FUNCTIONALIZATION OF THE ω-CHAIN OF PROSTANOIDS BY THE SELECTIVE OPENING OF THE HETEROCYCLE IN 3-ISOXAZOLYLCYCLOPENTANONE DERIVATIVES

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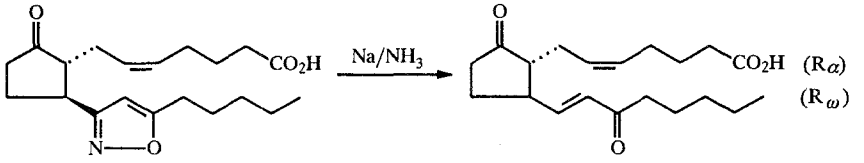
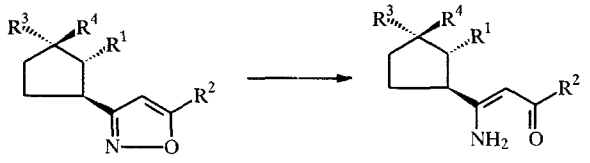
The reaction of reducing agents with functionalized isoxazole derivatives has been studied; 13-amino-15-ketoprostanoids have been synthesized.

Isoxazoles are being widely used in the construction of the carbon skeleton of organic compounds of different classes [1]. Thus, prostanoids are obtained from 3-isoxazole-substituted cyclopentanones, the heterocycle of which represents a latent bifunctional fragment of the prostanoid ω-chain to be constructed.



The 3-isoxazole-substituted cyclopentanones (I-X), described in [2, 3], were used in the present study for the synthesis of new analogs of prostaglandines, containing in the ω-chain an enaminoketone fragment, which can be obtained by the reducing splitting of the isoxazole ring in these compounds. The achievement of this conversion is related to the choice of selective reagents, which, by splitting the heterocycle, would not lose the ability of reducing the double bond and the carboxyl group in the α-chain.



I—X XI—XXIII

I, III, V, XIV, XVI, XXII R^1=$CH_2CH{=}CMe_2$; II, VII, X, XIII, XXIII R^1=$CH_2CH{=}CH(CH_2)_3COOMe$; IV, VIII R^1=$(CH_2)_3CH{=}CH(CH_2)_2COOMe$; VI, XVII R^1=CH_2CHO; IX, XII, XVIII, XIX, XXI R^1= =$(CH_2)_6COOMe$; XI R^1=$CH_2CH_2CHMe_2$; XV, XX R^1=$(CH_2)_7COOMe$; I, IX, XI, XXI, XXII R^2=Ph; II, IV—VIII, X, XII, XIII, XV—XX, XXIII R^2=C_5H_{11};III, XIV R^2=CH_2OH; I, II, IV, IX, XI—XIII, XV R^3=R^4=O;III, V, VII, XIV, XVI, XVIII R^3=β-OH, R^4=α-H; VI, VIII, X, XVII, XIX—XXIII R^3=α-OH, R^4=β-H

The reductive splitting of the simplest isoxazoles to enaminoketones by metals in acetic acid and catalytic hydrogenation, used successfully in [4], achieved little success in the given instance, due to the stability of the investigated isoxazole derivatives toward these reagents. Thus, mild hydrogenolysis of isoxazoles I and II (hydrogenation over 5% $Pd/BaSO_4$ in ethanol, reduction by iron in acetic acid) does not lead to opening of the heterocycle, while hydrogenation of compound I over 30% $Pd/BaSO_4$ for 48 h gives the enaminoketone XI with a yield of 8%.

The hydrogenation of compound II over Raney nickel in ethanol at the usual conditions leads to the formation of a mixture of enaminoketones with a reduced (XII) and unreduced (XIII) double bond in the α-chain in the ratio 1:1 and with a total yield of 83%; the mixture is difficult to separate by chromatography.

