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SYNTHESIS AND REDUCTIVE TRANSFORMATIONS OF ISOXALINO-PROSTANOIDS WITH AN ADDITIONAL HETEROCYCLIC FRAGMENT IN THE ω-CHAIN

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New analogs of 11-desoxyprostaglandins have been synthesised by the 1,3-dipolar cycloaddition of 2-(6-methoxycarbonylhexyl)-3-oxocyclopentanecarbonitrile oxide to alkenes – 13,15-isoxazalino-prostanoids with an additional heterocyclic unit in the ω-chain. Hydrogenolysis of the isoxazoline unit with Ra-Ni/$AlCl_3$ and conversions with the reducing agents ($NaBH_4$, $KBH(s\text{-}Bu)_3$) have been investigated.

Keywords: 11-desoxyprostanoids, 13,15-isoxazolinoprostanoids, hydrogenolysis, 1,3-dipolar cycloaddition.

One of the principle problems of the synthetic chemistry of prostaglandins is the preparation of modified analogs with more specific and long-acting effects than the natural compounds. Heteroanalogs of prostaglandins are compounds in which one of the carbon atoms of the prostane skeleton is replaced by a heteroatom, N, S, or O. Specific biological properties of prostanoids with nitrogen-containing units in the ω-chain have been noted [1,2].

In this study we have used the "isoxazole methodology" [3,4] to carry out the nitrile oxide synthesis of new 13,15*-isoxazolinoprostanoids based on a known synthon for 11-desoxyprostaglandins – 2-(6-methoxy-carbonylhexyl)cyclopent-2-en-1-one (**1**) – and vinyl derivatives of pyridine **2** and pyrrolidone **3** as dipolarophiles. Thus, adduct **4** was obtained by the conjugated 1,4-addition of nitromethane to compound **1**, the nitrile oxide **5** was formed under the influence of phenylisocyanate. Compound **5** then underwent 1,3-dipolar cycloaddition *in situ* with 2-vinylpyridine (**2**) or 1-vinylpyrrolid-3-one (**3**). The cycloadducts **6** and **7** are mixtures of isomers **a** and **b** which differ in chromatographic mobility and were separated by preparative TLC. All the spectroscopic parameters (IR, mass, ^{1}H- and ^{13}C-NMR) of both products appear to be practically identical. The pairs of cycloadducts **6a,b** and **7a,b** were therefore assigned as 15*-diastereoisomers of the isoxazilinoprostanoids, the formation of which arises from the nonstereospecific addition of the nitrile oxide to the C=C double bond of the dipolarophile.

* Here and below we have used the numbering of atoms used for prostaglandins for prostanoids and their predecessors.

