NEW TYPES OF STEROIDAL ISOXAZOLIDINES[1]

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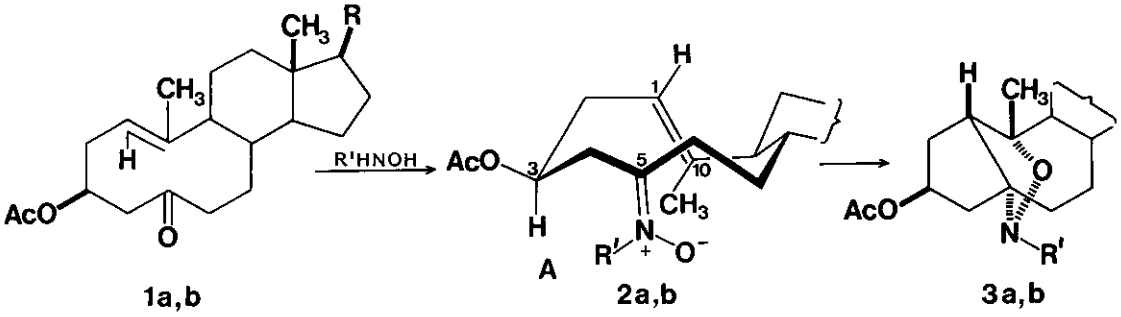
Abstract - Transannular nitrone 1,3-dipolar cycloaddition performed with (Z)-3β-acetoxy-$\Delta^{1(10)}$-unsaturated 5,10-secoketones 4a and 4b and N-methylhydroxylamine proceeds with acetic acid elimination to give mixtures of the respective Δ^{1}-unsaturated 3β,5β-epoxyimino compounds 7a and 7b, and Δ^{3}-unsaturated 1β,5β-epoxyimino derivatives 8a and 8b, while similar cycloaddition carried out with the (Z)-3β-hydroxy analogue 12 takes place without elimination at C(3) to produce only the 3β-hydroxy-1β,5β-epoxyimino compound 13. Under the same conditions, the corresponding 2,4-dien-1-ones 9a and 9b are formed as the minor products.

As previously reported,[2,3] when (E)-$\Delta^{1(10)}$-unsaturated 5-oxo-5,10-secosteroids (such as 1a and 1b) are treated with hydroxylamine or N-methylhydroxylamine in the presence of a proton donor catalyst, they are converted stereospecifically to the isoxazolidine derivatives 3a and 3b, respectively, in which the epoxyimino (-NR-O-) bridge is α-oriented and incorporated into the steroidal A-nor-B-homo system. These compounds arise from intramolecular 1,3-dipolar cycloaddition of the intermediary formed oximes or nitrones (2a and 2b, in the conformation of type A) to the olefinic double bond in the cyclodecene moiety of the 5,10-secosteroidal molecules (Scheme 1).



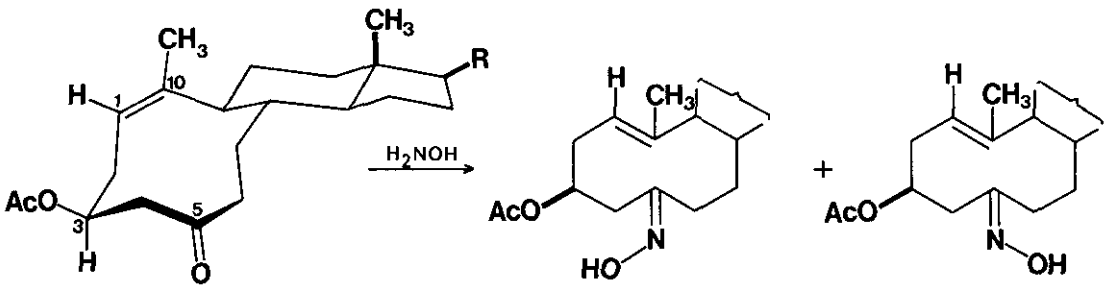
1a,b 2a,b 3a,b

a. R = C_8H_{17}; b. R = OAc R' = H or CH_3

Scheme 1

+Dedicated to Professor Sir Derek H. R. Barton on the occasion of his 70th birthday

However, when the corresponding (Z)-stereoisomeric 5,10-secoketones (4a and 4b, the ground state conformation of which is found to be of type B[4]) are treated with hydroxylamine under similar conditions, they are transformed only to syn- and anti-oximes 5a,b and 6a,b (Scheme 2).



