Alkylation of 2,3,6,11-tetrahydroanthra[2,1-*d*]isothiazole-3,6,11-trione and its S-oxide*

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The reactions of 2,3,6,11-tetrahydroanthra[2,1-*d*]isothiazole-3,6,11-trione with dimethyl sulfate, benzyl chloride, and allyl bromide afforded the corresponding 2-alkyl-2,3,6,11-tetrahydroanthra[2,1-*d*]isothiazole-3,6,11-triones and 3-(alkoxy)-6,11-dihydroanthra[2,1-*d*]isothiazole-6,11-diones. The reactions of 2,3,6,11-tetrahydroanthra[2,1-*d*]isothiazole-3,6,11-trione and its S-oxide with a formaldehyde—secondary amine system yielded 2-[(alkylamino)methyl]-2,3,6,11-tetrahydroanthra[2,1-*d*]isothiazole-3,6,11-triones and 2-[(alkylamino)methyl]-3,6,11-trioxo-2,3,6,11-tetrahydroanthra[2,1-*d*]isothiazole 1-oxides, respectively.

Key words: 2,3,6,11-tetrahydroanthra[2,1-*d*]isothiazole-3,6,11-trione, 3,6,11-trioxo-2,3,6,11-tetrahydroanthra[2,1-*d*]isothiazole 1-oxide, alkylation, aminomethylation.

Recently, we have reported[1] on the first synthesis of linear and angular 3,6,11-trioxoanthraisothiazoles based on intramolecular cyclization of *ortho*-(alkylthio)anthraquinonecarboxamides under the action of halogenating agents.

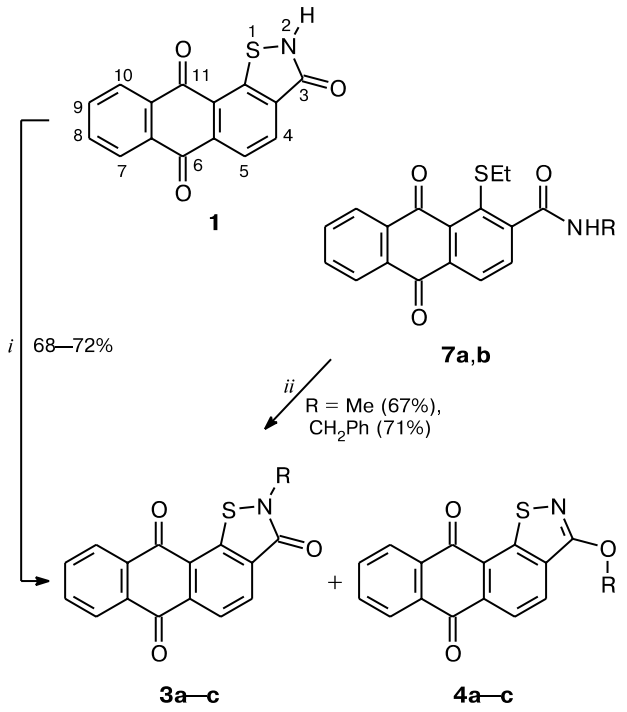
In the present study, we describe for the first time the synthesis of angular anthraquinonoisothiazoles by the reactions of nitrogen-unsubstituted 2,3,6,11-tetrahydroanthra[2,1-*d*]isothiazole-3,6,11-trione (**1**) and its S-oxide (**2**) with alkylating and aminoalkylating agents.

Results and Discussion

We found that isothiazolone **1** reacted with dimethyl sulfate, benzyl chloride, and allyl bromide in the presence of potassium carbonate to form mixtures of N- and O-alkylation products (**3a—c** and **4a—c**, respectively) (Scheme 1). It is advantageous to carry out the reaction in dimethylformamide in the presence of catalytic amounts of KI. Under these conditions, alkylation products **3a—c** and **4a—c** were obtained in 68—72% total yields. Products **3** and **4** were isolated from the mixtures by column chromatography.

In all cases, compounds **4a—c** were obtained as the major reaction products, but their proportion decreased

Scheme 1



R = Me (**a**), CH_2Ph (**b**), $CH_2CH{=}HC_2$ (**c**)

Reagents and conditions: *i*) Me_2SO_4 ($PhCH_2Cl$, $CH_2{=}CHCH_2Br$), K_2CO_3, KI, DMF, 45—50 °C; *ii*) SO_2Cl_2, CH_2Cl_2 (anhydrous).

