PHOSPHORINO[4,3-d]PYRIMIDINES. SYNTHESIS, PROPERTIES, AND RESOLUTION

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PHOSPHORINO[4,3-d]PYRIMIDINES. SYNTHESIS, PROPERTIES, AND RESOLUTION

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TO

My Wife and Son

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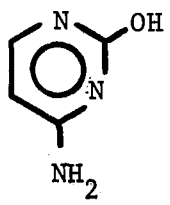
CHAPTER I

HISTORICAL

"A well known British chemist once said that there are four types of chemistry, organic, inorganic, physical, and pyrimidine."[29] The 1,3-diazine or pyrimidine ring occurs naturally in simple form as in cytosine (1), uracil (2), thymine (3), or in fused form such as adenine (4)



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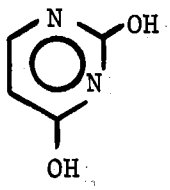

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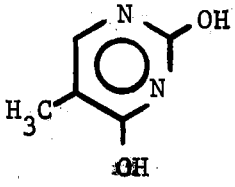

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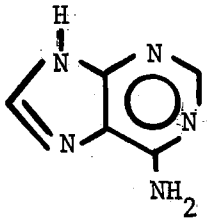
(a purine), riboflavin (5) (a pteridine), or tetrodotoxin (6) (a quinazoline).



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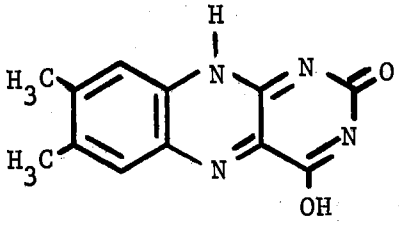

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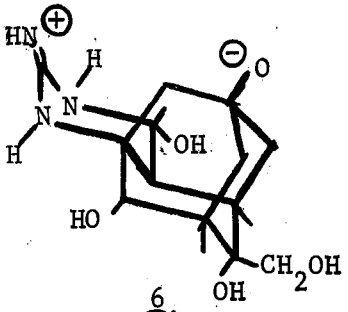

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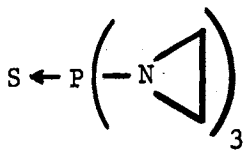
Pyrimidines in the form of N-glycosidic phosphates[164] (nucleotides) are the sole constituents of the nucleic acids, the building blocks of RNA and DNA. The pterins, aminopterin and amethopterin, and 6-mercaptopurine are antimetabolites which have been used extensively in the treatment of acute leukemia.[35] Another well known family of pyrimidines are

the barbiturates, which possess hypnotic activity.

In addition to the above-mentioned pterins, tris(1-aziridinyl)-phosphine sulfide (thiotepa) (7)[35] has long been a standard anticancer drug, clinically used in the chemotherapy of leukemia. This fact,



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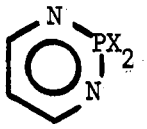

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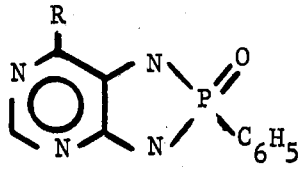

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coupled with the recently reported synthesis and activity of phosphorus analogs of pyrimidines of types 8[22,121,193,211] and 9[140] led us to postulate that pyrimidines substituted with phosphorus at the five and/or six positions (the biologically active positions)[27,168] might be of use in medicinal chemistry. Since quinazolines are substituted at the five and six positions of a pyrimidine nucleus, a phosphorus-substituted 5,6,7,8-tetrahydroquinazoline was selected as the entry into this new family of fused heterocycles. (The selection of a 5,6,7,8-tetrahydro derivative was dictated in part by the available phosphorus heterocyclic starting materials and will be discussed in Part III.)

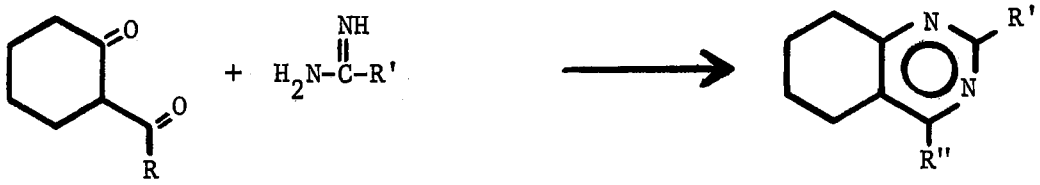
Quinazolines--Synthesis and Biological Activity

A. Synthetic Methods for 5,6,7,8-Tetrahydroquinazolines

The synthesis, reactions, and properties of pyrimidines have been extensively reviewed in the Weissberger and Taylor series THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS. Currently there are four volumes relating to pyrimidines in this treatise: The Pyrimidines[32] covering the literature

up to 1957; The Pyrimidines, Supplement I[31] which covers the literature into 1968; Fused Pyrimidines, Part I: Quinazolines[5] which includes only quinazoline literature into 1966; and Fused Pyrimidines, Part II: Purines[139], covering the literature to late 1970.

By far the most common and widely employed synthesis of 5,6,7,8-tetrahydroquinazolines is the base-catalyzed condensation of amidines or amidine analogs with β-dicarbonyl compounds.[5] The functionality may be



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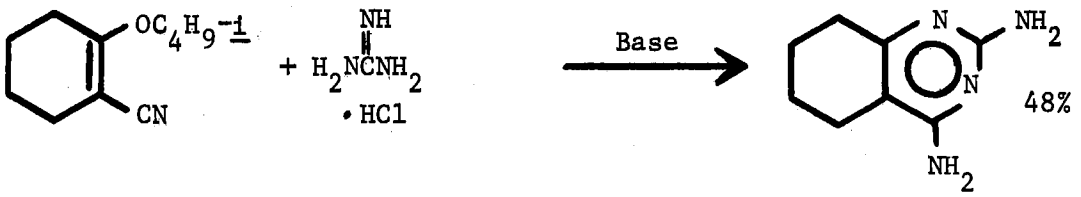
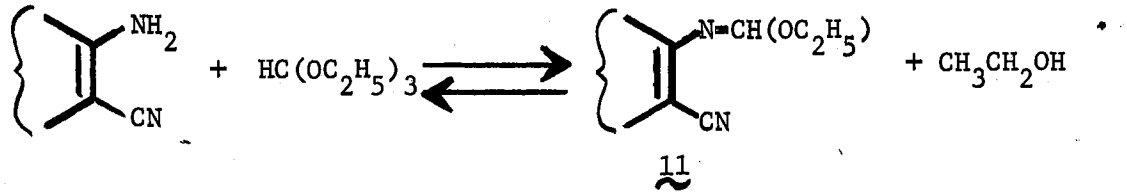
varied by the judicious selection of various amidine and amidine analogs available as reactants, such as ureas, thioureas, guanidines, etc. The yields generally range from 20-60%. Guanidine and thiourea seem to give higher yields than other "amidines". A further variance in functionality may be achieved in the use of different carbonyl components, e.g., β-keto aldehydes yield 4- and/or 6-unsubstituted quinazolines,[5] β-diketones form alkyl or aryl 4- and 6-substituted quinazolines,[5] and β-keto esters react to make quinazolinols (tautomeric quinazolinones). Jonak and co-workers[112] have recently prepared a series of 2-aminopyrimidin-4-ols from various β-keto esters and guanidine. The yields in these preparations ranged from 22% to 60%, and were typical of these types of condensation.

Another commonly employed synthesis of pyrimidines (applicable to quinazolines) is the condensation of 2-cyano enol ethers (derived from

β-keto nitriles)[139] with amides and amidines such as formamide,[59] thiourea,[12] and guanidine.[41,42,57,199] It is interesting to note that the parent β-keto nitriles do not react with guanidine to give diaminopyrimidines but yield aminotriazines instead.[200]

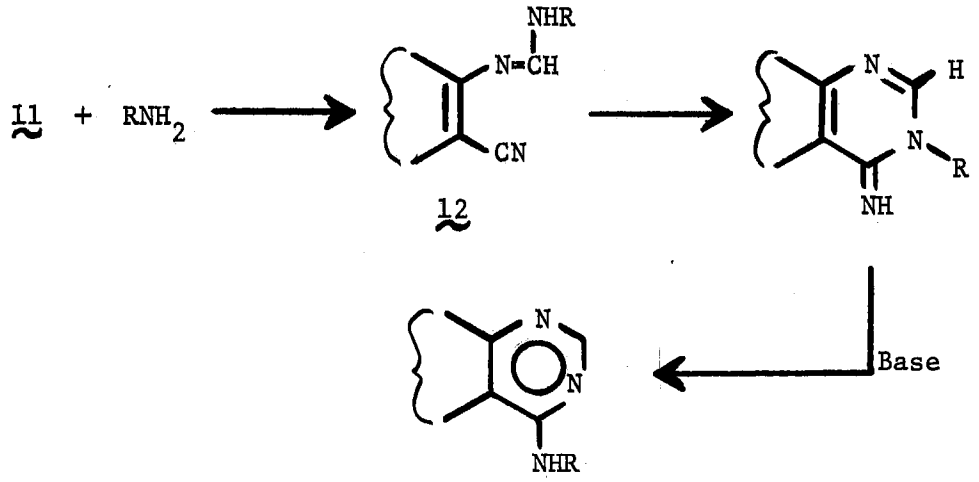


Taylor and coworkers[217,219,222,224] have been quite successful in utilizing 2-enamino nitriles (derived from Thorpe[202] cyclization of dicyano compounds) for the synthesis of both aromatic and saturated fused quinazolines and other fused pyrimidines. The key step in these synthetic routes is the formation of a highly reactive ethoxymethylene derivative 11 from the 2-enamino nitrile via reaction with triethyl orthoformate. (This reaction is often accelerated by the present of acetic anhy-

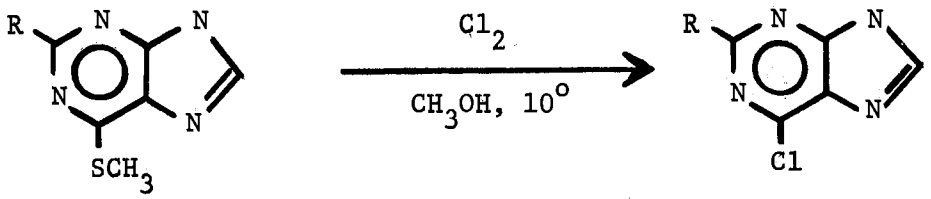


11

dride if acylation is slower than the formation of 11. The acetic anhydride probably favors product formation by removal of the ethanol by-product.) The intermediate 11 can then be cyclized with reagents such as ethanolic sodium hydrosulfide,[224] ethanolic ammonia,[217] ethanolic methylamine,[222] and some other amines.[219] The reaction of 11 with amines proceeds via intermediate formamidine 12, which undergoes an intramolecular addition to the nitrile group, and (where tautomerization to achieve aromatization is not possible) a subsequent base catalyzed ring-opening,



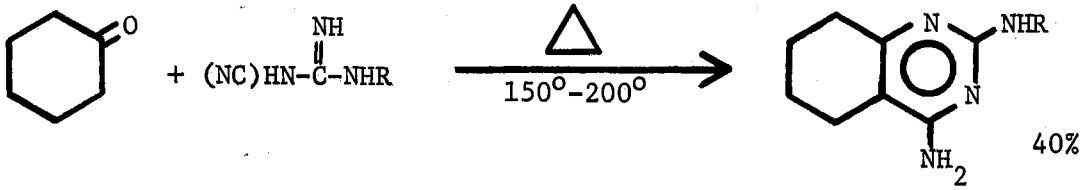
ring-closure process (Dimroth rearrangement) to achieve aromaticity.[30] The ring closure with sodium hydrosulfide is presumed to proceed by the same type of mechanism to form a 4-quinazolinethiol (tautomeric with 4-quinazolinethiones) in 60-97% yields. The mercaptopyrimidines are synthetically important because of the extreme facility with which they and their methyl derivatives may be converted to other functionalities, e.g., chloro, amino, etc. A slightly more versatile (alkyl or aryl groups may be placed at the 2-position), but overall inferior approach[224] is the acid-catalyzed condensation of thioamides (alkyl or aryl) and 2-enamino nitriles to form 4-mercaptopyrimidines.



89%[174]

Of particular importance (as will be discussed in Section B) in medicinal chemistry are the 2,4-diaminopyrimidines. The most readily

employed synthesis of this family of compounds is the condensation of a β-keto ester with guanidine to form a 2-amino-4-hydroxypyrimidine. These compounds may be converted with PCl_5 to 2-amino-4-chloro derivatives which may be subjected to ammonolysis to form a 2,4-diaminopyrimidines. While this reaction sequence is widely applicable, the overall yields are generally low (3-20% in a recently prepared series).[112] In the three-step reaction sequence involving methyl 2-oxocyclohexanecarboxylate the total yield of 2,4-diamino-5,6,7,8-tetrahydroquinazoline was only 23%.[168] For this reason, there has been recent interest in the development of one-step synthetic methods for the preparation 2,4-diaminoquinazolines. One of the most successful of these methods is the direct reaction of ketones and dicyandiamides[3,168] (N-cyanoguanidines) at

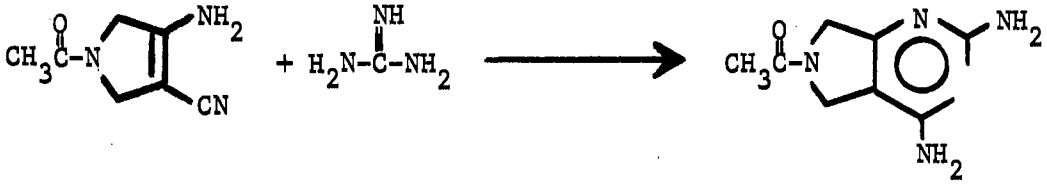


40%

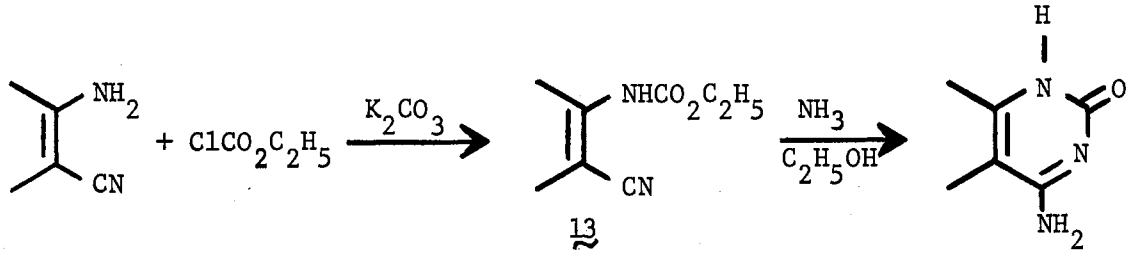
elevated temperatures. This reaction was shown to have considerable generality by the utilization of various acyclic and cyclic ketones with dicyandiamide to form diaminopyrimidines and quinazolines.[3,167,168] The use of N-substituted dicyandiamides with cyclohexanone led to 4-amino-2-alkylamino-5,6,7,8-tetrahydroquinazolines.[168]

2-Enamino nitriles and 2-cyano enol ethers are distinctly analogous compounds. However, the condensation of 2-enamino nitriles and guanidine to form 2,4-diaminopyrimidines has only recently[38,39,59,210] been reported. However, this type of condensation is quite common with aromatic o-amino nitriles and proceeds in 30% to 90% yields.[223] Similarly, 2-enamino nitriles can be made to condense with formamidine,[210] chloroformamidine,[194] formamide,[61] and benzamidine[79] to form the corresponding

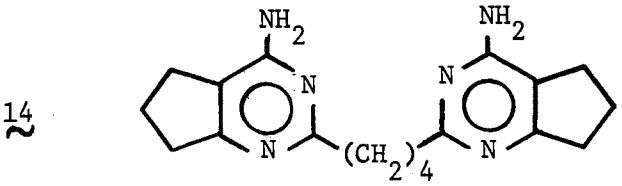
fused 4-aminopyrimidines.



Thorpe condensation products have also been employed for the formation of 2-pyrimidinone derivatives. The key step in this synthesis is the formation of a carbamate 13 from the 2-enamino nitrile and ethyl chloroformate. The carbamate may then be cyclized with ethanolic ammonia to form a 4-amino-2(1H)pyrimidinone.[59] Fusion of cyclic 2-enamino nitriles with urea[38,61] and thiourea[38,39,61,196] was also successful for the formation, respectively, of fused reduced 4-amino-2(1H)-pyrimidinones and the corresponding thiones. An excellent review of the chemistry of o-amino nitriles and 2-enamino nitriles covering the literature to 1970 is available.[223]

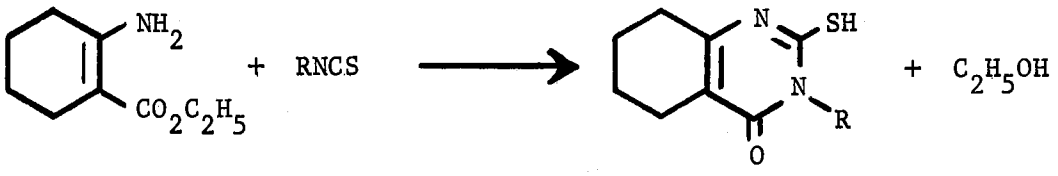


The utilization of Thorpe condensation products for fused pyrimidine synthesis is further illustrated by the recent report of the formation of 1,4-bis(4-amino-6,7-dihydro-5H-cyclopenta[d]pyrimidinyl)butane (14) in the reaction of adiponitrile and sodium alkoxide in alcohol.[239]

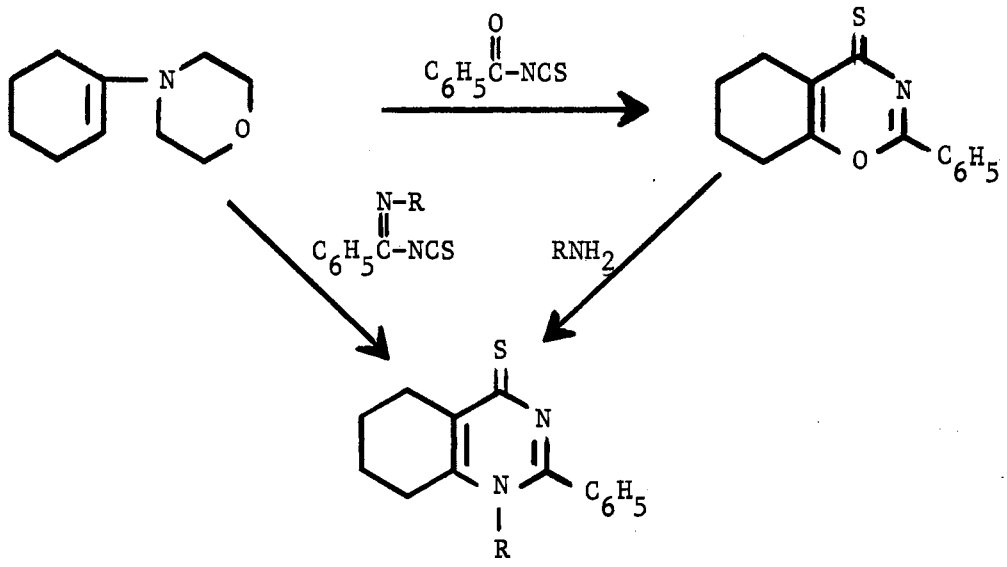


Other synthetic procedures for the preparation of 5,6,7,8-tetrahydroquinazolines that utilize cyclohexanone directly are condensations with N,N'-diarylthioureas at temperatures in excess of 150° to yield 1,3-diaryl-1,2,3,4,5,6,7,8-octahydro-quinazoline-2,4-dithiones.[205,206] The condensation of trisformamidomethane with cyclohexanone in the present of p-toluenesulfonic acid gives 5,6,7,8-tetrahydroquinazoline (10, R', R" = H) in 36% yield. The parent substance 10 (R' = R" = H) has also been obtained from the reaction of 2-chloro-1-cyclohexene-1-carboxaldehyde and formamide at 180° in 50% yield.[241,242]

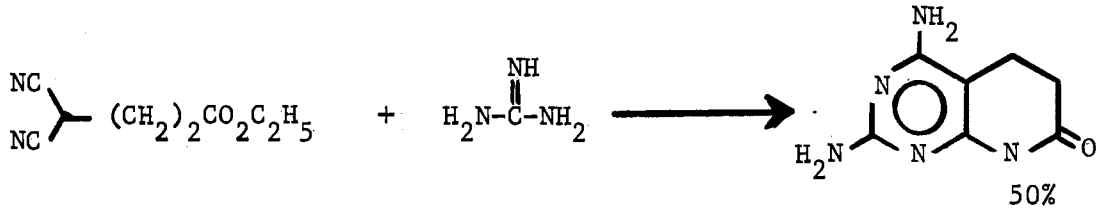
In addition to the cyclohexene derivative listed above, several other derivatives have found synthetic use. When ethyl 3,4,5,6-tetrahydroanthranilate and aryl isothiocyanates are heated together, 3-substituted-3,4,5,6,7,8-hexahydro-2-mercapto-4-quinazolinones[61,205] are formed when 2-morpholino-1-cyclohexene-1-carboxanilide reacts in an analogous manner to yield the corresponding 1,3-disubstituted octahydro-4-thio-2-quinazolinone. Simple enamines of cyclohexanone have been shown



to react with benzoyl isothiocyanate to form 5,6-tetramethylene-2-phenyl-1,3-oxazine-4-thiones.[36] Oxazines are valuable intermediates because they are readily converted to quinazolinethiones[36,106] by a variety of amines. De Stevens and co-workers[60] have generalized this type of reaction sequence by treating phenylbenzimidoyl isothiocyanates with enamines to form 1,4,5,6,7,8-hexahydro-1-aryl-2-phenylquinazolin-4-thiones.

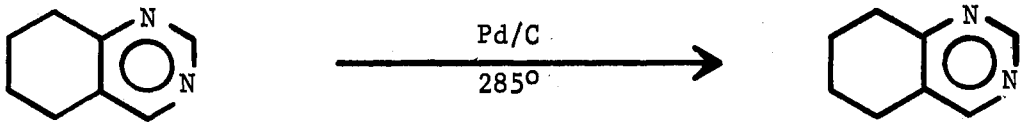


A recently reported[204] very unusual fused-pyrimidine synthesis from acyclic precursors deserves mention, albeit the yields are low, ca. 10-50%. The procedure involves the condensation of diethyl 2-cyanoglutarate or derivatives with guanidine or benzamidine to form the 2-amino- or 2-phenyl-5,6-dihydropyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione. If ethyl 4,4-dicyanobutyrate and guanidine are employed, the 2,4-diamino derivative is obtained.

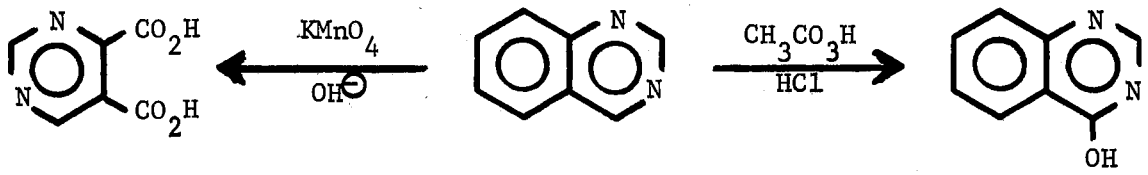


The determination of structure in quinazoline chemistry has for the most part depended upon synthesis for confirmation. However, there are a few reactions of general applicability which have been of importance in structure elucidation. 5,6,7,8-Tetrahydroquinazolines when heated in

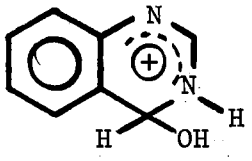
the presence of 10% Pd/C at about 285° are dehydrogenated to form quinazolines. The saturated quinazolines may then be readily correlated with the totally aromatic quinazolines to aid in structural elucidation.



The oxidative reactions of quinazolines have also been utilized for structure proof. Quinazolines are oxidized by alkaline potassium permangonate to 4,5-pyrimidinedicarboxylic acids, thus allowing correlation with pyrimidine derivatives. However, in acidic media quinazolines are oxidized to 4-hydroxyquinazolines (tautomeric 4-quinazolines). The



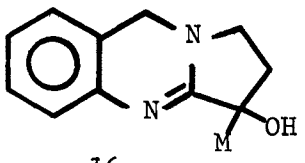
oxidation in the latter case is presumed to proceed via a hydrated cation, a known intermediate in aqueous solution of quinazolines, and thus analogous to the oxidation of a secondary alcohol to a ketone.



Quinazoline has been hydrolytically cleaved to o-aminobenzaldehyde by prolonged boiling with concentrated hydrochloric acid.

B. Biological Activity of Quinazolines

Quinazolines, i.e., 5,6-disubstituted pyrimidines, possess many of the biological activities of pyrimidines. "Some Pyrimidines of Biological and Medicinal Interest" is the title of a continuing series of review articles upon this subject.[29,45] The biological activities of quinazolines per se are discussed by Amarego[5] and a general bibliography of the literature in medicinal chemistry to 1969 is available.[69] There is a small group of alkaloids that possess the quinazoline structure. Among these naturally occurring bases are vasicine (16) (bronchodilator activity), febrifugine (17) (antimalarial activity), and arborine (18) (hypertensive action).[5]



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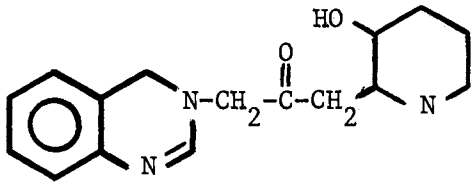

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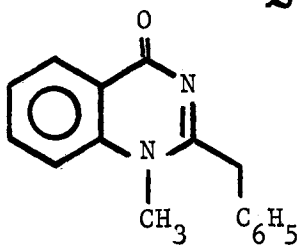

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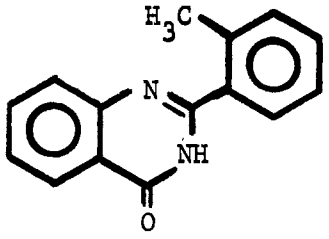
A biologically active saturated quinazoline is tetrodotoxin (6) (page one), one of the most potent non-protein neurotoxins known. Tetrodotoxin is found in the Japanese puffer fish and in the embryos of a California newt. Examples of synthetic quinazolines of biological interest are Methaqualone (19) and Quinethazone (20) (trade names). These products are marketed as a hypnotic and as a diuretic, respectively, under these and other trade names. Methaqualone (19) was found to be superior to

ethylphenylbarbituric acid as a hypnotic and possesses a low toxicity level (LD_{50} mouse, oral, 1 g./kg.).[5] It (19) has also been shown to act as an antitussive agent.[5] Synthetic quinazolines have also been shown to have hypotensive and antihistamine activity.



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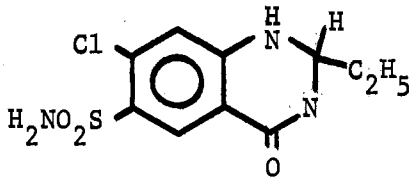

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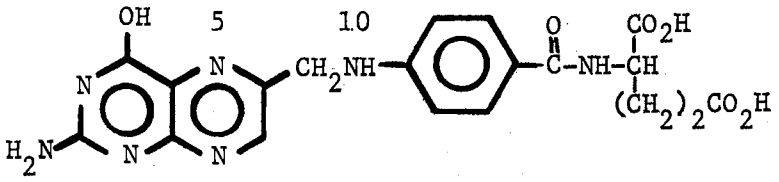
Perhaps the largest synthetic effort in quinazoline chemistry has been attempts to synthesize quinazolines which are potential growth factors. The impetus of this synthetic effort likely is due partly to the structural resemblence of quinazolines to the pterin system of folic acid (21), an essential growth factor.[110] In light of the importance of

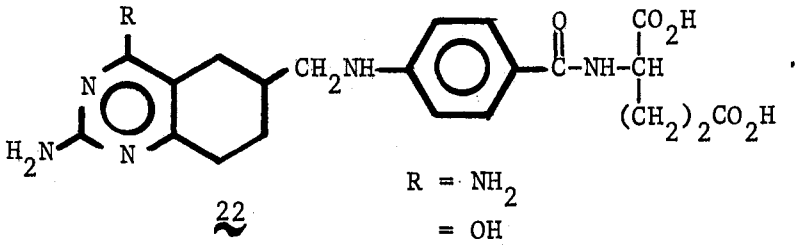


21

positions 5 and 10 in the metabolic transfer of one-carbon[119,165,179,187] segments, Baker and co-workers reasoned that substitution of methylene at either the N-5 or N-10 positions of folic acid could block the one-carbon transfer. Such a derivative might maintain enough structural identity to compete with folic acid and/or its derivatives and inhibit

growth. A large number of quinazolines have been synthesized with this end in mind.[5] As was mentioned on page one, aminopterin and amethopterin are standard anticancer drugs. These compounds have been shown to function in biological systems by non-competitive blocking of folic acid reduction to tetrahydrofolic acid, but the effect is reversible by the addition of folic acid and/or its derivatives.[109,229]

Kisluik has shown that tetrahydroaminopterin is a more potent folic acid antagonist in S. faecalis and P. cerevisiae than is aminopterin.[202] In a comparative study, DeGraw and coworkers prepared quinazoline 22.

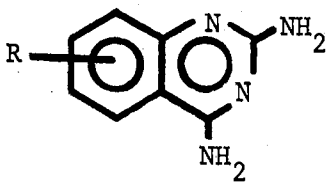


22

The quinazoline 22 (R = OH) when tested as a folic acid antagonist in cultures of P. cerevisiae (ATCC 8081) and S. faecalis (ATCC 8043) was found to be one-half and one-thirtieth, respectively, as active as aminopterin while 22 (R = NH_2) was eight and six times as effective as aminopterin. The observation was made that the 4-amino substituent may be of greater importance in folic acid inhibition than alterations at N-5 or N-10.[57] This conclusion is further supported by the work of Hitchings and coworkers[89] who found that most 2,4-diaminopyrimidines (simple or fused) acted as folic acid antagonists. 2-4-Diaminopyrimidines and quinazolines have also been shown to be active against Plasmodium gallinaceum and P. berghei.[42,91]

Compared to chloroguanide, a known antimalarial, 2,4-diamino-5-p-

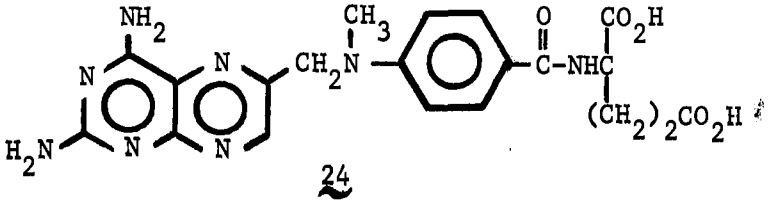
chlorophenyl-6-ethylpyrimidine is 60 times as active against P. gallinaceum and 200 times as active against P. berghei.[91] There has been a recent resurgence of interest in malarial chemotherapy resulting from the emergence of strains of Plasmodium falciparum that are resistant to many drugs in current use.[93] A series of 2,4-diaminoquinazolines recently reported[195] showed significant activity [ID_{50} (50% inhibiting dose) < 10 μg./ml.] against Streptococcus faecalis, Lactobacillus arabinosus, and Pediococcus cerevisiae. Most of the reported quinazolines were also active against KB cells (human epidermoid carcinoma) in culture.[195] Rosowsky and coworkers[195] proposed a structure-growth inhibitory activity relationship for substituted 2,4-diaminoquinazolines 23. The activity of the system seemed to depend on position of further substitution: 7- < 6,7-di < 6- < 5-. The activity seemed to be independent of substituent for CH_3, Cl, or CH_3O. 2,4-Diaminoquinazolines



R = CH_3,Cl,CH_3O

23

have shown significant anti-leukemic activity in L 1210 mouse Leukemia[107,212] and were found to be powerful inhibitors of dihydrofolate reductase from human leukemia cells.[110] These agents were just as effective as amethopterin (24) (AMP, the dihydrofolate reductase inhibitor presently used clinically). In the presence of quinazoline 25 at a concentration of 2×10^{-5} M the rate of uptake of tritium-labeled AMP (2×10^{-7} M) was reduced to 28% of that of the control in mouse L 1201 Leukemia cells.[110] An estimate of the activity of a dihydrofolate re-



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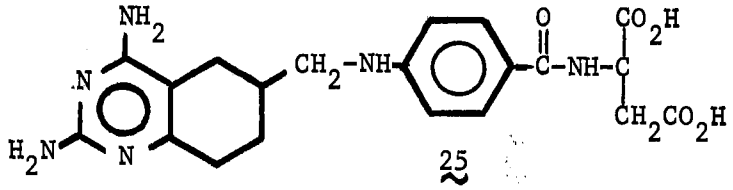

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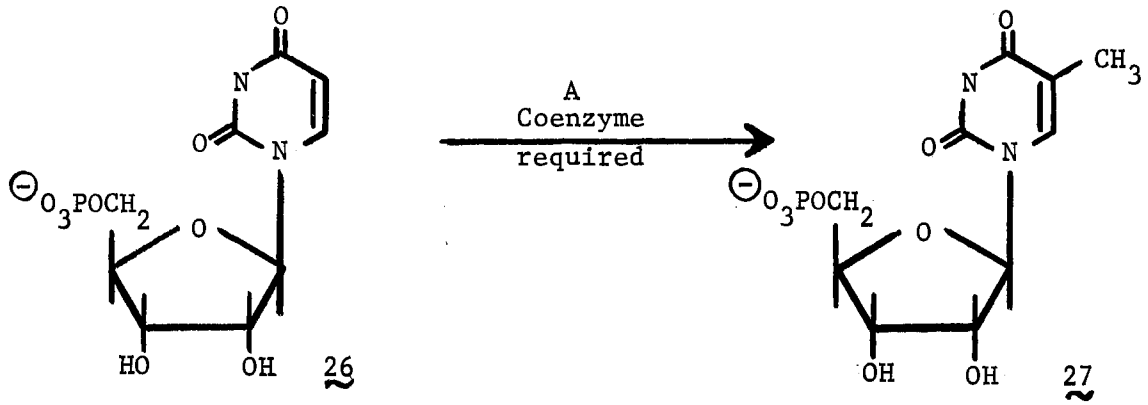
ductase inhibitor in vivo may be obtained by the measurement of its ability to inhibit uptake of radioactive deoxyuridine into DNA. This uptake necessitates the conversion of deoxyuridine monophosphate (26) to deoxythymindine monophosphate (27) a reaction which requires the coenzyme



26 27

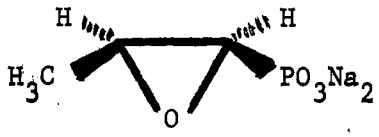
N^5,N^{10}-methylenetetrahydrofolate.[74] Johns coworkers[110] observed that 2,4-diaminoquinazolines (as compared to AMP) seemed to inhibit the incorporation of deoxyuridine to a greater extent than anticipated from their relative dihydrofolate reductase inhibition ability. A possible explanation of these results in a more rapid transport of the diaminoquinazoline than of AMP into leukemia cells. This type of phenomenon would also be applicable to the effect that 25 had upon the inhibition rate of AMP.

The fact that there were two papers[70,194] specifically relating to diaminopyrimidines presented in the Medicinal Chemistry Section at the 163rd ACS National Meeting in 1972 may be a small indication of current interest in the medicinal and synthetic aspects of these types of compounds.

Optically Active Phosphorus Compounds--Types Resolved and Methods Applicable

Optically active phosphorus compounds have been discussed in several recent reviews[116,144,16,163] of phosphorus stereochemistry. The resolution of quaternary phosphonium salts was reviewed by Chen,[43] while methods and reagents applicable to all types of resolutions have been summarized and discussed in two reviews published in 1971.[25,234] In general, all resolutions rely upon one of two basic processes: either (1) the racemate reacts with a chiral reagent to form diastereoisomers that are separable by conventional techniques, or (2) the enantiomers react with a chiral reagent at different rates, so that a kinetic resolution is effected.[26]

Some dissymetric phosphorus compounds possess a reactive functional group, or "handle". In this happenstance, workers have been quick to seize upon these functionalities as a means for resolution by conventional means. Thus, disodium and calcium (-)- and (+)-cis-(1,2-epoxypropyl)phosphonate (28) have been resolved from the appropriate functionalized phosphonate with (-)-menthol (29),[46,234] (+)-tartaric acid (30),[46] (+)-α-phenylethylamine (31),[46,234] calcium (+)-gluconate and calcium (-)-lactate. Aliphatic phosphonic acids have been resolved with the aid of quinine (32).[46] Several phosphorus thioacids[14,23,25,63,162] such as



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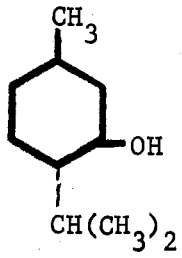

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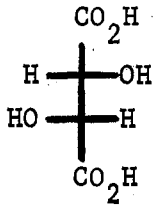

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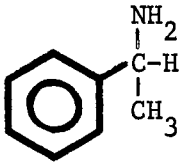

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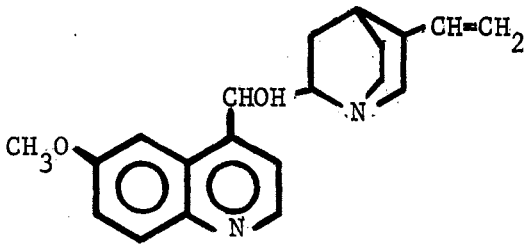
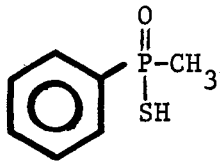


32

methylphenylphosphinothioic acid (33)[14] have been resolved by use of the common basic reagents, e.g., (+)-quinine (32), (+)-brucine (34), and (+)-α-phenylethylamine (31). The optical yields of the salts of 33 with



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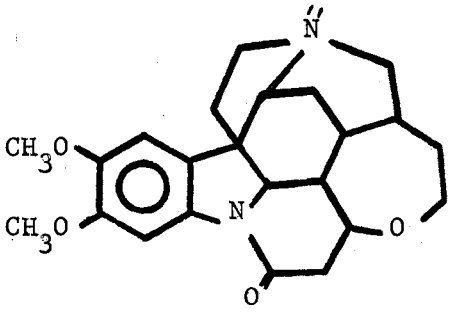

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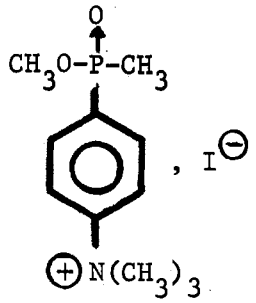
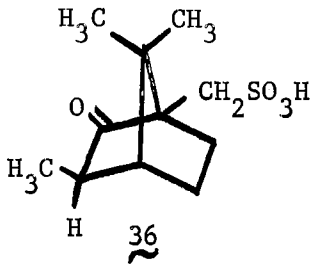


35

32 and 34 were 39% and 41%, respectively. Often the chiral phosphorus molecule has contained a functional group such as carboxyl[33,161] or amino[34,50,151] in an attached ligand. Coyne and coworkers were particularly successful in the resolution and regeneration of some amino sub-

stituted phosphinites[50,151] via anion exchange of their quaternary ammonium salts such as 35 with silver hydrogen D(-)-dibenzoyltartrate. Seiber and Tolkmith[208] were quite successful in their utilization of (+)-methyl-α-camphorsulfonic acid (36) to resolve the methiodide of racemic N,N-diethylamino-2-methylimidazol-1-yl phenylphosphinamidothioate (37). The imidazol ligand was then displaced stereospecifically to give 83% of the (+)-methyl ester ($[\alpha]_D^{20^\circ} = +73^\circ$), but the yield of the pure diastereomer was not reported. However, in these cases, one must be



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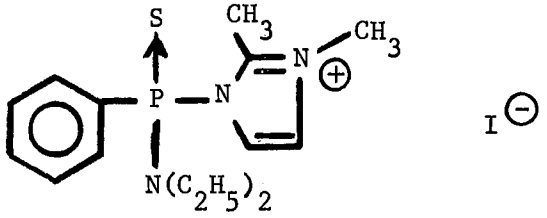
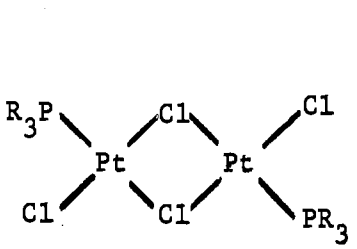


37

cognizant of the fact that the further the bonding site of the resolving agent is from the dissymetric center, the more difficult the resolution will be.[234]

The fact that phosphorus has a pair of unshared electrons was utilized by Chan[40] in his successful resolution of a phosphine via its inorganic platinum complex. The generalized method involves the reaction of a chiral phosphine with potassium chloroplatinite to form a trans-dichloro-bis(trialkylphosphine)platinum(II) (38). When compound 38 was boiled with $PtCl_2$, a binuclear compound 39 was formed. (+)-Deoxyephedrine (40) and 39 reacted to form separable diastereoisomers 41. Methanolic potassium cyanide was used to free the phosphine from the platinum complex.



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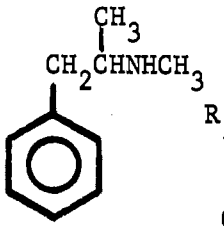

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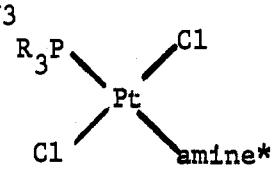
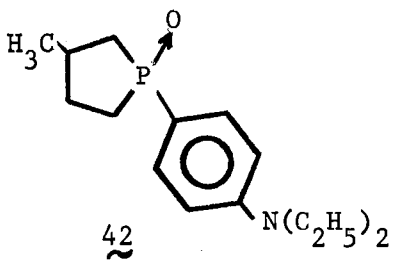


41

The resolution of enantiomeric quaternary phosphonium salts (the bromides) was initially[92] accomplished via anionic exchange to form diastereomeric (+)-camphor-10-sulfonates which were subsequently separated to the individual diastereomers. Since then a variety of optically active anionic resolving agents have been developed and successfully employed. These anions include (-)-menthoxyacetic acid,[83] hydrogen (+)- and (-)-dibenzoyltartrate,[38,44,98,101,117,125,157] camphor-10-sulfonic acid,[92,98] and α-bromocamphor-10-sulfonic acid. Such techniques have been successfully applied to cyclic,[92,44] alkyltriaryl,[113-115,238] dialkyldiaryl,[117] aryltrialkyl,[101,125,157] tetraalkyl,[240] spiro,[83] and di-phosphonium salts.[96] 3-Methyl-1-(p-diethylaminophenyl)-2-phospholene 1-oxide (42) (resolved via the camphor-10-sulfonate) is claimed to be the first chiral phosphocyclic compound resolved,[175] but Chen and Berlin[44] reported the resolution of 43 via the phosphonium hydrogen (-)- and (+)-dibenzoyltartrate shortly before this claim and Campbell and Way reported the resolutions of a 9-phosphafluorene in 1961.[33]



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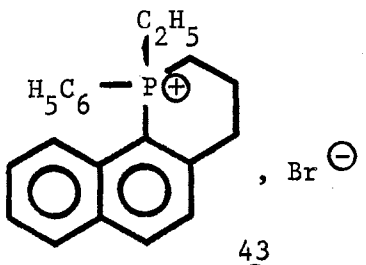
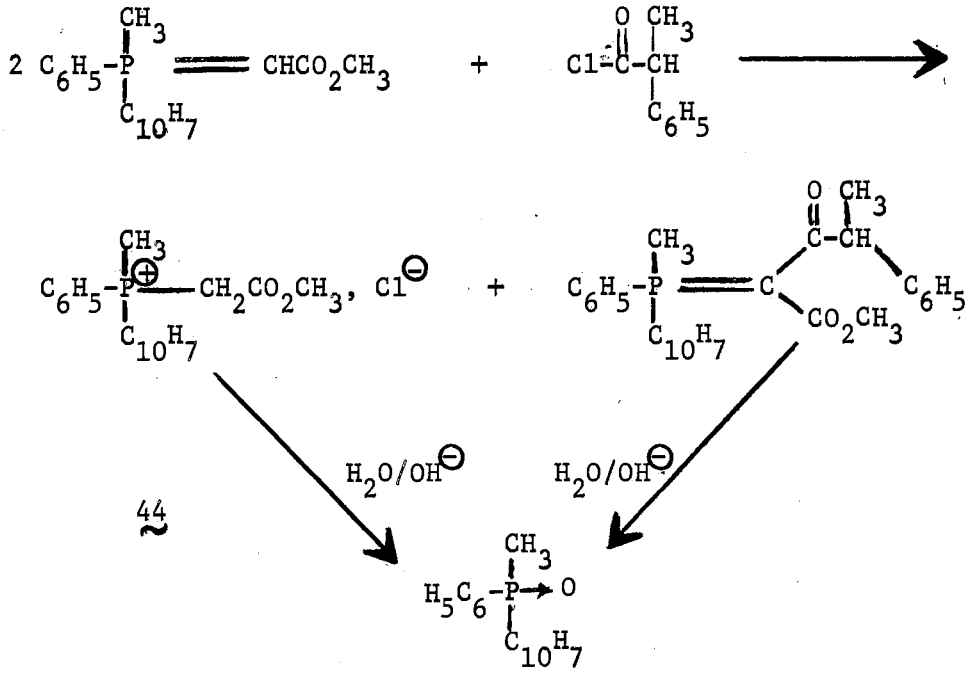


43

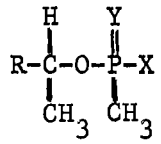
Another method that has been successfully applied to phosphorus compounds is kinetic resolution. An alkylidenephosphorane containing a chiral P atom underwent partial kinetic resolution[18] when treated with



an optically active acyl chloride. The specific rotation of 44 varied from -0.65° to +0.31° depending upon the acyl chloride used. Kinetic resolution is also observed in the reaction of alkoxycarbonylmethylene-triphenylphosphoranes containing a chiral center in the ester function, with optically active acyl halides. Optically active alcohols are obtained after hydrolysis of the reaction mixture.[18] The optical yield was as high as 31% in one case but generally was considerably lower, ca. 10%.

The separation of diastereoisomeric alkyl methylphosphonofluoridates 45 by gas-liquid chromatography has been achieved. While this is technically not a resolution, the techniques developed are certainly

relevant to the discussion at hand. Among other conclusions, the authors once again emphasize that as the distance between the asymmetric centers is increased, the ease of separation of diasteromers is decreased.



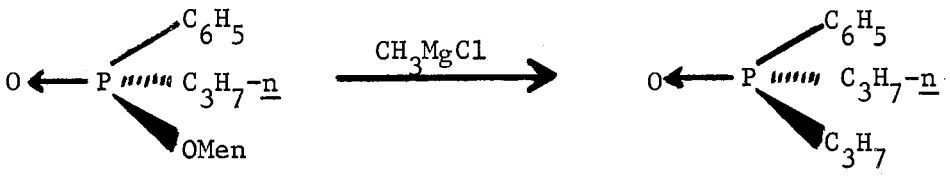
45

R = alkyl, alkenyl, alkynyl or $(CH_3)_2NCH_2$-

Y = O or S

X = F, H, or OCH_3

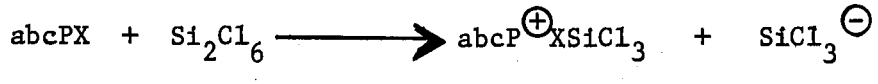
While optically active phosphine oxides may be readily obtained by the stereospecific alkaline hydrolysis of phosphonium salts, which proceeds with inversion of configuration,[92,101,116,144,156,163] Mislow and coworkers[123] have developed an alternative and more direct route to optically active phosphine oxides.[122,123,136,138,201] Their method involves the formation and separation of diastereomerically pure (-)-menthyl dialkylphosphinates[137] such as 46. These optically pure phosphinates can be stereospecifically cleaved with Grignard reagents[123] to form optically active phosphine oxides 47. Since the chirality found in 46 is R, as determined by x-ray analysis,[93] and since the chirality of



(R)-46 (R)-47

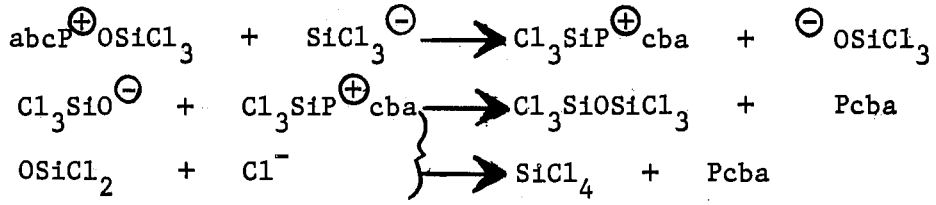
47 is R, by correlation with (+)-(S)-benzylmethylphenyl-n-propylphosphonium bromide,[178] the authors concluded that the reaction of Grignard reagents with phosphinates proceeds with net inversion of configuration.[123] (The same conclusion was reached by Benschop and coworkers in a different family of compounds.[15]) It was later shown that lithium reagents also react with phosphinates via inversion, but not as stereospecifically as Grignard reagents do, e.g., optical purities range from 35-95%.[138] Saeva, Rayner, and Mislow[201] have also been successful in the configurational correlation of sulfoxides and phosphine oxide via intersystem matching of Cotton effects.

The resolution of different types of phosphorus compounds has led to the stereochemical elucidation of many types of their reactions. Time and space preclude an all but a brief, cursory discussion and updating of these developments, which have been well reviewed.[116,144,156,163] Phosphine oxides have been reduced stereospecifically, with retention of configuration, by use of trichlorosilane (Cl_3SiH)[95] [70-80% yields], and phenylsilane ($C_6H_5SiH_3$)[65,149,150] [90% or better yields][Cl_3SiH/$(C_2H_5)_3N$ gave net inversion.[95]] Lithium aluminum hydride has been used to reduce an optically active phosphine oxide[34] to an optically active phosphine but has been shown to cause stereomutation prior to reduction in some cases.[87] Hexachlorodisilane (Si_2Cl_6) apparently reduces acyclic phosphine oxides with inversion (octachlorotrisilane gave the same results)[172,173] and cyclic phosphine oxides with retention.[56,173] In contrast, acyclic phosphine sulfides were reduced by hexachlorodisilane with retention of configuration.[243] The following mechanistic explanation of this anomaly was proposed:[243,172]

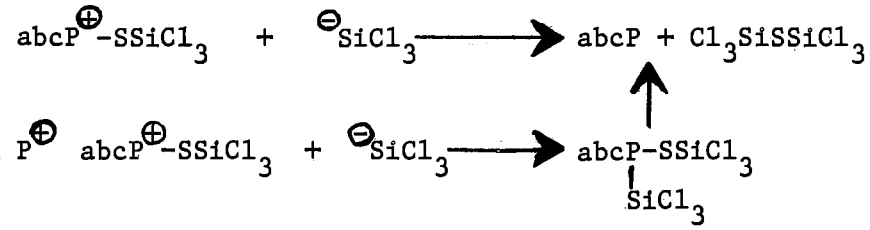


X = O
= S

if X = O, assume backside attack upon P by $SiCl_3^-$



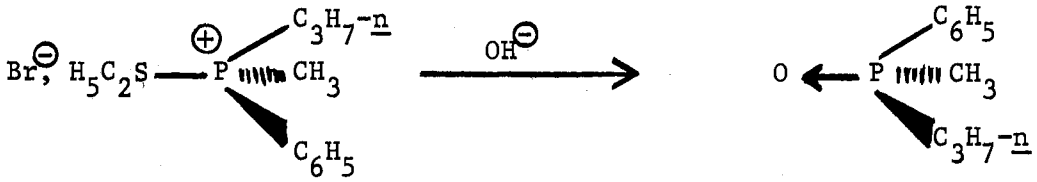
if X = S, assume attack upon S by $SiCl_3^-$



Hexachlorodisilane has been recommended as the most convenient reagent for use in preparing optically active phosphines[172] from phosphine oxides. The recommendation is based upon the ready availability of the silane, simplicity and mildness of reaction conditions, high conversion (ca. 80%) and high optical purity of product (generally 90% optically pure or greater as compared to a range of 50% and greater for trichlorosilane).[95,172]

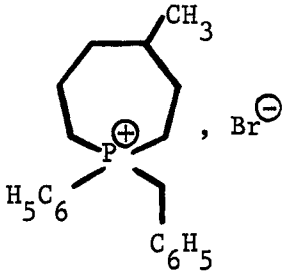
Acyclic phosphonium salts generally undergo basic hydrolysis to form phosphine oxides via inversion of configuration whereas cyclic phosphonium salts react with retention[100,116,144,148,156,163] of configuration. These conclusions have now been extended to include alkoxyphos-

phonium salts, both cyclic[56] and acyclic,[243] and to alkylmercaptophosphonium salts such as 48. An exception to this rule was recently re-



(-)-S-48 (+)-R

ported by Marsi,[148] who achieved complete inversion of configuration in the cleavage of cis- and trans-1-benzyl-4-methyl-1-phenylphosphepanium bromides 49. The methanolysis of O-menthyl S-methyl phenylphosphonothioate (50) to give an inverted product[73] is also consistent with the



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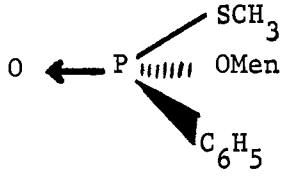
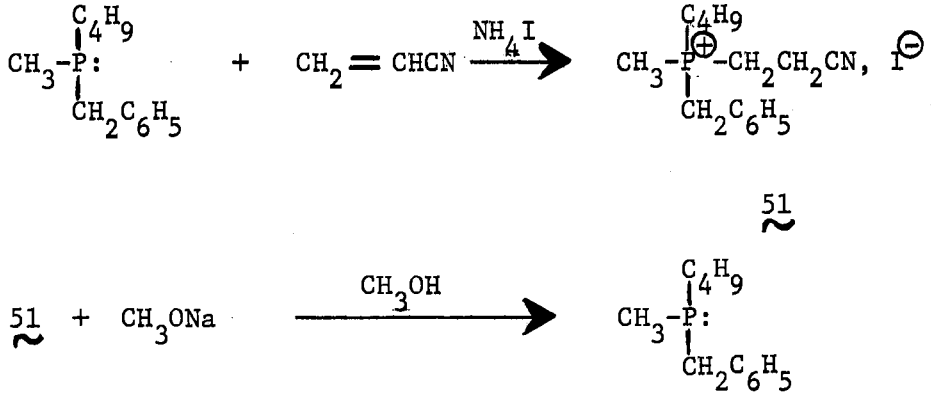


50

general trend although the alkaline hydrolysis of 50 reported previously gave a product with retention of configuration.[54] Compound 50 and methylmagnesium bromide react with retention of configuration.[64]

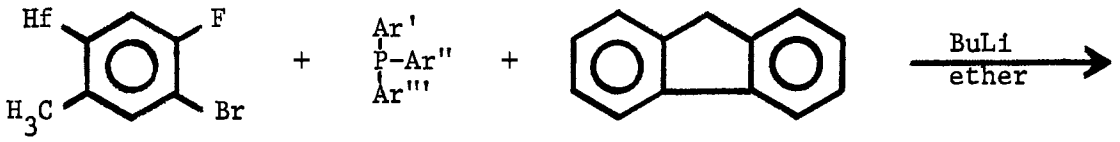
Some extremely interesting and novel methods of forming phosphonium salts for subsequent resolution have been developed. One of these was the reaction of acrylonitrile, ammonium iodide and a chiral phosphine to form a cyanoethylphosphonium iodide 51. Subsequent resolution via the

hydrogen dibenzoyltartrate and treatment of the resolved phosphonium salt with a sevenfold excess of sodium methoxide regenerated the free phosphine (not phosphine oxide) in optically active form.[240] Hence, a stereospecific reduction step is not necessary. Unfortunately, the



authors did not report the optical yield one might expect. A similar resolving procedure was reported by Wittig and coworkers.[237] Resolution was achieved by reaction of tertiary phosphines, paraformaldehyde, and (+)-camphor-10-sulfonic acid (only ½ equivalent) to form a hydroxymethylenetriarylphosphonium camphor-10-sulfonate. Predominately, the (+)-enantiomer reacts, precipitating the (+)-epimer. The (-)-enantiomer may be isolated from the mother liquor while the (+)-antipode may be regenerated from the hydroxymethylene salt by treatment with triethylamine to form the free phosphine. The (+)-antipode of phenyl-α-naphthyl-p-biphenylylphosphine was resolved in 86% optical yield by this method.[237]

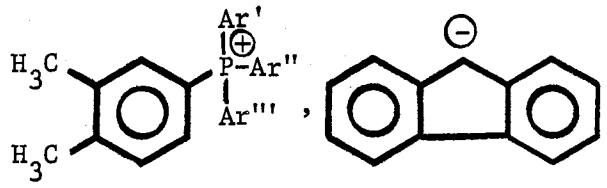
A new approach to the synthesis of phosphonium salts is the reaction of arynes and tertiary phosphines in the presence of fluorene to form a quaternary phosphonium fluorenide 52.[236] This reaction sequence when performed upon an optically active phosphine gave optically active phosphonium salt.



Ar' = C_6H_5

Ar" = p-tert-C_4H_9-C_6H_4

Ar''' = p-C_6H_5-C_6H_4



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The only remaining reported procedure for the conversion of an optically active phosphonium salt to an optically active phosphine is cathodic reduction. This was one of the earliest methods employed by Horner and coworkers[97,101] for the stereospecific cleavage of quaternary phosphonium salts. That cleavage proceeds with retention of configuration[97] was established as follows: The fact that enantiomeric phosphines were obtained from the same phosphonium salt, the (+) from one cathodic reduction and the (–) from two cathodic reductions, indicated that the reaction proceeded with retention of configuration if one assumes that quaternization occurs with retention of configuration. The yields of reduced products are 70-90%. (See Figure 1.)

The problem of determining optical purity has always been difficult in resolutions. NMR analysis of diastereomeric mixtures obtained when enantiomers are suitably derivatized by optically active reagents has been used to estimate enantiomeric ratios and consequently optical purity.[186] A reagent recently developed and employed for this purpose is (S)-(+)-2-bromo-1-methoxy-1-phenylethane (53)[37] which is made from (S)-(+)-O-methyl mandelate (54). If the methylene protons of 53 interfere with the spectrum, the dideutero compound is just as easily pre-

CR = Cathodic Reduction

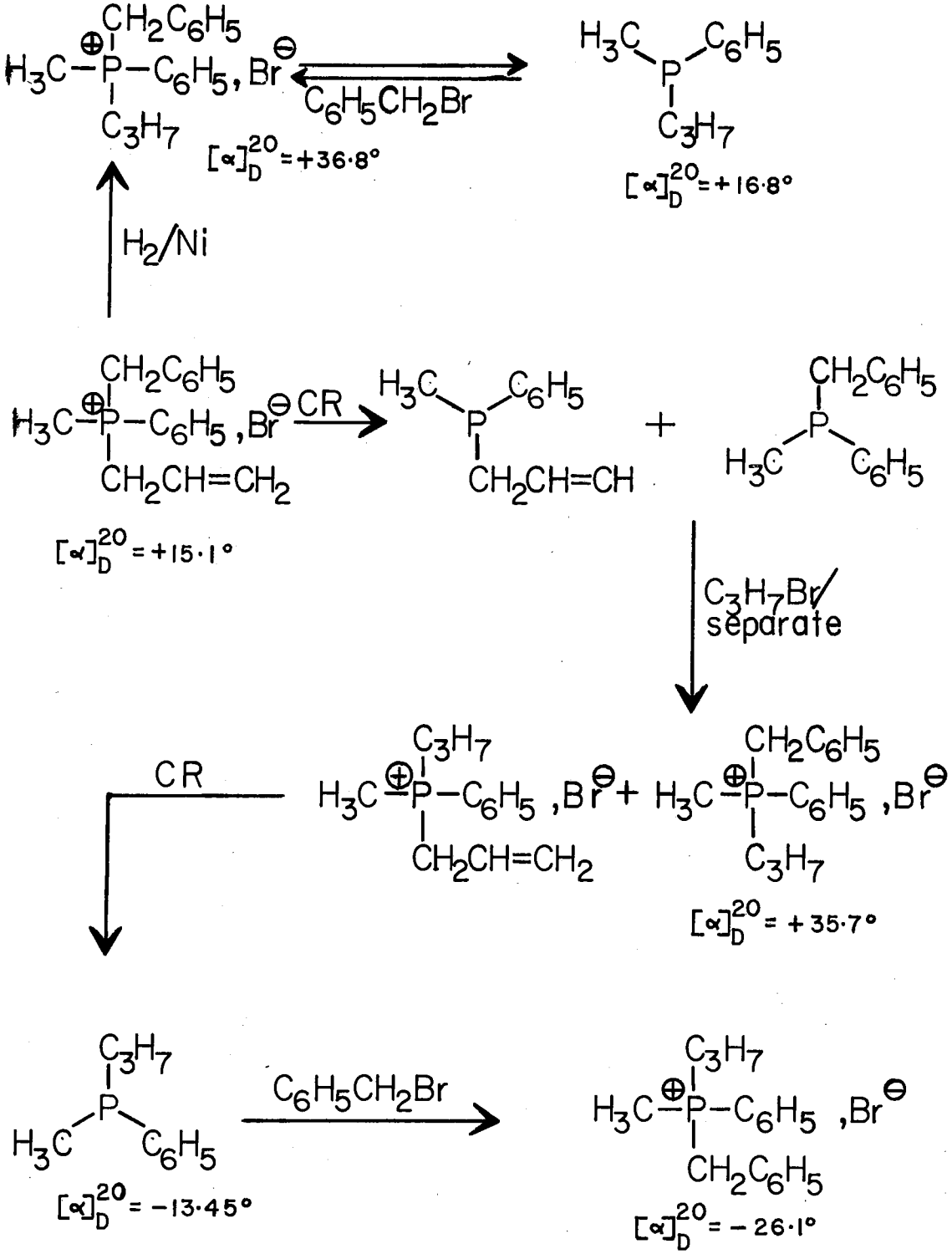
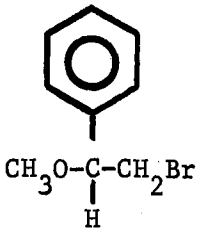


Figure I. Stereochemistry of Cathodic Reduction



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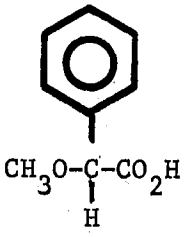

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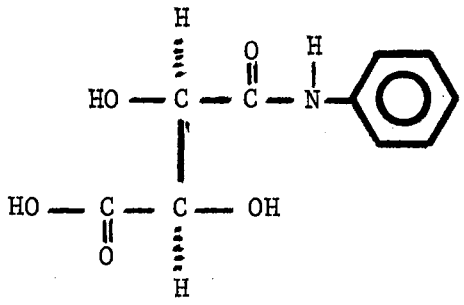
pared. For a series of chiral phosphines, reaction with 53 produced a pronounced doubling of the NMR lines with chemical shift differences 0.5 to 9.2 Hz.[37] Pirkle and coworkers[181] have utilized optically active 2,2,2,-trifluoro-1-phenylethanol as a solvent for a series of chiral phosphine oxides and achieved chemical shift differences of 1.4-3.2 Hz between enantiomeric protons. A new instrumental technique called CPL (circular polarization of luminescence) may be developed which would satisfy this problem.[58] The technique basically involves irradiation of a sample with circularly polarized light, which will preferentially excite one enantiomer. Consequently, the luminescence will be a measure of optical purity.

