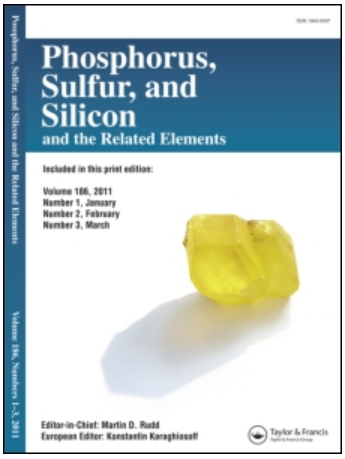

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

BENZODIAZA-, BENZOXAZA-, AND BENZODIOXAPHOSPHORINONES - FORMATION, REACTIVITY, STRUCTURE, AND BIOLOGICAL ACTIVITY

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To cite this Article Neda, Ion , Kaukorat, Thomas , Schmutzler, Reinhard , Niemeyer, Ulf , Kutscher, Bernhard and Pohl, Jörg(2000) 'BENZODIAZA-, BENZOXAZA-, AND BENZODIOXAPHOSPHORINONES - FORMATION, REACTIVITY, STRUCTURE, AND BIOLOGICAL ACTIVITY', Phosphorus, Sulfur, and Silicon and the Related Elements, 162: 1, 81 — 218
To link to this Article: DOI: 10.1080/10426500008045221
URL: http://dx.doi.org/10.1080/10426500008045221

Phosphorus, Sulfur and Silicon, 2000, Vol. 162, pp. 81-218
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BENZODIAZA-, BENZOXAZA-, AND BENZODIOXAPHOSPHORINONES – FORMATION, REACTIVITY, STRUCTURE, AND BIOLOGICAL ACTIVITY

ION NEDA[a], THOMAS KAUKORAT[a], REINHARD SCHMUTZLER[a*], ULF NIEMEYER[b], BERNHARD KUTSCHER[b], JÖRG POHL[b] and JÜRGEN ENGEL[b]

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(Received December 21, 1999)

1. INTRODUCTION

Although diverse phosphorus-containing heterocycles had been synthesized during the late nineteenth century already, work was still sparse in this area as recently as 1950 [1,2]. The realization, around 1950, of the importance of phosphorus-containing substances in biological processes resulted in intense activity in preparative organophosphorus chemistry, and in an upsurge of research on structural and mechanistic problems [3–6].

This post-1950 revolution in organophosphorus chemistry was followed by investigations of different organophosphorus heterocycles, including studies on reaction mechanisms, stereochemistry, and spectroscopic properties. The accumulation of general organophosphorus stereochemical studies and spectral work, documented in some texts [5,6], and in numerous reviews [7–20], laid the foundation for conformational studies. A concern for the conformational analysis of organophosphorus compounds emerged in the late 1960s, succeeding the major surge in conformational research,

* Corresponding Author.

which occurred between 1950 and 1965 [21–28]. Emphasis centered on the six-membered ring (phosphorine) system [20], interest in which was heightened because of its presence in biologically important substances, (1) the cyclic nucleotides adenosine 3′,5′-monophosphate (cyclic AMP) and guanosine 3′,5′-monophosphate (cyclic GMP), mediators of cell metabolism and proposed ubiquitous intracellular "second" messenger substances; (2) the antimetabolic, antitumor agent cyclophosphamide and its congeners; and (3) other pharmacological agents [29]. Certain biological aspects relating to phosphorinones are discussed in refs. [20,30].

Although six-membered phosphorus-containing ring systems, which derive from cyclohexane (phosphorines), were investigated in detail during the last decades, little is known about compounds of this type bearing an aromatic ring system as part of the heterocycle. For this reason, the present review article summarizes the preparation and chemistry of cyclic, phosphorus-containing derivatives originating from salicylic and anthranilic acid, and of their amides. Especially, with regard to the stereochemistry, interesting differences upon comparison to the phosphorus-containing cyclohexane derivatives (phosphorines), mentioned above, were expected. Because of the benzo group, which is part of the six-membered heterocycles in diaza-, oxaza- and dioxaphosphorinones, the formation of conformational equilibria "chair-chair" and "chair-tub" is restricted or impossible, which should affect, basically, the chemistry of these compounds.

Although phosphorus derivatives of salicylic acid have been known for well over a century, and were the subject of numerous investigations, the first review article dealing with this class of compounds appeared not before 1992 [31]. Monographs about the chemistry of phosphorus-containing compounds contain only a small amount of information about phosphorus derivatives of salicylic acid.

In contrast, benzodiaza- and benzoxazaphosphorinones are known only since about three decades (benzodiazaphosphorinones even only since 1978) and the interest in these classes of compounds has increased during the past few years. The combination of the above-mentioned compounds with the 2-chloroethylamino grouping, forming novel 2-chloroethylphosphamides, is of special interest, because of their chemical relationship to Cyclophosphamide [32]. In contrast to the enzymatic activation of Cyclophosphamide, the new compounds are expected to form cytotoxic species by hydrolysis of the P-O and P-N bonds, respectively. For this reason, selected examples of this class of compounds were investigated with regard to their antitumor activity.

In the following, besides a description of formation, chemical properties, and reactivity of diaza-, oxaza-, and dioxaphosphorinones, emphasis will be placed on the presentation of structure determinations of numerous compounds, obtained by X-ray crystal structure investigations.

The description of the formation and characterization of metal complexes of diaza-, oxaza-, and dioxaphosphorinones, all of which were synthesized during the last few years, forms an important part of this article, as well as the subsequent discussion of the biological activity of representative compounds.

2. BENZODIAZAPHOSPHORINONES

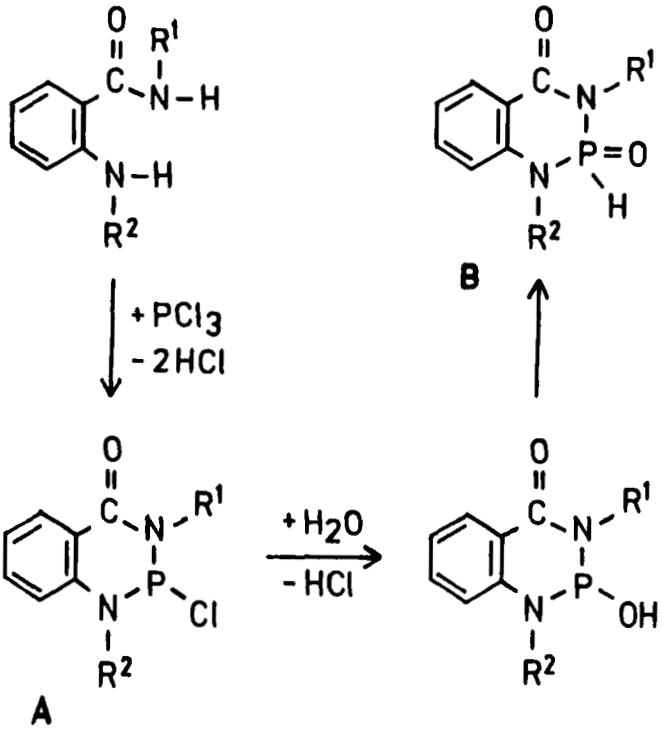
2.1. Introduction

The study of the chemistry of benzodiazaphosphorinones was started in 1978 by Coppola [33,34], with the investigation of the reaction of N,N′-substituted anthranilic amides with phosphorus trichloride according to Scheme 1.

Initially, the phosphorus(III) compounds of type **A**, originally expected, could not be isolated. Hydrolysis products of type **B** (Scheme 1) were exclusively obtained. Subsequently, only a few reports about derivatives of this heterocyclic system were published [35,36], until 1993, when the first fully characterized benzodiazaphosphorinone was synthesized [37]. This synthesis gave rise to further interest in benzodiazaphosphorinones, and within only two years, a large number of reports have appeared about compounds containing the benzodiazaphosphorinone ring system with phosphorus in coordination numbers three to five. A review of the results of these investigations is the subject of this account.

2.2. 1,3-Disubstituted 2-halo-2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-ones

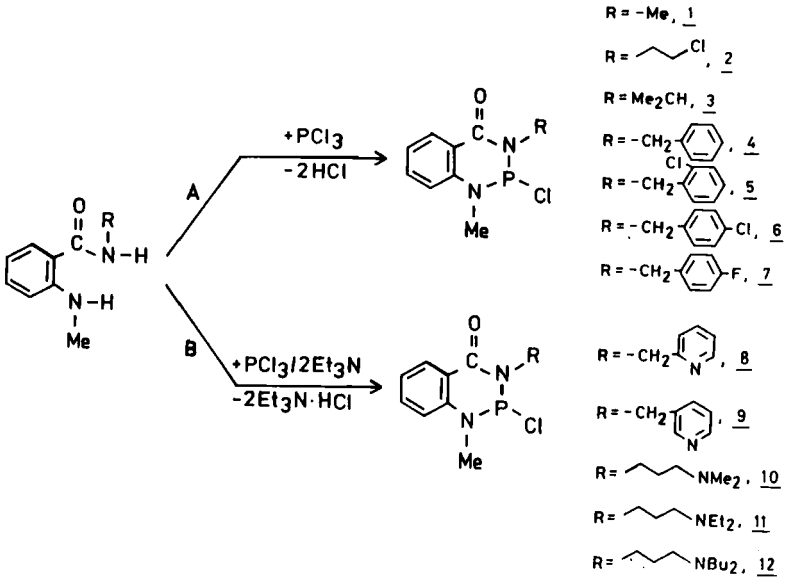
Nitrogen-substituted anthranilic amides, required in the preparation of halogen-substituted benzodiazaphosphorinones, can easily be formed by the reaction of isatoic acid anhydride with various primary amines [38].



SCHEME 1

The 2-chloro-substituted benzodiazaphosphorinones [37,39–42] can be synthesized, in principle, in two different ways (cf. Scheme 2): Either by direct reaction of the anthranilic amide and phosphorus trichloride in the absence of base (Route **A**) or by using triethylamine as HCl-acceptor (Route **B**).

Reaction conditions which guaranteed the exclusion of moisture, permitted the synthesis of 2-chloro-benzodiazaphosphorinones in high yield. In some cases, the use of base as an HCl-acceptor is unnecessary (formation of **1** – **7**). Because of the low basicity of the nitrogen atoms in the product, the formation of hydrochloride salts is ruled out [37,39,40]. Hydrogen chloride, formed during the reaction, is evolved upon increasing the temperature.



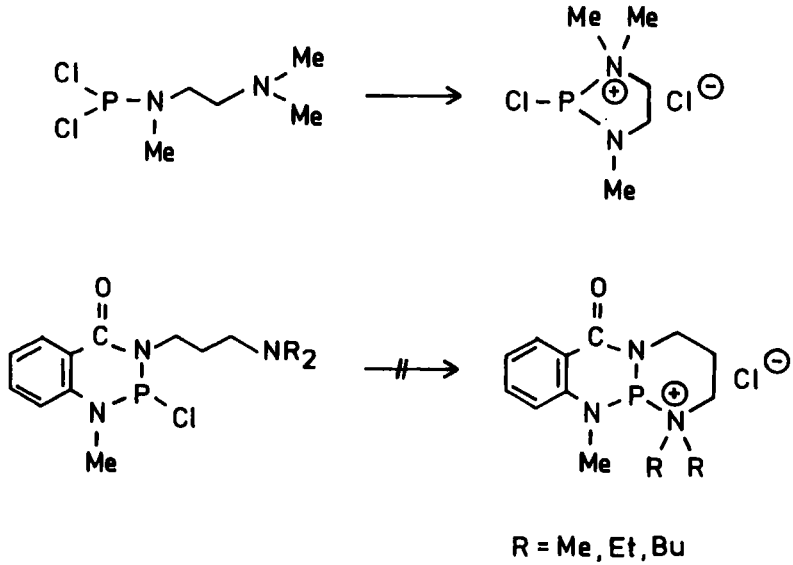
SCHEME 2

In some cases (formation of **8 – 12**), the presence of triethylamine as a base is necessary in order to avoid the formation of product/educt-hydrochloride mixtures, which are difficult to separate [41].

The synthesis of compounds **10 – 12** was carried out, in order to investigate possible intramolecular donor-acceptor-interactions between the nitrogen atom of the diorganoamino group and phosphorus. Such interactions are observed under certain conditions in phosphorus(III) compounds bearing the N,N′,N′-trimethylethylenediamine ligand [43]. Especially, the elimination of an anion favours the formation of a coordinative intramolecular, e.g. $Me_2N \rightarrow P$ bond, as shown in Scheme 3.

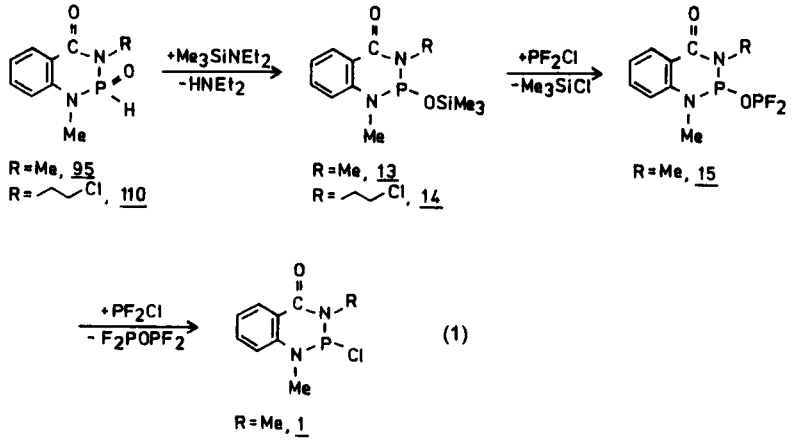
In contrast to the compounds containing the trimethylethylenediamine group, described in ref. [43], an intramolecular $R_2N \rightarrow P$ coordination could not be observed by ^{1}H-NMR spectroscopy for **10 – 12**, neither at room temperature nor at low temperature [41]. Presumably, the electrophilicity of the phosphorus atom is too low to induce a spontaneous coordinative N→P-bond.

A different way of formation of **1** is available in the reaction of the trimethylsiloxy-substituted benzodiazaphosphorinone **13** with chlorodifluoro-

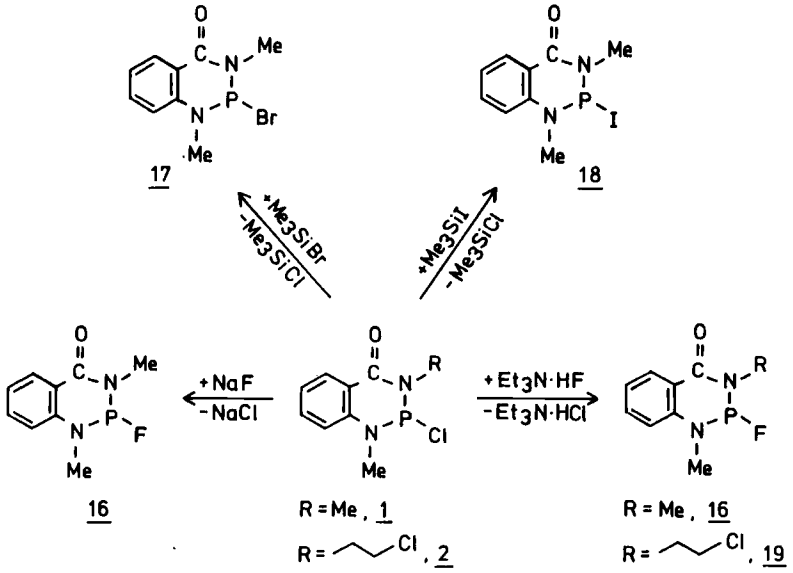


SCHEME 3

phosphine according to Eqn. (1) [44]. Compound **13** was synthesized by reaction of **95** (cf. Scheme 17) with diethylamino trimethylsilane.



The intermediate compound **15** is not stable at room temperature. Its existence could be confirmed only by NMR spectroscopy (^{1}H, ^{13}C, ^{19}F, ^{31}P) in solution at -20°C. The final product, compound **1**, was formed by the reaction of **15** with an additional equivalent of chlorodifluorophosphine. The μ-oxo-bis(difluorophosphine) [45], formed during the reaction, was detected by NMR spectroscopy. The exchange of the chlorine atom, bonded to phosphorus in some 2-chlorobenzodiazaphosphorinones for fluorine, bromine or iodine was effected, using different halogen exchange reagents [40,46], according to Scheme 4:



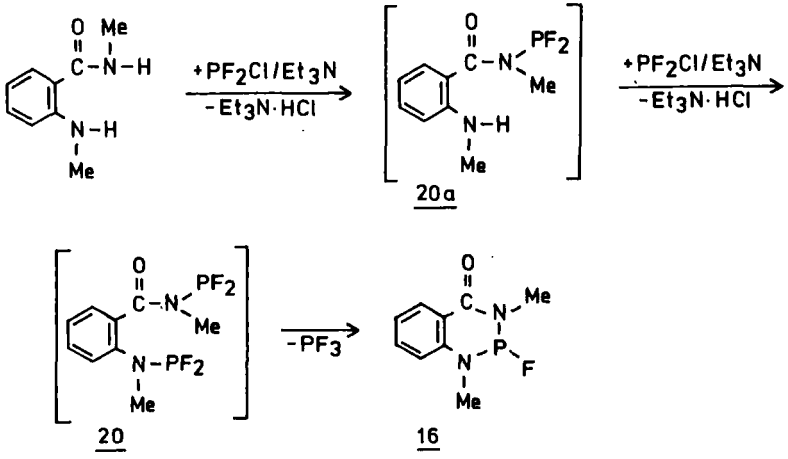
SCHEME 4

While the fluorine derivative **16** was formed by halogen exchange, using NaF in acetonitrile [46], the bromine- and iodine-substituted compounds, **17** and **18**, were prepared through the reaction of **1** with trimethylbromosilane and trimethyliodosilane, respectively [40].

A further possibility for the chlorine-fluorine exchange is the reaction of 2-chlorobenzodiazaphosphorinones with the acidic triethylamine-HF adduct in the presence of excess triethylamine. The chlorine-fluorine exchange, in these cases, occurs in high yield, and provides an excellent

and simple method of forming PF-compounds [40,47–51]. Both of the 2-fluoro-benzodiazaphosphorinones **16** and **19** were obtained, in accord to Scheme 4 in good yield, as described previously [52].

A third method of formation of 1,3-dimethyl-2-fluoro-2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-one, **16**, is the reaction of N,N′-dimethylanthranilic amide with chlorodifluorophosphine (Scheme 5) [44]:



SCHEME 5

In the presence of triethylamine, **16** was formed via the intermediates **20a** and **20**. The presence of **20** was confirmed by NMR spectroscopy during the reaction at -30°C. After allowing the reaction mixture to warm up to room temperature, compound **16** was formed by an intramolecular cyclization process, accompanied by the elimination of phosphorus trifluoride. The existence of the intermediate **20a** could not be proved, but its formation during the reaction seems plausible.

With regard to the reactions described above, the synthesis of all 2-halogenated derivatives of the most simple benzodiazaphosphorinone (1,3-dimethyl-2-halo-2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-one) succeeded, and their NMR spectroscopic properties could be compared [40,46].

Representative of all halogen derivatives **1, 16, 17**, and **18**, an X-ray crystal structure analysis was conducted for 1,3-dimethyl-2-fluoro-2,3-

dihydro-1H-1,3,2-benzodiazaphosphorin-4-one **16** [44] (Fig. 1). It confirmed the molecular structure, proposed on the basis of NMR- and mass spectral data.

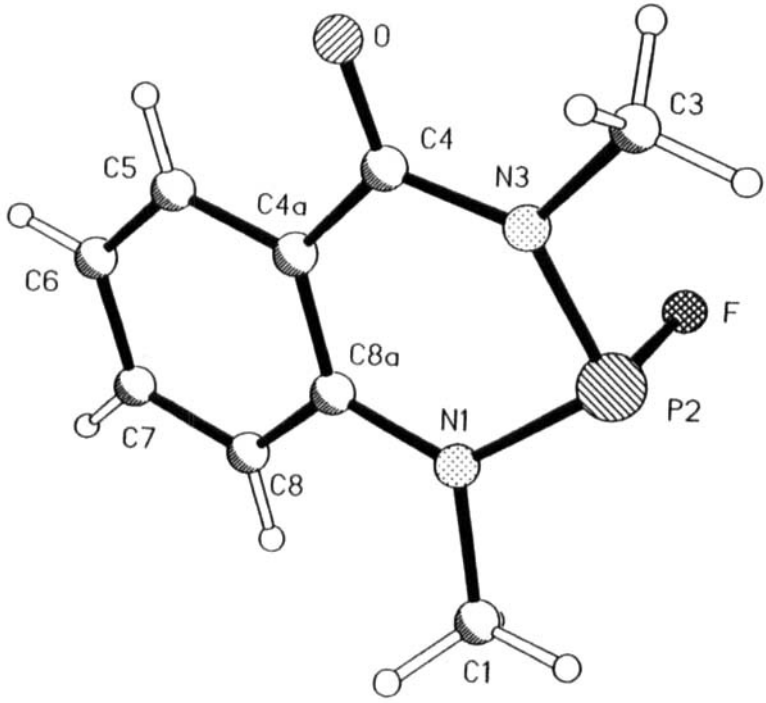
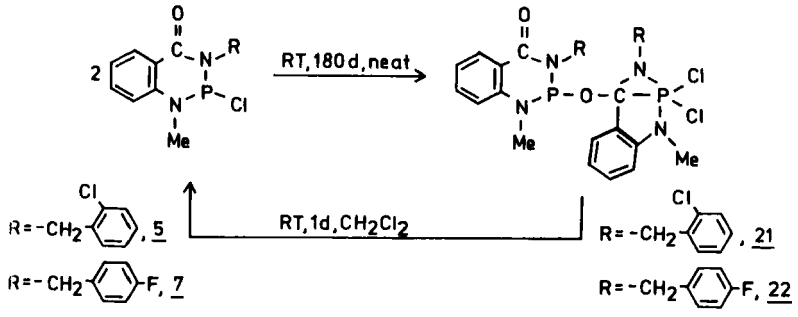


FIGURE 1 Structure of compound **16** in the solid state

Unusual behaviour was observed for the 2-chlorobenzodiazaphosphorinones **5** and **7**, bearing the o-chlorobenzyl- and p-fluorobenzyl substituent bonded to the nitrogen atom N3.

When the oily compounds **5** and **7** were stored without solvent and with exclusion of air at room temperature for six months, the formation of solids was observed in every case. Their NMR spectroscopic investigation suggests the formation of compounds **21** and **22**, presented in Scheme 6 [53].

When **21** and **22** were kept in solution (dichloromethane or chloroform) for one day, spontaneous conversion into the starting compounds **5** and **7** was observed [53].



SCHEME 6

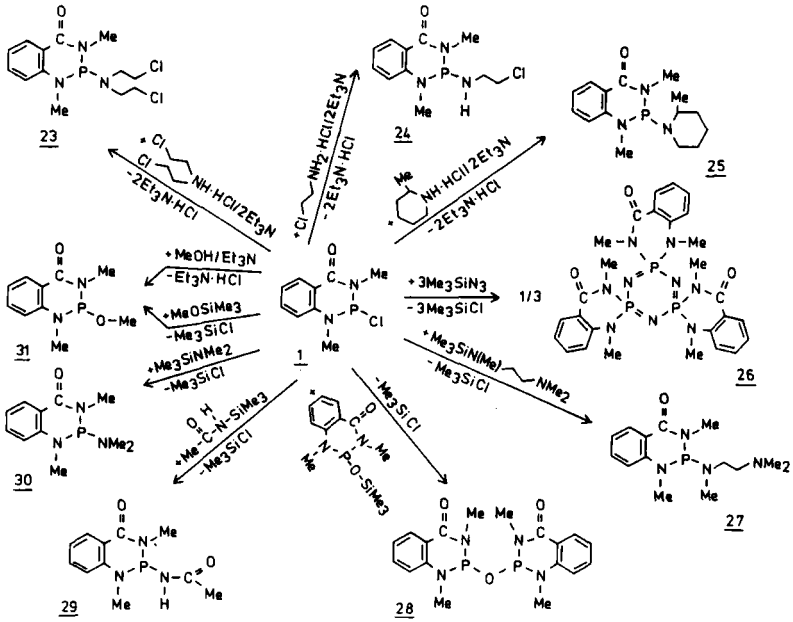
2.3. Substitution reactions on 3-substituted 1-methyl-2-chloro-2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-ones

N,N′-disubstituted 2-chloro-2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-ones bear a large synthetic potential. Because of the simple cleavage of the P-Cl bond, a variety of substitution reactions can be carried out.

In general, two different methods are significant in forming P-N- or P-O-bonds: (a) direct reaction of phosphorus-halogen-compounds with primary or secondary amines in the presence of a hydrogen-chloride acceptor (e.g. excess of the amine used in the reaction or a different base like triethylamine) [54], or (b) reaction of silylated amines and trimethylsiloxy derivatives with phosphorus halides, followed by removal of the trimethylsilylhalide [55]. According to these methods, the phosphorus- substituted 1,3-dimethyl-2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4- ones **23** – **31** were synthesized as described in Scheme 7 [37,40,44,46,52,60].

The synthesis of the bis(2-chloroethyl)amino- and 2-chloroethylamino-substituted compounds **23** and **24** [46] was carried out, using the corresponding hydrochloride derivatives, because the "free amines" were found to be unstable at room temperature. 2-Chloroethylamino-substituted compounds of phosphorus are of special interest. Because of the alkylating potential of the 2-chloroethylamino group [56–58], they exhibit cytostatic properties. The biological activity of 2-chloroethylamino substituted diaza-, oxaza- and dioxaphosphorinones is discussed in Chapter 5.

In addition to the NMR spectroscopic and mass spectrometric characterization of **23** and **24**, an X-ray crystal structure determination was carried



SCHEME 7

out for **23** [46], (Fig. 2). The results were compared to those obtained for several Cyclophosphamide derivatives.

Cyclophosphazenes are readily formed in the reaction of organophosphorus(III)-halogen compounds with trimethylsilyl azide [59]. Similar behaviour was observed for the reaction of **1** with trimethylsilyl azide [60]. The cyclotriphosphazene **26** was isolated only in moderate yield. In contrast, an attempt to react 2-chlorobenzodiazaphosphorinone, **2**, with trimethylsilyl azide, failed. Even the use of drastic reaction conditions (concentrated solution, high temperature) did not cause any reaction.

In the reaction of **1** with different N- or O-trimethylsilyl compounds, **27** – **31** were obtained with concomitant formation of trimethylchlorosilane. Compound **27** is another example of a compound, bearing the trimethylethylenediamine group bonded to phosphorus [37]. Compounds of this type were investigated in detail during the past few years [43] and, in all cases, the study of (mostly) spontaneous intramolecular $Me_2N \rightarrow P$ donor-acceptor interactions was of special interest. As described previously for the for-

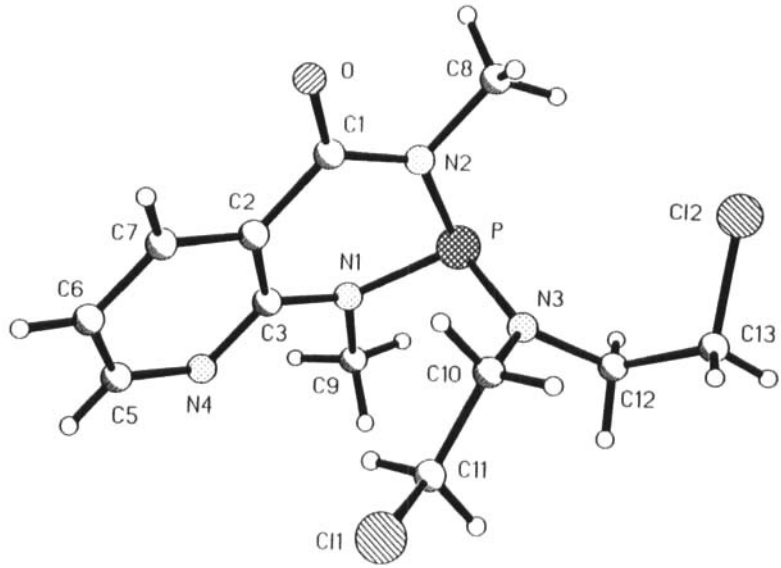


FIGURE 2 Structure of compound **23** in the solid state

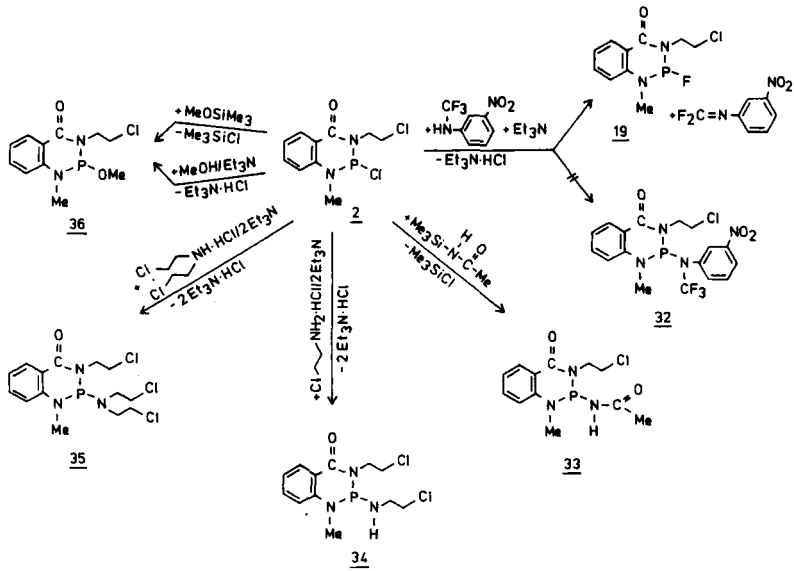
mation of **10** – **12**, no intramolecular $Me_2N \rightarrow P$ interaction was observed for **27** [37]. Such an interaction could easily be established by ^{1}H-NMR spectroscopy, because the $(CH_3)_2N$-proton resonance would be split into a doublet, resulting from $^3J(PH)$-coupling with ^{31}P.

Compound **28** was formed by reaction of **1** with the 2-trimethylsiloxy-substituted benzodiazaphosphorinone **13** [44] (cf. Scheme 7). Surprisingly, an equilibrium between the starting compounds **1** and 1,3-dimethyl-2-trimethylsiloxy-2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-one, and the product compound **28** and trimethylchlorosilane was observed in solution. The equilibrium could easily be shifted to the product side by evaporating the trimethylchlorosilane, which was formed during the reaction, in vacuo. In this manner, compound **28** could be isolated in good yield.

The formation of **29** and **30**, in good yield, took place in the reaction of **1** with N-trimethylsilyl acetamide and dimethylaminotrimethylsilane, respectively [40,46]. Compound **31** could be synthesized in a well known fashion in good yield either by reaction of **1** with methyl trimethylsilyl ether [61,62], or by reaction of **1** with methanol in the presence of triethylamine [52].

Compounds **23** – **31** were characterized by NMR spectroscopy, mass spectrometry and elemental analysis [37,40,44,46,52,60].

As for 2-chloro-1,3-dimethyl-2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-one, **1**, a number of substitution reactions were carried out for 2-chloro-3-chloroethyl-1-methyl-2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-one, **2**, as shown in Scheme 8:



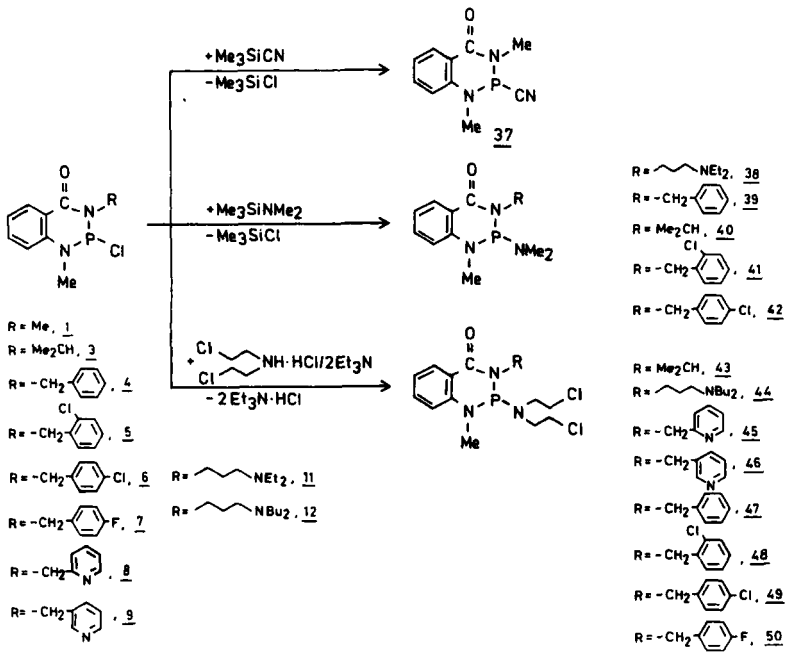
SCHEME 8

The reaction of **2** with N-trifluoromethyl-3-nitrophenylamine in the presence of triethylamine should lead to compound **32**, according to well known principles. Contrary to expectation, the formation of 3-chloroethyl-2-fluoro-1-methyl-2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-one, **19**, was observed [40]. In order to explain the reaction mechanism, which led to the formation of **19** from **2**, N-trifluoromethyl-3-nitrophenylamine was allowed to react with triethylamine. The formation of triethylamine hydrofluoride and N-difluoromethylene-3-nitrophenylimine was observed. In this way it could be proved that the halogen exchange in **2** was caused by triethylamine hydrofluoride formed during the reaction. Difluoromethyleneimine was observed as a side product in the reaction mixture [40]. The results are in agreement with literature data [47–51].

The synthesis of compounds **33** – **35** [39,40] was carried out as described for **23, 24** and **29**. The synthesis of **36** [52] was effected in a similar manner as described for **31**, in two different ways by reacting **2** either with methyltrimethylsilyl ether or with methanol in the presence of triethylamine as a base.

2.4. Reactions of various 3-substituted 2-chloro-1-methyl-2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-ones with trimethylsilyl cyanide, dimethylaminotrimethylsilane and bis(2-chloroethyl)amine hydrochloride

When **1** was allowed to react with trimethylsilyl cyanide in a 1:1 molar ratio, according to Scheme 9, compound **37** was obtained, bearing the cyano group at phosphorus [53]. The corresponding reaction of the chlorodiazaphosphorinones **3** – **6** and **11** with dimethylaminotrimethylsilane led to compounds **38** – **42** [39,42,53].



SCHEME 9

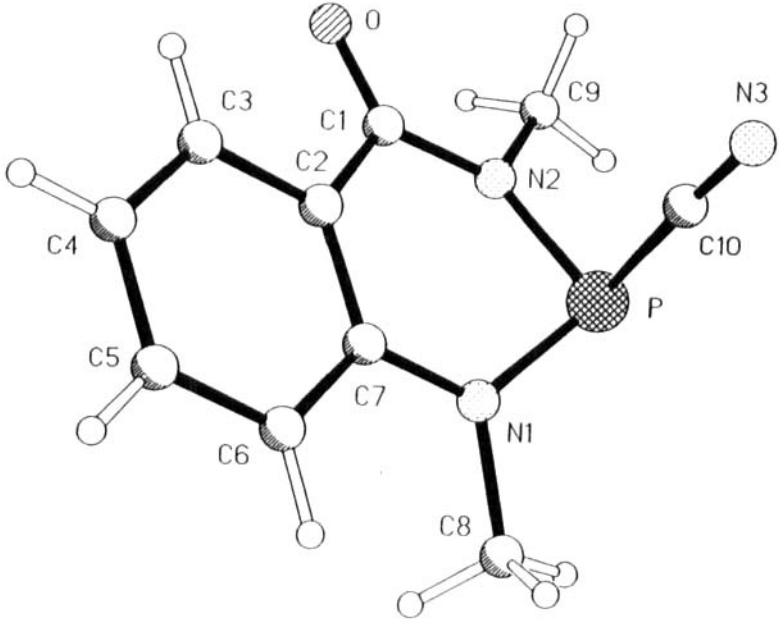


FIGURE 3 Structure of compound **37** in the solid state

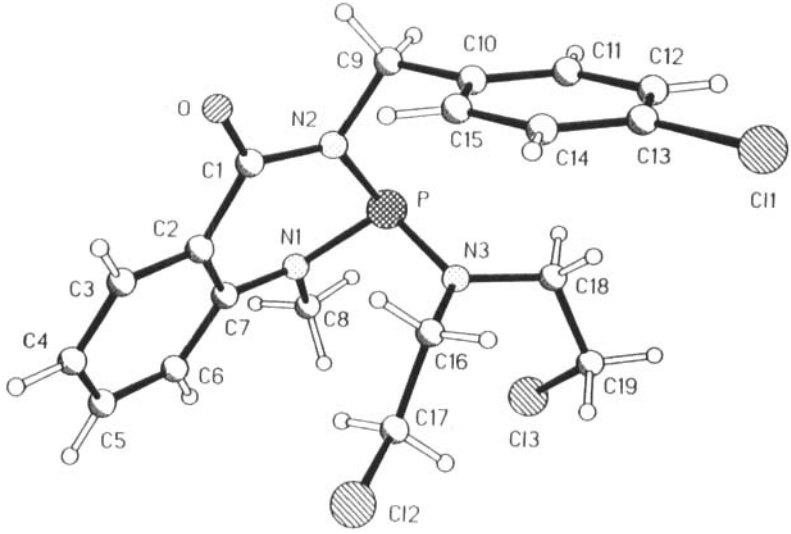


FIGURE 4 Structure of compound **49** in the solid state

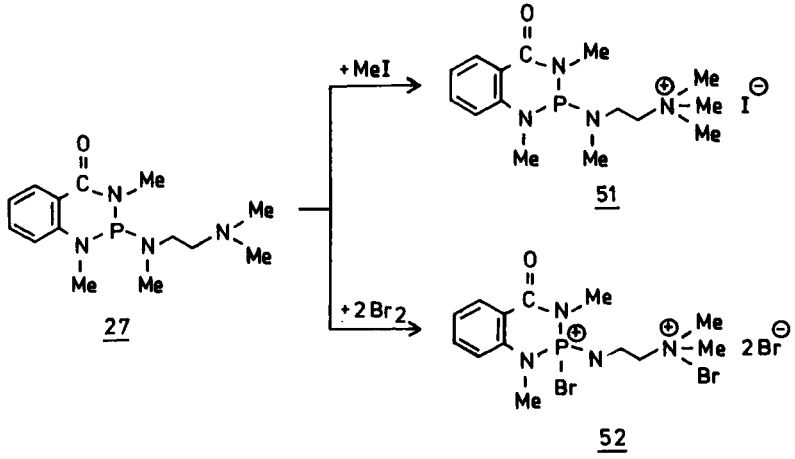
The advantage of this method, compared to the direct use of the unsilylated amines, is the proton-free course of the reaction, which avoids the protolytic P-N-cleavage in both starting compounds and reaction products. In addition, the isolation of the reaction products is quite easy because, instead of a solid hydrochloride, only the volatile trimethylchlorosilane is formed as a by-product. Compounds **43 – 50** were obtained by reaction of the corresponding chlorobenzodiazaphosphorinones **3, 5 – 9** and **12** with bis(2-chloroethyl)amine hydrochloride in the presence of triethylamine as a base [41,53].

