Synthesis and Conformational Study of 1,3,2-Oxazaphosphorino[4,3-*a*]isoquinolines: A New Ring System

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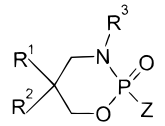
A set of 1,3,2-oxazaphosphorino[4,3-*a*]isoquinolines **6a,b**−**9a,b**, a new ring system, was synthesized, and their stereochemical and conformational analyses were performed by ^{1}H, ^{13}C, and ^{31}P NMR methods. X-ray measurements were also carried out to confirm the stereochemical assignments and conformational results obtained by means of NMR. Intermediate coupling constants ^{3}J(P,H) were found for compounds **7** and **9**; these do not relate to equilibria between previously reported conformers, but are indicative of new distorted conformational states in solution. The connecting isoquinoline and the steric interaction between the aromatic moiety and the Me-1 substituent can block the oxazaphosphorinane ring. The conformational behavior of compounds **6** and **8** was characterized by the usual chair-twist equilibrium.

Introduction

Oxazaphosphorinane derivatives have been compounds of interest for the past 20 years. A number of studies have been carried out on their biological activities and conformational behavior. Their antitumor activity is a valuable property,[1] and the conformational studies were rationalized by the clinical use of oxazaphosphorinane ring-containing compounds. On the other hand, the extreme sensitivity of the conformational behavior of the oxazaphosphorinane ring to the various substituents makes these compounds an excellent model for studies of the steric and electronic effects of functional groups in different positions.

In a series of publications, it was shown that the size of R^{3} and the steric and electronic properties of the substituents Z exert strong effects on the conformational equilibrium of the oxazaphosphorinane ring[2] **1**. Further, the sterically demanding substituents R^{1} and R^{2} (*tert*-butyl or phenyl) are readily able to force the system to occupy a twist conformation.[3] An exhaustive study has been carried out on oxazaphosphorinane derivatives fused with cyclohexane, in which the existence of separate conformations in equilibrium was revealed by low-temperature NMR measurements, because the conformers could be frozen out.[4]



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Fused oxazaphosphorinane ring systems with N-3 in a bridgehead position have also been synthesized with the aim of achieving lower systemic toxicity and greater selectivity, and their conformational properties have been discussed.[5]

Depending on the substituents on N-3, P, and C-5, the oxazaphosphorinane ring tends to occupy a conformational state other than chair. However, the unusual conformational behavior of these rings has been handled in terms of the chair−alternative chair and the chair-twist equilibrium, and the intermediate coupling constants ^{3}J(H,P) were used as unambiguous indicators of possible dynamic processes.[6]

In the present work, we report a systematic conformational study on 1,3,2-oxazaphosphorinane derivatives condensed with isoquinoline, and an example will be given where certain intermediate coupling constants ^{3}J(H,P) need not necessarily be considered indicators of an equilibrium between idealized conformational states.

Results and Discussion

The 1-methyltetrahydroisoquinoline-1-ethanol derivatives **3** and **5** were synthesized in two independent ways.

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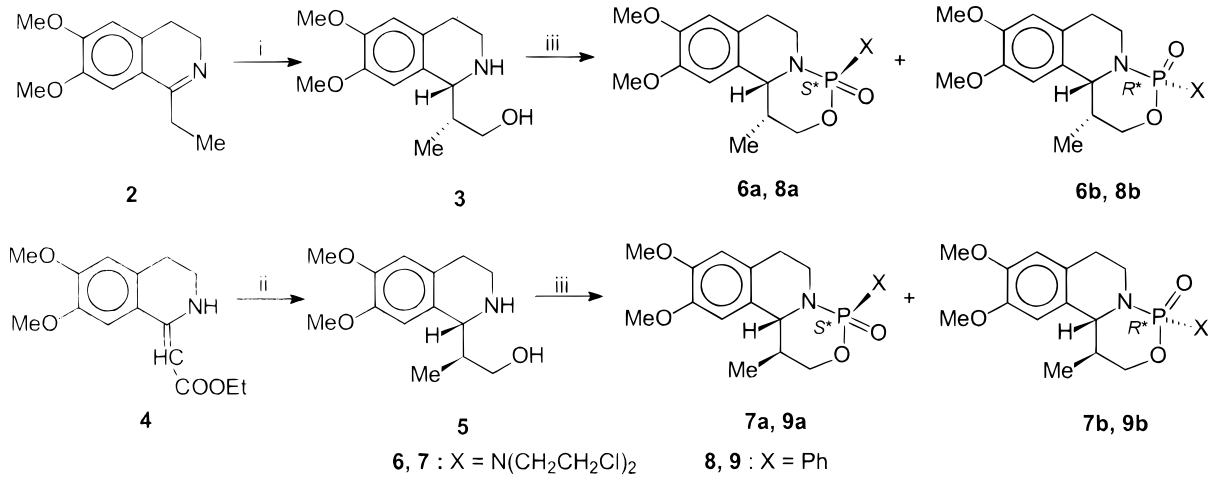
Scheme 1. Synthesis of the Studied Compounds[a]



[a] (i) CH_2O/NaOEt, then $NaBH_4$ and fractional crystallization, 51%; (ii) MeI, then Pt/H_2, then $LiAlH_4$ and fractional crystallization, 44%; (iii) Cl_2OPX/Et_3N or pyridine and column chromatography, 40−45%.

