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Synthesis and conformational analysis of phenyl-substituted 1,3,2-oxazaphosphino[4,3-*a*]- and 1,2,3-oxathiazino[4,3-*a*]isoquinolines

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Abstract

Through the ring closures of tetrahydroisoquinoline 1,3-amino alcohols bearing a phenyl group in the side-chain, diastereomers of novel 1- or 2-phenyl-substituted 1,3,2-oxazaphosphino[4,3-*a*]isoquinoline 4-oxides, and 1,2,3-oxathiazino[4,3-*a*]isoquinoline 4-oxides and 4,4-dioxides were prepared. NMR analysis and DFT calculations on the prepared tetrahydroisoquinoline-condensed 1,2,3-heterocycles revealed that their conformational equilibria of *cis*[1]*–trans–cis*[2] type are influenced by the relative configuration of P-4 in the 1,3,2-oxazaphosphinanes, and by the position of the phenyl group in the 1,2,3-oxathiazines.

Keywords: Phosphorus heterocycles; Sulfur heterocycles; Fused-ring systems; Conformational analysis; Molecular modelling

1. Introduction

Isoquinoline and its saturated derivatives are core units found abundantly among both naturally occuring and synthetic pharmacologically active compounds [1]. Because of their potential biological effects and wide-ranging synthetic applicability, the preparation and transformations of isoquinoline derivatives have acquired considerable significance in heterocyclic chemistry [2,3].

Angular fusion of the tetrahydroisoquinoline skeleton with another saturated heterocycle leads to new entities that often exhibit appreciable biological effects, e.g. 2-cyclohexylcarbonylhexahydropyrazino[2,1-*a*]isoquinolin-4-one (praziquantel) is applied as an anthelminthic drug [1], while 6-arylhexahydropyrrolo[5,1-*a*]isoquinolines have proved to be antidepressants [4], isoquino[1,2-*b*][1,3]benzoxazines possess an M_4 selective antimuscarinic effect [5], and multidrug resistance-modulating activity has been described for pyridazine-condensed 1,4-oxazino[3,4-*a*]isoquinolines [6,7].

The conformational equilibria of the angularly fused, saturated, nitrogen-bridged tricyclic systems have been studied thoroughly [8]. The heteroatoms, the substituents on the saturated rings and the relative configurations of the substituted carbon atoms have been reported to influence the predominant conformation of 1-, 2- and 4-substituted saturated 1,3-oxazino[4,3-*a*]-, pyrimido[6,1-*a*]- and 1,3,2-diazaphosphino[6,1-*a*]isoquinolines [9–12]. Conformational studies on the analogous 1,2,3-oxathiazino[4,3-*a*]- and 1,3,2-oxazaphosphino[4,3-*a*]isoquinolines have been performed for 1- or 2-methyl-substituted derivatives [13–15]; our present aim was therefore to prepare 1- or 2-phenyl-substituted 1,2,3-oxathiazino[4,3-*a*]- and 1,3,2-oxazaphosphino[4,3-*a*]isoquinolines and to investigate the effects of the phenyl substitution on the steric structures of these compounds. Since various derivatives of both 1,3,2-oxazaphosphinane and 1,2,3-oxathiazine are often

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applied as intermediates in organic synthesis [16–20], the present studies may contribute to a better understanding of the conformational aspects of these heterocyclic systems.

2. Experimental

Melting points were determined on a Kofler micro melting point apparatus and are not corrected. For column chromatography and for thin-layer chromatography, silica gel 60 (0.063–0.200 mm) and Merck Kieselgel 60F_{254} plates were used, respectively. Compounds **2a** and **2b** were prepared according to known procedures [10].

NMR spectra were recorded in $CDCl_3$ solution on a Bruker Avance 500 or Avance 300 spectrometer. For the ^1H and ^{13}C NMR spectra, TMS was applied as internal standard. During the ^{31}P NMR measurements, 85% H_3PO_4 was used as external standard.

Quantum chemical calculations were carried out with the *ab initio* program package GAUSSIAN 03 version C.02 [21].

The various conformations and configurations of all the studied compounds were preoptimized with the PM3 Hamiltonian [22,23]. The B3LYP density functional method was selected for all calculations. The method was based on the Becke three-parameter hybrid functionals [24] and the correlation functional of Lee et al. [25]. This method includes electron correlation effects.

A moderate split valence basis set 6-31G* [26] was used because of the size of the studied compounds. Polarization functions on hydrogen atoms were not used as no hydrogen-bonds exist in this series. All optimizations were carried out without any restriction at the B3LYP/6-31G* level of theory.

NMR chemical shifts were calculated by using the gauge-independent atomic orbital method (GIAO) [27]. This method determines the magnetic shielding of the ^1H and ^{13}C nuclei. The differences between these magnetic shieldings and those of the reference tetramethylsilane (TMS) are the chemical shifts. TMS GIAO calculations were made at the same level of theory.

The $^3J_{H,H}$ spin coupling constants [28,29] of the different conformations were determined at the B3LYP/6-31G* level of theory for comparison with the experimental values. These calculated spin–spin coupling constants consist of paramagnetic spin-orbit contributions, diamagnetic spin-orbit contributions, Fermi contact contributions and spin-dipolar contributions.

Calculations were carried out on the SGI cluster and on the Linux cluster.

2.1. (1R*,2'S*)-1-(2'-Hydroxy-2'-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (2c)

Compound **3** (17.39 g, 0.05 mol) was reduced with $NaBH_4$ (5.67 g, 0.15 mol) in the presence of $NaHCO_3$ (4.20 g, 0.05 mol) in MeOH (200 ml) to yield a 2:1 mixture of **2b** and **2c**, from which diastereomerically pure **2b** was obtained in 47% yield as described earlier [10]. The mother liquor remaining after filtration of the crude crystalline **2b** was evaporated in vacuo and the oily residue was crystallized from ether. The crystals were filtered off and recrystallized from iPr_2O–EtOAc to yield diastereomerically pure **2c**.

Yield 4.10 g (26%), mp 92–93 °C. The ^1H NMR spectrum of **2c** is in accordance with the literature [30] data on the (1*R*,2'*S*) isomer.

Anal. Calcd. for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.60; H, 7.19; N, 4.28.

2.2. General procedure for the preparation of 4-phenyl-substituted 1,3,2-oxazaphosphino[4,3-a]isoquinoline 4-oxides (4–6)

To an ice-water-cooled solution of amino alcohol 2 (0.94 g, 3 mmol) and Et_3N (0.61 g, 6 mmol) in anhydrous CH_2Cl_2 (50 ml), a solution of $PhPOCl_2$ (0.62 g, 3.2 mmol) in anhydrous CH_2Cl_2 (10 ml) was added dropwise over a period of 5 min. The mixture was allowed to reach room temperature under stirring and was then stirred at room temperature for a further 24 h. It was next transferred to a separatory funnel and was washed in turn with 5% HCl (2 × 25 ml) and with H_2O (2 × 25 ml). The organic phase was dried (Na_2SO_4) and evaporated in vacuo, and the crude product was purified by column chromatography, with EtOAc as eluent.

2.2.1. 4a

A white solid; yield 0.35 g (27%), mp. 182–184 °C (EtOAc–iPr_2O). ^1H NMR (500 MHz, $CDCl_3$): δ 7.81–7.48 (m, 5H, Ph), 7.22–7.09 (m, 5H, Ph), 6.59 (s, 1H, H-11), 6.37 (s, 1H, H-8), 4.90 (t, $J = 3.0$ Hz, 1H, H-11b), 4.73 (ddd, $J = 2.5$, 11.7, 18.6 Hz, 1H, H-2*eq*), 4.67 (ddd, $J = 4.5$, 6.3, 11.6 Hz, 1H, H-2*ax*), 3.91 (dddd, $J = 3.9$, 4.0, 7.1, 11.2 Hz, 1H, H-6*eq*), 3.84 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.22 (d, $J = 3.1$ Hz, 1H, H-1), 3.05 (ddt, $J = 2.0$, 2.7, 11.0 Hz, 1H, H-6*ax*), 2.35 (ddd, $J = 2.8$, 5.7, 15.2 Hz, 1H, H-7*eq*), 2.13 (ddd, $J = 4.5$, 10.7, 15.2 Hz, 1H, H-7*ax*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.8 (C-10), 147.7 (C-9), 137.8, 132.1, 131.2, 131.1, 130.8, 129.8, 129.5, 129.3, 129.1, 129.0, 127.9, 127.2, 125.1 (d), 111.3 (C-8), 109.6 (C-11), 71.8 (C-2), 58.5 (C-11b), 56.2, 55.9 (2× OCH_3), 48.8 (C-1), 40.6 (C-6), 29.1 (C-7).

Anal. Calcd. for $C_{25}H_{26}NO_4P$: C, 68.96; H, 6.02; N, 3.22. Found: C, 68.72; H, 6.13; N, 3.67.

2.2.2. 4b

A white solid; yield 0.28 g (22%), mp. 163–168 °C (EtOAc–iPr_2O). ^1H NMR (500 MHz, $CDCl_3$): δ 7.99–7.46 (m, 5H, Ph), 7.36–7.13 (m, 5H, Ph), 6.59 (s, 1H, H-11), 6.44 (s, 1H, H-8), 5.39 (t, $J = 3.7$ Hz, 1H, H-11b), 5.21 (ddd, $J = 3.4$, 4.0, 11.5 Hz, 1H, H-2*ax*), 4.53 (ddd, $J = 2.0$, 11.4, 21.3 Hz, 1H, H-2*eq*), 3.78 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.67 (br s, 1H, H-1), 3.27 (dddd, $J = 2.0$, 5.1, 9.0, 12.0 Hz, 1H, H-6*eq*), 3.00 (dt, $J = 2.9$, 12.2 Hz, 1H, H-6*ax*), 2.64 (ddd, $J = 4.9$, 12.3, 15.3 Hz,

1H, H-7*ax*), 2.42 (dd, $J = 2.3$, 15.5 Hz, 1H, H-7*eq*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.7 (C-9), 147.5 (C-10), 138.5, 133.2, 133.1 (d), 129.6, 128.7, 128.6, 128.0, 127.7, 126.9 (d), 111.5 (C-11), 109.0 (C-8), 70.4 (C-2), 57.5 (C-11b), 56.1, 55.8 (2× OCH_3), 45.6 (C-1), 42.0 (C-6), 28.6 (C-7).