For compounds **37** and **49**, X-ray crystal structures were determined [53] (Figs. 3 and 4) which confirmed the structures proposed in Scheme 9.

2.5. Oxidation reactions of 2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-ones, bearing different substituents at phosphorus and/or nitrogen

Reactions with methyl iodide and bromine

According to Scheme 10, the reaction of **27** with methyl iodide led to compound **51** [37]:



SCHEME 10

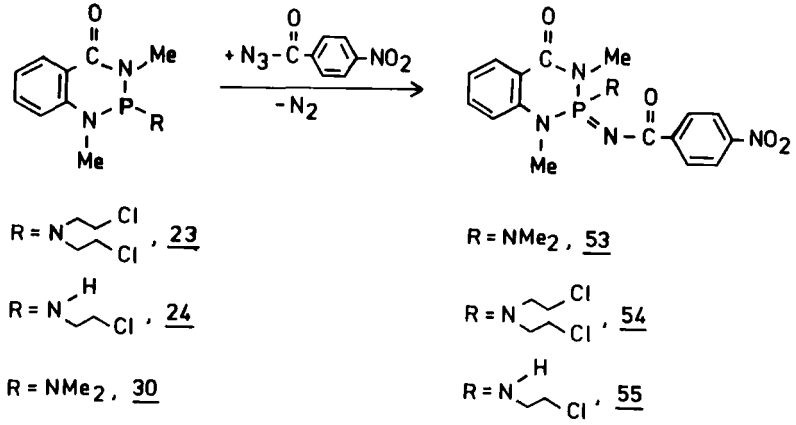
The formation of the ammonium iodide **51** by methylation of the nitrogen atom of the terminal dimethylamino group of the trimethylethylenedi-

amine unit in **27** was proved by NMR spectroscopy. An oxidative addition of the methyl group to phosphorus, followed by the formation of a phosphonium iodide or a spirocyclic azonium iodide by $Me_2N \rightarrow P$-coordination (cf. Scheme 3) was not observed. Similar behaviour was observed in the reaction of a compound, comparable to **27**, involving the diazaphosphetidinone ring system instead of the benzodiazaphosphorinone ring [63].

The reaction of **27** with elemental bromine took a different course. Even the use of different stoichiometric ratios of the starting compounds, and different reaction conditions consistently led to the formation of compound **52** in accord with Scheme 10. The unusual N-bromo-N,N-dimethylammonium-bromophosphoniumdibromide **52** was formed by bromination of both the phosphorus atom, and the nitrogen atom of the terminal dimethylamino group in **27**. The molecular structure of **52** was well established by detailed NMR- and IR-spectroscopic investigations, and by elemental analysis [37].

Reactions with 4-nitrobenzoyl azide

The reaction of phosphorus(III) compounds with covalent azides is well known as Staudinger-Reaction [64–66] and, together with the Kirsanov-Reaction, a common method of attaching aryl- or alkylimino groups to phosphorus. In this manner, according to Scheme 11, the reaction of **23**, **24** and **30** with 4-nitrobenzoyl azide led to the monomeric Staudinger products **53** – **55** [46,60]:

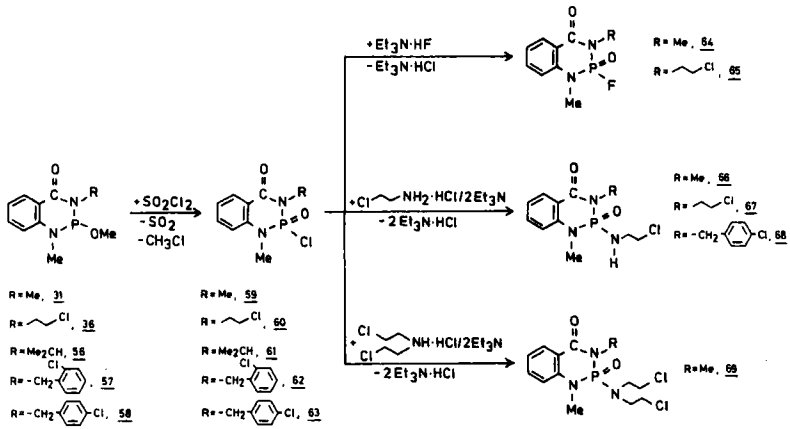


SCHEME 11

A dimerization of the phosphine imides, initially formed, leading to diazaphosphetidines, which often takes place during the Staudinger-Reaction, was not observed in the case of **53 – 55**.

Reactions with sulfuryl chloride and subsequent halogen substitution

According to Scheme 12, in the reaction of compounds **31** and **36** [52] and of **56 – 58** [53] with sulfuryl chloride, sulfur dioxide and methyl chloride as well as the N,N′-disubstituted 2-chloro-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-on-2-oxides **59, 60** [52] and **61 – 63** [53] were formed in good yield:



SCHEME 12

In a number of exchange reactions, the chlorine atom in compounds **59 – 63** was replaced by different methods for fluorine-, 2-chloroethylamino- or bis(2-chloroethyl)amino-substituents.

The use of the acidic triethylamine-3HF-adduct for chlorine/fluorine exchange in phosphorus chlorides is well known [47–51]. Phosphorus fluorides, were obtained in high yield [50]; according to this method, the same was observed for the formation of **64** and **65**, which were synthesized in the same manner, from **59** and **60** as starting compounds [52]. Aside from NMR spectroscopic and mass spectrometric methods, X-ray crystallography was also used to characterize **64** and **65** [52] (Figs. 5 and 6):

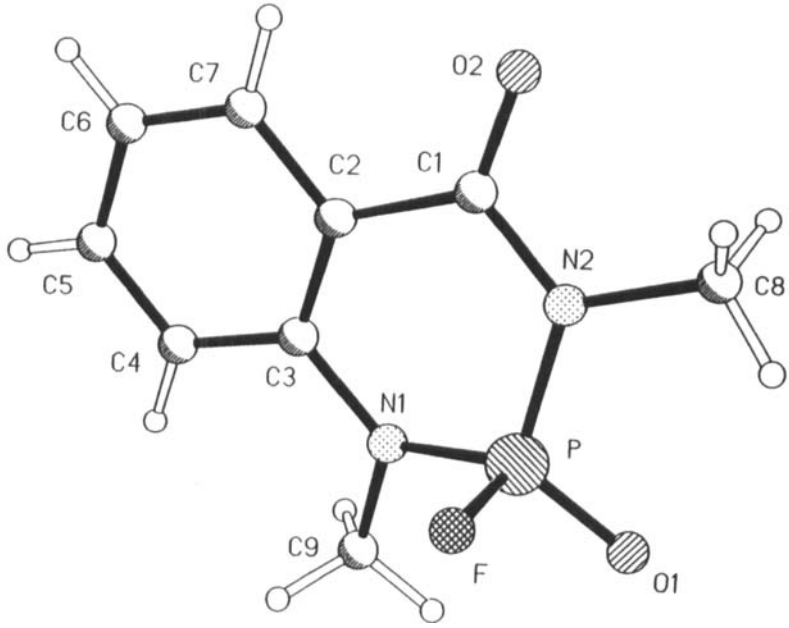


FIGURE 5 Structure of compound **64** in the solid state

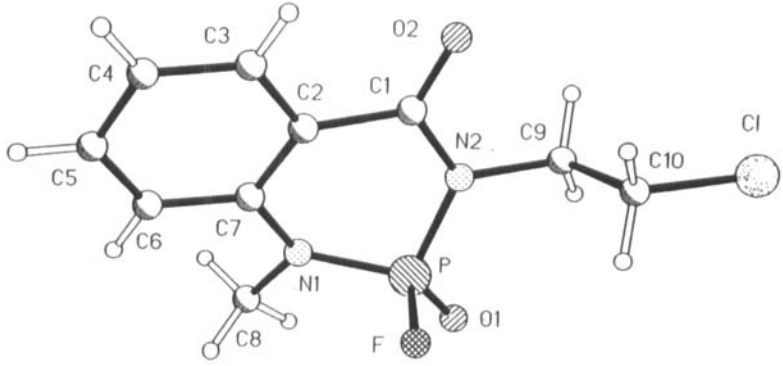


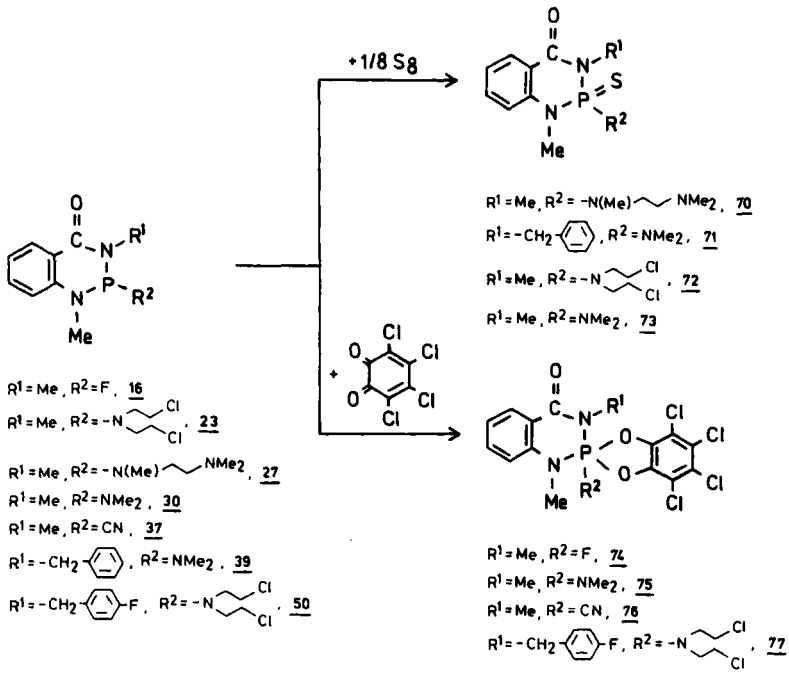
FIGURE 6 Structure of compound **65** in the solid state

The reaction of **59** and **60** with 2-chloroethylamine hydrochloride and of **59** with bis(2-chloroethyl)amine hydrochloride in the presence of triethyl-

amine as a base led to the expected substitution products **66, 67** and **69** [52]; likewise the reaction of **63** with 2-chloroethylamine furnished compound **68** [53].

Reactions with sulfur and tetrachloro-o-benzoquinone

In general, the oxidation of phosphorus(III) through elemental sulfur leads, exothermically, to phosphine sulfides [67,68]. The reaction of sulfur with the phosphorus(III) atom in **23, 27, 30** and **39**, according to Scheme 13, produced the well characterized thiobenzodiazaphosphorinones **70** [37], **71** [39] and **72, 73** [46]:



SCHEME 13

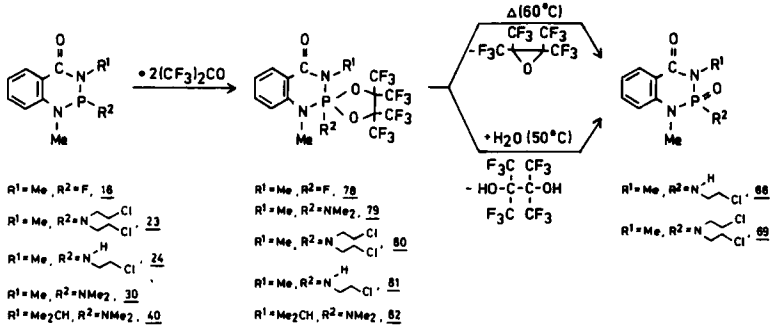
The reaction of o-benzoquinones with compounds of trivalent phosphorus is well known [69]. In general, the quinone system is added to the $\sigma^3\lambda^3$-phosphorus atom with formation of a phosphorane. While the spirophosphorane **74** (Scheme 13) was formed in low yield only in the

reaction of **16** with tetrachloro-o-benzoquinone [70], compound **75** was isolated in high yield [46], while the reactivity of **30** towards tetrachloro-o-benzoquinone was not very high and the resulting spirophosphorane, **75**, was not stable in solution [46]. Compounds **76** and **77** were also formed in good yield [53].

Reactions with hexafluoroacetone

There are numerous reports on the reaction of phosphorus(III) compounds with hexafluoroacetone [71–77]. In most cases, oxidative addition of two equivalents of hexafluoroacetone (as a perfluoropinacolyl group) to phosphorus(III) takes place.

While in the reaction of **16** with hexafluoroacetone only small amounts of compound **78** [70] (Scheme 14) were obtained, the reaction of **23, 24, 30** and **40** with two equivalents of hexafluoroacetone in every case led to the expected addition products **79** [46], **80, 81** [78] and **82** [53] in high yield:



SCHEME 14

In addition to the spectroscopic characterization of the spirophosphoranes **78** – **82**, representative of this class of compounds, an X-ray crystal structure determination was conducted for **79** [46] (Fig. 7).

Upon reaction of the perfluoropinacolyl substituted spirophosphoranes **80** and **81** with water at elevated temperature (Scheme 14), the phosphoryl compounds **66** and **69** were formed with loss of perfluoropinacol [78]. The formation of these compounds by a different route was described previously (cf. Scheme 12). A similar cleavage reaction of a phosphorus compound, accompanied by formation of perfluoropinacol, is also known [79].

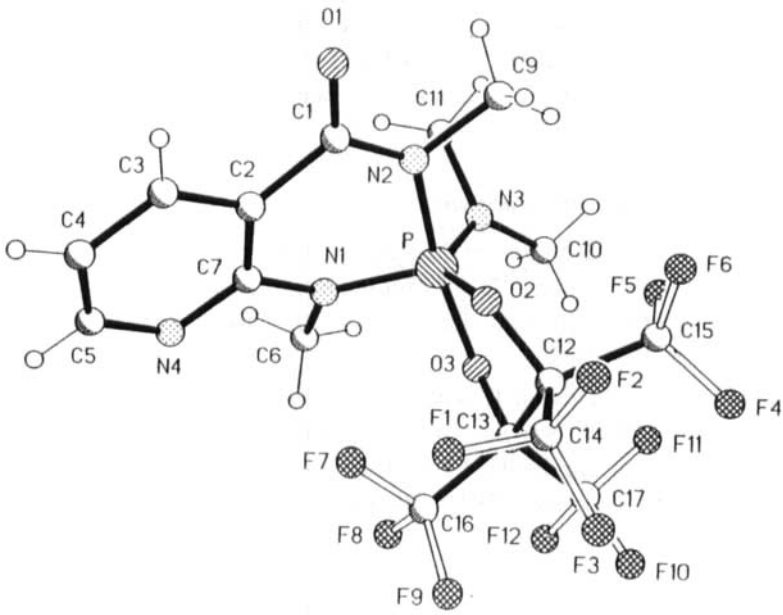


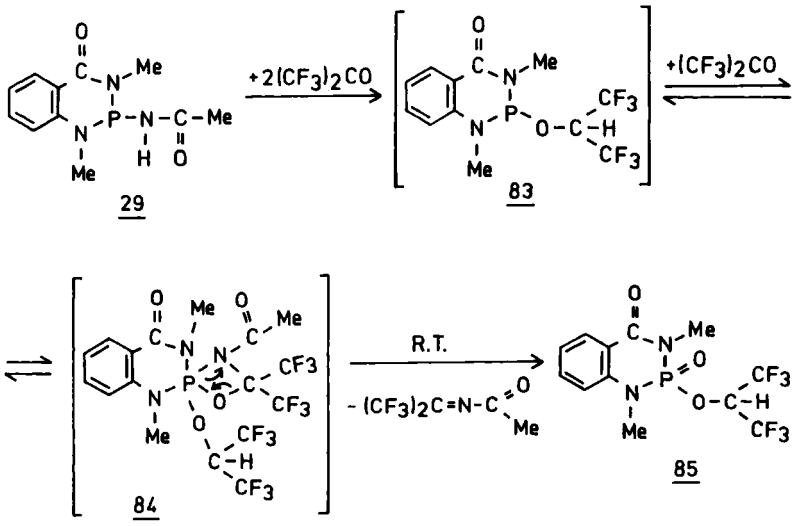
FIGURE 7 Structure of compound **79** in the solid state

Likewise, **66** and **69** were formed in small amounts by thermal decomposition of **80** and **81**. The reaction mechanism, proposed in Scheme 14, implying elimination of 1,1,2,2-tetrakis(trifluoromethyl)oxirane, has not been established with certainty [78].

The reaction of acetylaminobenzodiazaphosphorinone **29** with hexafluoroacetone took a different course from that shown in Scheme 14 (Scheme 15).

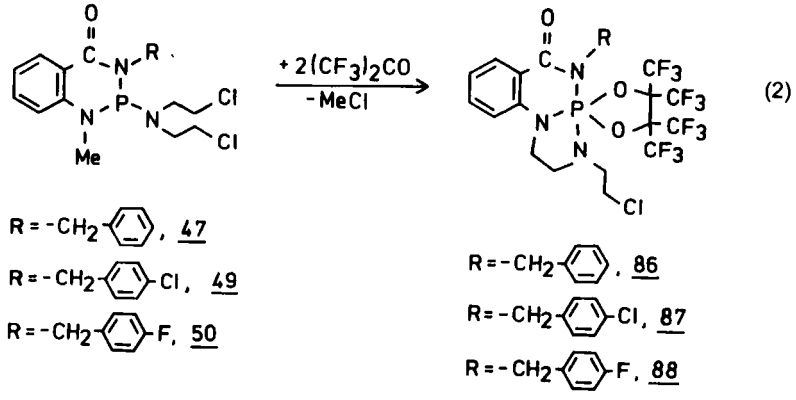
The benzodiazaphosphorinone oxide, **85**, was formed exclusively in good yield [78]. The formation of **85** occurred, presumably, by elimination of hexafluoroacetylimine via the undetected intermediates **83** and **84**. The formation of hexafluoroacetylimine was established by ^{19}F-NMR spectroscopy.

The proposed reaction mechanism seems plausible, because a similar reaction of acyclic aminophosphines $PX_2(NHR)$ (X=F, OPh; R= H, Me, ^{t}Bu, Ph) is known. Surprisingly, the reaction of 1-methyl-2-bis(2-chloroethyl)amino-2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-ones, bearing benzyl- or halobenzyl substituents at the nitrogen atom N3 in the heterocy-

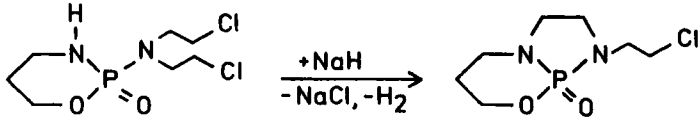


SCHEME 15

cle (compounds **47, 49** and **50**), with hexafluoroacetone took a different course than the reaction of the comparable compounds **23** and **24** with the same reagent (Scheme 14). In the former cases, besides the oxidative addition of two equivalents of hexafluoroacetone to the phosphorus(III) atom of **47, 49** und **50**, elimination of methyl chloride and intramolecular cyclization took place, forming the tricyclic phosphoranes **86** – **88** [53] (Eqn. (2)):



(2)



(3)

Similar results were observed for the reaction of 2-bis(2-chloroethyl) amino-2-oxo-1-hydro-1,3,2-oxazaphosphorinane (Cyclophosphamide) [80] with sodium hydride (Eqn. (3)) [81]. The use of sodium hydride was not necessary in the case of **86 – 88** and intramolecular cyclization occurred spontaneously in these cases. The unusual structures of **86 – 88** were established by NMR spectroscopic methods in addition to X-ray crystal structure determinations, conducted on these compounds (Figs. 8 – 10):

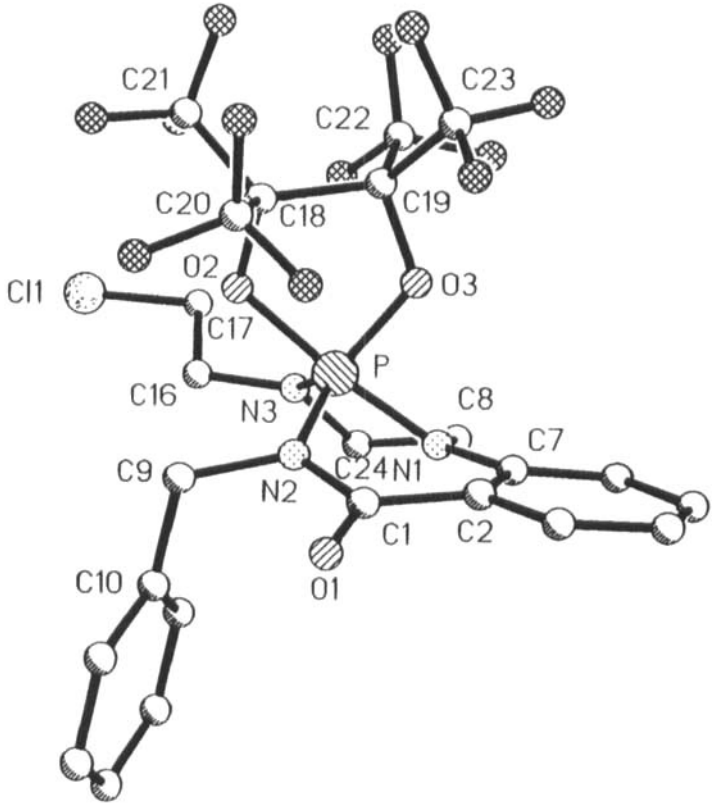


FIGURE 8 Structure of compound **86** in the solid state

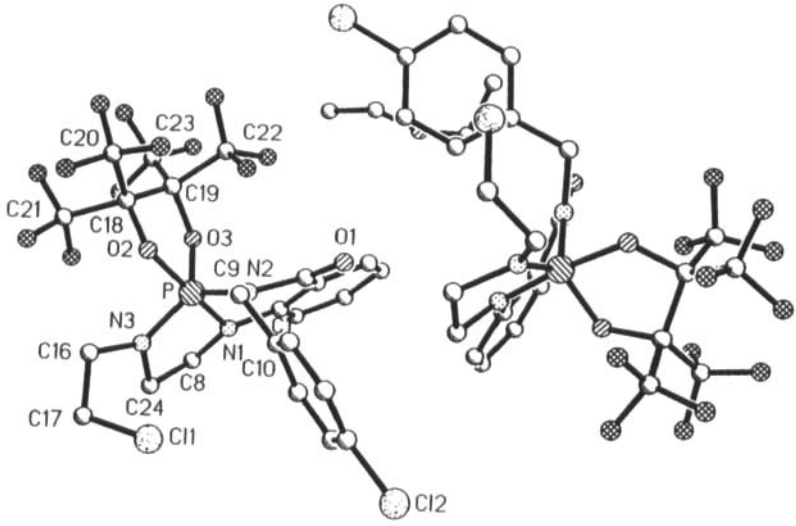


FIGURE 9 Structure of compound **87** in the solid state

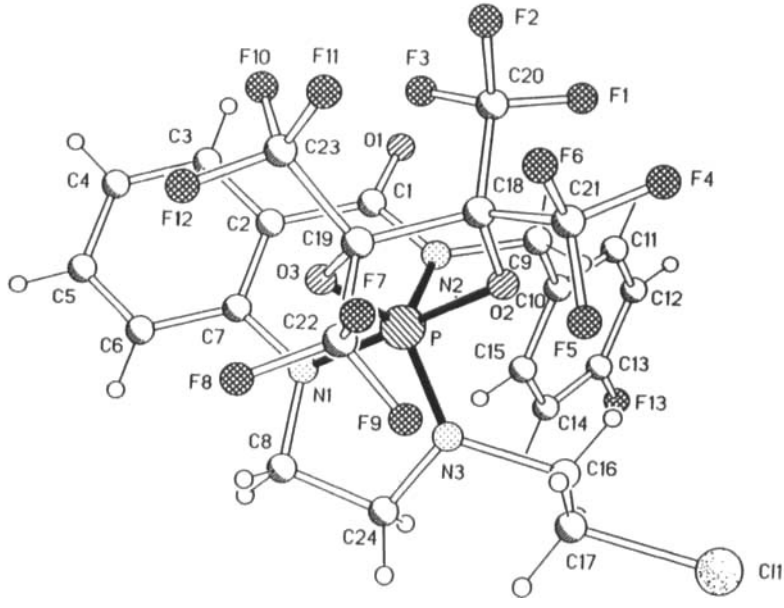
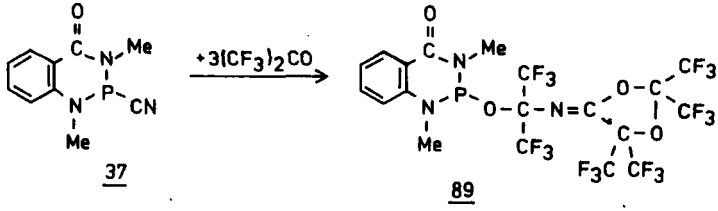


FIGURE 10 Structure of compound **88** in the solid state

In contrast to observations shown in Schemes 14 and 15, and in Eqn. (2), the reaction of the 2-cyano-substituted 1,3-dimethyl-2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-one **37** with excess hexafluoroacetone led to the formation of **89** (Eqn. (4)) [53]:

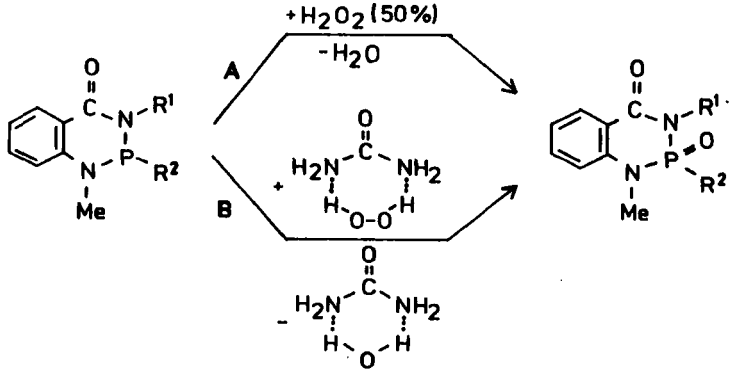


(4)

Three molecules of hexafluoroacetone were consumed in the formation of compound **89** from **37**. The formation of such reaction products is known from other reports [77].

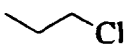
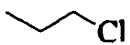
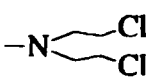
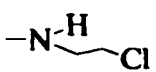
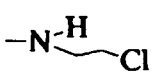
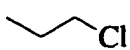
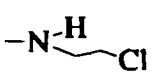
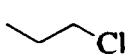
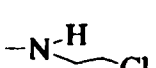
Reactions with hydrogen peroxide and hydrogen peroxide-urea-1:1-adduct

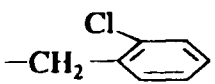
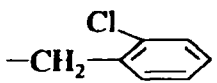
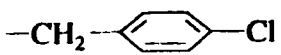
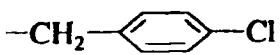
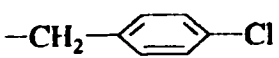
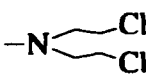
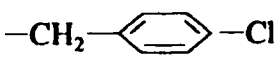
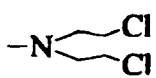
It is known that phosphorus(III) compounds are readily oxidized to the corresponding phosphoryl species, using aqueous hydrogen peroxide solution [68,82]. Another reagent used for this purpose is the hydrogen peroxide-urea-1:1-adduct $(NH_2)_2CO.H_2O_2$. In the first case, the reaction is conducted in an aqueous medium, while in the second case the reaction can be run in anhydrous media. In general, the yields of phosphoryl compounds are slightly better, when hydrogen peroxide-urea-1:1-adduct is used (Route B, Scheme 16), than in the case when aqueous H_2O_2-solution is used (Route A, Scheme 16).



SCHEME 16

TABLE I Appendix to Scheme 16

R^1	R^2	*No.*	R^1	R^2	*No.*
Me	F	16	Me	F	64
	F	19		F	65
Me		23	Me		66
Me		24			67
Me		27	Me		69
		34	Me		90
-$CHMe_2$	-NMe_2	40	-$CHMe_2$	-NMe_2	91

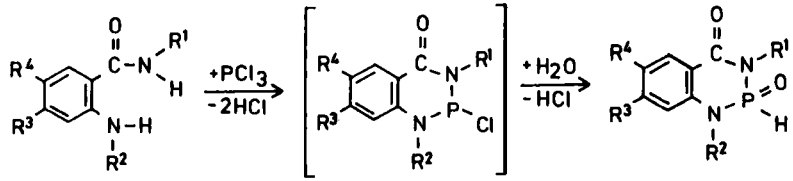
R^1	R^2	*No.*	R^1	R^2	*No.*
	-NMe_2	41		-NMe_2	92
	-NMe_2	42		-NMe_2	93
		49			94

Compounds **64, 65** [52], **66, 67, 69** [39], **90** [83] and **91 – 94** [53] were synthesized according to Scheme 16 by reacting the corresponding phosphorus (III) compounds with aqueous hydrogen peroxide solution (Route A) or hydrogen peroxide-urea-1:1-adduct (Route B).

The identity of all the above-mentioned compounds was established by NMR, IR-spectroscopy, mass spectrometry, and by elemental analysis [39,52,53,83].

2.6. 1,3-Disubstituted 2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-one-2-oxides

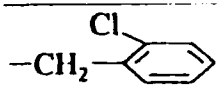
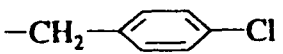
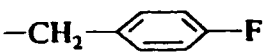
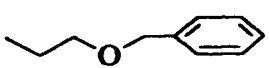
Anthranilamides [38] have been used as intermediates in the synthesis of various heterocycles. Their reactions with dimethylformamide [84] and phosgene [85] to form quinazolinones, with thionyl chloride to produce benzothiadiazinones [86], with nitrous acid to yield benzotriazinones [87], and with dimethylacetylene dicarboxylate to produce 1,4-benzodiazepine-3,5-diones [88] have been well documented. The treatment of anthranilamides with phosphorus halides was first investigated by Coppola et al. [33,34]. When N-substituted anthranilamides were allowed to react with phosphorus trichloride, benzodiazaphosphorinone oxides were produced (Scheme 17) [33,34,39,53]:

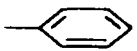
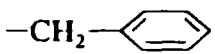


SCHEME 17

Presumably, small amounts of water led, through an intermediate (indicated in brackets), to compounds **95 – 118** (Compounds **95 – 104** [33], **105, 106** [39], **107 – 109** [53], **110 – 118** [34]). The intermediate could not be isolated by Coppola [33], but a variety of compounds of this type were synthesized [37,39–42] (Scheme 2). The existence of **95 – 118** was confirmed by NMR- and IR-spectroscopy and by elemental analysis. For **109**, an X-ray crystal structure determination was conducted (Fig. 11).

TABLE II Appendix to Scheme 17

R^1	R^2	R^3	R^4	*No*	R^1	R^2	R^3	R^4	*No.*
Me	Me	H	H	95		Me	H	H	107
Me	Me	Cl	H	96		Me	H	H	108
Me	Me	H	Cl	97		Me	H	H	109
Me	Me	-CH_2-O-CH_2-		98		Me	H	H	110
Et	Me	H	H	99		Me	H	H	111
-CH_2-CH=CH_2	Me	H	H	100		Me	H	H	112
	Me	H	H	101		Me	H	Cl	113

R^1	R^2	R^3	R^4	No	R^1	R^2	R^3	R^4	No.
Me	Et	H	H	102		Me	H	OMe	114
Me	$-CH_2-CH=CH_2$	H	H	103	Me		H	H	115
	Me	H	H	104	Me		H	H	116
$-CHMe_2$	Me	H	H	105	Me		H	Cl	117
	Me	H	H	106	Me		H	OMe	118

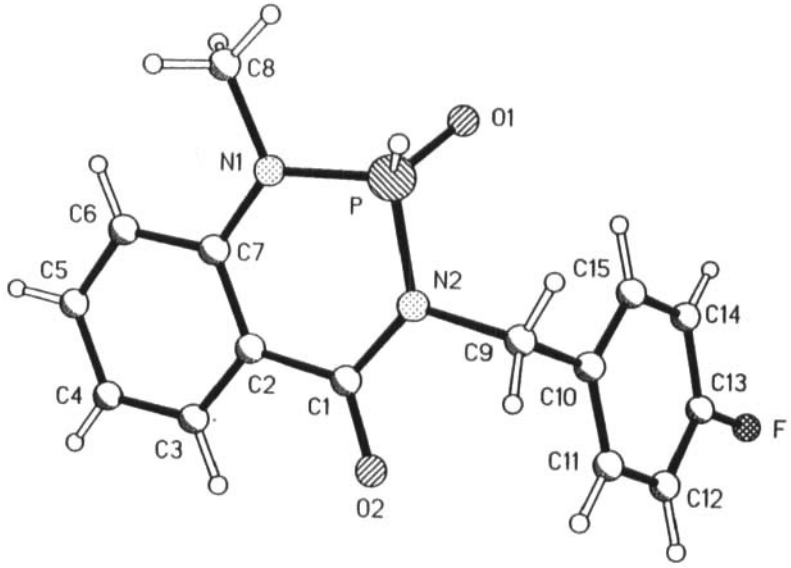
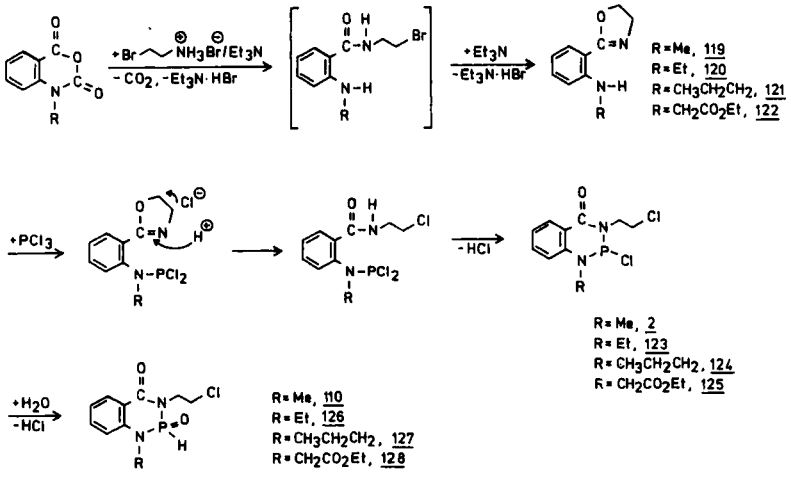


FIGURE 11 Structure of compound **109** in the solid state



SCHEME 18

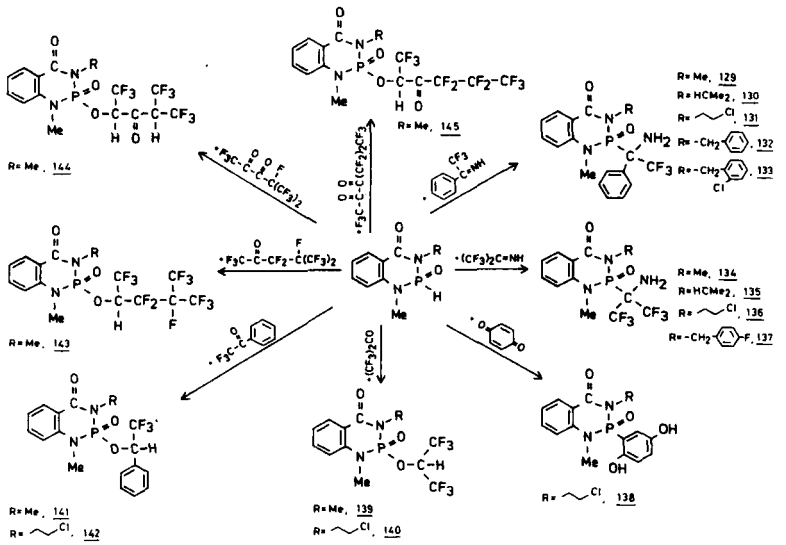
While Coppola reported the synthesis of the N-2-chloroethyl substituted 1,3,2-benzodiazaphosphorinone **110** by reaction of N-methylisatoic anhy-

dride with 2-chloroethylamine, followed by treatment of the intermediate anthranilamide derivative with phosphorus trichloride, the use of 2-bromoethylamine led to different reaction behaviour. When isatoic anhydride was allowed to react with 2-bromoethylamine (generated from its hydrobromide salt) in place of 2-chloroethylamine, oxazolines **119 – 122** were obtained [35] by cyclization of the expected intermediate anthranilamide derivatives (Scheme 18).

The structure of compounds **119 – 122** was confirmed by IR-, and ^{1}H-NMR spectroscopy, mass spectrometry, and elemental analysis [35]. Treatment of the oxazolines **119 – 122** with phosphorus trichloride in the presence of water produced via compounds **2, 123 – 125** the 1,3,2-benzodiazaphosphorinone-oxides **110, 126 – 128** in good yield. The reaction mechanism given in Scheme 18 was suggested.

2.6.1. Reactions of 3-substituted 1-methyl-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-one-2-oxides with perfluorinated mono- and diketones, and ketimines

It is known that phenyltrifluoromethylketimine reacts with dialkylphosphites under conditions of base catalysis [89]. Triethylamine catalysis was necessary also in order to bring about the reaction of different 1,3,2-benzodiazaphosphorin-4(1H)-one-2-oxides with phenyltrifluoromethylketimine to form compounds **129 – 133** [90] (Scheme 19):



SCHEME 19

Compounds **129 – 133** contain in their molecules two chiral centres (C and P), and exist as a mixture of two diastereomeric pairs, which can be distinguished by ^{1}H-, ^{19}F- and ^{31}P-NMR spectroscopy [90].

