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Reaction of Resorcinol and Its Derivatives with Urea Acetals

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Abstract—Reaction of 2-methylresorcinol and pyrogallol with urea acetals of various structures was studied. Depending on the structure of the acetal used, reaction was established to result in eiter calix[4]resorcinols containing urea fragment or in imidazolidin-2-one derivatives.

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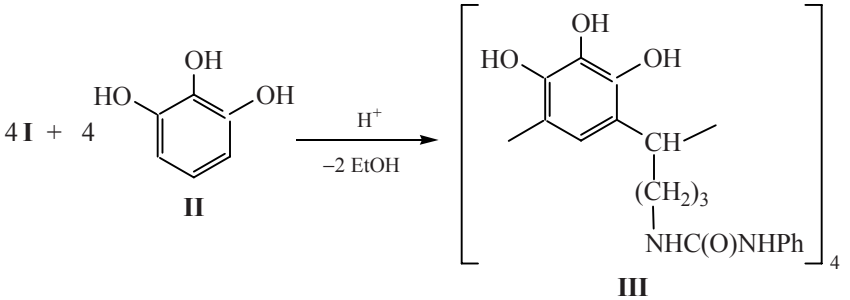
According to published data, the calixarene containing urea fragments can be used as anion selective complexing agents [1], as building blocks for molecular container constructions carcerands and carceplexes [2], and as stationary phases for the liquid chromatography [3, 4]. Considering these data, calix[4]resorcinols containing urea fragments at the molecule lower rim are of undoubted interest. Compounds of this type can possess biological activity and can be used as new synthetic platforms for construction of the new type supramolecular compounds.

We have show earlier that a convenient method of obtaining calix[4]resorcinols is reaction of functionalized acetals with resorcinol and its derivatives [5]. Aiming at the synthesis of calix[4]resorcinols involving urea fragments, we used 1-(4,4-diethoxybutyl)-3-phenylurea **I** obtained by reaction of 4,4-diethoxybutylamine with phenylisocyanate, in the reaction with resorcinol derivatives.

$$PhNCO + H_2N(CH_2)_3CH(OEt)_2 \rightarrow PhNHC(O)NH(CH_2)_3CH(OEt)_2.$$

I

The reaction of acetal **I** with pyrogallol **II** was carried out in the chloroform medium in the presence of trifluoroacetic acid. As a result, calix[4]resorcinol **III** was obtained, composition and structure of which were confirmed by elemental analysis and spectral methods.

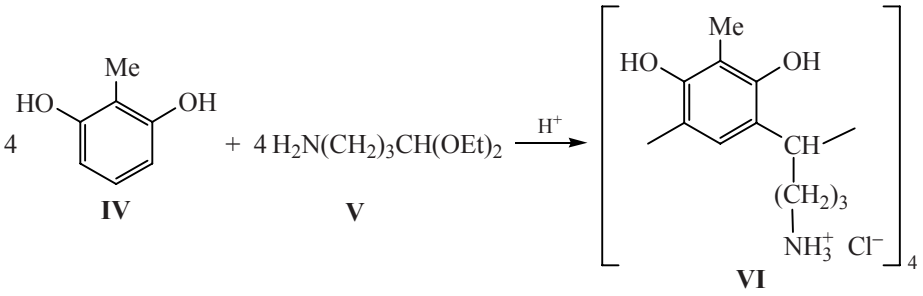


II **III**

Calixarene of the similar composition was also obtained by other way. Initially we carried out reaction of 2-methylresorcinol **IV** with 4,4-diethoxy-1-butylamine **V** in water–alcohol solution of hydrochloric acid, resulted in formation of calixarene **VI** containing ammonium fragments (Scheme 1).

