JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 3, 404–413 (1990)

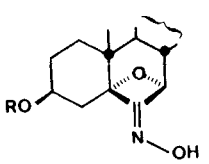
SYNTHESIS AND SPECTROSCOPIC PROPERTIES OF STEREOISOMERIC 5,7-OXIDO-6-HYDROXYIMINOCHOLESTANE DERIVATIVES

HELMUT DUDDECK
Lehrstuhl für Strukturchemie der Ruhruniversität Bochum, Postfach 10 21 48, D-4630 Bochum, FRG
JADWIGA FRELEK
Chair for Synthesis of Natural Products, Warsaw University, ul. Pasteura 1, PL-02093 Warsaw, Poland
DAVOR HORVATIĆ AND BISERKA KOJIĆ-PRODIĆ
Ruđer Bošković Institute, P.O.B. 1016, YU 41001 Zagreb, Yugoslavia
GÜNTHER SNATZKE*
Lehrstuhl für Strukturchemie der Ruhruniversität Bochum, Postfach 10 21 48 D-4630 Bochum, FRG
WOJCIECH J. SZCZEPEK
Chair for Synthesis of Natural Products, Warsaw University, ul Pasteura 1, PL-02093 Warsaw, Poland
PETRA WAGNER
Chair for Synthesis of Natural Products, Warsaw University, ul Pasteura 1, PL-02093 Warsaw, Poland

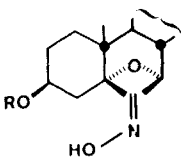
The four possible diastereomeric 5,7-oxido-6-hydroxyiminocholestanes and their *O*-acetates have been synthesized. The stereochemistry of one of the latter has been proved unequivocally by x-ray diffraction. Their ^{1}H and ^{13}C NMR and also their circular dichroism spectra are discussed. It is now also possible to determine unequivocally the stereochemistry of the ring-junction geometry and the oxime *E* or *Z* stereochemistry.

INTRODUCTION

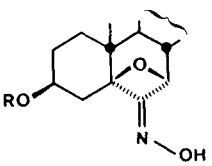
In contrast to the extensive studies of the chiropatical properties of ketones,[1] such studies on oximes have only rarely been published.[2,3] For oximes of saturated ketones, in no case have the differences between the circular dichroism (CD)-spectra of the *E* and *Z* isomers been described. In Warsaw University many such *E*/*Z* pairs have been synthesized, and here we discuss the structure elucidation and spectroscopic properties of some oxetanone oximes (**1**–**4**) containing an oxido bridge between C-5 and C-7 and the hydroxyimino function at C-6 in ring B of a steroid.†



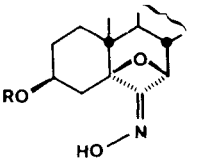
1a,b



2a,b



3a,b



4a,b

a R = H

b R = Ac

* Author for correspondence.

† Atomic coordinates for this structure and additional material have been deposited with the Cambridge Crystallographic Centre. The coordinates can be obtained from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

0894–3230/90/060404–10$05.00

Received 31 January 1989
Revised 22 September 1989

Table 1. Molecular geometry of steroid rings and oximino group

Ring A		Ring B		Ring C		Ring D	
Bond distances (Å)							
C-1 —C-2	1·537(9)	C-5 —C-6	1·551(8)	C-8 —C-9	1·559(8)	C-13—C-14	1·544(8)
C-2 —C-3	1.515(9)	C-6 —C-7	1.517(9)	C-9 —C-11	1·524(9)	C-14—C-15	1.516(8)
C-3 —C-4	1·520(9)	C-7 —C-8	1·522(9)	C-11—C-12	1·520(9)	C-15—C-16	1·548(9)
C-4 —C-5	1·524(9)	C-8 —C-9	1·559(8)	C-12—C-13	1·551(8)	C-16—C-17	1·546(8)
C-5 —C-10	1·546(9)	C-9 —C-10	1·560(8)	C-13—C-14	1·544(8)	C-17—C-13	1·563(8)
C-10—C-1	1·536(9)	C-10—C-5	1·546(9)	C-14—C-8	1·521(8)		
		C-5 —O-5	1·478(7)				
		C-7 —O-5	1·479(7)				
		C-6 —N-6	1·245(8)				
		N-6 —O-61	1·416(7)				
Bond angles (°)							
C-10—C-1 —C-2	112·2(5)	C-10—C-5 —C-6	110·1(5)	C-14—C-8 —C-9	106·9(4)	C-17—C-13—C-14	99·6(4)
C-1 —C-2 —C-3	110·0(5)	C-5 —C-6 —C-7	85·3(4)	C-8 —C-9 —C-11	109·9(5)	C-13—C-14—C-15	104·4(5)
C-2 —C-3 —C-4	112·8(5)	C-6 —C-7 —C-8	112·7(5)	C-9 —C-11—C-12	112·3(5)	C-14—C-15—C-16	103·7(5)
C-3 —C-4 —C-5	111·8(5)	C-7 —C-8 —C-9	107·1(5)	C-11—C-12—C-13	113·3(5)	C-15—C-16—C-17	107·1(5)
C-4 —C-5 —C-10	114·8(5)	C-8 —C-9 —C-10	111·1(5)	C-12—C-13—C-14	107·8(5)	C-16—C-17—C-13	103·4(4)
C-5 —C-10—C-1	106·7(5)	C-9 —C-10—C-5	107·1(4)	C-13—C-14—C-8	111·8(4)		
		C-4 —C-5 —O-5	110·0(5)				
		O-5 —C-5 —C-10	108·7(5)				
		O-5 —C-5 —C-6	86·5(4)				
		C-5 —O-5 —C-7	89·3(4)				
		C-5 —C-6 —N-6	143·3(6)				
		C-7 —C-6 —N-6	130·9(6)				
		C-6 —N-6 —O-61	111·5(5)				
Torsion angles (°)							
C-10—C-1 —C-2 —C-3	−61·2(7)	C-10—C-5 —C-6 —C-7	83·9(5)	C-14—C-8 —C-9 —C-11	−60·7(6)	C-17—C-13—C-14—C-15	46·7(5)
C-1 —C-2 —C-3 —C-4	54·7(7)	C-5 —C-6 —C-7 —C-8	−81·6(5)	C-8 —C-9 —C-11—C-12	56·0(6)	C-13—C-14—C-15—C-16	−35·1(5)
C-2 —C-3 —C-4 —C-5	−49·8(7)	C-6 —C-7 —C-8 —C-9	22·8(6)	C-9 —C-11—C-12—C-13	−52·5(7)	C-14—C-15—C-16—C-17	9·2(6)
C-3 —C-4 —C-5 —C-10	50·3(7)	C-7 —C-8 —C-9 —C-10	43·3(6)	C-11—C-12—C-13—C-14	52·2(6)	C-15—C-16—C-17—C-13	19·4(6)
C-4 —C-5 —C-10—C-1	−53·1(6)	C-8 —C-9 —C-10—C-5	−39·9(6)	C-12—C-13—C-14—C-8	−59·6(6)	C-16—C-17—C-13—C-14	−39·6(5)
C-5 —C-10—C-1 —C-2	58·4(6)	C-9 —C-10—C-5 —C-6	−27·8(6)	C-13—C-14—C-8 —C-9	64·3(6)		
		C-10—C-5 —C-5 —O-7	−84·8(5)				
		C-5 —O-5 —C-7 —C-8	87·2(5)				
		C-5 —O-5 —C-7 —C-6	−25·8(4)				
		O-5 —C-7 —C-6 —C-5	24·6(4)				
		C-7 —C-6 —C-5 —O-5	−24·6(4)				
		C-6 —C-5 —O-5 —C-7	25·2(4)				
		C-5 —C-6 —N-6 —O-61	8·0(1)				
		O-5 —C-7 —C-6 —N-6	−148·6(7)				

