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Two-fragment α-adrenolytics

4.* Synthesis of phosphorylated derivatives of 2-aryloxyethylamines and *N*-phenylpiperazine

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The reactions of 3-chloropropylphosphonates, 3-chloropropylthiophosphonates, or 3-chloropropylphosphinates with 2-aryloxyethylamines or *N*-phenylpiperazine afford the corresponding 3-(2-aryloxyethylamino)propylphosphonates and -phosphinates or 3-(4-phenylpiperazin-1-yl)propylphosphonates and -phosphinates. The compounds obtained exhibit α-adrenolytic and hypotensive activities, the latter being found to depend on the substituents at the P atom.

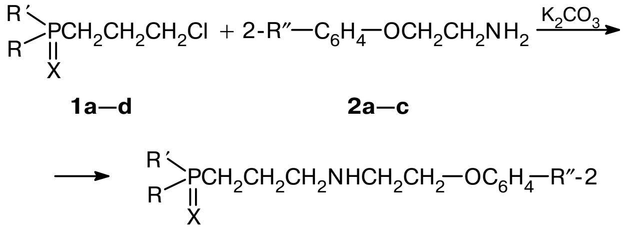
Key words: 2-aryloxyethylamines, *N*-phenylpiperazine, 3-chloropropylphosphonates, 3-chloropropylthiophosphonates, 3-chloropropylphosphinates, 3-(2-aryloxyethylamino)propylphosphonates, 3-(2-aryloxyethylamino)propylphosphinates, 3-(4-phenylpiperazin-1-yl)propylphosphonates, 3-(4-phenylpiperazin-1-yl)propylphosphinates, α-adrenolytic activity, hypotensive activity.

Previously, we described the synthesis of phosphorus-containing two-fragment α-adrenolytics either by addition of 2-aryloxyethylamines or *N*-arylpiperazines to dialkyl vinylphosphonates[2] or by alkylating *N*-phenylpiperazine with alkyl(3-haloalkyl)phenylphosphine oxides.[3] Among the products obtained, the best hypotensive activity was exhibited by compounds with an α-adrenolytic fragment separated from the phosphorus atom by three methylene groups.

The present work is devoted to the synthesis of such two-fragment α-adrenolytics by the *N*-alkylation of 2-aryloxyethylamines or *N*-phenylpiperazine with different 3-chloropropylphosphonates and -phosphinates, in order to elucidate how the environment of a tetracoordinated phosphorus atom influences the hypotensive activity of the compounds obtained.

We found that 3-chloropropyl-substituted phosphonates, thiophosphonates, and phosphinates (**1a—d**) react with 2-aryloxyethylamines (**2a—c**) in the presence of anhydrous potassium carbonate in boiling butanol to give the corresponding 3-(2-aryloxyethylamino)propylphosphonates, -phosphinates, or -thiophosphonates (**3a—i**) (Scheme 1).

Scheme 1



$$\mathrm{RR'P(X)CH_2CH_2CH_2Cl} + \text{2-R''}\mathrm{—C_6H_4—OCH_2CH_2NH_2} \xrightarrow{\mathrm{K_2CO_3}} \mathrm{RR'P(X)CH_2CH_2CH_2NHCH_2CH_2—OC_6H_4—R''\text{-}2}$$

1a—d **2a—c** **3a—i**

	R	R′	R″	X
1a	EtO	EtO	—	O
1b	Pr^iO	Pr^iO	—	O
1c	EtO	Ph	—	O
1d	EtO	EtO	—	S
2a	—	—	Me	—
2b	—	—	MeO	—
2c	—	—	F	—

	R	R′	R″	X
3a	EtO	EtO	Me	O
3b	EtO	EtO	MeO	O
3c	EtO	EtO	F	O
3d	Pr^iO	Pr^iO	Me	O
3e	EtO	Ph	Me	O
3f	EtO	Ph	MeO	O
3g	EtO	Ph	F	O
3h	EtO	EtO	Me	S
3i	EtO	EtO	MeO	S

