Synthesis and using of 10-hydroxy-3,3,6,6-tetramethyl-9-(4-hydroxy-3-methoxyphenyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dion as acid base titration indicator

© Anatoliy N. Pyrko
International Sakharov Environmental Institute of Belarusian State University, Minsk, Belarus

Abstract: The aim of this work is the synthesis of new 10-hydroxydecahydroacridine-1,8-dione derivative, determination of the structure and to study the possibility of using this compound as an indicator of acid-base titration. Environmentally friendly synthesis of 10-hydroxy-3,3,6,6-tetramethyl-9-(4-hydroxy-3-methoxyphenyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dion has been developed by one pot interaction of dimedone, hydroxylamine and 4-hydroxy-3-methoxybenzoic aldehyde in water-alcohol or water solution using citric acid or sodium dodecyl sulfate as catalysts, respectively. Purification of the synthesized compound was carried out by crystallization from ethanol. The obtained compound was characterised by $^1$H NMR, $^{13}$C NMR and UV-Vis spectroscopies. This substance in water-alcohol solution shows intense violet light absorption. Addition alkali induces red shift of absorption maximum to the blue region. UV irradiation of solution of this substance in alcohol induces two-band fluorescence in the visible region. One band disappears upon addition of a base in solution. The structure of the obtained compound was confirmed by high resolution mass-spectrometry analysis. In the mass-spectrum of 10-hydroxy-3,3,6,6-tetramethyl-9-(4-hydroxy-3-methoxyphenyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dion observed $[M+1]^+$ ion peak. The base peak corresponds to tricyclic fragment due to the elimination aromatic cycle from molecular ion. This substance is colorless in acidic and neutral and pink in base solutions. The acid dissociation constant of this compound in a water-alcohol solution was determined by the UV-Vis spectroscopic technique. It was shown that the obtained compound can be used as an indicator for the titration of strong acids and bases.

Keywords: organic synthesis, 10-hydroxydecahydroacridinedione derivative, acid dissociation constant, indicator for the acid-base titration, spectral methods

For citation: Pyrko AN. Synthesis and using of 10-hydroxy-3,3,6,6-tetramethyl-9-(4-hydroxy-3-methoxyphenyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dion as acid base titration indicator. Izvestiya Vuzov. Prikладnaya Khimiya i Biotekhnologiya = Proceedings of Universities. Applied Chemistry and Biotechnology. 2020;10(4):556–563. https://doi.org/10.21285/2227-2925-2020-10-4-556-563

УДК 547.835 + 543.06

Синтез и использование 10-гидрокси-3,3,6,6-тетраметил-9-(4-гидрокси-3-метоксифенил)-1,2,3,4,5,6,7,8,9,10-декагидроакридин-1,8-диона в качестве индикатора кислотно-основного титрования

А.Н. Пырко
Международный государственный экологический институт им. А.Д. Сахарова
Белорусского государственного университета, Минск, Беларусь

Резюме: Целью данной работы являлся синтез нового производного 10-гидроксидекагидроакридин-1,8-диона, определение структуры и изучение возможности использования этого соединения в качестве индикатора кислотно-основного титрования. Синтез 10-гидрокси-3,3,6,6-тетраметил-9-(4-гидрокси-3-метоксифенил)-1,2,3,4,5,6,7,8,9,10-декагидроакридин-1,8-диона проведен с учетом принципов «зеленой химии» взаимодействием димедона, гидроксиметанона и 4-гидрокси-3-метоксибензойного альдегида в экологически безопасном водно-спиртовом или водном растворе. В качестве катализатора использовалась лимонная кислота либо додецил сульфат натрия соответственно. Очистку синтезированного соединения осуществляли кристаллизацией из этанола. Полученное соединение характеризовали с помощью спектров $^1$H ЯМР, $^{13}$C ЯМР, поглощения и флуоресценции в УФ-видимой области. В водно-спиртовом растворе гидроксидекагидроакридиндиона наблюдается поглощение фиолетового света, максимум полосы поглощения которого смещается в область го-
INTRODUCTION

Heterocyclic compounds that include the 1,4-di-hydropropyridine fragment in their structure are of great interest to medical chemists [1–3] due to their wide range of biological effects. Compounds of this type have antihypertensive, antiviral, antioxidant antibacterial, antiviral, spasmylocic, contraceptive activity, without showing a mutagenic effect [4–6].

Decahydroacridinediones contain a 1,4-dihydropropyridine ring as structural fragment and are available via various versions of Hantsch synthesis [7–11]. These compounds exhibit a broad spectrum of biological activity [12–15]. Decahydroacridines with pesticidal activities have been detected [16]. The dyes of the decahydroacridine series have been intensively studied due to the application of them, in particular, as laser dyes and fluorescent markers [17].