SYNTHESIS

The two parent 6-ketones were prepared according to the procedure of Rowland and co-workers.[4,5] Oximation was achieved by treatment of these ketones with hydroxylammonium chloride in pyridine at room temperature. The respective diastereomeric oximes were unusually stable and each *E*/*Z* pair could easily be separated by column chromatography on silica gel.

DETERMINATION OF STRUCTURE OF **4b** BY X-RAY DIFFRACTION

X-ray experimental data

The crystals of **4b** were prepared from EtOH–H_2O at room temperature for x-ray analysis. Preliminary cell dimensions and the space group ($P2_12_12_1$) were determined from oscillation and Weissenberg photographs recorded with Cu Kα radiation; final cell dimensions [$a = 724{\cdot}6(1)$, $b = 1178{\cdot}0(5)$, $c = 3191{\cdot}3(8)$ pm] were refined from diffractometer measurements using 25 reflections in the range $6^\circ < \theta < 12^\circ$. A crystal of $0{\cdot}70 \times 0{\cdot}66 \times 0{\cdot}14$ mm^3 was used for data collection. Intensities were measured on an Enraf–Nonius CAD-4 diffractometer with graphite-monochromated Mo Kα radiation at 293 ± 1 K in the $\omega/2\theta$ scan mode [scan width in $2\theta = 0{\cdot}7 + 0{\cdot}3 \tan\theta(^\circ)$; scan rate, minimal = 1·03, maximal = 5·49° min^{-1}, aperture $2{\cdot}4 + 0{\cdot}9 \tan\theta(^\circ)$]; 7564 reflections were scanned ($+h$, $+k$, $\pm l$ up to 28° in θ), 3778 averaged reflections with 1040 observed reflections [2738 observed with $I \geqslant 3\sigma I$]. The intensity data were corrected for Lorentz and polarization effects but not for absorption.

The structure was solved by the direct method using SHELX86[6] and difference Fourier syntheses; refinement by full-matrix least-squares minimizing $\Sigma w(|F_o| - |F_c|)^2$ with final $w = [k\sigma^2F + gF^2]^{-1}$, $k = 1{\cdot}102$, $g = 0{\cdot}003$, using SHELX76.[7] A scale factor, atomic coordinates and anisotropic thermal parameters of non-H atoms were refined. The H atoms are introduced on stereochemical grounds and were refined on the constrained conditions (imposed by geometry of the pivot C atom) with isotropic thermal parameters. Residual electron density in the final map $-0{\cdot}3 < \Delta\rho < 0{\cdot}4$ e Å^{-3}; maximum shift/error = 0·441 (*y* for C-26). The low quality of the crystals and the large number of unobserved reflections affected the discrepancy factors: $R = 0{\cdot}138$, $R_w = 0{\cdot}107$. Scattering factors are those included in SHELX76.

Calculations were carried out on the IBM 4341 computer at the University Computing Centre, Zagreb, with SHELX86[6] and SHELX76[7] and the program for analysis of molecular geometry.[8]

Crystal and molecular structure of **4b**

Table 1 lists the molecular geometry of the steriod rings and the oximino group. Ring conformation and asymmetry parameters are given in Table 2. The atom numbering is according to IUPAC conventions and the *Atlas of Steroid Structure*.[9,10] Figure 1 and 2 show ORTEP[11] drawings in standard orientations for steroid molecules.[9,10] Figure 3 illustrates the stereo packing pattern viewed down the *b* axis.

