# Synthesis and steric structure of pyrrolidine- and piperidine-fused 1,3,4,2-oxadiazaphosphinanes

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**Dedicated to Prof. Lutz Tietze on the occasion of his 65th birthday**

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## Abstract

Pyrrolidine- and piperidine-fused 1,3,4,2-oxadiazaphosphinane 2-oxides were prepared by cyclization of the corresponding pyrrolidine- and piperidine-hydrazino alcohols by using phosphorus-containing reagents. Stereochemical and conformational analyses were carried out in order to determine the effect of the ring size on the conformational behavior of the nitrogen-bridged bicyclic system. It was found that the chair conformation in the pyrrolidine-fused 1,3,4,2-oxadiazaphosphinane 2-oxides can be shifted toward twisted or distorted conformations.

**Keywords:** 1,3,4,2-Oxadiazaphosphinanes, conformation

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## Introduction

1,3,2-O,N,P heterocycles have attracted great interest due to their valuable pharmacological effects and potential for synthetic applications.[1] The 1,3,2-oxazaphosphinane ring system is found in alkylating anticancer drugs (cyclophosphamide and ifosfamide), numerous derivatives of which have been prepared to determine their structure–activity relationships.[2] Compounds containing a 1,3,2-oxazaphosphinane moiety were recently reported to possess matrix metalloproteinase-inhibitory,[3] pesticidal[4] and antimicrobial[5] activities. Phosphorus-stabilized carbanions derived from chiral 1,3,2-oxazaphosphinane 2-oxides have been widely used in the diastereoselective formation of carbon–carbon bonds.[6]

In contrast with the thoroughly investigated 1,3,2-oxazaphosphinane 2-oxide derivatives, less attention has been paid to the preparation and transformations of the corresponding 1,3,4,2-oxadiazaphosphinane 2-oxides, containing an additional nitrogen atom in the heterocyclic ring.[7-10] The first representatives of this ring system were prepared with the aim of identifying potential antitumor agents. However, despite the close structural analogy, cyclophosphamide-

analog 1,3,4,2-oxadiazaphosphinane 2-oxides, and the homologous 1,3,4,2-oxadiazaphosphepine 2-oxides, exhibit negligible anti-leukemic activity.[9,10] There has been only one conformational investigation of this ring system: 4-methyl-2-phenoxy-1,3,4,2-oxadiazaphosphinane 2-oxide attains predominantly the chair conformation, with the P=O group occupying an axial position.[8]

As a follow-up of our stereochemical studies on 1,2,3,4-tetrahydroisoquinoline-condensed 1,3- and 1,2,3-heterocycles,[11] and on 1,3,4,2-oxadiazaphosphinane 2-oxides attached angularly or linearly to the tetrahydroisoquinoline ring,[12] we set out to prepare 1,3,4,2-oxadiazaphosphinane 2-oxides condensed with pyrrolidine and piperidine rings in order to investigate the effects of the substituents and the configurations of the substituted atoms on the predominant conformations of the nitrogen-bridged bicyclic systems.

## Results and Discussion

### Synthesis

The hydrazino alcohols **3** and **4** required for the synthesis of the 1,3,4,2-oxadiazaphosphinane derivatives were prepared from the corresponding amino alcohols **1** or **2**, the *N*-nitroso derivatives of which were reduced with LiAlH$_4$ according to literature procedures[13,14] (Scheme 1).



