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СИНТЕЗ 4-(2-ГИДРОКСИФЕНИЛ)-5,6,7,8-ТЕТРАГИДРОИЗОКСАЗОЛО [5,4-B]ХРОМЕН-5(4H)-ОНОВ

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Целью данной работы является синтез новых тетрагетероциклических соединений, представляющих интерес в качестве потенциальных биологически активных веществ, которые включают изоксазольный и хромоновый фрагменты в своей структуре. Синтез таких соединений осуществляли в две стадии. Конденсацией Кнёвенагеля 3-метил-1,2-изоксазол-5(2H)-она с салициловым альдегидом был получен (4Z)-4-(2-гидроксибензилиден)-3-метил-1,2-изоксазол-5(4H)-он. Для увеличения выхода продукта в этой реакции использовали избыток альдегида, равный половине эквивалентного количества. В качестве катализатора использовали пиперидин. Реакцию проводили путем кипячения компонентов в этилацетате. Реакцию полученного производного бензилиденизоксазола с циклогексан-1,3-дионом или димедоном проводили путем кипячения компонентов в этаноле без использования катализатора. Механизм взаимодействия включает гетеродиеновую конденсацию Дильса-Альдера с последующей дегидратацией одной молекулы воды. В результате получали 3-метил-4-(2-гидроксифенил)-5,6,7,8-тетрагидроизоксазоло [5,4-b]хромен-5(4H)-он и 3,7,7-триметил-4-(2-гидроксифенил)-5,6,7,8,9-тетрагидроизоксазоло[5,4-b]хромен-5(4H)-он. Очистка синтезированных соединений проводилась кристаллизацией из этанола. Все полученные соединения были охарактеризованы данными ИК, ^{1}H ЯМР и УФ спектроскопии. В спектре ^{1}H ЯМР имеются сигналы метильных групп изоксазольного кольца при 2,26, 2,29, 2,34 м.д. соответственно. В УФ-спектре плоской молекулы (4Z)-4-(2-гидроксибензилиден)-3-метил-1,2-изоксазол-5(4H)-она имеется максимум длинноволнового поглощения (400,9 нм), соответствующий совместной системе сопряженных связей изоксазольного и ароматического кольца. Структура полученных соединений была подтверждена данными масс-спектрометрического анализа высокого разрешения. В спектрах 3-метил-4-(2-гидроксифенил-5,6,7,8-тетрагидроизоксазоло[5,4-b]хромен-5(4H)-она и 3,7,7-триметил-4-(2-гидроксифенил)-5,6,7,8,9-тетрагидроизоксазоло [5,4-b] хромен-5(4H)-она имеется пик иона $[M + Na]^+$. Наличие пиков фрагмента $[M + Na - CO]^+$ и $[M + Na - CO - H_2O]^+$ подтверждает наличие гидроксильных и карбонильных групп в молекулах.

