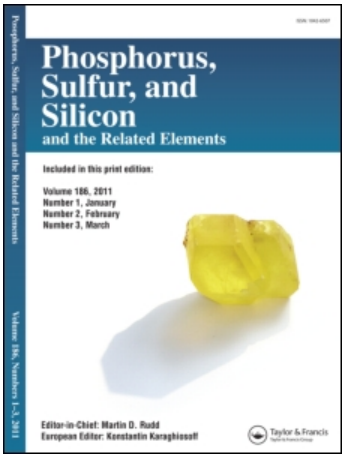

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SYNTHESIS OF 3-AMINO-2-OXO-1,2-OXAPHOSPHOLANES AND 3-AMINO-2-OXO-1,2-OXAPHOSPHORINANES

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SYNTHESIS OF 3-AMINO-2-OXO-1,2-OXAPHOSPHOLANES AND 3-AMINO-2-OXO-1,2-OXAPHOSPHORINANES

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Aminophosphonylation of 4-benzyloxy-2-butanone **1** and 5-hydroxy-2-pentanone **7** led to the phosphonic analogues of α-methylhomoserine which were cyclised under base catalysis to yield the 3-amino-2-oxo-1,2-oxaphospholane **4** or 3-amino-2-oxo-1,2-oxaphosphorinane **9**. ^{31}P-NMR analysis of the base catalysed cyclisation of **3** showed the influence of the reaction conditions on the course of the evolution of **4**.

Key words: Aminophosphonylation; α-amino-ω-hydroxyphosphonate; cyclic aminophosphonate; exocyclic cleavage; phosphonates.

INTRODUCTION

2-Oxo-1,2-oxaphospholane and 2-oxo-1,2-oxaphosphorinane are phosphorus analogues of lactones.[2] Because of the wide range of biological activities of lactones, the synthesis of their phosphorus congeners has attracted considerable interest. Most of them contain intracyclic or exo-methylene double bond,[3,4] hydroxy and/or alkyl substituents,[5–10] carboxylic or phosphonic ester substituents.[11,12] Although a 4-amino-2-oxo-1,2-oxaphosphol-3-ene has been recently reported,[13] no such cyclic compound with an α-amino group has been described. In the past decades, a variety of α-aminophosphonic acids and esters have been prepared, most of them bearing at least one hydrogen on the α carbon.[14] As part of our program on the study of α-disubstituted α-aminophosphonic acid derivatives, we became interested in the synthesis and chemical behaviour of ω-hydroxyalkyl α-aminophosphonic acids. We now report on the synthesis of the phosphonic analogues of α-methylhomoserine and their cyclisation to phosphorus containing heterocycles, which can be considered as structural analogues of the tuberculostatic *D*-cycloserine.[15]

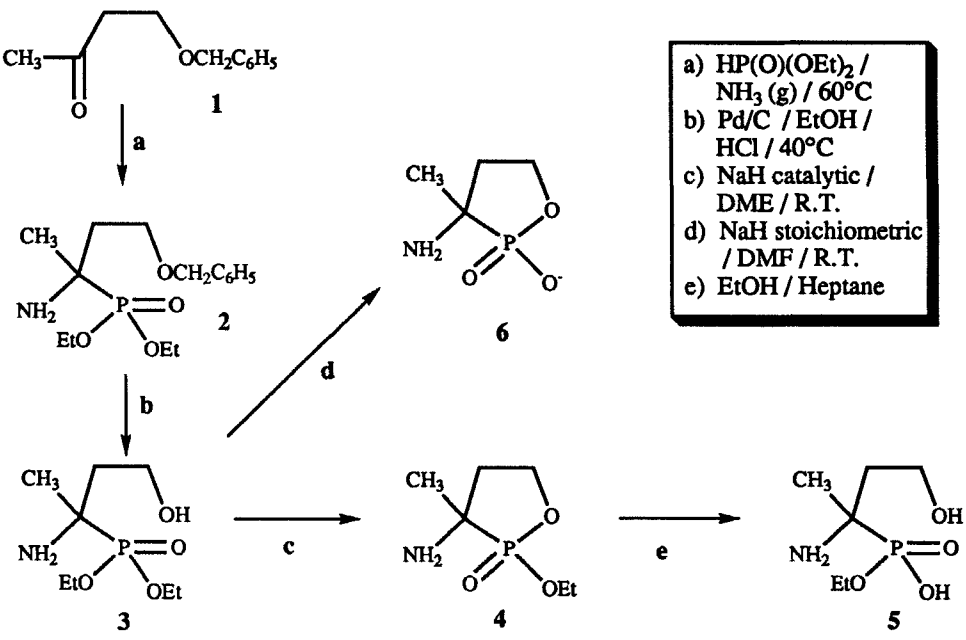
RESULTS AND DISCUSSION

Aminophosphonylation of 4-benzyloxy-2-butanone **1** was performed with ammonia and diethyl phosphite under the conditions of our modified procedure[16] of the Medved-Kabachnik reaction.[17] The aminophosphonic ester **2** was obtained in 65%

yield. Its debenzylation afforded the very hydroscopic diethyl 3-hydroxy-1-amino-1-methylpropylphosphonate **3** isolated as a monohydrate (Scheme 1).

