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Structure-Reactivity Relationship in 19-Methyl- and 19-Nor-5,10-secosteroids. Part 4. Intramolecular Nitrone 1,3-Dipolar Cycloadditions.†

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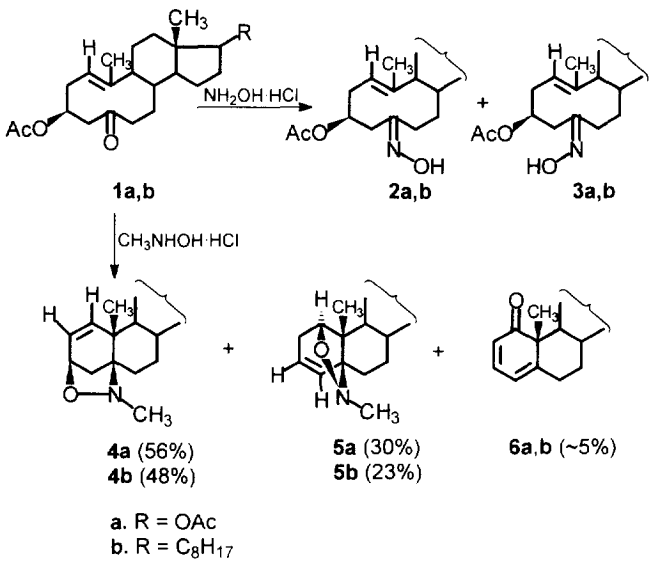
Abstract: The (*Z*)-19-nor-5,10-secosteroidal ketone **11** reacts with hydroxylamine hydrochloride to give the (*E*)- and (*Z*)-oximes **12** and **13**, while with *N*-methylhydroxylamine hydrochloride it undergoes transannular nitrone 1,3-dipolar cycloaddition to give isoxazolidines **14** and **15**, and an estratriene derivative **16**, originating from **14**. The (*E*)-19-nor-5,10-seco-ketone **17** undergoes intramolecular nitrone 1,3-dipolar cycloaddition with both hydroxylamine hydrochloride and *N*-methylhydroxylamine hydrochloride to produce, with the former reagent, a single isoxazolidine **18**, and with the latter, two regioisomers **22** and **23**. The reaction and stereochemical courses of the above transformations are compared with those previously observed for the corresponding 19-methyl analogues. Copyright © 1996 Published by Elsevier Science Ltd

Our previous studies on the reactivity of (*Z*)- and (*E*)-1,10-unsaturated 5,10-seco-5-ketones of the "normal", (*i.e.*, 19-methyl containing) steroid series **1** (Scheme 1) and **7** (Scheme 2),[1] towards hydroxylamine and *N*-methylhydroxylamine have shown the following.

The (*Z*)-seco-ketones **1a,b** react with hydroxylamine hydrochloride to give (Scheme 1) only a mixture of *E*- and *Z*-oximes **2a,b** and **3a,b**.[1a] However, upon heating with *N*-methylhydroxylamine hydrochloride, they undergo intramolecular cycloaddition (along with acetic acid elimination) to produce two types of structurally different isoxazolidines, the Δ^1-unsaturated compounds **4a** and **4b** (in 56% and 48% yield) and the Δ^3-unsaturated products **5a** and **5b** (in 30% and 23% yield) in which the 3β,5β- and 1β,5β-epoxyimino bridge, respectively, is incorporated into the natural steroid A/B-*cis*-5β,10β-configuration; the minor products in this reaction being 2,4-dien-5-ones **6a,b** (formed in about 5% yield).[2]

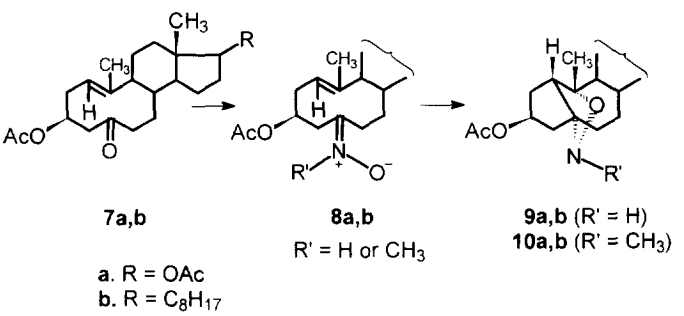
On the other hand, when the (*E*)-1(10)-unsaturated 5-oxo-5,10-secosteroids **7a,b** (Scheme 2) were treated with both hydroxylamine hydrochloride (R′ = H) and *N*-methylhydroxylamine hydrochloride(R′ = CH_3) they were converted regio- and stereoselectively in high yield (up to 95%), *via* the intermediately formed 1,3-dipolar oxime tautomers[3] or nitrones **8a** and **8b**,[4] respectively, to the isoxa-

† Dedicated to Professor Vladimir Prelog on the occasion of his 90th birthday.



Scheme 1

zolidine derivatives **9a,b** and **10a,b**, in which the epoxyimino bridge is α-oriented and incorporated into the steroidal A-nor/B-homo systems.[5]



Scheme 2

These results were explained in terms of different structural characteristics of the (*Z*)- and (*E*)-secosteroidal cyclodecenone systems.[6,7] It was also assumed that the reaction and stereochemical courses of the above intramolecular processes could depend, among other factors, upon the presence of the 19-methyl group at the C(10) end of the $\Delta^{1(10)}$-double bond.

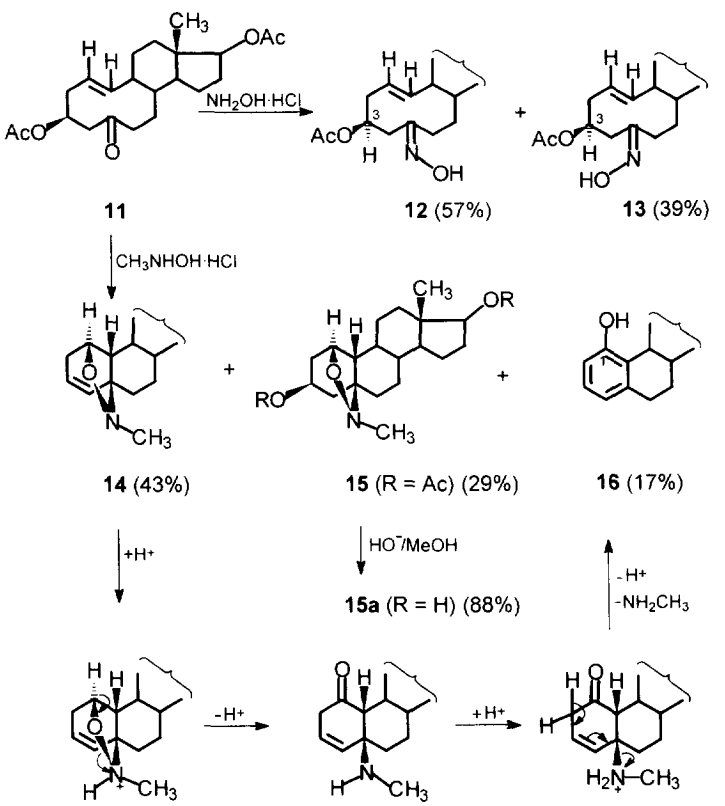
Therefore, in this paper similar nitrone 1,3-dipolar cycloadditions of the corresponding 19-demethylated compounds, *i.e.*, (*Z*)- and (*E*)-3β,17β-diacetoxy-19-nor-5,10-secoandrost-1(10)-en-5-ones **11** (Scheme 3) and **17** (Scheme 4),[8,9] were investigated and compared with those of the (*Z*)- and (*E*)-19-methyl analogues **1** and **7** described above. Such comparison seems to be justifiable because

according to the ^{1}H-NMR and ^{13}C-NMR spectral data the ground state conformations of the ten-membered rings of the (*Z*)- and (*E*)-19-nor-5,10-secosteroidal ketones **11** and **17**, respectively, and those of the corresponding 19-methyl derivatives **1** and **7**, respectively, are very similar in solution.[9]