n = 1: **3**
n = 2: **4**

**1**                                                        **2**
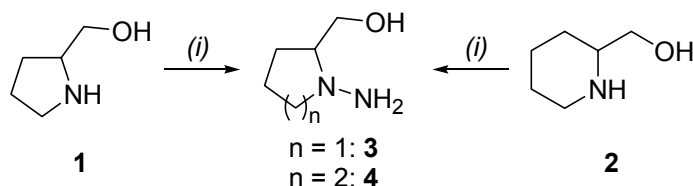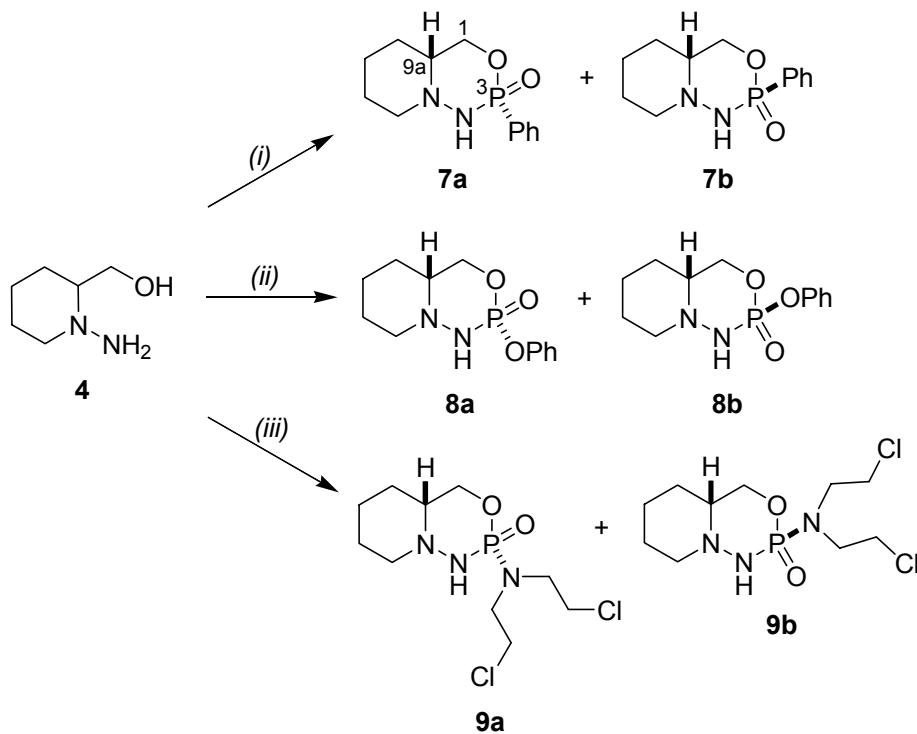
Reagents and conditions: *(i)*: see ref. 13.

**Scheme 1**

The cyclizations of compounds **3** and **4** with phenylphosphonic dichloride, phenyl dichlorophosphate and bis-(2-chloroethyl)phosphoramidic dichloride were performed at ambient temperature by using a procedure similar to that described earlier[12] resulting in 1,4,6,7,8,8a-hexahydropyrrolo[1,2-*d*][1,3,4,2]oxadiazaphosphinine 3-oxides **5** and **6** and 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*d*][1,3,4,2]oxadiazaphosphinine 3-oxides **7**, **8** and **9**, respectively (Schemes 2 and 3).
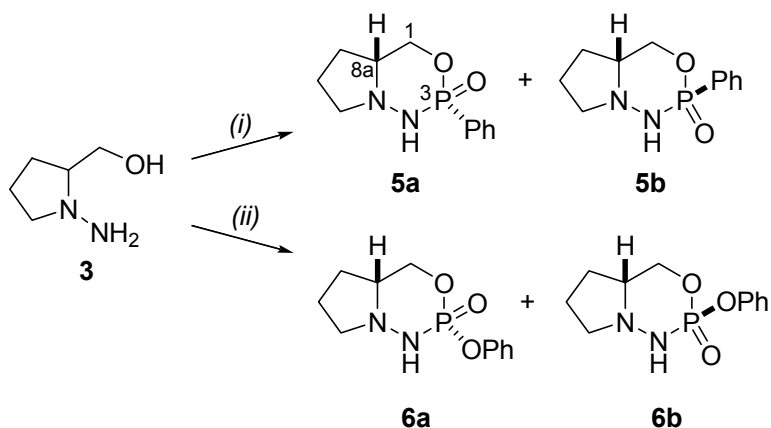
Reagents and conditions: *(i)*: PhPOCl$_2$, Et$_3$N, THF, R.T., 2 days, then column chromatography, 12% **(5a)**, 10% **(5b)**; *(ii)*: PhOPOCl$_2$, THF, R.T., 2 days, then column chromatography, 17% **(6a)**, 13% **(6b)**.