When a solution of the phosphonate **3** in 1,2-dimethoxyethane was treated with a catalytic amount of sodium hydride, 2-ethoxy-2-oxo-1,2-oxaphospholane **4** was obtained quantiatively as a crude oil. This compound was sufficiently stable to be identified by its spectral properties. However, when crystallisation of **4** was attempted in a (95%) ethanol-heptane mixture, white crystals of the monoethyl phosphonate **5**, isolated as a monohydrate, separated out. When the phosphonate **3** was treated with a stoichiometric amount of sodium hydride in anhydrous 1,2-dimethoxyethane, oxaphospholane **4** was obtained as a 1:1 mixture with a very hygroscopic side product identified as **6** by its spectroscopic properties. When the reaction was performed in *N*,*N*-dimethylformamide, only the oxaphospholane **6** was obtained in 58% yield after chromatography. Due to the facile hydrolysis of cyclic five-membered phosphonates, originally described by Westheimer[18] and Aksnes,[19] compounds **4** and **6** were never obtained analytically pure, although their spectroscopic properties could be determined.

The synthesis of the phosphorinane analogue **9** was performed by aminophosphonylation of the ketone **7** followed by base catalysed cyclisation. In this case, protection of the alcoholic function of **7** was unnecessary and diethyl 4-hydroxy-1-amino-1-methylbutylphosphonate **8** was directly obtained in 45% yield by aminophosphonylation of **7**. The cyclic compound **9** was obtained quantitatively by treatment of the phosphonate **8** with a catalytic amount of sodium hydride in anhydrous 1,2-dimethoxyethane, at 60°C for 5 hours. By contrast with **4** and in agreement with Westheimer studies,[18] opening of the 1,2-oxaphosphorinane ring was not observed for compound **9**, although traces of the diethyl phosphonate **8**



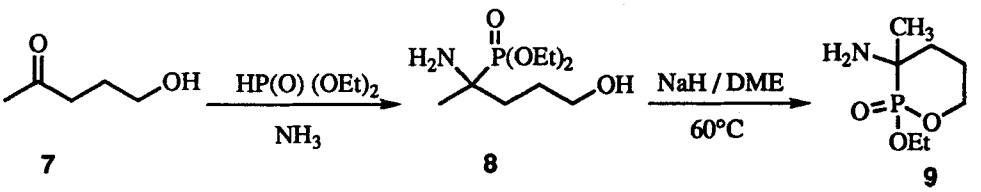
SCHEME 1

were detected by ^{1}H-NMR during attempted crystallisation of **9** in ethanol-heptane (Scheme 2).

The structures **5** and **6** were supported by the full analysis of their ^{1}H-NMR spectra (Tables I and II) which was achieved with the help of spectral simulation using a modified LAOCN 5 program[20] run on a Vax computer. The cyclic structure of **6** was characterised by a coupling between the C(5) protons and the phosphorus atom [$^3J_{H(5a)-^{31}P}$ = 8.72 Hz and $^3J_{(5b)-^{31}P}$ = 9.04 Hz] whereas no coupling was observed between the C(3) protons and the phosphorus in **5**. Moreover, the IR spectra of **5** and **6** showed an intense band at 2570 cm^{-1} and 2580 cm^{-1}, respectively, characteristic of the POH stretching frequency.[21]

^{1}H-NMR spectra of **3**, **4**, **8** and **9** were in agreement with the proposed structures but proved too complex to be fully analysed. Cyclisations of **3** to **4** and of **8** to **9** resulted in characteristic and reproducible changes of the corresponding IR spectra in the absorption range 1100–1000 cm^{-1} and around 900 cm^{-1}.

The ^{31}P chemical shifts of the aminophosphonic derivatives followed known trends. Phosphorus resonance in five-membered rings occurs well downfield of the phosphorus resonance in the six-membered analogues.[22] In our case, the difference between the phosphorus resonances of the five-membered and the six-membered ring compounds was: $\Delta(\delta 4-\delta 9)$ = 17.75 ppm. Moreover, cyclisation of the linear phosphonate **3** to a five-membered ring resulted in a strong downfield shift: +11.42

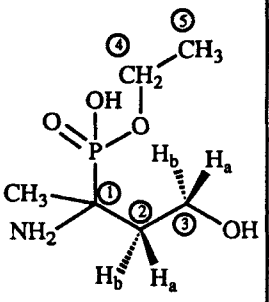


7 8 9

SCHEME 2

TABLE I

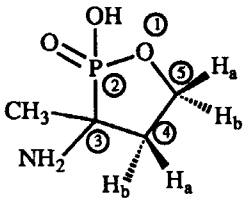
^{1}H-HMR data for compound **5** in D_2O



