STUDIES ON SOME ORGANOPHOSPHORUS COMPOUNDS : SPECTRAL PROPERTIES, BIOLOGICAL ACTIVITIES AND HYDROLYTIC PROPERTIES.

Thesis Submitted for the Degree of
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of the
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A C K N O W L E D G E M E N T

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S Y N O P S I S

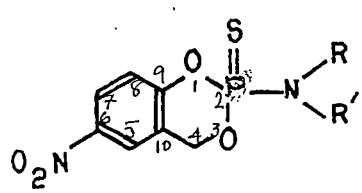
The work embodied in this dissertation is related to the investigation of some nitro-saligenin cyclic amidophosphorothionates with reference to their chemical, biochemical, insecticidal, fungicidal and other toxicological properties besides structural elucidations by chemical analyses and spectroscopic methods.

At the outset, in Part - I of this dissertation, a general introduction including anticholinesterase activities, chemical hydrolysis, NMR, IR, and Mass spectra of some organophosphorus pesticides has been presented. Common or trade names, chemical structures and other properties of some of them have been given in Appendix - I

Part - II of this thesis has been devoted to a short review describing the chemical, bio-chemical, insecticidal, fungicidal and other toxicological properties of saligenin cyclic phosphorus compounds with special emphasis on salithion (2-methoxy-4H-1,3,2-benzodioxaphosphorin-2-sulphide) discovered in 1963 by Prof. Eto., Prof. Oshima and their co-workers. Investigations have revealed that the biological activities of these compounds are greatly influenced by the exocyclic substituents on the phosphorus atom, and also by the substituents in benzene ring and/or in hetero-cyclic ring.

It was reported by Prof. Eto and his co-workers that 2-methoxy-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide (BD-8) was

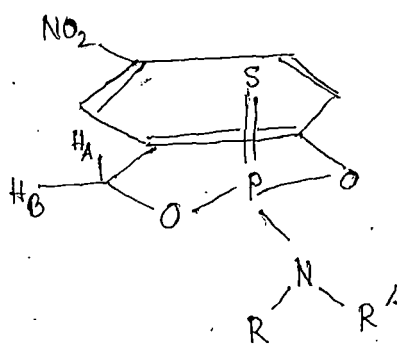
obtained as a paste after purification through silicic acid column chromatography and found to have about sixty times less insecticidal activity compared to salithion. However, it has been observed in this laboratory that the methoxy compound (BD-8) is a solid (m.p. 84°C), and has about 1.5 - 2 times greater oral insecticidal activity to Periplaneta americana than salithion. Moreover, introduction of an amide group in place of an alkyl ester group often gives organophosphorus esters fungicidal, nematocidal and other biological activities. There are many examples in literature which show that some phosphoramidothionates, phosphoramides or phosphonamides in which the phosphorus atom is attached directly to the nitrogen atom of an amine or a hetero-cyclic compound such as phthalamide, imidazole or triazole have very good fungicidal activity. These observations prompted us to undertake a systematic work on some nitro-saligenin cyclic alkylamidophosphorothionates. The work embodied in Part - III of this dissertation is related to the investigation of some 2-alkylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphides having the general structure (A)



where -NRR' = cyclohexylamido, morpholino, diethylamido, dimethylamido, isopropylamido, pyrrolidino, piperidino, or nonylamido group.

Part - III deals with the work related to the synthesis and structure determination of these cyclic phosphoramidothionates. The structures of these compounds have been established

by chemical analyses, UV, IR, Mass and ^{1}H, ^{13}C, ^{31}P - NMR spectral data. All compounds show common IR bands for P-O-C (alkyl), P-O-C (aryl) and for nitro group. They show common parent molecular ion in mass spectra; all compounds show an ion due to $(M - SH)^{+}$. From the study of the PMR spectral data of some 2-alkoxy/phenoxy/alkylamido, 6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphides it is fairly evident that the chemical shift difference of the protons H_A and H_B increases in going from 2-alkoxy to 2-alkylamido compounds, and that the 2-substituent at the same time increases in bulk, and probably spends more time in the conformation with the least steric interactions. The structure II appears to explain, to a reasonable extent, the reversal of the expected proton chemical shift order for the quasi-axial and quasi-equatorial protons, due to the position of the magnetically anisotropic P = S bond relative to the $-CH_2-$ group in the dioxaphosphorin ring.



^{13}C and ^{31}P NMR spectral data of some of these compounds, the temperature dependant of ^{1}H NMR spectra of the methoxy compound (BD-8) have been presented. It has been observed that as the temperature is varied, the rates of inter-conversions

of the conformers and their relative populations are also varied. This suggests that the methylene protons (H_{4A} & H_{4B}) are not equivalent to each other, and the dioxaphosphorin ring is conformationally mobile in solution.

All the compounds show good fungicidal activity against Helminthosporium spp. ; the isopropylamidophosphorothionate is the most effective compound, and its inhibitory effect is greater than that of Hinosan. All compounds have less oral insecticidal activity than salithion against P. americana. They are less toxic to male rats than salithion, and are not phytotoxic. For all compounds the HFAChE - housefly is more inhibited than the ChE - blood.

The rate of alkali hydrolysis is increased as the pH value increases from 7.7 to 11.85; the compounds containing the disubstituted amido groups are extremely resistant to hydrolysis compared to other compounds having the monosubstituted amido groups.

The biological activities and other data justify further examination of these phosphorothionates as potential pesticides.

C O N T E N T S

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PART I

PART - I

ORGANOPHOSPHORUS PESTICIDES : GENERAL INTRODUCTION

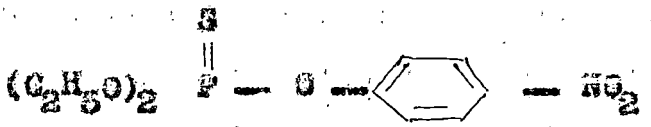
1. INTRODUCTION :

The pest, disease and weed situation are not static - they keep on changing. New physiological races evolve as a result of mutations in nature. Many insects and fungi develop resistant strains when the same insecticide or fungicide is used year after year. Similarly, by the use of the same herbicide, season after season there is often a shift in the weed flora and a number of resistant species become predominant. Even change in croping pattern change the pest, disease and weed situation - many pests, diseases and weeds of minor importance may assume major proportions. It has been often noticed that pests and diseases, virtually unknown and ignored suddenly become very alarming with the introduction of new crop varieties. Bacterial blight, tungrovirus, gall midge of paddy and Phalaris minor in wheat are only a few examples from our country.

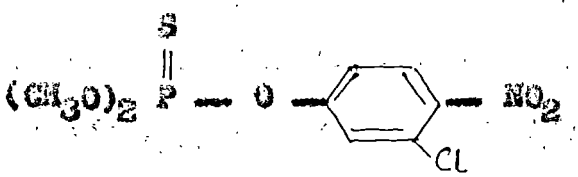
All these definitely point out that the existing pesticides, however efficient they may be cannot solve the pest problems permanently. New pesticides must be developed to combat various new situations. It should be a continuous search - a process of intensive and sustained research and development. Apart from

finding answers to new problems, research and development are also vital for finding pesticides which will be safer, more effective and selective, and above all more economic in the true sense and environmentally acceptable.

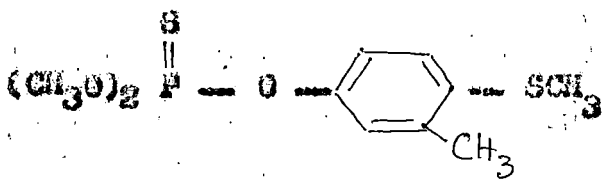
A particularly important group of pesticidal substances comprises phosphorus compounds, the importance of which have been steadily increasing in the recent past. Several new compounds of this group are used for insecticidal, acaricidal, nematocidal, anthelmintic, insect sterilizing, fungicidal, herbicidal, rodenticidal and other purposes. The development of new phosphorus compounds was for a long time dominated almost exclusively by one single guiding principle namely the 'Acyl Rule' of Schrader[1,2,3]. The great advancement in agricultural practice, scientific knowledge of the structure-activity relationship and mode of action of organophosphorus pesticides were achieved by the discovery of parathion by Schrader in 1944. Parathion is extremely toxic to mammals as well as to insects. Many less toxic pesticides have been synthesized by slight structural modification of parathion; for example, chlorthion (in 1952), fenthion (in 1958) and fenitrothion (in 1959) were discovered[3].



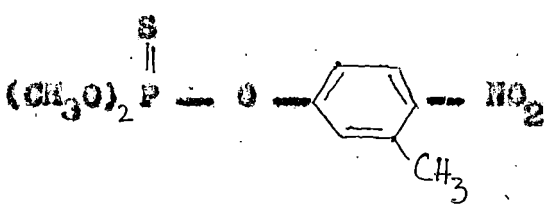
Parathion



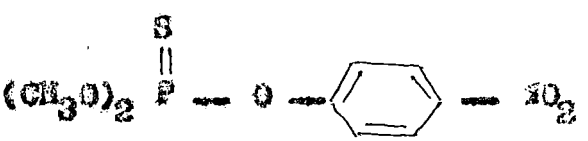
Chlorthion



Fenthion

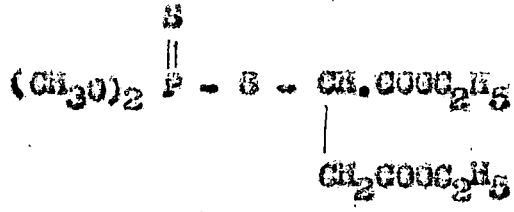


Fenitrothion

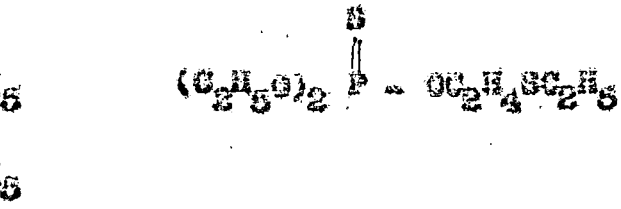


Parathion - methyl

Malathion was discovered in 1950 and demeton in 1951.



malathion



demeton - S

In 1952, the Perkow reaction was discovered, and many important vinyl phosphate esters have been introduced as practical pesticides. Since then several new compounds have been developed and are in commercial use[3]. Common or trade names, chemical structures and other properties of several organophosphorus pesticides have been given in Appendix-I.

2. REACTION WITH CHOLINESTERASE:

It is generally accepted that the organophosphorus compounds are toxic because they phosphorylate vital esterases, thus forming complexes that are either irreversible or do not readily release the enzymes[3]. The enzyme mainly affected is accepted to be cholinesterase, an enzyme that plays a vital role in hydrolysing acetylcholine. The reaction between acetylcholine (Ach) and cholinesterase (ChEn) takes place in three stages:

$$(CH_3)_3\overset{+}{N}C_2H_4O-\overset{O}{\overset{\|}{C}}-CH_3 + ChEH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (CH_3)_3\overset{+}{N}C_2H_4O-\overset{O}{\overset{\|}{C}}-CH_3/ChEH$$

Acetylcholine — Enzyme complex

At this stage there is an equilibrium between the enzyme and its substrate on the one hand and a complex of the two on the other.

$$(CH_3)_3\overset{+}{N}C_2H_4O-\overset{O}{\overset{\|}{C}}-CH_3/ChEH \xrightarrow{k_2} (CH_3)_3\overset{+}{N}C_2H_4OH + CH_3CO.ECh$$

Enzyme complex — Choline + Acetylated enzyme

The complex yields choline and acetylated enzyme in the second stage.

$$CH_3CO.ECh \xrightarrow[k_3]{H_2O} CH_3COOH + ChEH$$

Acetylated enzyme — Acetic acid + enzyme

The final stage is the deacetylation reaction in which the acetylated enzyme is hydrolysed to give the free enzyme and acetic acid.

The active center of acetylcholinesterase (AChE) is structurally complementary to its substrate acetylcholine which contains a trimethyl ammonium group with a positive charge on N and an ester linkage. The enzyme's active center contains a negatively charged anionic site, which binds the trimethylammonium group, and a relatively "nonspecific" esteratic site, which catalyzes the hydrolysis of the ester linkage. In the esteratic site there are basic (histidine, imidazole), serine hydroxyl, and acidic (tyrosine hydroxyl) groups (Fig. 1). The reaction between paraoxon and AChE is represented in Fig. 2. When the two chemicals interact there is a nucleophilic attack of the serine hydroxyl on the phosphorus atom that is aided by the acidic and basic groups present in the esteratic site of the enzyme. This results in the formation of a "reversible" complex that finally yields phosphorylated enzyme and *p*-nitrophenol. Aldridge[4] investigated the inhibition of cholinesterase by parathion and related compounds and found that the complex did not show significant reversibility. In other words, the inhibition of cholinesterase in this case followed first order kinetics and was bimolecular, i.e. :

$$K = \frac{1}{tI} \ln \frac{100}{b}$$

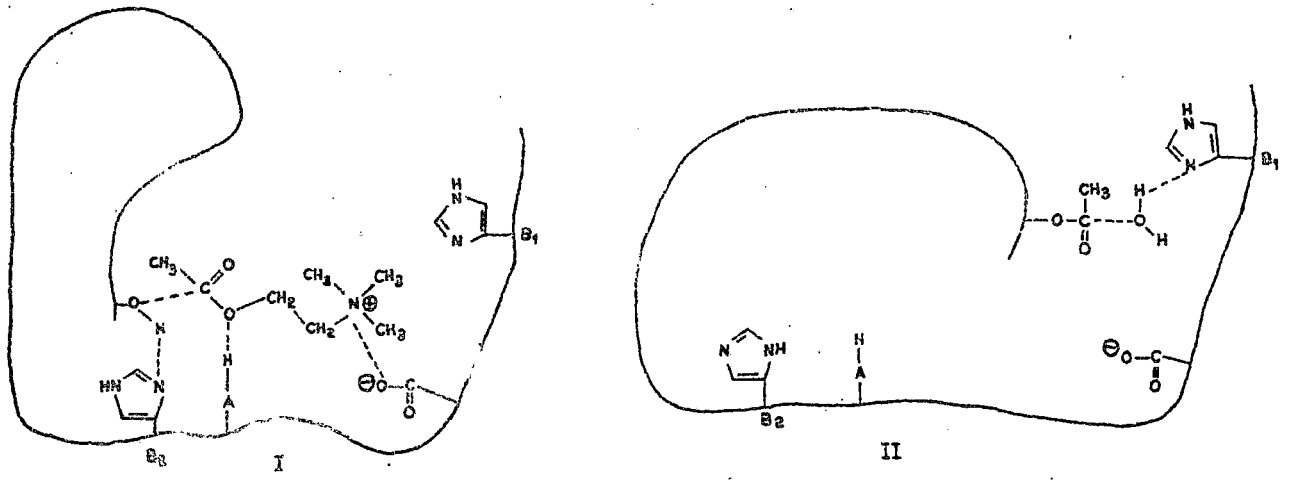


Fig. 1. Schematic Mechanism of action of AChE, after Krupka.
(I) Enzyme-substrate complex in AChE.
(II) Deacetylation of acetyl-AChE.

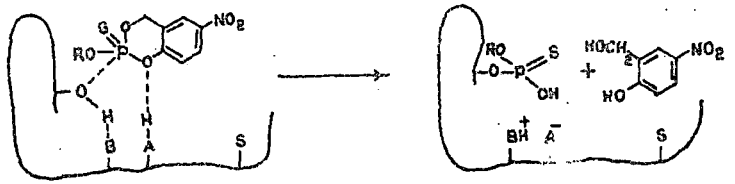


Fig. 2. Schematic mechanism of reaction of organophosphate with AChE.

where K = bimolecular rate constant,

t = time in minutes,

I = molar inhibitor concentration,

and, b = percentage residual activity.

Correlation between the reactivity of a organophosphorus compound and its cholinesterase inhibition, however, has not been ideal, and Main[6] introduced a kinetic treatment for the reaction that takes into account the reversibility of the complex. This reversibility is dependent on the affinity of the inhibiting compound for the active site of cholinesterase as well as on the rate of phosphorylation (Fig. 2). By utilizing different kinetic methods the values for K_i (affinity constant), k_p (phosphorylation constant), and k_b (bimolecular inhibition constant) may be determined[5,6].

If the acetylcholinesterase is destroyed, is irreversibly bound, or forms a complex from which it is released more slowly than under normal conditions, its substrate, acetylcholine, is not easily removed from the receptor surface of the muscle. This causes the muscle to be depolarized longer than usual and gives rise to several action potentials passing through the muscle. The result is a twitching of the muscle leading to tetanus and eventual paralysis of the muscle. Death in mammals occurs as a result of asphyxia caused by the paralysis of respiratory muscles.

3. CHEMICAL HYDROLYSIS:

Since most organophosphorus pesticides hydrolyse, their persistence and/or appearance of hydrolysis products may be obtained from kinetic studies. Hydrolysis rates of these compounds and their metabolites are of interest since chemical hydrolysis determines whether or not toxic residues will persist. The first-order half-lives of some common organophosphorus pesticides including some metabolites are listed in Table - 1 (7).

Table - 1.

Half-lives of some Organophosphorus Pesticides in Ethanol (Tem.70°C, pH 6.0, Buffer Solution (1:4)

Compound	Half-life hours	Compound	Half-life hours
Thimet oxon	0.60	Demeton-s	18.0
Dichlorvos	1.35	Morphothion	18.4
Thimet	1.75	Baytex	22.4
Trichlorphon	3.2	Vamidothion	25.4
Mecarbam	5.9	Menazon	27.6
Malaoxon	7.0	Paraoxon	28.0
Demeton-S-methyl	7.6	Thionazin	29.2
Malathion	7.8	Disulfoton	32.0
Thionazin-oxon	8.2	Diazinon	37.0
Parathion methyl	8.4	Ethion	37.5
Fenchlorphos	10.4	Parathion	43.0
Azinphosmethyl	10.4	Phenkapton	92.0
Sumithion	11.2	Chlorfenvinphos	93.0
Dimethoate	12.0	Carbophenothion	110.0
Thiometon	17.0	Dimefox	212.0
Methyl oxy-demeton	17.1		

The hydrolysis rate is dependent upon the chemical structure and reaction conditions such as pH, temperature, the kind of solvent used, and the existence of catalytic reagents[3]. In aqueous solution, between the pH range 1 to 5 many organophosphorus pesticides are most stable[8], and in this range (pH 1 to 5), the variation in pH of the solution has practically no effect on the hydrolysis rate. But the hydrolysis rate increases steeply at pH higher than 7, and all organophosphorus pesticides are much more unstable under alkaline conditions. Very good discussions on chemical structure and hydrolizability of various organophosphorus pesticides are given by Eto[3] and Faust[7].

4. INFRARED SPECTRA:

The IR spectra-structure correlations of organophosphorus compounds have been given by several workers[9-14]. The first set of organophosphorus group frequency correlations were furnished by Meyrick and Thomson[9] and by Gore[10]. These were based on relatively few compounds. By 1964 Thomas and Chittenden[11] were able to start publishing correlations based on data from 2300 compounds and by 1970 these workers[12] were able to publish organophosphorus group frequency correlations based on data from over 4000 compounds. Thomas[13] has recently revised all the existing correlations in the light of data from 5600 organophosphorus compounds. As a result of this, Thomas[13] has been able to demonstrate that by systematic applications of the correlations, it is possible to deduce a great deal of the structure of an unknown organophosphorus com-

pound on the basis of the IR spectrum. By the application of the correlations given by Thomas [13], Das [14] has been able to deduce the structures of 110 organophosphorus pesticides. A full list of correlations which have been proposed is given in the Table - II.

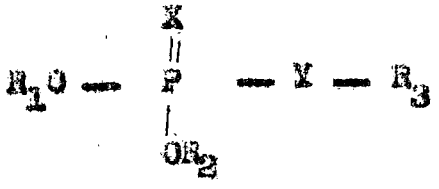
Table - II

a) Phosphorus-Oxygen Links:	
i) P = O (free)	1350-1250 cm^{-1} (s)
P = O (hydrogen bonded)	1260-1110 cm^{-1} (v.s)
ii) P-O-C (aliphatic)	1050-990 cm^{-1} (v.s.) and near 1150 cm^{-1}
P-O-C (ethyl)	1092-1008 cm^{-1} (v.s.) and 1170-1160 cm^{-1} (w)
P-O-C (methyl)	1060-1015 cm^{-1} (v.s.) and 1190 ± 10 cm^{-1} (w)
iii) P-O-C (aromatic)	1240-1190 cm^{-1} (s) and 995-850 cm^{-1} (s)
iv) P-O-P	970-900 cm^{-1}
b) Phosphorus-Sulphur Links:	
P = S (I)	862-674 cm^{-1}
P = S (II)	730-550 cm^{-1}
c) Phosphorus-Carbon Links:	
i) P - phenyl	1460-1425 cm^{-1} (m)
ii) P - alkyl	No useful correlations.
P - CH_3	1320-1280 cm^{-1}
d) Phosphorus-Halogen Links:	
P - Cl	580-440 cm^{-1} (s)
e) Phosphorus-Nitrogen Links:	
P - N	1665-870 cm^{-1}

It should be stated at once that not all of these correlations are of equal value, and that, whilst many of them are based upon the examinations of large number of compounds, others are only very tentative correlations based on a few compounds or on compounds of a limited type. The basis of each of these correlations has been well discussed by Thomas[13].

6. NMR SPECTRA:

The NMR spectra-structure correbations of organophosphorus compound have been given by several workers[15-18]. Babad et al[15] and Keith et al[16] reported the NMR spectra of some organophosphate insecticides in $CDCl_3$. Coupling constants and chemical shifts of some methyl and ethyl substituted organophosphate insecticides are given in Table-III and Table-IV. For compounds,



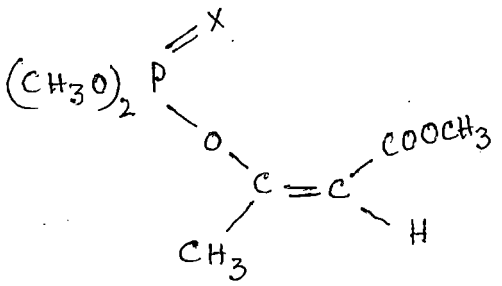
(1)

where R_1 and R_2 are both methyl groups, the methyl peak appears in the region δ = 3.9 to 3.7 ppm with $J(P\text{-}CH_3)$ = 11 to 16 Hz. Organophosphates in which R_1 and R_2 are both ethyl show methyl peaks at δ = 1.4 and methylene peaks in the region δ = 4.2 to 4.4. In this case, the $J(P\text{-}CH_3)$ and $J(P\text{-}CH_2)$ coupling constants are 0.8

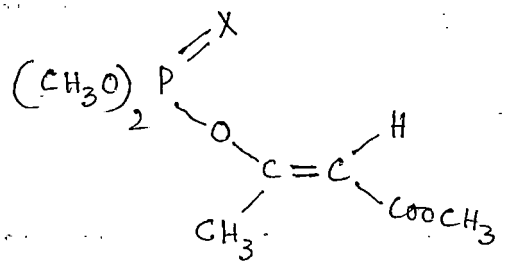
and 10 Hz. The chemical shifts of methyl and ethyl protons are quite comparable, between oxygen-containing organophosphate compounds and their sulfur analogs, but the coupling constants are something higher for compounds with a P = S bond than that with a P = O bond.

In many cases, it has been observed a further splitting in both the methyl proton peaks as well as methylene peaks. (Table-III & IV). This has been explained by Keith et al[16] on the basis of magnetic non-equivalence of methyl protons due to hindered rotation around one or more bonds of the phosphorus atom.

The cis-trans isomerism of organophosphorus compounds has also been detected by NMR. Isomerism is found when phosphorus is attached, by oxygen or sulfur, to a carbon-carbon double bond. The cis and trans isomers of phosdrin and its sulfur analogs are represented by the formula (2) and (3) and their coupling constants and chemical shifts are shown in Table-V.



(2)



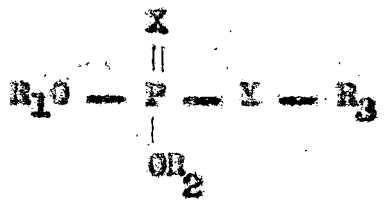
(3)

X = O or S

Some interesting results have been reported for phosphoramidate type compounds in which Y is a nitrogen atom. The NMR spectrum in the methyl region, when two methyl groups are attached to the nitrogen exhibits a pattern characteristic of hindered rotation around the partial carbon-

Table - III

Chemical shifts and coupling constants for methyl groups in various organophosphates.



(1)

Compound	R_1	R_2	R_3	X	Y	δCH_3	$J(P-CH_3)$ Hz
Bidrin	Me	Me	N,N-dimethyl cis-crotonamide	O	O	3.83	11.0
Ciodrin	Me	Me	α-methyl benzyl cis-crotonate	O	O	3.8	11.0
DDVP	Me	Me	2,2-dichlorovinyl	O	O	3.86	11.0
Dicapthon	Me	Me	2-chloro-4 nitro phenyl	S	O	3.92	14.0
Dimethoate	Me	Me	N-methylcarbamoylmethyl	S	S	3.8	15.0
Dimethoxon	Me	Me	N-methylcarbamoylmethyl	O	S	3.83	12.5
Guthion	Me		4-oxo-1,2,3 benzotriazin-3(4H)-yl-methyl	S	S	3.76	15.0

Contd.....

Table - III (Contd.....)

Compound	R_1	R_2	R_3	X	Y	δCH_3	$J(P-CH_3)$ Hz
Guthion (Oxygen analog)	Me	Me	4-oxo-1,2,3 benzotriazin-3(4H)-yl-methyl	O	S	3.81	12.0
Imidan	Me	Me	Phthalimidomethyl	S	S	3.77	15.0
Malaxon	Me	Me	1,2 dicarbethoxyethyl	O	S	3.83 3.82	13.0
Malathion	Me	Me	1,2 dicarbethoxyethyl	S	S	3.81 3.8	15.5
Mete-Systox R	Me	Me	2-(ethyl sulfinyl) ethyl	O	S	3.82	13.0
Methyl Parathion	Me	Me	4-nitro phenyl	S	O	3.87	14.0
Methyl Trithion	Me	Me	P-chlorophenyl thiomethyl	S	S	3.72	15.0
Naled	Me	Me	1,2 dibromo-2,2-dichloroethyl	O	O	3.92 3.91	12.0
Phosdrin	Me	Me	2-carbomethoxy 1-methylvinyl	O	O	3.75	11.0
Phosphamidon	Me	Me	2-chloro-2(N,N-diethylcarbamoyl)-1-methylvinyl	O	O	3.88 3.8	12.0
Ronnel	Me	Me	2,4,5 trichlorophenyl	S	O	3.9	14.0

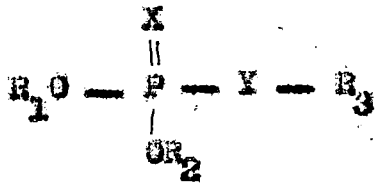
Contd.....

Table - III (Contd.....)

Compound	R_1	R_2	R_3	X	Y	δCH_3	$J(P-CH_3)$ Hz
Ruelene	Me	4-t-butyl-2-chloro-phenyl	methyl	O	NH	3.81	11.0
Tiguvon	Me	Me	4-methylthio-m-tolyl	S	O	3.81	14.0
Trichlorofon	Me	Me	1-hydroxy-2,2,2-trichloro-ethyl	O	-	3.91 3.9	11.0
Zytron	Me	2,4-di chloro-phenyl	isopropyl	S	NH	3.8	14.0

Table - IV

Chemical shifts and coupling constants for ethyl groups in various organophosphate (1)



(1)

Compound	R_1	R_2	R_3	X	Y	δCH_3	$J(P-CH_3)$ Hz	δCH_2	$J(P-CH_2)$ Hz
Co-Ral	Et	Et	3-chloro-4 methyl-2-ozo-2H benzopyran-7-yl	S	O	1.4	0.8	4.2	10.0
Diazinon	Et	Et	2-isopropyl-4-methyl 6-pyridinyl	S	O	1.38	0.8	4.34	9.5
Diazoxon	Et	Et	2-isopropyl-4-methyl 6-pyridinyl	O	O	1.39	1.2	4.33	8.0
Dioxathion	Et(2)	Et(2)	2,3-p-dioxane	S(2)	S(2)	1.36	-	4.17	10.0

Contd.....

Table - IV (Contd.....)

Compound	R_1	R_2	R_3	X	Y	δCH_3	$J(P-CH_3)$ Hz	δCH_2	$J(P-CH_2)$ Hz
Disulfoton	Et	Et	2-ethyl thioethyl	S	S	1.35	0.7	4.17 4.15	10.0
EPN	P-nitro phenyl	Et	Phenyl	S	-	1.36	0.5	4.27	10.0
Ethion	Et(2)	Et(2)	methylene	S(2)	S(2)	1.36	0.8	4.2 4.18	10.0
Paraoxon	Et	Et	4-nitrophenyl	O	O	1.39	0.9	4.26	8.5
Parathion	Et	Et	4-nitrophenyl	S	O	1.37	0.8	4.25	10.0
Phencapton	Et	Et	methyl(2,5-dichlorophenylthio)	S	S	1.36	0.8	4.18 4.16	10.0
Phorate	Et	Et	methyl thioethyl	S	S	1.38	0.8	4.18 4.17	10.0
Thionazin	Et	Et	2-pyrazinyl	S	O	1.41	0.8	4.35	9.0
Trithion	Et	Et	4-chlorophenyl-thiomethyl	S	S	1.33	0.8	4.12 4.09	10.0

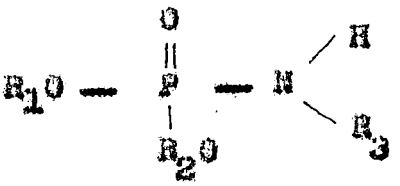
Table - V

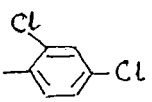
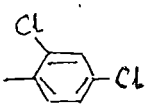
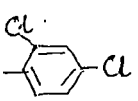
Chemical shifts and coupling constants in phosdrin isomers (2 and 3)

Compound	X	Chemical shift, δ				Coupling constant $J(CH_3-OP)$ Hz
		H	CH_3-O-P	CH_3O_2C	CH_3	
Cis Phosdrin	O	6.78	3.86	3.70	2.42	10.4
trans Phosdrin	O	6.30	3.88	3.67	2.15	11.2
Cis Thiono phosdrin	S	6.68	3.88	3.70	2.37	14.6
trans Thionophosdrin	S	6.36	3.82	3.67	2.10	14.6

Table — VI

Long-range coupling constants in phosphoramidates in $CDCl_3$ at Ambient temperature.



Substituent R_1	R_2	R_3	Coupling constant J(P-N-C-C-H) Hz
$-CH_3$		$-CH(CH_3)_2$	0.7
$-CH_3$		$-C(CH_3)_3$	0.8
$-CH_3$		$-CH_2-CH_3$	1.0
$-C_2H_5$	$-C_2H_5$	$-CH(CH_3)_2$	0.7
$-C_2H_5$	$-C_2H_5$	$-C(CH_3)_3$	0.7
$-C_2H_5$	$-C_2H_5$	$-CH_2-CH_3$	1.0

nitrogen double bond. The long-range $^{31}P - {}^{1}H$ coupling constant $J(^{31}P - N - CH_3)$, although less than 1 Hz, is always observable (Table - VI).

6. MASS SPECTRA:

The mass spectra of several organophosphorus pesticides have been reported by Danico[19], Jörg et al[20], Gillis et al[21] and Eto[3].

A significant rearrangement of two hydrogen atoms to phosphorus connected oxygens with the elimination of an alkyl group occurs at the first step of the fragmentation of trialkyl phosphates[3]. For example, triethyl phosphate decomposes with the following consecutive elimination of two ethylene molecules, giving finally the intense peak of $P(OH)_4^+$ (m/e 99).

$$(C_2H_5O)_3PO]^{+\cdot} \xrightarrow{-C_2} (C_2H_5O)_2\overset{+}{P}(OH)_2 \xrightarrow{-C_2H_4} C_2H_5O\overset{+}{P}(OH)_3$$

m/e 182 m/e 155 m/e 127

$$\downarrow -C_2H_4$$

$$\overset{+}{P}(OH)_4$$

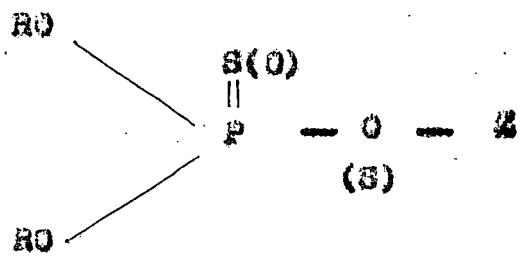
m/e 99

The fragment ion m/e 127 also decomposes in another way, accompanied by the elimination of water, as shown below:

$$C_2H_5\overset{+}{O}P(OH)_3 \xrightarrow{-H_2O} C_2H_5\overset{+}{O}PO(OH) \xrightarrow{-C_2H_4} \overset{+}{O}P(OH)_2$$

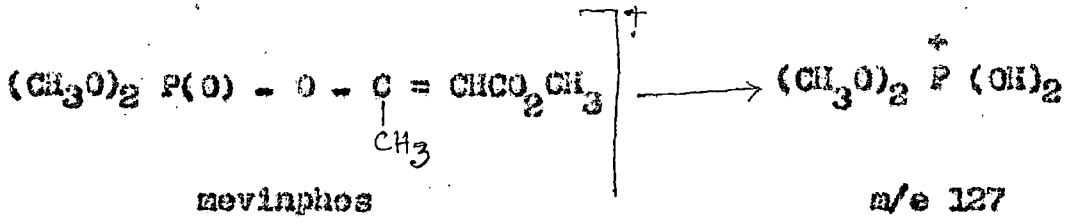
m/e 127 m/e 109 m/e 81

As the Z moiety of common organophosphorus pesticides shown below



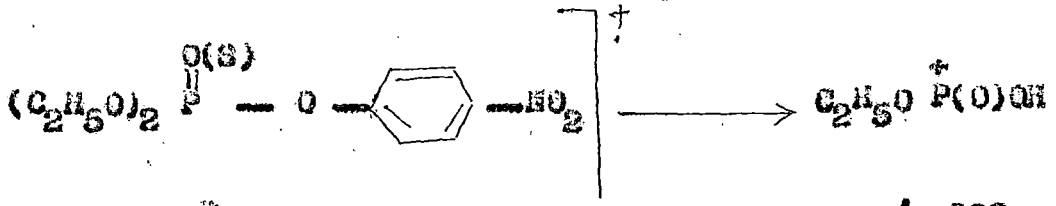
is complex, the successive rearrangement-fragmentation does not always give the final ion $\overset{+}{P}(OH)_4$(m/e 99) or $(RO)_3P\overset{+}{S}H$ (m/e 115).

The base peak ion (m/e 127) for mevinphos and phosphamidon is postulated to be formed by the double hydrogen rearrangement mentioned above.



mevinphos m/e 127

The mass spectrum of paraoxon is similar to parathion, and their base peak ion (m/e 109) is probably formed by the reaction shown below:

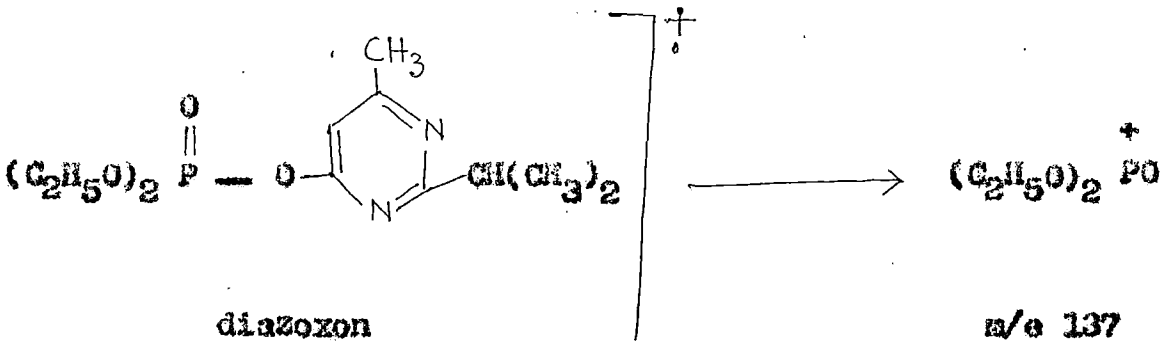


Paraoxon m/e 109

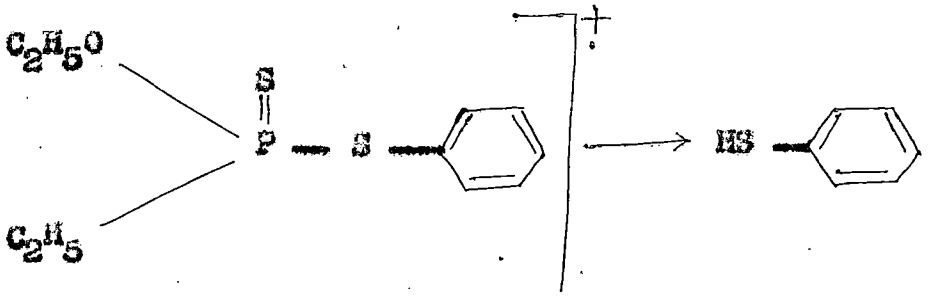
Paraoxon also gives relatively intense peaks of rearrangement fragment ions $\overset{+}{P}(OH)_4$ (m/e 99) and $OP(OH)_2^+$ (m/e 81). Another fragment ion, m/e 139 ($HO.C_6H_4NO_2^+$), may be formed due to α-cleavage of the molecular ion with hydrogen rearrangement.

Dimethyl phosphorothionates such as parathion-methyl and fenitrothion also give a fragment ion of m/e 109. Moreover, these methyl esters, almost without exception, give fragment ions of m/e 125, 93, 79, 63 and 47.

Diazoxon forms a base peak ion (m/e 137) which is found probably due to α-cleavage. This type of fragmentation is most common with almost all phosphorus esters, including O,O-dialkyl phosphates, phosphorothionates, phosphorothiolates, phosphorodithioates, and also O-alkyl alkylphosphonodithioates such as fonofos.

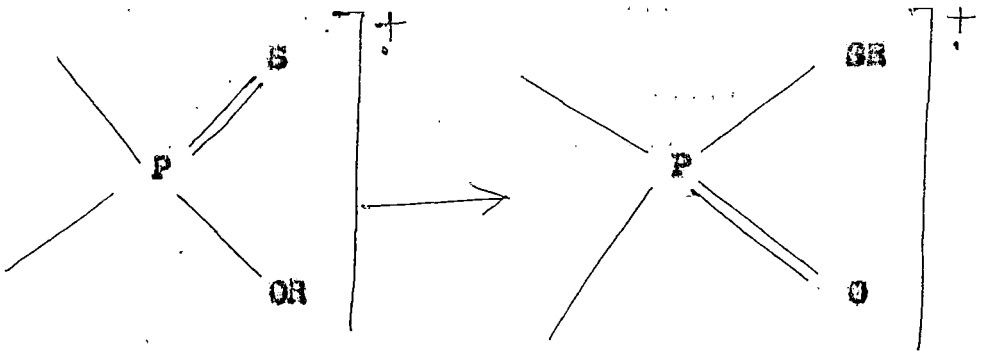


diazoxon m/e 137

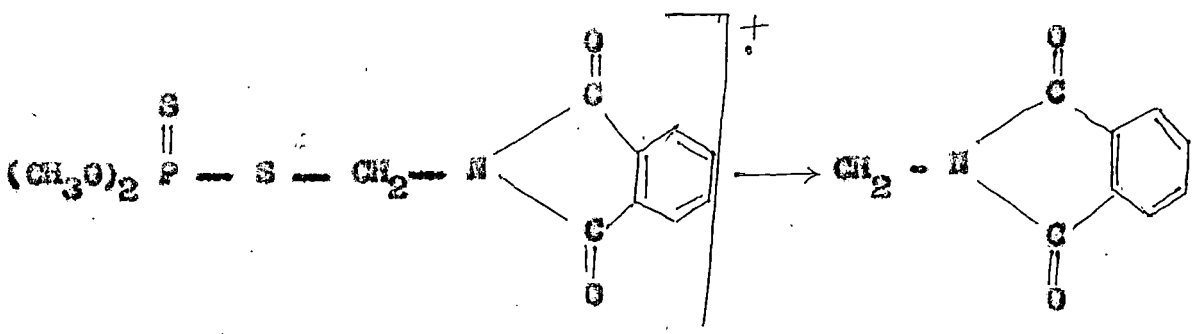


Fonofos m/e 110

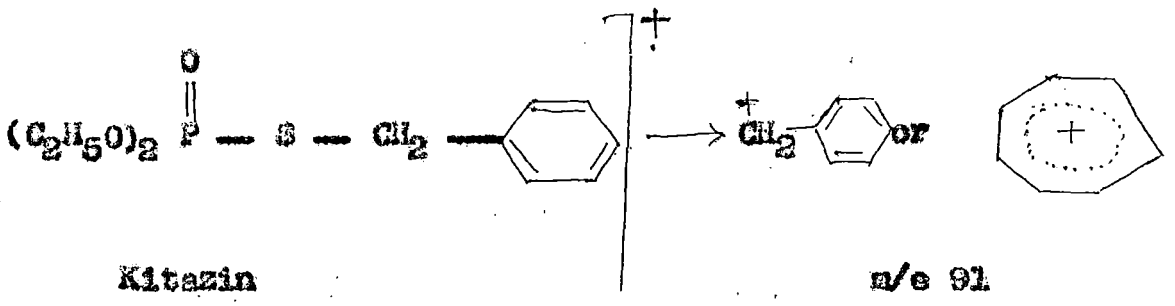
Cooks and Gerrard[22] observed that in case of some phosphorothionates a thiono-thiolo rearrangement may be induced by electron impact before any fission occurs:



In organophosphorus pesticides having a P-S-alkyl(Z) bond, β-cleavage at the S-alkyl bond takes place very often to form a relatively intense peak with the charge on the Z moiety. The base peaks of malathion (m/e 173), phosmet (m/e 160), azinphosmethyl (m/e 160) carbophenothion (m/e 157), and kitazin (m/e 91) are all due to the β-cleavage.

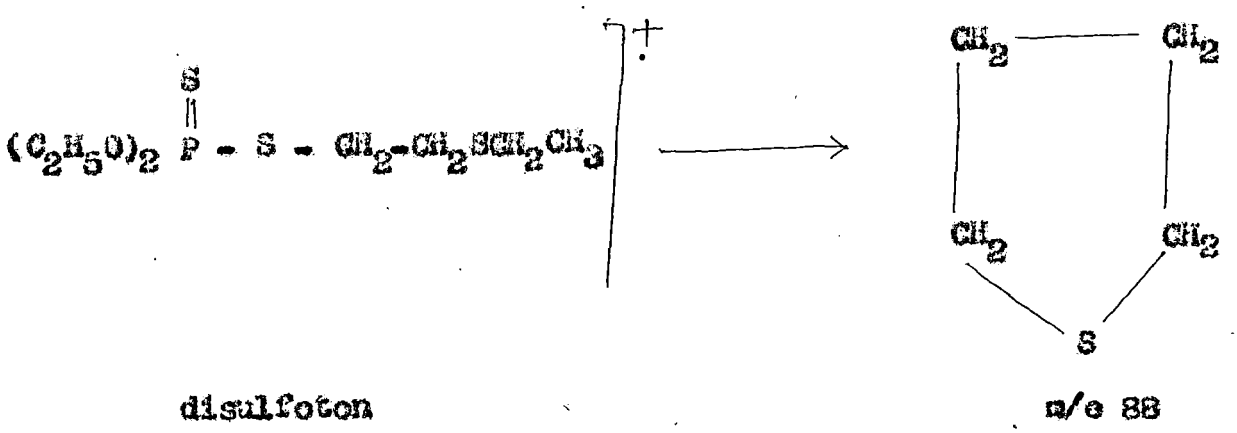


Phosmet m/e 160



Kitazin m/e 91

In some compounds, the β-cleavage occurs accompanied with rearrangement. The base peak of disulfoton (m/e 88) may be due to such a rearrangement forming tetrahydrothiofuran ion.



disulfoton m/e 88

The CI (chemical ionization) mass spectra of several organophosphorus pesticides were also reported[23]. The determination of metastable transitions in the mass spectra of Abate and Dicapthon by direct analysis of daughter ions was also reported[24].

R E F E R E N C E S.

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PART II

PART - II

REVIEW ON SALIGENIN CYCLIC PHOSPHORUS ESTERS HAVING PESTICIDAL ACTIVITY.

1. INTRODUCTION:

Discovery of saligenin cyclic phosphate as a biologically active metabolite of tri-o-cresyl phosphate (TOCP)[1,2,3] has led to the extensive studies on synthesis, chemical and biological properties of many related compounds[4,5]. Analogous cyclic phosphorus esters have been synthetically prepared for examination of their chemical properties[6,7] and biological activities[8,9]. The biological activities are not always coincident with the chemical reactivities and appear to be influenced by the size of an exocyclic substituent on the phosphorus atom. The TOCP-metabolite causes ataxia in hens but has no insecticidal activity, while its analogous cyclic phosphates carrying a small alkyl group have insecticidal activity[10]. Among the saligenin cyclic phosphorus compounds, salithion (2-methoxy-4H-1,3,2-benzodioxaphosphorin-2-sulphide) has been prepared in a large quantity and practically used as an insecticide in Japan[1,5].

This review describes how salithion has been discovered and developed as practical insecticide and also the chemical, pesticidal, biological and other properties of saligenin cyclic phosphorus compounds have been discussed.

2. DISCOVERY OF SALITHION AND RELATED COMPOUNDS:

It was the year 1930, when about 10,000 people in USA were striken with a flaccid paralysis of the lower limbs about 10 days after drinking an adulterated fluid, extract of Ginger[11]. This was due to the phosphate triester of ortho-cresol, so called TOCP, a contaminent present in the ginger extract. Also a similar big outbreak of paralysis took place in 1959 (in Morocco) from cooking oil contaminated with the lubricating oil of turbo-jet aircraft engines[12]. This was also due to o-cresyl phosphate (TOCP) poisoning. The phosphate triesters of cresol have been widely used in industries as plasticizers, lubricants, solvents, oil additives and fire-retardants.

Because of very sensitive to the delayed neurotoxic action of organophosphorus compounds, hens have been used for the assay of the neurotoxicity of triaryl phosphate. Aldridge and Barnes[13,1] observed that all neurotoxic triaryl phosphates except tri-p-ethyl phenyl phosphate have at least one alkyl group carrying the α-hydrogen atom on the ortho position. This structure-neurotoxicity relationship of triaryl phosphates is clearly understandable by the

isolation and characterization of the active metabolities of TOCP [2,3]. The main active metabolite (M) is ortho-tolyl saligenin cyclic phosphate (2-ortho-tolyloxy -4H-1,3,2 benzodioxaphosphorin-2-oxide). It is extraordinarily active in all the biological properties shown by TOCP; this compound (M) is about 100 times more potent to cause ataxia in hens than TOCP: (M) potentiated the toxicity of malathion 100 times by the dose of 20 mg/kg in mice, while TOCP 4 times by the dose 100 mg/kg; (M) is also ten million times more active than TOCP in the in vitro inhibition of plasma cholinesterase [4].

The conversion of TOCP into the cyclic phosphate proceeds via two steps [14] as shown in Fig. 1 : (i) the hydroxylation of the methyl group of TOCP by the mixed-function oxidases (mfo) and (ii) the cyclization by intra-molecular transphosphorylation of the intermediate, di-o-tolyl o-(α-hydroxy) tolyl phosphate, leaving one molecule of cresol. The later reaction takes place slowly in spontaneous manner and is greatly accelerated by the presence of plasma albumin [15].

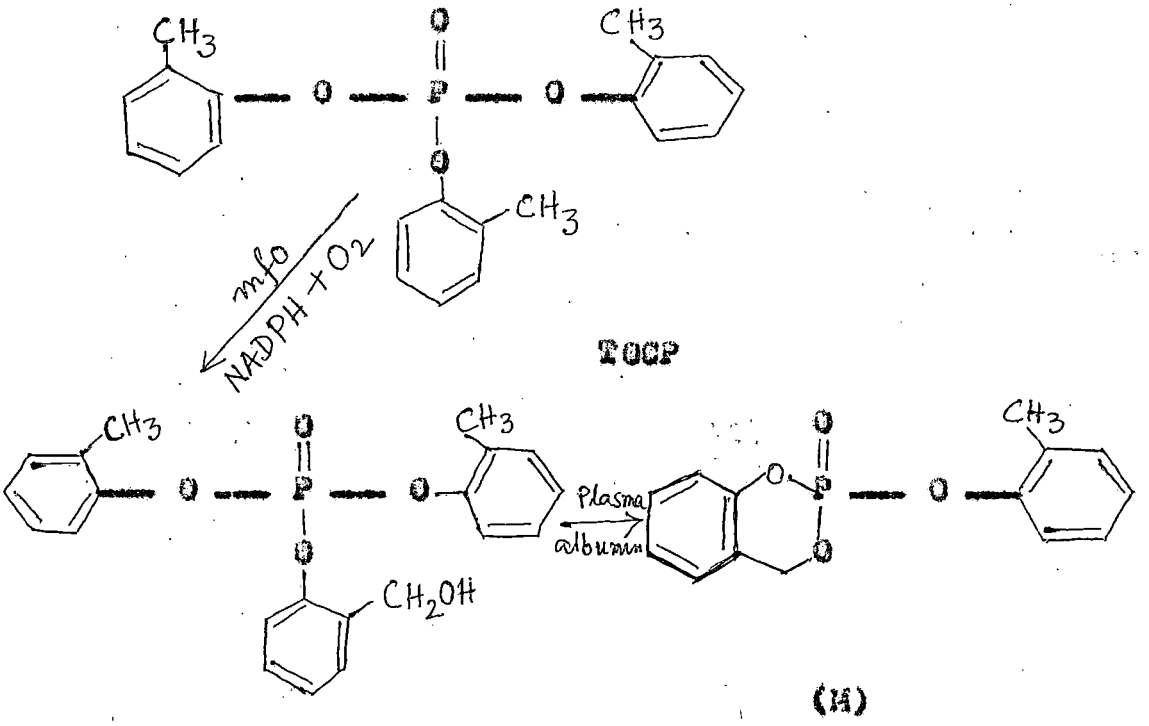


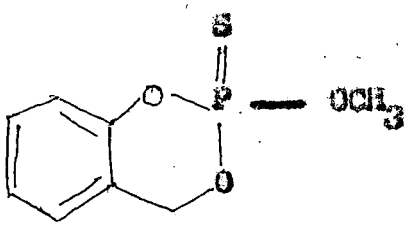
Fig. 1 Metabolic activation of TOCP.

Thus it is rational to presume that the triaryl phosphates having an o-alkyl group with the α-hydrogen atom may be similarly metabolized to give the corresponding active cyclic esters. In the cyclization reaction, no alkyl ester group participates as the leaving group (15). Actually, no aryl but alkyl saligenin cyclic phosphate is formed in vivo from alkyl di-o-tolyl phosphates (16). Such metabolic

activation of TOCP or its analogs have been observed in rats [14], hens [14], cats [17] and insects [16].

All aryl saligenin cyclic phosphates have showed no insecticidal activity but manifested a high delayed neurotoxicity to cause ataxia in hens; surprisingly the corresponding cyclic esters (both P = O and P = S compounds) having a small alkyl group on phosphorus revealed high insecticidal activity [2,8].

As a result of the aforesaid research "Salithion" (2-methoxy-4H-1,3,2-benzodioxaphosphorin-2-sulphide), an organophosphorus insecticide having a unique cyclic ester structure was discovered by the pesticide research group of Kyushu University [10] in 1963. Salithion was developed into a commercial insecticide in 1968 by Sumitomo Chemical Co. With the co-operation of Toa-Noyaku Co. (now Kumiai Chemical Co.) and Nikkasa Chemical Co. of Japan.

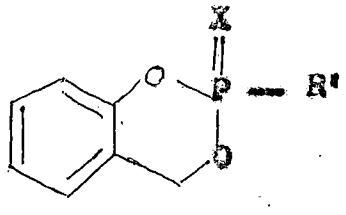


Salithion

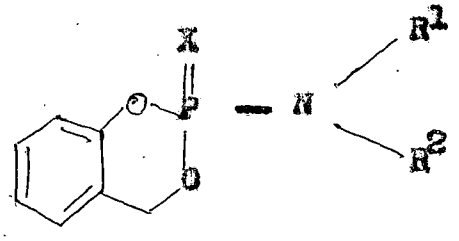
3. SYNTHESIS OF SALIGENIN CYCLIC PHOSPHORUS ESTERS:

The cyclic phosphate and phosphonate esters of saligenin are readily synthesised by condensation of saligenin and substituted phosphoryldichlorides in the presence of a dehydrochlorinating agent such as tertiary amine in a dry solvent like chloroform or toluene at low temperature[6]. In some cases where the reaction is affected difficultly by using the tertiary amine, the reaction has been made to proceed by heating the mixture for 10 to 20 hours in the presence of anhydrous potassium carbonate together with copper powder[18] instead of tertiary amine.

Such compounds, which are difficultly produced by the method employing a tertiary amine, include the compounds having X = S and R' = methoxy in formula (I) and X = S, R^1 = H and R^2 = alkyl containing more than one carbon atom or R^1 = R^2 = alkyl in the formula (II).



(I)



(II)

The process using potassium carbonate is made to proceed by a reaction between liquid and solid phases. Therefore, even if potassium carbonate is employed as finely divided powder form, it often causes a remarkable lowering and fluctuation of the yield[18]. Thus salithion was first prepared with inconsistent and, often, very low yield by heating (90°C) saligenin and methyl phosphorodichloridothionate in toluene for a long period (more than 15 hours) in the presence of anhydrous potassium carbonate together with copper powder as catalyst[19].

This difficulty, has been however, overcome later by applying the well-known Schotten-Baumann acylation procedure using an aqueous solution of sodium hydroxide (Fig. 2)

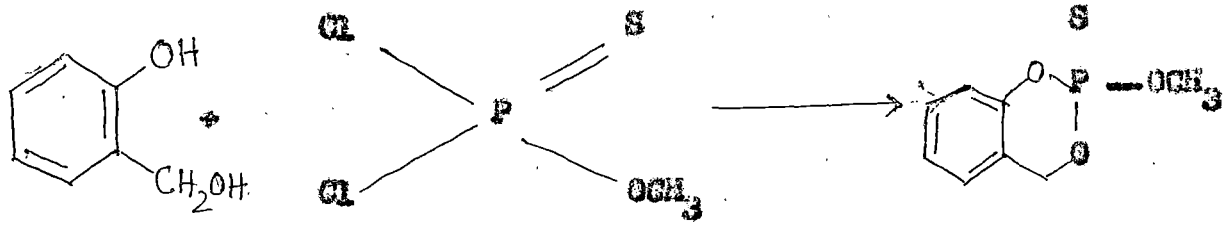


Fig. 2 Synthesis of Salithion.

Some typical examples are given below:

(a) Salithion (2-methoxy-4H-1,3,2-benzodioxaphosphorin-2-sulphide)[18]:

6.2 gm o-hydroxy benzyl alcohol was dissolved in 30-40 ml. 20 percent (by weight) sodium hydroxide aqueous solution. Methylthiophosphorodichloridate (8.3 - 11 gm) was then added dropwise to the above mixture at about 10°C with constant vigorous stirring. After the addition, stirring was continued for one hour, as a result, crystals were separated. 70 ml of chloroform or toluene was added to the reaction mixture and the stirring was continued for additional one hour. The organic layer was separated and washed with 2% sodium hydroxide, 0.5 (N)HCl and water, and dried over anhydrous sodium sulphate; the solvent was then removed at reduced pressure, and the solids thus separated, were recrystallized from methanol to give 6.5 - 7.6 gm (yield 60 - 70 percent) pure crystals of salithion, M.P. 52°C. Methylthiophosphorodichloridate can be prepared by the reaction of CH_3OH and $PSCl_3$ in presence of a base[20a,b].

(b) 2-alkoxy-6-nitro-4H-1,3,2-benzodioxaphosphorin 2-sulphide[21,22]:

These compounds were prepared by adding 1 mole 5-nitro saligenin in dried acetone dropwise to a mixture of alkylthiophosphorodichloridate (1 mole) and anhydrous potassium

carbonate (2 moles) in acetone at -5^{o} to $+5^{o}$C with constant vigorous stirring. After an additional stirring period of 1 - 3 hours at 0^{o} - 5^{o}C, the solids were filtered out of the reaction mixture and the solvent was removed at room temperature. The residual solid mass was dissolved in ethyl acetate and washed with ice cold water containing 5% sodium chloride. The ehtyl acetate phase was lyophilised and the solvent was removed at reduced pressure. For methoxy compound a semi-solid deep-brown paste was obtained; after standing for several days, the crude mass was solidified, and the solid, after washing several times, was recrystallized from methanol. All other compounds were solids[21].

(c) 2-ALKYLAMIDO-4H-1,3,2-BENZODIOXAPHERPHORIN-2-SULPHIDE/OXIDE[23]:

Saligenin cyclic phosphoramidates and phosphoramidothionates were synthesized from saligenin and appropriate phosphoramidic dichloride by the action of proper dehydrochlorinating agent. The reaction of saligenin with reactive dichloride as mono-alkyl phosphoramidic dichloride and some others was proceeded by the action of tertiary amine such as pyridine or triethylamine in cold condition. Liquid dichloride was usually added dropwise to the mixture of saligenin and the base in chloroform. Solid dichloride was however, dissolved

in cold chloroform with saligenin, then the amine was added dropwise to the chilled mixture. When the dichloride was less reactive as almost all phosphoramidothionic dichlorides, heating the mixture of reactants in toluene in the presence of anhydrous potassium carbonate and copper powder was useful. Typically, 2-methylamino-4H-1,3,2-benzodioxaphosphorin-2-oxide was prepared in the following procedure : To a mixture of saligenin, 9.2 gm, triethylamine, 15 gm, and 90 ml. chloroform, was dropwise added 12 gm methylphosphoramidic dichloride with stirring and cooling in an ice bath. After the completion of addition, the reaction mixture was kept overnight at room temperature, and then washed sequentially with ice-water, dil. HCl acid, aq. sodium bicarbonate solution and ice-water. The solvent was removed in vacuo after drying over anhydrous sodium sulphate. Crude crystals were recrystallized from benzene to yield pure crystals, m.p. 87°C (8 gm). Phosphoramidic and phosphoramidothionic dichlorides were prepared according to Michaeli's[24] method.

(d) Saligenin Cyclic Phosphorothiolates[25] :

Phosphorodichloridothiolates reacted with saligenin in the presence of solvent and pyridine or other tertiary amine at room temperature or at about 60°C. The products were purified by distillation in vacuo or recrystallization.

Typically, 2-Methylthio-4H, 1,3,2 benzodioxaphosphorin-2-oxide (MTBO) can be prepared in the following procedure:

To a mixture of saligenin (6.2 gm), pyridine (8 gm) and chloroform (100 ml), was added dropwise methyl phosphorodichloridothiolate (8 gm) with stirring at 20°C. After stirring for three hours, the reaction mixture was washed in sequence with water, dil. alkali, dil. HCl acid and water and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the residue was distilled *in vacuo* to give 3.2 gm of oil [b.p. 144-145°C (0.1 mm Hg)]. The oil solidified slowly at room temperature (m.p. of pure MTBO 44°C).

MTBO can also be synthesized from salithion by the following procedure[26]:

A mixture of salithion (20 gm, 0.0925 mole), potassium iodide (3 gm, 0.018 mole), methyl iodide (9 ml, 0.145 mole) and dimethyl formamide (20 ml) was kept at temperature 25°C for 24 hours. The mixture was then carefully concentrated to avoid complete dryness *in vacuo* and dissolved in chloroform (50 ml). Chloroform solution was washed with water (4 times) and dried over anhydrous sodium sulphate. After filtration, the filtrate was evaporated at reduced pressure to give MTBO (8.95 gm) in 45% yield. The residue was solidified on cooling. MTBO was recrystallized from ethanol at -15°C.

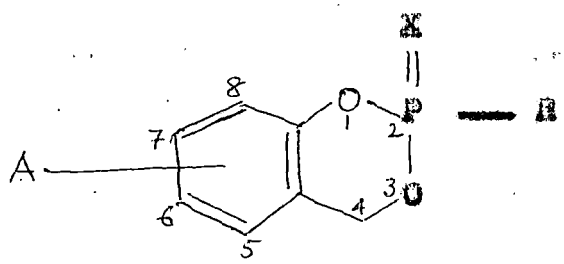
2-substituted-4H-1,3,2-benzodioxaphosphorin-2-sulphides including methoxy (salithion), alkylamino, alkylthio and arylthio derivatives were synthesized in good yield by the application of Schotten-Baumann acylation reaction (procedure 'a' given above); this method was very useful for the preparation of cyclic esters which were difficulty prepared by a tertiary amine method[27]. But, 6-nitro derivatives can be best prepared by the procedure 'b' mentioned above[21,22].

4. Other Saligenin Cyclic Phosphorus Esters:

The careful observation of literatures furnishes[18,19,25, 27,28,29,30] a variety of saligenin cyclic phosphorus esters in good numbers, which have been prepared and examined for insecticidal activity as well as other biological properties. They involve phosphates, phosphorothiolates, phosphoramidates, phosphonates and their thiono-analogs. A comprehensive but not a complete list of saligenin and ring substituted saligenin cyclic phosphorus esters is given in Table-I and Table-II.

Table - I

Substituted Saligenin Cyclic Phosphorus Esters with Physical Properties.



R	A	X	*Procedure	b.p. °C/mm Hg(m.p. °C)
OCH_3	H	S	(S)	55-56°C
OCH_3	H	O	(P)	110-2°/0.05
O-n-C_3H_7	H	O	(P)	129-32°/0.05
O-n-C_4H_9	H	O	(P)	150-4°/0.05
OC_2H_5	H	S	(P)	Liquid (not distilled)
OC_6H_5	H	S	(P)	(30°)
C_6H_5	H	S	(P)	(37°)
CH_3	H	O	(P)	140°/0.5 (35°)
C_2H_5	H	O	(P)	143-9°/0.3 (25°)
i-C_3H_7	H	O	(P)	(80°)
Sec-C_4H_9	H	O	(P)	110°/0.5
t-C_4H_9	H	O	(P)	(74°)
$CH = CH_2$	H	O	(P)	155°/2.5
CH_2Cl	H	O	(P)	160°/0.8 (51°)

Contd.....

Table - I (Contd.....)

R	A	X	*Procedure	b.p. °C/mm Hg(m.P. °C)
CH_2CH_2Cl	H	O	(P)	139-141°/0.1
CH_3	H	S	(P)	130°/0.6
C_2H_5	H	S	(P)	120°/0.6
1-C_3H_7	H	S	(P)	108°/0.6
CH_2Cl	H	S	(P)	146-155/0.4
OCH_3	6-CH_3	O	(P)	139-140/0.3
OC_2H_5	6-CH_3	O	(P)	152-156/0.3
OCH_3	7-CH_3	O	(P)	109/0.05
OC_2H_5	7-CH_3	O	(P)	112-118/0.05
O-n-C_3H_7	7-CH_3	O	(P)	141-147/0.1
C_6H_5	7-CH_3	O	(P)	(93-95)
$NHCH_3$	7-CH_3	O	(P)	(145-146)
OCH_3	8-CH_3	O	(P)	118-120/0.5
OC_2H_5	8-CH_3	O	(P)	165/0.6
OC_6H_5	8-CH_3	O	(P)	135-140/0.6
OCH_3	6-Cl	O	(P)	145-152/0.2
OC_2H_5	6-Cl	O	(P)	160/0.2
O-n-C_3H_7	6-Cl	O	(P)	167-169/0.15
O-n-C_4H_9	6-Cl	O	(P)	187/0.18
OC_6H_5	6-Cl	O	(P)	(89°)
$NHCH_3$	6-Cl	O	(P)	(148°)
OCH_3	8-Cl	O	(P)	170-171/0.15
OC_2H_5	8-Cl	O	(P)	151/0.18
O-n-C_3H_7	8-Cl	O	(P)	183/018

Table - I (Contd.....)

R	A	X	*Procedure	b.p.°C/mm Hg (m.p. °C)
O-i-C_3H_7	8-Cl	O	(P)	137/0.04
OC_6H_5	8-Cl	O	(P)	203/0.52 (54°)
$NHCH_3$	8-Cl	O	(P)	(128-129°)
OCH_3	6-CH_3	S	(S)	(34-35°)
OC_2H_5	6-CH_3	S	(S)	(71-72°)
O-n-C_3H_7	6-CH_3	S	(S)	158-160/0.2
OCH_3	7-CH_3	S	(S)	110-115/0.65
O-n-C_3H_7	7-CH_3	S	(S)	140-142/0.65
OCH_3	8-CH_3	S	(S)	68-70/0.15
OC_2H_5	8-CH_3	S	(S)	103-109/0.15
O-n-C_3H_7	8-CH_3	S	(S)	120-124/0.15
$NHCH_3$	8-CH_3	S	(S)	(30°)
OCH_3	6-C_6H_5	S	(S)	Oil**
OC_2H_5	6-C_6H_5	S	(S)	Oil**
O-n-C_3H_7	6-C_6H_5	S	(S)	Oil**
OCH_3	6-OCH_3	S	(S)	Paste**
OCH_3	6-$COCH_3$	S	(S)	Paste**
OCH_3	6-Cl	S	(P)	170-178/0.2
$NHCH_3$	6-Cl	S	(P)	176-180/0.25
SCH_3	6-Cl	S	(S)	160-170/0.2
OCH_3	8-Cl	S	(S,P)	(72-73°)
$NHCH_3$	8-Cl	S	(P)	(46-47°)

Contd.....

Table - I (Contd.....)

R	A	X	*Procedure	b.p.°C/mm Hg (m.p. °C)
SCH_3	8-Cl	S	(S)	Oil**
OCH_3	6-NO_2	S	(S)	Paste**
OCH_3	6-Cl	S	(S)	Paste**
	8-C_6H_5	S	(S)	
OC_2H_5	" "	S	(S)	Paste**
O-n-C_3H_7	" "	S	(S)	Paste**
OCH_3	6-C_6H_5	S	(S)	Paste**
	8-Cl			
OC_2H_5	" "	S	(S)	Paste**
O-n-C_3H_7	" "	S	(S)	Paste**
OCH_3	6,8-Cl	S	(S)	(57-58°)
OC_2H_5	"	S	(S)	Oil**
$NHCH_3$	"	S	(S)	Oil**
SCH_3	H	S	(S)	(69-70°)
SC_2H_5	H	S	(S)	145-147/0.2
S-n-C_3H_7	H	S	(S)	145-150/0.25
S-i-C_3H_7	H	S	(S)	140-143/0.1
S-C_2H_5	H	S	(S)	140-147/0.3
S-n-C_4H_9	H	S	(S)	160-167/0.25
S-C_6H_5	H	S	(S)	(79-80°)
SCH_3	H	O	(P)	144-145/0.1

Contd.....

Table - I (Contd.....)

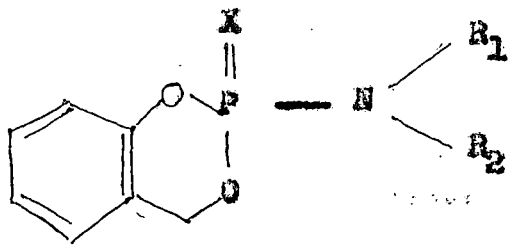
R	A	X	*Procedure	b.p. ^{o}C/mm Hg (m.p. ^{o}C)
SC_2H_5	H	O	(P)	140-145/0.04
S-n-C_3H_7	H	O	(P)	145-147/0.07
S-i-C_3H_7	H	O	(P)	156-158/0.1
S-n-C_4H_9	H	O	(P)	157-160/0.02
SC_6H_5	H	O	(P)	(88-89^{o})

* Pyridine (P) or aqueous sodium hydroxide solution (S) was used as dehydrogen chloride agent.

** These compounds were purified through silicic acid column chromatography.

Table - II

Saligenin Cyclic Phosphoramidates and Phosphoramidothionates with Physical Properties.



Code No.	R_1	R_2	X	*Procedure	b.p. °C/mm Hg (m.p. °C)
K-19	CH_3	H	O	A	(87)
K-22	C_2H_5	H	O	A	(68)
K-41	n-C_3H_7	H	O	A	135-140/0.5
K-40	i-C_3H_7	H	O	A	(84)
K-42	n-C_4H_9	H	O	A	(46-47)
K-10	C_6H_5	H	O	A	(131-133)
K-20	CH_3	CH_3	O	A	(121)
K-23	C_2H_5	C_2H_5	O	B	133-6/0.5 (44)
K-35	CH_3	H	S	A	120-123/0.2
K-37	C_2H_5	H	S	B	Undistilled liquid
K-36	CH_3	CH_3	S	B	118-122/0.2
K-38	C_2H_5	C_2H_5	S	B	110/0.2

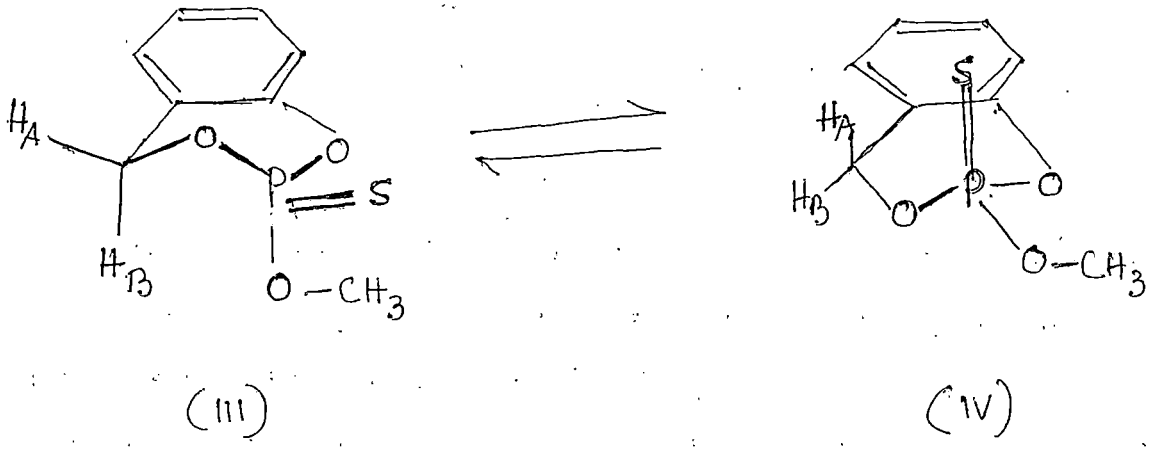
*Tertiary amine (A) or potassium carbonate (B) was used as dehydrogen chloride agent.

6. Chemical and Biological Properties of Salithion:

Here we concentrate our discussion to the important properties of salithion [5] relating to its structure, chemical and biological properties.

Pure salithion is a colourless crystalline powder: m.p. 55°-56°C; practically insoluble in water but easily soluble in acetone and benzene, moderately soluble in cyclohexane, toluene and xylene; vapour pressure 1.6×10^{-6} mm Hg at 25°C; UV λ_{max} nm(ϵ) 274(860), 267 (860). Salithion has a characteristic IR band at 1020 cm^{-1} for P-O-CH_2 in the hetero ring. NMR $\delta(CH_2)$ ppm ; 3.76 (3H, doublet, J_{PH} = 14 Hz, CH_3), 6.21 (2H, doublet, J_{PH} = 15 Hz, CH_2), 6.8 - 7.2 (4H, multiplet, benzene ring). The signal at upper field of the doublet at 6.21 ppm slightly splits further (1.5 Hz). This becomes much significant at -30°C, suggesting the methylene protons (H_A , H_B) are not equivalent with each other, but the

dioxaphosphorin ring is conformationally mobile in a solution (Fig. 3)



(III) (IV)

Fig. 3 Conformational change of salithion hetero ring.

X-ray crystallographic analysis shows that the hetero ring of salithion is a half chair form in which the sulfide group is in equatorial position (III). The strain in the ring appears little; the endocyclic O-P-O angle is 104°.

Salithion gives a characteristic fragmentation pattern in mass spectrometry[31]. It gives an intense peak of $[M - CH_3]^+$ (m/e 201) by β-cleavage occuring at the exocyclic ester group. Another fragmentation process is the direct loss of SH followed by the elimination of formaldehyde (Fig. 4).

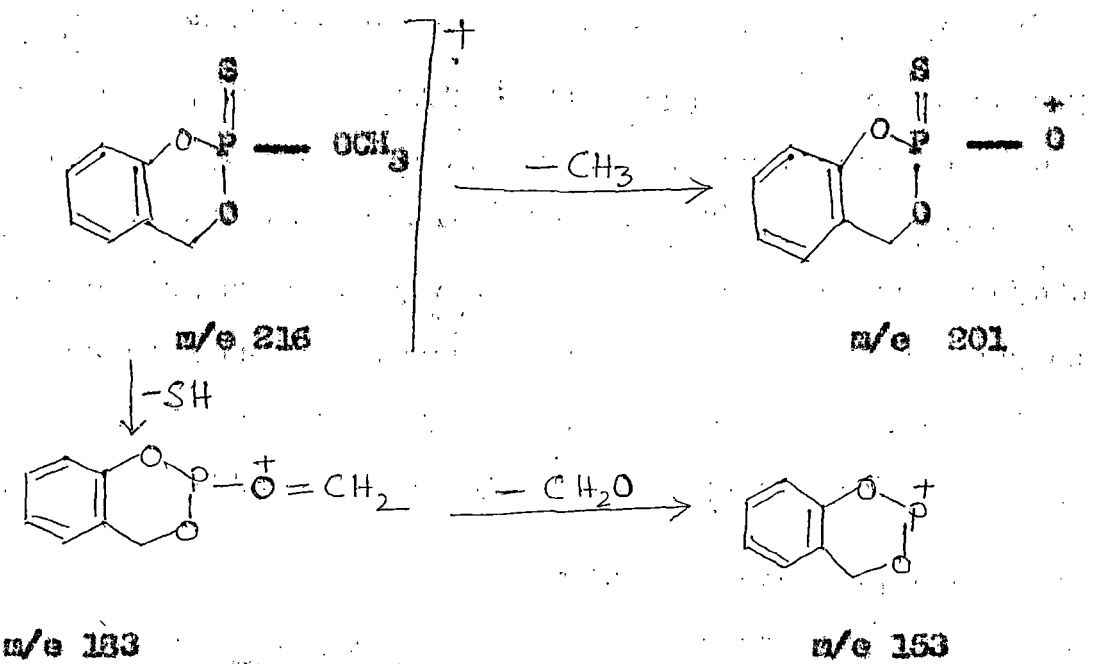


Fig. 4. Fragmentation of salithion in mass spectrometry.

Salithion is converted to its oxon analog (salioxon) by the action of bromine water. Since salioxon (2-methoxy-4H-1,3,2 benzodioxaphosphorin 2-oxide) is some thousands times more active in cholinesterase inhibition than salithion, an enzymatic method after the oxidation can be used for the residue analysis of salithion[32].

Salithion is converted into S-alkyl saligenin cyclic phosphorothiolates by heating with alkyl iodides (the Pistchimuka reaction)[33]. This reaction is accelerated in such polar compound as dimethyl formamide. Potassium carbonate also assists the reaction. When methyl iodide is used, isomerization occurs to give 2-methylthio-4H-1, 3,2-benzodioxaphosphorin-2-oxide (MTBO)[33,34]. Saligenin is demethylated to form the salt of saligenin cyclic phosphorothionic acid by the action of certain neucleophiles such as cyclohexylamine[5] and potassium dimethyldithiocarbamate[5,35]. The later reagent is particularly suitable for the preparation of MTBO by methylating the obtained salt with methyl iodide. MTBO is a unique phosphorylating agent[5]. The reactions of salithion are summarized in Fig. 6.

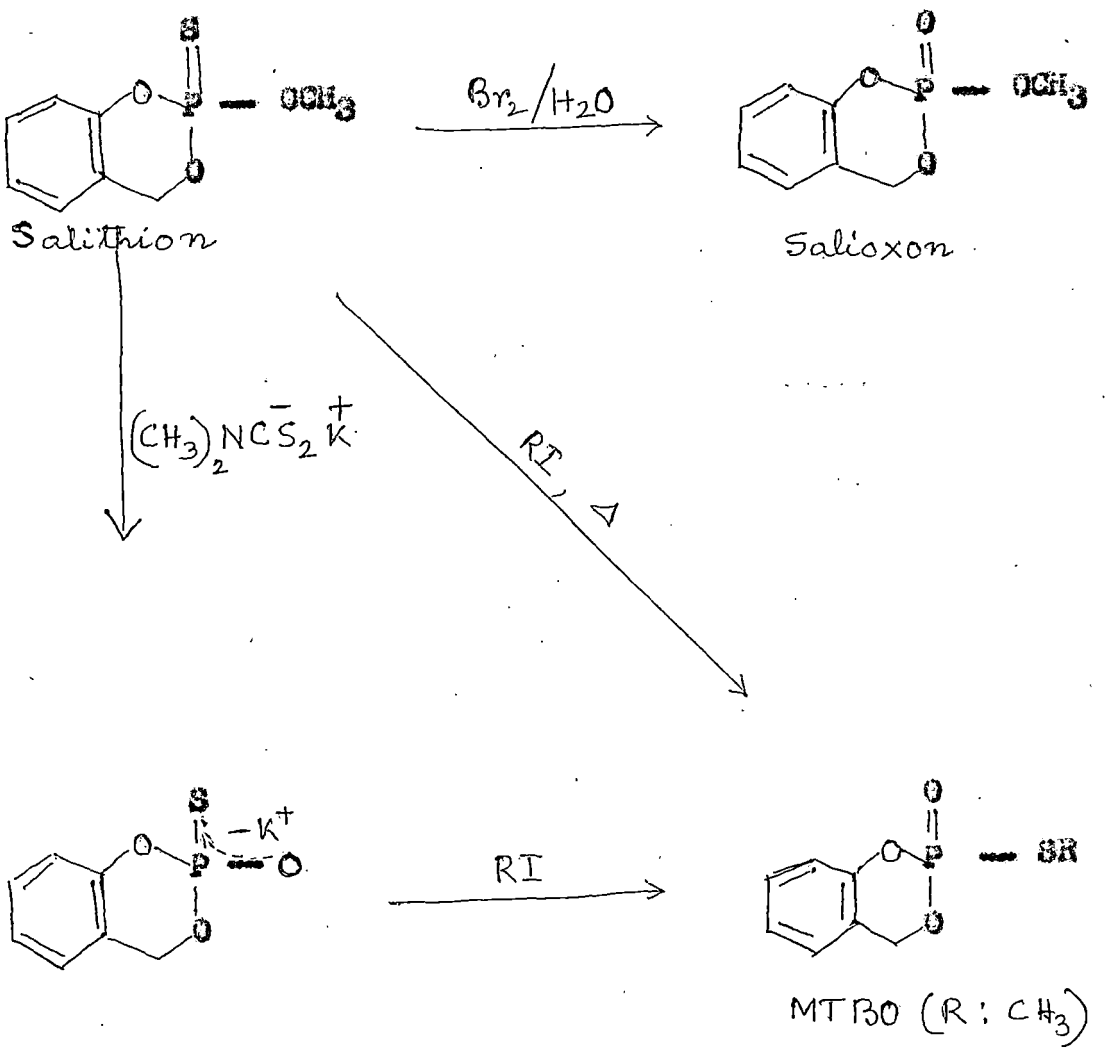


Fig. 5 - Reaction of Salithion.

Salithion is relatively unstable in storage. Some secondary amines, such as carbazole and N-phenyl α-napthylamine, stabilized the formulation (36). In a phosphate buffer (pH 7.7), salithion is hydrolysed slowly through opening of the hetero ring by the P-O (aryl) bond cleavage (5); the hydrolysis

rate constant (25^{o}) K = 2.4 x 10^{-4} min^{-1} . The rates of hydrolysis of the corresponding cyclic methylphosphonate, S-methyl phosphorothiolate (the thiolate isomer of salithion, MTBO), methyl phosphate (salioxon), and N-methyl phosphoramidate are, respectively 90, 60, 6 and 0.6 times greater than that of salithion. Salithion is completely hydrolyzed by heating at 100^{o}C for 5 minutes with N/6 sodium hydroxide to yield saligenin. The hydrolysis of salithion is shown in Fig. 6.