Earlier, we described the method synthesis of 10-hydroxy-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-diones [18]. These substances are colorless in acidic and neutral and pink in base solutions. That is why they can be suitable acid-base titration indicators.

Here in we wish to report our results on synthesis of 10-hydroxy-3,3,6,6-tetramethyl-9-(4-hydroxy-3-methoxyphenyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dione 1 and the possibility of using this compound as indicator of acid-base titration.

MATERIALS AND METHODS

In our article [18] the method synthesis of 10-hydroxy-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dion derivatives by three-component heterocyclization of dimedone, hydroxylamine with aldehydes in dry pyridine was described. The reaction of cyclization proceeds as a result of heating of equimolar quantities of dimedone and hydroxylamine hydrochloride in a solution of dry pyridine with addition of aromatic aldehyde, but pyridine is a toxic and foul-smelling substance, therefore, guided by the principles of "green chemistry" [19], we have excluded its use in the synthesis of decahydroacridinedione. The substance investigated was obtained by the interaction of dinedone 2, 4-hydroxy-3-methoxybenzoic aldehyde 4 (vanillin), hydroxylamine hydrochloride 3 and sodium acetate in a aqua-alcohol (1:1, 1:2 volume units) or in an aqueous solution. In the first procedure, citric acid was used as a catalyst, and in the second, sodium dodecyl sulfate, respectively. 10-Hydroxy-3,3,6,6-tetramethyl-9-(4-hydroxy-3-methoxyphenyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dione 1 was obtained with a good yield (83 and 92%, respectively).

This substance is colorless in acidic and neutral and pink in base solutions. That is why it can be suitable acid-base titration indicator. In water-alcohol solution hydroxydecahydroacridinedione 1 shows intense absorption with band maximum at 401.5 nm. Addition alkali induces red shift of absorption maximum to 502.5 nm. It is obvious that observed changes in the electronic absorption spectrum result from formation of anion (II) in alkaline solution (Fig. 2). Both absorption bands are wide and correspond to intramolecular charge transfer between donor and acceptor groups in the molecule. The presence of a negative charge in the donor part of the molecule (NO) increases the energy of the highest occupied molecular orbital (HOMO), which is responsible for red shift of charge-transfer band. Electron acceptors are two carbonyl groups.

By measuring the change in the optical density of absorption, proportional to the concentration of the painted form (II) depending on the pH-value of water or water-alcohol solutions of several hydroxy-decahydroacridinediones (I), we calculated the values of acid dissociation constant (K_acid) of this compound, which allows you to set the color changing pH range of the indicator. It is determined by the value of the constants: ΔpH_{ind} = pK_{acid} ± 1.
The reversible dissociation process $I \leftrightarrow II + H^+$ is characterized by dissociation constant:

$$K_{\text{diss}} = \frac{[H^+][II]}{[I]}$$  \hspace{1cm} (1)

Where: $[H^+]$, $[I]$ and $[II]$ are molar concentrations of proton, acid and its conjugate base (salt), respectively. To use this formula, it is necessary to determine the concentrations of all three components. Proton concentration was determined with a pH meter, a concentration of the base form - using spectrophotometric measurements. The mathematical expression for calculating the constants obtained as follows.

Denote the total concentration of both forms of $C_0$. The concentration of the main (colored) form denoted $C$, then the concentration of the acid form is $C_0 - C$ expression for the dissociation constant is:

$$K_{\text{diss}} = \frac{[H^+][C]}{C_0 - C}$$  \hspace{1cm} (2)

Bouguer – Lambert – Beer law [20] relates the molar concentration of the substance with the optical density of the maximum absorption of the solute (form):

$$D_{\text{max}} = C_M \cdot I \cdot \epsilon \quad \text{or} \quad C_M = \frac{D_{\text{max}}}{I \cdot \epsilon}$$  \hspace{1cm} (3)

where $D_{\text{max}}$ – the optical density of the absorption maximum; $C_M$ – its molar concentration; $I$ – cell width, cm; $\epsilon$ – molar extinction.

Using the expression of the optical density concentration, denoting $C_0 \cdot I \cdot \epsilon = D_0$ in the equation for the equilibrium constants have:

$$K_{\text{diss}} = \frac{[H^+] \cdot D_{\text{max}}}{D_0 - D_{\text{max}}} \quad \text{or} \quad K_{\text{diss}} (D_0 - D_{\text{max}}) = [H^+] \cdot D_{\text{max}}$$

If during the measurement the solution volume and the temperature does not change, then a number of successive measurements of pH values and corresponding densities longwave absorption maximum core mold (II) left side of the equation remains constant. Then, for two consecutive measurements (1 and 2) can be written:

$$K_{\text{diss}} \cdot D_0 = K_{\text{diss}} \cdot D_1 + [H^+] \cdot D_1 = K_{\text{diss}} \cdot D_2 + [H^+] \cdot D_2.$$
then

\[ K_{\text{diss}} = \frac{[H^+]_0 D_1 - [H^+]_0 D_2}{D_1 - D_2} \]  
(5)

