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ACID-PROMOTED PHOSPHONYL MIGRATION IN *N*-PHOSPHONYL-α-AMINOALCOHOLS. FROM *N*-(2-HYDROXYETHYL)PHOSPHONAMIDES TO *O*-(2-AMINOETHYL)PHOSPHONATES.[1]

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Abstract: *A novel acid-promoted N- to O-phosphonyl migration is described in N-(2-hydroxyethyl)phosphonamides giving O-(2-aminoethyl)phosphonates, a reaction which parallels the known N- to O-acyl migration in N-monoacyl-α-aminoalcohols.*

Transition-state analogs arise as one of the most promising mechanism-based enzyme inhibitors. This approach has been applied to the design of inhibitors against hydrolytic enzymes by using the tetrahedral phosphorus as a stable mimic of the tetrahedral carbon atom present in the intermediates.[2,3] The electronic structure of the phosphonate and phosphonamide groups makes them interesting candidates in the preparation of ester-hydrolyzing enzyme inhibitors and justifies the increasing interest in the synthesis of these type of compounds as well as on the study of their chemical properties.

During our continuing program on synthesis and biological evaluation of long-chain α-aminoalcohols and some *N*-acyl derivatives as antiinflammatory phospholipase A_2 inhibitors,[4] we have synthesized several *N*-phosphonyl-α-

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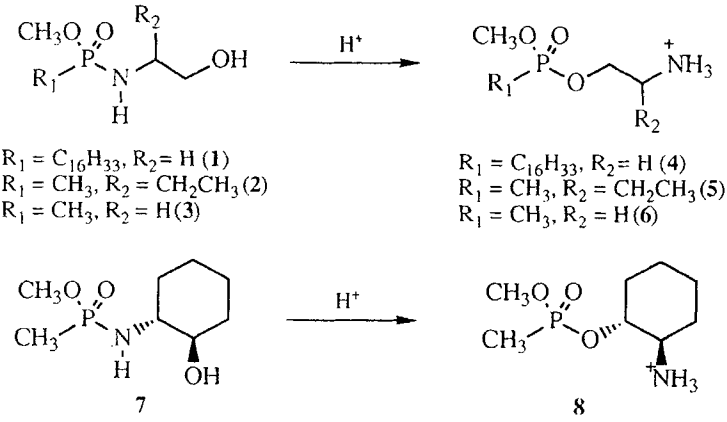

Scheme 1: Acid-promoted migration of phosphonyl group in phosphonamides **1-3** and **7**, leading to phosphonates **4-6** and **8**, respectively.

aminoalcohol compounds. These products have shown to be rather unstable towards hydrolysis as well as under acidic conditions.

Nitrogen to oxygen acyl group migrations have been extensively studied in *N*-acyl-α-aminoalcohols.[5] These compounds undergo *N*- to *O*-migration in the presence of acids, and the reverse *O*- to *N*-migration under basic treatment. Surprisingly, there are no reports of the equivalent phosphorus migration in the literature. This rearrangement has only formally been proposed as an intermediate in a multi-step rearrangement observed from the opened form of a 2-deoxy-2-phosphorylaminoglucose.[6]

In this communication we report for the first time the acid-promoted migration of the phosphonyl group in *N*-(2-hydroxyethyl)phosphonamides leading to *O*-(2-aminoethyl)phosphonates (*cf.* scheme 1), a process which is likely to occur through a mechanism similar to the above mentioned acyl migration. However, *O*-acyl derivatives can undergo the reverse process in alkaline media, whereas phosphorus analogs show only the described acid-promoted *N*- to *O*-migration. In this case, aqueous basic treatment leads exclusively to the *O*-phosphonate hydrolysis.

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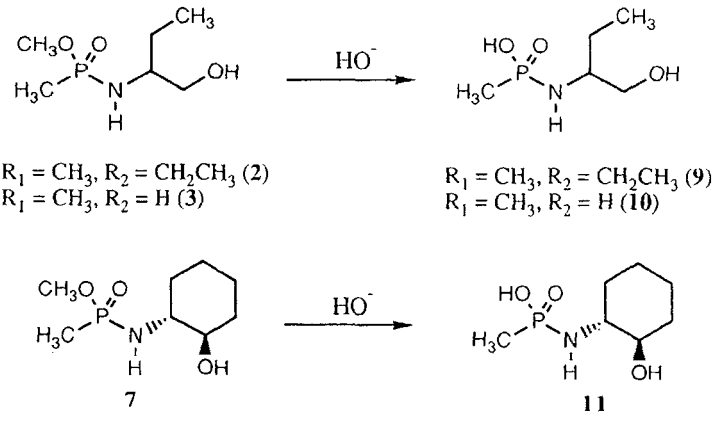

Scheme 2: Phosphonamides (**2**, **3** and **7**) *O*-methyl ester hydrolysis.

