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AN UNEXPECTED RESULT FROM THE REACTION OF HYDROXYMETHYL-2-OXAZOLIDINONES WITH ISOCYANATES

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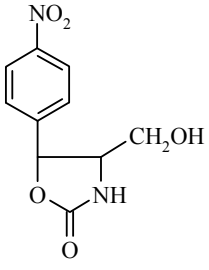
The reaction of hydroxymethyl-2-oxazolidinones with 4-chlorophenyl isocyanate and phenyl isocyanate was studied. It was established that the investigated hydroxymethyl-2-oxazolidinones can react with isocyanates either at the NH group alone or at the NH and OH groups.

Keywords: hydroxymethyl-2-oxazolidinone, 4-chlorophenyl isocyanate, phenyl isocyanate.

Urethanes have found use as drugs, such as Carbacholine and Proserin [1], pesticides Carbaryl, Carbofuran, and others [2]. Polyurethane fibers, glues, lacquers, and rubber are used widely in building and light industry.

At the same time compounds containing an oxazolidinone ring are widely known for their biological activity [3, 4].

Earlier we obtained isomeric (4*S*,5*S*)-4-hydroxymethyl-5-(4-nitrophenyl)-1,3-oxazolidin-2-one (**1**) and (1'*S*,4*S*)-4-[hydroxy(4-nitrophenyl)methyl]-1,3-oxazolidin-2-one (**2**) from (1*S*,4*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol [3, 4].



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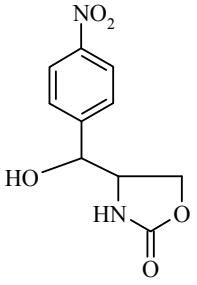

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Dedicated to L. I. Belen'kii on the occasion of his eightieth birthday.

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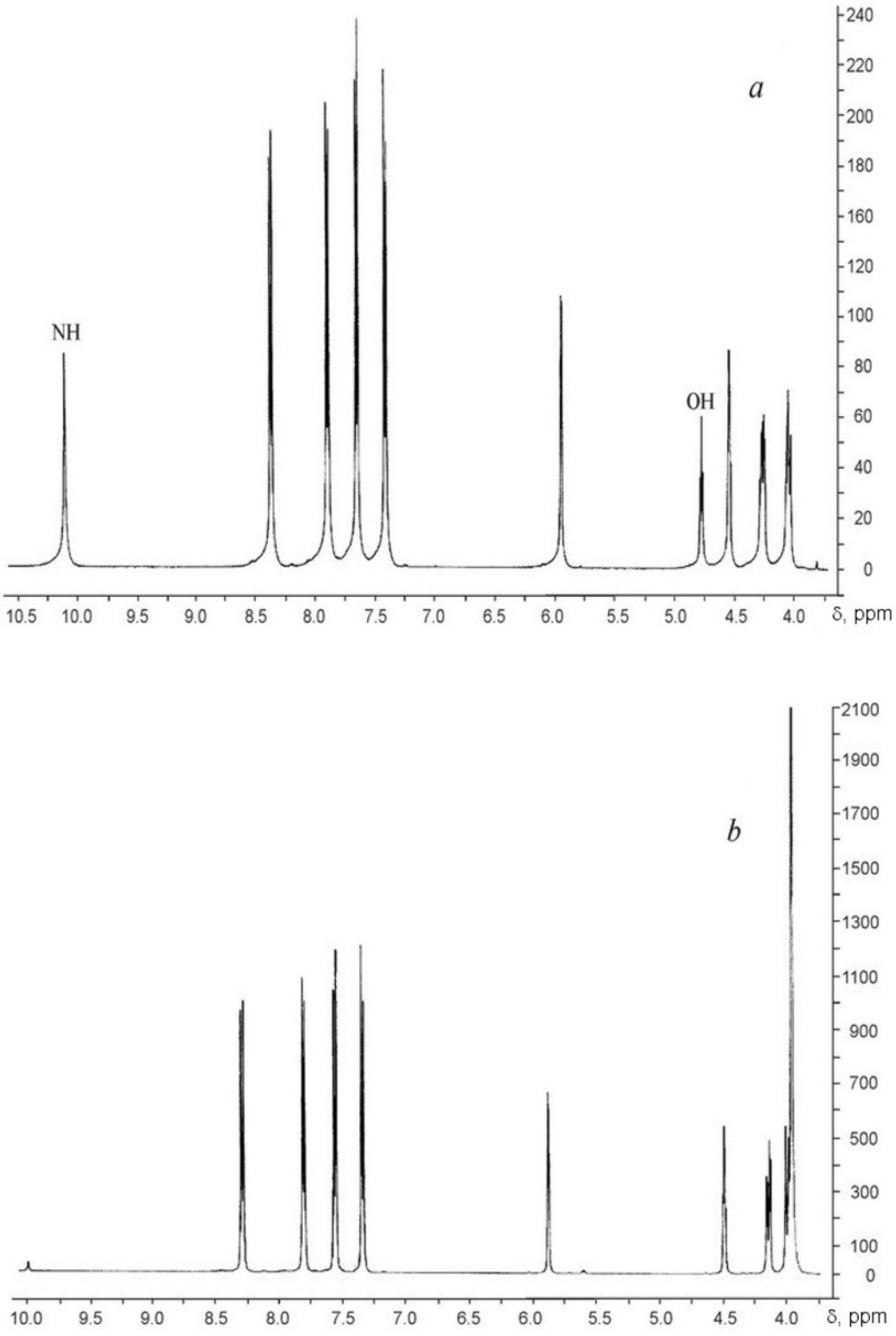


