Preparation of Acyclic and Cyclic Phosphoric Triamides and Diamido Esters

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Using phosphoryl chloride as a substrate, a series of *N*-bis(2-chloroethyl)phosphoric triamides (and diamido esters) was prepared. These acyclic products were cyclized to the 1,3,2-diazaphospholidine derivatives, which, in turn, could be cyclized again to the phosphotriamidate products of the 2,8-disubstituted 1-oxo-2,5,8-triaza-1-phosphabicyclo[3.3.0]octane system.

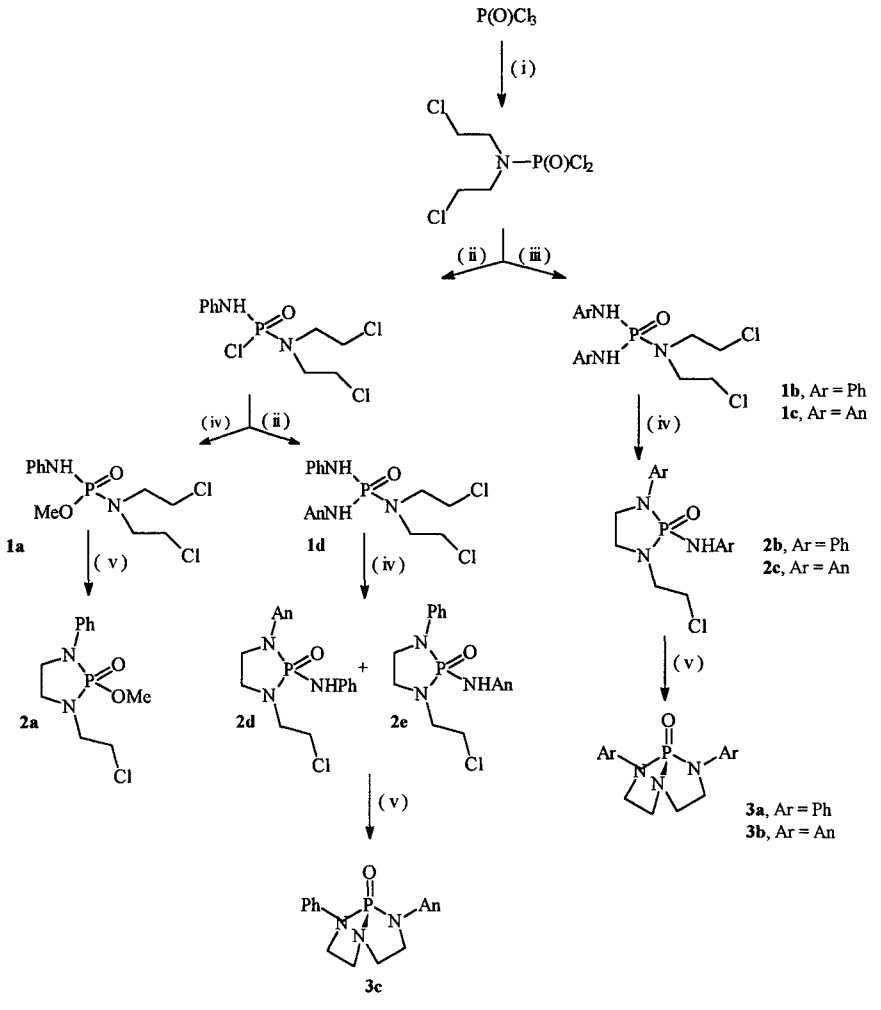
Amides of phosphoric acid display a wide spectrum of biological activity, the typical examples are *schradan* (octamethyl pyrophosphoramidate, systemic insecticide),[1] *aphamide* {*N,N'*-ethylenebis[*P,P'*-bis(1-aziridinium)-*N*-methyl]phosphoric triamide, insect chemosterilant}[2] or the family of *N*-phosphorylated nitrogen mustards known to arrest tumor growth.[3] The P(O)NHR functional group can serve as a simultaneous hydrogen bonding donor and acceptor,[4] and in this respect the behaviour of phosphoramidates shows distinct differences to that of the corresponding carboxylic amides.[5] We have recently found[6] that some chiral, racemic phosphoramidates can act as chiral recognition agents with respect to the optically active acids. The effect, based on the formation of diastereomeric hydrogen bonded complexes, depends on the torsion angle of the O=PNH function. Structure – reactivity studies called for efficient methods of preparation of a variety of non-cyclic, cyclic, and bicyclic phosphoramidates as hydrogen bonding substrates.