The use of bis(trifluoromethyl)ketimine led to compounds comparable to those described for phenyltrifluoromethylketimine [90] (Scheme 19). Likewise, the use of triethylamine as a catalyst was necessary for the less basic bis(trifluoromethyl) ketimine to form compounds **134 – 137**. The composition and structure of compounds **129 – 137** (partly unpublished) was confirmed by elemental analysis and mass spectrometric data, and by NMR spectroscopy. The structures of **134** and **137** were determined through single-crystal X-ray structure analyses [90] (Figs. 12 and 13):

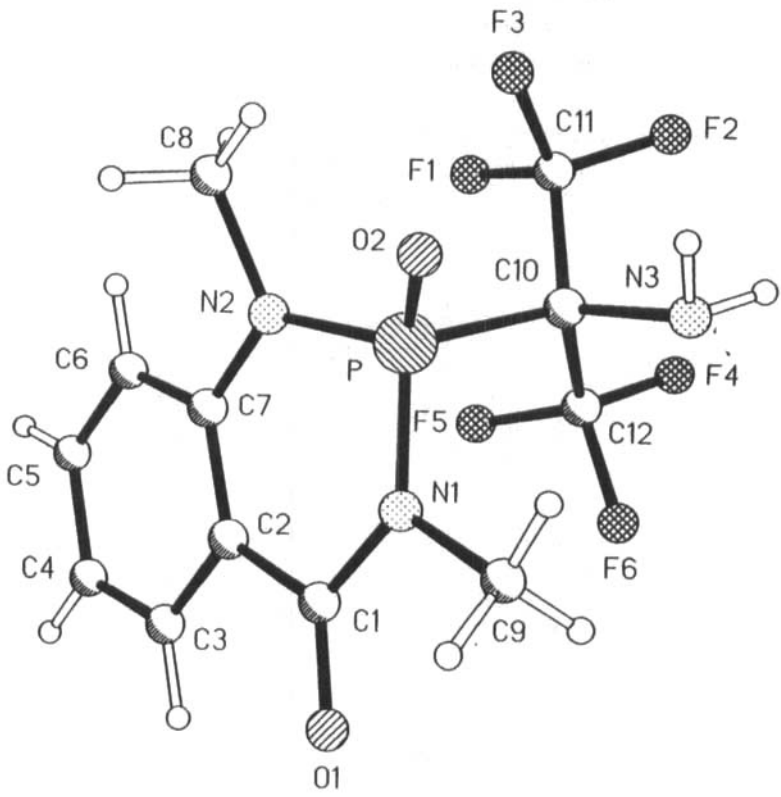


FIGURE 12 Structure of compound **134** in the solid state

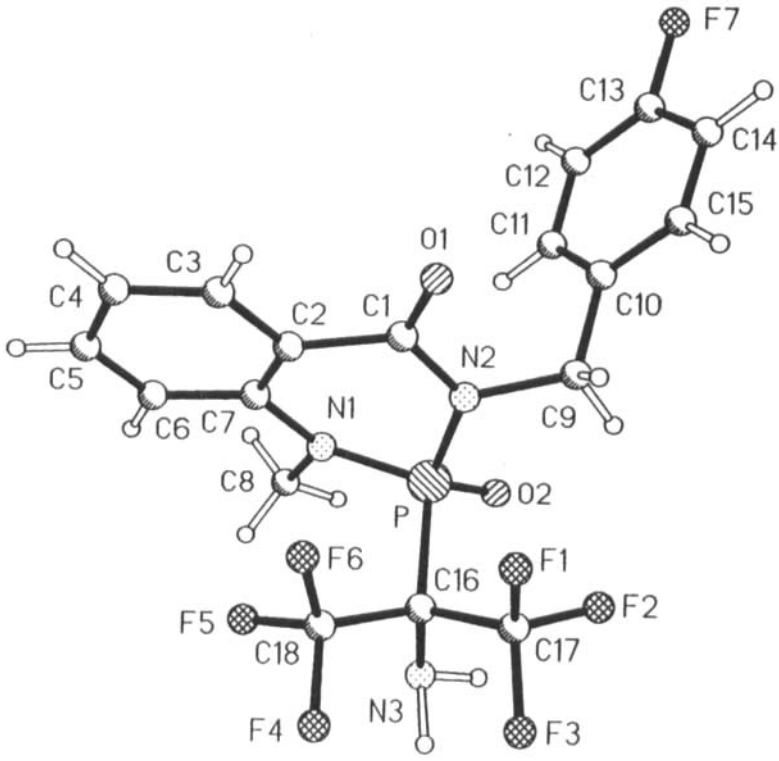


FIGURE 13 Structure of compound **137** in the solid state

While the reaction of 3-(2-chloroethyl)-1-methyl-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-one-2-oxide with p-benzoquinone in the presence of catalytic amounts of triethylamine led to the addition product **138** [91], no reaction was observed in an attempt to react the same compound with dialkyl- or alkyl-aryl-ketones. The polarization of the C(:O)-group of the non-fluorinated ketones, used in this reaction, was too low, and the ketones were, therefore, not sufficiently reactive. The formation of **138** was possible, because of a thermodynamic driving force (possibly aromatization) [92].

In contrast to non-fluorinated ketones, the use of hexafluoroacetone and trifluoroacetophenone in the presence of triethylamine as a catalyst led, in accord with Scheme 19, to compounds **139 – 142**. In these cases, addition

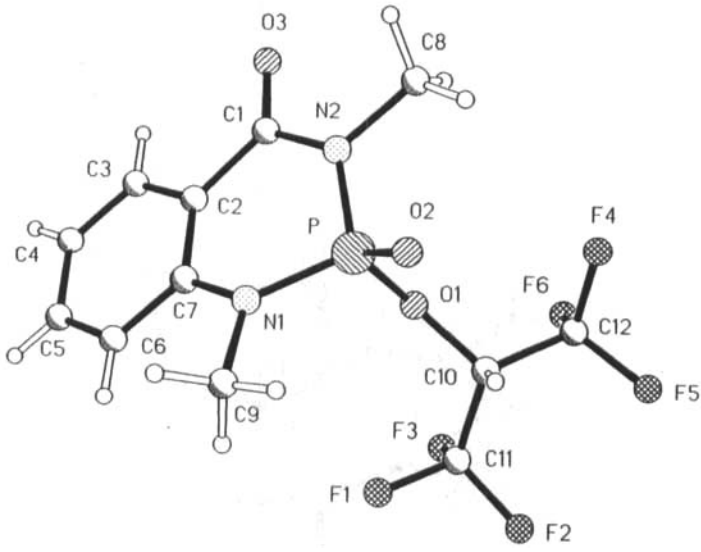


FIGURE 14 Structure of compound **139** in the solid state

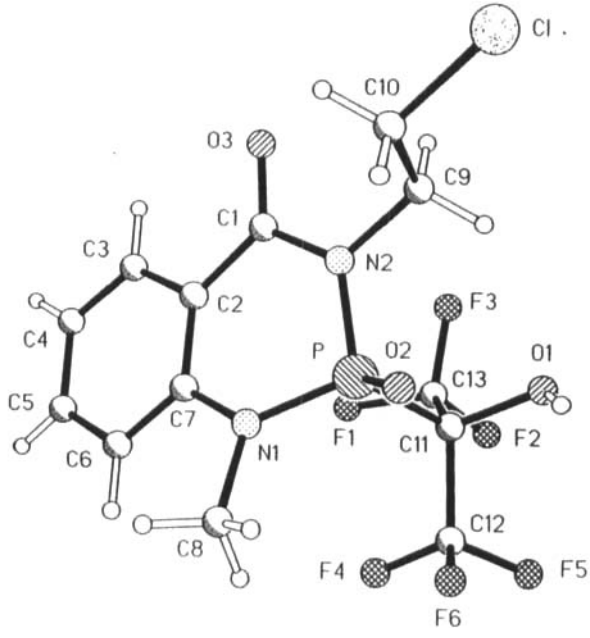


FIGURE 15 Structure of compound **140** in the solid state

of one molecule of the perfluorinated ketone to phosphorus was observed, forming a P-O-single bond and migration of the phosphorus-bonded hydrogen atom to the carbonyl-carbon atom. As a side reaction, the formation of small amounts of the isomeric "alcohol" was observed, produced by formation of a P-C-bond and migration of the hydrogen atom to the carbonyl-oxygen atom of the ketone [91]. The isomeric "alcohols" could not be isolated. However, the existence of such structural isomers is known [77,93–96].

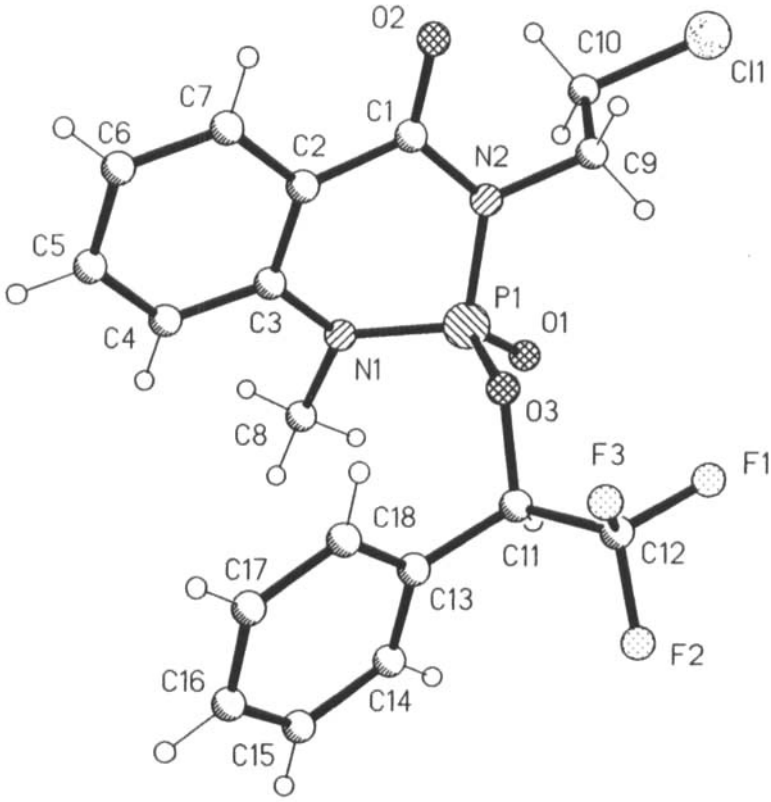


FIGURE 16 Structure of compound **141** in the solid state

The reaction of 1,3-dimethyl-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-one-2-oxide with perfluoro-methyl-isopropylketone, perfluoro-1-methyl-2-isopropyldiketone and perfluoro-1-methyl-2-n-propyl-

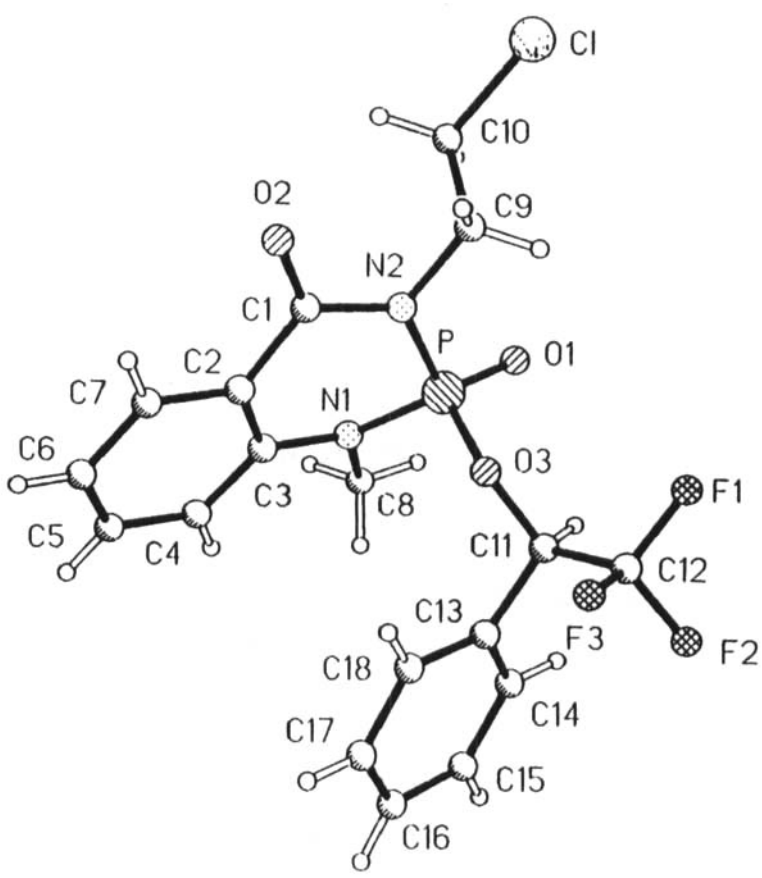


FIGURE 17 Structure of compound **142** in the solid state

diketone proceeded according to Scheme 19. The addition products **143** – **145** were formed in good yields [97]. Because the reaction products **143** – **145** have two asymmetric centres in their molecules (C-atom and P-atom, cf. Scheme 19), the formation of diastereomeric pairs was observed by NMR spectroscopy. In all cases, the formation of a P-O-C-bond and migration of the hydrogen atom from phosphorus to the carbonyl carbon atom took place. The isomeric HO-compounds, arising from the formation of P-C-bonds, and migration of hydrogen to the oxygen atom of the carbonyl group [77,93–96], were not observed.

Figs. 14 – 18 represent the results of the X-ray crystal structure investigations for compounds **139** – **142** and **145**. For **139, 141** (unpublished), **142**, and **145**, the structure of the P-O-C-isomer, which was formed as a main product according to Scheme 19, was established [91,97]. The X-ray crystal structure determination on a crystal of **140** proved the structure of the isomeric "alcohol", the side product of the reaction presented in Scheme 19 [91].

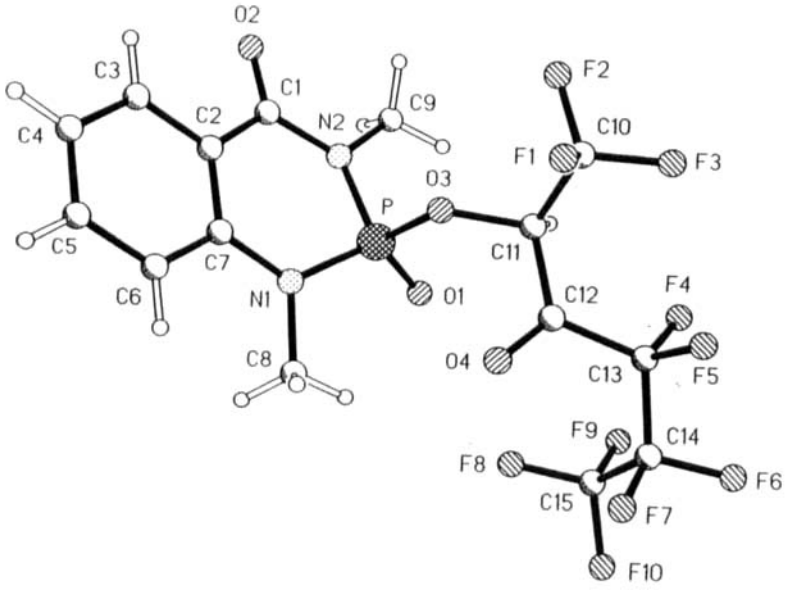


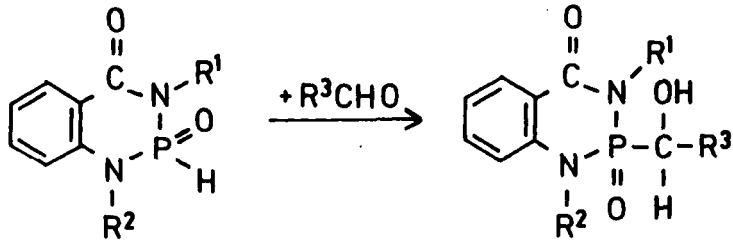
FIGURE 18 Structure of compound **145** in the solid state

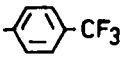
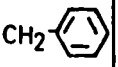
2.6.2. Reactions of 1,3-disubstituted 2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-one-2-oxides with aldehydes, isocyanates and isothiocyanates

Aldehydes

When different 2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-one-2-oxides were allowed to react with a variety of aldehydes, the alcohols **146** – **153** were isolated in good yield [98] (Scheme 20).

All compounds were characterized by NMR and IR-spectroscopy and elemental analysis. The asymmetric nature of the phosphorus atom plus the newly formed adjacent asymmetric carbon, carrying the hydroxy func-



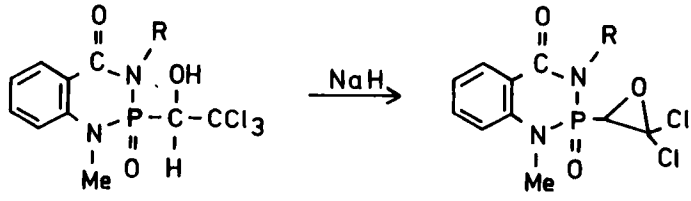
R^1	R^2	R^3	No.
Me	Me		146
	Me		147
Me	Me		148
Me	Me		149
Me	Me		150
Me	Me	CCl_3	151
Me		CCl_3	152
	Me	CCl_3	153

SCHEME 20

tion, resulted in a molecule with two chiral centres. The resulting mixture of diastereomers was responsible for the complexity of the NMR spectra [98].

Compounds **151 – 153** represent interesting intermediates, with the possibility of further transformations. It has been reported that the trichloromethylcarbinol function, when treated with base, forms a dichloro epoxide [99,100]. The general instability of this epoxide functionality usually requires its formation in situ, however in certain instances isolation and characterization have been achieved [101].

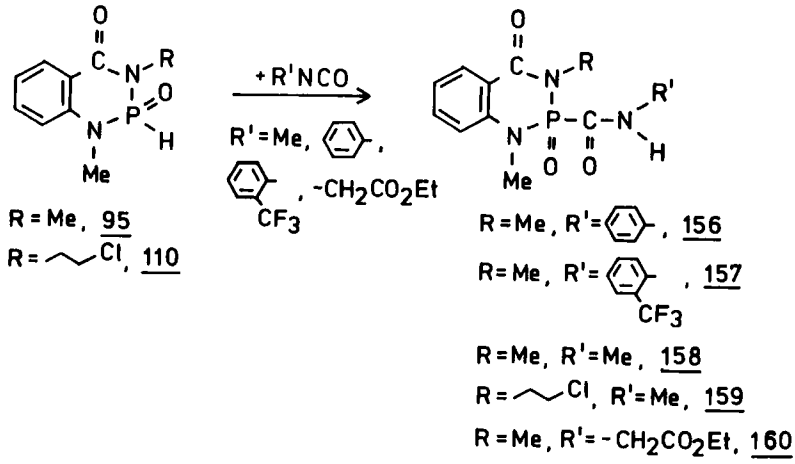
When a solution of **151** or **153** in dioxane was treated with sodium hydride, the stable dichloro epoxides **154** and **155** were formed (Eqn. (5)) [98]:



(5)

Isocyanates

While the condensation of 1,3,2-benzodiazaphosphorin-4(1H)-one-2-oxides with aldehydes did not require catalysts to produce the alcohols presented in Scheme 20, the reaction of some selected derivatives with isocyanates required the addition of one equivalent of triethylamine to form the reaction products **156** – **160** [98] (Scheme 21):



SCHEME 21

The identity of all compounds was well established by NMR and IR-spectroscopy, and by elemental analysis [98].

Isothiocyanates

A series of condensed 1,3,2-benzodiazaphosphorinones **164 – 183** was prepared by reaction of N-substituted 1,3,2-benzodiazaphosphorinone-2-oxides with aryl isothiocyanates in the presence of sodium hydride [35] (Scheme 22). All compounds presented in Scheme 22 were characterized by spectral data (NMR, MS) and by elemental analysis. In the case of **172**, the molecular structure was confirmed by a single crystal X-ray structure analysis (Fig. 19) [35]:

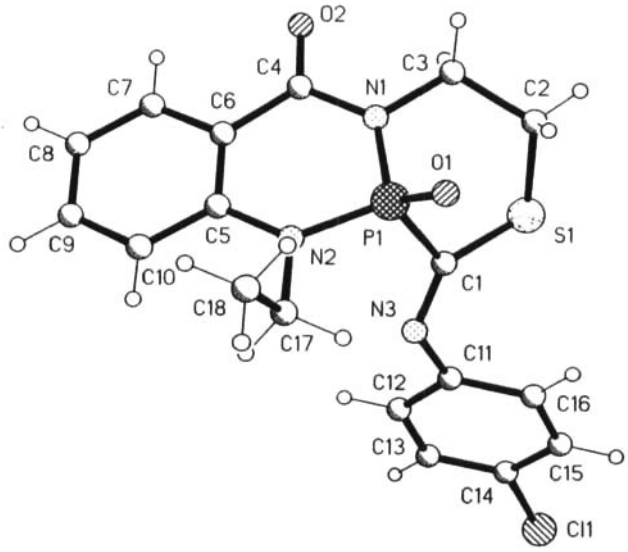
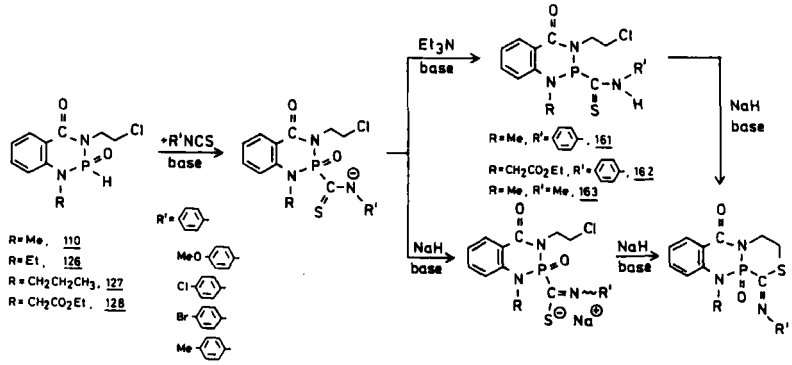
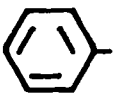
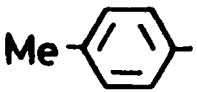
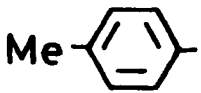
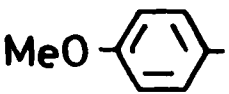
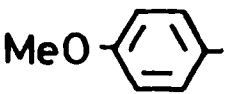
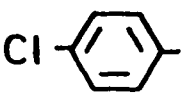
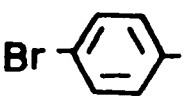


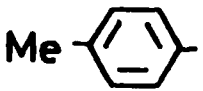
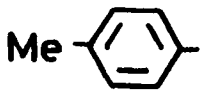
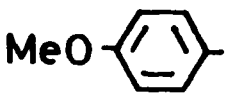
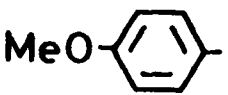
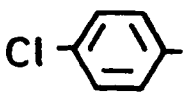
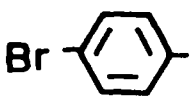
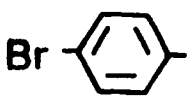
FIGURE 19 Structure of compound **172** in the solid state



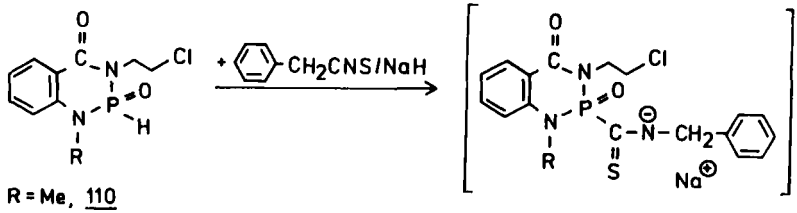
SCHEME 22

TABLE III Appendix to Scheme 22

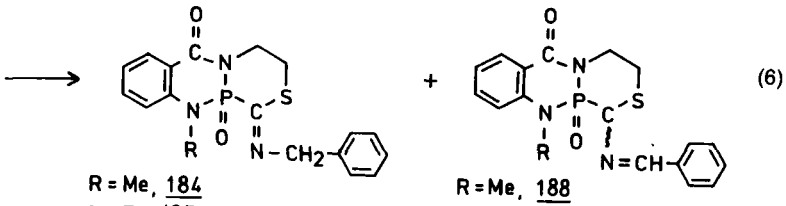
R	*R′*	*No*	*R*	*R′*	*No*
Me		164	$CH_2CH_2CH_3$		174
Me		165	$CH_2CH_2CH_3$		175
Me		166	$CH_2CH_2CH_3$		176
Me		167	$CH_2CH_2CH_3$		177
Me		168	$CH_2CH_2CH_3$		178

R	*R′*	*No*	*R*	*R′*	*No*
Et		169	CH_2CO_2Et		179
Et		170	CH_2CO_2Et		180
Et		171	CH_2CO_2Et		181
Et		172	CH_2CO_2Et		182
Et		173	CH_2CO_2Et		183

It was found that the use of different bases affected the direction of the reaction, and yield of the products. When triethylamine was used as the base, the final products were **161 – 163** [35,98]. Using sodium hydride as a base at the temperature of refluxing THF, compounds **164 – 183** were obtained [35]. When benzyl isothiocyanate was used instead of phenyl isothiocyanate, benzylimines and benzylideneamines **184 – 191** were also obtained [36] (Eqn. (6)):



R = Me, 110
R = Et, 126
R = $CH_2CH_2CH_3$, 127
R = CH_2CO_2Et, 128



(6)

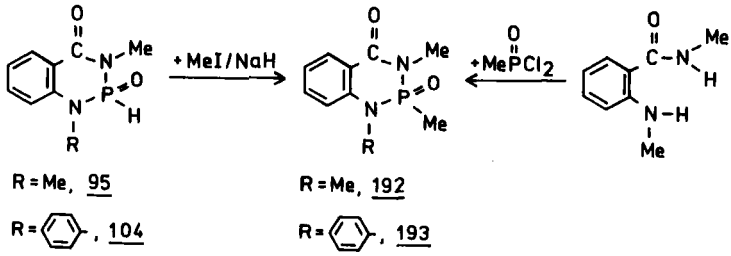
R = Me, 184
R = Et, 185
R = $CH_2CH_2CH_3$, 186
R = CH_2CO_2Et, 187

R = Me, 188
R = Et, 189
R = $CH_2CH_2CH_3$, 190
R = CH_2CO_2Et, 191

The tautomerization was observed for all the cases studied, except for R = Me. All compounds were characterized by ^{1}H-NMR and IR spectroscopy, mass spectrometry and elemental analysis. The molecular structure of **191** was further confirmed by X-ray diffraction data [36].

2.6.3. Reactions of 1-substituted 3-methyl-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-one-2-oxides with methyl iodide and with methylphosphonic dichloride

The treatment of **95** and **104** with methyl iodide in the presence of sodium hydride led to the formation of the P-methylated products **192** and **193** [34] (Eqn. (7)):



(7)

The structures of **192** and **193** were established by IR-spectroscopy (absence of the characteristic P-H absorption) and ^{1}H-NMR spectroscopy (absence of the characteristic P-H doublet, typical of **95** and **104**, and an additional P-CH_3 signal (doublet) in **192** and **193**). Additional proof of P-alkylation was provided by the treatment of N,N′-dimethyl anthranilamide with methyl phosphonic dichloride to also yield **192**. The spectral data of **192** obtained by both methods were identical [34].

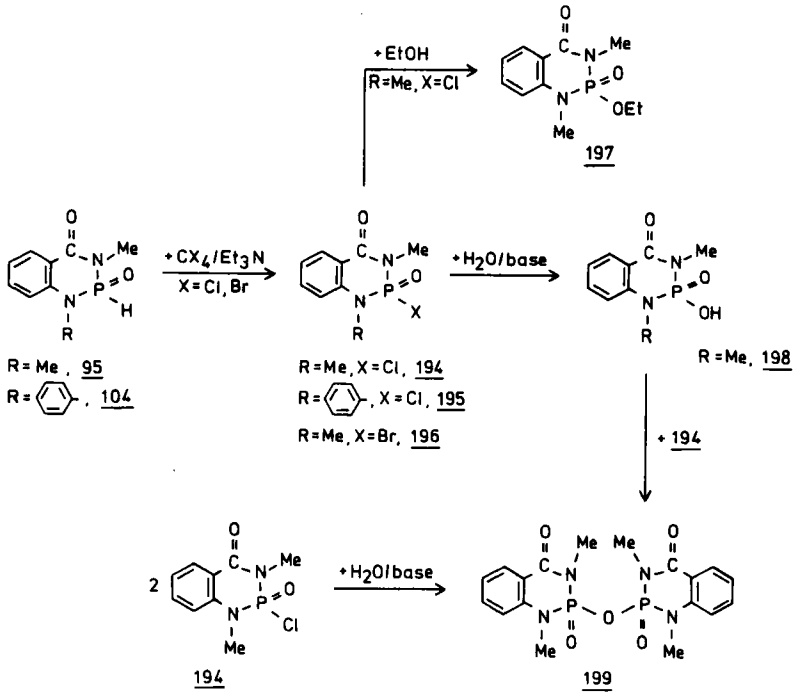
Attempts to react N,N′-dimethyl anthranilamide with bis(2-chloroethyl)amino phosphonic dichloride were unsuccessful. A reaction product analogous to **192** with the bis(2-chloroethyl)amino group as a substituent bonded to phosphorus could not be isolated, probably for electronic reasons [102].

2.6.4. Reactions of 1-substituted 3-methyl-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-one-2-oxides with tetrachloro- and tetrabromo methane and subsequent treatment with water

The phosphorus atom in **95** and **104** was readily chlorinated by treatment with tetrachloro methane in the presence of two equivalents of triethylamine [98] (Scheme 23).

Compounds **194** – **195** were isolated in high yield. The analogous 2-bromo-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-one-2-oxide **196** was prepared in somewhat lower yield by an analogous reaction with tetrabromo methane. Unlike in the previous reaction where tetrachloro methane was used as the solvent, the amount of tetrabromo methane was limited to only two equivalents due to the fact that it is a solid.

Compound **194** reacted readily with ethanol to furnish the 2-ethoxy-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-one-2-oxide **197** in quantitative yield [98] (Scheme 23).

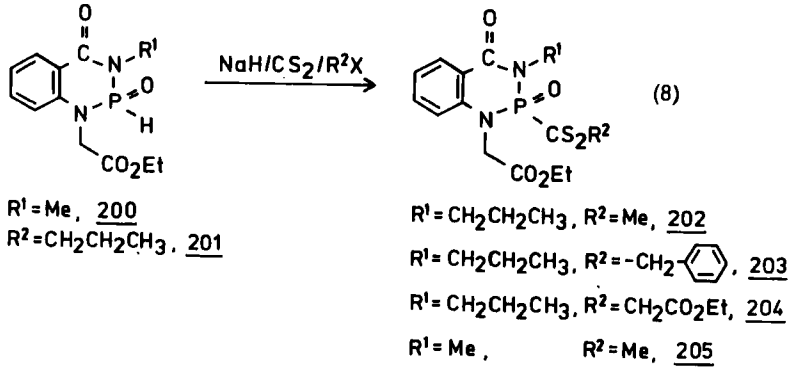


SCHEME 23

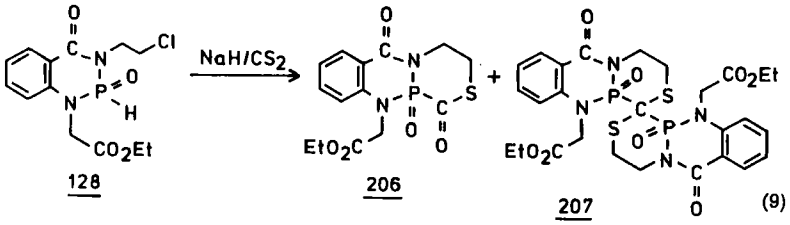
In the presence of catalytic amounts of water, compound **199** was formed by the base-catalyzed hydration of **194**, and subsequent reaction of the resulting 2-hydroxybenzodiazaphosphorinone **198** with another molecule of **194**. The reaction was very efficient, **199** being isolated in high yield. It is notable, that when **194** was intentionally treated with two equivalents of triethylamine in moist tetrahydrofuran, no detectable amount of **199** was formed [98].

2.6.5. Reactions of 1,3-disubstituted 2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-one-2-oxides with carbon disulfide, sodium hydride and triazine

The reaction of 3-methyl- and 3-propyl-substituted benzodiazaphosphorin-4(1H)-one-2-oxides **200** and **201** [103] with carbon disulfide and an alkyl halide in the presence of sodium hydride yielded the P-substituted products **202 – 205** (Eqn. (8)) [36,103].



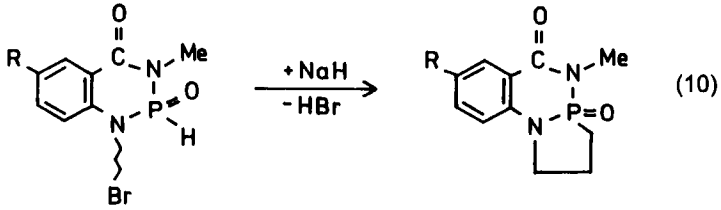
(8)



(9)

In contrast, when **128** was treated with carbon disulfide in the presence of sodium hydride, a mixture of different phosphorus heterocycles **206** and **207** was formed [36] (Eqn. (9)).

The formation of the tricyclic benzodiazaphosphorines **211 – 213** was observed, when the N-bromopropyl-substituted benzodiazaphosphorin-4(1H)-one-2-oxides **208 – 210** were treated with sodium hydride in accord with Eqn. (10) [34].

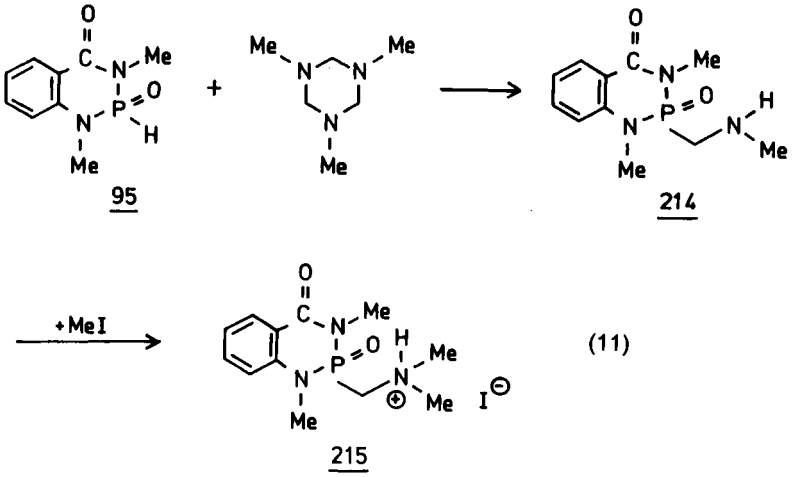


(10)

R=H, 208
R=OMe, 209
R=Cl, 210

R=H, 211
R=OMe, 212
R=Cl, 213

As expected, the reaction of **95** with 1,3,5-trimethyl-hexahydro-1,3,5-triazine led, according to Eqn. (11), to compound **214** [104] with the N-(methylamino)methyl substituent in α-position to phosphorus:



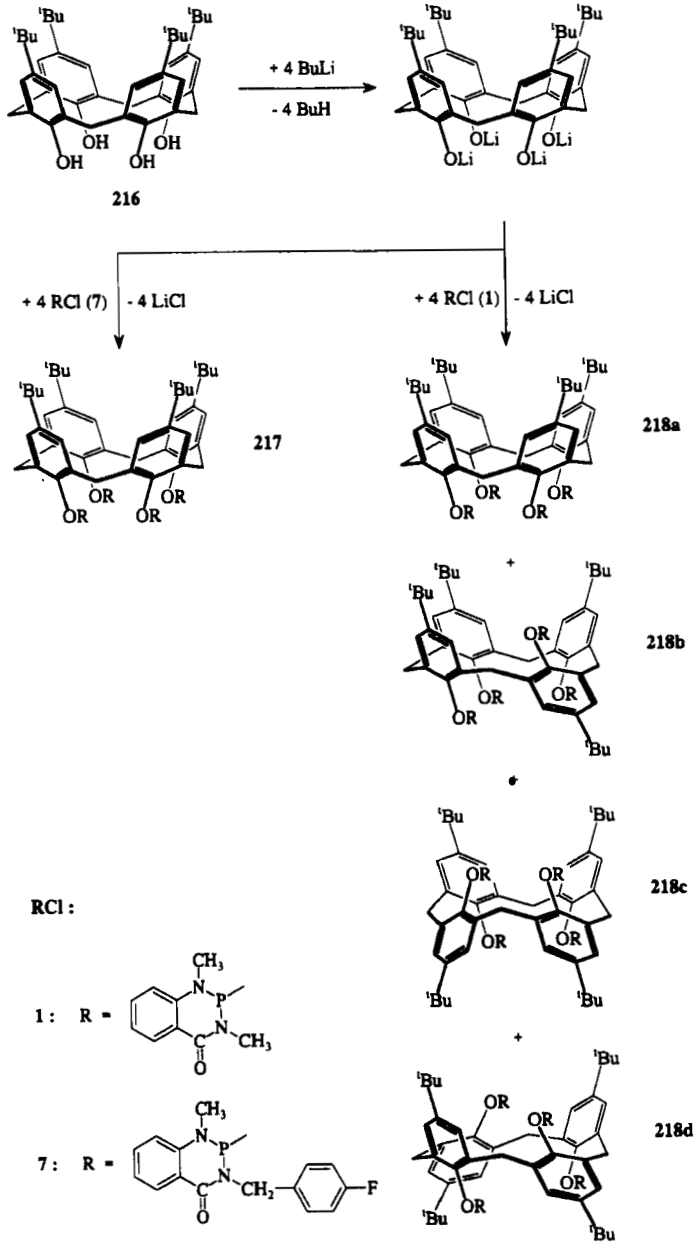
(11)

In addition to NMR spectroscopic and mass spectrometric characterization, IR-spectra in solution and in KBr were recorded on **214**, in order to establish the possibility of formation of an intramolecular P=O·····H interaction. While a hydrogen bridge bond was excluded in solution, weak interactions of this kind were observed in the solid state (KBr) by IR-spectroscopy [104].

A further reaction of **214** with methyl iodide formed the expected ammonium salt **215** [104], by methylation of the nitrogen atom of the methylamino group. Compound **215** was characterized unambiguously by spectroscopic methods.

2.7. Reactions of 3-substituted 1-methyl-2-chloro-2,3-dihydro-1,3,2-benzodiazaphosphorin-4-ones with calix[4]arenes

The investigation of the reaction of benzodiazaphosphorinones with calix[4] arenes [105] started about ten years ago, and it has attracted ever increasing interest since. These macrocyclic compounds are distinguished by some peculiarities, e.g. a hydrophilic and a hydrophobic part, a receptor space, and the possibility to functionalize donor atoms [106–111]. An inter-



SCHEME 24

esting use of the class of phosphorus- containing calix[4]arenes in science is obvious because of the ability of their phosphorus atom to exist in states of different oxidation and/or coordination number. Some phosphorus-containing calix[4]arenes are already known. Calix[4]arenes possess the ability to form different conformers [112]. After lithiation [110], the reaction of the calix[4]arene **216** with **7** furnished, according to Scheme 24, the stable cone conformer **217**, whose identity was proved by NMR spectroscopy [113].

