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Synthesis of 17-Dihydroisoxazolyl Steroids of the Androstane and Estrone Series*

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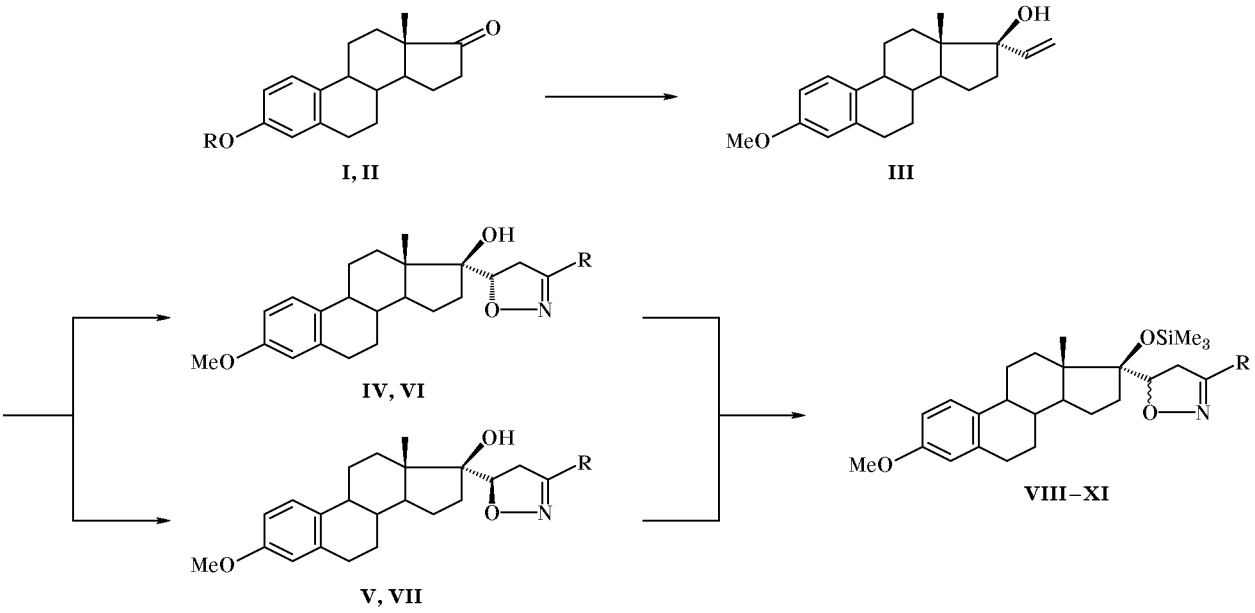
Abstract—1,3-Dipolar cycloaddition of nitrile oxides to 17β-hydroxy-17α-vinyl steroids of the estrone series proceeds both regio- and stereoselectively. The stereoselectivity of the process decreases in going to steroids of the androstane series. The major epimer has *S* configuration of the new chiral center.

We previously studied 1,3-dipolar cycloaddition of nitrile oxides to unsaturated steroid compounds with the double bond located at C^{20}, C^{22}, and C^{23} and examined properties of the resulting dihydroisoxazolyl derivatives [1–5]. In some cases, the stereoselectivity of the addition can be varied over a wide range through variation of the reactant structure [6].

The present communication reports on the results of our study on 1,3-dipolar cycloaddition of nitrile oxides to 17β-hydroxy-17-vinyl derivatives of the estrone and androstane series. The starting compound was estrone (**I**) whose 3-hydroxy group was protected by alkylation with dimethyl sulfate in the presence of sodium methoxide. We thus obtained methoxy

Scheme 1.



I, R = H; **II**, **IV**, **V**, **VIII**, **IX**, R = Me; **VI**, **VII**, **X**, **XI**, R = *i*-Pr; **VIII**, **X**: 5′*S*; **IX, XI**: 5′*R*.

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derivative **II** in 76% yield. It showed in the ^{1}H NMR spectrum a three-proton signal at δ 3.78 ppm from the methoxy group, whereas its IR spectrum lacked absorption typical of hydroxy group.

The Normant reaction of compound **II** with vinylmagnesium bromide in anhydrous THF at 0°C (3 h) afforded 88% of 17β-hydroxy-3-methoxy-17α-vinylestra-1,3,5(10)-triene (**III**) as an unsaturated compound which can be used as dipolarophile in 1,3-dipolar cycloaddition. Product **III** is formed as a result of the reagent approach from the least sterically hindered α-side of the steroid molecule. The vinyl proton signals in the ^{1}H NMR spectrum of **III** appeared as two doublets at δ 5.07 (J = 1 Hz) and 5.15 ppm (J = 17 Hz) and a doublet of doublets at δ 6.10 ppm (J_1 = 10, J_2 = 17 Hz). In the IR spectrum of **III** we observed stretching vibration band of the hydroxy group at 3440 cm^{-1}, while carbonyl absorption typical of initial ketone **II** was absent.

