1,3,2-Oxazaphosphinane analogs of phosphorylacetic acid derivatives: synthesis and properties

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Reactions of 2-AlkO-1,3,2-oxazaphosphinanes with alkyl *N*-haloacetylamino or *N*-chloromethyl-*N*-methoxycarbonylamino carboxylates mainly give products with retention (Alk = Me) and opening of the ring (Alk = Et). In aqueous solution, cyclic products with the *N*-isopropyl group are only stable, while the rest undergo hydrolysis with cleavage of the P—N bond of the ring. Oxazaphosphinane analogs of phosphorylacetamide and phosphorylacetohydrazide were synthesized.

Key words: 2-alkoxy-1,3,2-oxazaphosphinanes, 2-alkoxy-3-alkyl-1,3,2-oxazaphosphinanes, the Arbuzov rearrangement, alkyl haloacetylamino carboxylates, *N*-chloromethyl-*N*-methoxycarbonylglycine methyl ester, *N*-[(2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)acetyl]glycine methyl ester, hydrolysis, alkyl *N*-[(3-alkyl-2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)acetyl]amino carboxylates, *N*-{[(3-bromopropylamino)ethoxyphosphoryl]acetyl}glycine methyl ester, *N*-[(3-isopropyl-2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)methyl]-*N*-methoxycarbonylglycine methyl ester, *N*-({[*N*-(3-chloropropyl)-*N*-isopropylamino]methoxyphosphoryl}methyl)-*N*-methoxycarbonylglycine methyl ester.

Earlier,[1] we have described synthesis of 1,3,2-oxazaphosphinane analogs of phosphorylacetates with potential biological activity, in which, by analogy with carcinolytic cyclophosphamide, the oxazaphosphinane ring plays the role of a "carrier" of a pharmacophoric group to a cell through cell membranes.[2] It is known that condensation products of phosphorylacetic acid and amino acids, *e.g.*, with aspartic acid (PALA preparation), are strong carcinolytics[3] and the corresponding hydrazides exhibit antiamnestic, antihypoxic, and antidepressant activities.[4] In connection with this, it was of interest to synthesize a series of 1,3,2-oxazaphosphinane analogs of these and some structurally related compounds.

1,3,2-Oxazaphosphinane analogs of phosphorylacetic acid containing fragments of amino acid esters were synthesized by the Arbuzov reaction described in detail for the reactions of 2-alkoxy-3-alkyl-1,3,2-oxazaphosphinanes (**1**) with bromoacetates.[1] In the present work, compounds **1** reacted with alkyl *N*-haloacetylamino carboxylates (**2**) (Scheme 1).

Reactions with *N*-bromoacetyl derivatives were carried out in benzene at 20—50 °C, while those with *N*-chloroacetyl derivatives, in toluene at 100—110 °C. As with bromoacetates,[1] the reactions gave cyclic (**3**) and acyclic products (**4**). According to ^{31}P NMR data, their ratio is virtually independent of the nature of the substituent R^1 at the N atom in oxazaphosphinanes **1** but is determined by the substituent R^2 in the alkoxy group (Table 1). For instance, for R^2 = Me, cyclic products are dominant (the ratio **3** : **4** varies from 93 : 7 to 86 : 14), while for R^2 = Et, the major product is an acyclic one (**3** : **4** = 25 : 75)*. For pairs of compounds **3f**, **4g** and **3g**, **4h**, the ^{31}P NMR spectra in benzene show doubled signals due to diastereomeric anisochronism.

The use of oxazaphosphinane **1d** in the Arbuzov reaction with *N*-chloromethyl-*N*-methoxycarbonylglycine methyl ester (**5**) (Scheme 2) afforded cyclic (**6**) and acyclic products (**7**) in the 82 : 18 ratio (^{31}P NMR).

In this case, the ^{31}P NMR spectrum contained doubled signals because of hindered rotation about the C—N bond of the amide fragment (the intensity ratio of the higher-field and lower-field signals for both compounds **6** and **7** was ~ 3 : 7). Compound **6**, which is a derivative of aminomethylphosphonic acid, can also represent biological interest.[5]

All compounds **3** are crystalline solids that are well soluble in water. However, only compounds **3c—g** containing the *N*-isopropyl substituent are stable in aqueous solutions, probably because of the steric hindrances created by this group. Compound **3a** was completely hydrolyzed at 20 °C in 7 days with cleavage of the P—N bond of

* According to the ^{31}P NMR data, the yields of purified products **4b** and **3a** were 54 and 8%, respectively (see Experimental).

