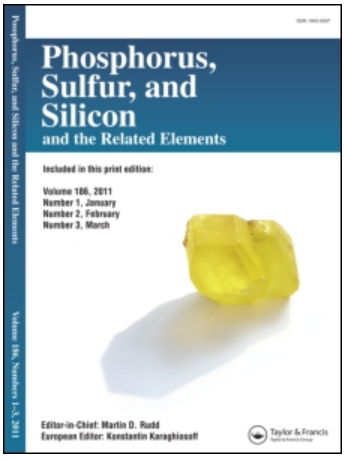

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SYNTHESIS OF METHYL ESTERS OF N-(O, O-DIETHYL-PHOSPHONOBENZYL)-2-AMINO-3-ARYL-PROPANOIC ACID

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SYNTHESIS OF METHYL ESTERS OF N-(O, O-DIETHYL-PHOSPHONOBENZYL)-2-AMINO-3-ARYL-PROPANOIC ACID

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Methyl esters of N-(O,O-diethylphosphonobenzyl-)-2-amino-3-aryl-propanoic acid were synthesized by the addition of diethylphosphite to Schiff bases of 2-amino carboxylic acids (L-phenyl-alanine and L-tyrosine). The compounds were obtained as a mixture of σ-diastereoisomers and the structures were confirmed by spectral methods.

Keywords: Methyl -N-(O,O -diethylphosphonobenzyl-)-2-amino-3-aryl-propanoic acid

INTRODUCTION

The comparatively easy addition of diethylphosphite to Schiff base[1] gives α-aminophosphonic acids after appropriate hydrolysis. These acids have important biological properties. Other methods including the simultaneous addition of ammonia and diethylphosphite[2–5] to aldehydes and ketones, followed by hydrolysis are described[6–11]. They are basic for the formation of α-aminophosphonic acids. By similar methods the optically active α-aminophosphonic acids[12,13] and N-substituted glycinephosphonic acids[14] are obtained. The preparation of N-phosphonobenzyl derivatives such as DL-(N-α-phosphonobenzyl) phenylalanine, DL-(N-α-phosphonobenzyl) tyrosine and some others are also published[15], but they were not characterized by chemical and spectral methods. We want to report the synthesis and spectral data of mixture of

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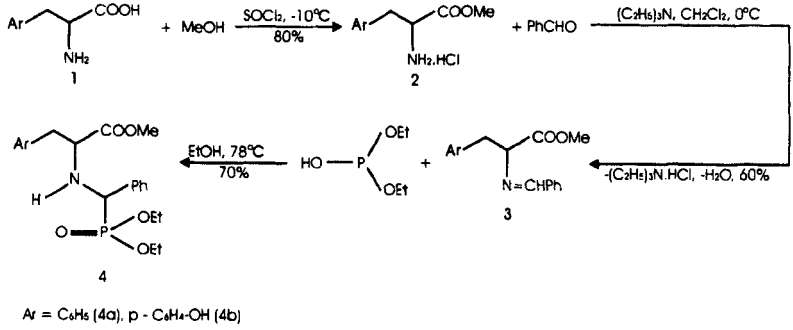
σ-diastereoisomers of esters of N-phosphonobenzylamino acids with similar structure.

RESULTS AND DISCUSSION

For the synthesis of the methyl esters of N-(O,O-diethylphosphonobenzyl-)-2-amino-3-aryl-propanoic acid **4** we have used a three-stage synthesis as it is shown in Scheme 1:



SCHEME 1

We carried out the esterification and preparation of the Schiff base of L-phenylalanine and L-tyrosine following the well known methods[16,17]. As a result were obtained the intermediate products of methyl-2-(benzylidenamino)-3-phenylpropanoat and methyl-2-(benzylidenamino)-3-(4-hydroxyphenyl) propanoat **3**. During this two-stage transformation the terminal carboxylic and amino functional groups were converted into methyl esters and benzyliden derivatives with very good yields. The increased basicity of azomethine group (**C=N**) allows the addition of diethylphosphite. We carried out the reaction by heating of the products **3** at 78°C in excess of diethylphosphite in absolute ethanol. The products **4** were obtained as colorful viscous liquids that crystallized with difficulty. Their purification was carried out by column chromatography. The content and structure of the methyl ester of N- (O,O-diethylphosphonobenzyl-)-2-amino-3-aryl propanoic acids **4** were confirmed by elemental analysis and spectral methods: IR, ^{1}H-NMR, ^{13}C- NMR, ^{31}P-NMR.