C - H	δ (ppm)	$J_{H_xH_y}$			J_{H_xP}	
		H_x	H_y	J (Hz)	H_x	J (Hz)
CH_3	1.50				CH_3	13.75
H_{2a}	1.97	H_{2a} H_{2a} H_{2a}	H_{2b} H_{3a} H_{3b}	-14.80 5.80 6.35	H_{2a}	11.23
H_{2b}	2.05	H_{2b} H_{2b}	H_{3a} H_{3b}	7.69 6.73	H_{2b}	10.28
H_{3a}	3.82	H_{3a}	H_{3b}	-11.24	H_{3a}	0
H_{3b}	3.87				H_{3b}	0
H_4	4.02	H_4	H_5	7.10	H_4	8.25
H_5	1.28	H_5	H_4	7.05		

TABLE II

^{1}H-HMR data for compound **6** in D_2O



C - H	δ (ppm)	$J_{H_xH_y}$			J_{H_xP}	
		H_x	H_y	J (Hz)	H_x	J (Hz)
CH_3	1.486				CH_3	13.74
H_{4a}	2.269	H_{4a} H_{4a} H_{4a}	H_{4b} H_{5a} H_{5b}	-13.75 7.39 5.38	H_{4a}	13.28
H_{4b}	2.294	H_{4b} H_{4b}	H_{5a} H_{5b}	7.16 7.75	H_{4b}	12.95
H_{5a}	4.091	H_{5a}	H_{5b}	-11.24	H_{5a}	8.72
H_{5b}	4.166				H_{5b}	9.04

ppm in the case of phosphonate ester **4** and +19.73 ppm for phosphonic acid monoester **6**. Such an effect has previously been reported in the phosphate series[21] as well as in the oxaphospholane series.[5a,5d,5f] On the other hand, cyclisation of the linear phosphonate **8** to a six-membered ring resulted in an upfield shift of 4.26 ppm. A similar phenomenon has also been observed in the phosphate series.[21]

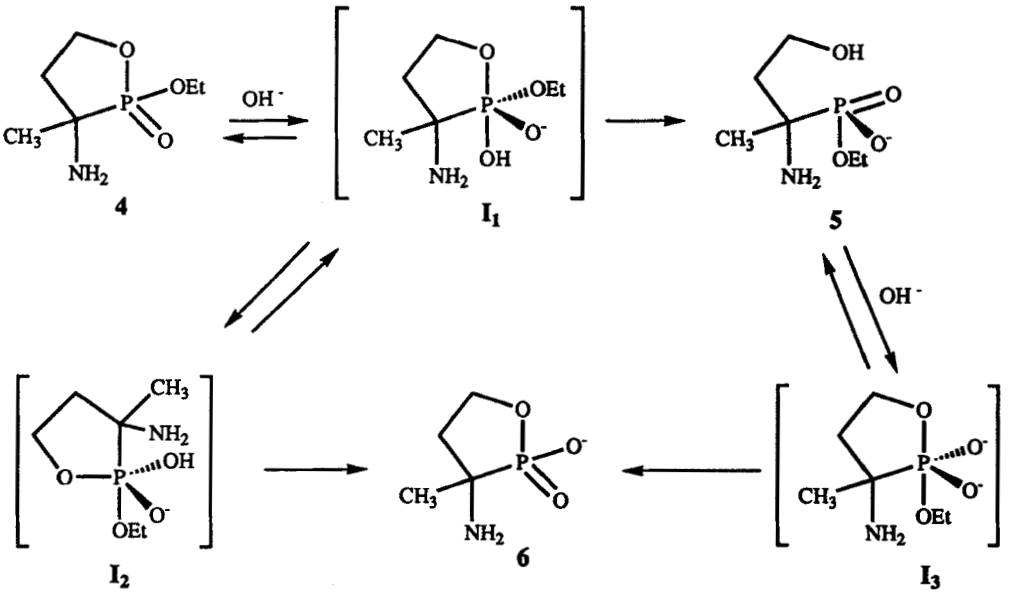
The influence of the reaction conditions, observed in the cyclisation of **3**, led us to investigate the correlations between **4**, **5** and **6**. From ^{1}H-, ^{13}C- and ^{31}P-NMR observations, it was not possible to detect the formation of the two diastereoisomers of **4**. However, during ^{31}P-NMR experiments, when the base was added portion-wise, new compounds were detected [**x** at δ41.5 ppm in C_6D_6 and **y** at δ35.5 ppm in a 5:2 DMF/C_6D_6 mixture], which could be assigned to the minor component of the diastereomeric pair, although more likely, as Kluger *et al.* observed in the case of ethyl phostonate,[23] a dimer resulting from the reaction of **3** on **4** cannot be excluded. Unfortunately, these compounds were only detected by ^{31}P-NMR but never isolated. In these ^{31}P-NMR experiments, a solution of **3** was treated with increasing quantities of base (NaH or CH_3ONa) in C_6D_6, DME or in Fluka pure DMF and the evolution of the various products **3**, **4**, **5**, **6** and **x** or **y** was monitored by ^{31}P-NMR. Addition of small amounts of base in C_6D_6 or in DME led to mixtures of **3**, **4** and **x**. With increasing quantities of base, **6** started to appear and became predominant when more than one equivalent of base was used. When these experiments were performed in DMF with increasing amounts of base, compounds **4**, **5**, **6** and **y** were formed all together in varying ratios. As **6** precipitated out of the mixture very quickly, the percentage determined by ^{31}P-NMR did not reflect the exact composition of the total mixture. However, the precipitate consisted only of **6** as indicated by the ^{31}P- and ^{1}H-NMR spectra. Thus, in DME or in C_6D_6, **4** appeared quickly, but its evolution to **5** and **6** was slow, requiring stoichiometric quantities of base. In DMF, **4** was also formed but reacted quickly to a complete range of products, even with catalytic amounts of base.

