STUDIES ON QUINONES

V. Anthra[1,2-c]-1,2,5-thiadiazole-6,11-diones and Their Reaction with Amines*

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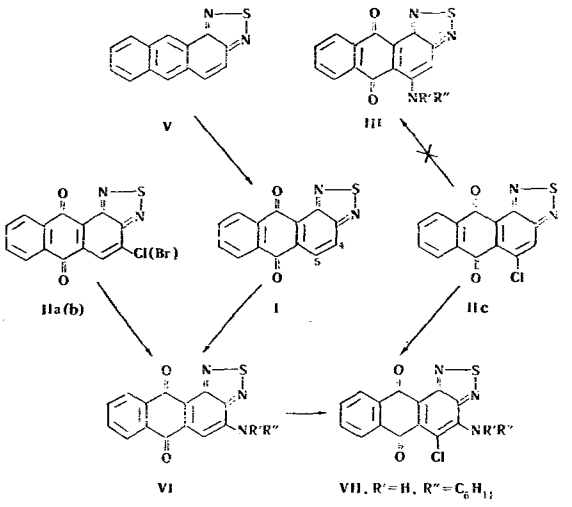
The reaction of 1,2-diaminoanthraquinones with thionyl chloride has given anthra[1,2-c]-1,2,5-thiadiazole-6,11-diones a new group of heterocyclic anthraquinone derivatives. In the reaction of anthra[1,2-c]-1,2,5-thiadiazole-6,11-dione (I) with primary and secondary amines, the amine residue enters position 4 and forms the corresponding 4-amino derivatives VI with a yield of up to 85%. The same compounds are obtained by the reaction of 4-haloanthra[1,2-c]-1,2,5-thiadiazole-6,11-diones (IIa, b). In 5-chloroanthra[1,2-c]-1,2,5-thiadiazole-6,11-dione (IIc), where it would appear, the halogen should be particularly mobile, the chlorine atom does not undergo exchange and, as in I, the replacement of the hydrogen in position 4 takes place. Some aspects of the influence of the thiadiazole ring on the anthraquinone nucleus are discussed.

The unusual reactivity of anthra[1,2-c]-1,2,5-selenadiazole-6,11-dione with respect to amines observed by one of us [2] prompted us to undertake the synthesis of previously unreported anthraquinone derivatives containing the 1,2,5-thiadiazole ring. Since benzo[c]-1,2,5-thia- and -selenadiazoles have similar properties [3], we also expected similarities in the anthraquinone series.



Anthra[1,2-c]-1,2,5-thiadiazole-6,11-diones can be obtained by using the general method for the synthesis of 1,2,5-thiadiazoles from o-diamines and thionyl chloride or thionylaniline [4]. Compounds I–III (Table 1) were obtained by heating 1,2-diaminoanthraquinones (IV) with thionyl chloride in organic solvents. Another route to the production of I consists in the cyclization of 1,2-diaminoanthracene by treating it with thionyl chloride and subsequent oxidation of anthra[1,2-c]-1,2,5-thiadiazole (V).

The anthraquinonethiadiazole I and its halogen derivatives II are stable light yellow crystalline substances the spectral characteristics of which are similar to those of the analogous selena and oxa compounds [2, 5]. The influence of the heteroatom on the position and intensity of the long-wave maximum of the quinonediazoles increases in the sequence O < S < Se (Fig. 1). The introduction of a halogen atom into position 4 of the thiadiazole causes a hypsochromic shift and into position 5 a bathochromic shift in the long-wave region and the appearance of a shoulder similar to that present in the spectrum of anthraquinoneoxadiazole.

The thiadiazole I reacts with primary or secondary amines and ammonia even more readily than anthraquinoneselenadiazole [2], forming the amino derivatives VI (Table 2). The reaction with aliphatic amines takes place on brief heating in the amine or in an organic solvent (dimethylformamide, dioxane, ethylene glycol), with a yield of up to 85%. The reaction with aromatic amines requires more severe conditions but is accelerated in the presence of salts of copper, cobalt, and some other metals as catalysts.

