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REACTION OF o-DIAMINOANTHRAQUINONES WITH ACETOACETIC ESTER AND CROTONIC ACID

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The reaction of 1,2 (and 2,3)-diamino-9,10-anthraquinones with acetoacetic ester and crotonic acid gave dihydro- and tetrahydroanthraquinonediazepinones, the structures of which were established on the basis of spectral data and chemical transformations.

The reaction of o-diaminoarenes with carbonyl compounds is one of the methods for the synthesis of 1,5-diazepine derivatives, many of which are of pharmacological value [1]. The first representatives of anthraquinonediazepines were recently obtained by the reaction of o-diaminoanthraquinones with mesityl oxide [2] and malonic ester [3]. In the present research in order to synthesize new representatives of this series of compounds we studied the possibility of the use of acetoacetic ester (AAE) and crotonic acid as the carbonyl components.

We found that a complex mixture of reaction products, from which we isolated acetoacetyl derivative III and diazepinones IV and V (the latter in the form of tautomeric forms Va and Vb), is formed when 1,2-diaminoanthraquinone (I) and AAE are heated in toluene by the method previously described for 2,3-diaminonaphthoquinone [4]. Diazepinone IV (55%) is the principal product, and V and III are obtained in 26 and 13% yields, respectively. The structures of the compounds obtained were established on the basis of analytical and spectral data (see Table 1).

The IR spectra of diazepinones IV and V at 1600-1700 cm^{-1} contain broad absorption bands that confirm the presence of carbonyl and amido groups. The presence of absorption bands in the high-frequency region (3100-3300 cm^{-1}) may constitute evidence for the presence of NH groups that participate in the formation of hydrogen bonds. In addition to the absorption bands that correspond to the amido and carbonyl groups of the quinone, frequencies that belong to the vibration of ketone C=O (1720 cm^{-1}) and amino group N–H (3320 and 3440 cm^{-1}) bonds are observed in the IR spectrum of III.

In addition to the signals of aromatic protons and protons of CH_2 and CH groups, the PMR spectra of diazepinones IV and Va contain signals of protons of NH groups, the position of which is in good agreement with the spectral data for similarly constructed compounds [2, 3]. The chemical shifts of the protons of the NH group in IV proved to be close (8.69 and 9.17 ppm), but the position of the protons of the NH group in Va differ substantially (8.7 and 11.3 ppm). The weak-field signal in the spectrum of diazepinone Va evidently belongs to the proton of the NH group in the 1 position, since it is adjacent to the carbonyl groups of the quinone and the heteroring. The deshielding effect of the carbonyl groups is also manifested in the diazepinone Vb molecule, the PMR spectrum of which at weak field (11.76 ppm) contains one signal from the proton of the NH group in the 1 position. In addition, in contrast to tautomers IV and Va, a signal of protons of the CH_2 group (in addition

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TABLE 1. Characteristics of the Synthesized Anthraquinone Derivatives

