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Reactions of 1-Acylamino- and 1-Methylsulfonylamino-2-aryloxy-4-hydroxy-9,10-anthraquinones with Secondary Amines

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Abstract—Reactions of 1-acylamino-4-hydroxy-2-phenoxy-9,10-anthraquinones with piperidine resulted in replacement of the phenoxy group by piperidino, while 1-methylsulfonyl-2-aryloxy-4-hydroxy-9,10-anthraquinones reacted with secondary amines to give products of nucleophilic substitution of hydrogen in position *3*.

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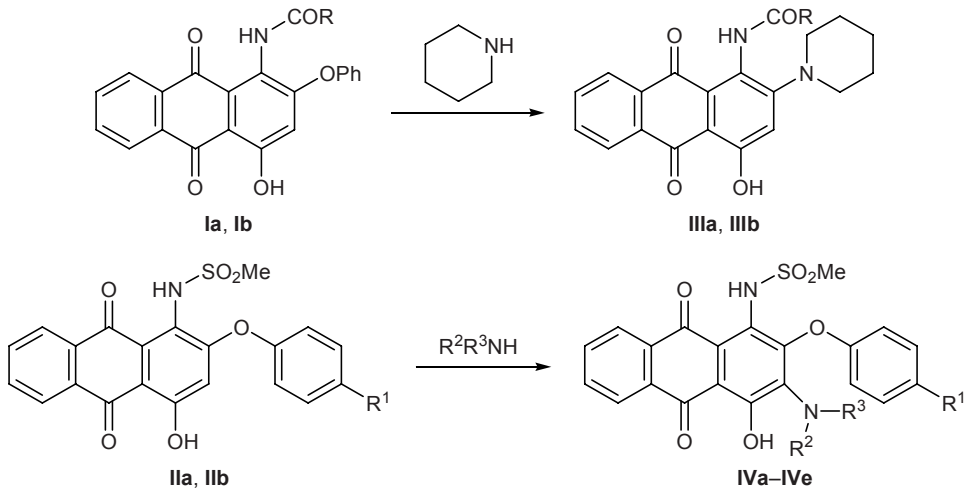
It is known that 1,4-dihydroxy-9,10-anthraquinone reacts with aliphatic amines at room temperature to give the corresponding 2-amino-1,4-dihydroxy-9,10-anthraquinones [1]. 1-Amino-4-hydroxy-9,10-anthraquinone reacts with strongly nucleophilic amines (such as piperidine and morpholine) only on prolonged heating at 80°C in excess reagent [2]; the reaction is not selective, and products of hydrogen substitution in positions *2* and *3* are formed. 1-Acetylamino-4-hydroxy-9,10-anthraquinone reacts with piperidine in a more selective fashion, yielding 1-acetylamino-3-piperidino-4-hydroxy-9,10-anthraquinone [2]. It was interesting to examine analogous amination reactions of 1-amino-4-hydroxy-9,10-anthraquinone derivatives having various acyl groups on the nitrogen atom and nucleofugal substituents in the 2-position.

In the present work we studied the behavior of 1-acylamino-2-aryloxy-4-hydroxy-9,10-anthraquinones **Ia** and **Ib** and 2-aryloxy-4-hydroxy-1-methylsulfonylamino-9,10-anthraquinones **IIa** and **IIb** in reaction

Scheme 1.



I, **III**, R = Me (**a**), Ph (**b**); **II**, **IV**, R^1 = H (**a**, **c**–**e**), *t*-Bu (**b**); **IV**, R^2R^3N = piperidino (**a**, **b**), pyrrolidin-1-yl (**c**), morpholino (**d**); R^2 = Me, R^3 = $HO(CH_2)_2$ (**e**).

with secondary amines. The amination of amides **Ia**, **Ib**, **IIa**, and **IIb** was carried out in DMF at 55–95°C. When the reaction was complete, the mixture was treated with a small amount of water, and the products (compounds **IIIa**, **IIIb**, and **IVa**–**IVe**; Scheme 1) were isolated by fractional crystallization and were then purified by recrystallization.

