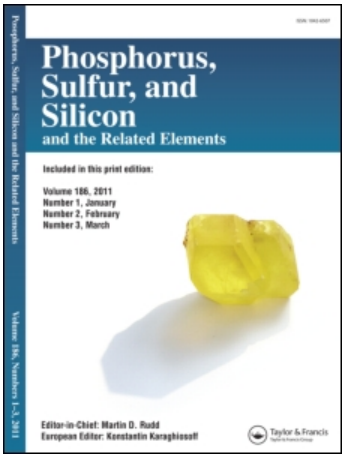

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SYNTHESIS OF SOME NEW CYCLIC AMINOPHOSPHONATES AND THEIR PHYSIOLOGICAL ACTIVITIES

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SYNTHESIS OF SOME NEW CYCLIC AMINOPHOSPHONATES AND THEIR PHYSIOLOGICAL ACTIVITIES

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The synthesis of 19 newly synthesized cyclic aminophosphonic acid derivatives was described and their biological activity studied. It was found, as in the case of the previously described series of acyclic analogues, that the phytotoxicity of the compounds, tested on aquatic plant *Spirodela oligorrhiza* depended mainly on their hydrophobic parameters. The most pronounced phytotoxicity, the measure of which was concentration of aminophosphonates causing 50% inhibition of plant growth (EC_{50}), exhibited compounds with not too long hydrocarbon substituent on the nitrogen atom (8–10 carbon atoms) and branched propyl groups on the phosphorus atom. The test had preliminary character and permitted to eliminate the less promising compounds for further studies.

Keywords: Aminophosphonates; Synthesis; Physiological activity

INTRODUCTION

First derivatives of aminomethanephosphonic acid were synthesized over 50 years ago[1]. They were found to exhibit interesting biological activity which motivated synthesis of a series of other organophosphorus compounds for potential biological application. Some of synthesized compounds fulfilled expectations and were subsequently used as potent herbicides.

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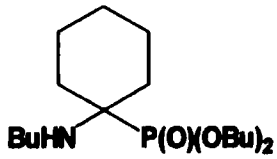
To those compounds belong such interesting herbicidal aminophosphonates as N-phosphonomethylglycine glyphosate[2–4] found in 1971, derivatives of aminomethylenebisphosphonic acids[5] synthesized in Japan in 1979, or Trakephon (N-n-butylaminocyclohexane phosphonic acid dibutyl ester)[6]:



Althought all those herbicides were intensively studied the mechanism of their toxic activity still remains unclear[7–9], with the exception of glyphosate[4].

Next an interesting class of cyclic plant growth modifiers are aminophosphonic acid derivatives of fluorene. They were intensively studied in the past 20 years, also in our laboratory[10–18]. Some of them were found to have high biological activity comparable to that exhibited by glyphosate. It was also found that the biological activity of the tested compounds strongly correlates with their lipophilic character and in this respect resembles the activity of Trakephon[19]. So, it is very probable that their action is connected with disrupting the function of plant membranes as postulated also by other authors[20]. Working on this assumption we have studied some new synthesized cyclic aminophosphonates differentiated by a kind of cyclic ring and substituents on phosphorus and nitrogen atoms and thus, representing different polarity and hydrophobicity. The primary aim was to determine whether the mentioned differentiation had any influence on phytotoxicity of the compounds studied that should help to understand better the mode of action of this class of compounds. A series of 19 new cyclic aminophosphonic acid derivatives were studied. Their toxicities were tested on aquatic plant *Spirodela oligorrhiza.*

MATERIALS AND METHODS

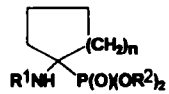
The compounds were synthesized by heating the carbonyl compound with the corresponding amine which yielded an imine which was used without

purification in the next step. After addition of dialkyl phosphite to the imine the reaction mixture was heated for several hours at elevated temperature. The final product was isolated and purified by column chromatography. All experimental data are given in the experimental part.

