CHAPTER 3

3. THIO ANALOGUES OF 1-OXO-2,8-DIARYL-2,5,8-TRIAZA-1λ^5-PHOSPHA-BICYCLO[3.3.0]OCTANE

3.1 Introduction

The synthesis of thiophosphoric amides with general structure **O** dates from 1857[1]. Most thiophosphoric amides can be prepared via the same routes as their phosphoryl counterparts. Thiophosphoramidates are usually formed via the simple reaction of $P(S)Cl_3$ or $P(S)Br_3$ with any primary or secondary amine[2]. Alternatively the aminophosphine can be prepared first which can then be transformed into the corresponding thio analogue with treatment of elemental sulphur[3,4,5].

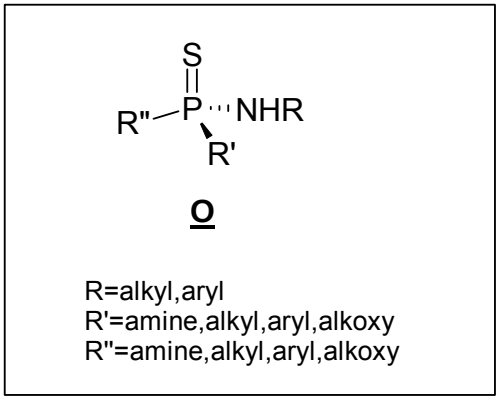


Figure 3.1 General structure of the thio-phosphoramidates.

N-Bis(2-chloroethyl)thiophosphoamidodichloridate[6] **8** and *N,N*-diethylthiophos-phoamidodichloridate[7] **8'** are very common substrates for preparing thiophospho-triamidates, but the second and third nucleophilic displacements almost always involve aliphatic amines.

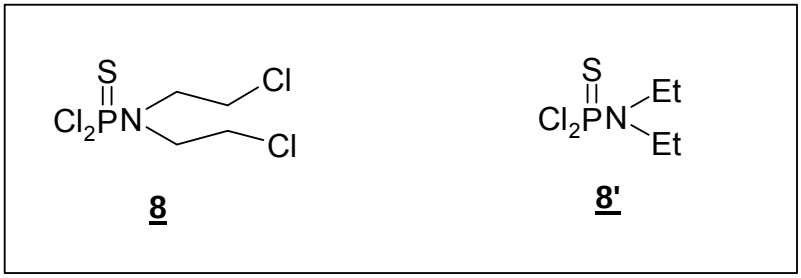


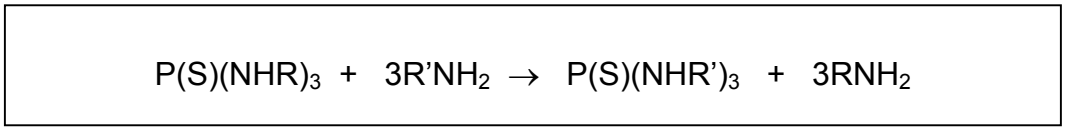
Figure 3.2 Substrates for preparing thiophosphoric triamides.

The phosphoryl oxygen in phosphonic chloro amides of the type RClP(O)NHR can be exchanged for sulphur when treated with $P(S)Cl_3$ in the presence of DMF as a catalyst.[8]

Phosphonic diamides with the general structure R"P(S)(NHR)(N'HR')[9,10] where R''=Aryl, R'=alkyl and R=alkyl or aryl substituents, can be prepared from $R"P(S)Cl_2$.

Numerous thiophosphorotriamides have been prepared over the years, but most attention was given to the symmetrically substituted thiophosphoric amides, (RNH)3P(S)[5,11,12] or unsymmetrical triamides containing only aliphatic substituents on nitrogen[13.] Compounds of the type $(R_2NH)_3P=S$, as well as N,N',N"-trialkyl-N,N',N"-triarylphosphoric triamides[3,14] are synthesized in very simple substitution reactions. The symmetrical thio derivatives can sometimes be prepared by treating the corresponding phosphoryl compound with P_4S_{10}. Existing examples are phosphorotriamides which contain either aliphatic or aromatic substituents on nitrogen.

Primary amine derivatives can undergo transamination in which aryl groups can be replaced by more strongly bonded alkyl groups, or in which a more volatile amine can be boiled off and the equilibrium shifted to the desired side. (**Scheme 3.1**) This method is also only applicable to symmetrically substituted compounds like $P(S)(NHR)_3$.



Scheme 3. 1 Transamination of thiophosphorotriamidates.

No examples have been reported of thiophosphortriamidates with general structure **P** (**Figure 3.3**) where only one of the *N*-substituents is aliphatic and the other two substituents are aromatic. This situation is similar to our compound **9a**, which was used as substrate in attempts to preprare our model compound **11a**.

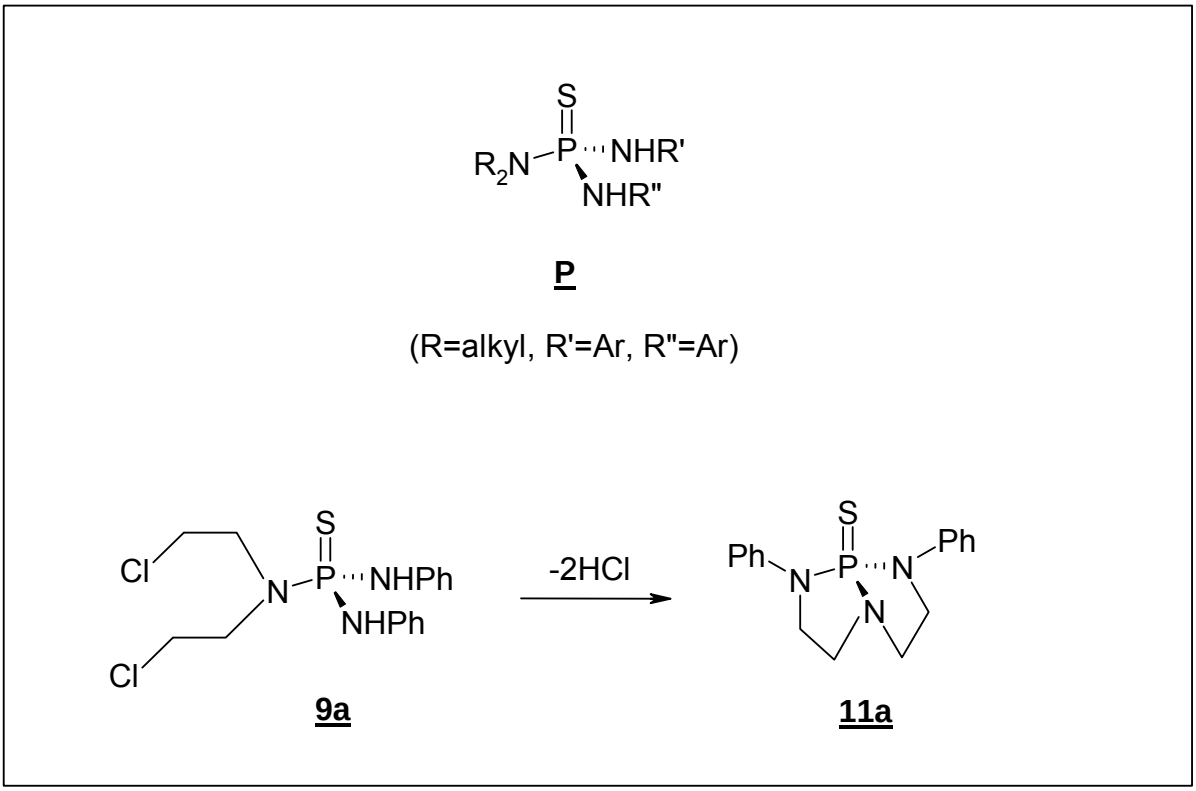


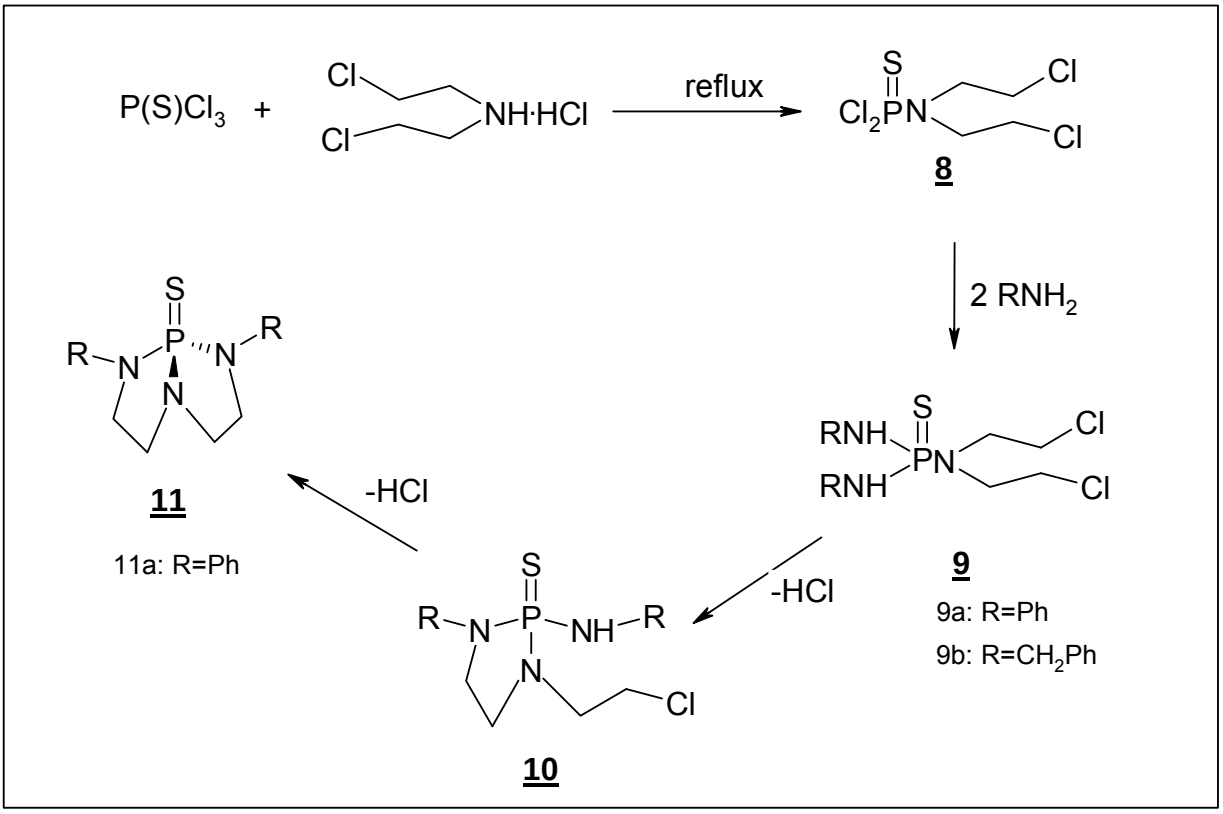
Figure 3.3 Thiophosphorotriamidates.

Although some of the thiophosphoamidodichloridates of the type $R_2NP(S)Cl_2$ are very resistant to nucleophilic attack, no problems were anticipated in obtaining the corresponding thio analogue **11a** via the same synthetic route as for the phosphoryl analogue **3a**.

3.2 Results and Discussion

3.2.1 Synthesis

The attempted route to product **11a**, according to the general sequence shown in **Scheme 3.2** turned out quite disappointing.



Scheme 3.2 Reaction pathway attempted for the preparation of the bicyclic thio analoque **11**.