Allyl alcohol **III** was brought into 1,3-dipolar cycloaddition with nitrile oxides generated *in situ* (to reduce self-condensation) from the corresponding aldehyde oximes by the action of *N*-chlorosuccinimide in the presence of triethylamine as a base. Using acetaldehyde oxime, we obtained a mixture of dihydroisoxazolyl derivatives **IV** and **V** which are epimers with respect to C$^{5'}$. The overall yield of **IV**/**V** was 93%, and the ratio, 10:1 (according to the ^{1}H NMR spectrum of the reaction mixture). Hence we can state that the reaction is highly stereo- and regioselective and that the major product is 17α-(dihydroisoxazol-5-yl) steroid which can readily be isolated by crystallization.

Starting from isobutyraldehyde oxime, a mixture of compounds **VI** and **VII** was formed in an overall yield of 83% and at a ratio of 5:1 (according to the ^{1}H NMR data). Both epimers were isolated in the pure state by column chromatography. The absolute configurations of the chiral centers in **VII** were determined by X-ray analysis [7]. The structures of the other dihydroisoxazolyl steroids were established by comparing the ^{1}H NMR spectra of the pure isomers. The signal from methyl protons of the 18-CH_3 group in (5′*S*)-**IV** and (5′*S*)-**VI** is located in a stronger field (δ 0.91–0.92 ppm) than the corresponding signal of their (5′*R*)-epimers. The 5′-H signal appears as a triplet at δ 4.82–4.84 ppm (J = 10 Hz) and δ 4.63–4.66 ppm (J = 10.5 Hz) for compounds of the (5′*S*)- and (5′*R*)-series, respectively. Methylene protons on C$^{4'}$ give a two-proton signal as a double doublet of doublets at δ 3.05 ppm (5′*S*; J_1 = 10, J_2 = 10.5, J_3 = 17 Hz) or 3.00 ppm (5′*R*; J_1 = 10, J_2 = 10.5, J_3 = 17 Hz). The spectra of compounds **IV** and **V** also contained three-proton singlets from methyl protons of the 3′-CH_3 group (δ 1.98–2.00 ppm); compounds **VI** and **VII** showed in the ^{1}H NMR spectra signals from protons of the 3′-$CH(CH_3)_2$ fragment: a multiplet at 2.70 ppm (1H) and a doublet at δ 1.20 ppm (6H). The IR spectra of dihydroisoxazolyl derivatives contained a band at 1610 cm^{-1}, belonging to stretching vibrations of the C=N bond in the isoxazole ring. The mass spectra of the products contained peaks of the molecular ions whose fragmentation patterns were consistent with the proposed structures.

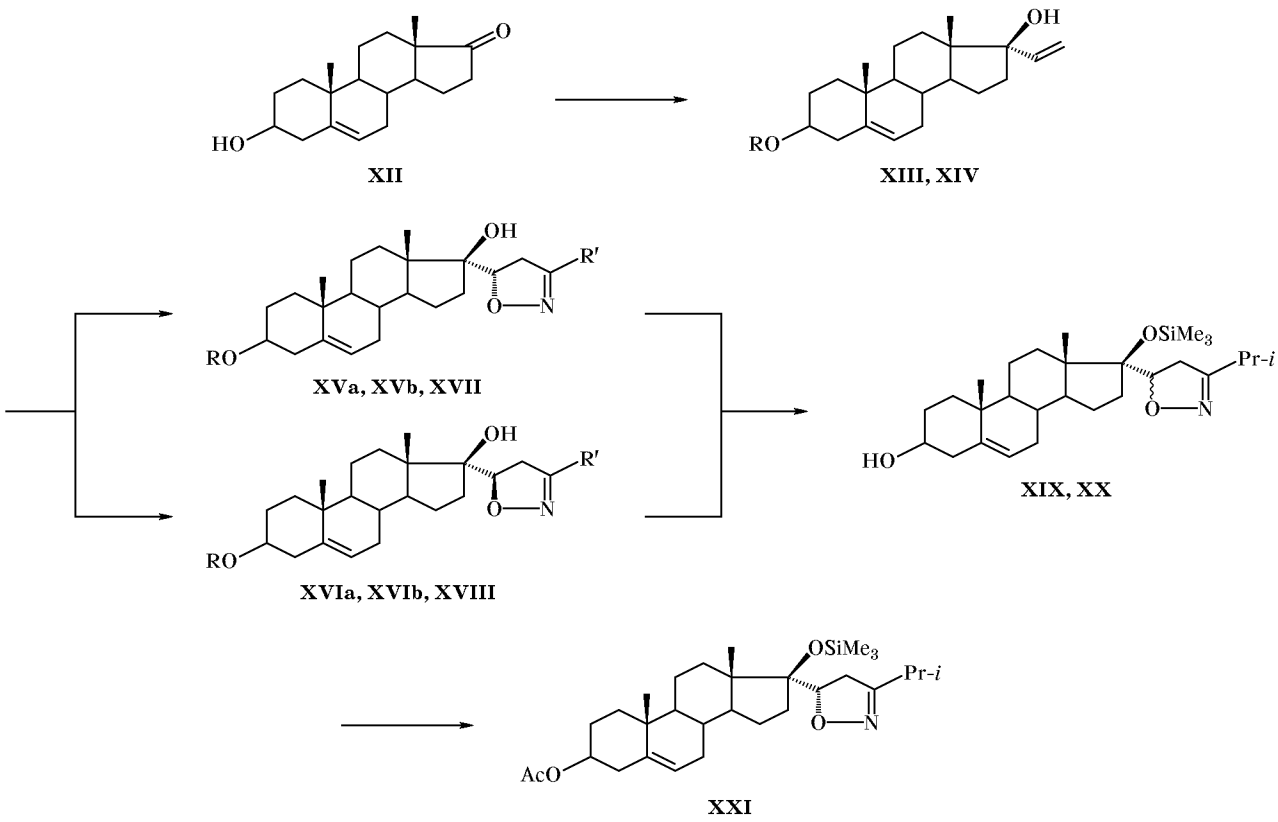
We failed to effect acetylation of the 17β-hydroxy group under various conditions. Treatment of epimeric mixture **IV**/**V** with chlorotrimethylsilane in methylene chloride in the presence of imidazole gave a mixture of trimethylsilyl ethers **VIII** and **IX** in an overall yield of 95%. Under the same conditions, from epimeric mixture **VI**/**VII** we obtained a mixture of ethers **X** and **XI**. These mixtures were separated into the pure epimeric trimethylsilyl ethers by chromatography. In the ^{1}H NMR spectra of **VIII**–**XI** we observed a singlet at δ 0.12 ppm from the trimethylsilyl group; also, a downfield shift of the 13-CH_3, 4′-H, and 5′-H signals was observed. No hydroxy group absorption was present in the IR spectra of these compounds.

