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The Synthesis of α-Amino Phosphonic Acids

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Only one amino phosphonic acid has been found in nature; Ciliatin (**1**), the β-amino acid, was isolated from rumen ciliate of a ruminant in 1959 by Horiguchi *et al.*[1] and later found by Quin in protozoa, in certain coelenterata, in some fresh-water mollusks, in bovine brain and in caprin liver.[2,3] Although none of the α-amino alkyl phosphonic acids has yet been found in living organisms, they possess a certain biological activity.[4] So it is interesting to know how the physical property and the biological activity will be affected by substitution of the carboxyl group with other acidic moieties, such as sulfonyl, arsenyl and phosphonyl groups, in the α-amino acid. In the first stage, several amino phosphonic acids were synthesized as analogues of essential amino acids.

Although many investigators have reported the synthesis of some amino phosphonic acids, especially aromatic or long-chain alkyl amino phosphonic acids,[5~12] synthesis of such compounds as in this paper has not been acomplished yet. Berlin *et al.*[11] synthesized the phosphonic acid starting from aromatic acyl chloride. This method served us for preparing our compounds starting from aliphatic acyl chlorides. Figure 1 shows the synthetic route of the valine-type derivative, α-amino-β-methyl propylphosphonic acid.

Diethyl *iso*-butyryl phosphonate (**3**), obtained by reaction of *iso*-butyryl chloride (**2**) with triethyl phosphite at room temperature, was converted to the corresponding oxime (**4**) by treating with hydroxylamine hydrochloride in absolute ethanol. The oxime (**4**) was hydrogenated over Raney-nickel catalyst to give

