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Reaction of 1-Aryl-3-(4,4-diethoxybutyl)ureas with Phenols. Synthesis of 2-Arylpyrrolidines

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Abstract—Acid-catalyzed reaction of phenols with 1-(4,4-diethoxybutyl)urea derivatives gave new 2-arylpyrrolidines containing 4-bromoresorcinol and hydroquinone fragments. The described reaction is advantageous due to its mild conditions and no necessity of using expensive or toxic catalyst.

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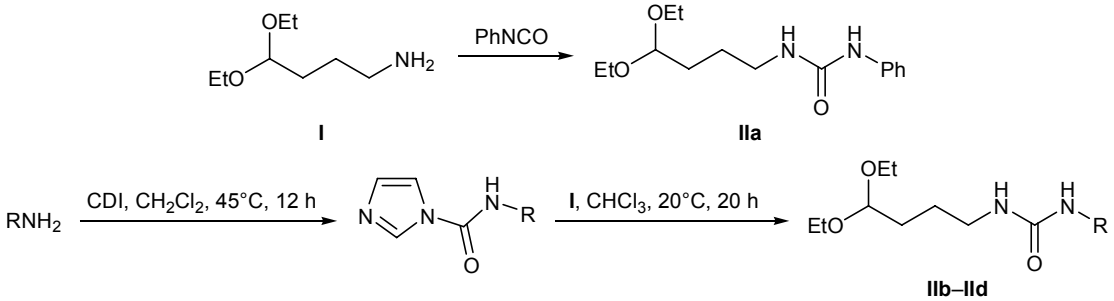
2-Arylpyrrolidines constitute an important class of heterocycles widely represented by both biologically active natural compounds and their synthetic analogs [1–3]. Known methods of synthesis of 2-arylpyrrolidines are based on two main approaches. The first of these implies modification of pyrrolidine ring already obtained in one or another way, and the second involves intra- or intermolecular cyclization with formation of pyrrolidine ring, where the aryl fragment is either included into the precursor molecule or introduced directly at the stage of formation of pyrrolidine ring [4–6]. The existing methods are generally multistep, and they require harsh conditions and toxic or expensive catalysts.

We previously studied reactions of 1-(4,4-diethoxybutyl)urea derivatives (γ-ureido acetals) with some phenols, such as resorcinol, 2-methylresorcinol, and pyrogallol [7]. These reactions produced 2-arylpyrrolidines in good yields. Important advantages of the proposed approach are mild reaction conditions and the use of accessible trifluoroacetic acid as catalyst.

It was interesting to elucidate whether less reactive phenols, in particular 4-bromoresorcinol and hydroquinone, could be involved in analogous reaction. Initial ureido acetals **IIa**–**IId** were synthesized as shown in Scheme 1. 1-(4,4-Diethoxybutyl)-3-phenylurea (**IIa**) was prepared by reaction of 4,4-diethoxybutan-1-amine with phenyl isocyanate. Acetals **IIb**–**IId** were obtained from the corresponding aromatic amines and 1,1′-carbonyldiimidazole (CDI) with subsequent treatment of the resulting *N*-aryl-1*H*-imidazole-1-carboxamides with γ-amino acetal **I** [7].

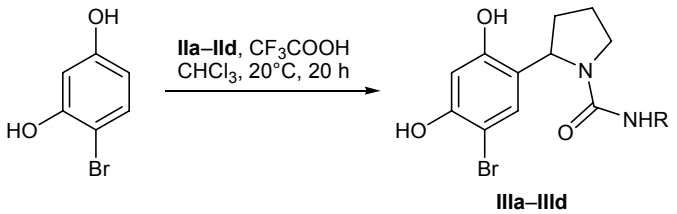
Acetals **IIa**–**IId** reacted with an equimolar amount of 4-bromoresorcinol in chloroform in the presence of 1 equiv of trifluoroacetic acid to give 2-arylpyrrolidines **IIIa**–**IIId** (Scheme 2). Likewise, the reaction of

Scheme 1.



CDI is 1,1′-carbonyldiimidazole; R = 4-$MeOC_6H_4$ (**b**), 4-BrC_6H_4 (**c**), 4-$O_2NC_6H_4$ (**d**).

