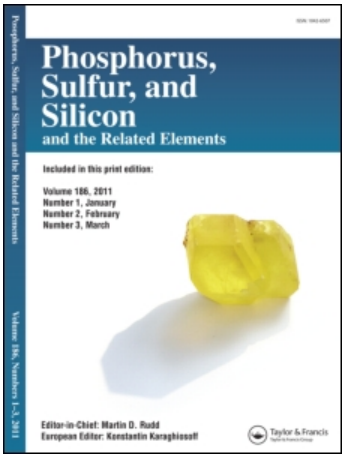

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G. A. Consiglio[a]; S. Failla[b]; P. Finocchiaro[a]; L. Siracusa[a]
[a] Istituto Chimico Facolta 7apos;di Ingegneria, Universita' di Catania, Catania, IT [b] Dipartimento di Ingegneria Chimica, dei Materiali delle Materie Prime e Metallurgiche, Università di Roma "La Sapienza", Rome, Italy

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ARYLIDENE BIS-(N-DIETHYL PHOSPHONOACETAMIDES). SYNTHESIS AND NMR CHARACTERIZATION

G.A. CONSIGLIO[a], S. FAILLA[b], P. FINOCCHIARO[a*] and L. SIRACUSA[a]

[a]Istituto Chimico Facolta' di Ingegneria, Universita' di Catania, V. le A. Doria, 6 – 95125 Catania (IT) and [b]Dipartimento di Ingegneria Chimica, dei Materiali delle Materie Prime e Metallurgiche – Università di Roma "La Sapienza" – Via del Castro Laurenziano, 7 – 00161 Rome, Italy

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Arylidene bis-(N-diethylphosphonoacetamides) have been prepered in good yield. All compounds are white crystalline powders soluble in low boiling point organic solvents. Characterization by ^{1}H-NMR technique indicates that the methyne proton appears in the aromatic region of the spectrum and the two methylene diastereotopic protons (CH_2P) give rise to a complex ABX system due to the coupling with the phosphorus atom, thus this pattern is very diagnostic for this tipe of compounds. The heteronuclear coupling was also investigated by $^{1}H\{^{31}P\}$-NMR spectroscopy.

Keywords: Organic diphosphonates; NMR and FAB-MS characterization; Arbuzov reactions

INTRODUCTION

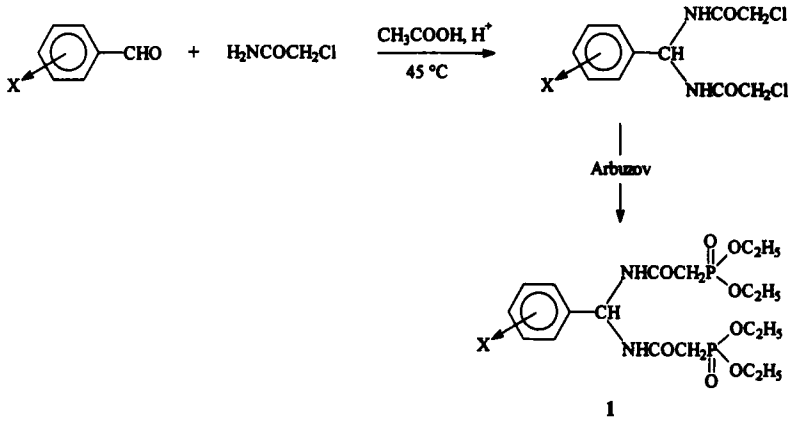
Alkyliden- and arylidene- bis-chloroacetamides which can be easily prepared by reacting aldehydes with two equivalents of chloro acetamides of fatty or aromatic acids were found to act as antihelmints and many different molecules of this class of compounds were tested for bactericides.[1] Furthermore, some aromatic chloroacetamides are also used as selective pre-emergent herbicides widely used in many agricaltural productions.[2,3] Thus, considering both the clinical and agricultural interests of such compounds and having in mind the information that the replacemet of the chlo-

* Corresponding Author: E-mail: pfinocchiaro@ic.ing.unict.it

roacetyl moiety by a phosphonoacetyl group could in many cases influence and increase the activity of some of these compounds, we decided to synthesized by the Arbuzov reaction using trialkyl phosphite[4,5] a variety of bis-N-(phosphonoacetyl) acids starting from arylidene-bis-chloroacetamides.