**Scheme 2**



Reagents and conditions: *(i)* and *(ii)*, see ref. 12; *(iii)* (ClCH$_2$CH$_2$)$_2$NPOCl$_2$, Et$_3$N, THF, R.T., 2 days, then column chromatography, 26% **(9a)**, 26% **(9b)**.

**Scheme 3**

In each case, two diastereomers (**a** and **b**) differing in the configuration of the phosphorus atom were formed; they were separated by column chromatography. No significant differences in the reactivities of the pyrrolidine- and piperidine-hydrazino alcohols or in the stabilities of the ring-closed, homologous products were observed in the reactions.

**Structure characterization**

The conformational behavior of the nitrogen-bridgehead saturated bicyclic 1,3,4,2-oxadiazaphosphinanes (**5-9**) can be described by an equilibrium of $cis^1$–$trans$–$cis^2$ type.[15] In the $trans$ structure, the A/B hetero rings are $trans$-connected, with a $trans$-diaxial arrangement of the hydrogen at the annelation (H-an) and the nitrogen lone pair. In the two other configurations, the hetero rings are $cis$-connected: for the $cis^1$-conformation, C-1 is in the inside, while for the $cis^2$ conformation, it is in the outside position (Figure 1). The phosphorus-containing 1,2,3-heterocycles are prone to participate in a conformational equilibrium involving chair, twisted chair and other distorted conformations.[1,16]
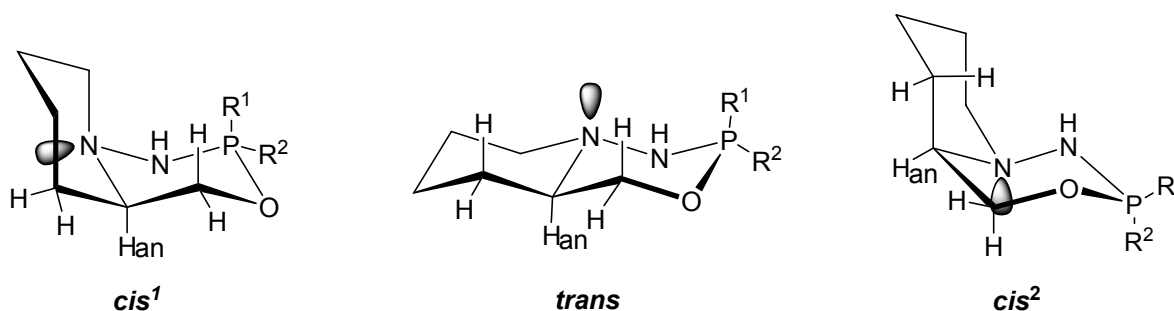


**Figure 1.** Possible ring connections of 1,6,7,8,9,9a-hexahydro-4$H$-pyrido[1,2-$d$][1,3,4,2]oxa-diazaphosphinanes.

The stereochemistry of the model compounds was determined in two steps. First, the predominant conformation was assigned on the basis of the characteristic $^3J$ couplings and NOE interactions. Second, the relative configuration of the P-phenyl substituent was observed by using the NOEs from the P-phenyl group to H-an (where applicable) and/or the significant differences in the chemical shifts for certain indicator nuclei.

The orientations of H-an (H-9a for **9**; H-8a for **5** and **6**) and the protons connected to the carbons adjacent to the annelation (H-1 and H-X; H-X: H-9 for **9**; H-8 for **5** and **6**) or the protons connected to the carbons adjacent to the nitrogen bridge (H-6) were assigned by using the vicinal coupling constants (Table 1) and the characteristic NOESY cross-peaks.

