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Synthesis of 2-Aminomethoxy-1-benzylsulfanylpentanes

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Abstract—Mannich condensation of 1-benzylsulfanylpentane with equimolar amounts of formaldehyde and secondary amine gave in 3–4 h at 45–50°C the corresponding 2-aminomethoxy-1-benzylsulfanylpentanes in 72–76% yield.

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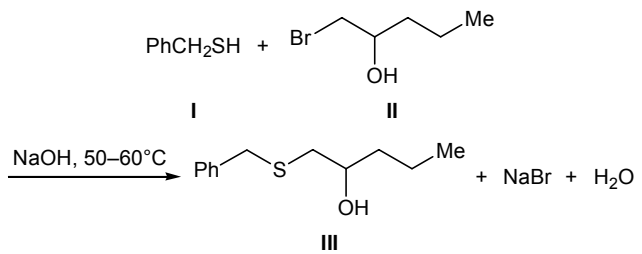
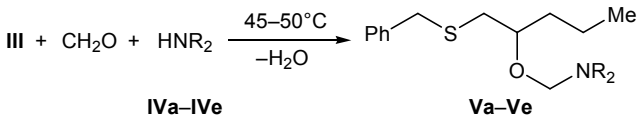
Organic compounds containing both nitrogen and sulfur atoms exhibit strong and diverse biological activity. Effective antiviral, antitumor, neurotropic, and antibacterial agents were found among such compounds [1]. Some nitrogen-and-sulfur-containing derivatives are used as antioxidant, anticorrosion, and antimicrobial dopes to fuels and oils [2]. An important problem is search for new N,S-containing compounds and improvement of general procedures for their synthesis [3].

Mannich reaction is widely used in the synthesis of organic compounds containing nitrogen and sulfur atoms [4]. While continuing our studies on the chemistry of dialkylamino derivatives of aryl(alkyl)-sulfanylalkanes [5], in the present work we synthesized aminomethoxy derivatives of 1-benzylsulfanylpentane and examined their antimicrobial activity. In the first step of our study we synthesized previously unknown 1-benzylsulfanylpentan-2-ol (**III**) by reaction of phenylmethanethiol (**I**) with an equimolar amount of 1-bromopentan-2-ol (**II**) in alkaline medium (40% aq. sodium hydroxide, 50–60°C, 3–4 h; Scheme 1). Alcohol **III** was then brought into Mannich condensation with formaldehyde and secondary amines **IVa**–**IVe** taken at an equimolar ratio. The Mannich reactions were carried out at 45–50°C (reaction time 3–4 h), and the products were new 2-aminomethoxy-1-benzylsulfanylpentanes **Va**–**Ve** (Scheme 2).

Scheme 1.



Scheme 2.



R = Et (**a**), Bu (**b**); R_2N = piperidino (**c**), morpholino (**d**), azepan-1-yl (**e**).

Alcohol **III** and amines **Va**–**Ve** were isolated as colorless liquids with a sharp odor. Compounds **Va**–**Ve** are insoluble in water but are readily soluble in organic solvents (ethanol, acetone, benzene, $CHCl_3$, CCl_4, etc.). Their structure was determined on the basis of their elemental compositions and IR, ^1H NMR, and mass spectra. The purity of the initial compounds and products and composition of the reaction mixtures were monitored by gas–liquid chromatography.

The IR spectrum of **III** contained a broad absorption band in the region of 3625 cm^{-1}, which is typical

of stretching vibrations of hydroxy group (ν_{OH}) in secondary alcohols; no such band was present in the IR spectra of **Va**–**Ve**. Compounds **III** and **Va**–**Ve** displayed in the IR spectra absorption bands at 2910–2895 and 2850–2830 cm^{-1} due to vibrations of C–H bonds in CH_3 and CH_2 groups, respectively. Stretching vibrations of aromatic C–C bonds in **Va**–**Ve** gave medium-intensity absorption bands at 1600–1585 and 1500–1400 cm^{-1}. Medium-intensity bands at 3100–3050 cm^{-1} belong to stretching vibrations of C–H bonds in the benzene ring. The IR spectra of **III** and **Va**–**Ve** also contained strong absorption bands in the region 700–650 cm^{-1} due to out-of-plane bending vibrations of C–H bonds (δ_{C-H}). Stretching vibrations of the C–O bonds appeared as a strong band at 1100–1050 cm^{-1}, and C–N vibrations gave rise to a medium-intensity band at 1250–1200 cm^{-1}. In the IR spectra of **Va**–**Ve** we also observed absorption bands in the region 735–730 cm^{-1}, which are typical of C–S stretching vibrations.

