SYNTHESIS OF ORGANOPHOSPHOROUS HYDRAZIDES AND STRUCTURALLY RELATED COMPOUNDS

A Thesis

Presented to

the Faculty of the College of Pharmacy

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

---

by

Suresh B. Sachanandani

December 1974

"DEDICATED TO MY BELOVED PARENTS WHOSE
UNCEASED FLOW OF LOVE HAS ALWAYS BEEN
A SOURCE OF INSPIRATION FOR ME."

ACKNOWLEDGEMENTS

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An Abstract of the Thesis

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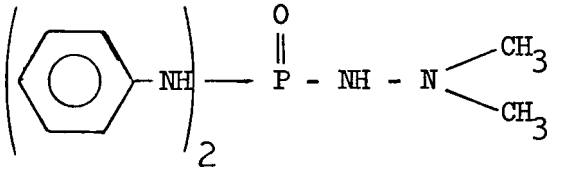
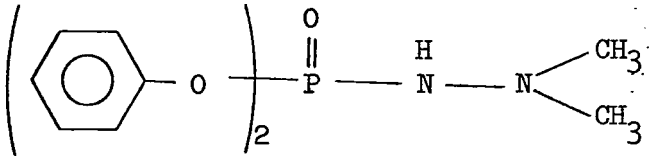
ABSTRACT

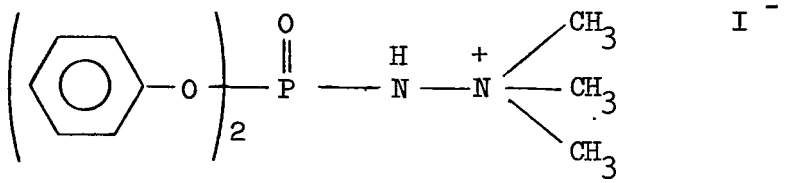
SYNTHESIS OF ORGANOPHOSPHOROUS HYDRAZIDES

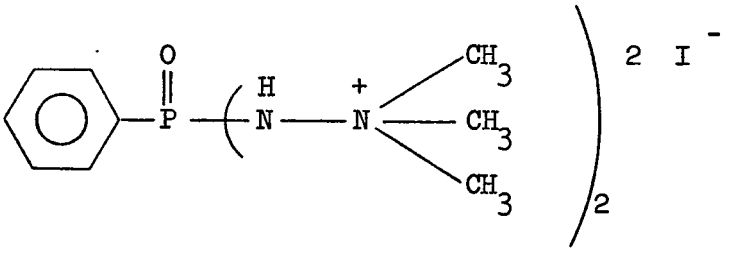
AND STRUCTURALLY RELATED COMPOUNDS.

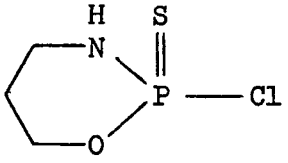
Quarternary ammonium compounds generally possess anticholinergic activity. An example of this is the ganglionic blocking agent, hexamethonium chloride: $(CH_3)_3\overset{+}{N}-(CH_2)_6-\overset{+}{N}-(CH_3)_3$ 2 Cl^-. Procarbzine, which has the structure: $(p\text{-}CH_3\text{-}NH\text{-}NH\text{-}CH_2)PhCONHCH(CH_3)_2$ is an antineoplastic agent. The hydrazine moiety in this compound appears with frequency in antineoplastic agents. Keeping these structure-activity relationships in mind, the following compounds were synthesized for biological evaluation.

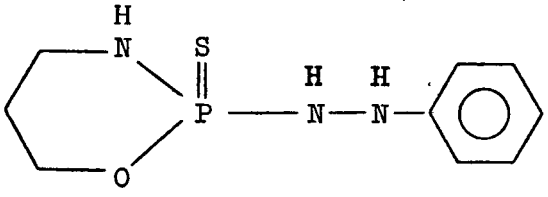
1. 

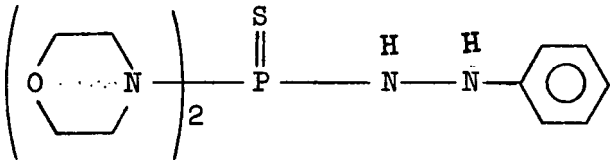
2. 

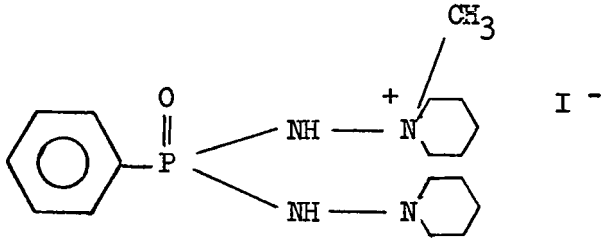
3. 

4. 

5. 

6. 

7. 

8. 

The first four compounds may possess antineoplastic and/or anti-cholinergic activity while the next four compounds may be active as anticancer and/or insecticidal agents.

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CHAPTER I

HISTORY AND INTRODUCTION

"Of all the strange things I have heard
of on this earth, the strangest of them
all is that men fear death..."

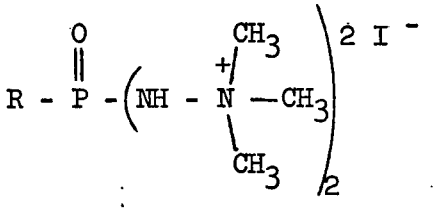
-Shakespeare

A survey of the medicinal chemical literature indicates that considerable interest has been shown in both quarternary amine compounds and agents possessing the hydrazine grouping. The former type of chemical compound has been widely studied with regard to its interaction with muscarinic and nicotinic receptors of the autonomic nervous system. Compounds containing the NH-NH moiety, on the other hand, have found application mostly as monoamine oxidase inhibitors but this grouping appears with frequency in anticancer agents and is an intricate part of the activity of at least one class of oncolytics, the methyl hydrazines.

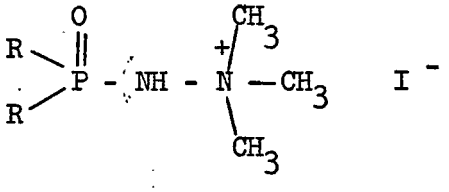
The current interest (1) in a class of compounds termed aminimides (Ia) prompted an investigation of these agents, their precursors and their phosphorous analogues, as potential therapeutic agents. Aminimides are of medicinal chemical interest since they contain both a quarternary nitrogen and a hydrazide linkage and are intraionic in nature. This latter property is expected to influence solubility and in vivo absorption.

Objective:

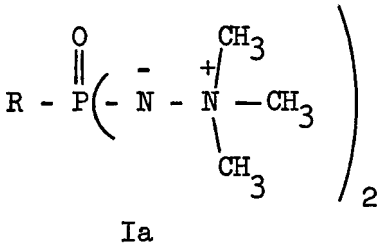
The purpose of this project was to synthesize a series of compounds I, Ia, Ib, II and IIa, and some structurally related compounds, and to subject samples of these compounds to preliminary pharmacological evaluation of antitumor and anticholinergic activity.



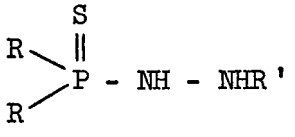
I



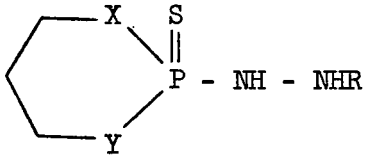
Ib



Ia



II



IIa

The compounds of type II and IIa, have shown some activity as contact insecticides on rice weevils (2). I will refer the new compounds of type II and IIa to the Ministry of Agriculture, Government of India. India has one-third of the world's rice growing land but its harvests have been largely hampered by lack of proper insecticides.

Background

A. Pharmacology

Anticholinergic drugs interfere with physiological functions that are dependent on cholinergic nerve transmission. These drugs do not prevent acetylcholine from being released at nerve endings, but they may compete with the liberated neurohormone for cholinergic receptor sites. Acetylcholine is the chemical transmitter at the post ganglionic parasympathetic nerve endings, as well as at autonomic ganglia and somatic neuromuscular junctions. Different types of anticholinergic drugs will antagonize the actions of acetylcholine at these three types of synapses. The anticholinergic drugs that will block somatic neuromuscular junction, and autonomic ganglia are termed curareform and ganglionic blocking drugs, respectively. The anticholinergics that mimic the effects of cutting the parasympathetic nerve supply to various organs are designated as parasympatholytics.

Muscarine mimics the actions of acetylcholine on the structures innervated by parasympathetic nerves; it is relatively inactive at autonomic ganglia and somatic neuromuscular junctions. Parasympatholytics that antagonize the actions of muscarine are also known as antimuscarinic agents. The classical parasympatholytic agent is atropine, and therefore anticholinergic drugs used to be referred to as atropinic agents.

Antimuscarinic agents inhibit the action of acetylcholine (ACh)

on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to ACh but lack cholinergic innervation; that is, they antagonize the muscarinic action of ACh. In general, antimuscarinic agents have much less effect on the action of ACh at other sites; however, high doses of atropine can block transmission at autonomic ganglia and skeletal neuromuscular junctions. The ratio of muscarinic to ganglionic blocking activity varies quite widely among the synthetic substitutes for atropine.

The major action of antimuscarinic agents is a competitive or surmountable antagonism to ACh and other muscarinic agents. The antagonism, therefore, can be overcome by increasing the concentration of ACh at receptor sites of the effector organ. The naturally occuring antimuscarinic drugs are the alkaloids of belladonna plants. Accurate study of the actions of belladonna dates from the isolation of atropine in pure form by Mein in 1831. Many semi-synthetic congeners of the belladonna alkaloids, usually quarternary ammonium derivatives, and a large number of synthetic antimuscarinic compounds have been prepared (Tables I and II).

A wide variety of compounds possess anticholinergic activity. Development of such compounds has been largely empiric and based principally on atropine as a prototype. Most medicinal chemists consider that the anticholinergic molecules have a primary point of attachment to cholinergic sites through the so-called cationic head; i.e., the positively charged nitrogen. In the case of the quarternary compounds there is no question of what is implied, but in the case of

tertiary amines one assumes, with good reason, that the cationic head is achieved by protonation of the amine at physiologic pH. It is undoubtedly true that a cationic head is far better than none at all; yet it is possible to obtain a typical competitive

PARASYMPATHETIC BLOCKING AGENTS

BELLADONNA ALKALOIDS AND CLOSELY ALLIED SYNTHETIC SUBSTANCES

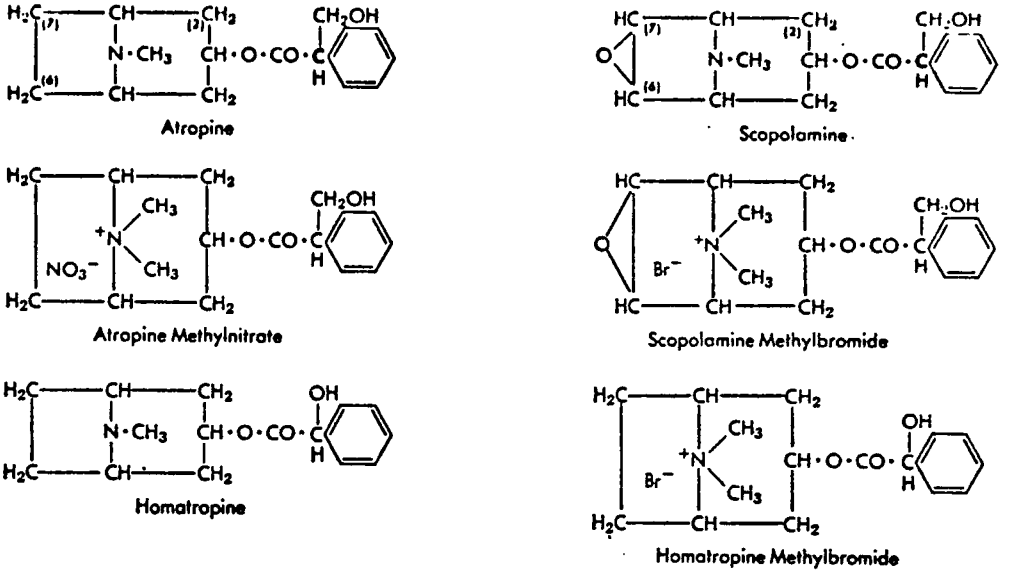
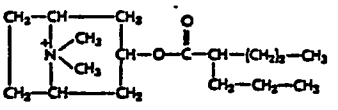
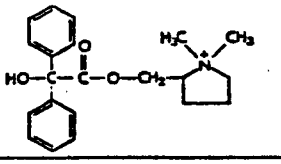
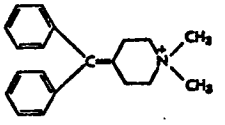
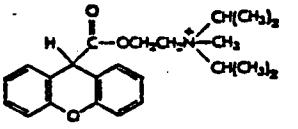
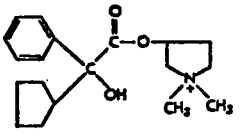
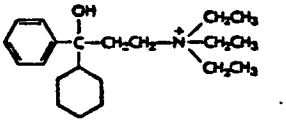
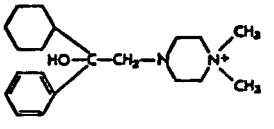
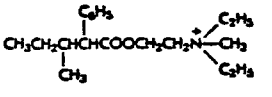
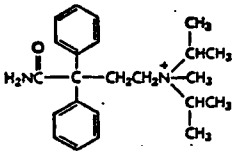
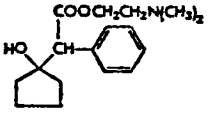
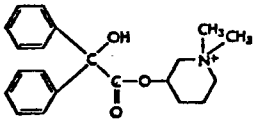
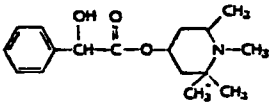
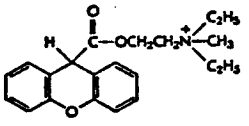
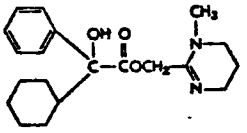
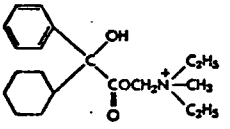
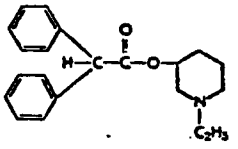
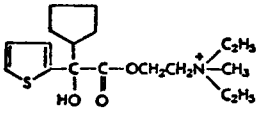
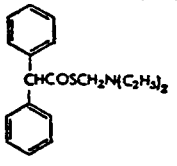


Table I (62)

block without a cationic head. That this is the case has been shown by Ariens and his co-workers (3) in the case of so-called carbocholines typified by benzyl carbocholine (III).

REPRESENTATIVE SYNTHETIC ANTIMUSCARINIC DRUGS

NONPROPRIETARY NAME	CHEMICAL STRUCTURES	NONPROPRIETARY NAME	CHEMICAL STRUCTURES
Quarternary Ammonium Anisotropine		Poldine	
Diphemanil, N.F.		Propantheline, U.S.P.	
Glycopyrrolate, N.F.		Tridihexethyl, N.F.	
Hexocyclium		Valethamate, N.F.	
Isopropamide, N.F.		*Other Synthetic Antim* Cyclopentolate, U.S.P.	
Mepenzolate, N.F.		Eucatropine, U.S.P.	
Methantheline, N.F.		Oxyphencyclimine, N.F.	
Oxyphenonium		Piperidolate	
Penthienate, N.F.		Thiphenamil	

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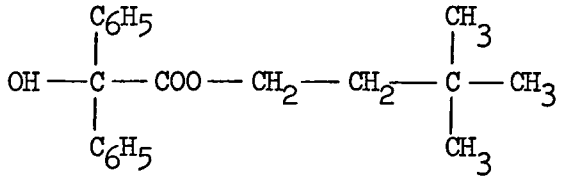


III

These compounds show a typical competitive action with acetylcholine, although they are less effective than the corresponding compounds possessing a cationic head.

Many of the highly potent compounds of this type possess an ester grouping, and it may be a necessary feature for the most effective binding. It is probable that it attaches to the receptor area at a positive site, similarly to acetylcholine.

At least one cyclic subsituent (phenyl, thienyl, etc.) is a feature of the molecule. The question of the superiority of the cyclic species used (i.e., phenyl, thienyl, cyclohexyl, etc.) appears not to have been explored in depth, although phenyl rings seem to predominate. Substituents on the aromatic rings seem to contribute little to activity.

An important comparison of the effects of several anticholinergic drugs was made by Herxheimer in 1958 (4).

The main differences in pharmacological properties are seen with those compounds having a quarternary ammonium structure.

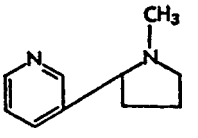
These drugs are poorly and unreliably absorbed after oral administration, and vaild comparisons of their potencies with those of the belladonna alkaloids can be made only after parenteral administration. Central effects are generally lacking, because these agents do not readily pass the blood-brain barrier. The quarternary ammonium compounds usually have a somewhat more prolonged action than do the natural alkaloids; little is known of the fate and excretion of most of these agents. The ratio of ganglionic blocking to antimuscarinic activity is greater than in compounds without the quarternary ammonium structure, and some of the side effects seen after high doses indicate that an element of ganglionic block may be present. Poisoning with quarternary ammonium compounds may also cause a curariform neuromuscular block, leading to respiratory paralysis. Toxic doses of these agents produce, therefore, the usual manifestations of antimuscarinic poisoning with additional effects of ganglionic and, rarely, neuromuscular block, but usually without striking CNS involvement.

Ganglionic blocking agents may be classified tentatively into two groups. The first group includes those drugs that initially stimulate the ganglia by an ACh-like action and then block because of a persistent depolarization (e.g., nicotine); this results in desensitization of the cholinoceptive site and a prolonged blockade. (5, 6)

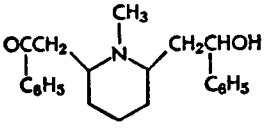
The blockade of autonomic ganglia produced by a second group

of blocking drugs, of which hexamethonium can be regarded as a prototype, does not involve prior ganglionic stimulation or changes in the ganglionic potentials. Such agents impair transmission by competing with ACh for ganglionic cholinoceptive sites and, in a manner analogous to the blockade of transmission at the neuromuscular junction by curare. Compounds in this group have no effect on nerve conduction or on the release of transmitter substance from the nerve terminals. It is this class of conventional ganglionic blocking agents (Table III) that is employed in therapy.

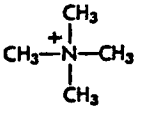
REPRESENTATIVE GANGLIONIC STIMULATING AGENTS



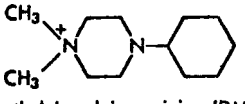
Nicotine



Lobeline



Tetramethylammonium (TMA)



Dimethylphenylpiperazinium (DMPP)

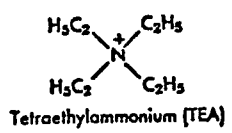
Table III (62)

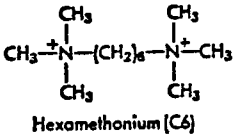
Although the ganglionic stimulating drugs have no essential therapeutic uses, they are of considerable interest as experimental tools for probing the complexities of ganglionic transmission.

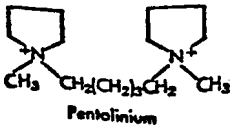
Ganglionic blocking drugs (Table IV) block transmission in autonomic ganglia without producing any preceeding or concomitant change in the membrane potential of the ganglionic cells. They produce ganglionic blockade by occupying receptor sites and by stabilizing the post-synaptic membranes against the action of ACh liberated from presynaptic nerve endings.

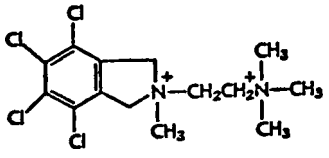
GANGLIONIC BLOCKING DRUGS

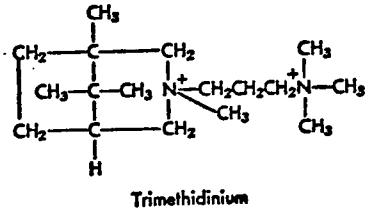
NON-DEPOLARIZING GANGLIONIC BLOCKING AGENTS

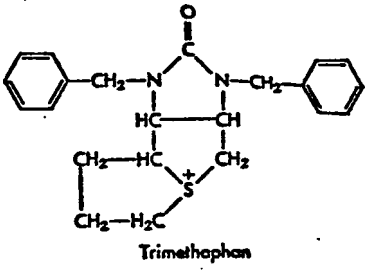

Tetraethylammonium (TEA)

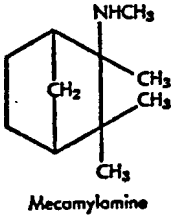

Hexamethonium (C6)


Pentolinium


Chlorisondamine


Trimethidinium


Trimethaphan


Mecamylamine

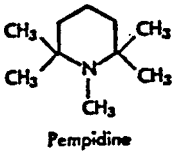
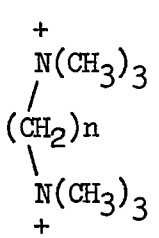

Pempidine

Table IV (62)

Although Marshall in 1913 (7) and Burn and Dale in 1915 (8) first described the "nicotine paralyzing" action of TEA on ganglia, and other investigators had reported certain additional pharmaceutical properties, TEA was largely overlooked until Acheson and Moe in 1946 (9) and Acheson and Pereira in 1946 (10) published their definitive analysis of the effects of the ion on the cardiovascular system and autonomic ganglia. Tetraethyl ammonium chloride and bromide were the first ganglionic blockers employed in therapy. Although one might assume that curariform activity would be a deterrant to their use, it has been shown that the curariform activity of the tetraethyl compound is less than 1 percent that of the corresponding tetramethyl compound. A few years after the introduction of the tetraethyl ammonium compounds, Paton and Zaimis (11) studied the usefulness of the bis-trimethyl ammonium polymethylene salts:



n=5 or 6, active as ganglionic blockers (feeble curariform activity)
n=9 to 12, weak ganglionic blockers (strong curariform activity)

The findings indicate that there is a critical distance of about 5 to 6 carbon atoms between the onium centers for good ganglionic blocking action.

