New Developments in Heterocyclic Chemistry of Phosphorus and Nitrogen*

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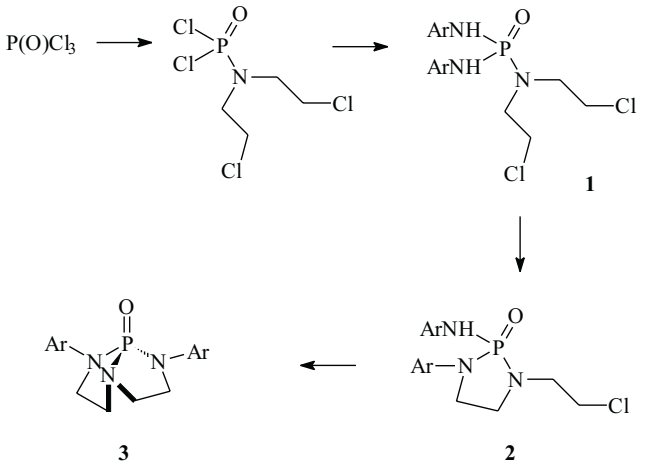
A series of phosphoric triamides of a general structure $(R_2N)_3P{=}O$ has been prepared. The series included non-cyclic structures, as well as structures in which the phosphorus and two (monocyclic structure), or three (bicyclic structure) nitrogen atoms were incorporated in the five-membered heterocyclic ring. The molecular parameters (particularly the N-P-N bond angles and P-N bond distances) were determined by X-ray diffraction, and they were correlated with the ^{31}

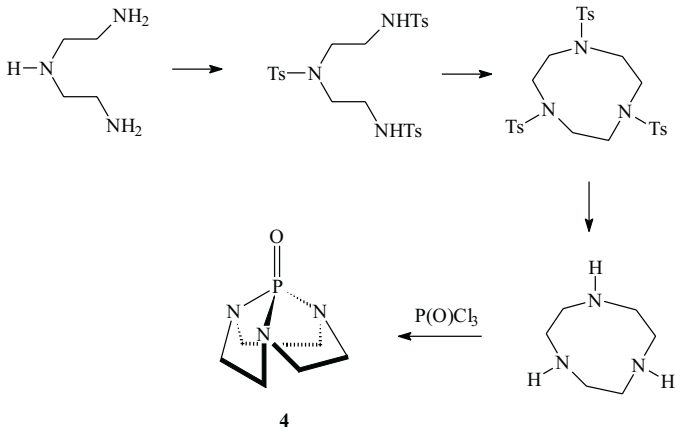
the ^{31}P NMR shielding parameters. For the PO_4 tetrahedral system (phosphate derivatives), extensive work by Gorenstein led to an empirical correlation between ^{31}P chemical shifts and the O–P–O bond angles [3]. According to that correlation, a decrease in the O–P–O bond angle results in a deshielding of the phosphorus nucleus; ionization of the phosphate function or the nature of the ester groups being of much lesser importance. For example, cyclic five-membered ring phosphate esters, with the endocyclic O–P–O bond angle less than 100°, are shifted downfield from their acyclic counterparts by up to 20 ppm [4]. Since the same substrates are several order of magnitudes more reactive in the nucleophilic cleavage of the P–O bond [5], the magnitude of the ^{31}P NMR chemical shift can therefore be related to the reactivity of the phosphoryl centre.

As an extension of that approach, we have decided to prepare a series of phosphoric triamides (PN_3O tetrahedral system) with variable values of the N–P–N bond angles, and to correlate the molecular geometry with the ^{31}P NMR chemical shifts, as well as to explore the new chemistry of the more strained systems. In our recent work [6], we have reported a synthetic sequence (Scheme 1) that produces three types of phosphoric triamides: noncyclic (**1**), monocyclic (**2**), and bicyclic (**3**); the latter two types incorporate phosphorus in one or two five-membered 1,3,2-diazaphospholidin-2-one rings. Additionally, a tricyclic compound, the 10-oxo-10-phospha-1,4,7-triazatricyclo[5.2.1.$0^{4,10}$]decane (**4**) was prepared in a pure state by some modification of an earlier literature report [7] (Scheme 2). Fortunately, compound **4**, and selected compounds **1**, **2**, and **3** were crystalline materials, suitable for X-ray diffraction studies. The ^{31}P NMR chemical shift values showed a dramatic variation within the series [from δ_P = 4.3 ppm for **1a** (Ar = Ph), to δ_P = 98.0 ppm for **4**], and were then correlated with the N–P–N bond angles and P–N bond distances yielding the relationship shown in Figure 1. Since the nature of the atoms bonded to phosphorus (N,N,N,O) is constant for all compounds studied, it may be concluded that the observed deshielding effect results not from any significant electronegativity changes, but from