To determine whether **5** and **6** were derived from **4**, two experiments were performed. When sodium hydride was added to a solution of the cyclic ester **4**(δ44 ppm) in C_6D_6, formation of compound **6**(δ40.7 ppm) was noted together with the

formation of a precipitate. When this precipitate was dissolved in CD_3OD, two ^{31}P-NMR signals were observed: δ41.8 ppm (assigned to **6**) and 27.3 ppm (assigned to the perdeuteromethyl ester of **5**), the latter increasing with time. When sodium hydride was added to a solution of **5** in DMF, followed by distillation of DMF, dissolution in C_6D_6 in the presence of 0.1 ml of ethanol, a mixture of **6** and **5** was obtained. However, a solution of **6** in CD_3OD (δ38.6 ppm) showed the formation of the perdeuteromethyl ester of **5**(δ27.3 ppm), thus indicating the facile solvolysis of the cyclic acid **6** in alcoholic solvents.

These facts led us to suggest the relationships between the various components of the reaction described in Scheme 3. With a catalytic amount of base, intramolecular cyclisation of **3** takes place, with elimination of ethanol, leading to the phospholane **4**. However, as compound **3** is a monohydrate, hydroxide anion will be present when a stoichiometric amount of base is used. A second reaction will then take place: addition of hydroxide ion to **4** leading to intermediate $\mathbf{I_1}$. The ring opening, facilitated by the ring strain release, takes place by elimination of the apical alkoxide group to give directly **5**. A similar intermediate of the $\mathbf{I_1}$ type is also involved in the ethanol-heptane crystallisation reaction, where hydrolysis of **4** occurs. In this case, the amine function may act as the base component.

In the presence of a strong base, in aprotic solvents, formation of **6** could then take place from **5**, by recyclisation to the dianionic intermediate $\mathbf{I_3}$, already postulated by Kluger,[24] leading eventually to **6**, which precipitates from the mixture and displaces the possible equilibrium. However, a second possibility would be a different evolution of intermediate $\mathbf{I_1}$, which, by pseudorotation according to Berry, will lead to intermediate $\mathbf{I_2}$ where the C-1 carbon and exocyclic ethoxy are now in apical position. Although this process is not favoured in simple unsubstituted oxaphospholanes,[23,24] the presence of the amino group in our compound could allow



SCHEME 3

C-1 to occupy the apical position and the ring oxygen, one of the equatorial positions. Exocyclic cleavage will then be permitted to lead to **6**.

The possibility of equilibrium reactions cannot be excluded. With the solvents used, precipitation occurred in the NMR tube modifying the observed results. However, addition of alcoholic solvents to dissolve these precipitates led to significant modifications of the ratio **5:6**. For example, when the spectrum of **6** (pure when taken in D_2O solution) was taken in CD_3OD, the presence of **5** was observed in 44%. Nevertheless, these ^{31}P-NMR studies showed the relations between the various components of the reaction mixture and their dependence on the reaction conditions.

