ХИМИЧЕСКИЕ НАУКИ

Original article
DOI: https://doi.org/10.21285/2227-2925-2022-12-1-8-14

Synthesis and biological testing for pesticidal activity of 8-azasteroids

Anatoly N. Pyrko

International Sakharov Environmental Institute
of Belarusian State University, Minsk, Republic of Belarus
Corresponding author: Anatoly N. Pyrko, pyrko@yandex.ru

Abstract. *The aim of the present study is the synthesis and testing for pesticidal activities of 2,3-dimethoxy-16,16-dimethyl-D-homo-8-azagona-1,3,5(10),13-tetraene-12,17a-one and 2,3-dimethoxy-16,16-dimethyl-d-homo-8-azagona-1,3,5(10),13-tetraene-12-imino-17a-one hydrochloride which could become the basis the basis of plant protection products. The first compound was obtained by condensation of 6,7-dimethoxy-2,3-dihydroisoquinoline with 2-acetyl-5,5-dimethylcyclohexane-1,3-dione. The second substance was synthesized by interaction of the first with ammonium chloride. 2-Acetyl-5,5-dimethylcyclohexane-1,3-dione was prepared by heating dimedone with acetic acid in polyphosphoric acid. 6,7-Dimethoxy-2,3-dihydroisoquinoline was synthesized in two steps. Boiling 2-(3,5-dimethoxyphenyl)ethylamine in formic acid gave the corresponding amide, which was cyclized in the presence of phosphorus oxychloride. The structure of the obtained compounds is confirmed by the data of IR, ^{1}H NMR, UV spectra and elemental analysis. In the IR absorption spectra of 2,3-dimethoxy-16,16-dimethyl-D-homo-8-azagona-1,3,5(10),13-tetraene-12,17a-dione and 2,3-dimethoxy-16,16-dimethyl-D-homo-8-azagona-1,3,5(10),13-tetraen-12-imino-17a-one hydrochloride, enaminodiketone bands are present (1535, 1580, 1615, 1625, 1670 cm^{-1}) and enimine ketone (1595, 1650, 3260 cm^{-1}) groups, respectively. Their UV absorption spectra recorded in ethanol contain two absorption bands (265.303 and 268.317 nm) corresponding to ππ* transitions of the same molecular fragments. The mass spectra of the two obtained tetracycles contain peaks of molecular ions. ^{1}H NMR spectra correspond to the structures of all obtained compounds The synthesized compounds were tested for certain types of insecticide (against Toxoptera graminum, Musca domestica, Meloidogyne incognita, Heliothis virescens, Diabrotica undecimpunctata howardi, Caenorhabditis elegans), fungicidal (against Drechslera, Erysiphe, Puccinia, Peronospora) and herbicidal (against Amaranthus retroflexus, Brassica rapa, Abutilon theophrasti, Alopecurus myosuroides, Avena fatua, Echinochloa crus galli) activities. Both synthesized compounds showed herbicidal activity against Amaranthus retroflexus, Brassica rapa, Abutilon theophrasti and insecticidal activity against Toxoptera graminum. Hydrochloride 2,3-dimethoxy-16,16-dimethyl-D-homo-8-azagon-1,3,5(10),13-tetraene-12-imino-17a-one showed insecticidal activity against Musca domestica and fungicidal activity against Drechslera.*

Keywords: *organic synthesis, heterocycles, azasteroids, herbicides, insecticides, fungicides*

For citation: Pyrko A. N. Synthesis and biological testing for pesticidal activity of 8-azasteroids. *Izvestiya Vuzov. Prikladnaya Khimiya i Biotekhnologiya = Proceedings of Universities. Applied Chemistry and Biotechnology.* 2022;12(1):8-14. (In English). https://doi.org/10.21285/2227-2925-2022-12-1-8-14.

CHEMICAL SCIENCES

Научная статья
УДК 547.92+632.95

Синтез и биологические испытания на пестицидную активность 8-азастероидов

Анатолий Николаевич Пырко

Международный государственный экологический институт имени А. Д. Сахарова
Белорусского государственного университета, г. Минск, Республика Беларусь
Автор, ответственный за переписку: Пырко Анатолий Николаевич, pyrko@yandex.ru

Аннотация. *Целью данного исследования является синтез и тестирование на пестицидную активность 2,3-диметокси-16,16-диметил-D-гомо-8-азагона-1,3,5(10),13-тетраен-12,17а-диона и гидрохлорида 2,3-диметокси-16,16-диметил-D-гомо-8-азагона-1,3,5(10),13-тетраен-12-имино-17а-она, которые*