The major therapeutic use of the ganglionic blocking agents is in the management of hypertensive cardiovascular disease.

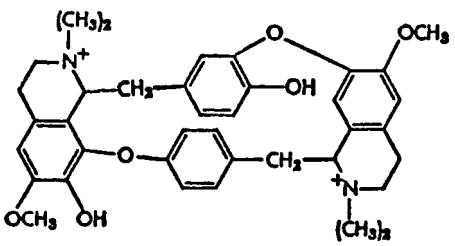
Neuromuscular blocking agents (Table V), on the basis of the primary mechanism by which they produce this effect, are classified either as competitive (stabilizing) agents, of which curare is the classical example, or as depolarizing agents, such as decamethonium. The neuromuscular blocking agents have also other important sites of action, including autonomic ganglia.

Curare has been employed for centuries by the Indians of South America for killing wild animals for food, death resulting from paralysis of skeletal muscles. However, until the 1940's curare was largely a pharmacological curiosity and the sporadic attempts to use it in therapy were severly limited by the lack of standardized preparations. Research on curare was greatly accelerated by the work of Gill (12), who, after prolonged and intimate study of the native methods of preparing curare, brought to the United States a sufficient amount of the authentic drug prepared from C. tomentosum to permit chemical and pharmacological investigation.

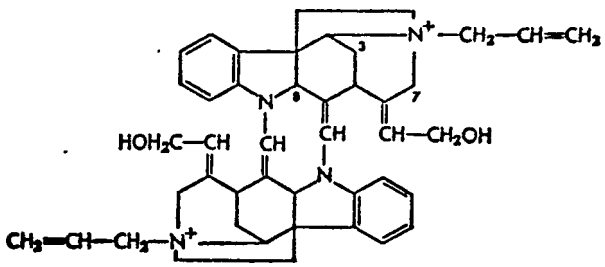
The functional relationship of curare to ACh focuses on the role of quarternary ammonium groups in curarimimetic agents. Only a few quarternary ammonium compounds, among them the simple esters of betaine, have been found to lack curarimimetic activity when properly tested, although many of them are quite weak. Many well known drugs (atropine, quinine, strychnine, etc.) show a marked increase in curarimimetic potency when their nitrogen atom is quarter-

STRUCTURAL FORMULAS OF MAJOR NEUROMUSCULAR BLOCKING AGENTS

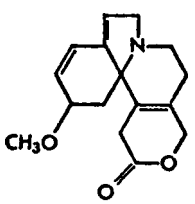
COMPETITIVE AGENTS



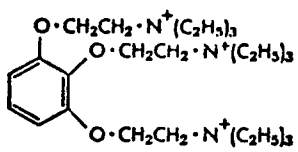
d-Tubocurarine



Diallyl-bisnortoxiferine

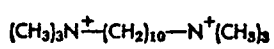


β-Erythroidine

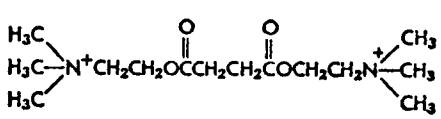


Gallamine

DEPOLARIZING AGENTS

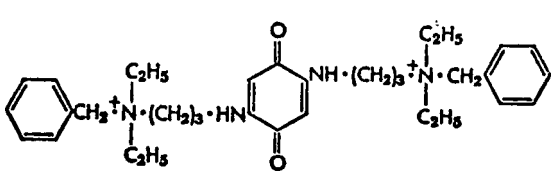


Decamethonium



Succinylcholine

COMBINED ACTION



Benzoquinonium

Table V (62)

nized. On the other hand, many non-quarternary ammonium compounds have a curare-like activity (quinine, nicotine, etc.). The curarimimetic activity of B-erythroidine and dihydro-B-erythroidine is actually abolished by quarternization of the nitrogen. Other atoms

can substitute for cationic quarternary nitrogen; thus, curarimimetic activity has been reported for sulfonium, phosphonium, arsonium, stibonium, and iodinium compounds.

Some essential factors that determine the activity of neuromuscular blocking agents of either the competitive or depolarizing class have been summarized by Cavallito (13, 14) as coulombic bonding characteristics, steric influences, and the lipophilic-hydrophilic balance of the molecule. These factors serve to illustrate the many obstacles to any simplified approach to structure-activity relationship in this group of compounds.

The structural features that distinguish competitive from primarily depolarizing neuromuscular blocking agents have received particular attention. From all the proposals made to date in this regard, a few generalizations can be drawn. The competitive or stabilizing agents are for the most part relatively bulky, rigid molecules (e.g., d-tubocurarine, the toxiferines, gallamine) whereas the depolarizing agents (e.g., succinylcholine) have generally a more slender, flexible structure.

Drugs that inhibit or inactivate acetylcholinesterase (AChE) are called anticholinesterases (anti-ChE agents). They cause ACh to accumulate at cholinergic sites, and thus are potentially capable of producing effects equivalent to continuous stimulation of cholinergic fibres throughout the central and peripheral nervous system. In view of the widespread distribution of cholinergic neurons, the anti-ChE agents as a group have assumed very extensive practical

application as toxic agents, in the form of agricultural insecticides and potential chemical warfare "nerve gases".

Shortly before and during World War II, a comparatively new class of highly toxic chemicals, the organophosphates, was developed chiefly by Schrader (15) of I. G. Farbenindustrie, first as agricultural insecticides and later as potential chemical warfare agents. The extreme toxicity of these compounds was found to be due to their "irreversible" inactivation of AChE, thereby exerting their effects for considerably longer periods than do the classical inhibitors. The following (Table VI) describes some of the representative organophorus insecticides.

N. N. Melinkov et al. (2) synthesized hydrazides of alkyl aryl thiophosphoric acids. Study of these compounds as contact insecticides showed that they had very weak activity.

Certain derivatives of methylhydrazine have shown considerable activity against rodent neoplasms (16-18) and in the treatment of Hodgkin's disease in man (19, 20). Procarbazine (N-Isopropyl-2-(2 methylhydrazine)-p-toluamide)IV) the most active member of the series, is metabolized in vivo through a number of intermediates to N-isopropylterephthalamic acid (21, 18, 22, 23). Hydrogen peroxide, an early oxidation product, may be essential to tumor inhibition (24). Compound IV inhibits DNA synthesis in vivo (25) but does not inhibit the synthesis of DNA, RNA or protein in vitro (26).

REPRESENTATIVE ORGANOPHOSPHORUS COMPOUNDS

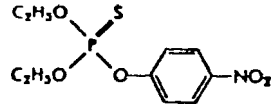
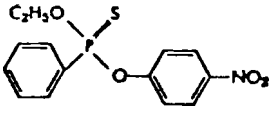
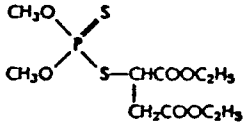
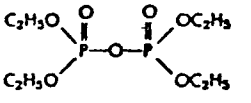
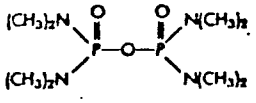
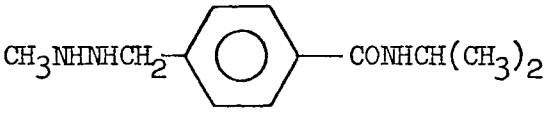
	Parathion, Thiophos, E 605 (see list of trade names in text) Diethyl O-(4-nitrophenyl) phosphorothioate	Widely employed agricultural insecticide, resulting in numerous cases of accidental poisoning
	EPN O-Ethyl O-(4-nitrophenyl) phenyl-phosphonothioate	Widely employed agricultural insecticide
	Malathion O,O-Dimethyl S-(1,2-dicarbethoxyethyl) phosphorodithioate	Widely employed insecticide of greater safety than parathion or EPN because of rapid metabolism by higher organisms
	TEPP Tetraethyl pyrophosphate	Early insecticide; tested clinically in glaucoma and myasthenia gravis
	OMPA, Schradan Octamethylpyrophosphortetramide	Insecticide; inactive *in vitro*, but metabolized by animals and plants to potent anti-ChE agent

Table VI (62)

The hydrazine moiety in this compound is of special significance as it frequently appears in antineoplastic agents. "The pre-

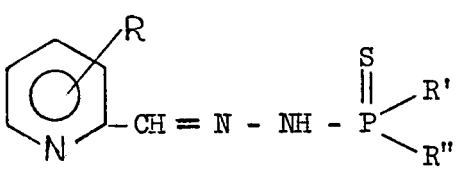


IV

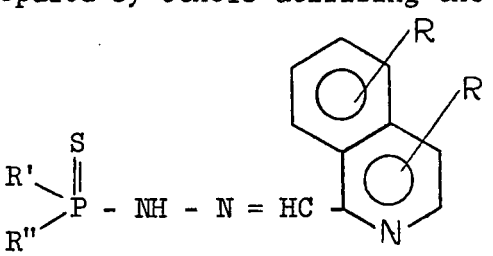
sence of this grouping in procarbazine and compounds such as indole-3-propionic acid hydrazide, α-hydrazino-ω-cyclohexylbutyric acid, 5 hydrazide l-glutamic acid, and 2-(4-nitroso-7-oxo-1, 3, 5-cycloheptatrien-1-yl) isonicotinic acid hydrazide is obvious, while in other agents its occurrence is less conspicuous. Various

thiadiazole, pyrazole, triazeno, and azapurine oncolytics also contain the N-N bond" (27). The hydrazino grouping, in a few cases, such as procarbazine and heterocyclic-2-carboxaldehyde thiosemicarbazones, is believed to be involved in the cytotoxic process via redox reactivity (21) or chelation (28), respectively. It has been reported that even hydrazine sulfate inhibits Walker carcinosarcoma by 28 to 94%, possibly through gluconeogenesis interference (29). It is also interesting to note that a phosphonothioic dihydrazide, $PhPS(NHNHPh)_2$, has demonstrated antitumor activity (30).

Although it is possible that compounds of the type II, IIa may act as antineoplastic agents, they can also be used as intermediates in the synthesis of compounds of the type V, Va. It is expected that derivatives of this nature will be prepared by others utilizing the information presented herein.



V



Va

Compounds of type V and Va are phosphorous analogues of the highly active formylheteroaromatic thiosemicarbozones (FHT). Optimal R substituents have been well characterized for the carbon congeners while terminal substituents (R' and R" in the case of V and Va) in these agents have been less thoroughly investigated. It is considered of interest to ascertain the effect on ribonucleoside

diphosphate reductase (RDR) and alkaline phosphatase (AP), and murine tumors produced by replacing the C-3' of FHT compounds with a phosphorous atom substituted with a variety of chemical groups or atoms.

Early work in this area includes the initial discovery of the antileukemic effect of pyridine-2-carboxaldehyde thiosemicarbazone by Brockman et al. (31) and the antitumor activity of 1-formylisoquinoline derivatives (32).

A fairly comprehensive summary (70 references) of the status of FHT oncolytics was published in a 1974 research article by French, Blanz, Shaddix, and Brockman (33). These authors reported good correlation between RDR inhibition activity in various in vivo and in vitro tumor systems.

B. Chemistry

A literature survey was made to seek the appropriate chemical procedures for the preparation of the proposed compounds. Subsequent to this, the schemes used for the actual synthesis and the primary studies leading to these are outlined.

The scientifically planned study of the organophosphorous compounds may be regarded as having begun in the early part of the nineteenth century by the work of Lassaigne who esterified the dehydrated phosphoric acids with alcohols.

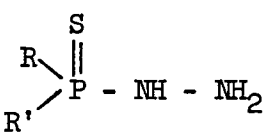
Until the 1860's, the purely synthetic aspect of organophosphorous compounds had most certainly been emphasized by Professor Carl Arnold August Michaelis, who during his long illustrious lifetime was unquestionably the outstanding leader in this subject, not only in Germany but in all the world. Professor Aleksandr Erminigeldovich Arbuzov may be regarded as a worthy successor to Michaelis both for his elaboration of methods of synthesis and for his very early attempt at unification of the basic principles of reactions of phosphorous compounds (34).

Among the British chemists who have contributed extensively to this subject are Frederick G. Mann and Walter C. Davies who carried out the extensive studies of phosphines and Professor Alexander R. Todd whose name is closely linked with the development of several new syntheses in the realm of substances related to nucleic acids.

The progress made in this field until 1949 has been fairly

well summed up by Kosolapoff (35), in his book Organophosphorus Compounds.

Fluck in his review of phosphorous-nitrogen chemistry provides basic information on thiophosphoric hydrazides, salts and esters (36). These, as well as phosphoric acid and diamidophosphoric hydrazides VI, have been reported where R and R' are small



VI

and includes those where R, R' = MeO or EtO (37, 38); R=Me, R'=EtO (39); R, R'=Me_2N OrEt_2N (37, 40); R=MeO or EtO, R'=MeNH (37) and R, R'=NaO (36, 41). Although the sulphur analogs of $(NH_2)_2PONH\text{-}NH_2$ and $(Me)_2PONHNH_2$ (42) are not reported it is expected that they can be prepared using standard procedures, e.g., the former compound can result from the reaction of thiophosphoryl chloride with hydrazine and then ammonia.

In 1973, Kosolapoff and Maier edited a 6-volume treatise which attempts to sum up most of the work in this field (43). In 1963, Nielson and Sisler (44) synthesized a series of substituted hydrazinophosphines, hydrazinophosphine oxides and hydrazinophosphine sulfides by the appropriate chlorophosphorous compounds. They made a detailed study of the n.m.r. and i.r. spectra of these compounds. The following table (Table VII) contains a list of the compounds they made and their n.m.r. data.

NUCLEAR MAGNETIC RESONANCE DATA [a, b]

Formula	Pattern splitting	Assignment	Chem. shift
$(C_6H_5)_2PNHN(CH_3)_2$[c]	Complex	H (C_6H_5)	1.9 τ
	Doublet	H (NH)	6.0 τ
	Singlet	H (CH_3)	6.8 τ
	Broad	P	−37.6 p.p.m.
$[(C_6H_5)_2P]_2NN(CH_3)_2$[d,e]	.....	H (C_6H_5)	(obscured)
	Singlet	H (CH_3)	7.52 τ
	Broad	P	−47.4 p.p.m.
$(C_6H_5)_2P(O)NHN(CH_3)_2$[e]	.....	H (−C_6H_5)	2.07 τ
	.....	H (*p*-C_6H_5, *m*-C_6H_5)	2.55 τ
	Doublet (18.8 c.p.s.)	H (NH)	5.53 τ
	Singlet	H (CH_3)	7.42 τ
	Broad	P	−22.0 p.p.m.
$(C_6H_5)_2P(S)NHN(CH_3)_2$[e]	.....	H (*o*-C_6H_5)	1.97 τ
	.....	H (*p*-C_6H_5, *m*-C_6H_5)	2.68 τ
	Doublet (21.5 c.p.s.)	H (NH)	6.21 τ
	Singlet	H (CH_3)	7.61 τ
	Broad	P	−57.3 p.p.m.
$(C_6H_5)_2P(O)N(CH_3)N(CH_3)_2$[e]	.....	H (*o*-C_6H_5)	2.12 τ
	.....	H (*p*-C_6H_5, *m*-C_6H_5)	2.61 τ
	Doublet (10.5 c.p.s.)	H (N-CH_3)	7.45 τ
	Singlet	H ($N(CH_3)_2$)	7.61 τ
	Broad	P	−28.2 p.p.m.
$(C_6H_5)_2P(O)N(C_2H_5)N(CH_3)_2$[e]	.....	H (*o*-C_6H_5)	2.06 τ
	.....	H (*p*-C_6H_5, *m*-C_6H_5)	2.51 τ
	Quadruplet (7 c.p.s.)	H (−CH_2−)	6.75 τ
	Doublet (*ca.* 7 c.p.s.)		
	Singlet	H (N-CH_3)	7.48 τ
	Triplet (7 c.p.s.)	H (CH_2-CH_3)	8.83 τ
	Broad	P	−26.2 p.p.m.
$(C_6H_5)_2P(S)N(C_2H_5)N(CH_3)_2$[f]	.....	H (*o*-C_6H_5)	1.82 τ
	.....	H (*p*-C_6H_5, *m*-C_6H_5)	2.46 τ
	Quadruplet (7 c.p.s.)	H (−CH_2−)	6.67 τ
	Doublet (8 c.p.s.)		
	Singlet	H (N-CH_3)	7.48 τ
	Triplet (7 c.p.s.)	H (CH_2-CH_3)	8.76 τ
	Broad	P	−66.4 p.p.m.
$C_6H_5P(S)(NHN(CH_3)_2)_2$[e]	.....	H (*o*-C_6H_5)	1.84 τ
	.....	H (*p*-C_6H_5, *m*-C_6H_5)	2.56 τ
	Doublet (27.3 c.p.s.)	H (NH)	6.33 τ
	Singlet	H (CH_3)	7.51 τ
	Broad, perhaps a septuplet (12 c.p.s.)	P	−61.1 p.p.m.
$P(O)(NHN(CH_3)_2)_3$[e]	Doublet (2.37 c.p.s.)	H (NH)	6.05 τ
	Singlet	H (CH_3)	7.45 τ
	Quadruplet (23 c.p.s.)	P	−12.5 p.p.m.

[a]Solvent $CDCl_3$ except where otherwise noted. [b]All phosphorous resonance spectra at 19.3 Mc. with H_3PO_4 as replaceable standard. [c]Proton resonance spectra at 56.4 Mc. with benzene as external standard. [d]Benzene solvent. [e]Proton resonance spectra at 60.0 Mc. with $(CH_3)_4Si$ as internal standard. [f]Proton resonance spectra at 60.0 Mc. with CH_3CHO as replaceable standard.

Also, shown in Figure 1 is an n.m.r. spectrum for one of their representative compounds. As most of the compounds were structurally similar to some of the synthetic intermediates reported herein, their work proved helpful in synthesis and characterization of these intermediates. For example, Fig. 1, depicts the splitting of NH proton, due to phosphorous, while the two methyl groups being unaffected

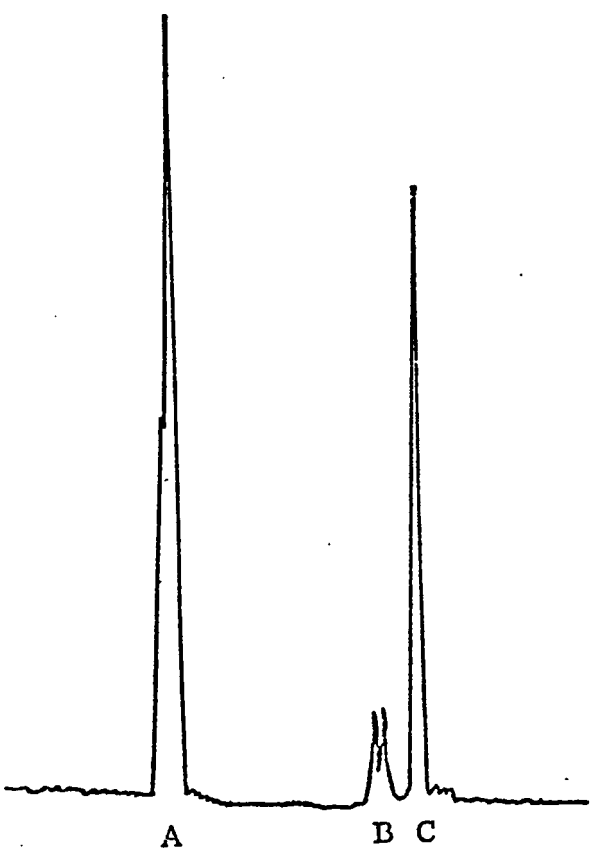


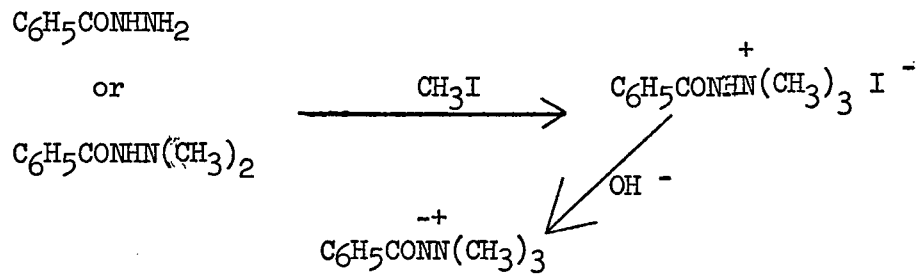
Fig. 1 - Proton n.m.r. spectrum of 2,2-dimethylhydrazinodiphenylphosphine in $CDCl_3$ solvent at 56.4 Mc. (44)

Peak	Area	Position p.p.m.	Type
A	10.2	-0.88	$-C_6H_5$
B	1.0	3.29	-NH
C	6.2	4.07	$-CH_3$

by P gave a singlet. In fact, the synthesis of one of the compounds of Neilson and Sisler, i.e., $C_6H_5P(O)NHN(CH_3)_2$, was repeated during this study mainly using their method and has been used as an intermediate for the synthesis of a quarternary hydrazide (III. A2, exp.).

