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α -FUNCTIONAL CYCLOALKYLPHOSPHONATES II. SYNTHESIS OF α -AMINOMETHYL AND α -(N-SUBSTITUTED)- AMINOMETHYLCYCLOALKYLPHOSPHONATES

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α -Aminomethylcycloalkylphosphonates **8** ($n = 2$ to 5) were prepared by catalytic hydrogenation of the corresponding α -cyanoalkylphosphonates **5**. The N-alkylation of **8** was realized through a metalation-alkylation sequence of their N-phosphorylated derivatives, while the carbethoxymethyl substituent was directly introduced on the primary amino groups. Finally, the various protective groups (phosphonic esters, phosphoramidates and carboxylic esters) were overall liberated by hydrolysis in concentrated HCl, leading to the corresponding α -aminomethyl-, α -(N-alkylated)-aminomethyl-, and α -(N-carboxymethylated)-aminomethylcycloalkylphosphonic acids **6**, **7-A** and **7-B**, respectively.

Key words: Cycloalkylphosphonates; aminophosphonates; phosphoramidates; aminophosphonic acids; (N-substituted)-aminophosphonic acids.

INTRODUCTION

Among the wide field of functional phosphonates, aminophosphonic acids and their derivatives have found extensive applications in various branches of industry.¹ Even more interest toward this class of compounds had showed since the discovery of their occurrence in the nature^{2–4} and owing to their biological (herbicidal, neurophysiological or antimicrobial) properties.^{5,6} Numerous methods of preparation of α -amino-, β -amino-, and ω -aminocarboxyalkylphosphonic acids appear regularly in the current chemical literature,⁷ including several contributions of our laboratory.^{8–13}

Up to now, few examples of aminocycloalkylphosphonates have been reported apart from the herbicide "Trakephon" **1**,¹⁴ phosphoranalogue **2** of cycloleucine¹⁵ and several α -aminocyclopropylphosphonates **3** prepared recently by Diel and Maier from the corresponding α -isocyanophosphonates;¹⁶ moreover, in the γ -serie, cyclic analogues **4** of 2-amino-4-phosphonobutanoic acid were synthesized and evaluated for their ability to inhibit excitatory transmission¹⁷ (Figure 1).

In the part I of this work, we described an effective route to α -cyanocycloalkylphosphonates **5** of various size *via* the bisalkylation of α -cyanomethylphosphonates by ω -dibromoalkanes.¹⁸ In the present paper, we illustrate the potentiality of these attractive intermediates by using them as precursors of α -aminomethyl- and α -(N-substituted)-aminomethylcycloalkylphosphonic acids **6** and **7** respectively, being new classes of aminophosphonic acids with an amine function in β position (Figure 2).

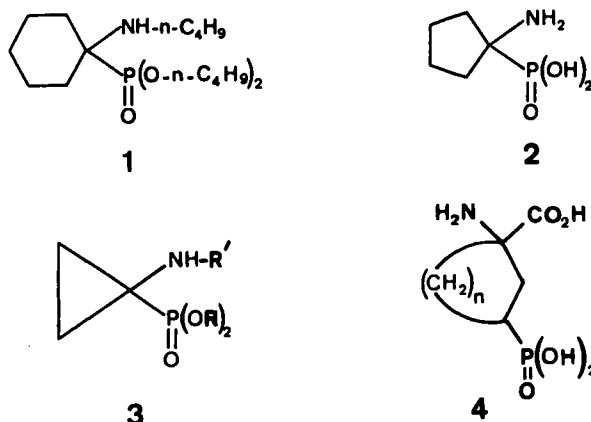


Figure 1

RESULTS AND DISCUSSION

Our strategy is based on the set of reactions represented on Scheme 1, where α -aminomethylphosphonates **8** play a decisive role.

Synthesis of dialkyl α -aminomethylcycloalkylphosphonates **8**

Reduction of **5** (reaction *a*) was cleanly realized in ethanol by hydrogen in presence of catalytic amount of commercial Raney Nickel, under standard conditions. The addition of a small amount of pulverized NaOH (5% molar)^{8,19,20} allows the reaction to be complete in 12 hours.

The crude phosphonates **8** were obtained pure (GC and ^{31}P -NMR) in quasi quantitative yields and used in such form for the rest of the synthesis. All these compounds are stable and they can be distilled. The boiling points of these new phosphonates are reported in the Table I. Our results confirm the efficiency of catalytic hydrogenation for the reduction of α -cyanophosphonates. Moreover, the smooth conditions of the procedure lead to very clean reactions and it is noteworthy that no ring opening, especially in the cyclopropane series,²¹ was observed.