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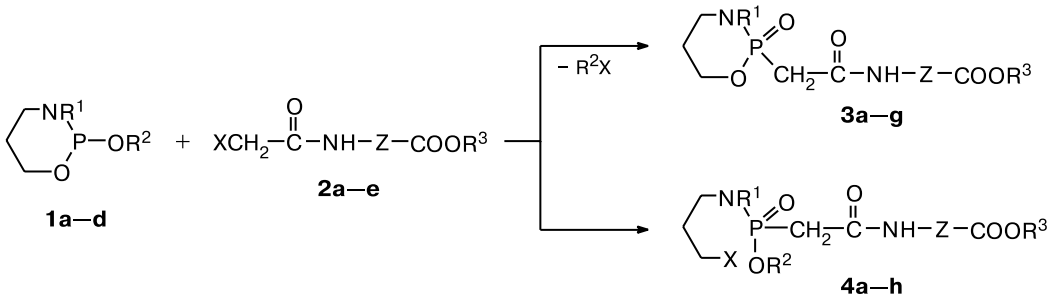
Scheme 1

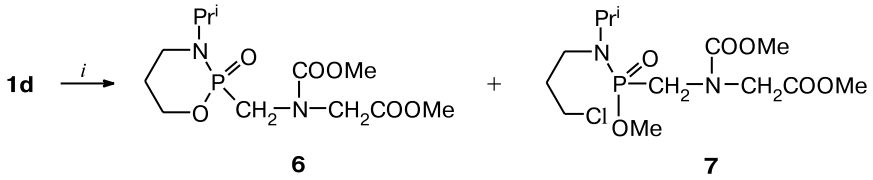


i. X = Br, C_6H_6, 20—50 °C; X = Cl, $CH_3C_6H_5$, 100—110 °C.

Compound	R^1	R^2	Compound	R^3	Z	X	Compound	R^1	R^3	Z
1a	H	Me	**2a**	Me	CH_2	Br	**3a**	H	Me	CH_2
1b	H	Et	**2b**	Et	CH_2	Cl	**3b**	Me	Me	CH_2
1c	Me	Me	**2c**	Et	CH_2CH_2	Cl	**3c**	Pr^i	Me	CH_2
1d	Pr^i	Me	**2d**	Et	$CH(CH_2COOEt)$	Cl	**3d**	Pr^i	Et	CH_2
			2e	Et	$CH(CH_2CH_2COOEt)$	Cl	**3e**	Pr^i	Et	CH_2CH_2
							3f	Pr^i	Et	$CH(CH_2COOEt)$
							3g	Pr^i	Et	$CH(CH_2CH_2COOEt)$

Compound	R^1	R^2	R^3	Z	X	Compound	R^1	R^2	R^3	Z	X
4a	H	Me	Me	CH_2	Br	**4e**	Pr^i	Me	Et	CH_2	Cl
4b	H	Et	Me	CH_2	Br	**4f**	Pr^i	Me	Et	CH_2CH_2	Cl
4c	Me	Me	Me	CH_2	Br	**4g**	Pr^i	Me	Et	$CH(CH_2COOEt)$	Cl
4d	Pr^i	Me	Me	CH_2	Br	**4h**	Pr^i	Me	Et	$CH(CH_2CH_2COOEt)$	Cl

Scheme 2

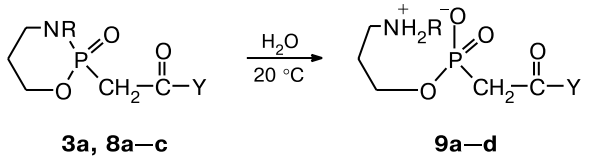


i. $ClCH_2N(COOMe)CH_2COOMe$ (**5**), C_6H_6, 80 °C.

the ring. This ring opening was confirmed by the absence of a spin-spin coupling between the C atom bound to the N atom and the P atom (^{13}C NMR). The hydrolysis yielded internal salt **9a**. Oxazaphosphinane analogs of alkyl phosphorylacetates, *viz.*, compounds **8a**—**c** described earlier,[1] hydrolyzed even more easily when merely exposed to atmospheric moisture to give salts **9b**—**d** (Scheme 3).

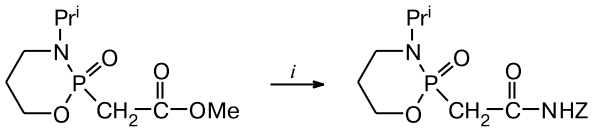
Treatment of methyl ester **10** (see Ref. 1) with a saturated solution of ammonia in methanol at room tempera-

Scheme 3



Compound	R	Y
3a, **9a**	H	$NHCH_2COOMe$
8a, **9b**	H	OMe
8b, **9c**	H	OEt
8c, **9d**	Me	OMe

Scheme 4



Reagents and conditions: NH_3 or $NH_2NH_2 \cdot H_2O$; MeOH, 20 °C.