Fig. 1. The ^{1}H NMR spectrum of compound **6**, *a* – in acetone-d_6, *b* – in acetone-d_6 in the presence of D_2O.

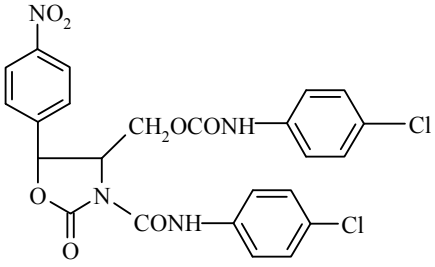
In the present work in order to obtain urethanes based on compounds **1** and **2** we studied their reaction with 4-chlorophenyl isocyanate (**3**) and phenyl isocyanate (**4**).

Treatment of (1*S*,2*S*)-2-ethoxycarbonylamino-1-(4-nitrophenyl)-1,3-propanediol with a mixture of water and a saturated solution of potassium carbonate in methanol (1:1) leads to the formation of a mixture of compounds **1** and **2**, from which it is fairly easy to produce compound **2** in the pure form. Compound **1** is difficult to obtain and is isolated by column chromatography followed by recrystallization [3, 4].

For this reason the first experiments were conducted between a mixture of compounds **1** and **2**, containing about 75% of compound **1**, and the isocyanate **3**. With the isocyanate **3** in an amount equimolar with the oxazolidin-2-one it was assumed on account of the difference in the reactivity of the secondary and primary OH groups that the urethane would only be produced from compound **1**. The reaction was conducted in boiling benzene for 24 h. After cooling the reaction mixture was filtered from the precipitate, which according to TLC proved to be mainly a mixture of the initial substances **1** and **2**. In the benzene solution up to six substances were detected, and four of them were in trace quantities.

Two main substances were isolated by column chromatography each with 25% yields. According to ^{1}H NMR data and to judge from the amount of each compound they were derivatives of compound **1**: (4*S*,5*S*)-3-[(4-chlorophenyl)carbamoyl]-4-{[(chlorophenyl)carbamoyl]oxymethyl}-5-(4-nitrophenyl)oxazolidin-2-one (**5**) and (4*S*,5*S*)-3-[(4-chlorophenyl)carbamoyl]-4-hydroxymethyl-5-(4-nitrophenyl)oxazolidin-2-one (**6**).