Results

The (*Z*)- and (*E*)-19-nor compounds **11** and **17** were treated with hydroxylamine hydrochloride and *N*-methylhydroxylamine hydrochloride, respectively, under experimental conditions similar to those applied in the 19-methyl series. The following comments can be made about the results.

When the (*Z*)-secoketone **11** in refluxing ethanolic solution was treated with hydroxylamine hydrochloride in the presence of pyridine (*ca.* 0.6 mol equiv. with respect to hydroxylamine hydrochloride), it was converted, similarly to the 19-methyl analogue **1**, only to the (*E*)- and (*Z*)-oximes



Scheme 3

12 and **13** (in 57% and 39% yield) (Scheme 3). The configuration of these isomers was deduced by comparison of ^{1}H-NMR chemical shifts of their 3α-H signals. In the (*Z*)-oxime **13**, due to the

deshielding by the oxime hydroxy group, this signal appears at lower field (δ = 5.92) than in the (*E*)-oxime **12** (δ = 5.35).

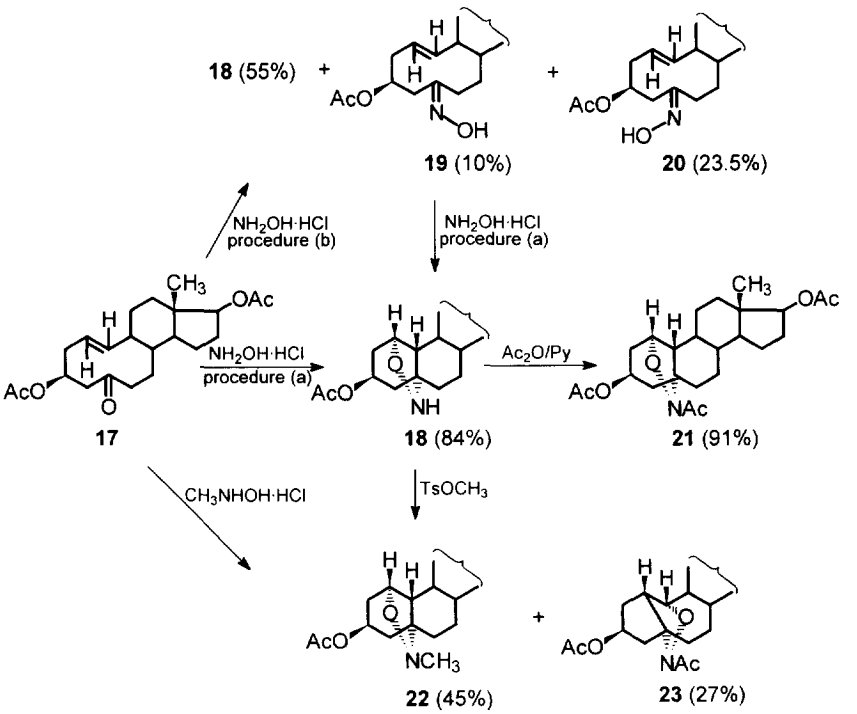
However, when the (*Z*)-19-nor-5,10-seco-ketone **11** was treated with *N*-methylhydroxylamine hydrochloride (in boiling ethanol/pyridine (1:1, v/v) solution for 24 h) (Scheme 3) it underwent exclusively transannular 1,3-dipolar nitrone cycloaddition, which, unlike the 19-methyl-seco-ketone **1**, took place both with and without acetic acid elimination, producing Δ^3-1β,5β-isoxazolidine **14** (in 43% yield) and 3β-acetoxy-1β,5β-isoxazolidine **15** (in 29% yield). In addition, 1-hydroxy-1,3,5(10)-estratrien-17β-yl acetate (**16**) was isolated (in 17% yield). It was found that this product is formed (Scheme 3) from the isoxazolidine **14** in the course of the reaction (see Experimental). In the 19-nor series the Δ^1-unsaturated 3β,5β-epoxyimino derivative, *i.e.*, the 19-nor-analogue of isoxazolidine **4a** was not obtained.

The structures of products **14** – **16** were deduced from their spectral characteristics and ascertained by X-ray analysis. Thus, the latter method unequivocally confirmed the presence of the Δ^3-double bond in isoxazolidine **14**,[10] the 1β,5β-stereochemistry of the epoxyimino bridge in compounds **14** and **15**[10] (actually, X-ray analysis in the latter case was performed on the more suitable crystals of the corresponding alcohol **15a**, obtained from acetate **15** by alkaline hydrolysis), and also the 1-position of the hydroxy group in the estratriene derivative **16**.[11]

The reaction of the stereoisomeric (*E*)-seco-ketone **17** with hydroxylamine hydrochloride (Scheme 4) was carried out: (a) in ethanol solution containing *ca.* 0.6 mol equiv. pyridine (with respect to hydroxylamine hydrochloride) at reflux for 28 h, and (b) in boiling ethanol/pyridine (1:1, v/v) for 4 h. In both cases the (*E*)-seco-ketone underwent regio- and stereoselectively intramolecular 1,3-dipolar nitrone cycloaddition to give isoxazolidine **18** (for (a): as the only product isolated in 84% yield, and for (b): as the main product obtained in 55% yield), in which the 1α,5α-epoxyimino bridge, contrary to the isoxazolidines **9** and **10** of the 19-methyl series, is part of the natural steroid A/B *trans* structure. Under the conditions of procedure (b) the corresponding (*E*)- and (*Z*)-oximes **19** and **20** were also isolated (in 10% and 23.5% yield, respectively). Both oximes were quantitatively transformed to the isoxazolidine **18** when treated with hydroxylamine hydrochloride under experimental conditions described in procedure (a).

The stereochemistry of oximes **19** and **20** was determined by similar method applied to the oximes **12** and **13** of the (*Z*)-1(10)-unsaturated series, *i.e.*, by comparing ^{1}H-NMR chemical shifts of their 3α-H signals. In oxime **20** (due to the deshielding by the oxime hydroxy group) this signal appears at a considerably lower field (δ = 5.95) than in oxime **19**, (δ = 5.40), thus indicating the *Z* configuration for the former, and the *E* configuration for the latter isomer.

