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Synthesis and Fungicidal Activity of the Quaternary Ammonium Salts of the 1,3,7-Substituted Dibenzothiophene-5,5-diones

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Abstract—A series of novel double quaternary ammonium salts based on 5,5-dioxo-5*H*-dibenzo[*b,d*]thiophene has been prepared via quaternization of the corresponding 3,7-bis(chloromethyl)dibenzothiophene-5,5-diones with various *N,N*-dimethylalkylamines. Pronounced fungicidal activity of the C^1-substituted quaternary ammonium salts has been observed.

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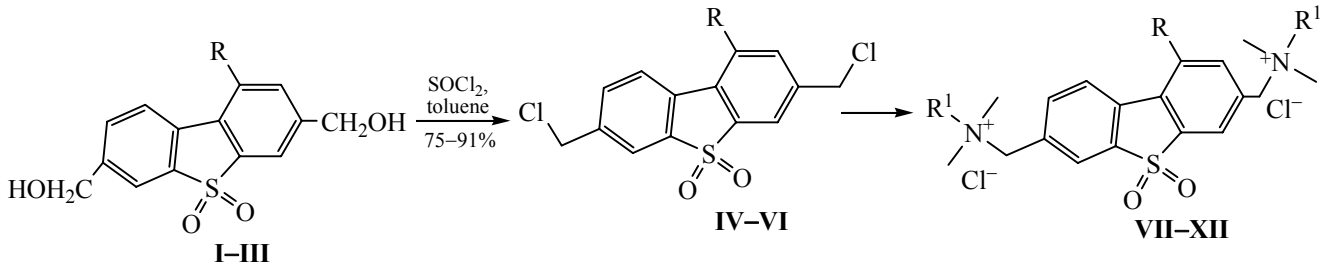
Sulfur-containing organic compounds are known for the broad range of biological activity: they act as as drugs [1, 2], pesticides [3], plants growth regulators [4], etc. A large group of such compounds comprises molecules containing sulfoxide and sulfonic moieties. Sulfanylamide drugs are used as chemotherapeutical antibacterial agents [1, 2]; 4,4-diaminodiphenylsulfone derivatives are applied as antileprotic, antiparasitic [5], anticancer [6], and antifungal [7, 8] agents. These compounds are noted for the low toxicity and absence of side effects; however, most of them are practically water-insoluble, which limits their application.

Quaternary ammonium salts belong to another class of biocide agents, soluble in water. This work, being a continuation of the studies [9, 10], reports on synthesis and fungicidal activity of new quaternary ammonium salts, containing a sulfonic group. The central part of their molecules was dibenzothiophene-5,5-dione or its 1-alkoxy derivative. The quaternary ammonium function was introduced in **VII–XII** at the C^3 and C^7 positions (see scheme).

The starting compounds to prepare the salts were 3,7-bis(hydroxymethyl)-5*H*-dibenzo[*b,d*]thiophene-5,5-dione (**I**) and its 1-alkoxy derivatives (**II**, **III**), their preparation was previously described in [10].

3,7-Bis(chloromethyl)dibenzothiophene-5,5-diones (**IV–VI**) were prepared with yields of 75–91% by refluxing of the primary alcohols (**I–III**) in toluene in the presence of two-fold (molar) excess of thionyl chloride.

Double quaternary ammonium salts (**VII–XII**) containing the dibenzothiophene-5,5-dione core were



I–III **IV–VI** **VII–XII**

R = H (**I, IV**), OCH_3 (**II, V**), OC_6H_{13} (**III, VI**); R = H, $R^1 = C_8H_{17}$ (**VII**); R = H, $R^1 = (CH_2)OH$ (**VIII**); R = OCH_3, $R^1 = C_8H_{17}$ (**IX**), R = OCH_3, $R^1 = CH_2CH_2OH$ (**X**); R = OC_6H_{13}, $R^1 = C_8H_{17}$ (**XI**); R = OC_6H_{13}, $R^1 = CH_2CH_2OH$ (**XII**).

prepared by quaternization of dimethylalkylamines (*N,N*-dimethyloctylamine, *N,N*-dimethylethanolamine) with 3,7-bis(chloromethyl) derivatives (**IV**–**VI**). The highest yield of the ammonium salts (67–88%) was achieved via 6–10 h refluxing of alcohol or acetonitrile solutions of the corresponding amines and chlorides taken in the ratio of 1:(2.3–5).