B — 4a,b

syn- — 5a,b

anti- — 6a,b

a. $R = C_8H_{17}$; b. $R = OAc$

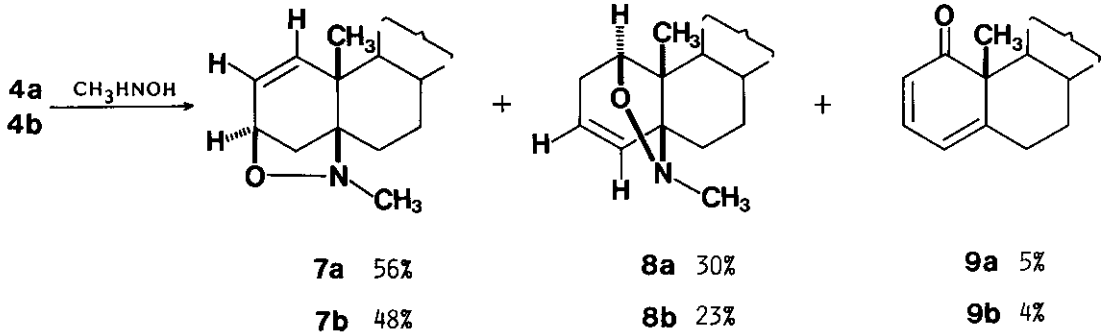
Scheme 2

The observed difference in reactivity between the (E)- and (Z)-5,10-secoketones in the reaction with hydroxylamine was explained by steric reasons; namely, in the (Z)-5,10-seco derivatives (contrary to the (E)-compound) the olefinic double bond and trigonal C(5) atom in the ground state conformation of the cyclodecenone ring are sterically too far apart to permit the internal 1,3-cycloaddition reaction to occur. In order to get more information concerning the importance of stereochemical factors influencing the reactivity of the (Z)-5,10-secosteroidal cyclodcenone ring in 1,3-dipolar cycloaddition processes, in the present study the behaviour of (Z)-3β-acetoxy-$\Delta^{1(10)}$-unsaturated 5-oxo-secosteroidal derivatives 4a and 4b, and the corresponding 3β-hydroxy analogue in the cholestane series 12, towards N-methylhydroxylamine, has been investigated.

RESULTS AND DISCUSSION

(Z)-3β-Acetoxy-$\Delta^{1(10)}$-unsaturated 5,10-secoketones 4a and 4b (prepared by oxidative fragmentation of the C(5)-C(10) bond in the corresponding 5α-hydroxy steroids[5,6]) were heated with N-methylhydroxylamine (in the form of its hydrochloride), in the presence of excess pyridine in refluxing ethanol for 24 h (when practically all starting material was consumed). The reaction mixtures were isolated and separated by column chromatography. It was found that under the above conditions both substrates 4a and 4b underwent transannular 1,3-dipolar nitrone cycloaddition (along with acetic acid elimination) to produce two types of structurally different isoxazolidine derivatives, in which the 3β,5β- or 1β,5β-epoxyimino bridge respectively, is incorporated into the "normal" steroid A/B cis-5β,10β-configuration (i.e. compounds 7a

and 7b, formed in 56% and 48% yield, and 8a and 8b, obtained in 30% and 23% yield). In addition, the 2,4-dien-1-ones 9a and 9b were isolated as the minor products (in about 5% yield) (Scheme 3).



a. R(17) = C_8H_{17}; b. R(17) = OAc

Scheme 3

Structures of all isolated products were determined on the basis of elemental microanalysis and spectral results (see Experimental). Moreover, the similarity in structures of the respective isoxazolidine derivatives of the cholestane and androstane series, i.e. compounds 7a and 7b, on the one hand, and 8a and 8b, on the other, was established by comparison of their physical characteristics, particularly the ^{1}H nmr and ^{13}C nmr spectral data. Selective chemical shifts relevant for the structural assignments are given in Tables 1 and 2.

Table 1. ^{1}H Nmr chemical shifts and coupling constants (Hz) in the isoxazolidine derivatives 7a, 7b, 8a, 8b

Protons (ppm)	3β,5β-compounds		1β,5β-compounds	
	7a	7b	8a	8b
H-C(1)	5.65 (d, J=10)	5.63 (d, J=10)	3.85 (s,br)	3.87 (s,br)
H-C(2)	5.85 (dxd, J=10, 5.5)	5.85 (dxd, J=10, 4.5)	H_α-2.18 (m)	H_α-2.20 (m)
			H_β-2.18 (m)	H_β-2.20 (m)
H-C(3)	4.38 (t, J=5.5)	4.38 (t, J=4.5)	5.87 (d, J=10)	5.91 (d,br, J=10)
H-C(4)	H_β-1.70 (dxd, J=11, 5.5)	H_β-1.72 (dxd, J=10, 4.5)	5.25 (d, J=10)	5.27 (d, J=10)
	H_α-2.55 (d, J=11)	H_α-2.54 (d, J=10)		
CH_3-N	2.59 (s)	2.58 (s)	2.63 (s)	2.63 (s)

