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Synthesis and Reductive Transformations of 11-Deoxyprostanoids with a 4,5,6,6a-Tetrahydro-3a*H*-cyclopenta[*d*]isoxazole Fragment in the ω-Chain

E. V. Koroleva, Ya. M. Katok, and F. A. Lakhvich

Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, ul. Akademika Kuprevicha 5/2, Minsk, 220141 Belarus
e-mail: evk@ns.iboch.ac.by

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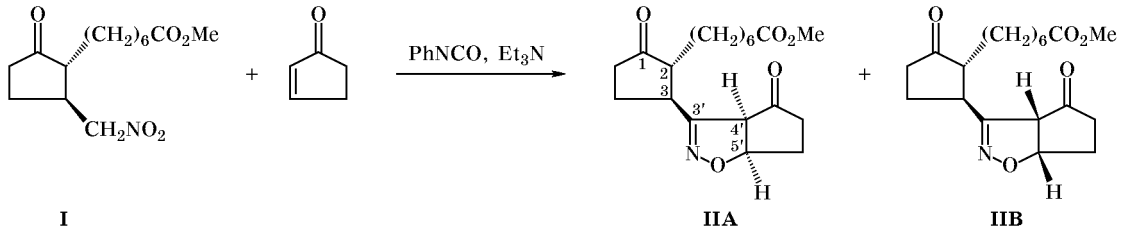
Abstract—A new prostanoid precursor with a 4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole fragment in the ω-chain was synthesized using the nitrile oxide technique. Its reduction afforded new 11-deoxyprostanoids with modified α- and ω-chains.

In continuation of our studies on the synthesis of modified prostaglandins (PG) by the nitrile oxide technique [1], we have obtained 3-[3-oxo-2-(6-methoxycarbonylhexyl)cyclopentyl]-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazol-4-one (**II**) from 2-(6-methoxycarbonylhexyl)-2-cyclopentenone which is a known synthon for 11-deoxyprostanoids. Compound **II** is the 1,3-dipolar cycloaddition product of nitrile oxide, generated *in situ* from 2-(6-methoxycarbonylhexyl)-3-nitromethylcyclopentanone (**I**), to 2-cyclopentenone. The cycloaddition is regioselective, and it yields a mixture of diastereoisomers **IIA** and **IIB** (1:1) differing by configuration of the asymmetric centers C^4 and C^5 (Scheme 1). Isomers **IIA** and **IIB** were separated by preparative thin-layer chromatography.

On the one hand, isoxazole derivatives **II** can be regarded as modified prostaglandins containing the natural α-chain and bicyclic cyclopentaisoxazole fragment in the ω-chain. According to published data, cycloalkyl groups as modifying units in PG molecules increase their stability in biological media and endow them with a specific prostanoid biological activity [2]. On the other hand, compound **II** can be used as convenient starting material for synthesis of other modified PG derivatives via reductive transformations of functional groups and isoxazole ring which possesses a latent functionality. In the present communication we report on reductive transformations of cyclopentaisoxazole **II** which were effected with the goal of obtaining a series of new modified 11-deoxyprostaglandins.

As starting compounds we used both isomeric mixture **IIA**/**IIB** and pure isomers **IIA** and **IIB**. Treatment of diastereoisomers **IIA** and **IIB** with potassium tris(*s*-butyl)hydridoborate (K-Selectride) [3]) at –45°C resulted in stereoselective reduction of one or two carbonyl groups to give, respectively, monohydroxy derivatives **IIIA** and **IIIB** or diols **IVA** and **IVB** in an overall yield of 80–95% (Scheme 2). The structure of hydroxy derivatives **III** and **IV** was confitmed by spectral data. Their IR spectra contained absorption bands from hydroxy groups in the region 3450–3500 cm^{-1}. In the ^1H NMR spectra we observed one

Scheme 1.



