Two-fragment α-adrenolytics
2.* Synthesis of alkyl(phenyl)[ω-(*N*-phenylpiperazino)alkyl]phosphine oxides

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A method for the synthesis of hypotensive alkyl(phenyl)[ω-(*N*-phenylpiperazino)alkyl]-phosphine oxides by reacting alkyl(ω-haloalkyl)phenylphosphine oxides with *N*-phenylpiperazine was elaborated. Phenyl[γ-(*N*-phenylpiperazino)propyl]propylphosphine oxide reacts with alkyl halides to give [γ-(*N*-alkyl-*N'*-phenylpiperazinio)propyl]phenyl(propyl)oxophosphine halides.

Key words: ethyl alkyl(phenyl)phosphinites, alkyl(ω-haloalkyl)phenylphosphine oxides, *N*-phenylpiperazine, alkyl(phenyl)[ω-(*N*-phenylpiperazino)alkyl]phosphine oxides, [γ-(*N*-alkyl-*N'*-phenylpiperazinio)propyl]phenyl(propyl)oxophosphine halides, hypotensive activity.

Previously,[1] it was shown that addition of β-aryloxyethylamines and *N*-arylpiperazines to dialkyl vinylphosphonates results in phosphonates whose phosphorus-bonded alkyl radical contains β-aryloxyethylamino and *N*-arylpiperazino groups. The compounds synthesized are superior to the original α-adrenolytics in the length of hypotensive effect.

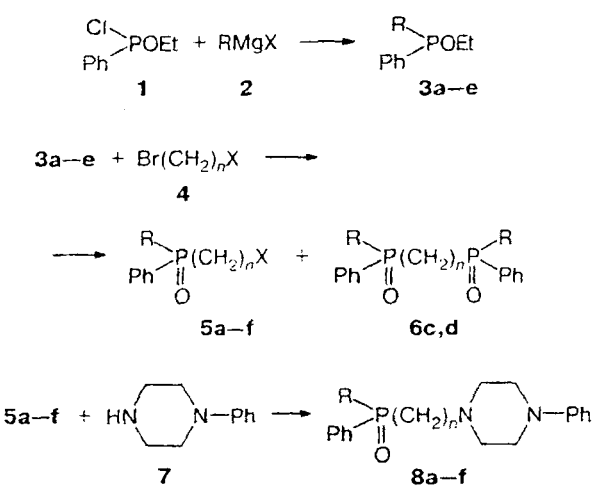
However, this way of phosphorylating amines can be used only to synthesize compounds with two methylene groups between the phosphorus and nitrogen atoms in an α-adrenolytic. A reaction of amines with haloalkane derivatives containing tetracoordinated phosphorus in the ω-position is a more versatile method for preparation of functionalized amines with another number of methylene groups.[2]

In continuation of investigations on the synthesis of two-fragment α-adrenolytics,[1] the above method was used for preparation of phosphine oxides with an *N*-phenylpiperazine fragment separated from the phosphorus atom by three or four methylene groups. The method includes a series of successive transformations (Scheme 1).

The reactions of ethyl chloro(phenyl)phosphonite (**1**) with the corresponding alkylmagnesium halides **2** were carried out under the conditions described previously[3] for the synthesis of **3b** and resulted in ethyl alkyl(phenyl)phosphinites **3a,c—e**. The yields, physicochemical constants, and data from elemental analysis for the compounds obtained are given in Table 1.

Phosphinites **3a—e** react with α,ω-dihaloalkanes **4** to give alkyl(ω-haloalkyl)phenylphosphine oxides **5a—f**. Note the occasional formation of 1,3-bisphosphorylated propanes **6c,d** (4 to 5% yield), although we used α,γ-bromochloropropane with halogen atoms differing in reactivity. The yields, physicochemical constants, data from elemental analysis, and ^{31}P NMR spectral parameters for **5a—f** and **6c,d** are presented in Table 2.

Scheme 1



n = 3, X = Cl, R = Me (**a**), Et (**b**), Pr (**c**), Bu (**d**), *n*-C_9H_{19} (**e**);
n = 4, X = Br, R = Pr (**f**)

The IR spectra of these compounds contain characteristic absorption bands at 1175—1185 cm^{-1} (ν(P=O)) and 1590—1600 cm^{-1} (ν_{arom}).

All phosphine oxides **5**, except for **5e,f**, were isolated from the reaction mixture by distillation *in vacuo*. In the distillation, phosphine oxide **5e** decomposes with strong

* For Part 1 see Ref. 1.

