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Electrophilic Substitution in the Dihydroquercitin System. Aminomethylation

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Abstract—Treating dihydroquercetin with formaldehyde and amines under conditions of Mannich reaction provided mono- and diaminomethyl derivatives of dihydroquercetin.

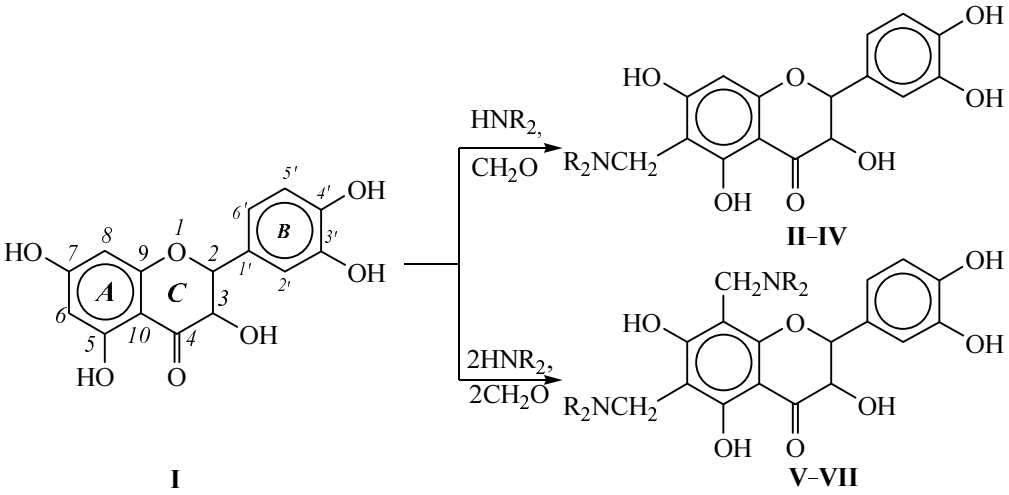
In extension of systematic investigations on the chemical features of dihydroquercetin [1, 2] we started to study its behavior in Mannich reaction. The process is well documented by examples of versatile phenols [3–5] and is widely used in syntheses. Yet important natural polyhydric phenols, flavanoids, were not involved into aminomethylation. We demonstrated that an available flavanoid dihydroquercetin (**I**) readily reacted with formaldehyde in the presence of secondary amines. The structure of final reaction products depends on the reagents ratio: both mono- and di(aminomethyl)dihydroquercetin can be obtained.

Reaction products **II–VII** are powdery solids. Their composition and structure were proved by elemental analysis and ^1H and ^{13}C NMR spectra.

It should be noted in particular, that the electrophilic substitution occurred solely in ***A*** ring even at the large excess of reagent and under more severe reaction condutions.

Aminomethylated dihydroquercetin form crystalline salts with mineral and organic acids soluble in water, for instance, tosylate **VIII**.

The structure of compound **VIII** was investigated by means of X-ray diffraction analysis. An independent part



NR_2 = morpholino (**II, V**), piperidino (**III, VI**), $N(Et)_2$ (**IV, VII**).

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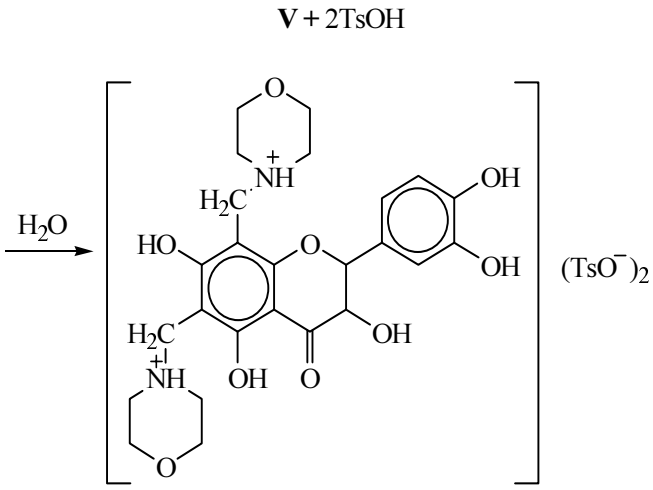

VIII

of its unit cell consists of two molecules of protonated dihydroquercetin derivative (cation), two tosylate anions, and three hydrate water molecules. Hence one of the *p*-toluenesulfonic acid molecules in preparation of salt **VIII** acts only as protonating agent and does not take part directly in building up the structure under study.

