Two-fragment α-adrenolytics
3.* Addition of primary amines to alkyl divinylphosphinates and phenyl(divinyl)phosphine oxide

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Primary alkylamines, β-aryloxyethylamines, or *N*-[β-(2-methoxyphenoxy)ethyl]-α,ω-diaminoalkanes react with alkyl divinylphosphinates or phenyl(divinyl)phosphine oxide to give the corresponding 4-alkoxy(4-phenyl)-1-alkyl-4-oxo-1,4-azaphosphorinanes. Reactions of the latter with mono- or dihaloalkanes afford 4-phosphapiperidinium halides. 1,4-Azaphosphorinanes containing a β-aryloxyethyl fragment exhibit hypotensive activity.

Key words: alkylamines, α,ω-diaminoalkanes, alkyl divinylphosphinates, phenyl(divinyl)phosphine oxide, 4-alkoxy(4-phenyl)-1-alkyl-1,4-azaphosphorinane 4-oxides, 4-alkoxy-1,1-dialkyl-4-oxo-4λ⁵-phosphapiperidinium halides, hypotensive activity.

Addition of primary and secondary amines to organophosphorus compounds containing a phosphorus-bound vinyl group is a convenient method for the synthesis of various β-aminoalkylphosphonates, -phosphinates, and -phosphine oxides,[2] including those exhibiting hypotensive activity.[3]

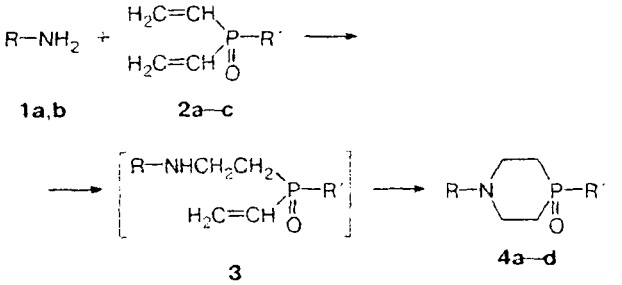
In contrast, reactions of compounds with two vinyl groups at the phosphorus atom, *e.g.*, divinylphosphinates and divinylphosphine oxides, with primary amines have not been studied so far (although, theoretically, they could result in not only linear but also cyclic products).

To synthesize heterocyclic compounds with nitrogen and phosphorus atoms, *viz.*, 1,4-azaphosphorinanes, we studied reaction of primary amines with alkyl divinylphosphinates and phenyl(divinyl)phosphine oxide.[4] It was found that methylamine (**1a**) and ethylamine (**1b**) react with alkyl divinylphosphinates (**2a,b**) or phenyl(divinyl)phosphine oxide (**2c**) in anhydrous ethanol at 60—70 °C to give 1 : 1 adducts (Scheme 1).

Studying the structures of these products (see below) suggests that the reaction does not stop at the stage of addition of amines to one vinyl group, and intermediate **3** undergoes intramolecular cyclization into 4-alkoxy(4-phenyl)-1-alkyl-1,4-azaphosphorinane 4-oxides (**4**).

The structures of compounds **4a—d** were confirmed by IR and ^{31}P and ^{1}H NMR spectroscopic data. The IR spectra of addition products **4a,b,d** exhibit characteristic absorption bands at 1050—1060 cm^{-1} (ν(P—O—C)) and 1220—1235 cm^{-1} (ν(P=O)) but do not contain bands at 1600—1660 cm^{-1} and 3000—3100 cm^{-1} typical of compounds with double bonds. The spectrum of azaphosphorinane **4c** shows bands at 1170 cm^{-1} (ν(P=O)), 1590 and 3050 cm^{-1} (ν(Ph)), and 2804 cm^{-1} (ν(Me—N)). None of the products obtained absorbs in the range of the secondary amino group R—NH—CH_2 (3300—3450 cm^{-1}), which, along with the absence of absorption for a vinyl group, proves them to be true azaphosphorinanes (cycloaddition products) rather than their precursors **3**, linear products of addition at only one vinyl group.