17-Hydroxy-17-dihydroisoxazolyl derivatives of the androstane series were obtained by 1,3-dipolar cycloaddition of nitrile oxides to vinyl steroid **XIII** which was synthesized from 3-hydroxyandrost-6-en-17-one (**XII**) by the Normant reaction. Compound **XIII** was brought into reactions with acetonitrile oxide and isobutyronitrile oxide, and its 3-*O*-acetyl derivative **XIV**, with acetonitrile oxide. As with the 19-nor analog, the cycloaddition was regioselective, but its stereoselectivity was very low. In the reaction with isobutyronitrile oxide, the ratio of epimeric products (5′*S*)-**XVII** and (5′*R*)-**XVIII** was 3:1, and with acetonitrile oxide almost equimolar mixtures of compounds **XVa**/**XVIa** and **XVb**/**XVIb** were formed (Scheme 2).

The structure of products **XV**–**XVIII** is proved by the presence of characteristic signals in their ^{1}H NMR spectra: one-proton triplets from 5′-H at δ 4.72–4.75 and 4.52–4.56 ppm for the (*S*)- and (*R*)-isomers, respectively, and one-proton multiplets from 4′-H at δ 2.80–3.18 ppm; vinyl protons signals typical of the initial olefin were absent.

Epimeric mixture **XVII**/**XVIII** was converted into 17-*O*-trimethylsilyl derivatives **XIX** and **XX** by treatment with a tenfold excess of chlorotrimethylsilane and imidazole in methylene chloride at room temperature. It was surprising that the 3-hydroxy group in **XVII** and **XVIII** remained unchanged (after treatment

Scheme 2.



XIII, **XVa**, **XVIa**, **XVII**, **XVIII**, R = H; **XIV**, **XVb**, **XVIb**, R = Ac; **XVa**, **XVb**, **XVIa**, **XVIb**, R′ = Me; **XVII**, **XVIII**, R′ = *i*-Pr; **XIX**: 5′*S*; **XX**: 5′*R*.

with water and extraction with chloroform). Therefore, this procedure can be regarded as a method for selective protection of the 17-hydroxy group in steroid compounds. Products **XIX** and **XX** showed in the ^{1}H NMR spectra signals from the trimethylsilyl group, and the 3-H signal did not shift downfield. The IR spectra contained an absorption band at 3415 cm^{-1} due to stretching vibrations of the 3-hydroxy group. The presence of the latter was additionally proved by acetylation with acetic anhydride in pyridine to obtain 3-acetoxy-17-trimethylsilyloxy steroid **XXI**. Its ^{1}H NMR spectrum contained a three-proton singlet from the acetoxy group, and a downfield shift of the 3-H signal was observed. The hydroxy group absorption disappeared from the IR spectrum, while bands typical of ester moiety appeared at 1760 and 1260 cm^{-1}.