The data in Table 1 show that H-an has two high vicinal couplings to the axial protons connected to the carbons adjacent to the annelation indicating that H-an is in an axial position and the hetero rings are $trans$-connected. The NOESY cross-peaks detected for H-an and H-6$_{ax.}$ corroborate the $trans$-connection of the hetero rings for all the compounds. The considerably lower $^3J$(H-1$_{eq.}$–P) values for **5b** and **6b** indicate significant conformational flexibility in the

oxadiazaphosphinane ring attached to the five-membered rings, potentially leading to the presence of twist and/or distorted conformations.

**Table 1.** Characteristic vicinal coupling constants, in Hz [a]

| $^3J$ (Hz) | H-1$_{ax.}$ –H-an | H-1$_{eq.}$ –H-an | H-X$_{ax.}$ –H-an | H-X$_{eq.}$ –H-an | H-1$_{ax.}$ –P | H-1$_{eq.}$ –P |
|---|---|---|---|---|---|---|
| **5a** | 9.8 | 3.3 | 10.3 | 3.0 | 1.8 | 18.1 |
| **5b** | 9.3 | 3.8 | 10.8 | 3.8 | 4.5 | 17.1 |
| **6a** | 10.1 | 3.3 | 10.6 | 3.5 | 1.8 | 19.4 |
| **6b** | 9.8 | 3.8 | 11.1 | 3.8 | 6.3 | 13.1 |
| **9a** | 9.6 | 3.8 | 10.1 | 3.5 | <1 | 18.6 |
| **9b** | 10.6 | 3.3 | 11.3 | 3.3 | <1 | 21.7 |

[a] For the meanings of H-an and H-X, see Figure 1.

As concerns the orientation of the P-substituent, P–R – H-1$_{ax.}$ NOE interactions could readily be detected in **9a**, **6a** and **5a**. It is a trend that H-1$_{ax}$ exhibits a relative downfield shift in compounds containing an axial P=O group (**9b**, **5b** and **6b**), this difference being augmented by the upfield shift of 1-H$_{ax.}$ in **5a** due to the ring current shielding of the axial Ph group (Table 2).

**Table 2**. Characteristic chemical shifts, in ppm ($\delta$ TMS = 0)

|  | H-1$_{ax.}$ | H-1$_{eq.}$ |
|---|---|---|
| **5a** | 3.93 | 4.44 |
| **5b** | 4.54 | 4.42 |
| **6a** | 4.29 | 4.39 |
| **6b** | 4.36 | 4.48 |
| **9a** | 3.92 | 4.16 |
| **9b** | 4.29 | 4.06 |

## Conclusions

Our results show that pyrrolidine- and piperidine-fused 1,3,4,2-oxadiazaphosphinane 2-oxides can conveniently be prepared by cyclization of the corresponding pyrrolidine- and piperidine-hydrazino alcohols with phosphorus-containing reagents (e.g. RPOCl$_2$). The relative stereo-chemistry of the ring junction is *trans* for all the compounds studied. The conformation of the oxadiazaphosphinane ring is chair for **9a** and **9b**, while the five-membered ring allows more flexibility for the phosphorus-containing heterocycles.

## Experimental Section

**General Procedures.**

The NMR spectra were recorded in $CDCl_3$ at 300 K on a Bruker AVANCE DRX 400 spectrometer. Chemical shifts are given in $\delta$ (ppm) relative to TMS as internal standard. Melting points were recorded on a Kofler hot plate microscope apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyzer. Chemicals were generally of highest purity. For column chromatography, Silica gel 60 (0.063-0.200 mm) was used. Merck Kieselgel 60F$_{254}$ plates were used for TLC. The hydrazino alcohols **3** and **4** were prepared according to literature procedures.[13] The syntheses and detailed NMR characterization of 1,3,4,2-oxadiazaphosphinanes **7a**, **7b**, **8a** and **8b** have been published earlier.[12]