In the resulting expression is absent \( D_0 \), which means there is no need to prepare a certain concentration of solution of the substance \( (C_0) \) and using the resulting expression eliminates the need to weigh the samples and measuring the volume of the solution, and thus eliminates the associated measurement errors. Obviously, the accuracy of determining the dissociation constant depends on the range of measurement. At high pH, the concentration of the acid form is insignificant and low-basic. In the first case, the denominator in the expression for the dissociation constant tends to zero in the second – the numerator. Comparable amounts of both forms are solutions in which the pH is close to \( pK_{\text{diss}} \), (at pH = \( pK \) concentrations of both forms of the same, that is, \( C = 0.5C_0 \)).

**EXPERIMENTAL**

Dimedone, hydroxylation hydrochloride, 4-hydroxy-3-methoxybenzoic aldehyde, sodium acetate and citric acid were acquired from Sigma-Aldrich and used without further purification. The UV-Vis absorption spectra were recorded on a UV-2501 PC spectrophotometer. Fluorescence spectra were measured on RF-5301 PC ("Shimadzu", Japan) spectrophotofluorimeter. The \( ^1\)H and \( ^{13}\)C NMR spectra of compound were examined on a Bruker Avance 500 spectrometer at 500 and 125 MHz, respectively; tetramethylsilane was used as internal reference. Chromatographic-mass spectrometric analysis was carried out on liquid hybrid chromatography mass spectrometer LTO Orbitrap Discovery (Thermo Electron Corporation, USA), which includes a linear Quadruple trap LTO XL and the orbital trap of high permission. Ionization of the sample was carried out by electrospray with using the source H-ESI II Ion Max. Calibration of linear and orbital traps LTO Orbitrap Discovery was carried out using a standard solution, containing caffeine (m/z 195), L-methionyl-arginyl-phenylalanine acetate (MRFA, m/z 524) and Ultra- mark 1621 (mixture of fluorinated phosphazines). As an internal calibrant during the removal of mass spectra indapamide was used (m/z 66.0674).

The progress of reaction and the purity of product was monitored by TLC on Silufol UV-254 plates using EtOAc–hexane (1:1) as eluent; spots were visualized under UV radiation or by treatment with iodine vapor, followed by calcination at 250–350 °C. The melting point was determined on a Boelius hot stage.

**Procedures for synthesis of 10-hydroxy-3,3,6,6-tetramethyl-9-(4-hydroxy-3-phenyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dion (1)**

1. A mixture of 2.8 g (20 mmol) of 5,5-dimethylcyclohexane-1,3-dione (dimedone), 1.52 g (10 mmol) of 4-hydroxy-3-methoxybenzoic aldehyde (vanillin) and 0.2 g of citric acid was stirred for one hour at room temperature in 50 ml of ethanol. Then 0.695 g (10 mmol) of hydroxylamine hydrochloride, 0.82 g (10 mmol) sodium acetate and 50 ml water were added thereto and stirred for another two hours. It was then diluted with 50 ml of water, and left to stand for 24 h. The precipitate was filtered off, washed with water (150 ml), and dried in air. Yield 3.41 g (83%), mp 184–186 °C. UV spectrum, EtOH, nm (log ε): 257 (4.13), 401.5 (3.77), \(^1\)H NMR spectrum (DMSO-\(d_6\)), δ ppm: 0.91 s (6H, 2Me), 0.99 s (6H, 2Me), 2.27 s (4H, 2CH\(_2\)), 2.51 (4H, 2CH\(_2\)), 3.60 s (3H, OMe), 5.75 s (1H, 9-H), 6.30–6.60 m (3H\(_{\text{arom.}}\)). \(^{13}\)C NMR spectrum (DMSO-\(d_6\)), δ ppm: 28.39 (4Me), 30.49 (C4,C5), 31.13 (C9), 32.01 (C3, C6), 47.07 (OMe), 55.84 (C2, C7), 111.17 (C8a, C9a), 111.36 (C\(_{\text{arom.}}\)), 111.48 (C\(_{\text{arom.}}\)), 115.42 (C\(_{\text{arom.}}\)), 119.12 (C\(_{\text{arom.}}\)), 132.43 (C\(_{\text{arom.}}\)), 144.36 (C\(_{\text{arom.}}\)), 147.92 (C4a, 10a), 189.03 (C1, C8). Found, %: C – 69.92; H – 7.13; N – 3.31. C\(_{52}\)H\(_{39}\)NO\(_5\). Calculated, %: C – 70.05; H – 7.10; N – 3.40.

