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

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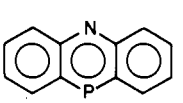
I. Introduction

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



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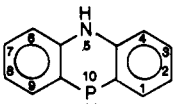

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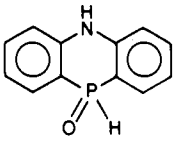
compound was prepared in 1888 by Schenk and Michaelis.[1] They reported that the interaction of diphenylamine and PCl_3 at elevated temperatures (followed by treatment of the reaction mixture with water) yields a white powder with the empirical formula $C_{12}H_{10}NOP$, and they suggested that the phosphorus 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 1960[5] that the substance was unambiguously shown to be a secondary phosphine oxide, viz. 5,10-dihydrophenophosphazine 10-oxide (3).



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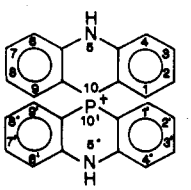
In 1971, it was reported[6] that a compound of empirical formula $C_{24}H_{18}ClN_2P$ was also formed by the interaction of Ph_2NH and PCl_3 at 200–220 °C. The chemical and spectral properties of this substance showed that it did not contain a P–H bond and that it was not a derivative of trivalent phosphorus. 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



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

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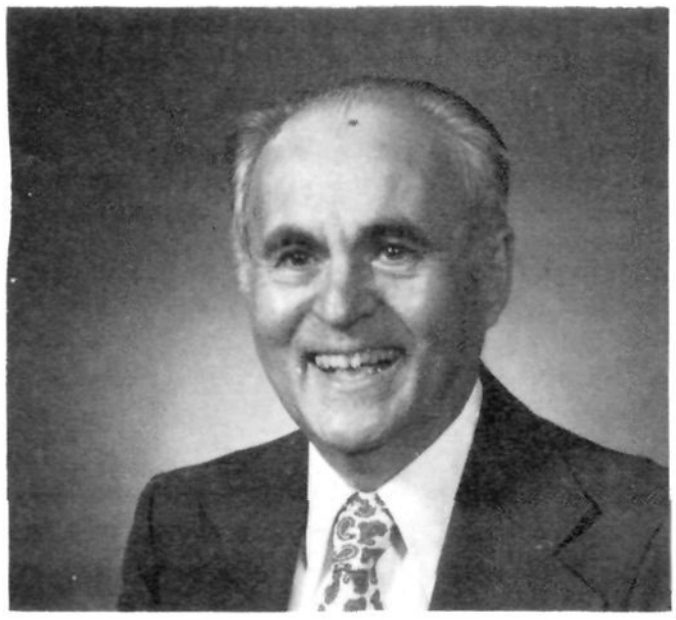


Leon D. Freedman was born in Baltimore in 1921 and completed his undergraduate education at Johns Hopkins in 1941. He then worked for 3 years in a U.S. Public Health Service Laboratory and became interested in organic derivatives of group 5A (group 15 in 1985 notation) elements. After serving in the U.S. Navy during 1944–1946, he returned to Johns Hopkins where he received his M.A. (1947) and Ph.D. (1949) degrees under A. H. Corwin. For the next 12 years he was employed by the Public Health Service and was mainly engaged in synthesis of novel organophosphorus compounds. In 1961 he joined the faculty at North Carolina State University where he is currently professor of chemistry. He is coeditor of Volume VI of *Organic Electronic Spectral Data* and coauthor of a monograph on organoarsenic, -antimony, and -bismuth compounds. He has also published numerous research and review papers.

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.

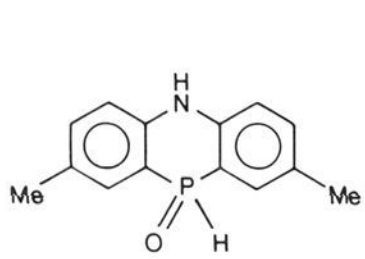
Most of the work on the 5,10-dihydrophenophosphazine ring system reported before 1970 was reviewed by F. G. Mann[8] in his monograph on heterocyclic derivatives of phosphorus, arsenic, antimony, and bismuth. A short review of the chemistry of the dihydrophenophosphazines was published in 1977 by Bokanov 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 Freedman[17] 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).



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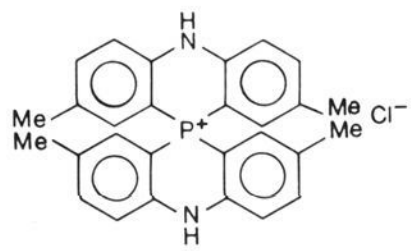

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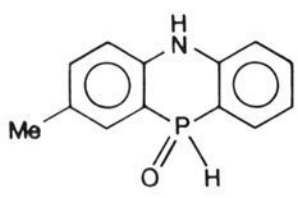

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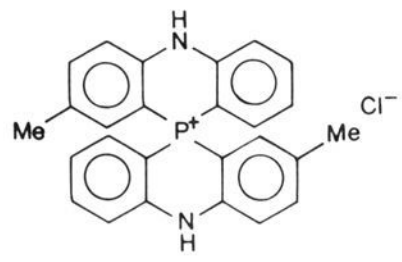

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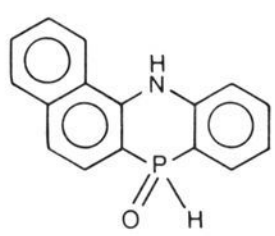

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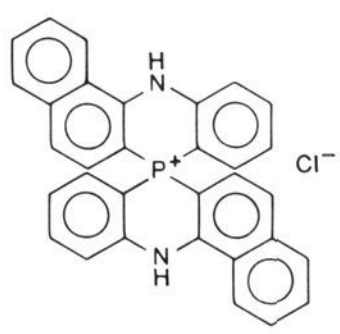

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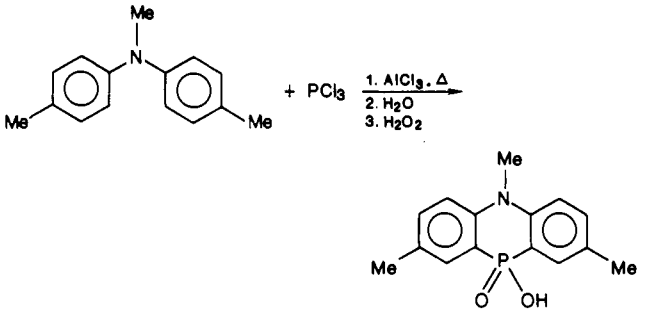
In contrast to the results obtained with the diarylamines, no reaction appears to occur when an *N*-methyldiarylamine and phosphorus trichloride are heated together.[3,17] In the presence of $AlCl_3$, *N*-methyldiphenylamine, and PCl_3 give a phosphonous dichloride $PhN(Me)C_6H_4PCl_2$.[1b] Although 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*-methyldi-*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]