Anal. Calcd. for $C_{25}H_{26}NO_4P$: C, 68.96; H, 6.02; N, 3.22. Found: C, 68.71; H, 6.18; N, 3.10.

2.2.3. **6a**

A white solid; yield 0.38 g (29%), mp. 232–234 °C (EtOAc–*i*Pr_2O). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82–7.49 (m, 5H, Ph), 7.48–7.32 (m, 5H, Ph), 6.64 (s, 1H, H-8), 6.50 (s, 1H, H-11), 5.27 (td, $J = 1.9$, 11.3 Hz, 1H, H-2), 4.67 (d, $J = 10.7$ Hz, 1H, H-11b), 3.88 (m, 1H, H-6*eq*), 3.86 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.42 (dddd, $J = 3.7$, 4.9, 8.6, 12.3 Hz, 1H, H-6*ax*), 3.01 (ddd, $J = 4.3$, 8.8, 15.5 Hz, 1H, H-7*ax*), 2.78 (td, $J = 4.1$, 15.7 Hz, 1H, H-7*eq*), 2.27 (ddd, $J = 2.7$, 3.8, 14.2 Hz, 1H, H-1*eq*), 2.19 (td, $J = 11.3$, 14.2 Hz, 1H, H-1*ax*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.0 (C-10), 147.8 (C-9), 140.1, 132.2 (d), 131.3 (d), 131.2, 129.2, 129.1, 128.7, 128.5, 127.5, 127.1, 127.0, 125.8, 111.9 (C-8), 108.9 (C-11), 79.6 (C-2), 56.2, 56.0 (2× OCH_3), 55.3 (C-11b), 42.8 (C-1), 40.1 (C-6), 29.7 (C-7).

Anal. Calcd. for $C_{25}H_{26}NO_4P$: C, 68.96; H, 6.02; N, 3.22. Found: C, 69.11; H, 6.15; N, 3.05.

2.2.4. **6b**

A white solid; yield 0.45 g (34%), mp. 150–153 °C (EtOAc–*i*Pr_2O). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00–7.46 (m, 5H, Ph), 7.40–7.31 (m, 5H, Ph), 6.63 (s, 1H, H-11), 6.55 (s, 1H, H-8), 5.82 (dt, $J = 1.6$, 11.8 Hz, 1H, H-2), 4.96 (d, $J = 11.0$ Hz, 1H, H-11b), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.40 (dddd, $J = 1.5$, 5.4, 10.0, 12.8 Hz, 1H, H-6*ax*), 3.07 (ddt, $J = 2.0$, 3.0, 12.5 Hz, 1H, H-6*eq*), 2.70 (t, $J = 16.4$ Hz, 1H, H-7*ax*), 2.69 (tdd, $J = 1.8$, 3.3, 14.1 Hz, 1H, H-1*eq*), 2.45 (d, $J = 15.8$ Hz, 1H, H-7*eq*), 2.23 (dt, $J = 11.8$, 13.9 Hz, 1H, H-1*ax*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.0, 147.8, 140.2, 133.3, 133.2, 132.7, 128.8, 128.6, 128.5, 128.2, 128.1, 126.7, 126.0, 112.0 (C-8), 108.2 (C-11), 76.9 (C-2), 56.2, 56.0 (2× OCH_3), 54.7 (C-11b), 42.0 (C-1), 41.5 (C-6), 28.5 (C-7).

Anal. Calcd. for $C_{25}H_{26}NO_4P$: C, 68.96; H, 6.02; N, 3.22. Found: C, 68.79; H, 5.91; N, 3.40.

2.3. General procedure for the preparation of 4-[bis(2-chloroethyl)amino]-substituted 1,3,2-oxazaphosphino[4,3-a]isoquinoline 4-oxides (7–9)

To a stirred solution of bis(2-chloroethyl)phosphoramidic dichloride (0.71 g, 3.2 mmol) in anhydrous CH_2Cl_2 (20 ml), a solution of amino alcohol **2** (0.94 g, 3 mmol) and Et_3N (0.61 g, 6 mmol) in anhydrous CH_2Cl_2 (20 ml) was added dropwise at room temperature over a period of 10 min. The mixture was stirred at room temperature for 48 h and the crystalline salts were then filtered off. The filtrate was evaporated in vacuo and the crude product was purified by column chromatography, with EtOAc as eluent.

2.3.1. **7b**

A white solid; yield 0.26 g (18%), mp. 129–132 °C (*i*Pr_2O). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14–7.07 (m, 5H, Ph), 6.68 (s, 1H, H-11), 6.33 (s, 1H, H-8), 5.03 (d, $J = 1.0$ Hz, 1H, H-11b), 4.80 (ddd, $J = 6.5$, 12.0, 12.5 Hz, 1H, H-2*ax*), 4.66 (ddd, $J = 3.0$, 11.5, 13.5 Hz, 1H, H-2*eq*), 3.91 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.71 (m, 4H, 2× CH_2N), 3.55 (ddd, $J = 4.0$, 7.5, 15.0 Hz, 1H, H-6*eq*), 3.44 (m, 4H, 2× CH_2Cl), 3.35 (td, $J = 3.0$, 6.0 Hz, 1H, H-1), 2.88 (tt, $J = 2.5$, 11.0 Hz, 1H, H-6*ax*), 2.22 (ddd, $J = 3.0$, 6.0, 15.0 Hz, 1H, H-7*eq*), 1.89 (ddd, $J = 4.5$, 11.0, 15.0 Hz, 1H, H-7*ax*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.0, 147.9, 137.8, 129.7, 129.2, 127.8, 127.2, 127.2 (C-11a), 125.0, 124.9 (C-7a), 111.3 (C-8), 109.8 (C-11), 71.4 (C-2), 59.1 (C-11b), 56.3, 56.0 (2× OCH_3), 49.4 (C-1), 49.2, 49.2 (2× CH_2N), 42.2, 42.2 (2× CH_2Cl), 40.0 (C-6), 28.7 (C-7).

Anal. Calcd. for $C_{23}H_{29}Cl_2N_2O_4P$: C, 55.32; H, 5.85; N, 5.61. Found: C, 55.52; H, 5.71; N, 5.69.

2.3.2. **9a**

A white solid; yield 0.31 g (21%), mp. 153–155 °C (*i*Pr_2O). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47–7.32 (m, 5H, Ph), 6.61 (s, 1H, H-8), 6.54 (s, 1H, H-11), 5.46 (td, $J = 3.0$, 12.0 Hz, 1H, H-2), 4.76 (td, $J = 3.0$, 11.0 Hz, 1H, H-11b), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.76 (tdd, $J = 4.5$, 7.0, 12.5 Hz, 1H, H-6*eq*), 3.69 (t, $J = 7.0$ Hz, 4H, 2× CH_2Cl), 3.48 (ddd, $J = 7.3$, 12.0, 14.8 Hz, 2H, CH_2N), 3.42 (ddd, $J = 6.5$, 11.2, 15.0 Hz, 2H, CH_2N), 3.20 (ddd, $J = 3.0$, 9.5, 12.8 Hz, 1H, H-6*ax*), 2.98 (ddd, $J = 4.8$, 9.8, 15.0 Hz, 1H, H-7*ax*), 2.67 (td, $J = 3.7$, 15.7 Hz, 1H, H-7*eq*), 2.33 (ddd, $J = 2.5$, 4.0, 14.4 Hz, 1H, H-1*eq*), 2.19 (td, $J = 11.5$ Hz, 14.4 Hz, 1H, H-1*ax*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.1, 148.0, 140.1, 128.8, 128.7, 127.5, 127.4, 127.3, 126.1, 111.9 (C-8), 109.0 (C-11), 80.4 (C-2), 56.3, 56.1 (2× OCH_3), 55.5 (C-11b), 49.2, 49.1 (2× CH_2N), 43.2 (C-1), 42.3, 42.3 (2× CH_2Cl), 40.7 (C-6), 29.5 (C-7).

Anal. Calcd. for $C_{23}H_{29}Cl_2N_2O_4P$: C, 55.32; H, 5.85; N, 5.61. Found: C, 55.51; H, 5.74; N, 5.69.

2.3.3. **9b**

A white solid; yield 0.20 g (13%), mp. 132–134 °C (*i*Pr_2O). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42–7.36 (m, 5H, Ph), 6.61 (s, 1H, H-8), 6.58 (s, 1H, H-11), 5.64 (d, $J = 12.0$ Hz, 1H, H-2), 4.78 (d, $J = 11.0$ Hz, 1H, H-11b), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.71 (m, 4H, 2× CH_2Cl), 3.70 (m, 1H, H-6*eq*), 3.62 (m, 2H, CH_2N), 3.48 (m, 2H, CH_2N), 3.00 (dt, $J = 3.0$, 12.0 Hz, 1H, H-6*ax*), 2.96 (dt, $J = 4.0$, 13.0 Hz, 1H, H-7*ax*), 2.65 (d, $J = 13.0$ Hz, 1H, H-7*eq*), 2.56 (td, $J = 1.5$, 14.0 Hz, 1H, H-1*eq*), 2.05 (td, $J = 12.0$, 14.0 Hz, 1H, H-1*ax*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.1, 147.8, 140.0, 128.9,

128.8, 128.0, 127.9, 127.9 (C-7a), 126.6 (C-11a), 126.0, 112.0 (C-8), 108.3 (C-11), 78.0 (C-2), 56.3, 56.1 (2× OCH_3), 55.9 (C-11b), 49.5, 49.5 (2× CH_2N), 42.7, 42.7 (2× CH_2Cl), 41.4 (C-6), 41.4 (C-1), 28.9 (C-7).

