

## Spectroscopic Properties of 6-Hydroximino-5 $\beta$ -Cholestane Derivatives

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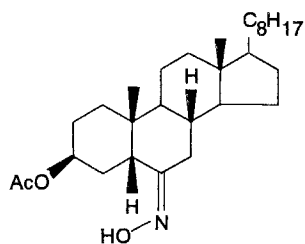
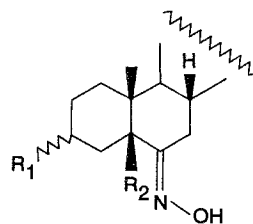
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**ABSTRACT** - The structures of 18 and the CD data of 13 6-hydroximinocholestane derivatives are presented. Oxime configurations were determined by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. An X-ray analysis of **11** has been performed.

Continuing our studies of the chiroptical properties of saturated steroidal ketoximes <sup>1</sup> we have synthesized a series of 6-hydroximinocholestanes with cis A/B ring junction (Fig.1). The oximes were obtained by direct oximation of the parent ketones with hydroxylammonium chloride in pyridine <sup>2</sup>. All 5 $\beta$ -substituted ketones gave single products. The E-configuration of the oxime hydroxyl group of these compounds followed from the presence of the strongly deshielded equatorial 7 $\beta$ -H signal <sup>2</sup> in their <sup>1</sup>H NMR spectra which lies in the range of  $\delta = 3.19 - 3.32$ . In the case of oximation of 3 $\beta$ -acetoxy-5 $\beta$ -cholestan-6-one both stereoisomeric oximes **1** and **2** were obtained according to the literature data concerning oximation of 5 $\beta$ -cholestan-6-one <sup>3</sup>. The more polar isomer **2** has the hydroxy group syn to C-7 as proven by the presence of the deshielded 7 $\beta$ -H signal at  $\delta = 3.15$ . The relative configuration of the oxime group of the less polar product **1** was found to be cis to C-5 because of the deshielding effect on 5 $\beta$ -H signal ( $\delta = 3.45$ ). The stereochemistry of the oximes **1**, **2**, **7**, **9**, **11** and **13** was independently confirmed by comparison of their <sup>13</sup>C NMR data with those of the parent ketones (Table 1). We have applied the known rule that on oxime formation the  $\alpha$ -syn carbons are shielded more than the  $\alpha$ -anti carbons <sup>4</sup>. The calculated shift parameters (Table 2) show that in case of the oximes **2**, **7**, **9**, **11** and **13** the most shielded signals, except those for C-6, correspond to the C-7 carbons. This clearly proves the E-configuration of the discussed oximes. By analogy, the oxime group in compound **1** was found to be in Z-configuration. In addition, the structure of **11** was confirmed by X-ray analysis (Fig. 2).

**Fig. 1:** Structures of 6-hydroximino-5 $\beta$ -cholestanes **1** - **13**, 6-keto-5 $\beta$ -cholestanes **14** - **18**, and of 6-hydroximino-5 $\alpha$ -cholestane derivatives **19** - **20**

**1****2**R<sub>1</sub> = β-OAc R<sub>2</sub> = H**3**

H OH

**4**

β-OH OH

**5**

β-Br OH

**6**

β-Cl OH

**7**

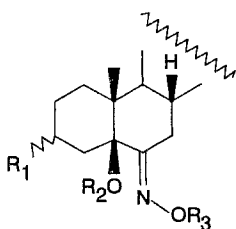
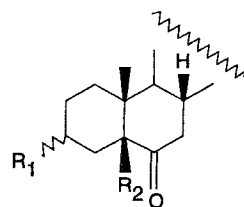
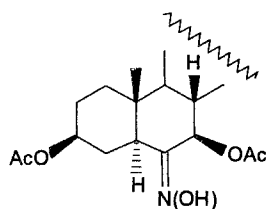
β-OAc OH

**8**

α-OH OH

**9**

α-OAc OH

**10** R<sub>1</sub> = β-OAc R<sub>2</sub> = H R<sub>3</sub> = Ac**11** β-OAc Ac H**12** β-OAc Ac Ac**13** α-OAc Ac H**14** R<sub>1</sub> = β-OAc R<sub>2</sub> = H**15** β-OAc OH**16** α-OAc OH**17** β-OAc OAc**18** α-OAc OAc**19** Z (syn to C-7)**20** E (anti to C-7)

**Table 1:**  $^{13}\text{C}$  chemical shifts of the 5 $\beta$ -cholestane oximes **1**, **2**, **7**, **9**, **11** and **13** and their parent ketones **14**, **15**, **16**, **17** and **18**.