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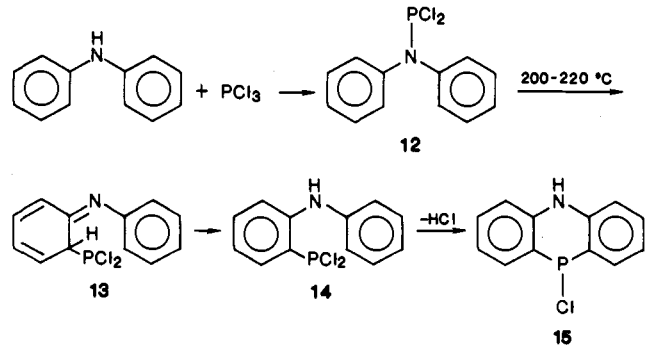
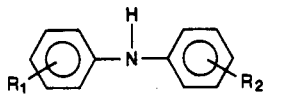
The phosphinic acid **11** is the only *N*-methyldihydrophenophosphazine derivative obtained via the condensation of PCl_3 and an aromatic amine.

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 work[17] showed that the dichloride **12** (which is readily prepared by the interaction of Ph_2NH and PCl_3 in ether at room temperature[20]) 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*-methyldiarylamines 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:



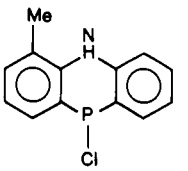
In the above mechanism, the rearrangement of **12** to **13** involves the transfer of the PCl_2 group to an ortho position and the formation of the type of intermediate usually postulated in electrophilic aromatic substitution. Rearomatization of **13** accompanied by transfer of a proton from carbon 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*-methyldiarylamines and PCl_3 requires little comment since the reaction of aromatic compounds with phosphorus trihalides under Friedel–Crafts conditions is well-known.[18b,23]

TABLE I. Diarylamines Studied[26]



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

In a review published in 1977, Bokanov and Stepanov[9] 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 reported[24] that a yellow solid sublimes out of the reaction mixture during the interaction of PCl_3 and 2-methyldiphenylamine or 3,5-dimethyldiphenylamine 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**. Furthermore, 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.



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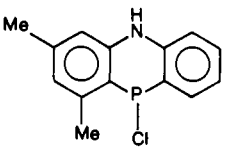
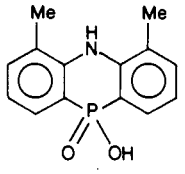


17

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, $(o\text{-}MeC_6H_4)_2NPCl_2$, 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



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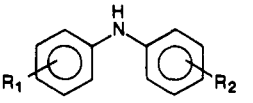
strongly suggest that the presence of two ortho substituents greatly interferes with the synthesis of dihydrophenophosphazine derivatives from diarylamines.

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 $(3\text{-}MeC_6H_4)(3\text{-}CF_3C_6H_4)NPCl_2$, 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.

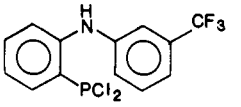
As mentioned above, the structures of the oxides

TABLE II. Diarylamines Studied[27]



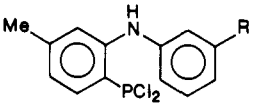
compd	R_1	R_2
19a	3-CF_3	H
19b	3-Me	H
19c	3-Me	3-CF_3
19d	3-CF_3	3-CF_3
19e	3,5-Me_2	H

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-



20a

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

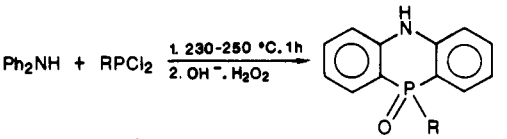


20b, R = H
c, R = CF_3

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 sulfur[28] shows the same type of regiospecificity observed in the investigation[27] 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 note[30] in the Russian literature has described the preparation of two tertiary phosphine oxides via the interaction of Ph_2NH and $MePCl_2$ or $PhPCl_2$:



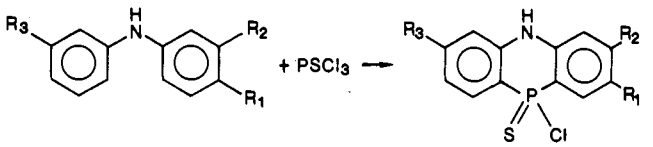
21a, R = Me
b, R = Ph

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 Thiophosphoryl Chloride

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 McHattie[31] in a British patent. Addi-

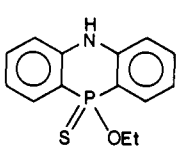


22a, $R_1=R_2=R_3=H$
b, $R_2=Cl$; $R_1=R_3=H$
c, $R_1=Cl$; $R_2=R_3=H$
d, $R_1=Me$; $R_2=R_3=H$
e, $R_2=R_3=Me$; $R_1=H$

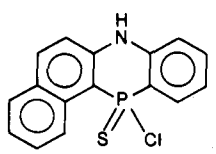
tional information about this work was obtained from McHattie by Mann and is included in the latter's monograph.[8] McHattie reported that the sulfide **22a** is best prepared by heating a mixture of Ph_2NH and $PSCl_3$ in an autoclave at 200 °C for 6 h. This procedure gives a crude hydrochloride of **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 regiospecificity 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*-methyldiphenylamine[3] and *N*-methyldi-*p*-tolylamine[17] 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 paper[34] 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



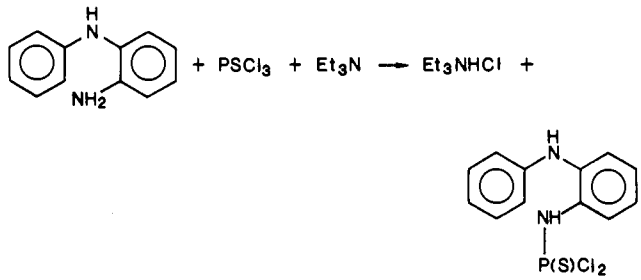
23a



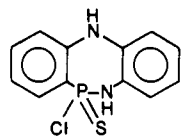
24

22a in a 52% yield by a similar reaction with Ph_2NH has been described in another paper[35] 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:



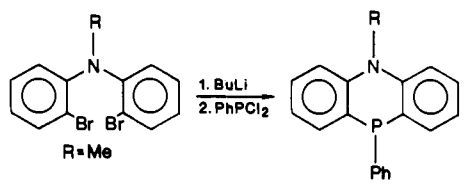
When the resulting product (obtained only as an oil) is heated for 6 h at 215 °C with a small amount of $AlCl_3$, cyclization occurs and the following seven-membered heterocycle can be isolated from the reaction mixture:



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 trilithio derivative $(o\text{-}LiC_6H_4)_2NLi$. 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.