**General method for ring-closure reactions.** To a stirred solution of the appropriate amino alcohol (**3** or **4**, 10 mmol) and triethylamine (2 eq.) in 80 mL of dry THF at RT was added dropwise a solution of the appropriate phosphorus-containing reagent (phenylphosphonic dichloride, phenyl dichlorophosphate or bis-(2-chloroethyl)phosphoramidic dichloride, 1 equiv.) in 30 mL of dry THF. The reaction mixture was stirred for 48 hours at RT and then filtered to remove triethylamine hydrochloride. The filtrate was evaporated to dryness.

**3-Phenyl-1,4,6,7,8,8a-hexahydropyrrolo[1,2-*d*][1,3,4,2]oxadiazaphosphinine 3-oxides 5a and 5b.** The crude product (ratio of the isomers 1:1, based on the $^1$H NMR spectrum) was purified by column chromatography, with ethyl acetate/methanol (9:1) as eluent. The more mobile diastereomer was crystallized by evaporation and was filtered from diethyl ether to yield isomer **5a** (0.29 g, 12%) as white crystals, which were recrystallized from diisopropyl ether– ethyl acetate, m.p. 201-204 ºC. $^1$H NMR ($CDCl_3$) $\delta$ 1.15-1.29 (m, 1H, H-8$_{ax}$), 1.68-1.88 (m, 3H, H-8$_{eq}$, H-7), 2.59 (q, 1H, $J$ = 8.6 Hz, H-6$_{ax}$), 2.74-2.82 (m, 1H, H-8a), 3.24 (dt, 1H, $J$ = 3.3, 8.6 Hz, H-6$_{eq}$), 3.93 (dt, 1H, $J$ = 1.8, 10.3 Hz, H-1$_{ax}$), 4.44 (ddd, 1H, $J$ = 3.3, 10.6, 18.1 Hz, H-1$_{eq}$), 4.63 (s, 1H, NH), 7.46 (dt, 2H, $J$ = 3.8, 7.3 Hz, *m*-Ar), 7.52 (dt, 1H, $J$ = 1.5, 7.3 Hz, *p*-Ar), 7.90 (ddd, 2H, $J$ = 1.5, 8.0, 13.6 Hz, *o*-Ar). $^{13}$C NMR ($CDCl_3$) $\delta$ 20.6 (C-7), 24.2 (C-8), 55.2 (C-6), 61.9 (C-8a), 72.9 (C-1), 128.3 (Ar), 128.8 (*m*-Ar), 130.5 (*o*-Ar), 131.7 (*p*-Ar). Anal. Calcd for $C_{11}H_{15}N_2O_2P$: C, 55.46; H, 6.35; N, 11.76. Found: C, 55.77; H, 6.18; N, 11.82.

The less mobile diastereomer was crystallized after the evaporation and was filtered from diethyl ether to yield isomer **5b** (0.24 g, 10%, m.p. 142-146 °C) as white crystals, with **5a** as minor impurity (ca 5:100 by $^1$H NMR). $^1$H NMR ($CDCl_3$) $\delta$ 1.55-1.67 (m, 1H, H-8$_{ax}$), 1.75-2.02 (m, 3H, H-8$_{eq}$, H-7), 2.75 (q, 1H, $J$ = 8.3 Hz, H-6$_{ax}$), 2.87-2.97 (m, 1H, H-8a), 3.49 (dt, 1H, $J$ = 4.0, 8.3 Hz, H-6$_{eq}$), 4.42 (ddd, 1H, $J$ = 3.8, 10.8, 17.1 Hz, H-1$_{eq}$), 4.54 (ddd, 1H, $J$ = 4.5, 9.56, 10.8 Hz, H-1$_{ax}$), 7.49 (dt, 2H, $J$ = 4.0, 7.6 Hz, *m*- Ar), 7.60 (dt, 1H, $J$ = 1.5, 7.6 Hz, *p*- Ar), 7.94 (ddd, 2H, $J$ = 1.5, 8.3, 13.1 Hz, *o*- Ar). $^{13}$C NMR ($CDCl_3$) $\delta$ 20.5 (C-7), 24.8 (C-8),

