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SYNTHESIS AND ISOMERISM OF 2-BENZOYL-5,12-DIMETHOXY-3-HETERYL-1,2,3,4-TETRAHYDRONAPHTHO[2,3-G]PHTHALAZINE-6,11-DIONES

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The cyclocondensation of the bielectrophile 2,3-bis(bromomethyl)-1,4-dimethoxyanthracene-9,10-dione with several heteroaryl-benzyl hydrazides with the formation of exofunctionalized tetracyclic quinoid systems was studied. Different numbers of products were isolated by liquid chromatography for different hydrazides. The products were identified as atropisomers. Generally, only one isomer was isolated for N²-(4,6-dimethylpyrimidin-2-yl)benzohydrazide, while two and three isomers were isolated for N²-(6-chloropyridazin-3-yl) benzohydrazide and for N²-(4-chlorophthalazin-1-yl) benzohydrazide, respectively. To determine their structure, modeling of the geometries and NMR spectra by DFT methods was performed. The structure of the obtained isomers was established based on ¹H, ¹³C NMR and NOESY spectra, the results well agree with the simulation results.

Keywords: 9,10-anthracenedione, hydrazide, cyclocondensation, atropisomerism, molecular modeling.

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Introduction

Quinoid compounds and nitrogen-containing heterocycles are widespread and important building blocks of natural molecules and important structures in synthetic chemistry. Heterocyclic quinone derivatives have been described in the literature as compounds exhibiting antithrombotic [1,2], antimicrobial [3] and anticancer activity [4,5]. Such wide applications determine the relevance of the choice of research objects aimed at developing synthetic approaches to polyfunctional compounds based on quinones and nitrogen heterocycles.

Establishing the spatial structure of organic molecules is an important task in the search for new biologically active compounds. The development of computational methods for predicting ¹H and ¹³C NMR shifts, together with the development of computer technology, allows modeling the structure of even sufficiently large organic molecules [6]. Today, the most attractive method for predicting the structure and spectral properties of organic molecules is a density functional theory (DFT) [7].

It is widely used for the analysis of the conformation of molecules due to its relatively low computational complexity and good results in the comparative analysis of homologous series of molecules [8]. Even with sufficient experimental data, DFT calculations can provide information that is very useful for interpreting the structure of the obtained compounds.

The study of the structure of atropisomers in solution for structurally similar substances based on the analysis of experimental and calculated ¹H NMR spectra at different temperatures is described elsewhere [9,10]. The equilibrium between atropisomers for the compounds reported in work [9] is observed at room temperature that can be explained by the low stiffness of the cycle. In our previous studies of the cycloaddition of 2,3-bis(bromomethyl)quinoxaline [10], isomeric forms were isolated as individual substances.

It was shown that the yield of atropisomers in the reaction is consistent with the calculations of their energies, with the predominant formation of the more energetically favorable isomer.

Experimental

Melting points were determined on a Buchi capillary melting point apparatus and are uncorrected. Element analyses were performed by the centre of Microanalyse of the Aix-Marseille University. ^1H NMR spectra were recorded on a Bruker AC 200 spectrometer. NOESY spectra were recorded using Bruker Avance 400MHz spectrometer with 60 ms mixing time. The ^1H chemical shifts are reported from TMS. LC-MS spectra were recorded using a chromatographic/mass-spectrometric system consisting of a high performance liquid chromatographer «Agilent 1100 Series» series equipped with mass-selective detector «Agilent LC/MSD SL».

The following adsorbent was used for column chromatography: silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC was performed on 5 cm×10 cm aluminium plates coated with silica gel 60 F254 (Merck) in an appropriate solvent.

The Gaussian 09, Revision B.01 package [15] has been used for all calculations carried out in this work with methods and Pople basis sets described in the main text. For the optimized structures, the confirmation of the energy minimum and thermochemical data were obtained using vibrational analysis on the same level of theory.