Isoxazolidine **18** was characterized as 1α,5-epoxyimino-19-nor-5α-androstane-3β,17β-diyl diacetate on the basis of analytical and spectral data (see Experimental). In addition, it was transformed with acetic anhydride in pyridine to the corresponding *N*-acetyl derivative **21**, the X-ray analysis of which confirmed the proposed structure.



Scheme 4

X-ray analysis and structure determination. - Crystal data of *N*-acetyl-1α,5-epoxyimino-19-nor-5α-androstane-3β,17β-diyl diacetate (**21**) are as follows: $C_{24}H_{35}NO_6$, M_r = 433.35, monoclinic, space group $P2_1$, a = 13.344 (2), b = 7.486 (1), c = 13.116 (2)Å, β = 117.31 (1)°; V = 1164.2(2)Å^3; D_x = 1.24 gcm^{-3} for Z = 2. The intensities of 4093 $h \pm k \pm l$ ($0 \le h \le 15$, $-9 \le k \le 8$, $-15 \le l \le 14$) were collected on a Huber four circle diffractometer using Cu$K\alpha$ graphite monochromatized radiation (λ = 1.54178 Å) up to 2θ = 135°. 3326 reflections were considered as observed ($I \ge 2.5\sigma$ (I)) and used in the structure refinement. The structure was solved by direct methods using SHELXS86[12] and refined using F first with isotropic and then anisotropic temperature factors with SHELX76.[13] 8 H atoms, located from a difference Fourier synthesis, were included in the refinement process; the positions of the other H atoms were calculated with C–H distances of 1.08 Å and H–C–H angles of 109.4°. At the end of the refinement a comparison of Friedel pairs shows a slight preference for the enantiomer represented here after. The final R value is 0.071. The list of atomic coordinates and molecular dimensions has been deposited with the Cambridge Crystallographic Data Centre.

The Figure is ORTEP plot[14] of the molecular structure of **21**, showing the numbering of the atoms.

The endocyclic torsion angles are summarized in Table 1.

All the three six-membered rings have chair conformations with only slight deformation.

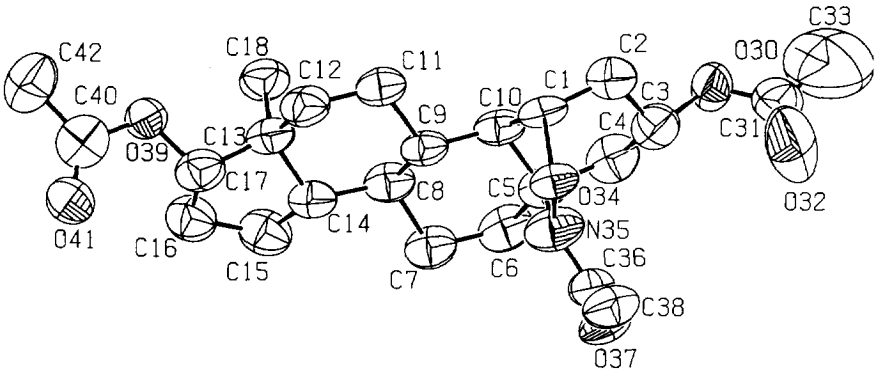


Figure. ORTEP Plot[14] of the crystal structure of **21**

Both pentagonal cycles C(5)-N(35)-O(34)-C(1)-C(10) and C(13)-C(14)-C(15)-C(16)-C(17) exhibit an envelope conformation with respectively C(10) and C(13) at the flap. A boat arrangement with a symmetry plane passing through C(3) and the middle of the O(34)-N(35) bond is observed for the 7-membered ring.

Table 1. - Endocyclic Torsion Angles (°) ($\sigma \leq 2°$)

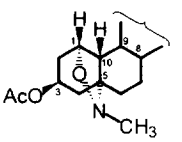
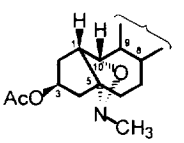
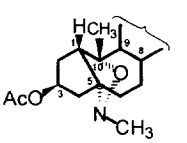
Ring	Torsion angles						
C(1)-C(2)-C(3)-C(4)-C(5)-C(10)	-61	46	-48	62	-69	71	
C(5)-C(6)-C(7)-C(8)-C(9)-C(10)	-46	53	-59	59	-52	46	
C(8)-C(9)-C(11)-C(12)-C(13)-C(14)	-51	51	-55	58	-60	57	
C(5)-N(35)-O(34)-C(1)-C(10)	-30	0	30	-48	46		
C(13)-C(14)-C(15)-C(16)-C(17)	47	-34	6	23	-43		
C(1)-C(2)-C(3)-C(4)-C(5)-N(35)-O(34)	52	46	-48	-46	85	0	-89

Treatment of (*E*)-19-nor-5,10-seco-ketone **17** with *N*-methylhydroxylamine hydrochloride (in boiling ethanol/pyridine (1:1, v/v) solution for 24 h) resulted in intramolecular nitrone 1,3-dipolar cycloaddition to give two regioisomers (Scheme 4), *i.e.*, the natural steroid A/B *trans* 1α,5α-epoxyimino derivative **22** (in 45% yield) and the A-nor/B-homo 5α,10α-isoxazolidine **23** (in 27% yield).

Structure **22** was confirmed by *N*-methylation of the isoxazolidine **18** with methyl *p*-toluene sulfonate (Scheme 4), which gave a product identical in all respect (m.p., mixed m.p. and spectral data) with the one obtained in the above reaction with *N*-methylhydroxylamine.

The A-nor/B-homo regioisomer **23** was identified on the basis of elemental microanalysis ($C_{23}H_{35}NO_5$) and spectral characteristics (particularly ^{1}H-NMR and ^{13}C-NMR data). Thus, the ^{1}H-NMR spectrum of **23** contains a triplet at δ 2.86 ppm, characteristic of the 1β–H in A-nor/B-homo 5α,10α-isoxazolidine systems.[5] Moreover, ^{13}C-NMR chemical shifts of **23** are very similar to those of the corresponding 19-methyl A-nor/B-homo analogue **10a**.[15] The selected ^{13}C-NMR data of the isoxazolidine derivatives **22**, **23** and **10a** relevant for the structural assignement are given in Table 2.