The presence of an enaminoketone fragment in the products of the reducing splitting of isoxazoles XI-XIII is confirmed by their physicochemical characteristics (Table 1). The IR spectra of the enaminoketones XI-XIII contain two strong bands at 1615 and 1530 cm^{-1}, which correspond to the stretching vibrations of the C=O— and C=C groups, and to the deformation vibrations of the NH fragment of the conjugated β-aminoenone, and bands of the stretching vibrations of the amino group at

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TABLE 1. Physicochemical Characteristics of 13-Amino-15-Ketoprostanoids (XI-XXIII)

Compound	IR spectrum	PMR spectrum, δ, ppm (J, Hz)	M^+	Yield, %
XI	1530, 1615, 1740, 3190, 3420	0,9 (6H, dd, Me); 1,1...2,6 (11H, m); 5,35 10,45 (2H, 2 br.s, NH); 5,87 (1H, s, HC=); 7,44& 7,85 (5H, m, Ph)	299	8
XII	1530, 1615, 1740, 3195, 3420	0,9 (3H, t, Me); 1,33, 1,6, 1,8...2,5 (26H, m, CH_2, CH); 3,69 (3H, s, OMe); 5,07 (1H, s, HC=); 5,5& 9,9 (2H, br. s, NH_2)	365	83
XIII	1530, 1620, 1740, 3195, 3420	0,9 (3H, t, Me); 1,31...2,5 (24H, CH_2, CH); 3,68 (3H, s, OMe); 5,12 (1H, s, HC=); 5,39 (2H, m, HC=CH); 6,0and 9,9 (2H, br.s, NH_2)	363	
XIV	1530, 1605, 3190, 3400	1,57& 1,66 (6H, s, Me); 1,88 (8H, m, CH_2, CH); 3,5 (2H, br.s OH); 4,08 (3H, m, CH_2OH, CHOH); 4,96 (1H, s, HC=); 5,1 (1H, t, HC=CMe_2); 6,5& 9,4 (2H, br.s, NH_2)	253	58
XV	1525, 1620, 1740, 3190, 3420	0,9 (3H, t, Me); 1,27...2,5 (28H, m, CH, CH_2); 3,69 (3H, s, OMe); 5,13 (1H, s, HC=); 5,35 & 9,90 (2H, br.s, NH)	379	60
XVI	1530, 1615, 3190, 3370	0,9 (3H, t, Me); 1,32...2,2 (17H, m, CH_2, CH); 2,37 (1H, dt, J=10,8 & 8,4, 3-H ring); 4,35 (1H, t, J=4,2, HCOH); 5,12 (1H, s, HC=); 5,2 (1H, t, HC=CMe_2); 6,22 (1H, s, NH); 9,9 (2H, br.s, NH, OH)	293	80
XVII	1530, 1615, 3200, 3370	0,9 (3H, t, Me); 1,31...2,1 (11H, m, CH_2, CH); 2,3 (2H, t, CH_2COO); 2,6 (2H, m, CH_2COH); 2,8 (1H, m, HC—CNH_2); 4,69 (1H, HC—O—C); 4,95 (1H, br.s, NH); 5,02 (1H, s, HC=); 5,1 (1H, m, HCOH); 6,0 (1H, br.s, OH); 9,89 (1H, br.s, NH)	267	98
XVIII+ XIX	1530, 1615, 1735, 3200, 3420	0,88 (3H, t, Me); 1,3...2,1 (24H, m, CH_2, CH); 2,25 (2H, m CH_2COO); 3,6 (3H, s, OMe); 3,95 (1H, m, H—COH)*; 4,2 (1H, t, H—COH)**; 5,07 (1H, s, HC=); 5,79& 9,7 (2H, br.s, NH_2)	367	55
XX	1530, 1615, 1735, 3210, 3400	0,88 (3H, t, Me); 1,27...2,45 (28H, m, CH_2, CH); 3,62 (3H, s, OMe); 4,27 (1H, t, H—COH); 5,13 (1H s, HC=); 5,8 & 9,9 (2H, br.s, NH)	381	80
XXI	1530, 1610, 1740, 3185, 3410	1,33...2,06 (15H, m, CH_2, CH); 2,26 (2H, t, CH_2COO); 2,48 (1H, d.t, J=10,8& 8,4, $HCCNH_2$); 3,44 (3H, s, OMe); 4,11 (1H, m, α-H—COH); 4,37 (1H, t, J=4, β-H—COH); 5,37 (1H, br.s, NH); 5,85 (1H, s, HC=); 7,4 & 7,9 (5H, m, Ph); 10,41 (1H, br.s, NH)	373	30
XXII	1530, 1605, 3180, 3410	1,64& 1,68 (6H, s, Me); 1,7...2,3 (7H, m, CH_2, CH); 2,53 (1H, d.t, J=10,8 & 8,4, HC—CNH_2); 4,35 (1H, t, J=4,2, H—COH); 5,2 (1H, t, HC=CMe_2); 5,8 (1H, s, HC=); 7,46 & 7,9 (5H, m, Ph); 5,4 & 10,4 (2H, br.s, NH_2)	299	30
XXIII	1530, 1630, 3190, 3420	0,89 (3H, t, Me); 1,29...2,32 (21H, m, CH_2, CH); 2,36 (1H, d.t, J=10,8 & 8,4 HC—CNH_2); 3,64 (3H, s, OMe); 4,24 (1H, t, J=4,2, HC—OH); 5,05 (1H, s, HC=); 5,16 & 9,9 (2H, br.s, NH_2); 5,36 (2H, m, HC=CH)	365	74