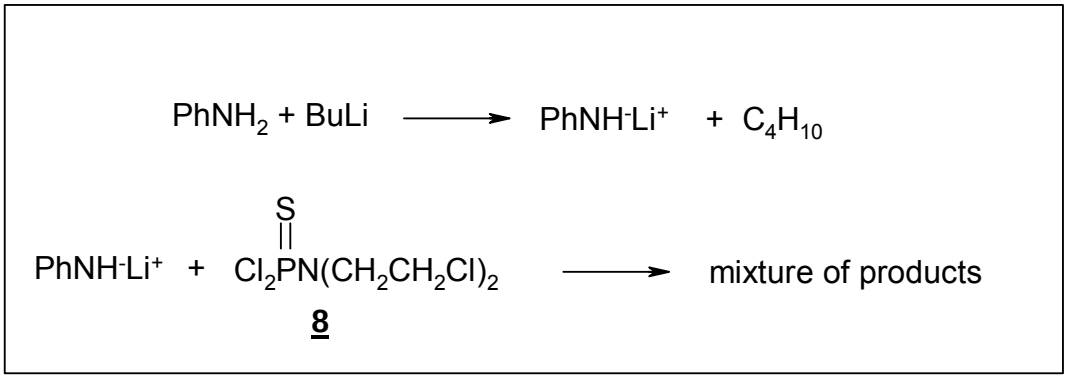
The first compound in the series, namely the *N*-bis(2-chloroethyl)-thiophosphoamidodichloridate **8** was prepared with a satisfactory yield and with the melting point in good agreement with the value reported in literature. All the attempts to substitute the two remaining chlorines for aniline residues were unsuccessful.

The known route to synthesize the noncyclic precursor **9** by reacting the *N*-bis(2-chloroethyl)thiophosphoamidodichloridate **8** with two moles of aniline and two moles of a base, failed under a variety of reaction conditions. The final product

couldn't be isolated in a state of satisfactory purity and with acceptable yield. The aniline in the presence of triethylamine proved to be not a strong enough nucleophile to replace the second and third chlorine atoms at the thio phosphoryl centre in compound **8**. This observation remains in disagreement with the reported preparations of thiophosphoric trianilides, $(ArNH)_3PS$ from $P(S)Cl_3$ and the aromatic amines. The phosphorous anilides, $(PhNH)_2PNMe_2$, were prepared via the transamination reaction, but it was due to the much higher reactivity of the P(III) substrates relative to the phosphoryl or thiophosphoryl analogues.

The noncyclic triamidate with aliphatic substituents on nitrogen (**9b,** R=$PhCH_2$) was prepared via the route shown in **Scheme 3.2**, but attempts to cyclize the compound led to the formation of an unexpected phosphorus containing product with a δ_P value of 5. The ^{31}P chemical shift of the desired product was expected to be much more down field[15]. No attempts were made to identify that product.

Different synthetic methods were then applied in order to introduce the two *N*-phenyl groups at the thiophosphoryl centre to arrive at the non-cyclic precursor **9a** (R=Ph). Lithium anilide was prepared to force the nucleophilic attack at phosphorus (**Scheme 3.3**), but this reaction was also unsuccessful. The reaction resulted in a complicated mixture of compounds and no single product could be isolated from the mixture.



Scheme 3.3 Attempted lithium anilide route to prepare substrate **9a**.

When the *N*-phenyl groups were introduced first to the $P(S)Cl_3$, in order to prepare the *N,N'*-diphenylphosphorothiochloridate **12a** (**Figure 3.4)**, a crystalline, unidentified phosphorus containing compound was formed.

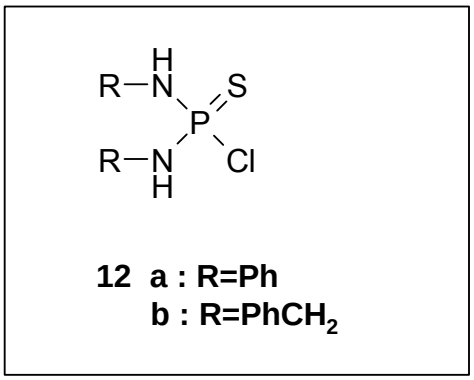
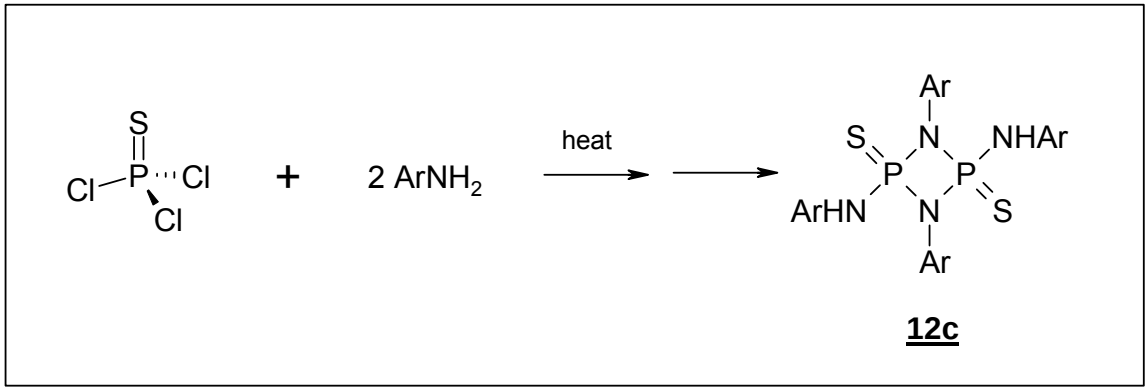


Figure 3.4 *N,N'*-disubstitutedphosphoro-thiochloridate.

Most aromatic amines react with PCl_3 / PCl_5 / $P(O)Cl_3$ / $P(S)Cl_3$ to form dimers rather than monomers. Our unknown compound could be the dimeric cyclophosphazane **12c** (**Scheme 3**).

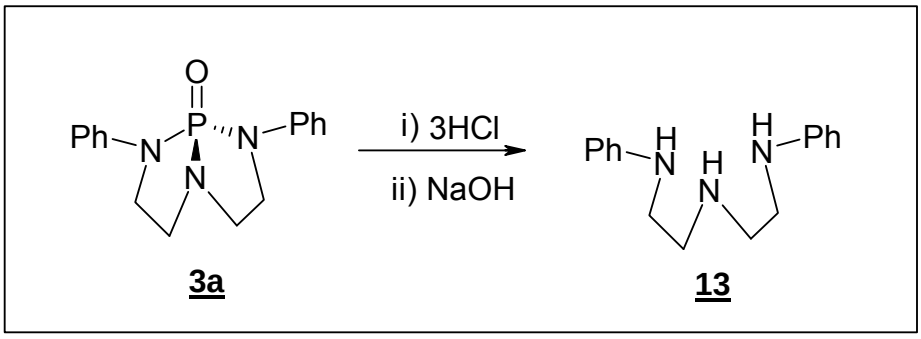


Scheme 3.4 Reaction of aniline with $P(S)Cl_3$.

The benzyl analogue **12b** was prepared in very pure state and in good yield, but attempts to replace the last chlorine at phosphorus by the mustard group, failed. No attempts were made to further investigate these reactions.

In the next attempt, the phosphoryl bicyclic compound **3a** was treated with $P(S)Cl_3$ in the presence of DMF in order to exchange the oxygen for sulphur, according to the report on the catalytic activity of DMF in that type of reactions. The crude product of that reaction contained a mixture of phosphorus containing compounds with the desired product (recognized by its characteristic ^{31}P NMR chemical shift, δ_P 81) only as a minor component. No attempts were made to isolate any of the reaction products. After standing on the shelf for more than a year, one product separated from the mixture as a semi-solid. The ^{31}P NMR revealed a single phosphorus containing compound with δ_P ~100 ppm, much more low field than the desired product which has δ_P ~81 ppm). Time didn't allow us to identify and characterize this compound.

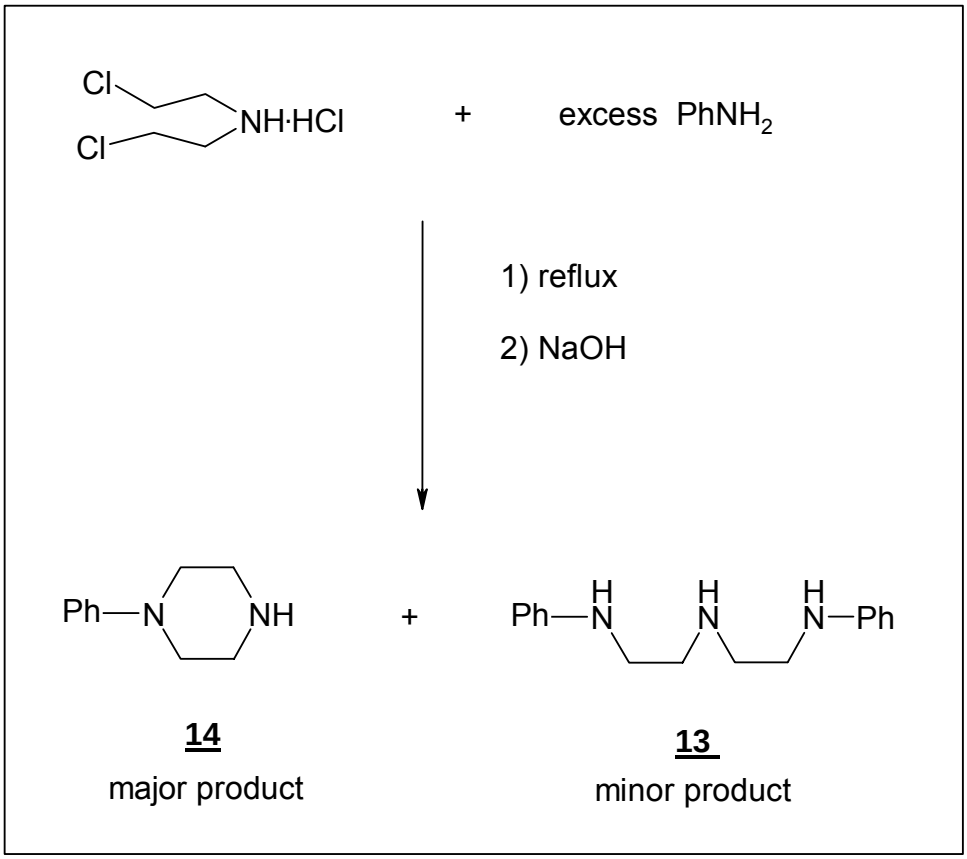
In the course of this work, triamine **13**, *N,N'*-diphenyl-bis(2-aminoethyl)amine, was prepared in our laboratory[16] which was then used to prepare the thio bicyclic derivative in a one pot reaction. The triamine was originally prepared by hydrolysis of all three P-N bonds in the phosphoryl bicyclic compound **3a** (R=Ph) by reacting it with concentrated aqueous hydrochloric acid (**Scheme 3.5**). The triamine trihydrochloride salt **13'** was isolated from this reaction in quantitative yield and needed no further purification.



Scheme 3. 5 Preparation of triamine **13** from phosphoryl bicyclic **3a**.

Cleavage of the three P-N bonds could also be achieved by reacting the bicyclic substrate with an excess of Me_3SiCl in MeOH. This is even a better reaction as all side products could be evaporated.

The *obvious* route for preparing the triamine **13** is reacting the mustard amine hydrochloride salt, bis(2-chloroethyl)ammonium chloride, with two moles of aniline. In agreement with the early experiment of Prelog and Driza[17] reported in 1933 we have demonstrated that the desired triamine is only formed as a minor product (~10%) and N-phenylpiperazine **14** is the major product of the reaction. After the first substitution by aniline, an intramolecular substitution is favoured above the second substitution by aniline, leading to the main product **14** (**Scheme 3.6**).