The ^{1}H NMR spectra of **III** and **Va**–**Ve** were consistent with the assumed structures. Compounds **III** and **Va**–**Ve** displayed in the mass spectra the corresponding molecular ion peaks and fragment ion peaks.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer. The ^{1}H NMR spectra were measured on a Bruker WP-400 spectrometer (400 MHz) from solutions in $CDCl_3$ using tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on a VG-7070E mass spectrometer. The densities d_4^{20} (g/cm^3) were determined by weighing precisely measured volumes, and the refractive indices n_D^{20} were measured using an IRF-22 refractometer. Chromatographic analysis of the reaction mixtures and products was performed on an LKhM-8MD chromatograph equipped with a thermal conductivity detector and a 300 × 3-mm steel column packed with 5% of polyethylene glycol succinate on Dinokhrom P; carrier gas helium, flow rate 40 cm^3/min; oven temperature 150°C, injector temperature 240°C.

1-(Benzylsulfanyl)pentan-2-ol (III). 1-Bromopentan-2-ol (**II**), 83.5 g (0.5 mol), was added dropwise to a mixture of 62 g (0.5 mol) of phenylmethanethiol (**I**) and 20 g (0.5 mol) of sodium hydroxide in 30 ml of water (a 40% solution) under vigorous stirring at 50°C. The mixture was stirred for 3–4 h at 50–60°C and cooled, 50 ml of benzene was added, the aqueous phase was separated, and the organic phase was washed with water until neutral washings and dried over $MgSO_4$. The solvent was distilled off, and the residue was distilled under reduced pressure. Yield 73.6 g (70%), bp 146–148°C (1 mm), n_D^{20} = 1.5476, d_4^{20} = 1.0528; MR_D = 63.42, calcd. 63.76. IR spectrum, ν, cm^{-1}: 3625 (OH), 2910 (CH_3), 2850 (CH_2), 3070 (C–H_{arom}), 1590 (C=C_{arom}), 1050 (C–O), 730 (C–S). ^{1}H NMR spectrum, δ, ppm: 0.9 t (3H, CH_3), 1.5 m (4H, CH_2), 2.5 t (2H, CH_2S), 2.8 m (OH), 3.5 t (OCH), 3.8 s (2H, PhC**H**$_2$), 7.30 m (1H, *p*-H), 7.34 m (2H, *m*-H), 7.36 m (2H, *o*-H). Mass spectrum, *m*/*z* (I_{rel}, %): 210 (10) $[M]^+$, 193 (100) $[M - OH]^+$, 179 (8) $[M - OH - CH_2]^+$, 138 (72) $[C_8H_{10}S]^+$, 135 (19) $[M - C_{11}H_9 - H_2O]^+$, 122 (6) $[C_7H_6S]^+$, 95 (50) $[PhCH_2]^+$. Found, %: C 68.34; H 8.56; S 15.12. $C_{12}H_{18}OS$. Calculated, %: C 68.54; H 8.62; S 15.24. *M* 210.34.

2-Aminomethoxy-1-benzylsulfanylpentanes Va–Ve (*general procedure*). Freshly distilled amine **IVa**–**IVe**, 0.03 mol, was added dropwise to a solution of 0.03 mol of alcohol **III** and 0.03 mol of formaldehyde (generated from paraformaldehyde during the process) in 30 ml of anhydrous benzene under stirring at 20–22°C. The mixture was stirred for 1 h at that temperature and for 3–4 h at 45–50°C. The solvent was distilled off, and the residue was distilled under reduced pressure.

