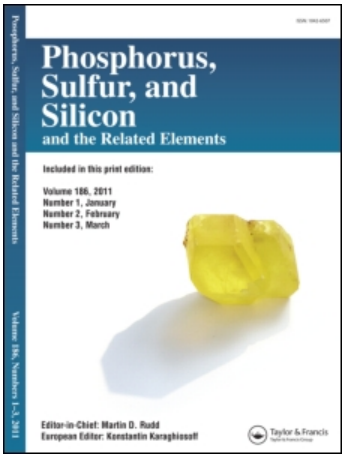

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I. Kraicheva[a]; P. Finocchiaro[b]; S. Failla[b]
[a] Bulgarian Academy of Sciences, Sofia, Bulgaria [b] Università di Catania, Catania, Italy

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SYNTHESIS AND NMR SPECTROSCOPIC STUDY OF A NEW BIS(AMINOPHOSPHONATE) WITH TERMINAL FURYL GROUPS

I. Kraicheva,[a] *P. Finocchiaro,*[b] *and S. Failla*[b]
Bulgarian Academy of Sciences, Sofia, Bulgaria[a] *and Università di Catania, Catania, Italy*[b]

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*1,3-Bis[*N*-methyl(diethoxyphosphonyl)-1-(2-furyl)]diaminobenzene has been synthesized through the addition of diethyl phosphite to the Schiff base* N,N′*-difurfurylidene-*m*-phenylenediamine. The compound has been characterized by elemental analysis, TLC, IR, and* ^{1}H, ^{13}C, *and* ^{31}P *NMR spectra. The NMR studies show that the reaction product is a mixture of two diastereomers (*meso *and racemic forms). The* ^{31}P *NMR data revealed 61% content for the predominant and 39% for the minor form.*

Keywords: Aminophosphonic acids; furan derivatives; NMR spectra; Schiff bases

INTRODUCTION

The importance of aminophosphonic acids and their derivatives is commonly known.[1] Compounds of this type are used widely in agrochemistry as antifungal agents,[2,3] as herbicides and plant growth regulators.[1,2] Some representatives find application in therapy and diagnostics medicine.[4–6] According to recent data, aminophosphonate derivatives are quite perspective for the design of therapeutic agents, including antitumor.[7–9] Considering the pharmacological importance of aminophosphonates as well as the biological activity of some furan derivatives,[10–12] it seems of interest to synthesize compounds combining the two pharmacophoric groups in the same molecule. It should be mentioned that data on the synthesis of aminophosphonate derivatives

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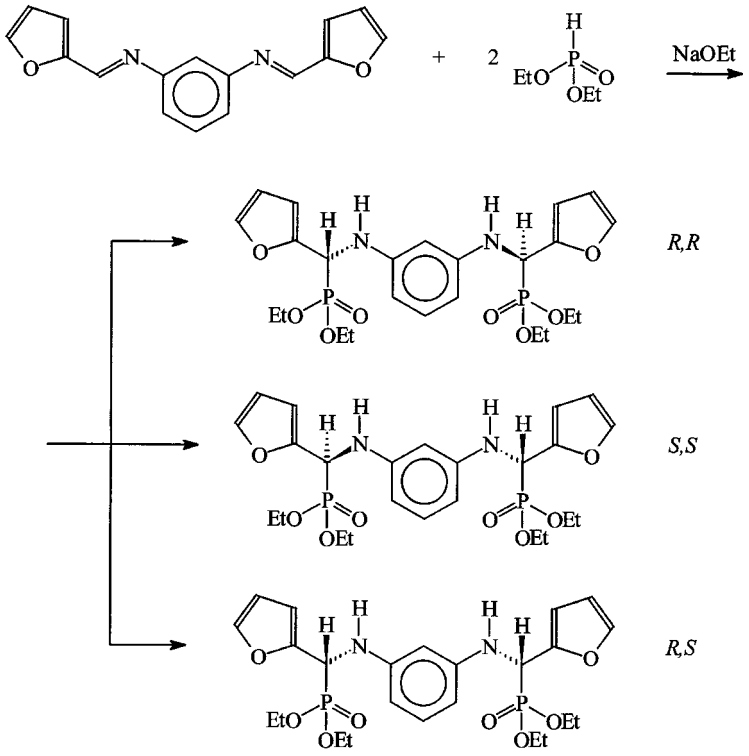
Address correspondence to I. Kraicheva, Institute of Polymers, Bulgarian Academy of Sciences, Acad. G. Bonchev Street, Block 103A, 1113 Sofia, Bulgaria. E-mail: kraicheva@yahoo.com

bearing furan moiety are relatively scarce.[13–18] Recently, new articles have appeared on the synthesis and stereochemistry of furan-containing aminophosphonates.[19,20] Preliminary results for the biological activity of some representatives have been promising.[21]

