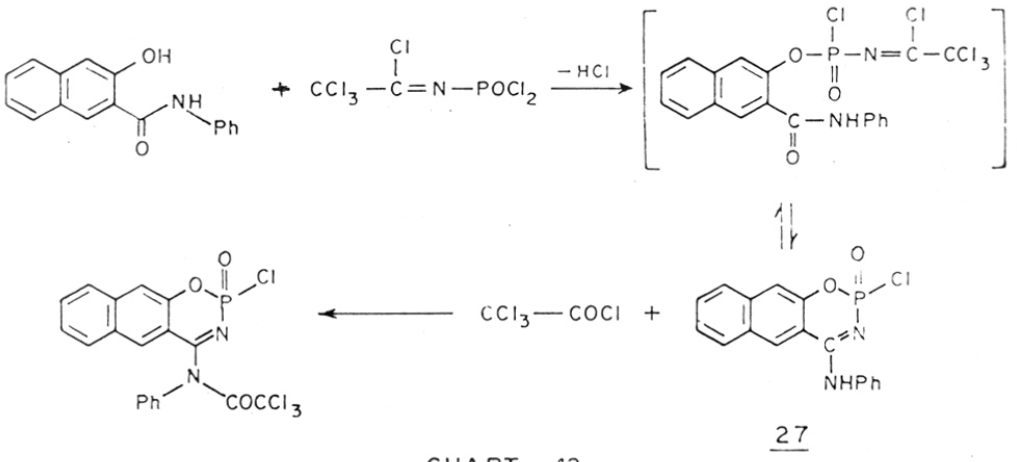


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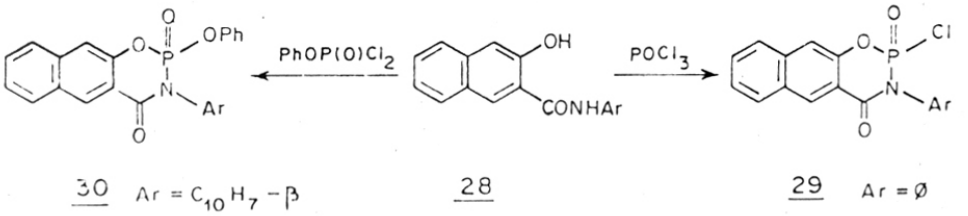
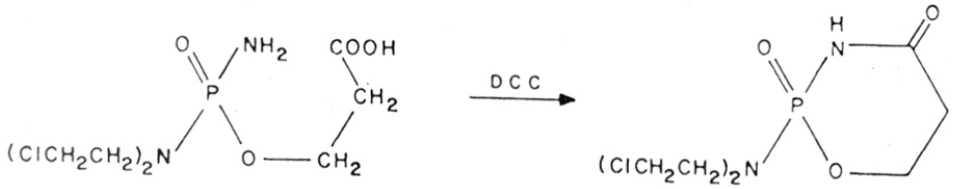
CHART – 12



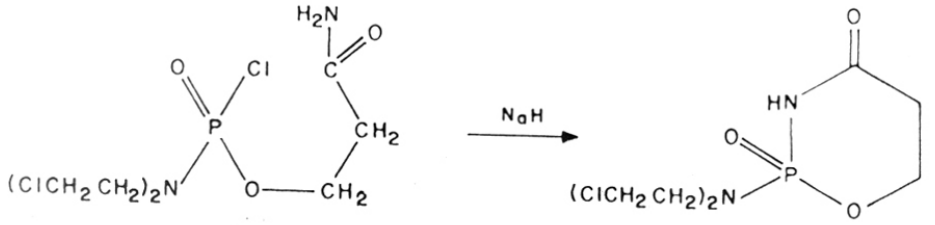
30 Ar = $C_{10}H_7$ – β 28 29 Ar = Ø

CHART – 13



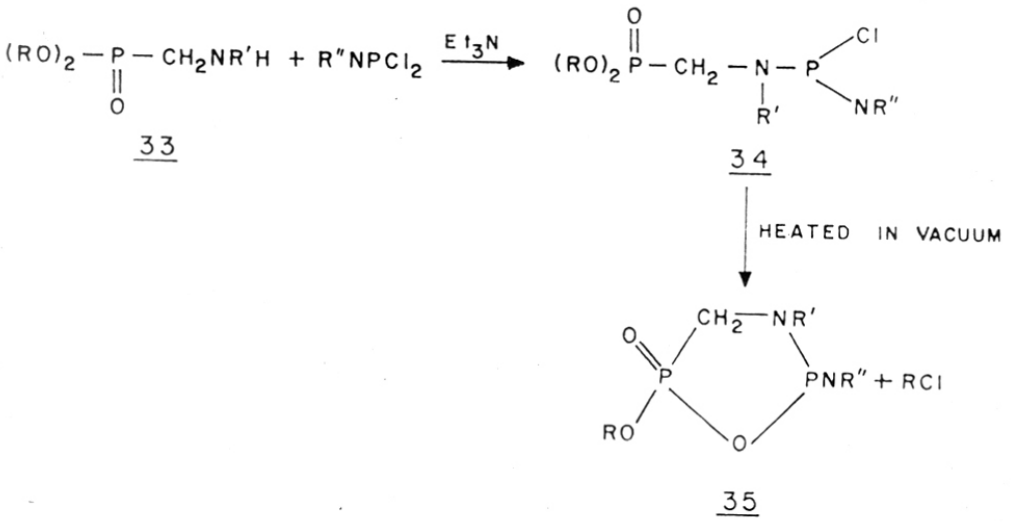
31 32

CHART – 14



32

CHART – 15



33 34 35

CHART – 16

[(Alkylamino)methyl]phosphoric esters 33 react readily with dialkylphophoramidous dichlorides in presence of triethylamine with formation of intermediate [(alkyl chloro(dialkylamino)phosphino)amino]methyl-phosphonic esters 34, which when treated in a vacuum lose alkyl chloride and are converted to substituted 1,3,2,5-oxaza-diphospholidene-5-oxides[20] 35 (Chart 16).

Charts 6 and 9 show the synthesis of tetrahydro-oxazaphosphorins and higher membered ring systems with nitrogen, oxygen and phosphorus. Compounds 19, 20, 29 and 30 consist of oxygen, nitrogen and phosphorus, in a ring system which is fused to an aromatic ring. The double bond in the heterocyclic ring is located at the ring junction of the heterocyclic and aromatic rings.

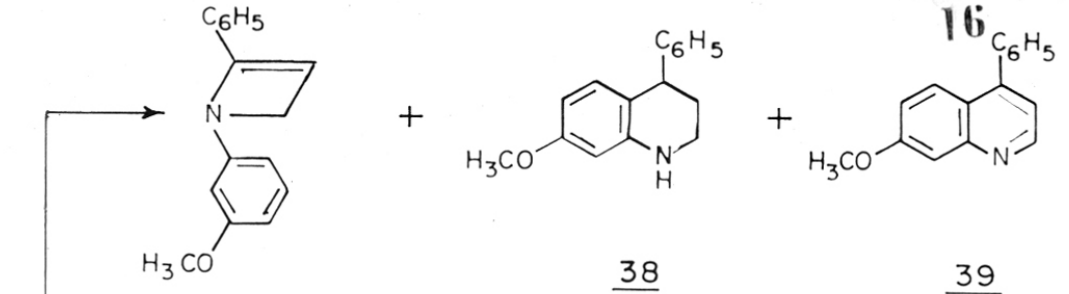
The synthesis of the parent 1,3,2-oxaza-phosphorin ring system is as yet unreported. The synthesis of dihydro-1,3,2-oxazaphosphorin was, therefore, interesting. The present chapter describes the synthesis of various substituted dihydro-1,3,2-oxazaphosphorins.

PRESENT WORK

Tilak et al in an unsuccessful attempt to synthesise azetines (e.g. 37) by the action of phosphorus oxychloride and triethylamine on aryl β-arylaminoethyl ketone 36 obtained corresponding 2-chloro-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide[21] 40, an unreported ring system along with compounds 38 and 39 (Chart 17).

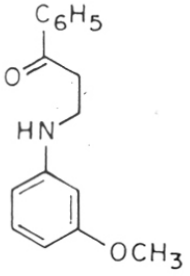
β-Dimethylaminopropiophenone hydrochloride[22] on interaction with primary amines such as aniline, p-chloroaniline, p-toluidine and p-anisidine yielded corresponding aryl β-arylaminoethyl ketones, which on treatment with phosphorus oxychloride and triethylamine gave corresponding dihydrooxazaphosphorins[21]. The substituents at the para position of the phenyl ring attached to the oxazaphosphorin ring at 6-position were changed (Chart 18). These compounds were tested for biological activity and few of them proved to be active against P-388 leukemia.

With the view to study the interrelation between antileukemic properties of compounds of this series and chemical structure and also hopefully to synthesise more active compounds, a number of compounds in this series with different substituents in both the phenyl rings were prepared.



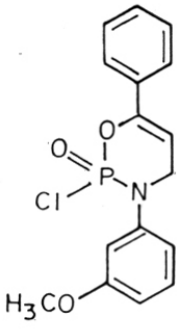
37 38 39

i) $POCl_3$, CH_2Cl_2 ,
24 hrs. at R. Temp.
ii) Et_3N at 0-5°



36

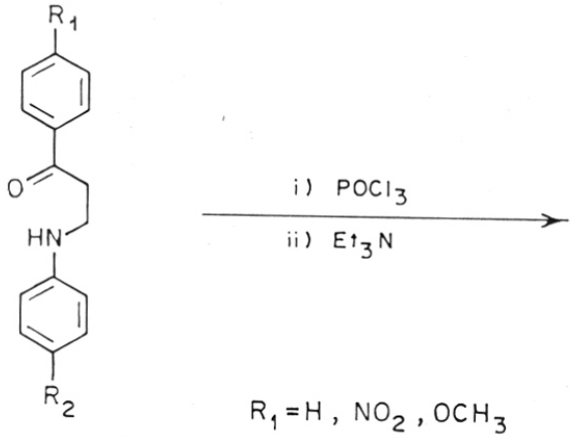
i) $POCl_3$, CH_2Cl_2
ii) Et_3N



+ 38 + 39

40

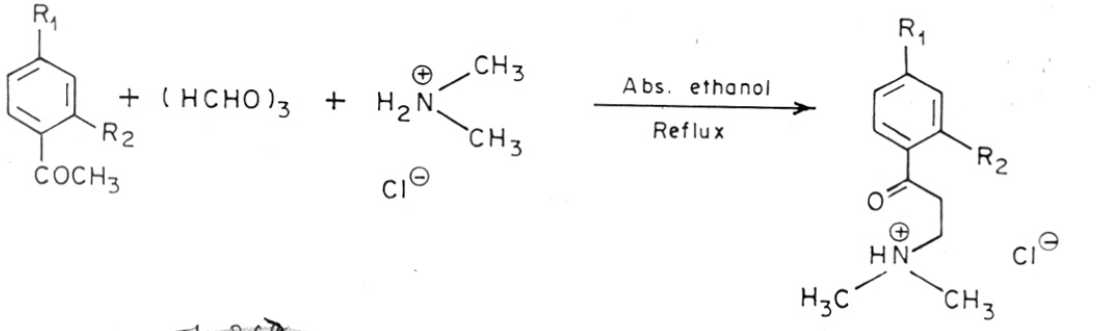
CHART – 17 .



$R_1 = H, NO_2, OCH_3$

$R_2 = H, Cl, CH_3, OCH_3$

CHART –18.



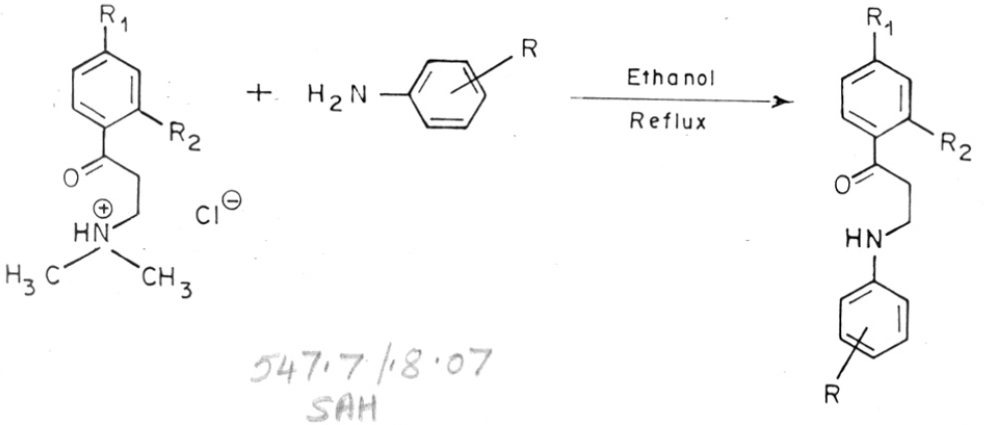
41 $R_1 = H$, $R_2 = H$

42 $R_1 = Cl$, $R_2 = H$

43 $R_1 = NO_2$, $R_2 = H$

44 $R_1 = \beta$-naphthyl, $R_2 = H$

45 $R_1 = Cl$, $R_2 = Cl$



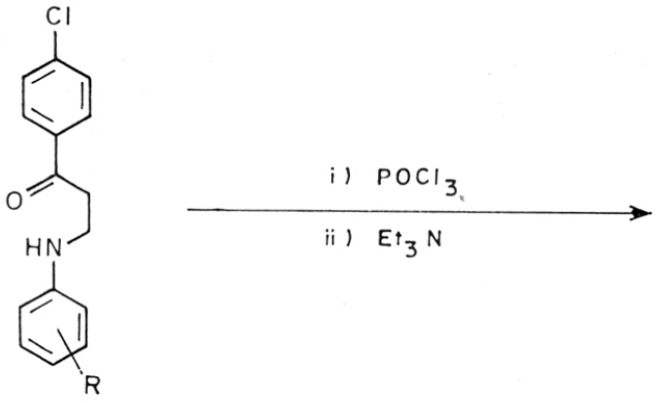
547.7/8.07
SAH

CHART – 19.

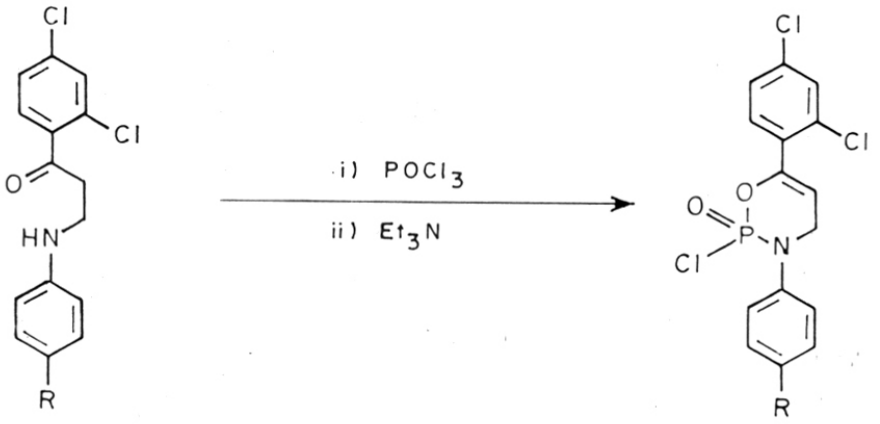
Acetophenone[22], p-chloroacetophenone when refluxed with paraformaldehyde and dimethylamine hydrochloride in absolute alcohol yielded β-dimethylaminopropiophenone hydrochloride 41 and ω-dimethylamino-p-chloropropiophenone hydrochloride 42 respectively. In a similar way 2,4-dichloro- ω -dimethylaminopropiophenone hydrochloride 43 was obtained from 2,4-dichloroacetophenone[23], paraformaldehyde and dimethylamine hydrochloride (Chart 19). The Mannich base hydrochlorides 42 and 45 on condensation with different monosubstituted primary aryl amines yielded respective substituted aryl β-arylaminoethyl ketones 46-50 and 56-59. The above aminoketones on treatment with phosphorus oxychloride and triethylamine in dry dichloromethane yielded the corresponding dihydro-oxazaphosphorins 51-55 and 60-63 (Chart 20).

Similarly, β-dimethylaminopropiophenone hydrochloride was condensed with disubstituted primary arylamines to yield aminoketones 64-66. The interaction of these aminoketones with phosphorus oxychloride and triethylamine in dichloromethane gave the corresponding dihydro-oxazaphosphorins 67-69 (Chart 21).

The synthesis of the dihydro-oxazaphosphorin 71 with disubstitution in both the phenyl rings at 3 and 6 positions was achieved by the reaction of aminoketone 70 with phosphorus oxychloride and triethylamine (Chart 22).

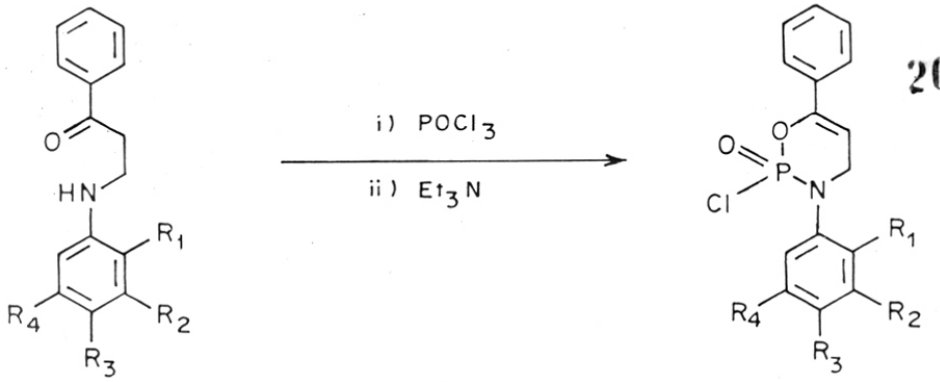


46	; R = H	51
47	; R = p−Cl	52
48	; R = p−CH_3	53
49	; R = o−OCH_3	54
50	; R = p−OCH_3	55



56	; R = H	60
57	; R = Cl	61
58	; R = CH_3	62
59	; R = OCH_3	63

CHART − 20.

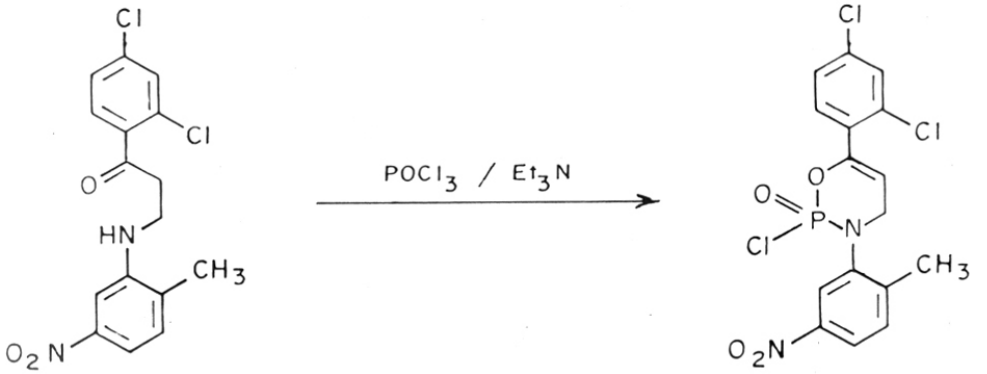


64 ; $R_1 = R_4 = H$, $R_2 = NO_2$, $R_3 = CH_3$, 67

65 ; $R_2 = R_3 = H$, $R_4 = NO_2$, $R_1 = CH_3$, 68

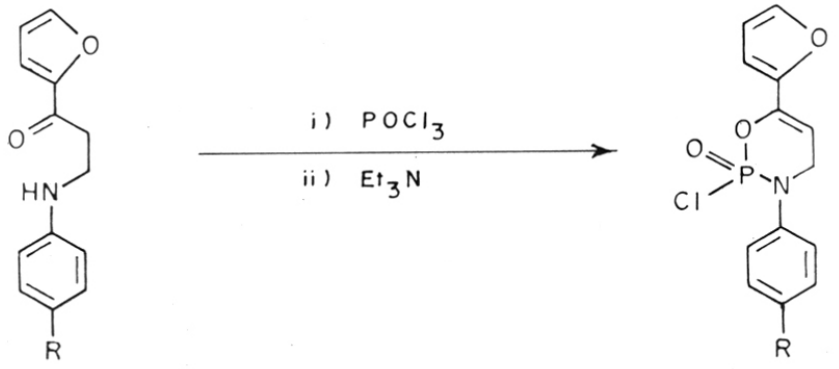
66 ; $R_2 = R_3 = H$, $R_1 = R_4 = Cl$, 69

CHART – 21.



70 71

CHART – 22.



72 ; $R = CH_3$

73 ; $R = OCH_3$

74

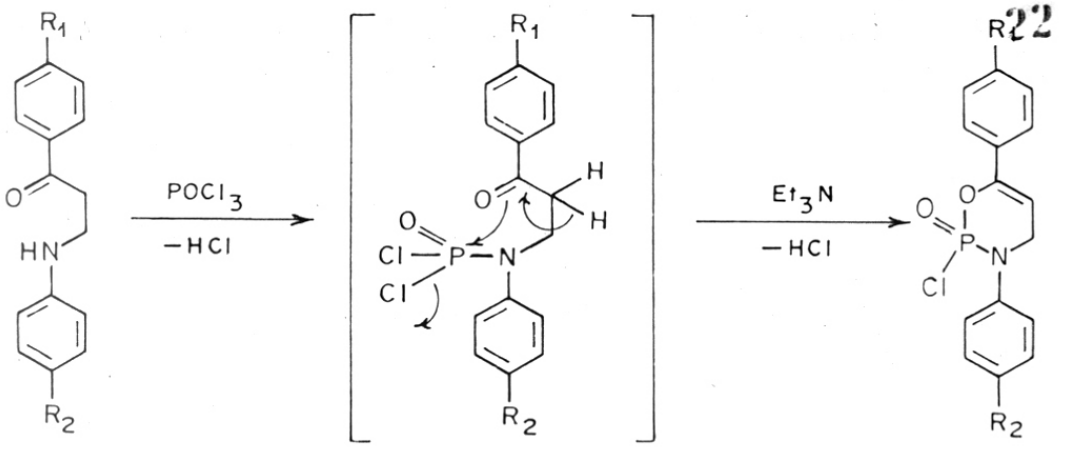
75

CHART – 23.

The aryl moiety at 6-position of the dihydro-oxazaphosphorin ring system was replaced by a hetero-cyclic ring such as furan, in the hope to increase the biological activity. 2-Furyl β-dimethylaminoethyl ketone hydrochloride[24] was prepared by condensation of 2-acetyl-furan[25], paraformaldehyde and dimethylamine hydrochloride in absolute ethanol. The resulting 2-furyl β-dimethyl-aminoethyl ketone hydrochloride was condensed with p-anisidine and p-toluidine to obtain respective amino ketones 72-73 which on treatment with phosphorus oxychloride and triethylamine gave corresponding dihydro-oxazaphospho-rins 74-75(Chart 23).

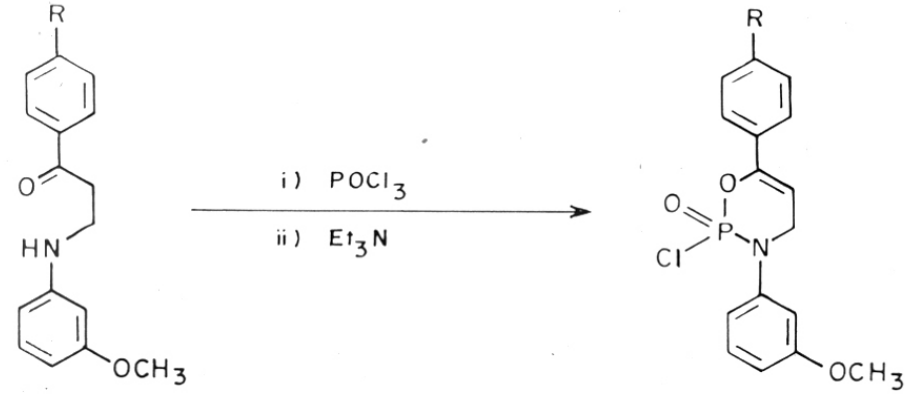
The mechanism of the formation of dihydro-oxazaphosphorins by the reaction of aryl β-arylaminoethyl ketones with phosphorus oxychloride and triethylamine has been suggested and confirmed earlier. The initial step in the reaction of amino ketones involves the phosphorylation of the arylamino group in the amino ketone to yield the intermediate B. Addition of triethylamine to this intermediate B, enolises the ketone. Finally cyclisation takes place forming a stable dihydro-oxazaphosphorin C by the expulsion of hydrogen chloride (Chart 24).

The Mannich base hydrochlorides of p-nitro-acetophenone, β-naphthylmethyl ketone, p-chloroaceto-phenone were condensed with m-anisidine to yield



B

CHART — 24



76 ; R = Cl

77 ; R = NO_2

78 ; R = β-naphthyl

79

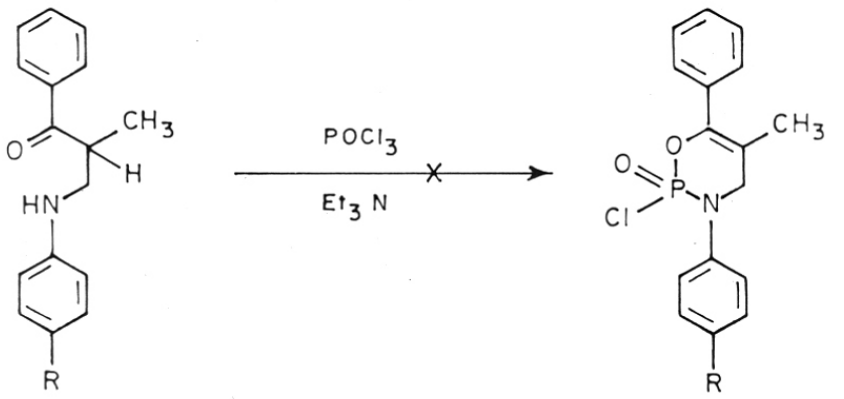
80

81

CHART — 25

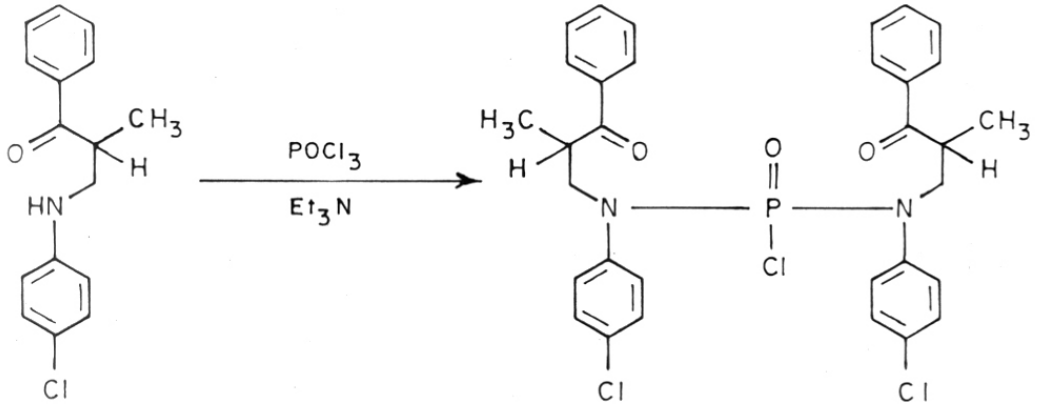
corresponding amino ketones 76-78. These aminoketones were reacted with phosphorus oxychloride and triethylamine to give corresponding dihydro-oxazaphosphorins 79-81 (Chart 25).

β-Dimethylaminopropiophenone hydrochloride[26], prepared by condensation of propiophenone, paraformaldehyde and dimethylamine hydrochloride in absolute ethanol, on condensation with primary aromatic amines, gave the respective aryl β-arylamino-α-methylethyl ketones. The latter, when treated with phosphorus oxychloride and triethylamine, surprisingly did not yield the corresponding dihydrooxazaphosphorins but gave dimers of the type 84 (Chart 26). The structures were conferred on the basis of spectral data such as NMR and IR. NMR spectra of the β-(p-chlorophenyl)amino-α-methylpropiophenone 82 showed doublet of a methyl group. The cyclised product of amino-ketone would show a singlet of the methyl group, but the NMR spectra of the final product 84 showed a methyl doublet, which indicated that the amino ketone had not cyclised, but two moles of aminoketone 82 had reacted with one mole of phosphorus oxychloride to form a dimer bis[N-(p-chlorophenyl)-N-β-benzoylpropylamino]chlorophosphine 84. The IR spectrum of this compound showed the absence of -NH group and the presence of a keto group which confirmed the open chain structure.



82 ; R = Cl

83 ; R = OCH_3



82

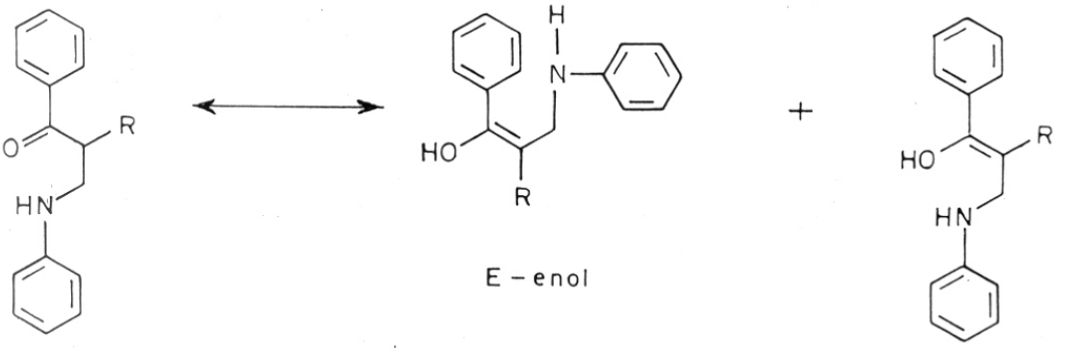
84

CHART — 26 .

The following explanation can be given for the unsuccessful synthesis of 3,5,6-substituted dihydro-oxazaphosphorins.

Amino ketones 85 may be existing in the two enol forms as E-enol 85a and Z-enol 85b (Chart 27). When R = CH_3, the E-enol form will be probably more stable than Z-enol form which will yield dimers as major isolated product. Formation of the Z-enol form is probably less favoured and consequently the cyclic dihydrooxazaphosphorine is therefore not formed. The reaction is generally carried out by dropwise addition of phosphorus oxychloride to the solution of aminoketone in dry dichloromethane, where more aminoketone is available to react with the second chlorine atom of phosphorus oxychloride, which might give rise to a dimer. Therefore, the reaction sequence was changed. A solution of aminoketone in dry dichloromethane was added dropwise to phosphorus oxychloride, but the same product was obtained. Sequence of addition of phosphorus oxychloride and triethylamine was also changed, but the product pattern was not altered.

2-(Dimethylaminomethyl)cyclohexanone hydrochloride was treated with aniline to give 2-anilinomethylcyclohexanone 86. The latter, on treatment with phosphorus oxychloride and triethylamine, did not yield the dihydro-oxazaphosphorin 87 (Chart 28).

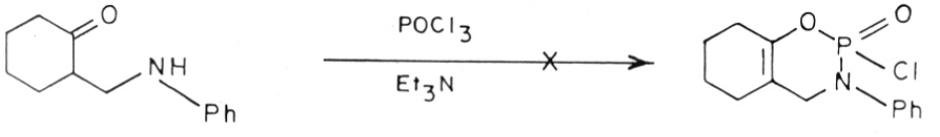


85

85 a

85 b

CHART – 27.



86

87

CHART – 28.

The synthesis of dihydro-oxazaphosphorins was also carried out in dry non-polar solvents like benzene, chloroform, ethyl acetate and dioxane. The sequence of the addition of phosphorus oxychloride and triethylamine was also changed but the yield of dihydro-oxazaphosphorins was not improved.

Among all the non-polar solvents used, dry dioxane was preferred to others, due to its miscibility in water. As triethylamine (excess), triethylamine-HCl and dioxane are soluble in water and the dihydro-oxazaphosphorins are insoluble, the reaction mixture on dilution in ice gave the dihydro-oxazaphosphorins as a precipitate which was then worked up as usual. Chromatographic purification of the product was found to be unnecessary and the reaction product could be purified readily only by crystallization.

EXPERIMENTAL

General method for preparation of Mannich base hydrochlorides from substituted acetophenones

Substituted acetophenones (0.5 mol), dimethylamine hydrochloride (0.65 mol), paraformaldehyde (0.22 mol) and absolute ethanol were taken in a round bottom flask. A few drops of HCl were added and the mixture was refluxed till all the paraformaldehyde dissolved. Excess of ethanol was removed under vacuum. The mixture was cooled, acetone (100 ml) was added and the mixture kept in deep freeze overnight. The solid which separated out was filtered and washed 2-3 times with acetone. The Mannich base hydrochlorides were crystallised from absolute ethanol.

In the case of 2,4-dichloroacetophenone the procedure was slightly modified.

2,4-Dichloroacetophenone (18.8 g; 0.1 mol), paraformaldehyde (10.8 g; 0.12 mol), dimethylamine hydrochloride (13.45 g; 0.16 mol) and absolute ethanol (40 ml) were refluxed together on a boiling waterbath till paraformaldehyde dissolved. Ethanol was then removed completely under vacuum. Dry benzene (50-60 ml) was added to the syrupy liquid and traces of water were then removed by using a Dean-Stark apparatus. Benzene was then completely

removed under vacuum. The residual reaction mixture was cooled and acetone (100 ml) added. The mixture was kept in deep freeze overnight. The solid which separated out was filtered and washed several times with acetone. The hydrochloride, on crystallisation from absolute ethanol, gave colourless needles, m.p. 131-133°. Yield - 53%.

[β-Dimethylaminoethyl]-2,4-dichlorophenyl-propiophenone hydrochloride thus obtained was sufficiently pure and was used as such for further reactions.

General method for preparation of aryl β-arylaminoethyl ketones.

A mixture of Mannich base hydrochlorides (0.1 mol), primary aryl amines (0.1 mol) in 50% ethanol (25-30 ml) was refluxed on a boiling waterbath for 2-3 hours. The reaction mixture was cooled, filtered and the residue washed thoroughly with water and ethanol. The resulting amino ketones were crystallised from absolute ethanol.

Whenever the reaction product obtained was an oil, the reaction mixture was extracted with chloroform. The chloroform extract was washed 2-3 times with water and then dried over anhydrous sodium sulphate. Chloroform was removed under vacuum. The dark syrupy liquid thus

obtained was then distilled to remove excess of unreacted primary arylamine. The ketone (residue) was chromatographed and then further purified by distillation under high vacuum.

The mp's, bp's and IR values of the amino-ketones are mentioned in Table 1.

General procedure for synthesis of 2-chloro-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxides

Method A

Aryl β-arylaminoethyl ketone (0.005 mol) and dry methylene chloride (20 ml) was taken in a R.B. flask. To this phosphorus oxychloride (1 g, 0.007 mol) was added and the mixture was stirred for 20-24 hrs at room temperature (protected from atmospheric moisture by drying tube filled with calcium chloride). The reaction mixture was then cooled in ice and triethylamine (dried over KOH pellets) (3.5 g) was added dropwise over a period of half an hour. The mixture was stirred further for 2 hours. The reaction mixture was worked up as described below.

Method B

A stirred solution of aryl β-arylaminoethyl ketone (0.005 mol) in dry methylene chloride (20 ml) and triethylamine (dried over KOH pellets) (3.5 g) was cooled to 0-5°. A solution of phosphorus oxychloride in dry methylene

chloride was then added dropwise during half an hour. The mixture was stirred for 24 hours at room temperature (protected from atmospheric moisture by drying tube filled with calcium chloride). The reaction was worked up as described below.

Method C

Aryl β-arylaminoethyl ketone (0.005 mol), phosphorus oxychloride (1 g; 0.007 mol) and dry dioxan (20 ml) were placed in R.B. flask. The mixture was stirred for 24 hours at room temperature under dry conditions. The mixture was then cooled to 0-5° and triethylamine (3.5 g) (dried over KOH pellets) was added dropwise in half an hour. Mixture was further stirred for 3-4 hours and poured over ice. The dihydro-oxazaphosphorins which separated out were isolated and finally crystallised from ethanol.

Following work-up procedures were followed:

(A) After the completion of the reaction, excess of methylene chloride was removed under vacuum and the residue was diluted with dry benzene. The triethylamine hydrochloride which precipitated out was filtered and the filtrate was concentrated under vacuum. The resulting syrup was adsorbed on silica-gel and loaded on a silica gel chromatographic column. The column was eluted with benzene.

2-Chloro-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxides were isolated from the first fraction. The column was then eluted with 5% ethyl acetate-benzene. This yielded the unreacted ketones.

(B) The reaction mixture was poured in ice-water and extracted with dichloromethane. The extract was washed 2-3 times with water. The dichloromethane layer after drying over anhydrous Na_2SO_4 was concentrated under vacuum and then chromatographed on a silica-gel column, using benzene as eluant. The first fraction yielded dihydro-oxazaphosphorins. The column was then washed with 5% ethyl acetate-benzene whereby the unreacted aminoketones were eluted out.

(C) In another procedure, instead of dichloromethane dry ethyl acetate was used as a solvent medium for the reaction. After completion of the reaction, mixture was poured in ice-water and extracted with ethyl acetate. The triethylamine-HCl, being less soluble in ethyl acetate than dichloromethane, was thus completely removed in 2-3 water washings. Ethyl acetate layer was then washed with dil. HCl and again with water. It was then dried over anhydrous Na_2SO_4 and ethyl acetate was completely removed under vacuum. The sticky residue thus obtained was treated with little cold ethanol. The solid dihydro-oxazaphosphorin which separated out was filtered, dissolved in benzene, and

decolourized with animal charcoal. The solution was filtered and the filtrate on concentration yielded dihydro-oxazaphosphorins as colourless needles. The main disadvantage of this method was that the dihydro-oxazaphosphorins were obtained in lower yields (30-40%).

Yields and m.p.'s of dihydro-oxazaphosphorins are recorded in Table 2. IR spectra of the dihydro-oxazaphosphorins show three prominent peaks in the region 1200-1300 cm^{-1} corresponding to P=O stretching frequency. NMR spectral data is recorded in Table 3 and the analytical data in Table 4.

Synthesis of 2-chloro-3-(p-anisyl)-6-(p-chlorophenyl)-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 55

4-Chlorophenyl β(p-anisyl)ethyl ketone (1.44 g; 0.005 mol) was dissolved in dry dioxane (20 ml). Phosphorus oxychloride (1 g; 0.007 mol) was added in one lot and the solution was stirred for 24 hours under the exclusion of moisture at room temperature. The white phosphoramidate complex separated out during the reaction. This was cooled to 0-5° and dry triethylamine (3.5 g) (dried over KOH pellets) was added dropwise in half an hour. The reaction was stirred for further 3-4 hours. The dark brown reaction mixture was then poured over ice. The solid which separated out was filtered and washed thoroughly with water to remove the

triethylamine-HCl, excess of triethylamine and dioxane. The residue consisting of dihydro-oxazaphosphorin was crystallised from ethyl alcohol when it gave colourless plates (1.3 g, yield 70.0%). m.p. 158°. (Found C, 51.7; H, 4.1; N, 3.5; P, 8.0 ; $C_{16}H_{14}Cl_2NO_3P$ requires C, 52.0 ; H, 3.8; N, 3.8; P, 8.4%).

NMR ($CDCl_3$, δ) p-$OCH_3C_6H_4$ at 3.8, s, 3p;
>C=C<u>H</u>-CH_2 at 5.8, q, 1p;
=CH-CH_2-N- at 4.2, m, 2p;
Aromatic protons at 6.8-7.8, m, 8p.

Mass M^+ 369.

Synthesis of 3-chloro-6-(2,4-dichlorophenyl) -3-(p-tolyl)-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 62

2,4-Dichlorophenyl β-(p-tolyl)aminoethyl ketone 58 (1.53 g; 0.005 mol) was dissolved in dry dichloromethane (20 ml). Phosphorus oxychloride (1 g; 0.007 mol) was then added and the mixture was stirred for 24 hours at room temperature. The reaction mixture was then cooled to 0-5° and dry triethylamine (3.5 g) (dried over KOH pellets) was added dropwise over a period of half an hour. The reaction mixture was further stirred for 2 hours and worked up as described in work-up procedure (A). The dihydro-oxazaphosphorin was isolated from the first fraction in

chromatography on silica-gel column, using benzene as eluant. Compound 62 crystallised from absolute ethanol in colourless needles, (1.29 g, yield 67.0%), m.p. 157°. (Found C, 49.2; H, 3.3; N, 3.3; P, 8.6; $C_{16}H_{13}Cl_3NO_2P$ requires C, 49.6; H, 3.4; N, 3.6; P, 8.0%).

NMR ($CDCl_3$, δ) $p\text{-}CH_3C_6H_4$- at 2.4, s, 3p;
>C=CH-CH_2- at 5.8, q, 1p;
=CH-CH_2-N- at 4.2, m, 2p;
Aromatic protons centred at 7.2, m, 7p.

Mass M^+ 387.

Synthesis of 2-chloro-3-(2'-methyl-5'-nitrophenyl)-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 68

A mixture of aryl β-(2'-methyl-5'-nitrophenyl) aminoethyl ketone 65 (1.38 g; 0.005 mol), phosphorus oxychloride (1 g; 0.007 mol) and dry benzene (20 ml) was stirred at room temperature for 20-24 hours. The mixture was then cooled to 0-5° and dry triethylamine (3.5 g) was added dropwise over a period of half an hour. The mixture was then stirred for additional 2 hours and filtered. The filtrate was chromatographed on a silica-gel column. The column was eluted with benzene. The first fraction gave dihydro-oxazaphosphorin 68 which crystallised from absolute ethanol in pale yellow needles (1.06 g, yield 58%), m.p. 107°. (Found C, 53.5; H, 3.7; N, 8.1; P, 9.5; $C_{16}H_{14}ClN_2O_4P$

requires C, 52.7; H, 3.8; N, 7.7; P, 8.5%).

NMR ($CDCl_3$, δ) o-CH_3Ar at 2.5, s, 3p;

$>C=C\underline{H}-CH_2$ at 5.8, q, 1p;

$=CH-C\underline{H_2}-\dot{N}-$ at 4.2, m, 2p;

Aromatic protons from 7.2-8.0, m, 8p.

Mass M^+ 364.

Synthesis of 2-chloro-3-(p-anisyl)-6-(2-furyl)-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 75

A solution of 2-furyl β-(p-anisyl)ethyl ketone 73 (1.22 g, 0.005 mol) in dry methylene chloride (20 ml) was added to dry triethylamine (3. 5 g). The mixture was cooled in ice and phosphorus oxychloride (1 g, 0.007 mol) was added dropwise. The mixture was stirred for 24 hours with exclusion of moisture. The reaction was then worked up as described in procedure (B). Chromatographic purification of the reaction product gave dihydro-oxazaphosphorin 75 which crystallised from absolute ethanol in colourless needles (0.970 g, yield 60.0%), m.p. 150°. (Found C, 52.4; H, 4.1; N, 3.9; P, 9.1; $C_{14}H_{13}ClNO_4P$ requires C, 51.6; H, 4.0; N, 4.3; P, 9.5%).

NMR ($CDCl_3$,δ) $>C=C\underline{H}-CH_2$ at 5.73, q, 1p;

$=CH-C\underline{H_2}-\dot{N}-$ at 4.46, m, 2p;

$-OC\underline{H_3}$ at 3.8, s, 3p;

Aromatic protons at 6.4-7.5, m, 7p.

Mass M^+ 325.

