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THE EXPERIMENTAL AND THEORETICAL STUDY OF TAUTOMERISM OF 3-SUBSTITUTED 2-METHYL-QUINOLINE-4 (1H)-ONES

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Key words: quinoline-4(1H)-ones; tautomerism; ^{13}C NMR-spectroscopy; quantum-chemical calculations

4-Hydroxy-/4-oxo tautomerism in the series of 3-substituted 2-methyl-quinolin-4(1H)-ones has been studied by ^{13}C NMR-spectroscopy and quantum-chemical methods in various approximations (restricted Hartree-Fock method, DFT and MP2) for the isolated molecules and for solutions using empirical correction of effects for solvents (PCM COSMO procedure). Substituents that are different in their nature have no significant influence on the value of the chemical shift of carbon in position C4 of the quinolone cycle. The only exception is the carbon shielding associated with the bromine atom in the molecule of 3-bromo-2-methyl-1,4-dihydroquinoline-4-one. Significant deshielding detected in all cases in ^{13}C NMR-spectra of the carbon nuclei in position 4 of the ring is in favour of the existence of all derivatives studied as 4-oxo forms in DMSO-d_6 solution. The experimental and calculated values for the chemical shift of carbon in position C4 of 4-oxo and 4-hydroxy isomers differ considerably and can be used as a criterion for assigning quinolin-4 (1H)-ones to a particular tautomeric form.

ЕКСПЕРИМЕНТАЛЬНІ ТА ТЕОРЕТИЧНІ ДОСЛІДЖЕННЯ ТАУТОМЕРІЇ СЕРЕД 3-ЗАМІЩЕНИХ 2-МЕТИЛХІНОЛІН-4(1H)-ОНІВ

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Ключові слова: *хінолін-4(1H)-они; таутомерія; ^{13}C ЯМР спектроскопія; квантово-хімічні розрахунки*

За допомогою ЯМР ^{13}C спектроскопії і квантово-хімічними методами в різних наближеннях (обмежений метод Хартрі-Фока, DFT і MP2) для ізольованих молекул і розчинів з використанням емпіричної корекції ефектів розчинників (процедура PCM COSMO) досліджена 4-гідрокси оксо-таутомерія в ряду похідних 3-заміщених 2-метилхінолін-4(1H)-онів. Різні за своїм характером замісники не чинять істотного впливу на значення хімічного зсуву вуглецю в положенні С4 хінолонового циклу. Виняток становить лише екранування вуглецю, пов'язаного з атомом брому в молекулі 3-бромо-2-метил-1,4-дигідрохінолін-4-ону. Значне дезекранування виявлене у всіх випадках у спектрах ЯМР ^{13}C для ядер вуглецю в 4-му положенні кільця вказує на користь існування всіх досліджених похідних у розчині в DMSO-d_6 у вигляді 4-оксо-форм. Експериментальні та розрахункові значення хімічного зсуву для вуглецю в положенні С4 для 4-оксо- і 4-гідрокси-ізомерів помітно відрізняються і можуть бути використані в якості критерію для віднесення хінолін-4 (1H)-онів до тієї чи іншої таутомерної форми.

ЭКСПЕРИМЕНТАЛЬНЫЕ И ТЕОРЕТИЧЕСКИЕ ИССЛЕДОВАНИЯ ТАУТОМЕРИИ СРЕДИ 3-ЗАМЕЩЕННЫХ 2-МЕТИЛХИНОЛИН-4(1H)-ОНОВ

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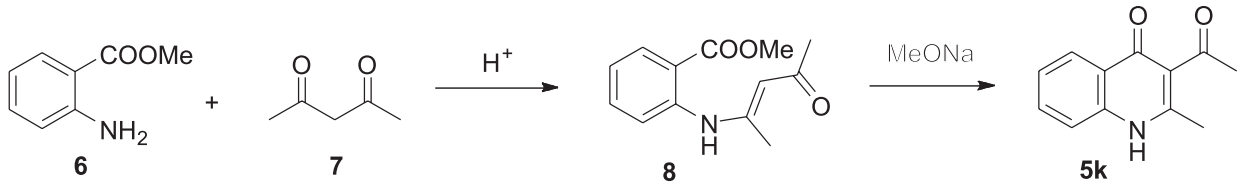
Ключевые слова: *хинолин-4(1H)-оны; таутомерия; ЯМР ^{13}C спектроскопия; квантово-химические расчеты*

