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Chemistry

AMIDOXIME-FUNCTIONALIZED (9,10-DIOXOANTRACEN-1-YL)HYDRAZONES

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Abstract. New (9,10-dioxoanthracen-1-yl)hydrazones containing amidoxime fragments were synthesized by the interaction of corresponding hydrazones of malonodinitrile, ethyl cyanacetate, ethyl acetoacetate, and acetylacetone with hydroxylamine in boiling dioxane in the presence of sodium acetate. It was established that the reaction of *N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)carbonohydrazonoyldicyanide **1** with NH_2OH leads to the formation of 2-(2-(9,10-dioxo-9,10-dihydroanthracen-1-yl)hydrazinylidene)-N^1,N^3-dihydroxymalonimidamide **2** as the major product, and 3-amino-2-(2-(9,10-dioxo-9,10-dihydroanthracen-1-yl)hydrazinylidene)-3-(hydroxyimino)propanamide **3** as a minor product. The ^{1}H, ^{13}C NMR and LC-MS data showed that the interaction of 9,10-dioxoanthracenylhydrazone of acetylacetone **5** by hydroxylamine is accompanied with the elimination of the acetyl fragment formed 1-[2-(2-(hydroxyimino) propylidene)hydrazinyl]anthracene-9,10-dione **9**. Possible mechanisms for the formation of amidoximes **3** and **9** are proposed. Quantum-chemical DFT calculations of the Gibbs free energy (ΔG) to determine conformational advantage of *Z*- or *E*-isomers for the amidoxime form of the derivatives **2,3,7-9** were carried out using the *M06-2X* hybrid method with *6-311++G(d, p)* basis set and the SMD solvation model in DMSO.

Keywords: 9,10-dioxoanthracenyl hydrazones, amidoximes, geometric isomerism, DFT calculations, *M06-2X/6-311++G(d,p)*

1. Introduction

Amidoxime compounds are valuable objects for organic and medicinal chemistry due to the presence of hydroxyimino and amino functions at one carbon atom. They are widely used as "building blocks" in the synthesis of various heterocyclic systems [1], as selective reagents for the determination of cations of toxic metals and for the development of metalloprotein inhibitors [2]. The attention of researchers to the use of the amidoxime fragment as a powerful pharmacophore in the development of effective prodrugs is connected with the transformation of amidoximes by enzymes into amides with the subsequent release of NO or their reduction to amidines (Fig. 1) [2, 3]. In particular, the use of amidoximes as antithrombotic agents has become widespread. *Ximelagatran* as a direct inhibitor of thrombin was the first known prodrug with the anticoagulant effect [4-7]. However, *Ximelagatran* is currently not used due to the high hepatotoxicity. Later, commercially available double prodrug *Dabigatran* (*Pradaxa*) as a thrombin inhibitor of oral administration with improved pharmacokinetic properties was developed [8]. Amidoxime-succinic acid ester of *Dabigatran* is a structural modification of *Pradaxa,* with a good solubility, rapid activation and bioavailability at the level of *Dabigatran etexilate* [9]. In addition, amidoxime-containing prodrugs with anti-protozoal (*Pentamidine* and its analogues) [10], antiviral (amidoxime derivative of *Oseltamivir*) [11] properties have been identified. Moreover, amidoxime prodrugs are known as serum protease inhibitors (*Upamostat*) [12], with antidiabetic and protective actions (*BGP-15*) [13].

On the other hand, compounds with antithrombotic and antioxidant actions were found among biologically active derivatives of 9,10-anthracenedione [14-18]. The recent results of the successful functionalization of amino derivatives of 9,10-anthracenediones are shown in the works [16-24]. It is the prompts to develop this direction.

Taking into account the fact that the concept of creating a prodrug is rapidly developing, the aim of this work is the synthesis of new derivatives of 9,10-anthracenedione functionalized with the amidoxime residue and the study of their chemical properties.

2. Experimental

The ^{1}H and ^{13}C NMR spectra of the synthesized compounds were obtained on a Varian Mercury-400 spectrometer (400 and 100 MHz, respectively) in

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solutions of DMSO-d_6, with TMS as an internal standard. LC-MS (liquid chromatography–mass spectrometry) spectra were recorded on Agilent 110\DAD\HSD\VLG 119562, ionization by electrospray at the atmospheric pressure (70 eV). Elemental analysis was performed on the PerkinElmer CHN-Analyzer series 2400. Melting points were measured on a Boetius device and are uncorrected. The individuality of the obtained compounds was monitored by TLC on Silufol UV-254 plates in a solvent system benzene : acetonitrile (6 : 1).