Scheme 1



Scheme 2



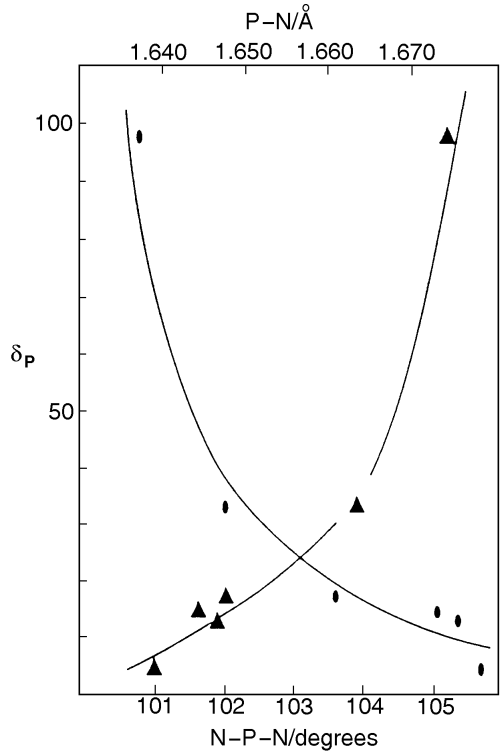


Figure 1. Effect of structural parameters on the ^{31}P NMR chemical shift of phosphoric triamides. ▲, δ_P *vs*. P–N bond distance; •, δ_P *vs*. N–P–N bond angle.

the changes in the nature of the P–N bonding that follow the changes in the molecular geometry. This conclusion can be corroborated by a comparison of the δ_P value for **4** (98.0) with that of $\delta_P = 23.3$ reported for $(Et_2N)_3PO$ [8]. For that pair of triamides any differences in the polar effects of the substituents can certainly be ignored, and the

dramatic deshielding effect of 74.7 ppm must reflect solely the difference in the geometry of the molecules. The results fully confirm earlier observations derived from the phosphate systems, and they demonstrate that even within a narrow range of structurally closely related substrates, variation in the geometry can lead to formidable changes in the shielding parameters at the phosphoryl centre.

The N–P–N bond angle decreases along the series indicating the shift of the hybridization of the phosphorus – nitrogen bonding orbitals from the sp^3 towards the unhybridized, p^3 (pyramidal) state. Such a trend should have a profound effect on other properties of the P–N bonding, such as bond length, hence the stability. For any covalent bond the less s-character in a hybrid atomic orbital, the further it lies from the bonded nuclei [8]. Examination of the available data on the P–N bond distances in various classes of organophosphorus compounds allowed us to arrange them into groups according to the decreasing P–N bond length resulting from the increasing s-character in the bonding orbital (Table 1). The variations in the bond length are large, and our value of the average P–N distance of 1.674 Å obtained for **4** locates this compound beyond the usual range of values observed for phosphoric triamides. The gradual decrease in the N–P–N bond angles is paralleled therefore by the stretching of the P–N bond towards the value obtained for the "pure" single bond in zwitterionic form of phosphoramidic acid, $^{-}HO_3P–NH_3^{+}$. When the average P–N bond distances obtained for the series **1**–**4** were used for the correlation with the δ_P values, a plot mirroring that obtained for the N–P–N bond angle effect was obtained (Figure 1). It is, to our knowledge, the first direct correlation of a P–X bond distance with the ^{31}P NMR shielding, and we propose it as a better measure of the effect of structural parameters on the NMR characteristics.

