Phosphorus, Sulfur, and Silicon, 1995, Vol. 101, pp. 261–266
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DIMETHYL ESTERS OF 1-AMINO-2-ARYLMETHYL CYCLOHEXYL PHOSPHONIC ACIDS. SYNTHESIS AND NMR CHARACTERIZATION

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(Received November 15, 1994; in final form November 30, 1994)

Dimethyl esters of amino-arylmethyl phosphonic acids containing a cyclohexyl moiety have been prepared in good yields. All compounds are white crystalline powders very soluble in low boiling point organic solvents. Characterization by ^{1}H-NMR techniques indicates that ortho substituents shift downfield the CH resonance, whereas ortho-carboxy groups, through hydrogen bonding with the NH group, yield a cyclic structure responsible of the dramatic downfield shift of the NH resonance.

Key words: ^{1}H-NMR characterization, crystalline, low-melting and very soluble amino-phosphonates, substrates for functionalization at the NH group.

INTRODUCTION

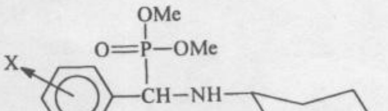
In our continuing efforts aimed at synthetizing new aryl-amino-methyl phosphonates and phosphonic acids mono-alkyl esters[1–6] we were interested in looking at the reactivity and the chemical properties of phosphonates possessing at least one cyclohexyl moiety linked to the —CH— or —NH— fragment. The potential interest of such new series of compounds can be summarized as follow:

i) The cycloalkyl moiety should enhance solubility in low boiling organic solvents.

ii) Reactivity at the —NH— functionality should be increased permitting an easy access to N-substituted amino phosphonates.

iii) Cycloalkyl groups, generally, impart specific agrochemical activities.

In this paper we wish to report on the synthesis and properties, together with their ^{1}H-NMR spectroscopic characterization, of different classes of variously substituted amino-arylmethyl cyclohexyl phosphonate esters of general formulas **1** and **2** given below:



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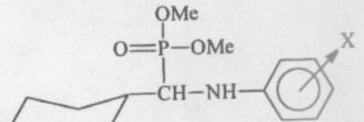

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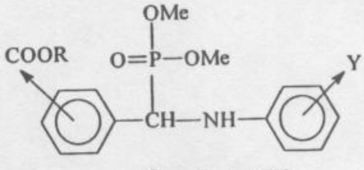
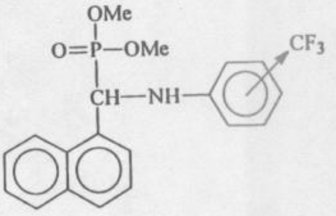
In addition, we shall describe the syntheses of compounds of general formula **3** in which one of the aryl rings is bearing a carboxy or carbomethoxy group in order to impart water solubility and derivatives **4** where the benzene ring is functionalized with a trifluoromethyl group and in addition a naphthyl ring is attached to the carbon-atom bearing the phosphonate group.



3 R = H, CH_3



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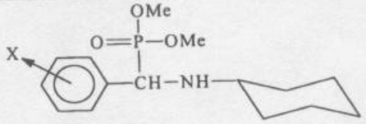
RESULTS AND DISCUSSION

In our approach to the synthesis of phosphonates **1–4** the best and simplest synthetic route was found in the direct addition (generally at room temperatures) of dimethyl phosphite to the corresponding Schiff bases, which are readily available through

TABLE I

Physical properties of **1**



N.	X	Yield %	m.p.°C	^{1}H-NMR δ ($CDCl_3$,TMS) CH [a]	NH [b]	O=P(OMe)$_2$ [c]
1a	4-F	29	46-48	4.22	2.30	3.55, 3.77
1b	4-CF_3	46	87-89	4.31	2.28	3.58, 3.78
1c	2-Cl	28	66-68	4.88	2.26	3.49, 3.86
1d	4-Cl	30	56-59	4.22	2.29	3.56, 3.77
1e	2,3-Cl_2	45	81-82	4.93	2.25	3.52, 3.87
1f	2,4-Cl_2	41	86-87	4.81	2.23	3.55, 3.86
1g	3,4-Cl_2	31	72-73	4.19	2.28	3.62, 3.77
1h†	2-OCH_3	43	79-80	4.85	2.28	3.48, 3.82
1i	3-OCH_3	80	63-66	4.20	2.34	3.52, 3.77
1j	4-OCH_3	82	53-55	4.18	2.32	3.52, 3.77
1k	2,5-$(OCH_3)_2$	91	74-76	4.81	2.30	3.52, 3.81
1l	3,4,5-$(OCH_3)_3$	35	55-58	4.17	2.38	3.57, 3.80

[a] doublet ($J_{HP} = 22 \div 23$ Hz)

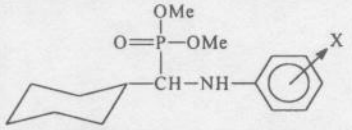
[b] broad singlet

[c] doublets ($J_{HP}=10 \div 12$ Hz)

† Calc. for $C_{16}H_{26}NO_4P$: C 58.76, H 7.95, N 4.28; found C 58.68, H 8.02, N 4.31.

