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Dedicated to Full Member of the Russian Academy of Sciences B.A. Trofimov on his 70th anniversary

Specificity of the Cyclization of 1-Alkyl(aryl)sulfonylamino-9,10-anthraquinones into Naphtho[1,2,3-*cd*]indol-6(2*H*)-ones

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Abstract—Cyclization of *N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)methanesulfonamides to 2,6-dihydronaphtho[1,2,3-*cd*]indol-6-ones in DMSO–KOH involves intermediate formation of 2,3-dihydroanthra[1,9-*cd*][1λ^6,2]thiazin-7-one 2,2-dioxides, whereas heterocyclization of *N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)-ethane- and -arenesulfonamides under analogous conditions occurs with participation of methylsulfonylmethanide.

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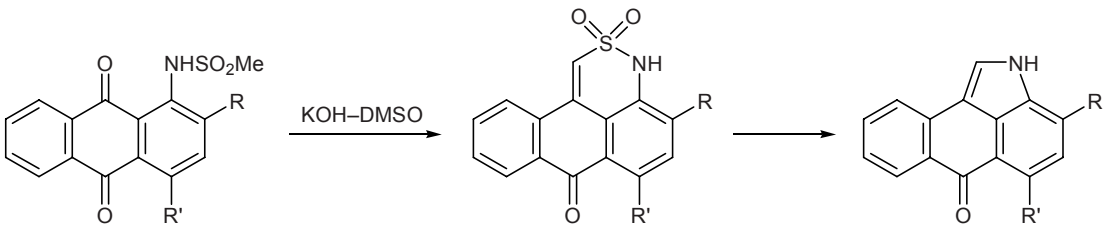
We previously [1] proposed a simple procedure for the synthesis of naphtho[1,2,3-*cd*]indol-6(2*H*)-ones **II** via cyclization of *N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)methanesulfonamides **I** in DMSO in the presence of potassium hydroxide. It was presumed that the cyclization **I** → **II** involves intermediate formation of 2,3-dihydroanthra[1,9-*cd*][1λ^6,2]thiazin-7-one 2,2-dioxides **IIIa**–**IIIc** (Scheme 1). The goal of the present work was to determine the scope of that cyclization and its mechanism. For this purpose, we examined transformations of compounds **I** having different substituents in the sulfonyl fragment under different conditions.

Unfortunately, we failed to obtain a wide series of 1-alkylsulfonylamino-9,10-anthraquinones because of low nucleophilicity of aminoanthraquinones. When reactions of 1-amino-9,10-anthraquinones with alkanesulfonyl chlorides were carried out under severe conditions (heating of the amine in excess butane- or phenylmethanesulfonyl chloride) decomposition of the reagents or products occurred. We succeeded in isolating only *N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)ethanesulfonamide (**Id**). Another synthetic approach to 1-R-sulfonylamino-9,10-anthraquinones is based on the reaction of sulfonamides with 1-halo-9,10-anthraquinones. However, it was successful only with arenesulfonamides. Therefore, we examined in detail the behavior of previously [1] synthesized *N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)methanesulfonamides **Ib** and **Ic**, as well as of newly prepared *N*-((9,10-dioxo-9,10-dihydroanthracen-1-yl)ethanesulfonamide (**Id**) in DMSO in the presence of bases.

We found that sulfonamides **Ib** and **Ic** in the system DMSO–KOH were converted into sultams **IIIb** and **IIIc** (Scheme 1) which were isolated and characterized by spectral and analytical data. Surprisingly, by