Compound	mp, °C (recrystallization solvent)	PMR spectrum (d_6-DMSO), ppm	Found				Empirical formula	Calculated			
			C, %	H, %	N, %	M		C, %	H, %	N, %	M
III	280—285 (methanol)	9,56 (1H, n.s., NH); 8,23—7,63 (7H,m, H^{4-8} quinone NH_2); 7,4 (1H, d, J=8 Hz, H^3 quinone); 3,7 (2H, s, CH_2); 2,26 (3H, s, CH_3)	66,6	4,1	8,7		$C_{18}H_{14}N_2O_4$	67,0	4,3	8,7	
IV	321—325 (chloroform)	9,17 (1H, n.s., NH); 8,69 (1H, n.s., NH); 8,17—7,74 (4H, m, H^{9-12} quinone); 7,45 (2H, s, $H^{6,7}$ quinone); 4,36 (1H, n.s., CH); 1,77 (3H, s, CH_3)	70,5	4,0	9,0	304					
Va	284—286 (nitrobenzene)	11,3 (1H, n.s., NH); 8,7 (1H, n.s., NH); 8,2—7,75 (4H, m, H^{9-12} quinone); 7,6 (1H, d, J=8 Hz, H^7 quinone); 7,05 (1H, d J=8 Hz, H^6 quinone); 4,55 (1H, n.s., CH); 1,90 (1H, s., CH_3)	71,1	3,8	9,1	304					
Vb	271—273,5 (benzene)	11,76 (1H, n.s., NH); 8,4—7,7 (5H, m., $H^{7,9-12}$ quinone); 7,5 (1H, d J=8 Hz., H^6 quinone); 3,23 (2H, s CH_2); 2,43 (3H, s, CH_3)[a]	70,7	4,1	8,9	304					
Va+Vb	265—270		70,8	3,6	9,0		$C_{18}H_{12}N_2O_3$	71,0	3,9	9,2	304
IX	286—288 (DMSO—methanol)	9,65 (1H, n.s., NH); 8,4—8,31 (6H, m, 6H quinone); 5.42 (1H, b.s., C=CH_2); 5,23 (1H, s., C=CH_2); 2,23 (3H, s., CH_3)[a]	71,3	4,0	8,9	304					
X	293—295	8,43—7,5 (6H, m, 6H quinone); 3,73 (2H, y., CH_2[b]); 2,76 (3H, s, CH_3)[c]	70,5	3,8	9,1	304					
XII	329—332 (DMSO)	11,34 (1H, n.s., NH); 8,16—7,61 (6H, m, 6H quinone); 5,5 (1H, n.s., C=CH_2); 5,27 (1H, s, C=CH_2); 2,2 (3H, s., CH_3)	71,1	3,6	9,2	304					
VI	322—325 (benzene)	10,5 (1H, n.s., NH); 10,0 (1H, n.s., NH); 8,35—7,7 (4H, m, H^{9-12} quinone); 7,51 (1H, d, J=8 Hz, H^7 quinone); 7,3 (1H, d, J=8 Hz., H^6 quinone); 4,13 (1H,m, CH); 1,42 (3H, d, J=6,5 Hz, CH_3)[d]	70,2	4,4	8,9	306					
VII	271—275 (benzene)	8,2—7,4 (6H, m, 6H quinone); 4,46 (1H,m, CH); 2,53 (2H,m, CH_2); 1,33 (3H, d, J=6 Hz, CH_3)[c]; 11,53 (1H, n.s., NH); 6,83 (1H, n.s., NH)	70,5	4,5	9,3	306	$C_{18}H_{14}N_2O_3$	70,6	4,6	9,2	306
XI	348—350 (DMSO)	8,26—7,36 (6H,m, 6H quinone); 4,43 (1H, m, CH); 2,56 (2H,m, CH_2); 1,33 (3H, d., J=6 Hz, CH_3)[c]; 9,90 (1H, n.s., NH); 7,06 (1H, n.s., NH)	70,1	4,5	9,0	306					
VIII	392—394 (DMSO—water)		68,1	3,1	10,1	264					
XIII	Did not melt up to 400°C (DMSO—methanol)		68,3	3,1	10,4	264	$C_{15}H_8N_2O_3$	68,2	3,0	10,6	264

[a] In $CDCl_3$. [b] Protonated form. [c] In CF_3CO_2H. [d] It was impossible to determine the position of the protons of the CH_2 group because of superimposition of the signals of the solvent.

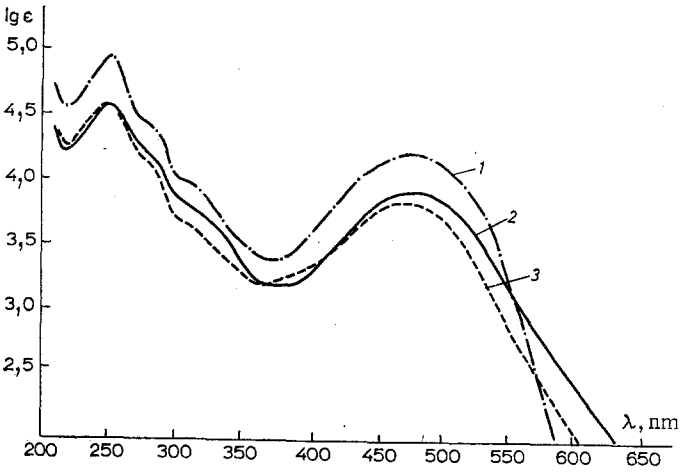
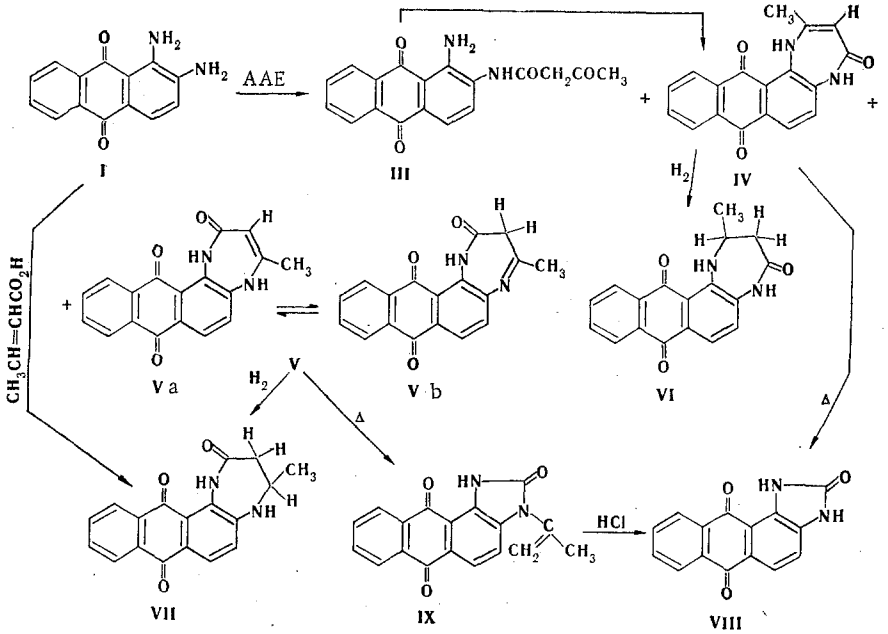


