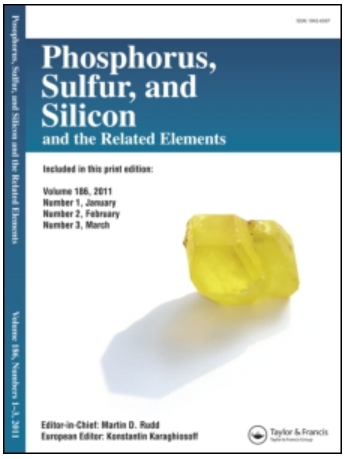

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SYNTHESIS, NMR INVESTIGATION AND FAB-MS CHARACTERIZATION OF 1-AMINO-2-ARYLMETHYL-DIPHOSPHONATE ESTERS

Salvatore Failla[a]; Paolo Finocchiaro[a]; Gerhard Hagele[b]; Roberto Rapisardi[c]
[a] Istituto Chimico, Facoltà di Ingegneria, Università di Catania, Catania, Italy [b] Heinrich-Heine-Universität Düsseldorf, Institute fur Anorganische Chemie und Strukturchemie, Universitätstrasse 1, Düsseldorf, Germany [c] Istituto C.N.R. Per la Chimica e la Technologia dei Materiali Polimerici, Catania, Italy

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SYNTHESIS, NMR INVESTIGATION AND FAB-MS CHARACTERIZATION OF 1-AMINO-2-ARYLMETHYL-DIPHOSPHONATE ESTERS

SALVATORE FAILLA,† PAOLO FINOCCHIARO,*†
GERHARD HAGELE‡ and ROBERTO RAPISARDI§

†*Istituto Chimico, Facoltà di Ingegneria, Università di Catania, Viale A. Doria, 6-95125 Catania, Italy;* ‡*Heinrich-Heine-Universität Düsseldorf, Institute fur Anorganische Chemie und Strukturchemie, Universitätstrasse 1, D-4000 Düsseldorf, Germany; and* §*Istituto C.N.R. Per la Chimica e la Technologia dei Materiali Polimerici, Viale A. Doria 6, I-95125 Catania, Italy*

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Variously substituted amino aryl-methyl-diphosphonate ethyl esters have been prepared in good yields by adding diethyl phosphonate to the corresponding Schiff bases. All compounds were characterized by NMR and MS-FAB techniques, which reveal the presence of peaks or fragmentation patterns very useful and diagnostic for constitutional assignment. Evidences for a stereospecific addition of diethyl phosphonate to the two —CH=N— sites in diaryl diimines have been observed. The presence of hetero-aromatic rings such as pyridine or azo-groups renders such compounds also very attractive for complexation studies towards metals; thus, these molecules are for potential uses in agrochemistry and bio-diagnostic medicine.

Key words: Amino-arylmethyl diphosphonate esters; preparation; spectroscopic properties; stereospecific synthesis.

INTRODUCTION

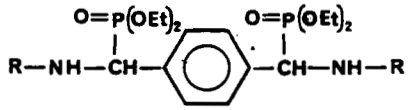
Recently we reported on the preparation and on the X-ray structure of O,O-diethyl-*N*,*N'*-ethyl-bis-phenylmethyl phosphonate[1] and the evidence of its stereospecific synthesis *via* addition of diethylphosphonate to the diaryl diimine precursor.[2]

Considering that amino-arylmethyl phosphonates are interesting compounds used as antifungal[3] and antibacterial agents[4] we decided to synthesize variously substituted derivatives in which two phosphonate groups are present in the same molecular unit. Furthermore, some of the prepared compounds possess ancillary groups (pyridine rings or azo-groups) which can render them potential complexing agents towards metals. In fact, lipophilic metal complexes can be of great interest for *in vivo* use in diagnostic medicine and in agro chemistry.

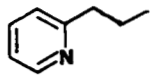
In this paper we wish to report on the synthesis and properties, together with their spectroscopic characterization, of various classes of amino-aryl-methyl diphosphonate esters, which are isolable intermediates for the preparation of amino-diphosphonic acids.

*Author to whom correspondence should be addressed.

