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THE CATALYTIC HYDROGENATION OF 3-(2-FLUOROPHENYL)- AND 3-(4-FLUOROPHENYL)-4,4-ETHYLENEDIOXYCYCLOPENTA[*d*]ISOXAZOLINES

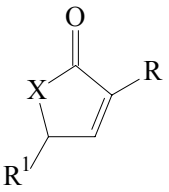
The catalytic hydrogenation of 3-(2-fluorophenyl)- and 3-(4-fluorophenyl)-4,4-ethylenedioxycyclopenta[*d*]isoxazolines led with good yields to corresponding fluorinated β-hydroxyketones. The synthesized compounds are precursors of new fluorinated prostanoids and carbocyclic analogs of acetogenins being of great interest as potential biologically active substances as well.

Key words: fluorinated prostanoids, acetogenins, catalytic hydrogenation, Raney nickel, isoxazolines, β-hydroxyketones.

Introduction. It is known that the introduction of a fluorine atom, which is similar in size to hydrogen atom but possesses high electronegativity [1] may play a remarkable role in medicinal chemistry [2–4]. Particularly, fluorinated analogues are usually more stable compounds [4], while keeping or improving the corresponding biological activity. Therefore, among the numerous pharmaceuticals which are sold all over the world, more than 150 drugs contain fluorinated compounds as active components [3, 4]. In this regard, the synthesis of new fluorinated analogues of natural compounds as perspective biologically active substances is of considerable interest.

Fatty acid oxidation processes taking place in vivo, result in the formation of compounds which are commonly called “oxylipins” [5]. Among them the most important products are acetogenins, thromboxanes, leukotrienes, carbocyclic oxylipins and particularly prostanoids. Prostanoids include along with prostaglandins (PGs) isoprostanes (isoPs), phytoprostans (PPs), their numerous analogues and others [6–8]. PGs possess an extremely high biological activity, which makes these compounds attractive for employment as drugs. However, their clinical use is constrained by a high chemical and metabolic instability of these compounds. In this regard, an actual task is the synthesis of more stable fluorinated prostanoids which exhibit more targeted and prolonged biological activity.

It should be noted a relatively new but sufficiently numerous group of acetogenins among the fatty acid metabolites which stand out for their structural typicality along with high and important biological activity [5, 9]. These compounds are known to possess insecticide, antiparasitic and immunoreglatory activity as well as an extremely powerful anti-cancer effect in some cases. As for their chemical structure acetogenins are characterized by a presence of five-membered (γ-laktone) cycle, in which commonly there is a double carbon-carbon bond. The size of an alkyl side chain (R) range from C17 to C37, while it may contain hydroxyl, carbonyl, tetrahydrofuran, epoxy and other groups:



Acetogenins
X = O; R^1 = H, OH, CH_3;
R= from C17 to C37,
with -OH, C=O, THF- and other groups.

There are also acetogenins with an atypical alkyl chain structure, for example without a cyclic ether moiety, etc. These compounds are marked by a general tendency to have an improved some biological activity characteristics.

The aim of this work is the synthesis of new fluorinated precursors of prostanoids and acetogenins carbocyclic analogs as well. Therefore we studied catalytic hydrogenation of ethyleneketal (1,3-dioxolane) derivatives of 4-oxocyclopenta [*d*]isoxazolines containing fluorophenyl substituent.

This work is a part of systematic investigations carried out at the Organic Chemistry department in the field of synthesis of analogues of biologically active complex natural compounds by nitrile oxide method [10–14].

Main part. The initial isoxazolines **2** (Scheme 1) were prepared previously [10] as a result of realization of the scheme which included: 1) synthesis of 2-cyclopentenone from dicyclopentadiene; 2) synthesis of the corresponding 4-oxocyclopentanisoxazolines **1** by 1,3-dipolar cycloaddition reaction of 2-cyclopentenone and nitrile oxides generated in situ from the corresponding hydroximoyl chlorides; 3) protection of keto group as dioxolane derivatives **2** (Scheme 1).

