ISOXAZOLINE APPROACH TO SYNTHESIS OF 7-KETOPROSTANOIDS

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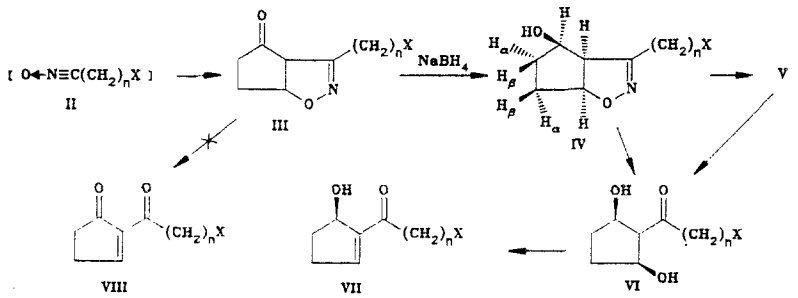
Synthones for 7-ketoprostanoids – 2-acylcyclopentenols – were synthesized from cyclopentenone and ω-nitroalkanoic acid esters in three steps that include the formation and reductive cleavage of cyclopentanoisoxazolines.

The use of 2-isoxazolines as universal polyfunctional synthones for obtaining diverse organic structures, including those for the modification and total synthesis of biologically important compounds [1, 2], is due to the ease of their formation and to the possibility of the realization of regio- and stereoselective processes involving the formation and transformation of the heterocycle and the construction in this way of the functionally substituted carbon skeleton of various types of substances. The idea of the use of nitrile oxides and cycloadducts based on them in the synthesis of prostanoids that was first advanced by us [3, 4] has recently undergone considerable development [5-7]. In the present paper we describe new synthones for 7-ketoprostanoids – 2-(ω-carbalkoxyalkyl-1-oxo)cyclopent-2-en-1-ols – in the synthesis of which the isoxazoline approach was used for the construction of the modified α chain of the prostanoid.

Cyclopentanoisoxazolines III were obtained by 1,3-dipolar cycloaddition of cyclopent-2-en-1-one to nitrile oxides II, which were generated from the corresponding ω-nitroalkanoic acid esters I [8, 9]. Cycloaddition occurs regioselectively with the formation of the isomer that corresponds to the "normal" relative orientation of the enone and dipole, in which the oxygen atom of the latter, which has increased electron density interacts with the most electron-deficient β-carbon atom of the dipolarophile.



I—VIII a $n=4$, X=COOEt; b $n=4$, X=CH(COOEt)$_2$; c $n=5$, X=COOEt

The reaction is a concerted process and is distinguished by cis stereospecificity; this is confirmed by the physicochemical data for the resulting adducts III. Let us examine the proof of their structure in the case of isoxazoline IIIa. Thus the methylidyne 3-H proton* shows up in the form of a multiplet at 5.38 ppm in the ^{1}H NMR spectrum (360 MHz) of the latter at weakest field. The second methylidyne 2-H proton shows up in the form of a doublet at 3.72 ppm with J_{23} = 8.7 Hz due to spin–spin coupling with the 3-H proton; this was confirmed by a double-resonance experiment and corresponds to a cis orientation of the 2-H and 3-H protons and, correspondingly, the rings. Coupling of the 3-H proton with two 4-H methylene protons (J_1 = 4.96 Hz, J_2 = 3.3 Hz) and long-range coupling with one of the 5-H protons (J = 2.2 Hz) were also established by means of double resonance. All of the 4-H and 5-H methylene protons of ketones III are chemically equivalent and resonate at 2.35 ppm. This is probably

*The numbering with respect to the cycloalkane.

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associated with flattening of the carbocycle in the presence of a relatively conformationally rigid bicyclic system, which increases the overall symmetry of the molecule.

Products could not be isolated from the reaction mixture in an attempt to cleave isoxazoline IIIa with Raney nickel in CF_3COOH [10]. This is evidently associated with the formation of unstable enediones VIII. In this connection the reduction of the carbonyl function of oxocyclopentanoisoxazolines III with sodium borohydride was undertaken, and hydroxycyclopentanoisoxazolines IV were obtained in 80-95% yields [11]. According to the results of TLC and data from the ^1H and ^{13}C NMR spectra, the reaction product is a single diastereomer with a cis orientation of the hydroxy group and the heteroring. The complete assignment of the signals in the ^1H NMR spectrum of IVa was made by means of double resonance (Table 1). The methylidyne 2-H proton shows up in the form of a triplet at 3.58 ppm as a consequence of coupling with the 3-H proton (J_{23} = 8.1 Hz, cis). The existence of the other diastereomer should have been expressed in the substantially smaller value of the J_{trans} constant for coupling with the 1-H proton, which would complicate the form of the 2-H signal, which shows up in the form of a doublet in the case of suppression of spin–spin coupling with the 3-H proton.

