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X-Ray Diffraction Study of the New Ecdysteroid Derivatives Containing Isoxazoline Ring in the Side Chain

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Abstract—Crystal and molecular structure of (2β,3β,14α,20R,5'R)-14,20-dihydroxy-20-(3'-isopropylisoxazolin-5'-yl)-2,3-isopropylidenedioxy-5β-pregn-7-en-6-one and (2β,3β,14α,20R,5'R)-20-hydroxy-20-(3'-methylisoxazolin-5'-yl)-14-trimethylsilyloxy-2,3-isopropylidenedioxy-5β-pregn-7-en-6-one was investigated by XRD analysis. Compounds crystallize in the orthorhombic [space group $P2_12_12_1$; a 11.751(2), b 12.146(2), c 19.660(4) Å] and hexagonal [space group $P6_1$; a 14.138(3), b 14.138(3), c 27.597(7) Å] crystal systems, respectively. These compounds, which resulted from the 1,3-dipolar cycloaddition of isobutyronitrile oxide or acetonitrile oxide to the corresponding steroid olefin, have 5'R-stereochemistry of the formed chiral center. The conformation of the side chain of molecules is stable due to the intramolecular hydrogen bonds.

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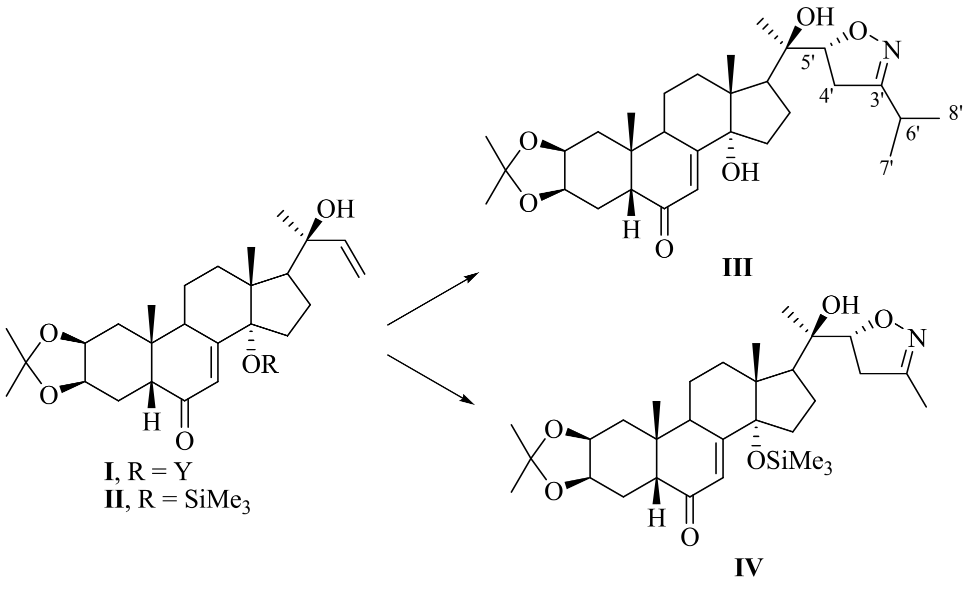
Recently we reported on the synthesis of new derivatives of ecdysteroids modified by isoxazoline ring in the side chain [1], which were obtained by 1,3-dipolar cycloaddition of nitrile oxides to 20-hydroxy-20-vinylsteroids **I** and **II**. It was shown that the 1,3-dipolar cycloaddition of nitrile oxides proceeded stereoselectively in each case to form a single stereoisomer. The configuration of the formed chiral center ($C^{5'}$) was determined using the method of circular dichroism by an empirical octants rule which related the sign and value of the molecular ellipticity of the band of the azomethine bond *n*–π* transition in the range of 212-220 nm to the conformation of isoxazoline ring and its disymmetrical environment



I, R = Y; **II**, R = SiMe$_3$.