С помощью ЯМР ^{13}C спектроскопии и квантово-химическими методами в различных приближениях (ограниченный метод Хартри-Фока, DFT и MP2) для изолированных молекул и растворов с использованием эмпирической коррекции эффектов растворителей (процедура PCM COSMO) исследована 4-гидрокси 4-оксо-таутомерия в ряду производных 3-замещенных 2-метилхинолин-4(1H)-онов. Различные по своему характеру заместители не оказывают существенного влияния на значение химического сдвига углерода в положении С4 хинолонового цикла. Исключение составляет лишь экранирование углерода, связанного с атомом брома в молекуле 3-бромо-2-метил-1,4-дигидрохинолин-4-она. Значительное дезэкранирование, обнаруженное во всех случаях в спектрах ЯМР ^{13}C для ядер углерода в 4-ом положении кольца, говорит в пользу существования всех исследованных производных в растворе в DMSO-d_6 в виде 4-оксо-форм. Экспериментальные и расчетные значения химического сдвига для углерода в положении С4 для 4-оксо- и 4-гидрокси-изомеров заметно отличаются и могут быть использованы в качестве критерия для отнесения хинолин-4(1H)-онов к той или иной таутомерной форме.

Quinoline-4-ones are a well known class of heterocyclic compounds, which have been intensively studied for several decades. First of all, the interest of researchers to various derivatives of quinoline-4-ones is based by diverse biological activity of these compounds, its study led to creation of new groups of highly effective drugs [1-4]. The structural features of quinoline-4-ones related to the possibility of the existence of prototropic tautomerism in the heterocycle are also interesting. Currently, in most publications, quinolin-4-ones are represented in the 4-oxo-form of tautomers **1**.

There are a number of works, in which tautomerism was purposively studied for the particular



Scheme 1

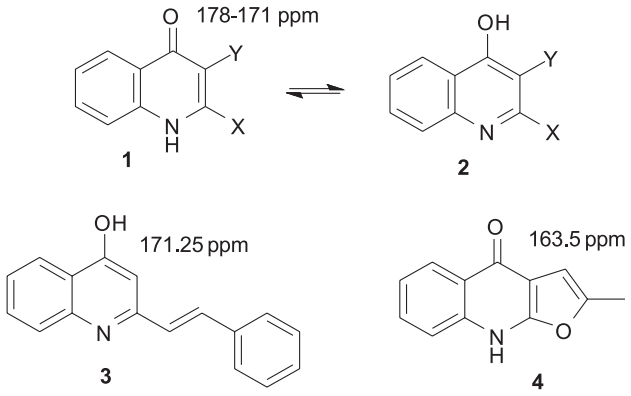


Fig. 1. Tautomeric forms of quinolin-4-ones.

series of quinoline-4-ones by NMR spectroscopy and X-ray analysis [5-7]. According to the data given in them the signal of C-4 carbon in the 4-oxo form **1** in the ^{13}C NMR-spectrum should have a chemical shift of more than 170 ppm. However, at the same time in literature some authors refer the C-4 carbon signal to 4-hydroxy or 4-oxo tautomeric form of quinolones, which may be illustrated by the structures of compounds **3** [8] and **4** [9] (Fig. 1).

The attempt to identify uniquely criterion for determining tautomeric forms of quinolin-4-ones in solutions was made using the method of NMR ^{13}C spectroscopy in combination with the quantum chemical calculations for a series of 3-substituted-2-methylquinoline-4(1H)-ones presented in Fig. 2. The ^{13}C NMR-spectra of 4(1H)-quinolin-4-one **5a** was taken from the Spectral Database for Organic Compounds (SDBS); the spectrum of 2-methyl-1H-quinolin-4-one **5b** was from the Sigma-Aldrich database.

Quinolin-4-ones **5c-g**, **k-m** were synthesized by the methods previously proposed [10, 11]. 3-Acetyl-2-methyl-1H-qinolin-4-one **5k** was prepared by the reaction of methyl anthranilate **6** with acetylacetone **7** followed by the intramolecular cyclization of enamine **8** (Scheme 1).

A special attention in the experiment was paid to quinoline-4-ones having carbonyl-containing groups in position 3. Such compounds can form an intramolecular hydrogen bond (IMHB), which presence can play a key role in the molecular stabilization in the form of 4-oxo or 4-hydroxy isomer.

In our study there were three types of quinolone-4-ones with the carbonyl group in position C-3: acid **5m**, aldehyde **5g** and acetylquinoline **5k**. According to the calculations carried out by the method of molecular mechanics with automatic optimization geometry in the case of acid **5m** both isomers are equally likely to form an intramolecular hydrogen bond with approximately the same length of 1.6 Å (Fig. 3).