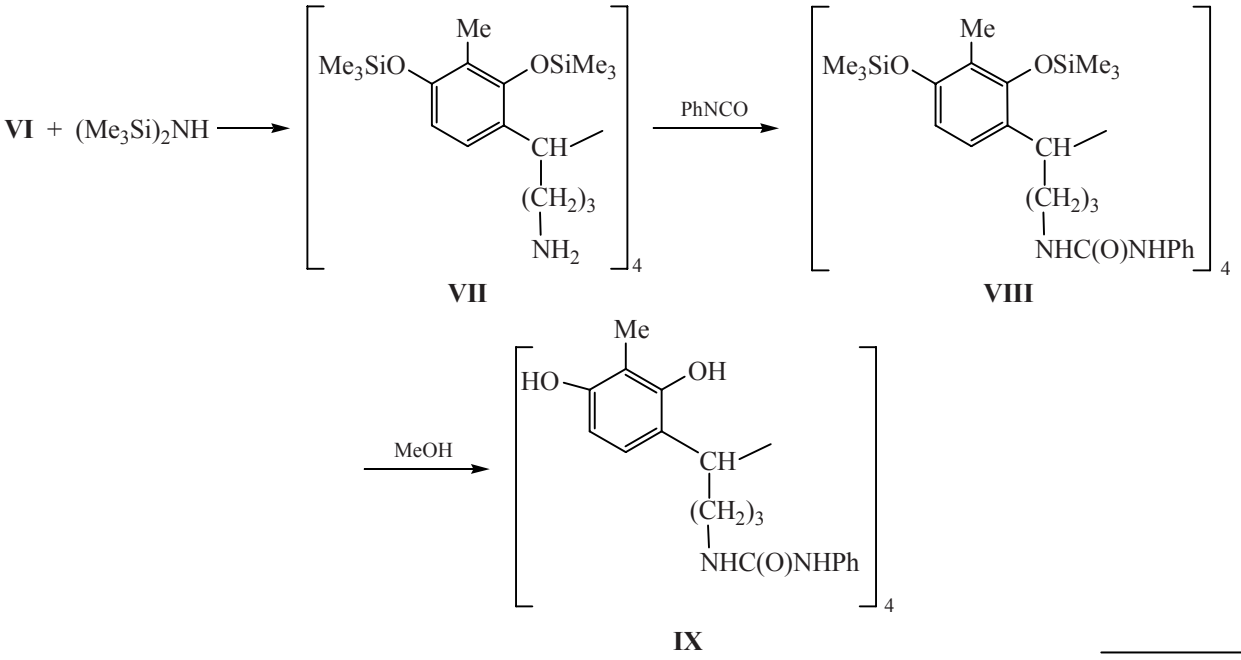
Treatment of calixarene **VI** with hexamethyldisilazane excess affords calixarene **VII** containing free primary amino groups. The latter reacts readily with phenylisocyanate to form calixarene **VIII** involving four urea fragments. Methanolysis of the crude compound **VIII** proceeds with desilylation re-

Scheme 1.



IV **V** **VI**

Scheme 2.



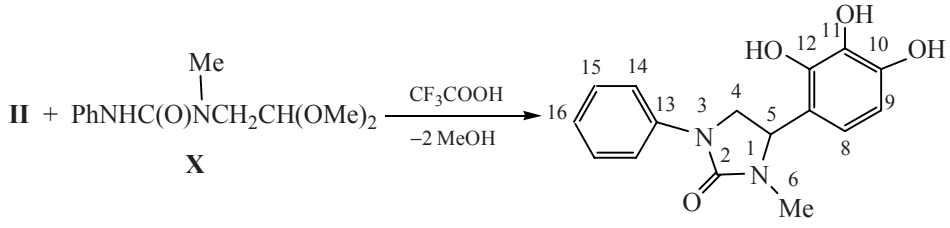
VII **VIII** **IX**

sulted in calixarene **IX**, which was isolated and characterized by elemental analysis, ^{1}H NMR and IR spectroscopy data (Scheme 2).

To elucidate influence of urea acetal structure, including the size of carbon chain binding urea and acetal fragments, on the synthetic result of reaction, we studied reaction of pyrogallol **II** with 1-(2,2-dimethoxyethyl)-1-methyl-3-phenylurea **X**, in which acetal and urea fragments are bound through two carbon links only. The result was found to be sufficiently unexpected: the reaction product was corresponding imidazolidin-2-one **XI** (Scheme 3).