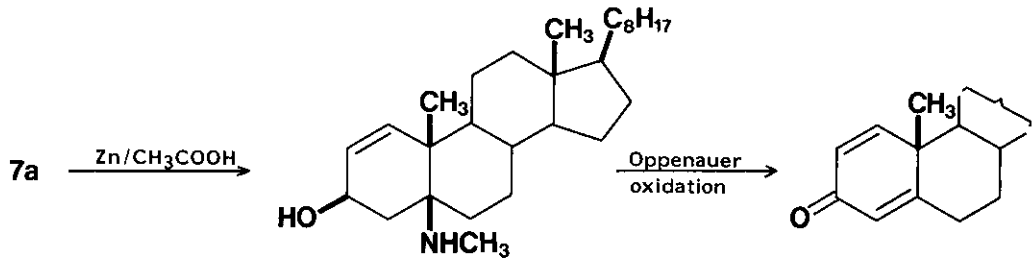
However, in order to make the distinction between the 3β,5β- and 1β,5β-isomeric pairs, the ^{1}H nmr double resonance method was used. Thus, by irradiating the center of the triplet at δ 4.38 ppm (H_α-C(3)) in the spectra of the isoxazolidine 7a and 7b, the olefinic H-C(2) signals (dxd at 5.85 ppm) and one of the methylene H_2C(4) proton signals (actually H_β-C(4), dxd at δ 1.70 ppm) both collapse to doublets, indicating that in the compounds 7a and 7b oxygen of the epoxyimino bridge is attached to the carbon atom located between the olefinic double bond and methylene group (this being possible only in the structures

of type 7). On the other hand, irradiation of the H_α-C(1) singlets at δ 3.85 ppm in the spectrum of 8a, and δ 3.87 ppm in the spectrum of 8b, in agreement with the proposed structure of type 8[7], was without effect on the coupling patterns of the olefinic H-C(3) protons appearing at δ 5.87 ppm in the spectrum of 8a and δ 5.91 ppm in the spectrum of 8b.

Table 2. Selected ^{13}C nmr chemical shifts (ppm/TMS) in the isoxazolidine derivatives 7a, 7b, 8a, 8b

Carbon atom	3β,5β-compounds		1β,5β-compounds	
	7a	7b	8b	8b
1	139.7 (d)	139.7 (d)	80.2 (d)	80.5 (d)
2	126.1 (d)	126.7 (d)	33.2 (t)	33.4 (t)
3	70.7 (d)	71.0 (d)	131.6 (d)	131.7 (d)
4	37.2 (t)	37.5 (t)	128.7 (d)	129.2 (d)
5	69.1 (s)	69.4 (s)	66.3 (s)	66.6 (s)
6	30.0 (t)	29.8 (t)	27.1 (t)	27.3 (t)
7	28.4 (t)	28.6 (t)	27.2 (t)	27.1 (t)
8	35.3 (d)	35.4 (d)	34.9 (d)	35.1 (d)
9	49.8 (d)	50.1 (d)	44.1 (d)	44.5 (d)
10	46.7 (s)	47.0 (s)	48.5 (s)	48.7 (s)
19	15.4 (q)	15.8 (q)	15.9 (q)	16.2 (q)
CH_3-N	41.5 (q)	41.8 (q)	37.9 (q)	38.2 (q)

Chemical evidence which unequivocally confirmed that the epoxyimino oxygen in isoxazolidine 7a[8] (and consequently also in isoxazolidine 7b) is attached to the C(3) position was obtained by its conversion to the known 1,4-cholestadien-3-one (11), effected by reductive cleavage of the epoxyimino bridge (with zinc and acetic acid) and subsequent Oppenauer oxidation of the resulting 5-methylamino-5β-cholest-1-en-3β-ol (10) (Scheme 4).

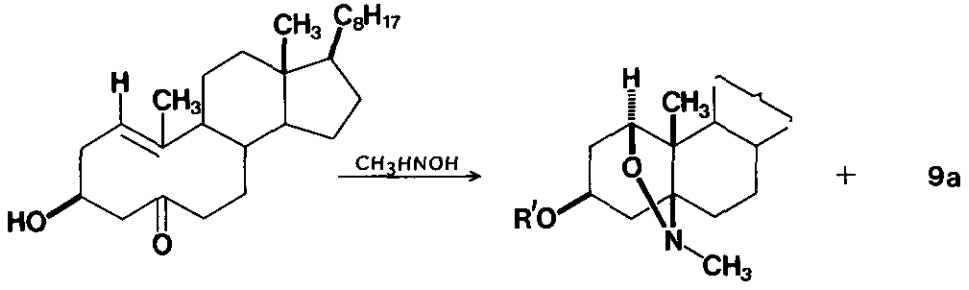


10 11

Scheme 4

3β-Hydroxy-5,10-secocholest-1(10)-en-5-one (12) (obtained by saponification of acetate 4a with methanolic potassium hydroxide[5]) was treated with N-methylhydroxylamine hydrochloride under conditions similar to

