Nucleophilic cleavage of 1-oxo-2,8-disubstituted-2,5,8-triaza-1λ^5-phosphabicyclo[3.3.0]octanes: a new route to eight- and five-membered heterocyclic systems

Zhengjie He, Susan Laurens, Xavier Y. Mbianda, Agnes M. Modro and Tomasz A. Modro*

Centre for Heteroatom Chemistry, Department of Chemistry, University of Pretoria, Pretoria 0002, South Africa

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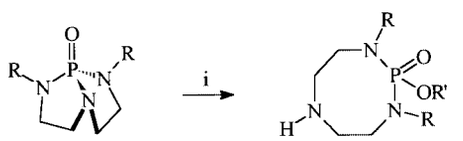
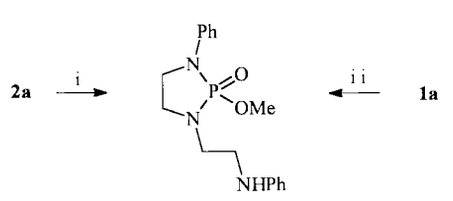
Five 1-oxo-2,8-disubstituted-2,5,8-triaza-1λ^5-phosphabicyclo[3.3.0]octanes **1** have been prepared and the nucleophilic cleavage of one of their P–N bonds has been studied. The acid-catalyzed alcoholysis involves in each case the cleavage of the P–N(5) bond, yielding the eight-membered monocyclic diamides **2**. In the base-catalyzed reaction, the *N*(2),*N*(8)-dialkyl substituted substrates **1** yielded the same products **2**, while for the *N*(2),*N*(8)-diaryl derivatives the exclusive cleavage of the P–N(2) (or P–N(8)) bond was observed yielding the isomeric 1,3,2-diazaphospholidine products **3**. Products **2** are stable as N(5) ammonium salts or *N*(5)-acyl derivatives, but as free bases they rearrange spontaneously to products **3** *via* the intramolecular N(5)→P nucleophilic attack accompanied with the P–N(2) (or P–N(8)) bond cleavage. The effect of the N(2)- and N(8)-substituents in **2** on the rate of the **2**→**3** rearrangement, as well as on the product distribution for the unsymmetrically disubstituted substrates has been investigated. The mechanism of the formation of products **3** *via* the rearrangement and *via* the direct **1**→**3** nucleophilic cleavage is discussed in terms of the reactivity of the attacking nucleophile, the electrophilicity of the phosphoryl center, and of the basicity of the departing amine in the P–N bond cleavage step.

A bicyclic phosphoric triamide system **1** has recently been prepared in our laboratory[1] and its chemistry is currently being investigated. The 2,8-diaryl substituted compounds **1** (**1**, R = Ar) have already demonstrated interesting chemical behavior leading to new heterocyclic products containing nitrogen and phosphorus incorporated in the ring skeleton. For example, metallation-induced migration of phosphorus from nitrogen to carbon yields new types of cyclic phosphonic and phosphinic amides,[2] and in the preceding communication we reported the acidic alcoholysis of the 2,8-diphenyl derivative, **1a** (**1**, R = Ph) (Scheme 1).[3] The primary product, the eight-membered cyclic diamide **2a** was found to rearrange spontaneously to the isomeric diazaphospholidine derivative **3a**, which could also be prepared directly from **1a**, *via* base-promoted alcoholysis (Scheme 2).[3]



Scheme 1 *Reagents and conditions*: i, R′OH, HCl, room temp.



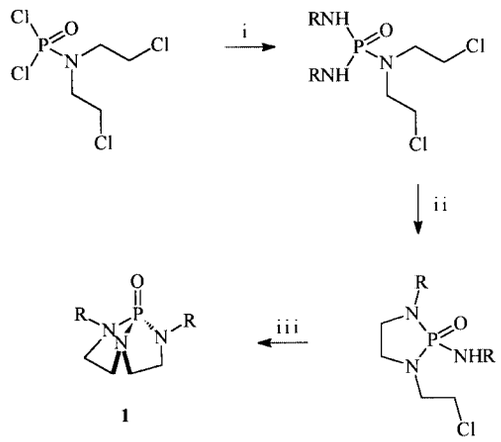
Scheme 2 *Reagents and conditions*: i, Benzene, reflux; ii, MeONa–MeOH, room temp.

Since the conversion **2**→**3** represents a new type of skeletal rearrangement involving ring contraction, we were interested in the mechanism of this transformation and the structural effects on the rate of the reaction. We were also interested in the structural effects on the regioselective cleavage of the P–N bond in **1** by nucleophilic reagents other than alcohols. Consequently, we now report the preparation of new substrates **1**, the ring-opening reactions of those products, and the reactivity of products **2** in their rearrangement to the corresponding derivatives **3**.

Results and discussion

Substrates

Two more substrates **1** (**1b**, R = 4-MeOC$_6$H$_4$, and **1c**, one R = Ph, one R = 4-MeOC$_6$H$_4$) were prepared before,[1] and their chemistry has now been studied in order to evaluate the electronic effect of the ring substituents on the regioselectivity of the P–N bond cleavage in **1** and on the rate of the rearrangement of **2**. The unsymmetrically substituted **1c** was of particular interest from the point of view of the selectivity in the **2**→**3** rearrangement reaction. In order to extend the study on substrates **1** substituted at the 2,8-nitrogen atoms with aliphatic groups, the synthesis of three additional models was undertaken: **1d** (R = CH_2Ph), **1e** (R = Et), and **1f** (R = Me). Since the preparation of **1** is based on a sequence of two 1,5-cyclization reactions (Scheme 3),[1] it was necessary to prepare the required precursors from the common substrate, $Cl_2P(O)N(CH_2CH_2Cl)_2$. We have found that the preparation and the isolation of *N*-alkyl substituted derivatives **1** were much more difficult than of those with *N*-aryl substituents. For **1e**, although we succeeded in arriving at the pure bicyclic product, we were not able to isolate its immediate precursor, the corresponding 1,3,2-diazaphospholidine, because the first and the second cyclizations (Scheme 3) proceeded with comparable rates. We were not able to prepare the simplest *N*-alkyl member of the group—**1f**. Although its precursor (the diazaphospholidine) was pre-



Scheme 3 *Reagents and conditions*: i, 2 RNH_2, 2 Et_3N, CH_2Cl_2, −20 °C; ii, MeONa–MeOH, 0 °C; iii, NaH, Bu_4NBr, benzene, room temp.

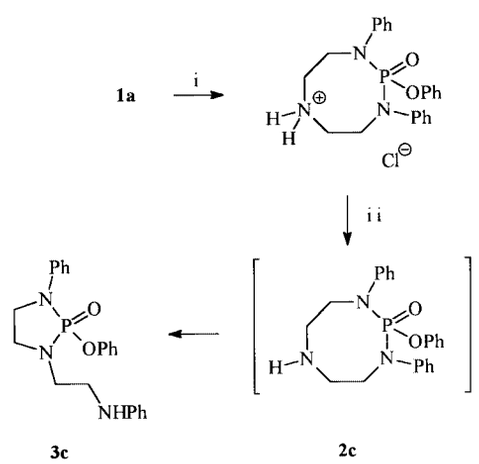
pared in a pure state and in large quantities, its further cyclization to the bicyclic product failed under a variety of conditions that led only to the recovery of the substrate or to advanced decomposition. The 2,8-dibenzyl derivative **1d** was prepared as a spectroscopically (^{31}P, ^{1}H NMR) pure compound, but the yields of the product varied from experiment to experiment, and we were unsuccessful in preparing crystals of **1d** suitable for X-ray diffraction.

Acid-catalyzed cleavage

All bicyclic compounds **1**, when treated with an alcohol containing one mole equivalent of HCl, underwent quantitative and regiospecific cleavage of the 'internal' P–N bond yielding the hydrochloride salt of the corresponding triazaphosphacyclooctane **2**, from which the free base **2** could be obtained upon neutralization. For the *N*-aromatic substrates the observed selectivity (the absence of the isomeric products **3**) was expected on the basis of the accepted mechanism of the acidic cleavage of the amidate P–N bond,[4] and can be explained by the higher basicity of the bridgehead N atom in **1**, responsible for the selectivity in the N-protonation pre-equilibrium step. For **1d** and **1e** the result of the alcoholysis was more difficult to predict, as all amide N atoms carry only alkyl substituents and should not differ much in basicity. Our recent ^{15}N NMR study of the P–N bonding in cyclic amides demonstrated however that the endocyclic nitrogen is always more shielded than the exocyclic N atom.[5] According to the data reported by von Philipsborn and Müller,[6] our ^{15}N NMR results suggest that the N atom incorporated into the ring should also be more basic; hence the bridgehead N atom in **1** should be more basic than the two other N atoms, each located in the single phospholidine ring. It would be however difficult to explain the observed selectivity for **1d** and **1e** solely in terms of the difference in basicity, as it would require a pK_a difference of approximately two units between the bridgehead and the 2,8-N atoms.† The other, independent factor is of a stereoelectronic nature. In the penta-coordinate intermediate (or transition state) of the substitution, the location of the bridgehead N(5) atom in the apical position (apical departure) allows the molecule to avoid a disfavored location of other ligands in the trigonal bipyramid structure. It seems therefore that the selectivity of the acidic alcoholysis of all substrates **1** is determined by the pre-equilibrium protonation step and by stereoelectronic effects.

