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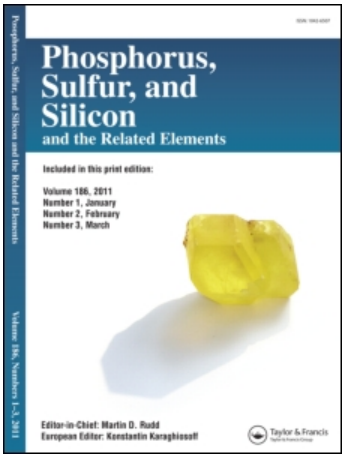


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# First Synthesis of γ,γ'-Diphosphonylketones and Their Reactivity in the Fischer Reaction

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# FIRST SYNTHESIS OF $\gamma,\gamma'$-DIPHOSPHONYLKETONES AND THEIR REACTIVITY IN THE FISCHER REACTION

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(Received November 22, 2001)

*Two synthetic methods leading to the new $\gamma,\gamma'$-diphosphonylketones **2** and **2′** are reported. The first method involves the base-catalyzed addition of diethylphosphite to diarylideneketones. The second one utilizes the reaction of triethylphosphite and ethoxydiphenylphosphine with $\beta,\beta'$-bis(dimethylamino)ketone hydrochlorides. On reaction with phenylhydrazine hydrochloride, compounds **2** and **2′** give the corresponding 2-(phosphonoethyl)3-(phosphonomethyl)indoles **3**. The structure of all obtained products is confirmed by NMR ($^1H$, $^{31}P$, $^{13}C$) and IR spectroscopy.*

*Keywords:* Diphosphonylketones; 2-(phosphonoethyl)3-(phosphonomethyl)indoles

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## INTRODUCTION

An increasing interest has been paid for several years to the synthesis of $\gamma$-ketophosphonates. Such interest has been stimulated by their promising applications as antihypertensive,[1] herbicide or fungicide agents.[2] Some of these compounds exhibit also activity as inhibitors of matrix-metalloprotease[3] and kininogenase.[4]

With the aim to broaden further the range of $\gamma$-ketophosphonates and pursuing our research program regarding the synthesis of phosphonylketones,[5–8] we report in the present investigation, two convenient and efficient methods for the synthesis of the new $\gamma,\gamma'$-diphosphonylketones from easily accessible diarylideneketones or $\beta,\beta'$-bis(dimethylamino)ketone hydrochlorides.

It is important to note, here, that diphosphorylated compounds are known for their useful properties ranging from pharmacological

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activities[9] to the metal-complexing ability.[10–12] For instance, in recent years, the use of some $\gamma,\gamma$-diphosphonylketones as a treatment for osteoporosis, has been proposed.[13]

Furthermore, and in order to explore the synthetic utility of the $\gamma,\gamma'$-diphosphonylketones synthesized, we show here that their reaction with phenylhydrazine hydrochloride carried out under the Fischer reaction conditions,[14–16] leads to a new class of phosphonoindoles. Our interest for these compounds is due to the well known interesting biological properties of indol derivatives.[17–19]

## RESULTS AND DISCUSSION

For the synthesis of $\gamma,\gamma'$-diphosphonylketones, we have used two different approches. The first one involved the base-catalyzed addition of diethylphosphite to diarylideneketones. The second approach utilizes the reaction of triethylphosphite and ethoxydiphenylphosphine with $\beta,\beta'$-bis(dimethylamino)ketone hydrochlorides.

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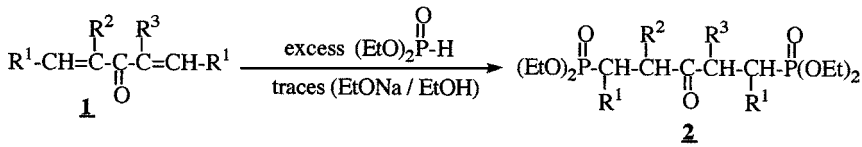
### Addition of Diethylphosphite to Diarylideneketones 1: Synthesis of $\gamma,\gamma'$-Diphosphonylketones 2

Treatment of diarylideneketones **1** with a large excess of diethylphosphite (10 equivalents), performed at room temperature, for 24 h and in the presence of a catalytic amount of sodium ethoxide in ethanol, led to the $\gamma,\gamma'$-diphosphonylketones **2**, in good yields (Scheme 1).