We report now the preparation of a series of phosphotriamidates (and diamido esters) **1** and **2** carrying as an essential structural feature the *N*-(2-chloroethyl) substituent, as well as their bicycloderivatives **3**, based on phosphoryl chloride as a common starting material (Scheme 1). Preparation of non-cyclic products **1** involved three subsequent nucleophilic displacements at the phosphoryl centre. The order of the nucleophilic reagents introduced at phosphorus is, however, important, and we found that best yields were always obtained when the bis(2-chloroethyl)amino group was substituted for the first chlorine atom in $POCl_3$. The phosphodiamidate ester **1a** could be obtained via two routes, however, for this and other related products, the best results were obtained if the methoxy group (as the methoxide anion) was introduced at the end of the sequence. The reason for a better selectivity is that when a substrate of the $R_2NP(O)Cl_2$ type is converted to a diamidochloridate, $R_2N(R'_2N)P(O)Cl$, the reactivity of the latter in the next substitution is drastically reduced. If, however, the amidodichloridate is converted to a monoester derivative, $R_2N(R'O)P(O)Cl$, the reactivities of both the substrate and the product are similar, and further substitution of the disubstituted product can also occur.

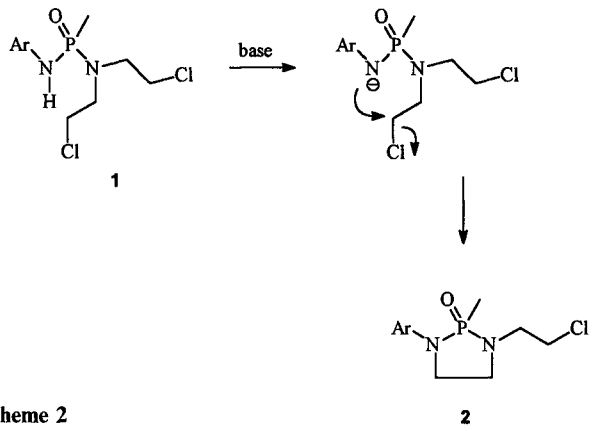
In agreement with our earlier reports,[7] all products **1** could be subjected to the 1,5-cyclization via deprotonation of the amide hydrogen and the intramolecular displacement of the β-chloro atom of the nitrogen mustard function (Scheme 2). Reaction of **1d** yielded two isomeric 1,3,2-diazaphospholidine derivatives **2d**, **2e** and only one of them was isolated as a pure material.

Structural assignment of the isolated product was not easy since the spectroscopic (^{31}P, ^{1}H, ^{13}C NMR, IR) characteristics of both compounds are very similar. Although the deprotonation of **1d** should involve the PhNH rather than the AnNH hydrogen (stronger acid), the reactivity of the latter conjugate base should be higher due to the electron-releasing effect of the *p*-MeO group. Analysis of the ^{1}H NMR spectrum of the purified material proved inconclusive. The ArNH signal was observed at $\delta = 6.29$ (d, $J_{HP} = 8.1$ Hz). For **2b** (containing an exocyclic PhNH group) the corresponding value is $\delta = 6.07$ (d, $J_{HP} = 7.2$ Hz), while for **2c** (possessing an exocyclic AnNH group) the value is $\delta = 5.85$ (d, $J_{HP} = 7.9$ Hz). The tentative identification of the isolated compound (^{31}P NMR: $\delta = 14.7$; mp 163.5–165.0 °C) as **2d** was finally based on its mass spectrum. Apart from the M^+ signal ($m/z = 365$, 367; 6.3, 2.3 %), the spectrum consisted of the signal at $m/z = 316$ ($M^+ - CH_2Cl$, fragmentation typical for the *N*-phosphorylated nitrogen mustards[8]), and of the base peak at $m/z = 177$. The peak corresponds to the formula $C_{10}H_{13}N_2O$ and can be envisaged as a result of the loss of CH_2Cl, followed by the fission of both endocyclic P–N bonds and yielding a fragment incorporating the *N*-*p*-anisyl group in an ethylenediamine system (Scheme 3). A corresponding signal at $m/z = 147$ ($C_9H_{11}N_2$), expected from the analogous fragmentation of **2e**, was absent in the MS of the purified product.