The monocyclic diamidoesters **2** are perfectly stable in the form of their ammonium salts or as the *N*(5)-acyl derivatives. The stability (and the behavior) of the neutral products **2** depends, however, on the nature of the nucleophilic group introduced at the phosphoryl center in the ring-opening reaction. When **1a** was treated with two mole equivalents of CF_3SO_3H in CH_2Cl_2, a white, hygroscopic solid precipitated out. The product, soluble in acetone, gave rise to a ^{31}P NMR signal of δ_P (acetone-d_6) = 6.6 ppm, and a ^{1}H NMR spectrum of the ring ethylene groups analogous to that of **2a** (*vide infra*). When the product was dissolved in THF containing triethylamine, only the starting **1a** was recovered after the work-up. We interpret this result as evidence for the reversibility of either the protonation, or the protonation followed by the ring-opening reaction. The initial, unstable product most likely represents either the triflate salt of the expected mixed phosphoric–sulfonic anhydride which undergoes, upon deprotonation, intramolecular displacement of the triflate ion leading to the starting material, or, simply, a triflate salt of the protonated **1a**. When **1a** was dissolved in $CDCl_3$ containing one mole equivalent of HCl, the ^{31}P NMR spectrum of the solution showed only a small low-field shift of the signal of the substrate, returning to its usual position upon the addition of Et_3N. This result contrasts sharply with the fast and facile cleavage of the P–N bond by solutions of HCl in aprotic solvents.[7]

The amide bond in **1** was found to be resistant to cleavage by phenols. No reaction was observed when **1a** was incubated at room temperature in a $CDCl_3$ solution containing phenol (or *p*-nitrophenol) and 1.1 mole equivalents of HCl. The reaction with phenol was, however, achieved under conditions of electrophilic catalysis. A CH_2Cl_2 solution of **1a** containing four mole equivalents of PhOH and 1.2 mole equivalents of Me_3SiCl produced, after 20 days at room temperature, a crystalline product (90%) identified as the hydrochloride salt of the expected phenyl ester. The salt was then deprotonated to the free base **2c**, but the latter product rearranged during isolation. Complete rearrangement of the neutral ester **2c** to the corresponding product **3c** was achieved after four days (Scheme 4). The failure



Scheme 4 *Reagents and conditions*: i, PhOH, Me_3SiCl, CH_2Cl_2, 20 days, room temp.; ii, K_2CO_3, CH_2Cl_2, 4 days.

to prepare the *p*-nitrophenyl ester analog of **2c** most likely resulted from the too low nucleophilicity of the *p*-nitrophenolate ion.

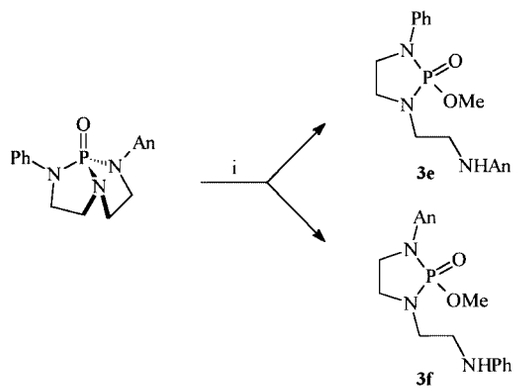
Both *N*-alkyl substituted substrates **1** (**1d**, **1e**) reacted with the HCl-containing methanol according to the reaction shown in Scheme 1, yielding the corresponding salts of the products **2d** (**2**, R = CH_2Ph, R′ = Me) and **2e** (**2**, R = Et, R′ = Me). The regiospecificity in this case probably results more from the stereoelectronic effects than from a small difference in the basicities of the non-equivalent nitrogen atoms.

Base-catalyzed cleavage

The mechanism of the base-catalyzed alcoholysis of **1** is much less clear. As reported in the communication, reaction of **1a** with sodium methoxide in methanol led directly to the diaza-

† Authors thank one of the referees for this comment.

phospholidine **3a**.[3] The same behavior was observed for other *N*-aryl substrates (**1b**, **1c**), so the products **3a** (**3**, R = Ph; R′ = Me), **3b** (**3**, R = Ph; R′ = Et),[3] **3d** (**3**, R = 4-MeOC$_6$H$_4$; R′ = Me), and **3e**, **3f** (**3**, R = one Ph and one 4-MeOC$_6$H$_4$; R′ = Me) could be prepared either by direct alcoholysis of **1**, or *via* the **2**→**3** rearrangement, which is sufficiently fast for the preparative purpose (as shown in Scheme 2). The rates of the direct **1**→**3** alcoholysis of the *N*-aryl substituted **1** (the cleavage of the P–NAr bond), followed by ^{31}P NMR spectroscopy, gave the following order of decreasing reactivity, as measured by the approximate half-lives in MeONa–MeOH at room temperature, for **1b**, **1c**, and **1a**: $t_{\frac{1}{2}} = 4$, 7, and 10 days, respectively ($k_{rel} \approx 2.5$, 1.4, 1.0). The highest reactivity of the *N*,*N*′-di-*p*-anisyl substrate **1b** shows that the reaction is accelerated by the higher basicity of the departing aromatic amine and indicates the involvement of proton transfer to the leaving group in the rate-determining step. Substrate **1c** gave, as expected, two isomeric products of methanolysis, **3e** and **3f** (Scheme 5).



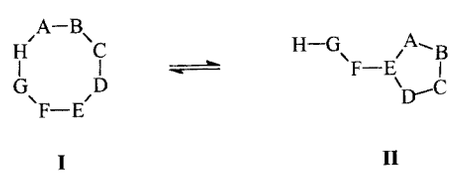
Scheme 5 *Reagents and conditons*: i, MeONa–MeOH, room temp.

Although only one isomer (**3f**) was successfully isolated in the pure state and fully characterized, the product ratio, **3e**:**3f** (determined by the integration of the ^{31}P NMR signals), remained greater than one during the course of the reaction, in agreement with the rate data. A similar preference for the cleavage of the P–NAn over the P–NPh bond in a mixed substrate was also observed in the **2**→**3** rearrangement (*vide infra*).

Both prepared *N*-alkyl substrates **1** (**1d**, **1e**) yielded exclusively in the base-catalyzed methanolysis the eight-membered cyclic products **2d** and **2e**, the same as the products obtained (in the form of the HCl salt) from methanolysis in the presence of HCl (*vide supra*). This result suggests that the cleavage of the P–N bond by MeO$^-$ may, in the case of the *N*-alkyl substrates **1**, follow a mechanism different from that operating for the *N*-aryl derivatives, and is driven by the cleavage of the more strained P–N(5) bond in the bicyclic system **1**. The difference between the *N*-aryl and *N*-alkyl substrates was also observed for their reactivity in the related **2**→**3** rearrangement (*vide infra*).

Rearrangement 2→3

The reported[3] rearrangement **2**→**3** stems from the 1,5-transannular interaction and results in a net ring contraction (Scheme 6); the observed spontaneity of the reaction indicates greater thermodynamic stability of the right-side isomer when **I** and **II** represent the 2,5,8-triaza-1λ^5-phosphacyclooctane, and



I **II**

Scheme 6

the 3-substituted 1,3,2λ^5-diazaphospholidine system, respectively. The transannular interactions involving nitrogen and a carbonyl carbon are well known,[8] and the N→P interaction in an eight-membered system was considered in the discussion of the hydrolysis of some cyclic phosphate aminoesters.[9] In all those cases, however, the ring structure of the substrate remains intact, and we found no literature precedents of the observed actual change in the cyclic molecular skeleton. Since the rearrangement involves the cleavage of one and the formation of another P–N bond accompanied by the nitrogen–nitrogen proton transfer, several mechanisms can be envisaged for the reaction, from fully concerted, to the 1,5-intramolecular nucleophilic N(5)→P attack yielding a P^V intermediate, followed by proton transfer and P–N(2) (or P–N(8)) bond cleavage.[3] Some indication of the bond changes occurring in the rearrangement could be obtained from the molecular parameters of the substrate's ground state.

