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Synthesis, Antimicrobial and Antifungal Activity of Double Quaternary Ammonium Salts of Biphenyls

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Abstract—The synthetic methods for new 2-, 2,2'-, and 3-substituted 4,4'-bis(chloromethyl)biphenyls were developed. Quaternization of them with various amines resulted in a series of new double quaternary ammonium salts containing the biphenyl moiety. The majority of the obtained compounds have a pronounced antifungal and antibacterial activity against the Gram-positive bacteria.

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In recent years, the synthetic approaches to various biphenyl derivatives and their biological activity were studied. Analysis of the scientific and patent literature indicates that the biphenyl group is used to create a wide range of the drugs and products for agriculture [1, 2]. Some biphenyl derivatives are patented and widely used in medicine as the antiandrogenic and hypotensive drugs [3, 4]. Antimicrobial preparations based on biphenyl derivatives are of great interest and are used in medicine and in agriculture [5–7]. However, an extremely low solubility in water is one of the drawbacks of the above-mentioned compounds, which impede their wide practical application.

Quaternary ammonium compounds belong to a special group that is used as disinfectants since the 30's of the last century. But the emergence of a variety of microbial strains resistant to the known antimicrobial agents necessitates the constant search for new compounds that exhibit bactericidal and fungicidal activity.

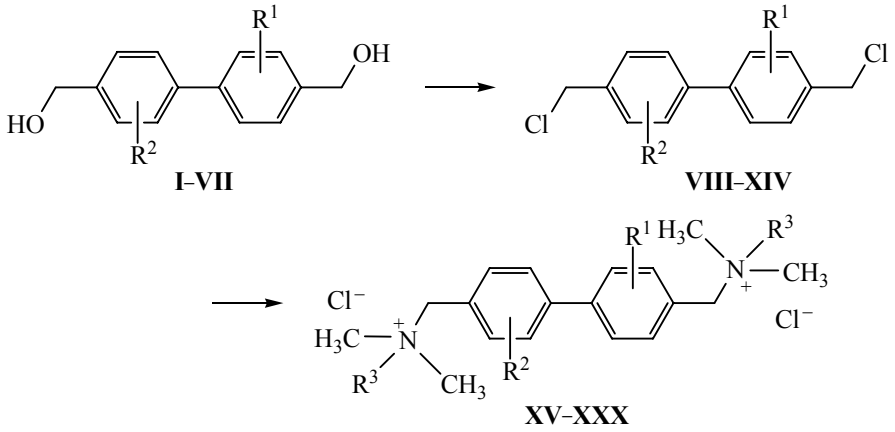
The aim of this work is the development of the synthetic methods for the quaternary ammonium salts containing biphenyl moieties, which are soluble in water, resistant to the temperature and the environment and are effective agents against the fungal and bacterial lesions in the agriculture and industry.

The quaternary ammonium salts **XV**–**XXX** were obtained via the quaternization of the tertiary amines (*N*,*N*-dimethylalkylamine, *N*,*N*-dimethylbenzylamine or *N*,*N*-dimethylaminoethanol) with the chloromethyl biphenyl derivatives, the 2-, 2,2'- or 3-substituted 4,4'-bis(chloromethyl)-1,1'-biphenyls **VIII**–**XIV**.

Benzyl alcohols **I**–**VII** readily reacted with thionyl chloride in dichloromethane or toluene at reflux to afford the corresponding bis(chloromethyl) derivatives **VIII**–**XIV** in an 85 yield %. 4,4'-Bis(chloromethyl)-3-nitrobiphenyl **XIV** was synthesized by the nitration of 4,4'-dichloromethylbiphenyl **VIII** with 96% nitric acid in acetic anhydride. The synthesis of the starting alcohols **I**–**VII** was performed as described in [8, 9].

