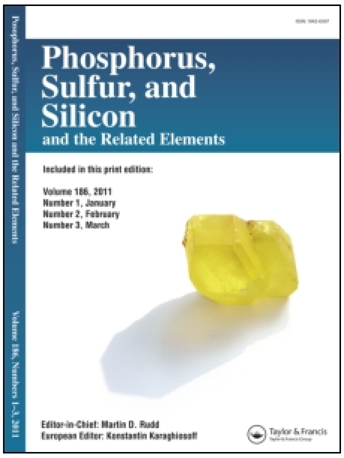

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

N_α,N_ω-DIPHOSPHONO-, DIPHOSPHINO-METHYL-*L*-α,ω-DIAMINOCARBOXYLIC ACIDS

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To cite this Article Natchev, Ivan A.(1988) 'N_α,N_ω-DIPHOSPHONO-, DIPHOSPHINO-METHYL-*L*-α,ω-DIAMINOCARBOXYLIC ACIDS', Phosphorus, Sulfur, and Silicon and the Related Elements, 37: 3, 143 — 148
To link to this Article: DOI: 10.1080/03086648808079029
URL: http://dx.doi.org/10.1080/03086648808079029

Phosphorus and Sulfur, 1988, Vol. 37, pp. 143–148
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N_α,N_ω-DIPHOSPHONO-, DIPHOSPHINO-METHYL-*L*-α,ω-DIAMINOCARBOXYLIC ACIDS

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(Received June 28, 1987; in final form January 6, 1988)

Treatment of *N*-hydroxymethylated lactames 1,4-diamino-*L*-butanoic acid—**1**, *L*-ornithine—**2**, and *L*-lysine—**3** is carried out with phosphorus trichloride to give the phosphonic acids **4**, **5** and **6**, and with methyldichlorophosphine to give the methylphosphinic acids **7**, **8** and **9**, which after alkaline hydrolysis liberate the carboxylic acids **10–15**. Analogously, from the *L*-lysine derivative—**16** and the aminomethylphosphonic acid derivative **18**, the acids **15** and **19** are obtained after hydrolysis. The herbicidal activity of the lysine derivative **15** is established.

RESULTS AND DISCUSSION

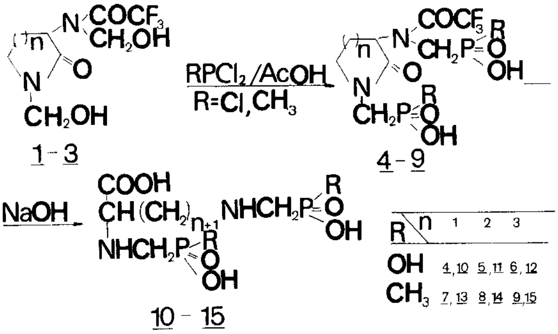
Pike[1] and Engelmann[2] were the first to carry out treatment of *N*-hydroxymethylated amides with phosphorus trichloride and acetic acid to *N*-phosphonomethylamide. Later, independently of each other, our laboratory[3] and Wong[4] succeeded in performing an analogous treatment of 1,4-dihydroxymethyl-2,5-piperazinedione.

Until now such an interaction of phosphorus trichloride with *N*-hydroxymethylated lactames is not described.

Considerably less investigations have been carried out with compounds containing amino- and amide group and alkyldichlorophosphines. Mastalerz[5] has treated carbonyl compounds (aldehydes and ketones) and alkylcarbamates with alkyl(aryl) dichlorophosphines and acetic acid, and after hydrolysis has obtained 1-aminoalkanephosphinic acids. Maier[6] subjected *N*-benzyglycine and formaldehyde to a treatment with alkyldichlorophosphine and an equivalent amount of water. After debenzylation, he obtained alkylphosphinic analogues of glyphosate. Till now, we have not noticed in the literature a description of the interaction of *N*-hydroxymethylated amides and lactames with methyldichlorophosphine and acetic acid.