RESULTS AND DISCUSSION

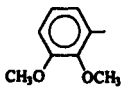
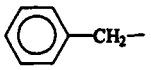
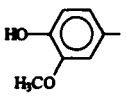
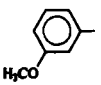
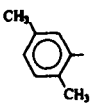
Bis-amides are very well known crystalline compounds easily obtainable from aldehydes or acetals and two equivalents of primary amides or halomethylamides and thus our precursors were prepared in good yield according to literature methods.[1,6–12] By refluxing the aryliden-bis-chloroacetamides with triethyl phosphite the desired bis-phosphonates were obtained in moderate yields (Scheme 1).



SCHEME 1

The structure of all synthesized compounds were supported by their proton and phosphorus magnetic resonance spectra, as well as by their FAB-MS spectra. In Table I are reported the salient physical data of the synthesized compounds.

TABLE I Diagnostic NMR Signals of bis-(N-Phosphono acethyl acids)[a] of General Formula 1: $ArCH[NHCOCH_2P(O)(OC_2H_5)_2]$

N.	Ar	^1H-NMR ($CDCl_3$, TMS)		
		δ_{CH_2-P} (ppm) ($^2J_{PH}$, Hz)	δ_{CH}	δ_{NH}
1a		2.88 (21)	6.67	7.95(d)
1b		2.82 (21)	[b]	7.72
1c		2.79 (20 5)	5.65	7.46(brs)
1d		2.89 (21)	[b]	8.15
1e		2.97 (20.5)	6.61	7.10(d)
1f		2.88 (21)	6.64	7.82(d)
1g		2.85 (21)	6.81	7.42(d)
1h		2.87 (20.8)	6.62	7.81(d)

[a]Full characterization of all compounds is reported in the experimental section.
[b]Masked by ArH resonances.

In the proton NMR spectra all signals are in the expected range of chemical shifts and the substitution pattern in the aromatic ring does not greatly affect their values. The methyne proton appears in the aromatic region of

the spectrum at *ca.* δ 6.6 ppm and resonate as a triplet or broad singlet due to the coupling with the adjacent NH protons, which in turn are at very low field (δ *ca.* 8.0 ppm) and possess the expected multiplicity (doublet or broad singlet).

Interestingly enough, the methylene groups attached to the phosphorus atom appear as a complex multiplet: this pattern is due to the proton-phosphorus coupling of each of the two diastereotopic methylene protons which in turn are coupled together. This pattern thus is very diagnostic for the type of compounds here described in which the system CH_2P is not a doublet due to the phosphorus coupling, but is a more complex ABX system where A and B are the two methylene diastereotopic protons and × is the phosphorus atom coupled with them. When the difference in chemical shifts between the two protons A and B is high enough two different quartetts (eight lines) are clearly in evidence in the proton spectrum of our bis-phosphonates. By the same token, the ethoxy groups attached to the phosphorus atoms reside in diastereotopic enviroment[13]and thus they give rise to two distinct triplets in the methyl region of the spectrum and two distinct quartetts for the methylene protons (Figure 1).

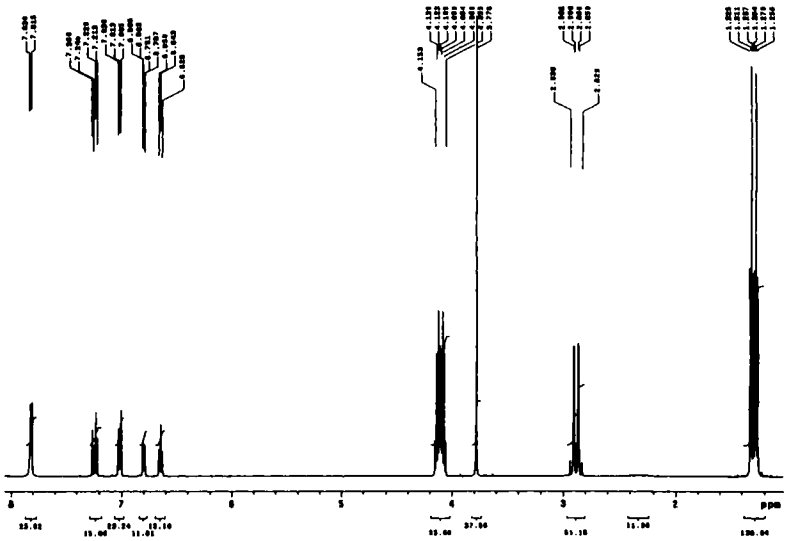
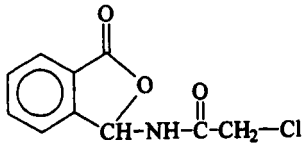
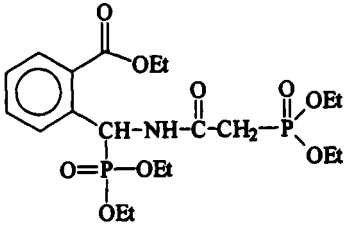


