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trans-HYDROXYLATION OF CYCLOPENT-5-ENE[*d*]ISOXAZOLINES

The title reaction has been studied as a variant of the cyclopentane ring functionalization of cyclopent-5-ene[d]isoxazolines as the key intermediates in total synthesis of aza- and oxo prostaglandin analogues by nitrile oxides approach. The oxidation, epoxides cleavage and hydrolysis of obtained monoesters and/or acylation lead with good yields to *trans*-5,6-dihydroxycyclopentanoisoxazolines or their acyl derivatives. The synthesized substances are the intermediates in total synthesis of prostaglandin analogues, as well as perspective biologically active compounds.

Introduction. This research was performed within the realization of multistep synthetic scheme of preparation of new nitrogen- and oxygen containing prostanoids on the basis of cyclopentenisoxazolines (Scheme 1) [1–10]. Within this approach the essential synthetic task is to introduce into the cyclopentane ring certain pharmacophore functional groups, in particular hydroxyl ones. In this regard, one of the stages of this scheme includes the cyclopentane ring functionalization of key intermediates **1**, which is possible due to the C = C bond.

Pharmacophore oxygen-containing groups could be introduced into the key cyclopentenisoxazolines using various methods. Previously we have developed the cyclopenteneisoxazolines **1** preparative *cis*-hydroxylation procedure by the action of potassium permanganate in the presence of interphase transfer catalysts via the Wagner reaction with the formation of corresponding *cis*-diols [6].

The purpose of this work is to reseacrh *trans*-hydroxylation of compounds **1**.

Main part. *Trans*-hydroxylation includes the C=C bond epoxidation of substrates with subsequent oxirane ring cleavage.

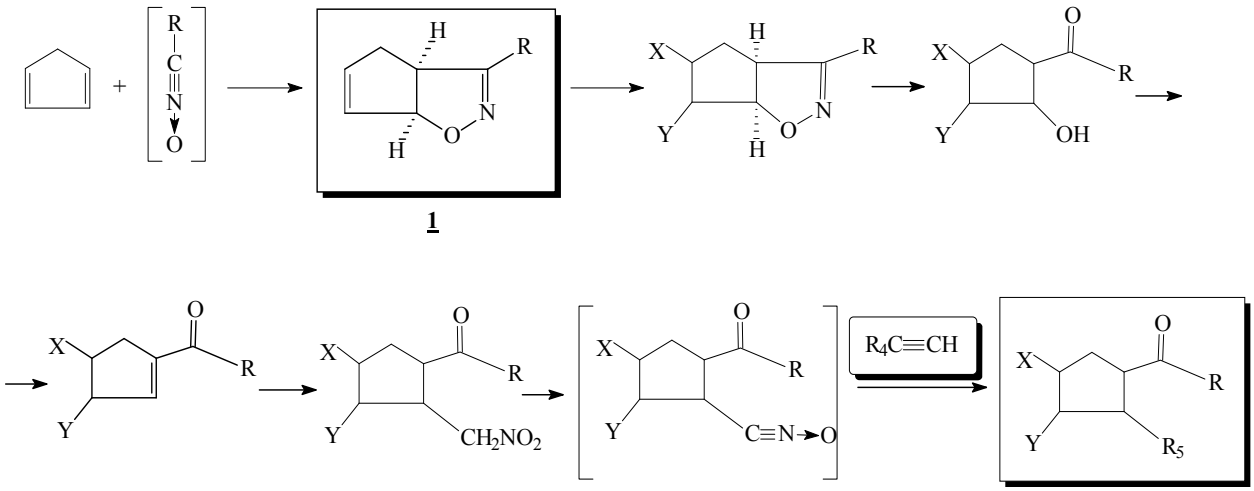
The oxidation of C=C double bond tis well known to introduce two vicinal hydroxyl groups and is possible by action of various reagents, including hydrogen peroxide as an available and cheap oxidizing agent.

