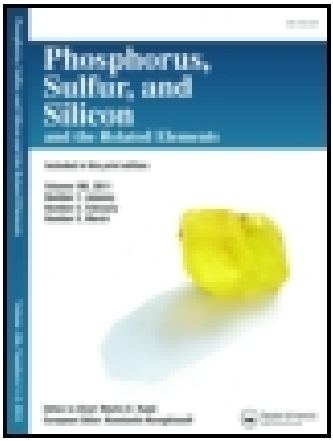

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SYNTHESIS AND NMR CHARACTERIZATION OF DIPHENYL α-(BENZYLOXYCARBONYLAMINO)-BENZYL-PHOSPHONATES AND DIPHENYL 1-(BENZYLOXYCARBONYLAMINO)-ALKYL PHOSPHONATES

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SYNTHESIS AND NMR CHARACTERIZATION OF DIPHENYL α-(BENZYLOXYCARBONYLAMINO)-BENZYL-PHOSPHONATES AND DIPHENYL 1-(BENZYLOXYCARBONYLAMINO)-ALKYL PHOSPHONATES

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A variety of the title phosphonic derivatives were synthesized in high yields starting from commercially available aldehydes. Complete NMR cheracterization is reported for all compounds, which are useful intermediates for the synthesis of the phosphorus analogs of natural enzymes or peptides.

Keywords: Phosphono-peptide intermediates; isomeric ratio; ^{1}H- and ^{31}P-NMR

INTRODUCTION

Phosphonopeptides are interesting compounds with attractive biological activity and therefore a rich literature has appeared concerning their synthesis.[1,6] The best route for the preparation of phosphorus analogs of natural enzymes or peptides, which could be obtained by replacing some amino acids with their phosphonic acid cognates or by inserting as additional moieties some aminophosphonic acids into a peptide chain, involves the synthesis of protected α-aminophosphonic acids.

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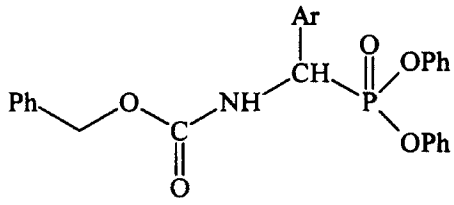
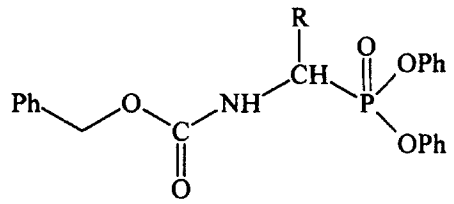
Futhermore, N-substituted α-aminophosphonic acid derivatives are attracting considerable interest for their use in agrochemistry,[7] as potential antitumoral agents[8] and for inhibiting enzymatic activity[9] and as antibacterial agents.[10] In addition, protected α-amminophosphonic acids, prepared by well established synthetic procedures, can be easily converted into their corresponding phosphonates bearing free ammino groups, which are stimulating great interest for their wide applications.[1,11]

Moreover, N-substituted α-aminophosphonic acid derivatives, as well as their cognates bearing free amino groups, can be used as curing agents for epoxy resins and other polycondensates in order to impart thermal resistance and/or fire-proofing and fire-retardant properties.[12–14]

Therefore, with such an idea in mind we synthesized a great variety of diphenyl α-(benzyloxycarbonylamino)-benzylphosphonates (**I**) and diphenyl 1-(benzyloxycarbonylamino)-alkylphosphonates (**II**), in order to fully characterize them by complete NMR analyses and for using such compounds for the purposes above described.



I



II

RESULTS AND DISCUSSIONS

The synthetic procedure for the preparation of compounds of type **I** and **II** is based on a three-component condensation reaction with benzylcarbamate, aldehydes and triphenylphosphite in the presence of acetic acid, adapted from the paper of Mastalerz *et al.*[15] Yields are good both for aliphatic as well as for aromatic aldehydes. Analytical characterization is reported in Tables I and II, as well in the experimental part.