those applied to the 3β-acetoxy derivatives 4a and 4b, i.e. in boiling ethanol-pyridine (1:1, v/v) for 8-10 h, when practically all starting material was consumed. Product analysis revealed that with this substrate, contrary to the 3β-acetoxy derivatives 4a and 4b, stereospecific intramolecular nitrone 1,3-cycloaddition took place without elimination at C(3), to produce as the only isoxazolidine derivative N-methyl-1β,5-epoxyimino-5β-cholestan-3β-ol (13)[10] (in 51% yield); the other isolated product being 2,4-cholestadien-1-one (9a) (isolated in 21% yield) (Scheme 5).



12

13 (R' = H) 51%

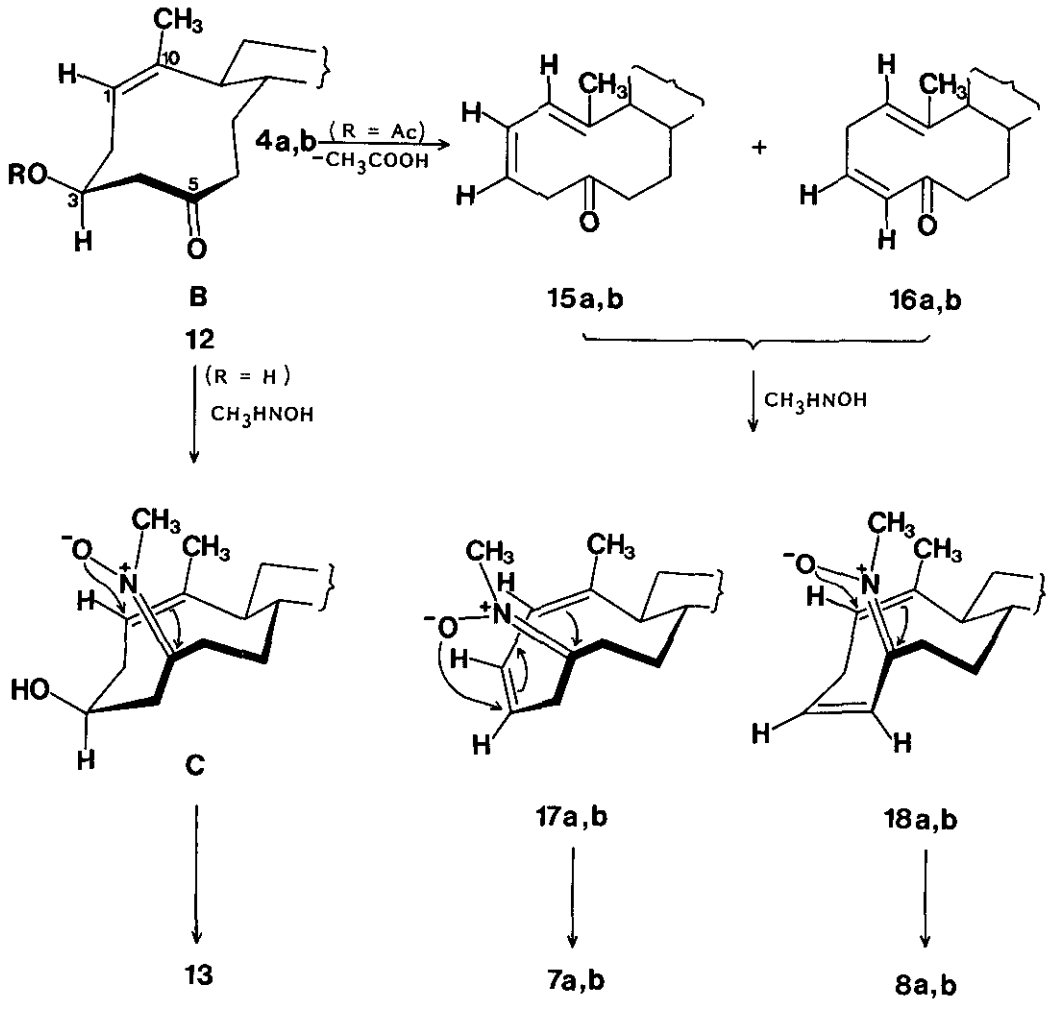
14 (R' = Ac)