The so prepared compounds purity was checked by thin-layer chromatography (Silufol UV-254 plates, toluene–ethyl acetate 5:1). Compounds **VII**–**XII** were water-soluble powders. Structure of **IV**–**XII** was elucidated from IR and ^{1}H NMR data, the composition was proved by elemental analysis. Structures, yields, and ^{1}H NMR spectral data of dibenzothiophene-5,5-dioxide derivatives **IV**–**XII** are given in Table 1.

In the ^{1}H spectra of the symmetric compounds (**IV**, **VII**, **VIII**) CH_2X methylene protons singlet was observed at 4.44–4.93 ppm. The signals of ammonium salts $N(CH_3)_2$ methyl group protons were observed as singlets as well, at 2.94 ppm (**VII**) and 2.96 ppm (**VIII**). Protons of methylene groups bound to nitrogen NCH_2 gave rise to triplets in lower field, at 3.00 ppm (J = 8.0 Hz) (**VII**) and 3.39 ppm (J = 4.8 Hz) (**VIII**). Substitution of dibenzothiophene fragment at 1 position disrupted the symmetry (compounds **V**, **VI**, and **IX**–**XII**), thus leading to splitting of the signals of methyl and methylene groups protons $N(CH_3)_2$ and CH_2X of the substituents at C^3 and C^7. Signals of dibenzothiophene core protons were located at 6.87–8.91 ppm (**IV**–**XII**), and their multiplicity definitely supported substitution at C^1, C^3, and C^7. The presence

Table 1. Structures, yield, and ^{1}H NMR data of bis(chloromethyl)dibenzothiophene-5,5-dioxides (**IV**–**VI**) and the salts (**VII**–**XII**)

