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Synthesis of Dialkylaminomethoxy Derivatives of 3-Aryloxy-1-(ethylsulfanyl)propanes

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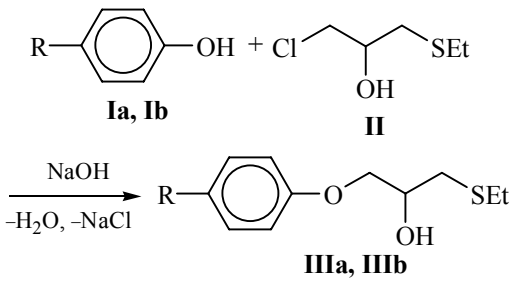
Organic compounds containing sulfur and nitrogen are widely used as antioxidant, anticorrosion, and antimicrobial additives to fuels and lubricants [1]. They are also biologically active compounds and are involved into the composition of pharmaceuticals [2]. The preparation of new series of compounds proceeding from accessible raw materials and refinement of the general synthetic procedures is highly urgent [3].

We reporet here on the results of syntheses and study of the properties of new dialkylaminomethoxy derivatives of 3-aryloxy-1-(ethylsulfanyl)propanes. To this end we first synthesized previously unknown sulfur-containing aryloxy alcohols **IIIa** and **IIIb** by reaction of phenols **Ia** and **Ib** with 1-chloro-3-(ethyl-sulfanyl)propan-2-ol (**II**) in alkaline medium (Scheme 1). The synthesis of alcohols **IIIa** and **IIIb** was carried out at equimolar ratio of initial compounds in alkaline medium (40% aqueous NaOH) at 70–75°C over 4–5 h, the yield of the alcohols was 70–72%.

Scheme 1.



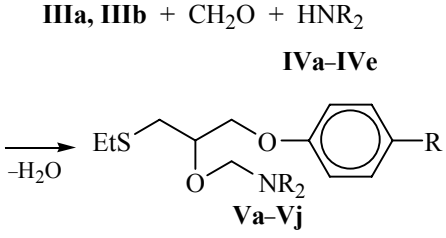
R = H (**a**), Me (**b**).

Further by Mannich condensation of alcohols **IIIa** and **IIIb** with formaldehyde and secondary amines **IVa–IVe** we obtained new representatives of dialkylaminomethoxy-3-aryloxy(ethylsulfanyl)propanes **Va–Vj** (Scheme 2).

The synthesis of amino derivatives **Va–Vj** was performed at 45–50°C over 4–5 h at equimolar amounts of the components. The yield of compounds **Va–Ve** from alcohol **IIIa** was 70–78%, of compounds **Vf–Vj** from alcohol **IIIb** attained 70–75%, the yield of *N,N*-dibutylamino derivatives **Vb** and **Vg** was somewhat higher (78 and 76% respectively).

The synthesized alcohols **IIIa** and **IIIb** and their amino derivatives **Va–Vj** are transparent foxy liquids. They are insoluble in water but well soluble in organic solvents (ethanol, acetone, benzene, CCl_4 etc.).

Scheme 2.



R = H (**Va–Ve**), Me (**Vf–Vj**); NR_2 = NEt_2 (**IVa, Va, Vf**), NBu_2 (**IVb, Vb, Vg**), piperidino (**IVc, Vc, Vh**), morpholino (**IVd, Vd, Vi**), $N(CH_2)_6$ (**IVe, Ve, Vj**).

The composition and structure of compounds obtained were established from the elemental analysis, IR, ^{1}H NMR, and mass spectra. The purity of compounds was checked by GLC. The IR spectra of compounds **IIIa** and **IIIb** contained broad absorption bands in the region 3350–3300 cm^{-1} characteristic of hydroxy group which were lacking in the spectra of compounds **Va–Vj**. In the IR spectra of compounds **Va–Vj** absorption bands were present in the 1220–1010 cm^{-1} characteristic of the C–N bond [4], and also in the region 2910–2895 and 2830–2820 cm^{-1} characteristic of vibrations of the C–H bond in the groups CH_3 and CH_2 respectively. ^{1}H NMR spectra of compounds synthesized have a typical pattern and also confirm the assigned structure. In the mass spectra (electron impact) of compounds **IIIa** and **IIIb, Va–Vj** the peaks were observed of the corresponding molecular ions and of their fragmentation products.

