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Preparation, Reactions, Structures, and Possible Uses of 5,10-Dihydrophenophosphazine Derivatives

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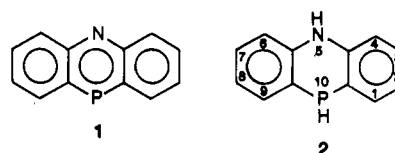
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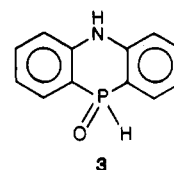
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I. Introduction

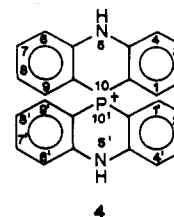
Phenophosphazine (1) has never been isolated, but numerous derivatives of 5,10-dihydrophenophosphazine (2) have been described in recent years. The first such



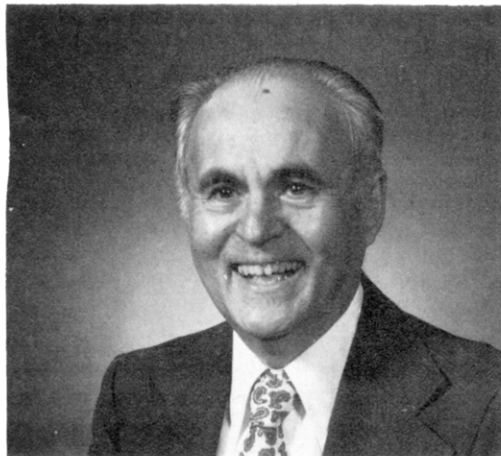
compound was prepared in 1888 by Schenk and Michaelis.¹ They reported that the interaction of diphenylamine and PCl_3 at elevated temperatures (followed by treatment of the reaction mixture with water) yields a white powder with the empirical formula $\text{C}_{12}\text{H}_{10}\text{NOP}$, and they suggested that the phosphorus atom in this substance might be a member of a ring system. Although the formation of a heterocyclic phosphorus compound by this procedure was confirmed in 1938,² 1956,³ and 1957,⁴ it was not until 1960⁵ that the substance was unambiguously shown to be a secondary phosphine oxide, viz. 5,10-dihydrophenophosphazine 10-oxide (3).



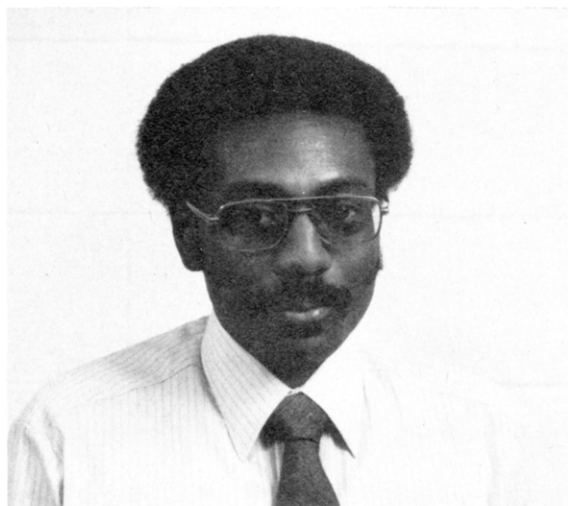
In 1971, it was reported⁶ that a compound of empirical formula $\text{C}_{24}\text{H}_{18}\text{ClN}_2\text{P}$ was also formed by the interaction of Ph_2NH and PCl_3 at 200–220 °C. The chemical and spectral properties of this substance showed that it did not contain a P–H bond and that it was not a derivative of trivalent phosphorus. The structure of the new compound was finally shown by an X-ray study^{6,7} to be 10,10'(5*H*,5'*H*)-spirobiphenophosphazinium chloride (4). This was the first spiro



phosphonium compound reported in which the phosphorus atom is a member of a ring that also contains



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Harold S. Freeman was born in Raleigh, NC, in 1951. He received a Bachelor of Science degree in Chemistry in 1972 from North Carolina Agricultural and Technical State University in Greensboro. He then joined Burroughs Wellcome Co., Research Triangle Park, NC. He maintained that full-time employment while earning the M.S. (1978) and Ph.D. (1981) degrees in organic chemistry from North Carolina State University at Raleigh under the direction of Leon D. Freedman. While at Burroughs Wellcome he published a number of papers on the design and synthesis of novel dopamine agonists as potential anti-Parkinson's agents. He became an Adjunct Assistant Professor of textile chemistry at North Carolina State University in 1981 and joined that department as an Associate Professor in 1982. His current research interests include the development of new fiber-reactive dyes, the photochemistry of dyes in polymer substrates, the synthesis of nongenotoxic dyes, and the analytical chemistry of dyes.

nitrogen; it was, in fact, one of the few spiro phosphonium compounds then known.

Most of the work on the 5,10-dihydropheno-

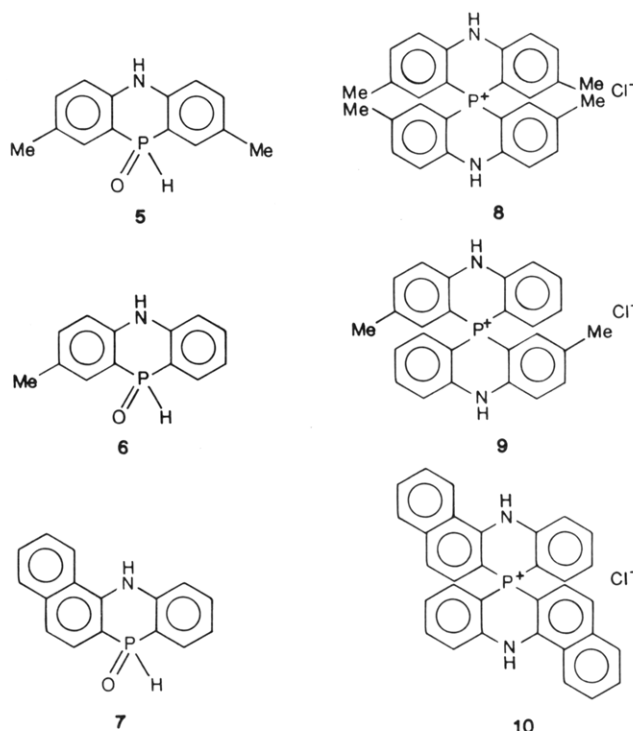
phosphazine ring system reported before 1970 was reviewed by F. G. Mann⁸ in his monograph on heterocyclic derivatives of phosphorus, arsenic, antimony, and bismuth. A short review of the chemistry of the dihydrophenophosphazines was published in 1977 by Bokanov and Stepanov.⁹ This paper is particularly valuable for its references to difficultly accessible Soviet sources. A brief discussion of derivatives of this ring system was also included in a 1977 review of polycyclic carbon-phosphorus heterocycles.¹⁰ Since 1977, there has been a flurry of papers that describe 5,10-dihydrophenophosphazine derivatives. This activity has doubtlessly been prompted by the ease of formation of many of these substances and by potential medical or industrial applications.

The present review is intended to be a comprehensive and critical survey of all published work on the preparation, reactions, structures, and possible uses of 5,10-dihydrophenophosphazine derivatives. It covers the literature as reported in *Chemical Abstracts* through July 1986. Work reported since the publication of Mann's monograph is discussed in greater detail.

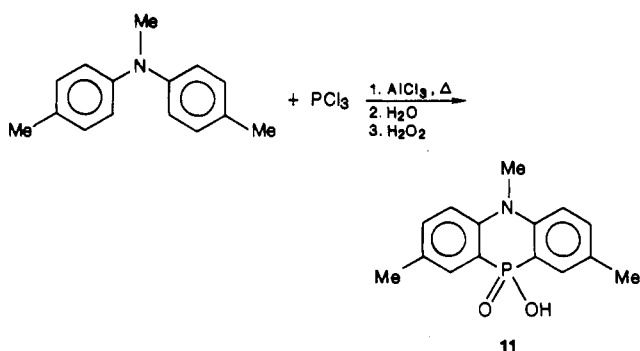
II. Synthesis of the Ring System

A. Interaction of Diarylamines and Phosphorus(III) Halides: Scope, Limitations, and Mechanism

After the publication of Häring's paper in 1960,⁵ a number of workers^{6,11–16} used the interaction of Ph_2NH and PCl_3 to obtain the phosphine oxide **3**. In 1975, Jenkins and Freedman¹⁷ were the first to report the extension of this reaction to other diarylamines. They found that the interaction of PCl_3 and di-*p*-tolylamine, 4-methyldiphenylamine, or *N*-phenyl-1-naphthylamine at 200–220 °C (followed by treatment of the reaction mixture with H_2O) gives the expected ring-substituted derivatives of the phosphine oxide **3** (i.e., **5–7**, respectively) and the phosphonium chloride **4** (i.e., **8–10**, respectively).

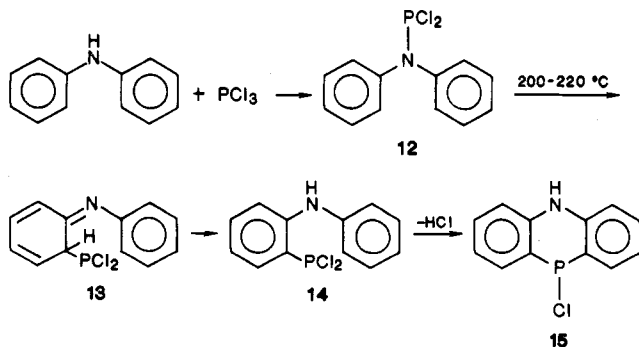


In contrast to the results obtained with the diarylamines, no reaction appears to occur when an *N*-methyl diarylamine and phosphorus trichloride are heated together.^{3,17} In the presence of AlCl_3 , *N*-methyl diphenylamine, and PCl_3 give a phosphonous dichloride $\text{PhN}(\text{Me})\text{C}_6\text{H}_4\text{PCl}_2$.^{1b} Although the orientation of the dichlorophosphino group has not been established, it has been generally assumed that this group enters para to the nitrogen.^{18a} When *N*-methyl di-*p*-tolylamine is heated with PCl_3 and a catalytic amount of AlCl_3 , ring positions ortho to the nitrogen are attacked, and a heterocyclic derivative of phosphorus is obtained:¹⁷



The phosphinic acid 11 is the only *N*-methyl dihydrophenophosphazine derivative obtained via the condensation of PCl_3 and an aromatic amine.