RESULTS AND DISCUSSION

The Schiff base *N*,*N*′-difurfurylidne-*m*-phenylenediamine was prepared by condensation of furfural and *m*-phenylenediamine.[22] Then addition of diethyl phosphite to its azomethine bonds was carried out and a new bis(aminophosphonate) with terminal furyl groups, 1,3-bis[*N*-methyl(diethoxyphosphonyl)-1-(2-furyl)]diaminobenzene, was synthesized. The reaction proceeds according to Scheme 1.



SCHEME 1

The reaction product is soluble in methanol, ethanol, chloroform, and benzene. Thin layer chromatograpy (TLC) of the product gave a single spot in each of the two eluting systems used. The elemental

analysis is consistent with its composition. In accordance with literature data,[16,23–25] the absorption bands of the corresponding groups were observed in the IR spectrum of the compound (see Experimental).

It is known[26] that the addition of dialkyl or diaryl phosphites to bis-imines should generate two diastereomeric products (*meso* and racemic forms) owing to the chirality of the groups present in the bis(aminophosphonate) molecule. Literature data concerning the stereochemistry of this reaction show that in some cases the addition of phosphites to achiral bis-imines gives only one of the two possible diastereomers,[20,26–28] while in other cases, depending on the type of the reagents, the formation of either only one or the two diastereomers (in 1:1 ratio) has been observed.[29]

In our case the NMR studies revealed that the reaction product is a mixture of the two possible diastereomeric forms: *R*,*S* (*meso*) and the enantiomeric pair *R*,*R* and *S*,*S*. (Scheme 1) The ^{1}H, ^{13}C, and ^{31}P NMR spectra demonstrated the occurrence of two sets of signals. Selected NMR parameters illustrating this finding are collected in Table I and the shape of some signals is shown in Figure 1. In the spectra taken in DMSO-d_6 and $CDCl_3$ solutions the signal of the methyne hydrogen of the CH(P) group appears as two distinct doublet of doublets each of them resulting from the coupling with ^{31}P nucleus and the NH proton of the diastereomers (Table I). In the spectra of the substances described

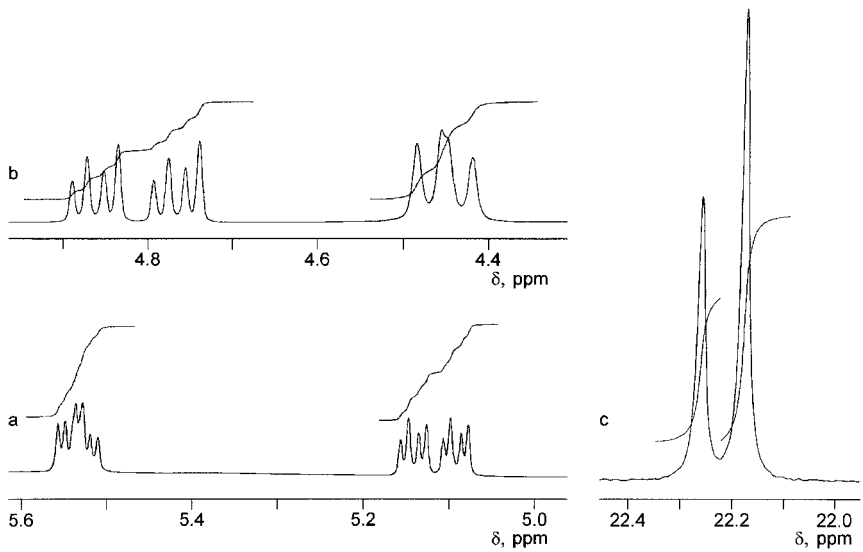


FIGURE 1 ^{1}H NMR spectra of CH(P) and NH regions in DMSO-d_6 (a) and $CDCl_3$ (b); $^{31}P\{^{1}H\}$ NMR spectrum (c) of the compound.