Formation of IMHB for 2-methyl-4-oxo-1,4-dihydroquinoline-3-carbaldehyde **5g** is more likely in the case of 4-hydroxy isomer **5'g** than in the quinolone structure since its calculated length is less by 0.7 Å. And in the case of 3-acetyl-2-methyl-1H-4-quinolin-4-one **5k** IMHB is only possible for the 4-hydroxy form of **5'k**, and it is almost impossible in 4-oxo form of **5k**. Therefore, we expected to see any changes in the values of the chemical shifts in the ^{13}C NMR-spectra at least in one case in this series of quinolones.

Undoubtedly, for clear interpretation of the experimental data of NMR spectroscopy it is necessary to carry out a comparative analysis of the C-4 chemi-

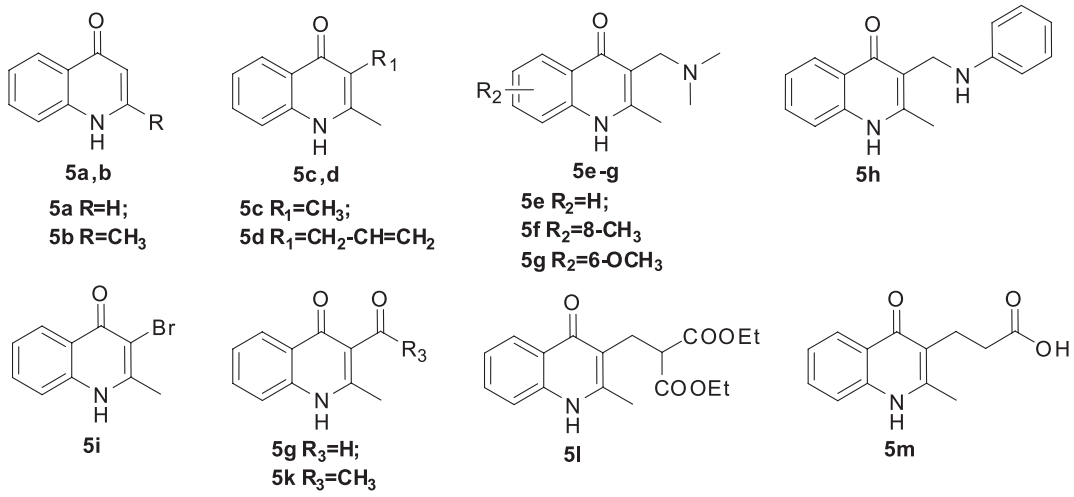


Fig. 2. The structures of quinolin-4-ones involved in studies of tautomerism using ^{13}C NMR-spectroscopy.

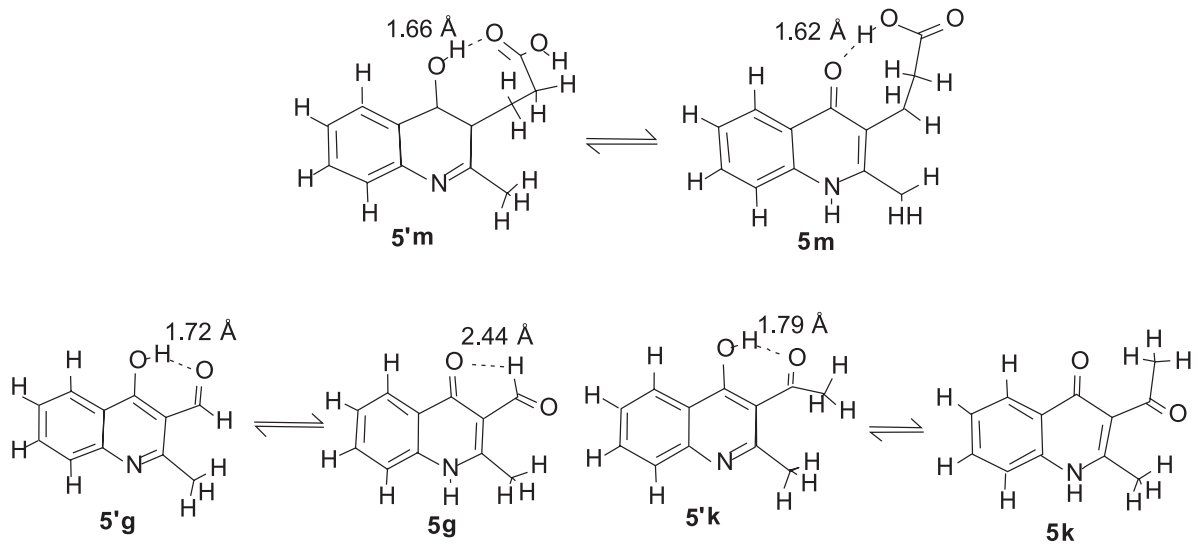
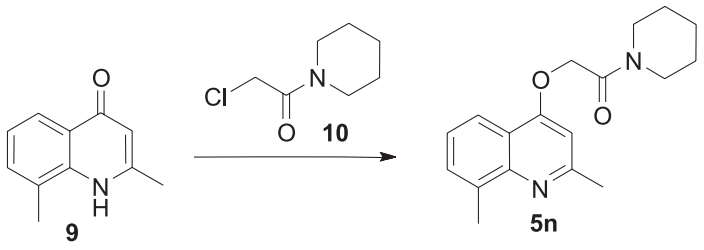