TABLE I

Physical properties of 

1

No.	R	Yield (in %)	m.p. (°C)	Recryst. solvent	^{1}H-NMR in $CDCl_3$ CHP	OCH_2	NH	CH_2CH_3	Others	^{31}P-NMR[a]	$[M + H]^+$
1a	4—$CH_3OC_6H_4$—	95	184	AcOEt	4.65 (d, J_p 22.7)	3.38 ÷ 4.51 (m)	[b]	0.95, 1.25 (t)	3.66 (s, OCH_3)	23.28	621
1b		10	89–90	AcOEt	4.04 (d, J_p 20.5)	3.79 ÷ 4.09 (m)	2.37 (br)	1.08, 1.21 (t)	2.92 (s, Py—CH_2CH_3—)	23.70	619
1c	Ph—N=N—Ph—	85	232–233	Toluene	4.85 (ABX, J_p 22.5)[c]	3.51 ÷ 4.25 (m)	5.68[c] (ABX, J 8)	0.98, 1.27 (t)		22.32	769
1d	c—C_6H_{11}—	46	112–115	AcOEt	4.17 (d, J_p 23.4)	3.69 ÷ 4.12 (m)	2.31 (br)	1.07, 1.28 (t)	1.16, 1.67 (m, c—C_6H_{11})	24.66	573

[a]Chemical shifts measured in $CDCl_3$ with 85% H_3PO_4 as external reference.
[b]Masked by OCH_2 resonances.
[c]See Figure 1 in the text.

RESULT AND DISCUSSION

Among the various possible synthetic routes reported in the literature for the preparation of amino-aryl-methyl phosphonate (on this respect see reviews quoted by Reference 3) the best and simplest one is the addition of dialkyl phosphonates to Schiff bases, which are readily available through the condensation of primary amines with aldehydes.

In our approach, and for all the compounds reported in this paper, we decided to follow this synthetic route using as starting materials diethyl phosphonate which was added to the appropriate diimine precursors in EtOH solution using NaH as catalyst.[5]

In Tables I–V are listed the physical properties of the synthesized compounds.

Generally, all samples are white crystalline materials, except for compounds **1c** and **2a** which are deeply red-coloured due to the presence of the Ph—N=N—Ph— chromophor; thus, these latter molecules, once hydrolized to the corresponding phosphonic acids, can be utilized for spectroscopic tritations in the visible region of the spectrum.

As far as the ^{1}H-NMR spectra are concerned, first of all, we remark that the aromatic or hetero-aromatic proton chemical shifts are not listed in the Tables because these protons resonate in the expected region of the magnetic field and they generally maintain the multiplicity already present in the precursor Schiff-bases.

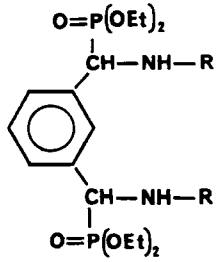
The methyne hydrogens of the groups —CH—P(O)(OEt)$_2$ generally resonate as a sharp doublet with a coupling constant H—P in the range of 20 ÷ 24 Hz, except in compounds **1c**, **2a**, and **5b** where the additional coupling with the NH proton generates an ABX pattern, as shown in Figure 1. In all these latter samples the CH resonances give rise to a four line pattern with J_{H-P} in the range of 18 ÷ 24 Hz and J_{H-NH} 8 ÷ 9 Hz, whereas the NH protons appear as a triplet with J_{NH-P} nearly equal to J_{NH-CH}. The observation of an ABX pattern only in compounds **1c**, **2a** and **5b** could be due to a slower exchange of the NH protons or to an increase of chemical shift difference due to the strong anisotropic moieties attached to the molecule, as already observed in cognate molecules.[8]

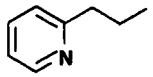
The methyl hydrogens of the ethoxy groups always appear as two distinct triplets *of equal intensity*, due to the close proximity of the stereocenter N—C—P. The alternative hypothesis that the observation of two distinct triplets for the ethoxy group arises from restricted rotation, on the NMR time scale, around the CH—P bond cannot, in principle, be excluded. Indications supporting such an idea come from preliminary force-field molecular mechanics calculations performed on diethyl α-amino-α-phenylmethyl phosphonate.[9]

In this respect it is worth noting that the addition H—P(O)(OEt)$_2$ to our diimines should generate, owing to the chiralities of the groups present in the diphosphonate molecule, two diastereomeric products (*meso* and racemic forms). However, the presence of only one signal observed in all our compounds for the methyne and ethoxy groups (apart from the expected multiplicity arising from the chirality of the molecule or restricted rotation processes) indicates that only one of the two possible diastereomers is formed stereospecifically in our addition reactions.