TABLE II

Physical properties of **2**



N.	X	Yield %	m.p.°C	^{1}H-NMR δ ($CDCl_3$,TMS)		
				CH [a]	NH [a]	$O{=}P(OMe)_2$ [b]
2a	2-CF_3	11	59-61	3.75	4.50	3.69, 3.74
2b	3-CF_3	28	116-118	3.71	4.11	3.66, 3.75
2c	2-F	37	52-53	3.70	4.10	3.70, 3.72
2d	4-F	53	116-118	3.60	6.55	3.72, 3.76
2e	2-COOH	29	164-166	3.84	8.20	3.71, 3.83
2f	4-COOH	59	208-209	3.77	4.80	3.66, 3.77
2g	2-$COOCH_3$	37	126-130	3.87	8.14	3.72, 3.85
2h	2-Cl	35	53-55	3.64	4.71	3.68, 3.74
2i	3-Cl	33	101-103	3.61	3.97	3.67, 3.74
2j†	4-Cl	73	144	3.60	-	3.66, 3.72
2k	2,3-Cl_2	45	84-85	3.64	4.70	3.68, 3.73
2l	2,5-Cl_2	23	137-138	3.56	4.58	3.70, 3.74
2m	3,4-Cl_2	31	133-135	3.56	4.11	3.70, 3.77
2n	3,5-Cl_2	70	172-173	3.60	4.30	3.68, 3.76
2o	2-OCH_3	24	52-55	3.62	4.27	3.67, 3.72
2p	2-OCH_3,5-Cl	31	97-98	3.62	4.56	3.67, 3.75
2q	4-N=N-Ph	20	168-170	3.70	4.46	3.67, 3.75

[a] ABX system

[b] doublets ($J_{HP} = 10 \div 12$ Hz)

† Calc. for $C_{15}H_{23}ClNO_3P$: C 54.30, H 6.94, N 4.22; found C 54.24, H 6.99, N 4.19.

the condensation of primary amines with aldehydes. Most of the aldimmine precursors of **1** and **2** were generally oily compounds at ambient temperatures and no attempts were made to purify them. Thus, the dimethyl phosphite was directly added to the crude reaction mixture and then, at the end of the reaction, the desired phosphonate was purified by recrystallisation from ethyl ether or from concentrated solutions of ethylacetate.

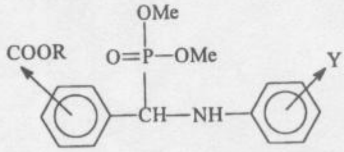
In the syntheses of phosphonates **3** and **4**, the Schiff-bases, generally high melting solids, were isolated and recrystallized before proceeding with the addition of dimethyl phosphite. In Tables I–IV are listed the physical properties of the synthetized compounds. All samples are white crystalline materials.

As far as the ^{1}H-NMR spectra are concerned, first of all, we remark that the aromatic or the cyclohexyl 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 hydrogen of the groups —CH—$P(O)(OMe)_2$ generally resonate as a sharp doublet with a coupling constant H—P in the range of 22 ÷ 24 Hz, except

TABLE III

Physical properties of **3**



N.	X	Y	Yield %	m.p.°C	^{1}H-NMR δ ($CDCl_3$,TMS)		
					CH	NH	O=P(OMe)$_2$^{a}
3a	H	2-COOH	67	153-155	4.98^b	8.70	3.65, 3.75
3b	H	4-COOH	71	148-150	4.86^c	6.13^c	3.44, 3.79
3c	H	2-$COOCH_3$	46	84-86	4.90^c	8.84^c	3.65, 3.70
3d†	4-OCH_3	4-COOH	97	110-112	4.83^b	6.0	3.47, 3.80
3e	4-OCH_3	2-$COOCH_3$	59	112-114	4.87^c	8.77^c	3.67, 3.75
3f	4-OCH_3	4-CF_3	65	-	4.75^b	5.10	3.47, 3.78

[a] doublets (J_{HP} = 10÷12)

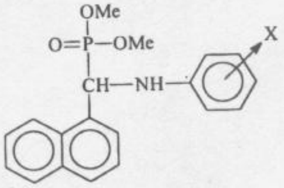
[b] doublet (J_{HP} = 24)

[c] ABX system

† Calc. for $C_{17}H_{20}NO_6P$: C 55.89, H 5.48, N 3.83; found C 55.82, H 5.52, N 3.80.