Compounds **1**,[7] **2**,[8] **3**[9] and **7**[10] have been synthesized *via* triethylamine-catalyzed coupling of the phosphonyl chloride and the corresponding amine in DMF. Purification was performed by column chromatography using either Florisil or Silica-gel as the stationary phase. Treatment of **1** with 0.1N HCl afforded transformation into **4** (*cf.* scheme 1),[11] which remains stable upon treatment with 1.5N LiOH at room temperature for 24 hours. Additionally, compound **2**, **3** and **7** led to the migration product **5**,[12] **6**[13] and **8**,[14] respectively, (*cf.* scheme 1) when treated with acetic acid (0.01N in chloroform).

Phosphonamides **1**-**3** and **7** respond in different manner to alkaline treatment. Compound **1** decomposes in 1.5N LiOH giving complete hydrolysis products, whereas the phosphonamide moiety of compounds **2**, **3** and **7** remains unaltered after this treatment and only the *O*-methyl ester function is hydrolyzed, leading to the acids **9**,[15] **10**[16] and **11**,[17] respectively (*cf.* scheme 2). Phosphonates **4** and **8** remain stable upon treatment with 1.5N LiOH at room temperature for 24 hours, therefore, the reverse *O*- to *N*-phosphonyl migration was not observed, thus differentiating from *N*-acyl derivatives of α-aminoalcohols that reverse the reaction in basic media.

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Table: Differential ^{13}C- and ^{1}H-NMR signals for phosphonamides (**1-3** and **7**) *vs.* phosphonates (**4-6** and **8**, respectively).

	^{13}C NMR (δ ppm)		^{1}H NMR (δ ppm)		
COMPOUND	NCH<u>C</u>HO	<u>C</u>H$_3$OP	NCHC<u>H</u>O	CH$_3$OP	C<u>H</u>$_2$P
Phosphonamide-**1**	63.28	50.52	3.01 (2H)	3.62	1.65 (2H)
Phosphonate-**4**	61.98	52.34	4.08 (2H)	3.70	1.54 (2H)
Phosphonamide-**2**	65.85	50.67	3.35-3.50 (2H)	3.50	1.40 (3H)
Phosphonate-**5**	61.38	52.90	N. A.	3.70	1.30 (3H)
Phosphonamide-**3**	62.98	50.57	3.60 (2H)	3.55	1.40 (3H)
Phosphonate-**6**	58.20	52.38	3.77-3.78 (2H)	3.70	1.52 (3H)
Phosphonamide-**7**	74.56	50.99	3.61 (1H)	3.35	1.22 (3H)
Phosphonate-**8**	71.32	52.22	3.40-3.58 (1H)	3.65	1.35 (3H)

^{1}H and ^{13}C NMR spectra were recorded on a Varian 300-MHz spectrometer. Chemical shifts (δ) are reported in ppm related to tetramethylsilane. N. A.: The signal could not be unambiguously assigned.

The structures of compounds **1-8** were elucidated on the basis of their NMR data. Significant differences were observed between ^{13}C NMR signals corresponding to the *O*-methyl (<u>C</u>H$_3$OP) and the NCH<u>C</u>HO groups, both C-signals unambiguously assigned from the coupling with the neighbouring phosphorus atom. ^{1}H NMR spectra also show some significative differences in the *O*-methyl (C<u>H</u>$_3$OP), the C<u>H</u>$_2$P and the NCHC<u>H</u>O H-signals (*cf.* table).