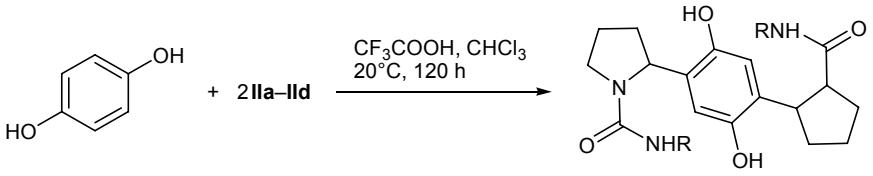
Scheme 2.



IIIa–IIId

R = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-BrC_6H_4 (**c**), 4-$O_2NC_6H_4$ (**d**).

Scheme 3.



IVa–IVd

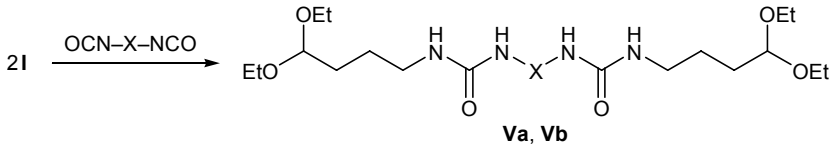
R = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-BrC_6H_4 (**c**), 4-$O_2NC_6H_4$ (**d**).

IIa–**IId** with hydroquinone at a ratio of 2:1 afforded phenylenedipyrrolidines **IVa**–**IVd** via substitution at the 2,5-positions of hydroquinone (Scheme 3). Among the examined phenols, hydroquinone turned out to be the least reactive, and target heterocyclic compounds **IVa**–**IVd** were isolated in poor yields after prolonged keeping of the reaction mixtures at room temperature. A probable reason is inconsistent effect of the hydroxy groups.

According to the NMR data, compounds **IVa**, **IVc**, and **IVd** were formed as mixtures of two diastereoisomers at a ratio of ~2:1. Compound **IVb** was isolated as a single diastereoisomer. It is now difficult to rationalize the observed difference in the stereochemical behavior of acetals **IIa**–**IId** in the reaction with hydroquinone. Unfortunately, we failed to isolate pure diastereoisomers of **IVa**, **IVc**, and **IVd** because of their very poor solubility in most solvents and small difference in the R_f values (<0.15).

It seemed also reasonable to synthesize compounds containing two pyrrolidine fragments on the basis of 4-bromoresorcinol. For this purpose, γ-amino acetal **I** was brought into reaction with hexamethylene and *p*-phenylene diisocyanates at a ratio of 2:1 to obtain bis-acetals **Va** and **Vb** [7] (Scheme 4). The reaction of **Va** and **Vb** with 2 equiv of 4-bromoresorcinol in

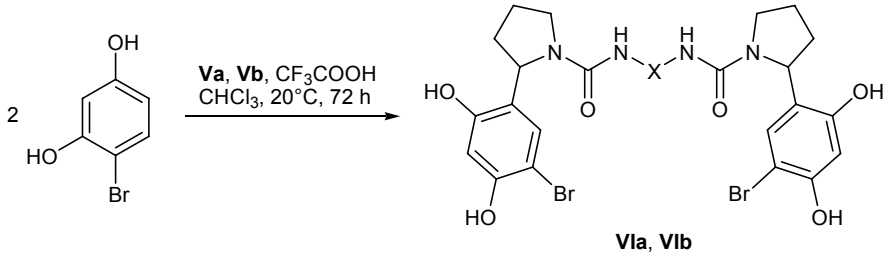
Scheme 4.



Va, **Vb**

X = $(CH_2)_6$ (**a**), 1,4-C_6H_4 (**b**).

Scheme 5.



VIa, **VIb**

X = $(CH_2)_6$ (**a**), 1,4-C_6H_4 (**b**).

chloroform in the presence of trifluoroacetic acid led to the formation of desired compounds **VIa** and **VIb** containing two pyrrolidine rings (Scheme 5). Compounds **VIa** and **VIb** could also be formed as mixtures of diastereoisomers. However, only one set of signals was observed in their NMR spectra, which may be due to both high diastereoselectivity of the reaction and very small difference in the chemical shifts of the respective nuclei in the two diastereoisomers. This problem requires further investigation.