The conformation of dihydroquercetin fragment in salt **VIII** where into positions *6* and *8* are introduced 1-aza-4-oxacyclohexyl substituents remained the same as in the initial flavanoid **I** (Fig. 1). In the crystal of compound **VIII** the molecules of cation, tosylate anion, and hydrate water form a three-dimensional framework of hydrogen bonds. It is noteworthy that in the crystal packing of compound **VIII** are present cation-anion pairs bound by strong N–H···O bonds (Fig. 2). A more detailed analysis of salt **VIII** geometry and crystal packing will be published elsewhere.

EXPERIMENTAL

^{1}H NMR spectra were registered from solutions in DMSO-d_6 on spectrometer Bruker AM-250 at operating frequency 250 MHz; chemical shifts were measured with respect to HMDS as external reference. ^{13}C NMR spectra were obtained on spectrometer Bruker AC-200 at operating frequency 50.32 MHz from solutions in DMSO-d_6, internal reference TMS. Adsorption chromatography was carried out on column packed with silica gel L 100/250 or L 40/100 μm. TLC was performed on Silufol UV-254 plates. The reaction progress was monitored and homogeneity of compounds obtained was checked by TLC, eluent benzene-dioxane, 1:3.

X-ray diffraction study. Crystals $C_{32}H_{39}N_2O_{13.5}S$ monoclinic, space group *Cc*, *a* 22.890(4), *b* 19.439(4), *c* 17.687(4) Å, β 110.939(5)°, *V* 7350(3) Å^3, *Z* 8, *M* 699.71, ρ_{calc} 1.256 g/cm^{-3}, μ(MoK_α) 1.52 cm^{-1}, *F*(000) 2930. Intensities of 22030 reflections were measured on diffractometer Smart CCD 1000K at 110 K [*l*(MoK_α) 0.71072 Å, ω-scanning, 2θ<50°], 11745 independent reflections (R_{int} 0.0342) were used for further refining. Structure **VIII** was solved by the direct method and refined by a least-squares procedure in full-matrix anisotropic-isotropic

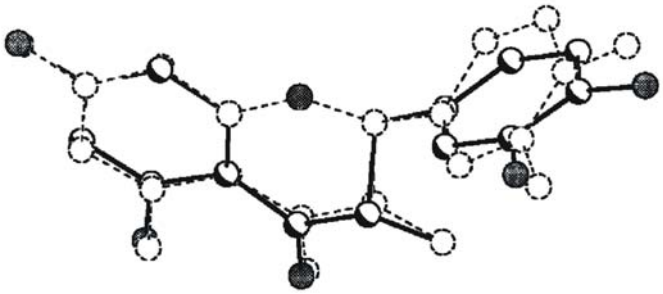

Fig. 1. Comparison of geometry of the dihydroquercetin fragments in salt **VIII** and compound **I** (the molecules are superimposed along the phenol group plane; molecule **VIII** is shown by dashed lines).