21%

Scheme 5

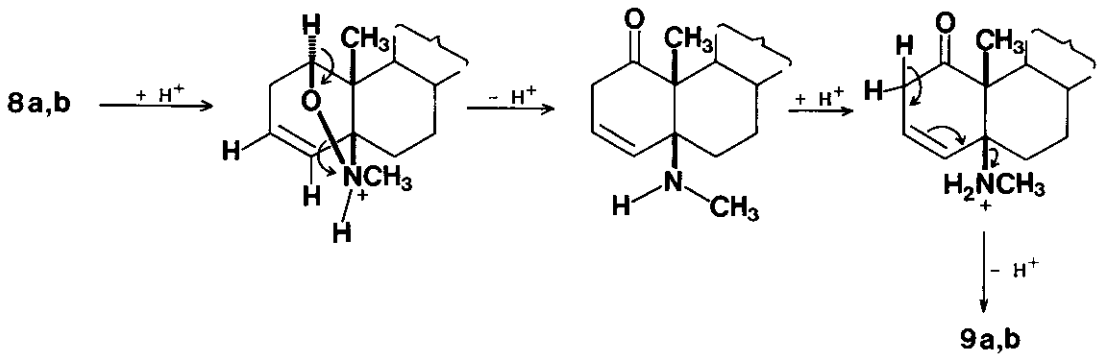
The obtained 3β-hydroxy derivative 13 was acetylated (with Ac_2O/pyridine) to give the corresponding 3β-acetate 14. In an attempt to eliminate the 3β-acetoxy group from compound 14 (in the form of acetic acid), it was refluxed with N-methylhydroxylamine hydrochloride in ethanol-pyridine for 24 h. However, the 3-acetoxyisoxazolidine 14 remained stable under the conditions used, thus indicating that it was not the precursor of the Δ^3-unsaturated 1β,5β-isoxazolidine 8a (formed in the intramolecular nitrone 1,3-dipolar cycloaddition of 3β-acetoxy-5,10-secoketone 4a).

From these results it follows that the chemical behaviour of the (Z)-3β-acetates 4a and 4b, and the corresponding 3β-hydroxycholestane analogue 12, towards N-methylhydroxylamine is determined by the less stable, but for transannular interactions more favourable conformation of the (Z)-cyclodecenone moiety in these 5,10-secosteroidal molecules, which could be of type C (Scheme 6). In these species the reacting centers, i.e. the nitrone grouping at C(5) and the olefinic (Z)-$\Delta^{1(10)}$-double bond, are suitably spatially oriented to undergo transannular 1,3-dipolar cycloaddition (whether synchronously as a supra-suprafacial [4+2] process[11], or as a two-step combination[12]) with formation of the "normal" steroid A/B cis-5β,10β-configuration and bridging at C(1) and C(5) by the epoxyimino grouping from the β-side. Such stereochemical course was actually observed with the (Z)-3β-hydroxy derivative 12 (Scheme 6).



Scheme 6

However, in the case of (Z)-3β-acetoxy derivatives 4a and 4b, it seems that the required conformation for transannular 1,3-dipolar cycloaddition is too strained to permit binding interaction leading to the isoxazolidine ring closure. Therefore, in these substrates the energetically more favourable process is the elimination of acetic acid in both C(2)-C(3) and C(3)-C(4) directions. The intermediary formed 1(10)Z,2(3)Z-dien-5-ones 15a,b[13] and 1(10)Z,3(4)Z-dien-5-ones 16a,b[13] react with N-methylhydroxylamine to produce the corresponding non-isolable nitrones 17a,b and 18a,b, respectively, which undergo spontaneous intramolecular cycloaddition; the isoxazolidine 7a,b being formed by nitrone 1,4-cycloaddition to the conjugated diene system in 17a,b, while the isoxazolidines 8a,b by nitrone 1,2-cycloaddition to the Z-$\Delta^{1(10)}$-double bond in 18a,b. The former process is the first example reported of nitrone 1,4-cycloaddition to the conjugated diene system.



Scheme 7

The minor components obtained in these reactions, i.e. 9a and 9b, probably arise from oxidative hydrolysis of 1β,5β-isoxazolidines 8a and 8b, respectively (Scheme 7), (which could take place in the course of the work-up procedure). The 3β-hydroxy derivative 12 reacted in a similar way with elimination of water (9a).

EXPERIMENTAL[14]

Mps: uncorrected. Prep. column chromatography: Silica gel 0.063-0.200 mm. TLC: control of reaction 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; uv spectra: Varian UV Super Scan 3 spectrophototmeter: λ_{max} nm (ε); ir spectra: Perkin-337 spectrophotometer; in cm^{-1}; nmr spectra: Bruker AM-360 (^1H (360 MHz), ^{13}C (90.55 MHz)), $CDCl_3$ soln. at rt, TMS as internal standard; chemical shifts in ppm as δ values; ms: Finnigan MAT Mass Spectrometer Model 8230. Light petroleum: fraction boiling at 40-60° C.