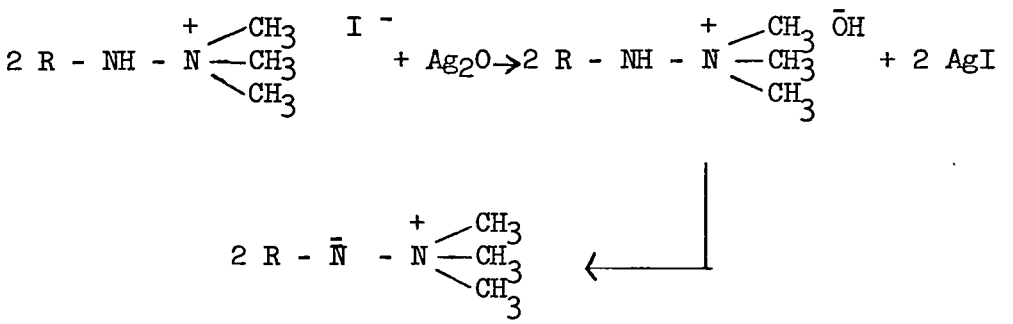
In 1973, W. J. McKillip et al. published a review of the chemistry of aminimides (45). They introduced aminimides as dipolar ions containing a cationic nitrogen bonded to an anion derived from a carboxyamide, $-CONN\equiv+$, sulfonamide, $-SO_2NN\equiv+$, cyanamide, $N\equiv CNN\equiv+$, or nitroamide, $NO_2NN\equiv+$. In all four structures, carbon substituents are attached to the quarternary nitrogen. Groups attached to the carbonyl portion may be either carbon, hydrogen, nitrogen, oxygen, or sulfur. The known sulfonyl analogs have a carbon moiety attached to the sulfur.

Many acylaminimides have been prepared by the following reactions (46):



The dialkyl hydrazides necessary for this preparation are best prepared by the action of an acid chloride (47) or anhydride on a 1,1-disubstituted hydrazine (48). Direct hydrazinolysis of esters with dimethyl hydrazine occurs only with formates, other esters of aliphatic or aromatic acids do not react (49).

The last step in the reaction to synthesize aminimides can probably also be achieved by Hoffman elimination as follows:



A reaction to convert an ester directly to an aminimide has been reported (50).

$$RNHC_2H_4COOCH_3 + NH_2\overset{+}{N}(CH_3)_3\bar{C}l \xrightarrow{NaOCH(CH_3)_2} RNHC_2H_4CO\overset{-+}{N}N(CH_3)_3 + NaCl$$

A general reaction to obtain quarternary ammonium compounds by alkylation has been described in great detail by Brasen and Hauser (51). An example they have cited is

$$C_6H_5CH_2N(CH_3)_2 + CH_3I \longrightarrow C_6H_5CH_2\overset{+}{N}(CH_3)_3I$$

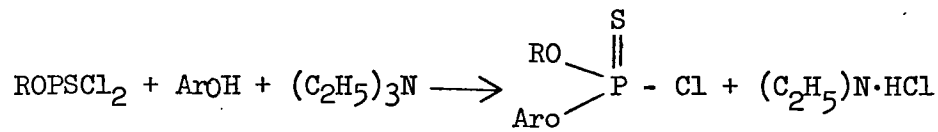
Reactions of the following kind have been described by A. G. Zenkevich et al. (2)

$$\begin{matrix} RO \\ ArO \end{matrix}\!\!>\!PSCl + 2\ NH_2 - NHR' \longrightarrow$$

$$\begin{matrix} RO \\ ArO \end{matrix}\!\!>\!PSNH - NHR' + R'NH - NH_2\cdot HCl$$

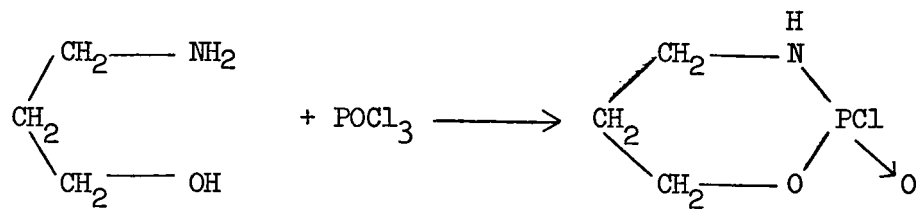
$$2\ PCl_3 + (RO)_2Mg \longrightarrow MgCl_2 + 2\ ROPCl_2$$

$$2\ ROPCl_2 + (RO)_2Mg \longrightarrow 2\ (RO)_2PCl + MgCl_2 \qquad (52)$$

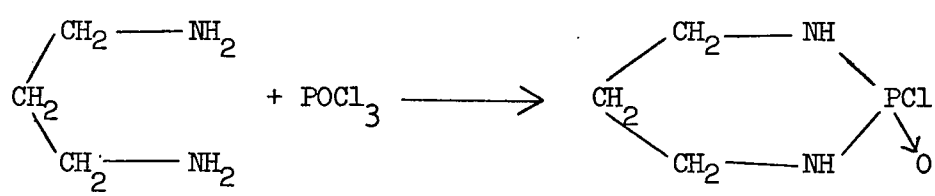


(53)

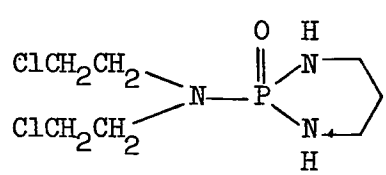
Iwamato et al. reported the following reaction (54)



Reactions of the following nature have posed a special problem.

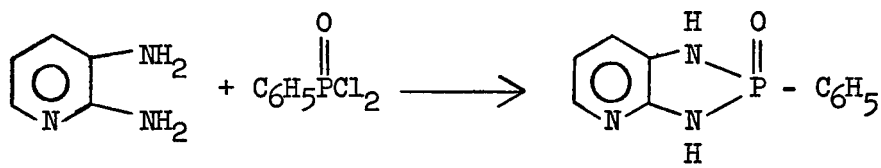


Friedman et al. (55) have reported their inability to isolate



No reason was cited for this. The investigators stated "This compound was never obtained pure despite our intensive efforts. Attempts to purify the oily products by the usual techniques, including chromatography and molecular distillation at 10^{-6} mm. pressure, were all unsuccessful. Treatment with liberal amounts of activiated carbon effected some improvement in purity as evidenced by analytical data".

Synthesis of the following nature has been reported using bromobenzene as the solvent (56).



Selection of proper solvent seems to play an important role in these kind of reactions.

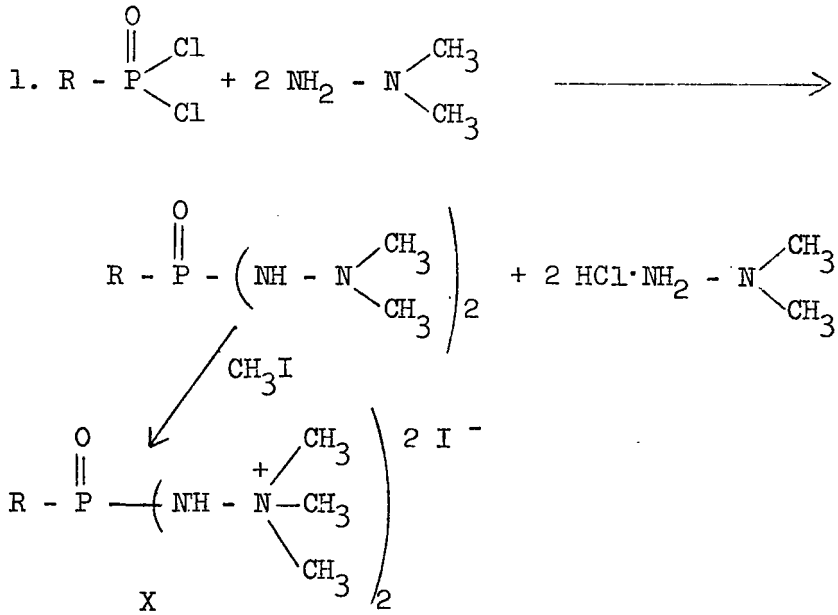
Conversion of ethyl and methyl esters to hydrazides using hydrazine and ethanol as the solvent has been reported by Peter A. S. Smith (57) and Andre Girard (58). Debo (59) has made several phosphoric and thiophosphoricdialkyl ester hydrazides

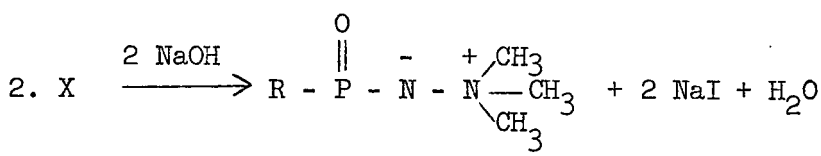
$$(R^1)(R^2)P\text{-}(Y)\text{-}X + H_2NNR^3R^4 + Na_2CO_3 \xrightarrow{H_2O}$$

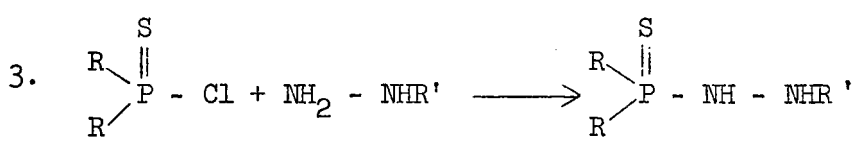
$$(R^1)(R^2)P(Y)NHNR^3R^4 + NaX + NaHCO_3$$

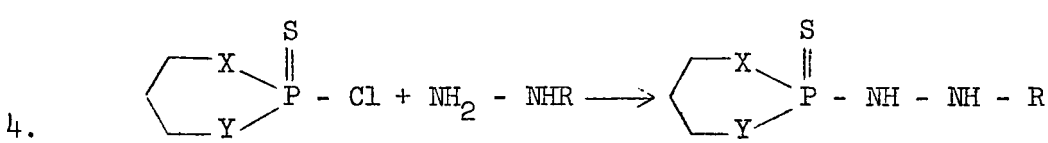
where Y=S or O and X=Cl. R^1 & R^2 are alkoxy, aryloxy, alkylamino and arylamino groups, while R^3 and R^4 are selected from the groups consisting of alkyl groups, aryl moieties and hydrogen.

The following general schemes have been used for the synthesis and attempted synthesis of proposed compounds:

1.


2.


3.


4.


CHAPTER II

EXPERIMENTAL

I. INTRODUCTION

Several compounds of the type I, Ia, II and IIa have been synthesized using the general scheme described at the end of the previous chapter. Some similar compounds which do not fall in the general category of the I, Ia and II, IIa type were also synthesized. Compounds of II and IIa type where R=C_6H_5 were also synthesized to help characterise compounds of the kind II and IIa. Chemicals and reagents were purchased from the various chemical companies listed below.

1. Aldrich Chemical Co. Inc.
   (a) 1-Phenylphosphonic dichloride
   (b) Diphenyl chlorophosphate
   (c) Phenyl dichlorophosphate
   (d) Ethyl dichlorophosphate
   (e) Diethyl chlorophosphate
   (f) Dimethyl hydrazine
   (g) Iodomethane
   (h) Phosphorous trichloride
   (i) 1, 3-diaminopropane
   (j) 3-amino-1-propanol
   (k) Succinyl hydrazide
   (l) Succinyl chloride

2. Eastman Organic Chemicals
   (a) Morpholine
   (b) Hydrazine
   (c) Triethylamine

3. Fischer Labs
   (a) Phenyl hydrazine

4. Alfa Inorganic
   (a) Thiophosphoryl chloride

The samples were dried by means of an Abderhalden drying apparatus using acetone as the heating solvent and phosphorous pentoxide as the desiccant. Compounds which possessed low melting points were dried in a desiccator using phosphorous pentoxide and the house vacuum line. Melting points for the compounds of type I and Ia were taken on Fischer-Johns apparatus and are corrected. Melting points for the compounds of type II and IIa were taken using Thomas-Hoover melting pt. apparatus. N.m.r. data were recorded on a varian T-60 n.m.r. spectrometer and reported in delta units. All n.m.r. samples were run in $CDCl_3$, DMSO or d-Acetone, as indicated, with tetramethyl silane as the internal standard. All of the representative n.m.r. spectra are included at the end of the experimental section. N.m.r. studies were used for both the identification of the products and in some cases to follow the course of reactions. Proton exchange using D_2O (involving NH & NH_2 protons) was also employed; in some spectras, peaks due to these protons were indistinct and have not been reported. Elemental analyses were performed by Atlantic Microlab, Inc., (Atlanta, Georgia).

The sections reporting the actual procedures used for the syntheses mentioned herein have been basically divided into two sub-divisions, namely, successful syntheses and attempted

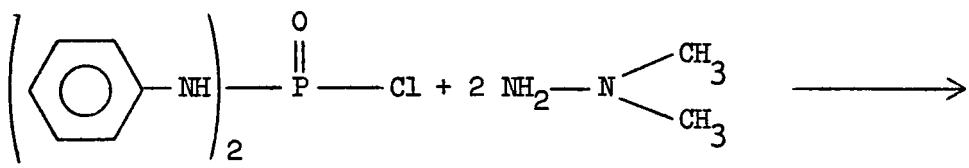
syntheses. The syntheses for which the assays of the newly formed compounds did not agree within 0.4% of theory or the product was not analyzed but used in attempted aminimide syntheses have been termed as attempted syntheses. Similarly, the syntheses for which the assays of the newly formed compounds did agree within 0.4% of theory, have been labeled as successful syntheses.

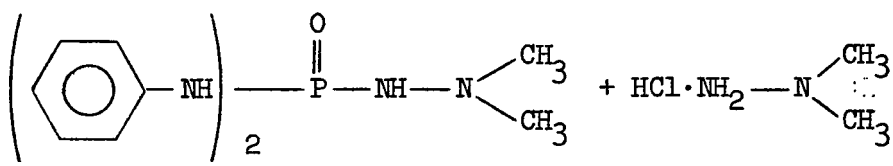
The attempted syntheses have been included herein as it was felt that the products were formed but difficulties were encountered in their purification. In most cases experimental elemental analyses were sufficiently close to theory and in all cases the n.m.r. studies strongly suggested that the desired product had been formed.

II. DIMETHYL HYDRAZINO (DI & MONO) SUBSTITUTED PHOSPHINE OXIDES

A. Successful Syntheses

1. N, N' - Diphenyl - N^2, N^2 - dimethyl phosphorodiamido hydrazide.





To a beaker containing 37.5 gms. (0.625 mole) of dimethylhydrazine in dioxane was added 66.8 gms. (0.25 mole) of solid N, N' - diphenyl phosphorodiamidic chloride with magnetic stirring and temperature maintained at 0-10°C using a salt-ice bath. The mixture was allowed to react over-night and then heated to about 80°C for one hour the next day to maintain fluidity of reaction condition. Dioxane was added to the beaker whenever the reaction mixture became too viscous for stirring.

The water insoluble product precipitated from dioxane upon addition of distilled water and the residue was recrystallised twice from ethanol. The product obtained melted at 164-67°C without decomposing; n.m.r. [a]: 7.77 (m, 10), 3.25 (s, 6).

Analysis of $C_{14}H_{19}N_4OP$ M.W. 290.31 (cal'd)

Calculated: C, 57.92%; H, 6.60%; N, 19.30%

Found: C, 58.06%; H, 6.69%; N, 19.16%

The phosphorodiamidic chloride used as the starting material was synthesized by the method used by Cook and co-workers (60).

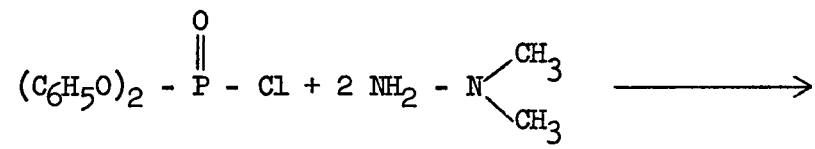
N, N' - Diphenyl phosphorodiamidic chloride.

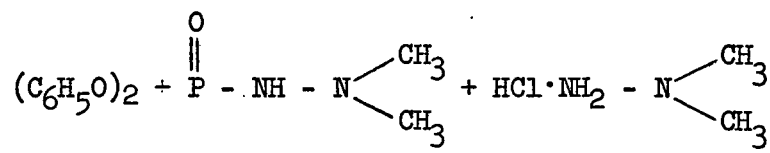
According to the method of Cook, et al., 76.5 gms. of phosphorus oxychloride in 250 ml. of anhydrous ether was placed in a three-neck, round-bottom, 1 liter flask equipped with thermometer, mechanical stirrer, and dropping funnel. Exactly 186.0 gms. of aniline in 250 ml. of anhydrous ether was added dropwise by means of the dropping funnel to the $POCl_3$-ether mixture over a one hour period with stirring. The temperature was maintained at 10 ± 5°C during this addition by means of an acetone-dry ice bath. The stirring was continued until the reaction mixture reached room temperature and was then allowed to stand over-night. The mixture was filtered by means of a large Buchner funnel and the suspended material was washed free of aniline hydrochloride with water. The remaining gray, granular mass was dried to yield 122.68 grams (92%) of impure product. Recrystal-

[a] In n.m.r. descriptions, s=singlet, d=doublet, t=triplet, m=multiplet

lisation from dilute ethanol yielded 80.0 gms. (60%) of product melting at 169-171°C.

2. Diphenyl ester of N^2, N^2-dimethyl phosphorohydrazidic acid.

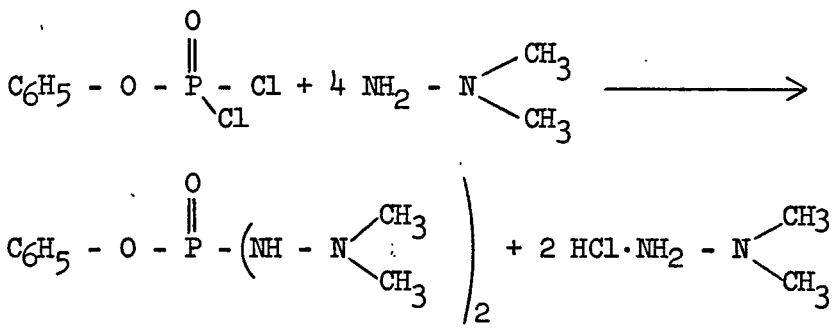




A solution containing 26.9 gms. (0.1 mole) of diphenyl chlorophosphate in anhydrous ether was placed in a two-necked 500-ml. round-bottom flask and to this was added 15.0 gms. (0.25 mole) of dimethyl hydrazine, slowly with stirring and temperature maintained below 25°C using ice-bath. The mixture was then refluxed at 40°C for 36 hours. The water insoluble product was washed free of the HCl salt and the cream coloured mass thus obtained gave a very white powder after long and repeated washings. The powder was dried using vacuum desiccator and melted at 77°C; n.m.r.: 7.3 (m, 10), 2.55 (S, 6).

B. Attempted Syntheses

1. Phenyl ester of bis(N^2, N^2 - dimethyl) phosphorohydrazidic acid.



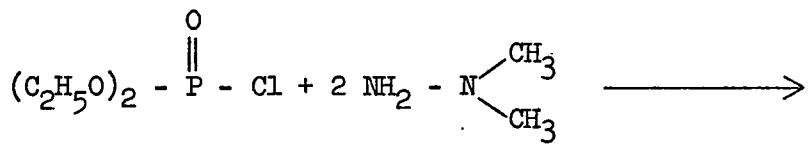
A solution of 21.1 gms. (0.1 mole) of phenyl dichlorophosphate in 20 ml. of dry benzene was added slowly with stirring to a solution of 24.04 gms. (0.4 mole) of 1, 1-dimethyl hydrazine in 20 ml. of dry benzene with temperature maintained at 0-5°C. The mixture then was warmed to room temperature, stirred for one hour and filtered after several washings with benzene, to eliminate 1, 1-dimethyl hydrazinium chloride. The filtrate was evaporated at room temperature and reduced pressure to give a white product which contained the impurity of 1, 1-dimethyl hydrazinium chloride. It was purified by repeated extractions from benzene and dried. The n.m.r. spectrum of this compound showing a singlet due to 12 equivalent methyl protons and a downfield multiplet due to 5 phenyl protons strongly indicated the formation of the expected product. The compound was sensitive to light (turned yellow on being exposed to light for several hours), was hygroscopic, and melted at 116°C, n.m.r.: 7.2 (m, 5), 2.55 (S.12).

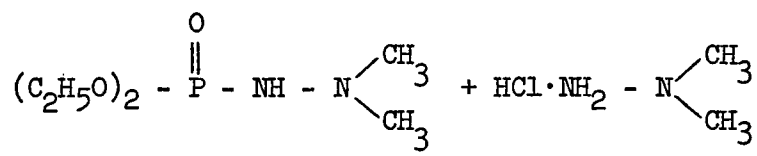
Analysis of $C_{10}H_{19}N_4O_2P$ M.W. 258.26 (cal'd)

Calculated: C, 46.51%; H, 7.42%; N, 21.69%

Found: C, 45.26%; H, 7.31%; N, 20.23%

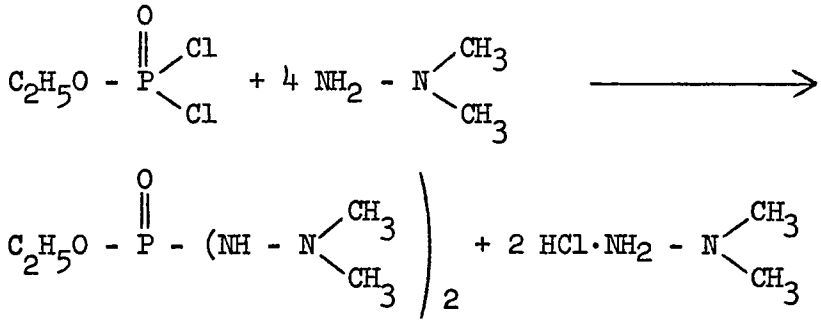
2. Diethyl ester of N^2, N^2 - dimethyl phosphorohydrazidic acid.





