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Synthesis of 9,11-Ethano-13,15-isoxazolinoprostanoids, PGH Analogs

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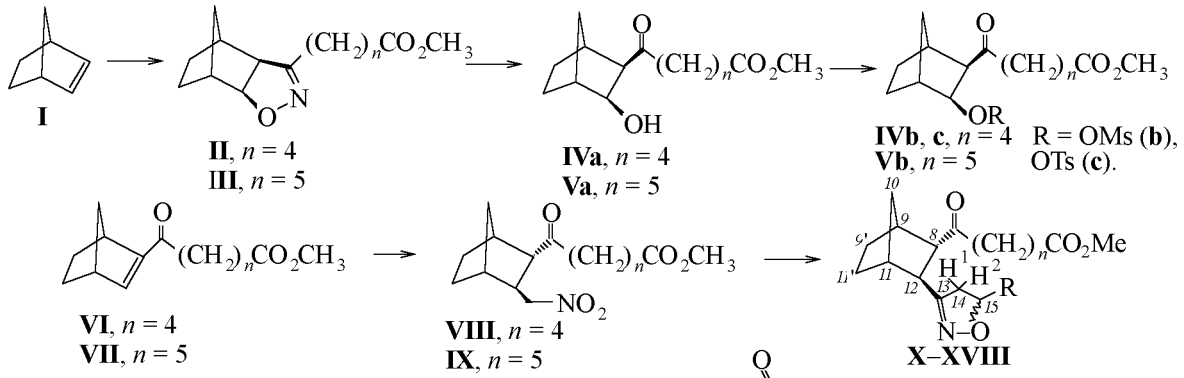
Abstract—The 1,3-dipolar addition to terminal alkenes of nitrile oxides generated from nitromethylene derivatives of bicycloheptane provided 9,11-ethano-13,15-isoxazolinoprostanoids with alkyl, phenyl, or additional heterocyclic fragment in the ω-chain.

The key role played by labile endoperoxides of prostaglandins (PGH) in the biosynthesis of the principal classic prostaglandins (PG), prostacycline (PGI_2), and thromboxanes (TX) attracts the attention of organic chemists to the development of procedures for preparation of stable analogs of these natural compounds. One of the most interesting approach to this target is the synthesis of bicyclo[2.2.1]heptane derivatives. Unlike labile PGH their 9,11-ethanoanalogs are chemically stable and promising as antagonists of the receptor of thromboxane A_2, a very active inductor of blood platelets aggregation [1]. Among the PG analogs especially interesting are isoxazolo- and isoxazolinoprostanoids, for pharmacologic tests have shown that many of these compounds are highly active and combine a pharmacological activity of cytoprotective, antiaggregation, and immunostimulating effect [2].

Nowadays several independent approaches to the synthesis of PGH analogs based on bicycloheptane exist differing mainly by the means of side chains formation. Thus at applying Diels–Alder reaction [3], organopalladium approach [4], and in the synthesis of carbaanalogs of PGH proceeding from (–)-norcamphor [5] the compounds obtained mainly possess unnatural configuration of centers to which the side chains are attached. The nitrile oxide method of introducing prostanoid side chains into the bicycloheptane molecule we have developed [6] makes possible preparation of compounds with the natural position of the α- and ω-chains in the molecule; therewith the 7-oxoprostanoid structure of the α-chain is predetermined.

In extension of the research aiming at the synthesis of carbocyclic analogs of PGH with the use of the nitrile oxide method we carried out a synthesis of a series of new 9,11-ethano-13,15-isoxazolinoprostanoids. In the syntheses under consideration the norbornene was used as initial compound. It reacted *in situ* with nitrile oxides furnishing products of 1,3-dipolar addition, bicyclo[2.2.1]heptanoisoxazolines (**II, III**).



n = 4 (**XI, XII, XIV, XVI, XVII, XVIII**), 5 (**X, XIII, XV**); R = C_5H_{11} (**X**), –N⟨O⟩ (**XI**), –O–⟨⟩–Cl (**XII, XIII**), Ph (**XIV, XV**), –⟨N⟩ (**XVI**), –⟨N⟩ (**XVII**), –N⟨N⟩ (**XVIII**).

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The reaction of 1,3-dipolar cycloaddition of nitrile oxides to bicyclo[2.2.1]heptene (I) occurred stereoselectively yielding di-*exo*-isoxazoline derivatives. In the ^{1}H NMR spectra of adducts **II, III** [6] appeared two doublets in the region 2.00 and 4.41 ppm with a coupling constant $^3J_{8,12}$ 8.4 Hz evidencing the di-*endo*-configuration of the protons H^8 and H^{12}.