TABLE I Selected NMR Parameters of 1,3-Bis[*N*-methyl(diethoxyphosphonyl)-1-(2-furyl)]diaminobenzene

	^{1}H-NMR parameters									^{13}C-NMR chemical shift, δ (ppm)			^{31}P-NMR chemical shift δ (ppm)
	Chemical shift, δ (ppm)				Coupling constant, J (Hz)								
Solvent	CH_3	OCH_2	CH(P)	NH	$^3J(CH_2CH_3)$	$^2J(CH(P))$	$^3J(CHNH)$	$^3J(NHCH)$	$^3J(NHP)$	CH_3	OCH_2	CH(P)	
DMSO-d_6	1.12 t	3.85 m	5.11 dd	5.52 dd[a]	7.00	24.25	10.25	9.00	4.50	16.45	62.84	47.47	22.18
	1.17 t	4.01 m	5.12 dd	5.54 dd[a]	6.75	24.50	10.50	10.25	4.25	16.54	62.95	50.01	22.26
	1.19 t				6.75					16.57	63.08		
										16.66	63.19		
$CDCl_3$	1.19 t	3.85 m	4.81 dd	4.45 dd[b]	7.06	23.98	9.22	9.00	7.25	16.18	63.20	48.70	
	1.29 t	4.10 m	4.82 dd		7.07	23.99	9.30			16.28	63.31	51.22	
										16.33	63.39		
										16.43	63.49		
DMF-d_7	1.12 t	3.98 m	5.12 dd	5.50 dd	7.12	23.91	10.25	10.32	4.99				
	1.18 t			5.51 dd	7.20			10.27	4.71				

[a]Partially overlapping doublets of doublets.
[b]Poorly resolved doublet of doublets

earlier,[17,18,20,26] the signal of the CH(P) proton has been observed as a sharp doublet or as a doublet of doublets. Two signals (two doublets) have been registered for this proton in the cases when the reaction product contains both diastereomers.[29]

In our case the two CH(P) signals have unequal intensity (Figure 1a,b). The NH proton gave a couple of doublet of doublets (partially overlapped), and a poorly resolved doublet of doublets shifted upfield, in the spectra taken in DMSO-d_6 and $CDCl_3$ respectively (Figure 1a,b). The two NH signals are well distinguished in the spectrum from DMF-d_7 solution (Table I). The D_2O exchange of the NH protons proceeds slowly. The nonequivalence of the two ethoxy groups of the compound was experimentally observed. Thus, three (in DMSO-d_6) and two (in $CDCl_3$ and DMF-d_7) triplets were identified for the methyl protons of these groups (Table I). In DMSO-d_6 and $CDCl_3$ spectra the signals of the methylene protons appear as a couple of multiplets in a ratio 3:1, that is, two of the methylene protons give a common multiplet shifted upfield.

The DMSO-d_6 spectrum revealed two sets of signals with unequal intensity for the aromatic protons ArH-2 and ArH-5 and for the proton FurH- 5 of the furan ring. The triplets assigned to ArH-2 are poorly resolved. The common signal for ArH-4,6 appears as two doublet of doublets in the $CDCl_3$ spectrum.

In the $^{13}C\{^1H, ^{31}P\}$ NMR spectra a pair of signals was registered for most of the carbon atoms. The largest difference in the chemical shift (ca. 2.5 ppm) was found for the two CH(P) carbon signals. Two couples of signals were observed for the methyl and methylene carbon atoms of the ethoxy groups. The assignment of the signals is based on the analysis of decoupled ^{13}C and 2D spectra of our product, and on literature data for similar compounds.[20,29,30]

In addition to the ^1H and ^{13}C NMR spectra, the $^{31}P\{^1H\}$ spectrum clearly shows that the addition of diethyl phosphite to *N*,*N*′-difurfurylidne-*m*-phenylenediamine leads to the formation of both diastereomeric forms: two singlets with unequal intensity were registered in this spectrum (Figure 1c) The intensity ratio of the signals revealed 61% content of the predominant diastereomer and 39% for the minor diastereomer.

EXPERIMENTAL

Starting Compounds

Diethyl phosphite (Fluka, *purum*) was purified by vacuum-distillation. The Schiff base *N*,*N*′-difurfurylidene-*m*-phenylenediamine was prepared from furfural (Fluka, *pract*.) and 1,3-phenylenediamine (Fluka,

purum) according to Berlin et al.,[22] using ethyl alcohol as solvent instead of benzene. Furfural was purified by vacuum-distillation under nitrogen atmosphere. All solvents were freshly distilled prior to use.