There are three asymmetric atoms in the structure of the products **4**: two carbons and one nitrogen atoms. As the initial amino acid carbon atom has S configuration, and the nitrogen atom has fast pyramidal inversion, we can expect only two σ-diastereoisomers (S,S and S,R) of each compound. The NMR data in Tables I and II show that the ratio of σ-diastereoisomers is approximately 3:2 (S,R:S,S). Similar data are obtained by ^{31}P-NMR spectra for **4a** 23.07 and 23.03 ppm (S,R:S,S) and for **4b** are 23.40 and 23.05 ppm (S,R:S,S) (in $CDCl_3$ ref. 85% H_3PO_4).

TABLE I ^{1}H-NMR Spectral Data of Compounds **4 a,b** in $CDCl_3$/TMS [δ, J(Hz)]

4	*a-S,R*	*a-S,S*	*b-S,R*	*b-S,S*
P-O-C-**CH**$_3$	1.16, 1.22	1.07, 1.21	1.09, 1.26	0.82, 1.16
	(t,J=7.2)	(t, J=7,1)	(t,J=7.1)	t,J=6.6)
	(t,J=6.9)	(t, J=7.0)	(t,J=7.1)	(t,J=7.1)
C-**CH**$_2$-Ph	2.93	2.91	2.87	2.86
	(m, J=5.8–8.5)	(m, J=5.8–7.5)	(m,J=5.7,10)	(m, J=5.6,8.6)
N-**H**	3.09	3.09		
CH-C-Ph	3.64	3.32	3.64	3.28
	(m,J=6.0, 7.4)	(m,J=5.8,8.3)	(m,J=2.2,5.6)	(m,J=3.7,4.6)
O-**CH**$_3$	3.65 S	3.39 S	3.89 S	3.67 S
P-**CH**-N	3.92	4.11	4.12	3.96
	(d,J=19.4)	(s, J=19.2)	(d,J=20)	(d, J=19)
P-O-**CH**$_2$-C	3.98, 4.01	3.87, 4.01	3.90, 4.11	3.75, 4.93
	(m,m,J=6–8)	(m,m, J=6–8)	(m,m,J=2–5)	(m,m,J=2–5)
	(m,m,J=6–8)	(m,m, J=6–8)	(m,m,J=2–5)	(m,m,J=2–5)
O-**H**			5–6	5–6
Ph	7.1–7.4	7.1–7.4	7.1–7.4	7.1–7.4
	(m,J=1–9)	(m,J=1–9)	(m,J=1–9)	(m,m,J=1)

There is an additional stabilization of the prepared compounds **4**, due to hydrogen bonds formation. In the IR spectra in a capillary layer of the iso-

lated products **4**, besides the absorption bands characteristic for the basic functional groups(see experimental), bands at 3325 cm^{-1} (for **4a**), at 3250 cm^{-1} (for **4b**) and at 1735–40 cm^{-1} corresponding to $\nu_{N-H}$and $\nu_{C=O}$ are present. However in $CHCl_3$ the frequencies of most bands are unchanged with the exception of those of $\nu_{C=O}$(decreasing to 1720 cm^{-1}) and of ν_{N-H} (increasing to 3620 cm^{-1} for **4a** and 3590 cm^{-1} for **4b**). These data suggest the existence of mainly intermolecular **N-H--- O=C** bonds in compounds **4**, when they are in a condensed state (capillary layer). And when they are in solution, intramolecular hydrogen bonds between **N-H** and **O=C** groups are formed instead[18]. This formation in one of the σ-diastereoisomer (S,R) is also preferred by some space factors, according to the configuration of the two asymmetric carbon atoms. It is confirmed by the better energetic stability of S,R diastereoisomers calculated by the help of Alchemy computer program for molecular mechanic in comparison with the S,S diastereoisomers.

