Two-fragment α-adrenolytics

1. Addition of β-aroxyethylamines and *N*-arylpiperazines to dialkyl vinylphosphonates

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Dialkyl β-(2-aroxyethylamino)ethylphosphonates, *N*-[β-(2-methoxyphenoxy)ethyl]-*N'*-[β-(diethoxyphosphoryl)ethyl]-α,ω-diaminoalkanes, and diethyl β-(*N*-arylpiperazino)ethylphosphonates were synthesized by the reactions of dialkyl vinylphosphonates with β-aroxyethylamines, *N*-[β-(2-methoxyphenoxy)ethyl]-α,ω-diaminoalkanes, and *N*-arylpiperazines, respectively. The compounds synthesized exhibit hypotensive and α-adrenolytic activities.

Key words: β-aroxyethylamines, *N*-[β-(2-methoxyphenoxy)ethyl]-α,ω-diaminoalkanes, *N*-arylpiperazines, dialkyl vinylphosphonates, dialkyl β-(2-aroxyethylamino)ethylphosphonates, *N*-[β-(2-methoxyphenoxy)ethyl]-*N'*-[β-(diethoxyphosphoryl)ethyl]-α,ω-diaminoalkanes, diethyl β-(*N*-arylpiperazino)ethylphosphonates, hypotensive activity, α-adrenolytic activity.

A search for efficient hypotensive drugs, in particular, α-adrenolytics, is a topical problem in medicine.

The present series of works is devoted to synthetic aspects of studies aimed at searching for compounds that exhibit α-adrenolytic and hypotensive activities. A working hypothesis, which determined the direction of a search and the structures of compounds synthesized, was based on the assumption that target compounds should contain two fragments. The first, specific fragment should be responsible for the affinity of the resulting compounds for α-adrenoreceptors of blood vessels. Based on the published data, we chose β-aroxyethylamino-, *N*-phenylpiperazino-, and 1,4-benzodioxan-2-ylmethylamino groups as these fragments.[1—4] The second, nonspecific fragment should contain groups capable of interacting with segments of an α-adrenoreceptor located in the vicinity of its active center. At particular distances between two fragments, this interaction can lead to strengthening of the lytic—receptor complex and the enhancement of the selectivity of action of compounds with respect to the α-adrenoreceptor. Different groups containing the phosphorus atom or heteroatomic rings were examined as nonspecific fragments.

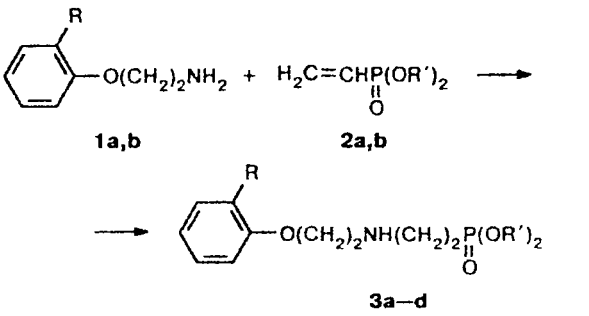
In this work, we report the synthesis of derivatives of the above-mentioned α-adrenolytics containing the four-coordinate phosphorus atom in the nonspecific fragment.

With the aim of preparing dialkyl β-[β'-(aroxy)ethylamino]ethylphosphonates and dialkyl β-(*N*-arylpiperazino)ethylphopshonates, we studied the reactions of β-aroxyethylamines and *N*-arylpiperazines with dialkyl vinylphosphonates.

It is known that the addition of amines to nonsaturated organophosphorus compounds, which was first reported by Pudovik,[5] proceeds exclusively at the β position regardless of the valence state and the environment about the phosphorus atom.[6] The reactions of the simplest primary and secondary amines with vinylphosphonates proceed without a catalyst. In some instances, they are accompanied by an exothermic effect.[5,7—9] In other cases, heating and the use of catalysts are necessary for the reactions to occur.[10]

We found that β-aroxyethylamines (**1**) reacted with dialkyl vinylphosphonates (**2**) upon heating (60—70 °C) of their mixtures in anhydrous ethanol for 6—8 h (Scheme 1).