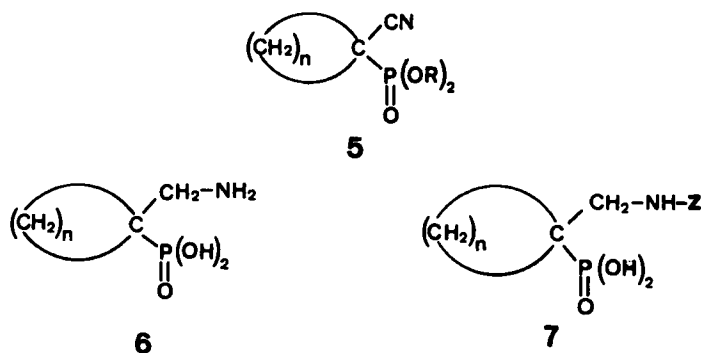
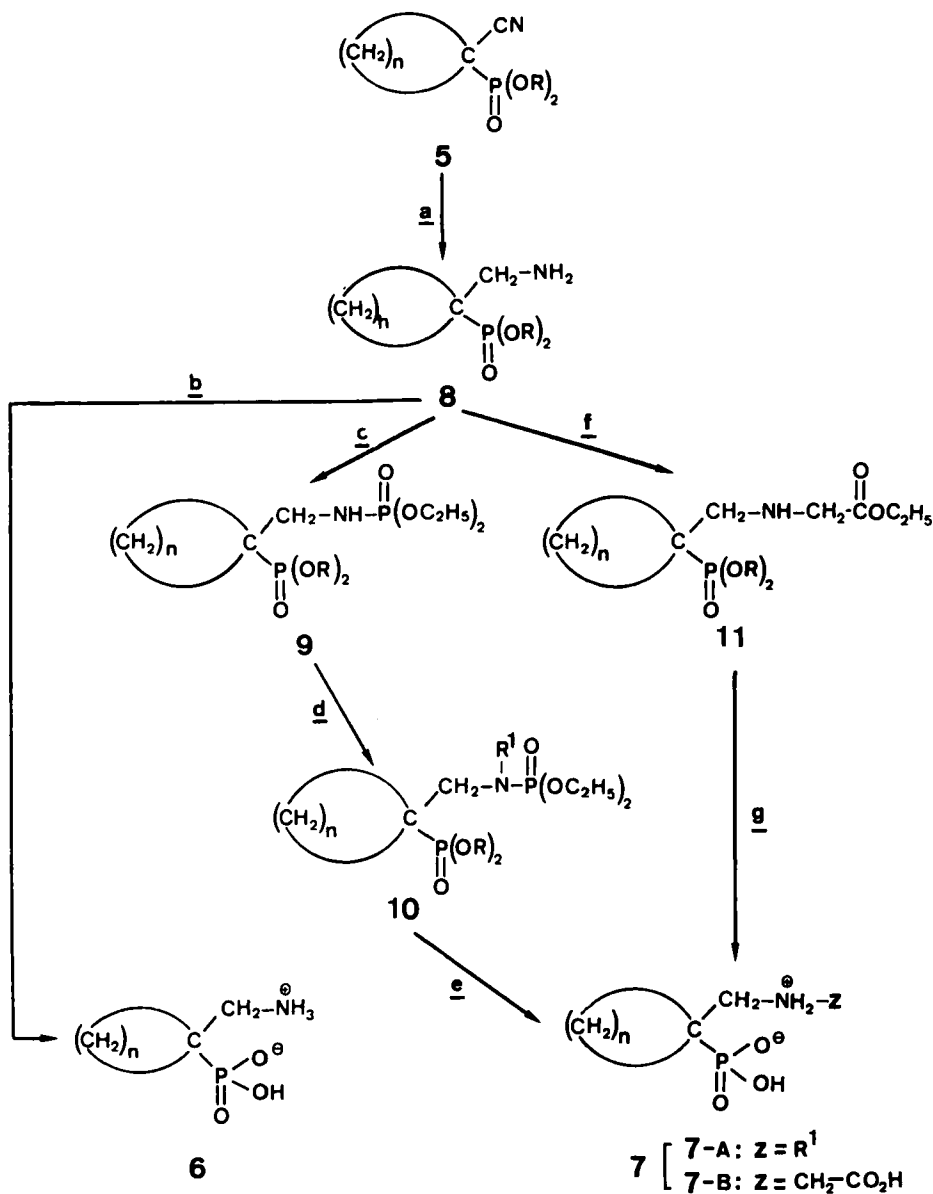


Figure 2



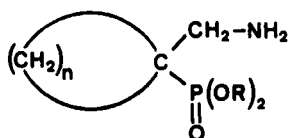
Scheme 1

The phosphonates **8** can be directly used for the preparation of α -aminomethylcycloalkylphosphonic acids **6** (reaction **b**) or as starting material to prepare the α -(*N*-substituted)-aminomethylcycloalkylphosphonic acids **7-A** (path **c** \rightarrow **d** \rightarrow **e**) or **7-B** (path **f** \rightarrow **g**).