2. A mixture of 1.4 g (10 mmol) of dimedone, 0.34 g of hydroxylation hydrochloride (NH\(_2\)OH - HCl), 0.42 g (5 mmol) of sodium acetate (NaOAc) in the presence of 0.2 g of sodium dodecyl sulfate (C\(_{12}\)H\(_{25}\)SO\(_4\)Na) as a catalyst was stirred in aqueous solution (20 ml H\(_2\)O) for 45 min. Then 0.76 g (5 mmol) of 4-hydroxy-3-methoxybenzaldehyde (vanillin) was added and stirred for 6 h at room temperature. For a deeper precipitation, potassium sulfate (K\(_2\)SO\(_4\)) was added to the aqueous solution. The precipitated green crystals were washed with 50 ml of water and dried in air. Crystalized from ethanol. The yield was 1.90 g (92%).

**Procedure for determining the dissociation constant.** The total solution volume was 100 ml, wherein 50 ml buffer and 50 ml of ethanol. Buffer was Triss – 1.21 g per 100 ml. Needless active substance is 5 mg. A pH meter for measuring the pH of the solution was adjusted to 6.86 by adding hydrochloric acid. Then poured into a cuvette 2 ml of the solution and the absorption spectrum was recorded on a spectrophotometer UV-2501 PC. Then, the pH was increased with concentrated KOH to pH 7.24, 7.61, 7.97, 8.41, 8.98, 9.73, 10.34, 10.79, 11.02 respectively, and re-measured with a spectrophotometer. Registration density maximum absorption was carried out at 502.5 nm. The pH measurements were taken at 20 °C using an HI 221 pH meter. The error of the ten definitions of the dissociation constant K for solutions of compound 1a was calculated as the root mean square error of the arithmetic mean (standard deviation) taking into account the Student coefficient of 2.26 for ten determinations for the confidence probability \( P = 0.95 \).

**RESULTS AND DISCUSSION**

The structure of the obtained compound is confirmed by the data of the \(^1\)H and \(^{13}\)C NMR, UV spectra, elemental and mass spectrometric analysis. The


\(^1\)H and \(^{13}\)C NMR spectra correspond to structure with symmetry plane passing through the C\(^2\) and N\(^{10}\) atoms [18]. Thus, in the \(^1\)H NMR spectrum of compound four methyl groups in positions 3, 6 and four methylene groups in 2, 4, 5, 7 positions appear as two singlets \((0.91:0.99 \text{ and } 2.27:2.51 \text{ ppm respectively})\). The \(^{13}\)C NMR spectrum exhibited 15 signals of 24 carbon atoms, because the signals of equivalent atoms coincide.

The structure of compound 1 was confirmed by high resolution mass-spectrometry data (Table 1). In the spectrum observed \([\text{M}+1]^+\) \((412 \text{ m/z})\), ion peak. The base peak \((288 \text{ m/z})\) corresponds to tricyclic fragment due to cleavages \((\text{C}^2-\text{C}^4_{\text{atom}})\) bond and the elimination aromatic cycle from molecular ion. Such type fragmentation was observed for other 9-aryldecahydroacridine-1,8-dione derivatives [21].

Results of measurements and calculations are given in the table 2. The resulting value \(pK_{\text{diss}}\), conversion process I \(\leftrightarrow\) II is \(7.425\pm0.016\). The value of the dissociation constant indicates the possibility of using this compound as an indicator for the titration of strong acids and bases. In this case, it is a better indicator than phenolphthalein and methyl orange, since its \(pK\) is close to the pH equivalence point (neutral medium pH = 7.0).

Irradiation of solution of this substance in alcohol \(\lambda_{\text{max}}\) \((370 \text{ nm})\) induces fluorescence at \(\lambda_{\text{max}}\) \(468\) and \(\lambda_{\text{max}}\) \(680\) nm. First band disappears upon addition of a base in solution. Irradiation of basic solution \((\lambda_{\text{max}}\) 500 nm) induces fluorescence at \(\lambda_{\text{max}}\) \(680\) nm (Fig. 3). The presence of two bands in the fluorescence spectrum of hydroacridinedion (I) in a neutral medium can be explained by its dissociation in an excited state and its transformation into an anion (II) (see Fig. 2). The long-wavelength band at \(680\) nm corresponds to the emission of an excited anionic form II. Since obtained hydroacridindion shows two emission bands in the visible region of fluorescent spectrum with large Stokes shift, it is of interest as fluorescent marker for studying biological molecules and supra-molecular structures.