Fig. 3. The lengths of the hydrogen bonds in the tautomeric forms of compounds **5m**, **5g**, **5k** calculated by the algorithm of the gradient descent in a MMFF94 force field.



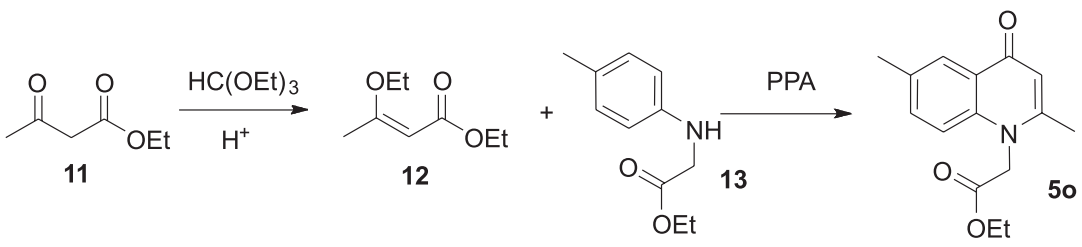
Scheme 2

cal shift values of the compounds studied with the values of the well-known structures of 4-hydroxy and 4-oxoquinolines. As model compounds 2,8-dimethyl-4-(2-oxo-2-piperidin-1-yl-ethoxy)quinoline **5n** (Scheme 1) and 2-(2,6-dimethyl-4-oxo-quinoline-1-yl)acetic acid **5o** were obtained (Scheme 2).

The synthesis of 4-alkoxyquinoline **5n** was carried out by alkylation of 2,8-dimethyl-quinolin-4(1H)-one **9** with 2-chloro-1-(piperidin-1-yl)ethan-1-one **10** in DMSO in the presence of K_2CO_3 according to the known method [12]. To obtain ethyl ester of 2-(2,6-dimethyl-4-oxo-quinoline-1-yl) acetic acid **5o** the condensation between ethyl 3-ethoxycrotonate **12** and ethyl N-(p-methylphenyl)glycine **13** with the subsequent high temperature cyclization of the intermediate was performed (Scheme 3).

For analytical criterion that would allow us to claim the existence of the compounds under research in 4-hydroxy or 4-oxo- tautomeric forms the chemical shift of the carbon atom in position C-4 was selected. In the ^{13}C NMR-spectra of the model compounds this signal is significantly different, it appears for 2,8-dimethyl-4-(2-oxo-2-piperidin-1-yl-ethoxy)quinoline **5n** at 160.65 ppm, and for ethyl 2-(2,6-dimethyl-4-oxo-quinoline-1-yl) acetic acid **5o** at 177.87 ppm, respectively.

According to the results of NMR-spectroscopy the spectra of all compounds studied contain the carbon nucleus signal C-4 at 175-177 ppm (Tab. 1). The spectrum of 3-bromo derivative **5i**, in which this signal is at 170.96 ppm, is out of the general picture. Such chemical shift to the strong field is obviously associated with the specific effect of the bromine atom in position 3. Another set of signals of the 4-hydroxy form was not observed in any spectra. This fact indicates the complete absence or rather small number of tautomeric 4-hydroxyquinolines that is not registered. When heating the solutions of the com-

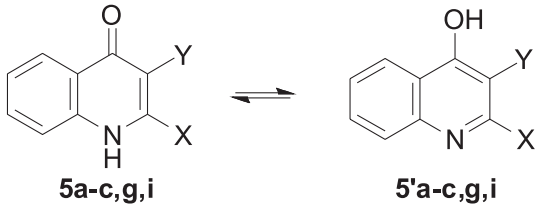


Scheme 3

Table 1

Chemical shifts of ^{13}C NMR (ppm) for the quinolone ring atoms of compounds **5a-m** in DMSO-d_6