A reductive cleavage of the isoxazoline ring effected by a system Raney Ni/$AlCl_3$/MeOH–H_2O [7] gave rise to hydroxyketones **IVa, Va** with a well formed 7-oxocarboxy prostanoid chain. The product of the heterocycle opening conserved the di-*exo*-orientation of the substituents in the bicycloheptane. The presence in the ^{1}H NMR spectrum of two doublets at 2.70 and 4.07 ppm with a coupling constant $^3J_{8,12}$ 7.2 Hz confirms the *cis*, *exo*-orientation of the substituents. No dehydration occurred on treating the ketoalcohols **IVa, Va** with methanesulfonyl chloride in pyridine; instead mesyl esters **IVb, Vb** were obtained. In triethylamine solution the reaction also finished at the stage of mesyl esters **IVb, Vb** formation. The tosyl chloride in pyridine also did not effect water elimination from hydroxyketones **IVa, Va**, and only tosylates **IVc, Vc** were obtained. The tosylates were also prepared in reaction of hydroxyketones **IVa, Va** with tosyl chloride in triethylamine.

The mesylates were prepared in higher yields by reacting hydroxyketones in benzene in the presence of a triple excess of pyridine (or triethylamine). At boiling of mesylates **IVb, Vb** in benzene with diazabicycloundecene (DBU) an elimination of methanesulfonic acid occurred to afford enones **VI, VII**. The latter form as readily when 1,1,4,4-tetramethylguanidine is used as demesylating agent. In this case the process is carried out at lower temperature, therefore the tarring of the reaction mixture is suppressed, and the enone yield increases to 80%.

The building up of the ω-chain by the nitrile oxide method involved a conjugate 1,4-addition of nitromethane to acylbicycloheptene **VI, VII** under Michael reaction conditions. The reaction proceeded stereoselectively; therewith the nitro group occurred in *exo*-position, and the acyl chain in the *endo*-position, and the products formed had the natural configuration of the α- and ω-chains. No isomeric products were detected in the reaction mixture. The addition of nitromethane to acylbicycloheptenes **VI, VII** in methanol in the presence of sodium methylate caused formation of a side reaction product, 7-oxo-7-(3-*exo*-methoxybicyclo[2.2.1]hept-2-*endo*-yl)-heptanoic acid, in 5 to 10% yield. Treating of acylbicycloheptene with nitromethane in benzene in the presence of tetramethylguanidine at room temperature afforded exclusively nitromethylene derivatives of bicycloheptane **VIII, IX**. The IR spectra of nitromethylene derivatives **VIII, IX** lack the strong absorption band of conjugated 7-oxo group at 1695 cm^{-1} that is characteristic of enone structure in compounds **VI, VII**, and appears a band inherent to an isolated 7-oxo group of the α-chain at 1710 cm^{-1}. The characteristic absorption bands of stretching vibrations of nitro groups are observed in the IR spectra of these compounds at 1555 and 1380 cm^{-1}. In the ^{1}H NMR spectra of nitro compounds **VIII, IX** appear characteristic signals of nitromethylene protons: a doublet of doublets at 4.12 ppm, and a doublet of doublets at 4.31 ppm ($^3J_{12,13}$ 7.8, $^2J_{13,13}$ 12.0 Hz). The *endo,exo*-configuration of substituents in positions *8* and *12* of the prostanoid skeleton is confirmed by the values of coupling constants and by multiplicity of signals of the appropriate protons, for instance, the chemical shift value and signal pattern of the *endo*-proton H^{12} are characteristic. No coupling is observed between the *endo*-protons of the bicycloheptane molecule and the bridgehead protons H^9 and H^{11}, only a coupling with H^8 protons and remote coupling with the bridging *anti*-proton [9]. The resonance signal from H^{12} proton appears at 2.85 ppm as a doublet of doublets with a vicinal constant $^3J_{8,12}$ 4.8 Hz and with a constant of the remote coupling with the bridging proton H^{10an} $^4J_{12,10an}$ 1.2 Hz. Unlike *endo*-protons, the *exo*-protons of the bicycloheptane moiety are involved in numerous couplings and have a complicated signal in the ^{1}H NMR spectrum in the region of 2.67 ppm.

Substituted nitromethylenebicycloheptanes **VIII, IX** are the key intermediates for the synthesis of 9,11-ethano-13,15-isoxazolinoprostanoids by the nitrile oxide method. By treating compounds **VIII, IX** with phenyl isocyanate nitrile oxides are generated which *in situ* are brought into 1,3-dipolar cycloaddition with olefin dipolarophiles. As the latter we used 1-heptene, 1-vinyl-2-pyrrolidone, styrene, *p*-chlorophenoxy-1-propene, 2-vinylpyridine, 4-vinylpyridine, *N*-vinylimidazole. The reaction was carried out in the presence of catalytic amounts of triethylamine. The addition of nitrile oxide proceeded stereoselectively furnishing isoxazolinoprostanoids **X–XVII** in over 85% yield. The reaction with N-vinylimidazole was an exclusion with the yield of adduct **XVIII** of 64%.