Table 1. Selected Chemical Shifts in $CDCl_3$ (δTMS = 0 ppm, $\delta CHCl_3$ = 77.7 ppm, δH_3PO_4 = 0 ppm)

	H-2eq	H-2ax	H-1	Me-1	H-11b	H-11	H-8	H-7eq	H-7ax	H-6ax	H-6eq	P	C-1	C-2	C-11a
6a	4.19	4.55	2.22	0.91	4.77	6.52	6.63	2.61	2.90	3.01	3.81	10.8	38.1	73.1	59.1
6b	4.16	4.78	2.33	0.89	4.85	6.58	6.60	2.59	2.89	2.89	3.60	16.8	35.1	71.9	59.7
7a	3.88	4.35	2.28	1.01	4.20	6.59	6.67	2.61	3.09	2.94	3.79	13.3	36.9	70.9	62.0
7b	4.10	4.19	2.30	1.23	4.24	6.64	6.71	2.69	2.91	3.15	3.55	13.2	36.7	70.7	61.4
8a	4.24	4.38	2.16	0.95	4.71	6.48	6.63	2.65	2.96	3.10	4.09	19.3	38.0	72.7	58.9
8b	4.20	4.93	2.44	1.05	5.00	6.62	6.55	2.41	2.73	2.94	3.17	24.5	35.8	71.1	58.2
9a	3.88	4.48	2.22	0.99	4.00	6.52	6.68	2.75	3.01	3.20	3.98	22.0	38.8	72.1	61.0
9b	4.22	4.29	2.51	1.36	4.40	6.50	6.76	2.46	2.57	3.14	3.53	19.8	37.5	69.8	60.8

Table 2. Selected Vicinal H, H and P, H Coupling Constants (Hz)

	P, 2eq	P, 2ax	P, 6ax	P, 6eq	P, 11b	1, 2ax	1, 11b	1, 2eq	6eq, 7ax	6eq, 7eq	6ax, 7ax	6ax, 7eq
6a	17.6	8.8	11.7	9.0	<1	3.7	2.6	2.2	5.2	4.3	10.9	2.7
6b	23.7	2.4	a	a	<1	1.7	2.2	1.5	6.7	2.3	12.4	1.7
7a	15.1	10.1	8.0	12.3	7.8	4.8	7.2	7.5	5.2	2.7	11.3	3.5
7b	20.0	7.3	5.4	7.4	7.3	11.2	8.3	3.9	5.8	4.2	9.6	4.7
8a	21.9	4.9	1.7	8.9	<1	2.8	4.0	2.3	4.4	3.1	11.3	2.8
8b	22.9	3.7	<1	10.3	<1	2.3	5.0	1.9	4.9	1.6	12.2	2.8
9a	10.7	16.1	6.8	10.8	4.6	4.6	8.3	7.7	4.2	3.5	10.1	3.3
9b	16.3	10.7	8.1	8.7	8.8	8.8	7.9	4.3	5.7	3.1	10.7	4.7

[a] Not resolvable.

The 1′-methyl-substituted homocalycotomine **3** was synthesized via a recently described method: formaldehyde addition to 1-ethyl-6,7-dimethoxy-3,4-dihydroisoquinoline **2**, followed by sodium borohydride reduction and fractional crystallization, resulted in a 51% overall yield of the diastereomerically pure amino alcohol **3** (Scheme 1).[7a] Its diastereomer **5** was prepared from the corresponding 1-(ethoxycarbonylmethylene)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **4** by C-1 alkylation with methyl iodide, followed by reduction according to the literature.[7b]

When amino alcohols **3** and **5** were reacted with the appropriate bis(2-chloroethyl)aminophosphonic dichloride or phenylphosphonic dichloride in the presence of Et_3N or pyridine, respectively, the two P-4 epimeric structures **a** and **b** of **6**−**9** were formed in nearly 1:1 ratio. The diastereomeric pairs **a** and **b** of **6**−**9** were separated by column chromatography on silica gel, with ethyl acetate as eluent.

