ISSN 1070-4280, Russian Journal of Organic Chemistry, 2020, Vol. 56, No. 2, pp. 287–291. © Pleiades Publishing, Ltd., 2020.
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Primary Amine–Promoted Ring Opening in Carbapenem-derived *p*-Nitrobenzyl Esters

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Received October 7, 2019; revised January 17, 2020; accepted January 20, 2020

Abstract—Ethylamine and ethanolamine react with 4-nitrobenzyl *(4R*,5*S*,6*S*)-3-[(2-furylmethyl)sulfanyl]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate, leading to the opening of the β-lactam ring by C^7–N bond cleavage accompanied and simultaneous amidation of the ester groups. In this anionoid transformation, the enamine–imine rearrangement followed by stereoselective protonation provides the formation of enantiomerically pure pyrrolidine derivatives: (2*S*,3*R*,4*S*)-*N*-ethyl-2-{(1*S*,2*R*)-1-[(ethylamino)-carbonyl]-2-hydroxypropyl}-4-[(2-furylmethyl)sulfanyl]-3-methyl-3,4-dihydro-2*H*-pyrrole-5-carboxamide and (2*S*,3*R*,4*S*)-4-[(2-furylmethyl)sulfanyl]-*N*-(2-hydroxyethyl)-2-[(1*S*,2*R*)-2-hydroxy-{[(2-hydroxyethyl)-amino]-carbonyl}propyl]-3-methyl-3,4-dihydro-2*H*-pyrrole-5-carboxamide.

Keywords: synthesis, carbapenem, ethanolamine, ethylamine, decyclization transformations, enamine–imine rearrangement

DOI: 10.1134/S1070428020020189

Carbapenems are top-ranked and widely used β-lactam antibiotics [1]. Carbapenems are obtained by chemical synthesis [2]. One of the costly stages in the synthesis of carbapenems **1** are hydrogenolysis of nitrobenzyl ester **2** and purification of acid **1**. The yields of acid **1** at this stage are generally as low as ~ 20–30% (Scheme 1) [3–6].

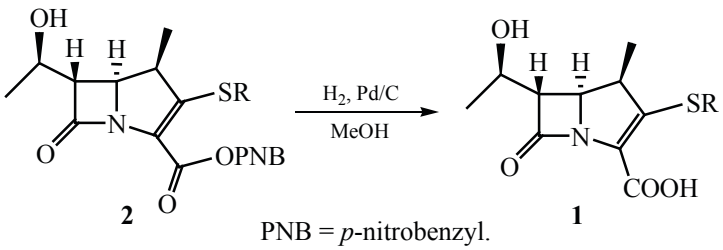
In view of the potential destructive potential of alkoxide and hydroxide anions in the course of isolation and purification of acid **1**, we studied the reaction of a model carbapenem **3** [7] with aqueous $EtNH_2$ and ethanolamine, assuming that, along with lactam ring opening, amidation in the ester moiety would occur to form, instead of compound **2**, the corresponding, more stable ethyl- and ethanolamides, which would ensure more unambiguous results in subsequent possible transformations.

Keeping a solution of compound **3** in THF with 2 equiv of 70% aqueous $EtNH_2$ at room temperature for 12 h gave cyclic imine **4**, enamine **5**, and *p*-nitrobenzyl alcohol **6**. The reaction of equimolar amounts of carbapenem **3** and monoethanolamine in THF (20°C, 12 h) occurred by a similar scheme, leading to compounds **7**, **8**, and **6** (Scheme 2).

As known, the opening of a strained β-lactam with hydroxy and amino nucleophiles involves formation of a tetrahedral intermediate followed by C^7–N bond cleavage [8–10]. A similar tetrahedral intermediate should take place in the case of amidation in the activated ester moiety of carbapenem **3**. The possible ways of formation of imine **4** is shown in Scheme 3.