Anal. Calcd. for $C_{23}H_{29}Cl_2N_2O_4P$: C, 55.32; H, 5.85; N, 5.61. Found: C, 55.09; H, 5.96; N, 5.72.

2.4. General procedure for the preparation of 1,2,3-oxathiazino[4,3-a]isoquinoline 4-oxides and 4,4-dioxides (**10–15**)

To an ice-salt bath-cooled solution of amino alcohol **2** (0.94 g, 3 mmol) and Et_3N (0.61 g, 6 mmol) in anhydrous CH_2Cl_2 (20 ml), a solution of $SOCl_2$ (0.40 g, 3.4 mmol) or SO_2Cl_2 (0.45 g, 3.3 mmol) in anhydrous CH_2Cl_2 (20 ml) was added dropwise over a period of 10 min. The mixture was stirred under ice-salt bath cooling for 3 h and was then allowed to warm to room temperature under stirring. It was stirred at room temperature for a further 48 h. The mixture was next transferred to a separatory funnel and washed in turn with a saturated aqueous solution of $NaHCO_3$ (2 × 10 ml) and then with H_2O (2 × 10 ml). The organic phase was dried (Na_2SO_4) and evaporated, and the crude product was purified by column chromatography, with EtOAc as eluent.

2.4.1. **10a**

A white solid; yield 0.73 g (68%), mp. 119–121 °C (*i*Pr_2O–EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.09 (m, 5H, Ph), 6.63 (s, 1H, H-11), 6.37 (s, 1H, H-8), 5.47 (dd, $J = 3.3$, 11.6 Hz, 1H, H-2*ax*), 5.43 (d, $J = 3.3$ Hz, 1H, H-11b), 4.13 (dd, $J = 1.2$, 11.6 Hz, 1H, H-2*eq*), 3.82 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.41 (ddd, $J = 2.7$, 4.7, 11.0 Hz, 1H, H-6*eq*), 3.35 (t, $J = 3.3$ Hz, 1H, H-1), 2.87 (dt, $J = 3.0$, 11.2 Hz, 1H, H-6*ax*), 2.76 (ddd, $J = 4.6$, 11.2, 15.3 Hz, 1H, H-7*ax*), 2.54 (td, $J = 2.7$, 15.3 Hz, 1H, H-7*eq*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.7, 147.6 (C-9 and C-10), 138.8, 129.8, 127.9, 127.2, 126.9, 125.4, 111.3 (C-8), 108.8 (C-11), 63.7 (C-2), 56.2, 55.8 (2× OCH_3), 49.6 (C-11b), 45.0 (C-1), 44.0 (C-6), 28.9 (C-7) ppm.

Anal. Calcd. for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90; S, 8.92. Found: C, 63.68; H, 5.46; N, 4.03; S, 9.00.

2.4.2. **11a**

A yellow solid, yield 0.61 g (57%), mp. 235–239 °C (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45–7.35 (m, 5H, Ph), 6.63 (s, 1H, H-11), 6.53 (s, 1H, H-8), 5.80 (dd, 1H, $J = 5.6$, 8.6 Hz, H-2), 4.56 (dd, 1H, $J = 6.0$, 8.8 Hz, H-11b), 3.86 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.56 (td, $J = 5.0$, 12.0 Hz, 1H, H-6*eq*), 3.34 (ddd, $J = 4.0$, 9.2, 12.4 Hz, 1H, H-6*ax*), 3.10 (ddd, $J = 5.4$, 9.2, 15.2 Hz, 1H, H-7*ax*), 2.77 (td, $J = 4.6$, 16.3 Hz, 1H, H-7*eq*), 2.60 (ddd, $J = 6.2$, 8.0, 14.2 Hz, 1H, H-1*eq*), 2.52 (ddd, $J = 6.0$, 9.1, 14.1 Hz, 1H, H-1*ax*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.7, 148.5, 139.9, 129.4, 129.4, 129.0, 128.5, 127.1, 126.9, 126.9, 112.4, 108.9, 70.4 (C-2), 56.8, 56.5 (2× OCH_3), 51.5 (C-11b), 40.8 (C-6), 39.4 (C-1), 29.2 (C-7) ppm.

Anal. Calcd. for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90; S, 8.92. Found: C, 63.12; H, 6.01; N, 3.78; S, 9.10.

2.4.3. **12a**

A white solid; yield 0.21 g (19%), mp. 124–125 °C (*i*Pr_2O–EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41–7.33 (m, 5H, Ph), 6.59 (s, 1H, H-11), 6.56 (s, 1H, H-8), 6.05 (dd, $J = 2.4$, 12.0 Hz, 1H, H-2), 5.23 (dd, $J = 2.8$, 11.8 Hz, 1H, H-11b), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.40 (ddd, $J = 4.6$, 8.0, 11.7 Hz, 1H, H-6*ax*), 3.33 (td, $J = 5.3$, 11.7 Hz, 1H, H-6*eq*), 2.96 (ddd, $J = 5.2$, 8.0, 15.9 Hz, 1H, H-7*ax*) 2.89 (td, $J = 5.0$, 15.9 Hz, 1H, H-7*eq*), 2.30 (td, $J = 11.9$, 14.2 Hz, 1H, H-1*ax*), 2.11 (td, $J = 2.7$, 14.2 Hz, 1H, H-1*eq*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.2, 148.0 (C-9 and C-10), 139.5, 128.9, 128.8, 127.5, 126.7, 126.7, 125.7, 125.7, 111.7 (C-11), 108.8 (C-8), 70.4 (C-2), 56.1, 56.0 (2× OCH_3), 47.1 (C-11b), 40.6 (C-6), 37.4 (C-1), 28.9 (C-7) ppm.

Anal. Calcd. for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90; S, 8.92. Found: C, 62.91; H, 5.52; N, 4.12; S, 9.35.

2.4.4. **13**

A white solid, yield 0.15 g, (13%), mp. 172–176 °C (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22–7.16 (m, 5H, Ph), 6.66 (s, 1H, H-11), 6.40 (s, 1H, H-8), 5.36 (d, $J = 3.2$ Hz, 1H, H-11b), 5.29 (dd, $J = 3.2$, 11.6 Hz, 1H, H-2*ax*), 4.80 (d, $J = 11.6$ Hz, 1H, H-2*eq*), 3.87 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.69 (td, $J = 5.6$, 11.2 Hz, 1H, H-6*eq*), 3.32 (t, $J = 3.2$ Hz, 1H, H-1), 3.17 (ddd, $J = 4.0$, 8.0, 11.6 Hz, 1H, H-6*ax*), 2.60 (td, $J = 4.8$, 16.0 Hz, 1H, H-7*eq*), 2.53 (ddd, $J = 4.8$, 8.4, 16.0 Hz, 1H, H-7*ax*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.5, 148.2 (C-9 and C-10), 135.5, 129.9, 128.9, 128.5, 128.3, 128.0, 125.6, 123.5, 111.5 (C-11), 109.8 (C-8), 65.9 (C-2), 56.2, 56.0 (2× OCH_3), 52.4 (C-11b), 44.1 (C-1), 43.1 (C-6), 29.8 (C-7) ppm.

Anal. Calcd. for $C_{19}H_{21}NO_5S$: C, 60.78; H, 5.64; N, 3.73; S, 8.54. Found: C, 61.03; H, 5.49; N, 3.81; S, 8.66.

2.4.5. **14**

A white solid; yield 0.12 g (11%), mp. 175–176 °C (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.31 (m, 5H, Ph), 6.62 (s, 1H, H-8), 6.54 (s, 1H, H-11), 5.85 (dd, $J = 3.2$, 12.0 Hz, 1H, H-2), 5.19 (dd, $J = 3.2$, 12.0 Hz, 1H, H-11b), 3.88 (dd, $J = 6.0$, 15.2 Hz, 1H, H-6*eq*), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.38 (dt, $J = 4.0$, 11.6 Hz, 1H, H-6*ax*), 3.10 (ddd, $J = 5.6$, 11.6, 16.4 Hz, 1H, H-7*ax*), 2.79 (td, $J = 3.0$, 16.4 Hz, 1H, H-7*eq*), 2.29 (td, $J = 12.0$, 14.8 Hz, 1H, H-1*ax*), 2.10 (td, $J = 3.2$, 15.2 Hz, 1H, H-1*eq*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.0, 148.5 (C-9 and C-10), 137.8, 129.9, 129.4, 127.6, 127.4, 126.8, 125.5, 125.2, 111.9, 109.6 (C-8 and C-11), 85.1 (C-2), 57.3 (C-11b), 56.6, 56.5 (2× OCH_3), 40.9 (C-6), 35.6 (C-1), 28.7 (C-7) ppm.

Anal. Calcd. for $C_{19}H_{21}NO_5S$: C, 60.78; H, 5.64; N, 3.73; S, 8.54. Found: C, 60.52; H, 5.77; N, 3.81; S, 8.39.