The assignment of the ^1H and ^{13}C NMR signals was straightforward via the application of the standard 2D methods, such as ^1H COSY45, NOESY, HMQC, and *J*-resolved spectra. During the measurement of the chemical shifts (Table 1) and coupling constants $^3J(H,H)$, especially for the second-order patterns, the iterative method implemented in the program PERCH[8] was used. The conventional *J*-resolved experiments facilitated the measurement of coupling constants $^3J(P,H)$ of interest in regard to the conformational states, since $^3J(H,H)$ is separated in the F1 domain and $^3J(P,H)$ can be observed in the F2 domain.[5a] Vicinal H,H and P,H coupling constants are shown in Table 2.

Determination of the Configurations. With respect to the relative configuration on the phosphorus, there is a series of diastereomer pairs **a** and **b**. The following indicators can be used to determine the orientation of the P═O double bond and the relative configuration: (i) ^{31}P chemical shifts,[9] (ii) proton chemical shift changes due to 1,3 diaxial interactions, (iii) ^{13}C chemical shift changes arising from the shielding effect of oxygen, (iv) the NOE effect between the substituent on the phosphorus and

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other ring protons or substituents. Measurement of the coupling constants ^1J(P,N) is also an approach to discover the phosphorus configuration,[10] but this was not utilized in this work.

The compounds with the same relative configurations on C-1 and C-11b exhibit similar differences as concerns the above features, and we therefore perform the stereochemical analysis relative to the phosphorus configuration for compounds **6** and **8** and compounds **7** and **9** separately.

Compounds 6 and 8. There is a significant difference between the ^{31}P chemical shifts of **a** and **b**. The shifts for **b** are downfield from those for **a**, which suggests that the P═O bond is axial in **b** and equatorial in **a**.

NOE cross-peaks can be observed from the methylene protons of the *N*-bis(chloroethyl) group in **6a** and from the aromatic protons of the phenyl group in **8a** to H-11b and H-2. This is possible when the substituents on the phosphorus occupy an axial position. There is a weak NOE from Me-1 to *N*-bis(chloroethyl) in **6b**, but, with regard to the estimated distance of the geometric center from the integrated intensity of the NOE cross-peak, the interaction can arise from the proximity of an axial Me-1 and an equatorial *N*-bis(chloroethyl) group.

The chemical shift for C-2 is upfield and that for H-2ax is downfield in **6b** and **8b** as compared with those in **6a** and **8b**, respectively. These facts confirm the axial position of P═O in compounds **b** and the equatorial position in compounds **a**.

Compounds 7 and 9. The ^{31}P and the ^{13}C chemical shifts in **a** and **b** do not exhibit a significant difference, which points to the similar orientation of the P═O bond despite the different configurations. The NOE cross-peaks from the methylenes of the *N*-bis(chloroethyl) group and the aromatic protons of the phenyl group to H-1 in **b** and to H11-b in **a** can serve as evidence of the pseudoequatorial position of the P═O bond in **7** and **9**.

The assignment of the relative phosphorus configuration could be made unequivocally by means of the NMR data as follows. Structures **a** possess an *S**, and structures **b** an *R**, relative configuration on the phosphorus.

Conformational Analysis. Idealized possible conformational states have been described for 1,3,2-oxazaphosphorinanes with various substituents.[4] Those structures were taken as starting point (Figure 1).

In connection with the conformations of the molecules, certain important points must be stated: (i) the *N*-bis(chloroethyl) group tends to occupy an equatorial position in consequence of its steric demand, (ii) the steric interaction between Me-1 and the aromatic ring has a great influence on the molecular conformation, (iii) the coordination of the bridgehead nitrogen is rather planar and there is a deviation of only ca. 0.1−0.12 Å from the planar arrangement, which makes the ring system distorted to a certain extent as compared with the idealized structures, while the nitrogen inversion causes only a slight difference between the cis and trans ring junctions, and (iv) the connecting isoquinoline moiety makes the phosphorinane ring somewhat rigid.

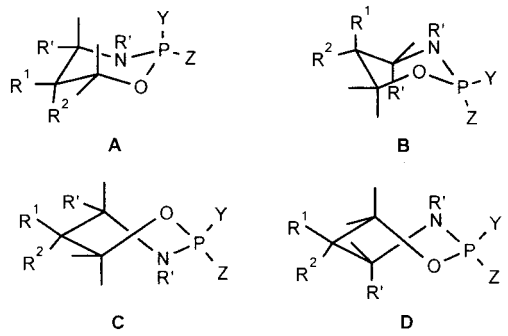

Figure 1. Oxazaphosphorinane conformations described earlier.

The conformations of the title compounds have been deduced mainly from the ^3J(H,P) and ^3J(H,H) data with the help of some crucial NOE interactions. Evaluation of the experimental data allows the compounds to be classified into two groups according to the patterns of coupling constants and NOE peaks.