We supposed that the result obtained is explained by a possibility of initial monomolecular hetero-

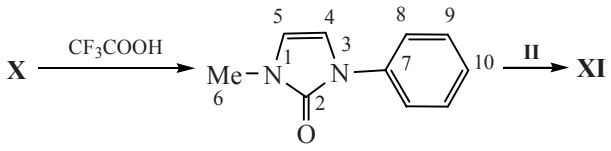
Scheme 3.



X **XI**

cyclization of acetal **X** into 1-methyl-3-phenylimidazol-2-one **XII** followed by reaction of the latter with pyrogallol. Actually we established by special experiment that acetal **X** under the reaction conditions (in the presence of trifluoroacetic acid) exerts cyclization into imidazole **XII**, which reacts with pyrogallol to form the final product **XI** (Scheme 4).

Scheme 4.



XII

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were registered on a Bruker AVANCE-600 device (600 and 150 MHz respectively). The IR spectra were recorded on a UR-20 device in the range of 400–3600 cm^{-1} (vaseline oil).

1-(4,4-Diethoxybutyl)-3-phenylurea (I). To a solution of 6.0 g of 4,4-diethoxy-1-butylamine in 12 ml of benzene was added dropwise 4.43 g of phenylisocyanate in 6 ml of benzene under argon atmosphere at 10–15°C. The reaction mixture was stirred for 1 h at 30°C. Then the solvent was removed and residue was recrystallized from benzene. Yield 9.2 g (65%), mp 66–68°C. IR spectrum, ν, cm^{-1}: 1580 (CH_{Ar}), 1634, 1593 (C=O), 3284 (NH). ^{1}H NMR spectrum [$(CD_3)_2C=O$], 20°C , δ, ppm: 1.14 t (6H, CH_3CH_2O, $^3J_{HH}$ 6.97 Hz), 1.60 q (4H, CH_2O, $^3J_{HH}$ 3.67 Hz), 3.23 q (2H, CH_2, $^3J_{HH}$ 5.87 Hz), 3.61 m (2H, CH_2), 3.47 m (2H, NCH_2) 4.50 t (1H, CH, $^3J_{HH}$ 5.13 Hz), 6.92 m (1H, *p*-CH_{Ar}), 7.22 m (2H, *m*-CH_{Ar}), 7.46 m (2H, *o*-CH_{Ar}), 7.86 s (1H, NH). Found, %: C 64.07; H 8.82, N 10.18. $C_{15}H_{24}N_2O_3$. Calculated, %: C 64.26; H 8.63; N 9.99.

4,5,6,10,11,12,16,17,18,22,23,24-Dodecahydroxy-2,8,14,20-tetra[3-(3-phenylureido)propyl]pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacoza-1(25),3,5,7(28),9,11,-13(27),15,17,19(26),21,23-dodecaene (III). A mixture of 0.3 g of acetal **I,** 0.14 g of pirogallol, 0.1 ml of trifluoroacetic acid and 3 ml of chloroform was heated for 25 h at 60°C. After the solvent removal the residue was reprecipitated from chloroform with pentane as a grey powder. Yield 0.25 g (64%), mp >250°C. IR spectrum, ν, cm^{-1}: 1608 (CH_{Ar}), 1653 (C=O), 3330 (OH). ^{1}H NMR spectrum (CD_3OD), 20°C , δ, ppm: 1.48 m (8H, CH_2), 1.98 m (8H, CH_2), 3.18 m (8H, CH_2), 4.42 m (4H, CH), 6.37 m (4H, CH_{Ar}), 6.93 m (4H, *p*-CH_{Ar}), 7.18 m (8H, *m*-CH_{Ar}), 7.27 m (8H, *o*-CH_{Ar}). Found, %: C 69.74; H 6.52; N 8.95. $C_{72}H_{80}N_8O_{12}$. Calculated, %: C 69.21; H 6.45; N 8.97.