C-No.	<b>1</b>	<b>14</b>	<b>2</b>	<b>15</b>	<b>7</b>	<b>16</b>	<b>9</b>	<b>17</b>	<b>11</b>	<b>18</b>	<b>13</b>
1	29.7	29.8	29.8	5.5	25.3	29.7	29.1	25.7	26.1	29.7	29.2
2	24.6	24.5	24.5	24.5	24.4	26.0	25.9	24.3	24.4	26.0	26.0
3	68.6	67.6	68.8	67.3	69.0	70.5	71.1	67.0	68.2	69.6	69.9
4	28.6	29.3	30.9	34.8	36.4	37.6	39.1	28.6	28.7	31.6	31.6
5	36.9	55.1	45.1	80.0	75.6	81.5	77.0	88.3	84.3	90.7	86.7
6	161.8	214.4	161.8	213.3	160.3	212.2	160.8	204.2	155.0	203.1	154.7
7	33.4	42.7	25.3	41.8	26.3	41.6	26.1	43.4	26.8	43.3	26.5
8	36.4	36.9	35.2	37.4	34.6	37.6	34.9	38.4	35.2	38.8	35.7
9	40.0	39.3	40.0	42.8	42.7	43.0	42.8	42.4	42.9	42.9	43.0
10	36.0	37.9	36.6	44.1	42.1	44.0	41.9	45.0	42.5	45.2	43.3
11	20.9	21.1	21.1	21.5	21.4	21.4	21.2	21.5	21.4	21.4	21.3
12	39.8	39.5	39.8	39.4	39.4	39.4	39.6	39.4	39.4	39.5	39.7
13	42.9	43.0	43.0	43.0	42.8	43.1	42.9	43.1	42.9	43.2	43.0
14	56.5	56.8	56.8	56.9	56.8	56.9	56.8	56.7	56.6	56.8	56.6
15	24.0	23.9	24.0	24.0	24.0	24.0	24.1	23.9	24.0	24.0	24.0
16	28.2	28.0	28.2	28.0	28.1	28.0	28.1	27.9	28.1	28.0	28.1
17	56.2	56.0	56.1	56.0	56.0	56.1	56.1	56.0	56.0	56.1	56.1
18	12.0	11.9	12.0	11.9	11.9	11.9	12.0	11.9	12.0	11.9	12.1
19	23.4	23.6	23.3	16.8	16.3	16.3	16.2	16.7	16.8	16.1	16.2
20	35.7	35.6	35.7	35.6	35.6	35.6	35.7	35.6	35.6	35.7	35.7
21	18.6	18.5	18.6	18.6	18.6	18.6	18.6	18.6	18.6	18.6	18.6
22	36.1	36.0	36.1	36.0	36.1	36.0	36.1	36.0	36.0	36.1	36.1
23	23.8	23.7	23.7	23.7	23.7	23.8	23.8	23.7	23.7	23.8	23.8
24	39.5	39.3	39.4	39.4	39.6	39.4	39.5	39.4	39.6	39.5	39.5
25	28.0	27.9	28.0	28.0	28.0	28.0	28.0	27.9	27.9	28.0	28.0
26	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5
27	22.8	22.7	22.8	22.8	22.8	22.8	22.8	22.7	22.7	22.8	22.8
OAc	21.5	21.2	21.4	21.5	21.6	21.3	21.4	21.2	21.3	21.2	21.3
	-	-	-	-	-	-	-	22.0	22.4	21.7	22.1
	170.7	170.2	170.6	170.9	170.9	170.1	170.7	169.7	170.1	169.6	170.0
	-	-	-	-	-	-	-	169.9	170.4	170.1	170.2