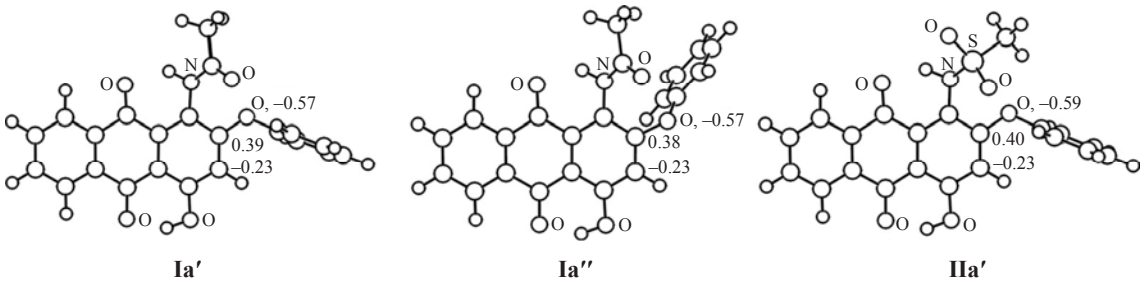
Analysis of the ^{1}H NMR and mass spectra of compounds **III** and **IV** indicates that the amination of acylamines **Ia** and **Ib** involves replacement of the phenoxy group in position *2* and that sulfonamides **IIa**–**IIe** react via replacement of hydrogen on C^3. The observed difference in the directions of nucleophilic attack on substrates **I** and **II** is difficult to explain taking into consideration only different electron-withdrawing properties of the acetyl (benzoyl) and methylsulfonyl groups. In fact, anthraquinones **Ia** and **IIa** are characterized by the same position of the long-wave absorption maximum in the electronic spectra (λ_{max} 436 nm). Similar blue shifts ($\Delta\lambda$ = 115 nm) in going from 1-amino-4-hydroxy-2-phenoxy-9,10-anthraquinone to compounds **Ia** and **IIa** suggest similar electronic effects of the acetyl and methylsulfonyl groups. Also, the chemical shifts of the 3-H proton in **Ia** and **IIa** differ only slightly (δ 6.50 and 6.55 ppm, respectively).

Quantum-chemical calculations performed at the B3LYP/6-31G(*d*) level of theory [3, 4] using Gaussian-98 software package [5] confirmed the above stated. The calculated charges on C^2 and C^3, as well as on the oxygen atom in the phenoxy group, in molecules **Ia** and **IIa** almost coincide in pairs (see figure). Figure shows the structures of two most thermodynamically favorable conformers of compound **Ia** (**Ia′** and **Ia″**), differing by orientation of the phenyl group. The calculated (B3LYP) Gibbs energy of conformer **Ia″** is higher by only 12.55 kJ/mol than that of **Ia′**. The phenyl group in molecule **IIa** cannot adopt orientation analogous to structure **Ia″** because of the presence of a bulky tetrahedral methylsulfonyl group. Therefore, the difference in the directions of amination of anthraquinones **I** and **II** may be explained as follows. The substitution of aryloxy group by amino is most likely to follow S_NAr mechanism. In the case of conformers **Ia′** and **IIa′**, nucleophile approach to the reaction center (carbon atom linked to the phenoxy group) is considerably hindered. Compounds **I** can undergo amination at the 2-position through conformer **Ia″**, whereas amination of **II** can occur only with conformer **IIa′** in which nucleophilic attack at the 2-position is strongly hindered for steric reasons. As a result, nucleophile attacks spatially more accessible carbon atom in position *3*.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DRX spectrometer (500 MHz) using DMSO-d_6 as solvent as tetramethylsilane as internal reference. The melting points were measured on a Boetius melting point apparatus. The molecular weights were determined from the mass spectra which were obtained on a Finnigan MAT-8200 spectrometer. The progress of reactions and the purity of products were monitored by TLC on Silufol plates using toluene–acetone (10:1) as eluent.

***N*-(4-Hydroxy-9,10-dioxo-2-phenoxy-9,10-dihydroanthracen-1-yl)benzamide (Ib).** A mixture of 1 g (3.06 mmol) of 1-amino-4-hydroxy-2-phenoxy-9,10-anthraquinone, 5 ml of toluene, and 0.5 ml of benzoyl chloride was stirred for 60 min at 100°C. After cooling, the precipitate was filtered off, washed with ethanol, and recrystallized from toluene. Yield 1.18 g (88%), mp 204–205°C. ^{1}H NMR spectrum, δ, ppm (hereinafter, primed locants refer to the benzoyl group): 6.51 s (1H, 3-H), 7.2 d (2H, *o*-H, J = 2.6 Hz), 7.30 t (1H, *p*-H, J = 2.5 Hz), 7.49 t (2H, *m*-H, J = 3.1 Hz), 7.56 t (2H, *m′*-H, J = 3.1 Hz), 7.63 t (1H,



Structures of the most thermodynamically favorable conformers of *N*-(4-hydroxy-9,10-dioxo-2-phenoxy-9,10-dihydroanthracen-1-yl)-acetamide (**Ib**) and *N*-(4-hydroxy-9,10-dioxo-2-phenoxy-9,10-dihydroanthracen-1-yl)methanesulfonamide (**IIa**), calculated by the B3LYP/6-31G(*d*) method; given are Mulliken charges on the C^2, C^3, and 2-O atoms.

p′-H, *J* = 2.5 Hz), 7.94 m (2H, 6-H, 7-H), 8.03 d (2H, *o*′-H, *J* = 3.2 Hz), 8.13 m (1H, 5-H or 8-H), 8.24 m (1H, 8-H or 5-H), 10.30 s (1H, NH), 13.30 s (1H, OH). Found, %: C 74.28; H 3.89; N 3.22. $C_{27}H_{17}N_1O_5$. Calculated, %: C 74.48; H 3.91; N 3.22.