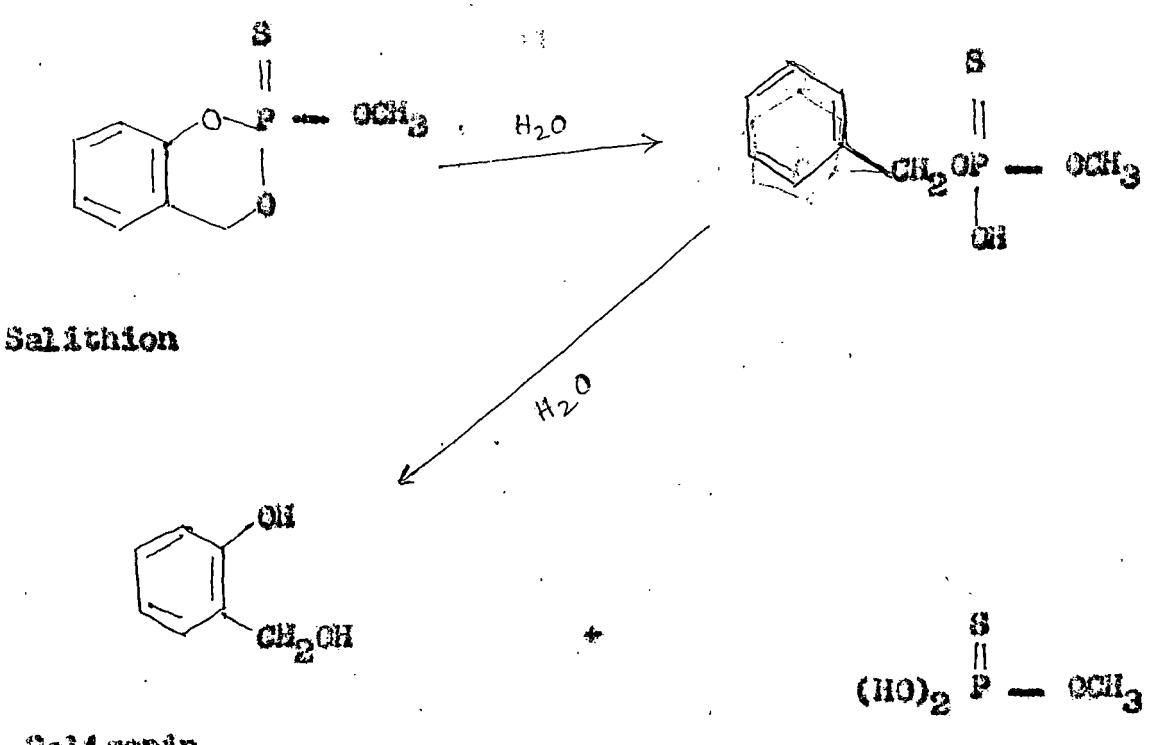


Fig. 6. Hydrolysis of Salithion.

Salithion is a wide-spectrum insecticide for use in orchards and vegetable gardens. It is particularly effective to control lepidopteran larvae, molaybugs, aphids and mites. It manifests the insecticidal action not only as contact and stomach poisons but also as a fumigant (37).

Salithion ^{32}P applied topically to houseflies rapidly absorbs into the body (42% after one hour). The major part was degraded in the body and about 4% of applied or 10% of absorbed salithion remains as salithion and salioxon for 24 hours. On the other hand, salithion ^{32}P administered orally to mice was rapidly degraded and excreted. After one hour, 78% of administered salithion was hydrolysed in the body. After 3 hour, 56.7% excreted and only 2.4% remained in the body (38).

Mihara et al (39) investigated the metabolism of salithion in rats and plants using ^{14}C-labelled compound. When rats were treated orally with salithion-4-^{14}C at the dosage of 9 mg/kg, 72, 82 and 91% of the radioactivity were excreted respectively after 12, 24 and 48 hours. The radioautograms of whole body showed a trace of radioactivity remained only in liver, kidney and lung after 24 hours. The radiocarbon was completely excreted during one week. This was also the case, even though the dosage was increased or repeated several times. No radioactive carbon dioxide was expired.

The metabolic pathways of salithion in rats and plants (1) have been studied . These are summarized (6) in Fig. 7.

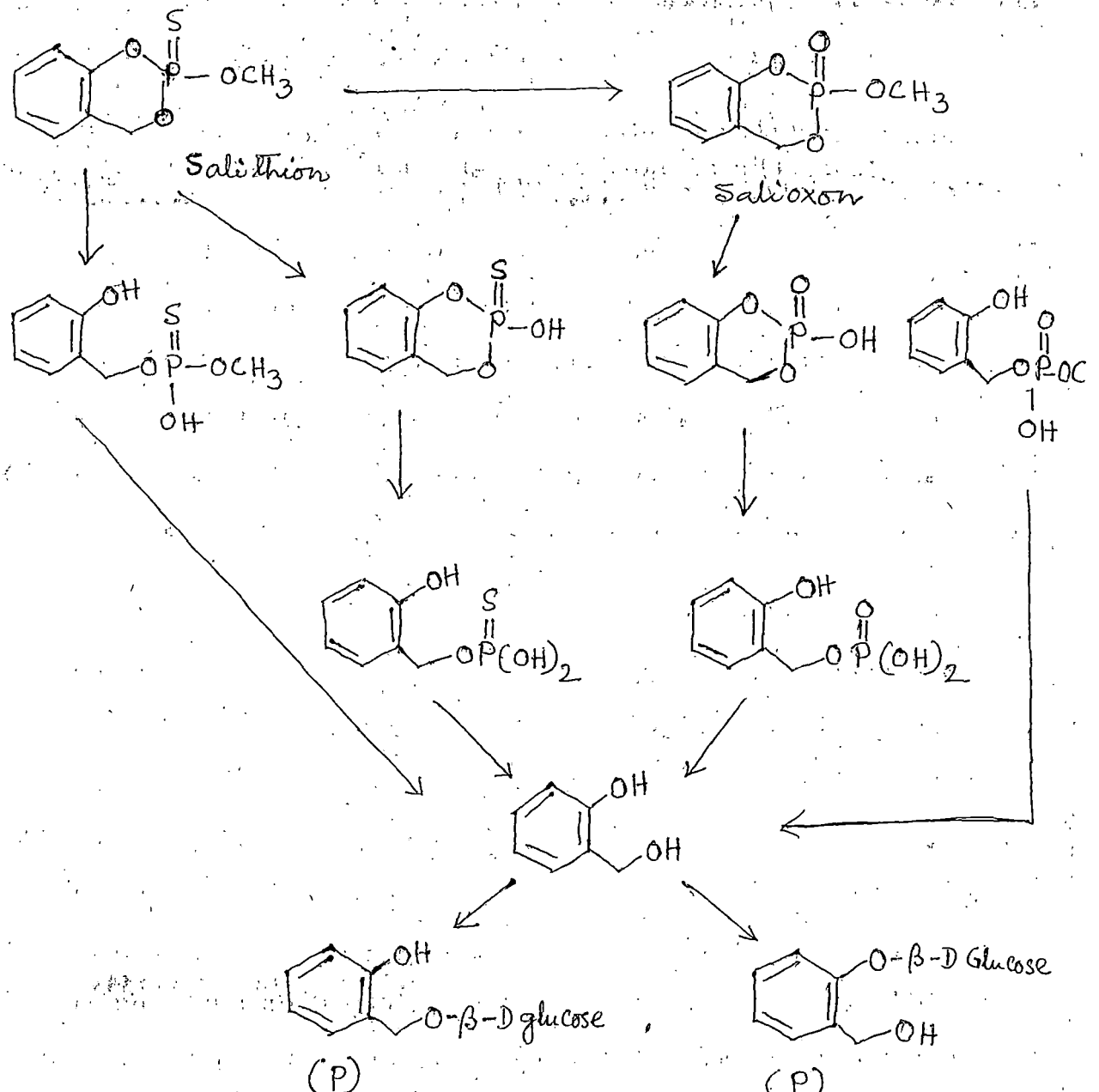


Fig. 7. Metabolic pathways of salithion in rats and plants (P-denotes the metabolite found in plant only).

It was shown that the biodegradation of salithion and salioxon proceeded through demethylation and ring-opening by P-O-aryl-bond cleavage. The metabolic pathways in plants only differed from those in glycoside conjugation of saligenin. About 10% of salithion absorbed was found in the bean plant whose roots had been soaked in the nutrient solution for 10 days. When salithion was applied on the leaves about 10% was absorbed into the tissues and slightly translocated into other leaves. Most of salithion applied on the leaves was vaporised. Vaporization of salithion from a nutrient solution was also observed. This causes a fumigant action to kill insects on the plants.

The acute toxicity of salithion for mamals was performed by Oshima[37]. The oral LD_{50} for mice is 91.3 mg/kg, for male rat 82-125 mg/kg, for female rat 102-130 mg/kg. The subcutaneous LD_{50} for male rat is 142 mg/kg and for female rat is 152 mg/kg. The acute oral LD_{50} for hen is 110 mg/kg.

Studies on the chronic toxicity of salithion was performed[5]. Rats fed for 24 months with 10 ppm salithion showed slight decrease in cholinesterase activities. No effect was observed in the rats fed with 3 ppm salithion. No histological lesion was found in any organs of rats fed with 100 ppm. In men and women administered orally 0.02 mg/kg/day of salithion for 21 days followed by 0.05 mg/kg/day for 14 days, no effect was found in the activity of erythrocyte acetylocholinesterase.

No effect was observed in fertility of rats for three generations fed with 10 ppm salithion. Carsinogenicity was not observed.

6. Chemical Hydrolysis of Saligenin Cyclic Phosphorus Esters.

The catalytic hydrolysis of saligenin cyclic phosphorus esters by phosphate ion has been reported (28b). The chemical reactivity of the cyclic phosphates with nucleophilic agents should be influenced by the electronic character of the substituent. The relative reaction rate may be theoretically predicted. The reaction rate for the following derivatives follows the order : butoxy < propoxy < ethoxy < methoxy < phenoxy < phenyl. Again in another series, the relative reaction rate is in the order NR_2 < NHR < OR < R. These have been supported experimentally (40,42,28a).

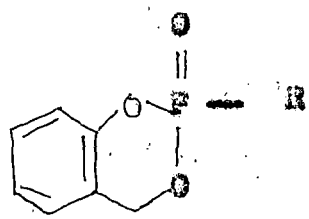
Saligenin cyclic phosphates were hydrolysed in pH 7.7 phosphate buffer to give O-hydroxy benzyl hydrogen phosphonates which gave chloroform-insoluble dyes with aminoantipyrine (6). This is a characteristic reaction of cyclic phosphorus ester of saligenin. The first order hydrolysis constants (K_{hyd}) are given in Table-III. Phosphonic acid esters are generally more unstable than phosphoric acid esters. The rate constants of alkyl phosphonates are about 10 times larger than those of corresponding phosphates. There is a smaller difference

between aromatic derivatives. Ethyl phosphonate is much stable than methyl phosphonate. The presence of unsaturation or chlorine makes the esters unstable.

It is interesting that, in the series of alkyl derivatives there is a relationship between rate constant and insecticidal activity (LD_{50}). [Table - III and Table-IV] The higher the reactivity is, the stronger the insecticidal activity. However, the aryl derivatives do not follow this relationship; they are more reactive than alkyl derivatives, but are almost non-insecticidal. The size of the substituent appears to be more important for biological activity than the electronic property of the substituent.

Table - III

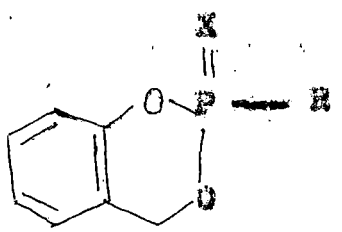
Hydrolysis rate constants of some saligenin cyclic phosphorus esters in phosphate buffer (pH 7.7) at 25°C.



R	K_{hyd} min^{-1}	R	K_{hyd} min^{-1}
CH_3	2.22×10^{-2}	OCH_3	1.42×10^{-3}
C_2H_5	4.25×10^{-3}	OC_2H_5	5.04×10^{-4}
$CH = CH_2$	1.39×10^{-2}	-	-
CH_2Cl	2.00×10^{-1}	-	-
CH_2CH_2Cl	1.41×10^{-2}	OCH_2CH_2Cl	2.58×10^{-3}
C_6H_5	1.23×10^{-2}	OC_6H_5	6.30×10^{-3}
NHC_6H_5	2.40×10^{-4}	$OC_3H_7(n)$	3.79×10^{-4}
$NHCH_3$	1.54×10^{-4}	$OC_4H_9(n)$	3.29×10^{-4}
$N(CH_3)_2$	Negligibly small.		

Table - XV

The relationship between rate-constant and insecticidal activity of some saligenin cyclic phosphorus esters.



X	R	K_{hyd} min^{-1}	LD_{50} (µg/female housefly)
O	CH_3	2.22×10^{-2}	0.19
O	C_2H_5	4.25×10^{-3}	0.17
O	$1\text{-}C_3H_7$	-	0.33
O	$Sec\text{-}C_4H_9$	-	7.0
O	$t\text{-}C_4H_9$	-	>10(0%)
O	$CH : CH_2$	1.39×10^{-2}	0.68
O	CH_2Cl	2×10^{-1}	<10 (60%)
O	CH_2CH_2Cl	1.41×10^{-2}	0.99
O	C_6H_5	1.28×10^{-2}	>10 (10%)
O	OCH_3	1.42×10^{-3}	0.035
O	OC_2H_5	5.04×10^{-3}	0.33

Contd.....

Table - IV (Contd.....)

X	R	K_{hyd} min^{-1}	LD_{50} (μg/female housefly)
O	O-n-C_3H_7	3.79×10^{-4}	7.1
O	O-n-C_4H_9	3.29×10^{-4}	>10 (40%)
O	O-CH_2CH_2Cl	2.68×10^{-3}	0.49
O	O-C_6H_5	6.30×10^{-3}	>10 (3)
O	$NHCH_3$	1.54×10^{-4}	0.05
O	$N(CH_3)_2$	negligibly small	0.40
O	NHC_6H_5	2.40×10^{-4}	>10 (5%)

7. Biological Activities and Structural Relationship.

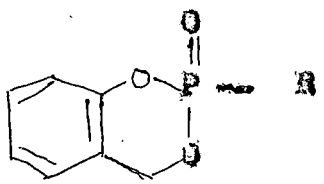
The saligenin cyclic phosphate esters have interesting biological activities. Some of them are neurotoxic, causing ataxia in higher animals. Others do not show such harmful activity but do have high insecticidal activity, systemic activity and fungicidal activity. Their biological activities include also synergism with organophosphorus insecticides, nematocidal and antifilarial activity. The specificity in

biological activities may be attributed to the steric effect of an exocyclic substituent group on the phosphorus atom as shown in Table-V. All aryl saligenin cyclic phosphates manifest a high delayed neurotoxicity to cause ataxia in hens and high synergistic activity with malathion (9,41). The arylphosphonate analogs showed similar biological activities but less neurotoxicity. On the other, the corresponding cyclic esters having a small alkyl group on phosphorus, i.e. 2-alkyl, 2-alkoxy-, and 2-alkylamino-4H-1,3,2-benzodioxaphosphorin 2-oxides, did not cause ataxia in hens with any sublethal doses and only weakly potentiated the toxicity of malathion (9). The interesting feature is that, the alkyl derivatives reveal high insecticidal activity, whereas, the aryl cyclic esters do not (8).

The specificity of saligenin cyclic phosphates in the biological activity relates to their selectivity in enzyme inhibition. These phosphates inhibit various serine enzyme by phosphorylation, producing probably salicyloxyphosphinylenzymes (14,4) (VI)(Fig. 8). This involves by opening of the cyclic ester structure at the P-O aryl bond. When the size of the exocyclic substituent R in (V) increases, the ester becomes a more selective inhibitor of aliesterase (42). Whereas, it becomes a more selective inhibitor of cholinesterase when the substituent is small. Thus the O-tolyl derivative (M), for example, is 130 times more selective to inhibit aliesterase than cholinesterase.

Table -V

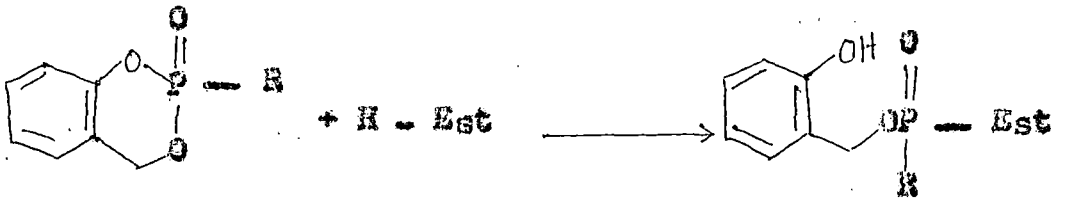
Effects of the exocyclic substituent (R) on biological activities of saligenin cyclic phosphate (V)



(V)

R	Delayed neurotoxicity MAD[a]	Synergism with malathion cotoxicity co-efficient		Insecticidal activity LD^c_{50}
		Mice	Houseflies[b]	
$OCH_3 - C_6H_4O$	2-5	16.7	7.8	(0)[d]
C_6H_5O	1.5-2	8.8	9.2	(3)[d]
C_6H_5	200	18.8	8.0	(0)[d]
C_2H_5	N.A.[e]	3.0	-	0.17
C_2H_5O	-	-	3.1	0.33
CH_3O	N.A.[e]	3.7	4.7	0.04
$(CH_3)_2N$	N.A.[e]	1.1	-	0.30

a. Minimum ataxia doese for hens in mg/kg.
b. A resistant strain.
c. 50% lethal dose by topical application to houseflies in μg/fly.
d. Percentage mortality at 10 μg/fly.
e. No ataxia signs evident with any sublethal dosages.



(V) (VI)

Fig. 8 Reaction of saligenin cyclic phosphates with esterase (R-Est)

Therefore, the exocyclic substituent of saligenin cyclic phosphate esters is regarded as the selectophore in the biological actions.

The heterocyclic structure of saligenin cyclic phosphorus esters is merely for the chemical reactivity of the phosphorus atom towards nucleophiles including the active site of esterase and is never requirement for the delayed neurotoxicity. As for example, although Tri-P-ethyl phenyl phosphate (TPEP) has the neurotoxicity [13], is unable to be transformed into a cyclic ester structure.

Johnson found "neurotoxic esterase" in nervous tissues which is specifically sensitive *in vivo* to neurotoxic organophosphorus esters [43]. The esterase is unlike acetylcholinesterase but similar to chymotrypsin and trypsin in the structure-activity relationship of inhibitors [44].

Although the structure-neurotoxicity relationship is too complicated to generalize, the neurotoxicity appears to be rather closely related to the structure of the non leaving group than that of the leaving group.

With this brief background of the relation of chemical structure to the biological activity of saligenin cyclic phosphorus esters, we will now discuss the specific activities such as insecticidal, synergistic, antiesterase, nematocidal, fungicidal etc.

7.(a) Insecticidal Activity (Table VI - XIV):

Various series of cyclic esters of saligenin derived from pentavalent phosphorus acids have been examined for insecticidal activity. They include phosphates [19], phosphoramidates [23], phosphorothiolates [25], phosphonates [28] and their thiono analogs (Table VI-XIV). The insecticidal activity of the esters appears to relate with the size of the exocyclic substituent on the phosphorus atom (Table-VI).

The cyclic esters in any series having an aryl group as an exocyclic substituent on the phosphorus atom have either poor or no insecticidal activity. In all the series, methyl derivatives are much more active than higher alkyl derivatives, except for phosphonate series (Table - XI) in which ethyl derivatives are more active than methyl derivatives. N, N-dialkyl phosphorami-

dates are much less active than mono-alkyl derivatives (Table-XIII). Thus saligenin cyclic methyl phosphate (Table -X), methyl phosphorothionate (Table-IX), N-methyl phosphoramidate, N-methyl phosphoramidothionate (Table-XIII), methyl phosphonothiolate and ethyl phosphonothiolate (Table-XI) are potent insecticides. It is interesting to note that the exocyclic substituent of the most active cyclic phosphorus ester in each series (OCH_3 , SCH_3 , $NHCH_3$, CH_3CH_2) differs from each other in electronic characteristics, but resembles in steric property such as the distance (about 2.9 Å) between phosphorus and carbon atom in the P-X-C function, if the bond angle of divalent sulfur is near 90° rather than 109.5°.

Furthermore, the introduction of any type of substituent at any position of the benzene ring and on the carbon atom of the hetero ring decreases the activity (29) (Table-VII). Thus, the simplest phosphorothionate, salithion, is the most effective insecticide in the whole series of saligenin cyclic phosphorus esters.

An outstanding contrast is observed in the effect of para-substitution between the salithion series and parathion series. Table (VIII) shows the effect of the electronic character of the substituent in the para-position of the phenolic ester group upon the insecticidal activity. Any substituents, either electron-withdrawing group or electron-releasing group decreases the insecticidal activity. Table-VIII shows that the

insecticidal activity of diethylphenyl phosphorothionates (II) is progressively increased by P-substitution of the phenyl ring in the increasing order of the electron withdrawing ability of the substituent, whereas neither electron withdrawing nor electron releasing group increases the activity of salithion (VIII). The P-O-C aryl bond of the hetero ring of saligenin cyclic phosphorus esters appear to be active enough to phosphorylate cholinesterase to kill insects without any electron-withdrawing group.

The systemic activity of some saligenin cyclic phosphoramidates against rice stem-borers and green rice leafhoppers on rice plants are observed (Table - XIII). Methyl phosphoramidate is more active than Schradan but less active than thimet against rice leafhoppers. Against rice stem-borers cyclic N-methyl phosphoramidothionate is superior to lindane and Diazinon. Salithion also shows more or less systemic activity against army worm and mite. No systemic activity has been observed in other compounds.

7.(b) NEMATOCIDAL ACTIVITY (Table XI and XIII, page-84 & 86).

Some saligenin phosphonothionates, phosphoramidates and phosphoramidothionates show nematocidal activity. Phosphoramidates and phosphoramidothionates are very effective to kill nematodes (Table - XIII)[8]. N-methyl phosphoramidate is most active in the series of saligenin derivatives against the non-parasitic soil nematode Rhabditis suspended in water[23]. Owing to the instability in water, the cyclic phosphates and

phosphonates are almost inactive, but their thiono analogs are effective against Rhabditis (Table XI, XIII).

Some saligenin cyclic aryl phosphonothionates are more effective as nematocides than the cyclic N-methyl phosphoramidate against the rice white tip nematodes, though they have very low insecticidal activity. Cyclic phenyl- and P-tolyl-phosphonothionates are the most effective nematocides in the series. These aryl phosphonothionates exhibit also a high activity against filaria in cotton rats (Litomosoides carinii)(5). It is interesting to note that these aryl phosphonothionates are poor insecticides, whereas they are more potent to kill nematodes than salithion, suggesting the cholinesterase or other critical target of nematodes may differ in nature from the insect cholinesterase.

The correlation between the structure and the nematocidal activity of phosphoramides and phosphoramidothionates are similar to that in the insecticidal activity for house fly.

7. (c) FUNGICIDAL ACTIVITY (Table XIV and XV, Page - 88,89).

Salithion has no fungicidal activity. But some saligenin cyclic phosphorothiolates have fungicidal activity (Table-XIV). These phosphorothiolate esters, particularly having an S-benzyl ester linkage, have activity to protect the rice plant from rice blast disease caused by the infection of Piricularia oryzae(46). The protective values against Piricularia oryzae

of the cyclic phosphorothiolates and related compounds are shown in the Table (XIV & XV). The data of some commercial fungicides including an organophosphorus compound, Hinson (O-ethyl S, S diphenyl phosphorodithioate) are shown in the Table (XIV) for comparison. The methyl-,ethyl-and n-butyl-phosphorothiolates have high fungitoxicity comparable to other commercial fungicides. The normal and isopropyl derivatives are less effective. Saligenin cyclic methyl phosphate and phosphorothionate (salithion) are highly active as insecticide but are almost inactive as fungicide. In the series of dialkyl benzyl esters of phosphorus acids, only S-benzyl phosphorothiolates are highly active as fungicide but the others e.g. phosphates, phosphorothionates and phosphorodithionates are inactive (45).

It is important to note that some cyclic phosphorothiolates have both the high insecticidal as well as fungicidal activity, with only exception in the case of S-benzyl-O.O-diethyl phosphorothiolate (Kitazin) which has weak insecticidal property but is a good fungicide and now used in practice for the control of rice blast disease.

7.(d) <u>ANTI - SH ENZYME ACTIVITY</u> (Table XV, Page -89).

The saligenin cyclic phosphorothiolates have high activity to alkylate (salicylate) mercaptans and to inhibit "SH-enzymes" such as yeast alcohol dehydrogenase (31). The activity seems to be related to fungicidal property but not with the

insecticidal activity.

I_{50} values for alcohol dehydrogenase of some saligenin cyclic phosphorus ester are shown in (Table-XV). Cyclic methyl and ethyl phosphorothiolates are most active in this series. On the other hand, cyclic phosphates have only weak activities, though they are potent inhibitors of esterases. Salithion i.e., methyl phosphorothionate which have high insecticidal property is almost inactive toward the enzyme.

The rate of alkylation reaction by the cyclic esters looks parallel with the hydrolysis rate of the ester and the alkylation proceeds with a considerable time lag. These facts suggest that the alkylation occurs after hydrolysis. Actually, the partial hydrolysate of saligenin cyclic esters react immediately with mercaptans. The reaction mechanism is shown in Fig. 9.

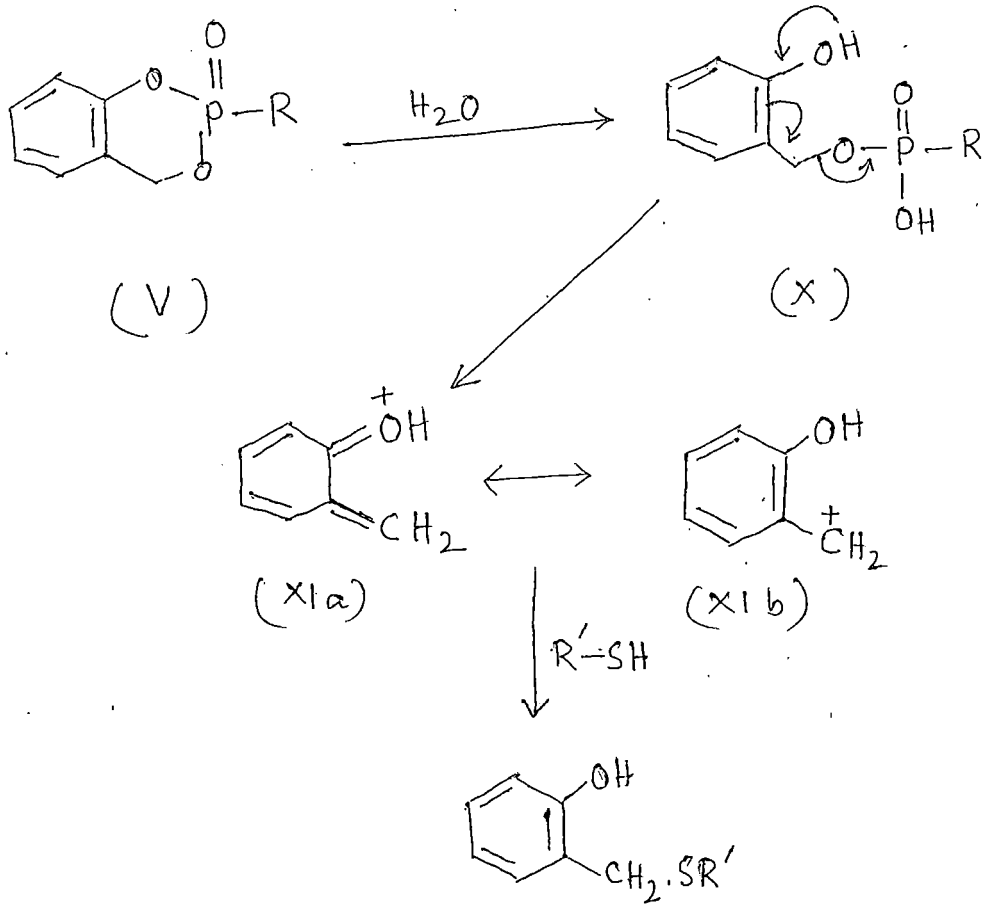


Fig. 9 A proposed mechanism for alkylation of Mercaptans with Saligenin cyclic phosphorus esters.

Saligenin cyclic phosphorothiolates are partially hydrolysed by opening of the heterocyclic P-O-C-aryl bond, more easily than phosphate esters. In Fig. 9, the cyclic ester (V) is hydrolyzed by the attack of hydroxide ion to yield salicyl phosphate (X). The electron releasing -OH group of (X) may convert to a carbonium ion (XIb) which may actually react with a SH group to give a thioester (XII).

Cyclic methyl and ethyl phosphorothiolates are much more active in hydrolysis, alkylation and the inhibition of "SH-enzyme" activities than the corresponding cyclic phosphates[31]. It seems reasonable to conclude that the decrease of electron density on phosphorus atom causes the high reactivity of the phosphorothiolates. This is supported by the lower P = O frequency (1280 cm^{-1}) of the phosphorothiolates in comparison with that of the phosphates (1310 cm^{-1}).

Further investigation shows (Table-XV) that there is an interesting correlation among the alkylating activity, the inhibitory activity against "SH-enzymes" and the antifugal activity of the cyclic esters. Cyclic methyl and ethyl phosphorothiolates are highly active in all three functions. Cyclic phosphates have very weak activities but they are potent inhibitors of esterases. These facts suggest that high inhibitory activity against "SH-enzymes" may be an important factor for the fungicidal activity of the cyclic phosphorothiolates.

7.(e) ANTIESTERASE ACTIVITY (Table-XVI, Page-90).

The relation of chemical structure to biological activities indicates that the specificity in biological activities of the saligenin cyclic phosphorus esters seem to be remarkably influenced by the steric characteristics of the exocyclic substituent on the phosphorus atom. This is evident when their specificities in enzyme inhibition (42) are compared.

The most insecticidal saligenin cyclic methyl phosphate (salioxon) is the strongest inhibitor of insect cholinesterase. However, the highly neurotoxic aryl phosphate is a poor inhibitor of cholinesterase, but is a very specific inhibitor of aliesterase (1,42). The less neurotoxic arylphosphonate occupies an intermediate position. In any series, when the size of the exocyclic substituent increases, the compound becomes a more selective inhibitor of aliesterase; in contrast, the compound carrying a small substituent is a more selective inhibitor of cholinesterase (Table-XVI). Aryl phosphonates are more specific inhibitors of pseudo-cholinesterase; alkyl phosphates are less specific and aryl phosphates are intermediate.

7.(f) SYNERGISTIC ACTIVITY (Table -XVII, XVIII and XIX Page-91-93).

Saligenin cyclic aryl phosphates and phosphonates have synergistic activity with malathion against insects and mites, particularly their resistant strain (46).

The joint action of the activity of some saligenin cyclic phosphorus esters with malathion has been examined by Eto et al (41) and compared with some phosphorus esters which are known as the synergists of malathion. Table-XVII shows that the aryl derivatives of saligenin cyclic esters are synergistic with malathion. They increase the toxicity of malathion 2.3 to 3.4 times at a 1:1 mixing ratio. The activities of them are more than propyl paraoxon but less than Dibrom and isopropyl paraoxon. 2-(o-toyloxy)-4H-1,3,2-benzodioxaphosphorin-2-oxide, and 7-methyl-2-phenyl-4H-1,3,2-benzodioxaphorin-2-oxide are the most synergistic against susceptible housefly among the tested cyclic esters. Alkyl derivatives of saligenin cyclic phosphorus esters are much less synergistic or even antigonistic.

Synergism of saligenin cyclic phosphorus esters with malathion in a resistant strain of housefly has been tabulated in Table-XVIII. In this case, the synergistic effect of saligenin cyclic phosphorus esters has remarkably been increased. Even the alkyl derivatives act as synergist of malathion. Thus all of present cyclic esters are more active than the other tested

organophosphorus synergists. Cyclic phenylphosphonate of methyl saligenin is the most effective synergistic against resistant housefly and increases the toxicity of malathion 14 times.

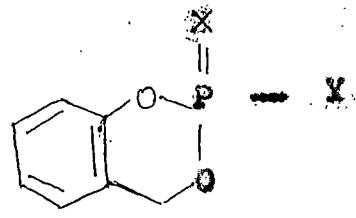
Synergistic effect on susceptible and resistant strains of green rice leaf hopper has been observed (41) and tabulated in Table (XIX). The toxicity of malathion to the susceptible insects becomes double by the addition of three saligenin cyclic phosphorus esters along with two other cyclic esters. Synergistic effect on resistant leaf hopper also increases by saligenin cyclic phosphorus esters but the values are lower than in the resistant housefly. They enhanced the toxicity of malathion 2.2 to 3.8 times.

The synergism appears to result primarily from the inhibition of detoxication of malathion. Phosphate action or esterase action can detoxify the toxicity of malathion. It has been observed for a great number of organophosphorus compounds that the synergism of malathion in mice and the degree of inhibition of ali-esterase in vivo are generally related (9). For insects, high esterase activity hydrolysing malathion is supposed to be partly responsible for malathion-resistance in some strains of mosquito, housefly and green rice leaf hopper (41).

Eto et al (42) have shown that aryl derivatives of saligenin cyclic phosphorus esters are the selective inhibitors of ali-esterase, whereas small alkyl derivatives are not so selective to ali-esterase inhibition. This appears to be responsible for their difference in synergistic properties.

Table - VI

Relation of structure to insecticidal activity (LD_{50} μg/housefly) of (VII)



(VII)

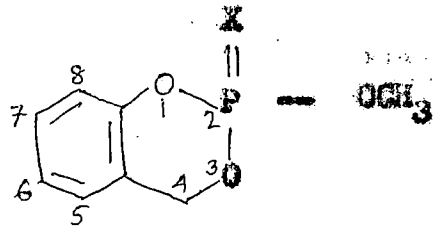
X / R	R		OR		SR		NHR	
	O	S	O	S	O	S	O	S
CH_3	0.13	0.31	0.04	0.05	0.09	0.18	0.05	0.04
C_2H_5	0.17	0.08	0.33	0.30	0.23	0.9	0.66	0.48
n-C_3H_7	0.33[a]	0.09[a]	7.1	-	2.34	2.2	1.50	-
n-C_4H_9	7.05[b]	-	(40)	-	6.30	10	(54)	-
C_6H_5	(0)	0.3	(3)	2.0	2.2	(0)	(5)	-

a = isopropyl, b = Sec-butyl.

Figures in parentheses are percentage mortality at 10 μg/fly.

Table - VII

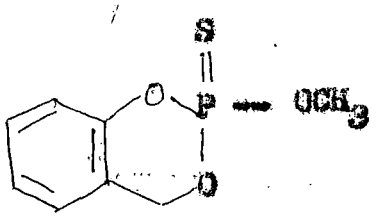
Effect of substituent (R) on insecticidal activity (LD_{50} μg/housefly)



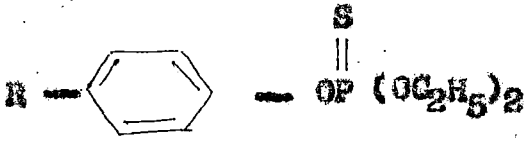
R	X	
	S	O
H	0.05 (Salithion)	0.035 (Saliozon)
4-CH_3	-	3.35
6-CH_3	2.00	0.1
7-CH_3	0.23	0.43
8-CH_3	1.30	2.0
6-Cl	1.75	0.09
8-Cl	0.13	0.23
β-CH_3	0.30	0.33
β-CH_3OCH_2	3.56	0.99
β-Cl	-	2.07

Table -VIII

Effect of P-substitution on insecticidal activity of Salithion (VIII) and parathion (IX) series.



(VIII)



(IX)

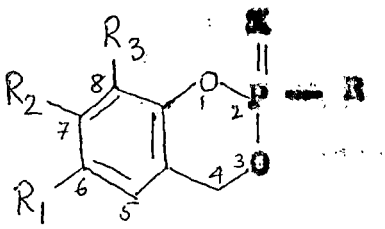
R	σ [a]	Relative insecticidal activity[b]	
		(VIII)	(IX)
OCH_3	-0.268	9.2	0.1
CH_3	-0.170	2.6	0.1
H	0.000	100.0	0.1
C_6H_5	+0.009	12.8	-
Cl	+0.226	3.0	0.33
$COCH_3$	+0.87	2.0	2.5
NO_2	+1.27	1.7	100.0

a = Hammett's substituent constant

b = Percentage of the most active compound in each series.

Table - IX

Insecticidal activity of Ring-substituted Saligenin Cyclic Phosphorus esters (thiono-compounds):



X	R_1 (6)	R_2 (7)	R_3 (8)	R	LD_{50} (µg/housefly)
S	CH_3	H	H	OCH_3	2.0
S	CH_3	H	H	OC_2H_5	>10
S	CH_3	H	H	O-n-C_3H_7	>10
S	H	CH_3	H	OCH_3	0.23
S	H	CH_3	H	OC_2H_5	3.0
S	H	CH_3	H	O-n-C_3H_7	7.5
S	H	H	CH_3	OCH_3	1.3
S	H	H	CH_3	OC_2H_5	3.0
S	H	H	CH_3	O-n-C_3H_7	7.5
S	H	H	CH_3	$NHCH_3$	3.6
S	C_6H_5	H	H	OCH_3	0.4
S	C_6H_5	H	H	OC_2H_5	0.5
S	C_6H_5	H	H	O-n-C_3H_7	1.0

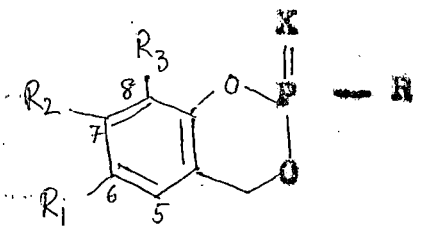
Contd.....

Table - IX (Contd.....)

X	R_1	R_2	R_3	R	LD_{50} (g/housefly)
S	OCH_3	H	H	OCH_3	0.55
S	$COCH_3$	H	H	OCH_3	2.5
S	Cl	H	H	OCH_3	1.75
S	Cl	H	H	$NHCH_3$	0.06
S	Cl	H	H	SCH_3	-
S	H	H	Cl	OCH_3	0.13
S	H	H	Cl	$NHCH_3$	0.09
S	H	H	Cl	SCH_3	-
S	Cl	H	C_6H_5	OCH_3	1.2
S	Cl	H	C_6H_5	OC_2H_5	3.0
S	Cl	H	C_6H_5	O-n-C_3H_7	>10
S	NO_2	H	H	OCH_3	3.0
S	C_6H_5	H	Cl	OCH_3	-
S	C_6H_5	H	Cl	OC_2H_5	-
S	C_6H_5	H	Cl	O-n-C_3H_7	-
S	Cl	H	Cl	OCH_3	0.3
S	Cl	H	Cl	OC_2H_5	4.0
S	Cl	H	Cl	$NHCH_3$	3.0

Table - X

Insecticidal activity of ring-substituted saligenin cyclic phosphorus esters (oxon-compounds).



X	R_1 (6)	R_2 (7)	R_3 (8)	R	LD_{50} (μg/housefly)
O	CH_3	H	H	OCH_3	0.1
O	CH_3	H	H	OC_2H_5	0.4
O	H	CH_3	H	OCH_3	0.43
O	H	CH_3	H	OC_2H_5	0.70
O	H	CH_3	H	O-n-C_3H_7	7.2
O	H	CH_3	H	C_6H_5	>10
O	H	CH_3	H	$NHCH_3$	0.14
O	H	H	CH_3	OCH_3	2.0
O	H	H	CH_3	OC_2H_5	2.1
O	H	H	CH_3	OC_6H_5	>10
O	Cl	H	H	OCH_3	0.09

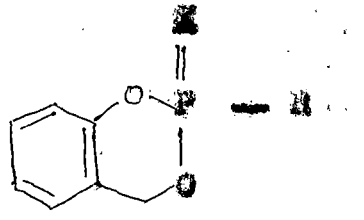
Contd.....

Table - X (Contd.....)

X	R_1 (6)	R_2 (7)	R_3 (8)	R	LD_{50} (μg/housefly)
O	Cl	H	H	OC_2H_5	0.13
O	Cl	H	H	O-n-C_3H_7	0.70
O	Cl	H	H	O-n-C_4H_9	2.5
O	Cl	H	H	OC_6H_5	>10
O	Cl	H	H	$NHCH_3$	0.09
O	H	H	Cl	OCH_3	0.23
O	H	H	Cl	OC_2H_5	0.15
O	H	H	Cl	O-n-C_3H_7	0.30
O	H	H	Cl	O-i-C_3H_7	-
O	H	H	Cl	OC_6H_5	>10
O	H	H	Cl	$NHCH_3$	0.30

Table - XI

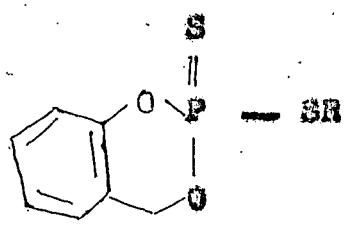
Saligenin cyclic phosphonates and phosphonothionates : toxicity, insecticidal and nematocidal activity.



X	R	LD_{50} µg/fly (Housefly)	LD_{50} mg/kg (House oral)	LD_{100} ppm (nematodes-Rhabditis)
O	CH_3	0.19	25-50	
O	C_2H_5	0.17	25-50	
O	1-C_3H_7	0.33	-	
O	Sec-C_4H_9	7.0	-	
O	t-C_4H_9	>10(0%)	-	
O	$CH = CH_2$	0.68	>100	
O	CH_2Cl	<10(60%)	25-50	
O	CH_2CH_2Cl	0.99	50-75	
O	C_6H_5	>10(0%)	-	
S	CH_3	0.31	5-10	25
S	C_2H_5	0.08	5-10	25
S	1-C_3H_7	0.09	-	-
S	CH_2Cl	1.14	25-50	25
S	C_6H_5	0.30	-	-

Table - XII

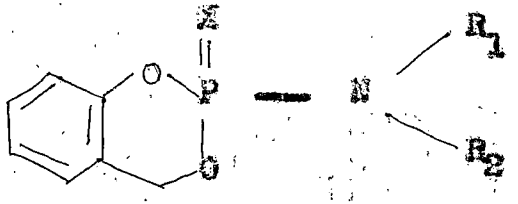
Insecticidal activity of Saligenin Cyclic Phosphorodithionates.



R	LD_{50} (μ g/fly)
CH_3	0.18
C_2H_5	9
n-C_3H_7	2.2
i-C_3H_7	6
$C_3H_5(CH_2-CH = CH_2)$	1.7
n-C_4H_9	10
C_6H_5	>10(0%)

Table - XII

Saligenin cyclic phosphoramidates and phosphoramidothionates : Insecticidal activity, toxicity and nematocidal activity:



X	R_1 / R_2	LD_{50} (µg/female House fly)	LD_{50} (µg/ug Rice stemborer)	LD_{50} µg/Rn (Green rice leaf-hopper)	LD_{50} mg/kg (Mouse)	Minimum conc.(ppm) to kill 100% nematodes-Rhabitis
O	NHMe	0.05	2.84	0.40	5-7.5	<10
O	NHEt	0.60	22.29	3.60	30-50	10-25
O	NH-n-Pr	1.50	33.60	33.0	>50	25-50
O	NH-i-Pr	3.44	103.34	>350	>50	50-100
O	NH-n-Bu	<10(54%)	>214	>400	>50	25-50
O	NH-Ph	>10(5%)	-	-	-	-
O	$N(Me)_2$	0.3	13.80	4.0	-	>200(10%)

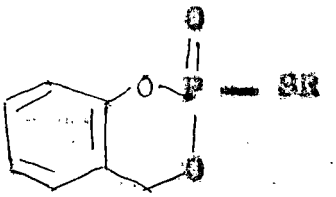
Contd.....

Table - XIII

X	$N\begin{smallmatrix}R_1\\R_2\end{smallmatrix}$	LD_{50} (µg/female House fly)	LD_{50} µg/gm (Rice stemborer)	LD_{50} µg/gm (Green rice leaf-hopper)	LD_{50} mg/kg (Mouse)	Minimum conc. (ppm) to kill 100% nematodes-Rhabditis
O	$N(Me)_2$	0.3	13.80	4.0	-	>200(10%)
O	$N(Et)_2$	>10(0%)	167.61	34.10	>50	100-150
S	NHMe	0.044	4.84	4.1	20-30	25-50
S	NH.Et	0.48	36.25	-	-	-
S	$N(Me)_2$	0.33	-	-	-	50-100
S	$N(Et)_2$	0.63	-	-	-	200(30%)
S	OMe (Salithion)	0.05	1.13	30.6	88	-
O	OMe (Salioxon)	0.035	2.16	1.8	52	-
Parathion		0.040	3.43	3.6	5-7	-
Malathion		0.060	-	0.8	347	-
D-D mixture (mixture of 1,3-dichloropropane and 1,2-dichloropropane)		-	-	-	-	>800(85%)

Table - XIV

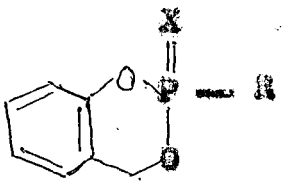
Insecticidal and fungicidal activity of saligenin cyclic phosphorothiolates:



R	LD_{50} µg/gm (oriental housefly)	Protective value % against Piricularia oryzae				Therapeutic value(%) to P.oryzae at 200 ppm
		200 ppm	100 ppm	50 ppm	25 ppm	
CH_3(HCBO)	3.00	100	100	100	84.8	7.1
C_2H_5	11.21	100	93.7	92.5	81.5	100
n-C_3H_7	94.50	100	57.1	34	-	-
i-C_3H_7	17.23	-	68.7	34.4	-	-
n-C_4H_9	211.8	100	91.7	93.3	75.6	97.6
C_6H_5	73.61	50.2	-	-	-	-
Salithion	1.60	52(at 500 ppm)	-	-	-	-
Kinosan	-	100	-	88.2	-	95.2(at 250 ppm)
Blasticidins	-	93.5	-	88.3	-	97.6
Pentachloro-benzyl alcohol	-	[illegible]	93.8	93.5	-	0

Table - XV

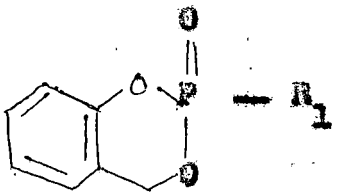
Chemical, Biological and Anti-Fungal activities of some saligenin cyclic phosphates and their thio analogs.



X	R	Hydrolysis %	Cysteine reacted %	I_{50} yeast alcohol dehydrogenase ($M \times 10^{-5}$)	Protective value against Piricularia oryzae % 50 ppm	500 ppm
O	SCH_3	86	66	4.5	100	-
O	SC_2H_5	81	60	4.4	93	-
O	OC_6H_5	55	46	6.8	-	-
O	OCH_3	17	10	62	-	65
S	OCH_3	5	5	100	-	62

Table - XI

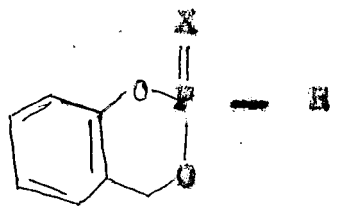
The Inhibition of Housefly, Human Blood and Horse Serum-Esterases by some Saligenin Cyclic Phosphorus Compounds.



R_1	R_2	Housefly I_{50} x 10^8 (M)		Human blood I_{50} x 10^8 (M)		Horse plasma I_{50} x 10^8 (M)	
		ChE	AliE	P-ChE	t-ChE	AliE	Malathionase
OCH_3	H (Salioxon)	7.6	8.4	1.8	17.0	230	620
OC_2H_5	H	13.2	2.1	1.6	25.0	240	-
O-n-C_3H_7	H	50.7	3.0	-	-	-	-
O-n-C_4H_9	H	37.5	2.3	-	-	-	-
OC_6H_5	H	15.5	1.4	0.5	12.0	120	120
C_6H_5	H	12.5	1.1	0.65	72.0	180	470
C_6H_5	CH_3	-	-	1.6	68.0	230	-
OPh-2-CH_3	H	-	-	1.3	39.0	200	-

Table X II

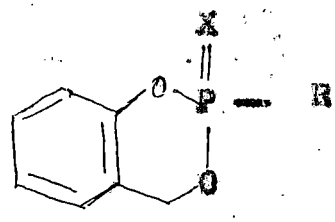
Joint action of some saligenin cyclic phosphorus esters and some other phosphoric esters with malathion against susceptible house flies.



X	R_1	R	LD_{50} µg/Fly alone	LD_{50} µg/Fly with malathion 1:1	Cotoxicity co-efficient.
Malathion			0.46		
O	H	OMe	0.02	0.06	0.6
O	H	OEt	0.16	0.14	1.7
S	H	OEt	0.11	0.22	0.8
O	H	OPh	c.10(30%)	0.38	2.3
O	H	O-o-Tol	c.10(40%)	0.26	3.4
O	H	Ph	c.10(60%)	0.36	2.5
O	Me	Ph	c.10(70%)	0.26	3.4
TOCP			>10(0%)	0.90	1.0
Dibrom			0.03	0.008	7.1
Propyl paraxon			0.10	0.11	1.5
Isopropyl paraoxon			0.22	0.06	4.9

Table - VIII

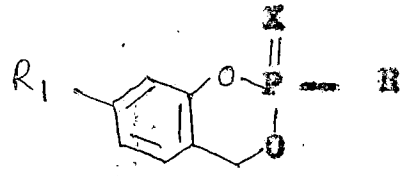
Synergistic effect of saligenin cyclic phosphorus esters with malathion against resistant house flies and comparison with other phosphate synergists.



X	R_1	R	LD_{50} µg/fly alone	LD_{50} µg/fly with malathion 1:1	Cotoxicity Co-efficient
Malathion			2·54		
O	H	OMe	0.15	0.06	4.7
O	H	OEt	0.40	0.22	3.1
S	H	OEt	0.20	0.10	3.6
O	H	OPh	>10(10%)	0.55	9.2
O	H	O-o-Tol	>10(10%)	0.65	7.8
O	H	Ph	>10(25%)	0.57	8.0
O	Me	Ph	0.10 (40%)	0.29	14.0
TOCP			>10(10%)	3.44	1.5
Dibrom			0.07	0.07	2.0
Propyl paraoxon			0.73	0.46	2.5
Isopropyl paraoxon			0.43	0.26	2.2

Table - XIX

Synergistic effect of saligenin cyclic phosphorus esters with malathion against susceptible and resistant green rice leafhopper.



X	R_1	R	LD_{50} (µg/susceptible g.r. leaf-hopper)		Cotoxicity Co-efficient	LD_{50} (µg/resistant g.r. leaf-hopper)		Cotoxicity Co-efficient
			alone	with malathion 1:1		alone	with malathion 1:1	
Malathion			0.003			0.021		
O	H	OMe	0.008	0.004	1.1	0.010	0.006	2.3
O	H	OEt	0.069	0.003	1.9	0.066	0.010	3.2
S	H	OEt	1.892	0.005	1.2	>2	0.019	2.2
O	H	OPh	0.240	0.003	2.0			
O	H	O-o-Tol	0.464	0.008	0.8	(0.0167)	0.015	2.2
O	H	Ph	0.218	0.005	1.2			

Table - XIX (Contd.....)

X	R_1	R	LD_{50}(µg/susceptible g.r. leaf-hopper)		Cotoxicity Co-efficient	LD_{50}(µg/resistant g.r. leaf-hopper)		Cotoxicity Co-efficient.
			alone	with malathion 1:1		alone	with malathion 1:1	
O	Me	Ph	3.120	0.003	2.0	>3	0.011	3.8
TOCP			>10	0.005	1.2	(>10)	(0.083)	1.1
Paraoxon			0.208	0.005	1.2	0.533	(0.069)	1.3
Propyl paraoxon			0.006	0.002	2.0	-	-	-
Isopropyl paraoxon			0.211	0.003	2.0	-	-	-

R E F E R E N C E S.

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PART III

PART - III

STUDIES ON SOME ORGANOPHOSPHORUS COMPOUNDS : SPECTRAL PROPERTIES, BIOLOGICAL ACTIVITIES AND HYDROLYTIC PROPERTIES.

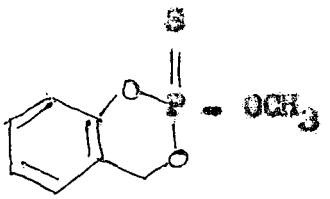
(2-alkylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide).

[Synthesis, spectral properties (^{1}H -, ^{13}C - and ^{31}P - NMR, UV, IR, and mass spectral), biological activities (insecticidal, fungicidal, and toxicological activities including antichôlinesterase properties), and hydrolytic properties of some 2-alkylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphides].

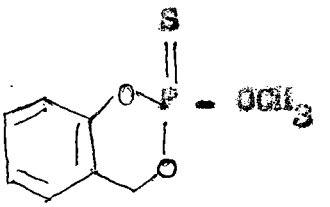
PART - III

AIMS AND OBJECTS OF THE PRESENT INVESTIGATION:

As stated previously (in PART - II) salithion (2-methoxy-4H-1,3,2-benzodioxaphosphorin-2-sulphide) was discovered in 1963 in the Laboratory of Pesticide Chemistry, Kyushu University, JAPAN[1], and developed into commercialization in 1968 by Sumitomo Chemical Company; many related compounds have been synthesized to study their chemical, biochemical, hydrolytic and biological properties including pesticidal activities. The unique structure of salithion comes from the active metabolite of tri-ortho-tolyl phosphate (TOCP)[2]. In spite of high neurotoxicity of the TOCP-metabolite, salithion causes no such toxicity. The introduction of any type of substituent at any position of the benzene ring decreases the insecticidal activity[3]. It has been reported[3] that the 2-methoxy-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide (BD-8) is obtained as a paste in the reaction of 5-nitro-saligenin with methyldichloridophosphorothionate after purification through silicic acid column chromatography; and, this methoxy compound has about sixty times less insecticidal activity compared to salithion[3]. However, it has been observed[4] in this laboratory that the methoxy compound (BD-8) is a white crystalline solid (m.p. 84°C), and has about 1.5-2 times greater oral insecticidal activity to cockroaches, Periplaneta americana (Linn) compared to salithion.

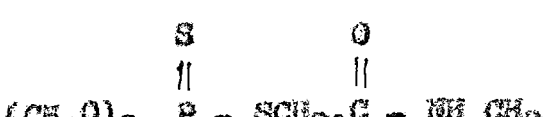


Salithion

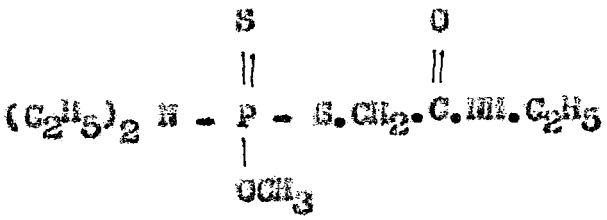


BD - 8 (m.p.-84°C)

Moreover, introduction of an amide group in place of an alkyl ester group often affords organophosphorus esters with fungicidal activity[5]. For example, although the insecticide dimethoate(I) [dimethyl S-(N-methylcarbamoylmethyl) phosphorothiolothionate] has no fungicidal activity, its dialkylphosphoramidate analogs, such as compound II, show some fungicidal as well as acaricidal activity[6].



I
Dimethoate

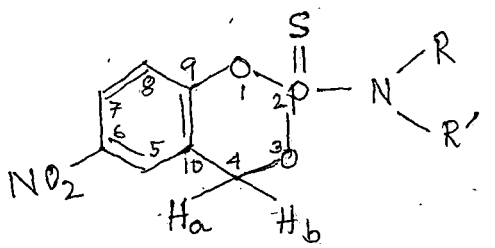


II
Compound- II

There are several other examples in literature from which it can be found that some phosphoramidothionates, phosphoramidothiolothionates, phosphoramides or phosphonamides in which the

phosphorus atom is attached directly to the nitrogen atom of an amine or a heterocyclic compound such as phthalimide, imidazole or triazole have very good fungicidal activity[5,7,8,9].

These observations prompted us to undertake a systematic work on some 2-alkylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphides having general structure (A),



(A)

where, alkylamido is cyclohexylamido, morpholino, dimethylamido, diethylamido, pyrrolidino, piperidino, isopropylamido or nonylamido. The work embodied in this dissertation is related to the investigation of the above mentioned compounds with reference to their chemical, pesticidal and toxicological properties besides structural elucidations by spectroscopic methods.

Actual Works:

(1) Syntheses of some organophosphorus compounds having general structure (A) mentioned above, are presented.

(ii) Spectral Properties: UV, IR, Mass and ^{1}H NMR spectral data of these compounds have been presented; ^{13}C and ^{31}P NMR spectra of only pyrrolidino and piperidino compounds as well as low temperature ^{1}H NMR spectral data of the methoxy compound (BD-8) have been given.

(iii) Biological Activities : Insecticidal, antifungal, anticholinesterase activities and phytotoxic properties have been studied; acute oral toxicity data on rats have also been presented.

(iv) Hydrolytic Properties: Chemical hydrolysis at alkaline pH have been given.

R E F E R E N C E S:

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3. Eto, M., Kobayashi, K., Sasamoto, T., Cheng, H.M., Aikawa, T., Kume, T., and Oshima, Y. : Botyu - Kagaku, 33, 73(1968)

4.(a) Das, B.K. : Pesticides, 15 3(1981).

(b) Das, B. K. : D.Sc. Thesis, Calcutta University, (1981).

5. Grapov, A.P. and Mel'nikov, N.N. : Russ. Chem. Rev., 42(9), 776 (1973).

6. Mandelbaum, Ya. A., Soifer, R.S., Mel'nikov, N.N., and Fedoseenko, L.G. : Khim - Sel'sk. Khoz., 6, 107 (1968)
[Chem. Abst., 69, 2087(1968)]

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A. MATERIALS AND METHODS

1. PURIFICATION OF SOLVENTS AND OTHER CHEMICALS:

Throughout the preparative and other part of the work, the organic solvents and other chemicals used were purified and dried according to Vogel[1]. All other chemicals and solvents occasionally used during the work were of standard commercial products of high quality (BM, BDH, SM and/or Fluka quality).

2. SPECTROSCOPIC METHODS:

Infrared spectra were recorded on Beckmann IR-20 spectrophoto meter in nujol mull. ^{1}H NMR spectra were obtained with Varian model A-60, EM-390, FT-80A, and WH-270 instruments in $CDCl_3$/Acetone - d_6 solvent using TMS as an internal reference; ^{13}C NMR spectra were recorded in the same FT-80A instrument at 20 MH_z; ^{31}P NMR spectra were obtained with FT-80A instrument at 32.2 MH_z, ^{13}C NMR spectra of nitro saligenin has been taken on WH-270 instrument at 67.89 MH_z low temperature ^{1}H NMR Spectra of the methoxy compound were taken on WH-270 instrument at 270 MH_z. UV spectra were obtained with Beckmann DU-2 spectrophotometer in absolute ethanol. Mass spectra were recorded on Varian model EM-600 and MS-30 instrument.

3. PREPARATION OF THIOPHOSPHORYL CHLORIDE ($PSCl_3$):

Thiophosphoryl chloride was prepared according to Moeller et al.[2]

4. PREPARATION OF 5-NITRO-SALIGENIN (2-HYDROXY-5-NITRO-BENZYL ALCOHOL):

The 2-hydroxy-5-nitro benzyl alcohol as one of the starting materials for the synthesis of nitro-saligenin cyclic alkylamido phosphorothionates was prepared in the following manner:

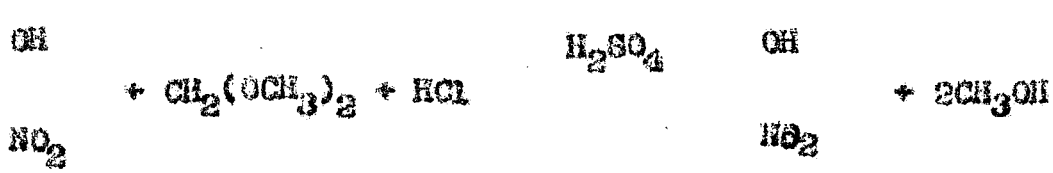
Preparation of the alcohol was done in two stages:

(i) preparation of the 2-hydroxy-5-nitro benzyl chloride, and

(ii) the hydrolysis of the said chloride.

4.(i) Preparation of 2-hydroxy-5-nitro-benzyl chloride.

The 2-hydroxy-5-nitro-benzyl chloride was prepared according to the method described in Organic Synthesis[3]. The reaction involved is:



The p-nitrophenol melting at above 112°C (Reidel, m.p. 114°C) was used for the preparation. The other ingradient methylal was synthesized afresh for every batch of preparation as follows:

760 ml. methanol was added to 400 gm anhydrous calcium chloride in a 3 lt. round bottomed flask equipped with a reflux condenser, 10.2 ml. Conc. hydrochloric acid was added; then with cooling and constant stirring, 400 gm of 37-40% formaldehyde was slowly dropped in through a dropping funnel. It took about 2 hours for complete addition of formaldehyde (the reaction was strongly exothermic). When all the formaldehyde had been added, the mixture was heated for a few minutes until the liquid boiled vigorously. The methylal came up quickly on the upper layer, and after an overnight standing was fractionally distilled. The 42-45°C fraction was collected and stored in a tightly stoppered bottle in cold (freezer) before it was used.

In a one-litre, three-necked round bottomed flask equipped with a mechanical stirrer, a short reflux condenser, and a bent glass tube reaching sufficiently below, were placed 50 gm (0.36 mole) p- nitrophenol, 650 ml Conc. HCl, 5 ml Conc. H_2SO_4 and 76 gm (1 mole) methylal. The reaction mixture was stirred while the temperature was maintained at an around 70+2°C for 4-5 hrs by means of a water bath. During this time HCl gas was bubbled into the reaction mixture through the bent glass tube. The 2-hydroxy-5-nitrobenzyl chloride began to separate as a solid after about one to one and half hour. At the end of the reaction, the mixture was cooled in a ice-bath for a period of 1-2 hour when more crystals separated. The solid materials, after filtration, was airdried for several hours to remove water; and then washed with benzene. The yield was about

40-45 gm. of a white product, m.p. 129-130°C.

4. (ii) HYDROLYSIS OF 2-HYDROXY-5-NITROBENZYL CHLORIDE:

The said chloride was taken as suspension in water and heated slowly; the crystals would go into solution while the impurities form a deep brown oily layer at the bottom of the container. The mixture was then boiled gently to ensure complete hydrolysis. The solution was quickly filtered while hot. The light yellow crystals of 2-hydroxy-5-nitrobenzyl alcohol separated as the filtrate got cooled; the product (m.p. 122-126°C) thus obtained was recrystallised from hot water; the crystals were filtered, washed with cold dioxen : benzene (1:9) mixture, and dried in vacuum.

m.p. 128°C (literature m.p. 128-129°C)[4];

R_f 0.74 (in methanol).

Analysis:

Found ; C, 49.68% ; H, 4.12% ; N, 8.25%;

Calc. for $C_7H_7O_4N$; C, 49.7% ; H, 4.14%; N, 8.28%

UV (Fig. 1) : λ_{max}^{EtOH} = 230 nm (7005), 318(8337), and 410 (3226) nm;

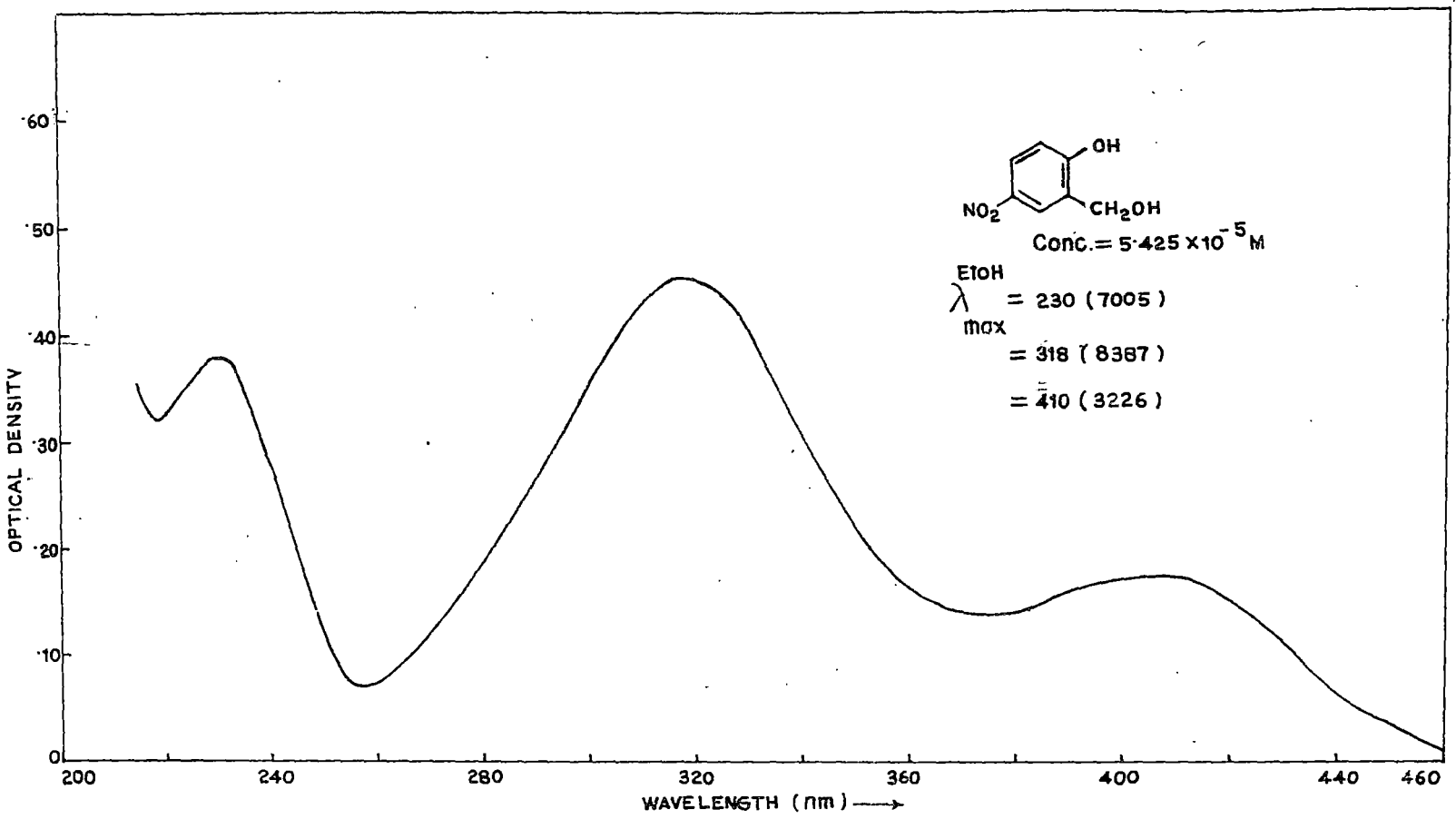
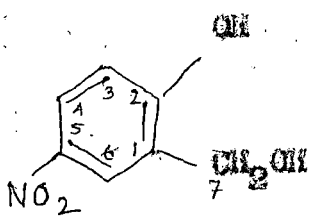


Fig. 1 UV– Visible Spectrum of 5– Nitro saligenin in Ethanol.

IR (Fig.2):

3450 and 3100 Cm^{-1}	: OH vibration;
1438 Cm^{-1}	: OH deformation Str. vibration;
1475 and 1335 Cm^{-1}	: asym. & sym. Str. of NO_2 group;
1610 and 1585 Cm^{-1}	: C = C Str;
1080 Cm^{-1}	: C - C - O
880, 860 and 825 Cm^{-1}	: 1 : 2 : 4 trisubstituted benzene ring vibration;
900 Cm^{-1}	: lone H- atom wagging of the phenyl ring;
750 and 735 Cm^{-1}	: C - N - O bending;
810 Cm^{-1}	: 2H (adjacent) of the ring.

^{13}C NMR (Fig.3):



Carbon Atom	(ppm)
C_7	60.18
C_3	116.02
C_6	124.01
C_1	124.91
C_4	130.41
C_5	141.89
C_2	161.47

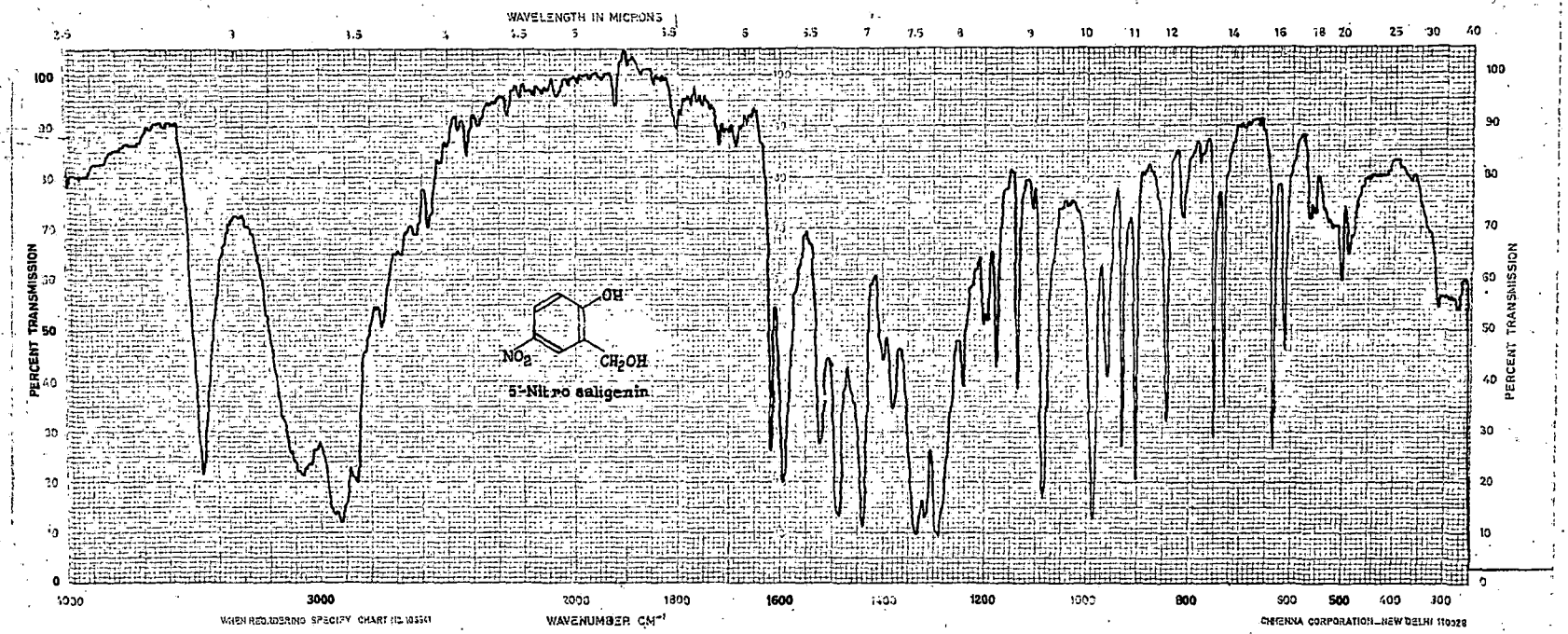


Fig. 2. IR spectrum of 5-Nitro-saligenin

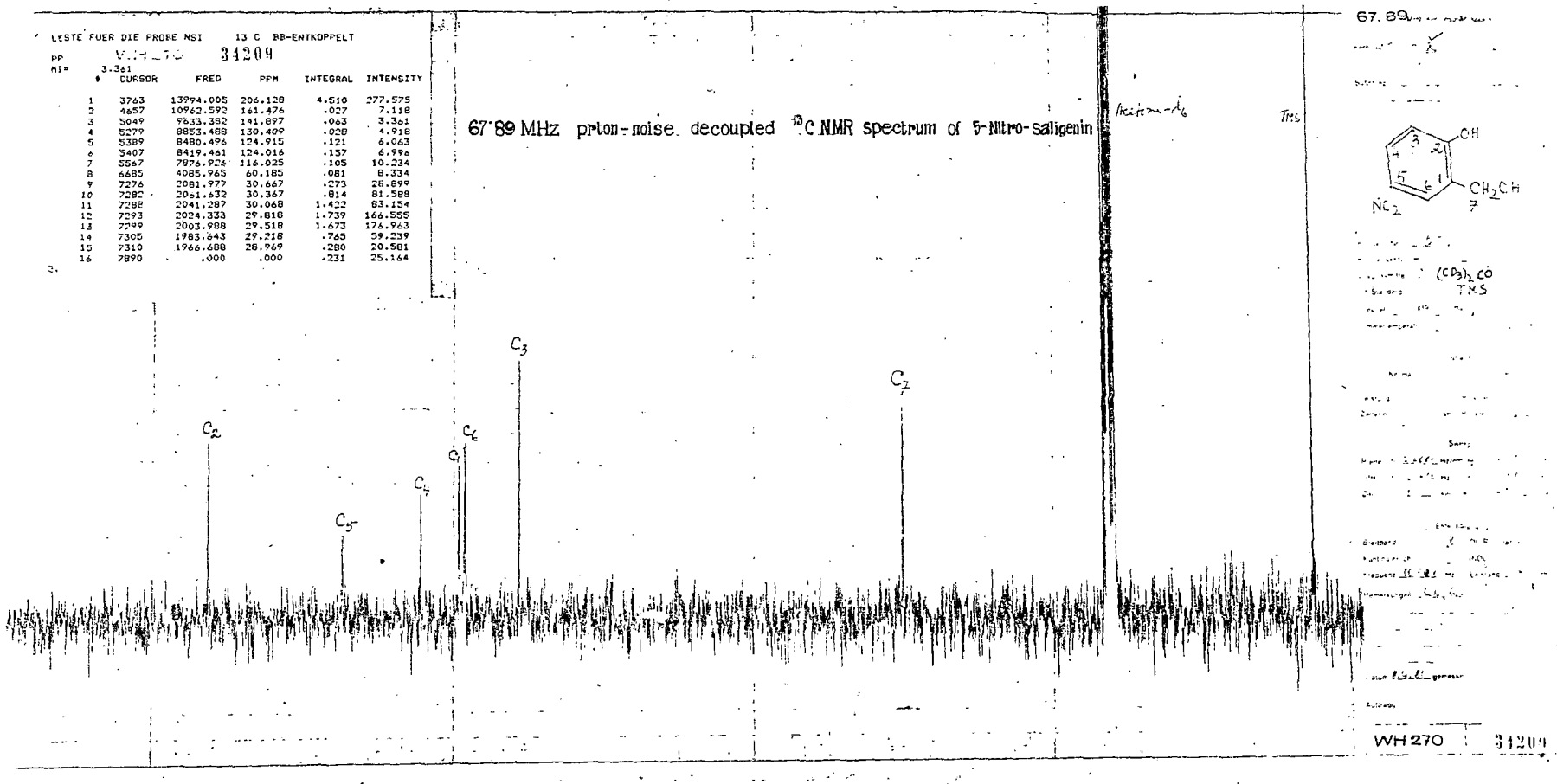

LESTE FUER DIE PROBE NSI 13 C BB-ENTKOPPELT
PP WH270 31209
MI= 3.361
# CURSOR FREQ PPM INTEGRAL INTENSITY
1 3763 13994.005 206.128 4.510 277.575
2 4657 10962.592 161.476 .027 7.118
3 5049 9633.382 141.897 .063 3.361
4 5279 8853.488 130.409 .028 4.918
5 5389 8480.496 124.915 .121 6.063
6 5407 8419.461 124.016 .157 6.996
7 5567 7876.926 116.025 .105 10.234
8 6685 4085.965 60.185 .081 8.334
9 7276 2081.977 30.667 .273 28.899
10 7280 2061.632 30.367 .814 81.588
11 7288 2041.287 30.068 1.422 83.154
12 7293 2024.333 29.818 1.739 166.555
13 7299 2003.988 29.518 1.673 176.963
14 7305 1983.643 29.218 .765 59.239
15 7310 1966.688 28.969 .280 20.581
16 7890 .000 .000 .231 25.164
67.89 MHz proton-noise decoupled ^{13}C NMR spectrum of 5-Nitro-Saligenin
Acetone-d_6
TMS
C_2
C_5
C_4
C_6
C_1
C_3
C_7
67.89
OH
CH_2CH
NO_2
$(CD_3)_2CO$
TMS
WH270 31209

Fig - 3

5. PREPARATION OF PHOSPHORAMIDOTHIOIC DICHLORIDES:

$$2RNH_2 + PSCl_3 \quad (2 \text{ mole}) \quad (1 \text{ mole}) \qquad RNH.P(S)Cl_2 + RNH_2.HCl$$

or

$$RNH_2 + PSCl_3 \quad (1 \text{ mole}) \quad (1 \text{ mole}) \xrightarrow[1 \text{ mole}]{\text{Triethylamine}} RNH.P(S)Cl_2 + \text{triethylamine-hydrochloride}$$

One mole $PSCl_3$ and two moles amine (or, one mole amine and one mole triethylamine) were allowed to react at 15° to -5°C in benzene/chloroform as solvent. The amine solution was added dropwise very slowly with constant vigorous stirring. After an additional stirring period, the solid particles (if present) were filtered off the reaction mixture and washed repeatedly with benzene/chloroform, Subsequently with 2% cold hydrochloric acid, then with cold saturated solution of sodium chloride. The benzene/chloroform phase was then dried with anhydrous sodium sulphate and filtered; evaporation *in Vacuo* gave the desired phosphoramidothioic dichloride; this dichloride was used as such for the subsequent reaction.

The different phosphoramidothioic dichlorides were prepared as follows:

5. (1) Cyclo hexylamidophosphoredichloridothionate (IA):

Thiophosphoryl chloride (16.9 gm; 0.1 mole) in 100 ml benzene was allowed to react with cyclohexylamine (19.8gg 0.2 mole)

in 20 ml benzene at -2° to 5°C; the amine solution was added dropwise very slowly with constant vigorous stirring. After an additional stirring period of two hours, the cyclohexylamine hydrochloride was filtered off, and the solution was washed with 2% cold hydrochloric acid saturated with sodium chloride, and then with cold saturated solution of sodium chloride. The benzene phase was then lyophilised with anhydrous sodium sulphate and filtered; evaporation *in Vacuo* gave the cyclohexylamidophosphorodichloridothionate. 16 gm (70% yield) white crystalline solid (m.p. 68-69°C) was thus obtained :

Analysis:

Found : C, 31.04% ; H, 5.20% ; N, 6.02% ; ($C_6H_{12}Cl_2NPS$)

Calc. for: C, 31.05% ; H, 5.21% ; N, 6.03%.

6. (11) Morpholinophosphorodichloridothionate (IB):

A solution of morpholine (8.7 gm; 0.1 mole) in 20 ml benzene was added dropwise to a stirred solution of thiophosphoryl chloride (8.45 gm; 0.05 mole) in 50 ml benzene at -5° to +5°C. The mixture was stirred at 5°C for 3 hr. and at room temperature for 16 hr. The mixture was worked up as in (IA). A clear viscous liquid which solidified after standing several days was obtained (7.0 gm; 64% yield,) m.p. 30-31°C,:

Analysis:

Found : C, 23.52% ; H, 3.94% ; N, 6.85% ; ($C_4H_8Cl_2NOPS$)

Calc. for: C, 23.54% ; H, 3.95% ; N, 6.86%.

5.(iii) N, N - Diethylamidophosphorodichloridothionate (IC):

Diethylamine was extracted in benzene from its aqueous solution by partition method, and its concentration was determined by volumetric method; before estimation of the amine the benzene phase was dried with anhydrous sodium sulphate.

7.3 gm (0.1 mole, 50.12 ml. benzene extract solution conc. 0.1466 gm/ml) diethylamine was allowed to react with thiophosphoryl chloride (8.45 gm, 0.05 mole) in 50 ml. benzene at -5^{o} to $+5^{o}$C and the mixture was worked up as in (IA). 8.0 gm (78% yield) liquid possessing camphor-like odour was thus obtained.

5.(iv) N, N - Dimethylamidophosphorodichloridothionate (ID):

N, N - Dimethylamine was extracted in chloroform from its aqueous solution by partition method and its concentration was determined by volumetric method; before estimation of the amine, the chloroform phase was dried with anhydrous sodium sulphate.