Scheme 1



1: R = Me (**a**), MeO (**b**) **3**: R = Me, R' = Et (**a**), Bu^n (**b**);
2: R' = Et (**a**), Bu^n (**b**) R = MeO, R' = Et (**c**), Bu^n (**d**)

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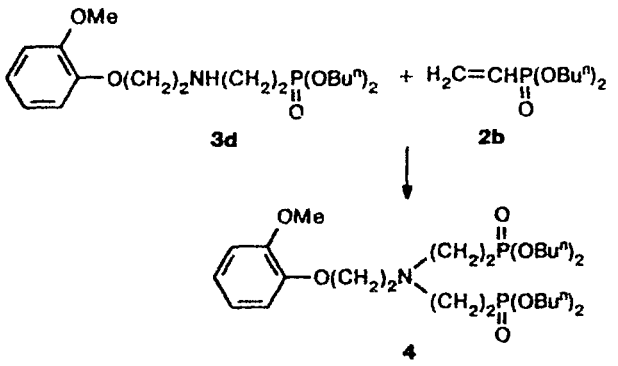
The resulting dialkyl β-[β′-(aroxy)ethylamino]ethylphosphonates (**3**) were isolated by vacuum distillation (from an Arbuzov flask) in 42—49% yields. The compounds were obtained in low yields due to resinification of the products in the course of distillation. When compound **3d** was isolated and purified on an apparatus for molecular distillation, the yield was 87% (the heater temperature was 260 °C (0.015 Torr), n_D^{20} 1.4929).

It was also found that compound **3d**, in turn, added to dibutyl vinylphosphonate upon boiling of a mixture of the reagents in anhydrous ethanol in the presence of catalytic amounts of sodium ethoxide to form *N,N*-bis[β-(dibutoxyphosphoryl)ethyl]-*N*-[β′-(2-methoxyphenoxy)ethyl]amine (**4**) (Scheme 2).

Scheme 2

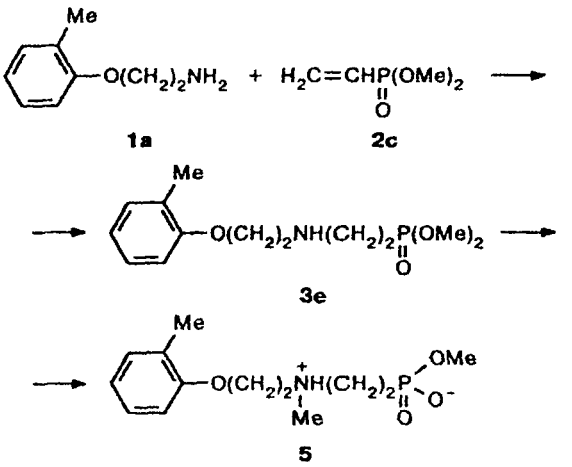


The course of the reaction was monitored by ^{31}P NMR spectroscopy. The initial spectrum of the mixture contained two signals at δ_1 30 and δ_2 16 corresponding to phosphonate **3d** and dibutyl vinylphosphonate, respectively. After refluxing of the reaction mixture for 6 h, the latter signal disappeared and the spectrum had only a signal at δ 30 corresponding to reaction product **4**. It should be noted that the chemical shifts in the ^{31}P NMR spectra of compounds **3d** and **4** have equal values due to the identity of the phosphorus atoms in these compounds. In the absence of a catalyst, the reaction did not occur and the ratio of the integral intensities of the above two signals in the spectrum of the reaction mixture remained unchanged even upon boiling for 45 h.

Compounds **3a—d** are viscous liquids, which are readily soluble in benzene, ether, dichloroethane, chloroform, and DMF. Their IR spectra do not contradict the structures assigned to these compounds and have characteristic absorption bands in the regions of 1260—1230 cm^{-1} (ν(P=O)) and 1590—1610 cm^{-1} (ν_{arom}) and a weak band in the 3310—3330 cm^{-1} region (ν(NH)).

