CHAPTER 2

2. N-ALKYL DERIVATIVES OF 1-OXO-2,8-DISUBSTITUTED-2,5,8-TRIAZA-1λ^5-PHOSPHABICYCLO[3.3.0]OCTANE

2.1 Introduction

The study on the bicyclic substrates **3** was extended to substrates substituted at the 2,8-nitrogen atoms with aliphatic groups, such as: R= Me, Et, $PhCH_2$. Of particular interest was the acid-catalyzed solvolysis of *N,N*-dialkyl derivatives **3**.

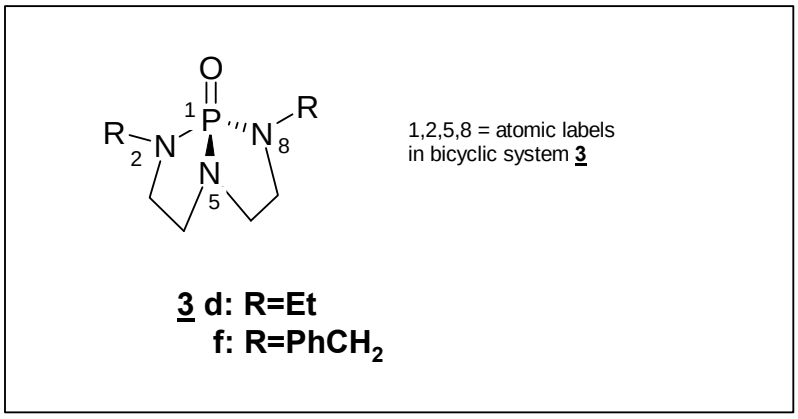


Figure 2.1 General structure of the bicyclic system.

For the *N*-aromatic substrates the observed selectivity of acidic cleavage of the P-N(5) bond was explained in terms of the higher basicity of the bridgehead nitrogen atom (see Chapter 1). In the *N*-aliphatic compounds the basicity of all three nitrogen atoms should be comparable, because all three nitrogen atoms are, apart from the involvement in the P-N bond, bonded to two aliphatic carbon atoms. These differences should have significant effects on the selectivity and the rate of the alcoholysis reaction as well as the **5** → **6** rearrangement.

2.2 Results and discussion

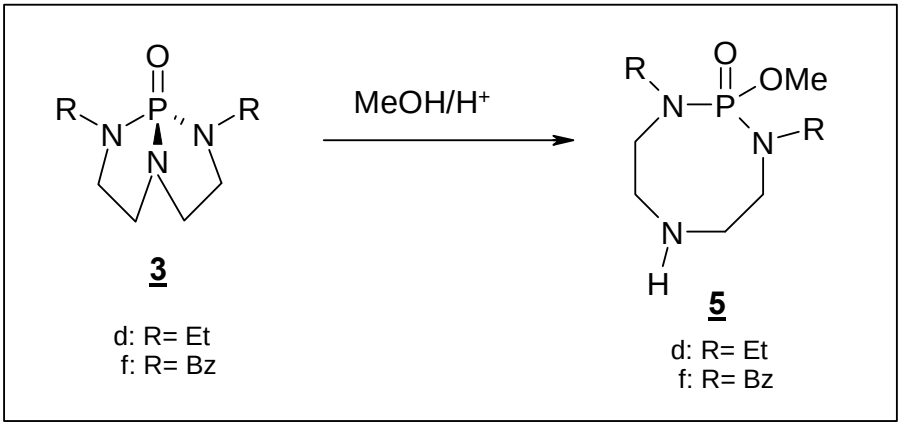
The preparation and the isolation of the *N*-alkyl derivatives of the bicyclic system **3** and their precursors proved to be much more difficult than of those with *N*-aryl substituents.

The pure 2,8-diethyl derivative, **3d** was prepared successfully. Although its immediate precursor was never isolated, it could be detected by ^{31}P NMR spectroscopy. In this case the first and second cyclizations proceeded with comparable rates which complicated the isolation of the intermediate products. All attempts to prepare the Me substituted derivative **3e** failed. Its immediate precursor, the triazaphospholidine **2e** , was isolated in a pure state and could be prepared in large quantities. The second cyclization was however unsuccessful under a variety of conditions. The benzyl derivative **3f** was prepared as a spectroscopically pure compound, but the reaction was difficult to reproduce. The yields varied between experiments. The *N*-alkyl derivatives of **3** were isolated as viscous oils and attempts to prepare crystals suitable for x-ray diffraction were unsuccessful.