Synthesis of α -(*N*-substituted)-aminomethylcycloalkylphosphonates

It is known that direct alkylation of primary amines by alkylhalides gives often a mixture of secondary and tertiary amines, difficult to separate. Conversely, the

TABLE I
Dialkyl α -aminomethylcycloalkylphosphonates 8

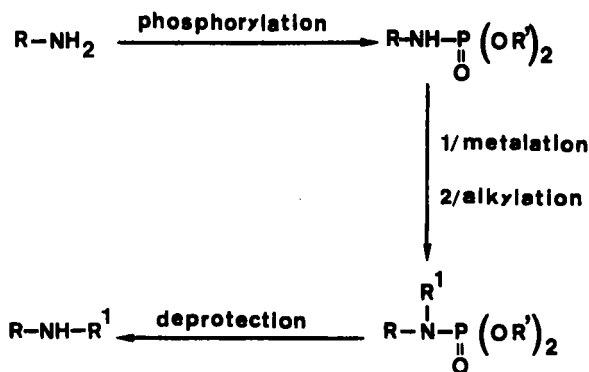


Entry	n	R	Yield %*	³¹ P-NMR (CDCl ₃)	BP°C/mmHg
				δ ppm	
1-a	2	C ₂ H ₅	94	28.92	83/0.5
1-b	2	i-C ₃ H ₇	95	27.19	96/0.5
1-c	2	n-C ₄ H ₉	95	31.44	110/0.5
1-d	3	C ₂ H ₅	95	29.83	86/0.5
1-e	3	i-C ₃ H ₇	97	28.40	98/0.5
1-f	3	n-C ₄ H ₉	96	30.05	118/0.4
1-g	4	C ₂ H ₅	98	33.44	90/0.5
1-h	4	i-C ₃ H ₇	98	31.33	100/0.5
1-i	4	n-C ₄ H ₉	97	33.36	132/0.5
1-j	5	C ₂ H ₅	97	31.63	95/0.5
1-k	5	i-C ₃ H ₇	96	30.58	105/0.5
1-l	5	n-C ₄ H ₉	97	32.01	140/0.2

*Yield of crude products; purity controlled by GC, ³¹P-, ¹H-NMR and IR measurements.

reduction of imines derived from these primary amines provides a useful and selective method for the preparation of mono-N-alkylated amines; this procedure, however, fails to be general and leads to moderate overall yields.^{22,23} We finally decided to use our previously reported method which consist in alkylation of the N-monophosphorylated amine.⁹ The protection of the nitrogen site by a phosphoryl group affords several advantages:

- the phosphorylation of a primary amine is rapid and quantitative;
- the obtained phosphoramidates are stable in basic medium and allow a facile N-alkylation through the phosphoramidic anion;
- the resulting N-alkylated phosphoramidate may be deprotected by mild acidic hydrolysis of the P—N bond (Scheme 2).



Scheme 2

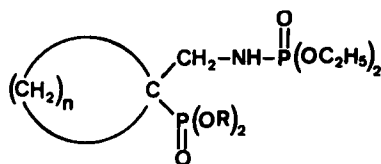
We applied this sequence to some α -aminomethylcycloalkylphosphonates **8**. The N-phosphorylation of the amino group (reaction *c*, Scheme 1) was accomplished by diethylchlorophosphate in presence of one equivalent of triethylamine, at room temperature, in chloroform.²⁴ The compounds **9** were isolated with excellent yields, in pure state after elimination of triethylammonium chloride and solvent. They are heat-resistant compounds (boiling points are given in Table II), but we used them in crude form for the subsequent step. We realized the following step (reaction *d*, Scheme 1) by the traditional metalation-alkylation sequence, using NaH (1 eq.) as metalating agent and one equivalent of alkylhalide in THF.²⁵ With allylbromide and dimethylsulfate, the reaction was complete after heating at 60°C for a few hours. Attempts of N-propylation by 1-bromopropane were unsuccessful. All the compounds **10** obtained are reported in Table III. Several efforts made to distil these high boiling compounds lead to their extensive degradation. Consequently, they were subjected to hydrolysis (section 3/) without further purification.

For the second series of N-substituted derivatives, we were concerned with the introduction of the carboxymethyl group in order to obtain a terminal glycinic rest with potential biological interest.²⁶ We applied the Diel and Maier's method¹⁶ to phosphonates **8** of the cyclopentyl and cyclohexyl series. This method consists in direct alkylation of a primary amino group by ethylbromoacetate (reaction *f*, Scheme 1). Using diisopropylethylamine as a bulky base, and catalytic amount of potassium iodide, in the boiling THF/cyclohexane mixture, readily leads to the phosphonates **11** in good yields (Table IV).