Continuing our studies on the synthesis of phosphono- and phosphino analogues and derivatives of the natural α-amino-carboxylic acids, we have chosen as starting substances the lactames of 1,4-diamono-*L*-butanoic acid,[7] *L*-ornithine[8] and of *L*-lysine.[9] The synthesis of the protected lactames **1–3** and the antispasmodic activity of *N*-ditrifluoroacetylated products will be published later.

Treatment of the di(hydroxymethyl)derivatives **1–3** with phosphorus trichloride was carried out by mixing simply the components with a small excess of chloride (Scheme 1). Without isolating the intermediate chlorinated products, the reaction



Scheme 1

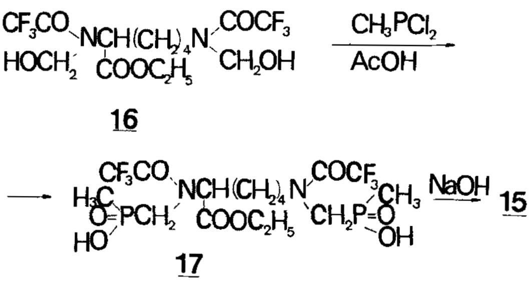
mixture is treated with acetic acid. Exclusion of humidity is necessary for the complete running of the interaction. Spectroscopic and elemental analysis showed that condensation with the two hydroxymethyl groups has taken place, giving the diphosphonomethyl derivatives **4–6** in yields of about 65–70%.

The interaction between the dihydroxymethylated lactames **1–3** and methyldichlorophosphine has a lower reactivity in comparison with phosphorus trichloride, it is better to carry out the interaction in an inert solvent medium (e.g. chloroform or tetrachloroethane) by boiling the components for 1 hour. Avoiding side reactions would require dry atmosphere and continuous removal of the hydrogen chloride released by passing dry argon, or nitrogen, through the reaction mixture. Without isolating the intermediate products, 1.2 eq. acetic acid is added dropwise within one hour and then the mixture is boiled for one hour. The volatile components are removed in vacuum and the reaction mixture is worked up as above. The yield of the methylphosphinic acid derivatives **7–9** is about 50–60%.

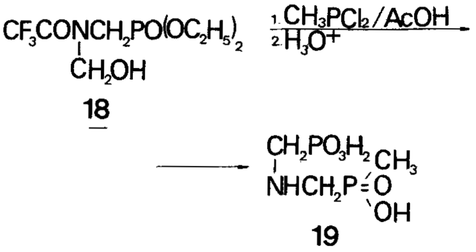
Simultaneous hydrolysis of the lactame and trifluoroacetyl groups was achieved by treatment of **4–9** with sodium hydroxide. The N_α,N_ω-diphosphonyl-, diphosphinylmethylated 1,4-diaminobutanoic acid, ornithine and lysine, **10–15**, were isolated with a yield of approx. 95%.

The same products, **10–15**, were isolated by treatment of the dihydroxymethyl derivatives **1–3** with triethylphosphite and diethoxymethylphosphonite (cf. our subsequent publications). With a view to check the versatility of the interaction discussed above, we performed experiments with N_α,N_ε-di(trifluoroacetyl)-N_α,N_ε-di(hydroxymethyl)-*L*-lysine ethyl ester, **16**, and *N*-trifluoroacetyl-*N*-hydroxymethyl-aminomethylphosphonic acid diethyl ester, **18** (cf. our subsequent publications).

Treatment of the lysine derivative **16** with methyldichlorophosphine and acetic acid gave the dimethylphosphinyl-derivative **17** with a yield of about 30%. Mineral acid hydrolysis of **17** led to the isolation of the *L*-lysine derivative **15**. The interaction of **18** with methyldichlorophosphine and acetic acid proceeds analogously. No isolation of the separate reaction products is necessary. The reaction mixture is subjected to acidic hydrolysis to give the acid **19** (yield about 45%, Scheme 2 and 3).



