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LETTERS TO THE EDITOR

Calix[4]resorcinols Modified with γ-Aminobutyric Acid Fragments

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The Mannich reaction involving amines, amino alcohols, aminoacetals, aminophosphonates, and aminophosphine oxides is one of the most convenient methods of functionalization of calix[4]resorcinols [1–5]. Thus obtained macromolecules are used as the supramolecular catalysts, extractants, and precursors in the synthesis of new macromolecular compounds [1, 6–8].

In the present work we investigated the possibility of modifying calix[4]resorcinol with γ-aminobutyric acid by the Mannich reaction. γ-Aminobutyric acid and its derivatives are used as neurotransmitters in the central nervous system [9]. Recently it was shown that the complex based on 5,11,17,23-tetra-*tert*-butyl-25,27-bis[carboxymethoxy]-26,28-dihydroxycalix[4]-arene with γ-aminobutyric acid has prolonged anticonvulsant activity [10]. Furthermore, amino acid molecules are often used as additional pharmacophore groups and are key intermediates in the synthesis of many biologically important molecules [11].

Interaction of calix[4]resorcinol **I** with formaldehyde and γ-aminobutyric acid **II** in aqueous ethanol medium at a ratio of the initial reactants of 1 : 4 : 4 led to the formation of the products of incomplete substitution of the macrocycle. In the ESI mass spectrum of the precipitate obtained there were the signals of *m*/*z* 716, 831, 946, indicating the presence of mono-, di-, and trisubstituted calixarene macrocycles, respectively.

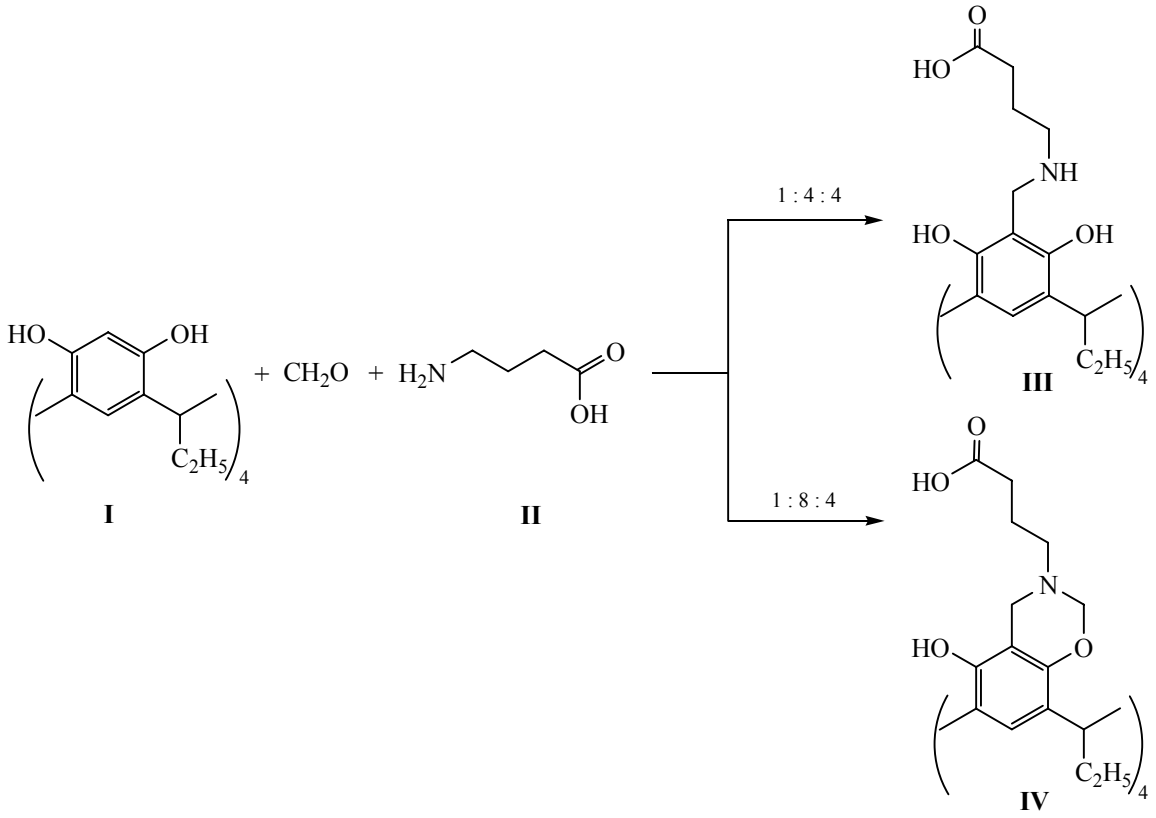
We found that the optimal solution for the reaction performing was ethanol–water–DMSO mixture allowing to obtain calix[4]resorcinol comprising four amino acid **III** fragments at the upper rim of the molecule in a yield of 68%.

The reaction of calix[4]resorcinol **I** with formaldehyde and γ-aminobutyric acid **II** in a ratio of 1 : 8 : 4 under reflux led to the formation of oxazine derivative **IV** in a high yield (Scheme 1).

