Synthesis some 4-substituted 9,10-anthraquinones

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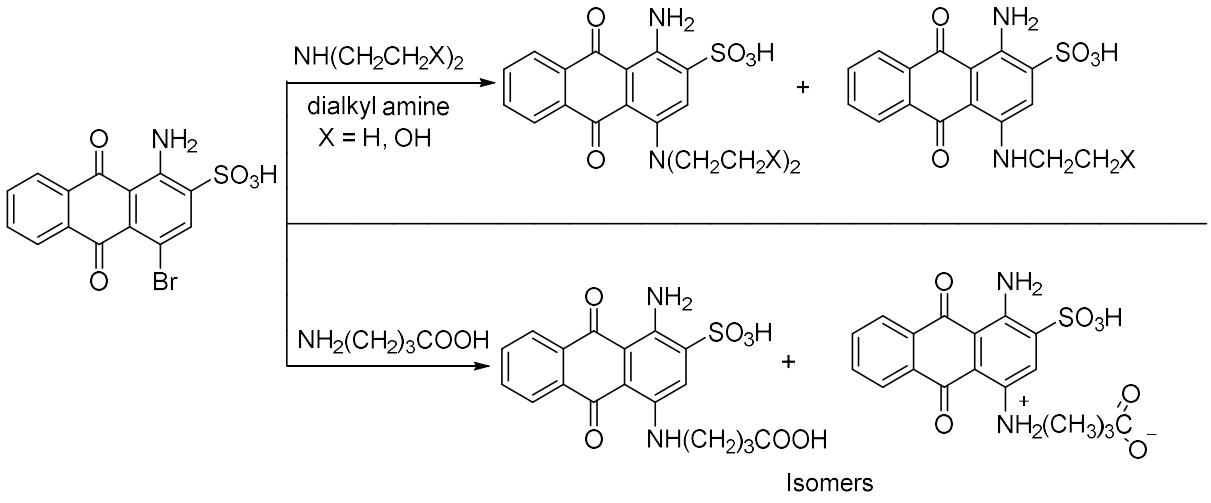
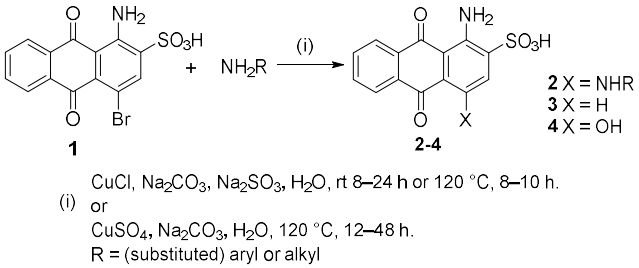
New 4-substituted 9,10-anthraquinones (6 compouds) with amino derivations fragments were synthesized through the substitution of the bromaminic acid by amines using the Ullmann coupling reaction. The structures of the synthesized compounds were determined using LC-MS, ^{1}H NMR, ^{13}C NMR spectroscopy, and elemental analysis data.



The classical and most widely used strategy for the synthesis of 4-substituted anthraquinone derivatives include the Ullmann coupling reaction [1-4], which involves the treatment of bromaminic acid **1**, with an amine in the presence of a copper catalyst (**Scheme 1**) [5-ally requires harsh conditions, e.g., high temperatures and long reaction times [9-12]; it suffers from mostly poor yields product **2** [13-15], and the formation of side-products, such as **3** and **4** [16-17].



Scheme 1. Classical synthesis of 4-substituted anthraquinone derivatives

Glanzel M. described [18] the anisotropy effect of the aromatic anthraquinone ring C, 3-H-proton is protonation by carbon atoms C-9 or C-10. He also described the effect of the methyl groups rotation of the substituted ring-D, and the fragmentation of the 3-H proton from the structure of the molecule, as shown in **Figure 1**.