Table 2. Selected ^{13}C-NMR Chemical Shifts (ppm/TMS) in the Isoxazolidine Derivatives **22**, **23** and **10a**

C-atom			
	22	**23**	**10a**
1	74.6 (*d*)	51.3 (*d*)	54.6 (*d*)
2	37.8 (*t*)	33.2 (*t*)	34.1 (*t*)
3	68.4 (*d*)	77.0 (*d*)	77.9 (*d*)
4	40.0 (*t*)	42.9 (*t*)	42.6 (*t*)
5	63.6 (*s*)	74.8 (*s*)	76.2 (*s*)
6	30.8 (*t*)	38.8 (*t*)	34.8 (*t*)
7	26.7 (*t*)	27.5 (*t*)	27.5 (*t*)
8	39.3 (*d*)	40.0 (*d*)	40.2 (*d*)
9	40.2 (*d*)	51.9 (*d*)	55.3 (*d*)
10	59.5 (*d*)	84.7 (*d*)	83.7 (*s*)
N–CH_3	35.7 (*q*)	35.4 (*q*)	34.7 (*q*)

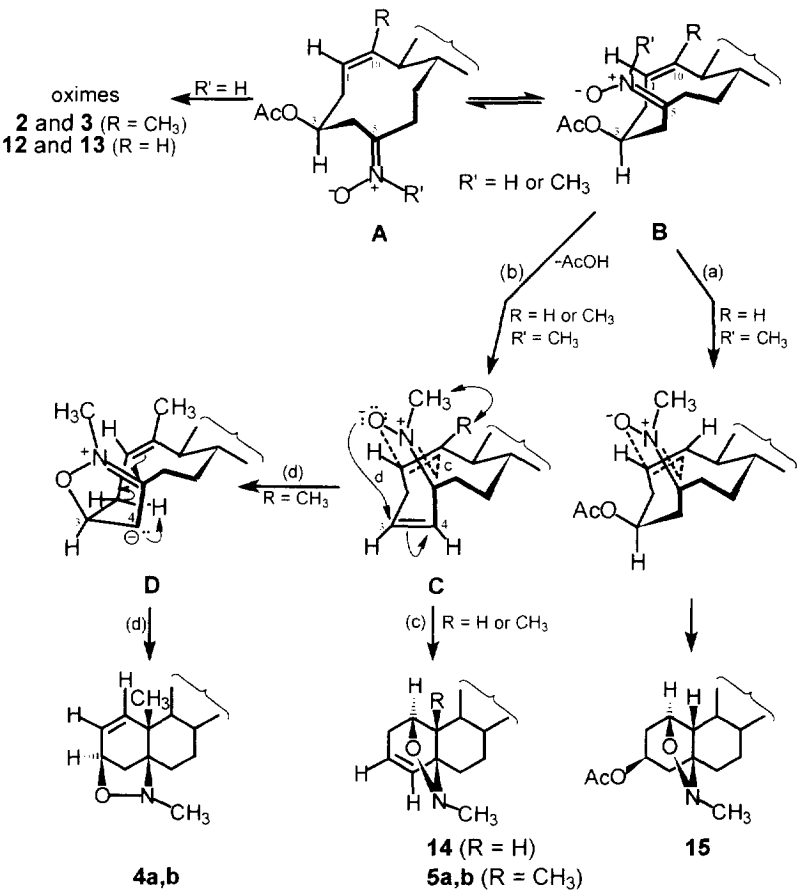
Discussion

Comparison of the results obtained for the (*Z*)-19-methyl- and (*Z*)-19-nor-, **1** and **11**, and (*E*)-19-methyl- and (*E*)-19-nor-5,10-secosteroidal derivatives, **7** and **17**, respectively, indicates that the

intramolecular reactivity of their cyclodecene systems towards hydroxylamine and *N*-methylhydroxylamine is highly dependent upon the presence (or the absence) of the methyl group at the C(10) reaction center. This effect can be rationalized by considering the possible reactive conformations of molecules involved in the respective transannular processes.

Z-Series

In the ground state conformation of the (*Z*)-5,10-secosteroidal nitrones of type **A**[16] (Scheme 5) the olefinic double bond and the trigonal C(5) atom are sterically too far appart to permit internal nitrone 1,3-cycloaddition. Therefore, in order to react intramolecularly the molecule must assume the less stable, but for transannular interaction a more appropriate conformation of type **B**,[17] which enables the formation of isoxazolidine derivatives with the natural A/B *cis* skeleton and the 1β,5β-configuration of the epoxyimino bridge; besides, for steric reasons, isoxazolidine ring closure requires the (*Z*)-configuration of the nitrone function.



Scheme 5

Actually, only the 19-nor-(*Z*)-seco ketone **11** reacts (partly) with *N*-methylhydroxylamine according to this reaction and stereochemical pathway (a) affording 3β-acetoxy isoxazolidine **15** as the minor product.

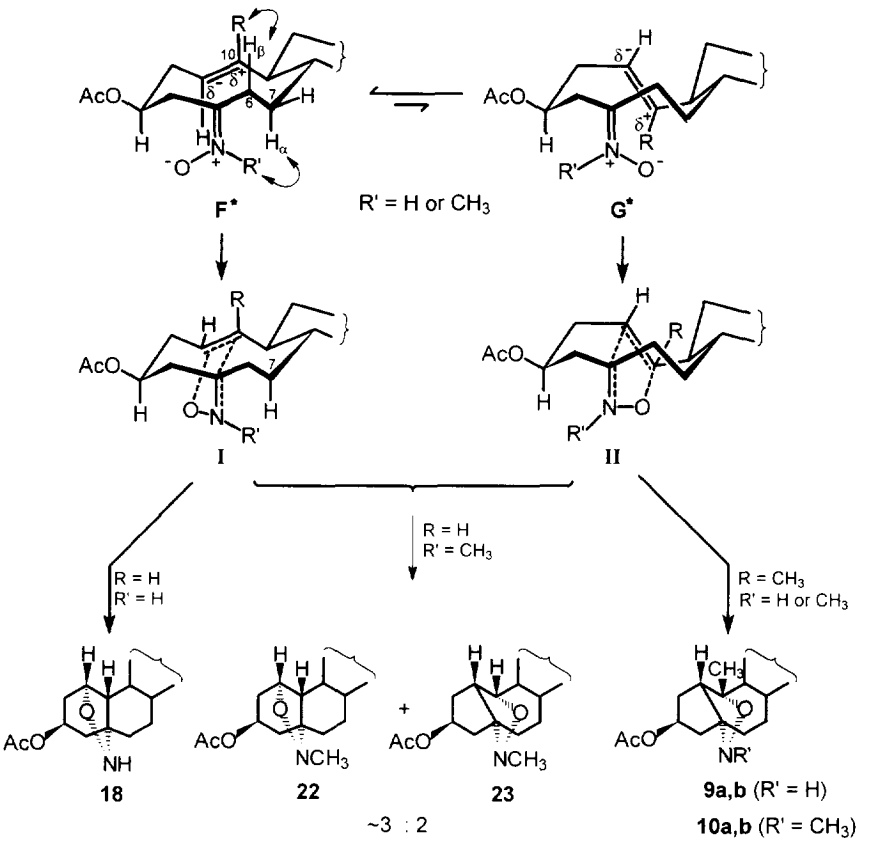
However, for the larger part of 19-nor-(*Z*)-ketone **11** and for 19-methyl analogues **1a,b** (exclusively) the required nitrone conformation **B** is too strained for transannular isoxazolidine ring closure. Therefore, in these cases the energetically more favourable process is the elimination of acetic acid (in the C(3)–C(4) direction, pathway (b)) to give a non-isolable nitrone intermediate of type **C**. In the 19-nor series this species (**C**, R = H) is readily transformed to the Δ^3-unsaturated isoxazolidine **14** as the result of nitrone 1,3-dipolar cycloaddition to the transannular $\Delta^{1(10)}$-double bond, following pathway (c).