Scheme 1



1: R = Me (**a**), Et (**b**);
2: R' = OMe (**a**), OEt (**b**), Ph (**c**);
4: R = Me, R' = OMe (**a**), OEt (**b**), Ph (**c**);
R = Et, R' = OEt (**d**)

^{31}P NMR spectra exhibit a singlet at δ 42—45 for **4a,b,d** and δ 23 for **4c**, which also supports this conclusion.

^{1}H NMR spectra are consistent with the proposed structure as well. Thus, P-bonded methylene groups in **4c** manifest themselves as a complex multiplet at δ

* For Part 2 see Ref. 1.

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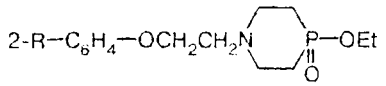
1.90—2.30 because of spin-spin coupling with ^{31}P nuclei. A multiplet signal at δ 2.80—3.10 was assigned to N-bonded methylene groups from chemical shifts for structurally similar molecular fragments.[5] Comparison between the integrated intensities of signals confirms that the peaks were assigned correctly.

Previously, we reported the synthesis of phosphonates[3] and phosphine oxides[1] containing an α-adrenolytic fragment in their phosphorus-bound alkyl substituent. In the present work, two-fragment α-adrenolytics with ring phosphorus and nitrogen atoms were obtained by reactions of divinylphosphinate (**2b**) with β-aryloxyethylamines **5** or *N*-[β-(2-methoxyphenoxy)-ethyl]-α,ω-diaminoalkanes (**6**).

β-Aryloxyethylamines **5** react with ethyl divinylphosphinate (**2b**) in boiling anhydrous ethanol for 2—3 h to give the corresponding 1-β-aryloxyethyl-4-ethoxy-1,4-azaphosphorinane 4-oxides (**7**).

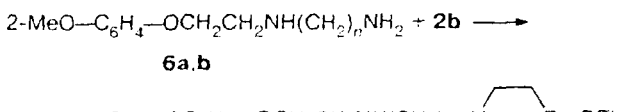


7a,b

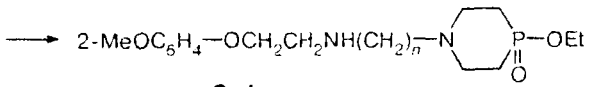
R = Me (**a**), MeO (**b**)

Like β-aryloxyethylamines, *N*-[β-(2-methoxyphenoxy)ethyl]-α,ω-diaminoalkanes (**6**) also react with divinylphosphinate **2b** to form 1-ω-[β-(2-methoxyphenoxy)-ethylamino]alkyl-4-ethoxy-1,4-azaphosphorinane 4-oxides (**8**), the reaction time being extended to 7—8 h (Scheme 2).

Scheme 2



6a,b



8a,b

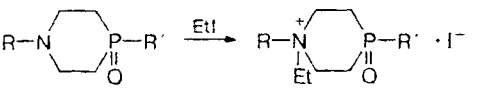
n = 2 (**a**), 4 (**b**)

Although compounds **6** contains both primary and secondary amino groups and either can add divinylphosphinate **2b**, only cycloaddition products **8a,b** were isolated in high yields under these reaction conditions. The secondary amino group is not involved here, as in the case of addition of compounds **6** to dialkyl vinylphosphonates.[3]

Azaphosphorinanes **7a,b** and **8a,b** are viscous liquids soluble in most organic solvents and dilute mineral acids. Their IR spectra show characteristic absorption bands at 1050—1055 (ν(P—O—C)), 1225—1230 (ν(P=O)), 1596—1605 (ν_{arom}), and 3040—3070 cm^{-1} (ν(=CH)) but do not contain bands at 1610—1660 cm^{-1} ($\nu(CH_2{=}CH)$). In addition, compounds **8a,b** absorb at 3320 cm^{-1} ($(CH_2)_2NH(CH_2)_n$), but there is no doublet in the range 3200—3500 cm^{-1} characteristic of an NH_2 group.

As tertiary amines, the 1,4-azaphosphorinanes synthesized react with mono- and dihaloalkanes to give heterocyclic ammonium salts. Thus, heating of azaphosphorinanes **4a,b,d** with a twofold molar excess of EtI at 60—65 °C for 2 h yielded 4-alkoxy-1-alkyl-1-ethyl-4-oxo-4λ^5-phosphapiperidinium iodides (**9a—c**)[6] (Scheme 3).