Access to the α -aminomethyl- and α -(N-substituted)-aminomethylcycloalkylphosphonic acids

The aminophosphonic acids **6** and **7** were obtained by hydrolysis of **8** and **10** or **11** respectively, in boiling hydrochloric acid (8N), for 12 hours. Moreover the hy-

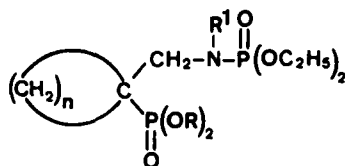
TABLE II
Dialkyl α -(N-diethoxyphosphoryl)-aminomethylcycloalkylphosphonates **9**



Entry	n	R	Yield %*	³¹ P-NMR (CDCl ₃) δ ppm		BP°C/mmHg
				P(O)—C	P(O)—N	
2-a	2	i-C ₃ H ₇	91	28.41	8.07	135/0.5
2-b	3	n-C ₄ H ₉	88	31.48	8.55	160/0.2
2-c	4	C ₂ H ₅	92	35.19	8.39	165/0.5
2-d	4	i-C ₃ H ₇	90	33.25	8.47	155/0.8
2-e	4	n-C ₄ H ₉	94	34.95	8.31	170/0.3
2-f	5	C ₂ H ₅	93	33.82	8.63	175/0.2
2-g	5	i-C ₃ H ₇	95	31.96	8.47	160/0.3
2-h	5	n-C ₄ H ₉	93	33.91	8.63	155/0.3

*Yield of crude products, pure in GC, ³¹P-, ¹H-NMR and IR spectroscopies.

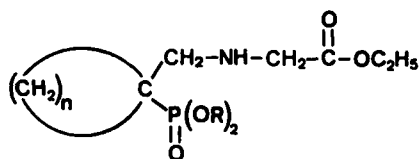
TABLE III

Dialkyl α -(N-alkyl, N-diethoxyphosphoryl)-aminomethyl cycloalkylphosphonates 10

Entry	n	R	R ¹	Yield %*	³¹ P-NMR (CDCl ₃) δ ppm	
					P(O)—C	P(O)—N
3-a	2	i-C ₃ H ₇	C ₂ H ₅	83	29.14	10.17
3-b	2	i-C ₃ H ₇	CH ₂ =CH—CH ₂	84	28.97	9.92
3-c	4	C ₂ H ₅	C ₂ H ₅	85	35.83	11.70
3-d	4	C ₂ H ₅	CH ₂ =CH—CH ₂	82	35.84	13.38
3-e	4	i-C ₃ H ₇	C ₂ H ₅	92	33.90	11.78
3-f	4	n-C ₄ H ₉	C ₂ H ₅	86	35.75	11.78
3-g	5	C ₂ H ₅	C ₂ H ₅	86	34.38	11.78
3-h	5	C ₂ H ₅	CH ₂ =CH—CH ₂	80	34.22	11.38
3-i	5	n-C ₄ H ₉	C ₂ H ₅	85	34.22	11.70

*Yield of crude products, pure in GC, ³¹P- and ¹H-NMR.

TABLE IV

Dialkyl α -(N-carbethoxymethyl)-aminomethylcycloalkylphosphonates 11

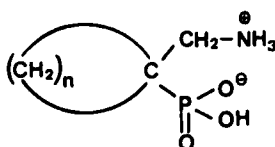
Entry	n	R	Yield %*	³¹ P-NMR (CDCl ₃) δ ppm
4-a	4	C ₂ H ₅	60	30.67
4-b	4	i-C ₃ H ₇	55	33.90
4-c	4	n-C ₄ H ₉	65	35.83
4-d	5	C ₂ H ₅	65	34.87
4-e	5	i-C ₃ H ₇	60	32.93

*Yield of purified products (chromatography on silicagel); purity controlled by GC, ³¹P-, ¹H-NMR and IR measurements.

drolisis of the phosphonic esters, these conditions were more than enough to break the P—N bond in 10 or to hydrolyse the carboxylic ester in 11.

Following this general procedure, phosphonates 8 gave α -aminomethylcycloalkylphosphonic acids 6 (reaction *b*, Scheme 1), whose main properties appear in Table V. Similarly, phosphonates 10 and 11 gave α -(N-substituted)-aminomethylcycloalkylphosphonic acids 7 (reaction *e* and *g* respectively) described in Table VI. The purification of aminoacids 6 and 7-B was achieved by addition of propylene oxide to an ethanolic solution of their hydrochlorides, from which they precipitated. On the other hand, we purified the aminoacids 7-A on an Amberlite Resin (IRA

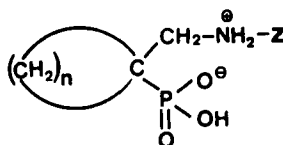
TABLE V
 α -Aminomethylcycloalkylphosphonic acids **6**



Entry	n	Yield %*	^{31}P -NMR (D_2O) δ ppm	MP $^\circ\text{C}$
5-a	2	65	22.45	>260
5-b	3	70	24.56	>260
5-c	4	75	26.89	>260
5-d	5	73	26.66	>260

*Yield of purified products; purity controlled by ^{31}P -, ^1H -NMR and elemental microanalysis (C, H, N: $\pm 0.3\%$ from calculated values).