**Table 2:**  $^{13}\text{C}$  substituent shift parameters for conversion of ketones to ketoximes\*.

C-No.	1	2	7	9	11	13
1	-0.1	0.0	-0.2	-0.6	+0.4	-0.5
3	+1.0	+1.2	+1.7	+0.6	+1.2	+0.3
4	-0.7	+1.6	+1.6	+1.5	+0.1	0.0
5	<u>-18.2</u>	-10.0	-4.4	-4.5	-4.0	-4.0
6	-52.6	-52.6	-53.0	-51.4	-49.2	-48.4
7	-9.3	<u>-17.4</u>	<u>-15.5</u>	<u>-15.5</u>	<u>-16.6</u>	<u>-16.8</u>
8	-0.5	-1.7	-2.8	-2.7	-3.2	-3.1
10	-1.9	-1.1	-2.0	-2.1	-2.5	-1.9
19	-0.2	-0.3	-0.5	-0.1	+0.1	+0.1

These values are differences between the  $^{13}\text{C}$  shifts of ketoximes and the corresponding ketones. Negative values indicate shieldings of the ketoxime signals. The underlined values correspond to  $\alpha$ -syn carbons.

**Table 3:** CD data of the oximes **1** through **13** in acetonitrile. Values are given as  $\Delta\epsilon$  ( $\lambda$ [nm]).

Compound	CE I	CE II
<b>1</b>	+0.89 (221)	
<b>2</b>	-5.53 (214)	+3.0 (196)
<b>3</b>	-7.55 (214)	+12.8 (196)
<b>4</b>	-6.19 (214)	+13.4 (195)
<b>5</b>	-6.54 (215)	+15.9 (196)
<b>6</b>	-7.74 (215)	+17.7 (196)
<b>7</b>	-6.12 (215)	+11.6 (196)
<b>8</b>	-7.07 (214)	+11.8 (196)
<b>9</b>	-7.92 (214)	+13.3 (192)
<b>10</b>	-6.52 (219)	+13.6 (199)
<b>11</b>	+1.30 (225)	
<b>12</b>	+1.92 (228)	
<b>13</b>	+1.04 (230)	

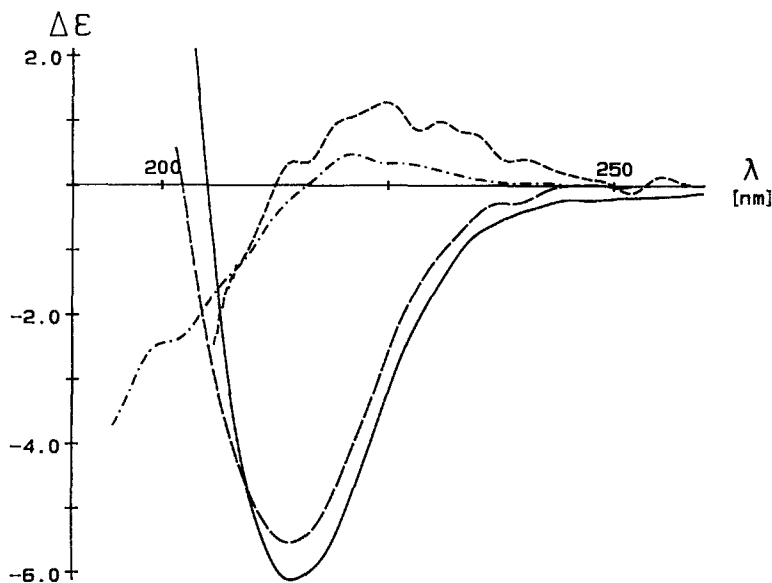
## CHIROPTICAL PROPERTIES

The CD data of all investigated oximes are collected in Table 3. 5-Hydroxy-6-hydroximino-5 $\beta$ -cholestanes (**3** - **9**) and 5-hydroxy-6-acetoximino-5 $\beta$ -cholestane (**10**) show two Cotton effects of opposite signs in the accessible range. The sign of the first Cotton effect (CE I) is always negative and its magnitude is slightly higher than that for the 5 $\beta$ -unsubstituted oxime **2** of the same oxime configuration. The observed sign of this Cotton effect agrees with the prediction by the chirality rule <sup>1</sup>. The second short-wavelength CE II is positive for all 5 $\beta$ -hydroxyoximes and about 4-6 times stronger than that on the unsubstituted oxime **2**.

The 5 $\beta$ -unsubstituted oxime **1** shows only one weak positive Cotton effect (CE I). The sign of this CE also fulfils the chirality rule <sup>1</sup>.