Studies on the physiological activity of the investigated compounds were done on aquatic plant *Spirodela oligorrhiza*. Two equal fronds were placed in an Erlenmayer flask containing modified Hoagland's solution[21]. The plants were cultivated under constant illumination 120 $\mu E\ m^{-2}s^{-1}$ at 25°C. After 8 days the dry weight of the plants was determined. Biomass data was expressed as percent control response. Calculation of the effective concentrations resulting in 50% growth inhibition (EC_{50}) compared with controls were calculated using non-linear regression for the logistic model (dose response)[22]. Each experiment was repeated at least three times.

All synthesized compounds had the general structure as given in Table I.

TABLE 1 Synthesized acyclic aminophosphonates and the values of their effective concentrations causing 50% inhibition of growth of *Spirodela oligorrhiza* (EC_{50})



Comp. No.	EC_{50} *[μM]*	R^1	R^2	*n*
1	61.0	n-C_4H_9	n-C_4H_9	2
2[a]	68.5	n-C_4H_9	n-C_4H_9	2
3	69.0	n-C_4H_9	n-C_4H_9	3
4	57.5	n-C_4H_9	n-C_4H_9	1
5	54.0	n-C_4H_9	iso-C_3H_7	2
6	3.35	n-C_8H_{17}	iso-C_3H_7	1
7	70.0	n-C_8H_{17}	C_2H_5	2
8	120.0	n-$C_{14}H_{29}$	n-C_4H_9	2
9	23.0	n-C_8H_{17}	n-C_4H_9	2
10	57.0	Sec-C_4H_9	n-C_4H_9	2
11	4.30	n-C_8H_{17}	n-C_4H_9	1
12	39.0	n-$C_{10}H_{21}$	iso-C_3H_7	3

13	0.20	n-$C_{10}H_{21}$	iso-C_3H_7	*2*
14	6.60	n-$C_{10}H_{21}$	n-C_4H_9	*2*
15	71.0	n-$C_{10}H_{21}$	n-C_4H_9	*1*
16	52.0	HO-C_2H_4	n-C_4H_9	*2*
17	67.5	n-C_8H_{17}	n-C_3H_7	*1*
18	>100.0	n-C_5H_{11}	n-C_4H_9	*1*
19[a]	>100.0	n-$C_{10}H_{21}$	n-C_4H_9	*2*

a. Compounds with incorporated tert-butyl groups into the ring.

RESULTS AND DISCUSSION

The values of concentrations of studied aminophosphonates inhibiting growth of *Spirodela oligorrhiza* in 50% oscillated between 10^{-4} and 10^{-7} M. The smallest values of EC_{50}, evidencing a very high physiological activity of aminophosphonates, were obtained for compounds nos 6, 11, 13 and 14. Those compounds exhibited far better physiological toxicity against *S. oligorrhiza* than the well-known cyclic pesticide Buminafos®[23] (62.0 μM). The toxicities of most of the other compounds were comparable which also makes them good potential herbicides.

The common feature of the most toxic compounds is a C_8H_{17} hydrocarbon chain at the nitrogen atom. A too long hydrocarbon chain drastically decreases the compound's efficiency (e.g., compound 8). This is the feature commonly observed for a series of amphiphilic compounds of biological activity[24–26] and may be the result of a phenomenon called interdigitation when the hydrocarbon chain of a compound can incorporate into the lipid phase of a cell membrane in such a way that its terminal group localizes in the opposite monolayer of the lipid bilayer thus stabilizing this bilayer[27]. Whether this is the reason or not, the obvious conclusion is that the more hydrophobic the compound is the better its phytotoxicity. A too long chain effect may be compensated by replacing n-C_4H_9 groups with iso-C_3H_7 groups (e.g. compound 12). The latter substituent decidely improves aminophosphonates phytotoxicities (see compounds 6 and 13). Contrary, compounds of diminished hydrophobicity or those with incorporated tert butyl groups into the ring (compound nos 2 and 19) exhibited decreased phytotoxic activity. General conclusion that may be drawn from

the results of the toxic tests seems to point at the lipid phase of biological membranes as a place where the interaction of the compounds studied with biological objects takes place. This conclusion confirm some studies on the interaction of some of the presented aminophosphonates with erytrocytes and planar lipid membranes. It was found that hemolysis of red cells and destabilization of lipid membranes depended mostly on hydrophobicity of aminophosphonates[28].