Bond lengths and angles are in agreement with a 3β, 5-substituted 5β-cholestane skeleton onto which a 3β-acetoxy-5β,7β-epoxy unit and the 17β-C_8-cholestane side-chain had been introduced (Table 1). The conformation of each particular ring (A, B, C, D) is described by the asymmetry parameters[9,10,12] in Table[2],

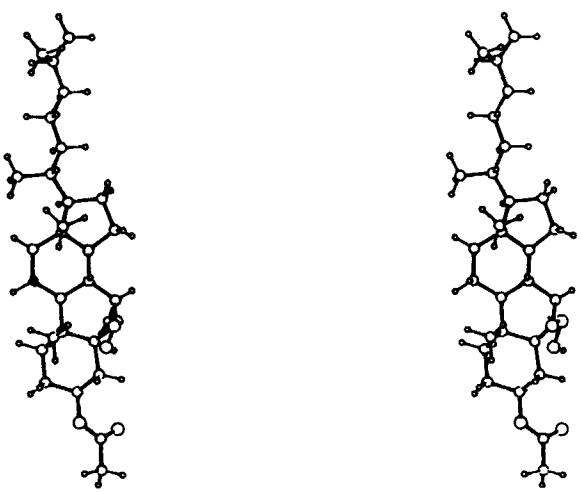


Figure 1. Stereoscopic projection of **4b** along the vectors through **l**(horizontal) = C-10 → C-13 and **w** = C-14 → C-12 (**l** × **w** perpendicular to the plane of the paper)

Table 2. Conformation of **4b**

Ring	Conformation	Asymmetry parameters	Mean *TA* (°)
A	Distorted chair	$C_s(1) = 1{\cdot}9$, $C_2(2{-}3) = 9{\cdot}9$	54·6
B	Distorted boat	$C_s(6) = 3{\cdot}7$, $C_s(5{-}10) = 41{\cdot}2$	49·9
C	Distorted chair	$C_s(8) = 2{\cdot}9$, $C_2(9{-}11) = 10{\cdot}3$	57·5
D	13β, 14α Half-chair	$C_s(13) = 12{\cdot}2$, $C_s(14) = 23{\cdot}0$; $C_2(13{-}14) = 7{\cdot}9$	30·0