FIGURE 1 ^{1}H-NMR spectrum of compound **1f** in $CDCl_3$

Interestingly enough, by reacting o-carboxyaldehyde with chloroacetamide in a molar ratio of 1:2 the condensation product yields the mono-adduct **2**, instead of the aryliden-bis-chloroacetamide derivative expected. This reaction is not unusual as we pointed out in a previous paper.[14] By refluxing **2** with excess of triethyl phosphite, compoud **3** was separated in good yields.



2



3

Molecule **3** possesses one stereocenter and thus all the ethoxy groups attached at phosphorus reside in diastereotopic positions; therefore in the methyl region of the ^{1}H-NMR spectrum four distinct triplets are expected plus the one belonging to the ethyl carboxylate group (see Figure 2a).

The methylene protons attached to the amide moiety are also diastereotopic giving rise to a doublet of doublet which is additionally splitted giving eight lines due to the coupling with the adjacent phosphorus atom ($^2J_{PH}$ = 21 Hz, $^2J_{HH}$ = 15 Hz); the methyne group due to the coupling with phosphorus and the NH group appears as a doublet of doublet ($^2J_{PH}$ = 23 Hz, $^3J_{HH}$ = 9.5 Hz), (Figure 2a). Futhermore, the heteronuclear coupling was investigated by ^{1}H{^{31}P}-NMR spectroscopy, which simplifies the pattern of the neighbouring hydrogens to the phosphorus atoms and clearly demostrates the assignement of the signals (Figure 2b). All other ^{1}H-NMR signals are in the range of chemical shifts expected for the formula assigned to **3**.

The ^{31}P{^{1}H}-NMR spectrum of **3** shows two singlets of equal intensity at δ = 21.708 and 22.405 ppm, indicating the presence, as expected, of two phosphonic moieties residing in diastereotopic positions.

In summary, the easy reaction above described allows to obtained in good yields molecule **3**, which possessing two different phosphonic moie-

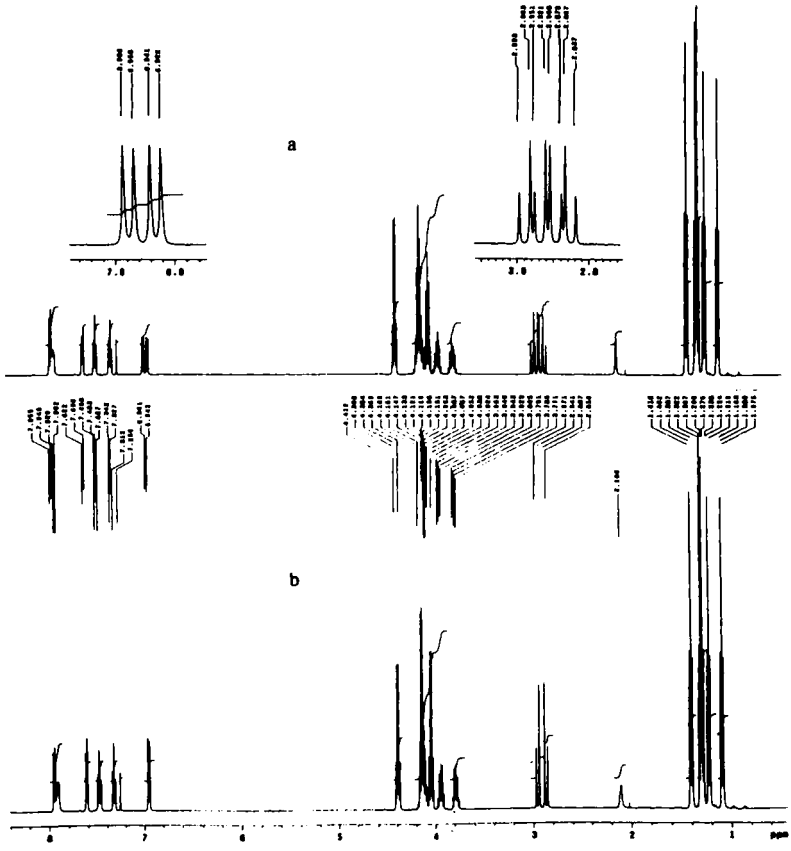


FIGURE 2 a) ^{1}H-NMR spectrum of compound **3** in $CDCl_3$; b) $^{1}H\{^{31}P\}$-NMR spectrum of compound **3** in $CDCl_3$

ties in strategic positions plus a carboxylic group, can act as a selective complexing agent for some molecules of biological interests.