In the ^{1}H NMR spectrum of compound **5** there are characteristic singlets for the two NH groups in the region of 9.25 and 10.04 ppm. In the ^{1}H NMR spectrum of compound **6** there is only one singlet for the NH group in the region of 10.10, there is a signal for the OH group in the region of 4.77 ppm, and the signals disappear after the addition of a drop of D_2O to the sample. Apart from its amount the fact that the compound is a monosubstituted derivative of compound **1** is also confirmed by the presence of a signal for OH that disappears when D_2O is added (Fig. 1).



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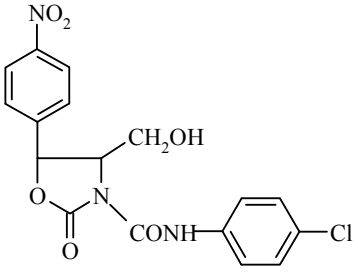

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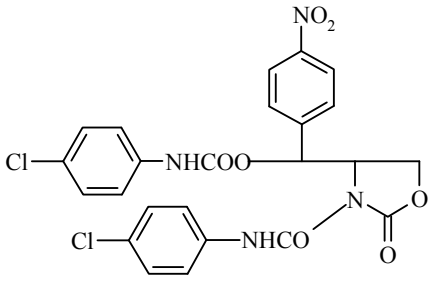
For the production of urethanes and ureas it is recommended to use anhydrous hydrocarbons such as benzene or toluene as solvents [5]. Realization of the reaction in THF gave compounds **5** and **6** in approximately the same ratio as with benzene. A disadvantage of THF is the fact that the excess of the initial compounds **1** and **2** dissolves in the reaction mixture and cannot be removed before chromatographic separation of compounds **5** and **6**.

The obtained results in our opinion are unexpected. They indicate a higher reactivity in this case for the NH group compared with the OH group. At the same time during the reaction of 4-hydroxymethyloxazolidin-2-ones with acid chlorides the OH group is more reactive. Earlier we obtained a series of esters based on compounds **1** and **2** [3, 4].

When the pure compound **2** was used as the initial oxazolidin-2-one it was not possible to realize the reaction either in benzene or in tetrahydrofuran even with an excess of the isocyanate **3**. At the same time with a mixture rich in compound **2** the reaction proceeds, and the main substance isolated from the reaction mixture is (1'*S*,4*S*)-3-[(4-chlorophenyl)carbamoyl]-4-{[(4-chlorophenyl)carbamoyloxy](4-nitrophenyl)methyl}oxazolidin-2-one (**7**).

On this basis mixtures rich in compound **1** were used in the reaction for the production of compound **5**, and mixtures rich in compound **2** were used for the production of compound **7**.



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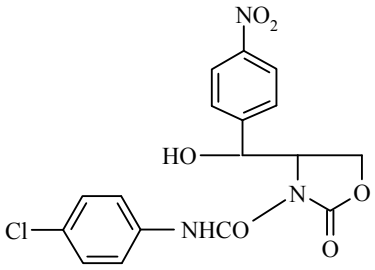

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Thus, compounds **5**-**8** can be obtained in the reaction of compounds **1** and **2** with the isocyanate **3** depending on the reaction conditions.

Analogous results were obtained in the reaction with the isocyanate **4**.

It should be noted that neither (4*S*,5*S*)-5-(4-nitrophenyl)-4-(propionyloxymethyl)oxazolidin-2-one nor (1'*S*,4*S*)-4-[(4-nitrophenyl)propionyloxymethyl]oxazolidin-2-one (the respective esters of compounds **3** and **4**) react with the isocyanates **3** and **4** in benzene, in THF, or in THF in the presence of pyridine or are acylated by dichloroacetyl chloride in chloroform in the presence of pyridine.