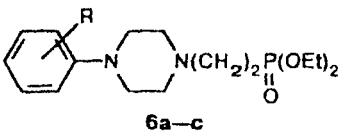
The reaction of β-(2-methylphenoxy)ethylamine with dimethyl vinylphosphonate (**2c**) under the conditions of the synthesis of phosphonates **3a—d** afforded a crystalline compound with the m.p. 186—187 °C. The elemental composition of this compound corresponded to the 1 : 1 addition product. However, the resulting compound was insoluble in benzene, ether, and dichloroethane and soluble in water. The IR spectrum of this compound had absorption bands in the regions of 1060 cm^{-1} (ν(P—O—C)), 1175 cm^{-1} (ν(P=O)), and 1240 cm^{-1} (ν(Ph—O—C)), a weak band at 3030 cm^{-1} (ν(=C—H)), and a broad strong band in the region of 2700—2250 cm^{-1} (ν(NH^+)). These data suggested that the reaction under consideration afforded methyl β-[methyl-β′-(2-methylphenoxy)ethylammonio]ethylphosphonate (**5**). The latter is apparently a product of alkylation of the nitrogen atom in dimethyl β-[β′-(2-methylphenoxy)ethylamino]ethylphosphonate (**3e**), which was initially formed, with the methoxy radical (Scheme 3).

Scheme 3



The formation of salt **5** under these conditions agrees with the published data because the alkylating ability of esters of phosphorus acids in reactions with amines is well known.[11]

The reactions of *N*-arylpiperazines with diethyl vinylphosphonate proceeded upon heating of a mixture of the reagents in anhydrous butanol at 100—115 °C for 6 h to form the corresponding diethyl β-(*N*-arylpiperazino)ethylphosphonates **6** in 70—80% yields.



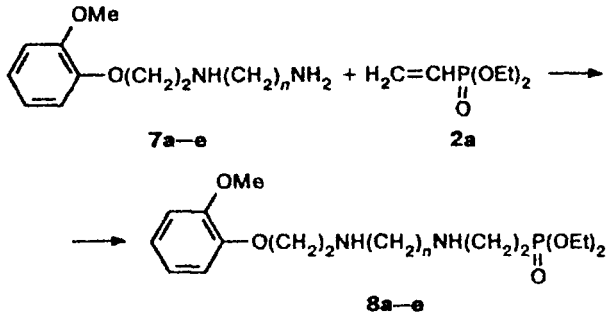
6a—c

R = H (**a**), 3-Me (**b**), 2,4-Me_2 (**c**)

Compounds **6** are viscous liquids soluble in organic solvents and insoluble in water.

The reactions of diethyl vinylphosphonate with *N*-[β-(2-methoxyphenoxy)ethyl]-α,ω-diaminoalkanes (**7**) were performed under the conditions of the synthesis of compounds **3a—d**. Compounds **7** contain primary and secondary amino groups. Addition of diethyl vinylphosphonate can occur at each of these groups. However, under these conditions only products of addition at the primary amino group, *viz.*, *N*-[β-(2-methoxyphenoxy)ethyl]-*N'*-[β-(diethoxyphosphoryl)ethyl]-α,ω-diaminoalkanes (**8**), were isolated in high yields (Scheme 4).

Scheme 4



n = 2 (**a**), 3 (**b**), 4 (**c**), 5 (**d**), 6 (**e**)

These compounds are viscous liquids readily soluble in alcohols, chloroform, dichloroethane, ether, and dilute acids.

The IR spectra of phosphonates **8a—e** in thin layers have absorption bands in the regions of 1030—1045 cm^{-1} (ν(P—O—C)), 1230—1260 cm^{-1} (ν(P=O)), and 1580—1600 cm^{-1} (ν_{arom}) and a weak band in the 3310—3330 cm^{-1} region (ν(NH)). The IR spectra of solutions of these compounds in CCl_4 (10-cm cell, $C \approx 10^{-4}$ mol L^{-1}) and trichloroethylene (1-cm cell, $C \approx 10^{-3}$ mol L^{-1}) have an absorption band at 3340 cm^{-1} corresponding to vibrations of secondary amines ν(NH) and do not contain absorption bands in the 3565—3410 cm^{-1} region typical of $\nu(NH_2)$.