In 1950, Kosolapoff^{19a} suggested that the primary product of the uncatalyzed interaction of Ph_2NH and PCl_3 is diphenylphosphoramidous dichloride, Ph_2NPCl_2 (12), which subsequently undergoes rearrangement and further condensation to yield a heterocyclic substance. Later work¹⁷ showed that the dichloride 12 (which is readily prepared by the interaction of Ph_2NH and PCl_3 in ether at room temperature²⁰) does indeed rearrange at 200–220 °C and does lose HCl to give, after treatment with H_2O , the same mixture of the oxide 3 and the phosphonium chloride 4 obtained via the direct interaction of Ph_2NH and PCl_3 at 200–220 °C. The failure of the *N*-methyl diarylamines to react with PCl_3 (except in the presence of AlCl_3) would seem to be a consequence of the inability of these amines to form phosphoramidous dichlorides. The formation of the dihydrophenophosphazine ring system by the interaction of Ph_2NH and PCl_3 appears to be consistent with the following sequence of reactions:



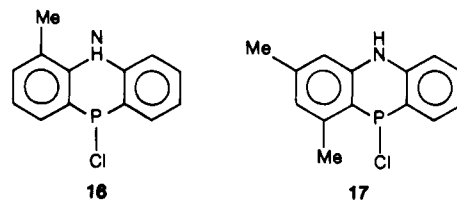
In the above mechanism, the rearrangement of 12 to 13 involves the transfer of the PCl_2 group to an ortho position and the formation of the type of intermediate usually postulated in electrophilic aromatic substitution. Rearomatization of 13 accompanied by transfer of a

TABLE I. Diarylamines Studied²⁶

R_1	R_2
4-Cl	H
4-Cl	4-Me
4-Cl	4-Cl
4-Br	4-Br
2,4-Br ₂	2,4-Br ₂
2-Me	H
2-Me	2-Me

proton from carbon to nitrogen yields the phosphonous dichloride 14. The latter compound, by analogy with similar phosphonous dichlorides,²¹ would be expected to undergo cyclodehydrohalogenation to give the phosphinous chloride 15; and hydrolysis of 15 would certainly yield the phosphine oxide 3.²² The mechanism of the formation of low and variable yields of the phosphonium chloride 4 is not obvious and has not been elucidated. The AlCl_3 -catalyzed interaction of the *N*-methyl diarylamines and PCl_3 requires little comment since the reaction of aromatic compounds with phosphorus trihalides under Friedel-Crafts conditions is well-known.^{18b,23}

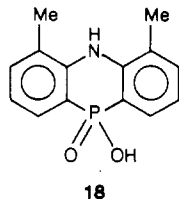
In a review published in 1977, Bokanov and Stepanov⁹ suggested that the main component of the mixture obtained by the uncatalyzed interaction of Ph_2NH and PCl_3 is not the phosphinous chloride 15 but rather a polymer containing phosphorus-nitrogen bonds. In 1981, however, it was reported²⁴ that a yellow solid sublimes out of the reaction mixture during the interaction of PCl_3 and 2-methyl diphenylamine or 3,5-dimethyl diphenylamine at about 210 °C. Although reproducible elemental analyses of these sublimates have not been obtained, their mass spectra clearly show that they are the phosphinous chlorides 16 and 17. Fur-



thermore, tertiary phosphines^{24,25} can be prepared by the addition of a Grignard reagent to an ether extract of the mixture obtained by the interaction of a diarylamine and PCl_3 at elevated temperatures. It seems probable that these ether extracts contain phosphinous chlorides, which can react with Grignard reagents. The synthesis of tertiary phosphines by this procedure is discussed in more detail in section IIIA.

The reaction of PCl_3 (or PBr_3) with a variety of diarylamines has been investigated in recent years. Thus, in 1981, the use of the amines listed in Table I was reported.²⁶ The three chloro-substituted diarylamines react with PCl_3 as expected and yield moderate amounts of secondary phosphine oxides and spiro phosphonium chlorides. The mixture obtained by the interaction of 4,4'-dibromodiphenylamine and PBr_3 (which reacts like PCl_3 with Ph_2NH) gives, upon hydrolysis, a solid that appears to consist mainly of the expected secondary phosphine oxide. The mass spectrum, however, exhibits a peak corresponding to a tri-

bromo derivative of the oxide 3. After it was learned that simply heating 4,4'-dibromodiphenylamine alone at 200 °C for 24 h produced some tribromodiphenylamine, further investigation of the interaction of the dibromo compound was abandoned. Unlike any other diarylamine studied, 2,2',4,4'-tetrabromodiphenylamine appears to undergo no reaction whatever with either PCl_3 or PBr_3 . It is not clear whether steric or electronic effects (or a combination of both) are responsible for this failure. The interaction of *N*-phenyl-*o*-toluidine and PCl_3 gives, after hydrolysis, the expected secondary phosphine oxide; no spiro phosphonium chloride, however, is isolated. No dihydrophenophosphazine derivatives are obtained by the direct interaction of di-*o*-tolylamine and PCl_3 . It is possible, however, to synthesize di-*o*-tolylphosphoramidous dichloride, $(o\text{-MeC}_6\text{H}_4)_2\text{NPCl}_2$, by refluxing a benzene solution of di-*o*-tolylamine and PCl_3 . Thermal decomposition of this dichloride and treatment of the reaction mixture with H_2O yield a small amount of a solid that can be oxidized to a phosphinic acid. Although this acid has not been obtained analytically pure, its mass and ^1H NMR spectra strongly indicate that it is the phosphinic acid 18. The results obtained with di-*o*-tolylamine



strongly suggest that the presence of two ortho substituents greatly interferes with the synthesis of dihydrophenophosphazine derivatives from diarylamines.

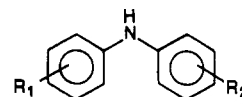
In a later investigation, the meta-substituted diarylamines listed in Table II were studied.²⁷ The first four compounds are of particular interest because of the possibility of isomeric products. Thus, two secondary phosphine oxides seem possible from each of the amines containing a single meta substituent (i.e., 19a and 19b). The amine with identical substituents in the 3- and 3'-positions (i.e., 19d) might give three isomeric oxides, while the amine with different substituents in these positions (i.e., 19c) seems capable of yielding four isomeric oxides. Furthermore, the presence of the meta-directing CF_3 group in 19a, 19c, and 19d might inhibit (or even prevent) the required electrophilic attack on the aromatic rings.

Each of the amines listed in Table II was heated with PCl_3 at 200–250 °C for 16–20 h, and the reaction mixtures were then treated with H_2O . The three amines containing an unsubstituted Ph group (i.e., 19a,b,e) yield modest amounts of dihydrophenophosphazine oxides; 3-methyldiphenylamine (19b) also gives a spiro phosphonium chloride (in about 18% yield). The other two amines (19c, 19d) give no organophosphorus compounds under these conditions. An oxide can be obtained, however, by converting 19c to the phosphoramidous dichloride $(3\text{-MeC}_6\text{H}_4)(3\text{-CF}_3\text{C}_6\text{H}_4)\text{NPCl}_2$, dehydrohalogenating this substance at 238 °C, and then treating the reaction mixture with H_2O . The bis(trifluoromethyl)amine 19d can also be converted to a phosphoramidous dichloride, but the latter substance can not be dehydrohalogenated even at 255 °C.

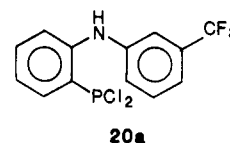
As mentioned above, the structures of the oxides

TABLE II. Diarylamines Studied²⁷

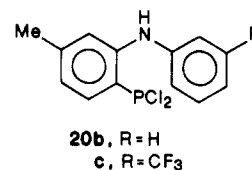
compd	R ₁	R ₂
19a	3-CF ₃	H
19b	3-Me	H
19c	3-Me	3-CF ₃
19d	3-CF ₃	3-CF ₃
19e	3,5-Me ₂	H



obtained from the amines 19a–c are not established by the method of synthesis employed. A ^1H NMR study, however, made it possible to show that the reactions of these amines are regiospecific and that the methyl and/or CF_3 groups are para to the phosphorus atom in the three oxides. Steric factors probably play a key role in determining the regiospecificity of these reactions. For example, the amine 19a probably gives the intermediate phosphonous dichloride 20a, formed by mi-



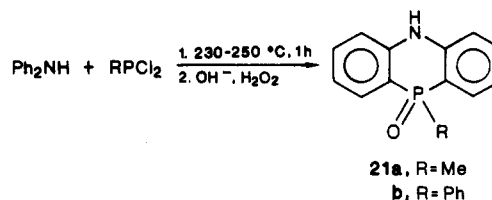
gration of a PCl_2 group from the nitrogen atom to an ortho position of the ring lacking the electron-withdrawing CF_3 group. Ring closure then occurs para (rather than ortho) to this bulky group. Similarly, amines 19b and 19c probably yield the intermediates 20b and 20c, respectively. The formation of these



substances seems likely, since the methyl-substituted ring is the more reactive one and since the position para to the methyl group is less hindered. Then, as in the case of 20a, ring closure occurs para to the trifluoromethyl group in 20c.

It is interesting that the conversion of the amines 19a and 19c to phenothiazines by reaction with sulfur²⁸ shows the same type of regiospecificity observed in the investigation²⁷ discussed above (i.e., the sulfur atom occupies the positions para to the ring substituents). It seems likely that the reaction of meta-substituted diarylamines with AsCl_3 obeys similar orientation rules.²⁹

A brief note³⁰ in the Russian literature has described the preparation of two tertiary phosphine oxides via the interaction of Ph_2NH and MePCl_2 or PhPCl_2 :

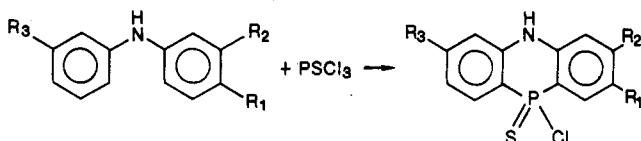


The oxides 21 were characterized by elemental analyses, mass spectra, and melting points. They were also converted to *N*-methyl derivatives by deprotonation with NaH and subsequent treatment with MeI (cf.

section IIIF). Further information on the reaction of diarylamines and phosphonous dichlorides has not yet been published.

B. Interaction of Diarylamines and Thiochlorophosphate

The formation of the thionophosphinyl chlorides **22** (10-chloro-5,10-dihydrophenophosphazine 10-sulfides) by the interaction of diarylamines and PSCl_3 was first described by McHattie³¹ in a British patent. Addi-

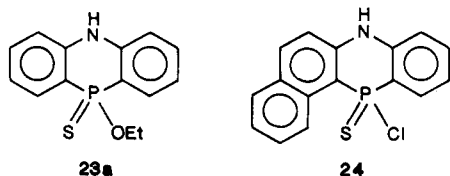


- 22 a.** $R_1 = R_2 = R_3 = \text{H}$
b. $R_2 = \text{Cl}; R_1 = R_3 = \text{H}$
c. $R_1 = \text{Cl}; R_2 = R_3 = \text{H}$
d. $R_1 = \text{Me}; R_2 = R_3 = \text{H}$
e. $R_2 = R_3 = \text{Me}; R_1 = \text{H}$

tional information about this work was obtained from McHattie by Mann and is included in the latter's monograph.⁸ McHattie reported that the sulfide **22a** is best prepared by heating a mixture of Ph_2NH and PSCl_3 in an autoclave at 200 °C for 6 h. This procedure gives a crude hydrochloride of **22a**, which loses HCl on being pulverized and then treated with boiling chlorobenzene. After insoluble impurities are removed by filtration, the chlorobenzene deposits the sulfide **22a** as pale yellow crystals. Instead of using an autoclave, one can add the mixture of Ph_2NH and PSCl_3 to *o*-dichlorobenzene, raise the temperature to 175 °C during a period of 3 h, and then maintain that temperature for 16 h. The yield of sulfide **22a** thus obtained, however, is much lower. McHattie apparently did not determine the actual positions of the chlorine and methyl groups in the sulfides **22b** and **22e** but assumed a pattern of regioselectivity similar to that later demonstrated in the reaction of meta-substituted diarylamines with PCl_3 (cf. section IIA).

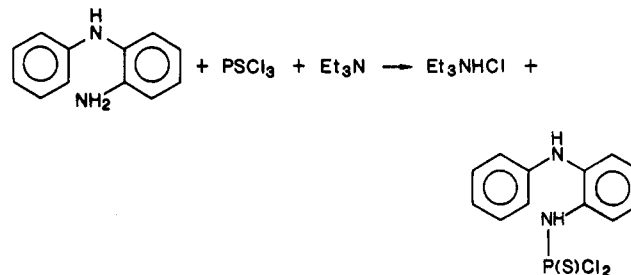
McHattie also investigated the reaction between *N*-methyldiphenylamine and PSCl_3 in a sealed tube at 190 °C for 6 h. When the reaction mixture is cooled, a solid is obtained that on digestion with boiling EtOH yields the ester **23a**. This loss of an *N*-methyl group resembles that which occurs when *N*-methyldiphenylamine is heated with AsCl_3 .^{32,33} It should be noted, however, that *N*-methyldiphenylamine³ and *N*-methyldi-*p*-tolylamine¹⁷ do not react with PCl_3 in the absence of a catalyst. In the presence of AlCl_3 the aromatic rings are attacked, but the *N*-methyl group is not eliminated (cf. section IIA).