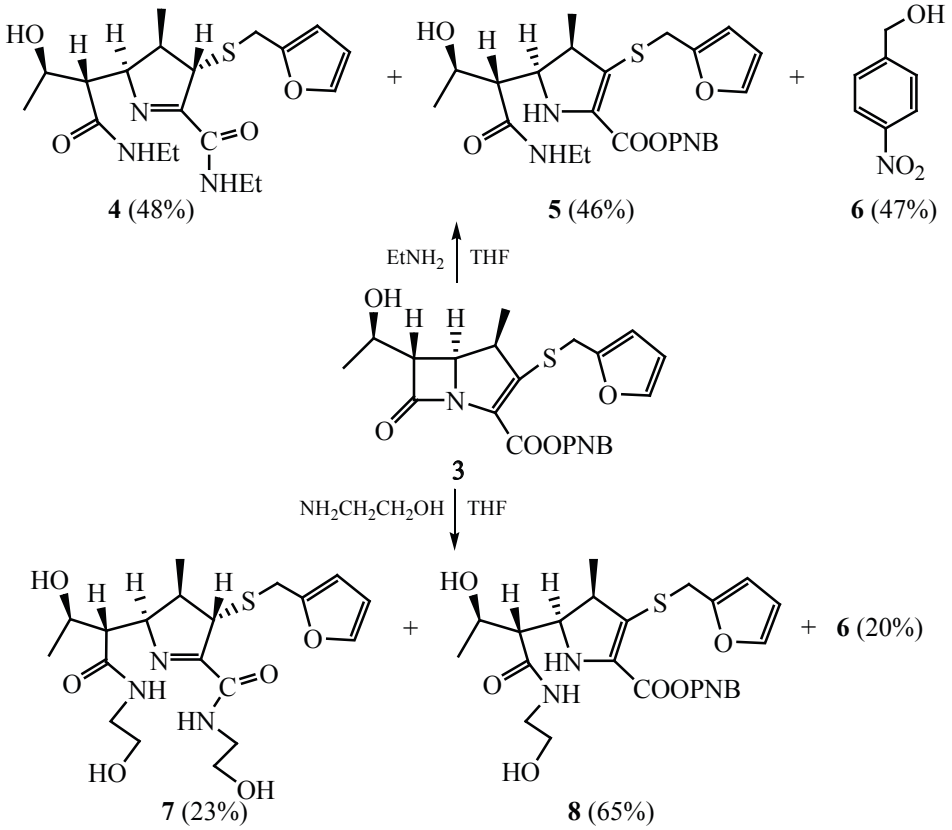
As seen from the scheme, *N*-centered carbanion **A** formed by lactam ring opening undergoes rearrangement

Scheme 1.



PNB = *p*-nitrobenzyl.

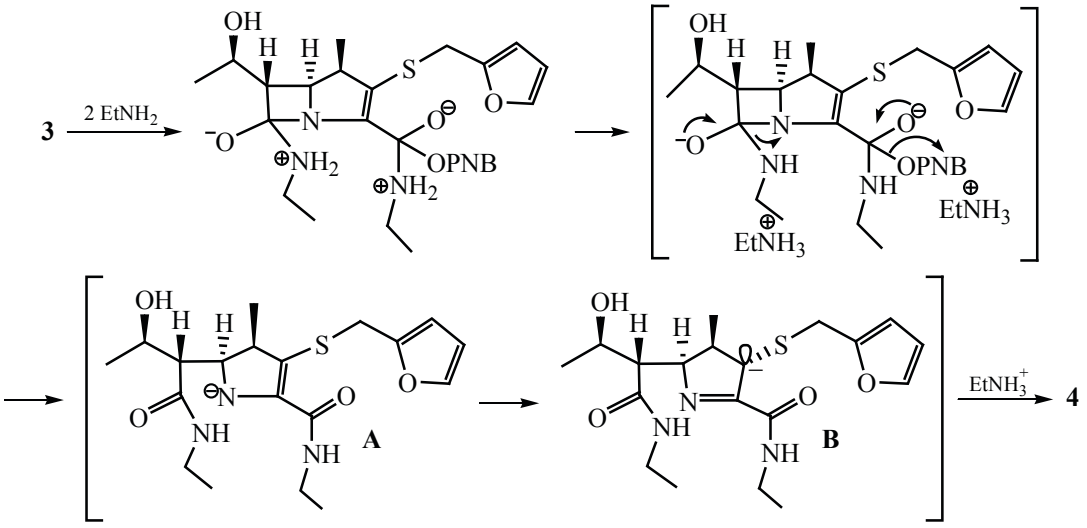
Scheme 2.



in a charged cyclic imine **B**, where the lone electron pair of the pyramidal anionic center points to the β region. This lifts the steric hindrances associated with the α orientation of the electron pair, and, finally, $EtNH_3^+$ protonated **B** to form imine **4**. A similar pathway is suggested for the formation of compound **7**.