The 4-H and 5-H protons, which are cis-oriented with respect to the C–O bonds of the isoxazoline ring and the hydroxy group (the β protons), are partially deshielded and show up at weaker field than the corresponding α protons. Their spin–spin coupling constant (SSCC) (4β, 5β) is 7 Hz, which confirms their relative cis orientation and, correspondingly, the cis orientation of the isoxazoline substituent and the hydroxy group of the carbocycle; the character of their spin–spin coupling corresponds completely to the theoretical splitting in the case of a β orientation of both the hydroxy group and the heteroring and differs substantially from that in the case of an α orientation of the hydroxy function and a β orientation of the heteroring. In addition, 2-acylcyclopentane-1,3-diol VIa with a symmetrical orientation of the hydroxy groups was obtained in the reductive cleavage of isoxazoline IVa under conditions that ensure retention of the configuration of the substituents (H_2/Raney nickel, H_3BO_3) [12]; this also confirms the proposed stereochemistry of hydroxycyclopentanoisoxazolines IV. In addition to this, it follows from an examination of molecular models of oxocyclopentanoisoxazolines III that it is difficult to explain, by steric factors only, the observed high stereoselectivity of the reduction as a consequence of primary attack by the hydride ion on the carbonyl function from the side opposite to the heteroring. All of the methylene protons of the ring become chemically nonequivalent on passing from ketone III to alcohol IV; this indicates a decrease in the flattened character of the five-membered carbocycle vis-à-vis retention of the conformationally rigid bicyclic system. In addition, the methylene protons in the side chain of alcohol IV also become chemically nonequivalent, evidently as a consequence of their diastereotopic character.

The conversion of cyclopentanoisoxazolines IV to the desired 2-acylcyclopent-2-en-1-ols VII was accomplished under the influence of Raney nickel in trifluoroacetic acid. In this case nickel not only displays catalytic properties but also reacts with the acid with the evolution of hydrogen. In addition, the presence of nickel ions in the reaction mixture evidently promotes dehydration of intermediate keto diol VI. Cyclopent-2-en-1-ols VII were isolated in 30-40% yields along with small amounts of keto diols VI as a result of a multistep process that includes the reductive opening of the isoxazoline ring, hydrolysis of intermediate hydroxy imine V, and dehydration of the resulting keto diol VI.

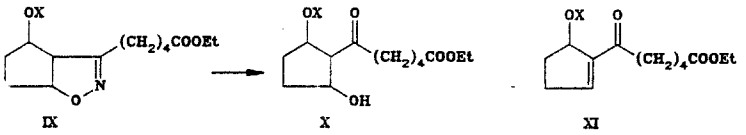
Thus, as a result of a three-step synthesis that includes the 1,3-dipolar cycloaddition of nitrile oxides, borohydride reduction of the keto function, and reductive cleavage of the isoxazolines, we were able to accomplish the introduction of the modified top chain of a prostaglandin into cyclopentanone. The 2-acylcyclopentenols VII* obtained are new intermediates in the total synthesis of prostaglandins that contain, in addition to the hydroxy function of the cyclopentane ring, a double bond activated by a carbonyl function in the side chain. In the synthesis of the desired synthone by the proposed method [14] it is particularly important that the dehydration of intermediate keto diols VI to the desired enones VII occurs directly under the conditions of reductive cleavage. Keto diol VIa was isolated in 75% yield from isoxazoline IVa when milder conditions were used [12]. However, the conversion of V Ia to the desired enone VIIa when the usual dehydrating agents (TsOH in ether, THF, benzene; CH_3ONa in methanol) were used was inefficient because of the occurrence of side processes, particularly the formation of the corresponding ethers.

*Compounds of this type were recently obtained [13] by an independent method.