Ключевые слова: изоксазолохромены, конденсация Кнёвенагеля, диеновая конденсация

SYNTHESIS OF 4-(2-HYDROXYPHENYL)-5,6,7,8-TETRAHYDROISOXAZOLO [5,4-B]CHROMENE-5(4H)-ONES

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The aim of this work is the synthesis of new tetraheterocyclic compounds of interest as potential biologically active substances that include the isoxazole and chromone moieties in their structure. The synthesis of such compounds was carried out with two stages. By Knoevenagel condensation of 3-methyl-1,2-isoxazol-5(2H)-on with salicylic aldehyde (4Z)-4-(2-hydroxybenzyliden)-3-methyl-1,2-oxazol-5(4H)-on was obtained. In this reaction an excess of half of the aldehyde equivalent was used to increase the yield of the product. Pyperidine was used as a catalyst. The reaction was carried out by boiling the components in ethyl acetate. The reaction of the resulting benzylidenisoxazole derivative with cyclohexane-1,3-dione or dimedone was performed by boiling the components in ethanol without the use of a catalyst. The interaction mechanism includes heterodiene Dielsa-Aldera condensation followed by dehydration of one water molecule. As a result, 3-methyl-4-(2-hydroxyphenyl-5,6,7,8-tetrahydroisoxazolo[5,4-b]chromene-5(4H)-one and 3,7,7-trimethyl-4-(2-hydroxyphenyl)-5,6,7,8,9-tetrahydroisoxazolo[5,4-b]chromen-5(4H)–one were obtained. Purification of the synthesized compounds was carried out by crystallization from ethanol. All the obtained compounds were characterised by IR ^{1}H NMR and UV spectroscopies. In ^{1}H NMR spectra there are signals of the methyl groups of the isoxazole ring of compounds at 2.26, 2.29, 2.34 ppm respectively. In the UV spectrum of a plane molecule of (4Z)-4-(2-hydroxybenzyliden)-3-methyl-1,2-oxazol-5(4H)-on there is a long-wave absorption maximum (400.9 nm) corresponding to the joint system of conjugated bonds of the isoxazole and aromatic rings. The structures of the obtained compounds were confirmed by high resolution mass-spectrometry analysis. In the spectra of 3-methyl-4-(2-hydroxyphenyl-5,6,7,8-tetrahydroisoxazolo[5,4-b]chromene-5(4H)-one and 3,7,7-trimethyl-4-(2-hydroxyphenyl)-5,6,7,8,9-tetrahydroisoxazolo[5,4-b]chromen-5(4H)–one the$[M + Na]^+$ ion peaks were observed. The presence of fragment peaks $[M + Na – CO]^+$ and $[M + Na – CO – H_2O]^+$ confirms the presence of hydroxy and carbonyl groups in the molecules.

Key words: isoxazole chromes, Knoevenagel condensation, diene condensation

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INTRODUCTION

Synthesis of new xanthene derivatives has received special attention due to their diverse array of biological activities such as antiinflammatory, antibacterial and antiviral activities [1-5]. They are one of the most widely distributed classes of natural compounds.

On the other hand, isoxazol scaffold represents an important class of heterocycles which have a wide range of pharmacological properties. A variety of biological activities has been reported for isoxazol derivatives such as protein-tyrosine phosphatase 1B (PTP1B) inhibitory, anticonvulsant, antifungal, HDAC inhibitory, analgesic, antitumor, antioxidant, antimicrobial, COX-2 inhibitory, anti-inflammatory, anticancer, antiviral, antituberculosis and antimycobacterial [6-13].

The condensation of two molecules of 1,3-cyclohexanediones with aromatic aldehydes usually produces 9-substituted octahydroxanthene [14-16] and tetrahydroxanthene derivatives with 2-hydroxyaromatic aldehydes [17]. The reaction mechanism involves the condensation of Knoevenagel of the molecule of cy-

clohexanedione with aldehyde and subsequent Michael addition of the second molecule to formed α, β-unsaturated diketone. The use of a heterocyclic 1,3-dicarbonyl compounds instead of a second cyclohexanedione molecule allows the preparation of a tetrahydroxanthene derivatives comprising a heterocycle as a substituent at the position 9 of the hydroxanthene fragment. Methods for conducting three-component condensation in one flask have been developed [2, 18]. This article describes the synthesis of tetracyclic compounds that include the isoxazole and chromone moieties in their structure.

MATERIALS AND METHOD

In order to exclude the possibility of formation of bis-adducts of condensation of salicylic aldehyde with two molecules of 1,3-cyclohexanedione or with two molecules of a heterocyclic 1,3-dicarbonyl compound, the synthesis of putative isoxazolotetrahydroxanthenes, including both the tetrahydroxanthene and isoxazole moieties, was carried out in two stages.

α, β-Unsaturated carbonyl compound **3** was obtained by the reaction of isoxazolone **1** with salicylic aldehyde **2** (Fig.). This substance was used in the reaction with cyclohexanediones **4a,b** for the synthesis of isoxazolotetrahydroxanthenes **8a,b**. To increase the yield of the Knoevenagel condensation product **3**, a 50% excess of aldehyde was used, since the formation of the bis-isoxazole derivative is possible in this reaction. Condensation of α, β-unsaturated carbonyl **3** and 1,3-cyclohexanediones **4a,b** was accomplished by heating the components in ethanol. The reaction was performed under catalist-free conditions. It was found that as a result of the experiment, not isoxazoloxanthene derivatives **8a,b** were obtained, but the isomeric structures **7a,b**.