Z = H (**11a**), NH_2 (**11b**)

Table 1. Effect of the structure of the starting compound **1** on the ratio of products **3** and **4** in its reactions with alkyl *N*-haloacetylamino carboxylates **2** and *N*-chloromethyl-*N*-methoxycarbonylglycine methyl ester **5** (^{31}P NMR (C_6H_6))

Starting reagents		δ[a]		Ratio of the yields of the products **3** : **4**
1	**2**, **5**	**3**	**4**	
1a	**2a**	22.5 (**3a**)[b]	30.0 (**4a**)[b]	86 : 14
1b	**2a**	21.8 (**3a**)	27.7 (**4b**)	25 : 75
1c	**2a**	21.8 (**3b**)	30.3 (**4c**)	92 : 8
1d	**2a**	20.1 (**3c**)	29.7 (**4d**)	91 : 9
1d	**2b**	20.0 (**3d**)[c]	29.9 (**4e**)[c]	86 : 14
1d	**2c**	21.0 (**3e**)[d,c]	30.4 (**4f**)[d]	93 : 7
1d	**2d**	19.3 (**3f, A**), 19.5 (**3f, B**)[e]	29.6 (**4g, A**), 29.7 (**4g, B**)	92 : 8
1d	**2e**	19.7 (**3g, A**), 20.1 (**3g, B**)	29.8 (**4h, A**), 29.9 (**4h, B**)	93 : 7
1d	**5**	18.9, 19.3 (**6**)	28.1, 28.5 (**7**)	82 : 18[f]

[a] Diastereomeric racemates whose signals are shifted upfield are designated as **A**, while those with low-field signals, as **B**.
[b] In MeOH.
[c] In toluene.
[d] In $CDCl_3$, δ: 20.8.
[e] In $CDCl_3$, a single signal at δ 19.8.
[f] 6 : 7.

ture gave the corresponding amide **11a**. In the reaction with hydrazine hydrate, hydrazide **11b** was obtained (Scheme 4).

The compositions and structures of the compounds obtained were confirmed by data from elemental analysis (Table 2) and $^{31}P\{^1H\}$, ^1H (Table 3), and ^{13}C NMR spectroscopy.

Experimental

NMR spectra were recorded on Bruker AMX-400 and Bruker Avance 300 instruments (400.13 and 300.13 MHz, respectively) in $CDCl_3$, CD_3OD, and D_2O with signals for the residual protons of the deuterated solvents as the internal standards (^1H), in benzene, toluene, $CDCl_3$, MeOH, CD_3OD, and D_2O with 85% H_3PO_4 as the external standard (^{31}P), and in CD_3OD with signals for the solvent as the internal standards (^{13}C).

The starting 2-alkoxy-1,3,2-oxazaphosphinanes **1** were prepared as described earlier.[6,7]

In some cases, products were isolated by column chromatography on SiO_2 (Aldrich, 130—270 mesh, compound : SiO_2 mass ratio 1 : 16) with hexane—acetone (100 : 1 → 1 : 1) or $CHCl_3$—MeOH (50 : 1 → 3 : 2) as eluents. Analysis of the fractions was performed by TLC on SiO_2 in hexane—acetone (3 : 2) or $CHCl_3$—MeOH (10 : 1 or 3 : 2).

***N*-[(2-Oxo-1,3,2λ^5-oxazaphosphinan-2-yl)acetyl]glycine methyl ester (3a) and *N*-{[(3-bromopropylamino)ethoxyphosphoryl]acetyl}glycine methyl ester (4b).** A flow of argon was passed through a solution of *N*-bromoacetylglycine methyl ester (**2a**) (1.49 g, 10 mmol) in C_6H_6 (2 mL) and a solution of phosphinane **1b** in C_6H_6 (2.5 mL) was slowly added dropwise so that the reaction temperature did not exceed 50 °C. After the temperature decreased to ambient, the reaction mixture was heated to 50 °C, kept for 1 h, and then analyzed by ^{31}P NMR spectroscopy (see Table 1). The solvent was removed *in vacuo* (final temperature 60 °C (1 Torr)). The residue (3.34 g) was chromatographed on SiO_2 with $CHCl_3$—MeOH (50 : 2 → 3 : 2) as the eluent. The yields of compounds **4b** and **3a** were 1.94 g (54%) and 0.19 g (8%), respectively (see Tables 2, 3).

Under the same conditions, compound **3a** was obtained from phosphinane **1a** (1.20 g, 8.86 mmol) and compound **2a** (1.86 g, 8.86 mmol). Chromatography followed by precipitation from MeOH with acetone gave product **3a** (1.05 g, 47%).

***N*-[(3-Methyl-2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)acetyl]glycine methyl ester (3b)** was obtained analogously from phosphinane **1c** (0.74 g, 5 mmol) and compound **2a** (1.05 g, 5 mmol). Chromatography followed by recrystallization from acetone gave compound **3b** (0.69 g, 52%).

***N*-[(3-Isopropyl-2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)acetyl]glycine methyl ester (3c)** was obtained under the same conditions from phosphinane **1d** (0.78 g, 4.4 mmol) and compound **2a** (0.92 g, 4.4 mmol) and recrystallized from acetone. The yield of compound **3c** was 0.83 g (64%).