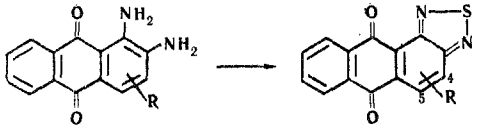
The amino derivatives VI formed by the reaction of II with amines are red and violet in color, which distinguishes them sharply from the blue 5-amino derivatives III obtained by the closure of the thiadiazole ring in the 4-alkylamino- and 4-arylamino-1,2-diaminoanthraquinones. The absorption band of III in the visible region of the spectrum is located 80–90 nm towards the long-wave region, has a lower intensity, and is considerably broader (Fig. 2). The IR spectrum of the 5-amino derivatives III has two bands of the stretching vibrations of CO at 1674 and 1634 cm^{-1} as a consequence of the participation of one of the carbonyl groups in the formation of an intramolecular hydrogen bond. The spectra of the amino compounds VI have only one band at 1674 cm^{-1}, which shows the location of the substituted amino group in the β position of the nucleus. This fact and the similarity of compounds VI to the 4-amino derivatives of anthraquinoneselenadiazole [2] give grounds for the assumption that in the thiadiazoles VI the amine residue is present in position 4.

The reactions of the 4- and 5-haloanthraquinonethiadiazoles with amines were used for proof. On being heated with cyclohexylamine, the 4-chloro- and the 4-bromo derivatives (IIIa and b) gave the same substance VId as was obtained from the quinone I, while 5-chloroanthraquinonethiadiazole (IIc) gave the cyclohexylamine derivative VII containing an atom of chlorine. The latter was also obtained by chlorinating VId with

*For part IV, see [1].

Table 1

Anthra[1,2-c]-1,2,5-thiadiazole-6,11-diones (I–III) Obtained from 1,2-Diaminoanthraquinones (IV)



IV I–III

Diamine	Thiadiazole	R[1]*	Mp °C (Solvent)	λ_{max}, nm (log ε)	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	N	S	C	H	N	S	
IVa	I	H	234—235 (acetic acid)	345 (4.03)	$C_{14}H_6N_2O_2S$	62.86 62.94	2.44 2.49	10.58 10.59	11.98 11.73	63.13	2.27	10.52	12.04	85
IVb	IIa	4-Cl	284—285 (chlorobenzene)	340 (4.02), 390 (3.68, shoulder)	$C_{14}H_5ClN_2O_2S$[3]*	55.65 55.76	1.72 1.75	9.23 9.47	10.40 10.26	55.93	1.68	9.32	10.66	71[2]*
IVc	IIb	4-Br	295—296 (chlorobenzene)	342 (3.92), 390 (3.74, shoulder)	$C_{14}H_5BrN_2O_2S$	48.83 48.71	1.57 1.64	8.17 8.25	9.28 9.51	48.71	1.46	8.12	9.29	68[2]*
IVd	IIc	5-Cl	250—251 (chlorobenzene)	355 (3.84), 390 (3.78, shoulder)	$C_{14}H_5ClN_2O_2S$[4]*	55.64 55.78	1.91 1.68	9.31 9.08	—	55.93	1.68	9.32	—	70[2]*
IVe	IIIa	5-NHC_6H_{11}	167—168 (benzene–n-hexane)	620 (3.41)	$C_{20}H_{17}N_3O_2S$	65.92 65.80	4.88 4.97	—	8.68 8.56	66.10	4.72	—	8.82	56
IVf	IIIb	5-$NHC_6H_4CH_3$-*p*	213—215 (benzene)	620 (3.46)	$C_{21}H_{13}N_3O_2S$	67.68 67.60	3.72 3.76	—	8.74 8.81	67.89	3.53	—	8.63	50
IVg	IIIc	5-$NHC_6H_4OCH_3$-*p*	244—245 (benzene)	620 (3.63)	$C_{21}H_{13}N_3O_3S$	64.78 64.67	3.35 3.44	—	8.02 8.00	65.10	3.38	—	8.28	52

[1]*The position in anthraquinonethiadiazole is given. [2]*In the absence of pyridine. [3]*Found, %: Cl 12.06, 12.15. Calculated, %: Cl 11.80. [4]*Found, %: Cl 11.90, 11.92; Calculated, %: Cl 11.80.

sulfuryl chloride. Consequently, the amine residue does in fact enter position 4 of the anthraquinonethiadiazole.