The initial 9,10-dioxoanthracenylhydrazones **1,3-5** were obtained according to the methods described in [25, 26].

2-(2-(9,10-Dioxo-9,10-dihydroanthracen-1-yl)hydrazinylidene)-N'^1,N'^3-dihydroxymalonimidamide 2. 0.3 g (3.7 mmol) of sodium acetate was added to 0.25 g (3.7 mmol) of hydroxylamine hydrochloride in 60 ml of dioxane at 293 K. The reaction mixture was maintained at constant stirring for 15 min, than 0.5 g (1.7 mmol) of *N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)carbonohydrazonoyldicyanide **1** was added. The reaction mixture was heated to 373 K and left at continuous stirring and heating for 2 h, cooled, diluted with 5-fold amount of water. The resulting precipitate was filtered off, washed with water, dried, extracted with hot acetonitrile, filtered off. The filtrate was evaporated to give product **2**. The yield was 80 %, m.p. 469–471 K. ^{1}H NMR spectrum, δ, ppm: 5.74 s (2H, NH_2), 6.17 s (2H, NH_2), 7.73 dd (2H, J = 20.2, 12.4 Hz, H Ar); 7.82-7.92 m (3H, H-Ar); 8.08-8.19 m (1H, H-Ar); 8.44 d (1 H, J = 7.5 Hz, H Ar); 10.09 br.s (1 H, OH); 10.24 br.s (1 H, OH); 13.74 br.s (1 H, NH). ^{13}C NMR spectrum, δ, ppm: 117.5, 119.9, 121.5, 122.0, 125.7, 126.6, 132.2, 133.1, 133.2, 133.3, 134.4, 135.6, 143.6 (C Ar); 145.4, 149.0 (C=NOH); 182.4, 184.1 (C=O). LC-MS spectrum, m/z (I_{rel}, %): 367 $[M+1]^+$ (100). Found % C: 55.68; H 3.92; N 22.98. $C_{17}H_{14}N_6O_4$. Calculated %: C 55.74; H 3.85; N 22.94.

3-Amino-2-(2-(9,10-dioxo-9,10-dihydroanthracen-1-yl)hydrazinylidene)-3-(hydroxyimino) propanamide 3. It was obtained as a residue after washing of the precipitate with hot acetonitrile to give compound **2** (see above). Yield 8 %, m.p. 493–495 K. ^{1}H NMR spectrum, δ, ppm: 5.97 s (2H, NH_2), 6.17 s (2H, NH_2), 7.74 dd (2H, J = 20.2, 12.4 Hz, H Ar); 7.85-8.01 m (2H, H Ar); 8.17–8.29 m (2H, H Ar); 8.42 d (1H, J = 7.5 Hz, H Ar); 10.31 br.s (1H, OH);14.56 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 118.8, 119.1, 121.7, 122.1, 124.4, 127.4, 131.1, 132.3, 133.7, 134.0, 135.1, 137.4, 145.1 (C Ar);149.5 (C=NOH); 162.4, 183.6, 184.9 (C=O). LC-MS spectrum, m/z (I_{rel}, %): 352 $[M+1]^+$ (100). Found, %: C 58.19; H 3.69; N 20.01. $C_{17}H_{13}N_5O_4$. Calculated, %: C 58.12; H 3.73; N 19.93.