***N*-[(3-Isopropyl-2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)acetyl]glycine ethyl ester (3d).** A flow of argon was passed at 100—110 °C through a solution of *N*-chloroacetylglycine ethyl ester (**2b**) (1.80 g, 10 mmol) in toluene (2 mL) and a solution of phosphinane **1d** (1.77 g, 10 mmol) in toluene (1 mL) was slowly added dropwise. The reaction mixture was kept at this temperature for 7 h (monitoring by ^{31}P NMR spectroscopy). Cooling of the mixture caused crystallization. The solvent was removed *in vacuo* and the residue was recrystallized from benzene—ether. The yield of compound **3d** was 2.29 g (75%).

***N*-[(3-Isopropyl-2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)acetyl]-β-alanine ethyl ester (3e)** was obtained under the same conditions from phosphinane **1d** (1.77 g, 10 mmol) and ethyl 2-(*N*-chloroacetylamino)propionate (**2c**) (1.94 g, 10 mmol) and recrystallized from ether. The yield of compound **3e** was 1.92 g (63%).

Diethyl *N*-[(3-isopropyl-2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)acetyl]aspartate (3f) was obtained analogously from phosphinane **1d** (1.77 g, 10 mmol) and diethyl *N*-chloroacetyl-DL-aspartate (**2d**) (2.66 g, 10 mmol) and recrystallized from benzene with ether. The yield of compound **3f** was 2.60 g (68%). According to ^{31}P NMR data, this compound was a mixture of diastereomeric racemates in a 23 : 77 ratio. Reprecipitation from CH_2Cl_2 with ether gave an 8 : 92 mixture of racemates (see Tables 1—3).

Diethyl *N*-[(3-isopropyl-2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)acetyl]glutamate (3g) was obtained analogously from phosphinane **1d** (1.77 g, 10 mmol) and diethyl *N*-chloroacetyl-DL-glutamate (**2e**) (2.80 g, 10 mmol) and recrystallized from benzene with ether. The yield of compound **3g** was 2.56 (65%). According to ^{31}P NMR data, this compound was a mixture of diastereomeric racemates in a 30 : 70 ratio. Recrystallization from acetone with ether gave the individual diastereomeric racemate **3g, A** (1.40 g, 36%; see Tables 1—3).

***N*-[(3-Isopropyl-2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)methyl]-*N*-(methoxycarbonyl)glycine methyl ester (6) and *N*-({[*N*-(3-chloropropyl)-*N*-isopropylamino]methoxyphospho-**

Table 2. Yields, melting points, and elemental analysis data for the compounds obtained

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)				Molecular formula
			C	H	N	P	
3a	47	130—131	38.21 / 38.40	6.04 / 6.04	11.17 / 11.20	—	$C_8H_{15}N_2O_5P$
3b	52	106—107	41.11 / 40.91	6.81 / 6.48	—	11.46 / 11.72	$C_9H_{17}N_2O_5P$
3c	64	138—139	45.21 / 45.20	7.26 / 7.24	9.54 / 9.58	—	$C_{11}H_{21}N_2O_5P$
3d	75	119.5—121	47.09 / 47.05	7.60 / 7.57	9.02 / 9.15	10.07 / 10.11	$C_{12}H_{23}N_2O_5P$
3e	63	82—83	48.70 / 48.74	7.91 / 7.87	8.71 / 8.74	—	$C_{13}H_{25}N_2O_5P$
3f	68[a]	127—128[b]	47.59 / 47.36	7.64 / 7.68	7.36 / 7.36	—	$C_{15}H_{29}N_2O_7P$
3g	36[c]	104.5—105.5[d]	50.03 / 50.24	7.71 / 7.69	6.84 / 6.89	—	$C_{17}H_{31}N_2O_7P$
4b	54[e]	—	33.51 / 33.44	5.48 / 5.61	—[f]	8.14 / 8.62	$C_{10}H_{20}BrN_2O_5P$
6	45	—	44.54 / 44.72	7.18 / 7.19	—	9.38 / 9.61	$C_{12}H_{23}N_2O_6P$
7	9	—	41.85 / 41.88	6.95 / 7.03	—	—	$C_{13}H_{26}ClN_2O_6P$
9a	96	197—198	35.91 / 35.82	6.52 / 6.39	10.21 / 10.44	—	$C_8H_{17}N_2O_6P$
9c	91	142—143	37.36 / 37.34	6.21 / 6.22	7.31 / 7.16	—	$C_7H_{16}NO_5P$
9d	90	141—143	36.42 / 35.90	7.27 / 7.32	6.03 / 5.98	13.39 / 13.23	$C_7H_{16}NO_5P \cdot 0.5H_2O$
11a	73	129—130	43.71 / 43.63	7.76 / 7.78	12.65 / 12.72	—	$C_8H_{17}N_2O_3P$
11b	41	129—130	40.93 / 40.85	7.70 / 7.71	17.96 / 17.86	—	$C_8H_{18}N_3O_3P$