2.4.6. *15*

A white solid; yield 0.11 g (10%), mp. 122–126 °C (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.35 (m, 5H, Ph), 6.62 (s, 1H, H-8), 6.54 (s, 1H, H-11), 5.85 (dd, $J = 2.6$, 12.0 Hz, 1H, H-2), 5.19 (dd, $J = 3.0$, 12.2 Hz, 1H, H-11b), 3.85 (m, 1H, H-6*eq*), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.38 (dt, $J = 3.8$, 11.6 Hz, 1H, H-6*ax*), 3.08 (ddd, $J = 5.8$, 11.4, 16.1 Hz, 1H, H-7*ax*), 2.80 (td, $J = 3.0$, 15.9 Hz, 1H, H-7*eq*), 2.28 (td, $J = 12.1$, 14.6 Hz, 1H, H-1*ax*), 2.11 (td, $J = 2.9$, 15.0 Hz, 1H, H-1*eq*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.6 (C-10), 148.1 (C-9), 137.4, 129.4, 129.0, 126.4, 126.1, 126.1 (C-7a), 125.1, 125.1 (C-11a), 111.6 (C-8), 109.3 (C-11), 84.6 (C-2), 56.8 (C-11b), 56.2, 56.1 (2 × OCH_3), 40.5 (C-6), 35.2 (C-1), 28.3 (C-7) ppm.

Anal. Calcd. for $C_{19}H_{21}NO_5S$: C, 60.78; H, 5.64; N, 3.73; S, 8.54. Found: C, 60.99; H, 5.72; N, 3.62; S, 8.39.

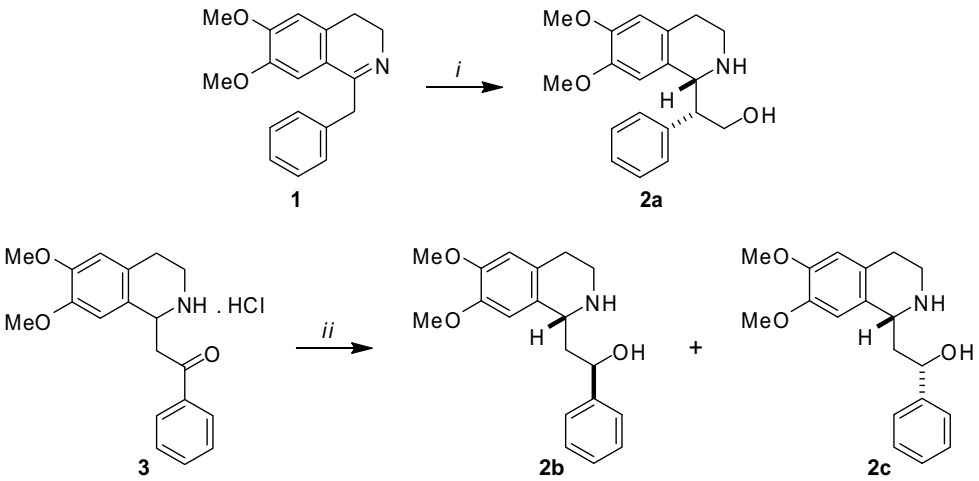
3. Results and discussion

3.1. Synthesis

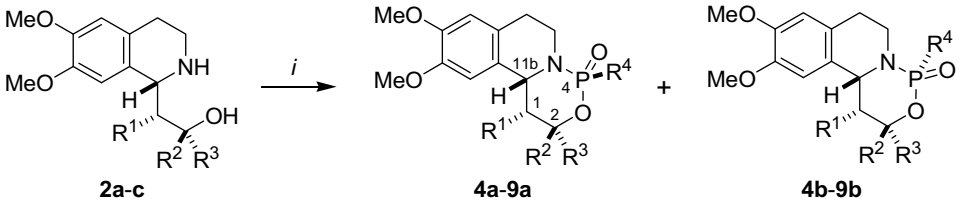
(1*R**,1'*R**)-1-(2'-Hydroxy-1'-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2a**), required for the synthesis of the target compounds, was prepared as a single diastereomer by reduction of the hydroxymethylated derivative of 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**1**) [10]. (1*R**,2'*R**)- and (1*R**,2'*S**)-1-(2'-hydroxy-2'-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2b** and **2c**) were obtained by $NaBH_4$ reduction of the corresponding β-amino ketone derivative **3** [10] and were separated by fractional crystallization (Scheme 1). Compound **3** was formed in good yield, by addition and subsequent decarboxylation of the oxo acid, prepared in situ by hydrolysis of the ethyl 3-oxo-3-phenylpropanoate, to 6,7-dimethoxy-3,4-dihydroisoquinoline.

The ring closures of the tetrahydroisoquinoline amino alcohols **2a–c** with $PhPOCl_2$ and bis(2-chloroethyl)phosphoramidic dichloride were carried out in anhydrous CH_2Cl_2 in the presence of Et_3N affording 1,3,2-oxazaphosphino[4,3-*a*]isoquinolines (**4–9**). The NMR spectra of the crude products indicated that the ratios of the diastereomers, differing in the *cis* or *trans* position of the *P*-substituent and the hydrogen at the annelation (H-11b), were only slightly influenced by the substituents on the phosphorus. The ring closure of **2a** with bis(2-chloroethyl)phosphoramidic dichloride proved to be highly diastereoselective in favour of the *trans* isomer (**7b**), since the *cis* counterpart (**7a**) could not be detected even in the crude product (Scheme 2). The *P*-epimeric diasteromers of **4**, **6** and **7** could be isolated by column chromatography, but all of our efforts to separate the diastereomers of **5** and **8** failed.

When amino alcohols **2** were reacted with $SOCl_2$ or SO_2Cl_2, 1,2,3-oxathiazino[4,3-*a*]isoquinoline 4-oxides (cyclic sulfamidites) **10–12** or 4,4-dioxides (cyclic sulfamidates) **13–15** were obtained (Scheme 3). The ^{1}H NMR spectra of the crude sulfamidites **10–12** indicated that each ring closure was highly diastereoselective. The highest selectivity was found for the 1-phenyl-substituted derivative **10**, when only one diastereomer could be detected in the crude product. For the 2-phenyl-substituted analogues **11** and **12**, although a mixture of S-4 epimeric products was formed, the *minor* diastereomers proved to undergo decomposition during the chromatographic purification process. A similar decomposition of the *minor* diastereomers was observed in the cyclizations towards the analogous 1- or 2-methyl-substituted tetrahydro-2*H*-1,2,3-oxathiazino[4,3-*a*]isoquinoline 4-oxides [17]. The ^{1}H NMR spectra demonstrated that the isolated products of cyclic sulfamidite type contained the S=O bond and the hydrogen at the annelation (H-11b) in the *cis* position (**a**).

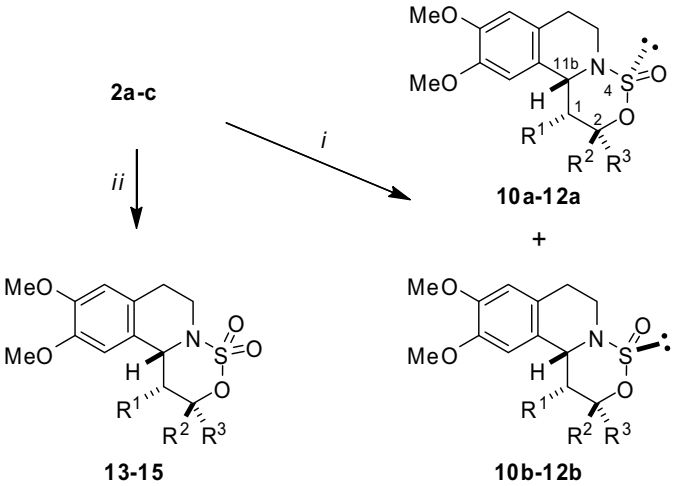


Scheme 1. Reagents and conditions: (i) 1—CH_2O, NaOEt, EtOH, rt; 2—$NaBH_4$, MeOH, 0 °C → rt, see Ref. [10]; (ii) $NaBH_4$, MeOH, 0 °C → rt, then rt, 3 h, then fractional crystallization.



Compd.	R^1	R^2	R^3	R^4	Diastereomer ratio (**a** : **b**) in the crude product
4	Ph	H	H	Ph	55 : 45
5	H	Ph	H	Ph	55 : 45
6	H	H	Ph	Ph	55 : 45
7	Ph	H	H	$N(CH_2CH_2Cl)_2$	~0 : ~100
8	H	Ph	H	$N(CH_2CH_2Cl)_2$	45 : 55
9	H	H	Ph	$N(CH_2CH_2Cl)_2$	45 : 55

Scheme 2. Reagents and conditions: (i) $PhPOCl_2$, CH_2Cl_2, Et_3N, 6 °C → rt, then rt, 24 h or $(ClCH_2CH_2)_2NPOCl_2$, CH_2Cl_2, Et_3N, rt, 48 h, 13–34%.



Compd.	R^1	R^2	R^3	Diastereomer ratio (**a** : **b**) in the crude product
10/13	Ph	H	H	~100 : ~0
11/14	H	Ph	H	78 : 22
12/15	H	H	Ph	84 : 16

Scheme 3. Reagents and conditions: (i) $SOCl_2$, Et_3N, CH_2Cl_2, –15 °C → rt, then rt, 50 h, 19–68%; (ii) SO_2Cl_2, Et_3N, abs. CH_2Cl_2, –15 °C → rt, then rt, 50 h, 10–13%.