As far as the proton NMR characterization is concerned we observe that for compounds of type **I** the most diagnostic peaks are due to:

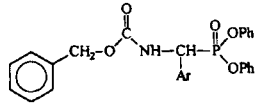
- the methyne hydrogen linked to the phosphonic group wich appears as a quartett because of the coupling with phosphorus ($^2J_{HP}$ ~ 21 Hz) and the NH group ($^3J_{HH}$ ~ 10 Hz), and whose chemical shift is sensitive to the electronic environment present in the molecule ranging from 5.4 to 6.0 ppm;
- the benzyloxymethylene group which appears as a quartett due to the chirality of the molecule and whose chemical shift is roughly centered at 5.10 ppm;
- the NH-CO group, very sensitive to hydrogen bond formation, appearing as a broad multiplet in the region of 6.0 ppm.

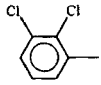
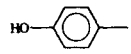
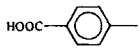
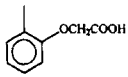
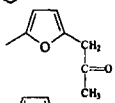
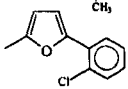
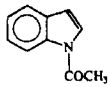
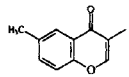
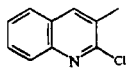
For compounds of type **II,** *i.e.*, the alkyl derivatives, the CH-P signal is shifted to higher fields and additional signals and as well as increasing complexity is arising from the presence of the aliphatic moiety. In the samples bearing a chiral aliphatic group doubling of the signals are in evidence due to the formation of both *threo* (**RR** and **SS**) and *erythro* (**RS** and **SR**) diastereomers. The presence of both diastereomers and their relative population can be more easily detected by ^{31}P-NMR analyses (see table II).

EXPERIMENTAL

Aldehydes, triphenyl phosphite, benzyl carbamate, acetic acid as well as solvents used were high purity commercial products from Aldrich. All syntheses were performed under a dry N_2 atmosphere. ^{1}H-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6, with Me_4Si as an internal standard using a Bruker AC-200 instrument operating at 200 MHz. Phosphorus NMR-spectra were recorded in $CHCl_3$ or DMSO at Düsseldorf University

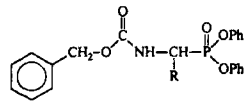
TABLE I Diagnostic NMR Peaks of Oxycarbanilinio Derivatives[a] of General Formula **I:**

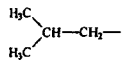
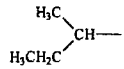
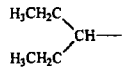
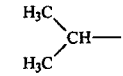
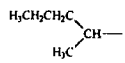
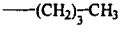
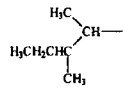


N	Ar	^{1}H-NMR ($CDCl_3$, TMS)		
		$\delta_{CH\text{-}P}$ (ppm) ($^2J_{PH}$, Hz)	$\delta_{CH_2\text{-}O\text{-}CO}$	$\delta_{NH\text{-}CO}$
Ia		6.30 (m)	5.07	6.20
Ib		5.80 (m)	5.12	5.90
Ic		5.49 (19.5)	5.12	6.11
Id		5.72 (23.2)	5.12	9.05
Ie		5.85 (23.0)	5.12	6.12
If		5.72 (m)	5.15	5.75
Ig		5.80 (m)	5.14	6.61
Ih		5.91 (22.5)	5.12	5.62
Ii		5.63 (21.0)	5.11	6.83
Ik		6.31 (22.5)	5.08	6.53

[a] Full characterization of all compounds is reported in the experimental section.