CONCLUSION

In conclusion, these studies have shown the possibility to prepare esters of ω-hydroxy α-amino alkylphosphonates and their cyclisation to oxaphospholanes or oxaphosphorinanes. The stability of these cyclic derivatives follows the known stability patterns of the parent systems, the oxaphospholanes being easily hydrolysed and the oxaphosphorinanes being more stable. Very recently, Vo-Quang *et al.* reported their results on the attempted synthesis of 3-amino-1,2-oxaphospholanes by cyclisation of the corresponding benzyloxycarbonyl protected amido linear derivatives. Unfortunately they were not able to selectively remove the BOC-protecting group to obtain the free amine. Our results show that their approach failed to yield the free 3-amino-1,2-oxaphospholanes because of the too harsh conditions required for the deprotection and not because of the too high lability which was postulated.[25]

EXPERIMENTAL

^1H- and ^{13}C-NMR spectra were recorded on Bruker AC 100 and 200, Varian 360A and Gemini 200 spectrometers, and the chemical shifts (δ) in ppm referred to internal TMS or TMPS (3-Trimethylsilyl-1-propanesulfonic acid, sodium salt) for D_2O solutions. Signal assignments were carried out by ^1H-^1H and ^1H-^{13}C 2D-correlation sequences. Proton-decoupled ^{31}P-NMR spectra were recorded on a Bruker AC 100 at 40.54 MHz and the chemical shifts (δ) referred to external 85% H_3PO_4. All J values are given in Hz. IR spectra were recorded on a Perkin-Elmer E 297 spectrophotometer. Chromatographic separations were performed using Merck silica gel 7734 (column chromatography) and Merck silica gel 7747 (preparative thin layer chromatography). Diethyl phosphite, sodium hydride and 5-hydroxy-2-pentanone **7** were Aldrich reagents and used as purchased, as well as 4-benzoyloxy-2-butanone **1** purchased from Fluka. 1,2-Dimethoxyethane was distilled from sodium-benzophenone. *N,N*-dimethylformamide was stirred over calcium chloride and distilled from calcium hydride. The *N,N*-dimethylformamide used in the ^{31}P-NMR study was puriss., absolute, dried over molecular sieves (H_2O < 0.01%) Fluka reagent.

Preparation of Diethyl 3-Benzyloxy-1-amino-1-methylpropylphosphonate **2**. Gaseous ammonia was bubbled through neat 4-benzyloxy-2-butanone **1** (5 g, 28 mmol) for 15 minutes. Diethyl phosphite (4.3 g, 31 mmol) was added and the reaction mixture stirred for 24 hours at 60°C under a continuous flow of ammonia. The reaction mixture was then poured into water (50 ml), acidified with concentrated HCl to pH 1 and extracted with diethyl ether (3 × 50 ml). Sodium carbonate was added to the aqueous layer up to pH 10 which was then saturated with potassium chloride and extracted with dichloromethane (5 × 30 ml). The organic layer was dried over sodium sulfate, filtered and evaporated to dryness, to give compound **2** (5.7 g, 65%) as an orange oil, IR (neat) 3370 (NH_2), 1225 (P=O), 1040 and 1015 (P—O—C) cm^{-1}; ^1H-HMR ($CDCl_3$) δ7.3 (5H, s, ArH), 4.5 (2H, s, Ph—CH_2), 4.1 (4H, pq, O$\underline{CH_2}CH_3$),

3.8–3.3 (2H, m, OCH_2CH_2C—P), 2.2–1.7 (2H, m, OCH_2CH_2C—P), 1.3 (3H, d, $^3J_{PH}$ 16, CH_3CP), 1.3 (6H, t, J 7, OCH_2CH_3); Anal. Calcd. for $C_{15}H_{26}NO_4P$: C, 57.13; H, 8.31; N, 4.44. Found: C, 57.14; H, 8.59; N, 4.20%.

Preparation of Diethyl 3-Hydroxy-1-amino-1-methylpropylphosphonate **3**. To a solution of **2** (2 g, 6.34 mmol) in ethanol (75 ml) and water (1 ml) was added concentrated HCl (0.5 ml) and 10% Pd on carbon (0.4 g). The system was evacuated, filled with hydrogen to a pressure of 1.3 atmosphere, warmed to 40°C and vigorously stirred for 5 hours. The mixture was filtered twice over Celite and evaporated to dryness. The residue was stirred efficiently in a mixture of dichloromethane (150 ml), water (1 ml) and sodium hydrogencarbonate (2 g) for 1 hour, then dried over sodium sulfate and filtered. After removal of the solvent under vacuum, compound **3** was obtained as a very hygroscopic orange oil (1.01 g, 77%), IR (neat) 3370 (NH_2), 1220 (P=O), 1160 (P—O), 1045 and 1025 (P—O—C), 760 (P—C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ4.23–4.0 (4H, dq, J 7 and $^3J_{PH}$ 7.15, OCH_2CH_3), 3.72 (2H, q, J 7.02, $HOCH_2CH_2C$), 2.0–1.5 (4H, m, CH_2CH_2C—P and NH_2), 1.48 (3H, d, $^3J_{PH}$ 16, CH_3CP), 1.35 (6H, t, J 7, OCH_2CH_3); ^{31}P-NMR ($CDCl_3$) δ29.44, (D_2O) δ32.88; ^{13}C-NMR ($CDCl_3$) δ16.36 (OCH_2CH_3, J 5.34), 21.40 [CH_3—C(1)], 37.84 (C-2, J 3), 51.66 (C-1, J 147.09), 58.26 (C-3, J 10.6), 62.30 and 62.40 (OCH_2CH_3, J 7.75 and 7.55, respectively); Anal. Calcd. for $C_8H_{20}NO_4P$, $1H_2O$: C, 39.50; H, 9.12; N, 5.76. Found: C, 40.20; H, 9.09; N, 5.58%.