The presence of the chloromethyl fragments in **VIII**–**XIV** was confirmed by the singlet signals of the methylene groups at 4.50–4.93 ppm (4H, CH_2Cl) in the NMR spectrum and the disappearance of the proton signals of the the hydroxy groups. The IR spectra of compounds **VIII**–**XIV** contain a strong band at 1180–1150 cm^{-1} belonging to the vibrations of the CH_2Cl moiety. The absorption band at 824–864 cm^{-1} corresponds to the C–Cl bond.

The reaction of bis(chloromethyl) derivatives **VIII**–**XIV** with the tertiary amines (trimethylamine, *N*,*N*-dimethyloctylamine, *N*,*N*-dimethylbenzylamine, or *N*,*N*-dimethylethanolamine) was performed in a solvent (ethanol or acetonitrile) under reflux over 4–8 h using 1 mol of the dichloride **VIII**–**XIV** and a 2–2.5-fold



I, **VIII**, $R^1 = R^2 = H$; **II**, **IX**, $R^1 = OH$, $R^2 = H$; **III**, **X**, $R^1 = OCH_3$, $R^2 = H$; **IV**, **XI**, $R^1 = OC_6H_{13}$, $R^2 = H$; **V**, **XII**, $R^1 = R^2 = F$; **VI**, **XIII**, $R^1 = F$, $R^2 = H$; **VII**, **XIV**, $R^1 = NO_2$, $R^2 = H$; **XV**, $R^1 = R^2 = H$, $R^3 = CH_3$; **XVI**, $R^1 = R^2 = H$, $R^3 = C_8H_{17}$; **XVII**, $R^1 = R^2 = H$, $R^3 = CH_2CH_2OH$; **XVIII**, $R^1 = OH$, $R^2 = H$, $R^3 = C_8H_{17}$; **XIX**, $R^1 = OH$, $R^2 = H$, $R^3 = CH_2CH_2OH$; **XX**, $R^1 = OCH_3$, $R^2 = H$, $R^3 = CH_3$; **XXI**, $R^1 = OCH_3$, $R^2 = H$, $R^3 = C_7H_7$; **XXII**, $R^1 = OCH_3$, $R^2 = H$, $R^3 = C_8H_{17}$; **XXIII**, $R^1 = OC_6H_{13}$, $R^2 = H$, $R^3 = C_8H_{17}$; **XXIV**, $R^1 = OC_6H_{13}$, $R^2 = H$, $R^3 = C_{18}H_{37}$; **XXV**, $R^1 = OC_6H_{13}$, $R^2 = H$, $R^3 = CH_2CH_2OH$; **XXVI**, $R^1 = R^2 = F$, $R^3 = C_8H_{17}$; **XXVII**, $R^1 = F$, $R^2 = H$; $R^3 = C_8H_{17}$; **XXVIII**, $R^1 = F$, $R^2 = H$; $R^3 = CH_2CH_2OH$; **XXIX**, $R^1 = NO_2$, $R^2 = H$, $R^3 = C_8H_{17}$; **XXX**, $R^1 = NO_2$, $R^2 = H$, $R^3 = CH_2CH_2OH$.

excess of the corresponding amine. The reaction progress was monitored by TLC.

The structure and composition of the synthesized compounds was confirmed by the IR and ^{1}H NMR spectroscopy (Table 1).

In the ^{1}H NMR spectra of the unsubstituted or symmetrically substituted biphenyls **XV**–**XVII**, **XXVI** the proton signals of the $N(CH_3)_2$ groups appear as a singlet at 2.91–2.96 ppm (12H) (**XVI**, **XVII**, **XXVI**). All the signals of methylene protons are in the range of 2.95–3.00 ppm (18H). The signals of the protons of the Ar–CH_2N and NCH_2 moieties appear in a weaker field (4.35–4.60 ppm) as the singlets and triplets (**XVII**), confirming the symmetry of these molecules.

The introduction of the substituents into the position 2 or 3 of the biphenyl fragment leads to destruction of the symmetry of molecules **XVIII**–**XXV**, **XXVII**–**XXX**, which causes separation of the proton signals of the $N(CH_3)_2$ fragment in the ^{1}H NMR spectrum. They appear as two singlets at 2.8–3.04 ppm.