Table 1. Typical P–N bond distances for organophosphorus compounds containing nitrogen.

Compound or class of compounds	Hybridization	P–N/Å	Reference
$^{-}HO_3P\text{-}NH_3^{+}$ [a]	sp^3	1.77	9
>P(O)-N< [a]	$sp^3 – sp^2$	1.61–1.65	10
>P(NR)-N< [a]	sp^2	1.52–1.60	11
P≡N [b]	sp	1.49	12

[a]Determined by X-ray diffraction. [b]Determined by gas-phase spectroscopy.

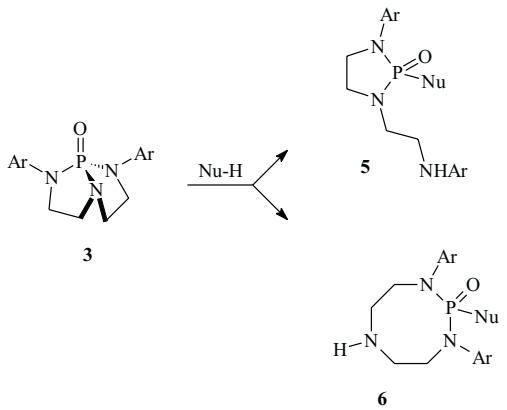
According to Letcher and Van Wazer [13], the ^{31}P chemical shift differences, $\Delta\delta$, are dominated by three terms affected by structural variations (Equation 1), where $\Delta\chi$ is the difference in electronegativity in the P–X bond, Δn_π the change in the π-electron overlap, $\Delta\Theta$ the change in the X–P–X σ bond angle, and C, k, and A are constants.

$$\Delta\delta = -C\Delta\chi_x + k\Delta n_\pi + A\Delta\Theta \quad (1)$$

Our results demonstrate that the two last terms in eq. (1) should not be treated independently, since the variation of the latter affects the former *via* the change in the π-electron overlap between nitrogen and the phosphorus nuclei. Another conclusion was that the observed variations in the P–N bond characteristics should be reflected by marked differences in the chemical behavior of the individual classes of the triamides of the series. Consequently, we have investigated some reactions of the new and attractive bicyclic system **3**, and the following parts of this paper report the results of that investigation.

The first reaction of choice was the nucleophilic (solvolytic) cleavage of the P–N bond(s). If limited to a single P–N bond, the cleavage of **3** can lead to a 1,3,2-diazaphospholidine derivative (**5**) ["*exo*" departure of N(2)], or to a novel, eight-membered heterocyclic system (**6**) ["*endo*" departure of N(5)] (Scheme 3). Extensive work by Haake *et al*. on the acidic cleavage of the phosphoramidate bond [14] has shown that the substrate, after activation *via* the N-protonation, undergoes the bimolecular, $S_N2(P)$ displacement by solvent molecule. It was expected therefore that under acidic conditions the regioselectivity governed by the first protonation site of the substrate (**3**) should involve the departure of the more basic N(5) atom. Our recent ^{15}N NMR spectroscopic studies [15] indicated a high degree of "p" character, hence high basicity, of N(5) in **3**. Alcoholysis of **3a** carried out in an alcohol containing one equivalent of dry HCl led, as expected, to the exclusive cleavage of the P–N(5) bond, yielding the corresponding 1-oxo-1-alkoxy-2,8-diphenyl-2,5,8-triaza-1λ^5-phosphacyclooctane **6a** (Ar = Ph; Nu = OMe) or **6b** (Ar = Ph; Nu = OEt) [16]. The solvolysis has been extended to other substrates **3**, and in all cases the acidic cleavage led to the corresponding **6** as the exclusive product. The new amidoesters **6** are rather unstable and undergo further changes upon purification, but they could be isolated and purified as stable hydrochloride salts, or N(5)-acyl derivatives. When free cyclic products **6** were stored as neat substances, or as solutions in aprotic solvents, they underwent slow change yielding another phosphorus-containing product. Full conversion could