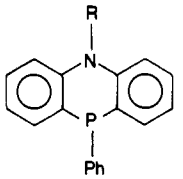
In the next few years, new methods for preparing *N*-alkyl-2,2′-dihalodiphenylamines were developed,[37] and it was found that it is indeed possible to convert these substances to the previously unknown 5-alkyl-5,10-dihydrophenophosphazine derivatives.[38] Thus, the interaction of *N*-methyl-2,2′-dibromodiphenylamine 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



25a. R = Me

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

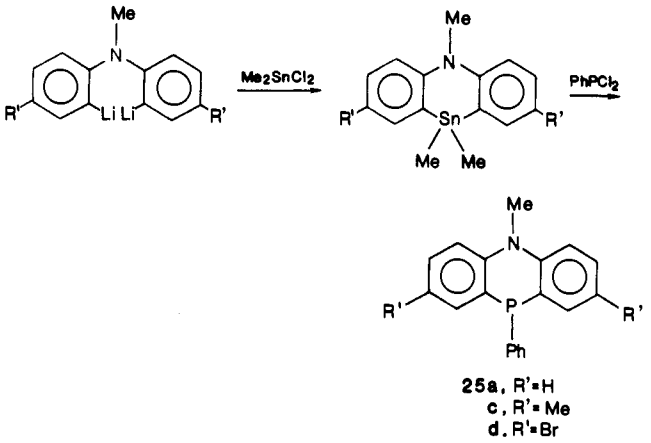
and the di-Grignard from *N*-ethyl-2,2′-dibromodiphenylamine yields 27.5% of the expected 5-ethyl derivative **25b**. Attempts to convert the *N*-alkyl-2,2′-



25b. R = Et

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.

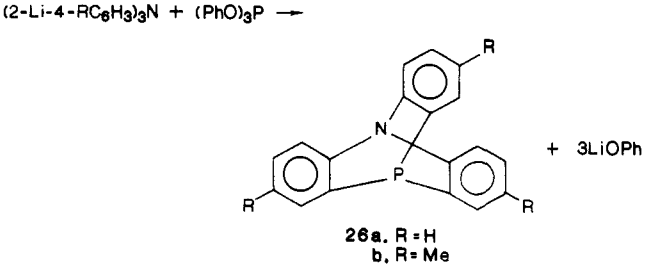
N-Methyl-2,2′-dilithiodiarylamines can be converted into heterocyclic tin compounds, which react with $PhPCl_2$ to give **25a,c,d**.[39] The interaction of the tin



25a, R′ = H
c, R′ = Me
d. R′ = Br

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**



26a, R = H
b, R = Me

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.

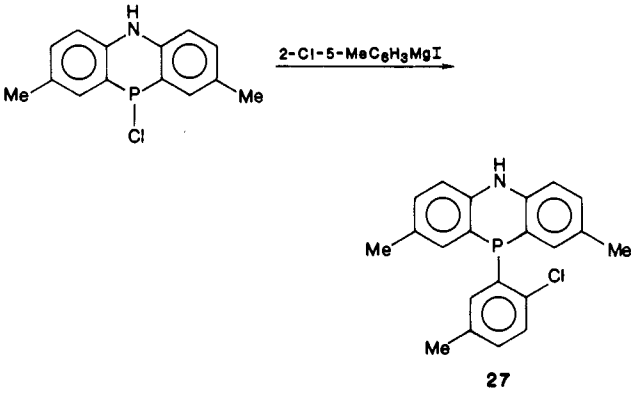
III. Reactions of 5,10-Dihydrophenophosphazine Derivatives

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

In 1938, Sergeev and Kudryashov[2] 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 authors[2] 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 Saunders[41] have found that the secondary oxide $Ph_2P(O)H$ reacts with either $SOCl_2$ or *N*-chlorosuccinimide to give the phosphinyl chloride $Ph_2P(O)Cl$. 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 $SOCl_2$.

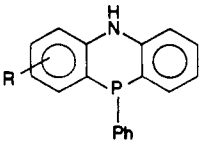
As previously mentioned in section IIA, there is considerable evidence that phosphinous chlorides are formed by the interaction of diarylamines and PCl_3 at elevated temperatures. In 1978, Hellwinkel and coworkers[25] allowed di-*p*-tolylamine and PCl_3 to react at about 200 °C and then extracted the 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:



27

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

The method used for preparing **27** has been extended[24] to the preparation of the tertiary phosphine **28a**.



28a, R = H
b, R = 4-Me
c, R = 1,3-Me_2

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 H_2O_2 in acetone.

The phosphinyl chloride **29** was first described by Häring;[5] it was prepared by treatment of the phosphinic acid **30** with $SOCl_2$ or with PCl_5 in $POCl_3$. Compound

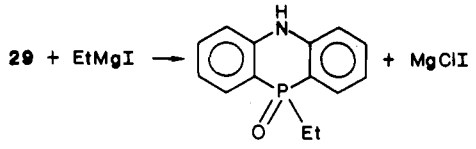
30 **29**

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 PCl_5 at about 100 °C.[12] The ease with

$$3 + PCl_5 \rightarrow 29 + HCl + POCl_3$$

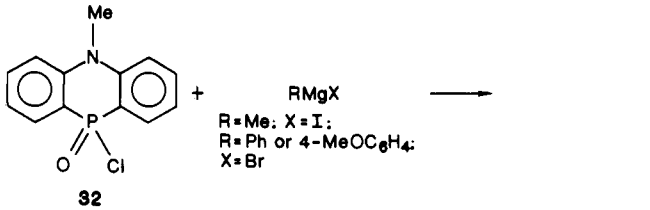
which secondary phosphine oxides like **3** can be prepared makes them convenient starting materials for the synthesis of the corresponding phosphinyl chlorides.

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.

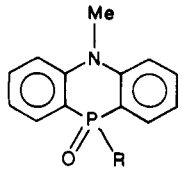


31

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 document[44] 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 reported[47] 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.