TABLE 1. Parameters of the Spectra of IIIa, IVa, VIa, and VIIa

Compound	IR spectrum, cm^{-1}	^1H NMR spectrum, δ, ppm (J, Hz)									
		2-H	3-H	4-H_α	4-H_β	5-H_α	5-H_β	CH_2COO	$CH_2C{=}O$	$CH_2C{=}N$	$(CH_2)_z$
IIIa	1600, 1735	3,72 d (8,7)	5,38 m (4,9; 3,3)	—	2,35 m		—	2,35 m	2,45 m		1,70 m
IVa	1615, 1735, 3500	3,58 t (8,4; 8,1)	4,95 q d (J_4=5,8; J_4=2,3; J_2=8,4)	1,79 m (J_{gem}=13, J_5=7,8)	2,04 q t (J_5=J_3= =2,3)	1,70 m (J_{gem}=12; J_1=9,3; J_4=2,3)	1,89 m (J_4=7,5; J_4=3,3; J_1=4,8)	2,33 t	2,45 and 2,69 m (J_{gem}=12)		1,67 m
VIa	1705, 1730, 3500	2,64 t (4,2)	4,60 m	—	1,99 m		—	2,33 t	2,64 t		1,67 m
VIIa	1665, 1730, 3500	—	6,85 m	—	1,84 m; 2,33 m; 2,45 m; 2,69 m;	—	—	2,33 m	2,69 m		1,67 m

We therefore investigated the possibility of the monodehydration of keto diol Xa in the form of its monohydroxy derivatives Xb-d, which were obtained for protection or to change the reactivity of one of the hydroxy group. Functionalization was carried out in the step involving hydroxycyclopentanoisoxazoline IXa. The resulting esters IXb-d were converted to the corresponding keto diol monoesters Xb-d under conditions of catalytic hydrogenation over Raney nickel (H_3BO_3/MeOH–H_2O); XIb-d were then subjected to dehydration with the formation of enones XIb-d.



IX—XI a X=H; b X=THP; c X=SO_2Me; d X=Ac; e X=Me

Thus tetrahydropyranyl (THP) ether Xb, which was obtained in 76% overall yield from IXa, was dehydrated with methanesulfonyl chloride [11] to enone XIb in 67% yield.

It was found that the free hydroxy group in mesyl ester Xc displays a greater tendency to undergo elimination than the mesyl group, since a small amount of hydroxy enone mesylate XIc is formed during its preparation. As a consequence of this, the exhaustive dehydration of Xc in the presence of p-TsOH in ether leads to derivative XIc instead of the expected XIa.

In the dehydration of monoacetate Xd under the influence of BF_3 etherate we were unable to obtain either the desired enone XIa or its acetate XId.

It was established that cyclopentanediol Xa itself undergoes monodehydration under the influence of cuprous acetate in a mixture of methanol and acetic acid; a mixture of two products, which were identified as enone XIa (18%) and its methyl ether XIe (45%), is formed.

Thus from a preparative point of view the most effective of the examined variants of the synthesis of enone XI with a protected hydroxy function from cyclopentanoisoxazoline IXa is the elimination of a hydroxy group through the mesylate of the monotetrahydropyranyl ether of diol Xb or the monodehydration of diol Xa under the influence of copper acetate. We used these methods together with the direct preparation of enone XIa by the reductive cleavage of hydroxycyclopentanoisoxazoline IXa with Raney nickel in trifluoroacetic acid.

EXPERIMENTAL

The IR spectra of KBr pellets (for the solid compounds) or films or solutions in CCl_4 (for the liquids and oils) were recorded with a UR-20 spectrometer. The ^1H and ^{13}C NMR spectra ($CDCl_3$) were obtained with Bruker WM-360 and Jeol PS-100 spectrometers with tetramethylsilane (TMS) as the internal standard. The mass spectra were obtained with a Varian MAT-311A spectrometer with direct introduction of the samples into the source at an ionizing-radiation energy of 70 eV. Monitoring of the course of the reactions and the purity of the compounds obtained was accomplished by TLC on Silufol UV-254 plates.

Ethyl 6-(8-Oxo-4-oxa-3-azabicyclo[3.3.0]oct-2-en-yl)hexanoate (IIIc). A few drops of triethylamine were added to a mixture of 1.61 g (19.6 mmole) of cyclopentenone, 1.17 g (5.8 mmole) of ethyl ω-nitroheptanoate (methods for the synthesis of esters I are presented in [8]), and 1.73 ml (16 mole) of phenyl isocyanate in 10 ml of dry benzene, and the mixture was stirred for 3 days at room temperature. The precipitated diphenylurea was separated, the solvent and excess reagents were removed by evaporation in vacuo, and the residue was chromatographed with a column packed with silica gel with gradient elution with an ether–hexane system to give 1.11 g (72%) of ethyl ester IIIc with mp 22-23°C. Oxoisoxazolines IIIa, b were similarly obtained. The physicochemical characteristics are presented in Tables 1 and 2.