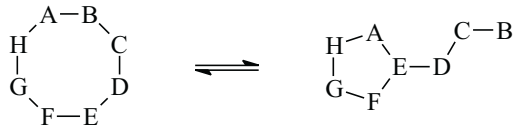
Scheme 3



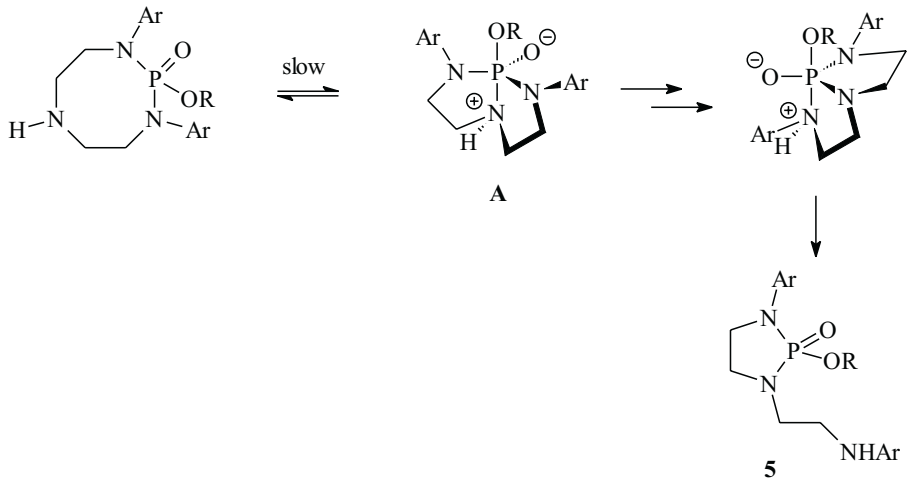
be achieved by refluxing **6** in benzene or THF, and the product was identified in each case as the isomeric 3-[2-(arylamino)ethyl]-2-oxo-2-alkoxy-1-aryl-1,3,2-λ^5diazaphospholidine (**5**, Nu = OR). The rearrangement **6** ⇒ **5** represents a new case of the **8** ⇒ **5** ring contraction (Scheme 4), and in our case can be described in terms of the intramolecular 1,5-nucleophilic attack of the amine nitrogen at the phosphoryl centre, followed by proton transfer and P–N bond cleavage. Although the reasons for which structure **5** represents the thermodynamically favored isomer in the **5/6** pair remain still unclear, and although the exact mechanism for the rearrangement needs to be worked out in detail, our investigation of the rearrangement of a series of substrates **6** (including the N-alkyl and N-benzyl-substituted compounds) [17] led to the following observations. (i) The reaction follows first-order kinetics; rate = k_1 [**6**]. (ii) Electron-donating substituents in the NAr function in **6** *decrease* the rate; similarly, for the N-alkyl and N-benzyl substituted substrates the rearrangement is much slower than for **6a**. (iii) The rearrangement is base-catalyzed; the catalysis may operate by increasing the nucleophilicity of the N(5) nitrogen atom (general base catalysis), or *via* the participation of the base's conjugate acid in the N(5) ⇒ N(2) proton transfer. According to the available data, we propose for the rearrangement a mechanism involving the rate-determining N(5) ⇒ P bond formation, resulting in the P(V) intermediate **A**, which then undergoes fast proton transfer, pseudorotation, and the product-determining cleavage of the P–N(2) bond (Scheme 5).

The change of the solvolysis medium from the ROH/H^+ system to a solution of sodium alkoxide in alcohol gave results that depend very much on the nature of the substituents at the N(2) and N(8) atoms in the substrate **3**. For the N-Ar substituted compounds, the selectivity was found to be rigorously opposite to that observed under the acidic conditions, and the diazaphospholidine derivatives **5** were the exclusive and direct reaction products. Since the effect of the substituents in the NAr groups was opposite to that observed for the rearrangement (the electron-donating groups *increasing* the reaction rate), we propose the mechanism similar to that shown in Scheme 5, but with the second, proton transfer rate-determining step, accelerated by the increase of the basicity of the nitrogen atom N(2) [or N(8)] (Scheme 6). All prepared N-alkyl substrates **3** yielded in the base-catalyzed alcoholysis exclusively the eight-membered cyclic products **6**, the same as the products obtained (in the form of the HCl salt) from the reaction in the presence of HCl. This suggests that in this case the reaction may follow a mechanism different from that operating for the N-aryl derivatives, driven by the cleavage of the more strained P–N(5) bond in the bicyclic system **3**.