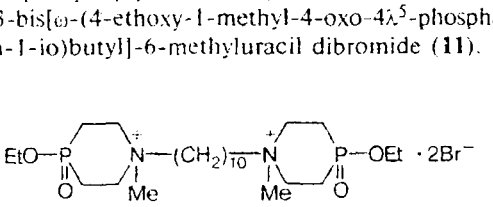
Scheme 3



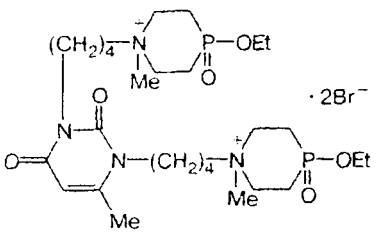
4a,b,d **9a—c**

9: R = Me, R′ = OMe (**a**), OEt (**b**);
R = Et, R′ = OEt (**c**)

The reaction of azaphosphorinane **4b** with 1,10-dibromodecane and 1,3-bis(ω-bromobutyl)-6-methyluracil results in the corresponding bisquaternary ammonium salts, namely, 1,10-bis(4-ethoxy-1-methyl-4-oxo-4λ^5-phosphapiperidin-1-io)decane dibromide (**10**) and 1,3-bis[ω-(4-ethoxy-1-methyl-4-oxo-4λ^5-phosphapiperidin-1-io)butyl]-6-methyluracil dibromide (**11**).



10



11

Phosphapiperidinium halides **9—11** are white crystalline substances soluble in alcohol and water. Their IR spectra contain characteristic absorption bands at 1030—1040 cm^{-1} (ν(P—O—C)) and 1220—1260 cm^{-1} (ν(P=O)). In addition, the spectrum of **11** shows two intense bands at 1660 and 1705 cm^{-1} typical of uracil ν(C=O).

Yields and physicochemical and analytical data on the compounds synthesized are presented in Tables 1 and 2.

1,4-Azaphosphorinanes **7a,b** and **8a,b** with a β-aryloxyethyl radical exhibit hypotensive activity. When injected intravenously into rabbits in a dose of 2.5 mg kg^{-1}, they induce fast decrease of blood pressure by 35 to 45%. After one hour, the hypotensive effect was 5 to 9%.

Table 1. Main characteristics of the 1,4-azaphosphorinanes synthesized

Compound	Yield (%)	B.p./°C (p/Torr)	n_D^{20}	d_4^{20}	Found / Calculated (%) C	H	N	P	Molecular formula	δ_P
4a	38	72–75 (0.03)	1.4805	1.0981	44.02 / 44.17	8.51 / 8.65	8.80 / 8.59	19.27 / 18.98	$C_6H_{14}NO_2P$	45
4b	61	75–77 (0.03)	1.4750	1.0836	47.30 / 47.45	9.17 / 9.10	8.80 / 7.91	17.72 / 17.48	$C_7H_{16}NO_2P$	42
4c	61	150–153[a] (0.008)	—	—	63.12 / 63.14	7.84 / 7.71	6.91 / 6.69	14.80 / 14.80	$C_{11}H_{16}NOP$	23
4d	53	77–80 (0.003)	1.4770	1.0675	50.16 / 50.25	9.47 / 9.49	7.29 / 7.33	15.49 / 16.20	$C_8H_{18}NO_2P$	44
7a	47	235–238[b] (0.001)	1.5010	1.1015	59.71 / 60.59	8.21 / 8.14	4.75 / 4.71	10.18 / 10.42	$C_{15}H_{24}NO_3P$	44
7b	40	240–243[b] (0.001)	1.5382	—	58.04 / 57.50	7.70 / 7.72	4.52 / 4.47	9.59 / 9.89	$C_{15}H_{24}NO_4P$	44
8a	93	[c]	—	—	57.33 / 57.29	8.22 / 8.20	7.62 / 7.86	8.20 / 8.69	$C_{17}H_{29}N_2O_4P$	44
8b	90	[c]	—	—	59.53 / 59.36	8.44 / 8.65	7.23 / 7.29	7.99 / 8.06	$C_{19}H_{33}N_2O_4P$	44

[a] M.p. 109–110 °C.
[b] The temperature of the heating element in a molecular distillation setup.
[c] Thick oil.