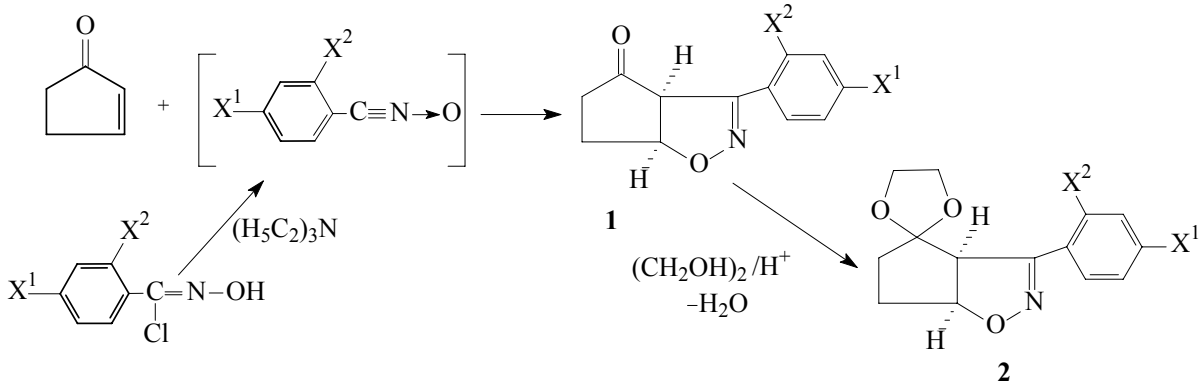
Thus obtained ketal (1,3-dioxolane) derivatives **2** (Scheme 2) were then subjected to a reductive cleavage of isoxazoline heterocycle by catalytic hydrogenation.

The catalytic hydrogenation of isoxazolines is known to proceed in mild conditions: under atmosphere of hydrogen at room temperature in the presence of catalytic amounts of the catalyst [11]. Employment of mild conditions is important because it is necessary to reserve the ketal protective group present in these compounds. In this regard, the employment of an alternative isoxazolines

reductive cleavage procedure by the action of Raney nickel in an aqueous solution of trifluoroacetic acid, which was previously used by us in the synthesis of more simple compounds without oxygen containing functional groups in the cyclopentane ring [12, 13] is unacceptable in the given case.

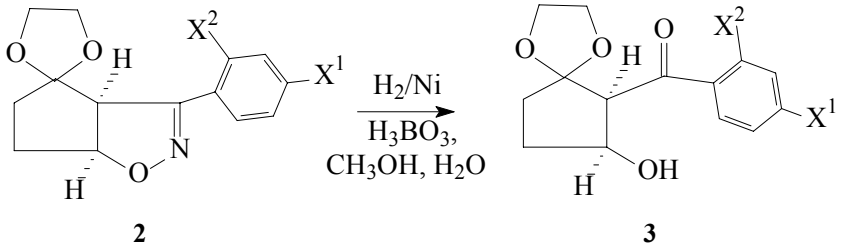
The reaction led to the corresponding β-hydroxyketones **3** in good yields (Scheme 2), while the relative *cis*-stereochemistry of hydroxyl group and acyl side chain being reserved. Thus, hydroxyketone **3a** was isolated in 74.4% yield as a result of catalytic hydrogenation of isoxazoline **2a.** Similarly, catalytic hydrogenation of 3-(2-fluorophenyl)-4,4-ethylenedioxacyclopenta[*d*] isoxazoline **2b** led to a formation of hydroxylketone **3b** (70.9% yield). In the last case, the formation of enone **4b** and ketone **5b** along with hydroxyketone **3b** was also observed when the freshly prepared catalyst was used (Scheme 3). The formation of these products can be explained by a sequence of following reactions: dehydratation of hydroxylketone **3** with the formation of enone **4** in which further reduction of C=C bond leads to a formation of ketone **5.** The isolation of these products was accomplished by a preparative thin layer chromatography (TLC).

