Synthetic applications of

bicyclic phosphoric triamides

by

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My family and friends;

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ABSTRACT

Bis(2-arylaminoethyl)amines cannot be efficiently prepared by the obvious route from bis(2-chloroethyl)amine and anilines, as intramolecular cyclisation to piperazine is favoured over a second substitution to form the open triamine. A series of bis(2-arylaminoethyl)amines was successfully prepared *via* a new and general route, the facile cleavage under acidic conditions of the corresponding bicyclic phosphoric triamides. In some cases, the resultant amines were functionalised further, eg. yielding the trihydrochloride salts and the tri-N-acetylated derivatives. The base hydrolysis of the bicyclic phosphoric triamides in turn, may lead to the formation of interesting amino acids or zwitterions, as demonstrated for one of the derivatives.

OPSOMMING

Bis(2-arielaminoetiel)amien kan nie doeltreffend volgens die logiese roete vanaf bis(2-chloroetiel)amien en die anilien voorberei word nie, aangesien intramolekulêre ringsluiting meer gunstig is as 'n tweede intermolekulêre substitusie, sodat die piperasien as hoofproduk verkry word. 'n Reeks bis(2-arielaminoetiel)amiene is voorberei deur gebruik te maak van 'n nuwe en algemene roete naamlik die suurhidrolise van die ooreenstemmende bisikliese fosfortriamiede. In sommige gevalle is derivate soos bv. die hidrochloriedsoute en die tri-N-asetiel derivate voorberei. Boonop kan interessante aminosure of zwitterione gevorm word wanneer die fosfortriamiede onder basiese toestande gehidroliseer word, soos aangetoon vir een van die derivate.

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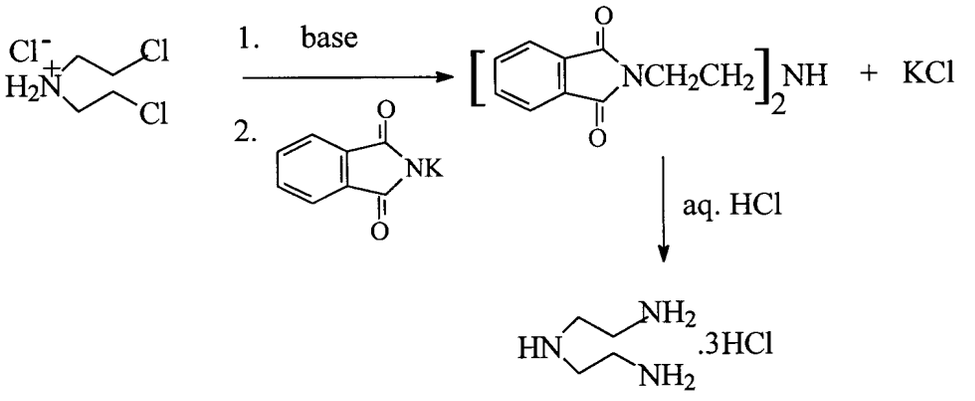
1. INTRODUCTION

1.1. Ethyleneamines

Ammonia- and amine-metal complexes are among the longest known and most intensively studied [1]. Amines may be subdivided into alkyl substituted or aryl substituted on the basis of significant chemical differences as demonstrated by their acid-base behaviour, eg. aniline (an aromatic amine), due to resonance stabilisation, is considerably less basic, $pK_b = 9.37$, and therefore less nucleophilic, than methylamine (an aliphatic amine) with $pK_b = 3.36$. The lone pair orbital on the nitrogen, which can overlap with an empty orbital on a metal, makes amines good σ-donor ligands. Primary and secondary amines can be deprotonated further, giving rise to *amido* (NR_2^-, a σ- and π-donor) and *imido/nitrene* (NR^{2-} σ- and double π-donor) ligands.

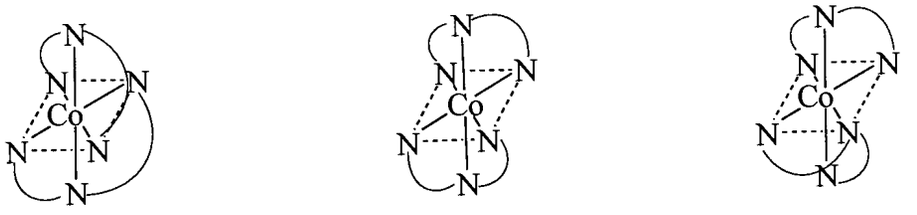
The ethyleneamines comprise a group of compounds having amino groups interconnected by ethylene group(s). Hofmann [2] was the first to isolate these compounds, chiefly ethylenediamine (*en*), from the reaction of ethylene dichloride and dibromide with ammonia. However, many side-products, mainly due to intramolecular cyclisation and polymerisation, were obtained when using his methods and some of the compounds were difficult to purify. Chemists like Mann [3], and Ueda and Kobayashi [4], improved the procedure, mainly by using the Gabriel synthesis which involves "protection" of the amine nitrogen by phthalimidation, followed by basic/acidic hydrolysis of the N-alkyl phthalimide (scheme 1).



Scheme 1: Gabriel synthesis of *dien*.

During this project, we were mainly concerned with diethylenetriamine (*dien*), and its derivatives, $R_2N\text{-}CH_2CH_2\text{-}N'R\text{-}CH_2CH_2\text{-}N''R_2$, where R= H and/or any substituent/s. This tridentate ligand can form both square planar and octahedral complexes and its complexation to Co(III), Cr(III), Cu(II) and Ni(II) has been particularly well studied. So, for example, it has long been known that three isomers [5] are formed when Co(III) octahedrally complexes with two equivalents *dien* (scheme 2).

meridional: *sym-facial:* *asym-facial:*

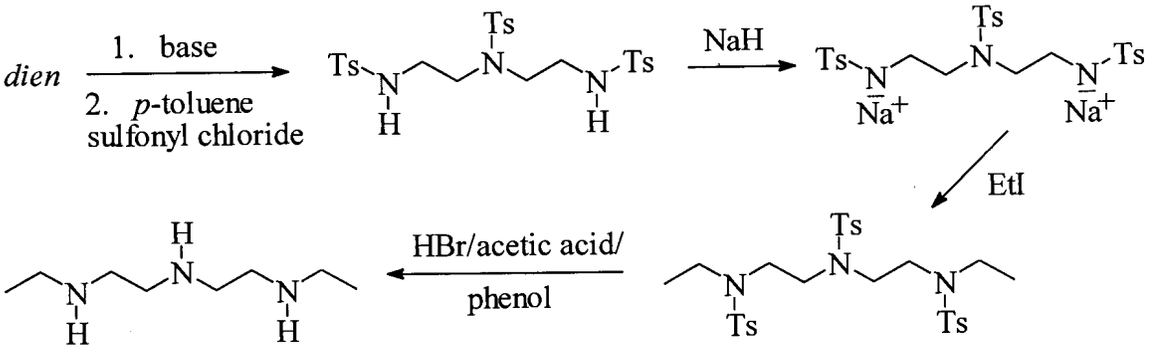


Scheme 2: Geometric isomers of Co(*dien*)$_2^{3+}$.

Derivatisation of *dien*, either through C- or N-substitution, affords interesting ligands, all of which can potentially coordinate a metal *via* two five-membered chelate rings. Many C- and N-alkylated derivatives have been prepared and their complexes studied. An obvious and generally used N-substitution method is the reaction of the free ligand with alkyl halides. In this way, N,N,N',N",N"-Me_5- and Et_5-*dien* may be prepared. A compound like N,N,N",N"-Et_4-*dien* can probably be prepared by reacting 2 equivalents diethylamine with bis(2-haloethyl)amine. Cyclisation cannot occur as the terminal N's are tertiary (see later). Complex ions of the latter ligand with palladium(II) and platinum(II), have played a prominent role in the elucidation of the substitution mechanisms of square-planar metal complexes [6]. For Pd(N,N,N",N"-Et_4-*dien*)X^+, it was proved that, contrary to predictions, the alkyl groups do not block the axial positions in a pseudo-octahedral arrangement, but that they are quite open [5], so bulky substituents do not seem to change complexation much. Wills *et al* used the Et_4 ligand to study Ti and V triads and managed to produce the first dialkylamidovanadium complex containing anionic ligands available for other transformations [7].

Large substituents like p-toluenesulfonyl (tosyl), picryl and benzoyl only monosubstitute the terminal nitrogens of *dien* due to steric hindrance and can be used to prepare the specific derivatives where all nitrogens are secondary (2° *dien*), eg. the

disodium salt of tritosylated *dien* is treated with 2 eq. of the alkyl halide, and the tosyl groups are removed by treatment with HBr/acetic acid/phenol [8] (scheme 3):

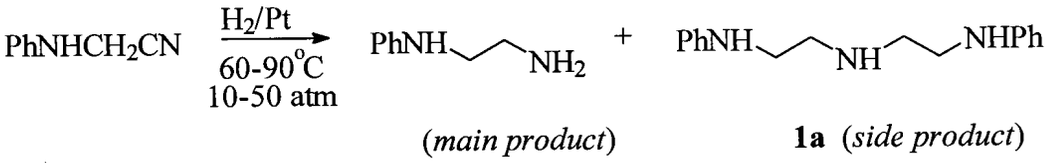


Scheme 3: Synthesis of N,N"-Et_2-*dien*.

For the unique case of bis(2-arylaminoethyl)amine, Ar-NH-CH_2-CH_2-NH-CH_2-CH_2-NH-Ar, the situation proved particularly difficult. Aryl halides won't react with *dien*, so the obvious route seems to be the reaction of the aniline with bis(2-chloroethyl)amine, a N-mustard compound which has been well studied in our laboratory. Prelog and Driza [9] reported on this experiment in 1933. When refluxing equal masses of bis(2-chloroethylamine) and aniline in methanol for 16 hours, they obtained N-phenylpiperazine and the mother liquor contained some bis(2-phenylaminoethyl)amine. The experiment was repeated under different conditions in our laboratory and proves that intramolecular cyclisation to the piperazine derivative is indeed favoured (see later).

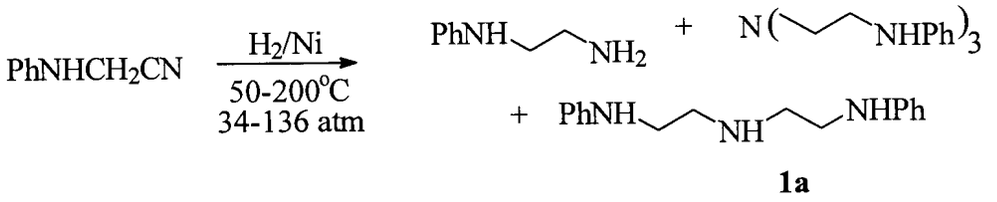
Bis(2-phenylaminoethyl)amine, **1a**, was isolated in small quantities (scheme 4) by Münch and Schlichting [10] (4a) and Salzberg [11] (4b), together with other amines, when reducing N-phenylglycinenitrile with a hydrogenating catalyst under pressure, and the products can be used as vulcanisation accelerators, antioxidants or insecticides:

(4a)



(*main product*) **1a** (*side product*)

(4b)



1a

Scheme 4: Reduction of N-phenylglycinenitrile under different conditions of temperature and pressure.

Furthermore, **1a** was obtained as a side-product (35%), together with N-phenylethylenediamine (65%), in the reaction of N-(2-chloroethyl)aniline with liquid ammonia [12]. Hence, to our knowledge, no clear-cut synthesis of **1a** in good yield has been accomplished.

The preparation of N'-phenyl-*dien* and precursors, by a modified Gabriel synthesis, has been reported [4]. N-substituted diethanolamine was first prepared by reacting chloroethanol with an arylamine in the presence of $CaCO_3$, followed by chlorination with thionyl chloride to give the bis(2-chloroethyl)amine. Reaction with potassium phthalimide, followed by hydrolysis with hydrazine hydrate, gave the N'-substituted bis(2-aminoethyl)amine (20%). The same compound was synthesised by Nakajima [13] *et al* in higher yield (80%). Instead of chlorinating N-substituted diethanolamine, they acetylated it and then followed the same procedure. N-phenyl-*dien* could also be prepared by this method.

Another analogous compound, N, N'-diphenyl-*en* (1,2-dianilinoethane), has been synthesised by various procedures. Gomez Aranda [14] *et al* discovered that in the presence of thallium(III) acetate, aromatic amines add to olefinic double bonds to give *vic*-bis[arylamino]-alkanes. So, for example, aniline reacted with ethylene to give N, N'-Ph_2-*en* (81%). It seems highly unlikely to form **1a** according to this mechanism as internal cyclisation or double addition of aniline to the olefinic bonds in a compound like bis(ethylene)amine would occur. The reaction of sodium acetanilide with 1,2-dibromoethane gives diacetylated N, N'-Ph_2-*en* (3.9%) and acid hydrolysis affords the amine hydrochloride (99%) [15]. This method was tested in our laboratory for the synthesis of **1a**, but did not work.

N, N'-Ph_2-*en* has found many applications. In 1953, it was discovered that it reacts with aldehydes in weakly acidic media to give imidazolidines [16], a useful analytical technique for "trapping" aldehydes selectively in the presence of ketones and other compounds thereby forming high-melting derivatives which can be quantitatively determined [17], eg. by gas-liquid chromatography. Hence, it became known as Wanzlick's reagent. Büchi [18] *et al* used this amine in a pharmacological study of ethylenediamides as pain killers.

Several organometallic complexes were prepared with this ligand. For example, by preparing $[Cu(C_6H_5NHCH_2CH_2NHC_6H_5)_2]$-$(ClO_4)_2$, it was shown that, contrary to previous findings, substituted ethylenediamines do not always, due to steric limitations, form hydroxy-bridged dinuclear complexes with small metals such as Cu(II) [19]. Another study on Pd(II) complexes used infrared spectroscopy to deduce the strength of metal-ligand interaction in substituted *en* complexes. N, N'-Ph_2-*en* coordinated weakest when compared to the N-alkylated derivatives, due to both inductive (low basicity) and steric factors, but the square planar complex was nevertheless isolated as a stable compound [20]. Pt(N-Ph-*en*)$_2^{2+}$ has also been prepared [5].

An interesting study by Gampp [8] *et al* revealed that derivatisation of *dien* may lead to the formation of pentadentate chelate complexes of Cu(II). Instead of the generally preferred tetragonal arrangement of ligands around Cu(II), distorted square pyrimidal or trigonal bipyramidal geometries may result. They used six ligands with the following parent structure: $RCH_2NHCH_2CH_2NHCH_2CH_2NHCH_2R$ (R= Me, CH_2-CN, CH_2-$C(O)NH_2$, CH_2-COOH, CH_2CH_2-NH_2 and CH_2-2-phenol). These can all be seen as derivatives of N-alkylated 2° *dien*, and are relatively easily prepared (some by specific methods). Using spectrophotometric pH titrations, the authors could deduce, by noticing the shifts from reference λ_{max}-values, which complex was formed at which pH. They found the latter four ligands to be pentadentate chelators when the amine groups were deprotonated.

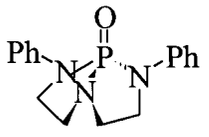
The possibility of wide variations of electronic (basicity and nucleophilicity) and steric nature when introducing substituents to the aromatic groups, as well as at the nitrogen atoms which can be further reacted, makes bis(2-arylaminoethyl)amines attractive derivatives of *dien*. The relatively large expected basicity difference between the dialkylated central N (diethylamine has $pK_b = 3.06$) and the aromatic terminal N's (N-

methylaniline has $pK_b = 9.15$), and the described "non-innocent" behaviour of aromatic amines w.r.t. complexation [5], may equip the ligand with unique coordinating properties.

1.2. Phosphoric amides

Phosphoric amides are considerably less widespread than carboxylic amides due to the remarkably low stability of the (O)P-N bond under acidic conditions. Their physical and chemical characteristics have long been studied in our laboratory. They have shown diverse biological activity (eg. as insecticides and, in the case of N-phosphorylated nitrogen mustards, as antitumour agents), and due to their ability to both donate and accept hydrogen bonds, some chiral, racemic phosphoramidates can act as chiral recognition agents by the formation of diastereomeric complexes.

During the past few years, a series of phosphoric triamides (and diamido esters etc.) were prepared in our laboratory. The main aim of this work was to study the physical characteristics of these compounds. In so doing, valuable structural and reactivity characteristics could be deduced by the correlation of, for example, X-ray crystallographic data and NMR properties. More recently, new heterocyclic phosphoric triamide systems which incorporated P in 5-membered rings, were prepared to evaluate the ^{31}P NMR shift dependence on N-P-N bond angles [21] :



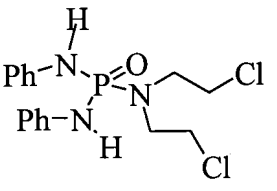
I

II

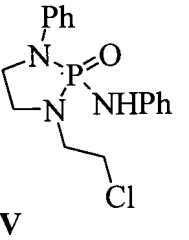
Scheme 5. Phosphoric triamides prepared before.

The results showed that, as amide nitrogens become increasingly incorporated into the rings, the N-P-N bond angles decrease, and the P nucleus becomes more and more deshielded. A high ^{31}P chemical shift (32 ppm) was therefore obtained for **I**, and an even higher shift (98 ppm) for **II**. A ^{15}N NMR study [22] then showed that each cyclisation to produce **I**, results in a drastic reduction in $^{1}J(P,N)$ coupling for both N-alkyl and N-phenyl nitrogens. This was due to the decreasing s-character of the N

bonding orbital, or increasing conjugation of the N lone pair with P (indicated by a high-frequency ^{15}N shift), which makes the N less basic than its exocyclic counterpart. Therefore, one would expect the endocyclic P-N bonds in **I** to be slightly less acid-labile than in the precursors (depicted below in scheme 6), according to the generally accepted mechanism of acid-hydrolysis of P-N bonds in phosphoric amides (see later).



III



IV

Scheme 6. Precursors of **I.**

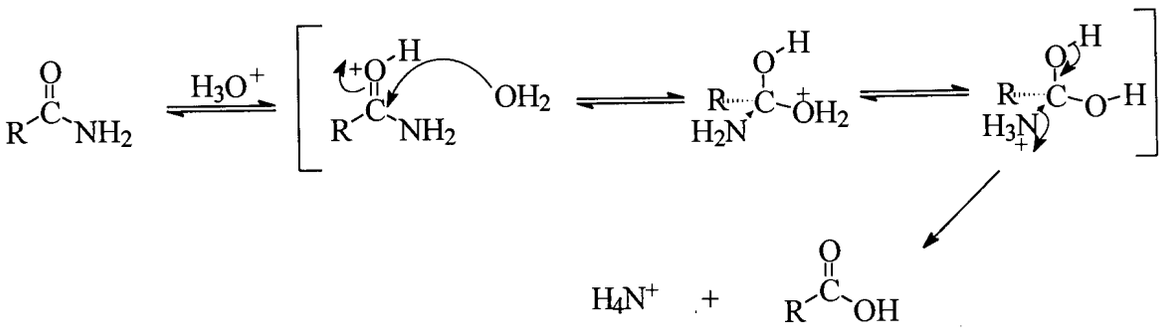
Furthermore, X-ray diffraction [23] revealed that the torsion angle O=P-N-H in **IV** was close to 0°, so that this function should be able to form a 1:1 H-bonded complex with the general structure R-Y(O)OH, thereby being a potential chiral recognition agent. This was further demonstrated when the diffraction data of an analogous compound, 1-phenyl-2-(benzylphenylamino)-2-oxo-3-(2-chloroethyl)-1,3,2-diazaphospholidine, in which the exocyclic phenyl was replaced by a benzyl group, clearly indicated an intramolecular C-H···O hydrogen bond [24].

1.3. Cleavage of the P-N bond in phosphoric amides

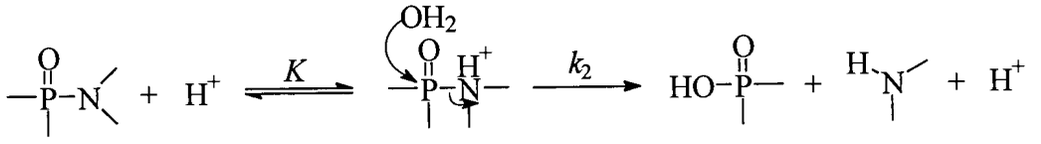
1.3.1. Acid hydrolysis

As mentioned before, the P-N bond in phosphoric amides is generally much more acid-labile than the C-N bond in carboxylic amides, eg. diphenyl phosphinamide hydrolyses 10^5 times faster than benzamide under acidic conditions [25]. This phenomenon has found synthetic application in the preparation of chiral organophosphorus compounds [26] and in the preparation of aliphatic amines by a modified Gabriel procedure [27]. The generally accepted mechanisms for the acid hydrolysis of amide bonds in phosphoric and carboxylic amides, respectively, are represented in scheme 7.