Fig. 1. Electronic absorption spectra in alcohol: 1) 2-N-acetyl-1,2-diaminoanthraquinone; 2) 2-N-acetoacetyl-1,2-diaminoanthraquinone; 3) 2-N-carbethoxyacetyl-1,2-diaminoanthraquinone.

to signals of aromatic and methyl protons) is present in the spectrum of diazepinone Vb. In the PMR spectrum of III the position of the protons of the amino group and the NH group coincides with the position of the analogous protons in the spectra of the 2-N-acyl derivatives of 1,2-diaminoanthraquinone [3]. A similarity in the UV spectra of the 2-N-acyl derivatives of 1,2-diaminoanthraquinone [5] and the spectrum of III was also established (see Fig. 1); this makes it possible to assume that it is the 2-N-acetoacetyl derivative of 1,2-diaminoanthraquinone.



The structures of III-V were also confirmed by their chemical transformations. When III is heated in acetic acid, it undergoes smooth conversion to diazepinone IV. Compounds IV and V undergo catalytic reduction to give tetrahydroderivatives VI and VII, respectively, whereas upon thermolysis they undergo rearrangement to the same compound, viz., imidazolone VIII, which, in agreement with the literature data [1], proceeds through a step involving the formation of isopropenyl derivatives. The thermolysis of the tautomeric forms of diazepinone V takes place more smoothly than the thermolysis of IV: Isopropenyl derivative IX, which, after hydrolysis [1], gives imidazolone VIII in almost quantitative yield, was isolated in 50% yield. The structures of imidazolones VIII and IX were confirmed by analytical and spectral data. In addition to absorption bands of quinone carbonyl groups at 1600-

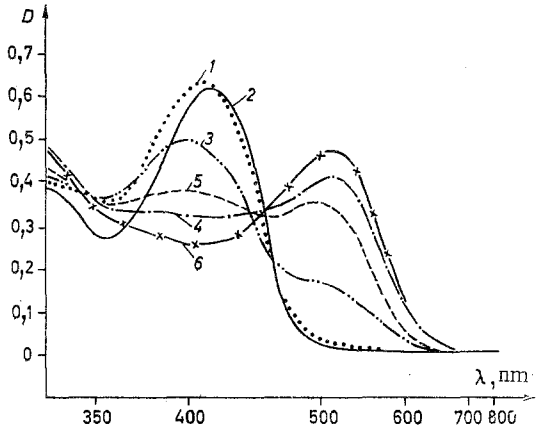
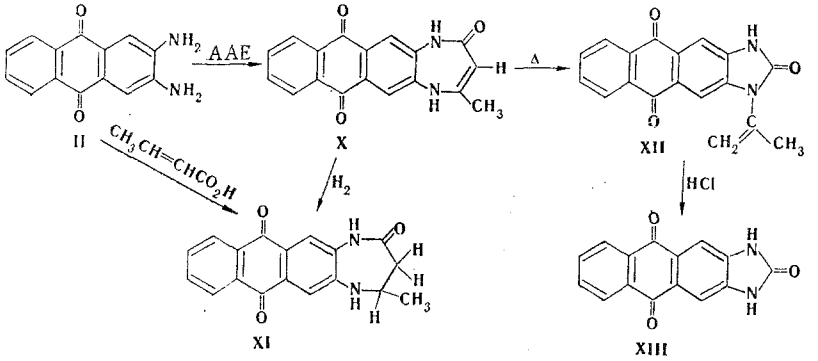


Fig. 2. Electronic absorption spectra of Vb: 1) in chloroform; 2) in carbon tetrachloride; 3) in alcohol; 4) in dimethyl sulfoxide; 5) in alcohol (after 24 h); 6) in dimethyl sulfoxide (after 24 h).