[a] The yield with respect to the mixture of diastereomeric racemates (23 : 77).
[b] The melting point of the mixture of diastereomeric racemates (8 : 92); for their 23 : 77 mixture, m.p. 116—119 °C.
[c] The yield with respect to one high-field diastereomeric racemate **3g (A)**; the yield of a mixture of the racemates was 68%.
[d] The melting point of individual diastereomeric racemate **3g (A)**; for the 30 : 70 mixture of racemates, m.p. 98—100 °C.
[e] The yield of compound **3a** in this reaction was 8%.
[f] Found/calculated (%): Br, 22.37/22.27.

ryl}methyl)-*N*-methoxycarbonylglycine methyl ester (7). A flow of argon was passed at 40 °C through a solution of *N*-chloromethyl-*N*-methoxycarbonylglycine methyl ester (**5**) (1.96 g, 10 mmol) in benzene (5 mL) and phosphinane **1d** (1.77 g, 10 mmol) was slowly added dropwise. The reaction mixture was heated at 80 °C for 6 h. The solvent was removed *in vacuo* (final temperature 60 °C (1 Torr)) and the residue (3.30 g) was chromatographed on SiO_2 with hexane—acetone as the eluent to give compound **7** (0.34 g, 9%) as an oil and compound **6** (1.46 g, 45%) as a glassy viscous substance (see Tables 1, 2).

3-Aminopropyl hydrogen [*N*-(methoxycarbonylmethyl)carbamoyl]methylphosphonate (9a). A solution of phosphinane **3a** (0.25 g) in water (5 mL) was kept at 20 °C for 7 days. The course of the reaction was monitored by ^{31}P NMR spectroscopy. The reaction mixture was concentrated to dryness *in vacuo* with addition of benzene and ethanol. The solid residue was recrystallized from ethanol. The yield of compound **9a** was 0.26 g (96%; see Tables 2, 3). ^{31}P NMR (H_2O), δ: 16.6. ^{13}C NMR (CD_3OD), δ: 28.06 (d, $C\underline{C}H_2C$, $^3J_{P,C}$ = 6.8 Hz); 36.22 (d, $\underline{C}H_2P$, $^1J_{P,C}$ = 121.4 Hz); 37.94 (s, $\underline{C}H_2NH_2$); 41.53 (s, $NH\underline{C}H_2C(O)$); 52.44 (s, $O\underline{C}H_3$); 62.74 (d, $\underline{C}H_2OP$, $^2J_{P,C}$ = 5.6 Hz); 170.48 (d, $PCH_2\underline{C}(O)$, $^2J_{P,C}$ = 5.2 Hz); 171.82 (s, $\underline{C}OOCH_3$).

3-Aminopropyl hydrogen ethoxycarbonylmethylphosphonate (9c) was obtained analogously from phosphinane **8b** (0.21 g, 1 mmol). Hydrolysis was completed in 1 day. The solvent was removed *in vacuo* and the residue was triturated with acetone.