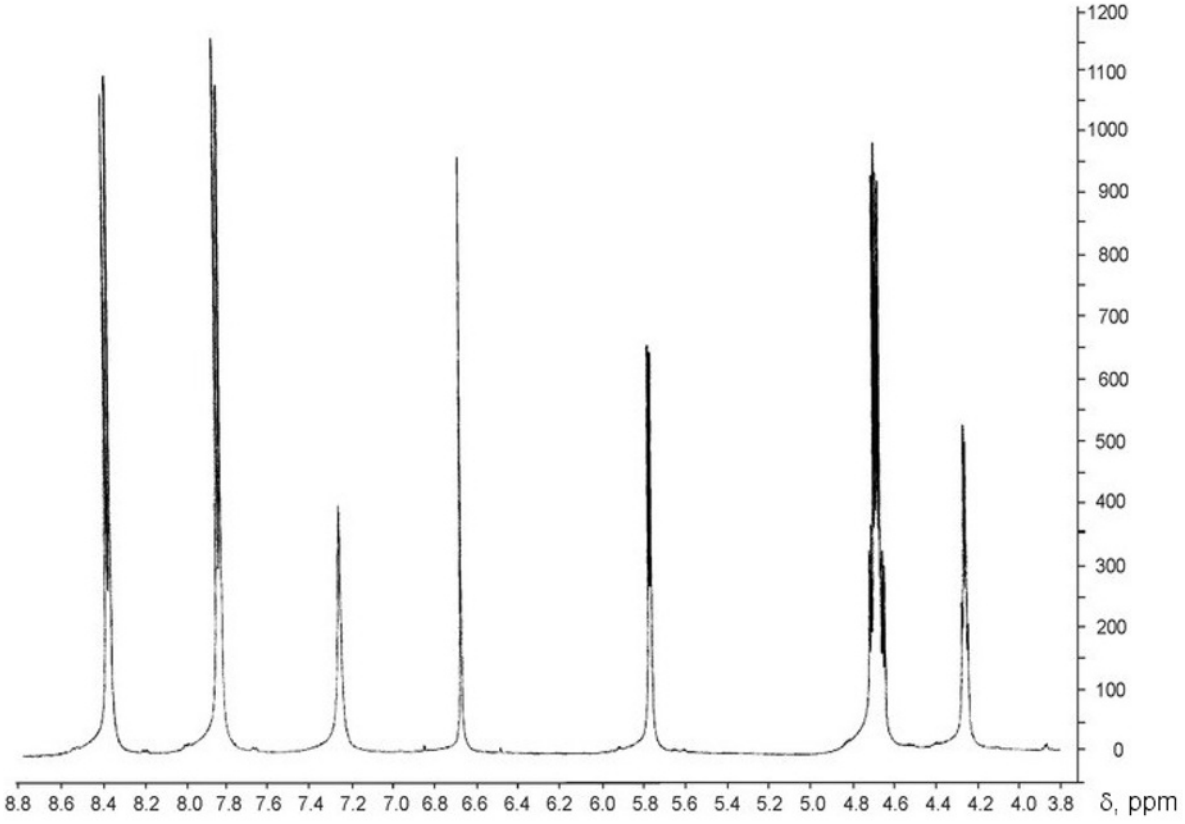

Fig. 2. The ^{1}H NMR spectrum of compound **9** in acetone-d_6.

A separate part of our work was devoted to analysis of the ^{1}H NMR spectra of the obtained compounds. In order to analyze the effect of a strong electron-accepting group on the position of the signals of the other groups the ester **9** was prepared, and its structure as (4*S*,5*S*)-4-[(dichloroacetoxy)methyl]-5-(4-nitrophenyl)oxazolidin-2-one was confirmed by X-ray crystallographic analysis [6].

The presence of the $COCHCl_2$ group in the molecule of compound **9** has practically no effect on the position of the signal for the NH group but strongly shifts the signal for the protons of the CH_2 group downfield. In the ^1H NMR spectrum (Fig. 2) it is seen that the protons of the CH_2 group are not equivalent. Their diastereotopic character shows up to the largest degree in compound **6**. In this compound the signals for the protons of the CH_2 group are not affected by strong electron-accepting groups and are upfield from the signal of the CH─N proton (Fig. 1). In compound **5** the signals of the CH_2 and CH–N protons are close and for this reason were not identified individually.