(7a)



(7b)



Scheme 7: Acid-catalysed hydrolysis of carboxylic (7a) and phosphoric (7b) amides.

In carboxylic amides, O-protonation is followed by the rate-determining formation of a tetrahedral intermediate (the A_0^2T mechanism), which can be greatly affected by the electrophilicity of the carbonyl C and steric congestion around the amide function. Once the intermediate has formed, proton transfer and amine displacement are expected to be rapid. In this case, the rate of hydrolysis has been shown to be less dependent on the basicity of the N.

In phosphoric amides, protonation at the N atom transforms the amine into an excellent leaving group so that bimolecular, direct displacement at P can occur when the water molecule attacks (the A-S_N2 mechanism). Because both protonation and substitution usually occur rapidly, the cleavage of the P-N bond is remarkably facile under acidic conditions. The nature of the substituents are expected to have only a weak effect on rate, since differences (eg. in N basicity or steric hindrance) should affect the protonation equilibrium and substitution step in opposite directions. However, according to the proposed mechanism, small variations in reactivity can be expected.

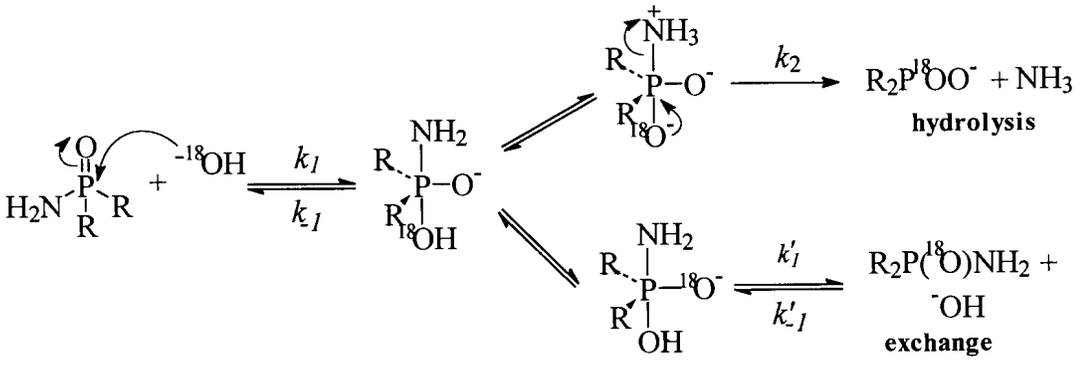
This was illustrated well by rate data collected in our laboratory when hydrolysing a series of dimethyl N-arylphosphoramidates [28], $(MeO)_2P(O)NHAr$, substituted in the

ring with alkyl groups. As expected, the rate of hydrolysis increased with increase in basicity (or pK_a). However, *ortho*-substituted amidates gave a linear plot (log k_{obs} vs pK_a) with a much steeper slope (0.90) than that of the *meta*- and *para*-substituted amidates (slope = 0.41). This was due to steric hindrance imposed by an alkyl group at the *o*-position which made *o*-substituted anilines less basic so that protonation of N occurred less readily. Bulkier substituents drastically enhanced the effect, hence the larger slope. For the *p*- and *m*-substituted anilines, only electronic factors played a significant role.

The mechanism of N-protonation followed by bimolecular displacement was also illustrated when a phosphoramidate with its N inside a 5-membered ring hydrolysed 4 x 10^3 times faster than the isomeric amide with N exocyclic [29]. This was explained by Westheimer's theory which predicts that, a S_N2 reaction involving a trigonal bipyramidal intermediate, followed by the displacement of an amine group, should occur more rapidly when the N is incorporated into a five-membered ring, a sterically favourable situation as the nucleophile attacks from the top axial position. The mechanism should therefore also be accompanied by an inversion of configuration in chiral phosphoramidates.

1.3.2. Alkaline hydrolysis

In contrast to acidic hydrolysis, alkaline hydrolysis rates for carboxylic and phosphoric amides are usually similar, indicating that they are equally susceptible to nucleophilic reaction. The mechanism, for phosphoric amides, may be depicted as follows [30]:



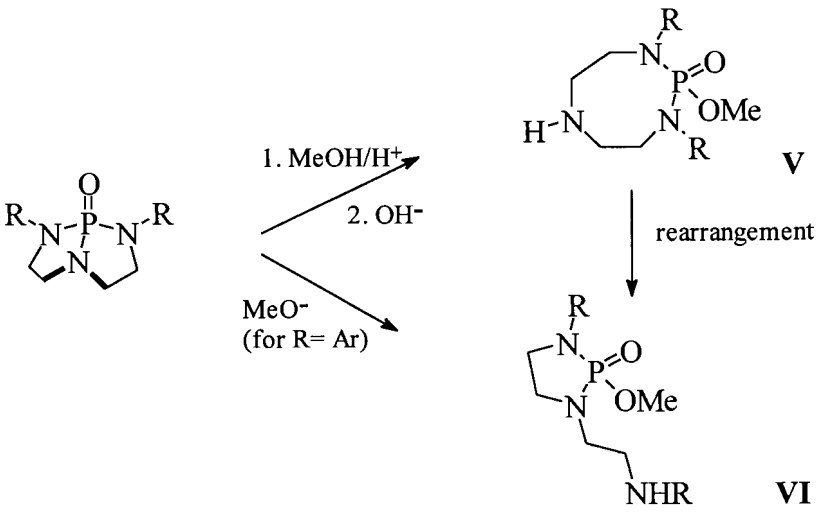
Scheme 8: Alkaline hydrolysis of the phosphoric amide bond.

Because OH^- is a very strong nucleophile towards tetracoordinate, pentavalent P [31], the relatively slow rates of alkaline hydrolysis indicate that an unactivated P-N bond is neither inherently labile nor very susceptible to nucleophilic attack. Furthermore, due to the proposed formation of a trigonal bipyramidal intermediate, stereoelectronic factors may play a large role in determining which P-N bond is cleaved in di- and triamidates. ^{18}O exchange studies [30] revealed some ^{18}O in unhydrolysed amide, which implied both proton transfer between O's and pseudorotation. Additionally, hydrolysis requires proton transfer after formation of the intermediate so that relative basicities of amide N's should be considered.

1.3.3. Alcoholysis

Acid- and base-catalysed alcoholysis should proceed via the same mechanisms described above. Due to the electron-donating tendency of alkyl groups, both alcohols and alkoxide ions can be expected to be generally more nucleophilic than their water counterparts, but their approach during nucleophilic attack may be more sterically hindered. Alcoholysis has been used in our laboratory in the preparation of several new heterocyclic compounds from the cyclic phosphoric triamides mentioned earlier, and these are now specifically discussed.

Acid-catalysed alcoholysis of all the bicyclic triamides (scheme 9) [32], yielded the eight-membered monocyclic diamides **V**. This result was expected on the basis of preferential protonation of the bridgehead N, due to its greater basicity, compared with the aryl-substituted N's, leading to regioselective cleavage of the central P-N bond. Greater basicity and a stereo-electronic effect (due to the tbp intermediate) accounted for the regioselective cleavage when R= alkyl. For R= Ar, the free amine product was found to rearrange spontaneously, following first-order kinetics, to the five-membered cyclic **VI**, at rates dependent on the aryl substituents. So, for example, rearrangement proceeded faster for Ar = Ph (refluxing in THF gave $t_{½}$ = 2.2 h) than when Ar = p-MeO-Ph ($t_{½}$ = 4.0 h), because more electron-donating p-MeO-Ph makes the P less electrophilic so that the $P\text{-}N_{bridgehead}$ bond reforms less rapidly. As expected, when R = alkyl, the rearrangement proceeded generally much slower.

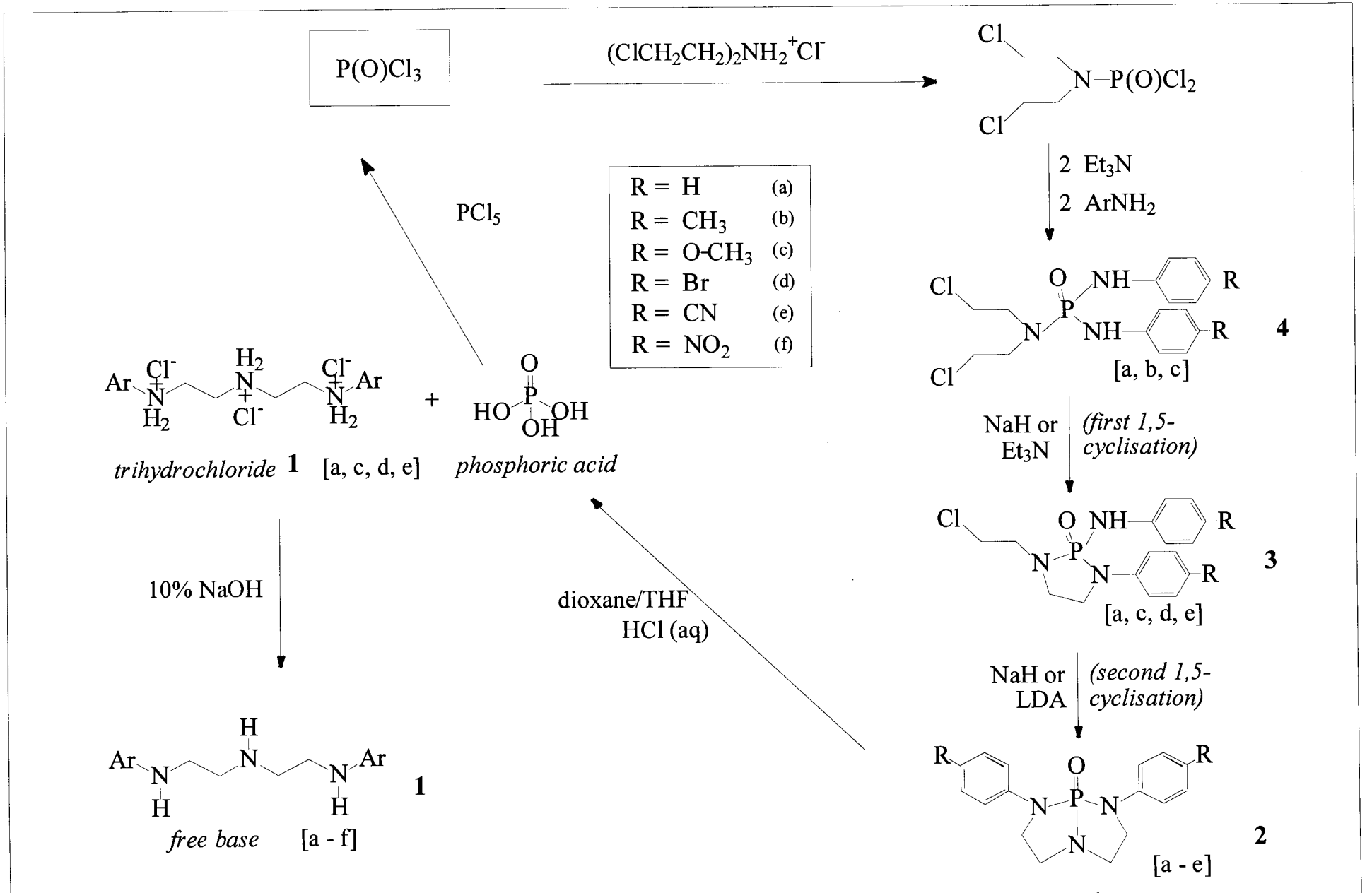


Scheme 9: Alcoholysis of the triamides can lead to two products.

On the other hand, base-catalysed alcoholysis yielded exclusively **VI** when R= Ar, but for R= alkyl, **V** was again obtained. This result was interpreted i.t.o mechanistic differences. MeO^- attack leads to the formation of a P(v) intermediate, which then undergoes rate-limiting proton transfer-assisted cleavage. Because the p-MeO-Ph N is more basic than the phenyl N, the overall rate of cleavage is faster for the former compound. For R= alkyl, cleavage was driven more by larger strain in the $P\text{-}N_{bridgehead}$ bond.

1.4. Synthesis of bis(2-arylaminoethyl)amines

On the basis of this experimental and theoretical knowledge, we could propose a new, general method for the synthesis of bis(2-arylaminoethyl)amines. Basically, instead of directly substituting bis(2-chloroethyl)amine or an analogous compound, which proved rather inefficient, we first protect the substrate from internal cyclisation to piperazine, by using the phosphoryl function, and then, by acidic hydrolysis, release the triamine from bicyclic triamide. $P(O)Cl_3$ can be regenerated through the reaction of phosphoric acid with PCl_5. The whole process, starting (and possibly ending) with $P(O)Cl_3$ as the substrate, and including all intermediate products (which need not necessarily be isolated), is shown in Scheme 10.



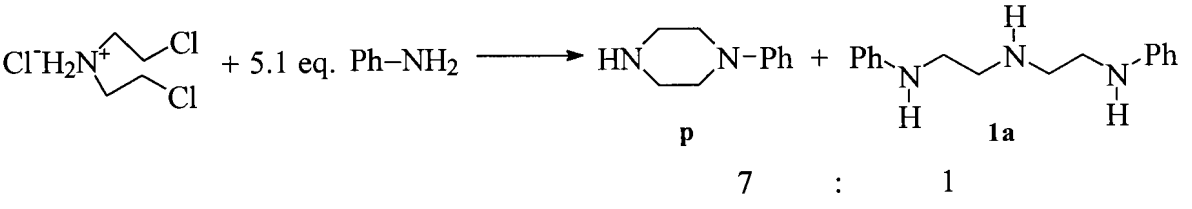
SCHEME 10: Synthetic route to bis(2-arylaminoethyl)amines. Isolated and characterised compounds are indicated in square brackets.

2. RESULTS AND DISCUSSION

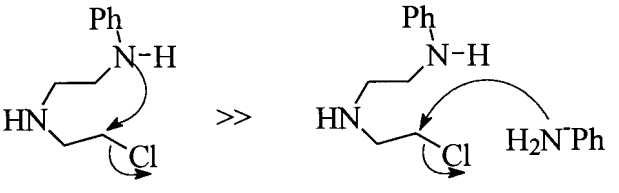
2.1. Control experiments for the synthesis of bis(2-phenylaminoethyl)amine 1a

2.1.1. From bis(2-chloroethyl)amine and aniline

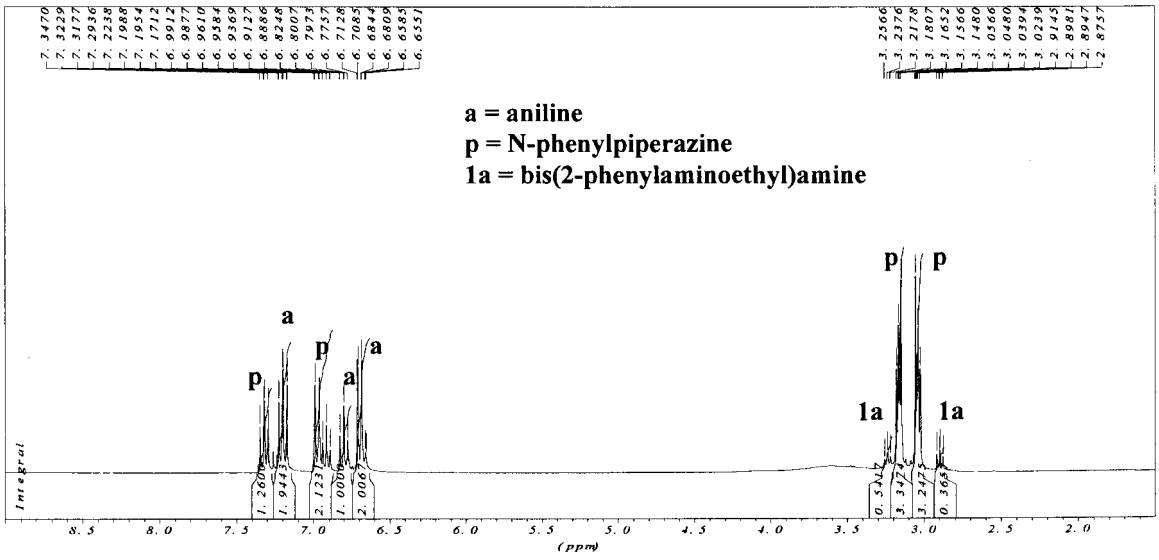
By refluxing a mixture of bis(2-chloroethyl)ammonium chloride and 5.1 equivalents aniline (**a**) in toluene for 24 hours, while monitoring the reaction at regular intervals by high-resolution ^{1}H NMR spectroscopy, it was found that intramolecular cyclisation (to piperazine) occurred in preference to a second substitution (i.e. the formation of **1a**). The final reaction mixture consisted of two portions, toluene-insoluble material (**P1**) and toluene-soluble material (**P2**). After neutralisation of both, followed by extraction with chloroform, neutral **P1** (which made up 97.3% of the total mass) contained N-phenylpiperazine (**p**) and bis(2-phenylaminoethyl)amine (**1a**) in a 7:1 ratio, and also aniline, **a** (which behaved both as substrate and base):



i.e. unimolecular 1,6-cyclisation was preferred over bimolecular substitution:

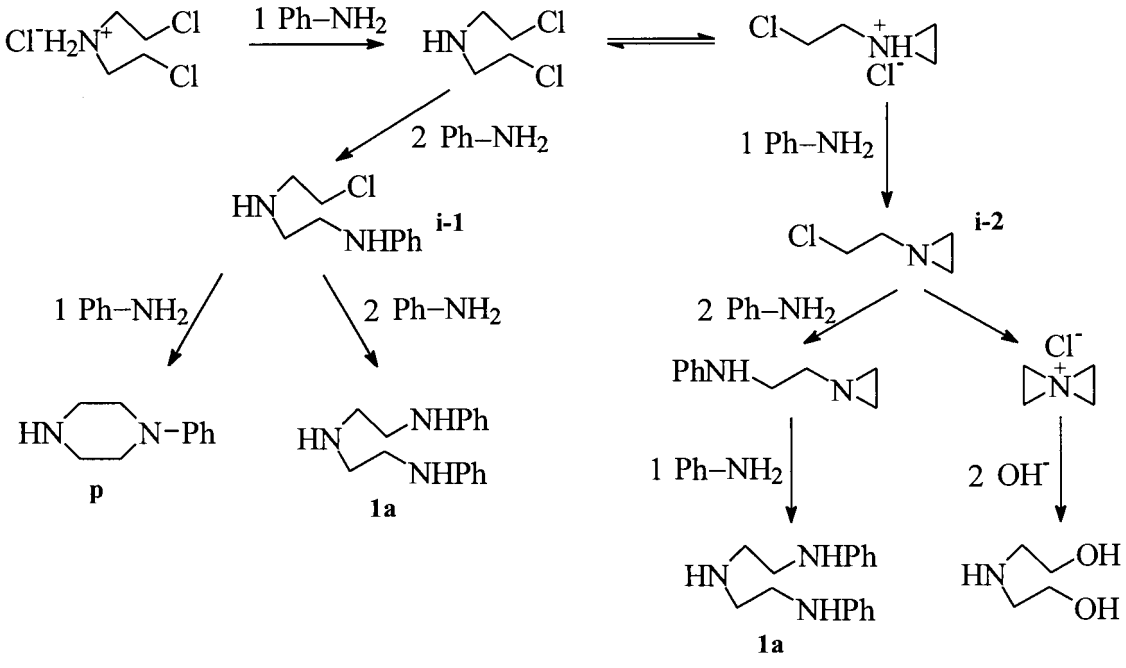


Scheme 11 shows the ^{1}H NMR spectrum of the **P1** mixture obtained after filtering and neutralising with 5% NaOH. NMR assignments were based on relative integrals and literature values [33] {for **a**: δ_H 7.12 (t, 2 m_{arom}), 6.73 (t, 1 p_{arom}), 6.61 (d, 2 o_{arom}) and for **p**: δ_H 7.25 (t, 2 m_{arom}), 6.91 (d, 2 o_{arom}), 6.83 (t, 1 p_{arom}), 3.11 (m, 4 CH_2N), 3.02 (m, 4 CH_2N)}, as well as the spectrum already obtained for **1a** (see *experimental*).