Experimental

All NMR spectra were taken on a Bruker Avance DRX 300 MHz instrument operating at 300.13 MHz (^{1}H) and 121.499 (^{31}P). IR spectra and elemental analysis were performed at the Institute of Organic Chemistry, Biochemistry and Biotechnology.

Imine synthesis

Method A

Carbonyl compound and corresponding amine were mixed in a molar ratio of 1:1.1 and dry potasium carbonate added. After 1 hr the product was filtered and the residue was evaporated on a warm water bath under reduced pressure. In all cases the product was pure enough for analysis and was used for aminophosphonate synthesis without further purification.

Method B

For low reacting carbonyl compounds a mixture of carbonyl compound with a 2–3 fold excess of butylamine and a catalytic amount of aluminium chloride was refluxed for a period of 2–3 hrs. Reaction was monitored by taking the IR spectra When the reaction was completed the mixture was dissolved in dry ethyl ether, dried over potasium carbonate, filtered and evaporated from a hot water bath under reduced pressure. The obtained imine was used without further purification.

Aminophosphonate synthesis

A mixture of imine and diethyl phosphite was heated at 70°C until the imine disappeared (by TLC method). It takes about 2–5 hrs. Then the mixture was dissolved in dry acetone to which the acetone solution of anhydrous oxalic acid was added and the mixture was kept at low temperatures. The oxalate was filtered off, and aqueous ammonia was added followed by

extraction of the free aminophosphonate with ether or chloroform. After drying over potasium carbonate the solvent was removed and the residue was crystallized. In the cases of noncrystalline aminophosphonates they were used without further purifications or their oxalates were crystallized before converting them to the free aminophosphonates.