56.6 (C-6), 62.5 (C-8a), 69.7 (C-1), 126.8 (Ar), 128.4 ($m$- Ar), 132.1 ($o$- Ar), 132.9 ($p$- Ar). Anal. Calcd for $C_{11}H_{15}N_2O_2P$: C, 55.46; H, 6.35; N, 11.76. Found: C, 65.89; H, 6.74; N, 11.31.

**3-Phenoxy-1,4,6,7,8,8a-hexahydropyrrolo[1,2-$d$][1,3,4,2]-oxadiazaphosphinine 3-oxides 6a and 6b.** The crude product (ratio of the isomers 1:2, based on the $^1$H NMR spectrum) was purified by column chromatography with ethyl acetate/$n$-hexane (9:1) as eluent. The more mobile diastereomer was crystallized by evaporation and was filtered from diethyl ether to yield isomer **6a** (0.43 g, 17%) as yellow crystals, which were recrystallized from ethyl acetate, m.p. 160-162 ºC. $^1$H NMR (CDCl$_3$) $\delta$ 1.32-1.46 (m, 1H, H-8$_{ax}$), 1.79-1.94 (m, 3H, H-8$_{eq}$, H-7), 2.62 (q, 1H, $J$= 8.6, H-6$_{ax}$), 2.80 (m, 1H, H-8a), 3.30 (dt, 1H, $J$ = 3.8, 8.6 Hz, H-6$_{eq}$), 4.29 (dt, 1H, $J$ = 1.8, 10.6 Hz, H-1$_{ax}$), 4.39 (ddd, 1H, $J$ = 3.3, 10.6, 19.4 Hz, H-1$_{eq}$), 4.57 (d, 1H, $J$ = 12.8 Hz, NH), 7.16 (t, 1H, $J$ = 7.1 Hz, $p$-Ar), 7.26-7.35 (m, 4H, Ar). $^{13}$C NMR (CDCl$_3$) $\delta$ 20.7 (C-7), 23.7 (C-8), 54.4 (C-6), 60.8 (C-8a), 73.2 (C-1), 120.6 ($m$- Ar), 124.9 ($p$- Ar), 129.5 ($o$- Ar), 150.6 (Ar). Anal. Calcd for $C_{11}H_{15}N_2O_3P$: C, 51.97; H, 5.95; N, 11.02. Found: C, 52.19; H, 5.77; N, 10.89.

The less mobile diastereomer was crystallized by evaporation and was filtered from diethyl ether to yield isomer **6b** (0.33 g, 13%) as yellow crystals, which were recrystallized from ethyl acetate, m.p. 119-123 ºC. $^1$H NMR (CDCl$_3$) $\delta$ 1.66-1.85 (m, 2H, H-8$_{ax.}$, H-7), 1.85-2.01 (m, 2H, H-8$_{eq}$, H-7), 2.94 (m, 1H, H-6$_{ax}$), 3.04 (m, 1H, H-8a), 3.32 (m, 1H, H-6$_{eq}$), 4.36 (dt, 1H, $J$ = 6.3, 11.1 Hz, H-1$_{ax}$), 4.48 (ddd, 1H, $J$ = 3.8, 11.1, 13.1 Hz, H-1$_{eq}$), 7.18 (dt, 1H, $J$ = 1.0, 7.6 Hz, $p$-Ar), 7.22-7.25 (m, 2H, $m$-Ar), 7.34 (dt, 2H, $J$ = 2.5, 7.6 Hz, $o$-Ar). $^{13}$C NMR (CDCl$_3$) $\delta$ 21.2 (C-7), 25.1 (C-8), 57.3 (C-6), 61.2 (C-8a), 70.6 (C-1), 120.9 ($m$- Ar), 125.3 ($p$- Ar), 130.1 ($o$- Ar), 150.6 (Ar). Anal. Calcd for $C_{11}H_{15}N_2O_3P$: C, 51.97; H, 5.95; N, 11.02. Found: C, 51.69; H, 6.07; N, 10.79.