Ethyl 6-(8-Hydroxy-4-oxa-3-azabicyclo[3.3.0]oct-2-en-2-yl)hexanoate (IVc). A solution of 0.33 g (1.24 mmole) of ethyl ester IIIc in 10 ml of absolute ethanol was added with stirring in the course of 30 min to a solution of 0.05 g (1.34 mmole) of sodium borohydride in 15 ml of absolute ethanol, after which the mixture was stirred for 10 min. The solvent was removed in vacuo, and the residue was diluted with water and extracted with chloroform. The combined extracts were washed with water and dried over magnesium sulfate. The residue obtained after evaporation of the solvent was chromatographed with a column packed with silica gel 40/100 by elution with hexane–ether (1:3) to give 0.274 g (82%) of ethyl ester IVc with

TABLE 2. Physicochemical Properties of Cyclopentanoisoxazolines III-IVb, c and Hydroxy Enones VIIb, c

Compound	mp, °C	IR spectrum, cm^{-1}	^1H NMR spectrum, δ, ppm, J, Hz
IIIb	Oil	1610, 1730, 1745	1,29 (6H, t, CH_3, $J=8$); 1,41—2,05 (8H, m, CH_2); 2,37 (4H, m, CH_2); 3,30 (1H, t, $J=7$); 3,67 (1H, d, 2-H, $J=10$); 4,20 (4H, q, CH_2, $J=8$); 5,33 (1H, m, 3-H)
IIIc	22—23	1610, 1740, 1745	1,24 (3H, t, CH_3, $J=8$); 1,36—2,44 (14H, m, CH_2); 3,59 (1H, d, 2-H, $J=8$); 4,03 (2H, q, CH_2, $J=8$); 5,18 (1H, m, 3-H)
IVb	37,0—38,5	1615, 1735, 3400	1,23 (6H, t, CH_3, $J=7$); 1,38—2,76 (12H, m, CH_2); 3,25 (1H, t, $J=9$); 3,45—3,57 (2H, m, H, OH); 4,05—4,48 (5H, m, H, CH_2); 4,84 (1H, m)
IVc	35—36	1620, 1730, 3440	1,23 (3H, t, CH_3, $J=7$); 1,34—2,34 (14H, m, CH_2); 3,50 (1H, t, $J=8$); 3,63 (1H, br.s, OH); 4,01 (2H, q, CH_2, $J=7$); 4,29 (1H, m, 1-H); 4,81 (1H, m, 3-H)
VIIb	Oil	1620, 1665, 1730, 1745, 3400	1,27 (6H, t, CH_3, $J=7$); 1,30—2,70 (12H, m, CH_2); 3,20 (2H, t, br.s, H, OH, $J=7$); 4,12 (4H, q, CH_2, $J=8$); 4,93 (1H, m); 6,68 (1H, m, 3-H)
VIIc	Oil	1615, 1665, 1735, 3460	1,20 (3H, t, CH_3, $J=8$); 1,23—2,68 (14H, t, CH_2); 3,44 (1H, br.s, OH); 4,00 (2H, q, CH_2, $J=8$); 4,88 (1H, m, 1-H); 6,64 (1H, m, 3-H)

mp 35-36°C. Ethyl esters IVa and IVb were similarly obtained. The physicochemical characteristics of IVa-c are presented in Tables 1 and 2.

The methods in [10, 12], which were set forth in detail in a preceding publication, were used for the reductive cleavage of hydroxycyclopentanoisozazolines IVa-c and IXa.

2-(1-Keto-6-carbethoxyhexyl)cyclopent-2-en-1-ol (VIIc). A 0.5-g sample of Raney nickel was added with stirring to a solution of 0.138 g (0.51 mmole) of hydroxycyclopentanoisoxazoline IVc in 5 ml of 85% trifluoroacetic acid, after which the mixture was stirred for 3 h, neutralized to pH 5 with a saturated aqueous solution of sodium bicarbonate, and extracted with chloroform. The combined extracts were washed with water and dried over magnesium sulfate. The residue after evaporation of the solvent was chromatographed with a column packed with silica gel 40/100 with gradient elution with hexane—ether to give 0.037 g (28%) of enone VIIc in the form of an oil.