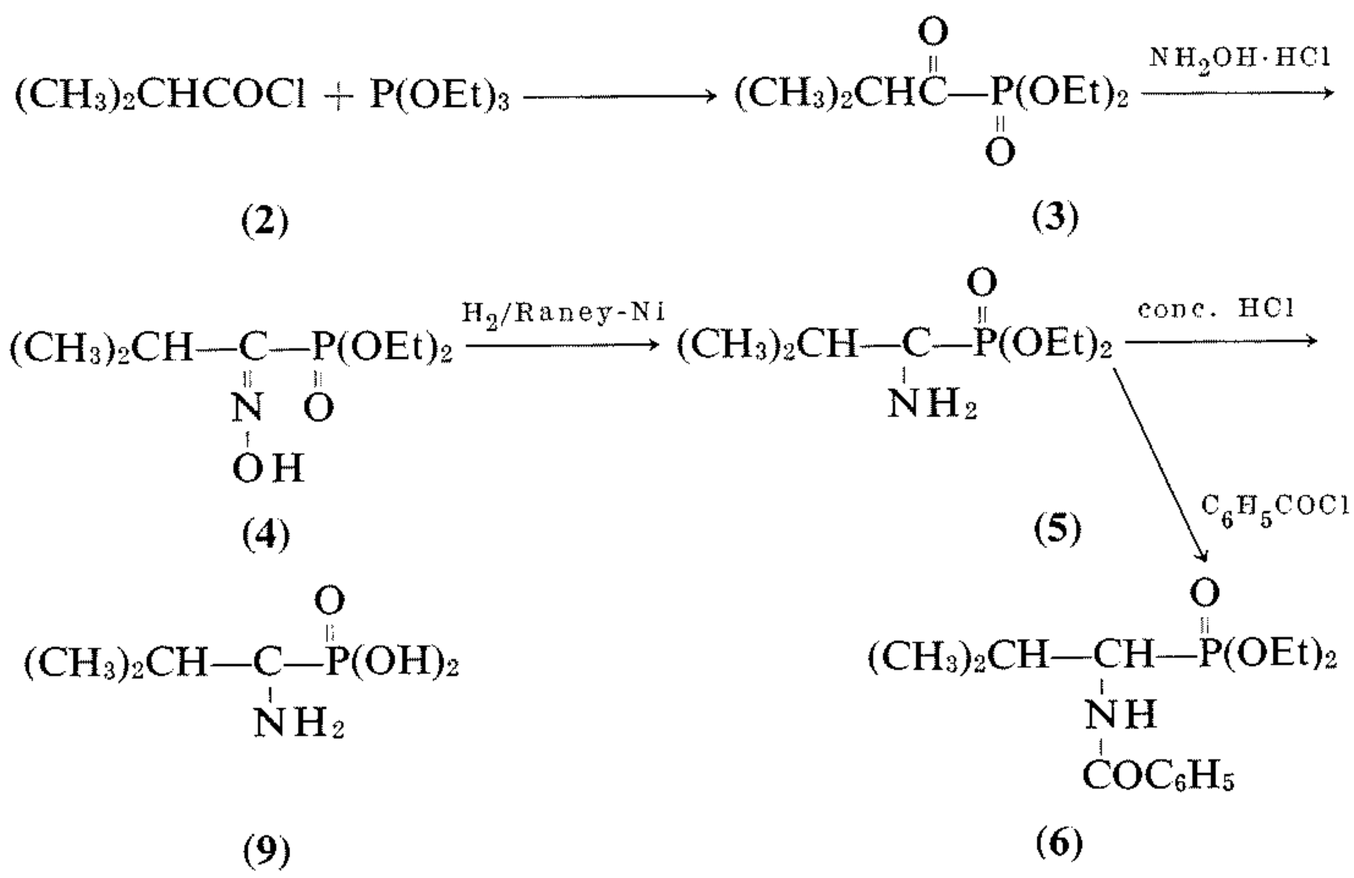

FIG. 1

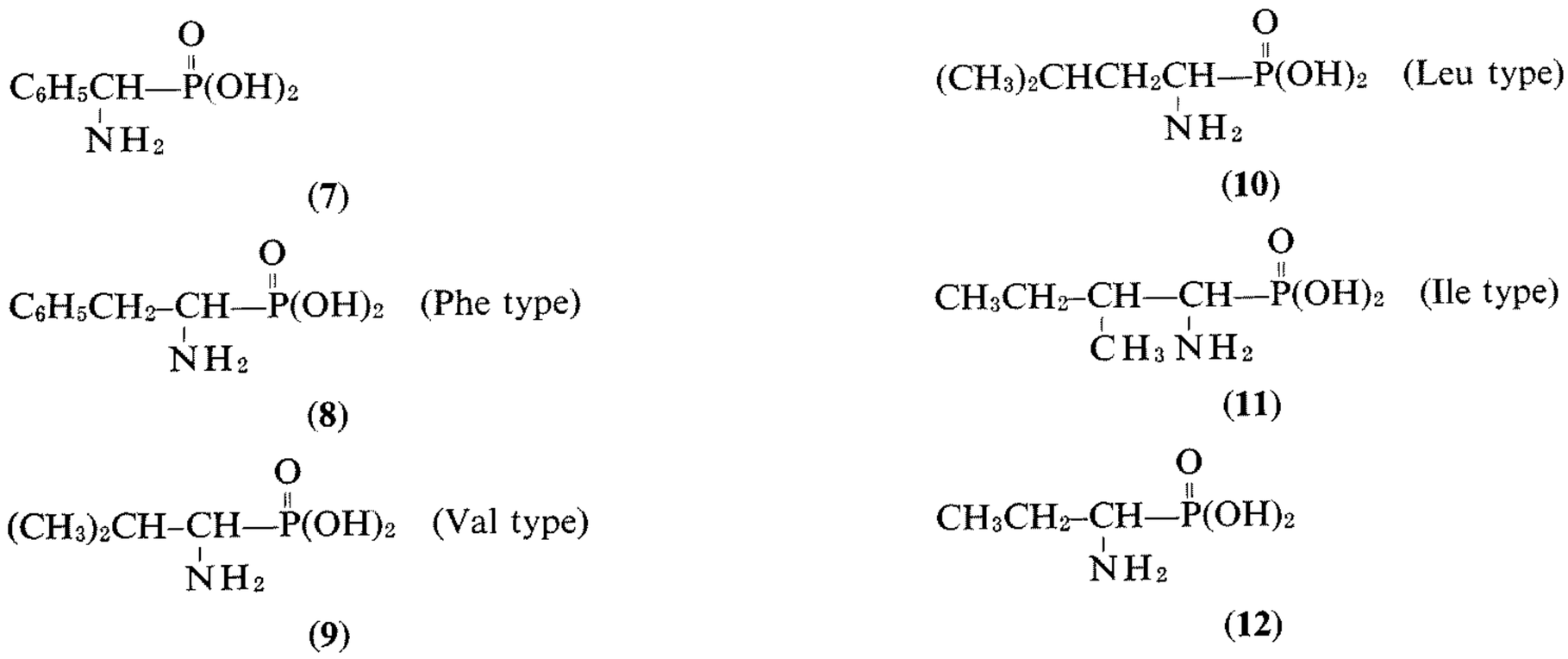

FIG. 2

diethyl α-amino-β-methylpropyl phosphonate (**5**) which was identified as its benzoyl derivative (**6**). The amino ester (**5**) was hydrolyzed with concentrated hydrochloric acid to afford the amino phosphonic acid (**9**). Figure 2 shows the structure of the phosphonic acids prepared in the present investigation.

Biological activities of these amino phosphonic acids are now under investigation and the detailed results will be reported elsewhere.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were determined with a Hitachi EPI-G21 spectrometr. The NMR spectra were determined with a Valian HA-100 NMR spectrometer.

Diethyl isobutyryl phosphonate (*3a*). Isobutyryl chloride (25.9 g) was added dropwise to triethyl phosphite (43.9 g) with stirring under nitrogen atmosphere at 30~40°C. After the addition had been complete, the mixture was allowed to stand overnight at room temperature. Distillation