This observation was further confirmed analyzing the ^{31}P-NMR spectra of our

TABLE II

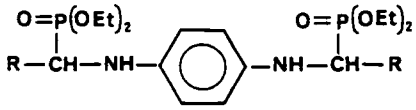
Physical properties of  2

No.	R	Yield (in %)	m.p. (°C)	Recryst. solvent	^{1}H-NMR in $CDCl_3$ CHP	OCH_2	NH	CH_2CH_3	Others	^{31}P-NMR[a]	[M + H]$^+$
2a	Ph—N=N—Ph—	80	226–228	Toluene	4.88 (ABX, J_p 24)[b]	3.38 ÷ 4.21 (m)	5.34[b] (ABX)	0.91, 1.28 (t)	—	22.35 (87.64%) 22.23 (12.36%)	769
2b		82	oil	—	[c]	3.71 ÷ 4.20 (m)	2.39(br)	1.08, 1.21 (t)	2.91 (s, Py—CH_2CH_2—)	23.44 (≥90%) 23.23 (≤10%)	619
2c	Ph—	70	176–180	EtOH	4.83 (m)	4.09, 3.71, 3.30, (q)	4.83(m)	0.87, 1.23 (t)		23.13 (≥92%) 23.02 (≤8%)	561

[a]Chemical shifts measured in $CDCl_3$ with 85% H_3PO_4 as external reference.
[b]See Figure 1 in the text.
[c]Masked by OCH_2 resonances.

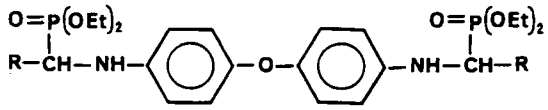
TABLE III

Physical properties of



3

and



4

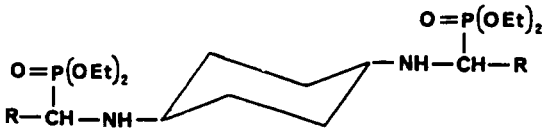
No.	R	Yield (in %)	m.p. (°C)	Recryst. solvent	^{1}H-NMR in $CDCl_3$				^{31}P-NMR[a]	[M + H]$^+$
					CHP	OCH_2	NH	CH_2CH_3		
3a	C_6H_5—	77	188–190[b]	EtOH	4.60 (d, J_p 23.4)	3.60 ÷ 4.24 (m)	3.20(br)	1.08, 1.24 (t)	23.53	561
3b	2-pyridyl	89	182–186	EtOH	4.84 (d, J_p 22.3)	4.11 ÷ 4.30 (m)	[c]	1.14, 1.24 (t)	22.19	563
4a	C_6H_5—	71	129–133	AcOEt	4.67 (d, J_p 24.1)	3.64 ÷ 4.14 (m)	[c]	1.03, 1.28 (t)	23.30	653

[a]Chemical shift measured in $CDCl_3$ with 85% H_3PO_4 as external reference.

[b]The same authors in two different articles (Reference 6 and 7) report different m.p.: 199–200 in Reference 6 and 193–194 in Reference 7. In any case NMR and MS characterizations were not given.

[c]Masked by OCH_2 resonances.

TABLE IV

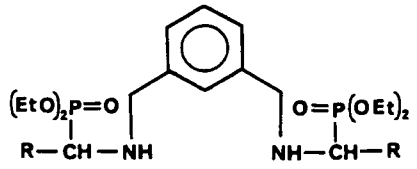
Physical properties of 

5

No.	R	Yield (in %)	m.p. (°C)	Recryst. solvent	^{1}H-NMR in $CDCl_3$					^{31}P-NMR[a]	[M + H]$^+$
					CHP	OCH_2	NH	CH_2CH_3	Others		
5a	C_6H_5—	60	152–155	EtOH	4.12 (d, J_p 21.2)	3.67 ÷ 4.12 (m)	2.35(br)	1.08, 1.25 (t)	1.88 (s, Cyclohexyl)	24.53	567
5b	c—C_6H_{11}—	96	85–89	Et_2O	2.74 (ABX, J_p 18.7)	3.93 ÷ 4.31 (m)	2.66(ABX)	1.32 (t)	1.20, 1.79(m, Cyclohexyls)	29.46	579

[a]Chemical shifts measured in $CDCl_3$ with 85% H_3PO_4 as external reference.