I **IIA** **IIB**

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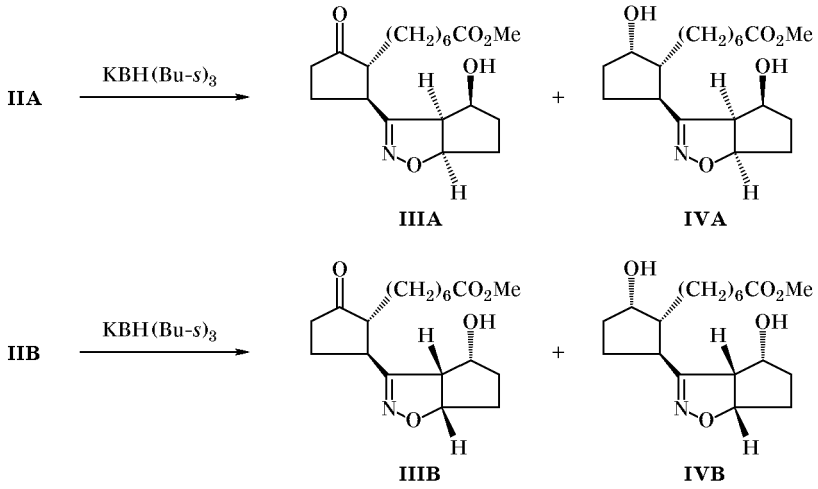
Scheme 2.

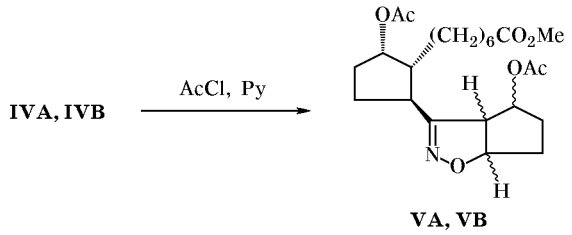


(compound **III**) or two (**IV**) one-proton signals from the OH protons in the region δ 4.30–4.45 ppm. These signals provide information on the selectivity of the reduction process. The signal at 4.30 ppm, which is present only in the ^{1}H NMR spectra of compounds **IV**, is a triplet with J = 3.0–3.5 Hz, indicating pseudo-equatorial orientation and β-configuration of the **H**–C–OH proton in the cyclopentane fragment (α-configuration of the hydroxy group; the procedure for determination of relative configuration was described by us in [4]).

Both mono- and dihydroxy derivatives **III** and **IV** show in the ^{1}H NMR spectra a signal at δ 4.40–4.45 ppm as a doublet of doublets (or quadruplet of doublets); J = 11.8, 8.5, 2.5 Hz. These parameters suggest pseudoaxial orientation and relative β-configuration of the **H**C–OH proton in the bicyclic fragment (ω-chain), in keeping with the data of [5]. The signals from the 4′-H, 5′-H, and 3-H protons of hydroxy derivatives **IV**, which are located in the α-positions with respect to the C–O and C=N bonds, are observed in a stronger field (by 0.2 ppm; see table) than the corresponding signals from compounds **II**.