могли бы стать основой средств защиты растений. Первое соединение было получено конденсацией 6,7-диметокси-2,3-дигидроизохинолина с 2-ацетил-5,5-диметилциклогексан-1,3-дионом. Второе – взаимодействием первого с хлористым аммонием. 2-Ацетил-5,5-диметилциклогексан-1,3-дион был получен нагреванием димедона с уксусной кислотой в полифосфорной кислоте. 6,7-Диметокси-2,3-дигидроизохинолин был синтезирован в две стадии. Кипячением 2-(3,5-диметоксифенил)этиламина в муравьиной кислоте получали соответствующий амид, циклизацию которого проводили в присутствии хлорокиси фосфора. Структура полученных соединений подтверждена данными ИК, ^{1}Н ЯМР, УФ-спектров и элементного анализа. В ИК-спектрах поглощения 2,3-диметокси-16,16-диметил-D-гомо-8-азагона-1,3,5(10),13-тетраен-12,17а-диона и гидрохлорида 2,3-диметокси-16,16-диметил-D-гомо-8-азагона-1,3,5(10),13-тетраен-12-имино-17а-она присутствуют полосы енаминодикетонной (1535, 1580, 1615, 1625, 1670 см$^{-1}$) и енаминокетонной (1595, 1650, 3260 см$^{-1}$) групп соответственно. В их УФ-спектрах поглощения, записанных в этаноле, имеются две полосы поглощения (265,303 и 268,317 нм), соответствующие ππ-переходам тех же фрагментов молекул. В масс-спектрах двух полученных тетрациклов присутствуют пики молекулярных ионов. ^{1}Н ЯМР-спектры соответствуют структурам всех полученных соединений. Синтезированные соединения были испытаны на некоторых видах инсектицидной (против Toxoptera graminum, Musca domestica, Meloidogyne incognita, Heliothis virescens, Diabrotica undecimpunctata howardi, Caenorhabditis elegans), фунгицидной (против Drechslera, Erysiphe, Puccinia, Peronospora) и гербицидной активности (против Amaranthus retroflexus, Brassica rapa, Abutilon theophrasti, Alopecurus myosuroides, Avena fatua, Echinochloa crusgalli). Оба синтезированные соединения показали гербицидную активность против Amaranthus retroflexus, Brassica rapa, Abutilon theophrasti и инсектицидную против Toxoptera graminum. Гидрохлорид 2,3-диметокси-16,16-диметил-D-гомо-8-азагона-1,3,5(10),13-тетраен-12-имино-17а-она проявил инсектицидную активность против Musca domestica и фунгицидную против Drechslera.*

Ключевые слова: *органический синтез, гетероциклы, азастероиды, гербициды, инсектициды, фунгициды*

Для цитирования: Пырко А. Н. Синтез и биологические испытания на пестицидную активность 8-азастероидов // Известия вузов. Прикладная химия и биотехнология. 2022. Т. 12. N 1. С. 8–14. https://doi.org/10.21285/2227-2925-2022-12-1-8-14.

INTRODUCTION

The high intensity of work on the chemistry of steroids is due to their enormous physiological and therapeutic value. The total synthesis of natural and related biologically active compounds is one of the important tasks of modern organic and bioorganic chemistry. Closely related to it are the problems of creating new drugs, chemical agents for protecting and regulating the growth of plants and animals, establishing the mechanism of action of natural and synthetic bioregulators, etc. [1–3].

The synthesis of modified steroids is an important direction in the chemistry of steroids, since the widespread use of steroid compounds as drugs poses the task of separating their pharmacological effect from hormonal action. One of the modifying factors that make it possible to increase the selectivity of the biological action of steroids is the introduction of a heteroatom into the steroid skeleton [4]. Nitrogen, oxygen, sulfur, selenium and phosphorus are commonly used as a heteroatom. Works on the synthesis of azasteroids were widely developed [5–8]. As a result of replacing the carbon atom with nitrogen, there are practically no changes in the structure of the steroid skeleton, however, the presence of a nitrogen atom with a free pair of electrons causes profound changes in biological activity. Azasteroids have a wide range of biological activity, in particular, antitumor, anti-inflammatory, anti-ulcer, antimicrobial [4–8]. Intensive research on complete synthesis, chemical modification and the study of biological activity in the 70–90s of the last century was carried out at the N. D. Zelinsky Institute of Organic Chemistry of the USSR Academy of Sciences and the Institute of Bioorganic Chemistry of the National Academy of Sciences of Belarus under the guidance of Academician of the National Academy of Sciences of Belarus A. A. Akhrem [9–13]. It was shown that 8-azasteroids [14, 15] represent a new class of low-molecular nonantigenic agents modulating immune functions of the human organism and animals. Both stimulators and depressants of immune response were found among compounds of this type. In addition to the creation of new medicines, an important task of the practical use of the results of scientific research in agriculture is the creation of new chemical plant protection products, since over time, the development of pest resistance to the drugs used is observed. This work is devoted to the synthesis and research on various types of pesticide activity of the 8-azaanalog of steroids.