TABLE V

Physical properties of 

6

No.	R	Yield (in %)	m.p. (°C)	Recryst. solvent	^{1}H-NMR in $CDCl_3$					^{31}P-NMR[a]	[M + H]$^+$
					CHP	OCH_2 + CH_2Ph	NH	CH_2CH_3	Others		
6a	Ph—	95	oil	—	[b]	3.42 ÷ 4.15 (m)	2.40(br)	1.21, 1.26 (t)		23.64	589
6b	c—C_6H_{11}	78	oil	—	2.75 (ABX, J_p 16)	3.72 ÷ 4.25 (m)	—	1.33 (t)	1.75, 1.96 (m, c—C_6H_{11})	24.48 (≈70%) 24.29 (≈30%)	601
6c	2-Py	45	oil	—	[b]	3.54 ÷ 4.25 (m)	2.88(br)	1.16, 1.26 (t)		22.66 (79%) 22.60 (21%)	591

[a]Chemical shifts measured in $CDCl_2$ with 85% H_3PO_4 as external reference.
[b]Masked by OCH_2 resonances.

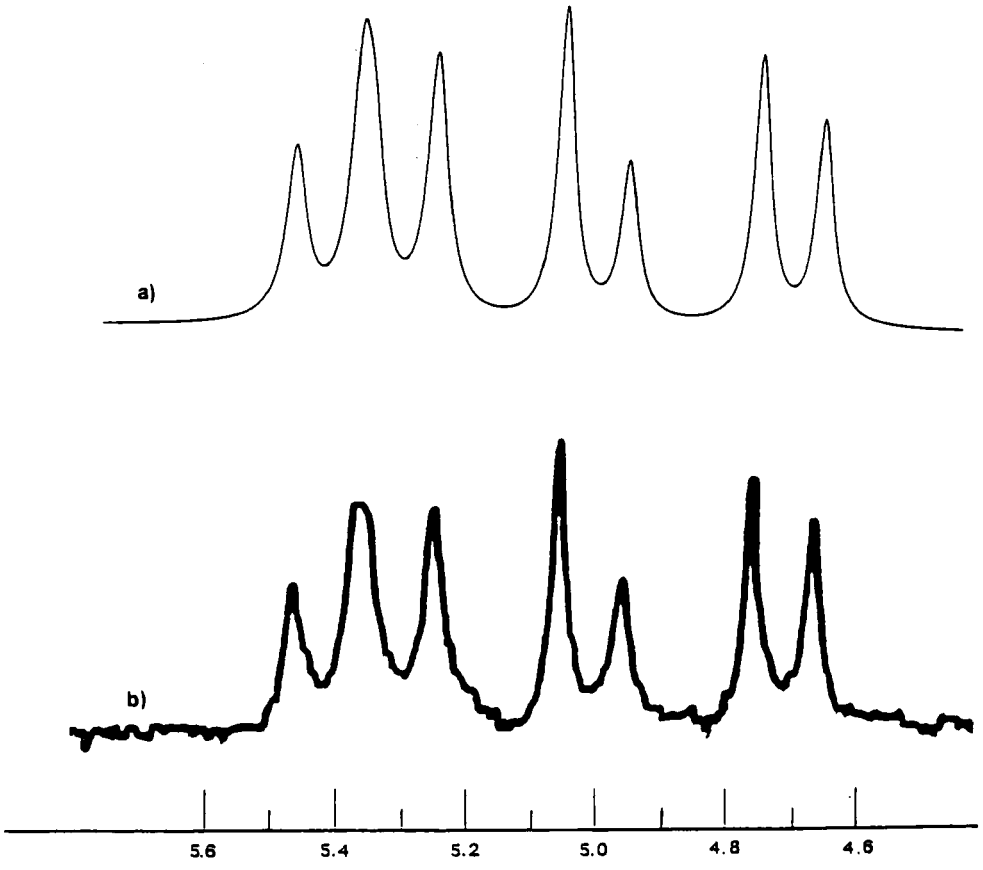


FIGURE 1 Vicinal $\overset{1}{P}—\overset{2}{CH}—\overset{3}{NH}$ coupling in $CDCl_3$ for compound **2a**: a) simulated (J_{12} = −27.4 Hz; J_{13} = 10.9 Hz; J_{23} = 8.8 Hz) and b) experimental.

samples. As reported in Tables I–V only one sharp phosphorus signal is observed in the majority of our samples, indicating that, in absence of accidental isochronies, only one diastereomer contributes to the structure. Even after several recrystallizations, in the mother liquors was still present the same diastereomer, as judged by the ^{31}P-NMR spectra (except where indicated).