*Compound XVIII.

**Compound XIX.

3180-3190 and 3400-3420 cm^{-1}. The PMR spectra show singlet signals of the olefinic proton at 4.96-5.87 ppm and of the protons (free and combined) of the amino group at 5.3-6.5 and 9.4-10.45 ppm.

The hydrogenation of the isoxazole III (with Raney nickel in ethanol) to the enaminoketone XIV is not accompanied by the reduction of the double bond in the α-chain; this is evidently due to steric hindrance, created by the gem-dimethyl grouping.

For the splitting of isoxazoles we have also used methods for the reduction with Raney nickel in the presence of acids, described in [5, 6]. Formation of the corresponding diketone is not taking place, which is characteristic for these methods of ring opening, where the initially formed enaminoketone can be subjected to acid hydrolysis. Thus, the isoxazole IV gives the enaminoketone XV with a reduced double bond in the α-chain. It had been established earlier in [9] that the corresponding enaminoketones are obtained with a preparative yield when the isoxazoles in methanol solution, containing nickel sulfate, are treated at −30°C with sodium borohydride. The reaction is generally applicable to isoxazole derivatives; it proceeds rapidly and is simple to carry out; it makes it possible to carry out a selective hydrogenolysis of isoxazole derivatives, containing substituents which are susceptible to reduction. By this method we have achieved the hydrogenolysis of isoxazoleprostanoids II, V-VIII. The splitting of the isoxazoles V and VI proceeds chemiselectively with the formation of the enaminoketones XVI and XVII.

In the reducing opening of the heterocycle in compounds VII and VIII the carboxyl group is not reduced; however, the double bond in the α-chain is not preserved and the enaminoketones XVIII and XX are formed. In the hydrogenolysis of compound II to the enaminoketone XIX the cyclic carbonyl group is reduced with 90% α-stereoselectivity.

The relative configuration of the hydroxyl group was determined from the PMR spectrum by using the general rules for the parameters of the prostanoid spectra. Of the two signals of the cyclic carbinol proton the triplet signal with 4.27-4.35 ppm was assigned to the pseudoequatorial β-proton H-COH of the enaminoketone isomer with an α-oriented hydroxyl group, and the multiplet signal at 3.95-4.15 ppm to the α-proton of the isomer with the β-oriented hydroxyl group. Thus, for example, the ratio of isomeric enaminoketones XII, by PMR spectral data, α-OH: β-OH = 4.1. From the formation of isoxazole I, the main product forms stereoisomer enaminoketone XII with the α-oriented hydroxyl group.