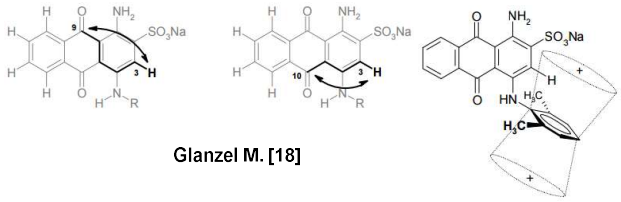


Figure 1. Structures of some 4-substituted 9,10-anthraquinone derivatives

Levsen K. [19], described the dissociation of $[M+H]^+$ ions of hydroxylethylamino-anthraquinone **5** (**Figure 2**), to the C-N bond as a result in the elimination of the hydroxyethyl radical ($^*CH_2CH_2OH$).

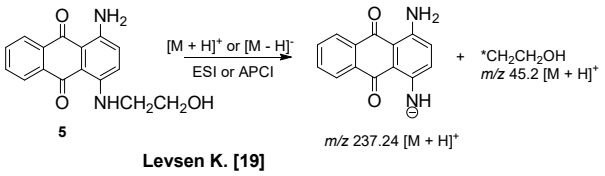


Figure 2. Dissociation 4-substituted 9,10-anthraquinone derivative **5**.

Mass spectrometry is a well recognized highly sensitive characterization method for 4-substituted anthraquinone derivatives [20], which we used for our study.

Experimental part

Material and methods

All materials purchased from commercial sources and used without purification. Melting points measured in open capillary tubes and uncorrected. The elemental analyses (C, H, N) performed using the Perkin-Elmer 2400 CHN analyzer and were within 0.4% of the theoretical values.

^1H, ^{13}C NMR spectra were recorded at Varian 400 spectrometer operating at 400 MHz frequency for ^1H and 100 MHz for ^{13}C experiments. The peaks were internally referenced to TMS (0.00 ppm) or to the residual undeuterated solvent signal. Peak multiplicities are reported as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, m= multiplet.

The chromatomass spectra were recorded on an Agilent 1100 Series high performance liquid chromatography equipped with a diode matrix with an Agilent LC/MS mass selective detector allowing a fast switching the positive/negative ionization modes. The reaction progress was monitored by the TLC method on Silica gel plates (DC-Fertigfolien ALUGRAM Xtra SILG/UV254, Germany).

Synthesis

General procedure for preparation of 4-substituted-9,10-anthraquinone 14-15, 17-20.

Bromaminic acid (0.01 mol), was dissolved in 40 ml hot water (70-80 °C), amino derivatives (0.01 mol), acid binding agent sodium bicarbonate (0.02 mol), copper sulfate (0.05 g) and ferrous sulfate (0.05 g) catalysts were then added to it. The reaction mixture stirred and heated to 90 °C. Maintained temperature 90 °C for 4 h under stirring. The product salted out by adding sodium chloride, cooled to room temperature, filtered and washed with 10% w/v brine solution.

1-Amino-4-[bis(2-hydroxyethyl)amino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonic acid **14**. Blue solid; yield: 46%, m.p. 295-297 ºC. LC/MS spectrum, m/z: 405,9 $[M+H]^+$; $C_{18}H_{18}N_2O_7S$; Calculated m/z: 407. ^{1}H NMR (400 MHz, DMSO-d6): δ 1.67 (d, 4H, NCH_2), 3.67 (d, J = 4.8 Hz, 4H, OCH_2), 7.49 (br s, 1H, H-3), 7.78 (m, 4H, ArH), 10.14 (s, 1H, OH), 10.79 (br s, 1H, OH); ^{1}H NMR (400 MHz, DMSO-d6 + CCl_4): δ 1.68 (d, 4H, NCH_2), 3.48 (d, 2H, OCH_2), 3.69 (d, 2H, OCH_2), 7.38 (br s, 1H, H-3), 7.74 (d, J = 7.6 Hz, 2H, ArH), 7.85 (m, 2H, ArH), 9.35 (s, 1H, OH), 10.14 (br s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d6): 39.31, 39.5, 39.7 (CH_2); 112.8, 119.51, 120.49, 123.55, 126.22, 129.37, 132.31, 133.19, 133.81, 134.68, 136.37, 137.35 (arom.); 182.00, 184.06 (C=O). Anal. Calcd for $C_{18}H_{18}N_2O_7S$: C, 53.07; H 4.42; N 6.87; S 7.86. Found: C, 53.10; H 4.4; N 6.9; S 7.8.