The successful use of the hydrogen D(-)-tartrate anion for the resolutions described previously will encourage investigators to investigate other dissymetric anions as resolving agents. The tartranilic acids[170] derived from D(-)- and L(+)-tartaric acid are a new and readily available addition to the number of reagents of potential use. Several bases which had been difficult to separate into the optical isomers were readily resolved with tartranilic acids.



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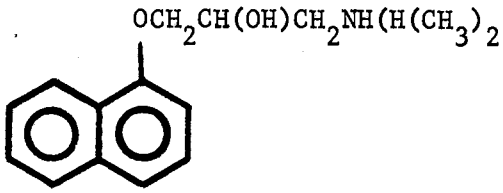

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The difficult problem of purification of the enantiomer which forms the more soluble diastereomer has recently been investigated.[135] The most common method is to utilize the antipode of the original resolving agent, thereby making the diastereomer of the enantiomer the less soluble. It has recently been shown that there is a marked difference in the solubilities of a racemic mixture and the pure enantiomer. Hence, after one enantiomer has been separated by the conventional means of diastereomer formation and purification, the remaining impure mixture of diastereomers can be converted to a non-equivalent mixture of enantiomers (enantiomer plus racemate). There is a difference in solubility of enantiomer and racemate. This difference was greatest (for the compounds studied) in hydrocarbons with small amounts of t-butylamine or 1-butanol added. Thus, an optically impure mixture of alcohol (56), $[\alpha]_D = +11.3^\circ$, was partially dissolved in petroleum ether with t-butylamine to yield a residue, $[\alpha]_D = +1.7^\circ$, and a solution of dissolved solid, $[\alpha]_D = +21.0^\circ$. Optically pure 56 has a $[\alpha]_D = +21.5^\circ$.

Pyramidal Inversion in Phosphorus

In 1954, Weston,[223] utilizing a valence force-field calculation,

predicted an inversion barrier height for trimethylphosphine of 22.0 kcal/mole. It took ten years before Horner and Winkler[99] experimentally tested this value. They reported a barrier height of 28-30 kcal/mole for the racemization of methyl-n-propylphenylphosphine. These studies have lent much impetus to the study of pyramidal inversion. There are several recent reviews upon the subject.[28,126,133,189]

There are several methods available for the determination of inversion barriers, not all of which are applicable to inversion about phosphorus. Of the molecular orbital methods available, the one most utilized for calculation of inversion barriers of phosphorus is a specially parameterized $CNDO_2$ program.[126,190] The MINDO scheme of Dewar and Shanshal[62] has been quite successfully applied to nitrogen inversion, but has not yet been applied to phosphorus. The following experimental methods for the determination of inversion barriers and their measurement limitations have been outlined by Rauk and coworkers[189]: microwave spectroscopy (barriers in the range of 0-5 kcal/mole); dynamic nuclear magnetic resonance (DNMR) (barriers in the range of 10-25 kcal/mole);[126] infrared and Raman spectroscopy (barriers in the range of 5-35kcal/mole); and kinetic measurements (racemization and epimerization) (20-40 kcal/mole). Of these experimental methods, only DNMR and kinetic measurements have been utilized greatly in the measurement of phosphorus inversion rates.

Since inversion is a unimolecular transformation and obeys first-order kinetics, a rate constant k can be determined by measurement of an observable quantity directly related to concentration, e.g., specific rotation, or absorbances (NMR, UV, IR) due to invertomers.[189] For racemization, k is generally calculated from the slope ($-k_{race}/2{,}303$) ob-

tained from a plot of log [α] vs. time. This rate constant k may then be utilized in the following expressions to generate the various measures of inversion energy:

$$\text{Arrhenius equation;} \quad k = Ae^{-E_a/RT}$$

The Arrhenius activation energy, E_a, may be calculated from the slope (E_a/2.303 R) of the best straight line plot of log k_{race} vs 1/T. Once E_a is evaluated, the Arrhenius preexponential factor (A) may be evaluated if desired.

$$\text{Eyring equation;} \quad \ln k = \ln(\underline{k}\ T/\underline{h}) - \Delta G^*/RT$$

The free energy of activation may be calculated from k using the Eyring relationship where $\underline{k}$ is the Boltzmann constant and $\underline{h}$ is Planck's constant. The transmission coefficient is generally assumed to be unity. The enthalpy of activation is related to the Arrhenius activation energy by the expression:

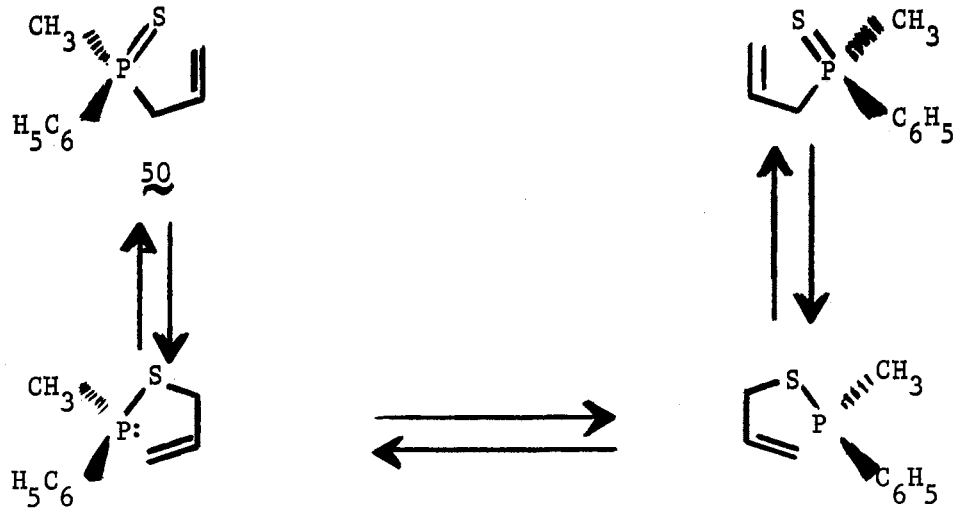
$$E_a = \Delta H^* + RT$$

The entropy of activation is related to the free energy of activation and the enthalpy of activation by the expression:

$$\Delta S^* = \frac{\Delta H^* - \Delta G^*}{T}$$

For simple inversion ΔS^* is expected, and usually found, to be close to zero. However, in the inversion of $\underset{\sim}{50}$, via sigmatropic rearrangement, values of 33 ± 2 kcal/mole and -18 e.u. for E_a and ΔS^* are calculated.[72] The large negative value for ΔS^* would be reasonable for a reaction with

a rigid, cyclic intermediate.

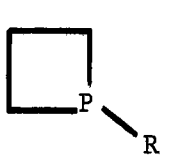


DNMR methods for determination of inversion barriers are much like those of classical kinetics, differing only in the nature and manner in which k is determined. The basic equation is:

$$k_c = \pi\Delta\nu/\sqrt{2}$$

where k_c is the rate of exchange at the coalescence temperature (T_c), i.e., where the maximum broadening of two peaks occurs just as they coalesce. The distance (in Hz) between the two absorption lines prior to coalescence is $\Delta\nu$. The limitations placed upon so simple a calculation are drastic. The two exchanging groups must be uncoupled and of equal population, and $\Delta\nu$ must be greater than the linewidth of the signals prior to exchange. Where a simple approach to k_c is precluded, a more laborious complete line shape analysis is necessary to calculate rates of exchange. However, there are now computer programs available for performing complete line shape analysis. A recent paper[124,67] indicates that the differences in k obtained by a complete line shape analysis and from the simplified equation [$k_c = \pi\Delta\nu/\sqrt{2}$] are often not great.

Several reviews on DNMR are available.[21,71] Tables I and II contain examples of the magnitude of inversion ba-riers encountered in acyclic and cyclic phosphorus derivatives. Prominant cyclic derivatives investigated are phosphetanes (57), phospholanes (58), isophosphindolines (62), phospholes (60), and phosphindoles (61).



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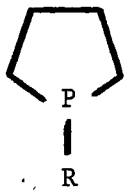

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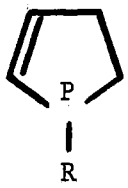

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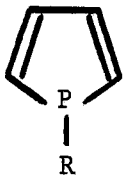

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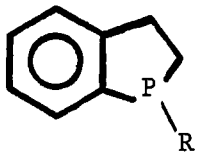

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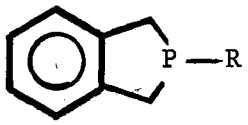

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As is evidenced in Tables I and II, inversion barriers in phosphorus are affected by many variables. There seems to be but little effect upon the inversion barriers of acyclic phosphines due to changes in substituent groups.[11] The ΔG^* for inversion of acyclic phosphines fall, for the most part, in a narrow array of values, 29-36 kcal/mole.[11] A general observation is that electron-withdrawing substituents in the para position of aryl-substituted phosphines result in a small lowering of the energy barrier to pyramidal inversion, compare 3a, 20a and 21a in

TABLE I

INVERSION BARRIERS IN CARBON-PHOSPHORUS HETEROCYCLES

No.	Compound	Barrier Parameters (ΔG^*, ΔH^* kcal/mole)	Method	Ref.
PHOSPHIRANES				
1c ≈	Phosphirane	80.4	E-CNDO$_2$	190
PHOSPHETANES				
2c ≈	1-t-Butyl-2,2,3,4,4-pentamethylphosphetane	28.2 ± 0.9 (ΔH^*) -8 e.u. (ΔS^*)	kinetic by NMR	51,52
3c ≈	1,2,2,3,4,4-Hexamethyl-phosphetane	stable to 163°/4 days	NMR	52
4c ≈	1-Methylphosphetane	44.3	E-CNDO$_2$	190
5c ≈	1-Phenyl-2,2,3,4,4-pentamethylphosphetane	29.8 ± 0.1 (ΔH^*) -8 e.u. (ΔS^*)	kinetic by NMR	52
PHOSPHINDOLINES				
6c ≈	1-Methyl-2-methylene phosphindoline	31.2	E-CNDO$_2$	190
7c ≈	3-Methyl-1-phenyl-phosphindoline	35.3 ± 0.5 (ΔG^*)	DNMR	24,67
8c ≈	1-Methylphosphindoline	36.4	E-CNDO$_2$	190

TABLE I (Continued)

No.	Compound	Barrier Parameters (ΔG^*, ΔH^* kcal/mole)	Method	Ref.
PHOSPHINDOLES				
9c ≈	3-n-Butyl-1-((d1)-2-phenyl-2-methoxyethyl-1,1-d_2)-2-phenylphosphindole	23.7 ± 0.5 (ΔG^*)	DNMR	24,67
10c ≈	1-(1,1-d_2-2-phenylethyl)-2-phenyl-3-n-butyl-phosphindole	23	DNMR	190
11c ≈	1,2-Dimethylphosphindol	23.2	E-CNDO$_2$	190
12c ≈	3-Ethyl-1-dimethylsilyl-2-phenylphosphindole	16.6 (ΔG^*)	DNMR	24
13c ≈	1-Methylisophosphindol	6.9	E-CNDO$_2$	190
14c ≈	1-Silylphosphindol	9.3	E-CNDO$_2$	190
PHOSPHOLANES				
15c ≈	1-Cyclohexyl-3-methyl-phospholane	39	estimation analogy	68,190
16c ≈	1,3-Dimethylphospholane	stable to 150°/3 days	NMR	150,149
17c ≈	1-Methyl-2,5-diketo-phospholane	18.0	E-CNDO$_2$	190

TABLE I (Continued)

No.	Compound	Barrier Parameters (ΔG^*, ΔH^* kcal/mole)	Method	Ref.
PHOSPHOLANES				
18c	1-Methyl-2,5-dimethylene-phospholane	31.7	E-CNDO	190
19c	3-Methyl-1-phenylphos-pholane	36.5 ± 0.5 (ΔG^*)	DNMR	67,68
20c	1-Methylphospholane	41.4	E-CNDO$_2$	190
21c	1-Methyl-2-phospholene	33.9	E-CNDO	190
22c	1-Methyl-3-phospholene	39.3	E-CNDO	190
PHOSPHOLES				
23c	2-Isopropyl-1,5-diphenyl-phosphole	15 ± 0.5 (ΔG^*)	DNMR	67
24c	1-Isopropyl-2-methyl-5-phenylphosphole	16.1 ± 0.5 (ΔG^*) 17.1 ± 0.4 (ΔH^*) 3.1 ± 1.1 e.u. (ΔS^*)	DNMR DNMR DNMR	67,68 68 68
25c	1-Isopropyl-2-methyl-5-(2-phenylethyl)phosphole	16.1 ± 0.5 (ΔG^*)	DNMR	67
26c	1-Methylphosphole	16.7	E-CNDO	190

TABLE I (Continued)

No.	Compound	Barrier Parameters (ΔG^*, ΔH^* kcal/mole)	Method	Ref.
PHOSPHOLES				
27c ≈	5-((d1)-2-Phenyl-2-methoxyethyl-1,1-d_2)-3-methyldibenzophosphole	26.3 ± 0.5 (ΔG^*)	DNMR	67
28c ≈	1-((d1)-2-Phenyl-2-methoxyethyl-1,1-d_2)-2-methyl-5-phenylphosphole	15.3 ± 0.5 (ΔG^*)	DNMR	67
29c ≈	1-Silylphosphole	6.0	E-CNDO$_2$	190
30c ≈	1,2,5-Trimethylphosphole	18.4	E-CNDO	190
PHOSPHORINANES				
31c ≈	9-Phenyl-9-phosphabicyclo[4,2,1]nonatriene	26.4	kinetic by NMR	118

TABLE II

INVERSION BARRIERS IN SELECTED ACYCLIC PHOSPHINES

No.	Compound	Barrier Parameters (ΔG^*, ΔH^* kcal/mole)	Method	Ref.
1a	Acetylisopropylphenylphosphine	19.4 (ΔG^*)	DNMR	66
2a	Allylmethylpropylphosphine	32.8 (ΔG^*) $k_{race} = 1.44 \times 10^5$ sec^{-1}	racemization	11
3a	p-Anisylmethylphenylphosphine	30.8 (ΔG^*) $k_{race} = 17.0 \times 10^5$ sec^{-1}	racemization	11
4a	Bis(dimethylsilyl)phenylphosphine	12.2 (ΔG^*)	DNMR	7
5a	Cyclohexylmethylpropylphosphine	35.6 (ΔG^*) $k_{race} = 4.27 \times 10^3$ sec^{-1}	racemization	11
6a	1,2-Dimethyl-1,2-bis (2,4,6-$d_3$phenyl)diphosphine	26.0 ± 2 (Ea)	kinetic by NMR	128,129
7a	1,2-Dimethyl-1,2-dibenzyl-diphosphine	24 (ΔG^* rotation-inversion)	DNMR	127
8a	1,2-Dimethyl-1,2-diphenyl-diphosphine	22.5 (ΔG^* rotation-inversion)	DNMR	127
9a	1,2-Dimethyl-1,2-di-p-tolyldiphosphine	22.5 (ΔG^* rotation-inversion)	DNMR	127

TABLE II (Continued)

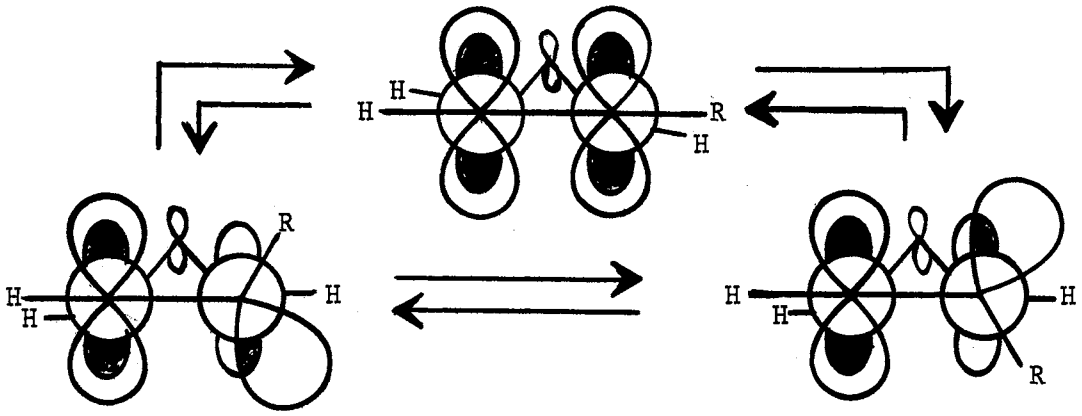
No.	Compound	Barrier Parameters (ΔG^*, ΔH^* kcal/mole)	Method	Ref.
10a ≈	Isopropylphenyltrimethoxysilyl-phosphine	17.1 (ΔG^*) 16.0 ($E_{inv.}$)	DNMR E-CNDO$_2$	8 8
11a ≈	Isopropylphenyltrimethyl-germylphosphine	21.4 (ΔG^*)	DNMR	7,9
12a ≈	Isopropylphenyltrimethyl-silylphosphine	18.9 (ΔG^*) 18.4 ($E_{inv.}$)	DNMR E-CNDO$_2$	9,10 7,8
13a ≈	Isopropylphenyltrimethyl-stannylphosphine	19.3 (ΔG^*)	DNMR	7,9
14a ≈	Methyl-p-tert-butylphenyl-phosphine	32.7 (ΔG^*)	DNMR	9,11
15a ≈	Methyl(o-methylmandeloyl) phenylphosphine	19.1 (ΔG^*) 19.3 (ΔG^*)	DNMR DNMR	66 66
16a ≈	Methylphenyl-3-propenylphosphine	32.8 (ΔG^*) $k_{race} = 1.44 \times 10^5$ sec^{-1}	racemization	11
17a ≈	Methylphenyl(dimethylphenyl-silyl)phosphine	19.1 (ΔG^*)	DNMR	10
18a ≈	(+)-Methylpropylphenyl-phosphine	29-31 (ΔG^*) 28.6 to 30.7 (Ea)	racemization racemization	94 99

TABLE II (Continued)

No.	Compound	Barrier Parameters (ΔG^*, ΔH^* kcal/mole)	Method	Ref.
19a	Methylphenylpropylphosphine	32.1 (ΔG^*) $k_{race} = 3.34 \times 10^5$ sec^{-1}	racemization	11
20a	Methylphenyl-p-tolylphosphine	30.3 (ΔG^*) $k_{race} = 30.6 \times 10^5$ sec^{-1}	racemization	11
21a	Methylphenyl-p-trifluoro-methylphenylphosphine	29.1 (ΔG^*) $k_{race} = 1.45 \times 10^7$	racemization	11
22a	Phosphine	37.2	LCAO-MO-SCF	134,68

Table II. This is in direct contrast to substituent effects found in cyclic systems. If other considerations are neglected, cyclic phosphines generally have a higher barrier to inversion than their acyclic analogs[28] because angle strain in the ring decreases the rate of inversion. That is, since the phosphine must ideally reach an sp^2-hybridized, planar transition state for inversion, bond angle strain would be much greater for cyclic systems in achieving this geometry than it would be for acyclic systems. This strain is well illustrated by comparison of the inversion barriers (Tables I and II) of phosphetane 4c and phospholane 20c (44.3 and 41.4 kcal/mole[190] respectively) with the previously cited acyclic phosphine inversion barriers. Likewise, one would expect to see a steric acceleration of inversion in a crowded and strained cyclic system but not in the acyclic system. This acceleration is observed in t-butylphosphetane 2c ($\Delta G^* = 28.2$ kcal/mole).[51,52] As stated above, the transition state for phosphorus pyramidal inversion involves an (sp^2-p)-hybridized phosphorus atom. Factors which would (1) enhance or detract from the sp^2 character of the central phosphorus atom, or (2) increase or decrease the amount of p character, would be manifested in a decrease or increase in the magnitude of the inversion barrier[126,189] respectively. There have been several experiments devised to test this idea, some with quite dramatic results.

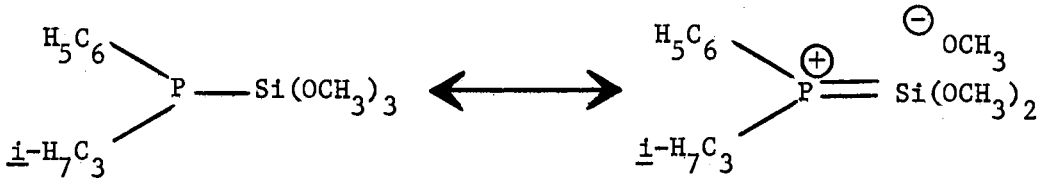
The inversion barrier of many phospholes (60) (page 32) is very low, ca. 16 kcal/mole, when compared to inversion barriers for other phosphines. This decrease in barrier height is attributed to stabilization of the transition state 63 via (3p-2p) delocalization[67,68] (see projection of phosphole following.)



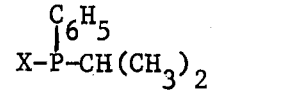
This stabilization is not significantly affected by alkyl or aryl substitution (24c, 25c, 28c, 30c) but annulation with either 1 or 2 benzo rings seems to be moderately destabilizing (9c, 27c).[67] The low inversion barrier (ca. 19-20 kcal) found in acylphosphines (1a and 15a) may well be attributed to the same effect.[66]

The lower energy barriers found for silylphosphines (12a, 17a)[9,10,160] and diphosphines (17a, 8a, 9a)[127] have long been attributed to (3p-3d) "orbital overlap". (This is also the reasoning used to explain similar effects in nitrogen inversion). Similarly, Baechler and coworkers[10] once postulated that the barrier to inversion of the germylphosphine 11a was higher than that of silylphosphine 12a because of more effective π-orbital (3p-3d) overlap in 11a. However, it has since been shown that the variance in the inversion barriers of substituted methylphenylphosphines with substituents on carbon 14a, silicon 12a, germanium 11a, and tin 13a (Table II) is directly proportional to the corresponding electronegativities.[9] "Apparently, for phosphines and perhaps for other inverting centers as well, inductive effects are indeed sufficient to account for a large proportion of the observed effect of heteroatomic substituents."[9] A similar effect upon the barrier to inversion in arsenic has recently been explained in like manner.[148] A recent example

of the lowering of a phosphine inversion barrier via substitution which is apparently the result of electronic factors other than electronegativity is that of the (trimethoxysilyl)phosphine 10a.[8] On a basis of electronegativity, one would predict an increase in the barrier height. Instead, a marked decrease in barrier height is found, approximately 2 kcal lower than for the corresponding trimethylsilyl derivative 12a. The observed lowering of the barrier height has been attributed to "negative hyperconjugation".[8]



The maximum amount of hyperconjugative delocalization would be expected in the planar transition state for inversion. Although π conjugation could (3p-3d) also be implicated in this phenomenon, the influences of hyperconjugation upon the inversion barrier of entirely first row elements has been well recognized.[126,189] In light of recent electronegativity studies there seems to be little basis to invoke π conjugation (3p-3d) for interpretation of the barrier magnitude in 10a. An $ECNDO_2$ calculation of the inversion barriers of a related series of compounds gave the following results.

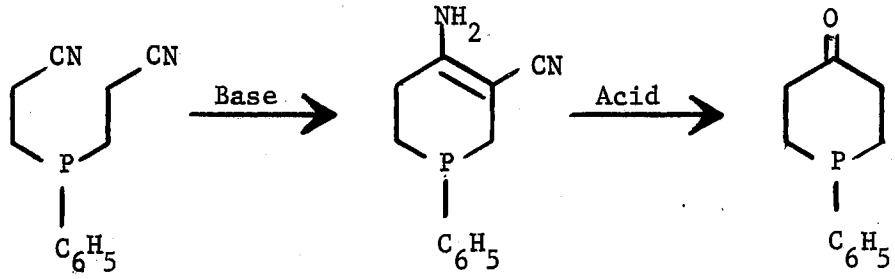


X	E_{inv} kcal/mole (calculated)
$Si(OCH_3)_3$	16.0
$Si(CH_3)_3$	18.4
$C(OCH_3)_3$	33.5
cyclohexylmethylpropylphosphine	36.3

While the analogy is not exact, the same type and magnitude of inversion barrier decrease is observed in the trimethoxymethane derivative, where 3p-3d delocalization is not possible,[8] as is observed in the trimethoxysilylphosphine.

IV. Phosphorinanones--Chemistry and Properties

Several general recent reviews covering the general topic of carbon-phosphorus heterocycles[16,43,143,146] and a bibliography[216] covering the literature to March, 1971 are available as general references in the area. 1-Phenyl-4-phosphorinanone was first reported in 1960 by Welcher, Johnson, and Wystrach.[232] Their synthetic method involved the classic Thorpe condensation of bis(cyanoethyl)phenylphosphine to form an intermediate 2-enamino nitrile which was subsequently hydrolyzed to the ketone 64.[232,76]



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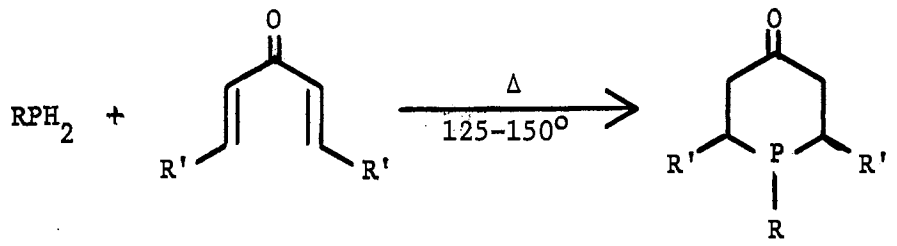
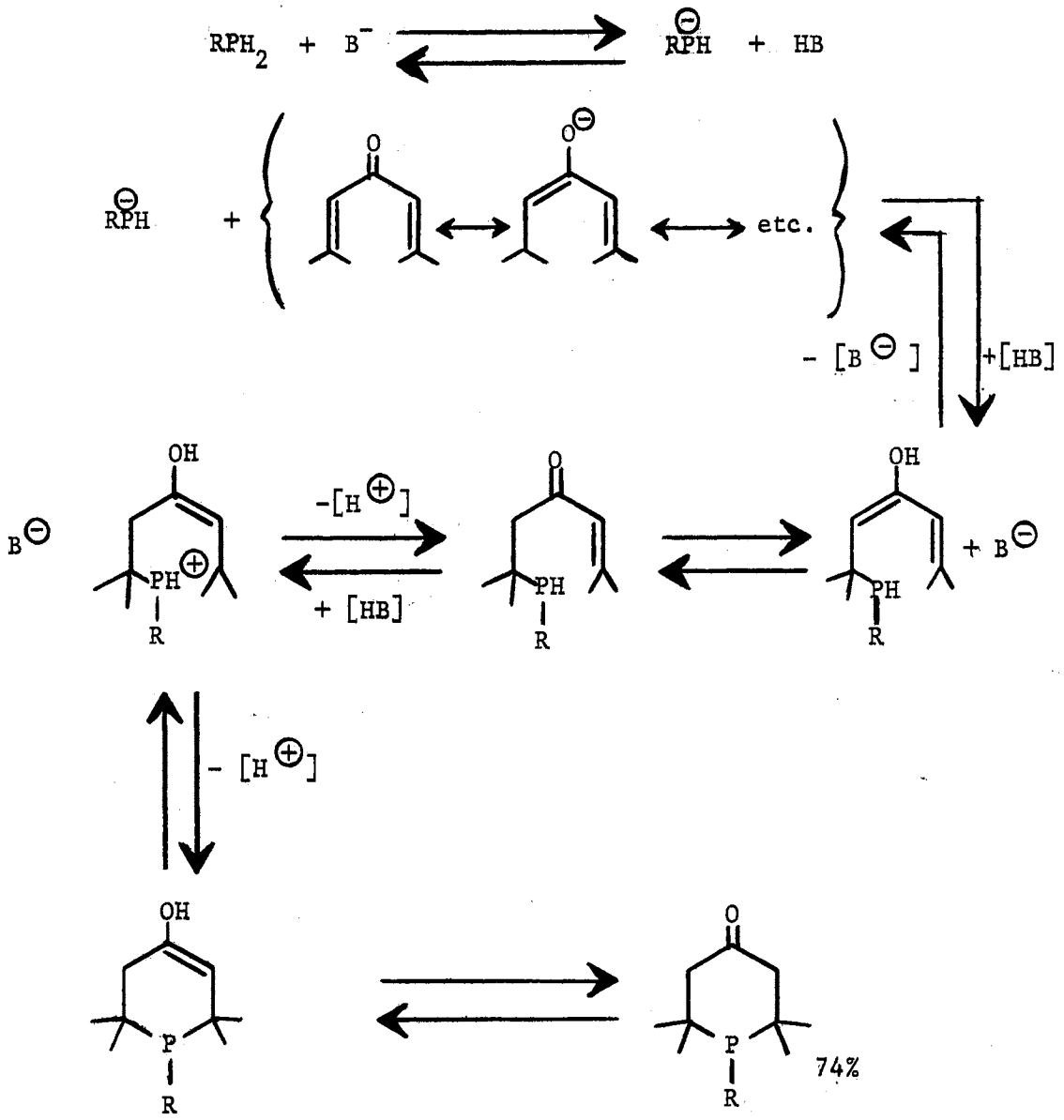
The 1-ethyl-[232] and the 1-methyl-4-phosphorinanones[184] are also obtained by the same route while several 2,6-disubstituted phosphorinanones have been prepared via the addition of monosubstituted phosphines to divinyl ketones.[230,231] Asinger and coworkers have modified this synthesis[6]



utilizing a basic catalyst and purpose of the following mechanism.



Interestingly these substituted phosphorinanones sublimed quite read-

ily.[6,143]

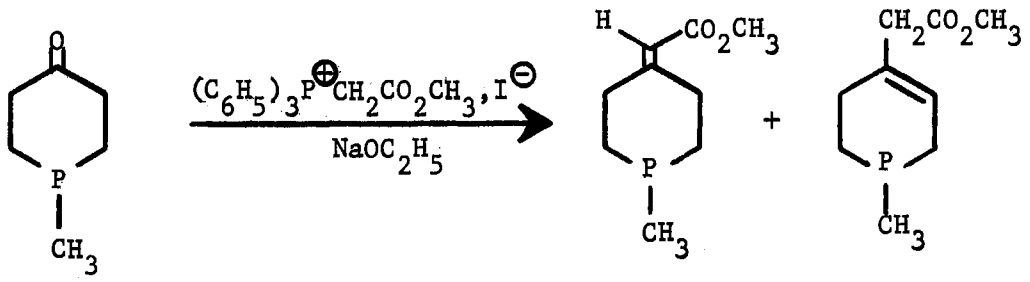
Phosphorinanones generally exhibit the properties expected of a simple phosphine and of a simple ketone. The phosphine oxides and sulfides of many of the known phosphorinanones have been prepared by standard procedures.[2,6,16,143] The common quaternary phosphonium salts, i.e., the methiodide and the benzyl bromide derivatives[16,143] have been prepared. The less common alkyl halides, heptyl bromide and dodecyl iodide, have also been employed for quaternization.[2] The keto function forms most of the common derivatives[16,143] such as phenylhydrazones,[76] p-nitrophenylhydrazones,[2] thiosemicarbazones,[152] semicarbazones,[232] dimethyl ketals,[151] and oximes.[2] Formation of these oximes needs to be reexamined in light of the recent report[152] of the oxidation of 1-methyl- and 1-ethyl-4-phosphorinanone by hydroxylamine. Martz and Quin[152] had need of the oxime derivative of these phosphorinanones for a proposed synthesis of the corresponding 4-aminophosphorinanane. However, the only products isolated were the 1-methyl- and 1-ethyl-4-phosphorinanone 1-oxide oxime.

R = CH_3
= C_2H_5

R = CH_3
= C_2H_5

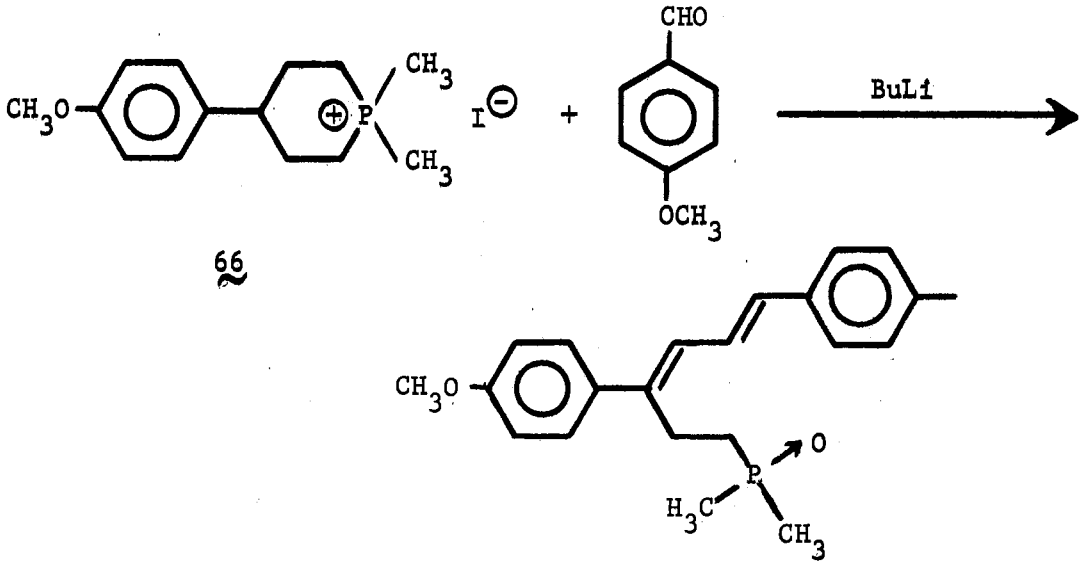
The synthesis of the 1-phenyl-4-aminophosphorinane has since been accomplished by Morris and Berlin[171] via reduction of the methoxyamine adduct. Phosphine oxidation was not encountered with methoxyamine. The p-tosylhydrazone was also prepared by these workers.[171] Phosphorinanones have also been utilized as substrates for the preparation of quinolines,[97] indoles,[76,77] and alkenes.[152,153,213] Similarly these heterocycles were useful in the synthesis of a series of secondary and tertiary alcohols via processes involving reduction[231] and Grignard[184,213] and Reformatsky reagents.[182,213] Likewise, certain phosphorinanones are precursors to a series of 1,4-disubstituted phosphorins.[147] These reactions have been discussed in the aforementioned reviews.[16,143]

Rather unusual chemistry of phosphorinanones and Wittig reagents has come to light in recent years. The Wittig reaction is known for its specificity. However, in reaction of 1-methyl-4-phosphorinanone (65) with the Wittig reagent derived from (methoxycarbonylmethyl)triphenylphosphonium iodide, migration of the double bond was observed.[183]



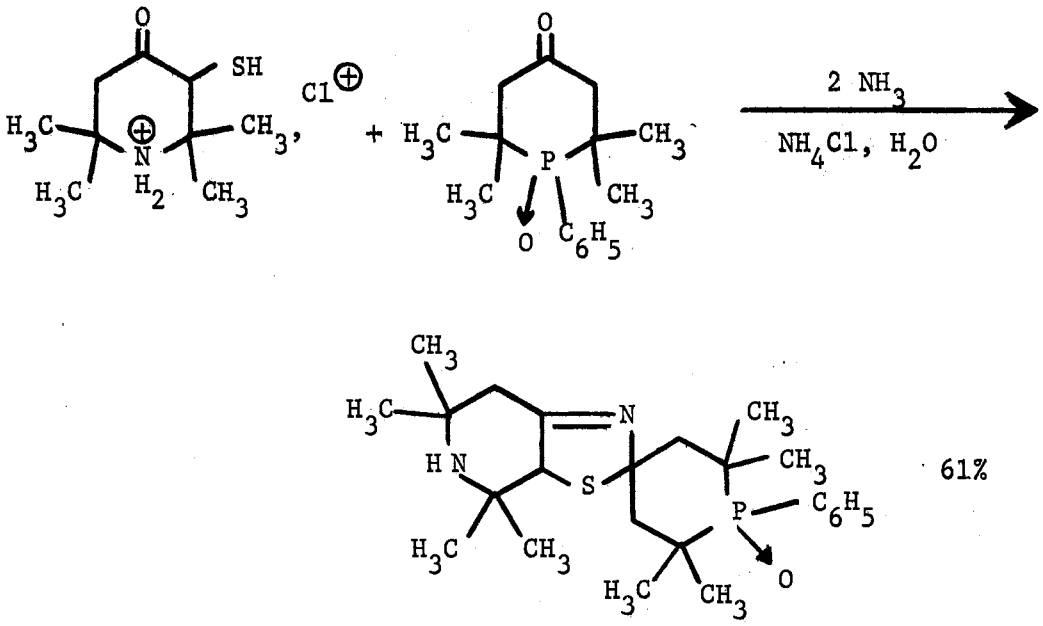
65

This rearrangement was attributed to intramolecular catalysis of enolization by the phosphine.[183] The Wittig reagent derived from 66 (a compound made from 65) reacts via ring opening to form dienes in which phosphorus is retained in the product.[132] In addition to the indoles and quinolines



66

mentioned above, 1-phenyl-4-phosphorinanone 1-oxide, 1-sulfide, and related compounds have been used to prepare thiazoline derivatives such as 67.[6]



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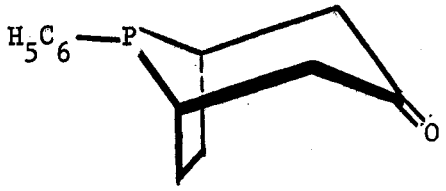
Some other heterocycles related to the simple 4-phosphorinanones are 68, 69, and 70. 8-Phenyl-8-phosphabicyclo[3,2,1]octan-3-one (68),



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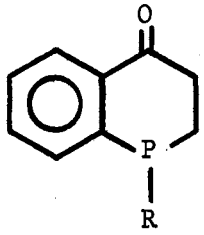
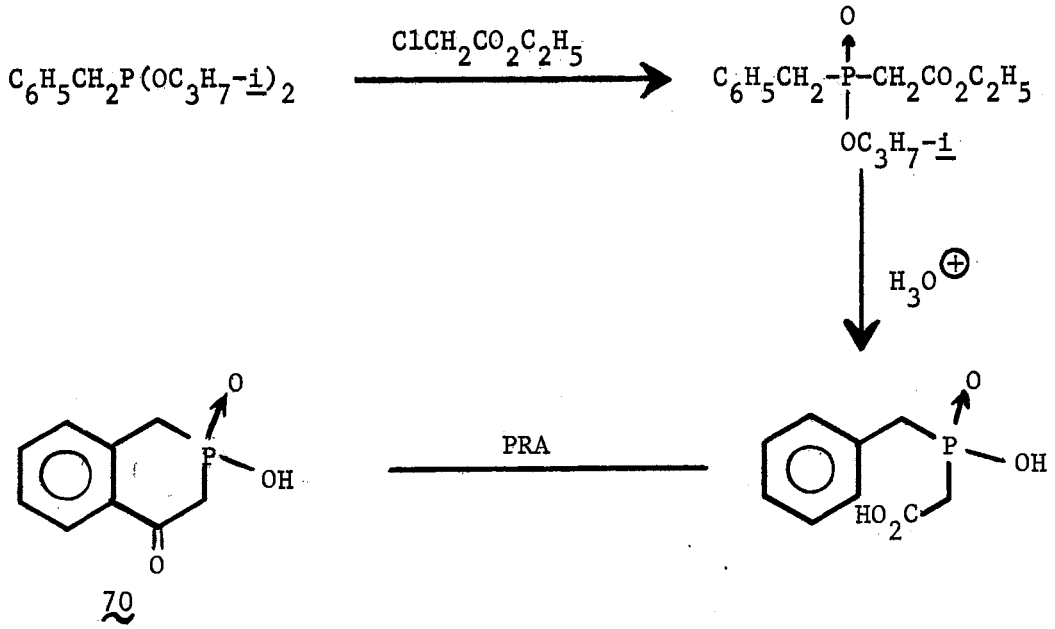


69

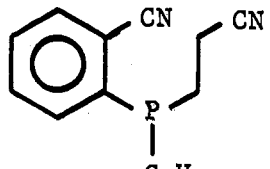
prepared in 47% yield by the addition of phenylphosphine to 2,6-cycloheptadien-1-one, is a rare example of a phosphorus bicyclo compound. The synthetic approach originated by Henning[130] for the preparation of tetrahydro-2-phosphinolin-4-one (70) is quite different from those methods previously discussed.



70

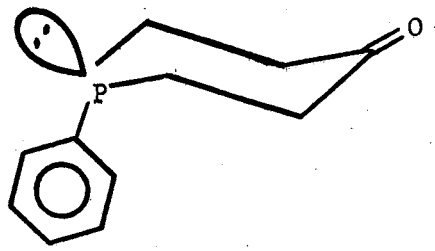
It is interesting to note that attempts to prepare β-[(p-methoxyphenyl)phenylphosphino]propanoic acid via acid hydrolysis of the ester or nitrile gave only (p-methoxyphenyl)methylphenylphosphine,[88] indicating

that 69 could not[75] be prepared by Henning's[86] cyclization. 1-Phenyl-1, 2,3,4-tetrahydro-4-phosphinolone (69, R = C_6H_5) has been obtained in 55% yield by Thorpe cyclization of 71 followed by hydrolysis.[75]



71

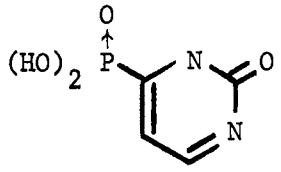
The stereochemistry of the phosphorinanones has been of considerable interest as discussed in the preceding section on optical activity and phosphorus inversion. X-ray single crystal analysis of 1-phenyl-4-phosphorinanon by Quin and coworkers[158] indicates that the phosphorinanone ring prefers a slightly flattened chair conformation with an axially phenyl group.[158] Similar analysis of the 1-phenyl-4-phosphorinanone dimethyl ketal also shows the chair form with axial phenyl orientation to be the favored conformation.[159] This is in agreement with the axial orientation of the hydrogen atom on phosphorus found in phosphacyclohexane[130,131] and in phosphacyclohexane 1-sulfide as determined by NMR analysis.



CHAPTER II

RESULTS AND DISCUSSION

Although various pyrimidines 8[22,121,193,211] with P in the 2-position, purines 9[140] with P in the 8-position, and pyrimidines with phosphorus and alkylphosphorus substituents 72[191] are known, cyclic carbon-phosphorus derivatives of pyrimidines, such as 5,6,7,8-tetrahydro-6-phosphorino[4,3-d]pyrimidine (73) (numbering and name approved by Chemical Abstracts)[141] have not been reported. One objective of this effort was to devise synthetic methods for the formation of the previously unknown phosphorino[4,3-d]pyrimidines and to initiate an investigation



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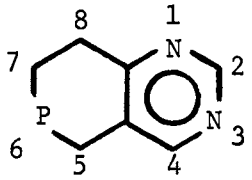


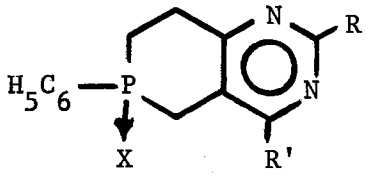
73

of the reactivity and stereochemistry of this prochiral family. The value of these compounds as potential chemotherapeutic agents is of particular interest in view of the biological activities observed in many compounds of similar structure (see Chapter I, part B).

Ten 4-substituted and 2,4-disubstituted 5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidines have been prepared (Table III). Additionally, four fused carbocyclic pyrimidines (one previously unreported)

TABLE III

5,6,7,8-TETRAHYDRO-6-PHENYLPHOSPHORINO[4,3-d]PYRIMIDINES



Compound Name	No.	X	R	R'	m.p.	Yield %
2,4-Diamino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine	74	-	NH_2	NH_2	221-222.5°	34[a] 13[b]
4-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine	75	-	H	NH_2	196-197°	7[c] 66[d]
5,6,7,8-Tetrahydro-6-phenylphosphorino-[4,3-d]pyrimidine-4-thio	76	-	H	SH	230-231.5°	26[e] 68[f]
5,6,7,8-Tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-d]pyrimidine 6-sulfide	77	S	H	SCH_3	146-48° s.t.	71
5,6,7,8-Tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-d]pyrimidine	78	-	H	SCH_3	96-98° s.t.	89
3-Ethyl-5,6,7,8-tetrahydro-4(3H)-imino-6-phenylphosphorino[4,3-d]pyrimidine	79	-	C_2H_5	=NH	147-149° s.t.	65

TABLE III (Continued)

Compound Name	No.	X	R	R'	m.p.	Yield %
4-(Ethylamino)-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine	80	-	H	NHC_2H_5	134-138° s.t.	70
2-Amino-5,6,7,8-tetrahydro-6-phenyl-phosphorino[4,3-d]pyrimidin-4-ol 6-sulfide	81	S	NH_2	OH	243-246° s.t.	67
5,6,7,8-Tetrahydro-2-methyl-6-phenyl-phosphorino[4,3-d]pyrimidin-4-ol 6-sulfide	82	S	CH_3	OH	269-271° s.t.	52
5,6,7,8-Tetrahydro-2-mercapto-6-phenylphosphorino[4,3-d]pyrimidin-4-ol 6-sulfide	83	S	SH	OH	345-348° s.t. (d)	80

[a]With 1 equivalent of base excess

[b]Neutral solution

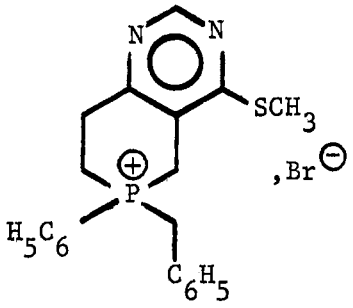
[c]Method A, formamidine acetate

[d]Method B, ethoxymethylene derivative and ethanolic ammonia

[e]Without acetic anhydride

[f]With acetic anhydride

were prepared as model compounds, illustrating the generality of a novel synthetic route for the generation of 2,4-diamino fused pyrimidines (Table IV). Where applicable, the phosphorino[4,3-d]pyrimidines have been shown to undergo the typical reactions of analogous pyrimidines, i.e., methylation and the Dimroth rearrangement. Phosphorino[4,3-d]pyrimidines also form quaternary salts as illustrated by the preparation of 5,6,7,8-tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinonia[4,3-d]pyrimidine salts (the bromide 88 and the diastereomeric hydrogen D(-,-)-dibenzoyltartrates ((±,-,-)-89)) and 4-amino-5,6,7,8-tetrahydro-6-phenylphosphorinonia[4,3-d]-pyrimidine bromide (90). The diastereomeric mixture of hydrogen D(-,-)-dibenzoyltartrates [D(-,-)-HDBT] 89 has been partially resolved to yield the pure diastereomer (+)-5,6,7,8-tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinia[4,3-d]pyrimidine



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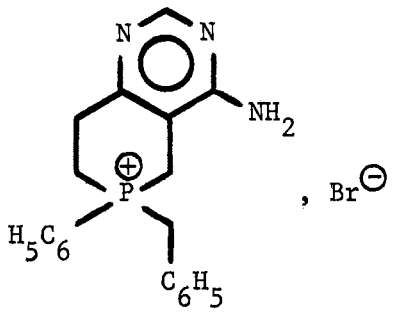

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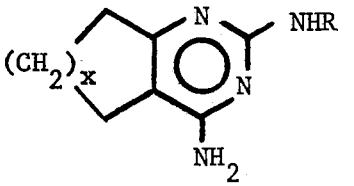
D(-,-)-HDBT salt ((+,-,-)-89), $[\alpha]_D^{25^\circ} = -14^\circ$ (c = 0.3000 g/25 ml., methanol), which undergoes metathesis with ammonium bromide to yield the pure (+) enantiomer (+)-88, $[\alpha]_D^{25^\circ} = +76^\circ$ (c = 0.2087 g/25 ml., methanol). There have been only four successful resolutions of a chiral carbon-phosphorus heterocycle reported previously in the literature[33,44,83,175] where P is the chiral center.

Synthesis of these fused pyrimidines has been achieved employing

TABLE IV

CARBOCYCLIC 2,4-DIAMINO FUSED PYRIMIDINES

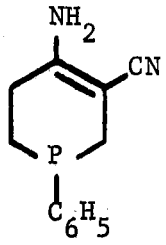


Compound Name	No.	X	R	m.p.	lit. m.p.	Yield %
2,4-Diamino-5,6,7,8-tetrahydroquinazoline	84	2	H	244-245°	243-245° [168]	34[a]
2,4-Diamino-6,7-dihydro-5(H)-cyclopentapyrimidine	85	1	H	231-232.5°	231° [168]	30[a]
4-Amino-2-methylamino-5,6,7,8-tetrahydroquinazoline	86	2	CH_3	202.5-203.5	204-205° [168]	13[a]
4-Amino-2-cyanoamino-5,6,7,8-tetrahydroquinazoline	87	2	CN	335-336 (d) 334-336 (d)		16[a] 18[b]

[a]Without base catalysis

[b]With base catalysis

three different synthetic pathways found in Figures 2, 3, and 4. The key starting material for Figures 2 and 3 was prepared by the known Thorpe cyclization of bis(cyanoethyl)phenylphosphine (91)[145,188] which gave 4-amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile (92).[76,232] Carbocyclic models, 2-aminocyclopentenecarbonitrile (93)[227] and 2-aminocyclohexenecarbonitrile (94),[235] were obtained by published procedures. The synthetic route outlined in Figure 2 consisted of the direct condensation of 2-enamino nitriles 92, 93, or 94 with guanidine and



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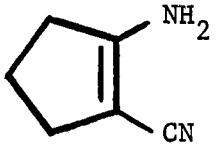

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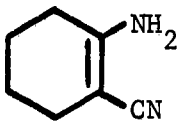
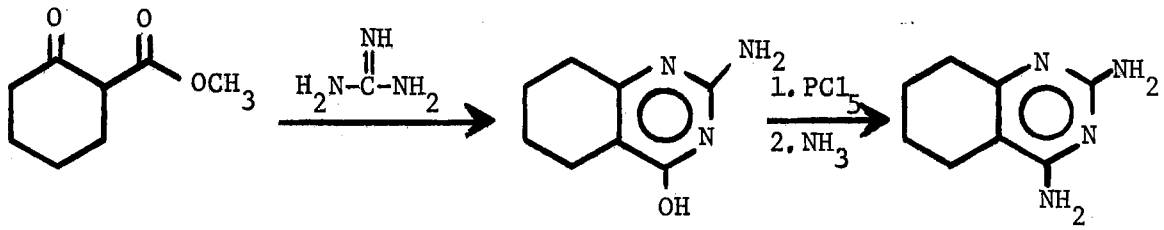
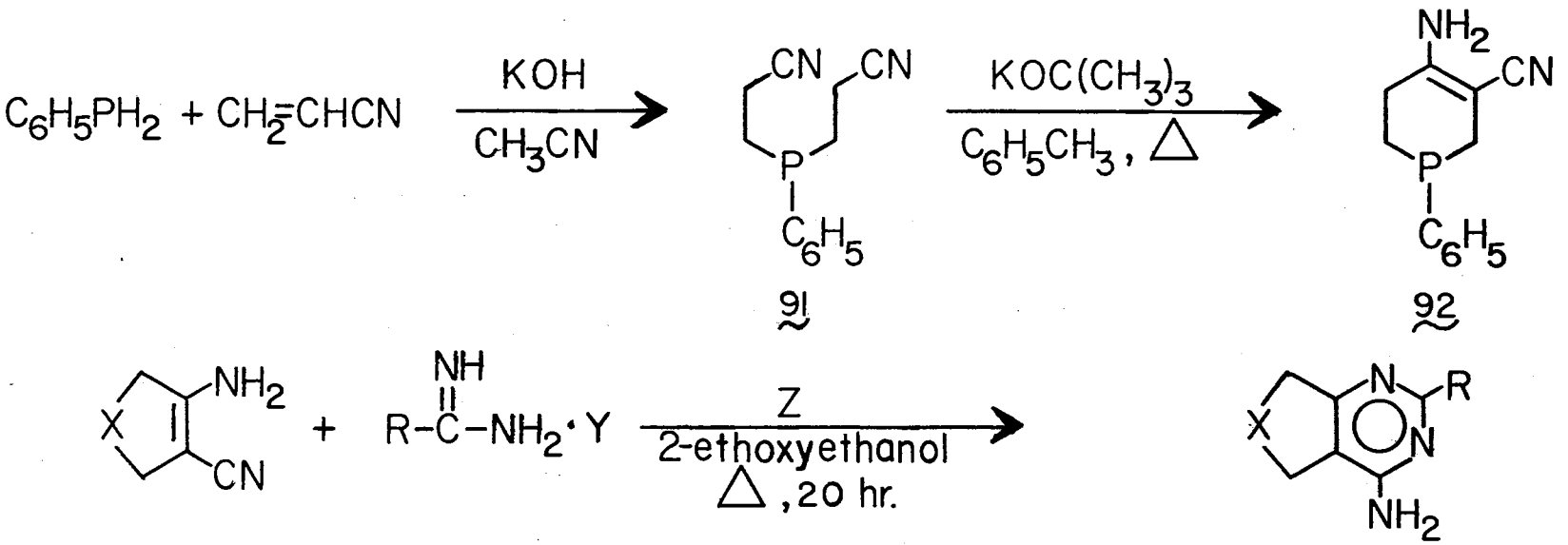


94

substituted guanidines to form 2,4-diamino fused pyrimidines. The yields obtained in this one-step synthesis of diaminopyrimidines (ca. 35% in the cases of simple guanidines) compare quite favorably with yields obtained by more standard multi-step methods, e.g., 23% for 84 from methyl 2-oxocyclohexanecarboxylate[168] as illustrated.



The second synthetic method employed, Figure 3, involved the reaction of 92 and triethyl orthoformate to form the ethoxymethylene deriva-



X	R/Y	Z(equivalents)	X	R
92 $-CH_2\underset{C_6H_5}{P}-$	NH_2/HCl	$KOC(CH_3)_3$ (2)	74 $-CH_2\underset{C_6H_5}{P}-$	NH_2
92 $-CH_2\underset{C_6H_5}{P}-$	H/CH_3CO_2H	CH_3CO_2H (1)	75 $-CH_2\underset{C_6H_5}{P}-$	H
94 $-CH_2CH_2-$	NH_2/HCl	$KOC(CH_3)_3$ (2)	84 $-CH_2CH_2-$	NH_2
93 $-CH_2-$	NH_2/HCl	$NaOCH_3$ (2)	85 $-CH_2-$	NH_2
94 $-CH_2CH_2-$	$NHCH_3/H_2SO_4$	$NaOCH_3$ (3)	86 $-CH_2CH_2-$	$NHCH_3$
94 $-CH_2CH_2-$	NHCN/——	$KOC(CH_3)_3$ (1)	87 $-CH_2CH_2-$	NHCN

Figure 2. Direct Formation of Diaminopyrimidines from 2-Enamino Nitriles.

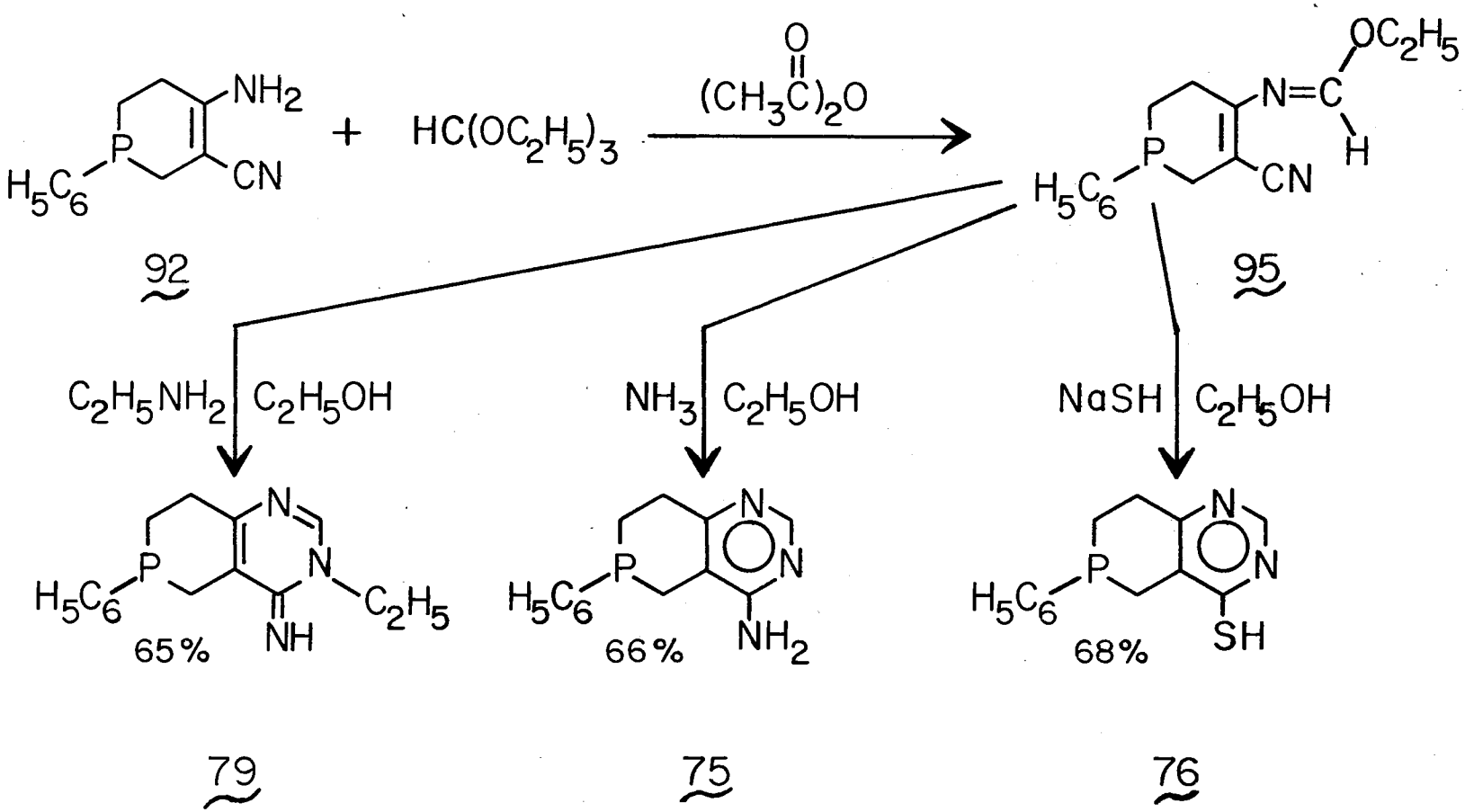


Figure 3. Formation of 4-Substituted Phosphorino[4,3-d]pyrimidines.