The presence of *N*-octyl fragment in compounds **XVIII**, **XXII**, **XXIII**, **XXVI**, **XXVII**, **XXIX** is confirmed by the appearance of the triplets of methyl protons at 0.63–0.69 ppm and the multiplet signals of methylene protons of the aliphatic chain at 0.97–1.13 (**XVIII**), 1.12–1.22 (**XXII**), 1.05–1.20 (**XXVI**, **XXVII**), 0.96–1.17 (**XXIX**), 0.82–1.68 (**XXIII**), 0.78–1.65 ppm (**XXIV**). The chemical shifts of the proton signals of two methylene groups of the CH_2CH_2OH fragment in **XVII**, **XIX**, **XXV**, **XXVIII**, **XXX** are virtually identical and appear as a multiplet in the range of 3.95–3.99 ppm. The singlets at 3.70–3.73 ppm correspond to the methoxy fragments in compounds **XX**–**XXII**. The aromatic protons of the biphenyl fragment appear as the multiplets in the range of 6.95–8.12 ppm.

The IR spectra of the obtained derivatives contain the strong absorption bands at 2973–2977, 2947 and 2873–2877 cm^{-1} (C–H) and 3150–3677 cm^{-1} (O–H), which confirm the presence of the dimethyl(hydroxy) alkylammonium groups. The stretching vibrations of the non-conjugated C–N groups appear as broad bands of low intensity in the range of 1223–1227 cm^{-1}.

The study of the antimicrobial activity of compounds **XV**–**XXX** was performed on the following strains of bacteria: Gram-negative *Escherichia coli* B, *Pseudomonas aeruginosa* PA01, *Pseudomonas putida* M, *Serratia marcescens*, *Pantoea herbicola* EH103, *Salmonella tyhpimurium* TA100; Gram-positive *Staphylococcus saprophyticus*, *Staphylococcus aureus*, *Bacillus subtilis* 494, *Sarcina lutea* according to [10]. All the substances were dissolved in the sterile distilled water and introduced into the nutrient broth for the microorganisms cultivation to the final concentrations from 500 to 5 μg ml^{-1}.