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(7) Compound **1** has been prepared as follows: 118 mg (1.93 mmols) of 2-aminoethanol, 117 mg (0.96 mmols) of DMAP and 195 mg (1.93 mmols) of TEA were dissolved in 10 mL of DMF in inert atmosphere. 400 mg (0.96 mmols) of *O*-methyl *n*-hexadecylphosphonyl chloride dissolved in 10 mL of dried CH_2Cl_2 were added dropwise. The mixture was kept stirring at room temperature during 30 minutes. The solvent was evaporated *in vacuo* giving 568 mg of crude product that was purified by column chromatography, using Florisil as stationary phase and CH_2Cl_2/CH_3OH (95:5) as eluent. 72 mg (16% yield) of pure **1** were obtained. ^1H NMR δ (ppm) 3.62 (m, 1H; NCH_2CH_2O); 3.62 (d J = 6, 3H; $C\underline{H}_3OP$); 3.31 (m, 1H; NCH_2CH_2O); 3.01 (m, 2H; NCH_2CH_2O); 1.79 (m, 2H; alkyl$CH_2C\underline{H}_2P$); 1.65 (m, 2H; alkyl$C\underline{H}_2CH_2P$); 1.10-1.35 (m, 26H; alkyl chain); 0.85 (dd J = 3 and 3, 3H; $C\underline{H}_3$alkyl); ^{13}C NMR δ (ppm) 63.28 (dt, $NCH_2\underline{C}H_2O$); 50.52 (dq, $\underline{C}H_3OP$); 43.88 (dt, $N\underline{C}H_2CH_2O$); 32.13 (t); 31.09 (t); 30.86 (t); 29.40-29.90 (t); 26.54 (dt, alkyl$\underline{C}H_2P$); 22.86 (t); 22.40 (dt, alkyl$\underline{C}H_2CH_2P$); 14.26 (q, alkyl$\underline{C}H_3$).

(8) Compound **2** has been prepared as indicated for phosphonamide **1**, starting with 1.04 g (11.67 mmols) of 2-aminobutanol and 1.0 g (7.78 mmols) of *O*-methyl methylphosphonyl chloride. After Silica-gel purification, 314 mg (20.1% yield) of pure **2** were obtained. ^1H NMR δ (ppm) 3.50 (d J = 6, 3H; $C\underline{H}_3OP$); 3.35-3.50 (m, 3H; OH and $NHCHC\underline{H}_2OH$); 2.85 (m, 1H; $NHC\underline{H}CH_2OH$); 1.25-1.50 (m, 2H; $CH_3C\underline{H}_2$); 1.40 (d J = 9, 3H; $C\underline{H}_3P$); 0.80 (dd J = 3 and 3, 3H; $C\underline{H}_3CH_2$). ^{13}C NMR δ (ppm) 65.85 (dt,

NCH$\underline{C}$H$_2$O); 55.09 (dd, NH$\underline{C}$HCH$_2$O); 50.67 (dq, $\underline{C}$H$_3$OP); 26.45 (dt, $\underline{C}$H$_2$CH$_3$); 13.24 (dq, $\underline{C}$H$_3$P); 10.74 (q, CH$_2\underline{C}$H$_3$).

(9) Compound **3** has been prepared as indicated for phosphonamide **1**, starting with 0.95 g (15.6 mmols) of 2-aminoetanol and 1.0 g (7.78 mmols) of *O*-methyl methylphosphonyl chloride. After Florisil purification, 117 mg (10.1% yield) of pure **3** were obtained. ^{1}H NMR δ (ppm) 3.60 (d J = 6, 3H; C$\underline{H}_3$OP); 3.60 (m, 2H; NHCH$_2$C$\underline{H}_2$OH); 2.95 (m, 2H; NHC$\underline{H}_2$CH$_2$OH); 2.40-2.60 (bs, 1H; N$\underline{H}$); 1.42 (d J = 9, 3H; C$\underline{H}_3$P). ^{13}C NMR δ (ppm) 63.15 (t, N$\underline{C}$H$_2$CH$_2$O); 50.70 (dq, $\underline{C}$H$_3$OP); 43.60 (t, NHCH$_2\underline{C}$H$_2$O); 12.35 (dq, $\underline{C}$H$_3$P).