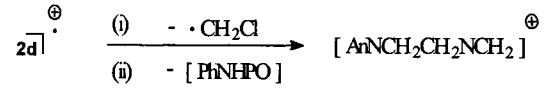
The monocyclic triamides **2b–2e** still contained the NH and the 2-chloroethyl functions and could be therefore cyclized to the bicyclic products **3** via another 1,5-intramolecular substitution. Compounds **2** were less acidic than **1** and the second cyclization required application of NaH as a base. Diazaphospholidines **2d** and **2e** or the mixture of both isomers, yielded the same product, the unsymmetrically substituted (chiral) bicyclic compound **3c**. Three types of the phoshoramidates prepared are characterized by specific ranges of the ^{31}P NMR chemical shift values (Table). The average δ values for **1b–1d**, **2a–2c**, and **3a–3c** are: 5.8 ± 0.6, 14.1 ± 0.7, and 33.8 ± 0.3, respectively. The regular deshielding effect observed upon each cyclization (average $+ 8.3 \pm 0.3$ ppm for the first, and $+ 19.7 \pm 0.5$ ppm for the second) undoubtedly reflects the changes in the N–P–N bond angles, which in turn affect the shielding parameters of the phosphorus nucleus. Gorenstein[9] correlated ^{31}P chemical shifts and O–P–O bond angles in phosphates and found that a decrease in the bond angle results in a deshielding of the P nucleus. Similar correlation was demonstrated for compounds with the S–P–S bond angle.[10] We conclude, that for phosphotriamidates, the



Scheme 1



Scheme 2



Scheme 3

^{31}P NMR spectra can be used to determine the presence (and the number) of the 1,3,2-diazaphospholidine rings in the molecule. We hope that both products **2** and **3**, as highly crystalline, chiral compounds, can find application as chiral recognition reagents, acting either via the hydrogen bonding interactions or via the inclusion effects. The presence of the aromatic groups opens the possibility of varying the ring substituents, which can modify the specific interactions between the reagent and an optically active substrate.

NMR spectra were recorded from $CDCl_3$ solutions on a Bruker AC 300 spectrometer and the ^{31}P chemical shifts are given relative to 85% H_3PO_4. For assignment purpose, both H-decoupled and H-coupled spectra were recorded. 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.

***N*-Bis(2-chloroethyl)-*N'*-phenylphosphodiamidochloridate:**
N-Bis(2-chloroethyl)phosphoamidodichloridate[7] (5.0 g, 19 mmol) and aniline (3.60 g, 39 mmol) were dissolved in CH_2Cl_2 (80 mL)

Table. ^{31}P NMR Spectra ($CDCl_3$) of Phosphoramidates and Diamido Esters **1–3**

Compound	δ
1a	10.4
1b	5.1
1c	6.3
1d	6.0
2a	18.9
2b	13.4
2c	14.7
2d	14.7
2e	13.7
3a	33.5
3b	34.1
3c	33.9

and the solution was stirred at r.t. for 240 h. Attempts to carry out the reaction at higher temperatures (refluxing CH_2Cl_2), hence for shorter periods, led to the formation of side products. After filtration and evaporation of the solvent, the crude product was purified by crystallization from benzene/hexane yielding colorless crystals (3.90 g, 64%); mp 77.5–78.5°C.

^1H NMR: $\delta = 3.40–3.60$ (8H, m, $4CH_2$), 6.24 (1H, d, $J_{HP} = 13.2$ Hz, NH), 6.95 (1H, t, $J_{HH} = 7.3$ Hz, p-H_{arom}), 7.00 (2H, d, $J_{HH} = 7.7$ Hz, 2 o-H_{arom}), 7.15 (2H, t, $J_{HH} = 7.8$ Hz, 2 m-H_{arom}).

^{31}P NMR: $\delta = 14.76$.

MS: $m/z = 320, 318, 316, 314$ (0.25, 6.9, 21.2, 22.3%, M^+), 269, 267, 265 (8.8, 52.1, 82.3%, $M^+ - CH_2Cl$), 231, 229 (8.3, 28.3%, $M^+ - CH_2Cl - HCl$), 92 (100%, $PhNH^+$).

Analysis ($C_{10}H_{14}Cl_3N_2OP$): Calc. C, 38.03; H, 4.44; N, 8.81. Found C, 38.63; H, 4.48; N, 8.83.