Compounds **3a—i** are thick liquids that are well soluble in organic solvents; when distilled *in vacuo*, they resinify vigorously. The IR spectra of compounds **3a—g** contain characteristic absorption bands at 1030—1040 cm^{-1} (ν(P—O—C)), 1220—1260 cm^{-1} (ν(P=O)), 1590—1605 cm^{-1} (ν(CC arom.)), and 3030—3070 cm^{-1} (ν(=C—H)), and a weak band at 3320—3330 cm^{-1} (ν(NH)). The IR spectra of thiophosphonates **3h,i** show the same characteristic bands, except for the ν(P=O) band, and a weak absorption band at 640 cm^{-1} (ν(P=S)).

Thus, under the chosen conditions, 2-aryloxyethylamines afford only monoalkylated products **3**, no matter what the nature of substituents at the phosphorus atom in the alkylating reagents. Dialkylation seems to contribute insignificantly to the reactions under discussion, though compounds **3** have a secondary amino group and therefore can be dialkylated. For example, phosphonate **3b** reacts with benzyl bromide **4** to

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* For Part 3 see Ref. 1.

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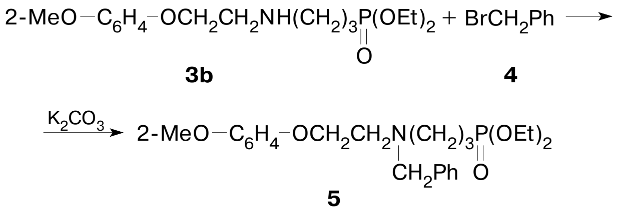
give diethyl 3-{benzyl[2-(2-methoxyphenoxy)ethyl]amino}propylphosphonate (**5**) (Scheme 2).

Scheme 2

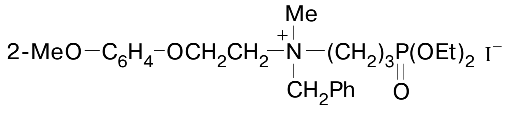


$$\text{2-MeO-C}_6\text{H}_4\text{-OCH}_2\text{CH}_2\text{NH(CH}_2)_3\text{P(O)(OEt)}_2\ (\mathbf{3b}) + \text{BrCH}_2\text{Ph}\ (\mathbf{4}) \longrightarrow$$

$$\xrightarrow{K_2CO_3} \text{2-MeO-C}_6\text{H}_4\text{-OCH}_2\text{CH}_2\text{N(CH}_2\text{Ph)(CH}_2)_3\text{P(O)(OEt)}_2\ (\mathbf{5})$$

However, even with the use of such a reactive alkylating agent as benzyl bromide, the secondary amino group is alkylated only in boiling butanol over 24 h.

In turn, compound **5**, which is a functionalized tertiary amine, reacts with MeI to form an ammonium salt, namely benzyl[3-(diethoxyphosphoryl)propyl]methyl[2-(2-methoxyphenoxy)ethyl]ammonium iodide (**6**).

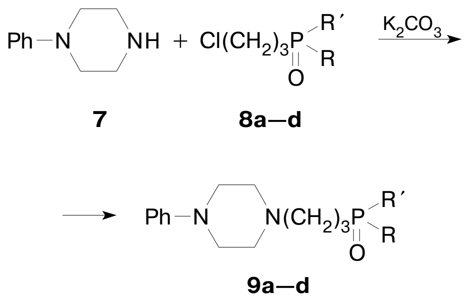


$$\text{2-MeO-C}_6\text{H}_4\text{-OCH}_2\text{CH}_2\text{-}\overset{+}{\text{N}}\text{(Me)(CH}_2\text{Ph)-(CH}_2)_3\text{P(O)(OEt)}_2\ \text{I}^-$$

6

Alkylation of *N*-phenylpiperazine (**7**) with *O*,*S*-diethyl (3-chloropropyl)thiophosphonate (**8a**), ethyl (3-chloropropyl)(dialkylamido)phosphonates (**8b**,**c**), or (3-chloropropyl)(dimethylamido)phenylphosphinate (**8d**) was carried out under the same conditions as in the synthesis of compounds **3** and afforded [3-(4-phenylpiperazin-1-yl)propyl]thiophosphonate **9a**, amidophosphonates **9b**,**c**, and phosphinate **9d**, respectively (Scheme 3).