Ketones VIIb (in 38% yield) and VIIa (in 41% yield) were obtained in the reductive cleavage of hydroxyisoxazolines IVa, b under similar conditions. The physicochemical characteristics of enones VII are presented in Tables 1 and 2.

1-Tetrahydropyranyloxy-2-(1-keto-5-carbethoxypentyl)cyclopent-2-ene (XIb). A 1-ml (0.927 g, 11 mmole) sample of dihydropyran and a catalytic amount of p-TsOH were added to a solution of 0.255 g (1 mmole) of isoxazoline IXa in 5 ml of dry methylene chloride, and the mixture was stirred for 30 min at 0°C and for 2 h at room temperature. It was then diluted with methylene chloride, and the mixture was washed with sodium bicarbonate, dried with sodium sulfate, and evaporated to give 0.342 g (97%) of IXb, which was subjected, without purification, to catalytic hydrogenation by the method in [12] to give 0.260 g of mono-THF-ether Xb in the form of an oil; the overall yield was 76% based on isoxazoline IXa.

A 0.3-ml (1.8 mmole) sample of methanesulfonyl chloride in 1 ml of triethylamine was added at 0°C to a solution of Xb in 4 ml of methylene chloride, after which the mixture was stirred for 1 h and evaporated. Another 1 ml of triethylamine was added, and the mixture was stirred for 1 day at room temperature. It was then diluted with methylene chloride, and the mixture was washed with water, dried, and evaporated. Preparative TLC [silica gel 5/40, ether—hexane (1:1)] of the residue gave 0.165 g (67%) of oily product XIb. IR spectrum (film): 1620, 1675, 1735 cm^{-1}. ^1H NMR spectrum: 6.88 (t, 1H, 3-H), 5.16 (d t), 4.95 (d t), 4.91 m, 4.73 m (2H), 4.12 (2H, q, $COOCH_2$), 4.04 m, 3.89 m (1H), 3.31 (m, 1H, CH_2—THP), mixture of diastereomers.

Monodehydration of 2-(1-Keto-5-carbethoxypentyl)cyclopentane-1,3-diol (Xa). A 0.5-ml sample of acetic acid and 15 ml of a solution of 1 g of copper(I) acetate monohydrate in 50 ml of dry methanol were added to 0.146 g (0.56 mmole) of diol Xa, and the resulting mixture was refluxed for 20 h. It was then diluted with water, and the diluted mixture was acidified with hydrochloric acid until the color of the solution changed. The mixture was extracted

with chloroform, and the extract was washed with a saturated solution of salt and filtered through a layer of aluminum oxide. Removal of the solvents and chromatography on plates with silica gel 5/40 in ether–hexane (3:1) gave 0.025 g (18%) of hydroxy compound XIa and 0.068 g (45%) of methoxy derivative XIe. IR spectrum (film): 1617, 1675, 1735 cm^{-1}. ^1H NMR spectrum: 6.92 (t, 1H, 3-H, J = 2.4 Hz), 4.67 (1H, d t, 1-H, J = 6.8 Hz, 2.4 Hz), 4.12 (2H, q) and 1.25 (3H, t, COOEt), 3.35 (3H, s, OMe), 1.66 (4H, m, 4-H and 5-H), 2.31 (2H, t, $CH_2C{=}O$).

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REDUCTIVE CLEAVAGE OF 4,5-CYCLOALKANOISOXAZOLINES*

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Different variants of the reductive cleavage of 4,5-cycloalkanoisoxazolines under the influence of Raney nickel in the presence of acids were studied. The compositions, structures, and properties of the reaction products are discussed.

The ease of formation of 2-isoxazolines as a result of 1,3-dipolar addition of nitrile oxides to substituted alkenes, the possibility of the selective modification of the heteroring, and the large number of transformations, particularly those with reductive character, associated with ring opening to give various structures (amino alcohols, hydroxy nitriles, enoximes, enones) make 2-isoxazolines convenient and flexible agents of organic synthesis for the construction of the carbon skeleton of the desired compound with the necessary difunctional fragment [2-4]. The general reaction of the reductive cleavage of 2-isoxazolines to β-hydroxy ketones or the products of their dehydration – α,β-unsaturated ketones – by the action of Raney nickel in an acidic medium, which was observed and described by us for the

*See [1] for our preliminary communication.

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