Only a few other workers have employed McHattie's method for preparing sulfides of type **22**. In 1981, a paper³⁴ from a Soviet laboratory reported that the interaction of *N*-phenyl-2-naphthylamine and PSCl_3 in *o*-dichlorobenzene at 175–176 °C for 10 h gives a 30% yield of the sulfide **24**. The preparation of the sulfide

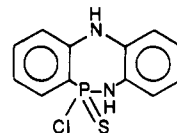


22a in a 52% yield by a similar reaction with Ph_2NH has been described in another paper³⁵ from the same laboratory. In that paper it was stated that catalytic amounts of PCl_3 promote the formation of **22a**.

A different type of heterocyclic compound has been obtained via the interaction of 2-aminodiphenylamine and PSCl_3 .³⁶ When these substances are heated for 7 h in boiling benzene in the presence of Et_3N , the primary amino group is first attacked:



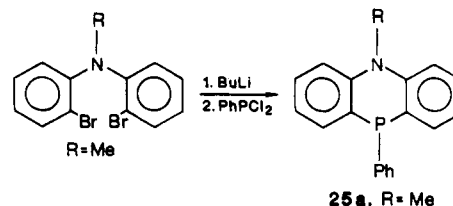
When the resulting product (obtained only as an oil) is heated for 6 h at 215 °C with a small amount of AlCl_3 , cyclization occurs and the following seven-membered heterocycle can be isolated from the reaction mixture:



C. Reaction of Organometallic Reagents with Phosphonous Dichlorides or Triphenyl Phosphite

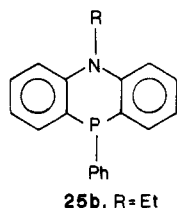
Jones and Mann,³ in 1956, were the first to attempt to use an organometallic reagent for the synthesis of the 5,10-dihydrophenophosphazine system. They treated 2,2'-dibromodiphenylamine with an excess of BuLi and showed that the bromine had been replaced with lithium. Presumably, they had obtained the trithio derivative (*o*- LiC_6H_4)₂NLi. Reaction of this substance with PhPCl_2 yielded a sticky yellow solid, which they were unable to characterize and believed was polymeric. They suggested that polymerization might be avoided if the 2,2'-dibromodiphenylamine is first converted to an *N*-alkyl derivative, but they were unsuccessful in their attempts to methylate the secondary amine.

In the next few years, new methods for preparing *N*-alkyl-2,2'-dihalodiphenylamines were developed,³⁷ and it was found that it is indeed possible to convert these substances to the previously unknown 5-alkyl-5,10-dihydrophenophosphazine derivatives.³⁸ Thus, the interaction of *N*-methyl-2,2'-dibromodiphenylamine and BuLi in Et_2O yields a dilithio derivative, which reacts with PhPCl_2 to give a 58% yield of the tertiary phosphine **25a**. The di-Grignard reagent prepared



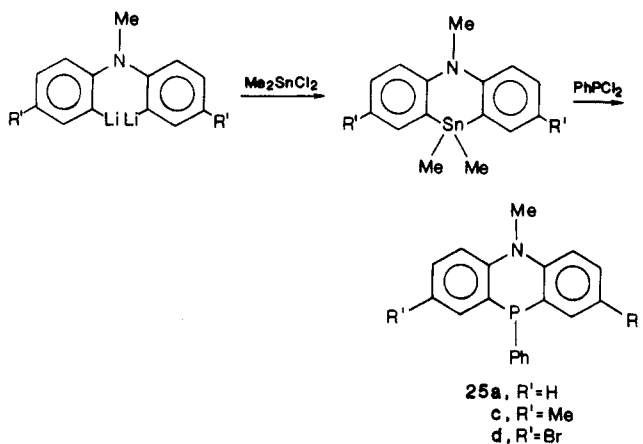
from this dibromo compound also reacts with the phosphonous dichloride and gives a 28% yield of **25a**. Similarly, the interaction of the phosphonous dichloride

and the di-Grignard from *N*-ethyl-2,2'-dibromodiphenylamine yields 27.5% of the expected 5-ethyl derivative **25b**. Attempts to convert the *N*-alkyl-2,2'-



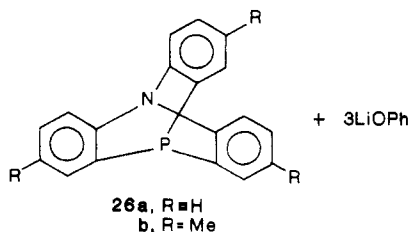
dichlorodiphenylamines to lithium derivatives have not been successful. Di-Grignard reagents can be obtained from the 2,2'-dichloro compounds, but the yields are low. Thus, only a 14.2% yield of **25b** is obtained from *N*-ethyl-2,2'-dichlorodiphenylamine.

N-Methyl-2,2'-dilithiodiarylamines can be converted into heterocyclic tin compounds, which react with PhPCl_2 to give **25a,c,d**.³⁹ The interaction of the tin



heterocycle and PhPCl_2 occurs at 180–210 °C, and the yields are in range of 36–55%. The replacement of tin by phosphorus is interesting, but this method seems to have no synthetic advantage over the direct reaction of the dilithio compound with the phosphonous dichloride. The latter method was, in fact, employed in this investigation in order to obtain authentic samples of the 5,10-dihydrophenophosphazines, but the yields obtained were not given.

Two azaphosphatriptycenes that are derivatives of 5,10-dihydrophenophosphazine have been prepared via organolithium compounds.^{25,40} The lithium reagents, prepared by the reaction of tris(*o*-bromoaryl)amines with BuLi, are only sparingly soluble in Et_2O . When a suspension of the tris(*o*-lithioaryl)amine in Et_2O is allowed to react with triphenyl phosphite in a mixture of the ether and THF, the azaphosphatriptycenes **26**



are obtained in yields of 22–30%. Since these yields are not always reproducible, another method for preparing the azaphosphatriptycenes has been devised.

This method is discussed in section IIIA.

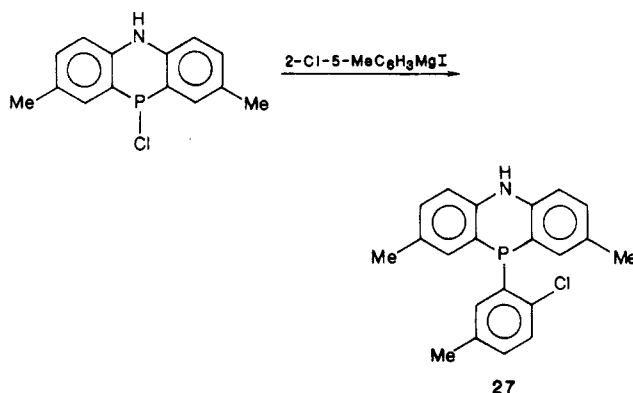
III. Reactions of 5,10-Dihydrophenophosphazine Derivatives

A. Phosphinous, Phosphinyl, and Thionophosphinyl Chlorides: Synthesis and Reaction with Grignard Reagents

In 1938, Sergeev and Kudryashov² claimed that the interaction of the secondary oxide **3** and SOCl_2 yields the phosphinous chloride **15**. They described the latter substance as a yellowish oil, which is soluble in excess SOCl_2 . Elemental analyses were not reported. The authors² did state, however, that treatment of **15** with NaOEt in absolute EtOH results in replacement of the chlorine with an ethoxy group. The new substance thus obtained was said to be a solid, mp 151.5–152 °C, and to give satisfactory combustion analyses.

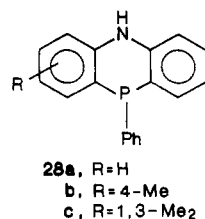
The work summarized in the above paragraph has never been confirmed. Hunt and Saunders⁴¹ have found that the secondary oxide $\text{Ph}_2\text{P}(\text{O})\text{H}$ reacts with either SOCl_2 or *N*-chlorosuccinimide to give the phosphinyl chloride $\text{Ph}_2\text{P}(\text{O})\text{Cl}$. Further investigation is required to ascertain whether it is indeed possible to obtain a phosphinous chloride by the interaction of a secondary phosphine oxide and SOCl_2 .

As previously mentioned in section IIA, there is considerable evidence that phosphinous chlorides are formed by the interaction of diarylamines and PCl_3 at elevated temperatures. In 1978, Hellwinkel and co-workers²⁵ allowed di-*p*-tolylamine and PCl_3 to react at about 200 °C and then extracted the cooled reaction mixture with ether. The resulting solution was then treated with an excess of (2-chloro-5-methylphenyl)magnesium iodide to yield the tertiary phosphine **27**. They assumed that the following reaction had occurred:



On treatment with potassium *tert*-butoxide, the phosphine **27** undergoes cyclodehydrohalogenation and gives the azaphosphatriptycene **26b**.

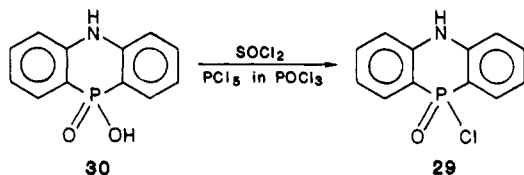
The method used for preparing **27** has been extended²⁴ to the preparation of the tertiary phosphine **28a**.



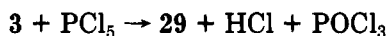
Two other tertiary phosphines (**28b,c**) have been ob-

tained by the reaction of the phosphinous chlorides 16 or 17 (obtained as described in section IIA) with an excess of PhMgBr. The phosphine 28a was accompanied by small amounts of the corresponding tertiary phosphine oxide 21b, presumably formed by air oxidation of 28a. Similarly, the phosphine 28b was accompanied by its oxide. The phosphine 28c was converted to the corresponding oxide by reaction with H₂O₂ in acetone.

The phosphinyl chloride 29 was first described by Häring,⁵ it was prepared by treatment of the phosphinic acid 30 with SOCl₂ or with PCl₅ in POCl₃. Compound

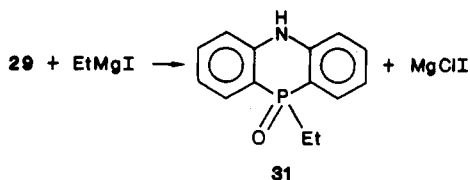


29 is a solid, mp 290 °C, and has been characterized by elemental analyses and IR.¹² Several later workers^{11,15,42,43} used Häring's methods to prepare 29; it has also been obtained by the interaction of the phosphine oxide 3 and PCl₅ at about 100 °C.¹² The ease with

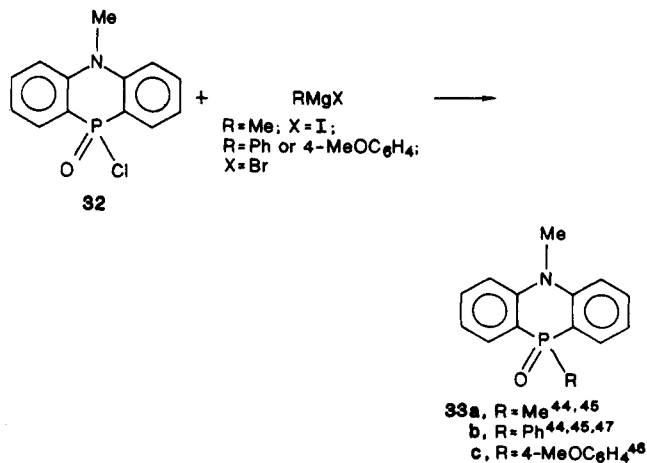


which secondary phosphine oxides like 3 can be prepared makes them convenient starting materials for the synthesis of the corresponding phosphinyl chlorides.

The tertiary phosphine oxide 31 has been obtained by the addition of the chloride 29 in 1,2-dimethoxyethane to a solution of EtMgI in ether.⁴² The structure of 31 was established by ¹H NMR and high-resolution mass spectral analysis.