Scheme 11.

The integrals were used to calculate the approximate product ratio as **a**:**p**:**1a** ~ 11:7:1. The **a** fraction accounts, of course, for the proportion which acted as base (deprotonation of the N-mustard salt, and neutralisation of formed HCl). Unreacted **a** should be neutral and soluble in toluene. Previously in our lab, we found that the nitrogen mustard liberated from its HCl salt can undergo intramolecular reactions leading to several other products. The total reaction scheme, including those side reactions, can be represented as in Scheme 12.



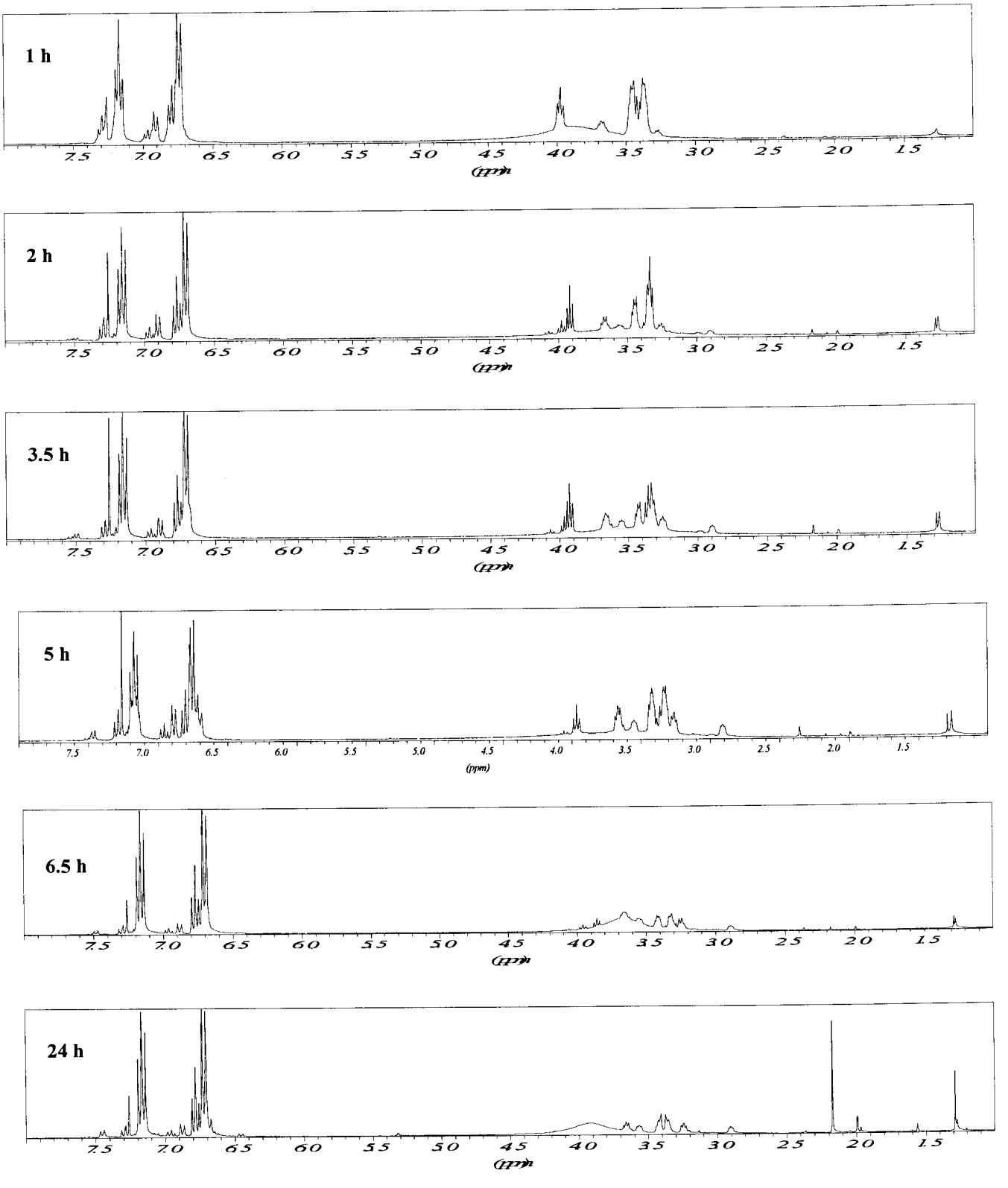
Scheme 12: Possible reactions which may occur during this experiment. The need for an excess of aniline is indicated.

While monitoring the reaction progress by ^{1}H NMR of **P2** (see scheme 13), it was difficult to discern all the peaks of intermediates and products. Although reference NMR shifts could be used, many reference spectra were recorded in D_2O (while we used $CDCl_3$), and even more importantly, due to the processing of the samples (see *experimental*), they were probably not representative of the reaction mixture, as only toluene-soluble compounds (**P2**) were monitored. Nevertheless, a few observations could be made (note that assignments are tentative):

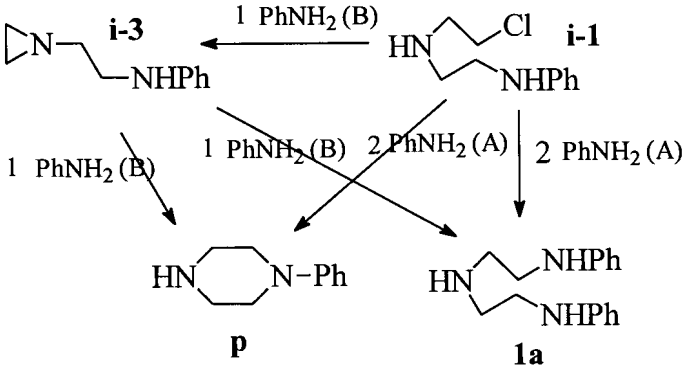
(i) After 1 hour, substitution had already occurred, as indicated by the presence of small signals of aromatic hydrogens next to the aniline proton signals. The product which formed, however, is puzzling. Firstly, although NMR signals were observed in a very similar region as expected for **p**, the *p*- and *o*-patterns (between δ_H 6.9–7.0) were interchanged, and the ethylene signals (at δ_H 3.3-3.5), of correct relative intensity, were different (downfield, and closer together) from those of **p**. The reference signals for **p** (at δ_H 3.02 and 3.11) were never observed during the course of the reaction, and only after processing of the toluene-insoluble portion, (scheme 11). Two possibilities exist:

1. **P** exists in solution in its monoprotonated form, with the proton at the more basic NH nitrogen. That would explain the difference in the NMR spectrum of the NCH_2CH_2N groups.

2. The hydrochloride salt of **p** was insoluble in toluene and the peaks belonged to more toluene-soluble intermediates, such as **i-1** or **i-3** (scheme 14). Because an aziridine singlet (δ_H = 2.18 [34]) of correct intensity was observed only after 24 hours, the peaks until that time were probably due to **i-1**. In this case, the prominent triplet present throughout at δ_H 3.9-4.0, are probably the CH_2Cl protons of **i-1**. Then the smaller triplet just downfield (δ_H 3.98), and gradually decreasing with time, could be due to the substrate N-mustard salt [34]. Note that, after 24 hours, these triplets had disappeared to be replaced by a previously overlapped broad peak indicative of N-H signals. Also, the aziridine singlet (δ_H = 2.18), which integrates for ~ 4 protons relative to the ethylene signals at ~ δ_H 3.3-3.5, indicates that, by this time, **i-3** (scheme 14) became predominant.



Scheme 13: Reaction progress monitored by ^{1}H NMR of toluene-soluble components, **P2**.



Scheme 14: Direct (A) and indirect (B) pathways to **p** and **1a**.

(ii) Because the spectrum of **1a** (ethylene signals at ~ δ_H 2.9 and 3.25) was already observed from 2 hours onwards, disubstitution had taken place by this time, but the concentration of **1a** hardly increased during the next 22 hours. It should be noted that the triplet at δ_H 3.25 overlaps another signal throughout the reaction. This signal, already visible after 1 hour as a triplet, together with signals at around δ_H 1.3 and 2, are thought to be due to **i-2** (scheme 12) [35].

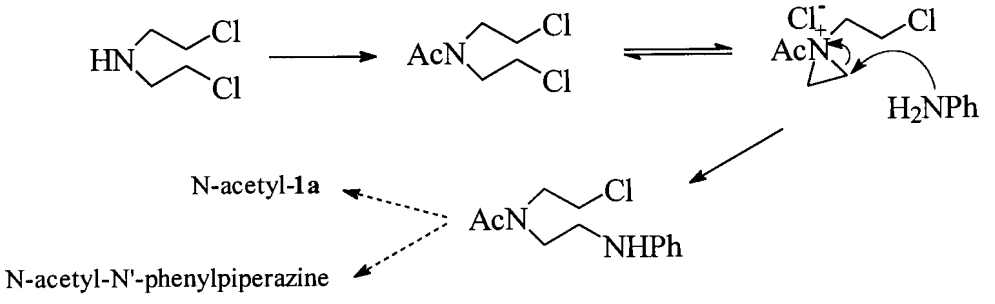
(iii) The triplets between δ_H 3.5–3.7 were difficult to assign. Either they belonged to **i-2** or to the free N-mustard base [34].

(iv) After treatment of **P1** with 5% NaOH, followed by extraction with chloroform (which resulted in the spectrum in scheme 11), a ^{1}H NMR, not shown here, was also obtained of the aqueous layer after evaporating it to dryness. This spectrum demonstrated the presence of small amounts of N,N-bis(2-hydroxyethyl)amine (see scheme 12), as indicated by triplets at δ_H 2.38 and 3.55 (lit.[35] δ_H 2.45, 3.39). This result confirms the validity of scheme 12 and again illustrates the complexity of the reaction.

Because our reaction proceeded in a heterogenous system, it is difficult to speculate on its detailed mechanism. Our result cannot be directly compared with the experiment of Prelog and Driza [9], since in the latter case only 1.5 mol-equiv. of aniline was reacted, and methanol was used as the solvent. The reaction was then much faster and only traces of **1a** were observed. Our results show that the intermediate **i-1** does not, under our conditions, necessarily cyclise to **p**, but in fact, is quite stable and can also produce the aziridine intermediate **i-3**.

Most importantly, though, the final product composition clearly demonstrates that intramolecular cyclisation to N-phenylpiperazine is considerably more favourable than disubstitution (directly or indirectly) of the N-mustard to form **1a**. This is therefore an inefficient method for its preparation.

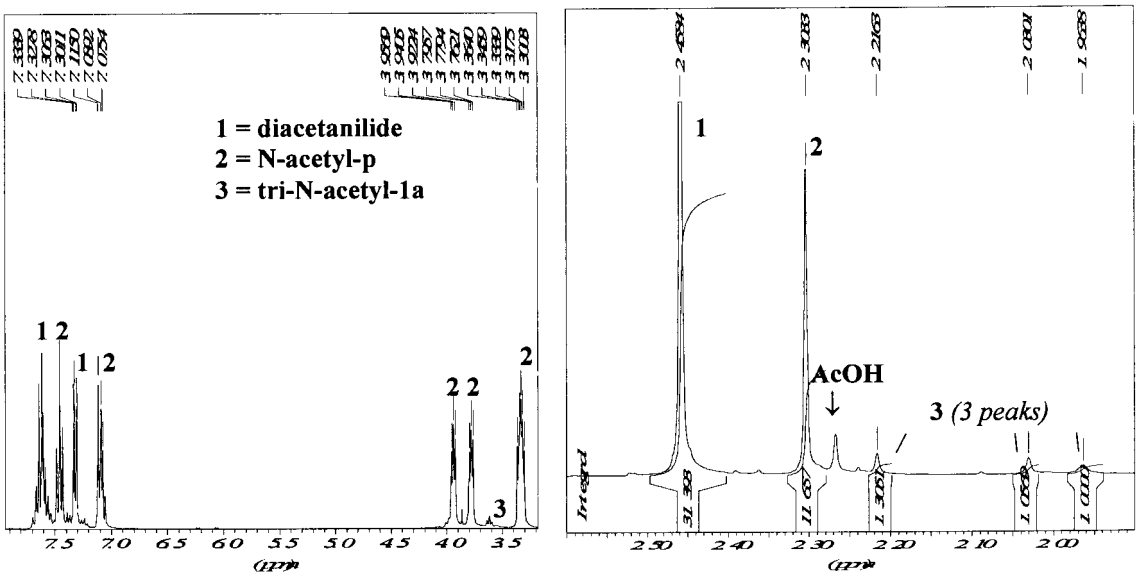
The literature supports our observations of aziridine intermediates. Experiments in our laboratory [36] proved that a well-known anticancer pro-drug, cyclophosphamide, bisalkylates nucleophiles through the same mechanism. Benn *et al* [37] proved that even N-aryl nitrogen mustards react with nucleophiles *via* the intermediacy of aziridinium ions. The positively charged N atom in an aziridinium ion makes the ethylene carbons more susceptible to nucleophilic attack [36]. Our reaction should therefore be accelerated by acetylating the N in bis(2-chloroethyl)amine (scheme 15). However, this cannot exclude N-phenylpiperazine formation:



Scheme 15: More reactive intermediates can still cause cyclisation to **p**.

Now, how about using acetanilide instead of aniline for the preparation of **1a** ? The N-acetyl group should prevent a second substitution at N, thus eliminating formation of **p**. This was attempted as the second control reaction (see 2.1.2).

Finally, the **P1** mixture obtained after treatment with NaOH (scheme 11) was acetylated by refluxing in Ac_2O. After work-up (see *experimental*), **1a**, **p** and **a** were all acetylated and the mixture gave a simple NMR spectrum (scheme 16), of which the integrals could be used again to estimate product composition. In this case, the acetyl methyl peaks were easily distinguished (from the literature [33] and the reference spectrum obtained for triacetylated **1a**- see later) and gave a good enough indication that the product composition was diacetanilide : N-acetylated **p** : N,N',N"-triacetylated **1a** ~ 16:12:1. N-acetylated **p** was successfully crystallised from the mixture.



Scheme 16: Acetylated product composition.

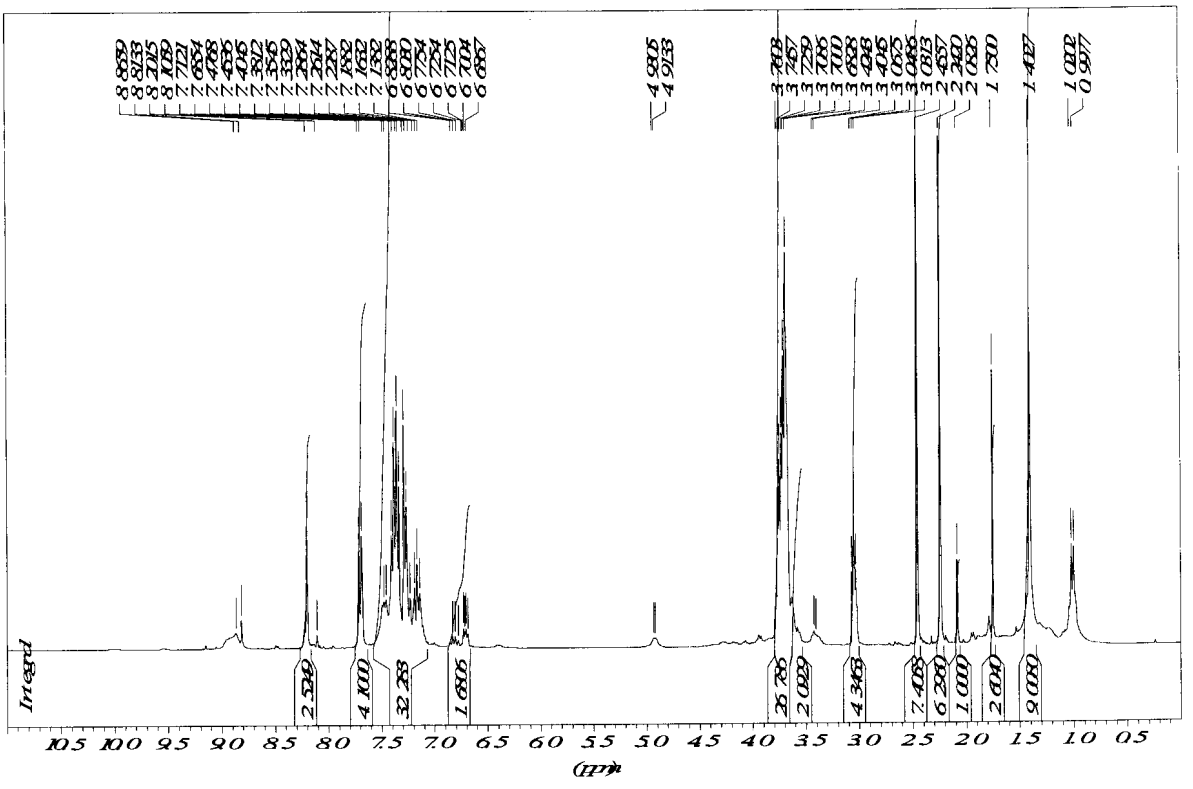
2.1.2. From bis(2-chloroethyl)amine and acetanilide

A mixture of bis(2-chloroethyl)ammonium chloride, 2 equivalents acetanilide and 3.1 equivalents Et_3N in toluene was stirred and heated at 50°C. The ^1H NMR of the reaction mixture after 24 hours was basically that of acetanilide [33] and triethylamine [δ_H 1.25 (t) and 2.94 (q)]. Two triplets at δ_H 3.0 and 3.7 were probably due to the free N-mustard. No reaction took place simply because acetanilide is too weakly nucleophilic (pK_b of amides is in the range of 14-16 [38]). Its nucleophilicity can be increased by treatment with NaH, and this was done in the third control experiment (2.1.3).

2.1.3. From bis(2-chloroethyl)amine and sodium acetanilide

Following the procedure used by Billman and Caswell [15] in synthesising N,N'-diphenyl-α,ω-diaminoalkanes, acetanilide was converted to sodium acetanilide by treatment with NaH in toluene. A solution of the N-mustard (previously deprotonated in 10% NaOH and extracted into toluene) was then added dropwise and a vigorous reaction ensued after 30 minutes. After it subsided, the mixture was heated gently for another 2 hours, then poured into water and cooled. At the phase interface, crystals of acetanilide formed on standing. The filtrate, which tested basic, was washed with water.

^{1}H NMR of both the toluene (scheme 17) and aqueous fractions were obtained after drying.



Scheme 17: ^{1}H NMR of the toluene fraction (experiment 2.1.3).

As seen from the above spectrum, a complex mixture of products was obtained by this method. Even after about a third (2.4 g) of the original acetanilide (7.5 g) crystallised, the mother liquor still contained a considerable amount, as indicated by the doublet at δ_H 7.7 (2 protons), the singlet at δ_H 2.2 (3 protons) and the triplet at δ_H 7.1 (1 proton) [lit [36]: δ_H 7.6, 2.1 and 7.0 respectively]. It could be speculated that the methyl signals at δ_H 2.4, 2.1 and 1.7 belong to N, N"-diacetylated **1a** and/or the monosubstituted N-mustard, but seeing that so much acetanilide was recovered, no effort was made to isolate any of the by-products as sufficient evidence already proved this method inferior to ours.

2.2. New synthetic route to bis(2-arylaminoethyl)amines

The synthesis of phosphoric triamide **4**, monocyclic triamide **3** and bicyclic triamide **2** in Scheme 10 (for R = H, MeO), together with the physical properties (NMR and structural studies) were described in detail by Huijie Wan [39]. The common starting material is phosphoryl chloride, which is first reacted with bis(2-chloroethyl)amine to give $Cl_2P(O)N(CH_2CH_2Cl)_2$ (in 100% yield). The phosphoryl center is then substituted twice with aniline derivatives and the resulting compounds can undergo base-promoted 1,5-cyclisations. In this project another few derivatives were synthesised using the same method, in some cases by modifying the reaction conditions. We were more interested in the triamines which resulted when **2** was acid-hydrolysed. For simplicity sake, we decided to incorporate in the triamides aniline derivatives substituted in the p-position (where R = Me, Br, CN, NO_2).