3.2. Structure

Similarly to those of nitrogen-bridged saturated bi- or polycycles, the stereostructures of the prepared 1,6,7,11b-tetrahydro-2*H*-1,3,2-oxazaphosphino[4,3-*a*]isoquinolines (**4–9**) and 1,6,7,11b-tetrahydro-2*H*-1,2,3-oxathiazino[4,3-*a*]-isoquinolines (**10–15**) can be characterized by a conformational equilibrium of *cis*[1]–*trans*–*cis*[2] type [9–15,31]. In the *trans* structure, the B/C hetero rings are *trans*-connected, with a *di-pseudoaxial* arrangement of H-11b and the nitrogen lone pair. In the two other conformations, the hetero rings are *cis*-connected: for the *cis*[1] conformation, C-1 is in the *pseudoaxial* (*inside*) position, while for the *cis*[2] conformation, C-1 is in the *pseudoequatorial* (*out-*

side) position relative to the tetrahydropyridine ring (Fig. 1).

The phosphorus can effect distortion in the heterocyclic ring. Earlier studies of the substituent effects on the conformational states of the 1,3,2-oxazaphosphinane ring [14,15,32] led to the conclusion that this ring could usually be characterized by a chair (as in Fig. 1) or a twist conformation.

The stereochemistry of the compounds was determined from the characteristic vicinal couplings, and the significant differences in the chemical shifts for the indicator nuclei, and by comparison of the measured and calculated NMR values. Both the energy differences between the preferred conformers and the stereochemistry in the frozen conformers, as calculated, were employed.

The orientation of H-11b was assigned by using the vicinal coupling constants between H-11b and H-1. We observed one small and one large coupling (except for **11a**), which excluded the *cis*[2] connection of the B/C rings.

Significant experimental and calculated coupling constants, displaying a good correlation, are given in Table 1; they support the assignments given later.

3.2.1. Configurations of 1,6,7,11b-tetrahydro-2H-1,3,2-oxazaphosphino[4,3-a]isoquinolines (4–9)

The configurations of these compounds could be determined from the chemical shifts of the phosphorus atom and of H-2*ax* and H-11b: H-2*ax* and H-11b have larger chemical shifts when X=O (X: P, S) is *axial*, due to the 1,3-*diaxial* effect (Table 2). In this conformation, the chemical shift of the phosphorus atom was found to be larger, as observed previously [20,21].

In order to complete the series of compounds **4**, **6**, **7** and **9**, the NMR parameters of **7a** were calculated because only

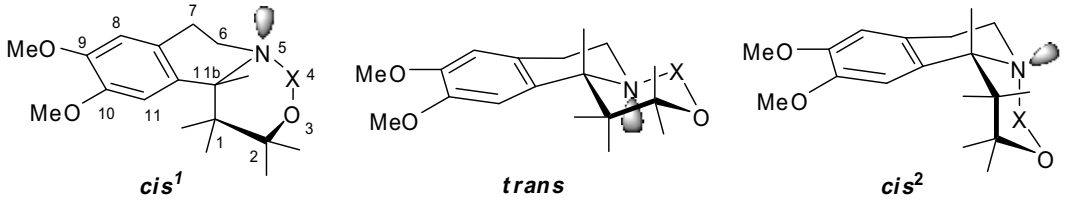


Fig. 1. Possible connections of the B/C rings in 9,10-dimethoxy-1,6,7,11b-tetrahydro-2*H*-1,3,2-oxazaphosphino- (X = P) and 1,2,3-oxathiazino[4,3-*a*]-isoquinolines (X = S).

Table 1
Selected vicinal coupling constants (in Hz)

Compound	H-1*ax*–H-11b		H-1*eq*–H-11b		Compound	H-1*ax*–H-11b		H-1*eq*–H-11b	
	Calcd.	Measured	Calcd.	Measured		Calcd.	Measured	Calcd.	Measured
4a	–[a]	–[a]	3.0	3.1	**4b**	–[a]	–[a]	4.1	3.7
6a	9.9	10.7	2.6	3.8	**6b**	9.8	11.0	2.4	3.3
7a	–[a]	–[b]	3.6	–[b]	**7b**	–[a]	–[a]	3.0	1.0
9a	10.1	11.0	1.8	4.0	**9b**	9.9	11.0	2.6	1.5
10a	–[a]	–[a]	3.6	3.3	**13**	–[a]	–[a]	3.4	3.2
11a	8.6	8.8	7.6	6.0	**14**	10.8	12.0	2.2	3.2
12a	10.6	11.8	3.1	2.7	**15**	10.8	12.2	2.9	3.0

[a] Missing value due to the lack of H-1*ax*.
[b] Missing value since **7a** was not formed in the ring-closure reaction.

Table 2
Selected chemical shifts (in ppm; $\delta_{TMS} = 0$ ppm, $\delta_{H3PO4} = 0$ ppm)

Compound	^{31}P		H-2*ax*		H-11b		C-2		C-6	
	Calcd.	Measured	Calcd.	Measured	Calcd.	Measured	Calcd.	Measured	Calcd.	Measured
4a	22.4	19.6	4.39	4.67	4.39	4.90	72.0	71.8	38.1	40.6
4b	31.6	24.1	5.23	5.21	5.45	5.39	68.5	70.4	40.8	42.0
6a	21.1	19.1	5.00	5.27	4.12	4.67	79.6	79.6	36.6	40.1
6b	30.0	21.8	5.82	5.82	5.29	4.96	76.1	76.9	39.8	41.5
7a	13.3	–[a]	4.51	–[a]	4.83	–[a]	69.1	–[a]	39.9	–[a]
7b	21.8	11.5	4.30	4.80	5.17	5.03	70.1	71.4	40.0	40.0
9a	15.3	10.9	5.07	5.46	4.49	4.76	83.9	80.4	39.3	40.7
9b	19.4	15.1	5.24	5.64	4.72	4.78	78.1	78.0	41.5	41.4

[a] Missing value since **7a** was not formed in the ring-closure reaction.

7b could be isolated and thus **7a** could not be studied experimentally.

3.2.2. Conformations of 1,6,7,11b-tetrahydro-2H-1,3,2-oxazaphosphino[4,3-a]isoquinolines (**4–9**)

*3.2.2.1. Compounds **4** and **7**.* There is a significant difference between the ^{31}P chemical shifts of **a** and **b**: the chemical shifts of the **b** isomers are downfield from those of the **a** analogues. The chemical shifts of H-2*ax* and H-11b are upfield for the **a** isomers as compared with the analogous **b** isomer (Table 2). This experimental information suggests the *axial* position of the P═O bond in **b** and the *equatorial* position in the **a** isomers.

The 1-phenyl group is *axial* and *trans* to H-11b, as shown by the small value of ^{3}J(H-1,H-11b) (3.0 Hz for **4a**, 3.7 Hz for **4b** and <1 Hz for **7b**). The chemical shift for C-2 is upfield and that for H-2*ax* is downfield in **4b** as compared with those in **4a**. These facts confirm the *axial* position of P═O in the **b** compound and the *equatorial* position in **a**.

The downfield shift (by 1.4 ppm) of C-6 in **4b** as compared with **4a**, in the absence of steric hindrance between Ph and H-6*ax* in the *cis*^{1} form, suggests that the connection of the B/C rings is *trans* for **4b** and *cis*^{1} for **4a**. The moderate values of the coupling constants between H-6 and H-7 in the ^{1}H NMR spectrum of **4a** suggest the possibility of two *cis*^{1} conformations in equilibrium. This is in accordance with the calculations as given in Fig. 2.

The same result with respect to the configuration and conformation was obtained for isomers **7**; H-2*ax* has a larger chemical shift than H-2*eq* which suggests the *axial* state of the P═O bond, with **7b** as the isolated isomer. The calculated and the measured values likewise correlated excellently, suggesting the *trans* connection of the B/C rings, which is favourable because of the *axial* 1-phenyl substituent.

*3.2.2.2. Compounds **5** and **8**.* The NMR spectra of the diastereomeric mixtures of **5** and **8** did not contain evaluable multiplets but only overlapping signals.

The theoretical calculations, however, revealed that the B/C heterorings are *trans*-connected in both **5b** and **8b**, with a twisted boat conformation of ring C, while in the isomers **5a** and **8a**, the B/C rings are *cis*^{1}-connected, with a chair conformation of ring C (Fig. 3).

*3.2.2.3. Compounds **6** and **9**.* We observed *trans-diaxial* coupling between H-1*ax* and H-11b in **6** and **9** (Table 3), which excludes the *cis*^{2}-connected form. The downfield shift (by 1.4 ppm for **6** and 0.7 ppm for **9**) of the C-6 resonances (Table 2) of isomers **b** with respect to the **a** analogues and the absence of steric hindrance in the *cis*^{1} form (because of the pure H-1*ax* and H-6*ax* positions concluded from the corresponding couplings) suggests a *trans* B/C connection for **b** and *cis*^{1} for **a**. The moderate values of the coupling constants between H-6 and H-7 in the ^{1}H NMR spectra of **6a** and **9a** point to the possibility of two *cis*^{1} conformations in

