Ring-ring isomerization in the series of *N*-(carbamoyl)-1-aryl-2,3,4,5,6,7-hexahydro-3-hydroxy-6,6-dimethyl-2,4-dioxo-1*H*-indole-3-carboxamides*

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N-(Carbamoyl)-1-aryl-2,3,4,5,6,7-hexahydro-3-hydroxy-6,6-dimethyl-2,4-dioxo-1*H*-indole-3-carboxamides upon dissolution in DMSO or DMF undergo a reversible isomerization to 5-(2-arylamino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-hydroxypyrimidine-2,4,6-(1*H*,3*H*,5*H*)-triones.

Key words: anilines, dimedone, *N*-arylenaminones, *N*-(carbamoyl)-1-aryl-2,3,4,5,6,7-hexahydro-3-hydroxy-6,6-dimethyl-2,4-dioxo-1*H*-indole-3-carboxamides, 5-(2-arylamino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-hydroxypyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones, dimethyl sulfoxide, ring-ring isomerization.

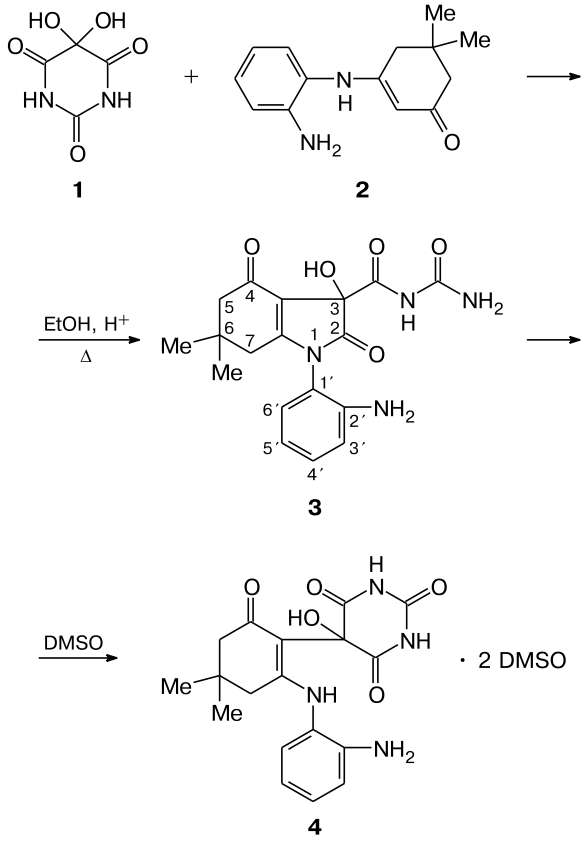
The ring-ring isomerization processes, in contrast to the ring-chain ones, are much rarer phenomena,[1—15] the more interesting is every new example.

Recently, it was reported that alloxane reacted with *N*-aryl-substituted enaminones, the condensation products of anilines with dimedone, to give polyfunctional indole derivatives.[16] We reacted alloxane **1** with 3-(2-aminophenyl)amino-5,5-dimethylcyclohex-2-en-1-one (**2**), the condensation product of *o*-phenylenediamine with dimedone, to obtain one of such derivatives: *N*-(carbamoyl)-1-(2-aminophenyl)-2,3,4,5,6,7-hexahydro-3-hydroxy-6,6-dimethyl-2,4-dioxo-1*H*-indole-3-carboxamide (**3**). The structure of compound **3** was confirmed by X-ray diffraction studies.[17]

The presence of the free amino group at *o*-position of the phenyl substituent makes compound **3** capable of the reactions, which are impossible for its analogs described in the work.[16] Thus, upon heating in CF_3COOH it undergoes recyclization to a spiro compound with the dibenzodiazepine and barbituric acid fragments.[17] Compound **3** was also found to undergo the ring-ring isomerization. In DMSO and DMF, it reversibly isomerizes to 5-[2-(2-aminophenyl)amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl]-5-hydroxypyrimidine-2,4,6(1*H*,3*H*,6*H*)-trione (**4**), which was isolated as a solvate with DMSO.[17] The recrystallization of solvate **4** from CH_3CN led to the recovery of compound **3** (see Ref. 17).

It seemed interesting to find out whether the ability to undergo the ring-ring isomerization is typical of only compound **3** or is a general property caracteristic of such group of indole derivatives.

Scheme 1



* Dedicated to Academician of the Russian Academy of Sciences V. I. Minkin on the occasion of his 80th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 0664—0667, March, 2015.