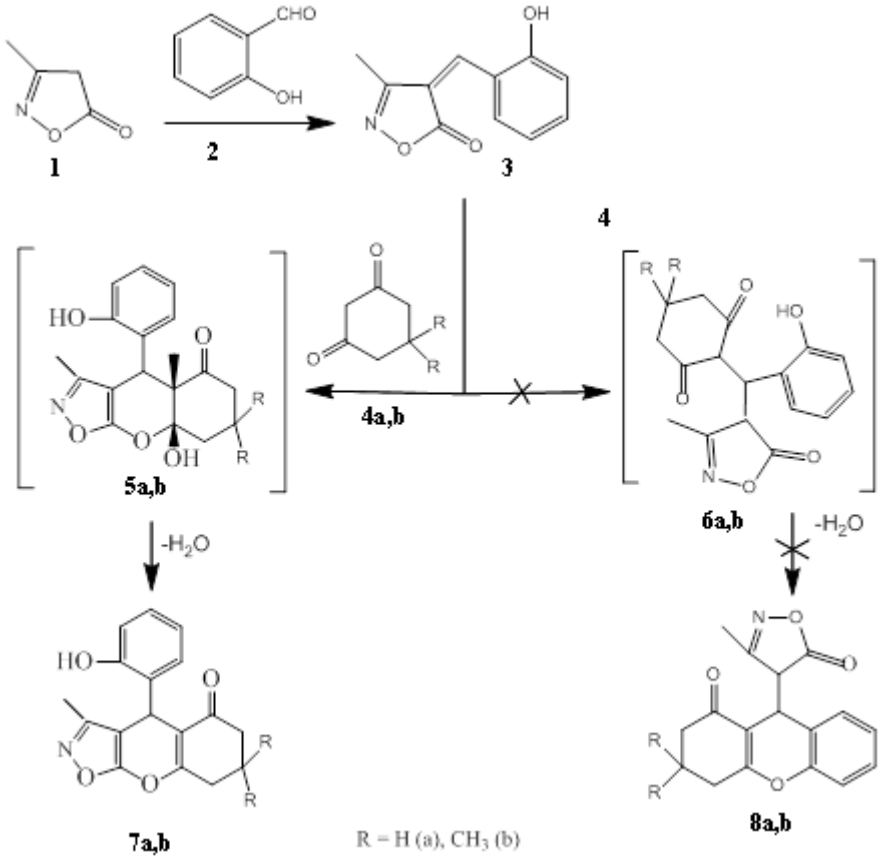

Fig. Scheme of synthesis of 4-(2-hydroxyphenyl-5,6,7,8-tetrahydroisoxazolo[5,4-b]chromene-5(4H)-ones
Рис. Схема синтеза 4-(2-гидроксифенил)-5,6,7,8-тетрагидроизоксазоло [5,4-b] хромен-5(4H)–он

EXPERIMENTAL

All compounds and solvents used were purchased from Sigma-Aldrich and used without further purification. The UV spectra were recorded on a Specord M-400 spectrophotometer. The IR spectra were obtained in KBr on a UR-20 spectrometer. The ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer at 200 and 50 MHz, respectively; tetramethylsilane was used as internal reference. The pro-

gress of reactions and the purity of products were 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 points were determined on a Boetius hot stage. Chromatographic-mass spectrometric analysis was carried out on liquid hybrid chromatography mass spectrometer LTQ Orbitrap Discovery (Thermo Electron Corporation, USA), which includes a linear Quadruple trap LTQ XL and the orbital trap of high permission. Ionization of the sample was carried out electrospray with using the source H-ESI II Ion Max. Calibration of linear and orbital traps LTQ Orbitrap Discovery was carried out using a standard solution, containing caffeine (m/z 195), L-methionyl-arginyol-phenylalanine acetate (MRFA, m/z 524) and Ultramark 1621 (micsture of fluorinated phosphazines). As an internal calibrant during the removal of mass spectra indapamide was used (m/z 66,0674).