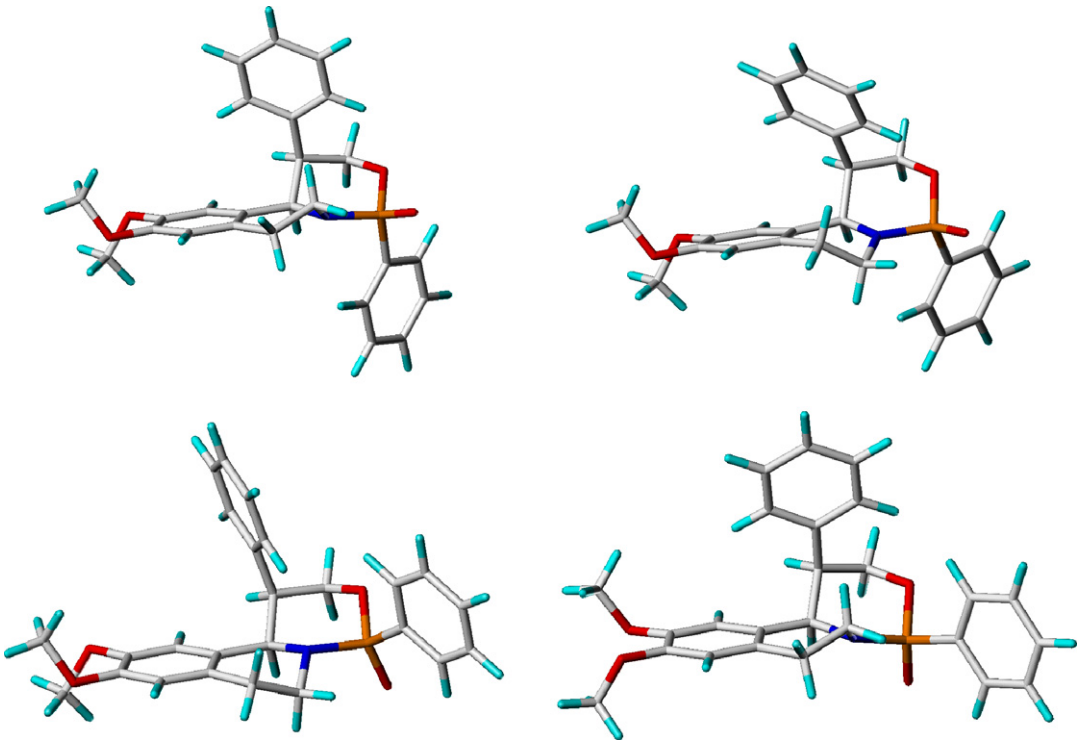


Fig. 2. Calculated global (left) and local (right) energy minima of **4a** (top, $\Delta E = 0.16$ kcal/mol) and **4b** (bottom, $\Delta E = 3.93$ kcal/mol).

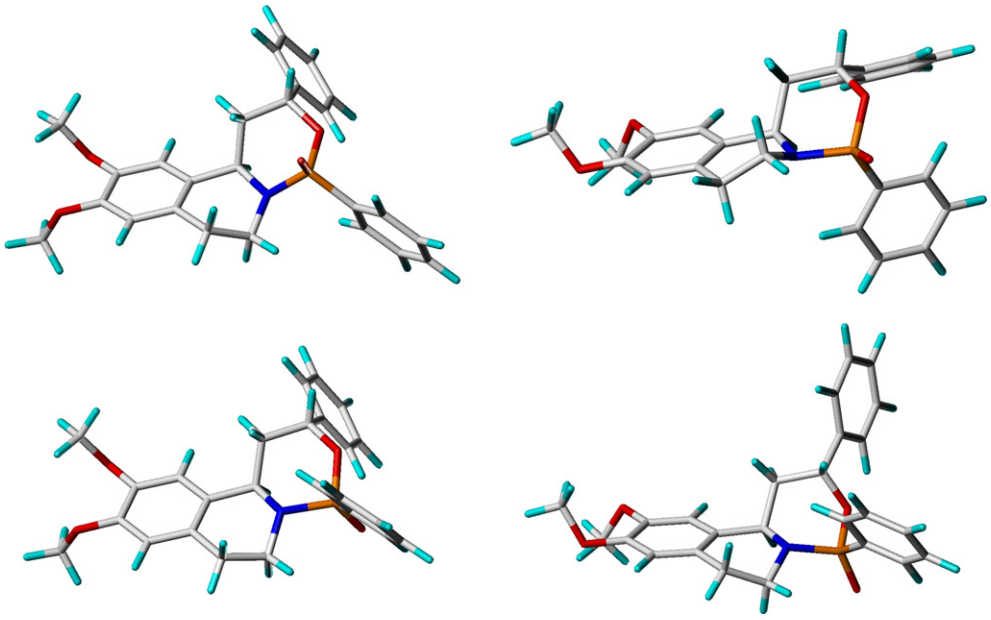


Fig. 3. Calculated global (left) and local (right) energy minima of **5a** (top, $\Delta E = 3.28$ kcal/mol) and **5b** (bottom, $\Delta E = 1.51$ kcal/mol).

equilibrium. This is in accordance with the calculations (*cf.* Table 3 and Fig. 4).

3.2.3. Configurations and conformations of 1,6,7,11b-tetrahydro-2H-1,2,3-oxathiazino[4,3-a]isoquinolines (*10–15*)

To determine the configurations of the sulfur atom in the sulfamidites, the theoretical ^{1}H NMR chemical shifts were analysed. They are nearly the same in the sulfamidites and sulfamidates if the S=O bond is *axial* (*cis* to the H-11b). Due to the 1,3-*diaxial* effect, H-11b and H-2*ax* have larger chemical shifts in the **a** isomers, where S=O is *axial*, than in the **b** isomers, where S=O is *equatorial* (Table 4). The experimental values of the isolated isomers correlated very well with the calculated chemical results on the **a** isomers. The calculated and experimental chemical shifts of the sulfones **13–15** are also given. Even if there is no stereochemical assignment, they impressively corroborate the quality of the theoretical calculations.

3.2.3.1. Compounds *10* and *13*.

The 1-phenyl-substituted compounds (**10a** and **13**) have ^3J(H-1,H-11b) values of

Table 3
Selected vicinal coupling data (in Hz)

Compound		H-1*ax*–H-2*ax*	H-1*eq*–H-2*ax*	H-1*eq*–H-2*eq*	H-6*ax*–H-7*ax*	H-6*ax*–H-7*eq*	H-6*eq*–H-7*ax*	H-6*eq*–H-7*eq*	P–H-2*ax*	P–H-2*eq*	P–H-11b
4a	Meas.	–[a]	6.3	2.5	10.7	2.8	4.0	<1	4.5	18.6	3.0
	Calcd.	–[a]	3.5	1.2	10.5	2.9	5.7	1.6	0.6	19.8	1.8
4b	Meas.	–[a]	3.4	1.9	12.3	2.3	5.0	<1	4.0	21.3	3.7
	Calcd.	–[a]	3.4	1.4	10.4	2.6	5.0	1.4	3.6	21.5	4.2
6a	Meas.	11.3	2.7	–[b]	8.8	3.7	4.3	4.1	1.9	–[b]	<1
	Calcd.	10.0	1.9	–[b]	10.3	2.6	5.1	1.8	2.6	–[b]	3.1
6b	Meas.	11.7	1.6	–[b]	10.0	1.5	<1	<1	1.6	–[b]	2.1
	Calcd.	10.0	2.0	–[b]	9.8	2.0	4.4	2.3	1.7	–[b]	0.1
7a	Meas.	–[a]	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]
	Calcd.	–[a]	10.3	3.1	10.7	2.6	5.2	2.1	1.1	21.9	2.0
7b	Meas.	–[a]	6.0	3.0	11.0	3.0	4.5	<1	12.5	13.5	1.0
	Calcd.	–[a]	3.7	1.0	10.4	2.9	5.9	1.6	1.1	21.9	2.0
9a	Meas.	12.0	2.5	–[b]	9.8	4.8	3.0	4.5	3.0	–[b]	3.5
	Calcd.	10.5	0.3	–[b]	9.1	0.9	2.6	2.1	0.8	–[b]	1.8
9b	Meas.	12.0	1.5	–[b]	13.0	<1	4.0	<1	<1	–[b]	<1
	Calcd.	10.2	2.0	–[b]	10.5	2.6	5.1	1.9	2.2	–[b]	2.6

[a] Missing value due to the lack of H-1*ax*.
[b] Missing value due to the lack of H-2*eq*.
[c] Missing value since **7a** was not formed in the ring-closure reaction.

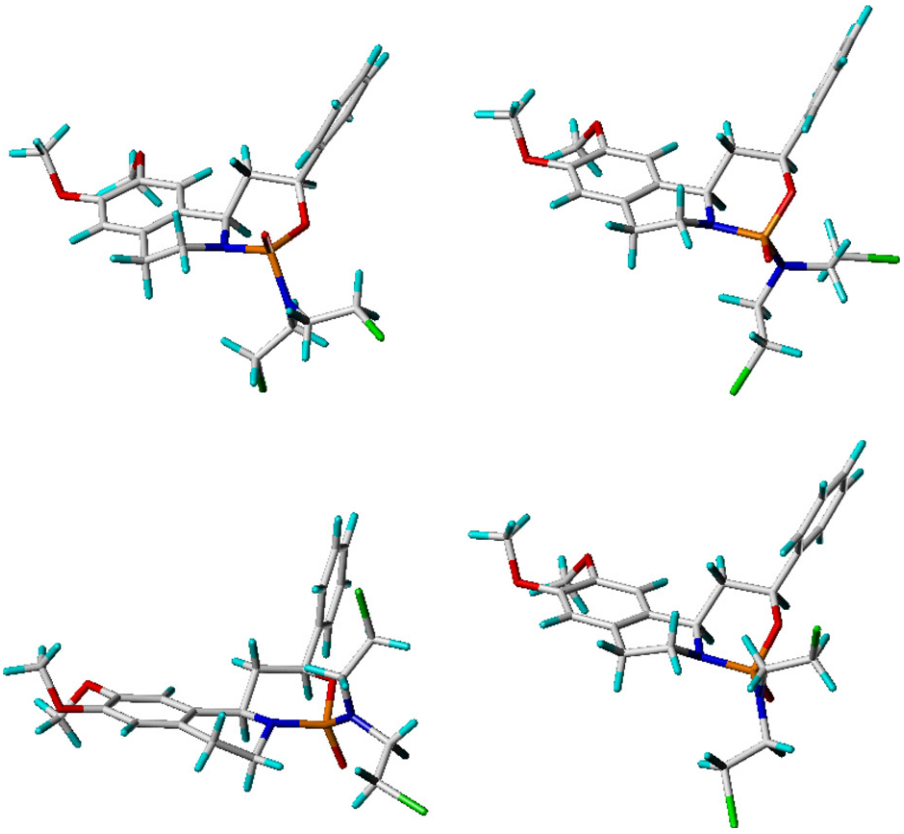


Fig. 4. Calculated global (left) and local (right) energy minima of **9a** (top, $\Delta E = 3.28$ kcal/mol) and **9b** (bottom, $\Delta E = 1.51$ kcal/mol).

