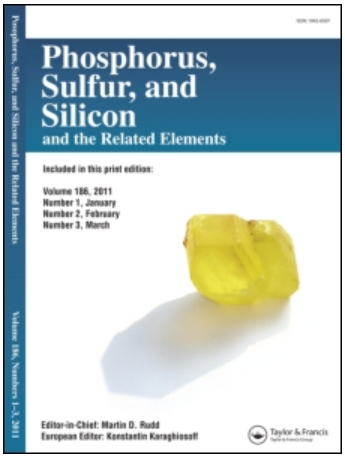

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Synthesis of New Cholesteryl and Adenosinyl Esters of 2-Furyl-*N*-phenylaminophosphonous Acids

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The synthesis of novel 2-furyl N-arylaminomethanephosphonous acids **2a**,**b** *and their cholesteryl and adenosinyl esters* **3a**,**b** *and* **4a**,**b**, *respectively, is presented.*

Keywords Adenosinyl aminophosphonites; aminophosphonous acids; cholesteryl aminophosphonites; formation of aminophosphonites

INTRODUCTION

The important biological function of aminophosphonic acids is well recognized.[1,2] Equally, the importance of 2-substituted furan derivatives as bioactive compounds is commonly known,[3] just to mention a series of nitrofurfural derived drugs such as nitrofurazone or nifurantoine[4] or the efficient anti-histamine agent ranitidine.[5]

Biological substances often bear in their structure a phosphorylated alcohol group, e.g., phospholipids, oligonucleotides, or carbohydrate phosphates.[6] Among them the synthesis and properties of mono- or dicholesteryl phosphites[7,8] has attracted much interest.

The synthesis of phosphites or phosphonates of various nucleosides is also of interest as they are derivatives of AMP, which could act as antimetabolites. The preparation of monophosphites of uridine and thymidine,[6,9] adenosine[10,11] or even mono-adenosinyl and mono-uridinyl esters of 1aminoethane phosphonic acid[12] was reported.

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Dedicated to Professor Jan Epsztajn from the University of Łódź, Poland, on the occasion of his 75th birthday.

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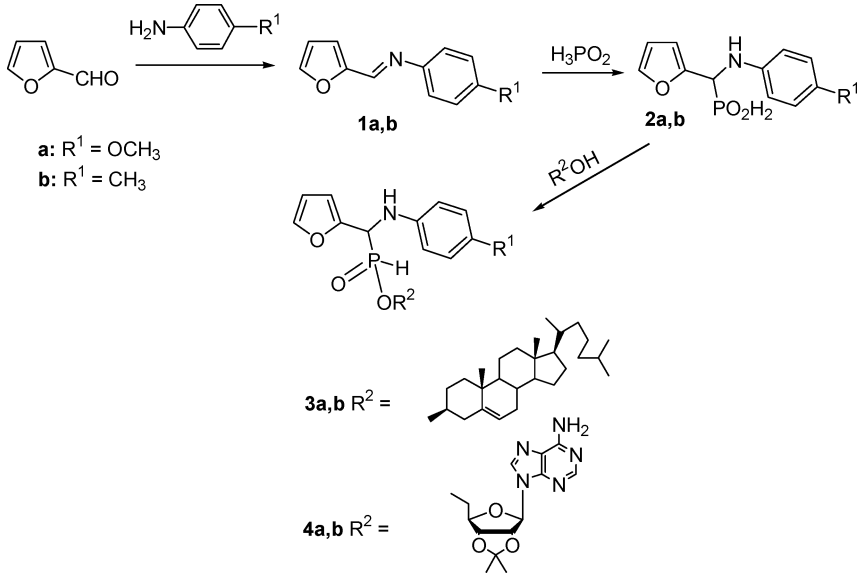
We have also contributed to this topic. In one of our previous papers, we reported the synthesis of cholesteryl and adenosinyl esters of *N*-substituted 2-furyl aminomethanephosphonous acids.[13] These compounds bear both furanic and aminophosphonous functions in their molecules combined with a biomolecule moiety and might be investigated with respect to their anti-metabolic action. As a continuation of our study, we report the synthesis of cholesteryl and *O*,*O*′-isopropylideneadenosinyl 2-furyl *N*arylaminomethanephosphonites, which were chosen in order to verify the reactivity of *N*aryl Schiff bases *vs.* the addition of hypophosphorous acid and the reactivity of *N*arylaminophosphonous acids *vs.* their condensation with cholesterol and adenosine.