Preparation of 3-Amino-2-ethoxy-3-methyl-2-oxo-1,2-oxaphospholane **4**. To a solution of compound **3** (0.9 g, 4 mmol) in freshly distilled anhydrous 1,2-dimethoxyethane (30 ml) was added a catalytic amount of sodium hydride (6 mg of an 80% dispersion in mineral oil, 0.05 eq) under argon. After 7 hours, the reaction mixture was filtered and the solvent removed to afford **4** (0.72 g, 100%) as an oil, IR (neat) 3370 (NH_2), 1240 (P=O), 1160 (P—O), 1040 and 1005 (P—O—C), 1130, 890 and 830 (ring), 765 (P—C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ4.45–3.87 (4H, m, OCH_2CH_2C and OCH_2CH_3), 2.6–1.73 (4H, m, OCH_2CH_2C and NH_2), 1.40 (3H, d, $^3J_{PH}$ 15.5, CH_3CP), 1.35 (3H, t, J 7, OCH_2CH_3); ^{31}P-NMR ($CDCl_3$) δ44.3; ^{13}C-NMR ($CDCl_3$) δ18.7 (OCH_2CH_3, J 5.16), 21.52 [CH_3—C(3)], 38.37 (C-4), 56.32 (C-3, J 148.64), 59.61 (C-5, J 7.15), 63.81 (OCH_2CH_3, J 6.65). Attempts of purification by distillation under vacuum gave a white oil (53%) with the same spectroscopic properties.

Preparation of Ethyl 3-Hydroxy-1-amino-1-methylpropylphosphonate **5**. An attempt of crystallisation of **4** in ethanol-heptane gave white crystals of **5**, slightly soluble in chloroform and in methanol and very soluble in water, m.p. 174°C, IR (nujol) 3370 (NH_2), 2570 (P—OH), 1180 (P=O), 1105, 1065 and 1040 (P—O) and (P—O—C), 790 (P—C) cm^{-1}; ^{1}H-NMR (D_2O, 200 MHz) see Table I; ^{31}P-NMR ($CDCl_3$) δ21.41, (D_2O) δ18.95; ^{13}C-NMR ($CDCl_3$) δ18.83 (OCH_2CH_3, J 5.46), 21.52 [CH_3—C(1)], 38.22 (C-2), 56.99 (C-1, J 151.63), 59.85 (C-3, J 7.6), 64.12 (OCH_2CH_3, J 7.025), (D_2O) δ18.69 (OCH_2CH_3, J 5.01), 21.45 [CH_3—C(1)], 38.24 (C-2), 56.59 (C-1, J 149.70), 59.72 (C-3, J 8.16), 63.95 (OCH_2CH_3, J 6.32); Anal. Calcd. for $C_6H_{16}NO_4P$, $1H_2O$: C, 33.49; H, 8.43; N, 6.51. Found: C, 34.06; H, 8.39; N, 6.55%.

Preparation of Sodium 3-amino-2-hydroxy-3-methyl-2-oxo-1,2-oxaphospholane **6**. To a stirred solution of **3** (1 g, 4.8 mmol) in *N,N*-dimethylformamide (30 ml) under argon, sodium hydride (0.16 g of a 80% dispersion in mineral oil) was added portionwise. After 4 hours, the reaction mixture was directly passed through a silica gel chromatography column (eluant: pentane-dichloromethane 1:1, followed by a linear gradient of methanol in dichloromethane, reaching 80% of methanol) to yield in the last fractions **6**, as a deliquescent yellow solid (0.42 g, 58%), IR (neat) 3370 (NH_2), 2580 (P—OH), 1190 (P=O), 1100, 1060 and 1015 (P—O) and (P—O—C), 890 (ring), 770 (P—C) cm^{-1}; ^{1}H-NMR (D_2O, 100 MHz) see Table II; ^{31}P-NMR ($CDCl_3$) δ41.32, (D_2O) δ38.68; ^{13}C-NMR (D_2O) δ23.57 [CH_3—C(3), J 2.5], 40.55 (C-4, J 12.8), 50.01 (C-3, J 131.2), 63.99 (C-5, J 6.3).