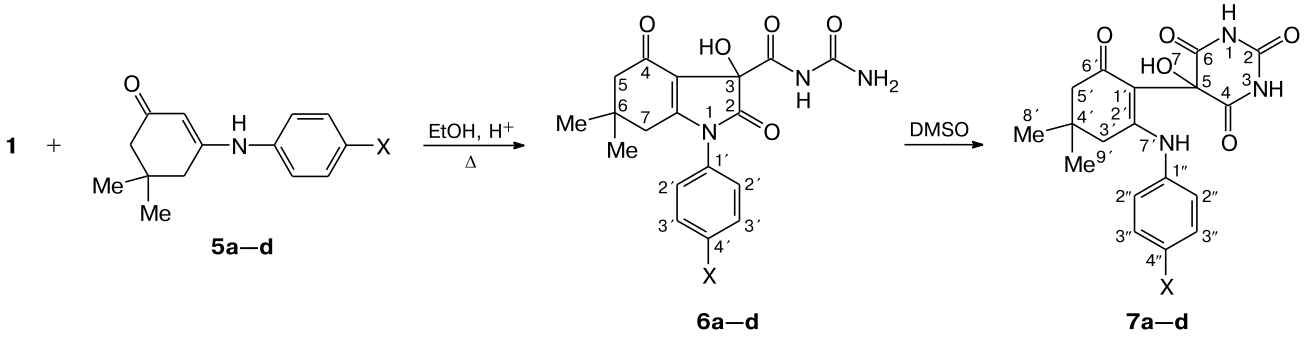
To obtain an unambiguous answer to this question, we had to have a full set of ^{1}H, ^{13}C, and ^{15}N NMR spectra for several analogs of compound **3**. For this purpose, we used our procedure described earlier[17] to synthesize four analogs of compound **3** from compound **5**: with phenyl (**6a**), *p*-fluoro- (**6b**), *p*-chloro- (**6c**), and *p*-bromophenyl (**6d**) substituents (Scheme 2). The compounds obtained by this procedure do not require further purification, since they crystallize from the reaction mixture in the spectrally pure form. The ^{1}H and ^{13}C NMR spectra of all four compounds recorded in DMSO-d_6 completely agree with the spectra given in the literature.[16] Like in the case of compound **3**, the number of signals in the ^{13}C NMR spectra of compounds **6a**—**d** was one signal short than the expected number for this structure. To make a full assignment of signals in the ^{1}H NMR spectra of the described compounds, we used a correlation sequence COSY, for the ^{13}C NMR spectra — HMBC and HSQC, for the ^{15}N NMR spectra — HMBC.

The unambiguous choice in favor of structures **7a**—**d** was made based on the correlation (HMBC) ^{1}H—^{15}N NMR spectra. They showed that upon dissolution of compounds **6a**—**d** in DMSO, the atom N(1) acquires a proton, that can be explained by the rearrangement to the structures **7a**—**d** (see Scheme 2).

The structures **7a**—**d** explain the inconsistency in the number of signals in the ^{13}C NMR spectra and the number of carbon atoms in the compounds: in the symmetric pyrimidinetrione ring atoms C(4) and C(6) are characterized by the same chemical shifts.

Figure 1 shows a correlation ^{1}H—^{15}N HMBC NMR spectrum of compound **7d**, which exhibits a number of cross-peaks for the signals of nitrogen nuclei N(7′)