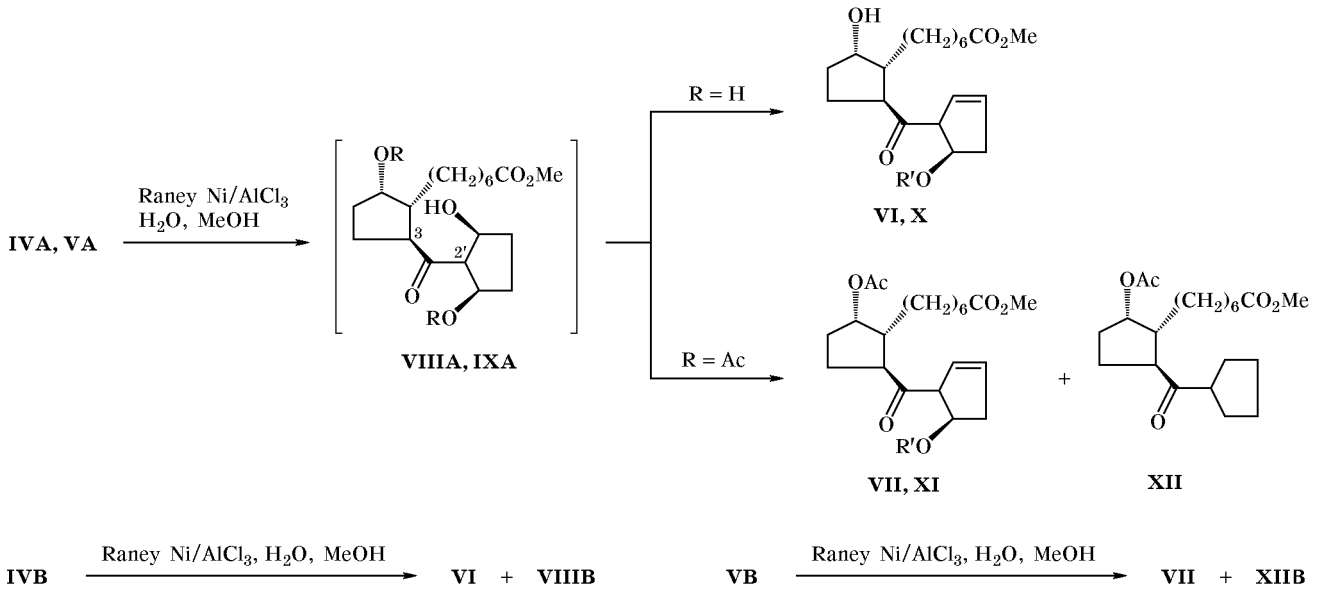
The reductive cleavage of cyclopentaisoxazole derivatives **IV** was effected by the action of Raney nickel in the system $AlCl_3$–methanol–water, where the reducing agent is hydrogen *in statu nascendi* [6]. The substrates were both isomeric mixture **IVA/IVB** and pure diols **IVA** and **IVB**, as well as their di-*O*-acetyl derivatives **VA** and **VB** which were prepared by treatment of **IVA** and **IVB** with acetyl chloride in pyridine (Scheme 3). The reduction of compounds **IV** and **V** resulted in formation of 5-methoxy-1-cyclopentenyl ketones **VI** and **VII**, respectively, in 60% yield (Scheme 4). The products were individual stereoisomers. Their structure was derived from the IR and ^{1}H NMR spectra. Ketones **VI** and **VII** characteristically showed in the IR spectra absorption of the enone system in the region 1650–1740 cm^{-1}; their ^{1}H NMR spectra contained signals from the 5′-H (δ 4.7 ppm, d.t) and 2′-H protons (δ 6.92–7.00 ppm, d.d) of the cyclopentene ring. The reduction of **IVA** gave product **VI** and an equal amount of its precursor **VIIIA**. Likewise, in the reaction with diastereoisomer **IVB** trihydroxy ketone **VIIIB** was also formed. These data support stereospecific character of the isoxazole ring cleavage. From diastereoisomeric mixture **IVA/IVB** we obtained a mixture of trihydroxy ketones **VIIIA** and **VIIIB** which were separated by preparative thin-layer chromatography. In all cases, the reduction of compounds **IV** was accompanied by formation of a small amount of dihydroxy ketone **X** (R′ = H; Scheme 4).

Scheme 3.



Unlike the initial cycloadducts, trihydroxy ketones **VIII** show in the IR spectra bands typical of stretching vibrations of both keto and hydroxy groups at 1710 and 3400–3550 cm^{-1}, respectively. The ^{1}H NMR spectra of **VIII** lack multiplet signals from 5′-H (δ 4.96 ppm); instead, a multiplet from the **H**COH proton appears at δ 4.58 ppm. A characteristic signal

Scheme 4.



III, **IV**, **VIII**, R = H; **V**, **IX**, R = Ac; **VI**, **VII**, R′ = Me; **X**, **XI**, R′ = H.

is also the triplet at δ 2.70 ppm, which was assigned to the 2′-H proton.

