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SYNTHESIS OF STEROIDS CONTAINING A VICINAL DIOL GROUP IN THE SIDE CHAIN VIA ISOXAZOLINE INTERMEDIATES*

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A sequence of conversions including 1,3-dipolar cycloaddition of nitrile oxides to steroid 22-enes and modification of the isoxazolines obtained by hydroxylation to the 4' position and splitting of the heterocycle leads to steroids with a polyfunctional open chain, 22,23-dihydroxy 24-ketones.

The problem of stereocontrolled synthesis of natural polyhydroxysteroids accounted for our interest in their promising new synthetic precursors, isoxazolinyl steroids [2]. We obtained a series of steroid compounds with a heterocycle in the side chain which were used in the synthesis of brassido steroids [3], ecdy steroids [4], sterols of marine organisms [5], etc. The strategy of these syntheses consisted in preparing heterocyclic adducts by reacting steroid olefins with nitryl oxides, opening the isoxazoline ring, and converting the acyclic compounds obtained.

An expansion of the synthetic potential of steroid isoxazolines can result from modification of 20-isoxazoline steroids followed by realization of the latent functionality of the heterocycle. As we know, the isoxazoline ring is stable toward many reactants, i.e., strong acids, mild reductants, or strong oxidants. One of the ways of modifying 2-isoxazolines is based on their ability to enter into substitution reactions. Under the action of strong bases, one of the allyl protons becomes detached to form an anion which is stable at −60 to 80°C and can react with various electrophiles [6, 7]. By this method, we synthesized steroid 4'-hydroxyisoxazolines and used them further to prepare steroids with a polyfunctional side chain. This approach is also of interest in that 4'-hydroxyisoxazolines cannot be obtained directly by 1,3-dipolar cycloaddition of nitryl oxides to steroid olefins.

In this paper we studied the possibility of modifying 3'-methyl-substituted derivatives, prepared for this purpose, of 20-isoxazolinyl steroids (IIa, IIIa) as well as their 3'-isopropyl-substituted analogs (IIb, IIIb), which we described elsewhere [8]. Hydroxylation of the indicated compounds to the 4' position of the heterocycle was carried out by use of a method employed in the synthesis of intermediates of amino sugars [6]. Thus, deprotonation of the isoxazoline ring of compounds II, III by lithium diisopropylamide with 3 equivalents of hexametapol and subsequent treatment of the anion obtained with trimethyl borate and oxidation of the 4'-borate formed with tert-butyl hydroperoxide in the presence of triethylamine led to the previously unknown 4'-hydroxyisoxazolinyl steroids (IVa, b, Va, b). The IR spectra of the compounds obtained show characteristic bands of stretching vibrations of the OH group at 3450 cm^{-1}. In place of the characteristic signal of methylene protons of the isoxazoline ring, the ESR spectrum shows a one-proton doublet signal of the carbinol proton at 4.92 (R = i-Pr) or 4.80 (R = Me) for 23R-isomers of IV, and in the case of 23S-isomers of V — at 4.81 (R = i-Pr) or 4.70 ppm (R = Me). The signals of the protons at the $C_{(22)}$ atom become simplified and are shifted to a stronger field by 0.3-0.32 ppm. The displacement of the signals of H_{Me} protons of the isopropyl group to a stronger field is significant.

Formation of 4'-hydroxyisoxazolines is also confirmed by their conversion to the corresponding acetates (VIa) and (VIIa, b); in the IR spectra of compounds VI and VII, this is manifested in the form of the band of stretching-vibrations of the ester group at 1750 cm^{-1} and 1250 cm^{-1} and in the ESR spectra, by signals of the protons of the CH_3CO group (2.13 ppm) and by a shift of the signals of the proton at the $C_{(4')}$ atom to a weaker field.

*For preliminary report see [1].