Compounds 6 and 8. The small ^3J(H1,H11b) and ^3J(H11b,P) values indicate that the relevant dihedral angles are close to the orthogonal, which rules out **B** and **D**. Vicinal coupling constants between H-2 and the phosphorus would allow a distinction between **A** and **C**, but the intermediate values of ^3J(H2eq,P) and ^3J(H2ax,P) do not permit the specification of a single conformation. The phosphorinane ring in **6** and **8** exists rather as a mixture of **A** and **C**. This is confirmed by the small coupling constants ^3J(H2eq,H1) and ^3J(H2ax,H1).

The conformation of the isoquinoline ring can be described as a flattened twist. This is demonstrated by the diaxial position of H-6ax and H-7ax and the NOE interaction between H-11b and H-6ax, from which a distance of 2.9 Å is estimated. This distance is reasonable if H-11b is axial to the isoquinoline ring, and the bridgehead nitrogen is almost planar.

Consideration of the above results points to the proximity of Me-1 and H-7ax and of H-1 and H-11, which allows NOE interactions (Figure 2). These cross-peaks are identified in the NOESY spectrum, as confirmation of the deduced conformation.

Compounds 7 and 9. The 11b*R**,1*S** relative configuration for these structures is associated with an increased ^3J(H1,H11b). The values 7.2−8.3 Hz for **7** and **9** are possible if the relation of the protons in question alternates between trans diaxial and diequatorial or if the dihedral angle is approximately 140° (distorted diaxial position). An intermediate value was measured for ^3J(H11b,P), which may be a result of a distorted conformational state (a PNCH dihedral angle of ca. 120°) or a fast dynamic process involving an axial−equatorial equilibrium for H-11b.

When the corresponding experimental data and the estimated dihedral angles are taken into account, if there is a fast exchange between an axial and an equatorial H-11b, it must be predominantly axial. This means that the aromatic ring and the methyl group would be in close proximity in most cases; however, this conformation should be considered unlikely because of the steric demands of both groups. We note that the steric demand

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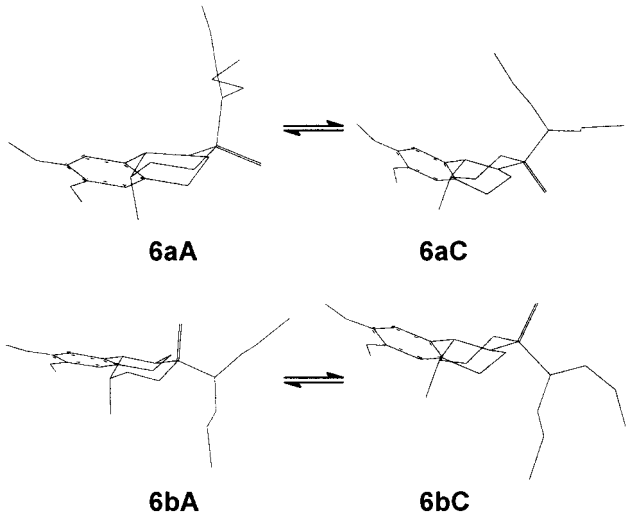

Figure 2. Conformational equilibrium of **6a** and **6b**. Computer-generated structures, using MM+ force field with the experimental data.

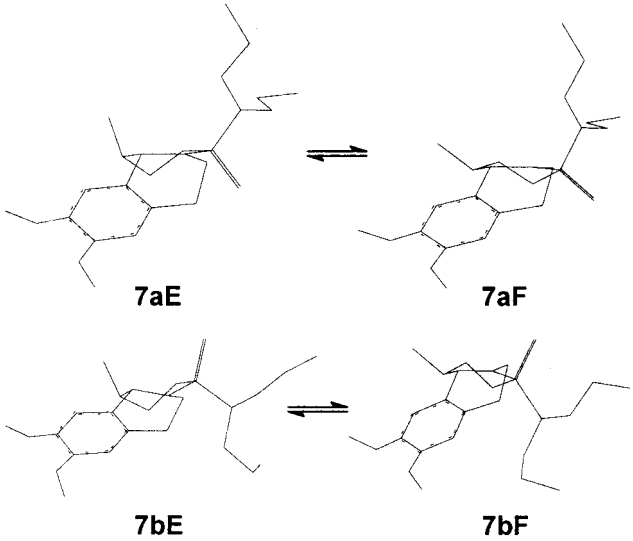

Figure 3. Conformational equilibrium of **7a** and **7b**. Computer-generated structures, using MM+ force field with the experimental data.

of the phenyl group is anisotropic, but in this case the free rotation of the equatorial phenyl into an energetically more preferred position is not allowed by the connecting dimethylene chain. We therefore consider that the dynamic process involving the change in the P−N−C−H11b dihedral angle can be eliminated as concerns the phosphorinane ring in **7** and **9**.