2.2.1. Synthesis of triamides 4 and 3

The S_N2 substitution of chlorides at the phosphorus in $Cl_2P(O)N(CH_2CH_2Cl)_2$ by anilines proved the most difficult and yield-determining step. This is because chlorine is a stronger electron-withdrawing atom than nitrogen so that the electrophilicity of the phosphoryl center is greatly reduced with each chlorine displacement. Seeing that nucleophilicity of the nitrogen increases with its basicity, more basic aniline derivatives should react faster. Table 1 arranges the pK_b values of *p*-substituted anilines in increasing order, i.e. basicity in decreasing order:

Table 1: pK_b values of *p*-substituted anilines used in this project.

Substituent, R (and representative letter)	*pK_b*
OCH_3 **(c)**	8.66
CH_3 **(b)**	8.92
H **(a)**	9.37
Br **(d)**	10.14
CN **(e)**	12.26
NO_2 **(f)**	13.00

From the table, we expect anisidine (**c**) to be most reactive and this was observed before [39]. Whereas aniline took 120 h to react completely with $Cl_2P(O)N(CH_2CH_2Cl)_2$, anisidine did so in 48 h. The least basic derivative, *p*-nitroaniline (**f**), proved unreactive in Wan's work. We found for the reaction with **f** that, in chloroform, almost no product was formed even when refluxing the reaction mixture. In THF, however, after stirring at room temperature for 7 days, two products [with δ_P –1 and 5.8 (presumably **4f**)], of combined concentration half that of the substrate (δ_P 18-20), were formed (note that these reactions could be followed directly by ^{31}P NMR using an internal standard). After refluxing another 7 days, an additional peak at δ_P 12.5 (presumably monocyclic **3f**) appeared, but the reaction mixture still contained mainly unreacted substrate and small amounts of the previously mentioned peaks. Although both chlorine substitutions took place with difficulty, it was demonstrated here that weakly nucleophilic aniline **f** does react, but that the reaction was slow and solvent-dependent. Because the p-nitrophenyl substituted triamine could be made more easily *via* another route (see later), none of the compounds in this mixture were characterised and the general route to **1f** was not pursued any further.

Surprisingly, p-aminobenzonitrile, **e** (only 0.74 pK unit more basic than its nitro-analogue) was much more reactive in *chloroform*. In this case, little reactivity was evident after 6 days at room temperature in THF, but after repeating the reaction in chloroform and refluxing for 17 h, all substrate was converted to: monosubstituted **5e** (δ_P *ca.* 0, roughly half of the total species present), disubstituted **4e** (δ_P 3.8, a quarter of the species) and monocyclic **3e** (δ_P 14.2, another quarter of the species). Refluxing for another 17 h, gave **3e** as roughly two-thirds of the total species present. A moderate yield of **3e** (19%) was obtained after crystallisation from the oily residue under dilute conditions. Two additional points were demonstrated here: large temperature-dependence of the reaction and ease of cyclisation of **4**→**3** under mildly basic conditions (Et_3N) for more acidic anilines. Wan commented on the base-dependence of these reactions: the nature of base used for each cyclisation was crucial in obtaining the desired product. In his case, where R = H and MeO, MeO^- was necessary to promote the first cyclisation to **3**. In our case, this cyclisation proceeded easier for **e** and **f** simply because less basic anilines yield more acidic anilides which can be more easily deprotonated.

Contrary to expectations, p-bromoaniline (**d**) did not react faster than **e**. In both chloroform and THF, under room temperature and reflux conditions, the reaction was complex in each case. The reaction was repeated several times and found to be rather irreproducible and very dependent on conditions of solvent, temperature and amount of base used. We still managed to isolate (see *experimental*) monosubstituted **5d** and monocyclic **3d** (6%). Although the reactions could be monitored by ^{31}P NMR, the spectra became very complex once reaction mixtures were heated, probably due to decomposition of **d** itself. Therefore, although **d** was reactive enough, its reactivity could not be easily compared with that of the other anilines. The best results were obtained when the reaction was carried out in THF, but unfortunately it was difficult to maintain strictly anhydrous conditions and partial hydrolysis of some phosphoramide bonds started taking place as reaction time increased. From our results, we propose that good yields of **3d** could be obtained when stirring the reaction for a longer period (typically 4 weeks) at room temperature in THF under anhydrous conditions.

As experienced before [39] for the more basic anilines, **a** (R= H) and **c** (R= MeO), **b** (R= Me) also presented less problems in this step than the anilines discussed so far. According to relative basicities, we expected the reaction time of **b** to be intermediate to that of **a** (120 h) and **c** (48 h). The reaction was, indeed, completed within 120 h. After purification by column chromatography, a moderate yield (57%) of **4b** was obtained. Note that, in this case, as for **a** and **c**, 1,5-cyclisation from **4**→**3** did not occur readily under mildly basic conditions (Et_3N) so that **3b** was not formed. Instead, **4b** underwent both cyclisations to the bicyclic triamide **2b** with NaH as the base (as dicussed below).

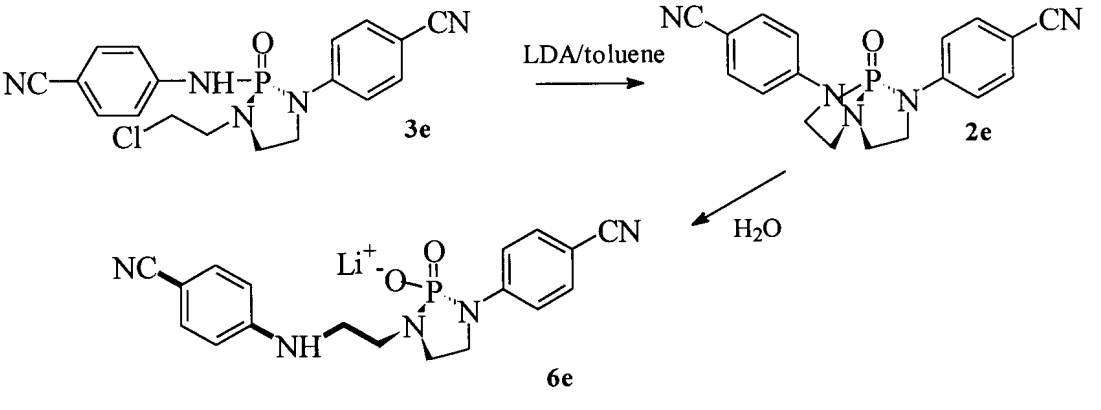
2.2.2. Synthesis of bicyclic triamides 2

This reaction was very straightforward for **b** and **d**. In both cases, an excess of NaH in THF gave good yields (91% for **b** and 79% for **d**). In both cases, at room temperature, the reaction seemed to be complete within an hour.

However, for **e**, drastic conditions were required to prepare bicyclic product **2e**, i.e. at least 2 hours of refluxing in toluene in the presence of a large excess LDA. When NaH was used as the base, a mixture of products was formed, as indicated by the ^{31}P NMR

spectrum of the reaction mixture, most of which precipitated out within two days. This was probably because hydride also reduced the nitrile groups to imines which polymerised, or to amines. Furthermore, **2e** was difficult to isolate and crystallise and a low yield (19%) was obtained. Compound **3e** was found to be weakly soluble in most common solvents and it is likely that this may be the reason for its reluctance to be deprotonated and to undergo cyclisation to **2e** at lower temperatures (<100 °C).

The **2e**-containing toluene fraction from the above-mentioned reaction was found to contain traces of another compound with δ_P 17.7-17.8. This chemical shift compared well to those of the 5-membered phosphoric diamidoesters obtained by alcoholysis of **2a** (δ_P 19.9 for the product of methanolysis and δ_P 18.5 [40] for the product of ethanolysis; see introduction). On repeating the experiment, it was decided to, once unstable **2e** had formed completely, hydrolyse it *in situ* by simply adding water. After washing the toluene layer with water, the aqueous layer was evaporated to a small volume by boiling and, on cooling, the product crystallised and was confirmed by both NMR and IR spectra to be the desired diamidophosphate (**6e**, scheme 18). Note that the phosphate and amino groups are all expected to be deprotonated as the pH of the mother liquor was made basic. Note also that the cyano-substituents were unaffected by boiling in aqueous LiOH for hours (when reducing the water volume), as demonstrated by the IR band at 2213.8 cm^{-1} (for C≡N, the IR frequencies are in the range 2210-2260 cm^{-1} [41]). ^{13}C NMR also confirmed the presence of a nitrile C (δ_C 119.5, lit. value: δ_C 119.5 [42]). Nitriles may be base-hydrolysed to amides at this temperature (and even to carboxylic acids and ammonia, though higher temperatures are usually required under these conditions) [43]. Compound **6e** (scheme 18) could also be used to generate the derived triamine (see later).



Scheme 18: *In situ* base hydrolysis of **2e**.

Finally, the melting point of **2e** was also lower than expected according to the trend observed throughout this work. For compounds **3**, **2** and **1** (together with its trihydrochlorides), the melting points generally increased in the following order: R= Ph (**a**) < MeO (**c**) < Me (**b**) < Br (**d**) < CN (**e**) < NO_2 (**f**), except for **2e** (mp 189-191°C), which was expected to melt at a higher temperature than **2d** (R= Br, mp 203-204°C). This was probably more due to impurities in the crystal lattice of **2e** than due to unusual bonding interactions in the pure compound. As commented earlier, crystallisation was difficult (2 weeks in acetone/hexane, 1:1, at 10 °C).

2.2.3. Synthesis of trihydrochlorides 1

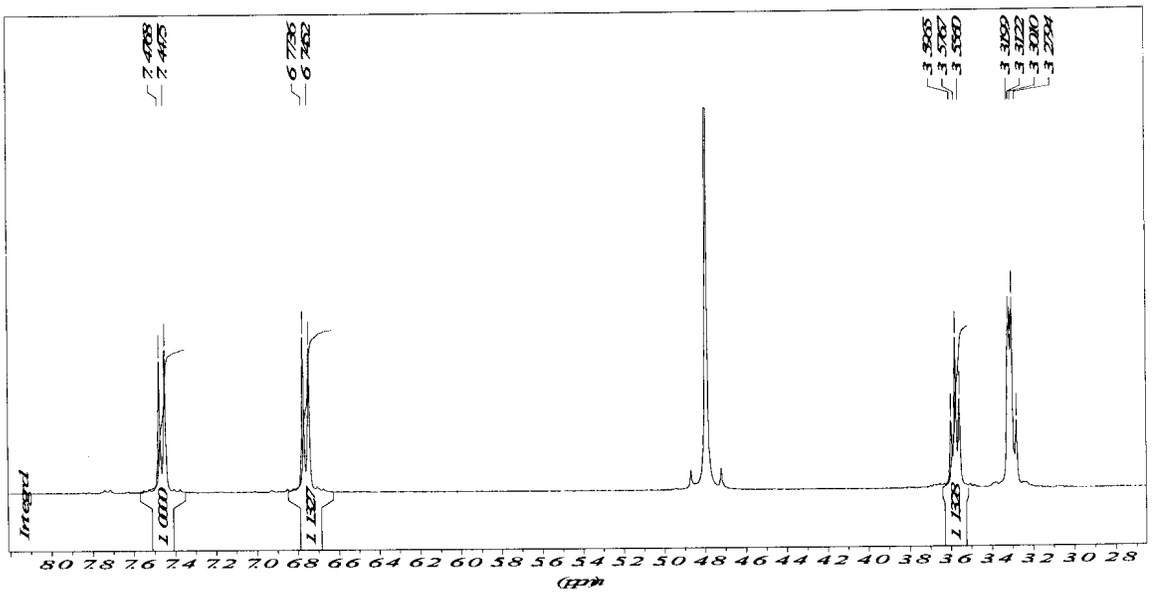
When bicyclic triamide **2**, dissolved in dioxane or THF solution, was treated with three or more equivalents HCl, either as 10% HCl or as conc. HCl, all three phosphoric amide bonds were cleaved rapidly (<24 hours) to yield phosphoric acid and triamine [bis(2-arylaminoethyl)amine] trihydrochloride **1** (scheme 10). Furthermore, as tested for **a**, **c** and **d**, when conc. HCl was used, it was found that the trihydrochlorides precipitated out of solution and, after filtering and drying, were pure materials. Their low solubility in all common solvents tested, except for methanol, made this method more efficient because no purification or work-up was necessary. The overall yield of the entire process, given in scheme 10, was improved for **1a** in this way (from ~ 50% to 70%, without precipitating further by reducing the mother liquor), by not isolating bicycle, i.e. compound **2a**. After cyclisation of **3a** using NaH, the product was already in THF solution, so that, after decanting the solution from the NaH deposit and neutralising with ethanol, acid was simply added to effect hydrolysis. Due to the presence of ethanol, some ethanolysis no doubt took place as well, but this did not interfere and the pure hydrochloride was precipitated.

It is interesting to note that compounds **1** can give rise to only partially protonated species, particularly in view of the much weaker basicity of the terminal nitrogens relative to the central N. Elemental analysis of the isolated products showed, however, that in all cases the triprotonated derivatives were formed.

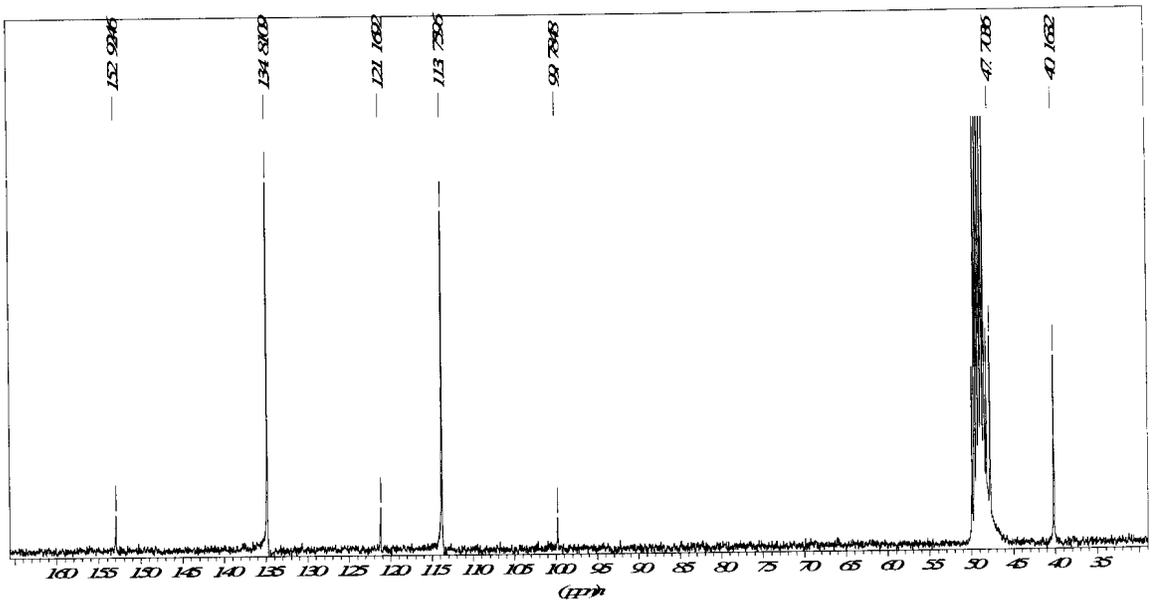
When the project was started, the lability of the P-N(Ar) bonds in **2a** and **2c** was doubtful, as crystal data showed these bonds to be quite short [40] due to extensive N→P

resonance donation and, according to the mechanism of acid hydrolysis (see introduction), P(O)-N(Ar) nitrogens, due to their low basicity, may undergo protonation only under higher acidity. However, although the P-N(Ar) bonds are certainly more stable than the central P-N bond in **2**, their hydrolysis under acidic conditions did not prove to be difficult. Although we used 3 equivalents of acid (or more) in our reaction and continued the reaction for 24 hours, it was later found for **2a** that only the addition of 1 drop of conc. HCl to 0.3 g of substrate in dioxane, was enough to bring about 100% conversion within 1 hour. However, the hydrolysis of **2c** was much slower as traces of the substrate were still apparent after 24 hours. It should be noted, however, that no reaction kinetics were studied for the hydrolysis because it was usually rapid and the techniques required for monitoring the process were beyond the scope of a synthetic project.

Because all hydrochlorides **1** were sufficiently soluble in methanol, their NMR spectra were recorded in CD_3OD. No unexpected trends were observed in these spectra. To illustrate the simplicity of their interpretation, the example of **1e** (R= CN) will be discussed here. Its ^{1}H and ^{13}C spectra are shown in scheme 19a and 19b.



Scheme 19a: ^{1}H NMR spectrum of the trihydrochloride of **1e** in MeOD.



Scheme 19b: ^{13}C NMR spectrum of the trihydrochloride of **1e** in MeOD.

In the ^{1}H spectrum, two ethylene triplets are easily distinguishable. The more upfield triplet at δ_H 3.30 is due to the more shielded NCH_2 protons and the one at δ_H 3.58 to the $ArNCH_2$ protons, less shielded due to the adjacent electron-withdrawing aryl function. The two doublets, at δ_H 6.76 and 7.46 are typical of p-substituted aromatic rings. The downfield doublet is due to the protons *ortho* to the electron-withdrawing cyano-group. For both ethylene and both aromatic signals, the respective coupling constants, J_{HH}, are equal as expected for neighbouring groups of equivalent protons. In the ^{13}C spectrum, five low-field signals are visible. One of them (at δ_C 121.2) belongs to the cyano-C. Due to the strong inductive electron-withdrawing effect of the cyano-substituent, the most shielded aromatic C is the ipso-C_{arom}. The o-C_{arom} is second most shielded for the same reason. The least shielded ethylene C (at δ_C 47.7) lies just outside the CD_3OD signal , at δ_C 49.0.

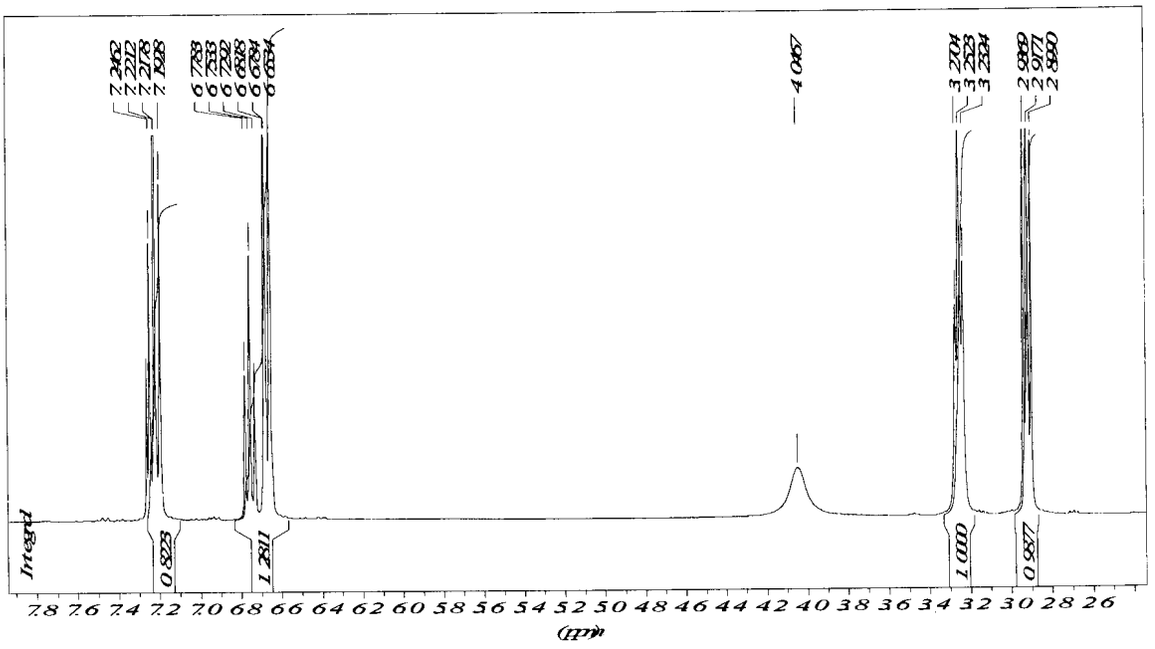
2.2.4. Synthesis of free triamines 1

The bis(2-arylaminoethyl)amines can be obtained either directly, by evaporating excess dioxane and water after completion of acid hydrolysis, and then stirring in an excess 10% NaOH, or indirectly, *via* the neutralisation of their hydrochlorides (which are isolated as explained above). For obvious reasons, the latter method gave the amines in higher purity. After hydrolysis and neutralisation, the product was simply extracted by

chloroform and washed with water. After drying the chloroform fraction, the yields obtained by both methods were very high (nearly 100%) for **1a** and **1c**, and, although they were viscous oils, it can be seen from the ^{1}H NMR spectrum of **1a** (see scheme 20 later), that it was obtained in good purity.