Table 1. Yields and ^{1}H NMR spectral parameters of the salts **XV**–**XXX**

Comp. no.	R^1	R^2	R^3	Yield, %	δ, ppm
XV	H	H	CH_3	87	2.95 s [18H, $N(CH_3)_3$], 4.37 s (4H, Ar–CH_2N), 7.48–7.69 m (8H_{Ar})
XVI	H	H	C_7H_7	89	2.94 s [12H, $N(CH_3)_2$], 4.41 s (4H, Ar–CH_2N), 4.43 s (4H, NCH_2), 7.10–7.69 m (18H_{Ar})
XVII	H	H	$(CH_2)_2OH$	56	2.79 t (4H, NCH_2, *J* 8 Hz), 2.94 s [12H, $N(CH_3)_2$], 3.32 t (4H, CH_2O, *J* 8 Hz), 4.43 s (4H, Ar–CH_2N), 7.50 d (4H_{Ar}, *J* 8 Hz), 7.69 d (4H_{Ar}, *J* 8 Hz)
XVIII	OH	H	C_8H_{17}	53	0.68 t (6H, CH_2CH_3, *J* 6.5 Hz), 0.95–1.20 m [20H, $(CH_2)_5$], 1.56–1.70 m (4H, CH_2), 2.86 s [6H, $N(CH_3)_2$], 2.87 s [6H, $N(CH_3)_2$], 3.00–3.06 m (4H, NCH_2), 4.26 s (2H, Ar–CH_2N), 4.31 s (2H, Ar–CH_2N), 6.93–6.98 m (2H_{Ar}), 7.25 d (1H_{Ar}, *J* 8 Hz), 7.40 d (2H_{Ar}, *J* 8 Hz), 7.49 d (2H_{Ar}, *J* 8 Hz)
XIX	OH	H	$(CH_2)_2OH$	69	2.95 s [12H, $N(CH_3)_2$], 3.36 t (4H, CH_2, *J* 5 Hz), 3.95 m (4H, CH_2), 4.37 s (2H, Ar–CH_2N), 4.44 s (2H, Ar–CH_2N), 6.97 s (1H_{Ar}), 7.00 d (1H_{Ar}, *J* 8 Hz), 7.28 d (1H_{Ar}, *J* 8 Hz), 7.45 d (2H_{Ar}, *J* 8 Hz), 7.51 d (2H_{Ar}, *J* 8 Hz)
XX	OCH_3	H	CH_3	79	2.99 s [9H, $N(CH_3)_3$], 3.01 s [9H, $N(CH_3)_3$], 3.72 s (3H, OMe), 4.39 s (4H, Ar–CH_2N), 4.41 s (4H, Ar–CH_2N), 7.10–7.60 m (7H_{Ar})
XXI	OCH_3	H	C_7H_7	57	2.81s [6H, $N(CH_3)_2$], 2.84 s [6H, $N(CH_3)_2$], 3.70 s (3H, OMe), 4.41s (2H, Ar–CH_2N), 4.42 s (2H, Ar–CH_2N), 4.43 s (4H, CH_2), 7.10–7.60 m (17H_{Ar})
XXII	OCH_3	H	C_8H_{17}	94	0.69 t (6H, CH_3), 1.12–1.22 m (20H, CH_2), 1.65 m (4H, CH_2), 2.86 s [6H, $N(CH_3)_2$], 2.88 s [6H, $N(CH_3)_2$], 3.03 s (4H, NCH_2), 3.73 s (3H, OMe), 4.26 s (2H, Ar–CH_2N), 4.31 s (2H, Ar–CH_2N), 6.95–7.75 m (7H_{Ar})
XXIII	OC_6H_{13}	H	C_8H_{17}	63	0.49–0.62 m (9H, CH_3), 0.82–1.18 m (32H_{aliph}), 2.82–2.92 m [12H, $N(CH_3)_2$], 3.67–3.73 m (2H), 4.22 c (2H, Ar–CH_2N), 4.28 c (2H, Ar–CH_2N), 6.83–7.62 m (7H_{Ar})
XXIV	OC_6H_{13}	H	$C_{18}H_{37}$	49	0.78–1.65 m (81H), 2.63–2.74 m (12H), 3.89–3.96 m (2H), 4.28–4.38 m (4H, Ar–CH_2N), 6.85–7.66 m (7H_{Ar})
XXV	OC_6H_{13}	H	$(CH_2)_2OH$	61	0.71 t (3H), 1.09–1.15 m (4H), 1.19–1.26 m (2H), 1.51–1.59 m (2H), 3.02 s [6H, $N(CH_3)_2$], 3.04 s [6H, $N(CH_3)_2$], 3.42–3.48 m (4H, NCH_2), 3.98 t (2H, CH_2O, *J* 6 Hz), 4.05–4.08 m (4H, Ar–CH_2O), 4.48 s (2H), 4.51 s (2H), 7.17–7.19 m (2H_{Ar}), 7.38–7.40 m (1H_{Ar}), 7.50–7.58 m (4H_{Ar})
XXVI	F	F	C_8H_{17}	65	0.65–0.69 m (6H), 1.05–1.2 m (20H), 1.66–1.74 m (4H), 2.91 s [12H, $N(CH_3)_2$], 3.14–3.16 m (4H), 4.58 s (4H, Ar–CH_2N), 7.62–7.68 m (2H_{Ar}), 7.80–7.84 m (2H_{Ar}), 7.88–7.92 m (2H_{Ar})
XXVII	F	H	C_8H_{17}	62	0.64–0.68 m (6H), 1.05–1.20 m (20H), 1.65–1.72 m (4H), 2.89 s [6H, $N(CH_3)_2$], 2.91 s [6H, $N(CH_3)_2$], 3.05–3.14 m (4H, NCH_2), 4.37 уш. s (4H, Ar–CH_2N), 7.27–7.52 m (2H_{Ar}), 7.47–7.54 m (3H_{Ar}), 7.57–7.61 m (2H_{Ar})
XXVIII	F	H	$(CH_2)_2OH$	86	2.97 s [6H, $N(CH_3)_2$], 2.98 s [6H, $N(CH_3)_2$], 3.36–3.42 m (4H, NCH_2), 3.95–3.99 m (4H, CH_2O), 4.46 br. s (4H, Ar–CH_2N), 7.29–7.33 m (2H_{Ar}), 7.47–7.52 m (3H_{Ar}), 7.56–7.60 m (2H_{Ar})
XXIX	NO_2	H	C_8H_{17}	73	0.65 t (6H, CH_2CH_3, *J* 6.5 Hz), 0.95–1.20 m [20H, $(CH_2)_5$], 1.62–1.75 m (4H, CH_2), 2.88 s [6H, $N(CH_3)_2$], 2.93 s [6H, $N(CH_3)_2$], 3.00–3.20 m (4H, NCH_2), 4.36 s (2H, Ar–CH_2N), 4.48 s (2H, Ar–CH_2N), 7.36 d (2H_{Ar}, *J* 8 Hz), 7.45 d (2H_{Ar}, *J* 8 Hz), 7.53 d (1H_{Ar}, *J* 8 Hz), 7.76 d (1H_{Ar}, *J* 8 Hz), 8.06 s (1H_{Ar})
XXX	NO_2	H	$(CH_2)_2OH$	69	2.99 s [6H, $N(CH_3)_2$], 3.03 s [6H, $N(CH_3)_2$], 3.40 t (2H, CH_2, *J* 4.5 Hz), 3.44 t (2H, CH_2, *J* 4.5 Hz), 3.99 m (4H, CH_2), 4.48 s (2H, Ar–CH_2N), 4.60 s (2H, Ar–CH_2N), 7.39 d (2H_{Ar}, *J* 8 Hz), 7.51 d (2H_{Ar}, *J* 8 Hz), 7.54 d (1H_{Ar}, *J* 8 Hz), 7.80 d (1H_{Ar}, *J* 8 Hz), 8.12 s (1H_{Ar})