Ethyl 3-amino-2-[2-(9,10-dioxo-9,10-dihydroanthracen-1-yl)hydrazinylden]-3-(hydroxyimino)propanoate 7. 0.15 g (1.8 mmol) of sodium acetate was added to 0.25 g (1.8 mmol) of hydroxylamine hydrochloride in 60 ml of dioxane at 293 K. The reaction mixture was maintained at constant stirring for 15 min, and 0.63 g (1.7 mmol) of ethyl 2-cyano-2-(2-(9,10-dioxo-9,10-dihydroanthracen-1-yl)hydrazinelyden)acetate **4** was added. The reaction mixture was heated to 373 K and kept at constant stirring for 2 h. Then the reaction mixture was cooled, diluted with 5-fold amount of water. The resulting precipitate was filtered, washed with water and dried. Yield 76 %, m.p. 521–523 K. ^{1}H NMR spectrum, δ, ppm: 1.34 t (3H, J = 7.2, CH_3); 4.41 q (2H, J = 7.2, CH_2); 6.17 s (2H, NH_2), 7.87 d (1H, J = 7.5 Hz, H Ar), 8.01-7.83 m (3H, H Ar); 8.13–8.20 m (3H, H Ar); 10.29 br.s (1H, OH); 13.94 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 14.9 (CH_3); 63.5 (CH_2); 117.8; 122.3; 123.6; 125.6, 126.1; 127.6; 131.0, 132.1; 133.0; 133.4; 133.7; 134.0; 136.8, 143.3 (C Ar);163.0, 182.7; 184.2 (C=O). LC-MS spectrum, m/z (I_{rel}, %): 381 $[M+1]^+$ (100). Found, %: C 60.06; H 4.19; N 14.79. $C_{19}H_{16}N_4O_5$. Calculated, %: C 60.00; H 4.24; N 14.73.

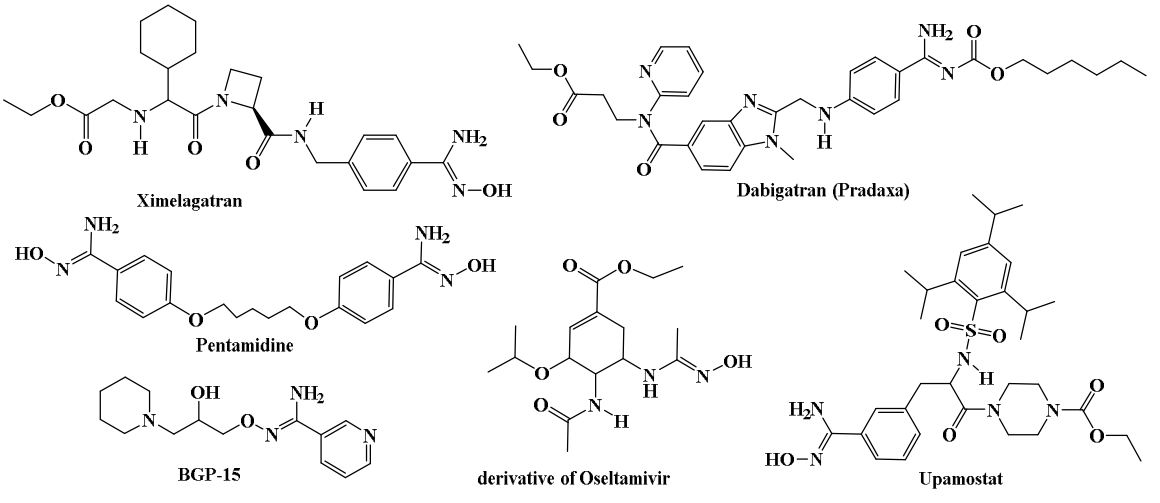


Fig. 1. Known prodrugs among amidoxime derivatives

Ethyl 2-[2-(9,10-dioxo-9,10-dihydroanthracen-1-yl)hydrazinylidene]-3-(hydroxyimino)butanoate 8. Obtained in a similar manner to the compound **7.** Yield 65 %, m.p. 491–493 K. ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, J=7.2, CH_3), 2.08 s (3H, CH_3); 4.45 q (2H, J=7.2, CH_2); 7.75 d (1H, J = 7.5 Hz, H Ar), 7.79-7.89 m (3H, H Ar), 8.05-8.13 m (3H, H Ar), 10.31 s (1H, OH), 14.31 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 13.1 (CH_3), 20.8 (CH_3), 62.7 (CH_2), 117.6, 121.8, 125.4, 127.57, 128.1, 130.8, 131.5, 133.2, 133.7, 135.0, 135.3, 135.8, 148.4 (C Ar), 163.4 (C=O), 183.5 (C=O), 185.7 (C=O). LC-MS spectrum, m/z (I_{rel}, %): 380 $[M+1]^+$ (100). Found, %: C 63.39; H 4.46; N 11.12. $C_{20}H_{17}N_3O_5$. Calculated, %: C 63.32; H 4.52; N 11.08.