The structure of the obtained compounds was confirmed by modern spectral methods of organic compounds analysis: ^{1}H NMR and ^{13}C NMR of spectroscopy (table). The PG numeration of atoms is used for discussion of the spectral data. Thus, the comparison of ^{1}H NMR spectrum of hydroxyketone **3a** (Fig. 1) with the spectrum of isoxazoline **2a** (Fig. 2) detects, that the most characteristic H-12 signal is shifted to a high shielding field and is observed at δ 4.83 ppm (instead of δ 5.24 ppm in the initial isoxazoline spectrum), while signals of dioxolane blocking group, benzene and cyclopentane ring are also observed as well.



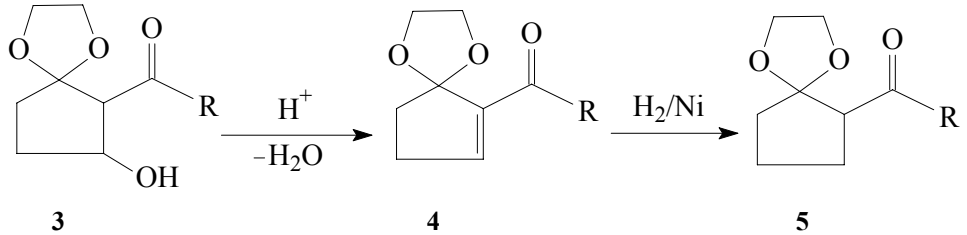
(**a**) X^1 = F, X^2 = H; (**b**) X^1 = H, X^2 = F

Scheme 1



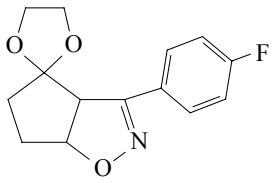
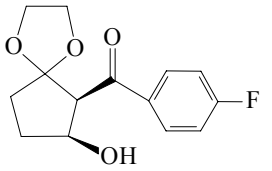
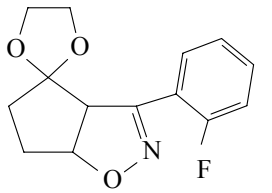
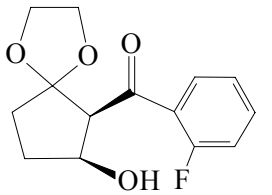
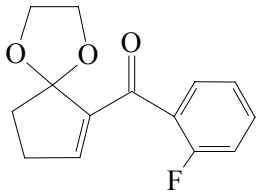
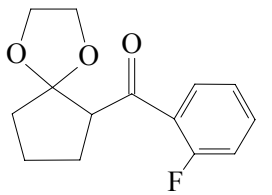
(**a**) X^1 = F, X^2 = H; (**b**) X^1 = H, X^2 = F

Scheme 2



Scheme 3

Comparison of characteristic signals in ^{1}H NMR spectra of the products of catalytic hydrogenation of 3-(2-fluorophenyl)- and 3-(4-fluorophenyl)-4,4-etylenedioxacyclopenta[*d*]isoxazolines