of the reaction mixture afforded diethyl isobutyryl phosphonate (3a, 43.9 g). Bp 75~83°C/3~4 mmHg, $N_D^{25.5}$: 1.4242, yield: 93.5%, IR ν_{max}^{film} cm^{-1}: 1690 (–CO–P–), 1260 and 1020 (–P(O)–$(OEt)_2$).

Diethyl benzoyl phosphonate (*3b*). Bp 120~125°C/2~3 mmHg, yield: 67.7%, IR ν_{max}^{film} cm^{-1}: 1655 (–CO–P), 1255 and 1040–1010 (–P(O)–$(OEt)_2$).

Diethyl phenyl acetyl phosphonate (*3c*). Bp 120~130°C/3 mmHg, yield: 72.0%, IR ν_{max}^{film} cm^{-1}: 1730 (–CO–P–), 1255 and 1030 (–P(O)–$(OEt)_2$).

Diethyl valeryl phosphonate (*3d*). Bp 75~85°C/3~4 mmHg, yield: 68.6%, IR ν_{max}^{film} cm^{-1}: 1690 (–CO–P–) 1260 and 1050–1010 (–P(O)–$(OEt)_2$).

Diethyl α-methyl butyryl phosphonate (*3e*). Bp 80~83°C/3 mmHg, yield: 84.5%, $N_D^{25.6}$=1.4272, IR ν_{max}^{film} cm^{-1}: 1690 (–CO–P–), 1255 and 1060–1010 (–P(O)–$(OEt)_2$).

Diethyl propionyl phosphonate (*3f*). Bp 75~80°C/3 mmHg, yield: 53.4%, IR ν_{max}^{film} cm^{-1}: 1695 (–CO–P–), 1260 and 1050–1010 (–P(O)–$(OEt)_2$).