2-Benzoyl-3-(6-chloropyridazine-3-yl)-5,12-dimethoxy-1,2,3,4-tetrahydro-naphtho[2,3-g]phthalazine-6,11-dione (3a)

2,3-Bis-bromomethyl-1,4-dimethoxyanthracene-9,10-dione **1** (0.884 g, 2.5 mmol) in 10 mL of DMF was added to stirred hydrazide **2a** (0.589 g, 2.5 mmol) and anhydrous potassium carbonate (0.685 g, 5.0 mmol) in 25 ml of DMF. The reaction mass was kept at room temperature and with constant stirring for 5 hours. The reaction was monitored by TLC and LC-MS. The reaction mixture was diluted with ice water and extracted with methylene chloride. The resulting organic phase was washed with water and dried over anhydrous sodium sulfate. After evaporation, the product was purified by chromatography using methylene chloride: diethyl ether (95:5) as eluent. A mixture of atropisomers was obtained with a total yield of 38%.

Isomer 1

Yield 0.27 g (27%), orange crystals, m.p. 171–173°C. ^1H NMR (Chloroform-*d*, 200 MHz): δ (ppm) 8.23–8.13 (m, 2H, quinone), 7.80–7.69 (m, 2H, quinone), 7.59 (d, $J=8.0$ Hz, 2H, Ph), 7.51–7.28 (m, 5H, quinoxaline, Ph), 6.11 (d, $J=18.0$ Hz, 1H, CH_2), 5.75 (br.d, $J=18.6$ Hz, 1H, CH_2), 4.33 (br.s, 2H, CH_2), 4.01 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3). ^{13}C NMR (Chloroform-*d*, 50 MHz): δ (ppm) 179.2,

179.0, 177.3, 159.7, 155.6, 152.9, 147.3, 135.7, 134.4, 133.8, 132.6, 130.7, 130.2, 129.2, 127.7, 126.5, 126.1, 121.5, 121.0, 116.6, 64.9, 64.8, 47.1, 45.1. Calculated ($\text{C}_{29}\text{H}_{21}\text{ClN}_4\text{O}_5$), %: C 64.39; H 3.91; Cl 6.55; N 10.36; O 14.79. Found, %: C 64.43; H 3.86; N 10.31. MS m/z : $[\text{M}+\text{H}]^+$ 541, 543. HPLC: $t_r=4.91$ min.

Isomer 2

Yield 0.11 g (11%), orange crystals, m.p. 184–186°C. ^1H NMR (Chloroform-*d*, 200 MHz): δ (ppm) 8.26–8.13 (m, 2H, quinone), 7.98 (d, $J=8.0$ Hz, 2H, Ph), 7.81–7.71 (m, 2H, quinone), 7.62 (d, $J=9.4$ Hz, 1H, quinoxaline), 7.54–7.38 (m, 3H), 7.32 (d, $J=9.4$ Hz, 1H, quinoxaline), 5.62 (br.s, 4H, 2CH_2), 4.23 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3). ^{13}C NMR (Chloroform-*d*, 50 MHz): δ (ppm) 182.3, 182.1, 175.2, 156.6, 154.4, 152.7, 146.1, 135.9, 134.4, 134.2, 131.5, 130.0, 129.5, 128.5, 127.0, 126.9, 126.7, 122.2, 122.0, 117.3, 62.0, 61.9, 44.2, 42.2. Calculated ($\text{C}_{29}\text{H}_{21}\text{ClN}_4\text{O}_5$), %: C 64.39; H 3.91; Cl 6.55; N 10.36; O 14.79. Found, %: C 64.41; H 3.89; N 10.33. MS m/z : $[\text{M}+\text{H}]^+$ 541, 543. HPLC: $t_r=5.48$ min.

2-Benzoyl-3-(4,6-dimethylpyrimidine-2-yl)-5,12-dimethoxy-1,2,3,4-tetrahydronaphtho[2,3-g]phthalazine-6,11-dione (3b)