Using the method for A2, 34.2 gms. (0.2 mole) of diethyl chlorophosphate was allowed to react with 30 gms. (0.5 mole) of 1, 1-dimethylhydrazine in dry benzene at 0-10°C. The reaction was allowed to continue over-night and was filtered next day to give 1, 1-dimethyl hydrazinium chloride on the filter and a filtrate which on evaporation under vacuum gave a yellowish liquid as the final product. This water soluble liquid was purified by repeated extractions from dry benzene. The n.m.r. spectrum for this compound shows a singlet due to equivalent methyl protons; a triplet and a multiplet; probably due to the ethyl group; thus indicating the presence of the desired compound.

3. Ethyl ester of bis (N^2, N^2 dimethyl) phosphorohydrazidic acid.

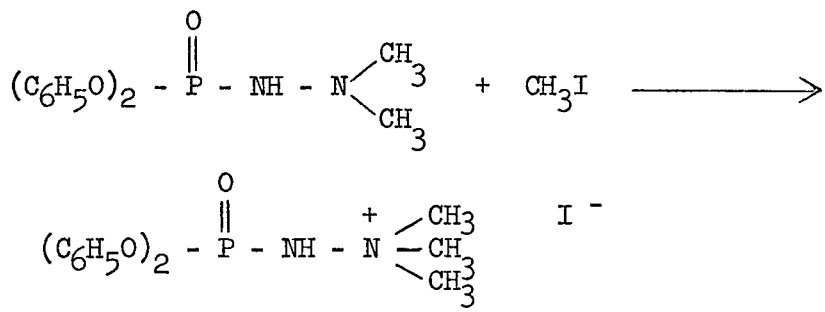


Using the method used for A2, 16.3 gms. (0.1 mole) of ethyl dichlorophosphate was allowed to react with 27 gms. (0.45 mole) of 1, 1-dimethyl hydrazine in dry benzene at 0-10°C. The reaction was run over-night and was filtered next day to give 1, 1-dimethyl hydrazinium chloride on the filter and a filtrate which on evaporation left behind a yellowish viscous liquid which was the final product and contained some impurity of 1, 1-dimethyl hydrazinium chloride. It was decided to use this water soluble intermediate without further purification. The n.m.r. spectrum of this product (not included in this monograph) showed a singlet due to 12 equivalent methyl protons, a triplet and a quadruplet due to the ethoxy group, along with some peaks due to the impurities present.

III. QUARTERNARY HYDRAZIDES

A. Successful Syntheses

1. Diphenyl ester of N^2, N^2, N^2-trimethyl phosphorohydrazinic acid iodide.



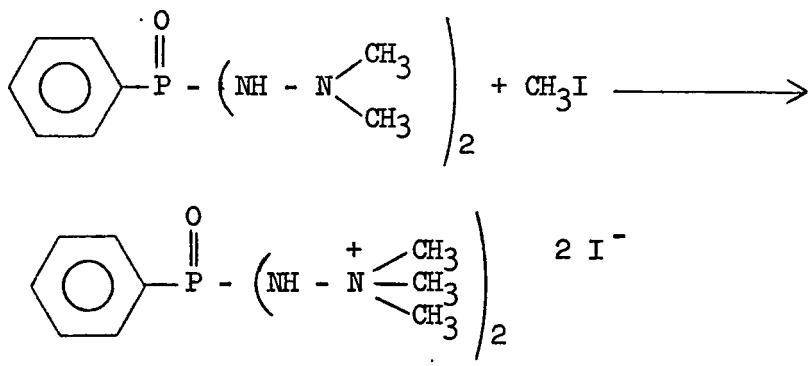
The methylation was carried out as described for B1. A concentrated solution of 5.8 gms. (0.02 mole) of the diphenyl ester of bis (N^2, N^2-dimethyl) phosphorohydrazidic acid was reacted with 8.5 gms. (0.06 mole) of methyl iodide over-night at room temperature. As no precipitate was observed the next day, the solution was concentrated under reduced pressure. A viscous solution was obtained which on addition of anhydrous ether and stirring gave a yellowish powder. On drying in an Abderhalden apparatus this powder lost its yellowish tinge. The white, water soluble product thus obtained gave a positive iodide test and melted at 134-36°C; n.m.r.: 7.25 (m, 10), 3.85 (S, 9).

Analysis of $C_{15}H_{20}N_2O_3PI$ M.W. 434.193 (cal'd)

Calculated: C, 41.49%; H, 4.65%; N, 6.45%; I, 29.23%

Found: C, 41.42%; H, 4.67%; N, 6.53%; I, 29.30%

2. P-Phenyl-N^2, N^2, N^2-trimethyl phosphonic dihydrazinium iodide.



The synthesis of this iodide was achieved as described for B1. A concentrated solution of 4.83 gms. (0.02 mole) of the hydrazide was reacted with 17.1 gms. (0.12 mole) of methyl iodide, overnight, at room temperature. Refluxing was avoided in order to prevent possible clevage of the phenyl group. Next day the white precipitate of the product was obtained, filtered and dried. This water soluble product melted at 184-85°C; n.m.r.: 7.9 (m, 5), 4.0 (S, 9).

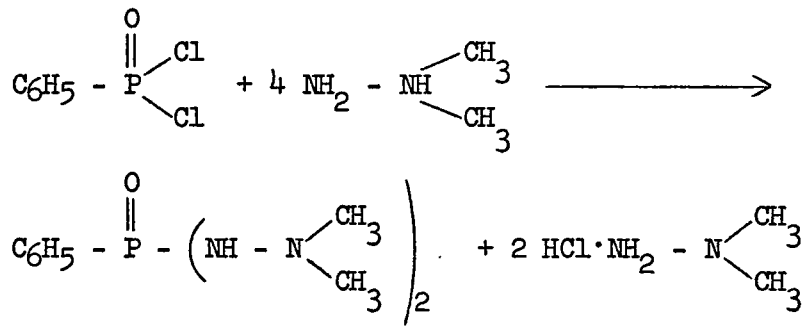
Analysis of $C_{12}H_{25}N_4OPI_2$ M.W. 526.15 (cal'd)

Calculated: N, 10.98%; I, 49.75%

Found: N, 10.77%; I, 49.54%

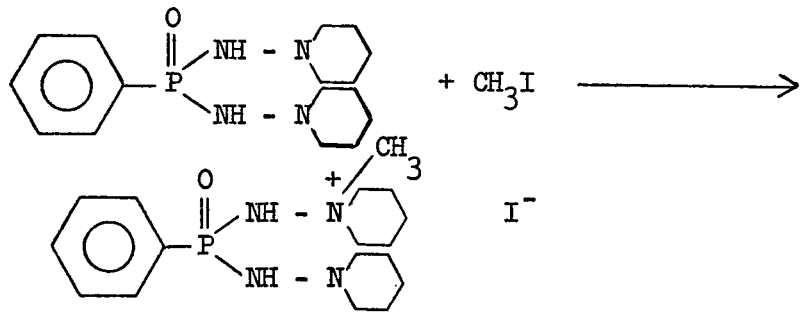
The phosphonic dihydrazide used as the starting material was synthesized by the method used by Nielsen and Sisler (1944).

P-Phenyl-N^2, N^2-dimethyl phosphonic dihydrazide.



According to the method of Nielsen and Sisler, over a one-hour period, 19.5 gms. (0.10 mole) of phenylphosphonic dichloride was added with stirring at 0-5°C to a solution of 25.0 gms. (0.42 mole) of 1,1-dimethyl hydrazine in 40 ml. of chloroform. After one hour of stirring at 60°C the mixture was filtered hot to give a non-quantitative yield of 1,1-dimethylhydrazinium chloride on the filter and filtrate which gave a positive test for chlorine. This results from the fact that 1,1-dimethylhydrazinium chloride is somewhat soluble in chloroform. The filtrate was evaporated to dryness and was purified by extracting several times with boiling benzene. (Nielsen and Sisler purified the final product by sublimation). The melting pt. for this white solid was 160-64°C and the compound was water soluble.

3. P-Phenyl N-(1-piperidinyl)-N'-(1-methyl-1-piperidinium) phosphonodiamide iodide.



The synthesis of this product was carried out as described for B.1. A concentrated solution of 6.7 gms. (0.03 mole) P-phenyl N, N'-(bis (1-piperidinyl) phosphonodiamide in commercial absolute ethanol was placed in a two-necked round-bottom flask. Dropwise addition of 12.8 gms. (0.09 mole) of methyl iodide was carried out with stirring. The reaction mixture was refluxed for 2 hours at 65°C. On cooling and adding a little amount of anhydrous ether, white precipitates of the iodide were obtained. Instead of expected dialkylation, monomethylation had occured. This was verified by n.m.r. studies and elemental analysis. The water insoluble product after drying, melted at 181-85°C.

Analysis of $C_{17}H_{30}N_4OPI$ M.W. 464.33 (cal'd)

Calculated: C, 43.97%; H, 6.51%; N, 12.07%

Found: C, 43.67%; H, 6.57%; N, 11.97%

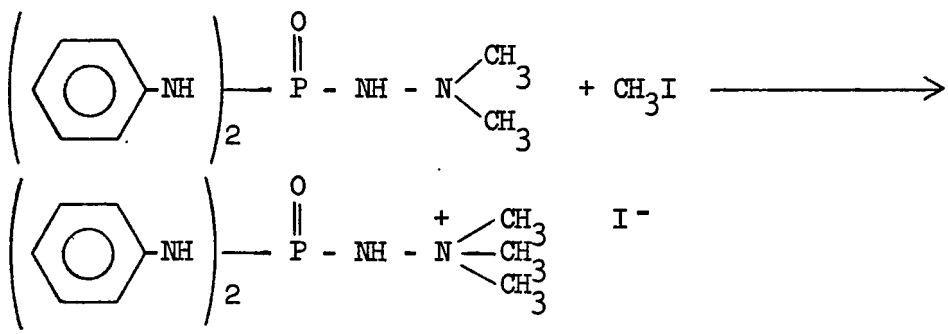
The phosphonodiamide used as the starting material was prepared by the method used by Cates and Lemke. (27)

P-Phenyl N, N'-(bis-(1-piperidinyl)phosphonodiamide.

According to the method of Cates and Lemke, a solution of 20 gms. (0.2 mole) of aminopiperidine and 20 gms. (0.2 mole) of triethyl amine in anhydrous ether was placed in a two-necked round-bottom flask. To this solution, 19.5 gms. (0.1 mole) of phenylphosphonic dichloride was added slowly with stirring. The reaction mixture was refluxed for about 3 hours. The voluminous white precipitate obtained was collected on a filter and washed free of chloride with water. The residue was recrystallized from alcohol-water and small white crystals were obtained which melted at 178-80°C.

B. Attempted Syntheses

1. N, N'-Diphenyl-N^2, N^2, N^2-trimethyl phosphordiamido hydrazinium iodide.



A concentrated solution of 7.3 gms. (0.025 mole) of N, N'-diphenyl -N^2, N^2-dimethyl phosphorodiamido hydrazide in commercial absolute ethanol was placed in a two-necked flask fitted with a dropping funnel, and a reflux condenser. The openings of the dropping funnel and condenser were protected from atmospheric moisture with drying tubes. Methyl iodide contained in the dropping funnel was added to the flask, slowly with stirring. After the addition was complete, the solution was boiled under reflux. White precipitate was obtained after a few minutes of refluxing but the refluxing was continued for one hour to ensure completion of reaction. After refluxing, the white precipitate was filtered and dried. This methylation was mainly carried out as described by Brasen and Hauser (51). The water-insoluble product melted at 162-64°C with decomposition. The n.m.r. spectrum of this compound showed a singlet due to the nine equivalent methyl protons and a downfield multiplet due to the

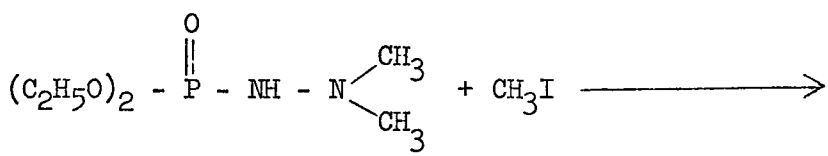
five phenyl protons, stongly suggesting that the expected compound was formed. N.m.r.: 7.0 (m, 10), 3.45 (S, 9).

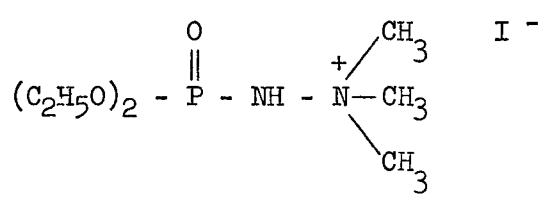
Analysis of $C_{15}H_{22}N_4OPI$ M.W. 432.246 (cal'd)

Calculated: N, 12.96%; I, 29.36%

Found: N, 14.32%; I, 21.78%

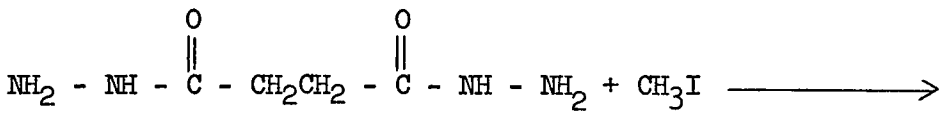
2. Diethyl ester of N^2, N^2, N^2-trimethyl phosphorohydrazinic acid iodide.

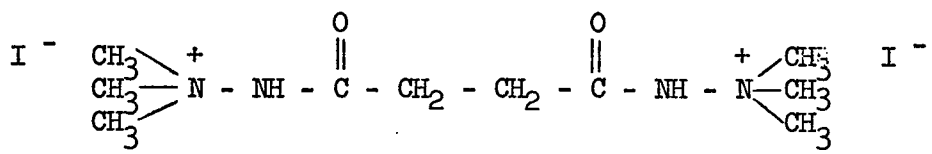




The synthesis of this iodide was carried out as described for B1. A concentrated solution of 19.6 gms. (0.1 mole) of the diethyl ester of N^2, N^2-dimethyl phosphorohydrazidic acid was reacted with 28.2 gms. (0.2 mole) of methyl iodide, over-night at room temperature. White precipitate of the water-soluble product was obtained, filtered and dried. The n.m.r. spectrum of this compound showed a singlet due to the nine equivalent methyl protons and a triplet and a multiplet reflecting the presence of two equivalent ethoxy groups; a strong indication that the expected compound had been formed. N.m.r.: 1.58 (t, 6), 3.8 (S, 9), 4.45 (m, 4).

3. Succinyl bis (N^2, N^2, N^2-trimethyl-hydrazinium iodide.)





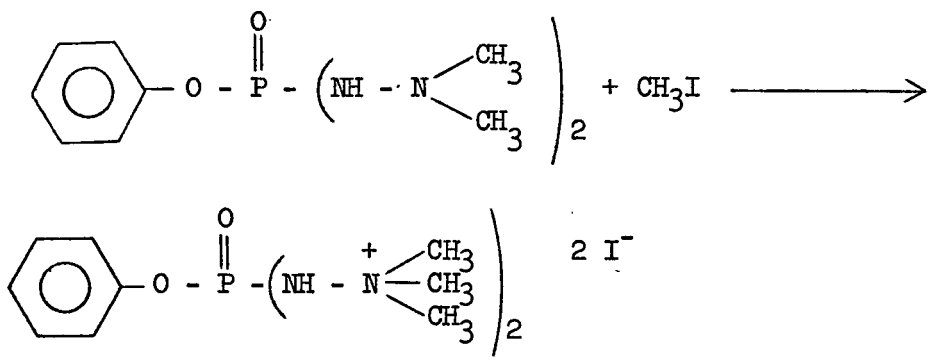
The synthesis of this iodide was carried out as described for B1. A solution of 7.3 gms. (0.05 mole) was placed in a one-necked flask fitted with a condenser and 75 gms. (1.4 mole) of methyl iodide was added to this flask slowly with stirring. The reaction mixture on being allowed to stand for a few days gave yellowish brown precipitate which was filtered, washed with methylene chloride and dried. The product decomposed on treatment with water and melted at 233-35°C. The n.m.r. spectrum of this compound consisting of one singlet due to the eighteen equivalent methyl protons and another singlet due to the four equivalent methylene protons strongly suggested that the expected product was formed. N.m.r.: 2.68 (S, 4), 3.7 (S, 18).

Analysis of $C_{10}H_{24}N_4O_2I_2$ MW 486.14

Calculated: C, 24.71%; H, 4.98%; N, 11.52%

Found: C, 22.68%; H, 4.77%; N, 10.61%

4. Phenyl ester of bis (N^2, N^2, N^2-trimethyl) phosphoro hydrazinic acid iodide.



The methylation was carried out as described for B1. A concentrated solution of 6.5 gms. (0.025 mole) of the phenyl ester of bis (N^2, N^2-dimethyl) phosphorohydrazidic acid, was placed in a two-necked flask and 12.77 gms. (0.09 mole) of methyl iodide was added dropwise with stirring. The reaction mixture was refluxed for about 2 hours, and on leaving it over-night at room temperature, white precipitate developed. This precipitate was filtered and more of the product was obtained by adding anhydrous ether to the filterate. This water soluble product was dried to give a melting point of 169-70°C. The n.m.r. of this product showed the expected singlet due to the eighteen equivalent methyl protons and a down field multiplet due to the five phenoxy protons along with some impurities; thus strongly suggesting the formation of the expected product. N.m.r.: 3.7 (S, 18), 7.3 (m, 5).

Analysis of $C_{12}H_{25}N_4O_2PI_2$ M.W. 542.15 (cal'd)

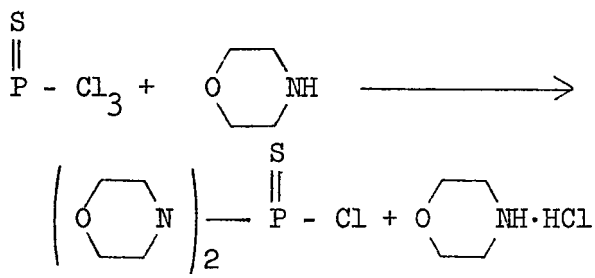
Calculated: N, 10.33%; I, 46.82%

Found: N, 11.74%; I, 54.16%

IV. THIOPHOSPHORYLATED HYDRAZIDES AND PHENYLHYDRAZIDES

A. Successful syntheses

1. P, P-Dimorpholino phosphorothioic chloride.



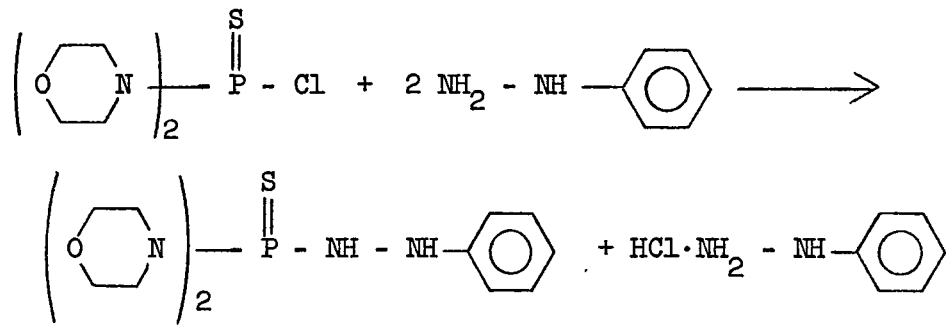
A solution of 15.3 gms. (0.09 mole) of thiophosphoryl chloride in 70 ml. of dichloromethane was placed in a three-necked flask. To this, a solution of 34.8 gms. (0.40 mole) of morpholine in 80 ml. of methylene chloride was added slowly with stirring and the reaction mixture was maintained at 5-10°C. After the addition of the amine was completed, the reaction mixture was warmed to room temperature and allowed to remain over-night. The white precipitate of morpholine hydrochloride was collected on a filter and the filtrate was evaporated in vacuo. The white crystals obtained were washed with water to get rid of the remaining chloride and other water soluble impurities, and the purified product after drying in an Abderhalden apparatus melted at 94-97°C; n.m.r.: 3.3 (m, 8), 3.8 (m, 8).

Analysis of $C_8H_{16}N_2O_2PSCl$ MW 270.74 (cal'd)

Calculated: C, 35.49%; H, 5.96%

Found: C, 35.92%; H, 7.18%

2. P, P-Dimorpholino-2-phenylphosphorothioic hydrazide.



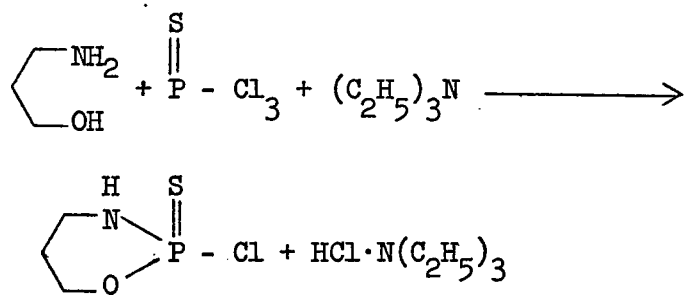
This synthesis was carried out under the same conditions as described for B1. In this case, the solution of 4.6 gms. (0.025 mole) of P-P-dimorpholino phosphorothioic chloride in 30 ml. of anhydrous ether was reacted with 7.7 gms. (0.06 mole) of phenylhydrazine. The product after being washed free of chloride and impurities with distilled water and drying in an Abderhalden apparatus melted at 173-75°C; n.m.r.: 3.2 (m, 8), 3.6 (m, 8), 7.1 (m, 5).