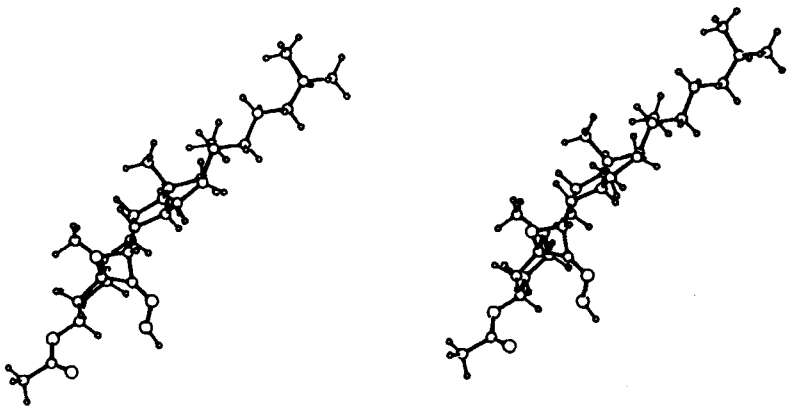


Figure 2. Stereoscopic ORTEP pair of **4b**

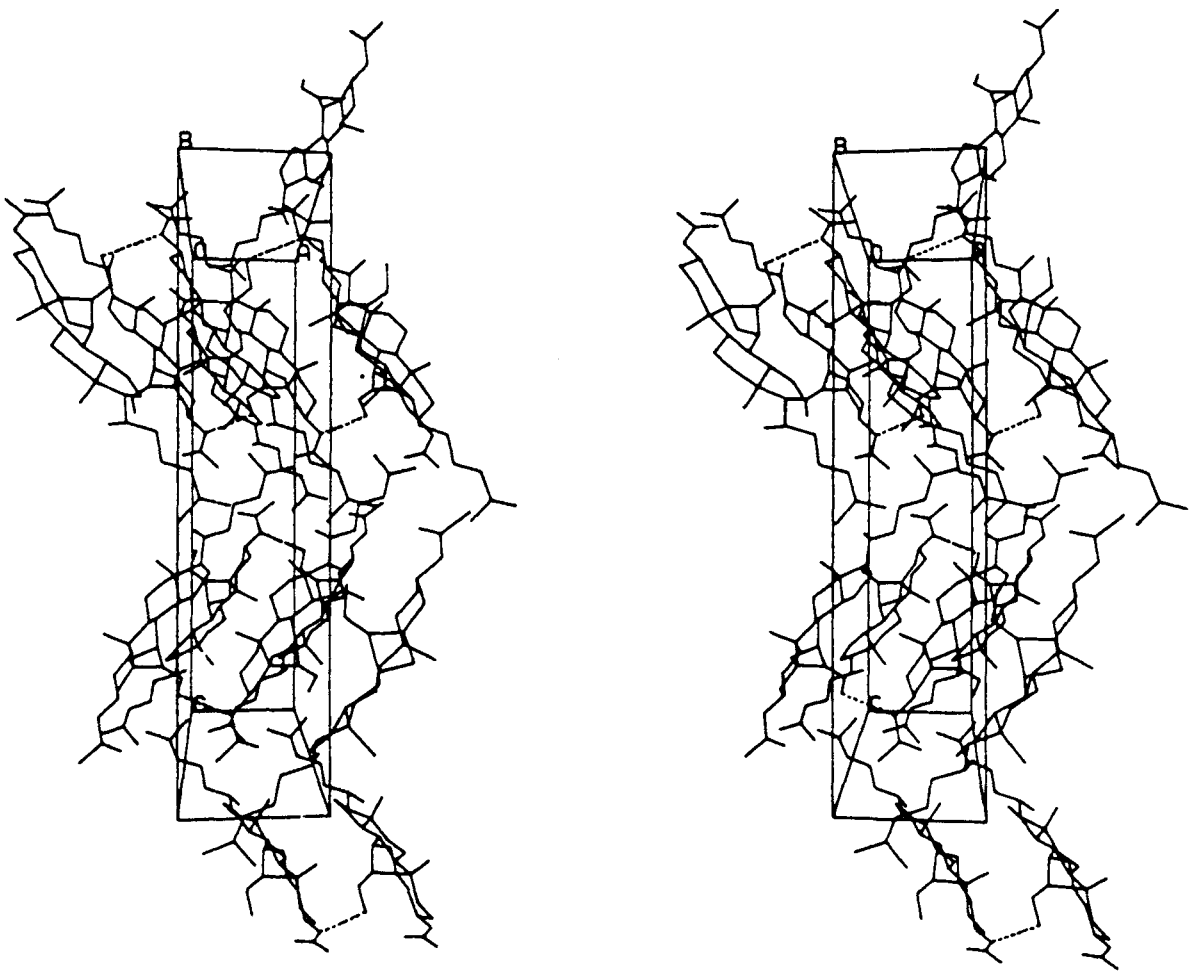


Figure 3. Stereo diagram of the molecular packing viewed down **b**; dotted lines connect hydrogen-bonded oximino and acetoxy groups, O—61—H···O-3 = 317·9(6) pm

Table 3. Torsional angles determining the ring junction conformations

	Ring junction	Torsional angle (°)	Remark
A/B	C-1 —C-10—C-5 —C-4	−53·1	quasi-*cis*
	C-9 —C-10—C-5 —C-6	−27·8	
B/C	C-10—C-9 —C-8 —C-7	+43·3	*trans*
	C-11—C-9 —C-8 —C-14	−60·7	
C/D	C-12—C-13—C-14—C-8	−59·6	*trans*
	C-17—C-13—C-14—C-15	+46·7	

and the overall skeleton conformation with ring junction torsional angles in Table 3. All rings exhibit distorted conformations caused by the 5β,7β-epoxy bridge in ring B. Although the C_s symmetry of ring B from C-6 to C-9 is retained, such a C_s axis through C-5 and C-10 is completely lost (Table 2).

The four-membered ring O-5—C-5—C-6—C-7 is puckered with a mean torsional angle (*TA*) of 25.0°; the same mode of puckering ($\langle TA \rangle = 25°$) and angle of puckering $\alpha = 35°$ is observed for cyclobutane.[12] The overall molecular conformation is defined by torsional angles along the bonds common to two rings according to the method described by Bucourt;[13] torsional angles at a junction of opposite signs describe a *trans* fusion, whereas such of identical signs refer to a *cis* junction. In the case of one trigonal carbon atom (C-6 in **4b**) the torsional angle at the junction A/B describes a quasi-*cis* fusion.[13] The influence of the 5β,7β-epoxy bond on the geometry of ring B cannot be neglected.

The conformation of the 17β-cholestane side-chain is described by a few torsional angles: C-17—C-20—C-22—C-23 = −168·8(5)°; C-21—C-20—C-22—C-23 = 64·4(7)°; C-20—C-22—C-23—C-24 = 174.2(6)°; C-22—C-23—C-24—C-25 = 174·1(7)°; C-23—C-24—C-25—C-26 = 30·0(1)°; and C-23—C-24—C-25—C-27 = 175.9(7)°. It appears as an extended chain; looking along C-24—C-25 the C-23—C-24 bond is *trans* to the C-25—C-27 bond, and the terminal methyl conformation is −*gauche, trans*. A detailed discussion on the conformation of the 17β-cholestane side-chain is given in Ref. 14.

Molecular packing is in the form of zig-zag layers running along the longest **c** axis (Figure 3) with the van der Waals contacts C-11···O-5 = 334·8(7) pm [$-x, y-1/2, -z-1/2$], C-32···O-31 = 330·1(9) pm [$x+1/2, -y-1/2, -z$]. A hydrogen bond between the oximino donor group and the 3β-acetoxy group [O-61—H-61···O-3 = 317·9(6) pm, H-61···O-3 = 226(2) pm, <O-61—H···O-3 = 148(2)°] connects zig-zag layers along **a**.

^{1}H AND ^{13}C NMR SPECTRA

The ^{1}H and ^{13}C NMR data of the oximes **1b**–**4b** are summarized in Tables 4–7. The signals were assigned with the aid of two-dimensional homo- and hetero-correlated spectroscopy (HH and HC COSY, respectively) and by comparison with data taken from published spectra for structurally related cholestane oximes in which the 5,7-oxido bridge is replaced by a 5-hydroxy group, and the C-7 atom being a methylene carbon.[15] In addition, all signals in both the ^{1}H and ^{13}C NMR spectra of **1a** appear very close to those of **1b** except those for C-2, C-3 and C-4, and for the protons attached to these carbons.

The alcohols **2a**/**2b**, **3a**/**3b** and **4a**/**4b** were not sufficiently soluble in chloroform, and a solvent change would have been necessary, leading to additional solvent-induced signal shifts, so we refrained from a detailed analysis of their NMR spectra. Anyway, there

Table 4. ^{1}H NMR (δ-scale) of alcohols **1a**–**4a** in DMSO-d_6

	1a	**2a**[a]	**3a**[a]	**4a**[a]
H-1	1·32/1·73			
H-2	1·16/1·60			
H-3	3·39		3·53	4·10
H-4	1·63/2·02			
H-7	4·67	4·63	4·76	4·57
H-8	1·37			
H-9	1·52			
H-11	1·42			
H-12	1·13/1·95			
H-14	1·35			
H-15	1·02/1·63			
H-16	1·24/1·79			
H-17	1·13			
H-18	0·62	0·62	0·66	0·67
H-19	0·78	0·78	0·91	0·89
H-20	1·32			
H-21	0·87	0·87	0·87	0·87
H-22	0·97/1·29			
H-23	1·09/1·32			
H-24	1·09			
H-25	1·48			
H-26	0·83	0·83	0·83	0·83
H-27	0·83	0·83	0·83	0·83
OH	4·89	4·62	4·84	4·53
N-OH	10·25	10·10	10·34	10·39
$J_{7,8}$ (Hz)	4·8		4·8	5·4

[a] Because of the small amounts of samples available, 2D spectra could not be registered, so other signals could not be identified unequivocally.