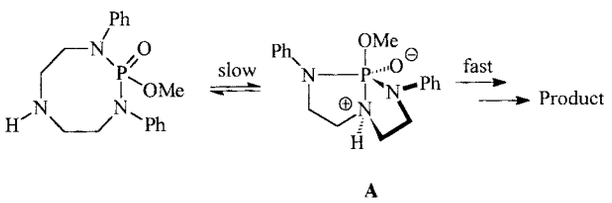
Until now, we have not succeeded in preparing crystals of any of the synthesized compounds **2** suitable for X-ray diffraction; purification and crystallization led inevitably to the rearrangement into products **3**. We have reported, however, the X-ray structure of the *N*-benzoyl derivative of **2b** (R = Ph; R′ = Et).[3] The structure revealed some features that might be considered relevant to the **2**→**3** interconversion. The non-bonded distance P···N(5) is 3.242 Å, shorter than the corresponding sum of the van der Waals radii (3.40 Å[10]). Although it could be taken as an indication of the incipient bonding between N(5) and P atoms, it is not reflected by any departure of the N(5) center from trigonal geometry (average C–N(5)–C bond angle is 119.7°). The P–N(2) and P–N(8) covalent bonds in the *N*(5)-benzoyl **2b** are non-equivalent; one (1.651 Å) lies within the range of 1.61–1.65 Å reported for phosphoramidates,[11] the other (1.688 Å) is closer to the value of 1.77 Å accepted for the 'pure' single P–N bond.[12] Those differences may, however, stem from the difference in the values of the two O=P–N–C(Ph) torsion angles thus it would be premature to consider the molecular parameters as an indication of an 'early stage'[13] of the intramolecular displacement of one of the *amide* nitrogens in **2** by the N(5) *amine* nitrogen atom.

The rates of the **2**→**3** rearrangement were measured for substrates **2** by means of the ^{31}P NMR spectroscopy. Since for each pair of compounds **2** and **3** differ significantly in their δ_P values, the kinetics of the rearrangement could be followed by measuring the change of the relative intensities of the ^{31}P NMR signals in the reaction system. The rate data are given in Table 1. Entry 1 contains results of the kinetic runs performed in order to confirm the unimolecular nature of the rearrangement. Although a *ca*. 20% decrease in the value of the first-order rate constant k_1 was observed upon the four-fold decrease of the substrate's initial concentration, we believe that the reaction follows, in principle, first-order kinetics, and that the variations in the k_1 value most likely reflect the changes in the nature of the reaction medium at the relatively high concentrations of the substrate. Entry 2 shows the effect of the substituent in the aromatic ring on the reaction rate. Each of the *p*-methoxy groups introduced onto the N–Ar function decelerates the reaction by a factor of about 1.5, making **2f** the *least reactive* in the series. It has to be noted that the substituent effect on the rate of the rearrangement for **2a**, **2f**, and **2g** is *opposite* to that observed for the cleavage of the corresponding substrates **1a**, **1b**, and **1c** by the MeO$^-$ ion (*vide supra*), although both reactions involve nucleophilic attack at the phosphoryl center (by the N(5) atom and by the MeO$^-$ ion, respectively), and cleavage of the same (P–N(2) or P–N(8)) bond. For both reactions we propose a common, associative mechanism, but with different rate-determining steps for each case. According to our model, the rate of the rearrangement is determined by the rate of the N(5)–P bond formation, resulting in the P(v) intermediate **A**, which then undergoes fast proton transfer and product-determining cleavage of the P–N(2) bond (Scheme 7). For the

Table 1 Rate data for the rearrangement **2**→**3**

Entry	Substrate (δ_p)	Product (δ_p)	Conditions and remarks	$k_1/10^{-5}$ s^{-1}	$t_{\frac{1}{2}}$/h
1	**2b** (12.2)	**3b** (18.5)	Refluxing THF (internal temp. 62 °C). Reaction followed to *ca.* 85% conversion. $[\mathbf{2b}]_o$ (M) =		
			(i) 0.030	4.8 ± 0.4	4.0
			(ii) 0.015	4.5 ± 0.2	4.3
			(iii) 0.0075	3.8 ± 0.08	5.1
2	**2a** (12.0)	**3a** (19.9)	Refluxing THF (internal temp. 62 °C). Reaction	8.9 ± 0.3	2.2
	2f (12.9)	**3d** (20.1)	followed to *ca.* 90% conversion. Substrate's initial	3.2 ± 0.1	6.0
	2g (13.8)	**3e** (19.3), **3f** (20.1)	concentration: 0.050 M	6.1 ± 0.2	3.2
3	**2a** (12.0)	**3a** (19.9)	$CDCl_3$, room temp. $[\mathbf{2a}]_o$ = 0.033 M	[a]	*ca.* 1200
	2a·HCl (12.7)	**3a** (19.9)	$CDCl_3$, excess of anhydrous K_2CO_3, room temp. $[\mathbf{2a}\cdot HCl]_o$ = 0.033 M	[a]	*ca.* 740
	2a·HCl (12.7)	**3a** (19.9)	$CDCl_3$ and 1.1 mole-equiv. Et_3N, room temp. $[\mathbf{2a}\cdot HCl]_o$ = 0.033 M	[a]	*ca.* 160
	2g (13.9)	**3e** (19.3), **3f** (20.1)	$CDCl_3$, room temp. Reaction followed to *ca.* 38% conversion. $[\mathbf{2g}]_o$ = 0.022 M	[a]	*ca.* 3000
4	**2e** (20.2)	**3g**[b] (26.5)	Refluxing THF (internal temp. 62 °C). Reaction followed to *ca.* 55% conversion.[c] $[\mathbf{2e}]_o$ = 0.050 M	1.9 ± 0.2	*ca.* 10
	2e (20.2)	**3g**[b] (26.5)	$CDCl_3$, room temp. Reaction followed to *ca.* 18% conversion. $[\mathbf{2e}]_o$ = 0.050 M	[a]	*ca.* 10500
5	**2d** (21.9)	**3h**[b] (27.3)	In MeOH–MeONa from **1d**, room temperature; $[\mathbf{1d}]_o$ = 0.020 M.	[a]	*ca.* 960
	2d (21.5)	**3h**[b] (25.9)	Refluxing THF (internal temp. 62 °C). Reaction followed to *ca.* 60% conversion.[d] $[\mathbf{2d}]_o$ = 0.050 M.	0.061 ± 0.020	*ca.* 320

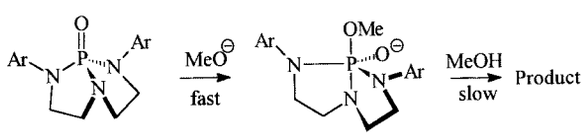
[a] Not enough data points collected to determine a reliable value of k_1. Approximate value of the half-life was determined from the [substrate] *vs.* time plot. [b] Not isolated and characterized (see Discussion). [c] Additional signals appeared in the ^{31}P NMR spectrum at higher conversions. [d] Approximate value; additional signals appeared in the ^{31}P NMR spectrum during the course of reaction.



A

Scheme 7

2a/**2f** pair of substrates, the less electron-donating phenyl substituents render the P atom in **2a** more electrophilic, thus making **2a** more reactive in the **2**→**3** rearrangement. For the base-catalyzed methanolysis of **1**, on the other hand, we propose that the P–O bond formation with a strongly nucleophilic MeO^- ion is fast, but the proton-assisted cleavage of the P–N(2) bond is rate-determining (Scheme 8). The more basic

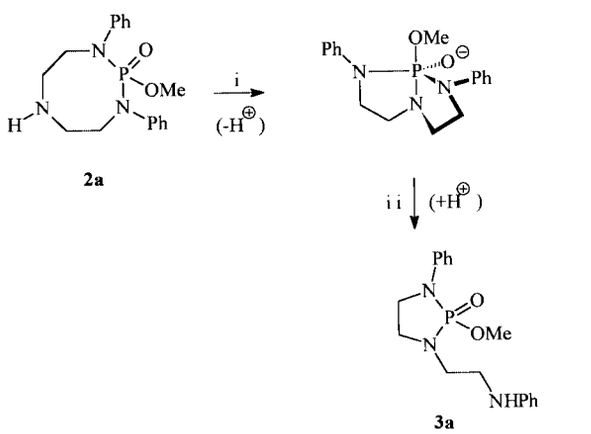


B

Scheme 8

N-*p*-anisyl function in **1b** makes the intermediate **B** more reactive in the second, dissociative step of the reaction.

Entry 3 in Table 1 gives evidence for the base-catalysis in the rearrangement. The reaction is significantly accelerated when instead of dissolving the free base of **2a** in $CDCl_3$, it was generated from its hydrochloride salt by adding an excess of base. After the free base was liberated, the excess of the base catalyzed the reaction; Et_3N (present in the homogeneous solution) being more effective than the solid K_2CO_3. 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 (Et_3NH^+, HCO_3^-) in the N(5)→N(2) proton transfer. The effect of a base on the rearrangement was also demonstrated in the behavior of **2a** in the attempted *N*-alkylation reaction. In an attempt to prepare the *N*(5)-methyl derivative of **2a**, the free base **2a** was treated with NaH in THF, followed by the addition of an excess of iodomethane. Instead of the expected N–Me derivative, the rearranged product **3a** was obtained. Since also no N-methylated derivative of **3a** was isolated, we propose that **2a**, upon deprotonation, forms a P(v) intermediate *via* the transannular N(5)→P interaction, and that the intermediate breaks down to **3a** during the protonation step (Scheme 9).