* Dedicated to Academician I. P. Beletskaya on the occasion of her anniversary.

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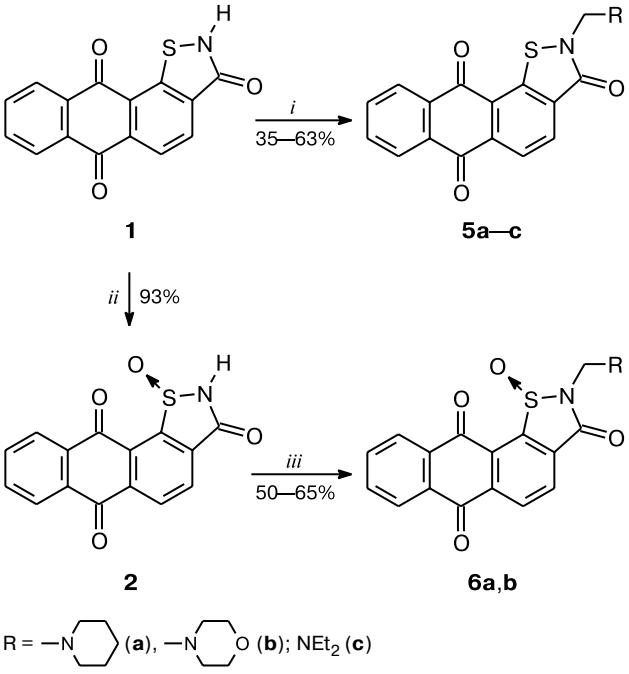
in the series dimethyl sulfate > benzyl chloride > allyl bromide.

Alkylating agent	Me_2SO_4	$PhCH_2Cl$	$CH_2{=}CHCH_2Br$
Products	**3a** : **4a**	**3b** : **4b**	**3c** : **4c**
Ratio	1 : 3	1 : 1.4	1 : 1.2

The predominance of O-alkylation products has been observed earlier in the reactions of benzoannelated isothiazolones with alkylating agents.[2] Compounds **4a—c** are the first representatives of angular anthraquinonoisothiazoles devoid of the oxo group at position 3 of the heterocycle.

Unlike alkylation, aminomethylation of isothiazolone **1** with a mixture of formaldehyde and secondary amine in DMSO proceeded regioselectively to produce *N*-aminomethyl derivatives **5a—c** (Scheme 2). This reaction pathway is typical of aminomethylation of cyclic amides[3] and imides[4] as well as of aminomethylation of isothiazolones.[5,6] Isothiazolone S-oxide **2**, which was prepared by oxidation of isothiazolone **1** with chlorine in wet CH_2Cl_2,[7] reacted with a formaldehyde—secondary amine system to yield aminomethylation products **6a**,**b**.

Scheme 2



Reagents and conditions: *i*) $HNEt_2$ (piperidine, morpholine), H_2CO (38% H_2O), DMSO, 50 °C; *ii*) Cl_2, CH_2Cl_2 (5% H_2O), 25 °C; *iii*) piperidine (morpholine), H_2CO (38% H_2O), DMSO, 50 °C.

The difference in the regioselectivity of the reactions of compound **1** with alkylating agents and the CH_2O—secondary amine system is probably attributed to the fact that these reactions proceeded by different mechanisms (nucleophilic substitution at the sp^3 carbon atom and electrophilic addition at the C=O bond, respectively). The addition of formaldehyde at the oxygen atom of the amide group is most unlikely, because this would require the intermediate formation of unstable formaldehyde hemiacetals.[5]

Anthraquinonoisothiazoles **3—6** are stable high-melting compounds poorly soluble in water and organic solvents. Their structures were confirmed by the data from NMR spectroscopy, mass spectrometry, and elemental analysis (Table 1).

The structures of isomeric alkylation products **3a—c** and **4a—c** were established by comparing the chemical shifts of the signals for the protons of the methylene (methyl) groups bound to the heteroatoms in the ^1H NMR spectra of the isomers. In the spectra of 3-alkoxyisothiazoles **4a—c**, these signals are observed at lower field than those found in the spectra of the corresponding isothiazolones **3a—c**. Compounds **3a**,**b** were identified as *N*-isomers by the independent synthesis from amides **7a**,**b** according to a procedure described earlier[1] (see Scheme 1).