Scheme 2



Scheme 3

The herbicidal activity of the lysine derivative **15** has been studied towards Sorghum Halepense. Quantities of 280 g/1000 m^2 killed the weed entirely in just two weeks. To compare the activity of the *D*-, *DL*- and *L*-forms, we employed the test of Tzibulskaya[10] with seeds from mono- and dicotyledons (cucumbers and wheat). The method correlates very well with the results from field experiments and can be successfully used to acquire preliminary information about the presence or absence of herbicidal activity in any compounds under investigation.

Thus, 96 hours after a 10^{-4} molar solution of *L*-**15** was applied to monocotyledons, its activity was found to be 100%. Dicotyledons, treated with the same concentration, showed 72.3% activity (a 10^{-4} molar solution comes up to 320 g active compounds per 1000 m^2. It is interesting to note that the *DL*-form possesses a statistically reliable herbicidal activity, which is almost equal to that of the *L*-form, whereas the *D*-form has a much higher activity. The low toxicity of the lysine derivative ($LD_{50} = 960$ mg/kg per os in mice), the pronounced herbicidal activity and, last but not least, the easy availability of *DL*-lysine and methyldichlorophosphine, promise excellent results with *DL*-**15** in further investigations and its eventual application in agriculture.

Surprisingly, the diphosphono-derivative, **12**, of *L*-lysine has a lower activity in comparison with that of **15**, while, reversely, its toxicity is higher.

The herbicidal and bactericidal activity of the phosphino-phosphono analogue of glycine, **19**, will be the subject of a separate investigation.

EXPERIMENTAL

1. General notes. Elemental analysis, IR-spectra, HPLC, GC, and $[\alpha]_D^{20}$—on a Perkin–Elmer instrument; ^1H NMR-spectra—on Jeol-100 MHz and Bruker-250 MHz; Mass-spectra—on LKB and

Varian; m.p.'s—on a Koefler apparatus; reagents and solvents—from Merck and Aldrich; TLC—silica gel plates, phosphomolybdate and ninhydrine detection.

2. *Synthesis of the diphosphonomethylderivatives* **4–9**. Each of the dihydroxy methylderivatives **7–9** (0.1 M) and phosphorus trichloride (30.21 g, 0.22 M) are placed in an Erlenmeyer flask, closed with a removable plug. The mixture is stirred magnetically for 1 hour at room temperature, and then stirring is kept up for another 15 mins. at 50–60°C. The volatile components are evaporated in vacuum to dryness. The resultant jelly-like mass is dissolved in dry tetrachloromethane (100 ml) and cold acetic acid (30.03 g, 0.5 M) is added. The mixture is left for 24 hours at room temperature and distilled in vacuum to dryness. Crushed ice (150 g) is added to the amber-coloured oily residue. An amorphous mass is separated, left overnight at room temperature, decanted and recrystallized from water to give:

L-*N*-Dihydroxyphosphonylmethyl-2-oxo-pyrrolidinyl-3-*N*-trifluoroacetyl aminomethylphosphonic acid, **4**: $C_8H_{13}F_3N_2O_8P_2$; 26.24 g (68.3%); m.p. approx. 220°C (decomp.); IR (KBr): 2860–2420, 2300–2100, 1750, 1645, 1310, 1250, 1180, 980, 820, 770, 625; ^{1}H NMR ($D_2O + NaOD$): 1.71 (2 H, m, NCH_2CH_2), 3.1–3.5 (6 H, m, $PCH_2 \times 2$, NCH_2CH_2), 4.44 (1 H, t, $COCHCH_2$), plus four exchangeable $PO_3H_2 \times 2$-protons, which appear as a broad band in DMSO-*d*; Mass-spect. (M^+/e): 384.142/fragments—95 (100%); R_f: 0.65 (*n*-BuOH·25% $NH_4OH = 4:1$); $[\alpha]_D^{20}$ +68.3°, $c = 1$, 0.1 N NaOH;