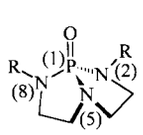
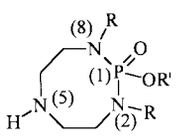
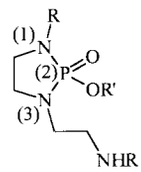
2a **3a**

Scheme 9 *Reagents and conditions*: i, NaH, THF, room temp.; ii, MeOH, room temp.

As in refluxing THF (entry 2 in Table 1), entry 3 shows that substrate **2g** is less reactive in the rearrangement than **2a**. Entry 4 gives rate data for the *N*-ethyl substrate, **2e**. The reaction is in this case (as for **2d**, entry 5) much less clean than for the *N*-aryl substrates; signals additional to those of **2e** and **3g** appear in the ^{31}P NMR spectrum at higher conversions. In agreement with the trend observed for the *N*-aryl substrates (entry 2), **2e** was found less reactive (by a factor of *ca.* five) than **2a**.

Rearrangement of **2d** (entry 5) was very slow and the reaction did not allow us to isolate and characterize the product **3h**. In the first experiment **1d** was used as a precursor for **2d**. When **1d** was dissolved in MeOH containing MeONa, it solvolyzed

Table 2 Labeling of compounds **1**, **2**, **3**

1	R	**2**	R	R′	**3**	R	R′
a	Ph	**a**	Ph	Me	**a**	Ph	Me
b	An[a]	**b**	Ph	Et	**b**	Ph	Et
c	Ph, An	**c**	Ph	Ph	**c**	Ph	Ph
d	CH_2Ph	**d**	CH_2Ph	Me	**d**	An	Me
e	Et	**e**	Et	Me	**e**	Ph (*endo*)	Me
						An (*exo*)	
f	Me	**f**	An	Me	**f**	An (*endo*)	Me
						Ph (*exo*)	
		g	Ph, An	Me	**g**	Et	Me
					h	CH_2Ph	Me

[a] An = 4-$MeOC_6H_4$.

relatively fast to **2d**: after four days the solution contained no **1d** (δ_P = 47.3), 98% of **2d** (δ_P = 21.9), and 2% of the product with δ_P = 27.3; the latter was, by analogy with previous systems, identified as the rearrangement product **3h**. The **2d**→**3h** interconversion was then followed in the usual way, yielding very slowly the final product with an approximate half-life of 960 h. In the absence of the base (MeO^-) the rearrangement was too slow to allow any rate determination. When **2d** (free base) was subjected to the rearrangement in THF at 62 °C, the conversion to the product with δ_P = 25.9 (the difference of $\Delta\delta_P$ = 1.4 with respect to the previous experiment was shown to result from the solvent effect) was accompanied by the formation of significant quantities of unidentified phosphorus containing products. The obtained value of $k_1 = 0.06 \times 10^{-5}$ s^{-1} is only approximate, but it demonstrates much lower reactivity of **2d** in the rearrangement as compared with the *N*,*N*′-diaryl and *N*,*N*′-diethyl analogs.

In conclusion, a new type of the molecular rearrangement (**2**→**3**) is a reasonably well understood process for the *N*,*N*′-diaryl substituted substrates (**2a**, **2b**, **2f**, **2g**). For the *N*,*N*′-dialkyl substituted compounds (**2d**, **2e**), the reaction is much more complex and the structure–reactivity relationship is much less clear. The chemistry of the latter, as well as of the related compounds **2** is currently studied in our laboratory.

Experimental

Solvents and commercially available substrates were purified by conventional methods. Melting points are uncorrected. For column chromatography Merck Kieselgel 60 (0.063–0.200 mm) was used as a stationary phase. Mass spectra were recorded on a Varian MAT-212 double focusing direct inlet spectrometer at an ionization potential of 70 eV. NMR spectra were recorded on a Bruker AC 300 spectrometer in $CDCl_3$, and the chemical shift values (δ) are given in ppm relative to the solvent (^1H, δ 7.24; ^{13}C, δ 77.0). ^{31}P NMR chemical shifts are given relative to 85% H_3PO_4 as external standard. Labeling of compounds **1**, **2**, **3**, together with the numbering of heteroatoms is given in Table 2.

Preparation of substrates

***N*,*N*-Bis(2-chloroethyl)phosphoramidic dichloride.** This was prepared according to the literature procedure.[14] The preparation of **1a**, **1b**, and **1c** has been described before.[1]

***N*,*N*-Bis(2-chloroethyl)-*N*′,*N*″-dibenzylphosphoric triamide.** A solution of *N*,*N*-bis(2-chloroethyl)phosphoramidic dichloride (0.256 g, 1.0 mmol) in ether (20 ml) was added dropwise with stirring at −70 °C to a solution of benzylamine (0.439 g, 4.1 mmol) in ether (10 ml). The mixture was kept at −70 °C for 2 h, allowed to warm up to room temperature and stirred for another 140 h. The precipitate (benzylammonium chloride) was filtered off and washed with ether (20 ml). The combined etheral solution was washed with water (2 × 20 ml) and cooled to 0 °C (without drying). Two layers separated, which, after 4 days, yielded the crystalline product at the interface of the layers. Colorless crystals, 0.385 g (97%); mp 83–85 °C. δ_P 17.5; δ_H 2.77 (2H, br dt, $^2J_{HP}$ 9.0, $^3J_{HH}$ *ca.* 6.0, 2 × NH), 3.39 (4H, dt, $^3J_{HP}$ 10.7, $^3J_{HH}$ 6.6), 3.60 (4H, t, $^3J_{HH}$ 6.7), 4.06–4.15 (4H, m), 7.22–7.34 (10H, m) (Found: C, 53.75; H, 6.24; N, 10.18. $C_{18}H_{24}N_3POCl_2$ requires: C, 54.01; H, 6.04; N, 10.58%). The structure of the product was confirmed independently by X-ray diffraction.[15]

3-(2-Chloroethyl)-2-oxo-2-benzylamino-1-benzyl-1,3,2λ^5-diazaphospholidine. A solution of the above phosphoric triamide (1.119 g, 2.8 mmol) in THF (100 ml) was added dropwise with stirring at room temperature to a solution of Bu^tOK (0.52 g, 4.6 mmol) in THF (100 ml). The mixture was then stirred at room temperature for 48 h. Water (150 ml) was added and the solution was extracted with ether (2 × 120 ml). The etheral solution was dried ($MgSO_4$), evaporated under reduced pressure and the crude product was purified by column chromatography (ethanol). The pure product was obtained as a pale-yellow viscous oil (0.64 g, 63%). δ_P 25.3; δ_H 2.98–3.04 (2H, m, NCH_2), 3.16–3.26 (4H, m, 2 × NCH_2), 3.51 (1H, t, $^3J_{HH}$ 6.5, one diastereotopic H of CH_2Cl), 3.52 (1H, t, $^3J_{HH}$ 6.5, second diastereotopic H of CH_2Cl), 3.83 (1H, dd, $^2J_{HH}$ 14.9, $^3J_{HP}$ 7.8, one diastereotopic H of CH_2Ph), 3.97 (2H, dd, $^2J_{HH}$ 10.7, $^3J_{HP}$ 6.8, two diastereotopic H's of CH_2Ph), 4.07 (1H, dd, $^2J_{HH}$ 14.8, $^3J_{HP}$ 6.8, one diastereotopic H of CH_2Ph), 7.22–7.31 (10H, m, 2 × Ph); δ_C 42.75 (d, $^2J_{CP}$ 3.6), 44.0 (d, $^2J_{CP}$ 13.1), 45.2 (s), 45.4 (s), 46.7 (d, $^2J_{CP}$ 5.1), 48.5 (d, $^2J_{CP}$ 5.0), 127.1 (s), 127.3 (s), 127.4 (s), 128.2 (s), 128.5 (s), 128.6 (s), 137.6 (d, $^3J_{CP}$ 5.1), 140.0 (d, $^3J_{CP}$ 6.2) (Found: C, 59.04; H, 6.86; N, 10.92. $C_{18}H_{23}N_3OPCl$ requires: C, 59.42; H, 6.37; N, 11.55%).