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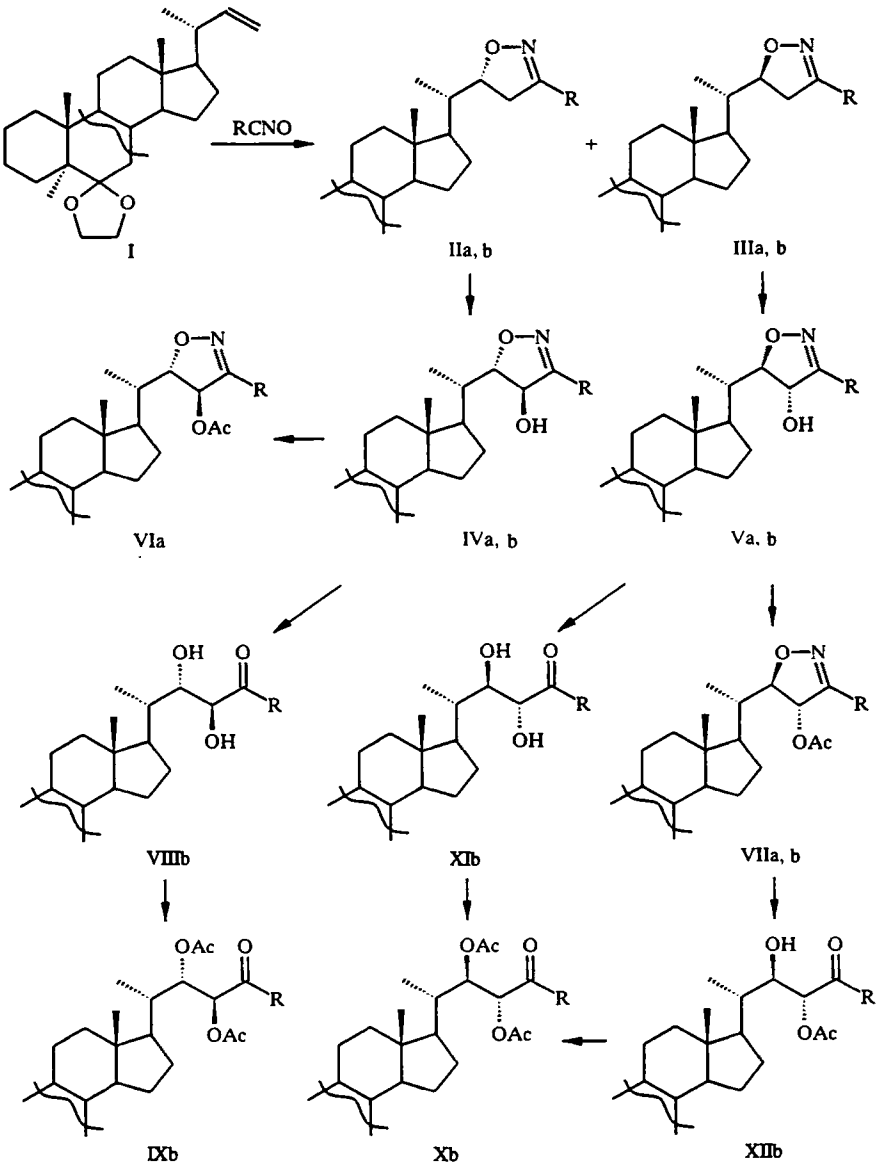

a R = Me, b R = *i*-Pr

It is clear from the data presented that the hydroxylation reaction, as expected, takes place regio- and stereoselectively, forming only an endo product with a trans configuration of the oxygen-containing substituents in the 4′ and 5′ positions; this is consistent with reported data [7] and confirmed by further chemical conversions of isoxazolinyl steroids IV-VII.

Conversion to compounds with an open side chain was accomplished by reductive splitting of isoxazoline IVb over Raney nickel in the presence of boric acid. The (22S), (23S)-dihydroxy 24-ketone (VIIIb) obtained has an IR spectrum with a broad band of stretching vibrations of the hydroxyl group (3430 cm^{-1}) and a strong band of stretching vibrations of the carbonyl group (1720 cm^{-1}). The ESR spectrum shows two one-proton multiplets (4.16 ppm and 4.35 ppm) corresponding to the protons at the $C_{(22)}$ and $C_{(23)}$ atoms. A characteristic feature is an appreciable shift of the signal of protons of the 21-methyl group to a weaker field.

Just as the 24-oxo-22,23-cis-diols described earlier [9], the 22,23-trans-diol VIIIb obtained is unstable and readily undergoes splitting at the $C_{(22)}-C_{(23)}$ bond to form the 22-aldehyde, and this substantially reduces the yield of the target product. Such decomposition can be prevented by converting the product to the corresponding diacetate (IXb). The IR spectrum of the latter contains absorption bands of the CH_3CO group (1750 cm^{-1} and 1240 cm^{-1}), which in the ESR spectrum are manifested in the form of two three-proton singlets; the signals of the protons at the $C_{(22)}$ and $C_{(23)}$ atoms are shifted (compared to the diol) to a weaker field (5.18 ppm and 5.38 ppm, respectively). The main fragments in the mass spec-