Scheme 3



R = EtO, R′ = EtS (**a**), Me_2N (**b**), Et_2N (**c**);
R = Ph, R′ = Me_2N (**d**)

The IR spectra of compounds **9a**—**d** are consistent with the structures proposed, showing characteristic absorption bands at 1190—1240 cm^{-1} (ν(P=O)), 1590—1603 cm^{-1} (ν(CC arom.)), and 3030—3070 cm^{-1} (ν(=C—H)); in addition, the spectra of **9a**—**c** contain a band at 1030—1045 cm^{-1} (ν(P—O—C)).

The yields, physicochemical characteristics, and elemental analysis data of the compounds synthesized are presented in Table 1.

The results obtained in the study of some of the synthesized phosphonates and phosphinates allow one to conclude that their hypotensive and α-adrenolytic activities are influenced both by the substituents in the phenyl ring of 2-aryloxyethylamino group and by the environment of the tetracoordinated phosphorus atom (Table 2). In particular, the hypotensive and α-adrenolytic activities of phosphorylated 2-(2-methoxyphenoxy)ethylamines are higher than those exhibited by compounds with other substituents in the phenyl ring of the α-adrenolytic fragment (*cf.* **3b** with **3a** and **3c**; **3i** with **3h**). When the P=O group is replaced by the P=S group, the compounds become less active (*cf.* **3a**,**b** and **3h**,**i**). Their activity also decreases in the presence of an Et_2N substituent at the phosphorus atom (**9c**), while less bulky EtS or Me_2N groups at the P atom insignificantly affect the activities of compounds **9a**,**b**. Attachment of a phenyl group directly to the phosphorus atom appreciably enhances the hypotensive activity of a compound and lowers its equally effective dose (*cf.* **3f** with **3b**).

Thus, phosphorylated 2-aryloxyethylamines and *N*-phenylpiperazines synthesized show pronounced α-adrenolytic activity and reduce blood pressure (BP). Phosphinate **3f** proved to be most effective; when injected intravenously into rabbits in a dose of 0.5 mg kg^{-1}, it reduces BP within 1 min by 45% from the initial level. After 2 h, BP remains below the initial level by 23%. Its pA_2 value, which characterizes the affinity of a compound for an α-adrenoreceptor, is equal to 7.8.

Experimental

IR spectra were recorded on a Specord-75 IR spectrometer (with a thin film or Vaseline oil between KBr plates) in the range 400—4000 cm^{-1}.

The starting *O*,*O*-diethyl (3-chloropropyl)phosphonate (**1a**),[4] triisopropyl phosphite,[5] diethyl phenylphosphonite,[6] diethyl thiophosphite,[7] 2-aryloxyethylamines **2a**,**b**,[8,9] and *N*-phenylpiperazine[10] were synthesized according to the known procedures, their physicochemical characteristics being very close to the literature data. Phosphonate **1b** and phosphinate **1c** were prepared by the action of 1,3-bromochloropropane on triisopropyl phosphite and diethyl phenylphosphonite, respectively (the Arbuzov rearrangement). The known[11] thiophosphonate **1d** was obtained by the reaction of 1,3-bromochloropropane with sodium diethyl thiophosphite, with the use of the procedure modified by us.[11] 2-(2-Fluorophenoxy)ethylamine (**2c**) was synthesized by the reaction of 2-(2-fluorophenoxy)ethyl bromide (**10**), prepared from 2-fluorophenol and 1,2-dibromoethane, with potassium phthalimide under the conditions described for the synthesis of amine **2b**.[8]