Diethyl α-amino-β-methylpropyl phosphonate (*5*). The phosphonate (**3**, 43.0 g) was added at once to the mixture of 19.0 g of $NH_2OH \cdot HCl$, 24.5 g of pyridine and 50 ml of anhydrous ethanol. The whole solution was allowed to stand for 48 hr with stirring at room temperature, and the solvent was removed *in vacuo*. The residual oil was added to the cold aqueous hydrochloric acid (100 ml) and extracted with CH_2Cl_2 (20 ml × 5). The extract was washed with dil. hydrochloric acid several times and then with water, aqeuous $NaHCO_3$ and water, successively. Concentration of the extract gave the crude oxime (**4**, 37.7 g). IR ν_{max}^{film} cm^{-1}: 3160 (–OH), 1235 and 1020 (–P(O)–$(OEt)_2$). The crude oxime (28 g) was hydrogenated over Raney-Ni (w-4) catalyst under 80 kg/cm^2 at 100°C for 10 min to afford the crude amino phosphonate (**5**, 22.6 g). IR ν_{max}^{film} cm^{-1}: 3400 (–NH_2), 1230 and 1020 (–P(O)–$(OEt)_2$). *N*-Benzoylderivative (6): mp 95.5~96.5°C, recrystallized from benzene-hexane. IR ν_{max}^{KBr} cm^{-1}: 3300 and 3250 (–NH–), 1650 (–CO–N), 1600 and 1580 (–C_6H_5), 1240 and 1040 (–P(O)–$(OEt)_2$), NMR $\tau_{TMS}^{CDCl_3}$: 8.88 (6H, doublet, J=7 Hz, $(CH_3)_2$–C–), 8.68 (6H, quartet, J=7 Hz, $(CH_3$–C–$)_2$–O–P), 5.84 (4H, sextet, Me–CH_2–O–P–O–CH_2–), 5.20~5.55 (1H, multiplet, –N–CH(–R)–P–), 3.2~3.4 (1H, broad doublet, –NH–CO–, disappeared by D_2O exchange), 2.1–2.65 (5H, multiplet, aromatic proton), *Anal.* Found: C, 57.42; H, 7.74; N, 4.42, Calcd. for $C_{11}H_{24}O_4NP$: C, 57.60; H, 7.72; N, 4.47.

Diethyl α-aminobenzyl phosphonate hydrochloride. Colorless needles (recrystallized from benzene-EtOH), mp 147~148°C, IR ν_{max}^{KBr} cm^{-1}: 3050~2550 ($-\overset{\oplus}{N}H_3\overset{\ominus}{Cl}$) 1600 (–$C_6H_5$), 1250 and 1030 (–P(O)–$(OEt)_2$), *Anal.* Found: C, 46.96; H, 6.22; N, 4.97; Cl, 12.48, Calcd. for $C_{11}H_{19}O_3NPCl$: C, 47.58; H, 6.51; N, 5.04; Cl, 12.75.

Diethyl α-benzoylamino-β-phenylethyl phosphonate. Colorless prism (recrystallized from benzene-hexane), mp 156.0~157.5°C, IR ν_{max}^{KBr} cm^{-1}: 3250 (–NH–), 1650 and 1530 (–CO–N), 1600 and 1580 (–C_6H_5) 1250, 1230 and 1050, 1030 (–P(O)–$(OEt)_2$), NMR $\tau_{TMS}^{CDCl_3}$: 8.72 (6H, double triplet J_{H-H}=7 Hz·J_{H-P}=9 Hz, $(CH_3$–C–$)_2$–O–P), 6.60~7.00 (2H, multiplet Ph-CH_2–C–P), 5.70~6.10 (4H, multiplet $(Me$–$CH_2)_2$–O–P) 5.75~6.25 (1H multiplet, –N–CH(–R)–P–), 2.80~3.00 (1H broad doublet, –NH–CO, disappeared by D_2O exchange) 2.20~2.80 (10H multiplet, aromatic proton), *Anal.*, Found: C, 62.93; H, 6.60; N, 3.85, Calcd for $C_{19}H_{24}O_4NP$: C, 63.25; H, 6.67; N, 3.89.