Thiophosphoryl chloride (8.45 gm ; 0.05 mole) in 50 ml chloroform was allowed to react with 4.5 gm (0.1 mole, 37.8 ml chloroform extract solution, conc. 0.1190 gm/ml) dimethylamine and the mixture was worked up as in (IA). 7.5 gm (84% yield liquid which solidified on standing as crystals (m.p. 32-33^{o}C) was thus obtained. This compound has camphor - like odour.

Analysis:

Found: C, 13.48% ; H, 3.39% ; N, 7.86% ;

Calc.for: $C_2H_4Cl_2NPS$; C, 13.50% ; H, 3.40% ; N, 7.87%.

5.(v) Isopropylamidophosphorodichloridothionate (IE):

Thiophosphoryl chloride (8.45 gm ; 0.05 mole) in 50 ml chloroform was reacted with 5.9 gm (0.1 mole, 24.8 ml chloroform extract solution, conc. 0.2379 gm/ml) isopropylamine, and the mixture was worked up as in (IA). 8.0 gm (83% yield) white crystalline solid (m.p. 35-36°C) was thus obtained.

Analysis:

Found : C, 18.74% ; H, 4.18% ; N, 7.27% ;

Calc. for : $C_3H_8Cl_2NPS$: C, 18.76% ; H, 4.20% ; N,7.29%.

5. (vi) Pyrrolidinophosphorodichloridothionate (IF):

Thiophosphoryl chloride (8.45 gm, 0.05 mole) in 50 ml chloroform was reacted with 7.1 gm (0.1 mole) pyrrolidine in 20 ml chloroform, and the mixture was worked up as in (IA). 8.5 gm product was obtained.

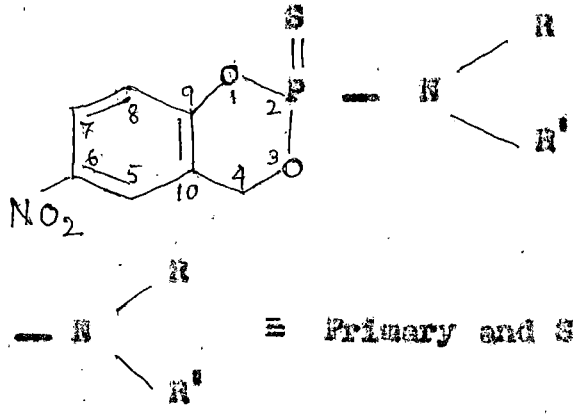
5. (vii). Piperidinophosphorodichloridothionate (IG):

Thiophosphoryl chloride (8.46 gm, 0.05 mole) in 50 ml chloroform was allowed to react with 8.5 gm (0.1 mole) piperidine in 20 ml chloroform. 9.0 gm product was obtained.

5.(viii) Nonylamidophosphorodichloridothionate (III):

This compound was prepared by taking $PSCl_3$ (4.1 gm), triethy-lamine (2.45 gm, 0.0242 mole), and n-nonylamine (3.47 gm, 0.0242 mole) in 100 ml. chloroform; the nonylamine in 30 ml. chloroform was added dropwise; after additional stirring for 3 hrs. the reaction mixture was washed twice with cold saturated sodium chloride solution. The chloroform phase was then dried with anhydrous sodium sulphate and filtered; evaporation in Vacuo gave 6.2 gm liquid nonylamidophosphorodichloridothionate.

6. PREPARATION OF 2 - ALKYLAMIDO-6-NITRO-4H-1,3,2 - BENZODIOXAPHOS-PHORIN-2-SULPHIDE:

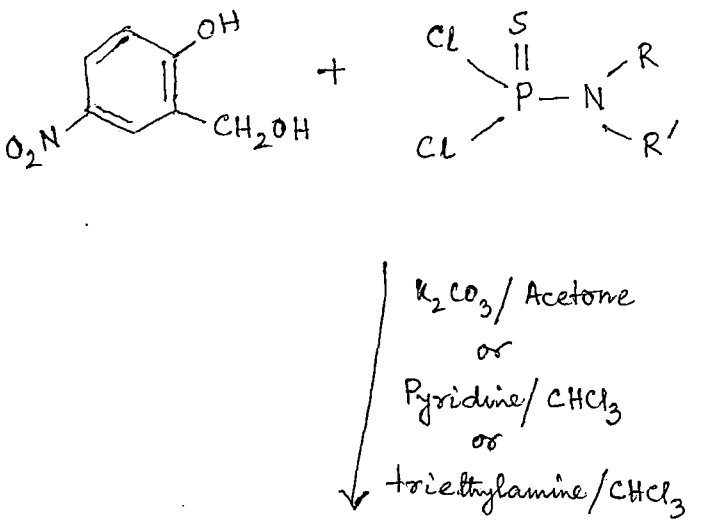


— N(R)(R') ≡ Primary and Secondary amines.

6. (a) GENERAL PROCEDURE:

2-alkylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-Sulphides were prepared by adding a solution of 2-hydroxy-5-nitro benzyl alcohol (5- nitro saligenin, 1 mole) in dry acetone to

1 mole of alkylamidophosphorodichloridothionate with cooling in an ice-bath. The anhydrous potassium carbonate (2 mole) was then added by instalments, with constant stirring. In some cases, good result was found by using 2 moles of pyridine or 2 moles of triethylamine in chloroform solution instead of anhydrous potassium carbonate. The temperature of the reaction mixture was strictly maintained below 5°C during the addition of potassium carbonate/pyridine/triethylamine. The condensation was accomplished by stirring at the temperature 5-27°C for an additional time of 12-16 hrs. The solid particles were filtered out of the reaction mixture and the solvent was removed under reduced pressure at room temperature. In some cases the crude product was directly recrystallised from methanol to give the pure compound; while in others an additional chloroform extraction was necessary prior to the recrystallisation. In the latter case, the crude product was extracted with chloroform and washed with 1% dil HCl (ice - cooled) and with cold water, repeatedly (three times). This was then dried with anhydrous sodium sulphate and the chloroform was subsequently removed under reduced pressure. The pure compounds were then obtained by recrystallisation from methanol.

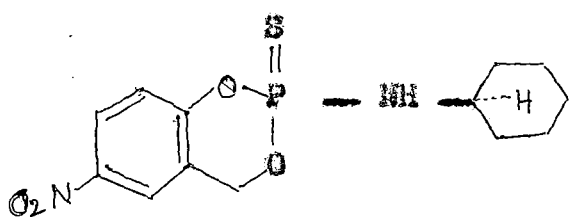


The different alkylamidophosphorothionates were prepared as follows:

6. (b) PREPARATION AND PROPERTIES OF SOME INDIVIDUAL ALKYLAMIDO-PHOSPHOROTHIONATES:

Melting points are uncorrected. Micro analyses were carried out by Alfred Bernhardt, West Germany.

6.(b)(i) 2-Cyclohexylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-Sulphide (BD-10):



This compound (BD-10) was prepared by condensation of 5-nitro saligenin (1.69 gm; 0.01 mole) and Cyclohexylamidophosphorodichloridothionate (2.32 gm, 0.01 mole) in presence of K_2CO_3 (2.76 gm ; 0.02 mole) in 75 ml acetone as solvent ; K_2CO_3 was added by instalments to the stirred solution at 0° to 5°C. After an additional stirring (2-3 hrs. at 0° to 5°C, and then 12-16 hrs. at room temperature), the solids were filtered off, and the solvent was removed. The crude product was washed with methanol saturated with n-heptane, and then the compound was recrystallised from hot methanol. 2.5 gm (76% yield) compound was obtained. BD-10 is a white crystalline solid, m.p. 125°C, practically insoluble in water, highly soluble in methanol, ethanol and benzene.

Analysis:

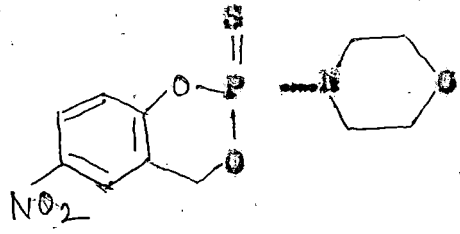
Found : C, 47.54% ; H, 5.19% ; N, 8.52% ;

Calc. for : $C_{13}H_{17}O_4N_2PS$: C, 47.56% ; H, 5.18% ; N, 8.53%.

Molecular Weight : 328.

A better yield (95%) was obtained by using pyridine (chloroform as solvent) instead of K_2CO_3 as dehydrogen chloride agent.

6.(b)(ii). 2-Morpholino-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-Sulphide (BD-11):



5-Nitro-Saligenin (1.69 gm, 0.01 mole), morpholinophosphorodichloridothionate (2.2 gm, 0.01 mole), and K_2CO_3 (2.76 gm, 0.02 mole) in 50 ml acetone gave 3 gm (90% yield) crude product; this was then dissolved in chloroform and washed with cold dilute HCl and water; after drying with anhydrous sodium sulphate the solvent was removed under reduced pressure. The solid mass was then recrystallised from hot methanol. 2.0 gm (60% yield) BD-11 was thus obtained; BD-11 is a white crystalline solid, m.p. 149°C, highly soluble

in acetone and chloroform, moderately soluble in methanol, ethanol and benzene.

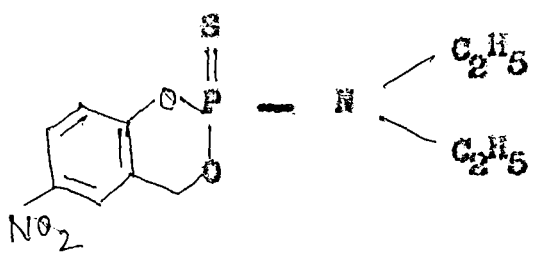
Analysis:

Found : C, 41.75% ; H, 4.10% ; N, 9.24%;

Calc. for : $C_{11}H_{13}O_5N_2PS$: C, 41.77% ; H, 4.11% ; N, 9.27%.

Molecular weight : 316.

6(b) (iii). 2- Diethylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-Sulphide (BD-12):



5-Nitro - Saligenin (1.69 gm, 0.01 mole), diethylamidophos-phorodichloridothionate (2.06 gm, 0.01 mole), and K_2CO_3 (2.76 gm, 0.02 mole) in 50 ml acetone gave BD-12 (2.8 gm, 90% yield) as white crystals (after working up as in BD-10), m.p. 105°C.

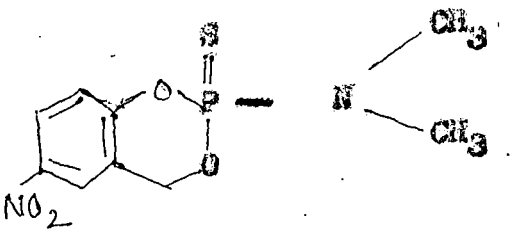
Analysis:

Found : C, 43.68% ; H, 4.94% ; N, 9.25%;

Calc. for : $C_{11}H_{15}O_4N_2PS$: C, 43.70% ; H, 4.96% ; N, 9.27%.

Molecular weight : 302.

6.(b)(iv). 2-Dimethylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-Sulphide (BD-13):



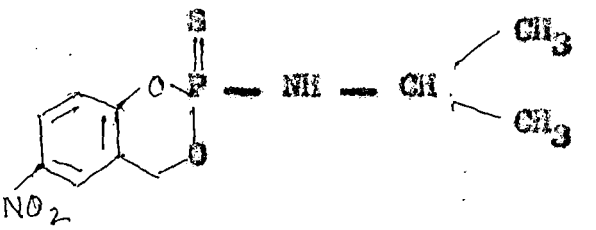
5-Nitro - Saligenin (1.69 gm, 0.01 mole), dimethylamido-phosphorodichloridothionate (1.78 gm, 0.01 mole), K_2CO_3 (2.76 gm, 0.02 mole) in 50 ml acetone gave BD-13 (2.0 gm, 75% yield) as white crystals (after working up as in BD-10), m.p. 128°C.

Analysis:

Found	: C, 39.40% ; H, 4.00% ; N, 10.19%;
Calc.for	: $C_9H_{11}O_4N_2PS$; C, 39.41% ; H, 4.01%; N, 10.21%.

Molecular weight : 274.

6.(b)(v). 2-Isopropylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-Sulphide (BD-14):



5-Nitro-Saligenin (1.69 gm, 0.01 mole) isopropylamidophos-phorodichloridethionate (1.92 gm, 0.01 mole), K_2CO_3 (2.76 gm, 0.02

mole) in 50 ml acetone gave ED-14 (2.0 gm, 70% yield) as white crystals, m.p. 98°C.

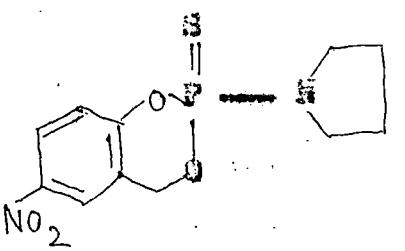
Analysis:

Found : C, 41.64% ; H, 4.50% ; N, 9.70%;

Calc. for : $C_{10}H_{13}O_4N_2PS$: C, 41.66% ; H, 4.61%; N, 9.72%.

Molecular weight : 288.

6.(b)(vi). 2-Pyrrolidino-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-Sulphide (ED-15):



5-Nitro - Saligenin (2.70 gm, 0.016 mole), pyrrolidinophosphorodichloridothionate (3.48 gm, 0.016 mole), K_2CO_3 (4.5 gm, 0.032 mole) in 50 ml acetone gave ED-15 (4 gm, 83% yield) as white crystals, m.p. 134°C.

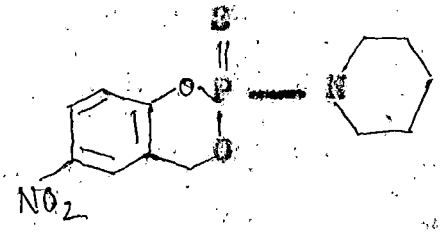
Analysis:

Found : C, 44.82% ; H, 4.27% ; N, 9.28%;

Calc. for : $C_{11}H_{13}O_4N_2PS$: C, 43.91% ; H, 4.32% ; N, 9.32%.

Molecular weight : 300.6.

6.(b)(vii). 2-Piperidino-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-Sulphide (BD-16):



8-Nitro-Saligenin (3.4 gm, 0.02 mole), piperidinophosphoro-dichloridothionate (4.36 gm, 0.02 mole), K_2CO_3 (5.5 gm. 0.04 mole) in 50 ml acetone gave BD-16 (5.5 gm, 87% yield) as white crystals, m.p. 130°C.

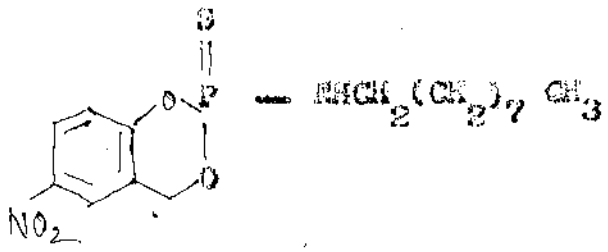
Analysis:

Found : C, 45.73% ; H, 4.71% ; N, 8.83%;

Calc. for : $C_{12}H_{15}O_4PS$: C, 44.71% ; H, 4.77% ; N, 8.90%.

Molecular weight : 314.6

8.(b) (viii). 2-Nonylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide (BD-17):



6-Nitro-saligenin (1.7 gm, 0.0103 mole) nonylamidophosphorodichloridothidonate (2.83 gm, 0.0103 mole), K_2CO_3 (2.9 gm, 0.0316 mole) in 50 ml acetone gave BD-17 (3.5 gm, 87% yield) as crystals, m.p. 64°C.

Analysis:

Found : C, 51.88% ; H, 6.69% ; N, 7.50%;

Calc. for : $C_{16}H_{25}O_4N_2PS$: C, 51.61% ; H, 6.72% ; N, 7.53%.

Molecular weight : 372.

7. ORAL INSECTICIDAL ACTIVITY ON COCKROACHES:

Insecticidal tests were performed on the American Cockroach, Periplaneta americana (Linn) according to Busvine with minor modifications[5]. Adults of P. americana weighing about 1 gm to 1.2 gm were collected in the month of May - June, 1980 from one particular location of the North Bengal University Campus. In the field they were never exposed to any organophosphorus insecticides. For preliminary experiment, ten roaches in each pot were exposed to different dosages of the compounds in dry sugar bait and after 48 hours the mortality was determined, and approximate 100% mortality (LC_{100}) value range (μg/gm basis) was found out.

To determine more precise LC_{100} value of each compound, one cockroach of known weight in each pot was exposed to known quantity of the alkylamidophosphorothionates progressively increasing its concentration by 1 μg for the dimethyl amido compound (range 15-20 μg/gm) and for the other compounds the concentration was increased by 2 μg/gm; for salithion and the methoxy compound (BD-8) the concentration was increased by 1 μg/gm. Each experiment was triplicated and the average LC_{100} value was found out by using the simple arithmetical procedure[6]. Before conducting the experiments on them, the cockroaches were kept starved for 24 hours. However, the varying susceptibility of male and female roaches to different compounds were ignored during the experiment.

8. ANTIFUNGAL ACTIVITY.

Helminthosporium Spp. was employed for the test of antifungal activity by using poisoned food technique[7]. Acetone solution of suitable quantity of the alkylamidophosphorothionates in sterile water containing 0.2 per cent Triton-X was incorporated into melted malt agar so as to get the concentration 5 - 100 ppm for the isopropylamido compound (BD-14) and 50 - 500 ppm for the other compounds in the media. The test medium was poured into sterile petridishes and after solidification the 7 mm 8 days old culture disc was placed asceptically at the centre of the petridish. Three replications on each test with appropriate control under same conditions were maintained. These petridishes were incubated at 26 ± 1°C for 48 hours and then the observations on the diameter of the colony were recorded. Percent inhibition over control was calculated following the equation given by Vincent[8].

9. ACCUTE ORAL TOXICITY TESTS ON RATS.

Oral toxicity testing was conducted on 6-12 months old male white albino rats, weighing 140-200 gm, each housed in separate compartments of a cage. All animals had free access to food and water. Different dosages of a compound were mixed with boiled fish and given to the animals at their habitual[9] feeding time. The mortality within 48 hours were recorded along with the toxic symptoms. Acute oral toxic dosage was found out by varying the amount of compound proportionately. The negligible amount

of compound wasted by the animal during dieting was roughly accounted for in determining the dosage.

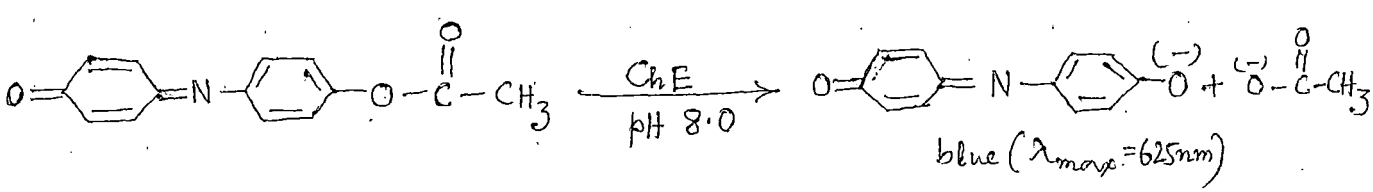
10. ANTICHOLINESTERASE ACTIVITY:

The organophosphorus compounds have a common pharmacological property which is the ability to inhibit the activity of a group of enzymes, especially acetyl cholinesterase (AChE), involved in the hydrolysis of esters of choline. Since these enzymes present widely in insects and mammals, the organophosphorus compounds, used as insecticides also exhibit high mammalian toxicity.

There are four major methods for assaying cholinesterase activity and effect of inhibitors. These methods are potentiometric, titrimetric, manometric and colorimetric.

10. (a) ANTICHOLINESTERASE ACTIVITY IN HOUSEFLY-HEAD HOMOGENATE:

The acetyl cholinesterase inhibition of housefly head brie (HFAChE) has been measured by colorimetric method of Kramer and Gamson[10,11], using indophenyl acetate as an internal substrate - indicator in 0.05 M phosphate buffer of pH 8.0. The enzymatic reaction for indophenyl acetate is as follows:



The reaction mixture contained 5 ml buffer containing housefly head brei (1 ml of this solution contained $\frac{1}{4}$ fly-head) and 0.15 ml indophenyl acetate (total volume = 5.15 ml, Conc. of indophenyl acetate $\sim 10^{-5}$M). The readings for control and sample were taken at 625 nm after exactly 30 minutes incubation.

10.(a)(i) REAGENTS:

1. Buffer solution: (0.05 M potassium dihydrogen phosphate): Clark and Lubs buffer of pH 8.0:

6.8 gm KH_2PO_4 dissolved in 500 ml of water was mixed with 475 ml of 0.1 N NaOH solution and diluted to 1 litre after the pH was adjusted to 8.0.

2. Indophenyl acetate : Working solution:

0.008 gm of indophenyl acetate when dissolved in 10 ml of absolute ethyl alcohol gave a 3.3×10^{-3} M solution so that the final concentration of the indophenyl acetate in the reaction vessel was always 9.6×10^{-5} M.

3. Glycerol solution:

10 ml of Glycerol was diluted to 100 ml with absolute alcohol.

4. Saline solution : 0.9%

9 gm of NaCl was dissolved in 1 litre distilled water.

5. Salt solution:

2.03 gm of Manganous chloride and 2.15 gm of NaCl were dissolved in 250 ml of water.

6. Preparation of working solution of acetylcholinesterase from housefly-heads:

About 500 houseflies (Musca domestica) closed in a glass vessel were stored in a deep freeze for 1-2 hours. They were then transferred in a container with finely broken dry ice, removed individually from the container, decapitated with a shaving blade and forceps. 400 heads were combined with 2 ml of salt solution and 2 gms of washed sand in a prechilled size No. 1 mortar. The heads were slowly ground, then transferred to 50 ml plastic centrifuge tube with one 3 ml aliquots of cold saline solution and two 5 ml aliquots of buffer solution. The head fragments were removed by centrifugation for 10 minutes at 10,000 r.p.m. in superspeed centrifuge at 4°C. The supernatant liquid was decanted into a graduated cylinder and the fragmented heads were mixed with 10 ml of buffer solution and centrifuged again at 10,000 r.p.m. This extraction procedure was repeated twice. The supernatant solutions were combined and the volume was adjusted to 80 ml with the buffer solution so that each ml was equivalent to 5 fly-heads. This solution was stocked frozen in deep freeze. One ml of this solution was diluted to 5 ml with buffer solution so that each ml of the diluted solution contained single fly-head and used for each set of the

experiment.

10.(a)(ii) METHOD:

A series of 15 ml pyrex beakers (numbered 1,2,3 ....etc.) containing different amounts of inhibitor (viz., BD-10/BD-11/etc.) in acetone along with one marked 'control' without inhibitors were arranged. 0.5 ml of glycerol solution was poured in each beaker including the 'control'. The acetone (in beaker 1,2,3, etc.) was removed by blowing cold air.

To the 'control' 5 ml of working enzyme-buffer solution was added and simultaneously the stop-watch was started. At the interval of exactly 2 minutes, 5 ml of the enzyme-buffer solution was added to each of the remaining beakers.

After exactly 30 minutes, 0.15 ml of the indophenyl acetate solution (3.3×10^{-3} M) was added to the beaker marked 'control' and subsequently to each beaker of the series at the interval of 2 minutes and then kept to be incubated at 30°C. After incubation for exactly 30 minutes the aborobances of 'control' and remaining solutions were successively noted in the spectrophotometer (Carl-Zeiss Specol, *ZV*) at 625 nm with reference to enzyme-buffer (reagent blank) solution.

Calculation:

$$\% \text{ Inhibition} = \frac{\text{Absorbance (Control)} - \text{Absorbance(Sample)}}{\text{Absorbance (Control)}} \times 100$$

11. ANTICHOLINESTERASE ACTIVITY IN GOAT-WHOLE BLOOD:

The method employed to determine the inhibition of the activity of acetyl cholinesterase in goat whole blood by organophosphorus compounds was by colorimetric method of Kramer and Gamson [10,11], using indophenyl acetate as an internal substrate-indicator in 0.05 M phosphate buffer of pH 8.0. The reaction mixture contained 5 ml of enzyme buffer solution (4.8 ml phosphate buffer solution along with 0.2 ml goat whole blood) and 0.15 ml indophenyl acetate (total volume = 5.15 ml, concentration of indophenyl acetate (~~total volume = 5.15 ml, concentration of indophenyl acetate~~ in the reaction mixture $\sim 10^{-5}$ M). The readings of 'control' and 'sample' were taken at 625 nm, after exactly 30 minutes incubation.

11. (a) MATERIALS AND METHOD:

(i) Material:

(a) Goat whole blood: 150 ml fresh blood was collected from goat and mixed with 15 mg ammonium oxalate (anticoagulating agent) in a 250 ml standard joint bottle and was shaken well. The bottle containing blood was then kept in the freezer at $0^{\circ}C$.

The other reagents e.g. (b) indophenyl acetate (c) phosphate buffer solution and (d) glycerol solution were prepared just as the same as mentioned in 10(a).

(11) Method:

The Anticholinesterase Activity in Goat whole blood was determined by the same method as described in 10(a). The only exception was that the contents of the beaker was filtered through a 4.25 cm Whatman No. 1 filter paper after exactly 29 minutes incubation and the absorbance of the filtrate was noted in spectrophotometer at 625 nm with reference to the filtrate of the enzyme-buffer solution and % inhibition was calculated in the same way as described in 10(a).

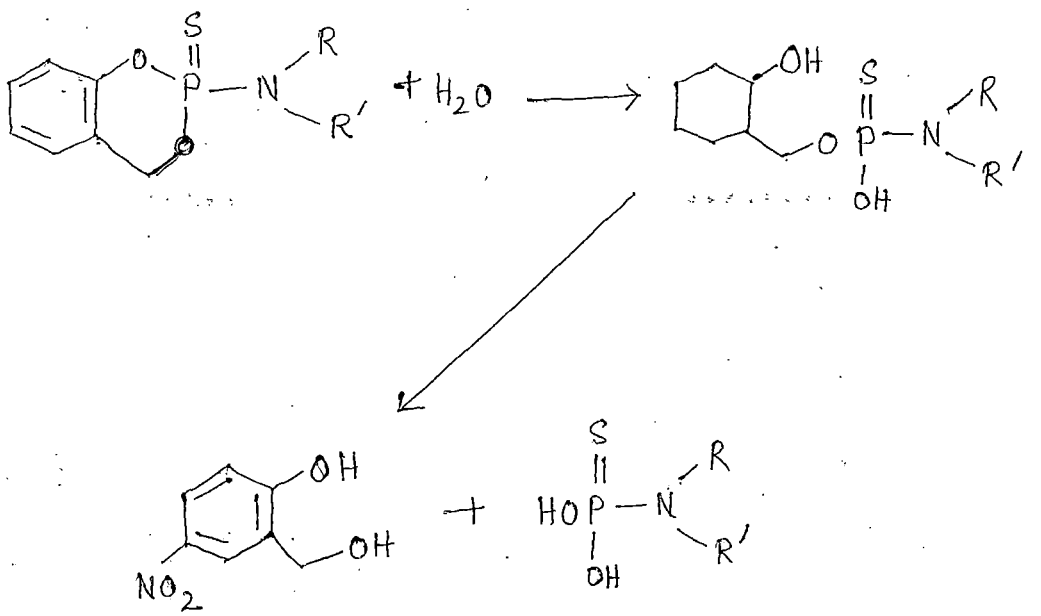
12. PHYTOTOXICITY TEST:

Phytotoxicity testing was conducted according to Eto et al (12). Acetone solution of the compounds mixed with fixed amount of water containing 0.2% Triton-X was prepared. 5 ml of this aqueous suspension containing 500, 250 or 100 ppm of the compounds was poured into a petridish bottom covered with absorbent cotton. Ten seeds of wheat (Triticum. Sp. UP 262 variety supplied by National Seed Corporation of India) were planed on the cotton and kept at room temperature (25-27°C) for five days. Occasionally 2-4 ml water was added in each petridish so that the seeds remained in moist condition. Each test was triplicated. Number of germination was counted after 5 days.

13. CHEMICAL HYDROLYSIS:

Since the nitro saligenin cyclic alkylamidophosphorothionates are analogous to salithion (13), it is envisaged to proceed

with the initial fission of aryl ester bond in dioxaphosphorin ring followed by the liberation of nitro saligenin.



Moreover, the reactivity of nitro saligenin cyclic phosphorothionates is not only effected by exocyclic substituents on the phosphorus atom but also it is significantly influenced by the presence of nitro group at the para position to phenolic -OH group in the benzene ring.

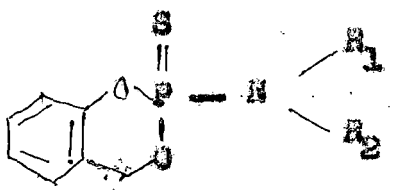
The chemical hydrolysis studies were performed in 0.0095 M NaOH solution in 50 per cent ethanol of pH 11.85 at 20°C. One ml of ethanol solution of the compounds was added with 9 ml of 0.0095 M NaOH solution (total volume 10 ml). The rate of hydrolysis was monitored by following the formation of nitro-saligenin anion at 400, 410, 420 and 430 nm in a Carl Zeiss Speckol UV spectrophotometer. UV spectra of the alk/lamidophosphorothionates and hydrolytic products were examined prior to Kinetic studies to show that overlap in relevant absorption peaks were not present. The concentration of the hydrolytic product was determined from the extinction co-efficient value of 5-nitro saligenin in the same 0.0095 M NaOH solution at the said wave lengths. The pseudo first order rate constants (K_{hyd}) were determined by the least squere regression analysis.

B. RESULTS AND DISCUSSION

B. RESULTS AND DISCUSSION:

1. SYNTHESIS.

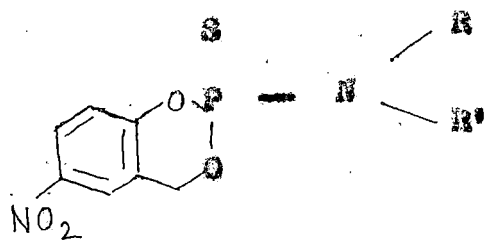
Only four saligenin cyclic phosphoramidothionates have so far been reported[14]. The physical properties and per cent yield of these compounds are given below.



Amido Group	Code No.	Yield percent	b.p. °C/mm Hg.
Methylamido	K - 35	20	120 - 123/0.2
Ethylamido	K - 37	-	Undistillable liquid.
Dimethylamido	K - 36	27	118 - 122/0.2.
Diethylamido	K - 38	13	110/0.2

All of them are liquids, and per cent yields are low (13-27%)[14]. The methylamido compound (K-35) has been prepared at -4°C using pyridine as dehydrogen - chloride agent in chloroform solution; the other three compounds (K-37, K-36, K-38) have been prepared at elevated temperatures (60-80°C) using anhydrous K_2CO_3 as dehydrogen -chloride agent and copper powder as catalyst in toluene with low yield.

We, however, succeeded to prepare the nitro-saligenin cyclic phosphoramidothionates (BD-10 to BD-17) in solid crystalline form with high yields (Table, given below):



Code No.	Amido Group	Yield (%)	m.p. (°C)
BD - 10	Cyclohexylamido	70 - 90	125
BD - 11	Morpholino	60 - 80	149
BD - 12	Diethylamido	80 - 90	105
BD - 13	Dimethylamido	75 - 80	128
BD - 14	Isopropylamido	70 - 80	98
BD - 15	Pyrrolidino	80 - 90	134
BD - 16	Piperidino	80 - 90	130
BD - 17	Nonylamido	80 - 90	64

The method[14] due to Eto *et al* by employing K_2CO_3 and copper powder at elevated temperature in benzene was tried for the preparation of the dimethylamido compound (BD-13); in that case, a pasty material was obtained from which it was difficult to get the pure compound.

Attempts had also been made several times to prepare the 2-methylamido-6-nitro-4H-1,3,2-benzodioxnphosphorin-2-sulphide, and

its ethylamido analog; unfortunately, in each case a viscous yellowish liquid was obtained. TLC of these liquids gave several spots indicating the presence of a number of compounds; the pure amidophosphorothionates could not be isolated from these liquid mixtures.

Cremlyn and Akhtar[15] had reported that the morpholinophosphorodichloridothionate is a liquid (b.p. 100-102/1.5 mm); Fusco and Bertulli[16] has also reported the same (b.p. 107-110/2 mm). We could, however, succeed to obtain the morpholinophosphorodichloridothionate in the form of white crystalline solid (m.p. 30-31°C).

2. SPECTRAL PROPERTIES:

The structures of the alkylamidophosphorothionates have been determined by chemical analysis and UV, IR, mass and NMR spectra. The analytical data along with the physical characteristics have been presented previously (Section A).

The spectral data for different alkylamidophosphorothionates are given below:

3. SPECTRAL DATA:

(1) 2-Cyclohexylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide (BD-10):

UV (Fig. 4): λ_{max}^{EtOH} = 290 nm (log ϵ = 4.051)

IR (Fig. 5):

1020 Cm^{-1} (s), P-O-C (alkyl);

1240 Cm^{-1} (vs) and 880-920 Cm^{-1} (s), P-O-C (aryl);

1515 Cm^{-1} (s), asym. str. of nitro group;

1340 Cm^{-1} (s), sym. str. of nitro group;

800 Cm^{-1} (s), P = S (I);

650 Cm^{-1} (m), P = S (II);

3300 Cm^{-1} (m), N - H str.;

1620 Cm^{-1} (w) and 1585 Cm^{-1} (m), two components of the substituted benzene ring "quadrant stretching" C = C vibrations;

1480 Cm^{-1} (m) and 1420 Cm^{-1} (m), two components of the substituted benzene ring "semicircle stretching" C = C vibrations;

740 Cm^{-1} (m), P - N str. (also aromatic C-H-O bending).

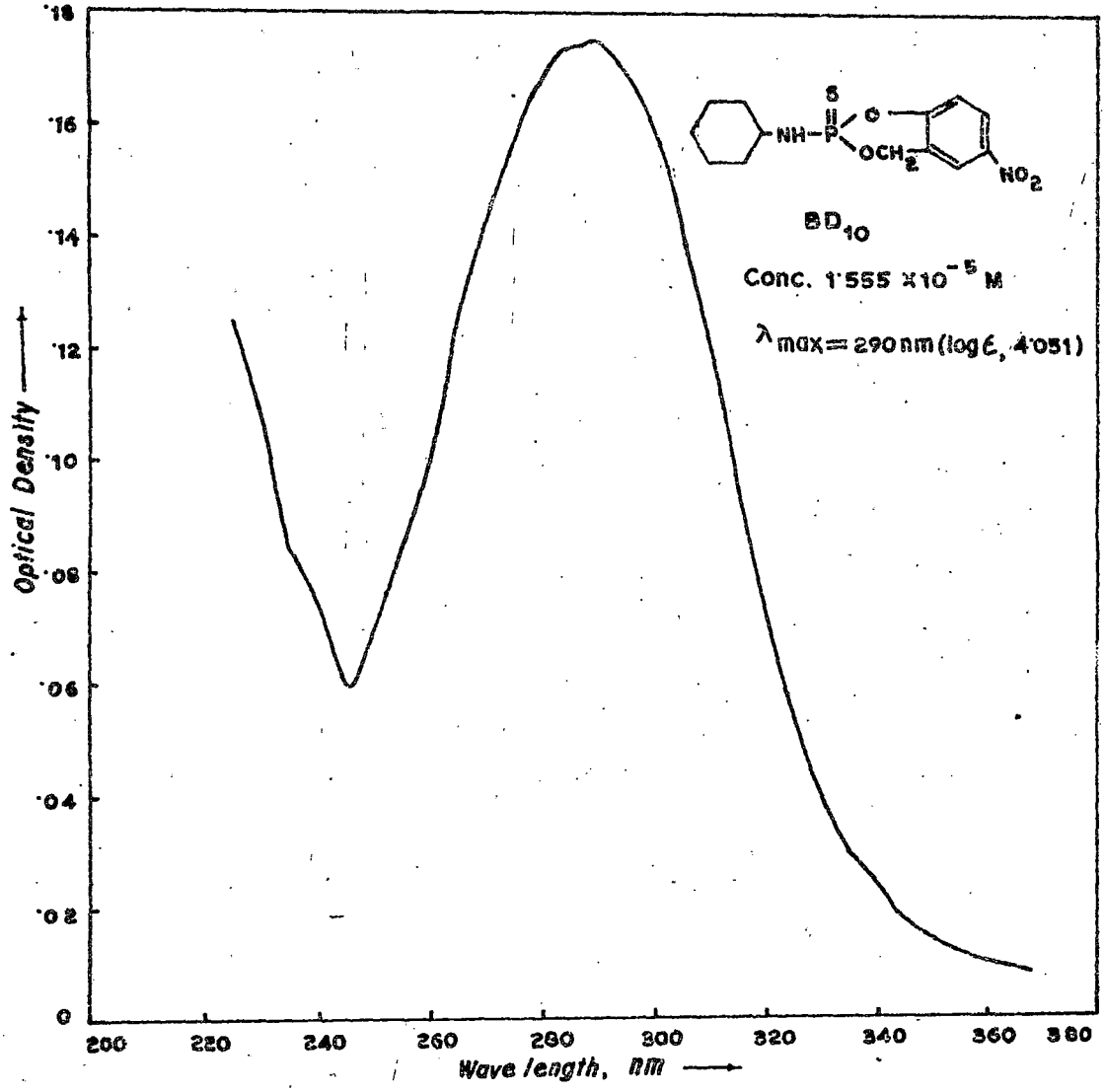


Fig. 4. UV spectrum of BD_{10} in ethanol

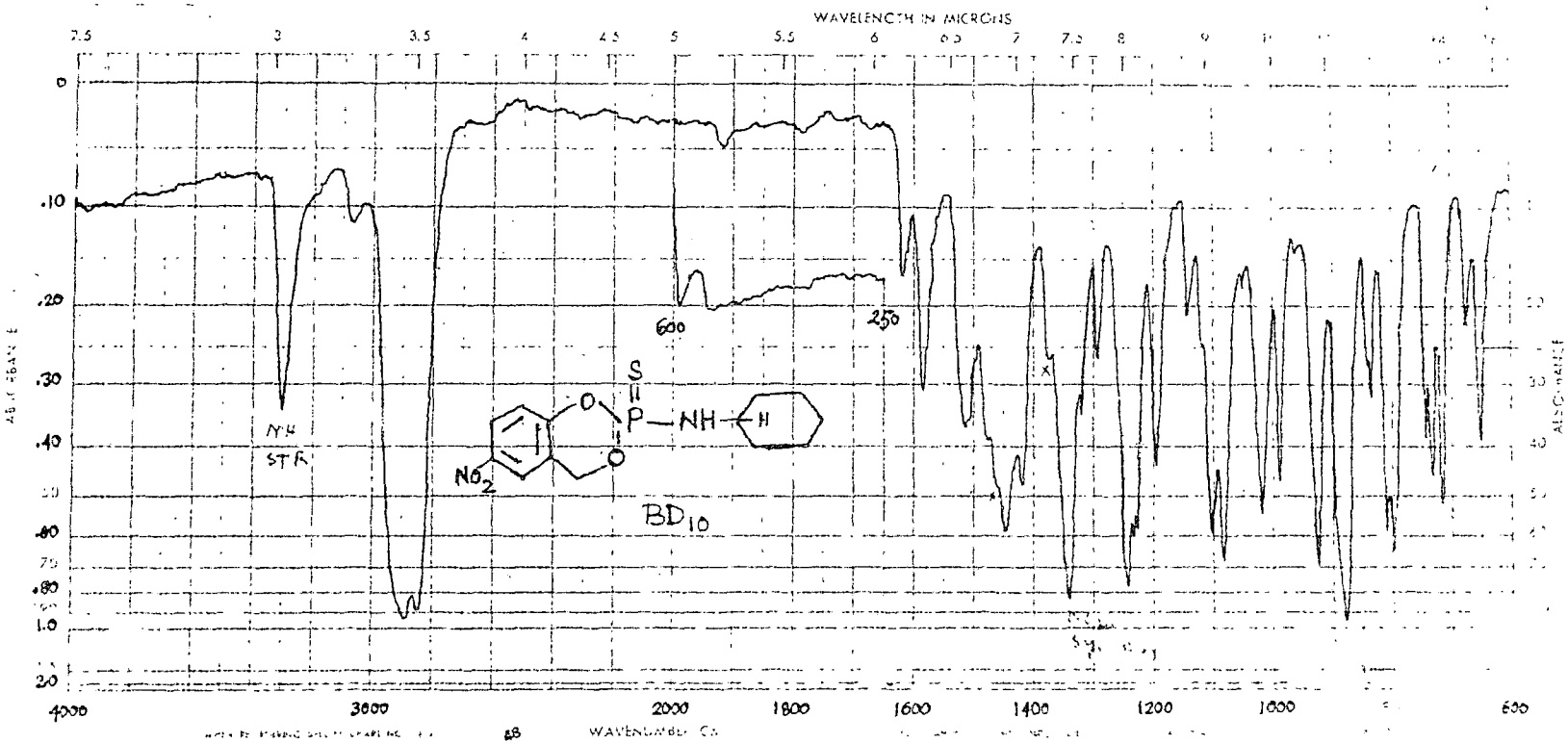


Fig. 5. IR spectrum of 2-Cyclohexylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide.

Mass (Fig. 6):

m/e	%RI
328 (M^+)	34.5
296	43.5
295 (base peak)	100
279	45.0
249	33.0
230	35.0
192	54.5
162	69.0

^1H NMR δ ($CDCl_3$) ppm (Fig. 7):

1.25 (2H, multiplet, $-CH_2-$ group at 4 position of the cyclohexylamine);

1.6 (4H, multiplet, two $-CH_2-$ groups at 3,3' position of the cyclohexylamine);

1.9 (4H, multiplet, two $-CH_2-$ groups at 2,2' position of the cyclohexylamine)

3.2 (1H, multiplet $-CH<$ group);

3.6 (1H, multiplet -P-NH- group);

5.45 (2H, Octet, $-CH_2-$ group in dioxaphosphorin ring);

7.1 (1H, doublet, J = 8.5 Hz, one aromatic hydrogen meta to nitro group);

8.05 (1H, doublet, one aromatic hydrogen ortho to both nitro group and $-CH_2-$ group of dioxaphosphorin ring);

8.2 (1H, multiplet, remaining one aromatic hydrogen)

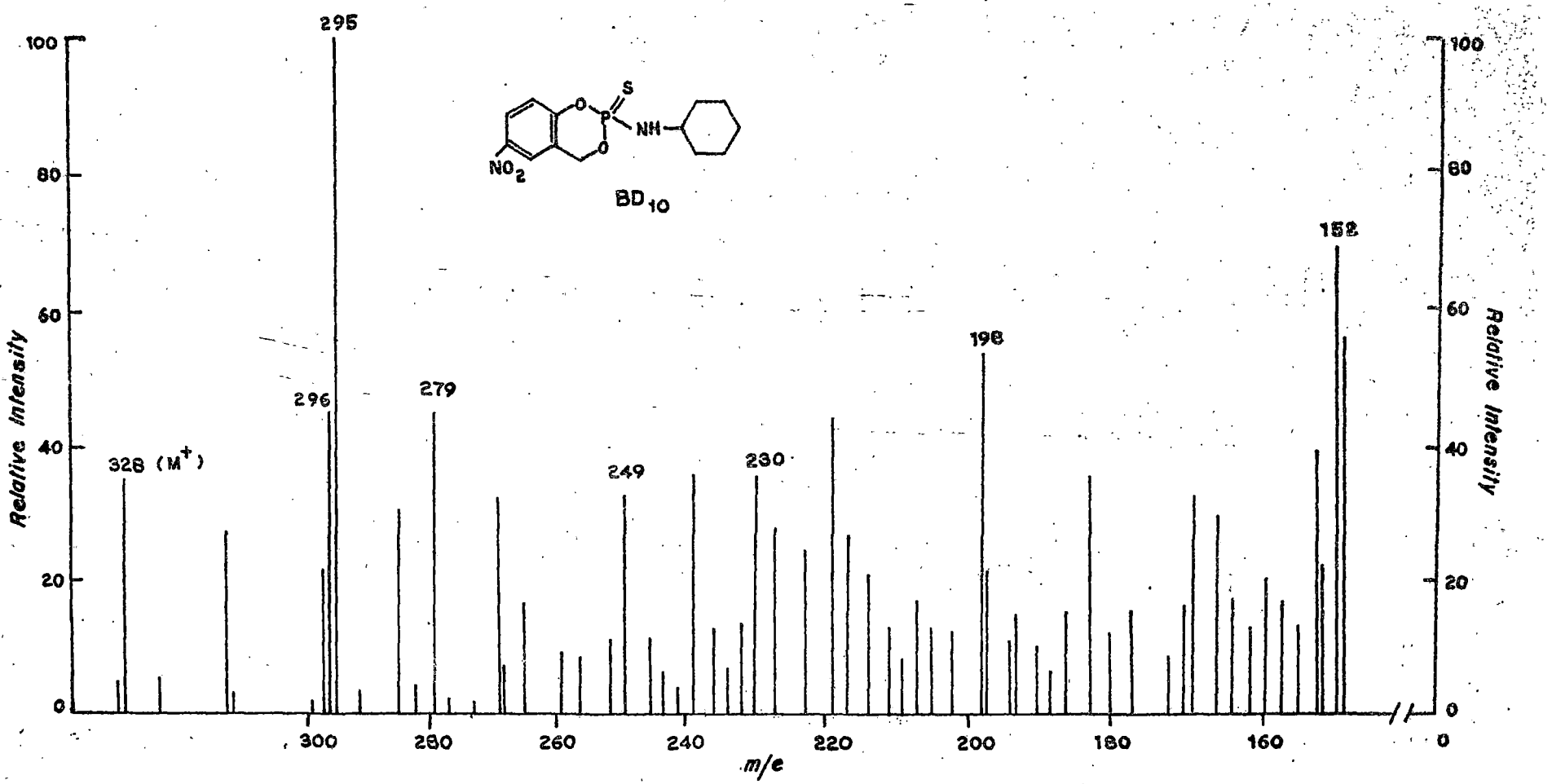


Fig. 6. Mass spectra of -2- Cyclohexylamido - 6- nitro 4H- 1,3.2 benzodioxaphosphorin-2- sulphide.

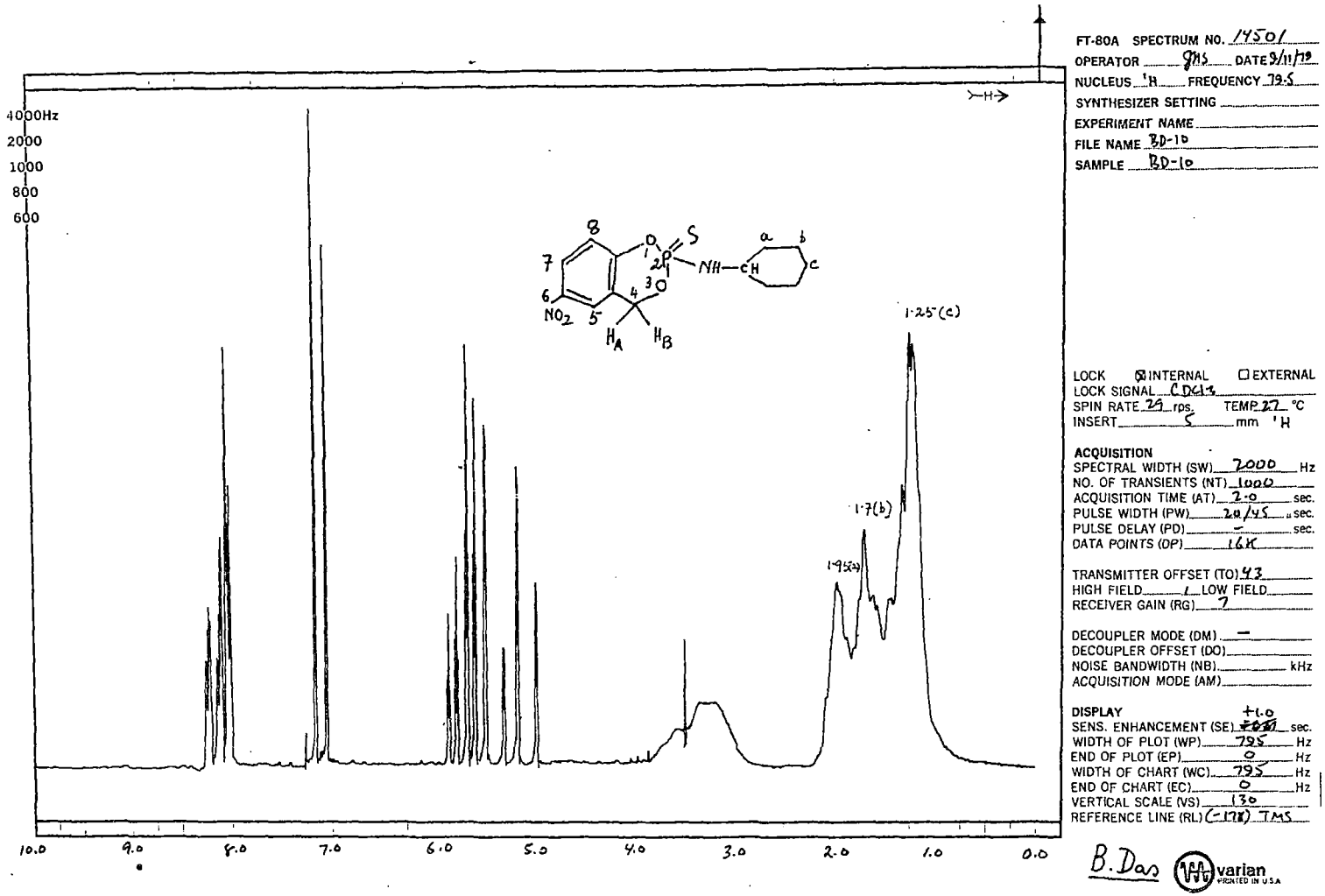


Fig. 7. ^1H NMR spectrum of 2-Cyclohexylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide.

(11) 2-Morpholino-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide (ED-11):

UV (Fig. 8): λ_{max}^{EtOH} = 274 nm (log ϵ = 4.908)

IR (Fig.9):

1020 Cm^{-1} (s) and 980 Cm^{-1} (vs), P-O-C (alkyl);
1250 Cm^{-1} (vs) and 886 Cm^{-1} (s), P-O-C (aryl);
1520 Cm^{-1} (s), asym. str. of nitro group;
1340 Cm^{-1} (vs), sym. str. of nitro group;
820 Cm^{-1} (s), P = S (I);
650 Cm^{-1} (m), P = S (II);
720 Cm^{-1} (m), P - N str. ;
1620 Cm^{-1} (w) and 1585 Cm^{-1} (m), benzene ring "quadrent stretching" vibrations.

Mass (Fig. 10):

m/e	%RI
316 (M^+)	43.0
284	60.0
283 (base peak)	100
230	48.6
198	70.0
152	46.4

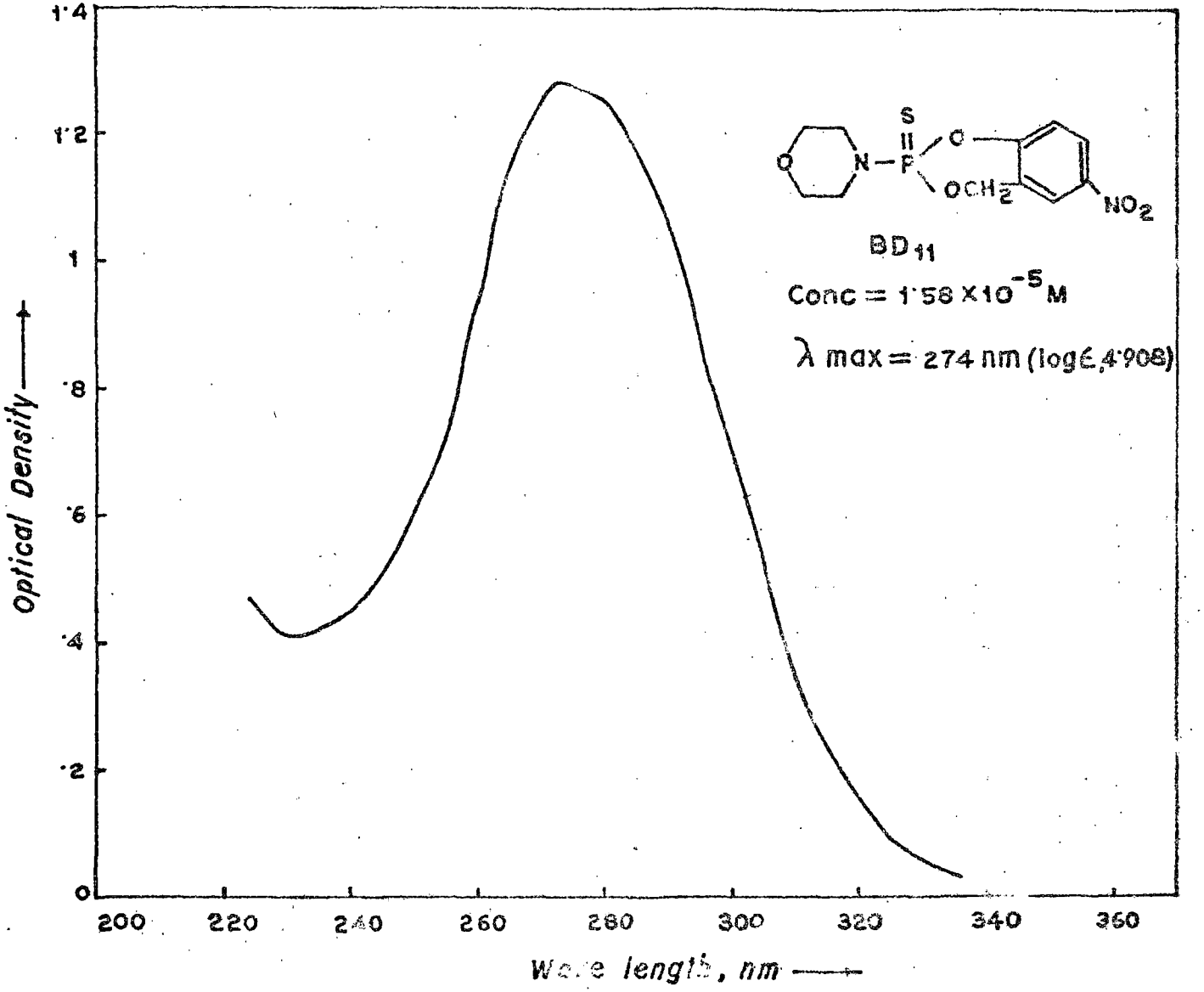


Fig. 8 UV spectrum of BD_{11} in ethanol

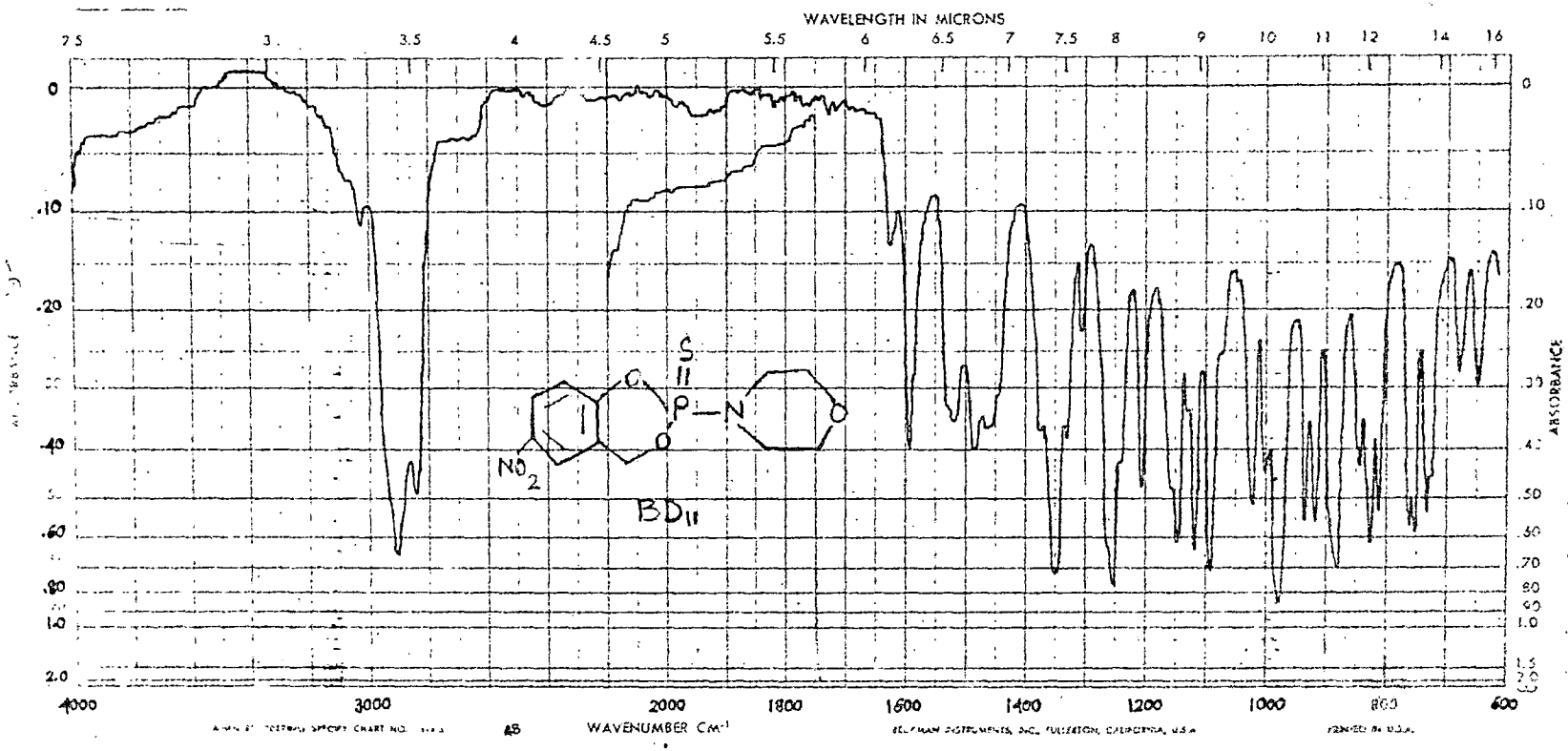


Fig. 9. IR spectrum of 2-Morpholino-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide

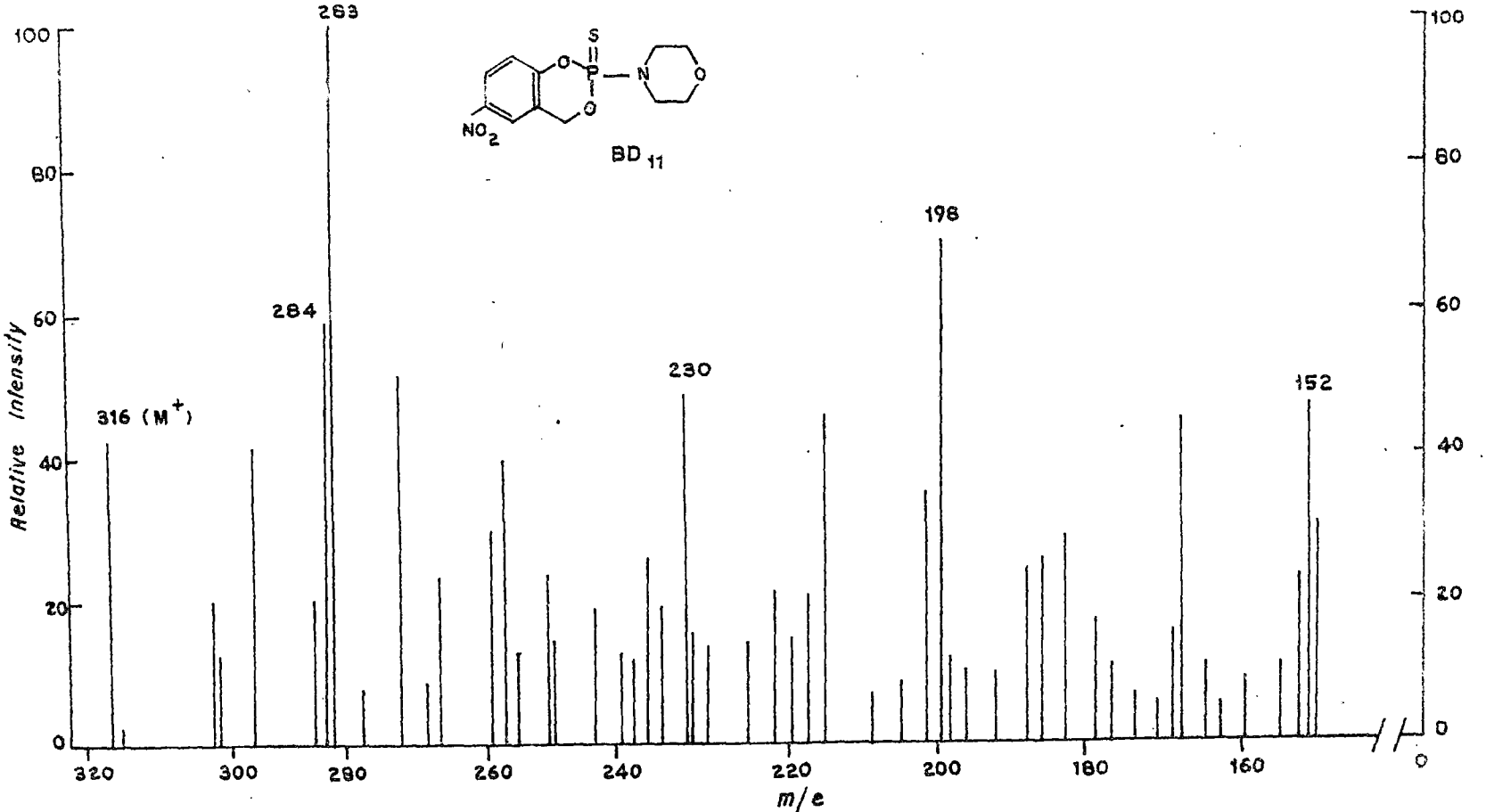


Fig. 10. Mass spectra of 2- Morpholino-6-nitro 4H-1,3,2 benzodioxaphosphorin-2 sulphide.

^{1}H NMR δ($CDCl_3$) ppm (Fig. 11):

3.6 (4H, multiplet, $-N(-CH_2-)(-CH_2-)$ group of the morpholine ring);

3.8 (4H, multiplet, $O(-CH_2-)(-CH_2-)$ group of the morpholine ring);

5.45 (2H, Octet, $-CH_2-$ group in dioxaphosphorin ring);

7.1 (1H, doublet, one aromatic hydrogen meta to nitro group);

8.05 (1H, doublet, one aromatic hydrogen ortho to both nitro group and $-CH_2-$ group of dioxaphosphorin ring);

8.2 (1H, multiplet, remaining one aromatic hydrogen).

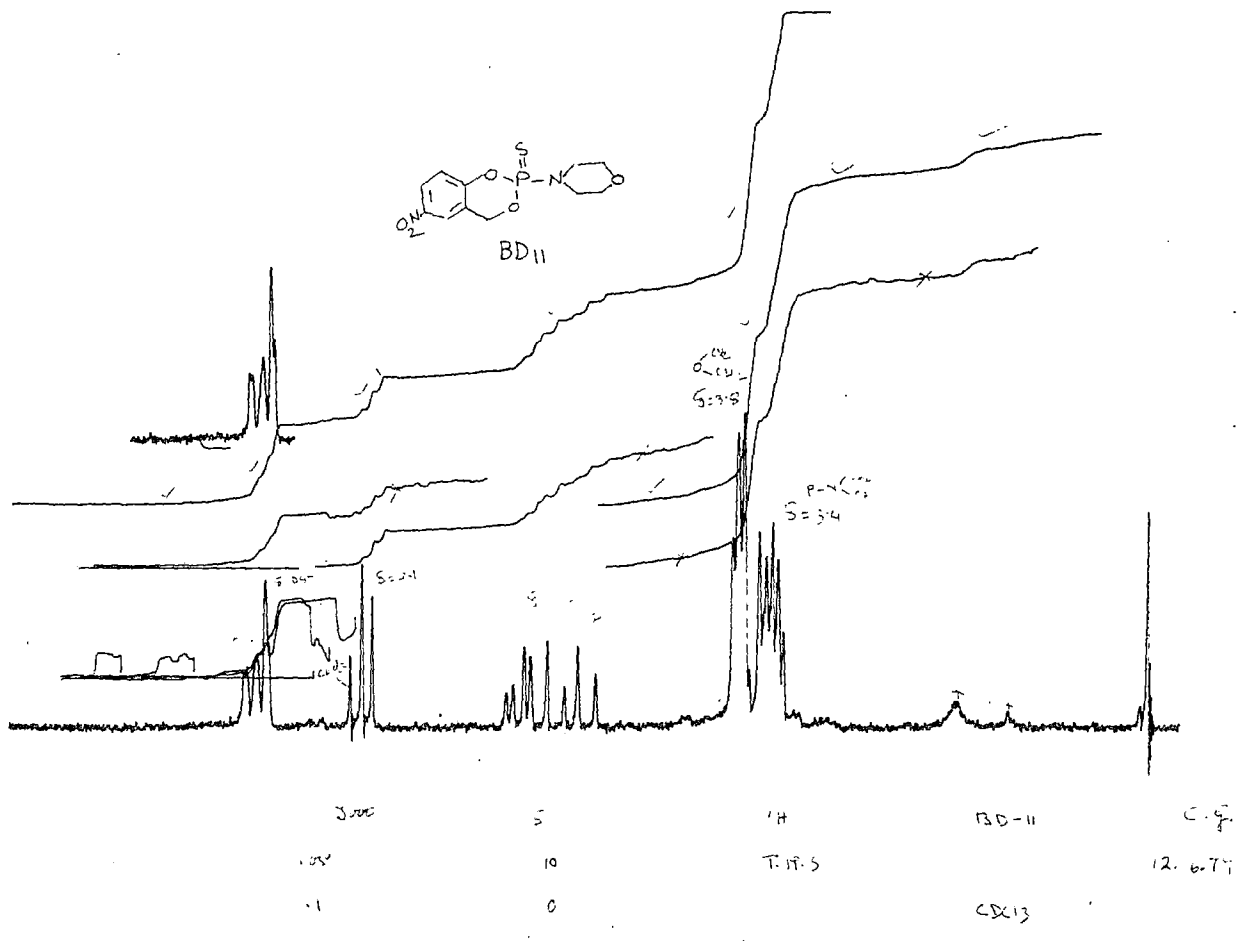


Fig. 11: 1

(iii) 2-N,N - Diethylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide (BD-12):

UV (Fig. 12): λ_{max}^{EtOH} = 295 nm (log ϵ =3.979)

IR (Fig.13):

1030 Cm^{-1} (vs), P-O-C (alkyl);
1235 Cm^{-1} (vs) and 880 Cm^{-1} (vs), P-O-C (aryl);
1515 Cm^{-1} (s), asym. str. of nitro group;
1345 Cm^{-1} (s), sym. str. of nitro group;
890 Cm^{-1} (s), P = S (I);
640 Cm^{-1} (m), P = S (II);
786 Cm^{-1} (m), P - N str.;
1620 Cm^{-1} (w) and 1585 Cm^{-1} (s), benzene ring "quadrant stretching" vibration.

Mass (Fig. 14):

m/e	%RI
302 (M^+)	25
269 (base peak)	100
198	40
152	10

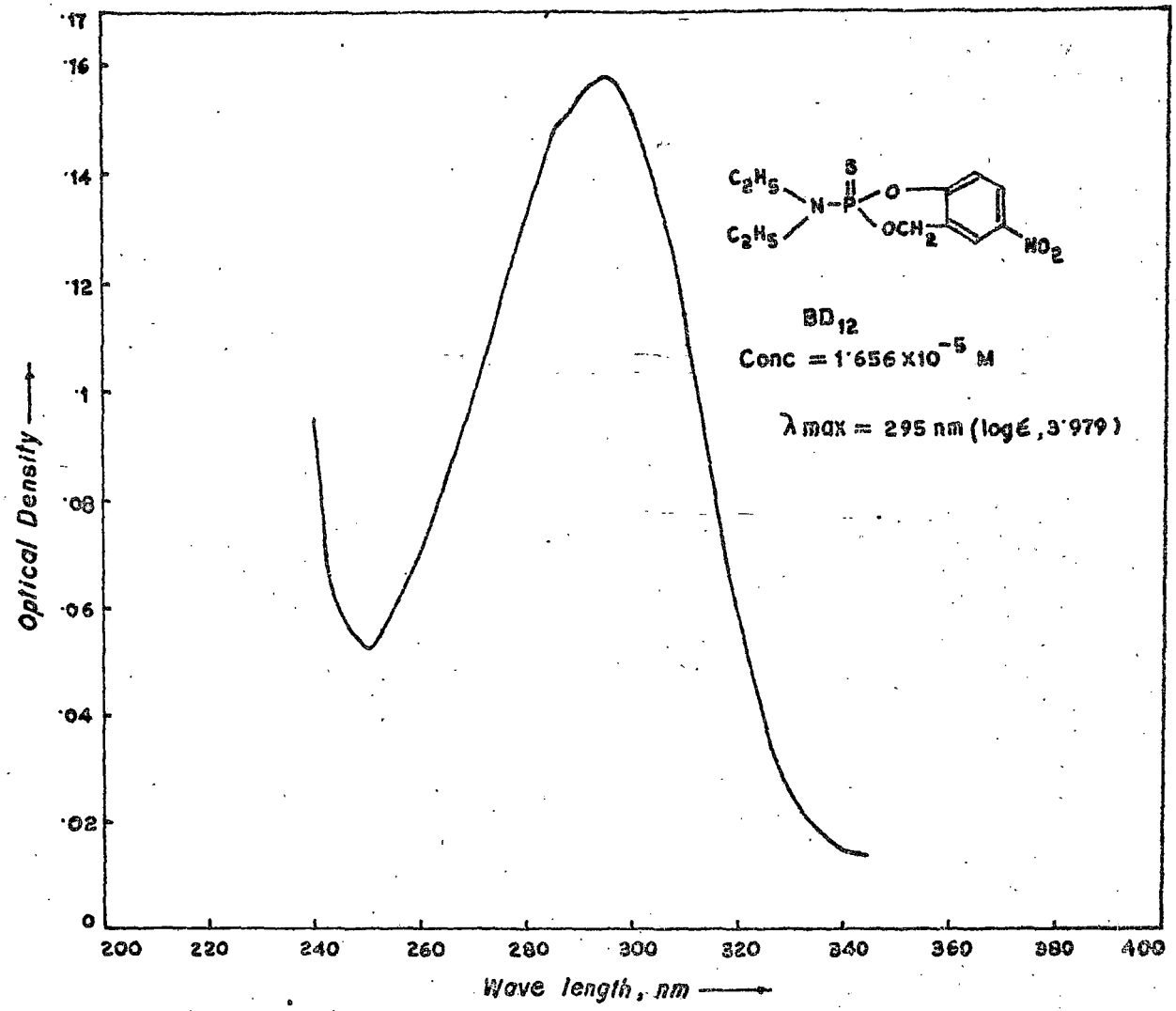


Fig. 12. UV spectrum of BD_{12} in ethanol

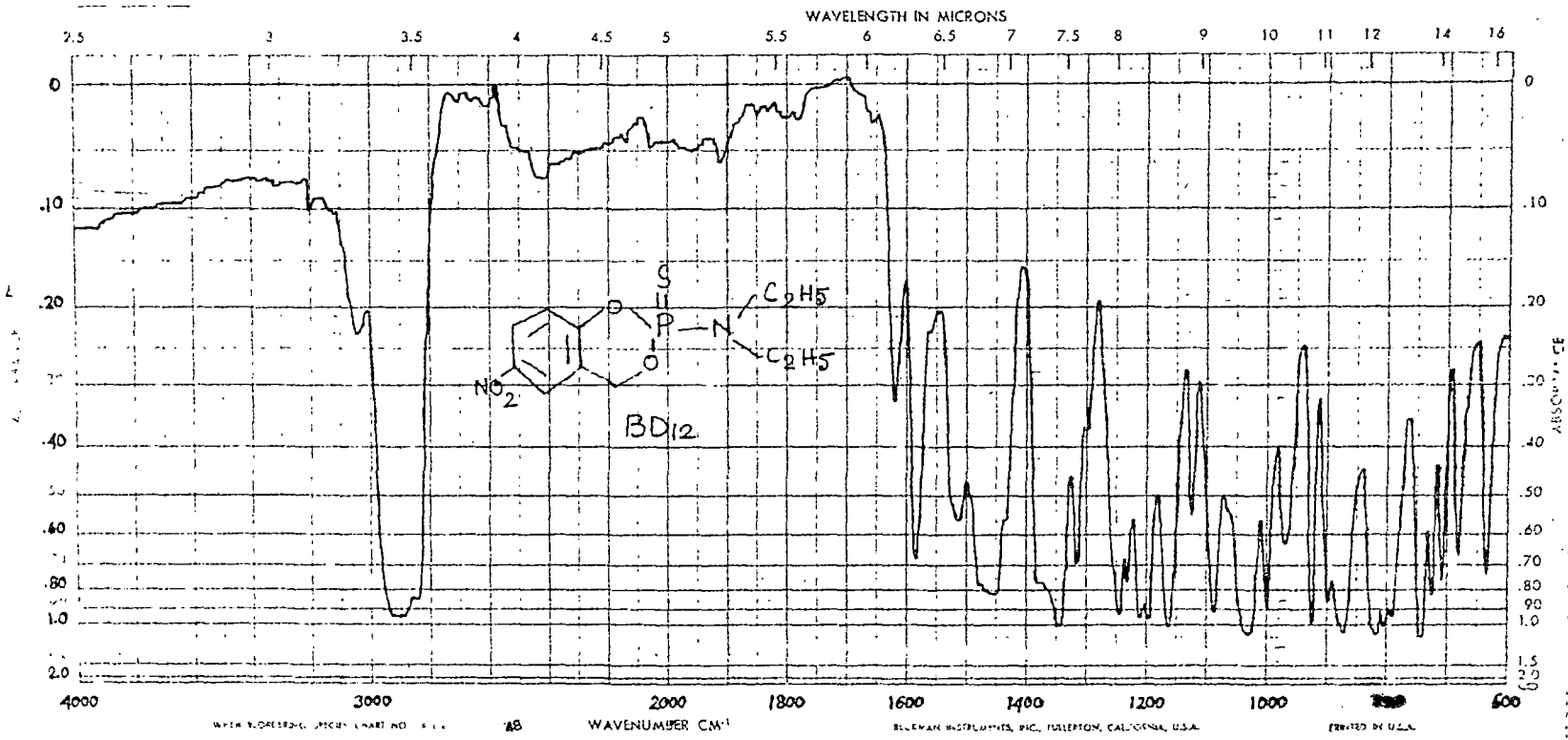


Fig. 13. IR spectrum of 2-N,N-Diethylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide.

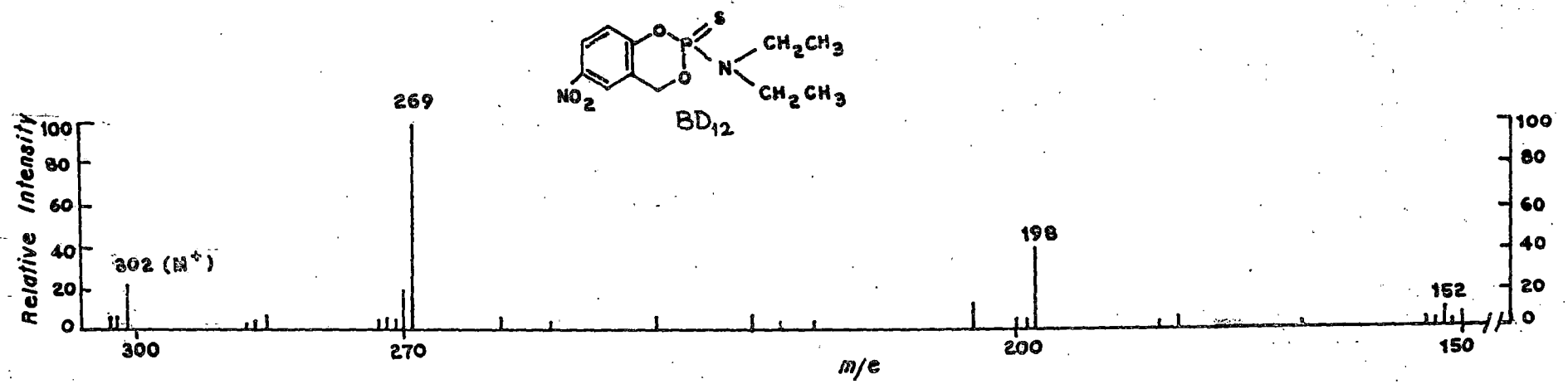


Fig. 14. Mass spectra of 2-diethyl amido-6-nitro 4H-1,3,2 benzodioxaphosphorin-2-sulphide.

^{1}H NMR δ ($CDCl_3$) ppm (Fig. 15):

1.15 (6H, triplet, J = 7.0, two $-CH_3$ groups);

3.4 (4H, multiplet, $-N\begin{matrix}\diagup CH_2- \\ \diagdown CH_2-\end{matrix}$ group);

5.4 (2H, multiplet, $-CH_2-$ group in the dioxaphosphorin ring);

7.05 (1H, doublet, one aromatic hydrogen meta to nitro group);

8.0 (1H, doublet, one aromatic hydrogen ortho to both nitro group and $-CH_2-$ group of dioxaphosphorin ring);

8.2 (1H, multiplet, remaining one aromatic hydrogen).