Compound	C2	C3	C4	C4′	C5	C6	C7	C8	C8′
5a	139.43	108.66	177.04	125.71	123.08	124.91	131.60	118.22	139.99
5b	149.46	108.26	176.57	124.40	124.66	122.51	131.24	117.61	140.02
5c	145.59	114.13	175.90	123.15	125.07	122.00	130.57	117.32	139.19
5d	146.42	116.03	175.04	123.25	124.92	122.11	130.70	117.23	139.03
5e	149.17	115.52	175.71	123.96	125.34	122.33	130.80	117.47	139.36
5f	150.11	115.61	175.75	123.97	125.80	122.29	131.93	123.26	138.14
5g	149.76	110.50	175.46	124.72	105.28	155.75	121.65	119.88	134.41
5h	149.02	115.77	175.42	123.69	125.02	122.43	130.98	117.31	139.08
5i	148.61	105.88	170.96	122.69	123.61	125.22	131.83	117.80	138.54
5g	156.15	114.05	177.59	126.17	124.93	124.89	132.98	118.52	139.02
5k	151.54	117.92	175.25	123.94	125.39	125.08	132.27	120.10	138.71
5l	147.21	114.08	175.70	122.64	124.76	123.20	131.25	117.51	139.15
5m	145.62	117.29	175.47	122.41	124.88	123.29	131.03	117.45	139.10



5a-c,g,i **5'a-c,g,i**

Scheme 4

pounds studied up to approximately 100°C the nature of spectra does not change, and it indicates stability of 4-oxo tautomers.

To interpret experimental results, including the shift of the carbon C-4 signal for 3-bromo-2-methyl-1H-quinoline-4-one **5i** we performed *ab initio* quantum chemical calculations for compounds **5a-c, g, i** in various approximations (Scheme 4).

Calculations conducted show that the relative energy is highly dependent on the method used. In the approximation of DFT (RI-BP86) for isolated molecules the relative stability of oxo-form **5** in all cases (except one) is significantly higher than that obtained for hydroxy tautomers **5'** (Tab. 2). The only exception is compound **5'g**, which is much more stable than isomer **5g** within the approximation used in the gas phase. Considering the effects of DMSO solvent and using the COSMO empirical procedure [13] the oxo-form is more preferred in all cases (however, Δ E value is the least in the case of **5g**). When using a more rigorous approximation MP2 for an isolated molecule structures **5'b**, **5'i** and **5'g** are characterised by a lower energy than the corresponding isomeric forms **5**. Moreover, in this case consideration of the solvent effects makes isomers **5** more favourable. Thus, the assumption concerning 4-oxo isomers in DMSO solution based on the data for ^{13}C NMR-spectra is confirmed by the conclusions drawn on the basis of analysis of the total energies of structures **5** and **5'**. For additional confirmation of the correctness of our conclusions the chemical shifts of ^{13}C NMR were calculated by the GIAO method [14] and using different approximations. The calculation results of shielding constants of ^{13}C nuclei in different approximations (Tab. 3) are consistent with the conclusions that the compounds studied exist in solution predominantly in the oxo form.

Consideration of the solvent effects is very important in order to achieve the quantitative agreement between the calculated values δC with the experimental values. In the series of 3-substituted-2-methyl-quinolin-4 (1H)-ones considered the satisfactory agreement with the experiment is achieved already in the DFT approximation (B3LYP) when using the COSMO procedure. At the same time, the effect of transition to a more strict MP2 approximation is less significant. The experimental values of ^{13}C NMR chemical shifts are in good agreement with the calculated values δC for oxo-forms **5**. The only exception is the carbon shielding associated with a bromine atom. However, this is consistent with the literature data, in which the similar effect for bromo heterocycles is observed.

Summarizing the results of ^{13}C NMR-spectroscopy and quantum chemical calculations it should be noted that the chemical shift value for carbon C4 calculated for the compounds in the form of **5** or **5'** differ significantly, and therefore, can be used as a criterion for assigning quinolin-4(1H) ones to 4-oxo or 4-hydroxy-forms.

Experimental Part

Melting points were determined by the open capillary method, and they were not corrected. ^1H NMR

Table 2

The values of the total energies (E), corrections to fluctuations at 0K (ZPE), the adjusted values of the total energies (E + ZPE), lower vibration frequencies (ν) and relative energies (ΔE, kcal/Mol) calculated in the approximation of B3LYP/6-311+G** (DFT), B3LYP/6-311+G** with empirical correction of the solvent effects (DFT/DMSO)