Diethyl α-benzoylamino-γ-methylbutyl phosphonate. Colorless prism (recrystallized from benzene-hexane), mp 140~141.5°C, IR ν_{max}^{KBr} cm^{-1}: 3250 (–NH–), 1645 and 1530 (–CO–), 1600 and 1580 (–C_6H_5), 1250 and 1020 (–P(O)–$(OEt)_2$), NMR $\tau_{TMS}^{CDCl_3}$: 9.04 (6H, doublet, Ja=5 Hz $(CH_3)_2$–C–C) 8.68 (6H double triplet J_{H-H}=7 Hz J_{H-P}=7.5 Hz $(CH_3$–C$)_2$–O–P 8.6~9.0 (1H, multiplet, Me_2CH–C–) 8.26 (2H broad singlet Me_2C–CH_2–C) 5.70~6.10 (4H, multiplet, $(MeCH_2)_2$C–O–P) 5.0~5.50 (1H, multiplet C–CH(–N)–P) 3.10~3.30 (1H broad doublet, disappeared by D_2O exchange, –NH–) 2.10~2.60 (5H aromatic proton), *Anal.* Found: C, 58.79; H, 8.02; N, 4.25, Calcd. for $C_{19}H_{26}O_4NP$: C,

58.75; H, 8.02; N, 4.28.

Diethyl α-benzoylamino-β-methylbuty phosphonate. Colorless prism (recrystallized from benzene-hexane), mp, 103.5～104.5°C, IR ν_{max}^{KBr} cm^{-1}: 3295 (–NH–), 1645 and 1530 (–CO–N), 1600 and 1850 ($-C_6H_5$), 1240 and 1030 (–P(O)–$(OEt)_2$), NMR $\tau_{TMS}^{CDCl_3}$: 8.70～9.20 (8H, 2–CH_3 and –CH_2– (alkyl chain) 8.66 (3H quartet J=6.5 Hz $(CH_3–C)_2$–O–P) 7.80～8.20 (1H multiplet Et–CH(Me)–C), 5.60～6.05 (2H, multiplet, $(Me–CH_2)_2$–O–P) 5.00～5.40 (1H, multiplet, –CH–N–CO–) 3.20～3.40 (1H, multiplet, –C–NH–CO–, disappeared by D_2O exchange), 2.10～2.60 (5H, aromatic proton), *Anal* Found: C, 58.97; H, 8.16; N, 4.32, Calcd. for $C_{19}H_{26}O_4NP$: C, 58.75; H, 8.02; N, 4.28.

Diethyl α-benzoylamino-propyl phosphonate. Colorless prism (recrystallized from benzene-hexane), mp 114～115°C, IR ν_{max}^{KBr} cm^{-1}: 3250 (–NH–), 1645 and 1520 (–CO–N–), 1600 ($-C_6H_5$), 1220 and 1020 (–P(O)–$(OEt)_2$), NMR $\tau_{TMS}^{CDCl_3}$: 8.94 (3H, triplet J=7 Hz, CH_3–C–C–), 8.68 (6H quartet, J=8 Hz, coupled with –CH_2 and –P–、$(CH_3–C)_2$–O–P), 7.85～8.40 (2H, multiplet, Me CH_2–C–P), 5.70～6.05 (4H, multiplet, $(Me–CH_2)_2$–O–P), 5.10～5.60 (1H, multiplet, –C–CH(–N)–P) 3.10～3.30 (1H, broad doublet, disappeared with D_2O exchange, –NH–CO–), 2.10～2.70 (5H aromatic proton), *Anal.* Found: C, 55.90; H, 7.40; N, 4.63, Calcd, for $C_{14}H_{22}O_4NP$: C, 56.20; H, 7.41; N, 4.68.