1. $C_{18}H_{38}NO_3P$; dibutyl ester of 1-N(butyloamino)-cyclohexyl phosphonic acid; yield: 27.76%, m.p. 92–95°C; ^{1}H-NMR($CDCl_3$): 4.10–3.97 (m, 4H, O-C$\underline{H}_2$); 2.71 (d*t, 2H, N-C$\underline{H}_2$, J_{HP}=3Hz, J=6.6Hz); 1.85–1.7 (m, 4H, O-CH$_2$C$\underline{H}_2$); 1.7–1.55 (m, 10H, 5*C$\underline{H}_{2(ring)}$); 1.5–1.3 (m, 8H, O-CH$_2$CH$_2$C$\underline{H}_2$, N-CH$_2$C$\underline{H}_2$C$\underline{H}_2$); 0.94 (t, 9H, O-CH$_2$CH$_2$CH$_2$C$\underline{H}_3$, N-CH$_2$CH$_2$CH$_2$C$\underline{H}_3$);
2. $C_{22}H_{46}NO_3P$; dibutyl ester 1-N(butyloamino)-p-t-butyl-cyclohexane phosphonic acid; yield: 81.78%, m.p. 99–104°C; ^{1}H-NMR: 4.08–4.01 (m, 4H, O-C$\underline{H}_2$); 2.73–2.71 (m, 2H, N-C$\underline{H}_2$); 1.85–1.84 (m, 2H, C$\underline{H}_{e2(ring)}$,C$\underline{H}_{d2(ring)}$); 1.68–1.63 (m, 7H, O-CH$_2$C$\underline{H}_2$, C$\underline{H}_{e'2(ring)}$, CHd'2(ring), CHb(ring); 1.48–1.38 (m, 12H, O-CH$_2$CH$_2$C$\underline{H}_2$, N-CH$_2$C$\underline{H}_2$C$\underline{H}_2$, C$\underline{H}_{c,c'2(ring)}$, C$\underline{H}_{f,f'2(ring)}$); 0.98–0.92 (t, 9H, O-CH$_2$CH$_2$CH$_2$C$\underline{H}_3$, N-CH$_2$CH$_2$CH$_2$C$\underline{H}_3$, J=7.4Hz); 0.86 (s, 9H, C-(C$\underline{H}_3$)$_3$);
3. $C_{19}H_{40}NO_3P$; dibutyl ester of 1-N(butyloamino)-cycloheptane phosphonic acid; yield: 66.14%; m.p. 90–94°C; ^{1}H-NMR ($CDCl_3$): 4.05 (d*t, 4H, O-C$\underline{H}_2$, J_{HP}=13,2Hz, J=6,5Hz); 2.71 (d*t, 2H, N-C$\underline{H}_2$, J_{HP}=2Hz, J=6.6Hz); 1.96–1.35 (m, 24H, 6*C$\underline{H}_{2(ring)}$, O-CH$_2$C$\underline{H}_2$C$\underline{H}_2$, N-CH$_2$C$\underline{H}_2$C$\underline{H}_2$); 0.98–0.90 (m, 9H, O-CH$_2$CH$_2$CH$_2$C$\underline{H}_3$, N-CH$_2$CH$_2$CH$_2$C$\underline{H}_3$);
4. $C_{17}H_{36}NO_3P$; dibutyl ester of 1-N(butyloamino)-cyclopentane phosphonic acid; yield: 85,81%; oil; ^{1}H-NMR: 4.07–4.03 (m, 4H, O-C$\underline{H}_2$); 2.70 (m, 2H, N-C$\underline{H}_2$); 2.2–1.8 (m, 2H, N-CH$_2$C$\underline{H}_2$); 1.62–1.70 (m, 10H, CH$_{2(ring)}$, O-CH$_2$C$\underline{H}_2$, N-CH$_2$CH$_2$C$\underline{H}_2$); 1.44–1.35 (m, 8H, C$\underline{H}_{2(ring)}$, O-CH$_2$CH$_2$C$\underline{H}_2$); 0.96–0.90 (m, 9H, O-CH$_2$CH$_2$CH$_2$C$\underline{H}_3$, N-CH$_2$CH$_2$CH$_2$C$\underline{H}_3$);
5. $C_{16}H_{34}NO_3P$ diisopropyl ester of 1-N(butyloamino)-cyclohexane phosphonic acid; yield: 100%; oil; ^{1}H-NMR: 4.65–4.5 (m, 2H, O-C$\underline{H}$); 2.63–2.62 (m, 2H, N-C$\underline{H}_2$); 1.56–1.51 (m, 6H, 2*CH$_{2(ring)}$, N-CH$_2$C$\underline{H}_2$); 1.32–1.28 (m, 6H, 2*CH$_{2(ring)}$, N-CH$_2$CH$_2$C$\underline{H}_2$); 1.22–1.20 (d, 12H, C-(CH$_3$)$_3$); 1.2–1.0 (m, 2H, CH$_{2(ring)}$); 0.84–0.82 (t, 3H, N-CH$_2$CH$_2$CH$_2$C$\underline{H}_3$);