1700 cm^{-1}, the absorption band of an amide carbonyl group at 1730 cm^{-1} that is characteristic for such compounds [6] is present in the IR spectra of these substances.

The tautomeric forms of diazepinone V, which have identical elementary compositions, were obtained by recrystallization from various solvents. Diazepinone Va is isolated from the reaction mixture in the form of red-brown crystals, after recrystallization of which from benzene, yellow crystals of tautomer Vb precipitate. The color of solutions of imine Vb in CCl_4 and chloroform is yellow (λ_{max} 412 and 410 nm, respectively); in DMSO the positions of the long-wave absorption maxima of Va and imine Vb are identical (510 nm) and do not change with time, whereas in alcohol the initial yellow color of the solution of imine Vb gradually changes to red, and, judging from the UV spectra (see Fig. 2), equilibrium is established between the enamine and imine forms. Heating and allowing the yellow crystals to stand at room temperature promotes their conversion to brown crystals. It is obvious that enamine form Va (red) is more stable than imine form Vb (yellow). The increased stability of the enamine forms of diazepinones IV and V, as well as their naphthoquinone analog [4], is evidently due to stabilization due to conjugation [7].



The fact that diazepinone X, which we obtained from 2,3-diaminoanthraquinone (II) and AAE, exists exclusively in the enamine form is also in agreement with this assumption. Like diazepinones IV and V, X undergoes catalytic reduction to give tetrahydro derivative XI; as a result of thermal rearrangement, it is converted to isopropenyl derivative XII, the acidic hydrolysis of which gave imidazolone XIII. The spectral data for XII and XIII are in agreement with the characteristics of compounds with similar structures [6].

Diamines I and II react readily with crotonic acid to give diazepinones VII and XI in high yields; the characteristics of these products were in complete agreement with the characteristics of the products of the reduction of diazepinones V and X, respectively. The formation of two isomeric products is possible in the case of diamine I; however, one substance, which proved to be identical to diazepinone VII, was obtained as a result of the re-

action. The formation of diazepinone VII rather than its isomeric VI constitutes evidence that the 1,4 addition of diamine I to crotonic acid proceeds exclusively with the participation of the amino group in the 2 position, whereas the α-amino group of the quinone participates in the analogous addition to mesityl oxide (under acid catalysis conditions, of course) [2].

EXPERIMENTAL

The IR spectra of KBr pellets or mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with Varian A-56/60A (60 MHz) and Bruker AG WP-80 (80 MHz) spectrometers with hexamethyldisiloxane as the internal standard (the chemical shifts are presented on the δ scale). The molecular weights of the compounds were determined by mass spectrometry with an MS-902 spectrometer (with a system for direct introduction of the samples) at 120°C.

2-N-Acetoacetyl-1,2-diaminoanthraquinone (III), 4,5-Dihydro-2-methyl-1H-anthra[1,2-b]-1,4-diazepine-4,8,13-trione (IV), 2,5-Dihydro-4-methyl-1H-anthra[1,2-b]-1,4-diazepine-2,8,13-trione (Va), and 2,3-Dihydro-4-methyl-1H-anthra[1,2-b]-1,4-diazepine-2,8,13-trione (Vb). A) A mixture of 2 g (8.4 mmole) of diamine I, 10 ml (77 mmole) of AAE, and 400 ml of toluene was refluxed with a Dean–Stark adapter for 18 h, after which it was cooled, and the violet precipitate was removed by filtration, washed with ether, and dissolved in chloroform. The chloroform solution was filtered through a thin layer of silica gel to give 1.4 g (55%) of diazepinone IV. IR spectrum: 1660, 1680 (C=O); 3090, 3230 cm^{-1} (NH).

The filtrate remaining after separation of IV was evaporated to half its original volume, and 0.25 g (10%) of a red-brown precipitate of diazepinone Va was removed by filtration. IR spectrum: 1620, 680 (C=O); 3130, 3200, and 3320 cm^{-1} (NH).

The residual reaction mass was chromatographed with a column filled with aluminum oxide (activity II) by elution with benzene to give 0.26 g (10%) of yellow crystals of diazepinone Vb. IR spectrum: 1650, 1700 (C=O); 3240-3260 cm^{-1} (NH).

Subsequent elution with chloroform gave 0.16 g (6%) of diazepinone Va (containing tautomer Vb) and 0.27 g (10%) of quinone III.