Comp. no.	R	R^1	Yield, %	^{1}H NMR, (DMSO-d_6), δ, ppm[a]
IV	H	–	91	4.93 s (4H, CH_2Cl), 7.59 d.d (2H, $H^{2,8}$ Dbt, J^{ortho} 8.5, J^{meta} 1.5 Hz,), 8.13 d (2H, $H^{4,6}$ Dbt, J^{meta} 1.5 Hz), 8.38 d (2H, $H^{1,9}$ Dbt, J^{ortho} 8.5 Hz)
V	OCH_3	–	77	4.05 s (3H, OCH_3), 4.84 s (2H, CH_2), 4.86 s (2H, CH_2), 7.53 s (1H H^2), 7.60 s (1H, H^4), 7.81 d (1H, H^8, J 1.5, 8.5 Hz), 8.01 s (1H, H^6), 8.27 d (1H, H^9)
VI	OC_6H_{13}	–	82	0.87 t (3H, CH_3, J 7 Hz), 1.29–1.32 m (4H, $(CH_2)_2$, 1.46 m (2H, CH_2), 1.83 m (2H, CH_2), 4.08 s (2H, OCH_2), 4.84 s (2H, CH_2), 4.86 s (2H, CH_2), 7.53 s (1H, H^2), 7.58 s (1H, H^4), 7.82 d.d (1H, H^8, J 1.5, 8.5 Hz), 8.02 s (1H, H^6), 8.21 d (1H, H^9, J 8.5 Hz)
VII	H	C_8H_{17}	46	0.61 t (6H, $CH_2\underline{CH_3}$, J 6.8 Hz), 0.95–1.10 m (20H, CH_2), 1.63 m (4H, $NCH_2\underline{CH_2}$, J 7.8 Hz), 2.94 s (12H, CH_3), 3.00 t (4H, $N\underline{CH_2}CH_2$, J 8.0 Hz), 4.44 c(4H, CH_2N), 7.46 d.d (2H, $H^{2,8}$ Dbt, J^{ortho} 8.0, J^{meta} 1.0 Hz), 7.87 d (2H, $H^{4,6}$ Dbt, J^{meta} 1.0 Hz), 8.15 d (2H, $H^{1,9}$ Dbt, J^{ortho} 8.0 Hz)
VIII	H	$(CH_2)_2OH$	82	2.96 s (12H, CH_3), 3.39 t (4H, $N\underline{CH_2}CH_2$, J 8 Hz), 4.00 s (4H, $NCH_2\underline{CH_2O}$, J 8 Hz), 4.45 s (4H, CH_2N), 7.33 d (2H, $H^{2,8}$ Dbt, J 8.0 Hz), 7.80 s (2H, $H^{4,6}$ Dbt), 7.90 d (2H, $H^{1,9}$ Dbt, J 8.0 Hz)
IX	OCH_3	C_8H_{17}	67	1.16 s (6H, $CH_2\underline{CH_3}$), 1.50–1.75 m (20H, CH_2), 2.17 m [4H, $N(CH_2\underline{CH_2})$], 3.43 s (3H, OCH_3), 3.48 s (6H, CH_3), 3.51 s (6H, CH_3), 3.55–3.70 m (4H, $N\underline{CH_2}CH_2$), 4.52 s (2H, CH_2N), 4.99 s (2H, CH_2N), 7.93 s (1H, $H^{4,6}$ Dbt), 8.09 s (1H, $H^{4,6}$ Dbt), 8.32 d (1H, H^8, J 7.5 Hz), 8.49 s (1H, H^2), 8.91 d (1H, H^9, J 7.0 Hz)
X	OCH_3	$(CH_2)_2OH$	77	3.05 s (6H, CH_3), 3.07 s (6H, CH_3), 3.44–3.51 m (4H, $N\underline{CH_2}CH_2$), 3.91 s (3H, OCH_3), 4.02–4.06 m (4H, $NCH_2\underline{CH_2O}$), 4.56 s (2H, CH_2N), 4.60 s (2H, CH_2N), 7.39 s (1H, $H^{4,6}$ Dbt), 7.56 s (1H, $H^{4,6}$ Dbt), 7.76 d.d (1H, H^8 Dbt, J^{ortho} 8.0, J^{meta} 1.0 Hz), 8.00 s (1H, H^2 Dbt), 8.22 d (1H, H^9 Dbt, J^{ortho} 8.0 Hz)
XI	OC_6H_{13}	C_8H_{17}	75	0.62–0.77 m (9H, $CH_2\underline{CH_3}$), 1.00–1.32 m (26H, CH_2), 1.52–1.77 m (6H, CH_2), 3.03 s (6H), 3.06 s (6H), 3.45–3.55 m (4H), 3.82–3.93 m (2H), 4.83–4.55 m (4H), 7.71 s (1H, $H^{4,6}$ Dbt), 7.89 s (1H, $H^{4,6}$ Dbt), 8.22 d (1H, H^8, J 7.5 Hz), 8.30 s (1H, H^2), 8.87 d (1H, H^9, J 7.5 Hz)
XII	OC_6H_{13}	$(CH_2)_2OH$	88	0.80 t (3H, CH_3, J 7 Hz), 1.19–1.22 m (4H), 1.29–1.32 m (2H), 1.65–1.69 m (2H, J 7 Hz), 3.11 s (6H), 3.13 s (6H), 3.55–3.84 (4H), 4.07 t (2H, OCH_2, J 7 Hz), 4.12–4.28 m (4H), 4.58 s (2H), 4.60 s (2H), 7.98 s (1H, $H^{4,6}$ Dbt), 8.17 s (1H, $H^{4,6}$ Dbt), 8.51 d (1H, H^8, J 7.5 Hz), 8.62 s (1H, H^2), 8.98 d (1H, H^9, J 7.0 Hz)

[a] Dbt – 5,5-dioxodibenzothiophene.

