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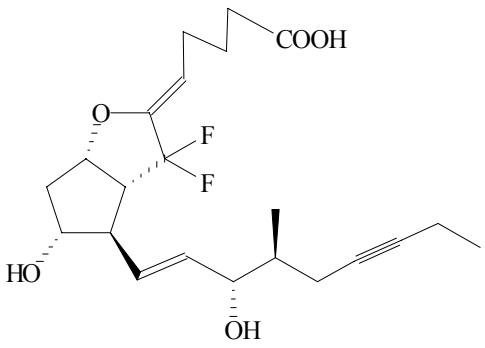
SYNTHESIS OF (2-FLUOROPHENYL)- AND (4-FLUOROPHENYL)-(2-NITROMETHYL)-METHANONES AS PRECURSORS OF FLUORINATED PROSTANOIDS

The synthesis of new fluorinated primary nitrocompounds – (2-fluorophenyl)- and (4-fluorophenyl)-(2-nitromethylcyclopentyl)methanones has been realized by the nitromethane 1,4-addition to 1-acylcyclopentenes, available by the reductive cleavage of corresponding cyclopent-5-en[*d*]isoxazolines. The obtained nitrocompounds are the precursors of new fluorinated prostaglandin analogues, which could be synthesized via the formation of second prostanoids side chain by nitrile oxides method.

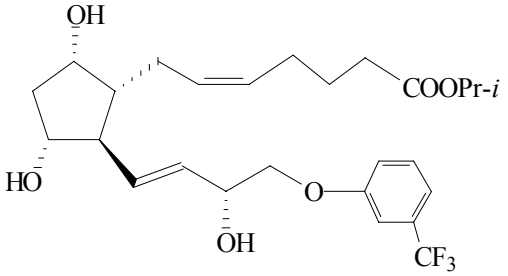
Introduction. Prostanoids along with acetogenins, thromboxanes and others are the most important forming *in vivo* products of fatty acids oxidation [1]. High biological activity and participation of such compounds in regulation of various physiological processes causes interest to their synthetic analogues, which have more directed and prolonged action. It should be mentioned that more than 150 drugs among numerous pharmaceuticals sold all over the world are fluorinated compounds [2–4]. Thus synthesis of fluorinated analogues acquires a particular importance since the introduction of fluorine atom which is similar to hydrogen in size, on the one hand, does not lead to significant change of molecules' steric structure [5].

On the other hand, substitution of hydrogen atoms by fluorine which possess high electron negativity can play a remarkable role in medical chemistry [2], particularly, causing improvement both of biological activity and stability of synthesized compounds [3]. Consequently synthesis of fluorinated analogues of prostaglandins (PG) is of particular interest. Thus 18,19-didehydro-7,7-difluoro-16-methyl PGI_2 (AFP-07) possesses good metabolic stability while keeping a strong activity as an inhibitor of platelet adhesion [2]. ***Travoprost*** acts as a PGF receptor agonist and is used for glaucoma treatment [2].

The aim of this work is to realize the first stage in the scheme of construction of prostanoids second side chain in fluorinated enone synthons by nitrile oxides method.



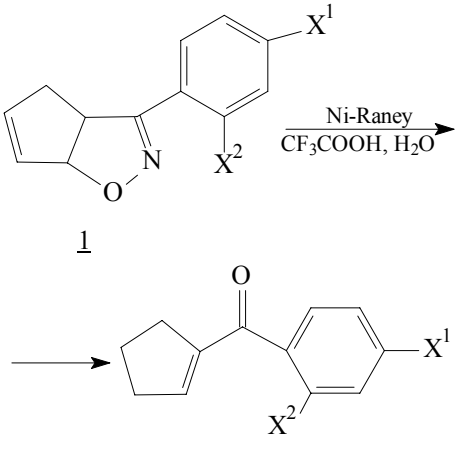
AFP-07



Travoprost

Main part. In order to realize this task the investigation of the first stage of present scheme has been accomplished, namely nitromethane addition to enones **2a** *и* **2b**. The latest were received earlier by the reductive cleavage of corresponding cyclopent-5-ene[*d*]isoxazolines **1a** and **1b** (scheme 1) [6].