Thiophosphonate **8a** and amidophosphonates **8b**,**c** were synthesized by the reaction of ethyl chloro(3-chloropropyl)phosphonate (**11a**) with ethanethiol and dimethyl- or diethylamine, respectively, while phenylphosphinamide **8d** was prepared from (3-chloropropyl)phenylphosphoryl chloride (**11b**) and dimethylamine. In turn, chlorophosphonate **11a** and phosphoryl chlo-

Table 1. Yields, physicochemical characteristics, and elemental analysis data of the compounds obtained

Compound	Yield (%)	B.p./°C (*p*/Torr)	n_D^{20}	d_4^{20}	Found/Calculated (%)					Molecular formula
					C	H	N	P	X	
1b	28	75—76	1.4475	—	44.31	8.28	—	12.62	14.34^a	$C_9H_{20}ClO_3P$
		(0.05)			44.54	8.31		12.76	14.61	
1c	62	225—230^b	1.5369	—	53.42	6.51	—	12.54	14.29^a	$C_{11}H_{16}ClO_2P$
		(0.001)			53.56	6.54		12.56	14.37	
2c	67	104—105	1.5165	—	62.03	6.46	8.94	—	12.12^c	$C_8H_{10}FNO$
		(10)			61.91	6.49	9.02		12.24	
3a	31	177—178	1.5038	1.0824	58.36	8.62	4.15	9.45	—	$C_{16}H_{28}NO_4P$
		(0.001)			58.33	8.56	4.25	9.40		
3b	43	235—240^b	1.5060	1.1254	55.81	8.39	4.00	8.76	—	$C_{16}H_{28}NO_5P$
		(0.001)			55.60	8.17	4.06	8.96		
3c	38	165—166	1.4943	—	54.12	7.49	4.26	9.08	—	$C_{15}H_{25}FNO_4P$
		(0.001)			54.04	7.56	4.20	9.29		
3d	34	225—226^b	1.4898	1.0591	60.62	9.10	3.78	8.53	—	$C_{18}H_{32}NO_4P$
		(0.001)			60.48	9.03	3.92	8.67		
3e	37	250—253^b	1.5392	1.0885	66.24	7.68	3.72	8.46	—	$C_{20}H_{28}NO_3P$
		(0.001)			66.46	7.81	3.88	8.57		
3f	35	265—268^b	1.5439	—	63.55	7.50	3.87	8.38	—	$C_{20}H_{28}NO_4P$
		(0.001)			63.65	7.47	3.71	8.21		
3g	37	245—250^b	1.5358	—	60.28	7.08	3.71	8.56	—	$C_{19}H_{25}FNO_3P$
		(0.001)			60.59	7.12	3.83	8.48		
3h	35	240—245^b	1.5077	1.0820	55.54	8.11	3.87	9.24	9.59^d	$C_{16}H_{28}NO_3PS$
		(0.001)			55.63	8.17	4.05	8.97	9.28	
3i	45	235—240^b	1.5112	1.1055	53.02	7.73	3.81	9.05	8.79^d	$C_{16}H_{28}NO_4PS$
		(0.001)			53.17	7.81	3.87	8.57	8.87	
5	23	^{e}	—	—	63.31	8.12	3.27	7.20	—	$C_{23}H_{34}NO_5P$
					63.42	7.87	3.21	7.11		
6	49	^{e}	—	—	49.71	6.50	2.68	5.40	24.50^f	$C_{24}H_{37}INO_5P$
					49.90	6.46	2.43	5.36	24.57	
8a	46	86—88	1.4961	1.1697	36.31	6.97	13.74^d	13.22	15.29^a	$C_7H_{16}ClO_2PS$
		(0.001)			36.44	6.99	13.89	13.43	15.37	
8b	71	89—90	1.4596	1.1175	40.96	7.89	6.63	14.21	16.52^a	$C_7H_{17}ClNO_2P$
		(0.001)			41.20	8.02	6.55	14.49	16.60	
8c	62	98—100	1.4598	1.0823	44.42	8.72	5.79	12.67	14.62^a	$C_9H_{21}ClNO_2P$
		(0.001)			44.70	8.76	5.79	12.81	14.67	
8d	89	143—146	1.5488	1.1686	53.95	6.97	5.61	12.54	14.38^a	$C_{11}H_{17}ClNOP$
		(0.001)			53.77	6.97	5.70	12.61	14.43	
9a	40	250—255^b	1.5190	1.0699	57.24	8.10	7.66	8.62	8.91^d	$C_{17}H_{29}N_2O_2PS$
		(0.001)			57.33	8.20	7.86	8.69	8.99	
9b	32	210—213^b	1.5350	1.0904	60.28	8.82	12.46	9.19	—	$C_{17}H_{30}N_3O_2P$
		(0.001)			60.15	8.90	12.38	9.12		
9c	41	240—245^b	1.5275	1.0679	62.04	9.55	11.35	8.21	—	$C_{19}H_{34}N_3O_2P$
		(0.001)			62.09	9.32	11.43	8.43		
9d	39	97—98^g	—	—	67.96	8.32	11.24	8.31	—	$C_{21}H_{30}N_3OP$
					67.89	8.14	11.31	8.34		
10	51	110—112	1.5330	—	43.68	3.78	—	—	36.32^h	C_8H_8BrFO
		(10)			43.88	3.68			36.44	
					—	—		—	8.54^c	
									8.68	
11a	47	72—74	1.4677	—	29.40	5.26	—	15.07	34.14^a	$C_5H_{11}Cl_2O_2P$
		(0.04)			29.29	5.41		15.11	34.59	
11b	49	132—133	1.5644	1.3844	45.46	4.70	—	12.96	29.78^a	$C_9H_{11}Cl_2OP$
		(0.001)			45.59	4.68		13.06	29.91	