By reductive cleavage of acetoxy derivatives **VA** and **VB** we obtained enone **VII**. Diacetoxy ketone **XI** (which can be regarded as a derivative of dihydroxy ketone **X**) was detected only by ^{1}H NMR spectroscopy. The formation of compounds **VI** and **VII** suggests that esterification is most likely to occur in parallel with the hydrogenation of the N–O bond. The major product of reductive cleavage of acetoxy compound **VB** was ketone **XII**. It can be formed by elimination of the hydroxy and acetoxy groups from intermediate triol **IX** and subsequent reductive transformations of the resulting cyclpentene or cyclopentadiene derivatives. The ratio of products **VII** and **XII** is 1:3; this indicates that the ability of hydroxy, acetoxy, and methoxy groups to be eliminated under the reduction conditions changes as follows: OAc > OH > OMe. Taking into account that the driving force of dehydration of intermediate trihydroxy ketones **VIII** and **IX** is just their ability to split off hydroxy or acetoxy group, it is obvious that elimination of acetic acid from intermediate **IX** to give product **VII** is more effective than dehydration of triol **VIII** to enone **VI**.

Compounds **VI**–**VIII**, **X**, and **XII** are analogs of $F_{1\alpha}$ 11-deoxyprostaglandins with modified ω-chain. The structure of products **VI**, **VII**, and **X** provides the possibility for further modifying the side ω-chain through its reactive enone moiety. In addition, compounds homologous to **VI**, **VII**, and **X** (with n = 3) can be regarded as precursors of 11-deoxy-7-oxoprostanoids having a carbocyclic fragment in the α-chain in the scheme proposed by us previously [5] for synthesis of modified 7-oxoprostaglandins. The procedure for introduction of prostanoid ω-chain into such compounds was developed in [1].

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer from samples prepared as thin films. The ^{1}H NMR spectra were obtained on a Bruker AC-200 instrument (200 MHz) using $CDCl_3$ as solvent and TMS as internal reference. The mass spectra (70 eV) were taken on a Varian MAT-311 spectrometer. Silica gel 40/100 μm (Czechia) was used for column chromatography. Thin-layer chromatography was performed on Silufol UV-254 (Serva) and Kieselgel 60F_{254} (Merck) plates in the systems hexane–ether (65:35) and chloroform–methanol (85:15); the spots were visualized by treatment with *p*-methoxybenzaldehyde. Glass plates with Kieselgel L 5/40 μm applied thereto were used for preparative TLC; eluent 5% of methanol in chloroform. The elemental compositions of the products (C, H, N) were in agreement with the expected values.

3-[2-(6-Methoxycarbonylhexyl)-3-oxocyclopentyl]-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]-