TABLE 1. Properties of the Synthesized Compounds*

Compound	Name	Empirical formula	Found, % / Calculated, %			Yield, %
			C	H	N	
IIa	(20S, 22R)-20(3-Methylisoxazolin-5-yl)-3α, 5-cyclo-6,6-ethylenedihydroxy-5α-pregnane	$C_{27}H_{41}NO_3$	75,41 75,83	9,50 9,66	3,35 3,28	64
IIIa	(20S, 22S)-20(3-Methylisoxazolin-5-yl)-3α, 5-cyclo-6,6-ethylenedihydroxy-5α-pregnane	$C_{27}H_{41}NO_3$	75,54 75,83	9,56 9,66	3,22 3,28	20
IVa	(20S, 22S, 23S)-20-(4-Hydroxy-3-methylisoxazolin-5-yl)-3α,5-cyclo-6,6-ethylenedihydroxy-5α-pregnane	$C_{27}H_{41}NO_4$	73,00 73,10	9,24 9,32	3,08 3,16	75*2
IVb	(20S, 22S, 23S)-20(4-Hydroxy-3-isopropylisoxazolin-5-yl)-3α,5-cyclo-6,6-ethylenedihydroxy-5α-pregnane	$C_{29}H_{45}NO_4$	73,68 73,84	9,54 9,62	2,87 2,97	56*2
Va	(20S, 22R, 23R)-20(4-Hydroxy-3-methylisoxazolin-5-yl)-3α,5-cyclo-6,6-ethylenedihydroxy-5α-pregnane	$C_{27}H_{41}NO_4$	73,10 72,89	9,32 9,36	3,16 3,11	76*2
Vb	(20S, 22R, 23R)-20(4-Hydroxy-3-isopropylisoxazolin-5-yl)-3α,5-cyclo-6,6-ethylenedihydroxy-5α-pregnane	$C_{29}H_{45}NO_4$	73,70 73,84	9,50 9,62	2,88 2,97	78*2
VIa	(20S, 22S, 23S)-20-(4-Acetoxy-3-methylisoxazolin-5-yl)-3α,5-cyclo-6,6-ethylenedihydroxy-5α-pregnane	$C_{29}H_{45}NO_5$	71,35 71,42	9,20 9,30	2,69 2,87	95
VIIa	(20S, 22R, 23R)-20(4-Acetoxy-3-methylisoxazolin-5-yl)-3α,5-cyclo-6,6-ethylenedihydroxy-5α-pregnane	$C_{29}H_{43}NO_5$	71,38 71,72	8,67 8,93	2,74 2,88	97
VIIb	(20S, 22R, 23R)-20-(4-Acetoxy-3-isopropylisoxazolin-5-yl)-3α,5-cyclo-6,6-ethylenedihydroxy-5α-pregnane	$C_{31}H_{47}NO_5$	72,34 72,48	9,03 9,22	2,59 2,73	96
VIIIb	(20S, 22S, 23S)-3α,5-Cyclo-6,6-ethylenedihydroxy-5α-cholestan-24-one-22,23-diol	$C_{29}H_{46}O_5$	73,20 73,38	9,64 9,77	–	70
IXb	(20S, 22S, 23S)-22,23-Diacetoxy-3α,5-cyclo-6,6-ethylenedihydroxy-5α-cholestan-24-one	$C_{33}H_{50}O_7$	70,83 70,94	8,95 9,02	–	80
Xb	(20S, 22R, 23R)-22,23-Diacetoxy-3α,5-cyclo-6,6-ethylenedihydroxy-5α-cholestan-24-one	$C_{33}H_{50}O_7$	70,85 70,94	8,93 9,02	–	80*3 47*4

*All compounds except IVb were obtained as oils; mp of compound IVb 100-101°C.

*2Yield calculated in terms of the initial isoxazolinyl steroid.

*3From compound VIIb.

*4From compound Vb.