The reactions of hydroquinone with acetals **Va** and **Vb** led to the formation of complex mixtures of products which we failed to isolate and identify.

In summary, we have synthesized new 2-arylpyrrolidine derivatives by reactions of 4-bromoresorcinol and hydroquinone with γ-ureido acetals. The described procedure is advantageous due to mild reaction conditions and the use of accessible inexpensive reactants.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker MSL 400 (400 MHz) and Bruker Avance 600 (150 MHz) spectrometers, respectively, from solutions in DMSO-d_6; the chemical shifts were determined relative to the residual proton and carbon signals of the deuterated solvent. The IR spectra were measured in KBr on a UR-20 spectrometer. The mass spectra (MALDI-TOF) were obtained on a Bruker Ultraflex III instrument using plastic and metal targets and 2,5-dihydroxybenzoic acid as matrix. The melting points were determined in glass capillaries on a Stuart SMP 10 melting point apparatus.

2-(5-Bromo-2,4-dihydroxyphenyl)-*N*-phenylpyrrolidine-1-carboxamide (IIIa). To a solution of 0.50 g (1.79 mmol) of 1-(4,4-diethoxybutyl)-3-phenylurea in 10 mL of anhydrous chloroform we added 0.34 g (1.79 mmol) of 4-bromoresorcinol and 0.20 g (1.79 mmol) of trifluoroacetic acid. The mixture was stirred for 3 days at room temperature, and the precipitate was filtered off, washed with chloroform, and dried for 2 h under reduced pressure (0.01 mm). Yield 0.19 g (28%), mp 153–154°C. IR spectrum, ν, cm^{-1}: 3419 (O–H), 2938, 2827 (N–H), 1639 (C=O), 1596 (C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 1.66–1.79 m (2H, CH$_2$), 1.80–1.89 m (1H, CH$_2$), 2.04–2.15 m (1H, CH$_2$), 3.41–3.49 m and 3.68–3.75 m (1H each, NCH$_2$), 5.06–5.11 m (1H, CHN), 6.47 s (1H, H$_{arom}$), 6.86 t (1H, H$_{arom}$, J = 7.39 Hz), 6.87 s (1H, H$_{arom}$), 7.16 t (2H, H$_{arom}$, J = 8.19 Hz), 7.40 d (2H, H$_{arom}$, J = 7.60 Hz). Mass spectrum: m/z 377 $[M + H]^+$. Found, %: C 54.41; H 4.42; Br 20.88; N 7.67. $C_{17}H_{17}BrN_2O_3$. Calculated, %: C 54.13; H 4.54; Br 21.18; N 7.43. M 377.24.

Compounds **IIIb**–**IIId** were synthesized in a similar way.

2-(5-Bromo-2,4-dihydroxyphenyl)-*N*-(4-methoxyphenyl)pyrrolidine-1-carboxamide (IIIb) was synthesized from 0.25 g (0.81 mmol) of 1-(4,4-diethoxybutyl)-3-(4-methoxyphenyl)urea and 0.15 g (0.81 mmol) of 4-bromoresorcinol in the presence of 0.09 g (0.81 mmol) of trifluoroacetic acid in 5 mL of anhydrous chloroform. Yield 0.24 g (73%), mp 218–219°C. IR spectrum, ν, cm^{-1}: 3281 (O–H), 2983, 2876 (N–H), 1632 (C=O), 1597 (C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 1.70–1.82 m (2H, CH$_2$), 1.84–1.93 m (1H, CH$_2$), 2.07–2.19 m (1H, CH$_2$), 3.42–3.51 m and 3.68–3.75 m (1H each, NCH$_2$), 3.69 s (3H, OMe), 5.08–5.13 m (1H, CHN), 6.51 s (1H, H$_{arom}$), 6.80 d (2H, H$_{arom}$, J = 9.05 Hz), 6.91 s (1H, H$_{arom}$), 7.33 d (2H, H$_{arom}$, J = 9.05 Hz). Mass spectrum: m/z 431 $[M + Na]^+$. Found, %: C 53.25; H 4.51; Br 19.39; N 7.01. $C_{18}H_{19}BrN_2O_4$. Calculated, %: C 53.08; H 4.70; Br 19.62; N 6.88. M 407.26.