In our opinion, the results of the reaction are determined mainly by steric accessibility of the lone electron pair of the nitrogen atom of the primary amino group in molecules **7a—e**. To the contrary, the NH group is sterically hindered due to the presence of the bulky 2-methoxyphenoxyethyl radical, which is in addition capable of forming intramolecular hydrogen bonds with the participation of amino groups.

Note that the initial compounds **7a,c—e** were prepared by the reactions of β-(2-methoxyphenoxy)bromoethane with the corresponding α,ω-diaminoalkanes taken in a four- to five-fold excess to reduce the probability of formation of products of replacement at both NH_2 groups. Compound **7b** was obtained by reduction of *N*-[β-(2-methoxyphenoxy)ethyl]-*N*-(β'-cyanoethyl)-amine (**9**), which was synthesized by addition of β-(2-methoxyphenoxy)ethylamine to acrylonitrile, with lithium aluminum hydride.

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

The resulting compounds were tested for hypotensive and α-adrenolytic activities. When introduced intravenously into rabbits in a dose of 2.5 mg per kg, the initial β-aroxyethylamines and *N*-arylpiperazines, which exhibit α-adrenolytic activity, caused a sharp decrease in the blood pressure (by 30—45% with respect to the initial level), which was regained within just 5—10 min. For these compounds, the value of pA_2, characterizing the degree of affinity of the competing adrenolytic for the α-adrenoreceptor and determined on vessels of an isolated rabbit ear, was 5—6.

Compounds **3a—d**, **6a—c**, and **8a—e**, containing the phosphorus atom, also exhibit hypotensive and α-adrenolytic activities. When introduced in a dose of 2.5 mg per kg, these compounds caused a sharp decrease in the arterial pressure (by 30—50% with respect to the initial value), the effect being retained at the 10—15% level for 30—60 min. For these compounds, the pA_2 values were in the range of 5.5—6.4.

Experimental

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

The IR spectra were obtained on a Specord-75 IR spectrometer in thin layers, as Nujol mulls between KBr plates in the 400—3600 cm^{-1} region, or in solutions in CCl_4 or trichloroethylene (the concentrations of the solutions were ~10^{-4}—10^{-3} mol L^{-1}).

Thin-layer chromatography was performed on Silufol UV-254 plates.

The initial compounds, *viz.*, β-(2-methoxyphenoxy)bromoethane, β-aroxyethylamines **1a,b**,[1,12] dialkyl vinylphosphonates **2a—c**,[13,14] phenylpiperazine,[15] 3-tolylpiperazine,[16] and 2,4-dimethylphenylpiperazine,[17] were synthesized according to known procedures. Their physicochemical constants coincide with the published data.

Diethyl β-[β'-(2-methylphenoxy)ethylamino]ethylphosphonate (3a). Diethyl vinylphosphonate (9.8 g, 0.06 mol) was added dropwise with intense stirring to a solution of β-(2-methylphenoxy)ethylamine (13.7 g, 0.09 mol) in anhydrous EtOH (20 mL) heated to 60 °C. The mixture was heated at 60—70 °C for 6 h and then the solvent was removed *in vacuo* (10 Torr). Distillation afforded product **3a** in a yield of 9.2 g.

Compounds **3b—d** were prepared analogously to **3a** from the corresponding dialkyl vinylphosphonates and β-(aroxy)ethylamines.

***N,N*-Bis[β-(dibutoxyphosphoryl)ethyl]-*N*-[β'-(2-methoxyphenoxy)ethyl]amine (4).** A solution of dibutyl β-[β'-(2-methoxyphenoxy)ethylamino]ethylphosphonate (3.3 g, 8.5 mmol), dibutyl vinylphosphonate (1.9 g, 8.5 mmol), and metallic Na (0.1 g) in anhydrous EtOH (30 mL) was refluxed for 6 h. After removal of ethanol, the residue was kept at 90 °C (0.001 Torr) for 40 min. Compound **4** was obtained as a viscous pale-brown oil in a yield of 5.2 g. The TLC data (Silufol, a 4 : 2 : 1 benzene—acetone—diethylamine mixture as the eluent): R_f 0.41.