6. $C_{19}H_{40}NO_3P$;diisopropyl ester of 1-N(oktyloamino)-cyclopentane phosphonic acid; yield: 22,3%; oil; ^{1}H-NMR: 4.67–4.57 (m, 2H, O-C<u>H</u>); 2.62–2.57 (t, 2H, N-CH_2); 1.85–1.80 (m, 2H, N-$CH_2C\underline{H}_2$); 1.68–1.55 (m, 6H, N-$CH_2CH_2C\underline{H}_2$, $2^*CH_{2(ring)}$); 1.28–1.16 (m, 24H, N-$CH_2CH_2CH_2(C\underline{H}_2)_4$, $2^*CH_{2(ring)}$, O-$CH(C\underline{H}_3)_2$); 0.79–0.75 (t, 3H, N-$(CH_2)_7CH_3$);
7. $C_{18}H_{38}NO_3P$; diethyl ester 1-N(oktyloamino)-cyclohexane phosphonic acid; yield: 48,8%; m.p. 81–83.5°C; ^{1}H-NMR: 4.3–4.2 (p, 4H, O-CH_2); 3.17–3.11 (t, 2H, N-CH_2); 1.8–1.57 (m, 8H, N-$CH_2C\underline{H}_2CH_2$, $2^*CH_{2(ring)}$); 1.39–1.21 (m, 20H, N-$(CH_2)_3(C\underline{H}_2)_4$, O-$CH_2C\underline{H}_3$, $3^*CH_{2(ring)}$); 0,78–0,76 (t, 3H, N-$(CH_2)_7C\underline{H}_3$);
8. $C_{28}H_{58}NO_3P$; dibutyl ester 1-N(tetradecanyloamino)-cyclohexane phosphonic acid; oil; ^{1}H-NMR: 4.06–3.99 (m, 4H, O-CH_2); 2.72–2.67 (m, 2H, N-CH_2); 1.76–1.59 (m, 12H, $2^*CH_{2(ring)}$, O-$CH_2C\underline{H}_2$, N-$CH_2C\underline{H}_2C\underline{H}_2$); 1.46–1.25 (m, 30H, O-$CH_2CH_2C\underline{H}_2$, N-$CH_2CH_2CH_2(C\underline{H}_2)_{10}$, $3^*CH_{2(ring)}$); 0.96–0.90 (t, 6H, O-$(CH_2)_3C\underline{H}_3$); 0.89–0.85 (t, 3H, N-$(CH_2)_{13}C\underline{H}_3$);
9. $C_{22}H_{46}NO_3P$; dibutyl ester 1-N(octyloamino)-cyclohexane phosphonic acid; yield: 92,09%; oil; ^{1}H-NMR: 4.07–4.0 (m, 4H, O-CH_2); 2.71–2.67 (m, 2H, N-CH_2); 1.76–1.59 (m, 12H, $2^*CH_{2(ring)}$, N-$CH_2C\underline{H}_2C\underline{H}_2$, O-$CH_2C\underline{H}_2$); 1.46–1.27 (m, 18H, O-$CH_2CH_2C\underline{H}_2$, $3^*CH_{2(ring)}$, N-$(CH_2)_3(C\underline{H}_2)_4$); 0.96–0.91 (t, 6H, O-$(CH_2)_3C\underline{H}_3$); 0.9–0.86 (t, 3H, N-$(CH_2)_7C\underline{H}_3$);
10. $C_{18}H_{38}NO_3P$; dibutyl ester 1-N(sec-butyloamino)-cyclohexane phosphonic acid; yield: 66.35%; oil; ^{1}H-NMR: 3.88–3.81 (m, 4H, O-CH_2); 3.0–2.9 (m, 1H, N-CH); 1.57–1.4 (m, 10H, O-$CH_2C\underline{H}_2$, $2^*CH_{2(ring)}$, N-$CHC\underline{H}_2$); 1.26–1.20 (m, 8H, O-$CH_2CH_2C\underline{H}_2$, $2^*CH_{2(ring)}$); 1.15–0.95 (m, 2H, $CH_{2(ring)}$); 0.88–0.85 d, 3H, N-$CHC\underline{H}_3$); 0.78–0.73 (t, 6H, O-$(CH_2)_3C\underline{H}_3$); 0.71–0.66 (t, 3H, N-$CHCH_2C\underline{H}_3$);
11. $C_{21}H_{44}NO_3P$; dibutyl ester of 1-N(octyloamino)-cyclopentane phosphonic acid; yield: 51,44%; oil; ^{1}H-NMR: 4,06–3,99 (m, 4H, O-CH_2); 2.67–2.63 (t, 2H, N-CH_2); 1.96–1.91 (m, 2H, N-$CH_2C\underline{H}_2$); 1.,8–1.57 (m, 10H, N-$CH_2CH_2(C\underline{H}_2)_3$, O-$CH_2C\underline{H}_2$); 1.43–1.29 (m, 8H, O-$CH_2CH_2C\underline{H}_2$, N-$(CH_2)_5C\underline{H}_2C\underline{H}_2$); 1.24 (s, 8H, $CH_{2(ring)}$); 0.93–0.88 (t, 6H, O-$(CH_2)_3C\underline{H}_3$); 0.86–0.82 (t, 3H, N-$(CH_2)_7C\underline{H}_3$);
12. $C_{23}H_{48}NO_3P$; diisopropyl ester of 1-N(decanyloamino)-cycloheptane phosphonic acid; yield: 75,96%; oil; ^{1}H-NMR: 4.7–4.62 (m, 2H, O-CH); 2.67–2.65 (m, 2H, N-CH_2); 2.48–2.44 (m, 2H, N-$CH_2C\underline{H}_2$);