By analogy with the published data,[3—6] compounds **5a—c** and **6a**,**b** were assigned the structures of 2-aminomethylisothiazolones. It is noteworthy that the signals for the protons of the methylene groups in the ^1H NMR spectra of *S*-oxides **6a**,**b** are nonequivalent due to the presence of the asymmetric sulfur atom in the molecule.

To summarize, we studied for the first time alkylation and aminomethylation of 3,6,11-trioxoanthraisothiazoles and used these reactions for the preparation of previously unknown representatives of this heterocyclic system.

Experimental

The ^1H NMR spectra were recorded in DMSO-d_6 on a Bruker AM-300 spectrometer (300.13 MHz). The chemical shifts were measured relative to Me_4Si as the internal standard. The mass spectra (EI) were obtained on an MS-30 Kratos instrument; the energy of ionizing electrons was 70 eV. The TLC analysis was carried out on Silpearl UV-250 silica gel (1 : 2 ethyl acetate—toluene as the eluent). The solvents were purified according to standard procedures.[8] The yields, melting points, and data from ^1H NMR spectroscopy and elemental analysis are given in Table 1.

3,6,11-Trioxo-2,3,6,11-tetrahydroanthra[2,1-*d*]isothiazole 1-oxide (2). A weak stream of gaseous chlorine was passed through a suspension of isothiazolone **1** (0.30 g, 1.06 mmol) in wet CH_2Cl_2 (5 mL) containing 5% water at 25 °C for 15 min. The reaction mixture was stirred for 4 h and poured into Pr^iOH (15 mL). The precipitate that formed was filtered off, washed with Pr^iOH (3×5 mL), and dried in air to afford S-oxide **2** in a yield of 0.29 g (93%). MS, m/z (I_{rel} (%)): 297 $[M]^+$ (22), 281 (9), 251 (100), 233 (10).

2-Alkyl-2,3,6,11-tetrahydroanthra[2,1-*d*]isothiazole-3,6,11-triones 3a—c and 3-alkoxy-6,11-dihydroanthra[2,1-*d*]isothi-

Table 1. Yields, melting points, and data from ^{1}H NMR spectroscopy and elemental analysis