Compounds **1d** and **1e** were crystalline as free bases so that, upon neutralisation in 10% NaOH, they precipitated out of solution. Both were therefore directly separable by filtration, and the yields were good (*ca.* 80%). The same applied to **1f**, although it was obtained by a different method (see later). Once again, the melting points followed the previously observed trend: **1d** (60-61.5°C) < **1e** (118°C) < **1f** (145-147.5°C). Interestingly, these melting points were similar to those of the corresponding anilines: p-bromoaniline (66°C), p-aminobenzonitrile (86°C) and p-nitroaniline (148°C).

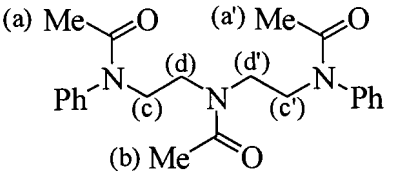
The ^{1}H and ^{13}C NMR spectra of **1** in $CDCl_3$ were, as for the hydrochlorides, so simple, that NMR alone could be used to confirm their identity. Both ^{1}H and ^{13}C NMR assignments could be based, in each case, on the assignments for the corresponding aniline derivative [33] because the spectra were so similar (see the example in scheme 20).



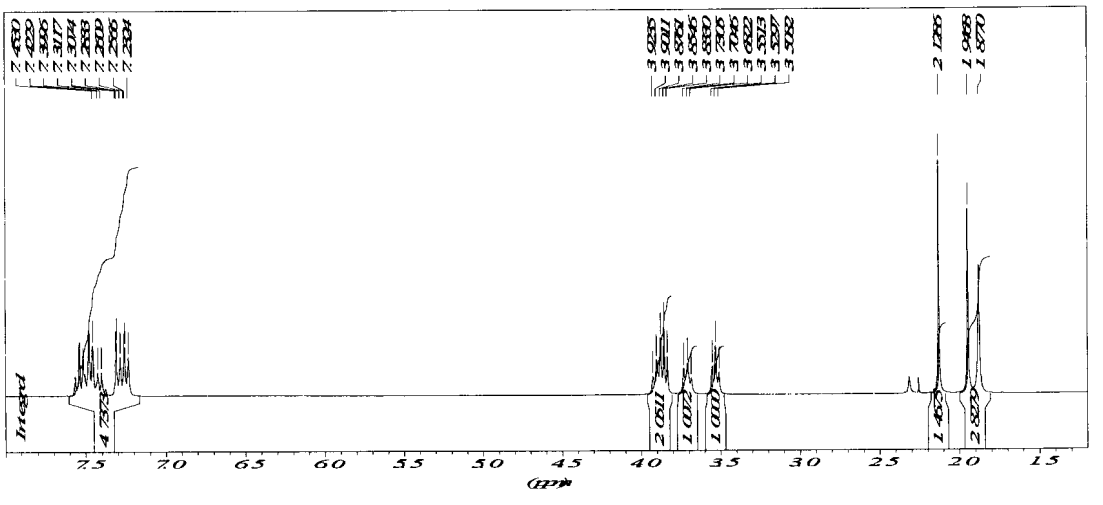
Scheme 20: ^{1}H NMR spectrum of **1a**.

2.3. Acetylation of triamines 1

Full N-acetylation of prepared triamines **1** was performed in order to obtain crystalline derivatives (especially of **1a** and **1b** which were viscous oils), more convenient for purification and identification. The tri-N-acetylated derivatives were prepared for **1a**, **1b**, **1c**, **1f** and they were fully characterised confirming the chemical identity of the parent amines. The NMR spectra (^{1}H and ^{13}C) of these acetamides showed some interesting features which are now discussed. The structural diagram of N, N',N"-tri-N-acetyl **1a** is given below:



At first glance, the ^{1}H NMR spectrum of the aliphatic hydrogens should consist of four signals: (b) (3H, s), (a) (6H, s), (c) (4H, t), (d) (4H, t). In reality, the spectrum, given below in scheme 21, was obtained: δ_H 1.78 (3H, s), 1.85 (3H, s), 2.03 (3H, s), 3.43 (2H, t, J = 6.5 Hz), 3.61 (2H, t, J = 7.1 Hz), 3.76 (2H, t, J = 6.5 Hz), 3.80 (2H, t, J = 7,2 Hz).



Scheme 21: ^{1}H NMR spectrum (300 MHz) of tri-N-acetyl **1a**.

The pattern was repeated for all tri-N-acetyl derivatives prepared, indicating the presence of *three* magnetically non-equivalent acetyl Me groups, i.e. (a) Me ≠ (a') Me, as well as four nonequivalent methylene groups, i.e. (c) CH_2 ≠ (c') CH_2, and (d) CH_2 ≠

(d') CH_2. The nonequivalence also applied for the aromatic protons. This was clearly seen in the spectra of the tri-N-acetylated di-p-substituted derivatives ; instead of the two doublets expected (2 o-H_{arom} and 2 m-H_{arom}), four doublets, of equal integrals, were distinguished. The ^{13}C NMR spectra demonstrated the nonequivalence too in that all signals expected to be singlets appeared as "doublets". The ^{1}H NMR chemical shifts of the N-acetyl methyl groups in the four derivatives prepared are given in table 2.

Table 2: ^{1}H NMR chemical shifts for the N-Ac methyl groups in the tri-N-acetyl derivatives of triamines **1**.

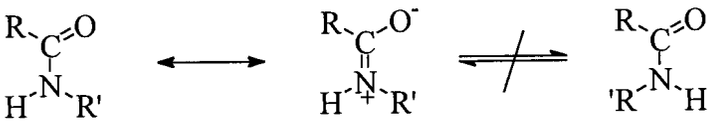
Parent amine	$\delta_{H(b)}$	$\delta_{H(a)}$	$\delta_{H(a')}$	$\Delta\ \delta_{H(a,a')}$
1a	2.02	1.77	1.84	0.07
1b	1.97	1.71	1.77	0.06
1c	2.02	1.74	1.80	0.06
1f	2.05	1.87	1.94	0.07

We assign the low-field signal to the central N-acetyl group, (b) Me ; the corresponding chemical shift values for N,N-dimethyl- or N,N-diethylacetamide are 2.09 ppm [44]. If this assignment is correct, the terminal acetyl methyl groups show magnetic nonequivalence with an almost constant value of the signal's separation. We interpret the observed nonequivalence i. t. o. the restricted rotation about the N-C(O) bonds at the terminal acetanilide functions *. The restriction of free rotation about the N-C(O) bond in amides, resulting from the resonance operating in the N-C=O function (scheme 22) is a well-recognised phenomenon [45].

Scheme 22: Resonance in the amide function.

* The restricted rotation can also operate at the central N-Ac function, but it should not lead to signal's separation because of the symmetrical substitution of the amide nitrogen.

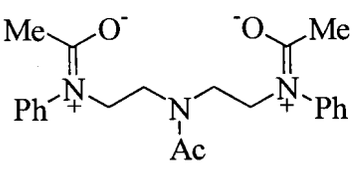
Amides can therefore be considered to be planar or nearly so. The energy of activation for rotation in typical amides is in the range of 12 to 25 kcal.mol^{-1} [46], and most of the secondary amides, R-C(O)NHR' exist in the form of a single stereoisomer. For example, the peptide bond formed between two amino acids has a trans geometry, preferable for steric reasons (scheme 23) [47]. In fact, it has been shown that most N-monosubstituted amides show a strong preference for the trans conformation [48].



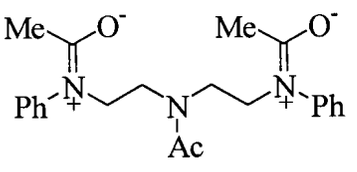
Scheme 23: General preference of secondary amides for the trans stereoisomer.

In unsymmetrically substituted N,N-dialkylamides, conformational preferences can be more rationally explained i. t. o. steric competition, eg. in the case of N-methyl-N-*alkyl* acetamides it was found that the cis isomer was increasingly preferred in the following sequence of *alkyl* groups (the fraction of the cis-conformer is given in brackets): R = Et (0.51), n-Bu (0.53), cyclo-C_6H_{11} (0.55), i-Pr (0.58) [48]. As can be seen, the cis preference is much less impressive here than the trans preference of secondary amides.

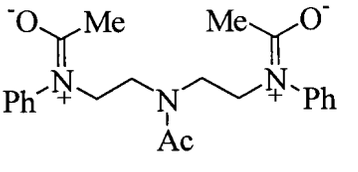
N-methylacetamide gives rise, in the ^{1}H NMR spectrum, to only one singlet for the Me-C(O) group, and one doublet (HCNH coupling) for the NMe. These signals were ascribed to the trans geometry [49]. When applied to the tri-N-acetyl derivatives of **1**, the resonance theory predicts that the compounds should be expected to exist as mixtures of three possible stereoisomers, as shown for the derivative of **1a** in scheme 24:



E,E-tri-N-acetyl1a



E,Z-tri-N-acetyl1a



Z,Z-tri-N-acetyl1a

Scheme 24.

Since in the ^{1}H NMR spectra of our tri-N-acetyl derivatives the three signals of the acetyl methyl groups appear with relative intensities of approximately 1:1:1, we conclude that the compounds exist predominantly either in the form of the E,Z stereoisomer, or as an approximately 1:1 mixture of the E,E and Z,Z stereoisomers. No attempts were made to separate those stereoisomers, and no variable-temperature NMR experiments were performed in order to determine the rotational barriers of the amide bonds. Such studies would be beyond the main objective of this project (preparation of triamines **1**), but they are high on the priority list of our research projects for the near future.

2.4. Nitration of tri-N-acetyl-1a

As mentioned before, **1f** was synthesised, not by the general procedure used for the other derivatives, but by nitration of the N,N',N"-triacetylated derivative of **1a**, a stable, crystalline compound. The most generally used reagent, a mixture of conc. H_2SO_4 and conc. HNO_3, was used for this purpose. The mechanism involves the production of the nitronium ion (NO_2^+), which substitutes a proton or protons on the aromatic ring.

Because aromatic amines become protonated under acidic conditions, the nitration proceeds with low selectivity. The conjugate acids are predominantly meta-directing [50], with a significant contribution of para-substitution ; the reaction of a free base (o/p orientation) cannot be ignored at lower acidities. The problem of selectivity is solved by converting substrates to their N-acetyl derivatives (acetanilides). Acetylation of the nitrogen atom suppresses protonation and eliminates meta-substitution, making the substituent exclusively o/p directing.

It has long been known [50] that, by varying both the ratio of H_2SO_4 to HNO_3, as well as the concentration of water in the reaction mixture, different ratio's of ortho- to para-substituted products can be obtained. The classical preparative textbook by Vogel [51] offers conditions of nitration under which para-selectivity is strongly favoured. The procedure involves dissolving acetanilide in a minimum amount of acetic acid and adding to it the HNO_3/H_2SO_4 mixture at temperatures <10 °C. The procedure was

applied to our tri-N-acetyl derivative of **1a** ; the only change involved extension of the reaction time from 1 hour to 48 hours to ensure complete conversion.

Under these conditions, we obtained *ca.* 100% crude yield of the di-p-substituted derivative (compared to 60% reported by Vogel). Both NMR spectroscopy and the melting point (sharp) indicated good purity of the product. Could di-p-substitution have occurred exclusively, and, if so, why? A few possibilities may be considered for N,N',N"-triacetyl-**1a**:

1. Steric hindrance at the o-positions is unusually great for this highly branched acetanilide.
2. Bonded and/or nonbonded interactions within the molecule electronically deactivated the o-positions more than expected.
3. It was our lucky day and the conditions were optimal by chance.

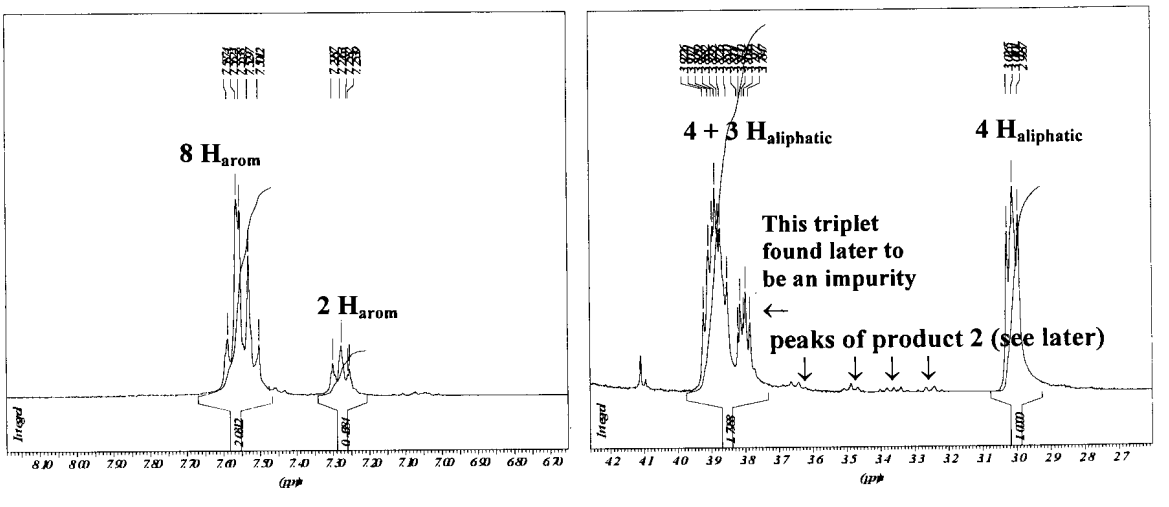
Once di-p-nitrophenyl-N,N',N"-triacetyl-**1a** was obtained, the acetyl groups could be removed by acidic hydrolysis to give, after neutralisation, the free triamine **1f**. This proved to be more difficult than expected. The usual method for p-nitroacetanilide entails the use of 70% H_2SO_4, but seeing that, at elevated temperatures, H_2SO_4 will be strongly oxidizing, we had to devise another method for hydrolysis. We decided to use an excess of 20% HCl and to reflux the reaction mixture for a longer period. Once a test sample was clear upon dilution with cold water (after 1 hour), the reaction was stopped. After neutralisation with 10% NaOH, an orange-yellow powder precipitated and was left to crystallise overnight before filtering the product. The desired compound (characterised also by elemental analysis, see experimental) was obtained, but in low yield (57%) for a simple hydrolysis. It was assumed that hydrolysis was not yet complete [the central N-Ac bond should be less labile than the (Ar)N-Ac bonds] when the reaction was stopped. When the reaction was repeated under conditions of excess of conc. HCl and refluxing for 3 hours, even less product, and of lower purity, was obtained. This was probably because decomposition took place under these harsh conditions. No attempts were made to improve the method, but this may certainly be achieved in future work.

2.5. Synthesis of a new amino acid or zwitterion

2.5.1. Base hydrolysis of 2a

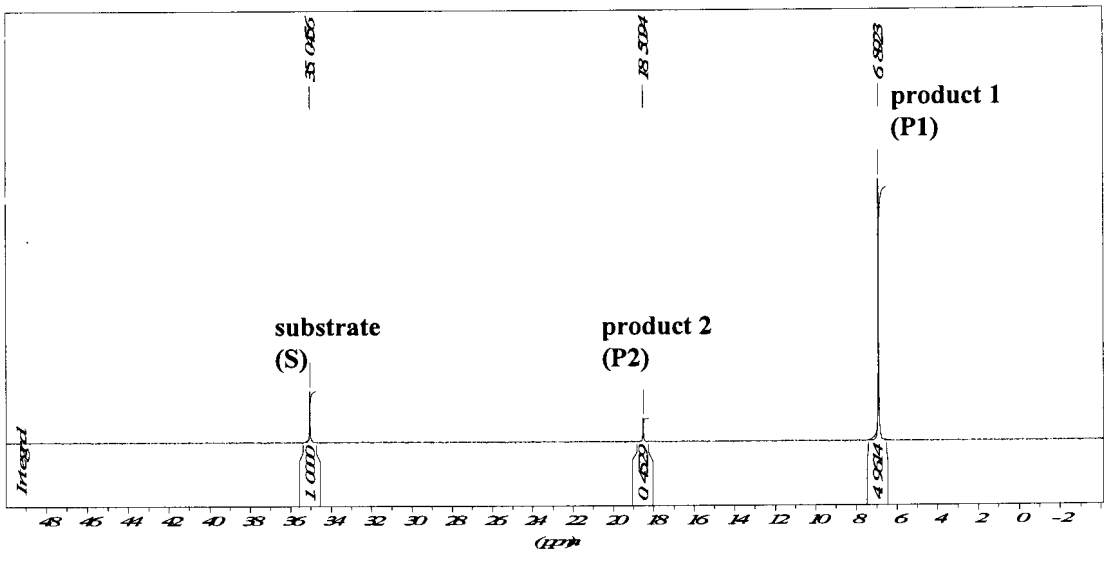
The behaviour of bicyclic triamide **2a** was also studied under conditions of simple base hydrolysis in dioxane. Exactly the same conditions were used as for the exhaustive acidic hydrolysis, except that 10% HCl was substituted for 10% NaOH. The reaction was monitored by ^{31}P NMR in a NMR tube using an internal standard. After 4 hours at room temperature, a *single* product peak (half the intensity of the substrate peak and at a chemical shift of δ_P 7.7) had appeared. After keeping the reaction for another 5 days, the peak did not visibly increase, therefore an equilibrium was established quite early. Increasing the temperature to 55°C, shifted the equilibrium further towards the product and, after another 97 hours, the substrate was almost completely converted. It should be noted that, a graph of substrate concentration versus time gave a hyperbolic function, indicative of a first-order reaction (see later).

After evaporating the dioxane, the residue was redissolved in water and excess substrate and impurities were removed by extraction with chloroform. The evaporated aqueous layer contained a product with δ_P 7.2, and with a ^1H NMR spectrum (in D_2O) shown below in scheme 25. Note that this compound still contained substantial amounts of salts like NaOH and NaCl:



Scheme 25.

When the reaction was repeated at 60 °C with 8 equivalents NaOH, an additional small ^{31}P peak at δ_P 18.5, due to product 2 (**P2**) was observed. The reaction, now giving two products, and forming at slightly different rates (as the ratio **P1** : **P2** decreased slowly with time- see later) actually occurred slower at this higher temperature (see kinetics later) so that, even after 120 hours, a considerable amount of substrate was left as seen from the ^{31}P spectrum obtained at that time (scheme 26):



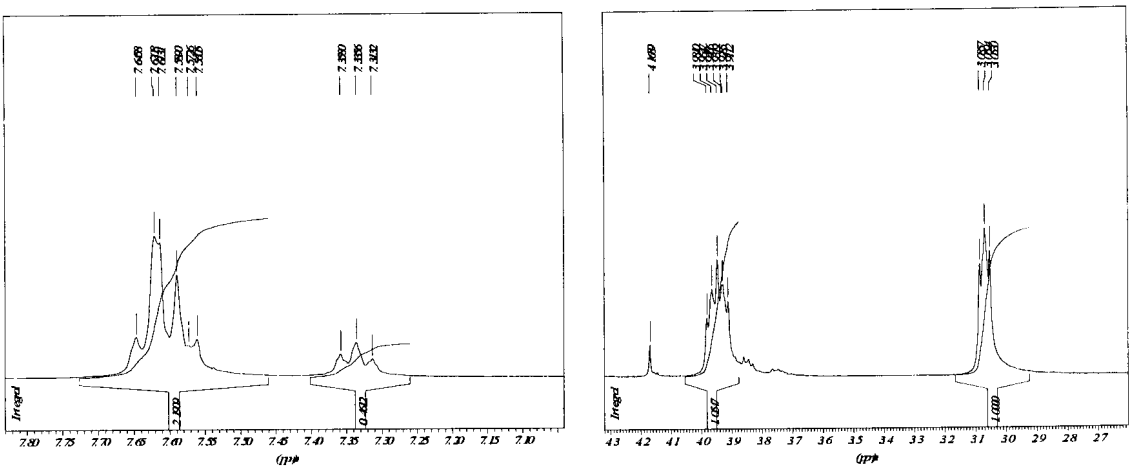
Scheme 26.