1.89–1.84 (m, 2H, N-$CH_2CH_2C\underline{H}_2$); 1.71–1.5 (m, 12H, N-$CH_2CH_2CH_2(C\underline{H}_2)_6$); 1.36–1.27 (d, 12H, O-$CH(C\underline{H}_3)_2$); 1.23 (s, 12H, $CH_{2(ring)}$); 0.87–0.82 (t, 3H, N-$(CH_2)C\underline{H}_3$);

13. $C_{22}H_{46}NO_3P$;diisopropyl ester of 1-N(decyloamino)cyclohexane phosphonic acid; yield: 68,76%; oil; ^{1}H-NMR: 4.76–4.64 (m, 2H, OCH), 2.75–2.69 (m, 2H, HN-$C\underline{H}_2$), 1.75–1.61 (m, 8H, $C\underline{H}_{2(ring)}$, HN-$CH_2C\underline{H}_2C\underline{H}_2$), 1.52–1.21 (m, 30 H, $C\underline{H}_{2(ring)}$, HN-$CH_2CH_2CH_2(C\underline{H}_2)_6$, O-$CH(C\underline{H}_3)_2$); 0.90–0.86 (t, 3H, $HN(CH_2)_9C\underline{H}_3$);
14. $C_{24}H_{50}NO_3P$; dibutyl ester 1-N(decyloamino)cyclohexane phosphonic acid; yield: 72,42%; oil; ^{1}H-NMR: 4.06–3.96 (m, 4H, OCH_2); 2.66–2.64 (m, 2H, HN-$C\underline{H}_2$); 1.64–1.54 (m, 12 H, $C\underline{H}_{2(ring)}$, HN-$CH_2CH_2CH_2CH_2$); 1.42–1.29 (m, 8H, OCH_2CH_2, $C\underline{H}_{2(ring)}$); 1.22 (m, 14 H, $OCH_2CH_2C\underline{H}_2$, HN-$CH_2CH_2CH_2CH_2(C\underline{H}_2)_5$); 0.92–0.81 (m, 9H, $OCH_2CH_2CH_2C\underline{H}_3$, HN-$(CH_2)_9C\underline{H}_3$);
15. $C_{23}H_{48}NO_3P$; dibutyl ester 1-N(decylamino)cyclopentane phosphonic acid; yield 76.79%, oil; ^{1}H-NMR: 4.05–3.98 (q, 4H, OCH_2); 2.67–2.62 (t, 2 H, NH-$C\underline{H}_2$); 1.68–1.58 (m, 12 H, $C\underline{H}_{2(ring)}$, $OCH_2C\underline{H}_2$, NH-$CH_2C\underline{H}_2C\underline{H}_2$); 1.40–1.22 (m, 20 H, $C\underline{H}_{2(ring)}$, $OCH_2CH_2C\underline{H}_2$, NH-$CH_2CH_2CH_2(C\underline{H}_2)_6$); 0.93–0.84 (m, 9 H, $O(CH_2)_3C\underline{H}_3$, NH-$(CH_2)_9C\underline{H}_3$);