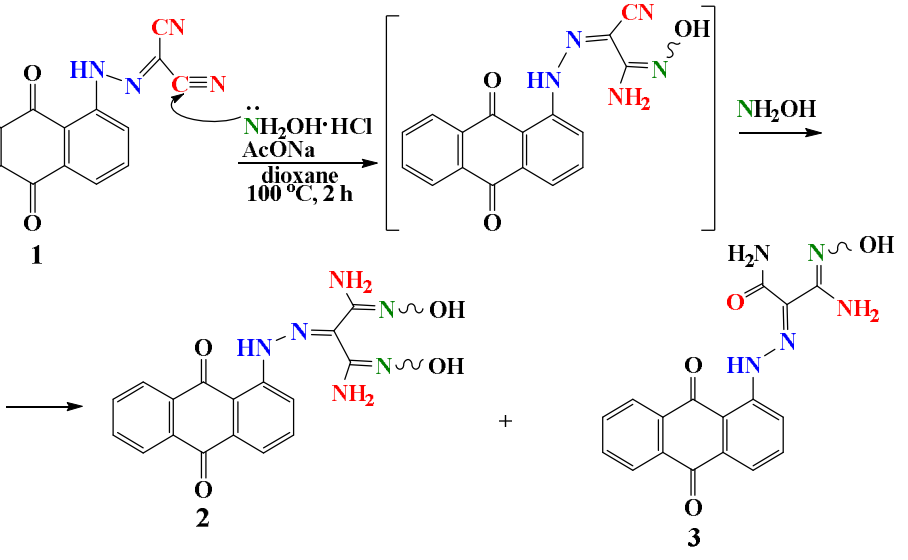
1-[2-(2-(Hydroxyimino)propylidene)hydrazinyl] anthracene-9,10-dione 9. Obtained in a similar manner to the compound **2.** Yield 88 %, m.p. 491–493 K. ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, CH_3), 7.88 dd (2H, *J = 7.5, 1.5 Hz*, H Ar); 7.91-7.95 (3H, H Ar); 8.17-8.21 m (3H, H Ar), 10.27 br.s (1H, OH), 13.39 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.5 (CH_3), 119.9, 121.6, 125.5, 126.3, 127.1, 132.3, 133.2, 134.2, 135.1, 136.3, 137.1, 139.6, 145.2 (C Ar); 185.5 (C=O), 183.6 (C=O). LC-MS spectrum, m/z (I_{rel}, %): 308 $[M+1]^+$ (100). Found, %: C 66.51; H 4.29; N 13.63. $C_{17}H_{13}N_3O_3$. Calculated, %: C 66.44; H 4.26; N 13.67.

Quantum-chemical density functional theory (DFT) calculations. Geometric optimization of all structures was carried out using the *M06-2X* hybrid method, the basic set *6-311++G(d,p)* of *Gaussian 09W* program package [27]. The solvation effect was calculated using the solvation model SMD (Solvation model based on density) in DMSO. The Gibbs free energy data were obtained using a vibration analysis.