Spectral parameters of compounds **II**–**VIII**, **X**, and **XII**

Comp. no.	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm, (*J*, Hz)							M^+
		2-H (5-H)	1-H	3-H	4′-H	5′-H	1′-H, 3′-H	other protons	
IIA	1440, 1465, 1610, 1740	2.42 ($J_{8,12}$ = 10)	–	3.00 m (d.d.d) (10, 10, 5.5)	3.74 (9.5)	5.44 m (d.d.d) (9.5, 5.0, 1.5)	–		349
IIB	1440, 1465, 1610, 1745	2.42 m		2.95 t.d (12.0, 11.0, 11.0, 6.0)	3.78 d (9.0)	5.44 m (d.d.d) (9.0, 5.5, 1.5)	–	3.66 (COOMe), 2.32 t (CH_2CO)	349
IIIA	1610, 1735, 3400	2.68 m		3.26 d.d.d (10.5, 10.5, 6.0)	3.66 t (8.5)	5.0 m (8.5, 3.5, 1.0)	4.45 d.d (1′-H) (8.5, 1.8)	3.66 (COOMe), 2.32 t (CH_2CO)	351
IVA	1620, 1730, 1710, 3450	–	4.30 t (3.0)	2.82 d.d.d (q) (10.8, 10.0, 2.8)	3.54 d.d (8, 7.5)	4.98 q	4.40 br.q (1′-H) (d.d) (8.2, 7.5)	2.52 (OH), 2.32 t (CH_2CO)	353
IVB	1620, 1730, 1710, 3400	–	4.30 t (3.5)	3.00 m	3.64 d.d (10.0, 9.4)	4.96 d.d (9.5, 6.2, 2.0)	4.40 d.d.d (1′-H) (11.8, 2.5, 8.5)	3.66 (COOMe), 2.32 t (CH_2CO)	353
VA	1235, 1380, 1440, 1735	–	5.02 d.d (9.0, 4.5)	2.6 m	3.72 d (8.0)	5.28 m	5.28 (1′-H)	3.66 (COOMe), 2.06 (CH_3CO), 2.32 t (CH_2CO)	437
VI	1620, 1675, 1710, 1740, 2825, 3400–3550		4.3 t (3.0)	3.28 m	–	4.7 d.t (HCOMe)	6.96 t (HC=, 3-H (2.5)	3.66 (COOMe), 3.38 (OMe), 2.3 t (CH_2CO)	352
VII	1250, 1380, 1620, 1675, 1710, 1740, 2825		5.28 t (3)	3.3 m		4.7 d.t (HCOMe) (5.8, 2.0)	7.0 d (HC=, 3′-H) (2.0)	3.66 (COOMe), 3.38 (OMe), 2.3 t (CH_2CO) (7.5), 2.06 (CH_3CO)	394
VIIIA	1710–1735, 3400–3550		4.34 t (2.5)	3.30 m	2.70 t (4.5)	4.58 m (1′-H, 3′-H)	4.58 m	3.66 (COOMe), 2.3 t (CH_3CO) (7.5)	356
X	1710–1735, 3400–3550		4.3 m (3.0)	3.30 m	–	5.14 t (1-H, 7.5)	6.92 t (HC=, 3′-H) (1.8)	3.66 (COOMe), 2.3 t (CH_3CO) (7.5)	338
XII	1250, 1375, 1450, 1680, 1710–1740		5.28 t (4)	2.92 m	2.92 m	–	–	3.66 (COOMe), 2.06 (CH_3CO), 2.3 t (CH_2CO)	366

isoxazol-4-one (II). 2-(6-Methoxycarbonylhexyl)-3-nitromethylcyclopentanone (**I**) [7], 0.001 mol, was dissolved in 15 ml of dry benzene, and excess 2-cyclopentenone (0.002–0.003 mol) and 0.004 mol of phenyl isocyanate were added. A few drops of triethylamine were added (until *N*,*N*′-diphenylurea began to separate from the solution), and the mixture was stirred with protection from atmospheric moisture for 24–48 h (until the initial nitro compound disappeared, TLC) at room temperature. In some cases, the mixture was heated at 40°C with stirring for the last 12 h. When the reaction was complete, the mixture was filtered through a layer of aluminum oxide, and the sorbent was additinally washed with a hexane–ether mixture.

The product was isolated by chromatography on silica gel using gradient elution with hexane–ether or chloroform–methanol mixtures.

3-[2-(6-Methoxycarbonylhexyl)-3-oxocyclopentyl]-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]-isoxazol-4-ol (III) and 3-[3-hydroxy-2-(6-methoxycarbonylhexyl)cyclopentyl]-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazol-4-ol (IV). A flask heated in a stream of argon was charged with 0.05 g of compound **II** in 7 ml of tetrahydrofuran (freshly distilled over lithium aluminum hydride). The solution was cooled to –45°C, and 1 ml of a 1 M solution of K-Selectride (Aldrich) was added through a syringe under stirring. The mixture was stirred for 4 h at –45°C, 1 ml of 30% H_2O_2 and 0.5 ml of a 5 M solution of potassium hydroxide were added at –20 to –5°C, and the mixture was stirred for 10 min at 0–5°C and diluted with 5 ml of water. Excess hydrogen peroxide was neutralized by adding small portions of MnO_2, and the mixture was evaporated. The resulting aqueous suspension was shaken with diethyl ether, and the extract was washed with water, dried over Na_2SO_4, and evaporated. The residue was subjected to column chromatography on silica gel using ether–hexane (20 : 80) as eluent or to preparative thin-layer chromatography using metanol–chloroform (5 : 95) as eluent.