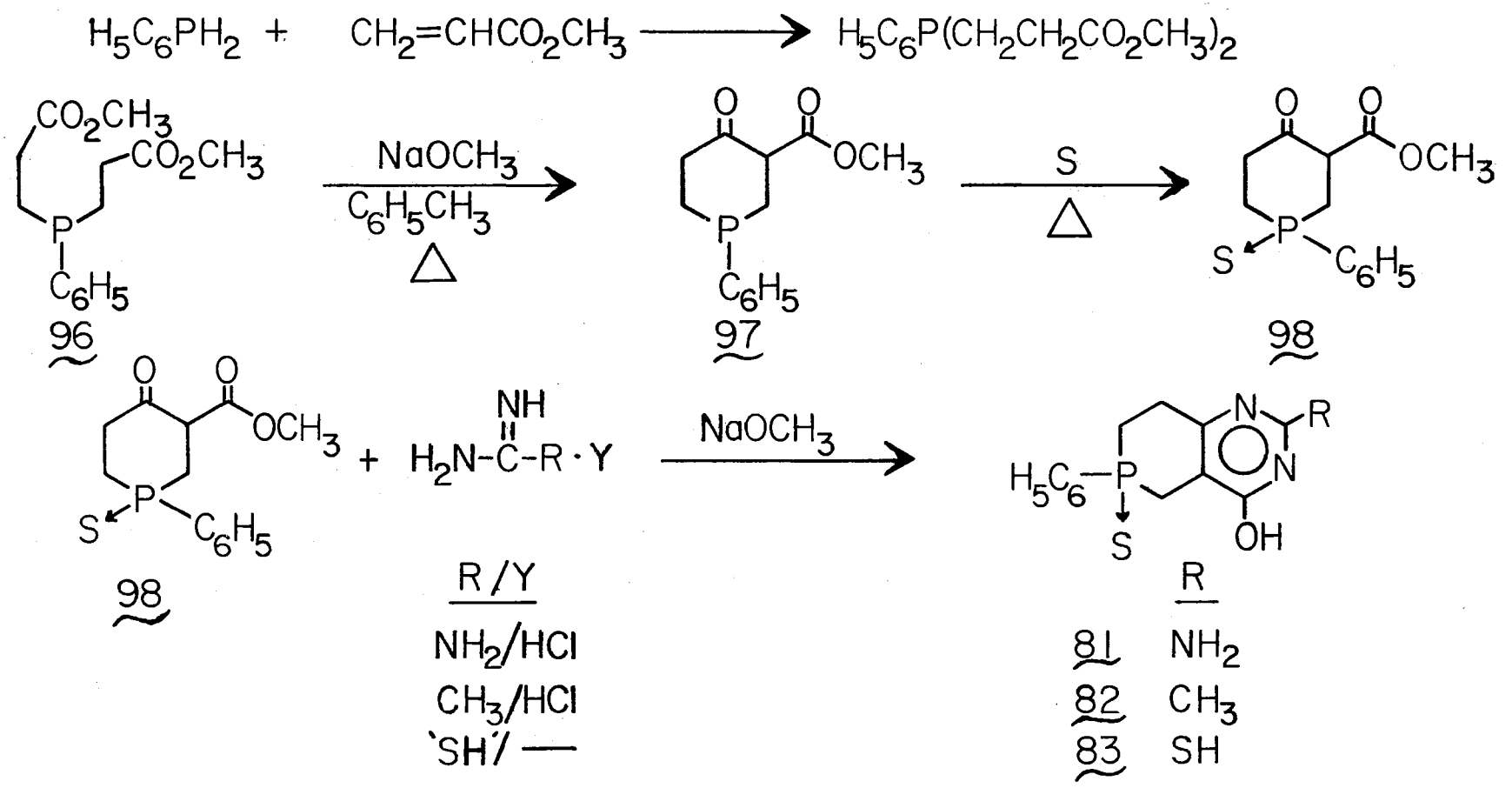
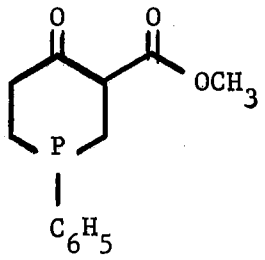


Figure 4. Formation of Pyrimidin-4-ols

tive 95. This derivative was then cyclized by use of basic reagents such as sodium hydrosulfide, ammonia and ethylamine to form the corresponding substituted pyrimidine.

Figure 4 outlines the third procedure employed for the synthesis of 6-phenylphosphorino[4,3-d]pyrimidines. The starting material for method three is a cyclic β-keto ester, probably the most common class of starting materials utilized for pyrimidine synthesis. Interestingly, even though the Thorpe cyclization of 91 is known,[76,232] the analogous Dieckmann cyclization of bis(carbomethoxyethyl)phenylphosphine (96), a known diester,[4] to form a cyclic β-keto ester has not been reported and remains novel to this work. The product of the cyclization, 97, was unstable to vacuum distillation and hence was treated with sulfur to form the solid derivative methyl 4-oxo-1-phenyl-3-phosphorinane-carboxylate 1-sulfide (98), which was utilized for pyrimidine synthesis.



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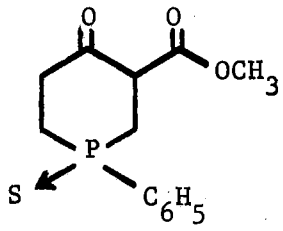

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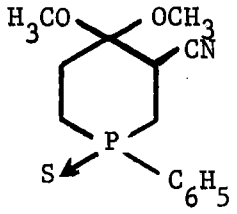


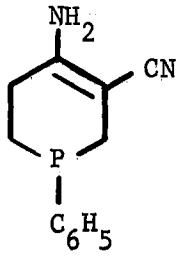
99

Attempted hydrolysis of the 2-enamino nitrile 92 employing standard methods for formation of β-keto esters[102-104] gave only the mixture of diastereomeric dimethyl ketals 99.

The structures of all new materials described herein are supported by IR, NMR, mass spectral and elemental analysis.

Preparation of 4-Amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile (92), 2-Aminocyclopentenecarbonitrile (93) and 2-Aminocyclohexenecarbonitrile (94)

The preparation of 2-enamino nitriles 92,[76,232] 93,[227] and 94[235] was readily accomplished by a modification of literature procedures.



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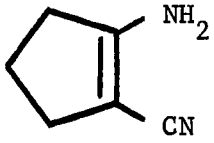

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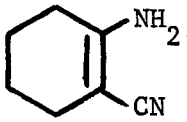

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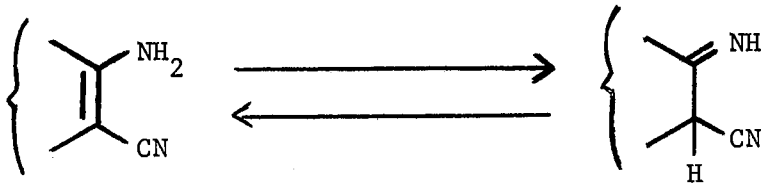
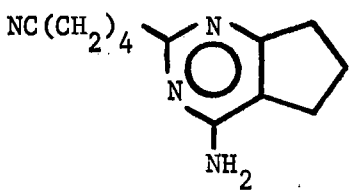
The availability of dry, anhydrous potassium tertiary-butyl alcoholate from MSA Research Corporation makes the Thorpe cyclization of the corresponding dinitrile in boiling toluene a relatively simple preparation. The precursor of 92, bis(cyanoethyl)phenylphosphine (91), was prepared from phenylphosphine via the procedure of Rauhut and coworkers,[119] while hexanedinitrile (adiponitrile) and heptanedinitrile (pimelonitrile), precursors of 93 and 94, respectively, are commercially available. Enamine nitriles 92 and 93 precipitated from the reaction mixture upon the addition of water; however, 94 remained in solution at this point. The toluene solution of 94 was concentrated to an oil before crystallization occurred. Enamine nitrile 94, a volatile solid with the odor of caramel, was most easily purified by sublimation while 92 and 93 were purified by crystallization from ethanol/water and chloroform, respectively. Typical yields of 70-95% are realized with minimal workup procedure. All three enamine nitriles show intense absorption in the infrared spectrum

at ca. 2.9μ and 3.0μ (N-H) and at 4.5μ (C≡N). The NMR integration (NH = 2H) indicates, as expected,[202] that tautomer 100 is the predominate isomer that exists in solution. Adiponitrile, when subjected to



100

Thorpe conditions, has been reported to yield both dimeric 101[227] and trimeric product 14.[239] While this difficulty was not encountered in the preparation of 92, 93, or 94, one should be aware of the possibility



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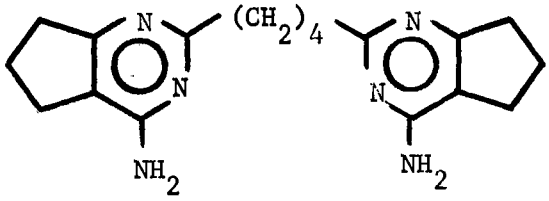
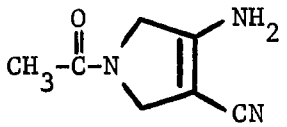


14

of this type of contaminant when utilizing these products in synthesis.

The Direct Formation of 2,4-Diaminopyrimidines From 2-Enamino Nitriles

The syntheses of 2,4-diaminopyrimidines have been summarized and contrasted[168] although the condensation of guanidine and the 2-enamino nutrile 102[38,39,210] and other 2-enamino nitriles[59] was omitted.



102

The preparation of the fused 4-amino and 2,4-diaminopyrimidines disclosed herein (see Scheme I) provide a further extension of this type of reaction and illustrate the utility of this route as a one-step synthesis of 2,4-diaminopyrimidines. Phosphorus in the system apparently does not greatly affect the reaction at carbon atoms two positions removed.

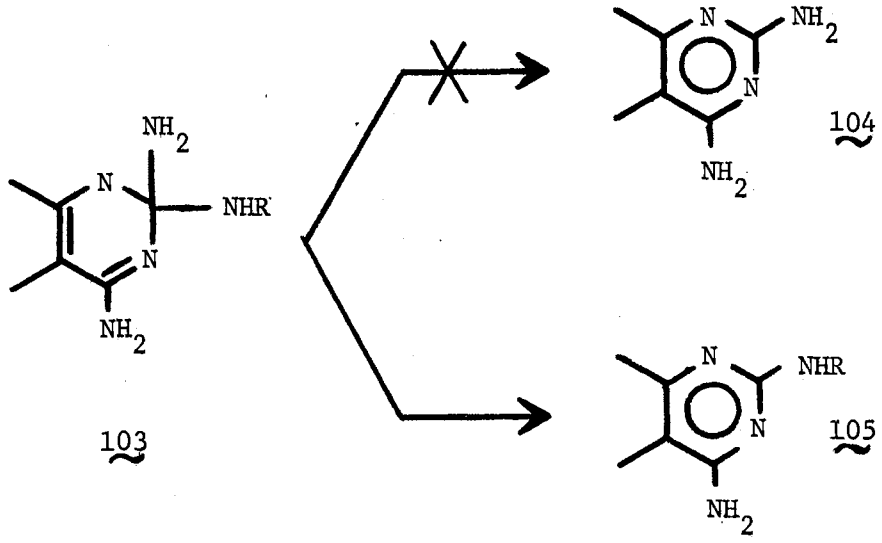
2-Enamino nitriles 92, 93, and 94 were shown to condense under the appropriate conditions with guanidine hydrochloride to form a series of diaminopyrimidines 74, 84, and 85, (see Tables III and IV for reaction conditions). Moreover, condensation of the 2-enamino nitrile 92 with formamidine acetate yields 4-amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine (75). 2-Enamino nitrile 94 and methylguanidine sulfate or cyanoguanidine gave 4-amino-2-methylamino-5,6,7,8-tetrahydroquinazoline (86) and 4-amino-2-cyanoamino-5,6,7,8-tetrahydroquinazoline (87), respectively.

While the yields obtained in this condensation are not outstanding, they are certainly comparable with those realized by Modest and coworkers[168] in the reaction of dicyandiamide and cyclic ketones. (The enamino nitriles are often precursors of cyclic ketones[202] via hydrolysis.) In other reported synthesis of 84 and 85 (the most common members of a rare class of compounds), the respective overall yields were 12% from cyclohexanone[57] and 18% from methyl 2-oxocyclopentanecarboxylate[197] and were achieved in laborious multistep procedures. Obviously, our method is superior in both efficiency of operation and time involved for comparable yields.

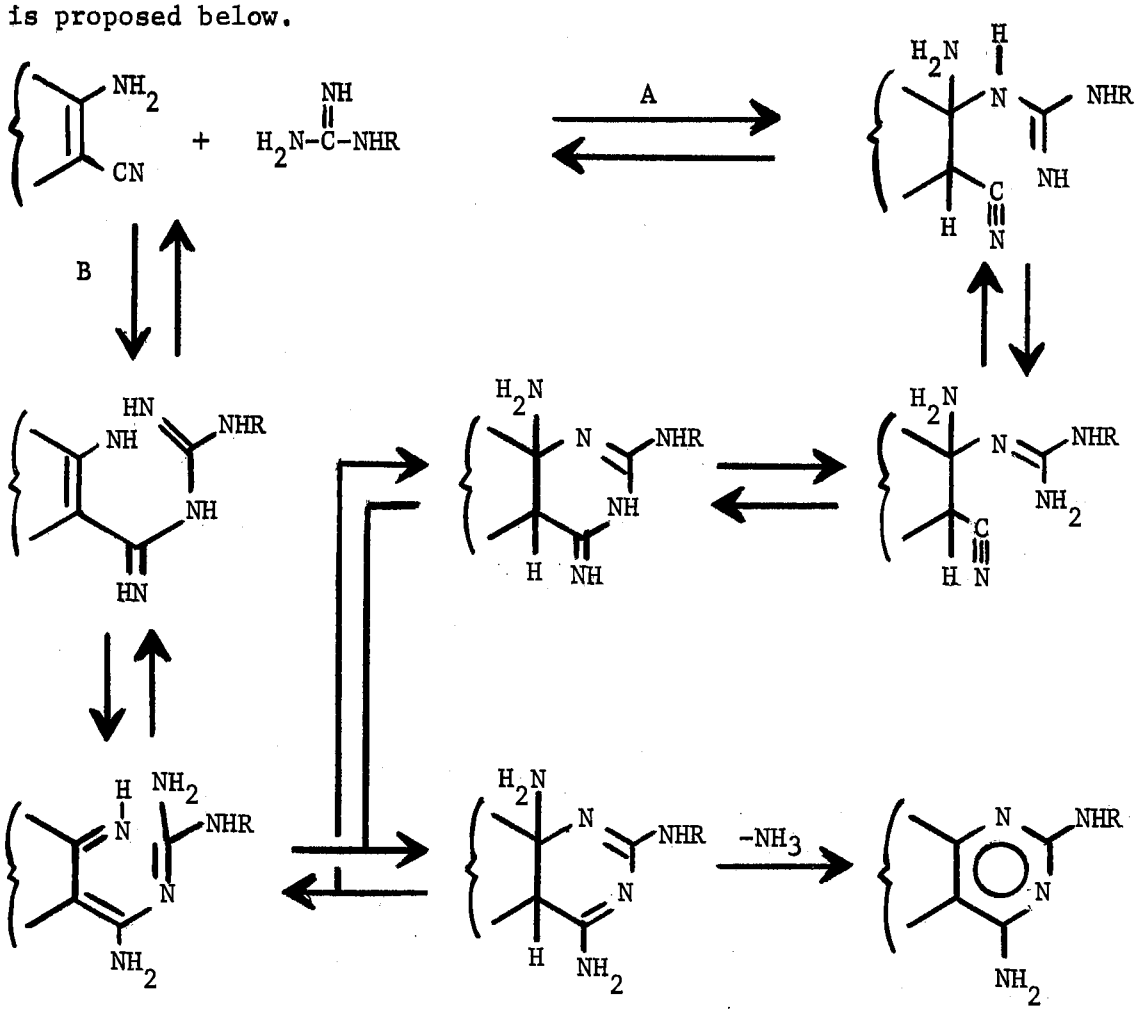
The conditions necessary for the above type of condensation to occur seem to vary on an individual basis. Cavalla[38] in his initial

communication utilized the guanidine acid salt without neutralization. Sheradasky and Southwick[210] have since employed a neutral or slightly basic solution. Pyrimidine 74 was prepared under basic conditions in higher yield than under neutral conditions. However, enamino nitrile 92 failed to condense with formamidine acetate under basic conditions, but condensation was realized in the presence of acetic acid. Enamino nitrile 94 does combine with cyanoguanidine equally well in basic and neutral conditions, but in low yield. In all cases, large quantities (50-80%) of the starting enamino nitrile were recovered from the reactions.

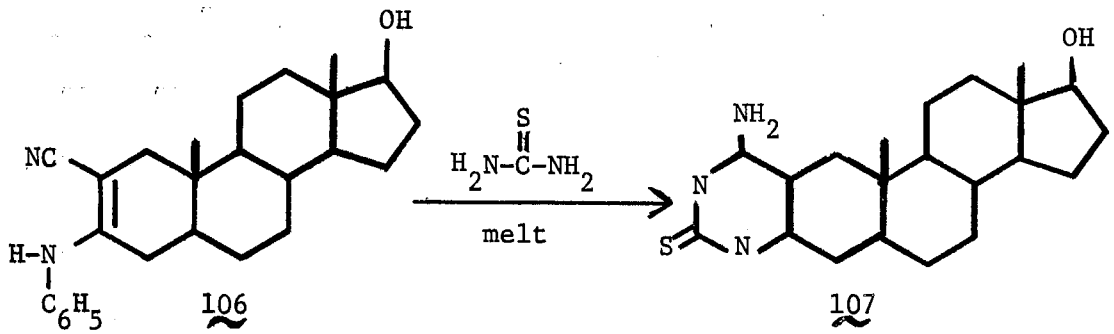
A literature search revealed that the mechanism of pyrimidine formation in this type of condensation apparently has not been rigorously investigated. The condensation of 2-enamino nitriles with unsymmetrical guanidines is evidence against any mechanism which would involve the guanidino carbon in any saturated state, i.e., for the formation of 103. If an intermediate such as 103 formed, one would expect diaminopyrimidine formation (such as 104 in conjunction with the generation of 105).



Only 105 is observed, however. A possible mechanism for the reaction is proposed below.



The reported[59] interaction of 2-enamino nitrile 106 with thiourea to form pyrimidine 107 supplies ancillary evidence for a mechanism similar to the preceding mechanism. Here again, surely the thiocarbonyl

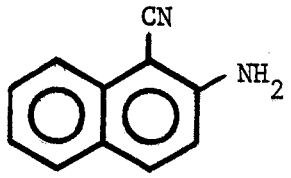


106 107

carbon atom must not achieve a saturated state, i.e. sp^3-hybridized, or a mixture of products would result. Similarly one might expect the loss of aniline from 106, but not the loss of benzene.

Differentiation between pathway A and pathway B is not easy and certainly not permitted from the experimental data available. Thompson implies[227] that Michael addition to the alkene is favored over addition to the nitrile in the proposed mechanism for dimerization of 93, i.e., pathway A is favored.

One might argue that pathway B is favored since 2-amino nitriles 108[196] and 109[61] are known to condense with guanidine. However, it should be noted that the condensation failed or proceeded in less than 10% yield in the case of several anthranilic nitriles 110.[223] The re-



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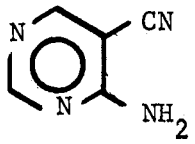

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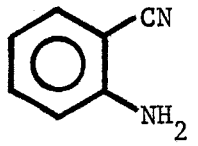
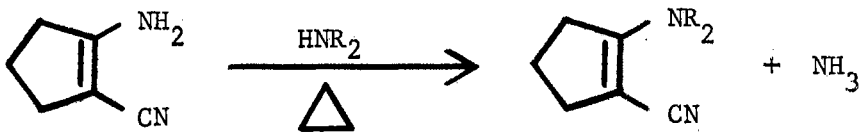


110

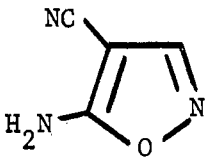
cent availability of substituted enamine nitriles via transamination[84] may supply the necessary starting materials to test some of the assumptions in the proposed mechanism.



The advantage of this one-step approach to the phosphorino[4,3-d]-pyrimidines is in the simplicity and relative mildness of reaction conditions as compared to the condensation procedure of Modest and Chatterjee,[168] which involved generation of melts at temperatures ranging from 160° to 200°.

The Formation of 4-Substituted-6-phenyl-phosphorino[4,3-d]pyrimidines

The importance and use of ethoxymethylene derivatives of 2-amino nitriles in the synthesis of 4-aminopyrimidines is well documented.[31] However, most of the 2-amino nitriles employed for pyrimidine synthesis have been aromatic in nature, e.g., 5-amino-4-isoxazolecarbonitrile (111),[219] 2-amino-3-thiophenecarbonitrile (112),[224] 2-amino-3-pyrrolecarbonitrile (113)[220] and other systems.[223] The ethoxymethylene derivative 114 is formed by boiling the corresponding 2-amino nitrile in excess 50:50 triethyl orthoformate and acetic anhydride for 1 to 4 hrs.[223] Subsequently, the solvents are removed by vacuum distillation, and the residue is treated with an anhydrous amine to effect pyrimidine formation. Derivatives such as 114 can and have been isolated[222] but are generally used as crude material. The cyclization is believed to occur



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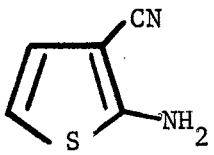

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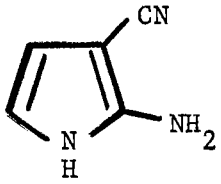

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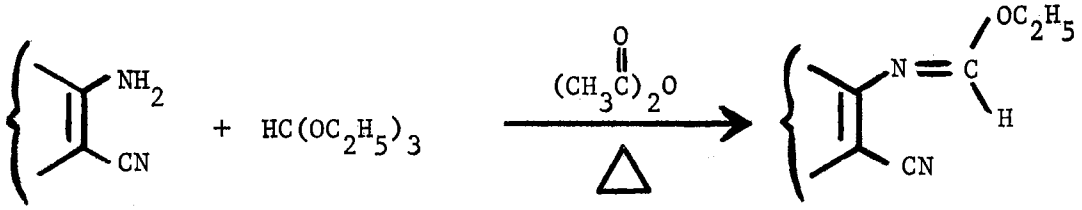
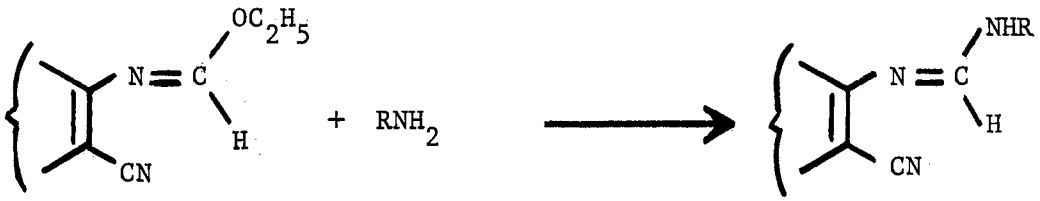
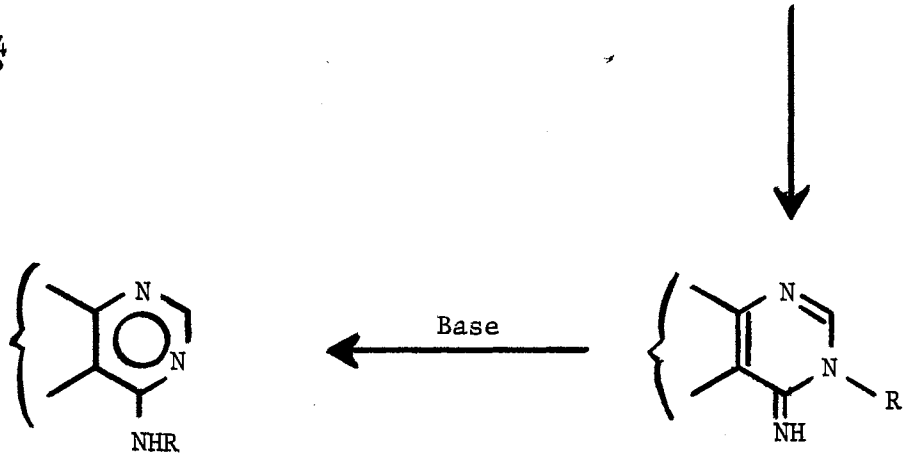


via the following intermediates:

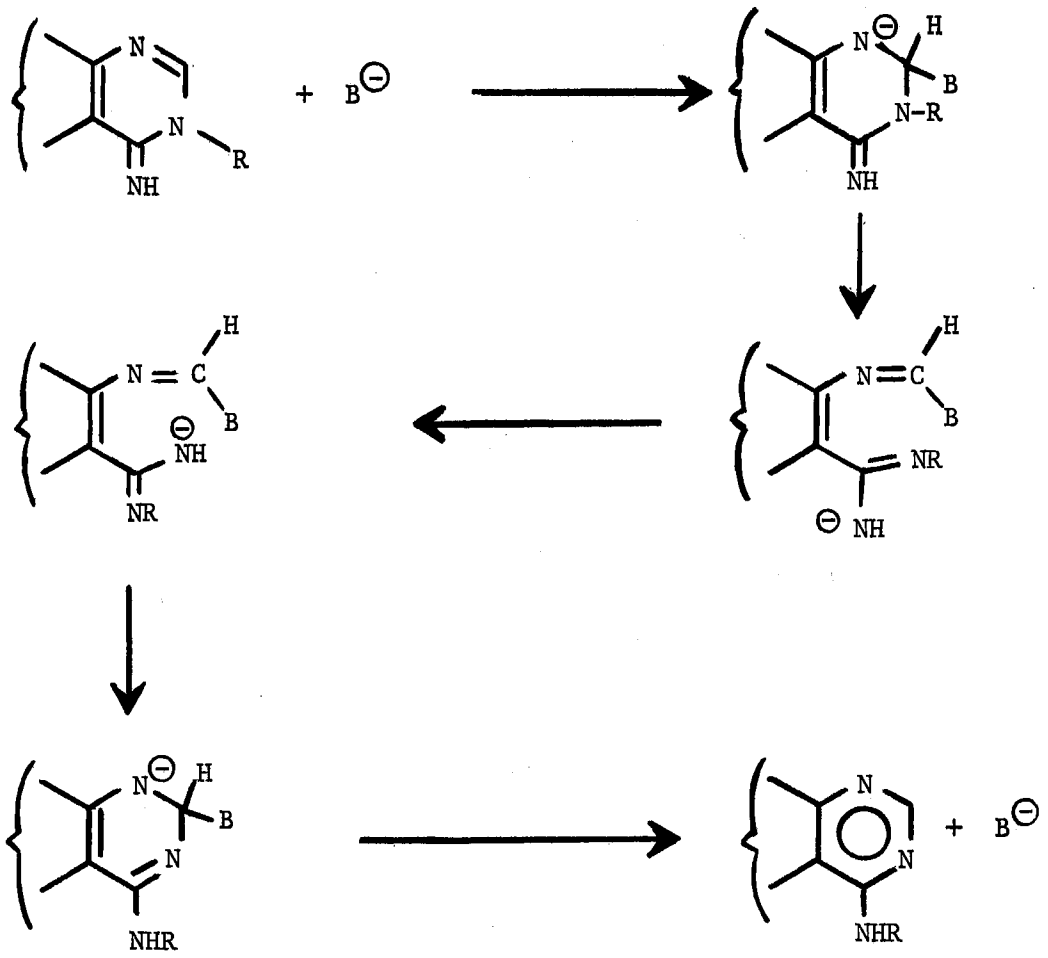


114



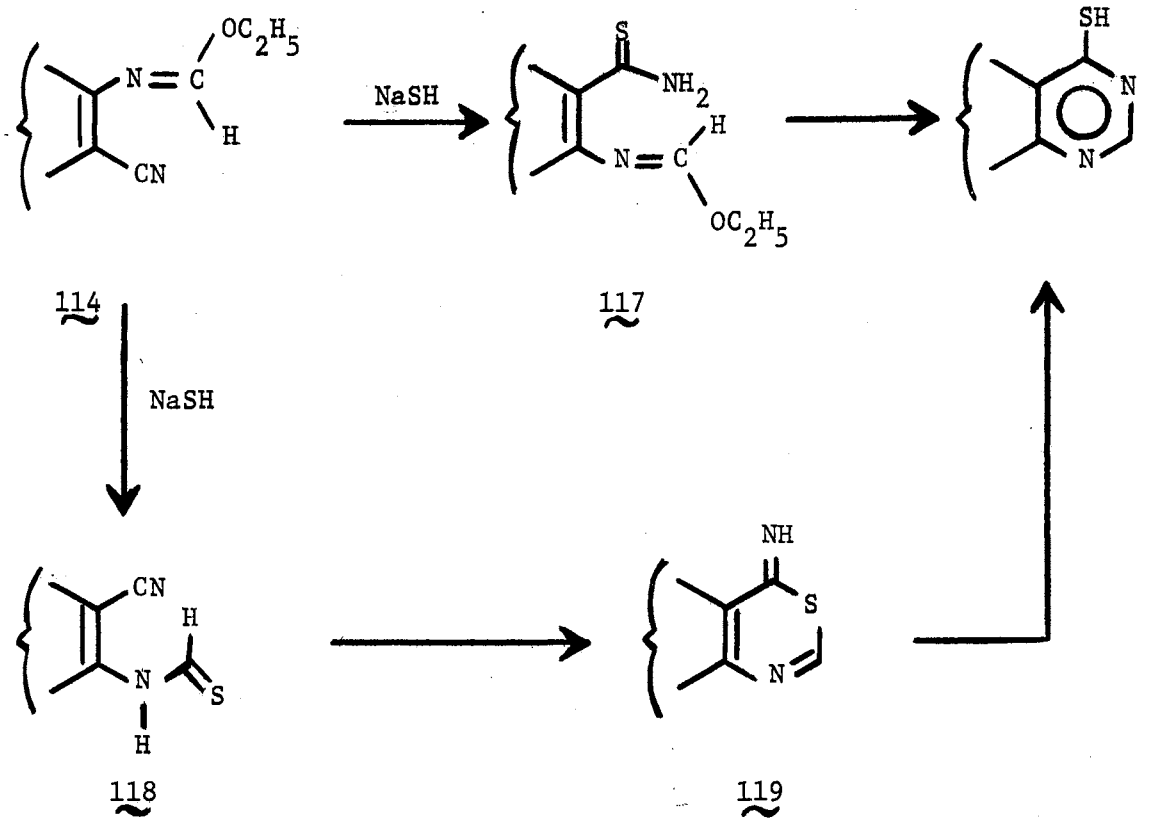
116 115

Compounds such as 115 are readily isolated, and the conversion of 115 to 116 is a classic example of the Dimroth rearrangement.[5,31,32,222] The mechanism proposed for this type of rearrangement is illustrated as follows:



Frequently, yields for this type of preparation range from 20% to 90%,[223] the major limiting factor being initial formation of the ethoxymethylene derivative. When acylation of the amine competes with the formation of the ethoxymethylene derivative, triethyl orthoformate has been used alone, but yields are generally lower.[224] The application of this synthetic procedure to the non aromatic 2-enamino nitriles has been reported and is seemingly becoming the method of choice as evidenced in the literature.[59,210,223]

Ethoxymethylene derivatives 114 have also been cyclized with anhydrous sodium hydrosulfide to form fused mercaptopyrimidines.[224] While the mechanism of this cyclization is not fully understood, the reaction is believed to proceed through either an intermediate ethoxymethylene-



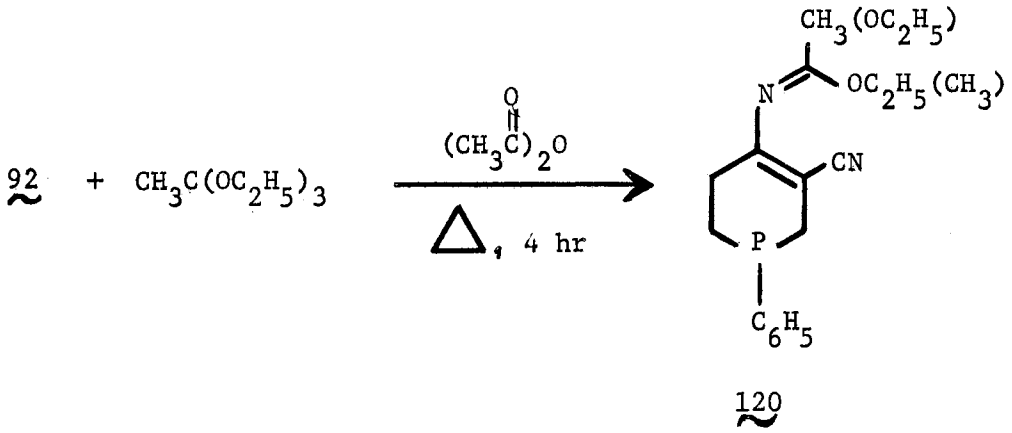
amino thioamide 117 or an intermediate 2-cyano thioformamide 118. Thioamide 117 could then cyclize to product (a known sequence)[224,225,209] or thioformamide 118 could cyclize to a 4-amino-m-thiazine 119, a known precursor to mercaptopyrimidines[226] under these conditions.

We now report that phosphorino[4,3-d]pyrimidines 75, 76, 79, and 80 can be prepared utilizing this type of reaction sequence (Figure 3). The narrow range of yields (65-68%) of 75, 76, and 79 is further evidence that the formation of the ethoxymethylene derivative is the limiting step in the sequence.[224] Thus, in spite of the large size of the phosphorus atom (covalent radius 1.10 A°)[176] compared to carbon (covalent radius 0.77 A°)[176] there is not sufficient strain in the six-membered C-P heterocycle to prevent formation of the fused system.

The importance of acetic anhydride to the initial condensation is clearly illustrated in the synthesis of 76. When an attempted formation

of 76 was made without the presence of acetic anhydride, the yield was only 26%. With acetic anhydride, the yield was increased to 66%. The function of the acetic anhydride seems to be to remove the ethanol formed in the reaction as ethyl acetate and thereby to drive the reaction to the right. This assumes that the initial formation of 114 is an equilibrium-controlled reaction. An interesting facet of the formation of 76 is that a small amount of the phosphine sulfide is formed. Evidently, the phosphine is capable of extracting sulfur from H_2S or NaSH (an apparent redox reaction). This type of reaction ($\geqslant P \rightarrow \geqslant P{\rightarrow}S$) appears to be rare although removal of sulfur from carbon[48,49] or phosphorus[17] is well known. A possibly analogous reaction previously discussed (see Historical part IV) is the formation of phosphine oxides by hydroxylamine.[152]

Interestingly, and in contrast to analogous examples in the literature,[198,218] the syn and anti adducts formed from triethyl orthoacetate and 92 have been prepared in 79% yield as a white crystalline solid. Reaction of 120 and sodium hydrosulfide failed to form the corresponding



120

mercaptopyrimidine in good yield. This suggested that the reactivity of the orthoester may not be the limiting factor in the extension of these synthetic routes to 2-substituted derivatives. Instead, the reactivity

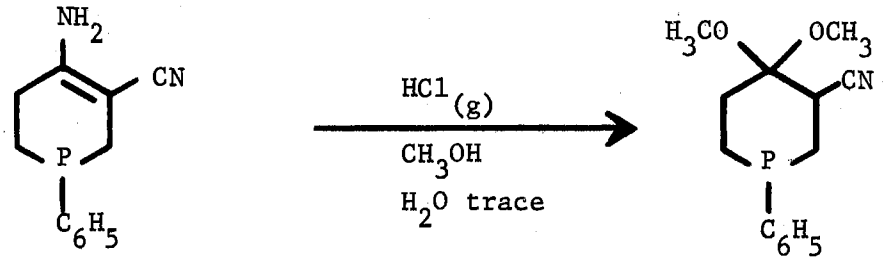
of the intermediate imidates, such as 120, may be limiting.

Phosphorino[4,3-d]pyrimidine 80 was obtained by the base-catalyzed Dimroth rearrangement of 79 in 70% yield. Both 79 and 80 sublime quite readily ($135\text{-}140^{\circ}/10^{-4}$ mm) but 80 has a tendency to form a glass which then crystallizes upon standing. The spectrum of 79 shows two sets of quartets for the N-methylene group, attributed to a syn-anti isomerism about the imine nitrogen. Brown did not report this splitting in his NMR discussion of the reactants and products of the Dimroth rearrangement.[30] The other proton resonances in the spectrum did not exhibit this additional splitting, possibly because of their distance from the imine hydrogen. Curiously, the NMR spectrum of 80 in $DCCl_3$ shows a complete doubling of all resonance lines in an approximate intensity ratio of 3:1. A Courtauld model of 80 indicates a large amount of hindered rotation of the $-NHC_2H_5$ group. This steric barrier to rotation may result in conformers in which the $-NHC_2H_5$ group is syn or anti to the P-phenyl ring. Experimental evidence supporting this explanation is (1), the relative intensity of the doubled spectrum is solvent-dependent, and (2) the spectrum is temperature-dependent with only one set of each resonances observable even at $125^{\circ}C$.

Preparation of Methyl 4-Oxo-1-phenyl-3-phosphorinanecarboxylate 1-sulfide (98)

A common synthesis of pyrimidines involves the condensation of amidines and amidine analogs with β-keto esters.[112] It is surprising that even though the Thorpe analog 92 has been known since 1960,[232] neither β-keto ester 98 (next page) nor the corresponding phosphine or any other derivatives has been reported.

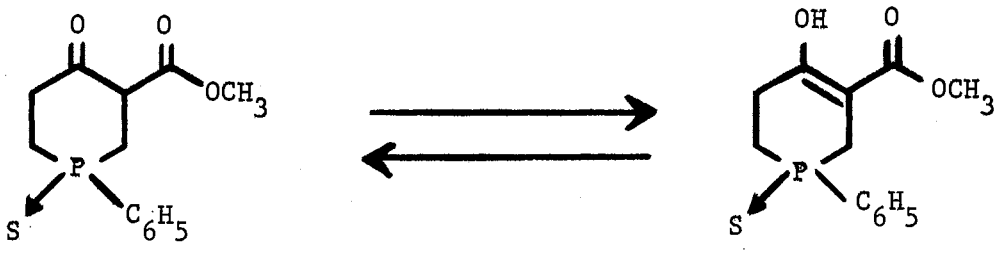
The attempted hydrolysis of 92 by known procedures[102-105] for the formation of β-keto esters from Thorpe products gave only the ketal 121, isolated as the sulfide 99. A well-known alternate route to cyclic



92 121

β-keto esters is the Dieckmann condensation of diesters.[202] The appropriate diester, bis(carbomethoxyethyl)phenylphosphine (96), for the formation of 121 was first reported in 1970.[4] The diester 96 was successfully cyclized with sodium/sodium methylate in boiling toluene to form 121. Attempts to purify 121 by vacuum distillation were thwarted by difficulties with decomposition; hence 121 was converted to the corresponding phosphine sulfide (98) by boiling in a mixture of chloroform and sulfur (see Scheme III). The overall yield, 96 → 97 → 98, was 45-60% for three preparations.

The 40.5 MHz NMR of 98 in methanol showed a not wholly unexpected, but moderately surprising, double ^{31}P absorption at δ -19.0 and δ -19.3 relative to H_3PO_4. This double absorption would be expected in molecules, such as 98, which have two asymmetric centers and thereby exist as a pair of diastereomers. However, the proton spectrum and integration of 98 indicate that 122, the enol of 98, predominates in chloroform solution. This enolization of 98 to 122 could result in equilibration of the diastereomers. If both diastereomers are observable in the ^{31}P



98 122

NMR spectrum, the cause may be the difference in solvent or may be an illustration of the extreme sensitivity of ^{31}P nuclei to minute changes in structure. The question remains unanswered, however.

Preparation of 6-Phenylphosphorino[4,3-d]-pyrimidin-4-ols

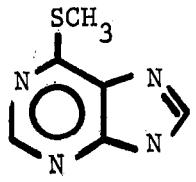
β-Keto esters have been shown to condense with amidines and amidine analogs under anhydrous, basic conditions.[5] Thus, 98 was condensed with guanidine hydrochloride, acetamidine hydrochloride, and thiourea under anhydrous basic conditions to yield, after neutralization, the corresponding 6-phenylphosphorino[4,3-d]pyrimidines 81, 82, 83 (Figure 4). The pyrimidinols are easily isolated and purified by solution in dilute base, decolorization of the solution with Nuchar, and subsequent acidification with dilute acetic acid to regenerate free pyrimidine. The mass spectra of these derivatives will be discussed in an ensuing section.

Of particular note in the proton NMR spectrum of these phosphorino-[4,3-d]pyrimidine 6-sulfides is the phenyl region. One may easily discern the ortho protons of the phenyl group down field from the remaining

aryl signals. This separation of the ortho protons was observed as a general characteristic of phosphine oxides, phosphine sulfides, and phosphonium salts in this family.

Reactivity of 5,6,7,8-Tetrahydro-6-phenylphosphorino[4,3-d]pyrimidines

Recent reports concerning the biological activity and potential chemotherapeutic usefulness of 6-(methylthio)purine[169] (123) and phosphonium salts such as 43,[43,207] prompted us to investigate the



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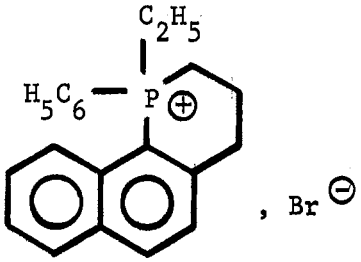

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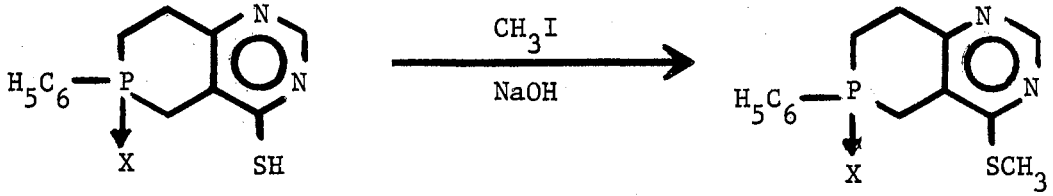
chemistry of 75 and 76. Of particular interest were the relative reactivities of the -SH vs C_6H_5P (alkylation vs quaternization), $-SCH_3$



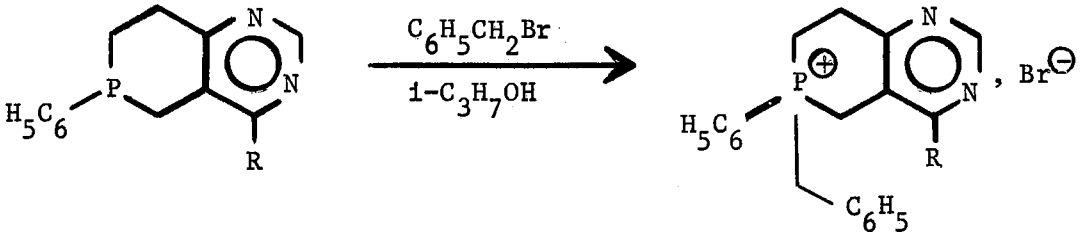
X = — (76)
= S (125)

X = — (77)
X = X (78)

vs $C_6H_5P<$, and $-NH_2$ vs $C_6H_5P<$ as competitive quaternizations. Specifically, whether it would be possible to methylate the thio function in the presence of a phosphine without carbon-phosphorus bond cleavage and whether it would be possible to quaternize a tertiary phosphine in the presence of a methylthio or amino functional group were the questions.

The methylation of 76 and phosphine sulfide to form the methylthio derivatives 78 (89%) and 77 (71%) was accomplished with 10% sodium hydroxide and methyl iodide. The methylthio derivatives 77 and 78 are surprisingly volatile and are readily purified by vacuum sublimation (80-90°/0.05 mm). Quaternization of phosphorus in 78 was not observed and there was also no evidence of carbon-phosphorus bond cleavage. Hence, with respect to methylation, 78 is an exact chemical analog of aminopyrimidinethiols in which one can methylate the mercapto group in the presence of the amino group.[32]

The formation of phosphonium salts 88 and 90 from phosphines 78 and 75, respectively, indicated that the tertiary phosphine in these phosphorino[4,3-d]pyrimidines is a stronger base and/or a more powerful nucleophile than the 4-methylthio or the 4-amino functions. The assignment of the phosphonium structure is rigorously supported by infrared,



R = SCH_3 (78) R = SCH_3 (88)

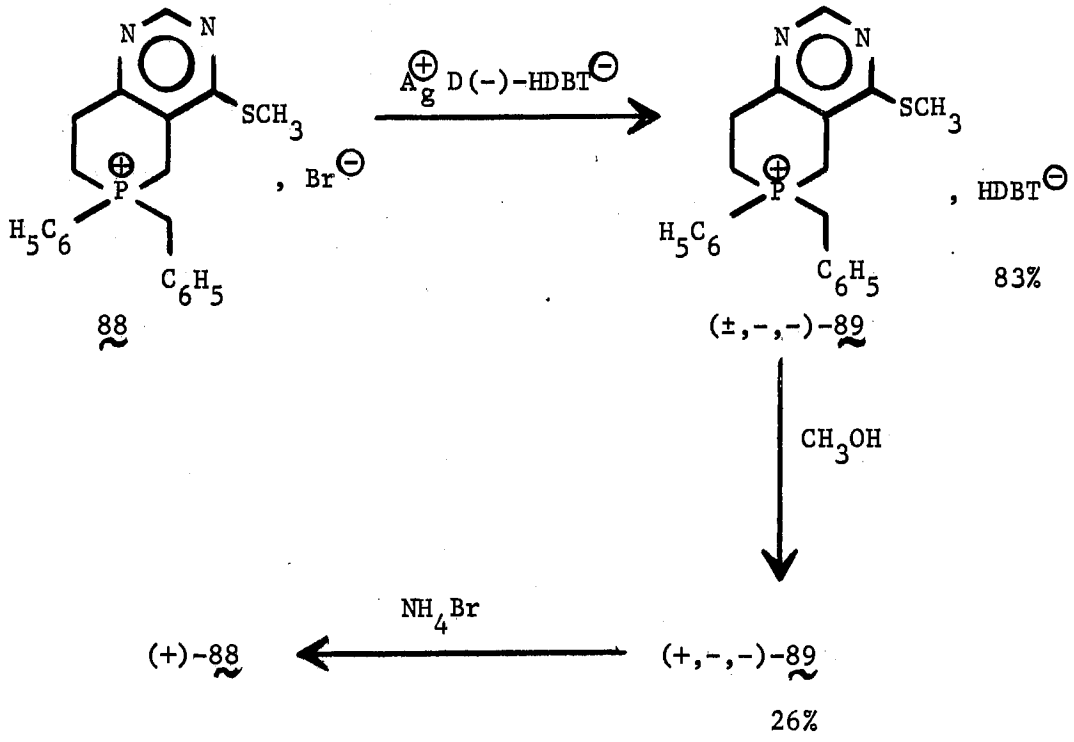
= NH_2 (75) = NH_2 (90)

NMR, mass spectral, and elemental analysis; except for the latter, the analyses are similar to those of the simpler precursor pyrimidines. However, most significantly, the highly positive ^{31}P NMR absorption of the phosphine precursors (ca. δ +44 relative to H_3PO_4; see Table VIII is shifted to a highly negative ^{31}P NMR absorption in the phosphonium salts (ca. δ -18; Table VIII.) This shift from positive to negative ^{31}P absorption is characteristic of a conversion from a phosphine to a phosphonium salt. The reaction is complete and specific for the phosphine as indicated by the loss of all absorption for ^{31}P at positive δ in the NMR.

The Partial Resolution of 5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinia[4,3-d]pyrimidine (-)-Hydrogen Dibenzoyltartrates (89)

The less negative diastereomer of the diastereomeric mixture 89 has been successfully prepared, separated, and shown to undergo metathesis with ammonium bromide to form (+)-88. Racemic 88 was treated with silver D(-)-hydrogen dibenzoyltartrate[78] in boiling methanol to form the mixture of diastereomers (+,-,-)-89 and (-,-,-)-89 in 83% yield. (Both diastereomers have a negative specific rotation; however, one is more negative than the other.) Subsequent separation of (+,-,-)-89 and (-,-,-)-89 was effected by repeated recrystallizations from a minimal amount of methanol. The more soluble (-,-,-)-89 has not been purified by this method. Four recrystallizations were sufficient to purify 375 mg. of (+,-,-)-89 to a constant specific rotation, $[\alpha]_D^{25^\circ} = -14^\circ$ (c = 0.3000 g/25 ml., methanol) and a sharp melting point, m.p. = 164.5° - 165° s.t. decomp. The constancy of the specific rotation upon recrystallization ([α] of the mixture of (+,-,-)-89 and (-,-,-)-89 had been

about -50°) and the sharpness of the melting point (the m.p. of the mixture had increased from 154-158°) strongly indicated that a pure isomer (+,-,-)-89 had been resolved. The yield of (+,-,-)-89 was 26% based upon the original mixture of (+,-,-)-89 and (-,-,-)-89 diastereomers.



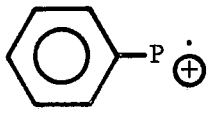
The pure diastereomer (+,-,-)-89 underwent satisfactory metathesis with ammonium bromide to form optically active (+)-88 ($[\alpha]_D^{25^\circ}$ = +76° (c = 0.2087 g/25 ml., methanol), 211 mg., 89%, m.p. 249-250°).

Both 88 and 89 have been characterized by spectral data and elemental analysis. The inclusion of solvent of crystalllization, or of stoichiometric amounts of dibenzoyltartaric acid or its anions, was an anticipated difficulty which was not encountered. Chen[43] reported the inclusion of a molecule of dibenzoyltartaric acid in resolved 74. He attributed this difficulty to the use of water as a solvent in the

initial formation of the tartrates of 74. Possibly we have circumvented this difficulty by employing anhydrous conditions although the exact cause of formation of such dual-component salts is unknown.

Mass Spectra of Phosphorino[4,3-d]pyrimidines and Related Heterocycles

Elucidation of the mass spectra of phosphorus-heterocyclic compounds is very rare in the literature (see reference 216 for a bibliographic listing for 1967-1971). Much of the available literature deals with 9-phosphafluorene and other related derivatives[47,80] or phosphoranes.[78] It is interesting that m/e 108 is a common ion in most of the mass spectra of C-P heterocycles recorded. This ion is generally attributed to the phenylphosphinidene cation (124)[47,78,80] and is also found as the base peak in the spectrum of phenylphosphine and diphenylphosphine.



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The mass spectra, utilizing a direct probe inlet, of all phosphorino-[4,3-d]pyrimidines prepared in this work are displayed in the Experimental section. The major fragment ions are tabulated in Tables V, VI, and VII. Moreover, the high resolution spectra of selected fragment ions of quinazoline 84 and phosphorino[4,3-d]pyrimidine 75 were obtained in an effort to specifically identify the fragment elemental composition. These results are shown in Figure 5 and Figure 6, respectively.

Surprisingly, the major fragmentation pathways seem to involve the saturated portion of the fused pyrimidine and not the pyrimidine ring

TABLE V

MAJOR FRAGMENT IONS IN PHOSPHORINO[4,3-d]PYRIMIDINES AND RELATED COMPOUND

No.	M* (RI) [M*-1(RI)]	M*-77	M*-109	Miscellaneous Fragment Ions m/e (RI) 10%
92 ≈	216 (100) [215 (19)]	139 (9)	107 (94)	54 (13), 67 (16), 78 (39), 80 (20), 94 (39), 108 (13), 109 (13), 188 (14), 217 (14)
74 ≈	258 (100) [259 (26)]	181 (17)	149 (15)	136 (12), 259 (15)
75 ≈	243 (100) [242 (33)]	166 (23)	134 (17)	107 (13), 244 (16)
76 ≈	260 (100) [259 (18)]	183 (21)	151 (16)	28 (11), 65 (11), 78 (12), 91 (25), 107 (11), 109 (13), 169 (42), 227 (20), 245 (17), 261 (18)
77 ≈	306 (100) [305 (13)]		197 (3)	63 (19), 65 (10), 91 (11), 92 (10), 109 (13), 135 (10), 165 (11), 243 (10), 260 (21), 271 (14), 273 (37), 290 (10), 291 (28), 304 (68), 307 (17), 308 (11)
78 ≈	274 (100) [273 (10)]	197 (3)	165 (4)	109 (10), 201 (11), 241 (33), 259 (27), 275 (27)
79 ≈	271 (80)	194 (27)	162 (28)	28 (12), 107 (10), 180 (100), 181 (10), 242 (11)
80 ≈	271 (100) [270 (13)]	194 (4)	162 (13)	180 (16), 228 (25), 243 (15), 256 (20), 272 (18)

TABLE VI

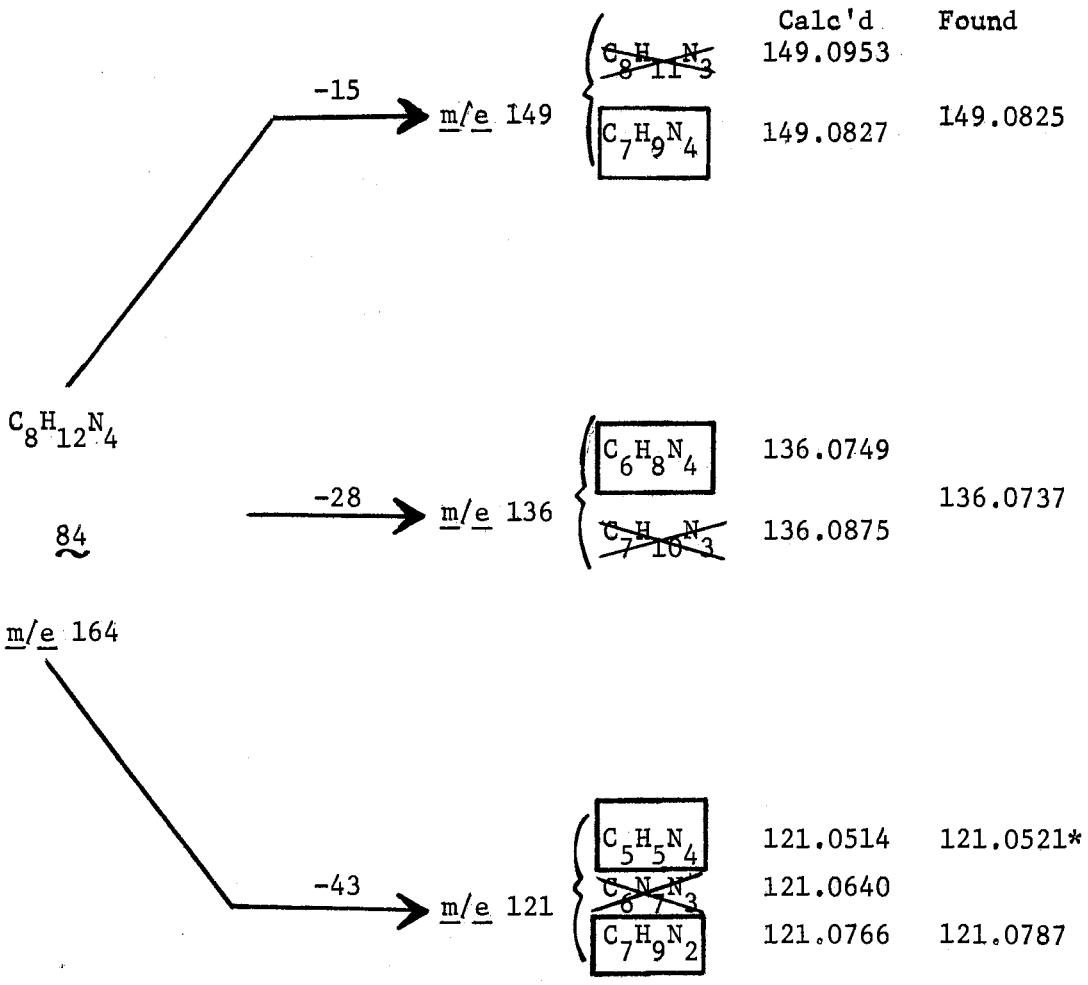
MAJOR FRAGMENT IONS IN THE MASS SPECTRA OF CARBOCYCLIC PYRIMIDINES

No.	M* (RI) [M*-1(RI)]	M*-28 ([M*-1]-28(RI)	M*-43 (RI)	m/e RI Common Ions 121	43	53	Miscellaneous Fragments m/e (RI) 10%
84	164 (100) [163 (49)]	136 (52) [135 (6)]	121 (9)	9	15	8	95 (10), 165 (10)
85	150 (96) 149 (100)		107 (23)	1	18	11	28 (17), 80 (11)
86	178 (48) [177 (33)]	150 (33) [149 (100)]		20	9	5	76 (15), 77 (13), 104 (11), 105 (12), 65 (15), 57 (13)
87	189 (100) [188 (49)]	161 (36) [160 (5)]	145 (5)	6	8	7	190 (12)

TABLE VII

MAJOR IONS IN THE MASS SPECTRA OF PHOSPHORINO[4,3-d]PYRIMIDINE P-SULFIDES AND RELATED COMPOUNDS

No.	M*(RI) [M*+1(RI)]	M*-32 [M*-33]	M*-141	Miscellaneous Fragments m/e (RI) 10%
81	291 (100) [292 (16)]	259 (14) 258 (47)	150 (75)	43 (11), 108 (33), 151 (11)
82	290 (92) [291 (15)]	258 (24) 257 (100)	149 (25)	42 (16), 109 (8)
83	308 (100) [309 (17)]		167 (12)	63 (11), 108 (27), 310 (11)
95	282 (100) [283 (14)]	250 (30) [249 (4)]	141 (16)	32 (22), 55 (38), 63 (23), 109 (54), 166 (11), 222 (44), 223 (11), 251 (11)



*m/e 121 is a doublet of approximate equal intensity

Confirmed □

Unobserved fragment ×

Figure 5. High Resolution Mass Spectra of 2,4-Diamino-5,6,7,8-tetrahydroquinazoline (84)

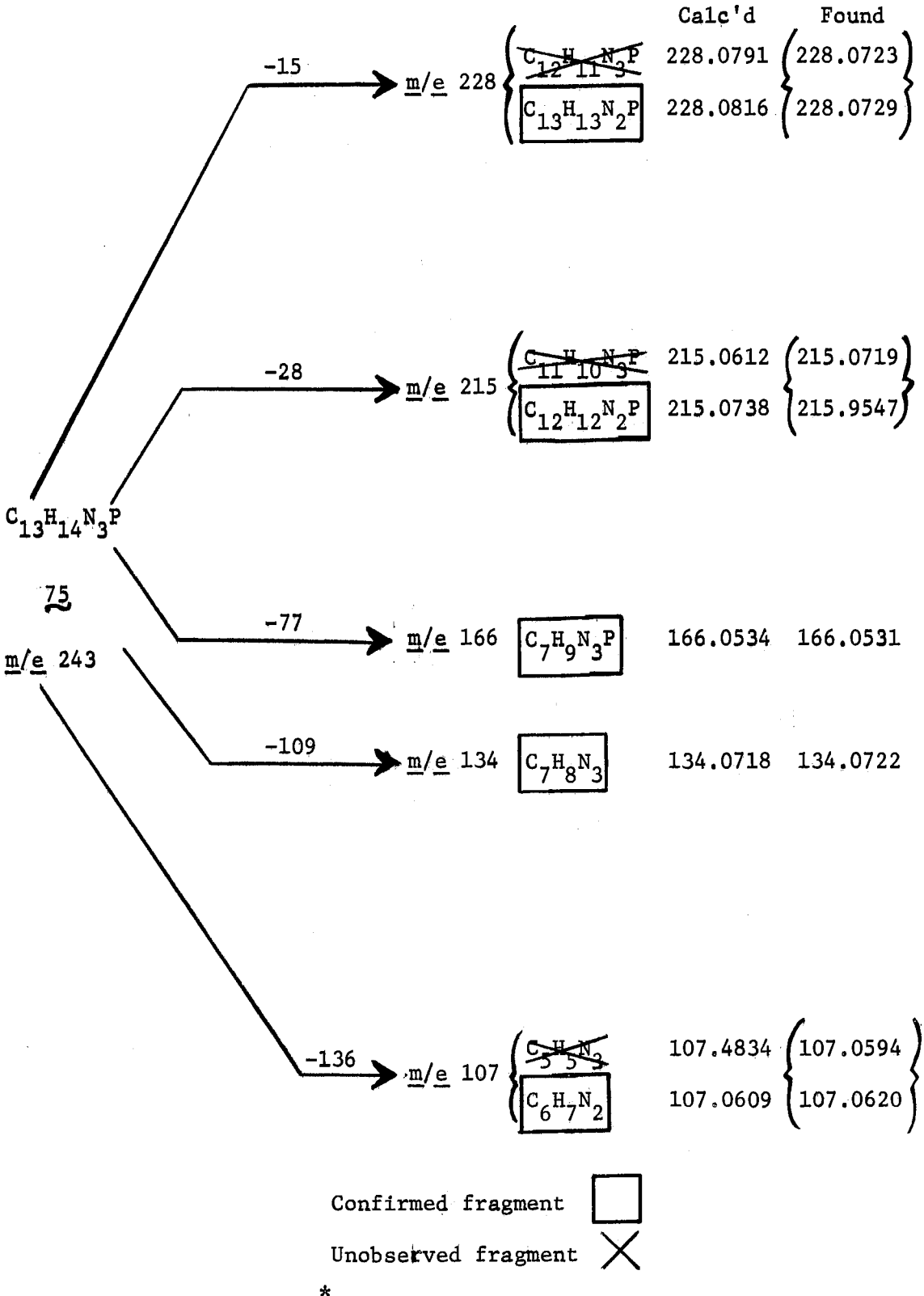


Figure 6. High Resolution Mass Spectra of 4-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine (75)

itself. For example, 84 shows fragment ions resulting from the loss of CH_3 (5%), C_2H_4 (52%), and C_3H_7 (4%) as either one-step or sequential-step fragmentations.

In the mass spectra of the phosphorus heterocycles, fragmentation via the phenylphosphinidene cation (124) (m/e 108) was often observed. However C_6H_5PH (m/e 109), confirmed by high resolution (Figure 6), was also observed as a major pathway in many of the fragmentation patterns. Other fragments from 75 supported by high resolution data are loss of CH_3 and loss of C_6H_5. The data for m/e 228 were conflicting and prevented any suggested structure.

The apparent fragmentation patterns of other phosphines seem to be analogous with 75. In some cases, fragmentation attributed to side chains complicates the spectrum. For example, 80 shows an apparent loss of CH_3, m/e 256 (20%); C_2H_4, m/e 243 (15%); C_2H_5N, m/e 228 (25%) attributed to the 4-ethylamino substituent.

Molecular ions have been reported in the mass spectrum of a few phosphonium salts.[1] However, the mass spectra of phosphonium salts 88 and 90 do not show molecular ions, but instead show the molecular weight less HBr as the largest major ion. These results are in concurrence with those obtained by Chen[43] although we feel the spectrum must result from volatility of the salt and not from thermal decomposition. The loss of HBr results from electron impact within the ionizing region of the spectrometer and not from thermal decomposition on the probe, or else HBr would be observed in the spectrum. HBr is not observed. This is not true in the case of 89, the hydrogen dibenzoyltartrate salt. In this case, decomposition of the sample occurs upon the probe at about 160°. Elimination of benzoic acid (identified by comparison with the known mass spectrum) is noted in the spectrum, and then the spectrum of the main sample is obtained at a probe temperature of ca. 200°. The

benzoic acid must come from decomposition and cannot be a contaminant because benzoic acid is volatile at room temperature in the mass spectrometer.