Structure	DFT					DFT/DMSO		MP2		MP2/DMSO	
	E, a.u.	ZPE, a.u.	E+ZPE, a.u.	n, cm-1	DE	E, a.u.	DE	E, a.u.	DE	E, a.u.	DE
5 a	-477.345654	0.135757	-477.209897	106.5	0.00	-477.365744	0.00	-475.933330	0.00	-475.9515218	0.00
5′a	-477.338215	0.135246	-477.202969	129.7	4.35	-477.352039	8.60	-475.933105	0.14	-475.9461474	3.37
5 b	-516.679100	0.162382	-516.516719	92.5	0.00	-516.699075	0.00	-515.138214	0.00	-515.156225	0.00
5′b	-516.671681	0.161554	-516.510128	19.6	4.14	-516.685188	8.71	-515.139847	-1.02	-515.152527	2.32
5 c	-556.007893	0.188892	-555.819001	-20.8	0.00	-556.029169	0.00	-554.341894	0.00	-554.358852	0.00
5′c	-555.999507	0.188459	-555.811049	39.9	4.99	-556.014397	9.27	-554.340858	0.65	-554.353037	3.65
5g	-630.055672	0.171518	-629.884154	48.9	0.00	-630.077493	0.00	-628.228111	0.00	-628.247202	0.00
5′g	-630.061769	0.170955	-629.890814	77.0	-4.18	-630.072610	3.06	-628.235378	-4.56	-628.245317	1.18
5 i	-3090.517761	0.152519	-3090.365242	56.2	0.00	-3090.541076	0.00	-3087.088197	0.00	-3087.106754	0.00
5′i	-3090.516992	0.151959	-3090.365034	67.4	0.13	-3090.527734	8.37	-3087.090644	-1.54	-3087.099345	4.65

Table 3

The calculated values of the isotropic magnetic shielding of ^{13}C (σ_{iso}) nuclei and ^{13}C NMR chemical shifts (δ) compared to the corresponding experimental values δ (Exp.)

Structure	Method of calculation	C2		C3		C4		C4′		C5		C6		C7		C8		C8′	
		σ_{iso}	δ	σ_{iso}	δ	σ_{iso}	δ	σ_{iso}	δ	σ_{iso}	δ	σ_{iso}	δ	σ_{iso}	δ	σ_{iso}	δ	σ_{iso}	δ
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
5 a	RI-BP86	48.0	134.5	65.6	116.9	5.9	176.6	48.9	133.6	51.3	131.2	56.0	126.5	49.5	133.0	63.8	118.7	39.7	142.8
	B3LYP	44.0	139.0	65.3	117.7	2.0	181.0	48.4	134.6	48.8	134.2	54.9	128.1	46.8	136.2	63.6	119.4	37.5	145.5
	PCM[a]	37.9	**140.1**	68.0	**110.0**	-0.7	**178.7**	50.2	**127.8**	52.2	**125.8**	54.6	**123.4**	44.8	**133.2**	60.0	**118.0**	36.2	**141.8**
	RHF	43.2	150.9	81.5	112.6	2.1	192.0	61.2	132.9	49.7	144.4	66.9	127.2	48.5	145.6	75.1	119.0	40.8	153.3
	RI-MP2	63.1	135.1	82.9	115.3	21.7	176.5	61.8	136.4	71.0	127.2	69.0	129.2	68.9	129.3	76.9	121.3	56.7	141.5
5′a	RI-BP86	29.7	152.8	78.2	104.3	18.3	164.2	58.8	123.7	57.6	124.9	54.5	128.0	50.2	132.3	47.7	134.8	27.7	154.8
	B3LYP	27.2	155.3	77.4	105.1	16.5	166.0	57.7	124.8	55.7	126.8	53.0	129.5	48.3	134.2	46.6	135.9	25.2	157.3
	RHF	27.1	167.0	90.7	103.4	20.9	173.2	68.0	126.1	60.1	134.0	63.3	130.8	52.9	141.2	56.4	137.7	28.3	165.8
	RI-MP2	49.2	133.3	90.4	92.1	35.8	146.7	70.5	112.0	77.0	105.5	67.2	115.3	69.7	112.8	61.1	121.4	44.7	137.8
Exp.	-		**139.4**		**108.7**		**177.0**		**125.7**		**123.1**		**124.9**		**131.6**		**118.2**		**140.0**