***N*-[1-(Benzylsulfanyl)pentan-2-yloxymethyl]-*N*-ethylethanamine (Va)** was synthesized from 6.3 g (0.03 mol) of compound **III**, 0.9 g (0.03 mol) of paraformaldehyde, and 2.19 g (0.03 mol) of diethylamine (**IVa**). Yield 6.4 g (72%), bp 152–153°C (1 mm), n_D^{20} = 1.5148, d_4^{20} = 0.9776; MR_D = 91.09, calcd. 91.01. IR spectrum, ν, cm^{-1}: 3070 (C–H_{arom}), 2900 (CH_3), 2840 (CH_2), 1600 (C=C_{arom}), 1200 (C–N), 1100 (C–O), 735 (C–S). ^{1}H NMR spectrum, δ, ppm: 1.0–1.18 m (9H, CH_3), 1.35 m (4H, CH_2), 2.65–2.95 m (6H, NCH_2, SCH_2), 7.36 m (2H, *o*-H), 3.40 t (OCH), 3.80 s (2H, PhC**H**$_2$), 4.20 d.d (2H, OCH_2N), 7.34 m (2H, *m*-H), 7.30 m (1H, *p*-H). Mass spectrum, *m*/*z* (I_{rel}, %): 295 (7) $[M]^+$, 223 (11) $[M - C_4H_{10}N]^+$, 192 (9) $[M - C_5H_{11}N - H_2O]^+$, 153 (72) $[M - C_8H_{10}S]^+$, 122 (100) $[C_7H_6S]^+$, 95 (36) $[PhCH_2]^+$, 72 (6) $[C_4H_{10}N]^+$. Found, %: C 68.88; H 9.82; N 4.70; S 10.75. $C_{17}H_{29}NOS$. Calculated, %: C 69.10; H 9.89; N 4.74; S 10.85. *M* 295.5.

***N*-[1-(Benzylsulfanyl)pentan-2-yloxymethyl]-*N*-butylbutanamine (Vb)** was synthesized from 6.3 g (0.03 mol) of compound **III**, 0.9 g (0.03 mol) of paraformaldehyde, and 3.87 g (0.03 mol) of dibutylamine (**IVb**). Yield 8.02 g (76%), bp 182–184°C (1 mm), n_D^{20} = 1.5024, d_4^{20} = 0.9481; MR_D = 109.5, calcd. 109.6. IR spectrum, ν, cm^{-1}: 3060 (C–H_{arom}), 2910 (CH_3),

2850 (CH_2), 1585 (C=C_{arom}), 1200 (C–N), 1050 (C–O), 735 (C–S). ^{1}H NMR spectrum, δ, ppm: 0.95 t (9H, CH_3), 1.35–1.45 m (12H, CH_2), 2.45–2.65 m (6H, SCH_2, NCH_2), 3.40 t (OCH), 3.80 s (2H, PhC**H**$_2$), 4.25 d.d (OCH_2N), 7.35 m (5H, C_6H_5). Mass spectrum, *m*/*z* (I_{rel}, %); 352 (6) $[M + H]^+$, 351 (27) $[M]^+$, 333 (27) $[M - H_2O]^+$, 193 (36) $[M - C_9H_{20}NO]^+$, 122 (100) $[C_7H_6S]^+$. Found, %: C 71.58; H 10.53; N 3.94; S 9.03. $C_{21}H_{37}NOS$. Calculated, %: C 71.74; H 10.60; N 3.98; S 10.43. *M* 351.61.

***N*-[1-(Benzylsulfanyl)pentan-2-yloxymethyl] piperidine (Vc)** was synthesized from 6.3 g (0.03 mol) of alcohol **III**, 0.9 g (0.03 mol) of paraformaldehyde, and 2.55 g (0.03 mol) of piperidine (**IVc**). Yield 6.83 g (74%), bp 176–178°C (1 mm), n_D^{20} = 1.5282, d_4^{20} = 1.0094; MR_D = 93.83, calcd. 93.60. IR spectrum, ν, cm^{-1}: 3050 (C–H_{arom}), 2895 (CH_3), 2850 (CH_2), 1585 (C=C_{arom}), 1250 (C–N), 1050 (C–O), 650 (C–S). ^{1}H NMR spectrum, δ, ppm: 0.95 t (3H, CH_3), 1.35 m (4H, CH_2), 1.63 m (6H, CH_2), 2.40 m (2H, SCH_2), 3.40 t (OCH), 3.80 s (2H, PhC**H**$_2$), 4.25 d.d (2H, OCH_2N), 7.35 m (5H, C_6H_5). Mass spectrum, *m*/*z* (I_{rel}, %); 307 (6) $[M]^+$, 289 (8) $[M - H_2O]^+$, 264 (5) $[M - C_3H_7]^+$, 204 (7) $[M - C_{15}H_{11}N - H_2O]^+$, 193 (5) $[C_{12}H_{17}S]^+$, 122 (100) $[C_7H_6S]^+$, 91 (78) $[PhCH_2]^+$. Found, %: C 70.16; H 9.43; N 4.51, S 10.34. $C_{18}H_{28}NOS$. Calculated, %: C 70.31; H 9.51; N 4.55; S 10.43. *M* 307.51.