However, the intermediate ^3J(H2ax,P) and ^3J(H2eq,P) values clearly point to a fast exchange between conformations with different P−O−C−H2ax and the same P−N−C−H11b dihedral angles.

The patterns of the coupling constants between H-6 and H-7 are the same as for **6** and **8**, where the twist conformation was determined. The diagnostic NOE cross-peak between H-11b and H-6ax was also observed in this case.

From the above results, and assuming a trigonal bridgehead nitrogen and a cis ring junction, stable conformation states can be modeled which differ from the structures reported in the literature, and which can be described as a distorted twist-boat (**E** and **F**) (Figure 3). For both structures, the simultaneous proximity of H-11 and H-1 and of H-11 and Me-1 is observed. The NOE interactions provide experimental evidence of this structural feature.

Variable-Temperature NMR Measurements. To freeze out the detected conformational processes, low-temperature NMR measurements were performed. No signal split could be observed, either in the ^{31}P spectra or in the ^{1}H spectra, even at 165 K. This suggests that the processes have low free energies of activation.

Conformer Populations. By means of the well-known procedure, the ratios of the conformers in equilibrium were estimated at 300 K.[3e] The accuracy of the calculation depends on the reference ^3J(P,H) values for axial and equatorial protons and the experimental error in the observed coupling constants. The POCH coupling constant of 2 Hz for an axial proton is generally accepted in the literature, but for the equatorial position values in the range ca. 21−24 Hz have been reported. Our observations and the published data on fused oxazaphosphorinane ring systems with nitrogen in a bridgehead position suggest that the upper limit of the range is a good estimation of the equatorial ^3J(H,P) for our model compounds.

Table 3. Quantitative Evaluation of the Conformational Equilibria

	composition (%)	ln K	ΔG_o (kJ/mol)
6aA	70	0.8	−2.1
6aC	30		
6bA	99	4.6	−11.5
6bC	1		
7aE	60	0.4	−1.0
7aF	40		
7bE	80	1.4	−3.5
7bF	20		
8aA	89	2.1	−5.2
8aC	11		
8bA	94	2.8	−6.9
8bC	6		
9aE	38	−0.5	1.2
9aF	62		
9bE	63	0.5	−1.3
9bF	37		

The conformational analysis clearly reveals that the connecting isoquinoline ring reduces the degree of freedom of the oxazaphosphorinane ring and rather blocks the conformation along the C1−C11b−N5−P4 chain. At the same time, the C1−C2−O3−P4 chain is fairly flexible. The conformation of the rigid part depends mostly on the relative configuration of C-1 and C-11b, which is due to the repulsive interaction between the sterically demanding aromatic moiety and the methyl group. A change in the configuration of the phosphorus does not affect the nature of the basic conformational behavior of the model compounds, but it has a decisive influence on the flexible part and therefore obviously on the conformational equilibrium.

The equilibrium is completely shifted toward the chair conformation (conformer **A**) in **6b** and **8b** (Table 3), because the *N*-bis(chloroethyl) and phenyl groups are in the preferred equatorial position, and the structure is therefore stable enough to prevent the depopulation of the chair form. The substituents on P═O are axial in **6a** and **8a**; the 1,3 diaxial repulsion therefore destabilizes the chair form and the ΔG_o values increase to −2.1 kJ/mol and −5.2 kJ/mol, respectively. According to the

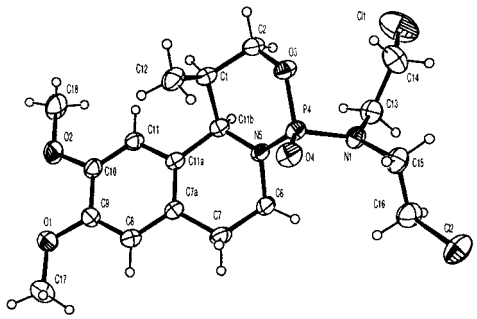

Figure 4. ORTEP perspective view of **6a**, showing the labeling system. Thermal ellipsoids are drawn at a 30% probability level.

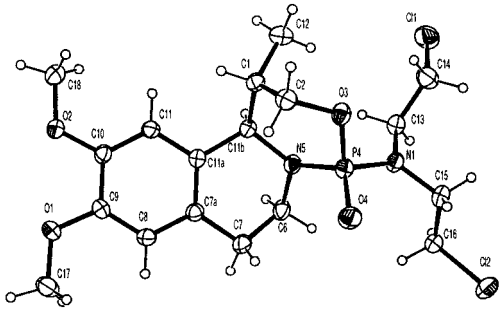

Figure 5. ORTEP perspective view of **7a**, showing the labeling system. Thermal ellipsoids are drawn at a 30% probability level.

literature, the destabilizing effect of an axial phenyl group is less than that of an axial *N*-bis(chloroethyl) group. The chair conformational state remains predominant, which may be due to the possible n−σ* interaction.[11]

A predominance of conformer **E** is observed for **7a**, **7b**, and **9b**, while the conformational equilibrium is shifted toward conformer **F** for **9a**. Since these conformations have not been described in the literature, we could find no data on a substituent effect relating to an equilibrium between **E** and **F**. We assume that the stereoelectronic effects play a minor role in **7** and **9**, in consequence of the distorted conformation. A valid interpretation of the measured conformer ratios requires a thorough substituent effect study with a wide range of functional groups on the phosphorus.