Analysis of $C_{14}H_{23}N_4O_2PS$ M.W. 342.40

Calculated: C, 49.11%; H, 6.77%; N, 16.36%

Found: C, 49.26%; H, 6.86%; N, 16.44%

3. 2-Chloro-1,3,2-oxazaphosphorine-2-sulfide.



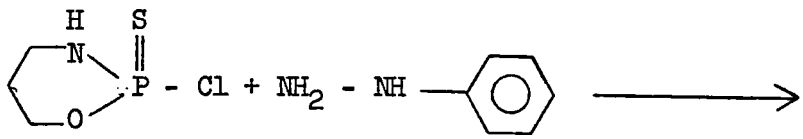
The synthesis was carried out as described for A1. A stirred solution of 8.3 gms. (0.11 mole) of 3-amino-1-propanol and 21.2 gms. (0.22 mole) of triethylamine in 80 ml. of bromobenzene, maintained at 5-10°C was treated dropwise with a solution of 17 gms. (0.1 mole) of thiophosphoryl chloride in 25 ml. bromobenzene. After the addition of the trichloride was completed, the reaction mixture was warmed to room temperature and allowed to react over-night. The white precipitate of triethylammonium chloride obtained was filtered and the filtrate repeatedly washed with water to remove the traces of triethylammonium chloride. Evaporation under vacuum at room temperature gave the pure white product which after drying, melted at 77-79°C; n.m.r.: 2.3 (m, 2), 3.4 (m, 2), 4.15 (S, broad hump, 1), 4.7 (m, 2).

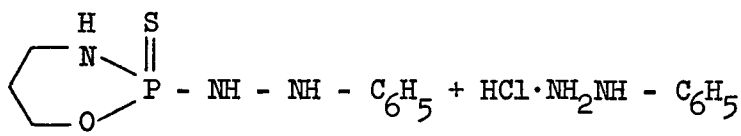
Analysis of $C_3H_7NOPSCl$ M.W. 171.50

Calculated: C, 21.0%, H, 4.11%; N, 8.16%

Found: C, 21.28%; H, 4.18%; N, 8.25%

4. 2-Phenyl-hydrazino-1,3,2-oxaza phosphorine 2-sulfide.





This synthesis was carried out as described for B1. A solution of 5.2 gms. (0.032 mole) of the monochloride in 30 ml. methylene chloride was reacted with 12.8 gms. (0.1 mole) of phenylhydrazine in 30 ml. of methylene chloride. The product after being washed free of chloride and impurities with distilled water and dried in an Abderhalden apparatus melted at 124-27°C; n.m.r.: 2.1 (m, 2), 3.5 (m, 2), 4.55 (m, 2), 7.3 (m, 5).

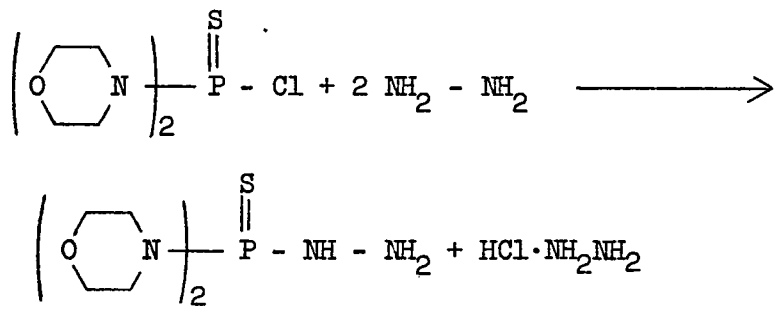
Analysis of $C_9H_{14}N_3OPS$ M.W. 243.27

Calculated: C, 44.44%; H, 5.80%; N, 17.27%

Found: C, 44.28%; H, 5.81%; N, 17.23%

B. Attempted Syntheses

1. P, P-Dimorpholino phosphorothioic hydrazide.



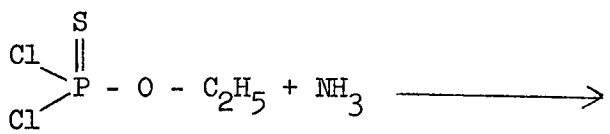
A solution of 4.6 gms. (0.25 mole) of P-P-dimorpholino phosphorothioic chloride in 30 ml. anhydrous ether was placed in a three-necked flask fitted with a reflux condenser, dropping funnel and a thermometer. Hydrazine (95%) from the dropping funnel (0.1 mole, 3.2 gms.) was added to the reaction vessel, slowly with stirring and the vessel temperature was maintained at 20°C. The reaction was allowed to proceed at 20°C for 2-4 hours and then at 35°C for 2 hours. The product obtained along with the hydrazinium chloride was washed with distilled water to get rid of the chloride, and dried in desiccator connected to a vacuum line; the dried product melted at 79-81°C. The n.m.r. spectrum for this compound contained a broad band for NH_2 protons which dissappeared on proton exchange with D_2O; n.m.r.: 2.8 (S, 2), 3.1 (m, 8), 3.7 (m, 8).

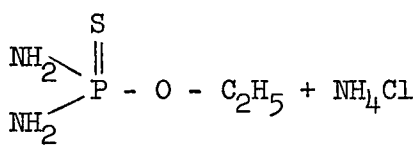
Analysis of $C_8H_{19}N_4O_2PS$ M.W. 266.31

Calculated: C, 36.08%; H, 7.19%; N, 21.04%

Found: C, 33.98%; H, 7.46%; N, 19.85%

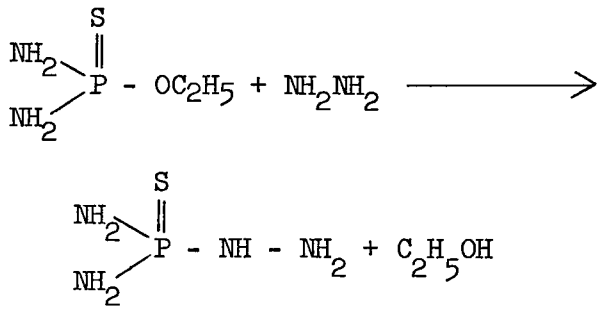
2. Ethyl ester of phosphorodiamidothioic acid.



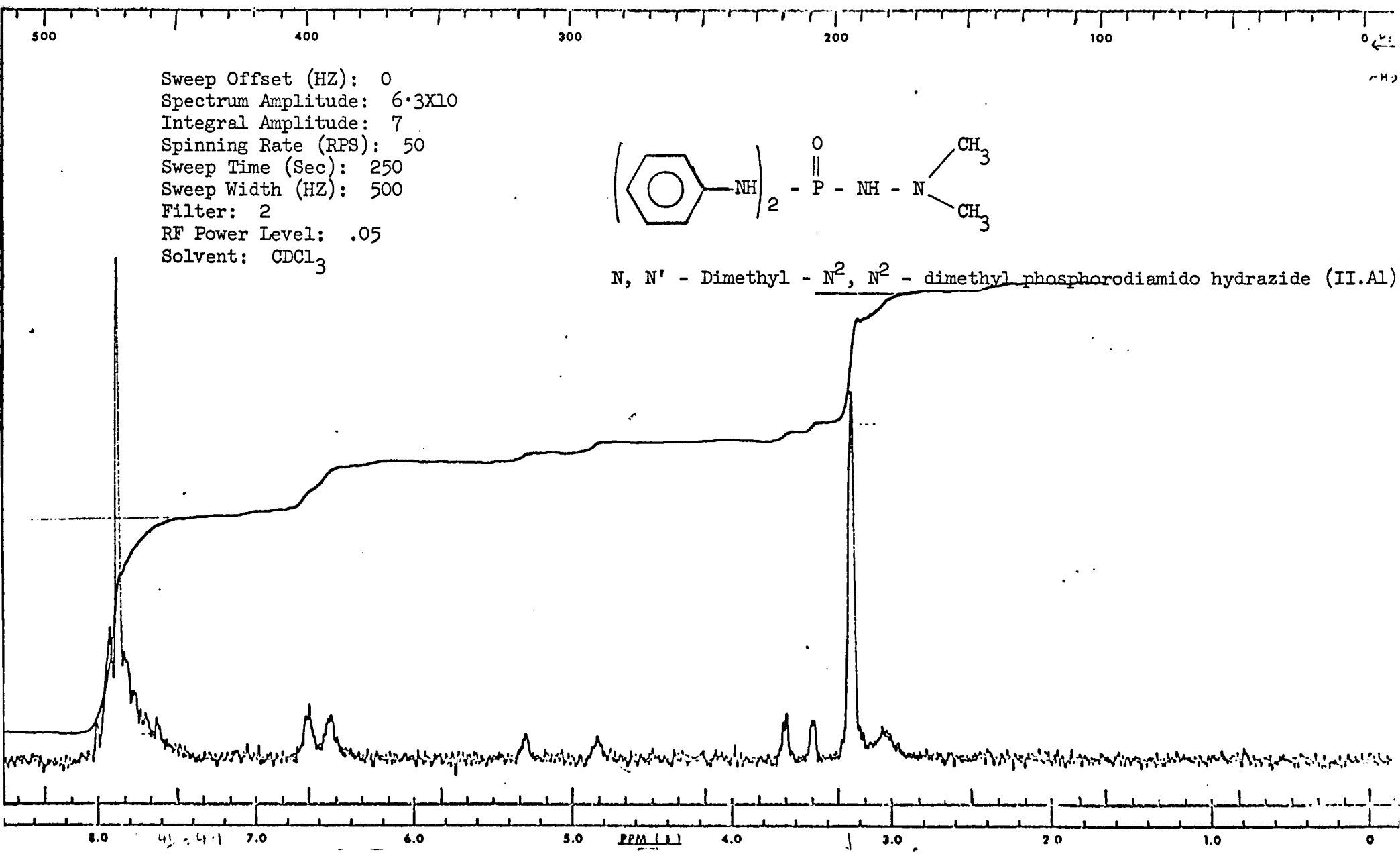


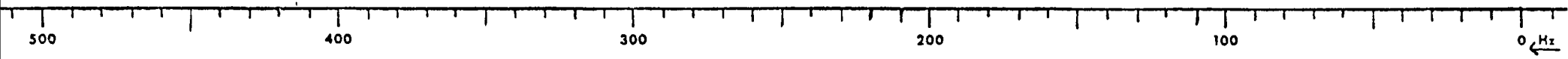
A stirred solution of 8.9 gms. (0.05 mole) of ethyl dichlorophosphate in 30 ml. of anhydrous ether was placed in a three-necked flask and ammonia was bubbled through it with the temperature being maintained below 20°C using a salt-ice bath. The reaction was considered completed when the temperature did not rise even after continuous flow of ammonia; the addition of ammonia was stopped and the reaction mixture was allowed to stand for 30 minutes. Ammonium chloride was removed by filtration and the filtrate on evaporation under vacuum gave the product, a colourless viscous liquid. The n.m.r. spectrum of this product gave a triplet and a multiplet (for CH_2 and CH_3 protons, respectively) indicative of the ethoxy group and a broad singlet for four NH_2 protons which disappeared on proton exchange with D_2O; n.m.r.: 1.98 (t, 3), 4 (S, broad hump, 4), 4.75 (m, 2).

3. Phosphorodiamidothioic hydrazide.

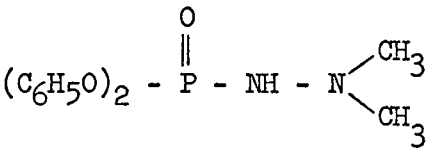


This reaction was carried out according to the method described by P.A.S. Smith (57). A solution of 95% hydrazine (3.2 gms., 0.1 mole) and 15 ml. of absolute ethanol is brought to a gentle boil in a 200-ml. two-necked flask provided with a magnetic stirrer, reflux condenser and dropping funnel. To this boiling stirred solution was added 4.6 gms. (0.032 mole) of the thioester at such a rate that a separate liquid phase did not accumulate in the reaction mixture. If unreacted ester is allowed to accumulate, some secondary hydrazide may be formed. The boiling was continued for 30 minutes after the completion of addition, and the contents of the flask were then cooled to room temperature with running water. The reaction mixture on evaporation under vacuum gave the product along with some unreacted thioester; this was shown by the n.m.r. studies. This mixture can be separated by high vacuum distillation, with the required hydrazide distilling first. On utilizing this distillation only the residue remaining was saved and it was the thioester as shown by its n.m.r. spectra, indicating that the fraction which had been distilled and discarded was probably the desired product; n.m.r.: (for the mixture): 1.45 (t), 3.55 (S, broad hump), 4.25 (m).

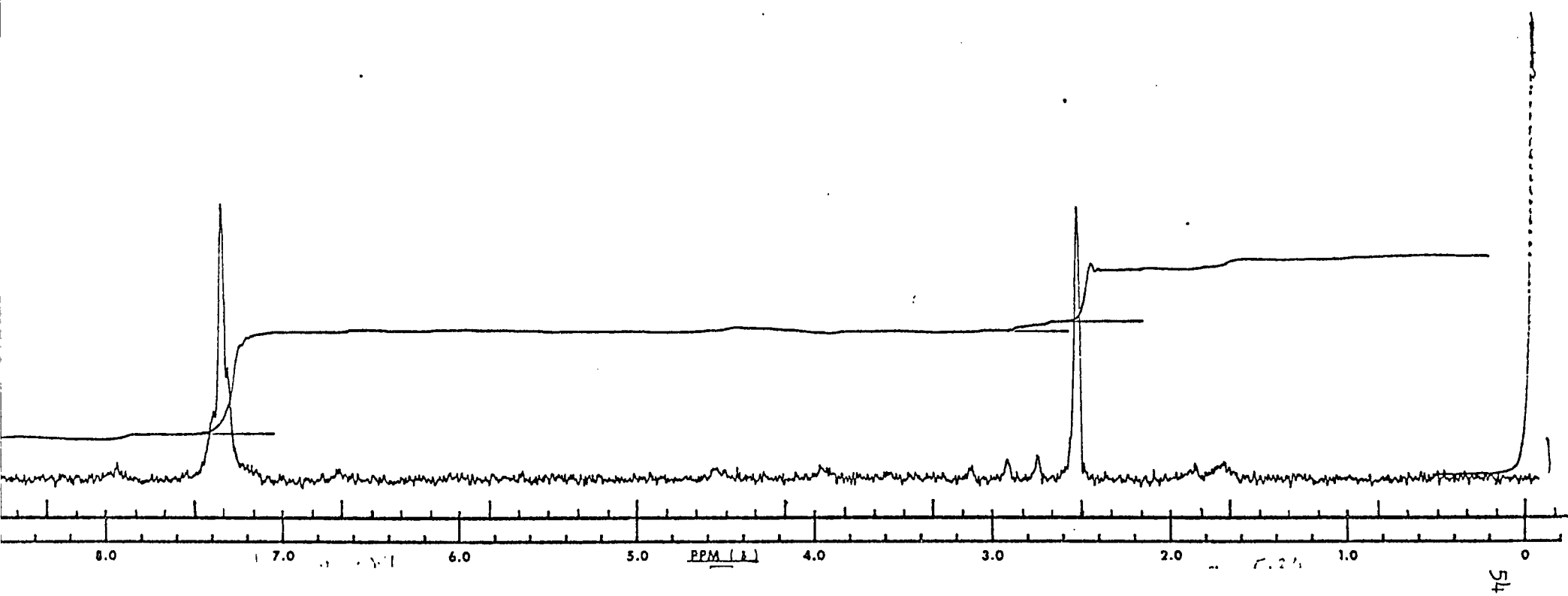

500
400
300
200
100
0
Sweep Offset (HZ): 0
Spectrum Amplitude: 6·3X10
Integral Amplitude: 7
Spinning Rate (RPS): 50
Sweep Time (Sec): 250
Sweep Width (HZ): 500
Filter: 2
RF Power Level: .05
Solvent: $CDCl_3$
$\left(\text{C}_6\text{H}_5\text{-NH}\right)_2 - \text{P}(=\text{O}) - \text{NH} - \text{N}(\text{CH}_3)_2$
N, N' - Dimethyl - N^2, N^2 - dimethyl phosphorodiamido hydrazide (II.A1)
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

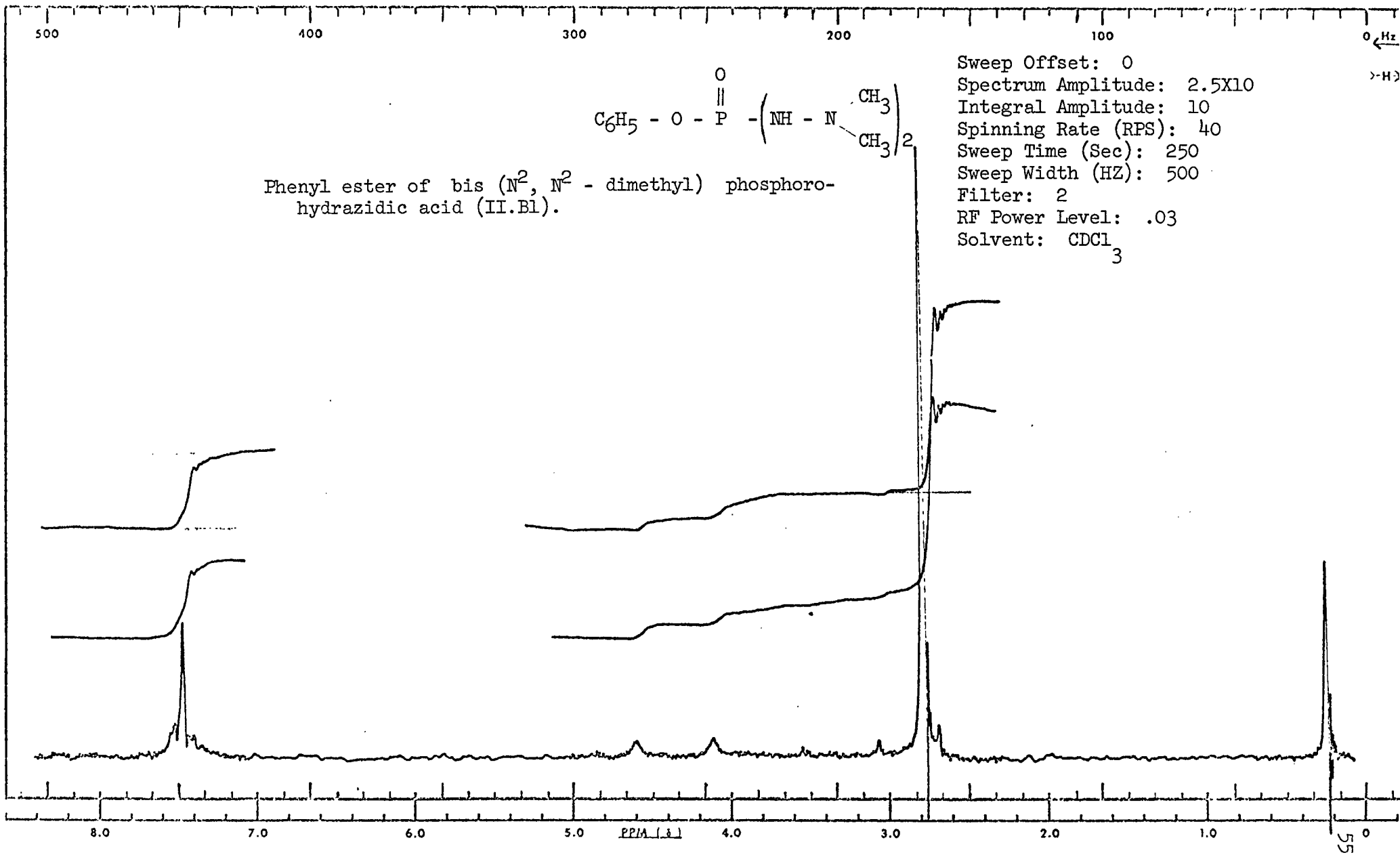


Sweep Offset (HZ): 0
Spectrum Amplitude: 5X10
Integral Amplitude: 6
Spinning Rate (RPS): 40
Sweep Time (Sec): 250
Sweep Width (HZ): 500
Filter: 2
RF Power Level: .05
Solvent: $CDCl_3$



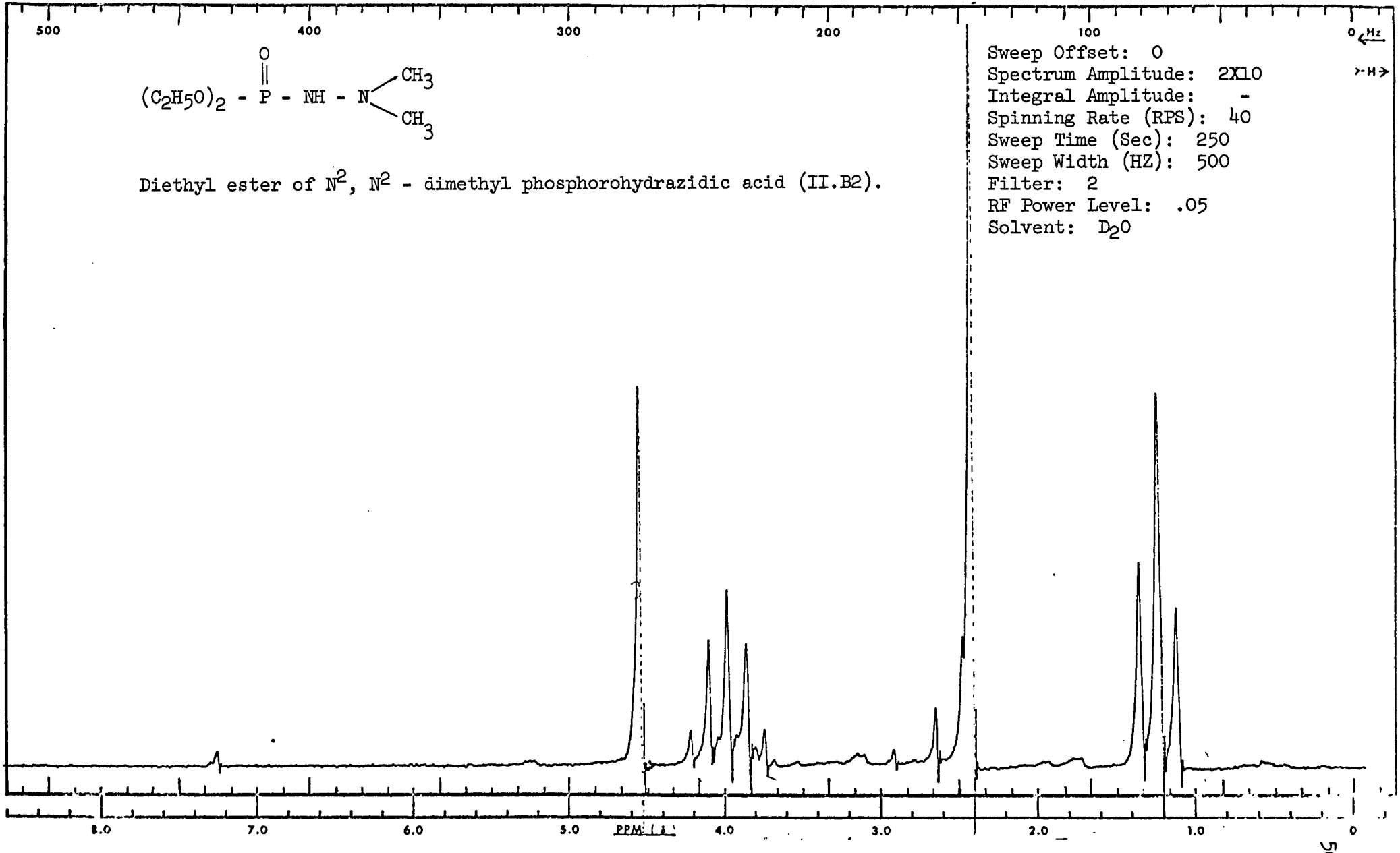
Diphenyl ester of - N^2, N^2 - dimethyl phosphorohydrazidic acid (II. A2).