(10) Compound **7** has been prepared as indicated for phosphonamide **1**, starting with 2.36 g (15.6 mmols) of 2-aminociclohexanol and 1.0 g (7.78 mmols) of *O*-methyl methylphosphonyl chloride. After Silica-gel purification, 1.03g (63.9% yield) of pure **7** were obtained. ^{1}H NMR δ (ppm) 4.70 (d, 0.5H, NH); 4.55 (d, 0.5H, NH); 3.61 (dd J = 3 and 6, 1H; C$\underline{H}$OH); 3.37 (d J = 6, 1.5H; C$\underline{H}_3$OP); 3.35 (d J = 6, 1.5H; C$\underline{H}_3$OP); 2.95 (bs, 1H; NHC$\underline{H}$); 2.49 (d, 0.5H, OH); 2.37 (d, 0.5H, OH); 1.70 (m, 2H; HOCHC$\underline{H}_2$); 1.40 (m, 2H; HNCHC$\underline{H}_2$); 1.22 (d J = 9, 3H; C$\underline{H}_3$P); 0.97 (m, 4H; Cy). ^{13}C NMR δ (ppm) 74.56 (dd, NCH$\underline{C}$HO); 57.63 (dd, NH$\underline{C}$HCHO); 51.00 (ddq, $\underline{C}$H$_3$OP); 34.33 and 34.10 (t, HNCH$\underline{C}$H$_2$ and HOCH$\underline{C}$H$_2$); 25.15 and 24.42 (t, Cy); 13.06 (ddq, $\underline{C}$H$_3$P).

(11) Conversion of **1** into **4** was achieved (*cf.* text) by shaking a solution in 0.1N HCl during 10 minutes. Compound **4**: ^{1}H NMR δ (ppm) 4.08 (m, 2H; NCH$_2$CH$_2$O); 3.70 (d J = 6, 3H; C$\underline{H}_3$OP); 1.78 (m, 2H; alkylCH$_2$C$\underline{H}_2$P); 1.54 (m, 2H; alkylC$\underline{H}_2$CH$_2$P); 1.10-1.40 (m, 28H; alkyl + NCH$_2$CH$_2$O); 0.85 (dd J = 3 and 3, 3H; C$\underline{H}_3$alkyl). ^{13}C NMR δ (ppm) 61.98 (dt, NCH$_2$CH$_2$O); 52.34 (dq, $\underline{C}$H$_3$OP); 32.14 (t); 30.93 (t); 30.71 (t); 29.40-29.90 (t); 25.37 (dt, alkylCH$_2$P); 22.88 (t); 22.50 (dt, alkyl$\underline{C}$H$_2$CH$_2$P); 16.65 (dt, N$\underline{C}$H$_2$CH$_2$O); 14.28 (q, alkylCH$_3$).

(12) The rearrangement of **2** into **5** was observed in a sealed NMR tube, dissolved in 0.01N acetic acid-*d* in chloroform-*d*, under inert atmosphere and during 20 hours. Compound **5**: ^{1}H NMR δ (ppm) 3.70 (d J = 6, 3H; C$\underline{H}_3$OP); 1.30 (d J = 9, 3H; C$\underline{H}_3$P); 0.80 (dd J = 3 and 3, 3H; C$\underline{H}_3$CH$_2$). ^{13}C NMR δ (ppm) 61.38 (dt, NCH$\underline{C}$H$_2$O); 52.90 (dq, $\underline{C}$H$_3$OP); 22.60 (dt, $\underline{C}$H$_2$CH$_3$); 20.70 (dd, NH$\underline{C}$HCH$_2$O); 12.00 (dq, $\underline{C}$H$_3$P); 9.92 (q, CH$_2\underline{C}$H$_3$).

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(13) The rearrangement of **3** into **6** was observed in a sealed NMR tube, dissolved in 0.01N acetic acid-*d* in chloroform-*d*, under inert atmosphere and during 20 hours. Compound **6**: ^{1}H NMR δ (ppm) 3.77-3.78 (m, 2H; $NHCH_2C\underline{H}_2O$); 3.70 (d J = 6, 3H; $C\underline{H}_3OP$); 3.25 (m, 2H; $NHC\underline{H}_2CH_2O$); 1.52 (d J = 9, 3H; $C\underline{H}_3P$). ^{13}C NMR δ (ppm) 58.20 (t, $NCH_2\underline{C}H_2O$); 52.38 (t, $NH\underline{C}H_2CH_2O$); 42.24 (dq, $\underline{C}H_3OP$); 10.88 (dq, $\underline{C}H_3P$).