TABLE II ^{13}C -NMR Spectral Data of Compounds 4 a,b in $CDCl_3$, ppm

4	*a-S,R ppm*	*a-S,S ppm*	*b-S,R ppm*	*b-S,S ppm*
P-O-C-CH_3	16.20	16.11	16.28	16.19
H_2C-Ph	39.53	39.17	38.53	38.39
-COO-CH_3	51.60	51.44	51.72	51.54
P-CH	60.17–61.64	57.75–59.77	60.01–62.16	57.56–59.64
N-CH	60.17–61.64	57.75–59.77	60.01–62.16	57.56–59.64
P-O-CH_2-C	63.2	62.91	63.52	63.27
C_6H_5	128.16–129.23	126.49–127.95	130.01–130.84	127.60–128.65
HO-C_6H_5			155.86	155.68
COO-CH_3	173.97	173.97	174.43	174.09

EXPERIMENTAL

The IR spectra were recorded on a Specord 75 IR (Carl Zeiss- Jena, Germany) spectrometer. ^1H- NMR, ^{13}C- NMR as and ^{31}P- NMR were taken

on a Bruker DRX 250 FT apparatus with external standart TMS at room temperature.

Preparations of Methyl Esters of N-(O,O-Diethylphosphonobenzyl-)-2-Amino-3-Aryl- Propanoic Acids 4

General Procedure

A solution of methyl-2-(benzylidenamino)-arylpropanoat **3** (2.67g, 10 mmole) and diethylphosphite (2 cm^3, 15 mmole) in absolute ethanol (10 cm^3) were stirred in a round bottomed flask. The reaction mixture was refluxed for 10 hours at 78°C. The end of the reaction is controlled by TLC. After this the mixture was filtered, and the solvent and the excess of the diethylphosphite removed on a rotavapor. The viscous liquid was purified by means of column chromatography using silicagel (Kieselgel 40, particlesize 0.06–0.200 mm, Merck) and as eluent toluene/methanol/ethylacetate at the ratio of 40/10/3(v/v/v). The yield of the methyl ester of N-(O,O-diethylphosphonobenzyl-)-2-amino-3-phenyl propanoic acid **4a** was 65–70%. Elemental analysis: Anal. Calcd. for $C_{21}H_{28}NO_5P$ (m. w. 405.2): C 62.20; H 6.97; N N 3.45%; Found: C 62.42; H 6.95; N 3.42 %; IR data: 1025–1050 cm^{-1} ($\nu_{C\text{-}O\text{-}CH3}$, $\nu_{P\text{-}O\text{-}C}$); 1210–1250 cm^{-1}($\nu_{P=O}$); 1735cm^{-1}($\nu_{C=O}$); 3325 cm^{-1}($\nu_{N\text{-}H}$). The yield of methyl ester of N-(O,O-diethylphosphonobenzyl-)-2-amino-3-(4-hydroxyphenyl) propanoic acid **4b** was 50–60%. Elemental analysis: Anal. Calcd. for $C_{21}H_{28}NO_6P$ (m. w. 421.2): C 59.84; H 6.71; N 3.24 %; Found: C 60.01; H 6.92; N 2.98%; IR data: 1030–1055cm^{-1} ($\nu_{C\text{-}O\text{-}CH3}$, $\nu_{P\text{-}O\text{-}C}$); 1220$cm^{-1}$($\nu_{P=O}$, $\nu_{C\text{-}N}$); 1740cm^{-1}($\nu_{C=O}$); 3250cm^{-1}($\nu_{N\text{-}H}$). The intermediate products **2** and **3** and diethylphosphite were obtained by known methods[16,17,19].

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