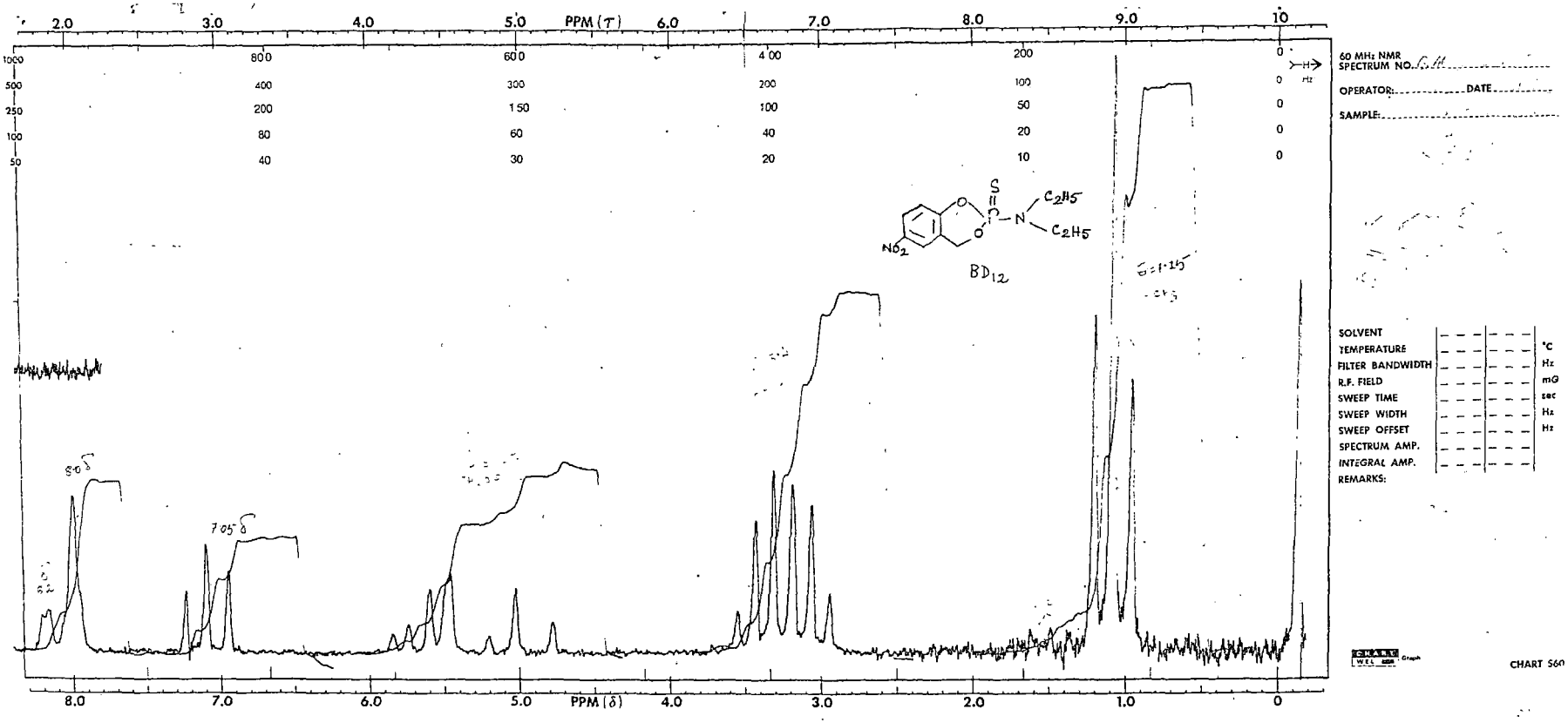


Fig. 15 - ^1H NMR of 2-N,N-Diethylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide

(iv) 2 - N, N- Dimethylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide (BD-13):

EtOH

UV (Fig. 16): λ_{max} = 295 nm (log ϵ =4.006)

IR (Fig. 17):

1010 Cm^{-1} (vs), P-O-C (alkyl);

1260 Cm^{-1} and 880 Cm^{-1} (s), P-O-C_6 (aryl);

1620 Cm^{-1} (s), asym. str. of nitro group;

1340 Cm^{-1} (s), sym. str. of nitro group;

820 Cm^{-1} (s), P = S (I);

645 Cm^{-1} (m), P = S (II);

780 Cm^{-1} (m), P - N str;

1620 Cm^{-1} and 1585 Cm^{-1}(s), benzene ring "quadrant stretching" vibration.

Mass (Fig. 18):

m/e	%RI
274 (M^+)	94.4
241	91.6
230	7.0
198 (base peak)	100
167	7.0
152	9.8

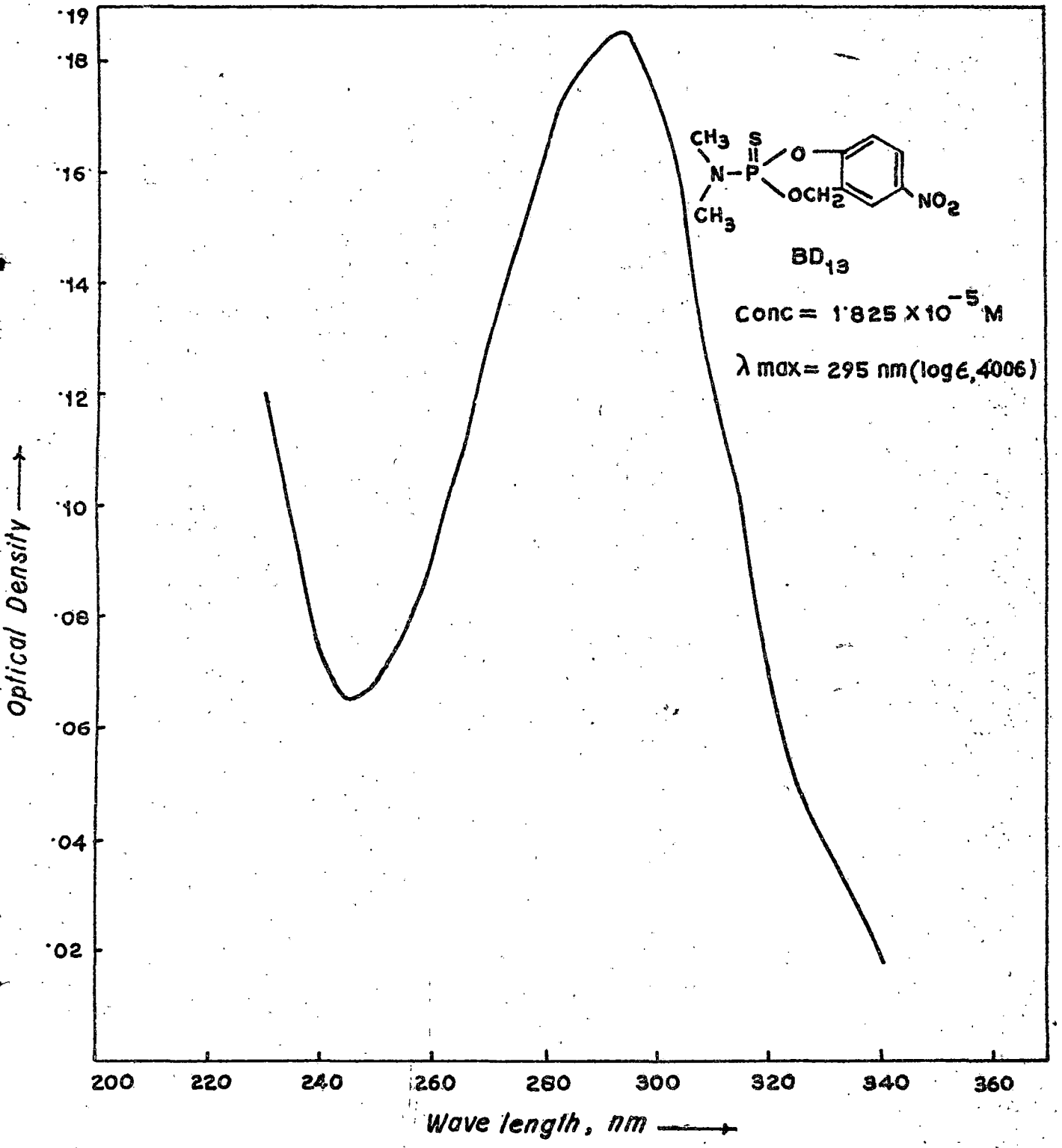


Fig. 16. UV spectrum of BD_{13} in ethanol.

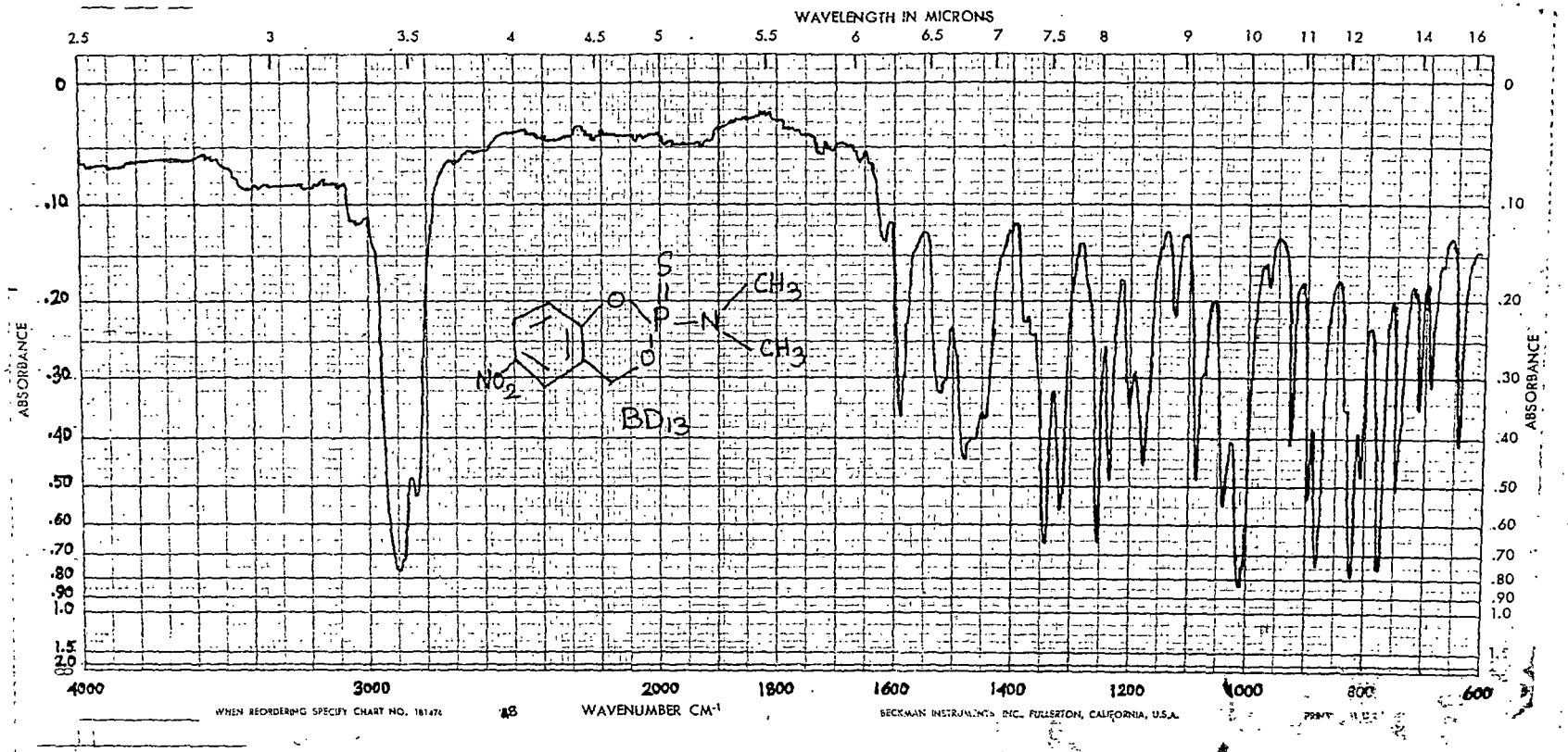


Fig. 17. IR spectrum of ~~2-~~ N,N-Diethylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide

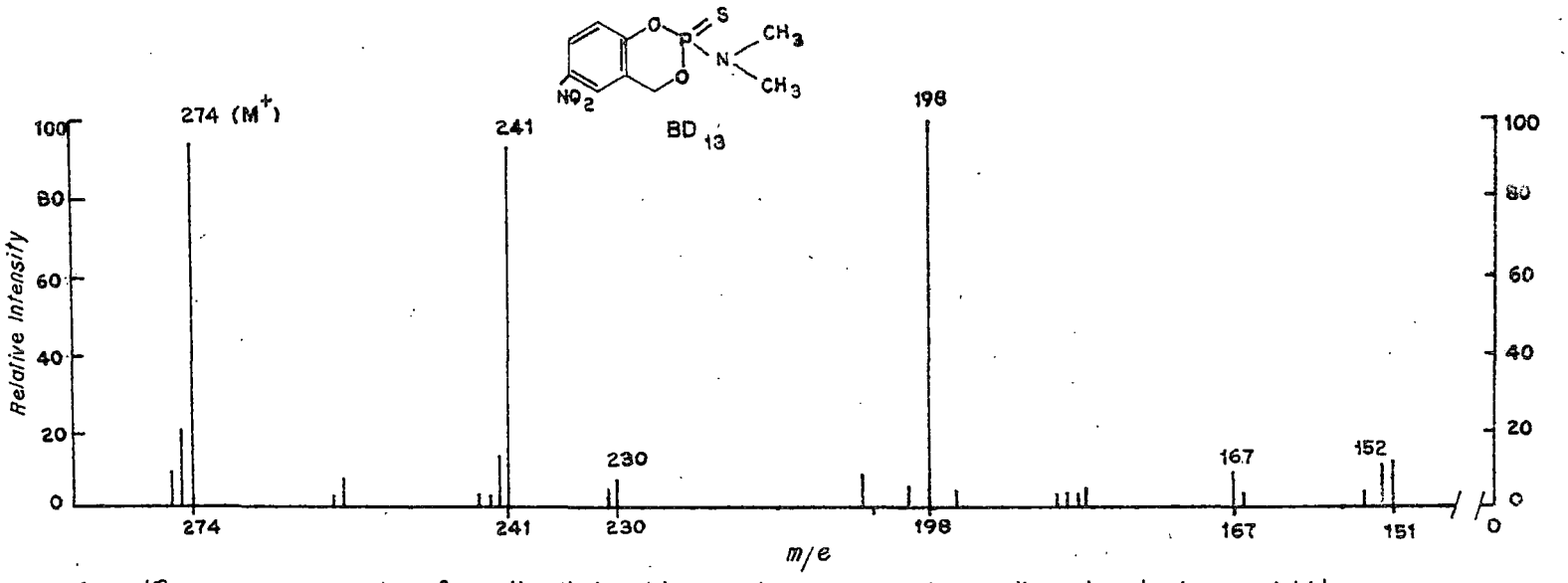


Fig. 18 Mass spectra of 2-dimethyl amido-6-nitro 4H-1,3,2 benzodioxaphosphorin-2 sulphide.

^1H NMR δ ($CDCl_3$) ppm (Fig. 19):

2.8 (6H, doublet, two $-CH_3$ groups in $-N(CH_3)_2$);

5.4 (2H, multiplet, $-CH_2-$ group in the dioxaphosphorin ring);

7.0 (1H, doublet, one aromatic hydrogen meta to nitro group);

8.0 (1H, one aromatic hydrogen ortho to both nitro group and $-CH_2-$ group of dioxaphosphorin ring);

8.18 (1H, multiplet, remaining one aromatic hydrogen).

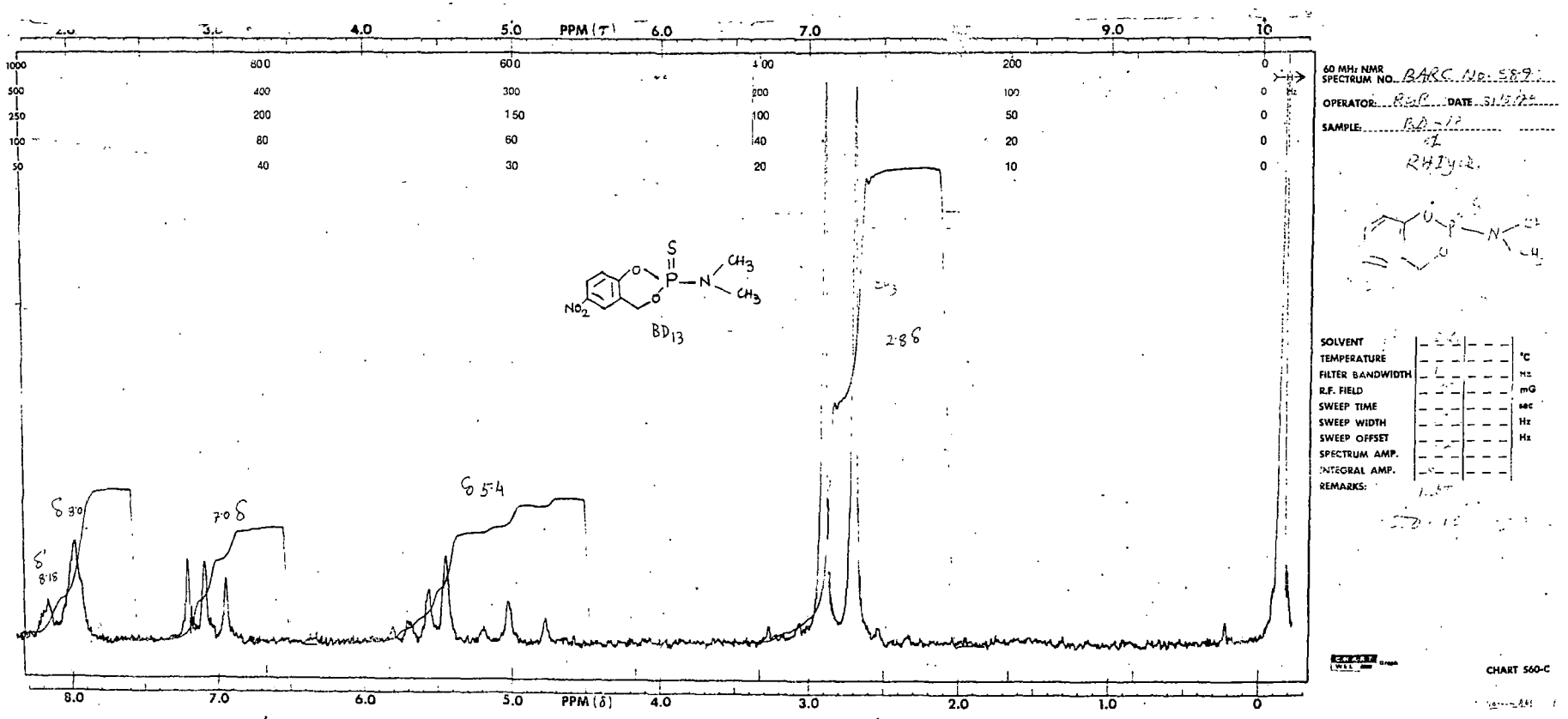


Fig. 19 – ^1H NMR spectrum of 2-N,N-Dimethylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide

(v) 2-Isopropylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide (BD-14):

EtOH

UV (Fig. 20): λ_{max} = 295 nm (log ϵ =3.915)

IR (Fig. 21):

1020 Cm^{-1} (vs), P-O-C (alkyl);

1240 Cm^{-1} (s) and 880 Cm^{-1} (s), P-O-C (aryl);

1515 Cm^{-1} (s), asym. str. of nitro group;

1340 Cm^{-1} (vs), sym. str. of nitro group;

800 Cm^{-1} (s), P = S (I);

660 Cm^{-1} (m), P = S (II);

1620 Cm^{-1} (w) and 1585 Cm^{-1} (s), benzene ring "quadrant stretching" vibration;

3290 Cm^{-1} (s), N - H str.

Mass (Fig. 22):

m/e	%RI
288 (M^+)	50
273	25
266	52
198 (base peak)	100
152	64

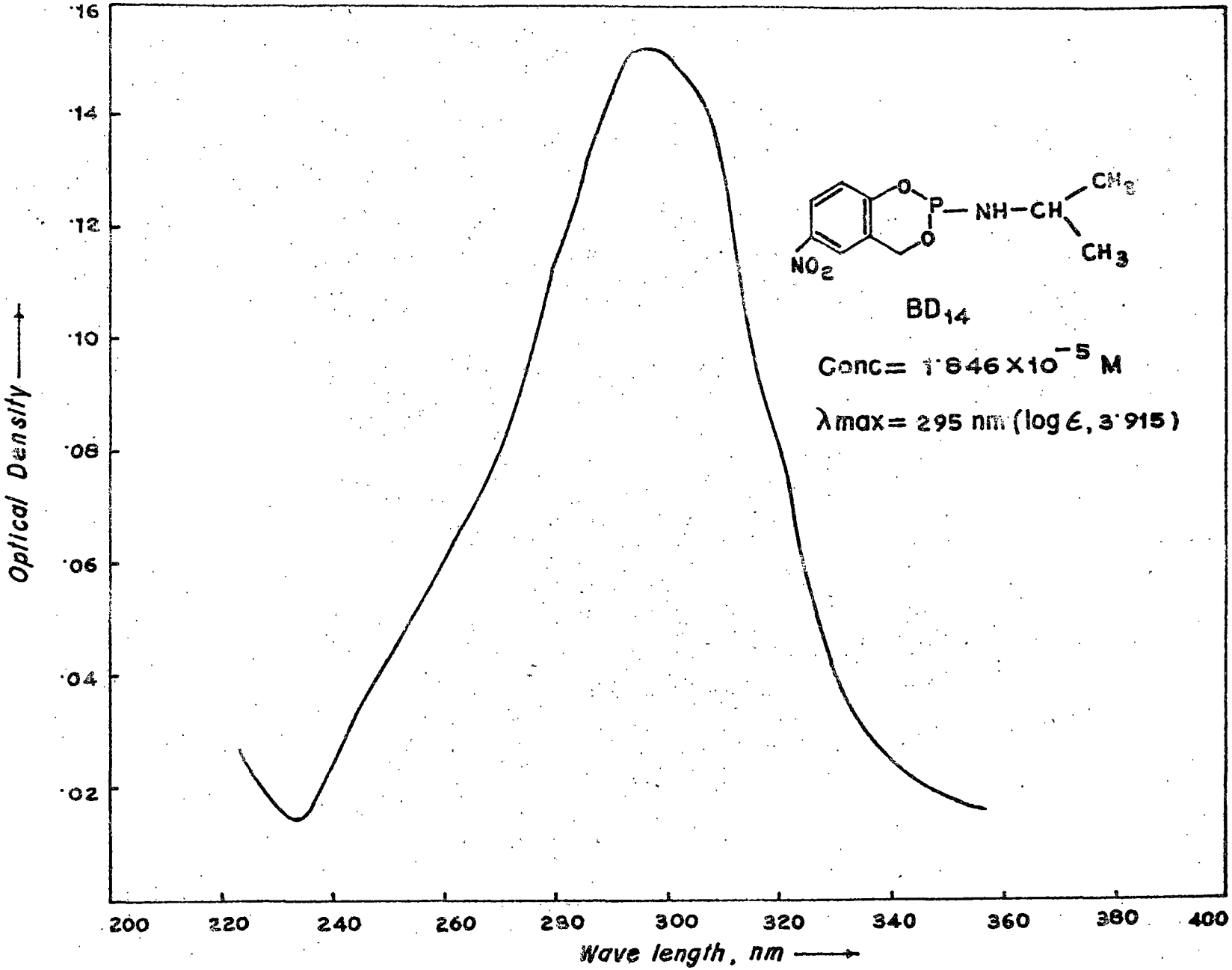


Fig. 20 UV spectrum of BD_{14} in ethanol

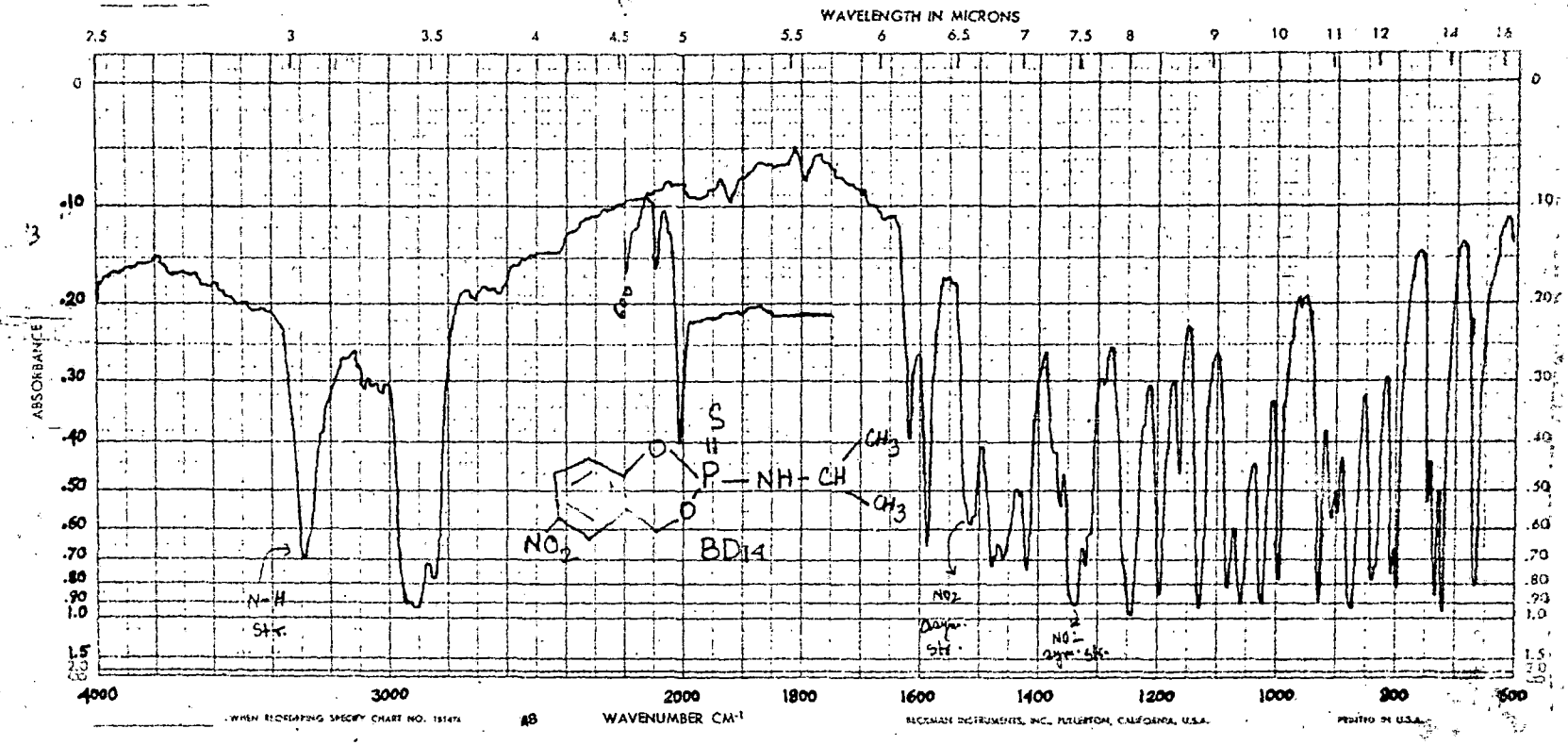


Fig. 21. IR spectrum of 2-Isopropylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide

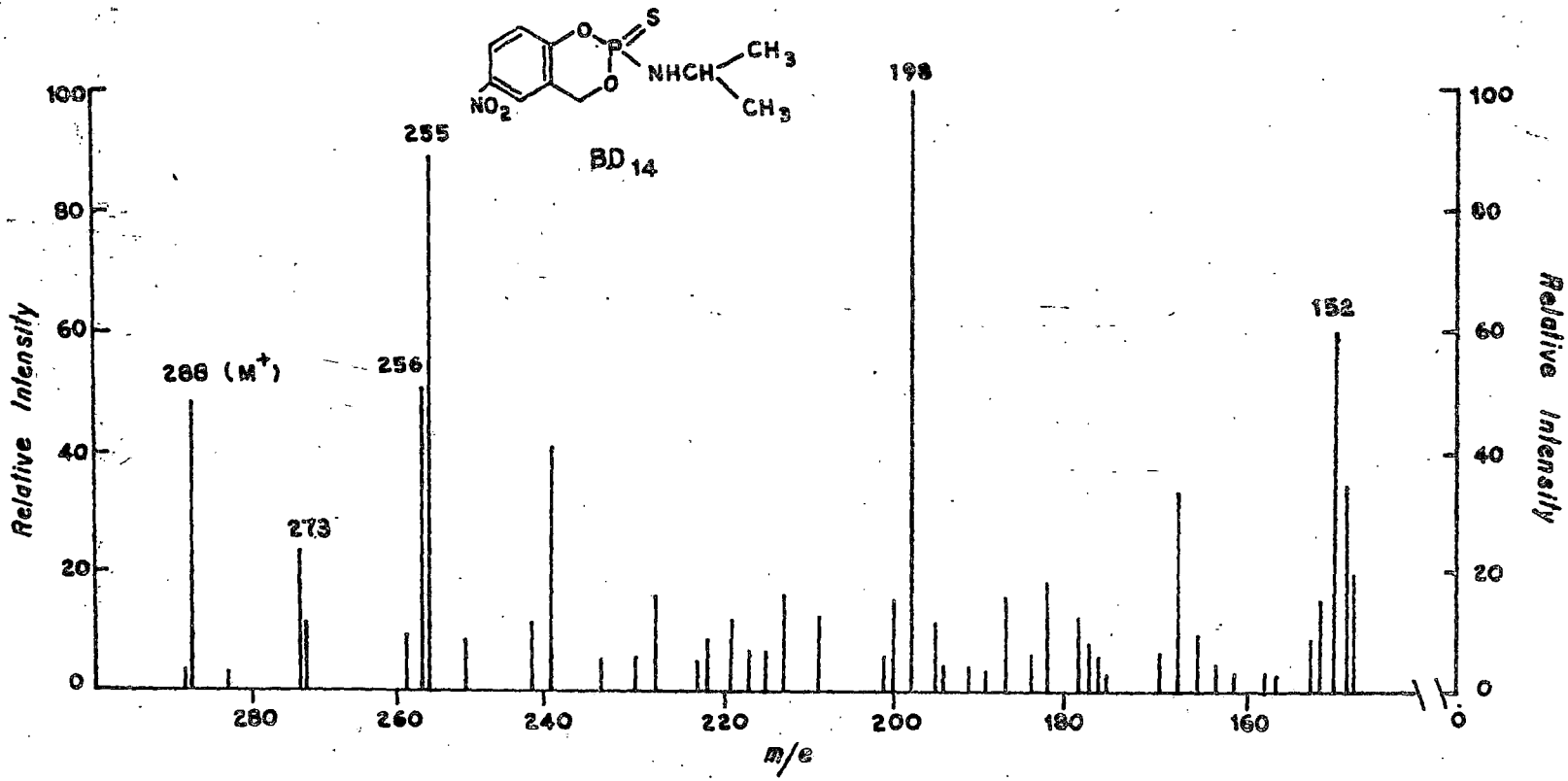


Fig. 22 Mass spectra of-2- Isopropylamido-6-nitro-4H-1,3,2 benzodioxaphophorin-2-sulphide.

^{1}H NMR $\delta(CDCl_3)$ ppm (Fig. 23):

1.25 (6H, doublet, $J = 7.0$, two $-CH_3$ groups);

3.46 (1H, multiplet, $-CH<$ group);

3.6 (1H, multiplet, $-NH-$group);

5.46 (2H, Octet, $-CH_2-$ group in dioxaphosphorin ring);

7.1 (1H, doublet, one aromatic hydrogen meta to nitro group);

8.05 (1H, doublet, one aromatic hydrogen ortho to both nitro group and $-CH_2-$ group of dioxaphosphorin ring);

8.2 (1H, multiplet, remaining one aromatic hydrogen).

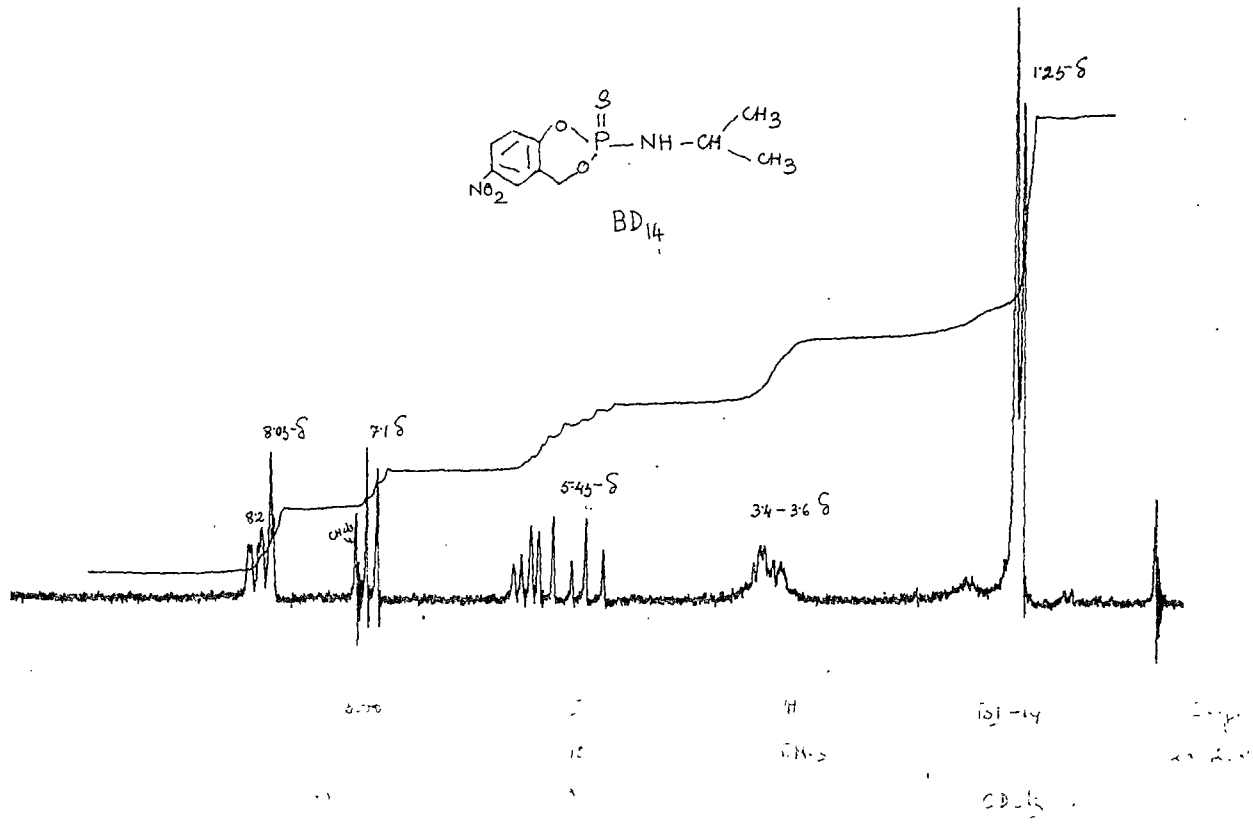


Fig. 23. ^1H NMR spectrum of 2- Isopropylamido- -6- nitro- 4H- 1, 3, 2- benzodioxaphosphorin -2- sulphide

(vi) 2-Pyrrolidino-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide (BD-15):

IR (Fig.24):

1030 Cm^{-1} (s), P-O-C (alkyl);
1250 Cm^{-1} (s) and 875 Cm^{-1} (s), P-O-C (aryl);
1520 Cm^{-1} (vs), asym. str. of nitro group;
1340 Cm^{-1} (vs), sym. str. of nitro group;
810 Cm^{-1} (s), P = S (I);
655 Cm^{-1} (s), P = S (II);
735 Cm^{-1} (m), P - N str.

Mass (Fig. 25):

m/e	%RI
300 (M^+)	21.4
267	100
198	25.7
148	11.4
116	80.0
70	35.7

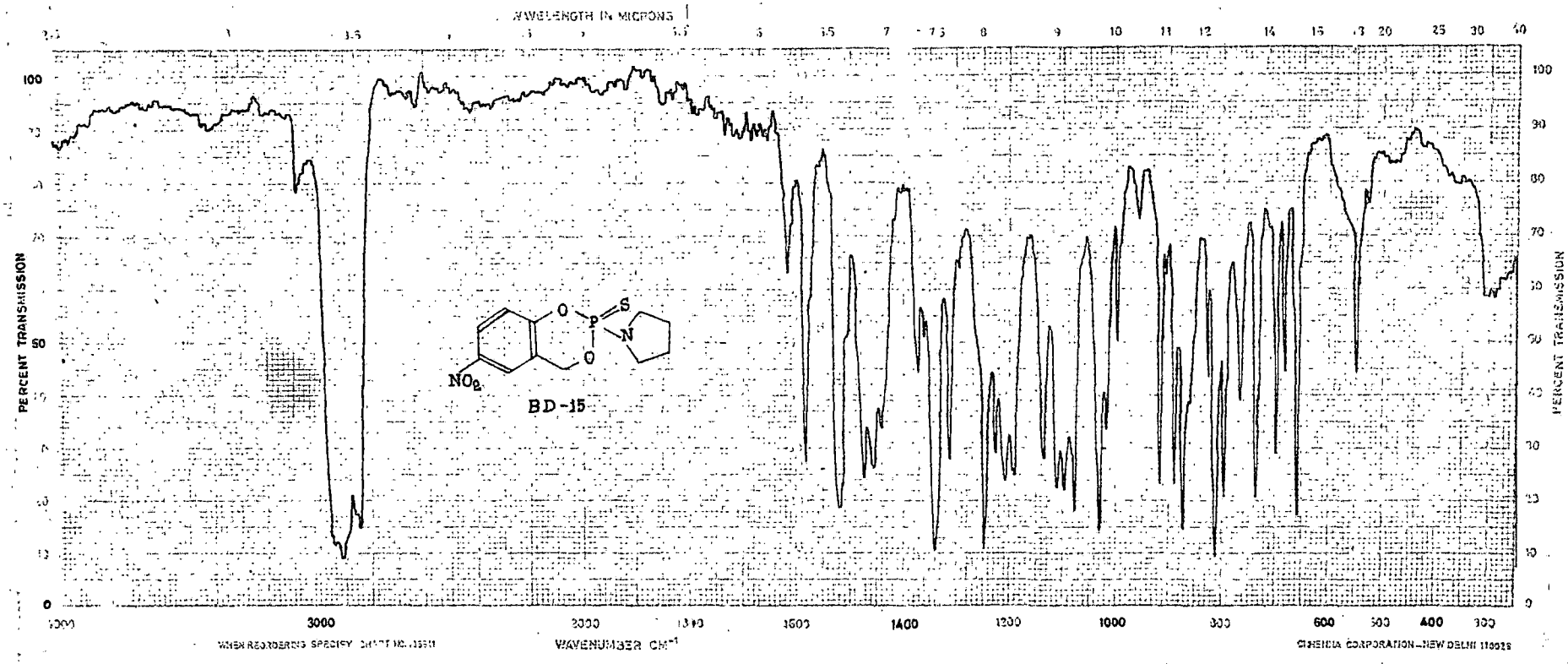
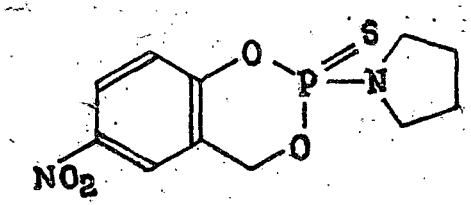


Fig. 24. IR spectrum of 2- Pyrrolidino - 6- nitro - 4H - 1,3,2- benzodioxaphosphorin - 2 - sulphide.

SPEKTRUM 23 VERDAMPFUNGSTEMPERATUR 120 GRAD
MOLEKUELPEAK: 300
MASSEN CHARAKTERISTISCHER IONEN:
267=300-SH

ANALYSE: 62907
==========

STH HA 015 00
ST.STEENKEN
MESSG:
AUSW :25-MAR-81
AUSWER: SCH



BD-15

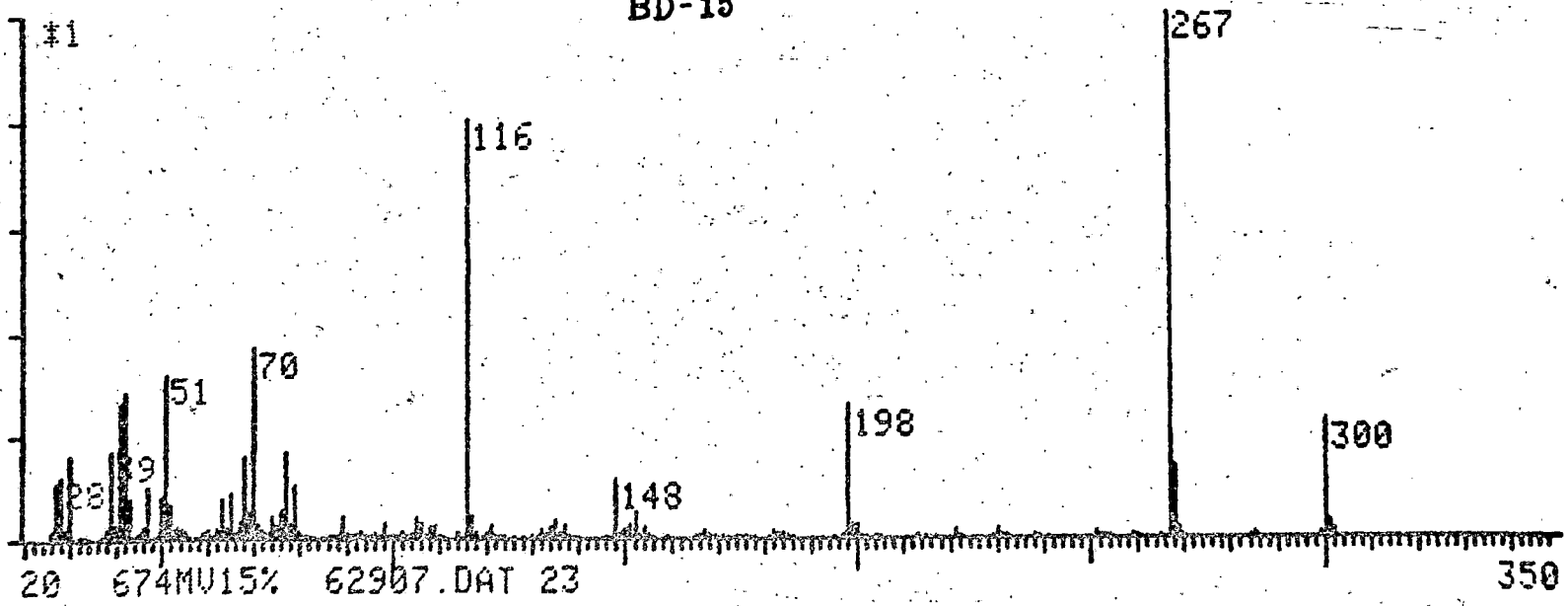


Fig. 25. Mass spectrum of 2-Pyrrolidino-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide

^1H NMR $\delta(CDCl_3)$ ppm (Fig. 26):

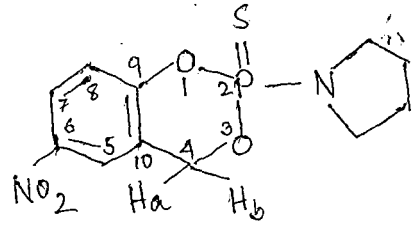
1.62 - 1.95 (4H, multiplet, two $-CH_2-$ groups at 2,2' positions of the pyrrolidine ring);

3.36 (4H, multiplet, two $-CH_2-$ groups adjacent to nitrogen);

5.26 and 5.66 (2H, $-CH_2-$ group in dioxaphosphorin ring);

7.06, 8.0 and 8.14 (due to aromatic hydrogens).

^{13}C NMR $\delta(CDCl_3)$ ppm (Fig. 27a - 27c):



Carbon atom	δ(ppm)	J(Hz)
$C_{2'}$	26.29	$^3J_{P-N-C_{1'}-C_{2'}}$ = 9.87
$C_{1'}$	47.68	$^2J_{P-N-C_{1'}}$ = 6.83
C_4	65.62	$^2J_{P-O-C_4}$ = 5.53
C_5	121.29	
C_{10}	121.51	$^3J_{P-O-C_9-C_{10}}$ = 12.38
C_7	124.81	$^4J_{P-O-C_9-C_8-C_7}$ = 0.93
C_6	143.03	
C_9	155.64	$^2J_{P-O-C_9}$ = 7.3

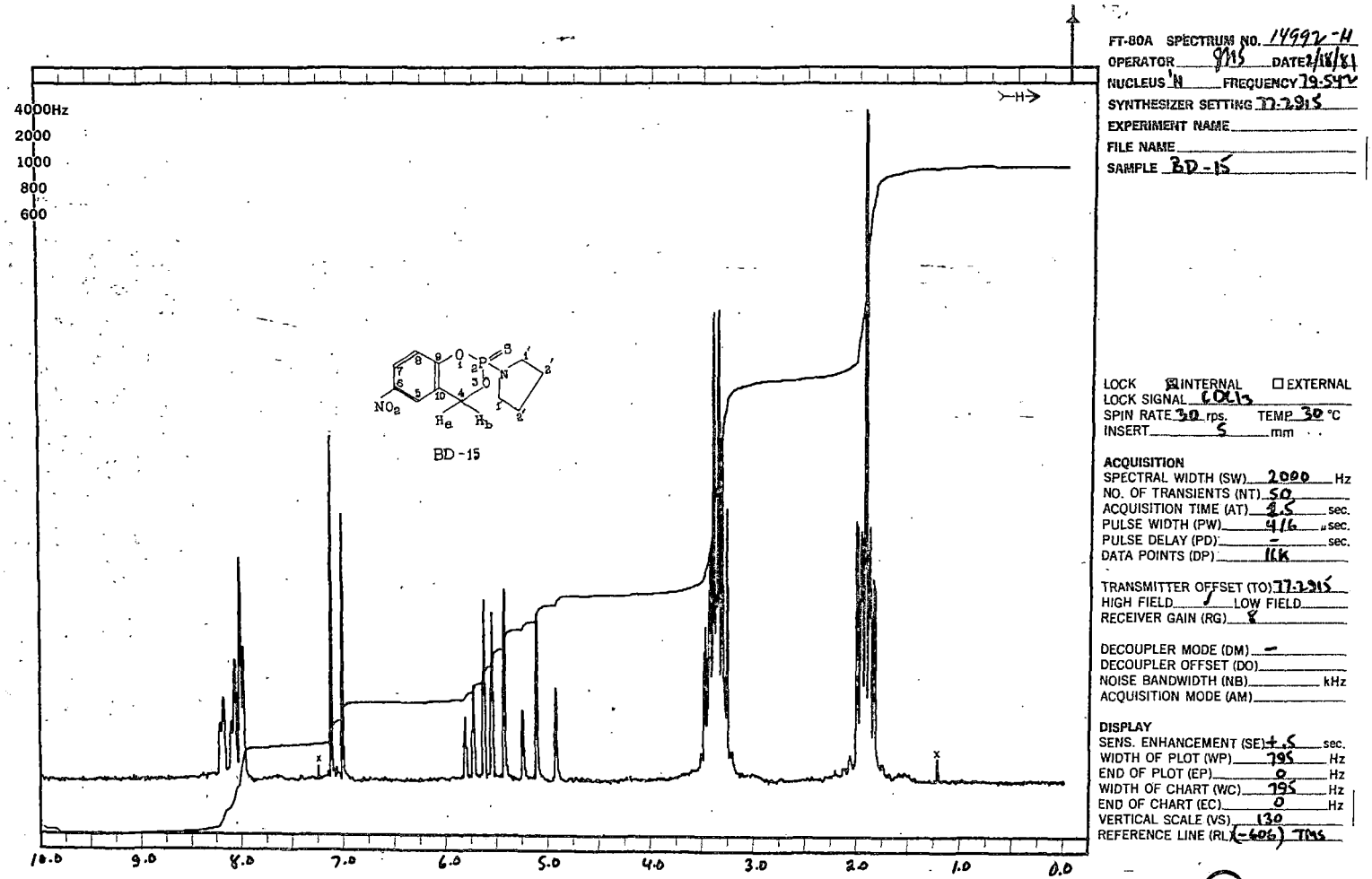
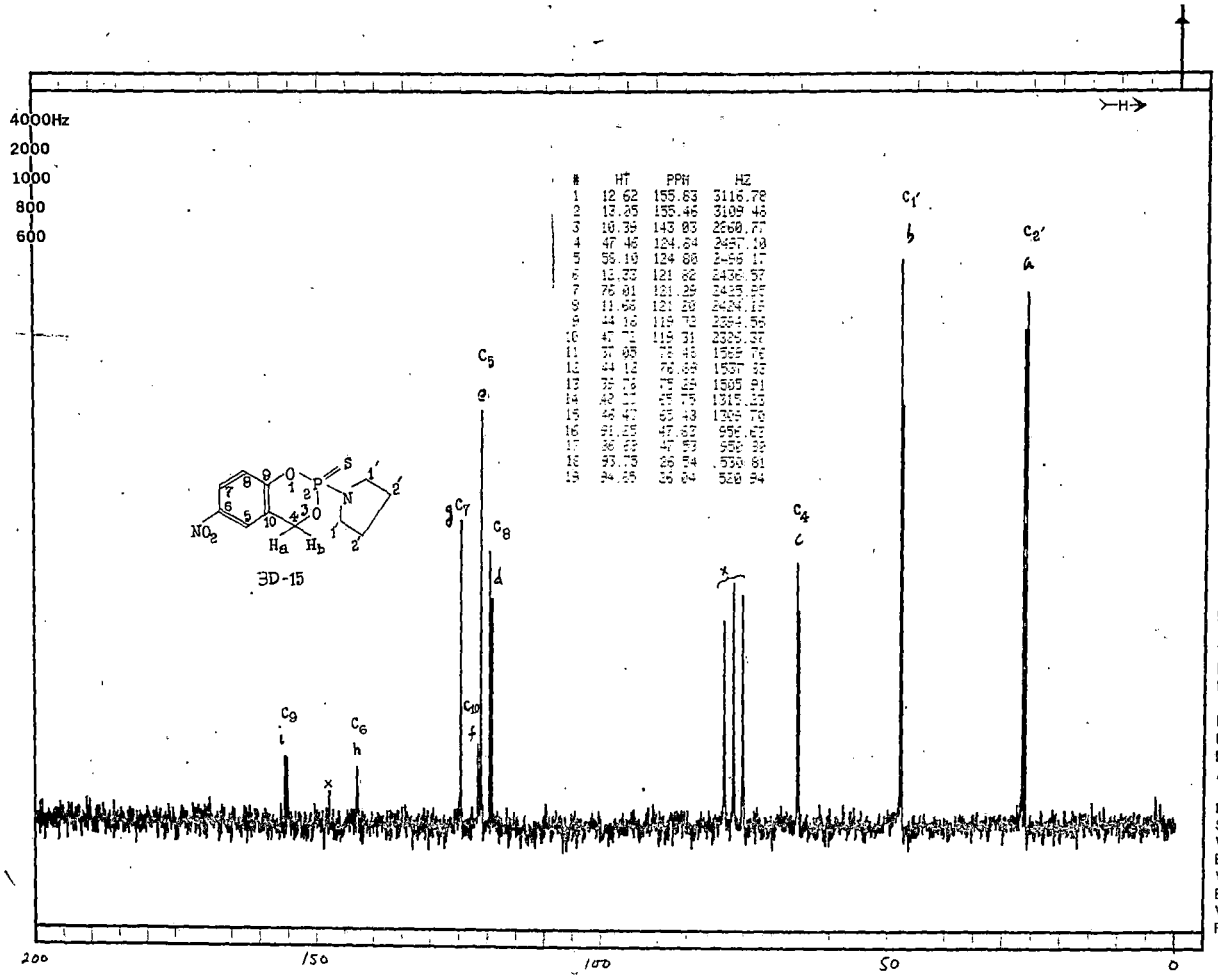


Fig. 26. ^1H NMR spectrum of 2-Pyrrolidino-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide



20·0 MHz proton noise-decoupled ^{13}C spectrum of BD-15 in $CDCl_3$

Fig. 27a

FT-80A SPECTRUM NO. 14992-6
OPERATOR GMS DATE 2/12/87
NUCLEUS ^{13}C FREQUENCY 20.0
SYNTHESIZER SETTING 17.7500
EXPERIMENT NAME
FILE NAME
SAMPLE BD-15

LOCK ☒ INTERNAL ☐ EXTERNAL
LOCK SIGNAL CDCl3
SPIN RATE 30 rps. TEMP 30 °C
INSERT 5 mm

ACQUISITION
SPECTRAL WIDTH (SW) 5000 Hz
NO. OF TRANSIENTS (NT) 11,000
ACQUISITION TIME (AT) 1.0 sec.
PULSE WIDTH (PW) 3/7 μsec.
PULSE DELAY (PD) sec.
DATA POINTS (DP) 16K

TRANSMITTER OFFSET (TO) 17.7500
HIGH FIELD ✓ LOW FIELD
RECEIVER GAIN (RG) 6

DECOUPLER MODE (DM) 1
DECOUPLER OFFSET (DO) 53
NOISE BANDWIDTH (NB) 2 kHz
ACQUISITION MODE (AM) 0

DISPLAY
SENS. ENHANCEMENT (SE) -2.0 sec.
WIDTH OF PLOT (WP) 4000 Hz
END OF PLOT (EP) 0 Hz
WIDTH OF CHART (WC) 4000 Hz
END OF CHART (EC) 0 Hz
VERTICAL SCALE (VS) 100
REFERENCE LINE (RL) 6682 TMS

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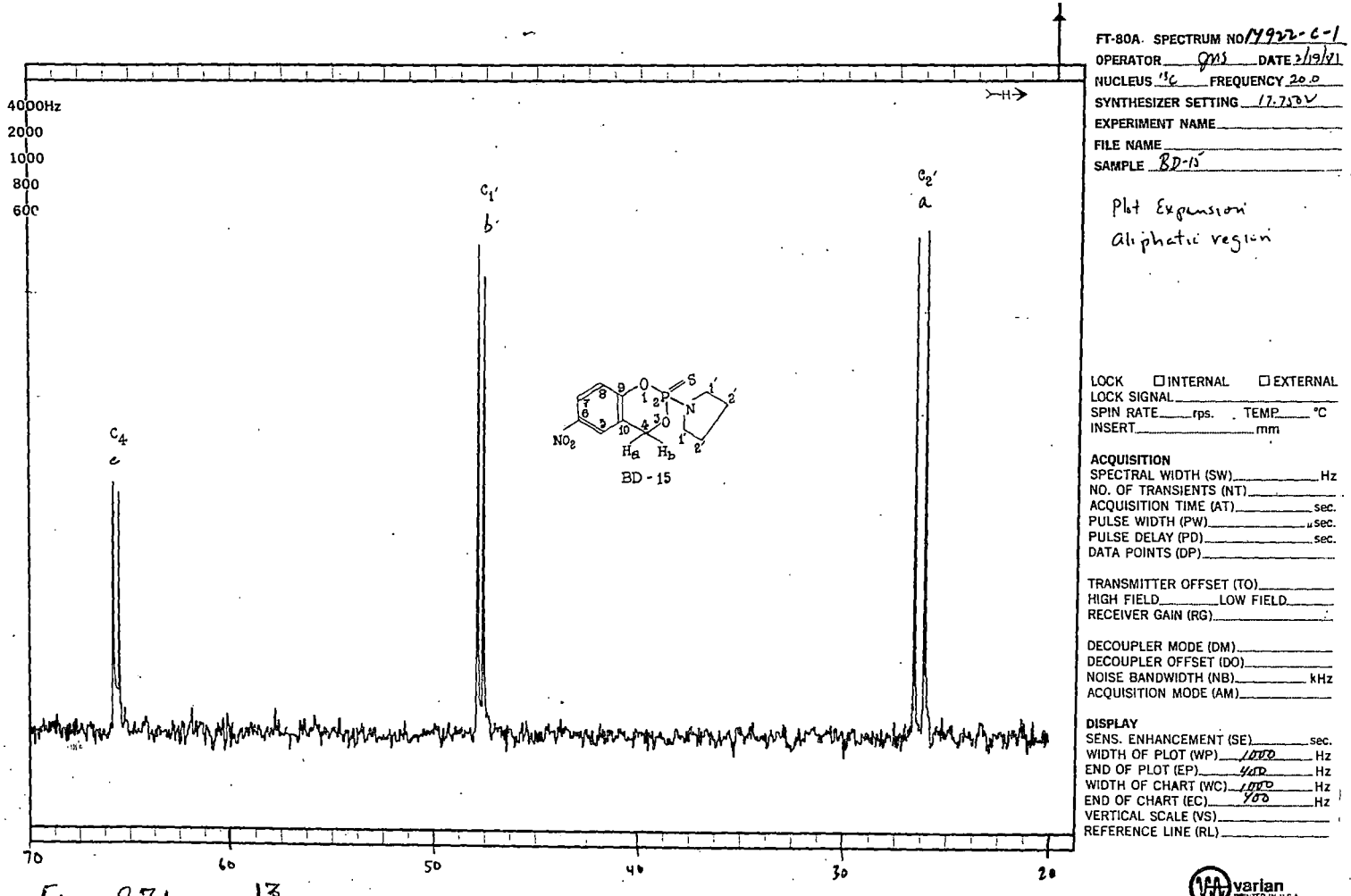


FT-80A. SPECTRUM NO 7922-C-1
OPERATOR QNS DATE 2/19/81
NUCLEUS ^{13}C FREQUENCY 20.0
SYNTHESIZER SETTING 17.750V
EXPERIMENT NAME
FILE NAME
SAMPLE BD-15

Plot Expansion
Aliphatic region

LOCK ☐INTERNAL ☐EXTERNAL
LOCK SIGNAL
SPIN RATE rps. TEMP °C
INSERT mm

ACQUISITION
SPECTRAL WIDTH (SW) Hz
NO. OF TRANSIENTS (NT)
ACQUISITION TIME (AT) sec.
PULSE WIDTH (PW) μsec.
PULSE DELAY (PD) sec.
DATA POINTS (DP)

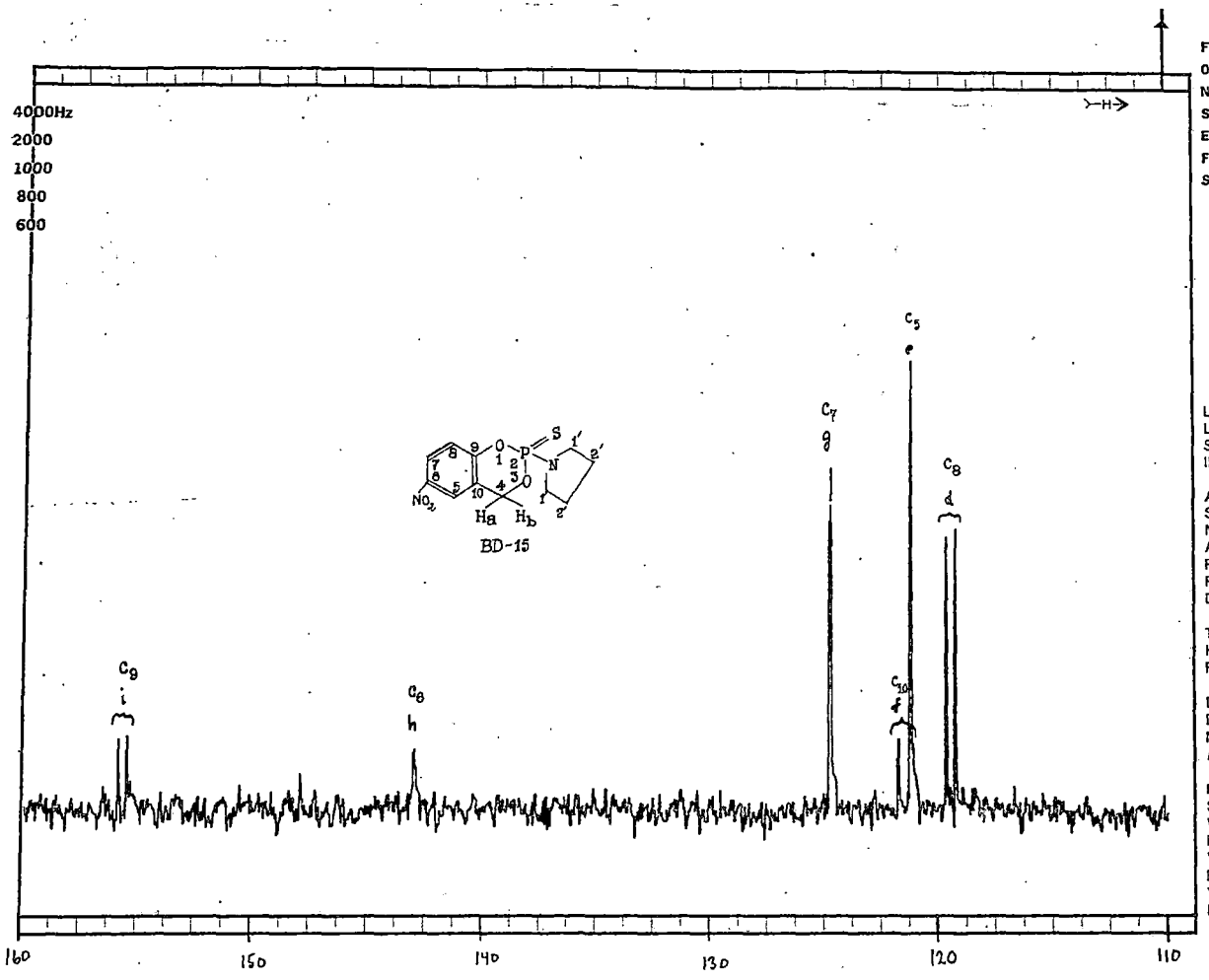
TRANSMITTER OFFSET (TO)
HIGH FIELD LOW FIELD
RECEIVER GAIN (RG)

DECOUPLER MODE (DM)
DECOUPLER OFFSET (DO)
NOISE BANDWIDTH (NB) kHz
ACQUISITION MODE (AM)

DISPLAY
SENS. ENHANCEMENT (SE) sec.
WIDTH OF PLOT (WP) 1000 Hz
END OF PLOT (EP) 400 Hz
WIDTH OF CHART (WC) 1000 Hz
END OF CHART (EC) 900 Hz
VERTICAL SCALE (VS)
REFERENCE LINE (RL)

varian PRINTED IN U.S.A.

Fig. 27b. ^{13}C NMR spectrum of BD-15 (Plot expansion: Aliphatic region)



FT-80A SPECTRUM NO. 14522-C-2
OPERATOR GMS DATE 7/19/81
NUCLEUS ^{13}C FREQUENCY 20.0
SYNTHESIZER SETTING 17.7507
EXPERIMENT NAME
FILE NAME
SAMPLE BD-15

Plot Expansion
Aromatic region

LOCK ☒ INTERNAL ☐ EXTERNAL
LOCK SIGNAL $CDCl_3$
SPIN RATE 30 rps. TEMP 30 °C
INSERT 5 mm

ACQUISITION
SPECTRAL WIDTH (SW) 5000 Hz
NO. OF TRANSIENTS (NT) 11,000
ACQUISITION TIME (AT) 1.0 sec.
PULSE WIDTH (PW) 3/7 μsec.
PULSE DELAY (PD) – sec.
DATA POINTS (DP) 16K

TRANSMITTER OFFSET (TO) 17.750
HIGH FIELD ✓ LOW FIELD
RECEIVER GAIN (RG) 8

DECOUPLER MODE (DM) 1
DECOUPLER OFFSET (DO) 53
NOISE BANDWIDTH (NB) -2 kHz
ACQUISITION MODE (AM) 0

DISPLAY
SENS. ENHANCEMENT (SE) -2.0 sec.
WIDTH OF PLOT (WP) 1000 Hz
END OF PLOT (EP) 7500 Hz
WIDTH OF CHART (WC) 1000 Hz
END OF CHART (EC) 7500 Hz
VERTICAL SCALE (VS) 100
REFERENCE LINE (RL) (-682) TMS

varian PRINTED IN U.S.A.

Fig. 27c. ^{13}C NMR spectrum of BD-15 (Plot expansion: Aromatic region)

(vii) 2-Piperidino-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide (BD-16):

IR (Fig. 28):

1025 Cm^{-1} (s), P-O-C (alkyl);
1245 Cm^{-1} (s) and 870 Cm^{-1} (s), P-O-C (aryl);
1515 Cm^{-1} (s), asym. str. of nitro group;
1340 Cm^{-1} (s), sym. str. of nitro group;
820 Cm^{-1} (s), P = S (I);
640 Cm^{-1} (m), P = S (II);
740 Cm^{-1} (s), P - N str.

Mass (Fig. 29):

m/e	%RI
314 (M^+)	17.1
281	100
198	7.1
130	82.9
84	12.9

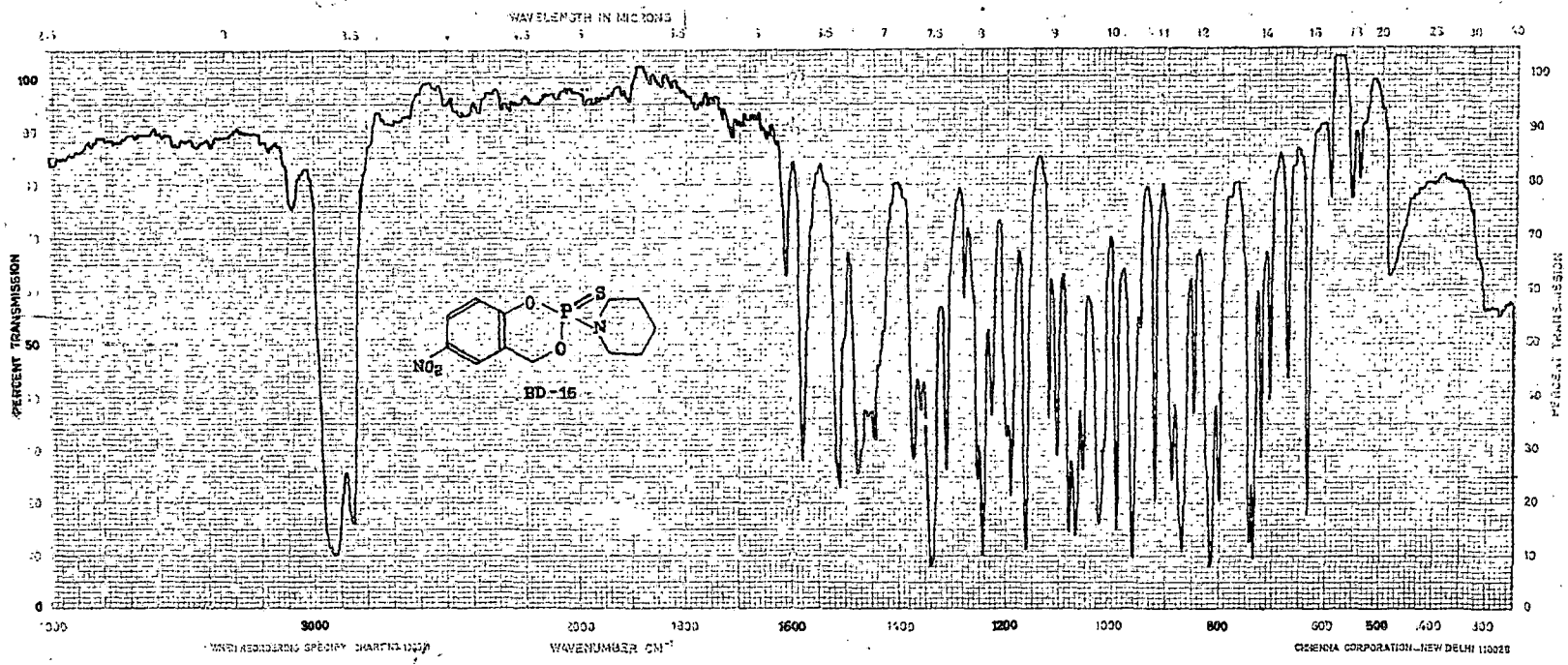
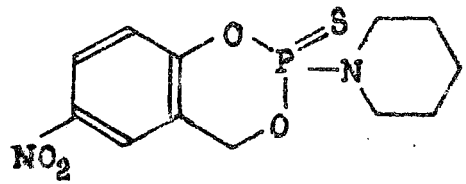


Fig. 28. IR spectrum of 2- Piperidino - 6- nitro - 4H - 1,3,2- benzodioxaphosphorin - 2- sulphide

SPEKTRUM 25 VERDAMPFUNGSTEMPERATUR 110 GRAD
MOLEKUELPEAK: 314
MASSEN CHARAKTERISTISCHER IONEN:
281=314-SH

ANALYSE: 62893

STH HA 016 00
ST STEENKEN
MESSG:
AUSW :25-MAR-81
AUSWER: SCH



BD-16

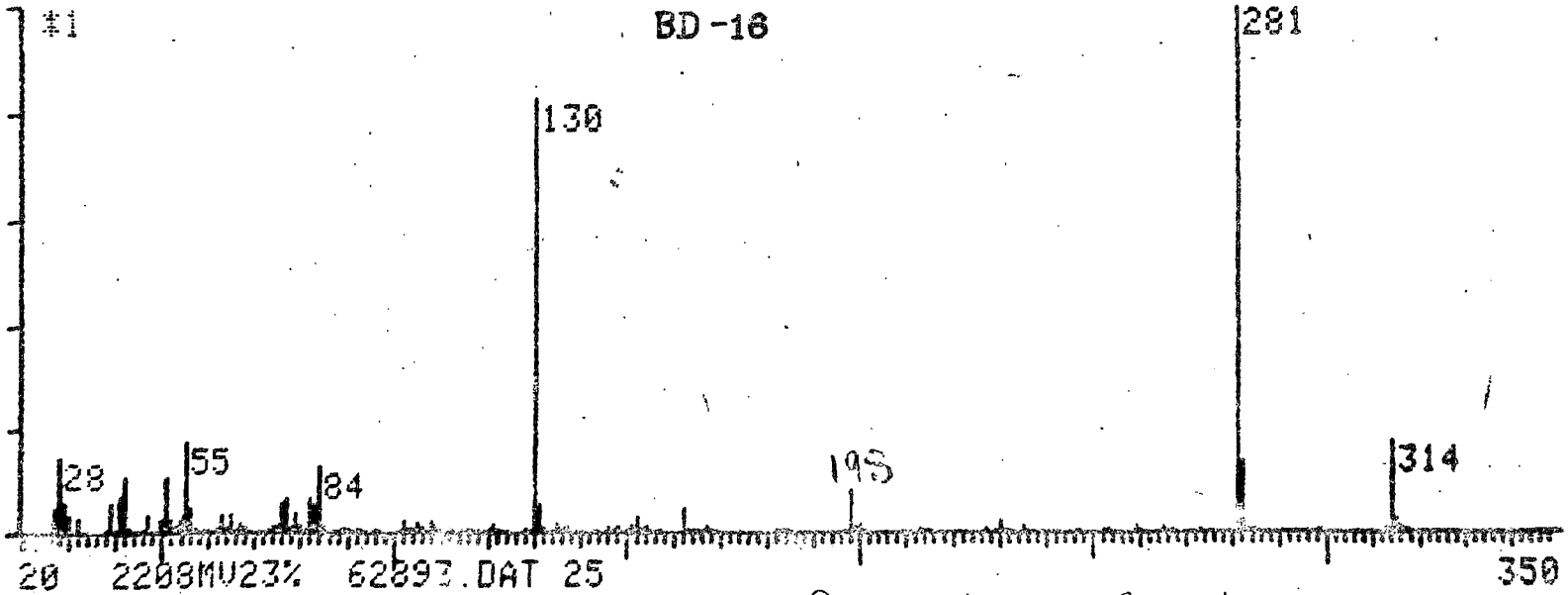


Fig. 29. Mass spectrum of 2-Piperidino-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide

^1H NMR δ ($CDCl_3$) ppm (Fig.30):

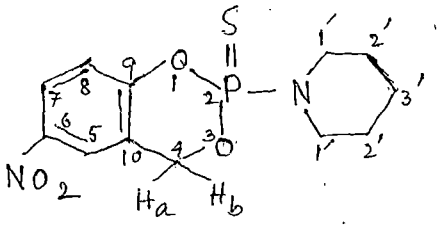
1.6 (6H, 3 $-CH_2-$ groups at 2',2' 3' positions of the piperidine ring);

3.15 - 3.5 (4H, multiplet, two $-CH_2-$ groups adjacent to nitrogen);

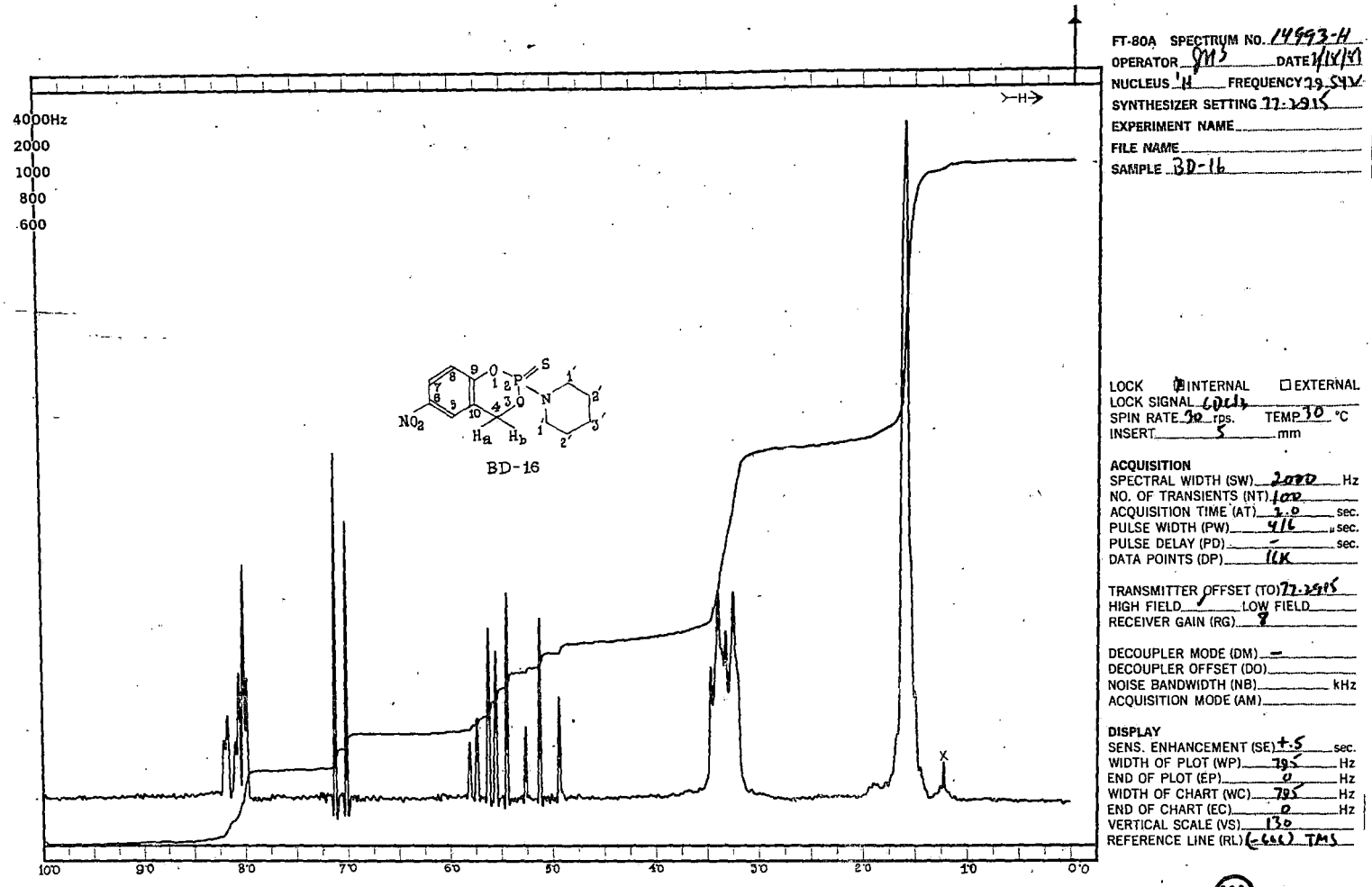
5.2 - 5.65 (2H, $-CH_2-$ group in dioxaphosphorin ring);

7.06, 8.0 and 8.14 (due to aromatic hydrogens).

^{13}C NMR δ ($CDCl_3$) ppm (Fig. 31a - 31b):



Carbon atom	δ (ppm)	J(Hz)	
C_3,	24.1	$^4J_{P-N-C_1',-C_2',-C_3'}$	=1.2
C_2,	25.93	$^3J_{P-N-C_1',-C_2'}$	=3.7
C_1,	46.25	$^2J_{P-N-C_1'}$	=3.6
C_4	66.11	$^2J_{P-O-C_4}$	=5.75
C_8	119.63	$^3J_{P-O-C_9-C_8}$	=8.22
C_5	121.32		
C_{10}	121.36	$^3J_{P-O-C_9-C_{10}}$	=11.38
C_7	124.75		
C_6	145.06		
C_9	155.84	$^2J_{P-O-C_9}$	=7.0



FT-80A SPECTRUM NO. 14993-H
OPERATOR SMS DATE 7/14/91
NUCLEUS ^1H FREQUENCY 79.54V
SYNTHESIZER SETTING 77.2915
EXPERIMENT NAME
FILE NAME
SAMPLE BD-16

LOCK ■ INTERNAL □ EXTERNAL
LOCK SIGNAL CDCl3
SPIN RATE 30 rps. TEMP 30 °C
INSERT 5 mm

ACQUISITION
SPECTRAL WIDTH (SW) 2000 Hz
NO. OF TRANSIENTS (NT) 100
ACQUISITION TIME (AT) 1.0 sec.
PULSE WIDTH (PW) 4/6 μsec.
PULSE DELAY (PD) – sec.
DATA POINTS (DP) 16K

TRANSMITTER OFFSET (TO) 77.2915
HIGH FIELD / LOW FIELD
RECEIVER GAIN (RG) 8

DECOUPLER MODE (DM) –
DECOUPLER OFFSET (DO)
NOISE BANDWIDTH (NB) kHz
ACQUISITION MODE (AM)

DISPLAY
SENS. ENHANCEMENT (SE) +.5 sec.
WIDTH OF PLOT (WP) 795 Hz
END OF PLOT (EP) 0 Hz
WIDTH OF CHART (WC) 795 Hz
END OF CHART (EC) 0 Hz
VERTICAL SCALE (VS) 130
REFERENCE LINE (RL) (-446) TMS

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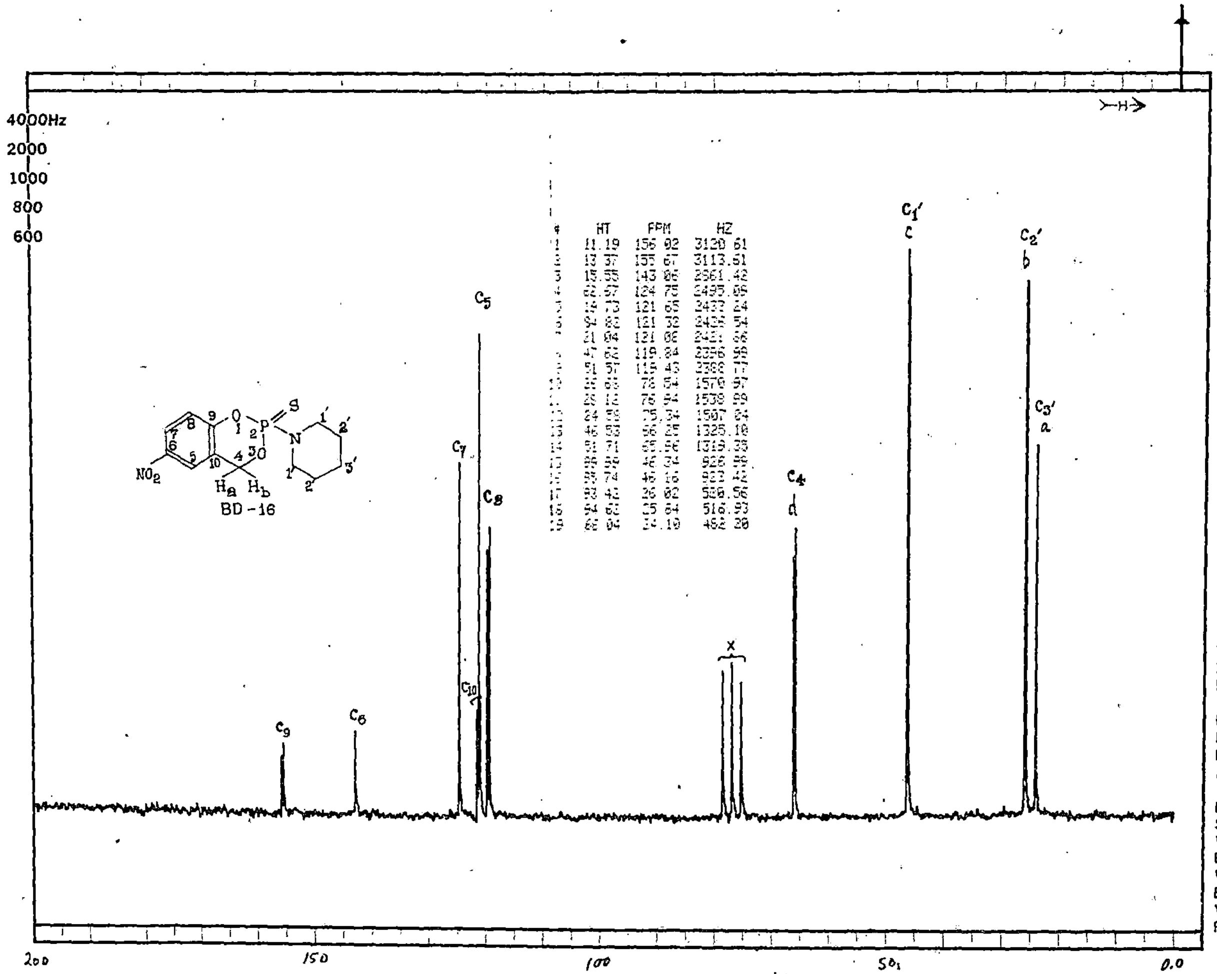
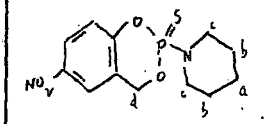
Fig. 30: ^1H NMR spectrum of 2-Piperidino-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide.