In compounds **7** and **10** [the products of the reaction of compound **2** with 4-chlorophenyl and phenyl isocyanate respectively] the protons of the CH_2 group are not affected by the electron-accepting groups, their signal lies in the upfield region compared with the signal for the proton of the CH–N group, and the diastereotopic effect shows up to an insignificant degree. As a result the signal is observed in the form of one complex multiplet.

EXPERIMENTAL

The ^1H NMR spectra were recorded in acetone-d_6 on Bruker Avance 500 instrument (500 MHz). The melting points were determined on a Kofler bench.

Dried Merck GR benzene with a water content of 0.0075%, Acros THF with a water content of less than 50 ppm, Acros extra dry chloroform with a water content of 0.005%, and Acros dichloroacetyl chloride were used in the reactions. Merck chromatographic plates with SiO_2 and SDS grade SiO_2 powder were used for chromatography, and all the products were isolated on a column of SiO_2 (3.5×40 cm) with 4:6 ethyl acetate−cyclohexane as eluent.

(4*S*,5*S*)-3-[(4-Chlorophenyl)carbamoyl]-4-[(chlorophenyl)carbamoyloxymethyl]-5-(4-nitrophenyl)-oxazolidin-2-one (5) and (4*S*,5*S*)-3-[(4-chlorophenyl)carbamoyl]-4-hydroxymethyl-5-(4-nitrophenyl)-oxazolidin-2-one (6). A. In a round-bottom flask fitted with a magnetic stirrer we placed a mixture of compounds **1** and **2** containing 75% of compound **1** (3 g, 12.6 mmol), the isocyanate **3** (1.4 g, 9.1 mmol), and benzene (50 ml). The mixture was boiled with stirring for 24 h. When the reaction mixture had cooled the precipitate, which consisted largely of a mixture of compounds **1** and **2**, was filtered off (1.6 g). The benzene was distilled on a rotary evaporator, and the residue was dissolved in benzene and chromatographed.

Compound **5** was obtained first (R_f 0.56). The yield was 1.3 g (25% calculated on compound **1**); mp 106-107°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 10.04 (H, br. s, NH); 9.25 (H, br. s, NH); 7.94-8.38 (4H, m, H arom); 7.35-7.66 (8H, m, H arom); 6.02 (H, d, *J* = 3.7, CH−O); 4.74-4.88 (3H, m, CH_2 + CH–N). Found, %: C 53.07; H 3.22; Cl 12.91; N 10.14. $C_{24}H_{18}C1_2N_4O_7$. Calculated, %: C 52.86; H 3.33; Cl 13.00; N 10.27.

Compound **6** was then obtained (R_f 0.31). The yield was 0.95 g (25.7% calculated on compound **1**); mp 177-178°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 10.10 (1H, br. s, NH); 7.89–8.38 (4H, m, H arom), 7.41-7.67 (4H, m, H arom); 5.95 (1H, d, *J* = 4.2, CH−O); 4.78 (1H, t, *J* = 5.8, OH); 4.55 (1H, m, CH−N); 4.02-4.07 and 4.24-4.28 (2H, 2 m, CH_2, H-a and H-b). Found, %: C 52.27; H 3.41; Cl 9.17; N 10.51. $C_{17}H_{14}ClN_3O_6$. Calculated, %: C 52.12; H 3.60; Cl 9.05; N 10.73.

B. In a flask fitted with a magnetic stirrer we placed a mixture of compounds **1** and **2** containing 75% of compound **1** (2.38 g, 10 mmol), the isocyanate **3** (3.84 g, 25 mmol), and benzene (50 ml). The mixture was boiled with stirring for 5-6 h. The end of the reaction was monitored by TLC, 10 ml of water was added to the reaction mixture, and the mixture was boiled for 1 h. After cooling the reaction mixture was transferred to a separating funnel, ethyl acetate (50 ml) was added, the mixture was washed with water and dried with Na_2SO_4, and the solvent was distilled. Compound **5** was isolated by column chromatography and was the main reaction product. The yield was 3.3 g (80% calculated on compound **1**); mp 106-107°C.

