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LETTERS TO THE EDITOR

Synthesis of Functionalized Diarylbutane Derivatives by the Reaction of 2-Methylresorcinol with γ-Ureidoacetals

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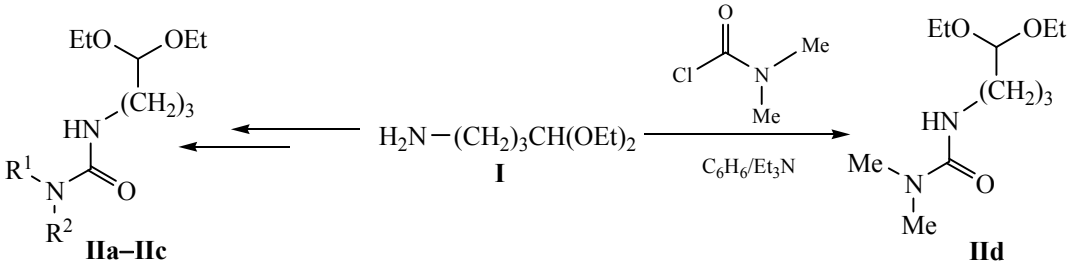
4-Nitrogen-containing diarylbutane derivatives are known for their pharmacological activity. These compounds are autophagy regulators [1] and epoxide hydrolase inhibitors [2]; they regulate concentration of γ-aminobutyric acid in the synaptic cleft [3, 4] and have antidepressant and anxiolytic effects [5].

Earlier we have studied the interaction of *N*-substituted acetals of aminoacetic aldehyde with a phenol in the presence of hydrochloric acid. This reaction led to the formation of amino-containing diarylethane derivatives with good yields [6, 7]. At the same time, we found that 4-aminobutanal acetals containing urea moiety in their molecules undergo intramolecular cyclization in the acidic medium in the presence of phenols to form the heterocyclic compounds: 2-arylpyrrolidine derivatives [8]. In this case formation of the corresponding diarylbutane derivatives has not been observed probably due to the high rate of intramolecular reaction as compared to intermolecular interaction with phenols, which may result in the formation of acyclic compounds. Since the rate of intermolecular processes enhances as concentration of reactants increases it was of interest to carry out this reaction in the presence of an excess of phenol to synthesize nitrogen derivatives of diarylbutane.

(4,4-Diethoxy)ureas **IIa**–**IId** were prepared from commercially available 4,4-diethoxy-1-butanamine **I**. Synthesis of compounds **IIa**–**IIc** has been previously described [9, 10]; compound **IId** was prepared by reacting 4,4-diethoxy-1-butanamine **I** with *N*,*N*-dimethylcarbamoyl chloride in the presence of triethylamine (Scheme 1).

Interaction of acetals **IIa**–**IIc** with an excess of 2-methylresorcinol in the presence of trifluoroacetic acid resulted in the formation of the corresponding diarylbutanes **IIIa**–**IIIc** modified with urea moieties. The yield of the target compounds was 42–88%. It

Scheme 1.



$R^1 = R^2 = H$ (**a**); $R^1 = H$, $R^2 = Ph$ (**b**); $R^1 = H$, $R^2 = p\text{-Br-}C_6H_4$ (**c**).