1-Oxo-2,8-dibenzyl-2,5,8-triaza-1λ^5-phosphabicyclo[3.3.0]-octane 1d. NaH (3.8 g, 158 mmol; large excess) and Bu_4NHSO_4 (0.1 g, 0.29 mmol) were added to a solution of the above phospholidine in THF (250 ml) and the mixture was stirred at room temperature for 45 h. The THF solution was decanted and the residue was washed several times with THF. The combined THF solution was evaporated under reduced pressure and the crude product was purified by column chromatography (THF). Pure **1d** was obtained as a slightly greyish viscous oil (0.43 g, 58%). δ_P 45.7; δ_H 2.79–3.01 (4H, m, 2 × NCH_2), 3.27–3.46 (4H, m, 2 × NCH_2), 4.02 (2H, dd, $^2J_{HH}$ 15.1, $^3J_{HP}$ 8.1, 2 H's of two CH_2Ph groups), 4.22 (2H, dd, $^2J_{HH}$ 15.1, $^3J_{HH}$ 7.4, 2H's of two CH_2Ph groups), 7.20–7.32 (10H, m); δ_C 47.9 (d, $^2J_{CP}$ 17.9), 48.5 (d, $^2J_{CP}$ 8.2), 50.2 (d, $^2J_{CP}$ 3.1), 127.2 (s), 128.0 (s), 128.4 (s), 150.1 (s) (Found: C, 61.62; H, 6.98; N, 11.58. $C_{18}H_{22}N_3OP{\cdot}H_2O$ requires: C, 62.60; H, 7.00; N, 12.17%).

***N*,*N*-Bis(2-chloroethyl)-*N*′,*N*″-diethylphosphoric triamide.** A large excess (*ca.* 10 ml) of Et_2NH was distilled off from a 70% aq. solution, dried and condensed in a flask immersed in ice. Ether (20 ml) was added and the solution was added dropwise with stirring to a solution of *N*,*N*-bis(2-chloroethyl)phosphoramidic dichloride (3.00 g, 11.6 mmol) in ether (20 ml) at −80 °C. The mixture was kept at −80 °C for 2 h and left overnight without cooling. Solvent was evaporated under reduced pressure, the residue was transferred to a Soxhlet apparatus and extracted with ether for 55 h. The solvent was evaporated from the extract yielding pure product, 3.09 g (97%); colorless solid, after recrystallization from ether, mp 69.3–70.5 °C. δ_P 18.5; δ_H 1.15 (6H, t, $^3J_{HH}$ 7.1), 2.27 (2H, br s), 2.96 (4H, dq, $^3J_{HH}$, $^3J_{HP}$

7.2, 8.8), 3.40 (4H, dt, $^3J_{HH}$, $^3J_{HP}$ 6.7, 10.7), 3.63 (4H, t, $^3J_{HH}$ 6.5) (Found: C, 34.55; H, 7.35; N, 15.18. $C_8H_{20}Cl_2N_3OP$ requires: C, 34.80; H, 7.30; N, 15.22%).

3-(2-Chloroethyl)-2-oxo-2-ethylamino-1-ethyl-1,3,2λ^5-diazaphospholidine. This compound was never isolated and characterized, but its formation and disappearance during the preparation of **1e** could be followed by ^{31}P NMR spectroscopy; δ_P (benzene) = 24.0.

1-Oxo-2,8-diethyl-2,5,8-triaza-1λ^5-phosphabicyclo[3.3.0]octane 1e. A mixture of the phosphoric triamide described above (1.00 g, 3.6 mmol), NaH (prewashed with benzene, 0.400 g, 16.6 mmol) and Bu_4NBr (0.27 g, 0.18 mmol) was stirred in benzene (100 ml) at room temperature for two days; the reaction progress was monitored by recording directly the ^{31}P NMR spectra of samples of the solution. An additional amount of NaH (0.400 g) was added and the stirring was continued for another two days. The ^{31}P NMR spectrum demonstrated full conversion and formation of a single phosphorus-containing product. The benzene solution was decanted, the residue was washed several times with benzene and the combined benzene solution was evaporated under reduced pressure. The crude product (viscous oil, 0.886 g, >100%) was purified by bulb-to-bulb distillation (oven temp. 200 °C/0.06 mmHg) yielding 0.475 g (65%) of the almost pure product; second bulb-to-bulb distillation (oven temp. 150–200 °C/0.07 mmHg) afforded pure **1e** (0.400 g, 58%) as a colorless viscous oil. δ_P 45.5; δ_H 1.08 (6H, t, $^3J_{HH}$ 7.2), 2.65–2.90 (6H, m), 2.90–3.16 (2H, m), 3.24–3.42 (4H, m); δ_C 14.6 (s), 40.5 (s), 47.6 (d, $^2J_{CP}$ 17.7), 48.5 (d, $^2J_{CP}$ 8.1); MS, *m*/*z* 203 (M^+, 51%), 188 ($M^+ - CH_3$, 70), 147 ($M^+ - 2C_2H_4$, 29), 146 ($M^+ - C_2H_4 - C_2H_5$, 39), 99 (100) (Found: C, 43.43; H, 9.11; N, 18.99. $C_8H_{18}N_3OP{\cdot}H_2O$ requires: C, 44.08; H, 9.11; N, 18.76%).

***N*,*N*-Bis(2-chloroethyl)-*N*′,*N*″-dimethylphosphoric triamide.** A solution of *N*,*N*-bis(2-chloroethyl)phosphoramidic dichloride (1.00 g, 3.90 mmol) in ether (5 ml) was added dropwise with stirring at −80 °C to a solution of methylamine (7.2 ml, 160 mmol) in ether (10 ml). The mixture was stirred for 2 h at −80 °C and allowed to warm up to room temperature. The solvent and the excess of methylamine was evaporated under reduced pressure, the residue was transferred to a Soxhlet apparatus and extracted with ether for 22 h. The product was obtained as white crystals (0.856 g, 89%), mp 92.1–93.7 °C. δ_P 20.7; δ_H 2.31 (2H, br s), 2.59 (6H, dd, $^3J_{HP}$ 12.1, $^3J_{HH}$ 5.8), 3.40 (4H, dt, $^3J_{HP}$ 10.6, $^3J_{HH}$ 6.5), 3.62 (4H, t, $^3J_{HH}$ 6.5); δ_C 26.4 (s), 42.2 (s), 49.0 (d, $^3J_{CP}$ 5.0); the ^{1}H-coupled spectrum showed the expected patterns of q, t, t, for the NMe, NCH_2, and CH_2Cl groups, respectively.

3-(2-Chloroethyl)-2-oxo-2-methylamino-1-methyl-1,3,2λ^5-diazaphospholidine. A solution of MeONa prepared from 0.750 g Na (32 mmol) in MeOH (37 ml) was added dropwise with stirring at 0–5 °C to a solution of the above phosphoric triamide (1.00 g, 4.0 mmol) in MeOH (25 ml). After 1 h the mixture was allowed to warm up to room temperature and was stirred for further 70 h. Methanol was removed under reduced pressure and the crude product was purified by column chromatography (EtOH). Viscous oil (0.428 g, 50%); δ_P 27.2; δ_H 2.41 (3H, dd, $^3J_{HP}$ 12.5, $^3J_{HH}$ 5.6, exocyclic NMe), 2.57 (3H, d, $^3J_{HP}$ 9.7, endocyclic NMe), 3.09–3.28 (4H, m), 3.57 (1H, t, $^3J_{HH}$ 6.6, one H of CH_2Cl), 3.58 (1H, t, $^3J_{HH}$ 6.5, one H of CH_2Cl); MS *m*/*z* 213, 211 (M^+, 5%, 15%), 162 ($M^+ - CH_2Cl$, 100), 133 ($M^+ - CH_2Cl - NMe$, 99), 119 ($M^+ - CH_2Cl - NMe - CH_2$, 56).

General procedure for the acidic alcoholysis of 1-oxo-2,8-disubstituted-2,5,8-triaza-1λ^5-phosphabicyclo[3.3.0]octanes 1

A solution of **1** (0.33–1.23 mmol) in an alcohol (5–20 ml) containing one mole equivalent of anhydrous HCl (*ca*. 0.1 M solution) was kept at room temperature until the ^{31}P NMR spectrum of a sample of the reaction mixture showed the complete disappearance of **1** (30 min–24 h). For slower reactions the acidity of the solution (pH = 4–5) was adjusted by the occasional addition of small volumes of alcoholic HCl. Alcohol was removed under reduced pressure and the hydrochloride salt (**2·HCl**) was isolated and characterized. The salts were then converted to the free bases **2** or to other derivatives of **2**, as described for individual products.

1-Oxo-1-methoxy-2,8-diphenyl-2,5,8-triaza-1λ^5-phosphacyclooctane 2a. *Hydrochloride salt.* Reaction time 24 h (100%). Purified by crystallization from $CHCl_3$–hexane; colorless crystals, mp 119.8–122.0 °C (decomp.). δ_P 12.7; δ_H 3.20–3.55 (4H, m), 3.36 (3H, d, $^3J_{HP}$ 11.2), 4.01 (4H, m), 7.19–7.46 (10H, m), 10.40 (2H, br d, NH_2^+); δ_C 45.5 (s), 46.5 (d, $^2J_{CP}$ 5.1), 54.0 (d, $^2J_{CP}$ 5.2), 126.6 (s), 126.8 (s), 129.7 (s), 142.2 (s) (Found: C, 55.28; H, 6.45; N, 11.30. $C_{17}H_{23}ClN_3O_2P$ requires: C, 55.51; H, 6.30; N, 11.42%).