[a] Analysis for Cl. [b] Temperature of the heater of the molecular distiller.
[c] Analysis for F. [d] Analysis for S.
[e] Oil. [f] Analysis for I.
[g] M.p., °C. [h] Analysis for Br.

Table 2. Hypotensive and α-adrenolytic activity of some of the compounds obtained

Compound	Dose[a] /mg kg^{-1}	Δp over the time (min)[b]					$p\mathrm{A}_2$[c]
		1	5	30	60	120	
3a	2.50	52	20	16	15	9	6.3
	1.25	40	14	8	—	—	6.3
3b	1.25	52	35	27	23	18	7.4
3c	1.25	36	20	16	15	11	6.2
3f	1.25	46	29	29	41	34	7.8
	0.5	45	25	22	23	23	7.8
3h	2.5	46	8	10	8	—	6.6
3i	2.5	60	25	27	29	22	—
9a	1.0	49	20	20	20	16	—
9b	1.5	47	32	22	16	13	—
9c	2.5	41	24	10	7	—	4.5

[a] Intravenous injection into rabbits.

[b] Δp is the reduction in blood pressure (% from the initial level).

[c] Determined in the vessels of a rabbit's isolated ear.

ride **11b** were obtained by the action of PCl_5 on phosphonate **1a** and phosphinate **1c**, respectively.

***O,O*-Diisopropyl (3-chloropropyl)phosphonate (1b).** Triisopropyl phosphite (50 g, 0.24 mol) was added dropwise at 135—140 °C to 1,3-bromochloropropane (75 g, 0.48 mol). The reaction mixture was heated at this temperature for 3 h, with removal of $\mathrm{Pr^iBr}$ (20.1 g, 68%). The excess of 1,3-bromochloropropane was removed, and the residue was distilled *in vacuo* to give compound **1b** (16.2 g, 28%). By analogy, ethyl (3-chloropropyl)phenylphosphinate (**1c**) was obtained from diethyl phenylphosphonite and 1,3-bromochloropropane in 62% yield.