^{31}P Nuclear Magnetic Resonance Spectra of Phosphorino[4,3-*d*]pyrimidines and Related Heterocycles

The ^{31}P NMR spectra of organophosphorus compounds is becoming increasingly important for structure elucidation. A complete review is available with numerous examples to aid in prediction of magnitude and direction of chemical shifts.[81] The chemical shift differences, relative to H_3PO_4, are very large in magnitude, covering a known range from about δ - 225 for PBr_3 to δ + 400 for P_4.[53]

The 40.5 MHz chemical shifts (Table VIII) determined in this effort show a large difference in magnitude for any particular ring change in position of substitution, or oxidation state of phosphorus. However, the chemical shift is fairly independent of a change in the substituent at the 4-position of the pyrimidine ring. (Compare 75, 76, 78, and 80 in Table IX.) Substituent changes at the 2-position seem to affect the chemical shift more drastically (compare 81 and 82), but insufficient data preclude a definitive conclusion. More phosphorino-[4,3-*d*]pyrimidines are needed before it can be ascertained whether a structure-chemical shift correlation holds.

In general, the ^{31}P chemical shifts observed for phosphorino[4,3-*d*]-pyrimidines are of the general magnitude and direction that one would predict for the phosphorus moiety, i.e., phosphine absorptions at positive δ and phosphonium and phosphine sulfides at negative δ. For exam-

TABLE VIII

^{31}P CHEMICAL SHIFTS OF C-P HETEROCYCLES

Compound	δ	Solvent	Concentration (%)
74	+ 51.9	DMSO	5
75	+ 44.0	DMSO	5
76	+ 44.6	DMSO	5
78	+ 44.4	CH_3OH	5
79	+ 39.6	DMSO	5
80	+ 44.7	DMSO	5
81	- 31.41	DMSO	5
82	- 39.0	DMSO	2
83	- 39.0	DMSO	5
88	- 18.6	$HCCl_3$	10
90	- 18.6	DMSO	10
91	+ 21.4	C_2H_5OH	10
92	+ 46.9	$HCCl_3$	5
95	+ 20.6	CH_3OH	50
96	- 19.0 and - 19.3	CH_3OH	20

ple, bis(cyanoethyl)-n-octylphosphine shows ^{31}P absorption at δ + 25.3[256] compared to 91, the phenyl analog, at δ + 21.4. The diester 95, δ + 20.6, is quite similar as one would predict. The phosphine pyrimidines, 74-76 and 78-80, have values typical of tertiary phosphines, e.g., dimethylphenylphosphine δ + 46.[257] The ^{31}P absorption of phosphorino-[4,3-d]pyrimidine 1-sulfides 81-83 (ca. -35) compare very closely to known ^{31}P chemical shifts of tertiary phosphine sulfides such as dimethylphenylphosphine sulfide, δ - 32.5.[258]

^{31}P chemical shifts of 88 and 90 are also in agreement with the reported corresponding chemical shifts of many phosphonium salts such as dimethyldiphenylphosphonium bromide, δ - 22.1. However, phosphonium salts have occasionally been reported to have positive δ values, e.g., a reported chemical shift of δ + 16.5.[259] A complete tabular summary of reported ^{31}P chemical shift is available covering the literature to 1967.[253]

Biological Activity

The determination of the biological potential of this family of phosphorino[4,3-d]pyrimidines has only just begun. However, results from the National Cancer Institute have been received describing the initial screening results observed in 92, 94, 74, 76, and 121. These compounds have been tested against L-1210 Lymphoid Leukemia and KB cell culture (human epidermoid carcinoma of the nasopharynx). A summary of these evaluation results is given below.

L-1210 Lymphoid Leukemia--Mean survival time

Host--mouse BDF_1

Vehicle--saline with Tween-80

Site--intraperitoneal

Tissue--ascitic fluid

Level--1 x 10^5 cells

Compound	Dose	Mean Survival Time Test/Control %
74	12.5 mg/kg.	98
76	100 mg/kg.	110
92	400 mg/kg.	100
94	100 mg/kg.	104
121	200 mg/kg.	101

While all compounds exhibited therapeutic activity, (such as a reduction of white blood cell count and other tests) a mean survival time-test animal-control animal ratio of 125% or greater is generally required for further experimental work. Most of these compounds were nontoxic at levels tested. However 74 was toxic at higher dose levels, e.g., 100-400 mg., and could only be tested at very low concentration levels.

KB Cell Culture--ED_{50} (concentration causing 50% inhibition of growth)

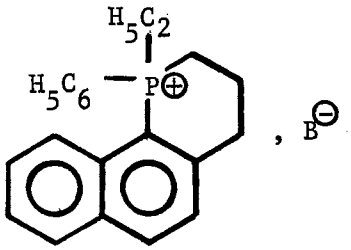
Host--cell culture tube assay

Vehicle--alcohol

Compound	ED_{50} g./ml.
74	0.32
76	0.01
92	0.01
94	0.3
121	0.27

These compounds were considered nontoxic and inactive for KB cells.

Recently reported testing data for phosphonium salt 43 against P-388 Lymphocytic Leukemia indicate a high level of activity. (Dose-6.25 mg./kg., median survival time of C57BL/6 mice, test/control ratio of 142%. Here again 125% T/C ratios are considered significant.) This high degree of activity is added encouragement that the phosphorinia-[4,3-d]pyrimidine bromides and other phosphorus heterocycles prepared in this work may be of chemotherapeutic value.



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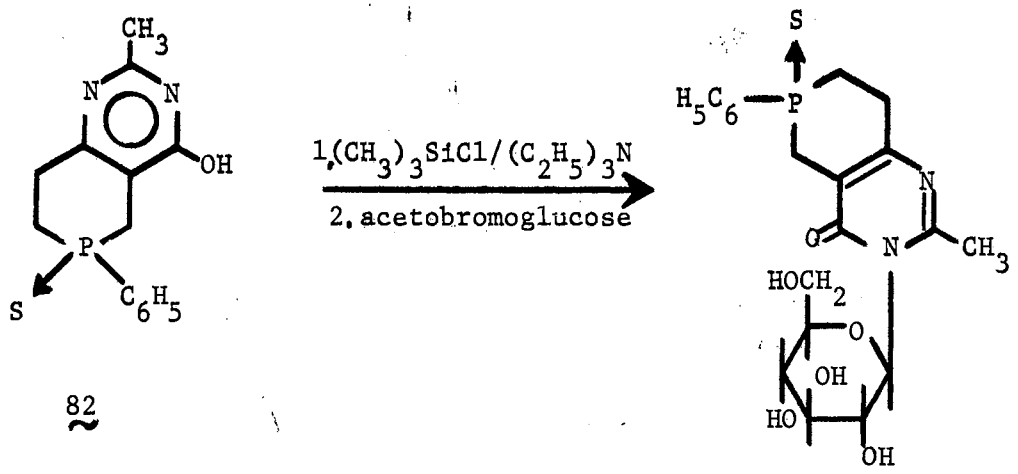
Suggestions for Further Work

The successful development of synthetic methods for the preparation of phosphorino[4,3-d]pyrimidines can be extended to the formation of many other functionalities. Additionally, the chemistry of pyrimidines reported herein should prove very interesting and provide new types of compounds for biological testing. For instance, pyrimidinols 81, 82, 83 should be relatively easy to alkylate by standard methods[31,32] to form nucleosides such as 126. If trimethylsilyl chloride were employed, reduction of the phosphine sulfide would likely not occur although the reduction properties of silanes and disilane with respect to P → X bonds are well known.[95,122] The formation of nucleoside derivatives could be of possible pharmaceutical importance by increasing the water solubility

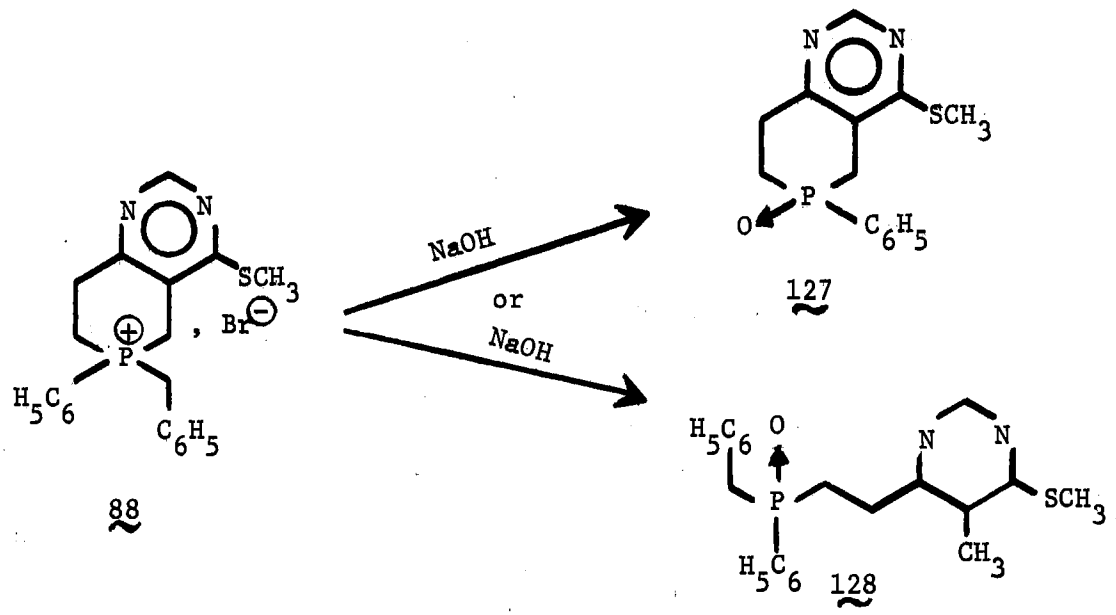


82

126

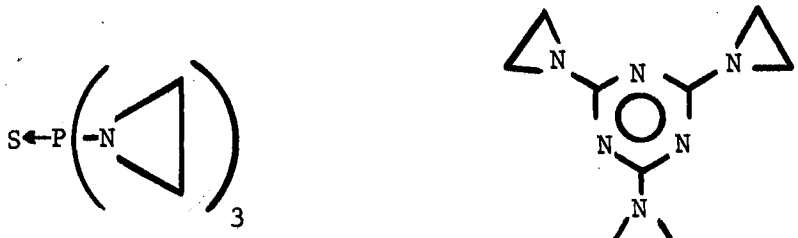
of the phosphorino[4,3-d]pyrimidines. Biological activities of nucleosides and parent pyrimidines and purines often differ markedly in activity.[13]

Since the resolution of (+)-88 has been affected, the groundwork has been laid for a possible stereochemical investigation of the base catalyzed cleavage of (+)-88. Of particular interest would be the position and product of cleavage, 127 or 128 since there are two "benzylic" positions in 88, and whether reaction with retention, inversion, or racemization occurs. A molecular orbital calculation on 88 might be of use in predicting the most stable anion and hence the direction of cleavage. The direction of cathodic reduction would also be of interest in view of the known stereochemistry, i.e., cleavage with retention of configuration. The group cleaved off is the one which would form the most stable anion.



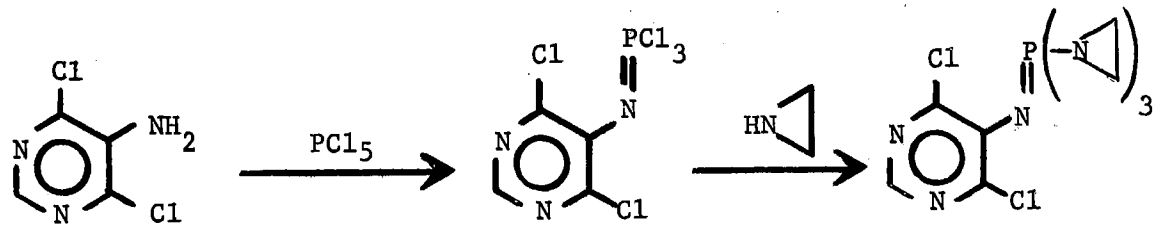
88 127 128

In light of the importance of tris(azaridinyl)phosphine sulfide (4) and 2,4,6-tris(azaridinyl)-s-triazine (129) in cancer chemotherapy, the



4 129

following reaction sequence[142] should be of immediate interest and obvious applicability to aminopyrimidine 75.



The synthetic methods for the preparation of phenylphosphorino-[4,3-*d*]pyrimidines described herein provide a basic starting point for the synthesis of many derivatives of this previously unknown family. Moreover, the phosphorino[4,3-*d*]pyrimidines prepared are probably of sufficient chemical and structural variations to allow an initial evaluation of the gross overall chemotherapeutic value of this family of heterocycles. The formation of phosphonium salt 90 is of particular significance in view of the success achieved in the resolution of (+)-88 via its D(-,-)-HDBT salt. This method of resolution may be generally applicable to the resolution of other members of this prochiral family. It is anticipated that the future chemistry and biological testing results of these phosphorus pyrimidines will be both interesting and fruitful.

CHAPTER III

EXPERIMENTAL[a-h]

Preparation of Bis(2-cyanoethyl)phenylphosphine (91). Phenylphosphine was cyanoethylated by a modification of a procedure by Rauhut and coworkers[145,188] as follows: Acrylonitrile (50.0 g., 0.94 mole was

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[a]Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

[b]Proton magnetic resonance spectra were taken on a Varian A-60 high resolution spectrometer and a Varian XL-100 high resolution spectrometer.

[c]^{31}P magnetic resonance spectra were taken on a Varian XL-100 high resolution spectrometer with a time averaging computer accessory (C-1024).

[d]Infrared spectra were taken on a Beckman IR-5A spectrophotometer with samples as films on sodium chloride or in potassium bromide pellets.

[e]Low resolution mass spectra were obtained on a LKB-9000 prototype, magnetic sector, GLC mass spectrometer, Biochemistry Department, Oklahoma State University.

[f]Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

[g]Rotations of optically active compounds were taken on a Rudolph polarimeter (O.C. Rudolph and Sons, Inc., Model 80, No. 722) which a circular scale reading to 0.001°, via a 2 dm. polarimeter cell.

[h]Commercially available reagents were used without further purification unless otherwise stated. Potassium t-butoxide was obtained from MSA Research Corp. and phenylphosphine was obtained from Pressure Chemical Co. and Stream Chemical Co.

added dropwise to a mechanically stirred mixture of phenylphosphine (50.0 g., 0.45 mole), acetonitrile (50 ml.) and aqueous potassium hydroxide (10 ml., 10 N). The rate of addition of acrylonitrile was controlled so that the temperature of the reaction mixture never exceeded 35°C. The reaction was moderated by cooling in an ice bath. After the addition was complete (ca. 45 min.), the reaction mixture was stirred for 2.5 hr at room temperature. The reaction mixture was diluted with 100 ml of ethanol and chilled to 0°C. The product started to crystallize, and the mixture was allowed to stand until crystallization was complete. The mixture was filtered and the product washed with 200 ml. of cold ethanol, the washings being combined with the filtrate. The product was dried at 60°/2 mm (80.5 g., m.p. 71-74°, 82%.) A product of higher quality (m.p. 73-74°, lit.[145,188] 73-74°) was obtained by recrystallization from ethanol. However, the crude material was sufficient for the following preparations. An additional 8.1 g. (9%) of 91 was recovered from the combined filtrate and washings after concentration. IR and NMR analysis (Plates I, II) support the proposed structure. The 40.5 MHz NMR spectrum (10% in $HCCl_3$) showed ^{31}P absorption at δ + 21.4 relative to H_3PO_4.

Preparation of 4-Amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile (92). The procedure of Welcher, Johnson, and Wystrach[232] was modified in the following manner. Bis(2-cyanoethyl)phenylphosphine (91) (21.6 g., 0.1 mole) dissolved in 250 ml. of dry toluene was added dropwise to a mechanically stirred, boiling solution of potassium t-butoxide (15 g., 0.13 mole) and 100 ml. of toluene. The mixture thickened when the addition was approximately 2/3 complete. After all of 91 had been added, the reaction mixture was stirred and boiled for an addi-

tional 3 hr. The mixture was subsequently cooled, hydrolyzed with 150 ml. of H_2O, and stirred for 30 min. while 92 precipitated. The mixture was filtered to yield 18.7 g. of 92 (dried at 78°/1 mm., m.p. 134.5-137°, 87%). Further purification of 92 was affected by recrystallization from C_2H_5OH/H_2O (m.p. 137.5-140°, lit.[232] 139.5-140°). The filtrate was separated, and the aqueous layer was extracted with two 50-ml portions of $HCCl_3$. The combined $HCCl_3$ extracts and toluene layer were evaporated to dryness, and the residue was recrystallized from C_2H_5OH/H_2O to yield an additional 1.5 g. of 92 (7%, total yield 94%). IR, NMR, and mass spectral analysis (Plates III, IV, V) support the proposed structure. The ^{31}P magnetic resonance absorption occurred at δ + 46.9 (5% in $HCCl_3$) relative to 85% H_3PO_4.

Preparation of 2-Aminocyclopentenecarbonitrile (93). The procedure used was essentially a modification of Thompson's[227] method. A solution of adiponitrile (21.6 g., 0.2 mole) in 300 ml. of dry toluene was added dropwise to a mechanically stirred, boiling solution of potassium t-butoxide (25.0 g., 0.223 mole) in 100 ml. of dry toluene. After the addition was complete (ca. 1 hr.), the mixture was stirred and boiled an additional 2 hours. The mixture was then cooled, hydrolyzed with 150 ml. of H_2O and stirred for 30 min. while the solid product separated. The heterogeneous mixture was filtered, and the dried residue was recrystallized from hot $HCCl_3$ to give 16 g. of 93 (m.p. 145-47°, lit.[227] 147-148°, 74%). IR and NMR analysis (Plates VI and VII) support the proposed structure of 93.

Preparation of 2-Aminocyclohexenecarbonitrile (94). A solution of pimelonitrile (24.4 g., 0.2 mole) in 250 ml. of dry toluene was added dropwise to a mechanically stirred, boiling solution of potassium t-

butoxide (25.0 g., 0.223 mole) in 100 ml. of dry toluene. After the addition was complete (ca. 45 min.), the mixture was stirred and boiled an additional 4 hours. The mixture was then cooled, treated with 150 ml. of H_2O, and stirred at room temperature for 30 minutes. A crystalline product did not separate. The layers were then separated, the aqueous layer was extracted twice with 100 ml. portions of $HCCl_3$, and the extracts were combined with the organic layer. Concentration of the organic layer upon the rotary evaporator gave a dark oil which crystallized upon standing. Sublimation (85°/0.1 mm.) of the resulting solid gave 94 as a clean white solid (m.p. 96-98.5° lit.[235] 98-99°, 18.0 g., 72%). The product is a quite volatile solid having an odor of burnt sugar. IR and NMR analysis (Plates VIII and IX) support the proposed structure.

Preparation of 2,4-Diamino-5,6,7,8-tetrahydro-6-phenylphosphorino-[4,3-d]pyrimidine (74). A mixture of the 2-enaminonitrile 92 (10.8 g., 0.05 mole), guanidine hydrochloride (4.8 g., 0.05 mole), potassium t-butoxide (10.8 g., 0.096 mole) and 2-ethoxyethanol (150 ml., freshly distilled) was boiled for twenty hours. After cooling, the reaction mixture was filtered to remove precipitated inorganic salts. The filtrate was diluted (150 ml. of H_2O) and allowed to stand until precipitation was complete. Filtration removed unreacted 2-enamino nitrile 92 (5.1 g., 47%). The filtrate was evaporated to near dryness and the precipitate that formed was suspended in water. Filtration gave the diamino pyrimidine 74 (4.5 g., 34%). Sublimation of the solid at 190-200°/0.003-0.001 mm. yielded an analytical sample of 74 (m.p. 221-222.5°). IR, NMR, and mass spectral analysis (Plates X, XI, and XII) support the proposed structure of 74.

Anal. Calcd. for $C_{13}H_{15}N_4P$: N, 21.71; P, 12.01.

Found: N, 21.64; P, 11.91.

The 40.5 MHz NMR spectrum of 74 showed ^{31}P absorption at δ + 51.9 (5% DMSO) relative to H_3PO_4.

Preparation of 4-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino-[4,3-d]pyrimidine (75)--Method A. A mixture of the 2-enamino nitrile 92 (10.8 g., 0.05 mole), formamidine acetate (10.4 g., 0.1 mole), glacial acetic acid (2.0 g., 0.033 mole) and 2-ethoxyethanol (100 ml., freshly distilled) was boiled for 20 hours. After cooling, the reaction mixture was filtered. The filtrate was diluted with an equal volume of H_2O and allowed to crystallize overnight. Subsequent filtration of the mixture gave unchange 92 and a solution of the product. The solution was evaporated to an oil, triturated with $HCCl_3$ (ca. 50 ml.), and filtered to yield crude 75. Sublimation of the crude material (190-200°/0.001-0.0005 mm.) gave pure 75 (0.9 g., 7%, m.p. 196-97°). IR, NMR, and mass spectral analysis (Plates XIII, XIV, and XV) support the proposed structure of 75. The 40.5 MHz NMR spectrum (5% in DMSO) showed ^{31}P absorption at δ + 44.03 relative to 85% H_3PO_4.

Anal. Calcd. for $C_{13}H_{14}N_3P$: N, 17.38; P, 12.78.

Found: N, 17.03; P, 12.59.

Preparation of 4-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino-[4,3-d]pyrimidine (75)--Method B. A mixture of the 2-enamino nitrile 92 (10.8 g., 0.05 mole), 80 ml. of triethyl orthoformate, and 80 ml. of acetic anhydride was boiled for 1 hour. The solution of ethoxymethylene derivative 95 was concentrated to a residual oil by distillation under vacuum (70°, 0.1 mm.). Anhydrous ethanol saturated with anhydrous ammon-

ia (C_2H_5OH/NH_3) (200 ml., saturated at 0°) was added to the residue and the solution was stirred overnight. (After approximately 5 hours of stirring, a precipitate formed.) The mixture was filtered and the residue was washed with 25 ml. of cold C_2H_5OH on the filter to yield 6.5 g. (m.p. 194-97°) of 75. The filtrate and washings were combined and evaporated to dryness on the rotary evaporator. Trituration of the resulting oil with acetone followed by filtration gave an additional 0.8 g. (m.p. 196-97°) of 75 for a total yield of 7.3 g. (66%) of 75, identical in every way to that prepared previously.

Preparation of 2,4-Diamino-5,6,7,8-tetrahydrouquinazoline (84). A mixture of the 2-amino nitrile 94 (12.2 g., 0.1 mole), guanidine hydrochloride (9.55 g., 0.1 mole), potassium t-butoxide (22.0 g., 0.2 mole), and 2-ethoxyethanol (250 ml., freshly distilled) was boiled for twenty hours. The cooled reaction mixture was filtered, diluted (250 ml. of H_2O), and allowed to crystallize (overnight). The mixture was filtered to yield 6.8 g. of tan needles, a mixture of starting material 94 and product 84. Sublimation of this mixture (70-80°/0.1 mm.) yielded a sublimate of 1.7 g. of starting material 94 (m.p. 96-98.5° s.t., lit.[235] 98-99°) and a residue of 5.1 g. of 84 (m.p. 244-245°, lit.[168] m.p. 243-245°). An additional 2.2 g. of 84 was obtained by evaporation of the filtrate to an oil which was triturated with acetone. The two fractions of 84 were combined and recrystallized (with the aid of Nuchar from C_2H_5OH/H_2O to yield 6.1 g. of 84 (m.p. 244-46°, 37%). Infrared absorption maxima (Plate XVI) agree with literature values[168] and NMR and mass spectra analysis (Plates XVII and XVIII) also support the proposed structure of 84.

Preparation of 2,4-Diamino-6,7-dihydro-5H-cyclopentapyrimidine (85). A mixture of the 2-amino nitrile 93 (21.6 g., 0.2 mole), guanidine hydrochloride (19.1 g., 0.2 mole), sodium methoxide (21.6 g., 0.4 mole), and 2-ethoxyethanol (300 ml., freshly distilled) was boiled for 20 hours. The cooled reaction mixture was filtered, diluted (300 ml. of water), and allowed to crystallize (ca. 2 hr.). The mixture was filtered to yield 12.2 g. of brown solid. This solid was triturated with warm $HCCl_3$ and filtered. The residue was recrystallized (with the aid of Nuchar) from hot C_2H_5OH/H_2O to yield 9.0 g. of 85 (m.p. 231-232.5°, lit.[168] m.p. 231-232°, 30%). Infrared absorption maxima (Plate XIX) agree with literature values,[168] and NMR and mass spectral analysis (Plates XX and XXI) also support the proposed structure of 85.

Preparation of 4-Amino-2-methylamino-5,6,7,8-tetrahydroquinazoline (86). A mixture of 2-amino nitrile 94 (12.2 g., 0.1 mole), methylguanidine sulfate (17.1 g., 0.1 mole), sodium methoxide (16.2 g., 0.3 mole) and 2-ethoxyethanol (300 ml., freshly distilled) was boiled for 20 hours. The cooled reaction mixture was filtered, diluted (300 ml. of H_2O), and allowed to crystallize (overnight). The mixture was filtered, and the filtrate (the crystals were unreacted 94) was concentrated (ca. 75 ml.) and diluted (300 ml. H_2O). After crystallization was complete, the mixture was filtered to yield 6.0 g. of tan crystals (m.p. 75-160°). Upon recrystallization from C_2H_5OH/H_2O the melting range narrowed (m.p. 149-190°). This product was further purified by sublimation (100°/0.1 mm.), which left a residue of 3.0 g. (m.p. 197-201°). A second recrystallization gave 2.2 g. of 86 (m.p. 202.5-203.5°, lit.[168] 204-205°, 13%). IR, NMR, and mass spectral analysis (Plates XXII, XXIII, XXIV) support the proposed structure of 86.

Preparation of 4-Amino-2-cyanoamino-5,6,7,8-tetrahydroquinazoline (87) (with base catalysis). A mixture of the 2-enamino nitrile 94 (12.2 g., 0.1 mole), N-cyanoguanidine (8.4 g., 0.1 mole), potassium t-butoxide, and 2-ethoxyethanol (125 ml., freshly distilled) was boiled for 20 hours. The cooled reaction mixture was filtered, diluted with an equal volume of H_2O and allowed to crystallize (ca. 2 hr.). Filtration of the mixture gave unreacted 94 and a solution of the product. The filtrate was decolorized with the aid of Nuchar and then acidified with 50% CH_3CO_2H. The precipitate which formed was filtered and dried to yield 87 (3.4 g., 18%, m.p. 334-336° decomp.). The product was characterized by comparison with an authentic sample as prepared previously.

Preparation of 4-Amino-2-cyanoamino-5,6,7,8-tetrahydroquinazoline (87) (without base catalysis). A mixture of the 2-enamino nitrile 94 (12.2 g., 0.1 mole), N-cyanoguanidine (8.4 g., 0.1 mole), and 2-ethoxyethanol (125 ml., freshly distilled) was boiled for 20 hours. The cooled reaction mixture was filtered and the residue recrystallized from hot C_2H_5OH/H_2O with the aid of Nuchar to yield pure 87 (3.0 g., 16%, m.p. 335-36° decomp.). IR, NMR, and mass spectral analysis (Plates XXV, XXVI, and XXVII) support the proposed structure of 87.

Anal. Calcd. for $C_9H_{11}N_5$: C, 57.14; H, 5.82; N, 37.04.

Found: C, 57.25; H, 5.77; N, 36.82.

Preparation of 5,6,7,8-Tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine-4-thiol (76). A mixture of the 2-amino nitrile 92 (9.0 g., 0.0416 mole) and triethyl orthoformate (100 ml.) was boiled for two hours. Volatiles were then removed by distillation under reduced pressure (70°, 0.05 mm.) to yield the crude ethoxymethylene derivative 95. Sodium hy-

drosulfide in anhydrous C_2H_5OH (300 ml., 1.5 N) was added and the mixture was boiled for 12 hours. The C_2H_5OH was removed by rotary evaporation and the residual solid was dissolved in hot H_2O (ca. 150 ml.). The aqueous solution was treated with decolorizing charcoal and filtered. The hot filtrate was acidified with glacial CH_3CO_2H (H_2S was evolved). The precipitated product was washed with water and ethanol, and dried. Two sublimations of the crude yellow product at 180-90°/0.002-0.001 mm. gave 3.1 g. (26%) of analytically pure phosphine 76 (m.p. 230-231.5°). IR, NMR, and mass spectral analysis (Plates XXVIII, XXIX, and XXX) support the proposed structure of 76. The 40.5 MHZNMR spectrum of 76 showed ^{31}P absorption at δ + 44.59 (5% in DMSO) relative to 85% H_3PO_4.

Anal. Calcd. for $C_{13}H_{13}N_2PS$: N, 10.77; P, 11.92; S, 12.31.

Found: N, 10.90; P, 11.80; S, 12.43.

In a second preparation, equal volumes of triethyl orthoformate and acetic anhydride were used. The yield of 76 was increased to 66% in what was otherwise an identical experiment.

Preparation of 5,6,7,8-Tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-d]pyrimidine 6-sulfide (77). Methyl iodide (0.79 g., 0.15 mole) was added to a solution of crude 125 (0.38 g., 0.13 mole) in 15 ml. of 10% NaOH. The mixture shaken vigorously and allowed to stand for 15 minutes while the product precipitated. The mixture was filtered and the residue was recrystallized from C_2H_5OH/H_2O. Subsequent sublimation (80-90°/0.05 mm.) of the residue gave 77 (0.28 g., m.p. 146-48° s.t., 71%). IR, NMR, and mass spectral analysis (Plates XXXI, XXXII, and XXXIII) support the proposed structure of 77.

Anal. Calcd. for $C_{14}H_{15}N_2PS_2$: N, 9.15; P, 10.14; S, 20.92.

Found: N, 9.02; P, 10.34; S, 20.76.

Preparation of 5,6,7,8-Tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-d]pyrimidine (78). Methyl iodide (3.0 g., 0.021 mole) was added to a solution of pyrimidine 76 (5.2 g., 0.02 mole) in 35 ml. of 2 N NaOH. The mixture was shaken vigorously and allowed to stand for 30 minutes while the product precipitated. The mixture was filtered, and the residue was washed with H_2O while on the filter and subsequently dried under vacuum (56°/1 mm.). The crude material was then sublimed (80-90°/0.1-.02 mm.) to yield 4.9 g. (89%) of pure 78, m.p. 96-98°. IR, NMR, and mass spectral analysis (Plates XXXIV, XXXV, XXXVI) support the proposed structure of 78. The 40.5 MH_3 NMR spectrum of 78 showed ^{31}P absorption at δ + 44.45 (5% in CH_3OH) relative to 85% H_3PO_4.

Anal. Calcd. for $C_{14}H_{15}N_2PS$: N, 10.22; P, 11.31; S, 11.68.

Found: N, 10.07; P, 11.16; S, 11.76.

Preparation of 3-Ethyl-5,6,7,8-tetrahydro-4(3H)-imino-6-phenylphosphorino[4,3-d]pyrimidine (79). A mixture of 2-enamino nitrile 92, 80 ml. of triethyl orthoformate and 80 ml. of acetic anhydride was boiled for 1 hr. Solution occurred as the mixture was heated. The color changed from straw to black during heating. The volatiles were then removed by vacuum distillation (60-80°/0.2-0.5 mm.) to yield the crude ethoxymethylene derivative 95 as a black oily residue. Anhydrous ethylamine (20 g.) in 200 ml. of absolute ethanol was added to crude 95 with stirring. After a short period of time (ca. 15 minutes), a large amount of precipitate formed. Stirring was continued overnight. The black reaction mixture was filtered, and the residue was washed on the

filter with 2 fifty-ml. portions of cold anhydrous ethanol to give 8.8 g. (65%, dried at 78°/1 mm.) of 79, as a clean white powder. Sublimation of this sample at 135-140°/0.0001-0.0005 mm. afforded an analytical sample, m.p. 147-149° s.t. IR, NMR, and mass spectral analysis (Plates XXXVII, XXXVIII, XXXIX) support the proposed structure of 79. The ^{31}P magnetic resonance absorption of 79 occurred at δ + 39.6 (5% in DMSO) from 85% H_3PO_4.

Anal. Calcd. for $C_{15}H_{18}N_3P$: N, 15.50; P, 11,44.

Found: N, 15.36; P, 11.22.

Preparation of 4-(Ethylamino)-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine (80). A mixture of the iminopyrimidine 79 (1 g.) and 50 ml. of NaOH (0.1 N) was boiled for 1 hour. The resulting oil was separated from the water and dissolved in $HCCl_3$. The $HCCl_3$ solution was evaporated to dryness on the rotary evaporator and the residual oil was dissolved in acetone. After two days, during which time no crystallization had occurred, the acetone solution was evaporated to dryness on the rotary evaporator to give 80 (0.7 g., 70%) as a crystalline solid. An analytical sample was obtained by sublimation at 135-140°/0.0001-0.0005 mm., m.p. 134-138° (s.t.) IR, NMR, and mass spectral analysis (Plates XL, XLI, XLII) support the proposed structure of 80. The ^{31}P magnetic resonance absorption of 80 occurred at δ + 44.74 (5% in DMSO) relative to 85% H_3PO_4.

Anal. Calcd. for $C_{15}H_{18}N_3P$: N, 15.50; P, 11.44.

Found: N, 15.45; P, 11.18.

Preparation of 4-(1-Ethoxyethylideneamino)-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile (120). A mixture of 2-enamino nitrile

92 (10.8 g., 0.05 mole), 80 ml. of triethyl orthoacetate, and 80 ml. of acetic anhydride was boiled for 4 hr. Solution occurred as the mixture was heated. The color changed very slowly from a light yellow to a dark amber. The volatiles were then removed by vacuum distillation (70°-80°/ 0.1-0.2 mm.) to yield crude 120 as a dark oil. Ethanol saturated with NH_3 (200 ml.) was added to crude 120, and the solution was stirred overnight. No crystallization occurred. The solvents were removed on the rotary evaporator and the resulting black oil was dissolved in 100 ml. of dry acetone and set aside. Solid material slowly precipitated during the next 3 days. The mixture was filtered, and the residue was dried and then sublimed to give pure 120 (10.4 g., 79%, m.p. 154-161°). NMR analysis (Plate XLIV) indicates that 120 is a mixture of syn and anti isomers. IR and mass spectral analysis (Plates XLIII and XLV) also support the proposed structure of 120.

Anal. Calcd. for $C_{16}H_{19}N_2OP$: N, 9.79; P, 10.84.

Found: N, 9.45; P, 10.69.

Preparation of 4-Oxo-1-phenyl-3-phosphorinanecarbonitrile dimethyl acetal 1-sulfide (99). A mixture of 2-enamino nitrile 92 (10.8 g., 0.05 mole), hydrochloric acid (20 ml., 12 M), water (20 ml.) and methanol (120 ml.) was boiled for 1 hr. The mixture was then evaporated to dryness on the rotary evaporator. Excess methanol was added during the evaporation. The residue was dissolved in methanol (120 ml.). The solution was then saturated with HCl gas and allowed to stand for 24 hr. at room temperature. The reaction was quenched by pouring the mixture into 300 ml. of ice water. The aqueous solution was made basic with 10% NaOH and then extracted twice with 75-ml. portions of $HCCl_3$ and twice

with 50-ml. portions of ethyl acetate. The organic extracts were combined, washed with 50 ml. of saturated NaCl, (followed by 50 ml. of H_2O), dried ($MgSO_4$) and evaporated to dryness upon the rotary evaporator. The resulting oil decomposed badly when attempts were made to vacuum distill the product. Therefore, the residual oil was dissolved in $HCCl_3$ (100 ml.) containing sulfur (1.6 g., 0.05 mole) and boiled for 1 hour. The solution was then concentrated to ca. 25 ml. and diluted with hexane to precipitate unreacted sulfur and some product. The precipitate was washed with CS_2 to remove excess sulfur. The hexane-chloroform solution was evaporated to dryness and the residue combined with the residue from the CS_2 washings. The combined residues, a mixture of the diastereomers of 99, were recrystallized from ethyl acetate/2-propanol to give 4.25 g. of mixed 99 (m.p. 145-168°, 29%). Subsequent recrystallization of the diastereomeric mixture from CH_3OH gave pure diastereomeric ketal 99 (m.p. 170-172°). IR and NMR (Plates XLVI and XLVII) support the proposed structure of 99.

Anal. Calcd. for $C_{14}H_{18}NO_2PS$: C, 56.95; H, 6.10; P, 10.51.

Found: C, 57.03; H, 6.26; P, 10.36.

Preparation of Bis(2-carbomethoxyethyl)phenylphosphine (96). Methyl acrylate (15.5 g., 0.18 mole) was added dropwise to a stirred mixture of phenylphosphine (10 g., 0.09 mole) potassium hydroxide (1 ml., 10 N), and acetonitrile (10 ml.). The reaction temperature was maintained between 20-35°C by controlled addition of phenylphosphine and/or by cooling in an ice bath. After addition was complete, the reaction mixture was stirred for 3 hr. at room temperature. The organic layer was separated, washed with two 15-ml. portions of saturated sodium chloride

solution, dried (anhydrous Na_2SO_4), and distilled to yield bis(2-carbomethoxyethyl)phenylphosphine (96) (b.p. 156-60/0.5-1.0 mm., lit.[4] 149-150°/1 mm., 13 g., 51%). IR and NMR (Plates XLVIII and XLIX) support the proposed structure of 96. The 40.5 MHz NMR spectrum of 96 (Plate L) shows ^{31}P absorption at δ + 20.62 (50% in CH_3OH) relative to 85% H_3PO_4.

Preparation of Methyl 4-oxo-1-phenyl-3-phosphorinanecarboxylate 1-Sulfide (98). A solution of bis(2-carbomethoxyethyl)phenylphosphine (96) (9.4 g., 0.033 mole) in 50 ml. of toluene was added dropwise to a boiling solution of sodium methoxide (1.8 g., 0.033 mole) in 150 ml. of toluene. After the reaction mixture had boiled for 2 hr., metallic sodium (0.7 g., 0.033 mole) was added and the mixture was stirred and boiled overnight. After cooling, the mixture was treated with 100 ml. of H_2O. The aqueous layer was separated and extracted three times with 50-ml. portions of $HCCl_3$, the extracts being combined with the organic layer. The combined organic layers were dried (Na_2SO_4) and evaporated to an oily residue. Attempts to distill this residue resulted in extensive decomposition; therefore, the residue was dissolved in 75 ml. of $HCCl_3$ and the solution was boiled for 1 hr. in the presence of sulfur (2.1 g., 0.066 mole). The $HCCl_3$ was removed via rotary evaporation, and the residue was recrystallized from CH_3OH/H_2O to yield 98 (4.2 g., m.p. 142-48°, 45%). IR, NMR, and mass spectral analysis (Plates LI, LII, and LIII) support the proposed structure of 98. The ^{31}P magnetic resonance absorption (Plate LIV) occurred as two broad multiplets at δ - 19.0 and δ - 19.3 (20% in CH_3OH) relative to 85% H_3PO_4.

Anal. Calcd. for $C_{13}H_{15}O_3PS$: C, 55.32; H, 5.32; P, 10.99; S, 11.34.

Found: C, 55.43; H, 5.42; P, 10.82; S, 11.15.

Preparation of 2-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino [4,3-d]pyrimidin-4-ol 6-Sulfide (81). The β-keto ester 98 (5.44 g., 0.02 mole), guanidine hydrochloride (1.91 g., 0.02 mole), and sodium methoxide (2.16 g., 0.04 mole) in 150 ml. of methanol were boiled for 3 hr. under an N_2 atmosphere. The reaction mixture was subsequently cooled and stirred at room temperature overnight. The mixture was then evaporated to dryness on the rotary evaporator, and the residue was dissolved in 150 ml. of H_2O. The pH of the solution was adjusted to pH 5-6 with glacial CH_3CO_2H, whereupon a small amount of H_2S was liberated. The precipitate which formed was filtered out and washed twice with H_2O while on the filter. The pink solid was recrystallized from DMSO and then dissolved in 10% NaOH and treated with Nuchar, the solution filtered, and the solid precipitated with 50% CH_3CO_2H. The solution and precipitation procedure was repeated two more times to give 81 (4 g., m.p. 243-246° s.t., 67%). IR, NMR, and mass spectral analysis (Plates LV, LVI, and LVII) support the proposed structure of 81. The ^{31}P magnetic resonance of 81 occurred at δ - 31.41 (5% in DMSO) relative to 85% H_3PO_4.

Anal. Calcd. for $C_{13}H_{14}N_3OPS$: N, 14.43; P, 10.66; S, 10.99.

Found: N, 14.54; P, 10.49; S, 11.06.

Preparation of 5,6,7,8-Tetrahydro-2-methyl-6-phenylphosphorino-[4,3-d]pyrimidin-4-ol 6-Sulfide (82). Acetamidine hydrochloride (0.95 g., 0.01 mole) and sodium methoxide (1.1 g., 0.02 mole) were mixed and stirred in 30 ml. of anhydrous ethanol for 10 min. at room temperature. The mixture was then filtered and added to a solution of β-keto ester 98 (2.2 g., 0.008 mole) in 50 ml. of ethanol. (The mixture turned orange in color.) The reaction mixture was boiled for 10 min. and then allowed

to stir overnight at room temperature. (The color darkened to black.) The mixture was subsequently boiled for 1 hr., cooled, and evaporated to dryness on the rotary evaporator. The brown oily residue was dissolved in 10% NaOH, treated with Nuchar, filtered, acidified with 50% CH_3CO_2H and filtered to yield 82 (1.2 g., m.p. 269-271° s.t., 52%). An analytical sample was prepared by thrice dissolving a sample of 82 in 6% NaOH, treating with Nuchar, and precipitating with 50% CH_3CO_2H. IR, NMR, and mass spectral analysis (Plates LVIII, LIX, and LX) support the proposed structure. The ^{31}P magnetic resonance absorption of 82 occurred at δ - 39.02 (2% in DMSO) relative to 85% H_3PO_4.

Anal. Calcd. for $C_{14}H_{15}N_2OPS$: N, 9.66; P, 10.69; S, 11.03.

Found: N, 9.57; P, 10.56; S, 11.08.

Preparation of 5,6,7,8-Tetrahydro-2-mercapto-6-phenylphosphorino-[4,3-d]pyrimidin-4-ol 6-Sulfide (83). Thiourea (2.2 g., 0.03 mole), sodium methoxide (1.5 g., 0.03 mole), and the β-keto ester 98 (5.6 g., 0.02 mole) were dissolved in 100 ml. of CH_3OH. The solution was then boiled for 4 hrs., cooled, and allowed to stir overnight. Precipitation occurred. The heterogeneous reaction mixture was evaporated to dryness on the rotary evaporator and the residue dissolved in 10% NaOH. The solution was treated with Nuchar and filtered, and the filtrate acidified with 50% CH_3CO_2H to precipitate crude 83. Purification was effected by dissolution in 10% NaOH, treatment with Nuchar, and precipitation with 20% CH_3CO_2H. This procedure was performed twice to give 4.8 g. (80%) of pure 83 (m.p. 344-346°). IR, NMR, and mass spectral analysis (Plates LXI, LXII, LXIII) support the proposed structure of 83. The ^{31}P magnetic resonance absorption of 83 occurred at δ - 39.0 (5% in DMSO) relative to

during the reaction. After ca. 10 min. of heating, AgBr precipitates as a gray solid. The mixture was cooled and filtered to give AgBr (0.78 g., 83%) and a rose-colored, CH_3OH solution of 89. The CH_3OH solution was concentrated on the rotary evaporator to ca. 20 ml., treated with 50 ml. of ethyl acetate, and allowed to stand overnight. The mixture was then filtered to give 1.9 g. of crude white 89 (m.p. 154-158°, $[\alpha]_D^{25°}$ = -46° (c = 0.2000 g./25 ml. methanol)). The filtrate was concentrated to ca. 20 ml., diluted with ethyl acetate, and filtered to give a second fraction of 89 as a rose-colored solid (1.0 g., m.p. 126-153°). Determination of the optical rotation of this fraction was not possible because of the color. The total yield was 2.9 g. (83%). The first fraction was leached with boiling 2-propanol to give a residue of 1.6 g., $[\alpha]_D^{25°}$ = -42° (c = 0.2000 g./25 ml., methanol). Several recrystallizations of the first fraction were required to produce a constant m.p. and specific rotation. The following data were recorded during the experiment.

No. of Recrystallizations	Solvent	Weight of Product	m.p.	$[\alpha]_D^{25°}$ Conc in CH_3OH)
Start	---	1.9 g	154-158(d)	-46° (0.01 g./ml.)
Leaching	i-C_3H_7OH	1.6 g	----	-42° (0.01 g./ml.)
1.	CH_3OH	1.05 g	164-165(d)	-18.5° (0.008 g./ml.)
2.	CH_3OH	.7 g	164.5-165°(d)	-14.16° (0.012 g./ml.)
3.	CH_3OH	.4 g	164.5-165°(d)	-14.23° (0.012 g./ml.)

The constancy of the melting point [m.p. 164.5-165°(d)] and specific

rotation ($[\alpha]_D^{25^\circ} = -14^\circ$) following successive recrystallizations strongly indicated that the separation of a pure diastereomer from the diastereomeric mixture had been achieved. The direction in which the rotation had changed, i.e., from negative toward positive, indicated that the diastereomer isolated was (+,-,-)-89.

The second fraction was recrystallized from CH_3OH/ethyl acetate to give 0.5 g. of material, $[\alpha]_D^{25^\circ} = -81^\circ$ (c = 0.2000 g./25 ml., methanol). Infrared and mass spectral analysis (Plates LXVII and LXVIII) support the proposed diastereomeric structure of (+,-,-)-89.

Anal. Calcd. for $C_{39}H_{35}N_2O_8PS$: C, 64.82; H, 4.84; N, 3.88; P, 4.29.

Found: C, 64.75; H, 4.87; N. 3.77; P, 4.17.

Metathesis of (+)-5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinia[4;3-d]pyrimidine Hydrogen D(-,-)-Dibenzoyltartrate-((+,-,-)-89) to (+)-1,2,3,4-Tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinia[4,3-d]pyrimidine Bromide ((+)-88). A solution of (+,-,-)-89 (0.375 g., 0.00052 moles) and NH_4Br (0.1 g., 0.001 mole) in 25 ml. of CH_3OH was boiled for 1 hr. and allowed to stand overnight. The CH_3OH was evaporated on the rotary evaporator and the residue extracted with 4 25-ml. portions of hot $HCCl_3$. The $HCCl_3$ extracts were evaporated to dryness on the rotary evaporator and the residue was recrystallized from CH_3OH/ethyl acetate to give 0.211 g. of enantiomer (+)-88 (m.p. 250-251°, 89%, $[\alpha]_D^{25^\circ} = +76^\circ$ (c = 0.2087 g./25 ml., methanol). The infrared spectrum of (+)-88 was identical to the infrared spectrum of racemic 88.

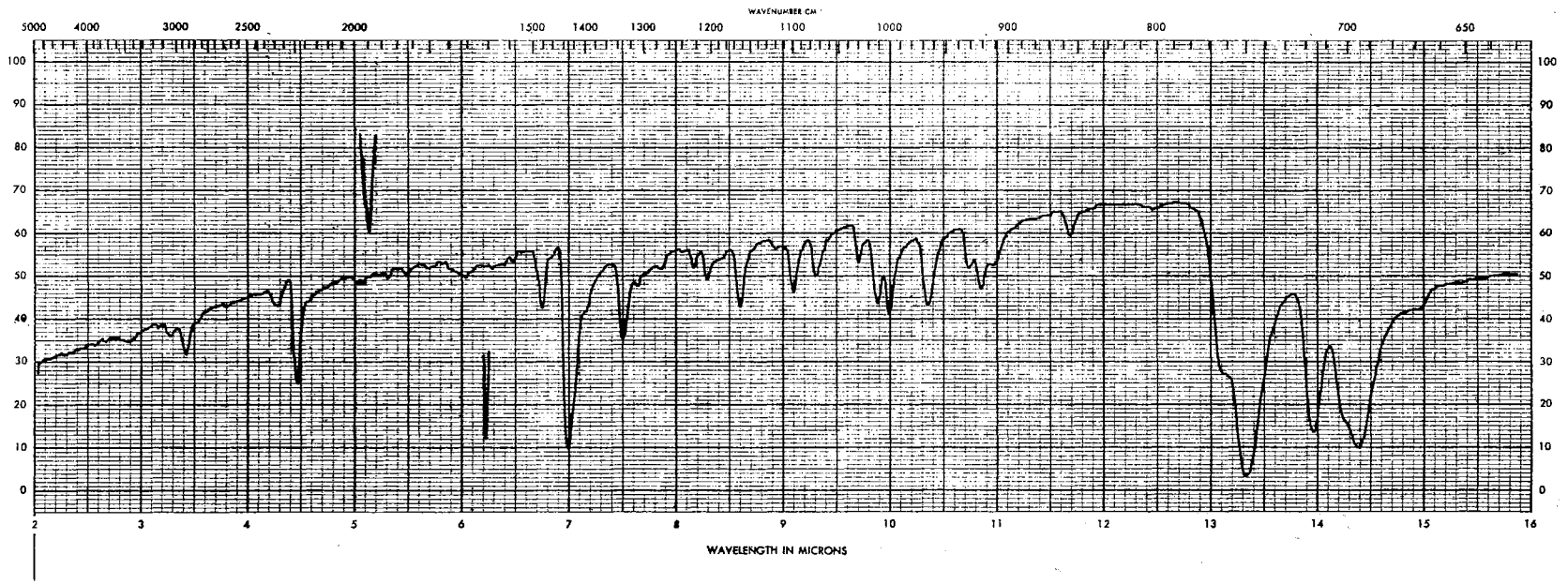
Preparation of 4-Amino-5,6,7,8-tetrahydro-6-benzyl-6-phenylphosphorinia[4,3-d]pyrimidine Bromide (90). Benzyl bromide (0.86/g., 0.01 mole) was added to a warm solution of pyrimidine 75 (1.22 g., 0.01 mole)

in 50 ml. of 2-propanol and the solution was boiled for 1 hr. The solution was subsequently concentrated to ca. 15 ml. on the rotary evaporator, diluted with 50 ml. of ethyl acetate, and allowed to stand overnight. The mixture filtered and the residue recrystallized from C_2H_5OH/ethyl acetate to give 1.6 g. of 90 (m.p. 248-251°, 79%). IR, NMR, and mass spectral analysis (Plates LXIX, LXX, LXXI) support the proposed structure of 90. The ^{31}P NMR spectrum (Plate LXXII) of 90 showed absorption at δ - 18.6 (10% in CH_3OH) relative to 85% H_3PO_4.

Anal. Calcd. for $C_{20}H_{21}BrN_3P$: N, 10.16; P, 7.49.

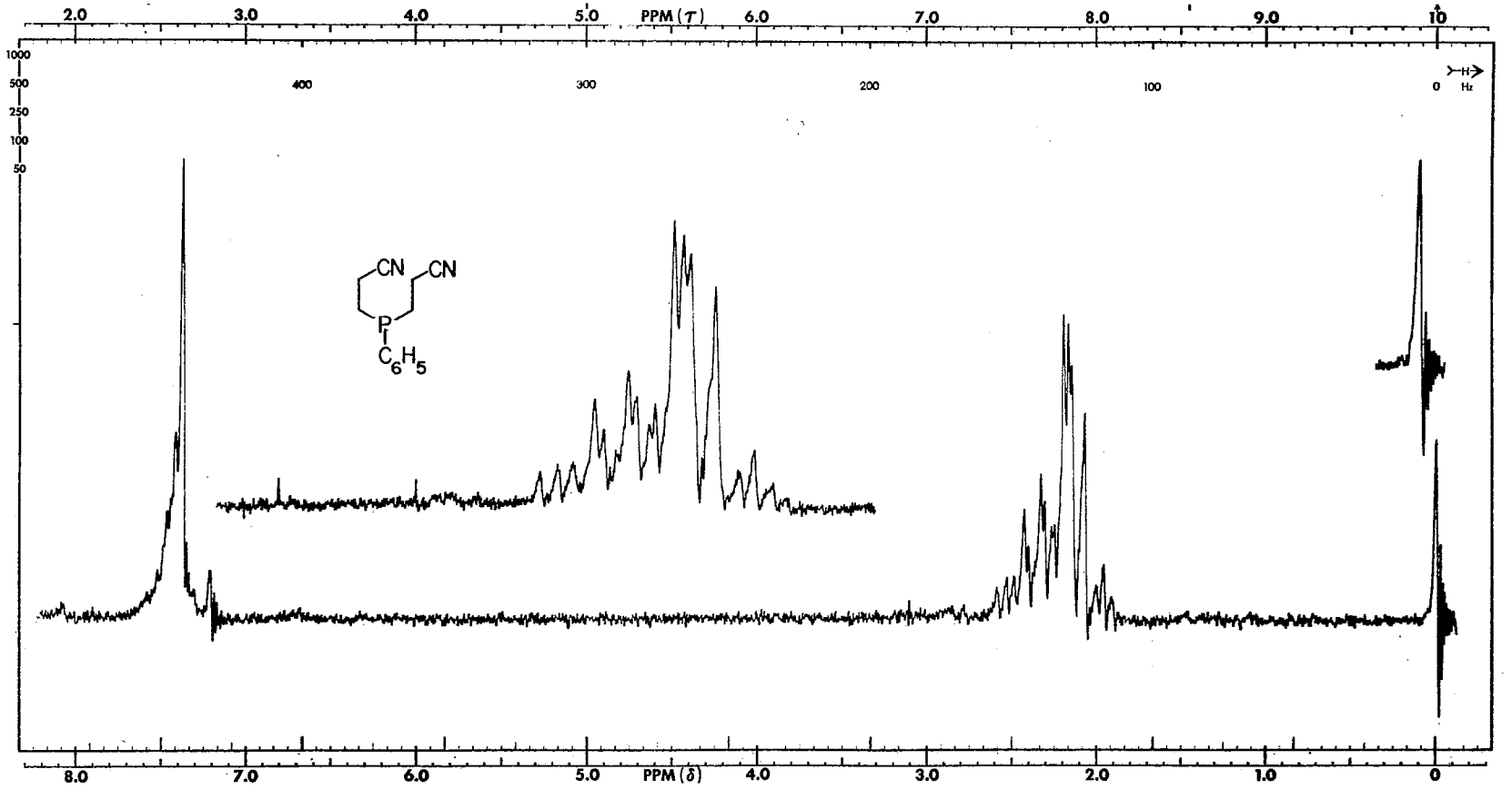
Found: N, 9.76; P, 7.22.