In contrast to previous observations [112], heating of a solution of **217** in toluene to reflux temperature did not lead to the transformation of the conformers. This observation was attributed to the fact, that the conformation in **217** is "frozen" by bulky groups, bonded to the oxygen atoms [113]. A different reaction took place when, after lithiation [110], **216** reacted with **1**. The formation of four conformers was observed by ^{31}P-NMR spectroscopy (cf. Scheme 24). The isomers **218a** – **218d** could not be separated by recrystallization or column chromatography from the isomeric mixture [110].

2.8. Metal complexes of benzodiazaphosphorinones

The chemistry of phosphorus(III) compounds with derivatives of transition metals has been investigated in detail, and there is a multitude of reports about phosphorus-containing metal complexes too numerous to describe in detail here [114]. Metal complexes with diazaphosphorinone ligands have been known for only a short time, and were described in the literature only sporadically until now [37,41,53,70,115]. In these cases, the elements chromium, molybdenum, tungsten, platinum and gold were used as the metal centers. We now summarize the chemistry of this class of compounds.

2.8.1. Reactions of olefin-metal(0) carbonyl derivatives of group 6 (metal = chromium(0), molybdenum(0), tungsten(0)) with substituted 2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-ones

Tetrahydrofuran-metal pentacarbonyls are well-known precursors in the synthesis of numerous mono-substituted carbonyl derivatives [116]. These complexes are obtained by irradiation of the corresponding hexacarbonyls in THF with a high pressure mercury lamp. They are not isolated, and are allowed to react with the respective ligand in situ. Reagents often used in the preparation of cis-disubstituted tetracarbonyl compounds of group 6

metals are olefin complexes of the type η^4-bicyclo[2.2.1]hepta-2,5-diene-metal tetracarbonyl (norbornadiene metal tetracarbonyl, $NorM(CO)_4$). In the starting compound $NorM(CO)_4$, the cis-configuration is already preformed through the norbornadiene substituent, bonded to the metal. This configuration is not preserved in every case during the formation of the phosphine complex. This is the case, especially, for monodentate ligands (monophosphorus(III) compounds), whose complexes tend to isomerize at higher temperature (Eqn. (12)), to form the thermodynamically more stable trans-substituted compounds [117]:

$$NorM(CO)_4 + 2L \xrightarrow[-Nor]{} cis\text{-}L_2M(CO)_4 \rightleftharpoons trans\text{-}L_2M(CO)_4 \qquad (12)$$

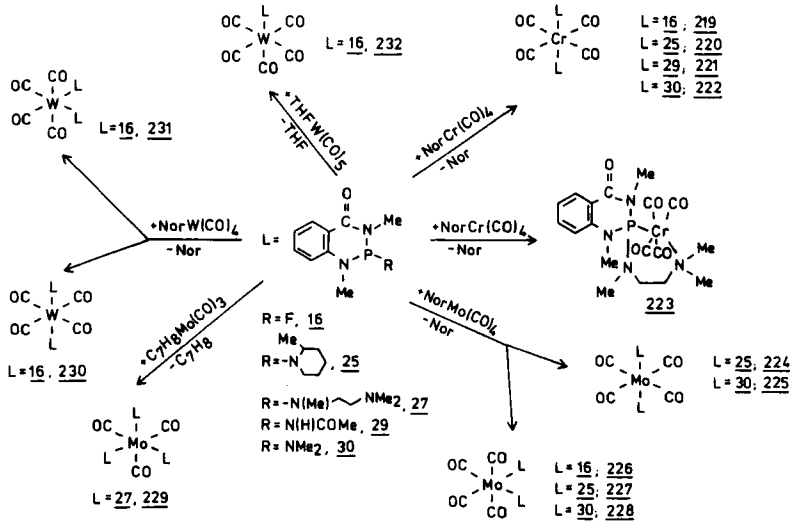
$M = Cr, Mo, W$

The rate of substitution and isomerization reaction depends, decisively, on the metal M, and on the ligand L [118]. The rate of olefin displacement for a certain ligand L decreases in the order Mo > W > Cr, while the rate of isomerization decreases in the opposite order, Cr > W > Mo. Thus, the probability of the formation of cis-configurated complexes for a certain ligand L is the highest when norbornadiene molybdenum(0) tetracarbonyl is used. For different ligands L, a dependence of the rate of isomerization on the cone angle Θ was observed. Likewise, an influence of the electronegativity of the substituent, bonded to the donor center (λ^3P atom), on the kinetics of the reaction was noted [118]. A further reagent, suitable as a precursor in the formation of phosphine complexes, is η^6-cycloheptatriene molybdenum(0) tricarbonyl. In this case, three coordination sites in the molecule are occupied through formation of facially or meridionally substituted complexes, respectively.

Infrared spectroscopy represents a simple physical method capable of providing information about the configuration of metal carbonyl complexes formed during reactions of substituted metal carbonyls and phosphines. To characterize the reaction products, it is important to know the number and the frequencies of the observed IR-resonances [119,120]. The number of resonances is determined by the symmetry of the molecule. With the assumption that all ligands are spherical, it is possible to determine the degree of substitution and the stereochemistry at the metal center [121] (local symmetry). In the case of strongly asymmetric ligands, the diagnostic value of IR-spectroscopy is possibly affected, because they can

cause a stronger decrease of symmetry than expected. Thus, an increase of wave numbers is possible. In addition, by interference of absorptions which are quite similar, the observed number of resonances can be lower than the theoretically expected number [122,123].

The preparation of the complexes **219, 226, 230 – 232** (ligand L = **16**) was effected by reaction of **16** with $NorM(CO)_4$ (M = Cr, Mo, W) and $(THF)W(CO)_5$ in a molar ratio of 2:1 according to Scheme 25:



SCHEME 25

In the case of the tetracarbonyl-Cr(0)-complex, only the trans isomer **219** was formed, while for the tetracarbonyl-Mo(0)-complex the expected cis isomer **226** was observed [70]. The cis-tetracarbonyl-W(0)-isomer **231** tended to isomerize at higher temperatures, showing a cis-trans-equilibrium with the thermodynamically more stable trans compound **230** [117]. Variable temperature ^{31}P-NMR investigations of a mixture of **230** and **231** did not show a significant temperature dependence of the cis-trans-equilibrium [70]. The monosubstitution of the THF-pentacarbonyl-W(0)-complex led to the expected compound **232** [70].

The need for long reaction times, required for the formation of **219, 226,** and **230 – 232** was established by the fact that the reactivity of the phos-

phorus atom was decreased by attaching a fluorine substituent to the donor center (phosphorus). Thus, the lower nucleophilic character of the ligand **16** led to lower substitution rates, which depend as well on the metal center M [118].

The dependence of the isomerization rate of the ligand L was discussed, comparing the reaction of different ligands L (L = **25, 29, 30**) with NorM(CO)$_4$(M = Cr, Mo). All compounds **220 – 222, 224, 225, 227, 228** (cf. Scheme 25) were formed in good yield at room temperature [70].

The reaction of **25** with NorM(CO)$_4$ (M = Cr, Mo) in a molar ratio of 2:1 led to compounds **220, 224** and **227** [70] (cf. Scheme 25) in moderate yield. The mixture of isomers **224** and **227** was separated by column chromatography. After substitution of norbornadiene in NorCr(0) tetracarbonyl by compound **30**, only the trans isomer **222** was formed; in the case of NorMo(0) tetracarbonyl, a mixture of the cis isomer **225** and the trans isomer **228** was observed. Compound **228** already isomerized at room temperature, forming an equilibrium with the more stable trans isomer **225**. Isomerization of **228** was explained by a steric effect, because the dimethylamino group, bonded to phosphorus in the ligand **30**, requires more space than the fluorine atom in the ligand **16** for which only the cis complex **226** is observed [70]. Electronic reasons (increased repulsion by free electron pairs of the nitrogen atoms in the heterocycle, of the nitrogen atom of the dimethylamino group and of the fluorine atom bonded to phosphorus) had a dominating influence on the formation of the trans isomers **219** and **222**, apart from the steric effect of the ligands. Additionally, the positive inductive effect of the dimethylamino group increased the nucleophilicity of the donor λ^3P-atom by increasing its electron density. This increased the rate of substitution as well (shorter reaction times).

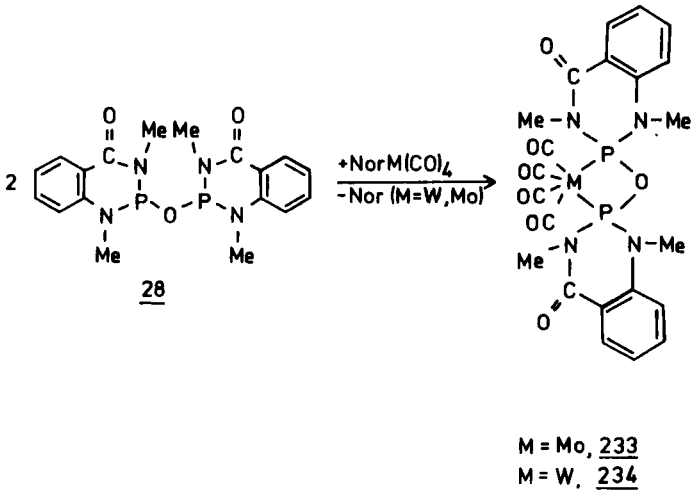
The reaction of **29** with NorCr(CO)$_4$ led to the expected trans complex **221**, while the synthesis of the corresponding molybdenum complex failed, because paramagnetic decomposition products were formed immediately in chlorinated solvents. Even under variable reaction conditions (solvent, temperature), it was not possible to isolate a molybdenum complex, comparable to **221**. The solvent influence on the kinetics and the mechanism of complexation was discussed, compared to the formation of compounds presented in Scheme 25 [70].

According to Scheme 25, in the reaction of **27** with NorCr(CO)$_4$ compound **223** [37] was formed, where substitution of norbornadiene occurred by chelation of a ligand molecule **27** via the phosphorus atom and the

nitrogen atom of the dimethylamino group. A similar reaction is described elsewhere in the literature [124].

The reaction of **27** with cycloheptatriene molybdenum tricarbonyl (Scheme 25) led to **229** as the sole product [37]. Neither chelation nor coordination via the nitrogen atom of the dimethylamino group to the metal center was observed [37]. All compounds, synthesized according to Scheme 25, were characterized by NMR, IR-spectroscopy, mass spectrometry and elemental analysis. A detailed discussion of IR- and ^{31}P-NMR data for compounds **219** – **232** is presented in ref. [70].

The reaction of the diphosphorus compound **28** with $NorM(CO)_4$ (M = Mo, W) provided the metal complexes **233** and **234**, according to Eqn. (13):



28 (13)

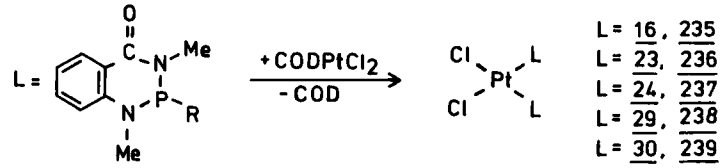
The formation of both chelate complexes occurred in good yield. Unambiguous characterization was possible by NMR and IR-spectroscopy, mass spectrometry and by elemental analysis [42].

2.8.2. Reactions of cyclooctadiene platinum dichloride {(COD)PtCl$_2$} with substituted 2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-ones

According to Pearson [125,126], platinum in the oxidation state +2 belongs to the class of "soft acids", showing a high affinity to phosphorus(III) compounds [127]. Cyclooctadienyl platinum dichloride ((COD)$PtCl_2$,

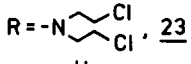
(COD = Cyclooctadiene)) is highly reactive towards phosphines, and forms the expected configuration of phosphine complexes under mild conditions. The reaction of $(COD)PtCl_2$ with several derivatives of benzodiazaphosphorinones leads to different platinum(II) complexes, as described below.

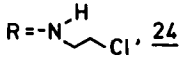
The reaction of **16, 29** and **30** with $(COD)PtCl_2$ furnished the platinum complexes **235, 238** and **239** [70], according to Eqn. (14):



(14)

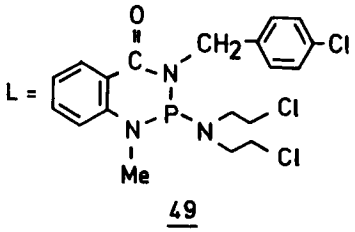
R = F, 16



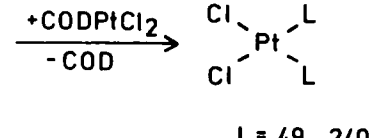


R = -N(H)COMe, 29

R = -NMe_2, 30



49



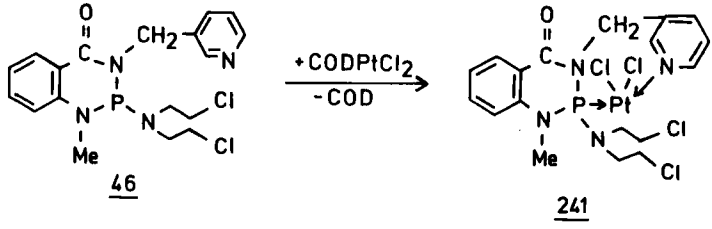
(15)

Attempts to react **25** with $(COD)PtCl_2$ failed. No coordination compound, containing the $PtCl_2$-fragment, was formed. This is due to the steric effect which seems to arise from the 2-methylpiperidino group in **25** [70]. The characterization of **235, 238** and **239** was effected, using different spectroscopic methods (IR, NMR, MS). Of special interest are ^{19}F- and ^{31}P-NMR investigations which indicate the geometry of the compounds. The cis geometry of these compounds was deduced from the magnitude of the $^1J(^{31}P^{195}Pt)$ coupling constant (cf. [128]). During the reaction of **16** with potassium tetrachloroplatinate (K_2PtCl_4), the cis substituted

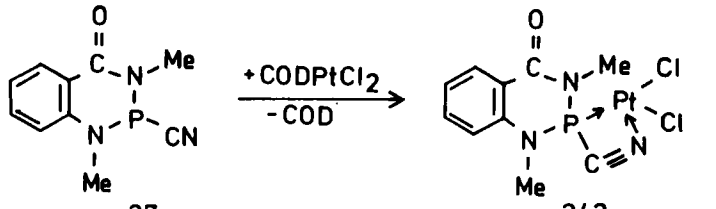
platinum(II) compound **235** was formed and not, as expected, the trans isomer [70]. The weak trans effect and π-acceptor ability of chlorine suggested a σ/π-synergism [96], which led primarily to a strengthening of σ-bonds. Because the fluorine atom bonded to phosphorus exerts a strong negative inductive effect on platinum, the synergetic interaction in **235** is quite strong and serves to explain the formation of the cis isomer **235** from potassium tetrachloroplatinate. In the case of the formation of the trans isomer, stabilization by back bonding from platinum to phosphorus would be irrelevant [128].

In the same manner as observed for **235, 238** and **239**, the reaction of **23, 24** and **49** with $(COD)PtCl_2$ led, according to Eqns. (14) and (15), to the formation of **236, 237** (Eqn. (14) [129]) and **240** (Eqn. (15) [53]). Because of the magnitude of the $^1J(PPt)$ coupling constant, the presence of **236, 237** and **240** as the cis isomers was suggested. The syntheses of these last three compounds were carried out mainly to check their use as potential cytostatic reagents, because strong biological activity was expected, resulting from the alkylating effect of the 2-chloroethyl amino group [56–58] in the presence of platinum. A more detailed discussion of this subject is found in Chapter 5.

The reaction of **46** with $(COD)PtCl_2$ formed, according to Eqn. (16), the complex **241**, showing a chelating coordination of the phosphorus atom and the nitrogen atom of the picolyl ligand to the metal center [41]:



46 241 (16)



37 242 (17)

Compound **241** is the first complex of this type, where instead of two monodentate ligands only one bidentate ligand is coordinated to platinum. Similar behaviour was observed for the reaction of **37** with $(COD)PtCl_2$, forming compound **242**, according to Eqn. (17) [53]. After coordination of the ligand **37** to platinum via the phosphorus atom, the second coordination site is occupied by the nitrogen atom of the cyano group. This structure is proved by ^1H- and ^{31}P-NMR spectroscopy, by mass spectrometry and by elemental analysis. Unfortunately, an X-ray crystal structure is not available to confirm the molecular structure unambiguously.

2.8.3. Reactions of tetrahydrothiophene chloro gold(I) {(THT)AuCl} with substituted 2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-ones

Coordination compounds, containing gold(I) as a metal center are well known [130]. An important application of these compounds is their use in therapeutic medicine. Like complexes of its "neighbouring element" platinum, gold complexes are used in many areas of medical treatment. Already at the end of the last century, $K[Au(CN)_2]$ was used successfully as a medication against tuberculosis, because of its antibacteriological effect [131]. The antiarthritic effect of some gold(I) compounds is known as well [132,133].

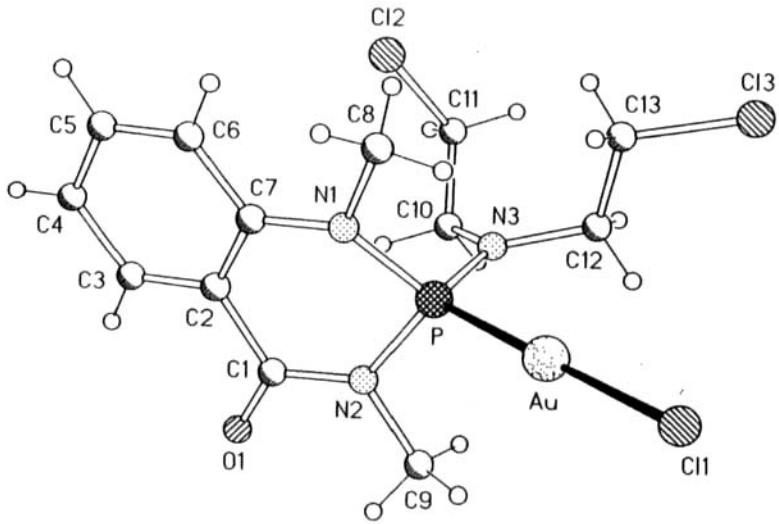


FIGURE 20 Structure of compound **245** in the solid state

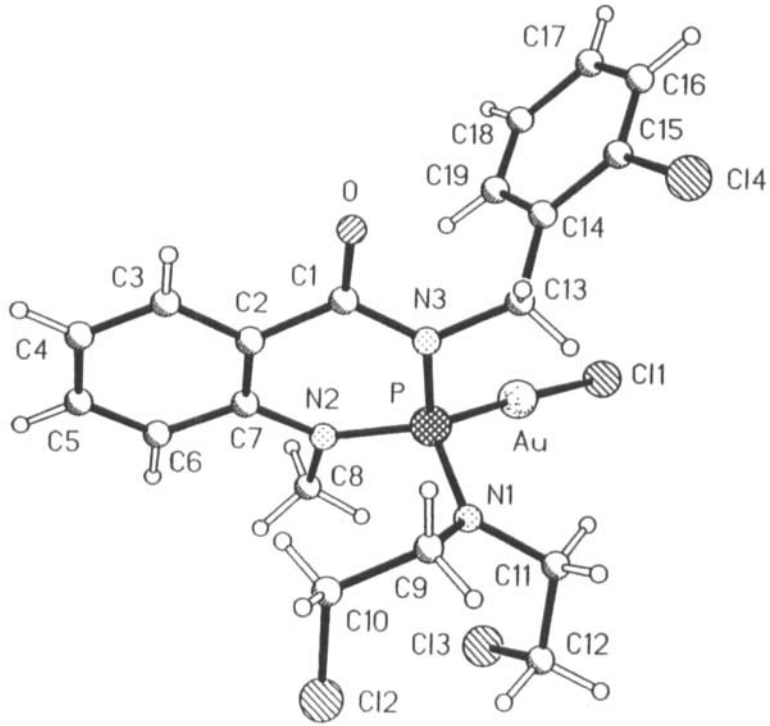
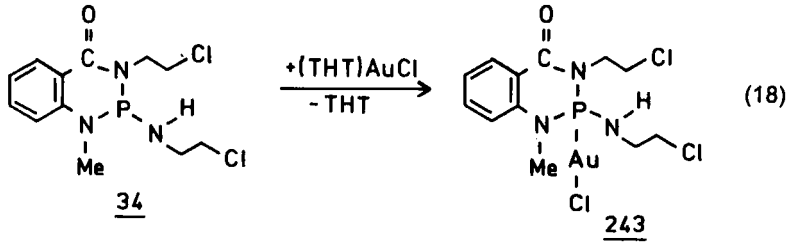


FIGURE 21 Structure of compound **246** in the solid state

The cytostatic effect of gold(I) complexes is also of importance. This effect can be influenced, mainly, by the nature of the ligands. One reason for this is the molecular size, which is important for the cell permeability. While some polymeric gold(I) thiolates are nearly ineffective, analogous phosphorus-containing, monomeric gold(I) thiolates of the type (RS) $Au(PR_3)$ reveal extreme cytotoxicity [134]. The cancerogenicity and mutagenicity of gold(I) complexes is comparably low, because according to the Pearson concept [125], gold(I) shows only low affinity to the potential donor atoms N and O in human DNA. Another advantage of gold(I) complexes, used in cancer therapy, is their much lower heavy metal toxicity, compared to platinum complexes (e.g. "Cisplatin", a well known cytostatic). Although the cancerostatic effect of gold(I) complexes cannot be explained fully, yet, both gold(I) and the coordinating ligand molecule

play an important role. When the free ligand shows cytotoxic behaviour but is not stable enough under "in vivo" conditions, complexation with gold(I) can stabilize this ligand, and can also facilitate the transport across the lipophilic cell membranes. Many phosphine gold(I) complexes meet both requirements, tetraedrically coordinated gold(I) [135–137] as well as linearly coordinated gold(I) [138].

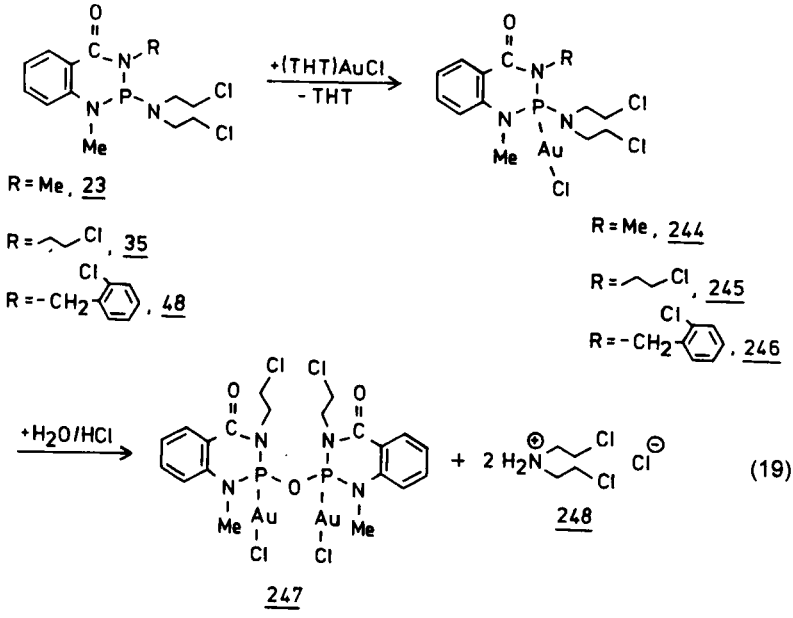
As discussed in Chapter 5, compounds containing the 2-chloroethyl grouping show biological activity, and thus are considered as potential cytostatics. A series of these compounds involving the benzodiazaphosphorinone ring system has been synthesized (cf. Chapter 2.4.) and were allowed to react with $(COD)PtCl_2$ (Eqns. (14) – (17)), in order to achieve an improvement of their cancerostatic properties. The possibility to synthesize phosphine gold(I) complexes easily by reaction of a suitable (2-chloroethylamino substituted) phosphine with tetrahydrothiophene gold(I) [130,139–141], gave the impulse for the synthesis and investigation of compounds, described in the following, which bear two totally different, cancerostatically active centers (2-chloroethylamino group and gold(I)). The reaction of **34** with tetrahydrothiophene chlorogold(I) led, according to Eqn. (18), to the complex **243** with linearly coordinated gold [129]. The characterization of **243** is based on NMR spectroscopy, mass spectrometry and elemental analysis.



34 243 (18)

The reaction of the 2-bis(2-chloroethyl)amino-1-methyl-2,3-dihydro-1H-1,3,2-benzodiazaphosphorin-4-ones **23, 35** and **48**, bearing different substituents at the nitrogen atom N3, with tetrahydrothiophene chlorogold(I) furnished, according to Eqn. (19), compounds **244 – 246** [115]. Compounds **244** and **246** were characterized by ^{31}P-NMR, elemental analysis, and X-ray crystal structure determinations (Figs. 20 and 21).

The reaction of **35** with (THT)AuCl was unusual. The formation of **245** could be proved unambiguously by ^{1}H- and ^{31}P-NMR spectroscopy and



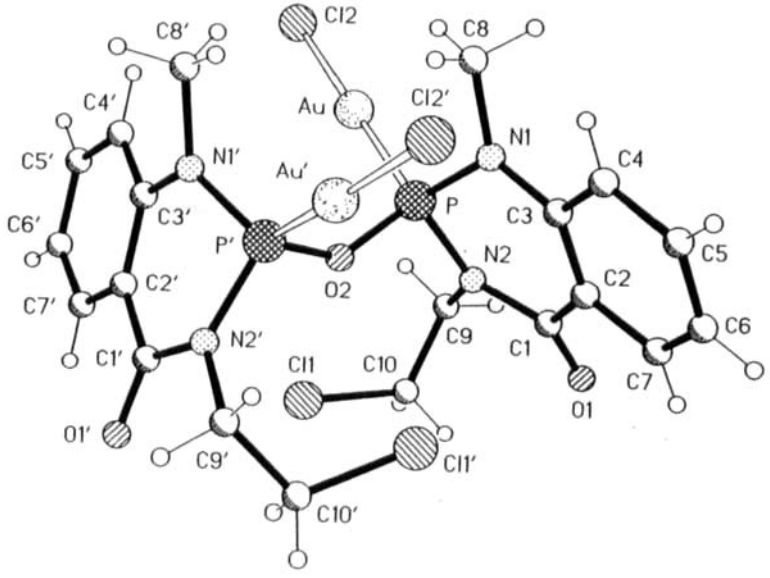


FIGURE 22 Structure of compound **247** in the solid state

by mass spectrometry immediately after mixing the starting compounds. After storage of **245** for six days in solution at −30 °C, the formation of **247** and **248** was observed according to Eqn. (19), probably due to the presence of small amounts of water. Both compounds, **247** and **248** were characterized by X-ray crystal structure determinations (Figs. 22 and 23). Apparently, the formation of the hydrolysis product **248** was preceded by a cyclization of the 2-chloroethylamino grouping, elimination of HCl, and formation of an aziridinium ring [57]. The hydrogen chloride, originating from this reaction, is probably absorbed by bis(2-chloroethyl)amine, forming the hydrochloride salt **248**. Bis(2-chloroethyl)amine is formed by hydrolysis and subsequent condensation of two molecules of **245** [115].

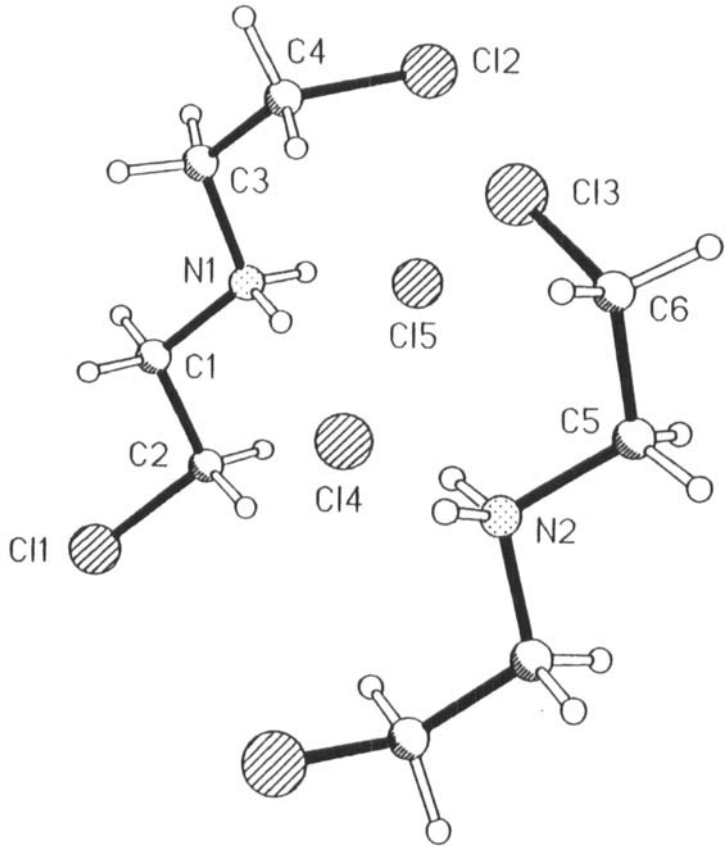


FIGURE 23 Structure of compound **248** in the solid state

A selection of compounds described before was checked with regard to their biological activity. The results are discussed in Chapter 5.

3. BENZOXAZAPHOSPHORINONES

3.1. Introduction

Benzoxazaphosphorinones were known only toward the late 1960ies. In contrast to benzodiazaphosphorinones, where two (equivalent) nitrogen atoms are bonded in α-position to the phosphorus atom in the heterocycle, benzoxazaphosphorinones can exist as two different structural isomers (**A, B**; Fig. 24), caused by different ring atoms (O, N) in α-position to the phosphorus atom in the heterocyclic system:

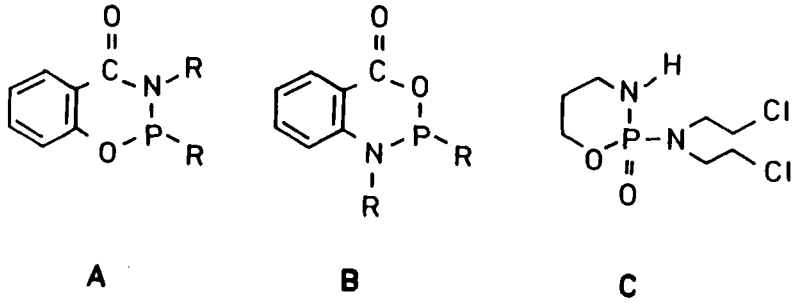


FIGURE 24 Two structural isomers of benzoxazaphosphorinones, **A** and **B**; Structure of Cyclophosphamide, **C**

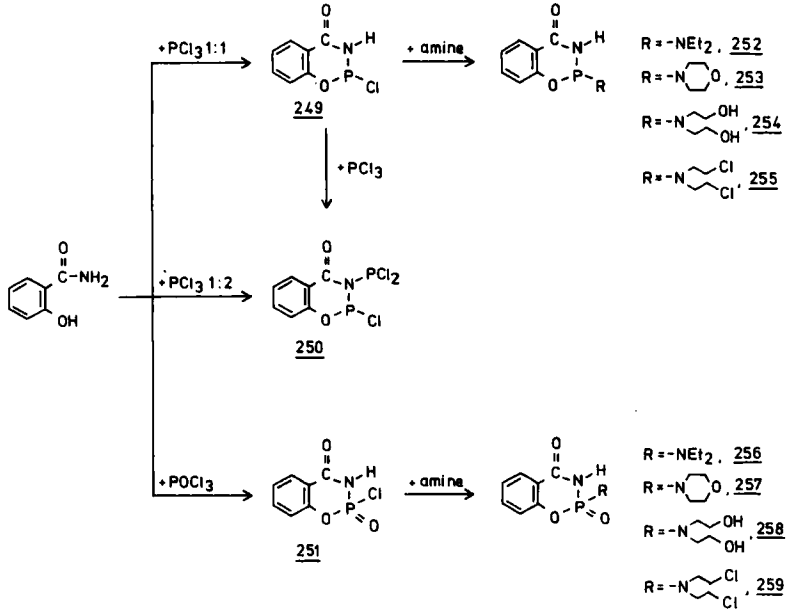
Compounds of type **A** can be synthesized easily by reaction of salicylamide with phosphorus(III) halides, while the formation of compounds of type **B** takes place via reaction of anthranilic acid with phosphorus(III) halides.

Intensive studies about chemistry and pharmacological properties of benzoxazaphosphorinones were caused by the discovery of the cytostatic properties of the related compound *Cyclophosphamide* [57] (**C**; Fig. 24). Its further development by introducing different substituents in *Cyclophosphamide* and modification of the heterocyclic ring system gave rise to

great interest in this class of compounds. Thus, many benzoxazaphosphorinones of types **A** and **B** were described in numerous publications. A summary is given in the following.

3.2. 2,3-Disubstituted 2,3-dihydro-4H-1,3,2-benzoxazaphosphorin-4-ones

Compounds of type **A** (Fig. 24) were obtained by reaction of salicylic acid amides with phosphorus(III) halides. The reaction of salicylic acid amide with phosphorus trichloride or phosphorus oxychloride in different stoichiometric ratios led to 2-chloro-2,3-dihydro-4H-1,3,2-benzoxazaphosphorin-4-one **249**, 2-chloro-3-(dichlorophosphino)-2,3-dihydro-4H-1,3,2-benzoxazaphosphorin-4-one **250** and 2-chloro-2,3-dihydro-1,3,2-benzoxazaphosphorin-4-on-2-oxide **251**, described in Scheme 26 [142,143].



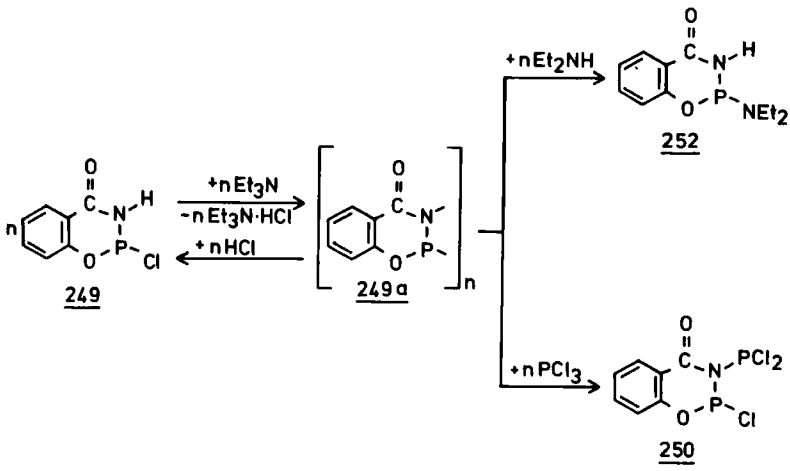
SCHEME 26

The use of an additional base as HCl-acceptor was not necessary for the preparation of **249 – 251**. Hydrogen chloride, formed during the reaction,

was expelled from the reaction mixture by heating. The reaction of phosphorus trichloride with salicylamide in an equimolar ratio formed compound **249** as the sole product in good yield, while the reaction in a molar ratio of 2:1 led to formation of **250** in nearly quantitative yield. Treatment of **249** with further phosphorus trichloride also formed compound **250** by phosphorylation of the nitrogen atom [142].

In the same manner as described for the formation of **249**, the reaction of salicylamide with phosphorus oxychloride in equimolar ratio led to compound **251**, according to Scheme 26 [143].

By treatment of **249** with excess triethylamine, the formation of a cyclic derivative, containing a two-coordinated phosphorus atom, was observed, accompanied by subsequent elimination of hydrogen chloride. This formation was followed by immediate oligomerization, forming compound **249a** [144] (cf. Scheme 27):



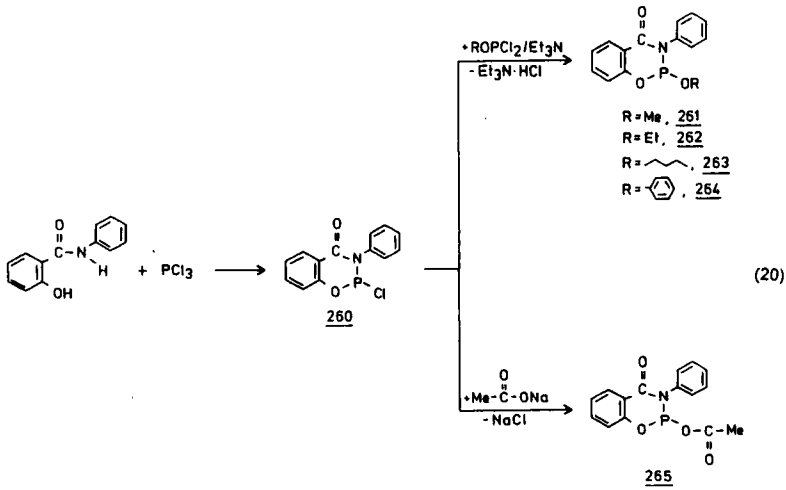
SCHEME 27

When **249a** was treated with dry, gaseous hydrogen chloride, the reverse reaction was observed, and the original acid chloride **249** was recovered.

When the oligomer **249a** was allowed to react with proton donors (e.g. Et_2NH) or halogen-containing reagents (e.g. PCl_3), the formation of compounds **250** and **252** via an addition reaction was observed [144]. Both compounds were already presented in Scheme 26.

The facile cleavage of the phosphorus-chlorine bond in **249** and **251** allowed further reactions of these compounds with secondary amines. According to Scheme 26, the reaction of **249** with different secondary amines led to the reaction products **252** [142,144] and **253 – 255** [143]. In all cases, an excess of amine was used, in order to bind the hydrogen chloride, formed during the reaction, as amine hydrochloride. In the same manner, **251** was allowed to react with diethylamine, bis(2-chloroethyl) amine, bis(2-hydroxyethyl)amine and morpholine to form compounds **256 – 259** (cf. Scheme 26) [143]. All reaction products, synthesized according to Scheme 26, were characterized unambiguously through their ^{31}P-NMR and IR-spectra, and elemental analyses. Compounds **253 – 259** were checked with regard to their cytostatic effect in animal tests [143].