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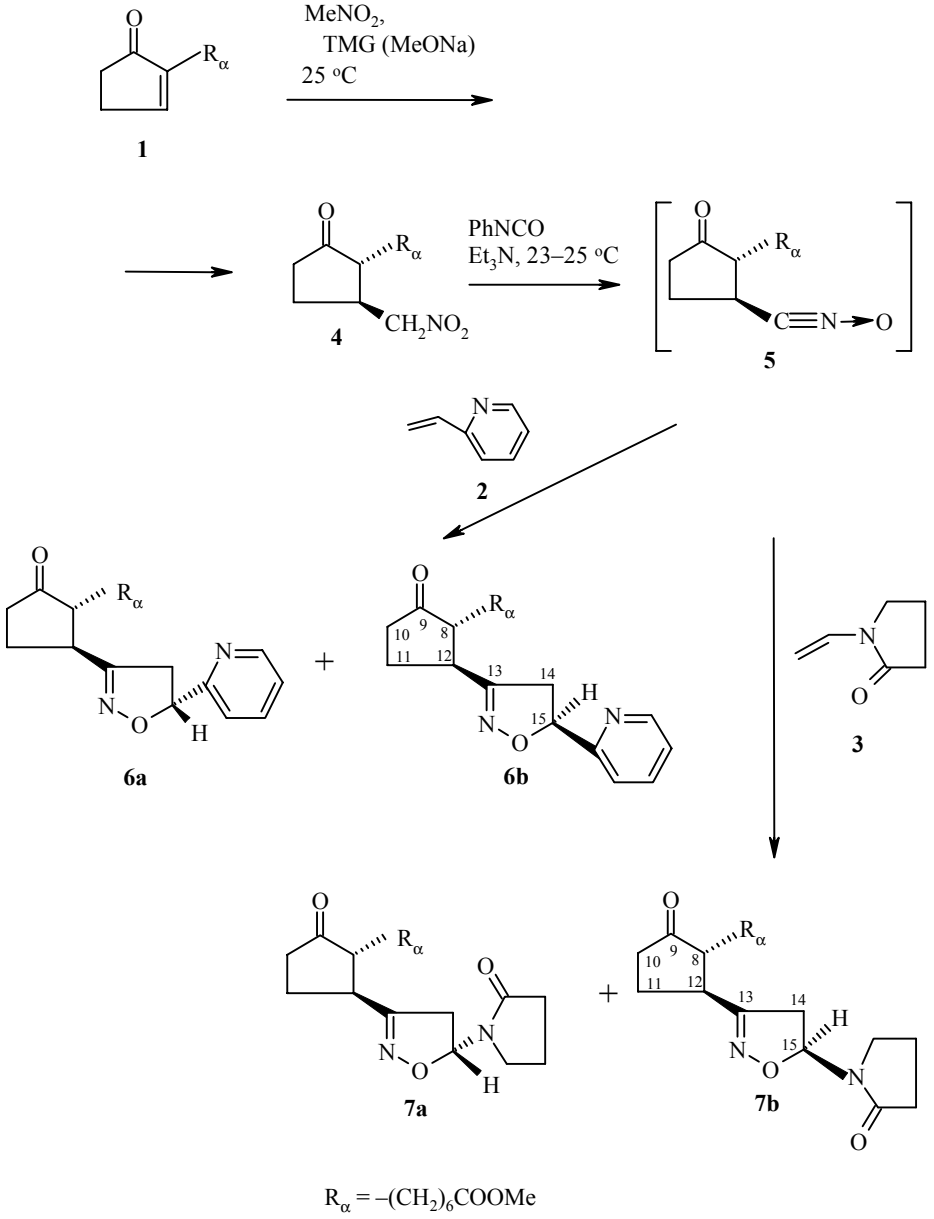

The structures of the 13,15-isoxazolinoprostanoids were confirmed from the spectroscopic data. For example, the mass spectra of the compounds prepared contain peaks corresponding to molecular ions and secondary ions expected from the proposed molecules of the cycloadducts. In the IR spectra, along with intense stretching vibrations for cyclic and ester C=O groups at 1740 cm^{-1}, a band of medium intensity was observed in the region of 1600 cm^{-1} corresponding to absorption of the C=N bond of the heterocycle. In the ^1H NMR spectrum of the diastereoisomers of the isoxazolinoprostanoids **6** there are signals of the heterocycle protons – two H-14 protons in the region of 3.3-3.5 ppm and the H-15 proton at 5.72 ppm. The considerable difference in the spectroscopic parameters of the protons H-14 and H-15 in the spectra of 2-pyridyl-substituted isoxazoline **6** and its structural isomer, the 4-pyridyl-substituted isoxazoline, which we reported earlier [6]. Thus, in the spectrum of the 4-pyridyl-substituted isoxazoline, the signals of the two H-24 protons differ by 0.6 ppm (2.92 and 3.50 ppm), whereas in compound **6** their chemical shifts are much closer (3.26 and 3.50 ppm). Proton H-15 (5.65 ppm) in the 4-pyridyl-substituted isoxazoline is more screened. Evidently these differences are connected with the differing influence of the aromatic ring of the pyridyl substituent on the electron density

distribution in the isoxazoline rings of these pyridyl-substituted isoxazolines. In compound **7** the signals of the two H-14 protons and the H-15 proton appear at 2.82, 3.18, and 6.50 ppm respectively.

The characteristic signal of H-12 in the spectra of compounds **6** and **7** appears at 3.00 ppm with coupling constant of 11.5-10.5 Hz. Similar values of $J_{8,12}$ are characteristic for the *trans*-diaxial orientation of the methyne protons in positions 8 and 12 carbocycles, which confirms the analogous nature of the mutually *trans* orientation of the α- and ω-chains of prostaglandins [7]. The signals of the protons of the methoxycarbonyl groups and the protons of the heterocyclic substituents at C-15 are also characteristic.

The 13,15-isoxazolinoprostanoids **6** and **7** are hetero-analogs of 11-desoxyprostaglandins of the E*-series with the ω-chain modified by some heteroatoms, present in two different heterocycles. Such prostanoids have the possibility of further modification by using functional groups and the latent susceptibility of the isoxazoline ring to reductive reactions.