X-ray Structures of 6a and 7a. In the solid state, the asymmetric units in **6a** and **7a** are comprised of independent molecules. The structures and the atom labeling schemes are depicted is Figures 4 and 5. Selected bond distances and torsional angles are presented in Tables 4 and 5.

The X-ray results clearly support the stereochemical assignments made on the basis of the NMR findings and provide experimental evidence for the planar arrangement of the bridgehead nitrogen. The sums of the bond angles around N-5 are 359.4° and 357.3° for **6a** and **7a**, respectively.

Figures 4 and 5 depict conformer **A** of **6a** and conformer **E** of **7a**, but the P4−N5−C11b−C1 torsion angles of −5.4° and 10.4° reveal that the oxazaphosphorinane ring is rather flattened for both structures, which is not

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Table 4. Selected Bond Distances (Å) and Angles (deg)[a] for 6a

Cl(1)−C(14)	1.745(5)	O(3)−C(2)	1.458(5)
Cl(2)−C(16)	1.782(5)	N(1)−C(13)	1.467(5)
P(4)−O(4)	1.475(3)	N(1)−C(15)	1.473(5)
P(4)−O(3)	1.581(3)	N(5)−C(11B)	1.473(5)
P(4)−N(5)	1.635(3)	N(5)−C(6)	1.477(5)
P(4)−N(1)	1.649(3)		
O(4)−P(4)−O(3)	113.08(17)	C(13)−N(1)−C(15)	117.0(3)
O(4)−P(4)−N(5)	117.23(18)	C(13)−N(1)−P(4)	119.7(3)
O(3)−P(4)−N(5)	103.58(16)	C(15)−N(1)−P(4)	121.9(3)
O(4)−P(4)−N(1)	108.91(17)	C(11B)-N(5)−C(6)	112.8(3)
O(3)−P(4)−N(1)	105.79(16)	C(11B)-N(5)−P(4)	128.5(3)
N(5)−P(4)−N(1)	107.51(17)	C(6)−N(5)−P(4)	118.1(3)
C(2)−O(3)−P(4)	123.6(3)		

[a] Esd's are given in parentheses.

Table 5. Selected Bond Distances (Å) and Angles (deg)[a] for 7a

Cl(1)−C(14)	1.775(3)	O(3)−C(2)	1.462(3)
Cl(2)−C(16)	1.792(3)	N(1)−C(13)	1.461(3)
P(4)−O(4)	1.466(2)	N(1)−C(15)	1.467(3)
P(4)−O(3)	1.583(2)	N(5)−C(6)	1.476(4)
P(4)−N(5)	1.645(2)	N(5)−C(11B)	1.480(3)
P(4)−N(1)	1.649(2)		
O(4)−P(4)−O(3)	114.66(12)	C(13)−N(1)−C(15)	116.9(2)
O(4)−P(4)−N(5)	116.54(13)	C(13)−N(1)−P(4)	122.60(19)
O(3)−P(4)−N(5)	102.23(11)	C(15)−N(1)−P(4)	120.54(19)
O(4)−P(4)−N(1)	109.61(12)	C(6)−N(5)−C(11B)	112.2(2)
O(3)−P(4)−N(1)	105.90(11)	C(6)−N(5)−P(4)	115.7(2)
N(5)−P(4)−N(1)	107.06(12)	C(11B)-N(5)−P(4)	129.44(18)
C(2)−O(3)−P(4)	114.69(17)		

[a] Esd's are given in parentheses.

reflected by the models created via the NMR data. A further difference is the distance between Me-1 and H-11 in **7a** relative to the solution structure. NOESY measurements point to similar H11−Me1 and H11−H1 distances. We note that the more populated conformers in solution can be observed in the solid state for **6a** and **7a**.

Conclusions

The oxazaphosphorinane ring is flexible enough to occupy all the possible theoretical conformational states. In this work, we have observed for **7** and **9** that the connecting isoquinoline and the steric interaction between the aromatic moiety and the Me-1 substituent can block the phosphorus-containing ring so that it populates distorted twist conformations with a planar bridgehead nitrogen. This results in intermediate ^3J(H11b,P) values, not due to equilibrium between previously reported conformational states, while the P−O−C−H dihedral angle remains flexible. For **6** and **8**, a conformational anomaly of this type was not observed, but the P−N−C−H dihedral angle is also blocked by the connecting isoquinoline ring. The equilibrium ratios for **6** and **8** can be explained by using earlier literature results.