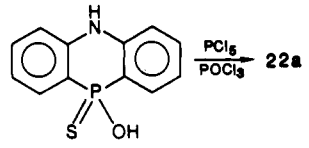
32



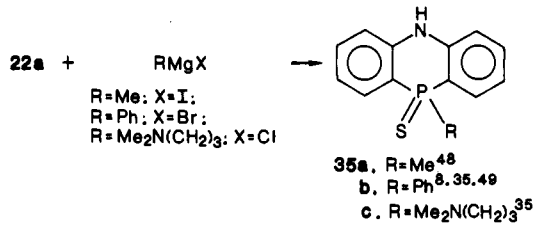
33a, R=Me[44,45]
b, R=Ph[44,45,47]
c, R=4-MeOC$_6$H$_4$[46]

According to a Russian review article,[9] the 2,8-dinitro derivative of **32** has been characterized, but the document[43] in which it is described is not accessible to us.

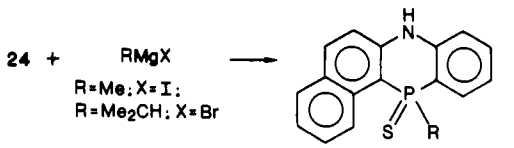
Thionophosphinyl chlorides are readily prepared by the interaction of diarylamines and $PSCl_3$ at elevated temperatures. This type of reaction has been discussed in section IIB. The parent compound **22a** can also be



34



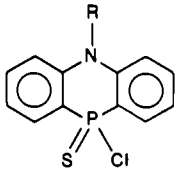
35a, R=Me[48]
b, R=Ph[8,35,49]
c, R=Me$_2$N(CH$_2$)$_3$[35]



36a, R=Me
b, R=Me$_2$CH

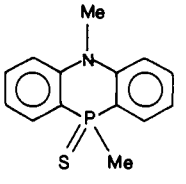
obtained by allowing the phosphinothioic acid **34** to react with PCl_5 in $POCl_3$.[5] Reaction of **22a** with an excess of a Grignard reagent yields the expected tertiary phosphine sulfide. The naphthalene derivative **24** reacts in a similar manner.[34]

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

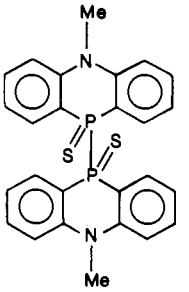


37a, R=Me
b, R=Et

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]



38



39

B. Reactions of the Secondary Phosphine Oxides

1. Oxidation to Acids

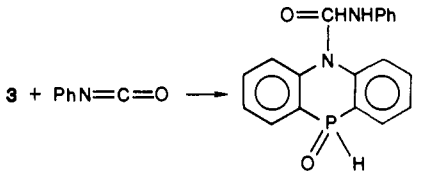
Secondary phosphine oxides are readily converted to the corresponding phosphinic acids. The acid **30** was first prepared by dissolving the oxide **3** in tetralin and boiling the resulting solution in air for a short time.[2,5] Oxidation of this oxide has also been accomplished with peracetic acid[5] and with NaOH in aqueous[43,52] or alcoholic[17] 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 H_2O_2 or alcoholic NaOH was used as the oxidizing agent in these cases.

Häring[5] reported that treatment of the oxide **3** with sulfur in hot acetic acid solution yields the phosphinothioic acid **34**, mp 213 °C. McHattie[8] apparently obtained the same acid by refluxing the thionophosphinyl chloride **22a** with an aqueous acetone solution of Na_2S 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. Mann[8] 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 workers[50] has described the preparation of **34** in a document that is not accessible to us; the abstract in *Chemical Abstracts* states that "cyclizing Ph_2NH with PCl_3 followed by treatment with S gave 32%" of **34**.

The reaction of the oxide **3** with Br_2 results in both oxidation and bromination. This result is discussed in section IIIC2.

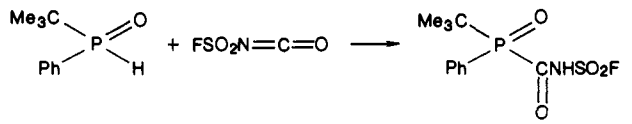
2. Addition to Unsaturated Compounds

Häring[5] 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

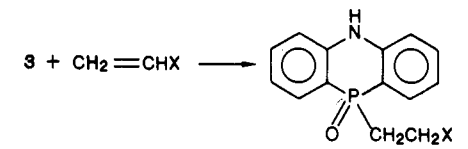


40

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]

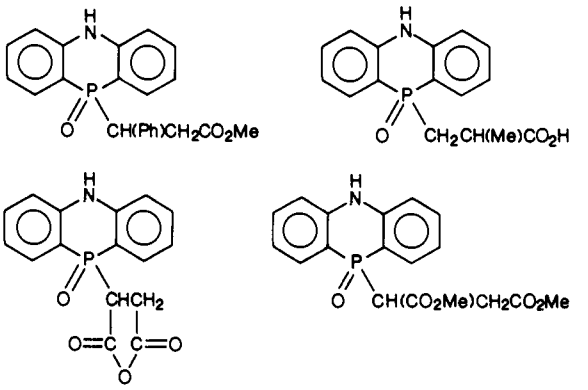


Like other secondary phosphine oxides, the oxide **3** adds to unsaturated compounds that contain activated double bonds. Thus, Levin and Gazizova[56] reported,

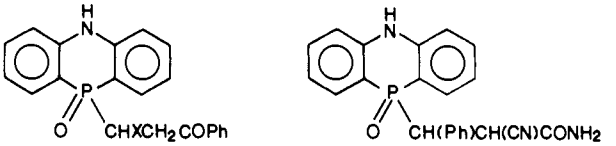


X = CN, CO_2H, CO_2Me, C(O)Me

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:

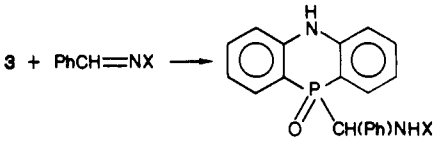


Several years later, Messinger[14] used base catalysis to effect the same type of addition reactions and thereby obtained the following compounds:

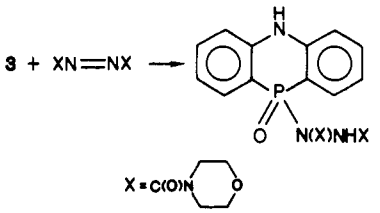


X = Ph, COPh

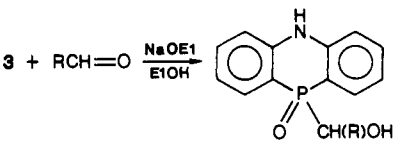
He also found that the oxide **3** adds to Schiff bases and to an azo diamide even in the absence of a catalyst. Addition reactions, however, were not observed with azobenzene or azo dicarboxylic esters.