1-Amino-4-[(2-hydroxyethyl)amino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonic acid **15**. ^{1}H NMR (400 MHz, DMSO-d6): δ 3.49 (d, 2H, CH_2), 3.69 (d, 2H, CH_2), 7.73 (s, 1H, H-3), 7.85 (t, J = 7.7 Hz, 2H, H-6, H-7), 8.25 (d, J = 8 Hz, 2H, H-5, H-8). ^{13}C NMR (100 MHz, DMSO-d6): 45.29 (CH_2); 60.24 (CH_2-OH); 109.38, 109.67, 121.16, 126.19, 126.36, 132.88, 133.03, 134.43, 134.47, 143.5, 143.79, 145.84 (arom.); 181.17, 182.12 (C=O). Anal. Calcd for $C_{18}H_{18}N_2O_7S$: C, 50.78; H 4.0; N 7.29; S 8.04. Found: C, 50.40; H 3.87; N 7.4; S 8.24.

4-[(4-Amino-9,10-dioxo-3-sulfo-9,10-dihydroanthracen-1-yl)-amino]butanoic acid **17**. Blue solid; yield 56%, m.p. 301-303 ºC. LC/MS spectrum: Found, m/z: 405,0 $[M+H]^+$; $C_{18}H_{16}N_2O_7S$; Calculated m/z: 405. ^{1}H NMR (400 MHz, DMSO-d6): δ 1.76 (d, 2H, NCH_2), 1.91 (d, 2H, CH_2), 2.32 (m, 2H, CH_2), 2.79 (s, 2H, OCH_2), 7.04 (s, 1H, H-3), 7.78 (s, 1H, ArH), 8.04 (s, 1H, ArH), 8.13 (s, 1H, ArH), 8.22 (s, 1H, ArH); ^{1}H NMR (400 MHz, DMSO-d6 + CCl_4): δ 1.82 (d, 2H, NCH_2), 1.98 (d, 2H, CH_2), 2.32 (d, 2H, CH_2), 2.83 (d, 2H, CH_2), 7.2 (br s, 1H, H-3), 7.73 (d, 2H, ArH), 8.05 (d, J = 8 Hz, 2H, ArH). ^{13}C NMR (100 MHz, DMSO-d6): 40.14, 42.24, 49.47, 53.22 (CH_2); 108.23, 113.48, 125.18, 125.9, 133.05, 134.73, 140.98, 143.98, 144.34, 145.34, 148.43, 154.95 (arom.); 181.43, 186.69 (C=O). Anal. Calcd for $C_{18}H_{16}N_2O_7S$: C, 53.33; H 3.95; N 6.91; S 7.9. Found: C, 53.3; H 3.9; N 6.9; S 8.1.

1-Amino-4-(1H-imidazol-1-yl)-9,10-dioxo-9,10-dihydroanthracene-2-sulfonic acid **18**. Yellow solid; Recr. from aceton yield 100%, m.p. 255-257 ºC. LC/MS spectrum: Found, m/z: 370,2 $[M+H]^+$; $C_{17}H_{11}N_3O_5S$; Calculated m/z: 370. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.8 (m, J = 8 Hz, 8H, ArH), 9.53 (s, 1H, SO_3H). Anal. Calcd for $C_{17}H_{11}N_3O_5S$: C, 55.13; H 2.97; N 11.35; S 8.65. Found: C, 55.10; H 2.9; N 11.37; S 8.63.