The *N*-methyl phosphinyl chloride 32 has been mentioned in a number of papers,^{9,44-47} but the method used for its synthesis has been described only in a document⁴⁴ that is not accessible to us. Treatment of 32 with a Grignard reagent leads to the formation of the expected phosphine oxides 33. It has also been re-

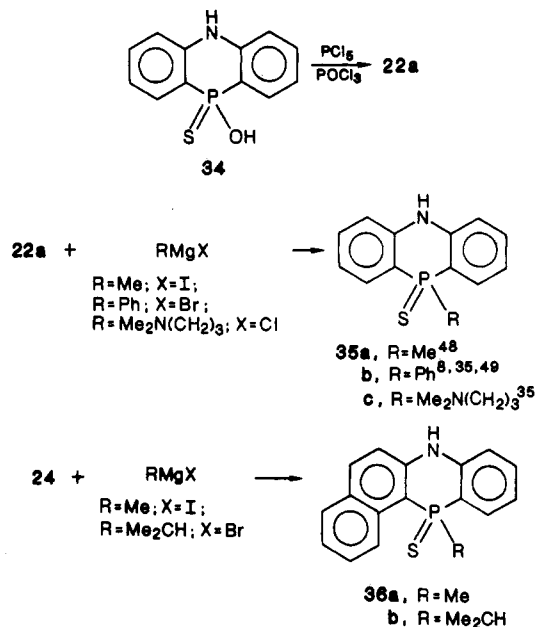


ported⁴⁷ that the reaction of 32 with 3.5 mol of PhMgBr

yields a 1:1 phenol adduct of 33b. The structure of this adduct is discussed in section IV.

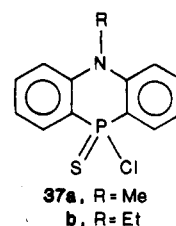
According to a Russian review article,⁹ the 2,8-dinitro derivative of 32 has been characterized, but the document⁴³ in which it is described is not accessible to us.

Thionophosphinyl chlorides are readily prepared by the interaction of diarylamines and PSCl₃ at elevated temperatures. This type of reaction has been discussed in section IIB. The parent compound 22a can also be

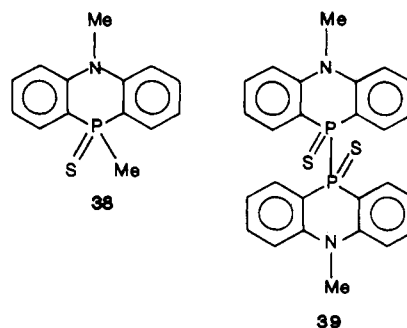


obtained by allowing the phosphinothioic acid 34 to react with PCl₅ in POCl₃.⁵ Reaction of 22a with an excess of a Grignard reagent yields the expected tertiary phosphine sulfide. The naphthalene derivative 24 reacts in a similar manner.³⁴

The *N*-alkylated thionophosphinyl chlorides 37 have been described,⁵⁰ but details of their preparation are not available to us. The reaction of 37a with MeMgI yields



a mixture of the tertiary phosphine sulfide 38 and the diphosphine disulfide 39.^{48,50} A possible mechanism by which Grignard reagents may react with some thionophosphinyl chlorides to form both tertiary phosphine sulfides and diphosphine disulfides has been discussed.⁵¹



B. Reactions of the Secondary Phosphine Oxides

1. Oxidation to Acids

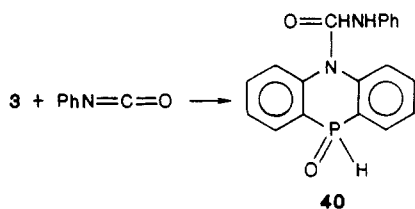
Secondary phosphine oxides are readily converted to the corresponding phosphinic acids. The acid **30** was first prepared by dissolving the oxide **3** in tetralin and boiling the resulting solution in air for a short time.^{2,5} Oxidation of this oxide has also been accomplished with peracetic acid⁵ and with NaOH in aqueous^{43,52} or alcoholic¹⁷ solution. The use of hydroxide ion as an oxidizing agent for secondary phosphine oxides was first described by Campbell and Stevens.⁵³ The mechanism of this interesting oxidation-reduction reaction was discussed by them and more recently by Granoth and co-workers.⁵⁴ The ring-substituted secondary phosphine oxides mentioned in section IIA have also been converted to phosphinic acids;^{17,26,27} alkaline H₂O₂ or alcoholic NaOH was used as the oxidizing agent in these cases.

Häring⁵ reported that treatment of the oxide **3** with sulfur in hot acetic acid solution yields the phosphinothioic acid **34**, mp 213 °C. McHattie⁸ apparently obtained the same acid by refluxing the thionophosphinyl chloride **22a** with an aqueous acetone solution of Na₂S and then acidifying the reaction mixture; his phosphinothioic acid, however, had a melting point of 304–306 °C. No explanation for the large difference in the melting points has been suggested. Mann⁸ has noted a number of cases in which the melting points reported by Häring and by McHattie differ significantly. More recently, a group of Russian workers⁵⁰ has described the preparation of **34** in a document that is not accessible to us; the abstract in *Chemical Abstracts* states that "cyclizing Ph₂NH with PCl₃ followed by treatment with S gave 32%" of **34**.

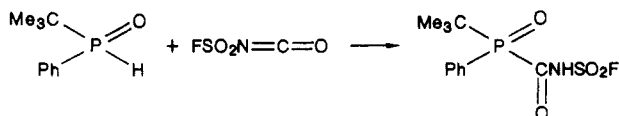
The reaction of the oxide **3** with Br₂ results in both oxidation and bromination. This result is discussed in section IIIC2.

2. Addition to Unsaturated Compounds

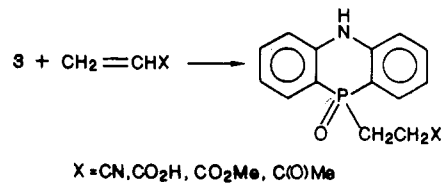
Häring⁵ reported that the interaction of the oxide **3** and phenyl isocyanate in hot DMF results in an attack on the nitrogen atom of the heterocyclic ring. Since



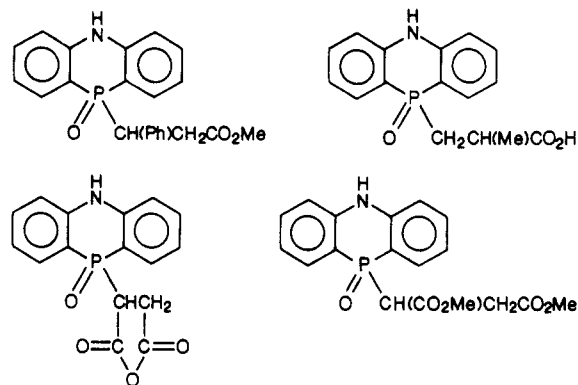
this formulation is supported only by elemental analyses, the correctness of structure **40** has been questioned.⁹ It should also be noted that it is possible for the P–H bond of a secondary phosphine oxide to add to the C–N double bond of an isocyanate.⁵⁵



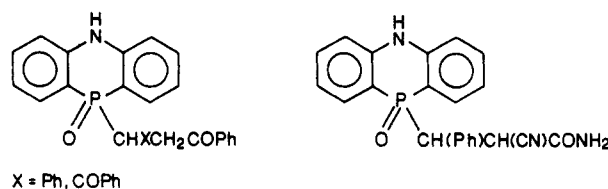
Like other secondary phosphine oxides, the oxide **3** adds to unsaturated compounds that contain activated double bonds. Thus, Levin and Gazizova⁵⁶ reported,



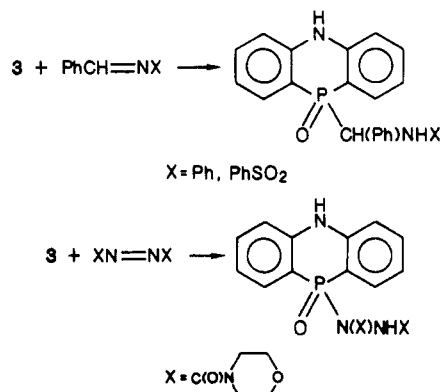
in 1966, that **3** reacts with acrylic acid derivatives and related compounds at 120–180 °C in the absence of a catalyst. They used similar reactions for the preparation of the following adducts:



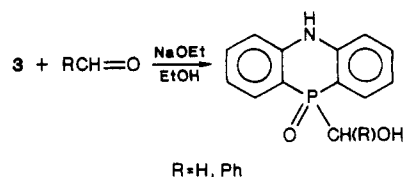
Several years later, Messinger¹⁴ used base catalysis to effect the same type of addition reactions and thereby obtained the following compounds:



He also found that the oxide **3** adds to Schiff bases and to an azo diamide even in the absence of a catalyst. Addition reactions, however, were not observed with azobenzene or azo dicarboxylic esters.

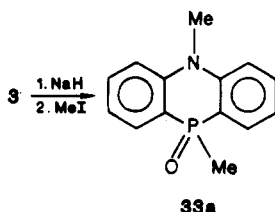


More recently, Petrov and co-workers⁵⁷ have prepared phosphinyl alcohols by the base-catalyzed interaction of the oxide **3** and an aldehyde. They also found that the reaction of **3** and the Schiff base PhCH=NPh yields the adduct earlier described by Messinger.¹⁴

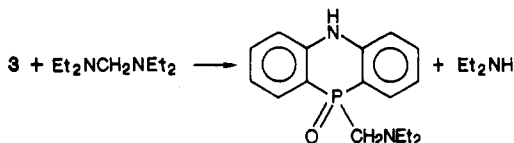


3. Other Reactions of the Secondary Phosphine Oxides

When the oxide **3** is dissolved in THF and treated first with NaH and then with MeI, both the phosphorus and nitrogen atoms are methylated.^{44,45} The interaction



of **3** and *N,N,N',N'*-tetraethylmethanediamine in boiling EtOH also yields a tertiary phosphine oxide.⁵⁷ Treatment of this oxide with picric acid gives a 1:1 adduct.



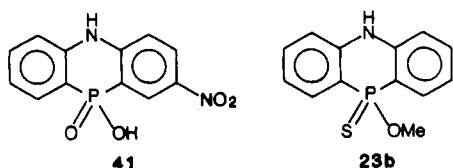
A crystalline hydrobromide or hydrochloride of **3** can be obtained by treatment of a hot acetic acid solution of **3** with the corresponding hydrogen halide.⁵ Both salts are readily hydrolyzed to **3**.

The conversion of the oxide **3** to the phosphinyl chloride **29** has been mentioned in section IIIA. The reaction of **3** with I₂ or Chloramine-T to yield a diphosphine dioxide is described in section IIIC2. The direct preparation of an ester and an amide from **3** is discussed in section IIID.

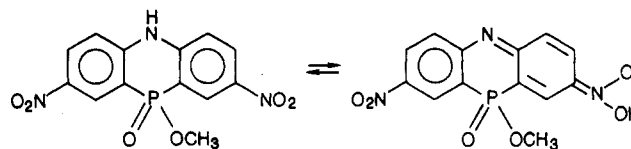
C. Electrophilic Substitution Reactions of the Aromatic Rings

1. Nitration

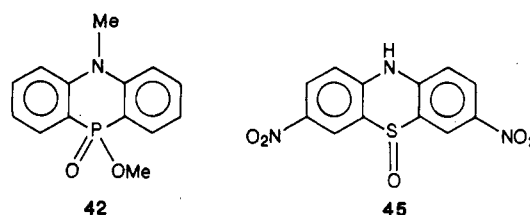
In the very first paper on the dihydrophenophosphazine system, Schenk and Michaelis^{1a} noted that the heterocyclic ring (in the substance we now know is the oxide **3**) must be rather stable since it is not disrupted by nitration. This statement was repeated in a second paper^{1b} from their laboratory, but neither publication gives any information about the nitro compound they obtained. In 1938, Sergeev and Kudryashov² reported that the interaction of the phosphinic acid **30** and HNO₃ in glacial acetic acid at 25 °C yields a mononitro derivative. Although they did not determine the orientation of the nitro group, they did note that the compound dissolves in alkali to give an intense bright red solution, a behavior that had previously been observed with the nitration product of the arsenic analogue of **30**.⁵⁸ Since Gibson and Johnson⁵⁹ have shown that the main product of mononitration of the arsenic acid is the 2-nitro derivative, it seems very likely that the nitro compound obtained by Sergeev and Kudryashov² has the analogous structure **41**.