TABLE VI
 α -(N-substituted)-aminomethylcycloalkylphosphonic acids **7**



Entry	n	Z	Yield %*	^{31}P -NMR (D_2O) δ ppm	MP $^\circ\text{C}$
6-a**	2	C_2H_5	50	32.58	>260
6-b	4	C_2H_5	65	29.13	>260
6-c	4	$\text{CH}_2=\text{CH}-\text{CH}_2$	68	29.61	155
6-d	4	CH_2-COOH	55	29.86	>260
6-e	5	C_2H_5	67	28.49	>260
6-f	5	$\text{CH}_2=\text{CH}-\text{CH}_2$	70	28.88	136
6-g	5	CH_2-COOH	52	31.15	>260

*Yield of purified products; purity controlled by ^{31}P -, ^1H -NMR and elemental microanalysis (C, H, N: $\pm 0.3\%$ from calculated values).

**Isolated as dihydrate (from microanalytical results).

410, OH form) in order to eliminate the hydrochloric acid, and the phosphoric acid coming from the phosphoramidic part of **10**. Finally, the high melting points of these aminophosphonic acids show that they must exist as inner salts.

CONCLUSION

Starting from readily available α -cyanocycloalkylphosphonates of various sizes, we have prepared, by economical process and on gram scale, new α -aminomethyl- and α -(N-substituted)-aminomethylcycloalkylphosphonic acids **6** and **7** respectively. The overall yields in purified aminoacids vary in the ranges of 70% for **6** (2 steps), 50% for **7-A** (4 steps) and 30% for **7-B** (3 steps).

EXPERIMENTAL

IR spectra were recorded with a Beckmann 4250 spectrophotometer. ^1H -NMR spectra were determined on a Varian T60 spectrometer with tetramethylsilane (TMS) as internal reference. ^{31}P -NMR spectra were determined on a Bruker WP90 spectrometer in reference to H_3PO_4 85%. Gas chromatographies (GC) were performed on a Girdel 300 chromatograph. Column chromatographies were carried out using Merck silica gel 60 (230–400 mesh) and Amberlite (IRA 410) ion exchange resin. Elemental microanalyses were realized on a Carlo Erba 1106 analyser. Melting points were determined with a Kofler apparatus and were uncorrected. The starting phosphonates **5** were prepared according to the previously described procedure (see Part I¹⁸).

Synthesis of dialkyl α -aminomethylcycloalkylphosphonates 8. As typical procedure, we describe the synthesis of the diisopropyl α -aminomethylcyclobutylphosphonate (entry 1-e, Table I): 8 g of the commercial Raney nickel catalyst (50% slurry in water) were washed with ethanol (3×15 ml) and introduced as ethanolic suspension in a standard laboratory hydrogenator. Then, 4.9 g (0.02 mol) of diisopropyl α -cyanocyclobutylphosphonate and 0.1 g (0.0025 mol) of pulverized NaOH were added. The mixture was vigorously stirred under H_2 at atmospheric pressure and room temperature. The theoretical volume of H_2 (960 ml) was consumed overnight. The end of the reaction was confirmed by GC and IR (disappearance of the $\nu_{\text{C}\equiv\text{N}}$ band at 2240 cm^{-1}) analyses. The mixture was then filtered and the solvent was removed from the filtrate under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 ml). The obtained solution was washed with H_2O (2×5 ml), dried on MgSO_4 and evaporated to give 4.83 g (yield: 97%) of the crude product, pure by GC and spectroscopic measurements. IR (neat, film), cm^{-1} : 3330–3310 (ν_{NH_2}); 1610 (δ_{NH_2}). ^1H -NMR (CDCl_3), δ ppm: 1.4 (d, 12H) [$(\text{CH}_3)_2\text{CH}-\text{O}$] $_2$; 1.7 (s, 2H) NH_2 (D_2O); 2.0 to 3.1 (m, 6H) $(\text{CH}_2)_3$; 2.8 (d, $^3J_{\text{PH}} = 20$ Hz, 2H) CH_2-N ; 4.7 (m, 2H) [$(\text{CH}_3)_2\text{CH}-\text{O}$] $_2$. All other products of Table I gave ^1H -NMR spectra in accordance with their corresponding phosphonic and cyclic parts. The position of the doublet of the CH_2-NH_2 group was found in the range of 2.7 to 2.8 ppm for all compounds; the value of the $^3J_{\text{PH}}$ coupling constant was 16 Hz for the cyclopropyl series ($n = 2$, entries 1-a to 1-c) and 20 Hz for the other series ($n > 2$, entries 1-d to 1-l).