***N*-(4-Hydroxy-9,10-dioxo-2-piperidino-9,10-dihydroanthracen-1-yl)acetamide (IIIa).** A mixture of 0.50 g (1.36 mmol) of amide **Ia**, 5 ml of DMF, and 1 ml of piperidine was stirred for 7 h at 70°C, 1 ml of water was added dropwise under stirring to the hot solution, the mixture was cooled to 18°C, and the precipitate was filtered off, washed with aqueous ethanol (1:1), water, and ethanol, dried, and recrystallized from toluene. Yield 0.31 g (62%), mp 95–97°C. ^{1}H NMR spectrum, δ, ppm: 1.60 s (6H, CH_2), 2.10 s (3H, CH_3), 3.01 m (4H, NCH_2), 6.53 s (1H, 3-H), 7.89 m (2H, 6-H, 7-H), 8.09 m (1H, 8-H or 5-H), 8.17 m (1H, 5-H or 8-H), 9.40 s (1H, NH). Found, %: C 69.33; H 5.51; N 7.45. $C_{21}H_{20}N_2O_4$. Calculated, %: C 69.23; H 5.49; N 7.69.

***N*-(4-Hydroxy-9,10-dioxo-2-piperidino-9,10-dihydroanthracen-1-yl)benzamide (IIIb).** A mixture of 1 g (2.33 mmol) of amide **Ib**, 6 ml of DMF, and 1 ml of piperidine was stirred for 15 h at 110°C, 1 ml of water was added dropwise under stirring to the hot solution, the mixture was cooled to 18°C, and the precipitate was filtered off, washed with aqueous ethanol (1:1), water, and ethanol, dried, and recrystallized from toluene. Yield 0.73 g (75%), mp 100–102°C. ^{1}H NMR spectrum, δ, ppm: 1.50 s (6H, CH_2), 3.30 m (4H, NCH_2), 6.82 s (1H, 3-H), 7.59 t (2H, *m*′-H), 7.61 t (1H, *p*′-H), 7.89 t (1H, 7-H or 6-H), 7.92 t (1H, 6-H or 7-H), 8.05 m (3H, 5-H or 8-H, *o*′-H), 8.20 d (1H, 8-H or 5-H), 10.11 s (1H, NH), 13.50 s (1H, OH). Mass spectrum: *m*/*z* 426 $[M]^+$. Found, %: C 73.24; H 5.39; N 6.66. $C_{26}H_{23}N_2O_4$. Calculated, %: C 73.23; H 5.39; N 6.57.

***N*-(4-Hydroxy-9,10-dioxo-2-phenoxy-3-piperidino-9,10-dihydroanthracen-1-yl)methanesulfonamide (IVa).** A solution of 1 g (2.48 mmol) of sulfonamide **IIa** in 7 ml of a 2:1 DMF–piperidine mixture was stirred for 6 h at 60°C, 1.5 ml of water was added dropwise under stirring to the hot solution, and the mixture was cooled to 18°C. The precipitate was filtered off, washed with ethanol, dried, and recrystallized twice from DMF–water (5:1). Yield 0.66 g (55%), mp 205–207°C. ^{1}H NMR spectrum, δ, ppm: 1.4 s (6H, CH_2), 3.00 m (7H, CH_3, NCH_2), 6.88 d (2H, *o*-H), 7.08 t (1H, *p*-H), 7.28 t (2H, *m*-H), 7.95 m (2H, 6-H, 7-H), 8.24 d (1H, 5-H or 8-H), 8.26 d (1H, 5-H or 8-H), 11.10 s (1H, NH), 14.20 br.s (1H, OH). Mass spectrum: *m*/*z* 492 $[M]^+$. Found, %: C 63.51; H 4.88; N 5.52; S 6.14. $C_{26}H_{24}N_2O_6S$. Calculated, %: C 63.41; H 4.88; N 5.69; S 6.50.