---

**Table 1.** Data of mass-spectrometric measurement for compound 1

| Calculated, m/z | Observed, m/z |
|----------------|--------------|
| 412.21185      | 412.21072    |
| 288.15942      | 288.15822    |

**Table 2.** The results determining of acid dissociation constant of decahydroacridine solution

| Number measuring | pH     | \([\text{H}^+]\) \(10^{-10}\) mol/l | D   | \(\text{K}_{m,n}^\circ\) | \(\text{K}_{m,n}^\circ\) \(10^{-8}\) | \(\text{pK}_{m,n}\) | \(\text{K}_{\text{average}} \pm \Delta K\) | \(\text{pK}_{\text{average}} \pm \Delta pK\) |
|-----------------|--------|------------------------------------|-----|------------------------|-----------------------------------|----------------|----------------------------------------|------------------------------------------|
| 1               | 6.86   | 1380.384                           | 0.153 | K\(_{1/2}\)       | 3.791                               | 7.421 | K\(_{\text{average}}\) \(\pm \Delta K\) | 7.424 \(\pm 0.016\) |
| 2               | 7.24   | 575.440                            | 0.282 | K\(_{1/3}\)       | 3.806                               | 7.420 | pK\(_{\text{average}}\) \(\pm \Delta pK\) |
| 3               | 7.61   | 245.471                            | 0.432 | K\(_{1/4}\)       | 3.761                               | 7.425 | pK\(_{\text{average}}\) \(\pm \Delta pK\) |
| 4               | 7.97   | 107.152                            | 0.556 | K\(_{1/5}\)       | 3.758                               | 7.425 | pK\(_{\text{average}}\) \(\pm \Delta pK\) |
| 5               | 8.41   | 38.904                             | 0.648 | K\(_{1/6}\)       | 3.753                               | 7.426 | 7.424 \(\pm 0.016\) |
| 6               | 8.98   | 10.471                             | 0.696 | K\(_{1/7}\)       | 3.748                               | 7.426 | 7.424 \(\pm 0.016\) |
| 7               | 9.73   | 1.862                              | 0.711 | K\(_{1/8}\)       | 3.746                               | 7.426 | 7.424 \(\pm 0.016\) |
| 8               | 10.34  | 0.457                              | 0.714 | K\(_{1/9}\)       | 3.742                               | 7.427 | \(\Delta pK_{\text{ind}} = \text{pK}_{\text{ind}} \pm 1\) |
| 9               | 10.79  | 0.162                              | 0.715 | K\(_{1/10}\)      | 3.741                               | 7.427 | \(\Delta pK_{\text{ind}} = \text{pK}_{\text{ind}} \pm 1\) |
| 10              | 11.02  | 0.095                              | 0.715 | K\(_{1/11}\)      | 3.739                               | 7.427 | \(\Delta pK_{\text{ind}} = \text{pK}_{\text{ind}} \pm 1\) |

\(K_{m,n}\) and \(\text{pK}_{m,n}\) are \(K_{\text{diss}}\) and \(\text{pK}_{\text{diss}}\) calculated using the formula (5) based on measurement of pH, D numbers m and n.
CONCLUSIONS

1. In accordance with the principles of green chemistry 10-hydroxy-3,3,6,6-tetramethyl-9-(4-hydroxy-3-methoxyphenyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dion has been synthesized by two environmentally benign methods using non-toxic reagents, solvents and catalysts.

2. The structure of obtained compound has been confirmed by the data of the \(^1\text{H}\) and \(^{13}\text{C}\) NMR, UV spectra, elemental and mass spectrometric analysis.

3. The acid dissociation constant of the resulting compound in hydroalcoholic solution was determined by the UV-Vis spectroscopic technique.

4. It has been shown that this compound can be used as an indicator for the titration of strong acids and bases.

5. Fluorescence spectra have been studied and it has been shown that this compound is of great interest as a fluorescent marker.

REFERENCES

1. Ozols YaYa, Pyrko AN, Lakkhiv FA, Vigante VA, Dubure RR, Dubur GYa, et al. Synthesis of decahydrophenanthridine-1,7-dione and hexahydroisoquinol-8-one derivatives in the reaction of 2-acetyl-2-cyclohexene-1-ones with conjugated enaminocarbonyl compounds. *Chemistry of Heterocyclic Compounds*. 1990;26(1):58–62. https://doi.org/10.1007/BF00506849

2. Ozols YaYa, Pyrko AN, Vigante BA, Dubure RR, Dubur GYa. Synthesis of phenyl-substituted derivatives of decahydro-1,7-phenanthridinedione and hexahydro-8-isouquinolone. *Chemistry of Heterocyclic Compounds*. 1992;28(5):530–534. https://doi.org/10.1007/BF00475250

3. Milkovic L, Vukovic T, Zarkovic N, Tatzber F, Bisenieks E, Kalme Z, et al. Antioxidative 1,4-dihydropyridine derivatives modulate oxidative stress and growth of human osteoblast-like cells *in vitro*. *Antioxidants*. 2018;7(9):1–23. https://doi.org/10.3390/antioxidants80900123