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Table 1. Main physicochemical characteristics and elemental analysis data for the phosphinites synthesized

Compound	Yield (%)	B.p./°C (p/Torr)	n_D^{20}	d_4^{20}	Found / Calculated (%)			Molecular formula
					C	H	P	
3a	41	89–90 (10)	1.5306	1.0035	61.12 / 64.28	7.58 / 7.79	18.48 / 18.42	$C_9H_{13}OP$
3c	49	60–63 (0.04)	1.5200	0.9657	67.05 / 67.33	8.28 / 8.73	15.64 / 15.78	$C_{11}H_{17}OP$
3d	55	72–73 (0.025)	1.5168	0.9644	68.92 / 68.55	9.26 / 9.11	14.76 / 14.73	$C_{12}H_{19}OP$
3e	48	130–132 (0.1)	1.4990	0.9171	72.53 / 72.82	10.57 / 10.42	10.94 / 11.04	$C_{17}H_{29}OP$

Table 2. Yields, physicochemical constants, elemental analysis data, and ^{31}P NMR spectral data for compounds **5a–f** and **6c,d**

Compound	Yield (%)	B.p. /°C (p/Torr)	M.p. /°C	Found / Calculated (%)			Molecular formula	δ_P
				C	H	P		
5a[a]	58	145–146 (0.006)	–	55.19 / 55.44	6.13 / 6.51	14.40 / 14.30	$C_{10}H_{14}ClOP$	38
5b	47	152–154 (0.01)	53–55	57.13 / 57.27	6.84 / 6.99	13.00 / 13.43	$C_{11}H_{16}ClOP$	38
5c	37	130–134 (0.001)	45–47	58.71 / 58.89	7.34 / 7.41	12.30 / 12.66	$C_{12}H_{18}ClOP$	39
5d	52	139–140 (0.001)	39–40	60.40 / 60.34	7.46 / 7.79	11.62 / 11.97	$C_{13}H_{20}ClOP$	38
5e	81	–	[b]	65.47 / 65.73	9.00 / 9.19	9.09 / 9.42	$C_{18}H_{30}ClOP$	36
5f	87	–	[b]	51.26 / 51.50	6.71 / 6.65	10.27 / 10.22	$C_{13}H_{20}BrOP$	39
6c	3.7	–	163–164	66.68 / 67.01	7.71 / 8.03	16.14 / 16.46	$C_{21}H_{30}O_2P_2$	38
6d	5.2	–	151–152	68.47 / 68.30	8.27 / 8.47	15.15 / 15.32	$C_{23}H_{34}O_2P_2$	38

[a] $n_D^{20} = 1.5575$.
[b] Oil.

resinification, while **5f** loses HBr to give but-3-enyl(phenyl)propylphosphine oxide. Elemental analysis showed that products **5e,f** obtained upon removal of α,ω-dihaloalkane *in vacuo* are sufficiently pure to be used in further syntheses without additional purification.

Phosphine oxides **5a–f** react with *N*-phenylpiperazine (**7**) in boiling BuOH in the presence of K_2CO_3 to give the target alkyl(phenyl)[ω-(*N*-phenylpiperazino)alkyl]-phosphine oxides (**8a–f**).

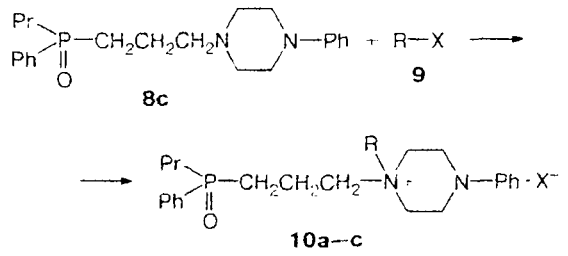
The IR spectra of compounds **8a–f** contain characteristic absorption bands at 1175–1180 cm^{-1} (ν(P=O)), 1595–1600 cm^{-1} (ν_{arom}), and 3030 and 3060 cm^{-1} (ν(=CH)).

The reactions of [γ-(*N*-phenylpiperazino)propyl]-phenyl(propyl)phosphine oxide (**8c**) with MeI, BnBr, and 1-(3-bromopropyl)-3,6-dimethyluracil afforded 1 : 1 adducts (data from elemental analysis). Although the phenylpiperazine fragment in **8c** contains two nitrogen atoms capable of forming quaternary derivatives, we believe that the reaction involves the N atom bonded to aliphatic substituents rather than the Ph-bonded one (Scheme 2).