Table 2. Physicochemical constants and analytical data for 4-phosphapiperidinium halides

Compound	Yield (%)	M.p./°C	Found / Calculated (%) C	H	N	P	Hal	Molecular formula	δ_P
9a	89	195–196	30.21 / 30.11	6.12 / 6.00	4.57 / 4.39	9.92 / 9.71	39.54 / 39.44	$C_8H_{19}INO_2P$	42
9b	97	209–210	32.37 / 32.44	6.40 / 6.35	4.21 / 4.20	9.38 / 9.30	37.90 / 38.09	$C_9H_{21}INO_2P$	41
9c	96	188–189	34.48 / 34.59	6.70 / 6.68	4.07 / 4.03	9.05 / 8.92	36.30 / 36.55	$C_{10}H_{23}INO_2P$	41
10	91	>90 decomp.	43.82 / 44.04	8.23 / 8.01	4.17 / 4.28	9.28 / 9.47	24.27 / 24.42	$C_{24}H_{52}Br_2N_2O_4P_2$	42
11	63	>72 decomp.	43.58 / 43.21	6.95 / 6.98	7.47 / 7.47	8.29 / 8.25	21.05 / 21.30	$C_{27}H_{52}Br_2N_4O_6P_2$	43

This effect is close to that produced by the acyclic β-(aryloxyethylamino)ethylphosphonates we synthesized previously.[3] Thus, the inclusion of phosphorus and nitrogen in a saturated six-membered ring insignificantly affects the hypotensive activity of compounds.

Experimental

IR spectra were recorded on a Specord 75IR spectrophotometer (thin film or Vaseline oil between KBr plates) in the range 400–4000 cm^{-1}. ^1H NMR spectra were recorded on a Bruker WM-250 spectrometer (250.13 MHz) with tetramethylsilane as the internal standard. ^{31}P NMR spectra were recorded on a KGU-4 instrument (10.2 MHz) with 85% H_3PO_4 as the internal standard. The starting alkyl divinylphosphinates **2a,b**,[7] phenyl(divinyl)phosphine oxide,[8] β-aryloxyethylamines **5a,b**,[9,10] and 1,3-bis(ω-bromobutyl)-6-methyluracil[11] were prepared according to the known procedures. Their physicochemical constants agree with the literature data.

4-Ethoxy-1-methyl-1,4-azaphosphorinane 4-oxide (4b). Methylamine (1.56 g, 0.05 mol) was passed with stirring through a solution of ethyl divinylphosphinate (**2b**) (7.2 g, 0.049 mol) in 100 mL of anhydrous ethanol. A temperature rise from 24 to 28 °C was observed. The reaction mixture was heated at 60–65 °C for 2 h, the ethanol was removed, and the residue was distilled *in vacuo* to give azaphosphorinane **4b** (5.3 g). ^1H NMR (C_6H_6), δ: 1.29 (t, 3 H, $CH_2-C\underline{H}_3$, $^3J_{HH}$ = 13.1 Hz); 1.65–2.09 (m, 4 H, $P(CH_2)_2$); 2.24 (s, 3 H, NMe); 2.32–2.88 (m, 4 H, $N(CH_2)_2$); 3.84–4.15 (m, 2 H, OCH_2).

Under similar conditions, **4-methoxy-1-methyl-1,4-azaphosphorinane 4-oxide (4a)** was obtained by addition of methylamine to methyl divinylphosphinate (**2a**).

4-Ethoxy-1-ethyl-1,4-azaphosphorinane 4-oxide (4d). A solution of KOH (7.6 g, 0.135 mol) in 30 mL of ethanol was added dropwise with stirring at 10 °C to a mixture of ethyl divinylphosphinate (**2b**) (16.5 g, 0.113 mol) and ethylamine hydrochloride (11 g, 0.135 mol) in 50 mL of ethanol. The temperature was maintained using external cooling. Then, the reaction mixture was heated and kept at 65—70 °C for 2.5 h. After one day, the precipitate that formed was filtered off and washed with ethanol. The ethanol was removed from the filtrate, and the residue was distilled *in vacuo* to give azaphosphorinane **4d** (11.4 g).