Apparatus and Conditions

The melting point of the product was determined on a Büchi 530 apparatus and is uncorrected. The IR spectrum was recorded on a Bruker IFS 113 Spectrophotometer in KBr disk. ^{1}H and ^{31}P NMR spectra in solvent DMSO-d_6 were registered on a Varian-Inova 500 MHz spectrometer at room temperature using TMS as internal reference and 85% H_3PO_4 as external reference. The remaining NMR spectra: ^{1}H (solvents $CDCl_3$ and DMF-d_7), $^{13}C\{^{1}H, ^{31}P\}$, DEPT, HH COSY, CH COSY, and CH COLOC (solvents DMSO-d_6 and $CDCl_3$) were taken on a Bruker DRX-250 250 MHz instrument at room temperature and TMS as internal standard. D_2O exchange was applied to confirm the assignment of the signals of NH protons.

The thin layer chromatograms were performed on Kieselgel-60 F_{254} plastic sheets (Merck) at room temperature. The samples were applied as methanolic solutions and the chromatograms were developed ascendingly with two eluting systems: a) ethyl acetate–tetrahydrofuran–methanol (12:3:1) and b) benzene–methanol (10:1). The spots were visualized under UV light and in an iodine vapour atmosphere.

Preparation of 1,3-Bis[*N*-methyl(diethoxyphosphonyl)-1-(2-furyl)]diaminobenzene

N,*N*′-difurfurylidene-*m*-phenylenediamine (10.56 g, 0.04 mol) and diethyl phosphite (13.80 g, 0.10 mol) were mixed in a flask, and a saturated solution of C_2H_5ONa was added dropwise with stirring until exothermicity ceased. The mixture was stirred for 2 h at room temperature, then for 2 h at 70–75°C. After cooling to room temperature the solid precipitate was washed with water and filtered. The crude product (12.98 g, 60%) was purified by recrystallization from ethanol. The colourless crystalline powder obtained was dried in vacuo to constant weight.

Yield: 11.08 g (51%); m. p. 141–149°C; $R_f = 0.80$ (a), 0.55 (b).

Analysis Calcd. for $C_{24}H_{34}N_2O_8P_2$: C, 53.33%; H, 6.30%; N, 5.19%. Found: C, 53.53%; H, 6.43%; N, 5.26%.

IR (KBr disk): $\tilde{\nu}$ (cm^{-1}): 3307 (ν_{NH}); 1613, 1500, 1443 ($\nu_{C=C}$(Ar, Fur)); 1243 ($\nu_{P=O}$); 1056, 1023 ($\nu_{P-OEt,C-O-C}$).

^{1}H-NMR, δ(ppm), J_{HH}(Hz): Solvent DMSO-d_6: 7.59 and 7.58 (2m, 2H, FurH-5); 6.74 and 6.73 (2t, $^{3}J = 8.00$ and 8.00, 1H, ArH-5); 6.41 (m, 4H,

FurH-3,4); 6.35 and 6.33 (2t, 1H, ArH-2); 6.13 (dd, $^3J = 8.00$, $^4J = 2.00$, 2H, ArH-4,6). Solvent $CDCl_3$: 7.39 (m, 2H, FurH-5); 6.93 (t, $^3J = 8.00$ 1H, ArH-5); 6.34 (m, 4H, FurH-3,4); 6.09 and 6.08 (2 dd, $^3J = 8.06$ and 8.05, $^4J = 1.68$ and 1.88, 2H, ArH-4,6); 5.96 (br. s., 1H ArH-2). Solvent DMF-d_7: 7.55 (m, 2H, FurH-5); 6.77 (t, $^3J = 7.98$, 1H, ArH-5); 6.41 (m, 5H, ArH-2, FurH-3,4); 6.20 (dd, $^3J = 8.01$, $^4J = 2.04$, 2H, ArH-4,6).

^{13}C-NMR, δ (ppm). Solvent DMSO-d_6: 150.38 and 150.33 (FurC-2); 148.02 and 147.82 (ArC-1,3); 142.92 (FurC-5); 129.52 (ArC-5); 111.04 (FurC-4); 109.13 and 109.02 (FurC-3); 104.62 and 104.50 (ArC-4,6); 98.75 and 98.56 (ArC-2). Solvent $CDCl_3$: 149.28 and 149.25 (FurC-2), 147.13 and 146.92 (ArC-1,3); 142.41 and 142.36 (FurC-5); 129.86 (ArC-5); 110.75 and 110.71 (furC-4); 108.73 and 108.61 (FurC-3); 104.98 and 104.91 (ArC-4,6); 99.41 and 99.24 (ArC-2).

Selected part of NMR parameters is given in Table I.

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