According to Eqn. (20) the reaction of salicylic acid anilide with phosphorus trichloride led to the formation of the benzoxazaphosphorine **260** [145]:

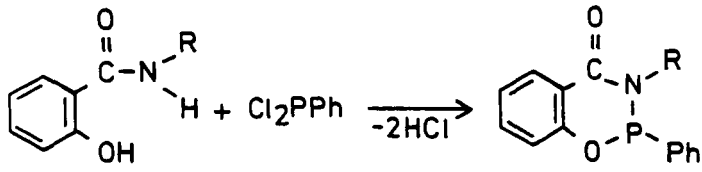


(20)

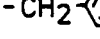
The reaction was carried out in hot benzene without addition of base. Further reaction of **260** with alkyl(phenyl)dichlorophosphites in the presence of triethylamine as a base led to the 2-alkoxy(phenoxy)-3-phenyl-5,6-benzo-1,3,2-oxazaphosphorin-4-ones **261 – 265** [145]. Compound **262** could also be obtained by treatment of **260** with ethanol in the presence of triethylamine. Compound **265** was obtained by reaction of **260** with sodium acetate.

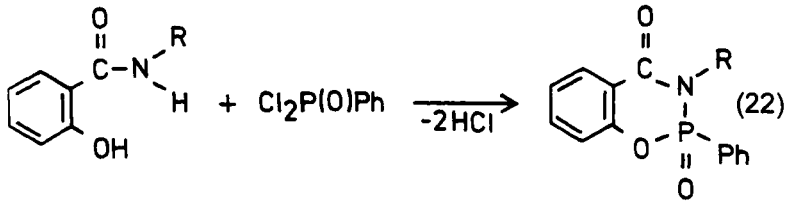
Previously it was shown [146] that the cleavage of salicylic acid and formation of the trialkyl phosphite occurred when alkyl o-benzoylene phosphites were treated with alcohol. The mixed cyclic anilides thus obtained reacted in a similar manner. From compound **262** and two molecules of alcohol, the anilide of salicylic acid and triethyl phosphite was obtained. The reaction of **262** with chlorine gave the corresponding phosphorus(V) derivative, 2-chloro-3-phenyl-5,6-benzo-1,3,2-oxazaphosphorin-4-one-2-oxide. Compound **264** also added chlorine, but the addition product could not be isolated in a pure state. Treatment of the crude adduct with acetic anhydride gave acetyl chloride, which confirmed the presence of P-Cl-bonds. The phosphorus-containing product was not isolated in this case due to the marked tarring of the reaction products [145].

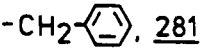
The reaction of salicylic acid amides with dichlorophenyl phosphine and dichlorophenyl phosphine oxide led, according to Eqns. (21) and (22) to the 2-phenyl-3-R-2,3-dihydro-1,3,2-benzoxazaphosphorin-4-one and –4-one-3-oxide derivatives **266** – **285** [147]:



(21)

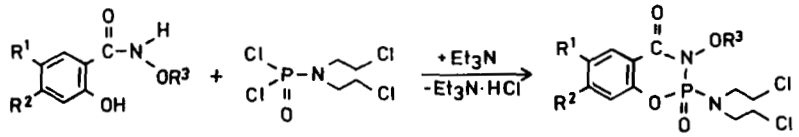
R=H, 266
R=Me, 267
R=Et, 268
R=$CH_2CH_2CH_3$, 269
R=  , 270
R=  , 271
R=  , 272
R=  , 273
R=$-NH_2$, 274
R= NH-Me, 275



R=H, 276
R=Me, 277
R=Et, 278
R=$CH_2CH_2CH_3$, 279
R=  , 280
R=  , 281
R=  , 282
R=  , 283
R=$-NH_2$, 284
R=-NH-Me, 285

Investigations about the synthesis of **266 – 285** proved the importance of using well dried solvents and starting compounds in order to achieve high yields of reaction products. Although N-methylsalicylic amide and $Cl_2P(O)Ph$ reacted very fast, in general, it was necessary to heat the reaction mixtures several hours to reflux temperature. The use of triethylamine, in order to bind the HCl formed, shortened the reaction time but reduced the yields by about 10–20%. The synthesis of compounds **266 – 275** (Eqn. (21)) occurred in quite good yield (>60%), while the reaction of N-methylsalicylic acid and $Cl_2P(O)Ph$ produced products only in moderate yield [147].

Some of the compounds, synthesized according to Eqns. (21) and (22) were investigated with regard to their pharmacological and antineoplastic effects [147]. The reaction of nitrogen-substituted salicylic amides with bis(2-chloroethyl)phosphoramide dichloride led, according to Eqn. (23), to the benzoxazaphosphorinone oxides, **286 – 289** [148]:

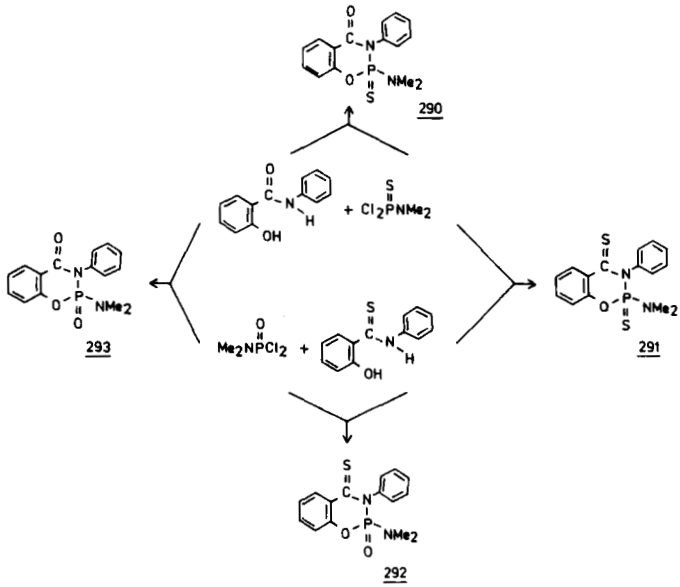


R^1	R^2	R^3	Nr
Cl	H	Me	286
H	Cl	Me	287
Cl	H	~	288
H	Cl	~	289

(23)

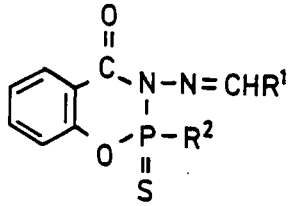
The reaction was conducted in the presence of triethylamine as a base. The synthesis of the bicyclic cyclophosphamide analogous products **286 – 289** was carried out in order to investigate their pharmacological properties [148].

Salicylamide was allowed to react with N,N′-dimethylphosphoramidothioic dichloride in the presence of triethylamine. Results from the identification of the crude product by thin layer chromatography, column chromatography and spectrometry, and by comparison with standard compounds indicated that not only two but four products (**290 – 293**) were formed under the above reaction conditions (Scheme 28) [149].

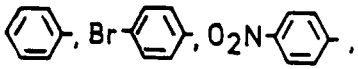


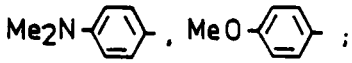
SCHEME 28

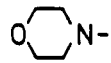
Based on the fact that thiophosphoryl chloride can be used as a sulfurizing agent for the transformation of amides into thioamides by its conversion to phosphoryl chloride [150], it is reasonable to assume that the four products are resulting from the combination of both sulfurization and cyclocondensation reactions as shown in Scheme 28.

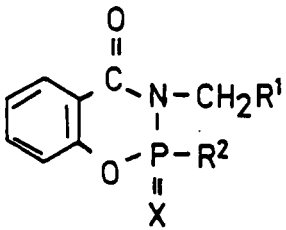


I

R^1 = 

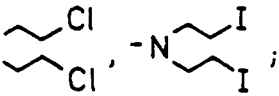


R^2 = Me_2N-, 



II

R^1 = heterocyclyl ;

R^2 = -OEt, $-NMe_2$,  ;

X = O, S

FIGURE 25 General types of benzoxazaphosphorinones, I and II

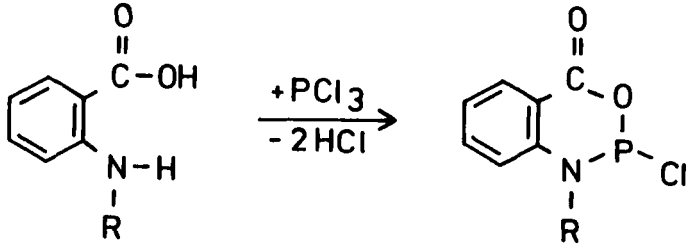
When an attempt was made to obtain product **291** by treating **290** with N,N-dimethylphosphoramidothioic dichloride under the aforementioned reaction conditions, **291** was not found, and only **290** was recovered. This result suggests that **291** was produced by the cyclocondensation of N,N-dimethylphosphoramidothioic dichloride with the intermediate thiosalicylanilide formed during the reaction.

The synthesis of a number of further benzoxazaphosphorinones of type **A** (Fig. 24) was described by some Chinese authors [151,152]. They are compounds of the general types **I** [151] and **II** [152] according to Fig. 25.

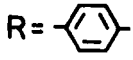
Because both references [151,152] are available only in the Chinese language (no English translation exists), only information from Chemical Abstracts can be presented here.

3.3. 1,2-Disubstituted 1,3-dihydro-4H-1,3,2-benzoxazaphosphorin-4-ones

Compounds of type **B** (Fig. 24) can be obtained by reaction of anthranilic acid or its nitrogen substituted derivatives and phosphorus halides. As described for the reaction of salicylic acid amide and phosphorus trichloride (cf. Chapter 3.2) the reaction of anthranilic acid or N-methyl anthranilic acid with phosphorus trichloride (Eqn. (24)) formed the corresponding 2-chlorobenzoxazaphosphorinones **294, 295** [153,154] and **296** [129]:



(24)

R = H, 294
R = Me, 295
R =  OEt, 296

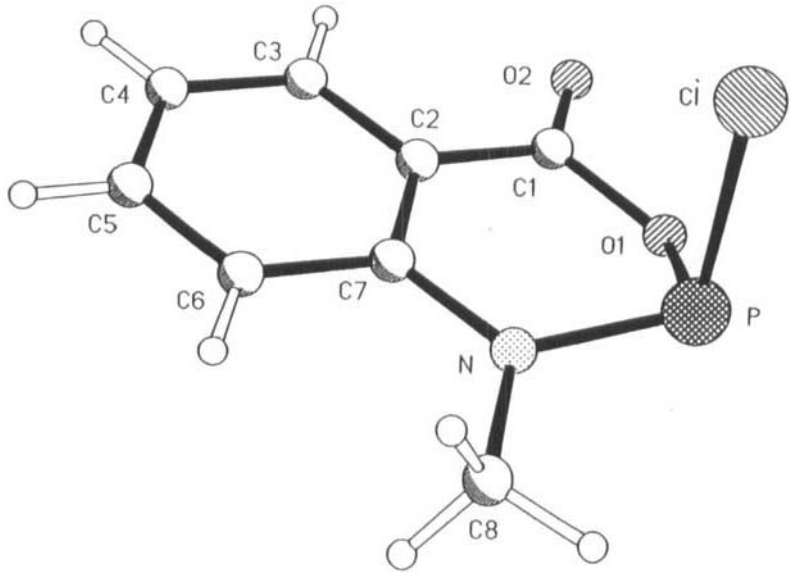
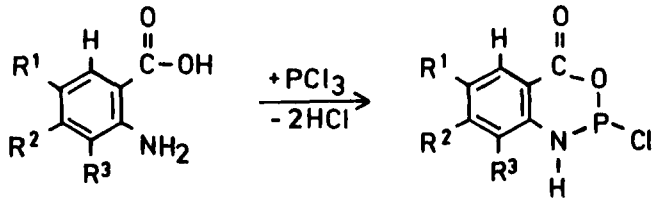


FIGURE 26 Structure of compound **295** in the solid state

The reaction products were characterized by ^{1}H-, ^{31}P-NMR and IR-spectroscopy, and by elemental analysis. For **295**, an X-ray crystal structure analysis was conducted (Fig. 26).



(25)

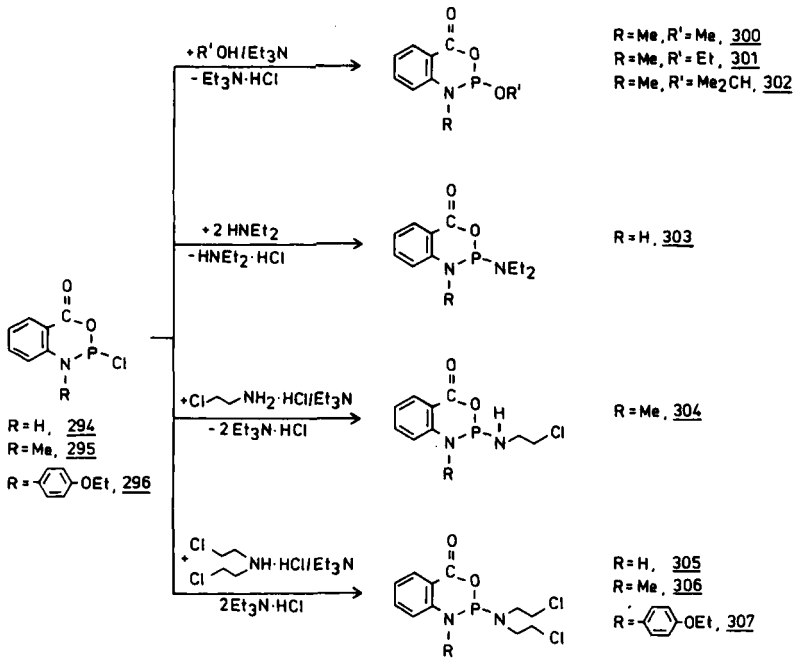
R^1	R^2	R^3	Nr
H	Cl	H	297
Cl	H	H	298
Cl	H	Cl	299

According to Eqn. (25), the reaction of some anthranilic acid derivatives, differently substituted at their aromatic ring system, and phosphorus

trichloride, led to the same results as described above [155]. All 2-chlorobenzoxazaphosphorinones **297** – **299** were isolated in good yield and characterized unambiguously by spectroscopic methods (NMR, IR, MS), and by elemental analysis.

Reactions of 2-chloro-1,3-dihydro-4H-1,3,2-benzoxazaphosphorin-4-one with alcohols or amines

The substitution of the chlorine atom in **294** – **296** by different groups R was effected in different ways, according to Scheme 29:



SCHEME 29

The reaction of **295** with different alcohols in the presence of triethylamine as hydrogen chloride acceptor, formed the corresponding phosphoramidites **300** - **302** [153]. Compound **303** was formed by reaction of **294** with excess diethylamine by simultaneous formation of diethylamine hydrochloride. An attempt to purify **303** by distillation failed. Decomposition and formation of diethylamine was observed [154].

The 2-chloroethylamino-substituted compounds **304 – 307** could be synthesized by reaction of **294 – 296** with the hydrochlorides of 2-chloroethyl amine and bis(2-chloroethyl)amine (Scheme 29) [129,156]. 2-Chloroethyl-substituted amino compounds were investigated intensively for some time because of their alkylating and, therefore, cytostatic effect (cf. Chapter 5). In order to synthesize **304 – 307**, the hydrochloride salts of the amines, mentioned above, were used, because the free amines are not stable at room temperature. By slow addition of triethylamine during the reaction of **295** and 2-chloroethylamine hydrochloride, the corresponding amine was released and the formation of **304 – 307** in good yield took place. Apart from NMR spectroscopic and mass spectrometric characterization of **304 – 307**, an X-ray crystal structure determination was carried out for **306** in order to prove the proposed structure (Fig. 27) [156].

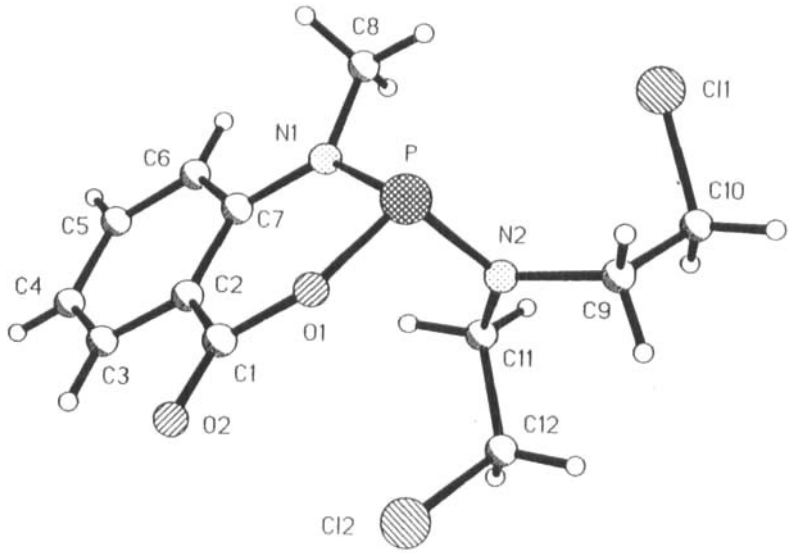
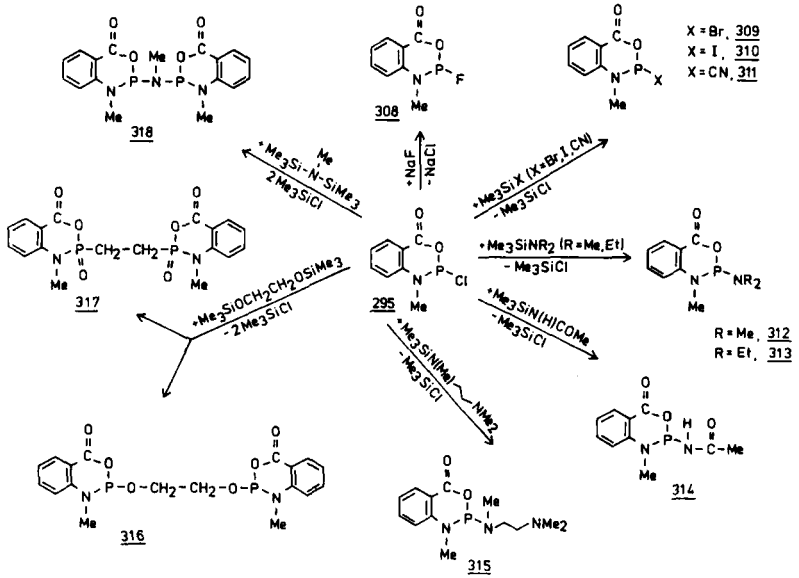


FIGURE 27 Structure of compound **306** in the solid state

It is noted that the heterocycle does not show the typical envelope conformation, but is nearly planar. The mean deviation from a plane through all ring atoms is only 3.0 pm.

Reactions of 2-chloro-1-methyl-1,3-dihydro-4H-1,3,2-benzoxazaphosphorin-4-one with trimethylsilylated compounds

The reaction of **295** with different trimethylsilylated compounds led to a multitude of substitution products (Scheme 30):



SCHEME 30

The advantage of reactions according to Scheme 30 is a proton-free course. Thus, the P-N- and P-O-bond cleavage reactions frequently observed and the formation of amine hydrochloride salts were avoided, which is often a reason for problems in purifying the products and for decreased yields. In all cases except one, a product of the reactions, presented in Scheme 30, is trimethylchlorosilane which can easily be removed by distillation.

The exchange of the chlorine atom in **295** via fluorine was possible by reaction of **295** with NaF in acetonitrile [157]. Although, P-Cl and P-F bond enthalpies are quite different and the relation is thermodynamically favourable (P-Cl 322 KJ/mole; P-F 503 KJ/mole [158]), the reaction is kinetically hindered because of the high energy transition state. It was necessary to use excess fluoride ion, and to heat the reaction mixture for several hours in order to isolate **308** in satisfactory yield.

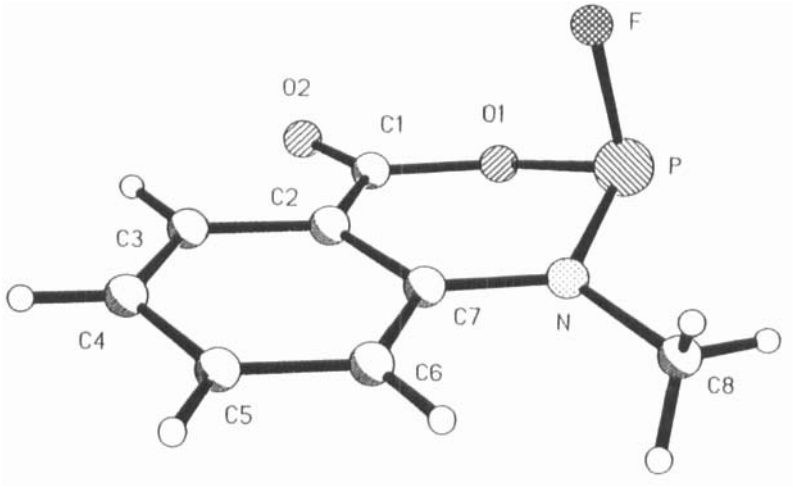


FIGURE 28 Structure of compound **308** in the solid state

For the formation of the analogous compounds of the heavier halogens **309** and **310**, the high driving force of formation of trimethylchlorosilane was utilized. As reagents for the reaction with **295**, bromo- and iodotrimethylsilane were used. The reaction products, **309** and **310**, could only be isolated in moderate yields [157]. The reaction of **295** with trimethylsilyl cyanide required drastic reaction conditions (high temperature), in order to synthesize **311** in good yield [157].

For compounds **295, 306, 308** and **311**, X-ray crystal structure determinations were conducted (Figs. 26 – 29) and the results were discussed in comparison [156,157]. Compounds **312** – **315**, containing exocyclic P-N-bonds, were formed in the same manner by reaction of **295** with trimethylsilyl substituted amines according to Scheme 30 [157].

The reaction of **295** with 1,2-bis(trimethylsiloxy)ethane in a molar ratio of 2:1 led to compounds **316** and **317** [156]. The formation of both **316** and **317** was postulated, based on ^{31}P-NMR spectroscopic observations. A detailed discussion of the structures **316** und **317** was impossible, because neither ^{1}H-NMR nor mass spectra and elemental analyses of both compounds differ significantly. The lack of solubility of the isolated products made it impossible to record a ^{13}C-NMR spectrum. It could not be proved beyond doubt whether **316** and **317** were formed independently from each other in approximately equal amounts, or if at first only compound **316** is

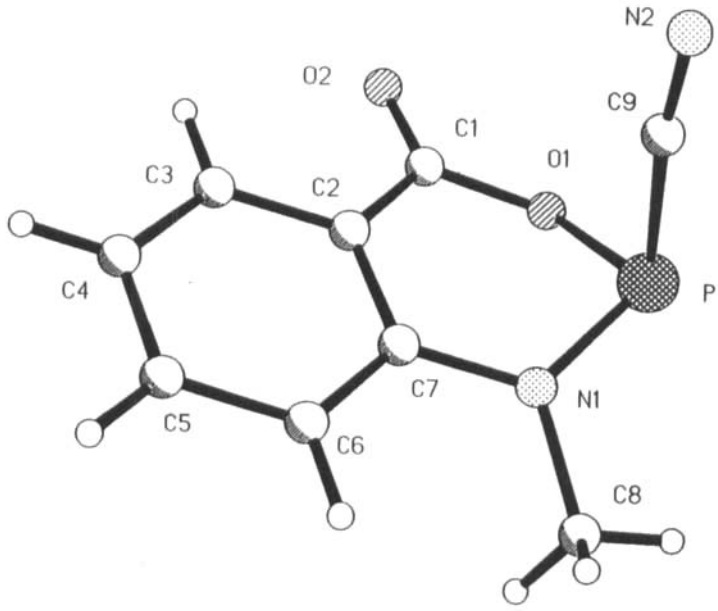


FIGURE 29 Structure of compound **311** in the solid state

formed, which rearranges, in part, into the phosphoryl compound **317** [156]. The reaction of **295** with heptamethyl disilazane led to **318** [156] (Scheme 30). Instead of an ethylene group (as in **316** and **317**), the methylamino group acts as a bridge between two benzoxazaphosphorinone units in **318**. Because of the absence of oxygen atoms in the bridging chain of **318**, the formation of structural isomers, as observed for **316/317**, was not possible.

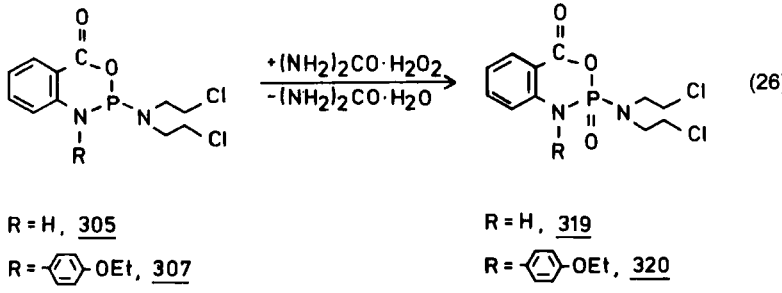
3.3.1. Oxidation reactions of 1,3-dihydro-4H-1,3,2-benzoxazaphosphorine-4-ones

Reactions with hydrogen peroxide or hydrogen peroxide-urea-1:1-adduct

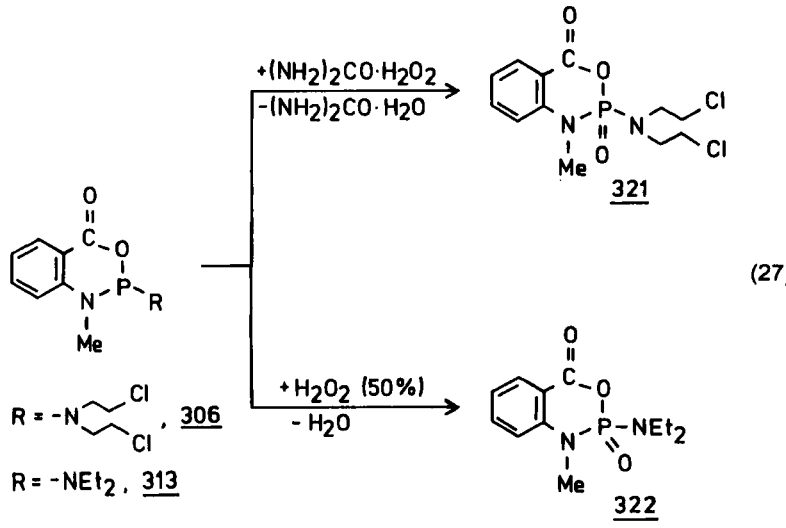
The oxidation of phosphorus(III) compounds to phosphoryl systems can be effected by aqueous hydrogen peroxide solution or by hydrogen peroxide-urea-1:1-adduct. In the former case, the reaction takes place in an aqueous medium, while in the latter case, an anhydrous reaction is ensured.

In order to avoid hydrolytic cleavage of the C-Cl bond or cleavage reactions on the heterocyclic system, the hydrogen peroxide-urea-1:1-adduct was chosen to form the phosphoryl systems **319 – 321** (Eqns. (26) and (27)) by oxidation of the phosphorus atoms in **305 – 307**. Compounds **319, 320** [129] and **321** were isolated in good yields and characterized by the usual methods [156].

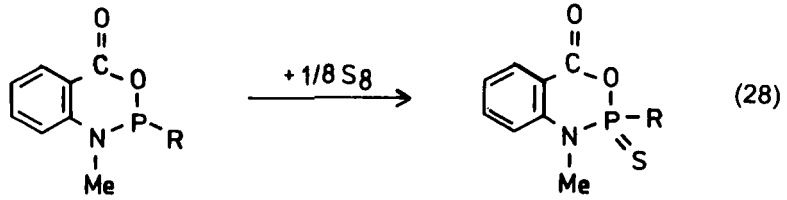
For the synthesis of **322, 313** was allowed to react with aqueous hydrogen peroxide solution. Compound **322** was isolated only in moderate yield. The use of $(NH_2)_2CO.H_2O_2$ as oxidizing agent under anhydrous conditions did not notably increase the yield of the reaction product. It is noted that, according to Eqn. (27), oxidation of **306** occurs in much higher yield than oxidation of **313**, independent of the oxidizing agent, although both starting compounds differ only in the terminal group of the diethylamino ligand [156].



(26)



(27)



(28)

R = NMe_2, **312**
R = NEt_2, **313**
R = N(H)COMe, **314**
R = N(Me)⌒NMe_2, **315**

R = NMe_2, **323**
R = NEt_2, **324**
R = N(H)COMe, **325**
R = N(Me)⌒NMe_2, **326**

The formation of **323** – **326** occurred according to the usual methods [156] by reaction of the corresponding starting compounds **312** – **315** with elemental sulfur (Eqn. (28)). All compounds, **323** – **326**, were characterized unambiguously. For **325**, an X-ray crystal structure determination was conducted (Fig. 30). Apart from an unusual planarity of the heterocycle, intramolecular hydrogen bonds between the hydrogen atom of the NH-grouping and the carbonyl oxygen atom of the N(H)COMe-grouping were observed [156].

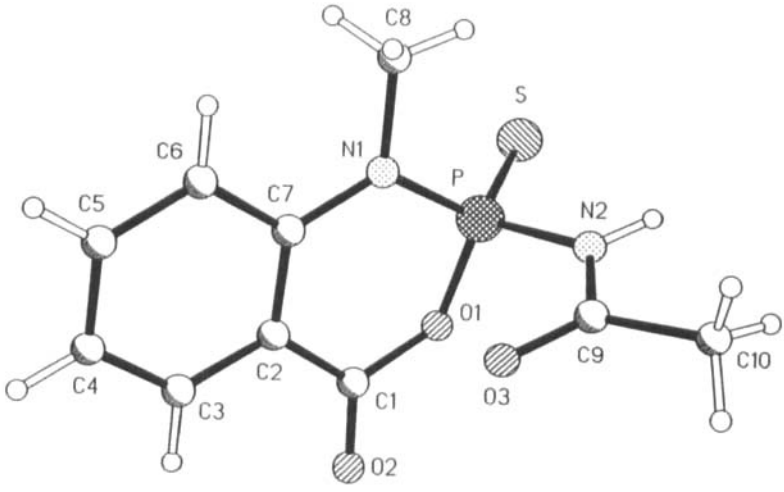
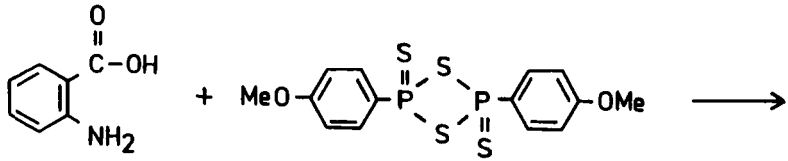


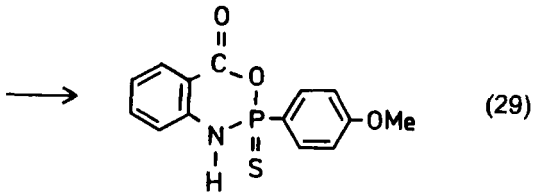
FIGURE 30 Structure of compound **325** in the solid state

Reactions with Lawesson's reagent

It has been found, that 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide (Lawesson's reagent) [159] is a most effective thiation reagent for ketones [160], carboxamides [161–164], esters [165–167], S-substituted thioesters [165], lactones [168], lactams [169], imides [169], enaminones [170], hydrazides [171], and hydrazones [172]. It also undergoes ring closure reactions with substrates containing two functional groups [167].

In contrast to previous observations, no thiation was observed in the reaction of Lawesson's reagent with anthranilic acid. According to Eqn. (29), benzoxazaphosphorin-4-one-2-sulfide **327** was formed [159]:





(29)

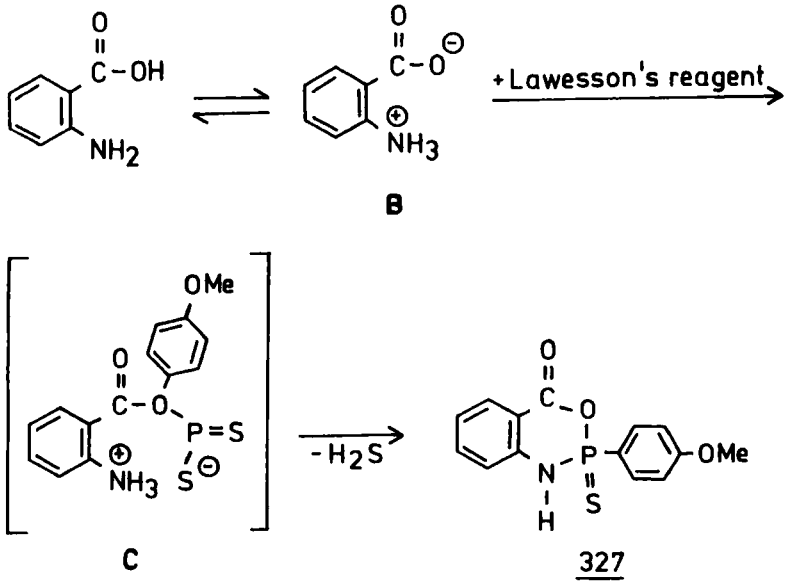
327

The structural proof for **327** is based on ^{1}H-, ^{13}C-, ^{31}P-NMR, IR-spectroscopy, and mass spectrometry. A mechanism for the formation of **327** is proposed in Scheme 31 [159].

It is assumed, that the carboxylate of the betaine **B** attacks Lawesson's reagent at phosphorus and not, as usual, at sulfur, giving a salt **C**, which at elevated temperature loses H_2S to give **327**. This reaction represents an unusual mode to form thiophosphoryl compounds of benzoxazaphosphorines.

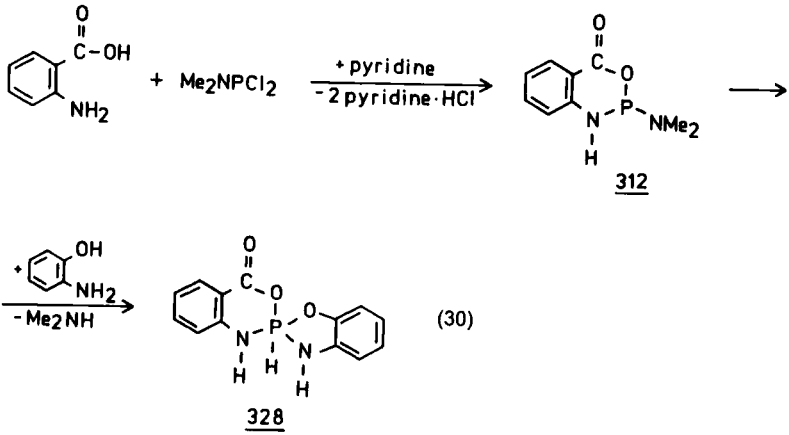
Reactions with orthoaminophenol

As shown in Eqn. (30), the reaction of anthranilic acid with dimethylamino dichlorophosphine led, at first, to the expected but not isolated



SCHEME 31

dimethylamino-substituted benzoxazaphosphorinone, **312**. Further reaction with orthoaminophenol led to the spirophosphorane, **328** [173]:

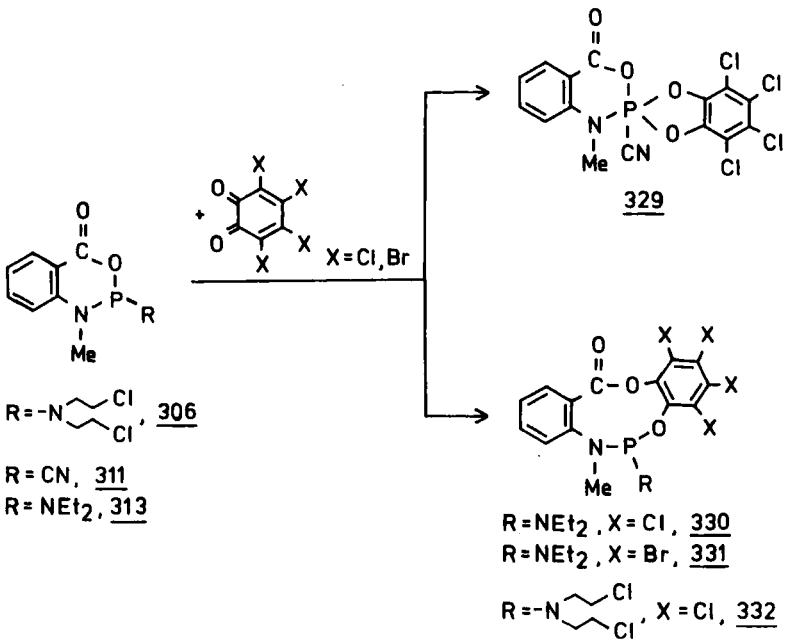


(30)

The reaction of **312** with o-aminophenol was unusual, because after separation of diethylamine and formation of a P-H bond, the spirophosphorane **328** was obtained. Although spirophosphoranes with a P-H bond are not stable in case their ring systems contain more than five atoms [174,175], **328** could be isolated and characterized. The stability of **328** was explained by the possibility of distribution of electron density by conjugation over both ring systems and the carbonyl group [173]. Compound **328** is the first stable spirophosphorane, exhibiting a P-H bond and bearing a ring system, consisting of more than five atoms.

Reactions with orthobenzoquinones

Only in one case, the reaction of 1-methyl-2-R-1,3-dihydro-4H-1,3,2-benzoxazaphosphorin-4-ones differently substituted at phosphorus with ortho-benzoquinones led, by oxidative addition of the quinone system to phosphorus, to the expected spirophosphorane. According to Scheme 32, reaction of **311** with tetrachloro-o-benzoquinone formed compound **329** [155].



SCHEME 32

The reaction of **306** with tetrachloro-o-benzoquinone and of **313** with tetrachloro- and tetrabromo-o-benzoquinone revealed unusual behaviour. In these cases, insertion of the quinone system into the heterocyclic ring of the phosphorus component and subsequent formation of a nine-membered heterocycle, containing a phosphoryl grouping, was observed. The unusual reaction behaviour presumably results from the low stability of the heterocyclic systems of **306, 311** and **313**. Thus, cleavage of a carbon-oxygen bond and insertion of the quinone is favoured and, according to Scheme 32, the formation of **330, 331** [176] and **332** [155] takes place.

Similar results were obtained by reaction of benzodioxaphosphorinones with carbonyl compounds. Insertion reactions of the carbonyl component into the heterocyclic system, accompanied by ring expansion, were observed [31]. For **330** as a representative compound, resulting from the unusual reaction presented in Scheme 32, an X-ray crystal structure determination was carried out (Fig. 31) which confirmed the proposed molecular structure [176].