| | 2a | 2b | 2c | 2d | 2e |
|---|---|---|---|---|---|
| $R^1$ | Ph |  |  | Ph | Ph |
| $R^2$ | H | H | H | $(CH_2)_2$ | $(CH_2)_3$ |
| $R^3$ | H | H | H | | |

**SCHEME 1**

The reaction was initially carried out with various amounts of diethylphosphite in order to optimize the reaction yield. We have found

**TABLE I** $\delta$ $^{31}$P in ppm and % of Diastereoisomers for Compounds **2**

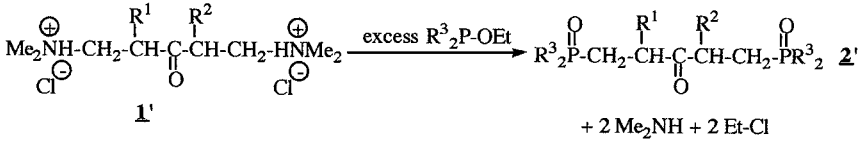
| | **2a**$_1$ | **2a**$_2$ | **2b**$_1$ | **2b**$_2$ | **2c**$_1$ | **2c**$_2$ | **2d**$_1$ | **2d**$_2$ | **2e**$_1$ | **2e**$_2$ |
|---|---|---|---|---|---|---|---|---|---|---|
| $\delta$ $^{31}$P | 28.4 | 28.3 | 27.5 | 26.8 | 26.5 | 26.1 | 29.5 | 26.6 | 29.2 | 29.1 |
| % dias | 52 | 48 | 59 | 41 | 55 | 45 | 54 | 46 | 53 | 47 |

that the use of 10 equivalents of diethylphosphite gave the best result (80–92% yield).

Compounds **2** were characterized on the basis of their $^{31}$P, $^{1}$H, and $^{13}$C NMR data, which indicate that they are obtained as a mixture of two diastereoisomers. The major will be designated by index 1 and the minor by index 2. The relative proportions of these diastereoisomers were estimated from the $^{31}$P NMR spectra where a singlet for each diastereoisomer is present (Table I).

## 2-2 Reaction of Triethylphosphite and Ethoxydiphenylphosphine with $\beta,\beta'$-bis(dimethylamino)ketone Hydrochlorides 1′: Synthesis of $\gamma,\gamma'$-Diphosphonylketones 2′

It is well known that $\beta$-(dialkylamino)ketone hydrochlorides react with phosphites under reflux to yield $\gamma$-ketophosphonates.[6,20–21] We show here that the extension of this reaction to $\beta,\beta'$-bis(dimethylamino)ketone hydrochlorides **1′** leads to the formation of $\gamma,\gamma'$-diphosphonylketones **2′** (Scheme 2).




| | **2'a** | **2'b** | **2'c** | **2'd** | **2'e** |
|---|---|---|---|---|---|
| $R^1$ | H | H | $(CH_2)_2$ | $(CH_2)_3$ | $(CH_2)_3$ |
| $R^2$ | H | H | | | |
| $R^3$ | OEt | Ph | OEt | OEt | Ph |

**SCHEME 2**

The reaction was achieved by heating under reflux for 6 h a mixture of **1′** in excess phosphite (5 equivalents).

The structures of compounds **2′** have been unambiguously characterised from their IR and NMR ($^{1}$H, $^{31}$P, $^{13}$C) spectral data.

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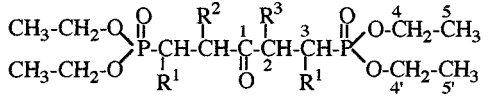
**TABLE II** $^{13}C$ NMR for Compounds **2**: $\delta$ in ppm ($J_{CP}$ in Hz)