The structure of prostanoids obtained was derived from their spectra. The IR spectra of isoxazolinoprostanoids **X–XVIII** compared with the spectra of

initial nitromethylene norbornane derivatives **VIII, IX** lack the characteristic absorption bands belonging to the stretching vibrations of N–O bonds of the nitro group and contain the bands of the N=C bond of isoxazoline in the region 1610 cm^{-1}. The position of the absorption band of the 7-oxo group from the α-chain is conserved at 1710 cm^{-1}.

The ^1H NMR spectra provide detailed information on the structure of the isoxazolinoprostanoids synthesized. A characteristic feature of these spectra is a complex signal in the region 4.50–6.43 ppm that at high resolution in the spectrum of compounds **XI–XVIII** appears as two doublets of doublets and corresponds to H^{15} in a mixture of isoxazoline epimers. In the spectrum of prostanoid **X** with a pentyl substituent the signal from the H^{15} proton is observed at 4.50 ppm. In going to aryl substituent in the heterocycle deshielding of the H^{15} proton occurs, and the respective resonance is shifted downfield by 1.18 and 1.01 ppm (δ 5.58 and 5.51 ppm for prostanoids with a phenyl substituent **XIV** and **XV** respectively). As compared to the proton H^{15} signal in the spectrum of prostanoid **X** this resonance in the spectra of prostanoids with pyridyl groups **XVI, XVII** is shifted by 1.13 and 1.04 ppm (δ 5.63 and 5.54 ppm for prostanoids **XVI** and **XVII** with 2-pyridyl and 4-pyridyl substituents respectively). Still greater shift of the signal is observed in the spectrum at introducing into the heterocycle of 2-oxopyrrolidyl group: it attains 1.93 ppm compared to the signal position in the spectrum of compound with an alkyl substituent. Therewith the signal pattern and coupling constants almost do not change.

The signal from H^{12} protons is observed in the region 2.87–3.56 ppm with a coupling constant $^3J_{12,8}$ ~4.7–5.0 Hz and it is shifted downfield with respect to the corresponding signal in the spectrum of the nitromethylene precursor by 0.5 ppm evidently due to the influence of the anisotropic C=N bond. In some cases it is overlapped with the doublet of doublets from one of isoxazoline protons, H^{14}. In the case of aryl substituents the signal of the proton H^{12} appears downfield (at 2.89–2.90 ppm in spectra of compounds **XIV, XV** with phenyl substituents). The pyridyl substituents cause still greater shift of the proton H^{12} signal, and the latter is observed at 3.27–3.56 ppm. The signal of proton H^8 appears as a triplet of doublets at 2.92–3.48 ppm with a vicinal coupling constant $^3J_{8,12}$ ~4.7–5.0 and *w*-constant $^4J_{8,9'}$ ~1.2–1.9 Hz. In the spectrum of prostanoid **XVIII** with an imidazole substituent the signals of the proton H^8 belonging to diastereomers are resolved. The resonance of the H^8 proton in this compound is observed at 3.36 and 3.48 ppm with an overall integral intensity corresponding to 1H. The multiplicity of proton signals from H^8 and H^{12} and coupling constants values show that the relative *endo,exo*-configuration of the prostanoid α- and ω-chains is conserved in the isoxazolinoprostanoids.

A set of signals in the range from 2.40 to 3.62 ppm corresponds to the signals from two protons of the isoxazoline ring H^{14} and appears as four doublets of doublets which as a rule are superimposed on each other in the spectra registered at operating frequency 200 MHz. This complex pattern is due to the presence of diastereomeric isoxazolines.

The cycloaddition reaction proceeds regioselectively in keeping with the general rules concerning the steric effects influence in cycloaddition of nitrile oxides to the terminal alkenes [10] resulting in formation of two diastereomeric pairs of adducts with a 3,5-disubstituted isoxazoline fragment. These diastereomers are of the same chromatographic mobility, and therefore they cannot be separated by chromatography. We succeeded in separation the isomeric isoxazolines only for isoxazolinoprostanoid **X** with a C_5H_{11} substituent. In the other cases the spectra of isomeric mixtures were registered, and the spectral parameters of isomers were different. The main difference consists in dissimilar chemical shifts of the H^{14} proton signals, therefore instead of one signal are seen two, and the H^{14} are also magnetically nonequivalent and appear as two doublets of doublets for a single isomer. As a result four doublets of doublets are observed in the spectrum with an overall integral intensity corresponding to two protons for H^{14} with a geminal coupling constant $^2J_{14,14}$ ~ 17–19 Hz and vicinal coupling constants $^3J_{14,15}$ ~ 5.2–7.0 and 8.0–10.0 Hz.