X = Ph, $PhSO_2$



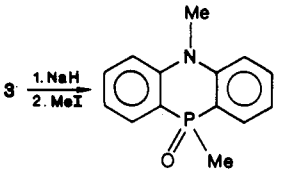
More recently, Petrov and co-workers[57] have prepared phosphinyl alcohols by the base-catalyzed interaction of the oxide **3** and an aldehyde. They also found that the reaction of **3** and the Schiff base PhCH=NPh yields the adduct earlier described by Messinger.[14]



R = H, Ph

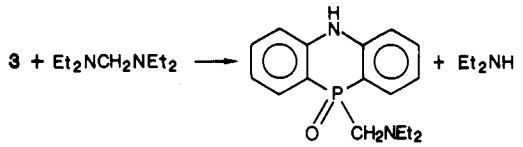
3. Other Reactions of the Secondary Phosphine Oxides

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



33a

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.



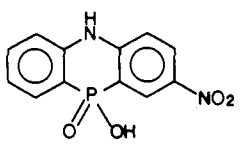
A crystalline hydrobromide or hydrochloride of **3** can be obtained by treatment of a hot acetic acid solution of **3** with the corresponding hydrogen halide.[5] Both salts are readily hydrolyzed to **3**.

The conversion of the oxide **3** to the phosphinyl chloride **29** has been mentioned in section IIIA. The reaction of **3** with I_2 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 Kudryashov[2] reported that the interaction of the phosphinic acid **30** and HNO_3 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 Johnson[59] have shown that the main product of mononitration of the arsinic acid is the 2-nitro derivative, it seems very likely that the nitro compound obtained by Sergeev and Kudryashov[2] has the analogous structure **41**.



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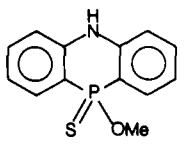
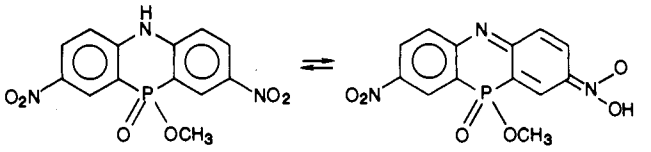
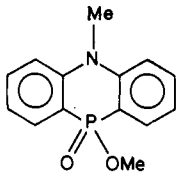


23b

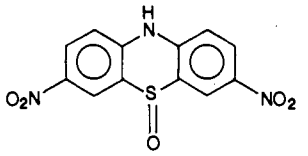
Much later, McHattie[8,31] found that the ester **23b** undergoes both oxidation and dinitration upon being refluxed with 1:1 aqueous HNO_3 for 30 min. He suggested that the nitro groups in the product occupy the positions para to the amino group, and he cited as evidence the fact that a solution of 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

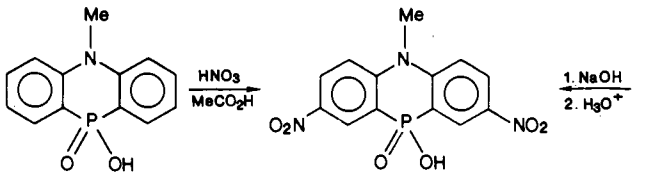


42

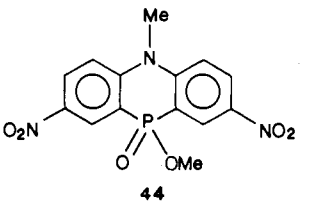


45

25 °C to the 2-nitro derivative **43** or the 2,8-dinitro derivative **44** by treatment with HNO_3 (*d* 1.42) in glacial acetic acid. When a 10-fold excess of HNO_3 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 HNO_3 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



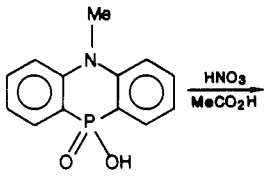
47 **46**



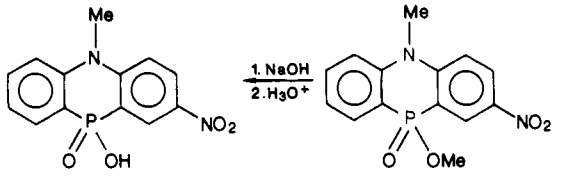
44

derivative **48** can be prepared[61] 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 HNO_3 in acetic acid.[45] Although the structure of the product was not proven, it was reasonably assumed that the nitro

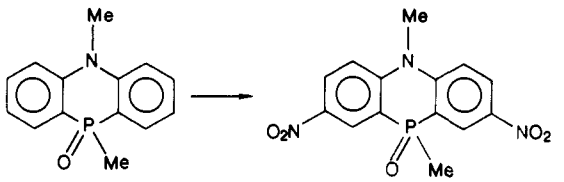


47



48 43

groups occupy the 2- and 8-positions.



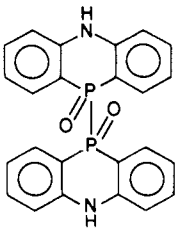
33a 49

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

Häring[5] has reported that the interaction of the phosphine oxide **3** and Br_2 (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.

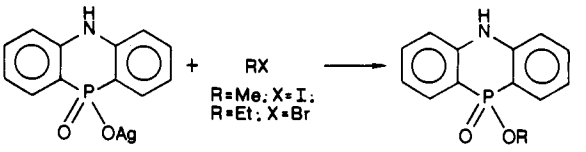
In contrast to the above results, the interaction of I_2 and **3** in DMF leads neither to nuclear halogenation nor to oxidation to a phosphinic acid.[5] Instead, 1 mol of I_2 reacts with 2 mol of **3** to yield exactly 2 mol of HI together with the following dioxide:



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 Kudryashov[2] 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

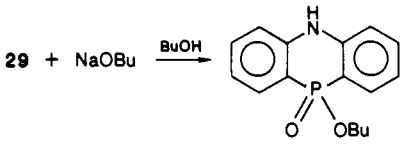


50a, R=Me
b, R=Et

reported a melting point of 112–114 °C for the methyl ester and 99 °C for the ethyl ester. Häring[5] 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-workers[57] have prepared the ethyl ester **50b** by the triethylamine-promoted reaction of the oxide **3** with CCl_4 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:

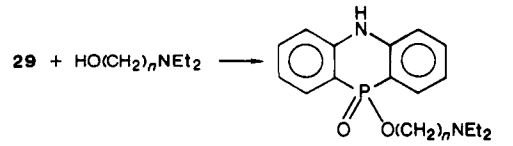
$$3 + CCl_4 + EtOH + Et_3N \rightarrow \mathbf{50b} + CHCl_3 + Et_3NH^+Cl^-$$

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



51

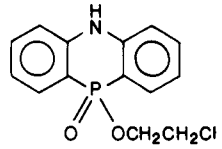
The (dimethylamino)alkyl esters **52**, on the other hand, were obtained by the direct reaction of the acid chloride **29** with an excess of the corresponding alcohol.[5] The benzyl ester of **30** was prepared by the interaction of the potassium salt of **30** and $PhCH_2Br$ in 2-propanol.[5]



52a, (*n*=2)
b, (*n*=3)

The French patent literature[62] describes the preparation of the chloroethyl ester **53** by heating the oxide **3** with ethylene oxide and CCl_4 in an autoclave at 100 °C. The yield of **53** was said to be greatly improved by the presence of small amounts of $TiCl_4$.

A number of esters of thiophenophosphazinic acid (**34**) have also been described. Häring[5] obtained the methyl ester **23b** by the interaction of the chloride **22a**



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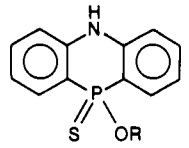
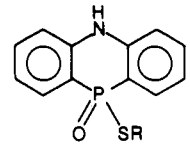
with NaOMe in MeOH. The isomeric thiolo derivative **54a** was obtained, however, when the acid **34** was treated with diazomethane. McHattie prepared **23a–e**



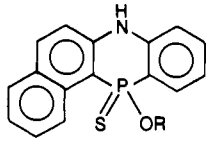
23a, R=Et
b, R=Me
c, R=Pr
d, R=Me_2CH
e, R=$CH_2CH_2NMe_2$



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

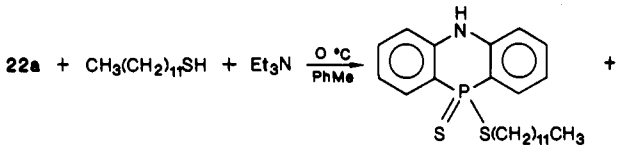
and a number of other thiono esters from the chloride **22a** and the nuclear-substituted chlorides **22b–e**; these esters are mentioned in Mann's book.[8] Cheplanova and Yarmukhametova[16] repeated Häring's method for preparing **23b** and used a similar procedure for **23a,c,d**. They noted, however, 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 reported[34] 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.



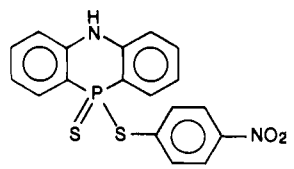
55a, R=Me
b, R=Me_2CH

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-



56

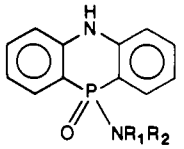
formation on the esters described in this patent is given in section VII. McHattie[8] prepared the *p*-nitrophenyl dithioate **57** by the reaction of the chloride **22a** with sodium *p*-nitrothiophenoxide in boiling benzene.



57

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. Häring[5] was the first to describe a 10-amino 10-oxide derivative. He obtained compounds **58a,b** by the interaction of the acid chloride



58a: R_1=H; R_2=$CH_2CH_2NEt_2$
b: R_1=H; R_2=$CH_2CH_2CH_2NMe_2$
c: R_1=Et; R_2=Et

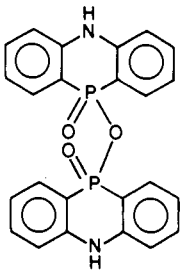
29 and an excess of the appropriate amine. He found that these amides were readily hydrolyzed by aqueous acids. A number of other amides have been prepared in a similar manner from **29** and are discussed in section VI. It has also been shown[57] that the amide **58c** can be obtained in good yield by heating the secondary phosphine oxide **3** with an excess of Et_2NH and CCl_4. The stoichiometry of this reaction presumably conforms to the following equation:

$$3 + 2Et_2NH + CCl_4 \rightarrow \mathbf{58c} + Et_2NH_2^+Cl^- + CHCl_3$$

The melting point of the amide thus obtained was 247 °C (compared to a reported[15] melting point of 244 °C when the compound was prepared by the interaction of the acid chloride **29** and an excess of Et_2NH).

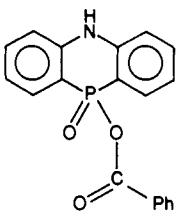
McHattie obtained a number of amides of thiophenophosphazinic acid (**34**) by heating a benzene solution of the acid chloride **22a** with ammonia or a primary or secondary amine. These amides are tabulated in Mann's book.[8] Several other amides of **34** were later prepared by a similar procedure[15] and are mentioned in section VI.

Häring[5] prepared phenophosphazinic anhydride (**59**) by the interaction of benzenesulfonyl chloride and the potassium salt of the acid **30**. The anhydride is in-



59

soluble in aqueous NH_3 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.



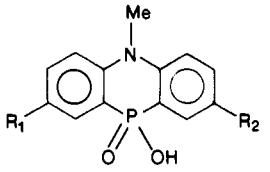
60

E. Dissociation Constants of Acid Derivatives

Dihydrophenophosphazine derivatives in which the phosphorus atom is part of a phosphinic acid group are sometimes referred to as phenophosphazinic 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 $AgNO_3$ yielded a silver salt. They also prepared a nitro derivative of the acid and showed that it was soluble in alkaline solution.

Häring[5] reported that phenophosphazinic 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 H_2O.) Mann[8] 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 H_2O would be approximately 3.1.