Table 5. ^{1}H NMR spectra of **1b-4b**[a]

	1b	**2b**	**3b**	**4b**
H-1	1·56/1·81	1·52/1·81	1·18/1·76	1·22/1·73
H-2	1·31/1·84	1·43/1·85	1·41/1·80	1·40/1·87
H-3	4·77	4·70	4·83	5·46
H-4	1·92/2·32	2·39/2·54	1·73/2·28	1·70/2·35
H-7	5·06	4·72	5·02	4·67
H-8	1·51	1·52	1·27	1·14
H-9	1·66	1·66	2·11	2·12
H-11	1·38	1·43	1·41	1·37
H-12	1·16/2·01	1·16/2·01	1·18/1·99	1·11/1·99
H-14	1·47	1·49	1·23	1·16
H-15	1·16/1·66	1·09/1·61	1·23/·162	1·14/1·57
H-16	1·24/1·84	1·28/1·85	1·30/1·85	1·22/1·79
H-17	1·16	1·19	1·14	1·08
H-18	0·66	0·64	0·69	0·69
H-19	0·89	1·01	1·01	1·01
H-20	1·35	1·39	1·39	1·33
H-21	0·88	0·88	0·87	0·88
H-22	0·98/1·28	0·94/1·33	0·97/1·35	0·97/1·27
H-23	1·10/1·31	1·14/1·33	1·14/1·37	1·08/1·27
H-24	1·10	1·09	1·10	1·10
H-25	1·42	1·49	1·48	1·48
H-26	0·83[b]	0·83[b]	0·83	0·83
H-27	0·84[b]	0·84[b]	0·83	0·83
CH_3CO	1·99	2·00	2·00	2·00
N-OH	8·03	7·42	7·62	7·62

[a] Solvent, $CDCl_3$; chemical shift values in ppm relative to CHC_3 ($\delta = 7.24$).
[b] May be interchanged.

is no reason to assume that the situation is different for these other pairs of oximes.

The stereochemistry of the 5,7-oxido bridge (α in **1b** and **2b**, β in **3b** and **4b**) can be deduced from ^{13}C signals only: the chemical shifts of the proton signals which can be identified easily (H-3, H-4α and H-7) are remarkably invariant on C-5/C-7 configuration inversion. The ^{13}C peak of best diagnostic value is that of C-19. In **1b** and **2b** this chemical shift is 16·4 and 16·8 ppm, respectively, whereas for **3b** and **4b** it is 13·5 and 13·8, respectively. Fortunately, this signal can be differentiated very easily from that of C-18 even without laborious full signal assignments, because its position is not obscured by other peaks in the spectrum, and can readily be identified as a methyl signal in the DEPT experiment. Undoubtedly, the reason for this observed differences of C-19 signal shifts is the different orientation of the oxime group. In the case of the α-oxido configuration (**1b** and **2b**), the oxime double bond is rather close to the 19-methyl group.

The situation is reversed if the stereochemistry of the oxime group (*E* in **1b** and **3b** and *Z* in **2b** and **4b**) is to be determined. Here, the ^{13}C NMR spectra are not very useful. Comparing the data for a given carbon in the pairs **1b/3b** and **2b/4b**, no chemical shift differences larger than 3 ppm can be observed, and in most cases these differences are even less than 2 ppm. Therefore, it would be dangerous to derive the oxime stereochemistry on the basis of such arguments. This finding is surprising since it is expected that the chemical shift difference for carbons adjacent to an oxime function would be at least 6 ppm owing to the presence or absence of a γ-*gauche* effect of the hydroxyl group.[16]

Apparently this rule is not valid to the same extent if the carbons involved are highly substituted and/or members of strained rings. The most diagnostic signal for the determination of the oxime stereochemistry is that of H-7. In the *E* configuration (**1b** and **3b**), this proton resonates at 5 ppm and thereby its signal is well separated from that of H-3. On the other hand, in **2b** and **4b** with *Z* configuration, H-7 has significantly smaller δ values (ca 4·7). It is interesting that in **4b** the H-3 chemical shift is extraordinary high (5·46 ppm), whereas in the other compounds δ values of 4·70–4·83 are observed. The reason is that **4b** is the only diastereomer in which the oxime-OH is very close to the α-positioned H-3, thus exerting a steric compression which generally leads to a paramagnetic ^{1}H signal shift.[17]

CD SPECTRA OF DIASTEREOMERIC OXIMES **1–4**

The CD of both the 5α- and 5β-isomers of 6-hydroxy-

Table 6. ^{13}C NMR (δ-scale) of alcohols **1a**–**3a** in DMSO-d_6[a] and of **1a** in $CDCl_3$[b]

C atom	In DMSO-d_6			**1a** in $CDCl_3$
	1a	**2a**	**3a**	
1	34·0	34·3	(c)	34·1
2	29.9	30.1	29.9	29.7
3	65.2	65.3	66.6	66.7
4	37.4	38.3	32.4	37.2
5	99.2	101.0	97.3	100.2
6	158.3	157.9	157.3	160.5
7	84.2	83.4	85.6	85.5
8	49.9	50.4	50.9	50.1
9	41.2	44.2	44.0	42.7
10	40.2	40.3	40.1	40.3
11	21.5	21.5	21.2	22.0
12	39.6	39.6	38.9	40.0
13	44.0	43.9	43.5	44.5
14	52.4	52.5	53.5	52.6
15	23.1	23.1	23.0	23.5
16	27.8	27.8	27.9	28.2
17	55.4	55.4	55.2	56.0
18	11.8	11.7	11.9	12.0
19	16.2	16.8	13.4	16.5
20	35.1	35.1	35.0	35.7
21	18.5	18.5	18.4	18.6
22	35.6	35.6	35.6	36.1
23	23.3	23.3	23.1	23.9
24	38.9	38.9	37.9	39.4
25	27.4	27.4	27.4	28.0
26	22.4	22.4	22.4	22.5
27	22.7	22.7	22.7	22.8

[a] Not enough material of **4a** was available to measure its ^{13}C NMR spectrum.
[b] Used for the assignment of the signal of its acetate **1b**.
[c] Not detected.