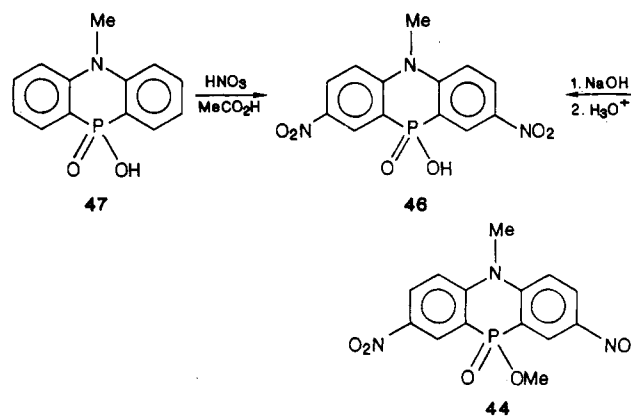
Much later, McHattie^{8,31} found that the ester **23b** undergoes both oxidation and dinitration upon being refluxed with 1:1 aqueous HNO₃ for 30 min. He suggested that the nitro groups in the product occupy the positions para to the amino group, and he cited as evidence the fact that a solution of the substance in dilute aqueous KOH has a deep purple color. The color, he believed, is due to the potassium salt of the aci form of the dinitro compound.



The nitration of three *N*-methyl-dihydrophenophosphazines has been studied in recent years. In 1976, it was shown^{43,60} that the ester **42** is easily converted at

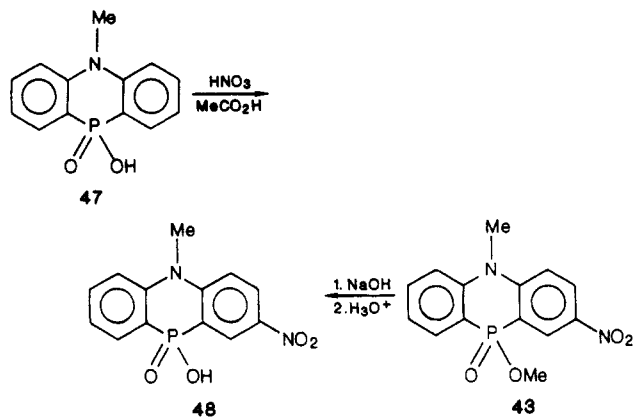


25 °C to the 2-nitro derivative **43** or the 2,8-dinitro derivative **44** by treatment with HNO₃ (*d* 1.42) in glacial acetic acid. When a 10-fold excess of HNO₃ is used and the reaction is allowed to proceed for 2.5 h, the mononitro compound **43** is obtained. Nitration with a 35-fold excess of HNO₃ for 6 h gives the dinitro compound **44**. The structure of **44** was deduced by ¹H NMR spectroscopy and by comparison of its UV spectrum with that of 3,7-dinitro-10*H*-phenothiazine 5-oxide (**45**).⁶⁰ Not surprisingly, the same dinitrated dihydrophenophosphazine **44** can also be obtained by nitration of the mononitro derivative **43**. Saponification of the dinitro compound **44** leads to the phosphinic acid **46**, which can also be obtained (in 90% yield) by the direct nitration of the phosphinic acid **47**. Similarly, the mononitro

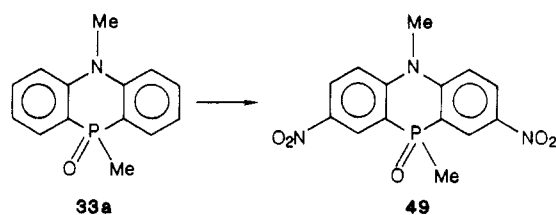


derivative **48** can be prepared⁶¹ by direct nitration of **47** or by saponification of the mononitrated ester **43** mentioned earlier in this paragraph.

The dinitration of the tertiary phosphine oxide **33a** has also been accomplished by the use of HNO₃ in acetic acid.⁴⁵ Although the structure of the product was not proven, it was reasonably assumed that the nitro



groups occupy the 2- and 8-positions.

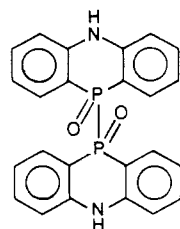


It is not surprising that the results summarized in this section indicate that the nitration of dihydrophenophosphazine derivatives yields compounds in which the nitro groups are para to the nitrogen atom of the ring and meta to the phosphorus atom. The amino group is, of course, strongly ortho,para-directing, while the phosphorus atom in the compounds discussed above has a partial positive charge and would be expected to be meta-directing.^{19b}

2. Halogenation

Häring⁵ has reported that the interaction of the phosphine oxide 3 and Br₂ (about 3 mol/mol of 3) in formic acid at 5 °C leads to both bromination of the ring and oxidation to a phosphinic acid. Although a mixture of bromo compounds of different bromine content is apparently formed, the main product is a dibromo-10-hydroxy-5,10-dihydrophenophosphazine 10-oxide. No information about the positions of the bromo substituents is available; nor is it known whether the bromination occurs before or after oxidation.

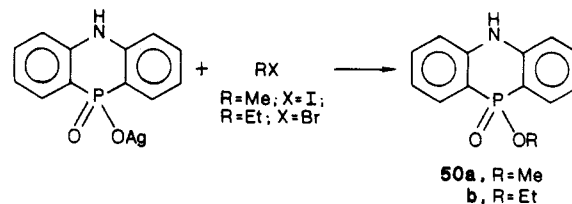
In contrast to the above results, the interaction of I₂ and 3 in DMF leads neither to nuclear halogenation nor to oxidation to a phosphinic acid.⁵ Instead, 1 mol of I₂ reacts with 2 mol of 3 to yield exactly 2 mol of HI together with the following dioxide:



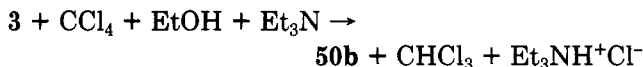
The same substance can also be obtained by allowing 3 to react with Chloramine-T in DMF. The dioxide crystallizes from MeOH with 2 mol of solvent and from formic acid with 1 mol of solvent. The latter solvate is very stable and is unaffected by heating at 180 °C (0.1 torr). Neither solvate melts below 340 °C.

D. Formation of Esters, Amides, and Anhydrides

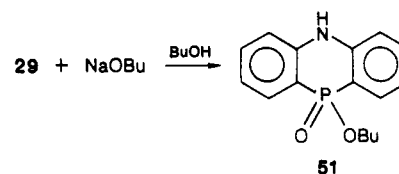
Sergeev and Kudryashov² were the first to report the synthesis of esters of the phosphinic acid 30. They converted the acid to the silver salt and then allowed the latter compound to react with MeI or EtI. They



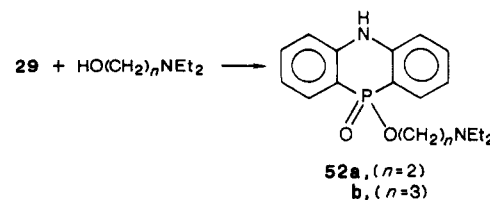
reported a melting point of 112–114 °C for the methyl ester and 99 °C for the ethyl ester. Häring⁵ prepared the methyl ester by three methods: (1) the interaction of the acid 30 and diazomethane; (2) treatment of the acid chloride 29 with NaOMe in MeOH; (3) the reaction of the potassium salt of 30 with dimethyl sulfate. All three methods yielded an ester with a melting point and mixture melting point of about 223 °C. There is no obvious explanation for the much lower melting point observed by the earlier workers.² The methyl ester 50a has been prepared as an intermediate in another laboratory by the interaction of the acid chloride 29 and NaOMe, but the melting point was not reported.⁴³ Petrov and co-workers⁵⁷ have prepared the ethyl ester 50b by the triethylamine-promoted reaction of the oxide 3 with CCl₄ and EtOH; they reported a melting point of 195 °C. Although they did not discuss the stoichiometry of this reaction, it probably conforms to the following equation:



The butyl ester 51 has been prepared by the interaction of the acid chloride 29 and NaOBu in BuOH.⁵

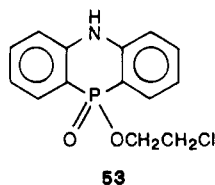


The (dimethylamino)alkyl esters 52, on the other hand, were obtained by the direct reaction of the acid chloride 29 with an excess of the corresponding alcohol.⁵ The benzyl ester of 30 was prepared by the interaction of the potassium salt of 30 and PhCH₂Br in 2-propanol.⁵

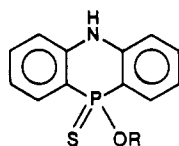


The French patent literature⁶² describes the preparation of the chloroethyl ester 53 by heating the oxide 3 with ethylene oxide and CCl₄ in an autoclave at 100 °C. The yield of 53 was said to be greatly improved by the presence of small amounts of TiCl₄.

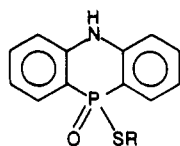
A number of esters of thiophenophosphazinic acid (34) have also been described. Häring⁵ obtained the methyl ester 23b by the interaction of the chloride 22a



with NaOMe in MeOH. The isomeric thiolo derivative **54a** was obtained, however, when the acid **34** was treated with diazomethane. McHattie prepared **23a-e**



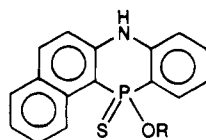
23a, R = Et
b, R = Me
c, R = Pr
d, R = Me₂CH
e, R = CH₂CH₂NMe₂



54a, R = Me
b, R = Et
c, R = Pr
d, R = Bu

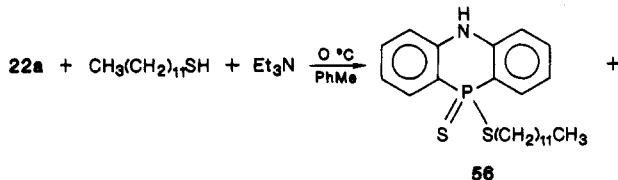
and a number of other thiono esters from the chloride **22a** and the nuclear-substituted chlorides **22b-e**; these esters are mentioned in Mann's book.⁸ Cheplanova and Yarmukhametova¹⁶ repeated Häring's method for preparing **23b** and used a similar procedure for **23a,c,d**. They noted, however, that a small amount of the isomeric thiolo ester was also formed in each reaction. They obtained the pure thiolo esters **54** by the interaction of the potassium salt of **34** and an appropriate alkyl halide.

It has also been reported³⁴ that the thiono esters **55a,b** are formed by the reaction of the chloride **24** with the appropriate sodium alkoxide. No mention was made of the concomitant formation of thiolo esters.

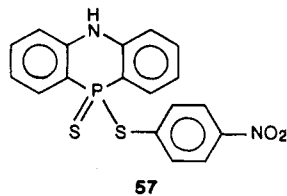


55a, R = Me
b, R = Me₂CH

Several esters of phenophosphazinic and thiophenophosphazinic acids have been mentioned in a Swiss patent.⁶³ In addition, the dodecyl dithioate **56** was said to be formed by the base-promoted interaction of the acid chloride **22a** and 1-dodecanethiol. Further in-



formation on the esters described in this patent is given in section VII. McHattie⁸ prepared the *p*-nitrophenyl dithioate **57** by the reaction of the chloride **22a** with sodium *p*-nitrothiophenoxide in boiling benzene.