Reduction of the keto groups of the carbocycle in compounds **6** and **7** with $NaBH_4$ and K selectride (potassium tris(*sec*-butyl)borohydride) permits formation of analogs of 11-desoxyprostaglandins of the F-series. In both cases the reaction gave 80-85% yields of the hydroxy derivatives **8** and **9** as mixtures of the 9α- and 9β-diastereomers with the composition 1:3 ($NaBH_4$) and 9:1 (K selectride).

The relative configuration of the 9-hydroxy groups of derivatives **8** and **9** was established from ^{1}H NMR spectra. We have described the principle for determining the relative configuration before [8]. Thus the triplet with $J \sim 5$ Hz at 4.28-4.32 ppm in the spectrum of the α-isomer is attributed to the pseudo-equatorial proton H-9β. Consequently the 9-OH group in the α-isomer has the α-configuration and is orientated *pseudo*-axially.

In contrast to the cyclodecomposition of (4-pyridyl)isoxazolines under the influence of K selectride which we described previously [9], cyclodecomposition products were not observed on treatment of (2-pyridyl)isoxazoline **6** with K selectride. This indicates the existence of electronic and stereochemical differences in the heterocyclic fragments of (2-pyridyl)- and (4-pyridyl)-isoxazolines which is in agreement with the different spectroscopic parameters of the heterocyclic fragments of these isomeric isoxazolines which were noted above.

Conversion of 13,15-isoxazolinoprostanoids into prostanoids with open ω-chains was carried out by reductive cleavage of the isoxazoline ring with Ra/Ni-$AlCl_3$-MeOH-H_2O [10]. As a result the hydroxy derivative **8** gave a 60-65% stereoisomeric mixture of keto diols **10**, while the enone **12** was isolated, along with the α- and β-keto diols **11**, in the case of the hydroxy derivative **9**.

The IR spectra of the keto diols **11** and **12** have characteristic OH stretches at 3400-3450 cm^{-1} and 13-C=O stretches at 1715 cm^{-1}. Characteristic stretches of the carbonyl groups of the R_ω ring and the ester group of the α-chain appear in the region 1740-1745 cm^{-1} as in the isoxazolineoprostanoid starting materials **6** and **7**.

In comparison with the isoxazolines **8, 9**, the characteristic doublet of doublets of the H-15 proton of the isoxazoline ring at 5.7 (**8**) and 6.5 ppm (**9**) is absent from the ^{1}H NMR spectrum and a characteristic signal of the H-15 (COH) at 5.24 and 5.85 ppm respectively appears, the chemical shifts of which indicate that the proton is close to the pyridine or pyrrolidinone ring. The methylene protons H-14 of the hydroxy ketone fragment appear as a multiplet at 3.02 ppm in the spectrum of compound **10**, while in the spectrum of compound **11** they appear as two signals differing by about 0.3 ppm.

Reductive cleavage of the 13,15-isoxazolinoprostanoids **6** with Ra-Ni–$AlCl_3$–MeOH–H_2O gave the diketone **13** in 70% yield. The 13,15-isoxazolinoprostanoid **7** was converted into the enone **14** in 50% yield. The corresponding diketone was not formed. The driving force for the formation of preparative amounts of the enones **12** and **14** in standard conditions for the splitting of the isoxazoline ring of the prostanoid **7** is probably the tendency to form a conjugated system including the heteroatom and keto group of the pyrrolidine ring.