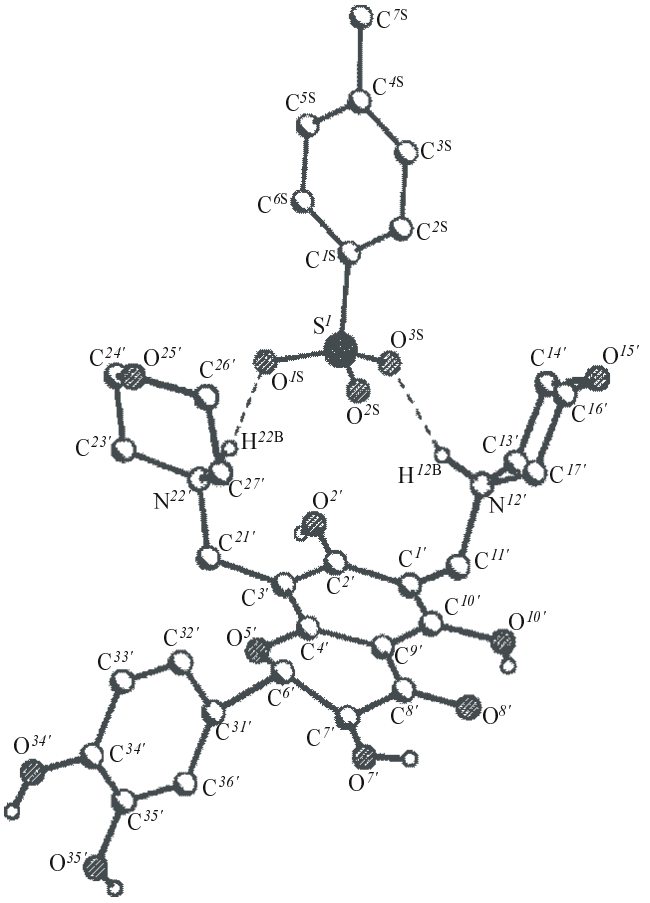

Fig. 2. General view of cation-anion pair in salt. **VIII**.

approximation along F^2. Hydrogen atoms of hydroxy groups and those linked to nitrogen were found from the difference Fourier syntheses of electron density and refined in the framework of *rider* model. Other hydrogen atoms were calculated from geometrical considerations and were refined in the framework of *rider* model. The final parameters of refinement: ωR_2 0.2002 (for all reflections), GOF 1.073, R_1 0.0938 [for 9434 reflections with $I > 2\sigma(I)$]. All calculations were carried out on IBM PC using SHELXTL-97 V5.10 software package [6].

6-(Morpholinomethyl)dihydroquercetin (II). A mixture of 0.05 g (1.6 mmol) of paraformaldehyde, 0.15 g (1.6 mmol) of morpholine, and 10 ml of 2-propanol was stirred at 60°C till complete homogenization. The solution obtained was added slowly to a solution of 0.5 g (1.6 mmol) of compound **I** in 2-propanol, and the reaction mixture was stirred at heating for 1.5 h. The reaction product gradually precipitated as light-yellow powder that was filtered off and washed in succession with ethanol, dioxane, benzene, and hexane, then it was dried in a vacuum till constant weight, yield 40%, mp 160–162°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.62 s [4H, N(CH$_2$)$_2$], 3.58 s (2H, CH$_2$), 3.78 s [4H, (CH$_2$)$_2$], 4.58 d [1H, C^{2}H, *J*(HH) 10.45], 5.00 d [1H, C^{3}H, *J*(HH) 10.41], 5.12 s (1H, C^{7}OH), 5.84 s (1H, C^{8}H), 6.86 s (1H, C$^{5'}$H), 6.91 s (1H, C$^{6'}$H), 7.05 s (1H, C$^{2'}$H), 7.93 s (1H, C$^{4'}$OH), 8.10 s (1H, C$^{3'}$OH), 10.95 s (1H, C^{3}OH), 11.90 s (1H, C^{5}OH). ^{13}C NMR spectrum, δ, ppm: 50.56 (C^{6}CH$_2$–N), 52.39 [2(NCH$_2$)], 66.02 [2(OCH$_2$)], 71.55 (C^3), 82.96 (C^2), 99.24 (C^8), 100.80 (C^6), 101.64 (C^{10}), 115.17 (C$^{2',5'}$), 119.14 (C$^{6'}$), 128.22 (C$^{1'}$), 144.96 (C$^{3'}$), 145.72 (C$^{4'}$), 159.21 (C^9), 160.48 (C^5), 167.99 (C^7), 197.71 (C^4). Found, %: C 59.64; H 5.07; N 3.57. $C_{20}H_{21}NO_8$. Calculated, %: C 59.55; H 5.21; N 3.47.

Compounds **III** and **IV** were prepared in a similar way.