Methyl *N*-Bis(2-chloroethyl)-*N'*-phenylphosphodiamidate (1a):
To a solution of *N*-bis(2-chloroethyl)-*N'*-phenylphosphodiamidochloridate (3.0 g, 9.4 mmol) in MeOH (10 mL) was added dropwise with stirring a solution of MeONa (0.51 g, 9.4 mmol) in MeOH (10 mL) at 0–5°C. The mixture was kept at r.t. for 2 h, filtered and evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (10 mL), washed with water (2 × 5 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Pure **1a** was obtained after column chromatography ($CHCl_3$/benzene, 2:1); colorless crystals (0.92 g, 75%); mp 80–81.5°C.

^1H NMR: $\delta = 3.40$ (4H, m, $2NCH_2$), 3.51 (4H, t, $J_{HH} = 7.1$ Hz, $2CH_2Cl$), 3.76 (3H, d, $J_{HP} = 11.4$ Hz, OCH_3), 5.43 (1H, d, $J_{HP} = 8.4$ Hz, NH), 6.98 (3H, m, 3 H_{arom}), 7.23 (2H, t, $J_{HH} = 7.8$ Hz, 2 m-H_{arom}).

^{13}C NMR: $\delta = 42.2$ (CH_2Cl), 49.6 (d, $J_{CP} = 4.1$ Hz, NCH_2), 52.4 (OCH_3), 117.8 (d, $J_{CP} = 6.8$ Hz, o-C_{arom}), 122.2 (p-C_{arom}), 129.4 (m-C_{arom}), 139.4 (*ipso*-C_{arom}).

^{31}P NMR: $\delta = 10.41$.

MS: $m/z = 314, 312, 310$ (1.8, 11.3, 16.8%, M^+), 276, 274 (2.4, 6.7%, $M^+ - HCl$), 263, 261 (33, 100%, $M^+ - CH_2Cl$), 170 (59.3%, $M^+ - NC_4H_8Cl_2$), 92 (93%, $PhNH^+$).

Analysis ($C_{11}H_{17}Cl_2N_2O_2P$): Calc. C, 42.44; H, 5.47; N, 9.00. Found, 42.65; H, 5.49; N, 8.92.

***N*-Bis(2-chloroethyl)-*N,N'*-diphenylphosphotriamidate (1b); Typical Procedure:**
A solution of *N*-bis(2-chloroethyl)phosphoamidodichloridate[7] (2.64 g, 10.2 mmol) in CH_2Cl_2 (10 mL) was added dropwise with stirring at −20°C to a solution of aniline (1.90 g, 20.4 mmol) and Et_3N (2.0 g, 20.0 mmol) in CH_2Cl_2 (20 mL) during 1 h. The mixture was allowed to warm to r.t. and kept for 120 h. The solution was washed with water (2 × 10 mL), dried ($MgSO_4$), evaporated under reduced pressure, and the crude product was purified by column chromatography ($CHCl_3$). Pure **1b** was obtained as a colorless solid (2.81 g, 74%); mp 170–171°C.

^1H NMR: $\delta = 2.86$ (2H, d, $J_{HP} = 10.0$ Hz, 2NH), 3.52–3.63 (8H, m, $4CH_2$), 6.85–7.30 (10H, 2Ph).

^{13}C NMR: $\delta = 43.3$ (CH_2Cl), 50.6 (CH_2N), 119.0 (d, $J_{CP} = 6.3$ Hz, o-C_{arom}), 122.0 (p-C_{arom}), 130.0 (m-C_{arom}), 143.0 (*ipso*-C_{arom}).

^{31}P NMR: $\delta = 5.12$.

Analysis ($C_{16}H_{20}Cl_2N_3OP$): C, 51.60; H, 5.38; N, 11.29. Found C, 51.13; H, 5.42; N, 11.11.

N-Bis(2-chloroethyl)-N',N''-bis(4-methoxyphenyl)phosphotriamidate **(1c)**:

Prepared from 4-methoxyaniline (1.90 g, 15.4 mmol) as described for **1b**. Purified by column chromatography ($CHCl_3$); colorless solid (2.0 g, 60%); mp 156–157°C.

^1H NMR: $\delta = 3.47$ (4H, m, $2CH_2N$), 3.64 (4H, t, $J_{HH} = 7.5$ Hz, $2CH_2Cl$), 3.72 (6H, s, $2OCH_3$), 6.56 (2H, d, $J_{HP} = 9.7$ Hz, 2NH), 6.78 (4H, d, $J_{HH} = 8.9$ Hz, 4 H_{arom}), 7.16 (4H, d, $J_{HH} = 8.9$ Hz, 4 H_{arom}).