Table 2. Fungicidal activity of the dioxodibenzothiophenes quaternary ammonium salts (**VII**–**XII**) at 100 μg ml^{-1}

Comp. no.	Mycelium growth inhibition coefficient *RF*, %							
	Alternaria alternata	*Aspergillus niger*	*Botrytis cinerea*	*Fusarium oxysporum*	*Monilia sp.*	*Mucor sp.*	*Penicillum lividum*	*Sclerotinia sclerotiorum*
VII	100	65	80	80	100	100	100	100
VIII	50	45	10	10	65	0	100	55
IX	60	20	20	20	0	0	100	50
X	15	0	20	50	30	0	0	80
XI	65	25	50	15	60	10	50	50
XII	75	40	30	15	40	0	35	40

of OCH_3 group was proved by the singlets at 3.43 ppm (**IX**) to 4.05 ppm (**V**). Methylene group protons of the aliphatic groups OC_6H_{13} and C_8H_{17} (**III**, **IV**, **VII**, **IX**, **XI**, and **XII**) produced multiplet signals at 1.00–2.77 ppm.

The IR spectra confirmed the structures of **IV**–**XII** as well. Intense bands were observed at 1395–1300 and 1170–1122 cm^{-1} assigned to sulfonic moiety. Bands assigned to C–Cl band were observed in the spectra of **IV**–**VI** at 875–870 cm^{-1}, the bands assigned to OH group of **VIII**–**X** appeared at 3422–3385 cm^{-1}. In the IR spectra of **VII**–**XII** the bands at 1468–1465 and 1073–1088 cm^{-1} were observed thus proving the presence of C–N bond. The bands at 1270–1241 and 1045 cm^{-1} (**V**, **VI**, and **IX**–**XII**) were assigned to C–O–C stretching.

We tested the fungicidal activity of the prepared compounds towards the following strains of phytopathogenic fungi (from the collection of Microbiology department, Belarus State University): *Alternaria alternata, Aspergillus niger, Botrytis cinerea, Fusarium oxysporum, Monilia sp., Mucor sp., Penicillum lividum,* and *Sclerotinia sclero-tiorum*. The fungicidal activity of **VII**–**XII** was determined according to [11], the results are given in Table 2.

From the presented data it is clear that the fungicidal activity of the studied compounds **VII**–**XII** was different. The highest activity, being comparable to that of nistatine, was observed in the case of unsubstituted dibenzothiophene-5,5-dione derivative (R = H, $R^1 = C_8H_{17}$) (**VII**); the growth inhibition coefficient *RF* was of 65 to 100%.

EXPERIMENTAL

The melting temperature was determined using the Kofler bench with Hanna HI 93530 electronic thermometer. ^{1}H NMR spectra were recorded with Bruker Avance-500 (500 MHz), and Tesla BS-587A (100 MHz) instruments; TMS was used as internal standard. IR spectra were recorded at 400–4000 cm^{-1} with Specord M-80, in KBr tablets. Solvents were purified and dried via the common procedures. The reactions were monitored with thin-layer chromatography (silica gel 60 A plates, F_{254}, Merck Art. 7734).