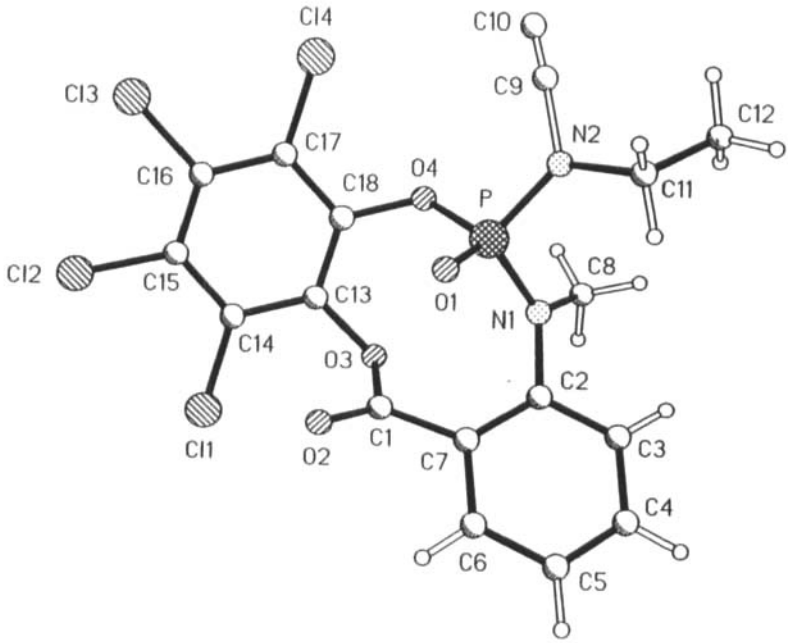
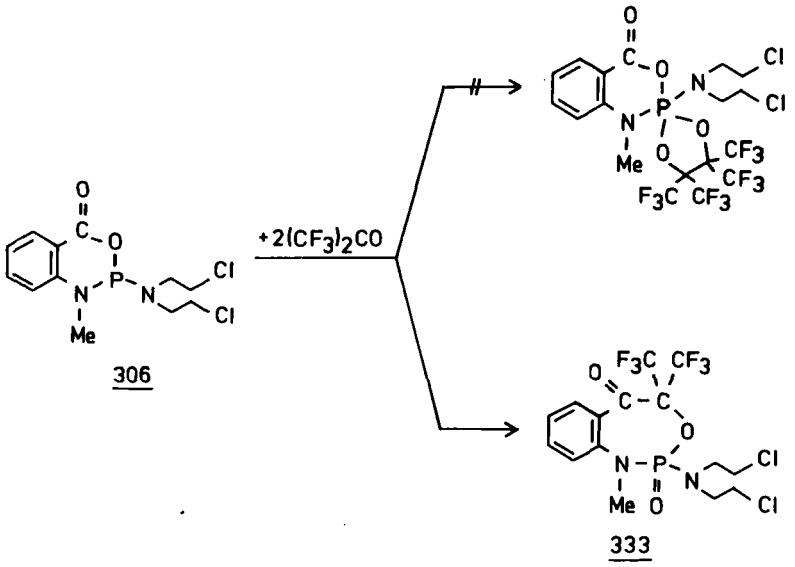


FIGURE 31 Structure of compound **330** in the solid state

Reactions with hexafluoroacetone

Similarly to observations made for the oxidative addition reactions of tetrachloro-o-benzoquinone towards **306**, the reaction of **306** with hexafluoroacetone did not lead to the expected bis(2-chloroethyl)amino substituted spirophosphorane.

Rather, as demonstrated in Scheme 33, by insertion of one molecule of hexafluoroacetone, an expansion of the phosphorinone ring by rearrangement (P-C → P-O-C), formation of a new C-C bond, and formation of **333** took place [178]:



SCHEME 33

The same reaction behaviour was previously observed only for dioxaphosphorinone derivatives [31,179] and for a diazaphosphetidinethione derivative [180]. With the formation of **333**, an oxazaphosphepine ring system was accessible for the first time, whose structure was confirmed by an X-ray crystal structure determination (Fig. 32) [179].

Reactions with perfluorinated α-diketones

Oxidative addition reactions of perfluorinated α-diketones with 1,3,2-oxazaphosphorinones were not known until now. Very interesting

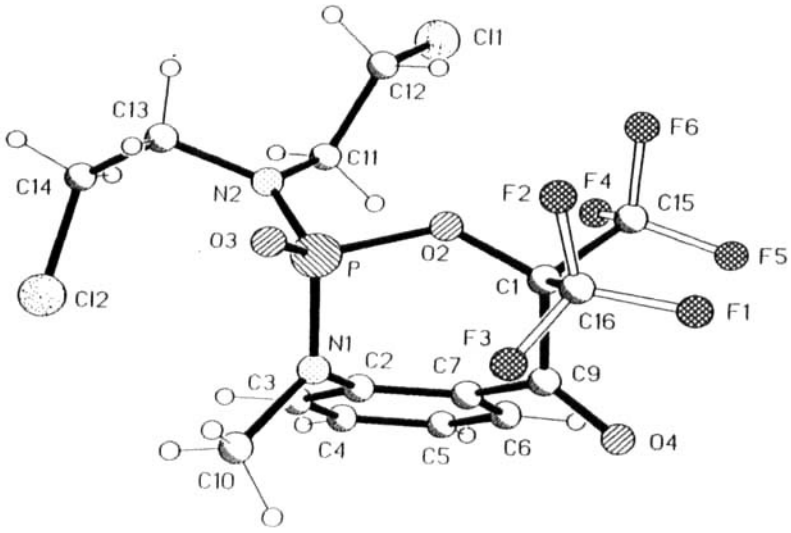
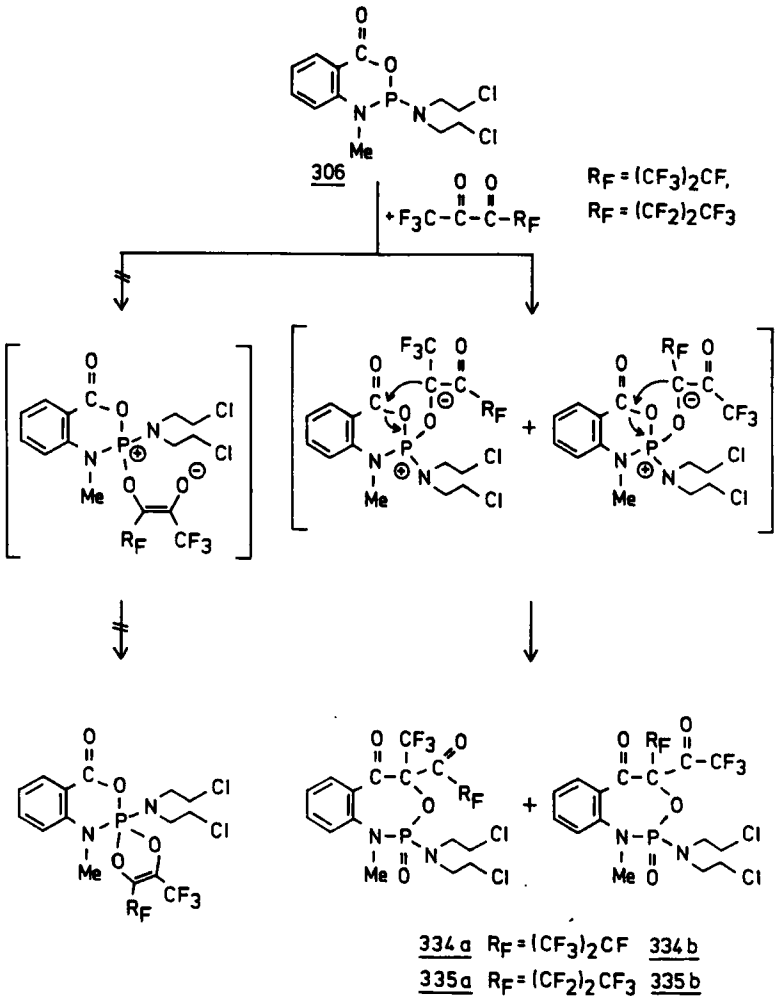


FIGURE 32 Structure of compound **333** in the solid state

proved the reaction of **306** with perfluoro-1-isopropyl-2-methyldiketone and perfluoro-1-propyl-2-methyldiketone. As shown in Scheme 34, the isomeric mixtures **334a/b** and **335a/b** [178] were formed under mild conditions in these cases.

An oxidative insertion reaction took place. An oxidative addition reaction and formation of spirophosphoranes (cf. Scheme 34) was not observed. A reaction mechanism, presented in Scheme 34, was proposed for the formation of **334a/b** and **335a/b**. In a primary step, the C=O-group is added to phosphorus by formation of the intermediates, written in brackets. The transition state was proved by ^{31}P-NMR spectroscopy during the reaction. The rearrangement of the cyclic P-O bond (P-O $\rightarrow$ P=O) in the intermediates and subsequent formation of a new C-C bond leads to expansion of the phosphorinone ring and formation of a seven-membered ring system. Identity and constitution of the isomeric mixtures **334a/b** and **335a/b** were confirmed by elemental analysis as well as mass spectrometry, IR-, ^{1}H-, ^{13}C-, ^{19}F- and ^{31}P-NMR spectroscopic investigations [178].



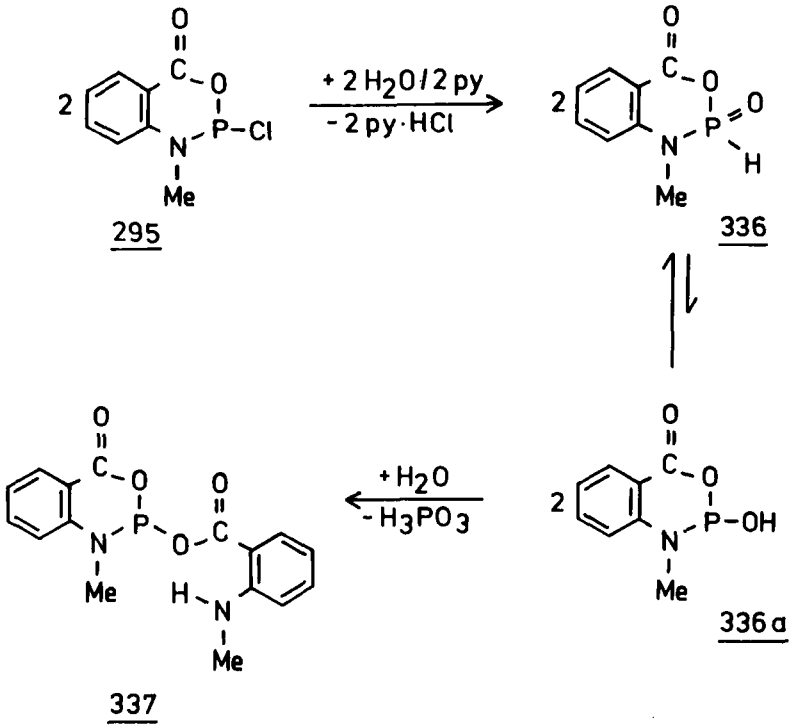
SCHEME 34

The proportion of the isomers **334a** and **335a** was much larger than that of the isomers **334b** and **335b** (ratio *ca.* 90%/10%). The reason for this observation is attributed to the higher polarizability of the $CF_3C(:O)$-group, compared to that of the $R_FC(:O)$-group ($R_F \neq CF_3$) in the diketones [178].

3.3.2. Unusual reactions of 2-chloro-1-methyl-1,3-dihydro-4H-1,3,2-benzoxazaphosphorin-4-one, 295

Reaction with water

The careful hydrolysis of **295** yielded, by substitution of the chlorine atom, compound **336**, which is in equilibrium with the tautomeric form **336a** (cf. Scheme 35) [176]:



SCHEME 35

The stability of **336** is quite low. Exposure of a solution of **336** in dichloromethane to moist air led to the observation of **337** after one day. Presumably, the reaction of two molecules of **336** (via the tautomeric form **336a**) formed, with participation of water and separation of phosphoric acid, compound **337**, by simultaneous cleavage of one of both heterocycles. The presence of phosphoric acid was proved in the reaction mixture by ^{31}P-NMR spectroscopy. Compound **337** was characterized by ^{1}H- and

^{31}P-NMR spectroscopy, by mass spectrometry, and by an X-ray crystal structure determination (Fig. 33) [176].

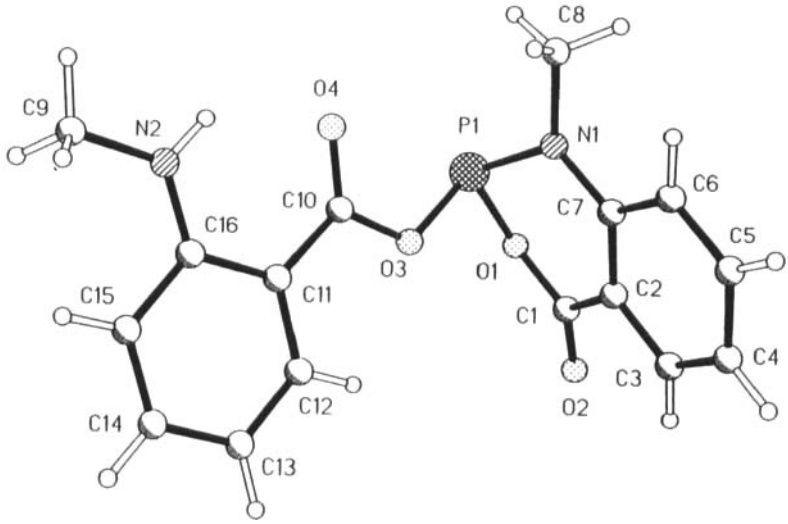
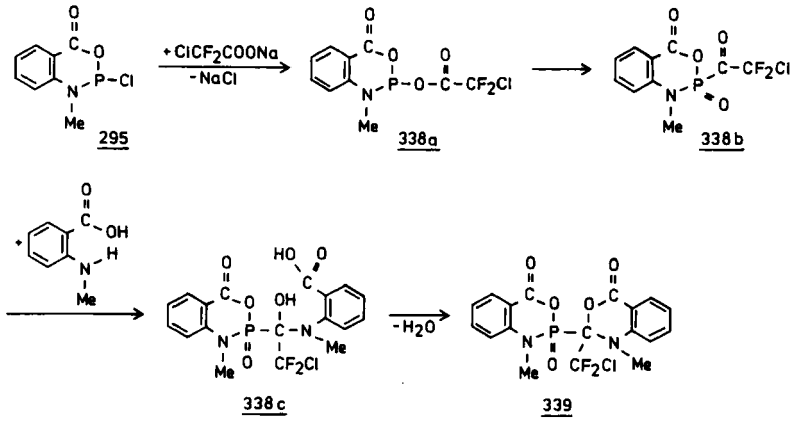


FIGURE 33 Structure of compound **337** in the solid state

Reaction with sodium chlorodifluoro acetate

According to Scheme 36, the reaction of **295** with sodium chlorodifluoro acetate should lead to compound **338a**, which, however, could not be observed. Instead, compound **339** was formed in an unusual way (Scheme 36) [176].

The formation of **339** was explained by reaction via the (unstable) intermediate **338a** which is formed, presumably, during the reaction by substitution of a chlorine atom in **295** for the chlorodifluoro acetoxy group. Compound **338a** immediately reacts by rearrangement to form **338b**. Subsequently, **338b** reacts with N-methylanthranilic acid to the (equally unstable) intermediate **338c**, followed by separation of water and rearrangement to the final product **339**. Catalytic amounts of water favoured the formation of N-methylanthranilic acid from **338a**, explaining the reaction of **338b** to form **338c**. Water which results from the transformation of **338c** into **339**, can participate in the first reaction step, according to Scheme 36, and favours the formation of N-methylanthranilic acid. The identity of **339**



SCHEME 36

was proved unambiguously by an X-ray crystal structure determination (Fig. 34) [176].

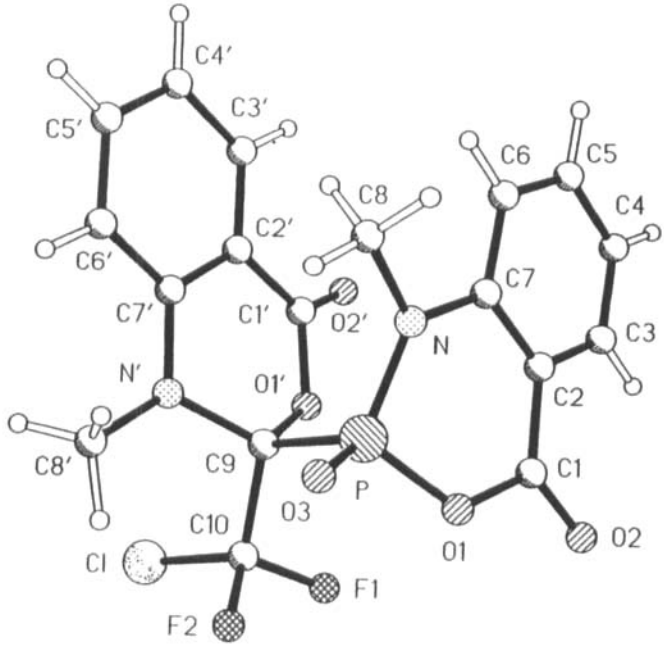
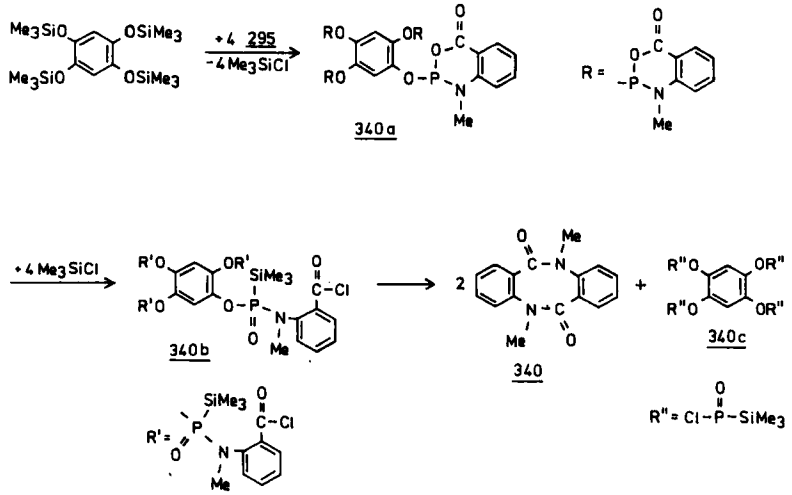


FIGURE 34 Structure of compound **339** in the solid state

Reaction with 1,2,4,5-tetrakis(trimethylsiloxy)benzene

According to Scheme 37, the reaction of **295** with 1,2,4,5-tetrakis(trimethylsiloxy) benzene did not lead to the expected compound **340a**, but to compound **340**, containing no phosphorus atom:



SCHEME 37

A reaction mechanism, depicted in Scheme 37, was proposed, based on ^{31}P-NMR spectroscopic and mass spectrometric data. The first reaction step is, presumably, the reaction of four molecules of **295** with 1,2,4,5-tetrakis(trimethylsiloxy)benzene with subsequent elimination of four molecules of trimethylchlorosilane and formation of an intermediate, **340a**. In an Arbuzov-type rearrangement, **340a** reacts with trimethylchlorosilane, formed in the first step, to form the (also unstable) intermediate **340b. 340b** forms, by intramolecular reaction, compounds **340** and **340c**. The existence of **340c** was confirmed by mass spectrometry (molecular ion) and ^{31}P-NMR spectroscopy. The main product **340** was characterized by elemental analysis and an X-ray crystal structure determination (Fig. 35) [176].

Reaction with 2,2′-bis(trimethylsiloxy)biphenyl

Unlike observations made for the reaction of 1,2,4,5-tetrakis(trimethylsiloxy) benzene with **295**, the reaction of **295** with 2,2′-bis(trimethylsi-

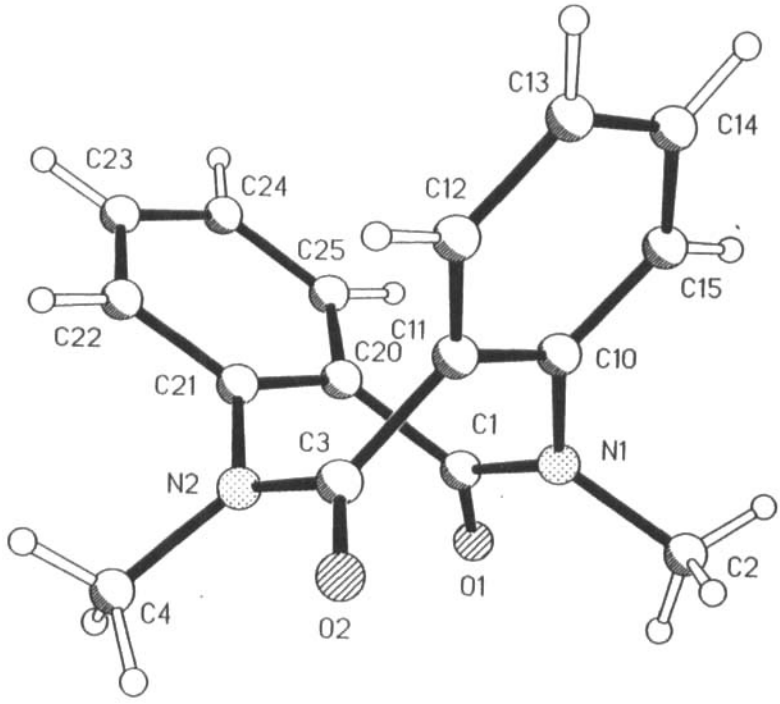
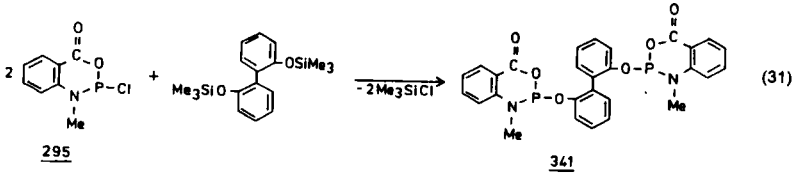


FIGURE 35 Structure of compound **340** in the solid state

loxy) biphenyl formed, according to Eqn. (31), by separation of trimethylchlorosilane, the expected compound **341**. The existence of **341** was proved by an X-ray crystal structure determination (Fig. 36) [176].



3.4. Metal complexes of benzoxazaphosphorinones

Similar considerations as for reactions with benzodiazaphosphorinones (cf. Chapter 2.8.) are made for reactions of the corresponding benzoxaza-

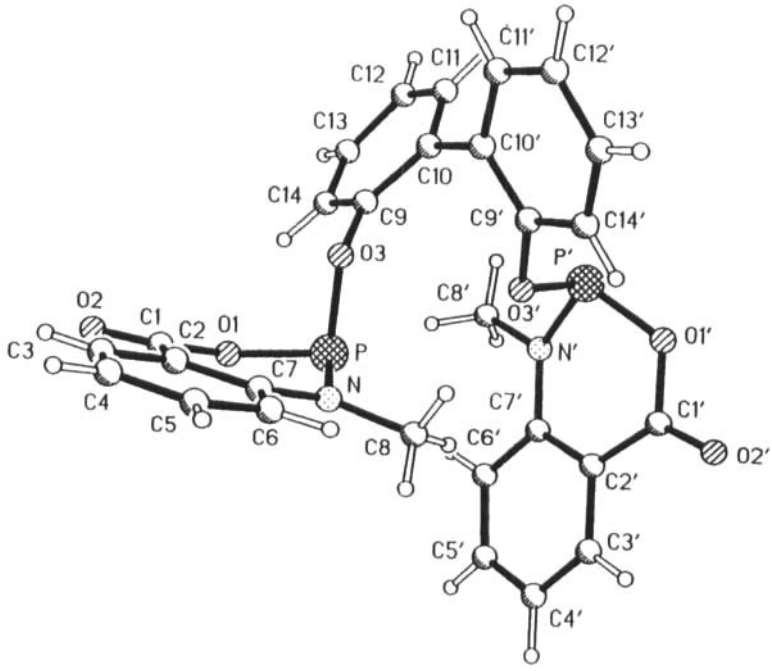


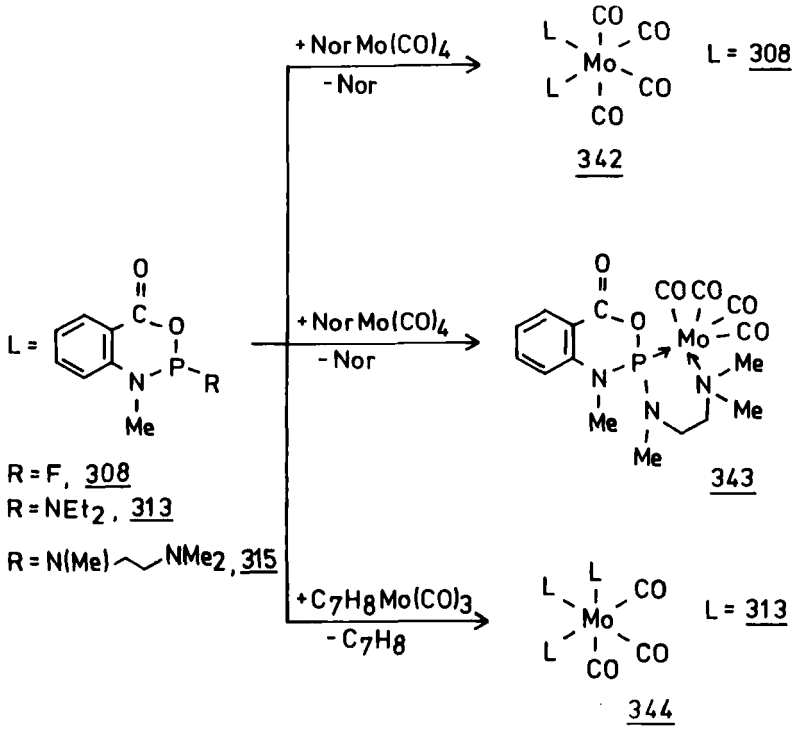
FIGURE 36 Structure of compound **341** in the solid state

phosphorinones with derivatives of transition metals. For benzoxazaphosphorinones, only coordination compounds containing molybdenum, platinum and gold are known until now. They are summarized in the following.

Reactions of olefin-molybdenum(0) carbonyl derivatives with substituted benzoxazaphosphorinones

According to Scheme 38, norbornadiene molybdenum tetracarbonyl (Nor)Mo(CO)$_4$ was allowed to react with **308** in a 1:2 molar ratio [181].

Although the nucleophilicity of the phosphorus atom in **308** is strongly reduced by the electron withdrawing effect of the fluorine substituent, compared to that of **313** and **315**, a short reaction time was sufficient in order to assure quantitative reaction in the synthesis of **342**. In contrast, the reaction of the related 1,3-dimethyl-2-fluoro-2,3-dihydro-1H-1,3,2-benzo-



SCHEME 38

diazaphosphorin-4-one **16** (with a more strongly nucleophilic phosphorus atom) with norbornadiene molybdenum tetracarbonyl required several days (cf. Chapter 2.8.). The cis-configuration of the coordination compound **342** (Scheme 38) was confirmed by ^{19}F- and ^{31}P-NMR spectroscopic investigations (characteristic magnitude of the PP-coupling constants). An X-ray crystal structure determination for **342** (Fig. 37) confirmed the postulated cis-conformation [181].

The reaction of **315** with norbornadiene molybdenum tetracarbonyl formed, according to Scheme 38, the chelate complex **343**, where coordination to the metal center takes place only by one ligand molecule **315** via the phosphorus atom and the nitrogen atom of the dimethylamino grouping. Similar reaction behaviour was observed for a 2-{[2-(dimethylamino)ethyl]methylamino}-1,3,2-benzodioxaphospholtetracarbonylchro-

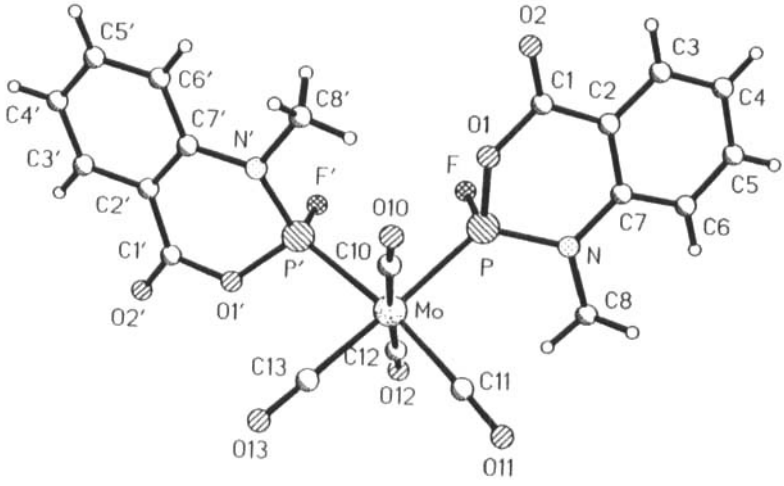


FIGURE 37 Structure of compound **342** in the solid state

mium(0)-complex [124]. The structure of **343** was confirmed, aside from NMR spectroscopy, mass spectrometry and elemental analysis, by an X-ray crystal structure determination (Fig. 38) [182].

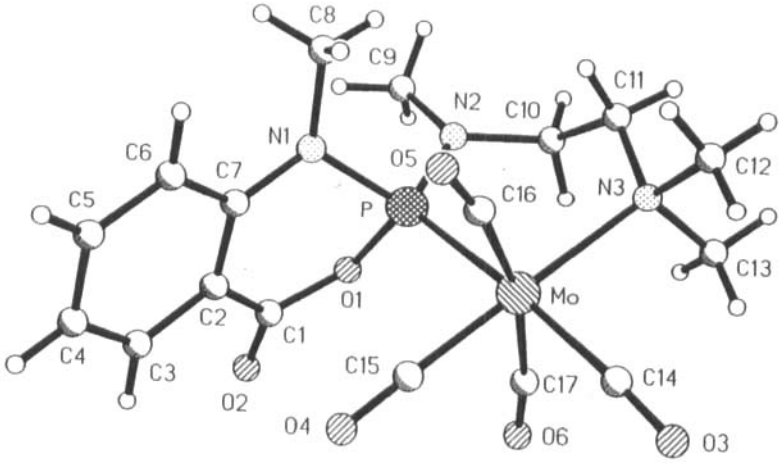


FIGURE 38 Structure of compound **343** in the solid state

The reaction of **313** with cycloheptatriene molybdenum tricarbonyl in a molar ratio of 3:1 formed, according to Scheme 38, several isomers. Aside from the expected fac-substituted product, the presence of the mer-substituted complex was established as well by ^{31}P-NMR spectroscopy. The formation of the fac-substituted complex is understandable, because of the decreasing effect on the ring strain in the sterically demanding coordination octahedron, due to this isomer [181]. Because the ^{31}P-NMR spectrum revealed several signals, the presence of rigid conformational isomers was assumed. It was not possible to separate these isomers by chromatography or fractional crystallization. Some crystals were obtained from the mixture of isomers, and one of them was investigated by an X-ray crystal structure analysis (Fig. 39). The fac-substituted isomer **344**, shown in Scheme 38, was confirmed [181].

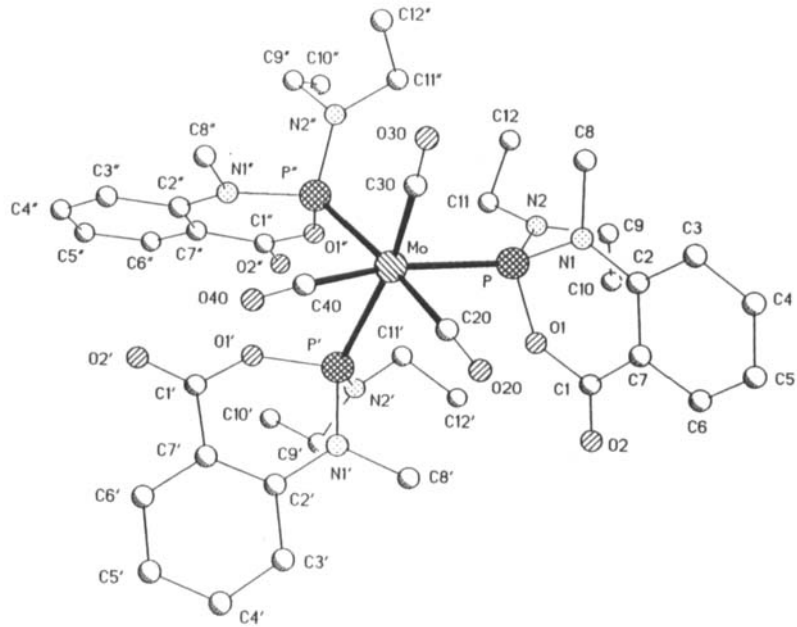
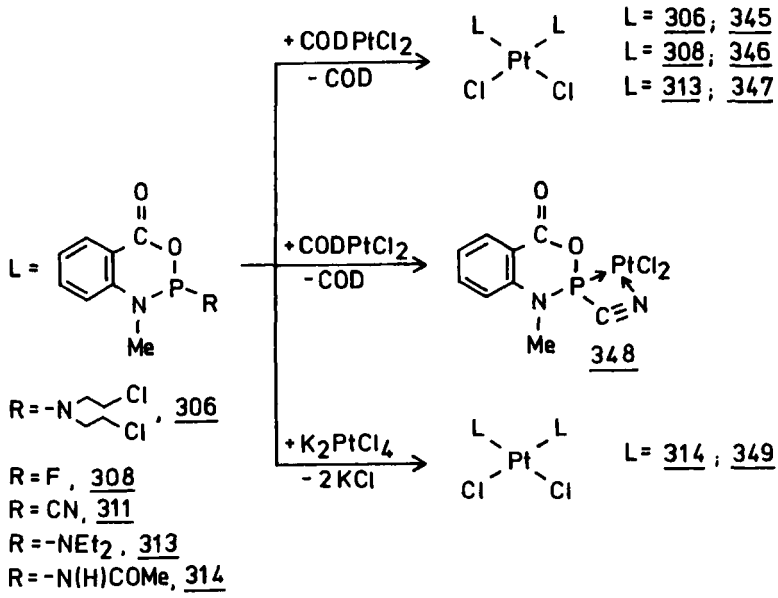


FIGURE 39 Structure of compound **344** in the solid state

Reaction of cyclooctadiene platinum dichloride {(COD)$PtCl_2$} with substituted benzoxazaphosphorinones

According to Scheme 39, several benzoxazaphosphorinones were allowed to react with (COD)$PtCl_2$ or K_2PtCl_4. Platinum(II) complexes of benzoxazaphosphorinones were isolated, comparable to those of benzodiazaphosphorinones (cf. Chapter 2.8.). In the same manner, the cis-substitution at the platinum metal in the coordination compounds was proved via the magnitude of ^1J(PtP)- and ^2J(PP) [181].



SCHEME 39

The reaction of **306, 308** and **313** with (COD)$PtCl_2$ yielded, in accord with Scheme 39, compounds **345 – 347** in good yield. Aside from NMR spectroscopic characterization, an X-ray crystal structure determination was carried out for **346**, providing evidence for the proposed structure (Fig. 40) [181].

The reaction of **311** with (COD)$PtCl_2$ was unusual. As described for the synthesis of **242** (Chapter 2.8.2.), coordination of only one ligand molecule **311** to platinum, via the phosphorus atom and the nitrogen atom of the

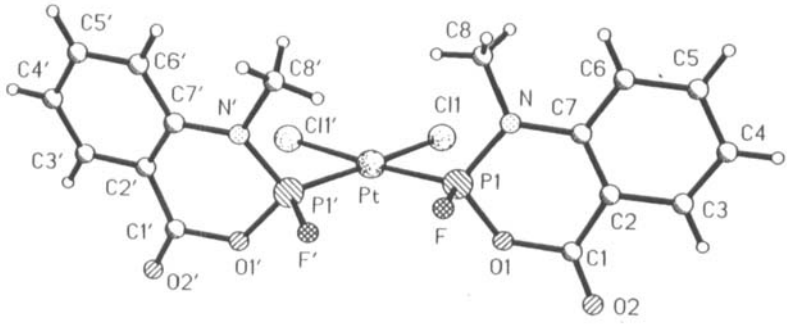


FIGURE 40 Structure of compound **346** in the solid state

cyanide group, was observed [53], leading to **348**. A reaction product of the type L_2PtCl_2 (L = ligand) was not observed.

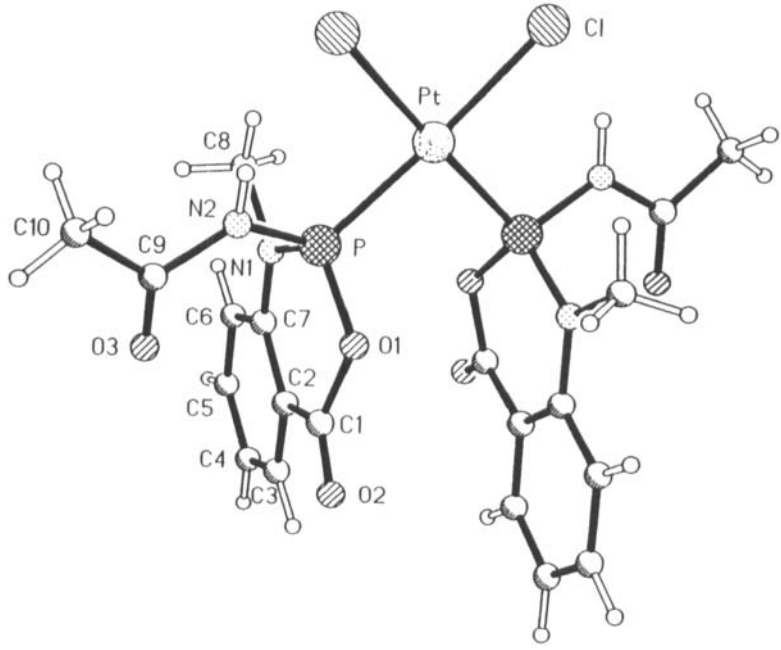


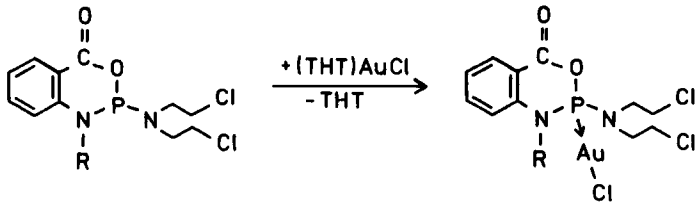
FIGURE 41 Structure of compound **349** in the solid state

The reaction of **314** with potassium tetrachloro platinate (K_2PtCl_4), conducted at room temperature, was significantly slower than analogous reactions with (COD)$PtCl_2$. Because of the lower reactivity of K_2PtCl_4, compared to (COD)$PtCl_2$, and the lower nucleophilicity of the phosphorus atom in **314**, caused by the electron withdrawing effect of the acetylamino group, **349** only could be obtained during a reaction time of no less than seven days [181]. The cis-configuration of **349** was established by ^{31}P-NMR spectroscopy, and by an X-ray crystal structure determination (Fig. 41) [181].