Scheme 2



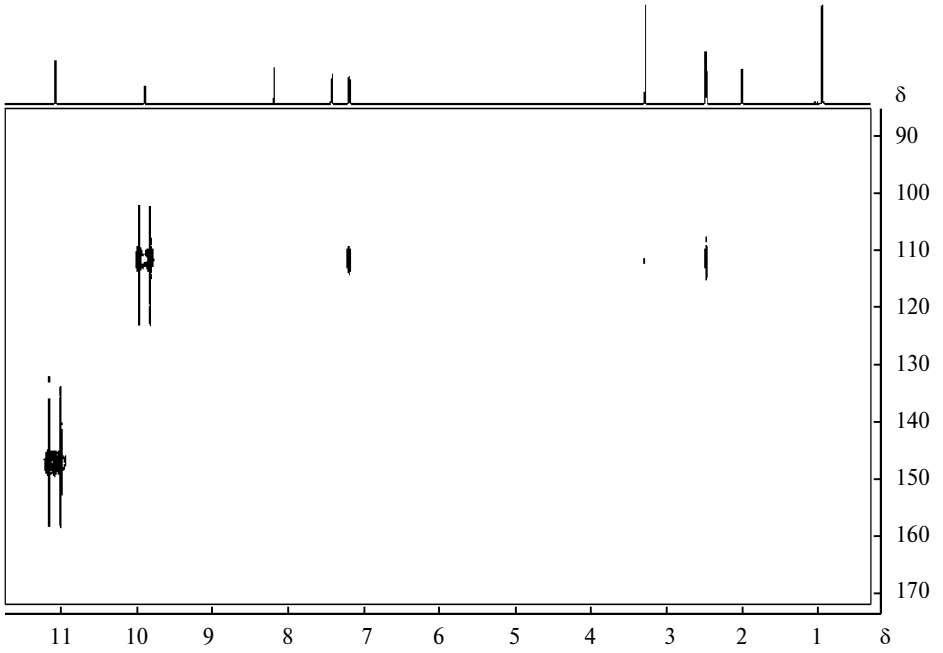


Fig. 1. ^{1}H—^{15}N HMBC correlation spectrum of compound **7d** (DMSO-d_6).

Table 1. ^{1}H, ^{13}C, and ^{15}N NMR chemical shifts for compounds **7a—d** (DMSO-d_6)

Atom	**7a**		**7b**		**7c**		**7d**	
	^{1}H	$^{13}C/^{15}N$	^{1}H	$^{13}C/^{15}N$	^{1}H	$^{13}C/^{15}N$	^{1}H	$^{13}C/^{15}N$
1(^{15}N)	11.06	147.00	11.06	148.77	11.08	147.00	11.08	147.00
2	—	150.29	—	150.30	—	150.26	—	150.25
3(^{15}N)	11.06	147.00	11.06	148.77	11.08	147.00	11.08	147.00
4	—	170.74	—	170.75	—	170.66	—	170.64
5	—	75.33	—	75.30	—	75.28	—	75.27
6	—	170.74	—	170.75	—	170.66	—	170.64
7	8.15	—	8.12	—	8.19	—	8.19	—
1′	—	106.84	—	106.81	—	107.40	—	107.47
2′	—	162.11	—	162.36	—	161.75	—	161.64
3′	2.47	40.69	2.39	40.55	2.47	40.61	2.48	40.60
4′	—	32.82	—	32.73	—	32.86	—	32.87
5′	2.00	48.79	1.99	48.77	2.00	48.77	2.00	48.77
6′	—	193.89	—	193.90	—	194.20	—	194.23
7′(^{15}N)	9.92	113.75	9.80	110.56	9.90	111.50	9.89	111.60
8′	0.94	27.40	0.93	27.41	0.95	27.35	0.95	27.87
9′	0.94	27.40	0.93	27.4	0.95	27.35	0.95	27.87
1″	—	138.08	—	134.45	—	137.12	—	137.54
2″	7.17	124.52	7.21	127.05	7.19	126.13	7.13	126.41
3″	7.39	129.29	7.22	115.97	7.43	129.13	7.55	132.05
4″	7.20	125.20	—	159.70	—	129.20	—	117.31

(δ 111.50) with protons H(7′) (a doublet at δ 9.90, ^{1}J = 90.4 Hz), besides, the nuclei N(7′) correlate with protons H(3′) (δ 2.47) and protons H(2″) (δ 7.19).

Atoms N(1) and N(3) (δ 147.00) in the pyrimidine fragment of the molecule correlate with the corresponding protons H(1) and H(3) (a doublet at δ 11.08, ^{1}J = 90.2 Hz).

The data of the described $^{1}H—^{15}N$ HMBC NMR spectrum unambiguously determine the environment of nitrogen atoms N(7′), N(1), and N(3).

Similar patterns were found in the correlation $^{1}H—^{15}N$ HMBC NMR spectra for all compounds **7a—d** (Tables 1 and 2).

In conclusion, a combination of the NMR data (see Tables 1 and 2) unambiguously indicates the isomerization of compounds **6a—d** to compounds **7a—d** upon dissolution in DMSO (see Scheme 2).

Attempted obtaining of complexes of compounds **6a—d** with DMSO (similar to **4**) was unsuccessful. The IR spectra of the colorless precipitates isolated from solutions of **6c** and **6d** in DMSO showed that they were not the starting compounds. A short-time mild heating of these precipitates in MeCOOH led to their quantitative transformation to the starting compounds **6a** and **6d**, thus demonstrating a reversibility of the isomerization taking place in DMSO.

Table 2. Some spin-spin coupling constants (J/Hz) for compounds **7a—d**

Compound	$^{1}J_{N(1),H} = {}^{1}J_{N(3),H}$	$J_{N(7'),H}$
7a	90.1	90.0
7b	89.7	91.2
7c	90.2	90.4
7d	89.5	91.0

Note. For compound **7b** $^{1}J_{F,H(4'')}$ = 242.6 Hz, $^{2}J_{F,H(3'')}$ = = 22.2 Hz, $^{3}J_{F,H(2'')}$ = 8.4 Hz, $^{4}J_{F,H(1'')}$ = 2.1 Hz.