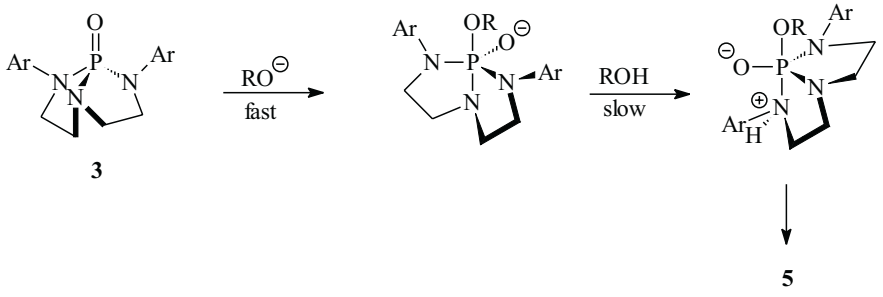
Scheme 4



Scheme 5



Scheme 6

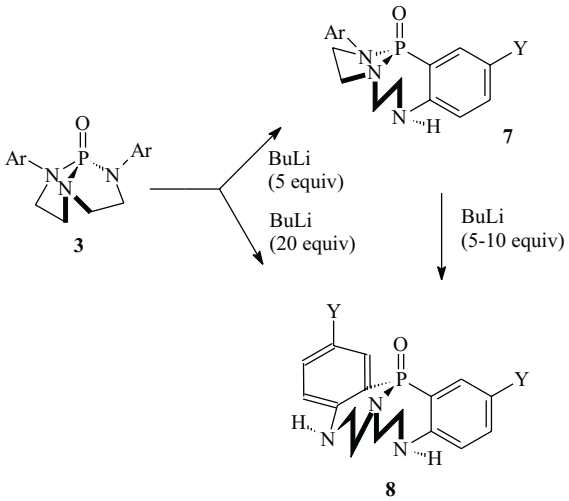


Next reactions studied for the triamide system **3** allowed us to prepare yet another, new types of heterocyclic products. Some years ago we reported the LDA-induced migration of phosphorus from nitrogen to aromatic carbon for simple phosphoric N-phenylamides [18]. In a similar approach, the lithiation (BuLi in THF) of **3** led, smoothly and with high yields, to the migration of the phosphorus atom from one, or both N-aryl nitrogen atoms to the *ortho*-carbon atoms of the corresponding aryl substituents [19]. As a consequence of that single, or double migration, a new type of bicyclic (fusion of the five- and seven-membered rings) phosphonic diamides (**7**), or bicyclic (fusion of two seven-membered rings) phosphinic amides (**8**) was prepared (Scheme 7). The N ⇒ C migration of phosphorus in **3** involves three steps: lithiation of the *ortho*-carbon in the N-Ar group, 1,3-phosphorus shift driven by the formation