Reaction of (Z)-3β-acetoxy-5,10-secocholest-1(10)-en-5-one (4a) with N-methylhydroxylamine. - A solution of 4a[5] (500 mg) and MeNHOH·HCl (500 mg) in EtOH (20 ml) and pyridine (20 ml) was refluxed for 24 h, then 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 25 g silica gel. Elution with benzene-light petroleum (1:1) gave 2,4-cholestadien-1-one (9a) (22 mg, 5%), mp 105° C (from acetone-light petroleum); $[\alpha]_D^{20}$ = -450.0°(c = 0.6, $CHCl_3$) (lit.[15] mp 100-101° C, $[\alpha]_D^{20}$ = -455°); uv (MeOH): 323 (5620) (lit.[15] 324 (5800)); ir (KBr): ν_{max} = 1655, 1620, 1560, 1460, 1450, 1440, 1375, 1360, 910, 820; ^1H nmr: δ = 0.72 (s, H_3C-18), 0.82 (two d, J=6 Hz, H_3C-26 and H_3C-27), 0.87 (d, J=6 Hz, H_3C-21), 1.25 (s, H_3C-19), 5.90 (d, J=7.5 Hz, HC-2), 5.97 (d, J=4.5 Hz, HC-4), 6.85 (dxd, J=7.5, 4.5 Hz, HC-3); m/z: 382 (M^+). Anal. Calcd for $C_{27}H_{42}O$ (382.63): C, 84.75; H, 11.07. Found: C, 84.80; H, 11.30. Elution with benzene gave starting 4a (17 mg, 3%). Benzene-diethyl ether (98:2) eluted 260 mg (56%) of N-methyl-3β,5-epoxyimino-5β-cholest-1-ene (7a), mp 104°C (from acetone-MeOH); $[\alpha]_D^{20}$ = +36.6° (c = 1.00, $CHCl_3$);

ir (KBr): ν_{max} = 3020, 1640, 1470, 1430, 1390, 1370, 1360, 1015; ^{1}H nmr: δ = 0.70 (s, H_3C-18), 0.86 (two d, J=6.5 Hz, H_3C-26 and H_3C-27), 0.90 (d, J=6.5 Hz, H_3C-21), 1.22 (s, H_3C-19), 1.70 (dxd, J=11, 5.5 Hz, $H_\beta C$-4), 1.98 (dxt, J=14, 4 Hz, $H_\alpha C$-6), 2.55 (d, J=11 Hz, $H_\alpha C$-4), 2.59 (s, H_3C-N), 4.38 (t, J=5.5 Hz, HC-3), 5.65 (d, J=10 Hz, HC-1), 5.85 (dxd, J=10, 5.5 Hz, HC-2); m/z: 413 (M^+). Anal. Calcd for $C_{28}H_{47}NO$ (413.69): C, 81.29; H, 11.45; N, 3.39. Found: C, 81.16; H, 11.29; N, 3.68. Further elution with benzene-diethyl ether (98:2) gave 139 mg (30%) of N-methyl-1β,5-epoxyimino-5β-cholest-3-ene (8a), mp 84° C (from acetone-MeOH); $[\alpha]_D^{20}$ = +24.8° (c = 0.85, $CHCl_3$); ir (KBr): ν_{max} = 3025, 1640, 1470, 1440, 1380, 1370, 900, 870, 800; ^{1}H nmr: δ = 0.70 (s, H_3C-18), 0.88 (two d, J=6.5 Hz, H_3C-26 and H_3C-27), 0.91 (d, J=6.5 Hz, H_3C-21), 1.98 (dxt, J=14, 4 Hz, $H_\alpha C$-6), 1.24 (s, H_3C-19), 2.18 (two m, H_2C-2), 2.63 (s, H_3C-N), 3.85 ((s,br, w/2=5 Hz, HC-1), 5.25 (d, J=10 Hz, HC-4), 5.87 (d,br, J=10 Hz, HC-3); m/z: 413 (M^+). Anal. Calcd for $C_{28}H_{47}NO$ (413.69): C, 81.29; H, 11.45; N, 3.39. Found: C, 81.47; H, 11.69; N, 3.61.

