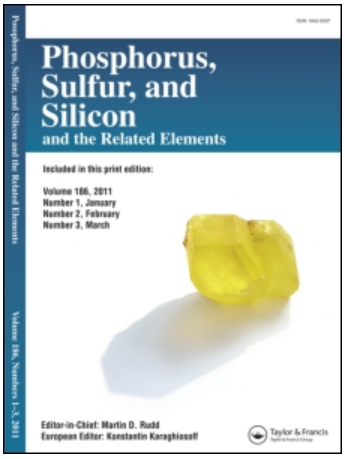

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OXYCARBANILINIO DERIVATIVES OF ARALKYLOXY-1-METHYLARYLPHOSPHONATES. SYNTHESIS AND CHARACTERIZATION

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OXYCARBANILINIO DERIVATIVES OF ARALKYLOXY-1-METHYLARYLPHOSPHONATES. SYNTHESIS AND CHARACTERIZATION

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The synthesis and the ^{1}H-NMR characterization of the title compounds is here described. These derivatives were prepared starting from salicylaldehyde which was alkylated at the phenolic hydroxyl group by the Williamson procedure and then converted into the corresponding α-hydroxy phosphoryl compound by triethyl phosphite in dry dioxane under a gaseous stream of HCl. The α-hydroxy phosphonic acid diethyl esters were then caused to react in dry CH_3CN at 50°C for a couple of days in order to yield the desired urethane, possessing a phosphonic group. The interest of the synthesized compounds lies in their potential biological and insecticide properties and as model compounds of phosphorus containing polyurethanes.

Keywords: Urethanes with phosphonic groups; ^{1}H-NMR characterization; α-hydroxy phosphonate intermediates

INTRODUCTION

Recently we reported on a new synthetic approach to α-hydroxy phosphoryl compounds[1] and on the characterization of alkyl ureas bearing the phosphonate group[2].

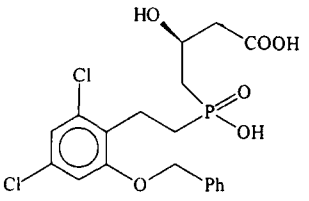
The first class of compounds comprises molecules which are useful intermediates in the synthesis of other α- and γ- substituted phosphonates and phosphonic acids[3,4] and which present significant biological activity[5,6] inhibiting enzymes such renin[7], EPSP synthase[8] and HIV protease[9].

The second class of substances, obtained by addition of isocyanates to 1-amino-1-aryl methyl phosphonates, represent model compounds for structur-

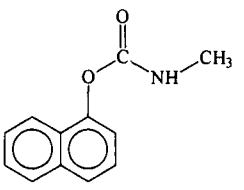
*Corresponding author.

ally defined polycondensates (polyureas) bearing the phosphonate moiety and could also serve in agrochemistry due to the presence of two active principles.

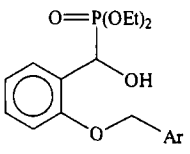
Considering that molecule **I** represents one inhibitor's example of 3-hydroxy-3-methylglutaryl coenzyme A-reductase (HMGR)[10], and, on a different field, compound **II** is one of the simplest and cheap insecticide, we decided to synthesize α-hydroxy phosphoryl compounds of general formula **III** and then, characterize the oxycarbanilinio derivatives **IV** in order to test their biological activity.



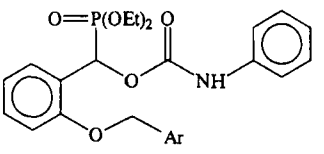
I



II



III



IV

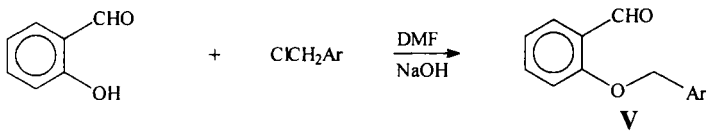
Furthermore, the synthesis and characterization of type **IV** molecules can be of utility in studies connected with the preparation of phosphorus containing polyurethanes[11] of which **IV** represent suitable model compounds.