In addition to the above described signals in the ^1H NMR spectra of the newly prepared prostanoids the characteristic signals of the substituents attached to the isoxazoline ring are observed. In the spectrum of **X** prostanoid with a pentyl substituent a triplet appears at 0.89 ppm from H^{20} protons ($^3J_{20,19}$ 6.2 Hz). In the spectra of pyridyl-substituted isoxazolinoprostanoids **XVI, XVII** the characteristic signals of the pyridyl moieties are located at 7.22, 7.46, 7.70, and 8.56 for 2-pyridyl and at 7.24 and 8.60 for 4-pyridyl. The coupling constants correspond to the published data [11]. Imidazole substituent is revealed in the spectrum as three broad singlets at 6.94, 7.13, 7.62 ppm corresponding to the protons $H^{4'}$, $H^{5'}$, $H^{2'}$ in the imidazole ring. The protons of the 2-oxopyrrolidyl group resonate in a strong field; they are

overlapped by the signals of the other protons and are coupled with each other. Therefore they appear as multiplets in the regions 1.92–2.14 ppm ($H^{4'}$), 2.26–2.55 ppm ($H^{3'}$),and 3.05–3.46 ppm ($H^{5'}$).

The biological activity of compounds synthesized was tested. It was found that the 9,11-ethano-13,15-isoxazolinoprostanoids possess immunodepressant activity.

EXPERIMENTAL

IR spectra were recorded on spectrophotometer UR-20 from thin films. ^{1}H NMR spectra were registered on spectrometer Bruker AC-200 (operating frequency 200 MHz) at 25°C from solutions in $CDCl_3$ or $CDCl_3$–CCl_4 (1:1), internal reference TMS. Chemical shifts are given in the δ scale. The structure of newly prepared compounds was established on the grounds of analysis of geminal, vicinal, and remote coupling constants in the double resonance spectra ^{1}H–^{1}H. Mass spectra were measured on Varian-MAT-311A instrument at ionizing electrons energy 70 eV, vaporizer temperature 120–150°C, ion source temperature 200°C.

The reaction progress was monitored and the purity and homogeneity of compounds synthesized was checked by TLC on plates Silufol UV-254, (Serva), DC-Plastikfolien Kieselgel 60 F_{254} (Merck) and DC-Alufolien Kieselgel 60 F_{254} (Merck) using solvent systems ethyl ether–hexane, 70:30; ether; ether–ethyl acetate, 95:5. The development was carried out under UV irradiation, with iodine vapor, and by a solution containing 5% of anisaldehyde, 5% of sulfuric acid, and 90% of ethanol. The products were separated by column chromatography on silica gel 40/100 μ (Czechia) at gradient elution with a mixture ethyl ether–hexane, chloroform–methanol, and also by preparative TLC on glass plates with adsorbent Silicagel LL_{254} 5/40 μ using as eluents mixtures ether–hexane, 10:90; chloroform–methanol, 90:10; and ether.

Compounds **II–IX** had characteristic identical to published data [6].

Methyl 7-oxo-9,11-ethano-12-(5-R-4,5-dihydro-3-isoxazolyl)-13,14,15,16,17,18,19,20-octanorprostanates X–XVIII. To a mixture of 1 mmol of nitromethylene derivative **VIII, IX** and an excess of alkene (1.1 mmol) dissolved in 5 ml of anhydrous benzene was added phenyl isocyanate (2 mmol). On addition of 5–8 drops of triethylamine the reaction mixture was stirred under anhydrous conditions for 24 h at room temperature till complete consumption of the initial nitro compound (TLC monitoring). On completion of the reaction 0.3 ml of water was added to destroy the excessive phenyl isocyanate, the mixture was stirred for 2 h more, the precipitate was filtered off and washed with benzene on the filter. To remove diphenylurea the reaction mixture was filtered through a bed of alumina, the reaction product was eluted with ether. The target compound was purified by column chromatography on silica gel at gradient elution with a mixture hexane–ether (in the case of *N*-vinylimidazole elution with chloroform–methanol mixture). For spectral analyses the samples were purified by preparative TLC on Silicagel LL_{254} 5/40 μ.