#	HT	PPM	HZ
1	11.19	156.02	3120.61
2	13.37	155.67	3113.51
3	15.55	143.06	2861.42
4	62.57	124.75	2495.05
5	19.73	121.65	2433.24
6	94.82	121.32	2426.54
7	21.04	121.08	2421.66
8	47.62	119.84	2396.98
9	51.57	115.43	2308.77
10	26.63	78.54	1570.97
11	26.12	76.94	1538.99
12	24.58	75.34	1507.04
13	46.53	66.25	1325.10
14	51.71	65.96	1319.33
15	88.59	46.34	926.99
16	35.74	46.16	923.42
17	93.42	26.02	520.56
18	94.62	25.84	516.93
19	68.04	24.10	482.20

FT-80A SPECTRUM NO. 14993-C
OPERATOR gms DATE 2/19/81
NUCLEUS 13C FREQUENCY 20.0
SYNTHESIZER SETTING 17.750V
EXPERIMENT NAME
FILE NAME
SAMPLE BD-16



LOCK ☒ INTERNAL ☐ EXTERNAL
LOCK SIGNAL CDCl3
SPIN RATE 30 rps. TEMP 30 °C
INSERT 5 mm

ACQUISITION
SPECTRAL WIDTH (SW) 5000 Hz
NO. OF TRANSIENTS (NT) 55408
ACQUISITION TIME (AT) 1.0 sec.
PULSE WIDTH (PW) 3/7 μsec.
PULSE DELAY (PD) – sec.
DATA POINTS (DP) 11K

TRANSMITTER OFFSET (TO) 17.750V
HIGH FIELD ✓ LOW FIELD
RECEIVER GAIN (RG) 8

DECOUPLER MODE (DM) 1
DECOUPLER OFFSET (DO) 53
NOISE BANDWIDTH (NB) 2 kHz
ACQUISITION MODE (AM) 0

DISPLAY
SENS. ENHANCEMENT (SE) -1.0 sec.
WIDTH OF PLOT (WP) 4000 Hz
END OF PLOT (EP) 0 Hz
WIDTH OF CHART (WC) 4000 Hz
END OF CHART (EC) 0 Hz
VERTICAL SCALE (VS) 100
REFERENCE LINE (RL) (-682) TMS

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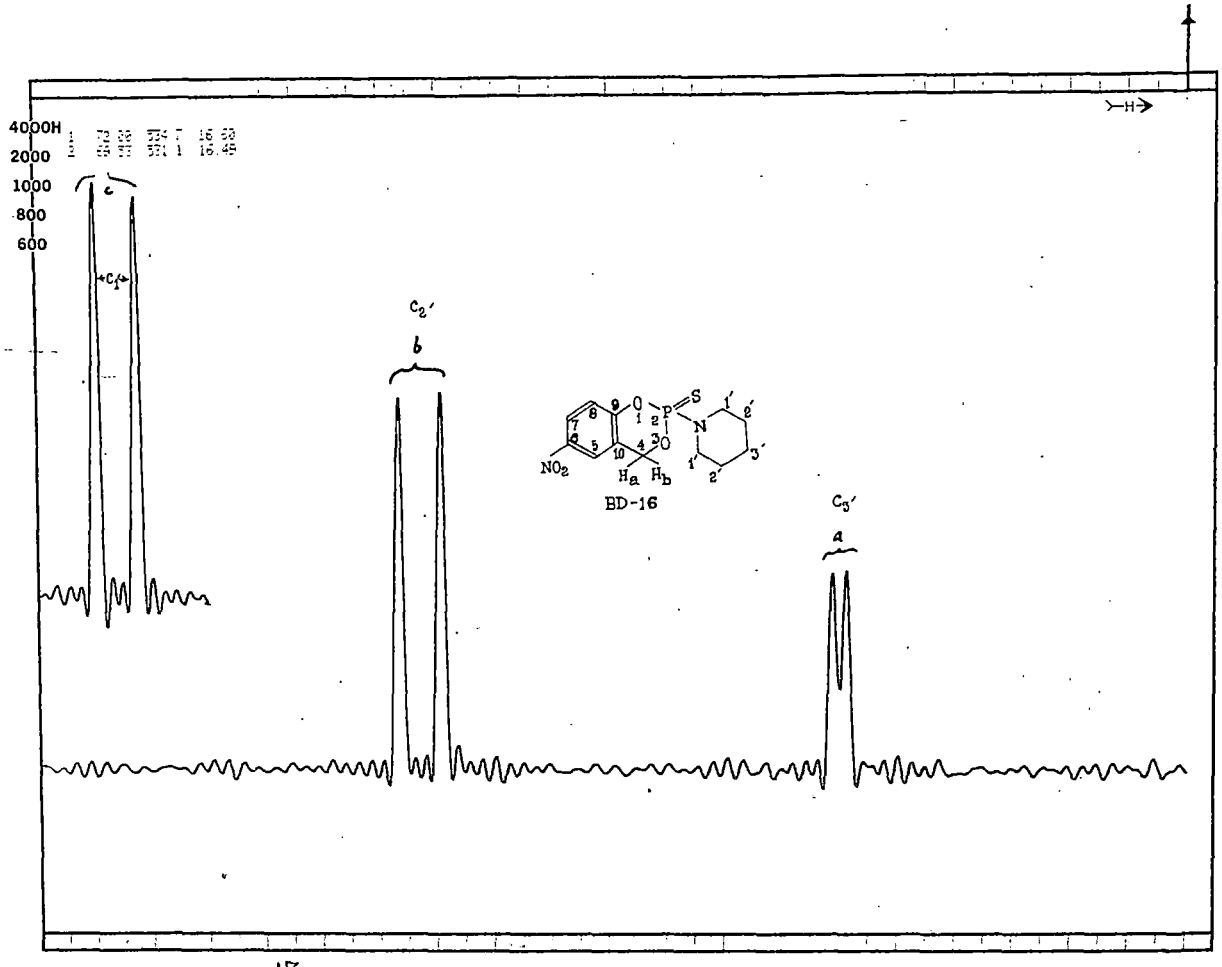
20.0 MHz proton noise-decoupled ^{13}C spectrum of BD-16 in $CDCl_3$

Fig- 31a



FT-80A SPECTRUM NO. 14993-c-1
OPERATOR Jms DATE 7/19/81
NUCLEUS FREQUENCY
SYNTHESIZER SETTING
EXPERIMENT NAME
FILE NAME
SAMPLE BD-16
Plot Expansion.

1	65.35	128.3	3.98
2	66.29	124.6	3.87
3	34.96	98.5	2.81
4	35.42	69.3	2.77

LOCK ☐ INTERNAL ☐ EXTERNAL
LOCK SIGNAL
SPIN RATE rps. TEMP °C
INSERT mm

ACQUISITION
SPECTRAL WIDTH (SW) Hz
NO. OF TRANSIENTS (NT)
ACQUISITION TIME (AT) sec.
PULSE WIDTH (PW) μsec.
PULSE DELAY (PD) sec.
DATA POINTS (DP)

TRANSMITTER OFFSET (TO)
HIGH FIELD LOW FIELD
RECEIVER GAIN (RG)

DECOUPLER MODE (DM)
DECOUPLER OFFSET (DO)
NOISE BANDWIDTH (NB) kHz
ACQUISITION MODE (AM)

DISPLAY
SENS. ENHANCEMENT (SE) +0.3 sec.
WIDTH OF PLOT (WP) 100 Hz
END OF PLOT (EP) Hz
WIDTH OF CHART (WC) 100 Hz
END OF CHART (EC) Hz
VERTICAL SCALE (VS) 72
REFERENCE LINE (RL)

varian PRINTED IN U.S.A.

Fig. 31.b.: ^{13}C NMR spectrum of BD-16 (Plot expansion)

(viii) 2-Nonylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide (BD-17):

IR (Fig. 32):

1030 Cm^{-1} (s), P-O-C (alkyl);
1250 Cm^{-1} (s) and 880 - 895 Cm^{-1} (s), P-O-C (aryl);
1520 Cm^{-1} (s), asym. str. of nitro group;
1340 Cm^{-1} (s), sym. str. of nitro group;
810 Cm^{-1} (s), P = S (I);
660 Cm^{-1} (s), P = S (II);
3310 Cm^{-1} (s), N - H str.;
1620 Cm^{-1} (w) and 1585 Cm^{-1} (m), two components of the substituted benzene ring "quadrant stretching" C = C vibrations;
740 Cm^{-1} (m), P - N str. (also aromatic C-H-O bending).

Mass (Fig. 33):

m/e	%RI
372 (M^+)	21.4
339	100
259	15.7
230	7.1
198	20
152	10

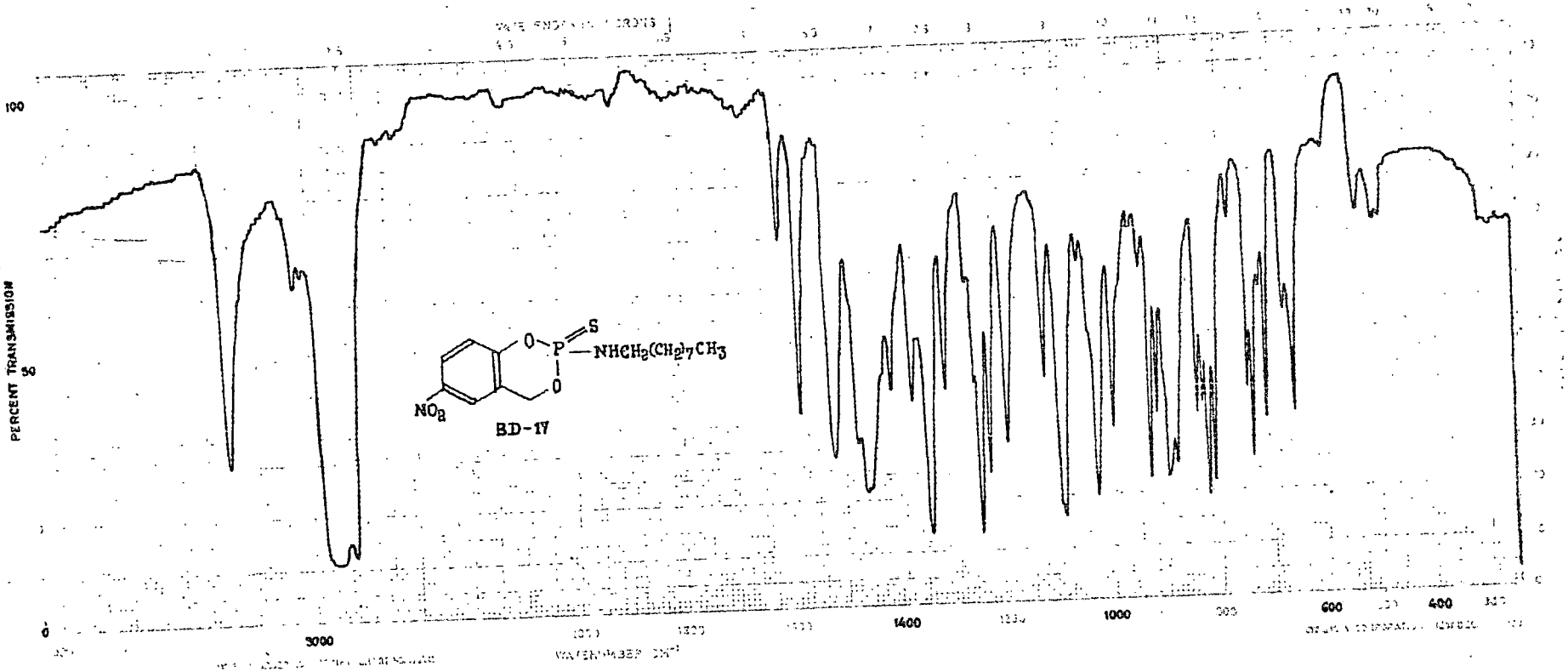


Fig. 32. IR spectrum of 2- Nonylamido – 6 - nitro – 4H - 1,3,2 - benzodioxaphosphorin – 2 - sulphide

SPEKTRUM 15 VERDAMPFUNGSTEMPERATUR 140 GRAD
MOLEKULARPEAK: 372
MASSEN CHARAKTERISTISCHER IONEN:
[illegible]-SH

ANALYSE: 62895

STN HA 017 : 0
ST.STEENKEN
MESSG:
AUSW :25-MAR-81
AUSWER: SCH

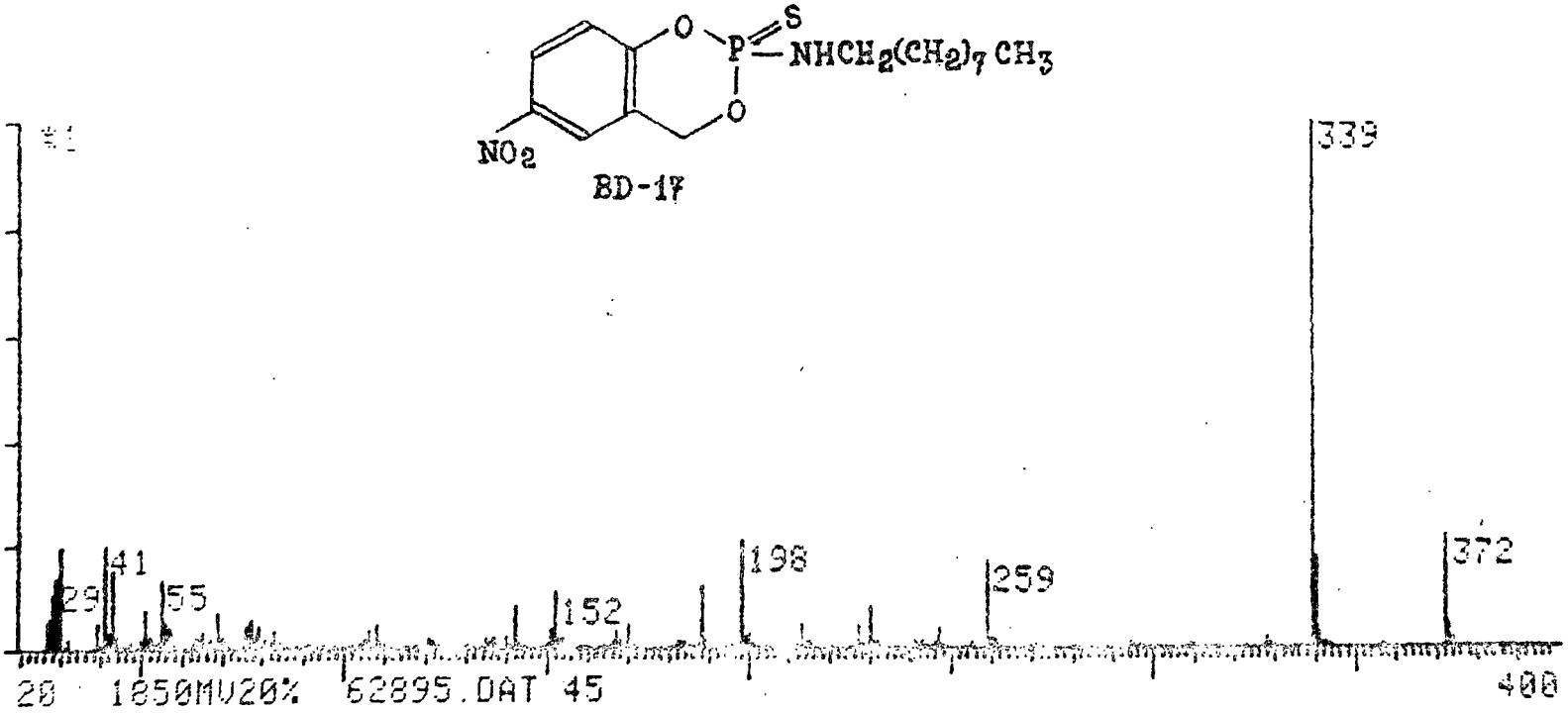


Fig. 33. Mass spectrum of 2-Nonylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide

4. INTERPRETATION OF IR SPECTRA:

The IR spectra of the nitro salicenin cyclic phosphoramidothionates have been analysed according to Thomas [17], Bellamy [18], Coltrup et al [19] and Das [20]. The common IR bands for all compounds are summarised below:

1010 - 1030 cm^{-1} (s), P-O-C (alkyl);

1235 - 1250 cm^{-1} (vs), P-O-C (aryl);

880 - 920 cm^{-1} (s), P-O-C (aryl);

1515 - 1530 cm^{-1} (s), asym. str. of nitro group;

1340 - 1345 cm^{-1} (s), sym. str. of nitro group;

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

640 - 660 cm^{-1}, P = S (II);

The thiono group is characterised by two IR absorption bands with frequencies in the normal ranges given by Thomas [17], as both are not observed in amidophosphates; of these two, the lower frequency band is assigned to P = S (II) bond stretching vibration frequency. The origin of the higher frequency band P = S (I) is uncertain, but whatever its origin, its diagnostic value is beyond doubt. In the nitro salicenin cyclic alkoxy/phenoxy compounds, Das et al. [20] have observed the two bands in the region : 650 - 775 cm^{-1}, P = S (II); and 780 - 820 cm^{-1}, P = S (I). It may be concluded that in these compounds the frequency of band I is only slightly affected by substitution (alkyl amido, alkoxy or phenoxy group to the phosphorus atom) and that of band II is affected to a greater extent. From the above data it can be observed that neither of the two bands shows

any systematic shifts which reflect changes in the inductive properties of the substituents, and this is not unexpected if they do indeed arise from mixed modes. It has also been observed that the P = S (I) band is of medium intensity while the intensity of the P = S (II) band is variable. This has also been reported by Thomas (17).

The frequencies of the P - N band for alkylamidophosphorothionates are : 740 cm^{-1} (BD-10), 720 cm^{-1} (BD-11), 785 cm^{-1} (BD-12), 780 cm^{-1} (BD-13), 785 cm^{-1} (BD-14), 740 cm^{-1} (BD-16) and 740 cm^{-1} (BD-17) ; we could not identify the P - N bond frequency in the iso-propylamido compound (BD-15). Workers have great difficulty in assigning the vibration frequency of the P - N bond. Thomas (17) has reviewed the assignments and correlations which have been proposed by other workers, and summarizes these as showing that P - N-(X) group is characterized by two absorption bands with frequencies in the ranges 645 - 887 cm^{-1} and 802 - 1150 cm^{-1}. He then proceeds to discuss indirect correlations for certain groups containing P - N bonds and finally concludes that, as all these indirect correlations have medium to strong absorption bands in the frequency range 789 - 1102 cm^{-1}, and as no consistent absorption band has been detected at lower frequencies, then this is the most reliable band for the identification of a P - N bond in an unknown molecule. As the P - N link must be expected to be mass sensitive, and therefore, the P - N absorption should show considerable frequency shifts with minor alterations in structure. Thomas (17) has noted a number of examples in which the P - N-link shows no absorption in the range quoted and also our experience confirms this. The P - N bond absorption frequency in iso-propyla-

ride compound (ED-14) could not be identified.

Although P - N absorption shows considerable frequency shifts, the N - H stretching vibrations occur in the normal frequency region:

3300 cm^{-1} in ED - 10
3290 cm^{-1} in ED - 14 ; and
3310 cm^{-1} in ED - 17.

The P-O-C (alkyl) group is characterized by a strong absorption band whose frequency lies between 1010 - 1030 cm^{-1}, while the band due to P-O-C (aryl) group is found in the region : 1235 - 1250 cm^{-1} ; this band is always accompanied by a second absorption band which has been attributed to either the sym. str. of the P-O-C (aromatic) system or to a separate P = O str. which is not so coupled. Thomas[17] strongly favours the latter explanation which is supported by the persistence of this band in both P-O-P and P-O-C compounds, and by the fact that in the latter the frequency is a linear function of the π-values (where, π is 'phosphorus-induction constant' for substituent groups, p. - 34, Ref. 17) of the substituents. This band lies between 880 - 920 cm^{-1} for all compounds; the frequency range quoted is that of the strongest band in this region. Although 1020 cm^{-1} band has been identified for the vibration of P-O-C (alkyl) group in the morpholino compound (ED-11), the 980 cm^{-1} band has strongest intensity in the 950 - 1050 cm^{-1} region. It may be possible that this 980 cm^{-1} band is due to P-O-C (alkyl) group vibration in the morpholino compound.

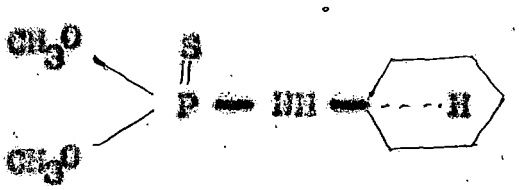
Two bands present in the ranges 1515 - 1520 cm^{-1} and 1340 - 1345 cm^{-1} are due to asym. and sym. str. of nitro group respectively (Bellamy, p. 335). The bands present at 1630 cm^{-1} and 1585 cm^{-1} are due to "quadrant stretching" C = C vibration of the aromatic ring (Colthup et al p. 224).

6. DISCUSSION ON MASS SPECTRA:

The mass spectra of these compounds have been analysed according to Cooks and Gerrard[22], Jörg et al[23], Ménico et al[24,25] and Gillis and Occolowitz[26].

All compounds show parent molecular ions. Fragmentation by loss of .SH radical is important; all compounds show an ion due to (parent molecule — SH)$^+$ and it is the base peak in spectra of cyclohexylamido (Fig. 6), morpholino (Fig. 10), diethylamido (Fig.14), pyrrolidino (Fig. 26), piperidino (Fig. 30), and morylamido (Fig.34) compounds; but m/e 198 is the base peak for both dimethylamido (Fig. 18) and isopropylamido (Fig.22) compounds.

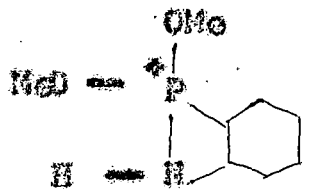
Cooks and Gerrard[22] reported that compounds of the type (A)



(A)

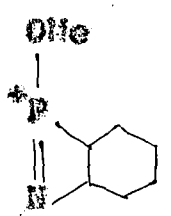
formed the base peak by loss of .SH radical directly from the molecular ion. By deuteration of the methyl group and the amino group

it was shown that the hydrogen of NH is abstracted from the cyclohexyl ring and not from the N - H entity. There was no preliminary hydrogen shift to sulphur. They postulated structure (B) for the product ion



(B)

By specific loss of the amino hydrogen, (B) further lost CH_3OH giving an ion for which they postulated structure (C)



(C)

These two structures (B and C) are supported by analogous fragmentations of the related compounds.

Following Cooks and Gerrard[22], we postulate the mass fragmentation processes for the different nitro saligenin cyclic amidophosphorothionates.

Cyclohexylamido compound shows m/e 295 ion as the base peak by the direct elimination of NH from the molecular ion peak

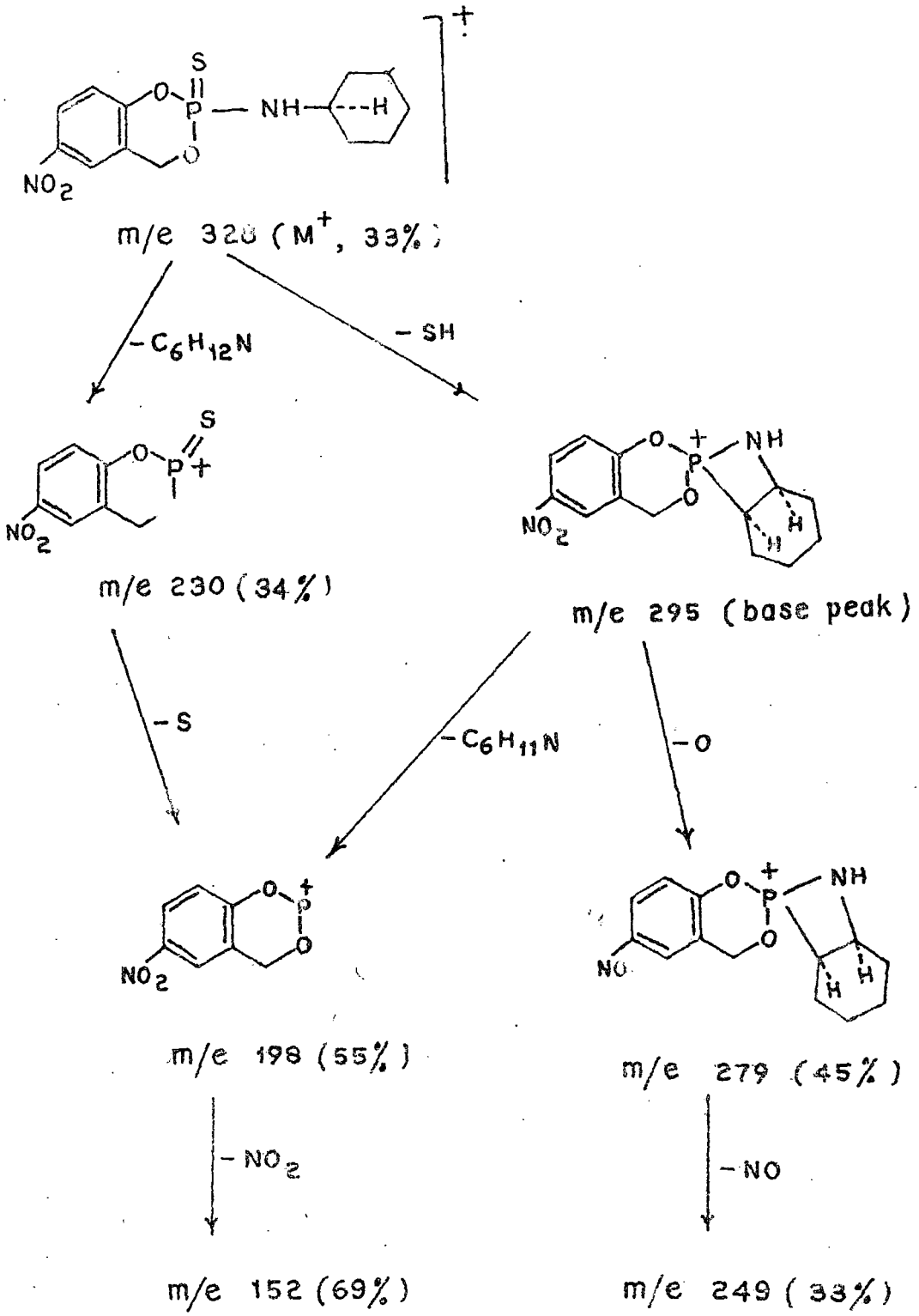
(m/e 333, % RI 33, Scheme-I). The ion (m/e 230, RI 34) is formed by the direct loss of $C_6H_{12}N$ from the molecular ion. The ion (m/e 198, RI 55) is formed by loss of S from the ion m/e 230 and also by the elimination of $C_6H_{11}N$ from the base peak ion. The ion (m/e 152, RI 69) is formed by the elimination of NO_2 from the ion m/e 198. The peak for m/e 270, RI 45 is observed due to the elimination of O from the base peak, and then the ion (m/e 249, RI 33) is formed by loss of NO from the ion, m/e 279.

In the case of morpholino compound the base peak shows for m/e 233 by the direct elimination of SH from the molecular ion peak (m/e 319, RI 43, Scheme-2). The ion (m/e 230, RI 43.6) and the ion (m/e 234, RI 60) are formed from the molecular ion peak by the direct loss of C_4H_8NO and S respectively. The ions (m/e 198, RI 70% and m/e 152, RI 45.4) have also been observed.

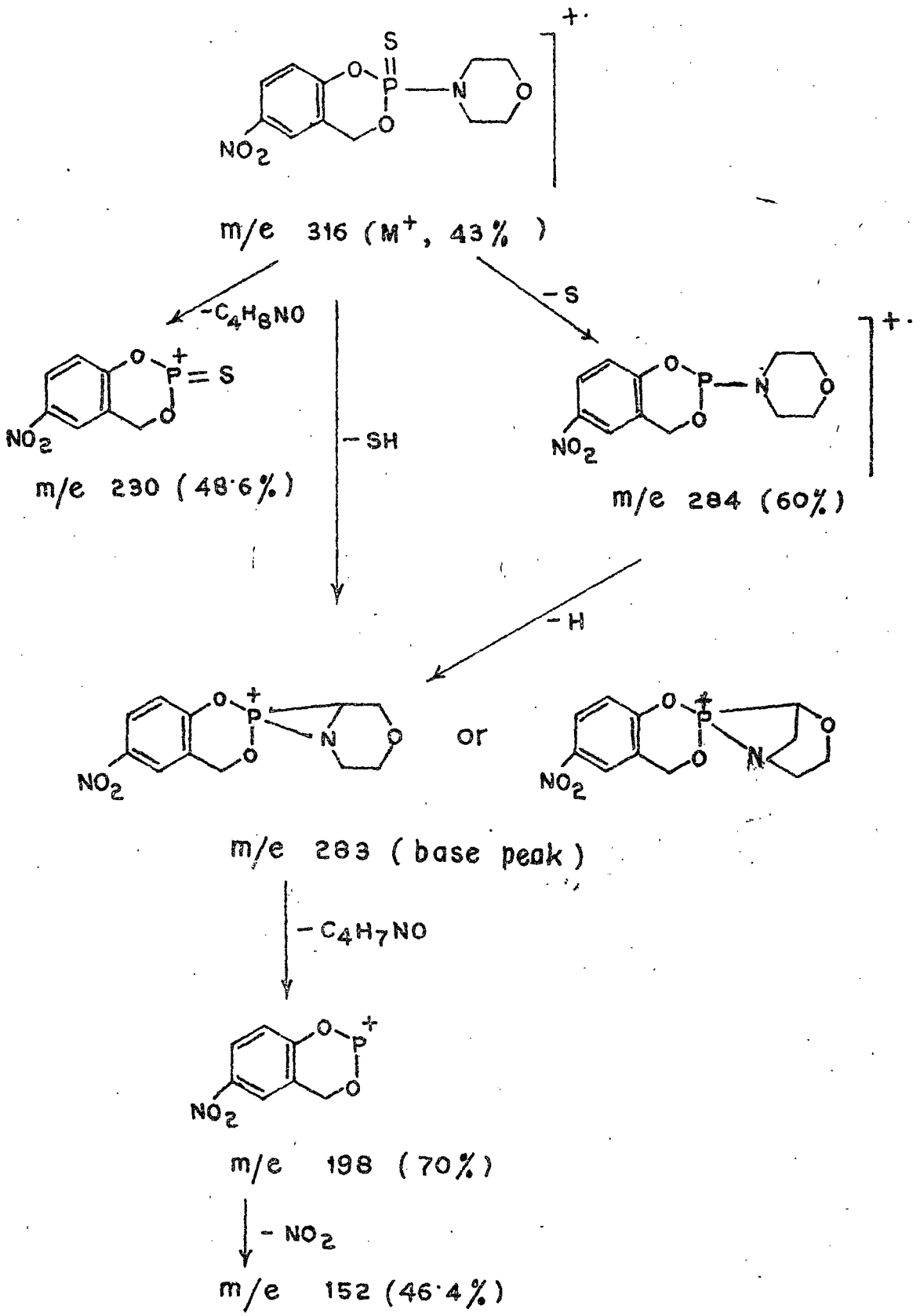
Diethylamido compound shows m/e 250 ion as the base peak by the direct elimination of SH from the molecular ion peak (m/e 302, RI 25, Scheme-3). The ions (m/e 198, RI 40 and m/e 152, RI 9.2) have also been observed like the other compounds.

In case of the dimethylamido compound the base peak ion is m/e 198 as mentioned earlier. The ion (m/e 241, RI 91.6) is observed by the direct loss of SH from the molecular ion. The ion (m/e 152, RI 9.2) has also been observed (Scheme-4).

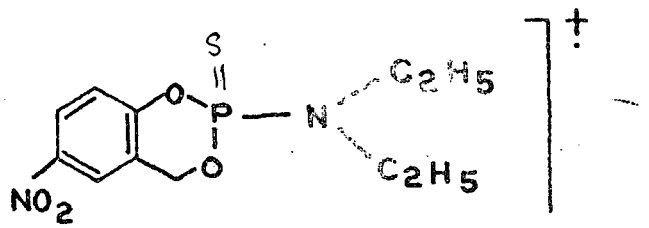
Isopropylamido compound also shows m/e 198 ion as the base peak. The ions (m/e 273, RI 25, m/e 255, RI 92 and m/e 230,



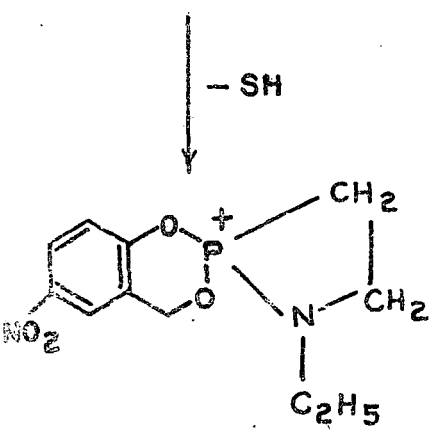
Scheme. Mass fragmentation of BD_{10}



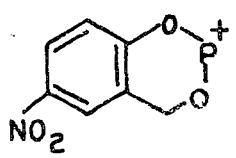
Scheme – Mass Fragmentation of BD_{11}



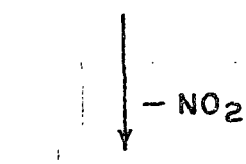
m/e 302 (M^+, 25%)



m/e 269 (base peak)

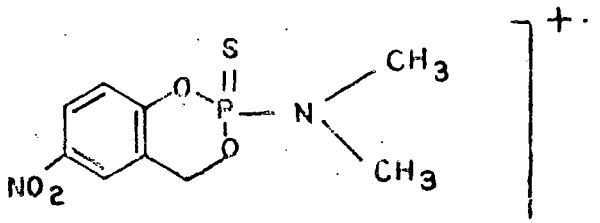


m/e 198 (40%)



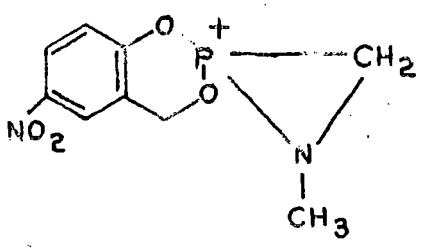
m/e 152 (9·2%)

Scheme. Mass Fragmentation of BD_{12}



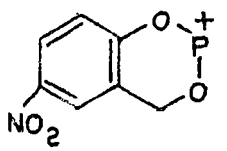
m/e 274 (M^+, 94·4%)

$\downarrow$ $-SH$



m/e 241 (91·6%)

$\downarrow$ $-C_2H_5N$



m/e 198 (base peak)

$\downarrow$ $-NO_2$

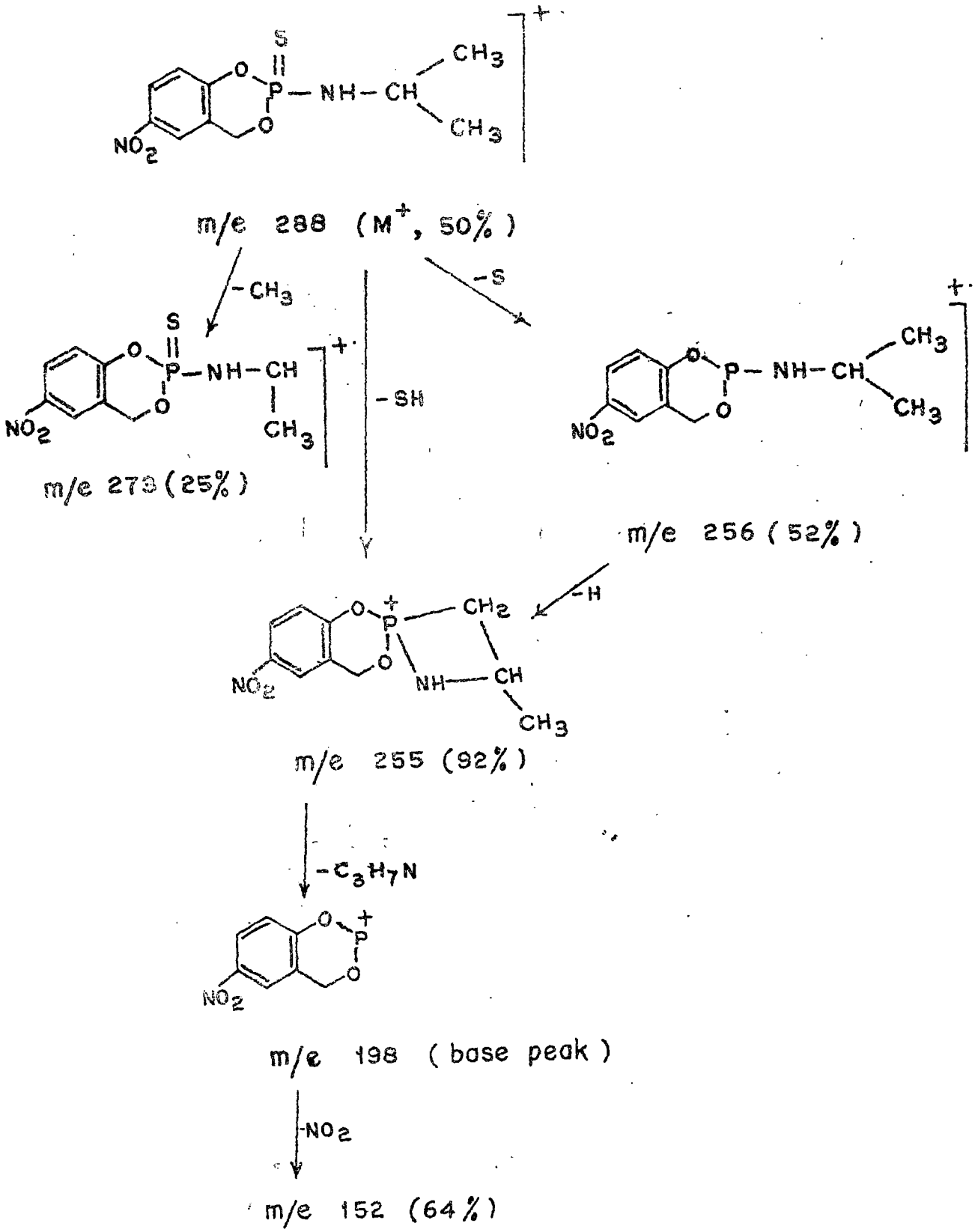
m/e 152 (9·2%)

RM 62) are observed by the direct loss of CH_3, OH and O respectively from the molecular ion peak. The ion m/e 255 may also be formed by the loss of H from the ion m/e 256. The ion (m/e 152, RM 64) is also observed as before (Scheme-5).

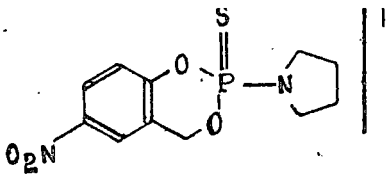
Pyrrolidine compound shows m/e 267 ion as the base peak by the direct elimination of OH from the M^+ ion peak (Scheme-6). The ion (m/e 116, RM 60.0) is formed by the direct loss of $C_7H_5NO_3$ from the base peak ion; the ion (m/e 106, RM 55.7) is formed by the direct loss of C_4H_7N from the base peak ion.

Piperidine compound shows m/e 281 ion as the base peak by the direct elimination of OH from the M^+ ion peak (m/e 314, RM 17.1, Scheme-7). The ion (m/e 198, RM 7.1) is formed by the direct loss of C_5H_9N from the base peak ion; the ion (m/e 130, RM 62.9) is formed by loss of $C_7H_5NO_3$ from the base peak ion.

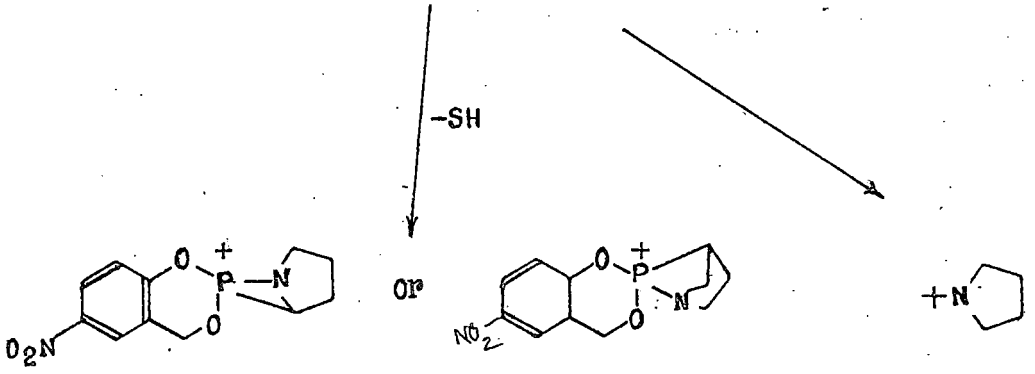
Benzylamide compound shows m/e 339 ion as the base peak by the direct elimination of OH from the parent molecular ion (m/e 372, RM 21.4, Scheme-8). The ion (m/e 259, RM 15.7) is formed by the direct loss of C_8H_{17} from the M^+ ion peak, the ion (m/e 198, RM 20) is formed by the loss of $C_9H_{19}N$ from the base peak ion. The ion (m/e 230, RM 7.1) is formed by the loss of CH_3N from the ion m/e 259.



Scheme 6 Mass Fragmentation of BD_{14}.

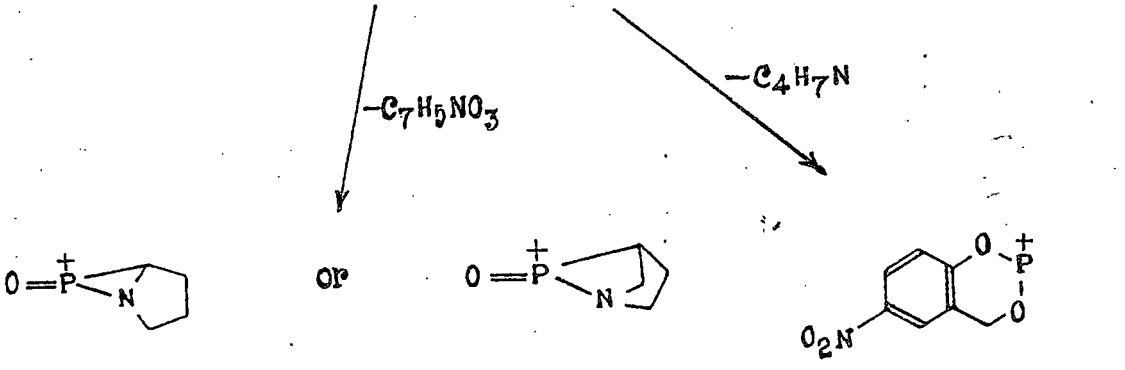


m/e 300 (M^+, 21.4%)



m/e 267 (base peak)

m/e 70 (35·7%)

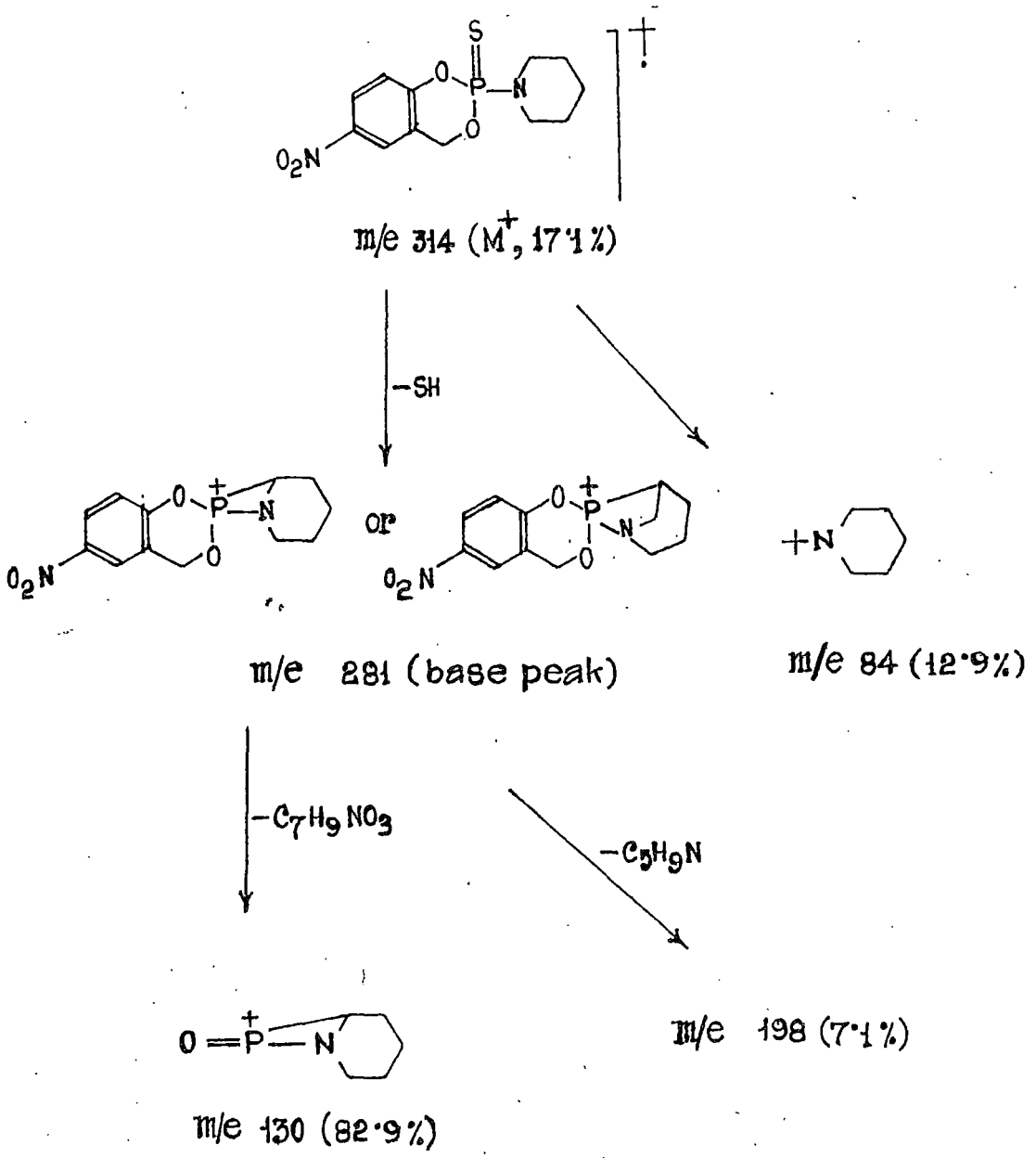


m/e 116 (80·0%)

m/e 198 (25·7%)

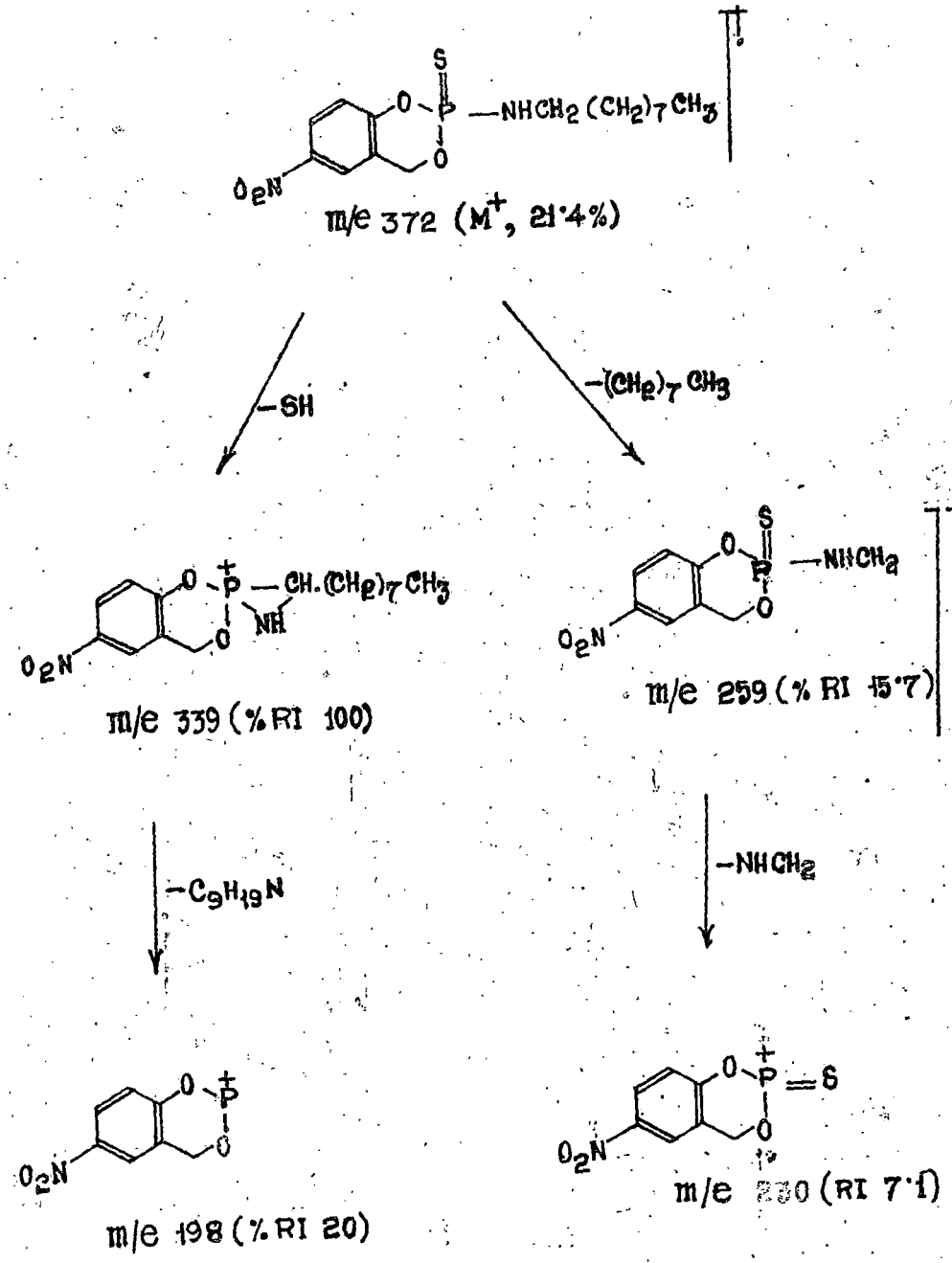
Scheme

Mass fragmentation processes in BD-15



Scheme – 7

Mass fragmentation of BD-16

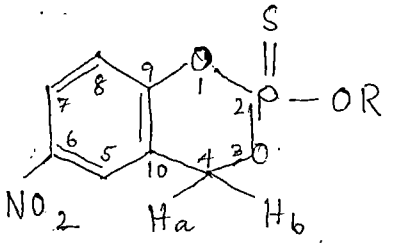


Scheme – 8

Mass fragmentation of BD-17

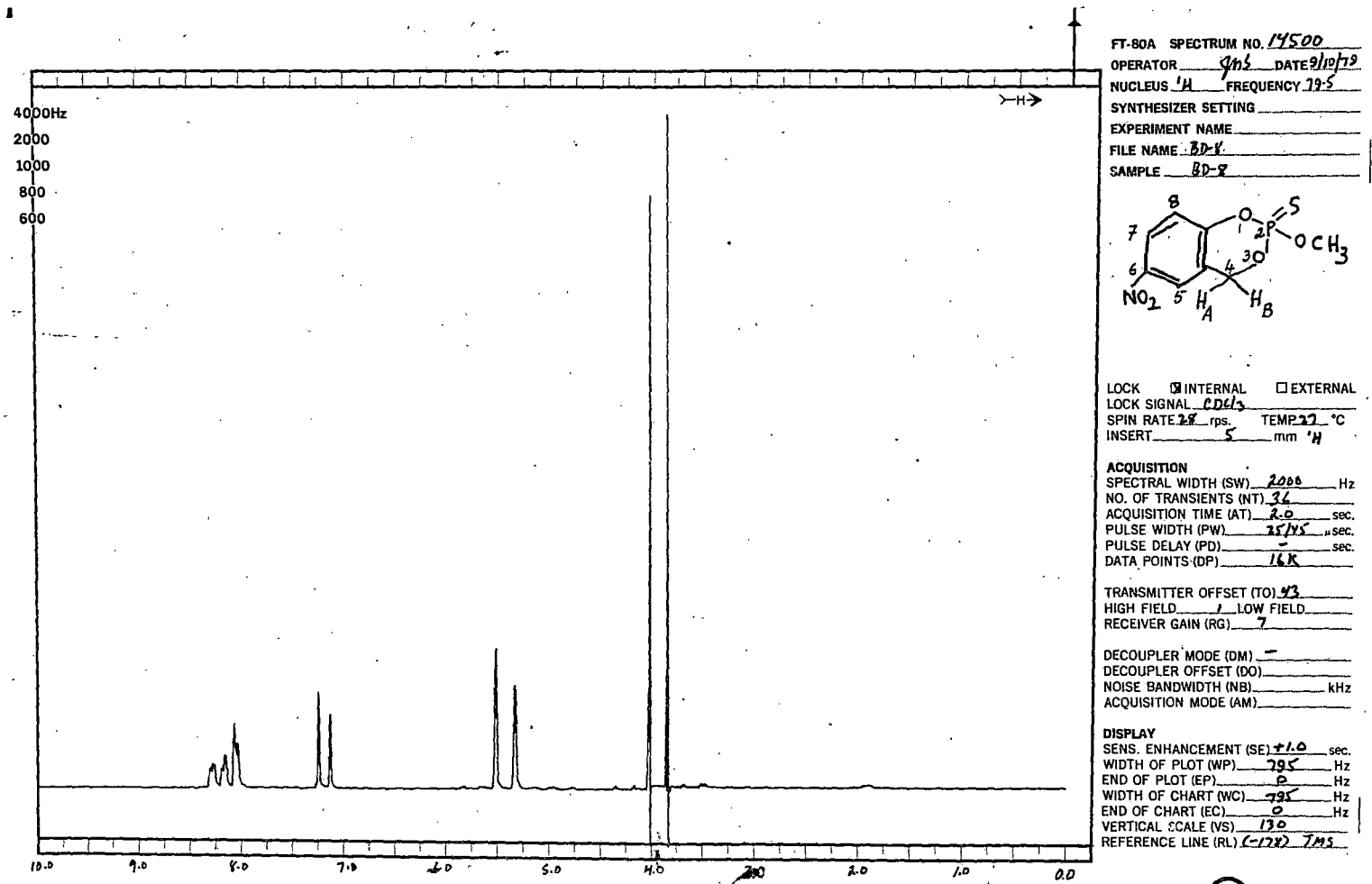
6. DISCUSSION ON NMR SPECTRA:

The ^1H NMR spectra of several 2-alkoxy/phenoxy-6-nitro-4H-1,3,2 benzodioxaphosphorin-2-sulphide have been reported by Das et al[21].



R = CH_3 (BD-8)
= C_2H_5 (BD-4)
= n-C_3H_7 (BD-3)
= n-C_4H_9 (BD-6)
= i-C_3H_7 (BD-5)
= i-C_4H_9 (BD-7)
= $C_2H_4OCH_3$ (BD-1)
= $C_2H_4OC_2H_5$ (BD-2)
= C_6H_5 (BD-9)

The ^1H NMR signal at δ =5.4 ppm in BD-1, BD-2, BD-9 and BD-10 (and also in other alkylamidophosphorothionates) is different from that of other compounds. Fig. 34 is the ^1H NMR spectrum of BD-8, Fig. 35 is the ^1H NMR spectrum of BD-9 and Fig. 7 is that of BD-10. If we study the three charts (Figs. 34,35 & 7) in the given order, it is fairly evident that the chemical shift difference of the protons H_{4A} & H_{4B} is increasing in going from BD-8 to BD-10. Also, the 2-substituent is at the sametime increasing in bulk, and probably spending more time in the conformation with the least steric interactions. In BD-10 (also in other alkylamidophosphorothionates), this may be mainly in one conformation; while in BD-8



FT-80A SPECTRUM NO. 14500
OPERATOR GNS DATE 9/10/79
NUCLEUS ^1H FREQUENCY 79.5
SYNTHESIZER SETTING
EXPERIMENT NAME
FILE NAME BD-8
SAMPLE BD-8

LOCK ☒ INTERNAL ☐ EXTERNAL
LOCK SIGNAL $CDCl_3$
SPIN RATE 28 rps. TEMP 27 °C
INSERT 5 mm ^1H

ACQUISITION
SPECTRAL WIDTH (SW) 2000 Hz
NO. OF TRANSIENTS (NT) 32
ACQUISITION TIME (AT) 2.0 sec.
PULSE WIDTH (PW) 25/45 μsec.
PULSE DELAY (PD) – sec.
DATA POINTS (DP) 16K

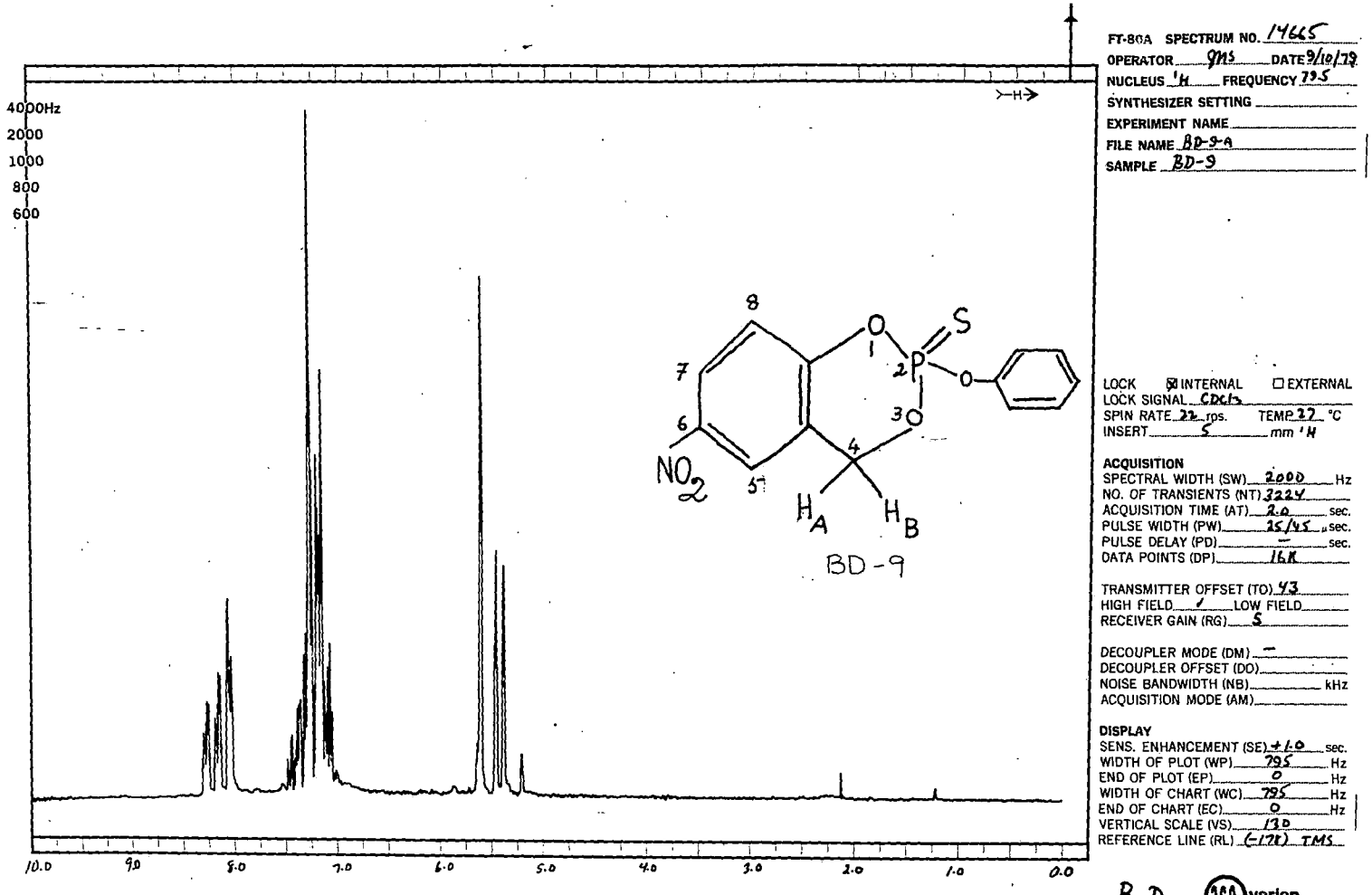
TRANSMITTER OFFSET (TO) 43
HIGH FIELD / LOW FIELD
RECEIVER GAIN (RG) 7

DECOUPLER MODE (DM) –
DECOUPLER OFFSET (DO)
NOISE BANDWIDTH (NB) kHz
ACQUISITION MODE (AM)

DISPLAY
SENS. ENHANCEMENT (SE) +1.0 sec.
WIDTH OF PLOT (WP) 795 Hz
END OF PLOT (EP) 0 Hz
WIDTH OF CHART (WC) 795 Hz
END OF CHART (EC) 0 Hz
VERTICAL SCALE (VS) 130
REFERENCE LINE (RL) (-172) TMS

B. Das varian PRINTED IN U.S.A.

Fig. 34. ^1H NMR spectrum of 2-Methoxy-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide.



FT-80A SPECTRUM NO. 14665
OPERATOR gns DATE 9/10/79
NUCLEUS ^1H FREQUENCY 79.5
SYNTHESIZER SETTING
EXPERIMENT NAME
FILE NAME BD-9-A
SAMPLE BD-9

LOCK ☒ INTERNAL ☐ EXTERNAL
LOCK SIGNAL CDCl3
SPIN RATE 22 rps. TEMP 27 °C
INSERT 5 mm ^1H

ACQUISITION
SPECTRAL WIDTH (SW) 2000 Hz
NO. OF TRANSIENTS (NT) 3224
ACQUISITION TIME (AT) 2.0 sec.
PULSE WIDTH (PW) 25/45 μsec.
PULSE DELAY (PD) — sec.
DATA POINTS (DP) 16K

TRANSMITTER OFFSET (TO) 43
HIGH FIELD / LOW FIELD
RECEIVER GAIN (RG) 5

DECOUPLER MODE (DM) —
DECOUPLER OFFSET (DO)
NOISE BANDWIDTH (NB) kHz
ACQUISITION MODE (AM)

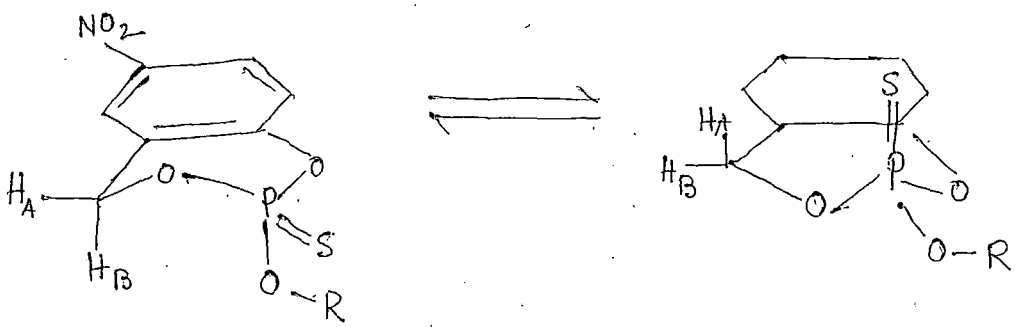
DISPLAY
SENS. ENHANCEMENT (SE) +1.0 sec.
WIDTH OF PLOT (WP) 795 Hz
END OF PLOT (EP) 0 Hz
WIDTH OF CHART (WC) 795 Hz
END OF CHART (EC) 0 Hz
VERTICAL SCALE (VS) 130
REFERENCE LINE (RL) (-172) TMS

B. Das varian PRINTED IN U.S.A.

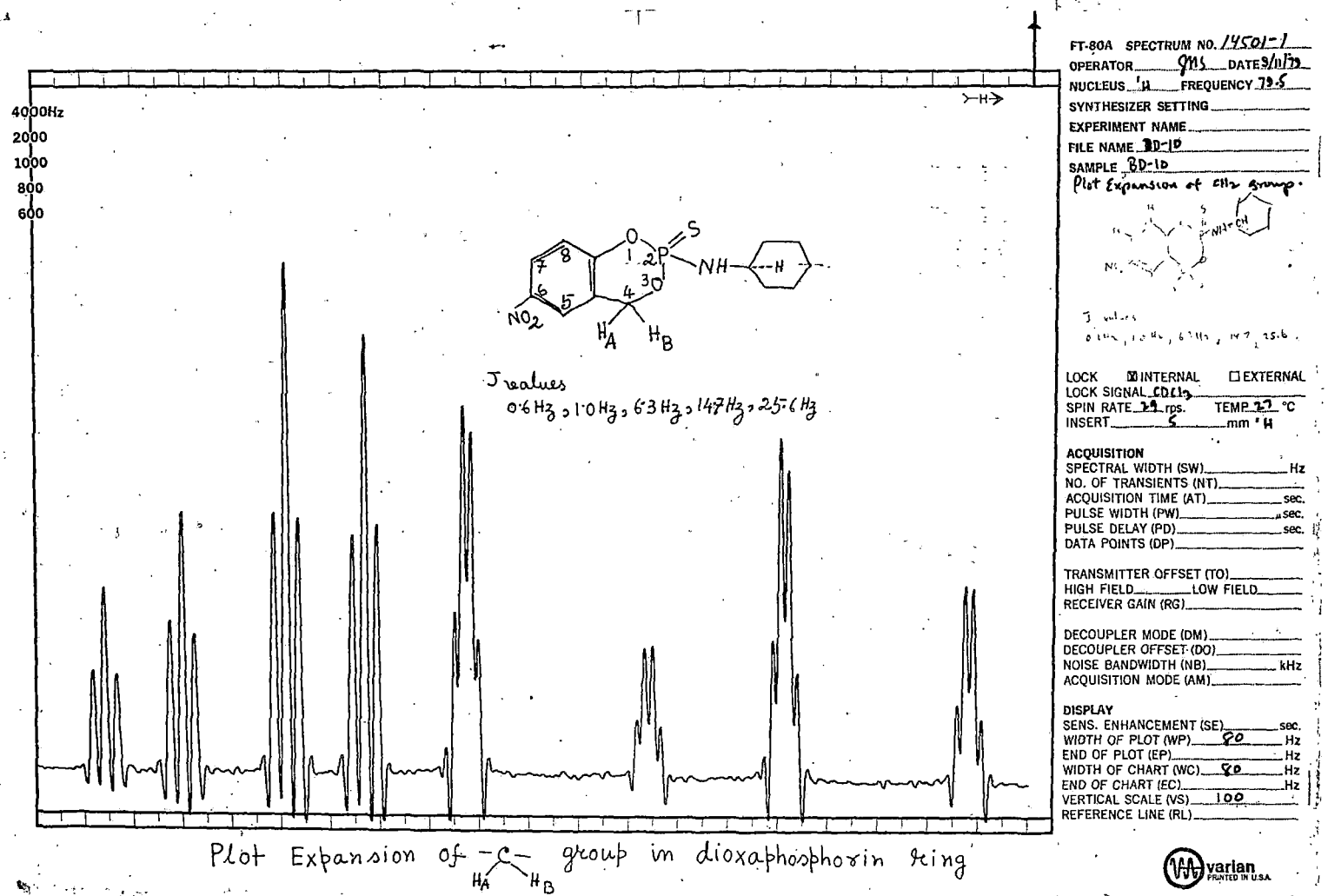
Fig. 35. ^1H NMR spectrum of 2-Phenoxy-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide.

(also in BD-4, BD-3, BD-6 etc.) it appears that both the chemical shift difference and the difference between $^{3}J_{P\text{-}O\text{-}C\text{-}H_{4A}}$ and $^{3}J_{P\text{-}O\text{-}C\text{-}H_{4B}}$ are quite small. This suggests that the molecule exists as an average of the two conformations with rapid interconversion between them. In the case of BD-9, it seems that an intermediate situation prevails, similar to BD-1 and BD-2.

In either of the conformations I & II



one of the couplings, $^{3}J_{P\text{-}O\text{-}C\text{-}H_{4A}}$ or $^{3}J_{P\text{-}O\text{-}C\text{-}H_{4B}}$ will be large and other one will be small, since the $P\text{-}O\text{-}C\text{-}H_4$ dihedral angle for one of them is close to 180° and for the other it is close to 60°. The plot-expansion of the 5.0 - 5.8 ppm region in BD-10 (Fig. 36) shows couplings of 0.6, 1.0, 6.3, 14.7 and 25.6 Hz. Since the 14.7 Hz coupling is certainly the geminal $^{2}J_{H_A\text{-}H_B}$ coupling constant, this then leaves 6.3 and 25.6 Hz as the two $^{3}J_{P\text{-}O\text{-}C\text{-}H}$ coupling



Plot Expansion of $-\underset{H_A}{\overset{H_B}{C}}-$ group in dioxaphosphorin ring

Fig. 36. Plot expansion of the $-CH_2-$ group (in BD-10), 5.0 – 5.8 ppm region.

constants. Consequently we can conclude that BD-10 is probably mainly in one conformation. On the other hand, the pattern found in BD-8 can only be explained by nearly equal (but not exactly) coupling constants and a small chemical shift difference in H_A and H_B, which requires rapid interconversion to give an average of the coupling constants and chemical shifts. BD-9 seems to be an intermediate case, similar to BD-1 and BD-2.

The small couplings seen in Fig. 36 arise from coupling to the aromatic ring protons H_5, H_7 and H_8. The conformation II seems less hindered for bulky substituent groups such as those in BD-9 and especially in BD-10. Therefore let us assume that in BD-10 conformation II predominates. In that case the dihedral angle of 180^0 belongs to H_B, and we can identify it as the upfield group of lines showing equal coupling of 0.6 Hz to the three aromatic protons H_5, H_7 and H_8. Proton H_A is more strongly coupled to H_5 and H_7 with $J = 1.0$ Hz, but not to H_8. This can be confirmed by spin-decoupling experiments shown in Fig. 37 and Fig. 38. In Fig. 37, aromatic protons H_5 and H_7 were irradiated at 8.1 ppm and the triplet structure of H_A disappeared; the quartet structure of H_B also collapsed due to irradiation of H_5 and H_7, which removed the effects of their spins, but the residual line width masks the remaining small coupling to H_8. However, in Fig. 38, in which only H_8 was irradiated, we can see that the quartets have become triplets as expected.

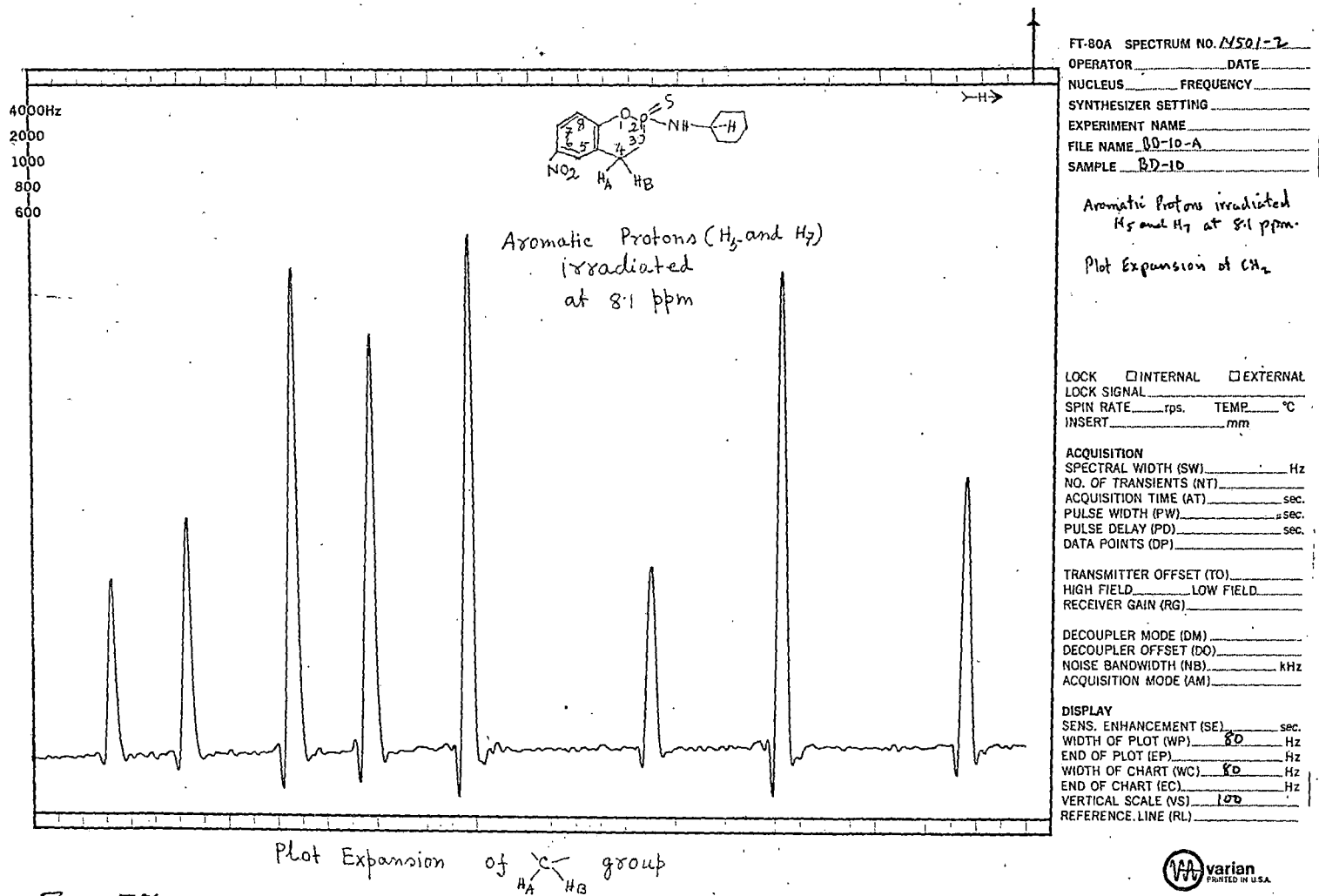


Fig. 37. Plot expansion of $-CH_2-$ group in BD-10 (aromatic protons H_5 and H_7 irradiated at 8·1 ppm)

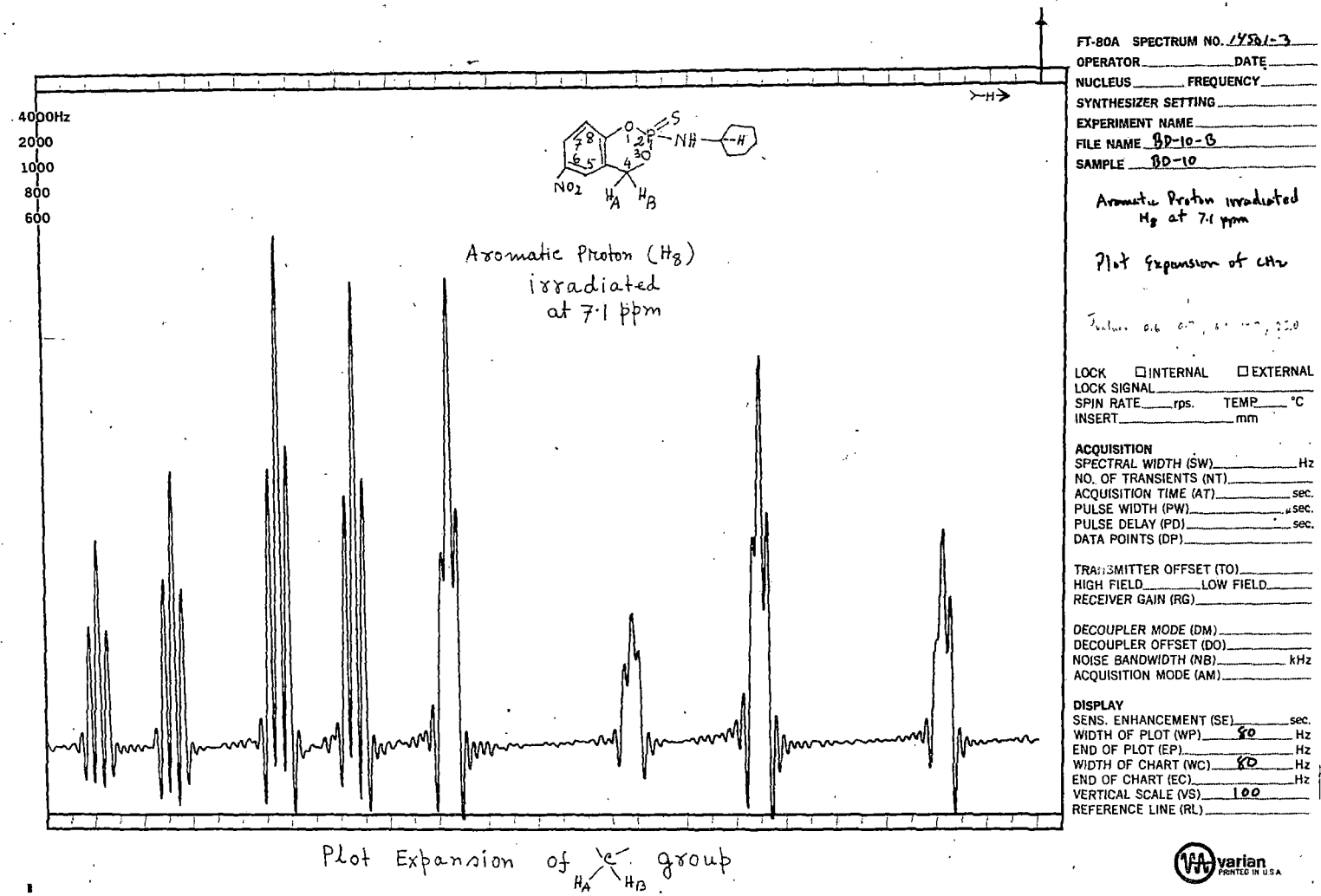
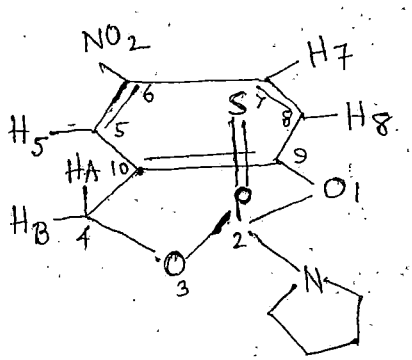
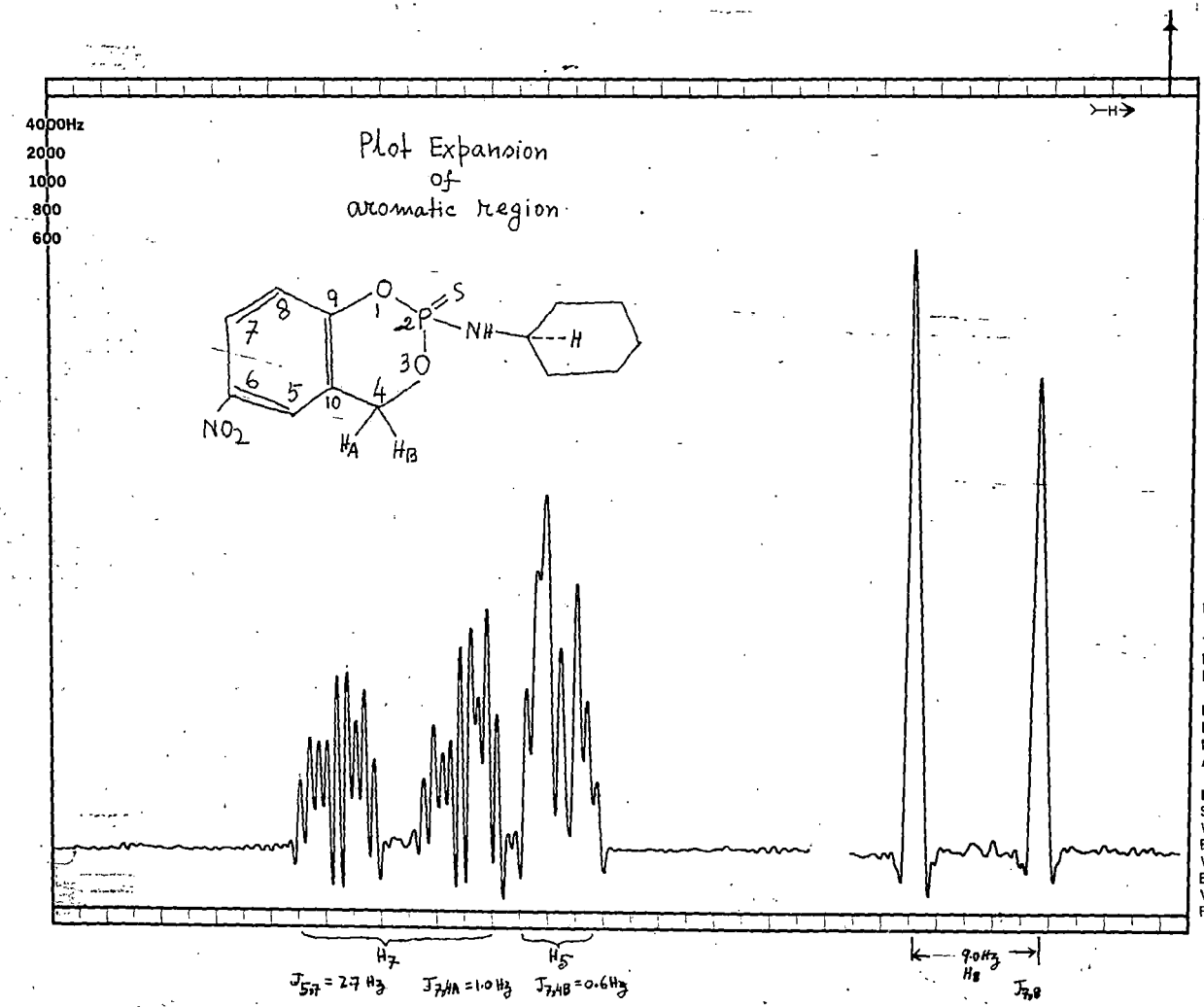


Fig. 38. Plot expansion of $-CH_2-$ group in BD-10 (aromatic proton H_8 irradiated at 7.1 ppm)

The plot expansion of the aromatic region (Fig. 39 for BD-10) shows the basic ABX pattern with the additional long range couplings to H_5 and H_7. The interpretation of this spectral region is facilitated by examining Fig. 40 in which the $-CH_2-$ group in the dioxaphosphorin ring was decoupled. In Fig. 40, H_7 appears as an eight line pattern. In Fig. 39, each line of this pattern is split by the protons H_{4A} and H_{4B} into triplets with 0.8 Hz spacing. This is the average of the actual couplings ($J_{H_7 - H_{4A}} = 1.0$ Hz ; $J_{H_7 - H_{4B}} = 0.6$ Hz), due to the fact that H_A and H_B are strongly coupled ($^2J_{H_A - H_B} = 14.7$ Hz) and separated by a small chemical shift.