Reaction of (Z)-3β-acetoxy-5,10-secoandrost-1(10)-en-5-one (4b) with N-methylhydroxylamine. - A solution of 4b[6] (300 mg) and MeNHOH·HCl (300 mg) in EtOH (15 ml) and pyridine (15 ml) was refluxed for 24 h and worked up as above. The residue was chromatographed on 15 g silica gel. Elution with benzene-light petroleum (1:1) gave 2,4-androstadien-1-one (9b) (11 mg, 4%), oil; ir (film): ν_{max} = 1735, 1680, 1630, 1570, 1480, 1450, 1390, 1380, 1250, 1045, 1025; ^{1}H nmr: δ = 0.75 (s, H_3C-18), 1.20 (s, H_3C-19), 2.00 (s, AcO-17), 4.56 (t, J=9 Hz, HC-17), 5.87(d, J=8 Hz, HC-2), 5.96 (d, J=5 Hz, HC-4), 6.85 (dxd, J=8, 5 Hz, HC-3); m/z: 328 (M^+). Elution with benzene-diethyl ether (99:1) gave starting 4b (13 mg, 4%). *Benzene-diethyl ether (97:3) eluted 132 mg (48%) of N-methyl-3β,5-epoxyimino-5β-androst-1-ene (7b)*, mp 161° C (from acetone-light petroleum); $[\alpha]_D^{20}$ = +8.4° (c = 1.25, $CHCl_3$); ir (KBr): ν_{max} = 3020, 1735, 1635, 1465, 1450, 1430, 1390, 1370, 1245, 1050, 1025, 1015, 760; ^{1}H nmr: δ = 0.82 (s, H_3C-18), 1.21 (s, H_3C-19), 1.72 (dxd, J=10, 4.5 Hz, $H_\beta C$-4), 2.03 (s, AcO-17), 2.15 (m, $H_\alpha C$-6), 2.54 (d, J=10 Hz, $H_\alpha C$-4), 2.58 (s, H_3C-N), 4.38 (t, J=4.5 Hz, HC-3), 4.61 (t, J=8 Hz, HC-17), 5.63 (d, J=10 Hz, HC-1), 5.85 (dxd, J=10, 4.5 Hz, HC-2); m/z: 359 (M^+). Anal. Calcd for $C_{22}H_{33}NO_3$ (359.51): C, 73.50; H, 9.25; N, 3.90. Found: C, 73.46; H, 9.47; N, 4.18. Elution with benzene-diethyl ether (96:4) afforded 63 mg (23%) of N-methyl-1β,5-epoxyimino-5β-androst-1-ene (8b) mp 165° C (from acetone-light petroleum); $[\alpha]_D^{20}$ = +5.3° (c = 0.93, $CHCl_3$); ir (KBr): ν_{max} = 3030, 1735, 1640, 1440, 1425, 1385, 1370, 1245, 1045, 1025, 900, 720; ^{1}H nmr: δ = 0.81 (s, H_3C-18), 1.26 (s, H_3C-19), 2.05 (s, AcO-17), 2.15 (m, $H_\alpha C$-6), 2.20 (two m, H_2C-2), 2.63 (s, H_3C-N), 3.87 (s,br, w/2=5 Hz, HC-1), 4.61 (t, J=9 Hz, HC-17), 5.27 (d, J=10 Hz, HC-4), 5.91 (d,br, J=10 Hz, HC-3); m/z: 359 (M^+). Anal. Calcd for $C_{22}H_{33}NO_3$ (359.51): C, 73.51; H, 9.25; N, 3.90. Found: C, 73.26; H, 9.07; N, 4.01.

Hydrogenolysis of N- methyl-3β,5-epoxyimino-5β-cholest-1-ene (7a). - To a stirred solution of 7a (160 mg) in 10 ml of AcOH-H_2O (9:1) was added 1 g of Zn-dust. After heating for 10 h at reflux, excess Zn was separated by filtration from the cooled reaction mixture and washed with 3% HCl. The filtrate was neutralized with 10% aq KOH and extracted with diethyl ether-CH_2Cl_2 (1:1). The organic layer was

washed with water, dried over Na_2SO_4 and evaporated to dryness. The residue (157 mg) was recrystallized from acetone-light petroleum to give 5-methylamino-5β-cholest-1-en-3β-ol (10) (143 mg, 89%), mp 112° C; $[\alpha]_D^{20}$ = +92° (c = 0.50, $CHCl_3$); ir (KBr): ν_{max} = 3600-3200, 1645, 1630, 1460, 1380, 1360, 1105, 760; ^{1}H nmr: δ = 0.66 (s, H_3C-18), 0.85 (two d, J=6.5 Hz, H_3C-26 and H_3C-27), 0.87 (d, J=6.5 Hz, H_3C-21), 1.04 (s, H_3C-19), 2.17 (dxd, J=9, 4 Hz, $H_\beta C$-4), 2.37 (s, H_3C-N), 2.50 (m, $H_\alpha C$-4), 4.05 (t,br, J=4 Hz, HC-3), 5.52 (d, J=10 Hz, HC-1), 5.77 (dxd, J=10, 4 Hz, HC-2); m/z: 415 (M^+). Anal. Calcd for $C_{28}H_{49}NO$ (415.71): C, 80.90; H, 11.88; N, 3.39. Found: C, 80.62; H, 11.68; N, 3.58.