B) A 0.4-g sample of acetoacetyl derivative III was refluxed in 5 ml of glacial acetic acid for 15-20 min, after which the mixture was cooled, and the precipitate was separated, washed with water, and dried to give 0.3 g (80%) of diazepinone IV. The IR spectrum was identical to the spectrum of diazepinone IV obtained in experiment A.

2,5-Dihydro-4-methyl-1H-anthra[2,3-b]-1,4-diazepine-2,7,12-trione (X). A mixture of 1 g (4.2 mmole) of diamine II, 2 ml (15.4 mmole) of AAE, and 150 ml of toluene was refluxed with a Dean–Stark adapter for 20 h, after which it was cooled, and the precipitate was separated and washed successively with chloroform, alcohol, and ether to give 1.1 g (86%) of X. IR spectrum: 1670 (C=O); 3310, 3355 cm^{-1} (NH).

2,3-Dihydro-1H-anthra[1,2-d]imidazole-2,6,11-trione (VIII) and 2,3-Dihydro-3-isopropenyl-1H-anthra[1,2-d]imidazole-2,6,11-trione (IX). A) A 0.1-g sample of diazepinone V was heated at 300°C for 5-10 min, after which it was cooled, and the melt was dissolved in chloroform and chromatographed on silica gel (elution with chloroform) to give 0.05 g (50%) of imidazolone IX and 0.01 g (13%) of imidazolone VIII.

An experiment was carried out similarly with diazepinone IV, and 0.02 g (20%) of imidazolone VIII was obtained.

B) A 0.1-g sample of imidazolone IX was refluxed in 15 ml of 2 N HCl for 3-4 h, after which the mixture was cooled and neutralized with ammonium hydroxide. The yellow precipitate of imidazolone VIII was separated. The yield was 0.08 g (90%). The IR spectra of the samples of imidazolone VIII obtained in experiments A and B were identical.

2,3-Dihydro-1-isopropenyl-1H-anthra[2,3-d]imidazole-2,5,10-trione (XII). A 0.3-g sample of diazepinone X was heated at 300°C for 5-10 min, after which it was cooled, and the melt was recrystallized from DMSO. The yield was 0.25 g (85%). IR spectrum: 1620, 1675, 1710-1730 (C=O); 3290 cm^{-1} (N–H).

2,3-Dihydro-1H-anthra[2,3-d]imidazole-2,5,10-trione (XIII). A 0.8-g sample of imidazolone XII was refluxed in 10 ml of 2 N HCl for 2 h, after which the mixture was cooled and neutralized with ammonium hydroxide. The precipitate was separated and reprecipitated from DMSO by the addition of methanol. The yield was almost quantitative. IR spectrum: 1620, 1680, 1720 (C=O); 3350 cm^{-1} (N–H).

2,3,4,5-Tetrahydro-4-methyl-1H-anthra[1,2-b]-1,4-diazepine-2,8,13-trione (VII). A) A mixture of 0.5 (2.1 mmole) of diamine I and 2 g (2.3 mmole) of crotonic acid was heated on a bath heated to 200°C for 30 min, after which it was cooled, and the melt was triturated with 20-30 ml of methanol. The mixture was poured into water, and the precipitate was separated and chromatographed on silica gel (elution with chloroform). The yield was 0.4 g (61%). IR spectrum: 1630, 1650 (C=O); 3340 cm^{-1} (N–H).

B) A solution of 0.1 mmole of V in 30 ml of absolute alcohol was hydrogenated over platinum oxide. After the calculated amount of hydrogen had been absorbed, the catalyst was removed by filtration, and the solvent was removed. The yield was 90%. The IR spectra of the substances obtained in experiments A and B were identical.

2,3,4,5-Tetrahydro-4-methyl-1H-anthra[2,3-b]-1,4-diazepine-2,7,12-trione (XI). A) This compound was obtained from 0.5 g (2.1 mmole) of diamine II and 2 g (2.3 mmole) of crotonic acid by the method presented for VII. The yield was 0.46 g (71%). IR spectrum: 1670-1690 (C=O); 3290, 3380 cm^{-1} (N–H).

B) This compound was obtained by reduction of diazepinone X by the method presented for VII. The yield was 90%. The IR spectra of the substances obtained in experiments A and B were identical.

2,3,4,5-Tetrahydro-2-methyl-1H-anthra[1,2-b]-1,4-diazepine-4,8,13-trione (VI). This compound was obtained by reduction of diazepinone IV by the method presented for VII. The yield was 52%. IR spectrum: 1660-1680 (C=O); 3220-3240 cm^{-1} (N–H).

The characteristics of the synthesized compounds are presented in Table 1.

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