MATERIALS AND METHODS

The starting compounds in the synthesis of imine **1** were 5,5-dimethylcyclohexane-1,3-dione (dimedone) existing in ketoenol form **2** and 2-(3,4-dimethoxyphenyl)ethylamine (veratrylmethylamine) **3**. There are many publications on the synthesis of 6,7-

dimethoxy-3,4-dihydroisoquinoline **4** [16–18]. We obtained this substance by the reaction of 2-(3,4-dimethoxyphenyl)ethylamine **3** with formic acid and cyclization corresponding formamide in toluene by heating with phosphorus oxychloride. Diketoenol **5** was obtained according to the previously developed method [19] by acylation of dimedone **2** with acetic acid in polyphosphoric acid. The synthesis of tetracycle **7** was carried out according to the AB → ABD → ABCD-scheme for constructing the tetracyclic steroid skeleton [20, 21] by the interaction of diketoenol (**5,** D-fragment) with dihydroisoquinoline (**4**, AB-fragment) without isolation of the intermediate tricycle (**6**, ABD-fragment, fig. 1). The reaction was carried out in non-toxic, environmentally friendly ethanol, which corresponds to the principles of "green" chemistry. We have developed an efficient method for synthesis of imine hydrochloride **1** from diketone **7** by the reaction of the latter with ammonium chloride (Fig. 1).

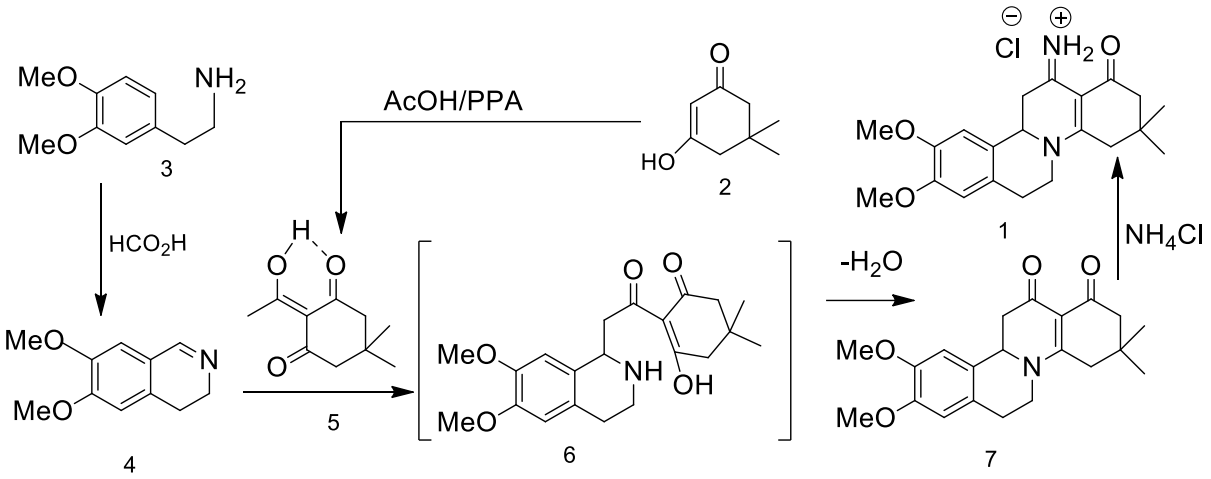

Fig. 1. Scheme of synthesis of 8-azasteroids **1** and **7**

Рис. 1. Схема синтеза 8-азастероидов **1** и **7**

EXPERIMENTAL

Dimedone, 2-(3,4-dimethoxyphenyl)ethylamine, o-phosphoric acid, phosphorus pentoxide and acetic acid were acquired from Sigma-Aldrich and used without further purification. IR spectra were obtained on a spectrophotometer UR–20 in KBr tablets. The UV-Vis absorption spectra were recorded on a UV-2501 PC spectrophotometer. The ^{1}H NMR spectra of compound were examined on a Bruker Avance 500 spectrometer at 500 MHz; tetramethylsilane was used as internal reference. Mass spectra were determined on a Varian MAT-311 instrument at an ionizing radiation energy of 70 eV. 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 Boetius hot stage.