***N*-[2-(4-*tert*-Butylphenoxy)-4-hydroxy-9,10-dioxo-3-piperidino-9,10-dihydroanthracen-1-yl]methanesulfonamide (IVb)** was synthesized in a similar way from 0.5 g (1.09 mmol) of compound **IIb**. Yield 0.32 g (55%), mp 216–218°C. ^{1}H NMR spectrum, δ, ppm: 1.4 s (6H, CH_2), 1.6 s [9H, $C(CH_3)_3$], 3.00 m (5H, CH_3, NCH_2), 6.88 d (2H, *o*-H), 7.28 d (2H, *m*-H), 7.95 m (2H, 6-H, 7-H), 8.24 d (1H, 5-H or 8-H), 8.26 d (1H, 8-H or 5-H), 11.10 s (1H, NH), 14.18 br.s (1H, OH). Found, %: C 65.23; H 5.66; N 4.49. $C_{30}H_{32}N_2O_6S$. Calculated, %: C 65.69; H 5.84; N 5.11.

***N*-[4-Hydroxy-9,10-dioxo-2-phenoxy-3-(pyrrolidin-1-yl)-9,10-dihydroanthracen-1-yl]methanesulfonamide (IVc).** Compound **IIa**, 1.1 g (2.72 mmol), was added to 4.5 ml of pyrrolidine, the mixture was stirred for 3 h at 40–45°C, 2 ml of DMF was then added, the mixture was heated to 60°C, 0.5 ml of water was added dropwise under stirring, and the mixture was cooled to 15°C. The precipitate was filtered off, washed with alcohol, and recrystallized from DMF–water (10:1). Yield 0.71 g (55%), mp 234–236°C. ^{1}H NMR spectrum, δ, ppm: 1.6 s (4H, CH_2), 3.50 m (7H, CH_3, NCH_2), 6.88 d (2H, *o*-H), 7.08 t (1H, *p*-H), 7.28 t (2H, *m*-H), 7.95 m (2H, 6-H, 7-H), 8.24 d (1H, 5-H or 8-H), 8.26 d (1H, 8-H or 5-H), 11.30 br.s (1H, NH), 14.60 br.s (1H, OH). Mass spectrum: *m*/*z* 478 $[M]^+$. Found, %: C 62.47; H 4.67; N 5.93; S 6.31. $C_{25}H_{22}N_2O_6S$. Calculated, %: C 62.76; H 4.60; N 5.86; S 6.69.

***N*-(4-Hydroxy-3-morpholino-9,10-dioxo-2-phenoxy-9,10-dihydroanthracen-1-yl)methanesulfonamide (IVd).** A solution of 1 g (2.48 mmol) of sulfonamide **IIa** in 10 ml of DMF–morpholine (1:1) was stirred for 20 h at 80°C, 1.5 ml of water was added dropwise under stirring to the hot solution, and the mixture was cooled to 18°C. The precipitate was filtered off, washed with ethanol, dried, and recrystallized twice from DMF–water (5:1). Yield 0.61 g (50%), mp 235–237°C. ^{1}H NMR spectrum, δ, ppm: 3.10 t (4H, OCH_2), 3.41 m (7H, CH_3, NCH_2), 6.92 d (2H, *o*-H), 7.12 t (1H, *p*-H), 7.36 t (2H, *m*-H), 7.96 m (2H, 6-H, 7-H), 8.24 d (1H, 5-H or 8-H), 8.26 d (1H, 8-H or 5-H), 11.00 br.s (1H, NH), 14.10 br.s (1H, OH). Found, %: C 60.97; H 4.57; N 5.90. $C_{25}H_{22}N_2O_7S$. Calculated, %: C 60.72; H 4.45; N 5.67.

***N*-{4-Hydroxy-3-[(2-hydroxyethyl)(methyl)-amino]-9,10-dioxo-2-phenoxy-9,10-dihydroanthra-**

cen-1-yl}methanesulfonamide (IVe) was synthesized in a similar way from 0.86 g (2.13 mmol) of compound **IIa** and 2-(methylamino)ethanol. Yield 0.63 g (64%), mp 190–192°C. ^{1}H NMR spectrum, δ, ppm: 3.41–3.11 m (10H, CH_3, CH_2), 4.45 s (1H, OH), 6.90 d (2H, *o*-H), 7.10 t (1H, *p*-H), 7.34 t (2H, *m*-H), 7.96 m (2H, 6-H, 7-H), 8.24 d (1H, 5-H or 8-H), 8.26 d (1H, 8-H or 5-H), 11.10 br.s (1H, NH), 14.20 br.s (1H, 4-OH). Mass spectrum: *m*/*z* 482 $[M]^+$. Found, %: C 60.20; H 4.70; N 5.74; S 6.31. $C_{24}H_{22}N_2O_7S$. Calculated, %: C 59.75; H 4.76; N 5.81; S 6.64.

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