Yield 0.43 g (43%), orange crystals, m.p. 184–186°C. ^1H NMR (Chloroform-*d*, 200 MHz): δ (ppm) 8.23–8.14 (m, 2H, quinone), 7.78–7.70 (m, 2H, quinone), 7.62 (dd, $J=7.4, 1.7$ Hz, 2H, Ph), 7.42–7.27 (m, 3H, Ph), 6.45 (s, 1H, pyrimidine), 6.08 (d, $J=17.5$ Hz, 1H, CH_2), 5.50 (d, $J=17.7$ Hz, 1H, CH_2), 4.46 (dd, $J=17.9, 17.4$ Hz, 2H, CH_2), 4.02 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 2.28 (s, 6H, 2CH_3). ^{13}C NMR (Chloroform-*d*, 50 MHz): δ (ppm) 182.3, 182.1, 174.7, 167.0, 160.0, 154.6, 153.1, 135.7, 134.4, 134.2, 131.5, 130.1, 128.5, 126.9, 126.7, 126.5, 122.2, 122.1, 110.7, 62.0, 61.9, 43.8, 42.3, 23.8. Calculated ($\text{C}_{31}\text{H}_{26}\text{N}_4\text{O}_5$), %: C 69.65; H 4.90; N 10.48; O 14.96. Found, %: C 69.72; H 4.93; N 10.44. MS m/z : $[\text{M}+\text{H}]^+$ 535. HPLC: $t_r=5.32$ min.

2-Benzoyl-3-(4-chlorophthalazine-1-yl)-5,12-dimethoxy-1,2,3,4-tetrahydronaphtho[2,3-g]phthalazine-6,11-dione (3c)

Total yield is 63%.

Isomer 1

Yield 0.20 g (35%), yellow crystals, m.p. 179–180°C. ^1H NMR (Chloroform-*d*, 200 MHz): δ (ppm) 8.86 (d, 1H, $J=8.4$ Hz, phthalazine), 8.12–8.19 (m, 2H, quinone), 8.07 (d, 1H, $J=8.4$ Hz, phthalazine), 7.99 (d, 2H, $J=7.1$ Hz, Ph), 7.79 (t, 1H, $J=7.7r2$ Hz, phthalazine), 7.70 (t, 1H, $J=7.6r2$ Hz, ArH), 7.63–7.67 (m, 2H, ArH), 7.37–7.51 (m, 3H, ArH), 5.73 (s, 4H, 2CH_2), 4.24 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3). Calculated ($\text{C}_{33}\text{H}_{23}\text{ClN}_4\text{O}_5$), %: C 67.06; H 3.92; Cl 6.00; N 9.48; O 13.54. Found, %: C

67.27; H 3.97; N 9.53. MS m/z : $[M+H]^+$ 591. HPLC: $t_r=5.56$ min.

Isomer 2

Yield 0.08 g (8%), yellow crystals, m.p. 168–171°C. $^1\text{H NMR}$ (Chloroform- d , 200 MHz): δ (ppm) 8.09–8.12 (m, 3H, quin., phthal.), 7.91 (d, 1H, $J=7.5$ Hz, phthalazine), 7.60–7.73 (m, 6H, Ar), 7.24–7.28 (m, 3H, Ph), 5.40 (dd, 2H, $J=18.3, 1.8$ Hz, CH_2), 4.70 (d, 1H, $J=18.3$ Hz, CH_2), 4.36 (d, 1H, $J=18.3$ Hz, CH_2), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3). Calculated ($\text{C}_{33}\text{H}_{23}\text{ClN}_4\text{O}_5$), %: C 67.06; H 3.92; Cl 6.00; N 9.48; O 13.54. Found, %: C 67.15; H 3.88; N 9.43. MS m/z : $[M+H]^+$ 591. HPLC: $t_r=5.92$ min.

Isomer 3

Yield 0.35 g (20%), yellow crystals, m.p. 185–187°C. $^1\text{H NMR}$ (Chloroform- d , 200 MHz): δ (ppm) 8.21 (d, 1H, $J=7.8$ Hz, phthalazine), 8.08–8.12 (m, 2H, quinone), 7.90 (t, 1H, $J=7.6 \times 2$ Hz, phthalazine), 7.85 (br.s, 1H, phthalazine), 7.65–7.69 (m, 2H, quinone), 7.45 (d, 2H, $J=7.4$ Hz, Ph), 7.24–7.40 (m, 3H, Ph), 4.20–6.00 (br.s., 4H, 2CH_2), 3.58–4.10 (br.s, 6H, 2OCH_3). Calculated ($\text{C}_{33}\text{H}_{23}\text{ClN}_4\text{O}_5$), %: C 67.06; H 3.92; Cl 6.00; N 9.48; O 13.54. Found, %: C 67.21; H 3.94; N 9.50. MS m/z : $[M+H]^+$ 591. HPLC: $t_r=4.23$ min.