Structure and composition of the synthesized compounds **III** and **IV** were confirmed by IR, NMR ^{1}H and ^{13}C spectroscopy, mass spectrometry (ESI) and elemental analysis data.

4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,23-tetrakis[*N*-(3-carboxypropyl)aminomethyl]-2,8,14,20-tetraethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (III). A solution of 0.35 g (3.34 mmol) of amino acid **II** in 5 mL of water, 0.28 g (3.34 mmol) of 37% aqueous solution of formaldehyde and 20 mL of dimethyl sulfoxide were added successively to a mixture of 0.5 g (0.83 mmol) of calix[4]resorcinol **I** in 5 mL of ethanol. The reaction mixture was stirred at room temperature for 8 h. The solvent was distilled off in vacuum. The residue was re-precipitated from chloroform to hexane, washed with water and dried in vacuum to constant weight. Yield 0.68 g (68%), mp 177–178°C. IR spectrum, ν, cm^{-1}: 1610 m (C=C$_{Ar}$), 1716 m, 1733 (C=O), 2734 br (NH$^+$), 3422 br (OH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.94 t (12H, 4C<u>H</u>$_3$CH$_2$, $^3J_{HH}$ 7.0 Hz), 1.99 br.s (8H, 4NCH$_2$C<u>H</u>$_2$), 2.23–2.27 m (8H, 4C<u>H</u>$_2$CH$_3$), 2.33 br.s (8H,

Scheme 1.



4CH$_2$COOH), 2.58 br.s (8H, 4NCH$_2$CH$_2$), 3.64 br.s (8H, 4CH$_2$Ar), 4.26 t (4H, 4CHCH$_2$, $^3J_{HH}$ 7.0 Hz), 7.20 s (4H, 4Ar-H), 10.88 br.s (4H, COH, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.2 (CH_2CH_3), 17.5 ($CHCH_2$), 26.2 (CH_2COOH), 30.0 ($NHCH_2CH_2$), 35.8 (CH), 40.29 (NCH_2CH_2), 48.9 ($ArCH_2N$), 111.3 ($C_{Ar}CH_2$), 122.5 ($C_{Ar}H$), 124.3 ($C_{Ar}CH$), 149.7, 150.9 ($C_{Ar}OH$), 176.8 (C=O). Mass-spectrum, *m*/*z*: 1061 $[M + H]^+$. Found, %: C 63.40; H 7.22; N 5.25. $C_{56}H_{76}N_4O_{16}$. Calculated, %: C 63.39; H 7.17; N 5.28.

2,12,22,32-Tetraethyl-4,14,24,34-tetrahydroxy-7,17,27,37-tetra-(3-carboxypropyl)-7,17,27,37-tetra-azanonacyclo[31.3(7).1.1^{3,11}.1^{13,21}.1^{23,31}1(41).3.5(10).·11(44).13.1^{23,31}.0^{5,10}.0^{15,20}.0^{25,30}.0^{35,40}]tetraconta[15(20),·21(43),23,25(30),31(42),33, 35(41)]dodecaene (IV). A mixture of 0.5 g (0.83 mmol) of calix[4]resorcinol **I** dissolved in 5 mL of ethanol, 0.43 g (4.16 mmol) of amino acid **II** in 5 mL of water and 0.67 g (8.33 mmol) of 37% aqueous formaldehyde and 20 mL of DMSO was heated for 2 h. The solvent was distilled off, the residue was re-precipitated from $CHCl_3$ into hexane, washed with water and dried in vacuum. Yield 0.96 g (74%), mp 257–259°C. IR spectrum, ν, cm^{-1}: 1637 m (C=C$_{Ar}$), 1717 m (C=O), 3385 br (C$_{Ar}$OH). ^{1}H NMR spectrum ($CDCl_3$) δ, ppm: 0.95 br.s (12H, 4CH$_2$CH$_3$), 1.84 br.s (8H, 2CH$_2$CH$_2$CH$_2$), 2.03 br.s (8H, 4CH$_2$COOH), 2.23–2.27 m (8H, 4CH$_2$CH$_3$), 2.56 br.s (8H, 4CH$_2$N), 3.81–3.84 m and 4.22–4.24 м (8H, 4CH$_2$Ar), 4.12 t (4H, 4ArCH, $^3J_{HH}$ 7.0 Hz), 4.9 m (8H, 4CH$_2$OAr), 7.19–7.21 m (4H, C$_{Ar}$H). Mass spectrum, *m*/*z*: 1109 $[M + H]^+$. Found, %: C 64.83; H 6.91; N 5.06; $C_{60}H_{76}N_4O_{16}$. Calculated, %:C 64.98; H 6.86; N 5.19.

^{1}H NMR spectra were recorded on a Bruker MSL 400 spectrometer operating at 400.13 MHz with respect to residual proton signals of the deuterated solvent ($CDCl_3$). ^{13}C NMR spectrum was registered on a Bruker Avance 600 spectrometer operating at 150.13 MHz. Mass spectra (ESI) were obtained on an AmazonX (Bruker Daltonik GmbH, Germany) spectrometer. IR spectra (KBr) were taken on a UR-20 spectrometer in the range of 400–3600 cm^{-1}. Melting points were determined in glass capillaries on a Stuart SMP 10 instrument.

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