2.2.1 Acid catalyzed alcoholysis

As with the 2,8-*N*-aryl derivatives, both *N*-alkyl substituted substrates reacted with the HCl-containing methanol according to the reaction shown in (**Scheme 2.1**), yielding the corresponding salts of the products[1] **5d** and **5f**.

The regioselectivity of the alcoholysis of the *N*-aryl substituted derivatives was explained in terms of the basicity of the different nitrogen atoms. In the *N*-alkyl derivatives all the amide nitrogen atoms carry only alkyl substituents and should not differ much in basicity. ^{15}N NMR studies of the P-N bonding in cyclic amides demonstrated however that the endocyclic nitrogen is always more shielded than the exocyclic nitrogen atom[2]. Following the arguments developed in an important contribution from Von Philipsborn and Müller[3], our NMR results suggest that the



Scheme 2. 1 Acid catalyzed methanolysis of **3**.

nitrogen incorporated into the ring should always be more basic, therefore the bridgehead N atom in compounds **3d** and **3f** should be more basic than the other two nitrogen atoms, each located in a single phospholidine ring. However, if the observed selectivity for **3d** (R=Et) and **3f** (R=$PhCH_2$) depended only on the basicity of the different nitrogens, it would require a pK_a difference of as much as approximately two units between the bridgehead nitrogen and the other two nitrogens. It has to be remembered, however, that in the pentacoordinate intermediate (the transition state) of the substitution, the location of the bridgehead N(5) atom is in the favourable apical position (apical departure). It seems therefore that the selectivity of the acid alcoholysis of all substrates **3** is determined by both the pre-equilibrium protonation step and by stereoelectronic effects.

2.2.2 Base catalyzed alcoholysis

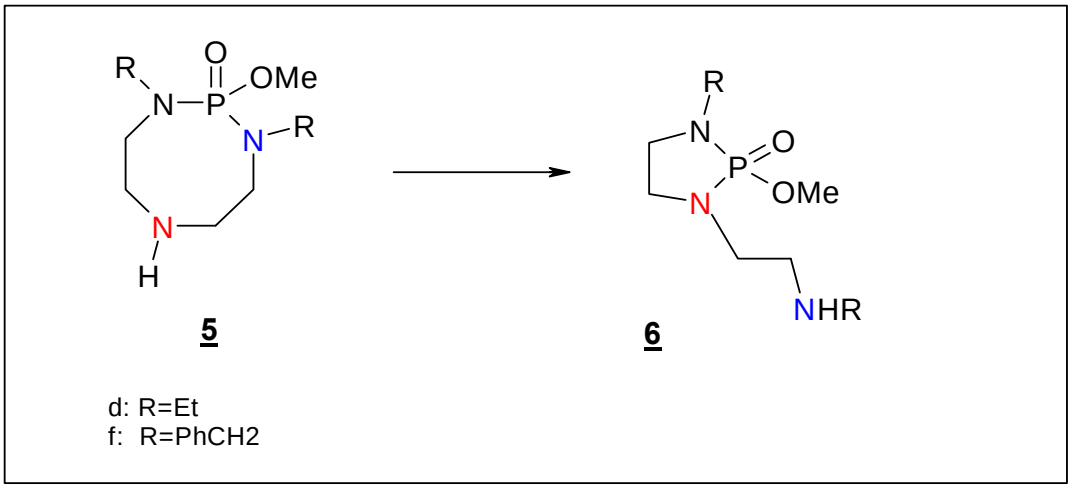
Both prepared *N*-alkyl substrates **3d** and **3f** yielded exclusively the eight-membered cyclic products in the base-catalyzed methanolysis, the same as the products obtained from methanolysis in the presence of HCl. This result suggests that the cleavage of the P-N bond by MeO^-, follows a mechanism 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. The difference between the *N*-

aryl and *N*-alkyl substrates was also observed for their reactivity in the related **5**→**6** rearrangement (see 2.3.3).

