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

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

Introduction

1,3,2-O,N,P heterocycles have attracted great interest due to their valuable pharmacological effects and potential for synthetic applications. 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. Compounds containing a 1,3,2-oxazaphosphinane moiety were recently reported to possess matrix metalloproteinase-inhibitory, pesticidal and antimicrobial 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.

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. 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).

![Scheme 1](image)

Reagents and conditions: (i): see ref. 13.

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): PhPOCl₂, Et₃N, THF, R.T., 2 days, then column chromatography, 12% (5a), 10% (5b); (ii): PhOPOCl₂, THF, R.T., 2 days, then column chromatography, 17% (6a), 13% (6b).

Scheme 2

Reagents and conditions: (i) and (ii), see ref. 12; (iii) (ClCH₂CH₂)₂NPOCl₂, Et₃N, 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. 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.

![cis$^1$](image1.png) ![trans](image2.png) ![cis$^2$](image3.png)

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

The stereochemistry of the model compounds was determined in two steps. First, the predominant conformation was assigned on the basis of the characteristic $^{3} J$ 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 $^{3} J$(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

<table>
<thead>
<tr>
<th></th>
<th>H-1 ax. –H-an</th>
<th>H-1 eq. –H-an</th>
<th>H-X ax. –H-an</th>
<th>H-X eq. –H-an</th>
<th>H-1 ax. –P</th>
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<tr>
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<td>3.3</td>
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</tr>
<tr>
<td>5b</td>
<td>9.3</td>
<td>3.8</td>
<td>10.8</td>
<td>3.8</td>
<td>4.5</td>
<td>17.1</td>
</tr>
<tr>
<td>6a</td>
<td>10.1</td>
<td>3.3</td>
<td>10.6</td>
<td>3.5</td>
<td>1.8</td>
<td>19.4</td>
</tr>
<tr>
<td>6b</td>
<td>9.8</td>
<td>3.8</td>
<td>11.1</td>
<td>3.8</td>
<td>6.3</td>
<td>13.1</td>
</tr>
<tr>
<td>9a</td>
<td>9.6</td>
<td>3.8</td>
<td>10.1</td>
<td>3.5</td>
<td>&lt;1</td>
<td>18.6</td>
</tr>
<tr>
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<td>11.3</td>
<td>3.3</td>
<td>&lt;1</td>
<td>21.7</td>
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</table>

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-Hax in 5a due to the ring current shielding of the axial Ph group (Table 2).

Table 2. Characteristic chemical shifts, in ppm (δTMS = 0)

<table>
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<tr>
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<th>H-1 ax.</th>
<th>H-1 eq.</th>
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<tr>
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<td>6a</td>
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<td>6b</td>
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<td>9a</td>
<td>3.92</td>
<td>4.16</td>
</tr>
<tr>
<td>9b</td>
<td>4.29</td>
<td>4.06</td>
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</table>

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. RPOCl2). The relative stereochemistry 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 CDCl₃ at 300 K on a Bruker AVANCE DRX 400 spectrometer. Chemical shifts are given in δ (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 60F₂₅₄ 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 ¹H 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 °C. ¹H NMR (CDCl₃) δ 1.15-1.29 (m, 1H, H-8ax), 1.68-1.88 (m, 3H, H-8eq, H-7), 2.59 (q, 1H, J = 8.6 Hz, H-6ax), 2.74-2.82 (m, 1H, H-8a), 3.24 (dt, 1H, J = 3.3, 8.6 Hz, H-6eq), 3.93 (dt, 1H, J = 1.8, 10.3 Hz, H-1ax), 4.44 (ddd, 1H, J = 3.3, 10.6, 18.1 Hz, H-1eq), 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). ¹³C NMR (CDCl₃) δ 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 C₁₁H₁₅N₂O₂P: 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 ¹H NMR). ¹H NMR (CDCl₃) δ 1.55-1.67 (m, 1H, H-8ax), 1.75-2.02 (m, 3H, H-8eq, H-7), 2.75 (q, 1H, J = 8.3 Hz, H-6ax), 2.87-2.97 (m, 1H, H-8a), 3.49 (dt, 1H, J = 4.0, 8.3 Hz, H-6eq), 4.42 (ddd, 1H, J = 3.8, 10.8, 17.1 Hz, H-1eq), 4.54 (ddd, 1H, J = 4.5, 9.56, 10.8 Hz, H-1ax), 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). ¹³C NMR (CDCl₃) δ 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_{2}O_{2}P: 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 °C. $^1$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, $J$ = 3.8, 8.6 Hz, H-1 ax), 4.39 (dd, 1H, $J$ = 3.8, 10.6 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), 132.1 (o-Ar). Anal. Calcd for C_{11}H_{15}N_{2}O_{3}P: 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 °C. $^1$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_{2}O_{3}P: C, 51.97; H, 5.95; N, 11.02. Found: C, 51.69; H, 6.07; N, 10.79.

3-[Bis-(2-chloroethyl)amino]-1,6,7,8,9a-hexahydro-4H-pyrido[1,2-d][1,3,4,2]oxadiazaphosphinine 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 °C. $^1$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_{2}N_{3}O_{2}P: 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 °C. $^1$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-6eq), 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-1eq), 4.29 (dt, 1H, J = 1.3, 11.3 Hz, H-1ax). 13C NMR: δ 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 C10H20Cl2N3O2P: C, 37.99; H, 6.38; N, 13.29. Found: C, 37.76; H, 6.52; N, 13.37.

References