TABLE 2. Spectral Properties of the Compounds Obtained

Compound	IR spectrum, cm^{-1}	Mass spectrum, m/z	ESR spectrum, δ, ppm, SSCC (J), Hz
IVb	1630	427 $[M]^+$, 412 $[M-Me]^+$	0,33 (1H, d.d., J_1 = 4,8, J_2 = 7,4, 4-H); 0,76 (3H, s, 18-Me); 0,88 (3H, d, J = 7,0, 21-Me); 1,02 (3H, s, 19-Me); 1,96 (3H, s, 3'-Me); 2,68 (2H, d, J = 10,0, 4'-H); 4,64 (1H, m, 22-H)
IIIa	1630	427 $[M]^+$, 412 $[M-Me]^+$	0,33 (1H, d.d, J_1 = 4,8, J_2 = 7,4, 4-H); 0,72 (3H, s, 18-Me); 0,90 (3H, d, J = 7,0, 21-Me); 1,02 (3H, s, 19-Me); 1,96 (3H, s, 3'-Me); 2,70 and 2,96 (2H, d.d, J_1 = 10, J_2 = 4, 4'-H); 4,70 (1H, m, 22-H)
IVa	3450	463 $[M]^+$, 448 $[M-Me]^+$, 421 $[M-i-Pr]^+$	0,34 (1H, d.d, J_1 = 4,8, J_2 = 7,4, 4-H); 0,74 (3H, d, J = 7,0, 21-Me); 0,78 (3H, s, 18-Me); 1,02 (3H, s, 19-Me); 2,04 (3H, s, 3'-Me); 4,32 (1H, m, 22-H); 4,80 (1H, d, J = 5, 4'-H)
IVb	3450	471 $[M]^+$, 456 $[M-Me]^+$, 429 $[M-i-Pr]^+$	0,31 (1H, d.d, J_1 = 4,8; J_2 = 7,4; 0,74 (3H, d, J = 7,1, 21-Me); 0,78 (3H, s, 18-Me); 1,02 (3H, s, 19-Me); 1,21 and 1,27 (6H, two d, 26- and 27-Me); 2,82 (1H, m, CHMe2); 4,34 (1H, m, 22-H); 4,92 (1H, d, J = 5, 4'-H)
Va	3450	463 [M+1], 448 $[M-Me]^+$, 421 $[M-i-Pr]^+$	0,34 (1H, d.d, J_1 = 4,8, J_2 = 7,4, 4-H); 0,75 (3H, d, J = 7,0, 21-Me); 0,80 (3H, s, 18-Me); 1,02 (3H, s, 19-Me); 2,04 (3H, s, 3'-Me); 4,34 (1H, m, 22-H); 4,70 (1H, d, J = 4,5, 4'-H)
Vb	3450	471 $[M]^+$, 456 $[M-Me]^+$, 429 $[M-i-Pr]^+$	0,31 (1H, d.d, J = 4,8, J = 7,4, 4-H); 0,71 (3H, s, 18-Me); 0,76 (3H, d, J = 7,0, 21-Me); 1,02 (3H, s, 19-Me); 1,22 and 1,28 (6H, two d, J = 7,0, 26- and 27-Me); 2,80 (1H, m, CHMe2); 4,34 (1H, m, 22-H); 4,81 (1H, d, J = 4,5, 4'-H)
VIa	1750, 1240	485 $[M]^+$, 470 $[M-Me]^+$, 425 $[M-AcOH]^+$	0,34 (1 d.d, J_1 = 4,8, J_2 = 7,4, 4-H); 0,74 (3H, s, 18-Me), 0,82 (3H, d, J = 7,0, 21-Me); 1,01 (3H, s, 19-Me); 1,96 (3H, s, 3'-Me); 2,06 (3H, s, Ac); 4,42 (1H, m, 22-H); 6,00 (1H, d, J = 5,0, 4'-H)
VIIa	1745, 1240	485 $[M]^+$, 470 $[M-Me]^+$, 425 $[M-AcOH]^+$	0,34 (1H, d.d, J_1 = 4,8, J_2 = 7,4); 0,72 (3H, s, 18-Me); 0,84 (3H, d, J = 7,0, 21-Me), 1,00 (3H, s, 19-Me); 1,98 (3H, s, 3'-Me); 2,14 (3H, s, Ac); 4,44 (1H, m, 22-H); 5,68 (1H, d, J = 4,5, 4'-H)
VIIb	1740, 1250	513 $[M]^+$, 498 $[M-Me]^+$, 471 $[M-i-Pr]^+$, 453 $[M-AcOH]^+$	0,33 (1H, d.d, J_1 = 4,8, J_2 = 7,4); 0,72 (3H, s, 18-Me); 0,80 (3H, d, J = 7,0, 21-Me); 1,02 (3H, s, 19-Me); 1,18 and 1,25 (6H, two d, 26- and 27-Me); 2,12 (3H, s, Ac); 2,71 (1H, m, CHMe2); 4,38 (1H, m, 22-H); 5,83 (1H, d, J = 4,5, 4'-H)
VIIIb	3430, 1720	474 $[M]^+$, 459 $[M-Me]^+$, 456 $[M-H_2O]^+$	0,33 (1H, d.d, J_1 = 4,8, J_2 = 7,4, 4-H); 0,74 (3H, s, 18-Me); 0,87 (3H, d, J = 7,0, 21-Me); 1,02 (3H, s, 19-Me); 1,12 and 1,14 (6H, d.d, J = 7,0, 26- and 27-Me); 3,06 (1H, m, CHMe2); 4,16 (1H, m, 22-H); 4,35 (1H, m, 23-H)
IXb	1750, 1240	558 $[M]^+$, 543 $[M-Me]^+$, 498 $[M-AcOH]^+$, 438 $[M-2AcOH]^+$	0,33 (1H, d.d, J_1 = 4,8, J_2 = 7,4; 0,72 (3H, s, 18-Me); 0,87 (3H, d, J = 7,0, 21-Me); 1,01 (3H, s, 19-Me); 1,06 and 1,18 (6H, two d, J = 7,0, 26- and 27-Me); 2,03 (3H, s, Ac); 2,14 (3H, s, Ac); 2,88 (1H, m, CHMe2); s, 5,18. (1H, d.d, J_1 = 2,5, J_2 = 7,0, 22-H); 5,38 (1H, d, J = 7,0, 23-H)
Xb	1750, 1240	558 $[M]^+$, 543 $[M-Me]^+$, 498 $[M-AcOH]^+$, 438 $[M-2AcOH]^+$	0,33 (1H, d, d, J_1 = 4,8, J_2 = 7,4, 4-H); 0,73 (3H, s, 18-Me); 1,02 (3H, s, 19-Me); 1,06 (6H, d, J = 7,0, 26- and 27-Me); 1,18 (3H, d, J = 7,0, 21-Me); 2,08 (3H, s, 2,16 (3H, s, Ac); 2,80 (1H, m, CHMe2); 5,32 (2H, m, 22- and 23-H)