Procedure for synthesis of 6,7-dimethoxy-3,4-dihydroisoquinoline **(4)**. A mixture of 36.2 g (0.2 mol) of 2-(3,5-dimethoxyphenyl)ethylamine **3** and 25 g of formic acid was boiled at a temperature of 185 °C for 4 hours. Then the excess acid was evaporated in vacuo and 200 ml of toluene and 120 ml of phosphorus oxychloride were added. The mixture was boiled for 3.5 hours. After cooling the mixture, 100 g of ice was slowly added. The acids were then carefully neutralized with solid potassium hydroxide and 300 ml of benzene were added. The toluene-benzene solution was dried over KOH, the solvent was evaporated, and the residue was distilled in vacuum (3 mm Hg, 150–155 °C). Received 20.63 g (54%) of the product, yellow oily liquid. ^{1}H NMR spectrum in $CDCl_3$, σ, ppm: 2.80 t (2H, J 7 Hz, 4-CH_2), 3.79 s (3H, OMe), 3.82 s (3H, OMe), 3.90 t (2H, J 7 Hz, 3-CH_2), 6.54 s (1H aromatic), 6.61 s (1H aromatic), 8.28 s (1H, 1-CH) Found%: C 68.98; H 6.90; N 7.38. $C_{11}H_{13}O_2N$. Calculated %: C 69.09; H 6.85; N 7.32.

Procedure for synthesis of 2-acetyl-5,5-dimethylcyclohexane-1,3-dion **(5)**. To 100 g of polyphosphoric acid (70 g of P_2O_5 + 30 ml of 85% H_3PO_4) was added with stirring at a temperature of 100 °C 13.8 g of glacial acetic acid and 14 g of dimedone **2**. Stirred at this temperature for 4 hours, then cooled to room temperature and slowly, (300 ml of water was added without overheating the mixture. Extracted with chloroform (5 × 50 ml), the extract was dried with anhydrous sodium sulfate. After evaporation of chloroform and the residue of acetic acid, the resulting oily liquid was passed through a layer of silica gel L – 100–400 μm, *l* 6 cm, eluting β-triketone **5** with 300 ml of hexane 16.8 g (92%) of the product was obtained. M.p. 34–36 °C, reported 34–36 °C [17]. ^{1}H NMR spectrum in CCl_4, σ, ppm: 1.10 s (6H, 2CH_3), 2, 48 s (4H, 2CH_2), 2.55 s (3H, CH_3), 18.05 s (enol. OH). Found %: C 65.82; H 7.83; $C_{10}H_{14}O_3$. Calculated %: C 65.91; H 7.74.

Procedure for synthesis of 2,3-dimethoxy-16,16-

dimethyl-D-homo-8-azagona-1,3,5(10),13-tetraene-12,17a-dione **(7)**. A mixture of 382 mg (2 mmol) 6,7-dimethoxy-3,4-dihydroisoquinoline **4** and 364 mg (2 mmol) 2-acetyl-5,5-dimethylcyclohexane-1,3-dione **1** in 10 ml of ethyl alcohol is heated at the boil for 3 hours. The crystals that precipitated after cooling the reaction mixture were filtered off and crystallized from ethanol. Received 494 mg (70%) of the product, mp 271–274 °C; recorded 268–271 °C [18]. IR spectrum (KBr), cm^{-1}: 1535, 1580, 1615, 1625, 1670. UV spectrum in ethanol, nm (ε): 265 (13500), 303 (18500). ^1H NMR spectrum in CF_3COOH, σ, ppm: 1.26 s (3H, 16-CH_3), 1.29 s (3H, 16-CH_3), 2.76 s (2H, 15-CH_2), 2, 82 m (2H, 11-CH_2), 2.86 t (2H, J 7 Hz, 6-CH_2), 2.97 s (2H, 17-CH_2), 3.83 s (3H, OMe), 3.86 s (3H, OMe), 3.90 t (2H, J 7 Hz, 7-CH_2), 4.82 qu (1H, proton X systems ABX, J_{AX} 12, J_{AX} 6 Hz, 9-CH), 6.56 s (1H aromatic), 6.60 s (1H aromatic). Mass spectrum (m/z) 355 $[M]^+$, 340 $[M - CH_3]^+$. Found %: C 70.91; H 7.02; N 4.01. $C_{21}H_{25}O_4N$. Calculated %: C 70.96; H 7.09; N 3.94.

Procedure for synthesis of 2,3-dimethoxy-16, 16-dimethyl-d-homo-8-azagona-1,3,5(10),13-tetraen-12-imino-17a-one hydrochloride **(1)**. A mixture of 3.55 g (10 mmol) of diketosteroid **7**, 24 ml of ethyl alcohol, 0.6 ml of 25% aqueous ammonia solution, 1.07 g (20 mmol) of ammonium chloride was stirred at room temperature for a day until the precipitate was completely dissolved. The mixture was kept at room temperature for two days. The precipitate that formed was filtered off, washed with a water–alcohol solution (1:1, 10 ml). It was dried in vacuum (8 mm Hg) over phosphoric anhydride at room temperature (20 °C). 2.50 g (64%) of imine hydrochloride **1** were obtained, mp 152–154 °C (dec.), recorded 154 °C [21]. IR spectrum (KBr), cm^{-1}: 1595, 1650, 3260. UV spectrum in ethanol, nm (ε): 268 (1550), 317 (12500). Mass spectrum (m/z) 354 $[M - HCl]^+$, 339 $[M – HCl - CH_3]^+$. Found %: C 64.41; H 7.00; N 6.98; Cl 9.02. $C_{21}H_{27}ClO_3N_2$. Calculated %: C 64.52; H 6.96; Cl 9.07; N 7.17.