1-Methyl-4-phenyl-1,4-azaphosphorinane 4-oxide (4c) was obtained by analogy with **4d** from phenyl(divinyl)phosphine oxide (**2c**) and methylamine hydrochloride. ^{1}H NMR ($CDCl_3$), δ: 1.90—2.30 (m, 4 H, $P(CH_2)_2$); 2.41 (s, 3 H, NMe); 2.80—3.10 (m, 4 H, $N(CH_2)_2$); 7.45—7.85 (m, 5 H, Ph).

1-[2-(2-Methylphenoxy)ethyl]-4-ethoxy-1,4-azaphosphorinane 4-oxide (7a). β-(2-Methylphenoxy)ethylamine (**5a**) (8.3 g, 0.055 mol) was added dropwise with stirring to a solution of ethyl divinylphosphinate (**2b**) (7.3 g, 0.05 mol) in 30 mL of anhydrous ethanol. A temperature rise from 22 to 27 °C was observed. The reaction mixture was refluxed for 2 h. Then, the ethanol was removed, and the residue was distilled on a molecular distillation setup to give azaphosphorinane **7a** (6 g).

1-[2-(2-Methoxyphenoxy)ethyl]-4-ethoxy-1,4-azaphosphorinane 4-oxide (7b) was obtained as described for **7a** from β-(2-methoxyphenoxy)ethylamine (**5b**) and ethyl divinylphosphinate (**2b**).

1-{2-[2'-(2-Methoxyphenoxy)ethylamino]ethyl}-4-ethoxy-1,4-azaphosphorinane 4-oxide (8a). A solution of ethyl divinylphosphinate (**2b**) (7.3 g, 0.05 mol) and 10.5 g (0.05 mol) *N*-[β-(2-methoxyphenoxy)ethyl]-1,2-diaminoethane (**6a**) in 50 mL of anhydrous ethanol was refluxed for 8 h. The ethanol was removed *in vacuo* (10—12 Torr), and the product was extracted with ether. The ether was removed, and the residue was kept at 90—100 °C (0.003 Torr) for 30 min to give compound **8a** (16.5 g).

1-{4-[2'-(2-Methoxyphenoxy)ethylamino]butyl}-4-ethoxy-1,4-azaphosphorinane 4-oxide (8b) was obtained in a similar way from *N*-[β-(2-methoxyphenoxy)ethyl]-1,2-diaminobutane (**6b**) and ethyl divinylphosphinate (**2b**).

1-Ethyl-4-methoxy-1-methyl-4-oxo-4λ^5-phosphapiperidinium iodide (9a). A mixture of azaphosphorinane **4a** (1.3 g, 0.008 mol) and EtI (2.5 g, 0.016 mol) was heated at 60—65 °C for 2 h. The excess of EtI was removed, and the residue was recrystallized from butanol to give compound **9a** (2.27 g).

Compounds **9b,c** were obtained by analogy with **9a** from the corresponding azaphosphorinanes **4b,d** and EtI.

1,1'-Decamethylenedi(4-ethoxy-1-methyl-4-oxo-4λ^5-phosphapiperidinium) dibromide (10). A mixture of azaphosphorinane **4a** (1.77 g, 0.01 mol) and 1,10-dibromodecane (1.5 g, 0.005 mol) was kept at ~20 °C for two days. The reaction mixture crystallized and was thoroughly triturated with anhydrous ether (30 mL). The crystals were filtered off, washed with ether, and dried *in vacuo* (0.02 Torr) at 40—50 °C to give compound **10** (2.98 g).

1,3-Bis[ω-(4-ethoxy-1-methyl-4-oxo-4λ^5-phosphapiperidin-1-io)butyl]-6-methyluracil dibromide (11). A solution of azaphosphorinane **4a** (1.77 g, 0.01 mol) and 1,3-bis(ω-bromobutyl)-6-methyluracil (1.98 g, 0.005 mol) in 30 mL of ethyl methyl ketone was refluxed for 14 h. The crystals that formed were filtered off, washed thoroughly with ether, and dried *in vacuo* (0.02 Torr) at 35—40 °C to give compound **11** (2.36 g).

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