Table 2. Activity of the quaternary ammonium salts **XV–XXX** with respect to the Gram-positive and Gram-negative bacteria[a]

Compound	Minimal inhibitory concentration, μg ml^{-1}									
	Escherichia coli B	*Pseudomonas Aeruginosa* PA01	*Pseudo-monas putida* M	*Serratia Marcecens*	*Pantoea Herbicola* EH103	*Salmonella Typhimurium* TA100	*Staphylo-coccus Saprophyticus*	*Staphylo-coccus aureus*	*Bacillus Subtilis* 494	*Sarcina lutea*
XV	>100	>500	>500	>500	>500	>250	>100	100	100	100
XVI	10	>100	100	>100	>100	>100	10	10	10	5
XVII	>500	>500	>500	>500	125	125	125	125	250	25
XVIII	>250	>250	>250	>250	>250	>250	>250	12.5	50	>250
XIX	>250	>250	>250	>250	>250	>250	>250	50	250	>250
XX	>500	>500	>500	>500	>500	>250	10	>100	100	10
XXI	100	>500	>500	>500	500	100	10	20	20	5
XXII	5	>100	>100	>100	20	10	5	5	5	5
XXIII	25	250	250	250	125	12.5	12.5	12.5	12.5	250
XXIV	>500	>500	>500	>500	>500	250	250	250	>500	12.5
XXV	>500	>500	>500	>500	500	250	12.5	12.5	12.5	12.5
XXVI	250	250	250	250	12.5	12.5	12.5	12.5	12.5	12.5
XXVII	12.5	>250	250	>250	125	12.5	12.5	12.5	25	12.5
XXVIII	>500	>500	>500	>500	500	250	12.5	12.5	>250	125
XXIX	>500	>500	>500	>500	250	250	250	12.5	25	>250
XXX	>500	>500	>500	>500	>500	250	>500	>500	>500	>250
Chlorohexidine	100	500	100	500	100	100	100	100	100	100

[a] The average data of three independent tests in the concentration range of 5–500 μg ml^{-1} of the substance in a medium.