Biological testing. The pesticide agents dealt with included insecticides (insect killers including adults, ova, and larvae), fungicides and phytotoxins (herbicides).

Fungi testing on plants was carried out by spraying substances on plants and included the following pathogenic fungi: *Drechslera, Erysiphe, Puccinia, Peronospora*. The effectiveness of the action of the compounds was determined in comparison with untreated plants.

Insect pests are the main factor in the loss of crop yields. The insecticidal activity of compounds **1,7** was tested against the following insects: *Toxoptera graminum, Musca domestica, Meloidogyne incognita, Heliothis virescens, Diabrotica undecimpunctata howardi, Caenorhabditis elegans.*

The herbicidal activity of the compounds was carried out against the following plants: *Amaranthus retroflexus, Brassica rapa, Abutilon theophrasti, Alopecurus myosuroides, Avena fatua, Echinochloacrus galli*.

RESULTS AND DISCUSSION

The synthesis of 12-imino derivative **9** by the reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline **4** with 2-(1-aminoethylidene)-5,5-dimethylcyclohexa-1,3-dione **8** obtained from 2-acetyl-5,5-dimethylcyclohexane-1,3-dione **5** was described in [22]. The reaction was carried out by boiling the mixture of components in ethanol for 72 hours or by heating the mixture in a sealed ampoule at a temperature of 100 degrees for 12 hours. The product yields were only 15% and 24%, respectively. The preparation of ketoimine hydrochloride **1** is described in [23]. The mixture of compounds **9** and **4** in a 3% isopropanol solution of HCl was heated in a sealed ampoule at a temperature of 150 °C for 8 hours (Fig. 2). The product yield was only 31.8%. We have developed a more efficient method for its synthesis from diketone **7** by the reaction of the latter with ammonium chloride. The product yield was 64%. Our method is energy-saving, as it is carried out without heating, and the product can be obtained in large quantities.

The structure of the obtained compounds was confirmed by the data of IR, NMR, UV spectra and elemental analysis. The IR absorption spectra of compounds **1,7** contain bands of the enaminodiketone (1535, 1580, 1615, 1625, 1670 cm^{-1}) eniminoketone (1595, 1650, 3260 cm^{-1}) groups, respectively. In their UV spectra there are two absorption bands (265.303 and 268.317 nm) corresponding to