Initially this approach has been studied on the model of the double bond oxidation of 3-phenylcyclopentenisoxazoline **1a** and 3-ethyl-derivative **1b** by the action of hydrogen peroxide in formic acid (Scheme 2). The reaction was carried out in 90% formic acid with 30% hydrogen peroxide. Obviously that the C=C bond oxidation proceeded both by the action of hydrogen peroxide as well as by performic acid formed in the reaction conditions.

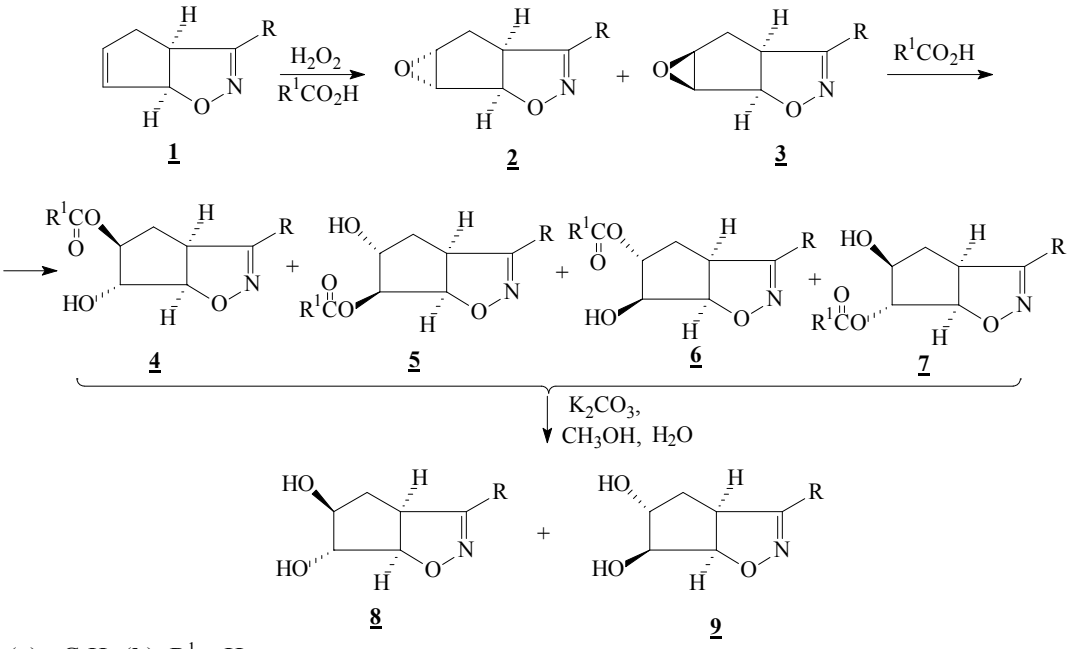
The formed stereoisomeric epoxides **2** and **3** were subjected to cleavage in the acidic media without isolation from the reaction mixture. Epoxide ring cleavage gave regio- and stereomeric monoformiates **4**–**7** (R^1 = H) with relative *trans*-location of substituents.

In accordance with theory the presence of 4 chiral centers makes it possible the existence of 16 stereoisomers for each regioisomer.

Meanwhile only 4 racemic mixtures of isomers **4**–**7** were obtained due to *cis*-fusion of isoxazoline and cyclopentane rings as well as stereoselectivity of epoxide ring opening by the action of nucleophile reagents. Ester group saponification with the formation of *trans*-dioles **8** and **9** led to resulted in diminution of regioisomers number.



Scheme 1



1 **2** **3** **4** **5** **6** **7** **8** **9**

R= -C_6H_5 (**a**); -C_2H_5 (**b**); R^1 = H

Scheme 2

Thus, in these conditions 3-phenylcyclopent-5-ene[*d*]isoxazoline **1a** was converted to stereoisomeric epoxides **2a** and **3a**, which further were subjected to the oxirane ring opening to form formiates **4a**–**7a** (R^1 = H).