TABLE - 1

MPS AND IR DATA OF AMINOKETONES

Compd. No.	MP in ^{o}C	IR values cm^{-1}	
		-NH	-C=O
46	124	3200	1680
47	116	3190	1670
48	151	3190	1680
49	87	3210	1690
50	133	3210	1690
56	47	3200	1700
57	78	3200	1700
58	65	3200	1700
59	BP $140^{o}/2x10^{-6}$ mm/Hg	3200	1700
64	105	3180	1670
65	121	3210	1670
66	70	3200	1660
70	127	3420	1690
72	67	3120	1660
73	73	3120	1650
76	85	3200	1670
77	115	3150	1670
78	102	3200	1670

TABLE - 2

MPS AND YIELDS OF DIHYDROOXAZAPHOSPHORINS

Compound No.	MP in °C	Yield in %
51	128	61.0
52	140	62.0
53	125	54.0
54	152	47.0
55	158	70.0
60	124	47.0
61	107	53.0
62	157	67.0
63	135	67.0
67	107	58.0
68	160	55.0
69	162	8.0
71	186	40.0
74	150	59.0
75	150	60.0
79	175	39.0
80	145	47.0
81	135	55.0

TABLE - 3

NMR SPECTRAL DATA OF DIHYDRO-OXAZAPHOSPHORINS

Compd. No.	>C=CH-CH$_2$	=CH-CH$_2$-N-	o,m,p-OCH$_3$	o,m,p-CH$_3$	Aromatic protons
51	1H,m,5.7	2H,m,4.4	-	-	9H,m,7.2-7.6
52	1H,dd,5.7	2H,m,4.4	-	-	8H,m,7.2-7.6
53	1H,m,5.9	2H,m,4.4	-	3H,s,2.4	8H,m,7.3-7.9
54	1H,dd,5.8	2H,m,4.3	3H,s,3.9	-	8H,m,6.9-7.8
55	1H,dd,5.8	2H,m,4.3	3H,s,3.8	-	8H,m,6.8-7.8
60	1H,dd,5.7	2H,m,4.2	-	-	8H,m,7.5
61	1H,dd,5.7	2H,m,4.2	-	-	7H,m,7.1-7.5
62	1H,dd,5.7	2H,m,4.2	-	3H,s,2.33	7H,m,7.1-7.5
63	1H,dd,5.8	2H,m,4.2	-	3H,s,4.0	7H,m,7.0-7.5
67	1H,dd,5.8	2H,m,4.5	-	3H,s,2.6	8H,m,7.3-8.1
68	1H,dd,5.77	2H,m,4.2	-	3H,s,2.56	8H,m,7.2-8.3
69	1H,dd,5.8	2H,m,4.3	-	-	8H,m,7.3-7.8
71	1H,dd,5.8	2H,m,4.2	-	3H,s,2.6	6H,m,7.2-8.4
74	1H,m,5.7	2H,m,3.8-4.2	-	3H,s,2.4	7H,m,6.4-7.4
75	1H,dd,5.73	2H,m,4.46	3H,s,3.8	-	7H,m,6.4-7.5
79	1H,dd,5.9	2H,m,4.35	3H,s,3.9	-	8H,m,6.9-7.8
80	1H, s,5.9	2H,m,4.1	3H,s,3.7	-	8H,m,6.7-8.2
81	1H, m,6.1	2H,m,3.5	3H,s,3.77	-	11H,m,6.8-8.3

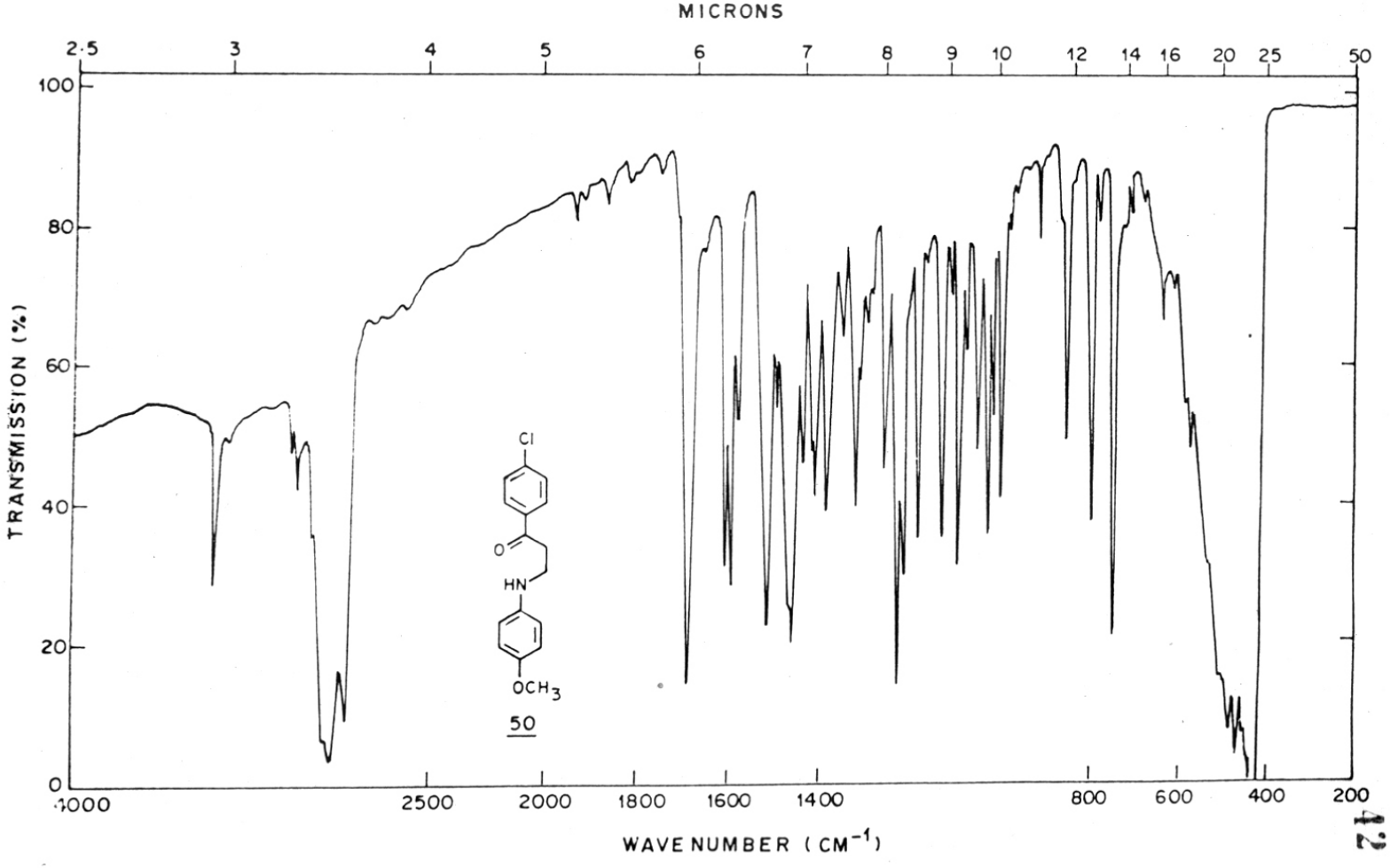
TABLE - 4 - ANALYTICAL DATA OF DIHYDRO-OXAZAPHOSPHORINS

Compd. No.		C	H	N	P
51	R	53.1	3.5	4.1	9.2
	F	52.2	3.6	4.5	9.6
52	R	48.2	2.9	3.7	8.3
	F	48.5	3.0	3.5	8.9
53	R	54.3	3.9	3.9	8.7
	F	54.0	3.9	3.6	8.0
54	R	52.0	3.8	3.8	8.4
	F	51.9	4.0	3.5	8.3
55	R	52.0	3.8	3.8	8.4
	F	51.7	4.1	3.6	8.0
60	R	48.2	2.9	3.7	8.3
	F	46.9	3.0	4.5	7.9
61	R	48.4	2.6	3.7	7.2
	F	47.8	2.5	3.2	7.7
62	R	49.6	3.3	3.6	8.0
	F	49.2	3.3	3.3	8.6
63	R	47.6	3.2	3.4	7.7
	F	48.6	3.3	2.9	7.8
67	R	52.7	3.8	7.7	8.5
	F	52.5	4.6	7.1	7.9
68	R	52.7	3.8	7.7	8.5
	F	53.5	3.7	8.1	9.5

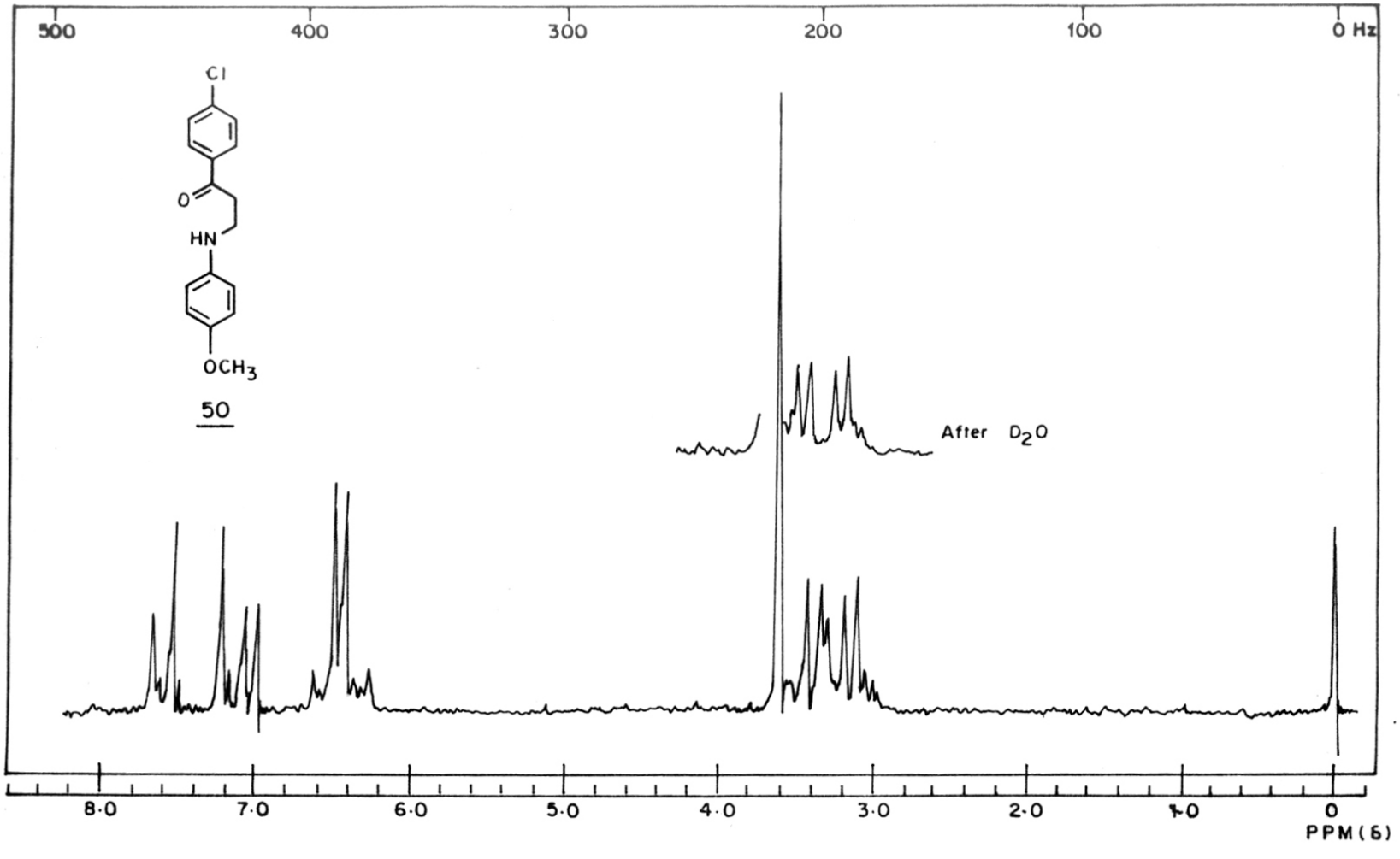
continued ....

Table 4 continued..

Compd. No.		C	H	N	P
71	R	44.4	2.7	6.5	7.1
	F	44.2	2.8	6.3	7.3
74	R	54.3	4.2	4.5	10.3
	F	53.9	4.1	4.9	9.9
75	R	51.6	4.0	4.3	9.5
	F	52.4	4.1	3.9	9.1
79	R	52.0	3.8	3.8	8.4
	F	51.5	3.8	3.4	8.4
80	R	50.5	3.6	7.4	8.1
	F	51.4	3.9	7.1	7.1
81	R	62.3	4.3	3.6	8.0
	F	61.9	4.6	3.3	7.1


MICRONS
2·5
3
4
5
6
7
8
9
10
12
14
16
20
25
50
100
80
60
40
20
0
TRANSMISSION (%)
4000
2500
2000
1800
1600
1400
800
600
400
200
WAVE NUMBER (CM^{-1})
Cl
O
HN
OCH$_3$

50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100
0 Hz
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HN
OCH3
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After D2O
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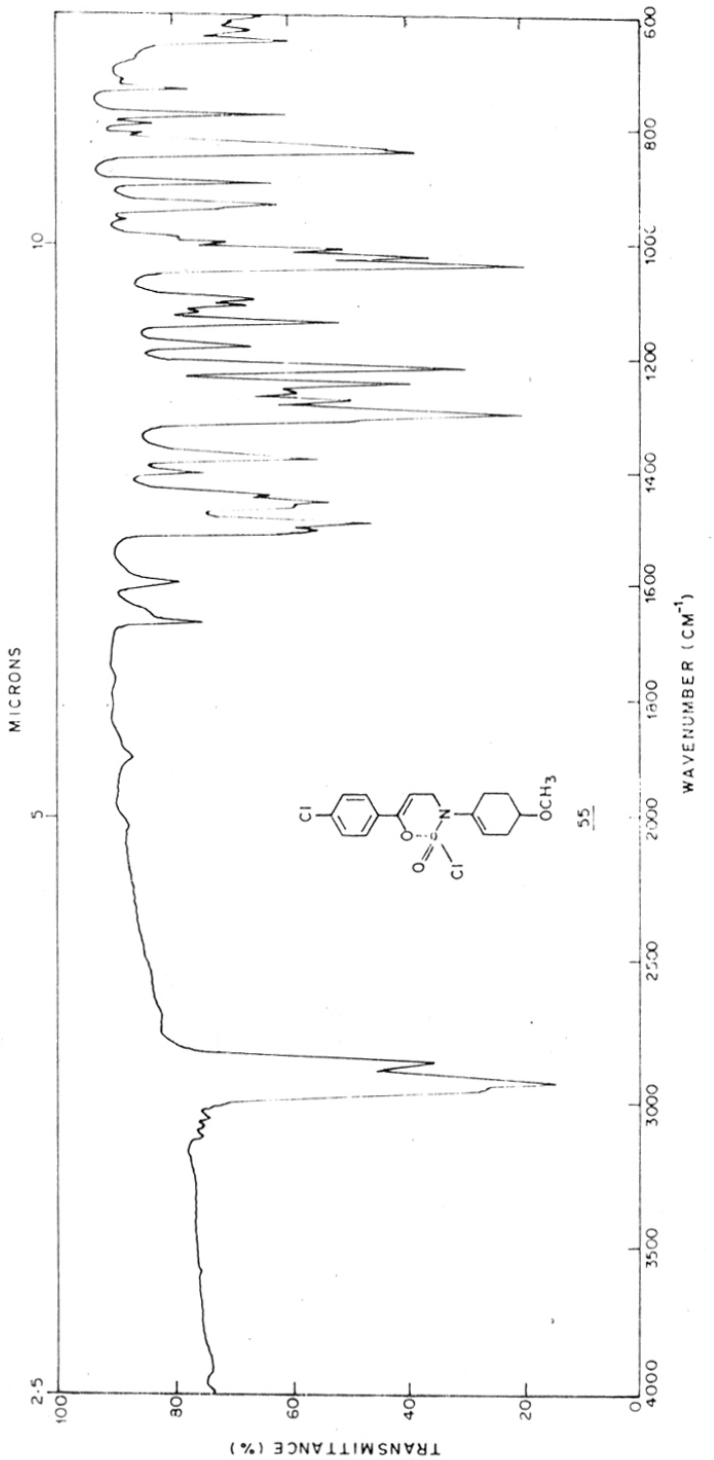
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)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80
60
40
20
0
2.5
5
10
MICRONS
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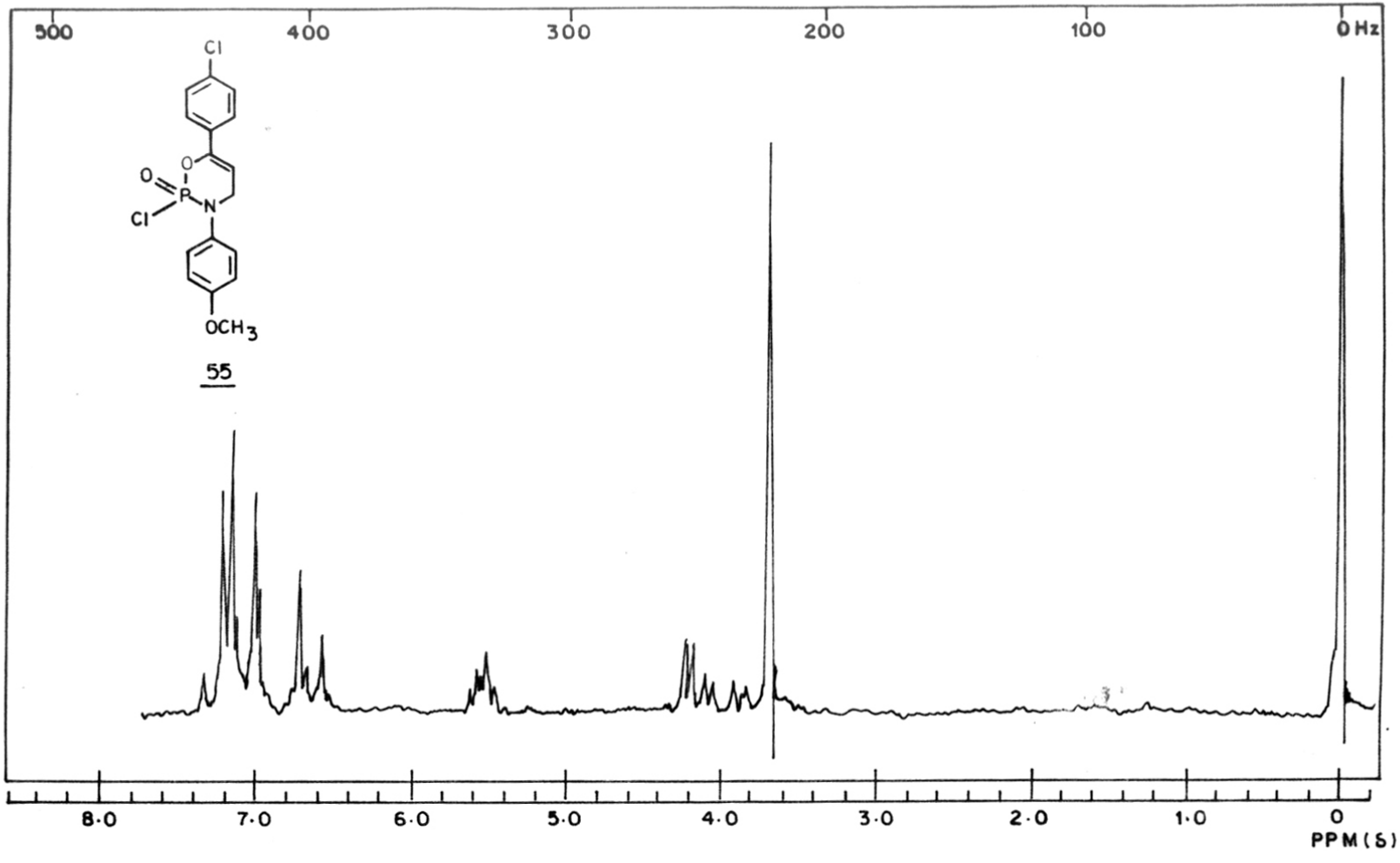
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER (CM⁻¹)
Cl
OCH3
O
S
N
O
Cl
55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N
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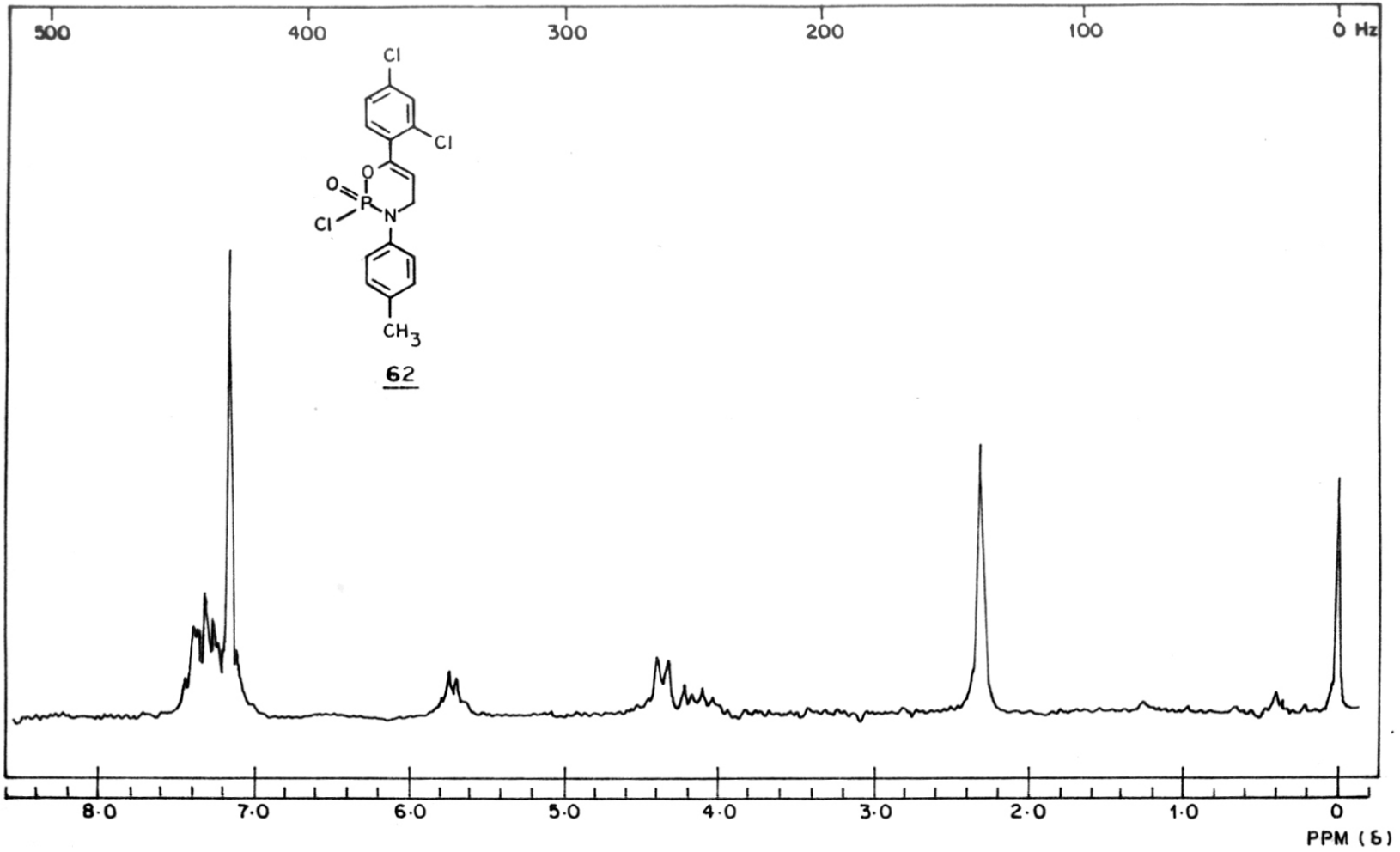
3·0
2·0
1·0
0
PPM (δ)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Cl
Cl
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P
N
Cl
CH3
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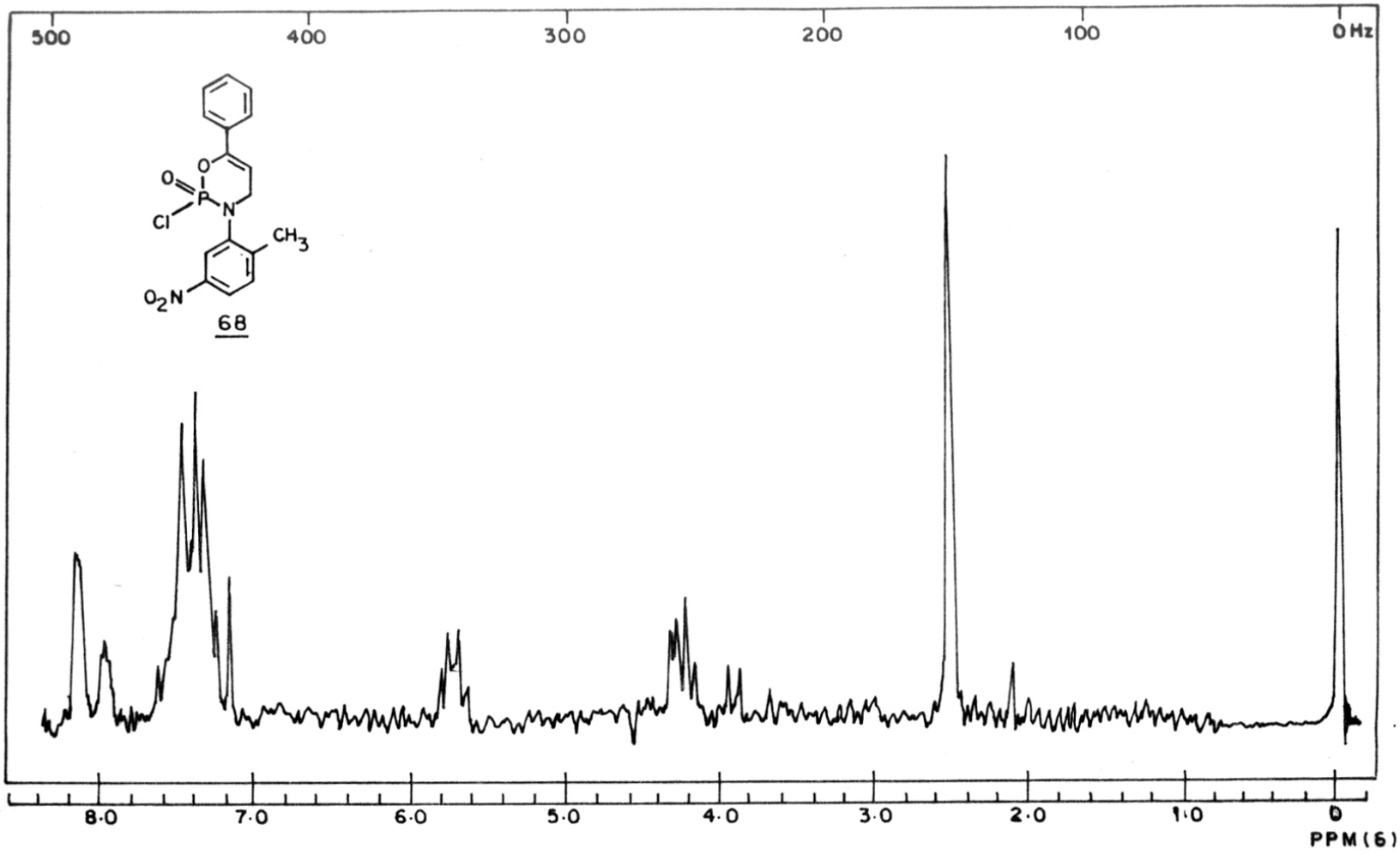
3·0
2·0
1·0
0
PPM (δ)

62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O
P
N
Cl
CH3
O2N
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5·0
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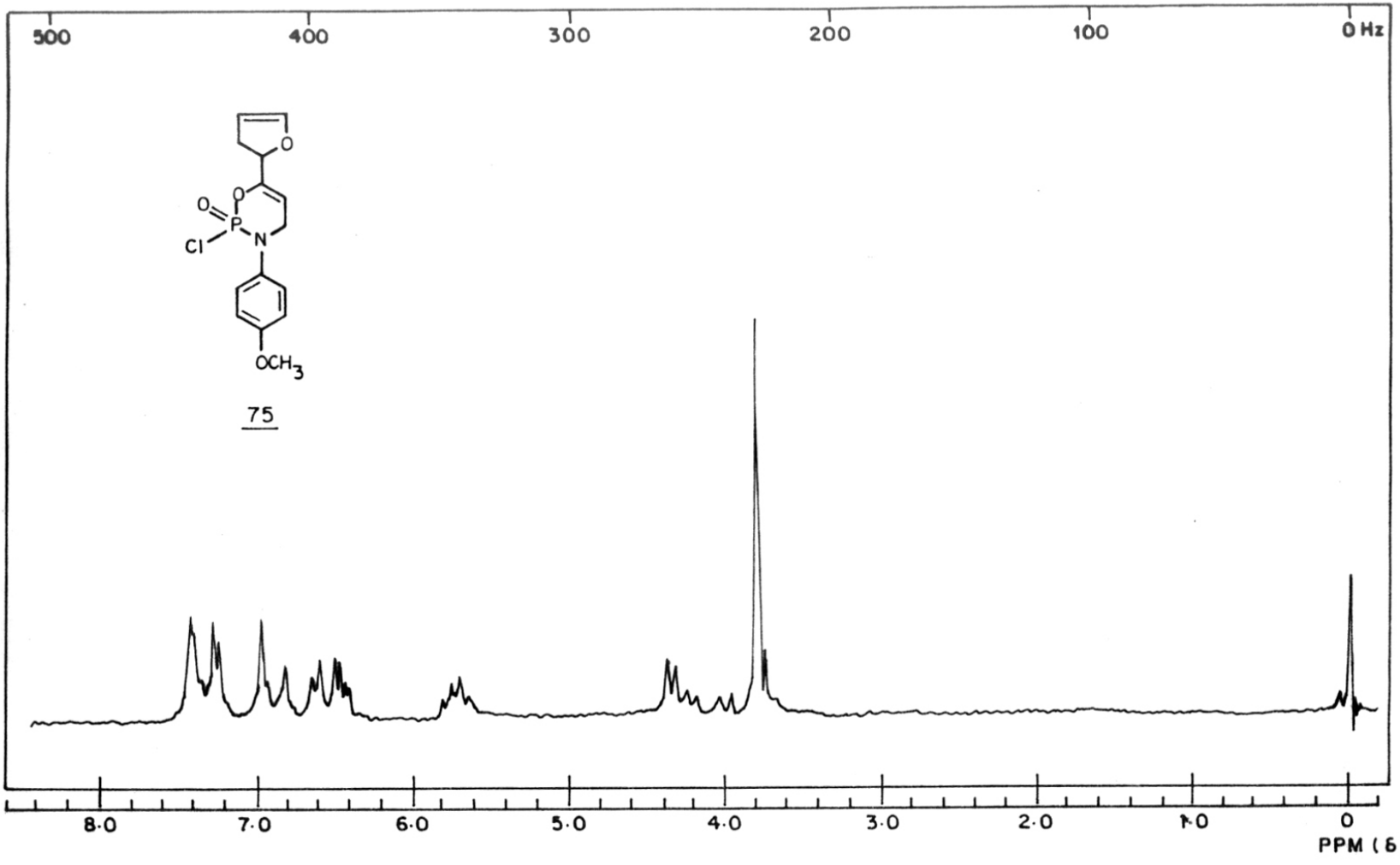
3·0
2·0
1·0
0
PPM (δ)

68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O
P
Cl
N
OCH3
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5·0
4·0
3·0
2·0
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0
PPM (δ)

75

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CHAPTER I : PART - B

SYNTHESIS OF 2-CHLORO-3-ALKYL-6-PHENYL-3,4-DIHYDRO-1,3,2-OXAZAPHOSPHORIN-2-OXIDES

Cyclophosphamide, [2-[bis(2-chloroethyl)amino] tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide], 1 is now widely used as an effective drug against lymphorecticular tumors and hemoblastoses[1]. Since its discovery, hundreds of compounds modelled on this basic structure have been prepared to obtain superior anticancer drugs. Recently three compounds; ifosphamide 2, trofosphamide 3 and sulfosphamide 4, which are derivatives of tetrahydro-oxazaphosphorin were synthesised[2]. These compounds have shown very promising results, especially ifosphamide which is receiving wide attention, because of its higher therapeutic Index (T.I. 24) and lower toxicity than cyclophosphamide (T. I. 20) against rat ascites sarcoma (Chart 1).

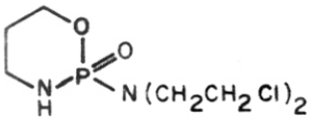
In the present chapter synthesis of such 3-alkyl substituted dihydro-oxazaphosphorins are described. As the dihydro-oxazaphosphorin is a new ring system, first reported from this laboratory, it was of interest to study the effect of these N-alkyl substituted dihydro-oxazaphosphorins on the biological activity against P-388 leukemia.

The precursors for the 3-alkyl substituted dihydro-oxazaphosphorins were 3-alkylaminopropiophenone hydrochlorides or oxalates. These amino ketone salts were reported to have good fungicidal activity[3] but could not be isolated in the free base form, as these were

reported to cyclise, in the basic medium, to give piperidinyl derivatives[4] (Chart 2). These amino ketone salts were prepared by different methods as reported in the literature. These are briefly described in the present context.

ω-t-Butylaminopropiophenone hydrochloride[5] 5 was prepared by heating t-butylamine hydrochloride, paraformaldehyde and acetophenone at 150° for half an hour. The aminoketone hydrochloride, on interaction with phosphorus oxychloride and triethylamine, yielded 2-chloro-6-phenyl-3-(t-butylamino)-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 6 (Chart 3).

ω-n-Butylaminopropiophenone oxalate 7 and ω-cyclohexylaminopropiophenone hydrochloride 8 were prepared according to Craig et al[4]. n-Butylamine and cyclohexylamine were heated on a waterbath with ω-dimethylaminopropiophenone to give the respective aminoketones. As these aminoketones always contained impurities of primary amines, their oxalates or hydrochlorides were prepared and crystallised to get pure aminoketones. The aminoketones 7 and 8 gave the corresponding dihydro-oxazaphosphorines 9 and 10 on treatment with phosphorus oxychloride and triethylamine (Chart 4).



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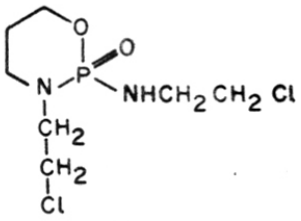

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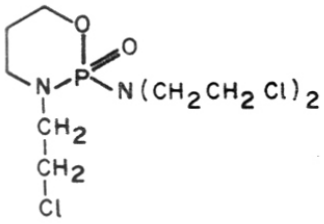

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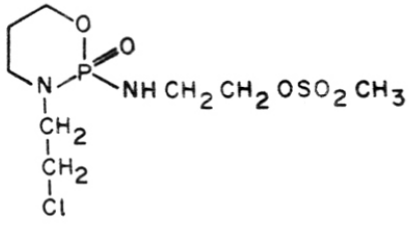
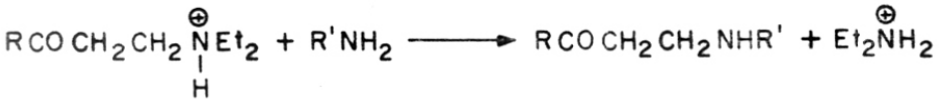
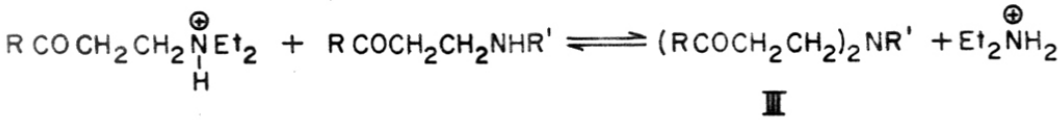


4

CHART - 1



I II



III

V IV

CHART - 2

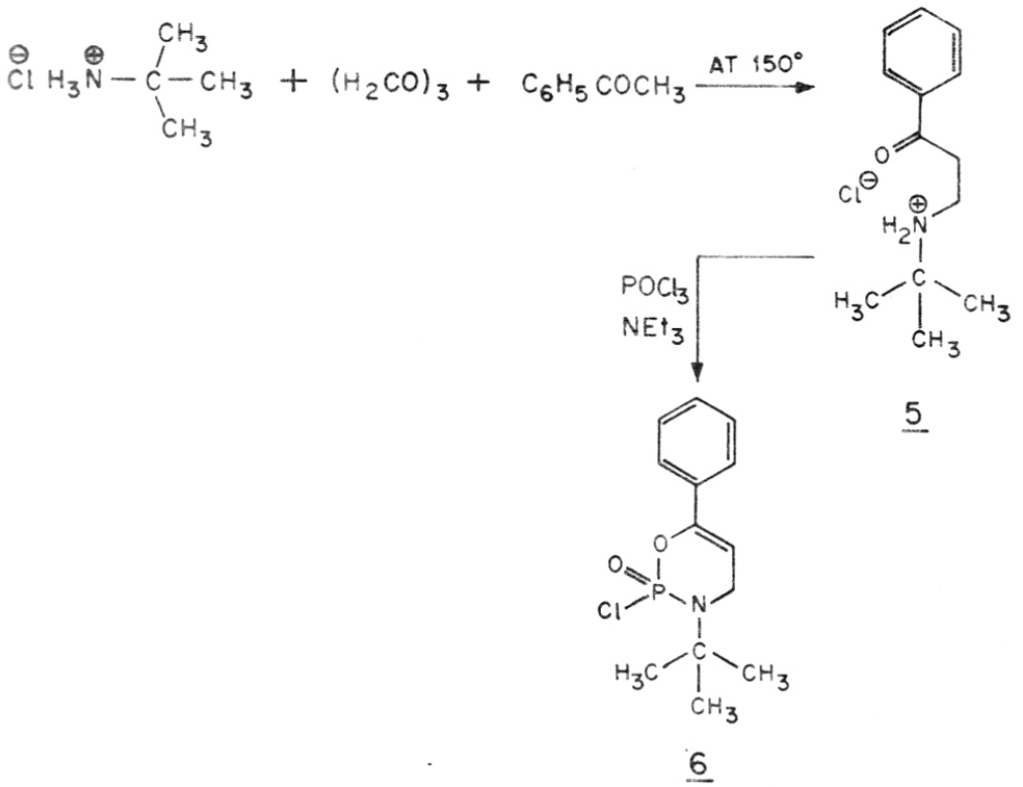
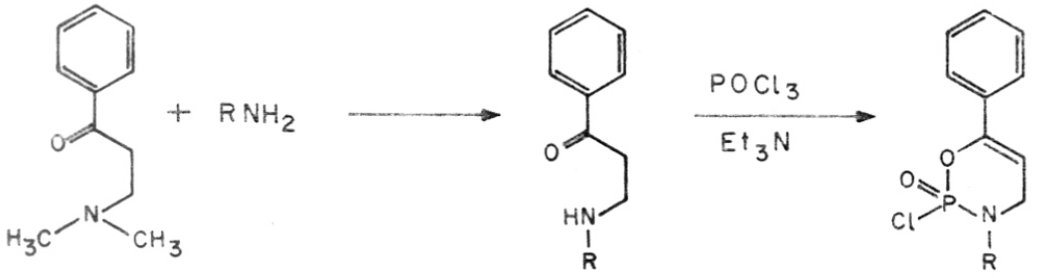


CHART - 3



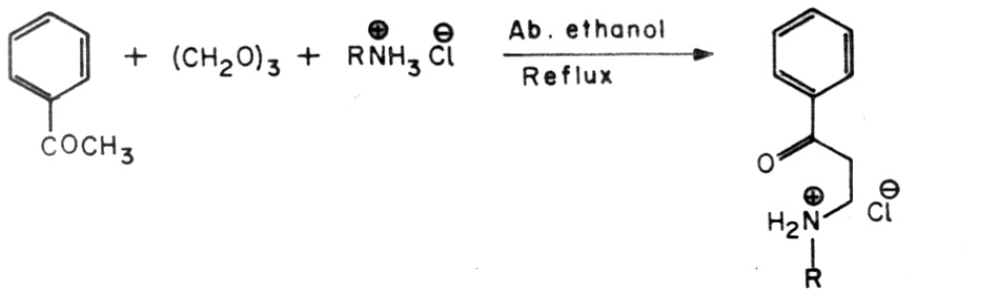
7 ; R = n-C4H9 (as Oxalate) 9

8 ; R = Cyclohexyl (as Hydrochloride) 10

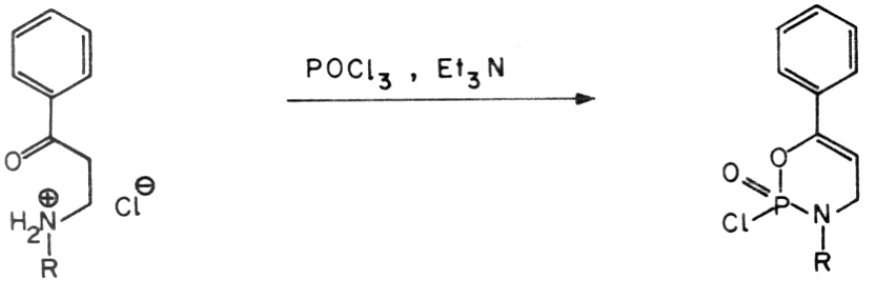
CHART - 4

ω-Benzylaminopropiophenone hydrochloride[6] 11 was obtained by the condensation of benzylamine hydrochloride, paraformaldehyde and acetophenone in absolute ethanol. The aminoketone hydrochloride 11 was treated with phosphorus oxychloride and triethylamine to give the corresponding dihydro-oxazaphosphorin 12 (Chart 5). In a similar way ω-(β-chloroethyl)aminopropiophenone hydrochloride 13 was prepared, by the condensation of β-chloroethylamine hydrochloride, paraformaldehyde and acetophenone in absolute ethanol. The aminoketone hydrochloride was reacted with phosphorus oxychloride and triethylamine to give 2-chloro-3-(β-chloroethyl)-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 14 (Chart 5).

ω-(β-Hydroxyethyl)aminopropiophenone hydrochloride 15, prepared as above on treatment with phosphorus oxychloride and triethylamine yielded compound 14. β-Hydroxy group was replaced by Cl by interaction with phosphorus oxychloride (Chart 6). Superimposable IR spectra, melting point and mixed melting point confirmed the compound as 2-chloro-3-(β-chloroethyl)-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 14. The structure was further confirmed by the absence of -OH group in the IR and NMR spectra of the reaction product.



11 , R = $CH_2C_6H_5$
13 , R = CH_2CH_2Cl
15 , R = CH_2CH_2OH

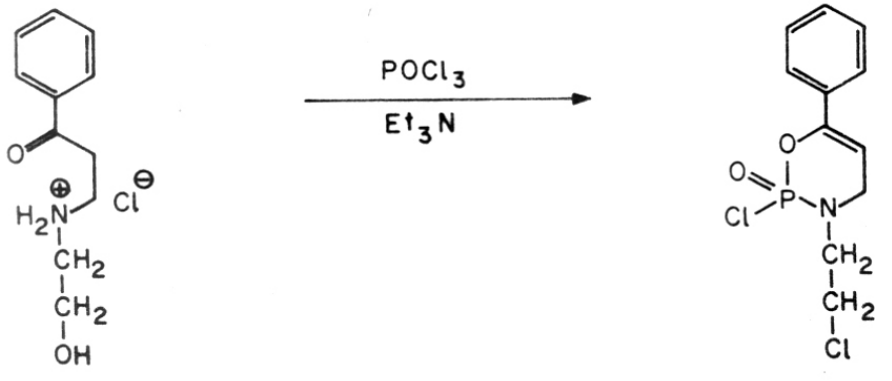


11
13

R = $CH_2C_6H_5$
R = CH_2CH_2Cl

12
14

CHART - 5



15

14

CHART - 6

The above dihydro-oxazaphosphorins were also obtained when phosphorus oxychloride and triethylamine were reacted with aminoketones. Aminoketones tend to cyclise to piperidinyl derivatives after some period in basic medium. Therefore, aminoketone salts were rapidly basified and immediately reacted with phosphorus oxychloride to form corresponding phospharamidate derivatives. These when treated with triethylamine gave dihydro-oxazaphosphorins.

EXPERIMENTAL

Preparation of ω -(β-chloroethyl)amino-propiophenone hydrochloride 13

β-chloroethylamine hydrochloride (11.5 g; 0.1 mol), paraformaldehyde (9.0 g; 0.1 mol) and acetophenone (24.0 g; 0.2 mol) were taken in a 100 ml round bottom flask. Absolute ethanol (30-40 ml) and conc. HCl (1 ml) were added to the mixture. The reaction mixture was then refluxed for 8-10 hours till all paraformaldehyde dissolved. Excess of alcohol was removed under vacuum. The reaction mixture was cooled, diluted with acetone (100 ml) and then kept in deep freeze overnight. The white solid which separated out was filtered, thoroughly washed with acetone, and crystallised from absolute ethanol when it gave ω -(β-chloroethyl) aminopropiophenone hydrochloride 13 as colourless needles m.p. 141°.

General method for the synthesis of 2-chloro-3-alkyl-6-phenyl-3,4-dihydrooxazaphosphorin--2-oxides

Method A : A mixture of ω -alkylaminopropiophenone hydrochlorides (0.005 mol), phosphorus oxychloride (0.007 mol) and dry dichloromethane was stirred at room temperature for 24 hours under exclusion of moisture. The mixture was then cooled to 0-5° and dry triethylamine (kept

over KOH pellets) (3.5 g) was added dropwise to the mixture in 30 minutes. The mixture was further stirred for two hours and then poured into ice-water and extracted with dichloromethane. The extract was washed 2-3 times with water and dried over anhydrous sodium sulphate. Dichloromethane was removed under vacuum and the residue was chromatographed on silica gel column using benzene as eluant. The first fraction gave 2-chloro-3-alkyl-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxides which were purified by crystallisation from ethanol.

Method B : In this method aminoketone salts were basified with sodium carbonate solution. The free base was then extracted with dichloromethane and dichloromethane layer was washed 2-3 times with water. The extract was dried over anhydrous sodium sulphate and excess dichloromethane was removed under vacuum. The work up was carried out fast as the free bases are reported to cyclise to piperidinyl derivatives. The ω-alkylaminopropiophenones (0.005 mol) were dissolved in dry dichloromethane then treated with phosphorus oxychloride (1 g; 0.007 mol). The mixture was stirred for 24 hours at room temperature under dry conditions. The mixture was then cooled to 0-5° with ice and dry triethylamine (kept over KOH pellets) (3.5 g) was added dropwise over a period of half an hour.

The mixture was stirred for two more hours. The reaction mixture was then worked up as described in Method A above.

2-Chloro-3(t-butyl)-6-phenyl-3,4-dihydro-1,3-2-oxazaphosphorin-2-oxide 6

ω -t-Butylaminopropiophenone hydrochloride 5 (1.03 g; 0.005 mol) was reacted with phosphorus oxychloride (1 g; 0.007 mol) and dry triethylamine (3.5 g) as described in Method A. 2-Chloro-3-(t-butyl)-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 6 thus obtained on crystallisation from benzene gave colourless needles (0.700 g, yield 45%), m.p. 200°. (Found: C, 54.0; H, 6.2; P, 11.4; $C_{13}H_{17}ClO_2NP$ requires C, 54.7; H, 5.9; P, 10.9%).

NMR ($CDCl_3$) $-\overset{|}{N}-C(C\underline{H}_3)_3$ at 1.5, s, 9p;
$-\overset{|}{C}=CH-C\underline{H}_2$ at 4.0, m, 2p;
$-\overset{|}{C}=C\underline{H}-CH_2$ at 5.5, d, 1p;
Aromatic protons at 7.3, s, 5p.

Mass M^+ 285.

2-Chloro-3-(n-butyl)-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 9

n-Butylaminopropiophenone 7 (1.02 g; 0.005 mol) was treated with phosphorus oxychloride and triethylamine as in Method B. 2-Chloro-3-(n-butyl)-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 9 was purified by distillation under high vacuum (0.800 g, yield 56%),

b.p. $160^{\circ}/4 \times 10^{-4}$ mm/Hg (Found C, 54.4; H, 5.8; P, 10.4; $C_{13}H_{17}ClNO_2P$ requires C, 54.7; H, 5.8; P, 10.8%).

NMR ($CDCl_3$, δ) $-\overset{|}{N}.CH_2\underline{CH_2}\underline{CH_2}\underline{CH_3}$ at 1.5, m, 7p;

$=CH-\underline{CH_2}-\overset{|}{N}-\underline{CH_2}$ at 3-4.4, m, 4p;

$\rangle C=\underline{CH}-CH_2$ at 5.7, q, 1p;

Aromatic protons centred at 7.4, m, 5p.

Mass M^+ 285.

2-Chloro-3-cyclohexyl-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 10

ω-Cyclohexylaminopropiophenone 8 (1.15 g; 0.005 mol) was reacted with phosphorus oxychloride (1 g; 0.007 mol) and triethylamine (3.5 g) to give compound 10 as a viscous oil (0.600 g, yield 44%).

NMR ($CDCl_3$, δ) Cyclohexyl protons centred at 1.5, m, 11p;

$=CH-\underline{CH_2}-\overset{|}{N}-$ at 3.2-4.3, m, 2p;

$\rangle C=\underline{CH}-CH_2$ at 5.8, q, 1p;

Aromatic protons centred at 7.4, m, 5p.

Mass M^+ 311.