Plate I



Bis(cyanoethyl)phenyphosphine (91), KBr Pellet

Plate II

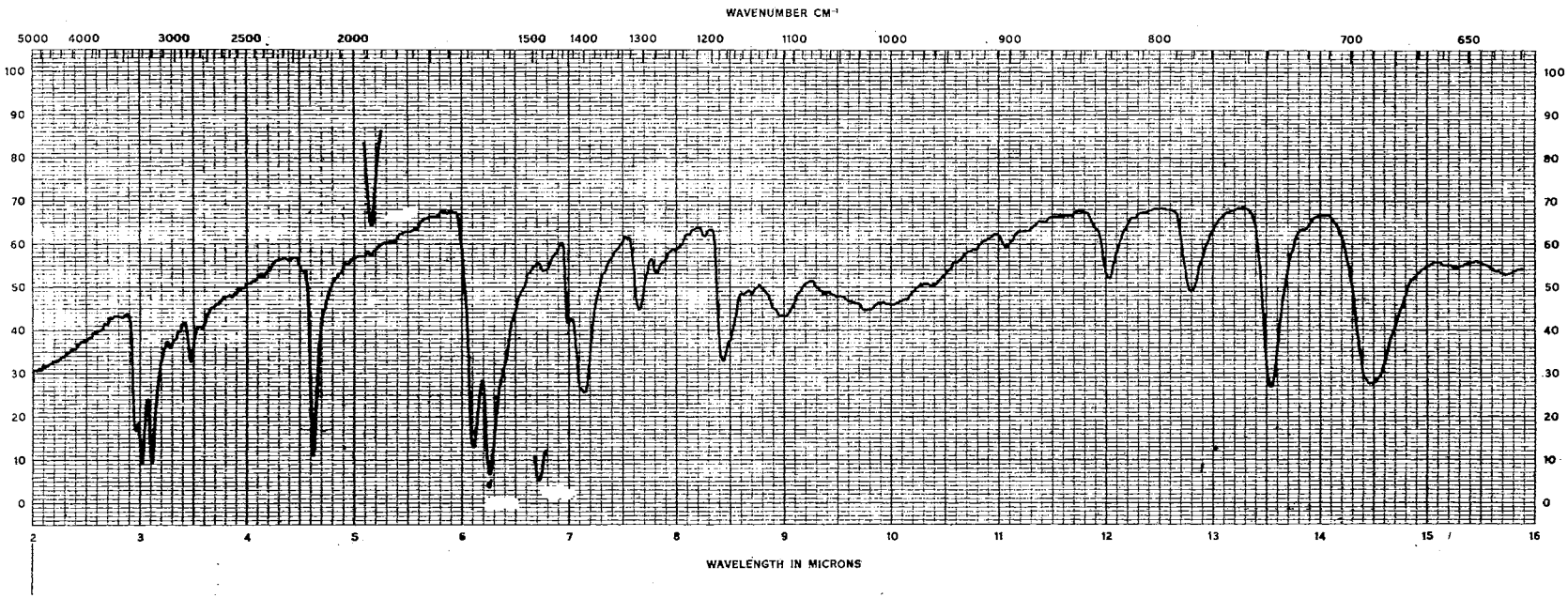


Bis(cyanoethyl)phenyphosphine (91)

Solvent. . . . . $DCCl_3$ O.F. . . . . 60 MHz F.B. . . . . 4 Hz R.F. . . . . 0.03 db

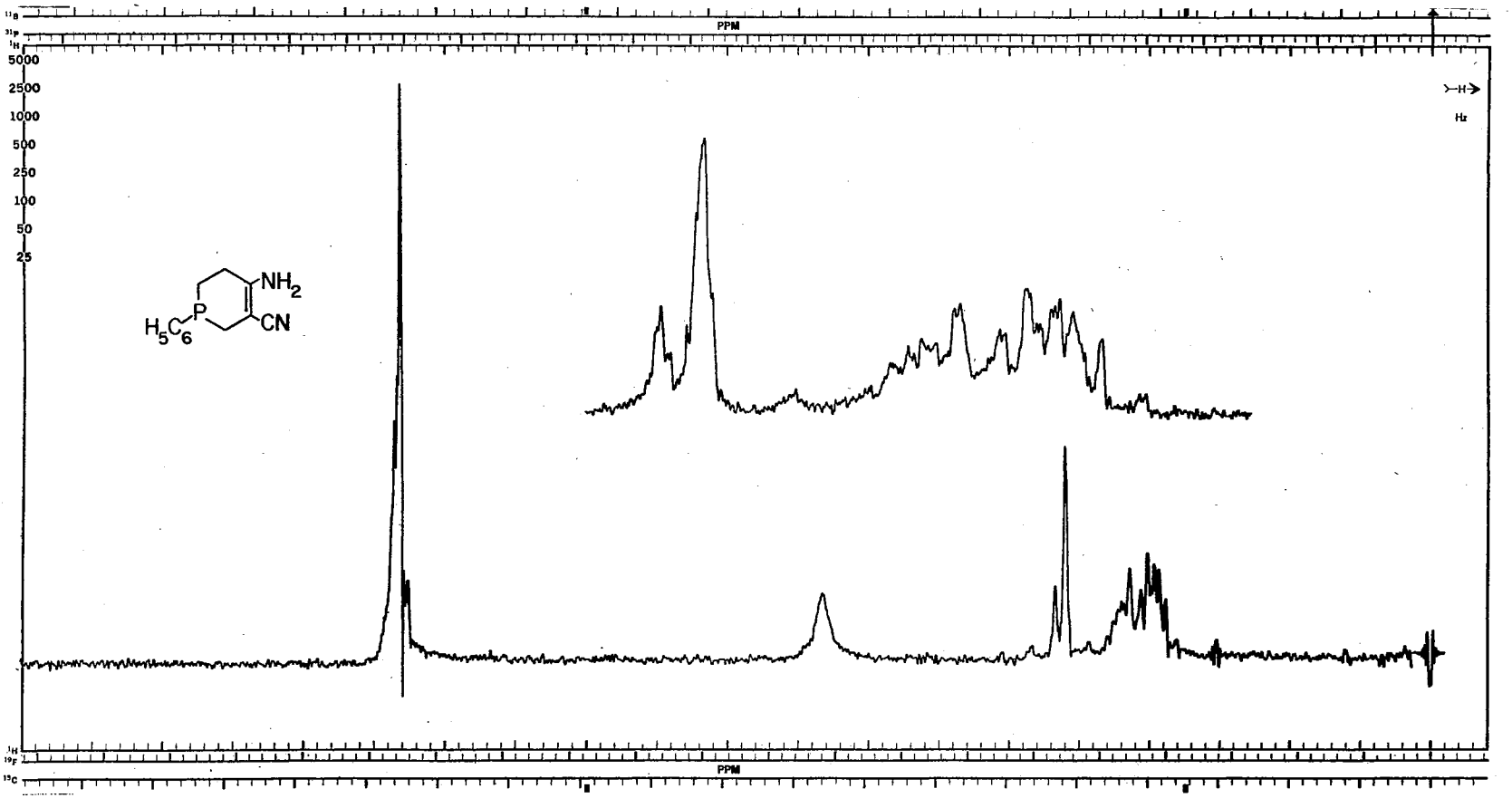
S.W. . . . . 500 Hz S.T. . . . . 250 sec S.O. . . . . 0 Hz S.A. 6.3

Plate III



4-Amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile (92), KBr Pellet

Plate IV

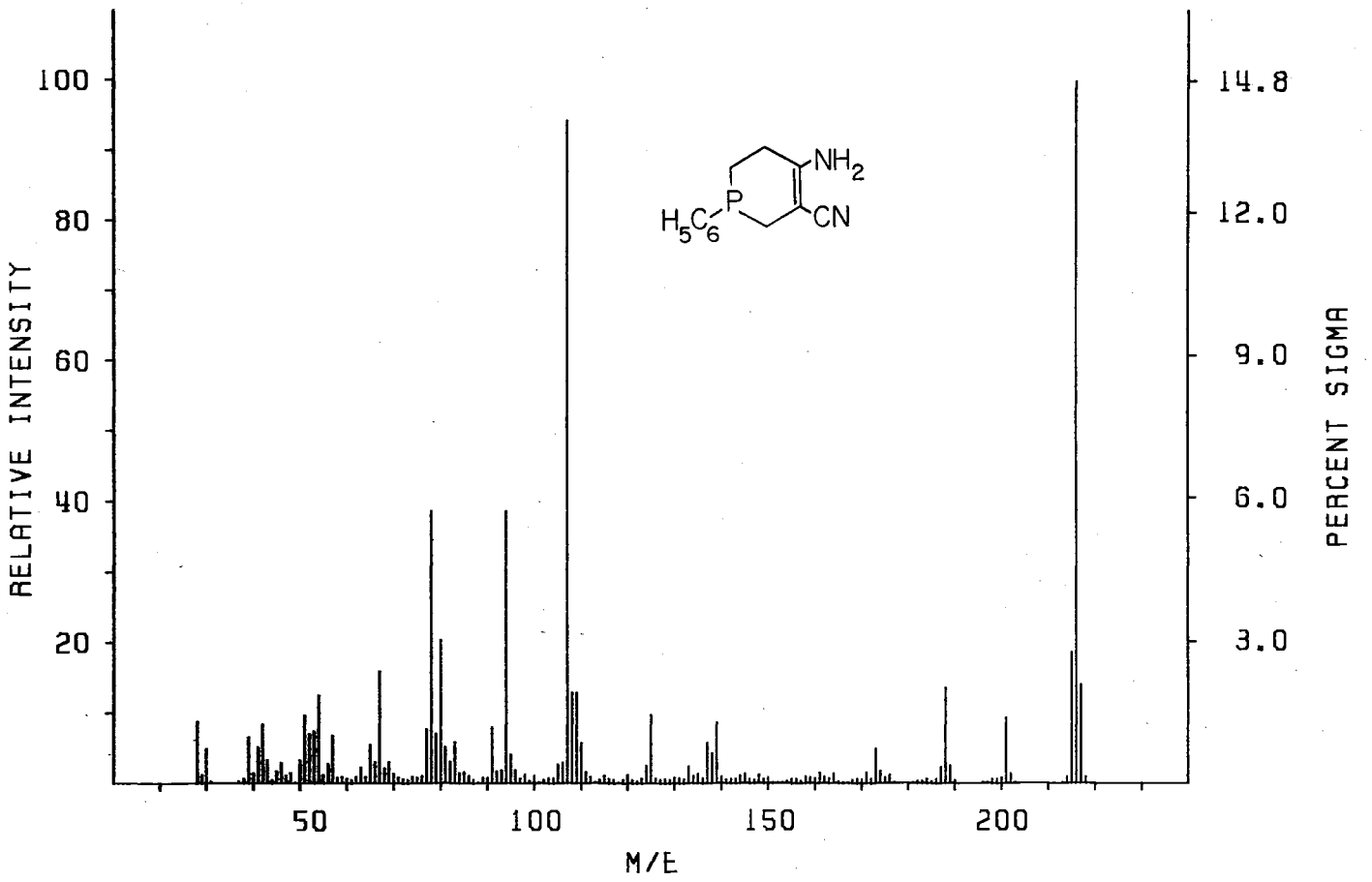


4-Amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile (92)

Solvent. . . $DCCl_3$ O.F. . . 100 MHz F.B. . . . . 2 Hz R.F. . . 60 db

S.W. . . . 1000 Hz S.T. . . 250 sec S.O. . . 83701 Hz S.A. . . 12.5 Lock. . . . HOMO

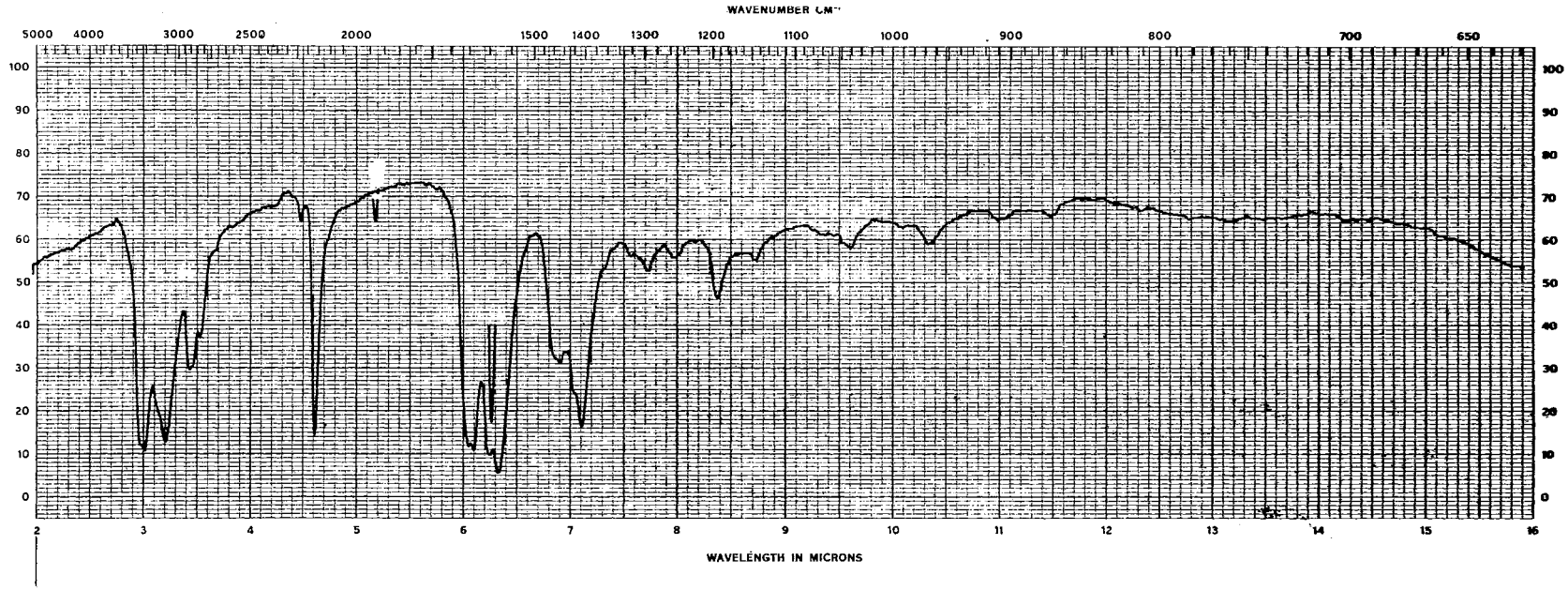
Plate V



4-Amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile (92)

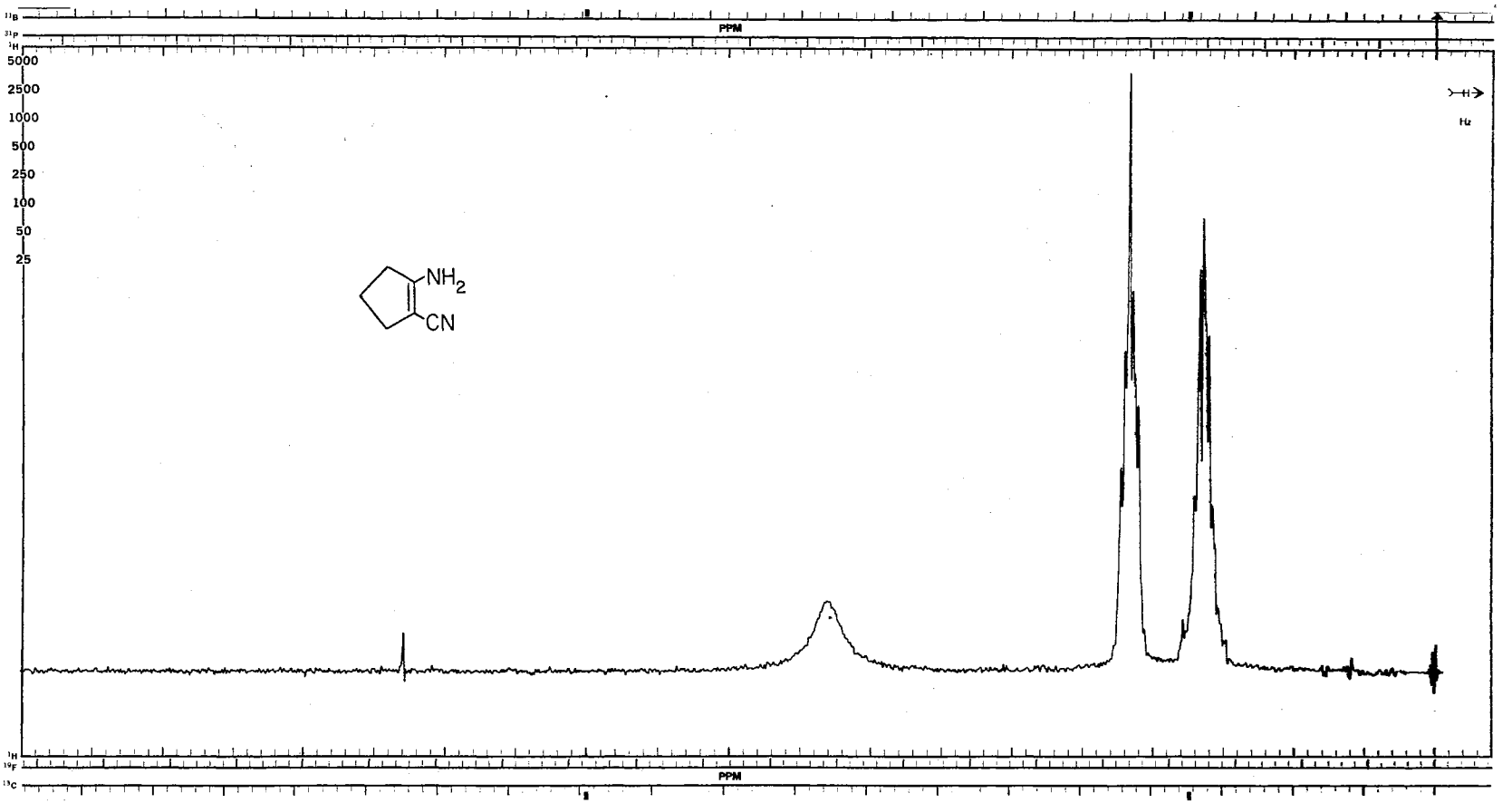
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....330° Probe °C....80°

Plate VI



2-Aminocyclopentene (93), KBr Pellet

Plate VII

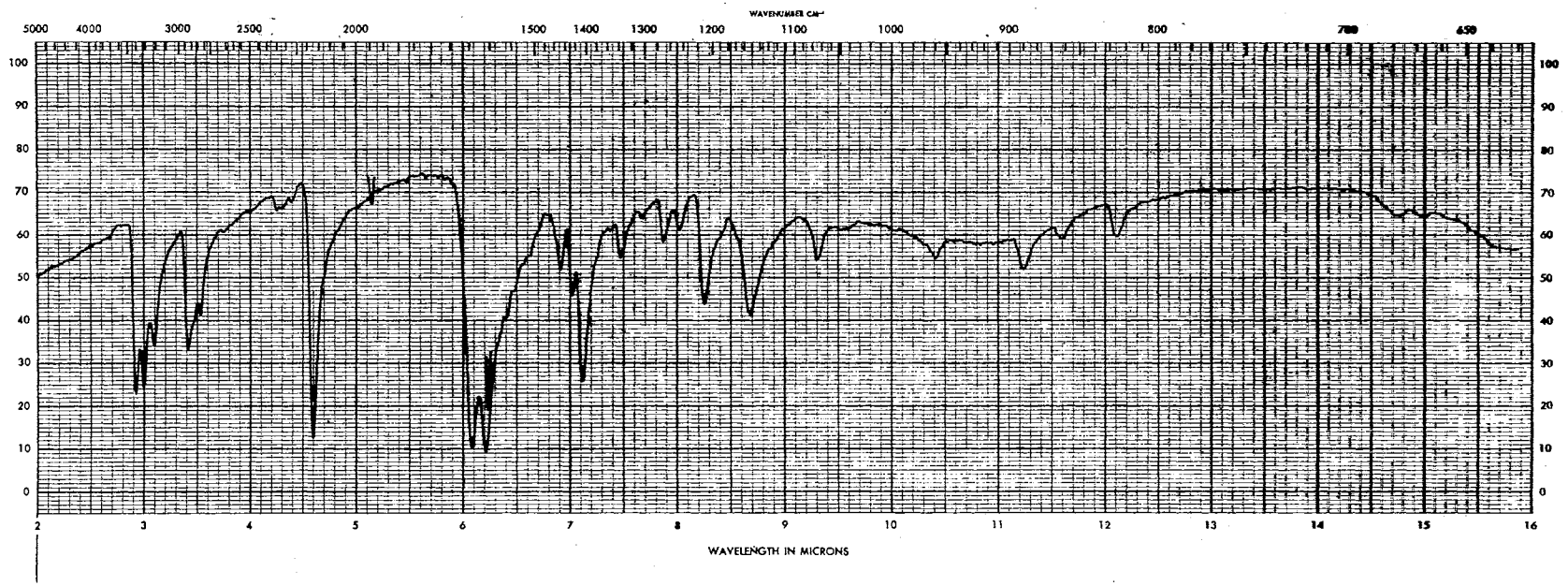


2-Aminocyclopentenecarbonitrile (93)

Solvent. . . $DCCl_3$ O.F. . . 100 MHz F.B. . . . . 1 Hz R.F. . . 60 db

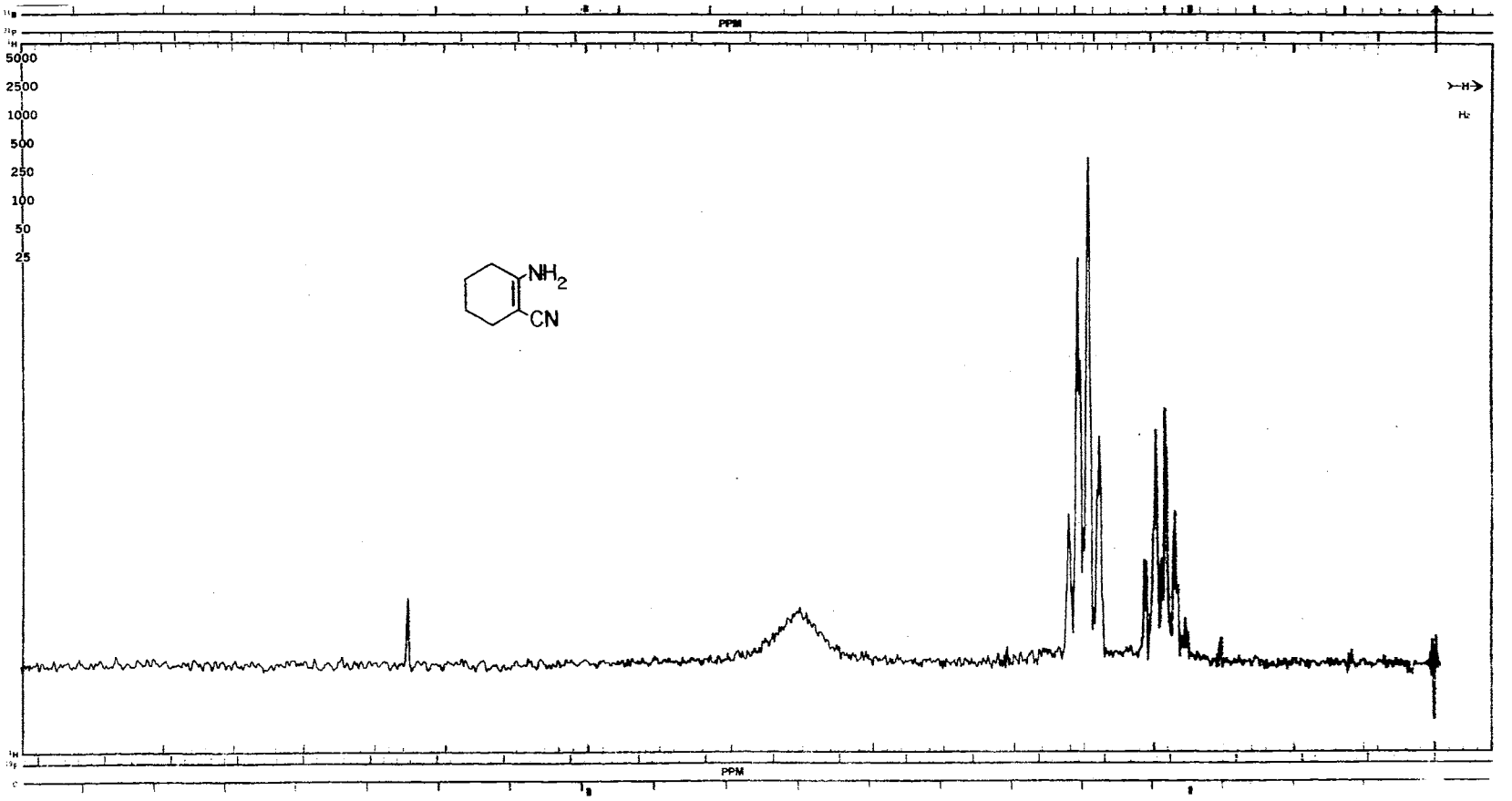
S.W. . . . 1000 Hz S.T. . . 500 sec S.O. . . 83701 Hz S.A. . . 12.5 Lock. . . . HOMO

Plate VIII



2-Aminocyclohexenecarbonitrile (94), KBr Pellet

Plate IX

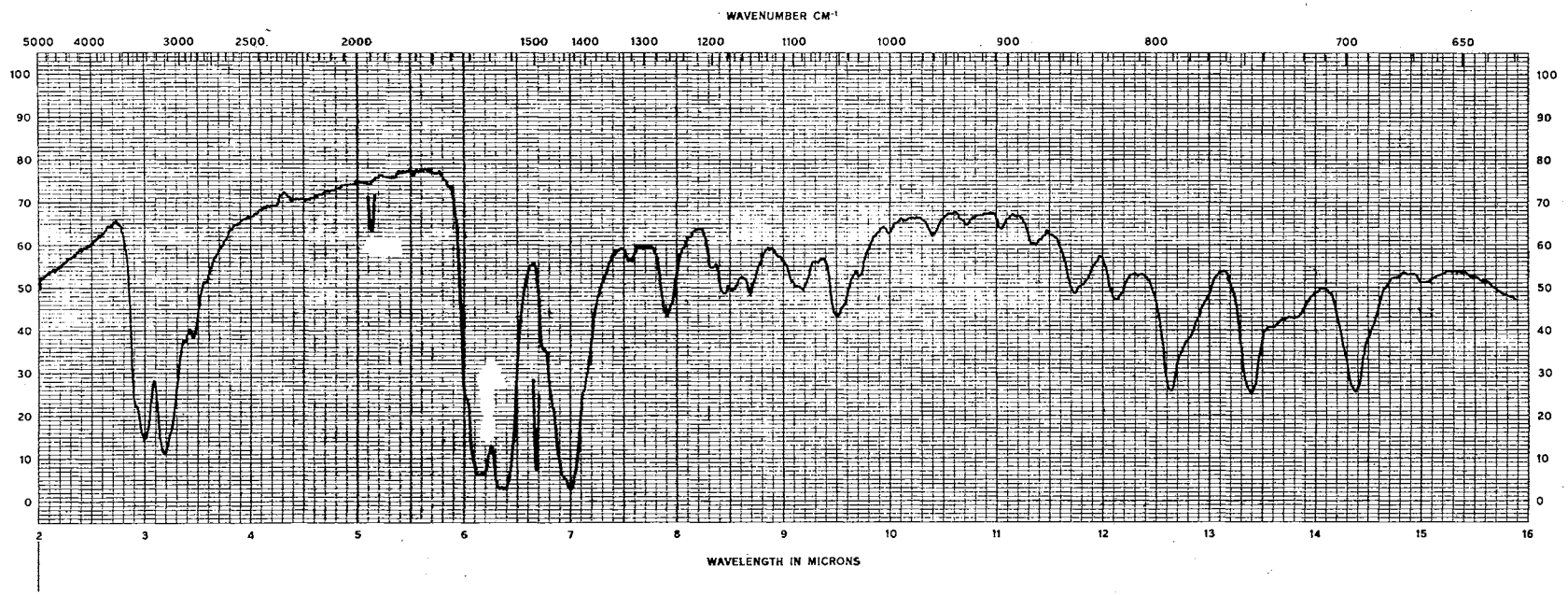


2-Aminocyclohexenecarbonitrile (94)

Solvent . . . $DCCl_3$ O.f. . . . 100 MHz F.B. . . . . 1 Hz R.F. . . 60 db

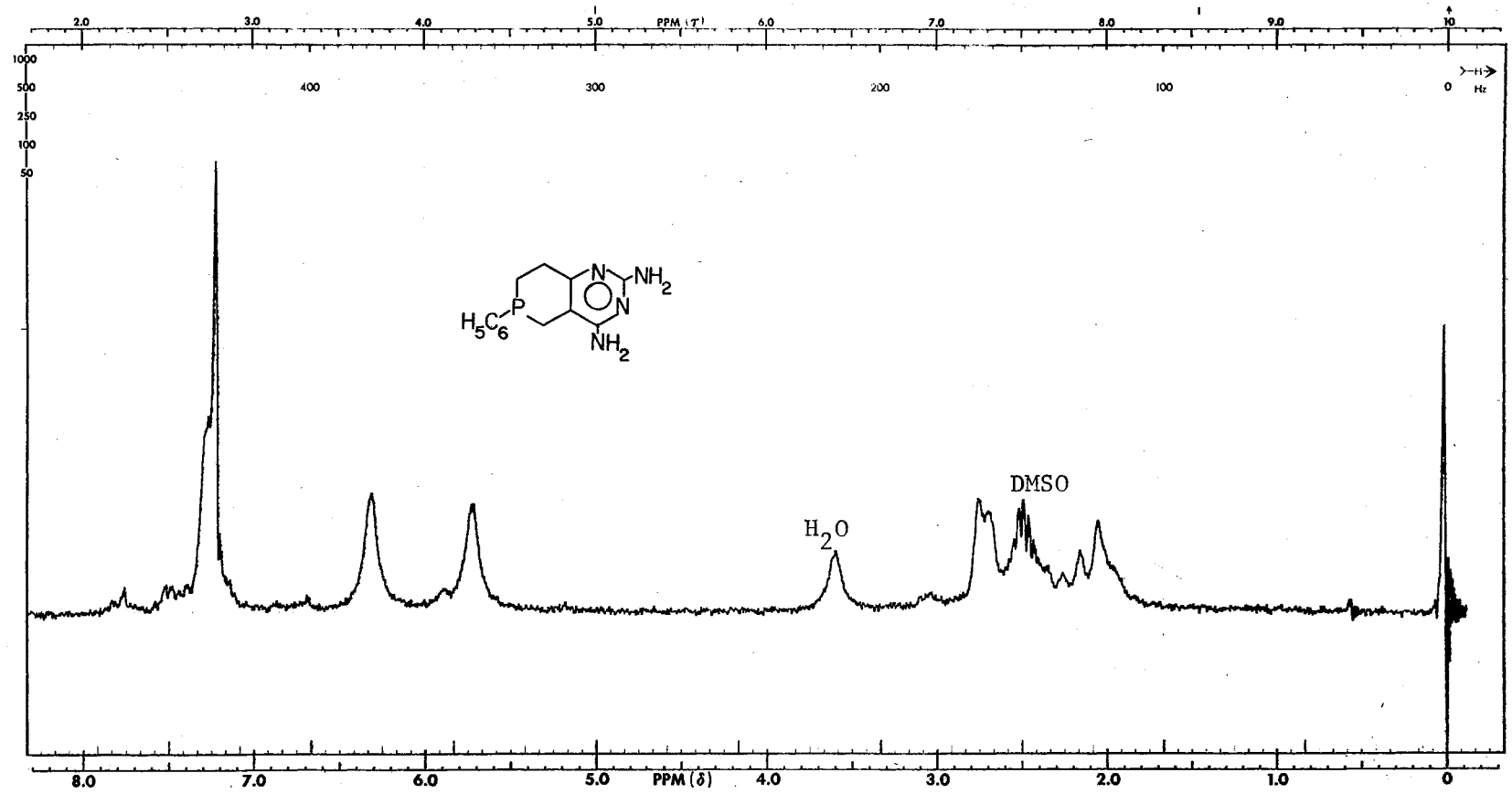
S.W. . . . 1000 Hz S.I. . . 500 sec S.O. . . 83701 Hz S.A. . . . 25 Lock . . . HOMO

Plate X



2,4-Diamino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine (74), KBr Pellet

Plate XI

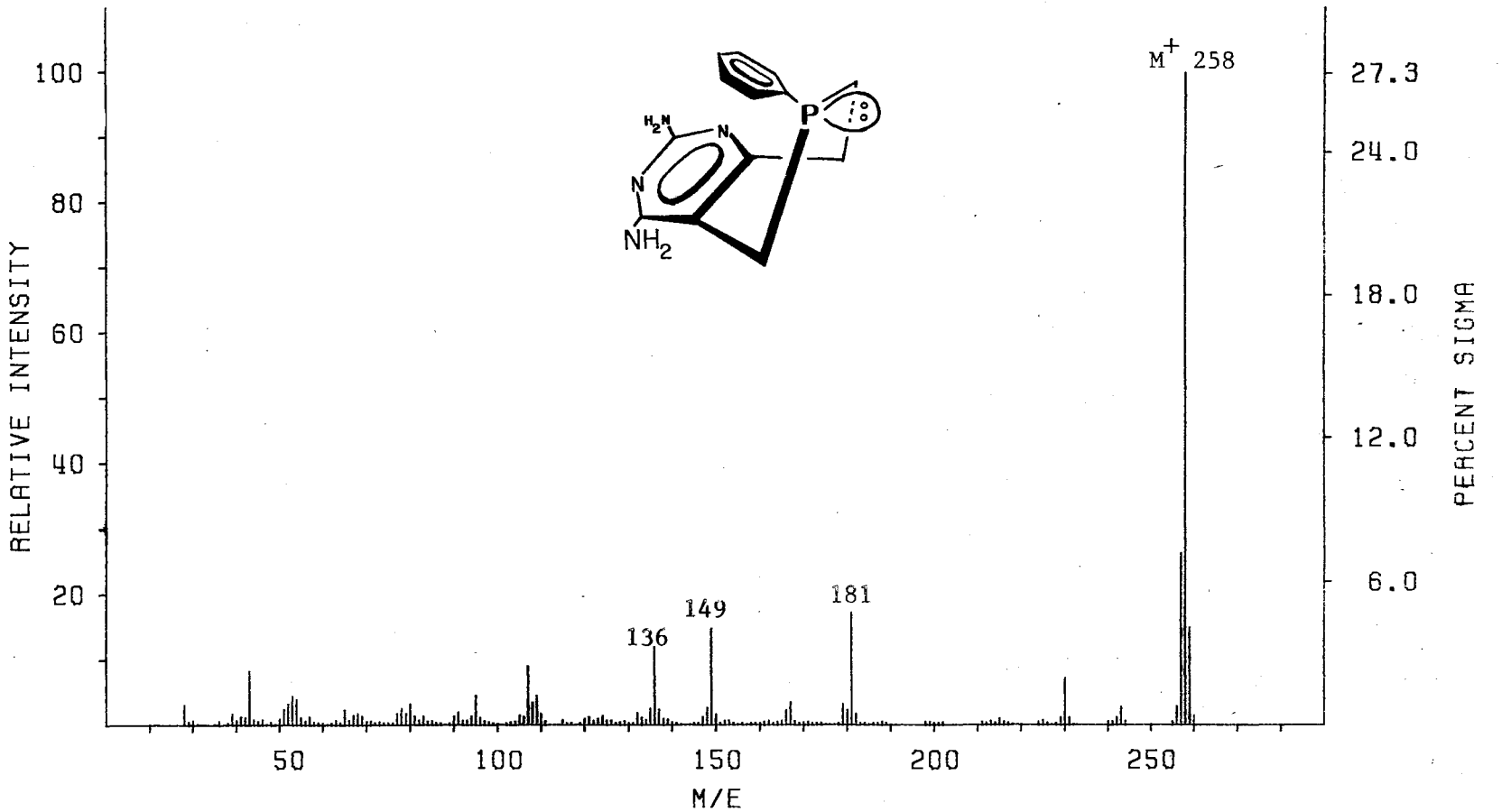


2,4-Diamino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine (74)

Solvent. . . . . DMSO-d_6 O.F. . . . . 60 MHz F.B. . . . . 4 Hz R.F. . . . . .05 db

S.W. . . . . 500 Hz S.T. . . . . 250 sec S.O. . . . . 0 Hz S.A. 6.3

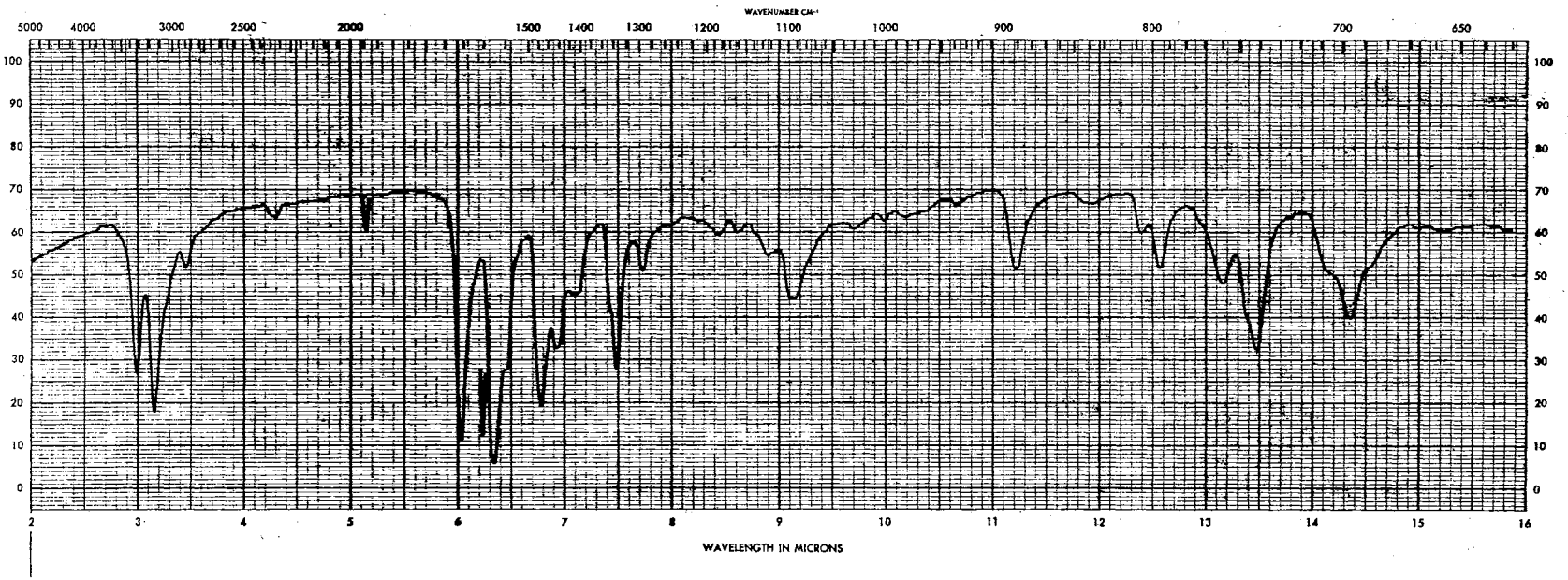
Plate XII



2,4-Diamino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine (74)

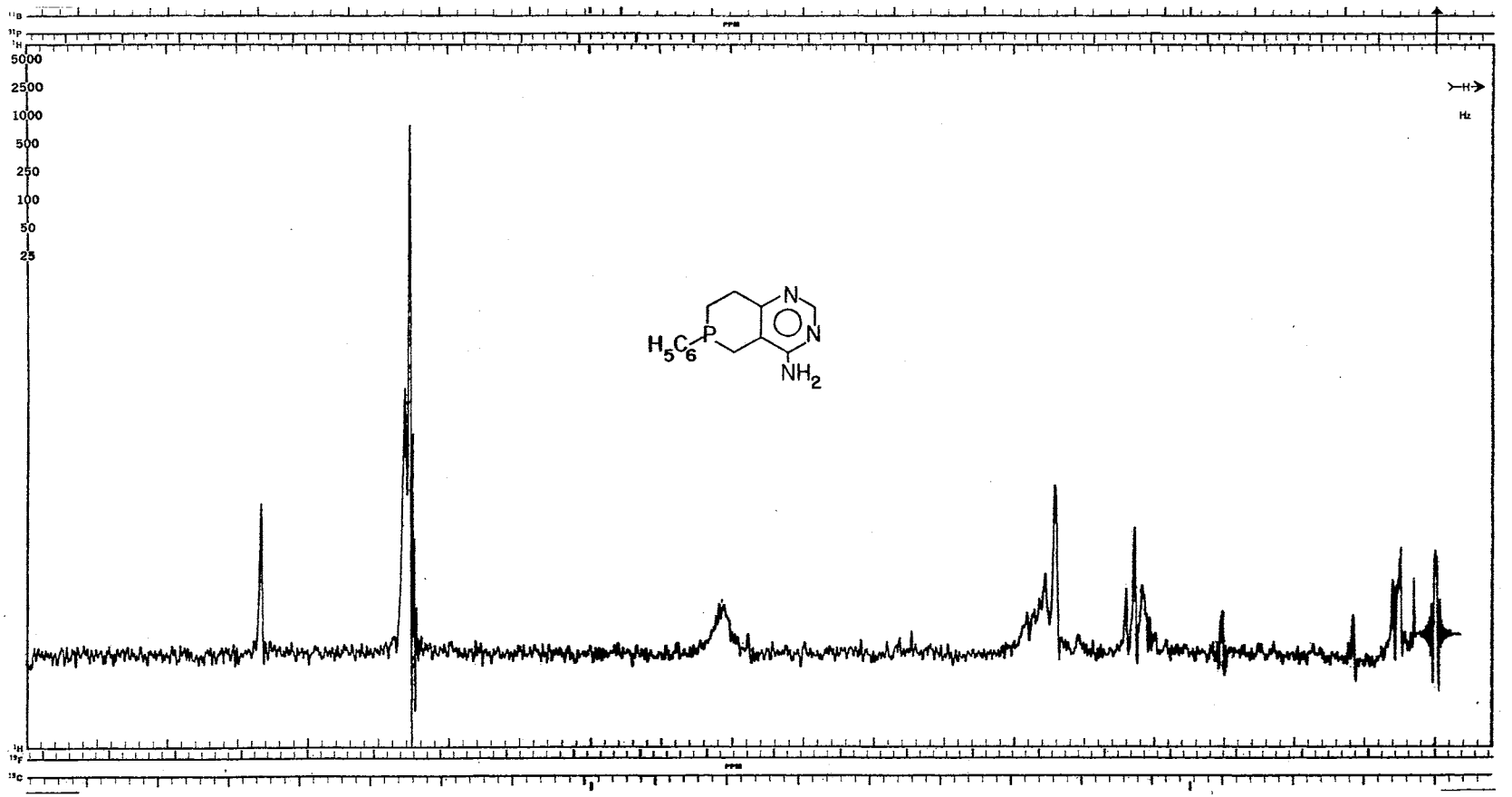
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....95°

Plate XIII



4-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine (75), KBr Pellet

Plate XIV

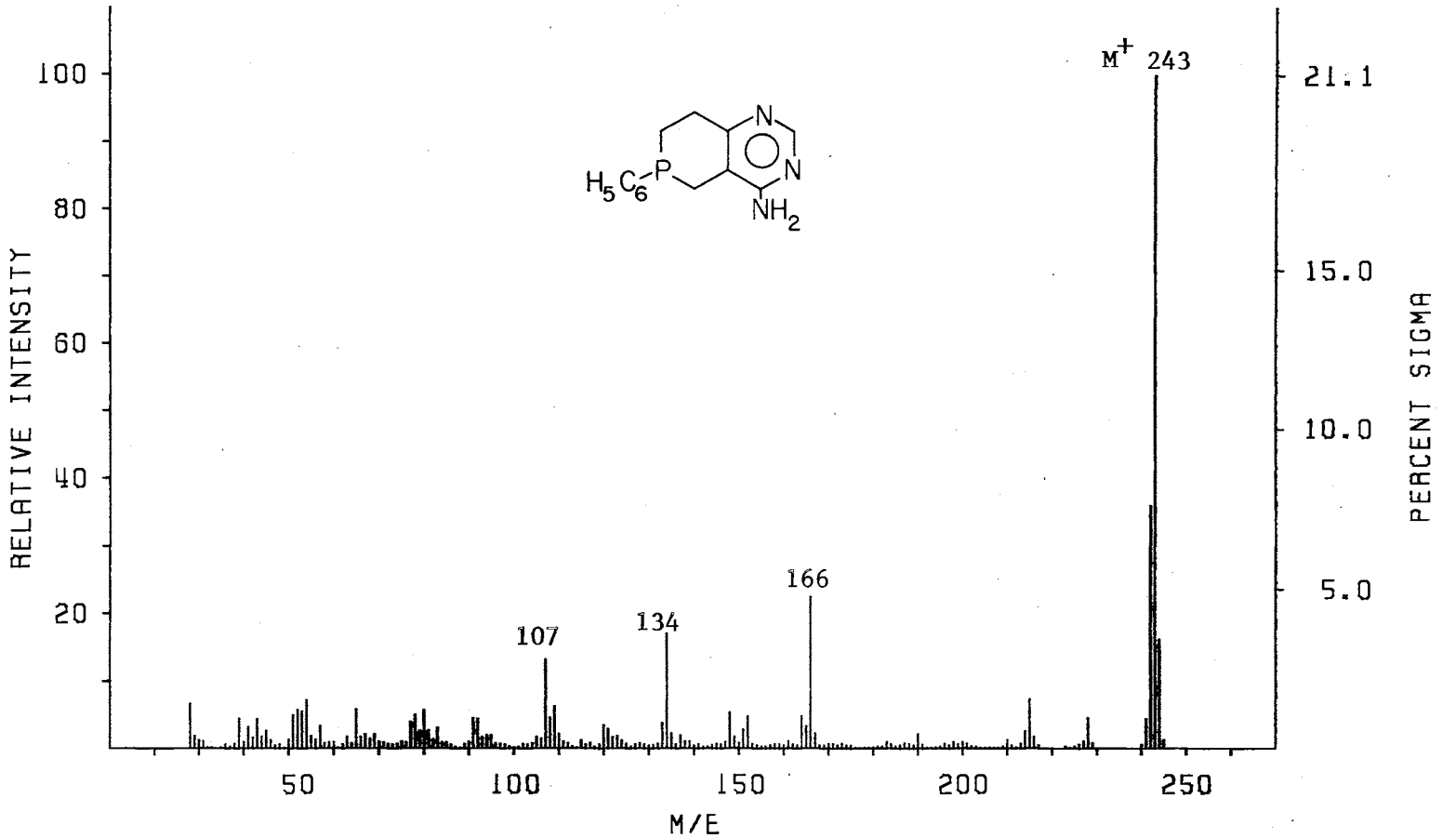


4-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine (75)

Solvent. . . $DCCl_3$ O.F. . . 100 MHz F.B. . . . . 2 Hz R.F. . . 63 db

S.W. . . . 1000 Hz S.T. . . 250 sec S.O. . . 83701 Hz S.A. . . . 25 Lock. . . HOMO

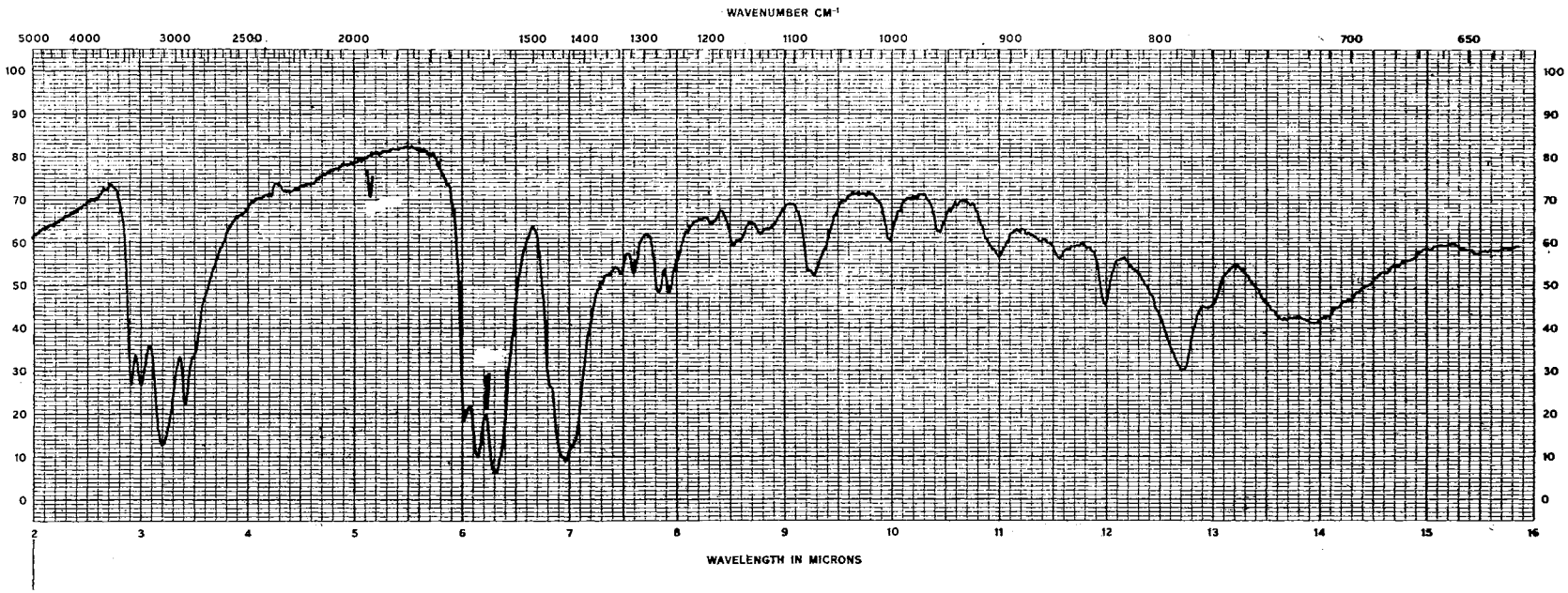
Plate XV



4-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine (75)

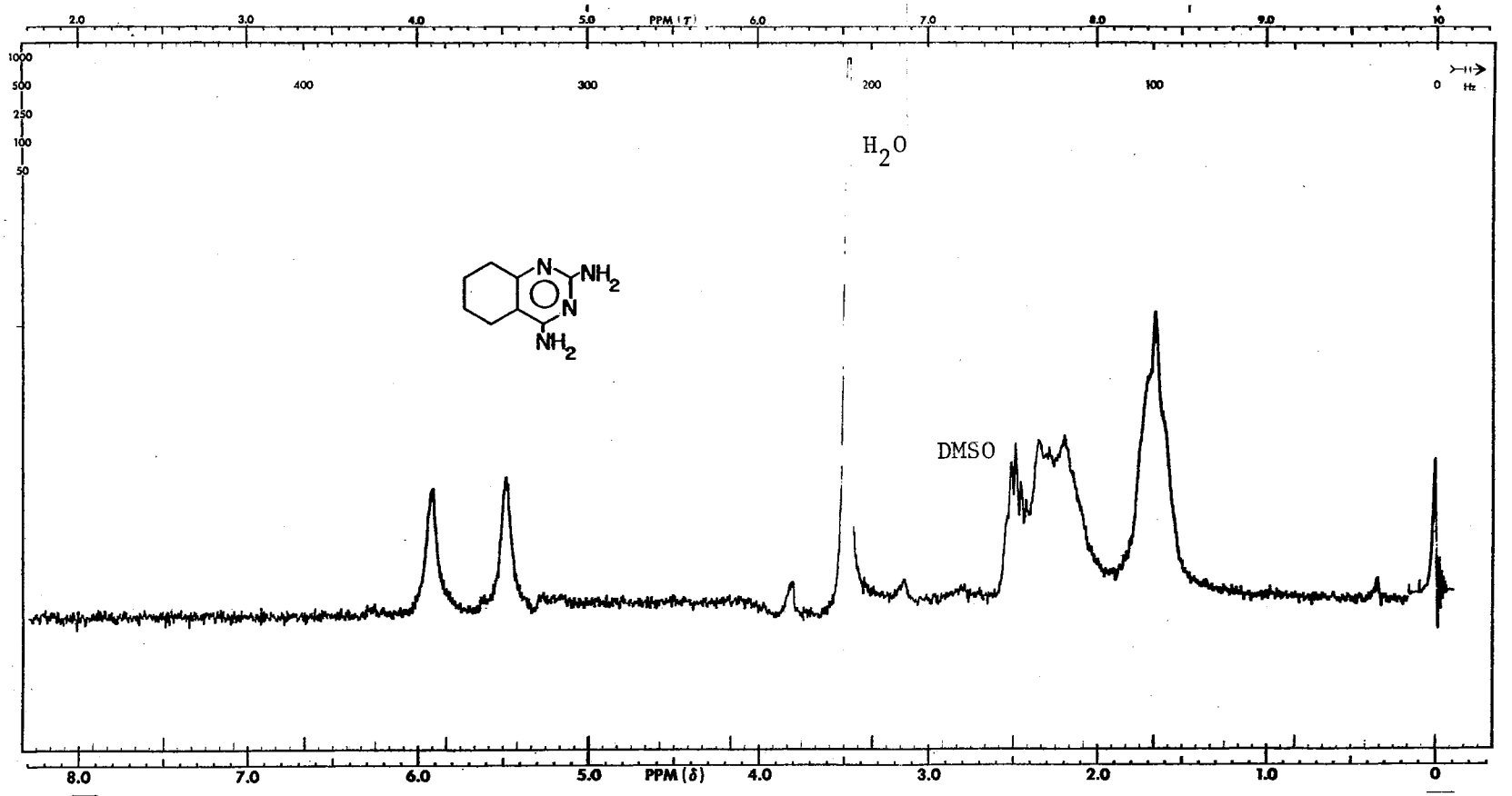
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....50°

Plate XVI



2,4-Diamino-5,6,7,8-tetrahydroquinazoline (84), KBr Pellet

Plate XVII

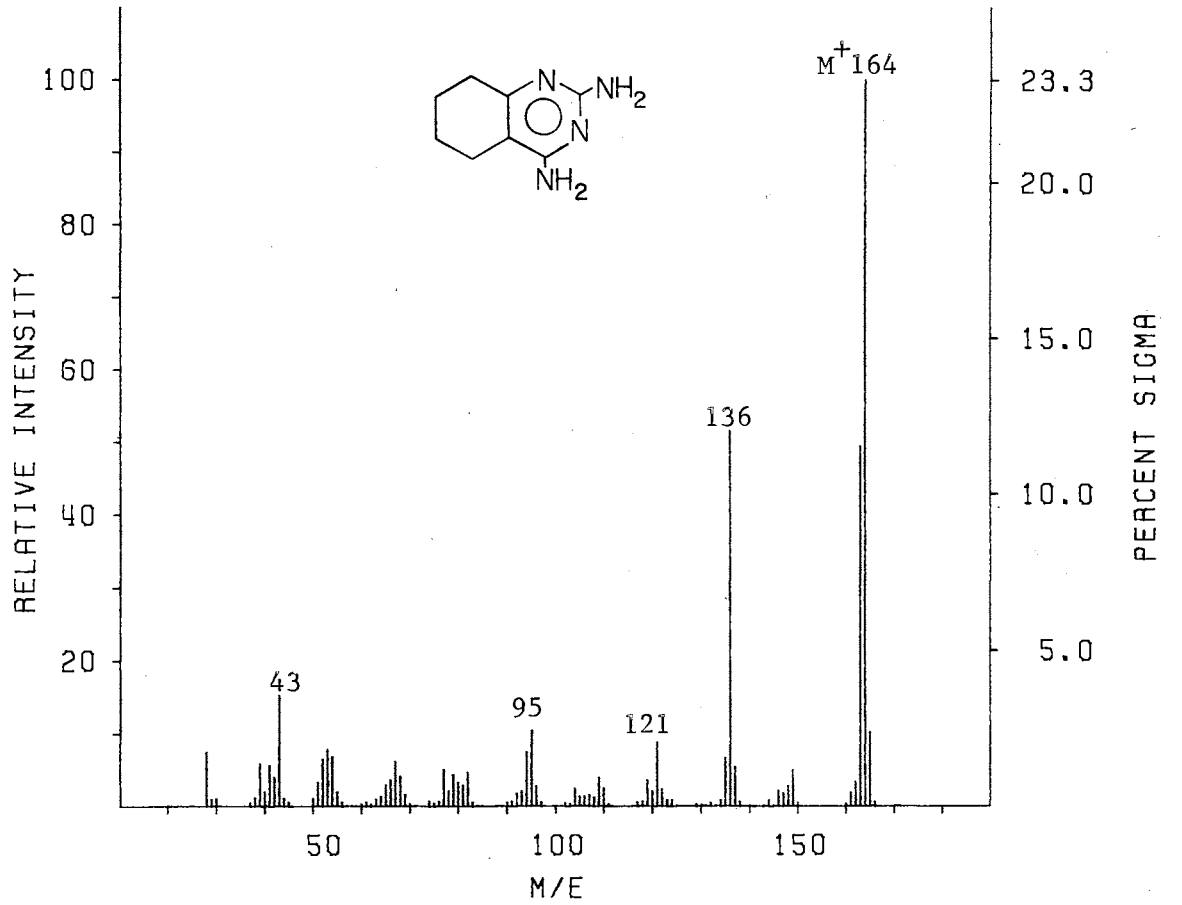


2,4-Diamino-5,6,7,8-tetrahydroquinazoline (84)

Solvent . . . . . DMSO-d_6 O.F. . . . . 60 MHz F.B. . . . . 4 Hz R.F. . . . . 0.07 db

S.W. . . . . 500 Hz S.T. . . . . 250 sec S.O. . . . . 0 Hz S.A. 12

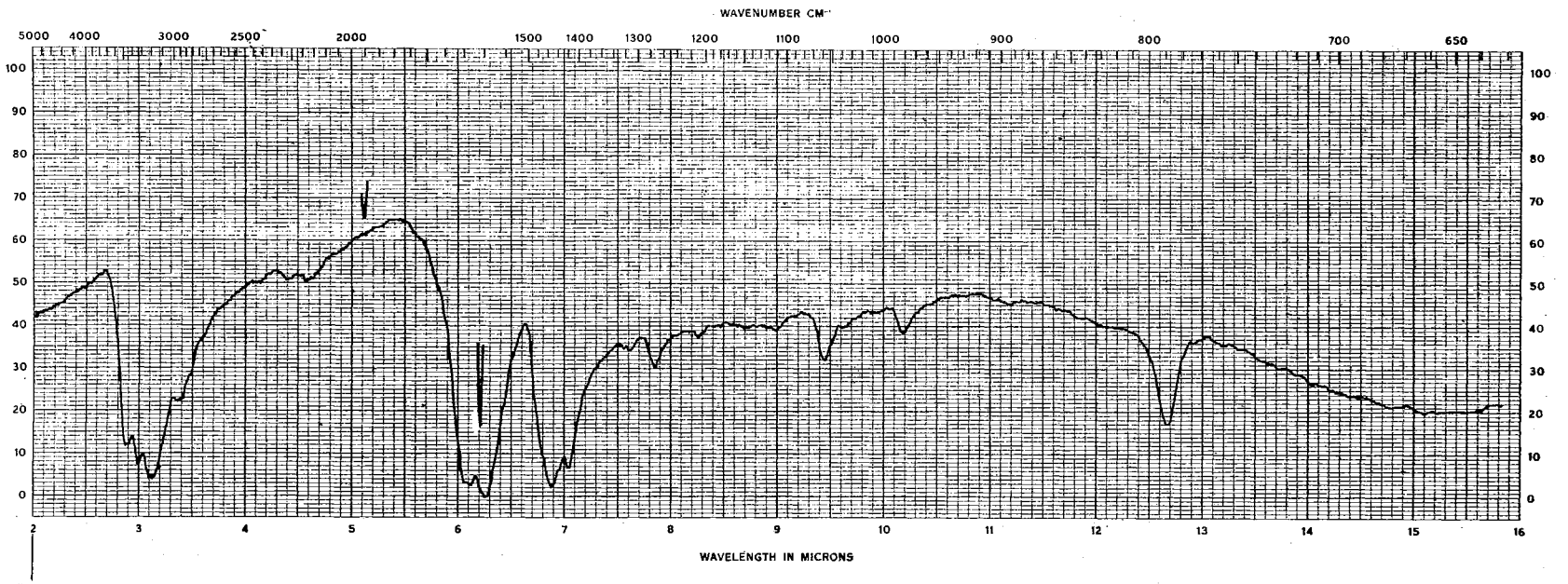
Plate XVIII



2,4-Diamino-5,6,7,8-tetrahydroquinazoline (84)

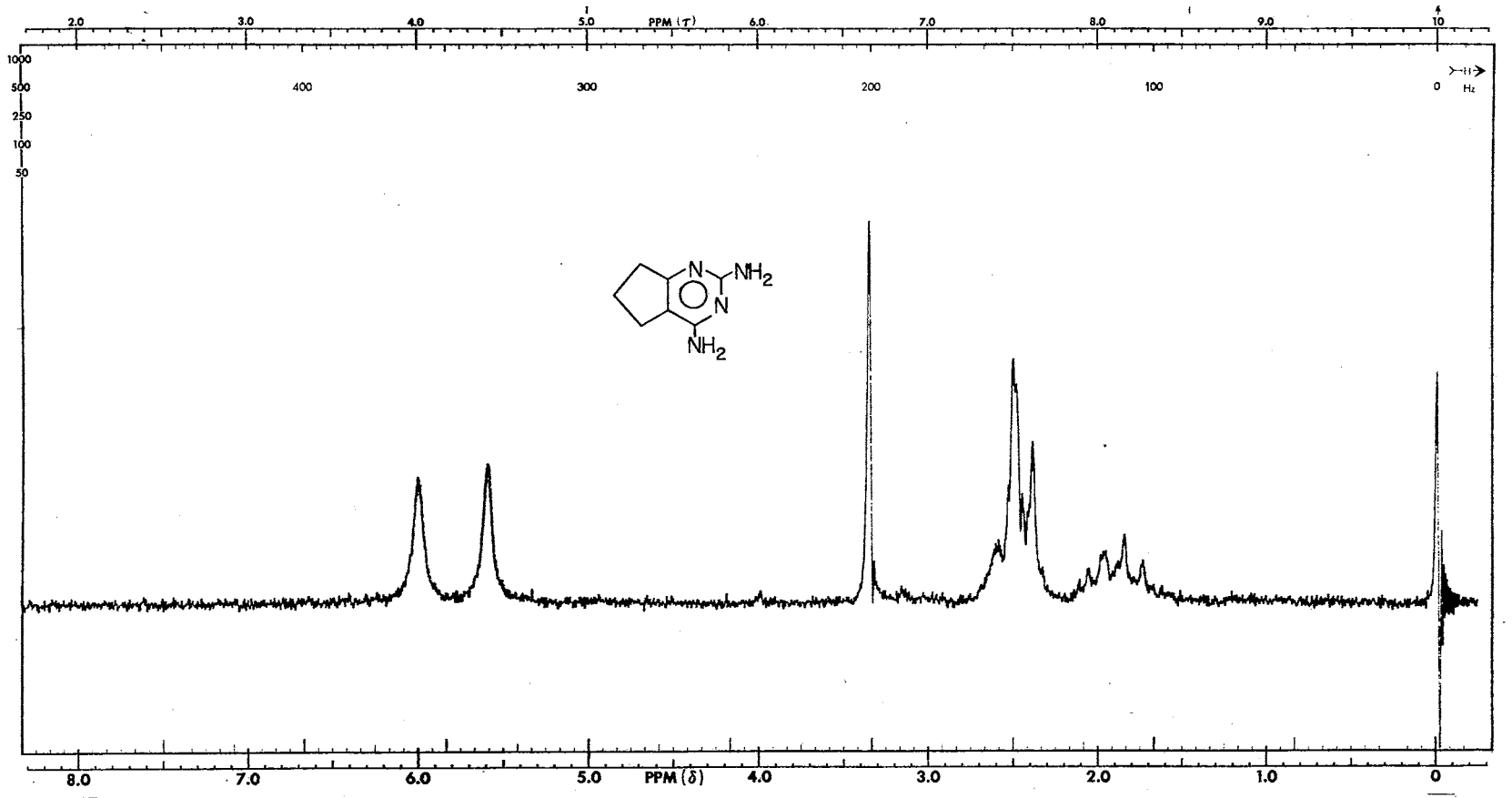
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....70°

Plate XIX



2,4-Diamino-6,7-dihydro-5-H-cyclopentapyrimidine (85), KBr Pellet

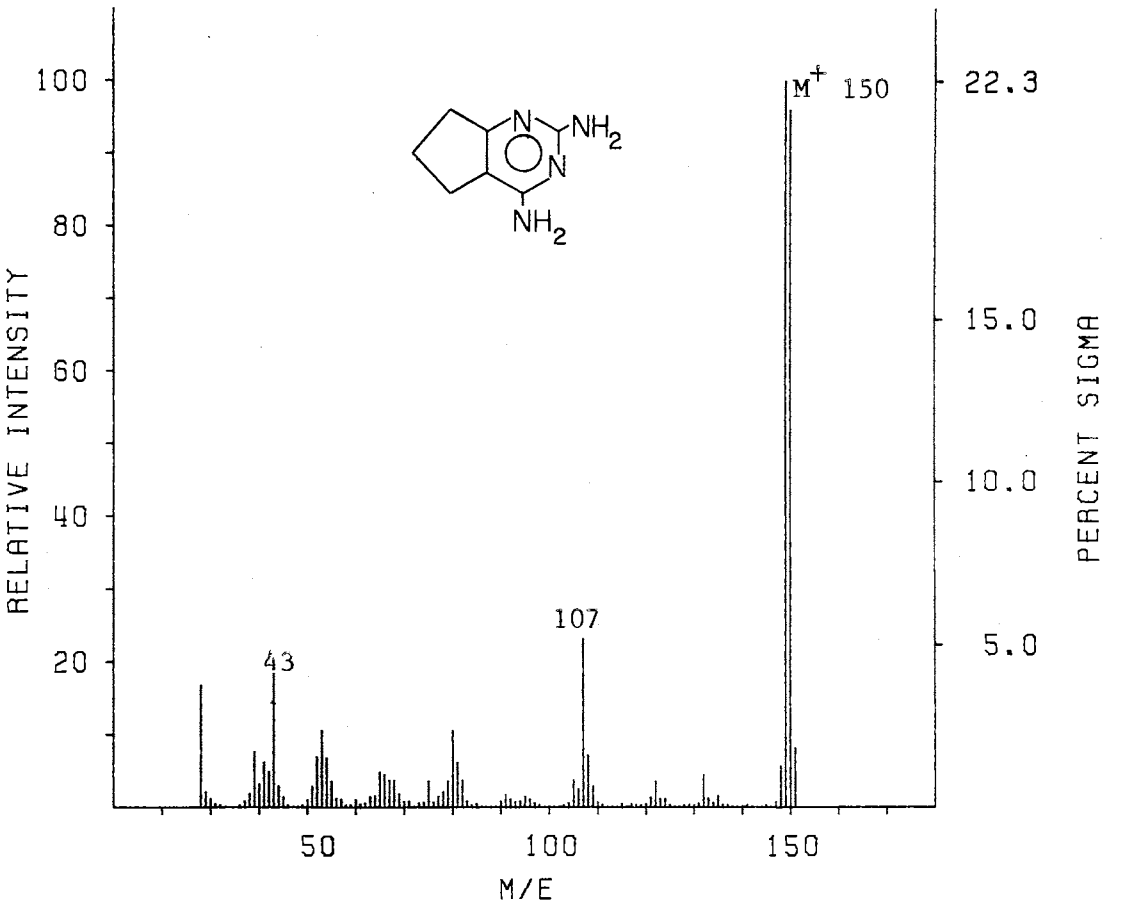
Plate XX



2,4-Diamino-6,7-dihydro-5H-cyclopentapyrimidine (85)

Solvent.	DMSO-d_6	O.F.	60 MHz	F.B.	4 Hz	R.F.	0.05 db
S.W.	500 Hz	S.T.	250 sec	S.O.	0 Hz	S.A.	10