Table 4
Experimental and calculated characteristic chemical shifts (in ppm; $\delta_{TMS} = 0$)

Compound	H-11b			H-2*ax*			H-2*eq*			C-2			C-6		
	Calcd. for **a**	Calcd. for **b**	Exp.	Calcd. for **a**	Calcd. for **b**	Exp.	Calcd. for **a**	Calcd. for **b**	Exp.	Calcd. for **a**	Calcd. for **b**	Exp.	Calcd. for **a**	Calcd. for **b**	Exp.
10	5.64	4.56	5.43	5.51	4.69	5.47	3.80	4.66	4.13	61.7	68.9	63.7	43.9	39.4	44.0
11	4.46	4.48	4.56	–[a]	–[a]	–[a]	5.13	5.60	5.80	70.6	76.5	70.4	41.9	45.1	40.8
12	5.37	4.53	5.23	5.86	5.06	6.05	–[b]	–[b]	–[b]	68.6	76.0	70.4	39.5	30.5	40.6
13	5.18		5.36	5.31		5.29	4.63		4.80	73.3		65.9	40.9		43.1
14	5.22		5.19	–[a]		–[a]	5.44		5.85	80.8		85.1	39.8		40.9
15	5.16		5.19	5.63		5.85	–[b]		–[b]	80.2		84.6	42.0		40.5

[a] Missing value due to the lack of H-2*ax*.
[b] Missing value due to the lack of H-2*eq*.

3.3 and 3.2 Hz. Consequently, the 1-phenyl group in the preferred conformation must be *axial* (in agreement with the theoretical calculations; *cf*. Fig. 5).

In the *cis*[1] structure, very strong steric hindrance can be expected between the phenyl group and H-6*ax*; thus, the *cis*[1] conformation could be excluded, and the connection of the B/C rings should be *trans*. This stereostructure is supported by the downfield shift of C-6 (2.9 ppm for **13** and 3.3 ppm for **10a** in comparison with the unsubstituted compounds [13]) and the absence of the phenyl substituent effect which is expected for the *cis*-connected B/C rings and corroborated by the quantum chemical calculations: the *trans*-anellated molecule is 0.46 and 1.76 kcal/mol more stable than the other conformer, which is actually *cis*[1] (*cf*. Fig. 5).

The chemical shifts of H-11b in **13** and **10a** are similar. The changes in the chemical shifts of H-2*ax*, H-6*ax* and H-6*eq* are moderate (0.18; 0.30 and 0.28 ppm) but in H-2*eq* there is a large chemical shift difference (0.67 ppm). This experimental NMR information suggest the *axial* position of the S=O bond in **10a**. Since the changes in the chemical shifts of C-2 and C-11b are similar (2.2 and 2.8 ppm) and that of C-6 is practically unchanged in **10a**, preference for the *trans* conformation can be concluded (Fig. 5).

The moderate values of the coupling constants between H-6 and H-7 in the ^{1}H NMR spectra of **10a** and **13** (Table 5) suggest the flexibility of ring B.

In order to complete the series of S-containing compounds (**10–15**), the NMR parameters of **10b–12b** were cal-

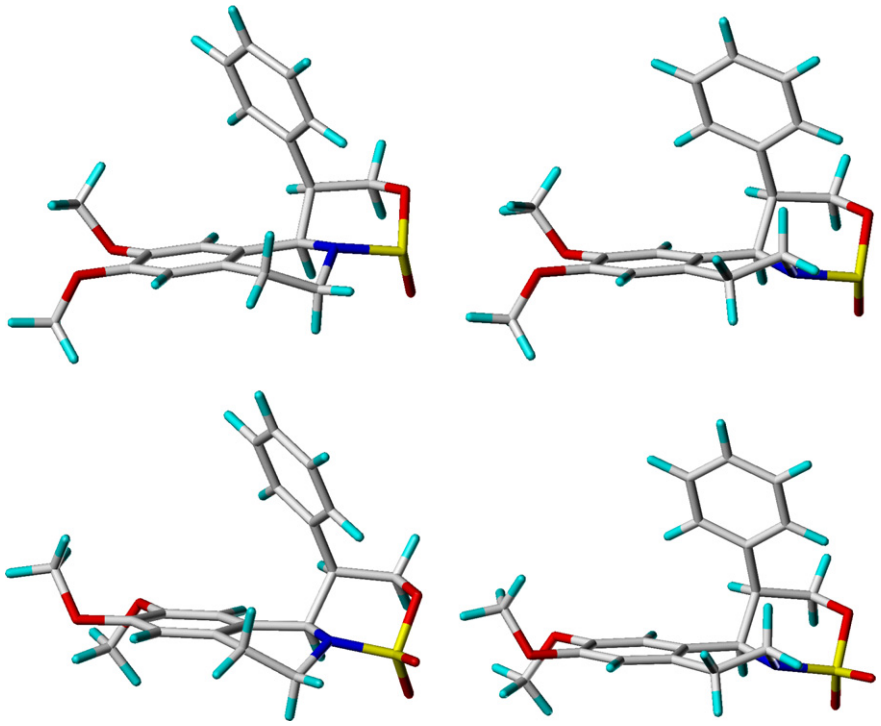


Fig. 5. Calculated global (left) and local (right) energy minimum conformations for **10a** ($\Delta E = 1.76$ kcal/mol, top) and for **13** ($\Delta E = 0.46$ kcal/mol, bottom).

Table 5
Selected vicinal coupling data (in Hz)

Compound		H-1*ax*–H-2*ax*	H-1*ax*–H-2*eq*	H-1*eq*–H-2*ax*	H-1*eq*–H-2*eq*	H-6*ax*–H-7*ax*	H-6*ax*–H-7*eq*	H-6*eq*–H-7*ax*	H-6*eq*–H-7*eq*
10a	Meas.	–[a]	–[a]	3.3	1.2	11.2	3.0	4.7	2.7
	Calcd.	–[a]	–[a]	3.5	1.2	10.3	2.4	4.6	2.1
10b	Meas.	–[a]	–[a]	–[b]	–[b]	–[b]	–[b]	–[b]	–[b]
	Calcd.	–[a]	–[a]	3.2	1.2	10.0	2.2	4.4	2.4
11a	Meas.	–[c]	6.0	–[c]	8.6	9.2	4.0	5.4	4.6
	Calcd.	–[c]	5.6	–[c]	9.8	10.2	2.9	5.8	1.4
11b	Meas.	–[c]	–[b]	–[c]	–[b]	–[b]	–[b]	–[b]	–[b]
	Calcd.	–[c]	5.8	–[c]	9.7	10.2	2.1	5.9	2.0
12a	Meas.	12.0	–[d]	2.4	–[d]	8.0	4.6	5.2	5.0
	Calcd.	10.1	–[d]	2.4	–[d]	10.4	1.5	5.9	2.3
12b	Meas.	–[b]	–[d]	–[b]	–[d]	–[b]	–[b]	–[b]	–[b]
	Calcd.	9.7	–[d]	2.0	–[d]	10.6	1.6	5.9	2.1
13	Meas.	–[a]	–[a]	3.2	<1	8.0	4.0	5.6	4.8
	Calcd.	–[a]	–[a]	3.5	1.0	10.3	2.2	4.5	2.4
14	Meas.	–[c]	12.0	–[c]	3.2	11.6	4.0	6.0	2.0
	Calcd.	–[c]	6.2	–[c]	1.1	10.5	1.3	5.9	2.3
15	Meas.	12.0	–[d]	2.6	–[d]	11.4	3.8	5.8	3.0
	Calcd.	10.3	–[d]	2.4	–[d]	10.6	1.3	5.8	2.3

[a] Missing value due to the lack of H-1*ax*.
[b] Missing value since **10b**, **11b** and **12b** could not be isolated.
[c] Missing value due to the lack of H-2*ax*.
[d] Missing value due to the lack of H-2*eq*.

culated because only the **a** isomers could be isolated; thus, **10b–12b** could not be studied experimentally. The calculations suggest *cis*[1] as the most stable conformation, which is 1.15 kcal/mol more stable than the *trans*-connected conformer.