Preparation of Diethyl 4-Hydroxy-1-amino-1-methylbutylphosphonate **8**. 5-Hydroxy-2-pentanone **7** (3 g, 3 mmol) was caused to react in the same way as for the preparation of compound **2**. The reaction mixture was poured into water, acidified to pH 1, saturated with potassium chloride and washed with dichloromethane (3 × 50 ml). Sodium carbonate was added to the aqueous phase until basic pH. The aqueous phase was then extracted with dichloromethane. The organic phase was dried, evaporated and column chromatography of the residue (eluant: dichloromethane-methanol 95:5) afforded **8** (3.2 g, 45%) as an oil, IR (neat) 3370 (NH_2), 1225 (P=O), 1160 (P—O), 1050 and 1030 (P—O—C), 755 (P—C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ4.08 (4H, dq, J_{HH} 7 and $^3J_{PH}$ 8.3, OCH_2CH_3), 3.64–3.4 (2H, m, CH_2CH_2OH), 2.7 (2H, m, NH_2), 1.85–1.54 (4H, m, P—C—CH_2CH_2C and P—C—CH_2CH_2C), 1.48 (1.5H, d, $^3J_{PH}$ 16, CH_3CP), 1.27 (1.5H, d, $^3J_{PH}$ 16.32, CH_3—C—P), 1.27 (6H, t, J 7.01, OCH_2CH_3); ^{31}P-NMR ($CDCl_3$) δ30.822; ^{13}C-NMR ($CDCl_3$) δ16.73 (OCH_2CH_3, J 5.5), 21.09 [CH_3—C(1)], 26.62 (C-3, J 10.88), 34.41 (C-2, J 4.07), 51.49 (C-1, J 147.33), 62.70 (C-4, J 3.86), 62.85 (OCH_2CH_3); Anal. Calcd. for $C_9H_{22}NO_4P$: C, 45.18; H, 9.27; N, 5.85. Found: C, 45.17; H, 9.23; N, 5.78%.

Preparation of 3-Amino-2-ethoxy-3-methyl-2-oxo-1,2-oxaphosphorinane **9**. **8** (1 g, 4.28 mmol) was caused to react under the conditions described above for the cyclisation of **3** to compound **4**. It afforded, after 5 hours at 60°C and work-up followed by preparative t.l.c. (eluant: chloroform-methanol 85:15), **9** (0.7 g, 88%) as a white oil, IR (neat) 3370 (NH_2), 1225 (P=O), 1155 (P—O), 1030 and 1000 (P—O—C), 930 and 860 (ring), 765 (P—C) cm^{-1}; ^{1}H-NMR (CD_3OD) δ4.35–4.15 (2H, m, OCH_2CH_2C), 4.16 (2H, dq, J_{HH} 6.98 and $^3J_{PH}$ 6.1, OCH_2CH_3), 2.2–1.61 (4H, m, CH_2CH_2C and CH_2CH_2C), 1.38 (3H, t, J 7.02, OCH_2CH_3), 1.36 (3H, t, J 7.08, OCH_2CH_3), 1.33 (1.5H, d, $^3J_{PH}$ 15.89, CH_3CP), 1.28 (1.5H, t, $^3J_{PH}$ 15.82, CH_3CP); ^{31}P-NMR ($CDCl_3$) δ26.556; ^{13}C-NMR ($CDCl_3$) δ16.87 (OCH_2CH_3, J 5.28), 23.90 (C-5, J 5.9), 24.10 [CH_3—C(3)], 38.73 (C-4), 49.70 (C-3, J 135.78), 63.64 (C-6, J 8.04), 71.70 (OCH_2CH_3, J 6.3); **9** gave a picrate, m.p. 207–210°C (dec.); Anal. Calcd. for $C_{13}H_{19}N_4O_{10}P$: C, 36.98; H, 4.54; N, 13.27. Found: C, 37.01; H, 4.70; N, 13.35%.

^{31}P-NMR Study of the Evolution of **3** *under Basic Conditions*. To a stirred puriss. dry DMF (Fluka) solution of **3**, portions (0.3 eq/mol) of sodium hydride were added under continuous argon bubbling. After each addition, the mixture was stirred for 5 min and an aliquot of 0.5 ml was transferred into a 5 mm NMR tube containing 0.2 ml of C_6D_6 to provide a lock. Since quantitiative analysis of ^{31}P-NMR is complicated by possible variation in Nuclear Overhauser Effect (NOE) and relaxation time between products, we employed a relaxation delay (25 s) that should be at least twice the relaxation time (T_1) of the phosphorylated products to prevent partial saturation of the signals.[24]