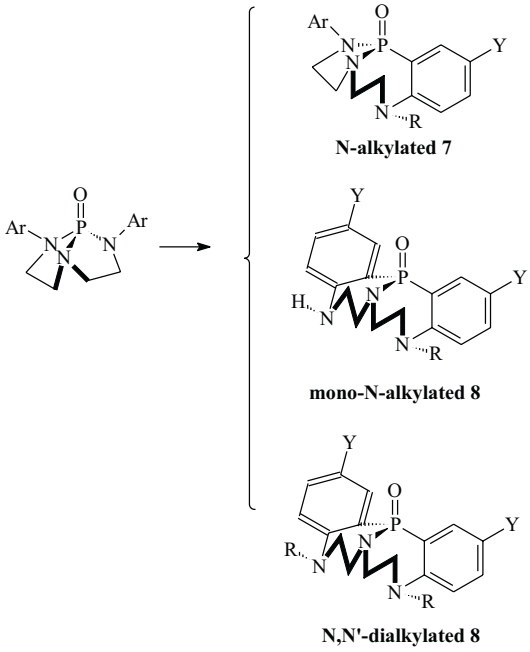
of a strong P–C bond together with the change of the C–Li to the N–Li bonding, and, finally, quenching of the N-lithiated amide function by a proton donor. Modification of the procedure, involving the replacement of a proton donor by an alkylating agent in the quenching step, allowed us to prepare the N-alkyl derivatives of phosphonamidates **7**, as well as the mono-N-alkyl derivatives (chiral at phosphorus), or di-N-alkyl derivatives (symmetrical) of the phosphinamidates **8** [20] (Scheme 8).

The availability of a new bicyclic system – the phosphonic diamides **7**, presented, as in the case of the bicyclic structure **3**, an interesting problem of the regioselectivity of the nucleophilic cleavage of a single P–N bond in substrate's molecule. Alcoholysis of **7** can, in principle, lead to two cyclic (seven-membered or ten-membered) phosphonic amidoesters. Again, the reaction was studied under the conditions of acidic, and basic catalysis, and, again, the reaction outcome depended on the reaction conditions [21]. The acid-catalyzed methanolysis was not selective and both P–N bonds in **7** were cleaved yielding a dimethyl ester of phenylphosphonic acid, substituted at the *ortho* position of the ring with the NH-$CH_2CH_2NHCH_2CH_2NHAr$ chain. We have, however, an evidence indicating that it is the P–NAr bond in **7** which is broken first, with the seven-membered cyclic phosphonic amidoester **9** formed as the intermediate product. Compound **9** is the exclusive product of a fully selective cleavage of **7** by the solution of MeONa in MeOH; the proposed mechanism for the reaction is presented in Scheme 9. According to that associative mechanism, addition of the methoxide ion to the substrate may produce two isomeric pentacoordinate intermedi-

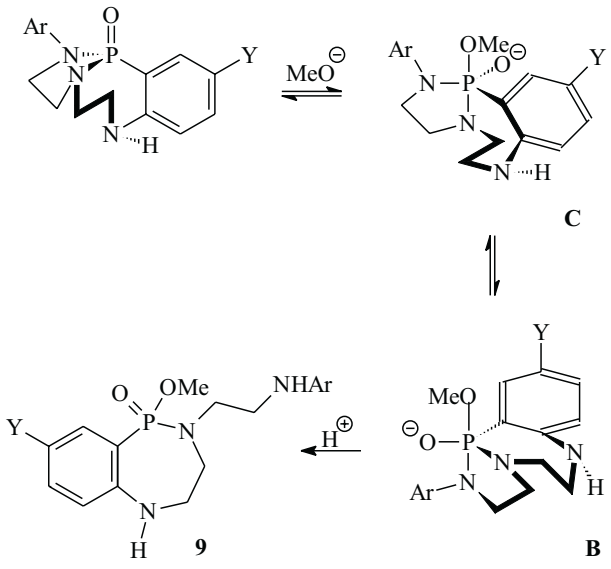
Scheme 7



Scheme 8



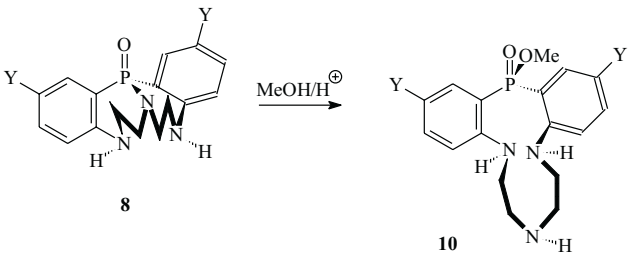
Scheme 9



ates (**B** and **C**) which differ with respect to the relative positions of the nitrogen atoms of the diazaphospholidine ring in the trigonal bipyramide structure. The X-ray structure of **7** (R = H; Ar = Ph) revealed the value of the N(bridgehead)–P–C(arom) bond angle of 107.7° [19]. Upon formation of the P(V) intermediate, that angle has either to undergo contraction to 90° (structure **C**, $\Delta = -17.7°$), or expansion to 120° (structure **B**, $\Delta = +13.3°$). Rigorous selectivity of the substitution clearly indicates that the seven-membered ring in **7** accommodates the latter change of the bond angle significantly easier than the former. Substrate **7** can therefore serve as a useful model for testing the angular effects operating in the addition – elimination mechanism of the substitution at cyclic phosphoryl substrates.