1-Amino-9,10-dioxo-4-(2-oxo-4-sulfanyl-idene-1,3-thiazolidin-3-yl)-9,10-dihydroanthra-cene-2-sulfonic acid **19**. Blue solid; Yield 14.3%, m.p. 285-288 ºC. LC/MS spectrum: Found, m/z: 435,2 $[M+H]^+$; $C_{17}H_{11}N_3O_5S$; Calculated m/z: 434. ^{1}H NMR (400 MHz, DMSO-d6): δ 3.32 (d, 2H, CH_2), 7.26 (s, 1H, H-3), 7.82 (d, J = 7.2 Hz, 2H, H-6, H-7), 8.33 (d, J = 8 Hz, 2H, H-5, H-8). Anal. Calcd for $C_{17}H_{10}N_2O_6S_3$: C, 46.89; S 22.06. Found: C, 46.85; S 22.00.

1-Amino-4-[(pyridin-3-yl)amino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonic acid **20**. Blue solid; Yield 15%, m.p. 250-251 ºC. LC/MS spectrum: Found, m/z: 394,2 $[M+H]^+$; $C_{19}H_{13}N_3O_5S$; Calculated m/z: 395. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.62 (s, 1H, H-3), 7.7 (d, 2H, H-5, H-7), 7.85 (t, J = 6.4 Hz, 3H, ArH), 8.08 (d, J = 6.4 Hz, 2H, H-5, H-8); ^{1}H NMR (400 MHz, DMSO-d6 + CCl_4): δ 7.63 (br s, 1H, H-3), 7.84 (t, J = 6.8 Hz, 2H, H-6, H-7), 7.96 (s, 1H, ArH), 8.00 (s, 1H, ArH), 8.10 (s, 1H, ArH), 8.17 (d, J = 6.8 Hz, 2H, H-5, H-8). ^{13}C NMR (100 MHz, DMSO-d6): 122.58, 124.42, 127.11, 127.40, 131.71, 133.22, 134.83, 135.58, 136.29, 140.89, 152.98, 173.58 (arom.); 180.82, 181.09 (C=O). Anal. Calcd for $C_{19}H_{13}N_3O_5S$: C, 57.73; H 3.29; N 10.63; S 8.1. Found: C, 57.7; H 3.3; N 10.7; S 8.17.

Results and discussion

Substitution with dialkyl amines **6-7** was starting according to the procedure described previously [21]. However, the desirable products were not obtained. In the case of nucleophilic substitution on diethanolamine (7) formed product **15** - 37% on the LC-MS (*m/z* 363.2 $[M+H]^+$). In the case of substitution brom on diethylamine (6), formations of side-product (4) was 28% (*m/z* 302.0 $[M+H]^-$). Then we used the general procedure (experimental data) for nucleophilic substitution in bromaminic acid (**Scheme 3**). In the case of substitution brom of diethanolamine (7), the product **15** was still present in LC-MS (*m/z* 364.0 $[M+H]^+$). The ^{13}C NMR spectra characteristic signals carbon (CH_2-CH_2-OH) was 45.29 and 60.24 ppm; the resonance signals for two carbonyl carbons 1-amino-4-[(2-hydroxyethyl)amino]-9,10-dioxo-9,10-dihydro-anthracene-2-sulfonic acid (15) at δ 181.17 and 182.12 ppm. Ullmann coupling reaction of bromaminic acid with diethylamine (6), leads to the formation product **13** (m/z 347.0 $[M+H]^+$), it was fixed using diode array detection (DAD).

The desired 4-diethanol-substituted product **14**, separated by HPLC. ^{1}H NMR is

present in 8 aliphatic protons of methylene groups in solvents (DMSO-d6) and (DMSO-d6+CCl_4), characteristic shifts of 5 aromatic protons at 7.38-8.24 ppm, respectively.