3,7-Bis(chloromethyl)-5*H*-dibenzo[*b,d*]thiophene-5,5-dione (IV). A mixture of 3,7-bis-(hydroxymethyl)-dibenzothiophene-5,5-dione **I** (2.76 g, 1.0 mmol), 10 ml of toluene, and 0.5 ml (~7 mmol, 3.5 eq.) of thionyl chloride were refluxed till HCl stopped releasing. The solvent was evacuated with the rotor evaporator; the residue was dissolved in 50 ml of hexane and purified by flash-chromatography. Yield 1.97 g (91%), colorless crystals, mp 159.0–161.5°C. IR spectrum, ν, cm^{-1}: 3063, 3043, 3020, 2977, 2940, 2873, 1463, 1447, 1420, 1400, 1327, 1310, 1290, 1273, 1260, 1257, 1213, 1160, 1150, 1090, 1077, 933, 900, 880, 827, 820, 733, 727, 710, 703, 680. Found, %: C 53.65; H 3.20. $C_{14}H_{10}Cl_2O_2S$. Calculated, %: C 53.68; H 3.22. *M* 313.21.

3,7-Bis(chloromethyl)-1-methoxy-5*H*-dibenzo-[*b,d*]thiophene-5,5-dione (V) was prepared similarly, from 3,7-bis(hydroxymethyl)-1-methoxy-5*H*-dibenzo-[*b,d*]thiophene-5,5-dione (**II**) and thionyl chloride. Yield 3.06 g (75%), mp 176–178°C. IR spectrum, ν, cm^{-1}: 2990, 2960, 2880, 1610, 1590, 1500, 1465, 1415, 1370, 1305, 1270, 1160, 1055, 935, 895, 875, 730. Found, %: C 52.41; H 3.42. $C_{15}H_{12}Cl_2O_3S$. Calculated, %: C 52.49; H 3.53. *M* 343.24.

3,7-Bis(chloromethyl)-1-hexyloxy-5*H*-dibenzo-[*b,d*]thiophene-5,5-dione (VI) was prepared similarly, from 1-hexyloxy derivative (**III**) and thionyl chloride. Yield 3.76 g (75%), mp 44–46°C. IR spectrum, ν, cm^{-1}: 2985, 2950, 2875, 1605, 1590, 1500, 1465, 1410,

1370, 1305, 1275, 1170, 1045, 935, 895, 870, 720. Found, %: C 57.84; H 5.14. $C_{20}H_{22}Cl_2O_3S$. Calculated, %: C 58.11; H 5.36. *M* 413.37.

Preparation of quaternary ammonium salts of 1,3,7-trisubstituted derivatives of 5,5-dioxodibenzothiophene (VII–XII) (general procedure). A mixture of bis(chloromethyl) derivative (**IV**–**VI**) and *N,N*-dimethyloctylamine or 2-(*N,N*-dimethylamino)-ethanol in the ratio of 1:(2.3–2.5) was refluxed with 20–50 ml of dehydrated acetonitrile or alcohol during 8–10 h. After the reaction, the precipitate formed was filtered off, washed with hot acetonitrile and hot hexane to remove the excess of the amine, and then dried under reduced pressure.

3,7-Bis[(*N,N*-dimethyl-*N*-octyl)ammoniummethyl]-5,5-dioxodibenzothiophene dichloride (VII) was prepared from 0.86 g (2.74 mmol) of 3,7-bis(chloromethyl)-5,5-dioxodibenzothiophene (**I**) and 1.0 g (6.36 mmol) of *N,N*-dimethyloctylamine. Yield 1.3 g (75%), mp > 150°C (decomp.). IR spectrum, ν, cm^{-1}: 3150–3650 br., 3033, 3020, 2970, 2940, 2870, 1627, 1503, 1497, 1483, 1470, 1460, 1450, 1407, 1383, 1330, 1253, 1223, 1093, 1080, 1073, 1027, 1020, 1000, 950, 903, 877, 870, 857, 833, 767, 757, 733, 707. Found, %: C 64.44; H 8.04. $C_{34}H_{56}Cl_2N_2O_2S$. Calculated, %: C 65.05; H 8.99. *M* 626.34.