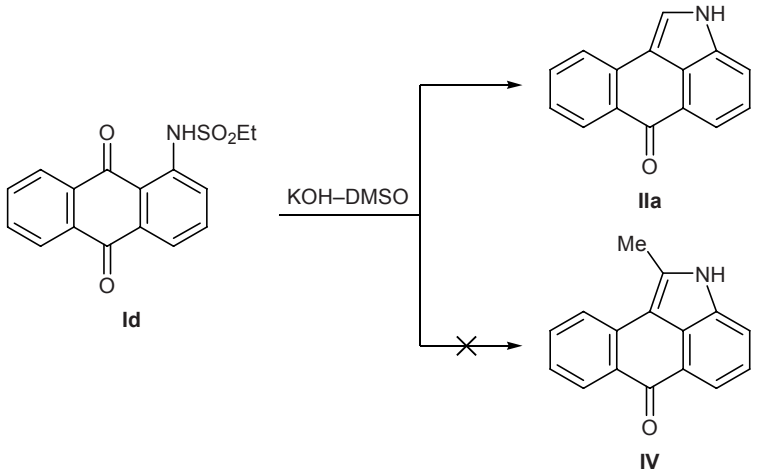
Scheme 1.



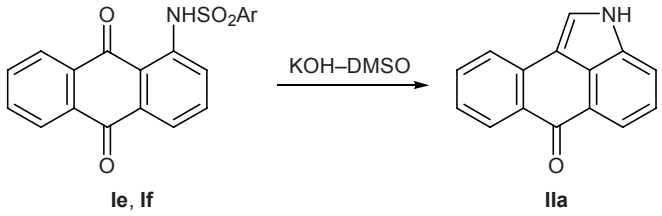
Ia–Ic **IIIa–IIIc** **IIa–IIc**

R = H (**a**), PhO (**b**), 4-MeC$_6$H$_4$O (**c**); R′ = H (**a**), HO (**b**, **c**).

Scheme 2.



Scheme 3.



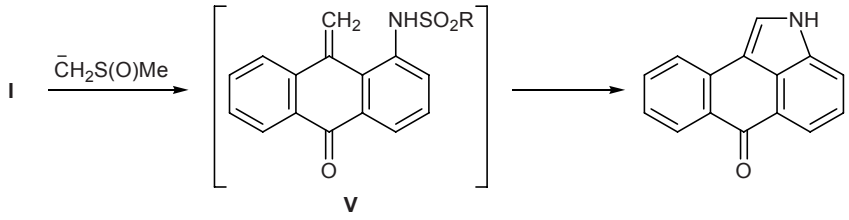
Ar = Ph (**e**), 4-MeC_6H_4 (**f**).

heating ethanesulfonamide **Id** in DMSO in the presence of KOH at 100–110°C we obtained naphthoindole **IIa** rather than expected 1-methylnaphtho[1,2,3-*cd*]-indol-6(2*H*)-one (**IV**) (Scheme 2). Moreover, under analogous conditions *N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)arenesulfonamides **Ie** and **If** were also converted into compound **IIa** (Scheme 3).

Presumably, the pyrrole ring is formed in the above reactions with participation of DMSO molecule. This assumption was confirmed by special experiment: heterocyclization of sulfonamide **Id** was carried out using ^{13}C-labeled dimethyl sulfoxide. The molecular weight of the product obtained in ^{13}C-DMSO was 220 a.m.u. (according to the MS data) against 219 for compound **IIa** isolated from unlabeled DMSO. On the other hand, the mass spectra of samples of **IIb** obtained in ^{13}C-DMSO and ^{12}C-DMSO were identical (*m*/*z* 327 $[M]^+$).

Obviously, the cyclization of *N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)methanesulfonamides **Ia**–**Ic** to naphtho[1,2,3-*cd*]indol-6(2*H*)-ones **IIa**–**IIc** follows the path proposed previously (**I** → **III** → **II**), while the transformation of analogous ethyl- and arylsulfonyl derivatives involves nucleophilic attack by the dimethyl sulfoxide anion with subsequent cyclization of intermediate methylene quinone **V** (Scheme 4). This mechanism is consistent with published data on the reactions of some ketones with a s suspension of KOH in DMSO, which leads to allyl alcohols [2]. The key stage in the reductive methylenation of ketones is addi-

Scheme 4.



R = Et, Ar.

tion of methylsulfonylmethanide at the carbonyl carbon atom [3].