Spectral data provide further evidence for the suggested assessment of the C^4 center. The B3LYP/6-311+G(d,p) geometry optimization of imine **4** with the *R*- and *S*-configuration of the newly formed chiral center C^4 predicted the spatial proximity of the H^4/H^3 and H^4/C^3–Me protons in the 4(*S*) diastereomer and NOE

Scheme 3.



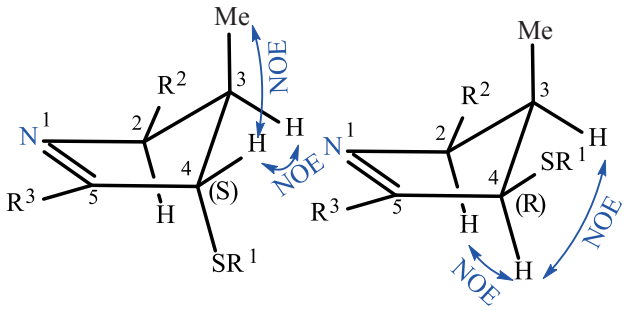


Fig. 1. Structures of the 4(*S*) and 4(*R*) diastereomers of compound **4**.

interactions for H⁴/H² and H⁴/H³ proton couples in the 4(*R*) diastereomer (Fig. 1). The NOESY spectrum of compound **4** (Fig. 2) showed cross peaks δ_H 3.92/2.40 ppm and 3.92/0.95 ppm, which, according to our assignments, corresponds to the 4(*S*) configuration. Furthermore, in was established that the H⁴–H³ dihedral angle in the 4(*S*) diastereomer is close to 90°, which is reflected in the ^{1}H NMR spectrum: H⁴ appears as a singlet at δ_H 3.92 ppm, and the doublet–quartet signal of H³ (δ_H 2.40 ppm, $^3J_{3-2}$ 5.7, $^3J_{3\text{-Me}}$ 7.1 Hz) shows no splitting from H⁴.

Using the example of carbapenem **3**, we could demonstrate 2 characteristic decomposition pathways of carbapenems under the action of primary amines. Experiments on the isolation of acid **1** after hydrogenolysis of PNB ester **3** showed formation of a mixture of hardly identifiable by-products. Note that compounds **4**, **5** and **7**, **8** present interest as novel biologically active structures and potential β-lactamase inhibitors [11].

EXPERIMENTAL

The IR spectra were obtained on a Shimadzu IR Prestige-21 spectrophotometer in mineral oil. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE-500 spectrometer at 500.13 (^{1}H) and 125.77 (^{13}C) MHz in $CDCl_3$ and $(CD_3)_2CO$. The chemical shifts in the ^{13}C NMR spectra were measured with reference to the carbon signals of $CDCl_3$ and $(CD_3)_2CO$ (δ_C 77.00 and 28.83 ppm, respectively) and in the ^{1}H NMR spectra, with reference to the residual proton signals of $CDCl_3$ and $(CD_3)_2CO$ (δ 7.27 and 2.07 ppm, respectively). The ESI(+) mass spectra were measured on a Shimadzu LCMS-2010EV instrument (syringe injection of a sample dissolved in chloroform/acetonitrile at a flow rate 0.1 mL/min, eluent acetonitrile–water, 95 : 5) in the positive ion mode, electrode potential 4.5 kV; interface capillary temperature 250°C, nebulizing gas (nitrogen) flow rate 1.5 L/min for APCI. The rotation angles were measured on a Perkin-Elmer 341 M instrument. The

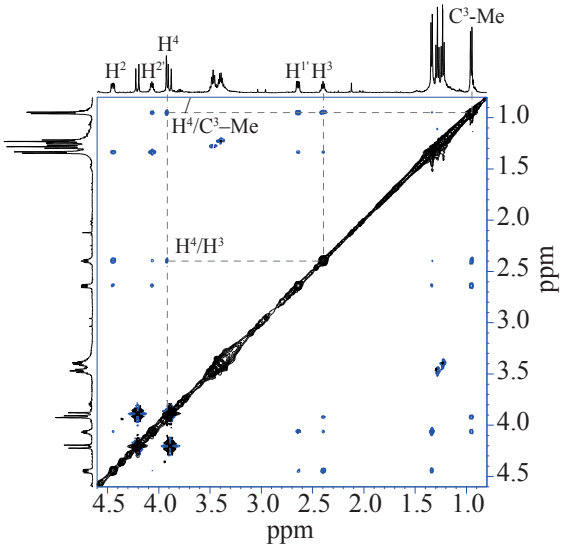


Fig. 2. {^{1}H, ^{1}H} NOESY spectrum of compound **4** (4*S*).

elemental analyses were obtained on a Euro-EA 3000 CHNS analyzer. Reaction progress was monitored by TLC on Sorbfil plates, spot visualization by spraying plates with a solution of anisaldehyde and sulfuric acid in ethanol and subsequent heating at 120–150°C. The synthesized compounds were isolated by column chromatography on a Macherey–Nayel silica gel (30–60 g per 1 g of compound). Solvents were purified by conventional procedures [12].