TABLE II Diagnostic NMR Peaks of Oxycarbanilinio Derivatives[a] of General Formula **II:**



N.	R	^{1}H-NMR ($CDCl_3$, TMS)			^{31}P-NMR
		$\delta_{CH\text{-}P}$ (ppm) ($^2J_{PH}$, Hz)	$\delta_{CH_2\text{-}O\text{-}CO}$	$\delta_{NH\text{-}CO}$	δP
IIa		4.52(19.6)	5.12	5.27	
IIb		4.52(m)	5.13	5.10	
IIc		4.58(20.2)	5.12	5.24	18.77(60.2%) 18.08(37.8%)
IId		4.67(20.3)	5.10	5.22	
IIe		4.41(19.5)	5.12	5.27	
IIf		4.55(20.1)	5.12	5.22	18.71(86.5%) 18.31(13.5%)
IIg		4.47(m)	5.13	5.18	
IIh		4.65(m)	5.12	5.20	

[a] Full characterization of all compounds is reported in the experimental section.

with a Bruker AM 200 MHz spectrometer with a resolution >0.003 ppm using 85% H_3PO_4 as external reference.

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

*General Procedure for Preparation of Diphenyl α-(benzyloxycarbonylamino)-Alkyl- or Aralkyl-phosphonates (**I** and **II**).* To a stirred solution of the aldehyde precursor (0.11 mol) and triphenyl phosphite (0.10 mol) in glacial acidic acid (50 ml) was added over a period of 30 minutes solid benzyl carbamate (0.10 mol) in small portions. After the addition was completed, the reaction mixture was warmed to 80 °C and stirred for one hour. The solvent was then evaporated in vacuo, the oilly residue was diluted with methanol (50 ml) and the solution left at – 24°C for 24 hrs. The white solid obtained was filtered and purified by crystallization from methanol.

Spectroscopic Characteristics of Compounds Listed in Table I

Ia ^{1}H-NMR ($CDCl_3$ TMS): 7.47 (m, 1H ArH,) 7.31–7.06 (m, 15H, ArH), 6.87 (m, 2H, ArH), 6.30 (m, 1H, CHP), 6.20 (m, 1H, NH), 5.07 (q, 2H, $ArCH_2$); 83 % yield, m.p. 122–123 °C. **Ib** ^{1}H-NMR ($CDCl_3$ TMS): 7.33–6.93 (m, 18H, ArH), 5.90 (m, 1H, NH), 5.80 (m, 1H, CHP), 5.12 (q, 2H, $ArCH_2$); 56 % yield, m.p. 107–109 °C. **Ic** ^{1}H-NMR ($CDCl_3$ TMS): 7.31–7.05 (m, 15H, ArH), 6.82 (d, $^3J_{HH}$ = 7.4 Hz, 2H, ArH), 6.55 (d, $^3J_{HH}$ = 7.4Hz, 2H, ArH), 6.11 (m, 1H, NH), 5.49 (q, $^2J_{PH}$= 19.5 Hz, 1H, CHP), 5.12 (q, 2H, $ArCH_2$); 39 % yield, m.p. 109–111 °C. **Id** ^{1}H-NMR (DMSO-d_6TMS): 9.05 (d, $^3J_{HH}$ = 10 Hz, 1H, NH), 7.96 (d, $^3J_{HH}$ = 8 Hz, 2H, ArH), 7.85 (dd, $^3J_{HH}$ = 8 Hz, 2H, ArH), 7.36–6.98 (m, 15H, ArH), 5.72 (q, $^2J_{PH}$ = 23.1 Hz, 1H, CHP), 5.12 (q, 2H, $ArCH_2$); 77 % yield, m.p. > 220°C. **Ie** ^{1}H-NMR ($CDCl_3$ TMS): 7.34–7.07 (m, 16H, ArH), 6.79 (m, 3H, ArH), 6.12 (d, $^3J_{HH}$ = 9.5 Hz, 1H, NH), 5.85 (q, $^2J_{PH}$ = 23 Hz, $^3J_{HH}$ = 10 Hz, 1H, CHP), 5.12 (q, 2H, $ArCH_2$), 4.49 (q, 2H, $ArOCH_2$); 86 % yield, m.p. 148–149 °C. **If** ^{1}H-NMR ($CDCl_3$ TMS): 7.34–7.02 (m, 15H, ArH), 6.45 (m, 1H, ArH), 6.36 (m, 1H, ArH), 5.75 (m, 1H, NH), 5.72 (m, 1H, CHP), 5.15 (q, 2H, $ArCH_2$), 4.95 (q, 2H, $ArCH_2$), 2.03 (s, 3H, CH_3); 35 % yield, m.p. 83–85 °C. **Ig** ^{1}H-NMR ($CDCl_3$TMS): 7.7 (d, $^3J_{HH}$= 7.5 Hz 1H, ArH), 7.41 (dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.5 Hz, 1H, ArH), 7.34–7.02 (m, 19H, ArH), 6.61 (br S, 1H, NH), 5.80 (m, 1H, CHP), 5.14 (q, 2H, $ArCH_2$); 38 % yield, m.p. 138–140 °C. **Ih** ^{1}H-NMR ($CDCl_3$