Methyl 7-oxo-9,11-ethano-12-(5-pentyl-4,5-dihydro-3-isoxazolyl)-13,14,15,16,17,18,19,20-octanorprostanate (X) was obtained as viscous oily substance (yield 0.21 g, 93%). IR spectrum, cm^{-1}: 1610 (νC=N of izoxazoline), 1711 (νC=O), 1739 (νCOOCH$_3$), 2960 ($\nu_{as}CH_2$), 2878 (ν_sCH_2), 1453 (δCH$_2$ sciss.). ^{1}H NMR spectrum, δ, ppm: 0.89 t (3H, CH$_3$, $^3J_{20,19}$ 6.2), 1.04–1.14 m (1H, $H^{11'}_{endo}$), 1.24–1.46 m (11H: $H^{9'}_{endo}$, $H^{9'}_{exo}$, H^{10}_{anti}, 4CH$_2$, α-chain and pentyl), 1.54–1.77 m (8H: H^{10}_{syn}, $H^{11'}_{exo}$, 3CH$_2$, α-chain and pentyl), 2.28–2.35 m (3H: 2.32 t, 2H, CH$_2$CO$_2$CH$_3$, $^3J_{2,3}$ 7.2; 1H, H^{11}), 2.30–2.52 m [3H: 2.44 t, 2H, CH$_2$C(O), $^3J_{6,5}$ 7.3; 2.47 d.d, 1H, H^{14-1}, $^3J_{14,14}$ 17.0, $^3J_{14,15}$ 7.3], 2.67 br.s (1H, H^9), 2.87 d.d (1H, H^{12}_{endo}, $^3J_{12,8}$ 4.8), 3.01 d.d (1H, H^{14-2}, $^2J_{14,14}$ 16.0, $^3J_{14,15}$ 10.0), 3.37 t.d (1H, H^9_{exo}, $^3J_{8,12}$ 4.8, $^4J_{8,9'}$ 1.9), 3.66 s (3H, CH$_3$O), 4.50 m (1H, H^{15}). Mass spectrum, [M^+]: 391.

Methyl 7-oxo-9,11-ethano-12-[5-(2-oxopyrrolidino)-4,5-dihydro-3-isoxazolyl]-2,13,14,15,16,17,18,19,20-nonanorprostanate (XI) was obtained as viscous oily substance (yield 0.18 g, 89%). IR spectrum, cm^{-1}: 1610 (νC=N of izoxazoline), 1724 (νC=O), 1749 (νCOOCH$_3$), 2963 ($\nu_{as}CH_2$), 2876 (ν_sCH_2), 1452 (δCH$_2$ sciss.). ^{1}H NMR spectrum, δ, ppm: 1.01–1.19 m (1H, $H^{11'}_{endo}$), 1.21–1.33 m (3H: $H^{9'}_{endo}$, $H^{9'}_{exo}$, H^{10}_{anti}), 1.33– 1.80 m (6H: H^{10}_{syn}, $H^{11'}_{exo}$, 2CH$_2$, α-chain), 1.92–2.14 m (2H, pyrrolidone, $H^{4'}$), 2.26–2.55 m [7H: 2H, CH$_2$CO$_2$CH$_3$, H^{11}, 2H, pyrrolidone, $H^{3'}$, 2H, CH$_2$C(O)], 2.73 br.s (1H, H^9), 2.97 br.s (1H, H^8_{exo}), 3.05–3.46 m (5H: 1H, H^{12}_{endo}, 2H, H^{14}, 2H, pyrrolidone, $H^{5'}$), 3.67 s (3H, CH$_3$O), 6.43 two d.d (1H, H^{15}). Mass spectrum, [M^+]: 390.

Methyl 7-oxo-9,11-ethano-12-[5-(4-chlorophenoxymethyl)-4,5-dihydro-3-isoxazolyl]-2,13,14,15,16,17,18,19,20-nonanorprostanate (XI) was obtained as viscous oily substance (yield 0.11 g, 90%). IR spectrum, cm^{-1}: 1610 (νC=N of izoxazoline), 1706

(νC=O), 1737 (νCOOCH$_3$), 2958 (ν_{as}CH$_2$), 2880 (ν_sCH$_2$), 1455 (δCH$_2$ sciss.), 1449, 1494, 1542, 1597 (νC=C arom). ^{1}H NMR spectrum, δ, ppm: 1.02–1.18 m (1H, $H^{11'}_{endo}$), 1.18–1.46 m (3H: $H^{9'}_{endo}$, $H^{9'}_{exo}$, H^{10}_{anti}), 1.52–1.78 m (6H: H^{10}_{syn}, $H^{11'}_{exo}$, 2CH$_2$, α-chain), 2.32 t (2H, $CH_2CO_2CH_3$, $^3J_{3,4}$ 7.2), 2.37 br.d (1H, H^{11}, $^3J_{11,11'}$ 4.2), 2.46 t [2H, $CH_2C(O)$, $^3J_{6,5}$ 6.8], 2.71 br.s (1H, H^9), 2.84 d.d (0.5H, $H^{14\text{-}1}_A$, $^2J_{14,14}$ 17.1, $^3J_{14,15}$ 6.8), 2.94 br.d (1H, H^{12}_{endo}, $^3J_{12,8}$ 5.0), 2.98–3.17 two d.d (0.5, $H^{14\text{-}1}_B$, 0.5H, $H^{14\text{-}2}_B$), 3.17 d.d (0.5H, $H^{14\text{-}2}_A$, $^2J_{14,14}$ 17.1, $^3J_{14,15}$ 11.0), 3.38 two t.d (1H, H^8_{exo}), 3.67 s (3H, CH$_3$O), 3.96 d (2H, H^{16}, $^3J_{16,15}$ 5.2), 4.88 m (1H, H^{15}, $^3J_{15,16}$ 5.2, $^3J_{15,14}$ 6.8), 6.81 d (2H, C$_6$H$_5$, $H^{2'}$, $H^{6'}$, ^3J 9.0), 7.23 d (2H, C$_6$H$_5$, $H^{3'}$, $H^{5'}$, ^3J 9.0). Mass spectrum, [M^+]: 447.