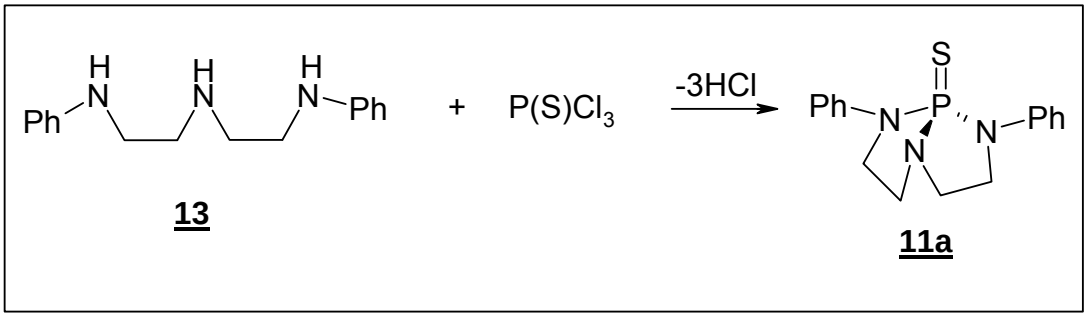
Scheme 3.6 Prepraration of triamine **13**.

Triamine **13** attracted our attention as a possible substrate in our quest for the product **11a**. It seemed reasonable that the condensation of **13** with $P(S)Cl_3$ in the presence of excess base, and under sufficient dilution, could serve as a

feasible route to **11a**, the compound which we have still failed to prepare via other routes.

The novel synthesis of the triamine **13** developed in our laboratory was however very time consuming and gave an overall yield of only 34% after six steps. A rather unconventional approach was applied to arrive at the triamine in large quantities. The "*N*-phenylpiperazine reaction" was carried out on a large scale (~60 g of substrate) in order to prepare a reasonable quantity of the triamine. The mustard amine hydrochloride salt and a large excess of aniline were refluxed in toluene for twenty four hours. The resultant mixture of amine salts was treated with large excess of aqueous NaOH to liberate the free bases, which were extracted with CH_2Cl_2. The triamine **13** was then precipitated with diethyl ether, together with some impurities, from the bulk of the *N*-phenylpiperazine. The triamine **13** (free base) was extracted from the precipitate with hot methanol from which it crystallizes out upon cooling. ^{1}H NMR and elemental analysis showed that in this way **13** can be preprared in a very pure state, and can be used in the planned synthesis of **11a**. It was possible therefore to demonstrate that the direct preparation of the triamines of the type **13** from the nitrogen mustard and aromatic amines can be of practical use, provided that one accepts great losses of the substrates which are converted to the piperazine derivative **14**.

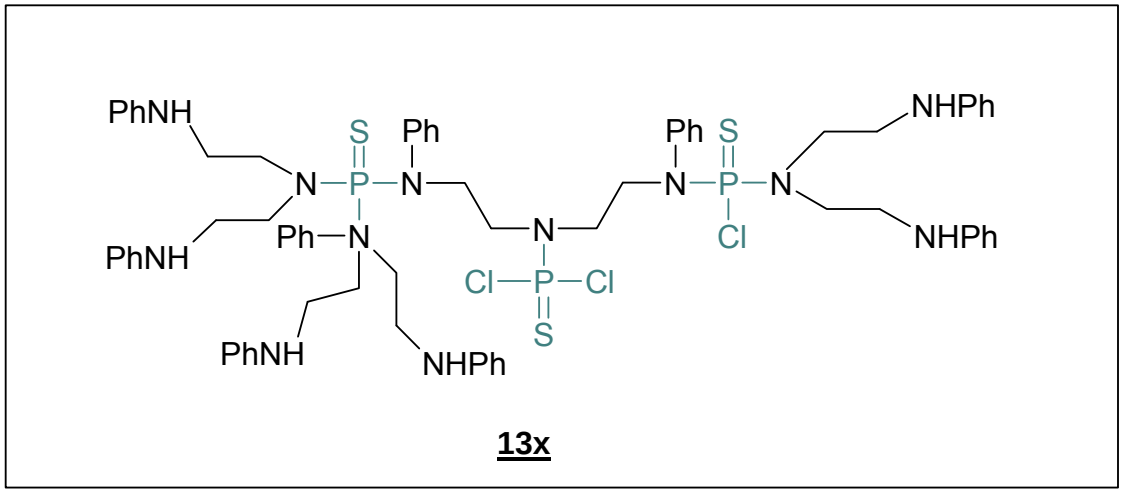
The bicyclic compound **11a** was then prepared by reacting the triamine **13** with $P(S)Cl_3$ (**Scheme 3.7**)[18] in the presence of a base.



13 **11a**

Scheme 3. 7 Preparation of the thiobicyclic compound **11a** from triamine **13**.

Triamine **13** has very low solublity in most organic solvents which limited the choices of reactions conditions. Triethylamine was chosen as a base necessary to neutralize three equivalents of HCl expected to be released. The substrate **13**, $P(S)Cl_3$ and Et_3N were mixed in a final molar ratio of 1:1.1:6 and with high dilution (7.5 mg of **13**/mL, 0.03 M). The high dilution was necessary to prevent the triamine molecule to react with $P(S)Cl_3$ at more than one reactive centre which might result in the formation of undesired chain products e.g. **13x** .



13x

Figure 3. 5 Expected condensation product from reaction of $P(S)Cl_3$ and triamine **13**.

A low boiling solvent (diethyl ether) was found to be possible as the medium for the first attempt of the reaction. Since we also expected polymerization to occur more likely at high temperatures, the boiling point of the solvent secured the low temperature of the reaction.

One mol of triamine **13** and 6 mol of triethylamine were dissolved in 50 mL of anhydrous diethyl ether. $P(S)Cl_3$ (1.1 mol) in 10 mL ether was added dropwise while stirring (-10 °C). The mixture was left to warm up to room temperature and then refluxed for ten days. Like before, the progress of the reaction was followed by ^{31}P NMR of the reaction mixture. The reaction was very slow but the intensity of the $P(S)Cl_3$ resonance signal was decreasing while new signals were growing. Finally all the intermediate signals were gone and only the signal of the product **11a** at 81 ppm was observed. The triethylammonium chloride was filtered off

and the filtrate washed with a 10% aqueous K_2CO_3 solution to keep the pH between 7 and 8. The solvent was evaporated and the crude product purified by column chromatography.

This reaction was repeated in anhydrous THF which lead to the formation of the product in shorter time, but resulted in a mixture of side products causing a much lower yield.

During one of these experiments, the water flow in the laboratory was cut off and the temperature of the reaction mixture ran out of control. All the solvent evaporated. After workup a very pure product **11a** was isolated with the yield comparable to previous experiments. This made us realize that the experiment can be caried out at much higher temperature without damaging our product. The synthesis of **11a** was then adjusted according to this observation. The triamine and $P(S)Cl_3$ were refluxed in toluene without using a base. The HCl which was formed in the reaction was boiled off while refluxing. After cooling, the insoluble side products were filtered off and the mixture washed with a 10% K_2CO_3 solution. The mixture was dried over $MgSO_4$ and the toluene evaporated under reduced pressure. A reasonably pure product **11a** crystallized from this mixture. A very pure compound was obtained after repeated crystallizations from toluene.

Another possible route to arrive at **11a**, which was not explored here, is to use tris(imidazolyl)thiophosphoric amide as starting material.

Attempts to prepare the unsubstituted bicyclic compound (R=H) via the route shown in **Scheme 3.7** using bis-(2-aminoethyl)amine as the substrate, resulted in a crystalline product with a ^{31}P NMR signal at δ_P ~100 ppm. This compound decomposed upon attempts of isolation.

NMR Analysis

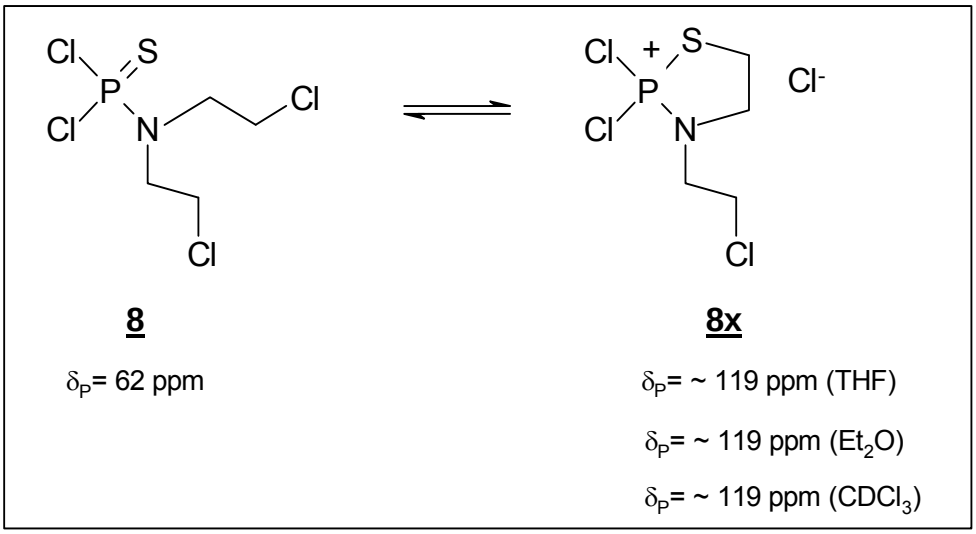
For the phosphoryl derivatives, the ^{31}P-NMR spectroscopy was very valuable in determining the chemical changes around phosphorus. As discussed in the introduction in Chapter 1, there is a correlation between the ^{31}P-NMR chemical shift and the structural differences in the phosphotriamidate series. This could be used to distinguish, with very high certainty, between the different compounds in the series without isolation of the individual compounds. The values reported in literature for those thio compounds which are most like the ones studied in this project, showed the same trend as in the phosphoryl derivatives. A regular downfield shift was observed for thio compounds with increasing number of nitrogens attached to phosphorus, but the differences are much smaller. With the thio-derivatives obtained in this work, it was not possible to unambiguously assign δ_P values to the different compounds. E.g. the ^{31}P chemical shift of substrate **8** differs from the next compound in the series, **9b** (R=Benzyl) by less than 1 ppm, but in the phosphoryl family the $\Delta\delta_P$ for the corresponding compounds was ~5 ppm.

Additional experiments

In the many attempts to prepare the phosphortriamide **9a** a new signal (δ_P 119) was sometimes observed in the ^{31}P NMR spectrum of the reaction mixture but after evaporation of the solvent, the signal disappeared completely. The substrate **8** used as the starting material to prepare **9a** was heated alone in THF, Et_2O and $CDCl_3$ respectively. The same signal (δ_P ~119) was observed in the solution, but after evaporation of the solvent the only signal observed was that of the substrate **8** at δ_P 62 ppm, and the ^{1}H NMR spectrum was unchanged.