The obtained 3-(4-methylphenoxy)-1-(ethylsulfanyl)-propanes **Va–Vj** were tested as antimicrobial agents in the medicine. They demonstrated a more pronounced antimicrobial activity than the preparations commonly used in the medicine (ethanol, phenol, acrinol, and nitrofungin). Thus they can be suggested for application as new efficient antimicrobial agents.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20 in the region 4000–400 cm^{-1}. ^{1}H NMR spectra were registered on a spectrometer Bruker WP-400 (400 MHz), solvent $CDCl_3$, chemical shifts reported with respect to TMS. Mass spectra were obtained on an instrument VG-7070E (ionizing electrons energy 70eV). The chromatography analysis of the reaction mixtures and testing the purity of compounds synthesized was performed on a chromatograph LKhM-8MD {steel column (3000 × 3 mm), stationary phase 5% poly(ethylene glycol) succinate on dinochrome P], carrier gas helium (40 cm^3/min), detector cataharometer, oven temperature 150°C, vaporizer temperature 240°C.

3-Phenoxy-1-(ethylsulfanyl)propan-2-ol (IIIa). To a mixture of 23.53 g (0.25 mol) of phenol and 10 g of NaOH in 15 ml of water at 70–75°C under vigorous stirring was added dropwise 38.67 g (0.25 mol) of alcohol **II**. The stirring was continued for 3–4 h. After cooling benzene was added to the mixture, the organic layer was washed with water to neutral washings, and dried with $MgSO_4$. On distilling off the solvent the residue was distilled in a vacuum. Yield 32.2 g (72%), bp 146–147°C (1 mm Hg), n_4^{20} 1.5508, d_4^{20} 1.1126. MR_D 60.86, calc. 60.87. IR spectrum, ν, cm^{-1}: 3350 (OH), 2920 (CH_3), 2880 (CH_2). ^{1}H NMR spectrum, δ, ppm: 1.36 t (3H, SCH_2CH_3), 2.1 s (OH), 2.5 t (2H, SCH_2), 2.75 d.d (2H, SCH_2CH), 3.7 m (OCH), 7.0 m (3H, *n-, m*-C_6H_5), 7.34 m (2H, *o*-C_6H_5). Mass spectrum, *m/z* (I_{rel}, %): 212 (10) $[M]^+$, 195 (100), 147 (20), 47 (25). Found, %: C 62.04; H 7.45; S 14.92. $C_{11}H_{16}O_2S$. Calculated, %: C 62.20; H 7.54; S 15.07. M 212.31.

3-(*p*-Tolyloxy)-1-(ethylsulfanyl)propan-2-ol (IIIb) was analogously obtained from 27.02 g (0.25 mol) of *p*-cresol (**Ib**) and 38.67 g (0.25 mol) of alcohol **II**. Yield 47.5 g (70%), bp 150–152°C (1 mm Hg), n_4^{20} 1.5448, d_4^{20} 1.0898. MR_D 65.64, calc. 65.51. IR spectrum, ν, cm^{-1}: 3200 (OH), 2920 (CH_3), 2870 (CH_2). ^{1}H NMR spectrum, δ, ppm: 1.34 t (3H, SCH_2CH_3), 2.35 s (3H, *n*-CH_3), 2.5 t (2H, SCH_2), 2.7 m (OH), 2.75 d.d (2H, SCH_2CH), 3.6 m (OCH), 6.85–7.10 m (4H, C_6H_4). Mass spectrum, *m/z* (I_{rel}, %): 226 (10) $[M]^+$, 209 (100), 105 (100), 59 (20). Found; %: C 63.53; H 7.92; S 14.02. $C_{12}H_{18}O_2S$. Calculated, %: C 63.68; H 8.01; S 14.16. M 226.32.

Dialkylaminomethoxy derivatives of aryloxy-substituted ethylsulfanylpropanes Va–Vj. To a solution of 0.02 mol of alcohol **IIIa** or **IIIb** and 0.02 mol of formaldehyde (which obtained from paraformaldehyde in the course of the reaction) in 30 ml of anhydrous benzene at 20–22°C was added dropwise while stirring 0.02 mol of freshly distilled amine **IVa–IVe**. The stirring was continued for 1 h at the same temperature, then 1–3 h at 40–50°C. On removing the solvent the residue was distilled in a vacuum.