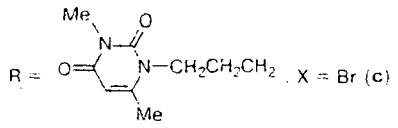
The structures of [3-(*N*-alkyl-*N'*-phenylpiperazinio)-propyl]phenyl(propyl)oxophosphine halides (**10a–c**) were confirmed by UV and IR spectroscopic data. In particular, the UV spectra of solutions of **8c** and **10a**, as well as those of dimethylaniline (**11**) and trimethylphenylammonium iodide (**12**), were recorded (the last two were model compounds containing a tertiary or quaternary nitrogen atom).

The spectrum of phosphine oxide **8c** shows an intense band at 249 nm, which was assigned, by analogy with that for dimethylaniline (252 nm), to a charge-transfer band.[4] This band is absent in the spectrum of iodide **12** because the lone electron pair of its nitrogen atom forms an additional bond. If the reaction of **8c**

Scheme 2



R = Me, X = I (**a**); R = Bn, X = Br (**b**);



with MeI involved the aromatic nitrogen atom, the spectrum of a reaction product would also contain no charge-transfer band at 249 nm. However, this is not the case. The spectra of phosphine oxide **8c** and its iodomethylate **10a** are very similar to each other. This suggests that they have the same Ph—N< absorbing fragment. Therefore, the structure of **10a** with the tetracoordinated aliphatic nitrogen atom corresponds to the iodomethylate of compound **8c**. The observed 9-nm hypsochromic shift of the above band maximum in the spectrum of **10a** against that for **8c** can result from redistribution of electron density in the molecule because of a positive charge on the aliphatic nitrogen atom.

The structure of **10a** was additionally confirmed by IR analysis of its capability for the formation of a hydrogen bond with phenol. It is known that the basicity of nitrogen sharply decreases when passing from aliphatic amines to aromatic ones. This results in a considerable difference between shift values of PhOH, $\Delta\nu$(OH), upon H-bonding with aliphatic[5] and aromatic[6] amines (400—500 cm^{-1} and 150—170 cm^{-1}, respectively). Thus, a $\Delta\nu$(OH) value can be used to unambiguously determine which nitrogen atom is involved in H-bonding. For this purpose, we recorded the IR spectra of a ternary mixture, *viz.*, "solvent—PhOH—substrate," for compounds **8c** and **10a** (molar ratio of PhOH : substrate <1). Because phosphine oxide **10a** is virtually insoluble in CCl_4, this traditional solvent was replaced by MeCN.

The IR spectrum of a MeCN—PhOH mixture contains an absorption band at 3400 cm^{-1} (ν(OH)), while a ternary MeCN—PhOH—**8c** mixture additionally absorbs at 3000 cm^{-1}. Therefore, $\Delta\nu$(OH) = 400 cm^{-1}, which indicates a hydrogen bond between PhOH and the aliphatic nitrogen atom of **8c**.[5]

In the case of a MeCN—PhOH—**10a** mixture, a broad band with a weighted mean at 3200 cm^{-1} corresponds to a PhOH—substrate associate. The $\Delta\nu$(OH) value for PhOH is equal to 200 cm^{-1}, thus suggesting the involvement of an aromatic nitrogen atom in H-bonding with PhOH.[6] The observed change of a proton-acceptor center in passing from **8c** to **10a** can be

Table 3. Yields, physicochemical characteristics, elemental analysis data, and ^{31}P NMR spectral data for phosphine oxides **8a—f** and **10a—c**

Compound	Yield (%)	M.p./°C	Found / Calculated (%)*				Molecular formula	δ_P
			C	H	N	P		
8a	51	103—104	70.46 70.15	7.92 7.95	8.24 8.18	9.23 9.05	$C_{20}H_{27}N_2OP$	38
8b	57	74—75	70.97 70.75	7.90 8.20	7.43 7.86	8.68 8.69	$C_{21}H_{29}N_2OP$	38
8c	54	110—111	70.17 71.32	8.40 8.43	7.62 7.56	8.48 8.36	$C_{22}H_{31}N_2OP$	37
8d	62	95—96	71.68 71.84	8.62 8.65	7.42 7.28	8.03 8.05	$C_{23}H_{33}N_2OP$	35
8e	65	92—93	74.06 73.97	9.39 9.53	6.38 6.16	6.79 6.81	$C_{28}H_{43}N_2OP$	37
8f	63	80—81	72.13 71.84	8.52 8.65	7.20 7.28	8.21 8.05	$C_{23}H_{33}N_2OP$	36
10a	73	177—178	53.81 53.90	6.40 6.69	5.28 5.48	6.52 6.04	$C_{23}H_{34}IN_2OP$	—
10b	62	165—167	64.95 64.31	6.98 7.07	5.15 5.17	5.76 5.72	$C_{29}H_{38}BrN_2OP$	—
10c	69	94—96	58.70 58.95	7.10 7.02	8.70 8.87	4.85 4.90	$C_{31}H_{44}BrN_4O_3P$	—