The only plausible explanation for this observation is that substrate **8** is capable of entering some reversible reaction of which the product **8x** can be formed only at higher temperatures, and then return to the initial stable compound **8**. The most likely reaction would be the intramolecular displacement of the chloride ion

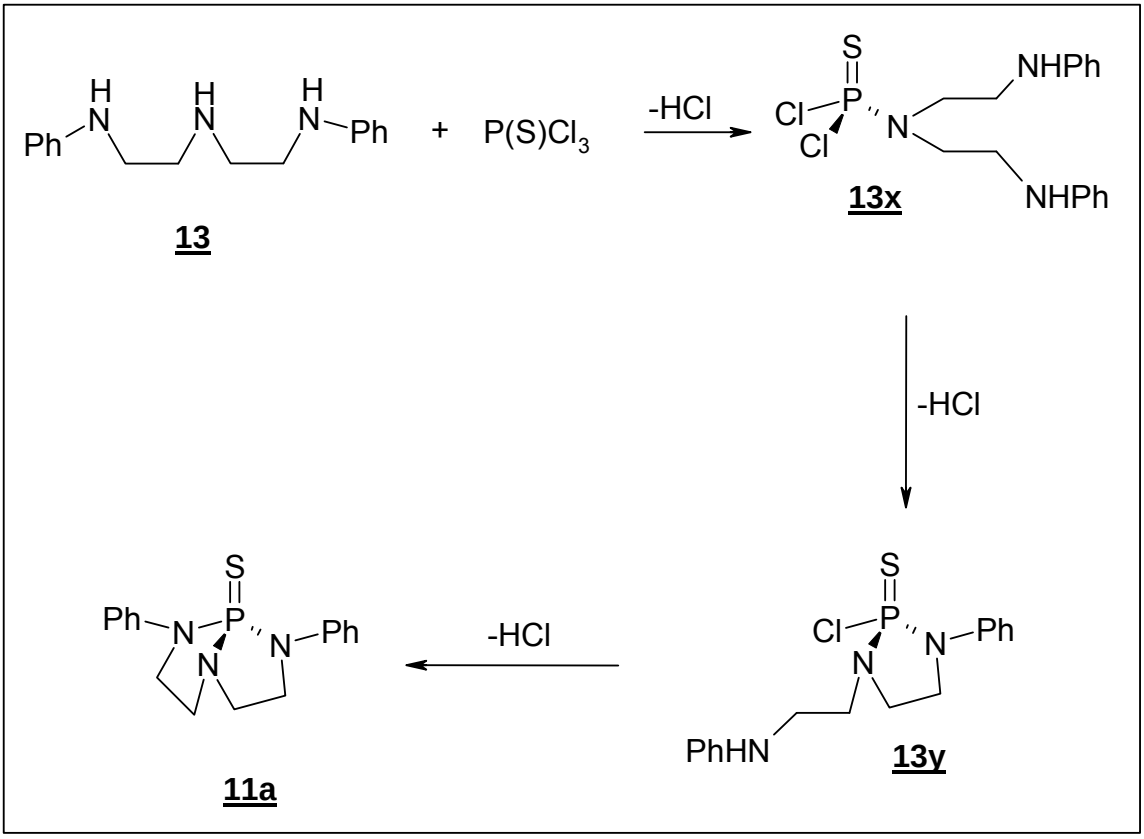
(**Scheme 3.8**)[19]. The nucleophilicity of the thiophosphoryl group will be discussed later in this chapter.



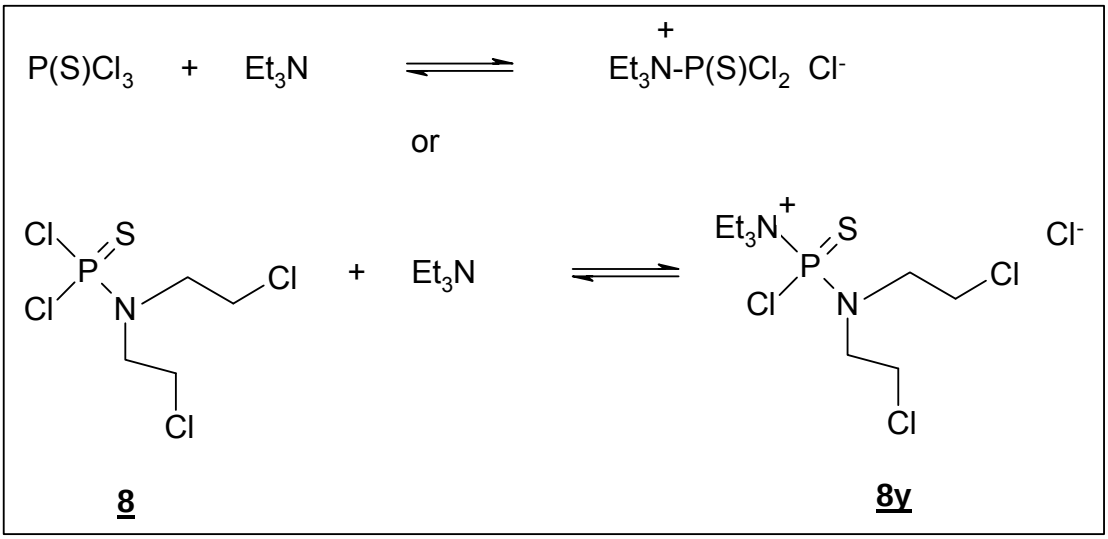
Scheme 3.8 Intramolecular displacement reaction of substrate **8**.

In almost all of the reaction mixtures where compound **8** or $P(S)Cl_3$ (δ_P 32) were used as a substrate and when triethylamine (Et_3N) was used as a base, a signal at δ_P ~43 was observed in the ^{31}P NMR spectra.

The resonance signal (δ_P ~43) also appeared in the reaction of triamine **13** with $P(S)Cl_3$. At first it was believed to be one of the intermediate substitution products **13x** or **13y** (**Scheme 3.9**), but these compounds were never isolated. The ^{31}P NMR signal at 63 ppm should rather be the monosubstituted intermediate **13x** because the chemical environment of phosphorus is basically identical as in compound **9a** which has δ_P 62.



Scheme 3. 9 Stepwise preparation of the thiobicyclic compound **11a** from triamine **13**.



Scheme 3. 10. Proposed equilibrium for reactions of **8** and $P(S)Cl_3$ and Et_3N.

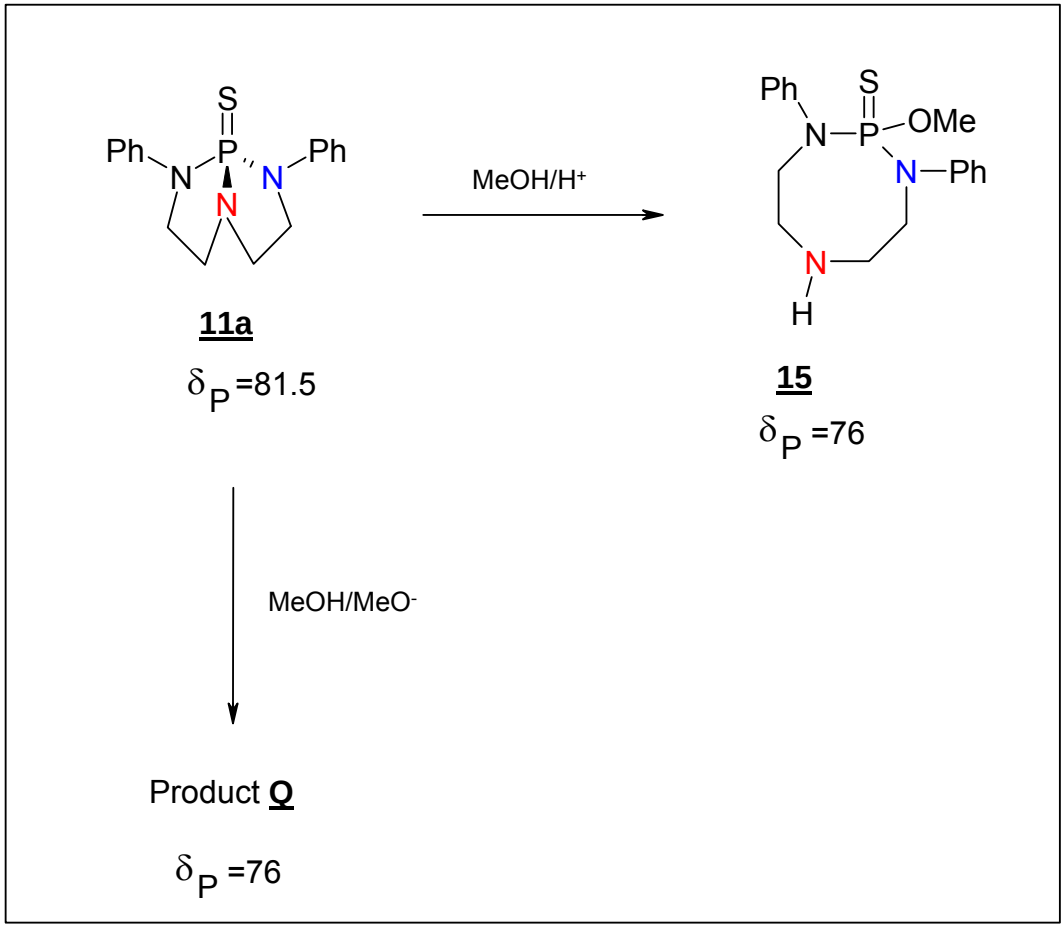
Equilibria like that shown in **Scheme 3.10** can be proposed. The ammonium species could be stabilized by adding $SbCl_5$ and formation of the non-nucleophilic $SbCl_6$-anion. This was not investigated any further.

3.2.2 Acid catalyzed alcoholysis

The first reaction studied for the new bicyclic compound **11a** was the acid catalysed solvolysis of the amide bond. A similar substitution reaction was expected like for the phosphoryl derivatives because the P-N bond is very unstable under acidic conditions[20] in a variety of amides derived from phosphorus acids. When the thiobicyclic compound **11a** was treated with methanol containing one mol equivalent of HCl, we observed the appearance of a new signal, only 5 ppm up field in the ^{31}P-NMR spectrum of the crude reaction mixture, with complete disappearance of the signal of the substrate. Reaction was completed in less than five minutes.

Under acidic conditions the product was stable in solution and could be isolated as a white solid after evaporation of methanol. ^{1}H-NMR spectrum indicated that it is the substitution product, the eight membered ring compound **15** (**Scheme 3.11**). The isolated product was not pure enough to give a reliable ^{13}C NMR spectrum. Therefore the crude product was analysed by GC-MS without further purification to confirm the structure of the compound.

The product **15** of the acid catalyzed reaction is stable as the neat hydrochloride salt. The hydrochloride salt was dissolved in chloroform and treated with aqueous K_2CO_3 to liberate the free amine. After decanting the aqueous layer, the organic layer was dried and without evaporation of the solvent, the ^{1}H-NMR of the sample was recorded. ^{1}H-NMR spectrum of the free amine **15'** did not correspond to the ^{1}H-NMR spectrum of the eight-membered ring compound **15** and ^{13}C NMR was not very useful because of the impurity of the sample.



Scheme 3.11 Alcoholysis of thiophosporyl bicyclic **11a**.

The splitting pattern of the aliphatic protons of the free base was distinctly different from that of the hydrochloride salt. The characteristic doublet for the methoxy protons has moved down field with 0.3 ppm and the coupling constant $^{3}J_{HP}$ changed from 13.9 Hz to 14.5 Hz. When the free base was isolated from the solvent as a grey viscous oil, and then send for NMR, the ^{31}P NMR spectrum indicated a mixture of phosphorus containing compounds which changed with time. ^{1}H NMR spectrum indicated the major fraction is the compound which results in the doublet with $^{3}J_{HP}$=14.5 and only 18 % of the product with $^{3}J_{HP}$=13.9. The corresponding free amine **15'** was never isolated in the pure form.

3.2.3 Base catalyzed alcoholysis

The change of the alcoholysis medium from the MeOH/H^+ system to a solution of sodium methoxide in methanol gave a ^{31}P-NMR signal at δ_P 76, the same as for the acidic methanolysis. This alcoholysis product is not the same as for the acidic alcoholysis. The ^{1}H NMR spectrum of product **Q** showed some distinct differences from the ^{1}H NMR spectrum of compound **15**.