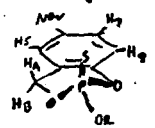
Fig. 41 and Fig. 42 are the plot expansions of BD-15 and BD-16 respectively. The $-CH_2-$ protons in the dioxaphosphorin ring are non-equivalent and have chemical shifts in both compounds of 5.2 ppm and 5.65 ppm. The coupling to the ^{31}P nucleus is 25 Hz for one the $-CH_2-$ protons and 6.6 Hz for the other. A Dreiding model of the molecules seems to have a stable conformation in which proton H_B is quasi-equatorial and proton H_A is quasi-axial.





FT-80A SPECTRUM NO. 14501-4
OPERATOR _____ DATE _____
NUCLEUS _____ FREQUENCY _____
SYNTHESIZER SETTING _____
EXPERIMENT NAME _____
FILE NAME _____
SAMPLE BD-10

Plot Expansion of aromatic region.



LOCK ☐INTERNAL ☐EXTERNAL
LOCK SIGNAL _____
SPIN RATE ____ rps. TEMP. ____ °C
INSERT _____ mm

ACQUISITION
SPECTRAL WIDTH (SW) _____ Hz
NO. OF TRANSIENTS (NT) _____
ACQUISITION TIME (AT) _____ sec.
PULSE WIDTH (PW) _____ μsec.
PULSE DELAY (PD) _____ sec.
DATA POINTS (DP) _____

TRANSMITTER OFFSET (TO) _____
HIGH FIELD _____ LOW FIELD _____
RECEIVER GAIN (RG) _____

DECOUPLER MODE (DM) _____
DECOUPLER OFFSET (DO) _____
NOISE BANDWIDTH (NB) _____ kHz
ACQUISITION MODE (AM) _____

DISPLAY
SENS. ENHANCEMENT (SE) _____ sec.
WIDTH OF PLOT (WP) 80 Hz
END OF PLOT (EP) _____ Hz
WIDTH OF CHART (WC) 80 Hz
END OF CHART (EC) _____ Hz
VERTICAL SCALE (VS) 100
REFERENCE LINE (RL) _____

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Fig. 39. Plot expansion of the aromatic region of BD-10

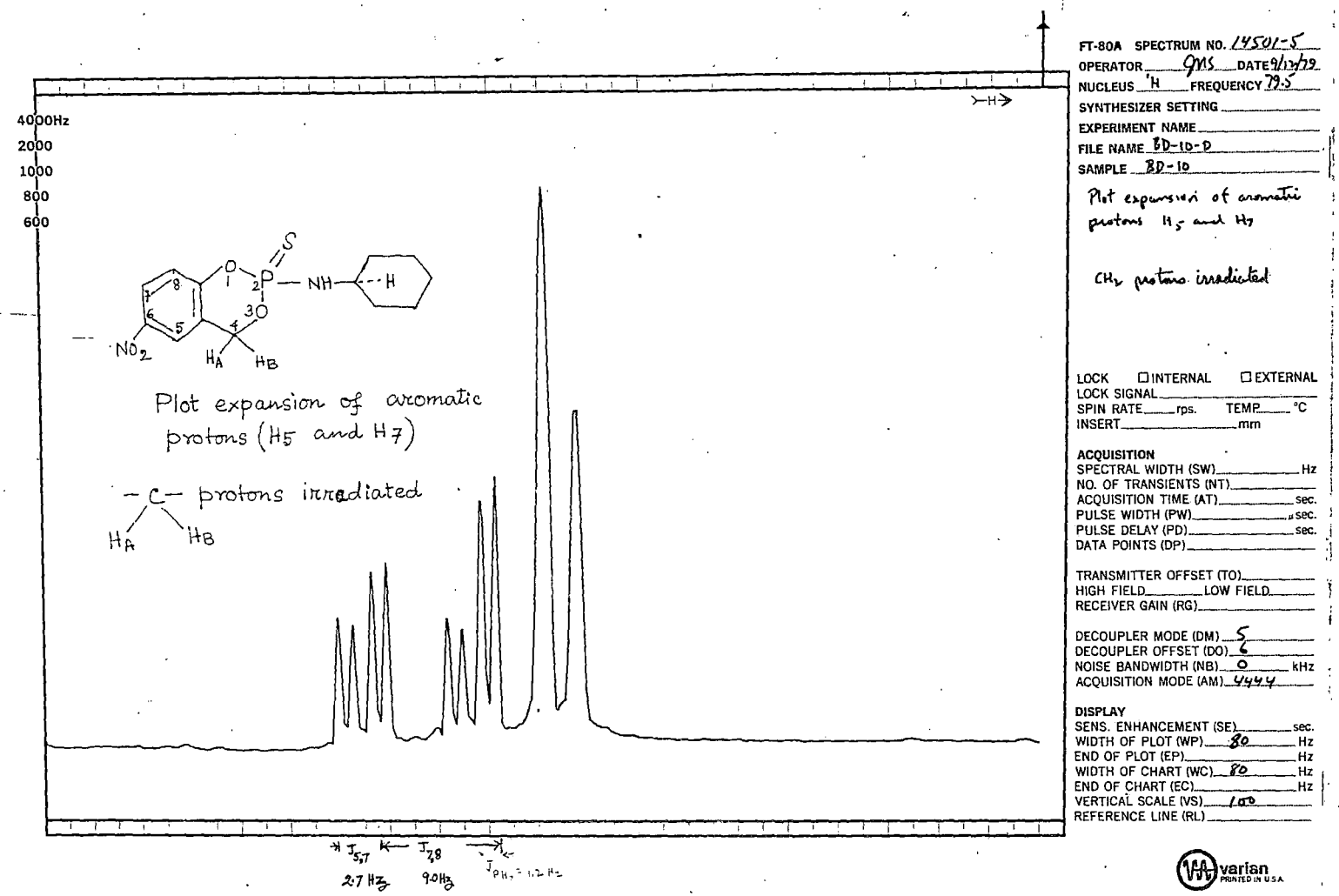
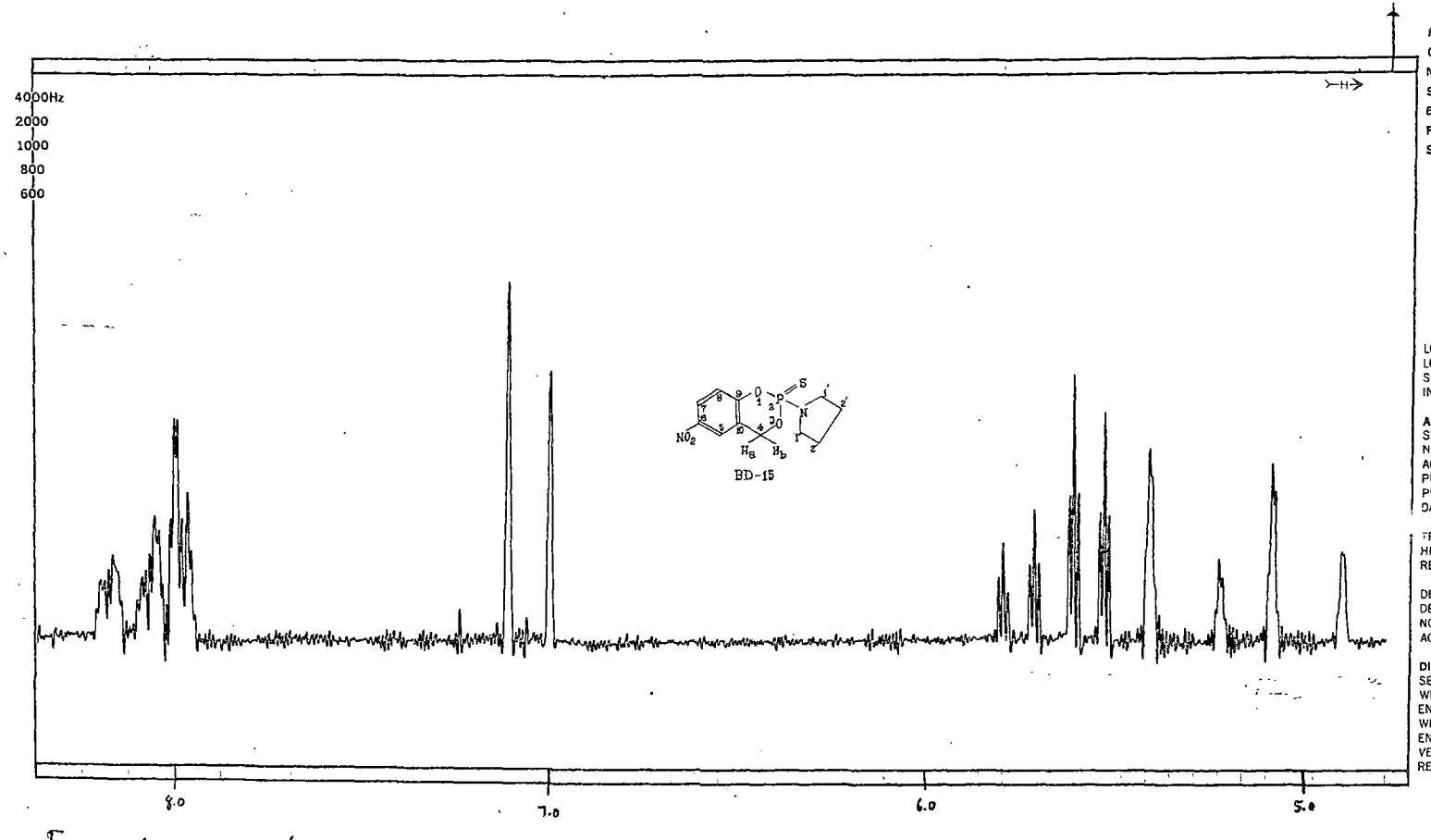


Fig. 40 : Plot expansion of the aromatic protons H_5 and H_7 in BD-10 with the $-CH_2-$ protons (in the dioxaphosphorin ring) irradiated.



FT-80A SPECTRUM NO. 14992-1
OPERATOR _____ DATE _____
NUCLEUS ^{1}H FREQUENCY _____
SYNTHESIZER SETTING _____
EXPERIMENT NAME _____
FILE NAME _____
SAMPLE BD-15

Plot Expansion
Scale: 1.0 Hz/Div.

LOCK ☐INTERNAL ☐EXTERNAL
LOCK SIGNAL _____
SPIN RATE ____rps. TEMP ____°C
INSERT _____ mm

ACQUISITION
SPECTRAL WIDTH (SW) _____ Hz
NO. OF TRANSIENTS (NT) _____
ACQUISITION TIME (AT) _____ sec.
PULSE WIDTH (PW) _____ μsec.
PULSE DELAY (PD) _____ sec.
DATA POINTS (DP) _____

TRANSMITTER OFFSET (TO) _____
HIGH FIELD _____ LOW FIELD _____
RECEIVER GAIN (RG) _____

DECOUPLER MODE (DM) _____
DECOUPLER OFFSET (DO) _____
NOISE BANDWIDTH (NB) _____ kHz
ACQUISITION MODE (AM) _____

DISPLAY
SENS. ENHANCEMENT (SE) _____ sec.
WIDTH OF PLOT (WP) _____ Hz
END OF PLOT (EP) _____ Hz
WIDTH OF CHART (WC) _____ Hz
END OF CHART (EC) _____ Hz
VERTICAL SCALE (VS) _____
REFERENCE LINE (RL) _____

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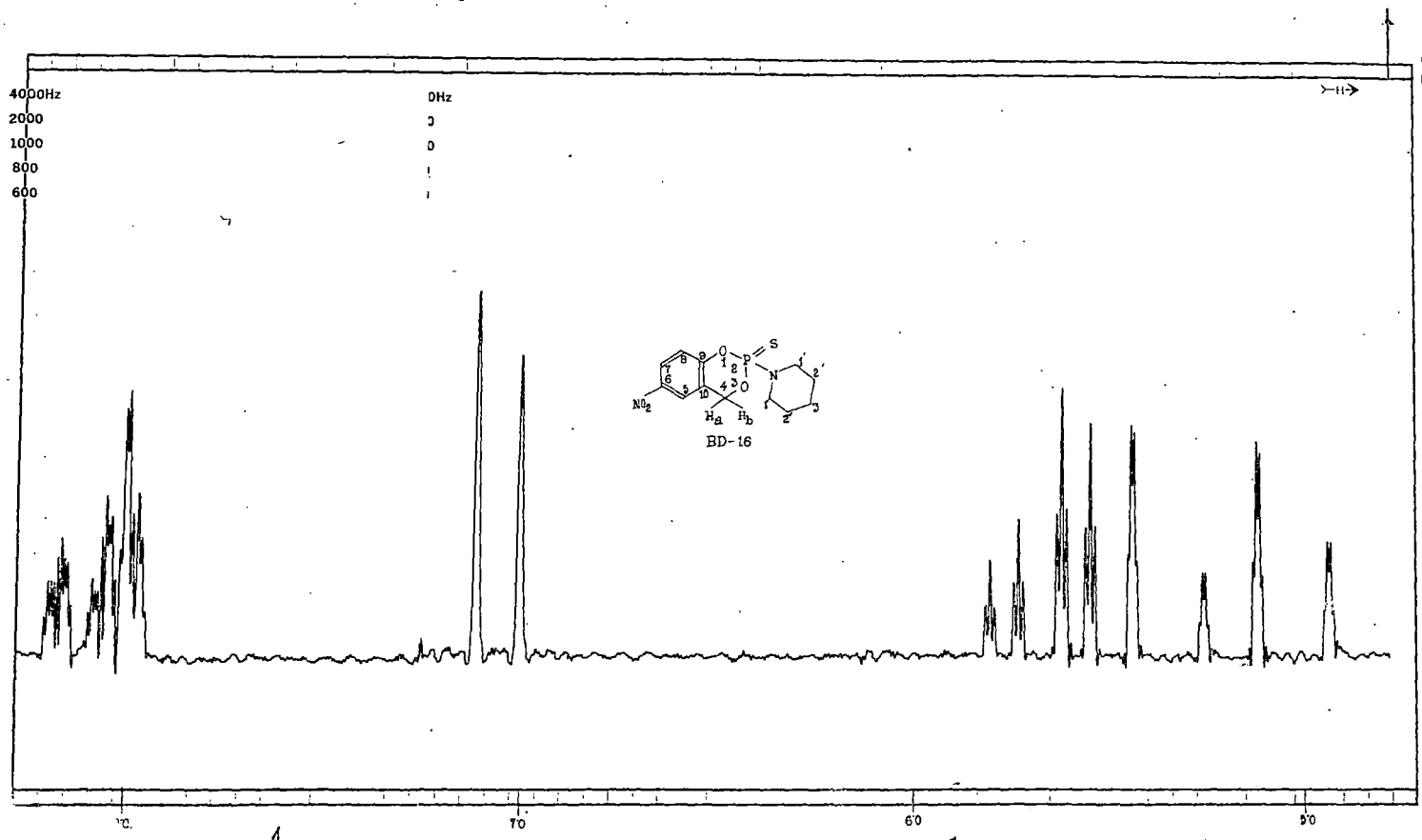
Fig. 41 ^{1}H NMR spectrum of BD-15 (Plot expansion)



BD-16

FT-80A SPECTRUM NO. 14993-1
OPERATOR _____ DATE _____
NUCLEUS ^1H FREQUENCY _____
SYNTHESIZER SETTING _____
EXPERIMENT NAME _____
FILE NAME _____
SAMPLE BD-16

Plot Expansion

Scale: 1.0Hz/div.

LOCK ☐INTERNAL ☐EXTERNAL
LOCK SIGNAL _____
SPIN RATE _____ rps. TEMP _____ °C
INSERT _____ mm

ACQUISITION
SPECTRAL WIDTH (SW) _____ Hz
NO. OF TRANSIENTS (NT) _____
ACQUISITION TIME (AT) _____ sec.
PULSE WIDTH (PW) _____ μsec.
PULSE DELAY (PD) _____ sec
DATA POINTS (DP) _____

TRANSMITTER OFFSET (TO) _____
HIGH FIELD _____ LOW FIELD _____
RECEIVER GAIN (RG) _____

DECOUPLER MODE (DM) _____
DECOUPLER OFFSET (DO) _____
NOISE BANDWIDTH (NB) _____ kHz
ACQUISITION MODE (AM) _____

DISPLAY
SENS. ENHANCEMENT (SE) _____ sec.
WIDTH OF PLOT (WP) _____ Hz
END OF PLOT (EP) _____ Hz
WIDTH OF CHART (WC) _____ Hz
END OF CHART (EC) _____ Hz
VERTICAL SCALE (VS) _____
REFERENCE LINE (RL) _____

varian PRINTED IN U.S.A.

Fig. 42: ^1H NMR spectrum of BD-16 (Plot expansion)

The assignment of the protons H_A and H_B in the spectrum is based on the coupling constants to the ^{31}P nucleus. The P-O-C-H dihedral angle is 180° for the quasi-equatorial proton H_B, and close to 60° for the quasi-axial proton H_A. Thus H_B is assigned to the 5.2 ppm proton ($^3J_{P-O-C-H_B}$ = 25 Hz) and H_A is assigned to the 5.65 ppm proton ($^3J_{P-O-C-H_A}$ = 6.5 Hz). This results in the quasi-equatorial proton having the smaller chemical shift, and the quasi-axial having the larger one, which is contrary to expectations based on aromatic ring current effects. However, the P = S bond also can exert the anisotropic magnetic effects and these might easily reverse the order of the chemical shifts. It is easier to live with this than with a violation of the Karplus-type relationship for spin-couplings which seems generally valid.

Proton H_8 is identified at 7.06 ppm by its 9 Hz coupling constant to proton H_7 at 8.14 ppm. This leaves proton H_5 at 8.0 ppm. Irradiation of H_5 and H_7 resulted in disappearance of the long range couplings which split H_B into quartets and H_A into triplets. Thus, H_B is coupled equally to all three aromatic protons with coupling constants of about 0.7 Hz, while H_A is coupled to two of the three aromatic protons with equal coupling constants of approximately 1.0 Hz. Since the quasi-axial and quasi-equatorial protons H_A and H_B interact differently with the sigma and pi electrons of the aromatic ring system, these differences in coupling are not surprising. In particular, the larger coupling for the quasi-axial proton seems in accord with the idea that

the bonding electron density for H_A is distributed along axes more or less perpendicular to the plane of the aromatic ring and that this allows more overlap with the ring pi-electron system whose maximum probablity function also lies above and below the plane of the ring.

Fig. 27a and Fig. 31a show the proton noise-decoupled ^{13}C spectra of BD-15 and BD-16 at 20.0 MHz. The saturated carbons 2 and 3 bonds from the phosphorus show splitting due to ^{13}C - ^{31}P spin coupling. These couplings are slightly different in BD-15 and BD-16. The coupling to the CH_2 carbon (C_4) in the dioxaphosphorin ring changes only from 5.53 Hz in BD-15 to 5.75 Hz in BD-16. This probably means that the conformation is almost the same, and this is in accord with the small difference in ^{13}C chemical shifts, 66.11 and 65.62 ppm. The change in $\delta(^{13}C)$ is only 0.5 ppm for this carbon (C_4), and since ^{13}C chemical shifts are often quite sensitive to conformation, it supports the similarity of the structures.

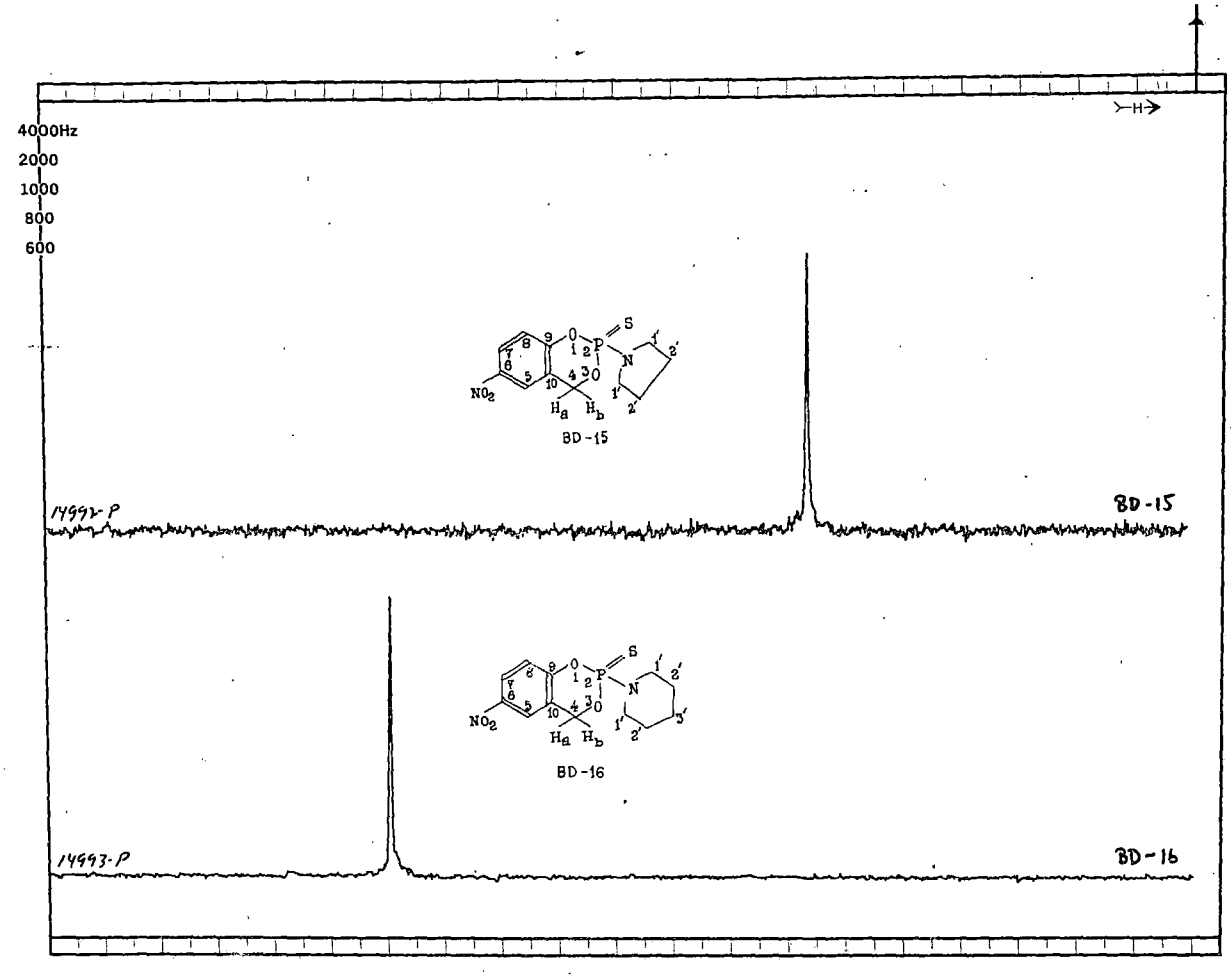
The CH_2's next to the nitrogen are coupled with J -values of 5.83 and 3.67 Hz respectively in BD-15 and BD-16. The CH_2's β to the nitrogen have J -values of 9.87 and 3.63 Hz. These large differences are due to the differences in the P-N-C bond angles for the 5- and 6- membered rings. Fig. 27b and Fig. 31b show the plot expansions of the aliphatic regions of ^{13}C spectrum in BD-15 and BD-16, clearly revealing the doubling of the lines due to the spin of the ^{31}P nucleus.

Fig. 27c is a plot expansion of the aromatic region of the ^{13}C spectrum of BD-15. Four of the ring carbons show measurable coupling to the ^{31}P nucleus. These couplings are:

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

The compound BD-16 shows smaller shifts for the carbons C_9 and C_{10} compared to those in BD-15 which again support a very minor difference in the conformations. Fig. 31b shows that the carbon γ to the ring nitrogen in BD-16 is coupled to the phosphorus with a 1.2 Hz coupling constant.

Fig. 43 is the 32.2 MHz ^1H broad-band decoupled ^{31}P NMR spectra of BD-15 and BD-16. Both compounds gave a sharp ^{31}P resonance line. There is a displacement of 3.63 ppm in the chemical shift for the phosphorus between the two compounds. Selective decoupling (Fig. 44, for BD-16) of the protons adjacent to the nitrogen (arrows) narrowed the otherwise broad line and showed that the ^{31}P is strongly coupled to protons H_A and H_B (attached to C_4). The couplings are reduced in this spectrum because the irradiation at 3.35 ppm partially collapses the couplings to the protons at 5.2 and 5.65 ppm. However, the ratio of the couplings is



14992-P

FT-80A SPECTRUM NO. 14993-P
OPERATOR JMS DATE 2/18/81
NUCLEUS ^{31}P FREQUENCY 32.203
SYNTHESIZER SETTING 29.951
EXPERIMENT NAME
FILE NAME
SAMPLE BD-16 / BD-15

^{31}P

Decoupled

Chemical shift difference is 3.63 ppm.

LOCK ☒ INTERNAL ☐ EXTERNAL
LOCK SIGNAL CDCl3
SPIN RATE 30 rps. TEMP 30 °C
INSERT 5 mm

ACQUISITION
SPECTRAL WIDTH (SW) 1000 Hz
NO. OF TRANSIENTS (NT) 1
ACQUISITION TIME (AT) 4.0 sec.
PULSE WIDTH (PW) 4 μsec.
PULSE DELAY (PD) - sec.
DATA POINTS (DP) 16K

TRANSMITTER OFFSET (TO) 29.951
HIGH FIELD ✓ LOW FIELD
RECEIVER GAIN (RG) 8

DECOUPLER MODE (DM) 1
DECOUPLER OFFSET (DO) 50
NOISE BANDWIDTH (NB) -7 kHz
ACQUISITION MODE (AM) 0

DISPLAY
SENS. ENHANCEMENT (SE) 0.0 sec.
WIDTH OF PLOT (WP) 1000 Hz
END OF PLOT (EP) 0 Hz
WIDTH OF CHART (WC) 1000 Hz
END OF CHART (EC) 0 Hz
VERTICAL SCALE (VS) 100
REFERENCE LINE (RL) —

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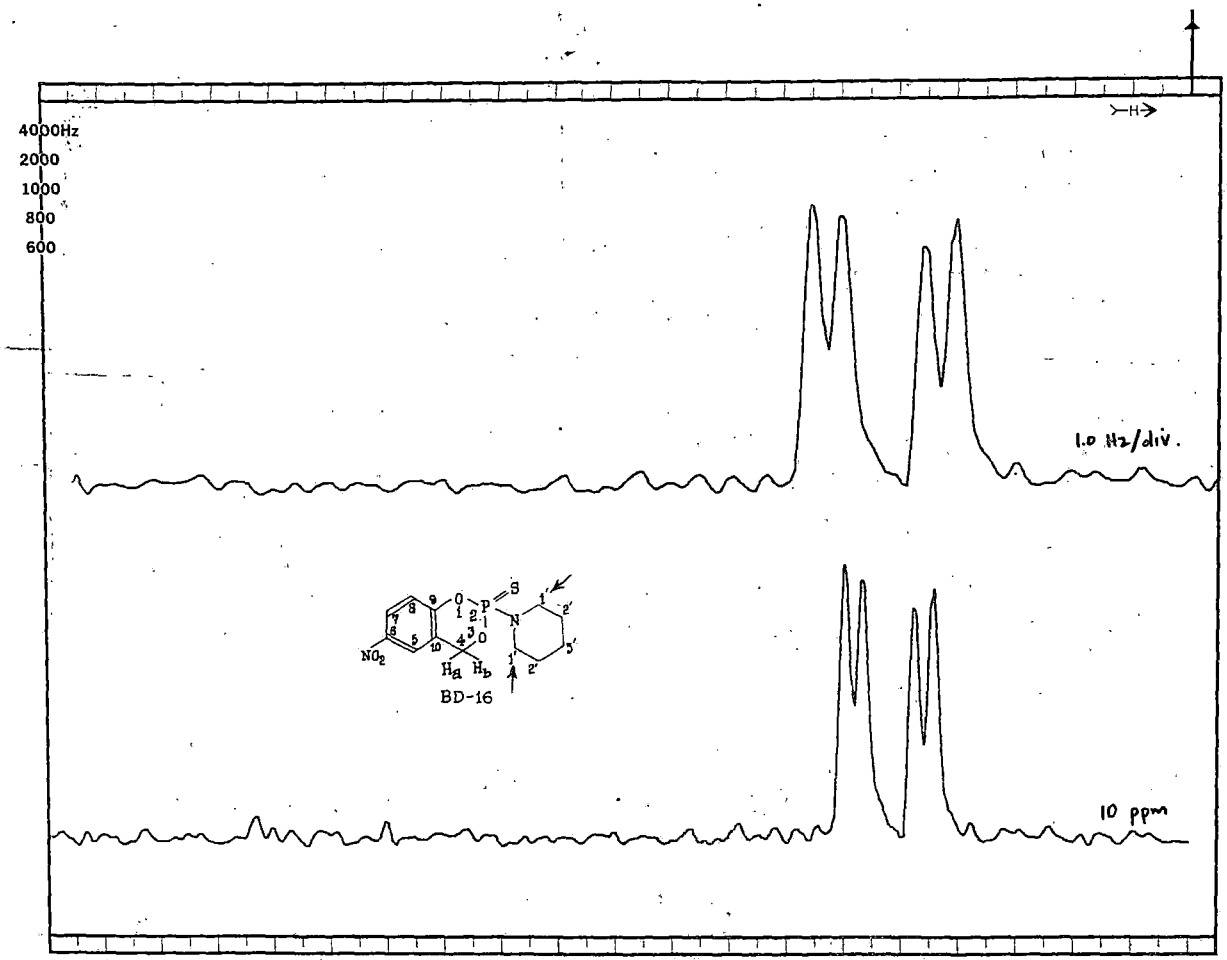
Fig. 43: ^{31}P NMR spectrum of BD-15 and BD-16 (^{1}H broad-band decoupled, chemical shift difference is 3.63 ppm)



FT-80A SPECTRUM NO. 4993-P-1
OPERATOR gms DATE 2/4/81
NUCLEUS ^{31}P FREQUENCY 32.203
SYNTHESIZER SETTING 29.951
EXPERIMENT NAME
FILE NAME
SAMPLE BD-16

^{31}P
Selective decoupling

LOCK ☒ INTERNAL ☐ EXTERNAL
LOCK SIGNAL $CDCl_3$
SPIN RATE 30 rps. TEMP 30 °C
INSERT 5 mm

ACQUISITION
SPECTRAL WIDTH (SW) 1000 Hz
NO. OF TRANSIENTS (NT)
ACQUISITION TIME (AT) sec.
PULSE WIDTH (PW) μsec.
PULSE DELAY (PD) sec.
DATA POINTS (DP)

TRANSMITTER OFFSET (TO) 29.951
HIGH FIELD / LOW FIELD
RECEIVER GAIN (RG) 8

DECOUPLER MODE (DM) 5
DECOUPLER OFFSET (DO) 6 (4280)
NOISE BANDWIDTH (NB) 0 kHz
ACQUISITION MODE (AM) 0

DISPLAY
SENS. ENHANCEMENT (SE) +0.5 sec.
WIDTH OF PLOT (WP) 32K/20K Hz
END OF PLOT (EP) Hz
WIDTH OF CHART (WC) Hz
END OF CHART (EC) Hz
VERTICAL SCALE (VS) 50/50
REFERENCE LINE (RL) —

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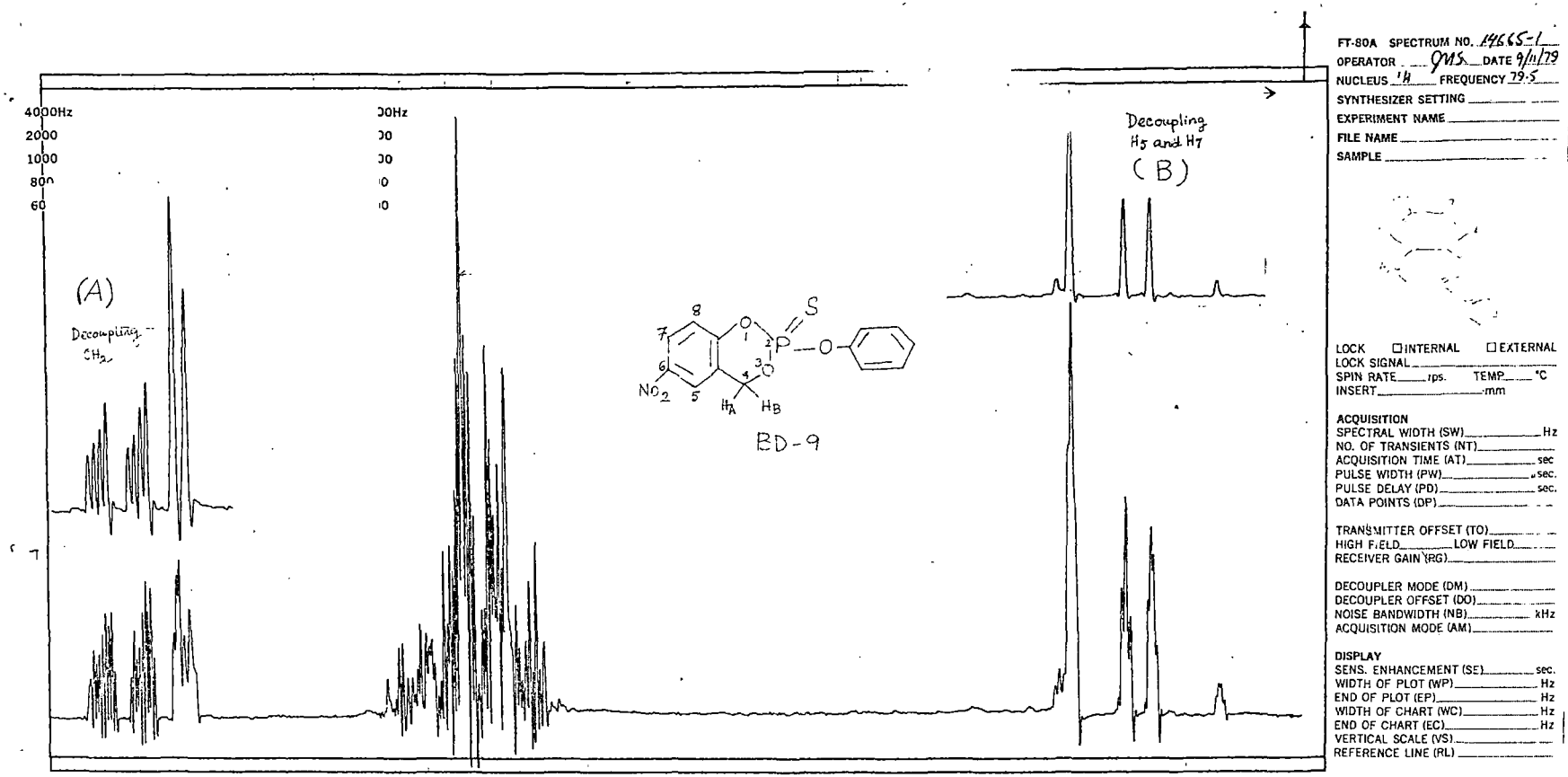
Fig. 44.: ^{31}P NMR spectrum of BD-16 (Selective decoupling)

still the same which is about 4:1. Selective decoupling of the protons for other compounds has not yet been performed.

Fig. 45 is a plot expansion of BD-9 [45(A) is the spectrum of the aromatic protons decoupled with $-CH_2-$ group, 45(B) is the spectral region of $-CH_2-$ group decoupled with H_5 and H_7; this spectrum (Fig. 45) shows that the same coupling patterns prevail in this molecule as found in BD-10, BD-15 and BD-16. The smaller separation of the lines in the CH_2 pattern of BD-9 compared to BD-10 indicates that the quasi-equatorial position of the 2-phenoxy substituent is only slightly favoured over the inverted form.

Fig. 46 shows that BD-8 also displays the long range couplings to the aromatic protons (Fig. 47 shows the CH_2 group and the $O-CH_3$). By irradiating the aromatic protons H_5 and H_7, shown in Fig. 48, the CH_2 group can be seen to be the AB part of the ABX pattern that arises from the CH_2 and the phosphorus. The geminal AB coupling is 14.5 Hz. The couplings $^3J_{P-O-C-H_A}$ and $^3J_{P-O-C-H_B}$ must be quite small. This is consistent with nearly equal populations of the two conformations.

The temperature dependant ^1H NMR spectra at 270 MHz in the temperature range -70^oC to $+50^oC$ (203^oK to 323^oK) of the methoxy compound (BD-8) have been given in Fig. 49 —74 . It is obvious from the charts that as the temperature is varied, the rates of



Scale : 1.0 Hz/division

Fig. 45. Plot expansion of BD-9 [45(A): aromatic protons decoupled with $-CH_2-$ group; 45(B): CH_2 group region decoupled with H_5 and H_7]

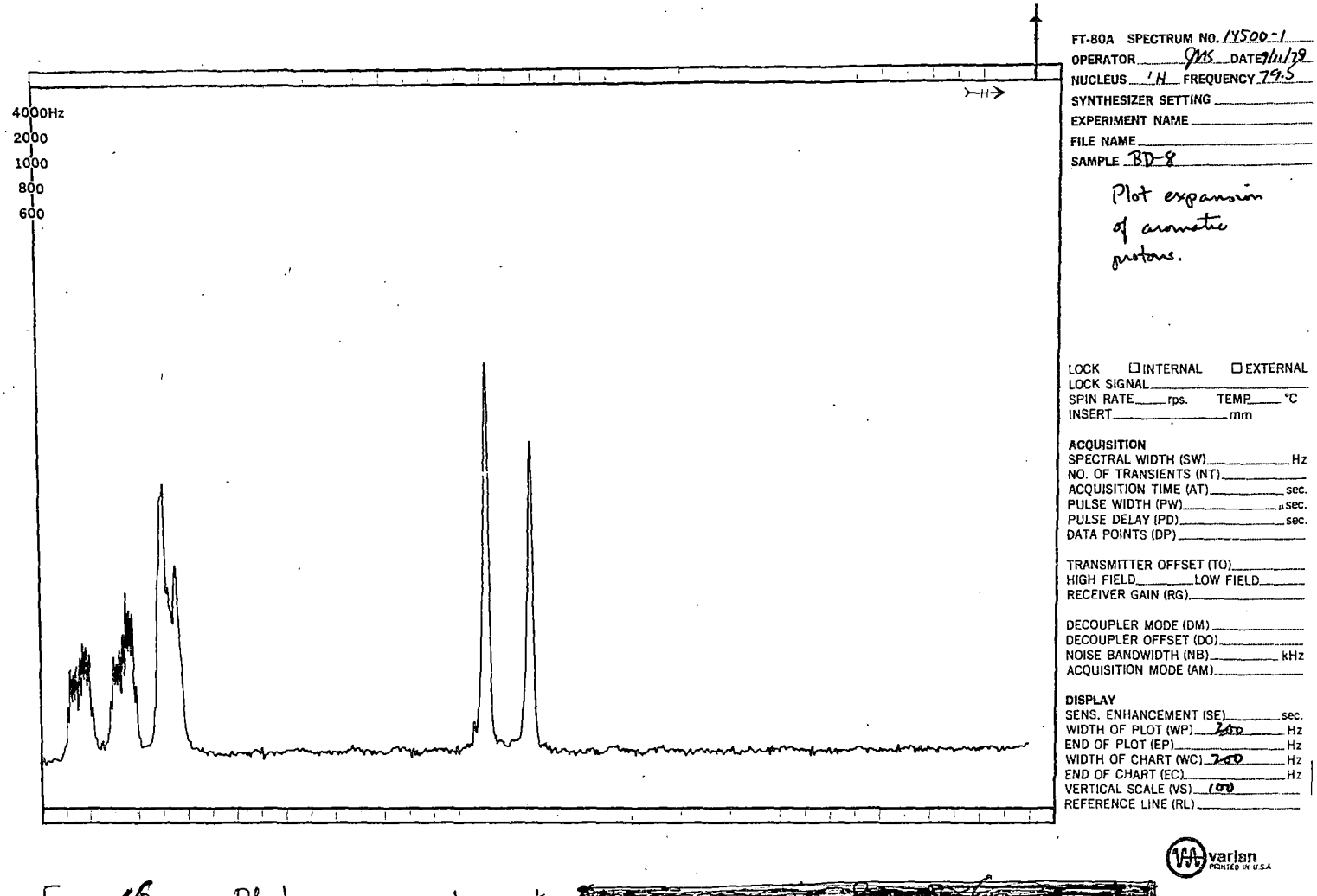
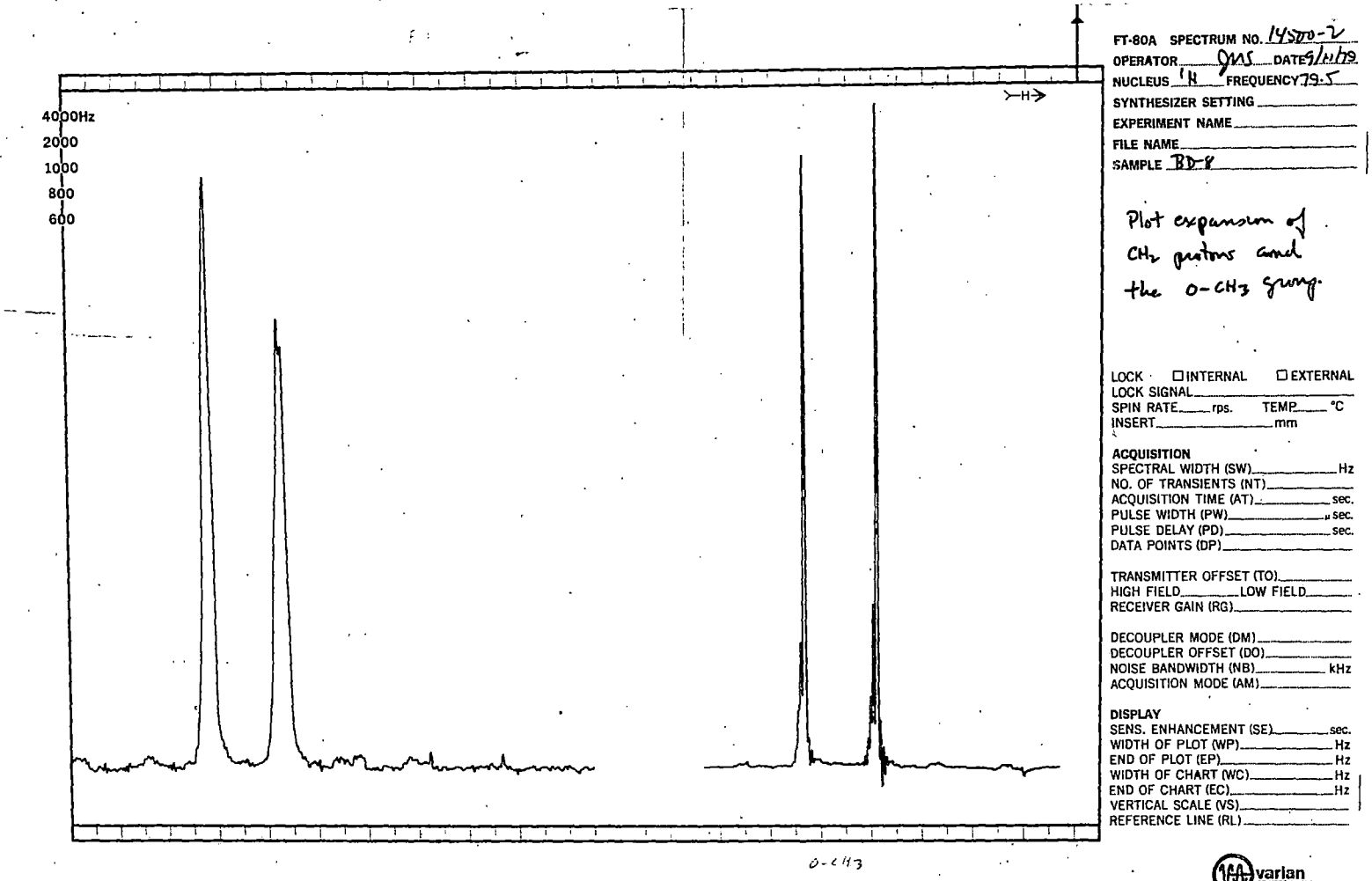


Fig. 48. Plot expansion of aromatic protons in BD-8



FT-80A SPECTRUM NO. 14500-2
OPERATOR GMS DATE 5/11/79
NUCLEUS 1H FREQUENCY 79.5
SYNTHESIZER SETTING
EXPERIMENT NAME
FILE NAME
SAMPLE BD-8

Plot expansion of CH_2 protons and the O-CH_3 group.

LOCK ☐INTERNAL ☐EXTERNAL
LOCK SIGNAL
SPIN RATE rps. TEMP °C
INSERT mm

ACQUISITION
SPECTRAL WIDTH (SW) Hz
NO. OF TRANSIENTS (NT)
ACQUISITION TIME (AT) sec.
PULSE WIDTH (PW) μsec.
PULSE DELAY (PD) sec.
DATA POINTS (DP)

TRANSMITTER OFFSET (TO)
HIGH FIELD LOW FIELD
RECEIVER GAIN (RG)

DECOUPLER MODE (DM)
DECOUPLER OFFSET (DO)
NOISE BANDWIDTH (NB) kHz
ACQUISITION MODE (AM)

DISPLAY
SENS. ENHANCEMENT (SE) sec.
WIDTH OF PLOT (WP) Hz
END OF PLOT (EP) Hz
WIDTH OF CHART (WC) Hz
END OF CHART (EC) Hz
VERTICAL SCALE (VS)
REFERENCE LINE (RL)

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Fig. 47. Plot expansion of CH_2 protons and the O-CH_3 group in BD-8

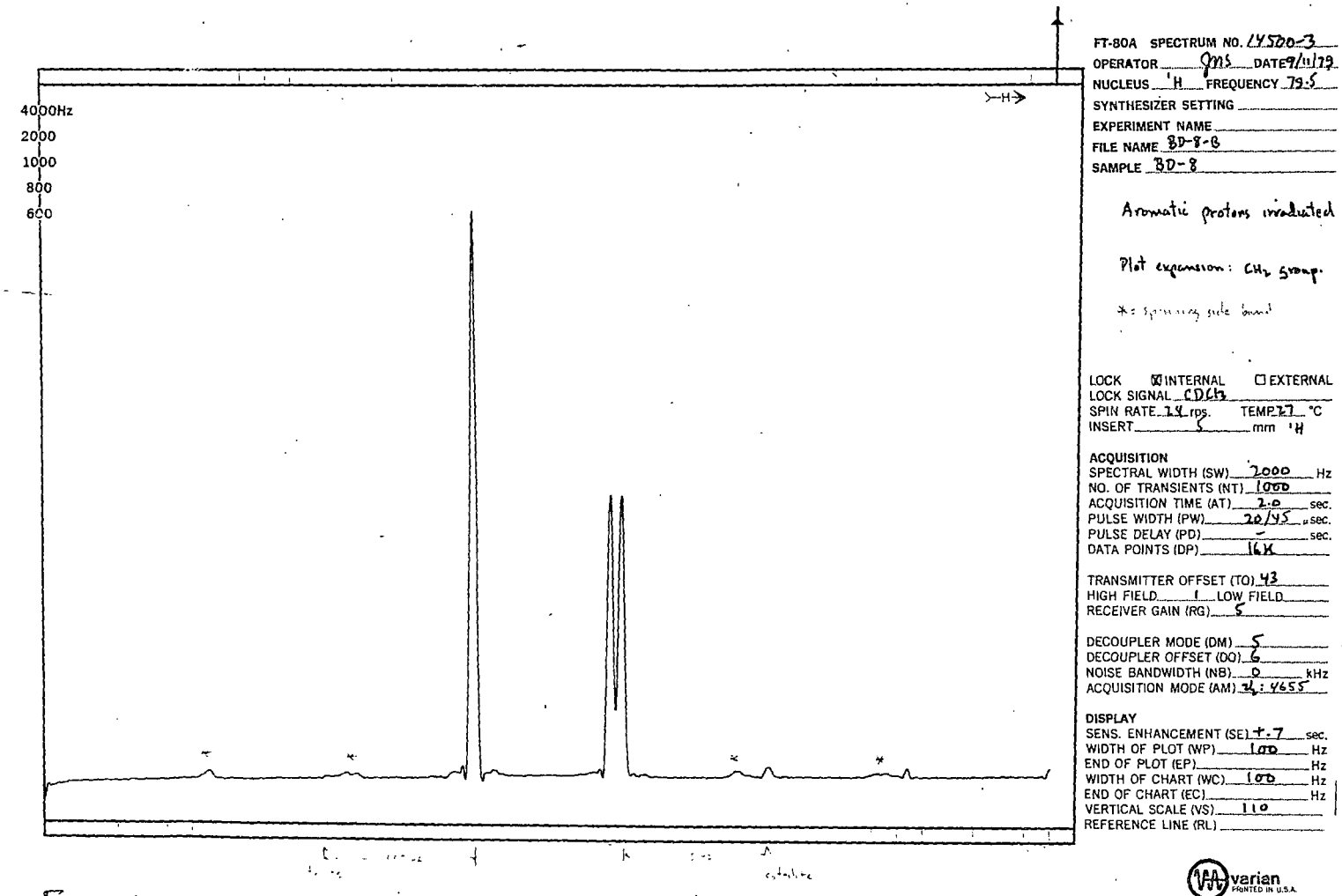


Fig. 48. Plot expansion: CH_2 group in BD-8 (aromatic protons irradiated)

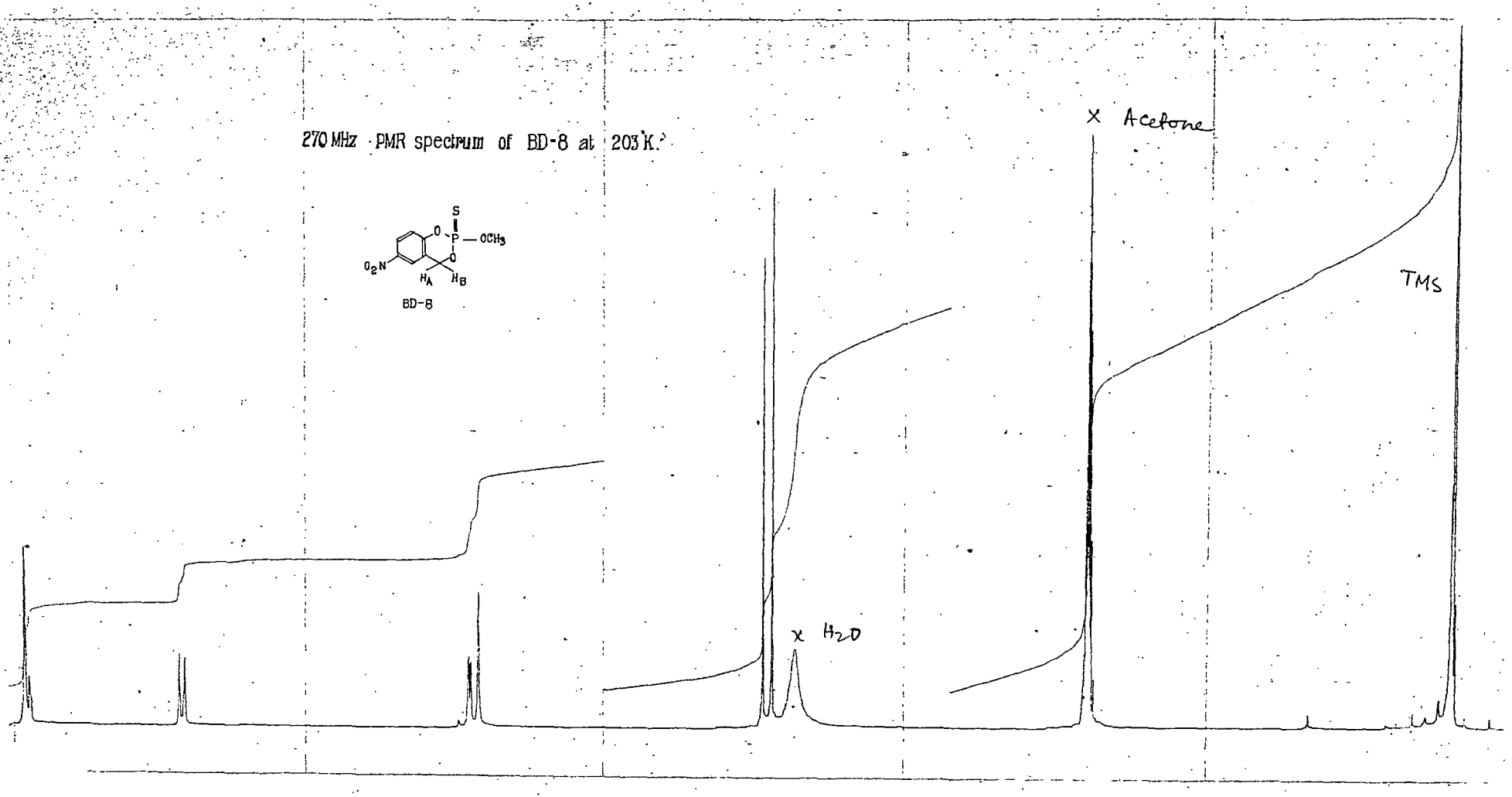
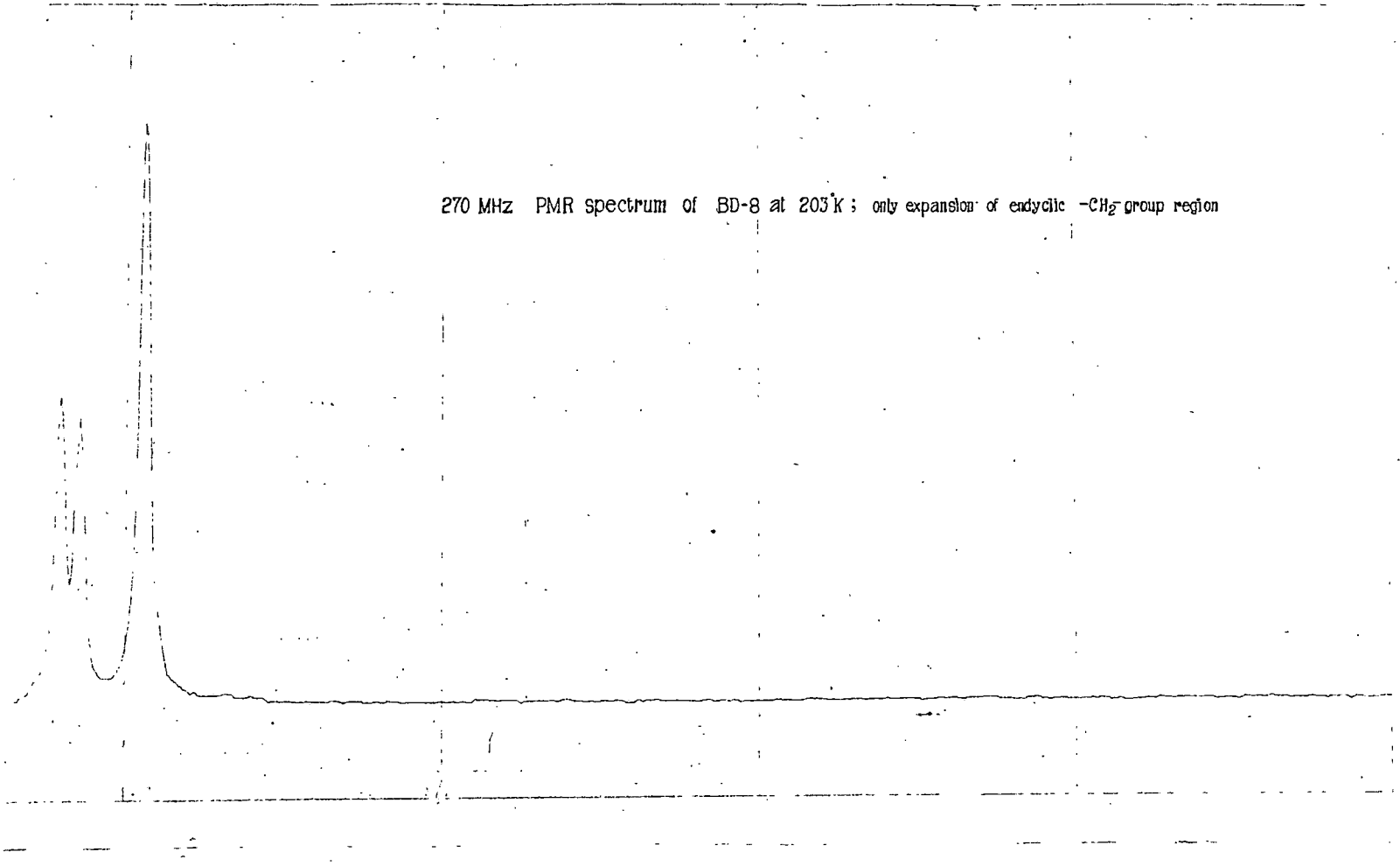