2-(*N,N*-Diethylaminomethoxy)-3-phenoxy-1-(ethylsulfanyl)propane (Va) was obtained from 4.25 g of compound **IIIa**, 0.6 g of paraform, and 1.46 g of diethylamine. Yield 4.3 g (72%), bp 158–160°C (1 mm Hg), n_4^{20} 1.5155, d_4^{20} 1.0213. MR_D 87.90, calc. 88.13. IR spectrum, ν, cm^{-1}: 2920 (CH_3), 2880 (CH_2), 1225 (C–N). ^{1}H NMR spectrum, δ, ppm: 1.36 t (3H, SCH_2CH_3), 1.62 t (6H, $2NCH_2CH_3$), 2.65–2.25 m (10H, OCH_2, $2NCH_2$, $2SCH_2$), 3.4 m (OCH), 4.2 d.d (2H, OCH_2N), 7.1 m (3H, *n-, m*-C_6H_5), 7.34 m (2H, *o*-C_6H_5). Found, %: C 64.46; H 9.04; N 4.63; S 10.66. $C_{16}H_{27}NO_2S$. Calculated, %: C 64.61; H 9.15; N 4.71; S 10.78.

2-(*N,N*-Dibutylaminomethoxy)-3-phenoxy-1-(ethylsulfanyl)propane (Vb) was obtained from 4.25 g (0.02 mol) of compound **IIIa**, 0.6 g of paraformaldehyde, and 2.58 g (0.02 mol) of dibutylamine (**IVb**). Yield 5.52 g

(78%), bp 184–186°C (1 mm Hg), n_4^{20} 1.5010, d_4^{20} 1.0976. MR_D 110.89, calc. 111.37. IR spectrum, ν, cm^{-1}: 2920 (CH_3), 2890 (CH_2), 1500 (C–C_{arom}), 1200 (C–N). ^{1}H NMR spectrum, δ, ppm: 0.95 m (6H, $2CH_3$), 1.34 m (3H, SCH_2CH_3), 1.55–1.65 m (8H, $4CH_2$), 2.55–2.70 m (10H, OCH_2, $2NCH_2$, $2SCH_2$), 3.4 m (OCH), 4.20 d.d (2H, OCH_2N), 7.0 m (3H, *n-, m*-C_6H_5), 7.35 m (2H, *o*-C_6H_5). Mass spectrum, m/z (I_{rel}, %): 353 $[M]^+$ (15), 282 (5), 147 (45), 119 (100), 98 (60), 75 (70). Found, %: C 67.78; H 9.89; N 3.88; S 8.95; $C_{20}H_{35}NO_2S$. Calculated, %: C 67.94; H 9.98; N 3.96; S 9.07. M 353.53.

2-Piperidinomethoxy-3-phenoxy-1-(ethylsulfanyl)propane (Vc) was obtained from 4.25 g of compound **IIIa**, 0.6 g of paraformaldehyde, and 1.72 g of piperidine (**IVc**). Yield 4.46 g (72%), bp 173–175°C (1 mm Hg), n_4^{20} 1.5312, d_4^{20} 1.0568. IR spectrum, ν, cm^{-1}: 2920 (CH_3), 2820 (CH_2), 1020 (C–N), 720 (C–S). ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, SCH_2CH_3), 1.65 t (6H, $3CH_{2cycle}$), 2.60–2.90 m (6H, OCH_2, $2SCH_2$), 3.3 m (OCH), 4.20 d.d (2H, OCH_2N), 7.0 m (3H, *p-, m*-C_6H_5) 7.34 m (2H, *o*-C_6H_5). Mass spectrum, m/z (I_{rel}, %): 309 (20) $[M]^+$, 235 (10), 147 (50), 119 (100), 75 (70), 47 (27). Found, %: C 65.89; H 8.76; N 4.46; S 10.26. $C_{17}H_{27}NO_2S$. Calculated, %: C 66.98; H 8.79; N 4.53; S 10.36. M 309.44.