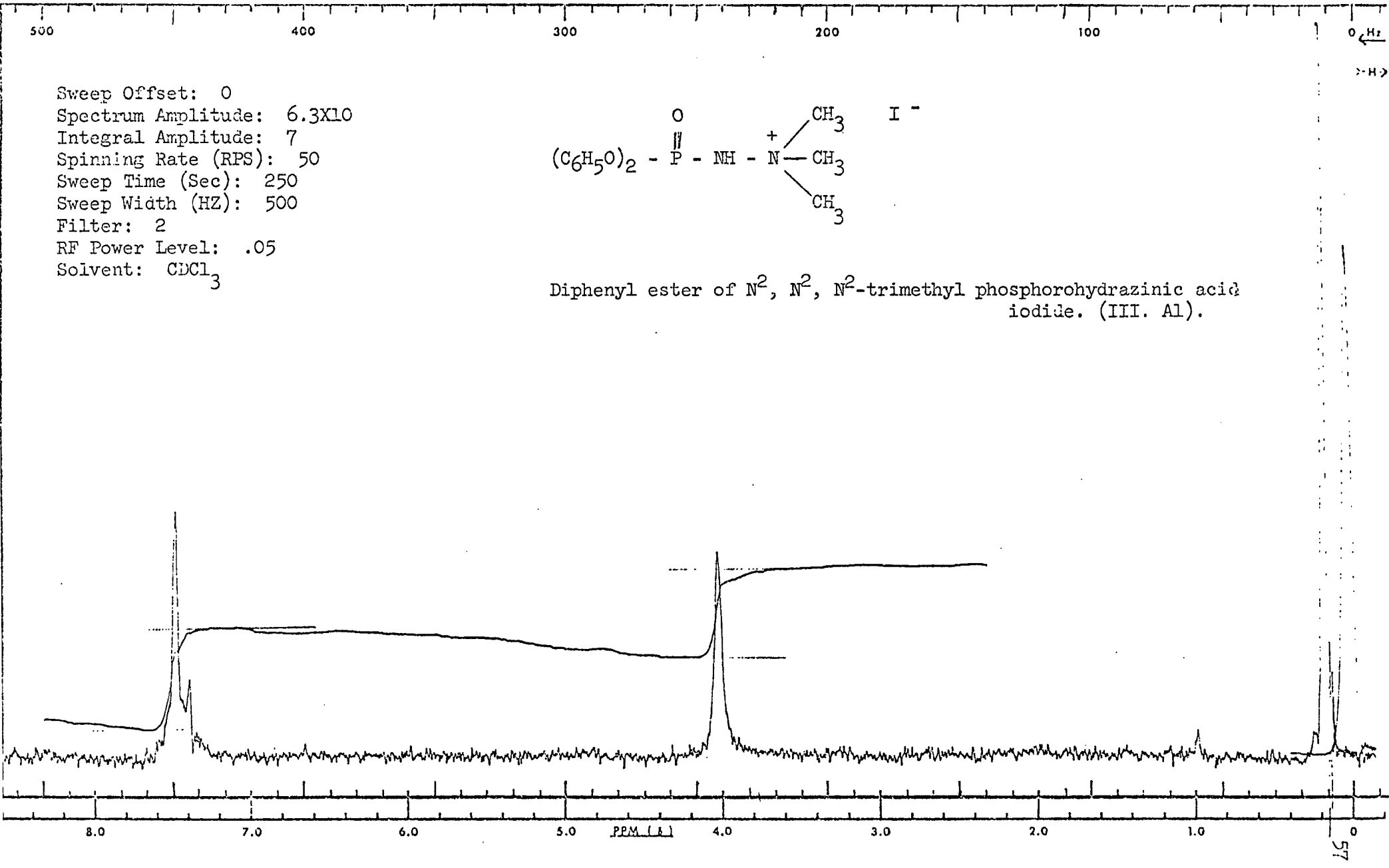
$$C_6H_5 - O - \overset{\overset{O}{\|}}{P} - \left(NH - N\begin{matrix}CH_3\\CH_3\end{matrix}\right)_2$$

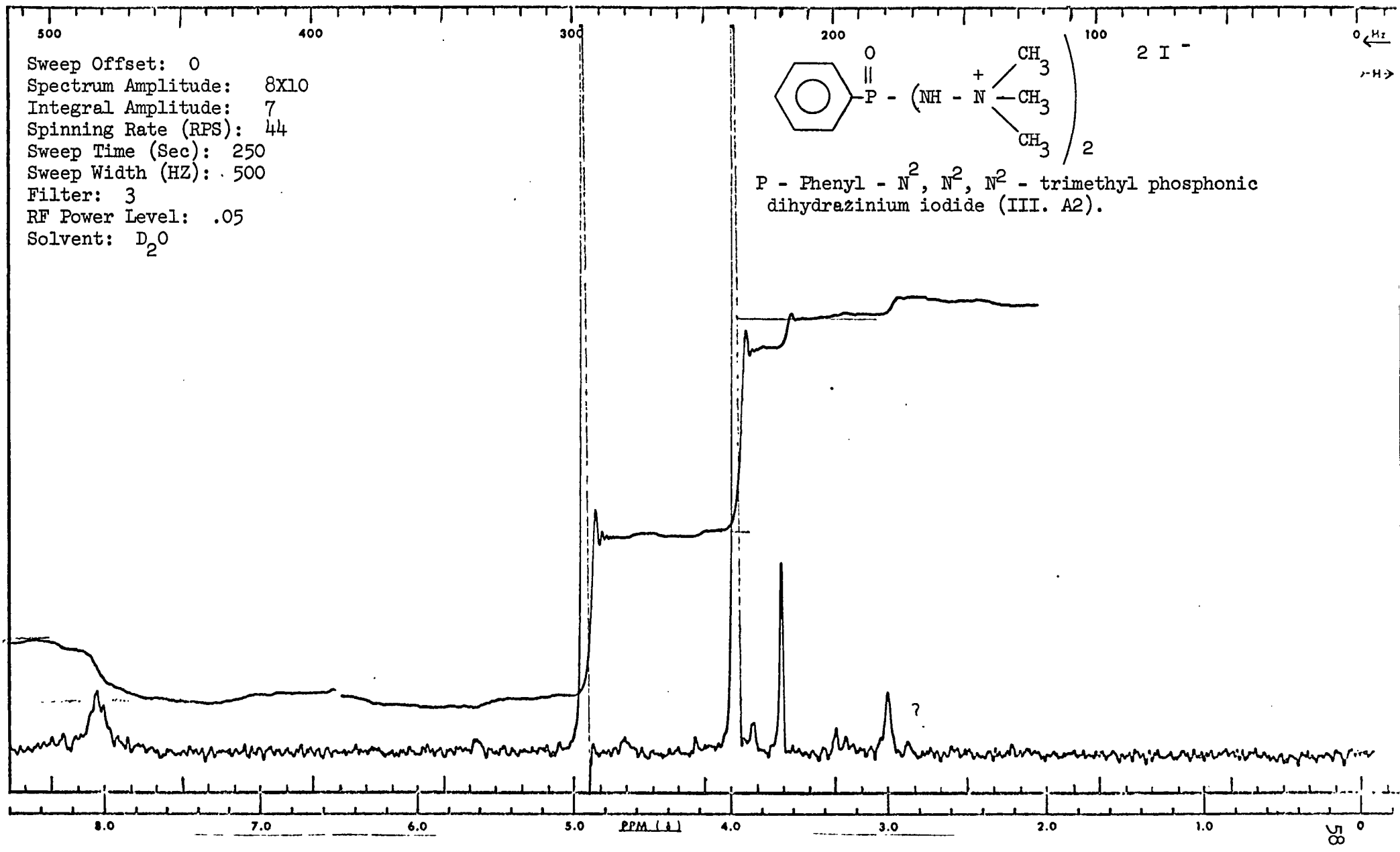
Phenyl ester of bis (N^2, N^2 - dimethyl) phosphoro-hydrazidic acid (II.B1).

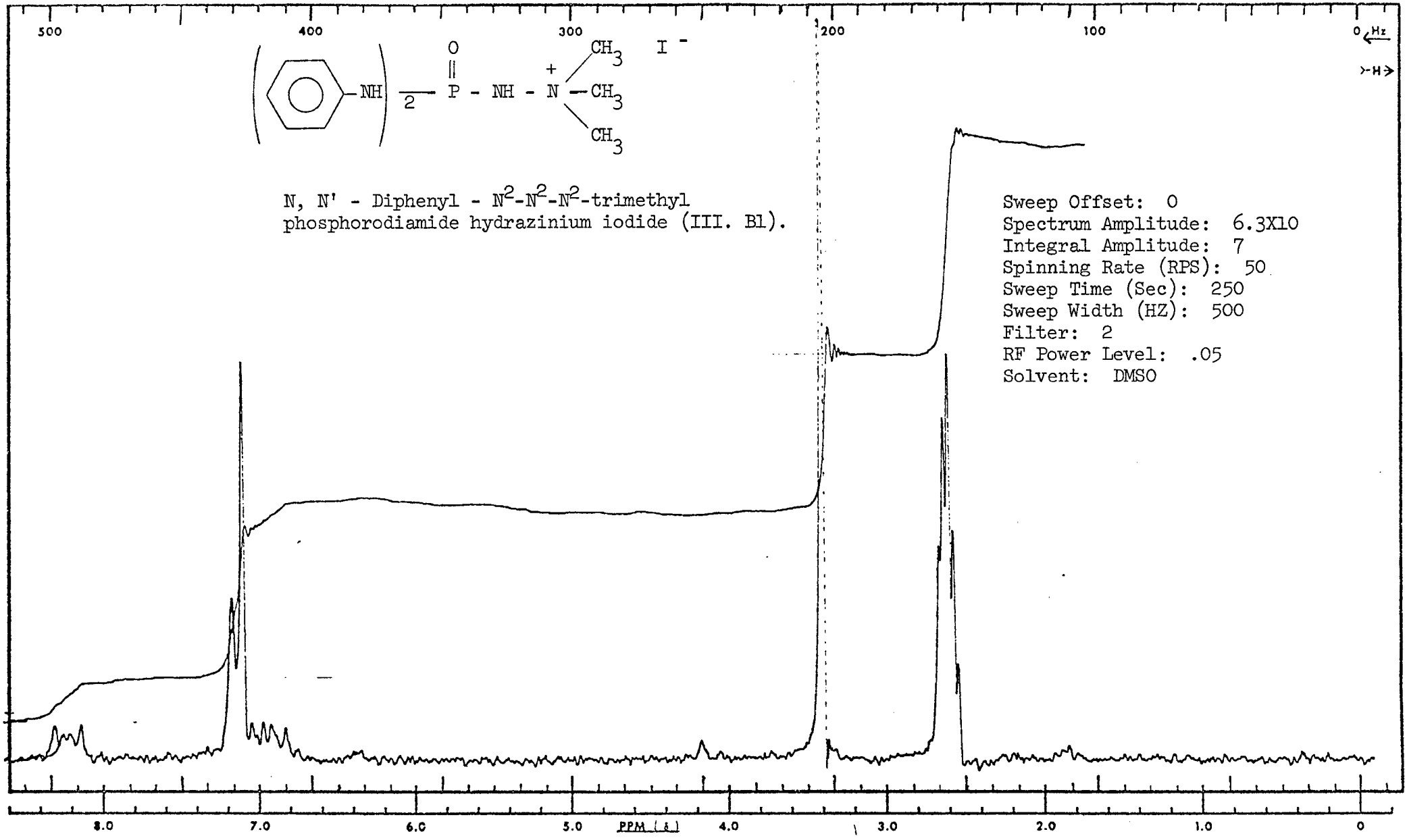


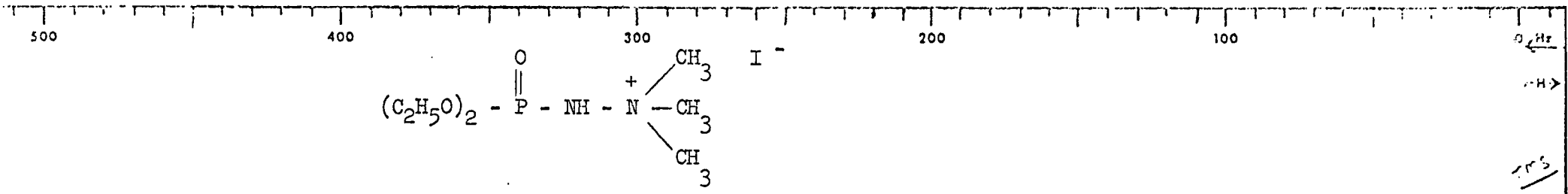
$(C_2H_5O)_2 - P(=O) - NH - N(CH_3)_2$

Diethyl ester of N^2, N^2 - dimethyl phosphorohydrazidic acid (II.B2).


500
400
300
200
100
0 Hz
Sweep Offset: 0
Spectrum Amplitude: 6.3X10
Integral Amplitude: 7
Spinning Rate (RPS): 50
Sweep Time (Sec): 250
Sweep Width (HZ): 500
Filter: 2
RF Power Level: .05
Solvent: CDCl3
(C6H5O)2 - P(=O) - NH - N+(CH3)2(CH3) I-
Diphenyl ester of N2, N2, N2-trimethyl phosphorohydrazinic acid iodide. (III. A1).
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

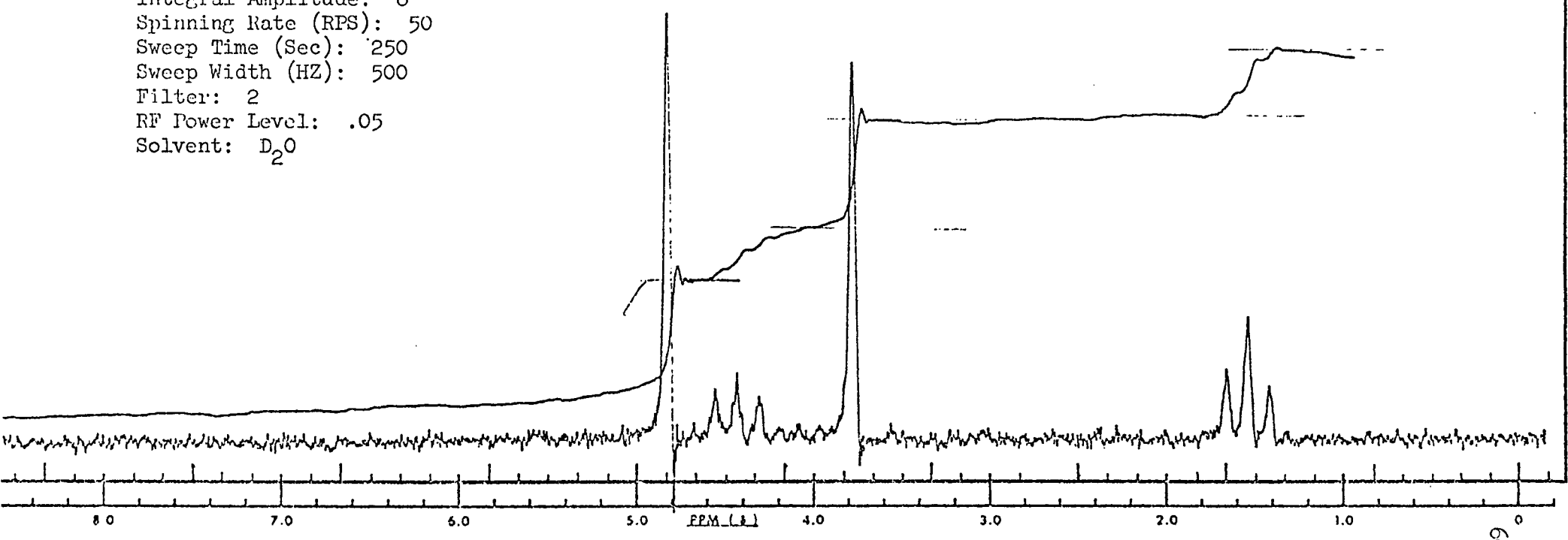

500
400
300
200
100
0 Hz
H
Sweep Offset: 0
Spectrum Amplitude: 8X10
Integral Amplitude: 7
Spinning Rate (RPS): 44
Sweep Time (Sec): 250
Sweep Width (HZ): 500
Filter: 3
RF Power Level: .05
Solvent: D2O
2 I -
P - Phenyl - N2, N2, N2 - trimethyl phosphonic dihydrazinium iodide (III. A2).
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