270 MHz PMR spectrum of BD-8 at 203°K.
S
O
P
OCH3
O
O2N
HA
HB
BD-8
x Acetone
TMS
x H2O

Fig- 49



270 MHz PMR spectrum of BD-8 at 203°K ; only expansion of endocic $-CH_2-$ group region

Fig - 50

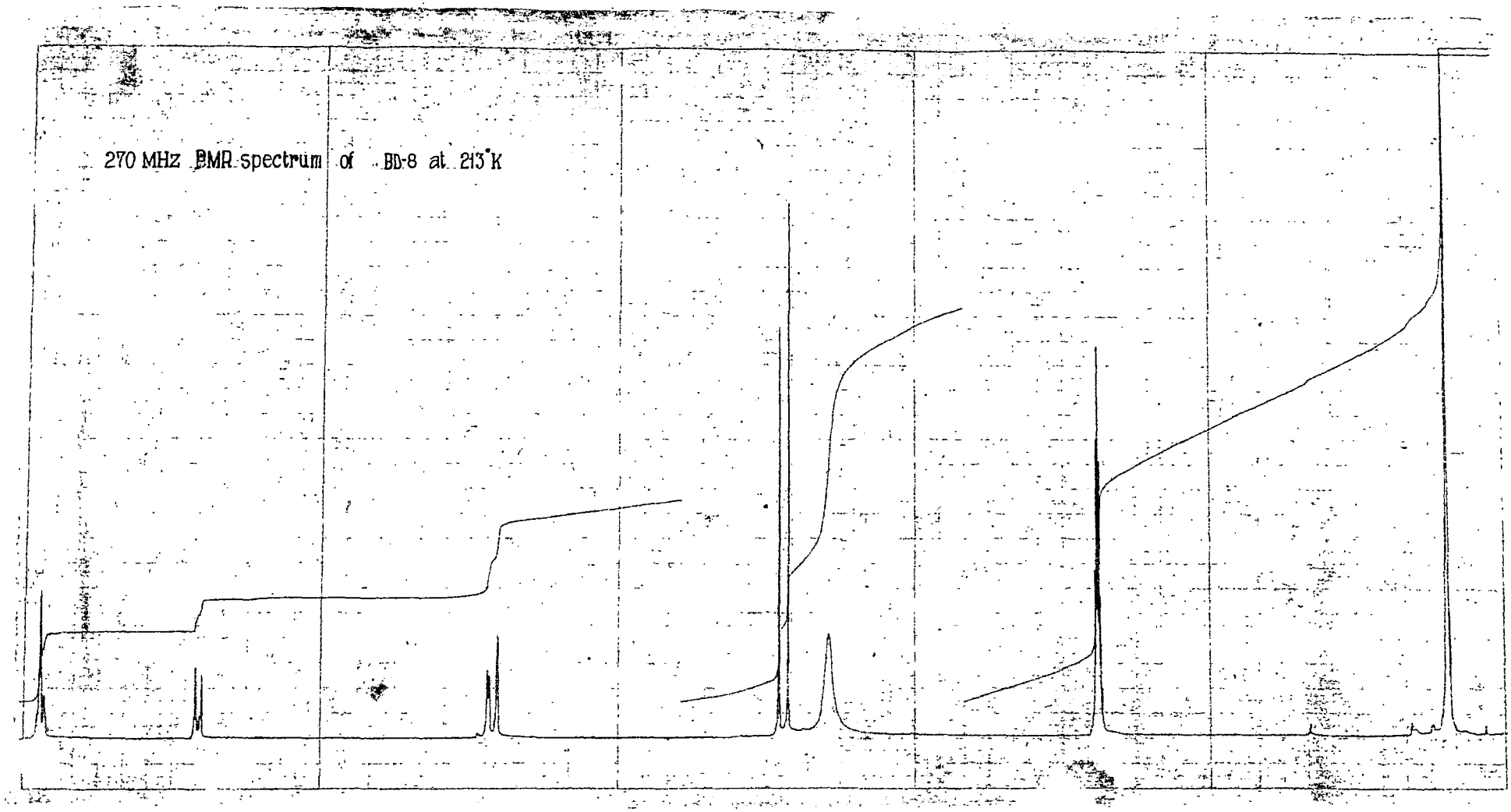


Fig-51

270 MHz PMR spectrum of BD-8 at 213°K ; only expansion of endocyclic $-CH_2-$ group region

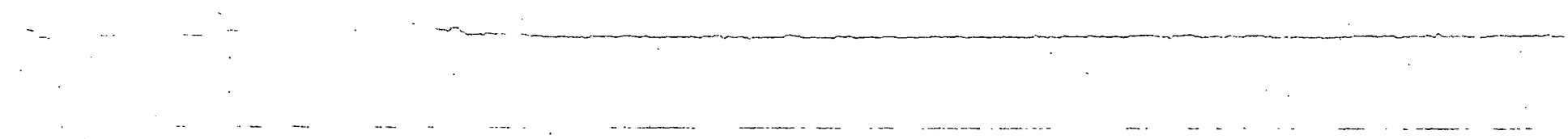


Fig- 52

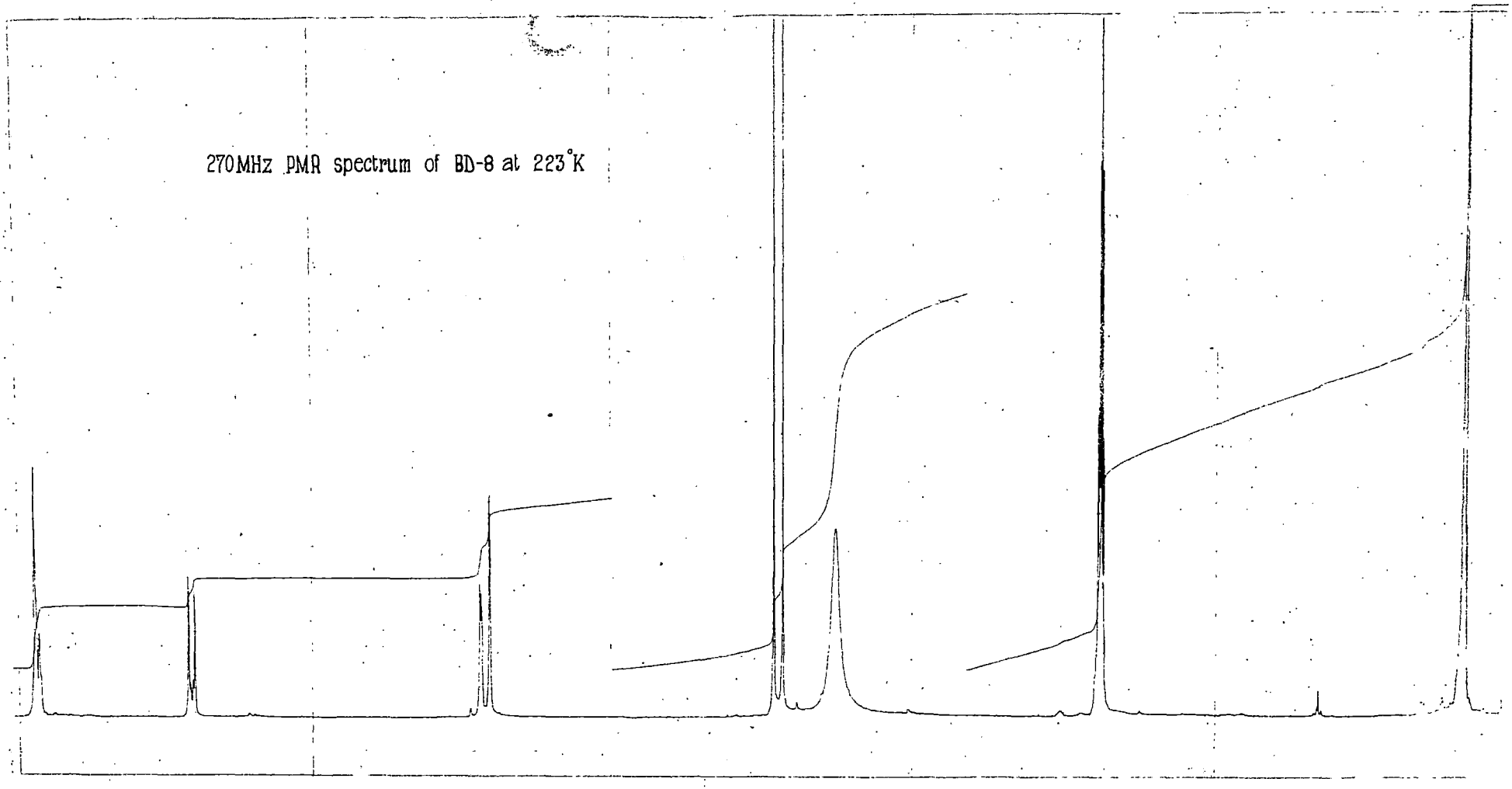


Fig - 53

270 MHz PMR spectrum of BD-8 at 223°K ; only expansion of endocyclic $-CH_2$ group region.

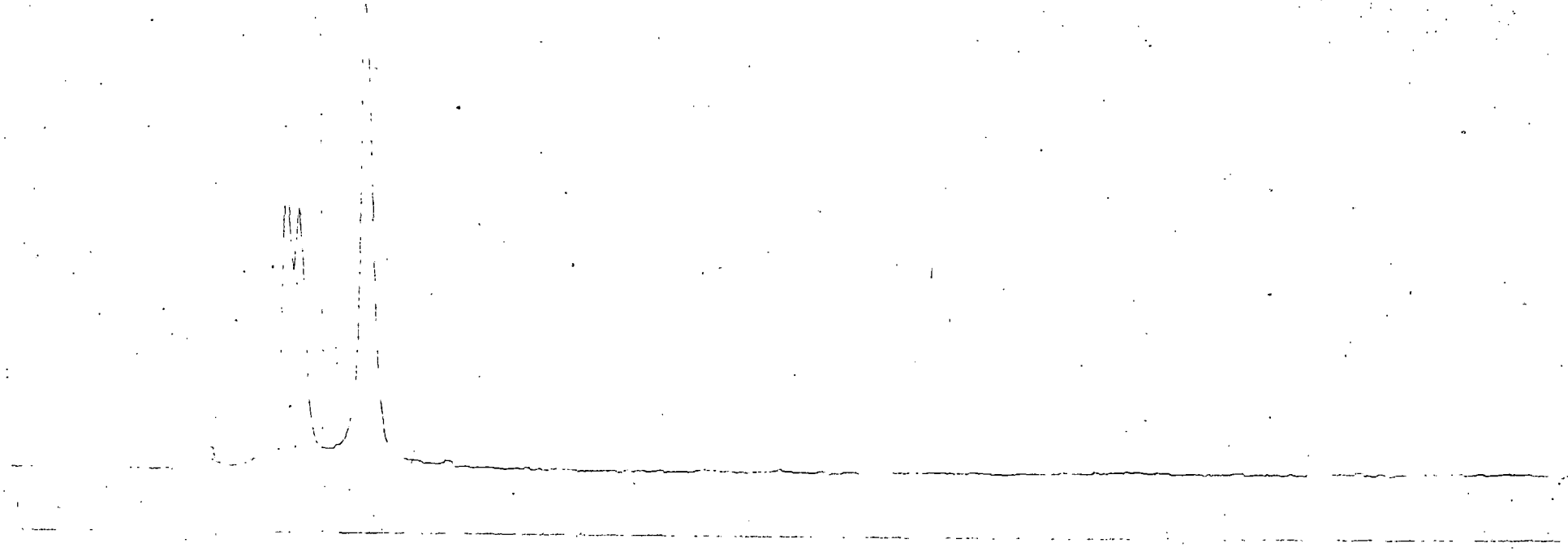


Fig - 54

70 MHz ... spectrum of BD-8 at 233°K.

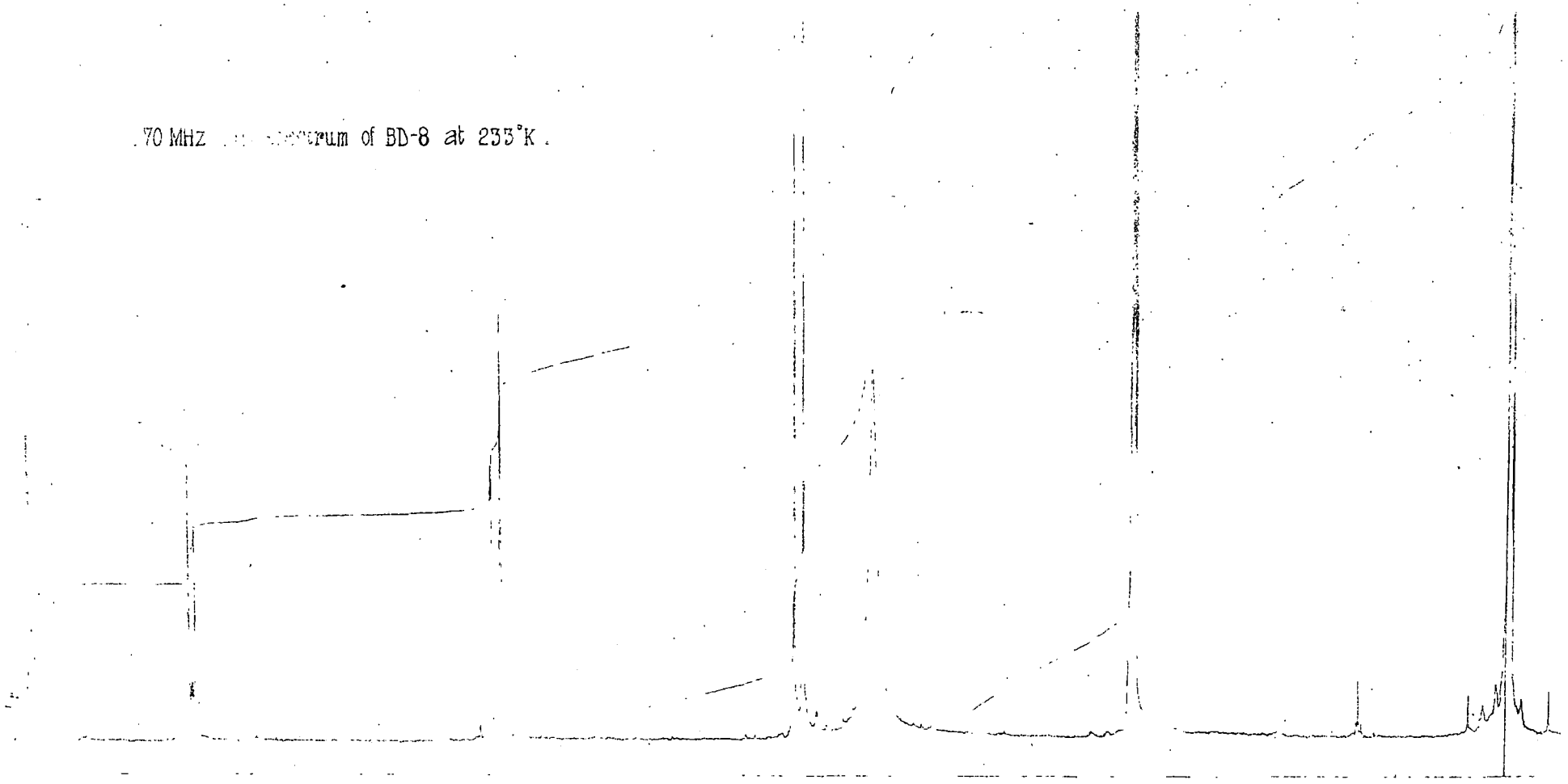


Fig - 55

270 MHz PMR spectrum of BB-8 at 233°K; only expansion of endocyclic $-CH_2-$ group region.

Fig - 56

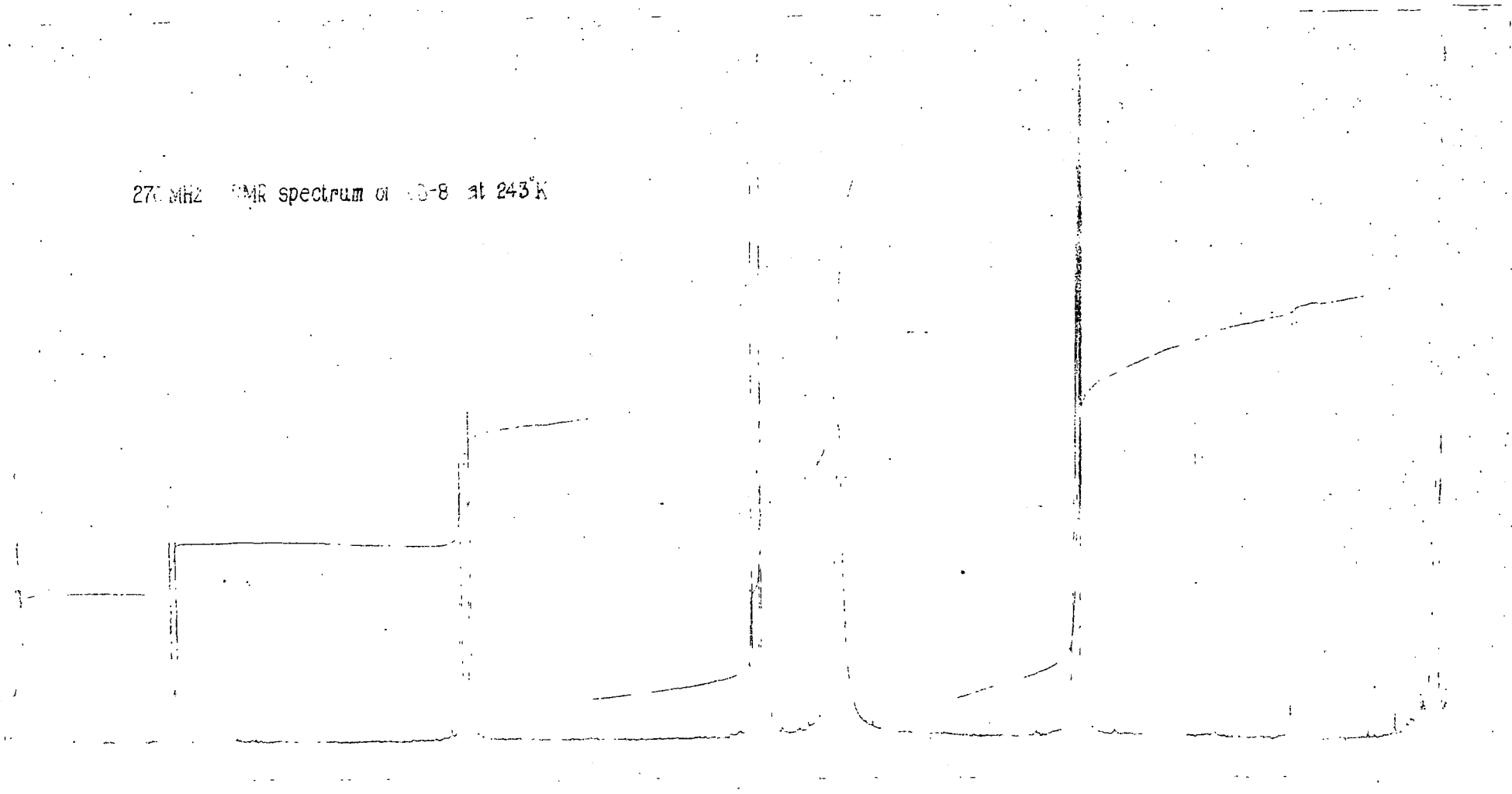


Fig-57

270 MHz PMR spectrum of BD-8 at 245°K ; only expansion of endocyclic $-CH_2-$ group region

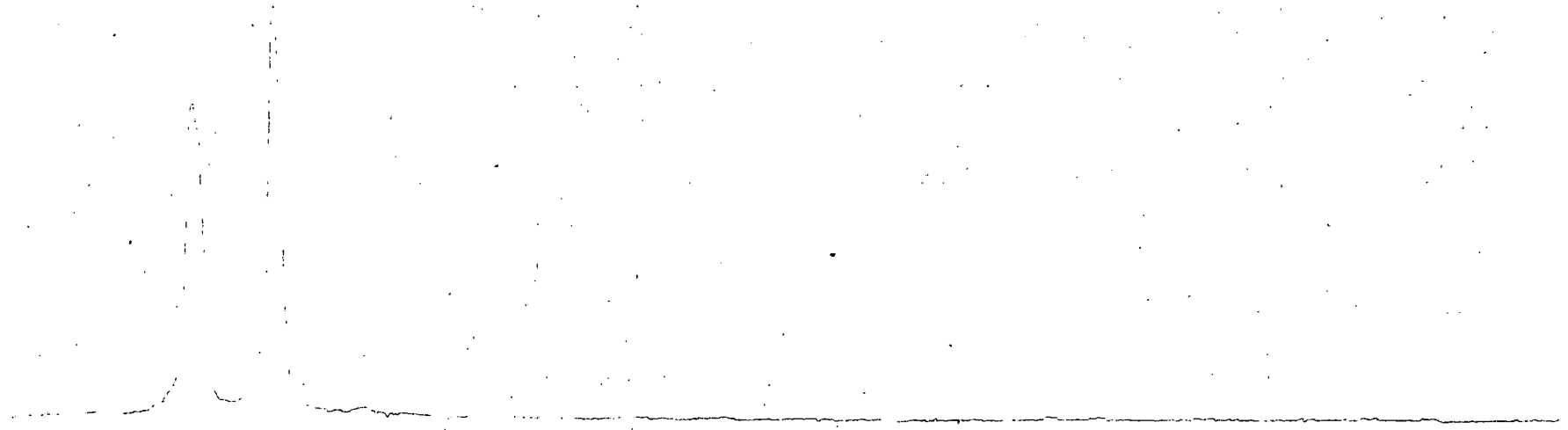


Fig- 58

270 MHz PMR spectrum of BD-8 at 253°K.

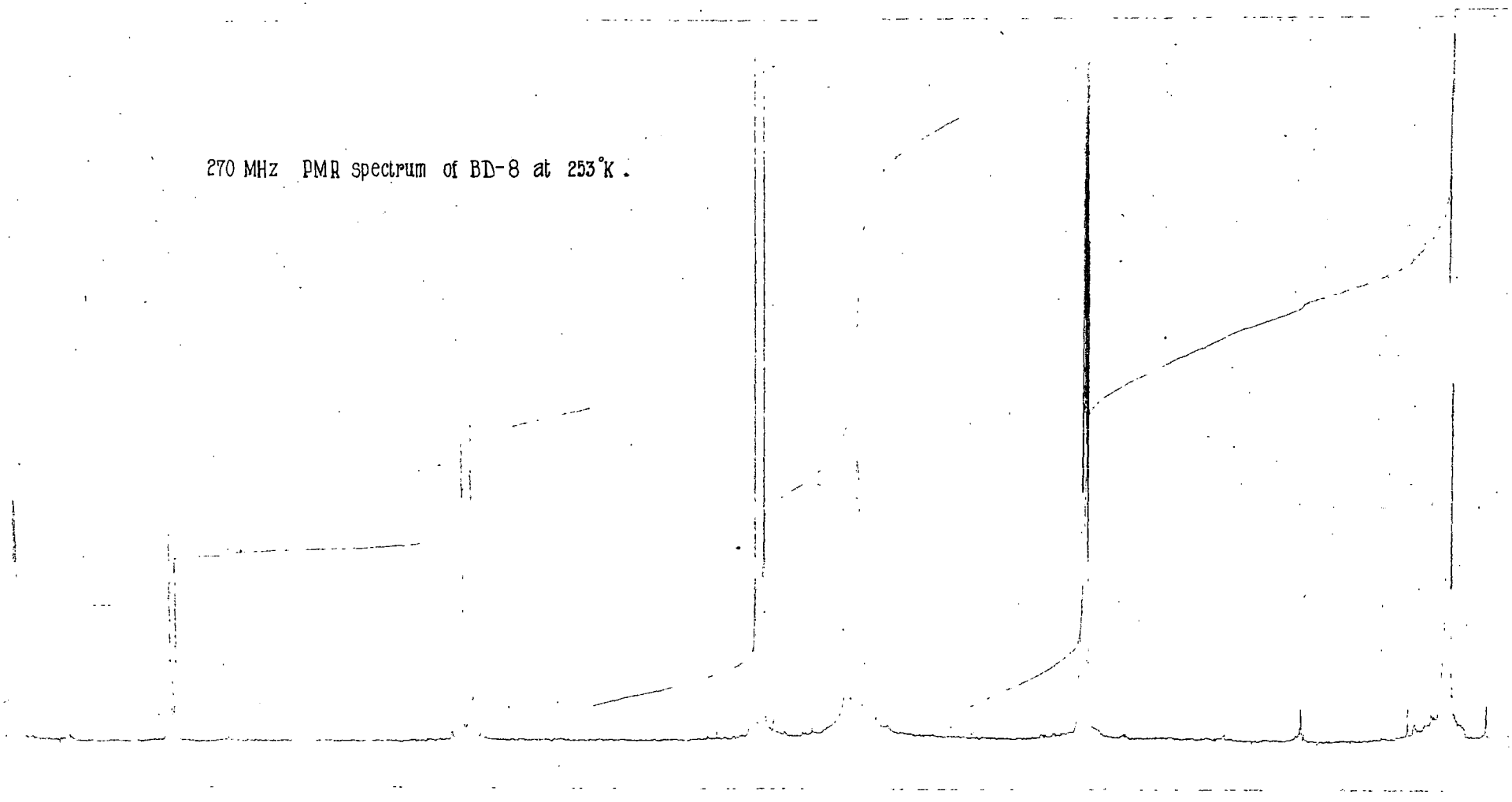


Fig - 59

270 MHz PMR Spectrum of BD-8 at 255°K ; only expansion of endocyclic $-CH_2-$ protons region

Fig- 60

270 MHz PMR Spectrum of BD-8 at 263°K

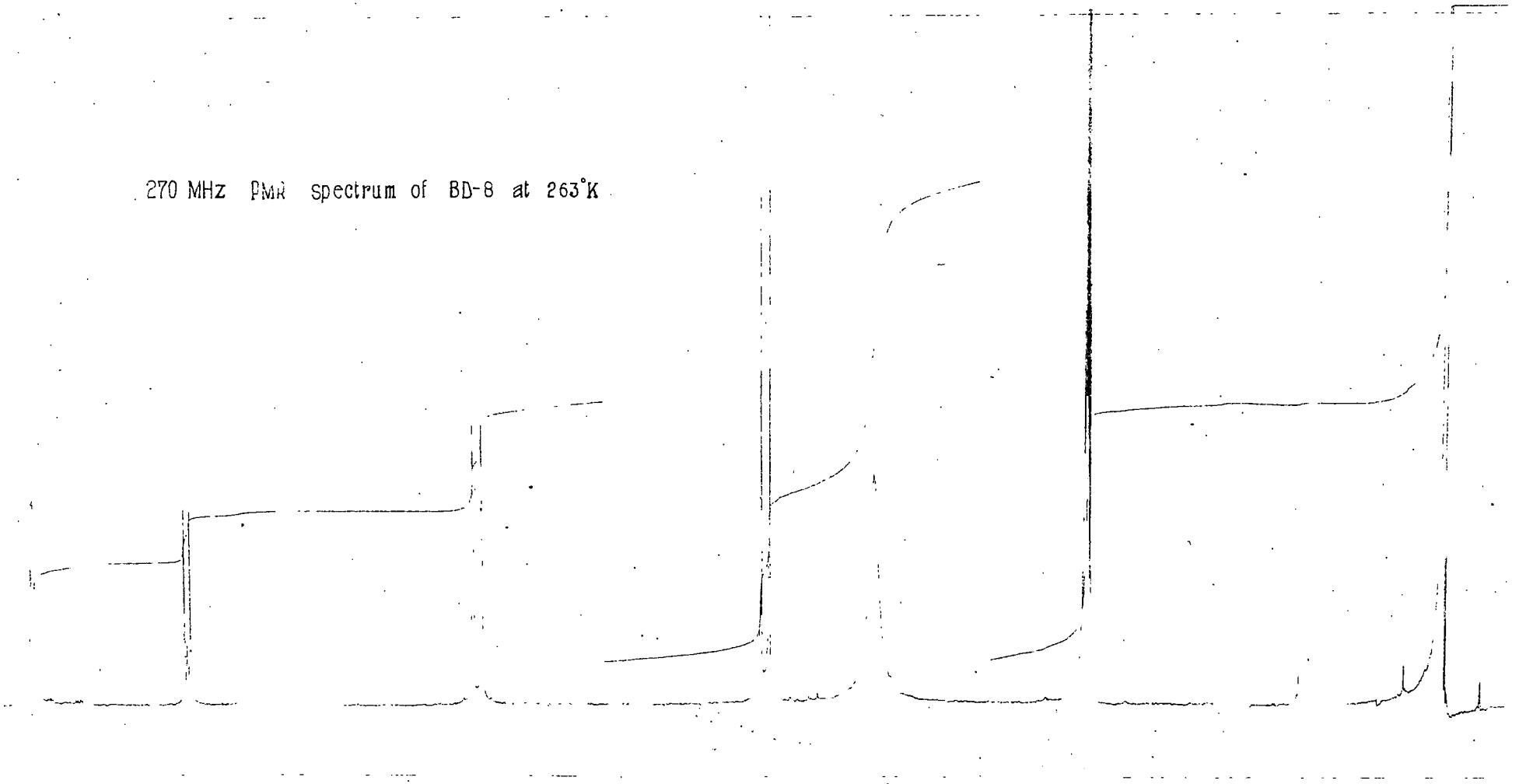


Fig- 61

270 MHz PMR spectrum of BD-8 at 263°K; only expansion of endocyclic $-CH_2-$ group region

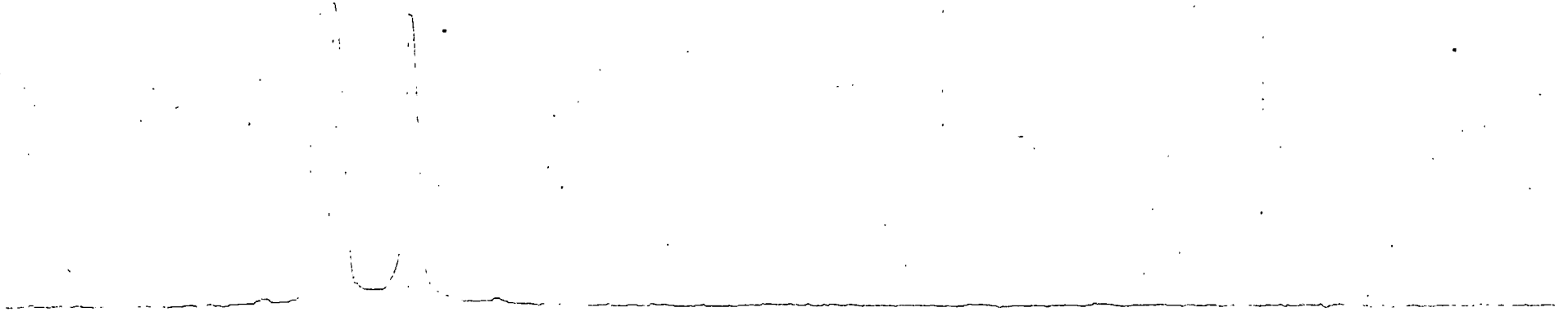
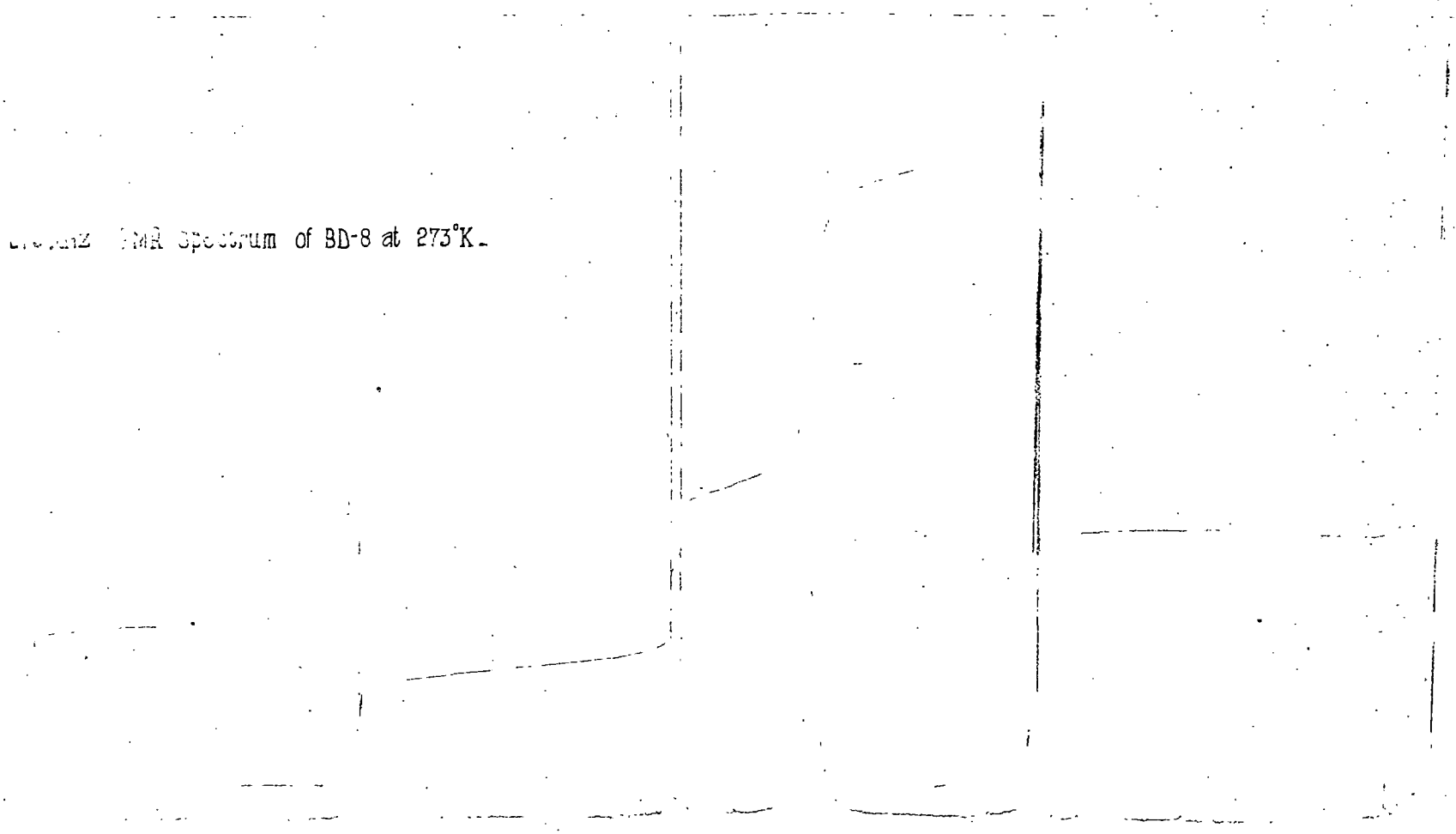


Fig- 62



100 MHz NMR Spectrum of BD-8 at 273°K.

Fig-63

270 MHz PMR spectrum of BD-3 at 273°K; only expansion of endocyclic $-CH_2-$ group region.

Fig- 64

270 MHz PMR spectrum of BD-8 at 283°K

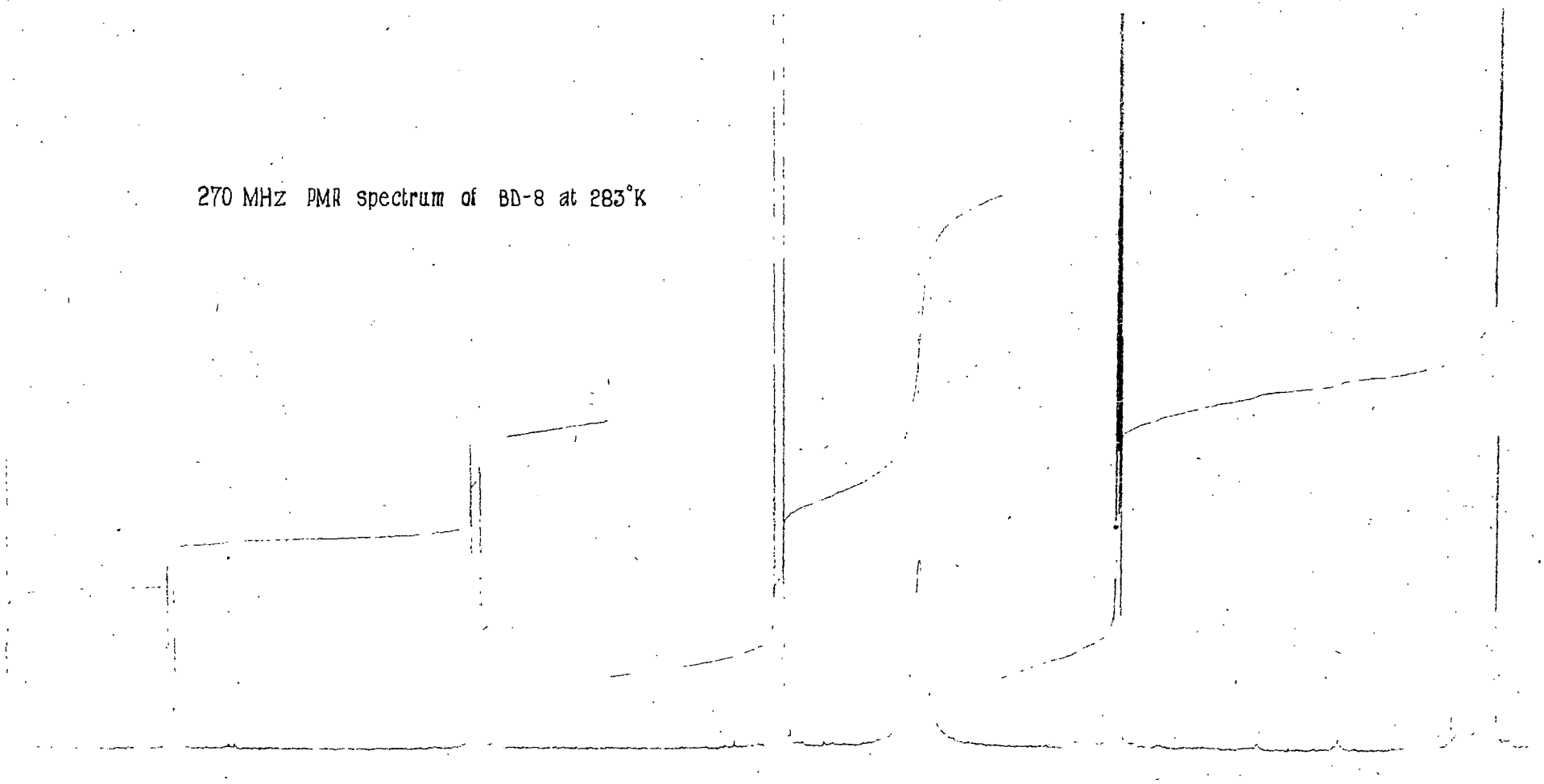


Fig- 65

270 MHz PMR spectrum of BD-8 at 283°K; only expansion of endocyclic $-CH_2$ group region.

Fig- 66

270 MHz PMR spectrum of BD-8 at 293°K

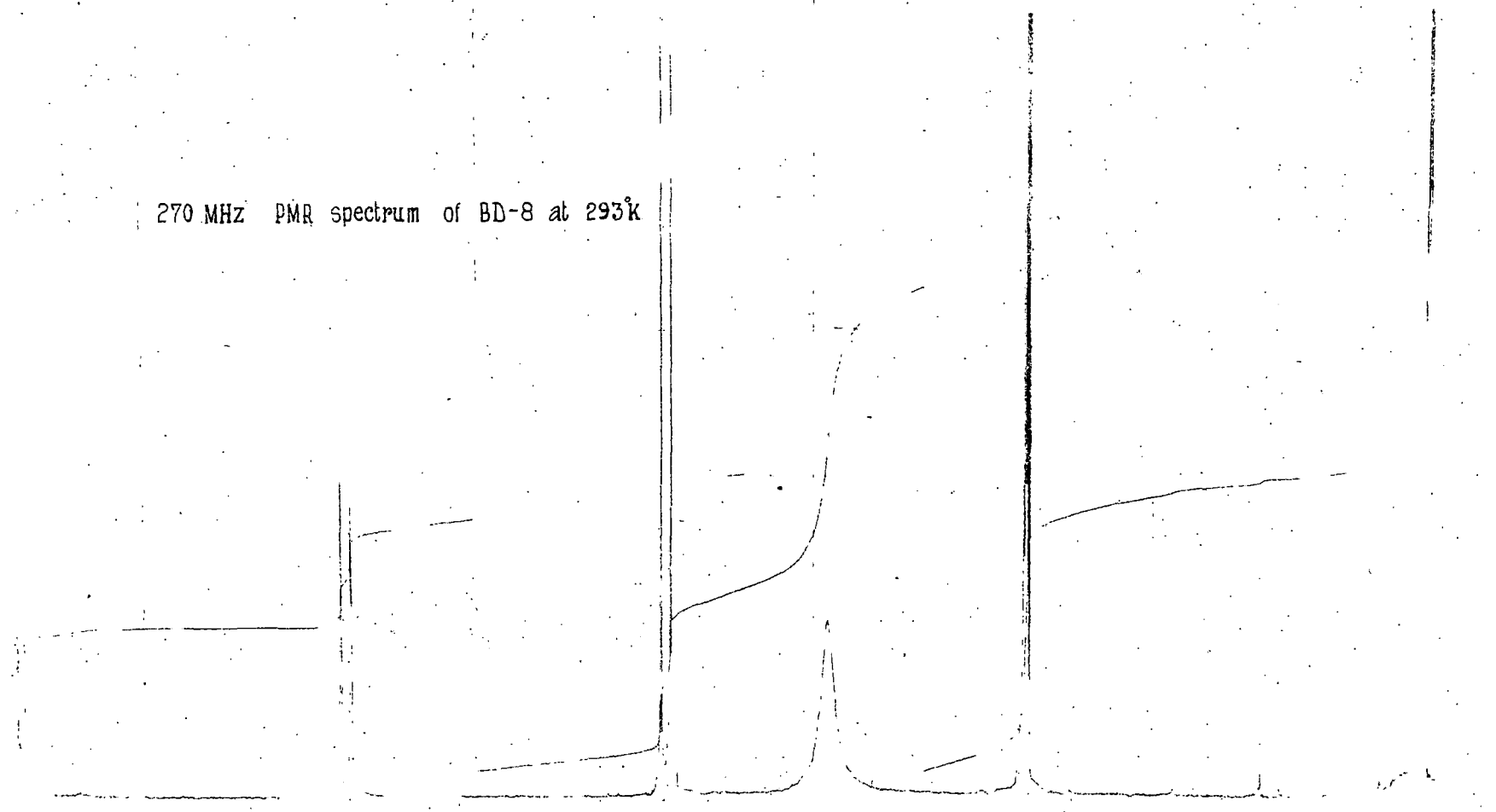


Fig- 67

270 MHz PMR spectrum of BD-8 at 293°K; only expansion of endocyclic $-CH_2-$ group region.

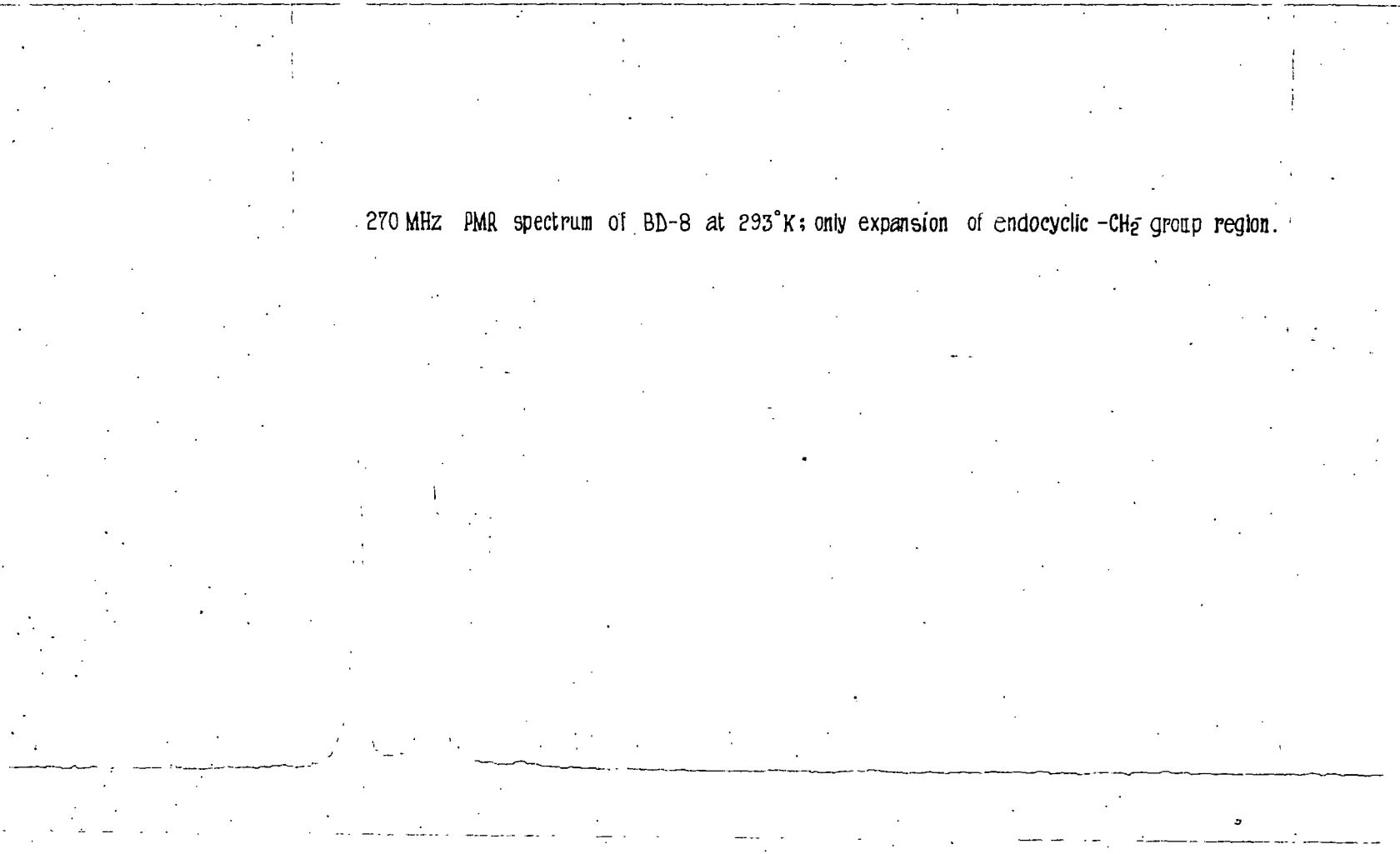


Fig - 68

270 MHz PMR spectrum of BD-8 at 303°K

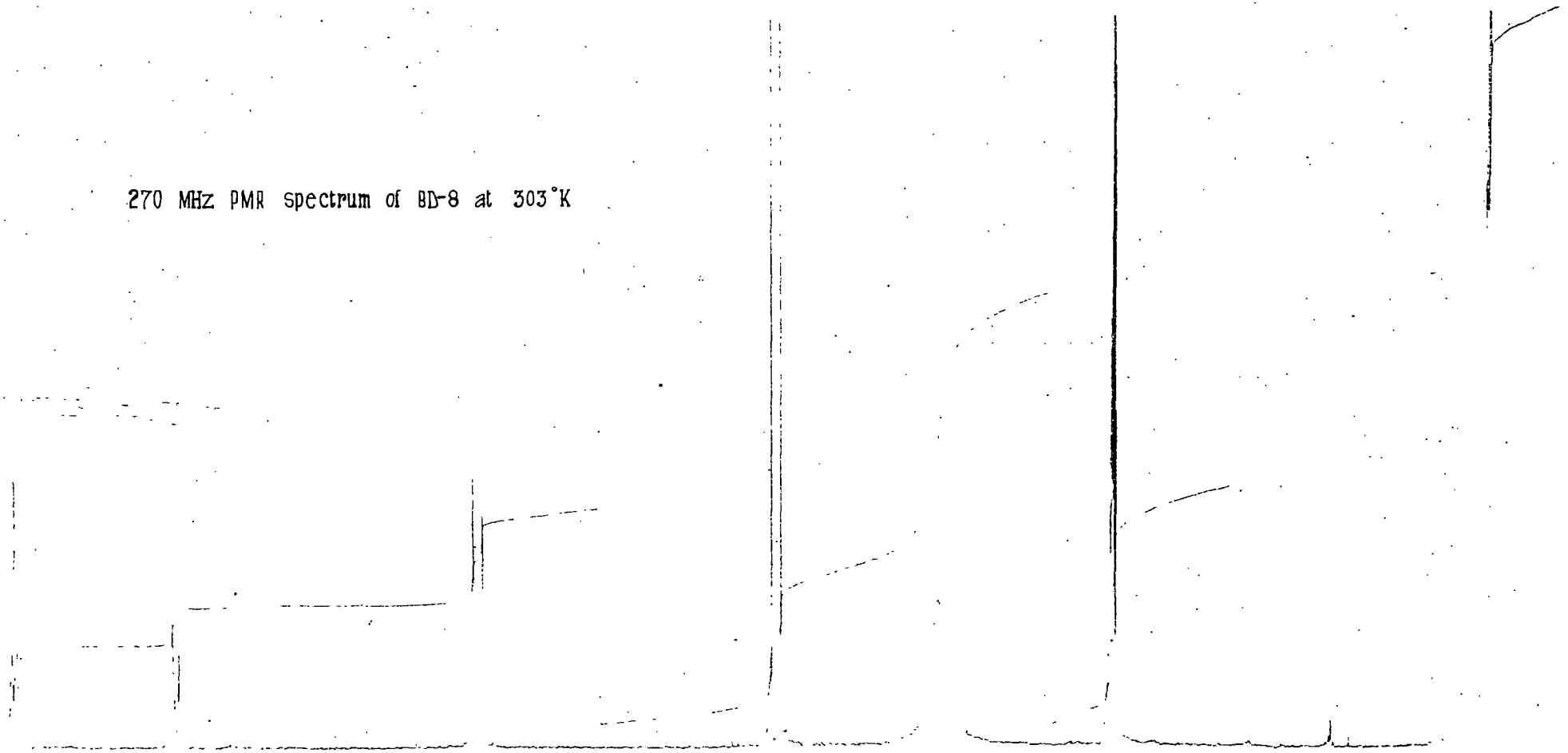


Fig - 69

270 MHz PMR spectrum of BD-8 at 303°K ; Only expansion of endocyclic $-CH_2-$ group region

Fig- 70

270 MHz PMR spectrum of [illegible]-B at 313°K

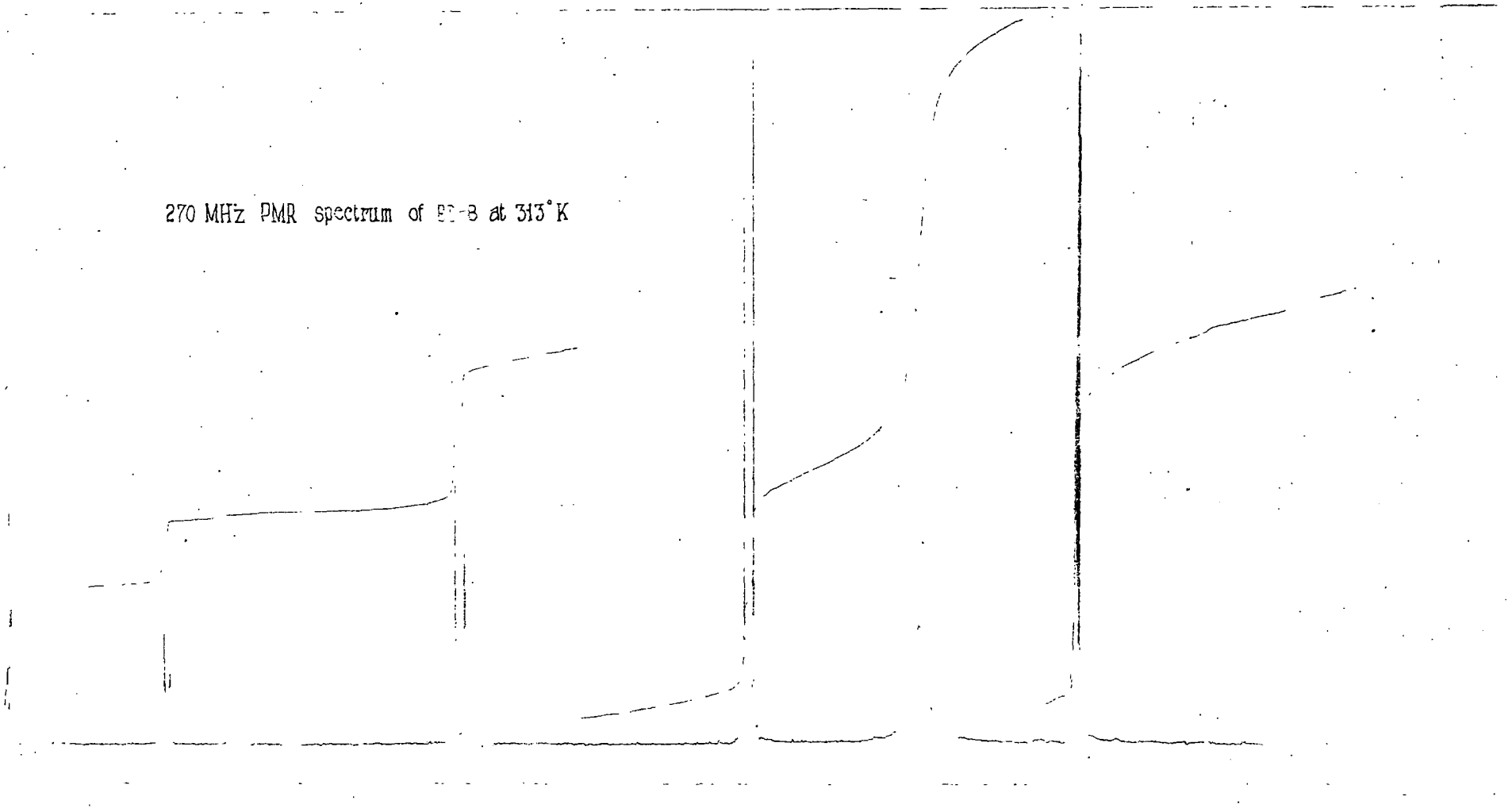


Fig- 71

270 MHz PMR spectrum of sD-8 at 313°K; only expansion of endocyclic $-CH_2-$ group region

Fig- 72

270 MHz PMR spectrum of BD-8 at 323°K.

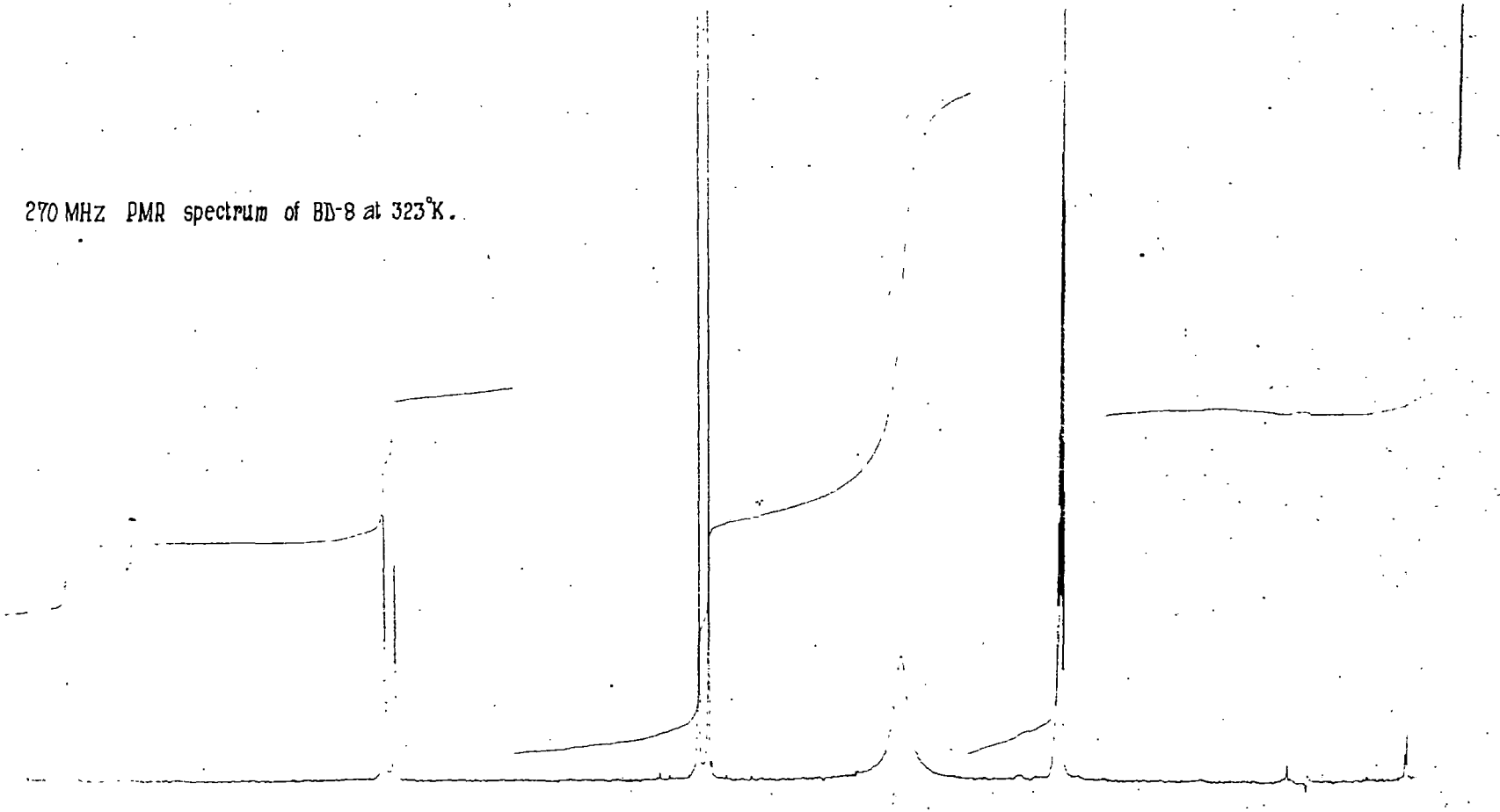


Fig- 73

270 MHz PMR spectrum of BD-8 at $323\,^{\circ}K$; only expansion of endocyclic $-CH_2-$ group region.

Fig- 74

interconversions of the conformers and their relative populations are also varied. It has also been observed that the signal at lower field of the doublet at 5.8 ppm splits further. This becomes much significant at -40°C (233°K); further splitting is observed at -70°C (203°K). This suggests that the methylene protons (H_{4A} & H_{4B}) are not equivalent to each other, and the dioxaphosphorin ring is conformationally mobile in solution.

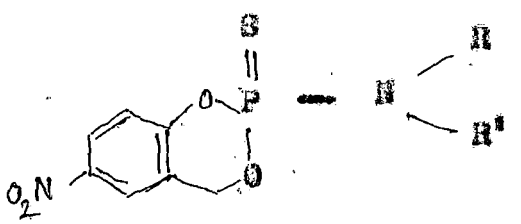
The ^{1}H NMR spectra of BD-10, and the ^{13}C, ^{31}P and ^{1}H NMR spectra of BD-15 and BD-16 seem to be in general accord with the structure II although they do not preclude another conformation (i.e., its inverted form, where oxygen and phosphorus lie below the plane of the aromatic ring). Further studies including X-ray crystal structure determination are in progress. However, it may be pointed out that the structure II appears to explain, to a reasonable extent, the reversal of the expected proton chemical shift order for the quasi-axial and quasi-equatorial protons, due to the position of the magnetically anisotropic P = S bond relative to the $-CH_2-$ group in the dioxaphosphorin ring.

7. INSECTICIDAL ACTIVITY:

The oral insecticidal activity data of the compounds against Cockroaches, P. americana (Linn), are listed in Table-1, and the results have been compared with that of salithion and the 2-methoxy-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide (BD-8).

Table - 1

Insecticidal activity against Cockroaches, P. americana



Amido group	Code No.	Conc. showing 100% mortality (LC_{100}) (µg/gm)
Cyclohexylamido	BD-10	50 - 60
Morpholino	BD-11	30 - 40
Diethylamido	BD-12	30 - 40
Dimethylamido	BD-13	15 - 20
Iso-propylamido	BD-14	60 - 75
Pyrrolidino	BD-15	>75
Piperidino	BD-16	>75
Nonylamido	BD-17	>75
S P — OCH_3 O	BD-8	3 - 9
Salithion	-	8 - 13

The data presented in Table-I reveal that all alkylamidophosphorothionates have less oral insecticidal activity than the methoxy compound (BD-8) and salithion; BD-8 has greater insecticidal activity than salithion. Dimethylamido compound has only 1.5 to 2 times less insecticidal activity compared to salithion; morpholino and diethylamido compounds show 3 to 4 times less insecticidal activity compared to salithion. The other compounds are almost noninsecticidal. In whole series of nitro saligenin cyclic alkyl/phenyl/amido phosphorothionates prepared in our laboratory, only the methoxy compound (BD-8) has greater insecticidal activity than salithion. The dimethylamido compound has 2 times greater insecticidal activity compared to diethylamido compound. Eto et al [14] observed the same in case of 2-dimethylamido —, and 2-diethylamido-4H-1,3,2-benzodioxaphosphorin-2-sulphides. Among the alkylamidophosphorothionates (BD-10 - BD-17) the dimethylamido compound has highest oral insecticidal activity to roaches.

8. ANTIFUNGAL ACTIVITY:

Table-2 shows the antifungal activity data of these compounds (BD-10 - BD-16) against Helminthosporium Sp. ; the data for Hinosan (O - ethyl S,S - diphenyl-phosphorodithionate) have also been presented.

Table - 2

Antifungal activity of the alkylamidophosphorothionates against H. Sp.

Code No	Percent inhibition over control after 48 hours Concentration in µg/ml					
	500	250	200	150	100	50
BD - 10	100.0	70.3	63.5	59.5	46.0	33.0
BD - 11	83.3	76.7	74.2	70.0	65.0	54.9
BD - 12	100.0	74.0	64.7	53.5	42.2	22.0
BD - 13	90.9	73.0	69.7	59.5	51.5	34.8
BD - 14	100.0	100.0	100.0	90.0	74.0	64.8
BD - 15	84.0	72.0	68.0	62.0	54.0	42.0
BD - 16	100.0	79.4	73.5	65.0	54.4	41.2
Kinosan	100.0	96.7	90.3	82.2	65.3	51.0

The results reveal that all these compounds show inhibitory effect on the growth of Helminthosporium. sp. Complete inhibition of the growth is observed in case of BD-10, BD-12, BD-14 and BD-16 (at 500 μg/ml); however, other compounds are also effective at higher concentrations. The isopropylamidophosphorothionate (BD-14) is the most effective compound; its inhibitory effect is greater than that of Hinosan. At the concentration 60 μg/ml Hinosan shows 51.0 percent growth inhibition but BD-14 shows 64.8 percent inhibition. Only the compound BD-14 shows complete inhibition at the concentration 300 μg/ml, while other compounds show inhibition within the range 60 to 75 percent at the same concentration. Although BD-12 shows 100 percent inhibition at 500 μg/ml, but at 50 μg/ml it shows only 22.0 percent inhibition.

9. PHYTOTOXIC PROPERTIES:

The phytotoxicity data against Triticum Spp. (U.P. 302 variety) for the alkylamidophosphorothionates (BD-10 to BD-16) are listed in Table -3.

The effects of nitro-saligenin cyclic alkylamidophosphorothionates on germination of wheat seed (Triticum Spp.)

Code No	Percent germination at different Conc.		
	500 ppm	250 ppm	100 ppm
BD - 10	90	100	100
BD - 11	90	100	100
BD - 12	100	100	100
BD - 13	100	100	100
BD - 14	100	100	100
BD - 15	100	100	100
BD - 16	100	100	100

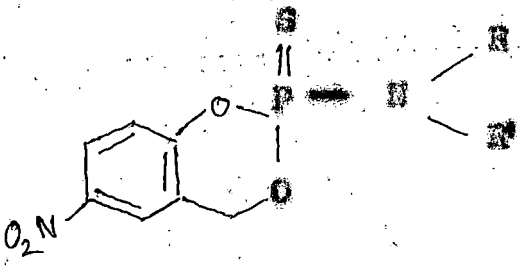
At 250 ppm and 100 ppm none of the compounds are phytotoxic to Triticum Spp. at 500 ppm BD-10 and BD-11 show slight phytotoxicity while other compounds are non-phytotoxic. In the case of BD-10 and BD-11 we observe 90 percent germination at 500 ppm.

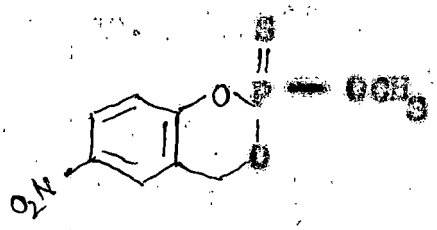
10. ACUTE ORAL TOXICITY ON RATS:

The acute oral toxicity data (LD_{50}) of the said alkylamidophosphorothionates on male rats are presented in table-4, and the results have been compared with salition and with the methoxy compound (BD-8).

Table - 4

Acute Oral toxicity on rats of the allylamidophosphorothionates



Amido group	Code No	LD_{50} (mg/kg) male rat
Cyclohexylamido	BD - 10	> 250
Morpholino	BD - 11	> 250
Diethylamido	BD - 12	150 - 250
Dimethylamido	BD - 13	125 - 250
Isopropylamido	BD - 14	> 250
	BD - 8	130 - 135
Sulithion	-	82

All compounds (BD-10 to BD-14) are less toxic than salithion. BD-12, BD-13 and BD-8 have greater toxicity to rats compared to other ketto saligenin cyclic phosphoramidothionates. Before death the rats were found to suffer from acute respiratory trouble. In some cases, a fluid with blood-stain oozed out of nostrils and eyes of the animals. In all cases, the decrease of spontaneous motor activity occurred after 2-4 hours. Salivation and irregular respiration were observed. In case of morpholino compound the colour of the rats became yellow after 20-30 hours; the yellow colour disappeared after 3-5 days. No other compounds showed this symptom.

The LD_{50} values given here are only after preliminary experiment and this requires further work for acurate LD_{50} value determination. However, the LD_{50} values given are appreciably fair to enable one to judge the relative toxicity of the compounds to male white albino rats.

11. ANTICHOLINESTERASE ACTIVITY:

The acetylcholinesterase inhibition data for housefly-head homogenate (HFAChE) and goat whole blood (blood - ChE) are listed in Table-5A - 5E (pp 187-191) and Table - 6A - 6E (pp 192-196) respectively; the molar I_{50} values calculated by least square programme are given below (Table-5). The data for only five compounds have so far been taken.

Table - 5

Anticholinesterase activity on housefly head homogenate and goat whole blood.

Code No.	Amido Group	I_{50}(M) x 10^5 (HFAChE) housefly	I_{50}(M) x 10^4 (ChE) goat whole blood
1	2	3	4
BD - 10	Cyclohexyl amido	2.86	1.81
BD - 11	Morpholino	5.43	1.04
BD - 12	Diethylamido	8.26	1.43
BD - 13	Dimethylamido	1.80	4.66
BD - 14	Isopropylamido	1.86	4.78

It has been observed that for any phosphoramidothionate (BD-10 to BD-14), the HFAChE is more inhibited than the ChE-blood. For the HFAChE, the I_{50} value increases in the order:

BD-13 < BD-14 < BD-10 < BD-11 < BD-12

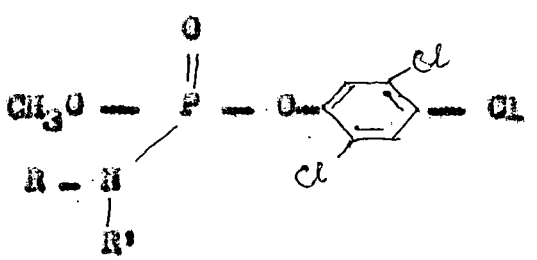
i.e, the antiacetylcholinesterase activity of the dimethylamido-phosphorothionate is highest, and that of the diethylamido analog is least. For the ChE-blood, the I_{50} value increases in the order:

BD-11 < BD-12 < BD-10 < BD-13 < BD-14

i.e. the anticholinesterase activity of the morpholino compound is most and that of the isopropylamido compound is least.

From the above results it may be concluded that the dimethylamido compound has good insect-acetylcholinesterase inhibitory activity, but the isopropylamido compound has least toxic effect on mammalian blood-cholinesterase. Previously it has been observed that the dimethylamido compound has also insecticidal activity (among the eight alkylamidophosphorothionates it has highest insecticidal activity), but the isopropylamido compound has highest antifungal activity.

Hansch and Deutsch[27] analysed the data obtained by Fukuto et al[28] from a series of methyl 2,4,5 - trichlorophenyl-N-alkyl phosphoramidates in order to clarify the effect of the



N-alkyl group on the inhibitory activity for the $HF^{A}ChE$. They observed that the logarithm of the bimolecular inhibition constant is correlated excellently with Taft's steric constant E_s and polar constant $\overset{*}{\sigma}$ of the substituent; the bulky isopropyl and tert-butyl groups decrease inhibition rates by steric interference. On the other hand, the ring substituents of methyl phenyl N-methyl phosphoramidates directly affect the antiacetylcholinesterase

activity (HFAChE) by virtue of the electronic and hydrophobic properties.[29] However, in a series of ethyl S-(substituted)-phenyl phosphoramidothiolates, no correlation was observed between the rates of cholinesterase inhibition and any of the free energy parameters for ring substituents[30]; moreover, the anticholinesterase activity (HFAChE) of phosphoramidothiolates is not always correlated with their insecticidal activity.

In case of nitro-saligenin cyclic phosphoramidothionates antiacetylcholinesterase activity is not correlated with their insecticidal activity. Among the five compounds (BD-10 to BD-14), only dimethylamido compound (BD-13) shows highest insecticidal activity, and also highest antiacetylcholinesterase activity. Although antiacetylcholinesterase activity of both dimethylamido and isopropylamido compounds are comparable (I_{50} is 1.80×10^{-5}M and 1.86×10^{-5}M respectively, Table-5, Column-3), the insecticidal activity of the dimethylamido compound is highest (LC_{100}=15-20 g/g) and that of the isopropylamido compound is least (LC_{100}=60-75 g/g). When the data for other nitro-saligenin cyclic phosphoramidothionates will be available we will try to find out the correlation between antiacetylcholinesterase activity and E_s, σ^* as well as π values of alkylamido groups. Previous studies[31] in this laboratory concerning the biological activities of some 2-alkoxy-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphides, a good correlation, as shown in the folloiwng equations, has been obtained between the anti-AChE activity (housefly) and σ^*, E_s^c as well

as π values:

$$-\log I_{50} = 4.9057\ \overset{*}{\sigma} + 7.3703 \quad \ldots\ldots\ldots \quad (1)$$

$$n = 6,\ r = 0.8142,\ s = 0.3413$$

$$= 0.8766\ E_s^c + 7.1550 \quad \ldots\ldots\ldots \quad (2)$$

$$n = 6,\ r = 0.7784,\ s = 0.3413$$

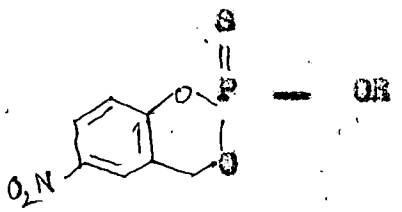
$$= -0.6737\ \pi + 7.7312 \quad \ldots\ldots\ldots\ldots \quad (3)$$

$$n = 6,\ r = 0.9351,\ s = 0.3413$$

$$= 1.7032\ \overset{*}{\sigma} + 0.0825\ E_s^c - 0.4781\ \pi + 7.6913 \ldots (4)$$

$$6 = 6,\ r = 0.9564,\ s = 0.3413$$

where, n is the number of data points used in the regression, r is the correlation co-efficient, and s is the standard deviation. Equation 4 gives the best fit to the experimental data. However, equation 3 also gives good fit as judged by correlation co-efficient value. These equations (3 & 4) show the great importance of the relative hydrophobic binding constant (π-value) of the exocyclic alkyl groups. By using equation 4 we have calculated the value of $-\log I_{50}$, and the results have been presented in the following table:



R	-log I_{50}(Calculated)	-log I_{50} (observed)
CH_3	7.4427	7.534
C_2H_5	7.0220	6.863
n-C_3H_7	6.7492	6.787
i-C_3H_7	6.5985	6.756
n-C_4H_9	6.4967	6.572
i-C_4H_9	6.5031	6.472

As mentioned earlier when the data for other cyclic amidophosphorothionates will be available we will try to find out the correlation between IIFAChE and E_s, as well as .

12. CHEMICAL HYDROLYSIS:

The alkaline hydrolysis for some alkylamidophosphorothionates have been carried out in 0.0095 M NaOH (in 50% ethanol) at 20°C. The hydrolysis data for each compound at different wave lengths (λ =400, 410, 420 and 430 nm) are listed in the tables 7A to 11 B (pp 197 - 214); the values of hydrolysis constant have been calculated by least square regression programme. The hydro-

lysis data have been summarised below (Table-7):

Table - 7

Hydrolysis of nitro-saligenin cyclic amidophosphorothionates; pH 11.85 (50% Ethanol), Temperature = 20°C

Code No	Amido Group	λ in mμ	K_{hyd} (min^{-1})	Average K_{hyd} (min^{-1})	$T_{1/2}$
1	2	3	4	5	6
BD-10	Cyclohexylamido	400	10.824×10^{-3}	10.364×10^{-3}	67 min
		410	10.364×10^{-3}		
		420	10.364×10^{-3}		
		430	9.903×10^{-3}		
BD-11	Morpholino	400	6.1413×10^{-5}	6.1413×10^{-5}	11286.6 min.
		410	6.1413×10^{-5}		
		420	6.1413×10^{-5}		
		430	6.1413×10^{-5}		
BD-13	Dimethylamido.	400	2.687×10^{-5}	2.878×10^{-5}	23896.5 min
		410	2.687×10^{-5}		
		420	3.07×10^{-5}		
		430	3.07×10^{-5}		
BD-17	Nonylamido	400	20.266×10^{-3}	19.4025×10^{-3}	35.72 min
		410	20.266×10^{-3}		
		420	19.345×10^{-3}		
		430	17.733×10^{-3}		
BD-15	Pyrrolidino	400	1.7835×10^{-5}	1.7632×10^{-5}	39500 min.
		410	1.7784×10^{-5}		
		420	1.7452×10^{-5}		
		430	1.7466×10^{-5}		
BD-16	Piperidino	400	1.0952×10^{-5}	1.162×10^{-5}	43312 min.
		410	1.2129×10^{-5}		
		420	1.1541×10^{-5}		
		430	1.1856×10^{-5}		

The average hydrolysis constants recorded in Table - 7 (Column-5) show that the nature of the amido group in the exocyclic side chain influences the stability of the compounds to alkaline hdyrolysis. The K_{hyd} increases in the order:

BD-16 < BD-15 < BD-13 < BD-11 < BD-10 < BD-17

i.e. the piperidino compound (BD-16) is most stable, and the nonylamido compound (BD-17) is least stable to alkaline hydrolysis. The cyclic phosphoramidothionates containing the disubstituted amido groups (piperidino, extremely resistant to hydrolysis compared to the other compounds having the monosubstituted amido groups (nonylamido and cyclohexylamido); probably the steric-interferences of the cyclohexylamido and nonylamido groups are less compared to that of the pyrrolidino, piperidino, dimethylamido and morpholino groups.

The hydrolysis of the saligenin cyclic esters proceeds with the initial fission of the endo-cyclic ester bond, and the cleavage of the exocyclic ester bond does not take place by alkaline hydrolysis (13). In our case, we could not detect any free amine in alkaline medium, and hence there is no cleavage in the P - N bond. Following the work of Eto (Ref. 13, p - 74, Equation-34) it may be proposed that the following reaction is taking place in course of alkaline hydrolysis:

Contrary to alkali hydrolysis in 0.0005 M NaOH these phosphoramidothionates show a good deal of resistance to the hydrolysis at pH 7.7 in phosphate buffer. For example, no detectable hudrolysis occurs even after 36 hours in case of morpholino, dimethylamido, pyrrolidino and piperidino compounds. However, the nonylamido and cyclohexylamido compounds show slight hydrolysis at pH 7.7 in phosphate buffer; the rate of hydrolysis (at pH 7.7) is less than that at pH 11.85. Therefore, it may be concluded that the rate of alkali hydrolysis is increased as the pH value increases from 7.7 to 11.85.

Salioxon, salithion and nitro-salithion (BD-8) which have been found as high insecticidal compounds in the series of saligenin cyclic phosphorus esters are rather unstable. The cyclic phosphoramidothionates presented here are more stable.

13. GENERAL CONCLUSIONS AND REMARKS:

(i) The dimethylamido compound (BD-13) shows greater insecticidal activity than other compounds to roaches; however, it has 1.5 to 2 times less insecticidal activity compared to salithion. The other compounds are non-insecticidal.

(ii) All compounds show antifungal activity against Helminthosporium spp. However, the isopropylamido compound (BD-14) is the most effective compound; its inhibitory effect is greater than that of Kinosan.

(iii) Except the cyclohexylamido (BD-10) and the morpholino (BD-11) compounds, none of the compounds are phytotoxic to Triticum spp. upto the concentration 500 ppm (the highest concentration used).

(iv) All compounds (BD-10 to BD-14) are less toxic to rats than salithion.

(v) From anticholinesterase activity studies it has been observed that for any phosphoramidothionate (BD-10 to BD-14), the HFAChE (housefly) is more inhibited than the ChE - blood. For the HFAChE, the activity of the dimethylamidophosphorothionate is highest, and that of the diethylamido analog is least. For the ChE - blood, the anticholinesterase activity of the morpholino compound is most, and that of the isopropylamido compound is least. It may be concluded that the dimethylamido compound has good insect-acetylcholinesterase inhibitory activity (it has also good insecticidal activity), but the isopropylamido compound has least toxic effect on mammalian blood - cholinesterase (it has good fungicidal activity).

(vi) From the chemical hydrolysis studies it has been observed that the compounds containing the disubstituted amido groups are extremely resistant to hydrolysis compared to other compounds having the mono-substituted amido groups.

(vii) All compounds show common IR bands due to P-O-C (alkyl), P-O-C (aryl), P=S, NO_2 groups etc. Although P-H absorption shows considerable frequency shifts, the N-H stretching vibrations occur in the normal frequency region.

(viii) All compounds show parent molecular ions. Fragmentation by loss of SH radical is important; all compounds show an ion due to (parent molecule - .SH)$^+$ and it is the base peak in spectra of cyclohexylamido, morpholino, diethylamido, pyrrolidino, piperidino, and nonylamido compounds; but m/e 198 is the base peak for both dimethylamido and isopropylamido compounds.

(ix) From the ^1H NMR spectral studies of the 2-alkoxy/alkylamido compounds it is fairly evident that the chemical shift difference of the two gesinal protons H_{4A} and H_{4B} (two protons of the CH_2 group in the dioxaphosphorin ring) is increasing in going from the methoxy (BD-8) to the cyclohexylamido (BD-10) compounds. Also the 2-substituent is at the same time increasing in bulk, and probably spending more time in the conformation with the least steric interactions. In BD-10 (also in other phosphoramidothionates), this may be mainly in one conformation (conformation II, p- 160), while in BD-8 it appears that both the chemical shift difference and the difference between $^3J_{P-O-C-H_{4A}}$ and $^3J_{P-O-C-H_{4B}}$ are quite small. This suggests that the molecule

exists as an average of the two conformations with rapid interconversion between them. In case of BD-9, it seems that an intermediate situation prevails. In case of BD-10, several plot expansions and decoupling experiments suggest that the quasi equatorial proton H_{4B} is assigned to the 5.2 ppm proton (J = 25.6 H_z) and the quasi-axial proton H_{4A} is assigned to the 5.6 ppm. proton (J = 6.3 Hz); the geminal coupling constant is 14.7 Hz. It has also been observed that the proton H_{4B} is coupled equally to the three aromatic protons H_5, H_7 and H_8 with J = 0.6. Hz; the proton H_{4A} is more strongly coupled to H_5 and H_7 with J = 1.0 Hz, but not to H_8.

From the temperature dependent ^1H NMR spectral study at 270 MHz in the temperature range -70°C to +50°C of the methoxy compound (BD-8), it is fairly evident that the methylene protons of the hetero ring are not equivalent to each other, and the dioxaphosphorin ring is conformationally mobile in solution.

From the ^{13}C NMR spectral study of the pyrrolidino and piperidino compounds (BD-15 and BD-16) it has been observed that the coupling (due to ^{31}P) to the CH_2 carbon (C_4) in the dioxaphosphorin ring changes only from 5.53 Hz in BD-15 to 5.75 Hz in BD-16. This probably means that the conformation is almost the same, and this is in accord with the small difference in ^{13}C chemical shifts, 66.11 and 65.52 ppm. The change in δ (^{13}C) is only 0.6 ppm for the carbon (C_4), and since ^{13}C chemical shifts are often quite sensitive to conformation, it supports the similarity of the

structures.

From ^{31}P NMR spectral studies it is fairly evident that the compounds (BD-15 and BD-16) are stable in one conformation (structure II).

Further studies including X-ray crystal structure determination are in progress.

(x) The biological activities and other data justify further examination of these phosphorothionates and other related compounds as potential pesticides.

TABLES AND REFERENCES

Table-5A

Acetylcholinesterase Inhibition in Housefly-head homogenate (HFAChE) at 30°C of ED-10.

(Phosphate buffer, pH 8.0; total volume = 5.15 ml/5 fly head, λ = 625; incubation time 30 min.)

Sets	Inhibitor* Conc. (μg)	O.D.	$\triangle$ O.D.	%Inhibition (Y)	I_{50} (M)
Control	-	0.67	0	-	
1	60	0.26	0.32	56.13	
2	50	0.28	0.29	50.87	
3	40	0.32	0.25	43.85	2.8611×10^{-5}
4	30	0.35	0.22	38.60	
5	20	0.405	0.165	28.90	

X* = log [Conc. of the inhibitor in μg]

Regression constants:

Y = mx + c

c = -44.5645

m = 56.1474

r = .9963

Table - 5B

Acetylcholinesterase Inhibition in Housefly-head homogenate (HFAChE) at 30°C of BD-11

Sets	Inhibitor* Conc.(g)	O.D.	ΔO.D.	%Inhibition (Y)	I_{50} (M)
Control	(-)	0.510	0	-	
1	50	0.310	0.200	39.21	
2	40	0.340	0.170	33.35	
3	30	0.370	0.140	27.45	5.4326×10^{-5}
4	20	0.415	0.096	18.60	
5	10	0.480	0.030	5.88	

X* = log [Cond. of the inhibitor in g]

Regression Constants: Y = mx + c

c = - 42.0753

m = 47.3029

r = 0.9983

Table-5C

Acetylcholinesterase Inhibition in Housefly-head homogenate (HFAChE) at 30°C of BD-12

(Phosphate buffer, pH 8.0; total volume 5.15 ml/ 5 fly head; λ=625; incubation time 30 min.)

Sets	Inhibition* Conc.(μg)	O.D.	$\triangle$O.D.	%Inhibition (Y)	I_{50} (M)
Control	(-)	1.05	0	-	
1	100	0.57	0.48	45.71	
2	80	0.59	0.46	43.81	
3	60	0.64	0.41	39.09	8.2601×10^{-5}
4	40	0.71	0.34	32.38	
5	20	0.80	0.25	23.81	
6	10	0.92	0.13	12.38	

X* = log [Conc. of the inhibitor in μg]

Regression constants : Y = mx + c

c = -20.6648

m = 33.5095

r = .9986

Table - 8D

Acetylcholinesterase Inhibition in Housefly head homogenate (HFAChE) at 30°C of BD-13

(Phosphate buffer, pH 8.0; total volume 5.15 ml/5 fly head; λ =626; incubation time 30 min.)

Sets	Inhibition* Conc. (μg)	O.D.	Δ O.D.	% Inhibition (Y)	I_{50} (M)
Control	(-)	1.05	0	-	
1	100	0.21	0.84	80.00	
2	80	0.27	0.78	74.28	1.80×10^{-6}
3	60	0.33	0.72	68.57	
4	40	0.42	0.63	60.00	
5	20	0.58	0.47	44.76	

X* = log [Conc. of the inhibitor in μg]

Regression constants : Y = mx + c

c = -20.0339

m = 49.8328

r = 0.9997

Table - 68

Acetylcholinesterase Inhibition in Housefly-head homogenate (HFAChE) at 30°C of BD-14

(Phosphate buffer, pH 8.0; total volume 5.15 ml/5 fly head; λ=625; incubation time 30 min.)

Sets	Inhibition* Conc. (μg)	O.D.	Δ O.D.	%Inhibition (Y)	I_{50} (M)
Control	(-)	1.06	0	-	
1	50	0.41	0.64	60.95	
2	40	0.46	0.59	56.18	
3	30	0.51	0.54	51.42	1.8642×10^{-5}
4	20	0.59	0.46	43.81	
5	10	0.71	0.36	32.38	

X* = log [Conc. of the inhibitor in μg]

Regression constants : Y = mx + c

c = -8.5553

m = 40.6143

r = 0.9999

Table - 6A

Acetylcholinesterase Inhibition in goat-whole blood of BD-10 at 30°C.

(Phosphate buffer, pH = 8.0; total volume = 5.15 ml/0.2 ml blood; λ = 625 nm; incubation time 30 min.)

Sets	Inhibitor* Conc.(µg)	O.D.	Δ O.D.	%Inhibition (Y)	I_{50} (M)
Control	(-)	0.69	-		
1	30	0.63	0.06	8.69	
2	40	0.60	0.09	13.04	
3	60	0.56	0.13	18.84	
4	80	0.515	0.175	25.36	1.810×10^{-4}
5	100	0.48	0.21	30.43	
6	120	0.46	0.23	33.33	

X* = log [Conc. of the inhibitor in µg]

Regression constants: $Y = mx + c$

$c = -53.8102$

$m = 41.7679$

$r = 0.9969$

Table - 6B

Acetylcholinesterase Inhibition in goat whole blood of BD-11 at 30°C.

(Phosphate buffer, pH = 8.0; total volume = 5.15 ml/0.2 ml blood; λ = 625 nm; incubation time 30 min.)

Sets	Inhibitor* Conc. (μg)	O.D.	Δ O.D.	%Inhibition (Y)	I_{50} (M)
Control	-	0.80	-		
1	30	0.69	0.11	13.75	
2	40	0.65	0.15	18.75	
3	60	0.58	0.22	27.50	
4	80	0.54	0.26	32.50	1.0426×10^{-4}
5	100	0.49	0.31	38.75	
6	120	0.45	0.35	43.75	

X* = log [Conc. of the inhibitor in μg]

Regression constants:

Y = mx + c

c = -59.8146

m = 49.2530

r = 0.9968

Table - 6C

Acetylcholinesterase Inhibition in goat whole blood of BD-12 at 30°C.

(Phosphate buffer, pH = 8.0; total volume = 5.15 ml/0.2 ml blood; λ = 625 nm; incubation time 30 min.)

Sets	Inhibitor* Conc.(μg)	O.D.	Δ O.D.	%Inhibition (Y)	I_{50} (M)
Control	-	0.65	-		
1	40	0.59	0.06	9.23	
2	60	0.53	0.12	18.46	
3	80	0.48	0.17	26.15	1.4259×10^{-4}
4	100	0.45	0.20	30.76	
5	120	0.42	0.23	35.38	

X* = log [Conc. of the inhibitor in μg]

Regression constants:

$y = mx + c$

$c = -78.8637$

$m = 54.9311$

$r = 0.9995$

Table - 6D

Acetylcholinesterase Inhibition in goat whole-blood of BD-15 at 30°C.

(Phosphate buffer, pH = 8.0; total volume 5.15 ml/0.2 ml blood; λ = 626 nm; incubation time 30 min.)

Sets	Inhibitor* Conc. (μg)	O.D.	$\triangle$ O.D.	%Inhibition (Y)	I_{50} (M)
Control	-	0.69	-		
1	30	0.65	0.04	6.15	
2	40	0.62	0.07	10.76	
3	60	0.58	0.11	15.94	
4	80	0.55	0.14	20.28	4.6564×10^{-4}
5	100	0.53	0.16	23.18	
6	120	0.51	0.18	26.08	

X* = log [Conc. of the inhibitor in μg]

Regression Constants:

Y = mx + c

c = -41.7889

m = 32.5769

r = 0.9996

Table -63

Acetylcholinesterase Inhibition in goat whole blood of BD-14 at 30°C.

(Phosphate buffer, pH = 8.0; total volume = 5.15 ml/0.2 ml blood; λ=625 nm; incubation time 30 min.)

Sets	Inhibitor* Conc. (μg)	O.D.	$\triangle$ O.D.	%Inhibition (Y)	I_{50} (M)
Control	-	0.55	-		
1	50	0.47	0.08	14.54	
2	100	0.42	0.13	23.63	
3	150	0.39	0.16	29.09	4.7805×10^{-4}
4	200	0.37	0.18	32.72	
5	250	0.35	0.20	36.36	

X* = log [Conc. of the inhibitor in μg]

Regression constants; $Y = mx + c$

$c = -38.0605$

$m = 30.8911$

$r = 0.9936$

Table - 7a

Chemical hydrolysis of BD-10 at λ=400 nm pH 11.85, 0.0095 M NaOH (in 50% Ethanol) ϵ=19090, Initial concentration, $C_o = 3.0 \times 10^{-5}$, temperature 20°C.

time (min) (X)	O.D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
5	0.04	0.20953	0.0314	
10	0.07	0.36668	0.0566	
15	0.092	0.48193	0.0760	
20	0.120	0.62860	0.1021	10.824×10^{-3}
25	0.142	0.74384	0.1237	
30	0.163	0.85385	0.1455	
35	0.184	0.96386	0.1683	
40.5	0.207	1.0843	0.1948	
45	0.223	1.1682	0.2142	
50.25	0.244	1.2782	0.2411	
54.75	0.259	1.3567	0.2614	
60	0.276	1.4458	0.2856	

Regression constants: $y = mx + c$

$c = 0.0085$

$m = 0.0047$

$r = 0.9999$

Table - 7b

Chemical hydrolysis of BD-10 at λ = 410 nm pH 11.85, 0.0096 N NaOH (in 50% Ethanol) ϵ =20090, Initial concentration $C_o = 3.0 \times 10^{-5}$ M, temperature 20°C.

Time (min) (X)	O. D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
5.5	0.047	0.23375	0.0363	
10.5	0.077	0.38328	0.0594	
15.5	0.103	0.51269	0.0814	
20.5	0.127	0.63216	0.1028	
25.5	0.150	0.74664	0.1243	10.364×10^{-3}
30.5	0.173	0.86112	0.1469	
35.5	0.195	0.97063	0.1698	
41.25	0.216	1.0752	0.1927	
45.75	0.236	1.1747	0.2168	
53.5	0.267	1.3290	0.2541	
55.25	0.273	1.3589	0.2620	
60.5	0.292	1.4535	0.2878	

Regression constants : $y = mx + c$

$c = 0.0096$

$m = 0.0045$

$r = 0.9997$

Table - 7a

Chemical hydrolysis of ED-10 at λ =420 nm pH 11.85, 0.0095 M NaOH (in 50% Ethanol) ϵ =18180, Initial concentration C_o = 3.0 x 10^{-5} M temperature 20°C.

time (min) (X)	O.D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
6	0.047	0.25853	0.0391	
11	0.072	0.39604	0.0615	
16.25	0.096	0.52805	0.0841	
21	0.117	0.64356	0.1049	
26	0.137	0.75358	0.1256	
31	0.157	0.86359	0.1474	10.364 x 10^{-3}
36	0.177	0.97360	0.1704	
41.75	0.197	1.0836	0.1946	
46.5	0.214	1.1771	0.2164	
51.75	0.234	1.2871	0.2434	
56	0.248	1.3641	0.2634	
61	0.264	1.4521	0.2874	

Regression constants:

$y = mx + c$

$c = 0.0104$

$m = 0.0045$

$r = 0.9997$

Table - 7d

Chemical hydrolysis of BD-10 at λ =430 nm pH 11.88, 0.0095 M NaOH (in 50% Ethanol) ϵ =14460, Initial concentration, $C_o = 3.0 \times 10^{-5}$ M, temperature 20°C.

time (min) (X)	O.D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
7.25	0.042	0.29066	0.0443	
11.75	0.06	0.41522	0.0647	
16.75	0.077	0.53287	0.0849	
21.75	0.094	0.65052	0.1061	
26.5	0.108	0.74740	0.1244	
31.5	0.125	0.86506	0.1477	9.903×10^{-3}
36.5	0.139	0.96194	0.1679	
42.5	0.156	1.0727	0.1922	
47.25	0.168	1.1626	0.2129	
52.75	0.185	1.2803	0.2417	
56.5	0.193	1.3356	0.2659	
61.5	0.205	1.4187	0.2781	

Regression constants:

$y = mx + c$

$c = 0.0125$

$m = 0.0043$

$r = 0.9997$

Table - 8a

Chemical hydrolysis of BD-11 at λ =400 nm pH 11.85, 0.0096 M NaOH (in 50% Ethanol) ϵ =19000, Initial concentration, C_o = 7.06 x 10^{-5} M temperature 20°C.

time (hrs) (X)	O.D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - (X) C_t}$	K_{hyd} (min^{-1})
5	0.098	0.51336	0.0328	
27.75	0.303	1.5872	0.1106	
52.5	0.423	2.2158	0.1636	6.1413×10^{-5}
75.33	0.46	2.4086	0.1813	
124.6	0.56	2.9335	0.2332	

Regression constants :

$y = mx + c$

$c = 0.0544$

$m = 0.0016$

$r = 0.9536$

Table - 8b

Chemical hydrolysis of BD-11 at λ=410 nm pH 11.85, 0.0095 M NaOH (in 50% Ethanol) ϵ = 20090, Initial concentration, C_o = 7.06 x 10^{-5} M, temperature 20°C.

time (hrs) (X)	O.D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
5	0.103	0.51269	0.0327	
27.75	0.316	1.5729	0.1095	
52.5	0.446	2.2150	0.1635	
75.33	0.49	2.4390	0.1841	6.1413×10^{-5}
124.6	0.6	2.9866	0.2388	

Regression constants :

$y = mx + c$

$c = 0.0526$

$m = 0.0016$

$r = 0.9599$

Table - 8c

Chemical hydrolysis of BD-11 at λ =420 nm pH 11.85, 0.0095 M NaOH (in 50% Ethanol) ϵ =18180, Initial concentration, $C_o = 7.06 \times 10^{-5}$ M, temperature 20°C.

time (hrs) (X)	O.D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
6	0.093	0.51155	0.0327	
27.75	0.284	1.5622	0.1086	
52.5	0.400	2.2002	0.1622	6.1413×10^{-5}
75.33	0.45	2.4752	0.1876	
124.6	0.54	2.9703	0.2371	

Regression constants:

$y = mx + c$

$c = 0.0527$

$m = 0.0016$

$r = 0.9589$

Table - 8d

Chemical hydrolysis of ED-11 at λ=430 nm pH 11.85, 0.0096 M NaOH (in 50% Ethanol) ϵ=14450, Initial concentration, $C_o = 7.06 \times 10^{-5}$ M, temperature 20°C.

time (hrs) (X)	O.D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
5	0.074	0.61211	0.0327	
27.75	0.220	1.5825	0.1055	
52.5	0.315	2.1799	0.1604	6.1413×10^{-5}
75.33	0.355	2.4567	0.1357	
124.6	0.428	2.9619	0.2362	

Regression constants: $y = mx + c$

$c = 0.0511$

$m = 0.0016$

$r = 0.9620$

Table - 9a

Chemical hydrolysis of BD-13 at λ=400 nm pH 11.85, 0.0095 M NaOH (in 50% Ethanol) ϵ =19000, Initial concentration, $C_o = 7.3 \times 10^{-5}$ M, temperature 20°c

time (hrs) (X)	O.D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
5	0.032	0.15763	0.0101	
28	0.138	0.72289	0.0463	
52.75	0.203	1.0634	0.0684	2.687×10^{-5}
75.25	0.24	1.2572	0.0821	
124.75	0.293	1.5348	0.1025	

Regression constants:

$y = mx + c$

$c = 0.0195$

$m = 0.0007$

$r = 0.9966$

Table-9b

Chemical hydrolysis of BD-13 at λ =410 nm pH 11.86, 0.0095 M NaOH (in 50% Ethanol) ϵ =20090, Initial concentration, $C_o = 7.3 \times 10^{-5}$, temperature 20°C.

time (hrs) (X)	O.D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
5	0.034	0.16924	0.0102	
28	0.143	0.71180	0.0446	2.687×10^{-5}
52.75	0.210	1.0453	0.0671	
75.25	0.255	1.2693	0.0830	
124.75	0.305	1.5182	0.1013	

Regression constants:

$y = mx + c$

$c = 0.0193$

$m = 0.0007$

$r = 0.9859$

Table - 9a

Chemical hydrolysis of BD-13 at λ=420 nm pH 11.85, 0.0095 M NaOH (In 50% Ethanol) ϵ=18180, Initial concentration, C_o = 7.3 x 10^{-5} M, temperature 20°C.

time (hrs) (X)	O.D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
5	0.028	0.15402	0.0093	
28	0.129	0.70957	0.0444	3.07×10^{-5}
52.75	0.183	1.0616	0.0682	
75.25	0.23	1.2651	0.0827	
124.75	0.28	1.5402	0.1029	

Regression constants:

$y = mx + c$

$c = 0.0117$

$m = 0.0008$

$r = 0.9600$

Table- 9d

Chemical hydrolysis of ED-13 at λ = 430 nm pH 11.85, 0.0095 M NaOH (in 50% Ethanol) ϵ =14450, Initial concentration, $C_o = 7.3 \times 10^{-5}$ M, temperature 20°C.

time (hrs) (X)	O.D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
5	0.022	0.15325	0.0092	
28	0.100	0.69204	0.0433	
52.75	0.147	1.0173	0.0652	3.07×10^{-5}
75.25	0.18	1.2457	0.0813	
124.75	0.221	1.5234	0.1021	

Regression constants:

$y = mx + c$

$c = 0.0110$

$m = 0.0008$

$r = 0.9648$

Table - 10n

Chemical hydrolysis of BD-17 at λ=400 nm pH 11.85, 0.0095 M NaOH (1n 60% Ethanol) ϵ =19090, Initial concentration, $C_o = 3.14 \times 10^{-5}$ M, temperature 20°C.

time (min) (X)	O.D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
4.6	0.072	0.37716	0.0556	
8.08 (8min 5Secs)	0.110	0.57622	0.0830	
10	0.130	0.68093	0.1062	
12	0.150	0.78573	0.1251	
16	0.180	0.94290	0.1551	20.266×10^{-3}
20	0.220	1.1524	0.1986	
23	0.240	1.2572	0.221	
26	0.262	1.3724	0.2405	
29	0.282	1.4772	0.2761	
35	0.316	1.6553	0.3259	
40	0.342	1.7915	0.3671	
45	0.368	1.9277	0.4133	

Regression constants:

$y = mx + c$

$c = 0.0194$

$m = 0.0038$

$r = 0.9997$

Table-10b

Chemical hydrolysis of BD-17 at λ=410 nm pH 11.85, 0.0095 M NaOH (in 50% Ethanol) ϵ =20090, Initial concentration, C_o = 3.14 x 10^{-5} M, temperature 20°C.

time (min) (X)	O.D.	C_t x 10^5 (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
5.25	0.07	0.34843	0.0511	
6	0.077	0.38323	0.0563	
10	0.127	0.63216	0.0976	
15	0.177	0.88104	0.1430	
20	0.227	1.085	0.1852	20.266 x 10^{-3}
25	0.265	1.3191	0.2382	
30	0.299	1.4783	0.2764	
35	0.333	1.6575	0.3259	
40	0.355	1.7670	0.3503	
45	0.373	1.8815	0.3971	

Regression constants:

$y = mx + c$

$c = 0.0083$

$m = 0.0088$

$r = 0.9911$

Table-10c

Chemical hydrolysis of BD-17 at λ=420 nm pH 11.85, 0.0095 M NaOH (in 60% Ethanol) ϵ = 18180, Initial concentration, $C_o = 3.14 \times 10^{-5}$ M, temperature 20°C.

time (min) (X)	O.D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
11	0.121	0.66557	0.1035	
16	0.168	0.92409	0.1514	
21	0.206	1.1276	0.1932	
26	0.237	1.3036	0.2330	19.345×10^{-3}
31	0.270	1.4861	0.2782	
36	0.295	1.6474	0.3230	
41	0.320	1.7602	0.3671	
46	0.342	1.8812	0.3970	

Regression constants:

$y = mx + c$

$c = 0.0152$

$m = 0.0084$

$r = 0.9994$

Table-10d

Chemical hydrolysis of BD-17 at λ=430 nm pH 11.85, 0.0095 M NaOH (in 50% Ethanol) ϵ = 14460, Initial concentration, C_o = 3.14 x 10^{-5}M, temperature 20°C.

time (min) (X)	O.D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
7.16 (7 min 10 secs)	0.063	0.43599	0.0649	
12	0.100	0.69204	0.1081	
17	0.130	0.89965	0.1466	
22	0.160	1.1073	0.1889	17.733×10^{-3}
27	0.186	1.2872	0.2291	
32	0.208	1.4394	0.2663	
37	0.228	1.5779	0.3032	
42	0.245	1.6955	0.3372	
47	0.260	1.7993	0.3696	

Regression constants:

$y = mx + c$

$c = 0.0165$

$m = 0.0077$

$r = 0.9990$

Table - 11a*

Chemical hydrolysis of BD-15 pH 11.85, 0.0095 N NaOH (in 50% Ethanol), Initial concentration, C_o = 2.12 x 10^{-5} M, temperature 20°C.