The Michael reaction was carried out at room temperature with stirring in dry nitromethane with tetramethylguanidine (TMG) until the initial enone would disappear. The reaction course monitoring was performed by analytic thin layer chromatography (Scheme 2).



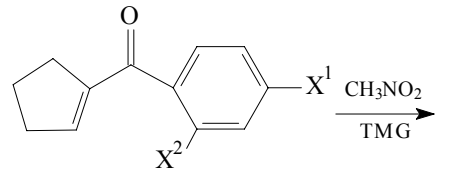
(**a**) $X^1 = F$, $X^2 = H$; (**b**) $X^1 = H$, $X^2 = F$

Scheme 1

Tetramethylguanidine plays role as a base which effects the activation of reagent (nitrome-

thane). The purification of the products was performed by preparative thin layer chromatography.

As a result of the reaction the corresponding nitromethyl derivatives **3a** (X^1 = F, X^2 = H) and **3b** (X^1 = H, X^2 = F) were prepared. Thus, the enone **2a** was converted to nitromethyl derivative **3a** in 75.0% yield. Similarly the nitrocompound **3b** was obtained from synthon **2b** in 47.4% yield. Within this research the formation of 1,2-adducts as well as of *cis*-isomers was not detected, which shows high chemo- and stereoselectivity of the reaction.



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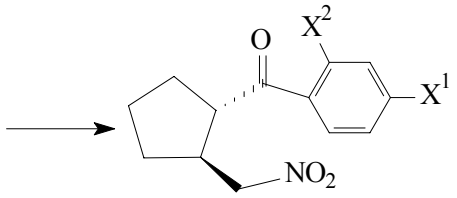

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(**a**) X^1 = F, X^2 = H; (**b**) X^1 = H, X^2 = F

Scheme 2

The structure of obtained compounds was proved by means of modern spectral methods of organic compounds analysis: proton magnetic resonance (PMR or ^{1}H NMR) and ^{13}C nuclear magnetic resonance (^{13}C NMR) spectroscopy.

Thus, in ^{1}H NMR spectrum of nitrocompound **3a** (Fig. 1) in comparison with initial enone **2a** spectrum (Fig. 2) the signal of vinyl proton with chemical shift 6.5 ppm disappears, while H-12 signal (PG atoms numeration is used for spectral data discussion) is shifted in high shielding field (2.99 ppm).

There are observed signals of chemically non-equivalent protons of nitromethyl group at 4.4 ppm, as well as H-8 signal (2.73 ppm) along with the signals of aromatic protons and protons of cyclopentane ring in spectrum of nitromethyl derivative **3a**.

Similar signals are detected in ^{1}H NMR spectrum of the product **3b**.

The structure of products of 1,4-addition of nitromethane to acylcyclopentenes is also proved by double resonance (spin decoupling), namely homonuclear decoupling experiments. Thus, the decoupling of CH_2NO_2 protons, simplified H-12 multiplet signal. These allowed to determine the H-12 and H-8 spin-spin coupling constant, which corresponded to relative *trans*-location of substituents in cyclopentane fragment. We have proved earlier *trans*-stereochemistry of Michael addition of nitromethane to similar enone synthons [7]. Thus, the reaction proceeded with high stereoselectivity, as there wasn't detected isomers with relative *cis*-stereochemistry of acyl and nitromethyl substituents among the reaction products.

As for ^{13}C NMR spectra of synthesized compounds the assignment of all signals to the corresponding C-atoms of the suggested structure has been accomplished. Thus, ^{13}C NMR spectrum of nitrocompound **3a** (Fig. 3) in comparison with spectrum of the initial enone (Fig. 4) contains the signal of nitromethyl group carbon at 78.67 ppm while C-8 and C-12 signals are shifted in high field and are detected at 49.64 (C-8) and 31.67 ppm (C-12). There are also signals of all other C-atoms of cyclopentane ring along with characteristic signals of carbonyl group (198.90 ppm) and *n*-fluorosubstituted benzene ring, for the latest being observed corresponding coupling constants due to spin-spin coupling with fluorine nuclei.