4Z-4-(2-Hydroxybenzylidene)-3-methylisoxazole-5(4H)-one (3). A mixture of 0.99 g (10 mmol) of isoxazolone **1**, 1.83 g (15 mmol) of salicylaldehyde **2** and three drops of piperidine in 20 ml of ethyl acetate was boiled for 15 min. After a day, the precipitated crystals were filtered and crystallized from ethanol. Yield 1.50 g (74%), m.p. 199-201 °C (from ethanol) (m.p. 198-200 °C [13]). IR spectrum, cm^{-1}: 1560, 1580, 1600 (C = C, C = O, C = N), 2750-3440 (OH). UV spectrum (EtOH), $\lambda_{max.}$, nm (log ε): 400.9 (4.10), 262.7 (3.78), 244.5 (3.70) .^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 2.26 (3H, s, CH_3), 6.93 (1H, d, J = 8.0 Hz), 7.04 (1H, t, J = 8.0 Hz), 7.53 (1H, t, J = 8.0 Hz), 8.01 (1H, s), 8.88 (1H, d, J = 8.0 Hz), 10.18 (1H, s).

3-methyl-4-(2-hydroxyphenyl)-5,6,7,8-tetrahydroisoxazolo[5,4-b]chromene-5(4H)-one (7a). A mixture of 1.02 g (5 mmol) of hydroxybenzylidesoxazolone **3** and 0.56 g (5 mmol) of cyclohexanedione **4a** in 20 ml of ethanol was boiled for 40 min, then cooled to room temperature. After 24 h, the precipitated crystals were filtered off, washed with alcohol and dried in air. Yield 1.41 g (89%), m.p. 218-220 °C (ethanol). IR spectrum, cm^{-1}: 1585, 1615, 1720 (C = C, C = O, C = N), 3060, 3450 (OH). UV spectrum (EtOH), λ_{max}, nm (log ε): 217.30 (4.16), 278.85 (4.07). ^{1}H NMR spectrum (DMSO-d_6, δ, ppm, J, Hz): 1.76 (1H, m), 1.92 (1H, m), 2.29 (3H, s, CH_3), 2.47 (2H, m), 2.65 (1H, m), 2.86 (1H, m), 4.89 (1H, s, H-9), 7.03 - 7.29 (4H, m, H Ar), 11.83 (1H, brs, OH). Found, %: C, 68.58; H 5.05; N, 4.79. $C_{17}H_{15}NO_4$. Calculated, %: C, 68.66; H, 5.09; N, 4.71.

3,7,7-trimethyl-4-(2-hydroxyphenyl)-5,6,7,8,9-tetrahydroisoxazolo[5,4-b] chromene-5(4H)-one (7b) was prepared in a similar manner from 1.02 g (5 mmol) of hydroxybenzylidenisoxazole **3** and 0.70 g (5 mmol) of dimedone **4b**. Yield 1.39 g (81%), m.p. 194-196 °C (ethanol). IR spectrum, ν, cm^{-1}: 1590, 1620, 1650, 1730 (C = C, C = O, C = N), 3175, 3445 (OH). UV spectrum (EtOH), λ_{max}, nm (log ε): 219.25 (4.12), 267.70 (4.12). ^{1}H NMR spectrum (CD_3OD, δ, ppm, J, Hz): 1.04 (3H, s, CH_3), 1.09 (3H, s, CH_3), 2.19 and 2.31, (2H, AB system, J_{AB} = 16 Hz, CH_2), 2.34 (3H, s, CH_3), 2.54 (2H, s, CH_2), 4.72 (1H, s, H-9), 6.95-7.23 (4H, m, Ar). Found, %: C, 70.22; H, 5.95; N, 4.40. $C_{19}H_{19}NO_4$. Calculated, %: C, 70.13; H, 5.89; N, 4.31.