***N*-[1-(Benzylsulfanyl)pentan-2-yloxymethyl]-morpholine (Vd)** was synthesized from 6.3 g (0.03 mol) of alcohol **III**, 0.9 g (0.03 mol) of paraformaldehyde, and 2.61 g (0.03 mol) of morpholine (**IVd**). Yield 6.96 g (75%), bp 182–184°C (2 mm), n_D^{20} = 1.5278, d_4^{20} = 1.0456; MR_D = 91.11, calcd. 90.72. IR spectrum, ν, cm^{-1}: 3060 (C–H_{arom}); 2900 (CH_3); 2840 (CH_2); 1600, 1500 (C=C_{arom}); 1250 (C–N); 1100 (C–O); 750 (C–S). ^{1}H NMR spectrum, δ, ppm: 0.95 t (3H, CH_3), 1.35 m (4H, CH_2), 2.60–2.80 m (10H, OCH_2, NCH_2, SCH_2), 3.20 quint (OCH), 3.80 s (2H, PhC**H**$_2$), 4.20 d.d (2H, OCH_2N), 7.30 m (5H, C_6H_5). Mass spectrum, *m*/*z* (I_{rel}, %): 309 (6) $[M]^+$, 291 (8) $[M - H_2O]^+$, 225 (3) $[M - C_4H_6NO]^+$, 210 (8) $[M - C_5H_9NO]^+$, 192 (5) $[M - C_5H_{11}NO_2]^+$, 99 (100) $[C_5H_9NO]^+$. Found, %: C 65.81; H 8.73; N 4.49; S 10.28. $C_{17}H_{27}NO_2S$. Calculated, %: C 65.98; H 8.79; N 4.53; S 10.36. *M* 309.47.

1-[1-(Benzylsulfanyl)pentan-2-yloxymethyl]azepane (Ve) was synthesized from 6.3 g (0.03 mol) of alcohol **III**, 0.9 g (0.03 mol) of paraformaldehyde, and 2.97 g (0.03 mol) of hexamethyleneimine (**IVe**). Yield 7.33 g (76%), bp 180–182°C (1 mm), n_D^{20} = 1.5268, d_4^{20} = 1.0062; MR_D = 98.21, calcd. 98.24. IR spectrum, ν, cm^{-1}: 3050 (C–H_{arom}); 2895 (CH_3); 2830 (CH_2); 1600, 1500 (C=C_{arom}); 1200 (C–N); 1050 (C–O); 735 (C–S). ^{1}H NMR spectrum, δ, ppm: 0.95 t (3H, CH_3), 1.35 m (4H, CH_2), 1.62 t (8H, CH_2), 2.60 m (4H, NCH_2), 3.35 t (OCH), 3.80 s (2H, PhC**H**$_2$), 4.20 d.d (2H, OCH_2N), 7.30 m (5H, C_6H_5), Mass spectrum, *m*/*z* (I_{rel}, %): 321 (5) $[M]^+$, 230 (5) $[M - C_6H_5N]^+$, 213 (8) $[M - C_6H_6NO]^+$, 138 (27) $[C_8H_{10}S]^+$, 91 (100) $[C_6H_5N]^+$. Found, %: C 70.75; H 9.66; N 4.33; S 9.89. $C_{19}H_{31}NOS$. Calculated, %: C 70.98; H 9.72; N 4.36; S 9.97. *M* 321.54.

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