(2*S*,3*R*,4*S*)-*N*-Ethyl-2-{(1*S*,2*R*)-1-[(ethylamino)-carbonyl]-2-hydroxypropyl}-4-[(furan-2-ylmethyl)-sulfanyl]-3-methyl-3,4-dihydro-2*H*-pyrrol-5-carboxamide (4) and 4-nitrobenzyl (4*R*,5*S*)-5-{(1*R*)-1-[(ethylamino)carbonyl]-2-methylpropyl}-3-[(furan-2-ylmethyl)sulfanyl]-4-methyl-4,5-dihydro-1*H*-pyrrol-2-cerboxylate (5). A 70% aqueous $EtNH_2$, 37 μL (0.46 mmol), was added to a stirred solution of 95 mg (0.21 mmol) of carbapenem **3** in 5 mL of THF, and the resulting mixture was stirred at room temperature for 12 h. The solvent was then evaporated, and the residue was subjected to column chromatography on SiO_2 (eluent CH_2Cl_2–CH_3OH, 80 : 1→10 : 1) to isolate 50 mg (48%) of enamine **4**, 38 mg (46%) of imine **5**, and 15 mg (47%) of alcohol **6**.

Imine 4. Light yellow oily liquid. $[\alpha]_D^{20}$ –107° (*c* 1.0, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 3420, 3360, 2955, 1703, 1680, 1655, 1445, 1225, 1100, 1030. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 0.95 d (3H, C³–CH_3, *J* 7.2 Hz), 1.23 t (3H, CH_3, *J* 7.2 Hz), 1.28 t (3H, CH_3, *J* 7.3 Hz), 1.34 d (3H, C²'–CH_3, *J* 6.3 Hz), 2.40 d.q (1H, H³, $^3J_{3-2}$ 5.7 Hz, $^3J_{3\text{-Me}}$ 7.1 Hz), 2.64 d.d (1H, H¹', $^3J_{1'-2}$ 9.8, $^3J_{1'-2'}$ 4.8 Hz), 3.30–3.50 m (4H, CH_2N), 3.89 d (1H, CH_2S, ^2J 14.8 Hz), 3.92 s (1H, H⁴), 4.05 d.q (1H, H²',

$^3J_{2'-1'}$ 4.8, $J_{2'\text{-Me}}$ 6.3 Hz), 4.20 d (1H, CH_2S, ^2J 14.8 Hz), 4.46 d.d (1H, H^2, $^3J_{2-1'}$ 9.8, J_{2-3} 5.7 Hz), 6.39 m ($2H_{furan}$), 6.58 t (1H, NH, J 5.3 Hz), 7.10 t (1H, NH, J 5.9 Hz), 7.45 s ($1H_{furan}$). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: 14.61 (CH_3), 11.64 (C^3–$\underline{C}H_3$), 20.17 (C$^{2'}$–$\underline{C}H_3$), 29.29 (CH_2S), 34.22 (CH_2N), 34.37 (CH_2N), 44.98 (C^3), 51.63 (C$^{1'}$), 55.01 (C^4), 67.55 (C$^{2'}$), 71.29 (C^2), 108.36 (CH_{furan}), 110.51 (CH_{furan}), 142.39 (CH_{furan}), 151.04 (C_{furan}), 161.17 (C^5–$\underline{C}$ONH), 170.43 (C^5), 172.93 (CONH). ^{15}N NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 114.45 (NH, C^5–CONHEt), 124.59 (NH, C$^{1''}$–CONHEt). Mass spectrum, *m/z* (I_{rel}, %): 396 (100) [M + H]$^+$. Found, %: C 57.59; H 7.52; N 10.48; S 8.25. $C_{19}H_{29}N_3O_4S$. Calculated, %: C 57.70; H 7.39; N 10.62; S 8.11.