**2**



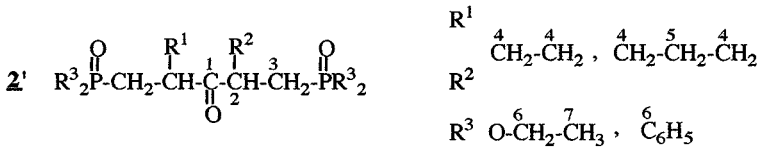
$R^1$ $C_6H_5$,  , 

$R^2$ $CH_2$-$CH_2$, $CH_2$-$CH_2$-$CH_2$

$R^3$

| | **2a** | **2b** | **2c** | **2d** | **2e** |
|---|---|---|---|---|---|
| $C_1$ | 203.3(15.1; **2a$_1$**) | 194.8(13.8; **2b$_1$**) | 201.8(14.9; **2c$_1$**) | 214.0(12.2; **2d$_1$**) | 206.4(12.5; **2e$_1$**) |
| | 203.7(14.3; **2a$_2$**) | 196.9(13.2; **2b$_2$**) | 202.5(14.4; **2c$_2$**) | 213.6(11.9; **2d$_2$**) | 205.8(12.3; **2e$_2$**) |
| $C_2$ | 43.4 | 41.8(**2b$_1$**) | 41.2(**2c$_1$**) | 49.2(**2d$_1$**) | 49.8(**2e$_1$**) |
| | | 44.2(**2b$_2$**) | 42.7(**2c$_2$**) | 51.5(**2d$_2$**) | 50.2(**2e$_2$**) |
| $C_3$ | 38.7(140.4; **2a$_1$**) | 34.0(146.1; **2b$_1$**) | 32.5(145.0; **2c$_1$**) | 41.5(146.2; **2d$_1$**) | 43.3(137.5; **2e$_1$**) |
| | 38.9(140.1; **2a$_2$**) | 33.9(145.2; **2b$_2$**) | 32.3(144.4; **2c$_2$**) | 43.2(138.8; **2d$_2$**) | 42.0(145.9; **2e$_2$**) |
| $C_4$ | 62.1–63.0 | 62.0–63.0 | 62.0–63.1 | 61.6–62.9 | 61.5–63.2 |
| $C_5$ | 16.1–16.4 | 15.7–16.2 | 15.6–16.2 | 15.5–16.0 | 15.7–16.1 |
| $C_6$ | 127.2–135.6 | 123.4–144.5 | 107.5–141.3 | 126.7–137.8 | 125.8–137.3 |
| $C_7$ | — | — | — | 23.3(14.7; **2d$_1$**) | 25.4(14.5; **2e$_1$**) |
| | | | | 25.2(4.6; **2d$_2$**) | 27.0(3.9; **2e$_2$**) |
| $C_8$ | — | — | — | — | 18.2(**2e$_1$**) |
| | | | | | 20.3(**2e$_2$**) |

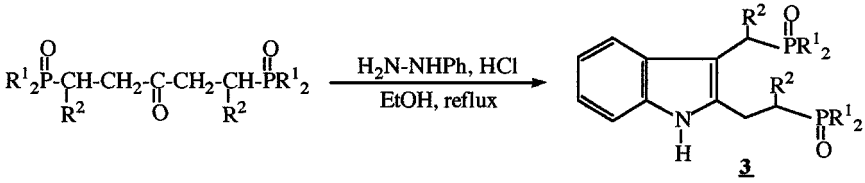
**TABLE III** $^{13}C$ NMR for Compounds **2′**: $\delta$ in ppm ($J_{CP}$ in Hz)



| | **2′a** | **2′b** | **2′c** | **2′d** | **2′e** |
|---|---|---|---|---|---|
| $C_1$ | 207.9(14.6) | 208.8(12.1) | 215.0(13.2) | 208.0(12.9) | 209.1(11.6) |
| $C_2$ | 40.4 | 42.7 | 43.8 | 44.5 | 42.9 |
| $C_3$ | 27.8(129.8) | 30.1(78.5) | 24.3(144.5) | 24.1(143.4) | 25.3(58.2) |
| $C_4$ | — | — | 36.2 | 35.2(5.5) | 37.1(5.2) |
| $C_5$ | — | — | — | 24.2 | 21.8 |
| $C_6$ | 61.8(6.4) | 127.8–135.5 | 61.0(6.2) | 60.5(6.4) | 127.8–135.3 |
| $C_7$ | 16.1(4.6) | — | 15.9(6.3) | 15.4(6.4) | — |