Therefore, we can conclude that the addition of diethyl phosphonate to symmetrical diimines proceeds stereospecifically with the predominant formation of only one of the two possible diastereomeric forms.

In previous papers[1,2] we reported evidences that in the reaction of diethyl phosphonate with *N,N'*-dibenzylideneethylenediamine only the *meso* stereoisomer was formed: reasoning by analogy we can tentatively propose that also in the reactions investigated in this paper the *meso* forms are predominantly produced.

Inspection of the ^{31}P chemical shifts reported in Tables I–V reveals that the latter are dramatically influenced by the substituents present in the molecule. In particular, as already observed in variously substituted 1-phenylamino-1-phenylmethane phosphonates,[8] electron withdrawing groups cause an upfield shift of the ^{31}P resonances.

TABLE VI

FAB-MS spectral data of samples listed in Tables I–V. Peak's intensities are reported in parenthesis

No.	$[M + H]^+$	$[2M + H]^+$	$[M + H - 138]^+$	$[M + H - (2 \times 138)]^+$	$[xM + R]^+$
1a	621 (35)	1241 (4)	483 (97)	345 (100)	643 (39)[a]
1b	619 (39)	1237 (3)	481 (38)	343 (100)	641 (7)[a]
					1259 (2)[b]
1c	769 (20)	—	631 (33)	493 (100)	791 (46)[a]
1d	573 (26)	1147 (10)	435 (100)	297 (51)	595 (33)[a]
					1007 (4)[c]
2a	769 (28)	1537 (2)	631 (18)	493 (100)	783 (20)[a]
					1559 (4)[b]
2b	619 (68)	—	481 (40)	343 (100)	
2c	561 (5)	1121 (7)	423 (45)	285 (100)	583 (20)[a]
					1143 (3)[b]
3a	561 (53)	1121 (11)	423 (100)	385 (69)	
3b	563 (55)	1125 (7)	425 (52)	287 (100)	
4a	653 (61)	1307 (12)	515 (100)	377 (97)	1168 (3)[c]
5a	567 (30)	1133 (4)	429 (50)	291 (100)	589 (5)[a]
5b	579 (4)	1157 (1)	441 (41)	303 (100)	601 (44)[a]
					1179 (3)[b]
6a	589 (16)	1177 (1)	451 (44)	313 (100)	1039 (1)[c]
6b	601 (20)	—	463 (23)	325 (100)	623 (3)[a]
6c	591 (15)	1181 (2)	453 (33)	315 (100)	613 (2)[a]

[a] x = 1, R = Na.
[b] x = 2, R = Na.
[c] x = 1, R = Fragment.

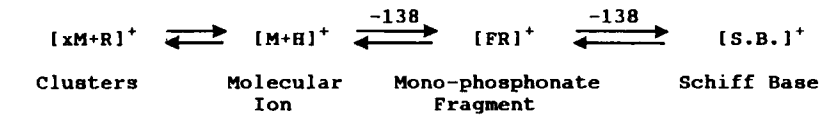
The addition reaction of H—P(O)$(OEt)_2$ at the precursor diimine was more carefully investigated by ^{1}H-NMR in the case of compound **3a**, and thus it was possible to ascertain that the reaction proceeds step-wise. The mono-phosphonate derivative (not isolated) was found to be formed in the first stage of the reaction‖; then, by further addition of another mole of H—P(O)$(OEt)_2$ the diphosphonate **3a** was formed, which precipitated from the reaction media.

The characterization of the samples reported in Tables I–V was also performed by FAB-MS technique. Inspection of Table VI indicates that a protonated molecular ion $[M + H]^+$ was observed in high intensity for all compounds, and the $[M + H - 138]^+$ ion or the $[M + H - (2 \times 138)]^+$ ion constitutes the base peak.