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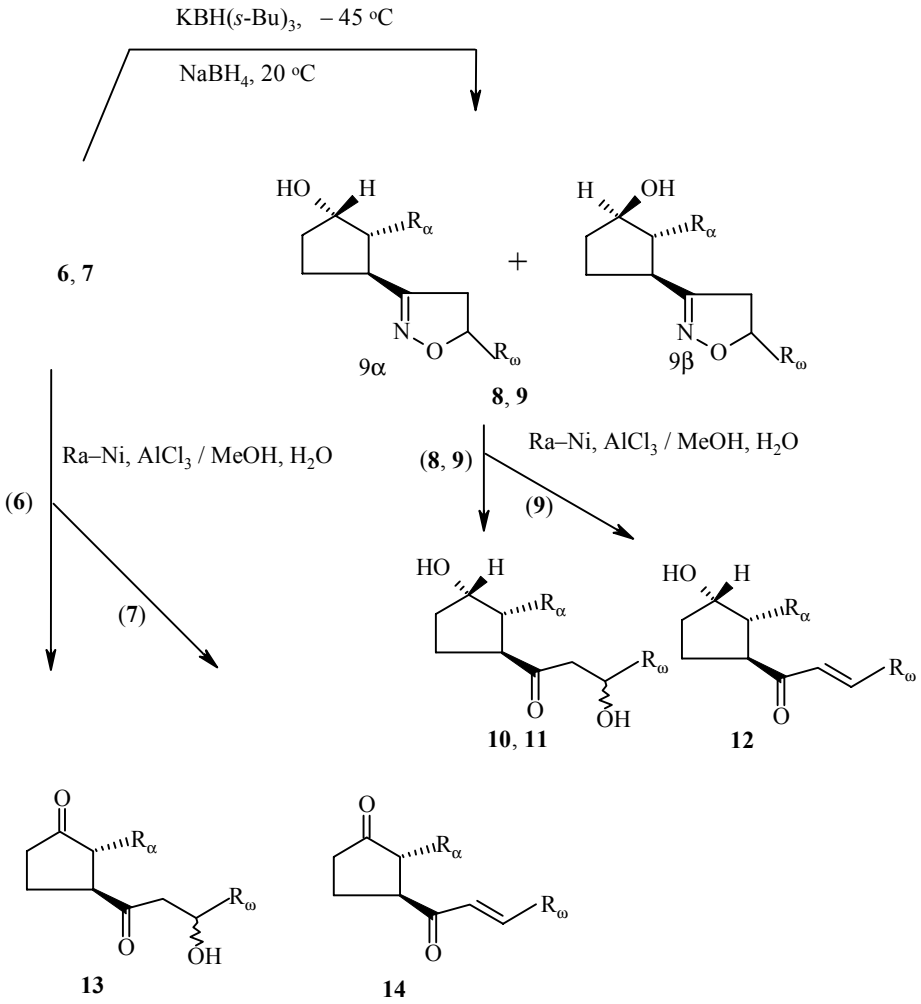
* Prostaglandins with a C=O group at C-9 of the prostane skeleton belong to the E-series, while those with an α-orientated OH groups at C-9 belong to the F-series [5].



Compounds **6-14** are analogs of 11-desoxyprostaglandins of the E- and $F_{1\alpha}$ series with modification of the smaller side chain. Data on the biological activity of the prostanoids synthesized are presented in a separate paper [11].

EXPERIMENTAL

IR spectra of films were recorded with a UR-20 spectrophotometer. ^{1}H NMR spectra of $CDCl_3$ solutions with TMS as internal standard were recorded with a Bruker AC-200 (200 MHz) spectrometer. Mass spectra were recorded with a Varian MAT-311 with an ionizing energy of 70 eV. Column chromatography was carried out on 40/100 μ silicagel (Czech), Silufol UV-254 (Serva) and Kieselgel 60 F_{254} (Merck) strips were used for TLC (85:15 chloroform:methanol, development with anisaldehyde). Preparative TLC was carried with Kieselgel L5/40 μ on glass strips (5% methanol in chloroform).

Methyl 11-Desoxy-13,15-(3',5'-isoxazolinyl)-9-oxo-15-(2'pyridyl)-16,17,18,19,20-pentanorprostanates – 2-(6-Methoxycarbonylhexyl)-3-[5-(2-pyridyl)-4-isoxazolin-3-yl]cyclopentan-1-one (6) and 11-Desoxy-13,15-(3',5'-isoxazolinyl)-9-oxo-15-(2'-oxopyrrolidin-1-yl)-16,17,18,19,20-pentanorprostanoic Acids – 2-(6-Methoxycarbonylhexyl)-3-[5-(2-oxopyrrolidin-1-yl)-4-isoxazolin-3-yl]cyclopentan-1-one (7). Phenyl-