TMS): 8.43 (d, $^3J_{HH}$ = 8 Hz, 1H, ArH), 7.75 (d, $^3J_{HH}$ = 7.5 Hz, 1H, ArH), 7.63 (m, 1H, ArH), 7.40 (t, $^3J_{HH}$ = 7.5 Hz, 1H, ArH), 7.32–6.91 (m, 17H, ArH), 5.91 (q, $^2J_{PH}$ = 22.5 Hz, 1H, CHP), 5.62 (d, $^3J_{HH}$ = 10 Hz, 1H, NH), 5.12 (q, 2H, $ArCH_2$) 2.46 (s, 3H, CH_3); 37 % yield, m.p. 187–188 °C. **Ii** ^{1}H-NMR ($CDCl_3$ TMS): 8.08 (d, $^4J_{HH}$ = 3 Hz, 1H, ArH), 7.98 (s, 1H, ArH), 7.47 (d, $^3J_{HH}$ = 8.5 Hz, 1H, ArH), 7.47–7.11 (m, 16H, ArH), 6.83 (d, $^3J_{HH}$ = 9 Hz, 1H, NH), 5.63 (q, $^2J_{PH}$ = 21 Hz, $^3J_{HH}$ = 9 Hz, 1H, CHP), 5.11 (q, 2H, $ArCH_2$) 2.44 (s, 3H, $ArCH_3$); 93 % yield, m.p. 176–178 °C. **Ik** ^{1}H-NMR ($CDCl_3$ TMS): 8.41 (s, 1H, ArH), 7.97 (d, $^3J_{HH}$ = 8 Hz, 1H, ArH), 7.7 (t, $^3J_{HH}$ = 8 Hz, 1H, ArH), 7.57 (d, $^3J_{HH}$ = 8 Hz, 1H, ArH), 7.43 (t, $^3J_{HH}$ = 8 Hz, 1H, ArH), 7.30–6.92 (m, 15H, ArH), 6.53 (br s, 1H, NH), 6.31 (q, $^2J_{PH}$ = 22.5 Hz, 1H, CHP), 5.08 (q, 2H, $ArCH_2$); 34 % yield, m.p. 147–149 °C.