The 5 $\beta$ -acetoxy-6-hydroximinocholestanes (**11** and **13**) and 5 $\beta$ -acetoxy-6-acetoximinocholestane (**12**) behave anomalously. Although they possess the same relative configuration as all 5 $\beta$ -hydroxyoximes, their CD curves show only one weak positive Cotton effect (CE I) at higher wavelengths (225 - 230 nm). The CD data obtained for 5 $\beta$ -acetoxyoximes **11** - **13** differ from those for isomeric 7 $\beta$ -acetoxy-6-hydroximinocholestanes **19** and **20** <sup>1</sup>. Compounds **19** and **20** containing also  $\beta$ -equatorial acetoxy substituents behave as expected giving negative and positive CE I around 220 nm, respectively. We are not able to explain the unusual chiroptical properties of **11** - **13**. They may be originated in a boat conformation of ring B in solution. In solid state and in an unpolar solvent (deuterated chloroform), however, we cannot detect such conformational effects.

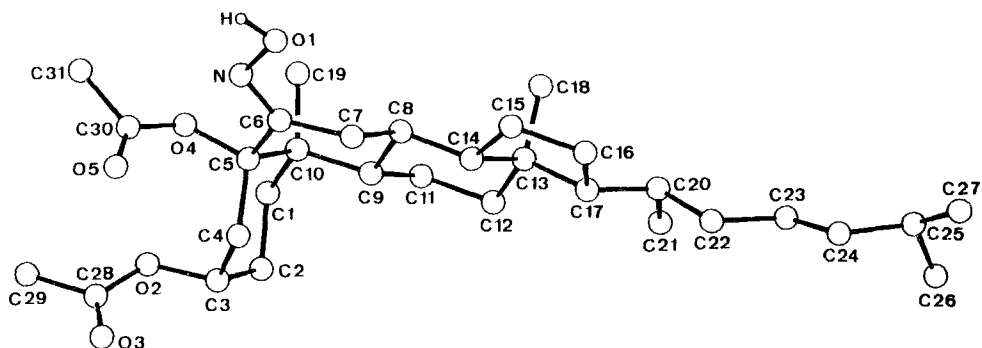
Fig.2: CD spectra of **1** (---), **2** (— — —), **7** (———), and **11** (-----); only CE I (200-250 nm)



## EXPERIMENTAL

Crystal data of **11**: Formula  $C_{31}H_{51}NO_5$ , mol wt 517.8  $g\text{mol}^{-1}$ , orthorhombic,  $P2_12_12_1$ ,  $a = 9.585(1)$ ,  $b = 10.815(1)$ ,  $c = 29.715(2)\text{\AA}^3$ ,  $Z=4$ ,  $d_{\text{calcd}} = 1.12\text{gcm}^{-3}$ ,  $\lambda = 1.54178\text{\AA}$ ,  $\mu = 5.55\text{cm}^{-1}$ , analytical absorption corrections (min = 1.072, max = 1.217),  $F(000) = 1136$ ,  $T = 20^\circ\text{C}$ , Enraf-Nonius CAD4 diffractometer,  $(\sin\theta/\lambda)_{\text{max}} = 0.63\text{\AA}^{-1}$ , 7627 reflections measured, 5989 unique reflections,  $R_{\text{av}} = 0.037$ , 4269 observed reflections [ $I > 2\sigma(I)$ ], solution by direct methods, all hydrogen atoms besides the hydroxyl (which was located in difference Fourier synthesis and included in the refinement procedure) were calculated and kept fixed during refinement, ADP included for non-hydrogen atoms, absolute configuration assigned according to  $\kappa = -0.07(30)^5$ ,  $R = 0.062$ ,  $R_w = 0.056$ ,  $\text{EOF} = 2.23$ , the crystal structure reveals an intermolecular hydrogen bond [ $\text{O}(1)-\text{O}(3)2.78\text{\AA}$ ,  $\text{O}(1)-\text{H}-\text{O}(3)163^\circ$ ]. Atomic coordinates, thermal parameters, bond lengths and angles are available on request from the Cambridge Crystallographic Data Centre.