*In the spectra of all compounds, the 3-H proton signal is in the form of a triplet with its center at 0.62 ppm; the multiplet signal of the ethylenedihydroxy group protons is located in the 3.68-4.08 ppm region.

trum of compound IXb are $[M-15]^+$ (detachment of methyl group), $[M-60]^+$ and $[M-120]^+$ (detachment of elements of acetic acid).

A comparison of the spectral characteristics of the prepared (22S), (23S)-isomers of diol VIIIb and its diacetate IXb with the characteristics of the known (22S), (23S)-isomers [9] makes it possible to confirm the configuration of the chiral center at the $C_{(23)}$ atom, formed in the hydroxylation reaction. In view of the fact that the stereochemistry of the center at the $C_{(22)}$ atom of molecules IV, VIII and IX does not change in the conversion chain discussed, in the case of the (22R)-isomer

of IIb, the parameters of the product of its hydroxylation and opening (if the hydroxylation proceeded to the cis position) should be the same as the parameters of the known (22S), (23R)-cis-diol and its diacetate, for which the following chemical shifts are characteristic in the ESR spectrum: 3.98 ppm (22-H) and 4.35 ppm (23-H) for the diol and 5.20 ppm and 5.28 ppm, respectively, for the diacetate [9]. However, despite the fact that the shape of the signals is similar, their position in the case of the products synthesized in this work differs appreciably: the chemical shifts are 4.16 ppm and 4.35 ppm for the diol VIIIb, and 5.18 ppm and 5.38 ppm for the diacetate IXb. Moreover, the clearly resolved signals in the spectra of the diacetates being compared make it possible to calculate SSCC [I]. Thus, for the diacetate of the cis-diol $J_{22,23}$ = 1 Hz [8], and for the diacetate of the trans-diol IXb $J_{22,23}$ = 7 Hz. These data also support the structural assignments made.

Conversion of 4′-hydroxyisoxazolinyl steroid Vb to the acyclic product (Xb) was carried out in two ways: first, by splitting the heterocycle of compound Vb, then by acetylating the unpurified diol (XIb). The yield of diacetate Xb was 47% in this case. Second, by opening the isoxazoline ring of the 4′-acetoxy derivative VIIb, then by acetylating the 23-acetoxy-22-hydroxy steroid (XIIb) formed. The yield of diacetate Xb in the second case was 80%, i.e., this method is preferable for converting 4′-hydroxyisoxazolinyl steroids into open-chain compounds. The proposed method makes it possible to form a 22,23-trans-vicinal dipole group, something that is difficult to accomplish otherwise. The presence of the 24-keto group can be used to synthesize a series of derivatives, as illustrated, in particular, by the preparation of the side chain of the (22S), (23S)-dolicholide [9].