6-(Piperidinomethyl)dihydroquercetin (III). Yield 75%, mp 200–202°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50 s [2H, CH$_2$(CH$_2$)$_2$], 1.59 s [4H, CH$_2$(CH$_2$)$_2$], 2.71 s [4H, N(CH$_2$)$_2$], 3.79 s (2H, CH$_2$), 4.40 d [1H, C^{2}H, *J*(HH) 10.44], 4.89 d [1H, C^{3}H, *J*(HH) 10.40], 5.05 s (1H, C^{7}OH), 5.63 s (1H, C^{8}H), 6.74 s (2H, C$^{5',6'}$H), 6.87 s (1H, C$^{2'}$H), 8.01 s (1H, C$^{4'}$OH), 8.10 s (1H, C$^{3'}$OH), 10.90 s (1H, C^{3}OH), 12.00 s (1H, C^{5}OH). ^{13}C NMR spectrum, δ, ppm: 22.66 [(CH$_2$)$_2$CH$_2$(CH$_2$)$_2$], 24.27 (CH$_2$CH$_2$CH$_2$), 52.28 [2(NCH$_2$)], 66.31 (C^{6}CH$_2$), 71.36 (C^3), 82.77 (C^2), 96.22 (C^8), 97.91 (C^6), 99.59 (C^{10}), 115.07 (C$^{5'}$), 115.29 (C$^{2'}$), 119.25 (C$^{6'}$), 128.38 (C$^{1'}$), 144.96 (C$^{3'}$), 145.69 (C$^{4'}$), 161.18 (C^9), 161.60 (C^5), 172.60 (C^7), 195.53 (C^4). Found, %: C 62.84; H 5.62; N 3.49. $C_{21}H_{23}NO_7$. Calculated, %; C 62.95; H 5.74; N 3.54.

6-(Diethylaminomethyl)dihydroquercetin (IV). Yield 45%, mp 200–202°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.14 t (6H, NCH$_2$CH$_3$), 2.86 q (4H, NCH$_2$CH$_3$), 3.89 s (2H, CH$_2$), 4.38 d [1H, C^{2}H, *J*(HH) 10.96], 4.93 d [1H, C^{3}H, *J*(HH) 11.01], 5.10 s (1H, C^{7}OH), 5.52 s (1H, C^{8}H), 6.73 s (2H, C$^{5',6'}$H), 6.86 s (1H, C$^{2'}$H), 7.97 s (1H, C$^{4'}$OH), 8.10 s (1H, C$^{3'}$OH), 11.05 s (1H, C^{3}OH), 12.00 s (1H, C^{5}OH). ^{13}C NMR spectrum, δ, ppm: 25.51 [2(CH$_2$CH$_3$)], 45.89 [2(CH$_2$CH$_3$)], 47.54 (NCH$_2$), 71.32 (C^3), 82.74 (C^2), 96.69 (C^8), 97.18 (C^6), 99.28 (C^{10}), 115.10 (C$^{5'}$), 115.31 (C$^{2'}$), 119.25 (C$^{6'}$), 128.54 (C$^{1'}$), 145.02 (C$^{3'}$), 145.72 (C$^{4'}$), 161.16 (C^9), 161.58 (C^5), 172.60 (C^7), 195.55 (C^4). Found, %: C 61.98; H 6.02; N 3.48. $C_{20}H_{23}NO_7$. Calculated, %: C 61.70; H 5.91; N 3.60.

6,8-Di(morpholinomethyl)dihydroquercetin (V). A mixture of 0.1 g (3.2 mmol) of paraformaldehyde, 0.3 g (3.2 mmol) of morpholine, and 10 ml of 2-propanol was stirred at 60°C till complete homogenization. The solution obtained was added slowly to a solution of 0.5 g (1.6 mmol) of compound **I** in 2-propanol, and the reaction mixture was stirred at slight heating for 1.5 h. The reaction product gradually precipitated as light-yellow powder that was filtered off and washed in succession with ethanol, dioxane, benzene, and hexane, then it was dried in a vacuum till constant weight. Yield 71%, mp 195–197°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.49 s [8H, N(CH$_2$)$_2$], 3.56 s (4H, CH$_2$), 3.58 s [8H, O(CH$_2$)$_2$], 4.45 d [1H, C^{2}H, *J*(HH) 10.97], 4.95 d [1H, C^{3}H, *J*(HH) 10.96], 5.23 s (1H, C^{7}OH), 6.75 s (2H, C$^{5',6'}$H), 6.88 s (1H, C$^{2'}$H), 8.00 s (2H, C$^{3',4'}$OH), 11.30 s (1H, C^{3}OH), 11.52 s (1H, C^{5}OH). ^{13}C NMR spectrum, δ, ppm: 50.57 (C^{6}CH$_2$N), 52.51 [4(NCH$_2$)], 60.39 (C^{8}CH$_2$N), 66.02 [4(OCH$_2$)], 71.55 (C^3), 82.95 (C^2), 99.24 (C^8), 100.80 (C^6), 101.64 (C^{10}), 115.17 (C$^{2',5'}$), 119.13 (C$^{6'}$), 128.22 (C$^{1'}$), 144.96 (C$^{3'}$), 145.72 (C$^{4'}$), 159.21 (C^9), 160.48 (C^5), 167.99 (C^7), 197.71 (C^4). Found, %: C 59.64; H 6.02; N 5.48. $C_{25}H_{30}N_2O_9$. Calculated, %: C 59.76; H 5.98; N 5.58.