***O,O*-Diethyl (3-chloropropyl)thiophosphonate (1d).** A solution of sodium diethyl thiophosphite (prepared from diethyl thiophosphite (30.8 g, 0.2 mol) and sodium (4.6 g, 0.2 mol) in 200 mL of anhydrous EtOH) was added dropwise with stirring at 30—35 °C to a solution of bromochloropropane (47.5 g, 0.3 mol) in 100 mL of anhydrous EtOH. The reaction mixture was refluxed for 4.5 h. The precipitate that formed was filtered off, and the filtrate was concentrated *in vacuo* (10 Torr). The product was extracted with ether (300 mL). The ethereal solution was washed with water and dried with $MgSO_4$. The ether was removed, and the residue was distilled *in vacuo* to give compound **1d** (27.15 g, 59%). B.p. 73—74 °C (0.002 Torr), d_4^{20} 1.1436, n_D^{20} 1.4871 (see Ref. 11).

2-(2-Fluorophenoxy)ethylamine (2c). A mixture of 2-(2-fluorophenoxy)ethyl bromide (**10**) (109.5 g, 0.5 mol) and potassium phthalimide (97.1 g, 0.55 mol) in 400 mL of DMF was stirred at 90—95 °C for 5 h and then poured into 700 mL of water. The precipitate that formed was filtered off, washed with hot water, dried, and added to a solution of hydrazine hydrate (25 g, 0.5 mol) in 500 mL of anhydrous EtOH. The resulting mixture was refluxed for 1 h, 18% HCl (125 mL) was added in portions of 25 mL, and stirring was continued at 90—100 °C for 1.5 h. The precipitate that formed was filtered off, and EtOH was removed from the filtrate. A 20% aqueous solution of KOH was added with stirring to the crystalline residue until pH 10 was reached. The product was extracted with $CHCl_3$ (2×100 mL), the extract was dried with $MgSO_4$, the solvent was removed, and the residue was distilled *in vacuo* to give compound **2c** (52.0 g, 67%).

2-(2-Fluorophenoxy)ethyl bromide (10). A mixture of 2-fluorophenol (112 g, 1 mol) and 1,2-dibromoethane (376 g, 2 mol) in 200 mL of water was heated to boiling, and a solution of NaOH (40 g, 1 mol) in 500 mL of water was added dropwise with stirring. The reaction mixture was refluxed for 7 h, and the organic layer was separated, dried with $MgSO_4$, and distilled to give compound **10** (111 g, 51%).

***O,S*-Diethyl (3-chloropropyl)thiophosphonate (8a).** Ethyl chloro(3-chloropropyl)phosphonate (**11a**) (26.65 g, 0.13 mol) was added dropwise at 10—13 °C to a solution of ethanethiol (8.06 g, 0.13 mol) and triethylamine (13.15 g, 0.13 mol) in 150 mL of anhydrous benzene. Then the reaction mixture was heated at 60 °C for 4 h. The precipitate that formed was filtered off, the filtrate was concentrated, and the residue was distilled to give thiophosphonate **8a** (13.8 g, 46%). IR (KBr), ν/cm^{-1}: 1040 (P—O—C), 1224 (P=O).

By analogy, ethyl (3-chloropropyl)(dimethylamido)phosphonate (**8b**) and ethyl (3-chloropropyl)(diethylamido)phosphonate (**8c**) were obtained from phosphonate **11a** and dimethyl- or diethylamine, respectively. The reaction of (3-chloropropyl)phenylphosphoryl chloride (**11b**) with dimethylamine yielded *N,N*-dimethyl-(3-chloropropyl)phenylphosphinamide (**8d**).