2.2.3 Rearrangement of the alcoholysis product

Both *N,N'*-dialkyl substituted compounds **5d** and **5f** rearranged to compounds **6d** and **6f**, but much slower than in the *N,N'*-diaryl analogues. [**Scheme 2.2**]

The rearrangement reaction was much less clean for *N*-alkyl than for the *N*-aryl derivatives. Additional signals to those of the rearrangement products appear in the ^{31}P NMR spectrum at higher conversions. In agreement with the trend observed for the *N*-aryl substrates, **5d** (R=Et) was found to be *ca.* five times less reactive than **5a**. The rearrangement of **5f** (R=PhCH$_2$) was very slow and the reaction did not allow us to isolate and characterize the product **6f**.



Scheme 2.2 Base catalyzed rearrangement of compound **5**.

In the first experiment (**entry 5, Table 2.1**) **3f** was used as a precursor for **5f**. When **3f** was dissolved in MeOH containing NaOMe, it solvolized relatively fast to **5f**; after four days the solution contained no **3f**, 98% of **5f** and 2% of the product **6f**. The **5**→**6** interconversion yielded very slowly the final product with an approximate half-life of 960 hours. In the absence of the base (MeO$^-$) the rearrangement was too slow to allow any rate determination.

Entry	Substrate	Product	Conditions	$K_1/10^{-5}$ s^{-1}	$t_{½}$/h
1	**5a'**	**6a'**	Refluxing THF (internal temp. 62 °C). Reaction followed to ca. 85% conversion. $[5a']_0$ (M) = (i) 0.03 (ii) 0.015 M (iii) 0.0075	4.8 ± 0.04 4.5 ± 0.2 3.8 ± 0.08	4.0 4.3 5.1
2	**5a** **5b** **5c**	**6a** **6b** **6c**	Refluxing THF (internal temp. 62 °C). Reaction followed to ca. 90% conversion. $[5a]_0$ = 0.050 M	8.9 ± 0.3 3.2 ± 0.1 6.1 ± 0.2	2.2 6.0 3.2
3	**5a**	**6a**	$CDCl_3$, room temp. $[5a]_0$=0.033 M	[a]	ca. 1200
	5a·HCl	**6a**	$CDCl_3$, room temp. , excess of anhydrous K_2CO_3 $[5a·HCl]_0$=0.033 M	[a]	ca. 740
	5a·HCl	**6a**	$CDCl_3$and 1.1 mole-equiv. Et_3N, room temp., $[5a·HCl]_0$=0.033 M	[a]	ca. 160
	5c	**6c, 6c'**	$CDCl_3$, room temp. Reaction followed to ca. 38% conversion $[5c]_0$=0.022 M	[a]	ca. 3000
4	**5d**	**6d**[b]	Refluxing THF (internal temp. 62 °C). Reaction followed to ca. 55% conversion.[c] $[5d]_0$=0.050 M	1.9 ± 0.2	ca. 10
	5d	**6d**[b]	$CDCl_3$, room temp. Reaction followed to ca. 18% conversion. $[5d]_0$=0.050 M	[a]	ca.10500
5	**5f**	**6f** [b]	In MeOH-MeONa from 3f, room temp; $[3f]_0$=0.020 M	[a]	ca.960
	5f	**6f** [b]	Refluxing THF (internal temp. 62 °C). Reaction followed to ca. 60% conversion[d]. $[5f]_0$=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. [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 the reaction.

Table 2.1 Rate data for rearrangement **5** → **6** for *N*-aryl and *N*-alkyl derivatives.

When the free base of **5f** was subjected to the rearrangement, the conversion to the product was accompanied by the formation of significant quantities of unidentified phosphorus containing products. The obtained k_1 value demonstrates much lower reactivity of **5f** in the rearrangement as compared with the *N,N'*-diaryl and *N,N'*-diethyl analogues.

For the *N,N'*-dialkyl substituted compounds, the rearrangement reaction is much more complex and the structure-reactivity relationship is much less clear than for the *N,N'*-aryl derivatives. The experimental difficulties and the more complex behavior of the *N,N'*-dialkyl derivatives made us to decide not to investigate these compounds further than the experiments discussed above, but, instead, to turn our attention to other, related systems.

2.3 Experimental

Solvents and commercially available substrates were purified by conventional methods immediately before use. Melting points were uncorrected. For column chromatography Merck Kieselgel 60 (0.063-0.200) was used as stationary phase. Mass spectra were recorded on a Varian MAT-212 double focussing 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 (^{1}H, δ 7.24; ^{13}C, δ 77.0). ^{31}P NMR chemical shifts are given relative to 85% H_3PO_4 as external standard.