3,7-Bis[(*N,N*-dimethyl-*N*-2'-hydroxyethyl)ammoniummethyl]-5,5-dioxodibenzothiophene dichloride (VIII) was prepared from 0.31 g (1 mmol) of 3,7-bis(chloromethyl)-5,5-dioxodibenzothiophene (**I**) and 0.5 ml (5.0 mmol, 5.0 eq.) of 2-(*N,N*-dimethylamino)-ethanol (**IIb**). Yield 404 mg (82%), mp ~ 150°C (decomp.). IR spectrum, ν, cm^{-1}: 3100–3677 br., 3030, 2977, 2940, 2870, 1630, 1483, 1470, 1410, 1390, 1327, 1253, 1223, 1163, 1100, 1077, 1067, 1033, 997, 943, 927, 910, 827. Found, %: C 63.08; H 7.51. $C_{22}H_{32}Cl_2N_2O_4S$. Calculated, %: C 53.76; H 6.56. *M* 490.15.

1-Methoxy-3,7-bis[(*N,N*-dimethyl-*N*-octyl)ammoniummethyl]-5,5-dioxodibenzothiophene dichloride (IX) was prepared from 1.72 g (5 mmol) of 1-methoxy-3,7-bis(chloromethyl)-5,5-dioxodibenzothiophene (**V**) and 2 g (12.7 mmol) of *N,N*-dimethyloctylamine. Yield 1.97 g (67%), mp > 170°C (decomp.). Found, %: C 63.84; H 8.32. $C_{35}H_{58}Cl_2N_2O_3S$. Calculated, %: C 63.90; H 8.90. *M* 656.35.

1-Methoxy-3,7-bis[(*N,N*-dimethyl-*N*-2'-hydroxyethyl)-ammoniummethyl]-5,5-dioxodibenzothiophene dichloride (X) was prepared from 0.2 g of **V** dichloride and 0.2 g of 2-(*N,N*-dimethylamino)ethanol. Yield 0.24 g (77%), mp > 170°C (decomp.). Found, %: C 52.76; H 6.64. $C_{23}H_{34}Cl_2N_2O_5S$. Calculated, %: C 52.97; H 6.57. *M* 520.16.

1-Hexyloxy-3,7-bis[(*N,N*-dimethyl-*N*-octyl)ammoniummethyl]-5,5-dioxodibenzothiophene dichloride (XI) was prepared from 0.14 g (0.33 mmol) **VI** dichloride and 0.15 g (0.95 mmol) of *N,N*-dimethyloctylamine. Yield 0.18 g (75%), mp > 150°C (decomp.). Found, %: C 66.54; H 9.14. $C_{40}H_{68}Cl_2N_2O_3S$. Calculated, %: C 66.00; H 9.42. *M* 726.435.

1-Hexyloxy-3,7-bis[(*N,N*-dimethyl-*N*-2'-hydroxyethyl)ammoniummethyl]-5,5-dioxodibenzothiophene dichloride (XII) was prepared from 0.53 g (1.28 mmol) of **VI** dichloride and 0.27 g (3.02 mmol) of 2-(*N,N*-dimethylamino)ethanol. Yield 0.66 g (88%), mp > 150°C (decomp.). Found, %: C 56.48; H 7.76. $C_{28}H_{44}Cl_2 \cdot N_2O_5S$. Calculated, %: C 56.84; H 7.50. *M* 590.23.

Determination of fungicidal activity of (VII–XII). The studied compounds **VII**–**XII** were dissolved in sterile distilled water and applied to the culture medium at the final concentration of 100 μg ml^{-1}. To cultivate the fungi, the potato agar was used after autoclaving for 30 min at 0.5 atm.

The fungi were plated with a microstreaker from the formed mycelium. The plates were incubated at 25°C, the results were recorded after 96 h. To compare the growth inhibition, the Ebbot equation was used:

$$RF = (D_k - D_0/D_k) \times 100,$$

with *RF* being the fungi growth inhibition coefficient (as compared with the reference), %; D_k is colony diameter in the reference experiment; D_0 is colony diameter in the experiment.

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