Results and discussion

As a continuation of our previous studies on the cyclocondensation of hydrazides and 1,4-bielectrophiles [10], we studied the reaction of 2,3-bis(bromomethyl)-1,4-dimethoxyanthracene-9,10-dione **1** with several hydrazides 2a,b,c. Cyclocondensation of hydrazides 2a,b,c occurred in DMF at room temperature in the presence of two equivalents of potassium carbonate as a base. The reaction gave compounds 3a,b,c with a condensed 4-cycle system (Scheme).

However, different numbers of products were observed for different R substituents on the LC-MS of the reaction mass. Thus, in the case of the reaction of hydrazide 2b, only one product was observed, while two and three reaction products were observed

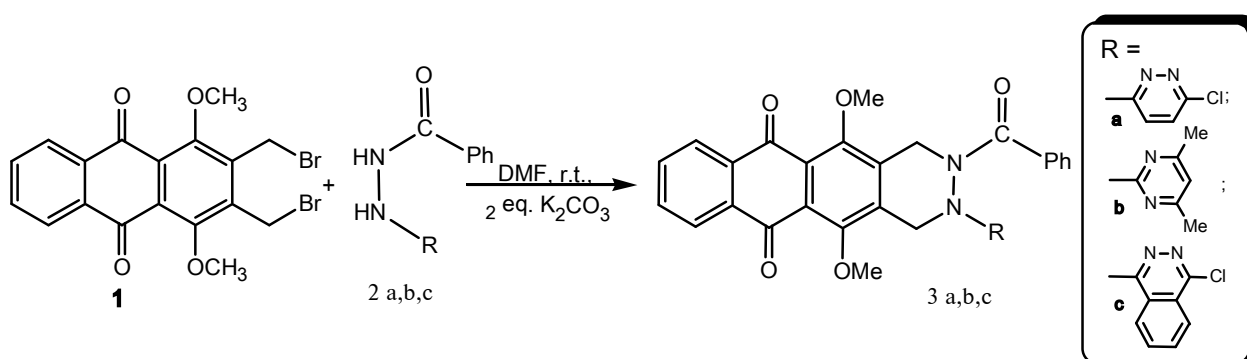
for hydrazide 2a and 2c, respectively. The resulting mixtures 3a and 3c were separated by preparative chromatography on silica gel (dichloromethane/diethyl ether, 95:5) and their components were isolated as individual substances. The results of LC-MS showed that the products formed with the corresponding substituent have the same molecular weight values corresponding to the above formula, but they exhibit some differences in NMR spectra. These products contain a six-membered pyridazine ring with benzoyl and heterocyclic substituents similar to the compounds that were previously studied [10], so we assumed the existence of similar atropisomers due to the complicated rotation of N–(C=O) bond and heterocyclic substituent.

In order to establish the spatial structure of the obtained atropisomers, a search for their possible geometries at the B3LYP/6-31G(d,p) level [11,12] was performed. A relaxed coordinate scan was performed with respect to the dihedral angles of the pyridazine ring substituents. NMR spectra at the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d,p) level in chloroform (PCM) [13] were also calculated for the found structures.

For compound 3c where a mixture of three substances was obtained, the relaxed 360° scan of the rotation of the benzoyl fragment revealed two minima (corresponding to the transition I_1-I_2). The scan of the rotation of the phthalazine substituent at the cis position –N–N–C=O system (for I_2) found another atropisomer (I_3), which corresponds to the location of the phthalazine cycle in the same plane with the quinoid fragment. The optimized geometries of the three isomers are shown in Figure.

The stability of the obtained atropisomers is explained by hydrogen bonds formation and significant spatial limitations of the rotation of the bulk phthalazine substituent and the delocalization of free electron pairs of nitrogens in the formed phthalazine cycle.