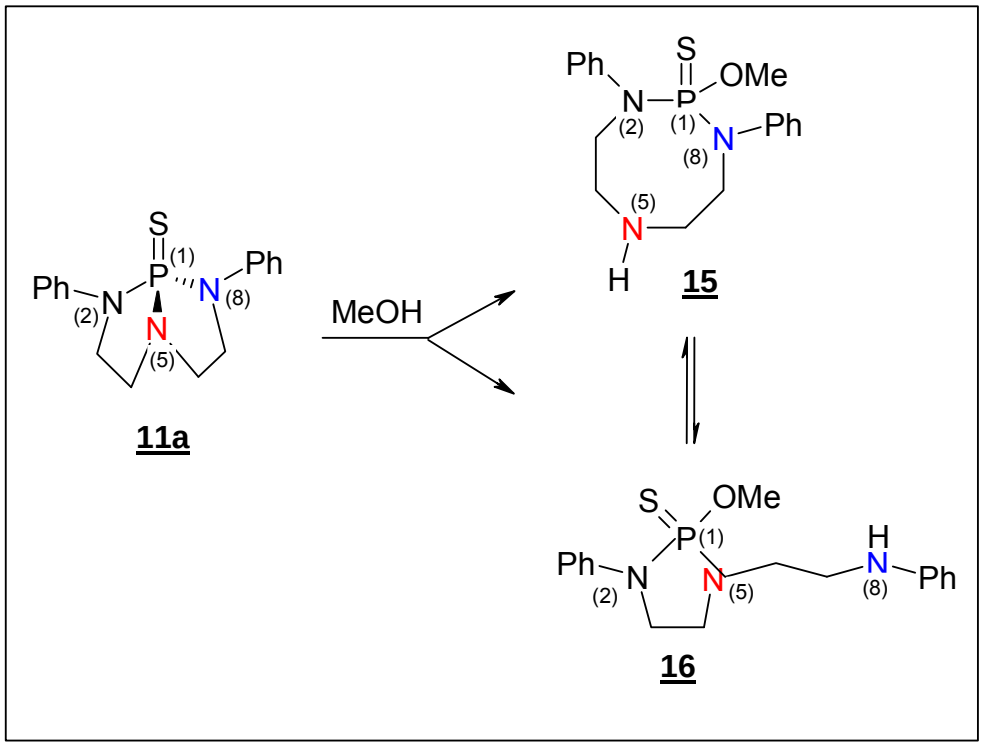
3.2.4 Rearrangement of the Alcoholysis Product , 15

Liberation of the free base of the alcoholysis product **15** resulted in a mixture of unknown phosphorus compounds. The free base was never isolated as a pure compound and therefore it was not possible to study the kinetics of the rearrangement of the eight-membered ring compound in analogy to the phosphoryl derivative.

Gas Chromatography-Mass Spectrometry (GC-MS) was employed to acquire information on the alcoholysis product **15**. Gas chromatography (GC) in combination with mass spectrometry (MS), is a technique with which the components of a complex mixture can be separated and identified even if present in amounts as low as 10^{-12} g. All forms of chromatography involve the partitioning of compounds between two phases, one mobile and one stationary. Each compound in a mixture partitions to a different degree between these two phases so that as they are carried along over a bed of the stationary phase, separation occurs. The components separated by gas chromatography are then eluted directly into the detector, in this case the mass spectrometer.

In the mass spectrometer the molecules are ionized in vacuum by a bundle of electrons. The fragmentation produces characteristic groups of ions of different masses. If the ions are separated according to their mass, a definite pattern of the number of ions present at each mass will be found. This pattern, the mass spectrum, is unique to a compound as fingerprints are to people. A compound can be identified by the mass spectrum.

From GC-MS analysis we got rather unexpected results. The analysis showed that the product contained two major compounds. One fraction contained the molecular ion of our expected product **15** (M^+ 347), but the fragmentation pattern revealed that *it is not* the substitution product, but in fact its isomer **16**. To form compound **15**, the P-N(5) bond is broken in compound **11a** and to form compound **16** the P-N(2)/P-N(8) bond is broken, giving the five-membered ring. The mass spectrum of that fraction, and the proposed fragmentation pattern are presented in **Figure 3.6** and **Scheme 3.13**, respectively.



Scheme 3.12 Cleavage of the P-N bonds in **11a**.

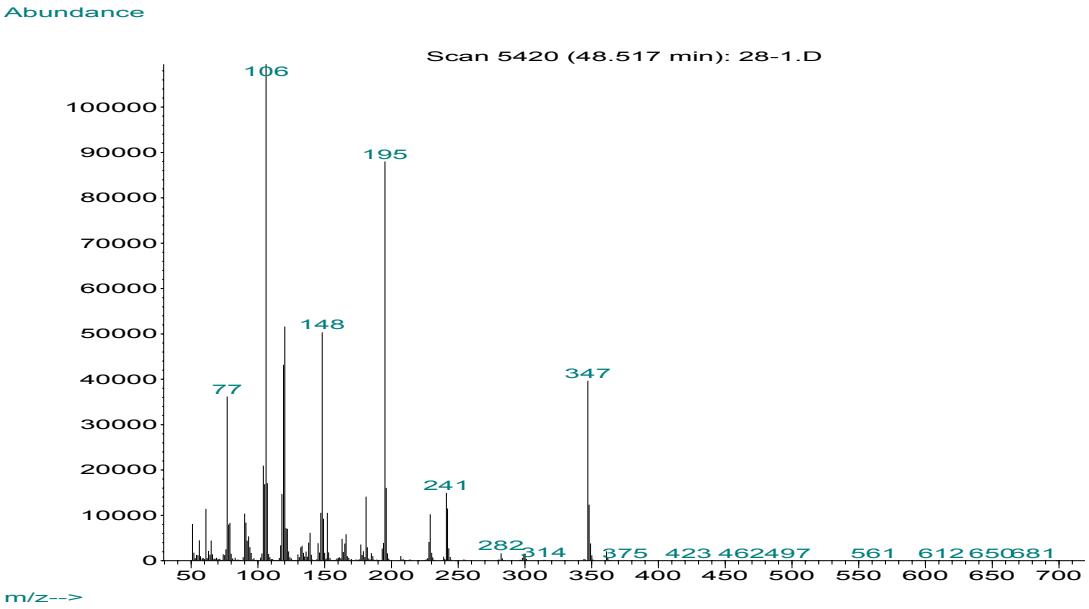


Figure 3.6 MS spectrum of fraction containing M^+ 347.

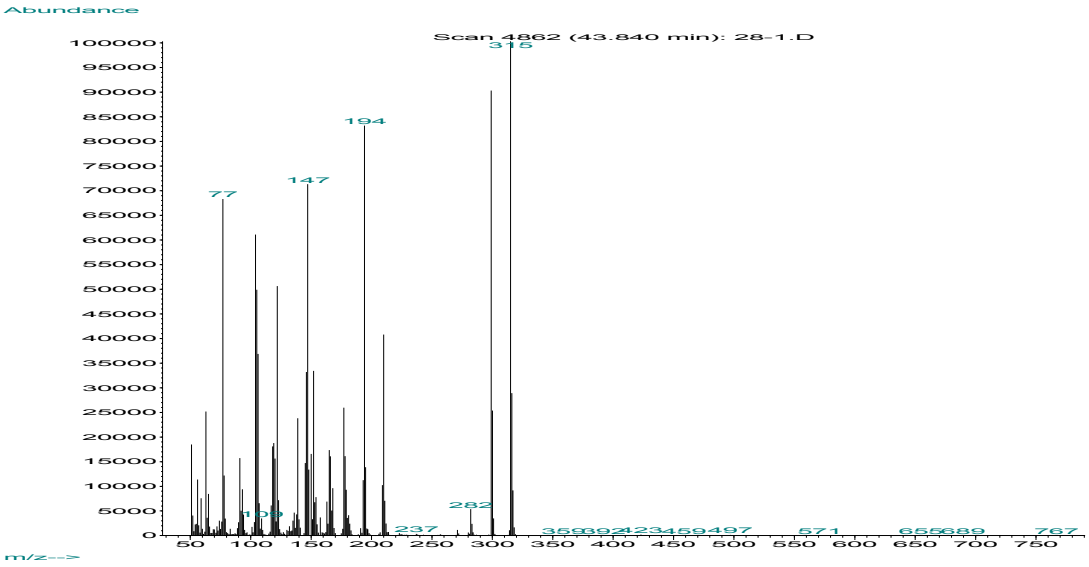
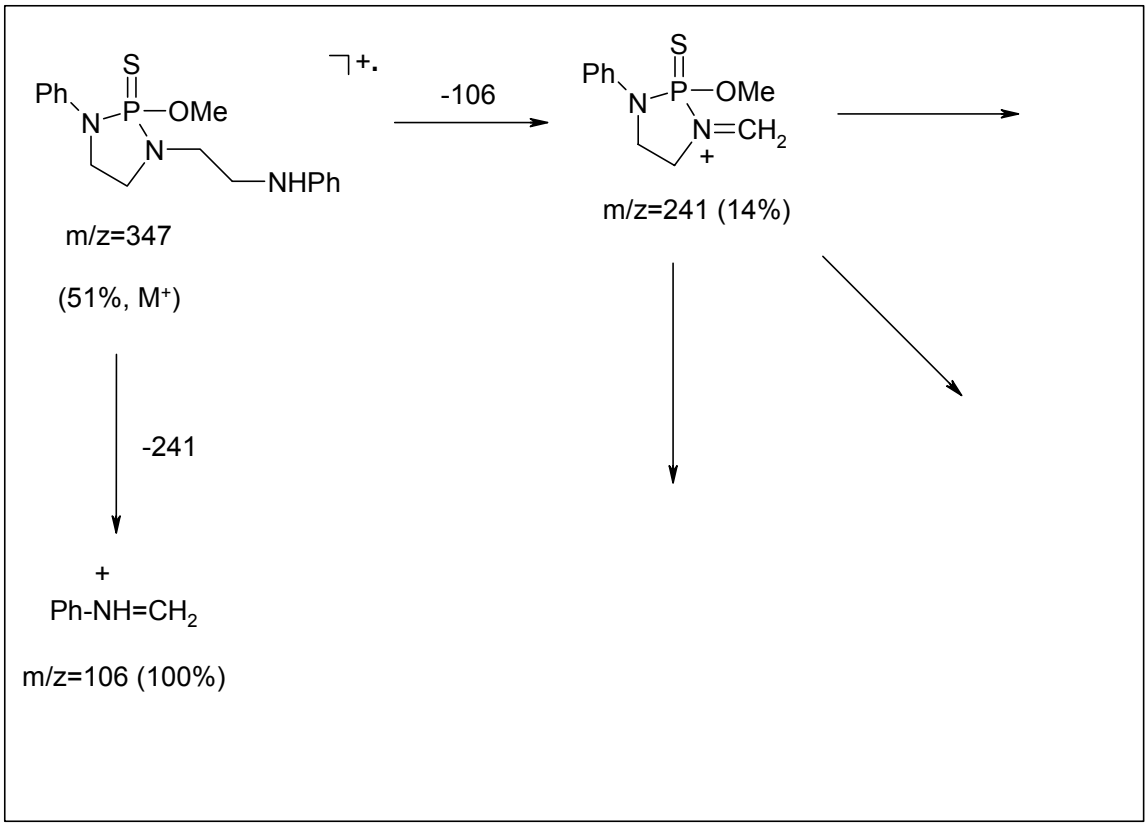


Figure 3.7 MS spectrum of fraction containing M^+ 299 and M^+ 315.