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)				Molecular formula	^{1}H NMR (δ, *J*/Hz)
			C	H	N	S		
2	93	322—325	60.62 60.60	2.33 2.37	4.73 4.71	10.91 10.79	$C_{15}H_7NO_4S$	7.90—8.04 (m, 2 H, H(8), H(9)); 8.14—8.26 (m, 2 H, H(7), H(10)); 8.31 (d, 1 H, H(4), *J* = 8.1); 8.53 (d, 1 H, H(5), *J* = 8.1); 11.82 (br.s, 1 H, NH)
3a	18 (67)*	272—276	65.29 65.07	2.95 3.07	4.84 4.74	10.78 10.86	$C_{16}H_9NO_3S$	3.42 (s, 3 H, NMe); 7.94—8.02 (m, 2 H, H(8), H(9)); 8.20 (d, 1 H, H(5), *J* = 7.2); 8.16—8.28 (m, 2 H, H(7), H(10)); 8.34 (d, 1 H, H(4), *J* = 7.2)
3b	27 (71)*	214—217	71.17 71.14	3.58 3.53	3.73 3.77	8.42 8.63	$C_{22}H_{13}NO_3S$	5.09 (s, 2 H, C$\underline{H}_2$Ph); 7.28—7.46 (m, 5 H, CH$_2$$\underline{Ph}$); 7.91—8.02 (m, 2 H, H(8), H(9)); 8.19—8.25 (m, 3 H, H(7), H(10), H(5)); 8.48 (d, 1 H, H(4), *J* = 7.2)
3c	33	226—227	67.27 67.28	3.65 3.45	4.36 4.36	10.01 9.98	$C_{18}H_{11}NO_3S$	4.51 (br.s, 2 H, NC$\underline{H}_2$CH=CH$_2$); 5.29—5.44 (m, 2 H, NCH$_2$CH=C$\underline{H}_2$); 5.92—6.12 (m, 1 H, NCH$_2$C$\underline{H}$=CH$_2$); 7.91—8.04 (m, 2 H, H(8), H(9)); 8.12—8.24 (m, 3 H, H(4), H(7), H(10)); 8.33 (d, 1 H, H(5), *J* = 7.3)
4a	53	259—260	65.00 65.07	3.19 3.07	4.60 4.74	10.88 10.86	$C_{16}H_9NO_3S$	4.20 (s, 3 H, OMe); 7.91—8.00 (m, 2 H, H(8), H(9)); 8.17—8.27 (m, 3 H, H(7), H(10), H(4)); 8.31 (d, 1 H, H(5), *J* = 8.2)
4b	41	195—197	71.05 71.14	3.74 3.53	3.89 3.77	8.76 8.63	$C_{22}H_{13}NO_3S$	5.59 (s, 2 H, OC$\underline{H}_2$Ph); 7.35—7.50 (m, 3 H, CH$_2$$\underline{Ph}$: *p*-H, *m*-H); 7.56 (d, 2 H, CH$_2$$\underline{Ph}$: *o*-H, *J* = 6.6); 7.86—7.98 (m, 2 H, H(8), H(9)); 8.09—8.22 (m, 3 H, H(7), H(10), H(4)); 8.28 (d, 1 H, H(5), *J* = 8.2)
4c	39	207—208	67.03 67.28	3.52 3.45	4.41 4.36	10.02 9.98	$C_{18}H_{11}NO_3S$	5.01 (br.s, 2 H, OC$\underline{H}_2$CH=CH$_2$); 5.27—5.69 (m, 2 H, OCH$_2$CH=C$\underline{H}_2$); 6.06—6.35 (m, 1 H, OCH$_2$C$\underline{H}$=CH$_2$); 7.73—8.03 (m, 2 H, H(8), H(9)); 8.10—8.51 (m, 4 H, H(4), H(5), H(7), H(10))
5a	55	199—202	66.55 66.65	4.62 4.79	7.45 7.40	8.51 8.47	$C_{21}H_{18}N_2O_3S$	1.35—1.55 (m, 2 H, N(CH$_2$CH$_2$)$_2$C$\underline{H}_2$); 1.56—1.76 (m, 4 H, N(CH$_2$C$\underline{H}_2$)$_2$CH$_2$); 2.67—2.84 (m, 4 H, N(C$\underline{H}_2$CH$_2$)$_2$CH$_2$); 4.76 (s, 2 H, NC$\underline{H}_2$N); 7.79—7.95 (m, 2 H, H(8), H(9)); 8.22—8.50 (m, 4 H, H(4), H(5), H(7), H(10))
5b	63	230—232	63.25 63.14	4.20 4.24	7.31 7.36	8.54 8.43	$C_{20}H_{16}N_2O_4S$	2.69—2.85 (m, 4 H, N(CH$_2$C$\underline{H}_2$)$_2$O); 3.65—3.83 (m, 4 H, N(C$\underline{H}_2$CH$_2$)$_2$O); 4.74 (s, 2 H, NC$\underline{H}_2$N); 7.78—7.93 (m, 2 H, H(8), H(9)); 8.21—8.46 (m, 4 H, H(4), H(5), H(7), H(10))
5c	35	158—160	65.72 65.55	5.01 4.95	7.72 7.64	8.68 8.75	$C_{20}H_{18}N_2O_3S$	1.20 (t, 6 H, N(CH$_2$C$\underline{H}_3$)$_2$, *J* = 7.2); 2.80 (q, 4 H, N(C$\underline{H}_2$CH$_3$)$_2$, *J* = 7.2); 4.85 (s, 2 H, NC$\underline{H}_2$NEt$_2$); 7.81—7.92 (m, 2 H, H(8), H(9)); 8.25—8.46 (m, 4 H, H(4), H(5), H(7), H(10))
6a	65	decomp. >265	64.02 63.94	4.67 4.60	7.11 7.10	8.17 8.13	$C_{21}H_{18}N_2O_4S$	1.22—1.42 (m, 2 H, N(CH$_2$CH$_2$)$_2$C$\underline{H}_2$); 1.39—1.61 (m, 4 H, N(CH$_2$C$\underline{H}_2$)$_2$CH$_2$); 2.51—2.70 (m, 4 H, N(C$\underline{H}_2$CH$_2$)$_2$CH$_2$); 4.61 (br.s, 2 H, NC$\underline{H}_2$N); 7.87—8.11 (m, 2 H, H(8), H(9)); 8.14—8.30 (m, 2 H, H(7), H(10)); 8.33 (d, 1 H, H(4), *J* = 8.2); 8.56 (d, 1 H, H(5), *J* = 7.2)
6b	50	254—256	60.73 60.60	4.27 4.07	7.29 7.07	8.04 8.09	$C_{20}H_{16}N_2O_5S$	2.55—2.78 (m, 4 H, N(CH$_2$C$\underline{H}_2$)$_2$O); 3.47—3.76 (m, 4 H, N(C$\underline{H}_2$CH$_2$)$_2$O); 4.56 (d, 1 H, NC$\underline{H}_2$N, *J* = 14.7); 4.75 (d, 1 H, NC$\underline{H}_2$N, *J* = 14.7); 7.92—8.11 (m, 2 H, H(8), H(9)); 8.17—8.31 (m, 2 H, H(7), H(10)); 8.36 (d, 1 H, H(4), *J* = 8.1); 8.57 (d, 1 H, H(5), *J* = 7.1)