In order to correlate the isolated compounds



Scheme. Synthesis of 2-benzoyl-5,12-dimethoxy-3-heteryl-1,2,3,4-tetrahydronaphtho[2,3-g]phthalazine-6,11-diones 3a–c

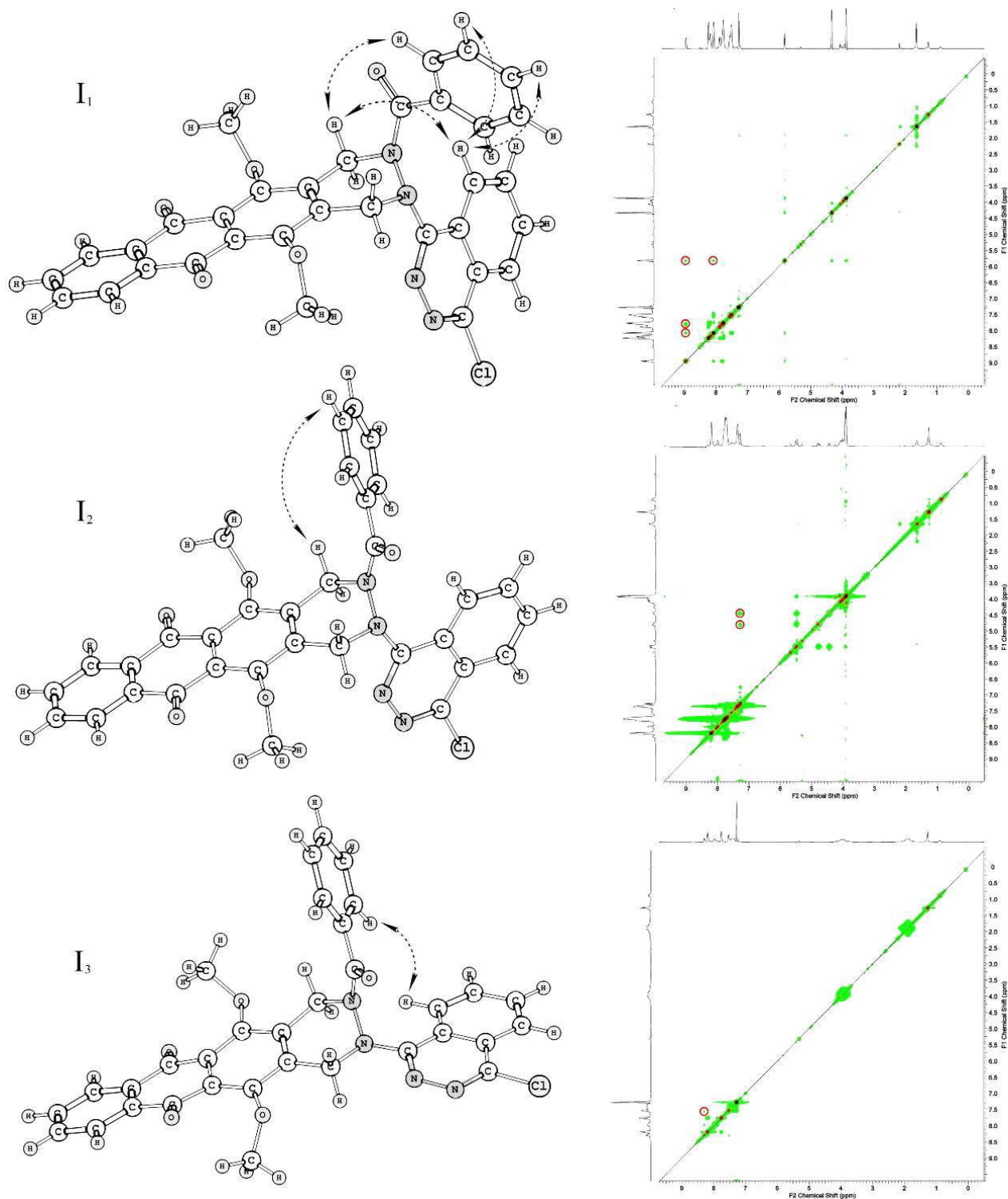
DFT calculated structures and NOESY spectra of isomers I₁ – I₃ of product 3c

Table 1
The chemical shift $\Delta\delta$, GIAO calculated/found from NMR of the isomeric forms (I_1 – I_3) of the product 3c