Spectroscopic Characteristics of Compounds Listed in Table II

IIa ^{1}H-NMR ($CDCl_3$ TMS): 7.34–7.07 (m, 15H, ArH), 5.27 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 5.12 (q, 2H, $ArCH_2$) 4.42 (dq, $^2J_{PH}$ = 19.6 Hz, 1H, CHP), 2.02 (m, 1H, Cyclohexyl), 1.70 (m, 5H, Cyclohexyl), 1.20 (m, 5H, Cyclohexyl); 91 % yield, m.p. 117–119 °C. **IIb** ^{1}H-NMR ($CDCl_3$ TMS): 7.33–7.06 (m, 15H, ArH), 5.13 (q, 2H, $ArCH_2$), 5.10 (d, $^3J_{HH}$ = 10 Hz, 1H, NH), 4.52 (m, 1H, CHP), 1.76 (m, 3H, $C\underline{H}_2C\underline{H}(CH_3)_2$), 0.97 (d, J_{HH} = 5.8 Hz, 6H, CH_3); 80 % yield, m.p. 124–126 °C. **IIc** ^{1}H-NMR ($CDCl_3$ TMS): 7.34–7.06 (m, 15H, ArH), 5.24 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 5.12 (q, 2H, $ArCH_2$), 4.58 (dq, $^2J_{PH}$ = 20.2 Hz, 1H, CHP), 2.15 (m, 1H, $C\underline{H}CH_3$), 1.42 (m, 2H, $C\underline{H}_2CH_3$), 1.10 (d, J_{HH} = 6.9 Hz, 3H, $CHC\underline{H}_3$), 0.97 (t, J_{HH} = 7.4 Hz, 3H, $CH_2C\underline{H}_3$). ^{31}P-NMR ($CDCl_3$, H_3PO_4 85%): 18.77 (60.2 %), 18.08 (37.8 %); 52 % yield, m.p. 109–111 °C. **IId** ^{1}H-NMR ($CDCl_3$TMS): 7.34–7.05 (m, 15H, ArH), 5.22 (d, $^3J_{HH}$ = 11.1 Hz, 1H, NH), 5.10 (q, 2H, $ArCH_2$), 4.67 (dq, $^2J_{PH}$ = 20.3 Hz, 1H, CHP), 1.86 and 1.31 (m, 4H, $C\underline{H}_2CH_3$), 1.56 (m, 1H, $C\underline{H}CH_2$), 0.99 (t, J_{HH} = 7.4 Hz, 3H, CH_3), 0.94 (t, J_{HH} = 7.4 Hz, 3H, CH_3); 30 % yield, m.p. 108–111 °C. **IIe** ^{1}H-NMR ($CDCl_3$TMS): 7.35–7.07 (m, 15H, ArH), 5.27 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 5.12 (q, 2H, $ArCH_2$), 4.41 (dq, $^2J_{PH}$ = 19.5 Hz, 1H, CHP), 2.41 (m, 1H, $C\underline{H}CH_3$), 1.1 (d, J_{HH} = 6.8 Hz, 6H, $CHC\underline{H}_3$). ^{31}P-NMR ($CDCl_3$, H_3PO_4 85%): 18.71 (86.5 %), 18.31 (13.5 %); 53 % yield, m.p. 106–108 °C. **IIf** ^{1}H-NMR ($CDCl_3$TMS): 7.35–7.06 (m, 15H, ArH), 5.22 (d, $^3J_{HH}$ = 9 Hz, 1H, NH), 5.12 (q, 2H, $ArCH_2$),

4.55 (dq, $^2J_{PH}$= 20.1 Hz, 1H, CHP), 2.24 (m, 1H, C<u>H</u>CH$_3$), 1.37 (m, 4H, CH_2), 1.1 (d, J_{HH} = 6.9 Hz, 3H, CHC<u>H</u>$_3$), 0.89 (t, J_{HH} = 6.9 Hz, 3H, $CH_2C\underline{H}_3$); 77 % yield, m.p. 98–101. **IIg** ^{1}H-NMR ($CDCl_3$TMS): 7.34–7.07 (m, 15H, ArH), 5.18 (m, 1H, NH), 5.13 (q, 2H, $ArCH_2$), 4.47 (q, $^2J_{PH}$ = 17.1 Hz, 1H, CHP), 1.72 (m, 2H, CH_2), 1.40 (m, 4H, CH_2), 0.87 (t, J_{HH} = 6.9 Hz, 3H, CH_3); 57 % yield, m.p. 95–97 °C. **IIh** ^{1}H-NMR ($CDCl_3$ TMS): 7.33–7.05 (m, 15H, ArH), 5.20 (m, 1H, NH), 5.12 (m, 2H, $ArCH_2$), 4.65 (m, 1H, CHP), 2.16 (m, 1H, CH), 1.49 (m, 1H, CH), 1.27 (m, 2H, CH_2), 1.11 (m, 3H, CH_3), 0.96 (m, 6H, CH_3). ^{31}P-NMR ($CDCl_3$, H_3PO_4 85%): 19.22 (24.7 %), 19.19 (43.6 %), 19.09 (31.7 %); 33 % yield, m.p. 111–113 °C.

Acknowledgements

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