4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,23-tetramethyl-2,8,14,20-tetra(3-ammoniochloridepropyl)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacoza-1(25),3,5,7-(28),9,11,13(27),15,17,19(26),21,23-dodecaene (VI). A mixture of 0.77 g of resorcinol **IV**, 1.0 g of acetal **V**, 2.5 ml of concentrated hydrochloric acid, 6 ml of ethanol and 6 ml of water distilled was heated for 8 h at 80°C. After the solvent removal the residue was washed twice with ethanol and dried in vacuum (20°C, 5 mm Hg, 24 h). Yield 1.37 g (24.0%), mp >250°C. IR spectrum, ν, cm^{-1}: 1600 (CH_{Ar}), 3320 (OH). ^{1}H NMR spectrum (D_2O), 20°C, δ, ppm: 1.59 m (8H, CH_2), 1.62 s (12H, CH_3), 2.34 m (8H, CH_2), 3.02 t (8H, CH_2, $^3J_{HH}$ 7.52 Hz), 4.36 t (4H, CH, $^3J_{HH}$ 7.88 Hz), 7.22 s (4H, CH_{Ar}). Found, %: C 57.01; H 6.95; Cl 15.01; N 6.0. $C_{44}H_{64}Cl_4N_4O_8$. Calculated, %: C 57.52; H 7.02; Cl 15.43; N 6.10.

4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,23-tetramethyl-2,8,14,20-tetra[3-(3-phenylureid)propyl]-pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacoza-1(25),3,5,7-(28),9,11,13(27),15, 17,19(26),21,23-dodecaene (IX). A mixture of 0.45 g of calixarene **VI** and 5 ml of hexamethyldisilazane (HMDS) was refluxed for 48 h to ammoniac release stopping and HMDS excess was removed under vacuum. The residue was dissolved into 5 ml of benzene. To this solution 0.23 g of phenylisocyanate was added dropwise and stirred for 14 h at 20°C. Then 5 ml ethanol was added and the reaction mixture was heated for 3 h at 50°C. After the solvent removal the residue was reprecipitated from chloroform with pentane. Yield 0.22 g (18.4%), mp >250°C. IR spectrum, ν, cm^{-1}: 1598 (CH_{Ar}), 1648 (C=O), 3338 (OH). ^{1}H NMR spectrum ($CDCl_3$), 20°C , δ, ppm: 1.34 m (8H, CH_2), 1.51 m (4H, CH_2), 1.95 m (4H, CH_2), 1.72 s (6H, CH_3), 2.09 s (6H, CH_3), 2.79 m (4H, CH_2), 3.35 m (4H, CH_2), 4.31 m (4H, CH), 6.45 m (4H, CH_{Ar}), 6.91 m (4H, *p*-CH_{Ar}), 7.11 m (8H, *m*-CH_{Ar}), 7.24 m (8H, *o*-CH_{Ar}). Found, %: C 69.00; H 6.12; N 8.41. $C_{72}H_{80}N_8O_{12}$. Calculated, %: C 69.21; H 6.45; N 8.97.

1-(2,2-Dimethoxyethyl)-1-methyl-3-phenylurea (X). A solution of 3.0 g of 2,2-dimethoxyethylmethylamine and 3.0 g of phenylisocyanate in 9 ml of benzene was heated for 1 h at 30°C. After the solvent removal the residue was recrystallized from benzene. Yield 3.9 g (65%), mp 66–68°C . IR spectrum, ν, cm^{-1}: 1461, 1580 (CH_{Ar}), 1634 (C=O), 3284 (NH). ^{1}H NMR spectrum

($CDCl_3$), δ, ppm: 3.04 s (3H, CH_3N), 3.41 s (6H, CH_3O), 3.43 d (2H, CH_2, $^3J_{HH}$ 5.30 Hz), 4.55 t (1H, CH, $^3J_{HH}$ 5.30 Hz), 7.22 m (5H, C_6H_5). Found, %: C 60.07; H 7.82, N 11.58. $C_{12}H_{18}N_2O_3$. Calculated, %: C 60.49; H 7.61; N 11.76.