EXPERIMENTAL

The ESR spectra were recorded on a Bruker WM-360 and a Bruker A-200 (operating frequencies, 360 MHz and 200 MHz, respectively) with TMS as internal standard. The IR spectra were obtained on a UR-20 instrument (in a film and a KBr pellet). The mass spectra were measured on a Varian MAT-311 instrument with 70-eV ionizing radiation. The melting point was determined on a Kofler micro hot stage.

The course of the reaction was followed by TLC on Merck silica gel plates. The column chromatography was carried out on Chemapol Silicagel L 5/40, 40/100, 100/160 and Merck Kieselgel 60.

Synthesis of 20-(3-R-Isoxazolinyl-5) Steroids (IIa, b, IIIa, b). To 10 mmole of N-chlorosuccinimide suspended in 20 ml of anhydrous chloroform and 0.04 ml of pyridine was added 10 mmole of acetaldehyde oxime or isobutyraldehyde, and the mass obtained was stirred for ~20 min. To the transparent solution formed was added at 20°C 2 mmole of steroid olefin I in 25 ml of chloroform, and after a brief agitation, 10 mmole of triethylamine was added (dropwise), then the reaction mass was stirred for 3 h. The solvent was evaporated off, and the corresponding isomeric products II and III were separated from the residue by column chromatography on silica gel (eluent, 7 : 1 hexane–ether).

4′-Hydroxylation of 20-Isoxazolinyl Steroids (IIa, b and IIIa, b). To a mixture of 2 ml of tetrahydrofuran, 3-4 mmole of hexametapol and 1.1 mmole of diisopropylamine at −65°C was added 0.7 ml of 1.6 N n-butyllithium, then after 10 min, 0.33 mmole of steroid II or III in 10 ml of tetrahydrofuran. The reaction mass was stirred for 30 min and cooled to −78°C, kept for 2 h at this temperature, then 2 mmole of trimethyl borate was added, and the mixture was stirred for 2.5 h. To the reaction mixture was then added 4.5 mmole of tert-butyl peroxide in 0.63 ml of triethylamine, and the mixture was kept at room temperature for 60 h. It was then treated with water and extracted with ether, the extract was dried with anhydrous sodium sulfate, and evaporated off, and products IV and V, respectively, were separated from the residue by column chromatography (eluent, 5 : 2 hexane–ether).

Cleavage of the Heterocycle of 20-(4-Hydroxy-3-isopropylisoxazolinyl-5) Steroids IVb, Vb and 20-(4-Acetoxy-3-isopropylisoxazolinyl-5) Steroid VIIb. To Raney nickel of brand W-2, saturated with hydrogen for 2 h, was added with stirring in ethanol 1 mmole of boric acid and a solution of 0.01 mmole of compound IVb in ethanol. The reaction mixture was stirred at room temperature for 5 h in a hydrogen atmosphere. When the reaction was complete (according to TLC data), the catalyst was filtered off, and the solvent was evaporated off. The residue was dissolved in ethyl acetate, and the solution was washed with water, then dried with anhydrous sodium sulfate, and evaporated. Product VIIIb was separated from the residue by column chromatography (eluent, 2 : 7 ether–hexane). The cleavage of compounds Vb and VIIb was carried out similarly; products XIb and XIIb obtained were correspondingly subjected to further acetylation without chromatographic purification (see below).

Acetylation of 4′-Hydroxyisoxazolinyl Steroids IVb and Va, b, 22,23-Steroid Diols VIIIb and XIb, and 22-Hydroxy-23-acetoxy Steroid XIIb. To a solution of 0.16 mmole of the initial steroid in 1 ml of pyridine was added drop-

wise 0.5 ml of acetic anhydride. The reaction mixture was kept for 18-20 h at room temperature, treated with water, and extracted with ether, and the extract was washed with a 0.5% HCl solution until the reaction was neutral; it was then dried over anhydrous sodium sulfate, the solvent was evaporated off, and the residue was dissolved in a small amount of chloroform and purified by passing through a layer of silica gel.

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