Presumably, intramolecular hydrogen bonding in sulfonamides **I** favors enhanced electrophilicity of the neighboring carbonyl group. For example, the same factor was assumed to be responsible for the amination of 1-hydroxy-9,10-anthraquinones with ammonia to 1-hydroxy-9-imino derivatives [4]. The proposed heterocyclization path is likely to be possible for other 1-amino-9,10-anthraquinone derivatives.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DRX spectrometer (500 MHz) from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The mass spectra were obtained on Finnigan MAT-8200 and Hewlett–Packard G1800A (GC–MS) instruments. The melting points were measured on a Boetius hot stage. The progress of reactions and the purity of products were monitored by TLC on Silufol plates using toluene–acetone (10 : 1) as eluent. Labeled dimethyl sulfoxide containing 99% of ^{13}C isotope (Isotec) was used.

Cyclization of 1-alkyl(aryl)sulfonylamino-9,10-anthraquinones Id–If into naphtho[1,2,3-*cd*]indol-6(2*H*)-one (IIa). Sulfonamide **Id–If**, 1.70 mmol, was dissolved in 10 ml of DMSO, 0.5 g (8.90 mmol) of finely powdered potassium hydroxide was added, and the mixture was stirred for 2 h at 100–110°C, cooled to 20°C, and poured into a mixture of 200 g of crushed ice and 10 ml of 36% hydrochloric acid. The precipitate was filtered off, dried, and twice recrystallized from toluene. Yield 68% (from **Id**), 60–62% (from **Ie** and **If**), mp 255–257°C. ^{1}H NMR spectrum, δ, ppm: 12.00 s (1H, NH), 8.45 br.s (1H), 8.32 d (1H, J = 7.8 Hz), 8.12 d (1H, J = 7.8 Hz), 7.97 d (1H, J = 7.5 Hz), 7.88 d (1H, J = 7.5 Hz), 7.70 br.t (1H, J = 7.0 Hz), 7.52 br.t (1H, J = 7.5 Hz), 7.42 br.t (1H, J = 7.0 Hz). Mass spectrum, m/z (I_{rel}, %): 219 (100) $[M]^+$, 190 (8.3) $[M - HCN - H_2]^+$, 163 (23.3) $[M - HCN - CO]^+$, 95 (10.0), 82 (13.3). Found, %: C 82.17; H 4.14; N 6.38. $C_{15}H_9NO$. Calculated, %: C 82.19; H 4.14; N 6.39. M 219.23.

4-Aryloxy-2,3-dihydroanthra[1,9-*cd*][1λ^6,2]thiazin-7-one 2,2-dioxides IIIb and IIIc (*general procedure*). Finely powdered potassium hydroxide, 0.25 g (4.45 mmol), was added to a solution of 1.70 mmol of sulfonamide **Ib** or **Ic** in 10 ml of DMSO, and the mixture was stirred for 8 h at 85°C and poured into 200 ml of 5% hydrochloric acid cooled to 0–5°C. The precipitate was filtered off, dried, and thrice recrystallized from toluene.

6-Hydroxy-4-phenoxy-2,3-dihydroanthra-[1,9-*cd*][1λ^6,2]thiazin-7-one 2,2-dioxide (IIIb). Yield 0.31 g (47%), mp 295–297°C. ^{1}H NMR spectrum, δ, ppm: 13.52 s (1H, OH), 12.01 br.s (1H, NH), 8.51 m (2H, 1-H, 7-H or 10-H), 8.34 d (1H, 10-H or 7-H), 7.91 t (1H, 9-H or 8-H), 7.80 t (1H, 8-H or 9-H), 7.55 t (2H), 7.38 t (1H), 7.35 d (2H), 6.44 s (1H, 5-H). Mass spectrum: m/z 391 $[M]^+$. Found, %: C 64.37; H 3.39; N 3.47; S 8.26. $C_{21}H_{13}NO_5S$. Calculated, %: C 64.45; H 3.25; N 3.58; S 8.18. M 391.40.