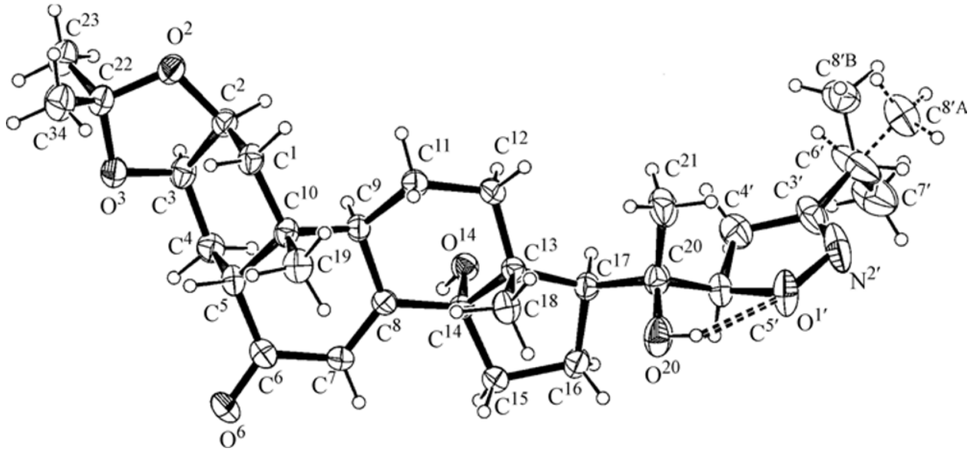


Fig. 1. Standard proection of molecule 2β,3β,14α,20R,5'R)-14,20-dihydroxy-20-(3'-isopropylisoxa-zolin-5'-yl)-2,3-isopropylidenedioxy-5β-pregn-7-en-6-one (**III**).

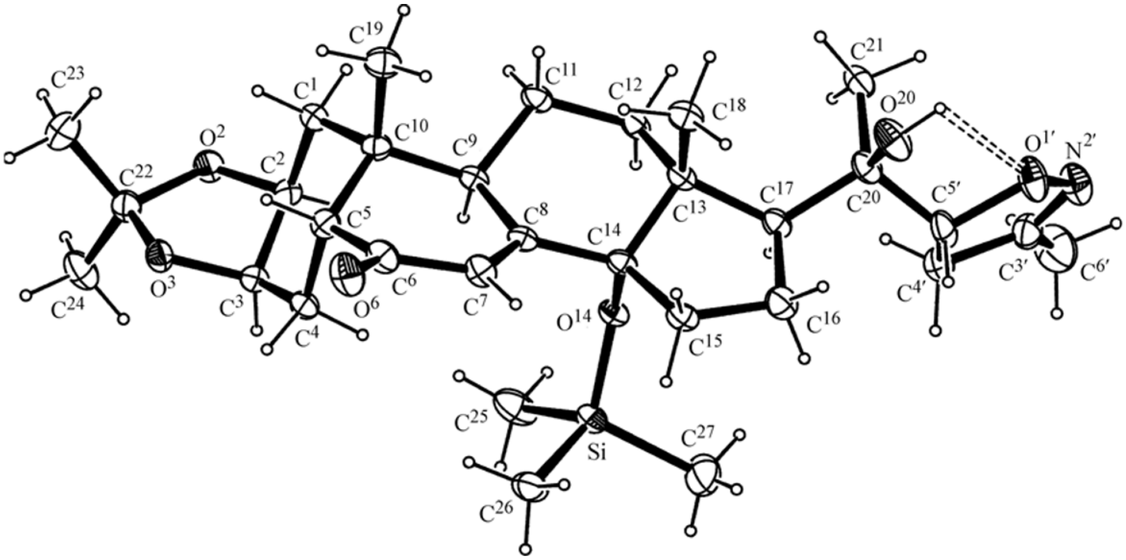


Fig. 2. Standard proection of molecule (2β,3β,14α,20R,5'R)-20-hydroxy-20-(3'-methyl-isoxazolin-5'-yl)-14-trimethylsilyloxy-2,3-isopropylidenedioxy-5β-pregn-7-en-6-one (**IV**).

[2]. The observed negative Cotton effect at a wavelength of 213 nm indicates the *R*-configuration of the new asymmetric center.

To confirm the validity of the assignment of the $C^{5'}$ center configuration in the resulting products and to study the structural features of the compounds of this group we performed an X-ray diffraction investigation of some compounds synthesized previously, namely derivatives **III** and **IV** with isopropyl and methyl substituents in the isoxazoline ring, containing free or protected 14-hydroxy group, respectively.