Ethyl chloro(3-chloropropyl)phosphonate (11a). Phosphorus pentachloride (104.1 g, 0.5 mol) was added in small portions at 30—35 °C to a solution of diethyl (3-chloropropyl)phosphonate (**1a**) (107.4 g, 0.5 mol) in 350 mL of anhydrous CCl_4. The reaction mixture was refluxed for 2 h until PCl_5 was completely dissolved. The solvent and $POCl_3$ were removed *in vacuo* (10 Torr), and the residue was distilled to give compound **11a** (48.2 g, 47%).

(3-Chloropropyl)phenylphosphoryl chloride (**11b**) was obtained by analogy with compound **11a** from ethyl (3-chloropropyl)phenylphosphinate (**1c**) and PCl_5.

Diethyl {3-[2-(2-methylphenoxy)ethylamino]propyl}phosphonate (3a). A solution of diethyl (3-chloropropyl)phosphonate (**1a**) (16.1 g, 0.075 mol) and 2-(2-methylphenoxy)ethylamine (**2a**) (11.3 g, 0.075 mol) in 250 mL of anhydrous $\mathrm{Bu^nOH}$ was refluxed with anhydrous K_2CO_3 (10.4 g, 0.075 mol) and stirring for 20 h. The precipitate that formed was filtered off, and the $\mathrm{Bu^nOH}$ was removed. The product was extracted with benzene (2×50 mL). Vacuum distillation gave compound **3a** (7.6 g, 31%).

Compounds **3b—i** were synthesized by analogy with **3a** from the corresponding 3-chloropropyl derivatives of phosphorus acids **1a—d** and 2-aryloxyethylamines **2a—c**.

Diethyl 3-{benzyl[2-(2-methoxyphenoxy)ethyl]aminopropyl}phosphonate (5). A solution of phosphonate **3b** (8.6 g, 0.025 mol) and benzyl bromide (4.3 g, 0.025 mol) in 150 mL of anhydrous $\mathrm{Bu^nOH}$ was refluxed with anhydrous K_2CO_3 (3.5 g, 0.025 mol) and stirring for 24 h. The precipitate that formed was filtered off, the butanol was removed, and the residue was chromatographed on Al_2O_3 in ether. The yield of compound **5** was 2.52 g (23%). IR (KBr), ν/cm^{-1}: 1035 (P—O—C), 1255 (P=O), 1598 (arom.), 3035, 3070 (=C—H).

Benzyl[3-(diethoxyphosphoryl)propyl]methyl[2-(2-methoxyphenoxy)ethyl]ammonium iodide (6). A solution of phosphonate **5** (2.18 g, 5 mmol) and MeI (0.78 g, 5.5 mmol) in 50 mL of anhydrous ethyl methyl ketone was heated at 65—70 °C for 13 h. Then the reaction mixture was poured into 200 mL of anhydrous ether. The resulting oil was separated, and reprecipitated with ether from anhydrous ethyl methyl ketone (40 mL). The yield of compound **6** was 1.42 g (49%).

***O*,*S*-Diethyl [3-(4-phenylpiperazin-1-yl)propyl]thiophosphonate (9a).** A mixture of chloropropylphosphonate **8a** (12.91 g, 0.056 mol), *N*-phenylpiperazine (11.85 g, 0.073 mol), and anhydrous K_2CO_3 (7.73 g, 0.056 mol) in 200 mL of anhydrous Bu^nOH was refluxed with stirring for 24 h. The precipitate that formed was filtered off, and the product was extracted with benzene (2×50 mL). The extract was washed with water and dried with $MgSO_4$. The benzene was removed, and the residue was distilled *in vacuo*. The yield of compound **9a** was 7.98 g (40%).

The same procedure was used to obtain compounds **9b—d** from ethyl (3-chloropropyl)amidophosphonates **8b**,**c** or phosphinamide **8d** and *N*-phenylpiperazine.

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