RESULTS AND DISCUSSION

2-Furyl aminophosphonous acids **2a**,**b** were synthesized following the published procedure[2,12] in a two-step reaction. Furfural was reacted with an aromatic amine to give the Schiff bases **1a**,**b**, which on addition of hypophosphorous acid afforded aminophosphonous acids **2a**,**b** in satisfactory yields (Scheme 1). The acids **2a**,**b** are new and were properly characterized by means of NMR spectroscopy and elemental analysis.



SCHEME 1

The condensation of the acids **2a**,**b** with cholesterol was carried out in the presence of dicyclohexylcarbodiimide (DCC) as a condensing agent in dichloromethane as solvent. The condensations of the acids **2a**,**b** with *O*,*O*′-isopropylidene adenosine were carried out under identical conditions. The reaction mixtures were refluxed for several days (up to 5 days).

The above reactions led either to the cholesteryl 2-furyl *N*-arylaminomethanephosphonites **3a**,**b** or to the adenosinyl (2-furyl)-*N*-arylaminomethanephosphonites **4a**,**b** in yields varying from 65 to 85%. In the case of the cholesteryl phosphonites **3a**,**b**, the ^{31}P NMR spectra showed four signals (two sets of two signals with similar chemical shifts). Similarly, in the ^{1}H NMR spectra corresponding sets of signals for the P—H and P—C—H protons were observed. This demonstrated the formation of four diastereoisomers, which was expected, because of the appearance of a second center of asymmetry situated at the phosphorus atom. The diastereoisomers were formed in unequal ratios, which would suggest the chiral assistance of the optically active cholesterol.

However, in case of the adenosinyl phosphonites **4a**,**b**, the ^{31}P NMR spectra showed only one broad signal. Also in the ^{1}H NMR spectra, only one set of signals for the P—H and P—C—H protons was observed. This indicates the exclusive formation of two diastereoisomers demonstrating the high chiral assistance of the adenosine molecule in the formation of a new center of chirality at phosphorus.

Unfortunately, the separation of the diastereoisomers failed because compounds **3a**,**b** and **4a**,**b** decomposed on silica gel and aluminum oxide.

EXPERIMENTAL

All solvents (POCh, Poland) were routinely distilled and dried prior to use. Amines, furfural, and *O*,*O*′-isopropylidene adenosine as well as cholesterol (Aldrich) were used as received. NMR spectra were recorded on a Varian Gemini 200 BB apparatus operating at 200 MHz (^{1}H NMR) and 81 MHz (^{31}P NMR). Elemental analyses were performed in the Center for Molecular and Macromolecular Science of the Polish Academy of Science in Łódź. Schiff bases **1a**,**b** were synthesized following the known procedures.[14,15]

Synthesis of Acids 2a,b: General Procedure

To furfural (1.92 g, 0.02 mol), the respective amine (0.02 mol) was added. After 1.5 h, 20 mL of methanol were added and the mixture was stirred at room temperature for 24 h. The solvent was evaporated *in vacuo*,

the residue was dissolved in 20 mL of dichloromethane and dried over anhydrous $MgSO_4$. The inorganic salt was filtered off and solvent was evaporated to give the Schiff base **1a**,**b** as light-brown oil in quantitative yield, which was dissolved in dioxane (20 mL). To this solution, hypophosphorous acid (1.32 g, 0.02 mol) was added, the mixture was refluxed for 5 h and stirred at room temperature for 24 h. The solid formed was collected by filtration, washed with 30 mL of dioxane and dried to give the acids **2a**,**b**.

N-(p-Methoxyphenyl)amino-2-furyl-methanephosphonous Acid (2a)

Yield: 2.20 g (44%); m.p. 172–174°C. Calcd. for $C_{12}H_{14}NO_4P$: C, 53.94; H, 5.28; N, 5.24%. Found: C, 53.68; H, 5.30; N, 5.17%. ^{1}H NMR (NaOD/D_2O): $\delta = 7.39$ (m, 1H, H^5_{fur}); 6.78 (broad s, 4H, *p*-C_6H_4); 6.97 (d, $^1J_{PH} = 531.1$ Hz, 1H, PH); 6.31 (m, 2H, H^3_{fur}, H^4_{fur}); 4.55 (d, $^2J_{PH} = 17.0$ Hz, 1H, CHP); 3.66 (s, 3H, OCH_3). ^{31}P NMR (D_2O): $\delta = 20.6$.