Methyl 7-oxo-9,11-ethano-12-[5-(4-chlorophenoxymethyl)-4,5-dihydro-3-isoxazolyl]-13,14,15,16,17,18,19,20-octanorprostanate (XIII) was obtained as viscous oily substance (yield 0.12 g, 90%). IR spectrum, cm^{-1}: 1610 (νC=N of izoxazoline), 1710 (νC=O), 1740 (νCOOCH$_3$), 2960 (ν_{as}CH$_2$), 2880 (ν_sCH$_2$), 1452 (δCH$_2$ sciss.), 1452, 1492, 1540, 1597 (νC=C arom). ^{1}H NMR spectrum, δ, ppm: 1.00–1.17 m (1H, $H^{11'}_{endo}$), 1.20–1.43 m (5H: $H^{9'}_{endo}$, $H^{9'}_{exo}$, H^{10}_{anti}, CH$_2$, α-chain), 1.55– 1.81 m (6H: 1H, H^{10}_{syn}, $H^{11'}_{exo}$, 2CH$_2$, α-chain), 2.31 t (2H, $CH_2CO_2CH_3$, $^3J_{3,4}$ 7.2), 2.37 br.d (1H, H^{11}, $^3J_{11,11'}$ 4.1), 2.41 t [2H, $CH_2C(O)$, $^3J_{6,5}$ 6.5], 2.69 br.s (1H, H^9), 2.82 d.d (0.5H, $H^{14\text{-}1}_A$, $^2J_{14,14}$ 17.3, $^3J_{14,15}$ 7.0), 2.92 br.d (1H, H^{12}_{endo}, $^3J_{12,8}$ 5.1), 2.88–3.23 two d.d (0.5, $H^{14\text{-}1}_B$, 0.5H, $H^{14\text{-}2}_B$), 3.14 d.d (0.5H, $H^{14\text{-}2}_A$, $^2J_{14,14}$ 17.3, $^3J_{14,15}$ 11.6), 3.35 two t.d (1H, H^8_{exo}), 3.66 s (3H, CH$_3$O), 3.93 d (2H, H^{16}, $^3J_{16,15}$ 5.4), 4.85 m (1H, H^{15}, $^3J_{15,16}$ 5.4, $^3J_{15,14}$ 7.0), 6.80 d (2H, C$_6$H$_5$, $H^{2'}$, $H^{6'}$, ^3J 9.0), 7.20 d (2H, C$_6$H$_5$, $H^{3'}$, $H^{5'}$, ^3J 9.0). Mass spectrum, [M^+]: 461.

Methyl 7-oxo-9,11-ethano-12-(5-phenyl-4,5-dihydro-3-isoxazolyl)-2,13,14,15,16,17,18,19,20-nonanorprostanate (XIV) was obtained as viscous oily substance (yield 0.29 g, 94%). IR spectrum, cm^{-1}: 1605 (νC=N of izoxazoline), 1709 (νC=O), 1739 (νCOOCH$_3$), 2955 (ν_{as}CH$_2$), 2880 (ν_sCH$_2$), 1455 (δCH$_2$ sciss.), 1433, 1495, 1555, 1605 (νC=C arom). ^{1}H NMR spectrum, δ, ppm: 1.02–1.11 m (1H, $H^{11'}_{endo}$), 1.21–1.42 m (2H: $H^{9'}_{endo}$, H^{10}_{anti}), 1.42–1.51 m (1H, $H^{9'}_{exo}$), 1.55–1.72 m (5H: $H^{11'}_{exo}$, 2CH$_2$, α-chain), 1.76 d.m (1H, H^{10}_{syn}, $^2J_{10,10}$ 9.2), 2.29–2,32 m (2H, $CH_2CO_2CH_3$), 2.44 br.d (1H, H^{11}, $^3J_{11,11'}$ 4.1), 2.46–2.51 m [2H, $CH_2C(O)$], 2.72 br.s (1H, H^9), 2.83 d.d (0.5H, $H^{14\text{-}1}_A$, $^2J_{14,14}$ 16.4, $^3J_{14,15}$ 8.1), 2.90 m (1H, H^{12}_{endo}), 2.96 d.d (0.5H, $H^{14\text{-}1}_B$, $^2J_{14,14}$ 11.6, $^3J_{14,15}$ 7.6), 3.31 d.d (0.5H, $H^{14\text{-}2}_B$, $^2J_{14,14}$ 17.4, $^3J_{14,15}$ 11.2), 3.40 d.d (0.5H, $H^{14\text{-}2}_A$), 3.46 two t.d (1H, H^8_{exo}), 3.68 s (3H, CH$_3$O), 5.58 two d.d (1H, H^{15}, $^3J_{14,15}$ 8.4, $^3J_{14,15}$ 10.9), 7.28–7.45 m (5H, C$_6$H$_5$). Mass spectrum, [M^+]: 383.