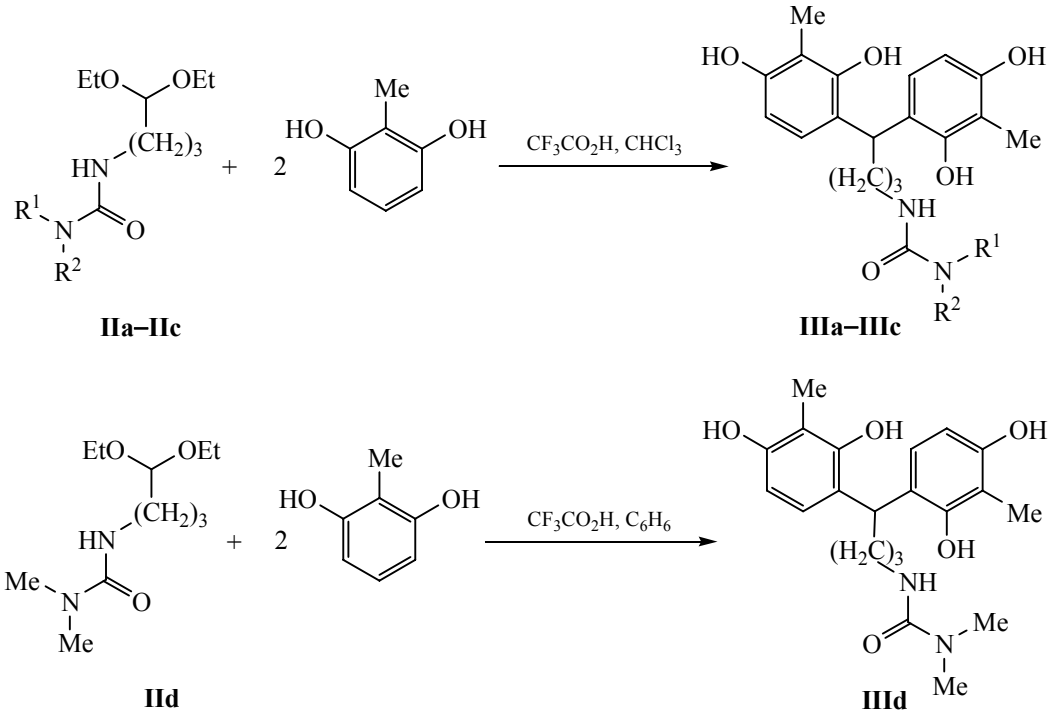
should be noted that the reaction of acetal **IId** having in its structure a tertiary nitrogen atom with 2-methylresorcinol under these conditions led to the formation of a complex mixture of the products, which isolation and identification was not succeeded. The title **IIId** was obtained with a yield of 84% by performing the reaction in benzene at room temperature (Scheme 2).

We have also studied the interaction of acetal **IId** with 2-naphthol in chloroform in the presence of trifluoroacetic acid. It was found that in the presence of 5-fold excess of 2-naphthol this reaction afforded dibenzoxanthene **IV** containing urea moiety in 22% yield. The composition and structure of the resulting compounds was confirmed by IR, NMR spectroscopy and mass spectrometry (MALDI) (Scheme 3).

In summary, depending on the ratio of the reactants the reaction of 2-methylresorcinol with γ-ureidoacetals can lead to either aryl-substituted 2-pyrrolidines and to novel diarylbutane derivatives modified with urea moieties.

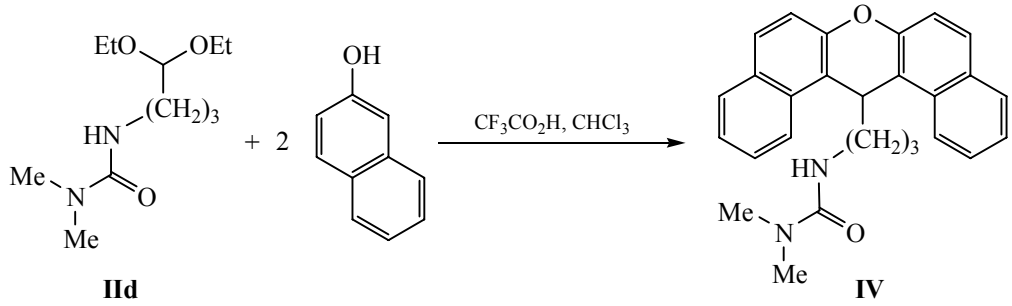
3-(4,4-Diethoxy)-1,1-dimethylurea (IId). *N*,*N*-Dimethylcarbamoyl chloride (2.5 g) was added dropwise with cooling (5–7°C) under argon to a solution of 3.74 g of 4,4-diethoxy-1-butanamine and 4.77 g of triethylamine in 27 mL of benzene. The

Scheme 2.