The nitration and hydrolysis of several esters of phenophosphazinic and thiophenophosphazinic acids

have been discussed in section IIIC1. Other reactions of these esters are mentioned in section IIIF.

A 5,10-dihydrophenophosphazine derivative having a 10-amino 10-oxide or a 10-amino 10-sulfide grouping may be regarded as an amide. Häring⁵ was the first to describe a 10-amino 10-oxide derivative. He obtained compounds **58a,b** by the interaction of the acid chloride



58a: R₁ = H; R₂ = CH₂CH₂NEt₂
b: R₁ = H; R₂ = CH₂CH₂CH₂NMe₂
c: R₁ = Et; R₂ = Et

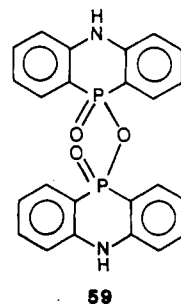
29 and an excess of the appropriate amine. He found that these amides were readily hydrolyzed by aqueous acids. A number of other amides have been prepared in a similar manner from **29** and are discussed in section VI. It has also been shown⁵⁷ that the amide **58c** can be obtained in good yield by heating the secondary phosphine oxide **3** with an excess of Et₂NH and CCl₄. The stoichiometry of this reaction presumably conforms to the following equation:



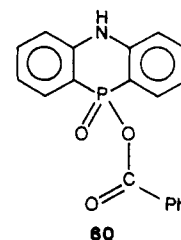
The melting point of the amide thus obtained was 247 °C (compared to a reported¹⁵ melting point of 244 °C when the compound was prepared by the interaction of the acid chloride **29** and an excess of Et₂NH).

McHattie obtained a number of amides of thiophenophosphazinic acid (**34**) by heating a benzene solution of the acid chloride **22a** with ammonia or a primary or secondary amine. These amides are tabulated in Mann's book.⁸ Several other amides of **34** were later prepared by a similar procedure¹⁵ and are mentioned in section VI.

Häring⁵ prepared phenophosphazinic anhydride (**59**) by the interaction of benzenesulfonyl chloride and the potassium salt of the acid **30**. The anhydride is in-



soluble in aqueous NH₃ or dilute alkali but can be hydrolyzed by boiling with 5 N NaOH. The mixed anhydride **60** is formed by heating the potassium salt of **30** with an excess of benzoyl chloride.

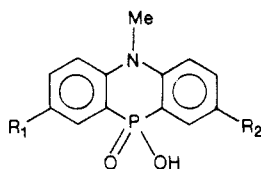


E. Dissociation Constants of Acid Derivatives

Dihydrophenolphosphazine derivatives in which the phosphorus atom is part of a phosphinic acid group are sometimes referred to as phenolphosphazinic acids.⁸ The parent compound **30** was first reported in 1938 by Sergeev and Kudryashov.² They noted that it was soluble in aqueous alkali and that it gave the correct neutralization equivalent on titration in aqueous EtOH with 0.1 N NaOH to the phenolphthalein endpoint. Treatment of a neutral solution of the acid with AgNO₃ yielded a silver salt. They also prepared a nitro derivative of the acid and showed that it was soluble in alkaline solution.

Häring⁵ reported that phenolphosphazinic acid (**30**) is a relatively strong monobasic acid with a pK_a of 3.1–3.2. This value was said to be potentiometrically determined, but the solvent used was not mentioned. (It should be noted that the acid has a very low solubility in H₂O.) Mann⁸ has stated that the acid gives a pK_a of 4.7 in 70% aqueous EtOH and estimated that the "true" pK_a value in H₂O would be approximately 3.1.

More recently, a group of Russian workers⁴⁶ have reported the dissociation constants of six phenolphosphazinic acid derivatives of the following type:



- 47:** R₁=H; R₂=H
61: R₁=H; R₂=Br
48: R₁=H; R₂=NO₂
62: R₁=NH₂; R₂=NO₂
63: R₁=Br; R₂=NO₂
46: R₁=NO₂; R₂=NO₂

The dissociation constants were determined by potentiometric titration in Me₂SO and were found to conform to the Hammett equation:

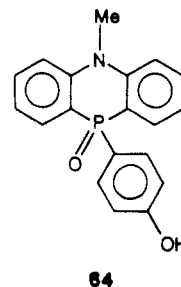
$$pK_a = (9.93 \pm 0.11) - (2.78 \pm 0.14)\Sigma\sigma$$

The σ values were taken from a review published in 1961 by Pal'm.⁶⁴ For comparison with these dissociation constants, the authors also determined the pK_a's in Me₂SO of the diarylphosphinic acids (*m*-RC₆H₄)₂PO₂H, where R = H, Me, or NO₂, and (*m*-O₂NC₆H₄)PhPO₂H. These values also obeyed the Hammett equation:

$$pK_a = (8.73 \pm 0.09) - (2.18 \pm 0.11)\Sigma\sigma$$

Since the value for the proportionality constant ρ is significantly higher for the pK_a's of the phenolphosphazinic acids (2.78 vs. 2.18), it seems likely that the influence of the substituents R and R' is transmitted to the phosphorus atom not only through the closest benzene ring but also through the bridge nitrogen atom. The fact that phenolphosphazinic acids are weaker than the corresponding diarylphosphinic acids suggests that the electron density is higher on the phosphorus atom of the heterocyclic compounds.

In the same paper⁴⁶ the Russian authors also compared the dissociation constants of several known phenols of the type RC₆H₄OH, where R = H, *p*-Br, *m*-O₂N, *p*-O₂N, or *p*-Ph₂P(O), with that of the phenolic derivative **64**, which incorporates the dihydrophenolphosphazine system. The dissociation constants were



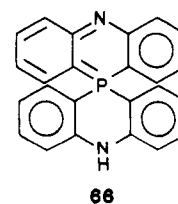
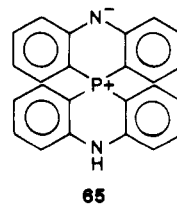
determined by potentiometric titration in aqueous isopropyl alcohol (H₂O to Me₂CHOH ratio of 20:1). Where R = H, *p*-Br, *m*-O₂N, or *p*-O₂N, the pK_a's gave an excellent correlation with known nucleophilic substitution constants σ^- :

$$pK_a = (12.55 \pm 0.06) - (2.33 \pm 0.08)\sigma^-$$

The above equation was then used to calculate substituent constants for the Ph₂P(O) group ($\sigma^- = 0.62 \pm 0.04$) and the 5,10-dihydro-5-methyl-10-oxophenolphosphaziny group ($\sigma^- = 0.58 \pm 0.04$). It was concluded that the phosphorus atom was so remote from the reaction center in these cases that the differences in their electronic effects were not manifest.

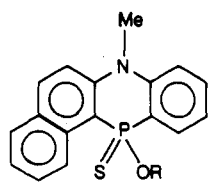
Thiophenolphosphazinic acid (**34**) was first prepared by Häring,⁵ who noted that it was soluble in aqueous Na₂CO₃ and that it could be reprecipitated with HCl. McHattie⁸ later prepared and characterized Et₃N and piperazine salts of the acid **34**. In 95% aqueous EtOH the acid gave a pK_a of 5.1, and it was estimated that the "true" pK_a value in aqueous solution would be approximately 3.5.

The spiro phosphonium chloride **4** and its ring-substituted derivatives appear to have acidic properties.^{6,7,17,26,27} Treatment of alcoholic solutions of these chlorides with aqueous NaOH yields fine yellow precipitates, which have not been rigorously purified since they are insoluble in H₂O and the common organic solvents (except for glacial acetic acid, which converts them to acetates). These yellow substances contain no chlorine, but their IR and mass spectra are virtually identical with the spectra of the corresponding chlorides; and they can be reconverted to the chlorides by treatment with HCl. It seems likely that the yellow substances have zwitterionic structures like **65** and are resonance stabilized through canonical forms of type **66**.

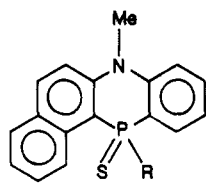


F. Miscellaneous Reactions

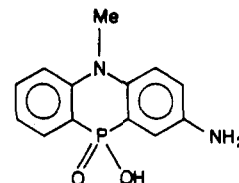
The NH group of a dihydrophenolphosphazine derivative can be alkylated by deprotonation with NaH and treatment of the resulting anion with an alkyl halide. The dimethylation of the secondary oxide **3** by this method has been noted in section IIIB3. A similar procedure has been employed for the N-methylation of the acid **30** to **47**,^{43,44,61} the esters **50a**, **55a**, and **55b** to **42**,^{43,44} **67a**,³⁴ and **67b**,³⁴ respectively, the tertiary phosphine oxides **21a** and **21b** to **33a**³⁰ and **33b**,³⁰ re-



67a, R = Me
b, R = Me₂CH

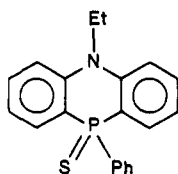


68a, R = Me
b, R = Me₂CH

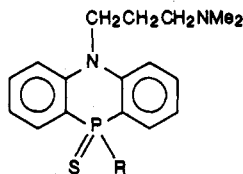


75

spectively, and the tertiary phosphine sulfides 36a and 36b to 68a³⁴ and 68b,³⁴ respectively. The tertiary phosphine sulfide 35b has been converted in an analogous manner to the *N*-ethyl compound 69⁴⁹ and the *N*-(dimethylamino)propyl compound 70a,³⁵ while the tertiary phosphine sulfide 35c has been similarly converted to the bis[(dimethylamino)propyl] compound 70b.³⁵

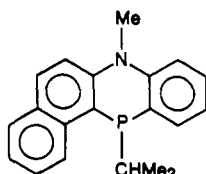


69

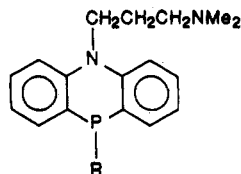


70a, R = Ph
b, R = Me₂N(CH₂)₃

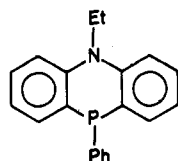
The tertiary phosphine sulfides 68b, 70a, and 70b mentioned in the paragraph above have been reduced (desulfurized) to the corresponding tertiary phosphines 71,³⁴ 72a,³⁵ and 72b,³⁵ respectively, by treatment with



71

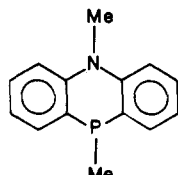


72a, R = Ph
b, R = Me₂N(CH₂)₃

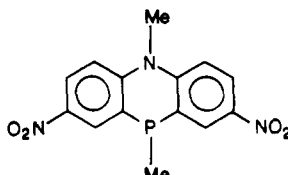


25b

sodium naphthalide. The *N*-ethyl compound 69 has also been converted to the corresponding tertiary phosphine 25b,⁵⁰ but details of this reaction are not available to us. The tertiary phosphine oxides 33a, 33b, and 49 have been reduced to the tertiary phosphines 73, 25a, and 74, respectively, by means of trichloro-



73



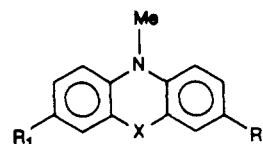
74

silane.⁴⁵ The polarographic reduction of the tertiary phosphine 74, the tertiary phosphine oxide 33a, and four other dihydrophenophosphazine derivatives is discussed later in this section.

The nitro compound 48 has been reduced with H₂ over nickel to the corresponding amino compound 75; and one of the nitro groups in the dinitro compound 46

has been reduced with Na₂S to give the monoamino derivative 62.⁶¹ The amino groups of both 62 and 75 have been converted with NaNO₂ in HBr to the corresponding diazonium bromides, which were then heated with aqueous CuSO₄ to yield the bromo compounds 63 and 61, respectively. Diazotization of 62 in HCl and subsequent reduction with H₃PO₂ gave the mononitro compound 48. The latter substance proved to be identical with the mononitro compound prepared by the nitration of the acid 47 or hydrolysis of the ester 43 (cf. section IIIC1).