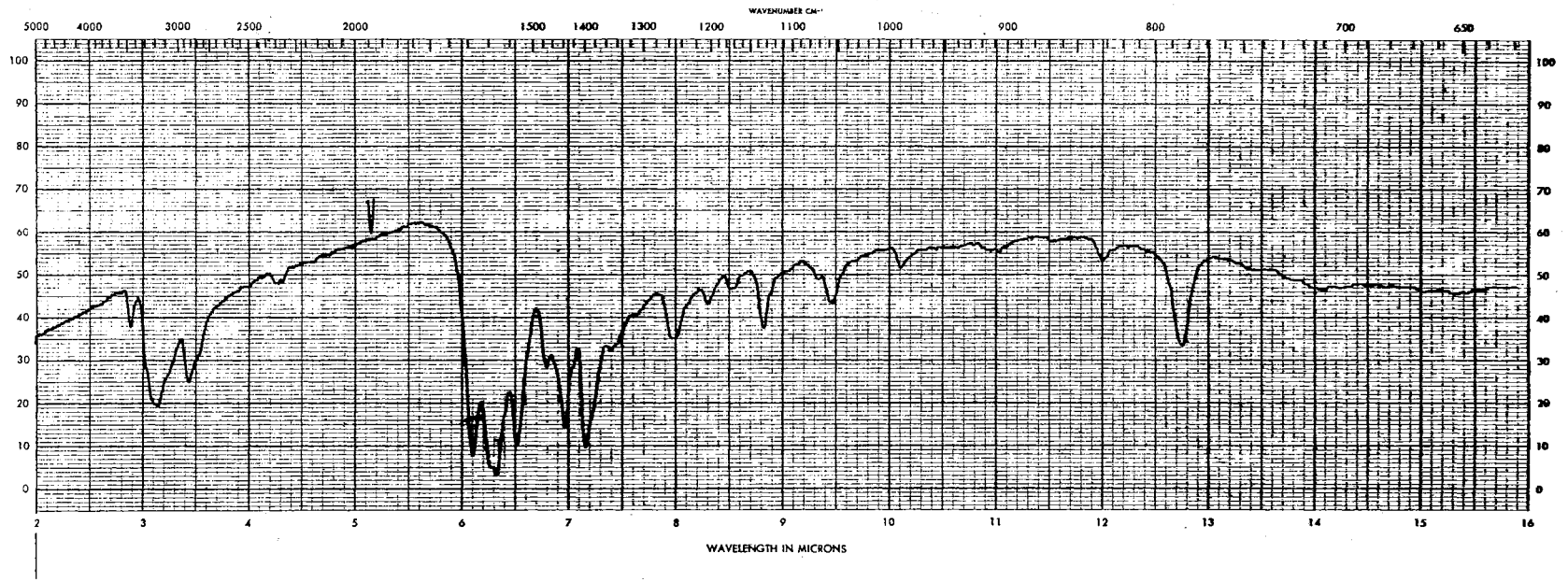
Plate XXI



2,4-Diamino-6,7-dihydro-5H-cyclopentapyrimidine (85)

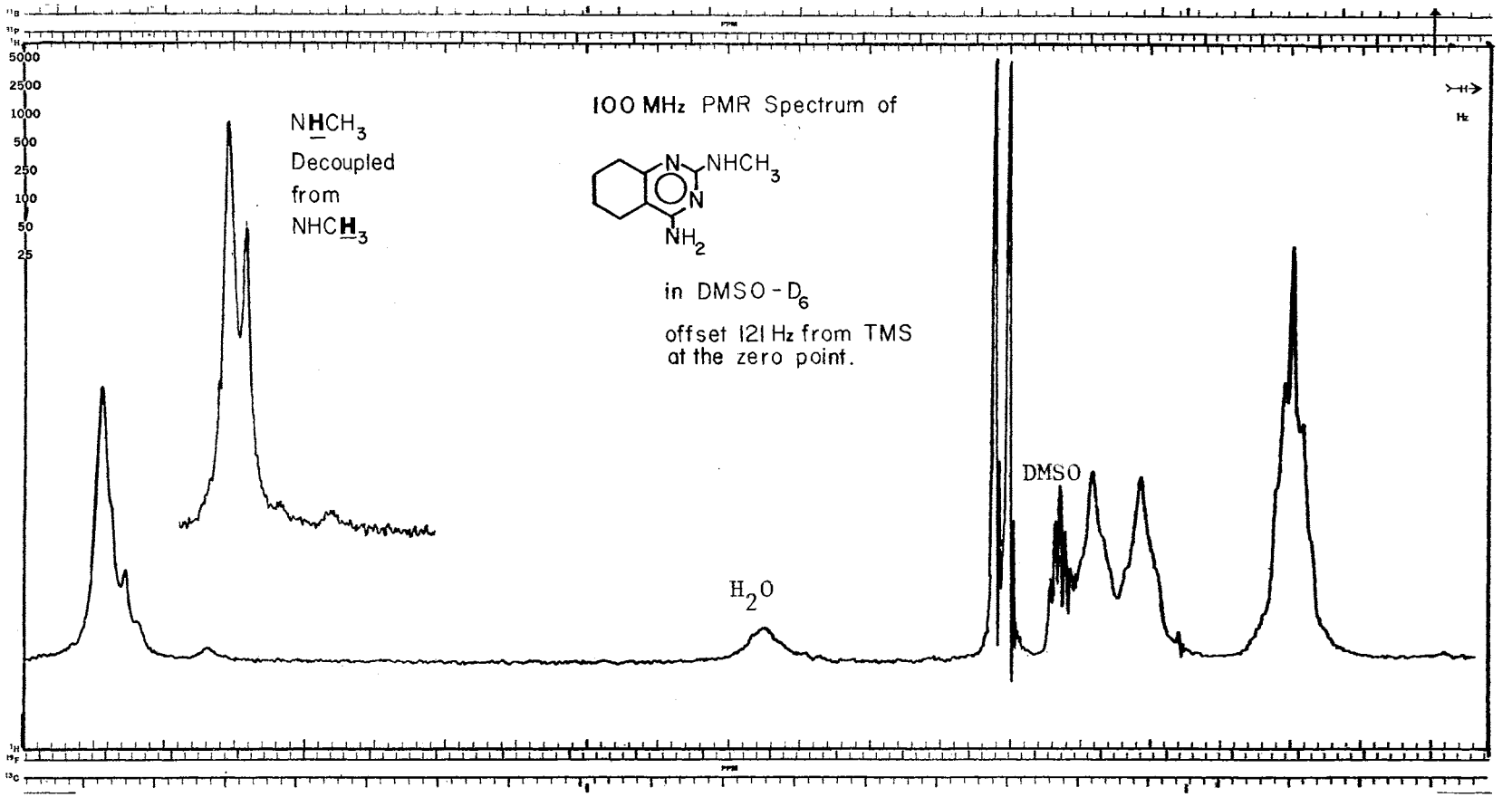
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....260° Probe °C....50°

Plate XXII



4-Amino-2-(methylamino)-5,6,7,8-tetrahydroquinazoline (86), KBr Pellet

Plate XXIII

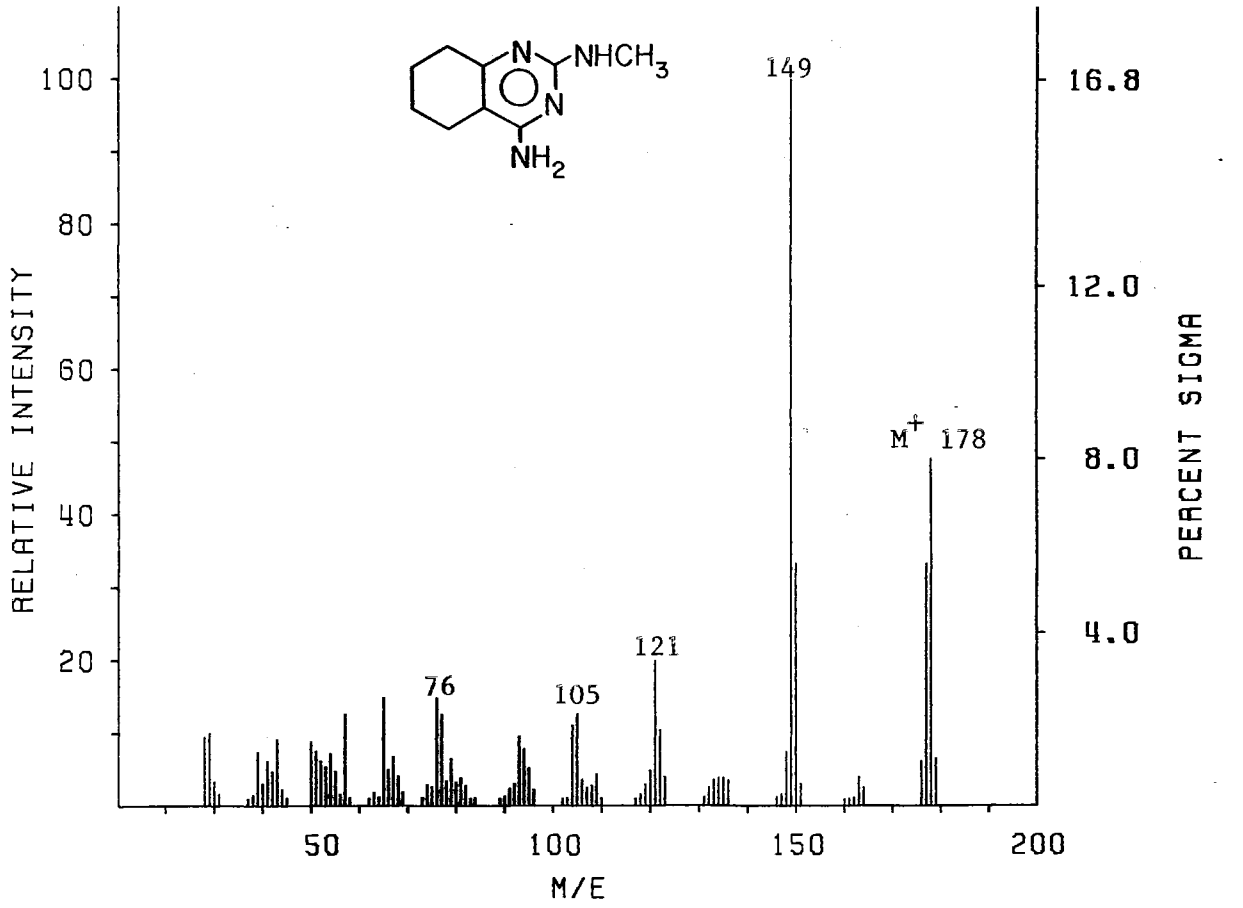


4-Amino-2-(methylamino)-5,6,7,8-tetrahydroquinazoline (86)

Solvent. . . DMSO-d_6 O.F. . . 100 MHz F.B. . . . . 2 Hz R.F. . . 74 db

S.W. . . . . 500 Hz S.T. . . 250 sec S.O. . . 83822 Hz S.A. . . 12.5 Lock. . . HOMO

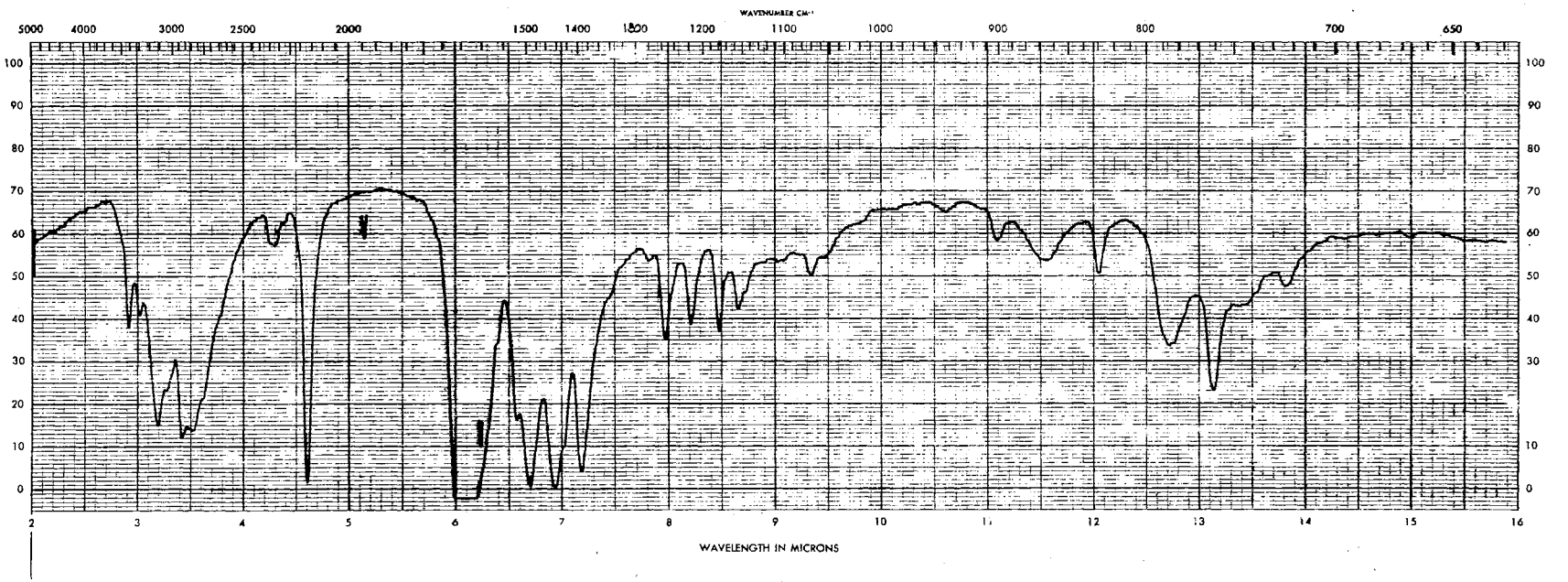
Plate XXIV



4-Amino-2-(methylamino)-5,6,7,8-tetrahydroquinazoline (86)

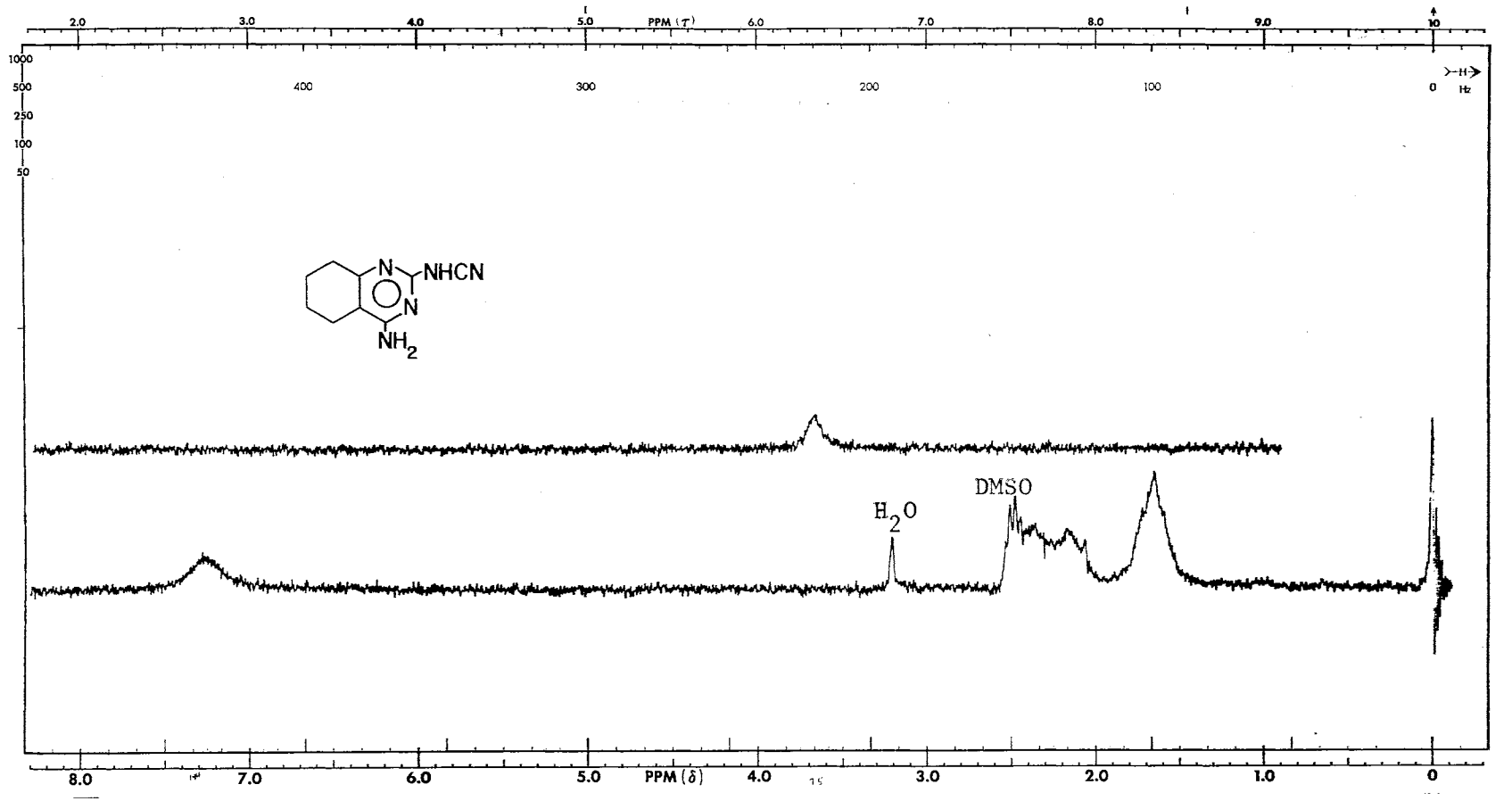
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....35°

Plate XXV



4-Amino-2-(cyanoamino)-5,6,7,8-tetrahydroquinazoline (87) KBr Pellet

Plate XXVI

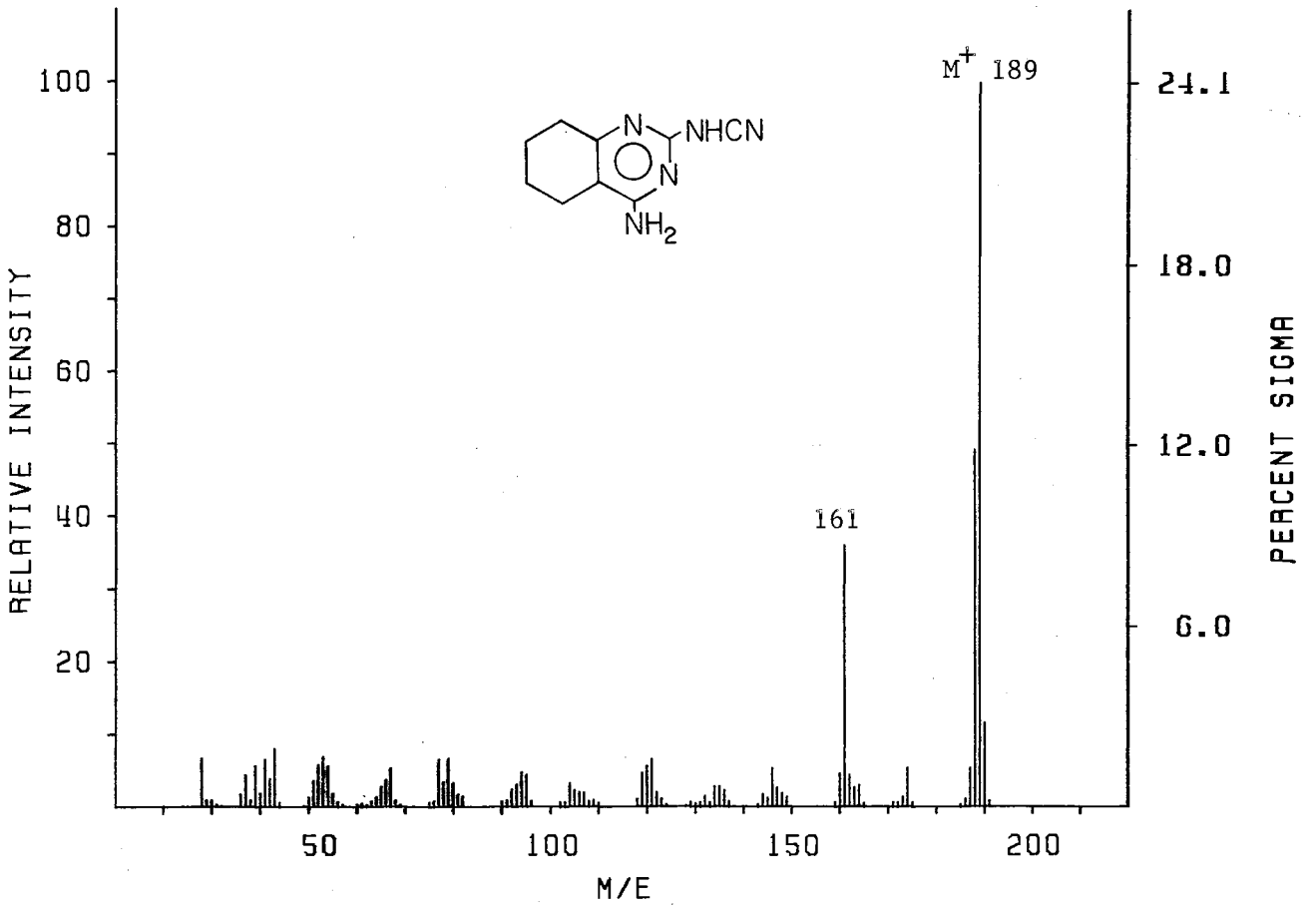


4-Amino-2-(cyanoamino)-5,6,7,8-tetrahydroquinazoline (87)

Solvent. . . . . DMSO-d_6 O.F. . . . . 60 MHz F.B. . . . . 4 Hz R.F. . . . . 0.05 db

S.W. . . . . 500 Hz S.T. . . . . 250 sec S.W. . . . . 0 Hz S.A. 12.5

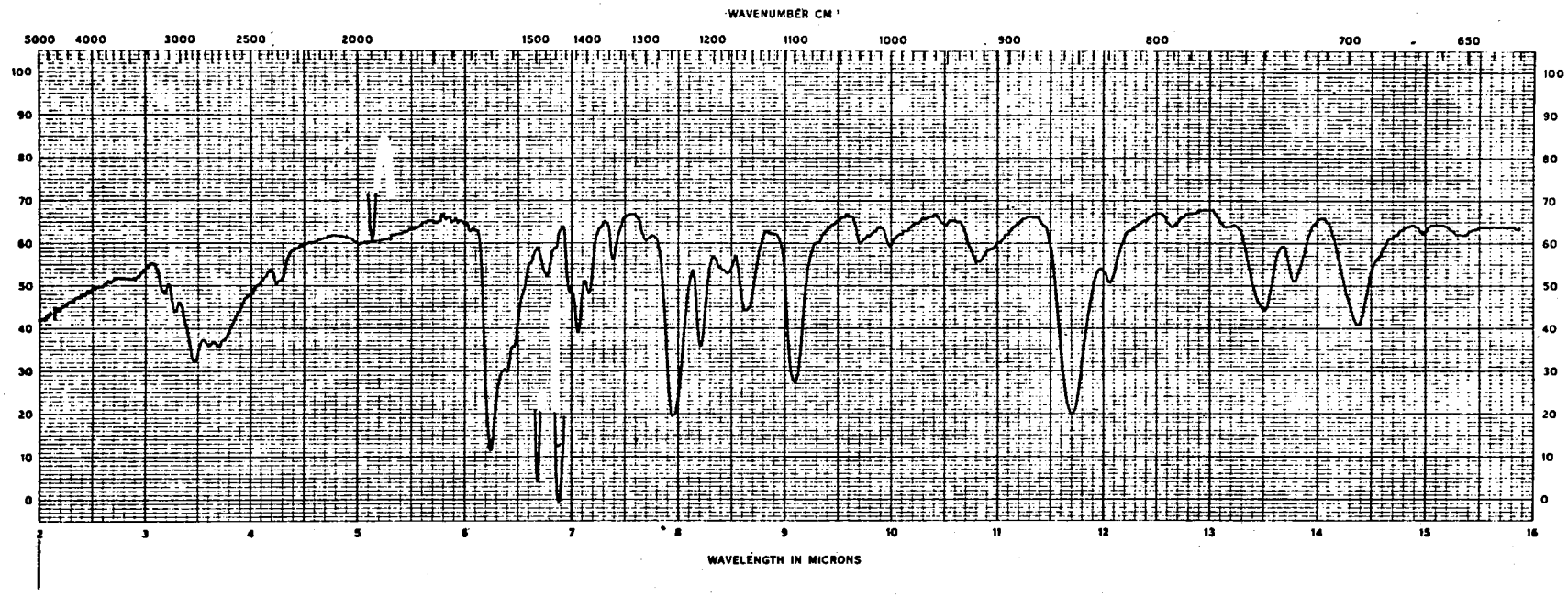
Plate XXVII



4-Amino-2-(cyanoamino)-5,6,7,8-tetrahydroquinazoline (87)

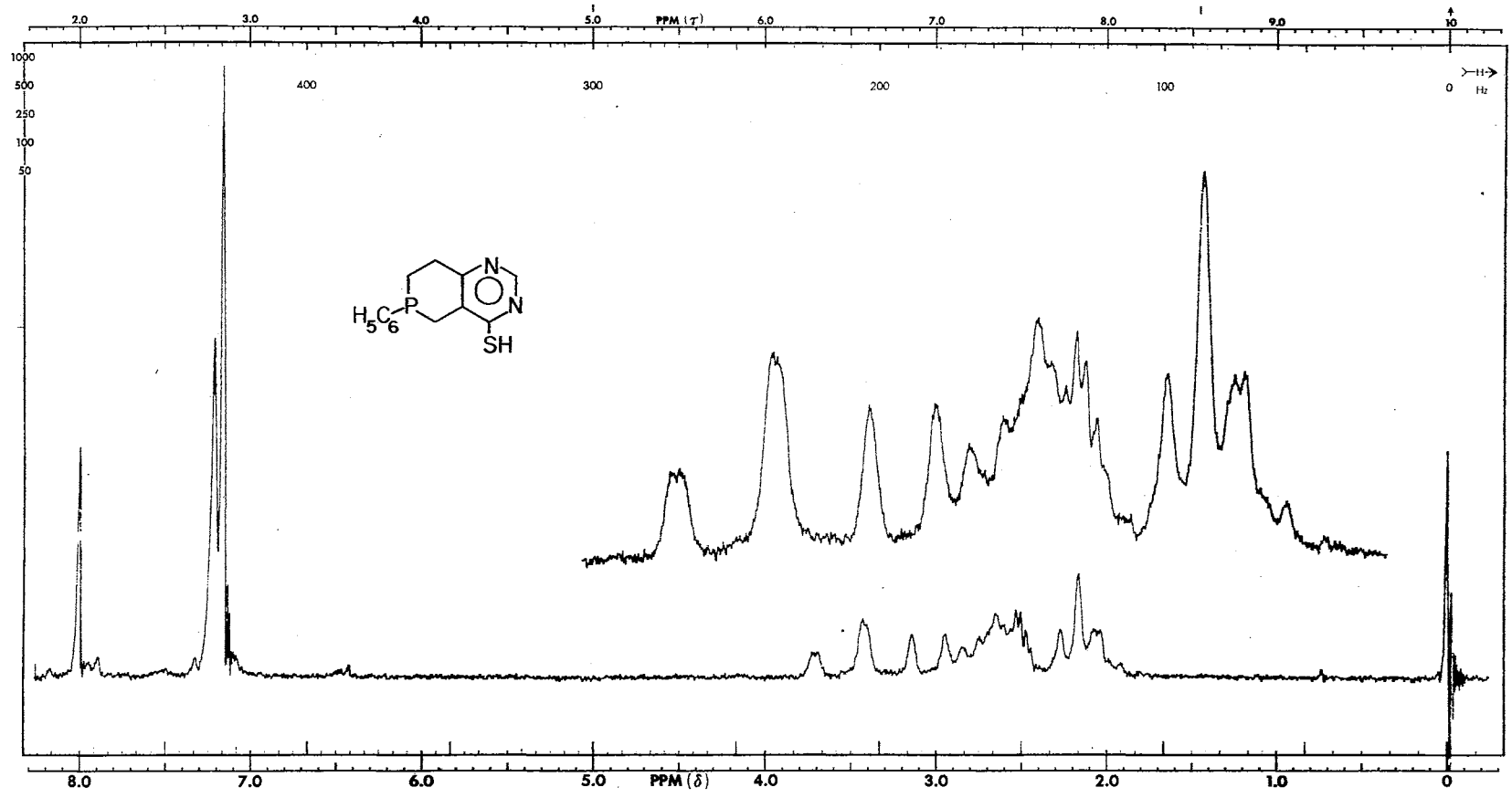
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....330° Probe °C....130°

Plate XXVIII



5,6,7,8-Tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine-4-thiol (76), KBr Pellet

Plate XXIX

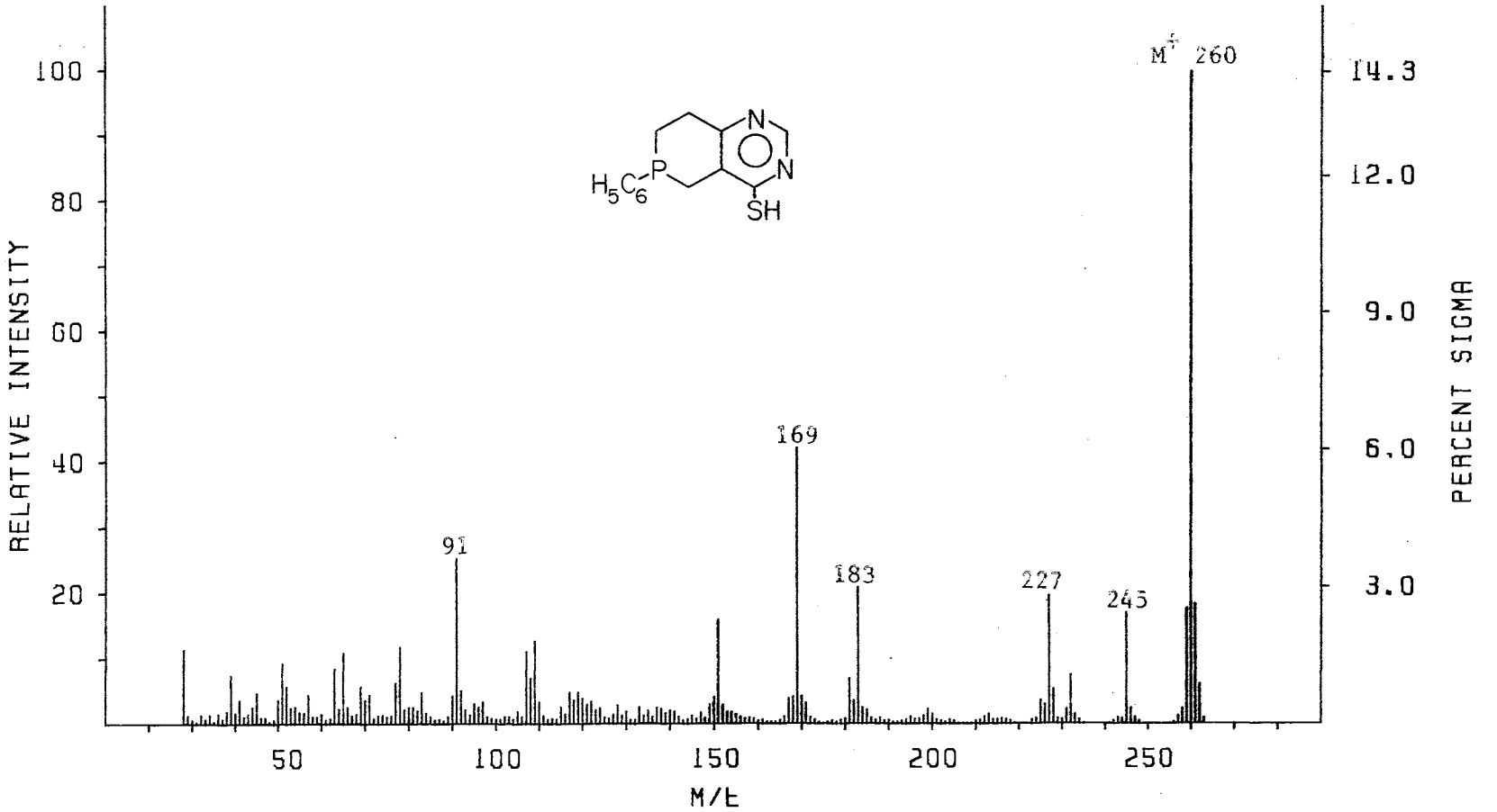


5,6,7,8-Tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine-4-thiol (76)

Solvent . . . . . DMSO-d_6 O.F. . . . . 60 MHz F.B. . . . . 4 Hz R.F. . . . . 0.035 db

S.W. . . . . 500 Hz S.T. . . . . 250 sec S.O. . . . . 0 Hz S.A. 4.0

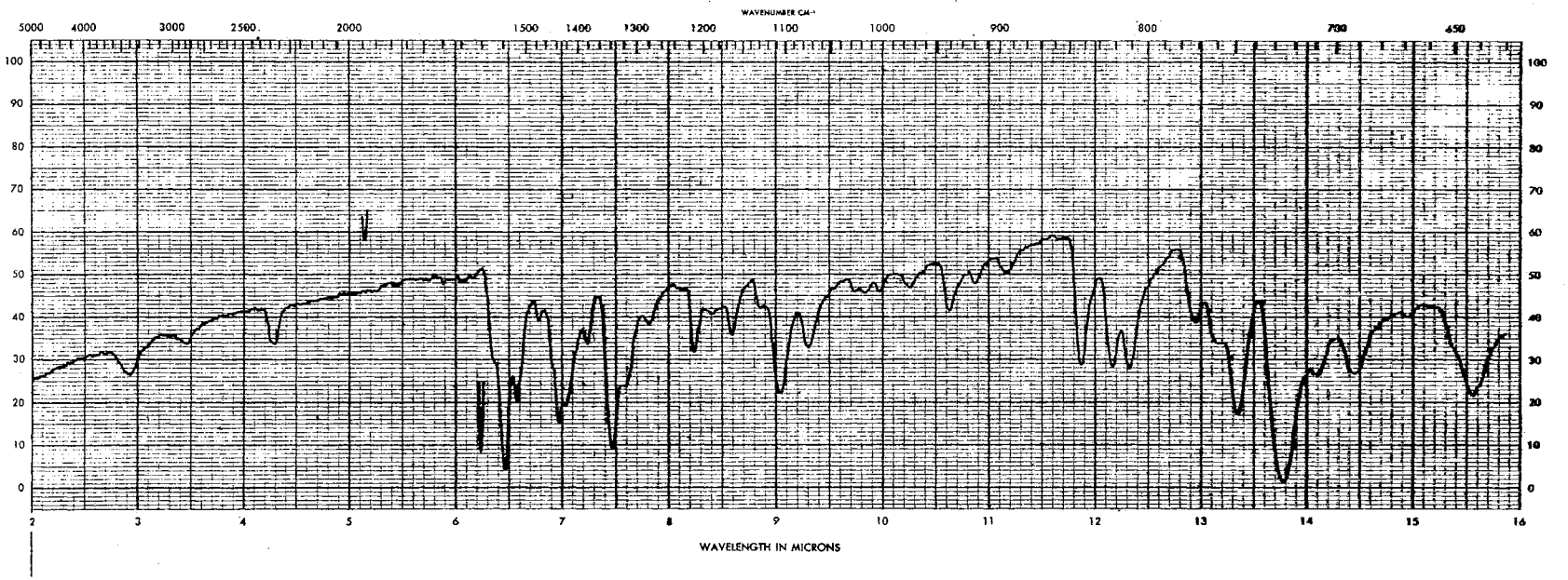
Plate XXX



5,6,7,8-Tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine-4-thiol (76)

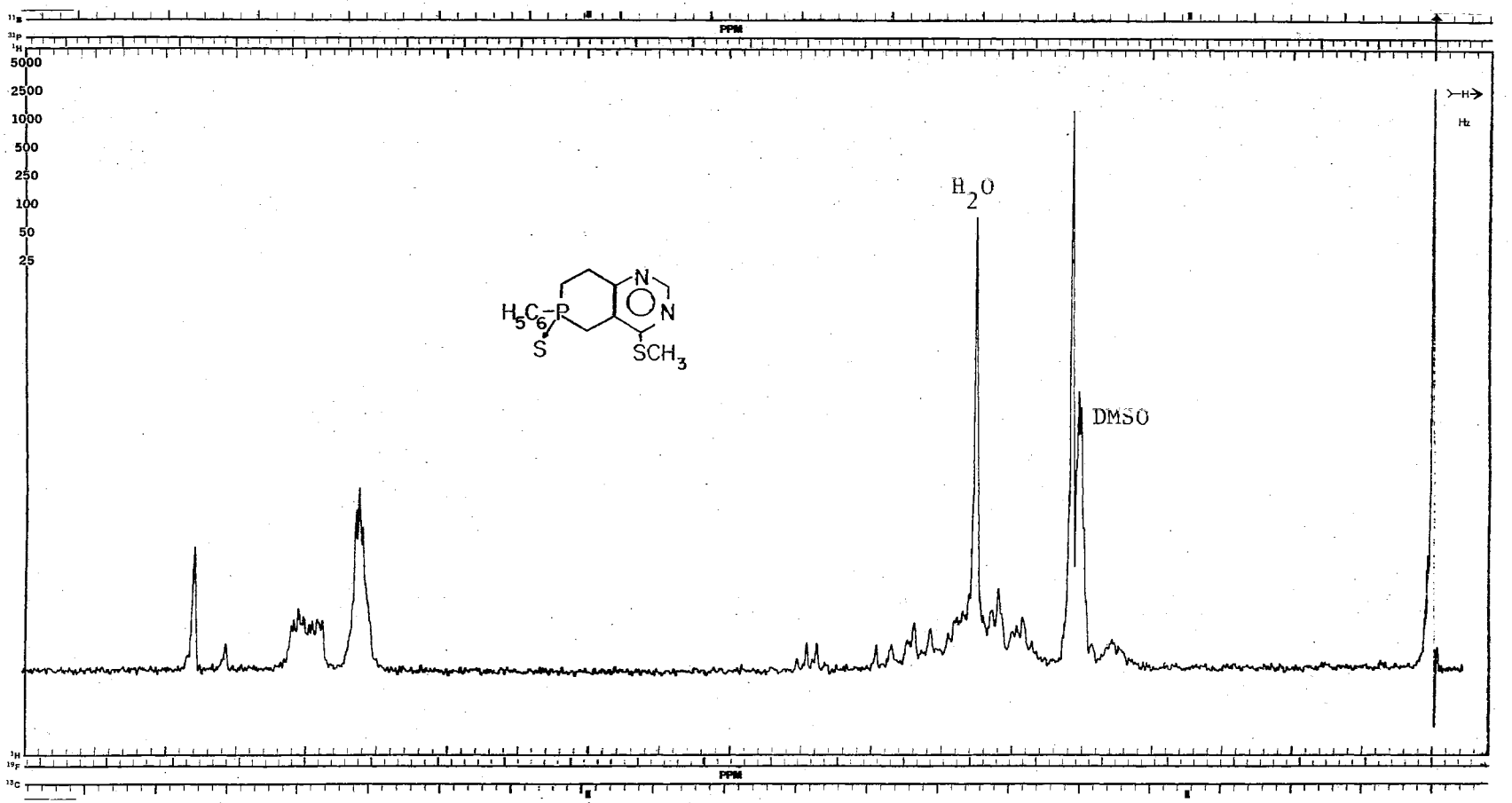
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....90°

Plate XXXI



5,6,7,8-Tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-d]pyrimidine 6-sulfide (77), KBr Pellet

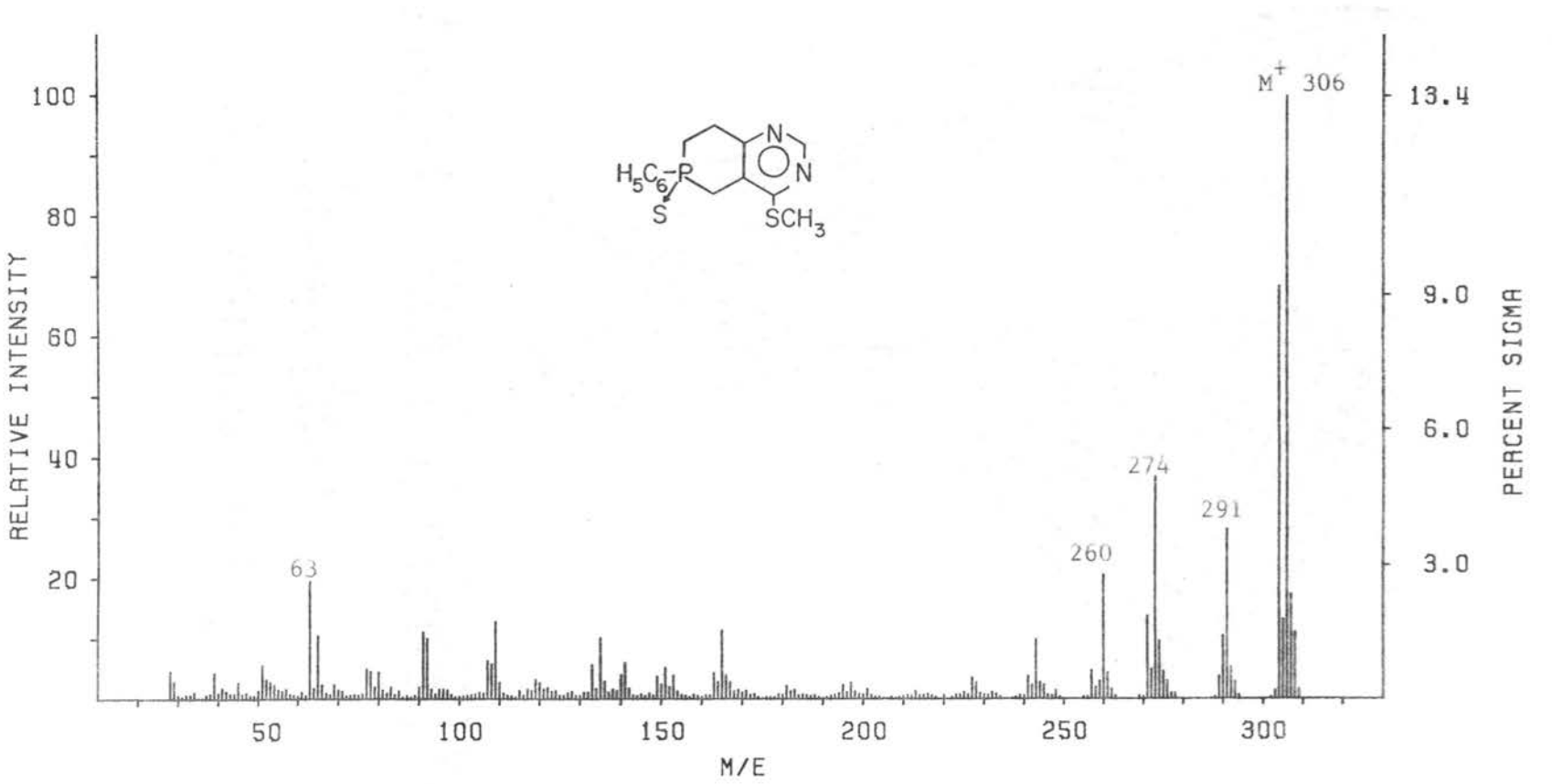
Plate XXXII



5,6,7,8-Tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-d]pyrimidine 6-Sulfide (77)

Solvent. . . DMSO-d_6 O.F. . . 100 MHz F.B. . . . . 1 Hz R.F. . . 73 db
S.W. . . . .1000 Hz S.T. . . 500 sec S.O. . . 86245 Hz S.A. . . . 16 Lock. . . . . ^2H

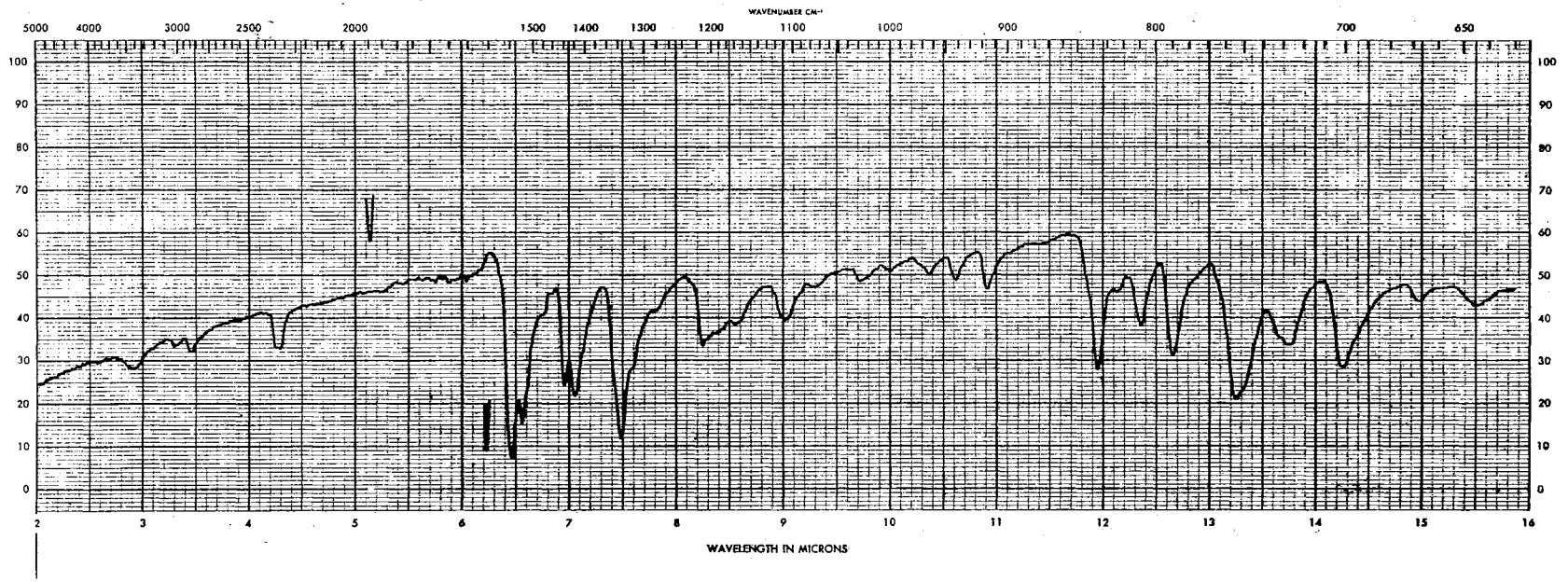
Plate XXXIII



5,6,7,8-Tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-d]pyrimidine 6-sulfide (77)

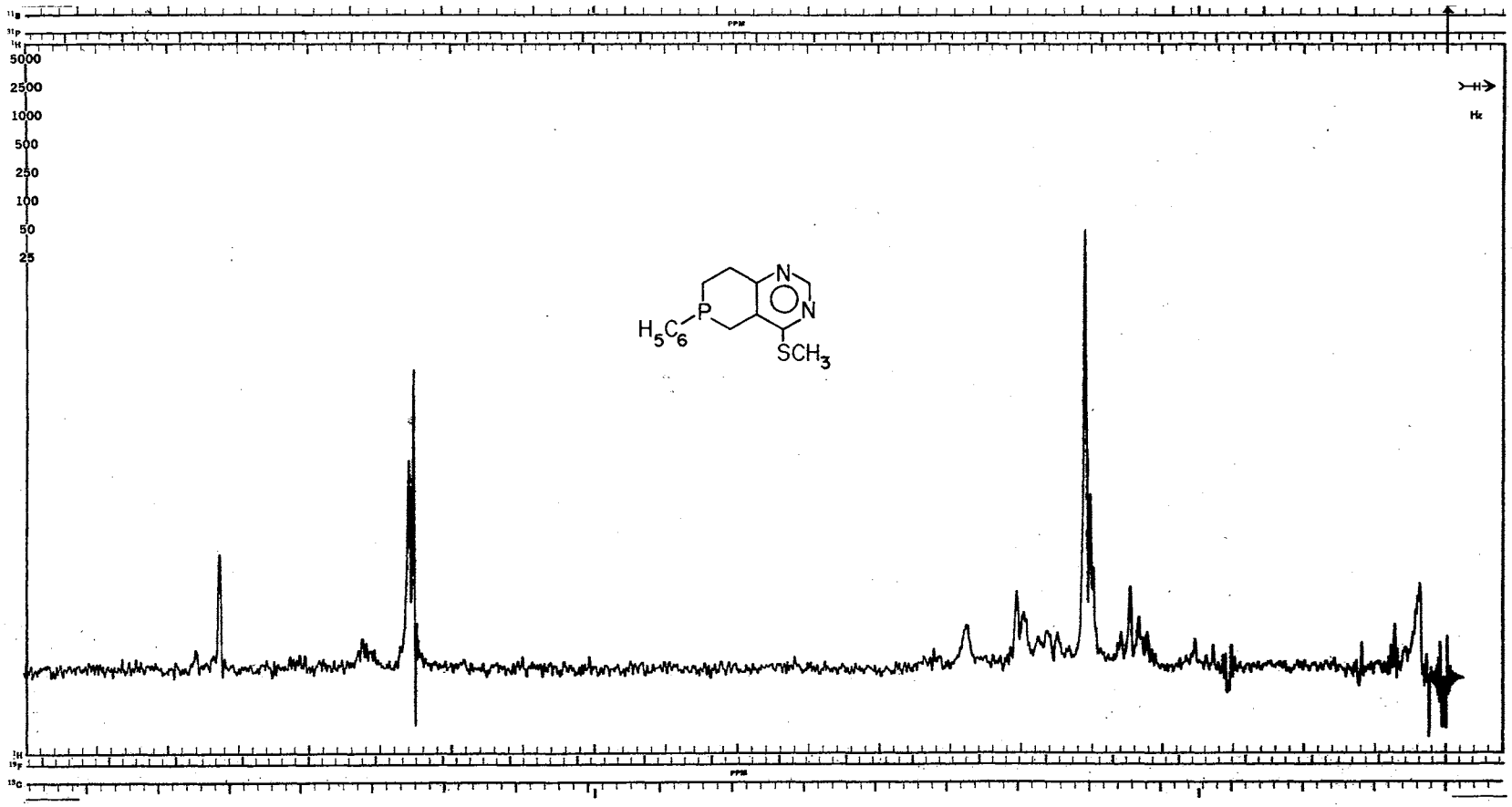
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....45°

Plate XXXIV



5,6,7,8-Tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-d]pyrimidine (78), KBr Pellet

Plate XXXV

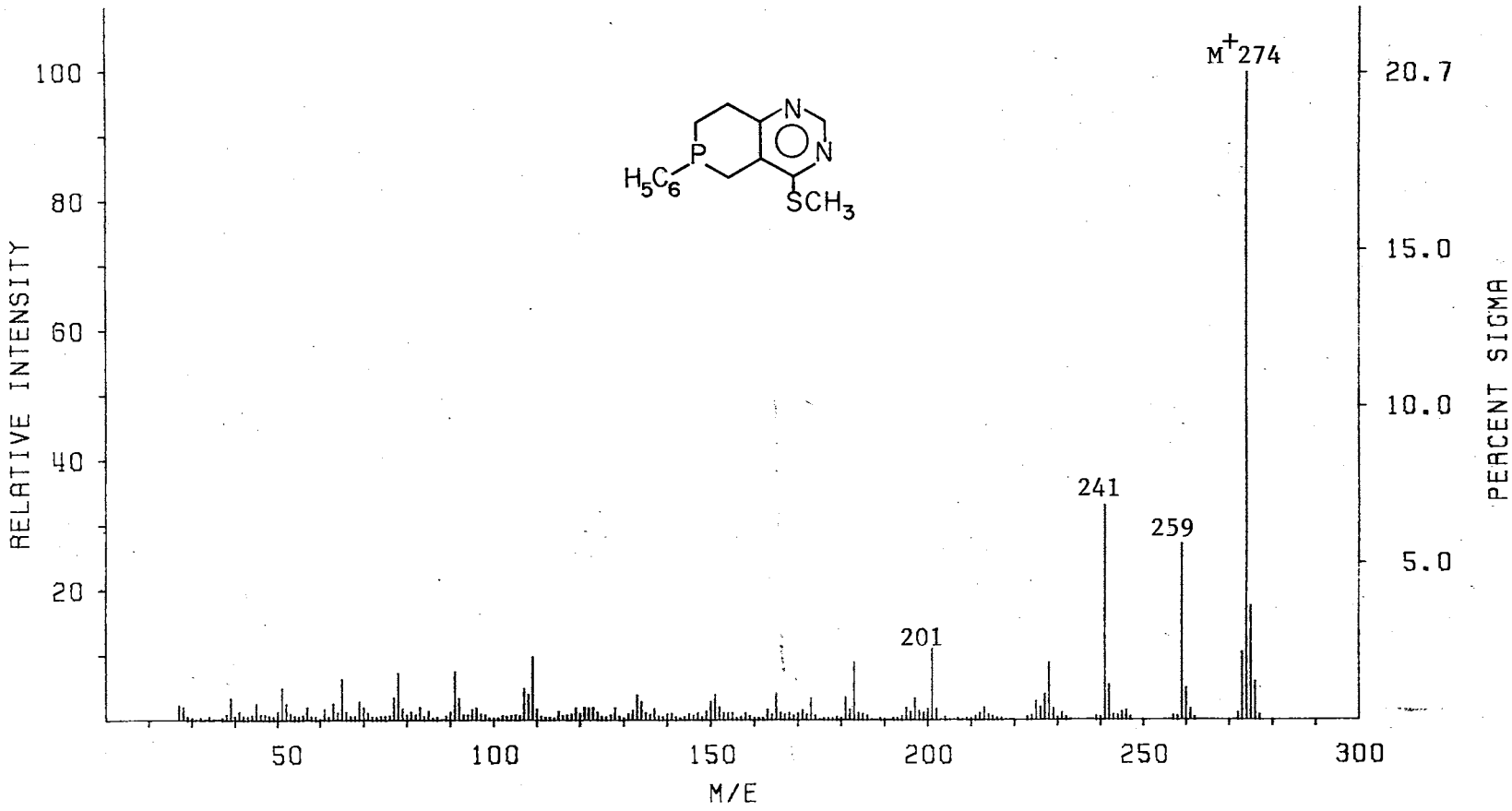


5,6,7,8-Tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-d]pyrimidine (78)

Solvent. . . DMSO-d_6 O.F. . . 100 MHz F.B. . . . . 2 Hz R.F. . . 58 db

S.W. . . . . 1000 Hz S.T. . . 250 sec S.O. . . 83701 Hz S.A. . . . 20 Lock. . . . ^1H

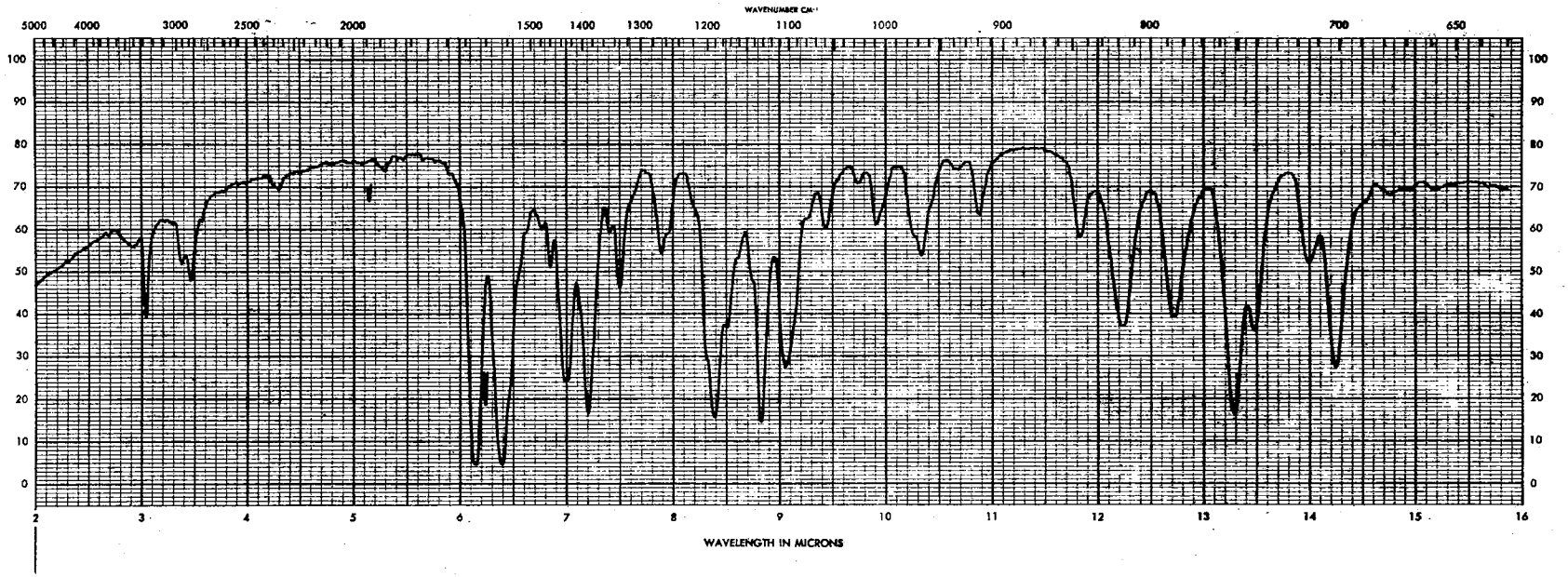
Plate XXXVI



5,6,7,8-Tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-d]pyrimidine (78)

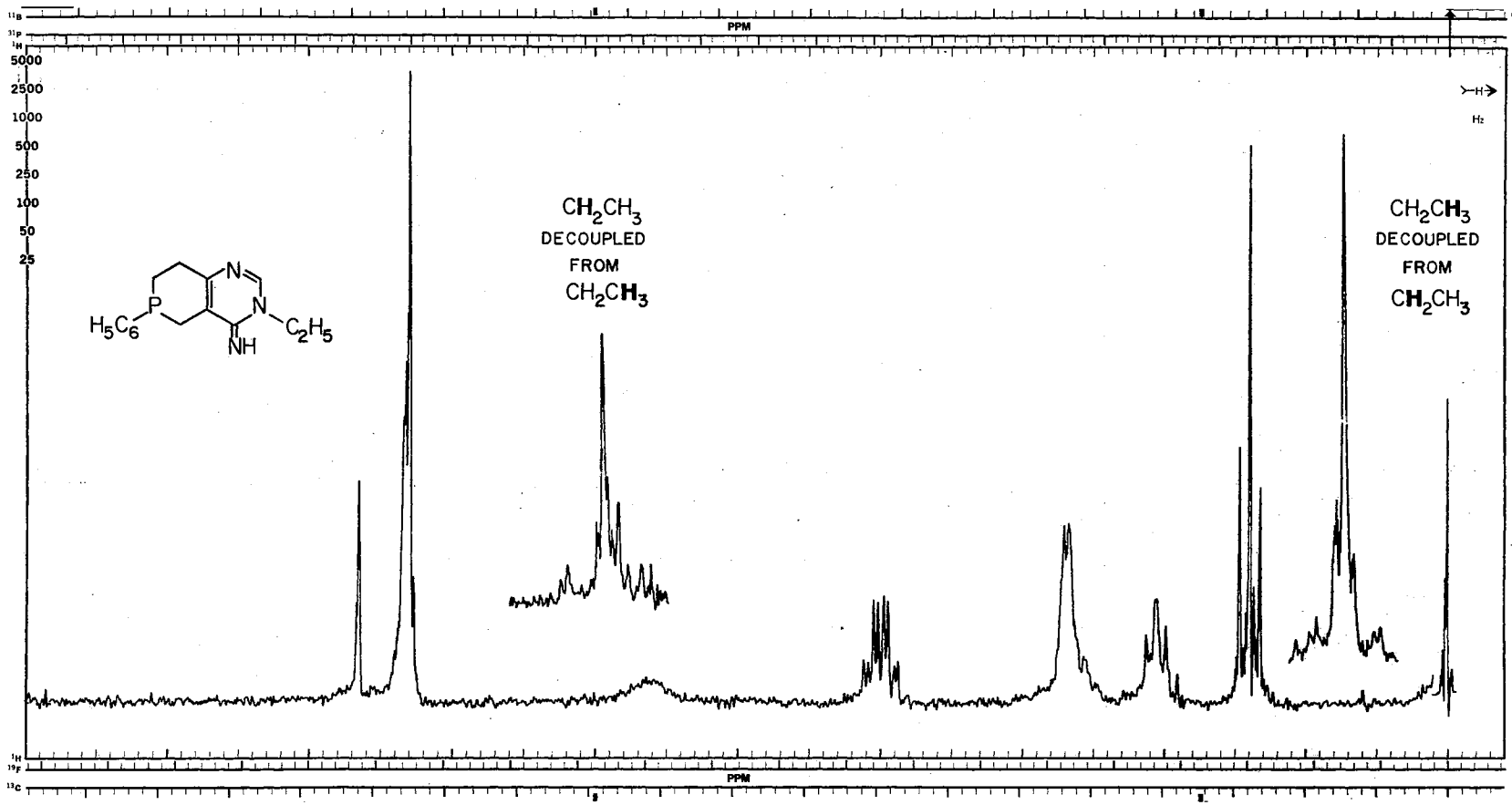
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....35°

Plate XXXVII



3-Ethyl-5,6,7,8-tetrahydro-4(3H)-imino-6-phenyl-phosphorino[4,3-d]pyrimidine (79), KBr Pellet