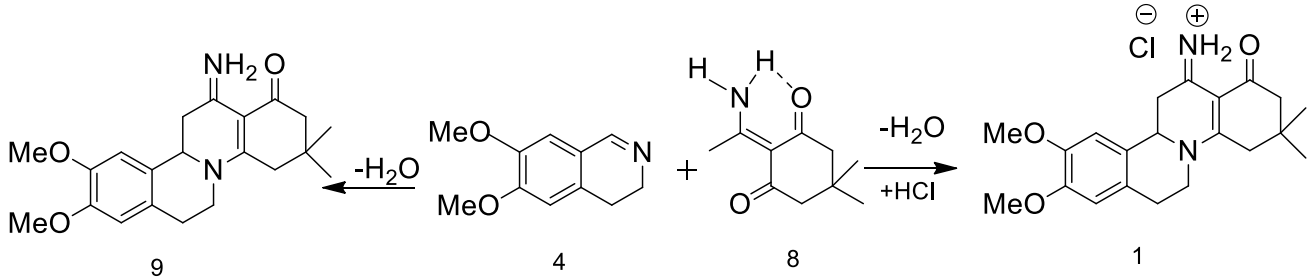

Fig. 2. Scheme of synthesis of 8-azasteroids **1** and **9**

Рис. 2. Схема синтеза 8-азастероидов **1** и **9**

ππ* transitions of the same fragments of molecules. It should be noted that there are many publications on the spectral properties of 8-azasteroids containing the enaminodicarbonyl group [24–26]. The ^{1}H NMR spectrum of compound **7** contains two signals of methyl protons (1.26 and 1.29 ppm), protons of methoxy groups (3.83 and 3.86 ppm). The quartet of the signal of the benzyl C^9H proton (4.82 ppm) represents the X-part of the ABX-system of the C^9H proton and the neighboring methylene group $C^{11}H_2$. The value of one of the constants of the spin-spin interaction of a benzyl proton with methyleneпprotons is greater than seven hertz (12 Hz), which indicates its axial orientation. The signals of the two aromatic protons appear as two singlets (6.56 and 6.60 ppm). The ^{1}H NMR spectrum of compound **1** is difficult to describe and interpret, as it contains a complex mixture of signals, probably due to the decomposition of iminohydrochloride in DMSO-d_6 solution. In addition, the presence of dynamic equilibrium in the process of iminohydrochloride conversion can lead to signal broadening. In the mass spectrum of compound **7** a peak of the molecular ion $[M]^+$ (355 m/z) and the ion corresponding to the elimination of the methyl group $[M - CH_3]^+$ (340 m/z) is observed. The mass spectrum of imine **1** contains a peak (354 m/z) corresponding to the elimination of the hydrogen chloride molecule $[M - HCl]^+$ and a peak (339 m/z) corresponding to the elimination of hydrogen chloride and the methyl group $[M - HCl - CH_3]^+$.

Insect pests are a major factor in the loss of the world's agricultural crops. Insecticidal activities of compounds (**1,7**) were tested against following insects: *Toxoptera graminum, Musca domestica, Meloidogyne incognita, Heliothis virescens, Diabrotica undecimpunctata howardi, Caenorhabditis elegans.* Test results are presented in Table 1.

The results of herbicidal activity are shown in Table 2 and expressed as percentage of the untreated control plants.

Fungus greenhouse tests were performed by spraying a substance on plants which then were inoculated with following phytopathogenic fungi: *Drechslera, Erysiphe, Puccinia, Peronospora*.

The compound efficacy is expressed by comparing the fungus development with and without product. Test results are shown in Table 3.

Table 1. Data showing insecticidal activity of the synthesized compounds **1** and **7**

Таблица 1. Данные инсектицидной активности синтезированных соединений **1** и **7**

Organism, insect stage	plant	days	dose	unites	Compound, biological effect	
					1	**7**
Toxoptera graminum, mixed	sorghum	6	0.1	ppm	3	3
Musca domestica, pupae	–	6	1.0	ug/well	3	1
Meloidogyne incognita, J2	–	5	5.0	ppm	1	1
Heliothis virescens, egg	–	8 6	0.6	ug/ well	1 1	1 1
Diabrotica undecimpunctata howardi, egg	cucumber	6	0.3	ppm	1	1
Caenorhabditis elegans, mixed	sorghum	7	5.0		1	1
key: 1 – 0–29% noticed death rate, 3 – 30–69% noticed death rate, 5 – 70–100% noticed death rate.						

Table 2. Data showing the herbicidal activity of the synthesized compounds **1** and **7**

Таблица 2. Данные гербицидной активности синтезированных соединений **1** и **7**

Plant	Dose, ppm	Compound, Biological effect, %	
		1	**7**
Amaranthus retroflexus	100	30	80
Brassica rapa	100	10	10
Abutilon theophrasti	100	30	10
Alopecurus myosuroides	100	0	0
Avena fatua	100	0	0
Echinochloa crus galli	100	0	0

Table 3. Data of the results of the study of antifungal activity of synthesized compounds **1** and **7**

Таблица 3. Данные результатов изучения антигрибковой активности синтезированных соединений **1** и **7**

compound	dose, ppm	The name of the fungus and the and Greenhouse test results			
		Drechslera	*Erysiphe*	*Puccinia*	*Peronospora*
1	100.00	100	0	0	0
7	100.00	0	0	0	0
key: 100 – The product is active. It causes an inhibition of desease development > 80%; 50 – The product is slightly active. It causes an inhibition of desease development > 50% <80%; 0 – The compound is regarded as inactive. It causes an inhibition of desease development < 50%.					

CONCLUSIONS

1. Two 8-azacyclic steroid analogues have been synthesized by an environmentally safe method, corresponding to the principles of “green” chemistry.

2. The structure of the obtained compounds was confirmed by the data of IR, UV, ^{1}H NMR spectra and elemental analysis.

3. Synthesized 8-azasteroids were tested for several types of pesticidal activity. Both compounds showed herbicidal activity against *Amaranthus retroflexus, Brassica rapa, Abutilon theophrasti* and insecticidal activity against *Toxoptera graminum*. 2,3-Dimethoxy-16,16-dimethyl-D-homo-8-azagon-1,3,5(10),13-tetraen-12-imino-17a-one hydrochloride showed insecticidal activity against *Musca domestica* and fungicidal activity against *Drechslera*.