Thus, our study showed that 1,3-dipolar cycloaddition of nitrile oxides to 17-hydroxy-17-vinyl steroids of the estrone series is characterized by high stereoselectivity which depends on the 1,3-dipole structure. The stereoselectivity of 1,3-cycloaddition to androstane derivatives is considerably lower.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker A-200 instrument (200 MHz) in chloroform-*d* using TMS as internal reference. The IR spectra were obtained on a UR-20 spectrometer from thin films or KBr discs. The mass spectra were measured using a Hewlett Packard 5970 mass-selective detector coupled with an HP 5890 gas chromatograph (DB-17 column). The melting points were determined on a Koefler heating block. The progress of reactions was monitored by TLC on Silufol UV-254 and Kieselgel 60 F_{254} (Merck) plates. Preparative chromatographic separation of product mixtures was performed on Kieselgel 60 silica gel (40/60 μm, Merck).

Estrone methyl ether. Metallic sodium, 3 g (0.13 mol), was added in small pieces under argon to 60 ml of anhydrous methanol. When the vigorous reaction ceased, 10 g (36.5 mmol) of estrone (**I**) dissolved in a small amount of anhydrous methanol was added. Dimethyl sulfate, 16 ml (0.13 mol), was slowly added (from a dropping funnel), the mixture

was refluxed for 5 h, 1.5 g (0.065 mol) of sodium methoxide and 16 ml (0.13 mol) of dimethyl sulfate were added, and the mixture was refluxed for an additional 4 h. The solvent was distilled off, the residue was diluted with water, and the product was extracted into chloroform. The extract was dried over sodium sulfate, the solvent was evaporated, and the residue was subjected to column chromatography on silica gel using toluene–ethyl acetate (98 : 2) as eluent. Yield 7.6 g (76%) of 3-methoxyestra-1,3,5(10)-trien-17-one (**II**). mp 184–185°C (from toluene–ethyl acetate). ^{1}H NMR spectrum, δ, ppm: 0.90 s (3H, 18-Me), 3.78 s (3H, OMe), 6.63 br.s (1H, 4-H), 6.72 d.d (1H, 2-H, J_1 = 8, J_2 = 2 Hz), 7.20 d (1H, 1-H, J = 8 Hz). IR spectrum (KBr), ν, cm^{-1}: 2920, 2880, 1745, 1620, 1510, 1460, 1260.

17β-Hydroxy-17-vinylsteroids III and XIII. A flask (which was preliminarily calcined) equipped with a dropping funnel and a reflux condenser (cooled with a dry ice–acetone mixture) was charged in a stream of argon with 1.1 g (54.8 mmol) of magnesium and several crystals of iodine. The mixture was heated until violet color appeared, cooled to 0°C, and a solution of 1.1 g (69.6 mmol) of vinyl bromide in 15 ml of anhydrous THF was added dropwise with stirring. A solution of 4.76 mmol of appropriate 17-oxo steroid in 15 ml of anhydrous THF was then added at 0°C, and the mixture was stirred for 3 h at room temperature, several drops of a saturated solution of ammonium chloride was added, and the mixture was extracted with ethyl acetate. The extract was dried over sodium sulfate and evaporated, and the residue was subjected to column chromatography on silica gel using toluene–ethyl acetate (9 : 1) as eluent.

17β-Hydroxy-3-methoxy-17α-vinylestra-1,3,-5(10)-triene (III). From 1 g of 3-*O*-methylestrone (**II**) we obtained 0.99 g (88%) of compound **III** as an oily substance. ^{1}H NMR spectrum, δ, ppm: 0.95 s (3H, 18-Me), 3.78 s (3H, OMe), 5.07 d (1H, 2′-H, J = 1 Hz), 5.15 d (1H, 2′-H, J = 9 Hz), 6.10 d.d (1H, 1′-H, J_1 = 10, J_2 = 17 Hz), 6.68 s (1H, 4-H), 6.75 d.d (1H, 2-H, J_1 = 8, J_2 = 2 Hz), 7.19 d (1H, 1-H, J = 8 Hz). IR spectrum (film), ν, cm^{-1}: 3440, 2935, 2880, 1620, 1510, 1460, 1260, 910.

3β,17β-Dihydroxy-17α-vinylandrost-6-ene (XIII) was synthesized from 2.75 g of androstane (**XII**). Yield 2.5 g (83%). mp 88–89°C (from hexane–ethyl acetate). ^{1}H NMR spectrum, δ, ppm: 0.90 s (3H, 18-Me), 1.02 s (3H, 19-Me), 3.52 m (1H, 3-H), 5.06 d (1H, 2′-H, J = 1 Hz), 5.15 d (2H, 2′-H, J = 9 Hz), 5.35 m (1H, 6-H), 6.03 d.d (1H, 1′-H, J_1 = 10, J_2 = 17 Hz). IR spectrum (KBr), ν, cm^{-1}: 3445, 2940, 2880, 1620, 1510, 1465, 1255, 910.