λ (nm)	time (hrs) (X)	O.D.	$C_t \times 10^5$	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
400	150	0.06	0.31430	0.0697	1.7835 x 10^{-5}
410	150	0.063	0.31359	0.0695	1.7784 x 10^{-5}
420	150	0.056	0.30803	0.0682	1.7462 x 10^{-5}
430	150	0.045	0.31142	0.0690	1.7456 x 10^{-5}

* This compound (BD-15) was extremely resistant to hydrolysis at pH 11.85; only after 150 hours readings were taken at λ =400, 410, 420 and 430 nm and K_{hyd} was calculated from these readings with the help of 1st order rate equation

$$K = \frac{1}{t} \log \frac{C_o}{C_o - C_t}$$

Table - 11b*

Chemical hydrolysis of BD- 16 pH 11.85, 0.0095 M NaOH (in 50% Ethanol), Initial concentration, $C_o = 1.67 \times 10^{-5}$ M, temperature 20°C.

λ (nm)	time (hrs) (X)	O.D.	$C_t \times 10^5$ (M)	$\log \frac{C_o}{C_o - C_t}$ (Y)	K_{hyd} (min^{-1})
400	150	0.038	0.19906	0.0428	1.0952×10^{-5}
410	150	0.044	0.21901	0.0474	1.2129×10^{-5}
420	150	0.038	0.20902	0.0451	1.1541×10^{-5}
430	150	0.031	0.21453	0.0463	1.1856×10^{-5}

*This compound (BD-16) also is extremely resistant to hydrolysis at pH 11.85; only after 150 hours readings were taken at λ=400, 410, 420 and 430 nm and K_{hyd} was calculated from these readings with the help of 1st order rate equation: $K = \frac{1}{t} \ln \frac{C_o}{C_o - C_t}$

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APPENDIX

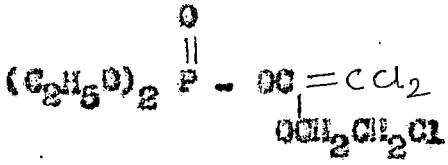
Appendix - 1

COMMON OR TRADE NAMES, CHEMICAL STRUCTURES AND OTHER PROPERTIES OF SOME ORGANOPHOSPHORUS PESTICIDES.

Common or trade name, Chemical name and Chemical structure.	Physical and biological properties.
A. PHOSPHATES	
1. Dichlorvos, DDVP, Vapona(R), Nuvan (Shell Oil Co.) $(CH_3O)_2$ P(O)-OCH = CCl_2 O, O-dimethyl O-(2,2 dichlorovinyl) phosphate.	Liquid; non-systemic, contact and stomach insecticide with fumigant action and low residual activity; has also acaricidal and anthelmintic property; LD_{50}, 80 mg/kg.
2. Dibrom(R), Naled (California Spray Chemical Corporation, 1956) $(CH_3O)_2P(O)$-OCH Br.$CBrCl_2$ O,O-dimethyl O-(1,2- dibromo-2,2-dichloro ethyl) phosphate.	Liquid (m.p. of pure compound is 26°C); Non-systemic insecticide and acaricide; LD_{50}, 430 mg/kg.

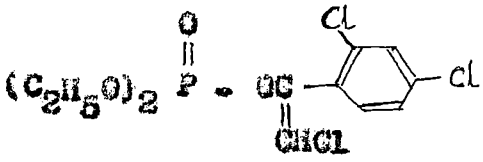
(Contd.)

3. Forestenon



Insecticide; LD_{50}, 7-10 mg/kg.

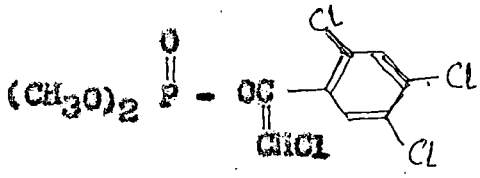
4. Chlorfenvinphos, Supona(R), Birlane(R)



O,O-diethyl O-[2-chloro-1-(2',4'-dichlorophenyl) vinyl] phosphate.

Liquid; non-systemic insecticide, used in soil and seed treatment; moderately persistent; LD_{50}, 10-40 mg/kg.

5. Tetrachlorvinphos, Gardona(R), Rabon(R) (Shell Development Co. 1966)



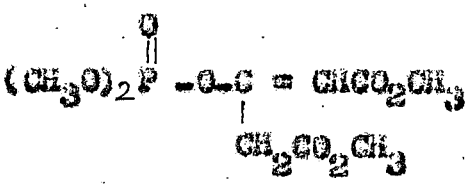
O,O-dimethyl O-[2-chloro-1-(2',4',5'-trichlorophenyl) vinyl] phosphate.

Solid, m.p. 62°C (α-isomer) 98°C (β-isomer) non-systemic, brief persistence selective insecticide, used to control diptera, lepidoptera and coleoptera and other pests; LD_{50}, 4,000 mg/kg.

(Contd.)

6. Bomyl(R)

(Allied Chemical Corp, Code No. GC-3707, 1959)

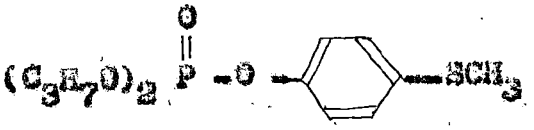


1,3 di(methoxy carbonyl)-1-propen-2-yl dimethyl phosphate.

Liquid; used for contact-residual treatment of insects and mites, LD_{50}, 32 mg/kg (R).

7.(a) Kayaphos(R), Propaphos

(Nippon Kayaku Co. 1968)



Di-n-propyl p-methyl thiophenyl phosphate.

Liquid; selective contact insecticide for rice stem-borers and greenrice leaf-hoppers; synergists of other organophosphorus insecticide; LD_{50}, 70 mg/kg.

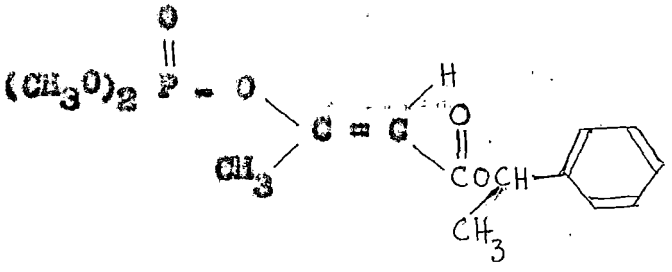
7.(b) GC-6506

Dimethyl homolog of Propahos.

Insecticide and acaricide for use in cotton; LD_{50}, 7 mg/kg.
Diethyl homolog is most toxic to mammals.

(Contd..)

8. Crotoxyphos, Ciodrin (R) (Shell Development Co. 1962).

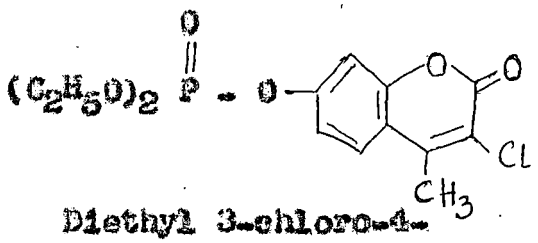


Dimethyl cis-1-methyl-2-(1-phenylethoxy carbonyl) vinyl phosphate.

Liquid; insecticide with no systemic activity, effective against ectoparasites on livestock by spray (for the control of flies, lice, mites and ticks on cattle and pigs by spray)

LD_{50}, 125 mg/Kg

9. Coroxon (Copper Technical Bureau 1961).



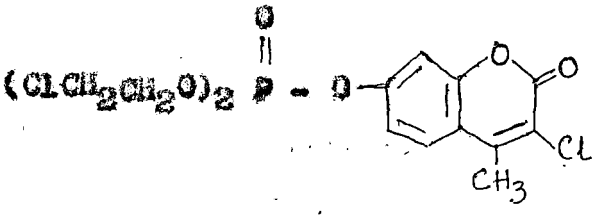
Diethyl 3-chloro-4-methylcoumarin-7 yl phosphate.

Solid, m.p. 72°C, animal systemic insecticide; LD_{50}, 12 mg/kg.

(Contd.)

10. Haloxon
(Copper Technical Bureau, 1962)

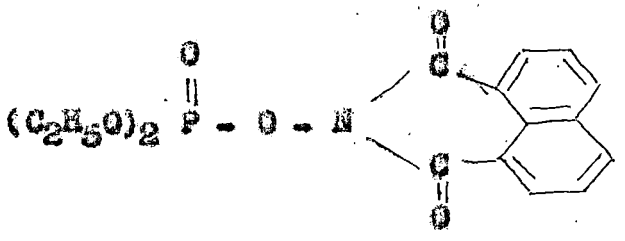
Solid, m.p. 92°C, has high anthelmintic properties but has no useful insecticidal properties; LD_{50}, 900 mg/kg.



Bis(2-chloroethyl) 3-chloro-4-methyl coumarin-7-yl-phosphate.

11. Maretin(R), Ronnetin(R), Napthelimide
(Bayer AG.)

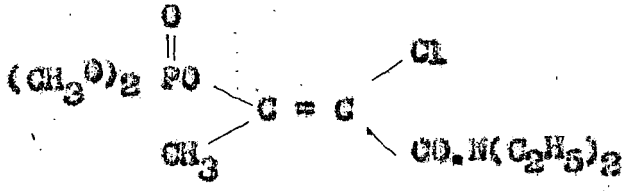
Solid, m.p. 196°C, has anthelmintic and insecticidal properties; LD_{50}, 75 mg/kg.



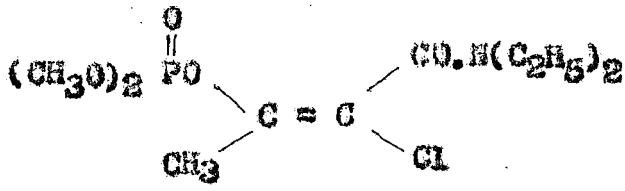
N-(diethoxyphosphinyloxy)-naphthalimide.

(Contd.)

12. Phosphamidon, Dimecron(R), Dicron(R) (Ciba Ltd.)



Cis (β-) isomer



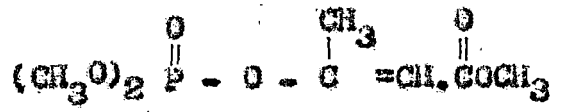
trans (∝) isomer

O,O-dimethyl O-(1-methyl-2-chloro-2-diethylcarbamoyl-vinyl) phosphate.

Liquid; systematic insecticide and acaricide with a little contact action, useful against sap-feeding and leaf-eating insects, particularly aphids, bugs, caterpillars (not Noctuidae), thrips, rice stem borers etc; LD_{50}, 15-28 mg/kg.

The Cis -isomer is more biologically active than trans-isomer.

13. Phosdrin(R), Mevinphos. (Shell Development Co. 1953)



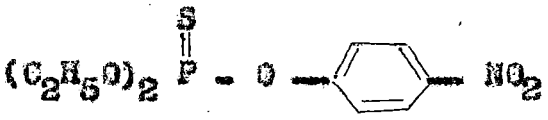
2-methoxy carbonyl-1-methylvinyl dimethyl phosphate.

Liquid; a contact and systemic insecticide and acaricide of short persistence, effective against sucking and chewing insects and mites; LD_{50}, 4-7 mg/kg.

(Contd.)

B. PHOSPHOROTHIONATES.

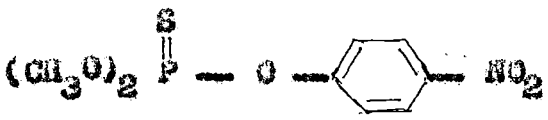
14. Parathion, Folidol(R);
(Bayer AG 1944)



O,O-diethyl O-paranitrophenyl phosphorothionate.

Liquid; wide spectrum insecticide; LD_{50}, 7 mg/kg.

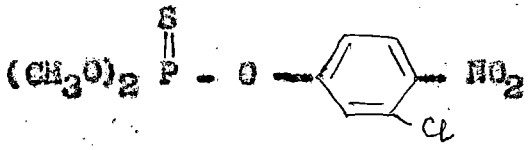
15. Methyl parathion.
(Bayer AG 1949)



O,O-dimethyl O-paranitrophenyl phosphorothionate.

Liquid; broad-spectrum; LD_{50}, 25-50 mg/kg.

16. Chlorothion(R)
(Bayer AG 1952)



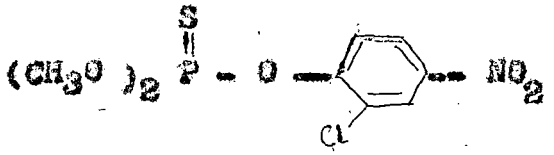
O,O-dimethyl O-(3-chloro-4-nitrophenyl) phosphorothionate.

Crystalline powder; for control of beetles, aphids, caterpillars
LD_{50}, 880 mg/kg.

(Contd.)

17. Di-capten(R), Dicapthon

(American Cyanamid Co. 1954)

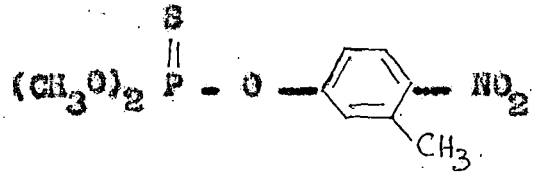


O,O-dimethyl O-(2-chloro-4-nitrophenyl) phosphorothionate.

Crystalline powder; for controlling household insects, aphids and boll weevils.

18. Sumithion(R), Folithion(R), Fenitrothion.

(Sumitomo Chemical Co. 1959)



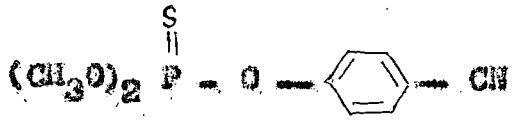
O,O-dimethyl O-(3-methyl-4-nitrophenyl) Phosphorothionate.

Liquid; broad-spectrum (as methyl parathion), specially for rice-stem borers, flies and mosquitoes in public health programme;

LD_{50}, 250-600 mg/kg.

(Contd.)

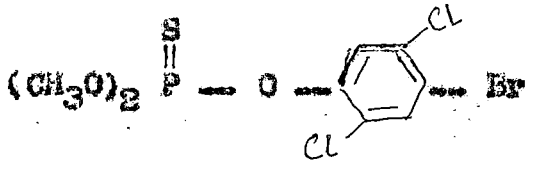
19. Cyanox(R), Cyanophos, CYAP
(Sumitomo Chemical Co. 1966)



O,O-dimethyl O-paracyanphenyl phosphorothionate.

Liquid; useful for controlling of rice-stem borers and pests of vegetables, fruits and ornamentals.

20. Bromophos, Nexion(R),
Brofene
(Boehringer Sohn and Cela Landwirtschaftliche Chem; Germany; 1961)

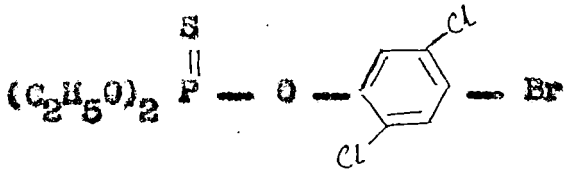


O, O-dimethyl O-(4-bromo-2, 5-dichlorophenyl) phosphorothionate.

Crystalline solid; m.p. 64°C non-systemic persistent insecticide and acaricide, particularly effective against diptera; ectoparasite control in livestock; LD_{50}, 3750 to 6100 mg/kg.

(Contd.)

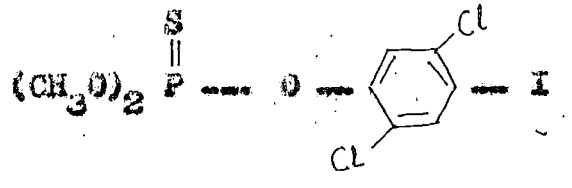
21. Bromophos ethyl.



0,0-diethyl O-(4-bromo-2, 5-dichlorophenyl) phosphorothionate.

Insecticide and acaricide; LD_{50}, 238 mg/kg.

22. Iodofenphos, Alfacron(R), Nuvanol N(R), Elocril (Ciba Ltd. 1966)

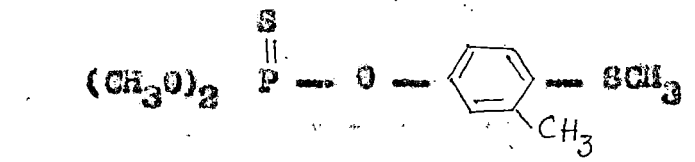


0,0-dimethyl O-(4-iodo-2, 5-dichlorophenyl) phosphorothionate

Colourless crystalline solid; m.p. 76°C; non-systemic contact and stomach insecticide and acaricide effective against a wide range of insect pests, LD_{50}, 2100 mg/kg.

(Contd.)

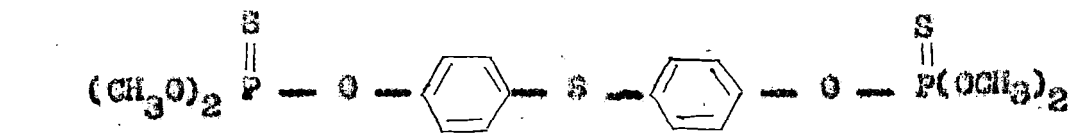
23. Baytex(R), Lebayacid(R), Fenthion.
(Bayer AG, 1958)



O,O-dimethyl O-(3-methyl-4-methylthiophenyl) phosphorothionate.

Liquid; general purpose insecticide with systemic action; particularly for fly and mosquito;
LD_{50}, 215 mg/kg (Male R)
615 mg/kg (Female R)

24. Abate(R), Biothion(R)
(American Cyanamid Co. 1965)



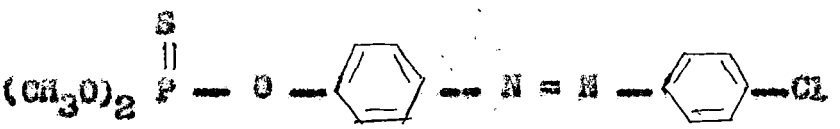
O,O,O',O'-tetramethyl O,O'-thiodi-p-phenylene phosphorothionate.

White solid; m.p. 30°C; control of mosquito larvae
LD_{50}, 2000-4000 mg/kg.

(Contd.)

25. Alamos(R), Siam(R), Azothoate (Soc. Montecatini, Italy, 1964).

Experimental insecticide and acaricide, particularly nontoxic to mammals.

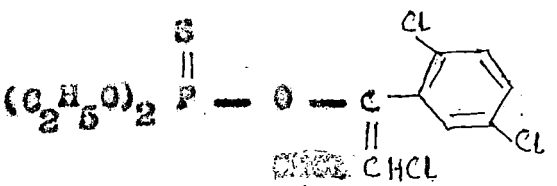


O,O-dimethyl O-[P-(P-chlorophenylazo) phenyl] phosphorothionate.

26. Akton(R) (Shell Development Co.)

Brown liquid; non-systemic insecticide, effective particularly for soil insects such as lawn chinch bugs; LD_{50}, 146 mg/kg.

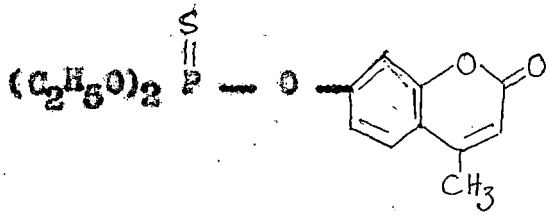
The methyl homolog and 2',4',5' trichloro analog of Akton are effective as housefly larvicide.



O,O-diethyl O-[2-chloro-1-(2',5'-dichlorophenyl) vinyl] phosphorothionate.

(Contd.)

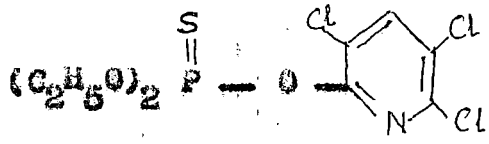
27. Potasan(R) (1947)



O,O-diethyl O-(4-methyl-7-cumarinyl) phosphorothionate.

Colourless crystalline solid, m.p. 38°C; stomach insecticide with weak contact activity; particularly effective against colorado potato beetles; LD_{50}, 42 mg/kg.

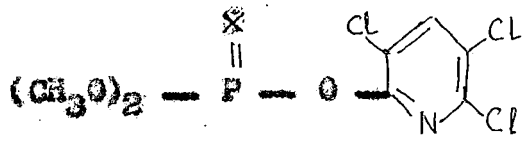
28. Dursban(R), Chloropyrifos (Dow Chemical Co. 1965)



O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothionate.

White crystalline solid, m.p. 43°C, moderately persistent insecticide, effective for controlling mosquito and fly larvae, sucking and chewing plant pests and soil pests, ticks on livestock; LD_{50} , 163 mg/kg.

29.



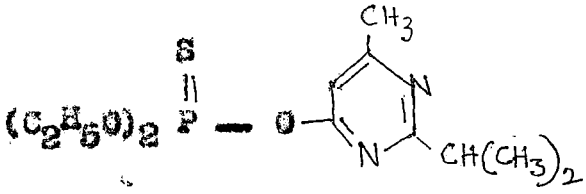
X = S Dowco 214

X = O Dowco 217

The methyl homolog (Dowco(R) 214) is more effective against adult mosquitoes but less effective against the larvae than chloropyrifos; its LD_{50} is 1,600 mg/kg.

(Contd.)

30. Diazinon, Basudin(R), Sgrolex(R) (1952)

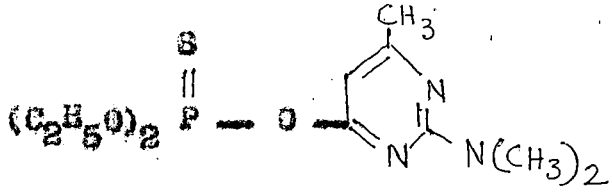


O,O-diethyl O-(2-isopropyl-4-methylpyrimidin-6 yl) phosphorothionate.

Liquid; it has long residual action and effective against soil, fruit, vegetable and rice-insects; LD_{50}, 108-250 mg/kg.

The n-propyl isomer of diazinon (Pyrazinon) is also effective as an insecticide; LD_{50}, 261 mg/kg.

31. Primiphos - ethyl (Imperial Chemical Industries, 1972)

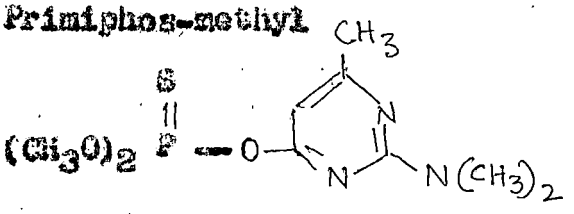


O,O-diethyl O-(2-dimethylamino-4-methylpyrimidin-6-yl) phosphorothionate.

Primiphos-ethyl is a liquid with broad insecticidal spectrum, particularly effective against diptera and coleoptera, it has also fungicidal activity; LD_{50}, 140-200 mg/kg.

(Contd.)

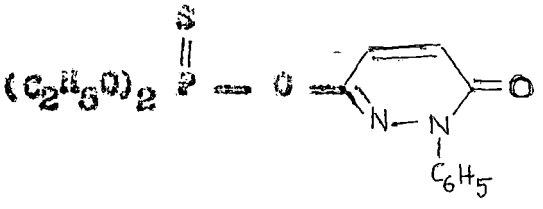
32. Primiphos-methyl



O,O-dimethyl O-(2-dimethylamino-4-methylpyrimidin-6-yl) phosphorothionate.

Primiphos-methyl is a liquid; it is an insecticide and acaricide with contact and fumigant activity; it is also used for stored products and for public health. LD_{50}, 2050 mg/kg.

33. Pyridafenthion, Ofnack(R) AC-12, 503 (Mitsui-Toatsu Chemicals, 1973).



O,O-diethyl O-(3-oxo-2-phenyl-2H-pyridazin-6 yl) phosphorothionate.

It is used for the control of rice stem borers.

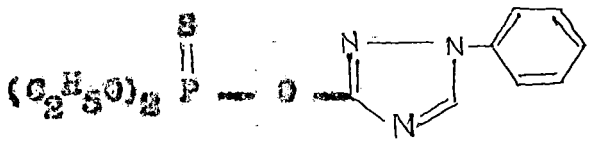
(Contd.)

34. Quinalphos, Bayrusil(R),
Diethquinalphion
(Bayer AG. 1965)

O,O-diethyl O-(2-quinoxalyl) phosphorothionate.

White crystalline powder, m.p. 36°C; contact and stomach activity, effective against both biting and sucking pests, especially against diamond-back moth; for control of mosquitoes and mites;
LD_{50}, 66 mg/kg.

35. Hostathion(R),
Triazophos, Hoe 2960;
(Farbwerke Hoechst 1967)

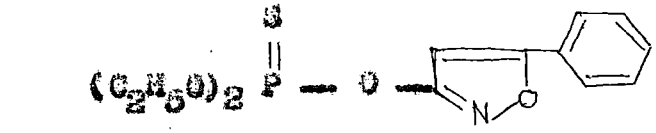


O,O-diethyl O-(1-phenyl-1,2,4-triazol-3yl) phosphorothionate.

Liquid; a non-systemic insecticide and acaricide, acting as a contact and stomach poison;
LD_{50}, 82 mg/kg.

(Contd.)

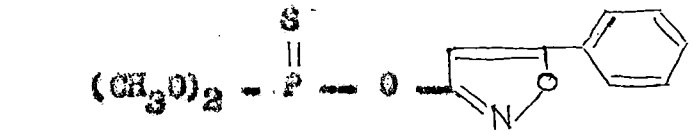
36. Isoxathion, Karphos(R)
(Sankyo Co. 1972)



0,0-diethyl O-(5-phenyl-3-isoxazolyl) phosphorothionate.

Liquid; a broad spectrum insecticide including scale insects and soil insects; LD_{50}, 112 mg/kg.

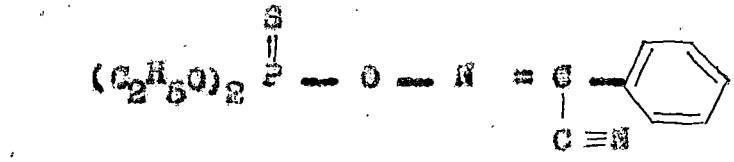
37. Dimex(R)



0,0-dimethyl O-(5-phenyl-3-isoxazolyl) phosphorothionate.

It is less toxic than the diethyl homolog; LD_{50}; 593-697 mg/kg (M).

38. Phoxim, Baythion(R), Valexon(R)
(Bayer AG. 1966)

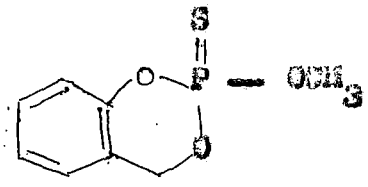


(Diethoxy phosphinothioyloxyimino) phenylacetonitrile.

Liquid; broad spectrum, contact and stomach poison; most useful against soil insects and stored products pests; LD_{50}, 2000 mg/kg.

(Contd.)

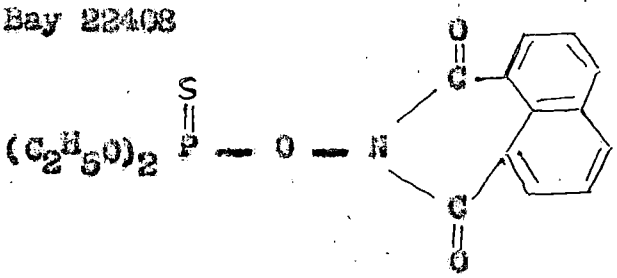
39. Salithion
(Sumitomo Chemical Co. 1968)



2-methoxy-4H-1,3,2-benzodioxaphosphorin-2-sulphide.

White crystalline powder, m.p. 56°C, a short lived insecticide for protection of fruits and vegetables;
LD_{50}, 102 mg/kg.

40. Bay 22408

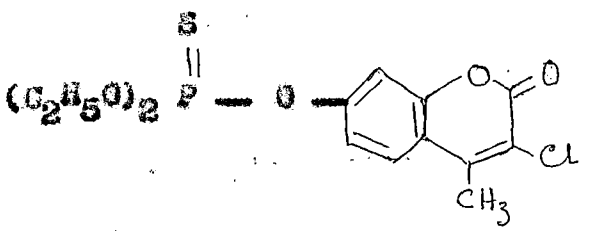


N-(diethoxyphosphinothioyloxy)-naphthalimide

Solid; insecticide, effective against mediterranean fruit flies;
LD_{50}, 500 mg/kg.

(Contd.)

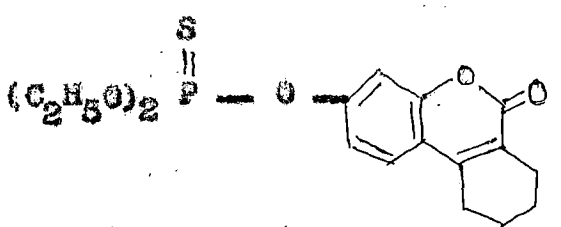
41. Coumaphos, Co-Ral(R), Asuntol(R), Muscatox(R)
(Montecatini, 1956)



Diethyl 3 chloro-4-methyl-coumarin-7-yl phosphoro-thionate.

Solid, m.p. 95°C, insecticide, useful to control ectoparasites on cattle, goats etc. by feed or spray; also effective against flies, mosquito larvae; active against gastro-intestinal nematodes and has synergistic activity with the anthelmintic agent phenothiazine;
LD_{50}, 90 to 110 mg/kg.

42. Coumithioate, Dition(R)
(Montacatini 1956)



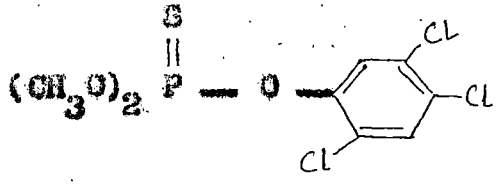
O,O-diethyl O-(3,4-tetra-methylene-7-coumarinyl) phosphorothionate.

Solid, m.p. 88-89°C; insecticide and miticide, useful for livestock pest control and for public health;
LD_{50}, 150 mg/kg.

(Contd.)

43. Bonnel, Trolene (R), fenchlorphos, Nemtor (R), Korlan (R)

(Dow Chem. Co. 1964)

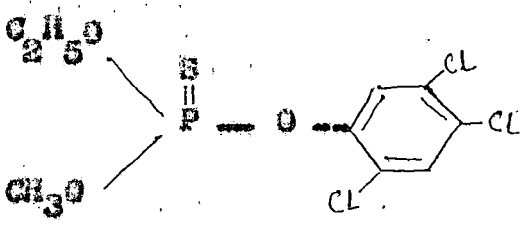


O,O-dimethyl O-(2,4,5-trichlorophenyl) phosphorothionate.

Solid, m.p. 40-42°C; animal systemic insecticide, effective to control cattle grub, lice, hornfly, screw-worm and ticks on livestock by oral administration; LD_{50}, 1250 - 1750 mg/kg.

44. Trichlormetaphos-3

(USSR)

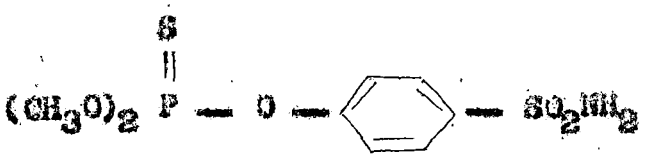


O-ethyl O-methyl O-(2,4,5-trichlorophenyl) phosphorothionate.

Liquid, insecticide, effective to control warble flies on cattle; useful against sucking insects, mites and midge larvae; LD_{50}, 330 - 800 mg/kg.

(Contd.)

45. Proban(R), Cythioate

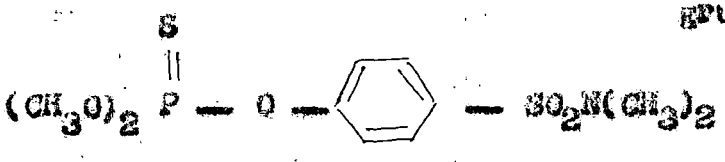


Solid, m.p. 43-42°C; useful for the control of ticks;

LD_{50}, 160 mg/kg.

O,O-dimethyl O-(P-sulfamoyl) phenyl phosphorothioate.

46. Famophos(R), Famphur
(American Cyanamid Co.)

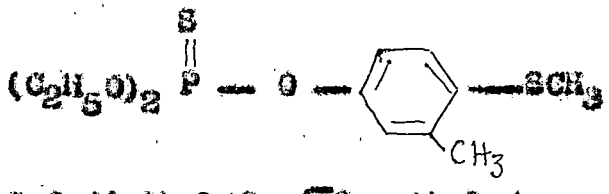


Solid, m.p. 55°C; systemic insecticide for cattle grubs;

LD_{50}, 35 mg/kg.

O,O-dimethyl O-[P-(dimethylsulfamoyl) phenyl] phosphorothionate.

47. Lucijet(R)



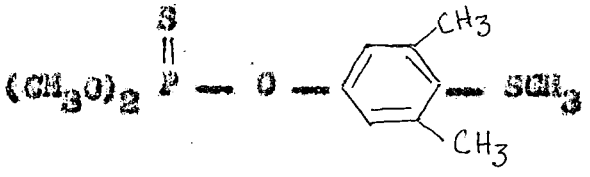
Liquid; insecticide effective against sheep blowfly larvae;

LD_{50}, 25 to 100 mg/kg.

O,O-diethyl O-[3-methyl-4-methylthiophenyl] phosphorothionate.

(Contd.)

48. Bay 37342

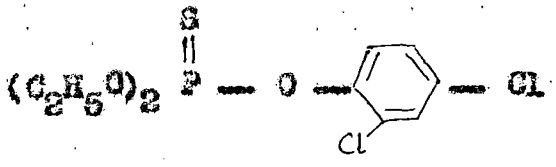


O,O-dimethyl O-(3,5-dimethyl-4-methylthiophenyl) phosphorothionate.

Liquid; animal systemic insecticide for the control of sheep botfly.

LD_{50}, 1000 mg/kg.

49. Nemacide(R), Dichlofenthion, VC-13 (Virginia-Carolina Chem. Corp.)



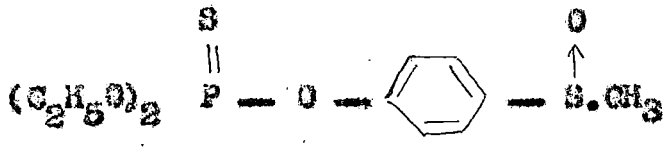
O,O-diethyl O-(2,4-dichlorophenyl) phosphorothionate.

Liquid; systemic, persistent nematocide and soil insecticide;

LD_{50}, 270 mg/kg.

(Contd.)

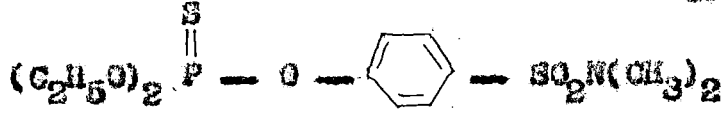
60. Dasanit (R), Fensulfothion, Terracur P (R)



O,O-diethyl O-(P-methylsulfinylphenyl) phosphorothionate.

Liquid; systemic, persistence nematocide and soil insecticide, it has also contact activity; LD_{50}, 4 to 10 mg/kg.

61. DSP; Kaya - ece (R) (Nippon Kayaku Co. 1966)

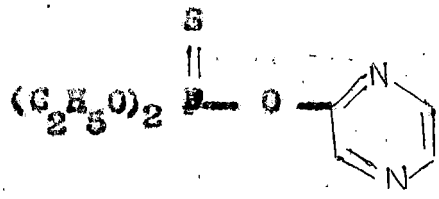


O,O-diethyl O-(P-dimethylsulfamoylphenyl) phosphorothionate.

Solid, m.p. 68 - 69°C; persistence nematocide and soil insecticide; LD_{50}, 65.4 mg/kg.

(Contd.)

52. Thionazin, Zinophos(R), Nemafos(R), Cynem(R) (American Cyanamid Co. 1966)



O,O-diethyl O-(Pyrazin-2-yl) Phosphorothionate.

Liquid; systemic soil insecticide and nematocide; persists about 4 weeks in soil;

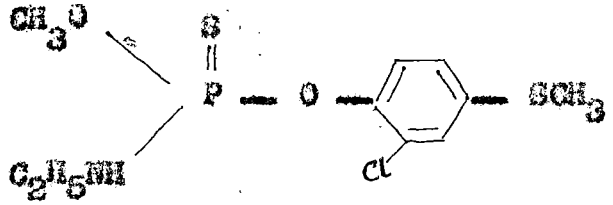
LD_{50}, 12 mg/kg.

(Contd.)

C. PHOSPHORAMIDES

53. Amidothioate, Hitemate(R)

(Nippon Kayaku Co. 1965)



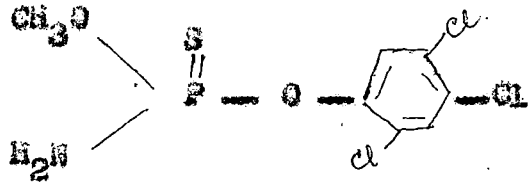
O-methyl O-(2-chloro-4-methylthiophenyl) N-ethyl-phosphoramidothionate.

Yellow oil; miticide, long residual activity and can be mixed with Bordeau mixture; kills both eggs and motive mites;

LD_{50}, 33 mg/kg (M).

54. Dow ET-15

(Dow Chem. Co.)



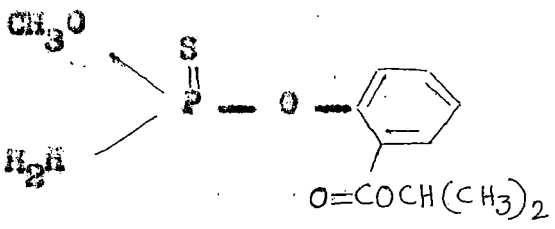
Methyl 2,4,5-trichlorophenyl phosphoramidothionate.

Insecticide;

LD_{50}, 710 mg/kg.

(Contd.)

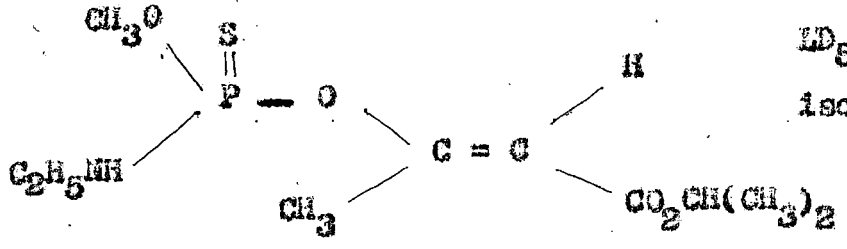
55. Optunal(R), isocarbophos.



O-(Isopropoxy carbonyl) phenyl methyl phosphoramidothionate.

Effective for colorado potato beetle and cotton insects; shows systemic activity against aphids and leaf rollers; LD_{50}, 50-100 mg/kg.

56. Compound 577 (Sandoz, 1972)

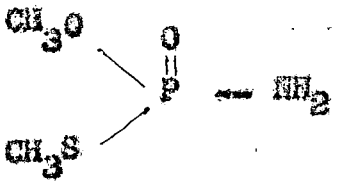


1-Isopropoxy carbonyl-1-propen-2-yl methyl N-ethyl phosphoramidothionate.

Experimental insecticide; trans isomer is more toxic than cis-isomer. LD_{50}, 122 mg/kg (Cis-isomer).

(Contd.)

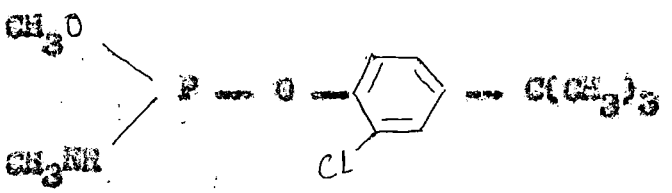
57. Monitor(R), Tamaron(R), Methamidophos.
(Bayer AG. 1964; Chevron Research Co. 1969)



O,S-dimethyl phosphoramido-thiolate.

Solid, m.p. 44.5°C; acaricide and broad spectrum insecticide with contact and systemic action; LD_{50}, 30 mg/kg.

58. Crufomate, Ruelene(R)
(Dow Chem. Co. 1959)

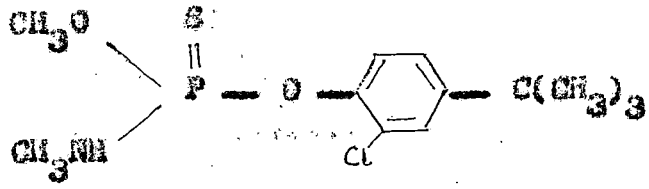


O-methyl O-(2-chloro-4-tert-butylphenyl) N-methyl-phosphoramidate.

Solid, m.p. 60°C; useful for the control of intestinal worms and warble flies.
LD_{50}, 770 to 1000 mg/kg.

(Contd.)

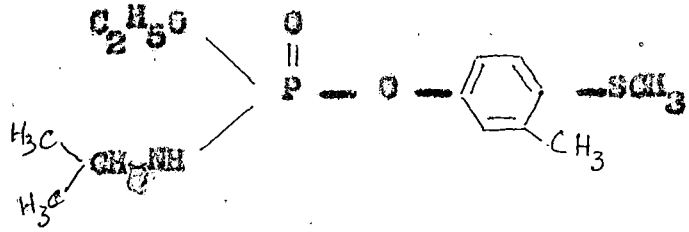
69. Narlene (R), Dowco 109 (R)
(Dow Chem. Co. 1968)



O-methyl O-(2-chloro-4-tert-butylphenyl) N-methyl-phosphoramidothionate.

Solid; effective to control cattle grubs and botflies on livestock and also as an anthelmintic.
LD_{50}, 1000 mg/kg.

60. Nemacur (R), Phenamiphos
(Bayer AG)

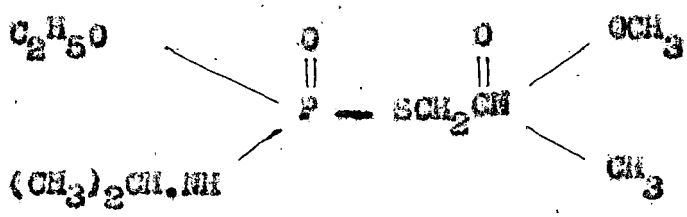


O-ethyl O-(3-methyl-4-methyl thiophenyl) N-isopropylphosphoramidate.

Solid, m.p. 49°C; systemic nematocide, effective against almost all nematode species below 6 ppm in soil for a long time (3 to 4 months)
LD_{50}, 15.3 - 19.4. mg/kg.

(Contd.)

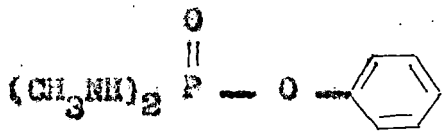
61. FCS 13. Nematocide.



O-ethyl S-(N-methoxy-N-methyl carbamoylmethyl) N-isopropyl phosphoramidothiolate.

62. Nellite (R), Dowco 169 (Dow Chem. Co)

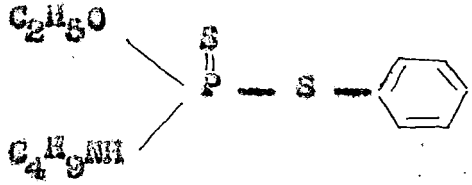
Solid, m.p. 105-106°C; systemic nematocide, specifically effective against root-knot nematode larvae; LD_{50}, 250 mg/k.



O-Phenyl N, N'-dimethyl phosphorodiamidate.

63. Phosbutyl

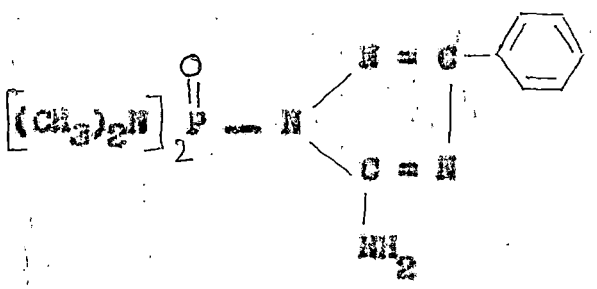
Liquid; fungicide, effective against mycelial cell formation, but not active against spore germination, LD_{50}, 300 mg/kg.



O-ethyl S-phenyl N-butyl-phosphoramidothiolothionate.

(Contd.)

64. Triamiphos, Wepsyn(R), Wepsin(R)

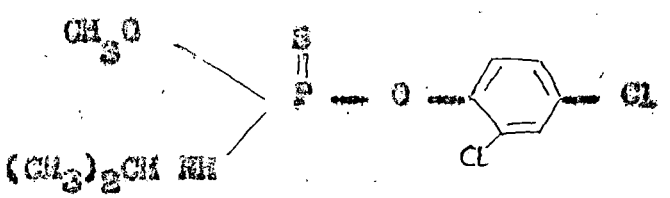


5-amino-1-[bis-(dimethylamino) phosphinyl]-3-phenyl-1,2,4-triazole.

Solid, m.p. 167 - 168°C insecticide and fungicide, effective against powdery mildew on apples and roses; useful as an acaricide with systemic properties.

LD_{50} , 20 mg/kg.

65. DMPA, Zytron(R) (Dow Chem. Co. 1959)

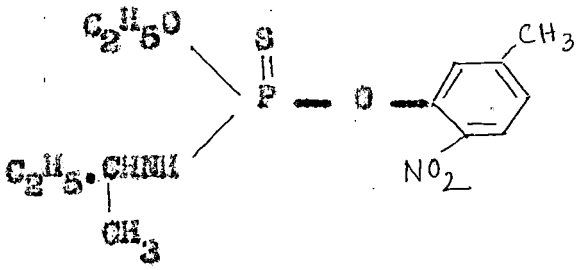


O-methyl O-(2,4 dichloro-phenyl) N-isopropylphos-phoramidothionate.

Solid, m.p. 51°C, pre-emergence selective herbicide for control of crabgrass in turf; LD_{50}, 270 mg/kg; it shows delayed neurotoxicity.

(Contd.)

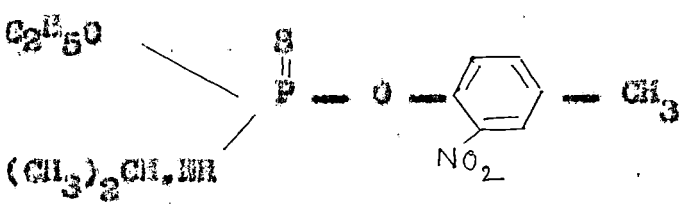
66. Cremart, S-2846
(Sumitomo Chem. Co)



O-ethyl O-(3-methyl-6-nitrophenyl) N-Sec.-butyl-phosphoramidothionate.

Liquid; pre-emergence herbicide, used in cereal, beans, cottons, carrot etc;
LD_{50}, 790 mg/kg. (male rat)

67. Amiprophos
(Nihon Nokushu Koyaku Co. 1971)



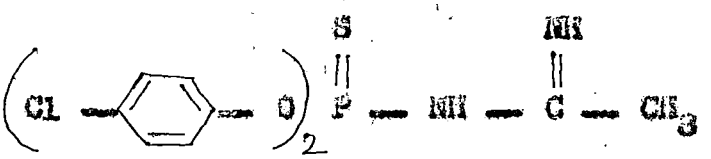
O-ethyl O-(2-nitro-4-methyl) N-isopropyl-phosphoramidothionate.

Herbicide;
LD_{50}, 720 mg/kg.

(Contd.)

68. Gophacide (R)

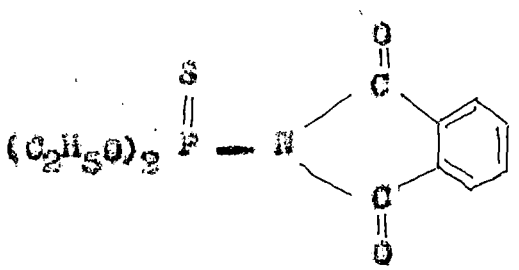
(Bayer AG)



O,O-di-(P-chlorophenyl) N-acetimidophosphoramidothionate.

Solid, m.p. 104-106°C; rodenticide; LD_{50}, 7.5 mg/kg.

69. Dowco 139



O,O-diethyl phthalimidophosphonothionate.

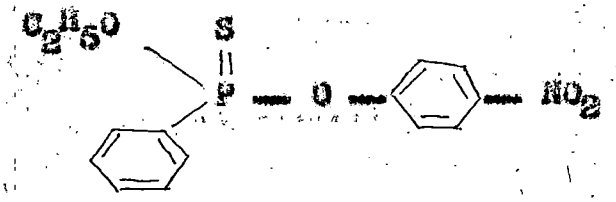
Solid, m.p. 83-84°C; fungicide, effective to control powdery mildew; shows curative and protective action; LD_{50}, 6,660 mg/kg.

(Contd.)

D. PHOSPHONOTHIONATES

70. EPN

(Du Pont. 1949)

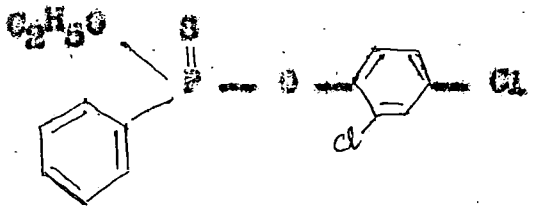


Ethyl P-nitrophenyl phenylphosphonothionate.

Light yellow crystalline solid, m.p. 36°C; insecticide and acaricide; potentiates the toxicity of malathion; shows delayed neurotoxicity; LD_{50}: 40 mg/kg (male rat) 13 mg/kg (female rat)

71. EPBP, S-Seven (R)

(Nissan Chemical Co. 1969)

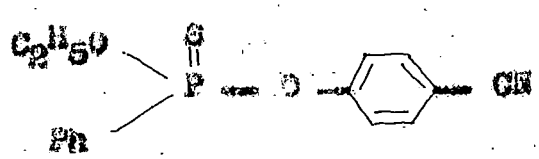


2,4 dicholorophenyl ethyl phenylphosphonothionate.

Liquid; soil insecticide (onion maggot); LD_{50}, 274 mg/kg (M)
Methyl ester homolog is more toxic than EPBP

72. Cyanofenphos, CYP, Surecide (R)

(Sumitomo Chemical Co. 1966)



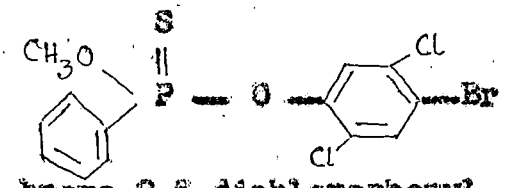
P-Cyanophenyl ethyl phenylphosphonothionate.

White crystalline powder, m.p. 83°C; insecticide rice stem borer, cotton boll worm etc; LD_{50}, 80 mg/kg.

(Contd.)

73. Phosvel(R), Leptophos, VCS - 566

(Velsicol Chemical Crop. 1965)



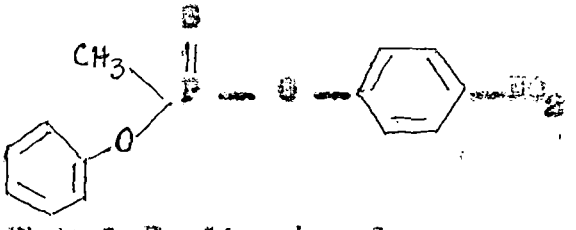
4-bromo-2,5-dichlorophenyl methyl phenylphosphonothionate.

White solid, m.p. 70.2°C; insecticide; controlling lepidopteran such as tobacco bud worms, cotton leaf worms, rice stem borers; has also fungicidal effect. LD_{50}, 90 mg/kg. It has no mutagenic or teratogenic properties.

74. Colep(R)

(Monsanto Co. 1962)

Insecticide.

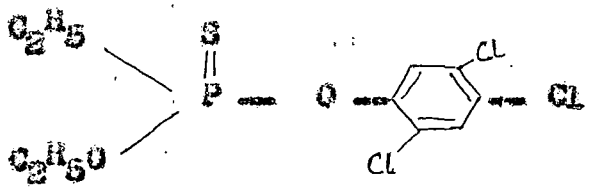


Phenyl P-nitrophenyl methylphosphonothionate.

(Contd.)

75. Trichloronate, Agritox (R), Agrisil (R), Phytosol (R) (Bayer AG 1960)

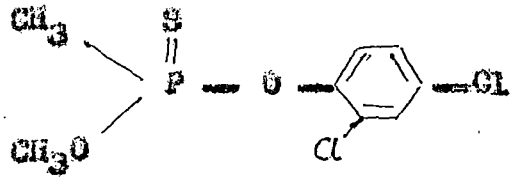
Liquid; nonsystemic, persistent soil insecticide (root maggots and wire - worms); LD_{50}, 50 mg/kg.



Ethyl 2,4,5 - trichlorophenyl ethylphosphonothionate.

76. Bay 30911

Systemic and contact insecticide with nematocidal activity; LD_{50}, 140 mg/kg.

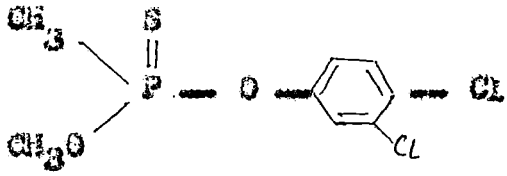


Methyl 2,4 - dichlorophenyl methylphosphonothionate.

(Contd.)

77. Bay 80833

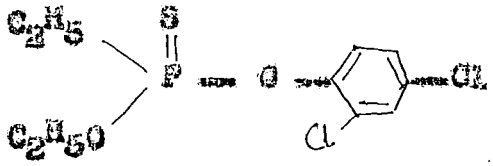
Soil insecticide.



Methyl 3,4-dichlorophenyl methylphosphonothionate.

78. Stauffer N 3054

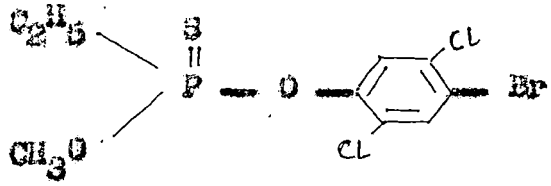
Insecticide;
LD_{50}, 75 mg/kg.



Ethyl 2,4-dichlorophenyl ethylphosphonothionate.

79. CELA K-41

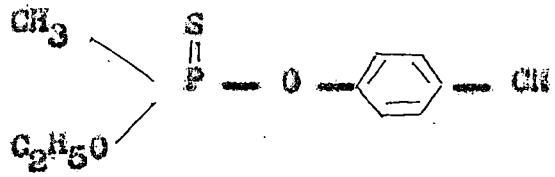
Insecticide and acaricide, 7 times more active than trichloro analog;
LD_{50}, 80 mg/kg.



4-bromo 2,5-dichlorophenyl methyl ethylphosphonothionate.

(Contd.)

80. Stauffer R-10341

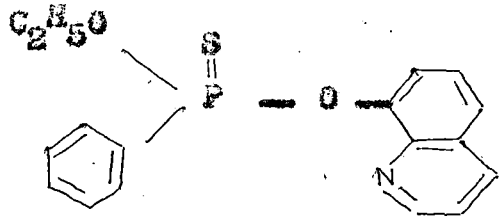


Ethyl 4-cyanophenyl methylphosphonothionate.

Insecticide, effective to resistant strain houseflies.

81. Becdip(R)

(Bayer AG)



O-ethyl O-(quinolin-8-yl) phenylphosphonothionate.

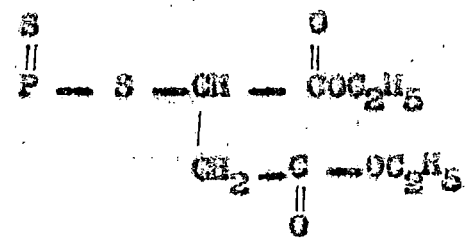
Acaricides; can be used to control ticks on livestock; LD_{50}, 150 mg/kg.

(Contd.)

E. PHOSPHOROTHIOLOTHIONATES.

82. Malathion, Cythion(R), Karbophos.
(American Cyanamid Co, 1950)

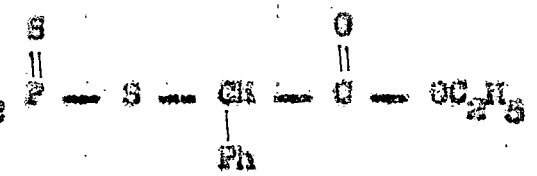
Liquid; safe general purpose insecticide with low mammalian toxicity; LD_{50}, 1375 mg/kg; contact and stomach poison.



O,O-dimethyl S-[1,2-di(ethoxycarbonyl) ethyl] phosphorothiolothionate.

83. Phenthoate, Cidial(R), dimephenthoate, Papthion(R), Elsan(R)
(Soc. Montecatini, Italy 1964).

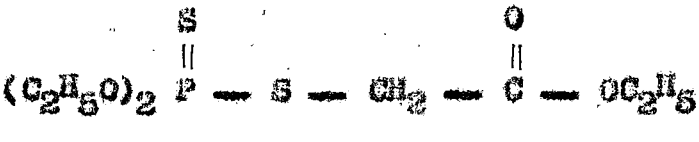
Liquid; broad spectrum insecticide and acaricide; LD_{50}, 4,700 mg/kg.



O,O-dimethyl S-[(α-ethoxycarbonyl) benzyl] phosphorothiolothionate.

(Contd.)

84. Acethion



Liquid; selective insecticide; LD_{50}, 1100 mg/kg; it is not used practically.

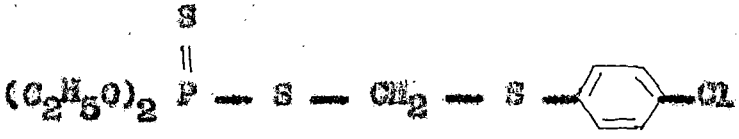
O,O-diethyl S-[ethoxy carbonyl-methyl] phosphorothiolothionate.

85. Chlormephos (Murphy Chemical Co. 1968).

Liquid; non systemic soil insecticide, particularly for control of larvae of coleoptera (wire worms); LD_{50}, 7 mg/kg.

O,O-diethyl S-chloromethyl phosphorothiolothionate.

86. Trithion(R), Gerrathion(R) Carbophenothion, Akarithion(R) (Stauffer Chemical Co. 1955)



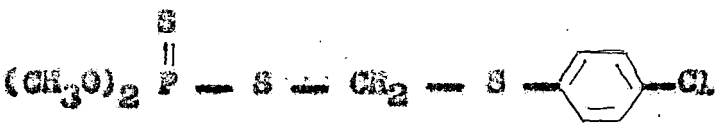
Liquid; insecticide and acaricide with long residual action; used for sucking plant pests, particularly mites; useful as a dip for cattle tick; LD_{50}, 30 mg/kg.

O,O-diethyl S-(P-chloro-phenyl-thiomethyl) phosphorothiolo-thionate.

(Contd.)

87. Methyl trithion(R), methyl carbophenothion
(Stauffer Chem. Co. 1958)

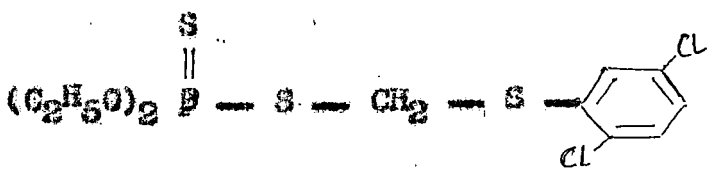
Liquid; for control of variety of insects and mites; particularly cotton boll weevil;
LD_{50}, 150 mg/kg.



O, O-dimethyl homolog of trithion(R)

88. Phenkapton, Phencapton(R)
(Geigy AG. 1956)

Liquid; nonsystemic, selective acaricide with prolonged action and effective against all development stages including eggs ;
LD_{50}, 200 mg/kg.

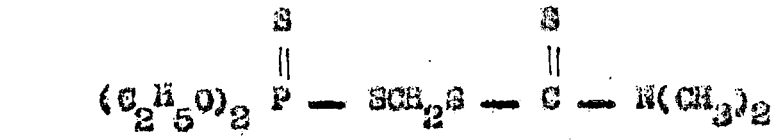


O,O-diethyl S-(2,5-dichlorophenylthiomethyl) phosphorothiolothionate.

(Contd.)

89. Azothion

(Farbwerke Hoechst, 1957)

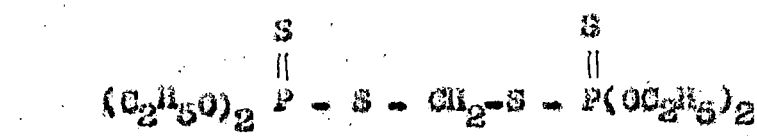


O,O-diethyl S-(N,N-dimethyl thiocarbamyl thiomethyl) phosphorothiolothionate.

Insecticide and acaricide; LD_{50}, 150 mg/kg.

90. Ethion, Nialate (R)

(Food Machinery and Chemical Crop. 1956)



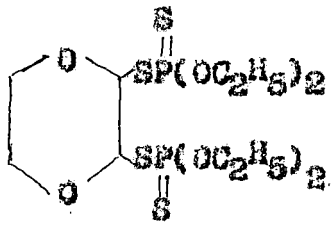
O,O,O',O'-tetraethyl S,S'-methylene bis (phosphorothiolothionate).

Liquid; for control of aphids, scales and mites; LD_{50}, 208 mg/kg.

Tetramethyl homolog is effective to bean leaf-lice and Tetranychus telarius.

(Contd)

91. Dioxathion, Delnav (R), Navadel (R) (Hercules Incorporated, 1954)

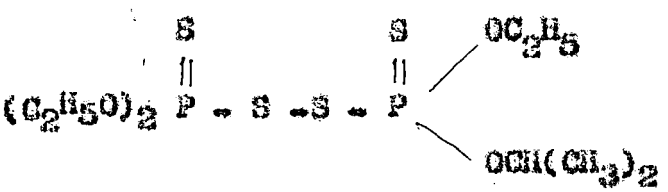


1,4 dioxan-2,3-ylidene bis (O,O-diethyl phosphoro-thiolothionate).

The methyl ester homolog has high insecticidal activity but low mammalian toxicity (LD_{50}, 300 mg/kg).

Liquid; non systemic acaricide and insecticide with a long residual effect and particularly useful to control mites on cotton and fruits and ticks, lice and hornfly on cattle; the cis-isomer is more toxic to both insects and mammals than the trans isomer; LD_{50}, 65-240 mg/kg (mixture of cis & trans).

92. Phostex (R) (Food Machinery and Chemical Corp. 1954)

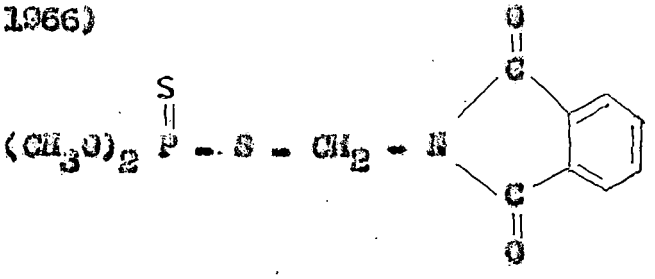


Diethoxy phosphinothionyl ethoxy isopropoxyphosphinothionyl disulphide.

Weak contact insecticide, but a highly effective miticide with a good ovicidal activity; LD_{50}, 2,500 mg/kg.

(Contd.)

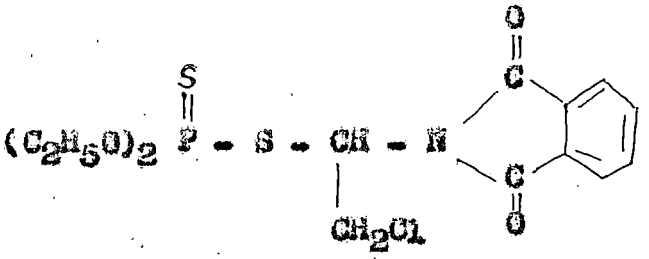
93. Phosmet, Imidan(R), phthalophos, Prolate(R) (Stauffer Chemical Co. 1966)



O,O-dimethyl S-(phthalimidomethyl) phosphorothiolothionate.

White crystalline solid, m.p. 72°C, acaricide and broad spectrum insecticide for sucking and chewing insects; LD_{50}, 230 mg/kg.

94. Dialifor, Torak(R) (Hercules Incorporated, 1965)



O,O-diethyl S-(2-chloro-1-phthalimidoethyl) phosphorothiolothionate.

Crystalline solid m.p. 67 - 69°C, insecticide and acaricide; LD_{50}, 5-97 mg/kg (depending on species and sex)

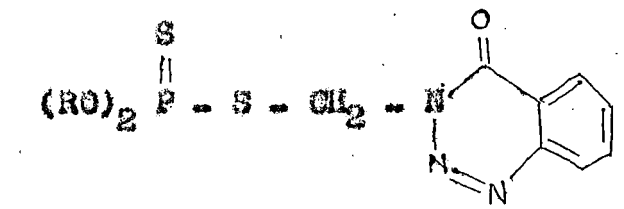
(Contd.)

95. (a) Azinphosmethyl, Guthion(R), Gusathion(R)

Azinphosmethyl: white crystalline solid m.p. 73-74°C, LD_{50}, 15 mg/kg.

(b) Azinphosethyl, Ethyl guthion, Gusathion A(R) (Bayer AG. 1953)

Azinphosethyl: Colourless needles, m.p. 53°C; LD_{60}, 17.5 mg/kg.



(a) R ≡ CH_3 azinphosmethyl

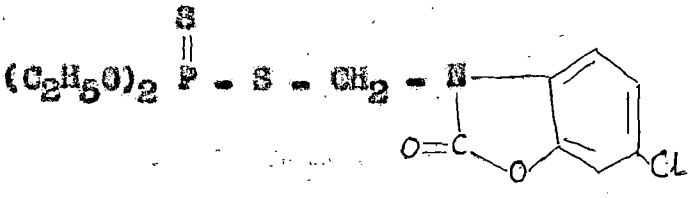
(b) R ≡ C_2H_5 azinphosethyl

Both are non-systemic insecticide and acaricide with long residual activity under neutral condition.

(a) Azinphosmethyl: O,O-dimethyl S-(~~ethyl~~-4-oxobenzo [illegible] - [1,2,3]- triazin-3 yl methyl) phosphorothiolothionate.

(Contd.)

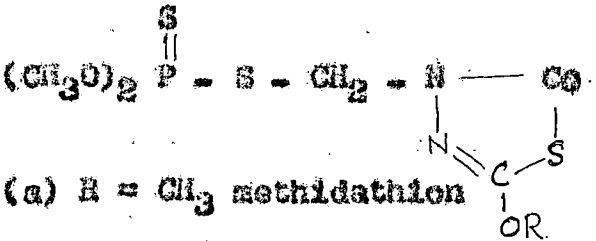
96. Zolone(R), Phosalone (Rhone-Poulenc, France 1961)



O,O-diethyl S-(6-chloro-2-oxobenzoxazolin-3-ylmethyl) phosphorothiolothionate.

Solid; m.p. 43°C; broad spectrum, non-systemic insecticide and acaricide; sap-feeding pests; LD_{50}, 120 mg/kg.

97. Methidathion, Supracide(R), Ustracide(R) (Geigy AG. 1963).



(a) R = CH_3 methidathion
(b) R = C_2H_5 lythidathion

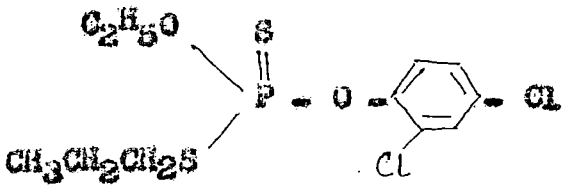
Methidathion:

O,O-dimethyl S-[(5-methoxy-2-oxo-1,3,4-thiadiazol-3-yl)methyl] phosphorothiolothionate.

(a) Methidathion: Solid, m.p. 39-40°C; non-systemic insecticide and acaricide with a wide spectrum; for controlling aphid, lepidopterous larvae (codling moth) and scales on fruit trees and cotton; LD_{50}, 26-48 mg/kg. (b) Ethoxy homolog (lythidathion), LD_{50}, 368-443 mg/kg) is useful specially against lepidopterous and dipterous larvae and orthoptera.

(Contd.)

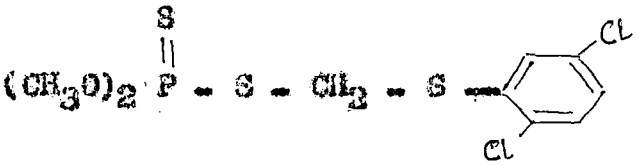
98. Tokuthion



O-ethyl S-propyl O-(2,4 dichlorophenyl) phosphoro-thiolothionate.

Experimental insecticide, effective to control mulbery mealybug, smaller tea tortrix, caterpillars etc; less toxic than the corresponding phosphoro-thionate.

99. Methyl Phenkapton (Geigy AG)

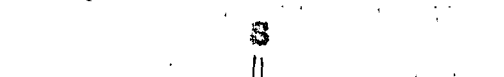


O,O-dimethyl S-(2,5-dichlorophenylthiomethyl) phosphorothiolothionate.

Acaricide and insecticide; LD_{50}, 375 mg/kg.

(Contd.)

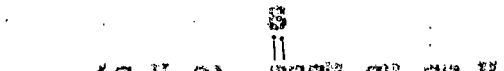
100. Thiometon, Ekatin(R), Dithiometasystox(R) (Sandoz Ltd.)



O,O-dimethyl S-(2-ethylthioethyl) phosphorothiolothionate.

Liquid; a systemic insecticide and acaricide with contact action; effective against aphids, sawflies, thrips, and mites; LD_{50}, 70-120 mg/kg.

101. Disulfoton, thiodemeton, Disyston(R), Dithiosystox (Bayer AG. 1966)



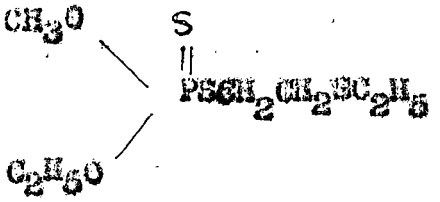
O, O-diethyl S-(2-ethylthioethyl) phosphorothiolothionate.

Liquid; a systemic insecticide and acaricide, used mainly for soil pest; seed dressing or granules to protect seedlings; effective against aphids on vegetables and fruits and carrot fly, leaf-hoppers on rice, vegetables, cotton and for some other pests.

(Contd.)

102. Tetrathion

(in Czechoslovakia)



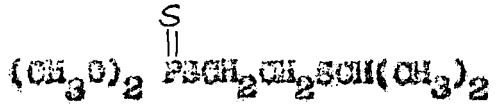
O-methyl O-ethyl S-(2-ethylthioethyl) phosphorothiolothionate.

Liquid; a systemic insecticide and acaricide, used mainly for soil pests; chemical and insecticidal properties are similar to thiometon and Disulfoton;

LD_{50}, 1.2 - 22.3 mg/kg (various animals)

103. Isothioate, Hasdon(R)

(Nihon Noyaku Co. 1972)



O,O-dimethyl S-(2-isopropylthioethyl) phosphorothiolothionate.

Liquid; a systemic insecticide and acaricide, effective against sucking plant pests by soil treatment or foliage spray;

LD_{50} , 200 mg/kg.

(Contd.)

104. Phorate, Thimet(R), timet (American Cyanamid Co. 1954)

$(C_2H_5O)_2 \overset{S}{\overset{\|}{P}}SCH_2SC_2H_5$

Liquid; a persistent systemic insecticide, used for the protection of seedlings from sap-feeding and soil insects; it has also some contact and fumigant action; LD_{50} , 2-4 mg/kg.

105. Am. Cy. 12008 (American Cyanamid Co. 1954)

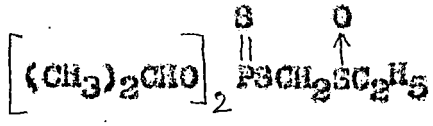
$(C_2H_5O)_2 \overset{S}{\overset{\|}{P}}SCH_2SCH(CH_3)_2$

O,O-diethyl S-(isopropylthiomethyl) phosphorothiolothionate.

Liquid; systemic insecticide with some contact activity; LD_{50}, 4 to 16 mg/kg (M).

(Contd.)

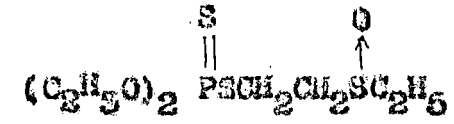
106. Aphidan, IPSP, PSP-204
(Hokko Chemical Co. 1964)



O,O-diisopropyl S-(ethylsulfinylmethyl) phosphorothiolothionate.

Liquid; a systemic insecticide, applied in soils to protect the plant from the attack of aphid; potatoes can be protected from aphid vector of virus diseases by treating the seed potatoes.
LD_{50}, 84.5 mg/kg.

107. Oxydisulfoton, Disyston-S(R), Disyston-Sulfoxide(R)
(Bayer AG. 1965)

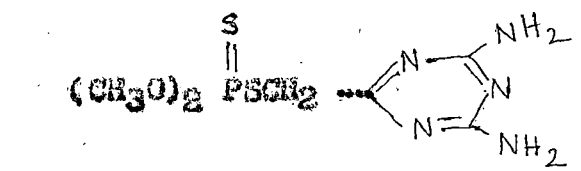


O,O-diethyl S-(2-ethylsulfinylethyl) phosphorothiolothionate.

Liquid; a persistent systemic insecticide and acaricide, particularly suitable for seed treatment against various vector (sap-sucking insects);
LD_{50}, 3.5 mg/kg.

(Contd.)

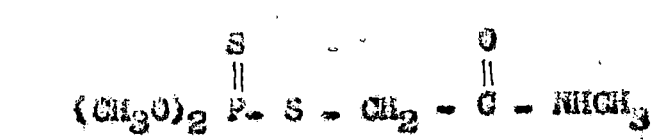
108. Menazon, azidithion, Saphizon(R), Bayfos(R) (Plant Protection Ltd. 1959)



0,0-dimethyl S-(4,6-diamino 1,3,5-triazin-2-ylmethyl) phosphorothiolothionate.

Crystalline solid, m.p. 166°C systemic aphicide, used by foliar spray, soil treatment, seed dressing and root dip; LD_{50}, 900 to 1,950 mg/kg.

109. Dimethoate, Rogor(R), Cygon(R),

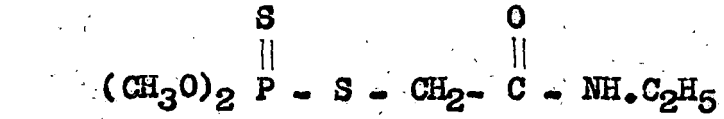


0,0-dimethyl S-(N-methylcarbamoylmethyl) phosphorothiolothionate.

Solid, m.p. 51-52°C; systemic and contact broad-range insecticide and acaricide; LD_{50}, 600 mg/kg (pure compd.) 150-300 mg/kg (technical product).

(Contd.)

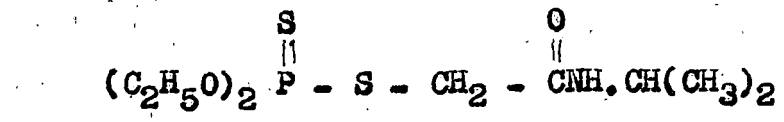
110. Ethoate - methyl,
Fitios B/77
(Bombrini Parodi-
Delfino, Italy).



0,0-dimethyl S-(N-
ethylcarbamoylmethyl)
phosphorothiolothionate.

Solid, m.p. 67-68°C;
insecticide and acaricide
with contact action,
particularly effective
against fruit-fly;
LD_{50}, 340 mg/kg.

111. Prothoate, Fostion$^{(R)}$,
Fac 20$^{(R)}$
(Soc. Montecatini. 1956)



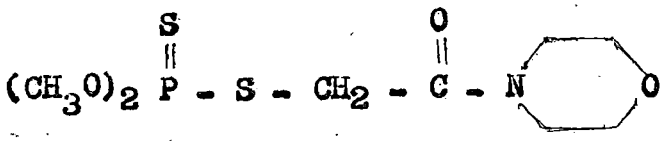
0,0-diethyl S-(N-
isopropylacarbamoylmethyl)
phosphorothiolothionate.

Crystalline solid, m.p.
28.5°C, acaricide and
insecticide with systemic
action, used mainly against
phytophagous mites and
some sap-sucking insects;
olive fly, cherry maggot;
LD_{50}, 10 mg/kg.

(Contd.)

112. Morphothion, Ekatin M(R), Ekatin F(R), Morphotox(R)
(Sandoz Ltd. 1956)

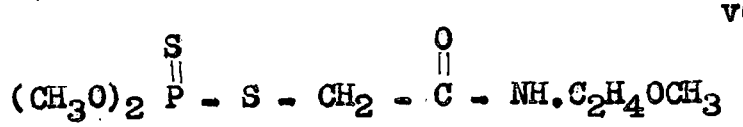
Crystalline solid, m.p. 63-64°C; a systemic and contact insecticide; LD_{50}, 190 mg/kg.



0,0-dimethyl S-(morphilino carbonylmethyl) phosphorothiolothionate.

113. Amidothion, Thiocron(R), Medithionate.
(Ciba Ltd. 1963)

Solid, m.p. 46°C; insecticide, sucking pests on cherries and vegetables; LD_{50}, 600-660 mg/kg.

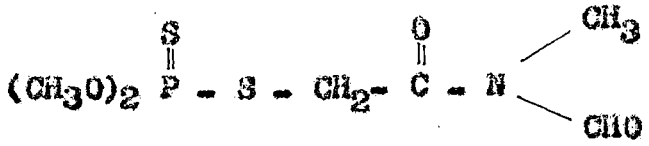


0,0-dimethyl S-(N-Methoxyethylcarbamoylmethyl) phosphorothiolothionate.

(Contd.)

114. Formothion, Anthio(R), Aflix(R)

(Sandoz Ltd. 1963)

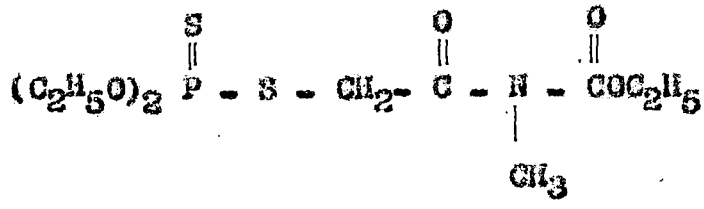


O,O-dimethyl S-(N-formyl-N-methylcarbamoylmethyl) phosphorothiolothionate.

Liquid; contact and systemic acaricide and insecticide, effective against both sucking and chewing pests; LD_{50} 375-535 mg/kg.

115. Mecarbam, Pestan(R), Murfotox(R), Afos(R)

(Murphy Chemical Ltd. 1961)

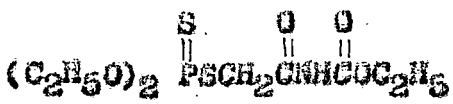


O,O-diethyl S-(N-ethoxycarbonyl-N- methylcarbamoylmethyl) phosphorothiolothionate.

Liquid; contace insecticide and acaricide with slight systemic action; persists in soil for several weeks; useful for control of sucking and chewing pests and root maggots of vegetables; LD_{50}, 36 mg/kg.

(Contd.)

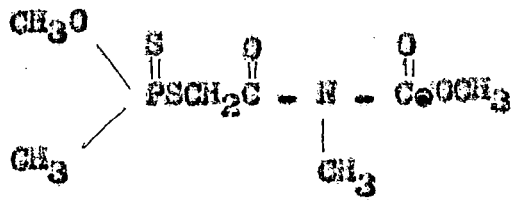
116. Bay 19586



N-desmethyl homolog of Mecarbam

Insecticide, effective against the oriental fruit fly and the melon-fly.

117. Mecarphos, Mecarphon (Murphy Chemical Ltd.)



S-(N-methoxycarbonyl-N-methylcarbamoylmethyl) methyl methylphosphorothiolothiolate.

Systemic insecticide; LD_{50}, 57 mg/kg.

(Contd.)

118. DMEP, Amiphos(R)

(Nippon Soda Co. 1966)

$(CH_3O)_2 P(=S)CH_2CH_2NHC(=O) - CH_3$

Dimethyl S-(2-acetamido-ethyl) phosphorothiolo-thionate.

Solid, m.p. 22-23°C; systemic acaricide and insecticide, useful to control sucking pests on fruits, vegetables, and ornamentals; LD_{50}, 400 mg/kg.