isocyanate (3 mmol) and triethylamine (0.1 ml) were added in turn to a solution of 2-(6-methoxycarbonyl)-3-nitromethylenecyclopentan-1-one (**4**) (1 mmol) and 2-vinylpyridine (**2**) (for **6**) or 1-vinylpyrrolidin-2-one (**3**) (for **7**) (3-5 mmol) in dry benzene (15 ml) in an argon atmosphere. The stirred mixture was carefully heated to 30-35°C until it became turbid. It was then kept at this temperature for 4 h, then for 36 h at room temperature, the residue was filtered off, placed on an Al_2O_3 and washed free form diphenyl urea with a mixture of diethyl ether and hexane. The product was eluted from the column with 20% methanol in ether. If necessary it was further purified by column chromatography on silicagel (eluant, diethyl ether with a gradient of methanol) or preparative TLC. The mixture of stereo isomers (1:1) of adduct **6** (85%) were obtained as an oily liquid. IR spectrum, ν, cm^{-1}: 1740, 1605, 1565, 1440, 1412, 820. ^{1}H NMR spectrum , δ, ppm (*J*, Hz): 1.20-2.00 (12H, m, 5-CH_2 R_ω-chain, H-11); 1.84 (1H, m, H-8); 2.26 (3H, m, CH_2COOMe, H-10); 2.45 (1H, dd, H'-10); 3.0 (1H, m, *J* = 11.5, H-12); 3.36-3.44 (2H, two dd, *J* =14.4, 10, H-14); 3.63 (3H, s, OCH_3); 5.70-5.76 (1H, dd, *J* = 10, 4, H-15); 7.24 t, 7.52 d, 7.74 t, 8.58 d (4H, H pyridine). Mass spectrum, *m/z*: 372.00 $[M]^+$. Found, %: C 67.52; H 7.56; N 7.50. $C_{21}H_{28}N_2O_4$. Calculated, %: C 67.72; H 7.58; N 7.52.

Compound 7 was obtained as an oily liquid in 85% yield as a mixture of stereo isomers (1:1). IR spectrum, ν, cm^{-1}: 1640, 1710, 1750. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.40-2.00 (15H, m, 5-CH_2 R_ω chain, H-8, H-11, CH_2 (pyrrolidine)); 2.38 (4H, t, *J* = 8.0, CH_2COOMe, H-10); 2.5 (2H, t, *J* = 8.0, CH_2CO (pyrrolidine)); 2.98 (1H, m, *J* = 10.5, H-12); 3.18 m, 2.82 dd (2H, *J* = 3, 17, H-14); 3.68 (3H, s, OCH_3); 6.50 (1H, dd, *J* = 3, 10, H-15); 3.34 (2H, m, NCH_2 (pyrrolidine)). Mass spectrum, *m/z*: 378.00 $[M]^+$. Found, %: C 63.69; H 8.01; N 7.38. $C_{20}H_{39}N_2O_5$. Calculated, %: C 63.47; H 7.99; N 7.40.

Methyl 11-Desoxy-9α-hydroxy-13,15-(3',5'-isoxazolinyl)-15-(2'-pyridyl)-16,17,18,19,20-pentanorprostanates – 1α-Hydroxy-2-(6-methoxycarbonylhexyl)-3-[5-(2-pyridyl)isoxazolinyl]cyclopentane (8) was prepared as an oil with a yield up to 75%. A solution of compound **6** (0.5 mmol) in THF (20 ml, freshly distilled from $LiAlH_4$) was placed in a flask heate in a stream of argon. The mixture was cooled to -45°C and K selectride (2.5 mmol as a 1 M solution in hexane (Aldrich)) was added to the stirred solution with a syringe. Stirring at -45°C was continued for 4 h, then at a temperature from -20 to -5°C 30% H_2O_2 (1 ml) and 5M KOH (0.5 ml) were added, stirring was continued for 10 min, then water (5 ml) was added at 0 to +5°C. The excess H_2O_2 was destroyed by addition of a small amount of manganese dioxide. The aqueous suspension was extracted with diethyl ether and the extract was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on a column or on a strip with silicagel, elution was with a methanol–chloroform mixture. IR spectrum, ν, cm^{-1}: 1475, 1580, 1600, 1750, 3450. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.20-2.00 (14H, m 5-CH_2 R_ω-chain, H-10, H-11); 2.12 (1H, m, H-8); 2.26 (2H, m, $\underline{CH_2}COOMe$); 2.90 (1H, q, *J* = 9.5, H-12); 3.14-3.54 (2H, m, H-14); 3.68 (3H, s, OCH_3); 4.28 (1H, t, *J* = 3.5, H-9); 5.70 (1H, dd, *J* = 6.0, 11.0, H-15); 7.24 t, 7.52 d, 7.74 t, 8.58 d (4H, H pyrid). Mass spectrum, *m/z*: 374.00 $[M]^+$. Found, %: C 67.17; H 8.10; N 7.50. $C_{21}H_{30}N_2O_4$. Calculated, %: C 67.36; H 8.07; N 7.48.