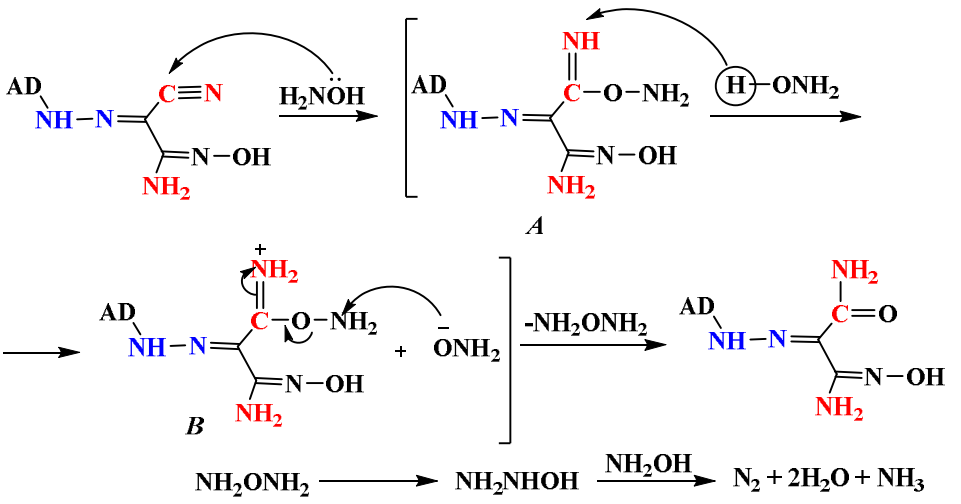
3. Results and Discussion

Taking into account the practical significance of amidoximes in the organic synthesis and medicinal chemistry, the new functionalized derivatives of dioxoanthracenylhydrazones were synthesized by an interaction of substitutes in the ylidene part of the compounds **1, 3-5** with hydroxylamine in a boiling dioxane. It should be noted, that the reaction in the classical proton solvent ethanol led to a low conversion of the starting compound, despite the long process duration (up to 50 h). Similar results with ethanol were observed in the synthesis of 9,10-dioxoanthrazylhydrazrazones with heterocyclic fragments [26]. Moreover, an excess of hydroxylamine (1:2.2) for the complete conversion of initial *N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)carbonohydrazonedicyanide **1** to **2** (Scheme 1) was required (control of TLC, eluent – benzene : acetonitrile). It was found that along with the main product **2**, the formation of minor product **3** takes place. Compound **3** was separated by a fractional crystallization.

In the ^{1}H and ^{13}C NMR spectra of dioximdiamide **2**, for which geometric Z/E isomerism in the amidoxime fragment is possible, a single set of signals was observed. It indicates the formation of only one geometric isomer. The ^{1}H NMR spectrum is characterized by two singlet signals of two amino groups at 5.74 and 6.17 ppm, aromatic protons within 7.67–8.45 ppm, singlets of two hydroxyl groups at 10.09 and 10.24 ppm, and a broad singlet of the amino group of the hydrazone moiety at 13.75 ppm. The ^{13}C NMR spectrum contains the corresponding carbon signals of the 9,10-anthracenedione ring (AD) and the hydrazone moiety, including two amidoxime residues (C=NOH) at 145.4 and 149.0 ppm.



Scheme 1. Interaction of *N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)carbonylhydrazonoyldicyanide **1** with hydroxylamine



Scheme 2. A plausible mechanism for the formation of minor product **3**

The formation of a single isomer of compound **2** is also confirmed by the presence of only one molecular ion peak (m/z) with a mass of 367 $[M+H]^+$ in LC-MS. The authors in the works [28–31] confirmed the existence of amidoximes with a free amino group in the form of an exclusively *Z*-isomer due to the presence of an intramolecular hydrogen bond between the NH group of the hydrazone moiety and the proton acceptor in the ylidene part of the molecule. Hence, it can be assumed that the hydrazone dihydroxymalonimidamide **2** also exists in the *Z,Z*-izomeric form.

Earlier, the authors [32, 33] had investigated the formation of minor amide products in various reaction conditions and proposed a mechanism for their production, which was adapted to describe a possible mechanism for the formation of by-product **3** (Scheme 2).