RESULTS AND DISCUSSION

α-Hydroxy phosphonic acid diethyl esters were easily prepared starting from salicylaldehyde according to the reaction Scheme I.

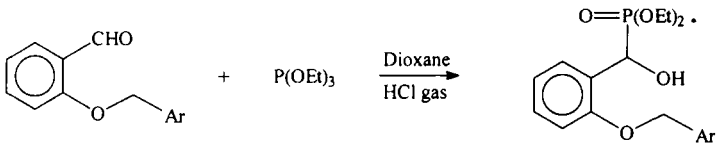
Reaction (**1**) was found to proceed in a very satisfactory way at 80°C for 30 ÷ 45 min and, generally, the aralkyloxy aldehyde **III** crystallized out in high yield (≥90%) from the reaction mixture on cooling.

The procedure described by reaction (**2**) was already reported by us[1] and also in this case yields and product's purity were excellent. Table I lists some physical properties together with the most diagnostic ^{1}H-NMR signals.



(1)

V

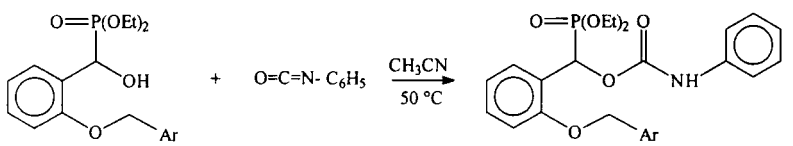


(2)

III

SCHEME 1

Once the α-hydroxy phosphonates **III** of our interest were in our hands they have been caused to react in anhydrous acetonitrile at 50°C for 3 or 4 days with a slight excess of phenyl isocyanate in order to obtain oxycarbanilino derivatives of general formulas **IV**, according to reaction (**3**). The use of a catalytic amount



(3)

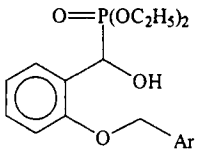
III IV

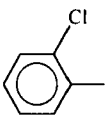
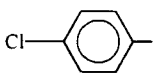
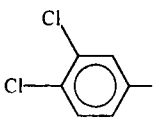
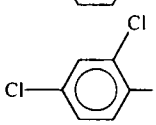
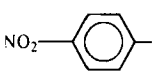
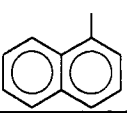
of tin octanoate helped very much for increasing the yields and for reducing the formation of N-phenyl isocyanurates.

The physical characteristics of the synthesized urethanes, together with the most diagnostic ^{1}H-NMR signals are listed in Table II. All products are white crystalline solids with high melting points and the main NMR features are the following:

i) The P(O)$(OEt)_2$ group still gives rise to two triplets at ca. 1.1 ÷ 1.3 ppm for the methyl signals, as in the precursor α-hydroxy phosphonates;
ii) The CH-P signal, appearing as a doublet, is very much downfield shifted by ca. 1.3 ppm when compared with the parent derivatives and thus this signal and its chemical shift is very diagnostic for assignment of the urethane structure;
iii) The ureidic NH proton is resonating at ca. 6.90 ÷ 7.10 ppm as expected for such a functional group and it is buried under the aromatic signals;

TABLE I Preparation of α-Hydroxy Phosphonates of General Formula **III**:



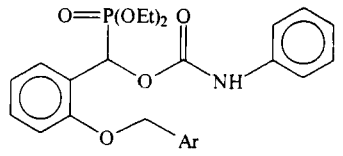
N.	Ar	Yield %	m.p. (°C)	^{1}H-NMR δ ($CDCl_3$, TMS)			
				δ_{PCH}[a] ($^2J_{PH}$, Hz)	δ_{CH_2}-Ar[b]	$\delta_{P(OCH_2CH_3)_2}$ $_{P(OCH_2CH_3)}$[c]	$\delta_{P(OCH_2CH_3)_2}$[d] $_{P(OCH_2CH_3)}$
IIIa		97	107–108	5.57(12.4)	5.21	4.12–3.95	1.24, 1.17
IIIb		80	100–101	5.50(12.0)	5.06	4.10–3.89	1.23, 1.15
IIIc		93	86–88	5.51(12.0)	5.05	4.13–3.94	1.26, 1.16
IIId		80	110–111	5.55(11.8)	5.17	4.12–4.03	1.25, 1.17
IIIe		96	120–122	5.55(12.0)	5.22	4.13–3.94	1.29, 1.19
IIIf		80	100–102	5.45(11.9)	5.54	3.98–3.63	1.125, 1.120

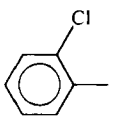
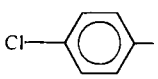
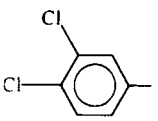
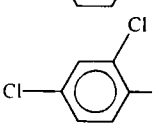
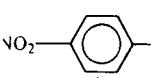
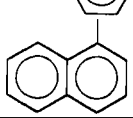
[a]Doublet, the $^2J_{PH}$ values are all negative.
[b]Singlet.
[c]Complex multliplet.
[d]Two methyl triplets ($^2J_{HH}$ = 7 Hz).

iv) The CH_2-Ar signal is not affected by the functionalization reaction performed at the α-hydroxy group, i.e., its chemical shift is almost the same in **III** and **IV**.

The characterization of the samples reported in Table II was also performed by the FAB-MS technique. For all compounds the protonated molecular ion $[M + H]^+$ was observed in high intensity, whereas the $[M + H - (HPO(OEt)_2]^+$ ion is always present and constitutes the base peak in relative intensity. The

TABLE II Preparation of Oxycarbanilinio Derivatives of General Formula **IV**:



N.	Ar	Yield %	m.p. (°C)	^{1}H-NMR δ ($CDCl_3$, TMS)			
				δ_{PCH}[a] ($^2J_{PH}$, Hz)	δ_{CH_2}-Ar[b]	$\delta_{P(OCH_2CH_3)_2}$[c] $_{P(OCH_2CH_3)}$	$\delta_{P(OCH_2CH_3)_2}$[d] $_{P(OCH_2CH_3)}$
IVa		56	141–143	6.84(13.6)	5.27	4.20–3.80	1.30, 1.13
IVb		58	150–152	~6.8[e]	5.13	4.21–3.80	1.30, 1.13
IVc		67	133–134	6.78(13.8)	5.12	4.24–3.80	1.32, 1.15
IVd		87	141–143	6.80(13.7)	5.23	4.23–3.91	1.31, 1.14
IVe		45	182–183	6.78(13.8)	5.28	4.21–3.82	1.31, 1.16
IVf		83	169–171	6.79(13.4)	5.62	4.09–3.75	1.20, 1.05

[a]Doublet, the $^2J_{PH}$ values are all negative.
[b]Singlet.
[c]Complex multiplet.
[d]Two methyl triplets ($^2J_{HH}$ = 7 Hz).
[e]Masked by ArH and NH signals.

region at relatively low masses is characterized by the presence of the ion at m/z 243, which may originate from the base peak by an α-scission of the aralkyloxy moiety.

In conclusion, this work reveals that functionalization of α-hydroxy phosphonates with isocyanates is a feasible reaction which proceeds slowly and in moderate to good yields. The interest of the synthesized compounds lies on their potential biological and insecticidal properties, whereas the reaction itself indi-

cates that polyurethanes and macrocycles containing the pendant phosphoryl moiety can be prepared once bis-α-hydrophosphonates[1] and bis-isocyanates are used.

EXPERIMENTAL

Aldehydes, triethyl phosphite, phenyl isocyanate, as well as other chemicals and 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 TMS as an internal standard using a Bruker AC-200 instrument operating at 200 MHz.