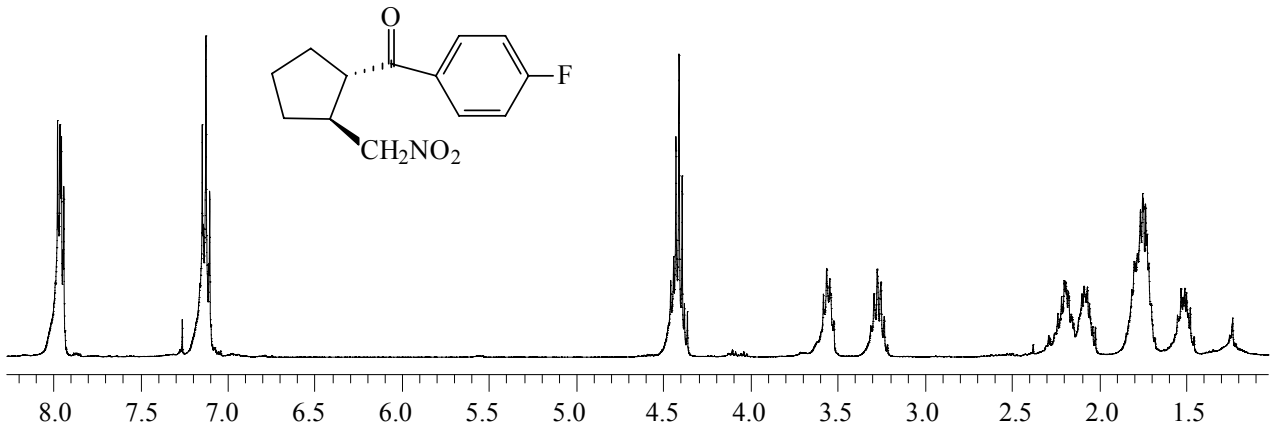


Fig. 1. ^{1}H NMR spectrum of (4-fluorophenyl)-(2-nitromethylcyclopentyl)methanone