Scheme 3.13 Proposed MS fragmentation pattern of product **15**.

All the main fragments and mass losses can be explained accepting for the first fraction the structure of **16**. It is known that compounds with a heteroatom attached to an aliphatic chain, undergo α-cleavage[21], i.e. the molecule is cleaved between the α- and β-carbon with respect to the heteroatom. The substitution product **15** wouldn't give the same fragmentation pattern after α-cleavage**.**

The molecular ion loses a fragment with a mass of 241 resulting in a base peak with a mass to charge ratio (*m/z*) of 106. At the same time, the mass loss of 106 and the appearance of a low intensity peak of *m/z*=241 is also observed. These peaks (m/z=241 and m/z=106) are both generated by the α-cleavage with different distribution of electrons into both fragments.

The compound that was detected in the ^{31}P-NMR spectrum (δ_P 76), is the substitution product **15**. Product **15** is then rearranging to its isomer **16** under

conditions of GC-MS analysis due to the high temperature or the basic groups present on the GC column. This rearrangement is in analogy with the rearrangement observed for the corresponding phosphoryl derivatives.

The other fraction obtained in the GC-MS experiment contained the molecular ion of the starting material **11a** (M^+ 315) as well as of its phosphoryl analogue **3a** (M^+ 299) (**Figure 3.7**). This was very surprising, because the signal of substrate **11a** disappeared completely in the ^{31}P-NMR spectrum of the reaction product. What was even more confusing was the presence of the oxygen analogue, which was never present in the reaction system in the first place!

If the two standard mass spectra of **11a** and **3a** (obtained independently from the genuine samples of those compounds; (**Fig. 3.8 & 3.9**) are superimposed, they give exactly the same result as that obtained for the second fraction (RT 43.840 min.) of our compound **15**.

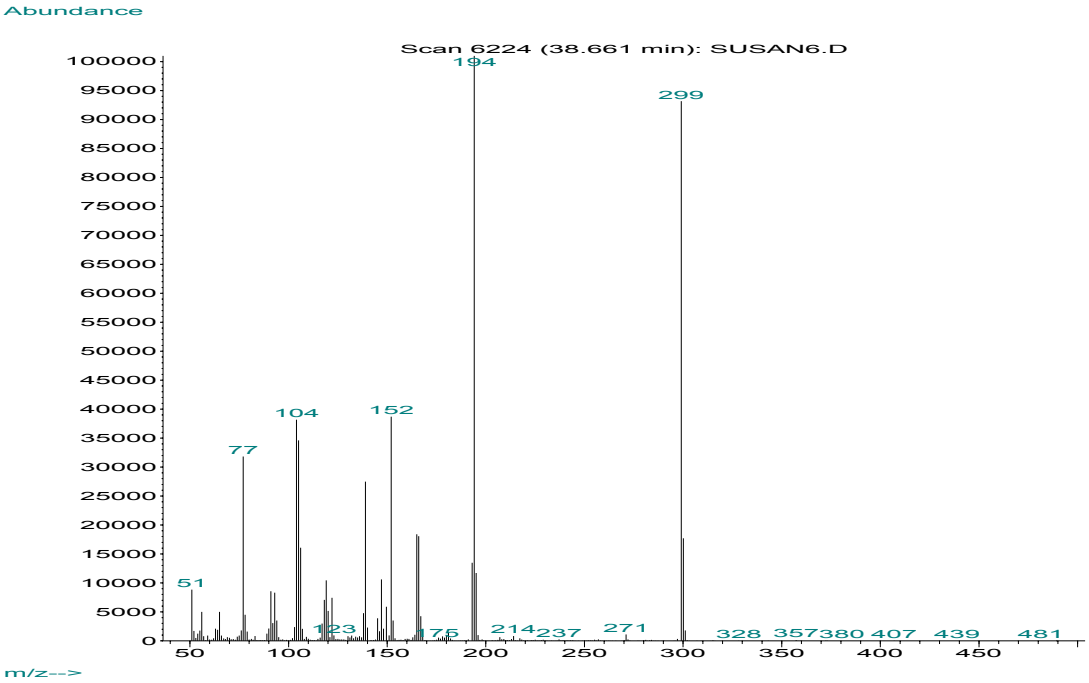


Figure 3.8 Standard MS spectrum of compound **3a**.

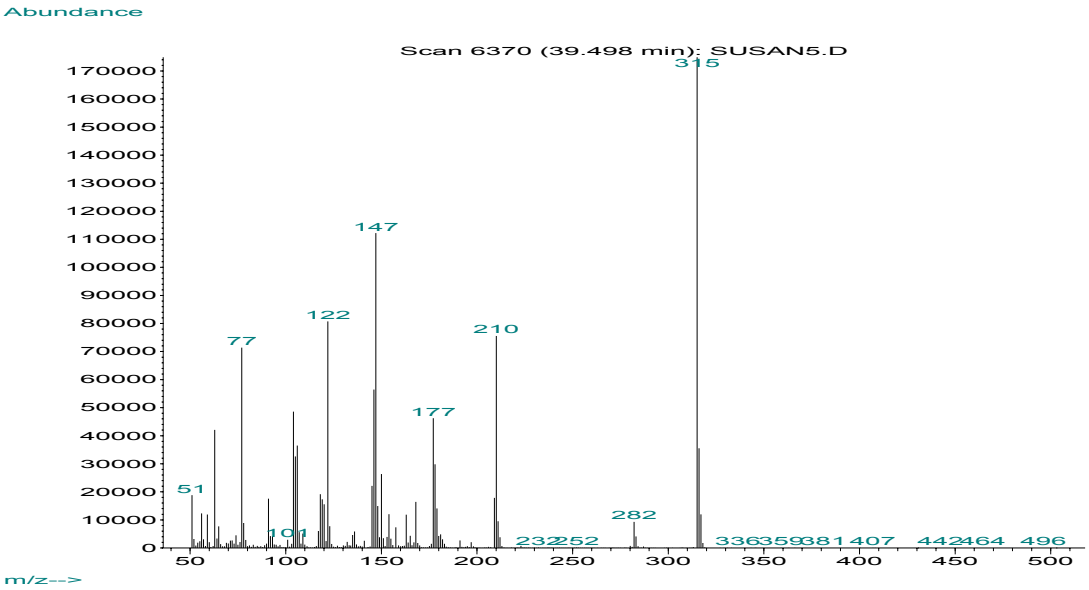
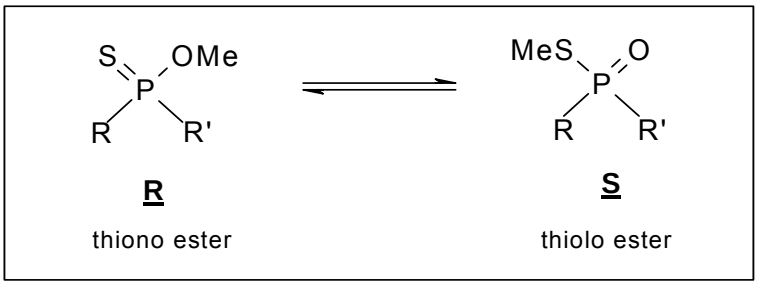


Figure 3.9. Standard MS spectrum of compound **11a**.

All the fragments and mass losses correspond to that of the standard spectra of the P=S (**11a**) and P=O (**3a**) containing bicyclic compounds.

Our explanation of the observed results is as follows. At high temperature, methyl esters of thiophosphoric acid, the thionophosphoric ester **R** can rearrange to the thiolophosphoric ester[22] **S** (**Scheme 3.14**).



Scheme 3.14. Thermal rearrangement of methyl thiophosphoric esters.

This rearangement was also observed in the mass spectra of a series of thionophosphate esters and amides studied by Cooks and Gerrard[23,24]. They

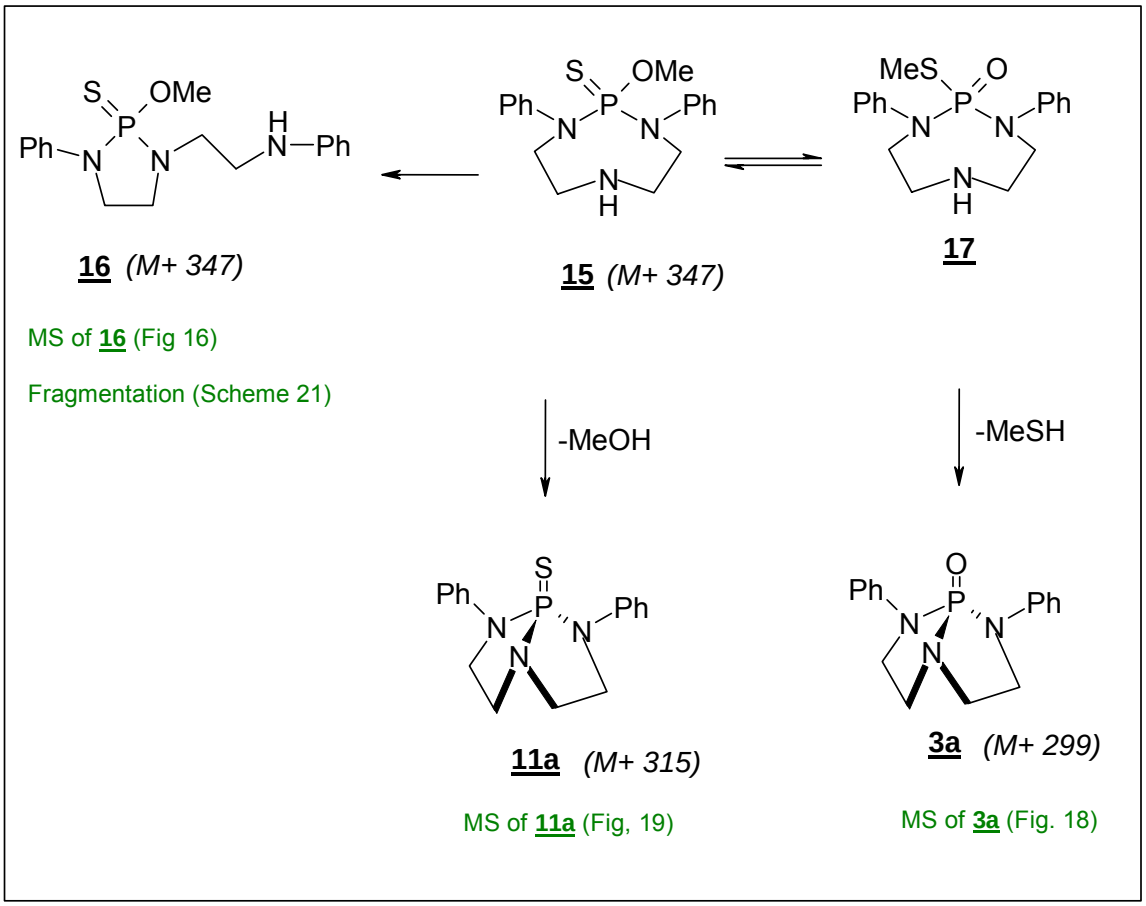
have established three important generalizations.

1. The molecular ion can rearrange before any fission occurs (**Scheme 3.14**). Spectra of thiono and thiolo esters were not identical. In the thiono isomer the ion M - CH3 is more prominent which indicated that the equilibrium between thiono and thiolo is not complete in the ion source. Spectra obtained at source temperatures of 60 and 200 degrees indicated that the rearrangement is of electron impact and not of thermal origin.