4. Thus, the conducted studies allow us to consider the search for substances with herbicidal, insecticidal and fungicidal activity among 8-azasteroids as promising.

REFERENCES

1. Ibrahim-Ouali M. Total synthesis of steroids and heterosteroids from BISTRO. *Steroids*. 2015;98(6):9-28. https://doi.org/10.1016/j.steroids.2015.02.014.

2. Kaplan W., Khatri H. R., Nagorny P. Concise enantioselective total synthesis of cardiotonic steroids 19-hydroxysarmentogenin and trewianin aglycone. *Journal of the American Chemical Society.* 2016;138 (22):7194-7198. https://doi.org/10.1021/jacs.6b04029.

3. Khatri H. R., Bhattarai B., Kaplan W., Li Zh., Long M. J., Aye Y., et al. Modular total synthesis and cell-based anticancer activity evaluation of ouabagenin and other cardiotonic steroids with varying degrees of oxygenation. *Journal of the American Chemical Society.* 2019;141(12):4849-4860. https://doi.org/10.1021/jacs.8b12870.

4. Iqbal A., Siddiqui T. A review on synthesis and biological activities of D-ring modified pregnenolone. *Steroids*. 2021;170(6):108827. https://doi.org/10.1016/j.steroids.2021.108827.

5. Martínez-Gallegos A. A., Guerrero-Luna G., Ortiz-González A., Cárdenas-García M., Bernès S., Hernández-Linares M. G. Azasteroids from diosgenin: synthesis and evaluation of their antiproliferative activity. *Steroids*. 2021;166(2):108777. https://doi.org/10.1016/j.steroids.2020.108777.

6. Brito V., Santos A. O., Almeida P., Silvestre S. Novel 4-azaandrostenes as prostate cancer cell growth inhibitors: synthesis, antiproliferative effects and molecular docking studies. *Comptes Rendus Chimie.* 2019;22(1):73-83. https://doi.org/S1631074818301838.

7. Huang L. H., Xu H.-D., Yang Z.-Ya., Zheng Y.-F., Liu H.-M. Synthesis and anticancer activity of novel C6-piperazine substituted purine steroid–nucleosides analogues. *Steroids.* 2014;82(4):1-6. https://doi.org/10.1016/j.steroids.2013.12.004.

8. Yao Zh., Xu Y., Zhang M., Jiang Sh., Nicklaus M. C., Liao C. Discovery of a novel hybrid from finasteride and epristeride as 5α-reductase inhibitor. *Bioorganic & Medicinal Chemistry Letters.* 2011;21(1):475-478. https://doi.org/10.1016/j.bmcl.2010.10.112.

9. Mikhalschuk A. L. On the 95th birthday of Afanasy Andreevich Akhrem. *Chemistry of Heterocyclic Compounds.* 2008;44:243-246. https://doi.org/10.1007/s10593-008-0039-z.

10. Mikhal’chuk A. L. The most important publications of A. A. Akhrem on the chemistry of heterocyclic compounds. *Chemistry of Heterocyclic Compounds.* 2008;44:247-252. https://doi.org/10.1007/s10593-008-0040-6.

11. Lakhvich F. A., Lis L. G., Akhrem A. A. Total synthesis of 8-azasteroids. *Russian Chemical Reviews.* 1984;53(6);582-612. http://dx.doi.org/10.1070/RC1984v053n06ABEH003076.

12. Gulyakevich O. V., Mikhal'chuk A. L. Mechanism for annelation ([2+4] cyclocondensation of schiff bases by β-dicarbonyl and β,β′-tricarbonyl compounds in amphiprotic media (review). *Chemistry of Heterocyclic Compounds.* 2008;44:253-262. https://doi.org/10.1007/s10593-008-0041-5.

13. Akhrem A. A., Lakhvich F. A., Pyrko A. N., Lis L. G. Heterocyclic analogs of steroids. xiii. new synthesis of 8-aza-16-oxasteroids. *Russian Journal of Organic Chemistry*. 1985;16(18):2565-2570. https://doi.org/10.1002/chin.198518300.

14. Akhrem A. A., Borisevich N. A., Gulyakevich O. V., Mikhal'chuk A. L., Raichyonok T. F., Tikhomirov S. A., et al. Specific fluorescence properties and picosecond transient absorption of 8-azasteroids. *Journal of Fluorescence.* 1999;9:357-361. https://doi.org/10.1023/A:1020596210145.

15. Rao H. S. P., Senthilkumar S. P. Review on the synthesis of 8-azasteroids. *Current Organic Chemistry.* 2004;8(15):1521-1528. https://doi.org/10.2174/1385272043369881.