## Reaction of $\gamma,\gamma'$-Diphosphonylketones 2 and 2′ with Phenylhydrazine Hydrochloride: Synthesis of 2-(Phosphonoethyl)3-(phosphonomethyl)indoles 3

In connection with our interest in the synthesis of heterocyclic compounds bearing phosphoryl groups,[22–23] we report here the indolization according to Fischer[14–16] of the $\gamma,\gamma'$-diphosphonylketones **2** and **2′** which leads to a new class of phosphorylated indoles. Thus, treatment of compounds **2** and **2′** with an equimolar amount of phenylhydrazine hydrochloride, using ethanol as solvent and heating the mixture under reflux for 12 h gives the 2-(phosphonoethyl)3-(phosphonomethyl)indoles **3** in good yields (Scheme 3).



| | **3a** | **3b** | **3c** | **3d** | **3e** |
|---|---|---|---|---|---|
| $R^1$ | EtO | EtO | EtO | Ph | EtO |
| $R^2$ | Ph |  |  | H | H |

**SCHEME 3**

The $^1H$, $^{13}C$, and $^{31}P$ NMR data confirm the structures of compounds **3** and are in accordance with some literature data.[16] The N–H proton shows a broad singlet at $\delta = 8.8$–$9.2$ ppm. The $^{13}C$ NMR spectra display

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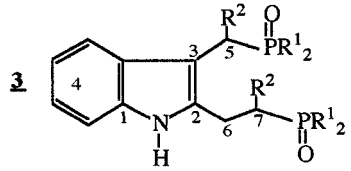
**TABLE IV** $^{13}C$ NMR for Compounds **3**: $\delta$ in ppm ($J_{CP}$ in Hz)




| | **3a** | **3b** | **3c** | **3d** | **3e** |
|---|---|---|---|---|---|
| $C_1$ | 138.5 | 139.1 | 139.5 | 138.8 | 138.3 |
| $C_2$ | 136.7(16.4) | 137.0(15.9) | 137.4(15.5) | 136.9(16.0) | 136.2(16.2) |
| $C_3$ | 102.5(8.2) | 103.4(8.5) | 104.2(8.0) | 103.8(7.5) | 104.0(7.8) |
| $C_4$ | 112.5–135.2 | 111.8–144.2 | 109.1–142.0 | 112.0–135.7 | 111.5–131.8 |
| $C_5$ | 44.9(138.5; **3a$_1$**) | 41.8(140.5; **3b$_1$**) | 41.3(139.4; **3c$_1$**) | 27.5(78.8) | 23.8(143.5) |
| | 45.3(138.3; **3a$_2$**) | 42.5(140.1; **3b$_2$**) | 41.5(139.0; **3c$_2$**) | | |
| $C_6$ | 32.6(4.0) | 32.0(3.7) | 31.7(3.9) | 33.9(3.0) | 32.2(3.5) |
| $C_7$ | 40.8(144.1; **3a$_1$**) | 39.8(145.5; **3b$_1$**) | 39.5(142.2; **3c$_1$**) | 25.6(80.3) | 21.0(144.7) |
| | 42.5(146.7; **3a$_2$**) | 40.1(146.2; **3b$_2$**) | 39.7(143.0; **3c$_2$**) | | |
| $C_8$ | 15.9–16.5 | 15.5–16.3 | 15.7–16.5 | 112.0–135.7 | 16.0–16.3 |
| $C_9$ | 62.0–63.3 | 61.8–63.2 | 62.0–63.4 | — | 61.9–62.2 |
| $C_{10}$ | 112.5–135.2 | 111.8–144.2 | 109.1–142.0 | — | — |

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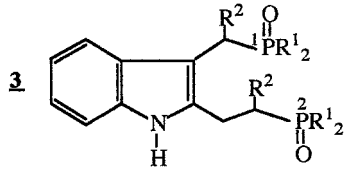
the characteristic signals of all carbons and particularly those corresponding to the indole ring (Table IV).

In addition, $^{31}P$, $^{1}H$, and $^{13}C$ NMR analysis of compounds **3a–c** shows, similar to the corresponding $\gamma,\gamma'$-diphosphonylketones (**2a–c**), a mixture of two diastereoisomers in an approximate 1:1 ratio which was estimated from the $^{31}P$ NMR spectra (Table V). Indexes 1 and 2 are attributed to the major and minor diastereoisomers respectively.