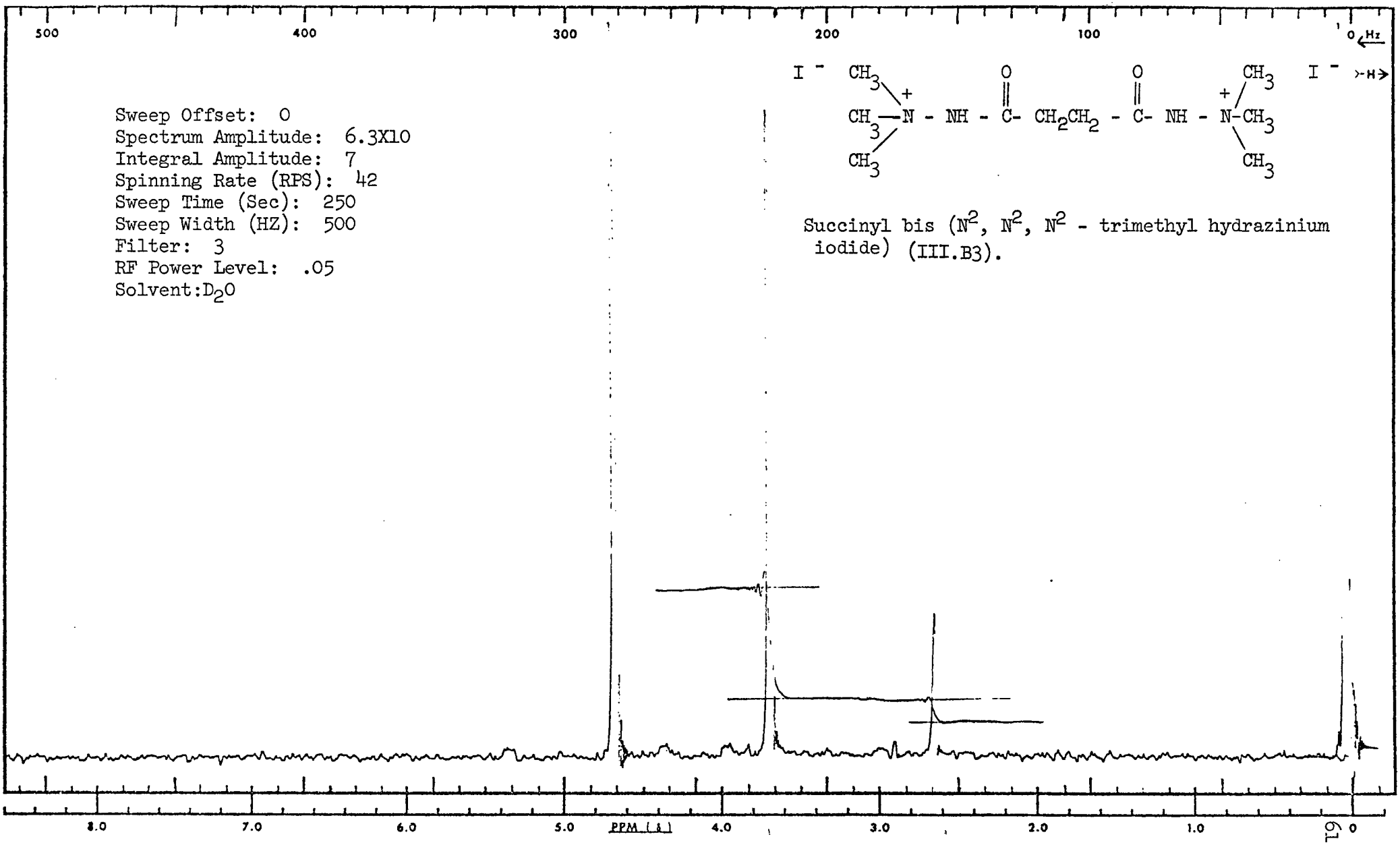

500
400
300
200
100
0 Hz
→H
NH
2
P - NH - N
CH3
CH3
CH3
I -
N, N' - Diphenyl - N2-N2-N2-trimethyl
phosphorodiamide hydrazinium iodide (III. B1).
Sweep Offset: 0
Spectrum Amplitude: 6.3X10
Integral Amplitude: 7
Spinning Rate (RPS): 50
Sweep Time (Sec): 250
Sweep Width (HZ): 500
Filter: 2
RF Power Level: .05
Solvent: DMSO
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0



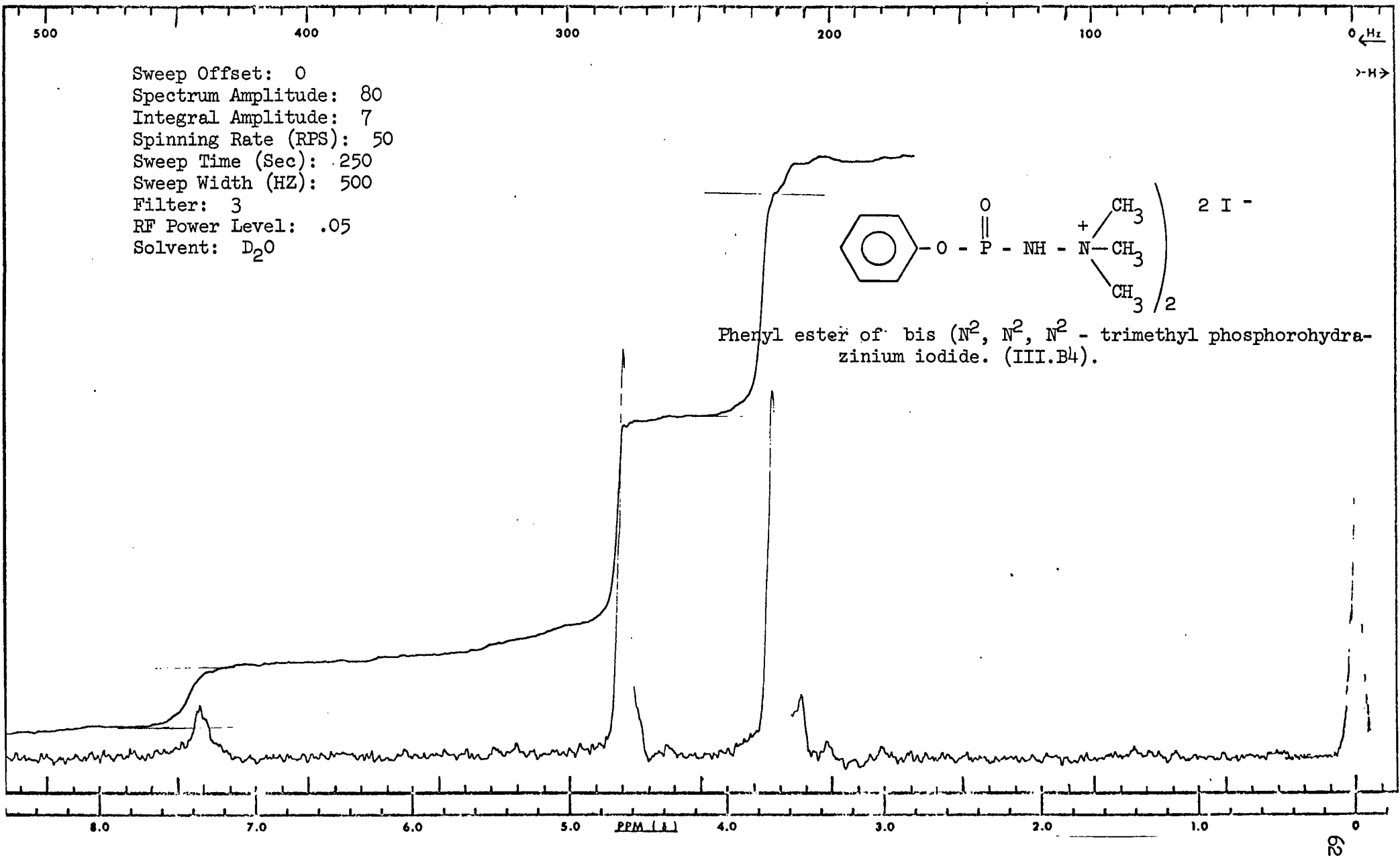
Diethyl ester of -N^2, N^2, N^2-trimethyl phosphorohydrazinic acid iodide (III.B2).

Sweep Offset: 0
Spectrum Amplitude: 6.3X10
Integral Amplitude: 6
Spinning Rate (RPS): 50
Sweep Time (Sec): 250
Sweep Width (HZ): 500
Filter: 2
RF Power Level: .05
Solvent: D_2O

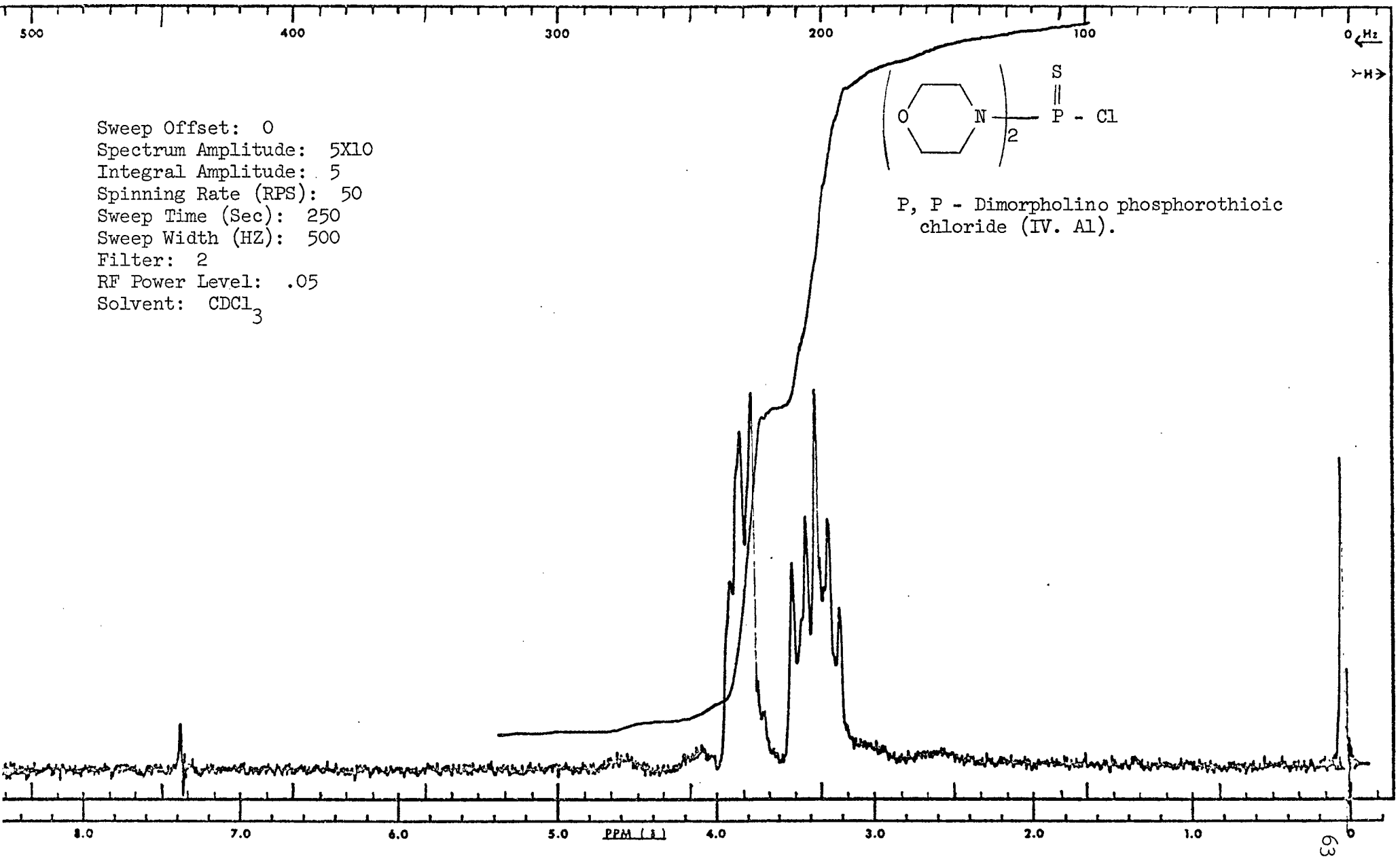


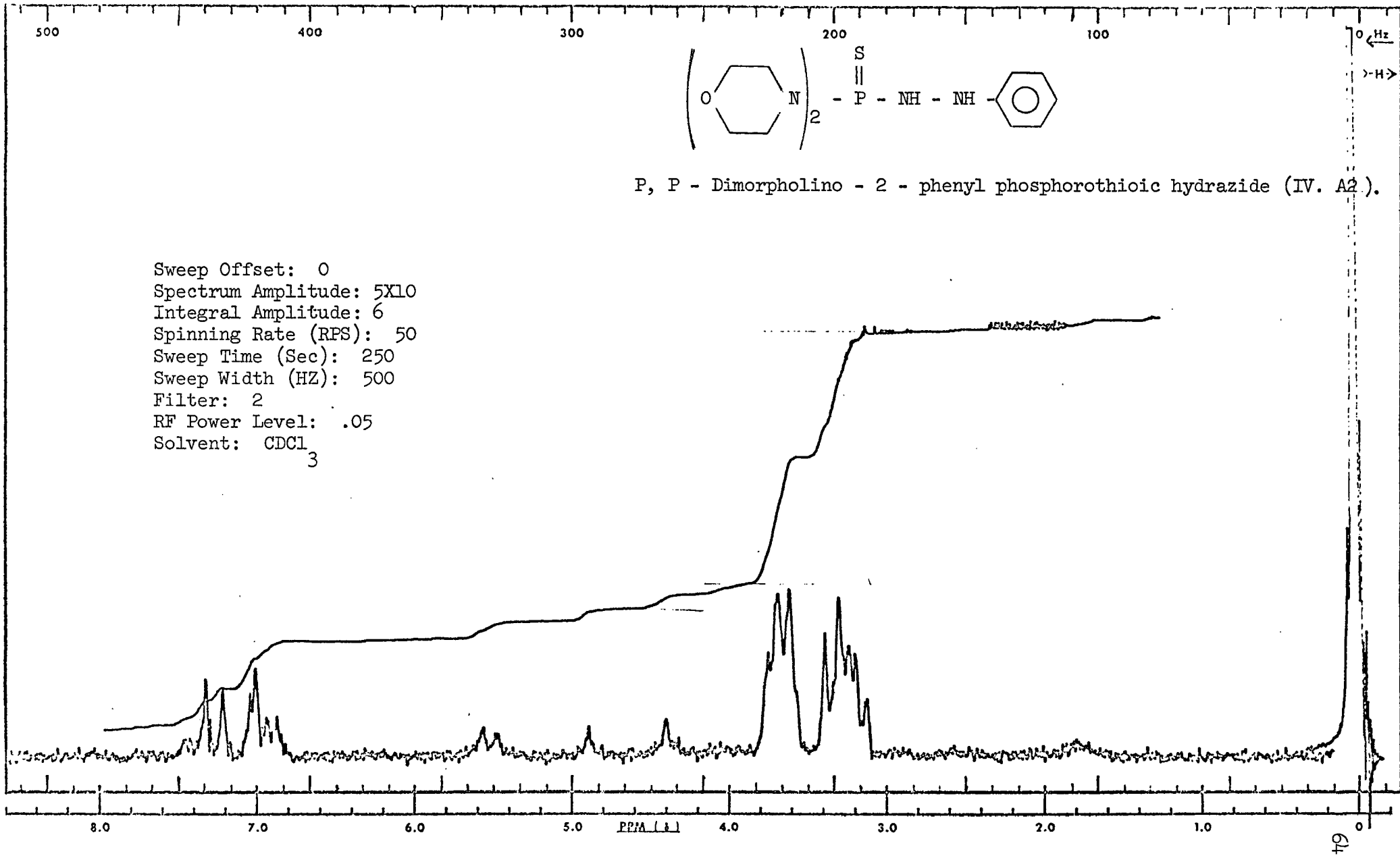


Succinyl bis (N^2, N^2, N^2 - trimethyl hydrazinium iodide) (III.B3).



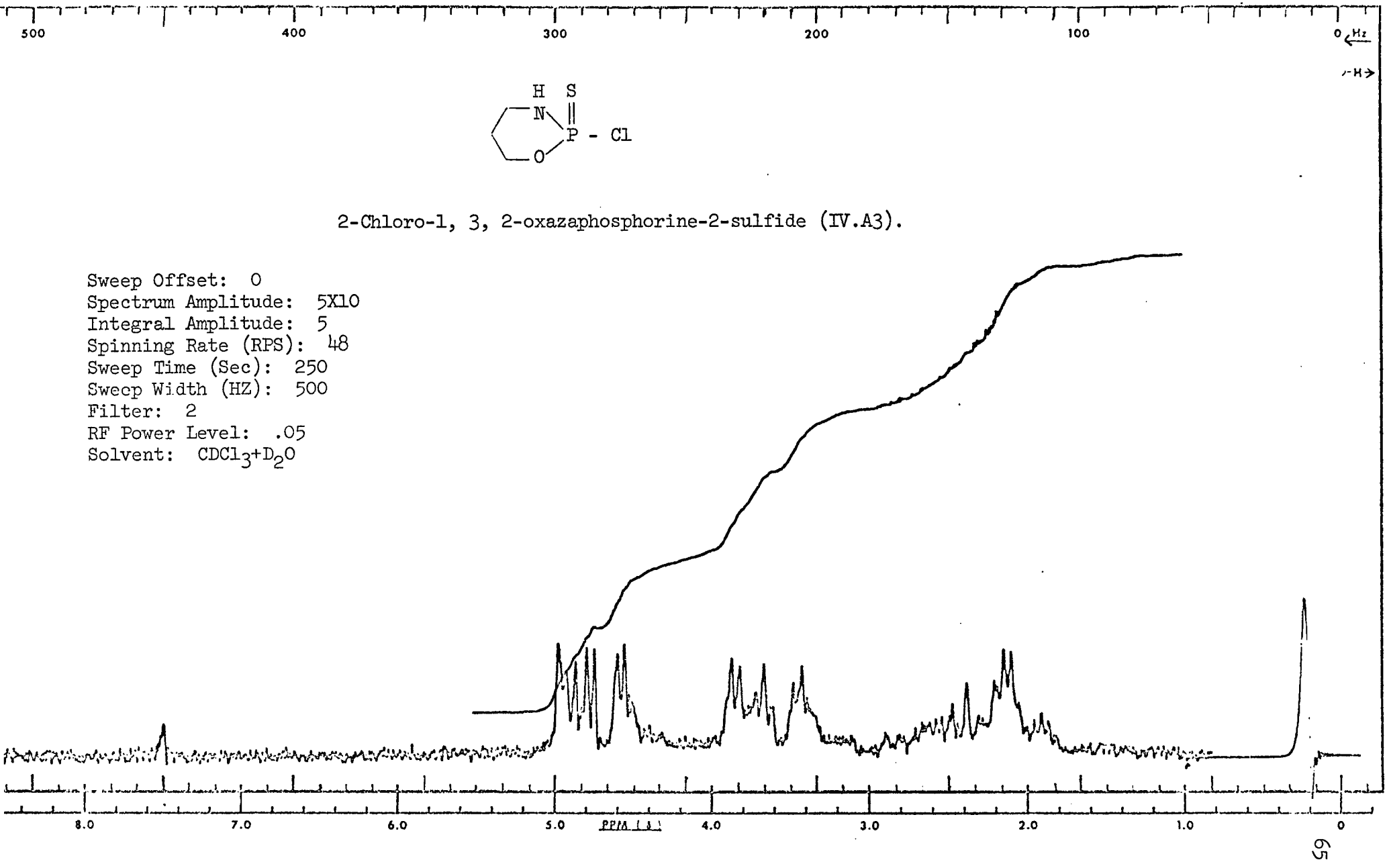
Phenyl ester of bis (N^2, N^2, N^2 - trimethyl phosphorohydrazinium iodide. (III.B4).


500
400
300
200
100
0 Hz
H
Sweep Offset: 0
Spectrum Amplitude: 5X10
Integral Amplitude: 5
Spinning Rate (RPS): 50
Sweep Time (Sec): 250
Sweep Width (HZ): 500
Filter: 2
RF Power Level: .05
Solvent: CDCl3
O
N
S
P - Cl
2
P, P - Dimorpholino phosphorothioic chloride (IV. A1).
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