Quinoxaline hydrogen numbers	$\Delta\delta$, ppm, GIAO calculated/found from NMR		
	Isomer 1	Isomer 2	Isomer 3
H ^{7'} –H ^{6'}	0.07/0.08	0.12/0.11	0.05/0.05
H ^{8'} –H ^{5'}	0.85/0.77	0.03/0.14	0.38/0.53
H ^{7'} –H ^{5'}	0.34/0.30	0.34/0.36	0.22/0.22

and the calculated geometries of molecules based on ¹H-NMR spectra, their GIAO calculation for three isomers was performed. The protons of the quinoid nucleus undergo virtually no change in chemical shift depending on the conformation, but its effect on the protons of the 4-chlorophthalazin-1-yl substituent is significant. The chemical shift of proton 8', 9.50 (I_1) undergoes the most significant changes; 8.91 (I_3) and 8.58 (I_2), due to the formation of hydrogen bonds of different strengths (found by NBO [14] analysis) in I_1 and I_3 , this proton does not form bonds in I_2 . The determined values of $\Delta\delta$ for protons in the 4-chlorophthalazine cycle agree well with the calculated values (Table 1). In addition, changes are observed in the position of the doublet of 2' and 6' protons of the benzene substituent: 7.98 (I_1); 7.62 (I_2) and 7.44 (I_3), which is due to the difference of the environment and the deformation of the substituent. The experimentally revealed significant difference in $\Delta\delta$ of this doublet and multiplet of three protons of the benzoyl substituent is also well reproduced in the calculations. Significant difference in the forms of methylene groups NMR signals can be explained by the different stiffness of the cycle and the formation of hydrogen bonds by its protons. A significant broadening of the signals of methoxyl groups in I_3 is also interesting. It can be explained by the twisting of the condensed quinoid system detected in the simulation, which leads to interaction with neighboring quinoid carboxyls due to the formation of weak hydrogen bonds.

The NOESY spectra (Figure) recorded for the studied atropisomers allowed us to unambiguously confirm the assignment of the calculated atropisomer to the structure I_1 according to the values of the signals corresponding to the interaction of the proton 8' phthalazine fragment with the methylene group and protons 2' and 6' of the benzoyl fragment. The long interatomic interactions in I_2 and I_3 were insignificant, which could be expected due to the large distances between the protons of the substituents and the broadening of their signals, so in this case the analysis of recorded and calculated ¹H NMR

Table 2
Calculated relative ΔG and relative yield of the isomeric forms (I_1 – I_3) of the product 3c

Isomeric form	Calculated relative ΔG , kcal mol ⁻¹	Relative yield, %
I_1	0	56
I_2	+2.5	12
I_3	+1.5	32

spectra was more informative. However, NOESY spectra also confirm the assignment made for these isomers.

The calculated Gibbs free energies of the isomeric forms (I_1 – I_3) of the product 3c, calculated at the B3LYP/6-31G(d,p) level, correlate with the experimental yields (Table 2).

For product 3a, two fractions were isolated, the results of LC-MS of which showed that both compounds have the same molecular weight values, and the recorded ¹H NMR spectra have slight differences, while ¹³C NMR spectra were almost identical. Thus, NMR spectra were uninformative for determination of the spatial structure of the obtained isomers. In the study of the structure of isomers (I_1 – I_3) of the product 3c, the correlation between the calculated ΔG isomers and their experimental yields was shown. This allowed assuming the structure of the obtained isomers on the basis of their experimental yields and calculated ΔG of the possible structures. For product 3a on M06-2X/6-31G(d,p) level, two minima were found for the rotation of the benzene substituent with a more energetically favorable trans-arrangement –N–N–C=O of the system, which allowed attributing the structure of isomer I_1 as trans- and I_2 as cis- (Table 3).

Table 3
Calculated relative ΔG and relative yield of the isomeric forms (I_1 and I_2) of the product 3a

Isomeric form	Calculated relative ΔG , kcal mol ⁻¹	Relative yield, %
I_1	0	71
I_2	+2.0	29

For hydrazide 2b, in the reaction of which only one isomer was obtained, DFT calculations also showed the possibility of the existence of two isomers of the product 3b that differ in the spatial arrangement of the benzene substituent. The differences between their GIAO in calculated ¹H and ¹³C NMR spectra were insignificant, but the difference in Gibbs free energies of possible products allowed us to attribute the structure of the obtained compound as a trans-

atropisomer. A high difference in ΔG of possible isomers (that is much higher than in the previous cases, 4.2 kcal mol⁻¹), explains the formation of only one of them during the reaction, more energetically advantageous (Table 4).