EXPERIMENTAL

Aldehydes, 2-chloroacetamide, triethyl phosphite as well as other 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 $CDCl_3$ with Me_4Si as an internal standard using a Varian Inova instruments operating at 200 or 500 MHz. Phosphorus NMR-spectra were recorded in $CHCl_3$ with a Varian Inova 500 MHz operating at 200 MHz, using 85% H_3PO_4as 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.

General Procedure for Preparation of Aryliden-bis-acetamide-phosphonic-acid diethyl esters

In a two-necked flask, equipped with a magnetic stirrer and a condenser with a nitrogen inlet, was placed 0.05 mol of an aryliden-bis-chloroacetamide compound, which were synthesised as reported in literature, and a certain amount (generally 20–30 ml) of freshly distilled $P(OC_2H_5)_3$. Then, the reaction mixture was heated at refluxing temperature for three hours. The solvent was removed under vacuum distillation and to the oily residue was added diethyl ether and the solution was maintained at – 20°C until a solid was formed. The crude product was then recrystallized from the appropriate solvent (generally a mixture of ethyl acetate/cyclohexane).

Spectroscopic Characterization of the Compounds Listed in Tables I

Ia m.p. = 68–69°C; ^{1}H-NMR (δ, $CDCl_3$, TMS): 7.95 (d, J_{HH} = 7.5 Hz, 2H, NH), 7.24–7.45 (m, 5H, ArH), 6.67 (t, J_{HH} = 7.5 Hz, 1H, CH), 4.09 (m, 8H, $\underline{CH_2}CH_3$), 2.88 (ABX, J_{HP} = 21 Hz, J_{HH} = 15 Hz, 4H, CH_2P), 1.26 (t, J_{HH} = 7Hz, 12H, $CH_2\underline{CH_3}$).

Ib m.p = .81–83°C; ^{1}H-NMR (δ, $CDCl_3$, TMS): 7.73 (d, J_{HH} = 7.5 Hz, 2H, NH); 7.06–6.84 (m, 4H, ArH + CH); 4.87 (m, 11H, $\underline{CH_2}CH_3$ + OCH_3); 3.86 (s, 3H, OCH_3); 2.82 (ABX, J_{HP}= 21 Hz, J_{HH} = 15 Hz, 4H, CH_2P); 1.26 (t, J_{HH} = 7Hz, 12H, $CH_2\underline{CH_3}$).

Ic m.p. = 85–87°C; ^{1}H-NMR (δ, $CDCl_3$, TMS): 7.46 (brs, 2H, NH); 7.28 (m, 5H, ArH); 5.66 (m, 1H, CH); 4.06 (m, 8H, $\underline{CH_2}CH_3$); 3.157 (d, J = 7 Hz, 2H, $ArCH_2$); 2.80 (ABX, J_{HP} = 20.5 Hz, 4H, CH_2P); 1.29 (m, 12H, $CH_2\underline{CH_3}$).

^{31}P-NMR (δ, $CDCl_3$, 85% H_3PO_4): 22.513 ppm

Id m.p. = 32–33°C; ^{1}H-NMR (δ, $CDCl_3$, TMS): 8.15 (d, J_{HH} = 8 Hz, 2H, NH); 6.83–7.26 (m, 4H, ArH); 4.11 (m, 8H, $\underline{CH_2}CH_3$); 2.89 (d, J_{HP} = 21 Hz, 4H, CH_2P); 1.29 (m, 12 H, $CH_2\underline{CH_3}$).

Ie m.p. = 118–120°C; ^{1}H-NMR (δ, $CDCl_3$, TMS): 7.10 (d, J_{HH} = 7.5 Hz, 2H, NH); 6.8–6.9 (m, 3H, ArH); 6.62 (t, J_{HH} = 7.5 Hz, 1H, CH); 4.09 (m, 8H, $\underline{CH_2}CH_3$); 3.88 (s, 3H, OCH_3); 2.97 (ABX, J_{HP} = 20.5 Hz, J_{HH} = 15 Hz, 4H, CH_2P); 1.28 (t, J = 7 Hz, 12H, $CH_2\underline{CH_3}$).