On the other hand, in the 19-methyl series (**C**, R = CH_3) similar cycloaddition reaction (pathway (c)) leading to isoxazolidines **5a,b** is considerably suppressed by the competing process which results in the formation of the isomeric Δ^1-unsaturated isoxazolidines **4a,b** (the **4a,b/5a,b** ratio being ~2:1). In this case, due to the repulsive interaction between the CH_3(19) and N–CH_3 methyl groups, the nitrone intermediate **C** follows an additional reaction course (d).[18,19] Its first step consists of attack of the negatively charged nitrone oxygen at the C(3) end of the olefinic Δ^3-double bond. In this way the negative charge from the nitrone oxygen is moved to the C(4) center, which participates in final stabilization *via* a six-membered ring species **D** to give isoxazolidines **4a,b**.

E-*Series*

For the (*E*)-5,10-secosteroidal nitrones two conformations, **F** and **G** (Scheme 6) (corresponding to the major and minor conformation, respectively, of the (*E*)-seco ketones **7a,b** and **17**)[6] can be envisaged. In both conformations the reaction centers are suitably (but mutually in different way) oriented for intramolecular nitrone 1,3-cycloaddition. Thus, the major conformation **F** could lead (*via* intermediate **I**) to isoxazolidines with the natural A/B *trans* steroid skeleton and 1α,5α-configuration of the epoxyimino bridge; for steric reason in this case the nitrone or 1,3-dipolar oxime tautomer function should possess the *Z*-configuration. On the other hand, the minor conformation **G** could give (*via* intermediate **II**) the A-nor/B-homo isoxazolidine derivatives with the 5α,10α-epoxyimino bridge, the ring closure requiring the *E*-configuration of the nitrone or 1,3-dipolar oxime tautomer group.

The results obtained have shown that the 19-methyl (*E*)-5,10-seco-ketones **7a,b** react with hydroxylamine hydrochloride and *N*-methylhydroxylamine hydrochloride exclusively in the minor conformation **G** to give the A-nor/B-homo isoxazolidines **9a,b** and **10a,b**, respectively. This is probably due: (i) to the more favourable orientation of the potential tertiary C(10) carbocationic site (with respect to the corresponding reaction centers of the nitrone group) in conformation **G**, as compared to conformation **F**; (ii) to the possibility of avoiding repulsive interaction between the CH_3–C(10) group and H_β–C(6) atom (which exists in conformation **F**); and, in the case of reaction with *N*-methylhydroxylamine hydrochloride, (iii) to the possibility of eliminating repulsive interaction between the N–CH_3 group and H_α–C(7) atom (which is present in conformation **F** when the nitrone function assumes the necessary (for ring closure) (*Z*)-configuration.



Scheme 6

*Partial charges refer only to 19-methyl derivatives (R = CH_3)

In accordance with the above considerations the 19-nor-(*E*)-5,10-seco-ketone **17**, in which: (i) the symmetrically substituted $\Delta^{1(10)}$-double bond has no orientational preference with respect to the approaching 1,3-dipole of the oxime tautomer, and (ii) in which the above mentioned repulsive interaction involving the CH_3–C(10) group is eliminated, reacts with hydroxylamine hydrochloride exclusively in the major conformation **F** producing isoxazolidine **18**.

However, in the reaction of this compound **17** with *N*-methylhydroxylamine hydrochloride both conformations **F** anf **G** participate. It seems that because of steric repulsion between the CH_3–N group and the H_α–C(7) atom existing in conformation **F**, the substrate molecules react also in conformation **G** (the natural steroid A/B-*trans* isoxazolidine **22** and the A-nor/B-homo isomer **23** being formed in a ratio of ~3 : 2).

From these results it be concluded that the reaction and stereochemical directing influence of the 19-methyl group in intramolecular processes of the 5,10-secosteroids with hydroxylamine hydro-

chloride and *N*-methylhydroxylamine hydrochloride arises primarily from steric interactions and, in the case of the (*E*)-19-methyl compounds, possibly also from electronic factors.

EXPERIMENTAL[20]

General. Removal of solvents was carried out under reduced pressure. Prep. column chromatography: silica gel 0.063-0.200 mm. TLC: control of reactions and separation of products on silica gel G (*Stahl*) with benzene/AcOEt 9:1 and 7:3, detection with 50% aq. H_2SO_4 soln. M.ps. uncorrected. UV spectrum: *Beckman DU-50* spectrometer, λ_{max} in nm (ε). IR spectra: *Perkin-Elmer-337* spectrophotometer; ν in cm^{-1}. NMR spectra: *Brucker AM-360* or *Varian FT80A* (^1H at 360 MHz or 80 MHz, ^{13}C at 90.55 MHz); $CDCl_3$ soln. at r.t., TMS as internal standard; chemical shifts in ppm as δ values, *J* in Hz. Mass spectra: *Finnigan-MAT 8230*. Light petroleum: fraction boiling at 40-60 °C.

Reaction of (Z)-*3β,17β-diacetoxy-19-nor-5,10-secoandrost-1(10)-en-5-one* (**11**)[9] *with hydroxylamine hydrochloride.* – A solution of **11** (200 mg) and NH_2OH·HCl (200 mg) + 0.14 ml pyridine (mol ratio 1:0.6) in EtOH (15 ml) was refluxed for 14 h, then poured into water and extracted with diethyl ether. The organic layer was washed with water, 5% aq. $NaHCO_3$ soln., water, dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on silica gel (8 g). Elution with benzene/AcOEt (90:10) gave (*E*)-(1(10)*Z*)-3β,17β-diacetoxy-19-nor-5,10-secoandrost-1(10)-en-5-one oxime (**12**) (119 mg, 57.2%), m.p. 193 °C (from acetone-light petroleum). $[\alpha]_D$ = + 117.2 (*c* = 1.00, $CHCl_3$). IR (KBr): 3460, 1750, 1738, 1660, 1250, 1030. ^1H-NMR (80 MHz): 0.75 (*s*, Me(18)); 1.98, 2.03 (2*s*, 2 AcO); 4.63 (*t*, *J* = 7, H-C(17)); ~5.35 (3*m*, H-C(1), H-C(3), H-C(10)); 7.90 (*br.s*, =N–OH). Anal. calc. for $C_{22}H_{33}NO_5$ (391.513): C 67.49, H 8.50, N 3.58; found: C 67.59, H 8.57, N 3.81.

Benzene/AcOEt (85:15) eluted (*Z*)-(1(10)*Z*)-3β,17β-diacetoxy-19-nor-5,10-secoandrost-1(10)-en-5-one oxime (**13**) (82 mg, 39.4%), m.p. 155 °C (from acetone-light petroleum). $[\alpha]_D$ = + 80.0 (*c* = 0.59, $CHCl_3$). IR (KBr): 3480-3200, 1745, 1735, 1660, 1250, 1240, 1025. ^1H-NMR (80 MHz): 0.75 (*s*, Me(18)); 1.99, 2.02 (2*s*, 2 AcO); 4.60 (*t*, *J* = 7, H-C(17)); ~5.35 (2*m*, H-C(1), H-C(10)); 5.92 (*m*, H-C(3)); 7.25 (*br.s*, =N–OH). Anal. calc. for $C_{22}H_{33}NO_5$ (391.513): C 67.49, H 8.50, N 3.58; found: C 67.71, H 8.62, N 3.85.