The compound number	Structural formula	H-8	H-12	H-10; H-11	α-chain
2a		3.87–3.94 m (2H, H-8 + + $H_{ethyleneket}$; J_1 = 9.2; J_2 = 6.7; J_3 = 1.5)	5.24 m (1H, H-12, J_1 = 9.0; J_2 = 6.8; J_3 = 4.7; J_4 = 1.9)	2.04–2.18 m (2H; H^A-11 + + H^B-11; J_1 = 13.9; J_2 = = 6.7; J_3 = 4.9); 1.86–1.94 m (1H, H^A-10; J_1 = = 12.8; J_2 = 10.5; J_3 = 7.6); 1.76–1.82 m (1H, H^B-10; J_1 = 12.8; J_2 = 10.5; J_3 = 6.1)	7.65 m (2H; H_{ar}-2' + + H_{ar}-6'; J_1 = 9.0; J_2 = = 5.4; J_3 = 2.1); 7.05 td (2H; H_{ar}-3' + H_{ar}-5'; J_1 = 9.0; J_2 = 2.1)
3a		3.91 d (1H, H-8; J = 6.9)	4.83 m (1H, H-12, J_1 = 7.2; J_2 = 6.9)	2.14 m (1H, H^A-11; J_1 = = 12.0; J_2 = 7.2); 2.04 m (1H, H^A -10; J_1 = 11.5; J_2 = = 9.0); 1.82 m (1H, H^B-10; J_1 = 13.3; J_2 = 9.4) 1.72 m (2H, H^B-11; J_1 = 11.8; J_2 = 9.0)	8.05 dd (2H; H_{ar}-2+ H_{ar}-6; J = 8.5); 7.09 t (2H; H_{ar}-3 + H_{ar}-5; J = 8.5)
2b		4.10 dd (1H, H-8, J_1 = 9.1; J_2 = = 3.2)	5.26 dd (1H, H-12, J_1 = = 9.1; J_2 = 4.7)	2.15 dd (1H; H^A-11; J_1 = = 13.8; J_2 = 7.3); 2.00–2.09 m (1H; H^B-11; J_1 = = 13.8; J_2 = 6.5; J_3 = 4.8); 1.90 td (1H, H^A-10; J_1 = = 12.8; J_2 = 7.4); 1.76 dd (1H, H^B-10; J_1 = 12.8; J_2 = 6.7)	7.78 dt (1H; H_{ar}-6'; J_1 = = 7.7; J_2 = 1.8); 7,35 m (1H; H_{ar}-4'; J_1 = 7.3; J_2 = 1.8); 7,16 dt (1H; H_{ar}-5'; J_1 = 7.6; J_2 = 1.0); 7.07 m (1H; H_{ar}-3'; J_1 = = 8.3; J_2 = 1.0)
3b		4.04 d (1H, H-8, J = 5.6)	4.46 dd (1H, H-12, J_1 = 6.7; J_2 = 5.9)	2.16 m (1H; H^A-11; J_1 = = 14.1; J_2 = 5.9); 1.96 m (1H; H^A-10; J_1 =13.6; J_2 = = 7.2; J_3 = 5.6); 1.86 m (1H, H^B-10; J_1 = 13.3; J_2 = 7.9); 1.77 m (1H, H^B-11; J_1 = 13.8; J_2 = 8.7; J_3 = 6.1)	7.75 dt (1H; H_{ar}-6; J_1 = = 7.7; J_2 = 1.8); 7.44 m (1H; H_{ar}-4; J_1 = 7.2; J_2 = = 1.8); 7,22 m (1H; H_{ar}-5; J_1 = 7.4); 7.12 m (1H; H_{ar}-3; J_1 = 8.7; J_2 = 8.4; J_3 = 7.7; J_4 = 2.0)
4b		–	6.76 dd (1H, H-12, J = = 2.6)	2.54 td (2H; CH_2-11; J_1 = = 6.9; J_2 = 2.8); 2.26 m (2H; CH_2-10; J_1 = 6.4)	7.76 dt (1H; H_{ar}-6; J_1 = = 8.4; J_2 = 1.5); 7.49 m (1H; H_{ar}-4; J_1 = 7.4; J_2 = = 2.0); 7.19 m (1H; H_{ar}-5; J_1 = 7.7; J_2 = 3.6); 7.12 m (1H; H_{ar}-3; J_1 = 8.7; J_2 = = 8.4; J_3 = 7.7; J_4 = 2.0)
5b		3.98 dd (1H, H-8, J_1 = 7.9; J_2 = 7.7)	1.77–1.92 m (4H; H^B-10 + CH_2-12 + + H^A-11)	1.86 m (1H; H^A-10; J_1 = = 13.1; J_2 = 8.7; J_3 = 4.3); 1.77–1.92 m (4H; H^B-10 + + CH_2-12 + H^A-11); 1.71 m (1H, H^B-11; J_1 = = 11.5; J_2 = 7.7; J_3 = 3.1)	7.70 dt (1H; H_{ar}-6; J_1 = = 7.7; J_2 = 1.8); 7.46 m (1H; H_{ar}-4; J_1 = 7.2; J_2 = = 4.9; J_2 = 1.8); 7.19 dt (1H; H_{ar}-5; J_1 = 7.7; J_2 = 1.0); 7.10 m (1H; H_{ar}-3; J_1 = 8.4; J_2 = 0.8)