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

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

General Synthetic Approach to 2-Aralkyloxybenzaldehydes (V)

To a stirred solution of salicylaldehyde (0.1 mol) in 100 ml of DMF were added, at room temperature, 4.0 g (0.1 mol) of NaOH dissolved in the minimum amount of water (few ml). The color turned yellowish indicating the formation of the phenoxy salt (in some cases precipitation of the yellow salt was observed). Then the reaction mixture was gently warmed in water bath and a solution of 0.1 mol of the desired substituted benzyl chloride in DMF was added. The reaction mixture was kept at ca. 80°C for 20–30 min and a copious precipitate of NaCl was observed. Then, the reaction was cooled down to room temperature and few ml of water were added. A crystalline product separated on standing which was filtered off, washed with water, dried and then recrystallized from EtOH. ^{1}H-NMR analyses were consistent with the expected formula **V** (see Scheme I) and yields were always greater than 90%.

General Procedure for Preparation of α-Hydroxy Phosphoryl 2-Aralkyloxy Compounds (III)

In a four-necked flask, equipped with a magnetic stirrer, gas inlet, thermometer, a condenser with a nitrogen inlet and a gas trap, 0.02 mol of the aralkyloxyben-

zaldehyde precursor **V** were dissolved in 25 ml of dry 1,4-dioxane and then an equimolar amount of triethyl phosphite was slowly added under nitrogen atmosphere at room temperature. To this stirred solution hydrogen chloride was bubbled for 15 min. and the temperature of the reaction was mantained below 25–30°C by external cooling. The reaction mixture was then stirred at room temperature for an additional hour, the solvent was removed under reduced pressure and the tick oil obtained was diluted with 20 ml of diethyl ether containing few drops of ethyl acetate, in order to allow it to crystallize in a white mass.

General Synthetic Approach to Oxycarbanilinio Derivatives IV

To a solution of the α-hydroxy phosphonate precursor **III** (0.01 mol) and a catalytic amount of tin octanoate in dry CH_3CN (50 ml) were added 0.025 mol of phenyl isocyanate and the solution heated to 50 °C under a dry N_2 atmosphere for three days. Then, the solvent was removed under reduced pressure and the crude white mass was treated with 20 ml of $CHCl_3$, in order to separate the isocyanurate formed in the reaction mixture. The chloroform solution was evaporated and the oxycarbanilinio derivative formed was crystallized from CH_3CN

Spectroscopic Characteristics of Compounds Listed in Table I

IIIa ^{1}H-NMR ($CDCl_3$, TMS): 7.62, 7.27, 7.03, 6.95 (m, 8H, ArH), 5.57 (d, $^2J_{PH}$—12.4 Hz, 1H, CHP), 5.21 (s, 2H, CH_2), 4.12-3.95 (m, 4H, OCH_2), 1.24 and 1.17 (t, 6H, CH_3). **IIIb** ^{1}H-NMR ($CDCl_3$, TMS): 7.59, 7.30, 7.00, 6.88 (m, 8H, ArH), 5.50 (d, $^2J_{PH}$—12.0 Hz, 1H, CHP), 5.06 (s, 2H, CH_2), 4.10-3.89 (m, 4H, OCH_2), 1.23 and 1.15 (t, 6H, CH_3). **IIIc** ^{1}H-NMR ($CDCl_3$, TMS): 7.60, 7.44, 7.02, 6.84 (m, 7H, ArH), 5.51 (d, $^2J_{PH}$—12.0 Hz, 1H, CHP), 5.05 (s, 2H, CH_2), 4.13-3.94 (m, 4H, OCH_2), 1.26 and 1.16 (t, 6H, CH_3). **IIId** ^{1}H-NMR ($CDCl_3$, TMS): 7.61, 7.41, 7.27, 7.03, 6.88 (m, 7H, ArH), 5.55 (d, $^2J_{PH}$—11.8 Hz, 1H, CHP), 5.17 (s, 2H, CH_2), 4.12-4.03 (m, 4H, OCH_2), 1.25 and 1.17 (t, 6H, CH_3). **IIIe** ^{1}H-NMR ($CDCl_3$, TMS): 8.25 (d, 2H, ArH), 7.64 (m, 3H, ArH), 7.24, 7.06, 6.86 (m, 3H, ArH), 5.55 (d, $^2J_{PH}$—12.0 Hz, 1H, CHP), 5.22 (s, 2H, CH_2), 4.13-3.94 (m, 4H, OCH_2), 1.29 and 1.19 (t, 6H, CH_3). **IIIf** ^{1}H-NMR ($CDCl_3$, TMS): 8.01, 7.85, 7.53, 7.25 7.04, (m, 11H, ArH), 5.54 (s, 2H, CH_2), 5.45 (d, $^2J_{PH}$—11.9 Hz, 1H, CHP), 3.98-3.63 (m, 4H, OCH_2), 1.125 and 1.120 (t, 6H, CH_3).