2. Rearrangement can give ions formed by joining two substituents, e.g. in the mass spectra of $P(S)(OPh)_2OMe$ were found ions of composition PhSPh, C_7H_7 and PhSMe. Ions of the composition PhOH and PhSH were also formed by hydrogen abstraction by one substituent from another.

3. Compounds with NHC_6H_6 substituents formed the base peak by loss of SH directly from the molecular ion. Deuteration of NH as well as the other substituents indicated that H is abstracted from the cyclochexyl ring; the loss of SH competes successfully with the McLafferty rearrangement, e.g. in compounds *i*-C_3H_8O-P(S)-, the ion M - SH was the base peak and the ion M - C_3H_8 was less than 5%.

According to our experimental results and the observations made by Cooks and Gerrard, our solvolysis product **15** (thiono ester) rearranges to the thiolo isomer. It can either lose methanol to form the substrate **11a** again, or the thiolo ester can lose MeSH directly to form the phosphoryl bicyclic compound **3a**. The following mechanism is proposed to explain the reappearance of the substrate **11a** as well as the phosphoryl bicyclic **3a** (**Scheme 3.15**).



Scheme 3.15 Proposed mechanism of the rearrangement of the thionoester **15**.

The alcoholysis reaction product **15** can therefore rearrange via three different reaction pathways. Firstly it can rearrange to the isomeric compound, the five membered ring **16**, lose MeOH to form substrate **11a** again or rearrange to the thiolo ester which can lose MeSH to form the phosphoryl bicyclic analogue **3a**.

3.2.5 Derivatives of 1-Thio-2,8-diphenyl-2,5,8-triaza-1λ^5-phosphabicyclo-[3.3.0]octane, 11a

Benzoylation

The hydrochloride salt **15** was treated with benzoylchloride in pyridine in order to prepare the *N*-benzoylated derivative **18.** ^{1}H NMR integrated for fifteen aromatic protons and eight aliphatic protons which was good indication that we have the benzoylated product. ^{31}P NMR spectrum contains a signal with the same

chemical shift as that of the substrate (compound **15).** All attempts to grow crystals suitable for X-ray analysis failed.

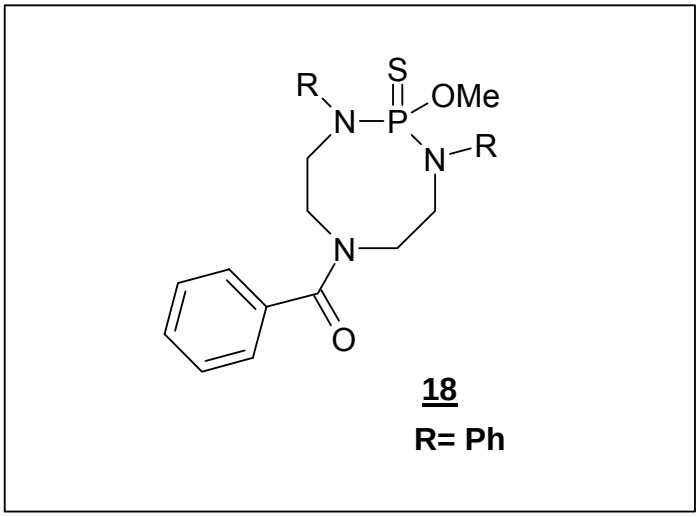
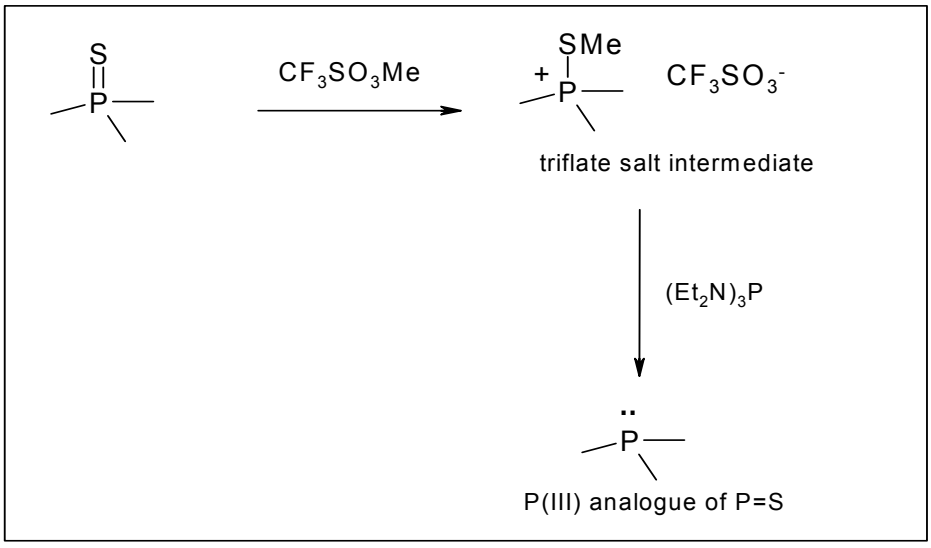


Figure 3.10 *N*-Benzoylated **15**.

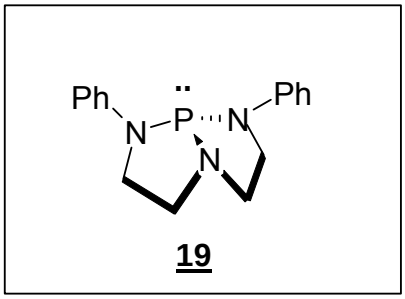
Reduction of the P=S bond

Omelanczuk[25,26] and co-workors decribed the reduction of thiophosphorus compounds by treating the 'P=S' compound with methyltriflate to form a stable intermediate product and then breaking the phosphorus-sulphur bond, leaving the phosphine [P(III)] analogue of the substrate.



Scheme 3.16 Reduction reaction to prepare P(III) analogues.

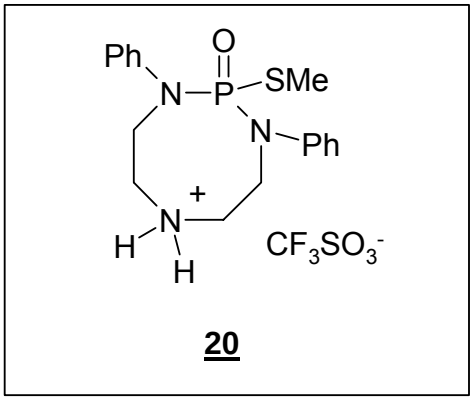
Compound **11a** was subjected to this same reaction conditions in order to prepare the phosphine triamide **19**, which we failed to prepare via the conventional route.



19

Figure 3.11 Phosphine derivative of bicyclic compound

Although the desired compound **19** was never isolated the reaction products were examined further. When the bicyclic compound **11a** was treated with the methyltriflate, a nonhomogeneous $CF_3SO_3^-$ salt was formed in 60 % yield (^{31}P 77.7 ppm. In attempts to crystallyze the salt, it was hydrolyzed, cleaving the P-N(5) bond, which lead to the thioloester **20**.



20

Figure 3.12 Triflate salt of the thiolo-ester.

The desulfurization reaction of the triflate salt resulted in many byproducts. The ^{31}P NMR signal at 104.5 ppm could possibly be assigned to the bicyclic

phosphine derivative **19**. The final reaction product couldn't be isolated in a state of satisfactory purity to do further analysis.

3.3 Experimental

3.3.1 Synthesis of new thio analogues

N,N-Bis(2-chloroethyl)thiophosphoramidic dichloride, 8

Rigorously dry bis(2-chloroethyl)ammonium chloride was dissolved in four mol-equivalents of freshly distilled $P(S)Cl_3$ and the solution was heated under reflux for 16 h. The excess of $P(S)Cl_3$ was distilled off and the product was purified by bulb-to-bulb distillation (20 °C/1 mm Hg);mp 32-34 °C (literature, mp. 33-34°C), 71%.

δ_P ($CDCl_3$): 62.6;

δ_H 3.87-4.04 (overlapping t and dt, 4 x CH_2).

The structure of the compound was confirmed by X-ray diffraction. (**Chapter 4**)

1-Thio-2,8-diphenyl-2,5,8-triaza-1λ^5-phosphabicyclo[3.3.0]octane, 11a

Bis(2-phenylaminoethyl)amine **13** (0.450 g, 1.8 mmol) and triethylamine (0.725 g, 7.2 mmol) were dissolved in rigorously anhydrous ether (50 mL). The solution was cooled to –10 °C, and freshly distilled $P(S)Cl_3$. (0.430 g, 2.5 mmol), dissolved in ether (10 mL), was added dropwise with stirring and cooling in the atmosphere of dry argon. The temperature of the mixture was kept between –20 and –10°C and was then allowed to warm up to room temperature. The precipitated triethylammonium chloride was filtered off and the filtrate was washed with a slightly basic aqueous solution (K_2CO_3). The filtrate was dried ($MgSO_4$), evaporated under reduced pressure, and the crude product (72%) was purified by column chromatography (CH_2Cl_2). The product (0.228 g, 41%) was obtained as colourless, crystalline material; m.p. 153 °C.

δ_P ($CDCl_3$): δ_P 81.5;

δ_H 3.21-3.31 (m, 2H), 3.62-3.78 (m, 4H), 3.83-3.92 (m, 2H), 7.01-7.06

(t, *J*=7.0 Hz, 2H), 7.16-7.25 (m, 8H);

δ_C 47.8 (s), 49.6 (d, *J*=16.2 Hz), 121.7 (s), 123.5 (s), 128.9 (s).

Elemental Analysis: $C_{16}H_{18}N_3PS$: Calculated: C, 60.93; H, 5.75; N, 13.32; S, 10.17% Found: C, 60.70; H, 5.85; N, 13.28; S, 9.98%.

The structure of the product was confirmed by X-ray diffraction. (**Chapter 4**)

Alternative procedure for the preparation of 11a

8.76 g of triamine **13** (free base) and 6.08 g of freshly distilled $P(S)Cl_3$ was refluxed in toluene (480 ml) for 14 days. The reaction mixture was allowed to cool down to room temperature , the undissolved material filtered off and the toluene solution washed with 10% K_2CO_3 (2x100 ml) and evaporated. The crude product was recrystallized from toluene several times to afford very pure colourless crystals. Yield: 57%, identical to previous product.

Bis(2-phenylaminoethyl)amine Trihydrochloride salt, 13'

1-Oxo-2,8-diphenyl-2,5,8-triaza-1λ^5-phosphabicyclo-[3.3.0]-octane **3a** which was used as the substrate was prepared as described before.[27] The product **3a** was not isolated, but the decanted reaction mixture was treated with 3 mol-equivalents of concentrated aqueous HCl. The solids were filtered off and washed with water. The product did not need further purification.

Yield: 86.5%, mp 220 °C (Lit. 203-206 °C).

δ_H (MeOD): 3.28 T, 4H, J_{HH}=5.9 Hz, 2 NCH_2), 3.49 (t, 4H, J_{HH}=6.0 Hz, 2 $ArNCH_2$), 6.67-6.71 (m, 6H, 4 o-H_{arom}, 2 p-H_{arom}), 7.15 (t, 4H, J_{HH}=6.0 Hz, 4 m-H_{arom})

δ_C (MeOH)41.1 (s, NCH_2), 48.1 (s, $ArNCH_2$), 114.3 (s, o-C_{arom}), 119.1 (s, p-C_{arom}), 130.3 (s, m-C_{arom}),149.1 (s, ipso-C_{arom}).

Free base, 13

The trihydrochloride salt (1.47 g) was mixed with 7 mL of 10 % aqueous NaOH. The mixture was stirred for several hours untill the free amine separated out as an oil. The amine was extracted with CH_2Cl_2 (4 x 20 mL). The CH_2Cl_2 solution was dried ($MgSO_4$) and the solvent evaporated leaving a dark brown oil.
Yield 0.662 g, 45%.