2-Chloro-3-benzyl-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 12

ω-Benzylaminopropiophenone 11 (1.15 g; 0.005 mol) was treated with phosphorus oxychloride and triethylamine as described in Method B to give compound 12. The latter crystallised from ethanol in colourless needles (0.717 g, yield 45%), m.p. 65°. (Found C, 60.1; H, 4.7; P, 10.5; $Cl_{16}H_{15}ClNO_2P$ requires C, 60.2; H, 4.7; P, 9.7%).

NMR ($CDCl_3$, δ) $\begin{matrix} \\ \\ \end{matrix}$ $\begin{matrix} \diagdown \\ \diagup \\ \diagdown \end{matrix}$ $\begin{matrix} C=CH-CH_2-N-CH_2 \text{ at 3-4, m, 4p;} \\ C=CH-CH_2 \text{ at 5.4, s, 1p;} \end{matrix}$

Aromatic protons at 7.2, s, 10p.

Mass M^+ 319.

2-Chloro-3-(β-chloroethyl)-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 14

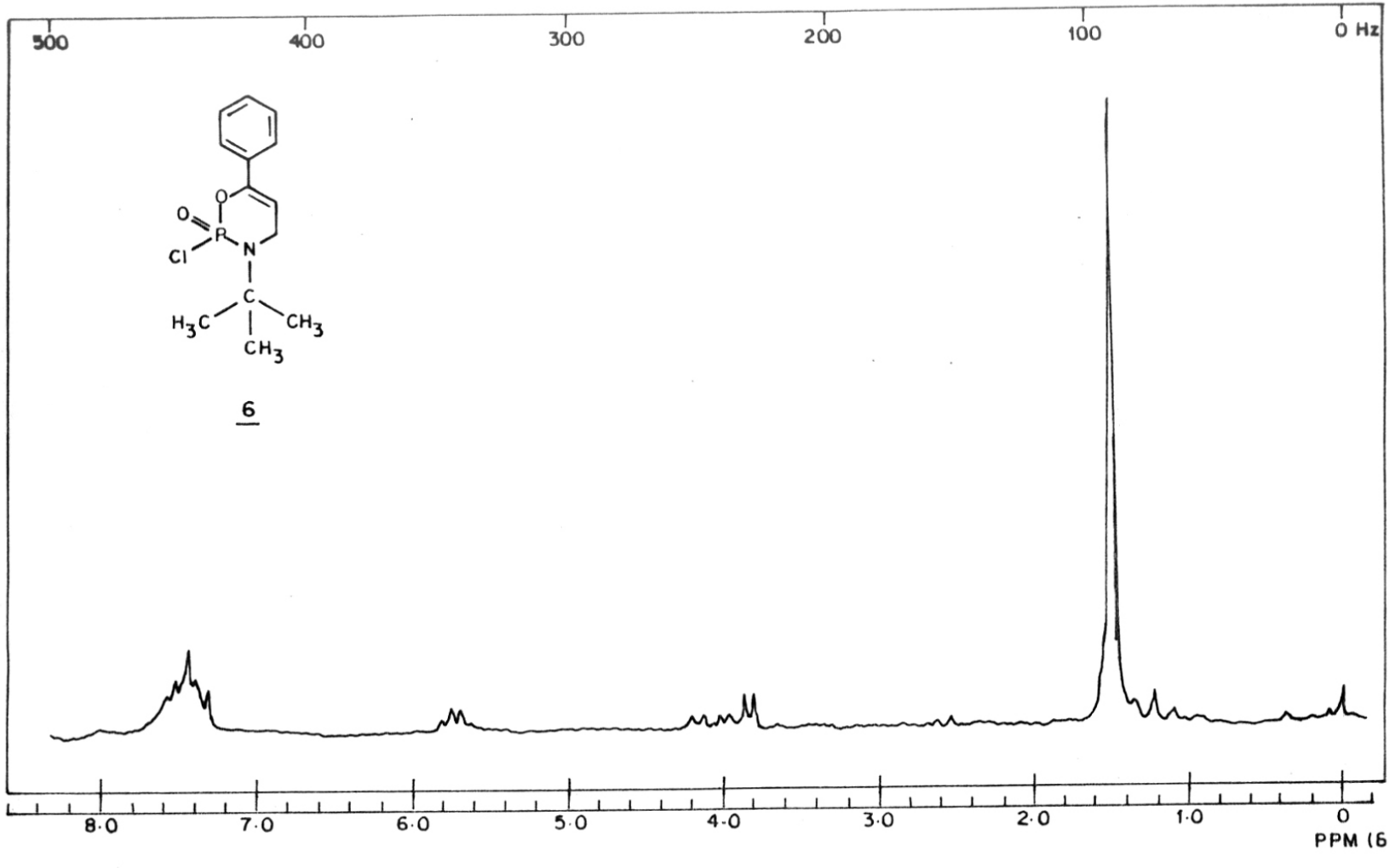
ω-(β-Chloroethyl)aminopropiophenone 13 (1.00 g; 0.005 mol) when treated with phosphorus oxychloride (1 g; 0.007 mol) and triethylamine (3.5 g) yielded 2-chloro-3-(β-chloroethyl)-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 14. The latter crystallised from absolute ethanol in colourless needles (0.725 g, yield 50%), m.p. 102°. (Found C, 44.8; H, 4.3; P, 11.8; $C_{11}H_{12}Cl_2NO_2P$ requires C, 45.3; H, 4.1; P, 10.6%).

NMR ($CDCl_3$, δ) $\rangle C=CH-\underline{CH_2}-\overset{+}{N}-\underline{CH_2}-CH_2$ at 3.2-4.3, m, 6p;

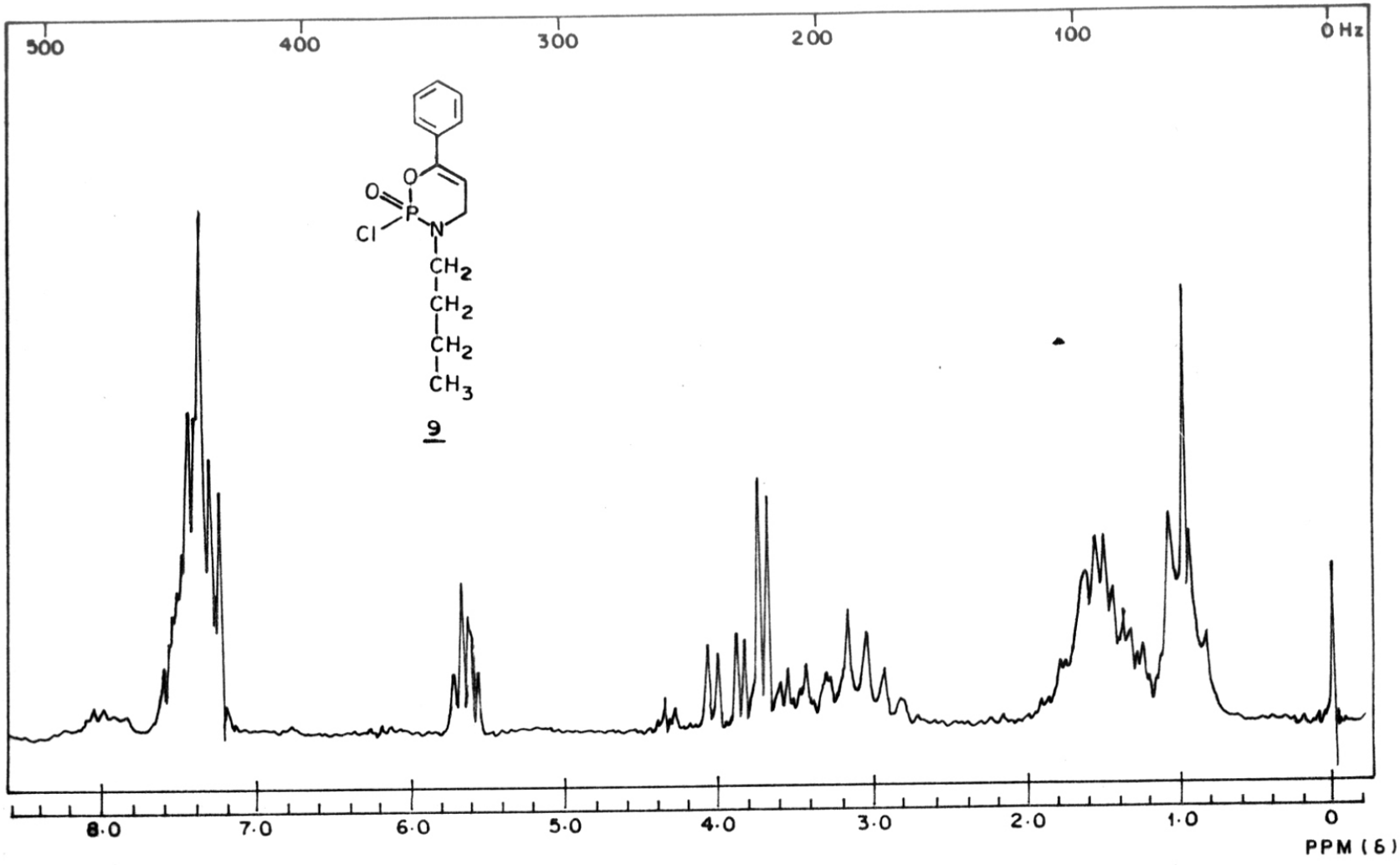
$\rangle C=\underline{CH}-CH_2$ at 5.6, q, 1p;

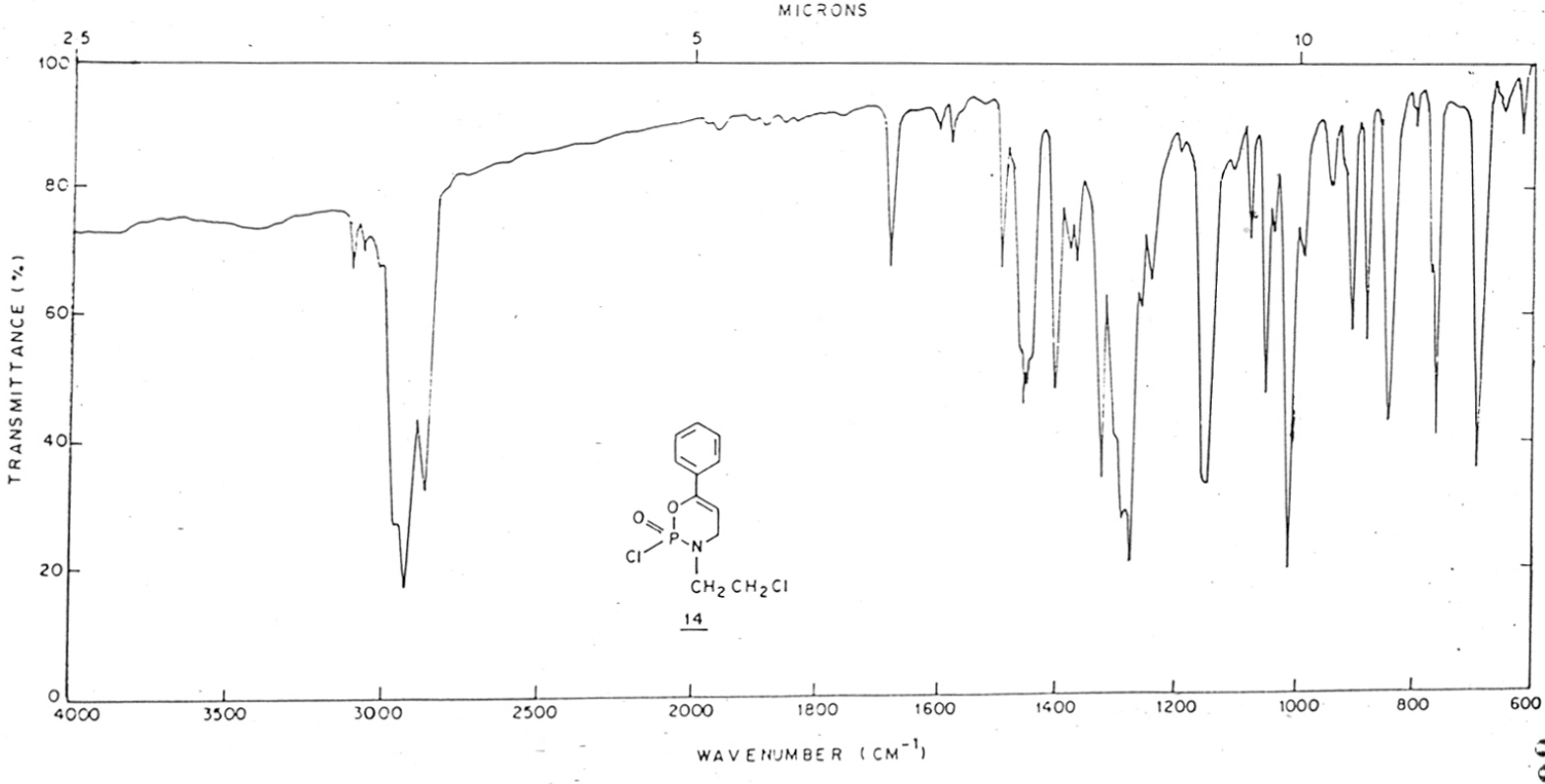
Aromatic protons centred at 7.4, m, 5p.

Mass M^+ 291.

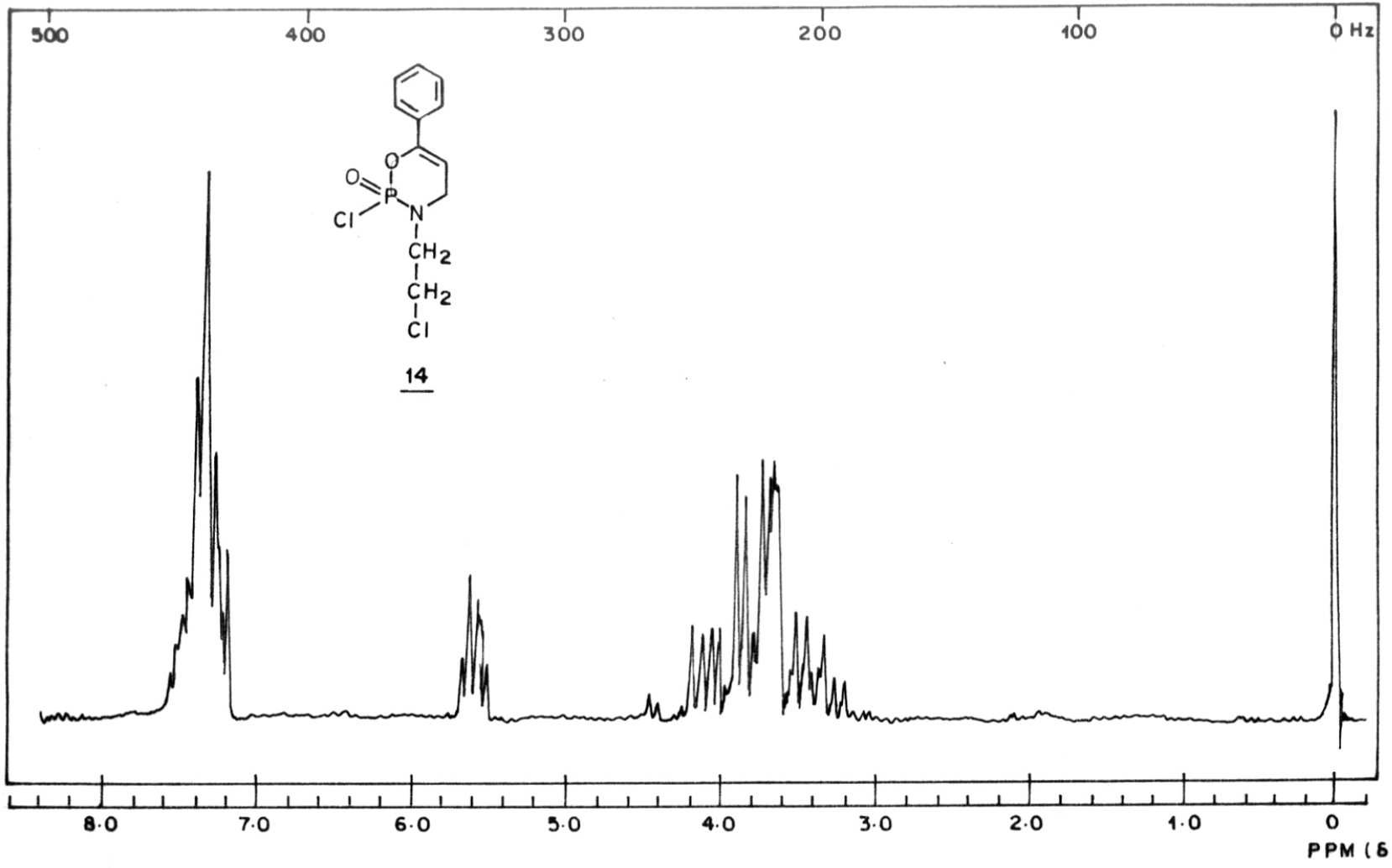

500
400
300
200
100
0 Hz
O
P
Cl
N
C
H_3C
CH_3
CH_3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

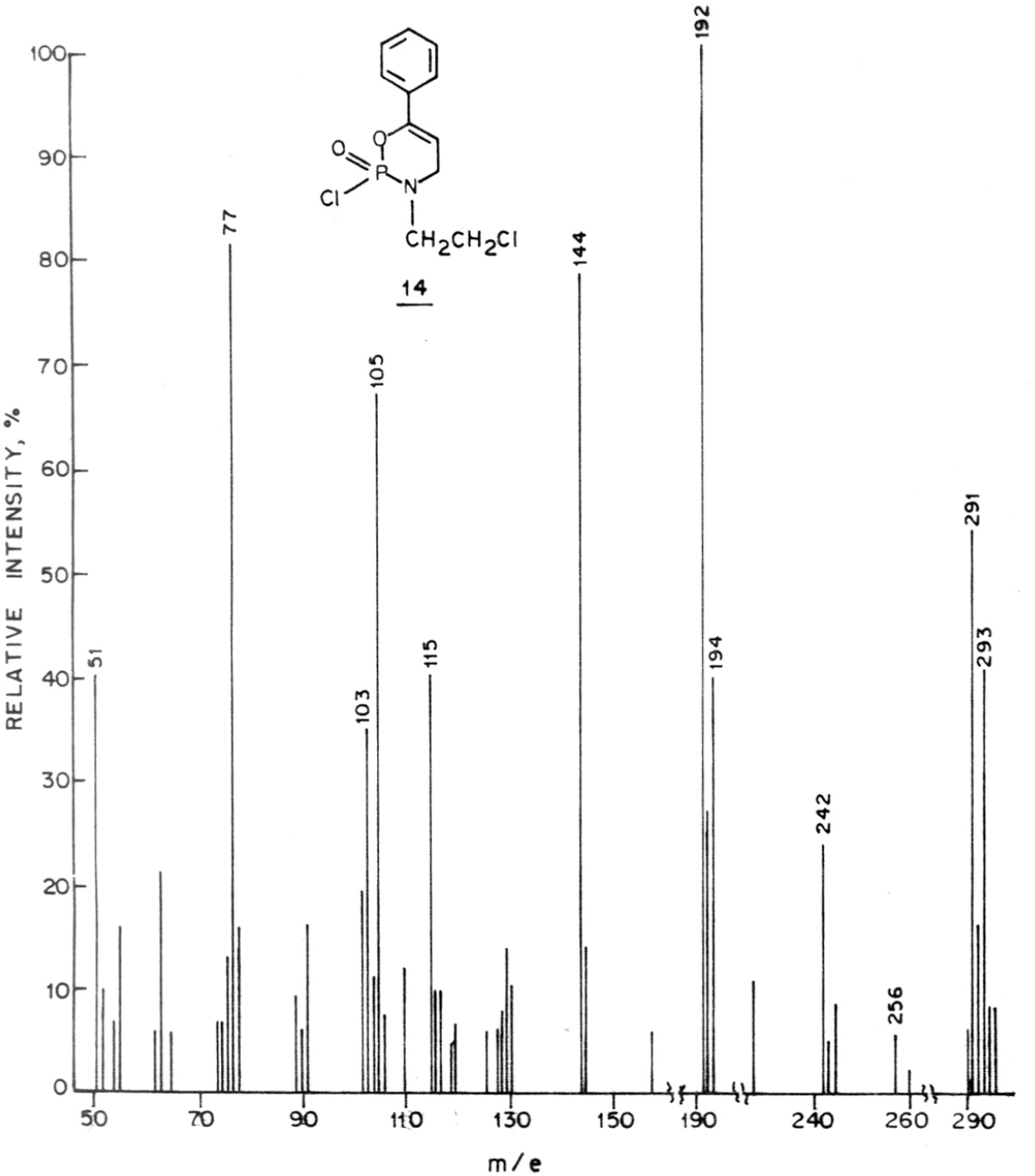
6


500
400
300
200
100
0 Hz
O
O
P
N
Cl
CH2
CH2
CH2
CH3
9
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
PPM (δ)


MICRONS
2.5
5
10
100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER (CM⁻¹)
O
O
P
Cl
N
CH2 CH2 Cl

14


500
400
300
200
100
0 Hz
O
O
P
N
Cl
CH2
CH2
Cl
14
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)


RELATIVE INTENSITY, %
m/e
14
CH2CH2Cl
Cl
O
P
N
O
51
77
103
105
115
144
192
194
242
256
291
293

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CHAPTER II : PART - A

SYNTHESIS OF SUBSTITUTED - 2 - CHLOROTETRAHYDRO-1,3,2 - OXAZAPHOSPHORIN - 2 - OXIDES.

INTRODUCTION

Arnold and Bourseaux[1,2,3] in 1958 first reported the synthesis of cyclophosphamide, viz. 2-bis(2-chloroethyl)-aminotetrahydro-1,3,2-oxazaphosphorin-2-oxide along with other cyclic N'-O-alkylene-N,N-bis(β-chloroethyl)diamido phosphates.

Cyclophosphamide is not only one of the most extensively used chemotherapeutic alkylating agents, but it has also become one of the most intensively studied. The interest shown in this drug is primarily due to two factors; its broad spectrum activity against human and animal tumors, and its complex metabolic pathway. Although considerable information is now available as regards metabolism of this drug, the reasons for its selectivity and effectiveness still remain obscure.

Various substituted derivatives of the parent oxazaphosphorin ring system have been synthesised in order to study their effect on the stereochemistry and biological activity. In many cases these derivatives failed to show biological activity. However, this effort has led to the synthesis of analogues of cyclophosphamide with better biological activity.

Many attempts have been made to introduce aromatic substituents at 3,4,5 and 6 positions in the oxazaphosphorin ring system. Hamacher, in an attempted synthesis of N-aryl substituted cyclophosphamide[4] 1 (R=4-$MeOC_6H_4CO$-) by the reaction of $(ClCH_2CH_2)_2NP(O)Cl_2$ 2 with 4-$MeOC_6H_4NH(CH_2)_3OH$ 3 obtained product 4. Similarly the reaction of $(ClCH_2CH_2)_2NP(O)Cl(O)(CH_2)_3Br$ 5 with $PhNH_2$ or of $(ClCH_2CH_2)_2NP(O)ClNHPH$ 6 with $Br(CH_2)_3$ OH gave $(ClCH_2CH_2)NP(O)(NHPh)O-(CH_2)_3Br$ 7 rather than 1 (R=H) (Chart 1).

Roca et al[5] reported the synthesis of 3-phenyl-substituted tetrahydro-oxazaphosphorins 9 by reacting 3-N-phenylamino-1-propanol 8 with $RP(O)Cl_2$ (Chart 2).

The Arbuzov reaction between suitably substituted 1,3,2-dioxaphosphorinanes and bromine gave an acyclic product 10. The latter, on condensation with a primary amine, gave an intermediate 11 which when treated with NaH in THF yielded 3-phenyl-substituted oxazaphosphorinanes[6] 12, 13 (Chart 3).

Compound 15 was obtained by treating $HO-CH_2-CH(CMe)_3-CH_2NHPh$ 14 with Me_2NPOCl_2[7] (Chart 4).

2-Oxo-2-phenoxy-6,6-diphenyl-1,3,2-oxaza-phosphorinane[8] 17 was prepared by treating $HOCPh_2(CH_2)_2NH_2$ 16 and $PhOPOCl_2$ (Chart 5).

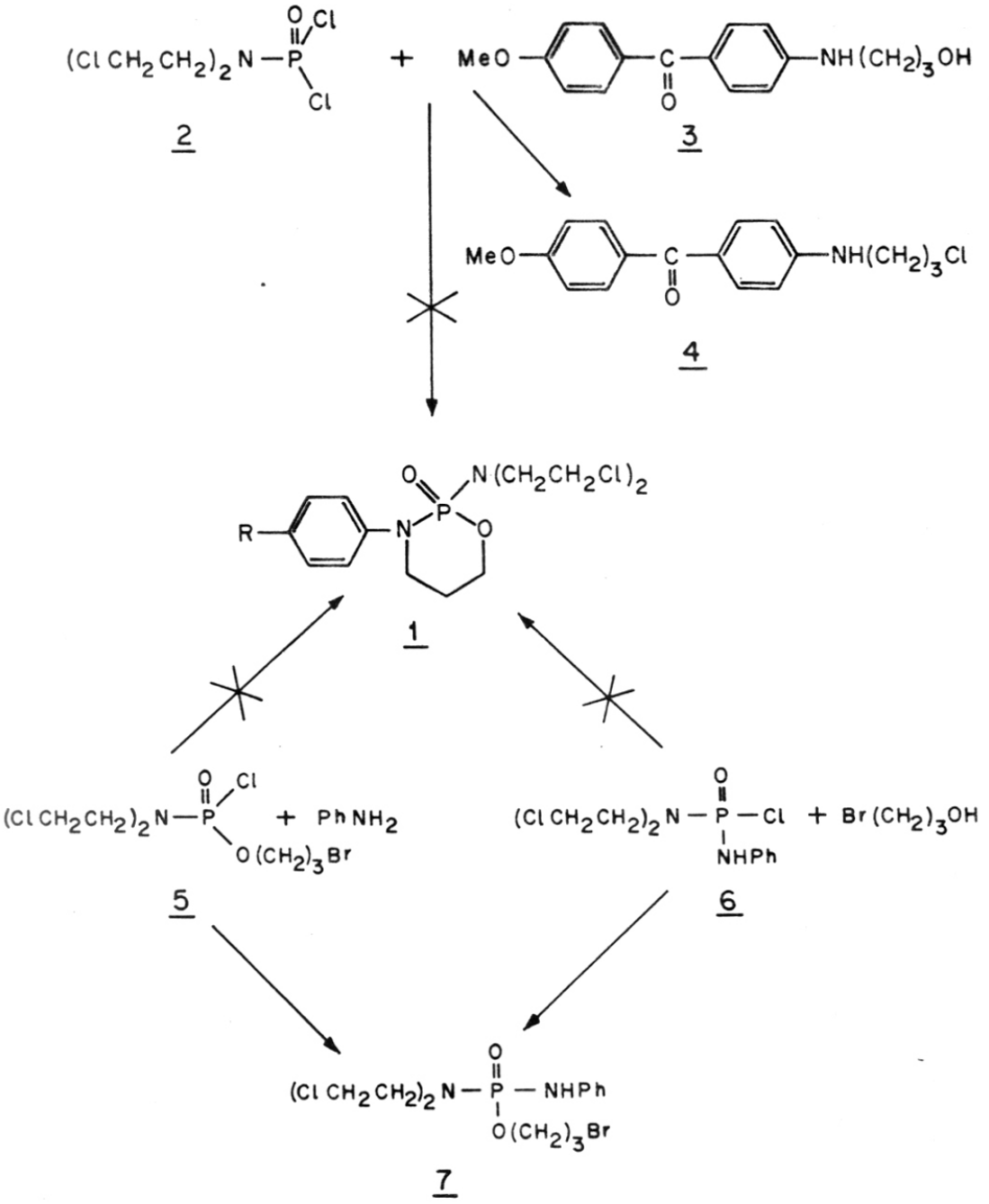
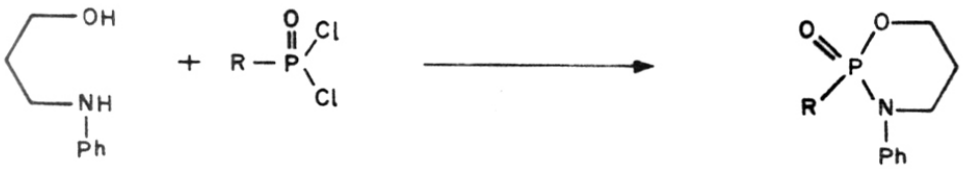
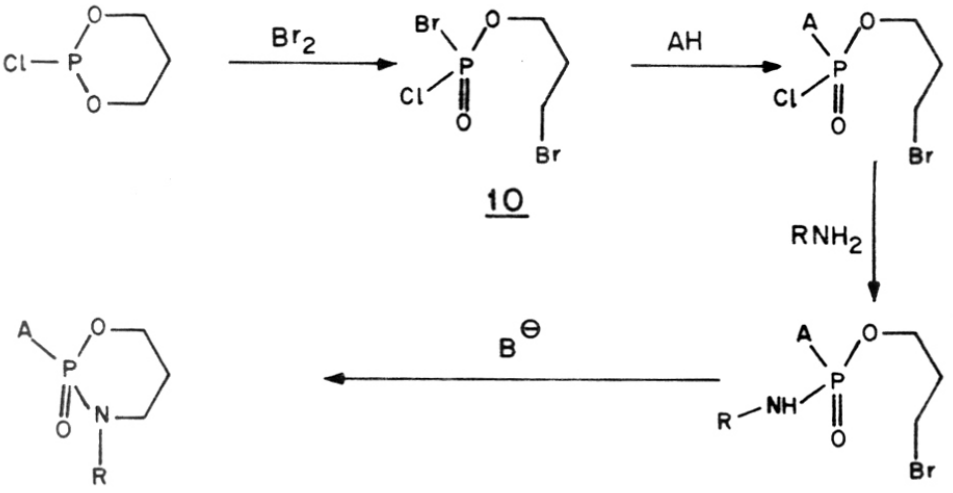

(Cl CH2 CH2)2 N — P(O)Cl Cl
2
+
MeO — C(=O) — NH(CH2)3OH
3
MeO — C(=O) — NH(CH2)3Cl
4
R — N — P(O) — N(CH2CH2Cl)2
1
(Cl CH2 CH2)2 N — P(O)Cl — O(CH2)3Br
+ PhNH2
5
(Cl CH2 CH2)2 N — P(O) — Cl
NHPh
+ Br(CH2)3OH
6
(Cl CH2 CH2)2 N — P(O) — NHPh
O(CH2)3Br
7

CHART – 1



8 Where R = OPh or NHPh 9

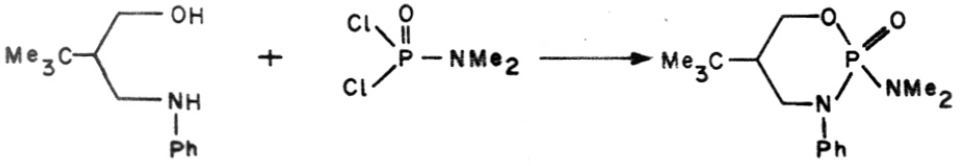
CHART – 2



10 11 12 , 13

Where R = C_2H_5 or C_6H_5

CHART – 3



14 15

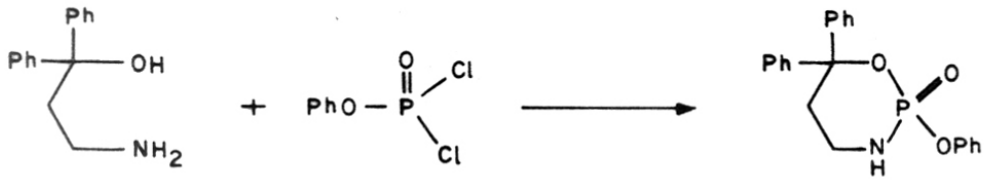
CHART – 4

4-Arylcyclophosphamides[9] 19 were obtained as mixtures of cis and trans isomers by treating $Cl_2P(O)N(CH_2CH_2Cl)_2$ with $RC_hH_4CH(NH_2)CH_2CH_2OH$ 18 (where R = H, 2-Me, 3-Me, 3-OMe, 4-OMe, 2-Cl, 3-Cl and 4-Cl) (Chart 6).

Compounds 20 and 21 synthesised by Eto et al[10] have oxygen, phosphorous and nitrogen in a ring system which is fused to an aromatic ring (Chart 7).

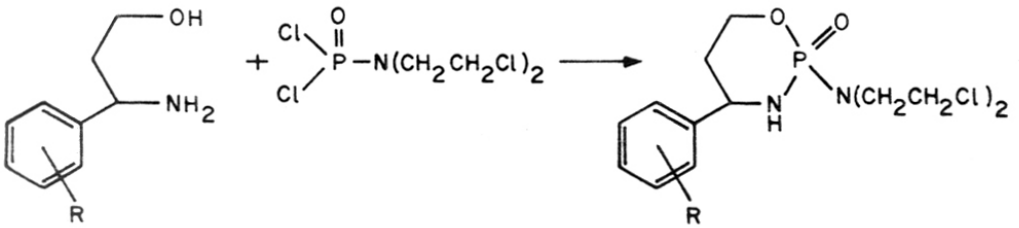
Literature survey revealed that 6-aryl-2-chloro or 2-chloro-3,6-diaryl derivatives, as well as compounds with fused saturated ring at 5 and 6 positions of the tetrahydro-oxazaphosphorin ring system have not been reported. Only a few derivatives with aromatic substituents in 4 and 5 positions are reported.

The present chapter describes the synthesis of 3,4,5,6-aryl/alkyl substituted tetrahydro-1,3,2-oxaza-phosphorin-2-oxides.



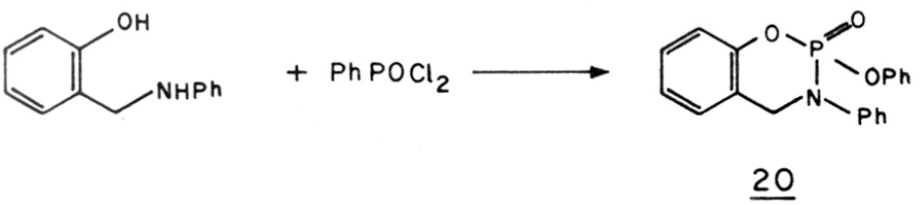
16 17

CHART – 5

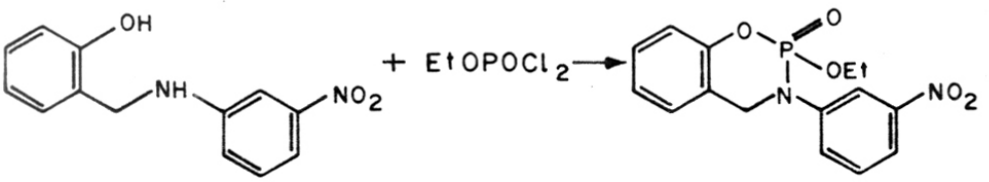


18 19

CHART – 6



20



21

CHART – 7

PRESENT WORK

The precursors, 1-aryl-3-N-arylamino-1-propanols, for the synthesis of 3,6-diaryl tetrahydro-1,3,2-oxazaphosphorins, were prepared by the reduction of corresponding aminoketones 22-23 with sodium borohydride in absolute ethanol. The relevant aminoketones were prepared by the interaction of corresponding Mannich base hydrochlorides with primary amines as described in the previous Chapter.

1-Aryl-3-N-arylamino-1-propanols 24-25 on treatment with phosphorous oxychloride in dry dichloromethane and followed by the interaction with triethylamine gave 2-chloro-3,6—diaryltetrahydro-1,3,2-oxazaphosphorin-2-oxides 26-27 (Chart 8).

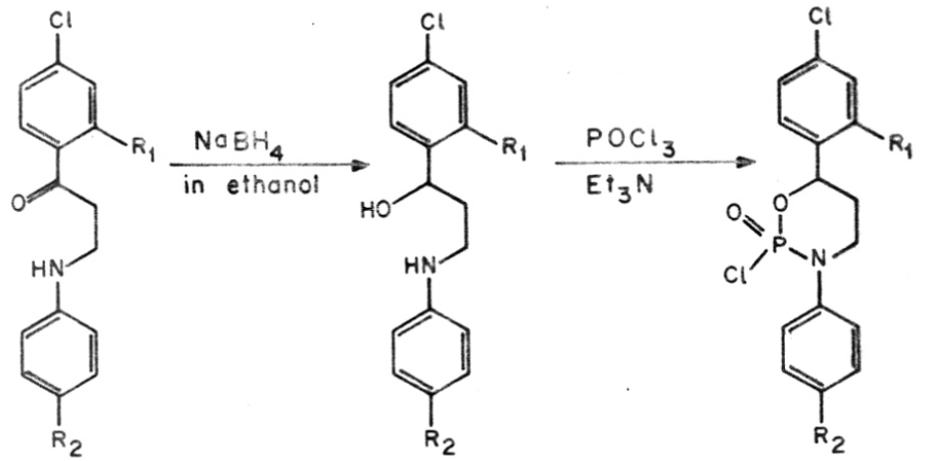
In the previous chapter, it was reported that the reaction of aryl β-aryl-∝-methylethylaminoketones 28-29 with phosphorus oxychloride and triethylamine did not yield the corresponding dihydro-oxazaphosphorins. Therefore, it was thought interesting to study the reaction of phosphorus oxychloride and triethylamine on 1-aryl-3-N-arylamino-2-methyl-1-propanols 30-31. The aminoketones 28-29, obtained by the condensation of β-dimethylamino-∝-methylpropiophenone hydrochloride and primary amines, were reduced by sodium borohydride in ethanol to the corresponding aminopropanols. The latter, 1-aryl-3-N-

arylamino-2-methyl-1-propanols, on treatment with phosphorus oxychloride and triethylamine, gave the desired 2-chloro-3,6-diaryl-5-methyltetrahydro-1,3,2-oxazaphosphorin-2-oxides 32-33 (Chart 9).

Compounds with substituents at 3 and 4 position and saturated six membered ring fused at 5 and 6 positions of tetrahydro-1,3,2-oxazaphosphorin ring system are so far not reported in literature. We have synthesised these compounds in the following manner.

β-Dimethylaminocyclohexanone hydrochloride[11] was condensed with aniline to give 2-anilinomethyl-cyclohexanone 34 which was then reduced to 2-anilinomethyl-cyclohexanol 35, by treatment with sodium borohydride. Reaction of 35 with phosphorus oxychloride and triethylamine yielded 2-chloro-3-phenyl-5,6-tetramethylene-tetrahydro-1,3,2-oxazaphosphorin-2-oxide 36.

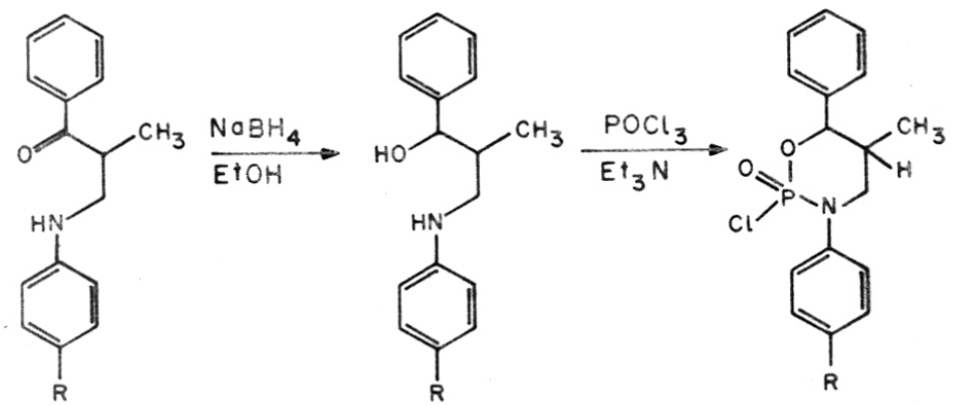
2-Chloro-3,4-diphenyl-5,6-tetramethylene-tetrahydro-1,3,2-oxazaphosphorin-2-oxide 39 was prepared similarly. Cyclohexanone and benzalaniline were condensed to give 2-(α-anilinobenzyl)-cyclohexanone[12] 37. The latter was then reduced to 2-(α-anilinobenzyl)-cyclohexanol 38 with sodium borohydride. The aminopropanol 38 when treated with phosphorus oxychloride and triethylamine yielded 39 (Chart 10).



22 — 24 — $R_1 = Cl$, $R_2 = CH_3$ — 26

23 — 25 — $R_1 = H$, $R_2 = CH_3$ — 27

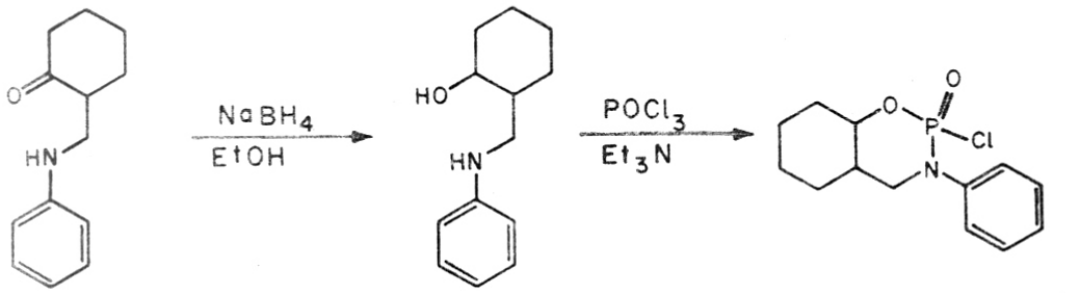
CHART - 8



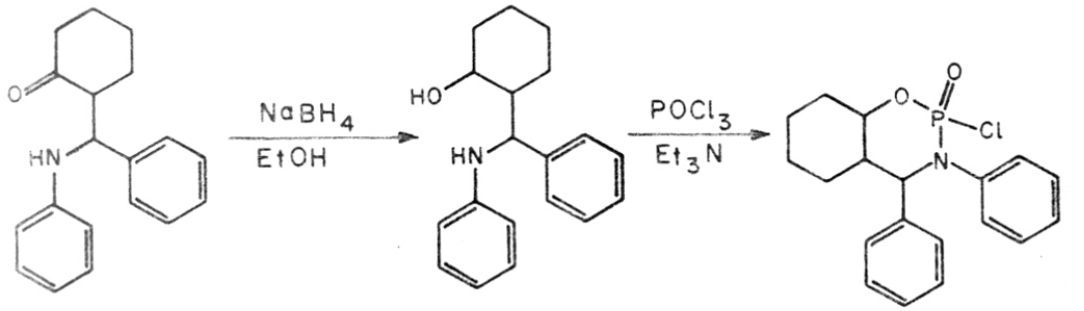
28 — 30 — R = H — 32

29 — 31 — $R = CH_3$ — 33

CHART - 9



34 35 36



37 38 39

CHART - 10

Mass spectra

The mass spectra of above substituted-tetrahydro-1,3,2-oxazaphosphorin-2-oxides reveal the following type of migration.

Localisation of charge on the doubly bonded oxygen atom of the exocyclic phosphoryl group leads to hydrogen atom abstraction from C-5 methylene group, followed by cleavage of C-O and C-N bonds. This fragmentation process results in the formation of strong peak of phenyl allyl ion (A) (Chart 11, Table 3).

The fragmentation process initiated by single hydrogen transfer from C-5 methylene to phosphoryl oxygen atom results in ring opening. This is followed by a second hydrogen migration of C-4 methylene to the phosphorus atom. Elimination of $O{=}\overset{\overset{OH}{|}}{\underset{\underset{H}{|}}{P}}{-}Cl$ from this intermediate ion results in the strongly conjugated heterodiene ion (B) which then eliminates hydrogen atom from ortho position of the phenyl ring by substitution-elimination reactions leading to N-aryldihydroquinoline ion (C). These sequences are shown in Chart 11.

In the mass spectra of 2-chloro-3-phenyl-5,6-tetramethylene tetrahydro-1,3,2-oxazaphosphorin-2-oxide 36 and its 4-phenyl-substituted analogue 39, formation of

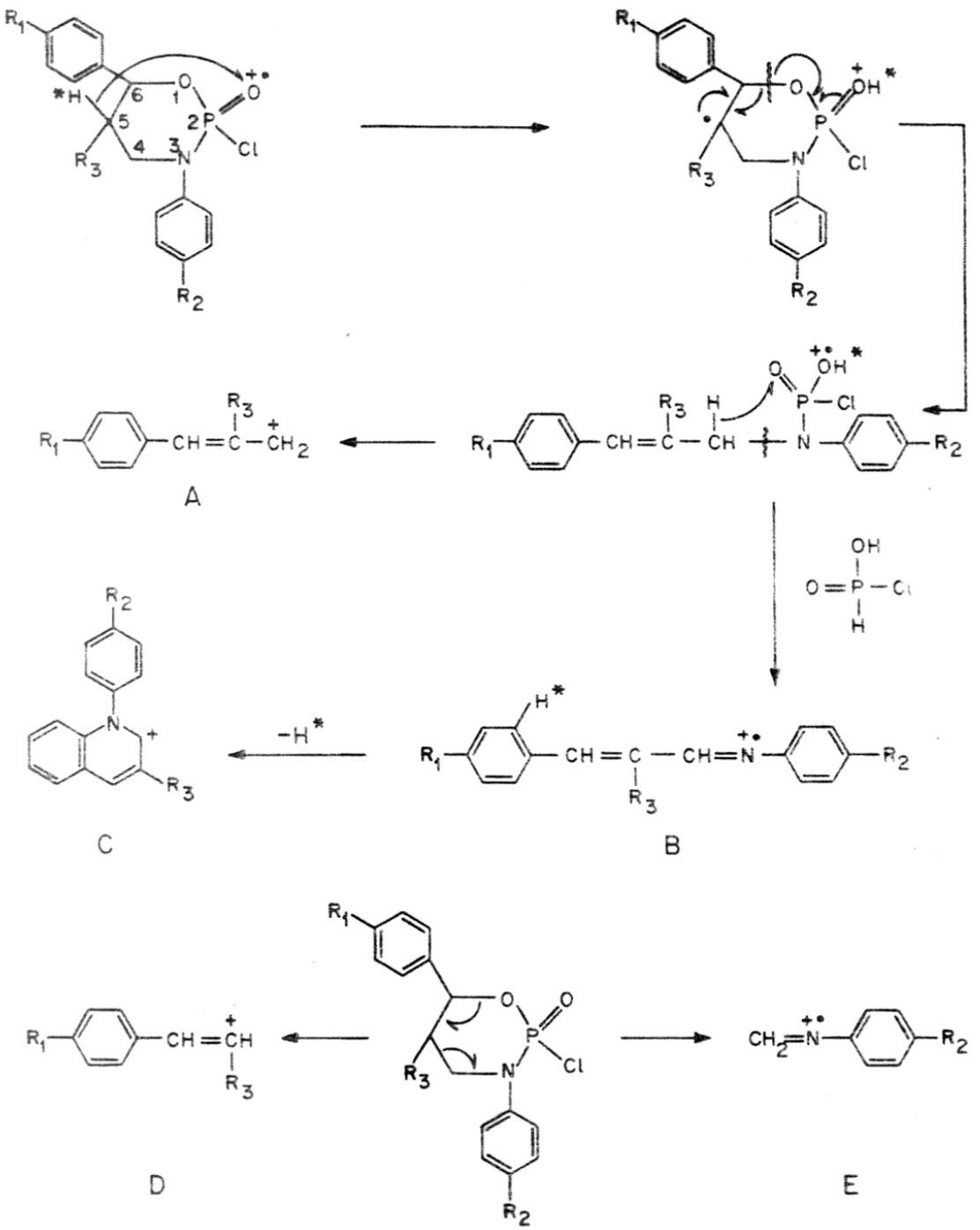
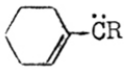


CHART – 11

stable phenylallyl ion by hydrogen migration is not possible. However, single hydrogen transfer from C-5 methylene followed by loss of cyclohexenyl (C_6H_9) radical results in the base peak at m/z 204 in the case of compound 36 and m/z 280 in the case of compound 39, the charge being stabilised by the phosphorus containing fragment. Similarly the peak at m/z 191 in the mass spectrum of 36 could be ascribed to the loss of cyclohexenyl substituted carbene  accompanied by another C-4 methylene hydrogen transfer to the phosphoryl function (Chart 12).