Figures 1 and 2 show the general view of molecules **III** and **IV**, respectively, in standard projections. By the XRD data the conformation of the steroid skeleton does not differ from that of the previously studied ecdysteroid structures [3–5]. The bonds and angles in the molecules are of common values. The spatial structure of the side chain of the considered steroid molecules **III** and **IV** is characterized by the torsion angles given in Table 4. The isoxazoline ring in the molecule **III** has $C^{4'}$–$C^{5'}$ *twist* conformation, while in the molecule **IV** it is practically planar with an average deviation of the ring atoms from the root-mean-square plane of 0.009(5) Å. In both compounds the hydroxy group O^{20}–H forms an intramolecular hydrogen bond with the oxygen atom $O^{1'}$ of heterocycle, which stabilizes the conformation of the molecule side chain

Table 1. Geometrical parameters (Å or deg) for hydrogen bonds in the crystal structure of **III** and **IV**

D–H···A	D–H		H···A		D···A		DHA angle	
	III	**IV**	**III**	**IV**	**III**	**IV**	**III**	**IV**
$O^{14}–H^{14}\cdots O^{2\,a}$	0.82	–	2.20	–	2.976(4)	–	158	–
$O^{20}–H^{20}\cdots O^{1'}$	0.82	0.82	2.38	2.43	2.735(5)	2.745(8)	107	104
$O^{20}–H^{20}\cdots O^{14\,b}$	0.82	–	2.19	–	2.902(4)	–	146	–
$C^{4'}–H^{4'1}–O^{6\,c}$	0.97	–	2.38	–	3.231(7)	–	146	–
$C^{4'}–H^{4'2}–N^{2'\,d}$	–	0.97	–	2.44	–	3.360(9)	–	142

[a] $(x – 1/2, y + 3/2, –z + 1)$; [b] $(–x + 1, y + 1/2, –z + 3/2)$; [c] $(–x + 1/2, –y + 2, z + 1/2)$; [d] $(x – y, x, z + 1/6)$.

(Table 1). Note that in the crystal the methyl group $C^{8'}$ of structure **III** is disordered over two positions with close occupancy.

The molecules of the structure **III** in the crystal are linked by the classical and non-classical hydrogen bonds (Table 1) to form a three-dimensional framework (Fig. 3). In the molecule of compound **IV** the non-classical hydrogen bonds form helical chains along the *c* axis (Fig. 4), which are connected only by the van der Waals interactions. Note that the crystal structures of the compounds contain cavities potentially accessible for the solvent of the volume 84 (**III**) and 177 Å^3 (**IV**), constituting 3.0 and 3.7% of the total cell volume, respectively. Nevertheless, as shown by analysis of the structure, these cavities do not contain *guest* molecules.

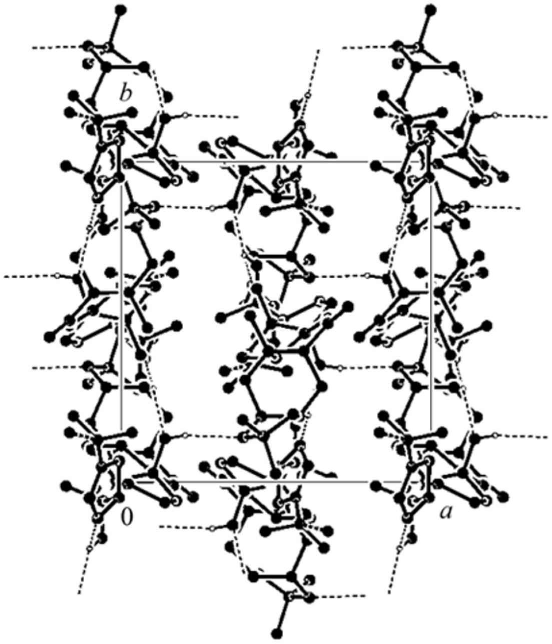


Fig. 3. Proection of crystal structure of 2β,3β,14α,20R,5'R)-14,20-dihydroxy-20-(3'-isopropylisoxazolin-5'-yl)-2,3-isopropyl-idenedioxy-5β-pregn-7-en-6-one (**III**) along *c* axis (dashed lines show hydrogen bonds; hydrogen atoms, not involved in hydrogen bonds are not shown).