Enamine 5. Colorless oily liquid. $[\alpha]_D^{20}$ –44° (*c* 1.0, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 3460, 3345, 2923, 1730, 1695, 1655, 1596, 1514, 1445, 1345, 1225, 1115, 1045, 895. ^{1}H NMR spectrum (500 MHz, acetone-d_6), δ, ppm: 1.03 d (3H, CH_3, J 6.8 Hz), 1.08 t (3H, CH_3, J 7.2 Hz), 1.14 d (3H, CH_3, J 6.2 Hz), 2.70 d.d (1H, H$^{1'}$, J 10.2, 5.6 Hz), 3.12–3.32 m (3H, H^4, CH_2N), 3.67 m (1H, H^5), 3.95 d (1H, CH_2S, J 14.6 Hz), 3.97 m (1H, H$^{2'}$), 4.10 d (1H, CH_2S, J 14.6 Hz), 4.24 br.s (1H, OH), 5.35 d (1H, OCH_2, J 13.7 Hz), 5.40 d (1H, OCH_2, J 13.7 Hz), 6.26 d ($1H_{furan}$, J 2.9 Hz), 6.35 d.d ($1H_{furan}$, J 2.9, 1.8 Hz), 7.20 br.s (2H, NH), 7.47 d ($1H_{furan}$, J 0.8 Hz), 7.72 d ($2H_{arom}$, J 8.7 Hz), 8.25 d ($2H_{arom}$, J 8.7 Hz). ^{13}C NMR spectrum (125 MHz, acetone-d_6), δ, ppm: 11.10 (CH_3), 14.29 (CH_3), 19.78 (CH_3), 28.36 (CH_2S), 33.57 (CH_2N), 42.82 (C^4), 53.40 (C$^{1'}$), 61.19 (C^5), 64.67 (CH_2O), 66.98 (C$^{2'}$), 107.54 (CH_{furan}), 110.52 (CH_{furan}), 123.44 (CH_{arom}), 128.07 (C^3), 128.55 (CH_{arom}), 134.94 (C^2), 142.94 (CH_{furan}), 143.94 (C_{arom}), 147.66 (C–NO_2), 151.75 (C_{furan}), 160.80 (CO_2), 171.80 (CONH). Mass spectrum, *m/z* (I_{rel}, %): 504 (100) [M + H]$^+$. Found, %: C 57.12; H 5.67; N 8.41; S 6.46. $C_{24}H_{29}N_3O_7S$. Calculated, %: C 57.24; H 5.80; N 8.34; S 6.37.

(2*S*,3*R*,4*S*)-4-[(Furan-2-ylmethyl)sulfanyl]-*N*-(2-hydroxyethyl)-2-((1*S*,2*R*)-2-hydroxy-{[(2-hydroxyethyl)amino]carbonyl}propyl)-3-methyl-3,4-dihydro-2*H*-pyrrol-5-carboxamide (7) and 4-nitrobenzyl (4*R*,5*S*)-3-[(furan-2-ylmethyl)sulfanyl]-5-((2*R*)-2-hydroxy-1-{[(2-hydroxyethyl)amino]carbonyl}propyl)-4-methyl-4,5-dihydro-1*H*-pyrrol-2-carboxylate (8). A solution of 0.10 g (0.22 mmol) of carbapenem **3** and 0.14 mL (0.24 mmol) of ethanolamine in 6 mL of dry THF was stirred at room temperature for 12 h. The solvent was then evaporated in a vacuum, and the residue was subjected to column chromatography on SiO_2 (CH_2Cl_2–CH_3OH, 80 : 1→10 : 1) to isolate 74 mg (65%) of enamine **8**, 22 mg (23%) of imine **7**, and 6 mg (20%) of alcohol **6**.