Spectroscopic Characteristics of Compounds Listed in Table II

IVa ^{1}H-NMR ($CDCl_3$, TMS): 7.40, 7.25, 7.04, 6.90 (m, 14H, ArH + NH), 6.84 (d, $^2J_{PH}$—13.6 Hz, 1H, CHP), 5.27 (s, 2H, CH_2), 4.20-3.80 (m, 4H, OCH_2), 1.30 and 1.13 (t, 6H, CH_3). FAB-MS: $[M + H]^+$ m/z = 504, 367 (base peak), 243. **IVb** ^{1}H-NMR ($CDCl_3$, TMS): 7.46, 7.33, 7.03, 6.83 (m, 15H, ArH + NH + CH), 5.13 (s, 2H, CH_2), 4.21-3.80 (m, 4H, OCH_2), 1.30 and 1.13 (t, 6H, CH_3). FAB-MS: $[M + H]^+$ m/z = 504, 367 (base peak), 243. **IVc** ^{1}H-NMR ($CDCl_3$, TMS): 7.68, 7.40, 7.22, 7.00, 6.87 (m, 13H, ArH + NH), 6.78 (d, $^2J_{PH}$—13.8 Hz, 1H, CHP), 5.12 (s, 2H, CH_2), 4.24-3.80 (m, 4H, OCH_2), 1.32 and 1.15 (t, 6H, CH_3). FAB-MS: $[M + H]^+$ m/z = 538, 401 (base peak), 243. **IVd** ^{1}H-NMR ($CDCl_3$, TMS): 7.70, 7.40, 7.26, 7.07, 6.90 (m, 13H, ArH + NH), 6.80 (d, $^2J_{PH}$—13.7 Hz, 1H, CHP), 5.23 (s, 2H, CH_2), 4.23-3.91 (m, 4H, OCH_2), 1.31 and 1.14 (t, 6H, CH_3). FAB-MS: $[M + H]^+$ m/z = 538, 401 (base peak), 243. **IVe** ^{1}H-NMR ($CDCl_3$, TMS): 8.24 (d, 2H, ArH), 7.74, 7.37, 7.25, 7.04, 6.89 (m, 12H, ArH + NH), 6.78 (d, $^2J_{PH}$—13.8 Hz, 1H, CHP), 5.28 (s, 2H, CH_2), 4.21-3.82 (m, 4H, OCH_2), 1.31 and 1.16 (t, 6H, CH_3). FAB-MS: $[M + H]^+$ m/z = 515, 378 (base peak), 243. **IVf** ^{1}H-NMR ($CDCl_3$, TMS): 8.15, 7.88, 7.70, 7.50, 7.30, 7.20, 7.00 (m, 17H, ArH + NH), 6.79 (d, $^2J_{PH}$—13.4 Hz, 1H, CHP), 5.62 (s, 2H, CH_2), 4.09-3.75 (m, 4H, OCH_2), 1.20 and 1.05 (t, 6H, CH_3). FAB-MS: $[M + H]^+$ m/z = 520, 383 (base peak), 243.

Acknowledgements

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