## EXPERIMENTAL SECTION

$^{1}H$, $^{31}P$, and $^{13}C$ NMR spectra were recorded with $CDCl_3$ as solvent, on a Bruker-300 spectrometer. The chemical shifts are reported in ppm

**TABLE V** $\delta$ $^{31}P$ in ppm and % of Diastereoisomers for Compounds **3**




| | **3a$_1$** | **3a$_2$** | **3b$_1$** | **3b$_2$** | **3c$_1$** | **3c$_2$** | **3d** | **3e** |
|---|---|---|---|---|---|---|---|---|
| $\delta$ $P_1$ | 27.9 | 27.6 | 28.6 | 28.5 | 27.5 | 27.3 | 31.0 | 28.3 |
| $\delta$ $P_2$ | 27.4 | 27.5 | 28.2 | 28.4 | 27.1 | 27.2 | 30.6 | 28.1 |
| % dias | 51 | 49 | 55 | 45 | 52 | 48 | — | — |

relative to TMS (internal reference) for $^{1}H$ and $^{13}C$ NMR and relative to 85% $H_3PO_4$ (external reference) for $^{31}P$ NMR. The coupling constants are reported in Hz. For the $^{1}H$ NMR, the multiplicities of signals are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, qp: quintet, m: multiplet.

IR spectra were recorded in $CHCl_3$, on a Perkin Elmer Paragon 1000 PC spectrometer.

Purification of products was performed by column chromatography using silica gel 60 (Fluka).

## Synthesis of Compounds 1 and 1′

The starting diarylideneketones **1**[24] and bis(dimethylamino)ketone hydrochlorides **1′**[25] were prepared according to reported procedures.

## Synthesis of γ,γ′-Diphosphonylketones 2

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To a mixture of diarylideneketone (0.01 mol) and diethylphosphite (0.1 mol), was added dropwise with stirring, a solution of 0.025 g of sodium in 0.5 mL of absolute ethanol. The reaction mixture was then stirred at room temperature for an additional 24 h. The excess of diethylphosphite was removed under reduced pressure then $CHCl_3$ (100 mL) was added. The organic phase was washed with water (2 × 50 mL), dried over $MgSO_4$ and concentrated in vacuo. The obtained residue was chromatographed on silica gel column using a mixture of ether and hexane 3/1 as eluent.

**2a**: Oil; Yield = 92%; $^{1}H$ NMR: $\delta = 1.02–1.30$ (m; 12H; C$\underline{H}_3$—$CH_2$—O); 2.93–3.23 (m; 4H; $CH_2$—C=O); 3.60–3.73 (m; 2H; CH—P=O); 3.83–4.13 (m; 8H; $CH_3$—C$\underline{H}_2$—O); 7.10–7.32 (m; 10H; H arom.); IR: $\nu_{C=O} = 1715$ $cm^{-1}$; $\nu_{P=O} = 1262$ $cm^{-1}$.

**2b**: Oil; Yield = 86%; $^{1}H$ NMR: $\delta = 1.06–1.25$ (m, 12H; C$\underline{H}_3$—$CH_2$—O); 2.82–3.14 (m; 4H; $CH_2$—C=O); 3.23–3.35 (m; 2H; CH—P=O); 3.80–4.12 (m; 8H; $CH_3$—C$\underline{H}_2$—O); 6.79–7.34 (m; 6H; H arom.); IR: $\nu_{C=O} = 1721$ $cm^{-1}$; $\nu_{P=O} = 1272$ $cm^{-1}$.

**2c**: Oil; Yield = 80%; $^{1}H$ NMR: $\delta = 1.03–1.24$ (m, 12H; C$\underline{H}_3$—$CH_2$—O); 2.98–3.27 (m; 4H; $CH_2$—C=O); 3.40–3.54 (m; 2H; CH—P=O); 3.89–4.16 (m; 8H; $CH_3$—C$\underline{H}_2$—O); 6.30–7.27 (m; 6H; H arom.); IR: $\nu_{C=O} = 1720$ $cm^{-1}$; $\nu_{P=O} = 1270$ $cm^{-1}$.