17-Dihydroisoxazolyl steroids IV–VII and XV–XVIII. Acetaldehyde oxime or isobutyraldehyde oxime, 17 mmol, was added dropwise to a suspension of 2.3 g (17 mmol) of *N*-chlorosuccinimide in 7 ml of chloroform and 0.07 ml of pyridine. The mixture was stirred until it became homogeneous, and a solution of 3.5 mmol of unsaturated steroid in 10 ml of chloroform was added. The mixture was stirred for a short time, and a solution of 2.5 ml (17 mmol) of triethylamine in 10 ml of chloroform was added very slowly in a dropwise manner (over a period of 3 h). The mixture was kept for 24 h at room temperature and washed with water. The organic layer was dried over sodium sulfate and evaporated, and the residue was subjected to column chromatography on silica gel using 5 : 1 hexane–ethyl acetate as eluent.

17β-Hydroxy-3-methoxy-17α-[(5*S*)-3-methyl-4,5-dihydroisoxazol-5-yl]estra-1,3,5(10)-triene (IV). From 1 g of olefin **III** and acetaldehyde oxime we obtained 1.1 g (93%) of isomeric mixture **IV**/**V** at a ratio of 10 : 1 (^{1}H NMR data). Recrystallization from hexane–ethyl acetate gave 0.3 g of the major isomer (**IV**). mp 183–184°C (from hexane–ethyl acetate). ^{1}H NMR spectrum, δ, ppm: 0.92 s (3H, 18-Me), 2.00 s (3H, 3′-Me), 3.05 d.d.d (2H, 4′-H, J_1 = 10, J_2 = 10.5, J_3 = 17 Hz), 3.78 s (3H, OMe), 4.84 t (1H, 5′-H, J = 10 Hz), 6.63 br.s (1H, 4-H), 6.72 d.d (1H, 2-H, J_1 = 8.6, J_2 = 2 Hz), 7.20 d (1H, 1-H, J = 8.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.8 q, 14.4 q, 24.0 t, 27.1 t, 28.2 t, 30.4 t, 34.6 d.d, 40.1 d, 41.1 t, 44.2 d, 47.7 s, 51.5 d, 55.9 q, 84.2 d, 85.1 s, 112.1 d, 114.4 d, 127.8 d, 133.2 s, 138.5 s, 156.9 s, 158.1 s. IR spectrum (KBr), ν, cm^{-1}: 3440, 2950, 2880, 1610, 1585, 1510, 1260. Mass spectrum, *m*/*z*: 369 $[M]^+$, 284 $[M-\text{heteroring}]^+$, 267 $[M-\text{heteroring}-H_2O]^+$, 227, 171, 147.

17β-Hydroxy-3-methoxy-17α-[(5*R*)-3-methyl-4,5-dihydroisoxazol-5-yl]estra-1,3,5(10)-triene (V) was isolated as an oily substance. ^{1}H NMR spectrum, δ, ppm: 0.95 s (3H, 18-Me), 1.98 s (3H, 3′-Me), 3.00 d.d.d (2H, 4′-H, J_1 = 10, J_2 = 10.5, J_3 = 17 Hz), 3.78 s (3H, OMe), 4.66 t (1H, 5′-H, J = 10.5 Hz), 6.63 br.s (1H, 4-H), 6.72 d.d (1H, 2-H, J_1 = 8.6, J_2 = 2 Hz), 7.20 d (1H, 1-H, J = 8.6 Hz). IR spectrum (film), ν, cm^{-1}: 3440, 2950, 2880, 1610, 1585, 1510, 1260. Mass spectrum, *m*/*z*: 369 $[M]^+$, 284 $[M-\text{heteroring}]^+$, 267 $[M-\text{heteroring}-H_2O]^+$, 227, 171, 147.

17β-Hydroxy-17α-[(5*S*)-3-isopropyl-4,5-dihydroisoxazol-5-yl]-3-methoxyestra-1,3,5(10)-triene (VI). From 0.8 g of olefin **III** and 4.5 ml of isobutyraldehyde oxime we isolated 0.86 g (83%) of a mixture of isomers **VI** and **VII** at a ratio of 5 : 1 (according to

the ^{1}H NMR data). mp 83–84°C (from hexane–ethyl acetate). ^{1}H NMR spectrum, δ, ppm: 0.91 s (3H, 18-Me), 1.20 d [6H, CH(C**H**$_3$)$_2$, J = 3 Hz], 2.70 m [1H, C**H**(CH$_3$)$_2$], 3.05 d.d.d (2H, 4′ = H, J_1 = 10, J_2 = 10.5, J_3 = 17 Hz), 3.78 s (3H, OMe), 4.82 t (1H, 5′-H, J = 10 Hz), 6.63 br.s (1H, 4-H), 6.72 d.d (1H, 2-H, J_1 = 8.6, J_2 = 2 Hz), 7.20 d (1H, 1-H, J = 8.6 Hz). IR spectrum (KBr), ν, cm^{-1}: 3440, 2940, 2880, 1610, 1580, 1510, 1470, 1400, 1260. Mass spectrum, *m*/*z*: 367 [*M*]$^+$, 346 [*M* – *i*-Pr]$^+$, 284 [*M* – heteroring]$^+$, 227, 171, 147.