Compounds **VI** and **VII** were prepared in a similar way.

6,8-Di(piperidinomethyl)dihydroquercetin (VI). Yield 70%, mp 201–203°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.58 s [12H, CH$_2$(CH$_2$)$_2$], 2.82 s [8H, N(CH$_2$)$_2$], 3.81 s (4H, CH$_2$), 4.36 d [1H, C^{2}H, *J*(HH) 11.00], 4.90 d [1H, C^{3}H, *J*(HH) 10.95], 5.00 s (1H, C^{7}OH), 6.74 s (2H,

$C^{5',6'}H$), 6.86 s (1H, $C^{2'}H$), 7.73 s (1H, $C^{4'}OH$), 8.30 s (1H, $C^{3'}OH$), 11.05 s (1H, $C^{3}OH$), 11.97 s (1H, $C^{5}OH$). ^{13}C NMR spectrum, δ, ppm: 22.65[2(CH_2)$_2$$\underline{C}H_2$($CH_2$)$_2$], 24.30 [2($\underline{C}H_2CH_2\underline{C}H_2$)], 52.61 [2($NCH_2$)], 66.35 ($C^{6}\underline{C}H_2$), 66.50 ($C^{8}\underline{C}H_2$), 71.00 ($C^{3}$), 82.67 ($C^{2}$), 96.50 ($C^{8}$), 97.41 ($C^{6}$), 99.19 ($C^{10}$), 115.37 ($C^{5'}$), 115.78 ($C^{2'}$), 119.84 ($C^{6'}$), 128.77 ($C^{1'}$), 144.73 ($C^{3'}$), 145.19 ($C^{4'}$), 161.19 ($C^{9}$), 161.63 ($C^{5}$), 161.79 ($C^{7}$), 193.71 ($C^{4}$). Found, %: C 64.97; H 6.77; N 5.73. $C_{27}H_{34}N_2O_7$. Calculated, %: C 65.06; H 6.83; N 5.62.

6,8-Bis(diethylaminomethyl)dihydroquercitin (VII). Yield 46%, mp 205–207°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.18 t (12H, CH_3), 2.85 q [8H, N(CH_2)$_2$], 3.56 s (1H, $C^{7}OH$), 3.85 s (4H, CH_2), 4.44 d [1H, $C^{2}H$, *J*(HH) 10.89], 4.87 d [1H, $C^{3}H$, *J*(HH) 10.89], 6.73 s (2H, $C^{5',6'}H$), 6.87 s (1H, $C^{2'}H$), 8.79 s (1H, $C^{4'}OH$), 9.33 s (1H, $C^{3'}OH$), 11.05 s (1H, $C^{3}OH$), 13.27 s (1H, $C^{5}OH$). ^{13}C NMR spectrum, δ, ppm: 25.64 [4($CH_2\underline{C}H_3$)], 45.95 [4($\underline{C}H_2CH_3$)], 47.54 ($N\underline{C}H_2C^{6}$), 47.53 ($N\underline{C}H_2C^{8}$), 71.32 (C^{3}), 82.74 (C^{2}), 96.69 (C^{8}), 97.18 (C^{6}), 99.30 (C^{10}), 115.10 ($C^{5'}$), 115.31 ($C^{2'}$), 119.27 ($C^{6'}$), 128.54 ($C^{1'}$), 145.0 ($C^{3'}$), 145.72 ($C^{4'}$), 161.16 (C^{9}), 161.55 (C^{5}), 172.60 (C^{7}), 195.54 (C^{4}). Found, %: C 63.29; H 7.25; N.93. $C_{25}H_{30}N_2O_7$. Calculated, %: C 63.35; H 7.17; N 5.08.

Tosylate VIII. 0.5 g (1 mmol) of compound **V** was dissolved in a water solution of 0.35 g (2 mmol) of *p*-toluenesulfonic acid. Salt **VIII** was separated from solution as light-yellow crystals, mp 275–276°C.

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