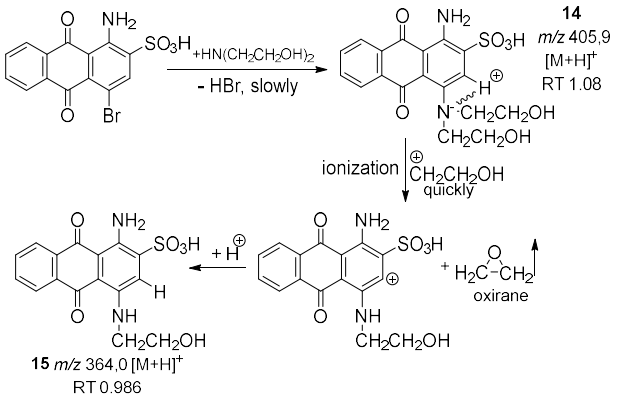
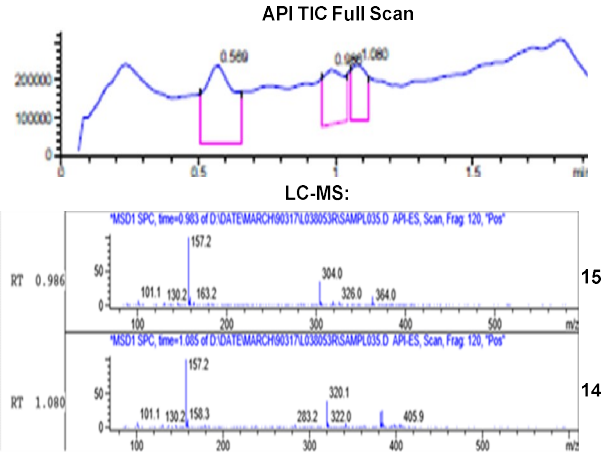


Figure 3. Proposed mechanism

The proposed mechanism for the formation of compound **15** (m/z 364.0 $[M+H]^+$) (**Figure 2**), depicted in the LC-MS spectrum (**Scheme 2**). And explains fragmentation 3-H-proton of the ethylhydroxyl radical which transformed into oxyran.