All signals observed in ^{1}H NMR spectrum of this sample were ascribed to corresponding protons in the proposed structure by double resonance experiments. A similar ^{1}H NMR spectrum was obtained for hydroxyketone **3b**.

In ^{13}C NMR spectrum of hydroxyketone **3a** there appears the signal of carbonyl C-atom at δ 196.38 ppm while the carbon atoms signals of ketal protective group along with the signals of C-8, C-12 and the benzene ring are also observed at corresponding values of chemical shifts.

Subsequent use of hydroxyketones **3** in synthesis of prostanoids and carbocyclic analogs of acetogenins involves their transformation to enones **4** according with the procedure previously devised [14].

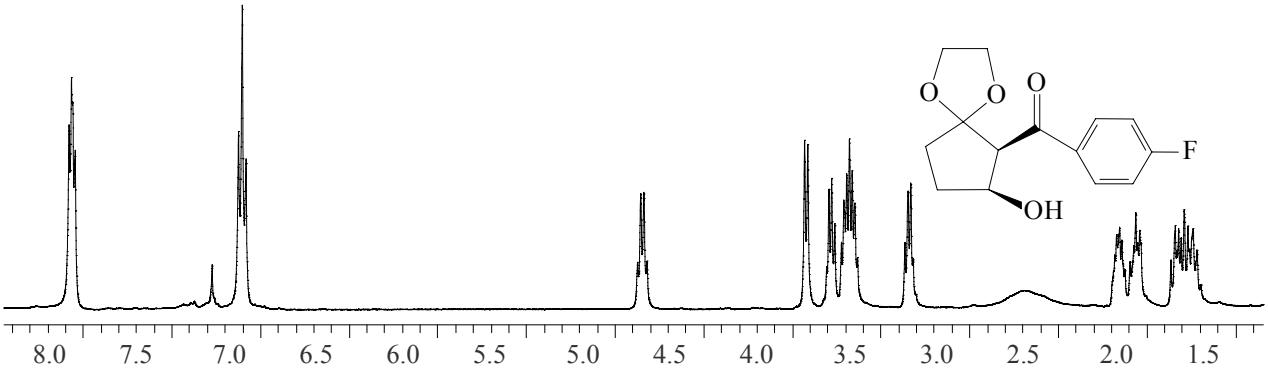


Fig. 1. ^{1}H NMR spectrum of (4-fluorophenyl)-(2-hydroxy-5,5-ethylenedioxacyclopentyl)methanone