By the action of potassium carbonate in aqueous methanol these formiates were subjected to hydrolysis without isolation from the reaction mixture. The obtained product was a mixture of stereoisomeric vicinal *trans*-dioles **8a**, **9a**, the total yield being 82%. Successive chromatography and fractional recrystallization allowed to isolate pure stereoisomer **8a**.

The structure of the obtained product correlates with its spectral data. Thus, wide intensive absorption band corresponding to valence vibrations of the O-H bond in the 3385–3400 sm^{-1} region is observed in the IR spectrum of diole **8a**. This gives evidence of the hydroxyl groups presence in the compound **8a**.

Proton signals corresponding to all structural fragments of the compound appear in the ^{1}H NMR spectrum, while vinyl proton signals of the initial cycloalkene **1a** disappear. Characteristic proton signals in 4th and 5th position of the isoxazoline heterocycle are observed at 4.12–4.24 and 4.92 ppm respectively, moreover spin-spin coupling constant (SSCC) of the latter with neighbouring carbinol proton was **2.5**Hz, which proves *trans*-location of these protons. The evident signal assignment and SSCC determination was accomplished using double-resonance method. Relative *trans*-location of H-10 and H-11 (PG numeration of atoms was used to facilitate the spectral characteristics comparison) was additionally confirmed for the acylation product because these proton signals overlapped in the diole **8a** spectrum. The ratio of stereoisomers **8a**: **9a** based on the ^{1}H NMR spectrum recorded for the reaction mixture is about 3: 1.

Similar results were revealed for the oxidation of 3-ethylcyclopent-5eno[*d*]isoxazoline **1b** by hydrogen peroxide.

Thus, the reaction proceeded stereoselectively and led to stereoisomers **8**, **9** with relative *trans*-location of the vicinal hydroxyl groups in the cyclopentane ring.

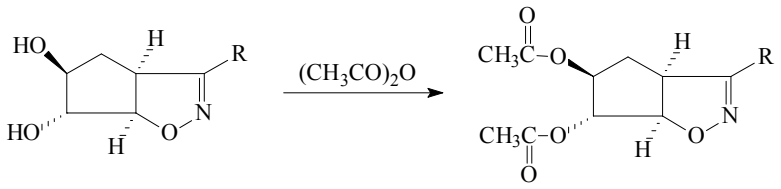
The reaction is characterized by high chemoselectivity, i.e. in the oxidation conditions the isoxazoline heterocycle C=N double bond proved to be stable towards the action of a reagent.

The obtained compounds with two vicinal hydroxyl groups displayed low chromatographic mobility. These could be readily dissolved in highly-polar solvents but were poorly soluble in chloroform. From this point of view acyl derivatives of dioles turned to be more accessible.

These derivatives were prepared by diole acylation. Thus, the diole **8a** by the action of acetic anhydride in the presence of catalytic amounts of sulfuric acid gave the corresponding diacetate **10a**, the yield being 59% (Scheme 3).

The absorption band of the hydroxyl group disappears while that of the ester group appears in the 1745 sm^{-1} region of the product **10a** IR spectrum.

In ^{1}H NMR spectrum the characteristic singlet signals of acetyl groups appear at 1.92 and 2.11 ppm. The shift of the H-10 and H-11 signals to a lower field is very illustrative being compared with the corresponding signals of the original diole spectrum because it is very significant due to the discreening effect of acetyl groups.



8a **10a**

Scheme 3

Moreover, H-11 appears as a singlet, indicating the relative *trans*- location of H-11, H-12 and H-10. Signal H-12 converts to a singlet by suppressing the H-8 signal during double resonance experiment. This is confirmed by the absence for the proton H-11 spin-spin coupling and is possible in case of *trans*-location of these protons.