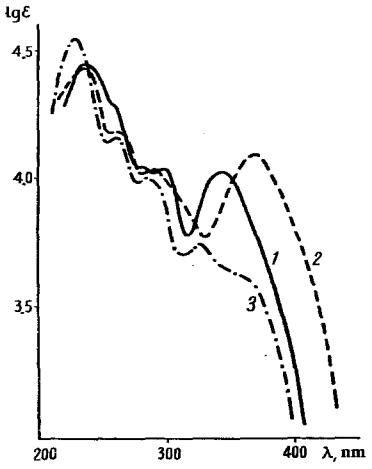


Fig. 1. UV spectra (in ethanol): 1) anthra[1,2-c]-1,2,5-thiadiazole-6,11-dione (I); 2) anthra[1,2-c]-1,2,5-selenadiazole-6,11-dione; 3) anthra[1,2-c]-1,2,5-oxadiazole-6,11-dione.

Such a direction of the reaction was unexpected on the basis of literature data. The 1,2,5-thiadiazole ring is a stable aromatic system with a closed sextet of π-electrons [6–8]. In its properties, benzo[c]-1,2,5-thiadiazole has much in common with naphthalene [8–10]. An increase in the double-bondedness in benzothiadiazole between the C_4 and C_5 and the C_6 and C_7 atoms has been established by X-ray [11] and chemical [8, 9, 12, 13] methods. In consequence of the electrophilic nature of the heterocycle, nucleophilic substitution in benzothiadiazole is facilitated, but to a greater extent in position 5 [14]. As is well known, in the anthraquinone molecule nucleophilic exchange takes place more readily in the α position. Thus, in anthraquinonethiadiazole the result of the concordant influences of the heterocycle and the anthraquinone nucleus should be mainly to activate the halogen atom in position 5 which is, at the same time, the α position of the anthraquinone. In actual fact, however, as mentioned above, the halogen atom in position 5 is not replaced but substitution of the hydrogen in position 4 takes place.

Since the reaction takes place without the participation of atmospheric oxygen part of the initial quinone evidently acts as the oxidizing agent necessary for the formation of the amino derivatives VI, being converted into a mixture of unidentified resinous substances.

It must be mentioned that neither the anthrathiadiazole V nor anthraquinone reacts with amines under the conditions of the reaction of I. The reaction can be considered as a nucleophilic 1,6-addition to a conjugated chain including a carbonyl group close to the heterocycle. In this case the role of the thiadiazole ring apparently consists in increasing the redox potential of the quinone and the introduction of a partially localized "diene" system conjugated with the carbonyl.

EXPERIMENTAL

Anthra[1,2-c]-1,2,5-thiadiazole (V). A mixture of 2.10 g (0.01 mole), of 1,2-diaminoanthracene obtained by the reduction of 1,2-anthraquinone dioxime [5], 120 ml of dioxane, 13.60 g (0.097 mole) of thionylaniline, and 15.80 g (0.2 mole) of pyridine was stirred at 70° C for 3 hr and poured into water, and the precipitate was chromatographed on alumina in chloroform. This gave 0.98 g (41%) of V in the form of lemon-yellow plates (from benzene) with mp 157–158° C. After 0.48 g (0.002 mole) of V had been boiled in 50 ml of acetic acid with 0.6 g of chromic anhydride and the product had been crystallized from acetic acid, 0.34 g (64%) of I was obtained, identical with that obtained from 1,2-diaminoanthraquinone. UV spectrum of V in ethanol [λ_{max}, nm (log ε) are given]: 250 (4.74), 310 (4.48), 330 (3.88 shoulder), 345 (3.73), 365 (3.56, shoulder), 383 (3.83), 403 (3.88). Found, %: C 71.45, 71.38; H 3.44, 3.63; N 11.62, 11.70; S 13.40, 13.23. Found $C_{14}H_8N_2S$, %: C 71.15; H 3.41; N 11.86; S 13.57.

Reaction of 1,2-diaminoanthraquinones (IV) with thionyl chloride. A solution of 3.15 g of pyridine in 10 ml of dioxane was slowly added to a mixture of 0.01 mole of IV, 60 ml of dioxane, and 7.14 g (0.06 mole) of thionyl chloride at 70° C, and the mixture was stirred for 30–60 min at the same temperature. After cooling, the reaction mixture was poured into water, and the precipitate was filtered off, washed with water, dried, and chromatographed on alumina; in the case of I and II the yellow band was eluted with chloroform, and in the case of III the blue band was eluted with benzene (Table 1).