17β-Hydroxy-17α-[(5*R*)-3-isopropyl-4,5-dihydroisoxazol-5-yl]-3-methoxyestra-1,3,5(10)triene (VII). mp 210–212°C (from hexane–ethyl acetate). ^{1}H NMR spectrum, δ, ppm: 0.95 s (3H, 18-Me), 1.20 d [6H, CH(C**H**$_3$)$_2$, J = 3 Hz], 2.70 m [1H, C**H**(CH$_3$)$_2$], 3.00 d.d.d (2H, 4′-H, J_1 = 10, J_2 = 10.5, J_3 = 17 Hz), 3.78 s (3H, OMe), 4.63 t (1H, 5′-H, J = 10.5 Hz), 6.63 br.s (1H, 4-H), 6.72 d.d (1H, 2-H, J_1 = 8.6, J_2 = 2 Hz), 7.20 d (1H, 1-H, J = 8.6 Hz). IR spectrum (KBr), ν, cm^{-1}: 3440, 2940, 2880, 1610, 1580, 1510, 1470, 1400, 1260. Mass spectrum, *m*/*z*: 367 [*M*]$^+$, 346 [*M* – *i*-Pr]$^+$, 284 [*M* – heteroring]$^+$, 227, 171, 147.

3β,17β-Dihydroxy-17α-[(5ξ)-3-methyl-4,5-didihydroisoxazol-5-yl]androst-6-ene (XVa/XVIa). From 0.5 g of compound **XIII** and acetaldehyde oxime we obtained 0.5 g (83%) of iosmeric mixture **XVa**/**XVIa** at a ratio of 6:5 (according to the ^{1}H NMR data) as an oily substance. ^{1}H NMR spectrum, δ, ppm: 0.84 s and 0.89 s (3H, 18Me), 1.02 s (3H, 19-Me), 1.94 s (3H, 3′-Me), 2.80–3.16 m (2H, 4′-H), 3.50 m (1H, 3-H), 4.32 br.s (1H, OH), 4.52 t and 4.72 t (1H, 5′-H, J = 10 Hz), 5.35 m (1H, 6-H).

3β-Acetoxy-17β-hydroxy-17α-[(5ξ)-3-methyl-4,5-dihydroisoxazol-5-yl]androst-6-ene (XVb/XVIb). From 0.6 g of compound **XIV** and acetaldehyde oxime we obtained 0.59 g (78%) of isomeric mixture **XVb**/**XVIb** at a ratio of 9:7 (according to the ^{1}H NMR data) as an oily substance. ^{1}H NMR spectrum, δ, ppm: 0.89 s and 0.92 s (3H, 18Me), 1.02 s (3H, 19-Me), 1.96 s (3H, 3′-Me), 2.04 s (3H, OAc), 2.86–3.18 m (2H, 4′-H), 4.38 br.s (1H, OH), 4.58 t and 4.78 t (1H, 5′-H, J = 10 Hz), 5.31 m (1H, 3-H), 5.35 m (1H, 6-H).

From 0.9 g of compound **XIII** and isobutyraldehyde oxime we obtained 0.66 g (60%) of isoxazolyl steroid **XVII** and 0.20 g (18%) of its isomer **XVIII**.

3β,17β-Dihydroxy-17α-[(5*S*)-3-isopropyl-4,5-dihydroisoxazol-5-yl]androst-6-ene (XVII). Oily substance. ^{1}H NMR spectrum, δ, ppm: 0.90 s (3H, 18-Me), 1.02 s (3H, 19-Me), 1.16 d [6H, CH(C**H**$_3$)$_2$, J = 7 Hz], 2.68 m [1H, C**H**(CH$_3$)$_2$], 3.02 m (2H, 4′-H), 3.52 m (1H, 3-H), 4.75 t (1H, 5′-H, J = 10.5 Hz), 5.35 m (1H, 6-H).

3β,17β-Dihydroxy-17α-[(5*R*)-3-isopropyl-4,5-dihydroisoxazol-5-yl]androst-6-ene (XVII). Oily substance. ^{1}H NMR spectrum, δ, ppm: 0.94 s (3H, 18-Me), 1.03 s (3H, 19-Me), 1.18 d [6H, CH(C**H**$_3$)$_2$, J = 7 Hz], 2.68 m [1H, C**H**(CH$_3$)$_2$], 2.82–3.18 m (2H, 4′-H), 3.54 m (1H, 3-H), 4.56 t (1H, 5′-H, J = 10 Hz), 5.35 m (1H, 6-H).