O-Acetyl derivatives **V** were obtained by treatment of compounds **IV** with acetyl chloride in the presence of pyridine, following a standard procedure.

1α-Hydroxy-2α-(6-methoxycarbonylhexyl)-3β-(5-methoxy-1-cyclopentenylcarbonyl)cyclopentane (VI), 1α-hydroxy-3β-(2,5-dihydroxycyclopentylcarbonyl)-2α-(6-methoxycarbonylhexyl)cyclopentane (VIII), and 1α-hydroxy-3β-(5-hydroxy-1-cyclopentylcarbonyl)-2α-(6-methoxycarbonylhexyl)-cyclopentane (X) or 1α-acetoxy-2α-(6-methoxycarbonylhexyl)-3β-(5-methoxy-1-cyclopentylcarbonyl)-cyclopentane (VII) and 1α-acetoxy-2α-(6-methoxycarbonylhexyl)-3β-(cyclopentylcarbonyl)cyclopentane (XII). To a solution of 0.54 mmol of isoxazole derivative **IVA** or **VA** in 30 ml of methanol we added 0.6 g of Raney nickel and then 0.1 g of $AlCl_3$ and 2 ml of water. The mixture was stirred for 12–48 h until the initial compound disappeared (TLC), filtered through a layer of silica gel, concentrated, diluted with water, and extracted with ether. The extract was dried over Na_2SO_4, and the solvent was removed. The residue was subjected to thin-layer chromatography on silica gel using methanol–chloroform (5 : 95) as eluent. Yield 60–75%.

REFERENCES

1. Akhrem, A.A., Lakhvich, F.A., Lis, L.G., Khripach, V.A., Antonevich, I.P., and Pap, A.A., *Zh. Org. Khim.*, 1981, vol. 17, no. 10, pp. 2242–2243; Lakhvich, F.A., Koroleva, E.V., Rubinova, I.L., and Yankova, T.V., *Izv. Akad. Nauk BSSR, Ser. Khim.*, 1987, no. 4, pp. 66–71; Lakhvich, F.A., Yankova, T.V., Koroleva, E.V., Lis, L.G., and Akhrem, A.A., *Zh. Org. Khim.*, 1988, vol. 24, no. 8, pp. 1665–1668.
2. Fried, J.E., Mehra, M.M., and Chan, Y.Y., *J. Am. Chem. Soc.*, 1975, vol. 96, no. 21, pp. 6759–6761; Collins, P.W., Gasiecki, A.F., Perkins, W.E., Gary, W.G., Jones, P.H., Bauer, R.F., and Gullikson, G.W., *J. Med. Chem.*, 1989, vol. 32, no. 5, pp. 1001–1006; Lakhvich, F.A. and Kozinets, V.A., *Itogi Nauki Tekh., Ser. Org. Khim.*, 1991, vol. 21, pp. 1–95.
3. Lakhvich, F.A., Koroleva, E.V., Antonevich, I.P., and Yankova, T.V., *Zh. Org. Khim.*, 1990, vol. 26, no. 8, pp. 1683–1687.
4. Lakhvich, F.A., Kozinets, V.A., Katok, Ya.M., and Koroleva, E.V., *Russ. J. Org. Chem.*, 1998, vol. 34, no. 8, pp. 1200–1204.
5. Lakhvich, F.A., Khripach, V.A., Antonevich, I.P., Yankova, T.V., Koroleva, E.V., and Akhrem, A.A., *Khim. Geterotsikl. Soedin.*, 1988, no. 7, pp. 966–971.
6. Kozikowski, A.P. and Adamczuk, M., *Tetrahedron Lett.*, 1982, vol. 23, no. 31, pp. 3123–3126.
7. Koroleva, E.V., *Izv. Akad. Nauk Belarusi, Ser. Khim. Nauk*, 1997, no. 4, pp. 90–98.