4. Mishnev A, Bisenieks E, Mandrika I, Petrosrka R, Kalme Z, Bruverea I, et al. Crystal structure and metabolic activity of 4-(thien-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydronquinoline-3-carboxylic acid ethoxycarbonylphenyl-methylester. *Acta Crystallographica. Section E*. 2018;74:1577–1579. https://doi.org/10.1107/S05670755180001425

5. Shekari F, Sadeghpour H, Javidnia K, Saso L, Nazari F, Firuzi O, et al. Cytotoxic and multidrug resistance reversal activities of novel 1,4-dihydropyridines against human cancer cells. *European Journal of Pharmacology*. 2015;746:233–244. https://doi.org/10.1016/j.ejphar.2014.10.058

6. Velena A, Zarkovic N, Troselj KG, Bisenieks E, Krauze A, Poikans J, et al. 1,4-Dihydropyridine derivatives: dihydronicotinamide analogues – model compounds targeting oxidative stress. *Oxidative Medicine Cellular Longevity*. 2016;216. Article ID 1892412. https://doi.org/10.1155/2016/1892412

7. Marjani AP, Khalafy J, Chitan M, Mahmoodi S. Microwave-assisted synthesis of acridine-1,8(2H,5H)-diones via a one-pot, three component reaction. *Iranian Journal of Chemistry and Chemical Engineering*. 2017;36(2):1–6.

8. Nalini V, Girija R. Synthesis, characterization and biological studies of 9-aryl substituted acridinecarboxylic derivatives by Hantzsch condensation. *International Journal of Current Research*. 2013;5(10):3076–3081.

9. Safaei-Ghomi J, Ghasezmizadeh MA, Zadeh S. ZnO nanoparticles: a highly effective and readily recyclable catalyst for the one-pot synthesis of 1,8-dioxodecahydroacridine and dioxocatohydroxanthene derivatives. *Journal of the Mexican Chemical Society*. 2013;57(1):1–7.

10. Xia J-J, Zhang K-H. Synthesis of N-substituted acridinediones and polyhydroquinoline derivatives in refluxing water. *Molecules*. 2012;17(5):5339–5345. https://doi.org/10.3390/molecules17055339

11. Kalalawe VG, Munde RD, Kagne RP, Nalini V, Girija R. Synthesis, characterization and biological studies of 9-aryl substituted acridinediones using ionic liquid as promoter. *International Journal of Green and Herbal Chemistry. Section B.*

12. Nakhi A, Srinivas PV, Rahman MS, Kishore R, Seerapu GPK, Kumar KL, et al. Amberlite IR-120H catalyzed MCR: design, synthesis and crystal structure analysis of 1,8-dioxodecahydroacridines as potential inhibitors of sirtuins. *Bioorganic and Medicinal Chemistry Letters*. 2013;23(6):1828–1833. https://doi.org/10.1016/j.bmcl.2013.01.026

13. Shchekotikhin YuM, Nikolaeva TG, Shub GM, Kriven’ko AP. Synthesis and antibacterial activity of substituted 1,8-dioxodecahydroacridines. *Pharmaceut-
tical Chemistry Journal. 2001;35(4):206–211.

14. Jezek J, Sebestic J, Hlavacek J. Biomedical applications of acridines: derivatives, syntheses, properties and biological activities a focus on neurodegenerative diseases. Springer International Publishing AG; 2017. 236 p. https://doi.org/10.1007/978-3-319-63953-6

15. Pesian NN, Akhteh N, Batmani H, Anil B, Šahin E. A facile and catalyst-free synthesis of hexahydroacridine-1,8(2H,5H) -dione and octahydroacridin-10(1H) -yl)thiourea derivatives: Inter- and Intramolecular Aza-Michael addition. Heterocyclic Communications. 2020;26(1):26–32. https://doi.org/10.1515/hc-2020-0005

16. Pyrko AN. Synthesis and biological testing for pesticidal activity of 9-aryl-n-aryl, alkyl substituted 1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione derivatives. Izvestiya Vuzov. Pririkladnaya Khimiya i Biotehnologiya = Proceedings of Universities. Applied Chemistry and Biotechnology. 2017;7(2):16–20. (In Russian) https://doi.org/10.212 85/2227-2925-2017-1-7-1-16-20

17. Gutsulyak KV, Manzhara VS, Mel’nik MV, Kalin TI. Relationship between the structure and photo-stability of decahydroacridine derivatives. Journal of Applied Spectroscopy. 2005;72(4):488– 494. https://doi.org/10.1007/s10812-005-0102-9

18. Pyrko AN. Synthesis and transformations of new 1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione derivatives. Russian Journal of Organic Chemistry. 2008;44(8):1215–1224. https://doi.org/10.1134/S1070428008080198