**3-[Bis-(2-chloroethyl)amino]-1,6,7,8,9,9a-hexahydro-4$H$-pyrido[1,2-$d$][1,3,4,2]oxadiaza-phosphinine 3-oxides 9a and 9b.** The crude product (ratio of the isomers 1:1, based on the $^1$H NMR spectrum) was purified by column chromatography, with ethyl acetate as eluent. The more mobile diastereomer was crystallized after the evaporation and was filtered from diethyl ether to yield isomer **9a** (0.82 g, 26%) as white crystals, which were recrystallized from diisopropyl ether, m.p. 73-76 ºC. $^1$H NMR (CDCl$_3$) $\delta$ 1.08-1.21 (m, 1H, H-9), 1.21-1.34 (m, 1H, H-8), 1.49-1.65 (m, 2H, H-9$_{eq}$, H-7), 1.68-1.79 (m, 2H, H-8$_{eq}$, H-7), 2.28 (1H, dt, $J$ = 2.5, 12.3 Hz, H-6), 2.43 (1H, tt, $J$ = 3.5, 10.1 Hz, H-9a), 3.17 (td, 1H, $J$ = 3.0, 11.3 Hz, H-6$_{eq}$), 3.34-3.53 (m, 2H, H-1'H-2'), 3.69 (2H, t, $J$ = 7.6 Hz, H-3', H-4'), 3.77 (d, 1H, $J$ = 7.1 Hz, NH), 3.92 (ddd, 1H, $J$ = 4.8, 9.6, 11.1 Hz, H-1), 4.16 (ddd, 1H, $J$ = 3.8, 11.1, 18.6 Hz, H-1$_{eq}$). $^{13}$C NMR (CDCl$_3$) $\delta$ 23.1 (C-8), 24.9 (C-7), 27.1 (C-9), 42.5 (C-3'), 49.5 (C-1',C-2',C-4'), 57.7 (C-6), 62.1 (C-9a), 72.8 (C-1). Anal. Calcd for $C_{10}H_{20}Cl_2N_3O_2P$: C, 37.99; H, 6.38; N, 13.29. Found: C, 38.31; H, 6.19; N, 13.44.

The less mobile diastereomer was crystallized by evaporation and was filtered from $n$- hexane to yield isomer **9b** (0.82 g, 26%) as a white solid, which was recrystallized from diisopropyl ether–ethyl acetate, m.p. 150-152 ºC. $^1$H NMR (CDCl$_3$) $\delta$ 1.18-1.36 (m, 2H, H-9, H-8), 1.54-1.60 (m, 1H, H-9$_{eq}$), 1.64-1.78 (m, 3H, H-8, H-7), 2.30 (td, 1H, $J$ = 7.1, 10.1 Hz, H-6$_{ax}$), 2.42 (tt, 1H,

$J$ = 3.3, 10.6 Hz, H-9a), 3.20 (td, 1H, $J$ =3.5, 10.1 Hz, H-6$_{eq}$), 3.35-3.48 (m, 1H, H-1'), 3.48-3.71 (m, 3H, H-2', H-3', H-4'), 4.06 (ddd, 1H, $J$ = 3.3, 11.3, 21.7 Hz, H-1$_{eq}$), 4.29 (dt, 1H, $J$ = 1.3, 11.3 Hz, H-1$_{ax}$). $^{13}$C NMR: $\delta$ 23.0 (C-8), 24.6 (C-7), 25.9 (C-9), 42.5 (C-3'), 48.9 (C-1',C-2',C-4'), 58.5 (C-6), 62.2 (C-9a), 71.4 (C-1). Anal. Calcd for $C_{10}H_{20}Cl_2N_3O_2P$: C, 37.99; H, 6.38; N, 13.29. Found: C, 37.76; H, 6.52; N, 13.37.