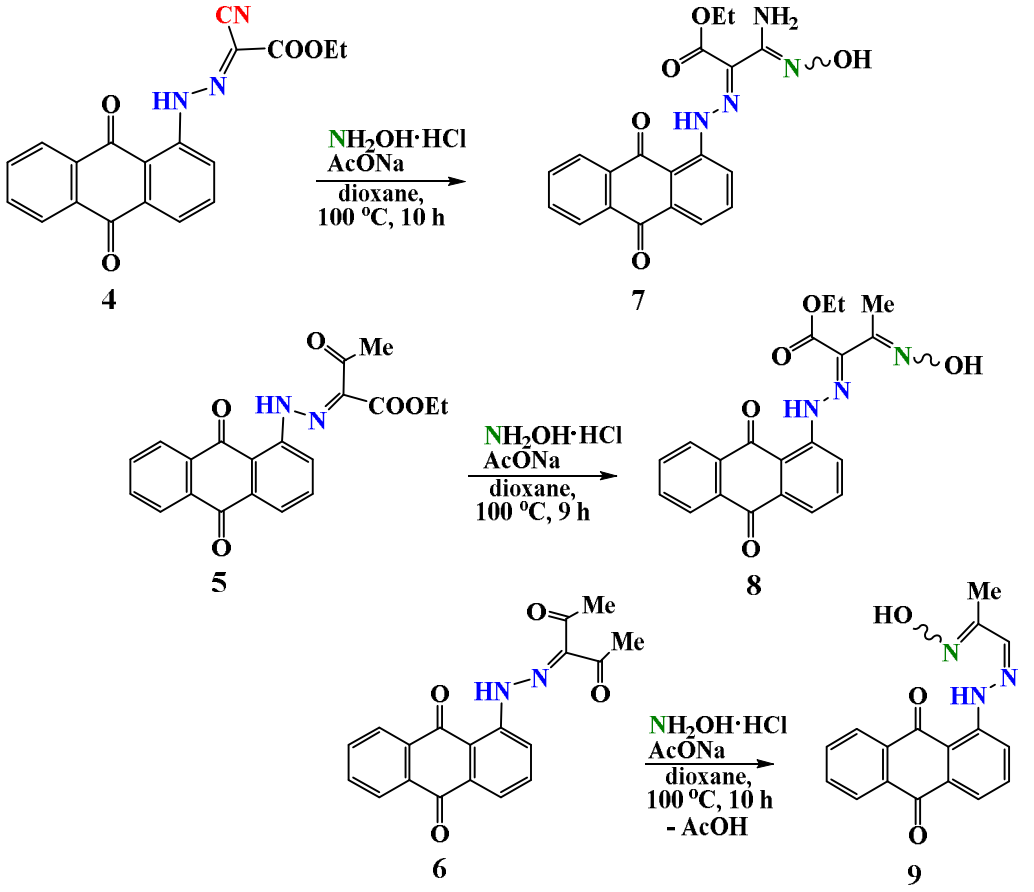
According to the proposed mechanism (Scheme 2), the formation of **3** begins from the attack of the carbon atom of the nitrile group with the oxygen atom of the second hydroxylamine molecule, which leads to the intermediate ***A***. The imine nitrogen atom of the intermediate ***A*** with a high electron density at the $–O–NH_2$ fragment pulls the proton out from the NH_2OH molecule (intermediate ***B***), leaving the oxygen atom negatively charged in the hydroxylamine. It facilitates the attack of the amino group. In the process of transformation, the unstable compound NH_2ONH_2 decomposed with the elimination of nitrogen, ammonia and water [32].

A reliable evidence of the formation of the amide structure **3** is the presence of the corresponding signals in the ^1H and ^{13}C NMR spectra. In particular, the ^1H NMR spectrum contains the signals of the protons of the 9,10-dioxoanthracene ring and characteristic signals of the substituent of the ylidene part of the molecule, namely the singlet signal of the amino group of the amide fragment at 5.97 ppm and singlet signals of the amidoxime residue. The last one was presented as singlet signals of two protons of the amino group at 6.17 ppm and proton of the hydroxy group at 10.31 ppm. The formation of the amide residue was also confirmed by the ^{13}C NMR spectrum, where the signals of the carbon atom of the amidoxime fragment C=NOH at 149.5 ppm, and the additional carbonyl group at 162.4 ppm are presented. Furthermore, there is only one molecular ion peak with a mass of 352 $[M+H]^+$ in the LC-MS spectrum.

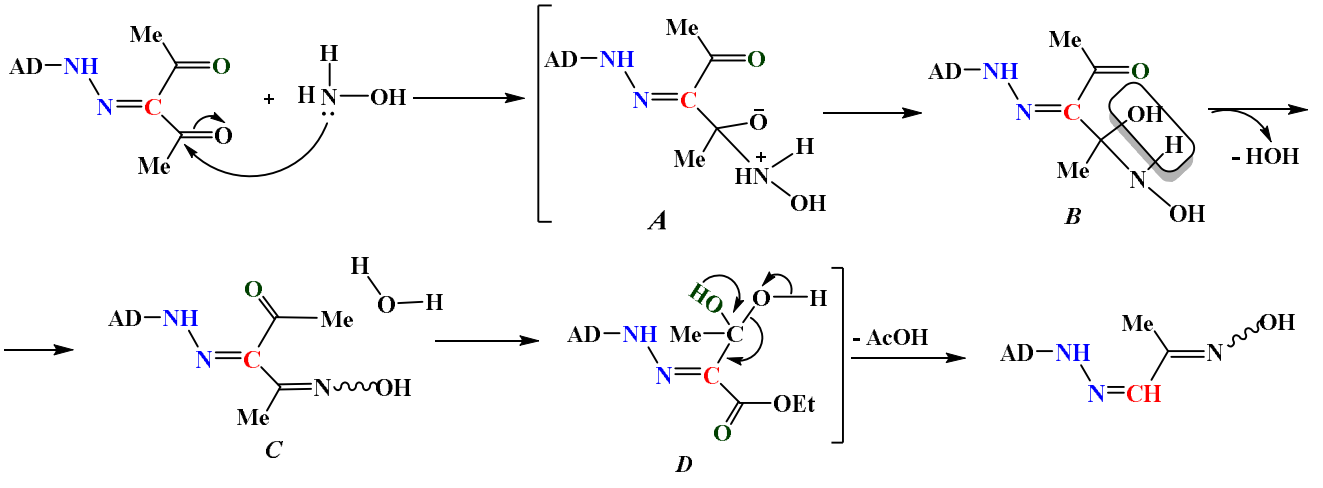
The interaction of hydrazones containing nitrile/acetyl and/or etoxycarbonyl fragments **4-6** with NH_2OH leads to the formation of ethyl 3-amino-2-[2-(9,10-dioxo-9,10-dihydroanthracene-1-yl)hydrazinylidene]-3-(hydroxyimino)propanoate **7**, ethyl 2-[2-(9,10-dioxo-9,10-dihydroanthracene-1-yl)hydrazinylidene]-3- (hydroxyimino)butanoate **8** and 1-[2-(2-(hydroxyimino) propylidene)hydrazinyl]anthracene-9,10-dione **9**.