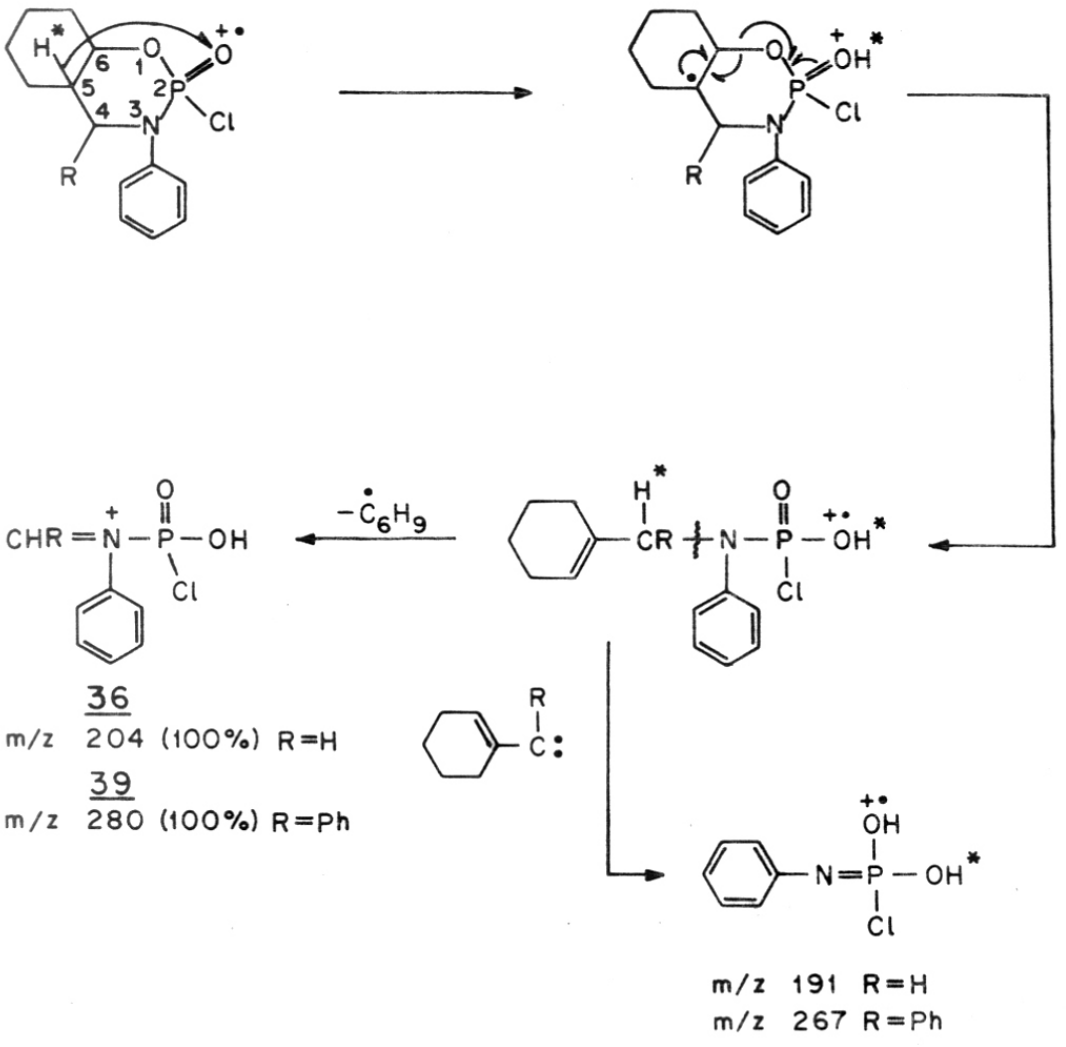

H*
O
+•
O
6
1
5
2P
4
3
N
Cl
R
+
O
OH*
P
Cl
N
R
H*
CR
N
P
O
+•
OH*
Cl
-C6H9
CHR=N
+
P
O
OH
Cl
36
m/z 204 (100%) R=H
39
m/z 280 (100%) R=Ph
R
C:
+•
OH
N=P
OH*
Cl
m/z 191 R=H
m/z 267 R=Ph

CHART -12

EXPERIMENTAL

General method for the synthesis of 1-aryl-3-N-arylamino-1-propanols

A mixture of aryl β-arylaminoethyl ketones (0.02 mol) and sodium borohydride (0.8 g; 0.02 mol) in ethanol (50 ml) was refluxed on a waterbath for 1-2 hours. After dilution with water (50 ml), the reaction mixture was acidified with dil. acetic acid and extracted with chloroform. Chloroform layer was washed with saturated sodium bicarbonate solution and then thoroughly with water. Chloroform layer was dried over anhydrous Na_2SO_4 and solvent removed to yield aminopropanols, which were crystallised from benzene. The mps, yields, analytical data and IR data of these compounds are given in Table 1.

General method for the synthesis of 2-chloro-3,6-diaryltetrahydro-1,3,2-oxazaphosphorin-2-oxides

To a solution of 1-aryl-3-N-arylamino-1-propanols (0.005 mol) in dry dichloromethane (20 ml), phosphorus oxychloride (0.007 mol) was added. The mixture was stirred for 20-24 hours at room temperature under exclusion of moisture. The mixture was cooled to 0-5° and dry triethylamine (3.5 g) was added dropwise over a period of 30 minutes. The mixture was further stirred for 2 hours. Excess of

dichloromethane was removed under vacuum and dry benzene (10 ml) was added. The mixture was filtered and the filtrate was again concentrated. The concentrated solution was chromatographed over silica-gel. The first fraction collected with benzene as eluant yielded 2-chloro-3,6-diaryltetrahydro-1,3,2-oxazaphosphorin-2-oxides. The mps, yields and analytical data of tetrahydro-oxazaphosphorins have been given in Table 2. NMR spectral data of these compounds is given in Table 3. Mass fragments are given in Table 4.

Synthesis of 2-chloro-5-methyl-6-phenyl-3-(p-tolyl)tetrahydro-1,3,2-oxazaphosphorin-2-oxide 33

A mixture of 1-phenyl-2-methyl-3-(p-tolyl)-1-propanol (1.26 g; 0.005 mol), phosphorus oxychloride (1 g; 0.007 mol) and dichloromethane (20 ml) was stirred for 20 hours at room temperature under exclusion of moisture. The mixture was then cooled to 0-5° and dry triethylamine (kept over KOH pellets) (3.5 g) was added dropwise over a period of half an hour. The mixture was stirred for two more hours. Excess of dichloromethane was removed under vacuum and dry benzene (10-20 ml) was added. The solution was filtered and the filtrate was concentrated under vacuum. The concentrated solution was adsorbed on a

silica gel column which was then eluted with benzene. The first fraction yielded 2-chloro-5-methyl-6-phenyl-3-(p-tolyl) tetrahydro-1,3,2-oxazaphosphorin-2-oxide 33 which crystallised from ethanol in colourless needles (0.837 g, yield 50%), mp 152°. (Found C, 60.3; H, 6.0; N, 3.8; P, 9.0; $C_{17}H_{19}ClNO_2P$ requires C, 60.8; H, 5.7; N, 4.1; P, 9.2%).

NMR ($CDCl_3$,δ) $-\underline{CH}-\overset{H}{\underset{CH_3}{\underset{|}{\overset{|}{C}}}}-\underline{CH_2}-$ at 0.8, d, 3p; p-$\underline{CH_3}C_6H_4$- at 2.3, s, 3p;

$-\underline{CH}-\underline{CH}-\underline{CH_2}-$ (CH$_3$ branch) at 3-3.8, m, 3p;

$-\underline{CH}-\underline{CH}-\underline{CH_2}-$ (CH$_3$ branch) at 5.1, dd, 1p;

Aromatic protons centred at 7.33, m, 9p.

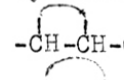
Mass M^+ 335.

2-Chloro-3-phenyl-5,6-tetramethylene-tetrahydro-1,3,2-oxazaphosphorin-2-oxide 36

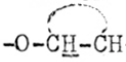
The mixture of 2-anilinomethylcyclohexanol 35 (1.02 g; 0.005 mol) and phosphorus oxychloride (1 g; 0.007 mol) in dry dichloromethane (20 ml) was stirred for 24 hours at room temperature under dry conditions. The mixture was then cooled to 0-5° and dry triethylamine (kept over KOH pellets) (3.5 g) was added dropwise. The reaction mixture was further stirred for 2 hours. The reaction

was worked up as described in the general method. Compound 35 was crystallised from ethanol in colourless plates (0.910 g, yield 64%), mp 130°. (Found C, 54.0; H, 6.1; N, 5.2; P, 10.4; $C_{13}H_{17}ClNO_2P$ requires C, 54.7; H, 6.0; N, 4.9; P, 10.8%).

NMR ($CDCl_3$, δ) Cyclohexyl protons at 1-2, m, 9p;



at 3-4, m, 2p;



at 4-5, m, 1p;

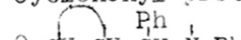
Aromatic protons at 7.4, s, 5p.

Mass M^+ 285.

2-Chloro-3,4-diphenyl-5,6-tetramethylene-tetrahydro-1,3,2-oxazaphosphorin-2-oxide 39

To a solution of 2-(α-anilinobenzyl)-cyclohexanol 38 (1.40 g; 0.005 mol) in dry dichloromethane (20 ml), phosphorus oxychloride (1 g; 0.007 mol) was added and the mixture was stirred at room temperature for 24 hours under exclusion of moisture. The mixture was cooled to 0-5° and dry triethylamine (kept over KOH pellets) (3.5 g) was added dropwise. The mixture was further stirred for 2 hours. The reaction mixture was worked up as described in the general method. Compound 39 crystallised from ethanol in colourless plates (1.1 g, yield 62%), m.p. 166°. (Found C, 62.8; H, 5.8; N, 4.1; P, 9.0; $C_{19}H_{21}ClNO_2P$ requires C, 63.1; H, 5.8; N, 3.8; P, 8.6%).

NMR ($CDCl_3$, δ) Cyclohexyl protons at 1-2.3, m, 9p;



at 4.3-4.6, dd, 2p;

Aromatic protons at 7.0, s, 10p.

Mass M^+ 361.

TABLE - 1

MP/BP, YIELDS, IR VALUES AND ANALYTICAL DATA OF AMINOPROPANOLS

Compd. No.	MP/BP in °C	IR values in CM^{-1} Solvent $CHCl_3$		Analytical data				Yields
		-NH	-OH		C	H	N	
24	102	3410	3620	R	62.1	5.5	4.5	80.0
				F	61.8	5.7	5.0	
25	114	3410	3620	R	69.8	6.5	5.1	84.0
				F	70.2	6.9	5.1	
30	$120/3.4 \times 10^{-3}$ mm/Hg Lit.[13] $115/3.4 \times 10^{-3}$ mm/Hg	3400	3600	R	-	-	-	70.0
				F	-	-	-	
31	$120/2 \times 10^{-4}$ mm/Hg	3400	3610	R	80.0	8.2	5.5	67.0
				F	79.8	8.3	5.5	
35	84 Lit.[14] 82	3400	3600	R	-	-	-	75.0
				F	-	-	-	
38	149	3400	3600	R	81.1	8.1	4.9	82.0
				F	80.7	8.1	5.0	

TABLE - 2

MPS, YIELDS AND ANALYTICAL DATA OF TETRAHYDRO-OXAZAPHOSPHORINS

Compound No.	MP in °C	Yield in %	Required R Found F	C	H	N	P
26	180	64.0	R	49.3	3.8	3.6	7.9
			F	49.5	3.3	3.8	7.8
27	154	56.0	R	54.0	4.5	3.9	8.7
			F	53.0	4.5	3.6	8.2
32	168	52.0	R	59.8	5.3	4.3	9.6
			F	59.9	5.3	4.5	9.1
33	152	50.0	R	60.8	5.7	4.1	9.2
			F	60.3	6.0	3.8	9.0
36	130	64.0	R	54.7	6.0	4.9	10.8
			F	54.0	6.1	5.2	10.4
39	166	62.0	R	63.1	5.8	3.8	8.6
			F	62.8	5.8	4.1	9.0

TABLE - 3

NMR VALUES OF TETRAHYDRO-OXAZAPHOSPHORINS

Compound No.		
26	$-\underline{CH}-CH_2-\underline{CH_2}-\underline{N}-$, $p-CH_3\underline{C_6H_4}-$	at 2.3, s, 5p;
	$-\underline{CH}-\underline{CH_2}-CH_2-\underline{N}-$	at 3.9, m, 2p;
	$O-\underline{CH}-CH_2-\underline{CH_2}-$	at 6.0, m, 1p;
	Aromatic protons	at 7.2-7.9, m, 6p.
27	$\underline{CH_2}-\underline{CH_2}-\underline{N}-$ and $p-\underline{CH_3}\underline{C_6H_4}$	at 2.3, d, 5p;
	$-\underline{CH}-\underline{CH_2}-CH_2-\underline{N}-$	at 2.9, m, 2p;
	$O-\underline{CH}-CH_2-\underline{CH_2}-$	at 5.5, m, 1p;
	Aromatic protons centered	at 7.3, d, 8p.
32	$-CH-\underline{CH}-CH_3$	at 0.8, d, 3p;
	$-CH-\underset{CH_3}{\underline{CH}}-\underline{CH_2}-$	at 2.6-3.8; m, 3p;
	$-\underline{CH}-CH-\underset{CH_3}{CH_2}-$	at 5.1, dd, 1p;
	Aromatic protons	at 7.5, s, 10p;

Table 3.. continued

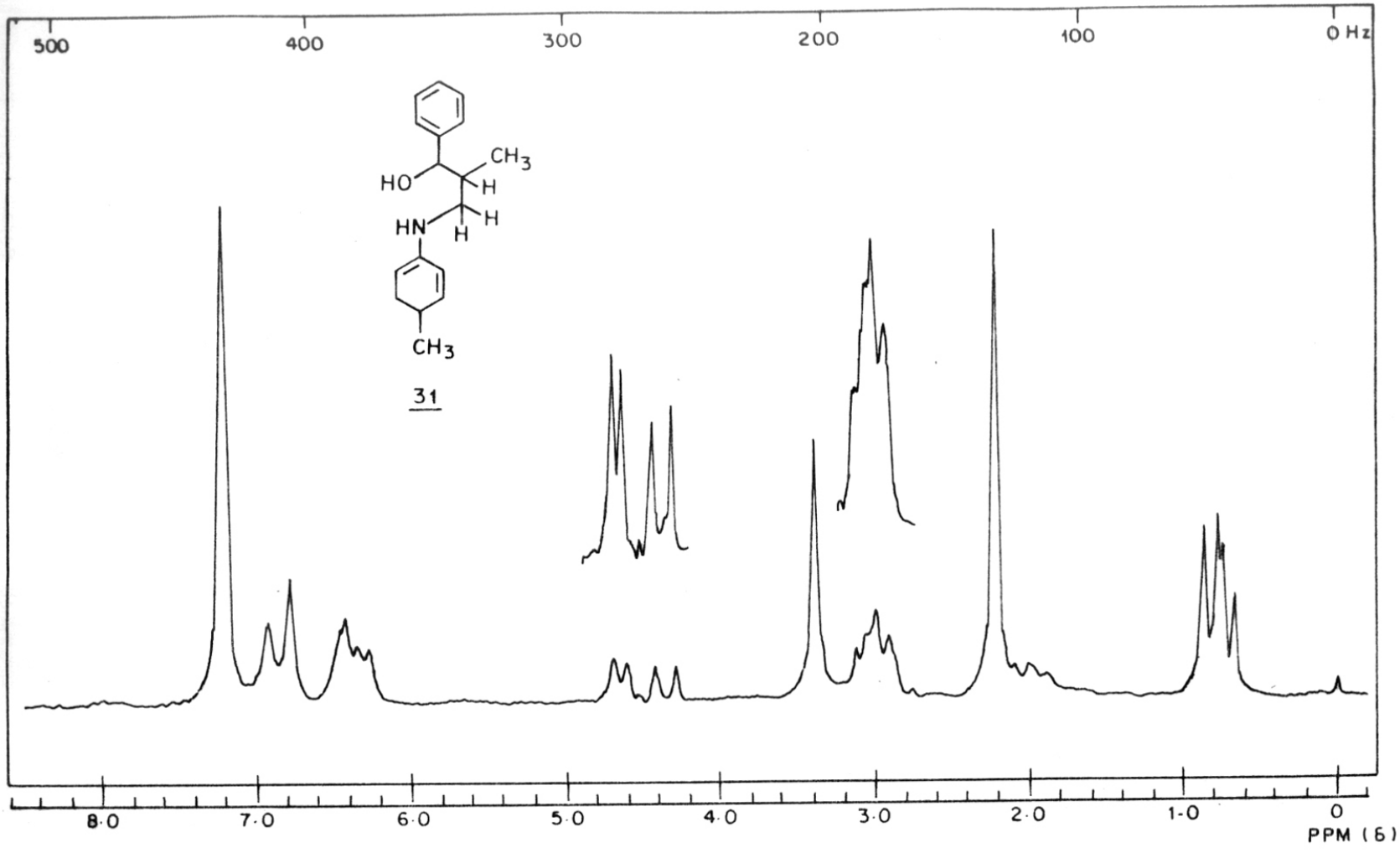
Table - 3 - continued...

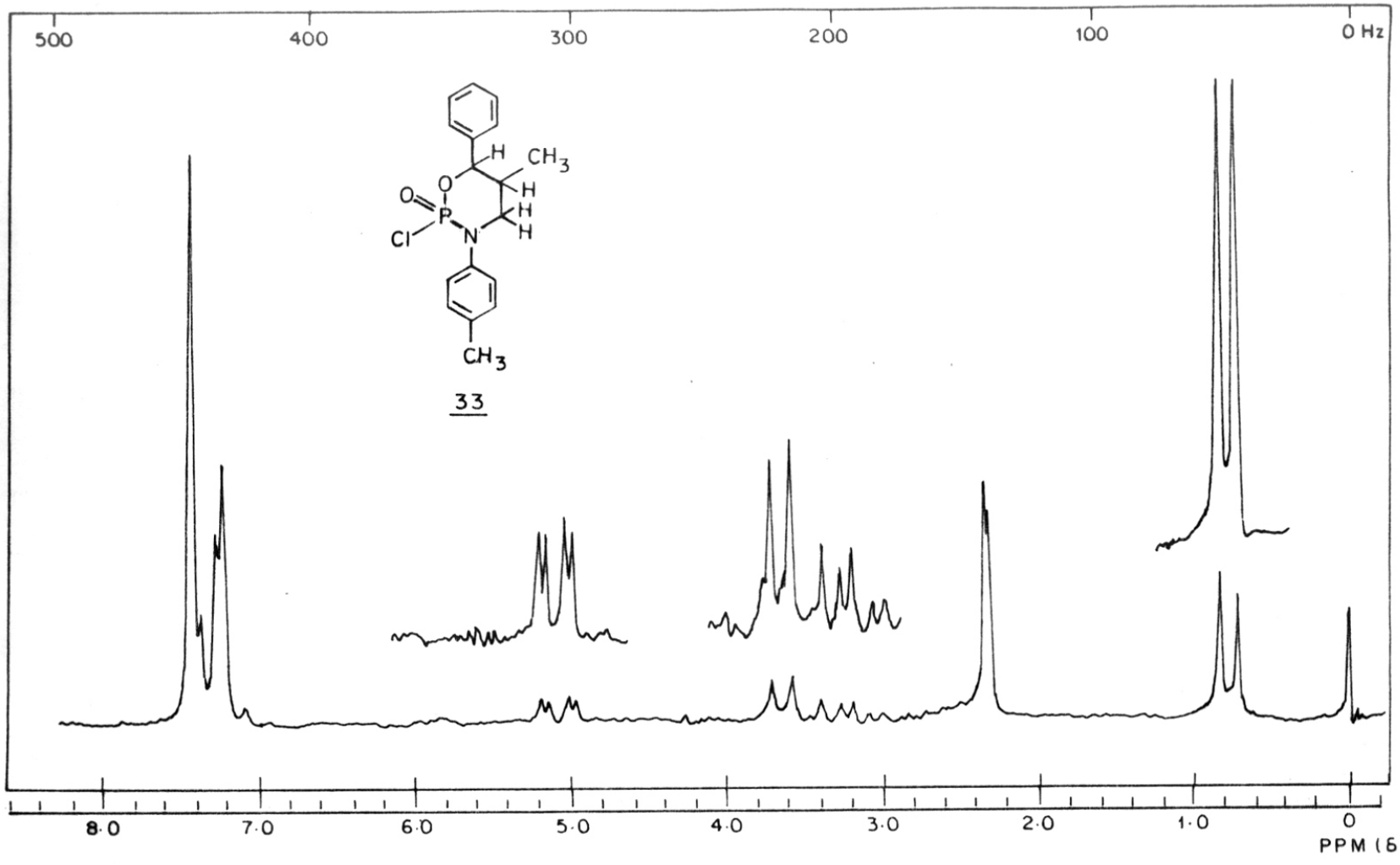
Compound No.		
	$-CH-\underset{\underset{CH_2}{|}}{CH}-\underline{C}H_3$	at 0.8, d, 3p;
33	$p\text{-}CH_3C_6H_4-$	at 2.3, s, 3p;
	$-CH-\underset{\underset{CH_3}{|}}{\underline{C}H}-\underline{C}H_2-$	at 3-3.8, m, 3p;
	$-\underline{C}H-\underset{\underset{CH_3}{|}}{CH}-CH_2-$	at 5.1, dd, 1p;
	Aromatic protons centered	at 7.33, m, 9p.
	Cyclohexyl protons	at 1-2, m, 9p;
	$-\underline{C}H-CH-\underline{C}H_2-N-$	at 3-4, m, 2p;
36	$-O-\underline{C}H-CH-$	at 4-5, m, 1p;
	Aromatic protons	at 7.4, s, 5p.
	Cyclohexyl protons	at 1-2.3, m, 9p;
39	$-O-\underline{C}H-CH-\underset{\underset{Ph}{|}}{\underline{C}H}-N-Ph$	at 4.3-4.6, dd, 2p;
	Aromatic protons	at 7, s, 10p.

TABLE - 4

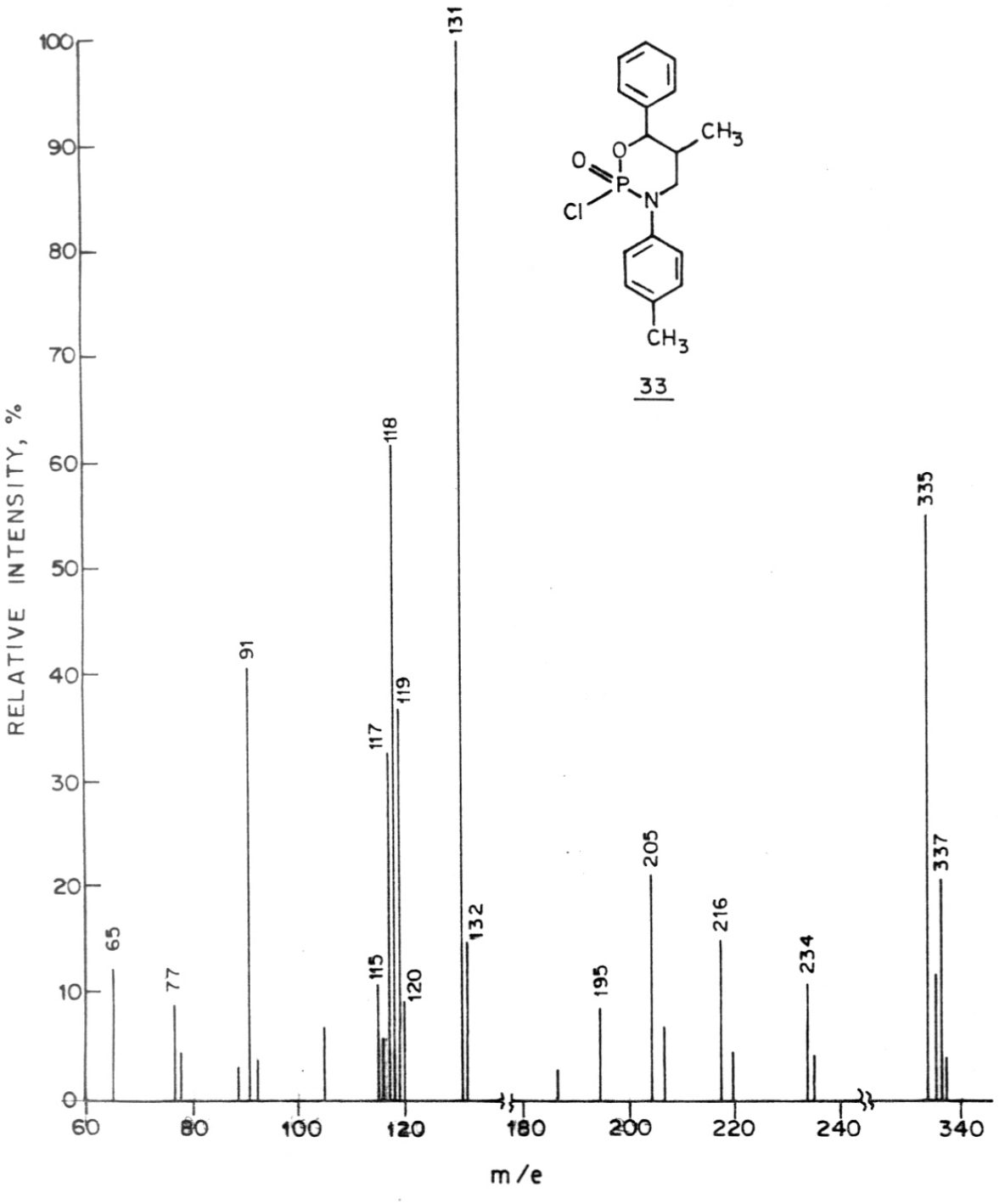
RELATIVE ABUNDANCE OF SOME CHARACTERISTIC IONS IN THE MASS SPECTRA OF TETRAHYDRO-1,3,2-OXAZAPHOSPHORIN -2-OXIDES

Compound No.	M^+	%	Single hydrogen transfer phenyl allyl ion A		Double hydrogen transfer hetero-diene ion B		C		D		E	
			m/z	%	m/z	%	m/z	%	m/z	%	m/z	%
26	389	15	185	100	289	6	288	4	172	15	119	46
27	355	21	151	100	255	4	254	8	118	16	119	25
30	321	33	131	100	221	33	220	20	118	64	105	38
31	335	55	131	100	235	4	234	11	118	62	119	37

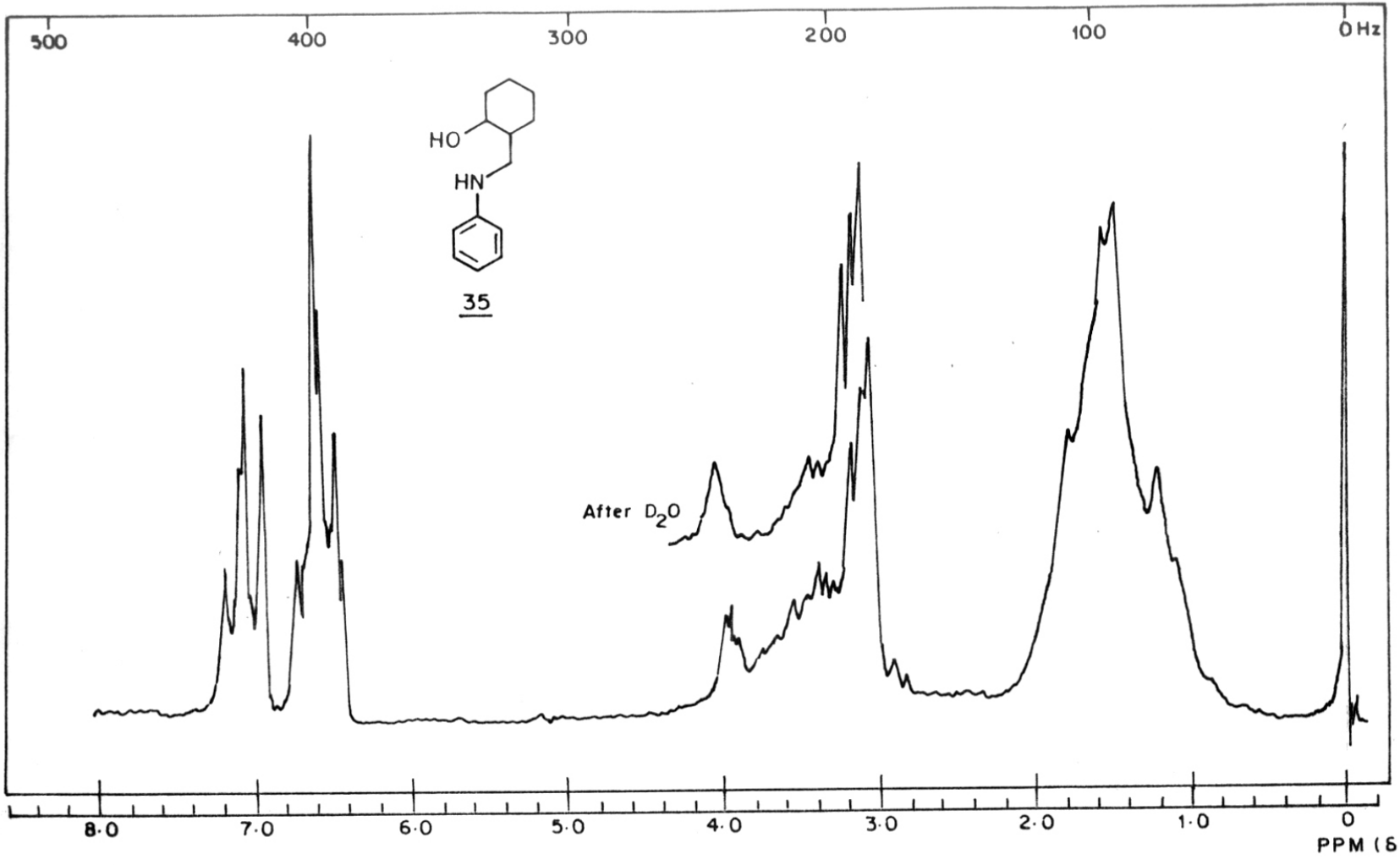

500
400
300
200
100
0 Hz
HO
CH3
H
H
HN
H
CH3
31
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

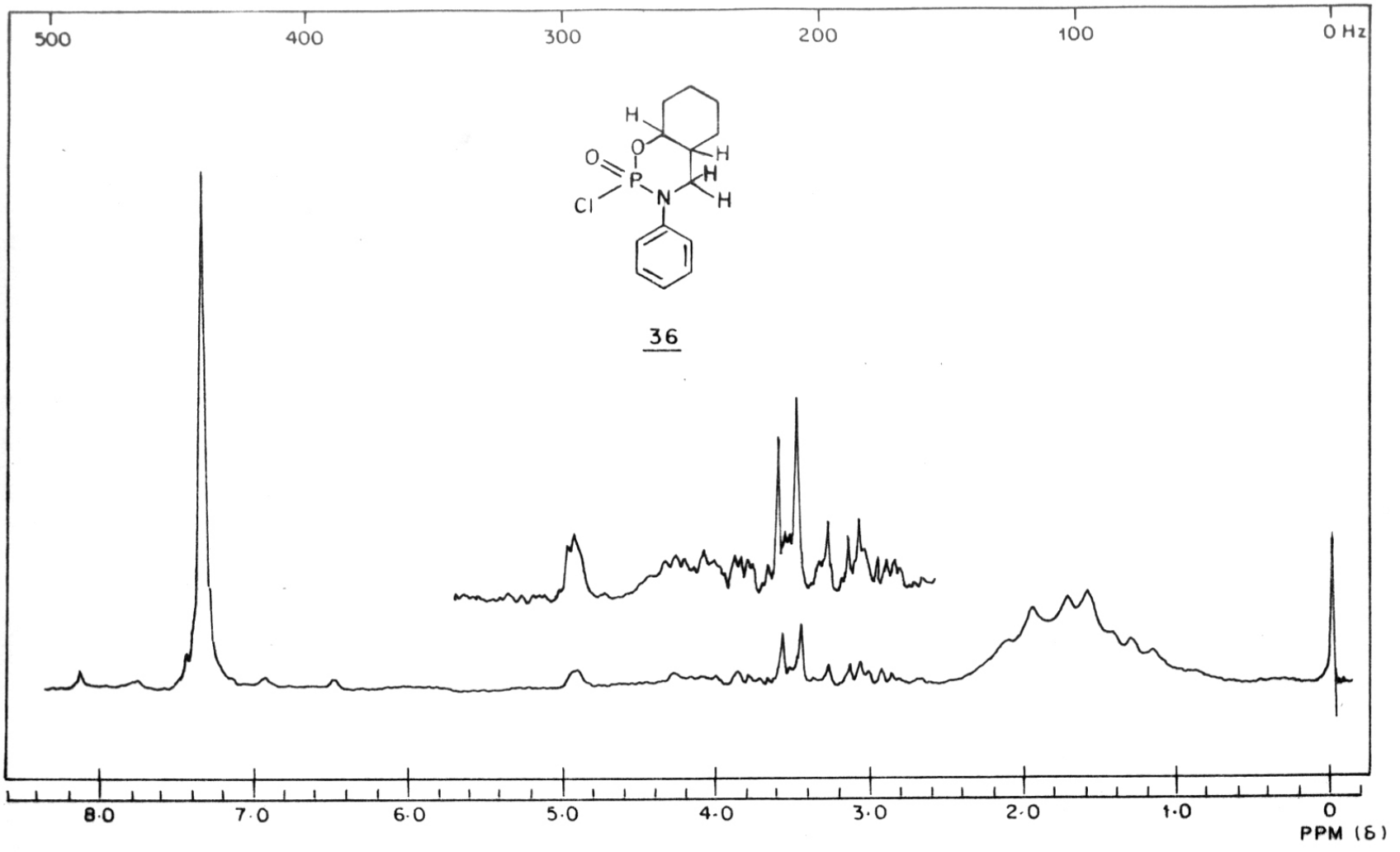

500
400
300
200
100
0 Hz
H
CH3
O
O
P
Cl
N
H
H
H
CH3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

33

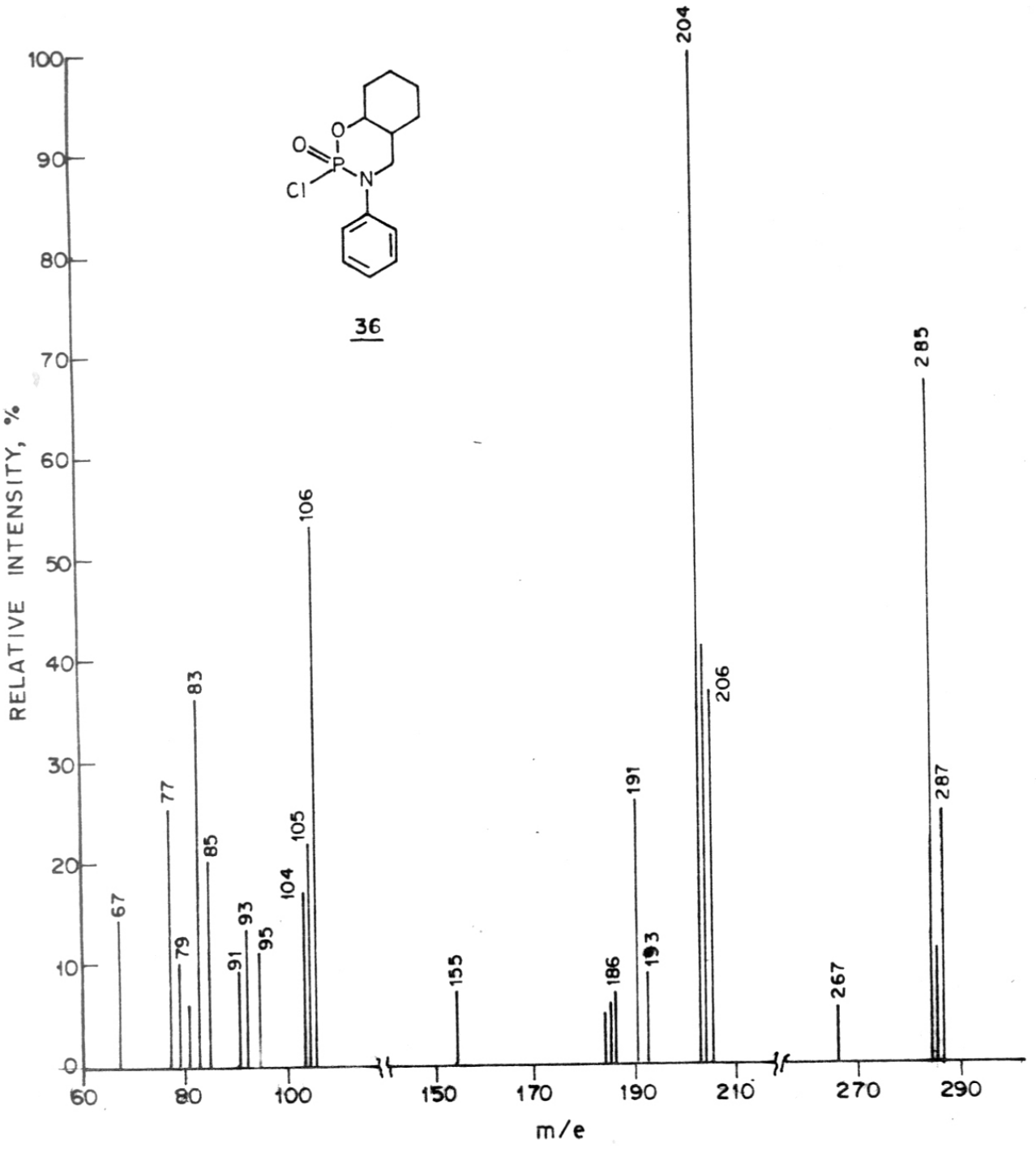

RELATIVE INTENSITY, %
m/e
131
118
91
119
117
335
337
205
216
234
132
65
77
115
120
195
CH3
O
P
N
Cl
CH3

33


500
400
300
200
100
0 Hz
HO
HN
35
After D_2O
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)



36


RELATIVE INTENSITY, %
m/e
100
90
80
70
60
50
40
30
20
10
0
60
80
100
150
170
190
210
270
290
67
77
79
83
85
91
93
95
104
105
106
155
186
191
193
204
206
267
285
287
O
O
P
Cl
N

36

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CHAPTER II : PART - B

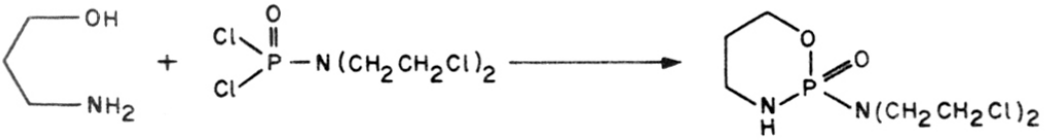
REACTIONS OF 2-CHLORO-3,6-DISUBSTITUTED-3,4-DIHYDRO-1,3,2-OXAZAPHOSPHORIN-2-OXIDES.

Various reactions of 2-chloro-3,6-disubstituted-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxides have been described in this chapter.

Nucleophilic substitution reactions at 2 position of the 1,3,2-oxazaphosphorinane derivatives have been extensively studied after the first synthesis of this ring system by Arnold et al[1] and particularly after its use in anticancer drugs. Various derivatives of tetrahydro-oxazaphosphorin ring system were obtained either by reacting 2-chloro tetrahydro-oxazaphosphorines with amines and alcohols or by treatment of substituted phosphoramidic dichlorides with aminopropanols in the presence of a base.

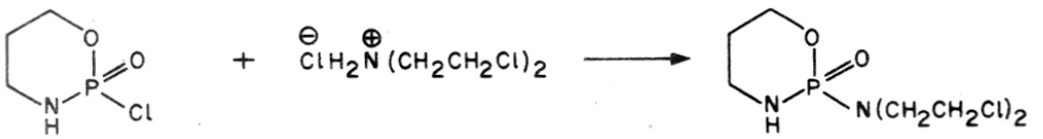
Arnold et al[1] synthesised 2 by the interaction of aminopropanols 1 with the dichloro-N,N-bis(β-chloroethyl)amidophosphate and trimethylamine in dioxane as a solvent (Chart 1). Similarly, compound 2 was synthesised by another pathway[2] by the reaction of 2-chlorotetrahydro-1,3,2-oxazaphosphorin-2-oxide 3 with N,N-bis(β-chloroethyl)-amine hydrochloride 4 in the presence of triethylamine in dichloromethane as solvent (Chart 2).

Interaction of 2-chloro-3-(β-chloroethyl)tetrahydro-1,3,2-oxazaphosphorin-2-oxide 5 with $HOCH_2CH_2NHR$ and R_1SO_2Cl 6 yielded derivatives[3] 7 (R=H, Et, CH_2CH_2Cl, $(CH_2)_3SO_3Me$, $CH_2CH_2SO_3Me$; R_1 = Me, Et, Pr, $CHMe_2$) (Chart 3).



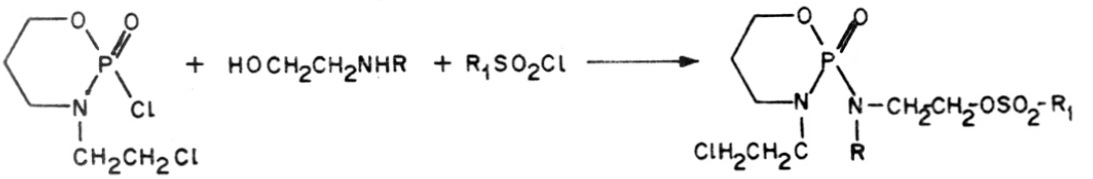
1 2

CHART - 1



3 4 2

CHART - 2



5 6 7

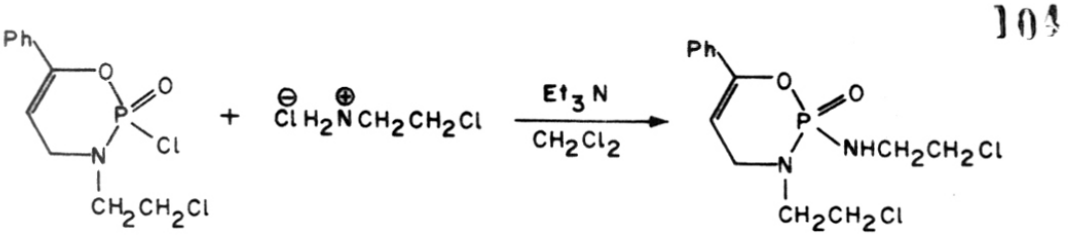
CHART - 3

PRESENT WORK

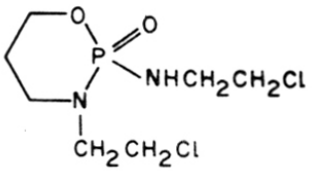
2-Chloro-3-(β-chloroethyl)-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 8 was treated with 2-chloroethylamine hydrochloride in presence of triethylamine to obtain compound 9 analogous to ifosphamide 10 a well-known anticancer drug (Chart 4). Similarly, compound 8 was reacted with methylamine and ethyleneimine to get compounds 11 and 12 respectively (Chart 5). Both chlorine groups present in compound 8 are reactive but substitution by nucleophiles takes place only at the 2 position. This was confirmed by the mass spectral fragmentation pattern. Replacement of chlorine of β-chloroethyl group would have shown loss of 98(PO_2Cl), instead, loss of 93 (PO_2NHCH_3) in 11 and ($PO_2NHCH_2CH_2Cl$) in 9 was observed.

Attempts to cyclise 2-(N-methylamino)-3-(β-chloroethyl)-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 11 in presence of bases such as pyridine, anhydrous K_2CO_3 in acetone, anhydrous K_2CO_3 in o-dichlorobenzene, and sodamide failed to give desired product 13 (Chart 6).

Interaction of the chloro-oxazaphosphorins 15, 16 and 17 with ethyleneimine, ammonia and methylamine in dichloromethane at room temperature yielded corresponding substituted derivatives 18, 19, 20 and 21 (Chart 7).