Free base **2a**. Anhydrous K_2CO_3 (0.69 g, 5.0 mmol) was added to a solution of **2a·HCl** (0.180 g, 0.50 mmol) in $CHCl_3$ (20 ml) and the mixture was stirred vigorously at room temperature for 24 h. After filtration (or centrifugation) the solution was washed three times with water (5 ml each), dried (Na_2SO_4) and evaporated under reduced pressure. **2a** was obtained as a white solid (0.166 g, 100%), mp 91.5–92.7 °C. δ_P 13.6; δ_H 1.84 (1H, br s), 2.73 (2H, ddd, $^3J_{HP}$ 6.7, $^3J_{HH}$ 14.7, 3.0), 3.03 (2H, ddd, $^3J_{HP}$ 7.0, $^3J_{HH}$ 14.6, 3.4), 3.50 (3H, d, $^3J_{HP}$ 11.3), 3.68 (4H, m), 7.05–7.10 (10H, m); δ_C 47.4 (s), 51.7 (d, $^2J_{CP}$ 4.7), 53.3 (d, $^2J_{CP}$ 5.1), 123.5 (d, J_{CP} 3.1), 124.1 (s), 129.3 (s), 143.2 (d, J_{CP} 4.5).

N-Benzoyl-**2a**. Described before;[3] δ_H 3.40–3.50 (2H, m), 3.55 (3H, d, $^3J_{HP}$ 11.3), 3.50–3.65 (1H, m), 3.70–3.85 (3H, m), 4.00–4.15 (1H, m), 4.15–4.30 (1H, m), 7.10–7.43 (15H, m); δ_C 41.6 (s), 49.0 (s), 49.5 (s), 49.7 (s), 53.5 (d, $^2J_{CP}$ 5.5), 129.4 (s), 130.0 (s), 136.3 (s), 142.4 (s), 143.8 (s), 172.5 (s); MS *m*/*z* 435 (M^+, 2%), 330 ($M^+ - PhCO$, 1.4), 317 (91), 235 (21), 214 (99), 119 (100), 105 (90), 77 (57).

N-Acetyl-**2a**. Obtained by acetylation of **2a** with Ac_2O in pyridine. White solid (74%), mp 144.5–145.9 °C (from benzene). δ_P 12.0; δ_H 1.90 (3H, s), 3.49 (3H, d, $^3J_{HP}$ 11.3), 3.35–4.08 (8H, m), 7.29–7.41 (10H, m); δ_C 21.9 (s), 45.9 (s), 48.3 (s), 49.1 (d, $^2J_{CP}$ 8.5), 49.3 (d, $^2J_{CP}$ 8.5), 53.4 (d, $^2J_{CP}$ 5.5), 123.7 (s), 125.0 (s), 129.4 (s), 143.8 (d, $^2J_{CP}$ 4.7), 171.3 (s); MS *m*/*z* 374 ($M^+ + 1$, 1%), 373 (M^+, 4), 255 (89), 214 (99), 119 (100), 106 (74) (Found: C, 61.10; H, 6.63; N, 11.05. $C_{19}H_{24}N_3O_3P$ requires: C, 61.11; H, 6.47; N, 11.25%).

N-Tosyl-**2a**. Obtained from **2a**, TsCl and pyridine in CH_2Cl_2 and purified by column chromatography (MeOH–CH_2Cl_2, 1 : 1). Colorless solid (51%), mp 69–70 °C. δ_P 11.7; δ_H 2.38 (3H, s), 3.19 (2H, m), 3.48 (3H, d, $^3J_{HP}$ 11.1), 3.45–3.51 (2H, m), 3.76–3.94 (4H, m), 7.13–7.64 (14H, m); δ_C 21.5 (s), 47.9 (s), 51.9 (d, $^2J_{CP}$ 4.9), 125.5 (s), 126.3 (s), 127.1 (s), 129.3 (s), 129.8 (s), 130.8 (s), 135.9 (s), 146.5 (d, J_{CP} 6.0) (Found: C, 56.84; H, 6.23; N, 8.13. $C_{24}H_{28}N_3O_4PS$ requires: C, 56.23; H, 5.85; N, 8.19%).

1-Oxo-1-ethoxy-2,8-diphenyl-2,5,8-triaza-1λ^5-phosphacyclooctane 2b. *Hydrochloride salt.* Prepared as for **2a**. Colorless crystals (100%), mp 114.8–116.8 °C (from acetone–hexane). δ_P 11.2; δ_H 0.90 (3H, t, $^3J_{HH}$ 7.3), 3.34 (4H, m), 3.72 (2H, dq, $^3J_{HP}$ 14.6, $^3J_{HH}$ 7.3), 4.01 (4H, m), 7.18–7.45 (10H, m); δ_C 15.8 (d, $^3J_{CP}$ 5.9), 45.5 (s), 48.4 (d, $^2J_{CP}$ 4.7), 63.7 (d, $^3J_{CP}$ 5.9), 126.5 (s), 127.0 (s), 129.6 (s), 142.4 (s) (Found: C, 56.18; H, 6.73; N, 10.90. $C_{18}H_{25}ClN_3OP$ requires: C, 56.62; H, 6.60; N, 11.00%).

Free base **2b**. Prepared as for **2a**. Colorless crystals (100%), mp 93.0–93.9 °C (from ether–hexane). δ_P 12.2; δ_H 1.10 (3H, t, $^3J_{HH}$ 7.2), 1.76 (1H, br s), 2.73 (2H, ddd, $^3J_{HP}$ 6.7, $^3J_{HH}$ 14.5, 3.1), 3.03 (2H, ddd, $^3J_{HP}$ 7.0, $^3J_{HH}$ 14.7, 3.4), 3.73 (4H, m), 3.92 (2H, dq, $^3J_{HP}$ 14.1, $^3J_{HH}$ 7.2), 7.07–7.42 (10H, m); δ_C 15.7 (d,

$^3J_{CP}$ 6.4), 47.5 (s), 51.7 (d, $^2J_{CP}$ 4.7), 62.9 (d, $^2J_{CP}$ 5.3), 122.5 (s), 123.6 (s), 124.0 (s), 143.4 (d, $^3J_{CP}$ 3.5) (Found: C, 62.81; H, 7.19; N, 12.29. $C_{18}H_{24}N_3OP$ requires: C, 62.60; H, 7.00; N, 12.17%).

N-Benzoyl-**2b**. Described before;[3] δ_H 1.08 (3H, t, $^3J_{HH}$ 7.1), 3.35–3.50 (2H, m), 3.50–4.30 (8H, m), 7.00–7.50 (15H, m); δ_C 15.8 (d, $^3J_{CP}$ 6.9), 46.1 (s), 48.2 (s), 49.2 (s), 49.6 (s), 63.0 (d, $^2J_{CP}$ 5.1), 123.0 (s), 125.6 (s), 128.1 (s), 129.3 (s), 136.3 (s), 142.4 (s), 143.8 (s), 144.2 (s), 172.0 (s); MS *m/z* 405 ($M^+ - C_2H_5O$, 6%), 331 (100), 300 (30), 228 (50), 119 (42), 105 (63).

1-Oxo-1-methoxy-2,8-di(4-methoxyphenyl)-2,5,8-triaza-1λ^5-phosphacyclooctane 2f. *Hydrochloride salt.* Prepared as for **2a**. Needles (100%), mp 155.1–156.6 °C (decomp.) (from $CHCl_3$–benzene, 1:1). δ_P 12.9; δ_H 3.15–3.45 (4H, m), 3.31 (3H, d, $^3J_{HP}$ 11.0), 3.76 (6H, s), 3.94 (4H, m), 6.84 (4H, d, $^3J_{HH}$ 6.8), 7.38 (4H, d, $^3J_{HH}$ 6.7), 9.99 (2H, br s, NH_2^+); δ_C 45.3 (s), 49.1 (d, $^2J_{CP}$ 5.1), 54.0 (d, $^2J_{CP}$ 5.9), 55.5 (s), 114.8 (s), 129.0 (s), 134.9 (s), 158.3 (s) (Found: C, 53.52; H, 6.45; N, 9.87. $C_{19}H_{27}ClN_3O_4P$ requires: C, 53.34; H, 6.36; N, 9.82%).

Free base **2f**. Prepared as for **2a**. Oil (93%); δ_P 12.9; δ_H 2.37 (1H, br s), 2.77 (2H, ddd, $^3J_{HP}$ 6.5, $^3J_{HH}$ 14.6, 3.3), 2.98 (2H, ddd, $^3J_{HP}$ 6.8, $^3J_{HH}$ 14.5, 3.5), 3.42 (3H, d, $^3J_{HP}$ 11.3), 3.63 (4H, m), 3.78 (6H, s), 6.85 (4H, m), 7.31 (4H, m); δ_C 46.6 (s), 51.8 (d, $^2J_{CP}$ 4.3), 53.4 (d, $^2J_{CP}$ 5.9), 55.5 (s), 114.5 (s), 129.0 (s), 134.9 (s), 158.3 (s).