It should be noted that the reaction of hydrazone of acetylacetone **6** with hydroxylamine in the boiling dioxane proceeds with the formation of 1-[2-(2-(hydroxyimino)propylidene)hydrazinyl]anthracene-9,10-dione **9**. There are no signals of the methyl group of the second acetyl fragment in the ^1H and ^{13}C NMR spectra of **9**. Only one molecular ion peak m/z with a mass of 308 $[M+H]^+$ is in the LC-MS spectrum. It indicates the elimination of the acetyl fragment. According to literature data [34, 35], a probable mechanism for the formation of hydrazone with the amideoxime residue **9** (Scheme 4) involves the reaction through the intermediates ***A-C***, followed by the elimination of acetic acid from the intermediate ***D***, analogously described in [18].

Analysis of the ^1H, ^{13}C NMR and LC-MS spectra of the obtained amidoxime derivatives **3**, **7-9** showed that these compounds also exist as a single geometric isomer.



Scheme 3. Interaction of 9,10-dioxoanrathenylhydrazones **4-6** with hydroxylamine



Scheme 4. A probable mechanism for the formation of hydrazone **9**

The stability of the *Z*/*E* configurations in amidoximes is an important indicator that plays a significant role in the affinity of a molecule to the active center of a biological target, affecting its pharmacological activity [36]. The Gibbs free energy (ΔG) is a thermodynamic characteristic, which allows everyone to theoretically estimate the stability of such isomers [36]. It is known that amidoximes can be represented by three general forms (amidoxime, iminohydroxylamine, aminonitrone), which are influenced by the nature of the solvent [37]. Based on the theoretical

studies of tautomerism between the general forms, the first form is more thermodynamically stable [38].

The amidoxime derivatives **2, 3, 7-9** exist in single isomeric forms, and are represented as single sets of signals in the solution of aprotic DMSO-d_6 in the ^{1}H and ^{13}C NMR spectra. Therefore, theoretical DFT calculations (ΔG) for the possible geometric isomers in the amidoxime form of the studied compounds were carried out. The DFT calculations were performed using the hybrid method *M06-2X*, basic set *6-311++G(d,p)* with the SMD solvation model in DMSO to determine the conformational advantage of the *Z*- or *E*-isomer (Table).

Calculated ΔG values for the possible geometric isomers of amidoxime derivatives 2, 3, 7-9

Compound	Possible isomer configuration	ΔG, kJ/mol
2	*1E,2E*	-135.731
	1E,2E,3Z	-138.147
	1E,3E	-135.363
	1Z,2Z,3E	-135.447
	1Z,3Z	**-138.830**
3	*2E,3E*	-135.476
	2E,3Z	-129.799
	2Z,3E	**-137.620**
	2Z,3Z	-132.382
7	*2E,3E*	-136.418
	2E,3Z	-138.959
	2Z,3E	**-143.364**
	2Z,3Z	-135.099
8	*2E,3E*	-132.391
	2E,3Z	-137.746
	2Z,3E	**-143.356**
	2Z,3Z	-140.601
9	*1E,2E*	-120.425
	1E,2Z	-122.866
	1Z,2E	**-127.509**
	1Z,2Z	-121.610