Reaction of (Z)-*3β,17β-diacetoxy-19-nor-5,10-secoandrost-1(10)-en-5-one* (**11**)[9] *with* N-*methylhydroxylamine hydrochloride.* – A solution of **11** (500 mg) and MeNHOH·HCl (500 mg) in EtOH/pyridine (1:1, v/v) (40 ml) was refluxed for 24 h, poured into water and extracted with diethyl ether. The organic layer was repeatedly washed with water, dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on silica gel (20 g). Elution with benzene afforded 1-hydroxy-estra-1,3,5(10)-trien-17β-yl acetate (**16**) (72 mg, 17.2%), m.p. 202 °C (from acetone-*n*-hexane). $[\alpha]_D$ = + 128.5 (*c* = 0.40, $CHCl_3$). UV (EtOH): 276 (1860), 283 (1850). IR (KBr): 3325, 1700, 1580, 1460, 1375, 1330, 1275, 1190, 1040, 790, 745. ^1H-NMR (360 MHz): 0.88 (*s*, Me(18)); 2.06 (*s*, AcO); 4.71 (*t*, *J* = 8, H-C(17)); 4.92 (*s*, HO-C(1)); 6.53 (*d*, *J* = 7.5, H-C(2)); 6.69 (*d*, *J* = 7.5, H-C(4)); 6.97 (*t*, *J* = 7.5, H-C(3)). ^{13}C-NMR: 171.2 (*s*, Me*C*OO); 154.8 (*s*, C(1)); 140.2 (*s*, C(10)); 126.5 (*s*, C(5)); 126.1 (*s*, C(3)); 121.9 (*d*, C(4)); 113.2 (*d*, C(2)); 82.9 (*d*, C(17)); 49.8 (*d*, C(14)); 44.6 (*d*, C(9)); 43.4 (*s*, C(13)); 40.4 (*d*, C(8)); 37.6 (*t*, C(12)); 31.4 (*t*, C(7)); 27.6 (*t*, C(16)); 25.7 (2*t*, C(6), C(11)); 23.3 (*t*, C(15)); 21.1 (*q*, *Me*COO); 12.5 (*q*, C(18)). MS: *m/z* = 314 ($M^{+\bullet}$, 100%), 254 ($M^{+\bullet}$ – 60, 36%). Anal. calc. for $C_{20}H_{26}O_3$ (314.428): C 76.40, H 8.33; found: C 76.67, H 8.17.

Benzene/Et_2O (80:20) eluted *N*-methyl-1β,5-epoxyimino-19-nor-5β-androst-3-en-17β-yl acetate (**14**) (199 mg, 43.4%), m.p. 171 °C (from acetone-light petroleum). $[\alpha]_D$ = + 58.4 (*c* = 0.62, $CHCl_3$). IR (KBr): 3020, 1735, 1465, 1435, 1375, 1260, 1050, 1030, 720. ^1H-NMR (360 MHz): 0.84 (*s*, Me(18)); 2.04 (*s*, AcO); 2.60 (*d*, *J* = 6, H-C(10)); 2.61 (*s*, Me–N); 4.32 (*br.s*, w/2 = 12 Hz, H-C(1)); 4.62 (*t*, *J* = 8.5, H-C(17)); 5.29 (*d*, *J* = 10, H-C(4)); 5.92 (*br.d*, *J* = 10, H-C(3)). ^{13}C-NMR: 171.3 (*s*, Me*C*OO); 130.0 (*d*, C(3)); 129.7 (*d*, C(4)); 82.9 (*d*, C(17)); 73.8 (*d*, C(1)); 63.3 (*s*, C(5)); 53.8 (*d*, C(10)); 49.1(*d*, C(14)); 43.6 (*s*, C(13)); 41.2 (*d*, C(9)); 41.1 (*q*, Me–N); 38.3 (*d*, C(8)); 36.8 (*t*, C(12)); 32.4 (*t*, C(2)); 32.2 (*t*, C(6)); 27.6 (*t*, C(16)); 27.0 (*t*, C(7)); 26.7 (*t*, C(11)); 23.8 (*t*, C(15)); 21.3 (*q*, *Me*COO); 12.5 (*q*, C(18)). MS: *m/z* = 345 ($M^{+\bullet}$, 100%). Anal. calc. for $C_{21}H_{31}NO_3$ (345.486): C 73.01, H 9.05, N 4.05; found: C 72.83, H 8.81, N 4.35.

Elution with benzene/Et_2O (1:1) gave *N*-methyl-1β,5-epoxyimino-19-nor-5β-androstane-3β,17β-diyl diacetate (**15**) (155 mg, 28.8%), m.p. 167 °C (from acetone-light petroleum). $[\alpha]_D$= + 77.3 (*c* = 0.55, $CHCl_3$). IR (KBr): 1735, 1730, 1460, 1425, 1370, 1260, 1255, 1025. ^1H-NMR (360 MHz): 0.84 (*s*, Me(18)); 2.04, 2.08 (2*s*, 2

AcO); 2.70 (*br.s*, w/2 = 20 Hz, Me–N); 4.34 (*br.s*, w/2 = 15 Hz, H-C(1)); 4.63 (*t*, *J* = 8.5, H-C(17)); 5.08 (*t*, *J* = 6.5, H-C(3)). ^{13}C-NMR: 171.4, 171.2 (2*s*, 2 Me*C*OO); 82.9 (*d*, C(17)); 72.9 (*d*, C(1)); 66.6 (*d*, C(3)); 49.4 (*d*, C(14)); 43.7 (*s*, C(13)); 41.8 (2*d*, C(9), C(8)); 40.7 (*q*, Me–N); 36.9 (*t*, C(12)); 32.2 (2*t*, C(6), C(2)); 27.7 (2*t*, C(16), C(7)); 27.0 (*t*, C(11); 23.9 (*t*, C(15)); 22.0 (*q*, *Me*COO); 21.5 (*q*, *Me*COO); 12.7 (*q*, C(18)). MS: *m/z* = 405 ($M^{+\bullet}$, 54%), 346 ($M^{+\bullet}$ – 59, 100%). Anal. calc. for $C_{23}H_{35}NO_5$ (405.540): C 68.12, H 8.70, N 3.45; found: C 67.92, H 8.47, N 3.65.

Oxidative hydrolysis of 1β,5-epoxyimino-19-nor-5β-androst-3-en-17β-yl acetate (**14**). - A solution of isoxazolidine **14** (30 mg) and *N*-methylhydroxylamine hydrochloride (30 mg) in ethanol/pyridine (1:1, v/v) (6 ml) was refluxed for 24 h. The mixture was worked up as above and chromatographed on silica gel (2 g). Elution with benzene afforded estratriene acetate **16** (15 mg, 54.9%); m.p., mixed m.p., IR and ^{1}H-NMR spectra were identical with those of the above described sample **16**.