1-Oxo-1-methoxy-2-phenyl-8-(4-methoxyphenyl)-2,5,8-triaza-1λ^5-phosphacyclooctane 2g. *Hydrochloride salt.* Prepared as for **2a**. Highly insoluble crystals (100%), mp 129.1–132.0 °C. δ_P 12.7; δ_H 3.15–3.50 (4H, m), 3.32 (3H, d, $^3J_{HP}$ 11.2), 3.76 (3H, s), 3.97 (4H, m), 6.85 (2H, d, $^3J_{HH}$ 6.7), 7.17–7.43 (7H, m), 10.00 (2H, br s); δ_C 45.4 (s), 45.5 (s), 48.7 (d, $^2J_{CP}$ 5.1), 49.0 (d, $^2J_{CP}$ 5.1), 54.0 (d, $^2J_{CP}$ 5.6), 114.8 (s), 126.4 (s), 126.7 (d, $^3J_{CP}$ 2.5), 129.2 (s), 129.6 (s), 134.7 (s), 142.4 (s), 158.4 (s) (Found: C, 53.83; H, 6.53; N, 10.36. $C_{18}H_{25}ClN_3O_3P$ requires: C, 54.34; H, 6.33; N, 10.56%).

Free base **2g**. Prepared as for **2a**. Oil (93%). δ_P 13.8; δ_H 1.97 (1H, br s), 2.74 (2H, m), 3.02 (2H, m), 3.46 (3H, d, $^3J_{HP}$ 11.3), 3.69 (4H, m), 3.77 (3H, s), 6.63–7.41 (9H, m); δ_C 47.1 (s), 47.7 (s), 51.8 (d, $^2J_{CP}$ 3.4), 53.0 (d, $^2J_{CP}$ 5.9), 53.2 (d, $^2J_{CP}$ 5.2), 55.5 (s), 114.5 (s), 122.9 (d, $^2J_{CP}$ 3.1), 123.8 (s), 127.1 (d, $^3J_{CP}$ 2.4), 129.3 (s), 136.2 (s), 143.3 (d, $^3J_{CP}$ 3.5), 157.2 (s).

Alternative preparation of hydrochloric salts 2b·HCl, 2f·HCl, 2g·HCl; general procedure

To a solution of **1** (0.33 mmol) in MeOH (5 ml), Me_3SiCl (0.039 g, 0.36 mmol) was added and the reaction mixture was stirred at room temperature for 4 h (full conversion was demonstrated by ^{31}P NMR spectroscopy). The solution was evaporated under reduced pressure yielding the corresponding **2·HCl** (100%). The products were sufficiently pure not to require further purification.

1-Oxo-1-methoxy-2,8-dibenzyl-2,5,8-triaza-1λ^5-phosphacyclooctane 2d. *Hydrochloride salt.* Prepared as for **2a**; reaction time 20 h. White solid (96%), purified by crystallization from $CHCl_3$–benzene (1:1), mp 250.4–256.0 °C. δ_P 18.7; δ_H 2.90–3.01 (2H, m), 3.10–3.18 (2H, m), 3.25–3.45 (4H, m), 3.68 (3H, d, $^3J_{HP}$ 11.2), 4.33 (2H, dd, $^3J_{HP}$ 9.5, $^2J_{HH}$ 15.2, two H's of the CH_2Ph groups), 4.43 (2H, dd, $^3J_{HP}$ 11.2, $^2J_{HH}$ 15.2, two H's of the CH_2Ph groups), 7.24–7.40 (10H, m), 9.98 (2H, br s) (Found: C, 57.94; H, 7.10; N, 10.07. $C_{19}H_{27}ClN_3O_3P$ requires: C, 57.65; H, 6.87; N, 10.61%).

Free base **2d**. Prepared as for **2a**. Oil (69%). δ_P 21.3; δ_H 1.98 (1H, br s), 2.52–2.61 (2H, m), 2.66–2.77 (2H, m), 2.90–3.08 (4H, m), 3.66 (3H, d, $^3J_{HP}$ 10.9), 4.14 (2H, dd, $^3J_{HP}$ 8.1, $^2J_{HH}$ 15.3, two H's of the CH_2Ph groups), 4.32 (2H, dd, $^3J_{HP}$ 9.4, $^2J_{HH}$ 15.4, two H's of the CH_2Ph groups), 7.22–7.39 (10H, m).

1-Oxo-1-methoxy-2,8-diethyl-2,5,8-triaza-1λ^5-phosphacyclooctane 2e. *Hydrochloride salt.* Prepared as for **2a**; reaction time 30 min. Colorless, hygroscopic crystals (98%). δ_P 18.8; δ_H 1.12 (6H, t, $^3J_{HH}$ 7.0), 3.08–3.39 (12H, m), 3.64 (3H, d, $^3J_{HP}$ 11.2); δ_C 14.5 (s), 42.2 (d, $^2J_{CP}$ 2.6), 43.2 (d, $^2J_{CP}$ 4.8), 45.3 (s).

Picrate salt, **2e·***PicH.* **2e**·HCl (0.067 g, 0.246 mmol) was dissolved in EtOH (0.5 ml) and the solution was added to a solution of picric acid (0.070 g, 0.307 mmol) in EtOH (1.25 ml). The solution was heated at 60 °C for 10 min and cooled. The precipitate was filtered off, washed with EtOH and dried. Yellow crystals (0.100 g, 81%), mp 144 °C. δ_P (D_2O) 21.1; δ_H (D_2O) 1.08 (6H, t, $^3J_{HP}$ 7.1), 3.00–3.22 (4H, m), 3.39–3.50 (8H, m), 3.73 (3H, d, $^3J_{HP}$ 11.4), 8.90 (2H, s) (Found: C, 38.70; H, 5.51; N, 17.90. $C_{15}H_{25}N_6O_9P$ requires: C, 38.80; H, 5.43; N, 18.06%).

Free base **2e**. **1e** (0.175 g, 0.86 mmol) was dissolved in MeOH (20 ml), a solution of MeONa (1.3 mole-equiv.) in MeOH (20 ml) was added and the solution was kept at room temperature, with the ^{31}P NMR spectra recorded periodically (substrate's signal at δ_P 47.7 being replaced by the signal at δ_P 22.7), $t_{\frac{1}{2}}$ *ca.* 65 h. After 13 days (*ca.* 4.8 half-lives) the solution was neutralized with the required volume of 0.73 M methanolic HCl and evaporated under reduced pressure. The residue was extracted with $CHCl_3$ (4 × 20 ml) and the combined $CHCl_3$ solution was evaporated under reduced pressure yielding **2e** (0.180 g, 89%) as a viscous oil. δ_P 19.9; δ_H 1.13 (6H, t, $^3J_{HH}$ 7.0), 3.05–3.32 (12H, m), 3.64 (3H, d, $^3J_{HP}$ 11.1); δ_C 14.4 (s), 42.1 (d, $^2J_{CP}$ 2.7), 43.0 (d, $^2J_{CP}$ 4.8), 44.8 (s) (Found: C, 45.60; H, 9.82; N, 17.51. $C_9H_{22}N_3O_2P$ requires: C, 45.94; H, 9.43; N, 17.86%).

Reaction of 1a with trifluoromethanesulfonic acid

1a (0.100 g, 0.33 mmol) was dissolved in CH_2Cl_2 (5 ml) and the solution was cooled to −50 °C. A suspension of CF_3SO_3H (0.100 g, 0.66 mmol) in CH_2Cl_2 (3 ml) was then added dropwise with stirring. The mixture was stirred at −50 °C for 1 h, and at room temperature for 2 h. White precipitate was formed and the ^{31}P NMR spectrum of the solution showed the complete disappearance of **1a**. The precipitate was collected; white, highly hygroscopic solid (0.100 g, 51%), soluble in acetone; δ_P [$(CD_3)_2CO$] 6.6. The solid (0.100 g) was dissolved in THF (10 ml) containing Et_3N (0.070 g) and the solution was stirred at room temperature. ^{31}P NMR spectroscopy showed the gradual disappearance of the signal at *ca.* 6.0 and the appearance of a signal at δ_P 32.2, confirmed to be the signal of **1a** by the addition of an authentic sample. After 6 h the reaction was complete; the solvent was evaporated under reduced pressure, the residue was dissolved in $CHCl_3$, washed with water and dried (Na_2SO_4). After evaporation of the solvent the white solid product (0.030 g, 30%) was purified by crystallization from THF–hexane (1:1) yielding pure **1a**, mp 150.0–151.2 °C (lit.[1] mp 148.0–149.5 °C); δ_P 33.5; ^1H NMR spectrum identical to that of an authentic sample of **1a**.