Table 7. ^{13}C NMR spectra if **1b**–**4b**[a]

	1b	**2b**	**3b**	**4b**
C-1	33·6	34·0	32·1	31·7
C-2	26·2	26·5	26·2	25·6
C-3	69·4	69·6	70·3	70·6
C-4	33·3	34·2	33·7	32·6
C-5	99·1	101·0	97·4	100·0
C-6	160·5	159·9	159·1	157·2
C-7	85·4	84·6	87·1	86·2
C-8	50·0	50·5	51·0	50·4
C-9	41·8	44·5	44·5	43·9
C-10	40·4	41·1	40·8	40·8
C-11	21·9	21·8	21·6	21·2
C-12	39·9	39·9	39·8	39·6
C-13	44·5	44·4	44·0	43·8
C-14	52·6	52·7	53·7	52·6
C-15	23·5	23·4	23·3	23·2
C-16	28·1	28·2	28·4	28·2
C-17	56·0	55·9	55·6	55·5
C-18	12·0	12·0	12·1	12·1
C-19	16·4	16·8	13·5	13·8
C-20	35·7	35·6	35·6	35·5
C-21	18·6	18·6	18·6	18·5
C-22	36·1	36·1	36·1	36·0
C-23	23·8	23·8	23·7	23·6
C-24	39·4	39·4	39·5	39·3
C-25	28·0	27·9	28·0	27·9
C-26	22·5	22·5	22·5	22·4
C-27	22·8	22·8	22·8	22·7
Ac	170·3	170·4	170·4	170·6
	21·3	21·3	21·3	21·3

[a] Solvent, $CDCl_3$; chemical shift values in ppm relative to $CDCl_3$ (δ = 77.0).

iminocholestanes show, as do all other oximes of saturated steriod ketones (to be published), two CD bands in the short-wavelength range of opposite signs. The first Cotton effect of the *anti*-oximes appears at 215 nm and is negative; the second is found below 200 nm and has a positive sign, irrespective of the configuration at C-5 (Table 8).

The carbocyclic ring system of **1** and **2** corresponds to that of a usual 6-hydroxyimino-steroid, but formation of the additional oxygen bridge may influence the signs of the Cotton effects, since one p orbital on the oxygen interacts with the π-MO of the oxime moiety, although

Table 8. CD data for the oximes **1a**–**4b** in acetonitrile (a) or hexafluoroacetone solution (b). Values are given as $\Delta\varepsilon_{max}(\lambda[nm])$.

Compound	*E*/*Z*	Cotton effect around 220 nm	Cotton effect around 200 nm	Additional CE
1a(a)	*E*	−11·24 (215)	+8·3 (199)	
(b)		−3·42 (230)	+7·9 (196)	+1·16 (250)
1b(a)	*E*	−10·52 (216)	+5·3 (200)	
2a(a)	*Z*	+4·92 (222)	−14·9 (203)	+10·7 (188)
(b)		+1·09 (234)	−9·1 (208)	
2b(a)	*Z*	+6·94 (223)	−18·9 (202)	+7·7 (188)
3a(a)	*E*	+2·07 (223)	−6·5 (204)	−0·43 (243)
3b(a)	*E*	+2·29 (221)	−6·0 (204)	
4a(a)	*Z*	−7·87 (222)	+3·2 (203)	
4b(a)	*Z*	−7·66 (221)	+4·6 (203)	

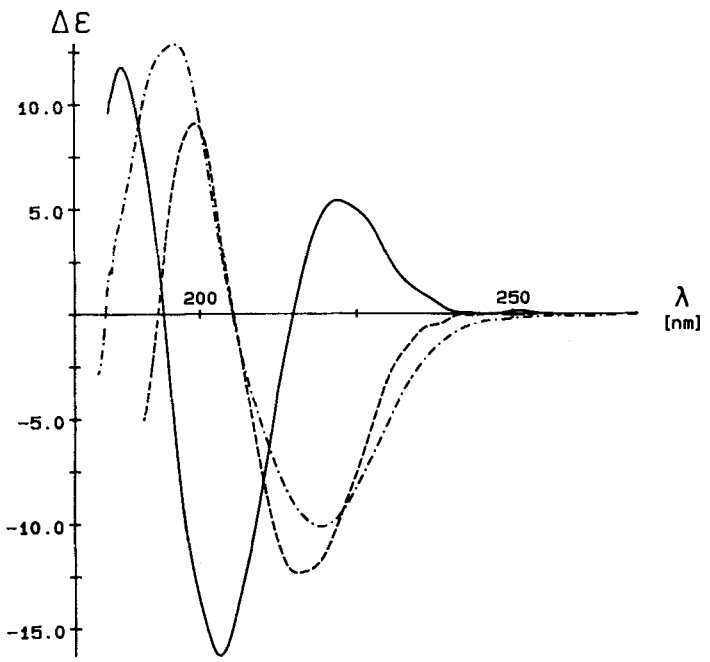


Figure 4. CD spectra of **1a** (– – – – – – –), **2a** (————) and (6*E*)-5α-methoxy-6-hydroxyimino-5α-cholestan-3α-ol (– · – · – · –) in acetonitrile solution

in achiral manner. The carbon skeleton of **3** and **4**, on the other hand, differs appreciably from that of a 5β-cholestane. Since, further, the CD spectra of the mentioned 6-oximes do not depend on the stereochemistry at C-5, for the corresponding pairs **1/3** and **2/4** the CDs are, however, enantiomorphic with each other, and no conclusion about the stereochemistry at C-5 for the 5,7-oxido compounds could be drawn from the chiroptical measurements alone.