Calc'd: C 25.01 H 3.41 N 7.29%
Found: C 25.42 H 3.22 N 7.16%

L-[*N*-(Dihydroxyphosphonylmethyl-2-oxo-piperidinyl-3)-*N*-trifluoroacetyl]aminomethylphosphonic acid, **5**: $C_9H_{15}F_3N_2O_8P_2$: 28.39 g (71.3%); m.p. approx. 200°C (decomp.); IR (KBr): 2820–2515, 2340–2090, 1700, 1650, 1305, 1245, 1080, 970, 800, 730, 645; ^{1}H NMR ($D_2O + NaOD$): 1.44 (4 H, m, $CH_2 \times 2$), 2..93 and 3.46 (4 H, d, $J = 14$ Hz, $PCH_2 \times 2$), 3.14 (2 H, t, NCH_2CH_2), 4.33 (1 H, t, $CHCH_2$); Mass-spect. (M^+/e): 398.168/fragments −95 (100%); R_f: 0.72 (in the above system); $[\alpha]_D^{20}$ +48.3° (in the above medium);

Calc'd: C 27.15 H 3.80 N 7.04%
Found: C 27.44 H 3.92 N 7.11%

D-, *DL*-, *L*-[*N*-(Dihydroxyphosphonylmethyl-2-oxo-hexahydroazepinyl-3)-*N*-trifluoroacetyl]aminomethylphosphonic acid, **6**: $C_{10}H_{17}F_3N_2O_8P_2$; 27.12 g (65.8%); m.p., the *D*-, *DL*-, and *L*-forms melt with decomposition at about 240°C; IR (KBr): 2800–2500, 2350–2100, 1750, 1645, 1305, 1240, 1085, 960, 810, 720, 630; ^{1}H NMR ($D_2O + NaOD$): 1.38 (6 H, m, $CH_2 \times 3$), 3.0–3.5 (6 H, m, $PCH_2 \times 2$, NCH_2CH_2), 4.18 (1 H, t, $CHCH_2$); Mass-spect. (M^+/e): 412.194/fragments −95(199%); R_f: +0.80 (in the above system); $[\alpha]_D^{20}$ +66.3° and −68.2° (in the above medium);

Calc'd: C 29.14 H 4.16 N 6.80%
Found: C 29.33 H 4.12 N 6.71%

3. *Synthesis of the methylphosphinomethylated* **7–9**. A mixture of each of the lactames **1–3** (0..1 M) and methyldichlorophosphine (25.79 g, 0.22 M) is boiled for 1 hour in dry tetrachloromethane (200 ml), accompanied by a continuous current of dry argon or nitrogen through the mixture. Cold acetic acid (15.01 g, 0.25 M) is gradually added for 1 hour. The mixture is boiled for another hour and evaporated in vacuum to dryness. The residue is worked up as above. Recrystallization with ethanol affords the following products:

L-[[*N*-(Hydroxy-methylphosphinyl)methyl]-2-oxo-pyrrolidinyl-3-*N*-trifluoroacetyl] aminomethylmethylphosphinic acid, **7**: $C_{10}H_{17}F_3N_2O_6P_2$; 20.26 g (53.3%); m.p. 251–254°C (decomp.); IR (KBr): 2740–2480, 2310, 2110, 1750, 1640, 1310–1240, 980–720, 630; ^{1}H NMR ($D_2O + NaOD$): 1.66 (2H, m, NCH_2CH_2), 1.89 and 2.18 (6 H, d, $J = 18$ Hz, $PCH_3 \times 2$), 3.1–3.6 (6 H, m, $PCH_2 \times 2$, NCH_2CH_2), 4.33 (1 H, t, $CHCH_2$), plus two exchangeable protons in DMSO-d_6, 10.4–10.7 (2 H, br., $POH \times 2$); Mass-spect. (M^+/e): 380.196/380; R_f: 0.68 (*n*-BuOH : pyr : AcOH H_2O = 16:2:5:1); $[\alpha]_D^{20}$ +78.2°, $c = 1$, 0.1 N, NaOH;