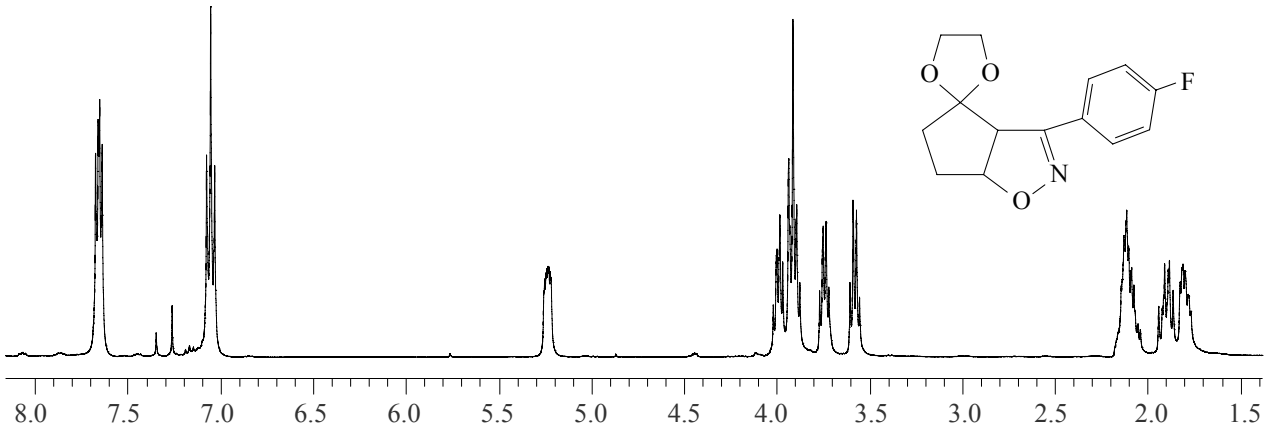
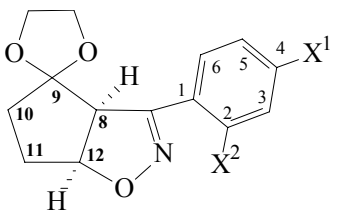


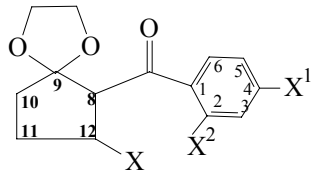
Fig. 2. ^{1}H NMR spectrum of 3-(4-fluorophenyl)-4,4-ethylenedioxacyclopenta[*d*]isoxazoline

Enones **4** occur to be carbocyclic analogues of acetogenins and are of considerable interest as perspective biologically active substances. On the other hand, these compounds along with hydroxyketones **3** are key intermediates in the synthesis of fluorinated prostanoids.

Experimental part. ^{1}H and ^{13}C NMR spectra of substances solutions in $CDCl_3$ were recorded on a Bruker AVANCE-400 spectrometer (400 MHz). Chemical shifts are reported in parts per million (δ, ppm) relative to hexamethyldisiloxane (HMDS) as an internal standard. Coupling constants *(J)* are given in Hz. The progress of the reactions was monitored by analytical TLC which was performed on silica gel plates Kieselgel 60 F_{254} (Merck), the eluent being ether – petroleum ether, visualization was effected with short-wave-length UV light (254 nm), with iodine or 4% solution of $KMnO_4$. The purification of solvents was performed according to standard procedures [15].

The following atoms numeration is used for spectral data discussion:





Catalytic hydrogenation of 3-(4-fluorophenyl)- or 3-(2-fluorophenyl)-4,4-ethylenedioxacyclopenta[*d*]isoxazoline. Catalytic amount of Raney nickel and 0.128 g (2.07 mmol) of boric acid were added to a stirred solution of 0.134 g (0.52 mmol) of isoxazoline **2a** in 8 ml of mixture of methanol : water (15 : 1). The reaction mixture was stirred at room temperature under hydrogen atmosphere until gas absorption ceased. After these the reaction mixture was filtered through a layer of aluminum oxide, which was then additionally eluted by ethanol. The solvent was distilled from the filtrate under reduced pressure, the residue was dissolved in ether and dried over anhydrous sodium sulfate.

After desiccant separation the ether was evaporated under reduced pressure to yield 0.126 g of crude product. The desired hydroxylketone was purified by a preparative TLC on silica gel, eluent: ether – petroleum ether. The yield of hydroxyketone **3a** was 0.094 g (74.4%).

Similarly, reduction of 0.1175 g (0.45 mmol) of 3-(2-fluorophenyl)-4,4-ethylenedioxacyclopenta[*d*]-isoxazoline gave 0.084 g of *cis*-(2-hydroxy-5,5-ethylenedioxacyclopentyl)-(2-fluorophenyl) methanone in 70.9% yield.