For the bacteria cultivation we used a liquid nutrient broth and nutrient agarized glucose-salt medium supplemented with 0.05% yeast extract. For the yeast cultivation we used the nutrient Saburo medium and a minimal agarized glucose-salt medium supplemented with 0.05% yeast extract. The minimal inhibitory concentrations (MIC) were measured in μg ml^{-1}. The data on the antimicrobial activity of **XV–XXX** are given in Table 2.

The data indicate that the investigated compounds **XV–XXX** inhibit the growth of the Gram-positive and Gram-negative bacteria and some of them have a pronounced antimicrobial activity. For most of the strains of Gram-negative and all Gram-positive bacteria the activity of the studied compounds is comparable to the activity of such well-known anti-septics as chlorhexidine. The lowest MIC values correspond to the *N*-dimethyloctyl derivatives **XVI**, **XXII**, **XXII**, **XXVI**, **XXVII**. In addition, the biological activity was significantly affected by the nature of the substituent in the biphenyl moiety. Thus, an alkoxy group at the C^2 atom of the biphenyl fragment leads to an increase in the biocidal properties against the Gram-positive and Gram-negative bacteria (**XXII**, **XXIII**). The antimicrobial activity of the compounds is independent of the composition of the used culture medium.

The fungicidal activity of the ammonium salts **XVIII–XXX** (Table 3) with respect to the strains of pathogenic fungi (*Alternaria alternata, Aspergillus niger, Botrytis cinerea, Fusarium oxysporum, Monilia sp., Mucor sp., Penicillum lividum, Sclerotinia sclerotiorum, Trichoderma Viridae*) was also investigated according to [11]. Thus, the quaternary ammonium salts based on the substituted biphenyls **XVIII–XXX** have a sufficiently high fungicidal activity. The most active are compounds containing the hydrophobic substituent at the C^2 atom of the biphenyl moiety. The derivative **XXIII** shows the inhibition

Table 3. Fungicidal activity of **XVIII–XXX**[a]

Compound	Coefficient of inhibition of the micelium growth, %								
	Alternaria alternata	*Aspergillus niger*	*Botrytis cineria*	*Fusarium oxysporum*	*Monilia sp*	*Mucor sp*	*Penicillum lividum*	*Sclerotinia sclerotiorum*	*Trichoderma viridae*
XVIII	54	61	54	33	51	2	40	12	[b]
XIX	12	18	13	8	16	3	20	58	[b]
XX	[b]	0	43	30	62	0	50	0	[b]
XXI	100	56	100	100	100	0	100	100	[b]
XXII	[b]	33	86	100	100	0	100	100	[b]
XXIII	100	100	100	100	100	100	100	100	100
XXIV	32	0	0	12	0	0	100	0	0
XXV	100	42	78	50	0	0	100	100	100
XXVI	100	100	92	75	0	100	100	100	78
XXVII	100	100	91	68	0	100	100	100	100
XXVIII	100	7	71	21	0	0	15	100	42
XXIX	60	15	23	17	78	0	10	100	[b]
XXX	35	15	27	33	0	0	0	81	[b]
Nystatin	100	100	100	100	100	100	100	100	100

[a] The data were obtained after 96 h, the concentration of the substances studied equals μg ml^{-1}. [b] Compounds were not tested.

coefficient about 100% against all nine strains of fungi.

EXPERIMENTAL

The melting points were measured on a Koefler heating block equipped with a Hanna HI 93530 electronic thermometer. The ^1H NMR spectra were recorded on a Tesla BS-567A and BS-587A (80 and 100 MHz, respectively) and Bruker Avance 500 spectrometers (500 MHz) from $CDCl_3$ or DMSO-d_6 solutions relative to internal TMS. The IR spectra were taken on a Specord M-80 instrument in the range of 400–4000 cm^{-1} from KBr pellets.