Plate XXXVIII

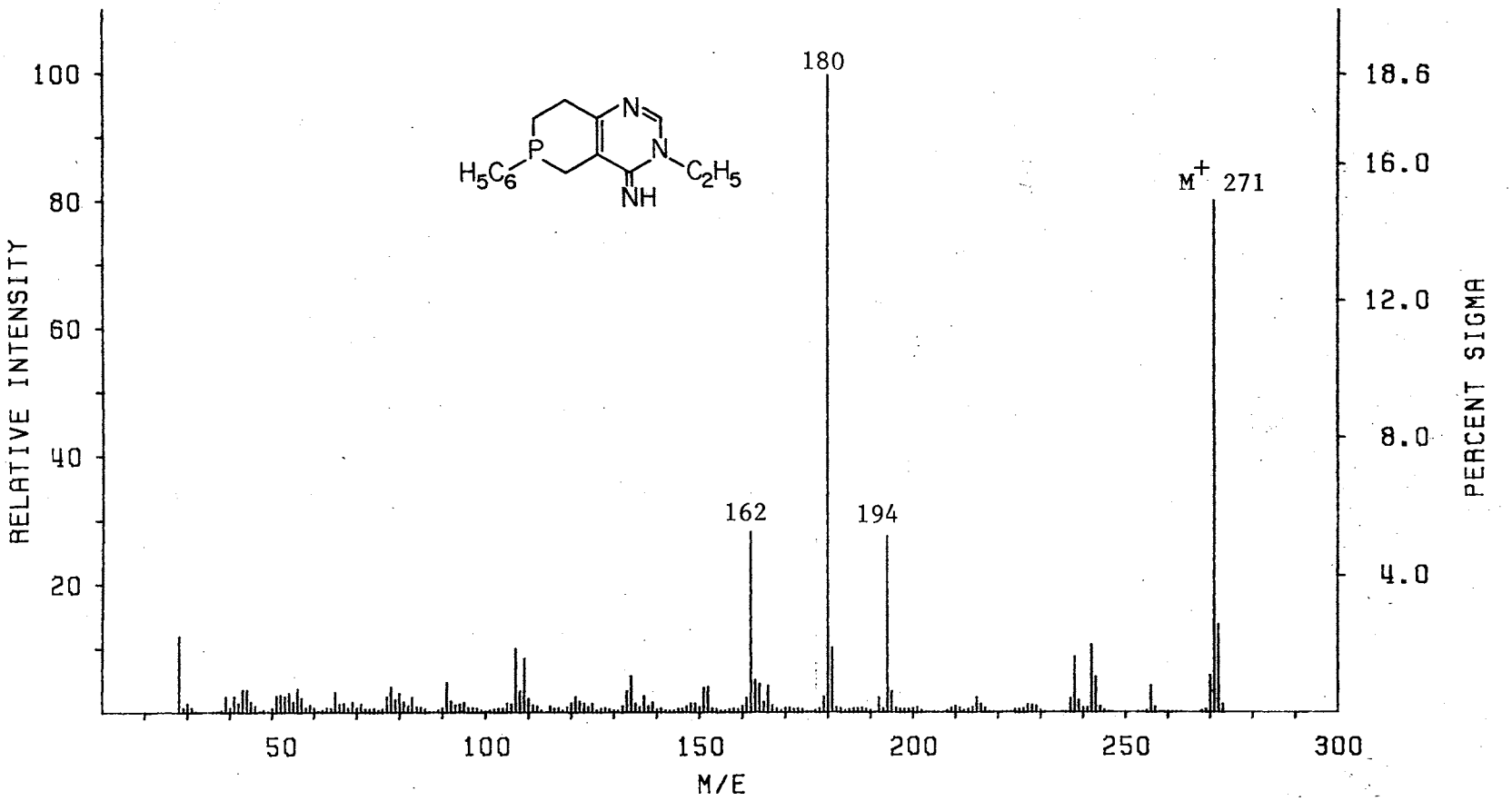


3-Ethyl-5,6,7,8-tetrahydro-4(3H)-imino-6-phenyl-phosphorino[4,3-d]pyrimidine (79)

Solvent. . . . $DCCl_3$ O.F. . . 100 MHz F.B. . . . . 1 Hz R.F. . . . . 65 db

S.W. . . . . 1000 Hz S.T. . . 500 sec S.O. . . 85767 Hz S.A. . . . . 20 Lock. . . . . ^2H

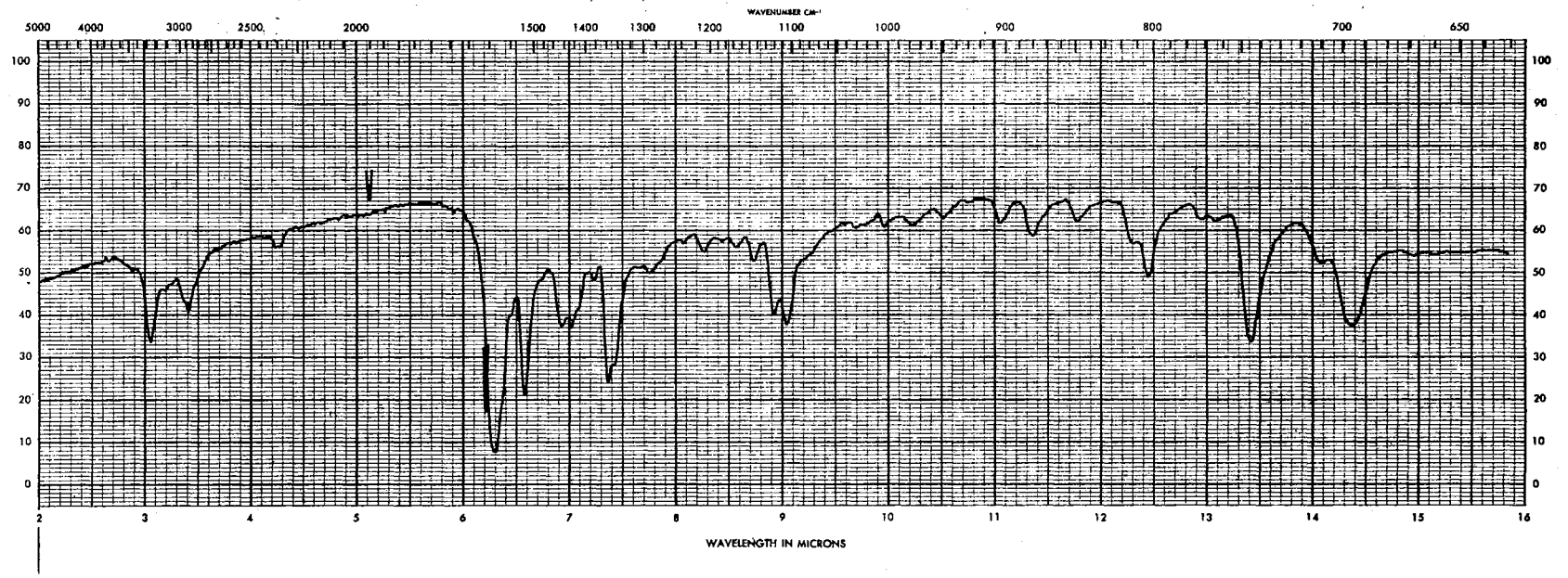
Plate XXXIX



3-Ethyl-5,6,7,8-tetrahydro-4(3H)-imino-6-phenyl-phosphorino[4,3-d]pyrimidine (79)

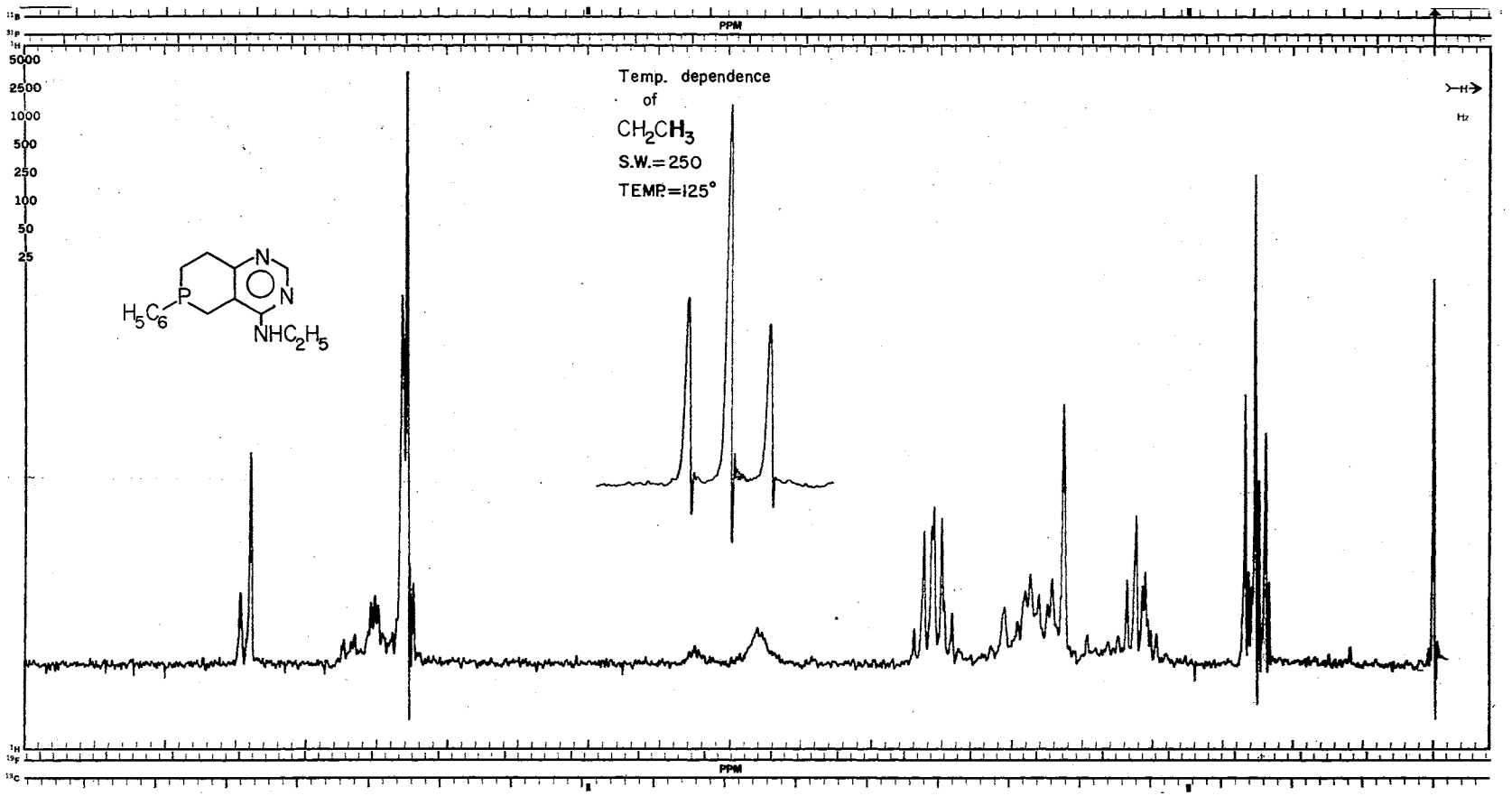
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....47°

Plate XL



4-(Ethylamino)-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine (80), KBr Pellet

Plate XLI

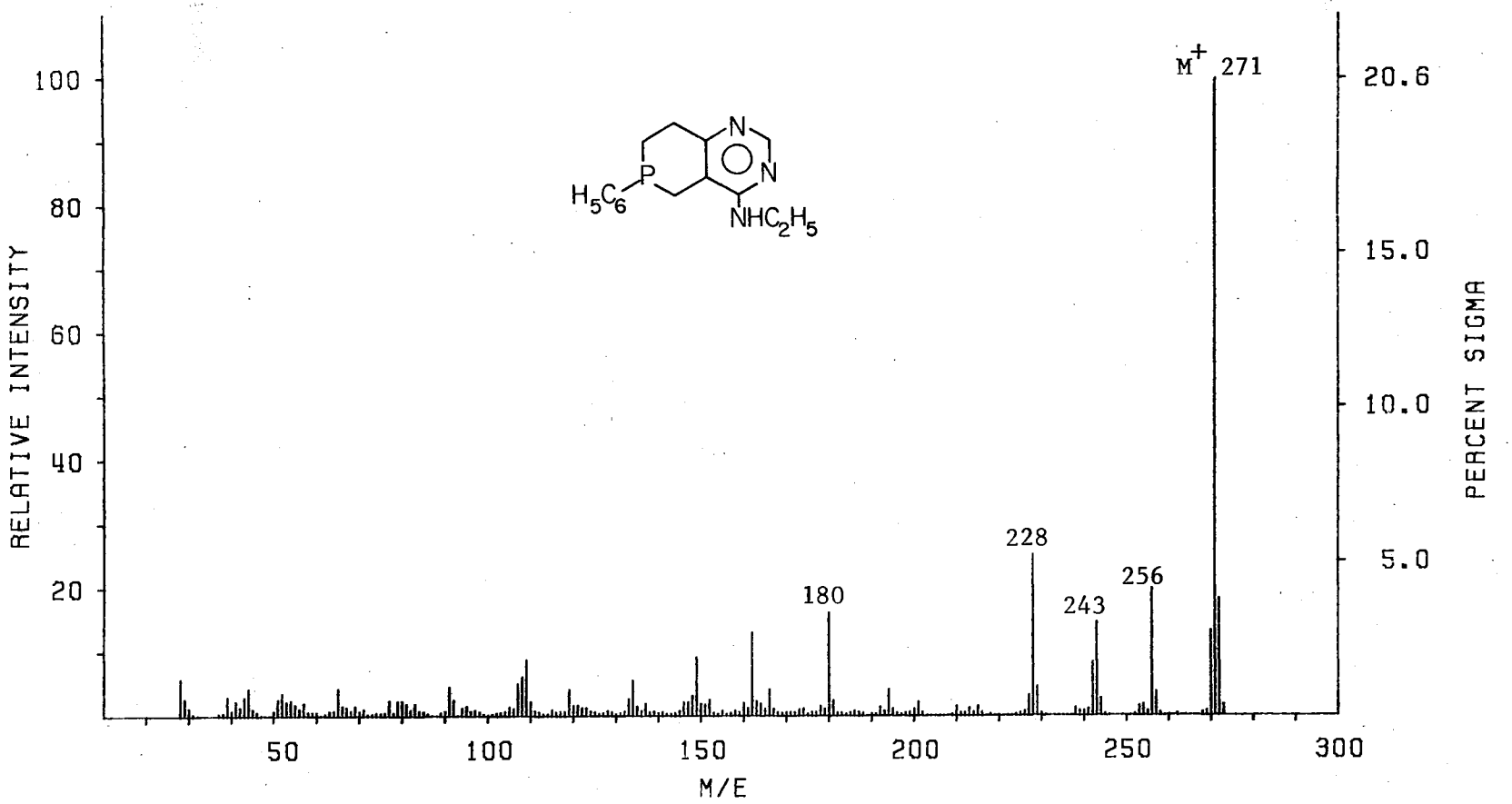


4-(Ethylamino)-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine (80)

Solvent. . . . $DCCl_3$ O.F. . . . 100 MHz F.B. . . . . 1 Hz R.F. . . . 65 db

S.W. . . . . 1000 Hz S.T. . . . 500 sec S.O. . . . 85767 Hz S.A. . . . . 20 Lock. . . . ^2H

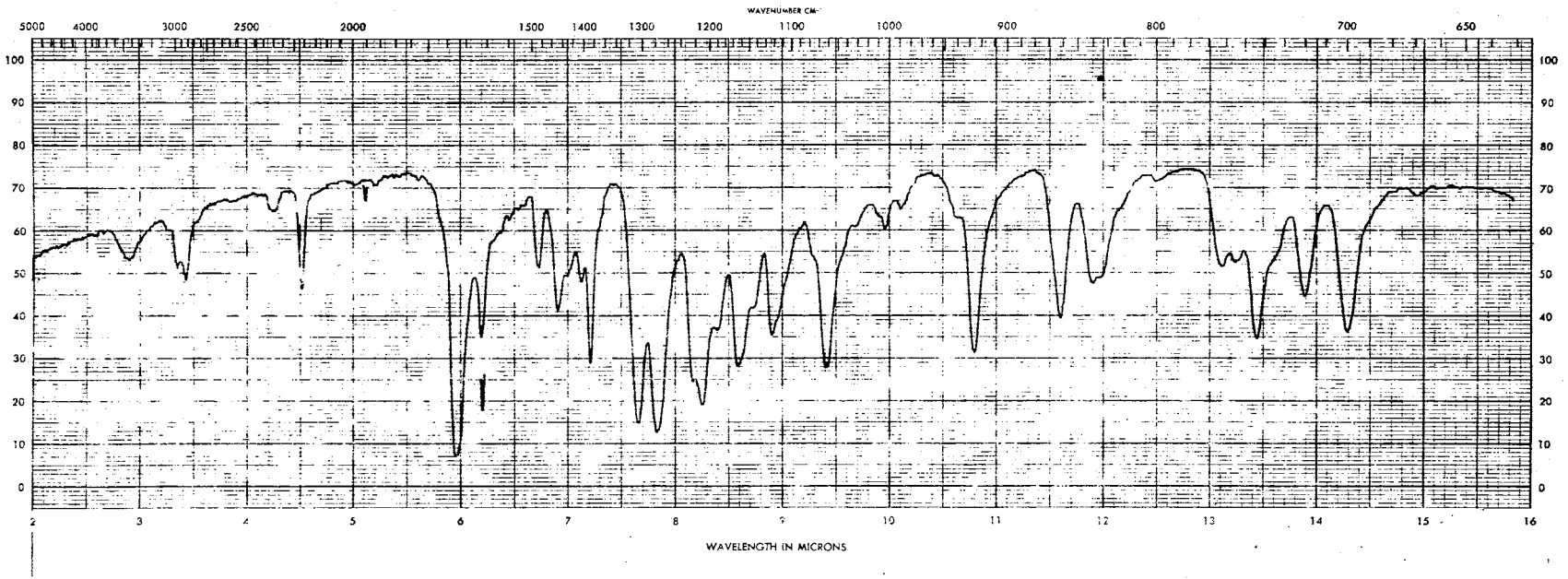
Plate XLII



4-(Ethylamino)-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine (80)

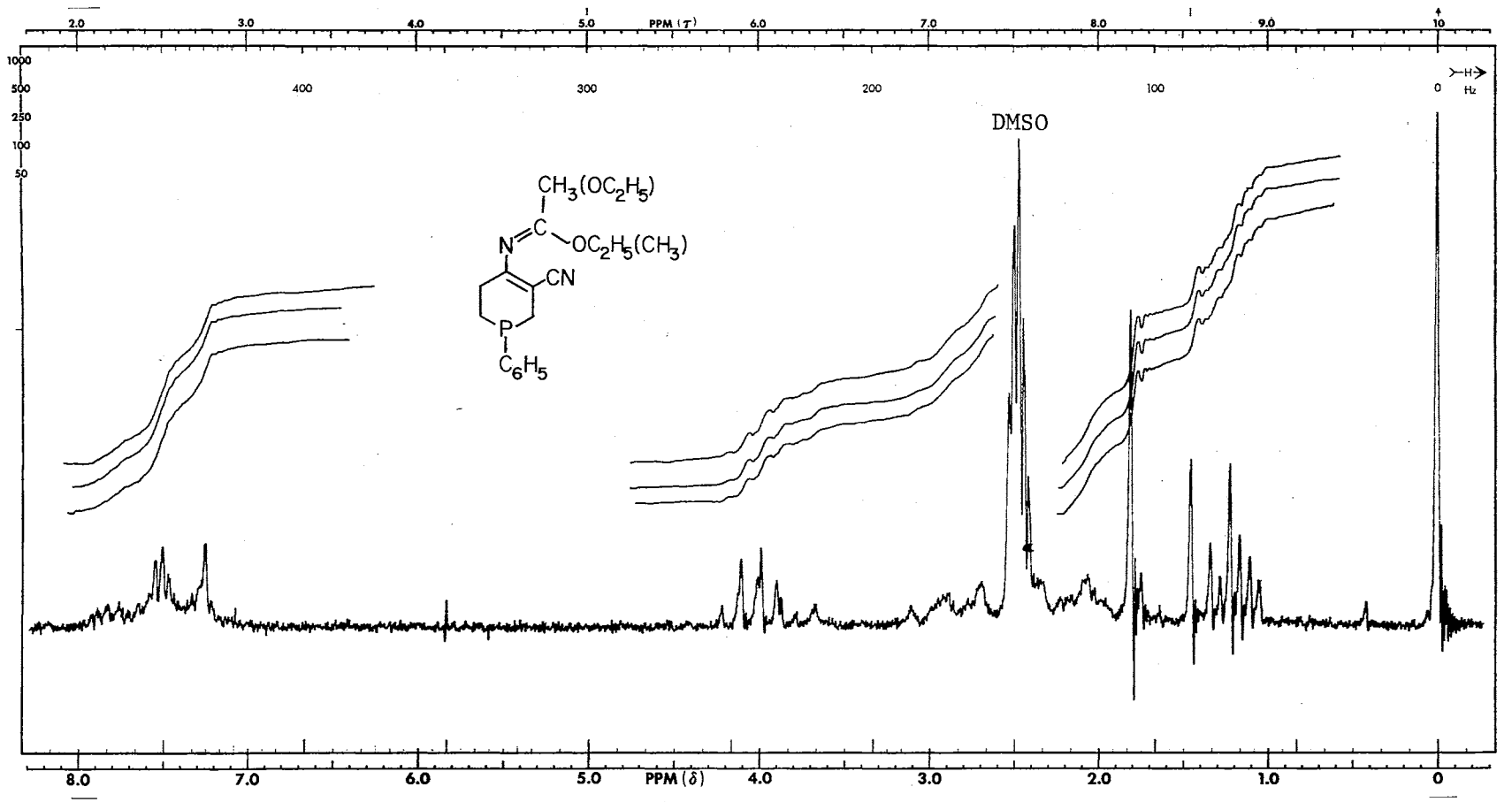
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....45°

Plate XLIII



4-(1-ethoxyethylideneamino)-1,2,5,6-tetrahydro-1-phenyl-phosphorin-3-carbonitrile (120), KBr Pellet

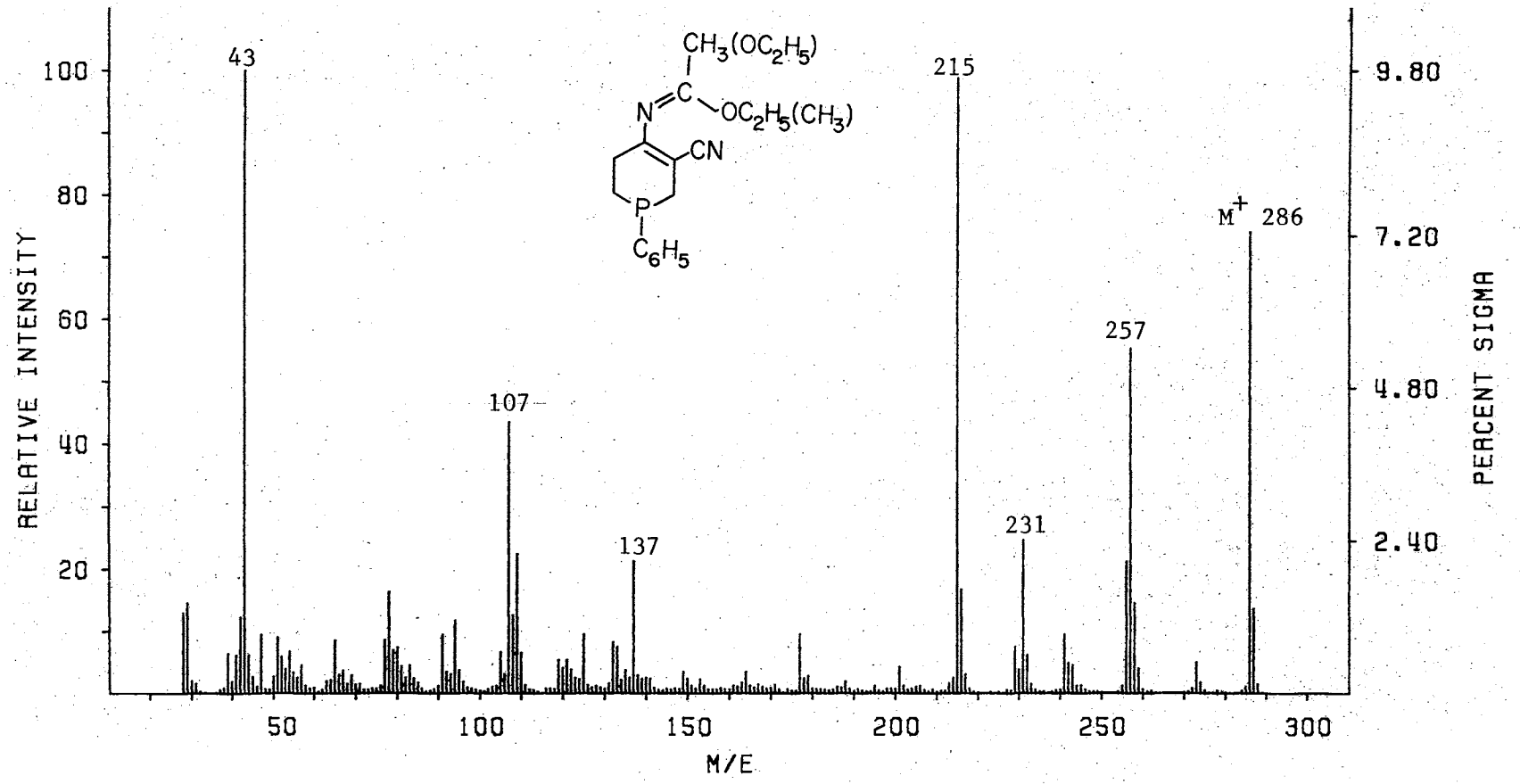
Plate XLIV



4-(1-Ethoxyethylideneamino)-1,2,5,6-tetrahydro-1-phenyl-phosphorin-3-carbonitrile (1.20)

Solvent.	DMSO-d_6	O.F.	60 MHz	F.B.	4 Hz	R.F.	0.05 db
S.W.	500 Hz	S.T.	250 sec	S.O.	0 Hz	S.A.	10

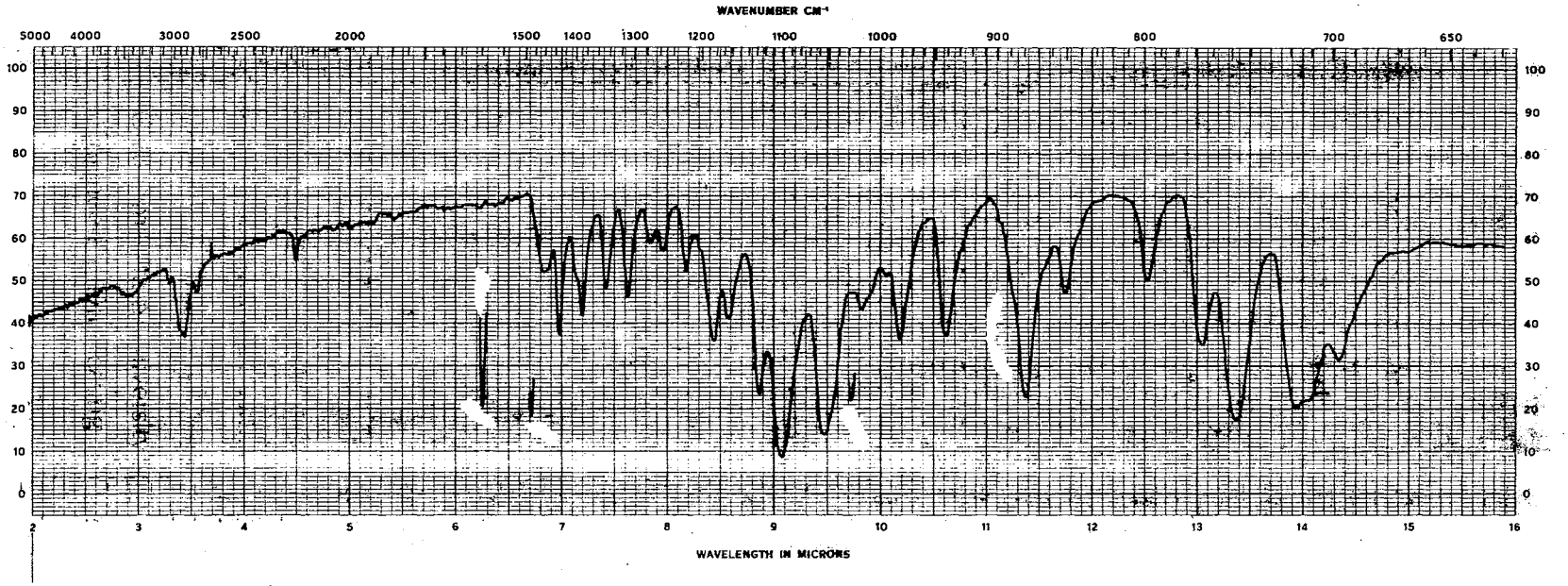
Plate XLV



4-(Ethoxyethylideneamino)-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile (120)

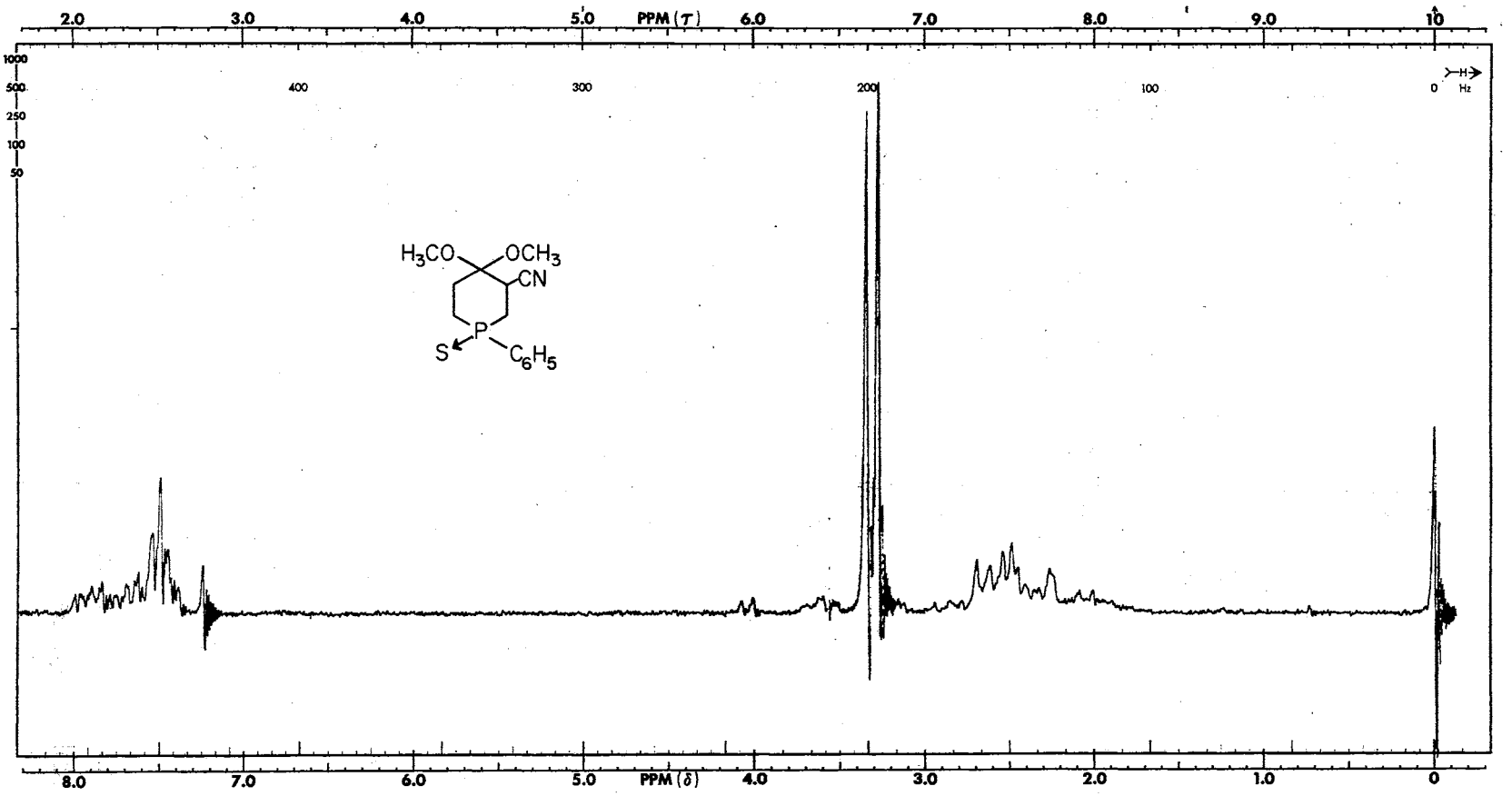
Inlet.....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....50°

Plate XLVI



4-Oxo-1-phenyl-3-phosphorinanecarbonitrile dimethyl acetal 1-sulfide (99), KBr Pellet

Plate XLVII

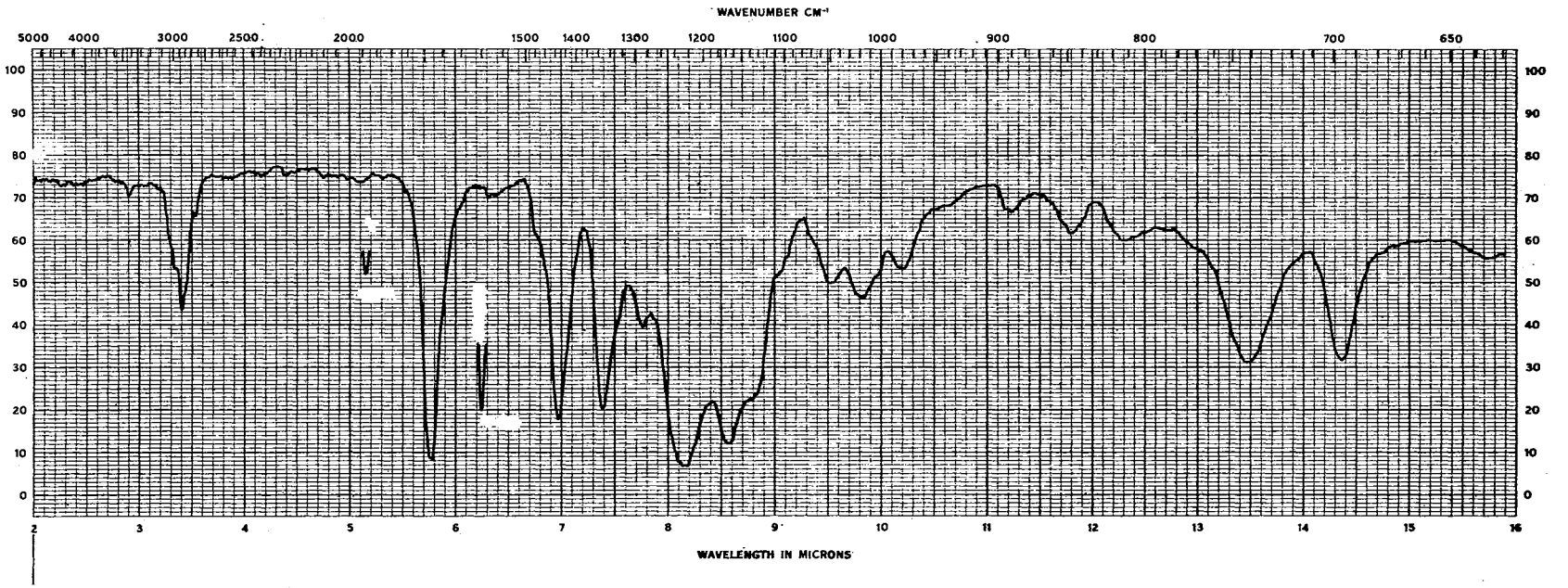


4-Oxo-1-phenyl-3-phosphorinanecarbonitrile dimethyl acetal 1-sulfide (99)

Solvent. . . $DCCl_3$ O.F. . . 60 MHz F.B. . . 4 Hz R.F. . . 0.04 db

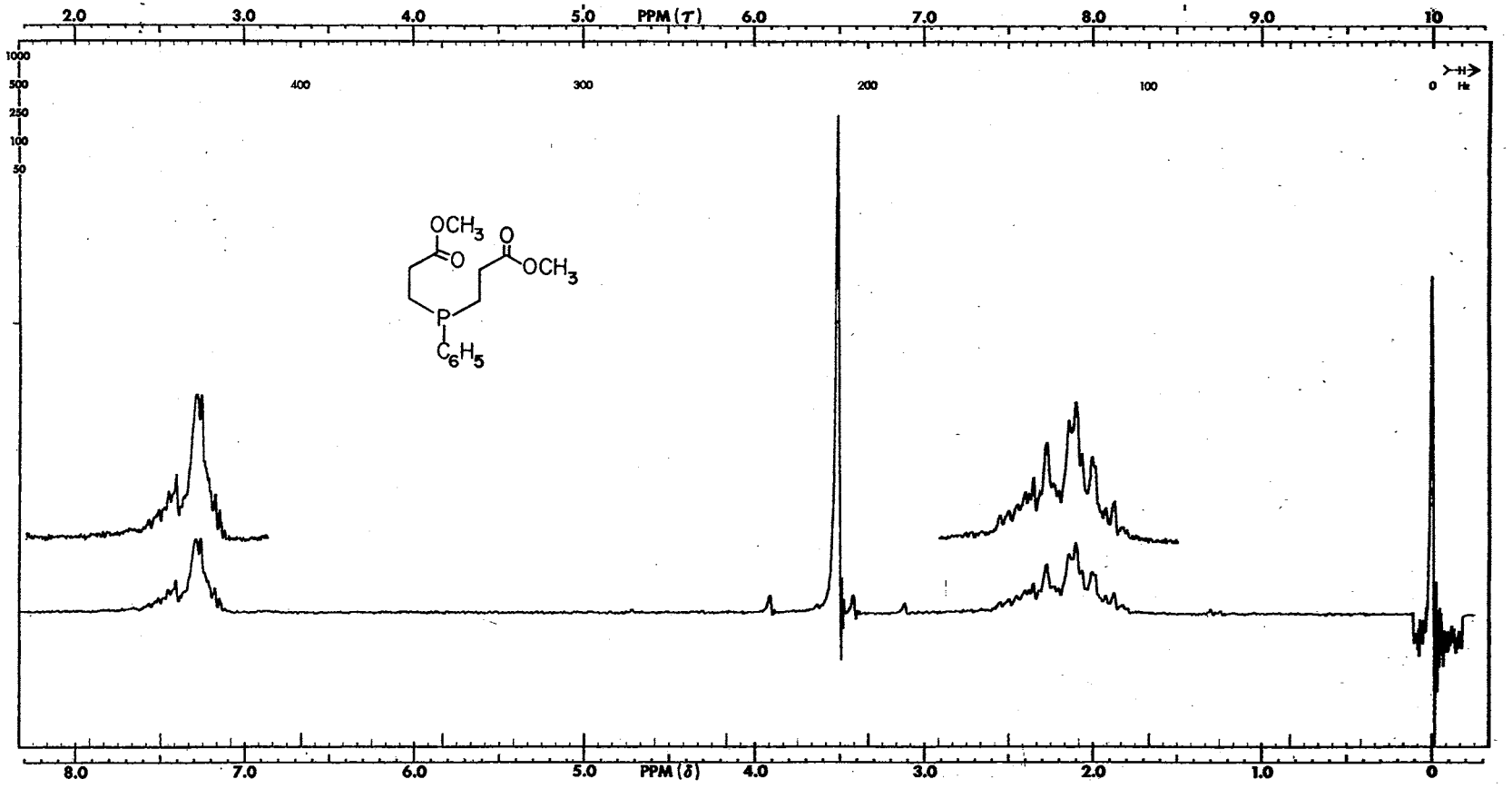
S.W. . . . 500 Hz S.T. . . 250 sec S.O. . . 0 Hz S.A. 4.0

Plate XLVIII



Bis(carbomethoxyethyl)phenylphosphine (96), Film on NaCl Plates

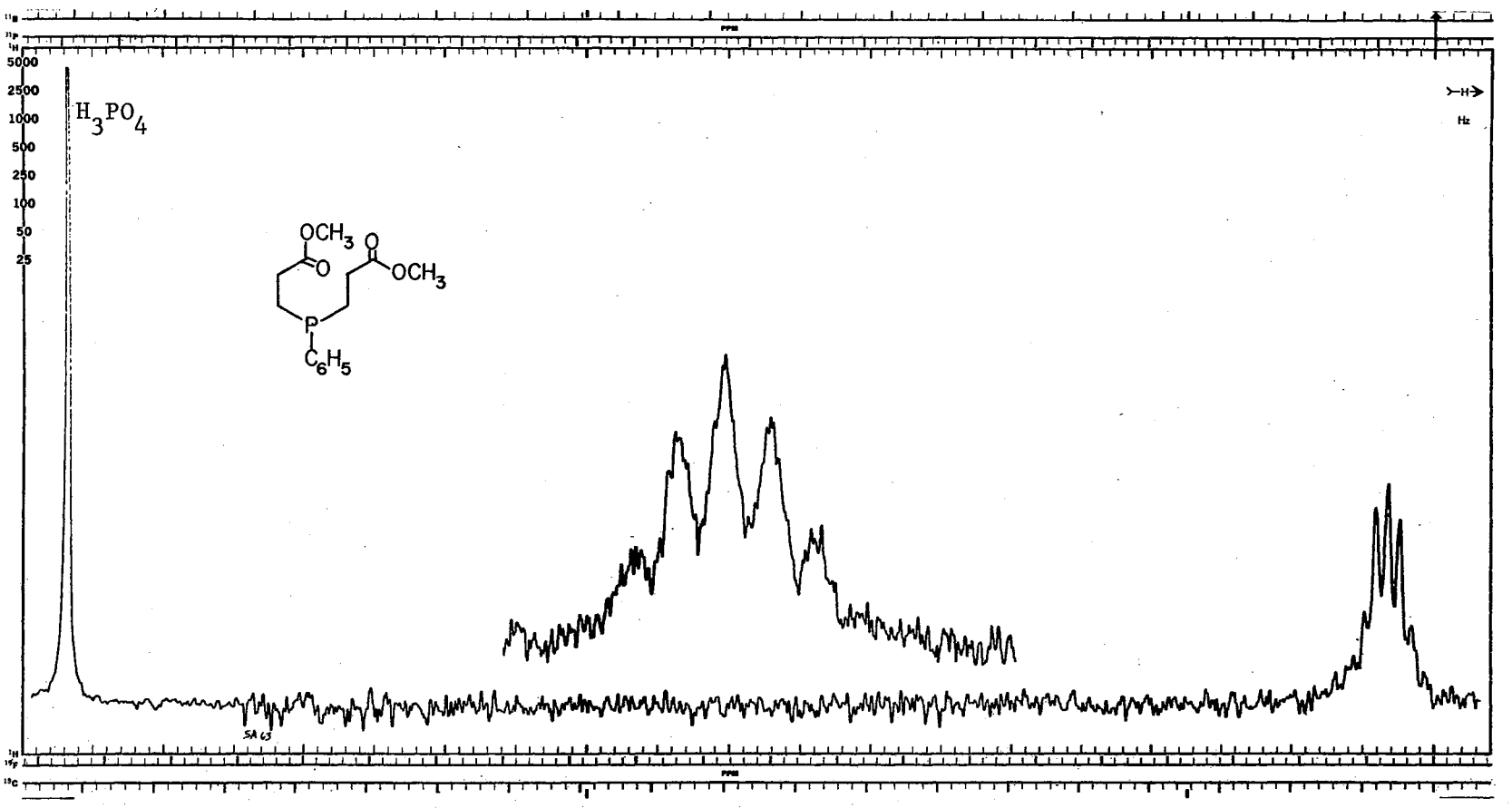
Plate XLIX



Bis(carbomethoxyethyl)phenylphosphine (96)

Solvent. . . . . $DCCl_3$	O.F. . . . . 60 MHz	F.B. . . . . 4 Hz	R.F. . . . . .01 db
S.W. . . . . 500 Hz	S.T. . . . . 250 sec	S.O. . . . . 0 Hz	S.A. 0.5

Plate L

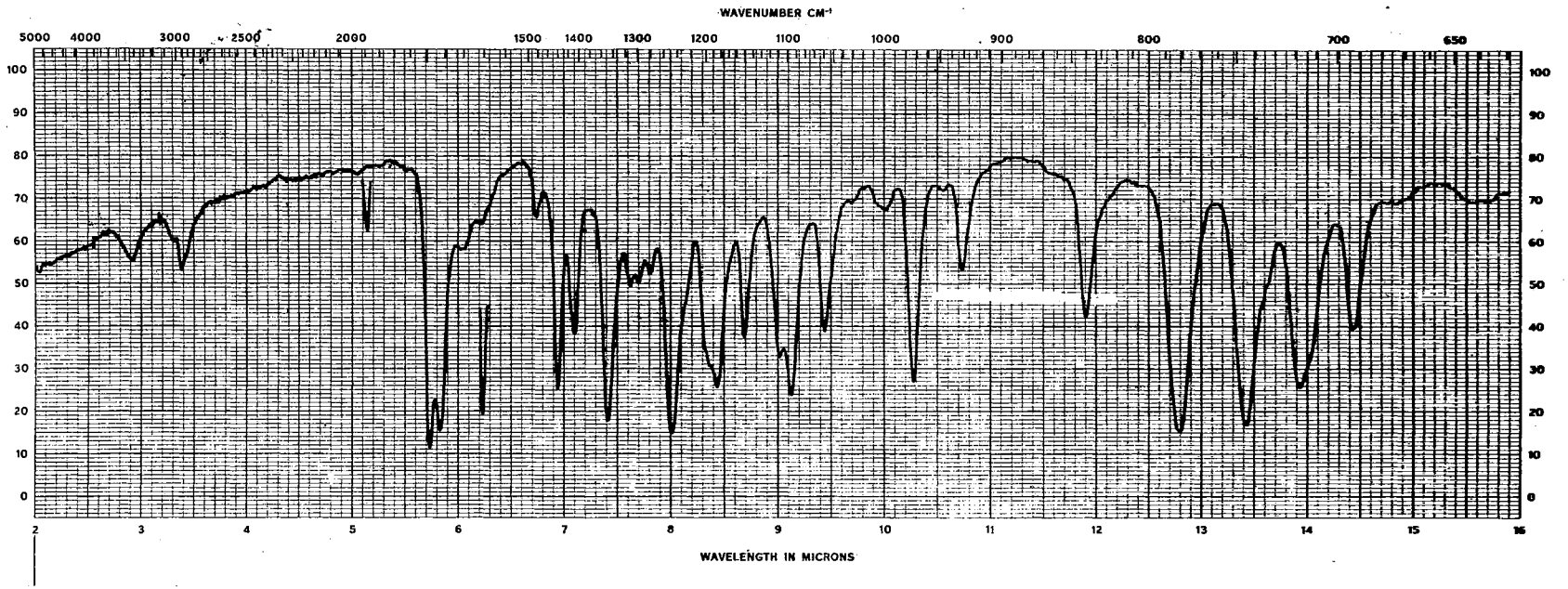


^{31}P Spectrum of Bis(carbomethoxyethyl)phenylphosphine (96)

Solvent. . . $HCCl_3$ O.F. . . 40.5 MHz F.B. . . . . 1 Hz R.F. . . 71 db Lock. . . 'H

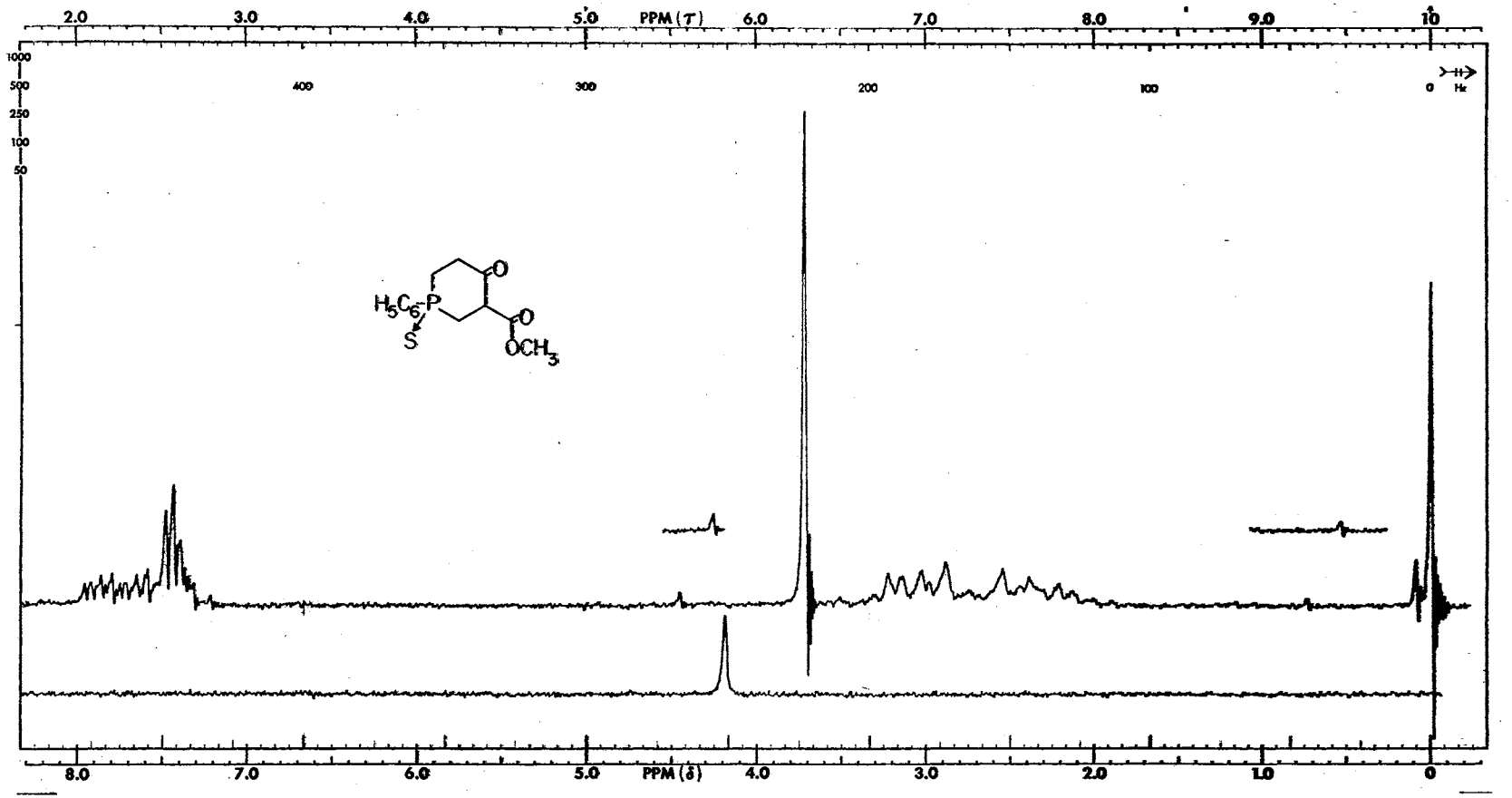
S.W. . . . 1000 Hz S.T. . . 250 sec S.O. . . 87735 Hz S.A. . . . 63

Plate LI



Methyl 4-oxo-1-phenyl-3-phosphorinanecarboxylate 1-sulfide (98), KBr Pellet

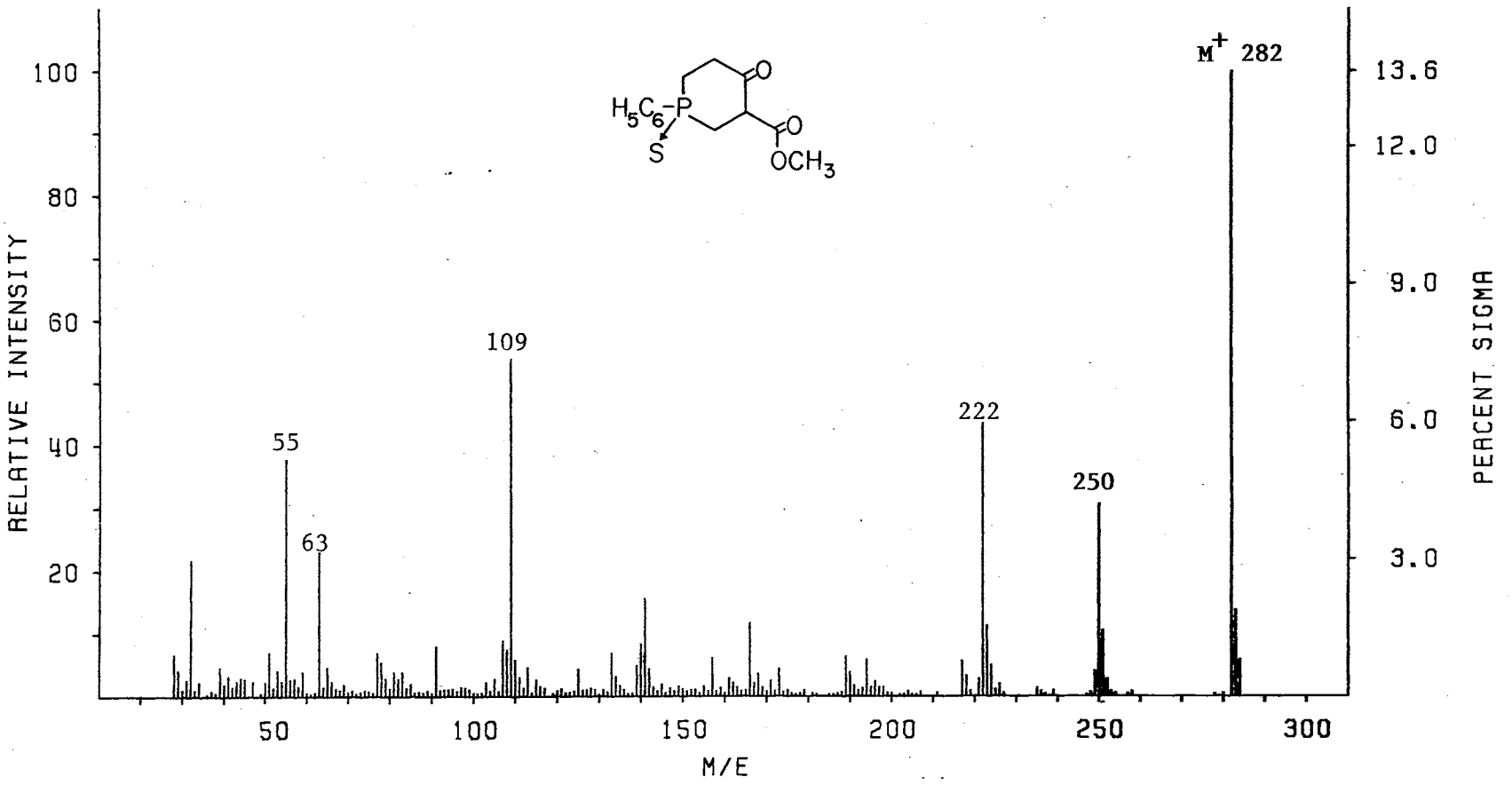
Plate LII



Methyl 4-oxo-1-phenyl-3-phosphorinanecarboxylate 1-sulfide (98)

Solvent. . . . . $DCCl_3$ O.F. . . . . 60 MHz F.B. . . . . 4 Hz R.F. . . . . 0.035 db

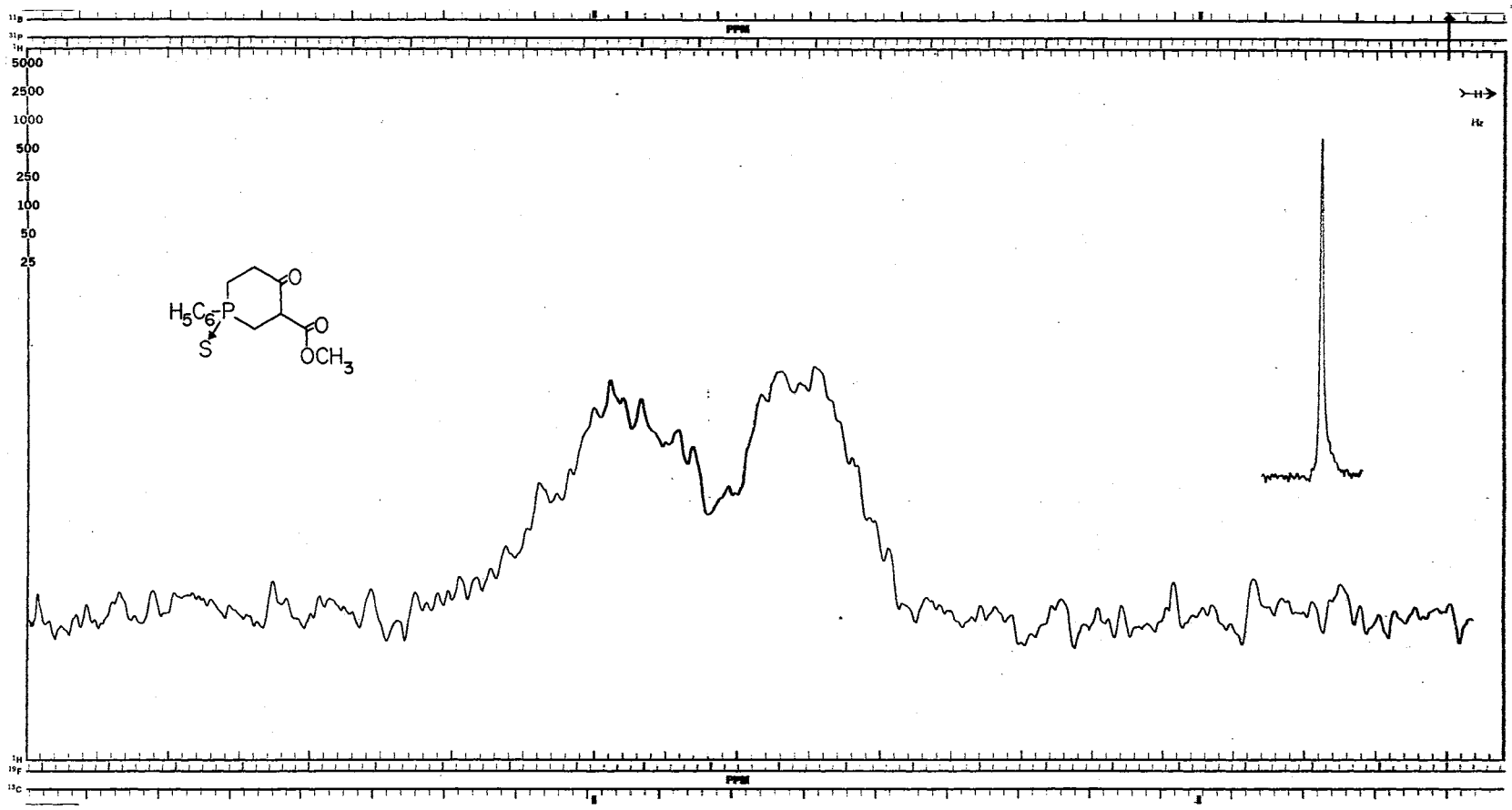
Plate LIII



Methyl 4-oxo-1-phenyl-3-phosphorinanecarboxylate 1-sulfide (98)

Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....35°

Plate LIV

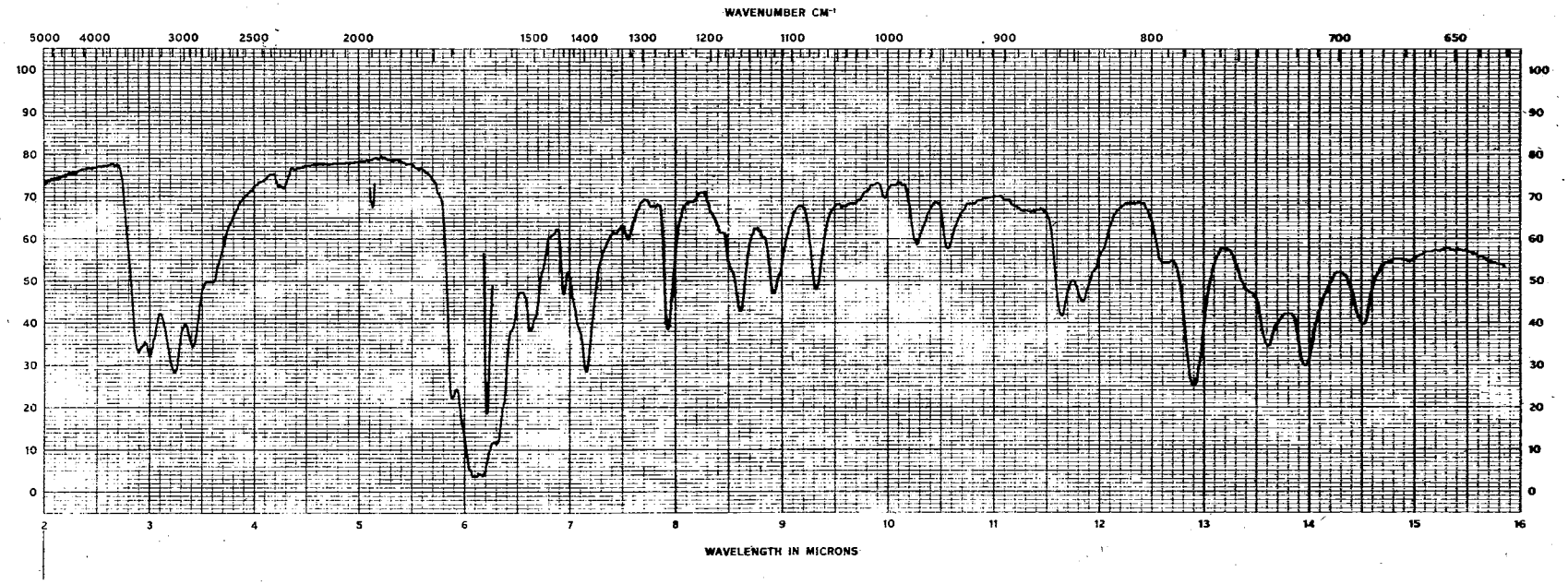


^{31}P Spectrum of Methyl 4-oxo-1-phenyl-3-phosphorinanecarboxylate 1-sulfide (98)