***cis*-(4-Fluorophenyl)-(2-hydroxy-5,5-ethylenedioxacyclopentyl)methanone** was obtained as oil in 74.4% yield.

^{1}H NMR, δ, ppm (*J*, Hz): 8.05 dd (2H; H_{ar}-2 + H_{ar}-6; *J* = 8.5); 7.09 t (2H; H_{ar}-3 + H_{ar}-5; *J* = 8.5); 4.83 m (1H, H-12, J_1 = 7.2; J_2 = 6.9); 3.91 d (1H, H-8; *J* = 6.9); 3.77 m (1H, $H_{ethyleneket}$, J_1 = 13.3; J_2 = = 7.2); 3.66 m (2H, $H_{ethyleneket}$; J_1 = 12.5; J_2 = 6.4); 3.33 m (1H, $H_{ethyleneket}$, J_1 = 13.3; J_2 = 7.2); 2,64 broad s (1H, OH); 2.14 m (1H, H^A-11; J_1 = 12.0; J_2 = 7.2); 2.04 m (1H, H^A -10; J_1 = 11.5; J_2 = 9.0); 1.82 m (1H, H^B-10; J_1 = 13.3; J_2 = 9.4) 1,72 m (2H, H^B-11; J_1 = 11.8; J_2 = 9.0).

^{13}C NMR, δ, ppm (*J*, Hz): 196.38 (C=O); 165.64 (*J* = 254; C_{ar}-4); 134.14 (C_{ar}-1); 131.53 (*J* = = 10; C_{ar}-2 + C_{ar}-6); 116.30 (C-9); 115.35 (*J* = 22; C_{ar}-3 + C_{ar}-5); 72.41 (C-12); 64.69 + 64.25 ($C_{ethyleneket}$); 62.42 (C-8); 35.87 (C-10); 30.92 (C-11).

***cis*-(2-Fluorophenyl)-(2-hydroxy-5,5-ethylenedioxacyclopentyl)methanone** was obtained as oil in 70.9% yield.

^{1}H NMP, δ, ppm (*J*, Hz): 7.75 dt (1H; H_{ar}-6; J_1 = = 7.7; J_2 = 1.8); 7.44 m (1H; H_{ar}-4; J_1 = 7.2; J_2 = = 1.8); 7.22 m (1H; H_{ar}-5; J_1 = 7.4); 7.12 m (1H; H_{ar}-3; J_1 = 8.7; J_2 = 8.4; J_3 = 7.7; J_4 = 2.0); 4.46 dd (1H, H-12, J_1 = 6.7; J_2 = 5.9); 4.04 d (1H, H-8, J_1 = 5.6); 3.79 m (1H, $H_{ethyleneket}$); 3.68 m (2H, $H_{ethyleneket}$; *J* = 13.6); 3.42 dd (1H, $H_{ethyleneket}$; J_1 = 13.1; J_2 = 6.4); 2.16 m (1H; H^A-11; J_1 = 14.1; J_2 = = 5.9); 1.96 m (1H; H^A-10; J_1 = 13.6; J_2 = 7.2; J_3 = = 5.6); 1.86 m (1H, H^B-10; J_1 = 13.3; J_2 = 7.9); 1.77 m (1H, H^B-11; J_1 = 13.8; J_2 = 8.7; J_3 = 6.1).

Catalytic hydrogenation of 3-(2-fluorophenyl)-4,4-ethylenedioxacyclopentane[*d*] isoxazoline using freshly prepared catalyst.