Alkaline hydrolysis of N*-methyl-1β,5-epoxyimino-19-nor-5β-androstane-3β,17β-diyl diacetate* (**15**). - Diacetate **15** (60 mg) in 2% methanolic KOH solution was stirred at room temperature overnight. The mixture was diluted with water and extracted with diethyl ether. The combined extracts were washed with water, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from acetone to give *N*-methyl-1β,5-epoxyimino-19-nor-5β-androstane-3β,17β-diol (**15a**) (42 mg, 88.3%), m.p. 208 °C. $[\alpha]_D$ = + 166.3 (*c* = 0.54, $CHCl_3$). IR (KBr): 3350, 1440, 1420, 1350, 1320, 1135, 1080, 1050, 1020, 995. ^{1}H-NMR (80 MHz). 0.75 (*s*, Me(18)); 2.58 (*s*, Me-N); 3.67 (*t*, *J* = 8, H-C(17)); 3.92 (*t*, *J* = 4.5, H-C(1)); 4.48 (*t*, *J* = 4.8, H-C(3)). MS: *m/z* = 321 (M^+, 100%). Anal. calc. for $C_{19}H_{31}NO_3$ (321.464): C 70.99, H 9.72, N 4.36; found C 70.81, H 9.74, N 4.52.

Reaction of (E)*-3β,17β-diacetoxy-19-nor-5,10-secoandrost-1(10)-en-5-one* (**17**)[9] *with hydroxylamine hydrochloride. (a) In the presence of 0.6 mol equiv. of pyridine.* – A solution of **17** (300 mg) and NH_2OH·HCl (300 mg) + 0.21 ml pyridine (mol ratio ~1:0.6) in EtOH (20 ml) was refluxed for 28 h and the mixture worked up as above. The residue (310 mg) was recrystallized from acetone-light petroleum) to give 1α,5-epoxyimino-19-nor-5α-androstane-3β,17β-diyl diacetate (**18**) (262 mg, 84.0%), m.p. 186 °C. $[\alpha]_D$ = –15.0 (*c* = 1.00, $CHCl_3$). IR (KBr): 3280, 1760, 1740, 1450, 1380, 1260, 1240, 1040. ^{1}H-NMR (360 MHz): 0.84 (*s*, Me(18)); 2.02, 2.05 (2*s*, AcO); 4.35 (*d*, *J* = 5.5, H-C(1)); 4.61 (*t*, *J* = 8 Hz, H-C(17)); 5.34 (*m*, H-C(3)); 5.75 (*br.s*, >NH). ^{13}C-NMR: 171.1, 170.1 (2*s*, 2 Me*C*OO); 82.6 (*d*, C(17)); 77.8 (*d*, C(1)); 69.1(*d*, C(3)); 62.0 (*s*, C(5)); 57.3 (*d*, C(10)); 49.5 (*d*, C(14)); 44.6 (*t*, C(4)); 43.0 (*s*, C(13)); 39.4 (*d*, C(9)); 39.1 (*d*, C(8)); 37.9 (*t*, C(12)); 36.5 (*t*, C(2)); 28.2 (*t*, C(6)); 27.5 (*t*, C(16)); 26.5 (*t*, C(7)); 25.4 (*t*, C(11)); 23.2 (*t*, C(15)); 21.3, 21.1 (2*q*, 2 *Me*COO); 12.1 (*q*, C(18)). Anal. calc. for $C_{22}H_{33}NO_5$ (391.513): C 67.49, H 8.50, N 3.58; found: C 67.60, H 8.63, N 3.83.

(b) In the presence of an excess of pyridine. - A solution of **17** (200 mg) and NH_2OH·HCl (200 mg) in EtOH/Py (1:1, v/v) (30 ml) was refluxed for 4 h, poured into water and the mixture worked up as above. The residue was chromatographed on silica gel (8 g). Elution with benzene/AcOEt (85:15) afforded (*E*)-(1(10)*E*)-3β,17β-diacetoxy-19-nor-5,10-secoandrost-1(10)-en-5-one oxime (**19**) (21 mg, 10.1%), m.p. 194 °C (from acetone-light petroleum). $[\alpha]_D$ = + 132.2 (*c* = 0.66, $CHCl_3$). IR (KBr): 3460, 3350, 1745, 1460, 1380, 1250, 1100, 1030. ^{1}H-NMR (80 MHz): 0.78 (*s*, Me(18)); 2.03, 2.05 (2*s*, 2 AcO); 4.65 (*t*, *J* = 7, H-C(17)); ~5.40 (3*m*, H-C(1), H-C(3), H-C(10); 7.60 (*br.s*, =N–OH). Anal. calc. for $C_{22}H_{33}O_5$ (391.513): C 67.49, H 8.50, N 3.58; found: C 67.72, H 8.46, N 3.80.

Further elution with benzene/AcOEt (85:15) gave (*Z*)-(1(10)*E*)-3β,17β-diacetoxy-19-nor-5,10-secoandrost-1(10)-en-5-one oxime (**20**) (49 mg, 23.6%), m.p. 113 °C (from acetone-light petroleum). $[\alpha]_D$ = + 107.0 (*c* = 1.00, $CHCl_3$). IR (KBr): 3600-3080, 1740, 1450, 1380, 1240, 1025. ^{1}H-NMR (80 MHz): 0.85 (*s*, Me(18)); 2.05, 2.07 (2*s*, 2 AcO); 4.65 (*t*, *J* = 7.5, H-C(17)); 5.40 (2*m*, H-C(1), H-C(10); 5.95 (*m*, H-C(3)); 7.45 (*br.s.*, =N–OH). Anal. calc. for $C_{22}H_{33}NO_5$ (391.513): C 67.49, H 8.50, N 3.58; found: C 67.64, H 8.78, N 3.71.

Benzene/AcOEt (80:20) eluted epoxyimino derivative **18** (115 mg, 55.3%).

N*-Acetylation of 1α,5-epoxyimino-19-nor-5α-androstane-3β,17β-diyl diacetate* (**18**). - A solution of isoxazolidine derivative **18** (200 mg) in Ac_2O (1.5 ml) and pyridine (1.5 ml) was stirred at r.t. for 12 h, poured into water and extracted with diethyl ether. The organic layer was successively washed with 5% aq. H_2SO_4 soln., water, 5% aq. $NaHCO_3$ soln. and water, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from acetone to give *N*-acetyl 1α,5-epoxyimino-19-nor-5α-androstane-3β,17β-diyl diacetate (**21**) (202 mg, 91.2%), m.p. 211 °C. $[\alpha]_D$ = + 70.2 (*c* = 1.00, $CHCl_3$). IR (KBr): 1745, 1735, 1730, 1650, 1450, 1370, 1250, 1235, 1180, 1050, 1030. ^{1}H-NMR (360 MHz): 0.83 (*s*, Me(18)); 2.01, 2.04, 2.12 (3*s*, 2AcO, Ac–N); 2.60 (*m*, H_α-C(2)); 2.70 (*dd*, *J* = 14, 7, H_α- C(4)); 4.32 (*d*, *J* = 5.5, H-C(1)); 4.62 (*t*, *J* = 8.5, H-C(17)); ~5.0 (*m*, H-C(3)). ^{13}C-NMR: 171.0, 170.0, 169.0 (3*s*, 2 Me*C*OO, Me*C*ON); 82.6 (*d*, C(17)); 76.2 (*d*, C(1)); 67.9 (*d*, C(3)); 64.5 (*s*,