Table 1. Yields, physicochemical characteristics, data of elemental analysis, and ^{31}P NMR spectra of the synthesized compounds

Compound	Yield (%)	B.p./°C (*p*/Torr)	n_D^{20}	d_4^{20}	Found / Calculated (%)				Molecular formula	δ ^{31}P
					C	H	N	P		
3a	49	159—161 (0.001)	1.5008	1.0881	57.33 57.13	8.38 8.31	4.23 4.44	9.77 9.82	$C_{15}H_{26}NO_4P$	29
3b	42	173—174 (0.001)	1.4921	1.0418	61.73 61.44	9.30 9.23	3.92 3.74	8.40 8.34	$C_{19}H_{34}NO_4P$	30
3c	44	163—164 (0.003)	1.5050	1.1160	54.28 54.37	7.85 7.91	4.20 4.23	9.41 9.35	$C_{15}H_{26}NO_5P$	29
3d	43	188—190 (0.001)	1.4958	1.0764	58.94 58.90	8.81 8.85	3.85 3.69	7.82 7.99	$C_{19}H_{34}NO_5P$	30
4	99	[a]	1.4644	—	57.22 57.31	9.10 9.12	2.26 2.30	9.99 10.19	$C_{29}H_{55}NO_8P_2$	30
5	38	186—187[b]	—	—	54.42 54.34	7.68 7.72	4.90 4.88	10.83 10.78	$C_{13}H_{22}NO_4P$	—
6a	77	175—177 (0.004)	1.5295	—	58.56 58.88	8.20 8.34	8.80 8.58	9.06 9.49	$C_{16}H_{27}N_2O_3P$	31
6b	72	187—188 (0.003)	1.5280	—	60.08 59.98	8.48 8.59	8.24 8.23	9.37 9.10	$C_{17}H_{29}N_2O_3P$	30
6c	81	180—182 (0.003)	1.5192	—	59.69 61.00	8.56 8.82	7.46 7.90	8.47 8.74	$C_{18}H_{31}N_2O_3P$	30
7a	60	130—132 (0.06)	1.5443	1.0939	63.23 62.82	8.87 8.63	13.63 13.32	—	$C_{11}H_{18}N_2O_2$	—
7b	60	120—123 (0.04)	1.5397	1.0819	64.37 64.26	9.18 8.99	12.22 12.49	—	$C_{12}H_{20}N_2O_2$	—
7c	82	150—151 (0.08); 46[b]	—	—	65.03 65.51	9.08 9.30	11.90 11.75	—	$C_{13}H_{22}N_2O_2$	—
7d	83	148—149 (0.04)	1.5290	1.0504	65.36 66.60	9.50 9.58	10.37 11.10	—	$C_{14}H_{24}N_2O_2$	—
7e	74	160—162 (0.005)	1.5250	1.0289	66.90 67.67	9.92 9.84	10.62 10.52	—	$C_{15}H_{26}N_2O_2$	—
8a	97	[a]	1.5131	1.1339	54.40 54.53	8.63 8.34	7.28 7.48	8.12 8.27	$C_{17}H_{31}N_2O_5P$	30
8b	98	[a]	1.5126	1.1203	55.80 55.66	9.08 8.56	7.19 7.21	7.30 7.97	$C_{18}H_{33}N_2O_5P$	30
8c	98	[a]	1.5085	1.1094	56.71 56.70	8.80 8.76	6.79 6.96	7.57 7.69	$C_{19}H_{35}N_2O_5P$	30
8d	99	[a]	1.5084	1.1027	57.50 57.67	9.37 8.95	6.17 6.73	7.06 7.44	$C_{20}H_{37}N_2O_5P$	30
8e	98	[a]	1.5066	1.0889	58.24 58.58	9.30 9.13	6.28 6.50	7.09 7.19	$C_{21}H_{39}N_2O_5P$	30
9	63	150—152 (0.005)	1.5350	—	65.19 65.45	7.45 7.32	12.38 12.72	—	$C_{12}H_{16}N_2O_2$	—

[a] Oil. [b] Melting point.