Imine 7. Colorless oily liquid. $[\alpha]_D^{20}$ –105° (*c* 1.0, CH_3OH). IR spectrum, ν, cm^{-1}: 3460, 3350, 2985, 1700, 1675, 1655, 1439, 1221, 1110, 1015. ^{1}H NMR spectrum (500 MHz, acetone-d_6), δ, ppm: 0.89 d (3H, CH_3, J 7.2 Hz), 1.20 d (3H, CH_3, J 6.6 Hz), 2.50 d.q (1H, H^3, J 7.2, 5.5 Hz), 2.60 d.d (1H, H$^{1'}$, J 9.7, 7.5 Hz), 3.30–3.70 m (8H, $2CH_2N$, $2CH_2OH$), 3.84 s (1H, H^4), 3.85 d (1H, CH_2S, J 14.7 Hz), 4.08 d.q (1H, H$^{2'}$, J 6.6, 7.5 Hz), 4.12 d (1H, CH_2S, J 14.7 Hz), 4.42 d.d (1H, H^2, J 9.7, 5.5 Hz), 6.35 s ($2H_{furan}$), 7.35 br.s (1H, NH), 7.45 s ($1H_{furan}$), 8.00 br.s (1H, NH). ^{13}C NMR spectrum (125 MHz, acetone-d_6), δ, ppm: 14.81 (CH_3), 21.07 (CH_3), 28.44 (CH_2S), 41.59 (CH_2N), 41.94 (CH_2N), 45.41 (C^3), 53.31 (C$^{1'}$), 55.51 (C^4), 60.66 and 60.83 (CH_2OH), 67.70 (C$^{2'}$), 73.50 (C^2), 107.89 (CH_{furan}), 110.37 (CH_{furan}), 142.39 (CH_{furan}), 151.66 (C_{furan}), 161.95 (CONH), 169.56 (C^5), 173.57 (CONH). Mass spectrum, *m/z* (I_{rel}, %): 428 (100) [M + H]$^+$. Found, %: C 53.47; H 6.72; N 9.69; S 7.62. $C_{19}H_{29}N_3O_6S$. Calculated, %: C 53.38; H 6.84; N 9.83; S 7.50.

Enamine 8. Colorless oily liquid. $[\alpha]_D^{20}$ –6° (*c* 1.0, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 3455, 3335, 2930, 1735, 1681, 1662, 1586, 1520, 1431, 1352, 1218, 1108, 1021, 887. ^{1}H NMR spectrum (500 MHz, acetone-d_6), δ, ppm: 1.05 d (3H, CH_3, J 6.7 Hz), 1.16 d (3H, C$^{2'}$–CH_3, J 6.3 Hz), 2.80 d.d (1H, H$^{1'}$, J 9.8, 5.5 Hz), 3.24 d.q (1H, H^4, J 6.7, 7.9 Hz), 3.35 m (2H, CH_2N), 3.60 t (2H, $C\underline{H}_2OH$, J 5.45 Hz), 3.67 d.d (1H, H^5, J 9.8, 7.9 Hz), 3.98 d (1H, CH_2S, J 14.6 Hz), 4.00 m (1H, H$^{2'}$), 4.12 d (1H, CH_2S, J 14.6 Hz), 5.34 d (1H, $C\underline{H}_2OPh$, J 13.8 Hz), 5.42 d (1H, $C\underline{H}_2OPh$, J 13.8 Hz), 6.28 d.d ($1H_{furan}$, J 3.0, 0.9 Hz), 6.36 d.d ($1H_{furan}$, J 3.0, 1.8 Hz), 7.37 t (2H, 2NH, J 5.7 Hz), 7.47 d.d ($1H_{furan}$, J 1.8, 0.9 Hz), 7.74 d ($2H_{arom}$, J 8.5 Hz), 8.25 d ($2H_{arom}$, J 8.5 Hz). ^{13}C NMR spectrum (125 MHz, acetone-d_6), δ, ppm: 11.96 (C^4–CH_3), 20.47 (C$^{2'}$–CH_3), 29.84 (CH_2S), 42.67 (CH_2N), 43.62 (C^4), 54.22 (C$^{1'}$), 61.83 (C^5), 61.88 (CH_2OH), 65.56 (OCH_2Ph), 67.72 (C$^{2'}$), 108.45 (CH_{furan}), 111.42 (CH_{furan}), 124.35 (CH_{arom}), 129.12 (C^3), 129.44 (CH_{arom}), 135.78 (C^2), 143.15 (CH_{furan}), 144.86 (C_{arom}), 148.56 (C_{arom}), 152.65 (C_{furan}), 161.67 (CO_2), 173.46 (CONH). Mass spectrum, *m/z* (I_{rel}, %): 520 (100) [M + H]$^+$. Found, %: C 55.61; H 5.72; N 7.97; S 6.02. $C_{24}H_{29}N_3O_8S$. Calculated, %: C 55.48; H 5.63; N 8.09; S 6.17.

ACKNOWLEDGMENTS

Analyses were performed using the equipment of the Khimiya Center for Collective Use, Ufa Institute of Chemistry, Ufa Federal Research Center, Russian Academy of Sciences.

FUNDING

The work was financially supported by the Russian Science Foundation (project no. 15-13-00039-P).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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