$R^1 = R^2 = H$ (**a**); $R^1 = H$, $R^2 = Ph$ (**b**); $R^1 = H$, $R^2 = p\text{-Br-}C_6H_4$ (**c**).

Scheme 3.



reaction mixture was stirred under cooling for 2 h. Then the precipitate was filtered off, the filtrate was evaporated in vacuum. Yield 4.39 g (81%), yellow oil. IR spectrum, ν, cm^{-1}: 1636 (C=O), 2926, 3039 (NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.93 t (6H, CH_3, $^3J_{HH}$ 7.1), 1.27–1.42 m (4H, CH_2), 2.63 s (6H, CH_3), 2.92–2.98 m (2H, CH_2). 3.18–3.27 m (2H, CH_2), 3.33–3.42 m (2H, CH_2), 4.19–4.24 m (1H, CH).

1-[4,4-Bis(2,4-dihydroxy-3-methylphenyl)butyl]-urea (IIIa). A solution of 0.5 g (2.45 mmol) of 1-(4,4-diethoxybutyl)urea in 10 mL of chloroform was added to a mixture of 0.92 g (7.35 mmol) of 2-methylresorcinol, 10 mL of anhydrous chloroform, and 0.28 g (2.45 mmol) of trifluoroacetic acid. The reaction mixture was stirred at room temperature of 10 h. The precipitate was filtered off, washed with diethyl ether and dried in vacuum. Yield 0.37 g (42%), mp > 250°C. IR spectrum, ν, cm^{-1} (KBr): 1597 (Ar), 1645 (C=O), 2878, 2923 (NH). ^1H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 1.37–1.46 m (2H, CH_2), 2.05 s (6H, CH_3), 2.20–2.35 m (2H, CH_2), 3.07–3.13 m (2H, CH_2), 4.37 t (1H, CH, $^3J_{HH}$ 7.8), 6.33 d (2H, CH_{Ar}, $^3J_{HH}$ 8.3), 6.86 d (2H, CH_{Ar}, $^3J_{HH}$ 8.5). Found, %: C 63.51; H 6.57; N 7.93. $C_{19}H_{24}N_2O_5$. Calculated, %: C 63.32; H 6.71; N 7.77.

1-[4,4-Bis(2,4-dihydroxy-3-methylphenyl)butyl]-3-phenylurea (IIIb) was obtained similarly from 0.50 g of 1-(4,4-diethoxybutyl)-3-phenylurea, 0.66 g of 2-methylresorcinol and 0.20 g of trifluoroacetic acid. Yield 0.39 g (50%), mp > 250°C. IR spectrum, ν, cm^{-1} (KBr): 1596 (Ar), 1647 (C=O), 2893, 2926 (NH). ^1H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 1.41–1.53 m (2H, CH_2), 2.03–2.07 m (2H, CH_2), 2.08 s (6H, CH_3), 3.18–3.25 m (2H, CH_2), 4.41 t (1H, CH, $^3J_{HH}$ 7.7), 6.36 d (2H, CH_{Ar}, $^3J_{HH}$ 8.4), 6.89 d (2H, CH_{Ar}, $^3J_{HH}$ 8.2), 6.96 t (1H, CH_{Ar}, $^3J_{HH}$ 7.3), 7.23 t (2H, CH_{Ar}, $^3J_{HH}$ 8.1), 7.33 d (2H, CH_{Ar}, $^3J_{HH}$ 7.6). Found, %: C 69.02; H 6.26; N 6.59. $C_{25}H_{28}N_2O_5$. Calculated, %: C 68.79; H 6.47; N 6.42.