^{13}C NMR: $\delta = 43.0$ (CH_2Cl), 50.4 (CH_2N), 55.6 (OCH_3), 115.0 (d, $J_{CP} = 9.1$ Hz, o-C_{arom}), 120.6 (m-C_{arom}), 135.5 (*ipso*-C_{arom}), 155.5 (p-C_{arom}).

^{31}P NMR: $\delta = 6.25$.

Analysis ($C_{18}H_{24}Cl_2N_3O_3P$): C, 50.00; H, 5.56; N, 9.72. Found C, 49.18; H, 5.53; N, 9.37.

3-(2-Chloroethyl)-2-methoxy-2-oxo-1-phenyl-1,3,2-diazaphospholidine (2a):
To a solution of **1a** (0.10 g, 0.32 mmol) in benzene (10 mL) were added NaH (0.016 g, 0.64 mmol) and Bu_4NBr (TBAB, 0.005 g, 0.016 mmol). The suspension was stirred vigorously for 15 min and filtered. The filtrate was washed with water until the pH of the aqueous layer was 7, dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Crude **2a** was obtained in 85% yield (0.075 g) and was purified by crystallization from benzene/hexane; mp 114–115°C.

^1H NMR: $\delta = 3.20–3.40$ (2H, m, NCH_2CH_2Cl), 3.57 (3H, d, $J_{HP} = 12.8$ Hz, OCH_3), 3.40–3.70 (6H, m, $CH_2Cl + NCH_2CH_2N$), 6.98 (1H, t, $J_{HH} = 7.4$ Hz, p-H_{arom}), 7.14 (2H, d, $J_{HH} = 8.4$ Hz, 2 o-H_{arom}), 7.29 (2H, t, J_{HH} 8.3 Hz, 2 m-H_{arom}).

^{13}C NMR: $\delta = 42.7$ (CH_2Cl), 43.2 (d, $J_{CP} = 14.3$ Hz, NCH_2CH_2N), 44.5 (d, $J_{CP} = 12.0$ Hz, NCH_2CH_2N), 47.4 (d, $J_{CP} = 4.7$ Hz, NCH_2CH_2Cl), 53.8 (d, $J_{CP} = 7.3$ Hz, OCH_3), 115.7 (d, $J_{CP} = 4.7$ Hz, o-C_{arom}), 121.7 (p-C_{arom}), 129.4 (m-C_{arom}), 141.0 (*ipso*-C_{arom}).

^{31}P NMR: $\delta = 18.94$.

MS: $m/z = 276, 274$ (15.7, 45.9%, M^+), 225 (100%, $M^+ - CH_2Cl$), 195 (57.7%), 105 (50.7%), 77 (19.8%).

Analysis ($C_{11}H_{16}ClN_2O_2P$): C, 48.09; H, 5.83; N, 10.20. Found C, 48.58; H, 5.87; N, 10.17.

3-(2-Chloroethyl)-2-oxo-1-phenyl-1-phenylamino-1,3,2-diazaphospholidine (2b); Typical Procedure:
To a solution of **1b** (0.50 g, 1.3 mmol) in MeOH (30 mL) was added dropwise with stirring a solution of NaOMe (70 mg, 1.3 mmol) in MeOH (10 mL) at 0–5°C. The mixture was stirred at 0–5°C for 1 h, allowed to warm up to r.t. and left for 24 h. After filtration, MeOH was evaporated under reduced pressure and $CHCl_3$ (50 mL) was added. The organic phase was washed with water (3 × 50 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue (95%) was recrystallized from benzene affording pure **2b** as a colorless solid; mp 190–191.5°C.

^1H NMR: $\delta = 3.32$ (2H, m, NCH_2CH_2Cl), 3.56 (2H, t, $J_{HH} = 6.7$ Hz, CH_2Cl), 3.50–3.65 (3H, m, $3NCH_2CHHN$), 3.68–3.81 (1H, m, NCH_2CHHN), 6.07 (1H, d, $J_{HP} = 7.2$ Hz, NH), 6.80–6.90 (4H, m, 4 H_{arom}), 7.10–7.30 (6H, m, 6 H_{arom}).