The solvents were purified and dried by the known methods. TLC was performed on a Fluka or Merck plates using a 60 F_{254} silica gel. The flash and column chromatography was performed using a Merck silica gel (Silica gel 60, 0.063–0.200 mm).

4,4'-Bis(chloromethyl)biphenyl (VIII) and its 2- or 2,2'-substituted derivatives (IX–XIV) (general procedure). A mixture of 4 mmol of the primary alcohol **I–VII** in 30–50 ml of toluene and 2.3 ml of thionyl chloride was heated until the evolution of hydrogen chloride ceased. The solvent was removed under reduced pressure. The residue was dissolved in 50 ml of hexane and filtered through 20 ml of silica gel. The solvent was evaporated in a vacuum.

4,4'-Bis(chloromethyl)-2-hydroxybiphenyl (IX). Yield 82.4%. IR (KBr), ν, cm^{-1}: 3420, 2970, 1616, 1579, 1401, 1181, 1121, 1024, 1007, 845, 815, 730, 702. ^1H NMR spectrum, δ, ppm (*J*, Hz): 4.75 s (2H, Ar-CH_2Cl), 4.76 s (2H, Ar-CH_2Cl), 7.34 d (1H_{Ar}, *J* 5), 7.60 d (2H_{Ar}, *J* 8), 7.67–7.69 m (2H_{Ar}), 8.14 d (2H_{Ar}, *J* 8). Found, %: C 62.86; H 4.93. $C_{14}H_{12}Cl_2O$. Calculated, %: C 62.94; H 5.02; Cl 26.54; O 5.99.

4,4'-Bis(chloromethyl)-2-methoxybiphenyl (X). Yield 85.6%. IR (KBr), ν, cm^{-1}: 3450, 2975, 2950, 1620, 1580, 1440, 1400, 1280, 1190, 1150, 1040, 1020, 855, 825, 740,720. ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.75 s (3H, OCH_3), 4.75 s (2H, Ar-CH_2Cl), 4.75 s (2H, Ar-CH_2Cl), 7.08 d (2H_{Ar}, *J* 8), 7.17 s (1H_{Ar}), 7.27 d (2H_{Ar}, *J* 8), 7.40–7.48 m (2H_{Ar}). Found, %: C 64.03; H 4.94. $C_{15}H_{14}Cl_2O$. Calculated, %: C 64.07; H 5.02; Cl 25.22; O 5.69.

4,4'-Bis(chloromethyl)-2-hexyloxybiphenyl (XI). Yield 86.1%. IR (KBr), ν, cm^{-1}: 3450, 2970, 2950, 1610, 1580, 1500, 1430, 1400, 1290, 1190, 1150, 1070, 1040, 860, 825, 740, 720. ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.81 t (3H, CH_3, *J* 6), 1.21–1.33 m [6H, $(CH_2)_3$], 1.61 m (2H, CH_2), 3.95 t (2H, OCH_2, *J* 6), 4.74 s (2H, Ar-CH_2Cl), 4.75 s (2H, Ar-CH_2Cl), 7.07 d (1H_{Ar}, *J* 8), 7.15 s (1H_{Ar}), 7.28 d (1H_{Ar}, *J* 8), 7.43 d (2H_{Ar}, *J* 8), 7.48 d (2H_{Ar}, *J* 8). Found, %: C 67.62; H 7.61. $C_{20}H_{27}Cl_2O$. Calculated, %: C 67.79; H 7.68; Cl 20.01; O 4.52.