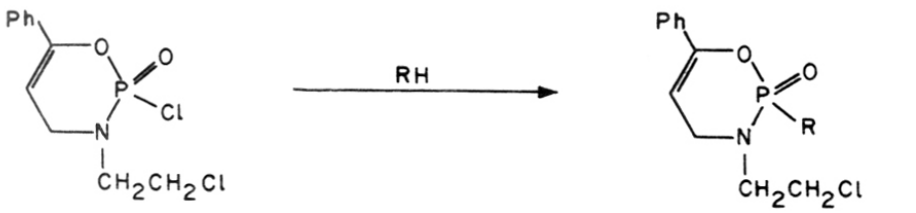


8 9



10

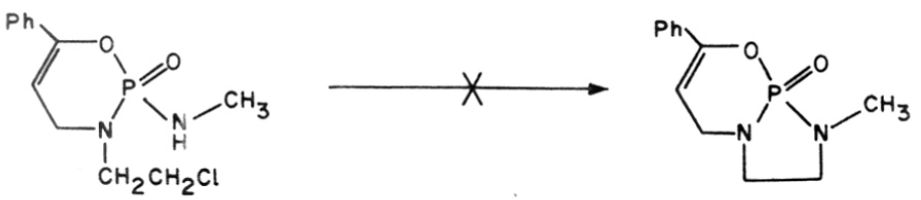
CHART – 4



8 11 ; R = NHCH$_3$

12 ; R = N

CHART – 5



11 13

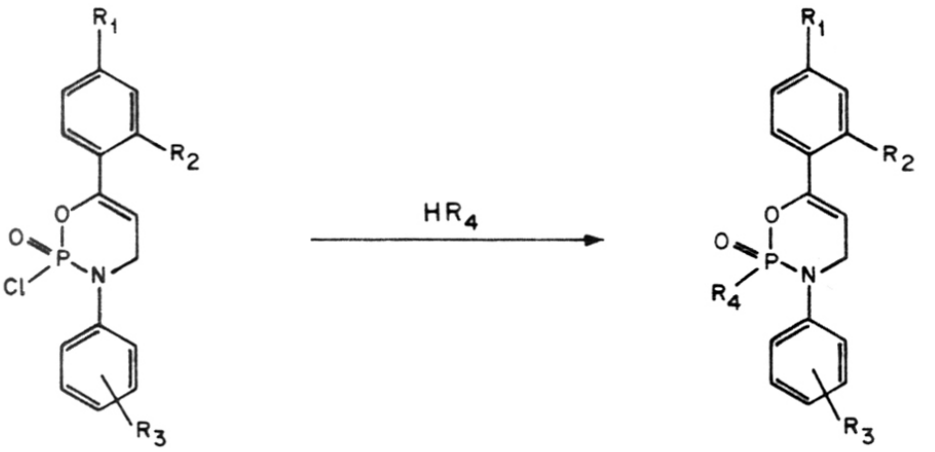
CHART – 6

Attempts to replace chlorine with cyano group were futile. 2-Chloro-3-(p-anisyl)-6-(p-chlorophenyl)-3, 4-dihydro-1,3,2-oxazaphosphorin-2-oxide 15 and sodium cyanide when stirred at room temperature in dichloromethane and also when refluxed in benzene did not yield a substituted product. However, compound 22 was obtained when chloro-oxazaphosphorin 15 and sodium cyanide were refluxed in dry acetone for 5-6 hours (Chart 8).

Replacement of chloro group in the dihydro-oxazaphosphorins by ethanethiol, anilino, phenoxy and thiophenoxy groups was attempted. However, these attempts failed to give desired replacement. The reactivity of aliphatic primary amines, secondary amines and alkoxy groups and unreactivity of anilino, thiol and phenoxy groups may be explained in the following manner.

Nucleophilic substitution reactions in tetrahydro-oxazaphosphorinanes take place by $S_N2(P)$ associative mechanism[4] involving pentacoordinated phosphorus intermediates. Substitution of leaving group by nucleophile, (a) when leaving group is axial, proceeds through a trigonal bipyramidal species, (b) when leaving group is equatorial, side ways attack across P=O, proceeds via square pyramidal intermediate[5] (Chart 9).

In the case of dihydro-oxazaphosphorins, the X-ray crystallographic structure of the compound 14 reveals



14 $R_1 = Cl$, $R_2 = H$, $R_3 = \underline{p} - CH_3$

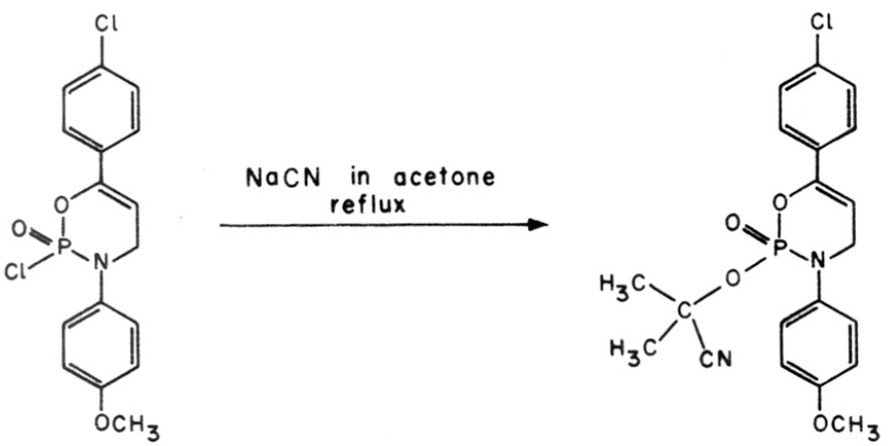
15 $R_1 = Cl$, $R_2 = H$, $R_3 = \underline{p} - OCH_3$; 18 ; $R_4 = N$

16 $R_1 = Cl$, $R_2 = H$, $R_3 = \underline{o} - OCH_3$; 19 ; $R_4 = N$

17 $R_1 = Cl$, $R_2 = Cl$, $R_3 = phenyl$; 20 ; $R_4 = NH_2$

21 ; $R_4 = NHCH_3$

CHART - 7



13 22

CHART - 8

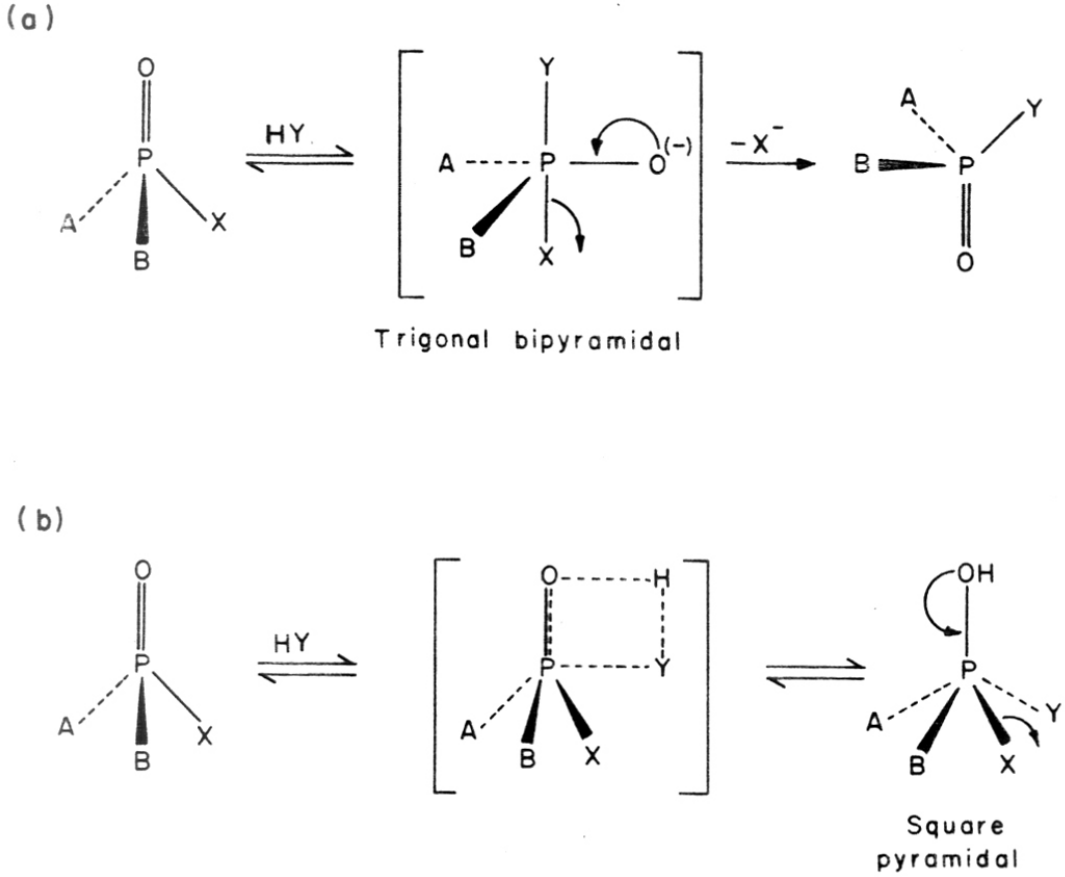


CHART - 9

that P=O is axial and chlorine is equatorial. This is supported by NMR spectral analysis of this compound described in Chapter III.

The first possibility of nucleophilic substitution in 14 via trigonal bipyramidal intermediate can be ruled out because of the unfavourable backside attack due to the hinderance by the oxazaphosphorin ring (Chart 10). It appears that in cases where the leaving group is equatorial as above, substitution via square pyramidal intermediate by sideways attack is the only operable mechanism. Out of the three possible sideways attack two are blocked viz. one by oxazaphosphorin ring and another by N-phenyl substituent. Nucleophile can only attack in a direction through ring oxygen and leaving group (Chart 11). By the above sideways attack the pentacoordinated phosphorus species has approximately the square pyramidal shape where the apex is occupied by O-P and the corners of the square by ring nitrogen, ring oxygen, nucleophile and the leaving group. Because of the cyclic structure as in 14, one of the angles viz. N-P-O is fixed by the ring to be approximately tetrahedral. This leaves smaller space for leaving group and and nucleophile to be accommodated in pentacoordinated phosphorus species compared to acyclic systems, resulting in buttressing strain. This strain is relieved when one of the ligands leaves forming tetrahedral phosphorus. When

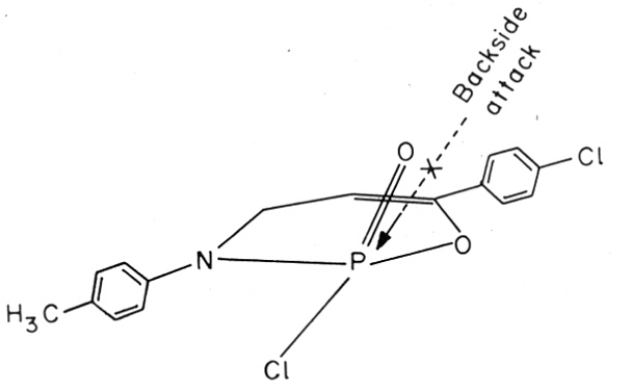


CHART 10

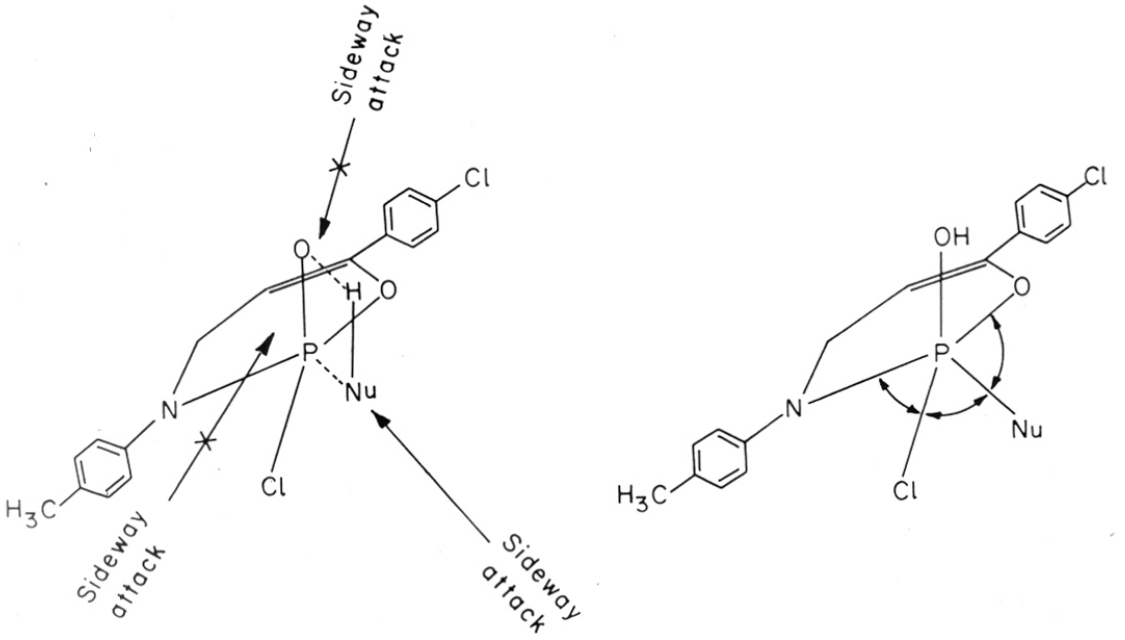


CHART 11

nucleophile is sterically bulky, formation of the above pentacoordinated intermediate itself may be unfavoured because of the buttressing strain. This may be the reason for the apparent unreactivity of bulkier aromatic amines and thiophenols. In these substitution reactions, the steric bulk rather than the nucleophilicity seems to decide the possibility of the reaction by a nucleophile.

EXPERIMENTAL

General method for synthesis of 2-substituted -3-alkyl/aryl-6-aryl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 11, 12 and 18-21

2-Chloro-3-alkyl/aryl-6-aryl-3,4-dihydro-1,3,2-oxazaphosphorins (0.001 mol) were reacted with amines (ammonia, methylamine and ethyleneimine) (0.002 mol) at room temperature using dichloromethane as solvent. The reaction mixture was poured into water after 30 minutes and the mixture extracted with dichloromethane. Dichloromethane layer was dried over anhydrous Na_2SO_4. After removal of dichloromethane the respective amino derivatives were obtained. The latter crystallised from ethanol in colourless needles.

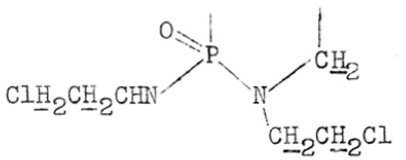
Yields, mp's and analytical data is given in Table 1.

Synthesis of 2-(β-chloroethylamino)-3-(β-chloroethyl)-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 9

A mixture of compound 8 (0.289 g ;0.001 mol), β-chloroethylamine hydrochloride (0.115 g ;0.002 mol) and triethylamine (0.5 ml ;0.004 mol) in dichloromethane was stirred for 30 minutes. The reaction mixture was then poured in ice-water and extracted with dichloromethane.

Dichloromethane layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The solid obtained was crystallised from ethanol to give colourless needles (0.284 g, 85%) m.p. 155°. (Found: C, 46.9; H, 4.9; N, 8.9; P, 8.8 ; $C_{13}H_{17}Cl_2N_2O_2P$ requires C, 46.7; H, 5.0; N, 8.3; P, 9.2%).

NMR ($CDCl_3$, δ)



at 3.7, m, 10p;

-NH at 4.3, m, 1p;

-C=CH-CH_2- at 5.6, s, 1p;

Aromatic protons at 7.4, m, 5p.

Mass M^+ 334.

Synthesis of 2-(N-methylamino)-3-(β-chloroethyl)-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 11

A mixture of compound 8 (0.289 g, 0.001 mol) methylamine hydrochloride (0.112 g, 0.002 mol) and triethylamine (0.5 ml, 0.004 mol) in dichloromethane was stirred for 30 minutes. The reaction mixture was then poured into ice-water and extracted with dichloromethane. Dichloromethane layer was dried over anhydrous Na_2SO_4,

filtered and concentrated to yield compound 11. This after crystallisation from ethanol gave colourless needles (0.258 g; 90%), m.p. 144°. (Found: C, 50.5; H, 5.6; N, 9.5; P, 10.2; $C_{12}H_{16}ClN_2O_2P$ requires C, 50.3; H, 5.6; N, 9.8; P, 10.8%).

NMR ($CDCl_3$, δ) $-NH-C\underline{H}_3$ at 2.63, d, 3p;

$-N\underline{H}$ and $=CH-C\underline{H}_2-\overset{|}{N}-C\underline{H}_2-C\underline{H}_2Cl$ at 3.63, m, 7p;

$-\overset{|}{C}=C\underline{H}-CH_2$ at 5.5, s, 1p;

Aromatic protons at 7.4, m, 5p;

Mass M^+ 286.

Synthesis of 2-(∝-cyanoisopropoxy)-3-(p-anisyl)-6-(p-chlorophenyl)-3,4-dihydro-1,3,2-oxazaphosphorin--2-oxide 22

A mixture of compound 15 (0.369 g; 0.001 mol) and sodium cyanide (0.098 g; 0.002 mol) in dry acetone (15 ml) was refluxed on waterbath for 5-6 hours. Excess of acetone was removed and residue was poured into water. This was then extracted with dichloromethane. Dichloromethane layer was dried over anhydrous Na_2SO_4 filtered and concentrated under vacuum. The liquid obtained which solidified after two hours was crystallised from absolute ethanol in colourless plates (0.271 g, yield 65%), m.p. 140°. (Found: C, 57.7; H, 5.2; N, 6.9; P, 7.4; $C_{19}H_{20}ClN_2O_4P$ requires C, 57.4; H, 4.8; N, 6.7; P, 7.4%).

NMR ($CDCl_3$, δ) $-O-\overset{CH_3}{\underset{CH_3}{C}}-CH_3$ at 1.8, d, 6p;

$-OCH_3$ at 3.8, s, 3p;

$=C-CH-CH_2$ at 4.1, m, 2p;

$=C-CH-CH_2$ at 5.6, m, 1p;

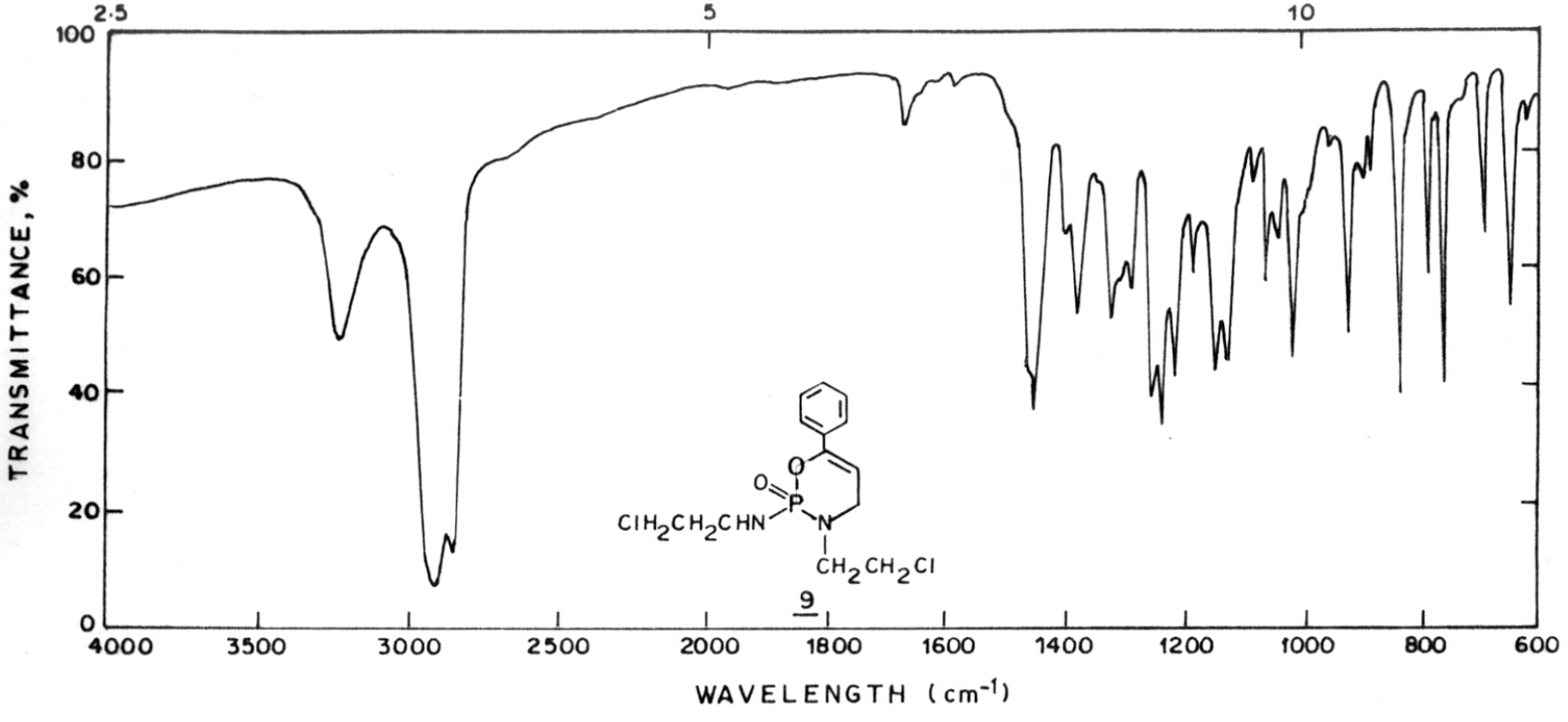
Aromatic protons at 6.8-7.6, m, 8p.

Mass M^+ 418.

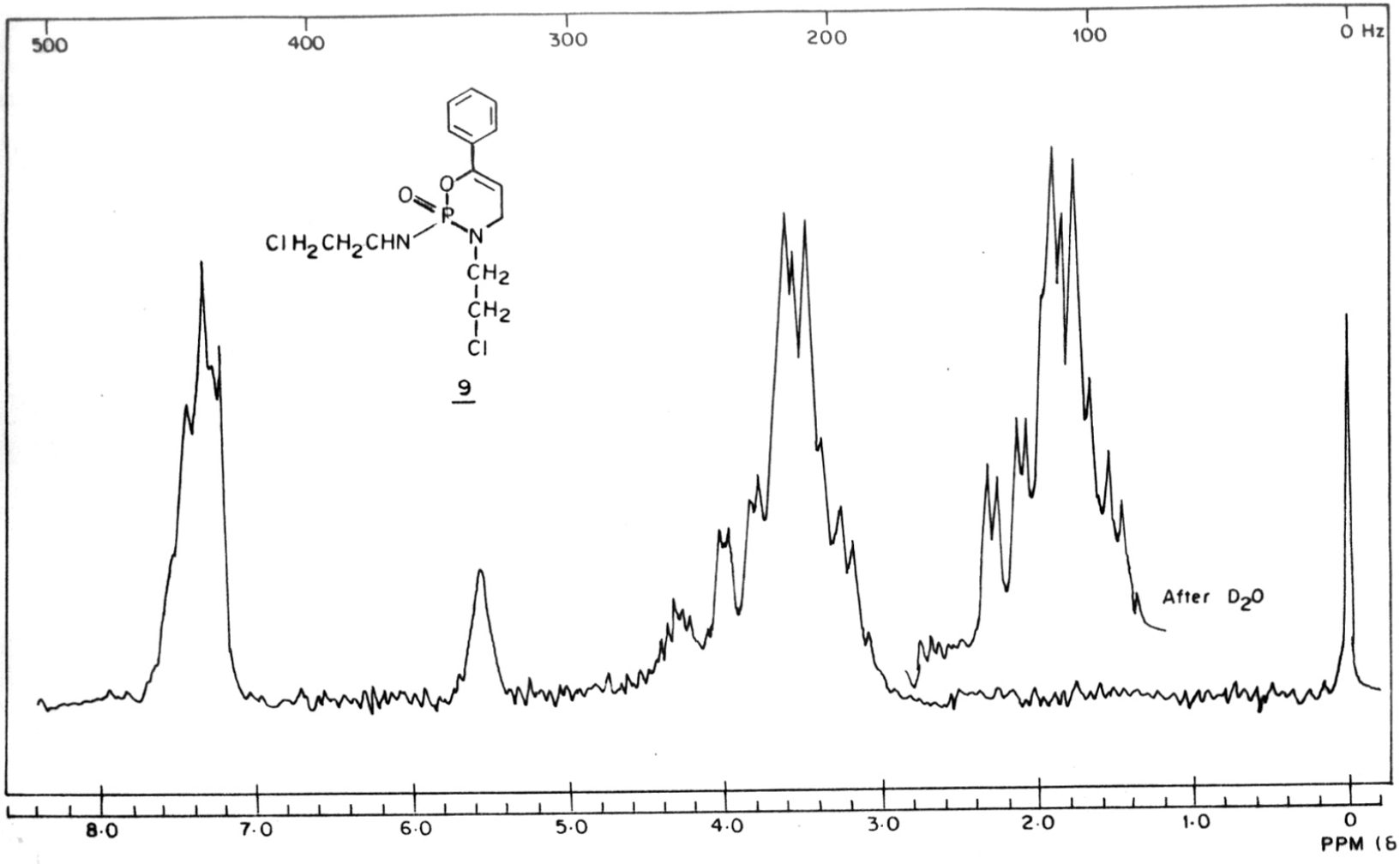
TABLE - 1

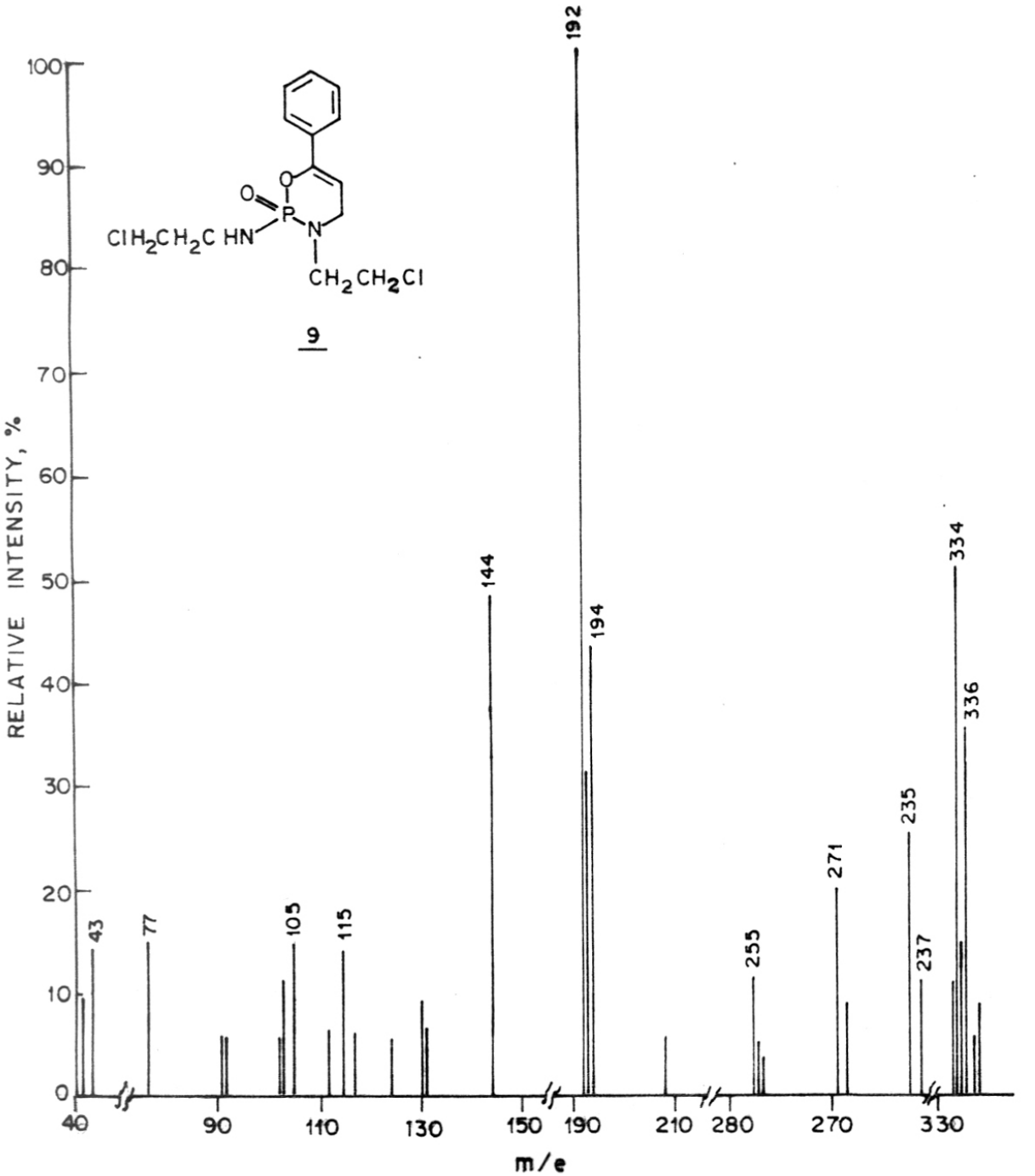
MPS, YIELDS AND ANALYTICAL DATA OF DIHYDRO-OXAZAPHOSPHORINS

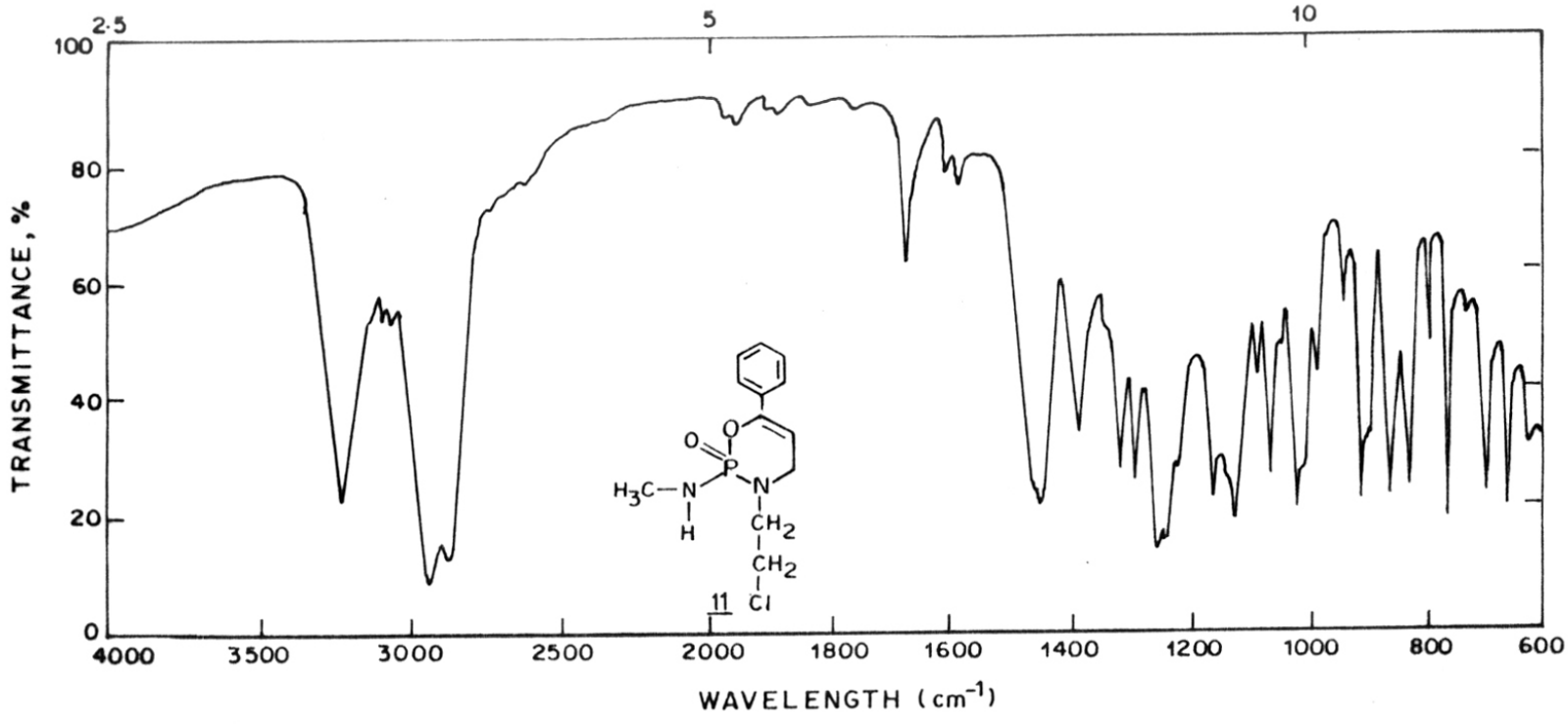
Compound No.	mp ^{o}C in	Yield in %		C	H	N	P
9	155	85	R	46.7	5.0	8.3	9.2
			F	46.9	4.9	8.9	8.8
11	144	90	R	50.3	5.6	9.8	10.8
			F	50.5	5.6	9.5	10.2
18	151	80	R	57.4	4.7	7.4	8.2
			F	57.0	4.6	7.1	7.8
19	153	82	R	57.4	4.7	7.4	8.2
			F	57.6	4.7	7.2	8.4
20	159	80	R	50.8	3.6	7.9	8.7
			F	51.2	3.8	8.2	8.3
22	140	65	R	57.4	4.8	6.7	7.4
			F	57.7	5.2	6.9	7.4


2.5
5
10
100
80
60
40
20
0
TRANSMITTANCE, %
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVELENGTH (cm-1)
ClH2CH2CHN
O
P
N
CH2CH2Cl

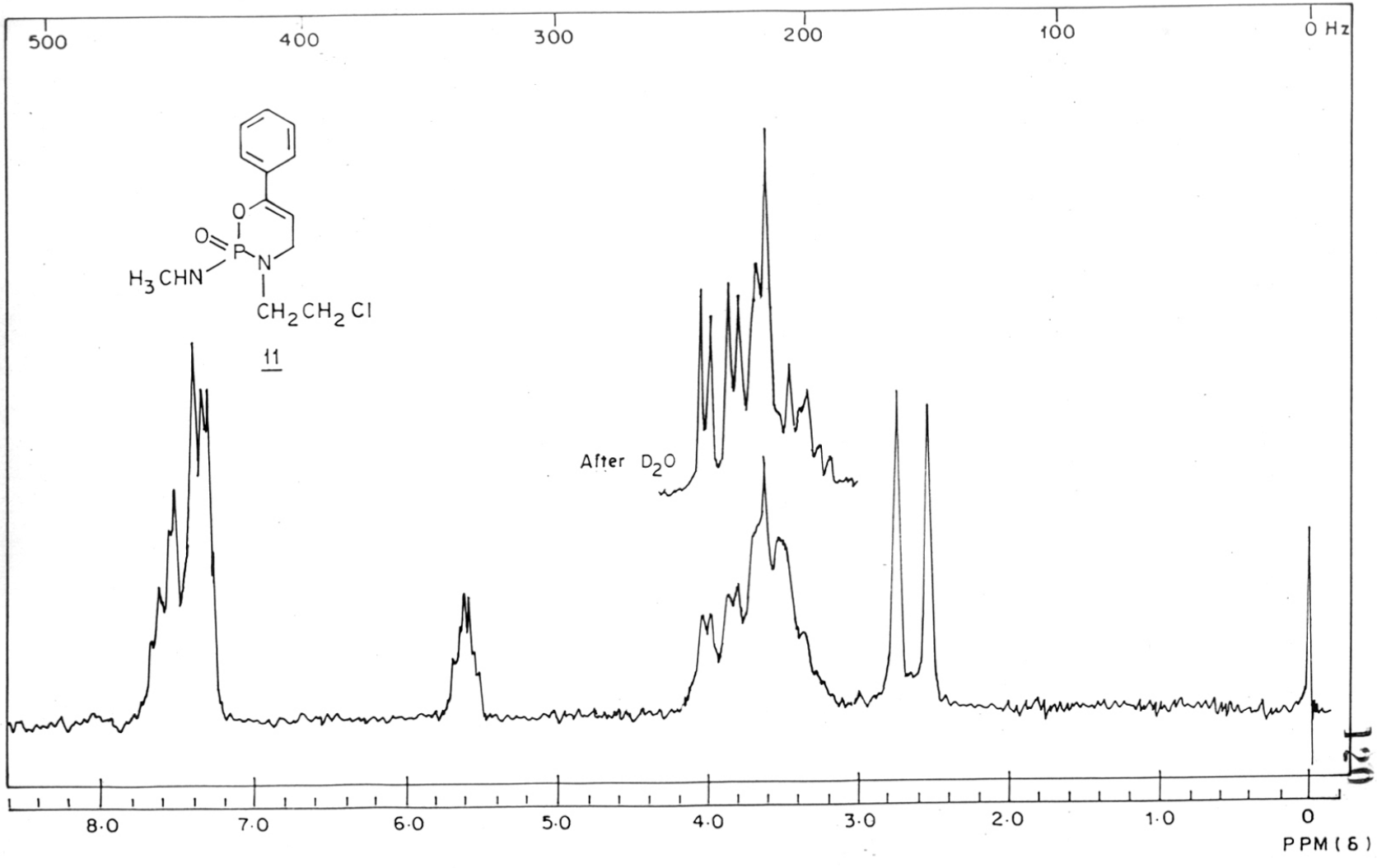
9

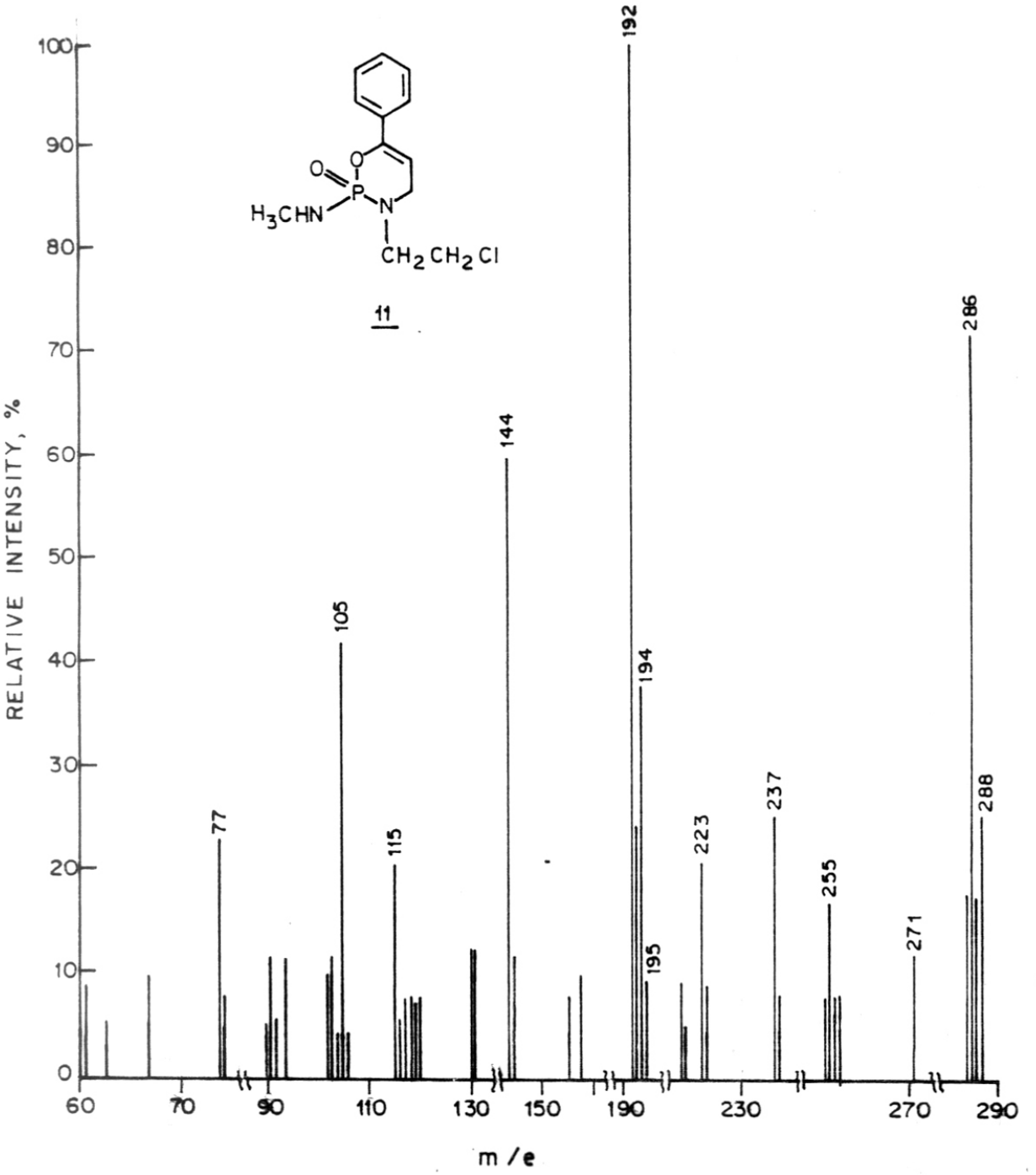

500
400
300
200
100
0 Hz
ClH2CH2CHN
CH2
CH2
Cl
9
After D2O
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)


100
90
80
70
60
50
40
30
20
10
0
RELATIVE INTENSITY, %
ClH2CH2C HN
O
P
O
N
CH2CH2Cl
9
192
144
194
334
336
235
271
237
255
105
115
43
77
40
90
110
130
150
190
210
280
270
330
m/e


2·5
5
10
100
80
60
40
20
0
TRANSMITTANCE, %
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVELENGTH (cm⁻¹)
O
O
P
H3C—N
H
N
CH2
CH2
Cl

11


500
400
300
200
100
0 Hz
O
O
P
N
H3CHN
CH2CH2Cl
11
After D2O
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)


192
286
144
105
194
77
115
223
237
288
255
271
195
RELATIVE INTENSITY, %
m / e
100
90
80
70
60
50
40
30
20
10
0
60
70
90
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130
150
190
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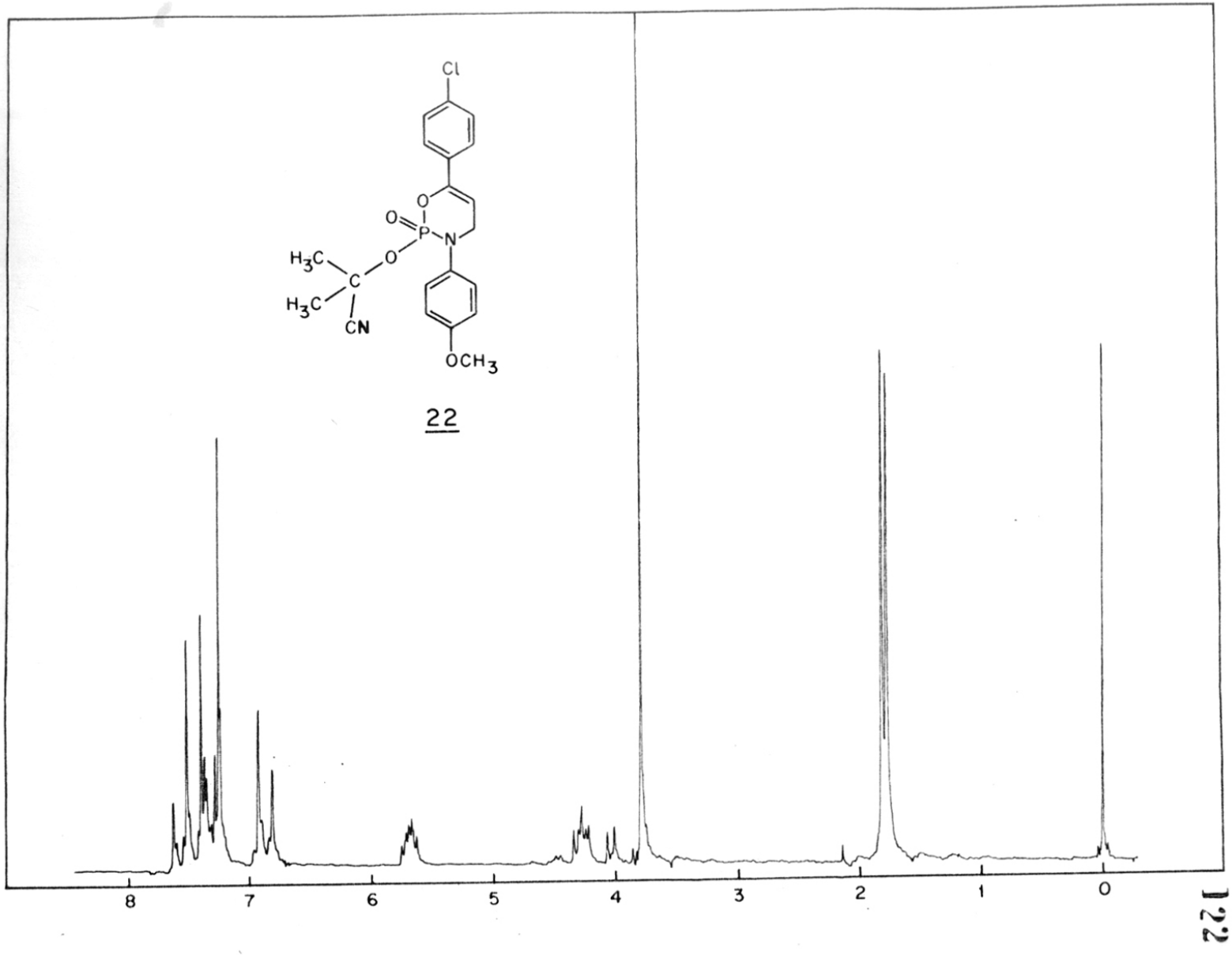
O
P
N
H3CHN
CH2 CH2 Cl

11



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J. Am. Chem.Soc., 100, 6388-94 (1978).

CHAPTER III

SPETRAL STUDIES OF 2-CHLORO-3,6-DISUBSTITUTED-3,4-DIHYDRO-1,3,2-OXAZAPHOSPHORIN-2-OXIDES.

[A] MASS SPECTRAL FRAGMENTATION MODES OF DIHYDRO-OXAZAPHOSPHORINS

INTRODUCTION

Information on the structure of organic compounds can be obtained by a variety of analytical techniques such as NMR and mass spectral data. During the last two decades there has been almost an explosive growth in the use of these techniques to solve structural problems of great complexity. Mass spectra of a variety of organic compounds have been examined both for the purpose of understanding the mechanism of fragmentation of molecular ions as also with a view to attempt the inverse operation of using the cracking pattern to determine the molecular structure[1,2,3]. The use of mass spectral data in the investigation of structures or providing support to structures determined by other physical methods such as IR, NMR spectra depends largely on empirical information provided by correlation studies on model known compounds. There are several investigations correlating certain fragmentations to the presence of a particular structural feature[1,4]. For example, cyclic molecules containing a double bond in a six membered ring have been shown to trigger Retro-Diel Alder Reactions producing a diene and a dienophilic ion. The presence of heteroatoms in the molecules like oxygen, nitrogen, sulfur or a metal leads to localization of charge which then directs further fragmentations (α or β-cleavages) with or without hydrogen transfer rearrangements.

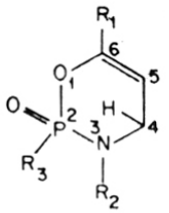
The rationalization of fragmentation processes in terms of classical theory of organic chemistry[1,4] are of value in solving problems of structure determination of closely related unknown compounds.

The present Chapter discusses the mass spectral fragmentation of substituted 3,4-dihydro-1,3,2-oxazaphosphorin-2-oxides (Chart 1). The fragmentation of these heterocyclic systems is of interest for the following reasons:-

(1) This phosphorus heterocyclic system is of interest in view of the presence of three different heteroatoms (oxygen, nitrogen and phosphorus) in close proximity in the ring. This should lead to wide variations in electronic charge distribution within the molecular ion under electron impact.