N-(p-Methylphenyl)amino-2-furyl-methanephosphonous Acid (2b)

Yield: 3.08 g (61%); m.p. 168–174°C. Calcd. for $C_{12}H_{14}NO_3P$: C, 57.37; H, 5.62; N, 5.58%. Found: C, 57.18; H, 5.78; N, 5.54%. ^{1}H NMR (NaOD/D_2O): $\delta = 7.37$ (m, 1H, H^5_{fur}); 6.98 (d, $J = 8.1$ Hz, 2H, *p*-C_6H_4); 6.72 (d, $J = 8.1$ Hz, 2H, *p*-C_6H_4); 6.95 (d, $^1J_{PH} = 531.3$ Hz, 1H, PH); 6.29 (m, 2H, H^3_{fur}, H^4_{fur}); 4.59 (d, $^2J_{PH} = 17.4$ Hz, 1H, CHP); 2.11 (s, 3H, CH_3). ^{31}P NMR (NaOD/D_2O): $\delta = 20.7$.

Synthesis of Esters 3a,b and 4a,b: General Procedure

To a suspension of the aminophosphonous acid **2a**–**d** (5 mmol) in dichloromethane (20 mL), 0.01 mol of cholesterol or isopropylidene adenosine and 5 mmol (1.04 g) of DCC were added. The mixture was then refluxed for 10 h with vigorous stirring, then stirred overnight at room temperature and this procedure was repeated during the next 7 days. The reaction mixture was filtered, the solid residue was washed with 20 mL of dichloromethane and then discarded. The filtrate was evaporated in vacuo, the residue was re-dissolved in 30 mL of chloroform, shaken with charcoal, filtered, and the eluent evaporated to obtain the pure product **3a**,**b** and **4a**,**b**.

Cholesteryl N-(p-Methoxyphenyl)amino-2-furyl-methanephosphonite (3a)

Yield: 3.01 g (95%); m.p. = 105–108°C. Calcd. for $C_{39}H_{58}NO_4P$: C, 73.67; H, 9.19; N, 2.20%. Found: C, 73.56; H, 9.21; N, 2.35%. ^{1}H NMR

($CDCl_3$): $\delta = 7.41$ (m, 1H, H^5_{fur}); 6.76 (d, $J = 8.8$ Hz, 2H, *p*-C_6H_4); 6.66 (d, $J = 8.8$ Hz, 2H, *p*-C_6H_4); 7.24 (d, $^1J_{PH} = 567.6$ Hz, 1H, PH); 7.15 (d, $^1J_{PH} = 569.4$ Hz, 1H, PH); 6.37 (m, 2H, H^4_{fur}, H^3_{fur}); 5.35 (m, 1H, HC=C); 4.79 (d, $^2J_{PH} = 17.1$ Hz, 1H, PCH); 4.73 (d, $^2J_{PH} = 16.8$ Hz, 1H, PCH); 4.21 (m, 1H, O-$CH_{cholest}$); 3.72 (s, 3H, OCH_3); 2.39 (m, 2H, $CH_{2cholest}$); 1.97–1.79 (m, 8H, $CH_{cholest}$); 1.6–1.3 (m, 8H, $CH_{cholest}$); 1.11 (m, 10H, $CH_{cholest}$); 1.01 (s, 3H, CH_3); 0.98 (d, $J = 9.0$ Hz, 3H, CH_3); 0.86 (d, $J = 6.6$ Hz, 6H, CH_3); 0.67 (s, 3H, CH_3). ^{31}P NMR ($CDCl_3$): $\delta = 28.4$, 28.3, 25.3, 25.2 (5:5:3:3).

Cholesteryl N-(p-Methylphenyl)amino-2-furyl-methanephosphonite (3b)