Fig. 3: Graphical representation of **11** from X-ray analysis



## General Procedures

Melting points were determined on a Boetius micro-melting point apparatus and are uncorrected. Unless otherwise stated optical rotations were measured on a Perkin-Elmer 241 polarimeter in chloroform solution, concentrations are given in  $g/100\text{ ml}$ . IR-spectra were recorded on an UR-20 spectrometer in KBr pellets, or on a Pye Unicam SP 1100 in chloroform solutions  $\{\lambda_{\text{max}}[\text{cm}^{-1}]\}$ .  $^1\text{H}$  NMR spectra were taken on Tesla BS 567, Bruker WP-80, or Bruker AM-400 spectrometers and CD spectra on a modified ISA-JOBIN-YVON Dichrograph Mark III  $\{\Delta\epsilon/\lambda [\text{nm}]\}$ . Column chromatography was performed on Kieselgel 60 (70-230 mesh) Merck. The synthesis of the oximes **7**, **11**, and oxime acetates **10** and **12** were reported earlier by us <sup>2</sup>.

Synthesis of the oximes **1 - 6**, **8 - 9** and **13**. To a solution of the corresponding ketone (0.5g) in 6 ml pyridine an excess of hydroxylamine hydrochloride (ca. 0.25g) was added and the reaction mixture was left for 2-5 days at room temperature. The progress of the reaction was monitored by TLC. After partitioning between water and ether or benzene the organic layer was purified by column chromatography and crystallized from the indicated solvent.

(6Z)-6-Hydroximino-5 $\beta$ -cholestan-3 $\beta$ -ol 3-acetate (**1**). Yield 45%; m.p. 174-177°C (hexane);  $[\alpha]_D$ : +10.4 (c= 1.2); IR (KBr): 3445, 3410, 3280, 1742, 1666, 1470, 1382, 1271, 1238, 1030;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ): 0.62 (s, 18-Me), 0.86 (s, 19-Me), 2.06 (OAc), 2.17 (dd, J=14.2 and 3.3 Hz, 7 $\beta$ -H), 3.45 (dd, J=13.1 and 4.0 Hz, 5 $\beta$ -H), 5.07 (nm, 3 $\alpha$ -H); Anal. found C 75.9; H 10.7; N 3.2:  $\text{C}_{29}\text{H}_{49}\text{NO}_3$  requires C 75.8; H 10.7; N 3.1.

(6E)-6-Hydroximino-5 $\beta$ -cholestan-3 $\beta$ -ol 3-acetate (**2**). Yield 25%; m.p. 139-141°C (hexane);  $[\alpha]_D$ : -11.3 (c= 1.3); IR (KBr): 3480, 1740, 1720, 1280, 1233, 1160, 1033;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ): 0.62 (18-Me), 0.85 (19-Me), 2.02 (OAc), 2.33 (dd, J=13.5 and 4.0 Hz, 5 $\beta$ -H), 3.15 (dd, J=14.2 and 3.1 Hz, 7 $\beta$ -H), 5.06 (nm, 3 $\alpha$ -H); Anal. found C 76.0; H 10.9; N 3.0:  $\text{C}_{29}\text{H}_{49}\text{NO}_3$  requires C 75.8; G 10.7; N 3.1.

(6E)-6-Hydroximino-5 $\beta$ -cholestan-5-ol (**3**). Yield 82%; m.p. 158-160°C (acetone);  $[\alpha]_D$ : +5.9 (c= 1.8); IR (KBr): 3300-3450, 1675, 1470, 1388, 1172, 984;  $^1\text{H}$  NMR (100 MHz,  $\text{CDCl}_3$ ): 0.64 (18-Me), 0.75 (19-Me), 3.21 (m, 7 $\beta$ -H); Anal. found C 77.6; H 11.1; N 3.1:  $\text{C}_{27}\text{H}_{47}\text{NO}_2$  requires C 77.6; H 11.3; N 3.4.

(6E)-6-Hydroximino-5 $\beta$ -cholestane-3 $\beta$ ,5-diol (**4**). Yield 80%. m.p. 100-102°C (methanol);  $[\alpha]_D$ : +26.2 (c= 1.3); IR (KBr): 3200-3620, 1665, 1472, 1390, 1165, 1100, 920;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ): 0.63 (18-Me), 0.80 (19-Me), 2.18 (dd, J=15.5 and 3.2 Hz, 4 $\beta$ -H), 3.22 (dd, J=14.6 and 3.6 Hz, 7 $\beta$ -H), 4.04 (nm, 3 $\alpha$ -H), 4.72 (nm, OH), 4.92 (s, OH), 8.70 (br m, NOH); Anal. found C 74.9; H 11.0; N 3.0:  $\text{C}_{27}\text{H}_{47}\text{NO}_3$  requires C 74.8; H 10.9; N 3.2.