Methyl 7-oxo-9,11-ethano-12-(5-phenyl-4,5-dihydro-3-isoxazolyl)-13,14,15,16,17,18,19,20-octanorprostanate (XV) was obtained as viscous oily substance (yield 0.25 g, 94%). IR spectrum, cm^{-1}: 1605 (νC=N of izoxazoline), 1712 (νC=O), 1742 (νCOOCH$_3$), 2960 (ν_{as}CH$_2$), 2880 (ν_sCH$_2$), 1454 (δCH$_2$ sciss.), 1438, 1495, 1555, 1605 (νC=C arom). ^{1}H NMR spectrum, δ, ppm: 1.05–1.15 m (1H, $H^{11'}_{endo}$), 1.27–1.40 m (4H: $H^{9'}_{endo}$, H^{10}_{anti}, CH$_2$, α-chain), 1.40–1.48 m (1H, $H^{9'}_{exo}$), 1.53– 1.69 m (5H: $H^{11'}_{exo}$, 2CH$_2$, α-chain), 1.73 d.m (1H, H^{10}_{syn}, $^2J_{10,10}$ 9.6), 2.27–2.34 m (2H, $CH_2CO_2CH_3$), 2.40 br.d (1H, H^{11}, $^3J_{11,11'}$ 4.2), 2.41–2.49 m [2H, $CH_2C(O)$], 2.70 br.s (1H, H^9), 2.84 d.d (0.45H, $H^{14\text{-}1}_A$, $^2J_{14,14}$ 16.8, $^3J_{14,15}$ 8.6), 2.89 m (1H, H^{12}_{endo}), 2.93 d.d (0.55H, $H^{14\text{-}1}_B$, $^2J_{14,14}$ 11.9, $^3J_{14,15}$ 7.8), 3.30 d.d (0.55H, $H^{14\text{-}2}_B$, $^2J_{14,14}$ 17.7, $^3J_{14,15}$ 11.4), 3.36 d.d (0.45H, $H^{14\text{-}2}_A$), 3.42 two t.d (1H, H^8_{exo}), 3.66 s (3H, CH$_3$O), 5.51 two d.d (1H, H^{15}, $^3J_{14,15}$ 8.04, $^3J_{14,15}$ 10.44), 7.26– 7.40 m (5H, C$_6$H$_5$). Mass spectrum, [M^+]: 397.

Methyl 7-oxo-9,11-ethano-12-[5-(2-pyridyl)-4,5-dihydro-3-isoxazolyl]-2,13,14,15,16,17,18,19,20-nonanorprostanate (XVI) was obtained as viscous oily substance (yield 0.31 g, 95%). IR spectrum, cm^{-1}: 1610 (νC=N of izoxazoline), 1729 (νC=O), 1759 (νCOOCH$_3$), 2964 (ν_{as}CH$_2$), 2883 (ν_sCH$_2$), 1450 (δCH$_2$ sciss.), 1489, 1565, 1590 (νC=C arom). ^{1}H NMR spectrum, δ, ppm: 1.00–1.17 m (1H, $H^{11'}_{endo}$), 1.22–1.45 m (3H: $H^{9'}_{endo}$, $H^{9'}_{exo}$, H^{10}_{anti}), 1.45–1.78 m (6H: 1.72 d.m, 1H, H^{10}_{syn}, $^2J_{10,10}$ 11.3; $H^{11'}_{exo}$, 2CH$_2$, α-chain), 2.32 t (2H, CH_2COOCH_3), 2.41 br.d (1H, H^{11}, $^3J_{11,11'}$ 5.7), 2.46 t [2H, $CH_2C(O)$], 2.71 br.s (1H, H^9), 2.95 t.d (1H, H^8_{exo}, $^3J_{8,12}$ 4.5), 3.17 d.d (0.5H: $H^{14\text{-}1}_A$, $^2J_{14,14}$ 17.2, $^3J_{14,15}$ 7.0), 3.28–3.43 m (2H: H^{12}_{endo}, 0.5$H^{14\text{-}1}_B$, 0.5$H^{14\text{-}2}_B$), 3.43–3.62 d.d (0.5H, $H^{14\text{-}2}_A$, $^2J_{14,14}$ 16.2, $^3J_{14,15}$ 6.2), 3.68 s (3H, CH$_3$O), 5.63 two d.d (1H, H^{15}, $^3J_{14,15}$ 7.0, $^3J_{14,15}$ 11.0), 7.22 d.d (1H, Py, $H^{5'}$, $^3J_{5',4'}$ 7.5, $^3J_{5',6'}$ 4.5),