α-Amino-β-methylpropyl phosphonic acid (*9*). Crude amino phosphonate (**5**, 20 g) was hydrolyzed by refluxing with 60 ml of conc. HCl for 48 hr. The reaction mixture was extracted with benzene to remove a neutral fraction, and the resulting aqueous layer was evaporated *in vacuo* to give a solidified crude product. Twice recrystallization from H_2O–MeOH afforded 8.9 g of pure α-amino-β-methylpropyl phosphonic acid (**9**). mp 276～278°C, yield from (3): 40.9%, IR ν_{max}^{KBr} cm^{-1}: 3100～2550 and 1590 (–NH_2), 2250 (–P(O)–$(\underline{OH})_2$), 1050 (–P(O)–), *Anal.* Found: C, 31.46; H, 7.94; N, 9.14, Calcd. for $C_4H_{11}O_3NP$: C, 31.39; H, 7.89; N, 9.13.

α-Amino benzyl phosphonic acid (*7*). Identified as its hydrochloride. Colorless needles (recrystallized from MeOH–H_2O), mp 287～289°C, yield from (3b): 40.2% IR ν_{max}^{KBr} cm^{-1}: 3050～2600 ($-\overset{\oplus}{N}H_3\overset{\ominus}{Cl}$), 1590 and 1510 ($C_6H_5$–), 1240 (–P(O)–OH), *Anal.* Found: C, 44.98; H, 5.65; N, 7.42, Calcd. for $C_7H_{11}O_3NPCl$: C, 44.90; H, 5.39; N, 7.49.

α-Amino-β-phenylethyl phosphonic acid (*8*). Colorless needles (recrystallized from MeOH–H_2O), mp 276～277°C, yield from (3c): 26.7%, IR ν_{max}^{KBr} cm^{-1}: 3050～2550 ($-\overset{\oplus}{N}H_3$), 2300 and 1240 (–P(O)–$(OH)_2$) 1600 and 1520 (C_6H_5–), *Anal.* Found: C, 47.38; H, 6.60; N, 6.08, Calcd. for $C_8H_{12}O_3NP$: C, 47.79; H, 5.97; N, 6.96.

α-Amino-γ-methylbutyl phosphonic acid (*10*). Colorless needles (recrystallized from MeOH–H_2O), mp 279～280°C, yield from (3d); 26.9%, IR ν_{max}^{KBr} cm^{-1}: 3100～2600 ($-\overset{\oplus}{N}H_3$), 2275 and 1180 (–P(O)–$(OH)_2$), 1600 (C_6H_5–), *Anal.* Found: C, 35.80; H, 8.48; N, 8.58, Calcd. for $C_5H_{14}O_3NP$: C, 35.70; H, 8.44; N, 8.38.

α-Amino-β-methylbutyl phosphonic acid (*11*). Colorless needles (recrystallized from MeOH–H_2O), mp 271～272°C, yield from (3e): 7.2%, IR ν_{max}^{KBr} cm^{-1}: 3100～2550 ($-\overset{\oplus}{N}H_3$), 2260 and 1180 (–P(O)–$(OH)_2$), *Anal.* Found: C, 35.21; H, 8.13; N, 8.53, Calcd. for $C_5H_{14}O_3NP$: C, 35.70; H, 8.44; N, 8.38.

α-Aminoethyl phosphonic acid (*12*). Isolated as its hydrochloride. Colorless needles (recrystallized from EtOH), mp 281～283°C, yield from (3f): 12.5%, IR ν_{max}^{KBr} cm^{-1}: 3400～2600 ($-\overset{\oplus}{N}H_3$), 2300 and 1180 (–P(O)–$(OH)_2$), *Anal.* Found: C, 21.08; H, 6.53; N, 8.10, Calcd. for $C_3H_{11}O_3NPCl$: C, 20.55, H, 6.32; N, 7.98.

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