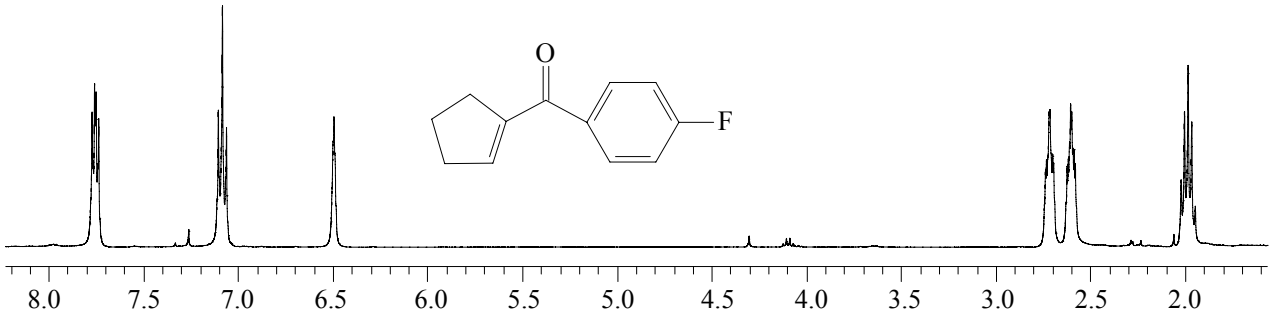


Fig. 2. ^{1}H NMR spectrum of (cyclopent-1-enyl)-(4-fluorophenyl)methanone

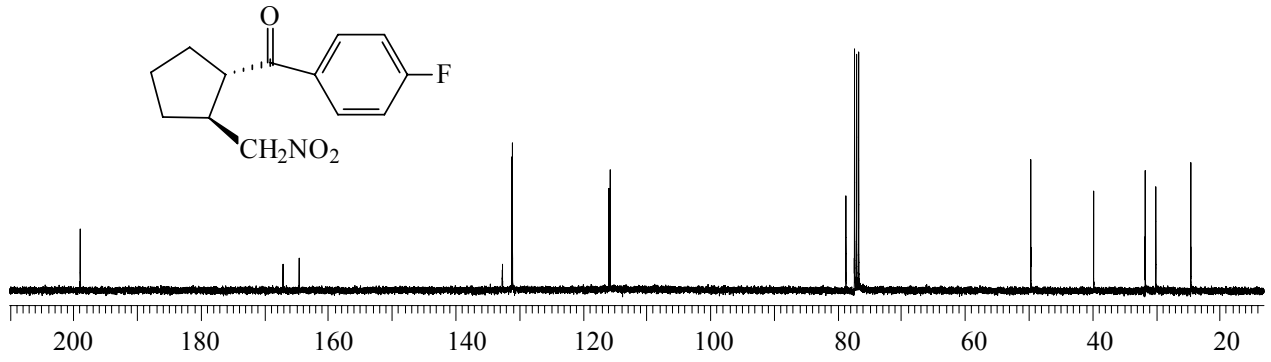


Fig. 3. ^{13}C NMR spectrum of (4-fluorophenyl)-(2-nitromethylcyclopentyl)methanone

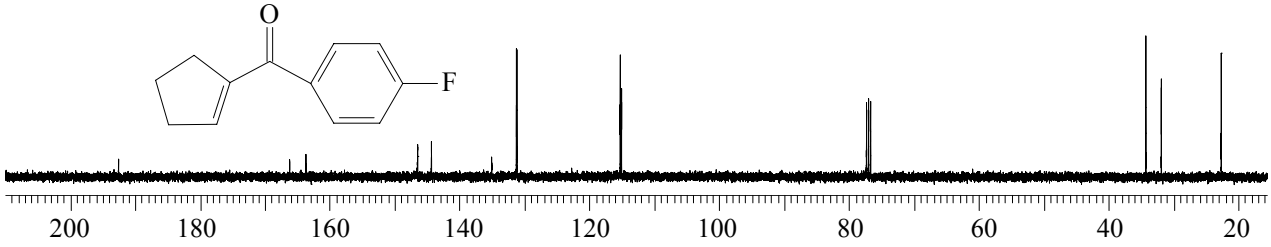
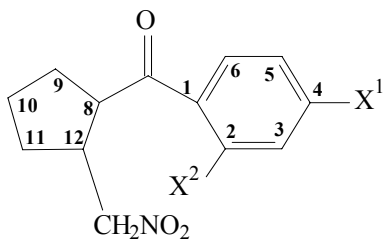


Fig. 4. ^{13}C NMR spectrum of (cyclopent-1-enyl)-(4-fluorophenyl)methanone

Experimental part. ^{1}H and ^{13}C NMR spectra of substances solutions in $CDCl_3$ with hexamethyldisiloxane (HMDS) as internal standard were recorded on Bruker AVANCE spectrometer (400 MHz). The reaction course was monitored by thin layer chromatography (TLC) on silica gel plates Kieselgel 60 F_{254} (Merck), the eluent being ether – light petroleum, developer: iodine or 4% $KMnO_4$ solution. The used solvents were purified according to standard procedures [8].

The following atoms numeration has been used for spectral data discussion:



Michael 1,4-addition of nitromethane to (cyclopent-1-enyl)-(4-fluorophenyl)- and (cyclopent-1-enyl)-(2-fluorophenyl)methanone. Tetramethylguanidine (5 drops) was added to a stirred solution of enone (0.46 mmol) in dry nitromethane (5 ml). Then the reaction mixture was stirred at room temperature until disappearance of the initial enone. The reaction proceeding control was carried out by analytic TLC. Then the reaction mixture was filtered through silica gel, which was eluted additionally by benzene, after that solvent was distilled under reduced pressure. The product was separated from the obtained residue by preparative TLC (eluent: ether – hexane).