Table 3. ^{1}H NMR spectra ($CDCl_3$) of the compounds obtained

Compound	δ, *J*/Hz
3a	1.77—1.82, 2.00—2.11 (both m, 1 H each, $CH_2C\underline{H}_2CH_2$); 2.95 (ABX system[a], 1 H, H_B, $CH_2P(O)$, $^2J_{H,H}$ = 14.5, $^2J_{P,H}$ = 17.0); 3.05 (ABX system, 1 H, H_A, $CH_2P(O)$, $^2J_{H,H}$ = 14.5, $^2J_{P,H}$ = 20.8); 3.31 (m, 2 H, $NC\underline{H}_2$); 3.60 (br.s, 1 H, $\underline{H}NP$); 3.74 (s, 3 H, $C\underline{H}_3O$); 3.80—3.91, 4.15—4.22 (both m, 1 H each, $C(O)C\underline{H}_2NH$); 4.25—4.32, 4.37—4.48 (both m, 1 H each, $C\underline{H}_2OP$); 7.37 (br.s, 1 H, $C(O)N\underline{H}$)
3b	1.83—1.89, 2.05—2.12 (both m, 1 H each, $CH_2C\underline{H}_2CH_2$); 2.71 (d, 3 H, $C\underline{H}_3N$, $^3J_{P,H}$ = 9.9); 2.93 (d, 2 H, $C\underline{H}_2P(O)$, $^3J_{P,H}$ = 18.6); 3.03—3.11, 3.15—3.21 (both m, 1 H each, $C\underline{H}_2NP$); 3.71 (s, 3 H, MeO); 3.94 (ABX system, 1 H, H_B, $NHC\underline{H}_2C(O)$, $^2J_{H,H}$ = 17.9, $^3J_{H,H}$ = 5.4); 4.06 (ABX system, 1 H, H_A, $NHC\underline{H}_2C(O)$, $^2J_{H,H}$ = 17.9, $^3J_{H,H}$ = 5.8); 4.20—4.38 (m, 2 H, $C\underline{H}_2OP$); 7.58 (br.s, 1 H, $C(O)N\underline{H}$)
3c	1.07, 1.18 (both d, 3 H each, $CHC\underline{H}_3$, $^3J_{H,H}$ = 6.8); 1.82—1.93, 1.98—2.08 (both m, 1 H each, $CH_2C\underline{H}_2CH_2$); 2.86 (ABX system, 1 H, H_B, $C\underline{H}_2P(O)$, $^2J_{H,H}$ = 14.8, $^2J_{P,H}$ = 18.0); 2.96 ((ABX system, 1 H, H_A, $C\underline{H}_2P(O)$, $^2J_{H,H}$ = 15.2, $^2J_{P,H}$ = 18.4); 3.01—3.08, 3.11—3.21 (both m, 1 H each, $C\underline{H}_2NP$); 3.72 (s, 3 H, $C\underline{H}_3O$); 3.89—3.95 (m, 1 H, $C\underline{H}CH_3$); 3.96 (ABX system, 1 H, H_B, $NHC\underline{H}_2C(O)$, $^2J_{H,H}$ = 18.0, $^3J_{H,H}$ = 5.2); 4.09 (ABX system, 1 H, H_A, $NHC\underline{H}_2C(O)$, $^2J_{H,H}$ = 18.0, $^3J_{H,H}$ = 6.0); 4.17—4.25, 4.29—4.38 (both m, 1 H each, $C\underline{H}_2OP$); 7.52 (br.s, 1 H, $C(O)N\underline{H}$)
3d	1.07, 1.18 (both d, 3 H each, $CHC\underline{H}_3$, $^3J_{H,H}$ = 6.8); 1.26 (t, 3 H, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.2); 1.79—1.88, 1.99—2.07 (both m, 1 H each, $CH_2C\underline{H}_2CH_2$); 2.86 (ABX system, 1 H, H_B, $C\underline{H}_2P(O)$, $^2J_{H,H}$ = 15.2, $^2J_{P,H}$ = 18.0); 2.96 (ABX system, 1 H, H_A, $C\underline{H}_2P(O)$, $^2J_{H,H}$ = 15.2, $^2J_{P,H}$ = 18.0); 3.01—3.08, 3.12—3.20 (both m, 1 H each, $C\underline{H}_2NP$); 3.89—3.96 (m, 1 H, $C\underline{H}CH_3$); 3.95 (ABX system, 1 H, H_B, $NHC\underline{H}_2C(O)$, $^2J_{H,H}$ = 18.0, $^3J_{H,H}$ = 5.2); 4.07 (ABX system, 1 H, H_A, $NHC\underline{H}_2C(O)$, $^2J_{H,H}$ = 18.0, $^3J_{H,H}$ = 6.0); 4.18 (q, 2 H, $C\underline{H}_2CH_3$, $^3J_{H,H}$ = 7.2); 4.18—4.26, 4.29—4.39 (both m, 1 H each, $C\underline{H}_2OP$); 7.47 (br.s, 1 H, $C(O)N\underline{H}$)
3e	1.07, 1.17 (both d, 3 H each, $CHC\underline{H}_3$, $^3J_{H,H}$ = 6.8); 1.24 (t, 3 H, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 6.8); 1.77—1.85, 1.99—2.05 (both m, 1 H each, $CH_2C\underline{H}_2CH_2$); 2.52 (t, 2 H, $CH_2C\underline{H}_2C(O)$, $^3J_{H,H}$ = 6.4); 2.78 (ABX system, 1 H, H_B, $C\underline{H}_2P(O)$, $^2J_{H,H}$ = 15.2, $^2J_{P,H}$ = 17.6); 2.88 (ABX system, 1 H, H_A, $C\underline{H}_2P(O)$, $^2J_{H,H}$ = 14.8, $^2J_{P,H}$ = 18.4); 2.99—3.07, 3.10—3.19 (both m, 1 H each, $C\underline{H}_2NP$); 3.50—3.56 (m, 2 H, $NHC\underline{H}_2CH_2$); 3.82—3.91 (m, 1 H, $C\underline{H}CH_3$); 4.14 (q, 2 H, $C\underline{H}_2CH_3$, $^3J_{H,H}$ = 7.2); 4.13—4.24, 4.27—4.37 (both m, 1 H each, $C\underline{H}_2OP$); 7.25 (br.s, 1 H, $C(O)N\underline{H}$)