δ_H 2.88(t, 4H, J_{HH}=5.7 Hz, $2NCH_2$), 3.21 (t, 4H, J_{HH}=5.7 Hz, 2 $ArNCH_2$), 4.01 (br S, 3H, 3NH), 6.63 (d, 4H, J_{HH}8.0 Hz, 4 o-H_{arom}), 6.71 (t, 2H, J_{HH}=7.5 Hz, 2 p-H_{arom}), 7.18 (dd, 4H, J_{HH}=8.0, 7.5 Hz, 4 m-H_{arom}

δ_C 44.3 (s, NCH_2), 49.1 (s, $ArNCH_2$), 113.6 (s, o-C_{arom}), 118.1 (s, p-C_{arom}), 129.9 (s, m-C_{arom}), 149.0 (s, ipso-C_{arom})

Alternative procedure for the preparation of 13

Rigorously dry bis(2-chloroethyl)ammonium chloride (60g) and 208g aniline (24 moles excess) was mixed with 500 mL toluene and refluxed gently for 24 hours. The mixture was cooled to room temperature and the white precipitate filtered off. The precipitate was washed with toluene. The white solid (mixture of amines HCl salts) was stirred in 700 mL solution of 10% NaOH for 24 hours, to liberate the free amines. The mixture was extracted with CH_2Cl_2 (3 X 240 mL), dried over $MgSO_4$ and the solvent was evaporated. Ether was added to the dark brown oil to precipitate the desired triamine from the mixture. The triamine was further purified by extraction with hot methanol which gave a very pure white solid.
Yield 4.9 g,11.8% ,mp 240-244 °C.
Elemental analysis: $C_{16}H_{21}N_3$ Calculated: C 75.30, H 8.24, N 16.47%,
Found: C 75.15, H 8.4 ,N 16.01%

***N,N*-Bis(2-chloroethyl)-*N',N"*-dibenzylthiophosphoric triamide, 9b**

1.468g (5.3 mmol) of substrate, *N,N*-bis(2-chloroethyl)thiophosphoramido dichloride was dissolved in 15 ml of anhydrous benzene. A mixture of 1.142 g (10.6 mmol) benzylamine and 1.08 g (10.7 mmol) triethylamine in 15 ml

anhydrous benzene was added dropwise while stirring. The mixture was refluxed ona waterbath for 10 hours and left to cool down to room temperature. The white precipitate which contained the product as well as triethylammoniumchloride was filtered off and washed with 10 mL benzene and then with 100 ml ice-cold water. The solid product was dried under vacuum and then recrystallized from CH_2Cl_2.

Yield 74%, mp 163-164 °C (Lit. yield 70-82%, mp.160,5-161,5 °C).

δ_P 64.1;

δ_H 2.77 (2H, br dt, $^2J_{HP}$ 9.0, $^3J_{HH}$ 8.19),
3.19-3.33 (6H, m,),
4.10-4.37 (4H, m),
7.22-7.34 (10H, m)
7.80-7.95 (2H, m)

Elemental Analysis: $C_{18}H_{24}N_3PSCl_2$ Calculated: C 51.9, H 5.77, N 10.1, S 7.7%
Found: C 51.78, H 5.9, N 10.00, S 7.32%.

N,N'-dibenzylthiophosphoro diamidochloride, 12b

Benzylamine (1.96 g, 0.02 mol) and triethylamine (2.2 g, 0.022 mol) was dissolved in 50 mL of anhydrous THF and cooled down to –10 °C. $P(S)Cl_3$ (1.70 g, 0.010 mol) in 100 mL of THF was added dropwise while cooling. The reaction mixture was kept at low temp for 2 hours and then left to warm up to room temperature.The white ppt was filtered off and the solvent evaporated. The crude product was dissolved in $CHCl_3$, washed with water (2x 50 mL) and dried ($MgSO_4$). After evaporation of the solvent the product was recrystallized from MeOH.

Yield: (70%), mp. 160-163 °C

δ_P 65.1

δ_H 4.22-4.26 (4H, d, $^3J_{HP}$),
7.33-7.45 ($10H_{arom}$, m),

δ_C 46.1 (s, $ArNCH_2$), 127.7 (s, o-C_{arom}), 128.0 (s, p-C_{arom}),
129.0 (s, m-C_{arom}), 140.2 (s, ipso-C_{arom})

Elemental Analysis: $C_{14}H_{16}N_2PSCl$. Calculated: C 54.1, H 5.15, N 9.02, S 10.3% Found: C 54.9, H 5.30, N 8.85, S 9.99%.

Alcoholysis product *Hydrochloride salt* **15?**

Compound **11a** (1.347 g, 4.28 mmol) was dissolved in 1000 mL of anhydrous methanol. A solution of Me_3SiCl in anhydrous methanol was added (0.477g) and stirred for 5 minutes. The solvent and volatile reaction products were evaporated. Yield 100% , mp 180 –182 °C .

δ_P 75

δ_H 3.21 (3H, d, $^3J_{HP}$ 13.81), 3.25-3.55 (4H, m), 3.8-4.05 (2H, m), 4.1-4.28 (2H, m), 7.2-7.55 ($10H_{arom}$, m)

Elemental analysis: $C_{17}H_{23}N_3OPSCl$ Calculated C 53.2, H 6.0, N 11.0, S 8.3% Found: C 53.17, H 6.12, N 10.11, S 7.80%.

Free base

0.285 g of the hydrochloride salt **15** was dissolved in 20 mL of $CHCl_3$. The solution was washed with 2 x 15 mL of 10 % K_2CO_3 , dried and the solvent evaporated. This product was used immediately for the benzoylation reaction. Yield: 73%.

***N*-Benzoylated alcoholysis product, 18**

0.188 g (0.5 mmol) of product **15** and 3 mL of dry pyridine was dissolved in 15 mL benzene. Benzoylchloride (0.250 g, 1.8 mmol) in 15 mL benzene was added dropwise while cooling (0 °C) and stirring . The reaction mixture was refluxed on a waterbath for 1 hour. A bright yellow precipitate was formed. The benzene solution was decanted and the yellow precipitate washed with benzene (2x20mL). The benzene was discarded. The yellow solid was dissolved in $CHCl_3$, washed with water, dried and the solvent evaporated under reduced pressure. The product was recrystallized from toluene. Yield 26.8%, mp. 161-165 °C.

δ_P 75 (74.9918)

δ_H 3.35 (3H, d, $^3J_{HP}$ 13.9), 3.44-3.56 (2H, m), 3.75-3.9 (3H, m), 3.95-4.15 (3H, m), 7.15-7.4 (15H, m)

δ_C (s, OCH_3), 46.86 (s, CH_2), 49.49 (s, CH_2), 51.64 (s, CH_2), 51.84 (s, CH_2), 127.04 (s, o-C_{arom}), 128.07 (s, p-C_{arom}), 129.21 (s, m-C_{arom}), 136.26 (s, ipso-C_{arom}), 172.1 (s, C=O)

Elemental analysis: $C_{24}H_{26}N_3O_2PS$ Calculated C 53.2, H 6.0, N 11.0, S 8.3%
Found: C 53.0, H 6.1, N 11.5, S 8.7%

3.3.2 GC-MS Analysis

A 1 μL aliquot of the sample was injected into the injection port of a Hewlett Packard 5890 series II "plus" gas chromatograph, using a HP 7683 auto injector. Data collection and instrument control was performed with a HP 59970 MC ChemStation. The injector port temperature was set to 250°C, and splitless injection was performed. Separation was achieved with a DB-1 capillary column, J & W Scientific (30m x 0.25 mm and 0.1 μm film thickness) at a helium flow rate of 1.0 mL/min. An initial oven temperature of 100°C was held for 3 minutes and subsequently raised at a rate of 5 °C/minute, up to 250°C, and then held for 40 minutes at that temperature. The column outlet was inserted directly into the ion source of a HP 5973 Mass Selective Detector (Hewlett Packard). The mass spectrometer was operated with a filament current of 300 μA and electron energy of 70 eV in the electron ionisation (EI) mode. The mass range scanned was 50-800 atomic mass units (amu). The transfer line was set at 280°C, and the quadrupole and source temperatures were 150°C and 230°C, respectively.

3.4 References

1. H. Schiff, *Ann.*, **101**,299 (1857).
2. J. Emsley, D. Hall, in *"The Chemistry of Phosphorus",* Harper and Row, London, (1976).
3. C. Stuebe, H.P. Lankelma, *J. Am. Chem. Soc.,* **78**, 976 (1956).

4. H-J. Vetter, *Z. Naturforsch,* **196**, 72 (1964).
5. H-J. Vetter, H. Nöth, *Chem. Ber.,* **96**, 1308 (1962).
6. V. Dorn, H. Welfle, *J. Prakt. Chem.,* **313(2)**, S218 (1971).
7. K. Sasse in Organische Phosphor-Verbindungen; Thieme: Stuttgart, 1964; part 2, p 749.
8. M.P. Coogan, M.J.P. Harger, *J. Chem. Soc. Perkin Trans. 2,* 2101 (1994).
9. C. Tang, H. Lang, Z. He, R. Chen, *Phosphorus, Sulphur and Silicon,* **114**, 123 (1996).
10. E.J. Reist, I.G. Junga, B.R. Baker, *J. Org. Chem.,* **25**, 666 (1960).
11. W. Autenrieth, P. Rudolph, *Ber.,* **33**, 2112 (1900).
12. P. Rudert, *Ber*., **26**, 565 (1893).
13. S. Fischer, J. Hoyano, L.K. Peterson, *Can. J. Chem.,* **54**, 2710 (1976).
14. A. P. Marchenko, A.M. Pinchuk, N.G. Feshchenco, *J. General Chem. USSR,* **43**, 1900 (1973) (Engl. 1887) *Russian Journal of General Chemistry.*
15. Phosphorus-31 NMR Spectroscopy in Stereochemical analysis, J.G. Verkade, L.D. Quin Ed (1987).
16. D.P. Pienaar, T.A. Modro, A.M. Modro, *Synthesis,*1315 (2000).
17. V. Prelog and G.J. Driza, *Coll. Czech. Chem. Commun.,* **5**, 497 (1933).
18. S. Laurens, V. Ichharam, T.A. Modro, *Heteroatom Chem.,* **12 (5)**, 327 (2001).
19. I.M. Aladzheva, D.I. Lobanov, O. V. Bykhovskaya, P. V. Petrovskii,T.A. Mastriukova, *Doklady Chemistry (Translation of the chemistry section of Doklady Akademii Nauk)*, **30-32**, 3881 (2003).
20. J. Rahil, P. Haake, *J. Am. Chem. Soc.,* **103**, 1723 (1981).
21. F.W. McLafferty, Interpretation of Mass Spectra, 3rd ed.;University Science Books: Mill Valley, 1980.
22. K. Sasse in Organische Phosphor-Verbindungen; Thieme: Stuttgart, 1964; part 2, pp 597, 668-670, 784.
23. R.G. Cooks, A.F. Gerrard, *J. Chem. Soc. B,*1327 (1968).
24. R.G. Gillis, J.L. Occoclowitz in *Analytical Chemistry of Phosphorus Compounds,* Ed. M. Halmann (1972).
25. J. Omelanczuk, M. Mikolajczyk, *Tetrahedron Lett.,* **25**, 2493 (1984).
26. J. Omelanczuk, M. Mikolajczyk, *J. Am. Chem. Soc.,* **101**, 7292 (1979).
27. H. Wan, T.A. Modro, *Synthesis*, 1227, (1996).