Synthesis of α -(*N*-diethoxyphosphoryl)-aminomethylcyclopropylphosphonates 9. As typical example, we describe the synthesis of the di-*n*-butyl α -(*N*-diethoxyphosphoryl)-aminomethylcyclohexylphosphonate (entry 2-g, Table II): to a solution of 1.17 g (6.7 mmol) of diethylchlorophosphate and 2.06 g (6.7 mmol) of di-*n*-butyl α -aminomethylcyclohexylphosphonate in CHCl_3 (10 ml) was dropped 1.5 g (15 mmol) of triethylamine in 5 ml of CHCl_3 . The resulting mixture was stirred at room temperature for 30 min, then hydrolyzed with H_2O (5 ml). The organic layer was washed with H_2O (2×5 ml), then dried over MgSO_4 and evaporated. The residue was mixed with diethylether (10 ml) and stored in the refrigerator overnight, until the triethylammonium chloride precipitated. The cold suspension was filtered and the filtrate evaporated and dried in vacuo to give 2.77 g (yield: 93%) of the crude product, pure in GC and ^{31}P -NMR. IR (neat, film) cm^{-1} : 3240 (ν_{NH}), 1240 and 1025 ($\nu_{\text{O}-\text{P}-\text{O}}$), 975 and 790 ($\nu_{\text{O}-\text{P}-\text{O}}$). ^1H -NMR (CDCl_3) δ ppm: 0.65 to 2.5 (m, 30H) [$\text{CH}_3(\text{CH}_2)_2-\text{CH}_2\text{O}$] $_2$, $(\text{CH}_3-\text{CH}_2\text{O})_2$, $(\text{CH}_2)_5$; 3.2 (dd, $^3J_{\text{PH}} = 24$ Hz, $^3J_{\text{HH}} = 7$ Hz, 2H) CH_2-NH ; 3.6 to 4.3 (m, 9H) [$\text{CH}_3(\text{CH}_2)_2-\text{CH}_2\text{O}$] $_2$, $(\text{CH}_3-\text{CH}_2\text{O})_2$, NH (D_2O). For all other products of Table II, the position of the double doublet (CH_2-NH) was found in the range of 2.9 to 3.2 ppm; the $^3J_{\text{PH}}$ coupling constant varied from 22 to 24 Hz for the larger cycles ($n > 2$, entries 2-b to 2-h) and was 16 Hz for the cyclopropylphosphonate (entry 2-a).

Synthesis of dialkyl α -(*N*-alkyl, *N*-diethoxyphosphoryl)-aminomethylcycloalkylphosphonates 10. As typical procedure, we describe the synthesis of the di-*n*-butyl α -(*N*-ethyl, *N*-diethoxyphosphoryl)-aminomethylcyclohexylphosphonate (entry 3-i, Table III): 0.20 g (5 mmol) of the commercial dispersion (60% in mineral oil) of NaH was washed twice and covered with anhydrous THF (10 ml). 0.4 g (2.6 mmol) of diethylsulfate in THF (5 ml) was added to the NaH suspension. Then, 1.89 g (4.6 mmol) of di-*n*-butyl α -(*N*-diethoxyphosphoryl)-aminomethylcyclohexylphosphonate in THF (5 ml) was dropped, under stirring. The mixture was refluxed for 6 h and stirring continued overnight at room temperature. H_2O (5 ml) was added and the aqueous layer washed with ether (2×10 ml). The organic layers were dried (MgSO_4) and the solvents removed in vacuo to give 1.87 g (yield: 85%) of the crude product pure in GC and ^{31}P -NMR. ^1H -NMR (CDCl_3) δ ppm: 0.65 to 2.6 (m, 33H) [$\text{CH}_3(\text{CH}_2)_2-\text{CH}_2\text{O}$] $_2$, $(\text{CH}_3-\text{CH}_2\text{O})_2$, $(\text{CH}_2)_5$, $\text{CH}_3-\text{CH}_2\text{N}$; 2.8 to 3.5 (m, 4H) $\text{CH}_2-\text{N}-\text{CH}_2$; 3.7 to 4.3 (m, 8H) [$\text{CH}_3(\text{CH}_2)_2-\text{CH}_2\text{O}$] $_2$, $(\text{CH}_3-\text{CH}_2\text{O})_2$. The *N*-allyl derivatives (entries 3-b, 3-d and 3-h, Table III) exhibit, in addition, the characteristic multiplet of the $\text{CH}=\text{CH}_2$ group between 5 and 5.9 ppm.