A study has been reported of the polarographic reduction of six dihydrophenophosphazine derivatives of the following type:



33a: R₁ = R₂ = H; X = P(O)Me
42: R₁ = R₂ = H; X = P(O)OMe
43: R₁ = H; R₂ = NO₂; X = P(O)OMe
44: R₁ = R₂ = NO₂; X = P(O)OMe
49: R₁ = R₂ = NO₂; X = P(O)Me
74: R₁ = R₂ = NO₂; X = PMe

DMF was used as the solvent, and 0.1 M Bu₄Ni was the supporting electrolyte. The polarogram of the mononitro compound 43 exhibited three waves. The first of these occurred at -1.21 V (relative to the saturated calomel electrode) and corresponded to a one-electron reversible process. There were four waves on each of the polarograms of the dinitro compounds (44, 49, 74), and it was concluded that the first two of these waves also represented one-electron processes. The third wave exhibited by each of the dinitro compounds corresponded to the irreversible transfer of six electrons and suggested the simultaneous reduction of two nitro groups to hydroxyamino groups. At the potential of the fourth polarographic wave, the reduction of the hydroxyamino groups and of the heterocyclic ring occurred. In fact, in the same region of reduction potentials (-2.6 to -2.7 V), the two unnitrated compounds (33a, 42) accepted one electron reversibly. The radical anions formed in the electrochemical reduction of the dinitro compounds 49 and 74 were studied by ESR spectroscopy.

Three spiro phosphoranes have been prepared by the addition of the azaphosphatriptycene (26b) to tetrachloro-1,2-benzoquinone, 3,5-di-*tert*-butyl-1,2-benzoquinone, or 9,10-phenanthraquinone.⁶⁶ The molecular structure of the adduct obtained with the first of these quinones is described in section IV.

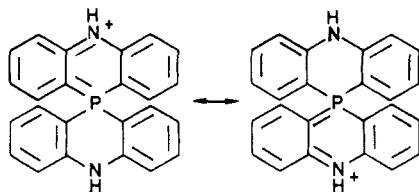
Aluminum chloride in benzene has been used to convert the methoxy-substituted tertiary phosphine oxide 33c to the corresponding phenol 64.⁴⁶ The acid dissociation constant of the latter compound has been discussed in section IIIIE.

A number of methiodides have been prepared by the reaction of MeI with dihydrophenophosphazine deriv-

atives, e.g. the tertiary phosphines **25a**,^{38a,44} **26a**,^{25,40} and **73**,⁴⁴ the esters **23e**⁸ and **52a**,⁵ and the amide **58a**.⁵ Structural information about these methiodides has not been reported.

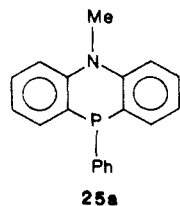
IV. Molecular Structures by X-ray Diffraction

The spiro phosphonium chloride **4** was the first phenophosphazine derivative to be studied by X-ray diffraction.^{6,7} The two tricyclic systems in the cation are essentially at right angles to one another. One tricycle is planar within experimental error; the other is distorted, with the two *o*-phenylene groups slightly tilted above the average plane of the tricycle. There is no obvious explanation for the observed difference between the two tricyclic systems, but there are several close intramolecular contacts that may be causing distortion. The two internal C–P–C bond angles (103.6, 103.7°) are identical within experimental error, and the four other C–P–C bond angles range from 110.7 to 114.0°. The average of these six angles is 109.5°, i.e. the regular tetrahedral angle. The four C–P bond distances vary from 1.764 to 1.774 Å. Since the estimated standard deviation is only 0.005 Å, the C–P bond distances in this cation appear to be significantly shorter than the normal C–P single-bond distance (e.g., 1.828 ± 0.003 Å in triphenylphosphine⁶⁷). They are, however, comparable to the cyclic C–P bond distances of 1.780 and 1.786 Å found in 1-benzylphosphole.⁶⁸ It seems possible that the C–P bonds in the spiro phosphonium cation may have some double-bond character. The C–N bonds in the cation are also unusually short: 1.370–1.382 Å (compared to 1.472 ± 0.005 Å for a "normal" C–N single bond⁶⁹). The observed shortening of the C–P and C–N bonds suggests that the spiro phosphonium cation may be resonance stabilized through canonical forms in which there is a formal positive charge on a nitrogen atom, e.g.



There are very few intermolecular close contacts in the crystal structure of the spiro phosphonium chloride. The closest approach of the chloride ion to the phosphorus atom is 4.39 Å. Both nitrogen atoms appear to be hydrogen bonded to chloride ions. One nitrogen–chlorine distance is 3.16 Å, while the other is 3.28 Å.

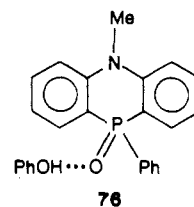
X-ray diffraction studies of several *N*-alkyl-5,10-dihydrophenophosphazine derivatives have been published in the Russian literature. The first⁷⁰ of these papers describes the crystal and molecular structure of 5-methyl-10-phenyl-5,10-dihydrophenophosphazine (**25a**). The tricyclic system of this molecule is distinctly



nonplanar. The central ring has a boat conformation

in which the phosphorus and nitrogen atoms are displaced by 0.55 and 0.32 Å from the plane of the four carbon atoms making up the bottom of the boat. The dihedral angle between the planar *o*-phenylene rings is 145.1°. The P–Ph bond occupies an axial position. The internal C–P–C angle is 97.2° while the other two C–P–C angles are 100.8 and 102.1°. These values are smaller than the average value of 103.0° for the C–P–C angles in Ph₃P and suggest (according to the authors⁷⁰) that the phosphorus atom in the phenophosphazine has a hybridization close to p³; i.e. all the 3p orbitals of the phosphorus atom take part in the formation of σ bonds, while the unshared pair of electrons is localized in an s orbital and cannot take part in conjugation. The internal C–P bond distances are 1.804 and 1.811 Å; the exocyclic C–P bond distance is 1.840 Å. The increased length of the exocyclic bond appears to be the result of steric interaction between the phenyl group bonded to the phosphorus atom and the *o*-phenylene rings of the tricyclic system. The bonds at the nitrogen atom have an essentially planar–trigonal configuration. Thus, the internal C–N–C angle is 121.6°, while the other two C–N–C angles are 117.7 and 117.9°. The exocyclic C–N distance is 1.460 Å, but the internal C–N distances are significantly shorter, viz. 1.393 and 1.394 Å. It was concluded that the geometry of the tricyclic system of the phenophosphazine is remarkably similar to the geometry of *N*-methylphenothiazine.⁷¹

A second Russian paper⁴⁷ describes a complete X-ray structural study of a 1:1 phenol adduct (**76**) of the oxide **33b**. As in compound **25a** (discussed in the above

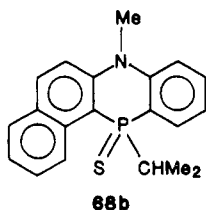


paragraph), the central heterocyclic ring in **76** is bent along the P...N axis and has the boat conformation; the dihedral angle between the planes of the *o*-phenylene rings is 149.3°. The phenyl group bonded to the phosphorus occupies an axial position, while the oxide group is equatorial. Comparison of the two compounds shows distinct differences in the C–P bond lengths and the C–P–C valence angles. Thus, the internal C–P bond lengths in the adduct are 1.761 and 1.773 Å, and the length of the exocyclic C–P bond is 1.796 Å. The internal C–P–C angle is 110.7°, while the other two C–P–C angles are 106.8 and 107.2°. The observed differences between the two compounds was ascribed to the difference in the hybridization of the phosphorus atom. The hydrogen bond in the adduct appears to be fairly strong. Thus, the O(phenol)...O(oxide) distance is only 2.68 Å; and the phenolic H...O(oxide) distance is 1.75 Å (compared with the sum of the van der Waals radii of 2.57 Å). The O–H...O bond angle is 155°. The strength of the hydrogen bond makes the adduct comparatively stable, and liberation of phenol occurs only when the adduct is heated to 160 °C (2 torr). As in other dihydrophenophosphazine derivatives, the internal C–N distances in **76** are short, viz. 1.382 (9) and 1.413 (7) Å; the exocyclic C–N distance is 1.489 (10) Å.

The X-ray structure of the tertiary sulfide **69** has also been determined in a Russian laboratory.⁴⁹ Like the

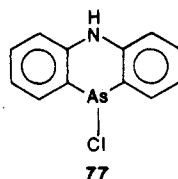
two compounds (**25a**, **76**) discussed above, this molecule is nonplanar and is bent along the P...N axis. The central heterocyclic ring has a boat conformation in which the phenyl substituent occupies an axial position and the sulfur an equatorial position. The dihedral angle between the *o*-phenylene rings is 138°. In short, the stereochemistry of the tricyclic system in the three compounds is quite similar. The average C-P-C valence angle in the sulfide is 103.6°, compared to 108.2° in the adduct **76** and 100.0° in the tertiary phosphine **25a**. The P=S bond length is 1.950 ± 0.005 Å. Because this bond is disposed equatorially, the sulfur atom is close to carbon atoms 1 and 9. In fact, the average distance between the sulfur and each of these carbon atoms is only 3.43 Å, which is less than the sum (3.55 Å) of the van der Waals radii. The effect of the P=S bond on the ¹H NMR signals of the protons attached to these carbon atoms is discussed by the authors.⁴⁹

A fourth paper⁷² in the Russian literature describes the crystal and molecular structure of the sulfide **68b**.



Once again, the heterocyclic ring has a boat conformation; the phosphorus and nitrogen atoms deviate from the bottom of the boat by 0.53 and 0.34 Å, respectively. The sulfur atom occupies an equatorial position, while the secondary carbon atom of the isopropyl group is found in an axial position. The P=S bond length, 1.951 (3) Å, and the average C-P-C angle (102.6°) are similar to the corresponding values for the sulfide **69** described in the above paragraph. The internal C-N distances are 1.39 (1) Å, while the exocyclic C-N distance is significantly longer, viz. 1.49 (1) Å.

It is interesting to compare the structural information reviewed in the above paragraphs with the results obtained by Camerman and Trotter⁷³ in an X-ray diffraction study of 10-chloro-5,10-dihydrophenarsazine (**77**). The molecule of the arsenic compound is only

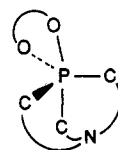


slightly folded about the As...N axis; the angle between the two *o*-phenylene rings is 169°20', and the chlorine atom is outside this angle. Each of these rings is thus displaced by only about 5° from a completely planar arrangement. The C-As bonds (mean length 1.917 ± 0.007 Å) and the C-N bonds (mean length 1.371 ± 0.009 Å) are significantly shorter than the corresponding normal single-bond distances. It is seen that the C-N bond distances in the arsenic compound are about the same as the internal C-N distances in **4**, **25a**, **76**, and **68b**; the C-N distances in **69** have not been reported. Camerman and Trotter suggested that the arsenic and nitrogen lone-pair electrons interact with the *o*-phenylene π electrons and in addition there may be d_π-p_π bonding between the π electrons and vacant 4d

orbitals of the arsenic atom.

Not surprisingly, the X-ray structure of the azaphosphatriptycene **26b**⁷⁴ differs in several important respects from the other 5,10-dihydrophenophosphazines discussed in this section. The restrictions imposed by the caged structure is found to lead to a narrowing of the C-P-C angle to a mean value of 93.3 (5)°. In contrast, the mean C-N-C angle of 107.0 (5)° approaches the regular tetrahedral angle. The mean C-P distance of 1.828 (8) Å and the mean C-N distance of 1.460 (13) Å are in good agreement with the normal single-bond values. Considerable distortion of the trigonal angles involved with the heterocyclic rings is necessary to enable the achievement of relatively small C-P-C angles. Thus, the mean value for the internal P-C-C angles within the cage is 115.6 (4)°, and for the external P-C-C angles the mean value is 124.0 (4)°.