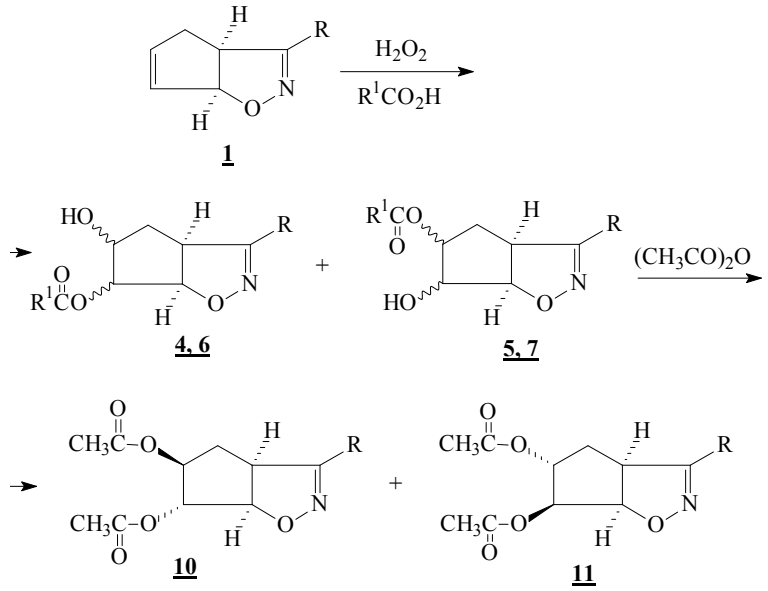
The preparation of diacetate **10a** prompted the idea to carry out the oxidation by hydrogen peroxide in acetic acid followed by complete monoester acylation i.e without initial monoester hydrolysis and intermediate isolation These could reduce the number of steps and simplify the experimental procedure. Such approach has been realized on cyclopentanisoxazoline (**1c**) as a model (Scheme 4). Oxidation being carried out by hydrogen peroxide (54%) in acetic acid at room temperature during 2 days. Formed as the intermediates the monoethers **4c**–**7c** ($R^1 = CH_3$) after aqueous treatment were subjected to a complete acylation by acetic anhydride in the presence of sulfuric acid initially at room temperature and then at 30-40°C. As a result, diacetates **10c**, **11c** have been isolated with an overall yield 51.2%.

It should be mentioned that in the realizing scheme of prostanoids synthesis the cyclopentanisoxazoline derivatives are further subjected to reductive cleavage of the isoxazoline heterocycle with the formation of the corresponding enones [6, 7] in which two chiral centers disappear. In this regard, the formation of a mixture of diastereomers **10**, **11** is not dramatical.

Experimental part. ^1H and ^{13}C NMR spectra of substances solutions in $CDCl_3$ or $CDCl_3$ with CD_3OD containing HMDS as an internal standard have been recorded with Bruker AVANCE spectrometer (400 MHz). The reaction courses was monitored by thin-layer chromatography (TLC) on silica gel plates Kieselgel 60 F_{254} (Merck), the eluent being ether – light petroleum, developer – iodine or 4% $KMnO_4$ solution.

Cyclopentanisoxazoline **1** synthesis is described in [1]. The used solvents were purified according to standard procedures [11].

Cyclopent-5-ene[*d*]isoxazolines 1 oxidation with hydrogen peroxide in formic acid. The isoxazoline **1a** (0.299 g, 0.0016 mol) was dissolved in of 90% formic acid (8 ml) with heating up to 80 °C. Then to the reaction mixture cooled to room temperature 30% hydrogen peroxide (0.8 ml) was added while stirring, the reaction mixture temperature being increased up to 35–40 °C.