2-(5-Bromo-2,4-dihydroxyphenyl)-*N*-(4-bromophenyl)pyrrolidine-1-carboxamide (IIIc) was synthesized from 0.25 g (0.70 mmol) of 1-(4-bromophenyl)-3-(4,4-diethoxybutyl)urea and 0.13 g (0.70 mmol) of 4-bromoresorcinol in the presence of 0.08 g (0.70 mmol) of trifluoroacetic acid in 5 mL of anhydrous chloroform. Yield 0.22 g (70%), mp 136–137°C. IR spectrum, ν, cm^{-1}: 3395 (O–H), 2976, 2863 (N–H), 1641 (C=O), 1592 (C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 1.66–1.79 m (2H, CH$_2$), 1.80–1.89 m (1H, CH$_2$), 2.03–2.14 m (1H, CH$_2$), 3.40–3.48 m and 3.66–3.74 m (1H each, NCH$_2$), 5.05–5.10 m (1H, CHN), 6.47 s (1H, H$_{arom}$), 6.84 s (1H, H$_{arom}$), 7.33 d (2H, H$_{arom}$, J = 8.92 Hz), 7.40 d (2H, H$_{arom}$, J = 8.92 Hz). ^{13}C NMR spectrum, δ$_C$, ppm: 23.56, 32.85, 47.14, 55.60, 98.25, 104.17, 113.47, 121.62, 123.51, 129.33, 131.45, 140.40, 153.44, 153.92, 154.49. Mass spectrum: m/z 456 $[M]^+$. Found, %: C 44.65; H 3.71; Br 34.83; N 6.42. $C_{17}H_{16}Br_2N_2O_3$. Calculated, %: C 44.76; H 3.54; Br 35.04; N 6.14. M 456.13.

2-(5-Bromo-2,4-dihydroxyphenyl)-*N*-(4-nitrophenyl)pyrrolidine-1-carboxamide (IIId) was synthesized from 0.10 g (0.31 mmol) of 1-(4,4-diethoxybutyl)-3-(4-nitrophenyl)urea and 0.06 g (0.31 mmol) of 4-bromoresorcinol in the presence of 0.04 g (0.31 mmol) of trifluoroacetic acid in 5 mL of anhydrous chloroform. Yield 0.07 g (57%), mp 139–140°C.

IR spectrum, ν, cm^{-1}: 3437, 3398 (O–H), 2945, 2869 (N–H), 1639 (C=O), 1595 (C=C_{arom}). ^1H NMR spectrum, δ, ppm: 1.66–1.79 m (2H, CH_2), 1.80–1.89 m (1H, CH_2), 2.06–2.17 m (1H, CH_2), 3.45–3.55 m and 3.73–3.80 m (1H each, NCH_2), 5.09–5.15 m (1H, CHN), 6.47 s (1H, H_{arom}), 6.85 s (1H, H_{arom}), 7.69 d (2H, H_{arom}, J = 9.29 Hz), 8.08 d (2H, H_{arom}, J = 9.29 Hz). Mass spectrum: m/z 422 $[M]^+$. Found, %: C 48.61; H 3.68; Br 18.62; N 9.72. $C_{17}H_{16}BrN_3O_5$. Calculated, %: C 48.36; H 3.82; Br 18.92; N 9.95. M 422.24.

2,2′-(2,5-Dihydroxybenzene-1,4-diyl)bis(*N*-phenylpyrrolidine-1-carboxamide) (IVa). To a solution of 0.50 g (1.79 mmol) of 1-(4,4-diethoxybutyl)-3-phenylurea in 10 mL of anhydrous chloroform we added 0.10 g (0.89 mmol) of hydroquinone and 0.10 g (0.89 mmol) of trifluoroacetic acid, and the mixture was stirred for 5 days at room temperature. The precipitate was filtered off, washed with ethanol (10 mL), and dried for 2 h under reduced pressure (0.01 mm). Yield 0.13 g (30%), mp >250°C. IR spectrum, ν, cm^{-1}: 3437, 3398 (O–H), 2869, 2727 (N–H), 1645 (C=O), 1595 (C=C_{arom}). ^1H NMR spectrum, δ, ppm: 1.74–1.86 m (4H, CH_2), 1.87–1.96 m (2H, CH_2), 2.11–2.24 m (2H, CH_2), 3.49–3.60 m (2H, NCH_2), 3.65–3.76 m (2H, NCH_2), 5.12–5.19 m (2H, CHN), 6.48 s (0.7H, H_{arom}), 6.51 s (1.3H, H_{arom}), 6.86–6.95 m (2H, H_{arom}), 7.16–7.24 m (4H, H_{arom}), 7.41–7.50 m (4H, H_{arom}). Mass spectrum: m/z 509 $[M + Na]^+$. Found, %: C 68.99; H 6.42; N 11.77; $C_{28}H_{30}N_4O_4$. Calculated, %: C 69.12; H 6.21; N 11.51. M 486.57.