^{13}C NMR: $\delta = 42.5$ (CH_2Cl), 43.5 (d, $J_{CP} = 13.4$ Hz, NCH_2CH_2N), 44.2 (d, $J_{CP} = 12.3$ Hz, NCH_2CH_2N), 46.5 (NCH_2CH_2Cl), 116.1 (d, $J_{CP} = 4.7$ Hz, o-C_{arom}), 118.9 (d, $J_{CP} = 6.3$ Hz, o'-C_{arom}), 121.6 (p-C_{arom}), 122.3 (p'-C_{arom}), 129.1 (m-C_{arom}), 129.2 (m'-C_{arom}), 135.7 (*ipso*-C_{arom}), 139.8 (*ipso'*-C_{arom}).

^{31}P NMR: $\delta = 13.40$.

MS: m/z = 337, 335 (22.2, 65.3%, M^+), 286 (100%, $M^+ - CH_2Cl$), 245, 243 (7.5, 21.9%, $M^+ - PhNH$), 106 (44.1%, $PhNHCH_2^+$), 77 (33.5%, Ph^+).

Analysis ($C_{16}H_{19}ClN_3OP$): C, 57.23; H, 5.66; N, 12.51. Found C, 57.71; H, 5.75; N, 12.29.

3-(2-Chloroethyl)-1-(4-methoxyphenyl)-2-[(4-methoxyphenyl)-amino]-2-oxo-1,3,2-diazaphospholidine (**2c**):

Prepared from **1c** as described for **2b**; crude yield: 95%; purified by crystallization from benzene; mp 192.5–193.5°C.

^{1}H NMR: δ = 3.29–3.61 (6H, m, $3CH_2N$), 3.58 (2H, t, J_{HH} = 7.0 Hz, CH_2Cl), 3.70 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 5.85 (1H, d, J_{HP} = 7.8 Hz, NH), 6.67 (2H, d, J_{HH} = 9.0 Hz, 2 *m*-H_{arom}), 6.76 (2H, d, J_{HH} = 9.1 Hz, 2 *m'*-H_{arom}), 6.78 (2H, d, J_{HH} = 8.9 Hz, 2 *o*-H_{arom}), 7.08 (2H, d, J_{HH} = 8.9 Hz, 2 *o'*-H_{arom}).

^{13}C NMR: δ = 42.5 (CH_2Cl), 44.2 (d, J_{CP} = 12.6 Hz, NCH_2CH_2N), 44.5 (d, J_{CP} = 11.4 Hz, NCH_2CH_2N) 46.7 (d, J_{CP} = 5.5 Hz, NCH_2CH_2Cl), 55.5 (OCH_3), 114.3 (d, J_{CP} = 4.8 Hz, *m*-C_{arom}), 114.6 (d, J_{CP} = 5.0 Hz, *m'*-C_{arom}), 118.1 (d, J_{CP} = 4.3 Hz, *o*-C_{arom}), 121.7 (d, J_{CP} = 6.0 Hz, *o'*-C_{arom}), 132.6 (*ipso*-C_{arom}), 134.6 (*ipso'*-C_{arom}), 154.8 (*p*-C_{arom}), 155.4 (*p'*-C_{arom}).

^{31}P NMR: δ = 14.68.

MS: m/z = 397, 395 (38, 100%, M^+), 275, 273 (9.3, 28.3%, $M^+ - AnNH$), 136 (19.1%, $AnNHCH_2^+$).

Analysis ($C_{18}H_{23}ClN_3O_3P$): C, 54.61; H, 5.81; N, 10.62. Found C, 54.77; H, 5.82; N, 10.51.

3-(2-Chloroethyl)-1-(4-methoxyphenyl)-2-oxo-2-phenylamino-1,3,2-diazaphospholidine (2d) and 3-(2-Chloroethyl)-2-[(4-methoxyphenyl)amino]-2-oxo-1-phenyl-1,3,2-diazaphospholidine (2e):

N-Bis(2-chloroethyl)-N'-(4-methoxyphenyl)-N''-phenylphosphotriamidate (**1d**):

To a solution of *N*-bis(2-chloroethyl)-*N'*-phenylphosphodiamidochloridate (1.0 g, 3.2 mmol) (*vide infra*) in CH_2Cl_2 (30 mL) were added 4-methoxyaniline (0.39 g, 3.2 mmol) and Et_3N (0.65 g, 6.4 mmol) and the solution was stirred at r.t. for 96 h. After that time ^{31}P NMR spectrum of a sample showed complete disappearance of the substrate. The solution was washed with water (3 × 80 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The crude product consisted of a single organophosphorus product **1d** (^{31}P NMR: δ = 6.0), which was subjected to cyclization without further purification.