**2d**: Oil; Yield = 87%; $^{1}H$ NMR: $\delta = 0.84–1.28$ (m; 12H; C$\underline{H}_3$—$CH_2$—O); 1.45–3.40 (m; 6H; cyclic H); 3.45–3.72 (m; 2H; CH—P=O); 3.82–4.15 (m; 8H; $CH_3$—C$\underline{H}_2$—O); 6.80–7.91 (m; 10H; H arom.); IR: $\nu_{C=O} = 1741$ $cm^{-1}$; $\nu_{P=O} = 1260$ $cm^{-1}$.

**2e**: Oil; Yield = 81%; $^{1}H$ NMR: $\delta = 0.87–1.33$ (m; 12H; C$\underline{H}_3$—$CH_2$—O); 1.37–3.26 (m; 8H; cyclic H); 3.63–3.72 (m; 2H; CH—P=O); 4.03–4.23

(m; 8H; $CH_3$—C$\underline{H}_2$—O); 6.91–7.86 (m; 10H; H arom.); IR: $\nu_{C=O} = 1712\ cm^{-1}$; $\nu_{P=O} = 1271\ cm^{-1}$.

## Synthesis of $\gamma,\gamma'$-Diphosphonylketones $\underline{2}'$

A mixture of $\beta,\beta'$-bis(dimethylamino)ketone hydrochloride (0.02 mol) and phosphite (0.1 mol) was heated under reflux for 6 h. After cooling, the excess of phosphite was removed under reduced pressure then $CHCl_3$ (100 mL) was added. The organic phase was washed with water ($2 \times 50$ mL), dried over $MgSO_4$ and concentrated in vacuo. The obtained residue was chromatographed on silica gel column using a mixture of ether and hexane 3/1 as eluent.

**$\underline{2}'$a**: Oil; Yield = 78%; $^{31}P$ NMR: $\delta = 29.2$; $^1H$ NMR: $\delta = 1.19$ (t; 12H; $^3J_{HH} = 6.4$; C$\underline{H}_3$—$CH_2$—O); 1.80–3.18 (m; 8H; $CH_2$—$CH_2$—C=O); 3.96 (qp; 8H; $^3J_{HH} = {}^3J_{PH} = 6.4$; $CH_3$—C$\underline{H}_2$—O); IR: $\nu_{C=O} = 1720\ cm^{-1}$; $\nu_{P=O} = 1260\ cm^{-1}$.

**$\underline{2}'$b**: Oil; Yield = 71%; $^{31}P$ NMR: $\delta = 30.8$; $^1H$ NMR: $\delta = 1.75$–3.20 (m; 8H; $CH_2$—$CH_2$—C=O); 7.12–7.95 (m, 20H, H arom.); IR: $\nu_{C=O} = 1718\ cm^{-1}$; $\nu_{P=O} = 1270\ cm^{-1}$.

**$\underline{2}'$c**: Oil; Yield = 82%; $^{31}P$ NMR: $\delta = 31.5$; $^1H$ NMR: $\delta = 0.90$ (t; 12H; $^3J_{HH} = 7.0$; C$\underline{H}_3$—$CH_2$—O); 1.25–2.47 (m; 10H; cyclic H and $CH_2$—P=O); 3.65 (qp; 8H; $^3J_{HH} = {}^3J_{PH} = 7.0$; $CH_3$—C$\underline{H}_2$—O); IR: $\nu_{C=O} = 1743\ cm^{-1}$; $\nu_{P=O} = 1262\ cm^{-1}$.

**$\underline{2}'$d**: Oil; Yield = 90%; $^{31}P$ NMR: $\delta = 31.8$; $^1H$ NMR: $\delta = 0.82$ (t; 12H; $^3J_{HH} = 7.1$; C$\underline{H}_3$—$CH_2$—O); 1.18–2.44 (m; 12H; cyclic H and $CH_2$—P=O); 3.59 (qp; 8H; $^3J_{HH} = {}^3J_{PH} = 7.1$; $CH_3$—C$\underline{H}_2$—O); IR: $\nu_{C=O} = 1714\ cm^{-1}$; $\nu_{P=O} = 1263\ cm^{-1}$.