As previously noted in section IIIF, the addition of *o*-quinones to the azaphosphatriptycene **26b** yields spiro phosphoranes.⁶⁶ The crystal and molecular structure of the adduct obtained with tetrachloro-1,2-benzoquinone has been determined by Hellwinkel and co-workers.⁶⁶ The phosphorus atom is in a slightly distorted trigonal-bipyramidal (TBP) environment, with one oxygen atom occupying an apical and the other an equatorial position:



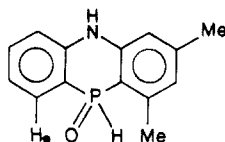
The most important deviation from an ideal TBP arrangement involves the angle between the two equatorial C-P bonds, which is only 100.8 (2)° instead of 120°. Nevertheless, the planarity of the three equatorial bonds is preserved, with the sum of the equatorial angles being 359.9°. The angle between the axial bonds is 172.9 (2)° and hence does not deviate greatly from linearity. The five-membered ring is planar, and the O-P-O angle is 86.2 (2)°. As is usually found in TBP molecules, axial bonds tend to be longer than similar equatorial bonds. Thus, the axial P-O bond distance is 1.816 (3) Å, while the equatorial P-O bond distance is 1.670 (3) Å. Similarly, the axial C-P distance is 1.869 (5) Å, and the equatorial C-P distances are 1.814 (5) and 1.815 (5) Å. The other bond distances in this molecule do not differ greatly from the corresponding distances in the parent azaphosphatriptycene **26b**.

V. Nuclear Magnetic Resonance Spectra of 5,10-Dihydrophenophosphazine Derivatives

Kupchik and Perciaccante³⁹ were the first to describe the ¹H NMR spectra of 5,10-dihydrophenophosphazine derivatives. Thus, they reported that the spectra of the tertiary phosphines **25a,c,d** exhibited singlets at δ 3.25, 3.18, and 3.37, respectively, which were assigned to the NMe protons, and a multiplet in the δ 6.6-7.9 region, which was assigned to the aromatic protons. The spectrum of the trimethyl compound **25c** contained an additional singlet at δ 2.3, which was assigned to the two methyl groups bonded to aromatic rings. It was also noted that the observed ratio of aromatic to aliphatic protons was relatively close to the theoretical ratio. Later workers obtained comparable ¹H NMR data for

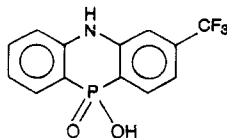
the phosphinic acids 11¹⁷ and 18,²⁶ the tertiary phosphines 26a,²⁵ 26b,²⁵ 27,²⁵ 28b,²⁴ 28c,²⁴ and 73,⁴⁵ the tertiary phosphine oxides 33a⁴⁵ and 33b⁴⁵ and the oxide²⁴ derived from 28c, the PMe derivative^{25,40} of the azaphosphatriptycene 26a, and nine 7,12-dihydrobenzo[a]phenophosphazine derivatives.³⁴ Additional ¹H NMR spectra have been recorded in the Russian literature, but they are in documents^{43,44,60} that are not readily available to us. According to the review of Bokanov and Stepanov,⁹ the ¹H NMR chemical shifts of the nonequivalent aromatic protons of the dinitro compound 44^{43,60} differ enough to make it possible to "decipher" the spectrum completely and to determine the orientation of the nitro groups.

As mentioned in section IIA, the structures of the dihydrophenophosphazine derivatives obtained via the interaction of PCl₃ and certain meta-substituted diarylamines were not unequivocally established by the method of synthesis employed. A ¹H NMR study,²⁷ however, made it possible to deduce their structures. One key to this problem was the detection of spin-spin coupling between the phosphorus atom and the aromatic hydrogens ortho to it. A study of the following secondary phosphine oxide (obtained from the amine 19e) was first studied, since there was no uncertainty about its structure:



This compound exhibited a P-H_a coupling constant of 13.8 Hz. Each of the dihydrophenophosphazine derivatives obtained from the amines 19a-c, however, exhibited coupling between the phosphorus atom and *two* ortho hydrogens. Accordingly, the 1- and 9-positions in these compounds must be occupied by hydrogen atoms, and the substituents on the aromatic rings must be in the 3-position or in both the 3- and 7-positions.

Bokanov and co-workers⁴⁹ have suggested that the magnetic anisotropy of the P=S bond in the tertiary phosphine sulfide 69 causes a downfield shift of the H-1 and H-9 signal (to δ 8.05) and, consequently, a distinct separation of this signal from the multiplet signal of the other aromatic protons (δ 7.2-7.4). It has also been shown (cf. Figure 1 of ref 27) that the H-1 and H-9 signals are separated in a similar manner from the signals of the other aromatic protons in the following phosphinic acid:



It seems possible that the downfield shifts noted in the ¹H NMR spectra of both this compound and 69 are caused by the electronic properties of the phosphorus atom.

The ³¹P NMR spectra of a number of 5,10-dihydrophenophosphazine derivatives have been recorded. The signs of the chemical shifts discussed in this review have been changed, when necessary, to conform to the current convention that downfield shifts are given positive

signs. In all cases the shifts have been given relative to the signal of 85% H₃PO₄. In 1969 Hellwinkel and Schenk⁴⁰ reported that the ³¹P chemical shift of the azaphosphatriptycene 26a occurred at an astonishingly high field strength: -80 ppm (CHCl₃) and -79 ppm (THF). They concluded that the lone pair on the phosphorus atom must have high s character and that the C-P-C bond angle must be about 90° (cf. section IV). The phosphonium iodide obtained by the methylation of 26a exhibited a ³¹P chemical shift of -4.75 ppm (CF₃CO₂H). This value indicates that the phosphorus atom in this compound is more strongly shielded than in triphenylmethylphosphonium iodide, $\delta(^{31}\text{P})$ +19.4. The results obtained by Hellwinkel and Schenk⁴⁰ were discussed in greater detail in a later paper²⁵ from the same laboratory. In this paper they also reported ³¹P NMR data for a number of other heterotriptycenes, including the azaphosphatriptycene 26b [$\delta(^{31}\text{P})$ -78.7, CDCl₃].

In 1973 Jenkins, Freedman, and Bordner⁷ reported that the ³¹P chemical shift of the phosphonium chloride 4 was -21 ppm (in either Me₂SO or CF₃CO₂H). This value, they believed, indicates that there is unexpectedly high electron density at the phosphorus atom and significant electron delocalization in the heterocyclic rings. These effects were rationalized by assuming that the phosphonium ion of 4 is resonance stabilized through canonical structures in which the positive charge is on nitrogen.

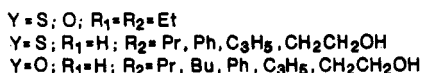
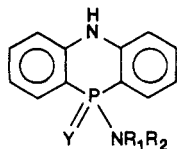
In 1977 Smirnov and co-workers⁴⁵ reported that the tertiary phosphines 25a, 73, and 74 exhibited ³¹P chemical shifts (in CDCl₃) of -43.0, -6.30, and -59.7 ppm, respectively. These values indicate, according to the authors, strong shielding of the phosphorus nucleus and localization of the unshared electrons on phosphorus. They also found that the chemical shifts of the phosphine oxides 33a and 33b in CDCl₃ were +9.4 and +5.0 ppm, respectively. In another paper³⁴ from the same laboratory, the chemical shifts of the thionophosphinyl chloride 24 and the tertiary phosphine sulfide 36b were reported to be +48.6 (THF) and +57.9 ppm (CDCl₃), respectively.

Negrebetskii⁷⁵ has studied the ¹³C NMR spectra of the tertiary phosphine 73 and its oxide 33a. He found that the values of the ²J_{PC} and ³J_{PC} constants in 73 were similar to the corresponding coupling constants in ortho-substituted triarylphosphines and in 1,6-diphosphatriptycene. It was concluded that the sign of these constants was positive and that their values depend mainly on the orientation of the unshared electron pair rather than on the nature of substituents on the aromatic rings. The changes in the J_{PC} constants noted on going from 73 to the oxide 33a were attributed to the increase of the s character of the orbitals of the phosphorus atom. It was also found that a decrease in the temperature at which the ¹³C NMR experiments were conducted led to an algebraic decrease in the ¹J_{PC} constants (if one assumes that ¹J_{PC} is negative for 73 and positive for 33a) and an upfield shift of the signals of the carbon atoms directly bonded to the phosphorus atom.

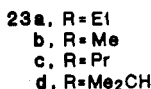
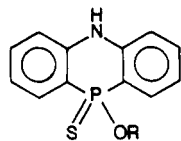
VI. Biological Properties of 5,10-Dihydrophenophosphazine Derivatives

Although a number of workers^{8,9,15,16,24} have suggested

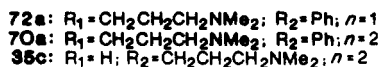
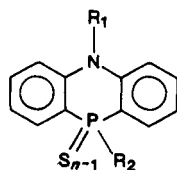
that dihydrophenophosphazine derivatives might be useful as therapeutic agents, no systematic investigation of the biological properties of these substances has yet been undertaken. Jones and Mann³ in 1956 reported that the oxide **3** has no apparent effect on schistosomiasis infection in mice. Four years later Häring⁵ appears to have studied some pharmacological properties of several derivatives of **3**; he noted only that none of the compounds he tested showed any interesting activity. The following year McHattie³¹ claimed in British patent that several of the dihydrophenophosphazine sulfides **22** that he had prepared possess anthelmintic properties, especially in ruminants. These claims prompted Cheplanova and Yarmukhametova¹⁵ in 1971 to synthesize 11 amides of the following type:



The compounds were said to be quite nontoxic toward warm-blooded animals (LD₅₀ > 1000 mg/kg). It was also stated that the anthelmintic activity of these substances was being studied, but the results have apparently not been published. A similar amide (Y = O, R₁R₂N = N-methylpiperazinyl) was prepared in 1962 by Schroeder and co-workers¹¹ and was tested against the E0771 (established) tumor in mice; no activity, however, was observed. The thiono esters **23** were described in a second paper by Cheplanova and Yarmukhametova¹⁶ and were said to be nontoxic toward warm-blooded animals (LD₅₀ > 500 mg/kg).

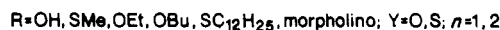
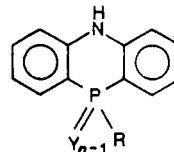


The influence of three (dimethylamino)propyl derivatives on the cardiovascular system has also been explored.³⁵ The compounds studied in this investigation included a tertiary phosphine and two sulfides. Hydrochlorides of these substances were injected intravenously into narcotized animals suffering from myocardial infarction. In doses of 10–20 mg/kg, this treatment resulted in transitory hypotension and bradycardia. Lower doses (1–5 mg/kg) appeared to have no effect on cardiac behavior.



VII. Practical Applications of 5,10-Dihydrophenophosphazine Derivatives

Only a few practical applications of dihydrophenophosphazine derivatives have been suggested. In 1957, it was reported⁴ in an obscure Russian journal that the oxide **3** could be used for the determination of titanium and uranium dioxide, but no further information about this method has been published. Ten years later it was claimed in an American patent^{38c} that 5-alkyl-10-phenyl-5,10-dihydrophenophosphazines are useful as additives for lubricating oils, greases, and hydraulic fluids that are to be employed in high-temperature environments (e.g., jet engines). These additives were said to be superior to any previously employed substance for inhibiting oxidation and for preserving contacting surfaces of moving parts. A Swiss patent⁶³ issued in 1972 claimed that certain dihydrophenophosphazine derivatives are effective stabilizers for paraffin oil when they are used with conventional stabilizers such as 2,6-di-*tert*-butyl-4-phenol and dilauryl thiodipropionate. The compounds described in the patent are of the following type:



More recently, the oxide **3** has been evaluated as a catalyst for the preparation of carbodiimides and polycarbodiimides by the decarboxylation of isocyanates.⁷⁶

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