Cyclization of **1d** *to a Mixture of* **2d** *and* **2e**:

To a solution of **1d** (1.3 g, 3.2 mmol) in MeOH (20 mL) was added dropwise with stirring a solution of NaOMe (26 mmol) in MeOH (30 mL) at 0–5°C. The mixture was allowed to warm up to r.t. and was kept for 20 h, until the ^{31}P NMR analysis showed the disappearance of **1d** and the formation of two products (^{31}P NMR: δ = 13.7; 45%, and 14.7; 55%). After filtration and evaporation of MeOH, $CHCl_3$ (30 mL) was added, the solution was washed with water until neutral, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product (mixture of **2d** and **2e**) was separated by repetitive crystallization from benzene/hexane. A single pure product **2d** was obtained in 30% yield; mp 163.5–165°C.

2d:

^{1}H NMR: δ = 3.32–3.46 (3H, m, 3CHN), 3.53–3.66 (5H, m, 3CHN, CH_2Cl), 3.60 (3H, s, OCH_3), 6.29 (1H, d, J_{HP} = 8.1 Hz, NH), 6.66 (2H, d, J_{HH} = 8.9 Hz, 2 *o*-H_{An}), 6.77 (2H, d, J_{HH} = 8.6 Hz, 2 *m*-H_{An}), 6.93 (1H, t, J_{HH} = 6.8 Hz, *p*-H_{Ph}), 7.17–7.27 (4H, m, 2 *o*-, 2 *m*-H_{Ph}).

^{13}C NMR: δ = 42.4 (d, J_{CP} = 4.2 Hz, CH_2Cl), 43.5 (d, J_{CP} = 13.1 Hz, CH_2N), 44.1 (d, J_{CP} = 12.3 Hz, CH_2N), 46.6 (d, J_{CP} = 5.1 Hz, CH_2N), 55.3 (OCH_3), 114.3 (*o*-C_{An}), 115.9 (d, J_{CP} = 4.7 Hz, *o'*-C_{Ph}), 121.4 (*m*-C_{An}), 121.9 (*p*-C_{Ph}), 129.0 (*m*-C_{Ph}), 132.4 (*ipso*-C_{An}), 141.2 (d, J_{CP} = 6.3 Hz, *ipso'*-C_{Ph}), 155.5 (*p*-C_{An}).

^{31}P NMR: δ = 14.76.

MS: m/z = 367, 365 (2.3, 6.3%, M^+), 316 (25.6%, $M^+ - CH_2Cl$), 177 (100%, $C_{10}H_{13}N_2O$).

Analysis ($C_{17}H_{21}ClN_3O_2P$): C, 55.86; H, 5.79; N, 11.49. Found C, 55.50; H, 5.85; N, 11.20.

Bicyclic Triamidates 3; General Procedure:

A solution of cyclic phosphoramidate **2** in benzene (7 mL per mmol of **2**) was added dropwise with stirring to a suspension of NaH (2 mol equiv) and Bu_4NBr (5 mol%) in the same volume of benzene at r.t. The mixture was stirred at r.t. for 6 h, filtered and the filtrate was washed with water until the aqueous layer was neutral. The benzene solution was dried (Na_2SO_4), evaporated under reduced pressure, and the crude product was purified by crystallization from benzene/hexane.

1-Oxo-2,8-diphenyl-2,5,8-triaza-1-phosphabicyclo[3.3.0]octane (**3a**):

Reaction time: 6 h; yield 90%; mp 148–149.5°C.

^{1}H NMR: δ = 3.15 (2H, m, J_{HP} = 11.3 Hz, J_{HH} = 14.6, 6.4, 3.1 Hz, 2CHN), 3.65 (2H, m, 2CHN), 3.74 (2H, m, 2CHN), 3.89 (2H, m, 2CHN), 6.93 (2H, m, 2 H_{arom}), 7.22 (8H, m, 8 H_{arom}).

^{13}C NMR: δ = 48.0 (d, J_{CP} = 7.0 Hz, NCH_2), 49.0 (d, J_{CP} = 19.5 Hz, $PhNCH_2$), 118.9 (d, J_{CP} = 3.4 Hz, *o*-C_{arom}), 122.2 (*p*-C_{arom}), 128.9 (*m*-C_{arom}), 142.0 (*ipso*-C_{arom}).

Additional NOE and COSY experiments confirmed the assignments of the signals.