Calc'd: C 31.39 H 4.51 N 7.37%
Found: C 31.46 H 4.33 N 7.37%

L-[[*N*-(Hydroxy-methylphosphinyl)methyl]-2-oxo-piperidinyl-3-*N*-trifluoroacetyl]aminomethylphosphinic acid, **8**: $C_{11}H_{19}F_3N_2O_6P_2$; 18.57 g (74.1%); m.p. 236–238°C (decomp.); IR (KBr): 2740–2480, 2315–2100, 1700, 1650, 1310–1250, 975–720, 630; ^{1}H NMR ($D_2O + NaOD$): 1.48 (4 H, m, $CH_2 \times 2$), 1.84 and 2.05 (6 H, d, $J = 18$ Hz, $\mathrm{PCH_3} \times 2$), 3.1–3.6 (6 H, m, $\mathrm{PCH_2} \times 2$, $\mathrm{NC\underline{H}_2CH_2}$), 4.30 (1 H, t, $\mathrm{C\underline{H}CH_2}$), plus two exchangeable $\mathrm{PO\underline{H}} \times 2$-protons; Mass-spect. ($\mathrm{M^+}$/e) 393.223/394; $\mathrm{R_f}$: 0.76 (in the above system); $[\alpha]_D^{20}$ +57.2°, $c = 1$, 0.1 N NaOH;

Calc'd: C 33.51 H 4.86 N 7.11%

Found: C 33.44 H 5.02 N 7.20%

D-, *DL*-, *L*-[[*N*-(Hydroxy-methylphosphinyl)methyl]-2-oxo-hexahydroacepinyl-3-*N*-trifluoroacetyl]aminomethyl-methylphosphinic acid, **9**: $\mathrm{C_{12}H_{21}F_3N_2O_6P_2}$; 21.88 g (53.6%); m.p. 262–265°C (*D*-form), 253–255°C (*DL*-form), 260–262°C (*L*-form); IR(KBr): 2750–2500, 2320–2100, 1750, 1650, 1310–1245, 980–720, 630; ^{1}H NMR ($\mathrm{D_2O}$ + NaOF): 1.34 (6 H, m, $\mathrm{CH_2} \times 3$), 1.92 and 2.40 (6H, d, $J =$ 18 Hz, $\mathrm{PCH_3} \times 2$), 3.1–3.6 (6 H, m, $\mathrm{PCH_2} \times 2$, $\mathrm{NC\underline{H}_2CH_2}$), 4.25 (1 H, t, $\mathrm{C\underline{H}CH_2}$), plus two exchangeable POH × 2-protons; Mass-spect. ($\mathrm{M^+}$/e): 408.250/408; $\mathrm{R_f}$: 0.83 (in the above system); $[\alpha]_D^{20}$ + 47.2° and −51.3°, $c = 1$, 0.1 N NaOH:

Calc'd: C 35.30 H 5.18 N 6.86%

Found: C 35.48 H 5.33 N 6.72%

4. *Synthesis of the diphosphono-, diphosphinocarboxylic acids* **10–15**. Each of the lactames **4–9** (0.1 M) is heated for 1 hour at 60–70°C in 2 N NaOH (200 ml). After acidification and distillation to dryness, the organic mass is extracted with boiling ethanol and recrystallized from water to give:

1,4-Bis(dihydroxyphosphonylmethylamino)-*L*-butanoic acid, **10**: $\mathrm{C_6H_{16}N_2O_8P_2}$; 28.26 g (92.3%); m.p. over 310°C; IR (KBr): 3420–2860, 2630, 2450–2100, 1755, 1550, 1250–1200, 1050–900; ^{1}H NMR ($\mathrm{D_2O}$ + NaOD): 1.7–2.2 (4H, m, $\mathrm{CH_2} \times 2$), 2.92 and 3.78 (4H, d, $J = 16$ Hz, $\mathrm{PCH_2} \times 2$), 4.21 (1 H, t, $\mathrm{C\underline{H}CH_2}$); Mass-spect. ($\mathrm{M^+}$/e): 306.148/306; $\mathrm{R_f}$: 0.39 (*n*-BuOH:pyr:AcOH = 16:2:5:1); $[\alpha]_D^{20}$ +55.5°, $c = 1$, 0.1 N NaOH;