By using the procedure, recommended for the splitting of isoxazoles to aminoalcohols [11] (Raney nickel in caustic), we obtained enaminoketones from the isoxazoles. Thus, by heating a methanol solution of isoxazoles I and IX with alkali and Raney nickel, the isoxazole ring is opened with the formation of the enaminoketones XXI and XXII. The reduction of the cyclic carbonyl group in the cyclopentanone derivatives is stereoselective and proceeds with the predominant formation of the isomer with the α-oriented hydroxyl group. Thus, for example the ratio of isomeric enaminoketones XII, by PMR spectral data, α-OH: β-OH = 4: 1. From the formation of isoxazole I, the main product forms, stereoisomer enaminoketone XII with the α-oriented hydroxyl group.

Of all the reagents for the reductive splitting of the oxazole ring studied molybdenum hexacarbonyl $Mo(CO)_6$ [12] is the most selective; it opens the heterocycle with a yield of up to 80% in polyfunctional isoxazole derivatives, which contain unsaturated bonds, sensitive toward reducing agents, carbonyl, and carboxyl functions.

Thus, refluxing of the isoxazole II in aqueous acetonitrile in the presence of catalytic amounts of $Mo(CO)_6$ gives with a yield of 80% the enaminoketone XIII, an analog of 11-desoxy-PGE_2. By the same method one obtains from the isoxazole X with a yield of 74% 11-desoxy-13-amino-15-dehydro-$PGF_{2\alpha}$ (XXIII), the structure of which has been confirmed by IR and PMR data, and mass spectra.

EXPERIMENTAL

The IR spectra were taken from a film or in CCl_4 solution on an UR-20 spectrophotometer. The PMR spectra were obtained on a Bruker WP-360 (360 MHz) spectrometer in $CDCl_3$ solution, with tetramethylsilane (TMS) as internal standard. The molecular masses were determined by mass spectrometry on a Varian MAT-311 spectrometer at an ionizing radiation of 70 eV. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 foils. The reaction products were separated and purified by column chromatography or preparative TLC on Kieselgel 60 F_{254} silica gel.

2α-Isopentyl-3β-(1-amino-3-oxo-3-phenylprop-2-en-1-yl)cyclopentan-1-one (XI, $C_{19}H_{25}NO_2$). Isoxazole I (227 mg, 0.93 mmole) in 20 ml ethanol is hydrogenated at 20°C and atmospheric pressure in the presence of 140 mg 30% $Pd/BaSO_4$ for 48 h. The catalyst is filtered off and the filtrate evaporated. Purification by preparative TLC gave 22 mg (8%) enaminoketone XI.

2α-(6-Methoxycarbonylhexyl)-3β-(1-amino-3-oxooct-1-enyl)cyclopentan-1-one (XII, $C_{21}H_{35}NO_4$) and 2α-[6-Methoxycarbonylhex(2,3)enyl]-3β-(1-amino-3-oxooct-1-enyl)cyclopentan-1-one (XIII, $C_{21}H_{33}NO_4$). Isoxazole II (90 mg, 0.25 mmole) in 10 ml ethanol is hydrogenated at 20°C and atmospheric pressure for 8 h in the presence of 80 mg Raney nickel. The catalyst is filtered off and the filtrate evaporated. The products are isolated by column chromatography on silica gel using gradient elution with the system hexane—ether. Yield 75 mg (83%) of a mixture of enaminoketones XII and XIII in the form of an oil.

2α-(Isopent-2-enyl)-3β-(1-amino-3-oxo-4-hydroxybuten-1-yl)cyclopentan-1β-ol (XIV, $C_{18}H_{29}NO_2$) is obtained in the same way from 60 mg isoxazole III with a yield of 35 mg (58%).