^{31}P NMR: δ = 33.50.

MS: m/z = 300, 299 (10.4, 52.5%, M^+), 195, 194 (13.1, 75.6%, $M^+ - PhNCH_2$), 105 (75.2%, $PhNCH_2^+$), 77 (99%, Ph^+), 28 (100%, C_2H_4).

Analysis ($C_{16}H_{18}N_3OP$): C, 62.21; H, 6.02; N, 14.02. Found C, 62.21; H, 6.04; N, 13.94.

2,8-Bis(4-methoxyphenyl)-1-oxo-2,5,8-triaza-1-phosphabicyclo-[3.3.0]octane (**3b**):

Reaction time: 5 h; yield: 92%; mp 168–169.5°C.

^{1}H NMR: δ = 3.12 (2H, m, J_{HP} = 11.1 Hz, J_{HH} = 14.2, 6.2, 3.3 Hz, 2CHN), 3.58 (2H, m, 2CHN), 3.85 (2H, m, 2CHN), 3.71 (6H, s, $2OCH_3$), 3.73 (2H, m, 2CHN), 6.71 (4H, d, J_{HH} = 8.9 Hz, 4 *m*-H_{arom}), 7.05 (4H, d, J_{HH} = 8.9 Hz, 4 *o*-H_{arom}).

^{13}C NMR: δ = 48.0 (d, J_{CP} = 6.9 Hz, NCH_2), 49.5 (d, J_{CP} = 19.8 Hz, $AnNCH_2$), 55.5 (OCH_3), 114.4 (d, J_{CP} = 5.2 Hz, *m*-C_{arom}), 120.9 (*o*-C_{arom}), 135.1 (*ipso*-C_{arom}), 155.2 (*p*-C_{arom}).

Additional NOE and COSY experiments confirmed the assignments.

^{31}P NMR: δ = 34.07.

MS: m/z = 359 (100%, M^+), 344 (12.6%, $M^+ - CH_3$), 224 (77.1%, $M^+ - AnNCH_2$), 135 (11.0%, $AnNCH_2^+$).

Analysis ($C_{18}H_{22}N_3O_3P$): C, 60.17; H, 6.13; N, 11.70. Found C, 60.40; H, 6.19; N, 11.61.

8-(4-Methoxyphenyl)-1-oxo-2-phenyl-2,5,8-triaza-1-phosphabicyclo-[3.3.0]octane (**3c**):

Reaction time: 5 h; yield 94%; mp 126.5–128°C.

^{1}H NMR: δ = 3.13 (2H, m, 2CHN), 3.65 (4H, m, 4CHN), 3.73 (3H, s, OCH_3), 3.86 (2H, m, 2CHN), 6.75 (2H, d, J_{HH} = 8.5 Hz, 2 *m*-H_{arom}), 6.89 (1H, t, J_{HH} = 7.8 Hz, *p*-H_{Ph}), 7.06 (2H, d, J_{HH} = 8.0 Hz, 2 *o*-H_{Ph}), 7.14 (4H, m, 4 H_{arom}).

^{13}C NMR: δ = 47.7 (d, J_{CP} = 7.1 Hz, NCH_2), 48.0 (d, J_{CP} = 7.7 Hz, NCH_2), 48.4 (d, J_{CP} = 20.2 Hz, NCH_2), 50.2 (d, J_{CP} = 20.0 Hz, NCH_2), 55.5 (q, J_{nc} = 143.2 Hz, OCH_3), 114.4 (*m*-C_{An}), 118.0 (*m*-C_{Ph}), 121.7 (*p*-C_{Ph}), 122.2 (*o*-C_{An}), 128.9 (*m*-C_{Ph}), 134.9 (*ipso*-C_{An}), 141.9 (*ipso*-C_{Ph}), 155.6 (*p*-C_{An}).

Additional proton-coupled ^{13}C NMR, NOE and COSY experiments confirmed the structure.

^{31}P NMR: δ = 33.87.

MS: m/z = 329 (M^+, 100%), 314 ($M^+ - CH_3$, 9.6%), 224 ($M^+ - PhNCH_2$, 42.6%), 194 ($M - AnNCH_2$, 46.1%), 135 ($AnNCH_2^+$, 37.6%), 105 ($PhNCH_2^+$, 8.9%).

Analysis ($C_{17}H_{20}N_3O_2P$): C, 62.01; H, 6.08; N, 12.76. Found C, 61.95; H, 6.12; N, 12.57.

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