Yield: 2.93 g (94%); m.p. 99–103°C. Calcd. for $C_{39}H_{58}NO_3P$: C, 75.57; H, 9.43; N, 2.26%. Found: C, 75.09; H, 9.40; N, 2.35%. ^{1}H NMR ($CDCl_3$): $\delta = 7.41$ (m, 1H, H^5_{fur}); 6.99 (d, $J = 8.2$ Hz, 2H, *p*-C_6H_4); 6.63 (d, $J = 8.2$ Hz, 2H, *p*-C_6H_4); 7.24 (d, $^1J_{PH} = 566.8$ Hz, 1H, PH); 7.16 (d, $^1J_{PH} = 569.6$ Hz, 1H, PH); 6.36 (m, 2H, H^4_{fur}, H^3_{fur}); 5.35 (m, 1H, HC=C); 4.85 (d, $^2J_{PH} = 17.0$ Hz, 1H, PCH); 4.80 (d, $^2J_{PH} = 16.5$ Hz, 1H, PCH); 4.23 (m, 1H, O-$CH_{cholest}$); 2.40 (m, 2H, $CH_{2cholest}$); 2.23 (s, CH_3, 3H); 1.97–1.81 (m, 8H, $CH_{cholest}$); 1.6–1.3 (m, 8H, $CH_{cholest}$); 1.10 (m, 10H, $CH_{cholest}$); 1.01 (s, 3H, CH_3); 0.99 (d, $J = 9.0$ Hz, 3H, CH_3); 0.89 (d, $J = 6.6$ Hz, 6H, CH_3); 0.67 (s, 3H, CH_3). ^{31}P NMR ($CDCl_3$): $\delta = 28.4$, 28.3, 25.3, 25.2 (5:5:3:3).

O,O′-Isopropylideneadenosinyl N-(p-Methoxyphenyl)amino-2-furyl-methanephosphonite (4a)

Yield: 2.73 g (98%); m.p. 69–72°C. Calcd. for $C_{25}H_{29}N_6O_7P$: C, 53.96; H, 5.25; N, 15.10%. Found: C, 53.75; H, 5.48; N, 15.44. ^{1}H NMR (DMSO-d_6): $\delta = 8.38$ (s, 1H, H^2_{ade}); 8.18 (s, 1H, H^8_{ade}); 7.64 (m, 2H, NH_2); 7.57 (m, 1H, H^5_{fur}); 7.00 (broad d, $^1J_{PH} = 541.2$ Hz, 1H, PH); 6.73 (d, $J = 9.3$ Hz, 2H, *p*-C_6H_4); 6.66 (d, $J = 9.3$ Hz, 2H, *p*-C_6H_4); 6.37 (m, 2H, H^3_{fur}, H^4_{fur}); 6.13 (d, $J = 2.9$ Hz, 1H, H^1_{rib}); 5.34 (dd, $J = 6.1$ and 3.1 Hz, 1H, H^2_{rib}); 4.96 (dd, $J = 6.1$ and 2.3 Hz, 1H, H^3_{rib}); 4.76 (d, $^2J_{PH} = 18.9$ Hz, 1H, CHP); 4.23 (m, 1H, H^4_{rib}); 3.61 (s, 3H, OCH_3); 3.54 (dd, $^3J_{PH} = 2.7$ Hz, $^3J_{HH} = 4.7$ Hz, 2H, H^5_{rib}); 1.54 (s, 3H, CH_3); 1.32 (s, 3H, CH_3). ^{31}P NMR ($CDCl_3$): $\delta = 22.1$.

O,O′-Isopropylideneadenosinyl N-(p-Methylphenyl)amino-2-furyl-methane phosphonite (4b)

Yield: 2.60 g (96%); m.p. 74–78°C. Calcd. for $C_{25}H_{29}N_6O_6P$: C, 55.55; H, 5.41; N, 15.55%. Found: C, 55.87; H, 5.78; N, 15.31%. ^{1}H NMR

(DMSO-d_6): $\delta = 8.38$ (s, 1H, H^2_{ade}); 8.19 (s, 1H, H^8_{ade}); 7.61 (m, 2H, NH_2); 7.58 (m, 1H, H^5_{fur}); 7.00 (broad d, $^1J_{PH} = 541.2$ Hz, 1H, PH); 6.86 (d, $J = 8.0$ Hz, 2H, p-C_6H_4); 6.66 (d, $J = 8.0$ Hz, 2H, p-C_6H_4); 6.37 (m, 2H, H^3_{fur}, H^4_{fur}); 6.13 (d, $J = 2.8$ Hz, 1H, H^1_{rib}); 5.34 (dd, $J = 6.0$ and 3.0 Hz, 1H, H^2_{rib}); 4.96 (dd, $J = 6.0$ and 2.1 Hz, 1H, H^3_{rib}); 4.81 (d, $^2J_{PH} = 18.9$ Hz, 1H, CHP); 4.23 (m, 1H, H^4_{rib}); 3.55 (dd, $^3J_{PH} = 2.2$ Hz, $^3J_{HH} = 3.8$ Hz, 2H, H^5_{rib}); 2.11 (s, 3H, CH_3); 1.54 (s, 3H, CH_3); 1.32 (s, 3H, CH_3). ^{31}P NMR ($CDCl_3$): $\delta = 22.1$.

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