Catalytic amount of freshly prepared Raney nickel and 0.0878 g (1.42 mmol) of boric acid were added to a stirred solution of 0.0914 g (0.347 mmol) of isoxazoline **2b** in a mixture prepared from 3.0 ml of methanol and 0.5 ml of water. The reaction mixture was stirred at room temperature under hydrogen atmosphere until gas absorption ceased. After these the reaction mixture was filtered through a layer of aluminum oxide, which was then additionally eluted by ethanol. The solvent was distilled from the filtrate under reduced pressure, the residue was dissolved in ether and dried over anhydrous sodium sulfate. Separation of drying agent and evaporation of ether under reduced pressure gave 0.1136 g of crude products. The latest separation was performed by a prepa-rative TLC on silica gel, eluent: ether-ether petro-leum ether. Thus there were obtained of *cis*-(2-fluorophenyl)-(2-hydroxy-5,5-ethylene-dioxacyclopentyl)methanone (0.0248 g, 26.8%), (2-fluorophenyl)-(5,5-ethylene-dioxacyclopent 1-enyl)-methanone (0.0069 g, 8.1%) and (2-fluorophenyl)-(2,2-ethylenedioxacyclopentyl)-methanone (0.0192 g, 22.2%).

(2-Fluorophenyl)-(5,5-ethylenedioxacyclo-pent-1-enyl)methanone was obtained as oil in 8.1% yield.

^{1}H NMP, δ, ppm (*J*, Hz): 7.76 dt (1H; H_{ar}-6; J_1 = 8.4; J_2 = 1.5); 7.49 m (1H; H_{ar}-4; J_1 = 7.4; J_2 = 2.0); 7.19 m (1H; H_{ar}-5; J_1 = 7.7; J_1 = 3.6); 7.12 m (1H; H_{ar}-3; J_1 = 8.7; J_2 = 8.4; J_3 = 7.7; J_4 = = 2.0); 6.76 dd (1H, H-12, *J* = 2.6); 4.28 m (2H, $H_{ethyleneket}$); 4.04 m (2H, $H_{ethyleneket}$); 2.54 td (2H; CH_2-11; J_1 = 6.9; J_2 = 2.8); 2.26 m (2H; CH_2-10; J_1 = 6.4).

(2-Fluorophenyl)-(2,2-ethylenedioxacyclo-pentyl) methanone is obtained as oil in 22.2% yield.

^{1}H NMP, δ, ppm (*J*, Hz): 7.70 dt (1H; H_{ar}-6; J_1 = 7.7; J_2 = 1.8); 7.46 m (1H; H_{ar}-4; J_1 = 7.2; J_2 = 4.9; J_2 = 1.8); 7.19 dt (1H; H_{ar}-5; J_1 = 7.7; J_2 = 1.0); 7.10 m (1H; H_{ar}-3; J_1 = 8.4; J_2 = 0.8); 3.98 dd (1H, H-8, J_1 = 7.9; J_2 = 7.7); 3.78 m (1H, $H_{ethyleneket}$; J_1 = 12.0; J_2 = 7.4); 3.70 m (1H, $H_{ethyleneket}$; J_1 = 12.0; J_2 = 7.4; J_3 = 4.4); 3.47 m (2H, $H_{ethyleneket}$; J_1 = 12.6; J_2 = 6.4); 1.86 m (1H; H^A-10; J_1 = 13.1; J_2 = 8.7; J_3 = 4.3); 1.77–1.92 m (4H; H^B-10 + CH_2-12 + H-11); 1.71 m (1H, H^B-11; J_1 = 11.5; J_2 = 7.7; J_3 = 3.1).

Conclusion. Thus, the results of the carried out research could be summarized as following:

– synthesis of new precursors of fluorinated prostanoids and carbocyclic analogs of acetogenins via the reductive cleavage of isoxazoline heterocycle of dioxolane derivatives of 4-oxocyclopenta[*d*]izoxazolines by catalytic hydrogenation was successfully performed;

– catalytic hydrogenation of fluorine containing cyclopenta[*d*]isoxazolines was accomplished in good yields;

– the obtained fluorine containing compounds are of interest as potential biologically active substances;

– new possibilities of nitrile oxide technology application in the synthesis of analogues of complex natural compounds have been demonstrated.

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