According to the data of DFT calculations, the stability of the *Z*/*E* isomers in the amidoxime fragment depends on the configuration and orientation of the substituents in the ylidene part of the molecule. In agreement with the values of ΔG, the *Z*-isomeric form of the hydrazone part prevails in all amidoximic derivatives **2, 3**, **7-9**. Moreover, the *Z*-isomeric form is confirmed by a presence of the bifurcated intramolecular hydrogen bond between the NH group of the hydrazone fragment and the proton acceptor in the ylidene moiety [18], which is observed as the characteristic low-field position of the proton signal of the NH group in the ^{1}H NMR spectra in the range of 13.39–14.56 ppm [18, 39]. Instead, different results on the *Z*/*E* configuration were obtained for the amidoxime fragment. In particular, it was found that in the case of compound **2**, the calculated data are in agreement with the experimental results of the study of the *Z,Z*-isomerism of bisamidoxime derivatives [40]. At the same time, according to the calculated ΔG values, the *E*-isomer of the amidoxime residue is predominated for compounds **3, 7–9**, which is consistent with a stabilization of the amidoxime fragment in the aprotic solvent DMSO [36].

4. Conclusions

The new amidoximes of 9,10-dioxoanthracenylhydrazones of malonodinitrile, ethyl cyanacetate, ethyl acetoacetate, and acetylacetone **2, 3, 7-9** as convenient reagents for obtaining various derivatives, and potentially biologically active substances, were synthesized. It was determined based on the results of ^{1}H, ^{13}C NMR and LC-MS spectra, that the obtained amidoxime compounds exist as one geometric isomer. The conformational preference of *Z*/*E* isomerism for the amidoxime-functionalized 9,10-dioxoanthracenylhydrazones was confirmed based on the results of the DFT calculations of the Gibbs free energy (ΔG). The *Z*-isomeric form of the hydrazone part for compounds **2, 3, 7-9** was experimentally confirmed due to the presence of the bifurcated intramolecular hydrogen bond between the NH-group of the hydrazone fragment and the proton acceptor in the ylidene moiety. It was shown that for amidoxime **2** the calculated data are consistent with the experimental results of the *Z,Z*-isomerism study of known in the literature bisamidoxime derivatives. According to

the calculated ΔG values, the *E*-isomer of the amidoxime residue was shown as probably the dominant form in DMSO for compounds **3, 7–9**.

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АМІДОКСИМ-ФУНКЦІОНАЛІЗОВАНІ (9,10-ДІОКСОАНТРАЦЕН-1-ІЛ)ГІДРАЗОНИ

Анотація. *Взаємодією (9,10-діоксоантраценіл-1)-гідразонів малонодинітрилу, етилових естерів ціанацетатної та ацетацетатної кислот, а також ацетилацетону із гідроксил аміном у киплячому діоксані у присутності ацетату натрію проведено модифікацію функціоналізованого гідразонного угруповання амідоксимними фрагментами. Встановлено, що реакція N-(9,10-діоксо-9,10-дигідроантрацен-1-іл)карбоногідразоноілдиціаніду **1** з NH_2OH приводить до утворення 2-(2-(9,10-діоксо-9,10-дигідроантрацен-1-іл)гідразиніліден)-N^1,N^3-дигідроксималонімідаміду **2** як основного та 3-аміно-2-(2-(9,10-діоксо-9,10-дигідроантрацен-1-іл)гідразиніліден)-3-(гідроксіміно)пропанаміду **3** як мінорного продукта. Методами ^1H, ^{13}C ЯМР-спектроскопії та хроматомас-спектрометрії встановлено, що взаємодія 9,10-діоксоантраценілгідразону ацетил ацетону **5** із гідроксиламіном супроводжується елімінуванням ацетильного фрагмента, наслідком чого є утворення 1-[2-(2-(гідроксіміно)пропіліден)гідразиніл]антрацен-9,10-діону **9**. Запропоновано вірогідні механізми утворення амідоксимів **3** та **9**. Проведені квантово-хімічні DFT-розрахунки вільної енергії ГіббсаΔG для амідоксимної форми похідних **2, 3, 7-9** гібридним методом M06-2X в базисному наборі 6-311++G(d,p) із використанням сольватаційної моделі SMD у ДМСО з метою визначення конформаційної переваги Z- або E-ізомерів.*

Ключові слова: *9,10-діоксоантраценілгідразони, амідоксими, геометрична ізомерія, DFT-розрахунки, M06-2X/6-311++G(d,p).*