Methyl 11-Desoxy-9-α-hydroxy-13,15-(3',5'-isoxazolinyl)-15-(2'-oxopyrrolidinyl-1')-16,17,18,19,20-pentanorprostanates – 1-α-Hydroxy-2-(6-methoxycarbonylhexyl)-3-[5-(2-oxopyrrolidin-1-yl)-isoxazolinyl]-cyclopentane (9) was made analogously to compound **8** in 70% yield. IR spectrum, ν, cm^{-1}: 1690, 1710, 1750, 3450. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.40-2.00 (16H, m, 5-CH_2 R_α-chain, H-10, H-11, CH_2 (pyrrolidine)); 2.16 (1H, m, H-8); 2.38 (2H, t, *J* =8.0, $\underline{CH_2}COOMe$); 2.50 (2H, t, *J* = 8.0, CH_2CO (pyrrolidine)); 2.88 (1H, q, *J* = 10.8, H-12); 3.16 m, 2.66 dt, 2.76 dt (2H, *J* = 3.0, 17.0, H-14); 3.68 (3H, s, OCH_3); 4.32 (1H, t, *J* = 3.5, H-9 at OH); 6.50 (1H, dd, *J* = 3.0, 10, H-15); 3.16 m, 3.34 m (2H, NCH_2 (pyrrolidine)). Mass spectrum, *m/z*: 380.00 $[M]^+$. Found, %: C 63.30; H8.46; N 7.39. $C_{20}H_{32}N_2O_5$. Calculated, %: C 63.14; H8.48; N 7.36.

Methyl 9α,11-Desoxy-15-dihydroxy-13-oxo-15-(2'-pyridyl)-16,17,18,19,20-pentanorprostanates – 1α-hydroxy-3-(3hydroxy-[1-oxo-3-(2-pyridyl)propyl]-2-(6-methoxycarbonylhexyl)cyclopentane (10). Raney nickel (0.60 g), then $AlCl_3$ (0.10 g), and water (2 ml) were added to a solution of compound **8** (0.54 mmol) in methanol (10 ml). The mixture was stirred for 12-24 h until the starting material had disappeared (monitored by TLC). The mixture was then filtered through a layer of silica gel, evaporated, diluted with water

and extracted with diethyl ether. The extract was dried over Na_2SO_4, the solvent was evaporated, and the residue was chromatographed one silicagel column with elution by a methanol–chloroform mixture. Yield of product 55-65%. IR spectrum, ν, cm^{-1}: 1580, 1605, 1715, 1745, 3450. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.20-2.00 (1H, m, 5-CH_2 R_ω chain, H-10, H-11); 2.12 (1H, m, H-8); 2.26 (2H, m, CH_2COOMe); 2.84 (1H, m, H-12); 3.02 (2H, m, H-14); 3.68 (3H, s, OCH_3); 4.28 (1H, t, H-9 at OH); 5.24 (1H, m, H-15); 7.24 t, 7.52 d, 7.74 t, and 8.58 d (4H, pyrid.). Mass spectrum, *m/z*: 377.00 $[M]^+$. Found, %: C 66.70; H 9.29; N 3.70. $C_{21}H_{31}NO_5$. Calculated, %: C 66.82; H 8.28; N 3.71.

Methyl 9α-11-Desoxy-15-dihydroxy-13-oxo-15-(2'-oxopyrrolidyl-1')-16,17,18,19,20-pentanorprostanates – 1α-Hydroxy-3-[3-hydroxy-1-oxo-3-(2-oxopyrrolidin-1-yl)propyl]-2-(6'-methoxycarbonylhexyl)cyclopentane (11) was prepared as an oil in 20% yield from compound **9** analogously to compound **10**. IR spectrum, ν, cm^{-1}: 1500, 1685, 1715, 1740, 3400. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.40-2.00 (17H, m, 5-CH_2 R_ω-chain, H-8, H-10, H-11, CH_2 (pyrrolidine)); 2.38 (2H, t, *J* = 8.0, CH_2COOMe); 2.50 (2H, t, *J* = 8.0, CH_2CO (pyrrolidine)); 2.90 (1H, m, H-12); 2.76 m and 3.03 m (2H, H-14); 3.16 m and 3.34 m (2H, NCH_2 (pyrrolidine)); 3.68 (3H, s, OCH_3); 4.28 (1H, t, *J* = 3.5, H-9 at OH); 5.85 (1H, m, H-15). Mass spectrum, *m/z:* 383.00 $[M]^+$. Found, %: C 62.80; H 8.70; N 3.64. $C_{20}H_{33}NO_6$. Calculated, %: C 62.64; H 8.67; N 3.65.