More recently, a group of Russian workers[46] have reported the dissociation constants of six phenophosphazinic acid derivatives of the following type:



47: R_1=H; R_2=H
61: R_1=H; R_2=Br
48: R_1=H; R_2=NO_2
62: R_1=NH_2; R_2=NO_2
63: R_1=Br; R_2=NO_2
46: R_1=NO_2; R_2=NO_2

The dissociation constants were determined by potentiometric titration in Me_2SO and were found to conform to the Hammett equation:

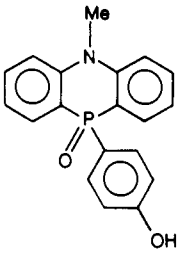
$$pK_a = (9.93 \pm 0.11) - (2.78 \pm 0.14)\sum\sigma$$

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 Me_2SO of the diarylphosphinic acids (m-$RC_6H_4)_2PO_2H$, where R = H, Me, or NO_2, and (m-$O_2NC_6H_4$)$PhPO_2H$. These values also obeyed the Hammett equation:

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

Since the value for the proportionality constant ρ is significantly higher for the pK_a's of the phenophosphazinic 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 phenophosphazinic 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 paper[46] the Russian authors also compared the dissociation constants of several known phenols of the type RC_6H_4OH, where R = H, p-Br, m-O_2N, p-O_2N, or p-$Ph_2P(O)$, with that of the phenolic derivative **64**, which incorporates the dihydrophenophosphazine system. The dissociation constants were



64

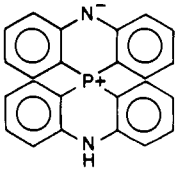
determined by potentiometric titration in aqueous isopropyl alcohol (H_2O to Me_2CHOH ratio of 20:1). Where R = H, p-Br, m-O_2N, or p-O_2N, the pK_a's gave an excellent correlation with known nucleophilic substitution constants σ^-:

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

The above equation was then used to calculate substituent constants for the $Ph_2P(O)$ group ($\sigma^- = 0.62 \pm 0.04$) and the 5,10-dihydro-5-methyl-10-oxophenophosphazinyl 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.

Thiophenophosphazinic acid (**34**) was first prepared by Häring,[5] who noted that it was soluble in aqueous Na_2CO_3 and that it could be reprecipitated with HCl. McHattie[8] later prepared and characterized Et_3N 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 H_2O 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**.



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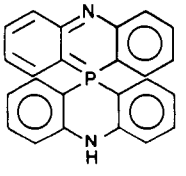
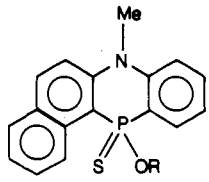


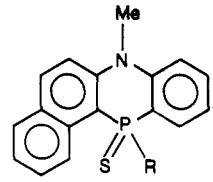
66

F. Miscellaneous Reactions

The NH group of a dihydrophenophosphazine 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-

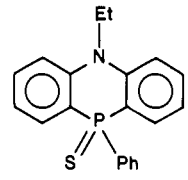


67a, R = Me
b, R = Me_2CH

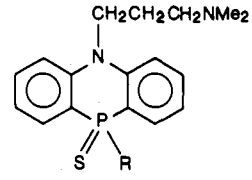


68a, R = Me
b, R = Me_2CH

spectively, and the tertiary phosphine sulfides **36a** and **36b** to **68a**[34] and **68b**,[34] respectively. The tertiary phosphine sulfide **35b** has been converted in an analogous manner to the *N*-ethyl compound **69**[49] 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]

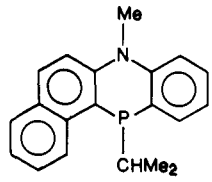


69

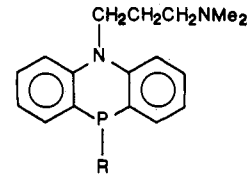


70a, R = Ph
b, R = $Me_2N(CH_2)_3$

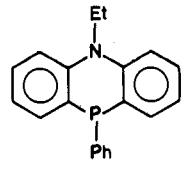
The tertiary phosphine sulfides **68b**, **70a**, and **70b** mentioned in the paragraph above have been reduced (desulfurized) to the corresponding tertiary phosphines **71**,[34] **72a**,[35] and **72b**,[35] respectively, by treatment with



71

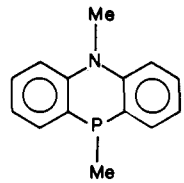


72a, R = Ph
b, R = $Me_2N(CH_2)_3$

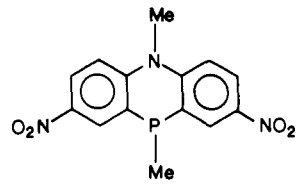


25b

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 trichlorosilane.[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.

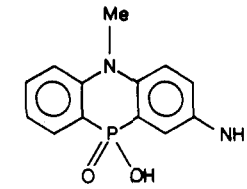


73



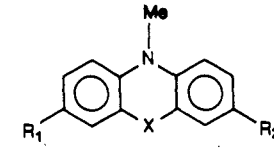
74

The nitro compound **48** has been reduced with H_2 over nickel to the corresponding amino compound **75**; and one of the nitro groups in the dinitro compound **46** has been reduced with Na_2S to give the monoamino derivative **62**.[61] The amino groups of both **62** and **75** have been converted with $NaNO_2$ in HBr to the corresponding diazonium bromides, which were then heated with aqueous $CuSO_4$ to yield the bromo compounds **63** and **61**, respectively. Diazotization of **62** in HCl and subsequent reduction with H_3PO_2 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).



75

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



33a: $R_1 = R_2 = H$; X = P(O)Me
42: $R_1 = R_2 = H$; X = P(O)OMe
43: $R_1 = H$; $R_2 = NO_2$; X = P(O)OMe
44: $R_1 = R_2 = NO_2$; X = P(O)OMe
49: $R_1 = R_2 = NO_2$; X = P(O)Me
74: $R_1 = R_2 = NO_2$; X = PMe

DMF was used as the solvent, and 0.1 M Bu_4NI 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.

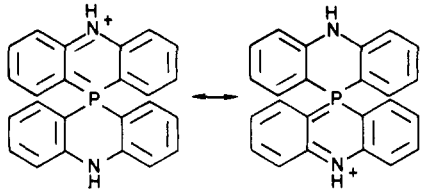
Aluminum chloride in benzene has been used to convert the methoxy-substituted tertiary phosphine oxide **33c** to the corresponding phenol **64**.[46] The acid dissociation constant of the latter compound has been discussed in section IIIE.

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.

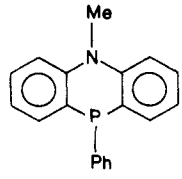
IV. Molecular Structures by X-ray Diffraction

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 triphenylphosphine[67]). 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 bond[69]). 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.