2α-(7-Methoxycarbonylheptyl)-3β-(1-amino-3-oxooct-1-enyl)cyclopentan-1-one (XV, $C_{22}H_{37}NO_4$). A solution of 60 mg (0.17 mmole) isoxazole IV in 10 ml methanol is treated with 100 mg $AlCl_3$ in 2 ml water, then with 600 mg Raney nickel and stirred for 4 h. The mixture is filtered through a layer of silica gel, evaporated, and diluted with water by a factor of 10. The solution is extracted with ether (3 × 50 ml), the extract is dried with Na_2SO_4 and the solvent evaporated. The residue is chromatographed on a column packed with silica gel, by eluting with a mixture of ether—hexane (1:4). The enaminoketone XV is obtained in the form of an oil with a yield of 48 mg (80%).

The hydrogenolysis of isoxazoles II, V-VIII with sodium borohydride in the presence of nickel salts is carried out by the procedure given in [9].

2α-(6-Methoxycarbonylhexyl)-3β-(1-amino-3-oxooct-1-enyl)cyclopentan-1α-ol (XIX) and -1β-ol (XVIII, $C_{21}H_{37}NO_4$) are obtained from isoxazoles II and VII, respectively.

1-Oxa-2-hydroxy-4-(1-amino-3-oxooct-1-enyl)bicyclo-[3,3,0]octane* **(XVII, $C_{15}H_{25}NO_3$)** is obtained from isoxazole VI.

2α-(Isopent-2-enyl)-3β-(1-amino-3-oxooct-1-enyl)cyclopentan-1α-ol (XVI, $C_{18}H_{31}NO_2$) and 2α-(7-methoxycarbonylheptyl)-3α-(1-amino-3-oxooct-1-enyl)cyclopentan-1α-ol (XX, $C_{22}H_{39}NO_4$) are obtained from isoxazoles V and VIII, respectively.

2α-(Isopent-2-enyl)-3β-(1-amino-3-oxo-3-phenylprop-1-enyl)cyclopentan-1α-ol (XXII, $C_{19}H_{25}NO_2$). A solution of 160 mg (0.54 mmole) of isoxazole I in 15 ml methanol is treated with 1 g Raney nickel powder; the solution is heated to 40°C, treated with 5 ml 1 M KOH, and stirred at 55-60°C for 2 h. The solution is filtered, the methanol evaporated, and the aqueous fraction extracted with ether (3 × 100 ml); the extract is dried, evaporated, and the residue chromatographed on a plate with silica gel with ether—hexane (4:1) as the eluent. The yield was 52 mg (30%) of the enaminoketone XXII in the form of an oil.

2α-(Methoxycarbonylhexyl)-3β-(1-amino-3-oxo-3-phenyl-prop-1-enyl)cyclopentan-1α- and -1β- ols (XXI, $C_{22}H_{31}NO_4$) as a mixture of isomers with respect to the $C_{(1)}$ atom are obtained in the same way from 180 mg (0.47 mmole) isoxazole IX, followed by treatment with diazamethane. Yield 55 mg (30%).

Enaminoketone XIII and 2α-[6-Methoxycarbonylhex(2,3)-enyl]-3β-(1-amino-3-oxooct-1-enyl)cyclopentan-1α-ol (XXIII, $C_{21}H_{35}NO_4$). The solution of 1 mmole isoxazole II or X in 20 ml acetonitrile is treated with 1 mmole water and 0.5 mmole molybdenum hexacarbonyl; the solution is refluxed for 8-24 h by checking the progress of the reaction by TLC. The mixture is diluted with hexane, filtered through Celite-545, and evaporated. The residue is chromatographed on a silica gel column by eluting the reaction product with ether. The enaminoketones XIII and XXIII, respectively, are obtained in the form of oils.

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*The name given is for the cyclic form of the compound.