Reactions of tetrahydrothiophene chlorogold(I) {(THT)AuCl} with substituted benzoxazaphosphorinones

The reaction of the benzoxazaphosphorinones **305** and **306** with tetrahydrothiophene chlorogold(I) furnished, according to Eqn. (32), the same results, as observed for the corresponding reactions of benzodiazaphosphorinones with tetrahydrothiophene chlorogold(I) (cf. Chapter 2.8.). Compounds **350** [129] and **351** [115] were isolated and characterized. The reaction of **341** with (THT)AuCl formed, according to Eqn. (33), the gold complex **352** [176]. An X-ray crystal structure determination was carried out for **352** (Fig. 42), providing the first X-ray crystal structure of a gold-containing compound, bearing the benzoxazaphosphorinone ring system. The results were compared to those of the uncoordinated starting compound, **341** [176].

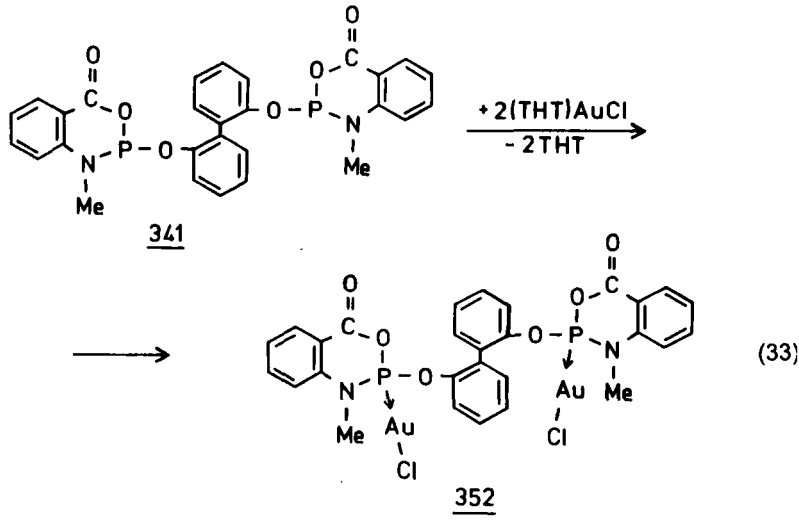
Compounds **350** – **352** are the first gold(I) coordination compounds, originating from a benzoxazaphosphorinone. Because of the presence of the bis(2-chloroethyl)amino grouping and the gold atom in **350** and **351**, these compounds are considered as potential cancerostatics.



(32)

R = H, **305**
R = Me, **306**

R = H, **350**
R = Me, **351**



341 352 (33)

4. BENZODIOXAPHOSPHORINONES

4.1. Introduction

Acyl derivatives of salicylic acid are used as drugs and microbiocides. Particular mention may be made of the use of acetylsalicylic acid as an analgesic and antipyretic. Many organophosphorus compounds show a wide spectrum of biological activity. The study of compounds whose molecules contain fragments of phosphorus acids and salicylic acid is of considerable interest in the search for new substances of practical importance. Although phosphorus derivatives of salicylic acid have been the subject of a large number of studies, the first review article about these compounds has been published only in 1992 [31]. Monographs on the chemistry of phosphorus compounds contain only few data on phosphorus derivatives of salicylic acid.

Phosphorus derivatives of salicylic acid deserve detailed examination not only because of their known and variable biological activity but also because of their unique reactivity, which differs sharply from that of the common acyl derivatives of phosphorus.

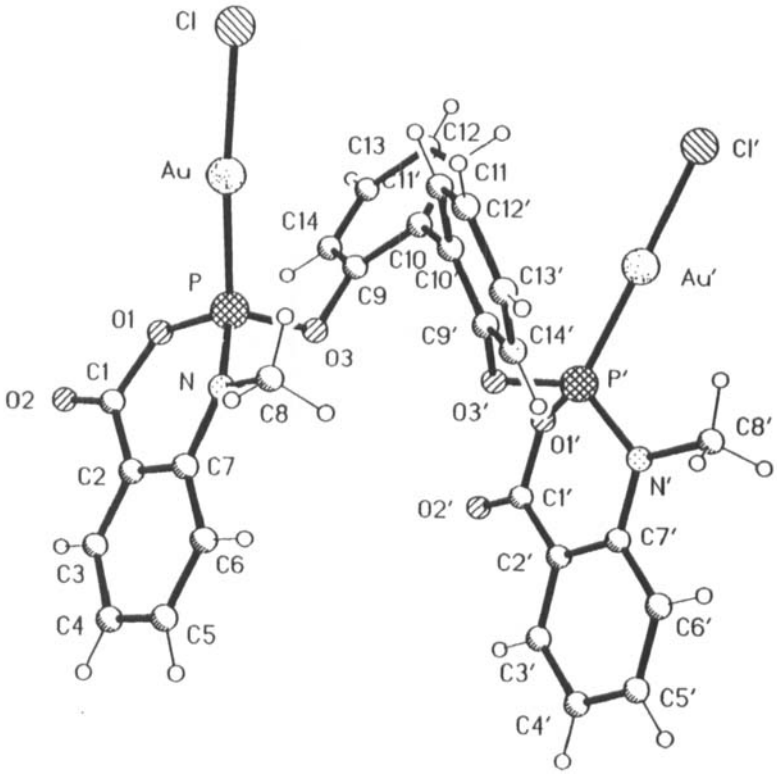


FIGURE 42 Structure of compound **352** in the solid state

Salicylic acid, unlike other hydroxybenzoic acids, contains in the ortho-position two functional groups capable of reacting with a central phosphorus atom to give cyclic and acyclic phosphorus-containing derivatives. The chemical properties of phosphorus-containing derivatives of salicylic acid are determined to a large extent by their cyclic or acyclic structure, and also depend on the coordination state of the phosphorus atom.

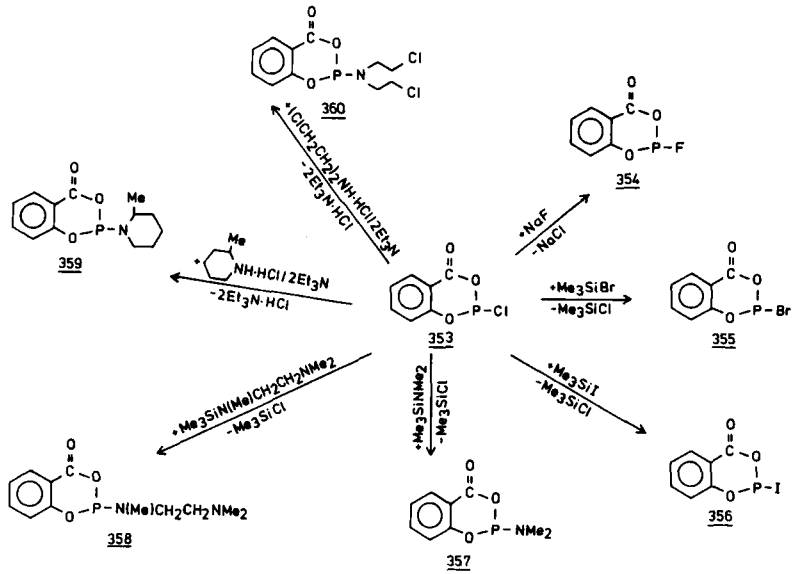
Because the chemistry of phosphorus derivatives of salicylic acid has been reviewed recently [31], in the following only some fundamental papers will be discussed, which appeared during the last few years and, therefore, are not covered in the review article mentioned above.

Phosphorus derivatives of salicylic acid were first obtained by Anschütz and his co-workers more than 100 years ago [183] by the reaction of sali-

cylic acid with phosphorus trichloride. This reaction can give several products, whose structures have been studied by a number of authors [183–192]. The main product of the reaction of salicylic acid and phosphorus trichloride is the 2-chloro-4H-1,3,2-benzodioxaphosphorin-4-one **353.** Compound **353** is the precursor for all reactions described in the following.

4.2. Substitution of chlorine in 2-chloro-4H-1,3,2-benzodioxaphosphorin-4-one 353

The reaction of 2-chloro-4H-1,3,2-benzodioxaphosphorin-4-one, **353**, with different reagents formed, according to Scheme 40, the substitution products **354 – 360** [193]:



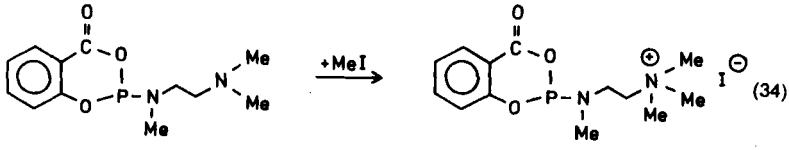
SCHEME 40

Although compounds **353 – 355** have been known for a long time, the synthesis was repeated in order to enable their characterization by modern spectroscopic methods [193]. Compound **354**, whose synthesis by reaction of **353** with potassium fluorosulfinate (KSO_2F) is known [194], could be

synthesized in yields twice as high by reaction of **353** with sodium fluoride in acetonitrile. NMR spectroscopic and mass spectrometric data of **354** were determined for the first time. Similarly, the synthesis of **355** from **353** and trimethylbromosilane was carried out in much higher yield, unlike by the known method [190] (reaction of salicylic acid and phosphorus tribromide). Characterization of **355** by ^{1}H-, ^{13}C- and ^{31}P-NMR spectroscopy as well as mass spectrometry completed the analytical data of this compound. The iodine compound, **356**, analogous to **353** – **355**, was synthesized by reaction of **353** with trimethyliodosilane, but could not be isolated. Spontaneous decomposition at room temperature with simultaneous elimination of elemental iodine was observed. The existence of **356** in the reaction mixture was proved by ^{1}H- and ^{31}P-NMR spectroscopy at –20 °C.

The reaction of **353** with primary or secondary amines in the presence of a base was described only in two cases [188,195]. Purification of the reaction products did not succeed in both cases. In contrast, the reaction of **353** with dimethylaminotrimethylsilane and N-trimethylsilyl-N,N′,N′-trimethylethylenediamine led, for the first time, to 2-dialkylamino substituted benzodioxaphosphorinones in high purity. The reaction of **353** with 1-methylpiperidine hydrochloride and bis(2-chloroethyl) amine hydrochloride formed compounds **359** and **360**, with **359** as an oily product. ^{13}C- and ^{31}P-NMR investigations on **359** confirmed the presence of two rotational isomers in solution, which could not be separated from each other.

During the reaction of **358** with methyl iodide, the formation of the ammonium iodide, **361**, was observed, according to Eqn. (34). The same behaviour was observed for the reaction of the corresponding diazaphosphorinone, **27**, with methyl iodide (cf. Chapter 2.5.). An alkylation of the phosphorus atom of **358** was not observed by ^{1}H-NMR spectroscopy.



358 **361** (34)

Attempts to react different amino-substituted derivatives of benzodioxaphosphorinones with norbornadiene molybdenum (or chromium) tetracarbonyl, or coordination compounds of platinum(0) and platinum(II), were

less successful. Displacement of norbornadiene by formation of phosphorus- and/or amino-substituted molybdenum (or chromium) tetracarbonyl complexes could be proved by NMR spectroscopy. A defined product could not be isolated from either of the reaction mixtures. Presumably, the reduced stability of the benzodioxaphosphorinone skeleton did not allow a uniform course of reaction. The presence of an electron-withdrawing carbonyl group in the heterocycle reduces the electron density at phosphorus to such a degree that no defined reaction product could be observed by ^{31}P-NMR spectroscopy.

A reaction of **357, 358** and **360** with cyclooctadiene platinum dichloride and potassium tetrachloro platinate could not be observed by NMR-spectroscopy, not even after a reaction time of four weeks at room temperature. Only the ^{31}P-NMR resonances of the starting compounds were observed [193].

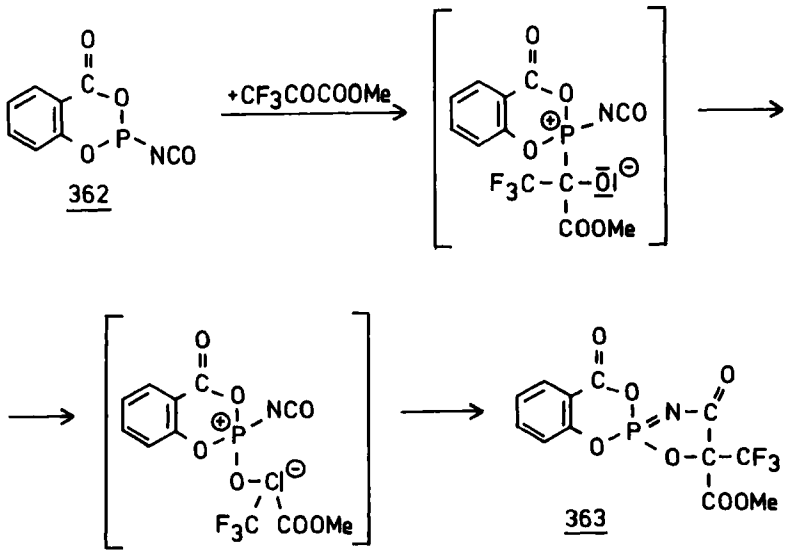
4.3. Reactions of 2-isocyanato-substituted 1,3,2-benzodioxaphosphorin-4-one, 362

2-Isocyanato-4H-1,3,2-benzodioxaphosphorin-4-one **362** was synthesized for the first time by reaction of the corresponding 2-chloro-derivative with sodium cyanate [196]. The reaction of **362** with methyl trifluoropyruvate formed, according to Scheme 41, compound **363** as product [196]. It is supposed that the reaction proceeds through an intermediate dipolar ion, subsequent phosphonate-phosphate rearrangement and the closure of a five-membered heterocycle with a P=N bond (cf. Scheme 41). The dynamics of the reaction of **362** with the trifluoropyruvic ester were studied by means of ^{31}P-NMR spectroscopy.

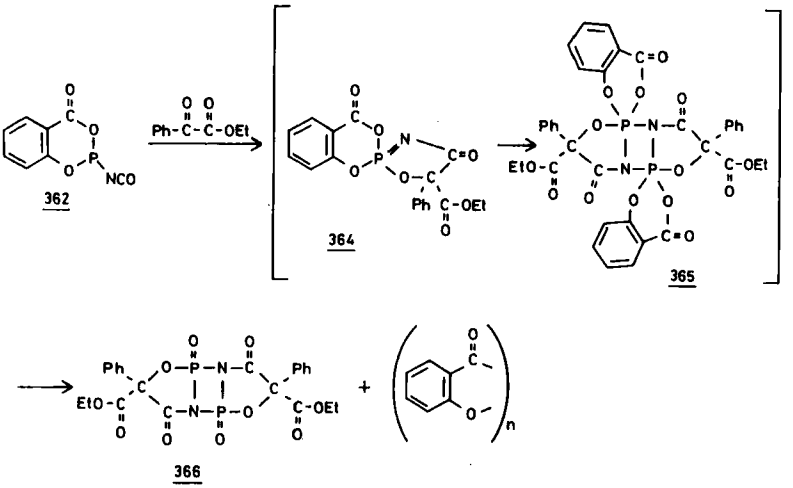
The reaction of **362** with α-ketocarboxylic esters, hexafluoroacetylacetone, salicylaldehyde and dimethyl trichloroacetylphosphonate as carbonyl reagents is described in ref. [197].

When **362** was allowed to react with ethyl benzoylformate, a crystalline solid was obtained according to Scheme 42. The isolated product was assigned the structure of the diazadiphosphetidine **366**.

The reaction is accomplished probably through the formation of the intermediate 1,3,2-dioxaphospholene, **364**, with a P=N bond, which undergoes dimerization to the diazadiphosphetidine, **365**. The latter decomposes under the reaction conditions with elimination of the salicylic fragment to give the final product, **366**. Diethyl mesoxalate reacts with **362** under

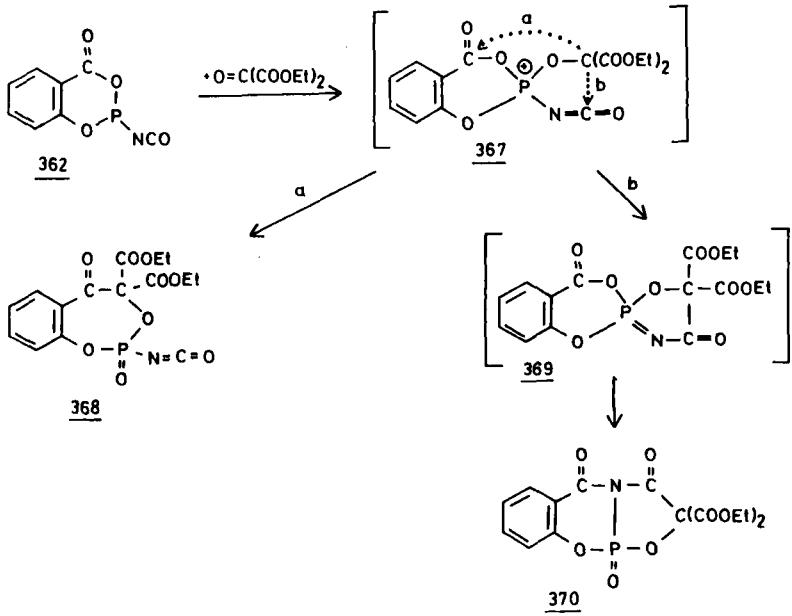


SCHEME 41



SCHEME 42

milder conditions and, according to Scheme 43, two products are formed in a ratio of ca. 60:40: 1,3,2-dioxaphosphepane, **368**, and phosphabicyclononane, **370**.



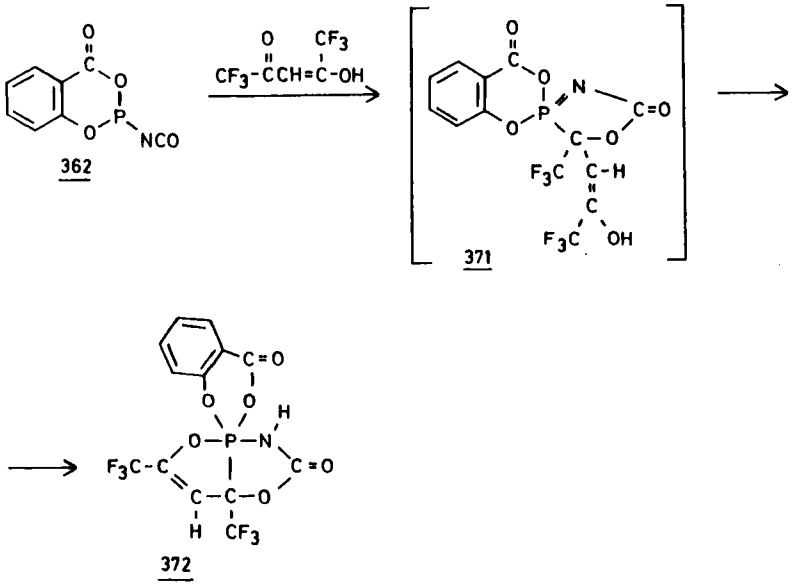
SCHEME 43

The carbanionic center in zwitterion **367**, which is formed by rearrangement of the initial zwitterion with the $^{+}$P-C-O^{-} bond, may attack either the endocyclic carbon (pathway a) or the exocyclic cumulenic carbon (pathway b). Pathway a gives 1,3,2-dioxaphosphepane, **368**. Pathway b leads, through the intermediate bicyclic dioxaphospholene **369** with a P=N bond, to the other reaction product, phosphabicyclononane, **370**.

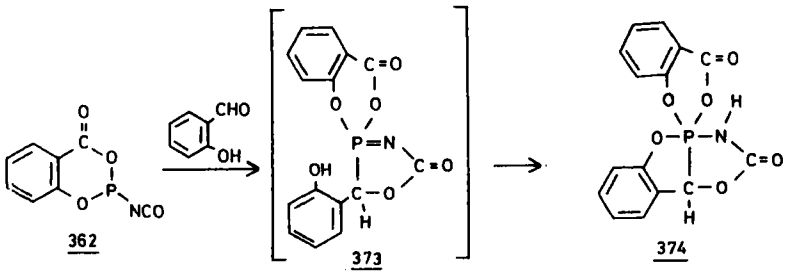
According to Scheme 44, the phosphite **362** reacts with hexafluoroacetylacetone specifically. Only the isocyanato group participates in the reaction with the salicylic fragment remaining unchanged.

This reaction proceeds similarly to the reaction of dimethyl phosphorisocyanatidites with hexafluoroacetylacetone, namely, at the carbonyl group of the β-diketone to form a five-membered ring with a P=N bond (compound **371**). Subsequent cyclization involving the enolic hydroxyl results in compound **372** with a five-coordinate phosphorus atom.

The stable crystalline solid compound **374** with a five-coordinate phosphorus atom was obtained in the reaction of **362** with salicylaldehyde (Scheme 45).



SCHEME 44

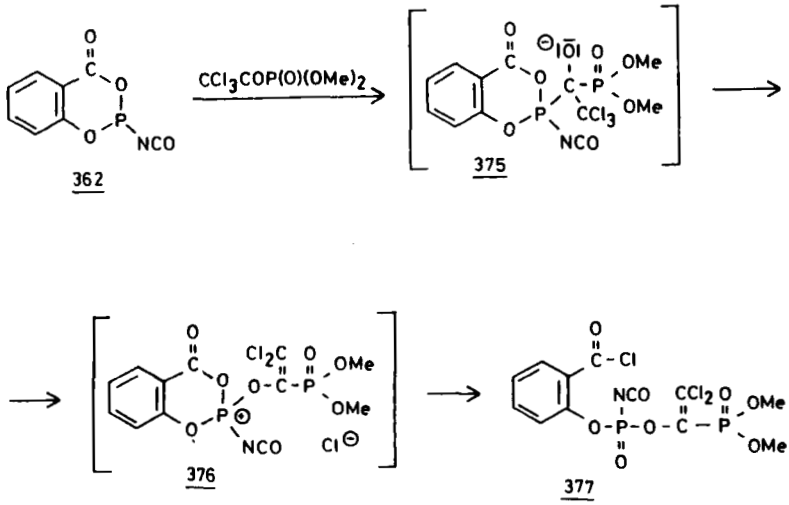


SCHEME 45

Compound **374** is formed, probably, by intramolecular addition of the phenolic hydroxy group to the P=N bond of the intermediate **373**.

Upon reaction with dimethyl trichloroacetylphosphonate **362** undergoes the Perkov reaction to give **377** (Scheme 46).

It is presumed that the attack by the P(III) atom on the carbonyl carbon results in the formation of the dipolar ion **375** with the $^{+}$P-C-O^{-}bond,



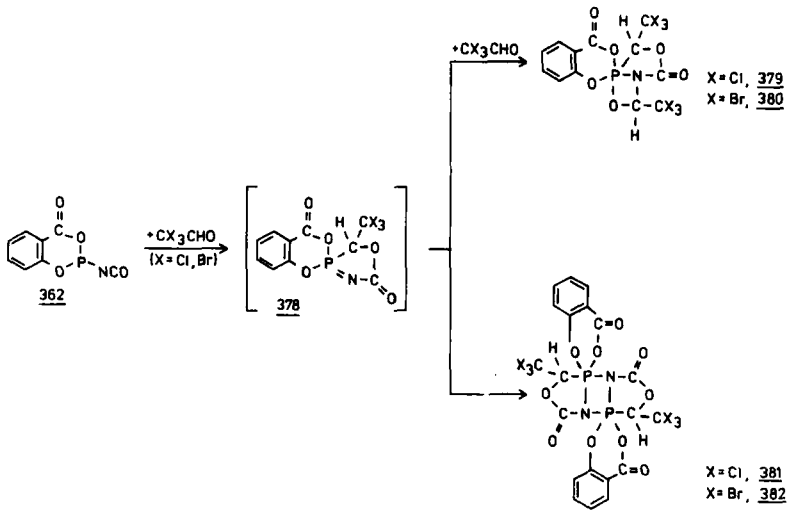
SCHEME 46

which is rearranged into the zwitterion with the P-O-C bond faster than the attack by the anionic center C-O⁻ on the carbonyl groups occurs. Zwitterion **376** is stabilized through cleavage of the anhydride fragment. Thus, in the reaction of **362** with dimethyl trichloroacetylphosphonate, cleavage of the salicylic ring occurs, where the acyl fragment is the leaving group.

When **362** was allowed to react with chloral and bromal, the course of the reaction was found to depend on the reaction conditions. Under mild conditions, the substituted diphosphatricyclodecanes **381** and **382** were obtained by condensation of equimolar amounts of the reactants. Under more vigorous conditions the reactants, by reaction in a 1:2 molar ratio, formed the substituted phosphabicyclo-heptanes **379** and **380** according to Scheme 47 [196].

By contrast, alkoxy-substituted 1,3,2-benzoxazaphosphorin-4-ones react with chloral with expansion of the ring to give a phosphepine ring [31,198].

Mixtures of monomeric and dimeric products were isolated when a stream of hexafluoroacetone was passed through a solution of **362** in dichloromethane at -25°C [196]. However, when alkoxy-substituted 1,3,2-benzoxazaphosphorin-4-ones were allowed to react with hexafluoroacetone, expansion of the ring was observed, accompanied by a P-C→P-O-C rearrangement to give a new C-C bond [195,199].



SCHEME 47

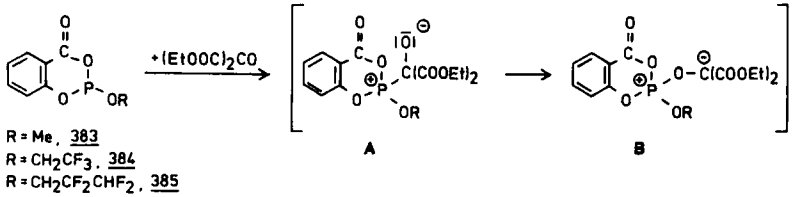
4.4. Reactions of 2-alkoxy-4H-1,3,2-benzodioxaphosphorin-4-ones with diethyloxomalonate

2-Alkoxy-4H-1,3,2-benzodioxaphosphorin-4-ones were recently shown [195,198] to be applicable to the preparation of novel seven-membered heterocycles, 1,4,2- and 1,3,2-dioxaphosphepanes, which can be used in the synthesis of functionally substituted ketones, and, in particular, of hexafluoroisopropyl-2-hydroxyphenyl ketone [199]. In the following, results are presented of an investigation of the reactions between the phosphorine derivatives **383 – 385** and diethyl oxomalonate [179].

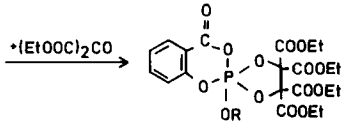
It turned out that diethyl oxomalonate readily reacted with compounds **383 – 385** to give the pentaalkoxyphosphoranes **386 – 388** (Scheme 48) [179].

Since such phosphoranes with a salicylic fragment were unknown, their structure was conclusively confirmed by ^{13}C-NMR spectroscopy.

When the reaction described in Scheme 48 was performed at uncontrolled temperatures (up to 140°C), new signals appeared in the ^{31}P-NMR spectra, suggesting thermal decomposition of the phosphoranes **386 – 388**. In the case of compound **387** the decomposition product was isolated by distillation. According to NMR spectral and elemental analysis data this



R = Me, 383
R = CH_2CF_3, 384
R = $CH_2CF_2CHF_2$, 385



R = Me, 386
R = CH_2CF_3, 387
R = $CH_2CF_2CHF_2$, 388

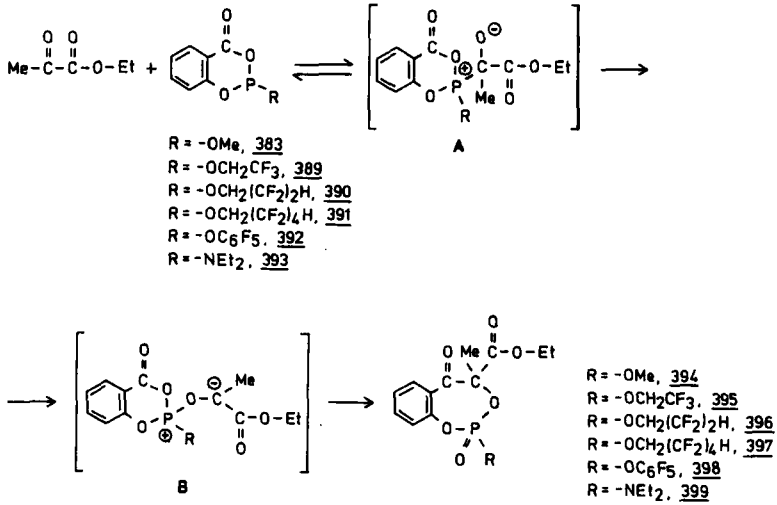
SCHEME 48

product was 2-(trifluoroethoxy)-4,4,5,5-tetrakis(ethoxycarbonyl)-1,3,2-dioxaphospholane-2-oxide, a compound containing no salicylic fragment [179].

4.5. Reactions of 2-substituted 4-oxo-5,6-benzo-1,3,2-dioxaphosphorinones with ethyl pyruvate, halo-substituted acetoacetic esters and methyl trifluoropyruvate

Ethyl pyruvate which reacts with ordinary phosphites to form derivatives of pentacoordinated phosphorus [200,201], reacts with phosphites **383, 389 – 393** [31] to give 1:1 addition products of the phosphate type (according to their δ(P) values). The structures of the 1,3,2-dioxaphosphepanes **394 – 399** were assigned to the products on the basis of ^{1}H-, ^{13}C-, ^{31}P-NMR and IR spectral data (cf. Scheme 49) [202].

The result of the reaction of salicyl phosphites **383, 389 – 393** with the α-keto ester ethyl pyruvate differs from that of chloral, where nucleophilic substitution of the sp^2 carbon atom readily occurs at the stage of the ion which is analogous to the bipolar ion **A**. In the case of methyl pyruvate, the bipolar ion **A** undergoes the phosphonate-phosphate rearrangement to ion **B**, which is stabilized due to substitution at the carbonyl group before it

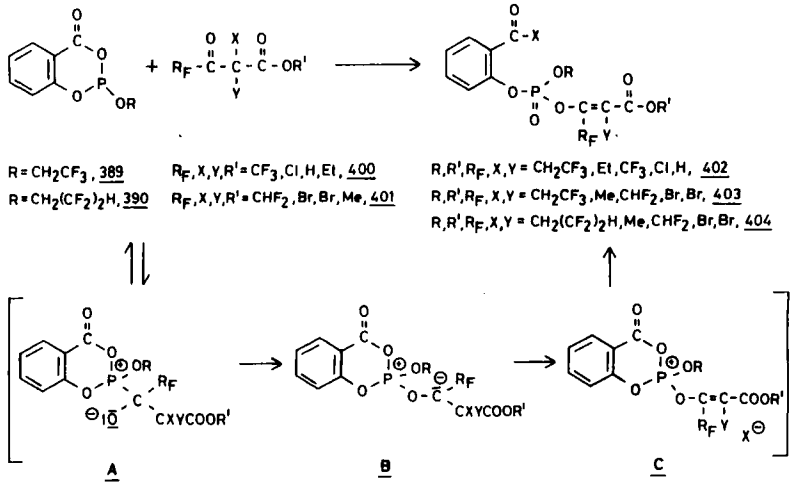


SCHEME 49

can add a second molecule of the α-keto ester methyl pyruvate, as in the case of ordinary phosphites, with the resultant formation of a new C-C bond.

The role of the phosphorus atom as a nucleophile in the rate-determining step was established by evaluating the reactivity of the phosphites, which decreases along the series **393** > **383** > **389** – **391** > **392**. The most active compound, **393**, reacts even at room temperature, while **392** is least active (190–210 °C), i.e. this series is in agreement with the decrease in the nucleophilicity of the phosphorus atom. A mixture of diastereomers is formed during the reaction; in the case of **393** the degree of stereoselectivity is low, whereas it is significant for **383, 389** – **392**. This suggests that in the case of **383** and **389** – **392** the thermodynamically more favourable diastereomer is formed under the reaction conditions, i.e., the bipolar ion **B** adopts the more favourable conformation for subsequent cyclization in the case of **383, 389** – **392**.

Unlike chloral and hexafluoroacetone, the compounds **400** and **401** do not form products of ring expansion with the salicyl phosphites **389** and **390**, that is, the selective loss of the anhydride fragment and the formation of the phosphates **402** – **404** takes place (Scheme 50) [203]:



SCHEME 50

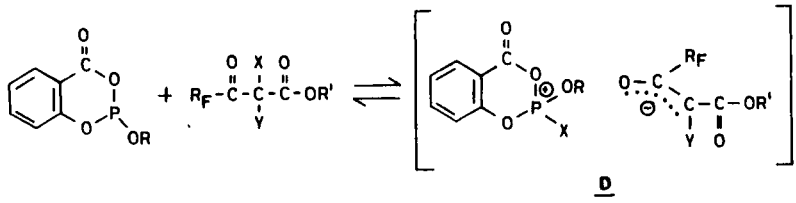
The reactions of salicyl phosphites with compounds **400** and **401** proceed according to the Perkov reaction. This reaction begins with attack by the P(III) atom on the carbonyl carbon atom, followed by rearrangement and the elimination of the C(:O)OP fragment. It is assumed, that fast transformation of the dipolar ion **A** into **B** and then into the vinyloxyphosphonium salt **C** takes place, with significantly higher rates of these two steps than of the intramolecular cleavage of the phosphorinone ring, forming the ions **A** and **B**. The alternative mechanism involving halogenophilic attack by phosphorus [204] would be expected to result in the formation of the products **E** containing a P-X bond (cf. Scheme 51).

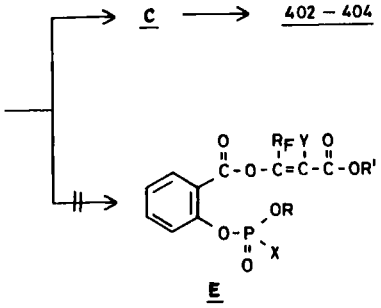
In the opposite case, predominant ligand exchange in the salt **D** rather than attack on the sp^2-carbon atom must be assumed.

As demonstrated in ref. [203], the halogenophilic mechanism must be preferred in the case of the bromo ketone **401**.

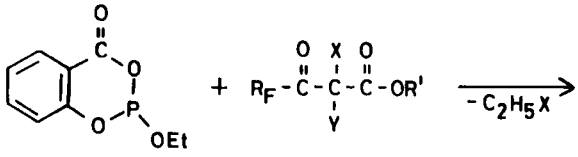
The reaction of the phosphite **405** (R = Et) with compounds **400** and **401** proceeds more readily, by two pathways as demonstrated in Scheme 52: the elimination of C_2H_5X and the cleavage of the acyl fragment.

The fact that the phosphite **405** reacts faster than its fluorinated analogues **389** and **390** shows that the rate-determining step includes nucleophilic attack at the phosphorus atom [203].





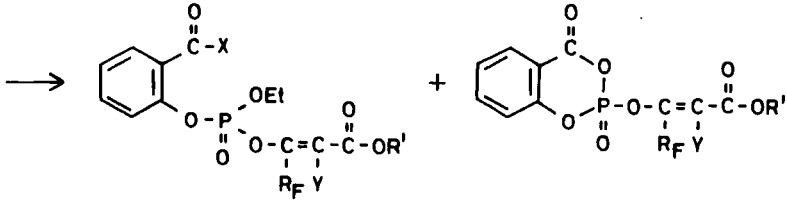
SCHEME 51



405

$R_F, X, Y, R' = CF_3, Cl, H, Et$, 400

$R_F, X, Y, R' = CHF_2, Br, Br, Me$, 401

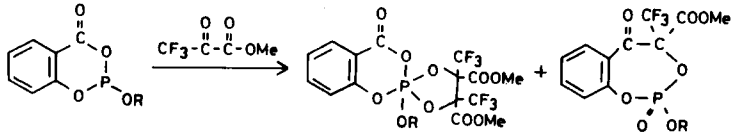


406 R', R_F, X, Y = Et, CF_3, Cl, H, 408

407 R', R_F, X, Y = Me, CHF_2, Br, Br, 409

SCHEME 52

Methyl trifluoropyruvate can react, unlike hexafluoroacetone, along two directions with the salicyl phosphites **369 – 371, 391** and **405** (Eqn. (35)). At low temperature (-40°C) in a solvent (ether, dichloromethane), on the addition of the phosphite to the carbonyl compound, the main or only products are the spirocyclic phosphoranes, **410 – 414**; when the temperature is not controlled (20–80°C), apart from the phosphoranes **410 – 414**, the ring enlargement products **415 – 419** are formed, the content of whose rises, depending on the nature of R, to 90% when the reaction is conducted at 80–120°C and the carbonyl compound is added to the salicyl phosphite [205].



(35)

369	R = Me	410	415
405	R = Et	411	416
370	R = CH_2CF_3	412	417
371	R = $CH_2(CF_2)_2H$	413	418
391	R = $CH_2(CF_2)_4H$	414	419

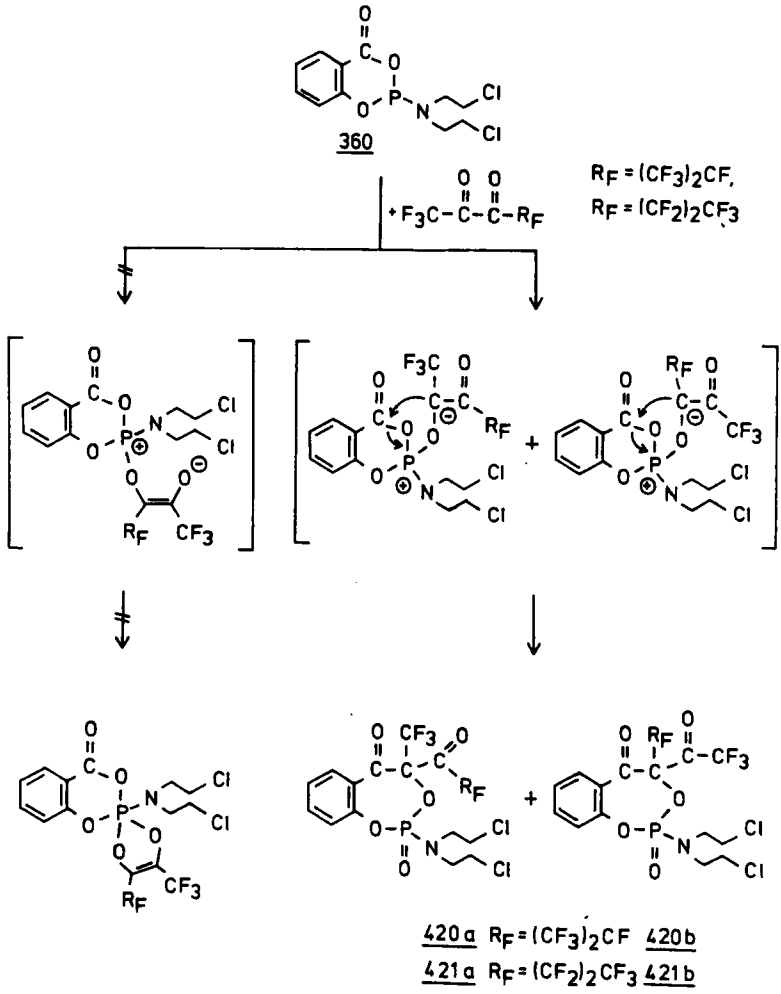
4.6. Reactions of 2-bis(2-chloroethyl)amino substituted 1,3,2-benzodioxaphosphorin-4-one with perfluorinated diketones

The reaction of 2-[2-bis(2-chloroethyl)amino]-1,3,2-benzodioxaphosphorin-4-one **360** with perfluoro-1-isopropyl-2-methyldiketone and perfluoro-1-propyl-2-methyl-diketone furnished, according to Scheme 53, by oxidative addition of the corresponding diketone to the heterocycle of **360**, the isomeric mixtures **420a/b** and **421a/b** [178].