**$\underline{2}'$e**: Oil; Yield = 83%; $^{31}P$ NMR: $\delta = 30.7$; $^1H$ NMR: $\delta = 1.10$–2.87 (m; 12H; cyclic H and $CH_2$—P=O); 7.12–7.90 (m; 20H; H arom.); IR: $\nu_{C=O} = 1712\ cm^{-1}$; $\nu_{P=O} = 1269\ cm^{-1}$.

## Synthesis of 2-(Phosphonoethyl)3-(phosphonomethyl)-indoles $\underline{3}$

A mixture of $\gamma,\gamma'$-diphosphonylketone (0.005 mol) and phenylhydrazine hydrochloride (0.005 mol) in 30 mL of absolute ethanol, was heated under reflux for 12 h. After removal of ethanol under reduced pressure, the residue was diluted with water (50 mL) and extracted with $CHCl_3$ ($2 \times 25$ mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The obtained residue was chromatographed on silica gel column using EtOAc as eluent.

**$\underline{3}$a**: m.p.°C = 108; Yield = 71%; $^1H$ NMR: $\delta = 0.85$–1.27 (m; 12H; C$\underline{H}_3$—$CH_2$—O); 2.80–3.24 (m; 2H; $CH_2$—C=C); 3.42–3.71 (m; 2H; CH—

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P=O); 3.82–4.18 (m; 8H; $CH_3$—C<u>H</u>$_2$—O); 6.84–7.40 (m; 14H; H arom.); 8.83 (broad s; 1H; N—H); IR: $\nu_{P=O} = 1268\ cm^{-1}$; $\nu_{NH} = 3466\ cm^{-1}$.

**3b**: m.p.°C = 114; Yield = 67%; $^1$H NMR: $\delta = 0.92$–$1.29$ (m; 12H; C<u>H</u>$_3$—$CH_2$—O); 2.37–2.65 (m; 2H; $CH_2$—C=C); 3.30–3.58 (m; 2H; CH—P=O); 3.79–4.10 (m; 8H; $CH_3$—C<u>H</u>$_2$—O); 6.98–7.90 (m; 10H; H arom.); 8.80 (broad s; 1H; N—H); IR: $\nu_{P=O} = 1260\ cm^{-1}$; $\nu_{NH} = 3450\ cm^{-1}$.

**3c**: m.p.°C = 110; Yield = 62%; $^1$H NMR: $\delta = 0.90$–$1.25$ (m; 12H; C<u>H</u>$_3$—$CH_2$—O); 2.54–2.78 (m; 2H; $CH_2$—C=C); 3.41–3.67 (m; 2H; CH—P=O); 3.87–4.15 (m; 8H; $CH_3$—C<u>H</u>$_2$—O); 6.42–7.50 (m; 10H; H arom.); 8.92 (broad s; 1H; N—H); IR: $\nu_{P=O} = 1265\ cm^{-1}$; $\nu_{NH} = 3462\ cm^{-1}$.

**3d**: m.p.°C = 98; Yield = 53%; $^1$H NMR: $\delta = 1.90$–$3.24$ (m; 6H; $CH_2$—P=O and $CH_2$—$CH_2$—P=O); 6.85–7.88 (m; 24H; H arom.); 9.12 (broad s; 1H; N—H); IR: $\nu_{P=O} = 1268\ cm^{-1}$; $\nu_{NH} = 3446\ cm^{-1}$.

**3e**: m.p.°C = 85; Yield = 57%; $^1$H NMR: $\delta = 1.16$ (t; 6H; $^3J_{HH} = 7.0$; C<u>H</u>$_3$—$CH_2$—O); 1.35 (t; 6H; $^3J_{HH} = 6.8$; C<u>H</u>$_3$—$CH_2$—O); 1.96–3.51 (m; 6H; $CH_2$—P=O and $CH_2$—$CH_2$—P=O); 3.95 (qp; 4H; $^3J_{HH} = {}^3J_{PH} = 6.8$; $CH_3$—C<u>H</u>$_2$—O); 4.08 (qp; 4H; $^3J_{HH} = {}^3J_{PH} = 7.0$; $CH_3$—C<u>H</u>$_2$—O); 6.82–7.50 (m; 4H; H arom.); 9.18 (broad s; 1H; N—H); IR: $\nu_{P=O} = 1265\ cm^{-1}$; $\nu_{NH} = 3452\ cm^{-1}$.

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