TABLE IV

Physical properties of **4**



N.	X	Yield %	m.p.°C	^{1}H-NMR δ ($CDCl_3$,TMS)		
				CH	NH	O=P(OMe)$_2$^{a}
4a	2-CF_3	30	85-88	5.69^b	5.74^b	3.25, 3.78
4b	3-CF_3	43	164-166	5.66^c	-	3.13, 3.82
4c	4-CF_3	50	157-160	5.66^b	-	3.12, 3.82
4d†	4-OCH_3	95	147-149	5.60^c	-	3.15, 3.82

[a] doublets (J_{HP} = 10÷11 Hz)

[b] ABX system.

[c] doublet (J_{HP} = 24 Hz)

† Calc. for $C_{20}H_{22}NO_4P$: C 64.69, H 5.93, N 3.77; found C 64.63, H 5.98, N 3.73.

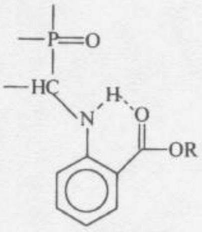
in all compounds of series **2** and in some derivatives of **3** where the additional coupling with the NH proton generates an ABX pattern. In all these latter samples the CH resonances give rise at least to a four line pattern with J_{H-P} in the range of 18 ÷ 24 Hz and J_{H-NH} 8 ÷ 9 Hz, whereas the NH protons appear as a triplet with J_{NH-P} nearly equal to J_{NH-CH}. The observation of an ABX pattern 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.[7]

The methyl hydrogens of the methoxy groups always appear as two distinct doublets of equal intensity, due to the close proximity of the stereocenter N—C—P. The alternative hypothesis that the observation of two distinct doublets for the methoxy groups arise from restricted rotation, on the NMR time scale, around the CH—P bond cannot, in principle, be excluded.

The chemical shift difference between the two doublets, as can be inferred from Tables I–IV, is very sensitive to the moiety attached to the methyne carbon bearing the phosphonate group. In particular going from cyclohexyl to 1-naphthalene the $\Delta\nu$ varies from ca. 0.05 ppm as in **2a** to 0.70 ppm as in **4c**. This effect is certainly due to the strong anisotropic ring current experienced by one of the methoxy groups attached to phosphorous which is lying in the close proximity of the aryl ring, whereas the other one is far away from it.

More interesting is the comparison of the CH—P chemical shifts: in all derivatives **1–3** bearing at least one *ortho-* substituent, inspection of Tables I–III reveals that in these compounds the CH resonance is very much shifted downfield when compared with that one of the *para-* or *meta-*substituted cognates. This downfield effect is even more dramatically evident looking at the NH resonance: in phosphonates **2e**, **2g**, **3a**, **3c**, **3e** which possess a carboxy or carbomethoxy group in the *ortho* position, the NH proton resonates below 8.00 ppm, whereas its unperturbed chemical shift ranges from 4.0 to 4.80 ppm for the *para-* or *meta-*derivatives **2** and occurs at 6.13 ppm for **3b**.

No doubt that this exceptional downfield effect is due to the formation of a hydrogen bond between the NH and the ortho carbonyl oxygen giving rise to a cyclic structure as indicated below:



EXPERIMENTAL

Amines, aldehydes, dimethylphosphite as well as solvents and all other chemicals 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 Bruker AC-250 instrument operating at 250 MHz.

Melting points were determined on a Büchi 530 melting point apparatus and are uncorrected. The Schiff base precursors were all prepared in high yield according to the procedure previously described.[3]

The compounds listed in Tables I–IV were synthetized by direct reaction between the Schiff bases and the phosphite according to the following general procedure:

To a stirred solution of the Schiff-base precursor (0.1 mol) in dry toluene (50 ml) was added dropwise 14 ml (0.15 mol) of $HP(O)(OMe)_2$ and a catalytic amount of NaH. After the addition was completed, the mixture was stirred for a few hours. The solvent was then evaporated and the oil residue was solidified by addition of diethyl ether and a few drops of ethylacetate. All the phosphonates synthesized are white solids, except for compound **2q** (Table II) which is red. They were recrystallized from a mixture of diethyl ether and ethylacetate. Microanalytical data are consistent with the molecular formulas and for one compound each of the type **1–4** data are reported as a footnote in Tables I–IV.

ACKNOWLEDGEMENTS

We thank C.N.R. and the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) for financial support.

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