Solvent. . . CH_3OH O.F. . . 40.5 MHz F.B. . . . . 1 Hz R.F. . . 75 db

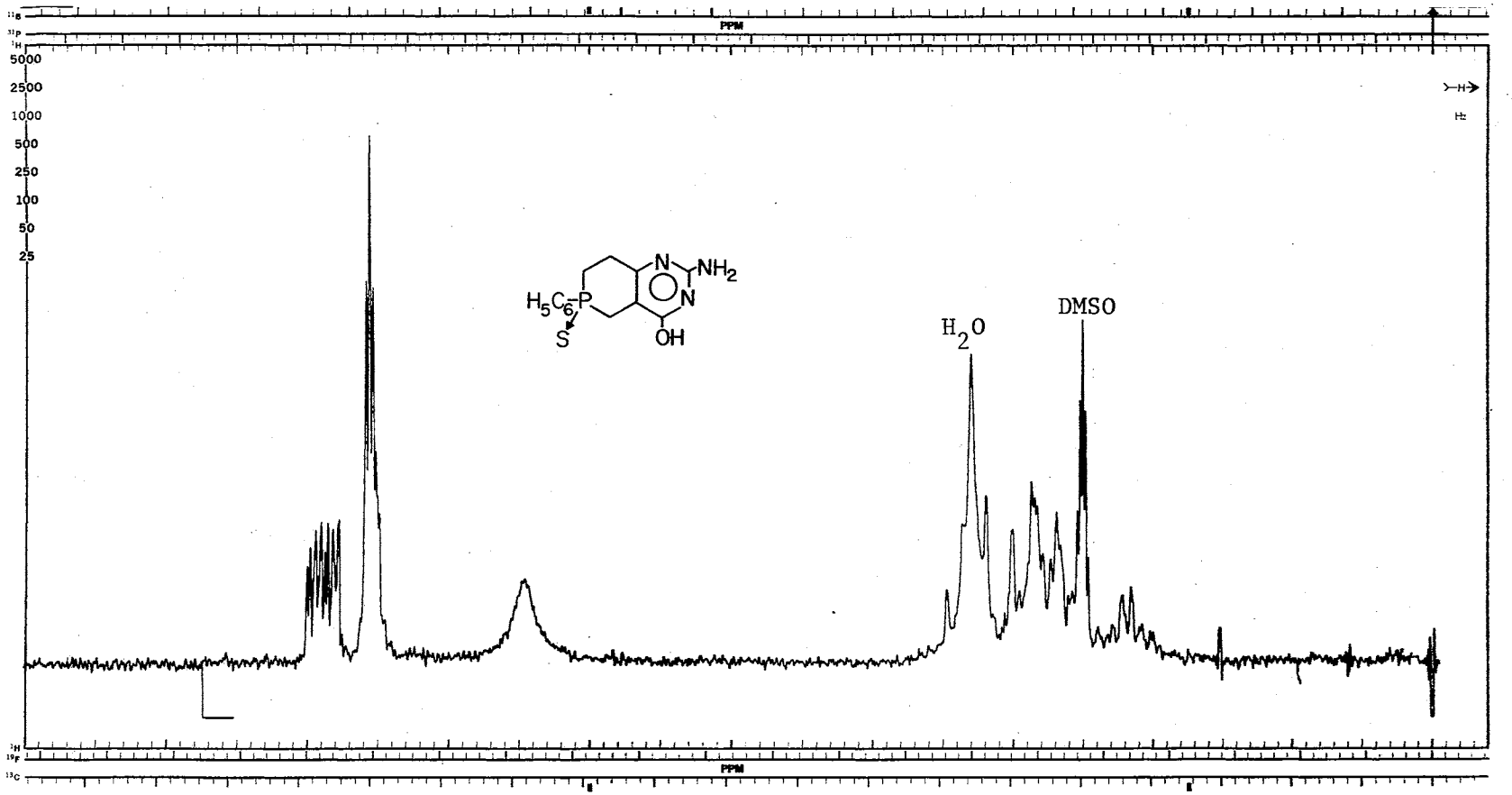
S.W. . . . 1000 Hz S.T. . . 250 sec S.O. . . 89735 Hz S.A. . . . 100 Lock. . .^1H

Plate LV



2-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidin-4-ol 6-sulfide (81), KBr Pellet

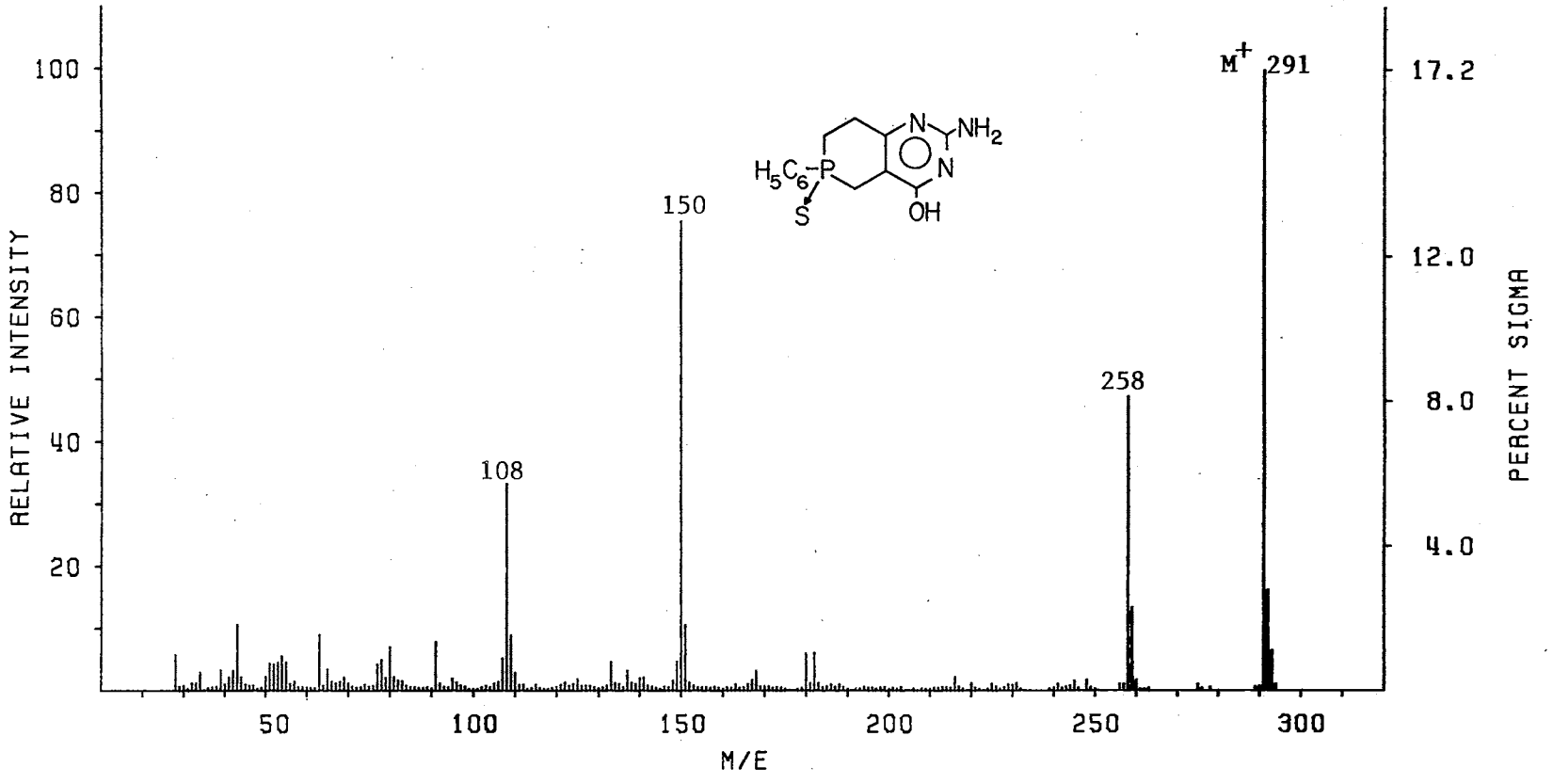
Plate LVI



2-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidin-4-ol 6-sulfide (81)

Solvent. . . DMSO-d_6 O.F. . . 100 MHz F.B. . . . . 1 Hz R.F. . . 65 db

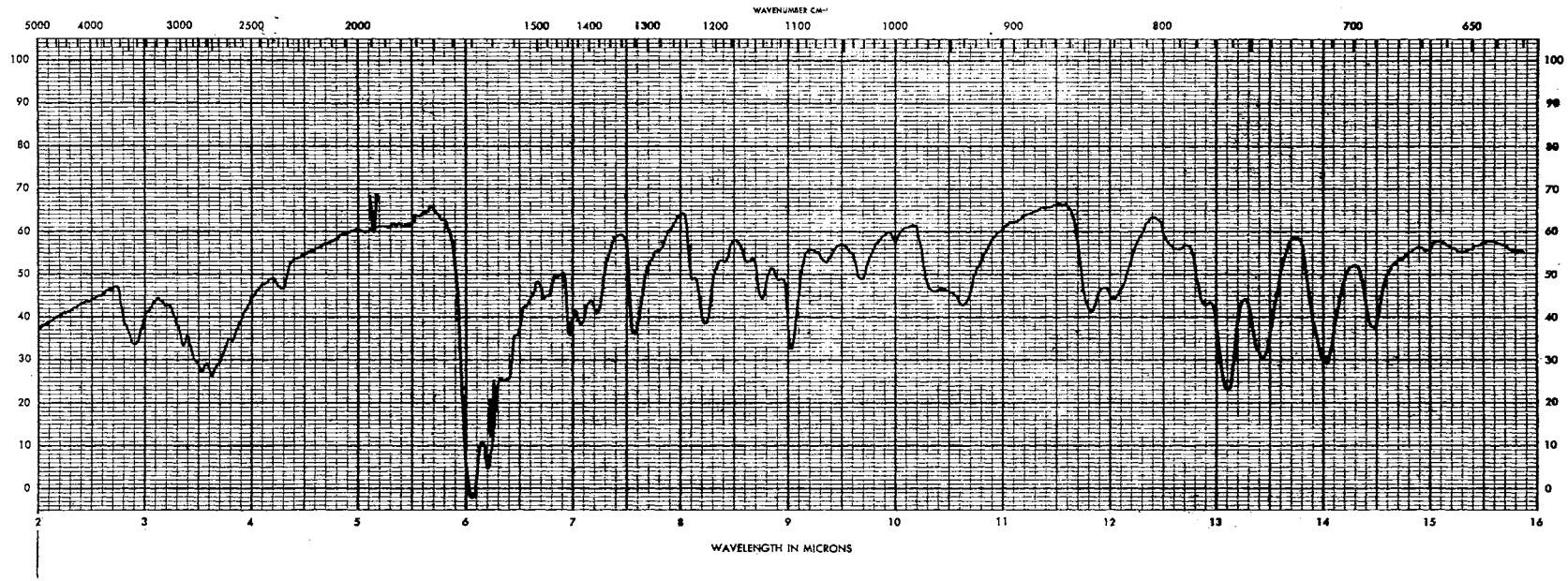
Plate LVII



2-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidin-4-ol 6-sulfide (81)

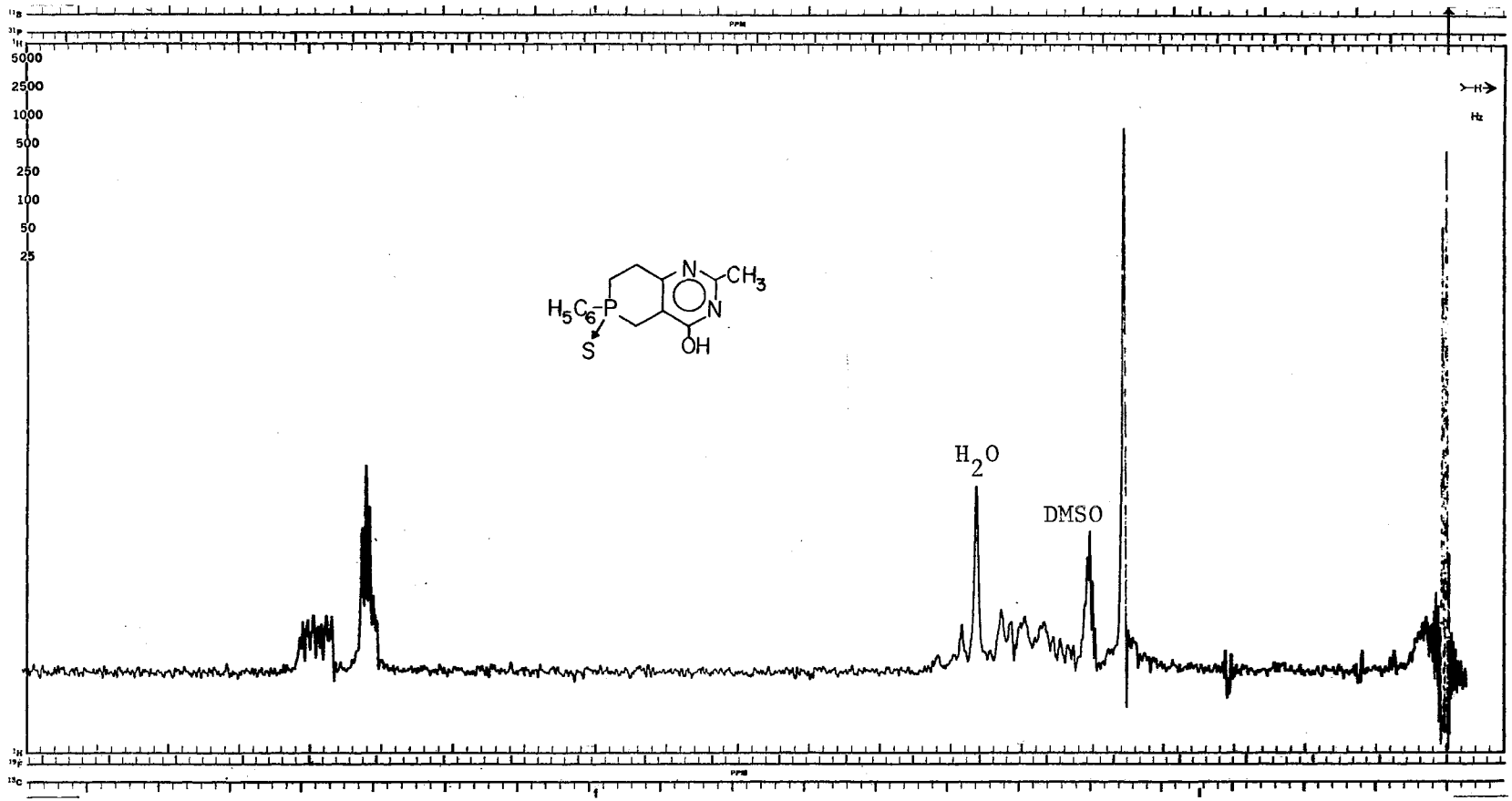
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....215°

Plate LVIII



5,6,7,8-Tetrahydro-2-methyl-6-phenylphosphorino[4,3-d]pyrimidin-4-ol 6-sulfide (82), KBr Pellet

Plate LIX

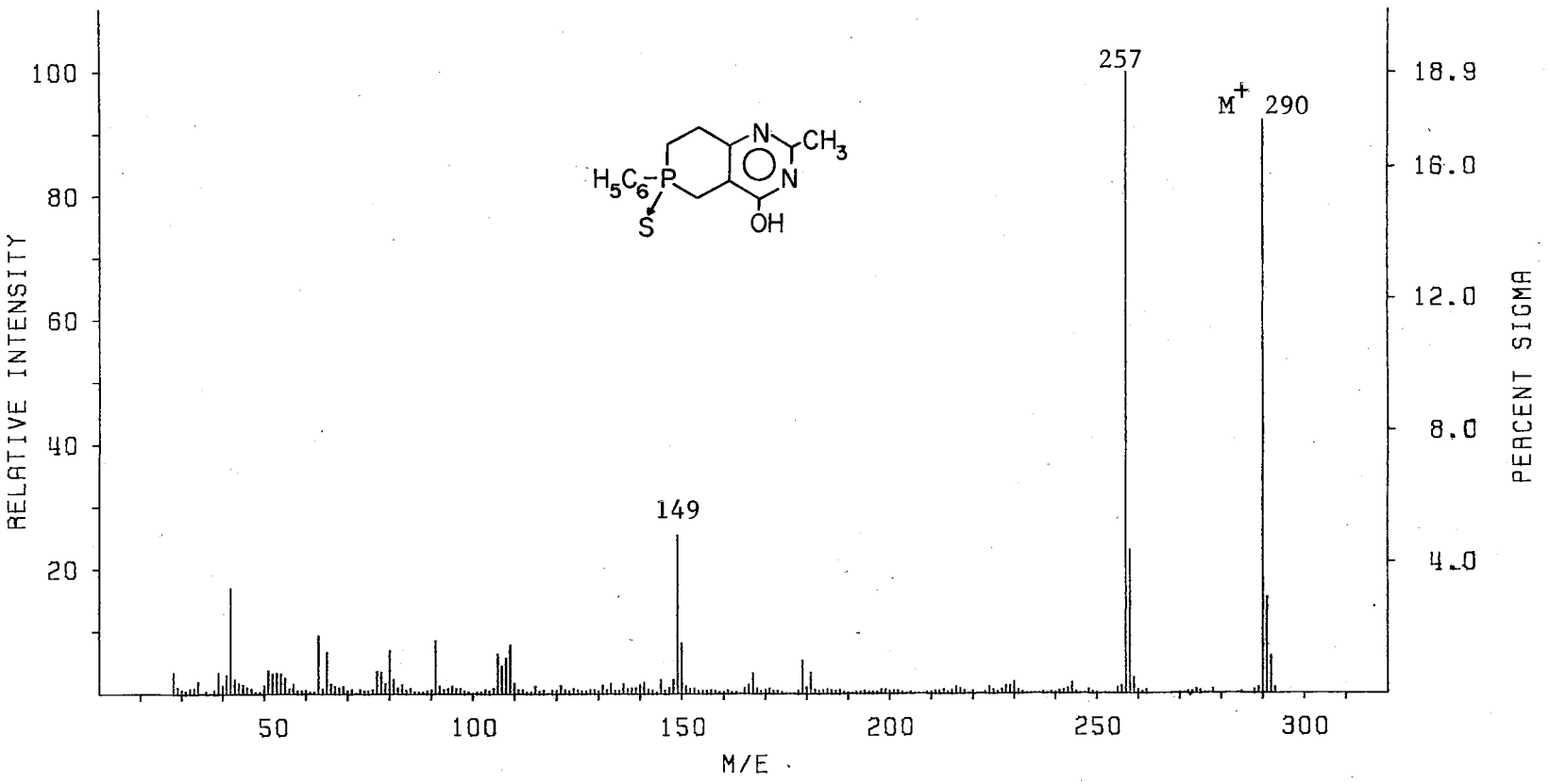


5,6,7,8-Tetrahydro-2-methyl-6-phenylphosphorino[4,3-d]pyrimidin-4-ol 6-sulfide (82)

Solvent. . . DMSO-d_6 O.F. . . 100 MHz F.B. . . . . 2 Hz R.F. . . 58 db

S.W. . . . . 1000 Hz S.T. . . 250 sec S.O. . . 83701 Hz S.A. . . . 16 Lock. . . . HOMO

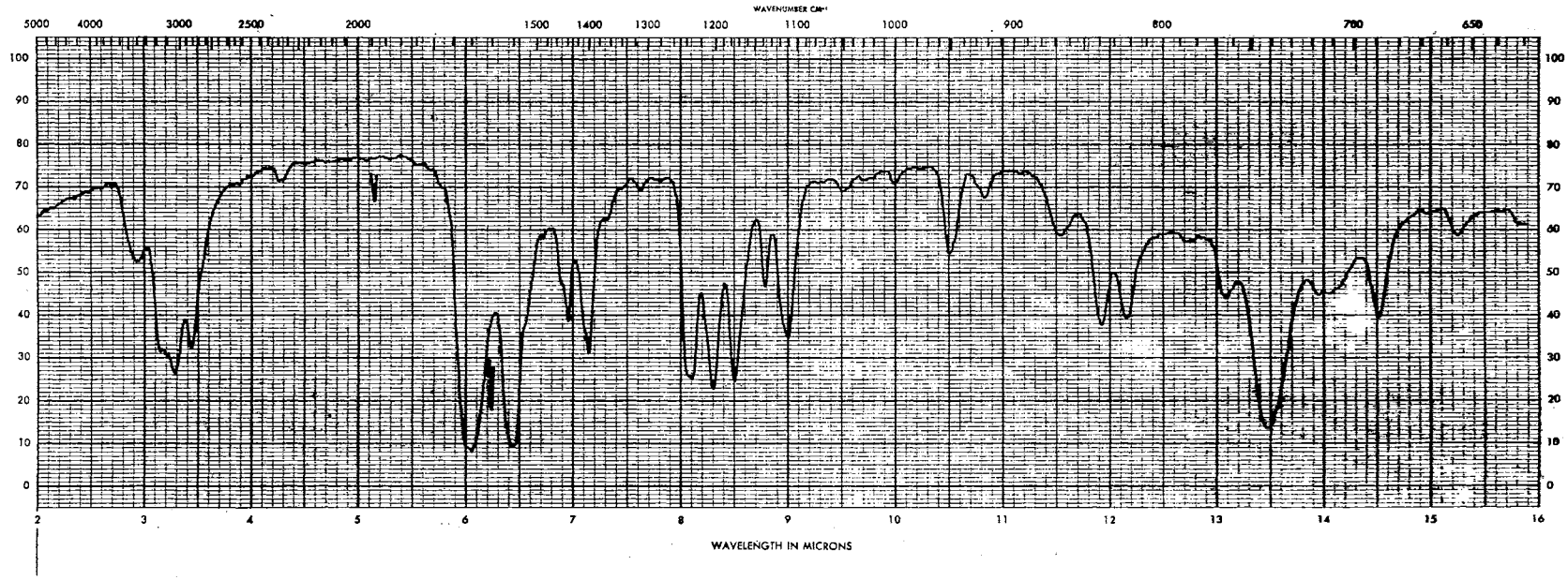
Plate LX



5,6,7,8-Tetrahydro-2-methyl-6-phenylphosphorino[4,3-d]pyrimidin-4-ol 6-sulfide (82)

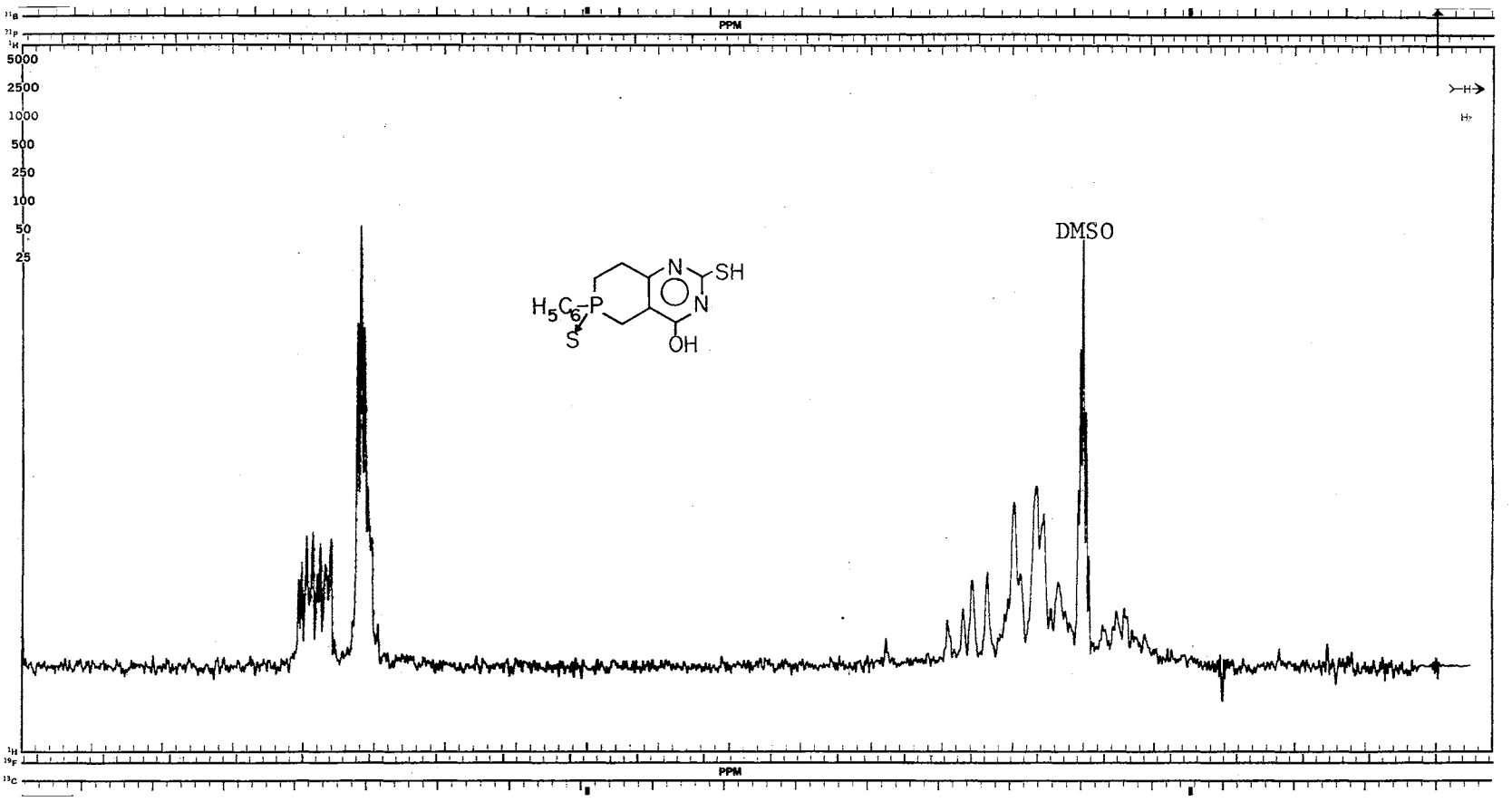
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....150° Probe °C....90°

Plate LXI



5,6,7,8-Tetrahydro-2-mercapto-6-phenylphosphorino[4,3-d]pyrimidin-4-ol 6-Sulfide (83), KBr Pellet

Plate LXII

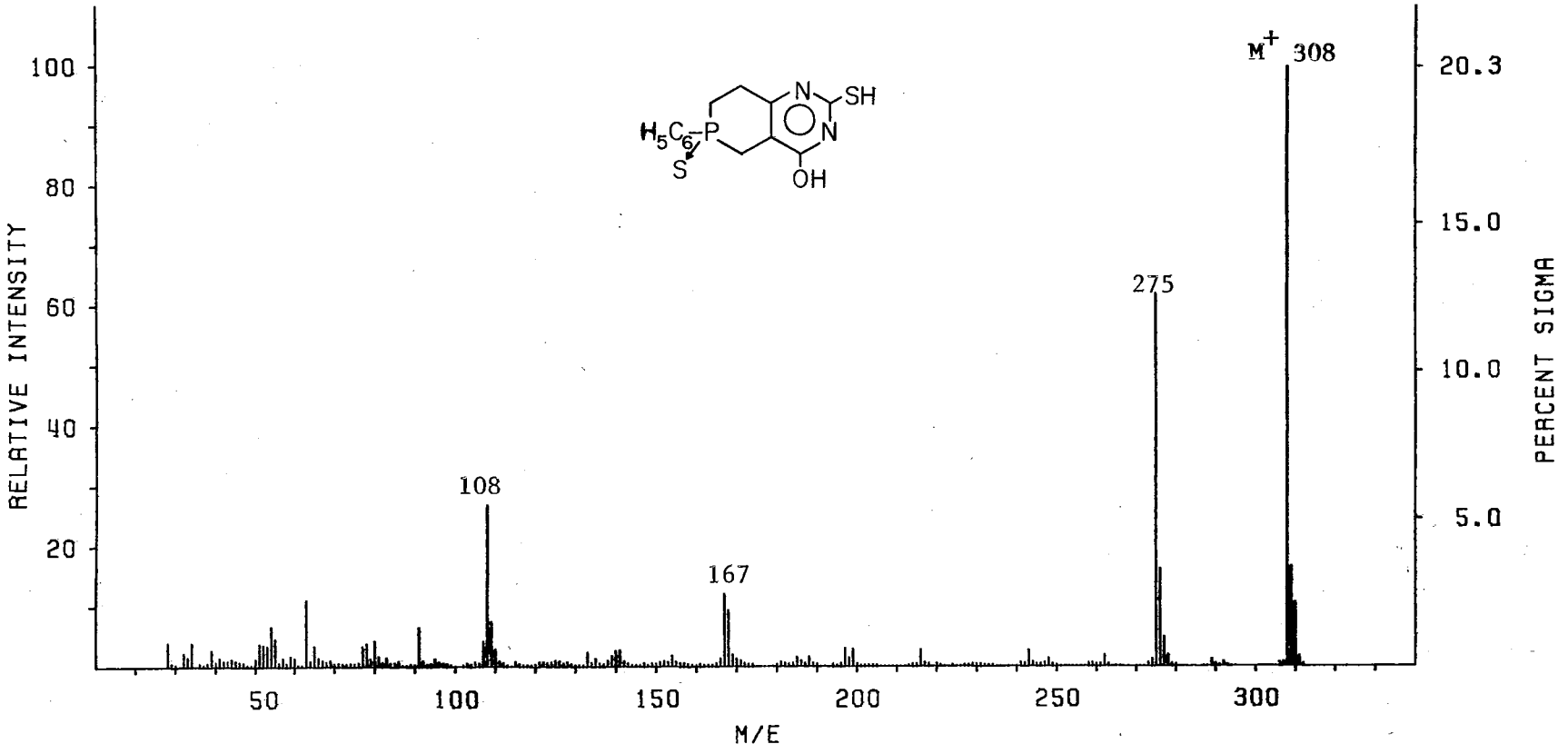


5,6,7,8-Tetrahydro-2-mercapto-6-phenylphosphorino[4,3-d]pyrimidin-4-ol 6-sulfide (83)

Solvent. . . DMSO-d_6 O.F. . . 100 MHz F.B. . . . . 1 Hz R.F. . . 65 db

S.W. . . . . 1000 Hz S.T. . . 500 sec S.O. . . 83701 Hz S.A. . . . 32 Lock. . . HOMO

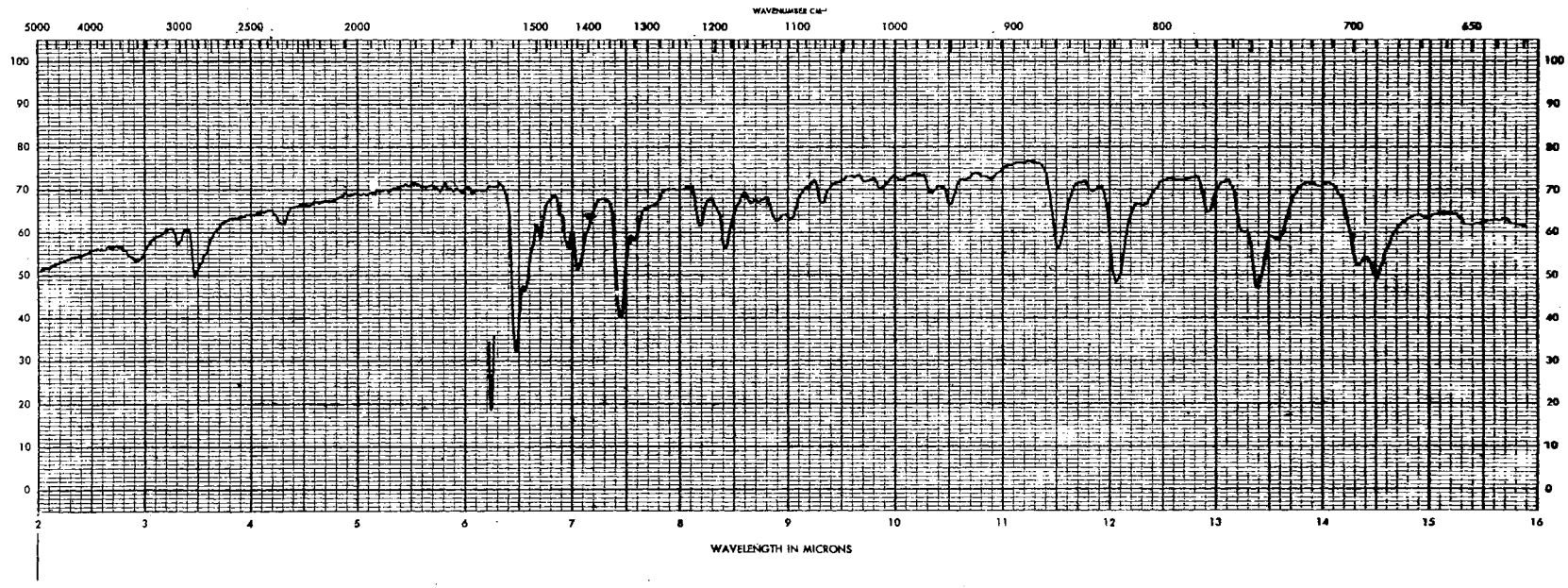
Plate LXIII



5,6,7,8-Tetrahydro-2-mercapto-6-phenylphosphorino[4,3-d]pyrimidin-4-ol 6-sulfide (83)

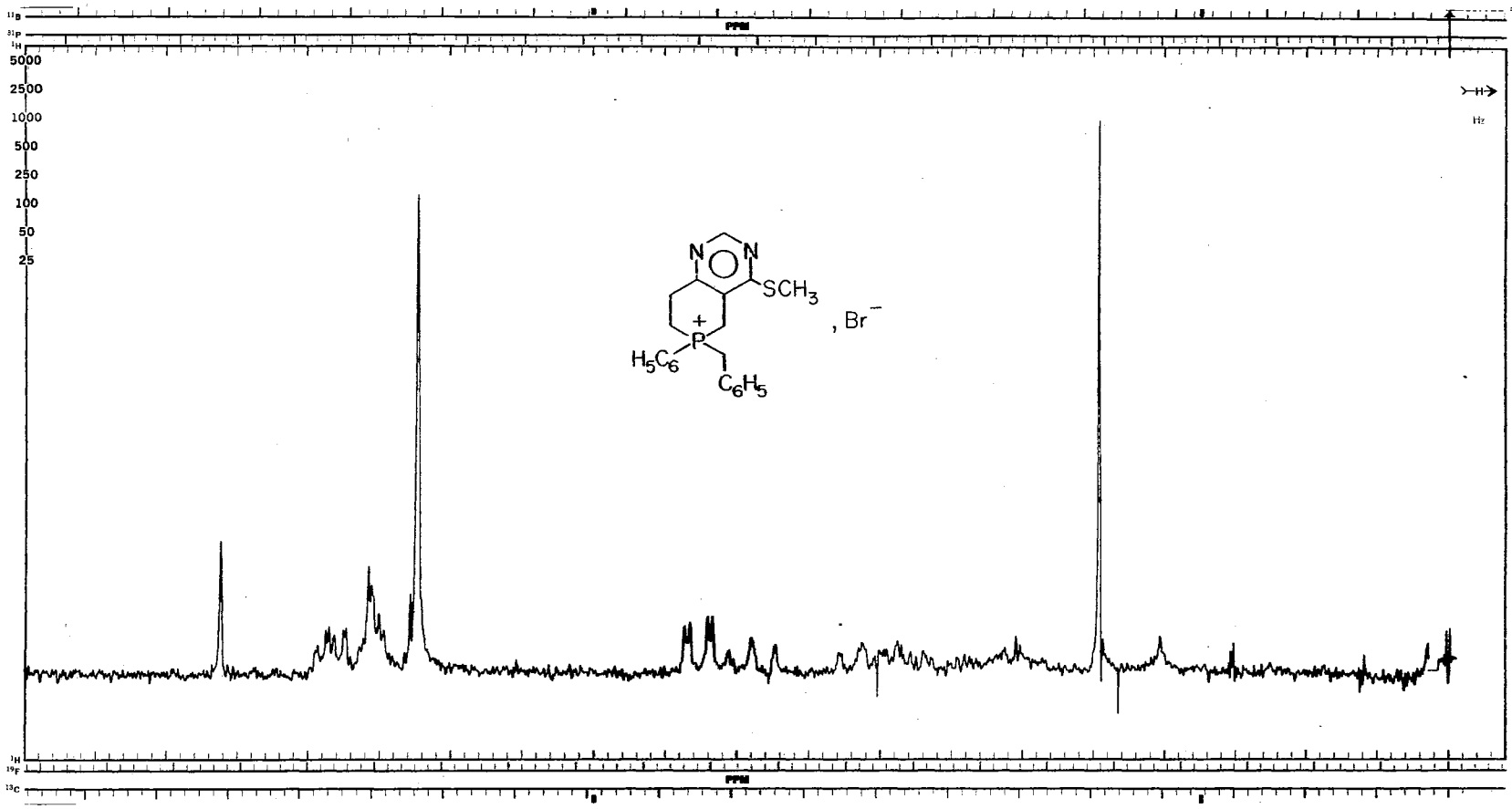
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....160°

Plate LXIV



5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinia[4,3-d]pyrimidine Bromide (88), KBr Pellet

Plate LXV

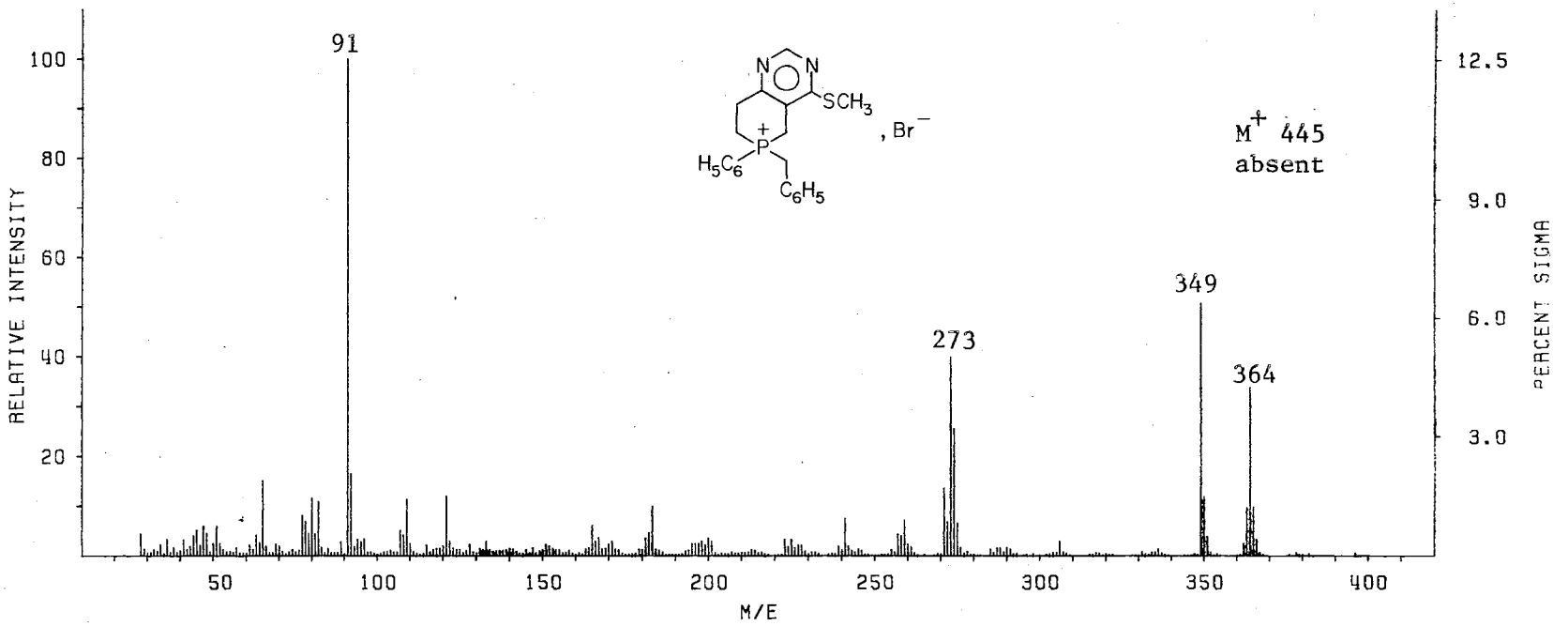


5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenyl-phosphorinia[4,3-d]pyrimidine Bromide (88)

Solvent. . . $DCCl_3$ O.F. . . 100 MHz F.B. . . . . 1 Hz R.F. . . . 62 db

S.W. . . . 1000 Hz S.T. . . 500 sec S.O. . . . 83701 Hz S.A. . . . . 25 Lock. . . . HOMO

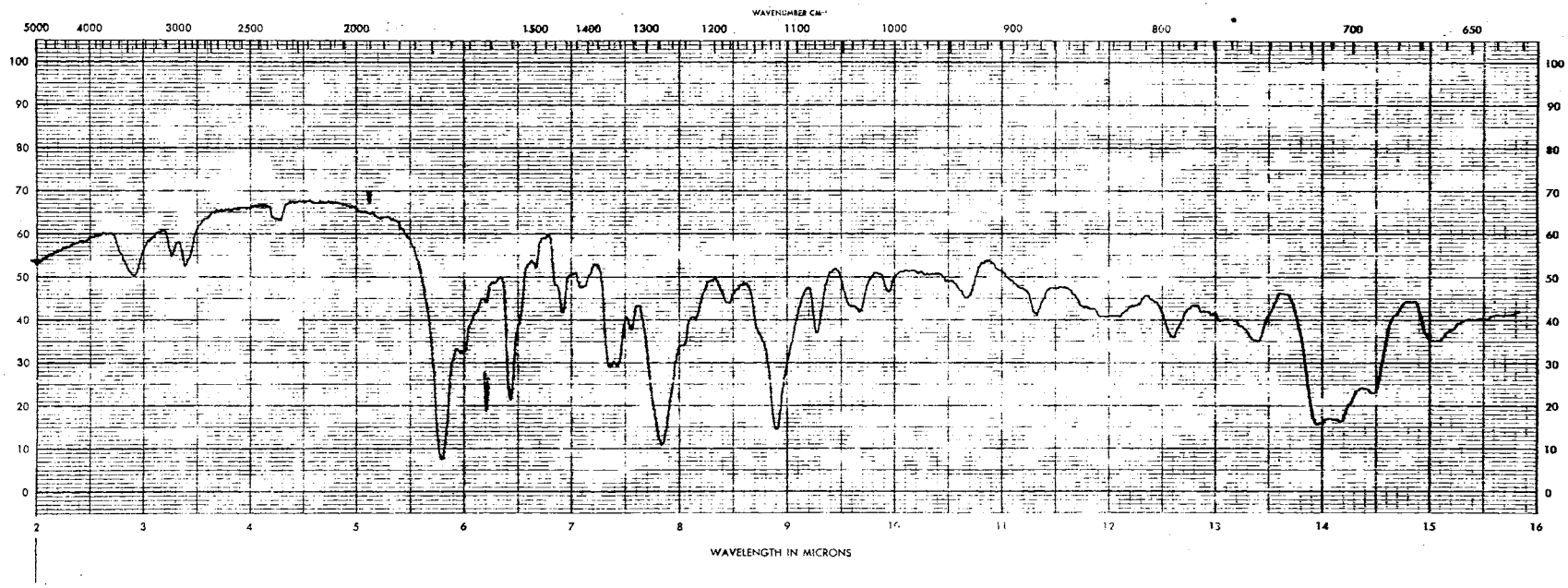
Plate LXVI



5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenyl-phosphorinia[4,3-d]pyrimidine Bromide (88)

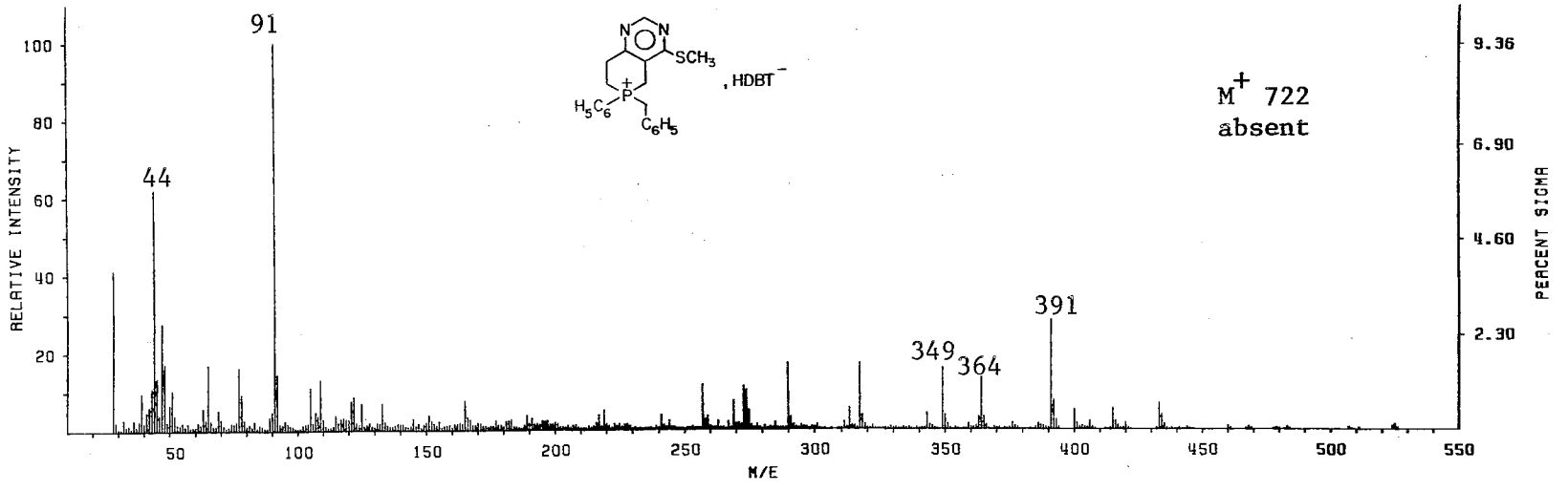
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....180°

Plate LXVII



(+)-5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenyl-phosphorinia[4,3-d]pyrimidine Hydrogen D(-,1)-Dibenzoyltartrate((+,-,-)-89) KBr, Pellet

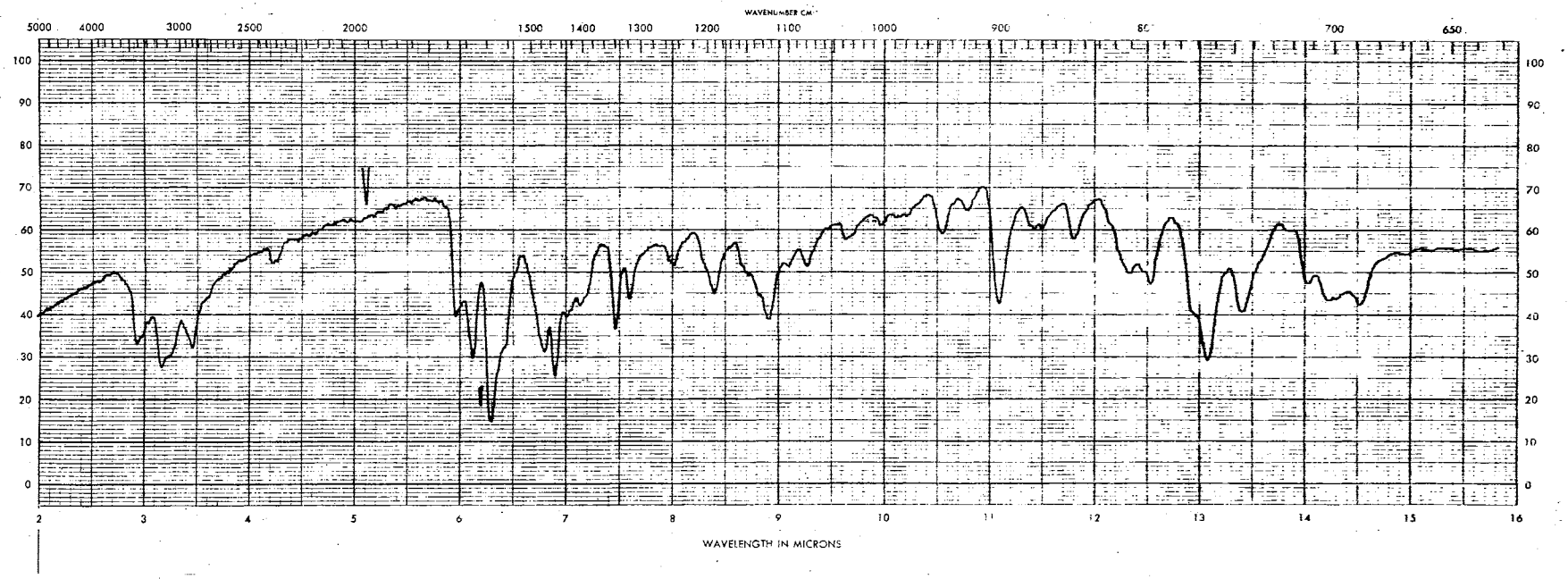
Plate LXVIII



(+)-5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenyl-phosphorinia[4,3-d]pyrimidine Hydrogen D(-,-)-Dibenzoyl-tartrate ((+,-,-)-89)

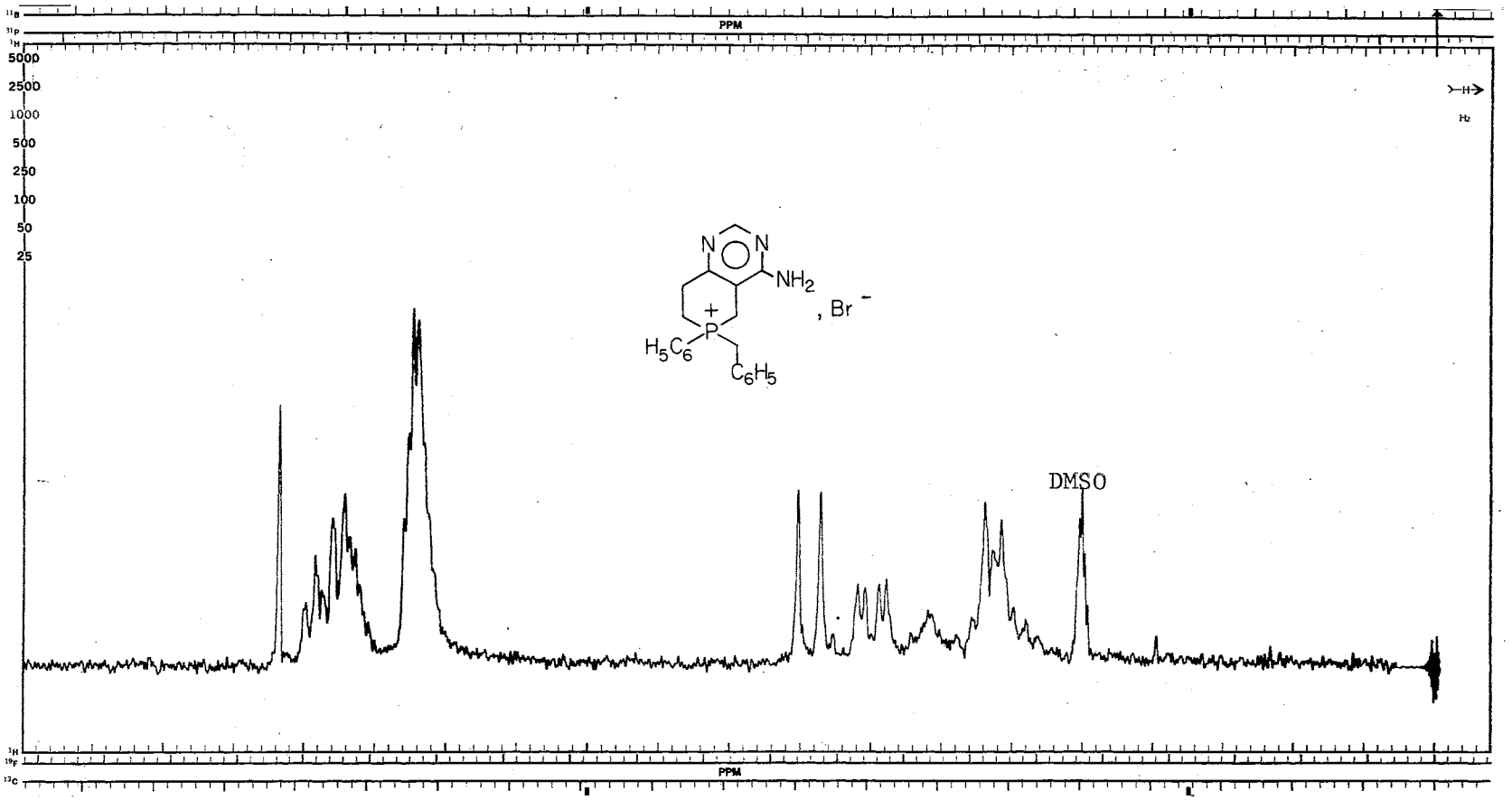
Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....163°

Plate LXIX



4-Amino-5,6,7,8-tetrahydro-6-benzyl-6-phenylphosphorinia[4,3-d]pyrimidine Bromide (90), KBr Pellet

Plate LXX

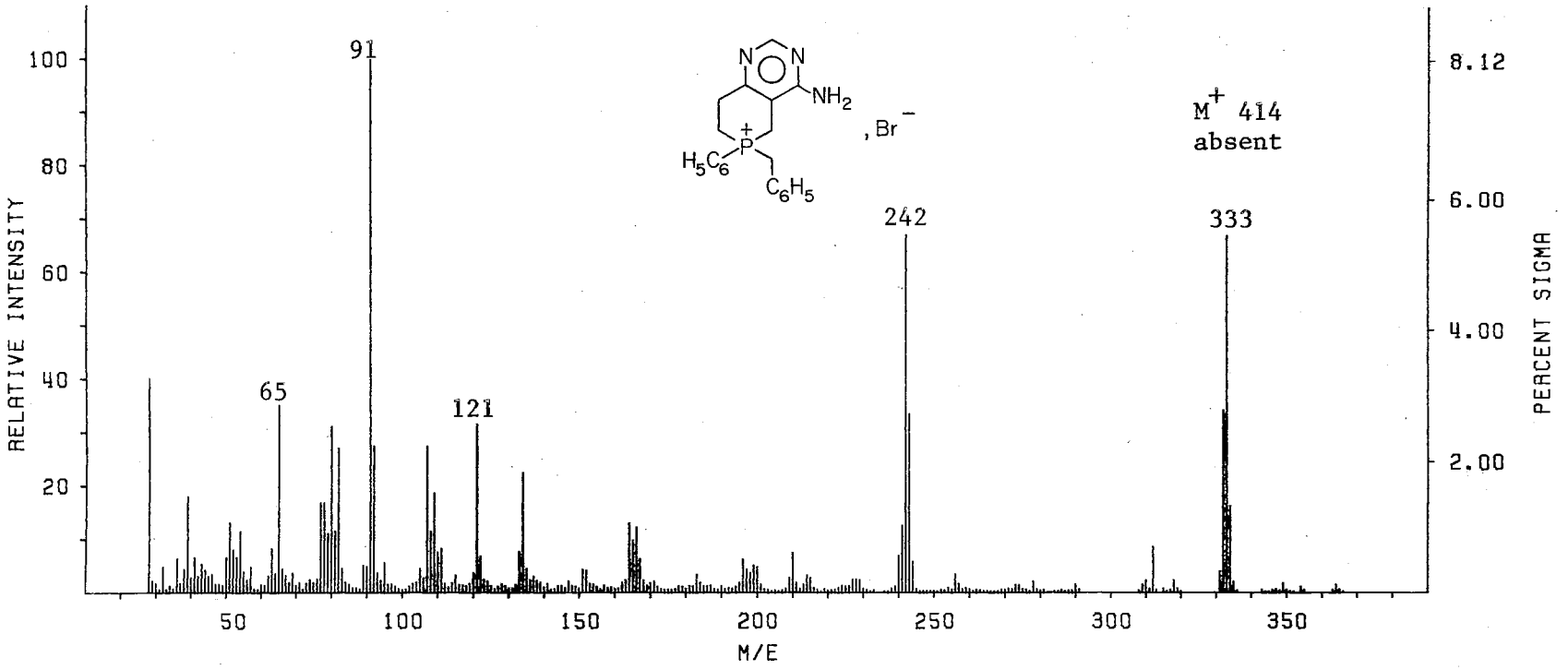


4-Amino-5,6,7,8-tetrahydro-6-beny-6-phenyl-phosphorinia[4,3-d]pyrimidine Bromide (90)

Solvent. . . DMSO-d_6 O.F. . . 100 MHz F.B. . . . . 2 Hz R.F. . . 65 db

S.W. . . . . 1000 Hz S.T. . . 250 sec S.O. . . 83701 Hz S.A. . . . 20 Lock. . . . . HOMO

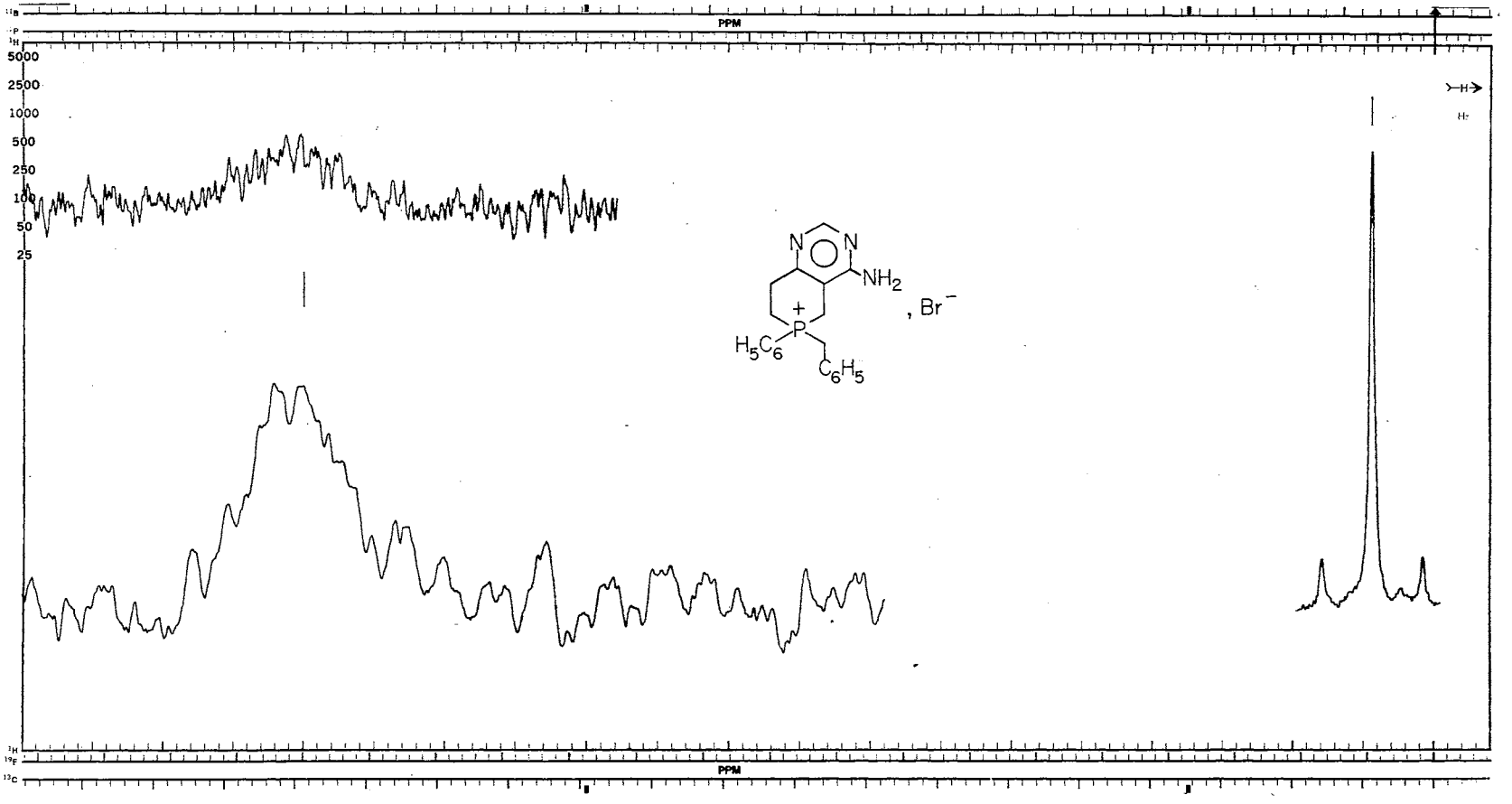
Plate LXXI



4-Amino-5,6,7,8-tetrahydro-6-benzyl-6-phenyl-phosphorinia[4,3-d]pyrimidine Bromide (90)

Inlet....Direct Probe Ionizing Voltage....70 eV Source °C....250° Probe °C....170°

Plate LXXII



^{31}P Spectrum of 4-Amino-5,6,7,8-tetrahydro-6-benzyl-6-phenylphosphorinia[4,3-d]pyrimidine Bromide (90)

Solvent. . . . CH_3OH O.F. . . . 40.5 MHz F.B. . . . 0.1 Hz R.F. . . . 80 db

S.W. . . . . 1000 Hz S.T. . . . 500 sec S.O. . . 88951 Hz S.A. . . . . 400 Lock. . . . ^1H

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