## References

1. Kivelä, H.; Zalán, Z.; Tähtinen, P.; Sillanpää, R.; Fülöp, F.; Pihlaja, K. *Eur. J. Org. Chem.* **2005**, 1189 and references cited therein.
2. (a) Colvin, O. M. *Curr. Pharm. Design* **1999**, *5*, 555. (b) Ludeman, S. M. In *From Nerve Agent to Anticancer Drug: The Chemistry of Phosphoramide Mustard*; Torrence, P. F., Ed.; Biomedical Chemistry; Wiley–Interscience: New York, 2000; pp 163-187.
3. (a) Sørensen, M. D.; Blæhr, L. K. A.; Christensen, M. K. *Int. Pat. Appl.* WO 02/06293; *Chem. Abstr.* **2002**, *136*, 118577. (b) Christensen, M. K.; Blæhr, L. K. A. *Int. Pat. Appl.* WO 03/059921; *Chem. Abstr.* **2003**, *139*, 117538.
4. Shipov, A. E.; Genkina, G. K.; Artyushin, O. I.; Mndzhoyan, Z. O.; Gushchin, B. E.; Chumakova, E. I.; Roslavtseva, S. A.; Eremina, O. Y.; Bakanova, E. I.; Kagan, Y. S.; Ershova, E. A.; Mastryukova, T. A.; Kabachnik, M. I. *Russ. Chem. Bull.* **1995**, *44*, 2147.
5. Reddy, P. V. G.; Kiran, Y. B. R.; Reddy, C. S.; Reddy, C. D. *Chem. Pharm. Bull.* **2004**, *52*, 307.
6. (a) Molt, O.; Schrader, T. *Synthesis* **2002**, 2633. (b) Pedrosa, R.; Maestro, A.; Pérez-Encabo, A.; Raliegos, R. *Synlett* **2004**, 1300.
7. (a) Cates, L. A. *J. Heterocycl. Chem.* **1973**, *10*, 111. (b) Cates, L. A.; Li, V.-S.; Basrur, J. P.; Saddawi, B. H.; Alkadhi, K. A. *J. Heterocycl. Chem.* **1985**, *22*, 183.
8. Arshinova, R.; Kraemer, R.; Majoral, J.-P.; Navech, *J. Org. Magn. Reson.* **1975**, *7*, 309.
9. Gadzhiev, G. Y.; Koroteev, M. P.; Budagov, V. A.; Ibragimov, S. I. *Zh. Obshch. Khim.* **1986**, *56*, 2648.
10. Takamizawa, A.; Matsumoto, S.; Iwata, T.; Sakai, S.; Makino, I. *Chem. Pharm. Bull.* **1977**, *25*, 1582.
11. (a) Zalán, Z.; Martinek, T. A.; Lázár, L.; Fülöp, F. *Tetrahedron* **2003**, *59*, 9117. (b) Zalán, Z.; Hetényi, A.; Lázár, L.; Fülöp, F. *Tetrahedron* **2005**, *61*, 5287.
12. Zalán, Z.; Martinek, T. A.; Lázár, L.; Sillanpää, R.; Fülöp; F. *Tetrahedron* **2006**, *62*, 2883.
13. Rosling, A.; Fülöp, F.; Sillanpää, R.; Mattinen, J. *Heterocycles* **1997**, *45*, 95.
14. Zalán, Z.; Lázár, L.; Fülöp, F. *Curr. Org. Chem.* **2005**, *9*, 357.
15. Crabb, T. A. In *Cyclic Organonitrogen Stereodynamics*; Lambert, J. B., Takeuchi, Y., Eds.; VCH: New York, 1992; p 253.
16. Martinek, T.; Forró, E.; Günther, G.; Sillanpää, R.; Fülöp, F. *J. Org. Chem.* **2000**, *65*, 316.