The products of the lithiation – induced double migration of phosphorus from the amide nitrogens to the aromatic carbons in **3** – the bicyclic (seven/seven-membered rings fusion) phosphinic amides **8** offered a new synthetic opportunity. Nucleophilic cleavage of the remaining P–N bond should lead to a novel, twelve-membered cyclic phosphinic derivative (**10**), an interesting structure from the point of a cyclic, polydentate ligand. Consequently, an acid-catalyzed methanolysis of **8** (Ar = Ph) was attempted, as for the bicyclic system **3**. Unexpectedly, the substrate proved quite resistant to the substitution reaction, contrary to the known susceptibility of the P(O)–N bond with respect to the acidic fission. The full ring opening reaction was finally achieved (Scheme 10), but only under conditions much more drastic than those typical for the phosphoric amide – ester transformation. When compared with a simple phosphinic analogue, $Ph_2P(O)NMe_2$ for which the rates of the acid-catalyzed cleavage are available in the literature [22], the relative rate of the P–N bond cleavage in **8** (corrected to the reaction conditions) was found to be $k_{rel} < 10^{-4}$. The crystal and molecular structure of the substrate molecule (**8**) has been determined [19], and revealed that the conformation of the bicyclic skeleton, together with the orientation of both fused aromatic rings, result in a serious steric hindrance for an approach of a nucleophile from the direction opposite to that of the P–N bond in **8**. Since the N(4), N(10)-dimethyl derivative of **8** was found to be even less reactive than the unsubstituted compound [23], it seems that the unusually low reactivity of the bicyclic amides **8** is of steric origin.

Scheme 10

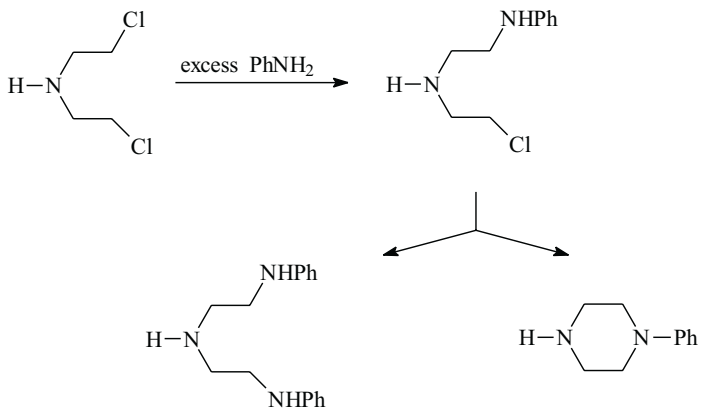


8 **10**

The structure of **10** was determined by X-ray diffraction, and some interesting observations about the hydrogen bonding pattern have been made [24]. The crystal packing consists of layers of molecules interconnected *via* a rather long N(2)–H...O=P hydrogen bond, and, possibly, another weak C–H...O=P hydrogen bond involving one methyl hydrogen of the P–OMe as a donor. The increased flexibility of the twelve-membered ring in **10** allows, however, the molecule to form one *intra*molecular hydrogen bond between the phosphoryl oxygen and the aromatic N(3)H group [N...O distance 2.797(3) Å, NHO angle 149(2)°]. The latter bonding destroys the molecular symmetry of **10** and twists the seven-atom section of the 12-membered ring into a specific conformation. In terms of the interatomic distance and angle of that intramolecular hydrogen bond in **10**, the bond is similar to that observed for H-bonded proteins, where the average N...O distance and the NHO angle for the N–H...O=C bond is reported as 2.87 ± 0.33 Å and 153 ± 7°, respectively [25]. If the intramolecular hydrogen bonding found in **10** is retained in solution, the molecule would contain two non-equivalent aromatic NH functions: the N(4)H group involved in bonding with the P=O group, and the "free" N(10)H group. This in turn should be reflected by the difference in such properties of those two amino groups as basicity, acidity, or complexation behavior. Those properties of **10** are currently studied in our laboratory.