* Found/Calculated (%): I, 24.23/24.47 (**10a**); Br, 14.39/14.76 (**10b**); 12.61/12.65 (**10c**).

due to the fact that the aliphatic nitrogen atom in **10a** is tetracoordinated and, accordingly, less basic than that in neutral **8c**; this is consistent with the structure proposed.

Hence, one can believe that reactions of *N*-phenylpiperazine derivatives with other alkylating reagents also involve an aliphatic nitrogen atom.

The yields, physicochemical characteristics, and ^{31}P NMR spectral parameters for compounds **8a—f** and **10a—c** are summarized in Table 3.

The hypotensive activity of phosphine oxides **8a—f** was studied. When injected intravenously into rabbits in a dose of 0.5 mg kg^{-1}, they quickly lower blood pressure by 30 to 40%. After two hours, the hypotensive effect was 13 to 20%.

Thus, phosphine oxides **8a—f** significantly outperform the previous compounds[1] both with respect to the dose causing the same effect and in effect duration.

Experimental

^{31}P NMR spectra were recorded on a KGU-4 instrument (10.2 MHz) with 85% H_3PO_4 as the internal standard.

IR spectra were taken on a Specord 75 IR spectrophotometer in the range 4000—400 cm^{-1} (thin film or Vaseline oil between KBr plates) and in the range 4000—2400 cm^{-1} (solutions in MeCN). Spectra of solutions ($C = 1 \cdot 10^{-2}$ to $4 \cdot 10^{-2}$ mol L^{-1}) in MeCN were recorded in 0.07-mm cells (KBr).

UV spectra were recorded on a Specord M40 spectrophotometer under standard conditions in the range of 200—350 nm. The concentration of solutions in MeOH was $5 \cdot 10^{-4}$ to $11 \cdot 10^{-4}$ mol L^{-1}, film thickness 0.211 and 1.00 mm. Solutions were prepared with the use of freshly distilled solvents (MeOH and MeCN).

The starting ethyl ethyl(phenyl)phosphinite (**3b**),[7] dichloro(phenyl)phosphine,[8] diethyl phenylphosphonite,[9] *N*-phenylpiperazine,[10] 1-(3-bromopropyl)-3,6-dimethyluracil,[11] and trimethylphenylammonium iodide[12] were prepared according to the known procedures. Their physicochemical constants agree with the relevant literature data.

Ethyl phenyl(propyl)phosphinite (3c). $PhP(OEt)_2$ (29.7 g, 0.15 mol) was added dropwise with stirring at 0 °C to a solution of $PhPCl_2$ (26.9 g, 0.15 mol) in 150 mL of anhydrous ether. The reaction mixture was kept at ~20 °C for 2 h, and then PrMgBr (0.3 mol) was added dropwise at −50 to −60 °C (the latter was preliminarily prepared in an ordinary way from PrBr (36.9 g, 0.3 mol) and Mg (7.3 g, 0.3 mol) in 150 mL of anhydrous ether). After one day, the precipitate that formed was filtered off and the ether was removed. The residue was distilled *in vacuo* to give compound **3c** (28.7 g). The synthesis was carried out in an atmosphere of dry argon.

Phosphinites **3a,d,e** were synthesized by analogy with **3c** from $PhPCl_2$ (0.15 mol), $PhP(OEt)_2$ (0.15 mol), and the corresponding alkylmagnesium halide (0.3 mol) prepared from Mg (0.3 mol) and MeI, BuBr, and nonyl bromide, respectively.