* The yield of the compounds in the reaction of amide **7** with SO_2Cl_2.

azole-6,11-diones 4a—c (general procedure). The alkylating agent (1.27 mmol, Me_2SO_4, $PhCH_2Cl$, or $CH_2{=}CHCH_2Br$), anhydrous K_2CO_3 (0.18 g, 1.30 mmol), and a catalytic amount of KI were added to a stirred suspension of isothiazole **1** (0.30 g, 1.06 mmol) in DMF (5 mL). The reaction mixture was stirred at 45—50 °C for 12 h and poured into 5% HCl (20 mL). The precipitate that formed was filtered off, dried in air, and recrystallized from a 2 : 1 EtOH—THF mixture. The resulting mixture of the corresponding N- and O-alkylation products **3a—c** and **4a—c** was separated into individual components by chromatography on a column with silica gel (L 40/100; toluene and then a 2 : 1 toluene—ethyl acetate mixture as the eluent).

Synthesis of 2-alkyl-2,3,6,11-tetrahydroanthra[2,1-*d*]isothiazole-3,6,11-triones 3a,b from *N*-alkyl-1-ethylthio-9,10-dioxo-9,10-dihydroanthracene-2-carboxamides 7a,b.[1] Sulfuryl chloride (0.10 mL, 1.24 mmol) was added with vigorous stirring to a suspension of amides **7a** or **7b** (0.92 mmol) in anhydrous CH_2Cl_2 (5 mL), after which the precipitate virtually immediately dissolved. After 5—8 s, the reaction product began to precipitate from the red solution. The reaction mixture was stirred at 15 °C for 1.5 h. The solvent was distilled off *in vacuo* and the precipitate was recrystallized from THF. Compounds **3a** and **3b** thus prepared were identical with the corresponding products synthesized by alkylation of isothiazolone **1** with Me_2SO_4 and benzyl chloride (see Table 1).

2-Alkylaminomethyl-3,6,11-trioxo-2,3,6,11-tetrahydroanthra[2,1-*d*]isothiazoles 5a—c and 2-alkylaminomethyl-3,6,11-trioxo-2,3,6,11-tetrahydroanthra[2,1-*d*]isothiazole 1-oxides 6a,b (general procedure). Isothiazolone **1** or *S*-oxide **2** (1.06 mmol) was stirred in DMSO at 45—50 °C until the reagents were completely dissolved. Then diethylamine, piperidine, or morpholine (1.50 mmol) and a 38% aqueous solution of formaldehyde (0.30 mL, 4.10 mmol) were successively added. The reaction mixture was stirred at 45—50 °C for 6 h, cooled to 20 °C, and kept for 3 h. The finely crystalline precipitate that formed was filtered off, washed with ethanol (3×10 mL), and dried in air to afford compounds **5a—c**, **6a**, and **6b**.

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