After processing the sample, as described previously for trial 1, a product with δ_P 11.2 was obtained. Its ^1H NMR looked similar to that obtained for trial 1 (scheme 25). In both cases, small peaks due to **P2** were observed, but only at 60 °C was **P2** visible during the reaction. This suggests that previously, when the reaction was carried out at 55 °C, it started forming only during work-up.

Carrying out the reaction at 80 °C with 4.5 equivalents of NaOH, produced the same results as before, at 60 °C. Although the substrate was depleted within 50 hours in this case, the two product peaks were present in a similar ratio (~ 1:10) as before, even after 144 hours. In this case, it seemed like both products formed at the same rate as their ratio remained constant during the course of the reaction.

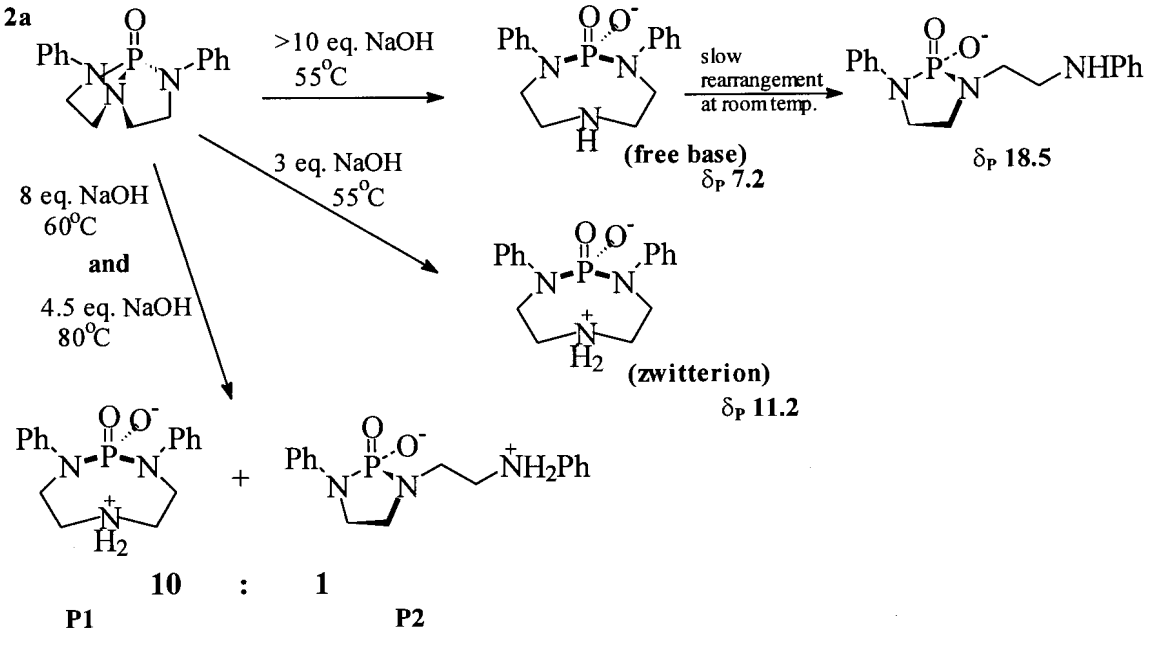
Then trial 1 (at 55 °C) was repeated on a large scale, except for one alteration: only 3 equivalents of 10% NaOH was added. After 10 days, the reaction mixture was cooled

and a product crystallised spontaneously to give fine, white crystals (mp 197-199 °C) of δ_P 11.2, and a ^{1}H NMR spectrum as shown in scheme 27:



Scheme 27.

Results obtained previously in our lab [32] for the alcoholysis of **2a** lead us to believe that the reactions shown in scheme 28 took place during these experiments, which are now discussed.



Scheme 28: Proposed reaction scheme for the base hydrolysis of **2a**, under specified conditions.

Firstly, the proton equivalence shown in the ^{1}H spectra, schemes 25 and 27, indicates a symmetrical molecule in D_2O solution. Secondly, the signals at δ_H 3.1 and 4.0 are of equal integrals and indicative of ethylene signals. As expected for **P1** (scheme 28), the 4 ethylene protons which absorb more downfield, couple with phosphorus to give a quintet. All calculated coupling constants are in agreement with expected values (see experimental). Furthermore, the aromatic signal at δ_H 7.34 integrates 2H and is probably due to two *p*-H_{arom} atoms and the multiplet at δ_H 7.60 accounts for the other 8 protons.

The ^{13}C spectrum shows the same symmetry and all the peaks were, as predicted, similar to those of the substrate, **2a** (see experimental).

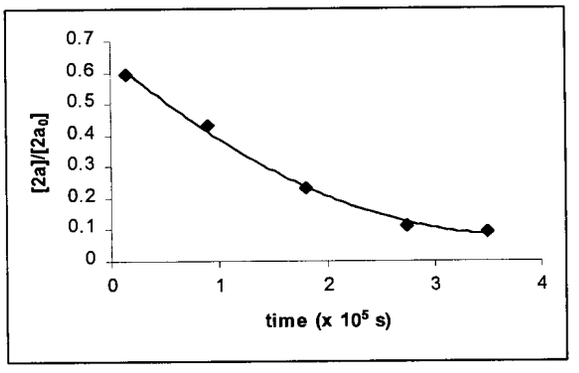
Most striking was the similarity of **P1**'s ^{31}P shift (δ_P 11.2) to that found for the 8-membered cyclic 1,3,2-diazaphospholidines obtained by acidic methanolysis (δ_P 13.6) and acidic ethanolysis (δ_P 10.6) [40]. These compounds, however, were found to rearrange with time to the 5-membered phospholidines (see *introduction*), which could also be obtained directly by base-promoted alcoholysis, giving δ_P 19.9 and δ_P 18.5, respectively, for the products of methanolysis and ethanolysis. These shifts resemble that of **P2** (δ_P 18.5, scheme 28), obtained when our reaction was carried out at temperatures above 60 °C. Because trace amounts of this compound were also obtained after work-up of the first experiment at 55 °C, even though it was not noticed during reaction monitoring, it is thought that, in the highly basic conditions, the free base was formed in that case [which also had a different ^{31}P chemical shift (7.2) than observed for the final product (11.2) formed under less basic conditions and thought to be the zwitterion]. This base could rearrange to the 5-membered cyclic diamidophosphate, **P2**, *via* the mechanism explained under "introduction" for the alcoholysis of **2a**. The zwitterion **P1**, on the other hand, cannot undergo the rearrangement because the aliphatic amine nitrogen of the eight-membered ring exists in the ammonium form, unable to form the necessary bond with phosphorus. The 8- to 5-membered ring rearrangement is therefore, as observed before for the alcoholysis products [32], a sensitive function of the acidity of the reaction medium. Note also that the triplet at *ca.* δ_H 3.8 in scheme 25 was much smaller in the spectrum of the pure zwitterion (scheme 27) and can now be considered an impurity.

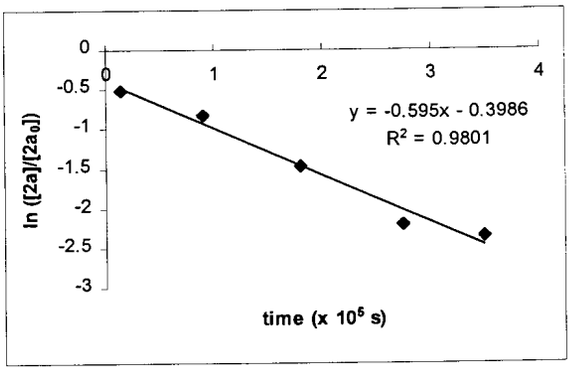
2.5.2. Kinetics

The kinetics of the reactions, which were approximately first-order w.r.t. substrate depletion at both 55°C and 60°C, were studied in an attempt to predict possible mechanisms. As substrate was depleted very rapidly at 80°C, this run is not included in the discussion.

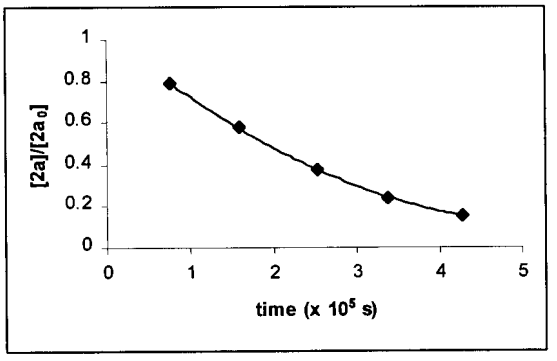
Table 3: Variation of substrate concentration with time.

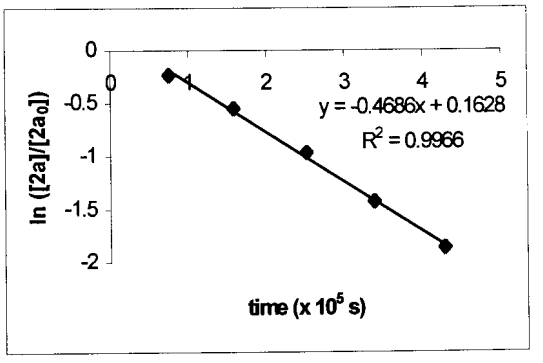
55 °C			60 °C		
time (10^{-5} s)	[2a]/[2a$_0$]	ln ([2a]/[2a$_0$])	time (10^{-5} s)	[2a]/[2a$_0$]	ln ([2a]/[2a$_0$])
0.144	0.594	-0.521	0.756	0.79	-0.236
0.900	0.433	-0.837	1.584	0.577	-0.55
1.80	0.23	-1.47	2.52	0.379	-0.97
2.74	0.111	-2.20	3.384	0.239	-1.43
3.49	0.094	-2.36	4.284	0.154	-1.87





Graph 1: Variation of [**2a**] with time, and plot of ln ([**2a**]/[**2a**$_0$]) against time, for base hydrolysis at 55 °C





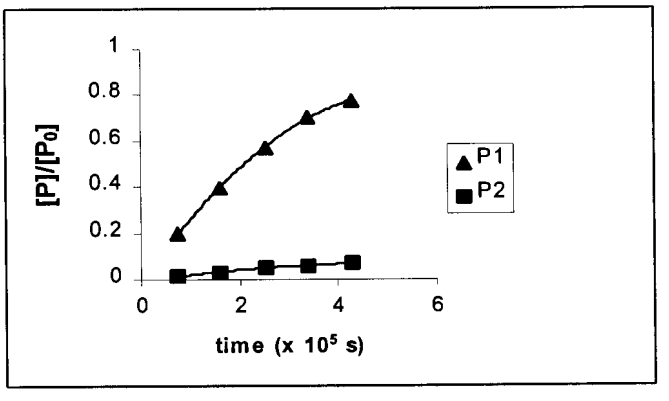
Graph 2: Variation of [**2a**] with time, and plot of ln ([**2a**]/[**2a**$_0$]) against time, for base hydrolysis at 60 °C.

From the slopes of the above linear plots, ln ([**2a**]/[**2a**$_0$]) against time, the rate constants, k_{obsd}, and half-lives, $t_{½}$, at 55 °C and 60 °C, could be determined:

Table 4: Rate constants, k_{obsd}, and half-lives, $t_{½}$, for base hydrolysis of **2a**.

Temperature	$k_{obsd}/10^{-6}$ **s**$^{-1}$	$t_{½}$**/h**
55 °C	5.95	32.4
60 °C	4.69	41.1

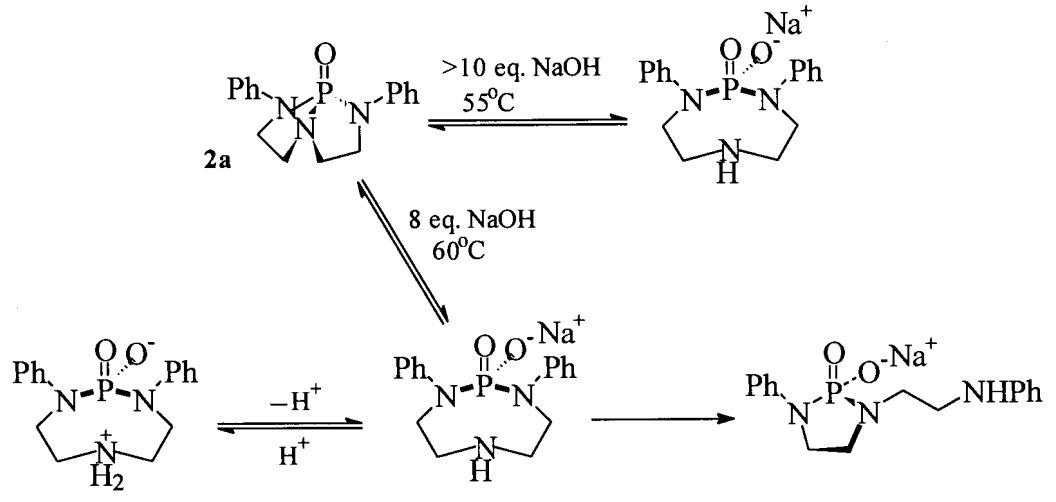
Graph 3 shows how the products' concentrations increased at 60°C:



Graph 3: Variation of products' concentrations with time, at 60°C.

As expected from le Chatelier's principle, the ln ([P]/[P$_0$]) vs time plots gave curves similar to those in graph 3 showing that the equilibria (scheme 29) shift the reaction

towards substrate formation as product concentration increases and lead to the deviation from simple first order kinetics. This is also the reason why the observed rate of substrate depletion (from the kinetic data obtained above, in table 4) is less at 60°C than at 55°C. Though the products form quicker at the higher temperature, their increased concentration increases the rate of the reverse reaction.



Scheme 29: Proposed equilibria involved during the alkaline hydrolysis of **2a**.

It should be noted that the real situation is more complex than depicted in scheme 29, eg. both the formation of products and the rearrangement of **P1→P2** are very pH-dependent and the two trials (at 55°C and 60°C) were carried out at different initial [OH^-] *and* different initial [**2a**].

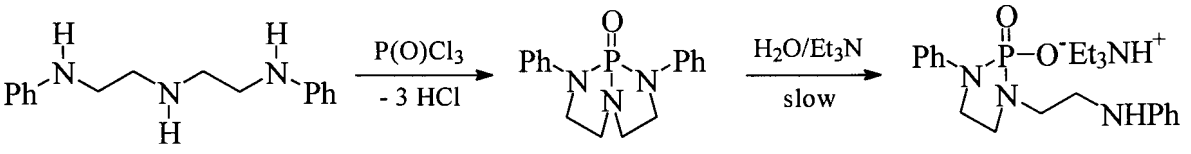
From the results, it may be assumed that **P1** was the kinetically favoured product because it formed first. Why would the formation of **P1** be favoured, at least initially, even at 80°C, especially when considering that *base alcoholysis* of **2a** formed *exclusively* the 5-mempered cyclic product [32] ? It is thought that the answer lies in the following considerations:

1. A pentacoordinate trigonal bipyrimidal intermediate forms during base-catalysed lysis of phosphoric amides (see introduction), and the location of the bridgehead N in the apical (leaving group) position avoids the disfavoured location of the N(Ph) groups of **2a**.
2. The central P-N bond in **2a** was found to be more strained (from crystal data) than the other two [40].

Finally, it should be noted that the zwitterion, proposed to have formed when repeating the reaction at 55°C under less basic conditions, should not rearrange to the 5-membered diamidophosphate as the protonated central N is not nucleophilic as in the free base. The reason why we could not prove beyond any doubt that this compound indeed formed was because elemental analysis failed due to its hygroscopic nature. However, the results certainly merit further investigation considering that **P1** is also an unusual amino acid.

2.6. Reactivity of 1a.

Free triamine **1a** was reacted with phosphoryl chloride in the presence of three equivalents Et_3N in order to demonstrate that it can be converted back to its precursor, **2a**. A dilute solution (0.16 M) of **1a**, $POCl_3$ and Et_3N in diethyl ether was kept under dry N_2 at room temperature and the reaction was monitored by ^{31}P NMR spectroscopy. The reaction was completed after *ca* 17 hours and showed almost exclusive formation of **2a** (δ_P 32.2; lit. δ_P 33.5 [52]), together with small amounts of a side-product (δ_P 20.8). The latter was identified as the corresponding 1,3,2-diazaphospholidine product **i**, formed from **2a** by the base-catalysed hydrolysis due to traces of water present in the reaction system. Under those conditions only very little polymerisation took place yielding an insoluble deposit which could be easily separated from the major product. The reactions are shown in Scheme 30.



1a **2a** **i**

Scheme 30.

Triamines **1** can be therefore "coupled" back to the phosphoryl group to form bicyclic triamides, and the reaction shown in Scheme 30 is currently used in our laboratory as a possible route to the P=S analogues of compounds **2** (bicyclic thiophosphoric triamides).

3. CONCLUSIONS

The obvious route to bis(2-arylaminoethyl)amines **1**, through the reaction of bis(2-chloroethyl)amine with anilines, proved inefficient due to preferential intramolecular cyclisation to N-arylpiperazine. By using the phosphoryl function as a protecting group, a new route was discovered to prepare **1** ; after preparing the corresponding bicyclic triamide, facile cleavage of the P-N bonds afforded the triamine in satisfactory yields. In this way, six derivatives were prepared by varying the nature of the p-substituent on the aromatic rings. The yield-determining step (synthesis of noncyclic triamide **4**) may be improved by optimising conditions of solvent, temperature and base, and carrying out the reaction under strictly anhydrous conditions. Because the very acidic aniline, p-nitroaniline (pK_b = 13), proved reactive towards the phosphoryl centre, the method seems generally applicable, also for the synthesis of unsymmetrically substituted **1**. Acetylation of **1** yielded tri-N-acetyl derivatives with interesting NMR spectroscopic properties. Highly regioselective nitration of tri-N-acetyl-**1a** was carried out. Base hydrolysis of the bicyclic triamide **2a**, yielded a potentially valuable amino acid. The reactivity of the triamine **1a** as a ligand with three reactive nucleophilic centres was confirmed when **2a** was reformed in solution from the reaction of **1a** with $P(O)Cl_3$.

Future work includes further functionalisation of **1**, eg. reduction of **1e** and **1f** to pentamines, potentially pentacoordinate ligands; hydrolysis of **1e** or oxidation of **1b** to the dicarboxylic acid; demethylation of **1c** which could lead to a variety of products. Crystal studies, together with variable-temperature NMR spectroscopy of tri-N-acetyl-**1a** should clarify the uncertainty around its apparent existence as either the E,Z isomer exclusively, or a 1:1 ratio of E,E and Z,Z isomers. The complexation of **1** with Cu(II), and with large metal ions such as Pt(II) and Pd(II) could lead to interesting and useful compounds. Titration of the 8-membered cyclic diamidophosphate may give important information regarding its stability and potential biological applications.

4. EXPERIMENTAL

NMR spectra were recorded from $CDCl_3$ solutions, unless stated otherwise, on a Bruker AC 300 spectrometer. Mass spectra were recorded on a Varian MAT-212 double focusing direct inlet spectrometer at an ionization potential of 70 eV. IR spectra were recorded from KBr pellets on a Bruker IFS 113 spectrophotometer. Melting points are uncorrected. Elemental analysis was performed at the department of Chemistry, University of Cape Town.

4.1. Control experiments for the synthesis of bis(2-phenylaminoethyl)amine

4.1.1. From bis(2-chloroethyl)amine and aniline

A mixture of bis(2-chloroethyl)ammonium chloride (2.9 g, 0.016 mol) and aniline (7.6 g, 0.082 mol) in 50 ml toluene was refluxed for 24 hours, while collecting 2 ml samples of the reaction mixture at regular intervals. Each sample was processed as follows: after cooling down to room temperature, it was filtered and the precipitate was washed with 1 ml toluene. The filtrate was roto-evaporated to dryness and, after drying under a vacuum of *ca* 10^{-2} mm Hg, the ^1H NMR spectrum was recorded in $CDCl_3$ (see 2.1.1.). After 24 hours, the reaction mixture was cooled and left overnight in a refrigerator. After filtering and washing the precipitate with a small amount of toluene, followed by evaporation of the filtrate as before, two products were obtained: P1 (toluene-insoluble precipitate) and P2 (toluene-soluble oil). Both products were stirred in 5% NaOH (P1 in 75 ml and P2 in 10 ml) for 2 hours, extracted with an equal volume of chloroform, and the chloroform solution was washed until the pH was *ca* 9. After drying ($MgSO_4$) and evaporation, followed by high-vacuum drying as before, of the solvent; the ^1H NMR spectra were obtained (see 2.1.1). Mass yields: P1 = 3.94 g (97.3%); P2 = 0.11 g (2.7%).