19. Beletskaya IP, Kustov LM. Catalysis as an important tool of green chemistry. Russian Chemical Reviews. 2010;79(6):493–515. https://doi.org/10.1010 70/RC2010v079n06ABEH004137

20. Christian GD, Dasgupta PK, Schug KA. Analytical chemistry. 7th revised ed. Washington: Wiley; 2013. 848 p.

21. Shchekotikhin YuM, Nickolaeva TG. Characteristics of the dissociative ionization of 9-aryl (hetaryl)-3,3,6,6-tetra- methyldecahydroacridine-1,8-diones under the influence of electron impact. Chemistry of Heterocyclic Compounds. 2004;40(8): 1031–1035. https://doi.org/10.1023/B:COHC.0000 46693.85136.ac

БИБЛИОГРАФИЧЕСКИЙ СПИСОК

1. Ozols Ya.Ya., Pyrko A.N., Lakhvich F.A., Vigante V.A., Dubure R.R., Dubur G.Ya., et al. Synthesis of decacyclophenanthridine-1,7-dione and hexahydroisoquinolin-8-one derivatives in the reaction of 2-acetyl-2-cyclohexene-1-ones with conjugated enamincarbonyl compounds // Chemistry of Heterocyclic Compounds. 1990. Vol. 26. Issue 1. P. 58–62. https://doi.org/10.1007/BF00506849

2. Ozols Ya.Ya., Pyrko A.N., Vigante B.A., Dubure R.R., Dubur G.Ya. Synthesis of phenyl-substituted derivatives of decahydro-1,7-phenanthridinedione and hexahydro-8-isouquinolone // Chemistry of Heterocyclic Compounds. 1992. Vol. 28. Issue 5. P. 530–534. https://doi.org/10.1007/BF00475250

3. Milkovic L., Vukovic T., Zarkovic N., Tatzber F., Bisenieks E., Kalme Z., et al. Antioxidative 1,4-dihydropyridine derivatives modulate oxidative stress and growth of human osteoblast-like cells in vitro // Antioxidants. 2018. Vol. 123.Vol. 7. Issue 9. P. 1–23. https://doi.org/10.3390/antiox7090123

4. Mishnev A., Bisenieks E., Mandrika I., Petrovskaya L., Kalme Z., Bruverea I., et al. Crystal structure and metabolic activity of 4-(thien-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethoxycarbonylphenylmethyl ester // Acta Crystallographica. Section E. 2018. Vol. E74. P. 1577–1579. https://doi.org/10.1107/S0569998018014251

5. Shekari F., Sadeghpour H., Javidinia K., Saso L., Nazari F., Firuzi O., et al. Cytotoxic and multidrug resistance reversal activities of novel 1,4-dihydropyridines against human cancer cells // European Journal of Pharmacology. 2015. Vol. 746. P. 239–244. https://doi.org/10.1016/j.ejphar.2014.10.058

6. Velena A., Zarkovic N., Trosej K.G., Bisenieks E., Krauze A., Poikans J., et al. 1,4-Dihydropyridine derivatives: dihydroxocotinamide analogues – model compounds targeting oxidative stress // Oxidative Medicine Cellular Longevity. 2016. Vol. 216. Article ID 1892412. https://doi.org/10.1155/2016/1892412

7. Marjani A.P., Khajafy J., Chitan M., Mahmoodi S. Microwave-assisted synthesis of acridine-1,8(2H,5H)-diones via a one-pot, three component reaction // Iranian Journal of Chemistry and Chemical Engineer. 2017. Vol. 36. Issue 2. P. 1–6.

8. Nalini V., Girija R. Synthesis, characterization and biological studies of 9-aryl substituted acridinedione derivatives by Hantzsh condensation // International Journal of Current Research. 2013. Vol. 5. Issue 10. P. 3076–3081.

9. Safaei-Ghomi J., Ghasemzadeh M.A., Zahedi S. ZnO nanoparticles: a highly effective and readily recyclable catalyst for the one-pot synthesis of 1,8-dioxo-decahydroacridine and dioxoactahydroxanthene derivatives // Journal of the Mexican Chemical Society. 2013. Vol. 57. Issue 1. P. 1–7.