In the work,[16] for all the obtained polyfunctional indole derivatives, the melting points are given within the 1—2 °C range. An impression was formed that these compounds are stable, melting sharply virtually in one point. In fact, all the colorless compounds **6a—d** obtained in this work are stable only until a certain temperature. Upon heating, they first turn dark and then decompose with the gas liberation and the formation of black melts. The 1—2 °C range means only the last step of decomposition, accompanied by a vigorous gas evolution. In the case of compounds **6a** and **6c**, the melting—decomposition points found by us are slightly higher than those indicated in the work,[16] whereas for **6b** it is lower. The largest difference (~30 °C) was observed for compound **6d**. We carried out its elemental analysis, which confirmed the analytical purity of this compound (see Experimental).

Experimental

Spectroscopic studies were carried out using facilities of the Molecular Spectroscopy Multi-user Center of the Southern Federal University. NMR spectra were recorded on a Bruker AVANCE-600 spectrometer.

Synthesis of compounds 3a—d (general procedure). Alloxane (0.19 g, 1 mmol) was dissolved in EtOH (5 mL) upon reflux, followed by addition of the corresponding compound **5a—d** (1 mmol) and heating until dissolution. Then, CF_3COOH (1 drop) was added to the mixture, which was brought to reflux and left to cool down to room temperature, rubbing with a glass rod. In many cases, crystallization began from a still warm solution. To obtain the maximal yields, the reaction mixture was allowed to stand for 12 h, a precipitate was filtered off, washed with cold EtOH and light petroleum, and dried.

***N*-(Carbamoyl)-1-phenyl-2,3,4,5,6,7-hexahydro-3-hydroxy-6,6-dimethyl-2,4-dioxo-1*H*-indole-3-carboxamide (6a).** After the reaction was complete, the mixture was cooled to room temperature, rubbing with a rod, when crystallization began, the mixture was placed in ice. The yield was 0.19 g (53%). A colorless compound, turns dark above 195 °C, m.p. 203—205 °C (decomp.) (*cf.* data in Ref. 16: m.p. 195—196 °C).

***N*-(Carbamoyl)-1-(4-fluorophenyl)-2,3,4,5,6,7-hexahydro-3-hydroxy-6,6-dimethyl-2,4-dioxo-1*H*-indole-3-carboxamide (6b).** Addition of a crystallization seed and rubbing with a rod initiated the crystallization from a warm solution. After standing of the mixture in ice for 1 h, the yield of the product was 0.16 g (43%). After standing of the mixture for 16 h, the yield was 0.26 g (59%). A colorless compound, turns dark above 175 °C, m.p. 188—190 °C (with decomp.) (*cf.* data in Ref. 16: m.p. 203—204 °C).

***N*-(Carbamoyl)-1-(4-chlorophenyl)-2,3,4,5,6,7-hexahydro-3-hydroxy-6,6-dimethyl-2,4-dioxo-1*H*-indole-3-carboxamide (6c).** The crystallization was initiated from a hot solution by rubbing with a rod, the reaction mixture rapidly grew dense. The mixture was cooled to room temperature and then in ice for 15 min. The yield of the product was 0.22 g (56%). A colorless compound, turns dark at 199—200 °C, m.p. 203—205 °C (with decomp.) (*cf.* data in Ref. 16: m.p. 199—200 °C).

***N*-(Carbamoyl)-1-(4-bromophenyl)-2,3,4,5,6,7-hexahydro-3-hydroxy-6,6-dimethyl-2,4-dioxo-1*H*-indole-3-carboxamide (6d).** The rubbing with a rod initiated rapid formation of a crystalline precipitate from a hot solution. After cooling in ice for 1 h, the yield of the product was 0.25 g (57%). A colorless compound, turns dark above 200 °C, m.p. 207—208 °C (with decomp.) (*cf.* data in Ref. 16: m.p. 235—237 °C). Found (%): C, 49.60; H, 3.88; Br, 17.88. $C_{18}H_{18}N_3O_5$. Calculated (%): C, 49.55; H, 4.16; Br, 18.32.

This work was financially supported by the Ministry of Education and Science of the Russian Federation (the Project Part of the State Assignment in Academic Area of the Southern Federal University, Theme No. 4.967.2014/K).

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Received December 9, 2014;
in revised form January 20, 2015