1

4, 6 **5, 7**

10 **11**

R= -C_6H_4-OCH_3-4 (**c**); $R^1 = CH_3$

Scheme 4

The reaction mixture was stirred for 18 h at room temperature. After the solvent evaporation as an azeotropic mixture with toluene yellow oil (0.706 g) was obtained and this was dissolved in methanol (30 ml) and refluxed with 0.6 g of K_2CO_3 for 2 h. Then reaction mixture was filtered through Al_2O_3 layer. The solvent was evaporated, the crude product was purified by preparative chromatography on neutral Al_2O_3 (eluent: 5% methanol solution in chloroform). The diole **8 a** was obtained as an oil (0.287 g, 82%) from which it crystallized (0.119 g). M.p. = 165–168 °C.

***trans*-5,6-Dihydroxy-3-phenylcyclo-pent[*d*]-isoxazoline 8 a.**

IR spectrum (KBr), sm^{-1}: 3385, 3400, 1605, 1580, 1505, 905.

^{1}H NMR spectrum ($CDCl_3$ + CD_3OD), δ, ppm (*J*, Hz): 7.68 m (2H) + 7.44 m (3H, C_6H_5), 4.92 dd (1H, H-12, J_1 = 10.5; J_2 = 2.5 Hz), 4.18 td (1H, 8-H, J_1 = 10.5 Hz; J_2 = 5.2 Hz), 4.01–4.12 m (2H H-10, H-11), 2.42–2.57 m (1H, H^A-9, J^{gem} = 14 Hz, J_2 = 9.5; J_3 = 5.5 Hz); 1.91– 1.94 m (1H, H^B-9, J^{gem} = 14 Hz, *J* = 5 Hz).

C^{13} NMR spectrum ($CDCl_3$ + CD_3OD) δ, ppm: 160.6 (C = N); 130.6; 129.3; 129.1; 127.5 (C_6H_5); 91.3 (C-12); 83.5 (C-11); 76.8 (C-10); 49.3 (C-8); 36.8 (C-9).

***trans*-5,6-Dihydroxy-3-ethylcyclopent-[*d*]-isoxazoline 8, 9 b**.

IR spectrum sm^{-1}: 3380, 3410, 1600.

^{1}H NMR spectrum ($CDCl_3$ + CD_3OD), δ, ppm (*J*, Hz): 4.72 dd (1H, H-12, J_1 = 10; J_2 = 2 Hz), 3.87 m (1H, H-11), 3.67 m (1H, H-10), 2.39–2.53 m (1H, H^A-9), 2.17–2.34 m (2H, CH_2CH_3), 1.72–1.84 m (1H, $H^Б$-9), 1.18 m (3H,-CH_2CH_3).

***trans*-Diole 8 a acylation.** One drop of concentrated sulfuric acid was added to a solution of diole **8a** (0.039 g, 0.0017mol) in of acetic anhydride (4 ml), the mixture being stirred at room temperature. The reaction mixture was neutralized by a saturated soda solution, and then extracted with ether. The organic layers were dried on magnesium sulfate. Evaporation of the solvent gave diacetate **10 a** (0.032 g, 59%).

***trans*-5,6-Diacetoxy-3-phenylcyclopenta-[*d*]isoxazoline 10 a.**

IR spectrum, sm^{-1}: 1745, 1610, 1585, 1555.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.65 m (2H) + 7.42 m (3H, C_6H_5-); 5.36 (1H, H-11); 5.04–5.10 m (2H, H-12, H-10); 4.28 td (1H, H-8; J_1 = 9,5 Hz; J_2 = 3 Hz); 2.46–2.61 m (1H, H^A-9, J^{gem} = 14.5 Hz; J_2 = 9.5; J_3 = 5 Hz); 2.20 m (1H, H^B-9, J^{gem} = 14.5 Hz; J_2 = 3 Hz); 2.11 s (3H; $OCCH_3$), 1.92 s (3H; $OCCH_3$).

C^{13} NMR spectrum ($CDCl_3$), δ, ppm: 170.0 + 169.2 ($OCCH_3$), 158.8 (C = N); 130.2; 128.9; 128.3; 126.9 (C_6H_5); 88.6 (C-12); 81.6 (C -11); 76.3 (C-10); 50.4 (C-8); 34.8 (C-9), 20.85 + 20.80 ($OCCH_3$).