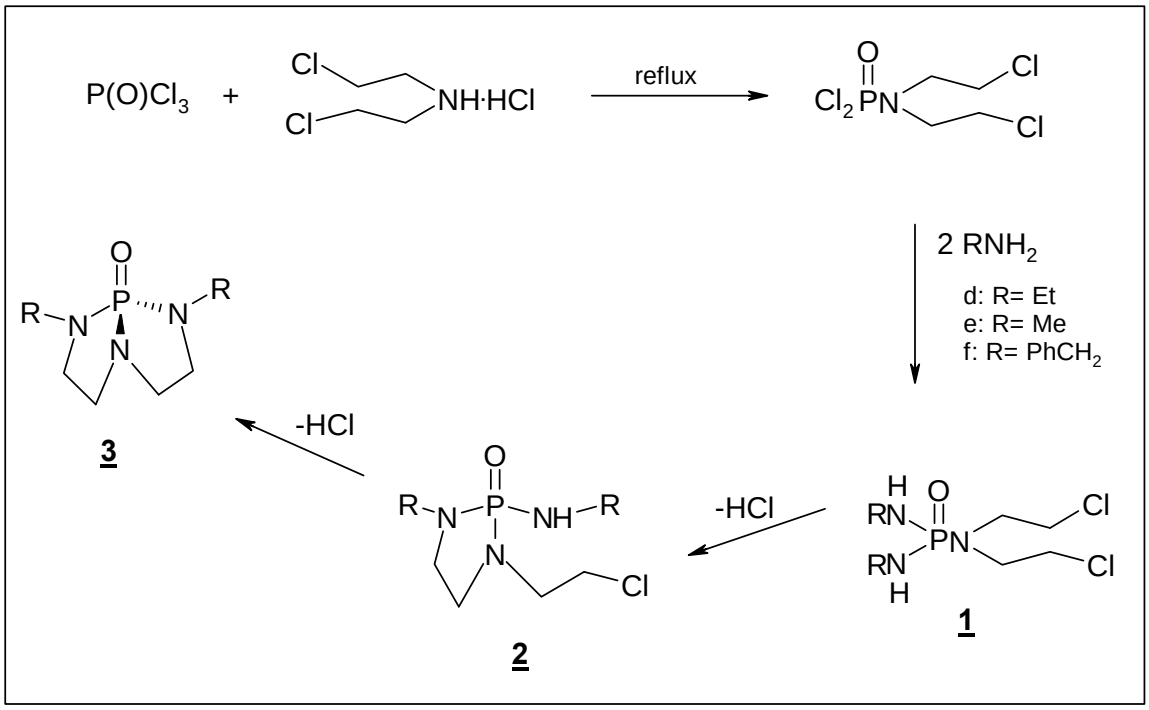
Preparation of substrates

The aliphatic derivatives were prepared via the same route as used for the *N*-aryl derivatives (**Scheme 2.3**)

***N,N*-Bis(2-chloroethyl)phosphoramidodichloride, 0**

The synthetic procedure was reported before[4].

90% yield, bp. 120-138 °C (~1mmHg), δ_P 18.0, Lit.: 94% yield, bp 98-99 °C (0.05 Torr), δ_P 13.1.



Scheme 2.3 Reaction pathway to prepare the bicyclic compound **3**.

N,N-Bis(2-chloroethyl)-*N',N"*-dibenzylphosphoric triamide, 1f

A solution of *N,N*-Bis(2-chloroethyl)phosphoramidodichloride (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 ethereal 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. Colourless crystals, 0.385 g (97%); mp 83-85 °C.

δ_P 17.5;

δ_H 2.77 (2H, br dt, $^2J_{HP}$ 9.0, $^3J_{HH}$ 6.6),
3.60 (4H, t, $^3J_{HH}$ 6.7),
4.06-4.15 (4H, m),
7.22-7.34 (10H, m)

Elemental Analysis: $C_{18}H_{24}Cl_2N_3OP$ Calculated: C, 54.01; H, 6.04; N. 10.58%.
Found: C, 53.75; H, 6.24; N, 10.18%.
The structure of the product was confirmed by X-ray diffraction.