Reaction of 1a with phenol

Hydrochloride salt. A solution of **1a** (0.200 g, 0.67 mmol), phenol (freshly distilled, 0.248 g, 2.64 mmol) and trimethylchlorosilane (0.086 g, 0.80 mmol) in CH_2Cl_2 (15 ml) was kept at room temperature for 20 days. The solvent and volatile products were removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (10 ml) and the product was precipitated by the dropwise addition of ether (30 ml) with stirring. The dissolving–precipitation procedure was repeated several times until **2c·HCl** (0.285 g, 89%) was obtained as a white solid, mp 87.0–92.0 °C. The ^{31}P NMR spectrum indicated that the purity of the product was *ca.* 90% and further purifications did not improve the quality of the product. δ_P 7.0; δ_H 3.20–3.80 (6H, m), 4.09 (2H, m), 6.68–7.47 (15H, m), 10.01 (2H, br d); δ_C 45.3 (s), 48.8 (d, $^2J_{CP}$ 4.4), 120.2 (d, $^2J_{CP}$ 4.4), 124.7 (s), 126.9 (s), 127.6 (s), 129.4 (s), 129.7 (s), 142.0 (s), 150.8 (d, $^2J_{CP}$ 5.8)

(Found: C, 58.17; H, 6.03; N, 9.56. $C_{22}H_{25}ClN_3O_2P·H_2O$ requires: C, 58.99; H, 6.03; N, 9.36%).

Free base. The reaction was repeated starting with **1a** (0.100 g, 0.33 mmol), phenol (0.124 g, 1.32 mmol) and Me_3SiCl (0.043 g, 0.40 mmol) in CH_2Cl_2 (15 ml) and after 20 days a large excess of finely powdered K_2CO_3 (2.30 g, 17.2 mmol) was added to the reaction mixture. After four days of vigorous stirring, the mixture was filtered and the filtrate was washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product (viscous oil) was purified by column chromatography (petroleum ether–AcOEt, 2:1) followed by crystallization from THF–hexane, yielding pure **3c** (0.078 g, 60% based on **1a**), needles, mp 112.0–114.1 °C. δ_P 14.8; δ_H 3.00–3.10 (2H, m), 3.25–3.42 (4H, m), 3.45–3.65 (2H, m), 4.44 (1H, br s), 6.59–7.35 (15H, m); δ_C 41.7 (s), 42.8 (d, $^2J_{CP}$ 13.0), 43.1 (d, $^2J_{CP}$ 14.4), 44.5 (d, $^2J_{CP}$ 4.6), 113.0 (s), 116.2 (d, $2J_{CP}$ 4.7), 117.6 (s), 121.2 (d, $^2J_{CP}$ 3.4), 122.0 (s), 125.1 (s), 129.3 (s) 129.6 (s) (Found: C, 67.40; H, 6.50; N, 10.34. $C_{22}H_{24}N_3O_2P$ requires: C, 67.14; H, 6.15; N, 10.68%).

Base-catalyzed methanolysis of 1-oxo-2,8-disubstituted-2,5,8-triaza-1λ^5-phosphabicyclo[3.3.0]octanes 1

General procedure. A solution of **1** (1.0 mmol) and MeONa (3.0 mmol) in MeOH (20 ml) was kept at room temperature while the reaction progress was monitored by ^{31}P NMR spectroscopy. When **1** had disappeared, the solution was neutralized with methanolic HCl, filtered and evaporated under reduced pressure. The crude product was purified as indicated for individual products. The following products were obtained.

3-[2-(Phenylamino)ethyl]-2-oxo-2-methoxy-1-phenyl-1,3,2λ^5-diazaphospholidine 3a. Described before,[3] but prepared again in a state of higher purity; reaction time 28 h, purified by column chromatography (AcOEt–petroleum ether, 1:1), followed by crystallization from THF–hexane, mp 115.0–116.0 °C (56%). δ_P 19.9; δ_H 3.43 (6H, m), 3.61 (3H, d, $^3J_{HP}$ 12.3), 3.63 (2H, m), 4.45 (1H, br s), 6.62–7.32 (10H, m); δ_C 41.6 (s), 43.2 (d, $^2J_{CP}$ 14.3), 43.3 (d, $^2J_{CP}$ 12.8), 44.4 (d, $^2J_{CP}$ 4.6), 54.3 (d, $^2J_{CP}$ 7.8), 112.8 (s), 115.7 (s), 117.4 (s), 121.7 (s), 123.5 (s), 129.3 (s), 129.4 (s), 137.6 (d, $^2J_{CP}$ 5.2) (Found: C, 61.52; H, 6.80; N, 12.55. $C_{17}H_{22}N_3O_2P$ requires: C, 61.62; H, 6.69; N, 12.68%).

3-{2-[(4-Methoxyphenyl)amino]ethyl}-2-oxo-2-methoxy-1-(4-methoxyphenyl)-1,3,2λ^5-diazaphospholidine 3d. Reaction time 25 days, purified by crystallization from THF–hexane, mp 120.5–121.6 °C (60%). δ_P 20.1; δ_H 3.30 (6H, m), 3.57 (3H, d, $^3J_{HP}$ 12.3), 3.66 (2H, m), 3.75 (3H, s), 6.60–7.10 (8H, m); δ_C 42.8 (s), 43.6 (d, $^2J_{CP}$ 13.3), 43.8 (d, $^2J_{CP}$ 14.6), 44.6 (d, $^2J_{CP}$ 4.4), 54.1 (d, $^2J_{CP}$ 7.7), 55.6 (s), 55.8 (s), 114.3 (s), 114.8 (s), 114.9 (s), 117.5 (d, $^2J_{CP}$ 4.5), 134.6 (s), 142.1 (s), 152.2 (s), 154.9 (s) (Found: C, 58.45; H, 6.72; N, 10.76. $C_{19}H_{26}N_3O_4P$ requires: C, 58.30; H, 6.70; N, 10.74%).

3-[2-(Phenylamino)ethyl]-2-oxo-2-methoxy-1-(4-methoxyphenyl)-1,3,2λ^5-diazaphospholidine 3f. Reaction time 42 days, two products separated by fractional crystallization from THF–hexane; **3f** (32%), colorless crystals, mp 109.7–110.4 °C. δ_P 20.1; δ_H 3.34 (6H, m), 3.58 (3H, d, $^3J_{HP}$ 13.8), 3.66 (2H, m), 3.76 (3H, s), 6.63–7.19 (9H, m); δ_C 41.7 (s), 43.4 (d, $^2J_{CP}$ 12.8), 43.8 (d, $^2J_{CP}$ 14.2), 44.5 (d, $^2J_{CP}$ 4.5), 54.2 (d, $^2J_{CP}$ 7.7), 55.6 (s), 112.9 (s), 114.8 (s), 117.6 (s), 118.0 (s), 129.3 (s), 134.6 (d, $^2J_{CP}$ 5.4) (Found: C, 59.99; H, 6.81; N, 11.70. $C_{18}H_{24}N_3O_3P$ requires: C, 59.82; H, 6.69; N, 11.63%).

Base-catalyzed methanolysis of 1-oxo-2,8-dibenzyl-2,5,8-triaza-1λ^5-phosphabicyclo[3.3.0]octane 1d

The reaction was monitored by ^{31}P NMR spectroscopy which showed the disappearance of **1d** (δ_P 47.3) and the formation of a new product (δ_P 21.9), which, in turn, gave way to the final product (δ_P 27.3), accepted as the rearrangement product **3h**. After four days the ^{31}P NMR spectrum revealed complete disappearance of **1d**, and the presence of **2d** (98%), together with 2% of **3h**. The **2d**→**3h** rearrangement was then followed by ^{31}P NMR spectroscopy yielding the approximate half-life of **2d** as $t_{\frac{1}{2}}$ = 960 h.

1-Oxo-1-methoxy-2,8-diethyl-2,5,8-triaza-1λ^5-phosphacyclooctane 2e. Reaction time 13 days. Crude **2e** (99%, δ_P 19.9) was treated with benzoyl chloride in pyridine, yielding *N-benzoyl*-**2e**, oil (45%), δ_P 20.0; δ_H 1.14 (6H, t, $^3J_{HH}$ 6.9), 3.08–3.38 (12H, m), 3.62 (3H, d, $^3J_{HP}$ 11.1), 7.35 (5H, br s) (Found: C, 56.90; H, 7.80; N, 12.16. $C_{16}H_{26}N_3O_3P$ requires: C, 57.05; H, 7.72; N, 12.38%).

Rate measurements for the 2→3 rearrangement

Specific conditions used in measuring the rates of the rearrangement are given in Table 1. At selected intervals samples of the reaction mixtures were placed in NMR tubes and ^{31}P NMR spectra were recorded. First-order rate constants were then calculated as $k_1 = \ln[(A + B)/A]/t$, where A and B represent the ^{31}P NMR integrals of the signals of **2** and **3**, respectively. For the rearrangement of **2e** and **2d**, where signals due to **2** and **3** were accompanied by additional (minor) signals, the latter were ignored in the calculations.

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