(2) Phosphorus containing antitumor drug cyclophosphamide and its metabolic products (having similar 1,3,2-oxazaphosphorinane cyclic skeleton) are at present being examined by the mass spectrometric technique[5]. Study of fragmentation of the dihydro and tetrahydro 1,3,2-oxazaphosphorin ring systems is, therefore, of interest for qualitative and quantitative identification.

(3) The substituted dihydro-1,3,2-oxazaphosphorine-2-oxide system may be studied vis-a-vis cyclohexene ring system in the carbocyclic series.



Compound No.	R_1	R_2	R_3
1	C_6H_4-Cl (p)	C_6H_5	Cl
2	C_6H_4-Cl (p)	C_6H_4-Cl (p)	Cl
3	C_6H_4-Cl (p)	$C_6H_4-OCH_3$ (p)	Cl
4	C_6H_4-Cl (p)	$C_6H_4-OCH_3$ (m)	Cl
5	C_6H_4-Cl (p)	$C_6H_4-OCH_3$ (o)	Cl
6	C_6H_4-Cl (p)	$C_6H_4-CH_3$ (p)	Cl
7	C_6H_4-Cl (p)	$C_6H_4-OCH_3$ (o)	N
8	C_6H_4-Cl (p)	$C_6H_4-OCH_3$ (p)	N
9	$C_6H_3-Cl_2$ (o, p)	C_6H_5	NH_2
10	$C_6H_3-Cl_2$ (o, p)	C_6H_5	$NHCH_3$
11	$C_6H_3-Cl_2$ (o, p)	$C_6H_4-CH_3$ (p)	Cl
12	$C_6H_3-Cl_2$ (o, p)	$C_6H_4-OCH_3$ (p)	Cl
13	$C_6H_3-Cl_2$ (o, p)	C_6H_5	Cl
14	$C_6H_3-Cl_2$ (o, p)	C_6H_4-Cl	Cl
15	C_6H_5	$C_6H_3-Cl_2$ (o, m)	Cl
16		$C_6H_4-OCH_3$ (p)	Cl
17	C_6H_5	CH_2CH_2Cl	Cl
18	C_6H_5	CH_2CH_2Cl	N
19	C_6H_5	CH_2CH_2Cl	$NHCH_3$
20	C_6H_5	CH_2CH_2Cl	$NHCH_2CH_2Cl$

CHART - 1

The carbocyclic system[6,7,8] has been extensively studied and it has been shown to undergo Retro-Diels Alder reaction (RDA). The mass spectral fragmentation modes of unsaturated six membered cyclic systems containing several heteroatoms has not been studied and their behaviour under electron impact is worth investigation. Before our results on this system are discussed, it may be pertinent to review RDA reactions in other systems.

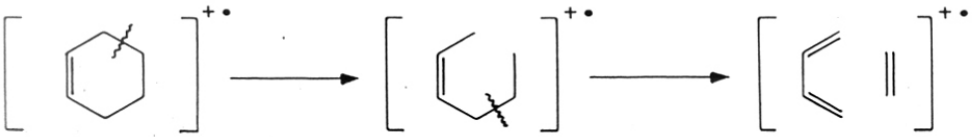
Many aspects of RDA reactions in carbocyclic systems have been thoroughly investigated[6,7,8]. Retro-Diels Alder fragmentation provides a unique method for structure determination in polycyclic compounds like steroids, terpenoids and natural products. The reaction has been shown to be highly stereospecific and it has been suggested that differences in the fragmentation of the stereoisomers could be used as a tool for the determination of ion structures[9].

The RDA reaction can occur by stepwise or concerted mechanism[6]. Based on the observed charge distribution between butadiene and/or ethylene, a stepwise mechanism was suggested by Djerassi et al[6 b,f]. The first step in the RDA fragmentation being allylic cleavage resulting in the formation of ring opened intermediate ion, followed by other simple cleavage resulting in the charged fragments. The abundance

of the two possible ions (butadiene and ethylene) (Chart 2, reaction 1) were found to correspond to the prediction of charge distribution based on Stevenson rule and energy consideration[6a]. The concerted mechanism resembles thermal electrocyclic RDA fragmentation (Chart 2, reaction 2). If electron impact RDA process occurs via concerted mechanism and if it follows the steric requirements of the thermally allowed process, then only cis-stereoisomers should be reactive. Mandelbaum et al[6e] have found that cis-isomers of tetra and pentacyclic diketones undergo RDA fragmentations, while the trans-isomers do not, and thus suggest that RDA process in these compounds occurs in one step by a concerted mechanism (Chart 2, reaction 2).

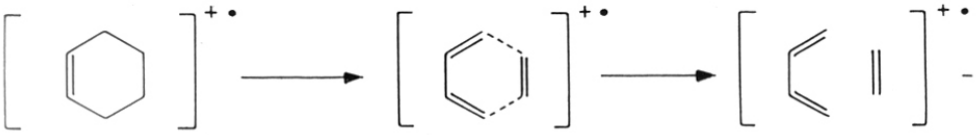
RDA fragmentations could be preceded by allylic isomerizations[8]. The allylic isomerization occurs in the molecular ion by 1,3-hydrogen shift or two successive 1,2 shifts. Unsubstituted and alkyl substituted cyclohexene systems have been shown to undergo several slow migrations of the double bond prior to RDA reactions[8a,8b]. Buchs et al[8c] have shown that in the mass spectra of alkyl substituted 2-cyclohexene-1-ol, formal RDA reaction operating from unrearranged molecular ion competes with RDA reaction proceeding from double bond migration. The competition between the two RDA processes has been reported to be dependent on the size and position of the olefinic moiety expelled[8c] (Chart 2, reaction 3).

STEPWISE RDA FRAGMENTATION



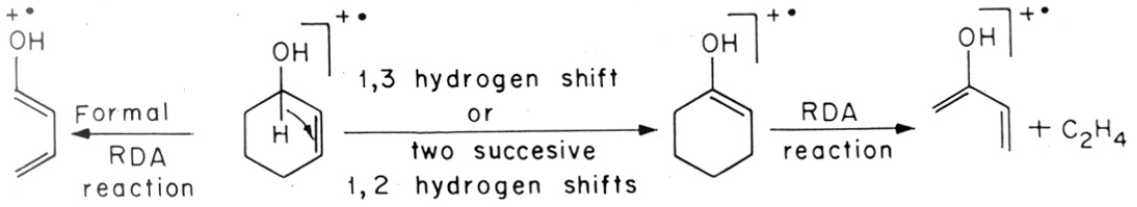
-----(1)

CONCERTED RDA FRAGMENTATION



-----(2)

ALLYLIC ISOMERISATIONS

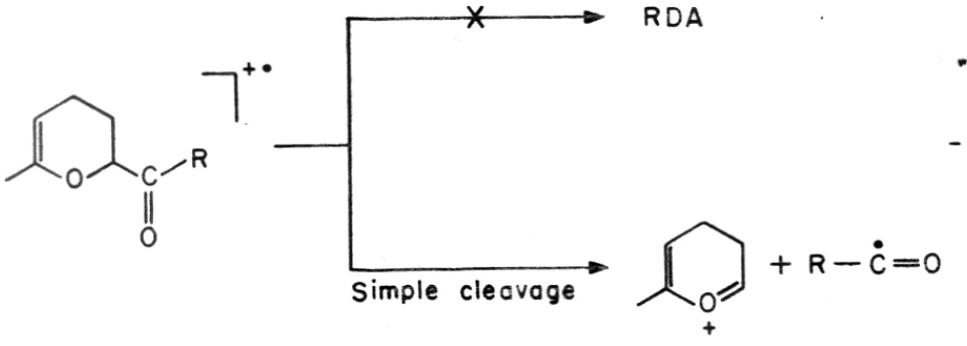


------(3)

CHART - 2 (Contd.)

Competition between RDA reaction and simple cleavage processes has been reported in the mass spectra of 2-substituted-2,3-dihydro-4H-pyrans[10]. It has been reported that electron donating substituents favour RDA reaction whereas electron attracting substituents like carbonyl in ester or ketone inhibit this reaction. This has been ascribed to the localization of charge on carbonyl oxygen by removal of non-bonding 'p' electron and weakening of C_2-C_7 bond, the charge being carried by α-cleavage products. In the spectra of electron donating alkoxy ethers removal of an electron from ether oxygen strengthens C=O bond and both RDA and α-cleavage products compete in the ether series (Chart 2, reactions 4 and 5).

The effect of substituent on the relative ion abundance of diene and ene fragments has been reported[6a,11] and the results indicate that the fragment of lower ionization potential carries the charge.



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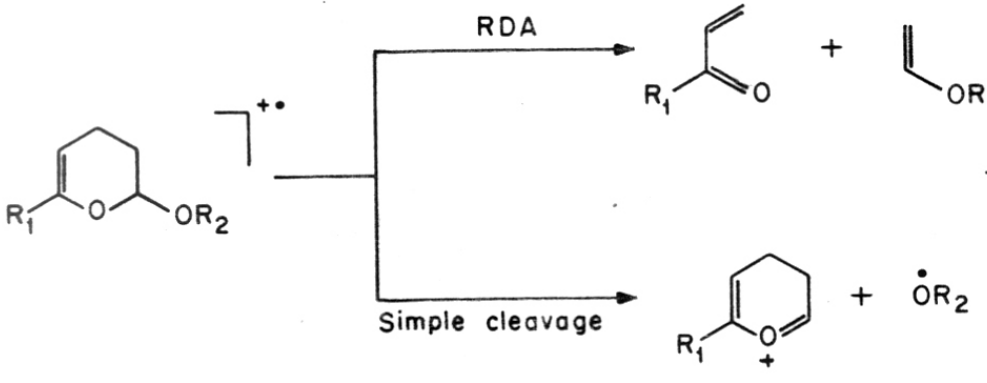


----- (5)

CHART - 2

PRESENT WORK

The relative abundance of the characteristic fragment ions in the mass spectra of substituted dihydro-1,3,2-oxazaphosphorinanes 1 to 20 (Chart 1) are reported in Table 1. All the compounds show abundant molecular ions.

One of the significant fragmentation modes of the molecular ion is the loss of substituted phenyl vinyl ketone (R_1-C(=O)-CH=CH_2) by Retro-Diels Alder reaction resulting in the formation of 'ene' fragment ion A (iminophosphorinanes). No metastable peak is observed for this process. This RDA fragmentation is illustrated for the compound 2-chloro-6-(p-chlorophenyl)-3-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin--2-oxide (1)(Fig. 1) (Chart 3). The relative intensity of this 'ene' fragment varies within wide limits being the base peak in the compounds 8,9,10,11 and 12 (which contain N-phenyl substituent), whereas it is absent in the compounds 17, 18, 19 and 20 (Table 1) bearing N-CH_2CH_2Cl substituent. The higher stability of 'ene' fragment A containing N-phenyl substituent could be due to formation of ylid ' (i.e. $\overset{+}{P} - \overset{-}{\ddot{N}} - C_6H_5$) type of bond and/or formation of cyclic intermediates formed by bond formation between phosphorus and phenyl ring[12,13]. Phenyliminophosphoranes are known to be stable to electron impact exhibiting strong molecular ions. The stability could be due to ylid[14] type of phosphorus-nitrogen bond which is known to be isoelectronic

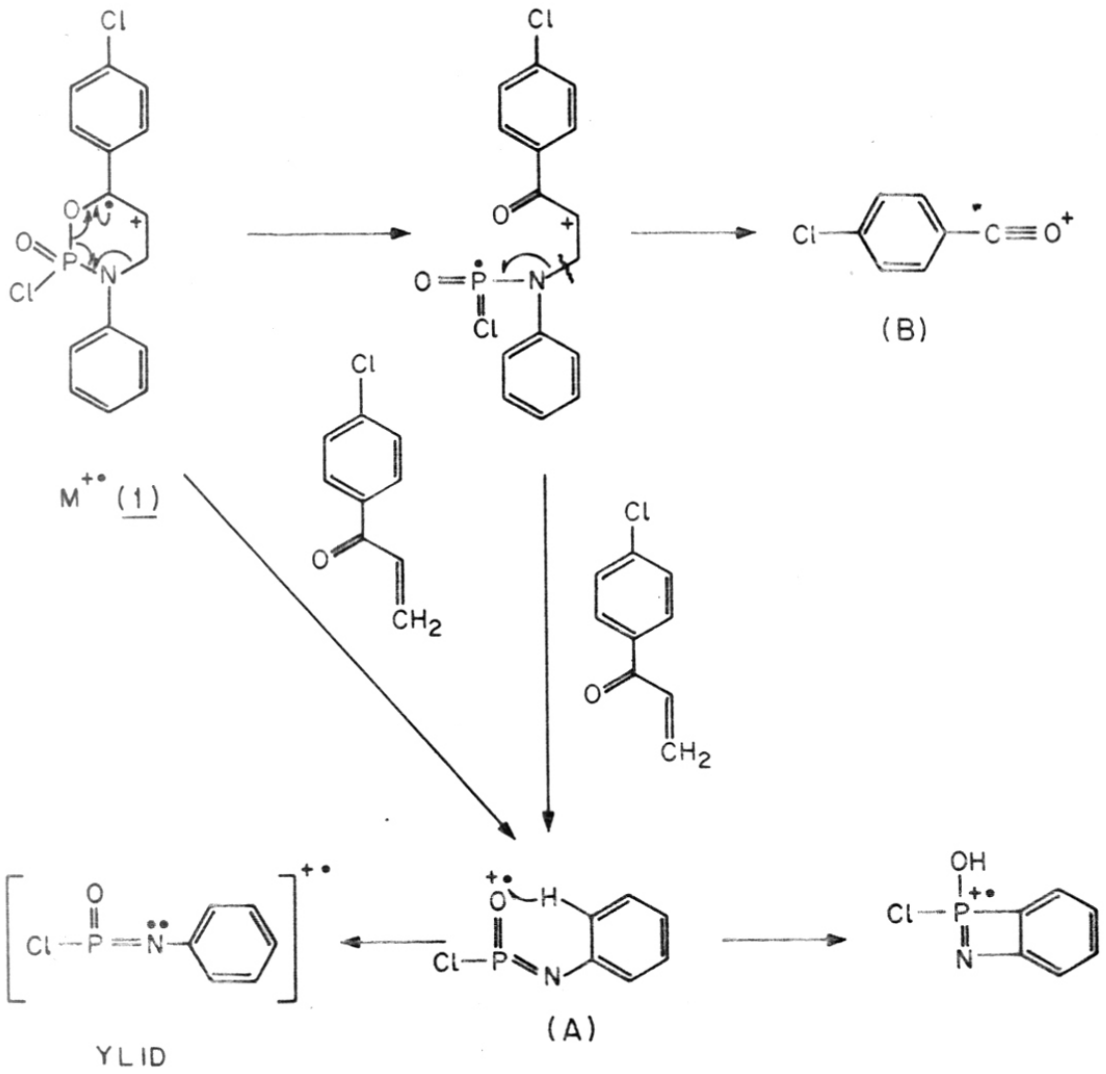


CHART - 3 : RDA FRAGMENTATION OF SUBSTITUTED 1,3,2-OXAZAPHOSPHORIN-2-OXIDES.

with phosphonium ylid bond[14]. The propensity of phosphorus to form phenylphosphonium cyclic intermediate ions has been reported in the mass spectral fragmentation of substituted 1,3,2-dioxaphosphorinanes[12] and phosphochloridothioate[13]. Formation of such type of cyclic intermediates is not possible in the compounds 17 to 20 and hence RDA fragmentation is not observed. This RDA process mostly occurs by stepwise mechanism. The initial step being the allylic cleavage which opens the ring followed by 'ene' fragment ion A. Observation of significant substituted benzoyl ion by simple cleavage of C_5-C_6 bond in the ring opened intermediate supports the stepwise mechanism (Chart 3).

In the carbocyclic system there are several examples of RDA fragmentation processes occurring after 1,3 hydrogen shift. These non-classical RDA reactions often compete with classical processes proceeding from unrearranged molecular ions. The present heterocyclic system also shows this type of behaviour. The mass spectra of the compounds 1, 2, 3 and 4 show strong peak (base peak) corresponding to loss of PO_2Cl from the molecular ion. This loss can occur directly from the unrearranged molecular ion but most probably it occurs as RDA fragmentation which is preceded by 1,3-hydrogen shift (Chart 4) or two consecutive 1,2-hydrogen shifts. The fragmentation is illustrated for the compound 2-chloro-6-(2,4-dichlorophenyl)-3-phenyl-3,4-dihydro-1,3,2-oxaza-

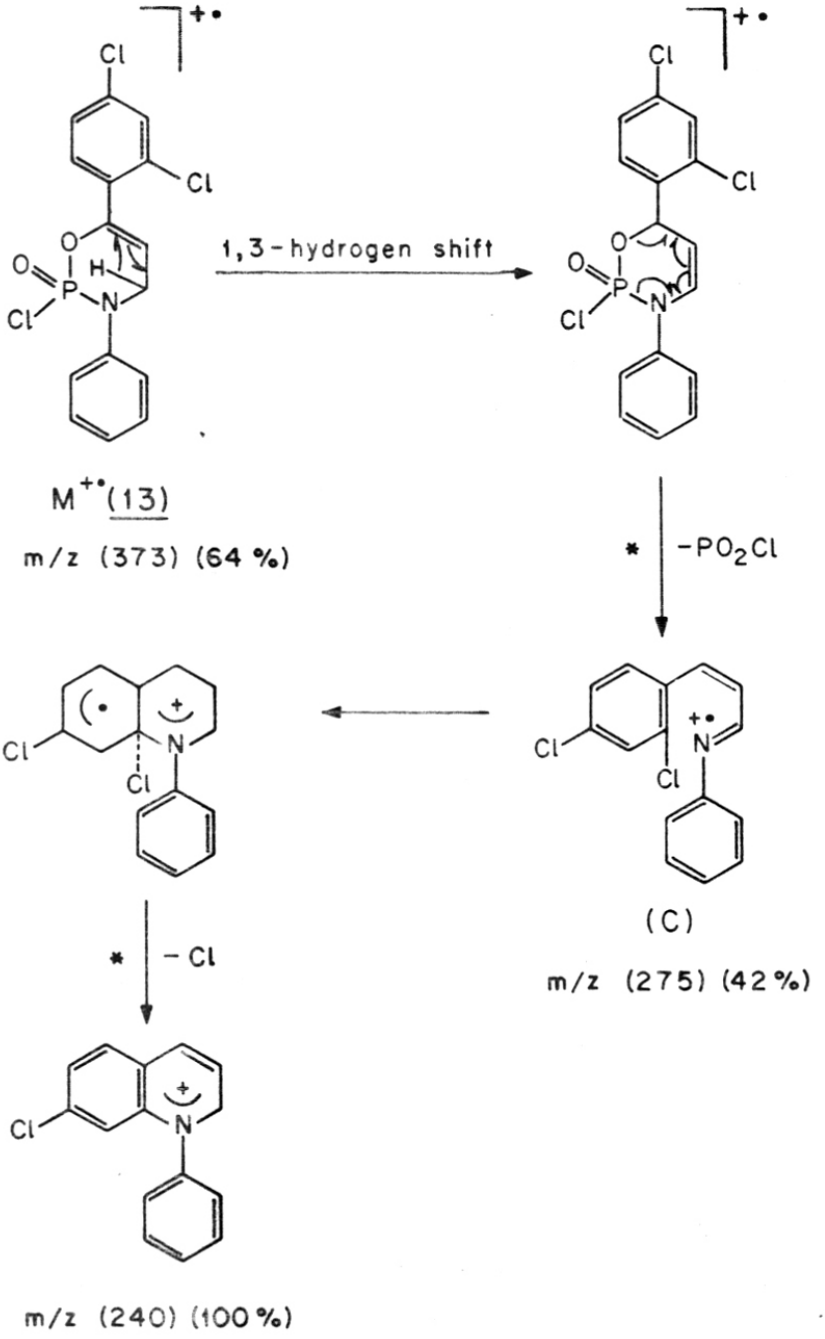


CHART-4 : RDA FRAGMENTATION PRECEDED BY ALLYLIC REARRANGEMENT.

phosphorin-2-oxide 13 (Fig.2). The relative importance of the two RDA processes was studied at different electron energies in compounds 13 and 16. At lower electron energies (12 eV) the ratio,

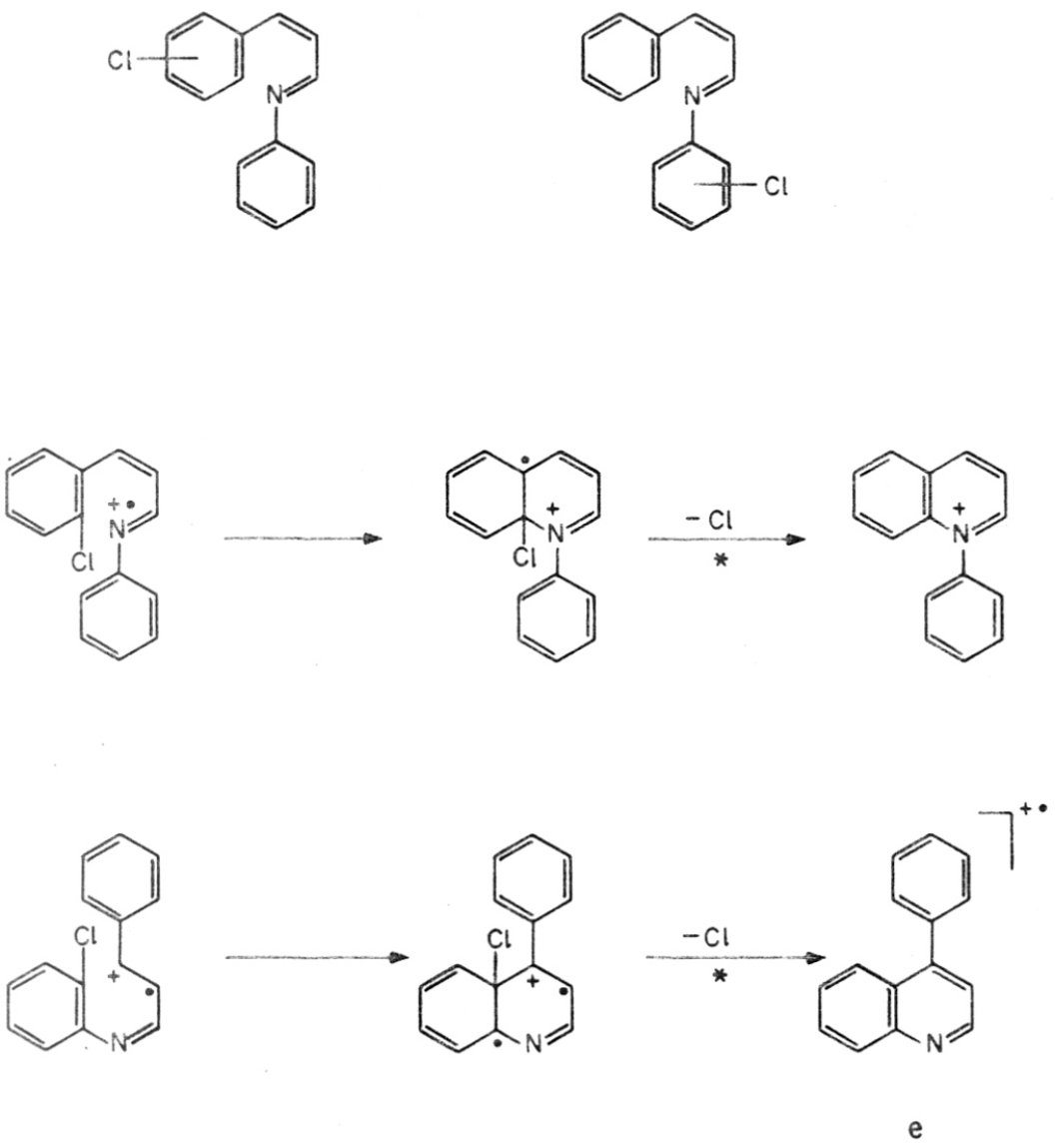
$$\frac{Z_C}{Z_A} = \frac{\%\text{ of Schiff base ion C}}{\%\text{ of 'ene' ion A}},$$

which is a measure of relative rate constants, was found to increase from 0.5 to 2 in 2-chloro-3-(2,4-dichlorophenyl) -6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 13 and from 2.7 to 3.8 in 2-chloro-6-(p-anisyl)-3-furyl-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 16. This shows that the RDA process producing Schiff base ion C is a slower process requiring less activation energy than that producing ion B. The observation of a broad metastable peak for the formation of ion C also supports the contention that the process is preceded by 1,3-hydrogen shift (Chart 4).

The further fragmentation of cycloreversion ion C is of interest and occurs predominantly by metastable loss of hydrogen atom in all the compounds. In the spectra of compounds 1 to 14, the α, β-unsaturated Schiff's base ion C shows loss of chlorine atom and is most significant in compounds 9 to 14, which contain chlorine atom in ortho and para- positions, are involved in the further fragmentation of this ion and is supported by metastable peak. The

first step being the electrophilic attack by the imino-nitrogen on the ortho-position of the phenyl ring resulting in the formation of dihydro-N-arylquinoline intermediate followed by elimination of ortho-substituent (Chart 5). Recently, Grützmacher et al[15] have shown operation of similar substitution-elimination processes in the spectra of benzalacetone, o-substituted benzoyl pyridine and stilbazole. Also in support of the above mechanism, it may be pointed out that similar quinoline ion structures have been ascribed to $(M-H)^+$ ions in the spectra of α, β-unsaturated oximes[16].

Another mechanism which is conceivable is that ortho-hydrogen of the N-phenyl ring is involved in the fragmentation of ion C. This elimination of ortho-hydrogen is favoured by electrophilic attack by the carbonium ion centre resulting in the intermediate formation of 4-aryl dihydroquinoline ion (e) (Chart 5). This mechanism is similar to solution chemistry behaviour. Recently, Shono et al[17] have described a versatile synthesis of tetrahydroquinoline in which carbonium ions formed as intermediates in the reactions of iminium ions with electron rich nucleophiles like styrene, cyclise to tetrahydroquinoline in the presence of Lewis acid.



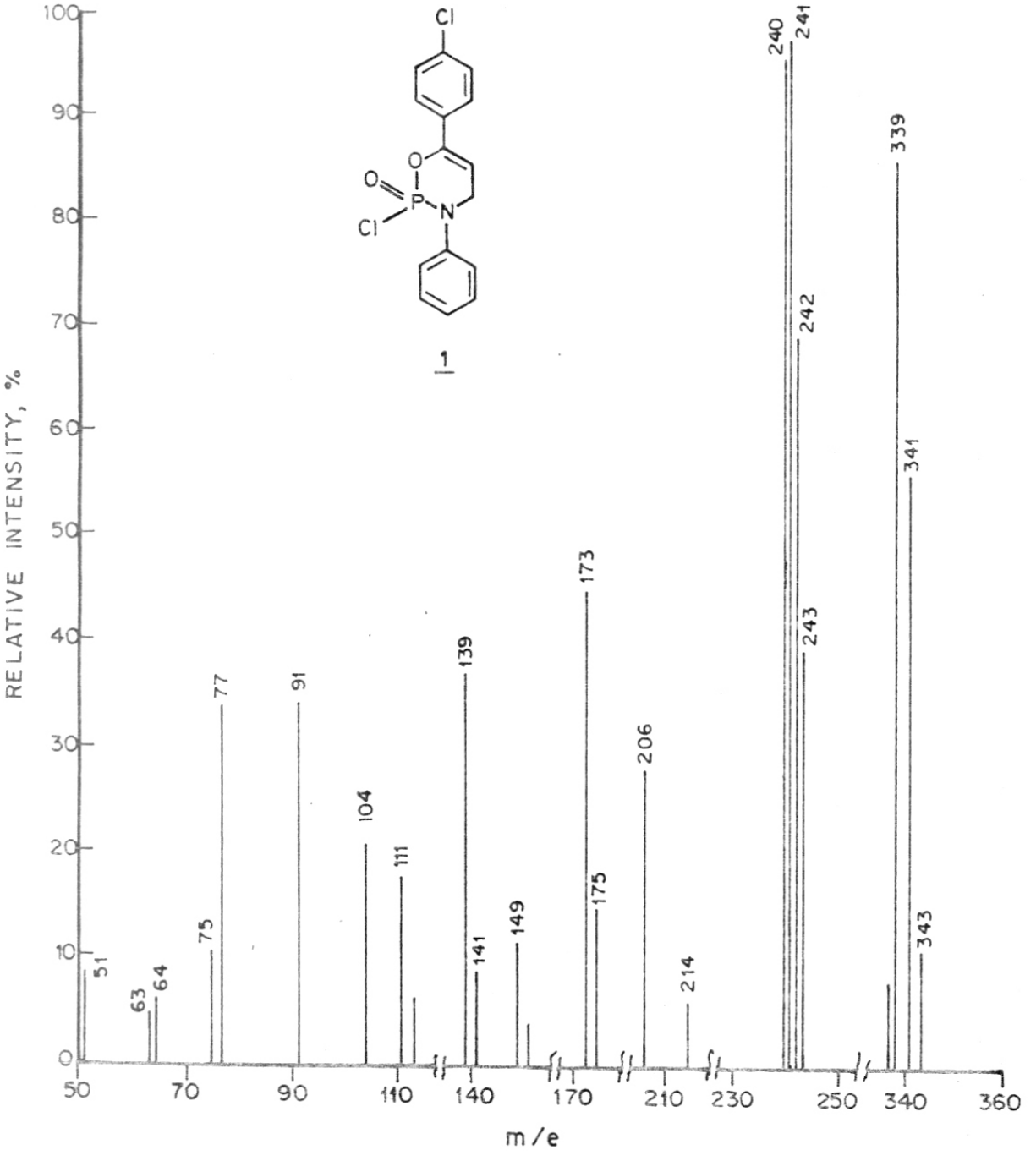
e

CHART-5 : INTRAMOLECULAR CYCLISATION / ELIMINATION REACTIONS.

In order to gain more information on the mechanisms of intramolecular cyclisation-elimination reactions chloro substituted (ortho, meta and para) α, β-unsaturated Schiff bases were examined. $(M-Cl)^+$ ion was most significant in the o-chlorocinnamylidene aniline whereas it was less significant in the corresponding meta and para isomer. Similarly, $(M-Cl)^+$ ion was about 6% in the cinnamylidene-o-chloroaniline and absent in cinnamylidene-m-chloroaniline and cinnamylidene-p-chloroaniline. This indicates that cyclisation is strongly favoured by charge localisation on the imino nitrogen whereas it is of less importance when electrophilic attack takes place by carbonium ion on the ortho-position. This result is expected in view of the fact that under electron impact, probability of the charge being localised on nitrogen is much more than that on the carbon.

TABLE - 1 - Relative abundance of characteristic ions in the mass spectra of substituted 3,4- dihydro-1,3,2-oxazaphosphorin-2-oxides

Compd. No.	$M^{+\cdot}$ m/e	% I	"ene" ion A		Aroyl ion B		Heterodiene ion C		$\overset{+}{C}$ - H		$\overset{+}{C}$-Cl	
			m/e	% I	m/e	% I	m/e	% I	m/e	% I	m/e	% I
1	339	86	173	40	139	38	241	100	240	98	206	28
2	373	38	207	40	139	40	275	100	274	33	240	38
3	369	34	203	70	139	14	271	100	270	80	236	0
4	369	17	203	34	139	54	271	100	270	50	236	8
5	369	45	203	25	139	12	271	12	270	6	236	0
6	353	19	187	17	139	16	255	36	254	20	220	2
7	369	100	210	82	139	29	271	11	270	16	236	0
8	376	36	210	100	139	6	271	11	270	3	236	0
9	354	33	154	100	173	15	275	14	274	22	240	52
10	368	50	168	100	173	21	275	18	274	28	240	64
11	387	53	187	100	173	20	289	55	288	24	254	51
12	403	30	203	100	173	10	305	47	304	0	270	0
13	373	64	173	84	173	84	275	42	274	33	240	100
14	407	72	207	15	173	40	309	52	308	20	274	100
15	373	50	241	39	105	88	275	61	274	100	240	15
16	325	25	203	36	95	20	227	100	226	10	192	0
17	291	54	159	0	105	67	193	27	192	100	158	6
18	298	45	166	0	105	52	193	55	192	63	158	37
19	286	72	140	0	105	42	193	34	192	100	158	10
20	334	51	202	0	105	14	193	34	192	100	158	0


RELATIVE INTENSITY, %
m/e
100
90
80
70
60
50
40
30
20
10
0
50
70
90
110
140
170
210
230
250
340
360
51
63
64
75
77
91
104
111
139
141
149
173
175
206
214
240
241
242
243
339
341
343
Cl
O
P
N
Cl
O

1

FIG. – 1.

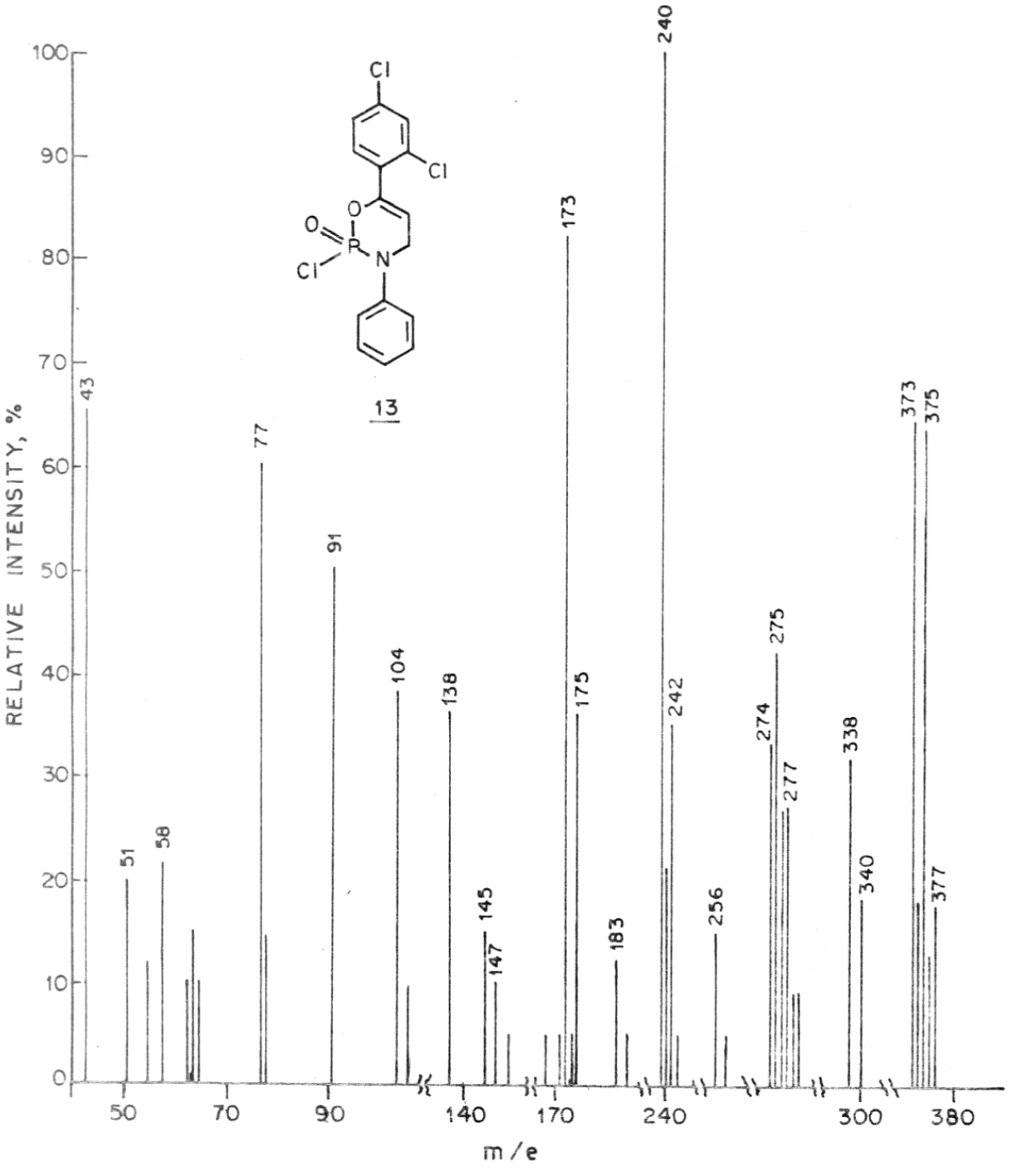

RELATIVE INTENSITY, %
m/e
13
43
51
58
77
91
104
138
145
147
173
175
183
240
242
256
274
275
277
338
340
373
375
377

FIG.- 2 .

(B) NMR SPECTRAL ANALYSIS OF DIHYDRO-OXAZAPHOSPHORINS

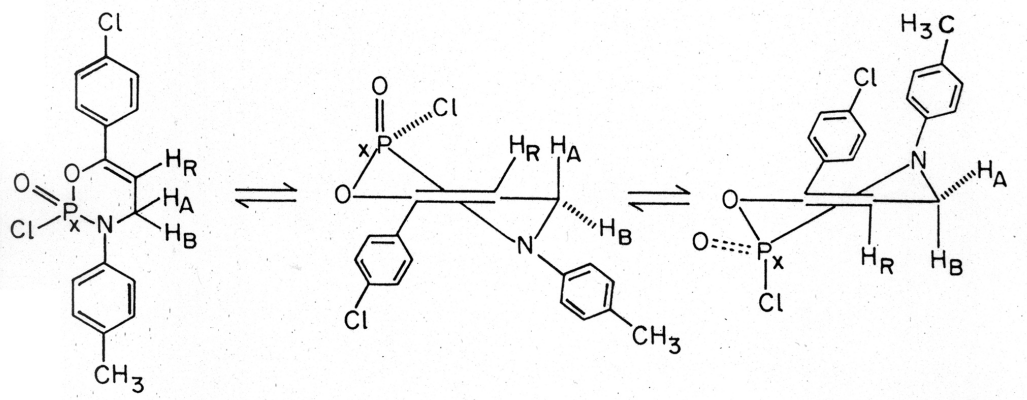


Fig. 3

NMR spectra of all the dihydro-oxazaphosphorins on 60 MHz (Fig. 4) show a complex pattern and spectra could not be analysed properly. 80 MHz (Fig. 5) and 100 MHz spectra recorded on a Varian FT 80A and Jeol FX 100 NMR spectrometers respectively, gave useful information and helped us to analyse the spectra.

The multiplicity of signals in the region 4.0 to 6.0 δ is suspected to be either due to two quasi chair conformers A_1 and A_2 or due to phosphorus couplings. To rule

out one of the possibilities, the spectrum of compound 6 was recorded at different spectrometer frequencies (60, 80 and 100 MHz). All the spectra did not show any change in line positions of the signals which showed that compound 6 does not have any conformers but the multiplicity is due to phosphorus couplings. The analysis of the PMR spectrum and ^{31}P NMR spectrum (36.4 - MHz) confirmed the latter argument.

The signals in the region 4.4 to 5.6 belong to a four spin system (ABRX) (Fig. 6). Methylene protons in the region 4.4 to 5.2 δ (show fifteen lines) constitute the AB part, the vinylic proton (multiplet, centered at 5.6 δ) is the R part, and phosphorus is the X part.

Proton H_A will couple with protons H_B, H_R and with phosphorus through nitrogen. Similarly, proton H_B will couple with protons H_A, H_R and with phosphorus. AB part in all should show sixteen signals but only fifteen signals are observed which may be due to overlapping of two signals. Irradiation at the centre of multiplet around 5.6 δ simplified the spectrum (i.e. the ABRX system has now become an ABX system) (Fig. 7). AB part showing eight signals, comprises of two AB type quartets (1,2,4,7 and 3,5,6,8) from which J_{AB} can be obtained. Analysis has been carried out on this decoupled spectrum

according to a method given by Abraham[18] and J_{AX}, ν_A and ν_B were calculated. These values are given below:

$J_{AB} = 16.9$, $J_{AX} = 3.4$, $J_{BX} = 24.1$

$\nu_A = 344.8$ Hz and $\nu_B = 327.7$ Hz where

ν_A = chemical shift of A,

ν_B = chemical shift of B.

Multiplicity of H_R (Fig. 8) can be explained as follows. H_R couples with H_A, H_B and phosphorus through oxygen as in the case of dioxaphosphoranes[19]. An attempt was made to find J_{RX} by irradiating the AB part (Fig. 9). This resulted in a doublet with separation of 2.7 Hz which is in agreement with the observed J (P-O-C-CH). J_{AR} and J_{BR} can be directly obtained from the spectrum (Fig. 6).

^{31}P NMR spectrum of compound 6 (Fig. 10) was recorded on a Brucker WH-90 spectrometer operating at 36.4 MHz for ^{31}P. The undecoupled spectrum shows two broad signals. The fine splittings could not be observed. These two broad signals after broad band decoupling show singlet.

Of the two possible conformers A_1 and A_2, the conformer A_1 may be more stable due to axial P=O bond. The large difference between the coupling constants J_{AX}

(3.4 Hz) and J_{BX} (24.1 Hz) can be explained on the basis of dihydral angle. The proton H_B (as shown in Fig. 3, A_1) is anti to P-N bond which will have a large coupling constant. H_A will be gauche to P-N bond which will have a small coupling constant.

The values of the coupling constants are given in the Table 2.

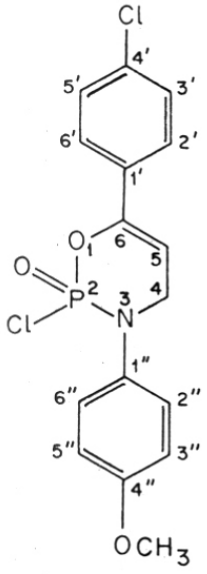
TABLE - 2

Protons	A	B	R	X
H_A	-	16.9	3.9	3.4
H_B	16.9	-	4.4	24.1
H_R	3.0	4.4	-	2.7

Interpretation of ^{13}C NMR spectra

Information obtained from PMR studies encouraged us to study coupling of phosphorus with various carbons in the dihydro-oxazaphosphorin ring systems.

^{13}C NMR spectra were recorded on Varian FT 80A NMR spectrometer operating at 20 MHz frequency. All the spectra were scanned in $CDCl_3$.



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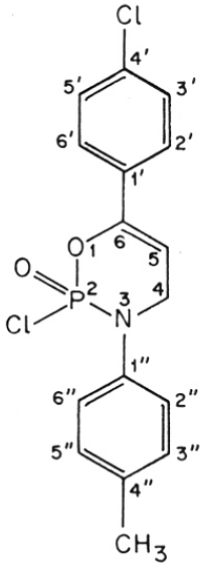
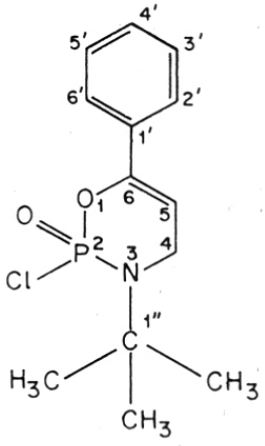


6



21

^{1}H broad band decoupled ^{13}C spectrum of compound 6 is given in Fig. 11. Comparison of ^{1}H broad band decoupled and off-resonance spectrum gave the following information.

Methyl carbon comes at 20.72 ppm. Methylene carbon (C-4) comes at 50.46 ppm as a doublet with coupling constant 2.15 Hz. Similarly vinylic carbon (C-5) comes at 100.86 ppm as a doublet with a separation of 10.23 Hz (J = 10.23 Hz).

Rest of the signals could not be assigned properly due to complexity. To make unambiguous assignments, ^{13}C NMR of 3 (Fig. 13) and 21 (Fig. 14) were studied, where the assignments are straightforward.

From the spectrum of compound 21 which does not have any phenyl substituent on nitrogen, one can easily assign C-6 carbon, position of which may not be expected to change in compounds 3 and 6. In compound 21 C-6 comes at 148.1 ppm as a doublet (J = 11.25 Hz). Hence the signals at 147.35 ppm for compound 6 (J = 9.95 Hz) and 147.35 ppm for compound 3 (J = 10.2 Hz) can be assigned for C-6 carbon.

By comparing the spectra of compounds 3 and 6, we could sort out the aromatic carbons of the two phenyl rings. Chemical shifts of the carbons of the chlorosubstituted phenyl ring are expected to be same. Hence, the signals at 125.8 ppm, 128.7 ppm, 130.35 ppm and 135.43 ppm of compound 6, can be assigned to C-3', C-5'; C-2', C-6'; C-1' (J = 8.68 Hz) and C-4' respectively.

In the spectrum of compound 3 (Fig. 13) it was observed that C-4" and C-3", C-5" showed coupling with phosphorus of the order of 2.15 Hz and 1.73 Hz respectively. C-4" has a pronounced downfield shift

158.76 ppm and C-3", C-5" have pronounced upfield shift 114.77 ppm compared to compound 6. So in compound 6 doublet at 130.03 ppm (J = 1.53 Hz) and doublet at 137.09 ppm (J = 2.01 Hz) can be assigned to C-3", C-5". and C-4" respectively. C-2" and C-6" come together at 124.83 ppm as a doublet (J = 4.54 Hz). The only remaining carbon C-1" can be assigned to a signal at 136.80 ppm which shows small splitting of 0.73 Hz. A similar splitting is observed for C-1" in compound 21.

The chemical shifts are given in Table 3 and ^{13}C-^{31}P coupling constants in Table 4.

TABLE - 3

CHEMICAL SHIFT* IN PPM

Carbon No.	Compound 3	Compound 6	Compound 21
C-4	50.95	50.46	57.78
C-5	100.88	100.86	100.97
C-6	147.36	147.35	148.10
C-1'	130.41	130.36	131.82
C-2',C-6'	128.70	128.69	128.34
C-3', C-5'	125.80	125.81	124.34
C-4'	135.44	135.43	129.16
C-1"	131.94	136.80	43.66
C-2",C-6"	126.84	124.83	-
C-3",C-5"	114.77	130.03	-
C-4"	158.76	137.09	-
CH_3	-	20.72	28.91
OCH_3	55.32	-	-

*Chemical shifts were measured with respect to $CDCl_3$ signal which comes at 76.9 ppm for TMS.