Reaction of phosphinite 3c with 1,3-bromochloropropane. Phosphinite **3c** (27.5 g, 0.14 mol) was slowly added dropwise to 1,3-bromochloropropane (44.1 g, 0.28 mol) at 140 °C under dry argon, the resulting EtBr being simultaneously removed. Then, the reaction mixture was heated at 140 °C for 1.5 h with removal of EtBr (14.1 g, 92%). An excess of 1,3-bromochloropropane was eliminated *in vacuo* (10 Torr), and the residue was distilled at 0.001 Torr to give (3-chloropropyl)phenyl(propyl)phosphine oxide (**5c**) (12.6 g). The crystallized still bottoms were recrystallized from ether to give 1,3-bis(phenylpropylphosphoryl)propane (**6c**) (2 g).

Under similar conditions, the corresponding alkyl(3-chloropropyl)phenylphosphine oxides **5a,b,d** and dioxide **6d** were obtained by reactions of phosphinites **3a,b,d** with 1,3-bromochloropropane.

Reaction of phosphinite 3c with 1,4-dibromobutane. Phosphinite **3c** (27.5 g, 0.14 mol) was added dropwise to 1,4-dibromobutane (190 g, 0.88 mol) at 135—140 °C in an atmosphere of dry argon. The reaction mixture was heated to 130—140 °C and kept at this temperature for 2 h with removal of EtBr (14.3 g). An excess of 1,4-dibromobutane was eliminated, and the residue was held at 90—100 °C (0.001 Torr) for 25 min to give crude 4-bromobutyl(phenyl)propylphosphine oxide (**5f**) (36.9 g).

Phosphine oxide **5f** (18.2 g, 0.06 mol) was twice distilled *in vacuo* to give but-3-enyl(phenyl)propylphosphine oxide (13.3 g, 71%), b.p. 128—130 °C (0.008 Torr), m.p. 46—47 °C. Found (%): C, 70.41; H, 8.50; P, 13.74. $C_{13}H_{19}OP$. Calculated (%): C, 70.24; H, 8.62; P, 13.93. IR (KBr), ν/cm^{-1}: 1180 (P=O); 1600 (Ph); 1660 (C=C); 3030, 3060 (=C—H).

(3-Chloropropyl)(nonyl)phenylphosphine oxide (**5e**) was obtained as described for **5f** from phosphinite **3e** (14 g, 0.05 mol) and 1,3-bromochloropropane (47.2 g, 0.3 mol).

Phosphine oxides **5a—f** and **6c,d** are soluble in MeCN, $CHCl_3$, DMF, alcohols, and benzene.

Butyl(phenyl)[3-(*N*-phenylpiperazino)propyl]phosphine oxide (8d). A solution of butyl(3-chloropropyl)phenylphosphine oxide (**5d**) (22.5 g, 0.087 mol) and compound **7** (15.6 g, 0.096 mol) in 300 mL of absolute BuOH was refluxed with stirring for 23 h in the presence of anhydrous K_2CO_3 (12 g, 0.087 mol). Then, the precipitate that formed was filtered off, and the BuOH was removed. Recrystallization of the residue from ether afforded phosphine oxide **8d** (20.7 g).

Compounds **8a—c,e,f** were synthesized in a similar way from the corresponding phosphine oxides **5a—c,e,f** and **7**.

Phosphine oxides **8a—f** are soluble in $CHCl_3$, DMF, MeCN, Et_2O, benzene, alcohols, and dilute acids.

[3-(*N*-Methyl-*N'*-phenylpiperazinio)propyl]phenyl(propyl)-oxophosphine iodide (10a). A solution of phosphine oxide **5c** (1.5 g, 0.004 mol) and MeI (0.57 g, 0.004 mol) in 50 mL of anhydrous benzene was heated to 60—70 °C and kept at this temperature for 12 h. The resulting oil was isolated. It crystallized upon addition of MeCOEt (10 mL). The crystals were filtered off and thoroughly washed with ether to give compound **10a** (1.52 g).

Compounds **10b** and **10c** were obtained in a similar way from phosphine oxide **8c** (1.5 g, 0.004 mol) and $PhCH_2Br$ (0.69 g, 0.004 mol) or (3-bromopropyl)-3,6-dimethyluracil (0.94 g, 0.004 mol), respectively.

UV (MeOH), λ_{max}/nm (log ε): **8c**: 216 sh (4.24), 221 sh (4.01), 249 (4.11), 270 (3.53)*; **10a**: 217 sh (4.55), 222 sh (4.51), 240 (4.32), 271 (3.42)*; $PhNMe_2$ (**11**): 200 (4.28), 252 (4.21), 299 (3.38); $PhNMe_3I$ (**12**): 204 sh (3.99), 208 sh (3.89), 221 (3.93).

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