6-Hydroxy-4-(4-methylphenoxy)-2,3-dihydroanthra[1,9-*cd*][1λ^6,2]thiazin-7-one 2,2-dioxide (IIIc). Yield 0.30 g (45%), mp 289–291°C. ^{1}H NMR spectrum, δ, ppm: 13.51 s (1H, OH), 12.01 br.s (1H, NH), 8.45 m (2H, 1-H, 7-H or 10-H), 8.05 d (1H, 10-H or 7-H), 7.78 t (1H, 9-H or 8-H, J = 7.2 Hz), 7.71 t (1H, 8-H or 9-H, J = 7.2 Hz), 7.25 m (2H), 7.05 m (2H), 6.49 s (1H), 2.42 s (3H, Me). Mass spectrum: m/z 405 $[M]^+$. Found, %: C 64.71; H 3.74; N 3.49; S 7.54. $C_{22}H_{15}NO_5S$. Calculated, %: C 65.18; H 3.70; N 3.45; S 7.90. M 405.42.

***N*-(9,10-Dioxo-9,10-dihydroanthracen-1-yl)-ethanesulfonamide (Id).** Ethanesulfonyl chloride, 1 ml, was added to a solution of 0.5 g (2.23 mmol) of 1-amino-9,10-anthraquinone in 5 ml of nitrobenzene. The mixture was stirred for 28 h at 100°C and cooled to 15°C, and the precipitate was filtered off, washed with alcohol, and recrystallized from 1,4-dioxane. Yield 2.45 g (78%), mp 187–188°C. ^{1}H NMR spectrum, δ, ppm: 11.90 s (1H, NH), 8.25–8.34 m (2H), 7.92–8.02 m (5H), 3.2 d (2H, CH_2), 1.49 d (3H, CH_3). Found, %: C 61.02; H 4.12; N 4.57. $C_{16}H_{13}NO_4S$. Calculated, %: C 60.95; H 4.13; N 4.44.

Cyclization of *N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)ethanesulfonamide (Id) into naphtho-[1,2,3-*cd*]indol-6(2*H*)-one (IIa) in ^{13}C-labeled DMSO. Sulfonamide **Id**, 0.02 g (6.35 μmol), was mixed with 0.1 ml of ^{13}C-DMSO and 0.02 g (0.036 mmol) of KOH, and the mixture was stirred for 2 h at 100–110°C. The mixture was cooled, neutralized with 1.5 ml of 10% hydrochloric acid, and treated with methylene chloride (2×2 ml). The extract was subjected to preparative thin-layer chromatography on a Silufol plate (width 20 cm) using toluene–acetone (10 : 1) as eluent. The product was extracted from the sorbent into diethyl ether, and the solution was concentrated and analyzed by gas chromatography–mass spectrometry. Mass spectrum, m/z (I_{rel}, %): 220 (100)

$[M]^+$, 191 (8.3) $[M - HCN - H_2]^+$, 164 (23.3) $[M - HCN - CO]^+$, 96 (10.0), 82 (13.3).

Cyclization of *N*-(4-hydroxy-9,10-dioxo-2-phenoxy-9,10-dihydroanthracen-1-yl)methanesulfonamide (Ib) into 5-hydroxy-3-phenoxynaphtho-[1,2,3-*cd*]indol-6(2*H*)-one (IIb) in ^{13}C-labeled DMSO. A mixture of 0.04 g (0.1 mmol) of sulfonamide **Ib**, 0.2 ml of ^{13}C-DMSO, and 0.04 g (0.072 mmol) of KOH was stirred for 2 h at 100–110°C. The mixture was cooled, neutralized with 1.5 ml of 10% hydrochloric acid, and extracted with methylene chloride (2×2 ml). The extract was subjected to preparative thin-layer chromatography on a Silufol plate (width 20 cm) using toluene–acetone (10:1) as eluent. The product was extracted from the sorbent into diethyl ether, and the solvent was distilled off. Mass spectrum: *m*/*z* 327 $[M]^+$ (cf. [1]).

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