Synthesis of dialkyl α -(*N*-carbethoxymethyl)-aminomethylcycloalkylphosphonates 11. For the synthesis of the compounds reported in the Table IV, we applied strictly the procedure described by Diel and

Maier¹⁶ for their syntheses of dialkyl α -(*n*-carbethoxymethyl)-aminocyclopropylphosphonates from the corresponding dialkyl α -aminocyclopropylphosphonates. For example (entry 4-e, Table 4), from 2.15 g (8.2 mmol) of diisopropyl α -aminomethylcyclopentylphosphonate, 1.37 g (8.2 mmol) of ethylbromoacetate, 1.05 g (8.2 mmol) of *N,N*-diisopropylethylamine, catalytic amount of KI, in the refluxed THF/cyclohexane (10 ml/5 ml) mixture, we isolated 1.57 g (yield: 55%) of purified (flash chromatography on silica gel; eluent, $\text{CH}_2\text{Cl}_2/\text{MeOH}$: 95/5) diisopropyl α -(*N*-carbethoxymethyl)-aminomethylcyclopentylphosphonate. $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.2 (t, 7 Hz, 3H) $\text{CH}_3\text{—CH}_2\text{O}$; 1.4 (d, 7 Hz, 12H) $[(\text{CH}_3)_2\text{CHO}]_2$; 1.2 to 2.4 (m, 10H) $(\text{CH}_2)_5$; 2.2 (s, 1H) $\text{NH}(\text{D}_2\text{O})$; 2.7 (d, $^3J_{\text{PH}} = 23$ Hz, 2H) $\text{CH}_2\text{—NH}$; 3.3 (s, 2H) $\text{NH—CH}_2\text{—COOEt}$; 3.8 to 5 (m, 4H) $[(\text{CH}_3)_2\text{CHO}]_2, \text{CH}_3\text{—CH}_2\text{O}$. For the other products of the Table IV, the $^1\text{H-NMR}$ spectra were in accordance with their structural formula (in particular, $^3J_{\text{PH}}$ varies from 23 Hz for the cyclopentyl series to 20 Hz for the cyclobutyl and the cyclohexyl series).

Synthesis of α -aminomethylcycloalkylphosphonic acids 6. As typical example, we describe the synthesis of the α -aminomethylcyclohexylphosphonic acid (entry 5-d, Table V): 3 g (12 mmol) of diethyl α -aminomethylcyclohexylphosphonate were refluxed for 24 h in HCl 8N (50 ml). After cooling, the mixture was diluted with water (100 ml) and extracted with CH_2Cl_2 (3×20 ml). The aqueous layer was evaporated, the residue was washed with water and evaporated again; this last operation was repeated 3 times. The resulting oil was dissolved in ethanol (10 ml) and propylene oxide was dropped in the solution until complete precipitation of the aminoacid, which was collected by filtration, dried and crystallized from the mixture $\text{EtOH}/\text{H}_2\text{O}$ (95/5) to give 1.74 g (yield 75%) of white crystals ($F > 260^\circ\text{C}$). $^1\text{H-NMR}$ (D_2O) δ ppm: 1.2 to 2 (m, 10H) $(\text{CH}_2)_5$; 3.3 (d, $^3J_{\text{PH}} = 21$ Hz, 2H) $\text{CH}_2\text{—NH}_2^+$. For the other aminophosphonic acids reported in Table V, the protons of the cyclic part were found as a broad multiplet (1.2 to 2 ppm) and the $\text{CH}_2\text{—N}$ protons as a doublet (3.2 ppm). The $^3J_{\text{PH}}$ coupling constant varies from 17 Hz (entry 5-a) to 19 Hz (entries 5-b and 5-c). The following microanalytical data were obtained for the successive entries of Table 5:

5-a: Calc. for $\text{C}_5\text{H}_{10}\text{NO}_3\text{P}$: C 31.78, H 6.62, N 9.27; found: C 31.5, H 6.4, N 9.1.

5-b: Calc. for $\text{C}_5\text{H}_{12}\text{NO}_3\text{P}$: C 36.36, H 7.27, N 8.48; found: C 36.1, H 7.1, N 8.2.

5-c: Calc. for $\text{C}_6\text{H}_{14}\text{NO}_3\text{P}$: C 40.22, H 7.82, N 7.82; found: C 40.0, H 8.0, N 7.6.

5-d: Calc. for $\text{C}_7\text{H}_{16}\text{NO}_3\text{P}$: C 43.52, H 8.29, N 7.25; found: C 43.3, H 8.5, N 6.9.