Scheme 2. Chromatomass-spectra

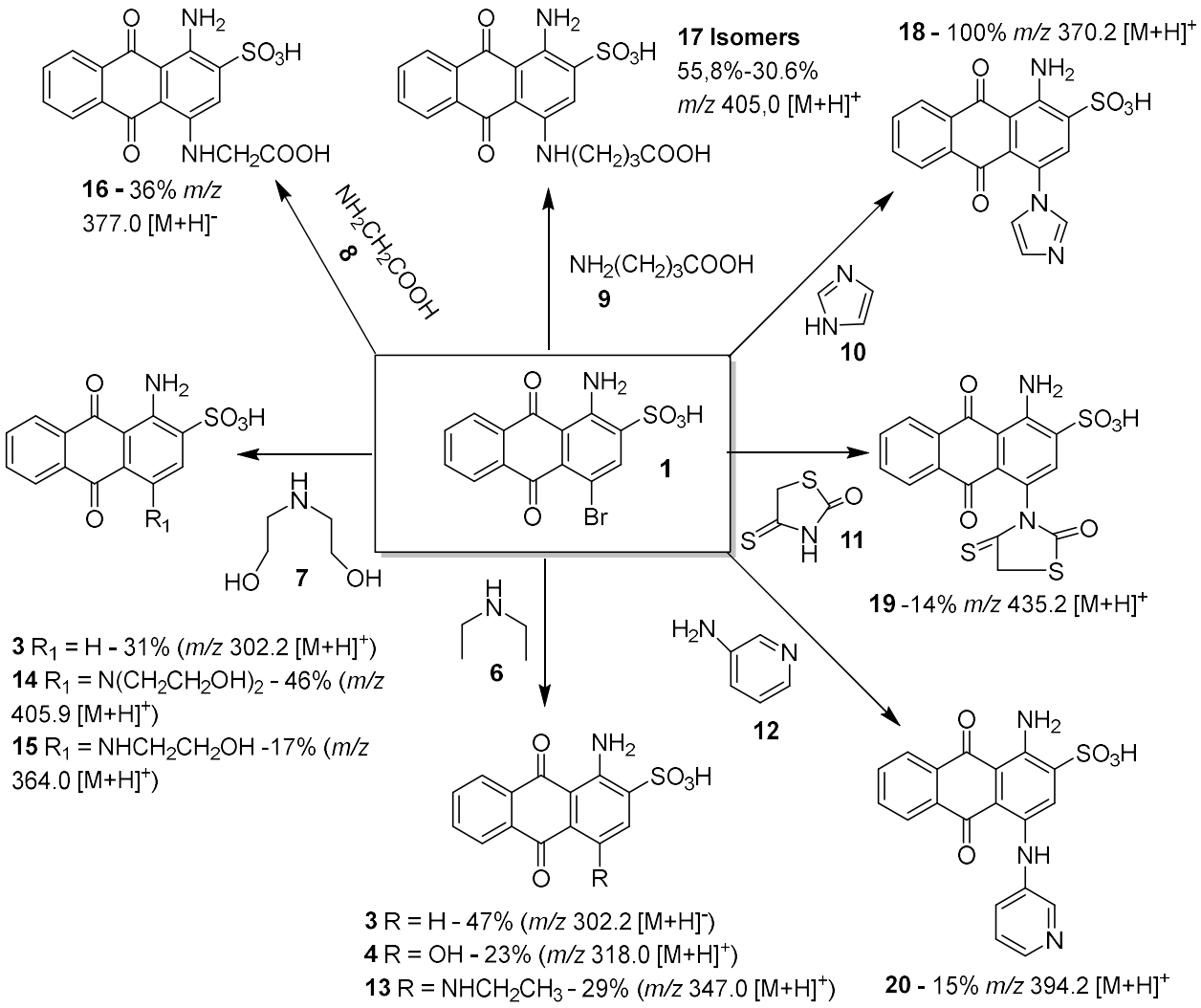
substitution by amino acids

In case substitution brom of glycine **8**, is formation of side-products **4** - 38.9% (*m/z* 318.2 $[M+H]^-$) and **3** was 24.5% (*m/z* 302.0 $[M+H]^-$). The poor yields of product **16** explained by the weak base of aminoacetic acid (8). Reaction of bromaminic acid with amino acid **9**, the formation of isomers **17** (*m/z* 405.0 $[M+H]^+$).

After purification by silica gel flash column chromatography, eluted with ethyl acetate:aceton 1:3 v/v, compound **17** was obtained. The ^1H NMR spectrum in (DMSO-*d6*) there are 6 aliphatic CH_2 methylene protons in the region at 1.76-2.79 ppm. The ^{13}C NMR spectra was characteristic signals carbon methylene groups in the region at 40.14-53.22 ppm.

substitution by heterocyclic amines

The yield of product **18** after recrystallization with acetone was 100% (*m/z* 370.2 $[M+H]^+$). The aromatic protons were visible as a multiplet of δ 7.7-7.8 ppm. In the case of substitution bromaminic acid with 3-aminopyridine (12), the yield of the main product **20** was 14.9% (*m/z* 394.0 $[M+H]^+$) the ^1H NMR spectrum nine aromatic protons appeared in the region of 7.62-8.24 ppm (DMSO-*d6*) and 7.63-8.17 (DMSO-*d6* + CCl_4).



Scheme 3. Synthesis of 4-substituted 9,10-anthraquinonsulfonic acids

The main undesirable product identified in all reactions was 1-amino-4-hydroxy-9,10-dioxo-9,10-dihydroanthracene 2-sulfonate (4, **Scheme 3**) formed by attack of the competing nucleophile hydroxide.

Conclusions

Fragmentation mechanisms of protonated 4-substituted-9,10-anthraquinones and its derivatives investigated by atmospheric pressure ionization with mass spectrometry (MS). The major fragmentation pathways were loss of the hydroxyethyl group (*CH_2CH_2OH) or ethyl group (*CH_2CH_3) from fourth position of the **C** ring. Determined LC/MS that as a result of nucleophilic substitution of brom on γ-aminobutyric acid, the final products are the isomers of compound **17**.

Acknowledgements

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