Oppenauer oxidation of 5β-methylamino-5β-cholest-1-en-3β-ol (10). - To a stirred solution of 10 (80 mg) in dry cyclohexanone (3 ml) and dry toluene (3 ml), aluminium isopropoxide (200 mg) in dry toluene (3 ml) was added and the mixture was refluxed for 1 h. After addition of saturated K,Na-tartarate (10 ml), the mixture was steam-distilled and the residue extracted with diethyl ether. The etherial extract was washed with water, dried over Na_2SO_4 and evaporated to dryness leaving an oily residue (75 mg), which was chromatographed on silica gel (3 g). Elution with benzene afforded cholesta-1,4-dien-3-one (11) (47 mg, 64%), mp 110°C (from acetone-MeOH); $[\alpha]_D^{20}$ = +27.7° (c = 0.50, $CHCl_3$); uv (MeOH): 244 (11950) (lit.[16] 108-110°C; $[\alpha]_D^{20}$ = +29.3°; uv (EtOH): 244 (12500)).

Reaction of (Z)-3β-hydroxy-5,10-secocholest-1(10)-en-5-one (12) with N-methylhydroxylamine. - A solution of 12[5] (330 mg) and MeNHOH·HCl (330 mg) in EtOH (10 ml) and pyridine (10 ml) was refluxed for 8 h and the mixture worked up as described above. The residue was chromatographed on silica gel (15 g). Elution with benzene-light petroleum (1:1) gave 2,4-cholestadien-1-one (9a) (67 mg, 21%), mp 105° C (from acetone-light petroleum); uv, ir and nmr spectra were identical to those observed for the previously described sample. Benzene-diethyl ether (95:5) eluted N-methyl-1β,5-epoxyimino-5β-cholestan-3β-ol (13) (193 mg, 51%), mp 129° C (from acetone-MeOH); $[\alpha]_D^{20}$ = +54.8° (c = 0.50, $CHCl_3$); ir (KBr): ν_{max} = 3380, 1465, 1450, 1440, 1380, 1310, 1120, 1100, 1060, 920, 905, 885, 775; ^{1}H nmr: δ = 0.70 (s, H_3C-18), 0.85 (two d, J=6.5 Hz, H_3C-26 and H_3C-27), 0.87 (d, J=6.5 Hz, H_3C-21), 1.22 (s, H_3C-19), 2.82 (s, H_3C-N), 3.95 (two m, HC-3 and HC-1); m/z: 431 (M^+). Anal. Calcd for $C_{28}H_{49}NO_2$ (431.71): C, 77.90; H, 10.85; N, 2.96. Found: C, 77.68; H, 11.03; N, 3.18.

Acetylation of N-methyl-1β,5-epoxyimino-5β-cholestan-3β-ol (13). - A solution of 13 (80 mg) in pyridine (1 ml) and Ac_2O (1 ml) was left at room temp. for 12 h and worked up in the usual way to give N-methyl-1β,5-epoxyimino-5β-cholestan-3β-ol acetate (14) (75 mg, 85%); mp 144° C (from acetone-MeOH); $[\alpha]_D^{20}$ = +16.0° (c = 0.50, $CHCl_3$); ir (KBr): ν_{max} = 1720, 1465, 1445, 1420, 1380, 1370, 1260, 1095, 1050, 1020, 890; ^{1}H nmr: δ = 0.65 (s, H_3C-18), 0.83 (two d, J=6.5 Hz, H_3C-26 and H_3C-27), 0.87 (d, J=6.5 Hz, H_3C-21), 1.15 (s, H_3C-19), 2.04 (s, AcO-3), 2.75 (s, H_3C-N), 3.85 (s,br, w/2=6 Hz, HC-1), 5.10 (m, HC-3); m/z: 473 (M^+). Anal. Calcd for $C_{30}H_{51}NO_3$ (473.75): C, 76.06; H, 10.85; N, 2.96. Found: C, 75.82; H, 10.97; N, 2.88.

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14. We wish to thank Dr. R. Tasovac (Microanalytical Laboratory, Faculty of Science, Belgrade) for carrying out elemental microanalyses. Spectral determinations were performed (^{1}H nmr and ^{13}C nmr) at Ciba-Geigy Limited, Basel, Switzerland (Dr. H. Fuhrer and Dr. G. Rist) and (ir and m/z) in the Laboratories for Instrumental Analysis, Faculty of Science, Belgrade (direction Prof. D. Jeremić).
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