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REFERENCES AND NOTES

1. Permanent address: Dip. Scienze dei Materiali e della Terra—Universita degli Studi, 60131 Ancona-Italy.
2. B. A. Arbuzov and D. K. Yarmukhametova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1767 (1960).
3. Y. Machida and I. Saito, *J. Org. Chem.*, **44,** 865 (1979).
4. J. N. Collard and C. Benezra, *Tetrahedron Lett.*, 3725 (1982).
5. a) A. E. Wroblewski, *Tetrahedron*, **39,** 1809 (1983); b) A. E. Wroblewski and W. T. Konieczko, *Monatsh. Chem.*, **115,** 785 (1984); c) A. E. Wroblewski, *Carbohydr. Res.*, **125,** C1 (1984); d) A. E. Wroblewski, *Z. Naturforsch., Teil B,* **40,** 407 (1985); e) A. E. Wroblewski, *Z. Naturforsch., Teil B,* **41,** 791 (1986); f) A. E. Wroblewski, *Tetrahedron,* **42,** 3595 (1986); g) A. E. Wroblewski, *Liebigs Ann. Chem.*, 1448 (1986); h) A. E. Wroblewski, *Liebigs Ann. Chem.*, 1854 (1986); i) A. E. Wroblewski, *Phosphorus Sulfur*, **28,** 371 (1986).
6. F. S. Mukhametov, L. V. Stepashkina and N. I. Rizpolozhenskii, *Zh. Obshch. Khim.*, **49,** 1756 (1979).
7. F. S. Mukhametov, L. V. Stepashkina, N. I. Rizpolozhenskii and R. R. Shagidullin, *Zh. Obshch. Khim.*, **52,** 272 (1982).
8. A. A. Nafikova, R. M. Aminova, F. S. Mukhametov, K. M. Enikeev, I. E. Ismaev and R. G. Gainullina, *Zh. Obshch. Khim.*, **57,** 336 (1987).
9. A. Pondaven-Raphalen and G. Sturtz, *Phosphorus Sulfur,* **36,** 39 (1988).
10. J.-R. Neeser, J. M. J. Tronchet and E. J. Charollais, *Can. J. Chem.*, **61,** 2112 (1983).
11. R. L. Bentley and J. Dingwall, *Synthesis*, 552 (1985).
12. a) E. Öhler and E. Zbiral, *Liebigs Ann. Chem.*, 229 (1991); b) E. Öhler and E. Zbiral, *Chem. Ber.*, **124,** 175 (1991); c) H. Kalchhauser and E. Öhler, *Helvetica Chim. Acta*, **74,** 417 (1991).
13. R. A. Abramovitch, M. Konieczny, W. Pennington, S. Kanamathareddy and M. Vedachalam, *J. Chem. Soc., Chem. Commun.*, 269 (1990).
14. For a review, see L. Maier, *Phosphorus Sulfur*, **14,** 295 (1983).
15. F. Bernheim, *Chemotherapy of Bacterial Infections VI—Drugs Used in the Treatment of Tuberculosis* in *Drill's Pharmacol. Med.* (McGraw Hill, New York, 1971), 4th ed., J. R. DiPalma, Ed., pp. 1713–1728.
16. Y. Berchadsky, N. Kernevez, F. Le Moigne, A. Mercier, L. Secourgeon, and P. Tordo, *Brit. UK Pat. Appl.*, GB 2,225,015 [Chem. Abstr. **113,** 191636w (1990)].
17. a) M. I. Kabachnik and T. Y. Medved, *Dokl. Akad. Nauk SSR*, **83,** 689 (1952); b) T. Y. Medved and M. I. Kabachnik, *Dokl. Akad. Nauk SSSR,* **84,** 717 (1952); c) M. I. Kabachnik and T. Y. Medved, *Izv. Akad. Nauk, Otd. Khim. Nauk*, 868 (1953); d) T. Y. Medved and M. I. Kabachnik, *Izv. Akad. Nauk, Otd. Khim. Nauk*, 314 (1954).

18. A. Eberhard and F. H. Westheimer, *J. Am. Chem. Soc.*, **87,** 253 (1965).
19. G. Aksnes and K. Bergesen, *Acta Chem. Scand.*, **20,** 2508 (1966).
20. LAOCN-5, QCPE-458, Chemistry Department, Indiana University, Bloomington, Indiana, 47405, USA; b) S. M. Castellano and A. A. Bothner-By, in *Computer Programs for Chemistry*, D. F. de Tar, Ed. (Benjamin, New York, Vol. I, 1968) pp. 10–39.
21. R. A. Y. Jones and A. R. Katritzky, *J. Chem. Soc.*, 4376 (1060).
22. M. J. Gallagher, in *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; J. G. Verkade and L. D. Quin, Ed., in *Methods in Stereochemical Analysis* (VCH Publishers Inc., Weinheim, 1987), Chapter 9, p. 297.
23. R. Kluger and S. D. Taylor, *J. Am. Chem. Soc.*, **112,** 6669 (1990).
24. S. D. Taylor and R. Kluger, *J. Am. Chem. Soc.*, **113,** 5714 (1991).
25. A.-M. Chollet-Gravey, L. Vo-Quang, Y. Vo-Quang and F. Le Goffic, *Synthetic Comm.*, **23,** 561 (1993).