4,4'-Bis(chloromethyl)-3-nitrobiphenyl (XIV). A mixture of 1.1 g (0.004 mol) of 4,4'-bis(chloromethyl)-biphenyl **VIII**, 10 ml of acetic anhydride, and 0.2 ml of 96% nitric acid was stirred at room temperature for 20 h, then poured into 100 ml of cold water. The reaction product was extracted with 20 ml of toluene, washed in succession with water, saturated sodium hydrogen carbonate solution, and water, and dried over anhydrous sodium sulfate. After the solvent removal, the target product was isolated by the column chromatography on silica gel eluting with hexane. Yield 0.84 g (71%). IR (KBr), ν, cm^{-1}: 3450, 2930, 2860, 1610, 1500, 1440, 1400, 1280, 1210, 1180, 1070, 820, 650, 600, 550. ^1H NMR spectrum, δ, ppm (*J*, Hz): 4.63 s (2H, Ar-CH_2Cl), 4.66 s (2H, Ar-CH_2Cl), 7.31 d (2H, *J* 8), 7.46 d (2H, *J* 8), 7.58 d (1H, *J* 8), 7.65 d (1H, *J* 8), 7.91 s (1H). Found, %: C 56.71; H 3.63. $C_{14}H_{11}Cl_2NO_2$. Calculated, %: C 56.78; H 3.74; Cl 23.94; N 4.74; O 10.80.

4,4'-Bis(chloromethyl)-2,2'-difluorobiphenyl (V). Yield 90.0%. IR (KBr), ν, cm^{-1}: 3022, 2923, 1623, 1514, 1413, 1131, 1010, 875, 740. ^1H NMR spectrum, δ, ppm (*J*, Hz): 4.59 s (4H, Ar-CH_2Cl), 7.16–7.23 m (4H_{Ar}), 7.31–7.40 m (2H_{Ar}). Found, %: C 62.37; H 4.02. $C_{14}H_{10}F_2Cl_2$. Calculated, %: C 62.48; H 4.12; F 7.06; Cl 26.34.

4,4'-Bis(chloromethyl)-2-fluorobiphenyl (VI). Yield 87.3%. IR (KBr), ν, cm^{-1}: 3032, 2963, 2918, 1623, 1495, 1431, 1278, 1151, 872, 741. ^1H NMR spectrum, δ, ppm (*J*, Hz): 4.60 s (2H, Ar-CH_2Cl), 4.64 s (2H, Ar-CH_2Cl), 7.19–7.26 m (2H_{Ar}), 7.40–7.45 m (1H_{Ar}), 7.46–7.49 m (2H_{Ar}), 7.52–7.57 m (2H_{Ar}). Found, %: C 58.47; H 3.41. $C_{14}H_{11}FCl_2$. Calculated, %: C 58.56; H 3.51; F 13.24; Cl 24.69.

***N*,*N*,*N*-trimethyl{4'-[(trimethylammonio)methyl]-[1,1'-biphenyl]-4-yl}methanaminium dichloride (XV) and {2-methoxy-4'-[(trimethylammonio)-methyl][1,1'-biphenyl]-4-yl}-*N*,*N*,*N*-trimethyl-methanaminium dichloride (XX).** A mixture of 1.0 g (4 mmol) of 4,4'-bis(chloromethyl)biphenyl **VIII** or **X** and 10 ml of a 33% solution of trimethylamine in ethanol was heated for 6 h. Then the solvent was evaporated. The crystalline residue was washed with hexane (2 × 20 ml) and dried in a vacuum.

Quaternary ammonium salts of biphenyl and its derivatives (XVI–XIX, XXI–XXX) (*general procedure).* A mixture of 4 mmol of 4,4'-bis(chloromethyl)-biphenyl **VIII** or substituted 4,4'-bis(chloromethyl)-biphenyls **IX–XIV** and 8.10 mmol of the corresponding tertiary *N*,*N*-dimethylamine in 25 ml of solvent (ethanol or acetonitrile) was refluxed for 4–8 h. Then the solvent was evaporated. The residue was refluxed in 20 ml of hexane for 20 min, filtered off and washed with hexane to remove an excess of the tertiary amine. The treatment was repeated two times, and the precipitate was dried in a vacuum without further purification. The purity of the obtained compounds was determined by TLC using a toluene–ethyl acetate mixture (5:1) as an eluent. All the salts **XV–XX** are powders, which are well soluble in water.

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