The results were comparable to those, described for the corresponding reactions of the benzoxazaphosphorinone **306** with α-diketones, mentioned above (cf. Chapter 3.3.1.). For this reason, they are not discussed here.

4.7. Reactions of 2-methoxy-4H-1,3,2-benzodioxaphosphorin-4-one with ethyl benzoylformate, 1,2-diphenylethanediol and benzylidenemethylamine

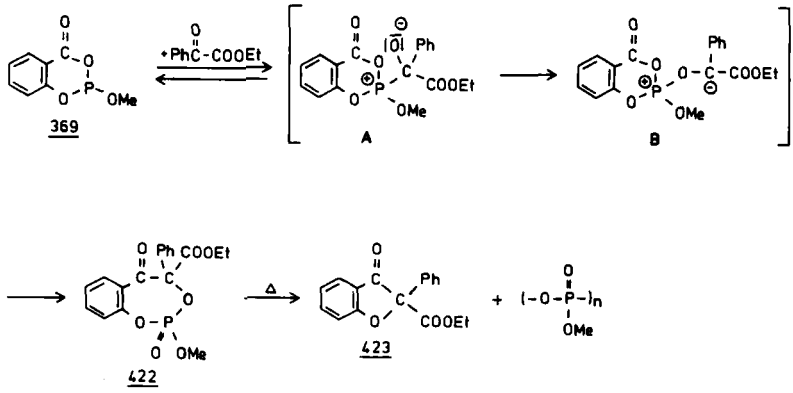
A further method to form seven-membered heterocycles from phosphorus(III)-containing derivatives of salicylic acid is the reaction of ethyl ben-



SCHEME 53

zoylformate with 2-methoxy-1,3,2-benzodioxaphosphorin-4-on **369** (Scheme 54) [206].

When ethyl benzoylformate was heated with **369**, the ring enlargement product **422** was formed. It is suggested, that the reaction probably begins with nucleophilic attack by the P(III) atom on the carbon atom of the carb-

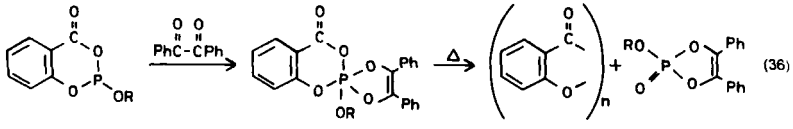


SCHEME 54

onyl group in ethyl benzoylformate. The bipolar ion **A** that is formed as a result of the P-C-O→P-O-C rearrangement [207] changes into the bipolar ion **B**. The latter is stabilized through nucleophilic substitution at the sp^2-carbon atom with the formation of a new C-C bond. Compound **422** was formed as a mixture of two diastereomers. An attempt at the vacuum distillation of **422** led to its complete dissociation with the formation of an organic compound not containing phosphorus. On the basis of elemental analysis and NMR spectroscopy this compound was assigned the structure of ethyl-2,3-dihydro-2-phenyl-3-oxo-2-benzofurancarboxylate **423**. Derivatives of 2,3-dihydro-2-phenyl-3-oxo-2-benzofurancarboxylic acid have not been described in the literature. There are only data on the isomeric 2,3-dihydro-2-oxo-3-phenyl-3-benzofurancarboxylic acid and its esters [208,209].

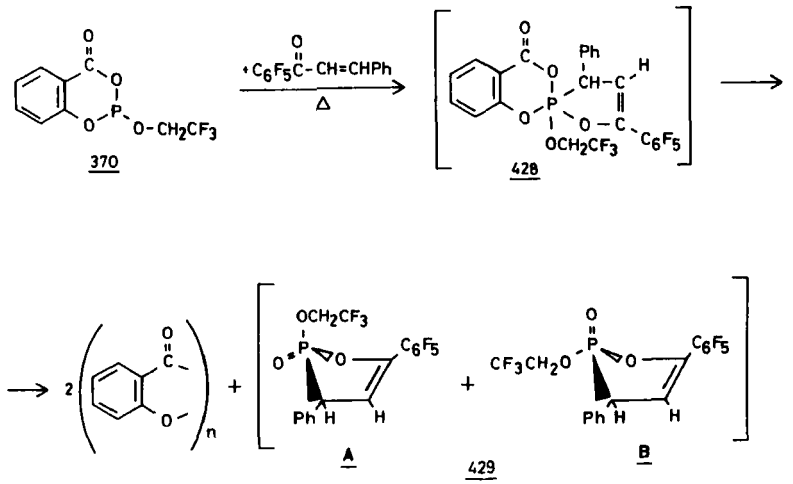
The salicyl phosphites **369** and **370** are less reactive towards benzil, and they give the spirophosphoranes **424** and **425** upon prolonged storage (Eqn. (36)) [210]. The latter are, however, unstable, and they readily split off the salicyl moiety upon heating to form the 1,3,2λ^5-dioxaphosphole-2-oxides **426** and **427**. The presence of a 1,3,2-dioxaphosphole ring in **426** and **427** was confirmed by ^{13}C-NMR spectroscopy.

The phosphite **370** requires heating to react with the ketone used in Scheme 55, even though the latter contains an acceptor pentafluorphenyl substituent. Just as with benzil, the phosphole oxide **429** proved to be the



R = Me, 369 R = CH_2CF_3, 370 R = Me, 424 R = CH_2CF_3, 425 R = Me, 426 R = CH_2CF_3, 427 (36)

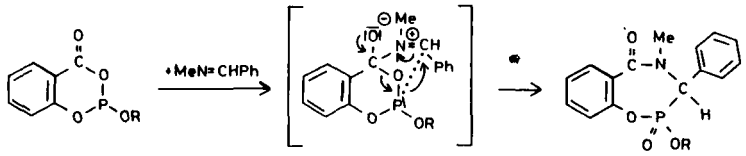
final product. It was isolated as a mixture of two diastereomers. The 1,4-addition product initially formed, the spirophosphorane **428**, is unstable, and decomposes under the reaction conditions, yielding the phosphole oxide **429** [210].



SCHEME 55

According to Eqn. (37), benzylidenemethylamine readily reacts (with heat evolution) with the salicyl phosphites **370** and **430**, yielding the new seven-membered heterocycles **431** and **432** [211]. The carbonyl carbon atom in benzaldehyde is more electrophilic than the C=N carbon in benzylidenemethylamine, therefore benzaldehyde does not react with the salicyl phosphites **370** and **430** even at 100°C. The high activity of benzylidenemethylamine towards **370** and **430** results from the fact that the imino nitrogen rather than phosphorus acts as a nucleophile here, and

the first reaction stage is attack by the nitrogen atom on the endocyclic carbonyl group of the phosphorus-containing heterocycle.



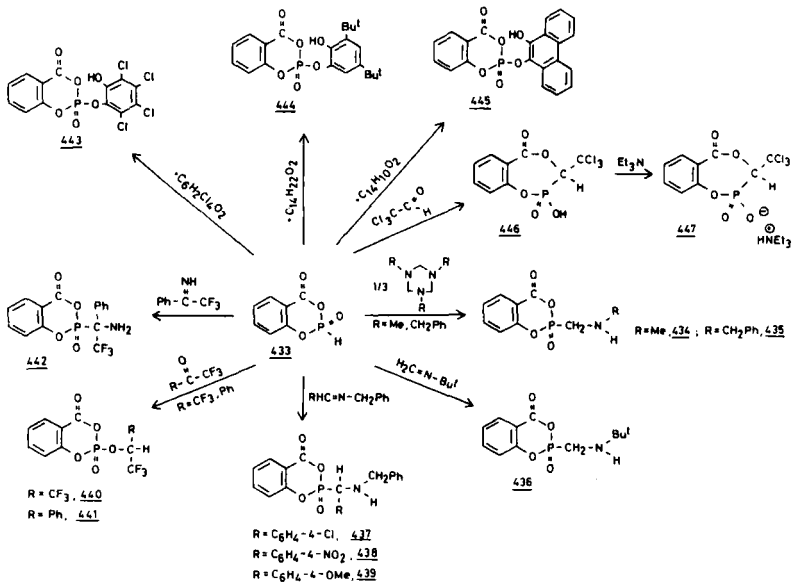
(37)

R = $CH(CF_3)_2$, 430
R = CH_2CF_3, 370

R = $CH(CF_3)_2$, 431
R = CH_2CF_3, 432

4.8. Reactions of 2-hydro-2-oxo-5,6-benzo-1,3,2λ^4-dioxaphosphorin-4-one with imines and carbonyl compounds

In the reaction of **433** with several nitrogen-substituted methyleneimines, $H_2C{=}NR$, compounds **434 – 436** were synthesized (Scheme 56) [212]:



SCHEME 56

Whereas methyleneimines with sterically demanding substituents (R = ^{t}Bu) are stable in their monomeric form, the condensation products of formaldehyde and methyl- or benzylamine trimerize spontaneously under normal conditions, forming 1,3,5-triorganohexahydro-1,3,5-triazines. For the synthesis of **434 – 436**, the trimeric derivatives of methyl- and benzylamine and the monomeric *tert.*-butylmethyleneimine were employed.

Compound **433** and the corresponding triazine were allowed to react under mild conditions, at 0°C, in dilute dichloromethane solution. In this manner, **434 – 436** could be isolated as colourless solids of high purity.

The reaction of **433** with a number of C-substituted methyleneimines, bearing a benzyl group at nitrogen, led to compounds **437 – 439**, with the benzodioxaphosphorinone grouping linked via phosphorus to a C-N bond system (Scheme 56). In contrast to compounds **434 – 436**, which exhibit a symmetrically substituted carbon atom (CH_2) bonded to phosphorus, compounds **437 – 439** are asymmetric at the carbon atom (CHR) bonded to phosphorus. Thus, the CH_2 protons of the benzyl group exhibit diastereotopic behaviour in the ^{1}H-NMR spectra.

The reaction of **433** with hexafluoroacetone led to compound **440** in only moderate yield (Scheme 56). The proposed structure of **440** was proved by NMR spectroscopic methods. Although it was expected, according to reports in the literature [93–95,213], the formation of the "alcohol form" (P-CRR′-OH) did not take place. Furthermore, although ring expansion (formation of a seven-membered ring) was observed in the reaction of hexafluoroacetone with 1,3,2-dioxaphosphorinones (trivalent phosphorus compounds) [195,199], no analogous reaction took place here. Trifluoroacetophenone was allowed to react with **433** in the presence of triethylamine. Because of the low reactivity of trifluoroacetophenone, the use of triethylamine as a catalyst was necessary. No reaction was observed when the reactants were mixed in the absence of base. As expected the reaction led to **441**, bearing a P-O-C fragment (Scheme 56). The small coupling constant ^{2}J(PC) of the CH carbon atom in its ^{13}C-NMR spectrum indicated the existence of **441** in the "ester form" (P-O-CRR′-H). The formation of 1:1 adducts exhibiting a P-C bond ("alcohol form") was not observed under the conditions of base catalysis. Because of the two chiral centers in **441**, the presence of two diastereoisomers was observed by ^{19}F- and ^{31}P-NMR spectroscopy.

A new method of synthesis of 1-aminofluoroalkylphosphonic acid esters, based on the addition of dialkylphosphites to the C=N bond of aryl-

trifluoromethylketimines, was reported in 1990 [214]. Previously, such reactions were unknown for ketimines bearing perfluoroalkyl groups and being unsubstituted at nitrogen. As recently as 1995, these investigations were extended to the reaction of various hydrophosphoryl compounds with phenyltrifluoromethylketimine [90].

The same results as described in the literature [90,214] were obtained when **433** was allowed to react with phenyltrifluoromethylketimine (Scheme 56). The use of triethylamine as a base was not necessary to prepare **442**. The effect of triethylamine as a catalyst in the reaction is probably to generate the corresponding anion from the PH moiety, which then attacks the ketimine. Apparently, in the case of **433** the basicity of the ketimine is sufficient for the generation of the required anion. Compound **442** was formed in good yield and in a state of high purity.

When o-quinones are employed in the reaction with hydrophosphoryl compounds, bonding to phosphorus occurs via one of the oxygen atoms of the quinone, forming 2-hydroxyarylphosphoric acid diesters [215,216]. Similar results were obtained in the reaction of **433** with a number of o-quinones, as demonstrated in Scheme 56. Because of its poor solubility in common organic solvents, it was impossible to record NMR spectra of **443**. In this case, only IR-spectroscopy, mass spectrometry and elemental analysis could be employed as a means of characterization. Compounds **444** and **445** were found to exhibit better solubility, and it was possible to record NMR spectra, which contributed to a full characterization. IR-spectroscopic investigations and the proton NMR signal of the hydroxyl group (strongly shifted to high frequency) indicate the existence of either an intramolecular or an intermolecular association via hydrogen bonds [217].

The reaction of **433** with chloral as a carbonyl compound led, according to Scheme 56, to a nontrivial result, namely formation of the ring expansion product **446**. Although ring expansion products were observed in the reaction of chloral with 1,3,2λ^3-dioxaphosphorinones [198], similar observations for 1,3,2λ^4-dioxaphosphorinones have not previously been described.

It should be noted that most of the ^{1}H-, ^{13}C- and ^{31}P-NMR resonances of **446** are doubled, because of the existence of two diastereoisomers. From the intensity of the signals, the isomeric ratio (a):(b) is *ca.* 60:40%.

Because it was not possible to define the structure of **446** unambiguously by NMR spectroscopy, an X-ray crystal structure determination was needed. Because no crystals suitable for an X-ray analysis could be

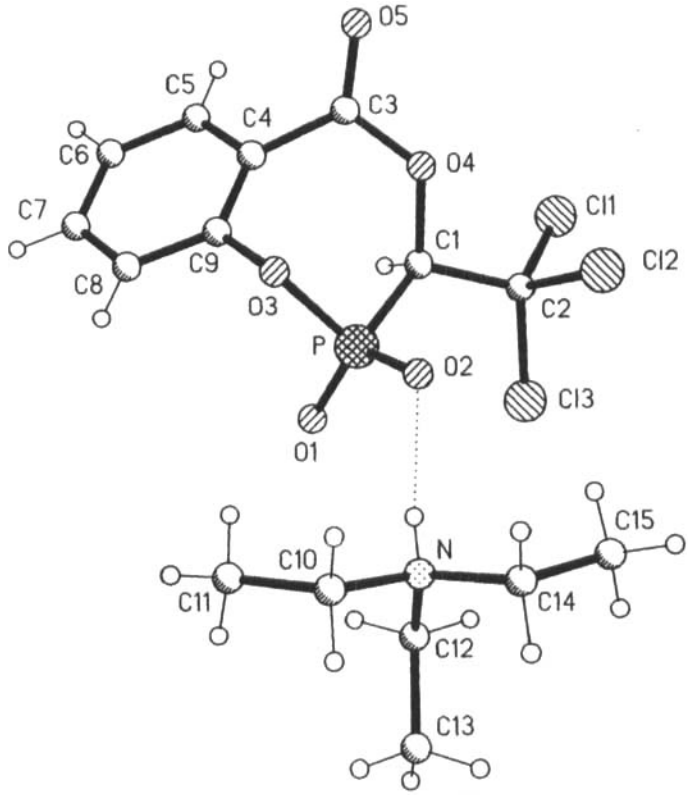


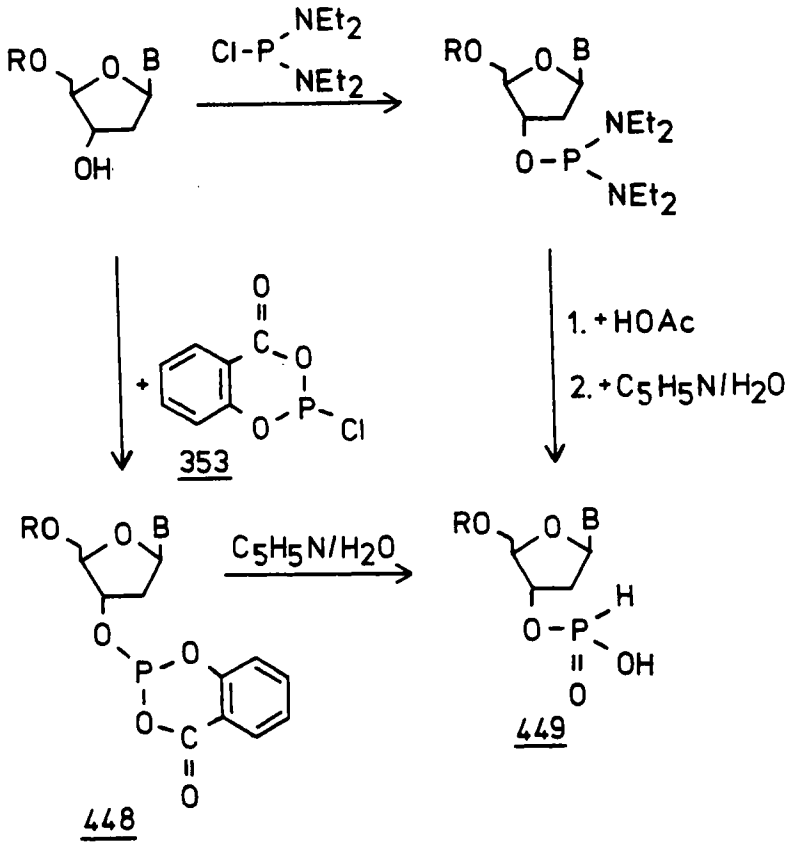
FIGURE 43 Structure of compound **447** in the solid state

obtained from **446**, it was therefore converted into the ammonium salt **447** by reaction with triethylamine. This salt was expected to exhibit better crystallization properties than **446**. According to Scheme 56, **447** was isolated in good yield, and single crystals of good quality could be obtained. The crystal structure determination (Fig. 43) confirmed the proposed structure of **447** [212].

4.9. 2-Chloro-4H-1,3,2-benzodioxaphosphorin-4-one 353 as protecting group in the synthesis of d-nucleoside-3-hydrogenphosphonates

H-phosphonates of nucleosides are versatile intermediates for the preparation of nucleic acid derivatives. A reliable and economical route to the

synthesis of hydrogenphosphonate derivatives of nucleosides involves the monofunctional phosphitylating reagent, 2-chloro-1,3,2-benzodioxaphosphorin-4-one, **353**, according to Scheme 57 [218]:



SCHEME 57

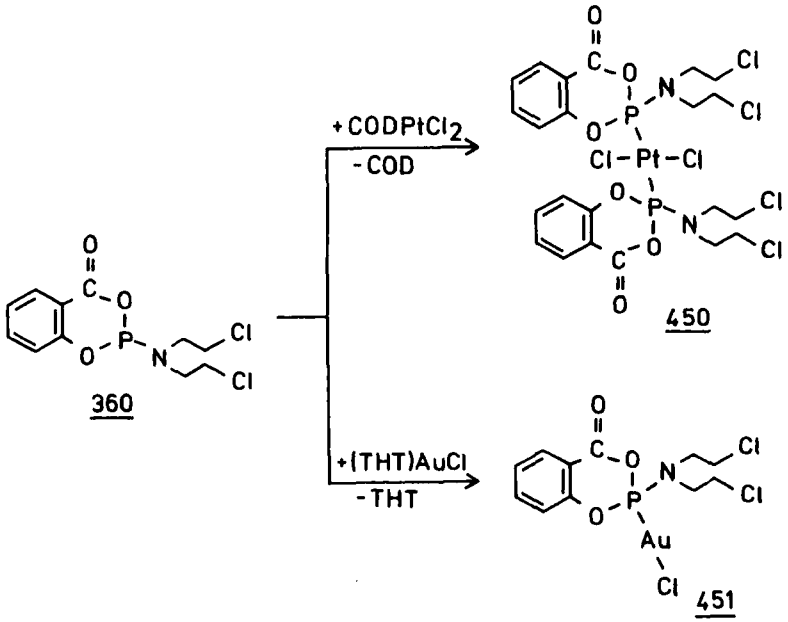
The reaction shown in Scheme 57 offers a good method to introduce the H-phosphonate function in nucleosides fast and under almost neutral conditions.

Such a process would eliminate the acid-hydrolysis step (which is necessary in the three-step route according to Scheme 57) and thus make this method more generally applicable.

The good yield of **449**, prepared via **448**, indicates that this approach may be a convenient and general route for the synthesis of compounds containing a H-phosphonate function [218].

4.10. Coordination compounds of 2-substituted 1,3,2-benzodioxaphosphorin-4-ones

Although benzodioxaphosphorinones have been known for more than one century, only a few of their coordination compounds are known until now. They were synthesized not before 1994. The only known complexes of this type of compound were prepared by reaction of 2-bis(2-chloroethyl)amino-4H-1,3,2-benzodioxaphosphorin-4-one with (COD)$PtCl_2$ and (THT)AuCl, according to Scheme 58 [115,129]:



SCHEME 58

Compounds **450** and **451** were characterized unambiguously [115,129]. In the case of **451** it was possible to conduct an X-ray crystal structure deter-

mination (Fig. 44); the first one of a transition metal complex, bearing the benzodioxaphosphorinone ring system:

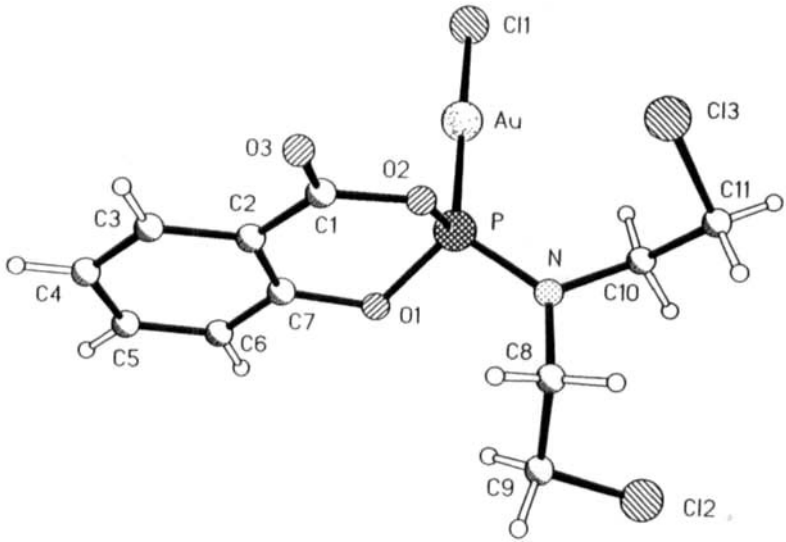


FIGURE 44 Structure of compound **451** in the solid state

The synthesis of **450** and **451** proved that the formation of coordination compounds with benzodioxaphosphorinones as ligands is possible, although, it does not seem to be easy in every case. In spite of some difficulties, which apparently accompany the coordination chemistry of benzodioxaphosphorinones, a huge, unexplored field is opened now, whose cultivation, hopefully, is not to be long in coming.

5. BIOLOGICAL ACTIVITY OF BENZODIAZA-, BENZOXAZA-, AND BENZODIOXAPHOSPHORINONES

The main aim in the development of effective antineoplastic drugs is, undoubtedly, to improve the selectivity, and to reduce undesirable side effects, e.g., in the case of many cytostatics, the damage to fast proliferating tissues, e.g. skin and gastrointestinal tissue toxicities (GI-tox).

TABLE IV Main groups of antineoplastic chemotherapeutics

Type	*Group*	*Chemical Short Name (INN-Term)*	
Alkylants	N-Mustard-Derivatives	Cyclophosphamide	
		Ifosfamide	
		Trofosfamide	
		Chlorambucil	
		Melphalan	
		Prednimustine	
	Ethylene Imine	Triethylenmelamine	
	Derivatives	Hexamethylmelamine	
		Thio-Tepa	
	Sulfonic Acid	Busulfan	
	Ester		
	Nitroso Urea	CCNU (Lomustine)	
	Compounds	BCNU (Carmustine)	
		ACNU (Nimustine)	
	Miscellaneous	Procarbazine	
		Dacarbazine	
		Cisplatin, Carboplatin, Lobaplatin	
		Estramustine Phosphate	
		Amsacrine	
Antimetabolites	Purine Antagonists	6-Mercaptopurine	
	Pyrimidine	5-Fluorouroacil	
	Antagonists	Tegafur	
		Cytarabine	
	Thymidine Antagonists	Hydroxycarbamide	
	Folic Acid Antagonists	Methotrexate	
Antibiotics		Actinomycin C	Dactinomycin
		Actinomycin D	
		Mitomycin	
		Daunorubicin	
		Doxorubicin	
		Aclarubicin	
		Epirubicin	

Type	*Group*	*Chemical Short Name (INN-Term)*
		Bleomycin
		Mitoxantron
Plant Alkaloids	Vinca Alkaloids	Vinblastine
		Vincristine
		Vindesine
	Podophyllines	Teniposide
		Etoposide
	Taxanes	Taxole
		Taxotere
Enzymes		L-Asparaginase

Especially, the toxicity to the bone marrow and the resulting changes in the differential white blood cell count often limit the administration of an otherwise effective substance. While many characteristic biochemical differences between tumor cells and normal cells are known, these differences are by far not as fundamental as those between procaryontic and eucaryontic cells. This causes the antibacterial chemotherapy to be much superior.

As shown in Table IV, cytostatics may be classified according to their mechanism of action, and to their origin. The largest group is comprised of the alkylating agents [219]. Many of the substances currently in use are known to exhibit some selectivity and, therefore, an acceptable therapeutical index while absolute selectivity is still far away.

One of the possibilities to reach this goal is the use of "prodrugs", i.e. drugs which are specifically activated at or in the target cell, or which are efficiently detoxified by non-target cells. In another approach the drug is conveyed at or into the target cell, or at least enriched there, i.e. "Drug Targeting".

Drug Targeting

Many concepts of drug targeting are based on the specific linkage of a pharmakon to the target cell, or on different receptor mechanisms between non-target cells and target cells. Also, quantitative differences can be taken advantage of. Melphalan, e.g., is a substance which consists of a N-mus-

tard group, and the amino acid phenyl alanine. A hypothesized increase in selectivity, due to different capacities for the transport of amino acids, could not be realized here, however. Hormones have also been used as carriers, thus, when the alkylating agent chlorambucil was covalently bonded to prednisolon, the resulting prednimustin with a presumed higher therapeutic index was obtained [220a].

A very recent successful exploitation of the targeting concept is the development of glufosfamide: here, an alkylating compound, i.e. isophosphoramidic mustard, which was formerly known as the active principle of the prodrug ifosfamide, was coupled to β-D-glucose, thus targeting this active principle to the transport proteins of glucose through cancer cell membranes [220b].

Prodrugs

An example of the preferred activation of a drug in the target tissue is the cleavage of stilbestrol diphosphate through acid phosphatase to stilbestrol. The comparatively high enzyme activity in the prostate and its cancer is used to release the active product ("Wirkform") from its water soluble "Transportform" [221]. Another concept approaches the hypoxy of many cancerous cells; otherwise inactive nitroaromatics with a nitrogen-mustard-side chain are to be given alkylating power by reduction in the acidic milieu of the target cell [222].

The prodrug concept includes cyclophosphamide which is broadly used since decades: the product, first synthesized in 1955 [80,223] was conceived as a prodrug. The initial hypothesis was, that an increased phosphoramidase activity in malignant cells should cleave the biologically inactive cyclic N-phosphamide ester, and should thus activate it in the target cell. In fact, however, cyclophosphamide was found to exhibit a good therapeutic index while the originally postulated mechanism of activation was later disproved [32,223].

Fig. 45 shows the metabolism of cyclophosphamide and its important reactions, according to the present knowledge. Cyclophosphamide, non-active and non-toxic in vitro, is activated in the liver through mixed-functional oxidases to 4-hydroxycyclophosphamide which is in equilibrium with its acyclic tautomer, aldophosphamide. Both isomers serve as transport vehicle, and are detoxified via oxidization either through aldehyde oxidase to 4-keto-cyclophosphamide or through NAD-dependent

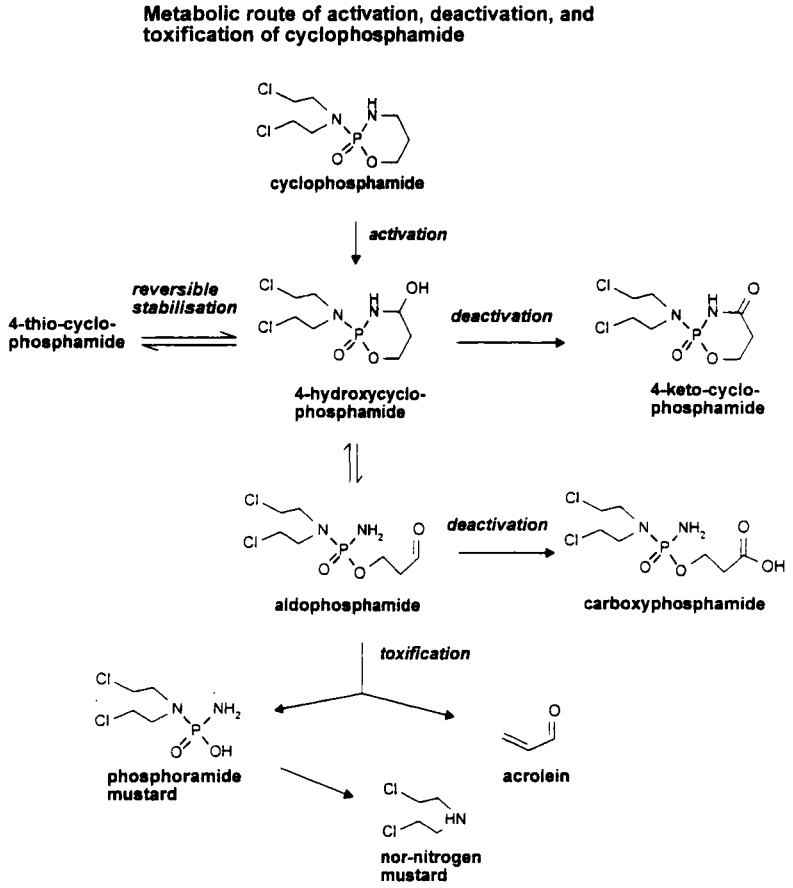


FIGURE 45 Metabolic route of activation, deactivation, and toxification of Cyclophosphamide

aldehyde dehydrogenase [57] to the main metabolite carboxyphosphamide, but most importantly, generate from aldophosphamide the cytotoxic metabolite, N,N-bis(2-chloroethyl)phosphoric acid diamide (phosphoramide mustard, (PM)) through base-catalyzed or enzyme-catalyzed (3′,5′-exonuclease) β-elimination of acrolein [224–226].

While the non-toxic carboxyphosphamide and 4-keto-cyclophosphamide are renally secreted [227], PM is known to display cytotoxic activity through alkylation of the N7 position at guanin, and formation of inter-strand-DNA-crosslinks [228]. This behaviour is due, essentially, to the mobility of the chlorine atom in the β-position to nitrogen [56–58].

Many observations suggest, that an improved detoxification of 4-OH-cyclophosphamide/aldophosphamide through the NAD-dependent aldehyde dehydrogenase in non-target cells, especially in bone marrow stem cells and committed progenitors, is the main reason for the comparatively favourable therapeutic index of cyclophosphamide, even though the role of some other metabolites has not been clarified conclusively [229].

The metabolism just discussed is also valid for the isomeric compound ifosfamide, although in this case, besides the 4-hydroxylation of ifosfamide another pathway of degradation becomes increasingly significant, more so than in the case of cyclophosphamide, i.e. the elimination of chloroacetaldehyde, induced enzymatically through the hydroxylation of the side-chain. This leads, compared to cyclophosphamide, to a decreased formation of the cytotoxic metabolite, N,N′-bis(2-chloroethyl)-phosphoric acid diamide (ifosfamide mustard, IPM) [230].

Cyclophosphamide (Endoxan®) and the related compounds ifosfamide (Holoxan®), trofosfamide (Ixoten®), and mafosfamide are the most important prodrug products displaying cytostatic action [32,223]. Their common structural feature is the 1,3,2-oxazaphosphorine ring.

Compounds with the 1,3,2-benzodiaza-, 1,3,2-benzoxaza- and the 1,3,2-benzodioxaphosphorine skeleton, with 2-chloroethylphosphoramide structures linked to it, may have also potential as antitumour agents. Their activation to cytotoxic metabolites may be effected through hydrolysis of P-O or P-N bonds (also by enzymatic catalysis). A large number of such compounds, whose synthesis is described in Chapters 2 – 4, have been tested in vitro and in vivo for their antitumour activity [231]. The results of these tests will be discussed in the following.

TABLE V Biological activity *in vitro*

No.	*44*	*45*	*54*	*67*	*69*	*80*	*138*	*236*	*241*
EC 90[a] [μg/ml]	*1.6*	*2*	*> 1*	*> 10*	*> 10*	*> 10*	*3.1*	*2.8*	*> 10*
No.	*243*	*244*	*305*	*306*	*321*	*350*	*360*	*382*	
EC 90[a] [μg/ml]	*3*	*not soluble*	*1.8*	*2.6*	*2.7*	*2.4*	*0.28*	*2.1*	

a. 90% Inhibition of colony formation of cells from murine L 1210 leukemia.

Table V lists data for the in vitro investigation of some selected compounds. In Table VI the results of in vivo investigations on some of these compounds are presented.

TABLE VI Biological activity *in vivo*

No.	*LD 50*[a] *[mg/Kg]*	*P 388*[b] *[mg/Kg]*	*ILS*[c] *[%]*
54	> 1000		
69	*ca.* 732	68.1 4x	0
236	464	147 1x	19
321	34	3.16 4x	5
350	732	215 1x	20
360	158	14.7 4x	- 8
382	*ca.* 340	31.6 4x	5
241	> 1000		

a. acute toxicity with single i.p. injection;
b. Mouse intraperitoneal single injection;
c. % increase in live span versus untreated control.

Most of the compounds listed in Table V, with EC 90 values below 10 μg/ml, reveal rather high direct cytotoxic activity in vitro.

Some of the compounds listed in Table VI are remarkably toxic in vivo (LD_{50} below 200 mg/Kg) but none of them showed anticancer activity against murine leukemia P 388.

The metabolic decomposition of cyclophosphamide leads, in the final stage, among other products, to acroleine, an aldehyde contributing to the toxicity of cyclophosphamide. Compounds **253 – 255** and **257 – 259** are benzene analogues of 4-ketocyclophosphamide. The condensed structure of the 4-ketocyclophosphamide group with benzene makes the in vivo formation of acrolein impossible and these compounds are perhaps less toxic than cyclophosphamide itself. In previous investigations, weak antineoplastic activity and low toxicity of the derivatives of 2-phenyl-2,3-dihydro-1,3,2-benzoxazaphosphorin-4-on-2-oxide was found [232]. Thus, compounds **253 – 255** and **257 – 259** were investigated for their antineoplastic effect on the development of L-1210 leukemia in mice [143].

The acute toxicity of **254, 255, 257 – 259** was similar to that of cyclophosphamide. Compound **253** was less toxic than cyclophosphamide. Compounds **255** and **259** given twice, in two therapeutic regimens, at a total dose of 1/2 LD_{50} revealed antineoplastic action against L-1210 leukemia. The animals treated, inoculated with L-1210 leukemia, lived twice as long as the untreated ones (control animals). The effect is weaker than that of cyclophosphamide which caused an increase in the life span by 330%.

The remaining four compounds did not reveal antineoplastic activity against L-1210 leukemia. As a result, only those compounds showed antineoplastic activity which carry the bis(2-chloroethyl)amino group in their molecule. This group is also present in cyclophosphamide.

The results of the investigations described above are presented in Tables VII and VIII.

TABLE VII Effects of 2-substituted 2,3-dihydro-1,3,2-benzoxazaphosphorin-4-ones and their 2-oxides on the development of L-1210 leukemia in mice (5 times administration; total dose 1/2 LD_{50})

Group	*Compound*	*LD_{50} mg/kg*	*Dose mg/kg*	*ILS (%)*	*Evaluation according to Geran [233]*
1	Not treated	---	---	---	-----
2	Cyclophosphamide	600	60 × 5	330	+
3	253	1000	100 × 5	0	-
4	254	750	75 × 5	13	-
5	255	750	75 × 5	100	+
6	257	620	62 × 5	0	-
7	258	750	75 × 5	13	-
8	259	750	75 × 5	100	+

TABLE VIII Effects of 2-substituted 2,3-dihydro-1,3,2-benzoxazaphosphorin-4-ones and their 2-oxides on the development of L-1210 leukemia in mice (3 times or 2 times administration; total dose 1/2 LD_{50})

Group	*Compound*	*Dose mg/kg*	*ILS (%)*	*Evaluation according to Geran [233]*
1	Not treated	---	---	-----
2	Cyclophosphamide	100 × 3	330	+
3	253	167 × 2	0	-
4	254	125 × 2	0	-
5	255	125 × 3	100	+
6	257	103 × 2	13	-
7	258	125 × 2	13	-
8	259	125 × 3	100	+

Compounds **255, 259** and cyclophosphamide were given three times. The remaining compounds were given twice, as the animals died before day 9.

The pharmacological investigation of **266, 267, 274, 276, 277** and **285**, which are characterized by NMR-spectroscopy, mass spectrometry and elemental analysis showed that compounds **266** and **277** were effective against leucemia L-1210 at a total dose of 1/2 LD_{50} (compound **266**, LD_{50} = 50 mg/Kg; compound **277**, LD_{50} = 1500 mg/Kg; ILS = 25% [232,233]). These investigations are promising because the compounds display antineoplastic activity even though they do not contain bis(2-chloroethyl)amino groupings.

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