Table 4
Calculated relative ΔG and relative yield of the isomeric forms (I₁ and I₂) of the product 3b

Isomeric form	Calculated relative ΔG , kcal mol ⁻¹	Relative yield, %
I ₁	0	100
I ₂	+4.2	0

Conclusions

As a result of cyclocondensation of 2,3-bis(bromomethyl)-1,4-dimethoxyanthracene-9,10-dione 1 with a number of heteroarylbenzylhydrazides 2a–c in DMF at room temperature for 5 hours in the presence of potassium carbonate as a base, a series of 2-benzoyl-3-heteroaryl-5,12-dimethoxy-1,2,3,4-tetrahydronaphtho [2,3-g]phthalazine-6,11-diones 3a-c was prepared. The reaction products were separated by liquid chromatography in the dichloromethane/diethyl ether system (95:5) and different numbers of atropisomers were isolated for different hydrazides. For N'-(4,6-dimethylpyrimidin-2-yl) benzohydrazide 2b, only one isomer was isolated with the yield of 43%, whereas two isomers were isolated for N'-(6-chloropyridazin-3-yl)benzohydrazide 2a (the yields being 27% and 11%) and three isomers were isolated for N'-(4-chlorophthalazin-1-yl)benzohydrazide 2c 3 (the yields being 35%, 20% and 8%). DFT modeling of possible structures of the obtained atropisomers showed the possibility of the existence of two isomers for 3a and 3b, and three isomers for 3c. Based on the analysis of experimental and GIAO simulated NMR spectra as well as the calculated ΔG of isomers, the calculated structures were assigned to the isolated compounds. For the product 3c, the assignment was confirmed by NOESY results. The isolation of only one isomer out of the two possible 3b is consistent with the high difference in their Gibbs energies (due to the formation of more stable product).

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СИНТЕЗ ТА ІЗОМЕРІЯ 2-БЕНЗОЇЛ-5,12-ДИМЕТОКСИ-3-ГЕТЕРИЛ-1,2,3,4-ТЕТРАГІДРОНАФТО [2,3-G] ФТАЛАЗИН-6,11-ДИОНІВ

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Досліджено циклоконденсацію біелектрофілу 2,3-біс(бромметил)-1,4-диметоксиантрацен-9,10-діона з низкою гетероїл-бензилгідразидів з утворенням екзофункціоналізованої тетрациклічної хіноїдної системи. Для різних гідразидів методом рідинної хроматографії було виділено різну кількість продуктів, які були ідентифіковані, як атропізомери: для N⁷-(4,6-диметилпіримідин-2-іл)-бензогідразиду виділено один ізомер, для N⁷-(6-хлорпіридазин-3-іл)-бензогідразиду – два ізомери, для N⁷-(4-хлорфталазин-1-іл)-бензогідразиду – три ізомери. З метою встановлення їх структури було виконано моделювання їх геометрії та спектрів ЯМР методами DFT. Структури отриманих ізомерів були встановлені на основі спектрів ¹H, ¹³C та NOESY, що добре узгоджується з результатами моделювання.

Ключові слова: 9,10-антрацендіон, гідразид, циклоконденсація, атропізомерія, молекулярне моделювання.

SYNTHESIS AND ISOMERISM OF 2-BENZOYL-5,12-DIMETHOXY-3-HETERYL-1,2,3,4-TETRAHYDRONAPHTHO[2,3-G]PHTHALAZINE-6,11-DIONES

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The cyclocondensation of the bielectrophile 2,3-bis-(bromomethyl)-1,4-dimethoxyanthracene-9,10-dione with several heteroaryl-benzyl hydrazides with the formation of exofunctionalized tetracyclic quinoid systems was studied. Different numbers of products were isolated by liquid chromatography for different hydrazides. The products were identified as atropisomers. Generally, only one isomer was isolated for N⁷-(4,6-dimethylpyrimidin-2-yl)benzohydrazide, while two and three isomers were isolated for N⁷-(6-chloropyridazin-3-yl)benzohydrazide and for N⁷-(4-chlorophthalazin-1-yl)benzohydrazide, respectively. To determine their structure, modeling of the geometries and NMR spectra by DFT methods was performed. The structure of the obtained isomers was established based on ¹H, ¹³C NMR and NOESY spectra, the results well agree with the simulation results.

Keywords: 9,10-anthracenedione; hydrazide; cyclocondensation; atropisomerism; molecular modeling.

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