Calc'd: C 23.54 H 5.27 N 9.15%

Found: C 23.77 H 5.01 N 9.11%

N_α,N_δ-Bis(dihydroxyphosphinylmethyl)-*L*-ornithine, **11**: $\mathrm{C_7H_{18}N_2O_8P_2}$; 28.91 g (90.3%); m.p. approx. 300°C (decomp.); IR (KBr): 3400–2850, 2630, 2435–2100, 1750, 1555, 1250–1200, 1030–895; ^{1}H NMR ($\mathrm{D_2O}$ + NaOD): 1.7–2.2 (6 H, m, $\mathrm{CH_2} \times 3$), 2.86 and 3.29 (4 H, d, $J = 16$ Hz, $\mathrm{PCH_2} \times 2$), 4.11 (1 H, t, $\mathrm{C\underline{H}CH_2}$); Mass-spect. ($\mathrm{M^+}$/e): 320.175/320; $\mathrm{R_f}$: 0.47 (in the above system); $[\alpha]_D^{20}$ +39.5°, $c = 1$, 0.1 N NaOH;

Calc'd: C 26.26 H 5.67 N 8.75%

Found: C 26.53 H 5.39 N 8.66%

N_α,N_ε-Bis(dihydroxyphosphonylmethyl)-*D*-, *DL*-, *L*-lysine, **12**: $\mathrm{C_7H_{20}N_2O_8P_2}$; 31.52 g (94..3%); m.p. over 310°C; IR (KBr): 3425–2855, 2640, 2450–2100, 1700, 1550, 1250–1200, 1055–905; ^{1}H NMR ($\mathrm{D_2O}$ + NaOD): 1.6–2.2 (8 H, m, $\mathrm{CH_2} \times 2$), 2.90 and 3.18 (4 H, d, $J = 16$ Hz, $\mathrm{PCH_2} \times 2$), 4.22 (1 H, t, $\mathrm{C\underline{H}CH_2}$); Mass-spect. ($\mathrm{M^+}$/e): 334.202/334; R_f: 0.55 (in the above system); $[\alpha]_D^{20}$ +48.3° and −50.2°, $c = 1$, 0.1 N NaOH;

Calc'd: C 28.75 H 6.03 N 8.38%

Found: C 28.92 H 5.92 N 8.42%

1,4-Di[(hydroxy-methylphosphinyl)methylamino]-*L*-butanoic acid, **13**: $\mathrm{C_8H_{20}N_2O_6P_2}$; 28.50 g (94.3%); m.p. 286–290°C (decomp.); IR (KBr): 3380–2500, 2300–2100, 1750, 1550–1480, 1305–1200, 1000–860, 720, 640; ^{1}H NMR ($\mathrm{D_2O}$ + NaOD): 1.7–2.8 (10 H, m, $\mathrm{CH_2} \times 2$, $\mathrm{PCH_3} \times 2$), 3.08 and 3.39 (4 H, d, $J = 14$ Hz, $\mathrm{PCH_2} \times 2$), 4.18 (1 H, t, $\mathrm{C\underline{H}CH_2}$); Mass-spect. ($\mathrm{M^+}$/e): 302.203/302; $\mathrm{R_f}$: 0.55 (DMF:dioxan? $\mathrm{CHCl_3}$ = 8:7:1); $[\alpha]_D^{20}$ +70.3°, $c = 1$, 0.1 N NaOH;

Calc'd: C 31.80 H 6.67 N 9.27%

Found: C 31.62 H 6.92 N 9.31%

N_α,N_δ-Di[(hydroxy-methylphosphinyl)methyl]-*L*-ornithine, **14**: $\mathrm{C_7H_{22}N_2O_6P_2}$; 28.81 g (91.1%); m.p. about 280°C (decomp.); IR (KBr): 3400–2500, 2310–2110, 1750, 1555–1485, 1300–1200, 1005–870, 720, 640; ^{1}H NMR ($\mathrm{D_2O}$ + NaOD): 1.7–2.8 (12 H, m, $\mathrm{CH_2} \times 3$, $\mathrm{PCH_3} \times 2$), 2.93 and 3.41 (4 H, d, $J =$ 14 Hz, $\mathrm{PCH_2} \times 2$), 4.18 (1 H, t, $\mathrm{C\underline{H}CH_2}$); Mass-spect. ($\mathrm{M^+}$/e): 316.230/316; $\mathrm{R_f}$: 0.63 (in the above system); $[\alpha]_D^{20}$ +57.6°, $c = 1$, 0.1 N NaOH;