This fact was the reason why the x-ray diffraction experiment was done for one of these compounds, and **4b** was chosen because it formed the most suitable crystals. Having thus unequivocally determined the stereochemistry for that compound, a combination of other spectroscopic methods led to the assignment of the correct configurations to all products **1–4**. It now turns out that the CD spectra of **1a/b** show not only the same signs for the two Cotton effects as the model oxime with 5α-configuration, but even the magnitudes of respective Cotton effects are the same, and the ring strain introduced by the oxygen bridge leads to only a very small bathochromic shift of these Cotton effects. We consider this to be a very important result since it indicates that both ring strain and orbital interaction are obviously of minor importance as long as such perturbations are introduced symmetrically to a mirror plane of the ring into which the oxime chromophore is built.

The chiral subunit comprised of the four-membered ring and the oxime grouping of **4** is obtained from that of **1** by mere rotation around the C = N axis by 180°, so one could naively expect that the Cotton effects for both these systems are alike. This is indeed the case, although the magnitudes of the individual Cotton effects differ somewhat. For the remaining two systems **2** and **3** by the same reasoning enantiomorphic CD curves should then appear, and such is also found. We can conclude from these results that the chiral 3-hydroxyiminooxetane unit governs the CD behaviour of these model steriods (3- refers here to the oxetane system, not to the steriod skeleton numbering).

EXPERIMENTAL

Melting points were determined on a Boetius micro-melting point apparatus and are uncorrected. Unless stated otherwise, optical rotations were measured on a Perkin-Elmer 241 polarimeter in chloroform solution; concentrations are given in g per 100 cm^3. IR spectra were recorded on a UR-20 spectrometer in KBr, or on a Pye Unicam SP 1100 spectrometer in chloroform solution. Unless stated otherwise, ^1H NMR and ^{13}C NMR spectra were taken on a Bruker AM-400 spectrometer in $CDCl_3$ under normal conditions. For $^1H-^1H$ and $^1H-^{13}C$ correlated two-dimensional spectra, standard Bruker software and parameter sets were

used.[18] CD spectra were recorded with an ISA–Jobin-Yvon Dichrograph Mark III instrument in acetonitrile. Column chromatography was performed on Kieselgel 60, 70–230 mesh (Merck).

For the usual work-up, the reaction mixture was partitioned between water and diethyl ether or benzene and the organic layer was washed twice with water, dried over anhydrous sodium sulphate and then evaporated under vacuum.

(6E)- and (6Z)-5α, 7α-Oxido-6-hydroxyimino-5α-cholestan-3β-ol. (**1a** and **2a**). A solution of 500 mg of 5α,7α-oxido-3β-hydroxy-5α-cholestan-6-one[5,19] and 500 mg of hydroxylammonium chloride in 10 cm^3 of pyridine was left at room temperature for 2 days. The raw material was chromatographed with benzene–diethyl ether. From the less polar fractions, 52 mg (10%) of **2a** were obtained by crystallization from acetone, m.p. 162–165 °C. $[\alpha]_D^{25} = +36{\cdot}0$ (THF, $c = 0.97$). IR: $\tilde{\nu} = 3630$, 1064, 1007, 903 cm^{-1}. $C_{27}H_{45}NO_3$ (MW431·6): calculated, C 75·13, H 10·51, N 3·24; found, C 75·10, H 10·55, N 3·20%.'

Crystallization of the residue of the more polar fractions from acetone gave 120 mg (23%) of **1a**, m.p. 198–202 °C. $[\alpha]_D^{25} = -84{\cdot}8$ ($c = 1{\cdot}08$). IR: $\tilde{\nu} = 3625$, 1060, 910, 893, 880 cm^{-1}. $C_{27}H_{45}NO_3$ (MW 431·6): calculated, C 75·10, H 10·51, N 3·24. found C 75·17, H 10·60, N 3·30%.

The combined mother liquours of the crystallizations afforded 325 mg (62%) of a mixture of **1a** and **2a**, which was rechromatographed.

(6E)- and (6Z)-5α, 7α-Oxido-6-hydroxyimino-5α-cholestan-3β-ol 3-acetate. (**1b** and **2b**). A 230-mg amount of 3β-acetoxy-5α, 7α-oxido-5α-cholestan-6-one,[5,19] dissolved in 5 cm^3 of pyridine, was treated and worked up as above with 250 mg of hydroxylammonium chloride. Chromatography with methylene chloride (alone and in mixture with diethyl ether) gave first 54 mg (23%) of **2b** as an oil. $[\alpha]_D^{25} = +2{\cdot}1$ ($c = 0.39$). IR: $\tilde{\nu} = 3620$, 1728, 1260, 1048, 915 cm^{-1}. $C_{29}H_{47}NO_4$ (MW 473·7): calculated, C 73·53, H 10·00, N 2·96; found, C 73·49, H 10·09, N 2·88%. This was followed by 160 mg (67%) of **1b**, m.p. 155–158 °C (hexane). $[\alpha]_D^{25} = -88{\cdot}8$ ($c = 1{\cdot}01$). IR: $\tilde{\nu} = 3620$, 1728, 1260, 1048, 912, 882 cm^{-1}. $C_{29}H_{47}NO_4$ (MW 473·7): calculated, C 73·53, H 10·00, N 2·96; found C 73·62, H 9·96, N 3·01%.