The initial diamines IVe, f were obtained from 4-chloro-1,2-diaminoanthraquinone as described previously [2]. IVg was synthesized similarly; blue-violet prisms (from benzene), mp 240–242° C. Found, %: C 70.12, 69.98; H 4.71, 4.65; N 11.39, 11.42. Calculated for $C_{21}H_{17}N_3O_3$, %: C 70.17; H 4.77; N 11.69.

6,11-Dihydroxyanthra[1,2-c]-1,2,5-thiadiazole. A solution of 2.66 g (0.01 mole) of I in acetic acid was stirred with a solution of 8 g of stannous chloride in 10 ml of concentrated hydrochloric acid and the mixture was boiled for 5 min. On cooling, 2.35 g (88%) of anthrahydroquinone separated out. Orange needles (from acetic acid), mp 208° C. Found, %: N 10.23, 10.09; S 11.72, 11.66. Calculated for $C_{14}H_8N_2O_2S$, %: N 10.44; S 11.95.

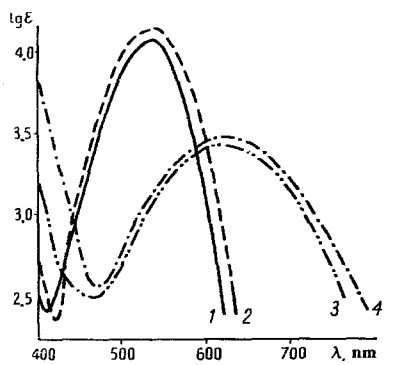
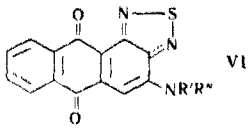


Fig. 2. Absorption spectra (in chloroform): 1) 4-cyclohexylaminoanthra[1,2-c]-1,2,5-thiadiazole-6,11-dione (VId); 2) 4-(4'-methylphenylamino)anthra[1,2-c]-1,2,5-thiadiazole-6,11-dione (VIg); 3) 5-cyclohexylaminoanthra[1,2-c]-1,2,5-thiadiazole-6,11-dione (IIIa); 4) 5-(4'-methylphenylamino)anthra[1,2-c]-1,2,5-thiadiazole-6,11-dione (IIIb).

Reaction of anthra[1,2-c]-1,2,5-thiadiazole-6,11-dione (I) with amines. a) A mixture of 2.66 g (0.01 mole) of I, 30 g of an amine, and 0.2 g of copper acetate was heated at 130–150° C for 2 hr. The excess of amine was eliminated by treatment with 5% hydrochloric acid, and the reaction product was washed with water, dried, chromatographed on alumina, eluted with chloroform, and crystallized from dioxane or chlorobenzene (Table 2).

Table 2



VI

Compound	NR′R″	Mp, °C	λ_{max}, nm	Empirical formula	Found, %				Calculated, %				Yield, %
					C	H	N	S	C	H	N	S	
VIa	NH_2	>330	522[1]*	$C_{14}H_7N_3O_2S$	—	—	14.69 14.77	11.19 11.25	—	—	14.94	11.40	68
VIb	$N(CH_3)_2$	264—265	550 (4.07)	$C_{16}H_{11}N_3O_2S$	62.21 62.40	3.67 3.56	13.38 13.37	10.84 10.77	62.13	3.58	13.58	10.37	77
VIc	$N(C_2H_5)_2$	206—207	560 (4.11)	$C_{18}H_{15}N_3O_2S$	64.16 64.10	4.45 4.35	12.44 12.66	9.39 9.35	64.07	4.48	12.46	9.51	70
VId	NHC_6H_{11}	214.5—215	538 (4.04)	$C_{20}H_{17}N_3O_2S$	66.22 65.95	4.31 4.42	11.44 11.25	8.77 9.06	66.10	4.72	11.56	8.82	85[2]*
VIe		259—260	530 (3.95)	$C_{18}H_{13}N_3O_3S$	61.59 61.83	4.01 4.07	11.78 11.58	—	61.53	3.73	11.96	—	80[2]*
VIf	NHC_6H_5	243—244	540 (4.13)	$C_{20}H_{11}N_3O_2S$	67.23 67.54	3.17 3.16	11.53 11.51	—	67.20	3.10	11.76	—	72
VIg	$NHC_6H_4CH_3$-*p*	244.5—245	548 (4.12)	$C_{21}H_{13}N_3O_2S$	67.67 67.52	3.90 3.60	11.28 11.41	8.62 8.37	67.89	3.53	11.33	8.63	68[3]*
VIh	NHC_6H_4Cl-*p*	306—307	540 (4.12)	$C_{20}H_{10}ClN_3O_2S$	61.22 61.53	2.32 2.60	10.92 11.16	8.15 7.98	61.31	2.57	10.73	8.18	72
VIi	$NHC_6H_4OCH_3$-*p*	265—265.5	555 (4.09)	$C_{21}H_{13}N_3O_3S$	64.93 64.72	3.32 3.69	10.76 10.50	8.19 8.13	65.10	3.38	10.85	8.28	75
VIj	$NHC_6H_4NH_2$-*p*	292—292.5	565[2]*	$C_{20}H_{12}N_4O_2S$	64.20 64.18	3.37 3.03	—	—	64.51	3.25	—	—	65