Cyclopent-5-en[*d*]isoxazoline 1c oxidation with hydrogen peroxide in acetic acid. The isoxazoline **1c** (0.5027 g, 0.0023 mol) was dissolved in acetic acid (10 ml) at room temperature. 54% Hydrogen peroxide (6.8 ml) was added to a resulted solution while stirring. The stirring continued for 48 h at ambient temperature. Na_2SO_3 was added, the solvent was removed on a rotary evaporator. According to the analytical TLC the obtained oil (0.685 g) was a mixture of dioles **8c**, **9c** and monoacetates **4c**–**7c**, R^1 = CH_3. The mixture was subjected to a complete acylation with acetic anhydride without separation.

The resulted crude product (0.685 g) was dissolved in acetic anhydride (5 ml) and 2 drops of concentrated sulfuric acid were added. The reaction mixture has been stirring at ambient temperature for 7 days. Then additional 3 ml of acetic anhydride and 2 drops of sulfuric acid were added as there remained starting compounds in the reaction mixture (according to TLC). The mixture was stirred at 30–40°C. The reaction mixture was further neutralized by $NaHCO_3$ solution, the organic products were extracted with ether (4 × 25 ml). The combined organic layers were washed with $NaHCO_3$ solution, then with brine and dried on anhydrous Na_2SO_4. The evaporation of solvent on a rotary evaporator gave 0.471 g of an oil which was purified by the preparative TLC on silica gel (2% ethanol in chloroform). As a result monoacetates **4c**–**7c** (R^1 = CH_3) (0.148 g) and diacetates **10c**, **11c** as a mixture of stereoisomers (0.268 g, 51.3% based on conversion of initial materials).

***trans*-5,6-Diacetoxy-3-(4-metoxyphenyl)-cyclopent[*d*]isoxazoline 10c.**

IR spectrum sm^{-1}: 2955, 2936, 2842, 1740, 1610, 1517, 1372.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.57 d (2H, $H_{arom.}$); 6.92 d (2H, $H_{arom.}$); 5.37 (1H, H-11), 5.06–5.09 m (1H, H-10); 5.04–5.09 d (1H, H-12, *J* = 9.9); 4.13–4.24 m (1H, H-8; J_1 = 9.8; J_2 = 3.16); 3.88 (3H, OCH_3); 2.47–2.55 m (1H, H^A-9, J^{gem} = 14.9; J_2 = 9.6; J_3 = 5.4 Hz); 2.36–2.44 m (1H, H^B-9, J^{gem} = 14.9; J_2 = 9.7, J_3= 5.8 Hz); 2.15 (3H; $OCCH_3$); 1.91 (3H; $OCCH_3$).

Conclusion. The oxidation of cyclopenteneisoxazolines by the action of hydrogen peroxide in an acid medium has been shown to give vicinal dioles or diacetates in **high overall yield**.

The reaction proceeded with high **chemoselectivity** with the participation of double C=C bond without affecting the double C=N bond of the isoxazoline heterocycle.

Hydroxylation is characterized by high **stereoselectivity**, producing dioles with relative *trans*-location of both OH-groups.

This method of cyclopenteneisoxazoline functionalization is characterized by **convenience and**

simplicity because a) it allows to accomplish several stages without laborious procedure of separation of isomeric products, b) very cheap and available reagents are used.

Different experimental methods which realize the introduction of hydroxyl groups either in *trans*- or in *cis*-relative position, provide an approach to the new prostaglandin analogues as well as open the wide possibilities to study the influence of the position and stereochemistry of the oxygen containing functions on prostanoids biological activity.

On the one hand, the obtained compounds are intermediates in the complete synthesis of nitrogen- and oxygen-containing prostanoids, on the other hand, they are of interest as perspective bioactive compounds.

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