10. Xia J.-J., Zhang K.-H. Synthesis of N-substituted acridinediones and polyhydroquinoline derivatives in refluxing water // Molecules. 2012. Vol. 17. Issue 5. P. 5339–5345. https://doi.org/10.3390/molecu les17055339

11. Kalalawe V.G., Munde R.D., Kagne R.P., Niwadange S.N., Gutte R.D. Synthesis of acridine derivatives using ionic liquid as promoter // International Journal of Green and Herbal Chemistry. Sec. B. 2018. Vol. 7. Issue 2. P. 188–193. https://doi.org/10.24214/UGHC/GC/7/2/18893

12. Nakhi A., Srinivas P.V., Rahman M.S., Kishore R., Seerapu G.P.K., Kumar K.L., et al. Amberlite IR-120H catalyzed MCR: design, synthesis and crystal structure analysis of 1,8-dio-
хиноэдекаэдронов как потенциальных ингибиторов сиртуин // Bioorganic and Medicinal Chemistry Letters. 2013. Vol. 23. Issue 6. P. 1828–1833. https://doi.org/10.1016/j.bmcl.2013.01.026

13. Shchekotikhin Yu.M., Nikolaeva T.G., Shub G.M., Kriven’ko A.P. Synthesis and antibacterial activity of substituted 1,8-dioxodecahydroacridines // Pharmaceutical Chemistry Journal. 2001. Vol. 35. Issue 4. P. 206–211.

14. Jezek J., Sebestic J., Hlavacek J. Biomedical applications of acridines: derivatives, syntheses, properties and biological activities a focus on neurodegenerative diseases. Springer International Publishing AG. 2017. 236 p. https://doi.org/10.1007/978-3-319-63953-6

15. Pesyan N.N., Akhteh N., Batmani H., Anil B., Şahin E. A facile and catalyst-free synthesis of hexahydroacridine-1,8(2H,5H )-dione and octahydroacridin-10(1H )-ylthiourea derivatives: Inter- and Intramolecular Aza-Michael addition // Heterocyclic Communications. 2020. Vol. 26. Issue 1. P. 26–32. https://doi.org/10.1515/hc-2020-0005

16. Пырко А.Н. Синтез и биологические испытания на пестицидную активность производных 1,2,3,4,5,6,7,8,9,10-декагидроакридиндиона-1.8 // Известия вузов. Прикладная химия и биотехнология. 2017. Т. 7. Н 2. С. 16–20. https://doi.org/10.21285/2227-2925-2017-7-1-16-20

17. Gutsulyak K.V., Manzhara V.S., Meţnik M.V., Kalin T.I. Relationship between the structure and photostability of decahydroacridine derivatives // Journal of Applied Spectroscopy. 2005. Vol. 72. Issue 4. P. 488–494. https://doi.org/10.1007/s10812-005-0102-9

18. Пырко А.Н. Synthesis and transformations of new 1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione derivatives // Russian Journal of Organic Chemistry. 2008. Vol. 44. Issue 8. P. 1215–1224. https://doi.org/10.1134/S1070428008080198

19. Beletskaya I.P., Kustov L.M. Catalysis as an important tool of green chemistry // Russian Chemical Reviews. 2010. Vol. 79. Issue 6. P. 493–515. https://doi.org/10.1070/RC2010v079n06ABEH004137

20. Christian G.D., Dasgupta P.K., Schug K.A. Analytical chemistry; 7th revised ed. Washington: Wiley. 2013. 848 p.

21. Shchekotikhin Yu.M., Nikolaeva T.G. Characteristics of the dissociative ionization of 9-aryl(hetaryl)-3,3,6,6-tetramethyldecahydroacridine-1,8-diones under the influence of electron impact // Chemistry of Heterocyclic Compounds. 2004. Vol. 40. Issue 8. P. 1031–1035. https://doi.org/10.1023/B:COHC.0000046693.85136.ac

INFORMATION ABOUT THE AUTHORS

Anatoliyi N. Pyrko,
Cand. Sci. (Chemistry). Associate Professor, Environmental Chemistry and Biochemistry Department, International Sakharov Environmental Institute of Belarusian State University, 23, Dolgobrodskaya St., Minsk, 220070, Belarus, e-mail: pyrko@yandex.ru

Contribution of the authors
Anatoliyi N. Pyrko carried out the experimental work, analyzed the experimental results and prepared the text of the manuscript. Author has exclusive author’s right and bear responsibility for plagiarism.

Conflict interests
The author declare no conflict of interests regarding the publication of this article.

The final manuscript has been read and approved by the author.

Заявленный вклад авторов
Пырко Анатолий Николаевич, к.х.н., доцент кафедры экологической химии и биохимии, Международный государственный экологический институт им. А.Д. Сахарова Белорусского государственного университета, 220070, г. Минск, ул. Долгобродская, 23/1, Республика Беларусь, e-mail: pyrko@yandex.ru

Заявленный вклад авторов
Пырко А.Н. выполнил экспериментальную работу, обобщил полученные результаты и написал рукопись. Автор имеет на статью исключительные авторские права и несет ответственность за плагиат.

Конфликт интересов
Автор заявляет об отсутствии конфликта интересов.

The article was submitted 28.10.2020; approved after reviewing 27.11.2020; accepted for publication 30.11.2020.