TABLE - 4

^{13}C-^{31}P COUPLING CONSTANTS IN HERTZ

Carbon No.	Compound 3	Compound 6	Compound 21
C-4	2.81	2.15	1.94
C-5	10.16	10.23	11.79
C-6	10.2	9.95	11.25
C-1'	8.75	8.68	7.79
C-1"	-	0.72	0.74
C-2",C-6"	4.95	4.54	-
C-3",C-5"	1.73	1.53	-
C-4"	2.15	2.01	-

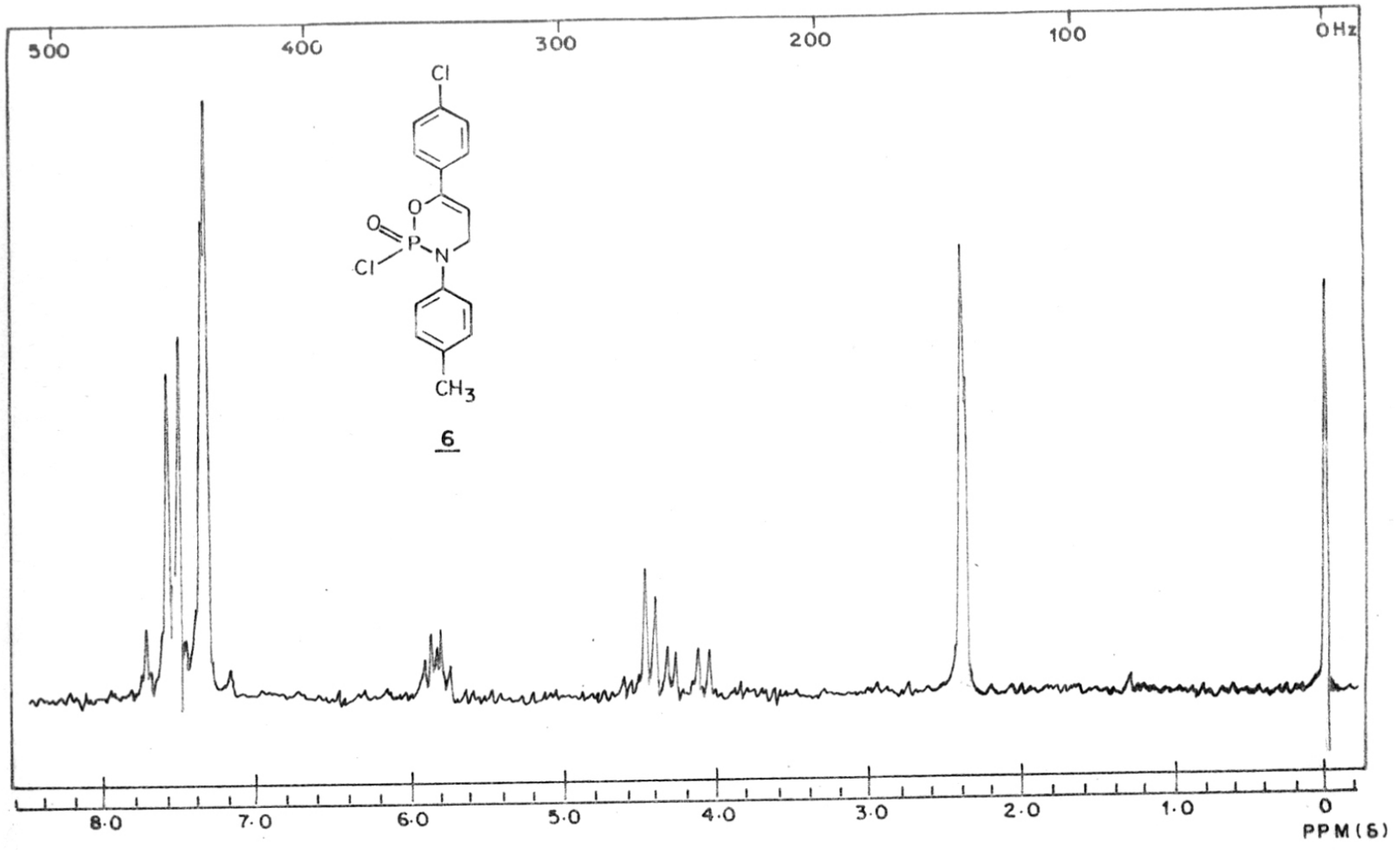

500
400
300
200
100
0 Hz
Cl
O
O
P
N
Cl
CH3
6
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG. – 4 .

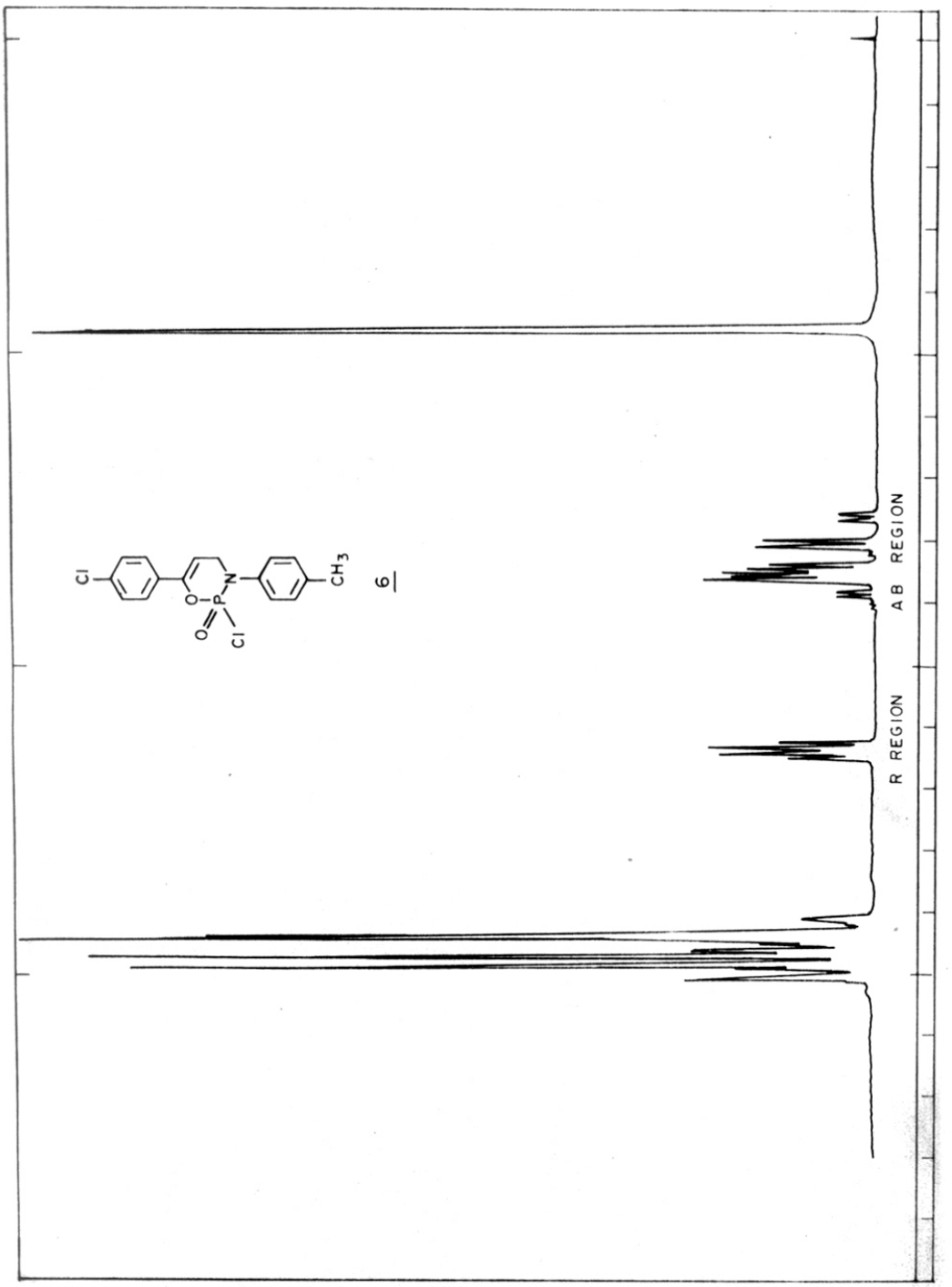


FIG. 5. 80 MHz PMR SPECTRUM OF COMPOUND 6

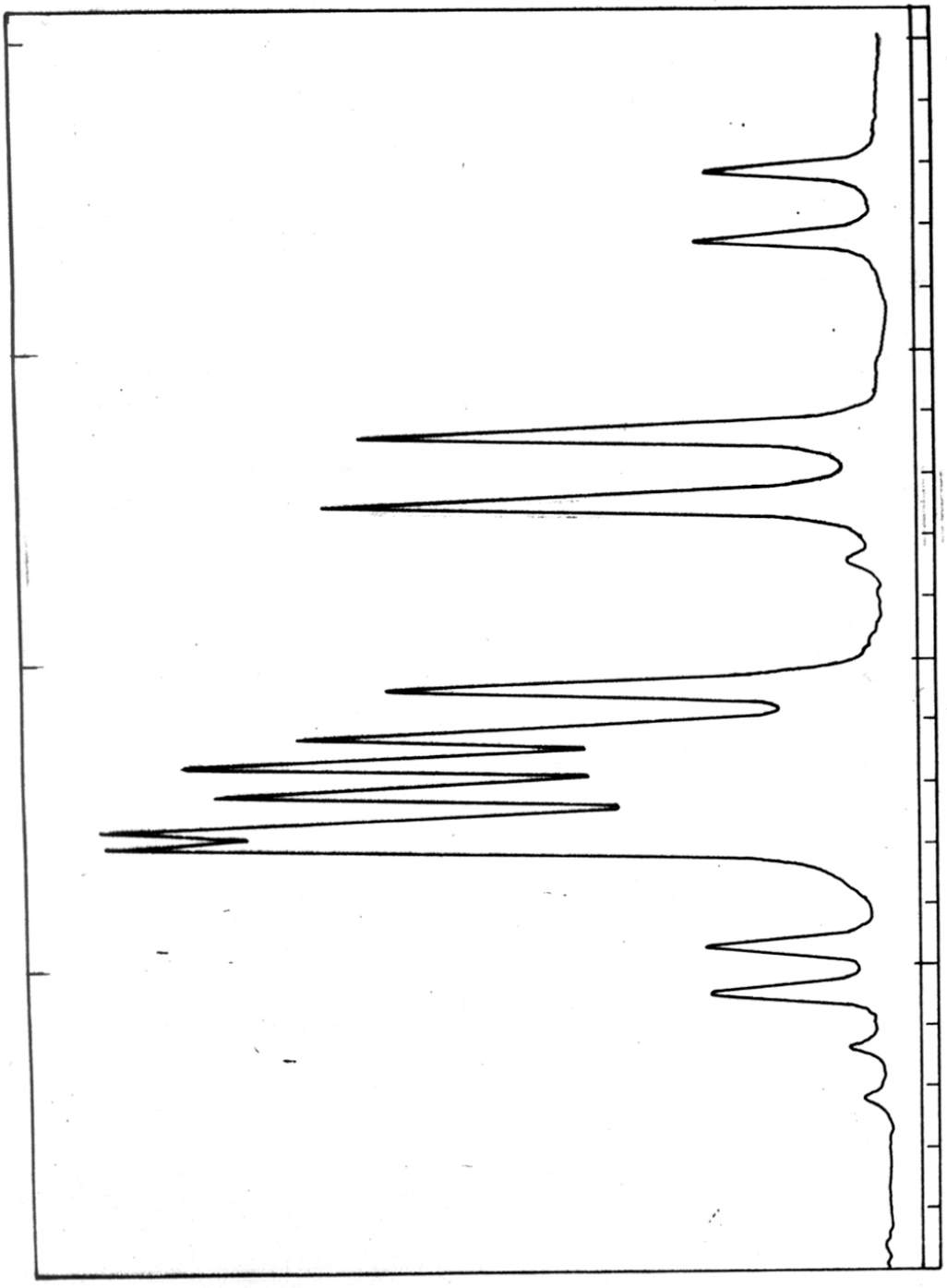


FIG. 6. EXPANDED AB REGION

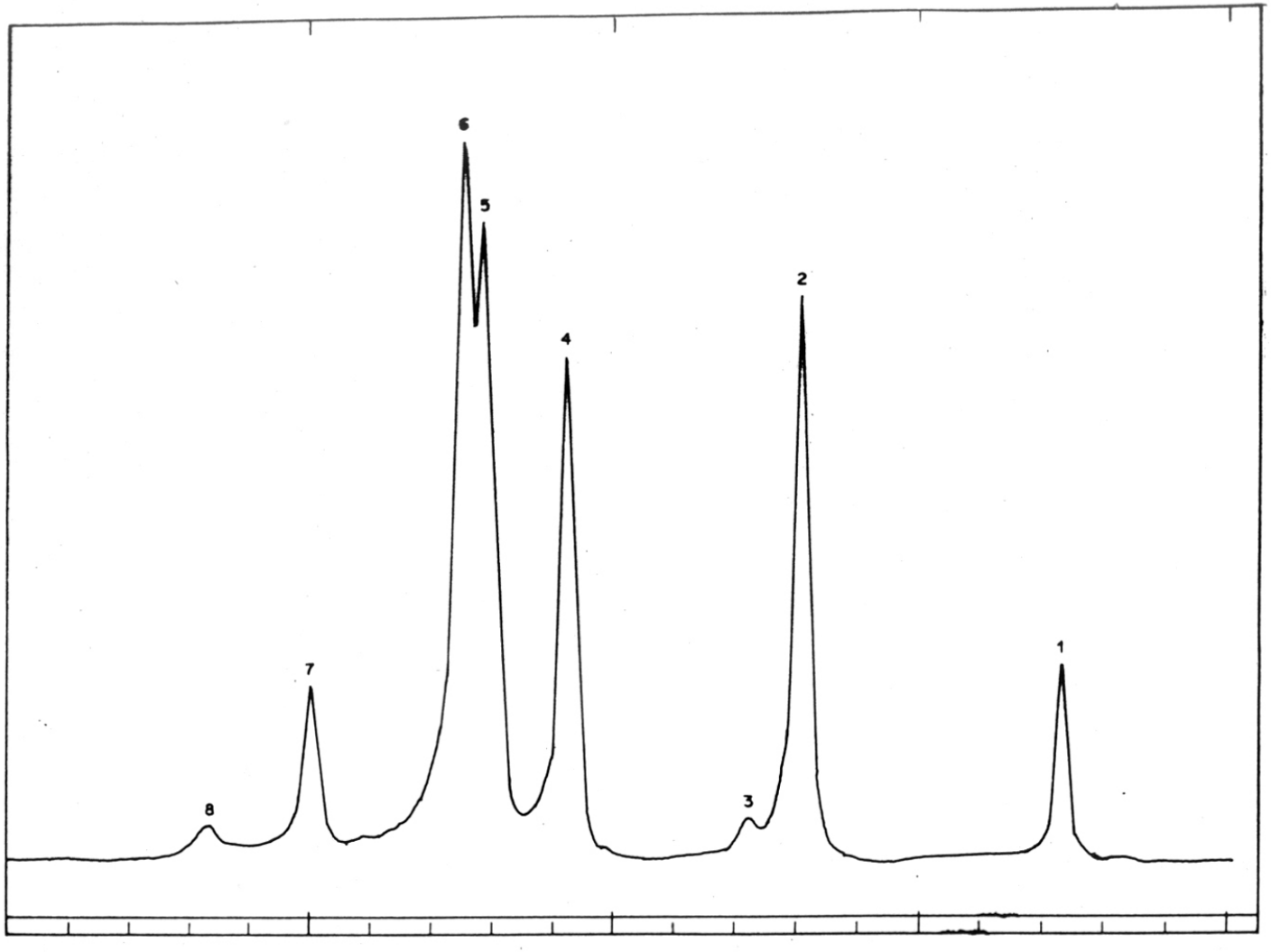


FIG. 7. EXPANDED AB REGION AFTER IRRADIATION OF R REGION

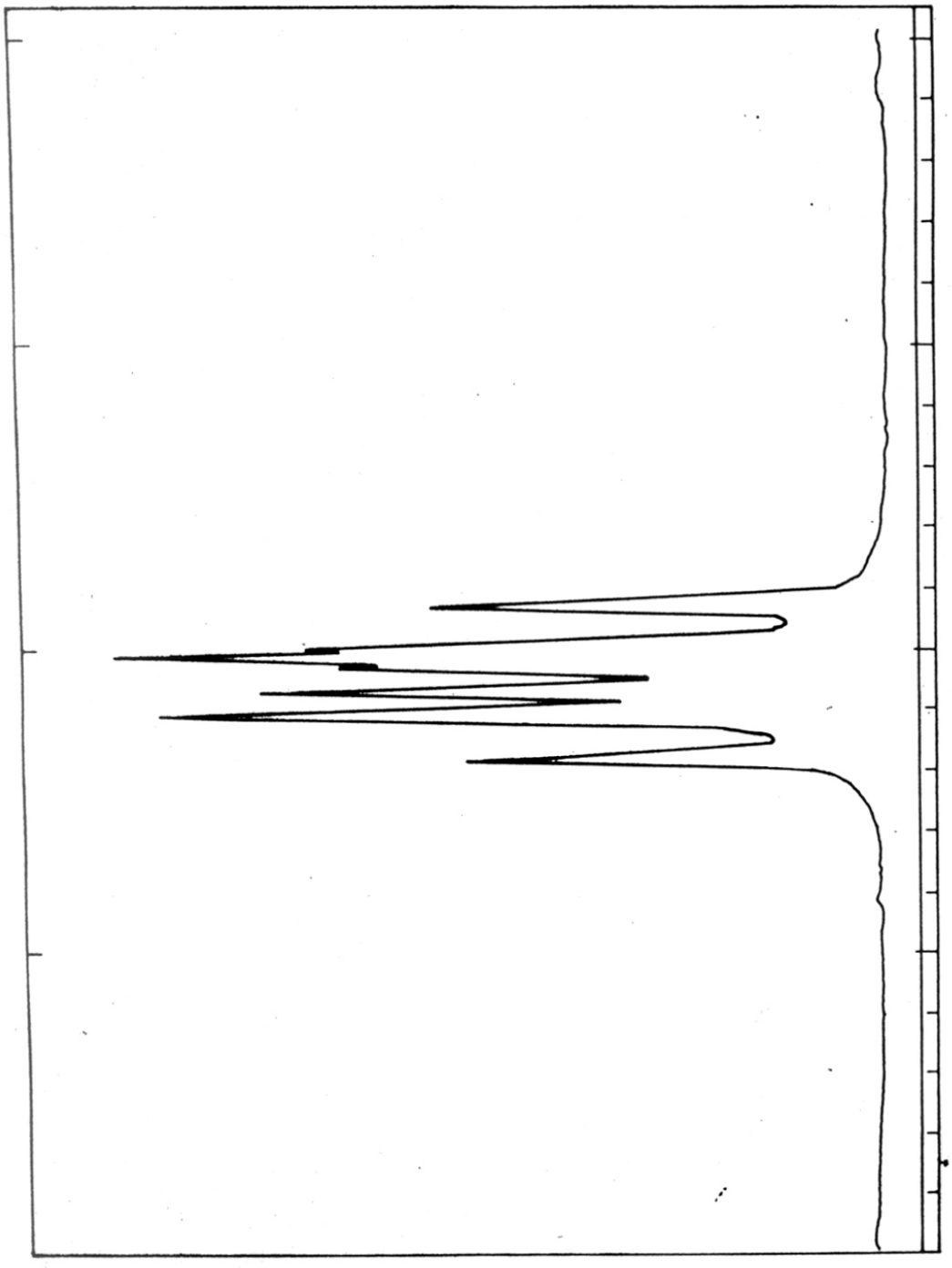


FIG. 8. EXPANDED R REGION

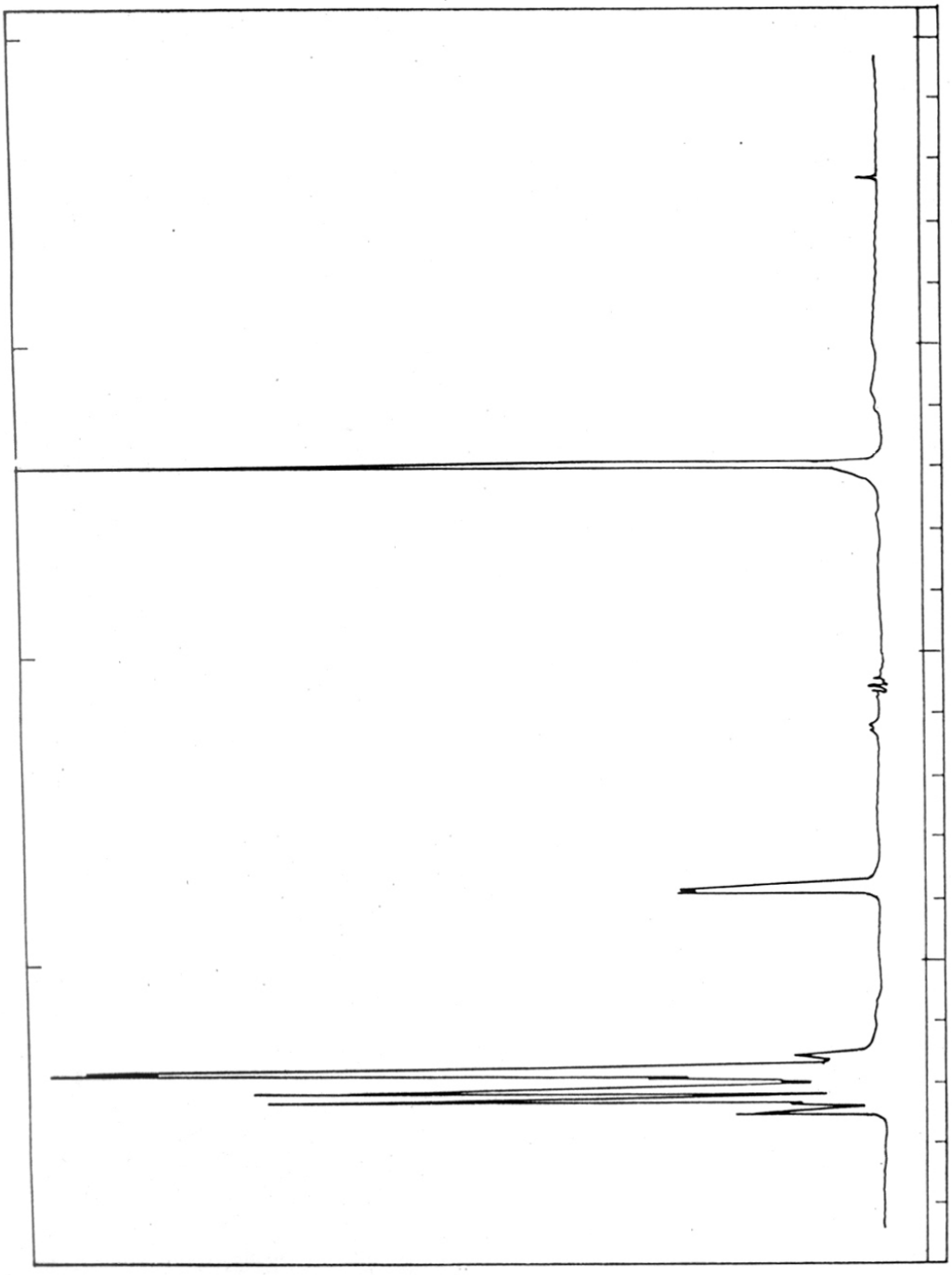


FIG. 9. SPECTRUM AFTER IRRADIATION OF AB REGION

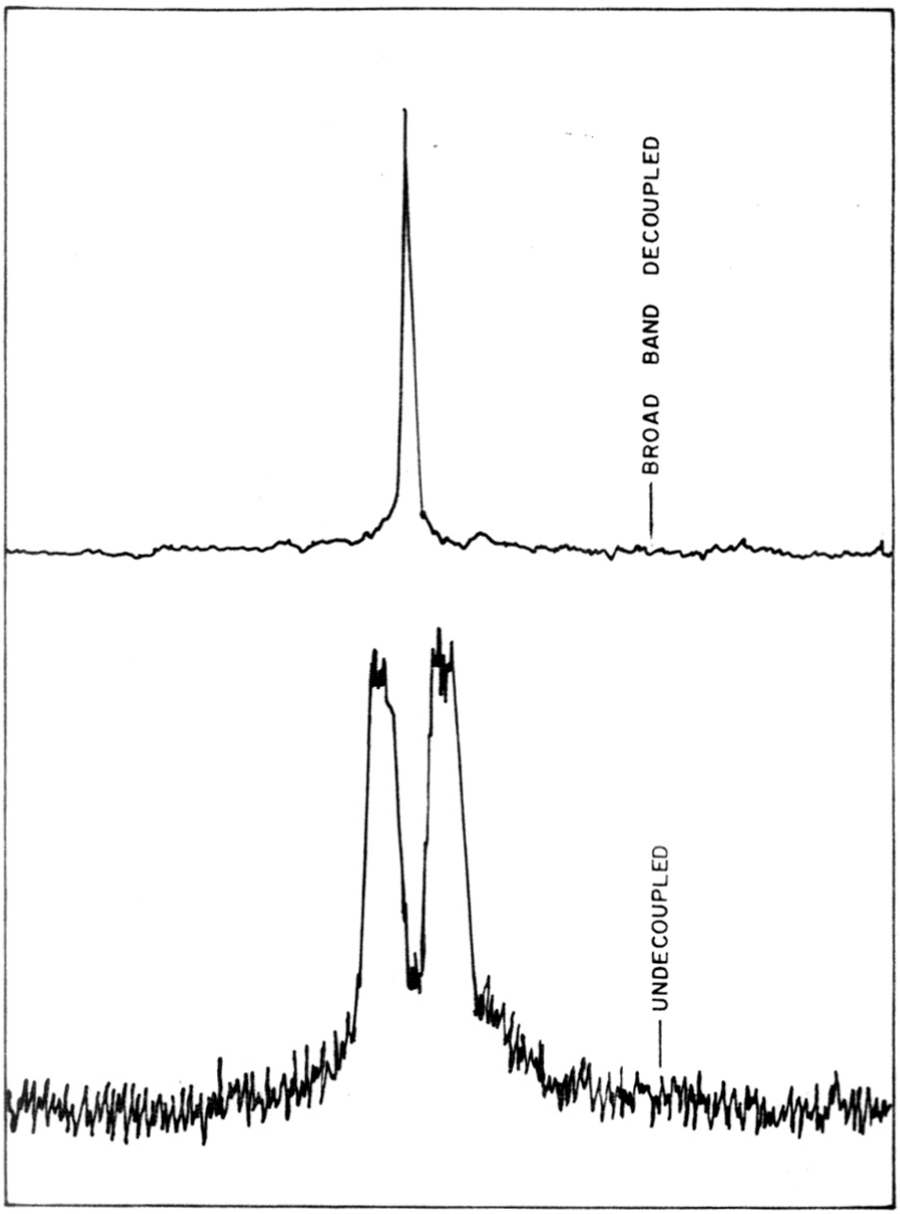


FIG. 10. ^{31}P SPECTRUM OF COMPOUND 6

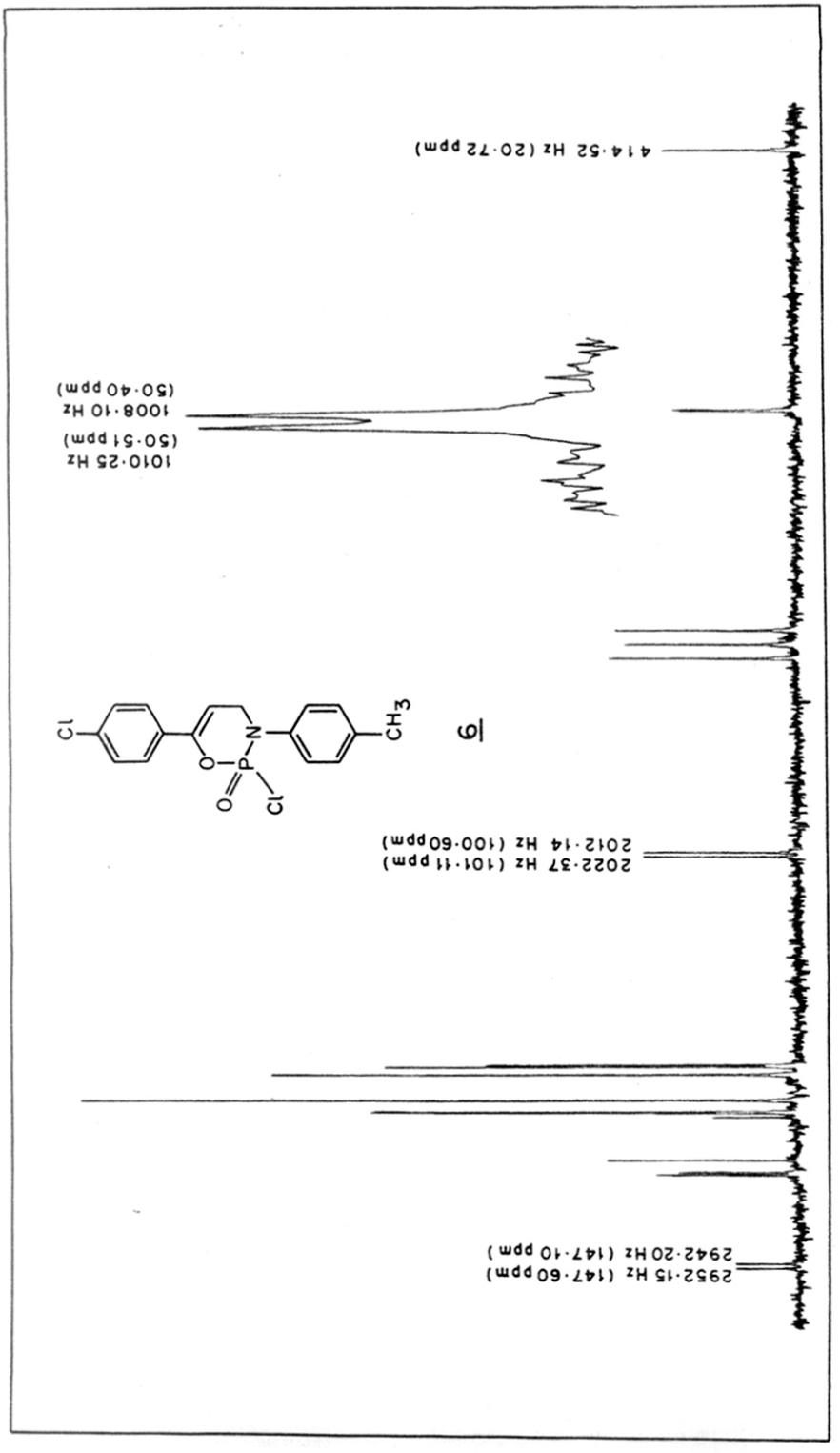


FIG. 11 : ^{13}C NMR SPECTRUM OF COMPOUND 6.

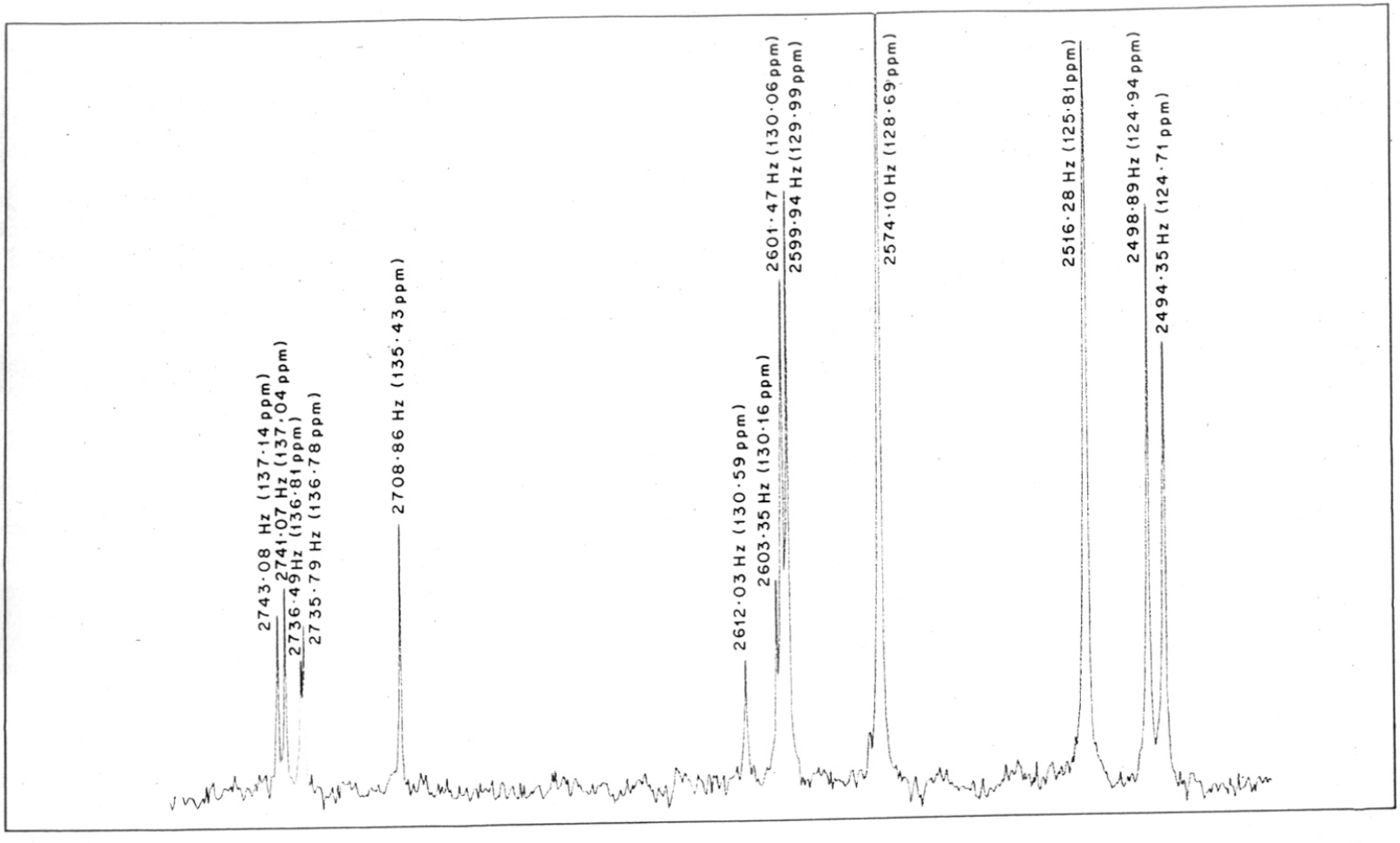
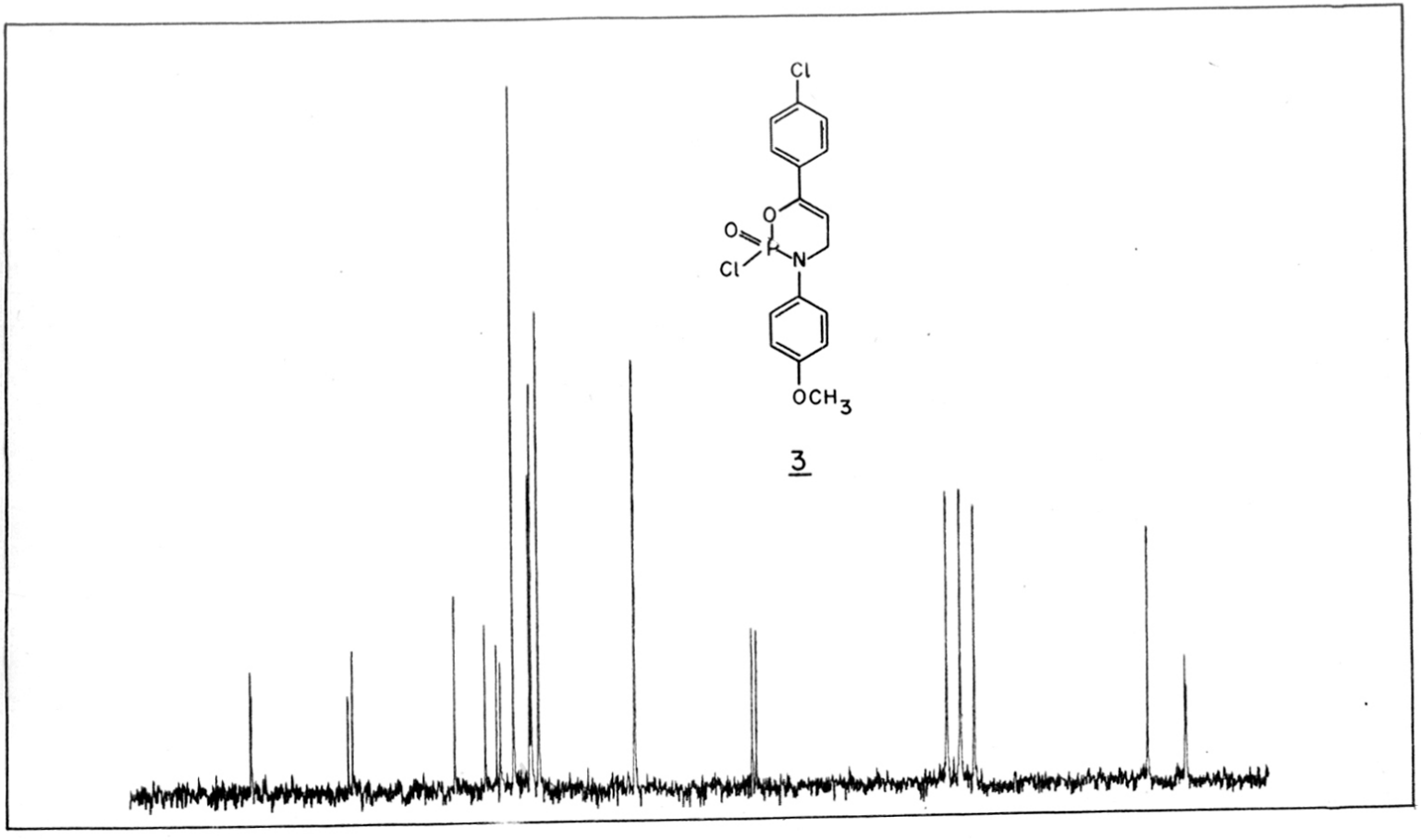
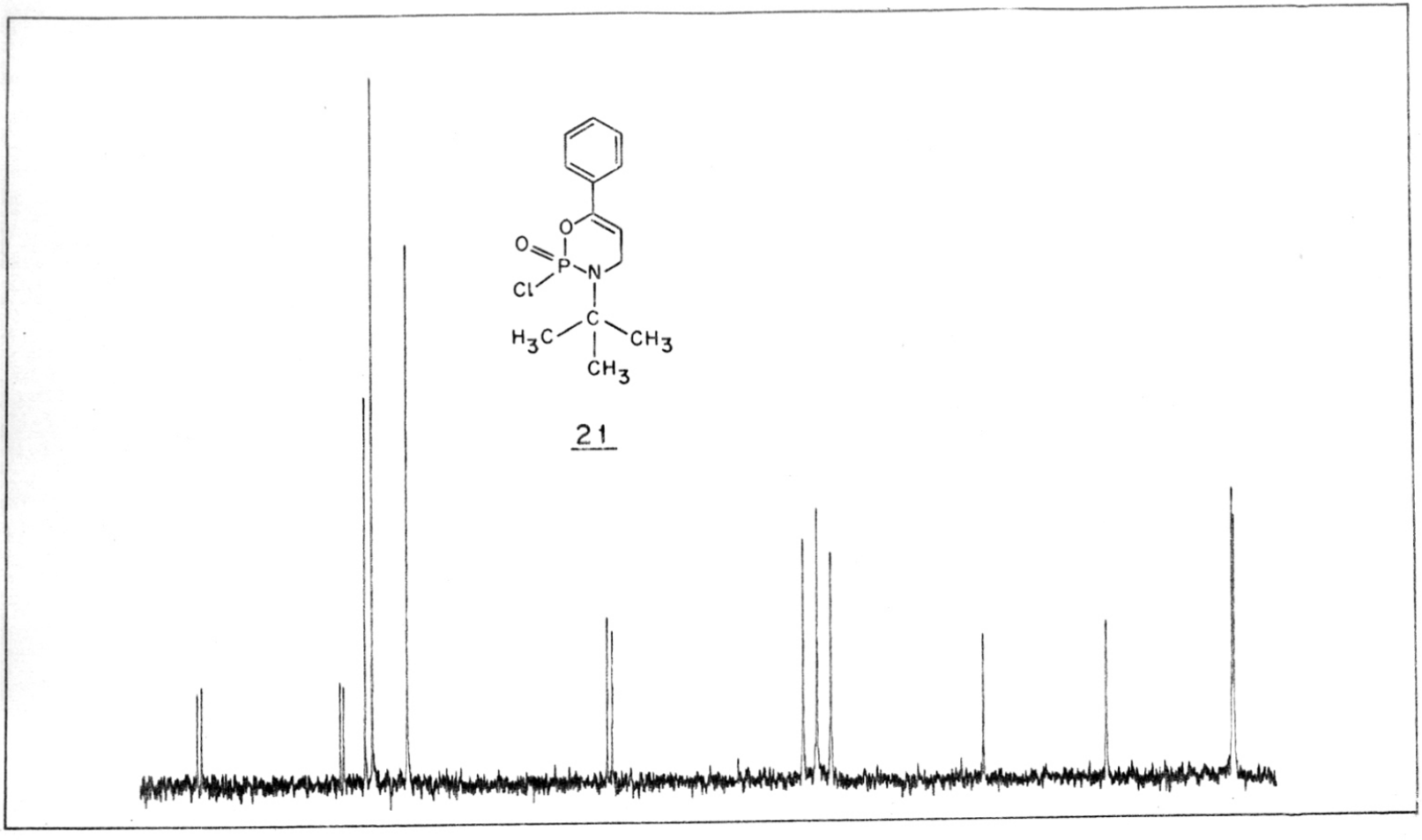


FIG. 12 : EXPANDED AROMATIC REGION OF COMPOUND 6



3

FIG. 13 : ^{13}C NMR SPECTRUM OF COMPOUND 3.



21

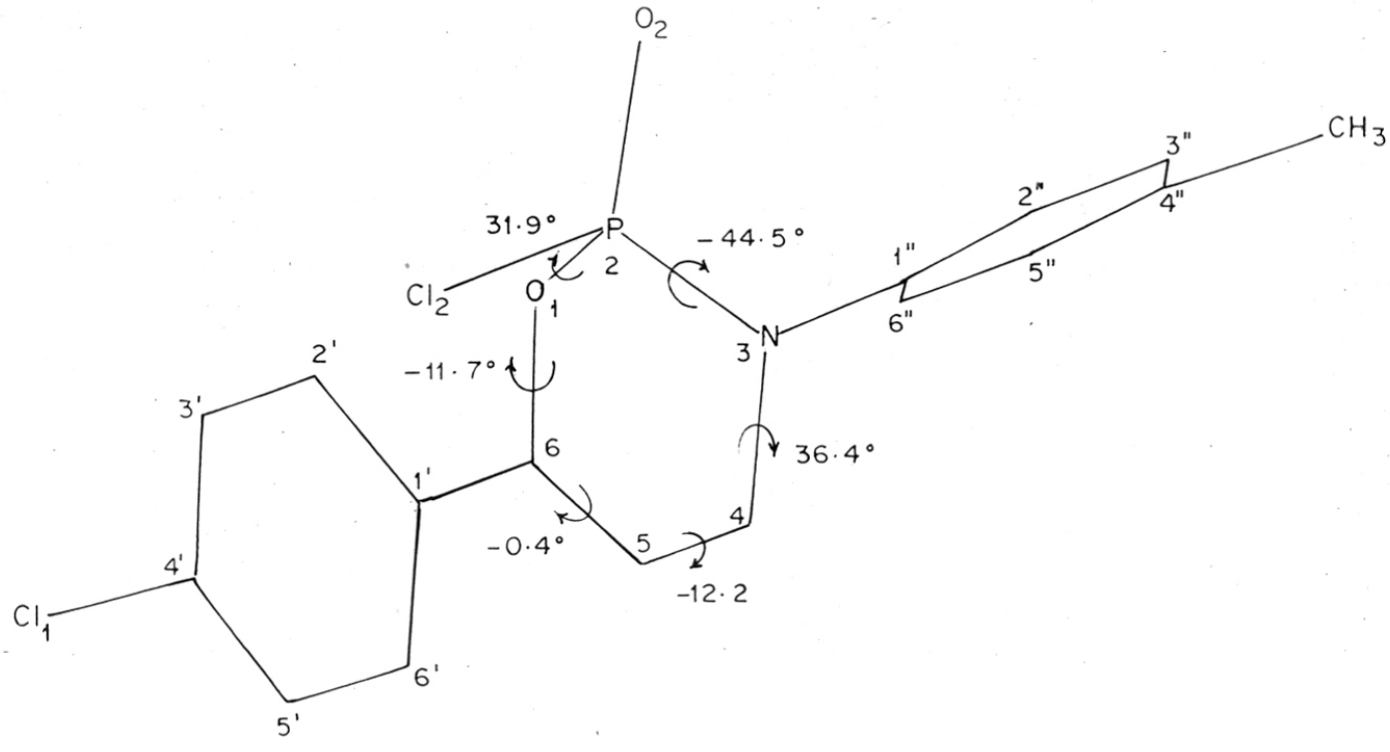
FIG. 14 : ^{13}C NMR SPECTRUM OF COMPOUND 21.

[C] X-RAY STRUCTURE OF DIHYDRO-OXAZAPHOSPHORIN*

X-ray crystal structure of 2-chloro-6-(p-chlorophenyl)-3-(p-tolyl)-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide 6, along with torsion angles is given in Chart 6. Bond lengths and bond angles of only dihydro-oxazaphosphorin ring are given in Tables 5 and 6 respectively.

X-ray crystal structure revealed that the dihydro-oxazaphosphorin 6 has half chair conformation and exocyclic O and Cl connected to phosphorus are in an axial and equatorial position.

* The above X-ray structure has been determined by Guru Row et al from NCL.



X-RAY CRYSTAL STRUCTURE OF COMPOUND 6

(WITH RING CONFORMATION ANGLE)

CHART – 6.

TABLE - 5

Bond length	A°	Bond length	A°
$P-O_2$	1.468	C_4-C_5	1.458
$P-Cl_2$	2.010	C_5-C_6	1.348
$P-N_3$	1.602	C_6-O_1	1.430
N_3-C_4	1.509	$P-O_1$	1.564

TABLE - 6

Bond angle	Angle$^{\circ}$	Bond angle	Angle$^{\circ}$
O_1-P-O_2	113.4	$N_3-C_4-C_5$	110.8
O_1-P-N_3	105.4	$C_4-C_5-C_6$	110.8
O_1-P-Cl_2	101.4	$C_5-C_6-O_1$	117.0
Cl_2-P-N_3	108.0	C_6-O_1-P	123.4
Cl_2-P-O_2	111.1	$O_1-C_6-C_1'$	110.8
O_2-P-N_3	116.3	$C_4-N_3-C_1''$	115.4
$P-N_3-C_4$	118.2	$P-N_3-C_1''$	121.4

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CHAPTER IV

SYNTHESIS OF SEVERAL DIMETHYL 2-AMINOTEREPHTHALATE DERIVATIVES : COMONOMERS FOR SYNTHESIS OF MODIFIED POLYESTER.