Trimethylsilyl ethers VIII–XI, XIX, and XX. To a solution of 0.54 mmol of epimeric mixture of 17-hydroxy-17-dihydroisoxazolyl steroid in 2 ml of methylene chloride we added 0.6 ml (2.7 mmol) of chlorotrimethylsilane and 0.2 g (2.7 mmol) of imidazole. The mixture was left to stand for 24 h at room temperature and washed with water, and the products were extracted into chloroform. The extract was dried over sodium sulfate and evaporated, and the residue was subjected to column chromatography on silica gel using 9:1 hexane–ethyl acetate as eluent.

From 0.3 g of epimeric mixture **IV**/**V** we obtained 0.36 g (95%) of a mixture of trimethylsilyl ethers **VIII** and **IX**.

3-Methoxy-17-[(5*S*)-3-methyl-4,5-dihydroisoxazol-5-yl]-17β-trimethylsiloxyestra-1,3,5(10)-triene (VIII). Oily substance. ^{1}H NMR spectrum, δ, ppm: 0.12 s (9H, OSiMe$_3$), 0.88 s (3H, 18-Me), 1.99 s (3H, 3′-Me), 2.62–3.14 m (3H, 4′-H and 6-H), 3.78 s (3H, OMe), 4.74 t (1H, 5′-H, J = 10 Hz), 6.63 s (1H, 4-H), 6.72 d.d (1H, 2-H, J_1 = 8.6, J_2 = 2 Hz), 7.20 d (1H, 1-H, J = 8.6 Hz). IR spectrum (film), ν, cm^{-1}: 2950, 2875, 1610, 1510, 1265.

3-Methoxy-17-[(5*R*)-3-methyl-4,5-dihydroisoxazol-5-yl]-17β-trimethylsiloxyestra-1,3,5(10)-triene (IX). Oily substance. ^{1}H NMR spectrum, δ, ppm: 0.12 s (9H, OSiMe$_3$), 0.85 s (3H, 18-Me), 1.97 s (3H, 3′-Me), 2.62–3.12 m (3H, 4′-H and 6-H), 3.78 s (3H, OMe), 4.56 t (1H, 5′-H, J = 10.5 Hz), 6.63 s (1H, 4-H), 6.72 d.d (1H, 2-H, J_1 = 8.6, J_2 = 2 Hz), 7.20 d (1H, 1-H, J = 2 Hz).

From 0.9 g of epimeric mixture **VI**/**VII** we obtained 1.05 g (94%) of trimethylsilyl ethers **X** and **XI**.

17α-[(5*S*)-3-Isopropyl-4,5-dihydroisoxazol-5-yl]-3-methoxy-17β-trimethylsiloxyestra-1,3,5(10)-triene (X). Oily substance. ^{1}H NMR spectrum, δ, ppm: 0.12 d (9H, OSiMe$_3$), 0.90 s (3H, 18-Me), 1.20 d [6H, CH(C**H**$_3$)$_2$, J = 7 Hz], 2.68 m [1H, C**H**(CH$_3$)$_2$], 2.80–3.06 m (3H, 4′-H and 6-H), 3.78 s (3H, OMe), 4.73 t (1H, 5′-H, J = 10 Hz), 6.63 br.s (1H, 4-H), 6.72 d.d (1H, 2-H, J_1 = 8.5, J_2 = 2 Hz), 7.20 d (1H, 1-H, J = 8.5 Hz). IR spectrum (film), ν, cm^{-1}: 2940, 2880, 1610, 1260.

17α-[(5*R*)-3-Isopropyl-4,5-dihydroisoxazol-5-yl]-3-methoxy-17β-trimethylsiloxyestra-1,3,5(10)-triene (XI). Oily substance. ^{1}H NMR spectrum, δ, ppm: 0.12 s (9H, $OSiMe_3$), 0.86 s (3H, 18-Me), 1.24 d [6H, $CH(CH_3)_2$, J = 7 Hz], 2.68 m [1H, $CH(CH_3)_2$], 2.80–3.06 m (3H, 4′-H and 6-H), 3.78 s (3H, OMe), 4.55 t (1H, 5′-H, J = 10.5 Hz), 6.63 br.s (1H, 4-H), 6.72 d.d (1H, 2-H, J_1 = 8.6, J_2 = 2 Hz), 7.20 d (1H, 1-H, J = 8.6 Hz). IR spectrum (film), ν, cm^{-1}: 2940, 2880, 1610, 1260.

From 0.9 g of epimeric mixture **XVII**/**XVIII**, using 10 equiv of chlorotrimethylsilane, we obtained 1.01 g (95%) of a mixture of 17-trimethylsiloxy derivatives **XIX** and **XX**.