(4-Fluorophenyl)-(2-nitromethylcyclopentyl)-methanone was prepared in 75.0% yield as an oil.

^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.96 dd (2H; H_{ar}-2 + H_{ar}-6; J = 9.0); 7.12 dd (2H; H_{ar}-3 + H_{ar}-5; J_1 = 8.7; J_2 = 8.4); 4.42 m (2H; CH_2NO_2; J_1 = = 12.5; J_2 = 7.4; J_3 = 6. 9); 3.56 m (1H; H-8; J_1 = = 7.4; J_2 = 7.2); 3.27 m (1H; H-12; J_1 = 9.0; J_2 = = 7.4; J_3 = 7.2); 2.19 m (1H; H^A-9; J_1 = 12.5; J_2 = = 8.2; J_3 = 7.4); 2.09 m (1H, H^A-11; J_1 = 12.3; J_2 = = 7.4); 1.75 m (3H, H^B-9 + 2H-10; J_1 = 12.5; J_2 =

= 12.3; J_3 = 7.2); 1.52 m (1H, H^B-11; J_1 = 12.5; J_2 = = 8.2).

^{13}C NMR spectrum, δ, ppm (*J*, Hz): 198.90 (C=O); 165.79 (*J* = 255; C–F); 132.60 (*J* = 3; C_{ar}-1); 131.07 (*J* = 10; C_{ar}-2 + C_{ar}-6); 115.85 (*J* = 22; C_{ar}-3 + C_{ar}-5); 78.67 (CH_2NO_2); 49.64 (C-8); 39.78 (C-11); 31.67 (C-12); 30.01 (C-9); 24.52 (C-10).

(2-Fluorophenil)-(2-nitromethylcyclopentyl)-methanone was prepared in 47.4% yield as an oil.

^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.81 m (1H; H_{ar}-6; J_1 = 7.7; J_2 = 1.8); 7.52 m (1H; H_{ar}-4; J_1 = =7.2; J_2 = 1.8); 7.23 m (1H; H_{ar}-5; J_1 = 7.7; J_2 = = 1.0); 7.11 dd (1H; H_{ar}-3; J_1 = 8.4; J_2 = 1.0); 4.48 dd (1H; $C\underline{H}^ANO_2$; J_1 = 12.0; J_2 = 6.7); 4.39 dd (1H; $C\underline{H}^BNO_2$); J_1 = 12.0; J_2 = 7.7); 3.49 m (1H; H-8; J_1 = 7.9; J_2 = 6.7); 3.26 m (1H; H-12; J_1 = = 7.9; J_2 = 7.4); 2.18 m (1H; H^A-9; J_1 = 12.0; J_2 = = 8.4); 2.6 m (1H, H^A-11; J_1 = 12.3; J_2 = 7.7); 1.76 m (3H, H^B-9 + CH_2-10; J_1 = 13.5; J_2 = 5.6); 1.49 m (1H, H^B-11; J_1 = 12.8; J_2 = 8.2).

^{13}C NMR spectrum, δ, ppm (*J*, Hz): 199.25 (*J* = = 9; C=O); 161.39 (*J* = 253; C–F); 134.60 (*J* = 9; C_{ar}-4); 130.87 (*J* = 2; C_{ar}-6); 125.36 (*J* = 12; C_{ar}-1); 124.59 (*J* = 4; C_{ar}-4); 116.63 (*J* = 23; C_{ar}-3); 78.91 (CH_2NO_2); 54.23 (*J* = 7; C-8); 39.77 (C-12); 30.43 (C-11); 30.17 (C-9); 24.24 (C-10).

Conclusion. Thus, the following results were obtained in this research:

– synthesis of fluorinated primary nitrocompounds as nitrile oxides precursors in the scheme of second PG side chain formation by nitrile oxides method was realized;

– Michael reaction proceeded with high chemo- and stereoselectively;

– new possibilities of nitrile oxides technology employment in the synthesis of complex natural compounds analogues were demonstrated.

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