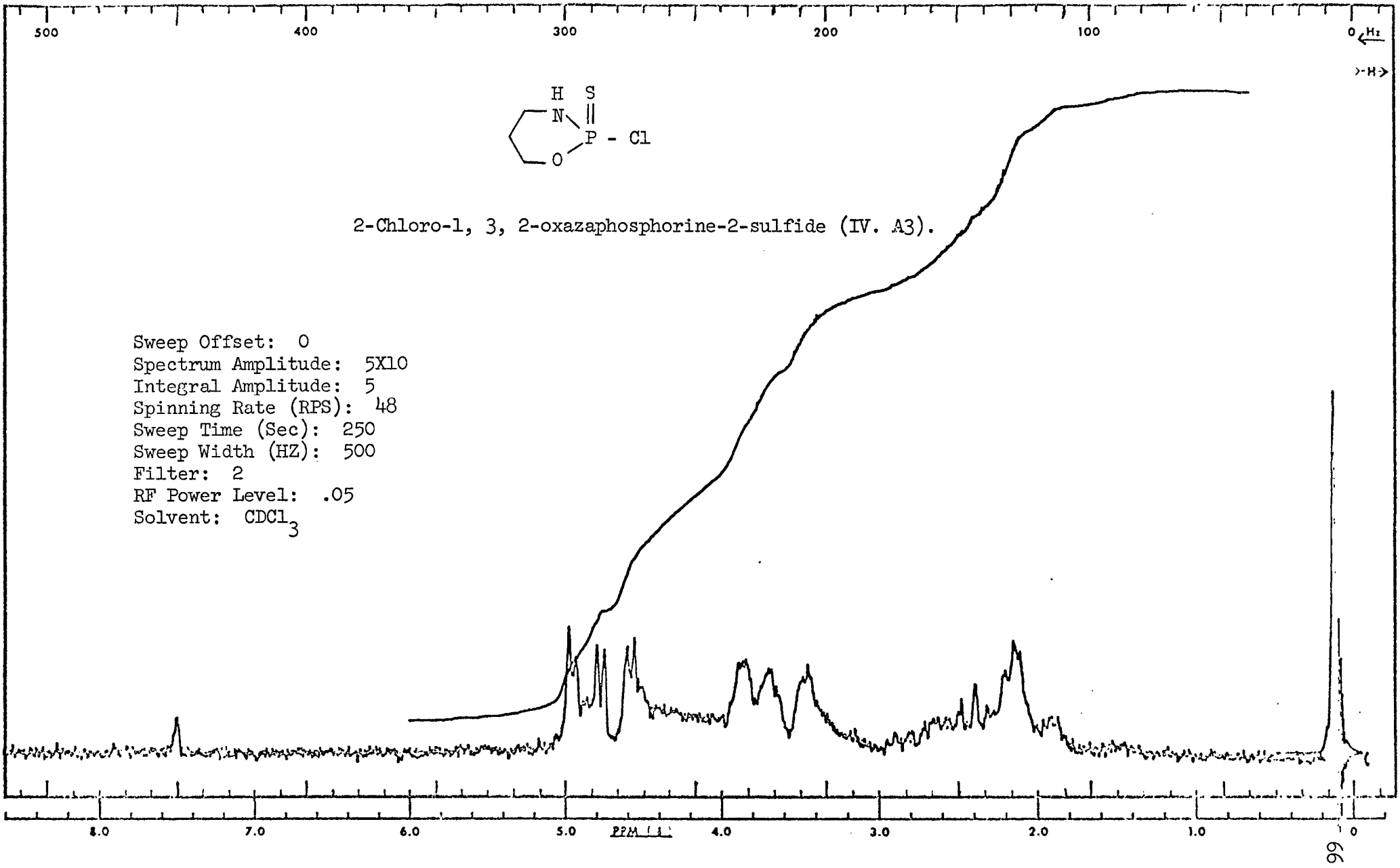


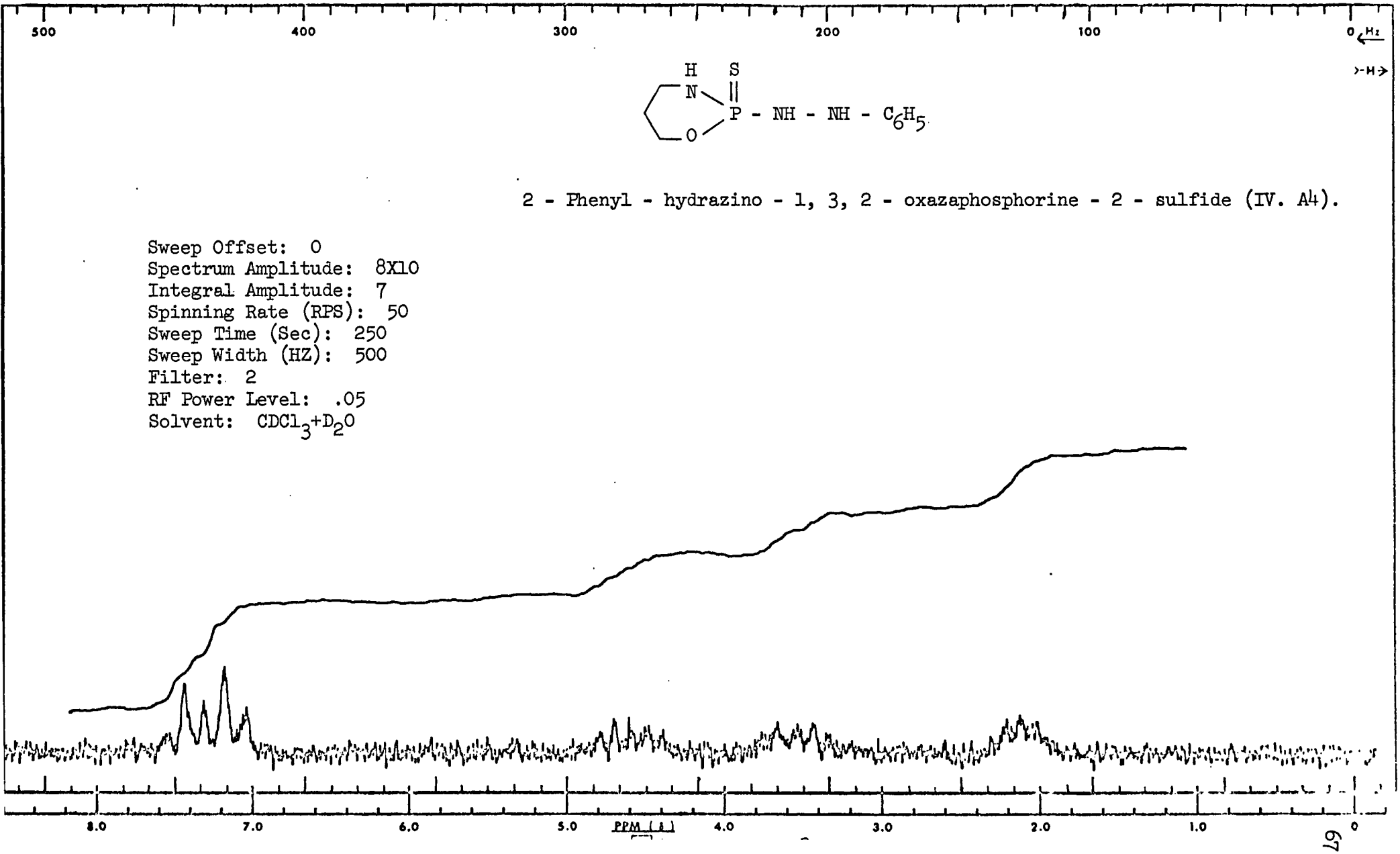
P, P - Dimorpholino - 2 - phenyl phosphorothioic hydrazide (IV. A2).

Sweep Offset: 0
Spectrum Amplitude: 5X10
Integral Amplitude: 6
Spinning Rate (RPS): 50
Sweep Time (Sec): 250
Sweep Width (HZ): 500
Filter: 2
RF Power Level: .05
Solvent: $CDCl_3$



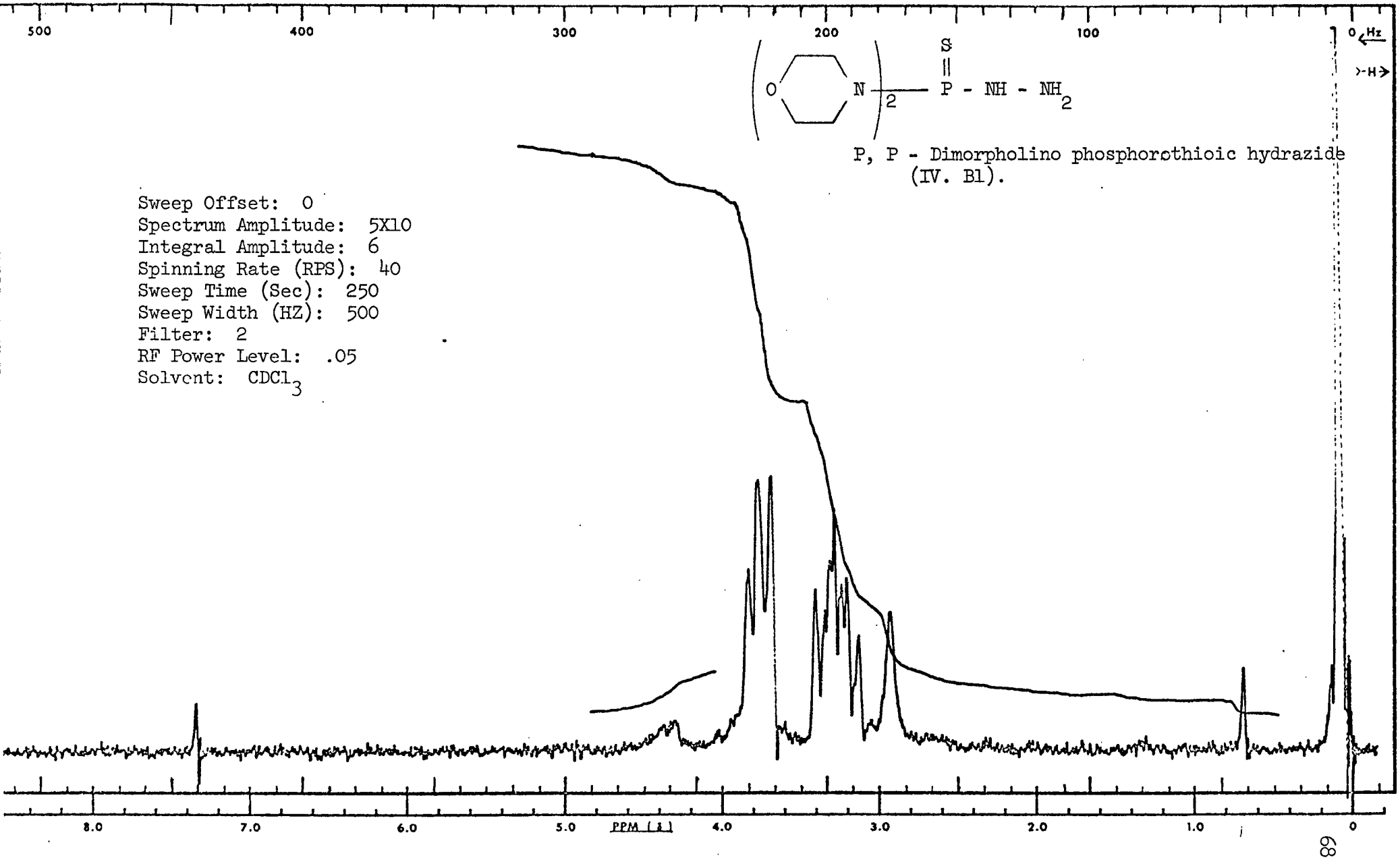
2-Chloro-1, 3, 2-oxazaphosphorine-2-sulfide (IV.A3).


500
400
300
200
100
0 Hz
H
S
N
P - Cl
O
2-Chloro-1, 3, 2-oxazaphosphorine-2-sulfide (IV. A3).
Sweep Offset: 0
Spectrum Amplitude: 5X10
Integral Amplitude: 5
Spinning Rate (RPS): 48
Sweep Time (Sec): 250
Sweep Width (HZ): 500
Filter: 2
RF Power Level: .05
Solvent: $CDCl_3$
8.0
7.0
6.0
5.0
PPM
4.0
3.0
2.0
1.0
0



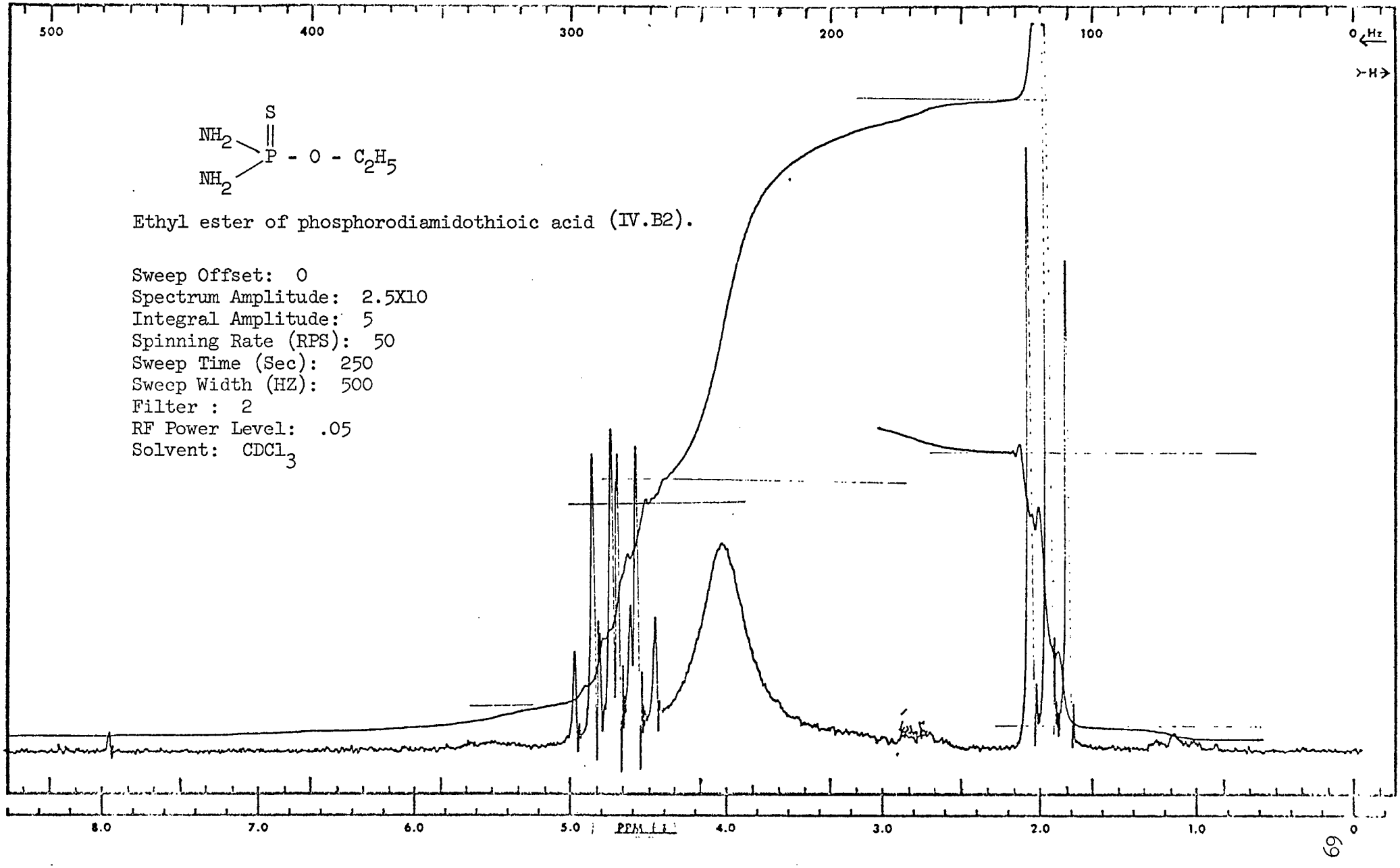
2 - Phenyl - hydrazino - 1, 3, 2 - oxazaphosphorine - 2 - sulfide (IV. A4).

Sweep Offset: 0
Spectrum Amplitude: 8X10
Integral Amplitude: 7
Spinning Rate (RPS): 50
Sweep Time (Sec): 250
Sweep Width (HZ): 500
Filter: 2
RF Power Level: .05
Solvent: $CDCl_3+D_2O$



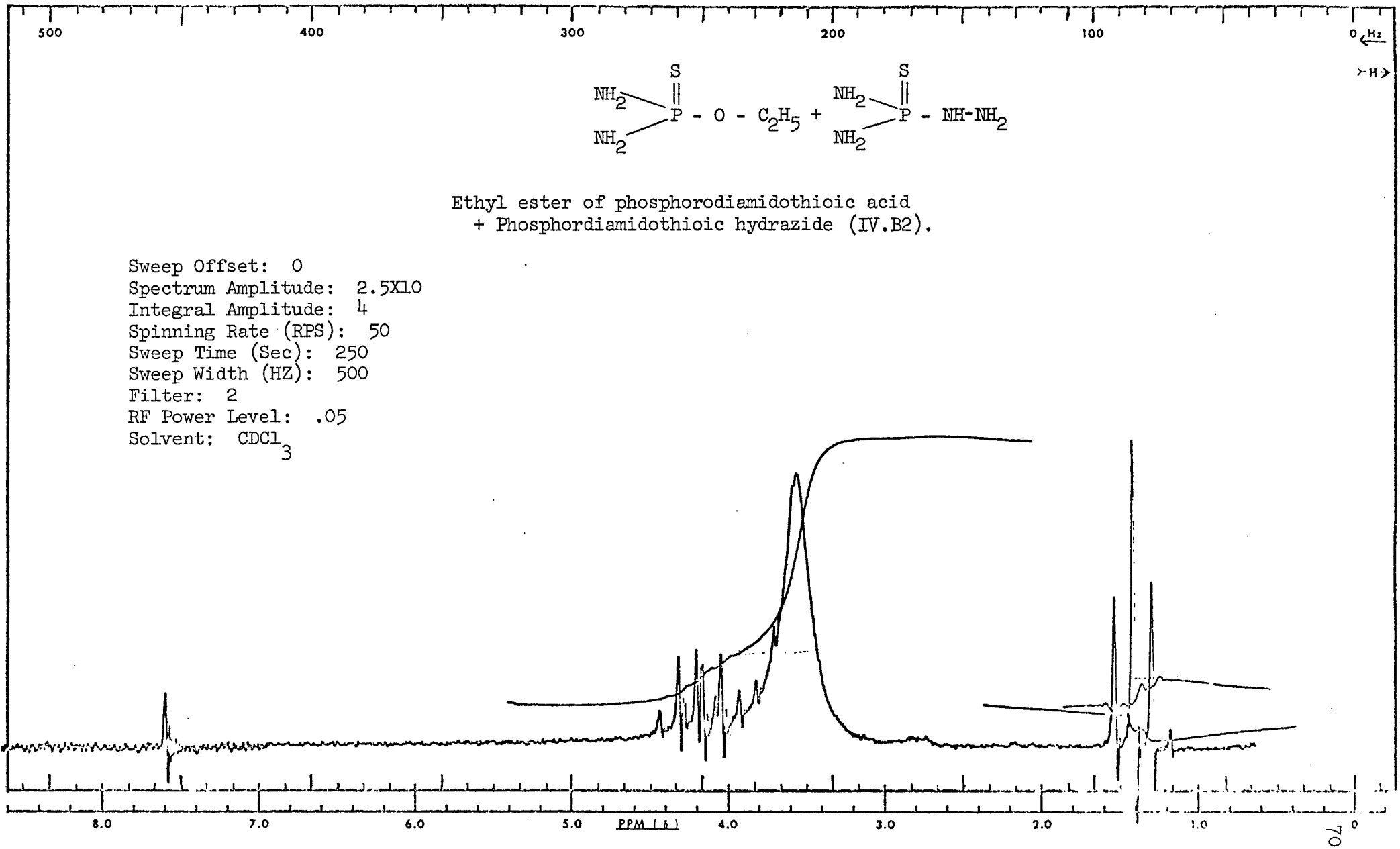
P, P - Dimorpholino phosphorothioic hydrazide (IV. B1).

Sweep Offset: 0
Spectrum Amplitude: 5X10
Integral Amplitude: 6
Spinning Rate (RPS): 40
Sweep Time (Sec): 250
Sweep Width (HZ): 500
Filter: 2
RF Power Level: .05
Solvent: $CDCl_3$



Ethyl ester of phosphorodiamidothioic acid (IV.B2).

Sweep Offset: 0
Spectrum Amplitude: 2.5X10
Integral Amplitude: 5
Spinning Rate (RPS): 50
Sweep Time (Sec): 250
Sweep Width (HZ): 500
Filter : 2
RF Power Level: .05
Solvent: $CDCl_3$



Ethyl ester of phosphorodiamidothioic acid
+ Phosphordiamidothioic hydrazide (IV.B2).

Sweep Offset: 0
Spectrum Amplitude: 2.5X10
Integral Amplitude: 4
Spinning Rate (RPS): 50
Sweep Time (Sec): 250
Sweep Width (HZ): 500
Filter: 2
RF Power Level: .05
Solvent: $CDCl_3$

CHAPTER III

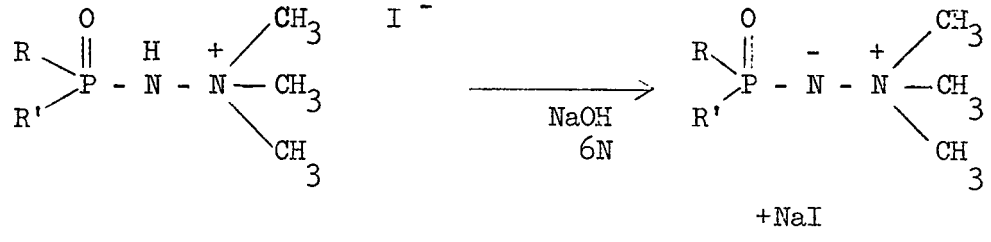
Conclusion

1. Several new organophosphorous hydrazides were successfully synthesized utilizing the proposed synthetic schemes.

2. In preparation of dimethyl hydrazino compounds the main problem was the separation of the product and 1, 1-dimethyl-hydrazinium chloride. Various means were tried; however the best method was the repeated extraction of the product using benzene in which the chloride is less soluble. The drawback of this procedure was that it was very laborious.

3. Formation of quarternary hydrazides using methyliodide as an alkylating agent was temperature dependent. In some cases, even at 50°C, clevage of the alkyl group on phosphorous was obtained. This was circumvented by carrying out the reaction at room temperature for long duration of time. This was made a general practice at least for the first attempt to carry out such reactions.

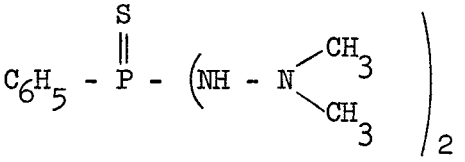
4. Aminimides were either not formed and/or could not be isolated using the reaction: -



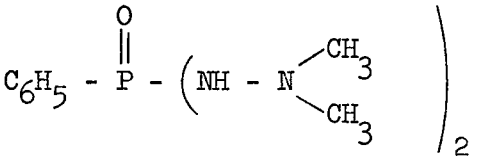
Water soluble quarternary amm. compounds did not react at all under

this situation.

5. Thiophosphorous compounds were generally low melting and water insoluble. Sulfur has a tendency to make the products water insoluble.

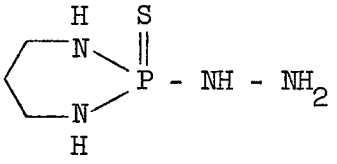


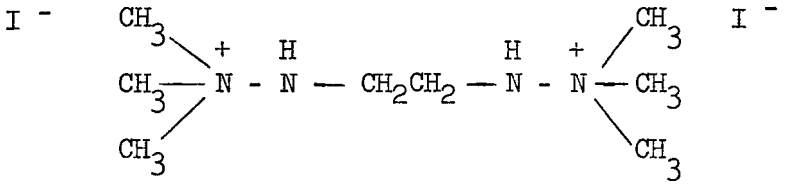
(water insoluble)



(water soluble)

6. General insolubility of the compounds of the following type in conventional organic solvents, also posed a great difficulty in their isolation and purification.





7. N.m.r. spectras and proton exchange studies using D_2O were very helpful in characterization of compounds.

8. There are reasons to believe that the compounds synthesized herein may exhibit oncolytic and/or ganglionic blocking activity.

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