4.1.2. From bis(2-chloroethyl)amine and acetanilide

Bis(2-chloroethyl)amine (0.20 g, 1.1 mmol) and acetanilide (0.33 g, 2.2 mmol) were dissolved in 15 ml toluene. After adding Et_3N (0.65 ml, 4.4 mmol), the reaction mixture

was heated at *ca* 50°C for 24 hours. A 2 ml sample was again processed as described under 4.1.1. ^{1}H NMR; acetanilide: 2.08 (3H, s, C*H*$_3$ of NAc), 6.98 (1H, t, 1 p-*H*$_{arom}$), 7.19 (2H, t, 2 m-*H*$_{arom}$), 7.50 (2H, d, 2 o-*H*$_{arom}$), 8.54 (1 H, N*H*); bis(2-chloroethyl)ammonium chloride: 3.03 (4H, t, 2 C*H*$_2$N), 3.69 (4H, t, 2 C*H*$_2$Cl); Et_3N: 1.25 (9H, t, 3 C*H*$_3$), 2.94 (6H, q, 3 NC*H*$_2$). These results indicate that no reaction took place.

4.1.3. From bis(2-chloroethyl)amine and sodium acetanilide

To acetanilide (7.5 g, 0.055 mol) in a 250 ml round-bottomed flask were added 50 ml toluene and NaH (6.3 g, 0.053 mol). The reaction mixture was refluxed with protection from moisture for 1.5 hour until white and pasty. After neutralising bis(2-chloroethyl)ammonium chloride (4.46 g, 0.025 mol) by stirring in 25 ml 5% NaOH, the neutral amine was extracted into 20 ml toluene. The toluene fraction was dried (Na_2SO_4) and filtered, before dropwise addition of this solution to the above reaction mixture, while stirring. After the vigorous ebullience subsided (1 hour), the reaction mixture was heated at *ca* 60°C for 1.5 hour. After pouring the reaction mixture into 25 ml water containing 0.5 ml conc. HCl and chilling it in the refrigerator for 24 hours, crystals formed at the phase interface. These were filtered, dried and identified by ^{1}H NMR spectroscopy (in $CDCl_3$) to be acetanilide (see 4.1.2.). Yield = 2.4 g. The filtrate consisted of toluene and aqueous fractions. After washing the toluene fraction with half the volume water, and the water fraction with half a volume toluene, the combined fractions were evaporated and their ^{1}H NMR spectra were recorded in $CDCl_3$ and D_2O respectively. The ^{1}H NMR spectrum of the toluene fraction showed a complex mixture of products (see 2.1.3.); few signals were observed in the ^{1}H NMR spectrum of the aqueous fraction.

4.2. Route to bis(2-arylaminoethyl)amines

Please note that the bicyclic phosphoric triamides **2a** (**2**, Ar = C_6H_5) and **2c** (**2**, Ar C_6H_4-p-OMe) were prepared as described before [52].

4.2.1. Preparation of triamides 4 and 3

N-Bis(2-chloroethyl)-N',N"-bis(4-methylphenyl)phosphotriamidate (4b)

A solution of N-bis(2-chloroethyl)phosphoamidodichloridate (6.60 g, 25.5 mmol) in CH_2Cl_2 (25 ml) was added dropwise with stirring at -20°C to a solution of 4-methylaniline (5.48 g, 51.0 mmol) and Et_3N (5.0 g, 50 mmol) in CH_2Cl_2 (25 ml). After warming to r. t. the mixture was kept stirring for 5 days. After filtering off the precipitate and washing with a small amount of CH_2Cl_2, the filtrate was washed with water (2 x 15 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product (13.4 g) was purified by column chromatography ($CHCl_3$). Pure **4b** was obtained (5.8 g, 63%); mp 124-129°C; ^{31}P NMR: 5.3.

3-(2-Chloroethyl)-1-(4-bromophenyl)-2-[(4-bromophenyl)-amino]-2-oxo-1,3,2-diazaphospholidine (3d)

A solution of N-bis(2-chloroethyl)phosphoamidodichloridate (5.0 g, 19 mmol) in $CHCl_3$ (25 ml) was added dropwise with stirring at *ca* 0°C to a solution of 4-bromoaniline (6.7 g, 39 mmol) and Et_3N (5.4 ml, 39 mmol) in $CHCl_3$ (50 ml) during one hour. After warming to r. t. the mixture was kept stirring for 99 hours, then refluxed * for another 48 hours. After washing the solution with water (2 x 25 ml), drying ($MgSO_4$) and evaporating under reduced pressure, the residue was redissolved in 50 ml THF, Et_3N (3 ml) was added and the mixture was stirred at r. t. for 24 hours, then refluxed * for 6 hours. After roto-evaporating the THF, the residue was dissolved in 50 ml $CHCl_3$ and washed with water (3 x 30 ml). After drying ($MgSO_4$) and filtering, the volume was halved by roto-evaporation. The product was crystallised by adding petroleum ether until an oil separated from solution which, after the addition of acetone crystallised to give pure, white crystals of **3d** (0.55 g, 6%); mp 221-222.5°C; ^{31}P NMR: 13.5; ^{1}H NMR: 3.24-3.36 (m, 1H, 1 NC*H*), 3.62 (t, 2H, J_{HH} = 6.1 Hz, ClC*H*$_2$), 3.41-3.76 (m, 5H, 5 NC*H*), 5.69 (d, 1H, J_{HP} = 6.7 Hz, N*H*), 6.72 (d, 2H, J_{HH} = 8.8 Hz, 2 o-H_{arom}), 7.02 (d, 2H, J_{HH} = 8.8 Hz, 2 o'-H_{arom}), 7.27 (d, 2H, J_{HH} = 8.8 Hz, 2 m-H_{arom}), 7.34 (d, 2H, J_{HH} = 8.8 Hz, 2 m'-H_{arom}); ^{13}C NMR: 42.3 (d, J_{CP} = 4.5 Hz, NCH_2CH_2Cl),

* Heating to these temperatures is not recommended as this was thought to be resposible for the low yield (due to decomposition of p-bromoaniline and/or products).

43.7 (d, J_{CP} = 13.5 Hz, NCH_2CH_2N), 44.0 (d, J_{CP} = 12.6 Hz, NCH_2CH_2N), 46.5 (d, J_{CP} = 5.3 Hz, $ClCH_2$), 114.5 (s, ipso-C_{arom}), 115.1 (s, ipso'-C_{arom}), 117.6 (d, J_{CP} = 5.4 Hz, o-C_{arom}), 120.5 (d, J_{CP} = 6.3 Hz, o'-C_{arom}), 132.1 (s, m-C_{arom}), 132.2 (s, m'-C_{arom}), 138.7 (s, p-C_{arom}), 139.8 (s, p'-C_{arom}); MS: *m/z* 493.0 (100%, M^+), 444.0 (85%, $-CH_2Cl$), 322.7 (35%, -ArNH), 171.9 (23%, $ArNH^+$).

Crystallisation from the mother liquor, by the same method as described above for **3d**, yielded the monosubstituted diamide, **N-(4-bromophenyl)-N'-bis(2-chloroethyl) chloro-phosphodiamidate (5d)** (0.2 g, 3%); mp 214-215°C; ^{31}P NMR: 0.0; ^1H NMR: 3.50 (t, 4H, J_{HH} = 5.9 Hz, 2 $ClCH_2$), 3.61 (m, 4H, J_{HH} = 6.2 Hz, J_{HP} = 12.7 Hz, 2 NCH_2), 7.19 (d, 2H, J_{HH} = 8.8 Hz, 2 o-H_{arom}), 7.49 (d, 2H, J_{HH} = 8.8 Hz, 2 m-H_{arom}); ^{13}C NMR: 41.6 (s, CH_2Cl), 49.1 (s, NCH_2), 118.3 (s, ipso-C_{arom}), 121.1 (d, J_{CP} = 7.2 Hz, 2 o-C_{arom}), 133.1 (s, 2 m-C_{arom}), 133.7 (s, p-C_{arom}); UV-sensitive compound which decomposed when stored at r. t.

3-(2-Chloroethyl)-1-(4-cyanophenyl)-2-[(4-cyanophenyl)-amino]-2-oxo-1,3,2-diazaphospholidine (3e)

A solution of N-bis(2-chloroethyl)phosphoamidodichloridate (5.59 g, 21.6 mmol) in THF (28 ml) was added dropwise with stirring at *ca* 0°C to a solution of 4-aminobenzonitrile (5.1 g, 43 mmol) and Et_3N (6.0 ml, 43 mmol) in THF (55 ml) during 0.5 hour. After warming to r. t. the mixture was stirred for 7 days. After roto-evaporating the THF, the residue was redissolved in 70 ml $CHCl_3$ and washed with water (3 x 30 ml). After drying ($MgSO_4$) and filtering, Et_3N (12 ml) was added and the mixture was refluxed for 17 hours. After washing with water (2 x 30 ml), and drying and filtering as usual, the volume was halved by roto-evaporation. The product was crystallised again by adding petroleum ether until an oil separated from solution which, after the addition of acetone crystallised to give pure, white crystals of **3e** (1.58 g, 19%); mp 233-234°C; ^{31}P NMR: 11.4; ^1H NMR: 3.27-3.39 (m, 1H, 1 NC*H*), 3.47-3.93 (m, 7H, 5 NC*H*, $ClCH_2$), 6.29 (d, 1H, J_{HP} = 6.7 Hz, N*H*), 6.95 (d, 2H, J_{HH} = 8.5 Hz, 2 o-H_{arom}), 7.20 (d, 2H, J_{HH} = 8.8 Hz, 2 o'-H_{arom}), 7.47 (d, 2H, J_{HH} = 8.5 Hz, 2 m-H_{arom}), 7.53 (d, 2H, J_{HH} = 8.8 Hz, 2 m'-H_{arom}); ^{13}C NMR: 42.8 (d, J_{CP} = 4.5 Hz, NCH_2CH_2Cl), 44.3 (d, J_{CP} = 13.5 Hz, NCH_2CH_2N), 44.4 (d, J_{CP} = 12.6 Hz, NCH_2CH_2N), 47.2 (d, J_{CP} = 5.4 Hz, $ClCH_2$), 105.9 (s, ipso-C_{arom}), 106.4 (s, ipso'-C_{arom}), 116.6 (d, J_{CP} = 4.5 Hz, o-

C_{arom}), 118.8 (d, J_{CP} = 7.2 Hz, o'-C_{arom}), 119.4 (s, *C*N), 119.5 (s, *C*N'), 134.3 (s, m-C_{arom}, m'-C_{arom}), 144.6 (s, p-C_{arom}), 145.2 (s, p'-C_{arom}); MS: *m/z* 384.8 (36%, M^+), 335.9 (100%, -CH_2Cl), 267.9 (24%, -ArNH).

4.2.2. Preparation of bicyclic triamides 2

2,8-Bis(4-methylphenyl)-1-oxo-2,5,8-triaza-1-phosphabicyclo-[3.3.0]octane (2b)

A solution of phosphotriamidate **4b** (4.89 g, 12.2 mmol) in THF (180 ml) was added dropwise with stirring to a suspension of NaH (4.72 g, 12.2 mmol) and Bu_4NBr (0.194 g, 2.44 mmol) in THF (180 ml). The mixture was stirred at r. t. for 18 hours, then the precipitate was left to deposit overnight. The solution was decanted and neutralised with 18 ml ethanol. After roto-evaporation of the THF/ethanol, the residue was dissolved in $CHCl_3$ (360 ml) and washed with water (3 x 180 ml). The chloroform layer was dried ($MgSO_4$), filtered, and evaporated and dried under high-vacuum as before. The product was purified by dissolving it in a minimum volume of $CHCl_3$ and precipitating with a large volume of cold hexane. Yield: 3.60 g (90%); mp 186-187°C; ^{31}P NMR: 33.7; ^1H NMR: 2.40 (s, 6H, 2 C*H*$_3$), 3.09-3.21 (m, 2H, 2 NC*H*), 3.59-3.80 (m, 4H, 4NC*H*), 3.84-3.94 (m, 2H, 2 NC*H*), 7.00 (d, 4H, J_{HH} = 8.5 Hz, 4 m-H_{arom}), 7.06 (d, 4H, J_{HH} = 8.5 Hz, 4 o-H_{arom}); ^{13}C NMR: 21.0 (s, *C*H$_3$), 48.3 (d, J_{CP} = 7.1 Hz, N*C*H$_2$), 49.4 (d, J_{CP} = 19.8 Hz, N*C*H$_2$), 119.4 (s, C_{arom}), 129.9 (s, C_{arom}), 132.0 (s, C_{arom}), 139.8 (s, C_{arom}). Analysis ($C_{18}H_{22}N_3OP$): Calc. C, 66.04; H, 6.77; N, 12.84. Found C, 65.88; H, 6.90; N, 12.49.

2,8-Bis(4-bromophenyl)-1-oxo-2,5,8-triaza-1-phosphabicyclo-[3.3.0]octane (2d)

A solution of 1,3,2-diazaphospholidine **3d** (0.30 g, 0.61 mmol) in THF (20 ml) was added dropwise with stirring to NaH (0.060 g, 0.63 mmol) and Bu_4NBr (0.020 g, 0.062 mmol) in THF (20 ml). The mixture was stirred at r. t. for 2 hours, then the precipitate was left to deposit overnight. The solution was decanted and neutralised with 2 ml ethanol. After roto-evaporation of the THF/ethanol, the residue was dissolved in $CHCl_3$ (30 ml) and washed with water (2 x 20 ml). The chloroform layer was dried ($MgSO_4$), filtered, and evaporated and dried under high-vacuum as before. Pure **2d** (lightly

coloured needles) was obtained by recrystallisation from chloroform/hexane (1:1). Yield: 0.22 g (79%); mp 203-204°C; ^{31}P NMR: 32.9; ^{1}H NMR: 3.12-3.24 (m, 2H, 2 NC*H*), 3.56-3.67 (m, 2H, 2 NC*H*), 3.73-3.93 (m, 4H, 4 NC*H*), 7.06 (d, 4H, J_{HH} = 9.0 Hz, 4 o-H_{arom}), 7.30 (d, 4H, J_{HH} = 8.8 Hz, 4 m-H_{arom}); ^{13}C NMR: 48.6 (d, J_{CP} = 7.2 Hz, NCH_2), 49.9 (d, J_{CP} = 19.8 Hz, $ArNCH_2$), 115.8 (s, ipso-C_{arom}), 121.1 (d, J_{CP} = 3.6 Hz, o-C_{arom}), 132.6 (s, m-C_{arom}), 141.6 (s, p-C_{arom}); MS: *m/z* 458, 457, 456 (77, 99, 100%, M^+). Analysis ($C_{16}H_{16}Br_2N_3OP$): Calc. C, 42.02; H, 3.53; N, 9.19. Found C, 41.98; H, 3.65; N, 9.05.

2,8-Bis(4-cyanophenyl)-1-oxo-2,5,8-triaza-1-phosphabicyclo-[3.3.0]octane (2e)

A solution of 1,3,2-diazaphospholidine **3e** (0.14 g, 0.36 mmol) in toluene (10 ml) was added dropwise with stirring to LDA (0.50 g, 0.4 mmol) and a spatula tip of Bu_4NBr in toluene (10 ml). The mixture was refluxed for 3 days. After roto-evaporating the mixture to dryness, the residue was dissolved in chloroform (15 ml) and washed with water (2 x 10 ml), dried ($MgSO_4$) and roto-evaporated to dryness. Pure **2e** was obtained by crystallisation from the oily residue, by dissolving it in the minimum amount of acetone and adding an equal volume of hexane, then keeping the solution at *ca* 10°C for two weeks. Yield: *ca* 0.08 g (64%); mp 189-191°C; ^{31}P NMR: 32.1; ^{1}H NMR: 3.19-3.31 (m, 2H, 2 NC*H*), 3.61-3.75 (m, 2H, 2 NC*H*), 3.79-4.01 (m, 4H, 4 NC*H*), 7.30 (d, 4H, J_{HH} = 8.5 Hz, 4 o-H_{arom}), 7.49 (d, 4H, J_{HH} = 8.6 Hz, 4 m-H_{arom}); ^{13}C NMR: 48.7 (d, J_{CP} = 7.2 Hz, NCH_2), 50.1 (d, J_{CP} = 19.7 Hz, $ArNCH_2$), 106.1 (s, ipso-C_{arom}), 119.0 (d, J_{CP} = 3.6 Hz, o-C_{arom}), 119.5 (s, *C*N), 134.0 (s, m-C_{arom}), 146.7 (s, p-C_{arom}).

The 5-membered cyclic diamidophosphate 6e

Exactly the same method was employed as above for the preparation of **2e**, except for using 0.80 g (2.1 mmol) of the 1,3,2-diazaphospholidine **3e**, and adjusting the amounts of other reagents and the volumes of solvents. However, while monitoring the reaction using ^{31}P NMR with an internal standard, a peak at δ_P 17.8 (previously conspicuous in trace amounts during the synthesis of **2e**) grew rapidly as the reaction progressed. As explained in section 2.2.2., hydrolysis of **2e** took place to yield **6e**, which was now obtained by washing the reaction mixture (after refluxing for 34 hours) with an equal

volume of water, thereby extracting water-soluble **6e**. The volume of the aqueous layer was halved by boiling on a hot plate. Pure **6e** crystallised from the solution by cooling (0.15 g, 19%); mp 241.5-242.5°C; ^{31}P NMR (D_2O): 20.2; ^{1}H NMR (D_2O): 3.09-3.26 (m, 4H, 4 NC*H*), 3.39 (t, 2H, J_{HH} = 6.1 Hz, 2 NC*H*), 3.49-3.56 (m, 2H, 2 NC*H*), 6.80 (d, 2H, J_{HH} = 8.8 Hz, 2 o-H_{arom}), 7.12 (d, 2H, J_{HH} = 8.8 Hz, 2 o'-H_{arom}), 7.55 (d, 2H, J_{HH} = 8.8 Hz, 2 m-H_{arom}), 7.67 (d, 2H, J_{HH} = 8.8 Hz, 2 m'-H_{arom}); ^{13}C NMR (D_2O): 41.4 (d, J_{CP} = 7.2 Hz, NCH_2), 43.4 (d, J_{CP} = 12.6 Hz, NCH_2), 43.9 (d, J_{CP} = 8.1 Hz, NCH_2), 44.7 (d, ClCH_2), 97.2 (s, ipso-C_{arom}), 100.2 (s, ipso'-C_{arom}), 113.2 (d, J_{CP} = 4.5 Hz, o-C_{arom}), 115.2 (d, J_{CP} = 4.5 Hz, o'-C_{arom}), 121.6 (s, *C*N), 122.3 (s, *C*N'), 134.2 (s, m-C_{arom}), 134.5 (s, m'-C_{arom}), 148.0 (s, p-C_{arom}), 152.9 (s, p'-C_{arom}); IR: υ_{CN} = 2213.8 cm^{-1}.

4.2.3. Preparation of the bis(2-arylaminoethyl)amines 1 and their hydrochlorides

All data for the specific derivatives, including their preparations, are given in table 5.

(i) General procedure:

To a solution of approximately 0.10 g **2** (**6e** for the preparation of **1e**, see above) in 1,4-dioxane or THF (10 ml) was added dropwise with stirring 3 – 6 mol-equivalents of HCl (as a 10% aqueous solution, or as conc. aqueous solution), and the solution was stirred at room temperature for 24 h. For **1a, 1c, 1d and 1e** the corresponding trihydrochloride salts precipitated out when conc. HCl was used, and were isolated by cooling the mixture to 10°C and filtration.

For a direct isolation of free amines **1** most of dioxane and water was removed under reduced pressure, at least 6 mol-equivalents of NaOH (as a 5% aqueous solution) was added to the residual paste (pH > 9), and the mixture was stirred at room temperature for 1 h. (Crystalline derivatives **1d** and **1e** were directly isolated at this stage by filtering and washing with water). The mixture was diluted twice with water, extracted with chloroform, and the chloroform solution was washed with water until pH of *ca* 8 was reached. After drying ($MgSO_4$) and evaporation of the solvent under reduced pressure, the product was kept under a vacuum of *ca* 10^{-2} mm Hg for 1 h. (The same procedure was employed when the free triamines were obtained from the isolated, pure trihydrochlorides).