2-Morpholinomethoxy-3-phenoxy-1-(ethylsulfanyl)propane (Vd) was obtained from 4.25 g of compound **IIIa**, 0.6 g of paraformaldehyde, and 1.74 g of morpholine (**IVd**). Yield 4.79 g (74%), bp 173–175°C (1 mm Hg), n_4^{20} 1.5366, d_4^{20} 1.1066. MR_D 87.84, calc. 87.98. IR spectrum, ν, cm^{-1}: 2900 (CH_3), 2860 (CH_2), 1200 (C–N), 730 (C–S). ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, SCH_2CH_3), 2.6–2.8 m (14H, $3OCH_2$, $2NCH_2$, $2SCH_2$), 3.20 t (OCH), 4.2 d.d (2H, OCH_2N), 7.0 m (3H, *p-, m*-C_6H_5), 7.34 m (2H, *o*-C_6H_5). Found, %: C 61.52; H 8.01; N 4.43; S 10.20. $C_{16}H_{25}NO_3S$. Calculated, %: C 61.70; H 8.09; N 4.50; S 10.30.

2-Hexamethyleneiminomethoxy-3-phenoxy-1-(ethylsulfanyl)propane (Ve) was obtained from 4.25 g of compound **IIIa**, 0.6 g of paraformaldehyde, and 1.98 g hexamethyleneimine (**IVe**). Yield 4.72 g (73%), bp 182–184°C (1 mm Hg), n_4^{20} 1.5308, d_4^{20} 1.0526. MR_D 95.05, calc. 95.37. IR spectrum, ν, cm^{-1}: 2920 (CH_3), 2850 (CH_2), 1200 (C–N), 730 (C–S). ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, SCH_2CH_3), 1.65 t (8H, CH_{2cycle}), 2.6–2.9 m (10H, OCH_2, $2NCH_2$, $2SCH_2$), 3.25 t (OCH), 4.20 d.d (2H, OCH_2N), 7.0 m (3H, *p-, m*-C_6H_5), 7.34 m (2H, *o*-C_6H_5). Mass spectrum, m/z (I_{rel}, %): 323 (10), 225 (6) $[M - C_6H_{12}N]^+$, 194 (17) $[C_{11}H_{23}OS]^+$, 133 (36) $[M - C_9H_{20}NO]^+$, 119 (72) $[M - C_{10}H_{23}OS]^+$, 75 (100). Found, %: C 66.71; H 8.96; N 4.25; S 9.82. $C_{18}H_{29}NO_2S$. Calculated, %: C 66.83; H 9.04; N 4.33; S 9.91. M 323.19.

2-(*N,N*-Diethylaminomethoxy)-3-(*p*-tolyloxy)-1-(ethylsulfanyl)propane (Vf) was obtained from 4.25 g of compound **IIIb**, 0.6 g of paraformaldehyde, and 1.46 g of diethylamine (**IVa**). Yield 4.36 g (70%), bp 164–165°C (1 mm Hg), n_4^{20} 1.5150, d_4^{20} 1.0148. MR_D 92.55, calc. 92.78. IR spectrum, ν, cm^{-1}: 2910 (CH_3), 2890 (CH_2), 1215 (C–N). ^{1}H NMR spectrum, δ, ppm: 0.95 t (6H, $2CH_3$), 1.36 t (3H, SCH_2CH_3), 2.35 s (3H, *p*-CH_3), 2.60–2.80 m (10H, $2NCH_2$, OCH_2, $2SCH_2$), 3.25 m (OCH), 4.20 d.d (2H, OCH_2N), 6.85–7.10 m (4H, C_6H_4). Mass spectrum, m/z (I_{rel}, %): 311 (10) $[M]^+$, 239 (15), 147 (45) 119 (100), 101 (45), 75 (60), 47 (30). Found, %: C 65.41; H 9.30; N 4.42; S 10.19. $C_{17}H_{29}NO_2S$. Calculated, %: C 65.55; H 9.38; N 4.49; S 10.29. M 311.19.

2-(*N,N*-Dibutylaminomethoxy)-3-(*p*-tolyloxy)-1-(ethylsulfanyl)propane (Vg) was obtained from 4.52 g of compound **IIIb**, 0.6 g of paraformaldehyde, and 2.58 g of dibutylamine (**IVb**). Yield 5.59 g (76%), bp 208–209°C (1 mm Hg), n_4^{20} 1.5038, d_4^{20} 0.9812. MR_D 110.89, calc. 111.37. IR spectrum, ν, cm^{-1}: 2920 (CH_3), 2890 (CH_2), 1020 (C–N). ^{1}H NMR spectrum, δ, ppm: 0.95 m (6H, $2CH_3$), 1.35 t (3H, SCH_2CH_3), 1.35–1.65 m (8H, $4CH_2$), 2.35 sC (3H, p-CH_3), 2.60–2.80 m (10H, $2NCH_2$, $2SCH_2$, OCH_2), 3.2 m (OCH), 4.22 d.d (2H, OCH_2N), 6.85–7.10 m (4H, C_6H_4). Mass spectrum, m/z (I_{rel}, %): 367 (19) $[M]^+$, 306 (5), 119 (100). Found, %: C 71.59; H 10.52; N 3.77; S 8.67. $C_{21}H_{37}NO_2S$. Calculated, %: C 71.74; H 10.60; N 3.81; S 8.72. M 367.56.