3-(2-Chloroethyl)-2-oxo-2-benzylamino-1-benzyl-1,3,2λ^5-diazaphospho-lidine, 2f

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^{t}OK (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 extracted with ether (2 ×120 ml). The ethereal solution was dried ($MgSO_4$), evaporated under reduced pressure and the crude product was purified by column chromatography (ethanol). The 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)

Elemental Analysis: $C_{18}H_{23}ClN_3OP$ requires: C, 59.42;H, 6.37;N, 11.55%.
Found: C, 59.04; H, 6.86; N, 10.92%

1-Oxo-2,8-dibenzyl-2,5,8-triaza-1λ^5-phosphabicyclo[3.3.0]-octane (3f).

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). The pure compound was obtained as a slightly grayish 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)

Elemental Analysis: $C_{18}H_{22}N_3OP{\cdot}H_2O$ requires: C, 62.60;H, 7.00:N, 12.17%
Found: C, 61.62;H, 6.98;N, 11.58%.

***N,N*-Bis(2-chloroethyl)-*N',N"*-dimethylphosphoric triamide (1e).**

A solution of *N,N*-Bis(2-chloroethyl)phosphoramidic dichloride (1.00 g, 3.90 mmol) in ether (5 ml) was aded 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 2.31b (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 (2e) .

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), 3.09-3.028 (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).

***N,N*-Bis(2-chloroethyl)-*N',N"*-diethylphosphoric triamide (1d)**

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 ºC. The mixture was kept at –80 ºC for 2h 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 ºC.

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)

Elemental Analysis: $C_8H_{20}Cl_2N_3OP$ Calculated: C, 34.80; H, 7.30;N, 15.22%
Found: C, 34.55; H, 7.35; N, 15.18%

3-(2-Chloroethyl)-2-oxo-2-ethylamino-1-ethyl-1,3,2λ^5-diazaphospholidine (2d).

This compound was never isolated and characterized, but its formation and disappearance during the preparation of "bicyclic" **3d** 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 (3d).

A mixture of the phosphoric triamide described above (1.00 g, 3.6 mol), NaH (prewashed with benzene, 0.400g 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) afford pure **3d** (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)

Elemental analysis: $C_8H_{18}N_3OP{\cdot}H_2O$ requires: C, 44.08; H, 9.11; N, 18.76%
Found: C, 43.43; H, 9.11; N, 18.99%.

1-Oxo-1-methoxy-2,8-dibenzyl-2,5,8-triaza-1λ^5-phosphacyclooctane (5f).

Hydrochloride salt: A solution of **3f** (0.33g,1.23 mmol) in MeOH (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 **3f**. Reaction time was about 20h. The acidity of the solution (pH= 4-5) was adjusted by the occasional addition of small volumes of methanolic HCl. MeOH was removed under reduced pressure and the hydrochloride salt (**5·HCl)** was isolated and characterized. White solid (96%), purified by crystallization from $CHCl_3$ –benzene (1:1), mp 250.4-256.0 ºC.

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), 7.24-7.40 (10H,m), 9.98 (2H, br s)

Elemental analysis: $C_{19}H_{27}ClN_3O_3P$ requires: C, 57.65; H, 6.87; N, 10.61%
Found: C, 57.94; H, 7.10; N, 10.07%.

Free base **5f':** The salt were then converted to the free base **5f'.** Anhydrous K_2CO_3 (0.69 6, 5.0 mmol) was added to a solution of **5f·HCl** (0.180g, 0.5 mmol) in $CHCl_3$ (20 ml) and the mixture was stirred vigorously at room temperature for 24 h. After filtration, the solution was washed three times with water (3 × 5 ml),

dried (Na_2SO_4) and the solvent evaporated under reduced pressure. **5f'** was obtained as an 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 (5d).

Hydrochloride salt. Prepared as for **5f**; reaction time 30 minutes. 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, **5d**·*PicH.* The **5d**·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 ºC for 10 min. and cooled. The precipitate was filtered off, washed with EtOH and dried. Yellow crystals (0.100 g, 81%), mp 144 ºC.

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)

Elemental analysis: $C_{15}H_{25}N_6O_9P$ requires: C, 38.80; H, 5.43; N, 18.06%
Found: C, 38.70; H, 5.51; N, 17.90%.

Free base of 5d.

Substrate **3d** (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), $t_{½}$ *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 **5d'** (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)

Alternative preparation of hydrochloride salts 5d and 5f; general procedure

To a solution of **3** (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 **5·HCl** (100%). The products were sufficiently pure not to require further purification.

2.4 References

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