RESULTS AND DISCUSSION

The structures of the obtained compounds are confirmed by the data of the ^{1}H NMR, UV, IR spectra, elemental and chromatographic-mass spectrometric analysis. Thus, in the UV spectrum of a plane molecule [19] of benzylidenisoxazolone **3**, there is a long-wave absorption maximum (400.9 nm) corresponding to the joint system of conjugated bonds of the isoxazole and aromatic rings. Both π-bond systems of the compounds **7a,b** are separated by C-9 saturated carbon atom, so in their spectra long-wavelength peaks shift to the short-wavelength region (278.85 and 267.70 nm respectively). In ^{1}H NMR spectra there are signals of the methyl groups of the isoxazole ring of compounds **3, 7a,b** at 2.26, 2.29, 2.34 ppm respectively. The presence of a chiral carbon atom (C-9) in molecules **7a,b** defines nonequivalence of geminal protons of methyl and methylene groups therefore their signals do not coincide.

The presence of a one-proton singlet signal (4.89 and 4.72 ppm) in the spectra of each of them, corresponding to the methine proton in position **4** of the tricyclic fragment, is a confirmation of the conformity of the assigned structure. In the case of alternative structures **8a,b** in the spectra of these compounds in the region of 3 -5 ppm there would be two one-proton doublets of interacting protons.

The structures of compounds **7a,b** were confirmed by high resolution mass-spectrometry data (Table). In the spectra of both compounds observed $[M + Na]^+$ ion peaks. The presence of fragment peaks $[M + Na – CO]^+$ and $[M + Na – CO – H_2O]^+$ confirms the presence of hydroxy and carbonyl groups in the molecules.

Table

Data of mass-spectrometric measurement for compounds 7a,b
***Таблица*. Данные масс-спектрометрических измерений соединений 7a,b**

compound	Calculated m/z	Observed m/z	Simulated formulaion	Mass measurement error (Δppm)	Mass resolving power (R)
7a	320.08933	320.08902	$C_{17}H_{15}O_4NNa$ $[M + Na]^+$	-0.966	39801
	292.09441	292.09464	$C_{16}H_{15}O_3NNa$ $[M +Na - CO]^+$	0.770	42104
	274.08385	274.08423	$C_{16}H_{13}O_2NNa$ $[M + Na – CO -H_2O]^+$	1.390	41204
7b	348.12063	348.12036	$C_{19}H_{19}O_4NNa$ $[M + Na]^+$	-0.773	38401
	320.12571	320.12570	$C_{18}H_{19}O_3NNa$ $[M +Na - CO]^+$	-0.05	41004
	302.11515	302.11528	$C_{18}H_{17}O_2NNa$ $[M + Na – CO -H_2O]^+$	0.36	40404

Obviously, if the reaction of the unsaturated carbonyl compound **3** with cyclohexadiones **4a,b** occurred by the Michael addition to form the intermediate tricycles **6a,b**, followed by cyclization with the participation of the more active ketone carbonyl, dehydration would result in the formation of compounds **8a,b**, but not **7a,b**. Compounds **7a,b** formation mechanism includes a hetero Diels-Alder reaction to form adducts **5a,b**. Their dehydration gives the products **7a,b**.

It should be noted that the α, β-unsaturated carbonyl compound **3** is a latent form of the cross-conjugated endion system of the easily react with enolic dienophiles via heterocyclization of Diels-Alder. At the same time, a pyran cycle is formed [20-22].

CONCLUSION

In conclusion, a convenient method for the synthesis of (2-hydroxyphenyl)-5,6,7,8-tetrahydro-isoxazolo[5,4-b]chromene-5(4H)-ones have been developed.

It was shown that (4Z)-4-(2-hydro-xybenzyliden)-3-methyl-1,2-oxazol-5(4H)-on reacts with cyclohexane-1,3-dions following the pattern of a hetero Diels-Alder reaction with the formation of 4-(2-hydroxyphenyl) -5,6,7,8-tetrahydro-isoxazolo [5,4-b] chromene-5(4H)-one derivatives.

Two new substances were obtained and characterized.

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