INTRODUCTION

Polyethylene terephthalate (Dacron, Terylene) a commercial man-made fibre was first synthesised by British Scientists J. R. Whinfeld and J. T. Dickson in 1941. Since then polyster fibres have taken a leading position in the market among the synthetic textile fibres. This is mainly due to the dimensional stability, good appearance and easy care-properties of fabrics made from these fibres. However, limitations encountered in the development of polyester fibre for clothing are due to the difficulty in dyeing, the problem of pilling and the hard touch of clothing.

Poor hydrophilicity and dye uptake pose difficulties in dyeing polyester fabrics. Diffusion of the dye into individual fibres and eventual dye adsorption depends largely on the physics and chemistry of the fibre structure and its ability to be modified before or during dyeing. The two main structural features of fibres which govern their dyeability are (1) permeability, or the ease with which dye molecules diffuse into the fibre matrix and (2) the presence of polar functional groups in the molecular chains of the fibre. These two features mainly depend on the crystalline and amorphous (non-crystalline) regions in the polyester. The crystalline regions provide strength and rigidity whereas amorphous regions provide

flexibility and permeability for the dye molecules. The ratio of crystalline to amorphous material has a significant influence on the maximum draw ratio, dyeability and other properties of man-made fibres. Polyester fibre being a highly crystalline material has compact structure (with very small interspaces in between the two linear chains). This makes the dye difficult to diffuse into the fibre matrix.

Copolymerisation offers a very useful means of influencing the crystallinity of the polymer, altering the crystalline-amorphous regions ratio. Since 1953, many attempts have been made to copolymerise a number of compounds along with terephthalic acid (or its dimethyl-ester) and ethylene glycol to improve dyeability, hydrophilicity and antistatic properties. Few of the commercial fibres which were so developed are given below:-

Polyethylene terephthalate/ sodium-5-sulfoisophthalate[1]	du Pont in 1958	Dacron 64
Polyethylene terephthalate/ isophthalate[2]	Beaunit in 1958	Vycron or Toyobo polyester
Polyethylene terephthalate/ p-hydroxybenzoic acid[3,4]	Nitiray in 1964	NRC polyester

The above copolymerized polyester fibres were prepared with a view to increase the dyeability for basic dyes.

When aliphatic long chain carboxylic acid was employed as a third component[5,6] the resulting copolyesters showed better affinity for disperse dyes and higher resistance to abrasion. In particular instances, the introduction of an acetal linkage to a side chain made the polymer reactive to certain chemicals[7], or an acetal group in a main chain made cross-linking by an after treatment possible[8]. Copolyesters from a third component containing sulfur and/or silicone showed an excellent resistance to heat, and when phosphorus was incorporated, anti-fnflammability was imparted to the polymers. Copolyesters containing chlorine showed good resistance against hydrolysis and the action of bacteria[9]. Recently polyethylene glycol was incorporated in the polyester to increase its hydrophilicity[10].

Attempts have been made to incorporate amino groups into copolymers to provide sites having affinity for the sulfonic acid (direct and acid) dyes commonly used for cotton and wool[11,12]. However, there are as yet no commercial fibres of the above types on the market.

From the above literature survey, it was observed that numerous compounds have been copolymerised to increase dyeability, hydrophilicity and feel of the polyester at the cost of mechanical properties of the fibre. However, the monomers containing various functional groups

which were copolymerised with dimethyl terephthalate (DMT) were almost invariable derivatives of isophthalic acid and its dimethyl ester. Consequently the linearity of the polymers which is the characteristic of polyesters derived from DMT was affected by incorporation of isophthalic acid (and its dimethyl ester) in the polyester chain. It was, therefore, considered interesting to prepare monomers having structure similar to dimethyl terephthalate containing some functional groups, which may improve the dyeability of the fibre without affecting linearity of the polymer chain.

Further literature survey indicates that no attempts have been made to cross-link polyesters derived from DMT by copolymerisation of DMT and bis-DMT derivatives where two DMT moieties have been linked by suitable bridges. The present work makes one such attempt.

The present chapter describes the synthesis of some monomers and copolyesters. However, the work was handicapped by numerous difficulties due to lack of facilities. It has therefore not been found possible to take it to its logical conclusion by carrying out studies such as dyeability, antistatic properties, strength, etc. on the synthetic copolyesters prepared presently. This aspect of the work will be undertaken later in this laboratory.

PRESENT WORK

Thermofixation of the reactive azo dye, 2-hydroxy-5-methyl-4'-sulfonazidoazobenzene 1 with polyester fibre led to chemical bonding of the generated sulfonyl nitrene with the fibre substrate. Tilak et al[13,14] suggested that the nitrene insertion in the polyester fibre was most likely to occur through insertion in the aromatic ring of the polyester fibre than in the aliphatic region of the fibre substrate.

Thermolysis of 1 with dimethyl terephthalate yielded compounds 3 and 4. Dye 1 when thermolysed with polyester and the dyed fibre subsequently hydrolysed gave compounds A and B which after esterification gave compounds 3 and 4. This showed that the dye 1 reacts with polyester fibre with the formation of covalent bonds (Chart 1).

In a similar manner in the model experiment of thermal decomposition of p-toluenesulfonyl azide[15] 5 (model for sulphonazido dyes) in dimethyl terephthalate (model for polyester), dimethyl 2-p-toluenesulfonamido-terephthalate 6 and 2,5-dicarbomethoxy-1-p-toluene sulfonyl-1H-azepine 7 were obtained (Chart 2). Based on the above observations it was thought interesting to incorporate some functional groups like sulfonamido in the polyester backbone.

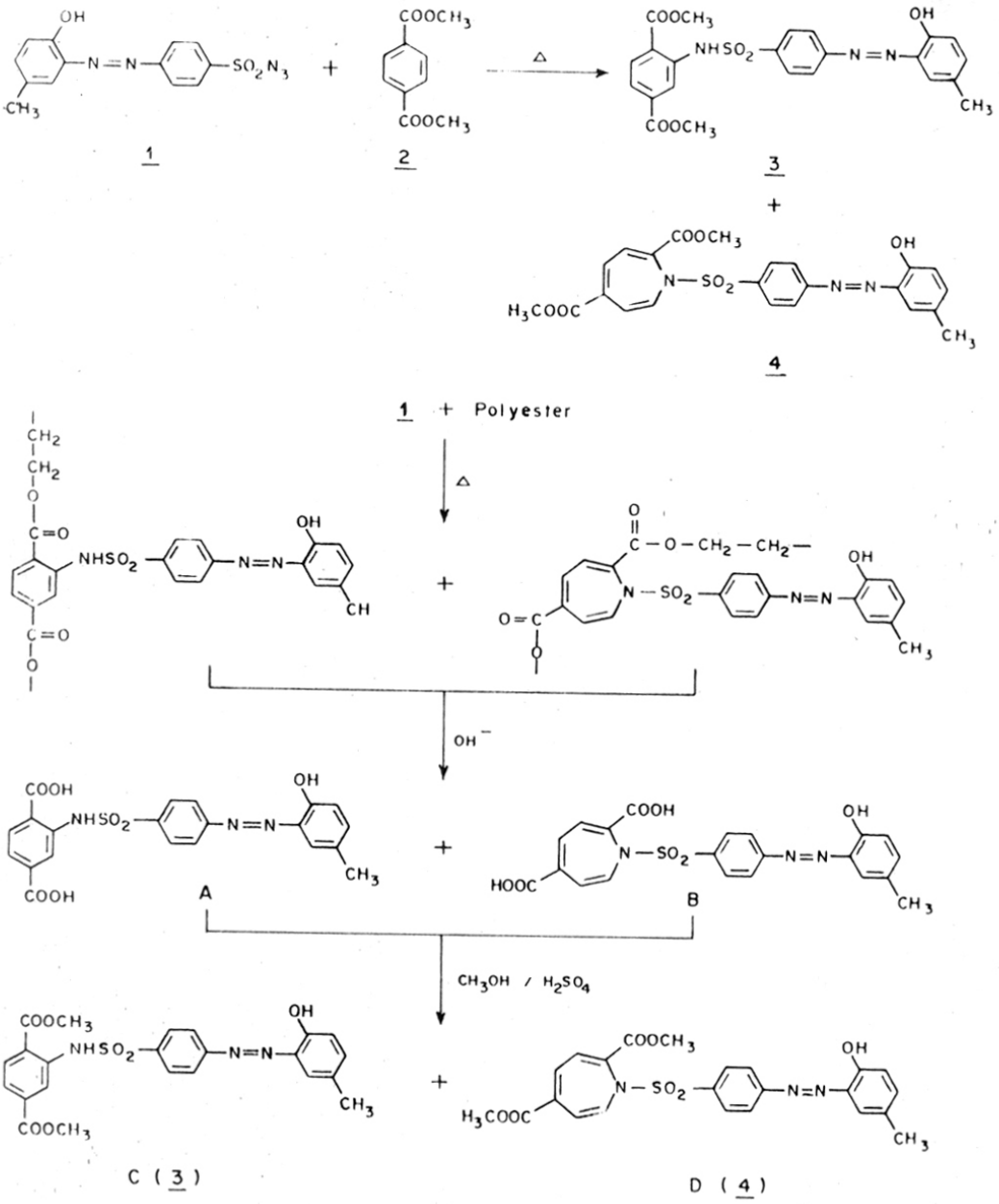
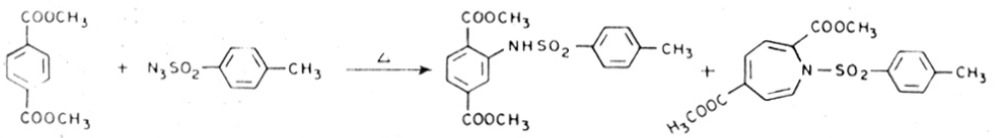


CHART – 1.

To confirm the formation of sulfonamido derivative 6 earlier workers tried unsuccessfully, to prepare it by the reaction of p-toluenesulfonylchloride and dimethyl 2- aminoterephthalate 17 in various acid binding agents.

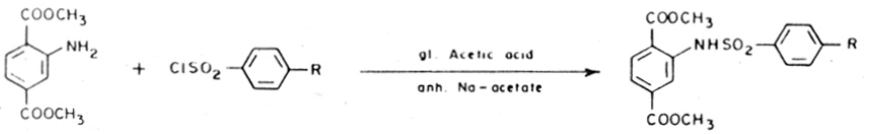
The above reaction did not go smoothly due to weak basic character of dimethyl 2-aminoterephthalate. The reaction was found to proceed in glacial acetic acid medium using anhydrous sodium acetate as acid binding agent. p-Toluenesulfonyl chloride and p-acetamido-benzenesulfonyl chloride[16] on interaction with dimethyl 2-aminoterephthalate in glacial acetic acid in presence of anhydrous sodium acetate gave dimethyl 2-p-toluene-sulfonamidoterephthalate 6 and dimethyl 2-p-acetamido-benzenesulfonamidoterephthalate 10 respectively (Chart 3).

With a view to prepare cross linked polyesters we prepared two hitherto unknown comonomers, dimethyl 1,3-benzenedisulfonamido-bis-terephthalate 12 and dimethyl 1,5-naphthlenedisulfonamido-bis-terephthalate 14. These were prepared by condensation of dimethyl 2-amino-terephthalate 17 with 1,3-benzenedisulfonyl chloride[17] 11 and with 1,5-naphthalenedisulfonyl chloride[18] 13 respectively (Chart 4).



2 5 6 7

CHART – 2.

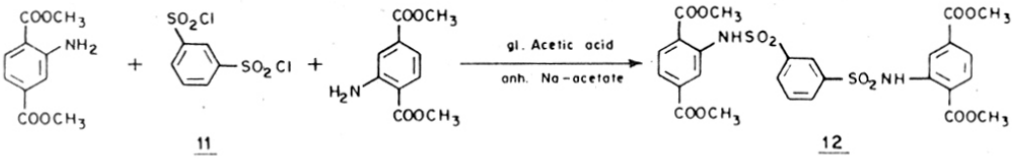


17

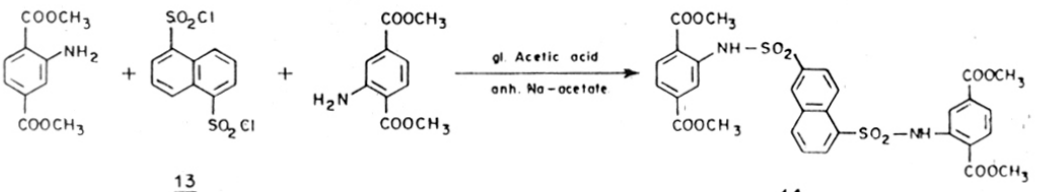
8 R = CH_3 6

9 R = $NHCOCH_3$ 10

CHART – 3.



11 12



13 14

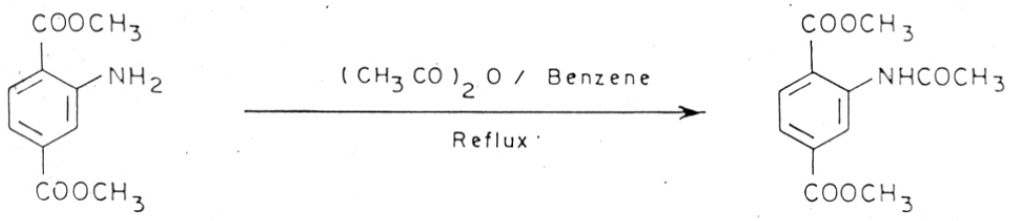
CHART – 4.

Dimethyl 2-acetamidoterephthalate[19] 15 was prepared by refluxing dimethyl 2-aminoterephthalate 17 and acetic anhydride in benzene (Chart 5).

Dimethyl 2-aminoterephthalate 17, a precursor for all these comonomers was prepared by the procedure described by Ivanova et al[20]. Dimethyl 2-nitro-terephthalate prepared by nitration of dimethyl terephthalate with fuming nitric acid (1.52 d) and fuming sulfuric acid (1.9 d), was reduced with stannous chloride and methanolic hydrochloric acid to give dimethyl 2-aminoterephthalate (Chart 6).

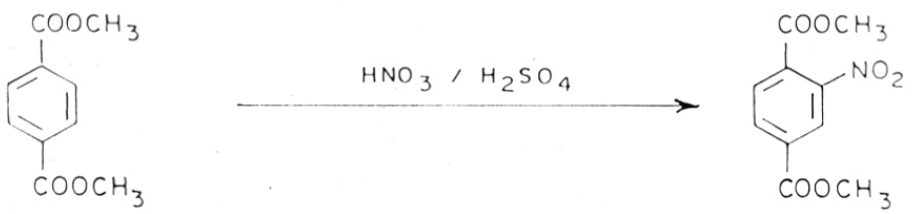
The general polyester condensation reaction is carried out in two steps (1) ester exchange reaction and (2) polycondensation reaction. In the first step, intermediate bis-β-hydroxyethyl terephthalate (BHET) is formed along with methanol. Methanol is distilled out at the end of the first step. In the polycondensation step the temperature of the reactor is increased to 270-285°. Excess ethylene glycol is distilled out under high vacuum and molten charge (polyester) is taken out.

The standard polyester was first prepared by the condensation of dimethyl terephthalate and ethylene glycol for comparative study. Dimethyl 2-p-toluene-sulfonamido terephthalate 6 and dimethyl 2-acetamido-



15

CHART – 5.



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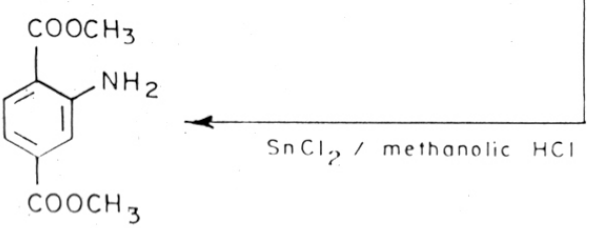


17

CHART – 6.

terephthalate 15 were then copolymerised with dimethyl terephthalate and ethylene glycol. The copolymers were prepared by taking 0.5, 1.0, 1.5, 2.0 and 5.0 mol % compounds 6 and 15 on the basis of dimethyl terephthalate content in the initial reactor feed. The melting points and inherent viscosities were measured (Table 1). It was observed that as the percentage of third component was increased, the melting points were decreased. The viscosities were measured on Cannonfeld A 100 viscometer is s-tetrachloroethane:phenol 60:40 mixture. The co-polyesters above 0.5 viscosities were selected, as polymers having an η inherent above about 0.5 may be melt spun or pressed into textile films. The differential thermal analysis (DTA) of these three samples indicates that only the sample containing 2% of compound 15 shows a significant drop in peak area indicating loss of crystallinity[21] which gives an indirect proof for the change in fibre structure brought about by incorporation of some functional groups. Such a copolymeric polyester fibre may have better affinity towards acid dyes.

TABLE - 1

MPS AND VISCOSITY MEASUREMENTS

	Viscosity η inherent	M.P. in ^{o}C
Standard polyester	0.56	258
Copolyester with 0.5% 15	0.55	251
Copolyester with 2% 15	0.52	245
Copolyester with 1% 6	0.44	246
Copolyester with 2% 6	0.54	242

EXPERIMENTAL

Synthesis of dimethyl 2-p-toluene sulfonamidoterephthalate 6

Dimethyl 2-aminoterephthalate (4.18 g; 0.02 mol), p-toluenesulfonyl chloride (4.95 g; 0.026 mol) and gl. acetic acid (AR grade) (20 ml) were heated to reflux. Finely powdered anhydrous sodium acetate was added in 0.82 g, 0.41 g, 0.205 g, and 0.205 g quantities at regular interval of 10 minutes. Final addition of 0.41 g was made and mixture was poured over ice. The brown mass which separated out was filtered, washed thoroughly with water and crystallised from benzene when it gave 6 as colourless needles, (6.16 g, yield 85%), m.p. 170°. (Found C, 56.3; H, 4.8; N, 3.6; $C_{17}H_{17}NO_6S$ requires C, 56.2; H, 4.7; N, 3.9%).

NMR ($CDCl_3$, δ) : p-CH_3 C_6H_4- at 2.4, s, 3p;
-OCH_3 at 3.95, d, 6p;
Aromatic protons at 7.2-8.3, m, 7p;
-NH (exchangeable) at 10.55, s, 1p.

IR(nujol) ν_{max} 3000, 1750, 1600, 1590, 1500, 1440, 1400, 1380, 1340, 1300, 1250, 1200, 1180, 1120, 1100, 1000, 970, 950, 920, 900, 860 cm^{-1}.

Mass M^+ 363.

Synthesis of dimethyl p-acetamido-benzene-sulfonamidoterephthalate 10

Dimethyl 2-aminoterephthalate (4.18 g; 0.02 mol), p-acetamidobenzenesulfonyl chloride (6.0 g; 0.026 mol) and gl. acetic acid (20 ml) were refluxed. Anhydrous sodium acetate was added in 0.82 g, 0.41 g, 0.205 g, and 0.205 g quantity. On work up as above, the title compound was obtained which on crystallisation from ethanol gave colourless plates (6.5 g, yield 80%), m.p. 176°. (Found C,53.5; H, 5.0; N, 7.3; $C_{18}H_{18}N_2O_7S$ requires C, 53.2; H, 4.4; N, 6.9%).

NMR ($AsCl_3$, δ) $-COCH_3$ at 2.2, s, 3p;
$-OCH_3$ at 3.9; d, 6p;
$-NHCOCH_3$ at 8.1, s, 1p;
Aromatic protons at 7.3-8.2, m, 7p;
$-NHSO_2R$ at 10.55, s, 1p.

IR(nujol) ν_{max} 3300, 3240, 2900, 1730, 1710, 1680, 1590, 1570, 1500, 1420, 1370, 1330, 1300, 1250, 1120 and 1080 cm^{-1}.

Mass M^+ 406.

Synthesis of dimethyl 1,3-benzene-disulfonamido-bis-terephthalate 12

To a stirred mixture of dimethyl 2-amino-terephthalate (1.04 g; 0.005 mol) and gl. acetic acid (10 ml) heated to 80° was added 1,3-benzenedisulfonyl chloride (0.892 g; 0.0032 mol). The mixture was heated to boil and anhydrous sodium acetate 0.2050, 0.1025, 0.0512, 0.0512 and 0.1025 g, was added at the 5-10 minutes time intervals. The mixture was further refluxed for 20 minutes. The mixture was then poured on ice and the brown solid obtained was filtered and dried. After two crystallisations from ethanol, the above product gave the title compound as a white solid (1.86 g, yield 60%), m.p. 163°. (Found C, 50.6; H, 4.1; N, 4.3; $C_{26}H_{24}N_2O_{12}S_2$ requires C, 50.3; H, 3.9; N, 4.5%).

NMR ($CDCl_3$, δ) $-OCH_3$ at 3.9, d, 12p;
Aromatic protons at 7.1-8.3, m, 9p;
$-NH$(exchangeable) at 10.2, s, 2p.

IR(nujol) ν_{max} 3000, 1700, 1670, 1550, 1500, 1430, 1400, 1380, 1340, 1290, 1240, 1200, 1170, 1140, 1120, 1000, 950, 900, 820, 760 cm^{-1}.

Mass M^+ 620.

Synthesis of dimethyl 1,5-naphthalene-disulfonamido-bis-terephthalate 14

To a boiling mixture of dimethyl 2-amino-terephthalate (1.04 g; 0.005 mol), gl. acetic acid (10 ml) and 1,5-naphthalenedisulfonyl chloride (1.05 g; 0.0032 mol) was added 0.205, 0.1025, 0.0572, 0.0572, 0.1025 g of anhydrous sodium acetate as above. After refluxing under stirring for 30-40 minutes, the mixture was poured on ice, filtered and the residue dried (1.84 g, yield 55%). The reaction product decomposes at 250°. (Found C, 52.9; H, 4.1; N, 4.3; $C_{30}H_{26}N_2O_{12}S_2$ requires C, 53.7; H, 3.9, N, 4.2%).

NMR ($CDCl_3$, δ) $-OCH_3$ at 3.9, d, 12p;
Aromatic protons at 7.4-8.9, m, 12p;
$-\underset{|}{N}H$ at 10.5 , s, 2p.

IR(nujol) ν max 3200, 1700, 1670, 1560, 1500, 1460, 1400, 1370, 1340, 1300, 1240, 1180, 1160, 1120, 1080, 1000, 950, 920, 900, 840, 820, 760 cm^{-1}.

Synthesis of polyethylene terephthalate and copolyesters

All ingredients used for the reaction were of high purity. Dimethyl terephthalate was purified by crystallisation from ethanol. Ethylene glycol was

purified by refluxing it for one hour with 2% metallic sodium and subsequent distillation. Antimony trioxide and zinc acetate (AR grade) were used as such.

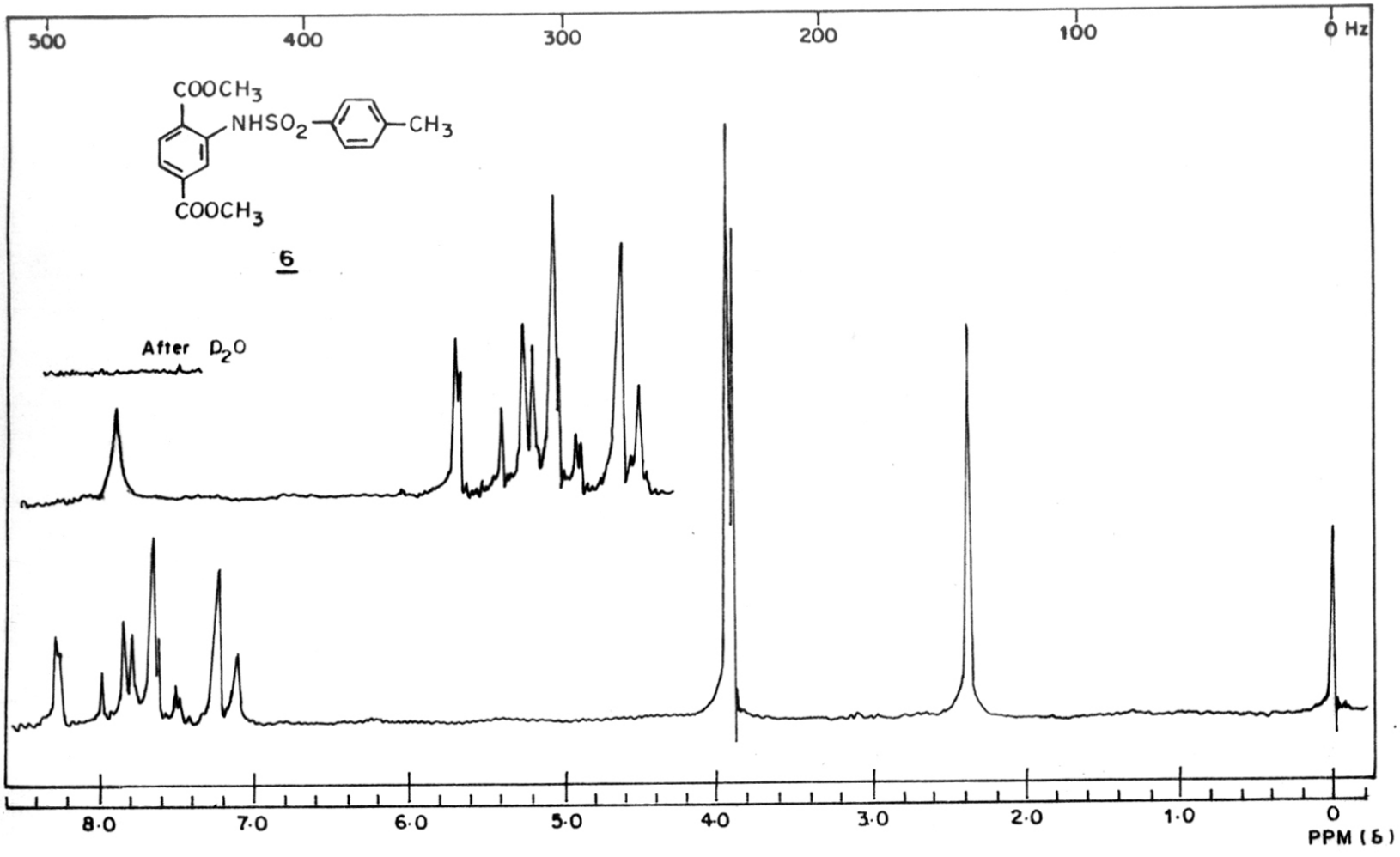
The polymerization reaction was carried out in a hard glass polymer tube having one inlet for nitrogen and other for distillation. The tube was charged with dimethyl terephthalate (19.4 g; 0.1 mol), ethylene glycol (14.2 g; 0.23 mol), zinc acetate (0.046 g) and antimony trioxide (0.072 g). The tube was dipped half-way into the dimethyl phthalate bath. The charge was kept molten by heating to 197°, and nitrogen gas was introduced at the bottom through a fine capillary tube. After one hour when methanol evolution ceased, the temperature was raised to 200° and maintained for three hours. The temperature was then slowly increased to 283° (during this period excess of ethylene glycol distilled over). Nitrogen flow was then stopped and vacuum was applied slowly. The pressure was brought down to 0.5 mm in about 15 minutes. After three hours, the tube was again filled with nitrogen and then removed from dimethyl phthalate bath and allowed to cool. The polymer (i.e. polyester) was taken out from the tube and powdered.

The copolymers were prepared in a similar manner. Dimethyl 2-acetamidoterephthalate 15 was added as

0.5, 1.0, 1.5 and 2.0 mol % of dimethyl terephthalate content in initial monomer feed. Dimethyl 2-p-toluene-sulfonamido terephthalate 6 was added as 0.5, 1.0 and 2.0 mol % of dimethyl terephthalate content in the initial monomer feed. The various quantities of materials used are given below in Table 2.

TABLE - 2

Mol %	DMT gms.	Compd. 15(g)	Compd. 6 (g)	Zinc acetate(g)	Antimony trioxide(g)
0.5	19.2695	0.1305	-	0.046	0.072
1.0	19.1390	0.2610	-	0.046	0.072
1.5	18.8780	0.5220	-	0.046	0.072
2.0	18.3560	1.0440	-	0.046	0.072
0.5	19.2185	-	0.1815	0.046	0.072
1.0	19.1370	-	0.2630	0.046	0.072
2.0	18.8740	-	0.5260	0.046	0.072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CH3
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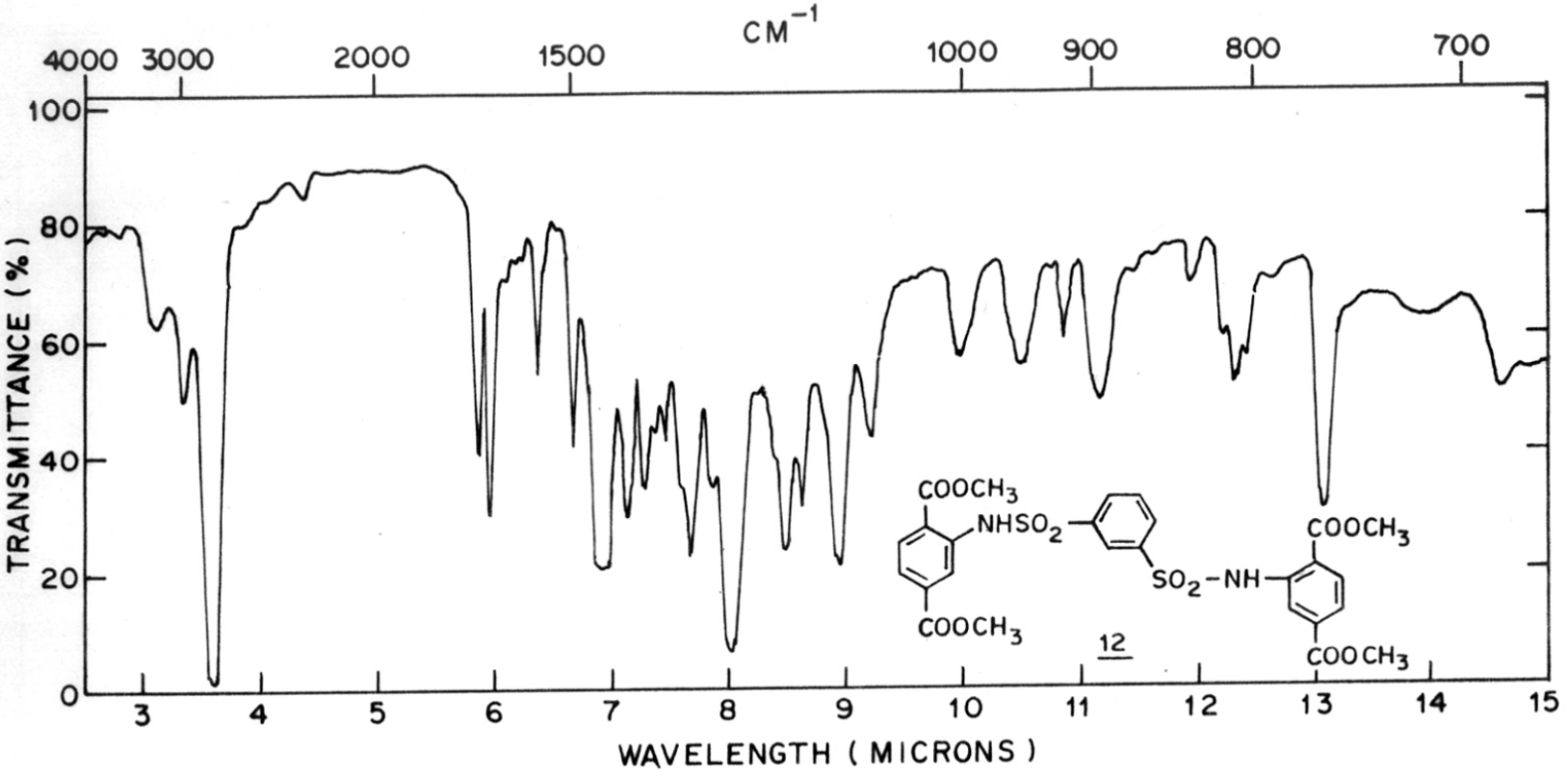
PPM (δ)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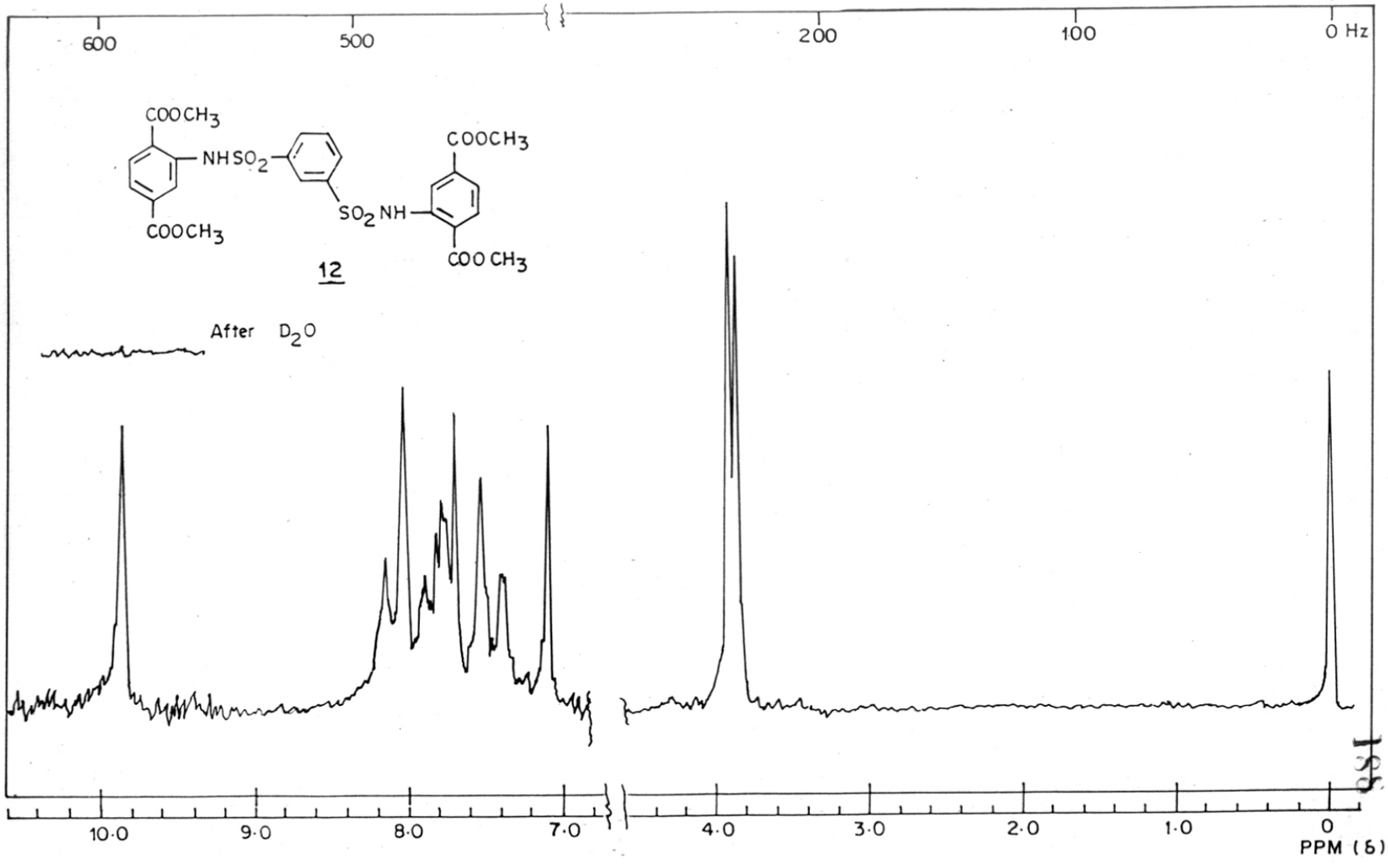
COOCH$_3$
COOCH$_3$

12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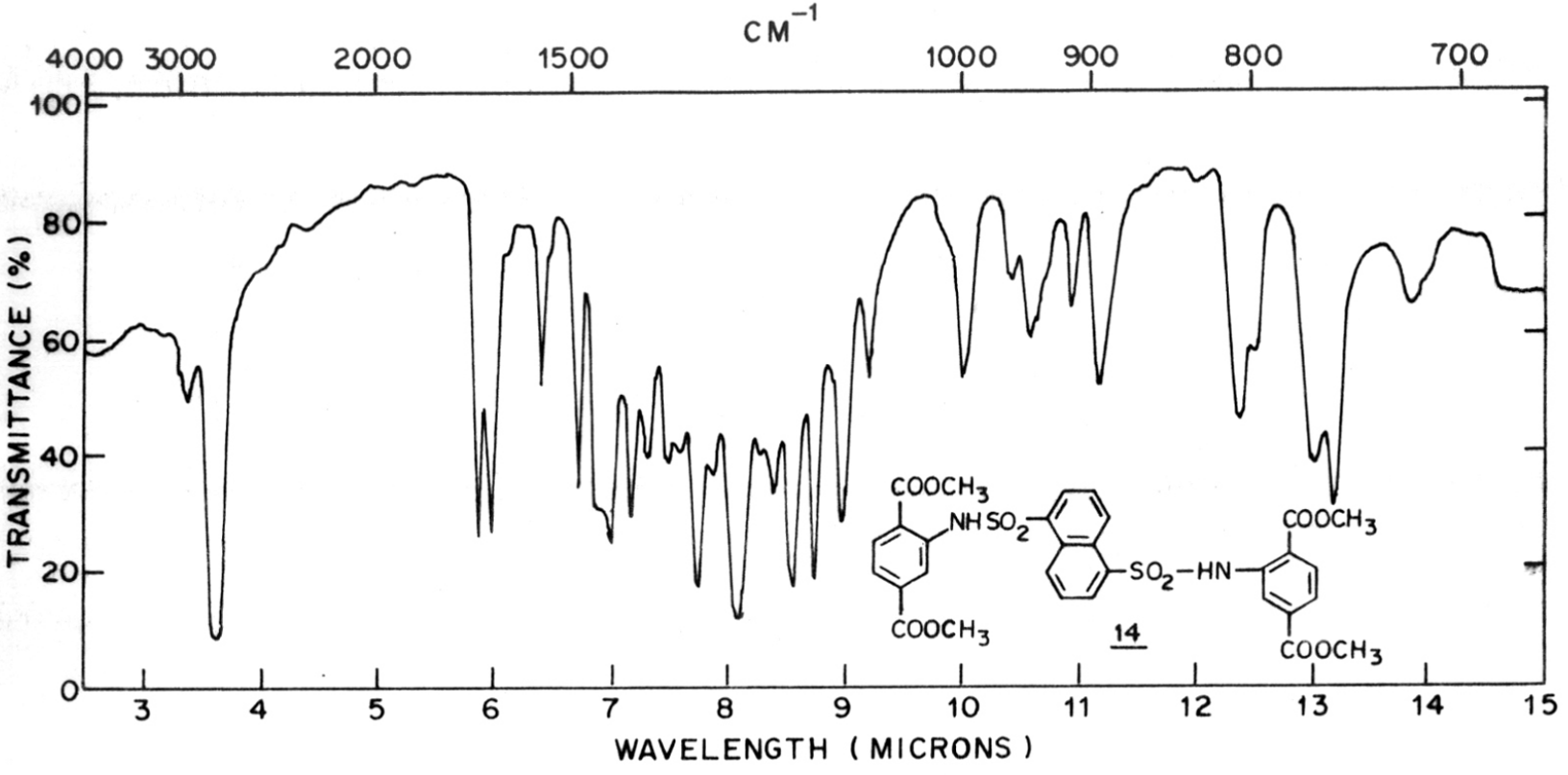
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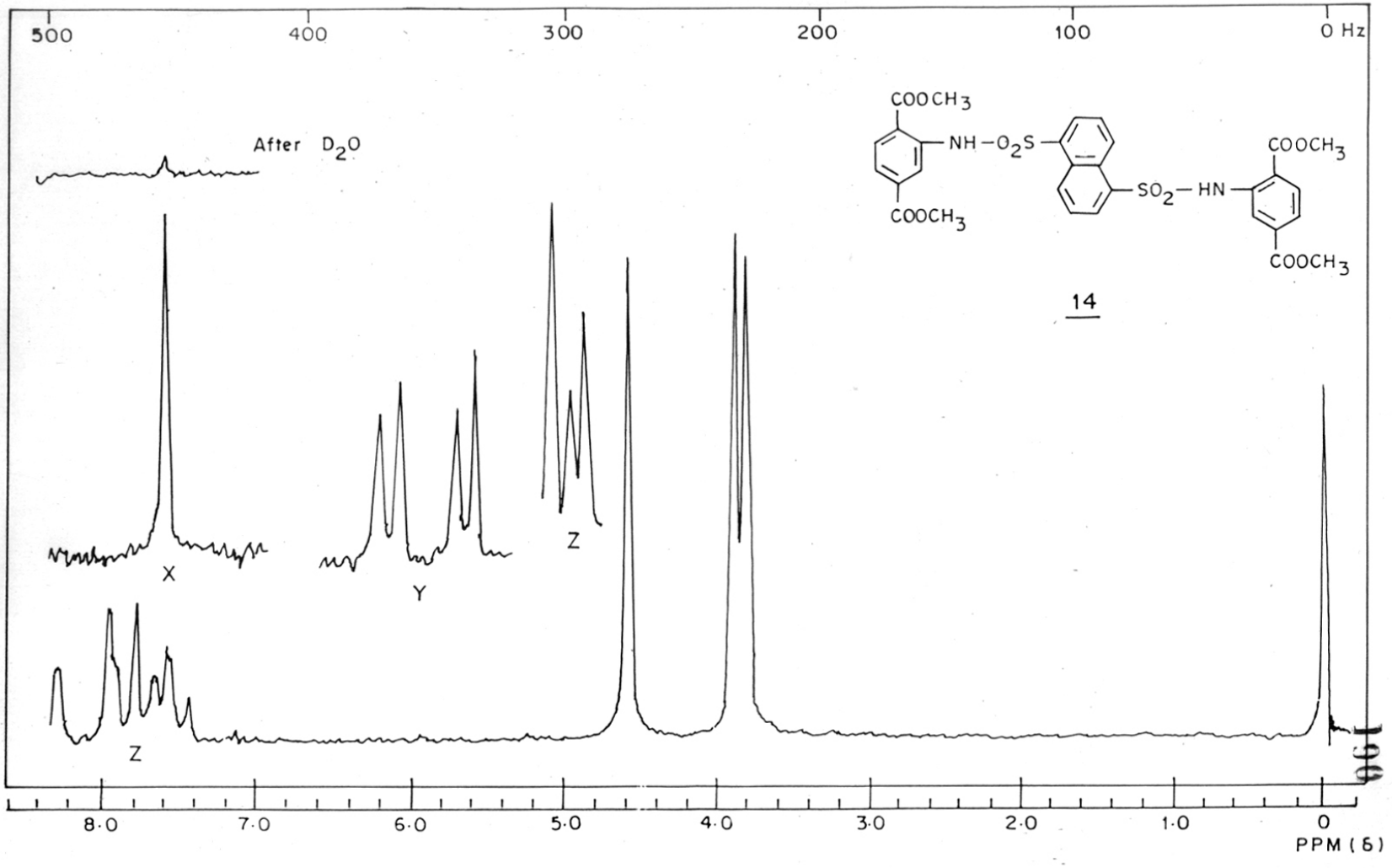
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Z
Z
$COOCH_3$
NH
O_2S
SO_2
HN
$COOCH_3$
$COOCH_3$
$COOCH_3$
$COOCH_3$
14
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

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SUMMARY

The thesis is submitted in the following chapters.

CHAPTER-I

PART - A

A brief review of earlier work, relevant to that discussed in this Chapter, is presented.

2-Chloro-3,6-diaryl-3,4-dihydro-1,3,2-oxaza-phosphorin-2-oxides were obtained by the interaction of phosphorus oxychloride and triethylamine with aminoketones. These aminoketones were prepared by the condensation of different monosubstituted base hydrochlorides of various aromatic ketones such as acetophenone, p-chloroacetophenone, p-nitroacetophenone, 2,4-dichloroacetophenone, 2-acetylfuran and 2-acetylnaphthalene. The synthesis of these, hitherto unreported, 2-chloro-3,6-diaryl-3,4-dihydro-1,3,2, oxaza-phosphorin-2-oxides is exhaustively covered in this Chapter.

PART - B

Synthesis of several new 2-chloro-3-alkyl-6-phenyl-3,4-dihydro-1,3,2-oxazaphosphorins is described in this Chapter.

CHAPTER - II

PART - A

Whereas a large number of cyclophosphamides have been reported earlier in view of the high anti-leukemic activity of the commercially important drugs Endoxan and

Ifosphamide, surprisingly, 3,6-diaryltetrahydro-oxaza-phosphorins as well as compounds with substituents at 3 and 4 position with a fused saturated ring at 5,6 positions are unreported.

Aryl β-arylaminoethyl ketones were reduced with sodium borohydride to give corresponding aminopropanols. These aminopropanols, when treated with phosphorus oxychloride and triethylamine, yielded substituted 2-chlorotetrahydro-1,3,2-oxazaphosphorin-2-oxides. The synthesis of these compounds is described in this Chapter.

PART - B

Various nucleophilic substitution reactions of 2-chloro-3,6-disubstituted-3,4-dihydro-1,3,2-oxaza-phosphorin-2-oxides and the plausible mechanism for apparent unreactivity of some nucleophiles with dihydro-oxazaphosphorins is discussed in this part.

CHAPTER - III

[A] Mass spectral fragmentation modes of 2-chloro-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxides with various substituents at 2,3 and 6 positions have been discussed in this section.

[B] NMR spectra of all the dihydro-oxazaphosphorins show a complex pattern and multiplicity of signals

cannot be explained properly. 80 MHz spectrum gave useful information and helped us to solve the problem. Chemical shifts and various coupling constants viz. geminal, vicinal and phosphorus couplings as well as ^{31}P spectrum is recorded in this section. ^{13}C NMR spectra are also studied in detail for three compounds and line positions for all carbons are assigned. ^{13}C-^{31}P coupling constants are also calculated. The analysis of these ^{1}H, ^{31}P and ^{13}C NMR spectra is described in this section.

[C] X-ray crystallographic structure of 2-chloro-3-(p-chlorophenyl)-6-(p-tolyl)-3,4-dihydro-1,3,2-oxazaphosphorin-2-oxide, along with bond angles, bond lengths and torsion angles of only dihydro-oxazaphosphorin ring, is given in this section.

CHAPTER - IV

Dimethyl terephthalate being one of the monomers in polyester synthesis, various derivatives of dimethyl 2-aminoterephthalate were prepared.

The synthesis of these compounds as well as the copolymerisation of these compounds is covered in this Chapter.

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