Experimental Section

The NMR spectra were recorded in $CDCl_3$ solution at 300 K on a Bruker AVANCE DRX 400 spectrometer, with the deuterium signal of the solvent as the lock. During ^1H and ^{13}C NMR measurements, TMS was applied as internal standard; for the ^{31}P NMR spectra, 85% H_3PO_4 was used as external standard. Samples were dissolved in 0.5 cm^3 solvent and placed in 5 mm Aldrich NMR tubes. Nitrogen bubbling was used to degas samples. For the low-temperature measurements, CS_2 was used as solvent.

1D spectra were evaluated with the help of PERCH software. For evaluation of the NOESY spectra and integration of the cross-peaks, NMRView[12] was used.

X-ray Diffraction Studies. All data were collected on a Rigaku AFC5S diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.71069$ Å) in the ω-2θ scan mode at room temperature. The lattice parameters were calculated by least-squares refinements of 25 reflections. The weak reflections [$I < 10\sigma(I)$] were rescanned up to two times. For **6a** and **7a**, 3899 and 3802 reflections, respectively, were collected [$2\theta_{max} = 50°$]. The data were corrected for Lorentz and polarization effects.

The structures were solved by direct methods (SIR92)[13] and refined by full-matrix least squares techniques (SHELXL-97)[14] to an R1 value of 0.0560 (wR2 = 0.1203) for **6a** and of 0.0398 (wR2 = 0.1007) for **7a**. These final *R* values are based on the reflections with $I > 2\sigma(I)$. The heavy atoms were refined anisotropically. The hydrogen atoms on the aliphatic ring carbons were refined with fixed isotropic temperature factors ($1.2U_{eq}$ of the carrying atom), and the remaining hydrogen atoms were included in the calculated positions with fixed isotropic temperature factors (1.2 or 1.5 times U_{eq} of the carrying atom). Calculations were performed with teXsan for Windows[15] crystallographic software. The Figures were drawn with ORTEP-3 for Windows.[16] (The final atomic coordinates and full lists of bond lengths and angles for **6a** and **7a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC).)

Crystal data for **6a**. $C_{18}H_{27}Cl_2N_2O_4P$, $M_r = 437.29$, monoclinic, space group $P2_1/n$ (No. 14), lattice parameters: $a = 14.301(3)$, $b = 7.389(2)$, $c = 21.149(2)$ Å, $\beta = 108.53(1)$, $Z = 4$, $V = 2118.9(7)$ Å^3, $D_c = 1.371$ g/cm^3, μ(Mo Kα) = 0.408 mm^{-1}, $F(000) = 920$, $T = 294$ K; colorless prisms, crystal dimensions 0.24 × 0.26 × 0.30 mm.

Crystal data for **7a**. $C_{18}H_{27}Cl_2N_2O_4P$, $M_r = 437.29$, monoclinic, space group $P2_1/c$ (No. 14), lattice parameters: $a = 13.085(3)$, $b = 7.845(2)$, $c = 20.747(2)$ Å, $\beta = 105.68(1)$, $Z = 4$, $V = 2050.4(7)$ Å^3, $D_c = 1.417$ g/cm^3, μ(Mo Kα) = 0.421 mm^{-1}, $F(000) = 920$, $T = 294$ K; colorless plates, crystal dimensions 0.24 × 0.32 × 0.34 mm.