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Continuation of Table 3

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
5 b	RI-BP86	37.2	145.3	65.4	117.1	5.4	177.1	51.0	131.5	51.5	131.0	56.3	126.2	49.4	133.1	64.8	117.7	39.8	142.7
	B3LYP	33.3	149.7	66.0	117.0	1.5	181.5	50.2	132.8	49.1	133.9	55.4	127.6	46.9	136.1	64.3	118.7	37.2	145.8
	PCM[a]	26.6	**151.4**	68.4	**109.6**	-1.0	**179.0**	51.7	**126.3**	52.5	**125.5**	55.0	**123.0**	44.8	**133.2**	60.7	**117.3**	36.1	**141.9**
	RI-MP2	53.2	145.0	82.7	115.5	21.3	176.9	63.7	134.5	71.2	127.0	69.5	128.7	69.1	129.1	77.4	120.8	56.4	141.8
5′ b	RI-BP86	19.7	162.8	78.2	104.3	18.0	164.5	59.9	122.6	57.8	124.7	55.0	127.5	50.0	132.5	48.6	133.9	28.1	154.4
	B3LYP	17.2	165.8	77.7	105.3	16.5	166.5	59.1	123.9	56.1	126.9	53.7	129.3	48.3	134.7	47.4	135.6	26.0	157.0
	PCM[a]	15.0	163.0	75.2	102.8	14.8	163.2	58.6	119.4	55.8	122.2	52.8	125.2	47.4	130.6	48.5	129.5	26.8	151.2
	RI-MP2	40.4	157.8	90.3	107.9	35.8	162.4	71.4	126.8	77.3	120.9	67.4	130.8	69.9	128.3	61.1	137.1	45.4	152.8
Exp.	-		**149.5**		**108.3**		**176.6**		**124.4**		**122.5**		**124.7**		**131.2**		**117.6**		**140.0**
5 c	RI-BP86	39.8	142.7	58.0	124.5	7.0	175.5	52.8	129.7	50.7	131.8	56.5	126.0	50.0	132.5	64.9	117.6	41.2	141.3
	B3LYP	36.1	146.9	58.8	124.2	3.0	180.0	51.7	131.3	48.4	134.6	55.6	127.4	47.3	135.7	64.4	118.6	38.3	144.7
	PCM[a]	29.6	148.4	60.7	117.3	1.7	176.3	53.0	125.0	52.0	126.0	55.2	122.8	45.5	132.5	60.8	117.2	37.4	140.6
5′ c	RI-BP86	21.5	161.0	70.9	111.6	19.8	162.7	60.3	122.2	58.2	124.3	55.1	127.4	51.0	131.5	48.6	133.9	30.2	152.3
	B3LYP	19.1	163.9	70.5	112.5	18.5	164.5	59.1	123.9	56.4	126.6	53.6	129.4	49.1	133.9	47.4	135.6	27.8	155.2
	PCM[a]	16.8	161.2	66.9	111.1	17.6	160.4	58.9	119.1	56.3	121.7	52.6	125.4	48.1	129.9	48.6	129.4	28.6	149.4
Exp.			145.6		114.1		175.9		123.2		125.1		122.0		130.6		117.3		139.2
5 g	RI-BP86	26.3	156.2	61.4	121.1	9.4	173.1	46.5	136.0	49.9	132.6	54.1	128.4	48.8	133.7	63.8	118.7	41.7	140.8
	B3LYP	23.5	159.5	61.0	122.0	1.0	182.0	47.6	135.4	48.6	134.4	53.2	129.8	45.7	137.3	63.2	119.8	38.5	144.5
	PCM[a]	19.2	158.8	61.4	116.6	-1.6	179.6	49.6	128.4	51.6	126.4	52.1	125.9	42.9	135.1	59.5	118.5	36.8	141.2
5′ g	RI-BP86	19.1	163.4	67.3	115.2	6.7	175.8	57.2	125.3	54.4	128.1	53.9	128.6	45.7	136.8	48.0	134.5	27.5	155.0
	B3LYP	16.5	166.5	67.4	115.6	6.1	176.9	57.7	125.3	52.8	130.2	52.8	130.2	44.0	139.0	47.3	135.7	25.1	157.9
	PCM[a]	14.7	163.3	66.7	111.3	5.6	172.4	58.1	119.9	52.7	125.3	51.4	126.6	42.0	136.0	47.9	130.1	25.3	152.7
Exp.			156.2		114.1		177.6		126.2		124.9		124.9		133.0		118.5		139.0
5 i	RI-BP86	37.9	**144.6**	47.9	**134.6**	10.8	**171.7**	53.1	**129.4**	50.3	**132.2**	55.8	**126.7**	49.1	**133.4**	65.0	**117.5**	42.0	**140.5**
	B3LYP	33.5	**149.5**	51.3	**131.7**	7.5	**175.5**	51.8	**126.2**	48.2	**134.8**	54.6	**128.4**	46.7	**136.3**	64.1	**118.9**	39.3	**143.7**
	PCM[a]	27.2	**150.8**	56.1	**121.9**	5.1	**172.9**	52.7	**125.3**	51.6	**126.4**	53.7	**124.3**	44.4	**133.6**	60.3	**117.7**	38.0	**140.0**
5′ i	RI-BP86	22.6	**159.9**	57.8	**124.7**	22.7	**159.8**	58.6	**123.9**	57.1	**125.4**	54.2	**128.3**	49.9	**132.6**	48.7	**133.8**	31.5	**151.0**
	B3LYP	33.5	**149.0**	51.3	**131.2**	7.5	**175.0**	51.8	**130.7**	64.1	**118.4**	54.6	**127.9**	46.7	**135.8**	64.1	**118.4**	39.3	**143.2**
	PCM[a]	18.0	**160.0**	58.4	**119.6**	19.2	**158.8**	58.3	**119.7**	55.4	**122.6**	51.6	**126.4**	46.5	**131.5**	48.3	**129.7**	29.0	**149.0**
Exp.			**148.6**		**105.9**		**171.0**		**122.7**		**125.2**		**123.6**		**131.8**		**117.8**		**138.5**