(6E)-6-Hydroximino-3 $\beta$ -bromo-5 $\beta$ -cholestan-5-ol (**5**). Yield 92%; m.p. 128-133°C (hexane);  $[\alpha]_D$ : +21.9 (c= 1.5); IR (KBr): 3470, 1668, 1472, 1390, 1215, 1055, 920, 720;  $^1\text{H}$  NMR (100 MHz,  $\text{CDCl}_3$ ): 0.65 (18-Me), 0.83 (19-Me), 2.61 (dd, J=16.1 and 4.2 Hz, 4 $\alpha$ -H), 3.26 (m, 7 $\beta$ -H), 3.87 (br m, OH), 4.67 (nm, 3 $\alpha$ -H); Anal. found C 65.5; H 9.1; N 2.9:  $\text{C}_{27}\text{H}_{46}\text{BrNO}_2$  requires C 65.3; H 9.3; N 2.8.

(6E)-6-Hydroximino-3 $\beta$ -chloro-5 $\beta$ -cholestan-5-ol (**6**). Yield 86%; m.p. 155-158°C (hexane);  $[\alpha]_D$ : +23.2 (c= 1.3); IR (KBr): 3480, 1670, 1475, 1450, 1392, 1238, 1055, 920, 726;  $^1\text{H}$  NMR (100 MHz,  $\text{CDCl}_3$ ): 0.65 (18-Me), 0.83 (19-Me), 2.51 (dd, J=16.1 and 4.4 Hz, 4 $\alpha$ -H), 3.28 (m, 7 $\beta$ -H), 3.87 (m, OH), 4.54 (nm, 3 $\alpha$ -H); Anal. found C 71.8; H 10.2; N 3.1:  $\text{C}_{27}\text{H}_{46}\text{ClNO}_2$  requires C 71.7; H 10.2; N 3.1.

(6E)-6-Hydroximino-5 $\beta$ -cholestane-3 $\alpha$ ,5-diol (**8**). Yield 90%; m.p. 168-170 (benzene);  $[\alpha]_D$ : +1.8 (c= 1.5); IR (KBr): 3400, 1663, 1170, 1058;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ): 0.61 (18-Me), 0.72 (19-Me), 3.19 (d like, 7 $\beta$ -H), 3.99 (nm, OH), 4.05 (br m, 3 $\beta$ -H), 8.46 (s, NOH); Anal. found C 75.0; H 10.8; N 3.3:  $\text{C}_{27}\text{H}_{47}\text{NO}_3$  requires C 74.8; H 10.9; N 3.2.

(6E)-6-Hydroximino-5 $\beta$ -cholestane-3 $\alpha$ ,5-diol 3-acetate (**9**). Yield 85%; m.p. 195-196°C (acetone-hexane);  $[\alpha]_D$ : +17.4 (c= 1.3); IR (KBr): 3440, 1714, 1660, 1273, 1170, 1053;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ): 0.62 (18-Me), 0.75 (19-Me), 1.99 (OAc), 2.07 (t, J=12.1 Hz, 4 $\alpha$ -H), 3.23 (dd, J=14.1 and 3.6 Hz, 7 $\beta$ -H), 4.04 (s, 5 $\beta$ -OH), 5.13 (br m, 3 $\beta$ -H), 7.87 (s, NOH); Anal. found C 73.1; H 10.6; N 3.0:  $\text{C}_{29}\text{H}_{49}\text{NO}_4$  requires C 73.2; H 10.4; N 2.9.

(6E)-6-Hydroximino-5 $\beta$ -cholestane-3 $\alpha$ ,5-diol 3,5-diacetate (**13**). Yield 86 %; oil;  $[\alpha]_D$ : -52.0 (c= 1.1); IR (nujol): 3350-3510, 1748, 1660, 1470, 1371, 1244, 1170, 1065, 1030;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ): 0.63 (18-Me), 0.82 (19-Me), 1.98 (OAc), 2.18 (dd, J=13.9 and 11.8 Hz, 4 $\alpha$ -H), 3.19 (dd, J=13.5 and 4.1 Hz, 7 $\beta$ -H), 4.76 (br m, 3 $\beta$ -H), 7.82 (s, NOH); Anal. found C 72.0; H 10.1; N 2.6:  $\text{C}_{31}\text{H}_{51}\text{NO}_5$  requires C 71.9; H 9.9; N 2.7.

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