3β-Hydroxy-17α-[(5*S*)-3-isopropyl-4,5-dihydroisoxazol-5-yl]-17β-trimethylsiloxyandrost-6-ene (XIX). Oily substance. ^{1}H NMR spectrum, δ, ppm: 0.12 s (9H, $OSiMe_3$), 0.86 s (3H, 18-Me), 1.02 s (3H, 19-Me), 1.21 d [6H, $CH(CH_3)_2$, J = 7 Hz], 2.68 m [1H, $CH(CH_3)_2$], 2.86 m (2H, 4′-H), 3.54 m (1H, 3-H), 4.63 t (1H, 5′-H, J = 10 Hz), 5.36 m (1H, 6-H). IR spectrum, ν, cm^{-1}: 3415, 2950, 1760, 1250, 1100, 845.

3β-Hydroxy-17α-[(5*R*)-3-isopropyl-4,5-dihydroisoxazol-5-yl]-17β-trimethylsiloxyandrost-6-ene (XX). Oily substance. ^{1}H NMR spectrum, δ, ppm: 0.12 s (9H, $OSiMe_3$), 0.90 s (3H, 18-Me), 1.03 s (3H, 19-Me), 1.21 d [6H, $CH(CH_3)_2$, J = 7 Hz], 2.68 m [1H, $CH(CH_3)_2$], 2.89 m (2H, 4′-H), 3.53 m (1H, 3-H), 4.46 t (1H, 5′-H, J = 10 Hz), 5.35 m (1H, 6-H). IR spectrum, ν, cm^{-1}: 3415, 2950, 1760, 1250, 1100, 845.

Acetylation of steroid alcohols XIII and XIX. Compound **XIII** or **XIX**, 0.2 mmol, was dissolved in 1 ml of pyridine, and 0.5 ml of acetic anhydride was dropwise added. The mixture was left to stand for 18–20 h at room temperature and was then diluted with water, and the product was extracted into ether. The extract was washed with 0.5% hydrochloric acid until neutral reaction, dried over anhydrous sodium sulfate, and evaporated. The residue was dissolved in a small amount of chloroform, and the solution was passed through a layer of silica gel. Yield 90–95%.

From 3,17-diol **XIII** we obtained 95% of 3β-acetoxy-17β-hydroxy-17α-vinylandrost-6-ene (**XIV**). Oily substance. ^{1}H NMR spectrum, δ, ppm: 0.91 s (3H, 18-Me), 1.03 s (3H, 19-Me), 2.04 s (3H, OAc), 5.06 d (1H, 1′-H, J = 1 Hz), 5.15 d (2H, 2′-H, J = 9 Hz), 5.30 m (1H, 3-H), 5.37 m (1H, 6-H). IR spectrum (KBr), ν, cm^{-1}: 3440, 2940, 2880, 1740, 1620, 1510, 1465, 1260, 910.

From 3-hydroxy-20-dihydroisoxazolyl-17-trimethylsiloxy steroid **XIX** we obtained 3-acetoxy-17α-(3-isopropyl-4,5-dihydroisoxazol-5-yl)-17β-trimethylsiloxyandrost-6-ene (**XXI**). Oily substance. ^{1}H NMR spectrum, δ, ppm: 0.12 s (9H, $OSiMe_3$), 0.86 s (3H, 18-Me), 1.03 s (3H, 19-Me), 1.16 d and 1.19 d [6H, $CH(CH_3)_2$, J = 7], 2.04 s (3H, OAc), 2.68 m [1H, $CH(CH_3)_2$], 2.86 m (2H, 4′-H), 3.61 m (2H, 3-H and 5′-H), 5.38 m (1H, 6-H). IR spectrum (film), ν, cm^{-1}: 2980, 2960, 2880, 2860, 1745, 1480, 1450, 1385, 1370, 1255.

REFERENCES

1. Khripach, V.A., Litvinovskaya, R.P., and Baranovskii, A.V., *Zh. Org. Khim.*, 1990, vol. 26, no. 6, pp. 1274–1278.
2. Khripach, V.A., Litvinovskaya, R.P., Baranovskii, A.V., and Akhrem, A.A., *Dokl. Akad. Nauk SSSR*, 1991, vol. 318, no. 3, pp. 597–600.
3. Verenich, A.I., Govorova, A.A., Galitskii, N.M., Baranovskii, A.V., Litvinovskaya, R.P., and Khripach, V.A., *Zh. Strukt. Khim.*, 1992, no. 5, pp. 552–554.
4. Khripach, V.A., Litvinovskaya, R.P., and Drach, S.V., *Zh. Org. Khim.*, 1993, vol. 29, no. 4, pp. 717–723.
5. Litvinovskaya, R., Drach, S., and Khripach, V., *Mendeleev Commun.*, 1995, no. 6, pp. 215–216.
6. Litvinovskaya, R.P., Koval', N.V., and Khripach, V.A., *Khim. Geterotsikl. Soedin.*, 1998, no. 2, pp. 267–273.
7. Litvinovskaya, R.P., Lyakhov, A.S., Drach, S.V., Khripach, V.A., and Govorova, A.A., *Russ. J. Gen. Chem.*, 2000, vol. 70, no. 9, pp. 1476–1479.