*3.2.3.2. Compounds **11** and **14**.* We observed *trans*-^3J(H,H) coupling between H-1*ax* and H-11b in **14** (Table 1). This excludes the *cis*[2] conformation for this compound. Moreover, the chemical shift of C-6 is similar in **14** and in the unsubstituted sulfamidate (40.9 ppm) [13]. In the *cis*[1] form,

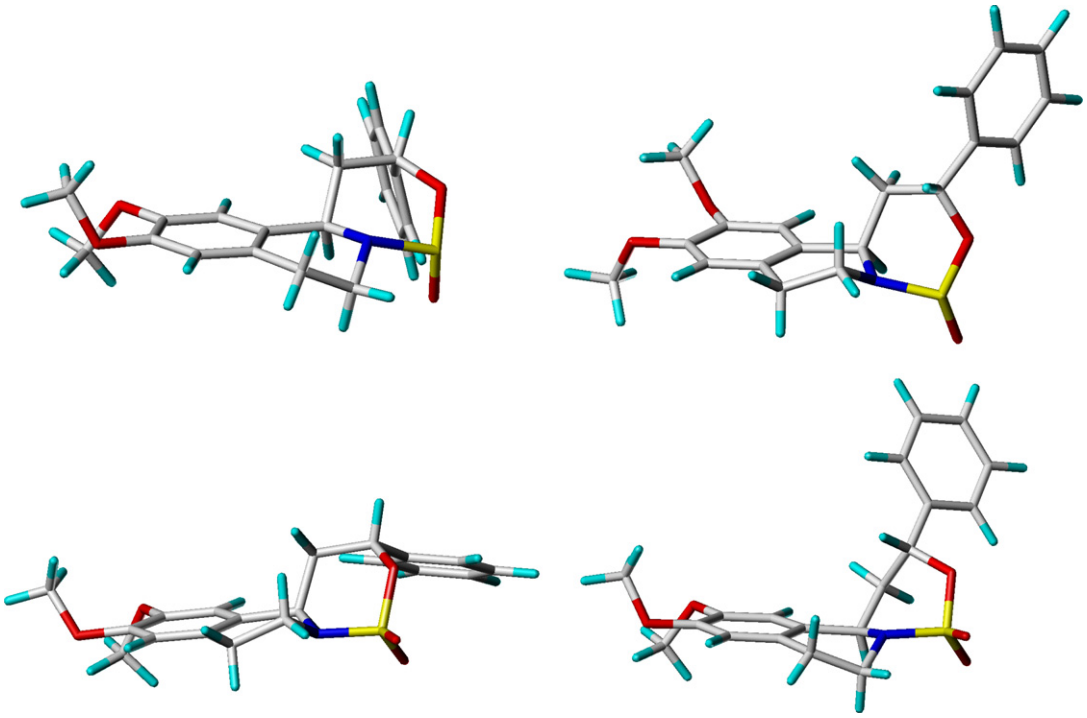


Fig. 6. Calculated global (left) and local (right) energy minimum conformations for **11a** ($\Delta E = 0.9$ kcal/mol, top) and **14** ($\Delta E = 0.6$ kcal/mol, bottom).

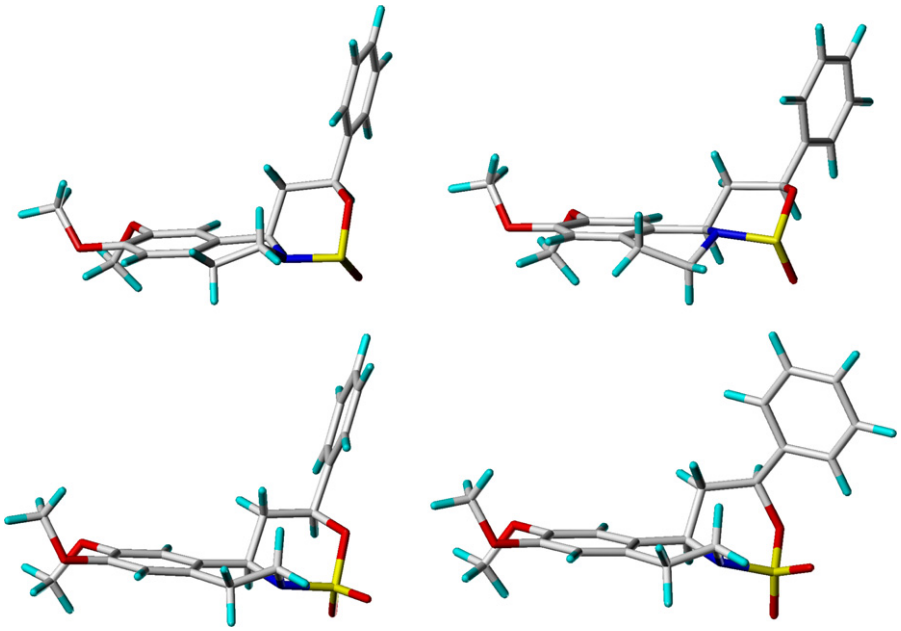


Fig. 7. Calculated global (left) and local (right) energy minimum conformations for **12a** ($\Delta E = 0.9$ kcal/mol, top) and **15** ($\Delta E = 9.5$ kcal/mol, bottom).

H-1*ax* and H-6*ax* are very close and this causes an upfield shift in the C-6 signal. The chemical shift of C-11b is upfield in **15** as compared with **14**, which suggests the *axial* position of the phenyl group in **14** and the *equatorial* position in **15**. Accordingly, the chemical shift of H-2 is larger because of the anisotropic neighbouring effect of the S=O bond in the 1,3-*diaxial* position [33]. Except for the effects of the phenyl substitution (downfield shifts in C-1 and C-2), no significant changes were observed for the ^{1}H and ^{13}C NMR chemical shifts of the unsubstituted compound as compared with **14**. Hence, *cis*[1] can be regarded as the preferred conformer.

For **11a**, ^{3}J(H-1*ax*–H-11b) and ^{3}J(H-1*eq*–H-11b) are 8.8 and 6.0 Hz, respectively, which suggest the *equatorial* position of H-11b on the oxazaphosphinane ring; ^{3}J(H-1*ax*–H-2) and ^{3}J(H-1*eq*–H-2) are 8.6 and 5.6 Hz, which indicate a

Table 6
Stereochemical assignments for **4**–**15**

Compound	Steric position of H-11b and the P-substituent or the S=O group	Stereochemistry of the junction of the hetero rings
4a	*cis*	*cis*^{1}
4b	*trans*	*trans*
6a	*cis*	*cis*^{1}
6b	*trans*	*trans*
7b	*trans*	*trans*
9a	*cis*	*cis*^{1}
9b	*trans*	*trans*
10a	*cis*	*trans*
11a	*cis*	*trans*-*cis*^{1}
12a	*cis*	*cis*^{1}
13	–	*trans*
14	–	*cis*^{1}
15	–	*cis*^{1}

boat or a stereoheterogeneous conformation of ring C. Although the *ab initio* calculations show that the *trans*-connected chair form is 0.9 kcal/mol more stable than the *cis*^{1}-connected twisted boat form, the measured values accord with the conformational equilibrium of the two preferred conformations (Fig. 6).

The calculations for **11b** suggest the *cis*^{1} conformation (with a twisted structure in ring C), as the most stable which is 0.88 kcal/mol more stable than the *cis*^{1}-connected chair form.

*3.2.3.3. Compounds **12** and **15**.* *Trans*-^{3}J(H,H) coupling was observed between H-1*ax* and H-11b in the 2-phenyl-substituted derivatives **12a** and **15** (Table 4); this excludes the *cis*^{2} conformation in these compounds.

In **15**, the chemical shift of C-6 is similar to that in the unsubstituted sulfamidate (40.5 ppm) [13]. In the *cis*^{1} form, H-1*ax* and H-6*ax* are very close. This causes an upfield shift in the C-6 signal. Further, the chemical shift of H-2 is increased because of the anisotropic neighbouring effect of the S=O bond in 1,3-*diaxial* position [33]. Apart from the phenyl substituent effects (downfield for C-1 and C-2), no significant changes were observed for the ^{1}H and ^{13}C chemical shifts of the unsubstituted compound as compared with **15**; thus, the preferred conformer can be regarded as that with the *cis*^{1} B/C connection.

The chemical shifts of H-6*ax* and H-11b are virtually the same in the sulfamidate **15** and the sulfamidite **12a**. The change in H-2*ax* is moderate (0.20 ppm). The chemical shift of C-6 is practically the same in **12a**, which suggests the same preferred conformation (*cis*^{1}).

The moderate values of the coupling constants between H-6 and H-7 in the ^{1}H NMR spectra of **12a** and **15** point to the possibility of two *cis*^{1} conformations in equilibrium, as corroborated by the theoretical calculations (Fig. 7).

For **12b**, the calculations suggest that the *cis*^{1} conformation is 3.33 kcal/mol more stable than the energetically next most stable conformer (Table 6).

4. Conclusions

Diastereomers of novel 1- or 2-phenyl-substituted 4-[bis(2-chloroethyl)amino]- or 4-phenyl-9,10-dimethoxy-1,6,7,11b-tetrahydro-2*H*-1,3,2-oxazaphosphino[4,3-*a*]isoquinoline 4-oxides (**4–9**), and 9,10-dimethoxy-1,6,7,11b-tetrahydro-2*H*-1,2,3-oxathiazino[4,3-*a*]isoquinoline 4-oxides (**10–12**) and 4,4-dioxides (**13–15**) were prepared by ring-closure reactions of phenyl-substituted tetrahydroisoquinoline-1-ethanols with appropriate P- or S-containing agents.

NMR analysis and theoretical DFT calculations on the prepared tricycles revealed that the conformations of the 1- or 2-phenyl-substituted tetrahydro-1,3,2-oxazaphosphino[4,3-*a*]isoquinoline 4-oxides (**4–9**) depend neither on the position of the phenyl substituent nor on the relative configuration of C-2. The geometry of the connection of the B/C ring is influenced only by the relative configuration of P-4, independently of the substituent on the phosphorus atom: compounds containing a P=O group in the *trans* position relative to H-11b (diastereomers **a**) could be characterized by the *cis*^{1} conformation, while their *cis* counterparts (diastereomers **b**) contained *trans*-connected B/C rings. For the 1- or 2-phenyl-substituted tetrahydro-1,2,3-oxathiazino[4,3-*a*]isoquinoline 4-oxides and 4,4-dioxides, the position of the phenyl substitution exerted a significant effect on the predominant conformation: the connection of the B/C rings proved to be *trans* for the 1-phenyl-substituted derivatives (**10a** and **13**) while the conformational equilibria of the 2-phenyl-substituted analogues (**11a**, **12a**, **14**, **15**) were found to be shifted towards the *cis*^{1} form, independently of the relative configuration of C-2.

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