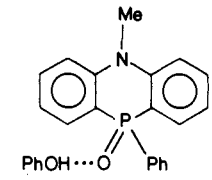
X-ray diffraction studies of several *N*-alkyl-5,10-dihydrophenophosphazine derivatives have been published in the Russian literature. The first[70] of these papers describes the crystal and molecular structure of 5-methyl-10-phenyl-5,10-dihydrophenophosphazine (**25a**). The tricyclic system of this molecule is distinctly



25a

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 Ph_3P and suggest (according to the authors[70]) that the phosphorus atom in the phenophosphazine has a hybridization close to p^3; 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 paper[47] 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



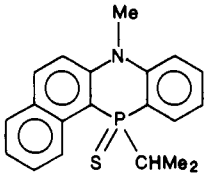
76

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 ^{1}H NMR signals of the protons attached to these carbon atoms is discussed by the authors.[49]

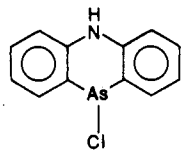
A fourth paper[72] in the Russian literature describes the crystal and molecular structure of the sulfide **68b**.



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 Trotter[73] in an X-ray diffraction study of 10-chloro-5,10-dihydrophenarsazine (**77**). The molecule of the arsenic compound is only

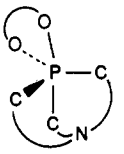


77

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 coworkers.[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:



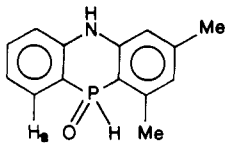
The most important deviation from an ideal TBP arrangement involves the angle between the two equatorial C–P bonds, which is only 100.8 (2)° instead of 120°. Nevertheless, the planarity of the three equatorial bonds is preserved, with the sum of the equatorial angles being 359.9°. The angle between the 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 Perciaccante[39] were the first to describe the ^{1}H 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 ^{1}H NMR data for

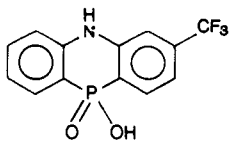
the phosphinic acids **11**[17] and **18**,[26] the tertiary phosphines **26a**,[25] **26b**,[25] **27**,[25] **28b**,[24] **28c**,[24] and **73**,[45] the tertiary phosphine oxides **33a**[45] and **33b**[45] and the oxide[24] derived from **28c**, the PMe derivative[25,40] of the azaphosphatriptycene **26a**, and nine 7,12-dihydrobenzo[*a*]phenophosphazine derivatives.[34] Additional ^{1}H 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 ^{1}H 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 PCl_3 and certain meta-substituted diarylamines were not unequivocally established by the method of synthesis employed. A ^{1}H 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-workers[49] 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 ^{1}H NMR spectra of both this compound and **69** are caused by the electronic properties of the phosphorus atom.

The ^{31}P 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% H_3PO_4. In 1969 Hellwinkel and Schenk[40] reported that the ^{31}P chemical shift of the azaphosphatriptycene **26a** occurred at an astonishingly high field strength: −80 ppm ($CHCl_3$) 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 ^{31}P chemical shift of −4.75 ppm (CF_3CO_2H). This value indicates that the phosphorus atom in this compound is more strongly shielded than in triphenylmethylphosphonium iodide, $\delta(^{31}P)$ +19.4. The results obtained by Hellwinkel and Schenk[40] were discussed in greater detail in a later paper[25] from the same laboratory. In this paper they also reported ^{31}P NMR data for a number of other heterotriptycenes, including the azaphosphatriptycene **26b** [$\delta(^{31}P)$ −78.7, $CDCl_3$].

In 1973 Jenkins, Freedman, and Bordner[7] reported that the ^{31}P chemical shift of the phosphonium chloride **4** was −21 ppm (in either Me_2SO or CF_3CO_2H). 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.

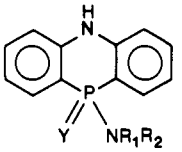
In 1977 Smirnov and co-workers[45] reported that the tertiary phosphines **25a**, **73**, and **74** exhibited ^{31}P chemical shifts (in $CDCl_3$) of −43.0, −6.30, and −59.7 ppm, respectively. These values indicate, according to the authors, strong shielding of the phosphorus nucleus and localization of the unshared electrons on phosphorus. They also found that the chemical shifts of the phosphine oxides **33a** and **33b** in $CDCl_3$ were +9.4 and +5.0 ppm, respectively. In another paper[34] 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 ($CDCl_3$), respectively.

Negrebetskii[75] has studied the ^{13}C 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 ^{13}C 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

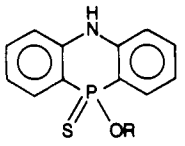
Although a number of workers[8,9,15,16,24] have suggested

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 Mann[3] in 1956 reported that the oxide **3** has no apparent effect on schistosomiasis infection in mice. Four years later Häring[5] 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 McHattie[31] 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 Yarmukhametova[15] in 1971 to synthesize 11 amides of the following type:



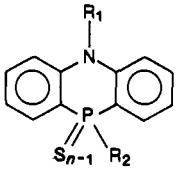
Y = S; O; $R_1 = R_2 = Et$
Y = S; $R_1 = H$; R_2 = Pr, Ph, C_3H_5, CH_2CH_2OH
Y = O; $R_1 = H$; R_2 = Pr, Bu, Ph, C_3H_5, CH_2CH_2OH

The compounds were said to be quite nontoxic toward warm-blooded animals (LD_{50} > 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, R_1R_2N = *N*-methylpiperazinyl) was prepared in 1962 by Schroeder and co-workers[11] 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 Yarmukhametova[16] and were said to be nontoxic toward warm-blooded animals (LD_{50} > 500 mg/kg).



23a. R = Et
b. R = Me
c. R = Pr
d. R = Me_2CH

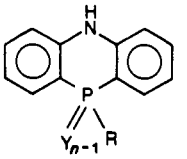
The influence of three (dimethylamino)propyl derivatives on the cardiovascular system has also been explored.[35] The compounds studied in this investigation included a tertiary phosphine and two sulfides. Hydrochlorides of these substances were injected intravenously into narcotized animals suffering 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.



72a: $R_1 = CH_2CH_2CH_2NMe_2$; R_2 = Ph; *n* = 1
70a: $R_1 = CH_2CH_2CH_2NMe_2$; R_2 = Ph; *n* = 2
35c: R_1 = H; $R_2 = CH_2CH_2CH_2NMe_2$; *n* = 2

VII. Practical Applications of 5,10-Dihydrophenophosphazine Derivatives

Only a few practical applications of dihydrophenophosphazine derivatives have been suggested. In 1957, it was reported[4] 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 patent[63] 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:



R = OH, SMe, OEt, OBu, $SC_{12}H_{25}$, morpholino; Y = O, S; *n* = 1, 2

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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