7.46 d.d (1H, Py, $H^{3'}$, $^3J_{3',4'}$ 7.5), 7.70 t.t (1H, Py, $H^{4'}$, $^3J_{4',3'}$ 7.5, $^3J_{4',5'}$ 7.5, $^4J_{4',6'}$ 2.0), 8.56 br.d (1H, Py, $H^{6'}$, $^3J_{5',6'}$ 4.5, $^4J_{4',6'}$ 2.0). Mass spectrum, [M^+]: 384.

Methyl 7-oxo-9,11-ethano-12-[5-(4-pyridyl)-4,5-dihydro-3-isoxazolyl]-2,13,14,15,16,17,18,19,20-nonanorprostanate (XVII) was obtained as viscous oily substance (yield 0.15 g, 82%). IR spectrum, cm^{-1}: 1610 (νC=N of izoxazoline), 1720 (νC=O), 1752 ($\nu COOCH_3$), 2960 ($\nu_{as}CH_2$), 2880 (ν_sCH_2), 1455 (δCH_2 sciss.), 1511, 1561 (νC=C arom). ^{1}H NMR spectrum, δ, ppm: 1.07–1.17 m (1H, $H^{11'}_{endo}$), 1.20–1.48 m (3H: $H^{9'}_{endo}$, $H^{9'}_{exo}$, H^{10}_{anti}), 1.48–1.78 m (6H: 1.74 d.m, H^{10}_{syn}, $H^{11'}_{exo}$, $2CH_2$, α-chain), 2.25 br.d (1H, H^{11}), 2.32 t (2H, $CH_2CO_2CH_3$), 2.46 t [2H, $CH_2C(O)$], 2.73 br.s (1H, H^9), 2.85 d.d (1H, H^{14}), 2.92 t.d (1H, H^8_{exo}), 3.27–3.56 s (2H, H^{12}_{endo}, H^{14}), 3.68 s (3H, CH_3O), 5.54 two br.d (1H, H^{15}, $^3J_{14,15}$ 10.7, $^3J_{14,15}$ 11.0), 7.24 br.d (2H, Py, $H^{2'}$, $^3J_{2',3'}$ 5.0), 8.60 br.d (2H, Py, $H^{3'}$, $^3J_{2',3'}$ 5.0). Mass spectrum, [M^+]: 384.

Methyl 7-oxo-9,11-ethano-12-[5-(1-imidazolyl)-4,5-dihydro-3-isoxazolyl]-2,13,14,15,16,17,18,19,20-nonanorprostanate (XVIII) was obtained as viscous oily substance (yield 0.08 g, 64%). IR spectrum, cm^{-1}: 1612 (νC=N of izoxazoline), 1708 (νC=O), 1739 ($\nu COOCH_3$), 2959 ($\nu_{as}CH_2$), 2880 (ν_sCH_2), 1455 (δCH_2 sciss.). ^{1}H NMR spectrum, δ, ppm: 1.06–1.18 m (1H, $H^{11'}_{endo}$), 1.32–1.56 m (3H: $H^{9'}_{endo}$, $H^{9'}_{exo}$, H^{10}_{anti}), 1.56–1.80 m (6H: H^{10}_{syn}, $H^{11'}_{exo}$, $2CH_2$, α-chain), 2.35 br.t (2H, $CH_2CO_2CH_3$), 2.40 two br.d (1H, H^{11}), 2.50 br.t [2H, $CH_2C(O)$], 2.67 br.s (1H, H^9), 3.01–3.22 m (2H: 3.04 br.d, 0.5H, H^{12}_{endo}, $^2J_{12,8}$ 4.7, 3.08 br.d, 0.5H, H^{12}_{endo}, 0.5H, $H^{14\text{-}1}_A$, 0.5H, $H^{14\text{-}1}_B$), 3.36 t.d (0.5H, H^8_{exo}), 3.44–3.66 m (1.5H: 3.48 t.d, 0.5H, H^8_{exo}; 3.49 d.d, 0.5H, $H^{14\text{-}2}_B$, $^3J_{14,15}$ 9.0; 3.60 d.d, 0.5H, $H^{14\text{-}2}_A$, $^2J_{14,14}$ 18.6, $^3J_{14,15}$ 9.6), 3.70 s (3H, CH_3O), 6.35 br.d (1H, H^{15}, $^3J_{15,14}$ 9.0), 6.94 br.s (1H, pyrazole, $H^{4'}$), 7.13 br.s (1H, pyrazole, $H^{5'}$), 7.62 br.s (1H, pyrazole, $H^{2'}$). Mass spectrum, [M^+]: 373.

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