16. $C_{16}H_{34}NO_3P$; dibutyl ester 1-N(etanoloamino)cyclohexane-phosphonic acid; yield:?; oil; ^{1}H-NMR: 4.19–4.12 (m, 4 H, OCH_2); 3.77–3.74 (t, 2 H, NH-$C\underline{H}_2$); 3.30–3.27 (t. 2 H, NH-$CH_2C\underline{H}_2$); 2.11–2.06 (m, 2 H, $C\underline{H}_{2(ring)}$); 1.87–1.81 (m, 2 H, $C\underline{H}_{2(ring)}$); 1.67–1.59 (m, 14 H, $OCH_2C\underline{H}_2C\underline{H}_2$, $C\underline{H}_{2(ring)}$); 0.85–0.79 (m, 6 H, $O(CH_2)_3C\underline{H}_3$);
17. $C_{19}H_{40}NO_3P$; dipropyl ester of 1-N(n-octylamino)cyclopentane phosphonic acid; yield: 80.8%, (gel: ^{1}H-NMR: 4.04–3.97 (m, 4 H, OCH_2); 2.7–2.65 (t, 2 H, NH-$C\underline{H}_2$); 1.98–1.94 (m, 2 H, NH-$CH_2C\underline{H}_2$); 1.76–1.61 (m, 10 H, NH-$CH_2CH_2(C\underline{H}_2)_5$); 1.38–1.25 (m, 12 H, $C\underline{H}_{2(ring)}$, $OCH_2C\underline{H}_2$); 0.99–0.92 (t, 6 H, $OCH_2CH_2C\underline{H}_3$); 0.88–0.84 (t. 3 H, NH-$(CH_2)_7C\underline{H}_3$);
18. $C_{18}H_{38}NO_3P$; dibutyl ester 1-N(n-pentyloamino)cyclopentane phosphonic acid; yield: 90.97%, oil; ^{1}H-NMR: 4.11–4.01 (m, 4 H, OCH_2); 2.69–2.67 (m, 2 H, N-$C\underline{H}_2$); 1.97–1.95 (m, 2 H, HN-$CH_2C\underline{H}_2$); 1.77–1.62 (m, 10 H, $C\underline{H}_{2(ring)}$, $OCH_2C\underline{H}_2$, HN-$CH_2CH_2C\underline{H}_2$); 1.44–1.3 (m, 10 H, $C\underline{H}_{2(ring)}$, $OCH_2CH_2C\underline{H}_2$, HN-$CH_2CH_2CH_2C\underline{H}_2$); 0.96–0.88 (m, 9 H, $O(CH_2)_3C\underline{H}_3$, NH-$(CH_2)_4C\underline{H}_3$);

19. $C_{28}H_{58}NO_3P$; dibutyl ester 1-N(n-decylamino)p-tetrabutylocyclohexane phosphonic acid; yield: 80.9%, oil; ^{1}H-NMR: 4.06–4.0 (m, 4 H, OCH_2); 2.69–2.67 (m, 2 H, HN-C$\underline{H}_2$); 1.84–1.83 (m, 2 H, HN-$CH_2C\underline{H}_2$); 1.66–1.59 (m, 6 H, $OCH_2C\underline{H}_2$, HN-$CH_2CH_2C\underline{H}_2$); 1.46–1.34 (m, 10 H, $OCH_2CH_2C\underline{H}_2$, $HN(CH_2)_3CH_2CH_2CH_2$); 1.3–1.25 (m+s, 14 H, $C\underline{H}_{2(ring)}$, HN-$(CH_2)_6CH_2CH_2CH_2$); 0.96–0.91 (t, 9 H. $O(CH_2)_3C\underline{H}_3$, HN-$(CH_2)_9C\underline{H}_3$); 0.84 (s, 9 H, C-$(C\underline{H}_3)_3$);

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