(ii) *In situ* hydrolysis of **2a**

After the reaction of **4a** (9.0 g, 24.2 mmol) with NaH (as described before [52]) in THF solution, the mother liquor was decanted and neutralised with 30 ml ethanol. To the neutralised solution was added 9 ml conc. HCl, dropwise and with stirring. White precipitate of trihydrochloride **1a** formed immediately; it was left to crystallise in the refrigerator overnight, filtered, washed with 30 ml acetone and dried. The yield by this method was 6.1 g (69% from **4a**).

4.3. Acetylation of triamines 1

Specific data are given in table 5.

General Procedure:

A solution of amine **1** in acetic anhydride (*ca* 8 ml per 1 g of **1**) was heated under reflux for 2 h and poured into cold water (*ca* 6 ml per 1 ml of Ac_2O). The solution was extracted with $CHCl_3$ (*ca* 1 ml per 3 ml of water used), the $CHCl_3$ solution was washed twice with equal volumes of water and once with half of the volume of 5% aq. Na_2CO_3 (pH *ca* 8). After drying ($MgSO_4$) and evaporation of the solvent under reduced pressure, the triacetate was purified by crystallisation.

4.4.1. Nitration of tri-N-acetyl 1a

Tri-N-acetyl derivative of **1a** (1.0 g, 2.62 mmol) was dissolved in glacial acetic acid (6 ml) and conc. H_2SO_4 (6 ml) was added with stirring. A mixture of HNO_3 (0.5 ml) and conc. H_2SO_4 (0.4 ml) was added dropwise with stirring and cooling (inside temperature below 10°C). The solution was allowed to warm to room temperature and stirred for a further 48 h. Cold water (50 ml) was added slowly while cooling the flask in ice; the precipitated yellow product was filtered off, washed with water and dried. The product crystallised after keeping it in a refrigerator. Data are given in table 5.

4.4.2. Hydrolysis of the Nitration Product (Preparation of 1f):

A suspension of the above product (0.20 g, 0.42mmol) in 20% aq HCl (3 ml) was heated under reflux for 1 h. The hot mixture was poured into cold water (20 ml) and neutralised with 10% aq. NaOH with cooling. The mixture was kept in a refrigerator overnight and the precipitated product was filtered off and dried.

4.5. Base hydrolysis of 2a

1. In a NMR tube, a few milligrams of **2a** was dissolved in 0.5 ml dioxane to which was added 0.5 ml of 50% aq. NaOH. The reaction was kept at r. t. and monitored by ^{31}P NMR spectroscopy. After 2 days, the mixture was heated at 55°C for a period of 97 hours (see 2.5.). After extraction of excess substrate and organic impurities into an equal volume of $CHCl_3$, the aqueous layer was roto-evaporated and the ^{1}H NMR spectrum of the residue was recorded in D_2O.

2. In 5 ml dioxane was dissolved **2a** (0.090 g, 0.30 mmol). To the solution was added 10% aq. NaOH (1 ml, *ca* 8 eq.). The mixture was heated at 60°C for 166 hours, while monitoring the reaction again (see 2.5.). Work-up as above (1.)

3. In 6 ml dioxane was dissolved **2a** (0.10 g, 0.33 mmol). To the solution was added 10% aq. NaOH (0.6 ml, *ca* 4.5 eq.). The mixture was heated at 80°C for 143 hours, while monitoring the reaction again (see 2.5.). Work-up as above (1.)

4. In 20 ml dioxane was dissolved **2a** (0.40 g, 1.3 mmol). To the solution was added 10% aq. NaOH (1.6 ml, *ca* 3 eq.). The mixture was heated at 55°C for 10 days. The pure zwitterion (see 2.5.) crystallised on cooling and was filtered and washed with *ca* 5 ml each of chloroform, dioxane and acetone. After drying, a powdery white salt was obtained (0.31 g, 73%); mp 197-199°C; ^{31}P NMR (D_2O): 11.2; ^{1}H NMR (D_2O): 3.07 (t, 4H, J_{HH} = 4.9 Hz, 2 NCH_2), 3.95 (m, 4H, J_{HP} = 10.4 Hz, J_{HH} = 5.1 Hz, 2 OPNCH_2), 7.34 (t, 2H, J_{HH} = 6.7 Hz, 2 p-H_{arom}), 7.56-7.65 (m, 8H, 4 o-H_{arom}, 4 m-H_{arom}); ^{13}C NMR (D_2O): 47.1 (s, NCH_2), 51.1 (s, OPNCH_2), 123.3 (s, p-C_{arom}), 124.1 (d, J_{CP} = 3.6 Hz, o-C_{arom}), 129.5 (s, m-C_{arom}), 146.2 (s, ipso-C_{arom}).

4.6. Reaction of 1a with phosphoryl chloride

A solution of $POCl_3$ (0.05 ml, 0.5 mmol) in diethyl ether (4 ml) was added dropwise, with stirring under N_2, to a solution of crude **1a** (0.2 g, 0.8 mmol) and Et_3N (0.2 ml, 1.4 mmol) in diethyl ether (5 ml) at *ca* -10°C during 0.5 hour. After warming to r. t. the mixture was kept stirring for 68 hours and monitored by ^{31}P NMR spectroscopy (see 2.6). The reaction was completed after *ca* 17 hours and showed almost exclusive formation of the bicyclic precursor **2a** (δ_P 32.2; lit. δ_P 33.5 [52]), together with small amounts of a side-product (δ_P 20.8).

Table 5: Triamines 4-$XC_6H_4NHCH_2CH_2NHCH_2CH_2NHC_6H_4$-4-X **1** and their derivatives

Compound	X	Preparation	Data for **1**	Derivatives
1a	H	Hydrolysis of **2a** (0.84 g, 2.8 mmol)	Yield: 0.72 g (100%); oil. ^{1}H NMR: 2.88 (t, 4H, J_{HH} = 5.7 Hz, 2 NCH_2), 3.21 (t, 4H, J_{HH} = 5.7 Hz, 2 ArNCH_2), 4.01 (br s, 3H, 3 NH), 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}); ^{13}C NMR: 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}).	*Trihydrochloride*. Mp 203-206°C. ^{1}H NMR (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}); ^{13}C NMR: 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}). *N,N',N"-triacetyl* (63%). Mp 111-113°C (from $CHCl_3$/pet ether, 2:1). ^{1}H NMR: 1.78 (s, 3H, CH_3 of NAc), 1.85 (s, 3H, CH_3 of NAc), 2.03 (s, 3H, CH_3 of NAc), 3.43 (t, 2H, J_{HH} = 6.5 Hz, NCH_2), 3.61 (t, 2H, J_{HH} = 7.1 Hz, NCH_2), 3.76 (t, 2H, J_{HH} = 6.5 Hz, ArNCH_2), 3.80 (t, 2H, J_{HH} = 7.2 Hz, ArNCH_2), 7.16 (d, 2H, J_{HH} = 7.2 Hz, 2 o-H_{arom}), 7.20 (d, 2H, J_{HH} = 7.0 Hz, 2 o-H_{arom}), 7.28-7.47 (m, 6H, 2 p-H_{arom}, 4 m-H_{arom}); ^{13}C NMR: 21.9 (s, CH_3 of Ac), 23.2 (s, CH_3 of Ac), 44.0, 46.8, 47,4, 48.8 (s, NCH_2), 128.1, 128.3 (s, o-C_{arom}), 128.4, 128.8 (s, p-C_{arom}), 130.3, 130.6 (s, m-C_{arom}),

				143.87, 143.93 (s, ipso-C_{arom}), 171.3, 171.4, 171.8 (s, C=O). [a]
1b	CH_3	Hydrolysis of **2b** (2.00 g, 6.11 mmol)	Yield: 1.15 g (67%); oil. ^{1}H NMR: 2.25 (s, 6H, 2 ArCH_3), 2.89 (t, 4H, J_{HH} = 5.8 Hz, 4 NCH), 3.21 (t, 4H, J_{HH} = 5.8 Hz, 4 ArNCH), 3.71 (s, 3H, 3 NH), 6.56 (d, 4H, J_{HH} = 8.3 Hz, 4 o-H_{arom}), 6.99 (d, 4H, J_{HH} = 8.0 Hz, 4 m-H_{arom}); ^{13}C NMR: 21.0 (s, ArCH_3), 44.7 (s, NCH_2), 49.2 (s, ArNCH_2), 113.8 (s, o-C_{arom}), 127.4 (s, p-C_{arom}), 130.4 (s, m-C_{arom}), 146.8 (s, ipso-C_{arom}). [b]	*N,N',N"-triacetyl* (81%). Purified by column chromatography (SiO_2, acetone/$CHCl_3$, 1:1); oil. ^{1}H NMR: 1.71 (s, 3H, ArCH_3), 1.77 (s, 3H, ArCH_3), 1.97 (s, 3H, CH_3 of NAc), 2.28 (s, 3H, CH_3 of NAc), 2.31 (s, 3H, CH_3 of NAc), 3.36 (t, 2H, J_{HH} = 6.1 Hz, 2 NCH), 3.53 (t, 2H, J_{HH} = 7.0 Hz, 2 NCH), 3.65-3.73 (m, 4H, 4 ArNCH), 6.98 (d, 2H, J_{HH} = 8.0 Hz, 2 o-H_{arom}), 7.02 (d, 2H, J_{HH} = 8.3 Hz, 2 o-H_{arom}), 7.10 (d, 2H, J_{HH} = 8.0 Hz, 2 m-H_{arom}), 7.14 (d, 2H, J_{HH} = 8.2 Hz, 2 m-H_{arom}); ^{13}C NMR: 21.5 (s, ArCH_3), 21.8 (s, CH_3 of NAc), 23.0 (s, CH_3 of NAc), 43.8, 46.7, 47.3, 48.7 (s, NCH_2), 127.8, 127.9 (s, o-C_{arom}), 130.8, 131.1 (s, m-C_{arom}), 138.2, 138.6 (s, p-C_{arom}), 141.2, 141.3 (s, ipso-C_{arom}), 171.4, 171.5, 171,7 (s, C=O). [c]
1c	OCH_3	Hydrolysis of **2c** (0.30 g, 0.83 mmol)	Yield: 0.25 g (95%); oil. ^{1}H NMR: 2.88 (t, 4H, J_{HH} = 5.7 Hz, 2 NCH_2), 3.18 (t, 4H, J_{HH} = 5.8 Hz, 2 ArNCH_2), 3.70 (br s, 3H, 3 NH), 3.75 (s, 6H, 2 OCH_3), 6.60 (d, 4H, J_{HH} = 8.8 Hz, 4 m-	*Trihydrochloride*. Mp 207-209.5°C. ^{1}H NMR (CD_3OD): 3.49 (t, 4H, J_{HH} = 6.3, 2 NCH_2), 3.73 (t, 4H, J_{HH} = 6.2 Hz, 2 ArNCH_2), 7.04 (d, 4H, J_{HH} = 8.8 Hz, 4 m-H_{arom}), 7.36 (d, 4H, J_{HH} = 8.8 Hz, 4 o-H_{arom}); ^{13}C

			H_{arom}), 6.78 (d, 4H, J_{HH} = 9.0 Hz, 4 o-H_{arom}); ^{13}C NMR: 45.4 (s, NCH_2), 49.3 (s, ArNCH_2), 56.5 (s, OCH_3), 115.0 (s, m-C_{arom}), 115.6 (s, o-C_{arom}), 143.4 (s, ipso-C_{arom}), 152.9 (s, p-C_{arom}).	NMR: 45.3 (s, NCH_2), 47.2 (s, ArNCH_2), 56.3 (s, OCH_3), 116.6 (s, m-C_{arom}), 123.3 (s, o-C_{arom}), 125.2 (s, ipso-C_{arom}), 160.7 (s, p-C_{arom}). [d] *N,N',N''-triacetyl* (90%). Oil. ^{1}H NMR: 1.68 (s, 3H, CH_3 of NAc), 1.74 (s, 3H, CH_3 of NAc), 1.95 (s, 3H, CH_3 of NAc), 3.35 (t, 2H, J_{HH} = 6.1 Hz, 2 NCH), 3.51 (t, 2H, J_{HH} = 6.9 Hz, 2 NCH), 3.62-3.67 (m, 4H, 4 ArNCH), 3.71 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 6.80 (d, 2H, J_{HH} = 8.5 Hz, 2 m-H_{arom}), 6.84 (d, 2H, J_{HH} = 8.8 Hz, 2 m-H_{arom}), 6.99 (d, 2H, J_{HH} = 8.8 Hz, 2 o-H_{arom}), 7.01 (d, 2H, J_{HH} = 8.8 Hz, 2 o-H_{arom}); ^{13}C NMR: 21.7 (s, CH_3 of NAc), 22.9 (s, CH_3 of NAc), 43.7, 46.5, 47.3, 48.6 (s, 4 NCH), 55.88 (s, OCH_3), 55.92 (s, OCH_3), 115.2, 115.6 (s, 2 m-C_{arom}), 129.1, 129.2 (s, 2 o-C_{arom}), 136.4, 136.5 (s, 2 ipso-C_{arom}), 159.4, 159.6 (s, 2 p-C_{arom}), 171.75 (s, C=O), 171.84 (s, C=O).
1d	Br	Hydrolysis of **2d** (0.10 g, 0.22 mmol)	Yield: 0.075 g (83%); mp 60-61.5°C. ^{1}H NMR: 2.97 (t, 4H, J_{HH} = 5.7 Hz, 4 NCH), 3.27 (t, 4H, J_{HH} = 5.5 Hz, 4 ArNCH), 4.15 (br s, 3H, 3 NH), 6.58 (d, 4H, J_{HH} = 8.8 Hz, 4 o-H_{arom}), 7.33 (d,	*Trihydrochloride*. Mp 214-216°C. ^{1}H NMR (CD_3OD): 3.26 (t, 4H, J_{HH} = 5.9 Hz, 4 NCH), 3.46 (t, 4H, J_{HH} = 5.9 Hz, 4 ArNCH), 6.62 (d, 4H, J_{HH} = 8.5 Hz, 4 o-H_{arom}), 7.23 (d, 4H, J_{HH} = 8.8 Hz, 4 m-H_{arom}); ^{13}C

			4H, J_{HH} = 8.5 Hz, 4 m-H_{arom}); ^{13}C NMR: 44.3 (s, NCH_2), 49.0 (s, ArNCH_2), 109.8 (s, ipso-C_{arom}), 115.2 (s, o-C_{arom}), 132.6 (s, m-C_{arom}), 148.0 (s, p-C_{arom}).	NMR: 41.1 (s, NCH), 47.8 (s, ArNCH), 110.8 (s, ipso-C_{arom}), 116.1 (s, o-C_{arom}), 133.0 (s, m-C_{arom}), 148.0 (s, p-C_{arom}). [e]
1e	CN	Neutralisation of the trihydrochloride salt, prepared by hydrolysis of the corresponding 1,3,2-diazaphospholidine (see Discussion)	Yield: 0.050 g (82%); mp 118°C. ^{1}H NMR: 2.93 (t, 4H, J_{HH} = 5.7 Hz, 4 NC*H*), 3.26 (t, 4H, J_{HH} = 5.4 Hz, 4 ArNC*H*), 4.61 (br s, 3H, 3 N*H*), 6.56 (d, 4H, J_{HH} = 8.3 Hz, 4 o-H_{arom}), 7.42 (d, 4H, J_{HH} = 8.5 Hz, 4 m-H_{arom}); ^{13}C NMR: 43.4 (s, NCH), 48.6 (s, ArNCH), 99.8 (s, ipso-C_{arom}), 113.0 (s, o-C_{arom}), 121.0 (s, *C*N), 134.5 (s, m-C_{arom}), 152.0 (s, p-C_{arom}).	*Trihydrochloride.* Mp 211-212°C. ^{1}H NMR (CD_3OD): 3.30 (t, 4H, J_{HH} = 6.1 Hz, 4 NC*H*), 3.58 (t, 4H, J_{HH} = 6.1 Hz, 4 ArNC*H*), 6.76 (d, 4H, J_{HH} = 8.5 Hz, 4 o-H_{arom}), 7.46 (d, 4H, J_{HH} = 8.8 Hz, 4 m-H_{arom}); ^{13}C NMR: 40.2 (s, NCH), 47.7 (s ArNCH), 99.8 (s, ipso-C_{arom}), 113.8 (s, o-C_{arom}), 121.2 (s, *C*N), 134.8 (s, m-C_{arom}), 152.9 (s, p-C_{arom}); IR: ν_{CN} = 2214.3 cm^{-1}. [f]
1f	NO_2	From triacetyl derivative of **1a**, via nitration followed by hydrolysis	Yield: 0.083 g (57%). Yellow powder, mp 145-147.5°C. ^{1}H NMR: 2.97 (t, 4H, J_{HH} = 5.7 Hz, 4 NC*H*), 3.32 (t, 4H, J_{HH} = 4 ArNC*H*), 4.89 (br s, 3H, 3 N*H*), 6.54 (d, 4H, J_{HH} = 9.3 Hz, 4 o-H_{arom}), 8.09 (d, 4H, J_{HH} = 9.3 Hz, 4 m-H_{arom}); ^{13}C NMR:	*N,N',N"-triacetyl.* (100%). Yellow powder, mp 99-102°C. ^{1}H NMR: 1.87 (s, 3H, CH_3 of NAc), 1.94 (s, 3H, CH_3 of NAc), 2.05 (s, 3H, CH_3 of NAc), 3.43 (t, 2H, J_{HH} = 6.5 Hz, 2 NC*H*), 3.63 (t, 2H, J_{HH} = 7.2 Hz, 2 NC*H*), 3.79 (t, 2H, J_{HH} = 6.3 Hz, 2 ArNC*H*), 3.87 (t,

		(0.20 g, 0.42 mmol)	43.6 (s, NCH), 48.6 (s, ArNCH), 111.9 (s, o-C_{arom}), 127.1 (s, m-C_{arom}), 139.1 (s, ipso-C_{arom}), 153.9 (s, p-C_{arom}). [g]	2H, J_{HH} = 7.2 Hz, 2 ArNC*H*), 7.40 (d, 2H, J_{HH} = 9.0 Hz, 2 o-H_{arom}), 7.44 (d, 2H, J_{HH} = 9.0 Hz, 2 o-H_{arom}), 8.28 (d, 2H, J_{HH} = 9.0 Hz, 2 m-H_{arom}), 8.32 (d, 2H, J_{HH} = 8.8 Hz, 2 m-H_{arom}); ^{13}C NMR: 22.0 (s, *C*H$_3$ of NAc), 23.4 (s, *C*H$_3$ of NAc), 44.1, 46.9, 47.8, 49.2 (s, 4 NCH), 125.9, 126.2 (s, o-C_{arom}), 129.0, 129.2 (s, m-C_{arom}), 128.2, 130.8 (s, ipso-C_{arom}), 147.5, 149.5 (s, p-C_{arom}), 170.8, 172.0 (s, *C*=O); IR: ν_{NO2} = 1521.8 cm^{-1}.

[a] Analysis ($C_{22}H_{27}N_3O_3$): Calc. C, 69.27; H, 7.13; N, 11.01. Found C, 69.50; H, 7.31; N, 10.86. [b] Analysis ($C_{18}H_{25}N_3$): Calc. C, 76.28; H, 8.89; N, 14.83. Found C, 76.10; H, 9.00; N, 14.65. [c] Analysis ($C_{24}H_{31}N_3O_3$): Calc. C, 70.39; H, 7.63; N, 10.26. Found C, 70.15; H, 7.80; N, 10.14. [d] Analysis ($C_{18}H_{28}Cl_3N_3O_2$): Calc. C, 50.89; H, 6.64; N, 9.89. Found C, 50.61; H, 6.99; N, 9.35. [e] Analysis ($C_{16}H_{22}Br_2Cl_3N_3$): Calc. C, 36.78; H, 4.24; N, 8.04. Found C, 36.48; H, 4.38; N, 7.91. [f] Analysis ($C_{18}H_{22}Cl_3N_5$): Calc. C, 52.13; H, 5.35; N, 16.88. Found C, 51.85; H, 5.50; N, 16.42. [g] Analysis ($C_{16}H_{19}N_5O_4$): Calc. C, 55.65; H, 5.54; N, 20.28. Found C, 55.40; H, 5.61; N, 19.89.

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