1-[4,4-Bis(2,4-dihydroxy-3-methylphenyl)butyl]-3-(4-bromophenyl)urea (IIIc) was obtained similarly from 0.02 g of 1-(4-bromophenyl)-3-(4,4-diethoxybutyl)urea, 0.01 g of 2-methylresorcinol and 0.01 g of trifluoroacetic acid. Yield 0.02 g (88%), mp 157–158°C. IR spectrum, ν, cm^{-1} (KBr): 1596 (Ar), 1649 (C=O), 2876, 2928 (NH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.29–1.43 m (2H, CH_2), 1.83–1.92 m (2H, CH_2), 1.97 s (6H, CH_3), 3.03–3.12 m (2H, CH_2), 4.33–4.42 m (1H, CH), 6.30 d (2H, CH_{Ar}, $^3J_{HH}$ 8.4), 6.76 d (2H, CH_{Ar}, $^3J_{HH}$ 8.5), 7.29–7.39 m (2H, CH_{Ar}), 7.41–7.51 m (2H, CH_{Ar}). Found, %: C 58.03; H 5.40; Br 15.68; N 5.21. $C_{25}H_{27}BrN_2O_5$. Calculated, %: C 58.26; H 5.28; Br 15.50; N 5.44.

3-[4,4-Bis(2,4-dihydroxy-3-methylphenyl)butyl]-1,1-dimethylurea (IIId) was obtained similarly from 0.12 g of 3-(4,4-diethoxybutyl)-1,1-dimethylurea, 0.12 g of 2-methylresorcinol and 0.06 g of trifluoroacetic acid in 10 mL of anhydrous benzene. Yield 0.16 g (84%), mp 175–177°C. IR spectrum, ν, cm^{-1} (KBr): 1595 (Ar), 1646 (C=O), 2861, 2892, 2923 (NH). ^1H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 1.40–1.51 m (2H, CH_2), 1.92–2.01 m (2H, CH_2), 2.04 s (6H, CH_3), 2.07 s (6H, CH_3), 3.14–3.23 m (2H, CH_2), 4.35–4.42 m (1H, CH), 6.34 d (2H, CH_{Ar}, $^3J_{HH}$ 8.3), 6.86 d (2H, CH_{Ar}, $^3J_{HH}$ 8.5). Found, %: C 64.78; H 7.04; N 7.46. $C_{21}H_{28}N_2O_5$. Calculated, %: C 64.93; H 7.27; N 7.21.

3-{3-(14*H*-Dibenzo[*a*,*j*]xanthen-14-yl)propyl}-1,1-dimethylurea (IV) was obtained similarly from 0.41 g of 3-(4,4-diethoxybutyl)-1,1-dimethylurea, 1.27 g of 2-naphthol and 0.23 g of trifluoroacetic acid in 10 mL of anhydrous chloroform. Yield 0.16 g (22%), mp 189–190°C. IR spectrum, ν, cm^{-1} (KBr): 1595 (Ar), 1648 (C=O), 2865, 2892 (NH). ^1H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 1.10–1.21 m (2H, CH_2), 2.06–2.14 m (2H, CH_2), 2.63 s (6H, CH_3), 2.82–2.87 m (2H, CH_2), 5.69 t (1H, CH, $^3J_{HH}$ 4.1), 7.37 d (2H, CH_{Ar}, $^3J_{HH}$ 8.9), 7.48 t (2H, CH_{Ar}, $^3J_{HH}$ 7.1), 7.66 t (2H, CH_{Ar}, $^3J_{HH}$ 7.2), 7.83 d (2H, CH_{Ar}, $^3J_{HH}$ 9.1), 7.91 d (2H, CH_{Ar}, $^3J_{HH}$ 8.6), 8.38 d (2H, CH_{Ar}, $^3J_{HH}$ 8.5). Mass spectrum, *m*/*z* (I_{rel}, %): 411 (100) $[M]^+$. Found, %: C 79.18; H 6.18; N 7.01. $C_{27}H_{26}N_2O_2$. Calculated, %: C 79.00; H 6.38; N 6.82.

^1H NMR spectra were recorded on a Bruker Avance 600 spectrometer with an operating frequency of 600 MHz with respect to residual proton signals of the deuterated solvents. IR spectra were taken on a spectrometer UR-20 in the range of 400–3600 cm^{-1}. The solid samples were analyzed from KBr pellets or a suspension in vaseline oil. Melting points were determined in glass capillaries on a Stuart SMP 10 instrument.

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