C(5)); 57.7 (*d*, C(10)); 49.4 (*d*, C(14)); 43.0 (*s*, C(13)); 40.1 (*d*, C(9)); 39.9 (*t*, C(4)); 39.3 (*d*, C(8)); 37.5 (*t*, C(2)); 36.6 (*t*, C(12)); 31.2 (*t*, C(6)); 27.5 (*t*, C(16)); 26.5 (*t*, C(7)); 25.1 (*t*, C(11)); 23.2 (*t*, C(15)); 22.3, 21.2, 21.1 (3*q*, *Me*CON, 2 *Me*COO); 12.1 (*q*, Me(18)). Anal. calc. for $C_{24}H_{35}NO_6$ (433.551): C 66.49, H 8.14, N 3.23; found: C 66.30, H 8.30, N 3.52.

Reaction of (E)-3β,17β-*diacetoxy-19-nor-5,10-secoandrost-1(10)-en-5-one* (**17**)[9] *with* N-*methylhydroxylamine hydrochloride.* – A solution of **11** (200 mg) and $CH_3NHOH{\cdot}HCl$ (200 mg) in EtOH/pyridine (1:1, v/v) (20 ml) was refluxed for 24 h, poured into water and worked up in the usual way. The residue was chromatographed on silica gel (10 g). Benzene/diethyl ether (98:2) fractions contained unchanged starting material **11** (30 mg, 15%). Elution with benzene/diethyl ether (95:5) afforded *N*-methyl-1α,5-epoxyimino-19-nor-5α-androstane-3β,17β-diyl diacetate (**22**) (97 mg, 45.0%), m.p. 111 °C (from acetone-light petroleum). $[\alpha]_D$ = + 32.5 (c = 0.85, $CHCl_3$). IR (KBr): 1735, 1450, 1375, 1245, 1050, 1030. ^{1}H-NMR (360 MHz): 0.83 (*s*, Me(18)); 2.03, 2.05 (2*s*, 2 AcO); 2.72 (*s*, Me–N); 4.22 (*d*, *J* = 6.5, H-C(1)); 4.59 (*t*, *J* = 9, H-C(17)); 5.46 (*m*, H-C(3)). ^{13}C-NMR: 171.2, 170.5 (2*s*, 2 Me*C*OO); 82.9 (*d*, C(17)); 74.6 (*d*, C(1)); 68.4 (*d*, C(3)); 63.6 (*s*, C(5)); 59.5 (*d*, C(10)); 49.2 (*d*, C(14)); 43.0 (*s*, C(13)); 40.2 (*d*, C(9)); 40.0 (*t*, C(4)); 39.3 (*d*, C(8)); 37.8 (*t*, C(2)); 36.6 (*t*, C(12)); 35.7 (*q*, Me–N); 30.8 (*t*, C(6)); 27.6 (*t*, C(16)); 26.7 (*t*, C(7)); 24.9 (*t*, C(11)); 23.3 (*t*, C(15)); 21.2 (2*q*, 2 *Me*COO); 12.1 (*q*, Me(18)). MS: *m/z* = 405 (M^+, 26%), 346 (M^+– 59, 20%). Anal. calc. for $C_{23}H_{35}NO_5$ (405.540): C 68.12, H 8.70, N 3.45; found: C 68.43, H 8.93, N 3.62.

Benzene/diethyl ether (93:7) eluted *N*-methyl-5,10α-epoxyimino-19-nor-5(10→1)*abeo*-1β(*H*)-5α-androstane-3β,17β-diyl diacetate (**23**) (58 mg, 26.9%), m.p. 149 °C (from acetone-light petroleum). $[\alpha]_D$ = –2.2 (*c* = 0.50, $CHCl_3$). IR (KBr): 1735, 1445, 1370, 1245, 1045, 1025. ^{1}H-NMR (360 MHz): 0.84 (*s*, Me(18)); 2.04 (2*s*, 2 AcO); 2.62 (*s*, Me–N); 2.86 (*t*, *J* = 9, H-C(1)); 3.89 (*s*, H-C(10)); 4.62 (*t*, *J* = 8.5, H-C(17)); 5.28 (*m*, H-C(3)). ^{13}C-NMR: 171.2, 170.7 (2*s*, Me*C*OO); 84.7 (*d*, C(10)); 82.6 (*d*, C(17)); 77.0 (*d*, C(3)); 74.8 (*s*, C(5)); 51.9 (*d*, C(9)); 51.3 (*d*, C(1)); 49.6 (*d*, C(14)); 43.6 (*s*, C(13)); 42.9 (*t*, C(4)); 40.0 (*d*, C(8)); 38.8 (*t*, C(6)); 37.1 (*t*, C(12)); 35.4 (*q*, Me–N); 33.2 (*t*, C(2)); 27.5 (2*t*, C(7), C(16)); 26.7 (*t*, C(11)); 23.7 (*t*, C(15)); 21.4, 21.2 (2*q*, 2 *Me*COO); 12.6 (*q*, C(18)). MS: *m/z* = 405 (M^+, 100%). Anal. calc. for $C_{23}H_{35}NO_5$ (405.540): C 68.12, H 8.70, N 3.45; found: C 68.32, H 8.60, N 3.55.

N-*Methylation of* 1α,5-*epoxyimino-19-nor-5*α-*androstane-3*β,17β-*diyl diacetate* (**18**). – A solution of isoxazolidine derivative **18** (100 mg) and methyl *p*-toluenesulfonate (40mg) in benzene (10 ml) was refluxed for 16 h. After cooling the mixture was diluted with diethyl ether, washed with saturated aq. $NaHCO_3$ soln. and water, dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on silica gel (5 g). Benzene/diethyl ether (95:5) eluted *N*-methylisoxazolidine derivative **22** (73 mg, 70.5%), m.p. 111-112 °C (from acetone-light petroleum), undepressed by admixture with an authentic sample. IR and ^{1}H-NMR spectra were identical with those of the product **22** obtained from seco-ketone **17** and CH_3NHOH.

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16. The nitrone conformation of type **A** corresponds to the only ground state conformation found for the (*Z*)-cyclodecenone rings in 5,10-secosteroidal ketones **1** and **11** in solution.[7,9]
17. Failure of (*Z*)-seco ketones **1** and **11** to undergo transannular cycloaddition with hydroxylamine hydrochloride may be due to insufficient stabilization of the transition state for isoxazolidine ring closure of the 1,3-dipolar oxime tautomer in conformation **B** (Scheme 5, R' = H).
18. About details on the proposed mechanism see Ref. 19.
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