2-Piperidinomethyleneoxy-3-(*p*-tolyloxy)-1-(ethylsulfanyl)propane (Vh) was obtained from 4.52 g of compound **IIIb**, 0.6 g of paraformaldehyde, and 1.74 g of piperidine. Yield 4.62 g (71%), bp 191–193°C (1 mm Hg), n_4^{20} 1.5296, d_4^{20} 1.0459. MR_D 95.48, calc. 95.37. IR spectrum, ν, cm^{-1}: 2920 (CH_3), 2830 (CH_2), 1020 (C–N). ^{1}H NMR spectrum, δ, ppm: 0.95–1.18 (6H, $3CH_{2cycle}$), 1.36 t (3H, SCH_2CH_3), 2.35 s (3H, *p*-CH_3), 2.60–2.90 m (10H, OCH_2, NCH_2, SCH_2), 3.24 quintet (OCH), 4.20 d.d (2H, OCH_2N), 6.95–7.21 m (4H, C_6H_4). Mass spectrum, *m/z* (I_{rel}, %): 323 (10) $[M]^+$, 262 (5), 208 (15), 147 (40), 119 (100), 98 (55), 75 (70), 47 (30). Found, %: C 66.70; H 8.96; N 4.27; S 9.81. $C_{18}H_{29}NO_2S$. Calculated, %: C 66.83; H 9.03; N 4.32; S 9.91. M 323.19.

2-Morpholinomethoxy-3-(*p*-tolyloxy)-1-(ethylsulfanyl)propane (Vi) was obtained from 4.52 g of

compound **IIIb**, 0.6 g of paraformaldehyde, and 1.74 g of morpholine. Yield 4.88 g (75%), bp 193–195°C (1 mm Hg), n_4^{20} 1.5314, d_4^{20} 1.0891. MR_D 92.52, calc. 92.48. IR spectrum, ν, cm^{-1}: 2900 (CH_3), 2840 (CH_2), 1200 (C–N). ^1H NMR spectrum, δ, ppm: 1.34 t (3H, SCH_2CH_3), 2.35 s (3H, *n*-CH_3), 2.60–2.80 m (14H, NCH_2, $3OCH_2$, $2SCH_2$), 3.2 quintet (OCH), 4.20 d.d (2H, OCH_2N), 6.95–7.20(4H, C_6H_4). Mass spectrum, *m/z* (I_{rel}, %): 325 (10) $[M]^+$, 264 (15), 119 (100), 47 (25). Found, %: C 62.62; H 8.28; N 4.25; S 9.76. $C_{17}H_{27}NO_3S$. Calculated, %: C 62.74; H 8.36; N 4.30; S 9.85. M 325.17.

2-Hexamethyleneiminomethoxy-3-(*p*-tolyloxy)-1-(ethylsulfanyl)propane (**Vj**) was obtained from 4.5 g of alcohol **IIIb**, 0.6 g of paraformaldehyde, and 1.98 g of hexa-methyleneimine (**IVe**). Yield 4.93 g (73%), bp 193–195°C (1 mm Hg), n_4^{20} 1.5300, d_4^{20} 1.0455. MR_D 99.73, calc. 100.02. IR spectrum, ν, cm^{-1}: 2920 (CH_3), 2840 (CH_2), 1060 (CN). ^1H NMR spectrum, δ, ppm: 1.35 (3H, SCH_2CH_3), 1.65 m (8H, $4CH_{2cycle}$), 2.35 s (3H, *p*-CH_3), 2.6–2.9 m (10H, $2NCH_2$, OCH_2, $2SCH_2$), 3.34 t (OCH), 4.20 d.d (2H, OCH_2N), 6.85–7.10 m (4H, C_6H_4). Found, %: C 66.59; H 9.18; N 4.09; S 9.42. $C_{19}H_{31}NO_2S$. Calculated, %: C 67.61; H 9.26; N 4.15; S 9.50.

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