The X-Ray analysis data show that the new asymmetric center of the stereoisomers formed at adding nitrile oxides to the ecdysteroid 20-hydroxy-20-vinyl derivatives has the *R*-configuration.

EXPERIMENTAL

20-Hydroxy-20-isoxazolinylsteroids **III** and **IV** were synthesized by 1,3-dipolar cycloaddition of isobityronitrile oxide and acetonitrile oxide, respectively, to olefins **I** and **II** as described in [1]. The single crystals were obtained by the slow evaporation of the saturated methanol–water solution of compound **III** and hexane-ethyl acetate solution of compound **IV**.

The three-dimensional sets of intensities for the molecules **III** and **IV** were collected on an automatic diffractometer Nicolet *R*3*m* (MoK_α-radiation, graphite monochromator, θ/2θ-scanning) at room temperature.

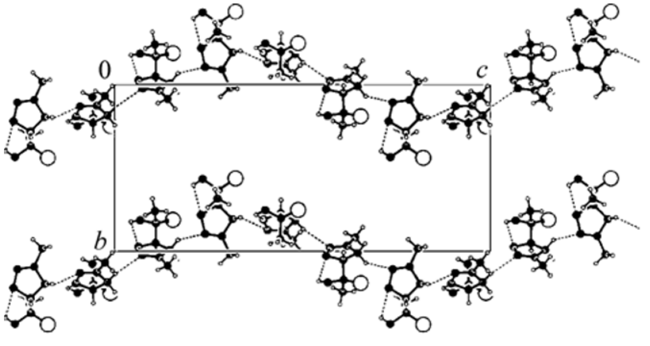


Fig. 4. Proection of crystal structure of (2β,3β,14α,20R,5'R)-20-hydroxy-20-(3'-methyl-isoxazolin-5'-yl)-14-trimethylsilyloxy-2,3-isopropylidenedioxy-5β-pregn-7-en-6-one (**IV**) along *a* axis(dashed lines show hydrogen bonds, steroid fragment is represented as a sphere of large radius).

Table 2. Crystal data for structures of **III** and **IV**

Parameter	Compound	
	III	**IV**
Empirical formula	$C_{30}H_{45}NO_6$	$C_{31}H_{49}NO_6Si$
Molecular mass	515.67	559.80
Crystal system	Orthorhombic	Hexagonal
Space group	$P2_12_12_1$	$P6_1$
Unit cell parameters		
a, Å	11.751(2)	14.138(3)
b, Å	12.146(2)	14.138(3)
c, Å	19.660(4)	27.597(7)
V, Å^3	2806.0(9)	4777.1(19)
Z	4	6
d_{calc}, g cm^{-3}	1.221	1.168
Extinction coefficient, cm^{-1}	0.084	0.115
Crystal size, mm	0.40×0.36×0.26	0.46×0.30×0.20
θ_{min}, θ_{max}, deg	1.97, 27.56	1.66, 26.56
Reflections collected/independent	3836/3632 [$R_{(int)} = 0.0268$]	8786/3390 [$R_{(int)} = 0.0593$]
Refinement method	Full matrix least square method on F^2	Full matrix least square method on F^2
GOOF on F^2	1.025	1.011
$R_1/wR_2[I > 2\sigma(I)]$	0.0624/0.1491	0.0540/0.1023
R_1/wR_2(all data)	0.1013/0.1783	0.1282/0.1292
$\Delta\rho_{max}/\Delta\rho_{min}$, e/Å^3	0.624/–0.282	0.114/–0.133

The unit cell parameters were determined and refined from 25 reflections. The structures were solved by the direct methods (SIR2004 [5]), the refinement was carried out in a full-matrix anisotropic approximation for non-hydrogen atoms (SHELXL-97 [6]). The positions of the hydrogen atoms were calculated geometrically and refined in the *rider* model. The absolute structures of **III** and **IV** were not determined from the XRD data and were taken on the basis of known configuration of chiral centers of the precursor molecules, which remain unchanged during the synthesis of **III** and **IV**. Illustrations were made using the programs ORTEP-3 [7] and PLATON [8]. The crystal data and the structure refinement parameters obtained by the least squares method are given in Table 2.

Crystallographic information for the compounds is deposited in the Cambridge Structural Database: CCBC 757216 (**III**) and CCBC 757217 (**IV**).

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