The $[M + H - 138]^+$ ion corresponding to the monophosphonate molecule, was generated by the easy loss of diethyl phosphonate $HPO(OEt)_2$ m/z 138. The region at relatively low masses is characterized by the presence of the ion $[M + H - (2 \times 138)]^+$, which is the base peak or the second peak in relative intensity. This ion may originate from the monophosphonate ion by a loss of a neutral molecule of diethyl phosphonate (see Scheme 1).

In all spectra peaks due to cluster ions $[xM + R]^+$ are observed. A cluster with peak at m/z 23 mass unit above the molecular ion strongly indicates cationization of our molecules with Na. The source of this metal ion contamination is probably due to the synthetic procedure used. A cluster with peak, at m/z $[2M + H]^+$ mass unit with relative intensities in the range 1–15%, is also present in all spectra. This later peak and some other cluster ions may originate from a beam-surface reaction indicating that probably some association occurs among the molecular ion with neutral molecule and fragments.

‖$C_{24}H_{27}N_2O_3P$, ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.02 and 1.29 (t, J_{HH} 7 Hz, $CH_2C\underline{H}_3$, 6H), 3.75–4.22 (m, OCH_2 + NH, 5H), 4.79 (d, J_{HP} 24.2 Hz, 1H), 6.62 (d, J_{HH} 8.8 Hz, ArH, 2H), 7.11 (d, J_{HH} 9.1 Hz, ArH, 2H), 7.37 (m, ArH, 8H), 8.42 (s, CH=N, 1H); ^{31}P-NMR δ (ppm): 23.20.



SCHEME 1

Fragmentation patterns involving clusters were also observed for peptides,[10] dicarboxylic acid,[11] and phosphonium salts.[12] In the later compounds the detection of both ions, i.e., the cation C^+ and the cluster ion $[C_2X]^+$ (where X is the anion), allows the determination of the relative molecular masses of the salt molecule and its ionic components, i.e., cation and anion.

EXPERIMENTAL

Amines, aldehydes, diethylphosphonate as well as solvents and all other chemicals used were high purity commercial products from Aldrich, which were further purified before use. All syntheses were performed under a dry N_2 atmosphere.

^{1}H-NMR spectra were recorded in $CDCl_3$ with Me_4Si as an internal standard using a Bruker WP-80 or AC-250 instrument operating at 80 and 250 MHz, respectively. Phosphorus NMR-spectra were recorded at Düsseldorf University with a Bruker AM 200 MHz spectrometer with a resolution of ≥0.003 ppm using 85% H_3PO_4 as external reference.

Mass spectra were obtained using a double focusing Kratos MS 50S instrument equipped with a standard FAB source and DS 90 data system. 3-Nitro-benzylalcohol was used as matrix.

Melting points were determined on a Büchi 530 melting point apparatus and are uncorrected.

The Schiff base precursors were all prepared in high yield from aldehydes and amines according to the following example.

Precursor of **1b**. An ethanolic solution (200 ml) of terephthaldicarboxaldehyde (5.7 g, 42.5 mmol), at reflux temperature, was added 10.4 g of 2-(2-aminoethyl)pyridine (85 mmol) dissolved in 50 ml of EtOH. After few minutes, and upon cooling, an orange precipitate was formed, which was filtered off and recrystallized from EtOH, to give 14 g (97%) of the desired Schiff base, m.p. 108–110°C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.20 (t, J_{HH} 7.2 Hz, CH_2Py, 4H), 4.05 (t, J_{HH} 7.2 Hz, N—CH_2, 4H), 7.18 (m, PyH, 4H), 7.52 (m, PyH, 2H), 7.71 (s, ArH, 4H), 8.22 (s, CH=N, 2H), 8.55 (m, PyH, 2H).

Some of the used Schiff bases were already reported in the literature and, in such cases, the physical properties given and found were coincident.

Compound **1b**. A stirred solution of the Schiff base precursor (8.5 g, 25 mmol) in dry ethanol (100 ml) was added dropwise 9 ml of $HP(O)(OEt)_2$ (65 mmol) and a catalytic amount of NaH.

After the addition was completed, the mixture was warmed at reflux for two hours. The solvent was then evaporated and to the oily residue were added a few drops of ethylacetate. White crystal very slow were formed on standing and were collected by filtration to give **1b** (3 g, 4.9 mmol 20%) m.p. 88–90°C.

The compounds listed in Tables I–V have been obtained in the same way.

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