Synthesis of α -(*N*-substituted)-aminomethylcycloalkylphosphonic acids 7. The α -(*N*-carboxymethyl)-aminomethylcycloalkylphosphonic acids **7-B** (entries 6-b and 6-g, Table VI) were obtained from the corresponding dialkyl phosphonates **11** by acidic hydrolysis and precipitation with propylene oxide using exactly the same procedure as for the sequence **8** \rightarrow **6**. For the α -(*N*-alkyl)-aminomethylcycloalkylphosphonic acids **7-A** (entries 6-a, -b, -c, -e and -f, Table VI), the acidic hydrolysis and the subsequent washings were the same ones again. The oily residue was dissolved in water (to obtain a 1.5% w/w solution) and passed through a column of Amberlite IRA 410 previously set into OH form. The column was eluted with aqueous acetic acid (5% w/w) and the fraction pH 7 to pH 3 collected. This fraction evaporated gave aminophosphonic acids as white solids, pure by $^1\text{H-NMR}$ and elemental analysis. The following data refer to the successive entries of Table VI:

6-a: $^1\text{H-NMR}$ (D_2O) δ ppm: 0.4 to 1 (m, 4H) $(\text{CH}_2)_2$; 1.2 (t, 7 Hz, 3H) $\text{CH}_3\text{—CH}_2\text{N}$; 2.6 to 3.4 (m, 4H) $\text{CH}_2\text{—N—CH}_2$. Anal. calc. for $\text{C}_6\text{H}_{14}\text{NO}_3\text{P—2H}_2\text{O}$: C 33.48, H 8.37, N 6.51; found: C 33.1, H 8.1, N 6.7.

6-b: $^1\text{H-NMR}$ (D_2O) δ ppm: 1.1 (t, 7 Hz, 3H) $\text{CH}_3\text{—CH}_2\text{N}$; 1.1 to 2 (m, 8H) $(\text{CH}_2)_4$; 2.4 to 3.2 (m, 4H) $\text{CH}_2\text{—N—CH}_2$. Anal. calc. for $\text{C}_8\text{H}_{18}\text{NO}_3\text{P}$: C 46.37, H 8.69, N 6.76; found: C 46.1, H 8.4, N 6.5.

6-c: $^1\text{H-NMR}$ (D_2O) δ ppm: 1.2 to 2.4 (m, 8H) $(\text{CH}_2)_4$; 3.2 (d, $^3J_{\text{PH}} = 20$ Hz, 2H) $\text{CH}_2\text{—N}$; 3.8 (~d, 6 Hz, 2H) $\text{N—CH}_2\text{—CH=}$; 5.4 to 6.2 (m, 3H) —CH=CH_2 . Anal. calc. for $\text{C}_9\text{H}_{18}\text{NO}_3\text{P}$: C 49.31, H 8.21, N 6.39; found: C 49.5, H 8.1, N 6.2.

6-d: $^1\text{H-NMR}$ (D_2O) δ ppm: 1.2 to 2.4 (m, 8H) $(\text{CH}_2)_4$; 3.2 (d, $^3J_{\text{PH}} = 20$ Hz, 2H) $\text{CH}_2\text{—N}$; 3.9 (s, 2H) $\text{CH}_2\text{—COOH}$. Anal. calc. for $\text{C}_8\text{H}_{16}\text{NO}_4\text{P}$: C 40.50, H 6.75, N 5.90; found: C 40.3, H 6.4, N 5.6.

6-e: $^1\text{H-NMR}$ (D_2O) δ ppm: 1.2 (t, 7 Hz, 3H) $\text{CH}_3\text{—CH}_2\text{N}$; 0.9 to 2 (m, 10H) $(\text{CH}_2)_5$; 2.7 to 3.4 (m, 4H) $\text{CH}_2\text{—N—CH}_2$. Anal. calc. for $\text{C}_9\text{H}_{20}\text{NO}_3\text{P}$: C 48.86, H 9.04, N 6.33; found: C 48.7, H 9.3, N 6.5.

6-f: $^1\text{H-NMR}$ (D_2O) δ ppm: 1 to 2 (m, 10H) $(\text{CH}_2)_5$; 3.4 (d, $^3J_{\text{PH}} = 20$ Hz, 2H) $\text{CH}_2\text{—N}$; 3.8 (~d, 6 Hz, 2H) $\text{N—CH}_2\text{—CH=}$; 5.4 to 6.1 (m, 3H) —CH=CH_2 . Anal. calc. for $\text{C}_{10}\text{H}_{20}\text{NO}_3\text{P}$: C 51.50, H 8.58, N 6.00; found: C 51.2, H 8.3, N 6.3.

6-g: $^1\text{H-NMR}$ (D_2O) δ ppm: 0.8 to 2 (m, 10H) $(\text{CH}_2)_5$; 3.4 (d, $^3J_{\text{PH}} = 21$ Hz, 2H) $\text{CH}_2\text{—N}$; 3.9 (s, 2H) $\text{CH}_2\text{—COOH}$. Anal. calc. for $\text{C}_9\text{H}_{18}\text{NO}_4\text{P}$: C 43.02, H 7.17, N 5.57; found: C 43.1, H 7.4, N 5.8.

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