If m.p. = 75–76°C; ^{1}H-NMR (δ, $CDCl_3$, TMS): 7.822 (d, J_{HH} = 7.5 Hz, 2H, NH); 7.26–6.78 (m, 4H, ArH); 6.64 (t, J = 7.5 Hz, 1H, CH); 4.12 (m, 8H, $\underline{CH_2}CH_3$); 4.05 (s, 3H, OCH_3); 2.88 (ABX, J_{HP} = 21 Hz, J_{HH} = 15 Hz, 4H, CH_2P); 1.29 (t, J = 7 Hz, 12H, $CH_2\underline{CH_3}$).

Ig m.p. = 43–45°C, ^{1}H-NMR (δ, $CDCl_3$, TMS): 7.42 (d, J_{HH} = 7.5 Hz, 2H, NH); 7.22 (m, 1H, ArH); 7.0 (m, 2H, ArH); 6.81 (t, J = 7.5 Hz, 1H, CH); 4.08 (m, 8H, $\underline{CH_2}CH_3$); 2.85 (ABX, J_{HP} = 21 Hz, J_{HH} = 15 Hz, 4H, CH_2P); 2.35 (s, 3H, $ArCH_3$); 2.29 (s, 3H, $ArCH_3$); 1.27 (t, J_{HH} = 7.5 Hz, 12H, $CH_2\underline{CH_3}$).

Ih m.p. = 89–90°C; ^{1}H-NMR (δ, $CDCl_3$, TMS): 7.81 (d, J_{HH} = 7.4 Hz, 2H, NH); 7.05–7.26 (m, 4H, ArH); 6.62 (t, 1H, CH); 4.11 (m, 8H, $\underline{CH_2}CH_3$); 2.88 (d, J_{HP} = 20.8 Hz, 4H, CH_2P); 2.30 (s, 3H, $ArCH_3$); 1.28 (m, 12H, $CH_2\underline{CH_3}$).

Compound **2**: m.p. = 158–160°C; yield 38 %; ^{1}H-NMR (δ, $CDCl_3$, TMS): 7.94 (d, J_{HH} = 7.5 Hz, 1H, ArH); 7.76 (t, J_{HH}= 7.5 Hz, 1H, ArH); 7.66 (t, J_{HH} = 7.5 Hz, 1H, ArH); 7.57 (d, J_{HH} = 7.5 Hz, 1H, ArH); 7.22 (d, J_{HH} = 9.5 Hz, 1H, NH); 7.15 (d, J_{HH} = 9.5 Hz, 1H, CH); 4.18 (s, 2H, CH_2Cl). FAB-MS: m/z = 226 (base peak) $[M+H]^+$, m/z = 228 (35%) $[M+H+2]^+$.

Compound **3**: m.p. = 80–82°C; yield 65%; ^{1}H-NMR (δ, $CDCl_3$, TMS): 7.94 (d, J_{HH} = 7.5 Hz, 1H, ArH); 7.91 (dd, J_{HH} = 9.5 Hz, J_{HP} = 5.5 Hz, 1H, NH); 7.61 (d, J_{HH} = 7.5 Hz, 1H, ArH); 7.48 (t, J_{HH} = 7.5 Hz, 1H, ArH); 7.33 (t, J_{HH} = 7.5 Hz, 1H, ArH); 6.95 (dd, J_{HH} = 9.5 Hz, J_{HP} = 23 Hz, 1H, CHP); 4.39 (q, J_{HH} = 7 Hz, 2H, $O\underline{CH_2}CH_3$); 4.13 (m, 4H, $O\underline{CH_2}CH_3$); 3.94–3.78 (m, 4H, $O\underline{CH_2}CH_3$) 2.91 (ABX, J_{HH} = 15 Hz, J_{HP} = 21 Hz, 2H, CH_2P); 1.40 (t, J_{HH} = 7 Hz, 3H, $OCH_2\underline{CH_3}$); 1.30 (t, J_{HH} = 7 Hz, 3H, $OCH_2\underline{CH_3}$); 1.29 (t, J_{HH} = 7 Hz, 3H, $OCH_2\underline{CH_3}$); 1.22 (t, J_{HH} = 7 Hz, 3H, $OCH_2\underline{CH_3}$); 1.09 (t, J_{HH} = 7 Hz, 3H, $OCH_2\underline{CH_3}$). ^{31}P-NMR (δ, $CDCl_3$): 22.40 and 21.71 ppm. FAB-MS: m/z = 494 (base peak) $[M+H]^+$, m/z = 516 (32%) $[M + Na]^+$.

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