(1'*S*,,4*S*)-3-[(4-Chlorophenyl)carbamoyl]-4-[(4-chlorophenyl)carbamoyloxy(4-nitrophenyl)methyl]-oxazolidin-2-one (7). In a flask fitted with a magnetic stirrer we placed a mixture of compounds **1** and **2** containing 75% of compound **2** (2.38 g, 10 mmol), the isocyanate **3** (3.84 g, 25 mmol), and benzene (50 ml). The mixture was treated as described in the previous experiment (method B). Compound **7** was isolated by column chromatography and was the main reaction product. The yield was 3.5 g (85% calculated on compound **2**); mp 143-145°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.91 (1H, br. s, NH); 9.45 (1H, br. s, NH); 7.78-8.32 (4H, m, H arom); 7.36-7.60 (8H, m, H arom); 6.49 (1H, d, *J* = 4.0, CH–O); 5.25-5.30 (1H, m, CH–N); 4.72-4.78 (2H, m, CH_2). Found, %: C 53.11; H 3.45; Cl 13.09; N 10.14. $C_{24}H_{18}Cl_2N_4O_7$. Calculated, %: C 52.86; H 3.33; Cl 13.00; N 10.27.

(4*S*,5*S*)-4-(Dichloroacetoxy)methyl-5-(4-nitrophenyl)oxazolidin-2-one (9). In a round-bottom flask fitted with a magnetic stirrer we placed a mixture of compounds **1** and **2** containing 75% of compound **2** (4.76 g, 20 mmol), chloroform (50 ml), and pyridine (4.7 g, 60 mmol). With cooling to 0-5°C and with stirring we added dropwise dichloroacetyl chloride (4.5 g, 40 mmol). As the acid chloride was added the initial compound dissolved. The reaction was monitored by TLC. At the end of the reaction 20 ml of water was added to the reaction mixture, and the mixture was stirred for 2-3 h. Compound **9** separated in the form of crystals, which were filtered off, washed on the filter with 1 N hydrochloric acid solution and with water, and dried with Na_2SO_4. The yield was 4.5 g (95% calculated on compound **1**); mp 159-160°C (alcohol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.83-8.38 (4H, m, H arom), 7.25 (1H, br. s, NH); 6.67 (1H, s, $CHCl_2$); 5.75 (1H, d, *J* = 4.9, CH–O); 4.62-4.69 (2H, m, CH_2); 4.22-4.24 (1H, m, CH–N). Found, %: C 41.54; H 2.93; Cl 20.41; N 8.11. $C_{12}H_{10}Cl_2N_2O_6$. Calculated, %: C 41.28; H 2.89; Cl 20.31; N 8.02.

(1'*S*,4*S*)-4-[(4-Nitrophenyl)(phenylcarbamoyl)methyl]-3-(phenylcarbamoyl)oxazolidin-2-one (10). From of a mixture of compounds **1** and **2** containing 75% of compound **2** (2.38 g, 10 mmol), the isocyanate **4** (3.84 g, 25 mmol), and benzene (50 ml) under the conditions of the previous experiment we obtained compound **10**, which was the main reaction product. The yield was 2.9 g (82% calculated on compound **2**); mp 135-137°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.86 (1H, br. s, NH); 9.30 (1H, br. s, NH); 7.77-8.33 (4H, m, H arom); 7.07-7.80 (10H, m, H arom); 6.51 (1H, d, *J* = 4.1, CH–O); 5.25-5.28 (1H, m, CH–N); 4.73-4.78 (2H, m, CH_2). Found, %: C 60.72; H 4.15; N 11.58. $C_{24}H_{20}N_4O_7$. Calculated, %: C 60.50; H 4.23; N 11.76.

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