General Procedure for the Preparation of 4-[Bis(2-chloroethyl)amino]-9,10-dimethoxy-1-methyl-4-oxo-1,6,7,-11b-tetrahydro-1,3,2-oxazaphosphorino[4,3-*a*]isoquinoline (6a, 6b and 7a, 7b). The amino alcohol (**3** or **5**) (2.51 g, 10.6 mmol) was allowed to react at room temperature with bis(2-chloroethyl)aminophosphoryl dichloride (2.74 g, 10.6 mmol) and triethylamine (2.15 g, 21.2 mmol) in dry ethyl acetate under a nitrogen atmosphere. The reaction mixture was stirred for 48 h and then filtered to remove triethylamine hydrochloride. The clear solution was subjected to rotary evaporation. The ^{31}P NMR spectrum of the crude product revealed two diastereomeric products in nearly 1:1 ratio. The product (3.8 g of **6** and 4.1 g of **7**) was column chromatographed on neutral silica gel, with ethyl acetate as eluent. From the rapidly eluting isomer were isolated **6a** (0.8 g, mp 152−154 °C) and **7a** (0.9 g, mp 131−132 °C) and from the more slowly eluting isomer were isolated **6b** (0.8 g, colorless oil) and **7b** (0.6 g, mp 103−105 °C) in pure form. For the X-ray analysis, compound **6a** was recrystallized from ethyl acetate. ^{13}C NMR ($CDCl_3$) **6a**: δ 11.4, 30.0, 38.3, 41.0, 42.5, 49.5, 56.3, 56.5, 59.2, 73.3, 109.3, 112.0, 126.0, 128.6, 147.9, 148.3; **6b**: δ 11.0, 29.1, 35.2, 41.0, 42.8, 50.0, 56.2, 56.4, 59.7, 71.3, 108.7, 112.1, 126.8, 127.8, 147.9, 148.1; **7a**: δ 16.4, 29.7, 37.12, 42.4, 42.6, 49.6, 56.4, 56.6, 62.3, 71.2, 111.1, 112.6, 126.8, 129.4, 146.6, 148.8; **7b**: δ 16.8, 29.0, 36.8, 42.2, 42.7, 49.8, 56.4, 56.6, 61.5, 70.8, 109.4, 112.4, 128.5, 128.7, 147.3, 148.4. Anal. Calcd for $C_{18}H_{27}Cl_2N_2O_4P$: C, 49.44; H, 6.22; N, 6.41. Found for **6a**: C, 49.34; H, 6.19; N, 6.51. Found for **6b**: C, 49.11; H, 6.21; N, 6.48. Found for **7a**: C, 49.40; H, 6.20; N, 6.60. Found for **7b**: C, 49.18; H, 6.06; N, 6.38.

General Procedure for the Preparation of 9,10-Dimethoxy-1-methyl-4-phenyl-4-oxo-1,6,7,11b-tetrahydro-1,3,2-oxazaphosphorino[4,3-*a*]isoquinoline (8a, 8b and 9a, 9b). To a solution of the amino alcohol (**3** or **5**) (2.51 g, 10.0 mmol) and anhydrous pyridine (1.58 g, 20.0 mmol) in anhydrous toluene (400 mL) at 6−10 °C under a nitrogen atmosphere was added a solution of phenylphosphonic dichloride (2.15 g, 11.0 mmol) in anhydrous toluene (100 mL) dropwise over a period of 1 h. When the addition was complete, anhydrous pyridine (1.68 g, 20.0 mmol) in anhydrous toluene (40 mL) was added, and the mixture was left to stand overnight at room temperature. The reaction mixture was washed consequently with water (3 × 100 mL), hydrochloric acid (3M, 2 × 100 mL), and sodium hydroxide (3 M, 2 × 100 mL) and then dried (Na_2SO_4), and the solvent was removed to afford a pale-yellow oil. The ^{31}P NMR spectrum of the crude product revealed two diastereomeric products in nearly 1:1 ratio. The crude product was column chromatographed on neutral aluminum oxide, with ethyl acetate as eluent. From the rapidly eluting isomer were isolated **8a** (0.88 g, mp 150−153 °C) and **9a** (0.60 g, mp 75−77 °C) and from the more slowly eluting isomer were isolated **8b** (1.01 g, mp 189−190 °C) and **9b** (0.70 g, mp 133−135 °C) in pure form. For the X-ray analysis, compound **8a** was recrystallized from ethyl acetate. ^{13}C NMR ($CDCl_3$) **8a**: δ 11.0, 30.2, 38.1, 41.2, 56.3, 56.4, 59.0, 72.8, 108.9, 112.0, 126.3, 128.9, 129.2, 131.1, 131.2, 132.2, 148.0, 148.3; **8b**: 11.2, 29.0, 35.7, 41.6, 56.3, 56.5, 58.2, 72.1, 108.5, 112.1, 127.1, 128.2, 129.0, 133.1, 133.3, 133.4, 148.2, 148.3; **9a**: 16.3, 30.4, 36.5, 41.0, 56.3, 56.5, 60.8, 71.9, 111.7, 112.4,126.5, 129.1, 129.3, 131.8, 132.2, 132.5, 147.1, 148.5; **9b**: 17.9, 28.5, 37.6, 42.6, 56.3, 56.7, 61.0, 69.9, 109.2, 112.5, 128.1, 128.8, 128.9, 132.2, 132.5, 132.7, 147.3, 148.2. Anal. Calcd for $C_{20}H_{24}NO_4P$: C, 64.34; H, 6.48; N, 3.75. Found for **8a**: C, 64.20; H, 6.51; N, 3.62. Found for **8b**: C, 64.30; H, 6.41; N, 3.68. Found for **9a**: C, 64.11; H, 6.39; N, 3.88. Found for **9b**: C, 64.26; H, 6.54; N, 3.90.

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