3f	1.08, 1.18 (both d, 3 H each, $CHC\underline{H}_3$, $^3J_{H,H}$ = 6.8); 1.24, 1.25 (both t, 3 H each, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.1); 1.85—1.91, 1.95—2.05 (both m, 1 H each, $CH_2C\underline{H}_2CH_2$); 2.76—2.96 (m, 2 H, $CHC\underline{H}_2C(O)$); 2.90 (ABX system, 1 H, H_B, $C\underline{H}_2P(O)$, $^2J_{H,H}$ = 16.8, $^2J_{P,H}$ = 4.8); 2.98 (ABX system, 1 H, H_A, $C\underline{H}_2P(O)$, $^2J_{H,H}$ = 16.8, $^2J_{P,H}$ = 4.8); 3.01—3.09, 3.12—3.21 (both m, 1 H each, $C\underline{H}_2NP$); 3.78—3.90 (m, 1 H, $C\underline{H}CH_3$); 4.14, 4.20 (both q, 2 H each, $C\underline{H}_2CH_3$, $^3J_{H,H}$ = 7.1); 4.23—4.29, 4.32—4.39 (both m, 1 H each, $C\underline{H}_2OP$); 4.82 (dt, 1 H, $NHC\underline{H}CH_2$, $^3J_{H,H}$ = 8.0, $^3J_{H,H}$ = 6.0); 7.57 (d, 1 H, $N\underline{H}CH$, $^3J_{H,H}$ = 7.9)
3g	1.16, 1.25 (both d, 3 H each, $CHC\underline{H}_3$, $^3J_{H,H}$ = 6.6); 1.30, 1.34 (both t, 3 H each, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.1); 1.88—1.99, 2.21—2.32 (both m, 1 H each, $CH_2C\underline{H}_2CH_2$); 2.01—2.13 (m, 2 H, $CHC\underline{H}_2CH_2$); 2.37—2.55 (m, 2 H, $CH_2C\underline{H}_2C(O)$); 2.96 (d, 2 H, $C\underline{H}_2P(O)$, $^2J_{P,H}$ = 18.2); 3.06—3.29 (m, 2 H, $C\underline{H}_2NP$); 3.88—4.01 (m, 1 H, $C\underline{H}CH_3$); 4.18, 4.25 (both q, 2 H each, $C\underline{H}_2CH_3$, $^3J_{H,H}$ = 7.1); 4.22—4.30, 4.33—4.46 (both m, 1 H each, $C\underline{H}_2OP$); 4.63 (dt, 1 H, $NHC\underline{H}CH_2$, $^3J_{H,H}$ = 7.5, $^3J_{H,H}$ = 5.5); 7.46 (d, 1 H, $N\underline{H}CH$, $^3J_{H,H}$ = 7.5)
9a[b]	1.99 (quint, 2 H, $CH_2C\underline{H}_2CH_2$, $^3J_{H,H}$ = 6.0); 2.82 (d, 2 H, $C\underline{H}_2P(O)$, $^2J_{P,H}$ = 20.2); 3.14 (t, 2 H, $C\underline{H}_2N$, $^3J_{H,H}$ = 6.5); 3.74 (s, 3 H, MeO); 3.99—4.03 (overlapping, 4 H, $C\underline{H}_2P(O)$, $NHC\underline{H}_2C(O)$)
9b[b]	2.00 (br.s, 2 H, $CH_2C\underline{H}_2CH_2$); 2.89 (d, 2 H, $C\underline{H}_2P(O)$, $^2J_{P,H}$ = 20.9); 3.15 (br.s, 2 H, $C\underline{H}_2N$); 3.71 (s, 3 H, MeO); 4.00 (br.s, 2 H, $C\underline{H}_2OP$)
9c[c]	1.46 (t, 3 H, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.8); 2.17 (quint, 2 H, $CH_2C\underline{H}_2CH_2$, $^3J_{H,H}$ = 6.1); 2.99 (d, 2 H, $C\underline{H}_2P(O)$, $^2J_{P,H}$ = 20.4); 3.29 (t, 2 H, $C\underline{H}_2N$, $^3J_{H,H}$ = 6.8); 4.22 (q, 2 H, $OC\underline{H}_2CH_3$, $^3J_{H,H}$ = 6.0); 4.34 (q, 2 H, $C\underline{H}_2OP$, $^3J_{P,H}$ = $^3J_{H,H}$ = 7.2)
9d[c]	1.92 (br.s, 2 H, $CH_2C\underline{H}_2CH_2$); 2.63 (s, 3 H, NMe); 2.74 (d, 2 H, $C\underline{H}_2P(O)$, $^2J_{P,H}$ = 27.4); 3.08 (br.s, 2 H, $C\underline{H}_2N$); 3.23 (s, 3 H, OMe); 3.95 (br.s, 2 H, $C\underline{H}_2OP$)
11a	1.09, 1.18 (both d, 3 H each, $CHC\underline{H}_3$, $^3J_{H,H}$ = 6.8); 1.82—1.88, 1.99—2.09 (both m, 1 H each, $CH_2C\underline{H}_2CH_2$); 2.81 (ABX system, 1 H, H_B, $C\underline{H}_2P(O)$, $^2J_{H,H}$ = 14.8, $^2J_{P,H}$ = 17.6); 2.91 (ABX system, 1 H, H_A, $C\underline{H}_2P(O)$, $^2J_{H,H}$ = 14.8, $^2J_{P,H}$ = 18.0); 3.00—3.08, 3.13—3.23 (both m, 1 H each, $C\underline{H}_2NP$); 3.85—3.97 (m, 1 H, $C\underline{H}CH_3$); 4.17—4.25, 4.30—4.39 (both m, 1 H each, $C\underline{H}_2OP$); 5.50, 7.03 (both s, 1 H each, $\underline{H}_2NC(O)$)
11b	1.08, 1.17 (both d, 3 H each, $CHC\underline{H}_3$, $^3J_{H,H}$ = 6.8); 1.80—1.89, 1.98—2.08 (both m, 1 H each, $CH_2C\underline{H}_2CH_2$); 2.82 (ABX system, 1 H, H_B, $C\underline{H}_2P(O)$, $^2J_{H,H}$ = 15.2, $^2J_{P,H}$ = 18.0); 2.91 (ABX system, 1 H, H_A, $C\underline{H}_2P(O)$, $^2J_{H,H}$ = 15.2, $^2J_{P,H}$ = 18.0); 3.00—3.08, 3.11—3.21 (both m, 1 H each, $C\underline{H}_2NP$); 3.70 (br.s , 2 H, $N\underline{H}_2$); 3.83—3.93 (m, 1 H, $C\underline{H}CH_3$); 4.17—4.25, 4.29—4.38 (both m, 1 H each, $C\underline{H}_2OP$); 8.30 (s, 1 H, $N\underline{H}NH_2$)