(6E)-5β,7β-Oxido-6-hydroxyimino-5β-cholestan-3β-ol. (**3a**). A 760-mg amount of 5β,7β-oxido-3β-hydroxy-5β-cholestan-6-one[4] was treated with 750 mg of hydroxylammonium chloride in 20 cm^3 of pyridine as described above. Chromatography on silica gel with methylene chloride–diethyl ether and diethyl ether gave 716 mg (91%) of crude oxime, which afforded from acetone 505 mg (64%) of **3a**, m.p. 246–255 °C (decomp.). $[\alpha]_D^{25} = +26.9$ (THF, $c = 1{\cdot}005$). IR: $\tilde{\nu} = 3630$, 926, 897, 815 cm^{-1}. $C_{27}H_{45}NO_3$ (MW 431·7): calculated, C 75·13 H10.51, N 3·24; found, C 75·08, H 10·49, N 3·18%.

(6E)- and (6Z)-5β,7β-Oxido-6-hydroxyimino-5β-cholestan-3β-ol 3-acetate. (**3b** and **4b**). A 777-mg amount of 3β-acetoxy-5β,7β-oxido-5β-cholestan-6-one[4] in 15 cm^3 of pyridine was treated with 750 mg of hydroxylammonium chloride as described above and chromatographed with benzene–diethyl ether mixtures. Crystallization of the less polar fractions from methanol gave 337 mg (42%) of **3b**, m.p. 81–84 °C. $[\alpha]_D^{25} = +21.9$ ($c = 1.04$). IR: $\tilde{\nu} = 3400$, 1748, 1248, 1052, 940 cm^{-1}. $C_{29}H_{47}NO_4$ (MW 473·7): calculated, C 73·53, H 10·00, N 2·96; found, C 73·63, H 10·05, N 2·91%.

Crystallization of the more polar eluates from methanol gave 70 mg (9%) of **4b**, m.p. 180–183 °C. $[\alpha]_D^{25} = -62.9$ ($c = 1{\cdot}04$). IR: $\tilde{\nu} = 3516$, 1750, 1232, 1040, 910 cm^{-1}. $C_{29}H_{47}NO_4$ (MW 473·7): calculated, C 73·53, H 10·00, N 2·96; found, C 73·48, H 10·08, N 3·00%.

The combined mother liquours afforded 363 mg (45%) of a mixture of **3b** and **4b**.

(6Z)-5β,7β-Oxido-6-hydroxyimino-5β-cholestan-3β-ol. (**4a**). A solution of 16 mg of **4b** in 16 cm^3 of methanol–diethyl ether (3:1) was treated at room temperature with an excess of 5% aqueous NaOH for 30 min. Usual work-up and filtration through a short silica gel column gave 13 mg (89%) of **4a**, m.p. 231–235 °C (decomp., from methanol). $[\alpha]_D^{25} = -52{\cdot}7$ ($c = 1.01$). IR: $\tilde{\nu} = 3620$, 890, 840 cm^{-1}. $C_{27}H_{45}NO_3$ (MW 431·7): calculated C 75·13, H 10·51, N 3·24; found, C 75·17, H 10·46, N 3·16%.

ACKNOWLEDGEMENTS

G. S. thanks the Deutsche Forschungsgemeinschaft, Fonds der Chemischen Industrie, and Hoechst AG for valuable financial help, and J. F. and W. J. S. the Deutsche Forschungsgemeinschaft and Polska Akademia Nauk for grants. D. H. and B. K. -P. thank Prof. L. Golić (University of Ljubljana) for data collection, and Ph. B. Strong (Medical Foundation of Buffalo, Buffalo, USA) for stereo drawings.

REFERENCES

1. *c.f* D. N. Kirk, *Tetrahedron* **42**, 777 (1986).
2. *c.f* M. Legrand and M. J. Rougier, in *Stereochemistry, Fundamentals and Methods*, edited by H. B. Kagan, Vol 2, p. 33. Thieme, Stuttgart (1977).
3. A. Bodor, J. Breazu, J. Miklós, B. Demian and F. Kerek, *Tetrahedron* **36**, 1785 (1980).
4. A. T. Rowland, P. J. Bennett and T. S. Shoupe, *J. Org. Chem.* **33**, 2426 (1968).

5. A. T. Rowland, R. S. Drawbaugh and J. R. Dalton, *J. Org. Chem.* **42**, 487 (1977).
6. G. M. Sheldrick, in *Crystallographic Computing 3*, edited by G. M. Sheldrick, C. Krüger and R. Goddard, p. 175. Oxford University Press, Oxford (1985).
7. G. M. Sheldrick, *SHELX76, Program for Crystal Structure Determination*, University of Cambridge, Cambridge (1983).
8. M. Nardelli, *Comput. Chem.* **7**, 95 (1983).
9. W. L. Duax and D. A. Norton (Eds), *Atlas of Steroid Structure*, Vol. 1, p. 7. Plenum, New York (1975).
10. J. F. Griffin, W. L. Duax and C. M. Weeks (Eds), *Atlas of Steroid Structure*, Vol. 2. Plenum, New York (1984).
11. C. K. Johnson, *ORTEP*, Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, TN (1965).
12. W. L. Duax, C. M. Weeks and D. C. Rohrer, *Top. Stereochem.* **9**, 271 (1976).
13. R. Bucourt, *Top. Stereochem.* **8**, 159 (1974).
14. W. L. Duax, J. F. Griffin, D. C. Rohrer and C. M. Weeks, *Lipids* **15**, 783 (1980).
15. H. Duddeck, J. Frelek, W. J. Szczepek and W. J. Rodewald, *Bull. Chem. Soc. Ethiop.* **1**, 18 (1987).
16. G. E. Hawkes, K. Herwig and J. D. Roberts, *J. Org. Chem.* **39**, 1017 (1974).
17. H. Duddeck and M. Kaiser, unpublished results.
18. H. Duddeck, M. Kaiser and D. Brosch, *Magn. Reson. Chem.* **23**, 548 (1985).
19. R. Hanna, G. Maalouf and B. Muckensturm, *Tetrahedron* **29**, 2297 (1073).