Calc'd: C 34.18 H 7.01 N 8.48%

Found: C 33.92 H 7.14 N 8.26%

N_α,N_ε-Di[(hydroxymethylphosphinyl)methyl]-*D*-, *DL*-, *L*-lysine, **15**: $C_{10}H_{24}N_2O_6P_2$; 31.74 g (96.1%); m.p. about 280°C (decomp.); IR (KBr): 3400–2500, 2310–2110, 1755, 1550–1475, 1310–1205, 1000–880, 720, 640; ^{1}H NMR (D_2O + NaOD): 1.6–2.8 (14 H, m, $CH_2 \times 4$, $PCH_3 \times 2$), 3.00 and 3.33 (4 H, d, $J = 14$ Hz, $PCH_2 \times 2$), 4.27 (1 H, t, $C\underline{H}CH_2$); Mass-spect. (M^+/e): 330.257/330; R_f: 0.71 (in the above system); $[\alpha]_D^{20}$ +70.1° and −68.3°, $c = 1$, 0.1 N NaOH;

Calc'd:	C 36.37	H 7.32	N 8.48%
Found:	C 36.48	H 7.44	N 8.56%

5. Synthesis of the methylphosphinyl derivatives with hydroxymethyl compounds **16** *and* **18.** The same method, as in Item 3, is used. With **18**, when the interaction between methyldichlorophosphine and acetic acid is over, the mixture is boiled for 6 hours in 20% hydrochloric acid. The following products are isolated (**16** affords **17**, and **18–19**):

N_α,N_ε-Di[(hydroxy-methylphosphinyl)methyl]-N_α,N_ε-ditrifluoroacetyl-*D*-, *DL*-, *L*-lysine ethyl ester, **17**: $C_{16}H_{26}F_6N_2O_8P_2$; 16.12 g (29.3%); oil, b.p., cannot be distilled without decomposition at 100°C/6.10^{-4} Torr; IR (film): 2720–2500, 2430–2100, 1750–1700, 1650, 1310–1245, 980–840, 730; Mass-spect. (M^+/e): 550.327/fragments—93 (100%); R_f: 0.88 (n-BuOH:pyr.:AcOH:H_2O = 16:2:5:1) and 0.36 ($CHCl_3$:C_6H_6:MeOH = 9:3:1); $[\alpha]_D^{20}$ +77.9° and −82.3°, $c = 1$, 0.1 N NaOH;

Calc'd:	C 34.92	H 4.76	N 5.09%
Found:	C 35.18	H 4.55	N 5.12%

When the substance **17** is heated in 1 N NaOH in a water bath and then acidified, the product *D*-, *DL*-, *L*-lysine is obtained with a yield of 86.3% (**15**). The spectral data are identical with that of the one prepared in Item 4.

N-[(Hydroxy-methylphosphinyl)methyl]aminomethylphosphonic acid, **19**: $C_3H_{11}NO_5P_2$; 9.20 g (45.3%); m.p. approx. 280°C (decomp.); IR (KBr): 2840–2480, 1555, 1300, 1250–1000; ^{1}H NMR (D_2O + NaOD): 1.85 (3 H, d, $J = 18$ Hz, PCH_3), 2.86 and 3.02 (4 H, d, $J = 16$ Hz, $PCH_2 \times 2$); Mass-spect. (M^+/e): 203.072/203; R_f: 0.33 (n-BuOH:25% NH_4OH = 4:1);

Calc'd:	C 17.87	H 5.46	N 6.90%
Found:	C 18.28	H 5.78	N 7.11%

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