16. Aksenov N. A., Malyuga V. V., Abakarov G. M., Aksenov D. A., Voskressensky L. G., Aksenov A. V. Synthesis of 3,4-dihydroisoquinolines using nitroalkanes in polyphosphoric acid. *Russian Chemical Bulletin*. 2019;68:1047-1051. https://doi.org/10.1007/s11172-019-2518-z.

17. Shimizu M., Orita H., Hayakawa T., Suzuki K., Takehira K. Oxidation of 1,2,3,4-tetrahydroisoquinolines to 3,4-dlhydrolsoqulnollnes with molecular oxygen catalyzed by copper(i1) chloride. *Heterocycles*. 1995;41(4):773-779. https://doi.org/10.3987/COM-94-6991.

18. Akhrem A. A., Moiseenkov A. M., Krivoruchko V. A., Lakhvich F. A., Poselenov A. I. Approach to synthesis of 8-azasteroids. *Russian Chemical Bulletin.* 1972;21(9):2078-2083. https://doi.org/1007/BF00854629.

19. Pyrko A. N. Method of preparation of cyclic β-triketones. *Zhurnal organicheskoi khimii = Russian Journal of Organic Chemistry*. 1991;27(10):1981-1982. (In Russian).

20. Akhrem A. A., Titov Yu. A. *Total steroid synthesis*. New York: Plenum Press; 1970. 306 p.

21. Blickenstaff R. T., Ghosh A. C., Wolf G. C. *Total synthesis of steroids*. New York: Academic Press; 1974. 318 p.

22. Pshenichny V. N., Gulyakevich O. V., Khripach V. A. Interaction of 6,7-dimethoxy-3,4-dihydroxy isoquinoline with enamines 2-acetyl-5,5-dimethyl-1,3-cyclohexanediones. *Proceedings of the Academy of Science of BSSR. Chemical series.* 1986;(5):114-116.

23. Gulyakevich O. V., Mikhal'chuk A. L., Khripach V. A. Enamino ketones. Annelation of cyclic Shiff bases with 2(1-aminoethylidene)-1,3-cyclohexanones. *Zhurnal organicheskoi khimii = Russian Journal of Organic Chemistry*. 1991;27(1):187-188. (In Russian).

24. Borisevich N. A., Raichyonok T. F., Sukhodola G. B., Tolstorozhev V. A., Shashilov A. A. Absorption and fluorescence of 8-azasteroids in the gas phase. *Journal of Applied Spectroscopy.* 2005;72 (1):49-58. https://doi.org/10.1007/s10812-005-0030-8N.

25. Borisevich N. A., Dubovskii V. L., Mikhal'chuk A. L., Raichenok T. F., Tikhomirov S. A., Tolstorozhev G. B. Photochemical processes in aqueous solutions of immunoactive 8-azasteroid. *Journal of Applied Spectroscopy*. 2003;70:545-549. https://doi.org/10.1023/a:1026146430668.

26. Bagnich S. A., Gulyakevich O. V., Mikhalchuk A. L. Spectral-luminescent properties of 12-oximino derivatives of 8-Aza-*D*-Homogona-12,17*a*-Diones and their concentration dependence. *Journal of Fluorescence.* 2008;18:277-283. https://doi.org/10.1007/s10895-007-0267-0.

INFORMATION ABOUT THE AUTHOR

Anatoly N. Pyrko,
Cand. Sci. (Chemistry), Associate Professor,
Department of Environmental Chemistry
and Biochemistry,
International Sakharov Environmental Institute
of Belarusian State University,
23, Dolgobrodskaya St., Minsk, 220070, Belarus,
pyrko@yandex.ru
https://orcid.org/ 0000-0002-5838-1681

Contribution of the author

Anatoly N. Pyrko carried out the experimental work, on the basis of the results summarized the material and wrote the manuscript.

Conflict interests

Author declares no conflict of interests regarding the publication of this article.

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

Information about the article

The article was submitted 01.03.2022.
Approved after reviewing 15.03.2022.
Accepted for publication 21.03.2022.

СВЕДЕНИЯ ОБ АВТОРЕ

А. Н. Пырко,
к.х.н., доцент кафедры экологической химии
и биохимии,
Международный государственный
экологический институт имени А. Д. Сахарова
Белорусского государственного университета,
220070, г. Минск, ул. Долгобродская, 23/1,
Республика Беларусь,
pyrko@yandex.ru
https://orcid.org/ 0000-0002-5838-1681

Вклад автора

А. Н. Пырко выполнил экспериментальную работу, на основании полученных результатов провел обобщение и написал рукопись.

Конфликт интересов

Автор заявляет об отсутствии конфликта интересов.

Автор прочел и одобрил окончательный вариант рукописи.

Информация о статье

Поступила в редакцию 01.03.2022.
Одобрена после рецензирования 15.03.2022.
Принята к публикации 21.03.2022.