1-Methyl-3-phenylimidazol-2-one (XII). A mixture of 4.0 g of urea **X**, 2.1 g of trifluoroacetic acid and 25 ml of chloroform was heated for 4 h at 60°C. After the solvent removal the residue was washed with diethyl ether. Yield 2.45 g (90.8%), mp 117°C. IR spectrum, ν, cm^{-1}: 1595 (CH_{Ar}), 1642 (C=C), 1679 (C=O). ^1H NMR spectrum ($CDCl_3$), 20°C, δ, ppm: 3.28 s (3H, HC^6), 6.29 d (1H, HC^4, $^3J_{HH}$ 2.93 Hz), 6.54 d (1H, HC^5, $^3J_{HH}$ 2.93 Hz), 7.21 t (1H, HC^{10}, $^3J_{HH}$ 7.33 Hz), 7.38 t (2H, HC^9, $^3J_{HH}$ 7.92 Hz), 7.59 d (2H, HC^8, ^3J 8.21 Hz). Found, %: C 68.43; H 6.21; N 16.54. $C_{10}H_{10}N_2O$. Calculated, %: C. 68.95; H 5.79; N 16.08.

3-Methyl-1-phenyl-4-(2,3,4-trihydroxyphenyl)-imidazolydin-2-one (XI). To a mixture of 1.6 g of pyrogallole, 1.58 g of trifluoroacetic acid and 25 ml of chloroform was slowly added dropwise a solution of 3.0 g of urea **X** in 15 ml of chloroform. The reaction mixture was heated for 8 h at 60°C. After the solvent removal the residue was dissolved into 3 ml of chloroform and kept overnight. The precipitate was filtered off and washed with 50 ml of diethyl ether. Yield 2.93 g (80.7%), mp 150–151°C. IR spectrum, ν, cm^{-1}: 1600 (CH_{Ar}), 1692, 1653 (C=O), 3337 (OH). ^1H NMR spectrum (CD_3OD), δ, ppm: 2.67 s (3H, HC^6), 3.61 d. d (1H, HC^4, $^2J_{HH}$ 8.88 Hz, ^3J 6.79 Hz), 4.07 t (1H, HC^5, $^3J_{HH}$ 9.40 Hz), 4.87 d. d (1H, HC^4, $^2J_{HH}$ 9.66 Hz, $^3J_{HH}$ 7.05 Hz), 6.41 d (1H, HC^9, $^3J_{HH}$ 8.36 Hz), 6.51 d (1H, HC^8, $^3J_{HH}$ 8.36 Hz), 6.97 t (1H, HC^{16}, $^3J_{HH}$ 7.31 Hz), 7.25 t (2H, HC^{15}, $^3J_{HH}$ 8.09 Hz), 7.48 d (2H, HC^{14}, $^3J_{HH}$ 7.84 Hz). ^{13}C NMR spectrum (CD_3OD), δ, ppm: 29.57 (C^6, $^1J_{CH}$ 137.84 Hz), 51.86 (C^4, $^1J_{CH}$ 145.95 Hz), 55.39 (C^5, $^1J_{CH}$ 145.40 Hz), 108.34 (C^9, $^1J_{CH}$ 161.43 Hz), 118.40 (C^{14}, $^1J_{CH}$ 158.66 Hz), 118.49 (C^7), 119.29 (C^{15}, $^1J_{CH}$ 159.22 Hz), 123.70 (C^{16}, $^1J_{CH}$ 160.32 Hz), 129.84 (C^8, $^1J_{CH}$ 158.66 Hz), 141.85 (C^{13}), 134.49 (C^{11}), 147.23, 146.18 (C^{10}, C^{12}), 160.30 (C^2). Found, %: C 63.56; H 5.25; N 9.53. $C_6H_{16}N_2O_4$. Calculated, %: C 63.99; H 5.37; N 9.33.

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