Compounds **IVb**–**IVd** were synthesized in a similar way.

2,2′-(2,5-Dihydroxybenzene-1,4-diyl)bis[*N*-(4-methoxyphenyl)pyrrolidine-1-carboxamide] (IVb) was obtained from 0.30 g (0.97 mmol) of 1-(4,4-diethoxybutyl)-3-(4-methoxyphenyl)urea and 0.05 g (0.48 mmol) of hydroquinone in the presence of 0.11 g (0.97 mmol) of trifluoroacetic acid in 10 mL of anhydrous chloroform. Yield 0.03 g (12%), mp >250°C. IR spectrum, ν, cm^{-1}: 3386, 3199 (O–H), 2953, 2888, 2834 (N–H), 1646 (C=O), 1598 (C=C_{arom}). ^1H NMR spectrum, δ, ppm: 1.69–1.80 m (4H, CH_2), 1.81–1.91 m (2H, CH_2), 2.03–2.17 m (2H, CH_2), 3.42–3.51 m (2H, NCH_2), 3.61–3.70 m (2H, NCH_2), 3.65 s (6H, OCH_3), 5.06–5.14 m (2H, CHN), 6.43 s (2H, H_{arom}), 6.75 d (4H, H_{arom}, J = 8.56 Hz), 7.30 d (4H, H_{arom}, J = 8.40 Hz). Mass spectrum: m/z 569 $[M + Na]^+$. Found, %: C 65.67; H 6.57; N 10.05. $C_{30}H_{34}N_4O_6$. Calculated, %: C 65.92; H 6.27; N 10.25. M 546.62.

2,2′-(2,5-Dihydroxybenzene-1,4-diyl)bis[*N*-(4-bromophenyl)pyrrolidine-1-carboxamide] (IVc) was synthesized from 0.25 g (0.69 mmol) of 1-(4-bromophenyl)-3-(4,4-diethoxybutyl)urea and 0.04 g (0.35 mmol) of hydroquinone in the presence of 0.08 g (0.69 mmol) of trifluoroacetic acid in 5 mL of anhydrous chloroform. Yield 0.05 g (21%), mp >250°C. IR spectrum, ν, cm^{-1}: 3266 (O–H), 2864, 2878 (N–H), 1651 (C=O), 1588 (C=C_{arom}). ^1H NMR spectrum, δ, ppm: 1.73–1.86 m (4H, CH_2), 1.87–1.97 m (2H, CH_2), 2.08–2.24 m (2H, CH_2), 3.49–3.59 m (2H, NCH_2), 3.65–3.76 m (2H, NCH_2), 5.15–5.22 m (2H, CHN), 6.46 s (1.4H, H_{arom}), 6.48 s (0.6H, H_{arom}), 7.32–7.41 m (4H, H_{arom}), 7.42–7.53 m (4H, H_{arom}). Mass spectrum: m/z 667 $[M + Na]^+$. Found, %: C 52.73; H 4.65; Br 24.58; N 8.84. $C_{28}H_{28}Br_2N_4O_4$. Calculated, %: C 52.91; H 4.38; Br 24.80; N 8.70. M 644.36.