The last transformation of the bicyclic system **3** reported here is its exhaustive hydrolysis. Ammonia and amines represent one of the most common types of σ-donors in coordination chemistry, and the polyamines with the typically 1,2- or 1,3-location of the amino groups are widely used as polydentate chelating ligand structures [26]. The β,β′-diaryl substituted "diethylenetriamine", Ar-NH-CH_2CH_2-NH-CH_2CH_2-NH-Ar (**11**), is an interesting example of that group because of the possibility of wide variations of its electronic and steric effects that may be achieved by introducing substituents to the aromatic groups, as well as at the nitrogen atoms of the 1,4,7-triazaheptane skeleton. The β,β′-diphenyl derivative (**11a**, Ar = Ph), although a simple compound, is very difficult to prepare. The most obvious route to **11** seems to be the reaction between bis(2-chloro-ethyl)amine and aniline; Prelog and Driza demonstrated long ago [27] that the major product of this reaction is N-phenylpiperazine. We have repeated Prelog's experiment and found that the intermediate monosubstitution product undergoes intramolecular cyclization rather than the second substitution with a preference of *ca* 7: 1 (Scheme 11). Having the bicyclic phosphoric triamide system **3** available in our Laboratory (*vide supra*), we have developed an efficient and general method for the preparation of the triamines **11** *via* the hydrolytic cleavage of all three P–N bonds in the parent triamide substrates **3** (Scheme 12). A series of the triamines **11** was prepared [28], and the products were isolated in the form of their trihydrochloride salts (highly insoluble, crystalline materials, easy to isolate and purify) and/or as free bases, and they were identified by NMR (^{1}H, ^{13}C) spectroscopy, MS, elemental analysis, and by conversion to the tri-N-acetyl derivatives.

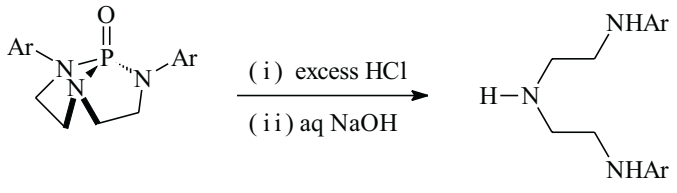
Scheme 11



11a (minor) **(major)**

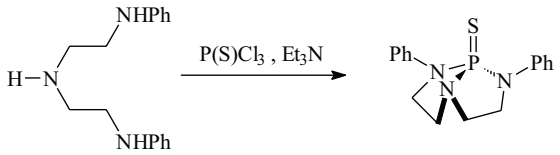
The prepared triamines **11** are currently engaged in the preliminary experiments as chelating ligands for different metal ions. Apart of that application, compounds **11** help us to solve some synthetic problems encountered in our further work on the heterocyclic chemistry of organophosphorus compounds. Since the chemistry of the bicyclic system **3** proved so rich and rewarding, we have decided to prepare their thiophosphoryl analogues and to study the effect of substituting the sulfur atom for oxygen at the phosphoryl center on the reactivity of the system. Unfortunately, the obvious route to the "thio-**3**" using $Cl_2P(S)N(CH_2CH_2Cl)_2$ as the starting material (see Scheme 1) failed to yield the final product in a state of satisfactory purity and with acceptable yield. The first "thio-**3**" was however obtained recently *via* a direct condensation of $P(S)Cl_3$ with the triamine **11a** (Scheme 13), and its structure has been confirmed by X-ray diffraction [29]. The chemistry of that new type of a heterocyclic thiophosphoryl system is now investigated in our Laboratory.

Scheme 12



11

Scheme 13



11a **' thio-3a '**

Acknowledgments

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