1* Saturated solution. 2*In the absence of copper acetate. 3*In the absence of copper acetate 60% of VIg and 20% of the initial I were obtained.

b) To a solution of 0.01 mole of I in 200 ml of dimethylformamide containing 0.2 g of copper acetate was added 11.0 g of diethylamine or 15.8 g of a 30% solution of dimethylamine, and the mixture was heated at 75° C for 2 hr, after which it was poured into 500 ml of 5% hydrochloric acid. The reaction product was crystallized from chlorobenzene (**VIb**) or was chromatographed and eluted with chloroform (**VIc**). Under analogous conditions, the passage of a current of ammonia into a solution of I gave compound **VIa**, and boiling a solution of I with 3.24 g (0.03 mole) of p-phenylenediamine gave compound **VIj** (Table 2).

Reaction of 4-haloanthra[1,2-c]-1,2,5-thiadiazole-6,11-diones (IIa, b) with amines. a) A mixture of 0.01 mole of **IIa** or **IIb** and 25 ml of cyclohexylamine was boiled for 10 min, and the reaction product was separated as described above in example (a). In both cases an 85–89% yield of a substance with mp 214–215° C giving no depression of the melting point in admixture with authentic **VId** synthesized from I was obtained.

b) A mixture of 0.01 mole of **IIa**, 100 ml of ethylene glycol, 3.22 g (0.03 mole) of p-toluidine, and 0.001 mole of copper acetate was stirred at 150° C for 2 hr. After isolation and purification, 2.71 g (73%) of **VIg**, identical in melting point and IR spectrum with that prepared from I, was obtained.

5-Chloro-4-cyclohexylaminoanthra[1,2-c]-1,2,5-thiadiazole-6,11-dione (VII). a) A solution of 3.00 g (0.01 mole) of **IIc** in 25 ml of cyclohexylamine was boiled for 10 min, and the **VII** was isolated as described above. Yield 2.7 g (69%); light red plates (from dioxane), mp 213–214° C.

b) A boiling solution of 3.63 g (0.01 mole) of **VId** in 100 ml of chloroform was treated with 1.6 ml (0.02 mole) of sulfuryl chloride. Judging from a chromatographic sample, the chlorination reaction was complete in a few minutes. After the chloroform had been evaporated, the residue was washed with water and was recyrstallized from dioxane. This yielded 2.0 g (50%) of a substance giving no depression of the melting point in admixture with the substance isolated in case (a) and identical with it in respect of its IR and UV spectra. Found, %: C 60.40, 60.81; H 4.01, 3.90; Cl 8.92, 9.15; N 10.40, 10.35; S 8.04, 8.28. Calculated for $C_{20}H_{16}ClN_3O_2S$, %: C 60.37; H 4.05; Cl 8.91; N 10.55; S 8.06.

The UV spectra were measured on an SF-4 instrument in ethanol or, for compound III, chloroform, in solutions with concentrations of 10^{-4} and 0.2×10^{-4} M; the IR spectra were recorded on an IKS-14 spectrometer in tablets of KBr.

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