Methyl 11-Desoxy-9α-hydroxy-13-oxo-14-en-15-(2'-oxopyrrolidyl-1')-16,17,18,19,20-pentanorprostanates – 1α-Hydroxy-2-(6-methoxycarbonylhexyl)-3-[1-oxo-3-(2-oxopyrrolodin-1-yl)propen-2-yl]-cyclopentane (12) was obtained as an oil in 70% yield analogously to compound **11**. IR spectrum, ν, cm^{-1}: 1660, 1630, 1690, 1750, 3475. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.40-2.00 (15H, m, 5-CH_2 R_ω-chain, H-8, H-10, H-11, CH_2 (pyrrolidine)); 2.38 (2H, t, *J* = 8.0, CH_2COOMe); 2.50 (2H, t, *J* = 8.0, CH_2CO (pyrrolidine)) 3.12 (1H, m H-12); 3.68 (3H, s, OCH_3); 4.32 (1H, t, *J* = 3.5, H-9); 5.58 (1H, d, *J* = 14.5, H-14); 8.04 (1H, d, *J* = 14.5, H-15); 3.16 m and 3.34 m (2H, NCH_2 (pyrrolidine)). Mass spectrum, *m/z*: 365.00 $[M]^+$. Found, %: C 65.87; H 8.54; N 3.85. $C_{20}H31NO_5$. Calculated, %: C 65.73; H 8.55; N 3.83.

Methyl 11-Desoxy-15-hydroxy-9,13-dioxo-15-(2-pyridyl)-16,17,18,19,20-pentanorprostanates – 3-[3-Hydroxy-1-oxo-3-(2-pyridyl)propyl]-2-(6-methoxycarbonylhexyl)cyclopentan-1-one (13) was obtained analogously to compound **10** from compound **6** as an oil in 65-70% yield. IR spectrum, ν, cm^{-1}: 1580, 1605, 1715, 1750, 3450. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.20-2.00 (13H, m, 5-CH_2 R_ω-chain, H-8, H-11); 2.26 (4H, m, CH_2COOMe, H-10); 3.02 (1H, m, H-12); 3.12 (2H, dd, H-14); 3.68 (3H, s, OCH_3); 5.26 (1H, m, H-15); 7.24 t, 7.52 d, 7.74 t, and 8.58 d (4H, H pyrid.). Mass spectrum, *m/z*: 375.00 $[M]^+$. Found, %: C 67.00; H 7.76; N 3.74. $C_{21}H_{29}NO_5$. Calculated, %: C 67.18; H 7.78; N 3.73.

Methyl 11-Desoxy-14-en-9,13-dioxo-15-(2'-oxopyrrolidyl-1')-16,17,18,19,20-pentanorprostanate – 2-(6-methoxycarbonylhexyl)-3-[1-oxo-3-(2-oxopyrrolidin-1-yl)propen-2-yl]cyclopentan-1-one (14) was obtained analogously to compound **10** from compound **7** as an oil in 70% yield. IR spectrum, ν, cm^{-1}: 1600, 1630, 1690, 1750. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.40-2.00 (15H, m 5-CH_2 R_ω-chain, H-8, H-11, CH_2 pyrrolidin.); 2.38 (4H, t, *J* = 8.0, CH_2COOMe, H-10); 2.50 (2H, t, *J* = 8.0, CH_2C (pyrrolidine)) 3.24 (1H, m, *J* = 11.0, H-12); 3.68 (3H, s, OCH_3); 5.64 (1H, d, *J* = 14.5, H-14); 8.14 (1H, d, *J* = 14.5, H-15); 3.60 (2H, t, NCH_2 pyrrolidin.). Mass spectrum, *m/z*: 363.00 $[M]^+$. Found, %: C 65.89; H 8.06; N 3.84. $C_{20}H_{29}NO_5$. Calculated, %: C 66.09; H 8.04; N 3.85.

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