To simulate the effect of the solvent (DMSO) the CPCM (polarizable conductor calculation model) was used [15].

spectra were recorded on Varian VXR-300 (300 MHz), and Bruker Avance-400 (400 MHz) devices in DMSO-d_6 solution, the internal standard was TMS. ^{13}C NMR-spectra were recorded on a Bruker Avance-400 (100 MHz) device in DMSO-D_6 solution, the internal standard was TMS. The methods of synthesis and characteristics of compounds **5c-g**, **k-n** were given in the studies [10-12].

3 Acetyl-2-methyl-1H-quinolin-4-one 5k. Boil 0.02 Mol of methylanthranilate, 0.02 Mol of acetylacetone and 0.1 g of *n*-toluenesulfonic acid in 100 ml of benzene in a Din-Stark apparatus for 6 h to complete separation of water. Distill benzene under vacuum, then to the residue add sodium methylate solution prepared from 0.02 mol of metallic sodium and 200 ml of absolute methanol. Boil the reaction mixture for 30 min. Cool the flask contents and dilute with 200 ml of water. Filter the precipitate obtained and crystallize from ethanol. Yield – 65%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.10 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.66 (ddt, *J* = 8.4, 6.9, 1.1 Hz, 1H), 7.52 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.34 (ddt, *J* = 8.0, 6.9, 0.9 Hz, 1H), 2.49 (s, 2H), 2.42 (s, 2H).

2-(2,6-Dimethyl-4-oxoquinolin-1-yl)acetic acid 5o. Add 12.7 ml (0.1 Mol) of ethyl acetoacetate to 18.3 ml (0.11 Mol) of triethyl orthoformate with 0.1 ml of the concentrated sulphuric acid, stir the reaction mixture and allow to stand overnight. Dilute the reaction mixture with 100 ml of water and neutralize with K_2CO_3 solution. Extract the ether layer separated with chloroform, dry over anhydrous $CaCl_2$, filter, and distill chloroform. To the resulting ethyl-*trans*-3-ethoxycrotonate add 19.33 g (0.1 Mol) of N-(p-methylphenyl)glycine ethyl ester and 100 ml of o-xylene. Heat the mixture to boiling with parallel distillation of ethanol released during the reaction. Remove o-xylene under vacuum. To the residue add 100 g of polyphosphoric acid, and heat the mixture at the temperature of 140°C with vigorous stirring for 2 h. After cooling dilute the reaction mixture with water and neutralize to pH = 7. Filter the precipitate formed, dry and crystallize from ethanol. M. p. – 130-132°C. Yield – 31%.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.51 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 6.06 (s, 1H), 5.16 (s, 2H), 4.19 (q, *J* = 7.0 Hz, 2H), 2.40 (s, 3H), 2.38 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

Conclusions

To assess the possibility of tautomeric transformations among 3-substituted-2-methylquinoline-4(1H)-ones some compounds with substituents that are different in their nature in position 3 of the quinolone cycle and model compounds – 2,8-dimethyl-4-(2-oxo-2-piperidin-1-yl-ethoxy)-quinoline and 2-(2,6-dimethyl-4-oxo-quinoline-1-yl)acetic acid have been synthesized. By using ^{13}C NMR-spectroscopy 4-hydroxy-/4-oxo-tautomerism has been studied in the series of derivatives of 3-substituted-2-methylquinoline-4(1H)-ones.

Significant deshielding observed in all cases in ^{13}C NMR-spectra of the carbon nuclei in position 4 of the ring indicates the existence of all derivatives studied as 4-oxo forms in DMSO-d_6 solution.

The data of quantum-chemical calculations in various approximations (restricted Hartree-Fock method, DFT and MP2) are in good agreement with the experimental results of ^{13}C NMR. The chemical shift values for C4 carbon in the 4-oxo form (175-177 ppm) and 4-hydroxy form (160 ppm) significantly differ, and therefore, they can be used as a criterion for assigning quinolin-4 (1H)-ones to a particular tautomeric form.

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