[a] Hereafter, AB is the part of the ABX-spin system, where X stands for the phosphorus atom.
[b] In D_2O.
[c] In CD_3OD.

The precipitate was separated and recrystallized from ethanol—acetone to give compound **9c** (0.20 g, 91%; see Tables 2, 3). ^{31}P NMR (H_2O), δ: 15.7. ^{13}C NMR (CD_3OD), δ: 13.80 (s, $CH_2\underline{C}H_3$); 28.51 (d, $C\underline{C}H_2C$, $^3J_{P,C}$ = 6.0 Hz); 35.38 (d, $\underline{C}H_2P$, $^1J_{P,C}$ = 121.3 Hz); 37.61 (s, $\underline{C}H_2NH_2$); 61.27 (s, $O\underline{C}H_2CH_3$); 62.33 (d, $\underline{C}H_2OP$, $^2J_{P,C}$ = 5.6 Hz); 169.77 (d, $PCH_2\underline{C}(O)$, $^2J_{P,C}$ = 6.4 Hz).

3-Methylaminopropyl hydrogen methoxycarbonylmethylphosphonate (9d). Phosphinane **8c** underwent hydrolysis by atmospheric moisture on storage to give crystalline product **9d**. Trituration with acetone gave the title compound in 90% yield (see Tables 2, 3). ^{31}P NMR (H_2O), δ: 15.8; (CD_3OD), δ: 14.8.

3-Aminopropyl hydrogen methoxycarbonylmethylphosphonate (9b) was obtained analogously, m.p. 150—153 °C (see Table 3). ^{31}P NMR (H_2O), δ: 15.7.

(3-Isopropyl-2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)acetamide (11a). Dry NH_3 was passed through a stirred solution of phosphinane **10** (0.70 g, 3 mmol) in anhydrous MeOH (5 mL) (the process was exothermic) until the temperature decreased to ambient. The reaction mixture was left for 7 days (monitoring by ^{31}P NMR spectroscopy). The solvent was removed *in vacuo* and the residue was recrystallized from benzene with acetone. The yield of amide **11a** was 0.48 g (73%). ^{31}P NMR (MeOH), δ: 22.3; ($CDCl_3$), δ: 20.7 (see Tables 2, 3).

(3-Isopropyl-2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)acetohydrazide (11b). A flow of argon was passed through a solution of hydrazine hydrate (0.14 g, 2.8 mmol) in dry MeOH (2 mL) and phosphinane **10** (0.66 g, 2.8 mmol) in MeOH (2 mL) was added dropwise. The course of the reaction was monitored by ^{31}P NMR spectroscopy. After 15 days, the solvent was removed *in vacuo* at 20 °C. The glassy residue was triturated with a mixture of benzene and ether and recrystallized from benzene. The yield of hydrazide **11b** was 0.27 g (41%). ^{31}P NMR (MeOH), δ: 21.8; ($CDCl_3$), δ: 20.3 (see Tables 2, 3).

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