Methyl β-[methyl-β′-(2-methylphenoxy)ethylammonio]ethylphosphonate (5). A solution of β-(2-methylphenoxy)ethylamine (12.1 g, 0.08 mol) and dimethyl vinylphosphonate (5.4 g, 0.04 mol) in anhydrous EtOH (20 mL) was heated at 60—70 °C for 8 h. After removal of the solvent, an excess of amine was distilled off on an apparatus for molecular distillation at a heater temperature of 130—133 °C (0.01 Torr). The resulting viscous liquid crystallized out. The crystals were thoroughly washed with anhydrous ether. Salt **5** was obtained in a yield of 4.38 g.

Diethyl β-(*N*-3-tolylpiperazino)ethylphosphonate (6b). A solution of diethyl vinylphosphonate (8.2 g, 0.05 mol) and *N*-3-tolylpiperazine (10.6 g, 0.06 mol) in anhydrous Bu^{n}OH (50 mL) was heated at 100—115 °C for 6 h. Distillation *in vacuo* afforded product **6b** in a yield of 12.2 g.

Compounds **6a,c** were prepared under the conditions of the synthesis of **6b** from diethyl vinylphosphonate and *N*-phenylpiperazine and *N*-(2,4-dimethylphenyl)piperazine, respectively.

***N*-[β-(2-Methoxyphenoxy)ethyl]-α,β-diaminoethane (7a).** β-(2-Methoxyphenoxy)bromoethane (46.2 g, 0.2 mol) was slowly added dropwise to ethylenediamine (60.1 g, 1 mol) heated to 80 °C, the temperature of the reaction mixture being maintained. Then the reaction mixture was stirred at 80 °C for 5 h. An excess of ethylenediamine was distilled off *in vacuo* (10 Torr). A 20% aqueous solution of KOH (100 mL) was added dropwise to the residue. The product was extracted with chloroform, the extract was dried with $MgSO_4$, the chloroform was removed, and the residue was distilled *in vacuo*. Product **7a** was isolated in a yield of 25.2 g.

Compounds **7c—e** were prepared analogously to **7a** from the corresponding α,ω-diaminoalkanes and β-(2-methoxyphenoxy)bromoethane.

***N*-[β-(2-Methoxyphenoxy)ethyl]-α,γ-diaminopropane (7b).** A solution of compound **9** (22.5 g, 0.1 mol) in anhydrous benzene (100 mL) was slowly added dropwise to a solution of lithium aluminum hydride (5.43 g, 0.14 mol) in anhydrous ether (300 mL) at 35 °C. The reaction mixture was refluxed for 2 h and then cooled to 15—18 °C. Water (5 mL), a 20% aqueous solution of NaOH (5 mL), and water (16 mL) were successively added dropwise to the reaction mixture, the temperature being maintained. The precipitate was filtered off and washed with benzene. The solvents were removed from the filtrate *in vacuo* (10 Torr) and the residue was distilled. Product **7b** was obtained in a yield of 13.7 g.

***N*-[β-(2-Methoxyphenoxy)ethyl]-*N'*-[β-(diethoxyphosphoryl)ethyl]-α,β-diaminoethane (8a).** Diethyl vinylphosphonate (8.2 g, 0.5 mol) was slowly added dropwise to a solution of *N*-[β-(2-methoxyphenoxy)ethyl]-α,β-diaminoethane (10.5 g, 0.05 mol) in anhydrous EtOH (200 mL) heated to 60 °C. The mixture was stirred for 5 h at the temperature of boiling ethanol. Ethanol was removed and the residue was kept at 90 °C (0.001 Torr) for 40 min. Product **8a** was obtained in a yield of 18.2 g.

Compounds **8b—e** were prepared analogously to **8a** from diethyl vinylphosphonate and the corresponding *N*-[β-(2-methoxyphenoxy)ethyl]-α,ω-diaminoalkanes **7b—e**.

***N*-[β-(2-Methoxyphenoxy)ethyl]-*N*-(β-cyanoethyl)amine (9).** A mixture of β-(2-methoxyphenoxy)ethylamine (25 g, 0.15 mol), acrylonitrile (15.9 g, 0.3 mol), and hydroquinone (0.5 g) was heated at 78 °C for 5 h. An excess of acrylonitrile was distilled off. Vacuum distillation of the residue afforded product **9** in a yield of 25.9 g.

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