2,2′-(2,5-Dihydroxybenzene-1,4-diyl)bis[*N*-(4-nitrophenyl)pyrrolidine-1-carboxamide] (IVd) was synthesized from 0.10 g (0.31 mmol) of 1-(4,4-diethoxybutyl)-3-(4-nitrophenyl)urea and 0.02 g (0.16 mmol) of hydroquinone in the presence of 0.04 g (0.31 mmol) of trifluoroacetic acid in 5 mL of anhydrous chloroform. Yield 0.02 g (19%), mp >250°C. IR spectrum, ν, cm^{-1}: 3343 (O–H), 2921, 2876 (N–H), 1668 (C=O), 1597 (C=C_{arom}), 1558, 1333 (NO_2). ^1H NMR spectrum, δ, ppm: 1.75–1.87 m (4H, CH_2), 1.88–1.97 m (2H, CH_2), 2.11–2.22 m (2H, CH_2), 3.54–3.66 m (2H, NCH_2), 3.71–3.81 m (2H, NCH_2), 5.19–5.22 m (2H, CHN), 6.45 s (1.4H, H_{arom}), 6.47 s (0.6H, H_{arom}), 7.72–7.83 m (4H, H_{arom}), 8.08–8.17 m (4H, H_{arom}). Mass spectrum: m/z 599 $[M + Na]^+$. Found, %: C 58.19; H 5.14; N 14.29. $C_{28}H_{28}N_6O_8$. Calculated, %: C 58.33; H 4.89; N 14.58. M 576.57.

***N*,*N*′-(Hexane-1,6-diyl)bis[2-(5-bromo-2,4-dihydroxyphenyl)pyrrolidine-1-carboxamide] (VIa).** To a solution of 0.39 g (0.80 mmol) of 1,1′-(hexane-1,6-diyl)bis[3-(4,4-diethoxybutyl)urea] in 10 mL of anhydrous chloroform we added 0.30 g (1.60 mmol) of 4-bromoresorcinol and 0.08 g (0.70 mmol) of trifluoroacetic acid, and the mixture was stirred for 3 days at room temperature. The precipitate was filtered off, washed with ethanol (10 mL), and dried for 2 h under reduced pressure (0.01 mm). Yield 0.11 g (21%), mp 136–137°C. IR spectrum, ν, cm^{-1}: 3197 (O–H), 2916, 2726 (N–H), 1672 (C=O). ^1H NMR spectrum, δ, ppm: 1.09–1.18 m (4H, CH_2), 1.26–1.36 m (4H, CH_2), 1.67–1.73 m (4H, CH_2), 1.74–1.83 m (2H, CH_2), 1.98–2.10 m (2H, CH_2), 2.85–3.03 m (4H, CH_2), 3.22–3.32 m (2H, NCH_2), 3.42–3.52 m (2H, NCH_2), 4.88–

4.92 m (2H, CHN), 5.84 br.s (2H, NH), 6.46 s (2H, H_{arom}), 6.80 s (2H, H_{arom}). Mass spectrum: *m*/*z* 707 $[M + Na]^+$. Found, %: C 48.95; H 5.44; Br 23.05; N 8.43. $C_{28}H_{36}Br_2N_4O_6$. Calculated, %: C 49.14; H 5.30; Br 23.35; N 8.19. *M* 684.43.

***N*,*N*′-(Benzene-1,4-diyl)bis[(5-bromo-2,4-dihydroxyphenyl)pyrrolidine-1-carboxamide] (VIb)** was synthesized in a similar way from 0.30 g (0.62 mmol) of 1,1′-(benzene-1,4-diyl)bis[3-(4,4-diethoxybutyl)-urea] and 0.23 g (1.24 mmol) of 4-bromoresorcinol in the presence of 0.07 g (0.62 mmol) of trifluoroacetic acid. Yield 0.39 g (92%), mp 213–214°C. IR spectrum, ν, cm^{-1}: 3404 (O–H), 2896, 2826 (N–H), 1638 (C=O), 1593 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 1.67–1.80 m (4H, CH_2), 1.81–90 m (2H, CH_2), 2.04–2.17 m (2H, CH_2), 3.34–3.48 m (2H, NCH_2), 3.65–3.74 m (2H, NCH_2), 5.06–5.11 m (2H, CHN), 6.49 s (2H, H_{arom}), 6.88 s (2H, H_{arom}), 7.25 br.s (4H, H_{arom}). Mass spectrum: *m*/*z* 699 $[M + Na]^+$. Found, %: C 49.48; H 4.37; Br 23.42; N 8.54. $C_{28}H_{28}Br_2N_4O_6$. Calculated, %: C 49.72; H 4.17; Br 23.63; N 8.28. *M* 676.36.

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