(14) The rearrangement of **7** into **8** was observed in a sealed NMR tube, dissolved in 0.01N acetic acid-*d* in chloroform-*d*, under inert atmosphere and during 5 days. Compound **8**: ^{1}H NMR δ (ppm) 3.40-3.58 (m, 2H; $NHCHC\underline{H}O$); 3.65 (d J = 6, 3H; $C\underline{H}_3OP$); 3.00-3.25 (m, 2H; $NHC\underline{H}CHO$); 1.30-1.60 (m, 4H; $NHCHC\underline{H}_2$ and $OCHC\underline{H}_2$), 1.35 (d J = 9, 3H; $C\underline{H}_3P$), 1.10-1.30 (m, 4H; Cy). ^{13}C NMR δ (ppm) 71.32 (t, $NHCH\underline{C}HO$); 57.58 (dq, $NH\underline{C}HCHO$); 52.22 (t, $\underline{C}H_3OP$); 34.50 and 34.23 (t, $HNCH\underline{C}H_2$ and $HOCH\underline{C}H_2$), 24.88 and 24.52 (t, Cy), 11.44 (dq, $\underline{C}H_3P$).

(15) Hydrolysis of **2** to give acid **9** was achieved by treatment with aqueous 1.5N LiOH during 2 hours at room temperature. Compound **9**: ^{1}H NMR δ (ppm) 3.28 (dd J = 3 and 7, 1H; $NHCHC\underline{H}_2OH$); 3.17 (dd J = 5 and 7, 1H; $NHCHC\underline{H}_2OH$); 2.75 (m, 1H; $NHC\underline{H}CH_2OH$); 1.26 (m, 1H; $CH_3C\underline{H}_2$); 1.11 (m, 1H; $CH_3C\underline{H}_2$); 1.05 (d J = 11, 3H; $C\underline{H}_3P$); 0.72 (dd J = 5 and 5, 3H; $C\underline{H}_3CH_2$). ^{13}C NMR δ (ppm) 68.28 (t, $NHCH\underline{C}H_2OH$); 56.00 (d, $NH\underline{C}HCH_2OH$); 27.70 (dt, $CH_3\underline{C}H_2$); 16.44 (dq, $\underline{C}H_3P$); 11.24 (q, $\underline{C}H_3CH_2$).

(16) Hydrolysis of **3** to give acid **10** was achieved by treatment with aqueous 1.5N LiOH during 2 hours at room temperature. Compound **10**: ^{1}H NMR δ (ppm) 3.28 (dd J = 3 and 7, 1H; $NHCHC\underline{H}_2OH$); 3.32 (m, 2H; $NHCH_2C\underline{H}_2OH$); 2.72 (m, 1H; $NHC\underline{H}_2CH_2OH$); 2.45 (bs, 1H; NH); 1.00 (d J = 11, 3H; $C\underline{H}_3P$). ^{13}C NMR δ (ppm) 64.96 (t, $NHCH_2\underline{C}H_2OH$); 45.15 (t, $NH\underline{C}H_2CH_2OH$); 15.86 (dq, $\underline{C}H_3P$).

(17) Hydrolysis of **7** to give acid **11** was achieved by treatment with aqueous 1.5N LiOH during 24 hours at room temperature. Compound **11**: ^{1}H NMR δ (ppm) 8.29 (bs, 1H; $P(O)O\underline{H}$); 3.08 (bs, 1H; $N\underline{H}$); 2.92 (m, 1H; $NHCHC\underline{H}OH$); 2.45 (m, 1H; $NHC\underline{H}CHOH$); 1.60 (m, 2H; $C\underline{H}_2CHOH$); 1.43 (m, 2H; $C\underline{H}_2CHNH$); 1.05 (d J = 6, 3H; $C\underline{H}_3P$); 1.00 (bs, 4H; Cy). ^{13}C NMR δ (ppm) 77.72 (d, $NHCH\underline{C}HOH$); 58.33 (d, $NH\underline{C}HCHOH$);

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35.71 (t, $\underline{C}H_2CHOH$); 35.26 (t, $\underline{C}H_2CHNH$); 26.92 (t, Cy); 26.85 (t, Cy); 16.31 (dq, $\underline{C}H_3P$).

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