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^{1}H and ^{13}C NMR study of a series of C-9-substituted 19-norsteroids

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epoc ABSTRACT: The ^{1}H and ^{13}C NMR spectra of a series of 9-substituted 19-norsteroids were completely assigned using a series of 2D NMR experiments, which included ^{1}H–^{1}H COSY, NOESY and ^{1}H–^{13}C heteronuclear HETCOR and HMQC. For second-order spin systems, chemical shifts and coupling constants were obtained by simulation of the experimental spectrum. Criteria were deduced to characterize the stereochemistry of these different compounds (multiplet pattern of H-8β and variation of chemical shifts). The results allow the easy determination of the configuration at C-9. Conformational changes resulting from the substitution were studied by NMR and molecular modeling calculations (AM1). Copyright © 2001 John Wiley & Sons, Ltd.
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KEYWORDS: steroids; C-9 substitution; configuration; conformation; ^{1}H NMR; ^{13}C NMR; AM1 calculation

INTRODUCTION

The role of the conformation in structure–activity relationship of steroid hormones has attracted attention for a long time and high-field NMR spectroscopy is increasingly being used to complement x-ray crystallographic methods and to probe the sometimes subtle differences which may occur between solid-state and solution conformations. Amino steroids have been studied as potent inhibitors and probes of the active site of cytochrome P-450_{SCC} by binding at the heme iron, e.g. in the biosynthesis of pregnenolone from 22-aminocholesterol.[1–3]

Considering the large range of potential biological activities, the regio- and stereoselective functionalization of 3-oxygenated estra-1,3,5(10)-trienes is an area of considerable importance in steroid chemistry.

A series of 10 C-9-monosubstituted steroids, in which the proton at C-9 of 3-methoxy-(or 3-hydroxy)-estra-1,3,5(10)-trienes was regio- and stereospecifically replaced by an azido, a cyano, an acetamido, a methylammonium or a methylacetamido group, were synthesized (Scheme 1).[4,5] ^{1}H and ^{13}C NMR spectroscopy were used to characterize the stereochemistry at C-9 and to study the conformational changes produced by 9α or 9β substitution.

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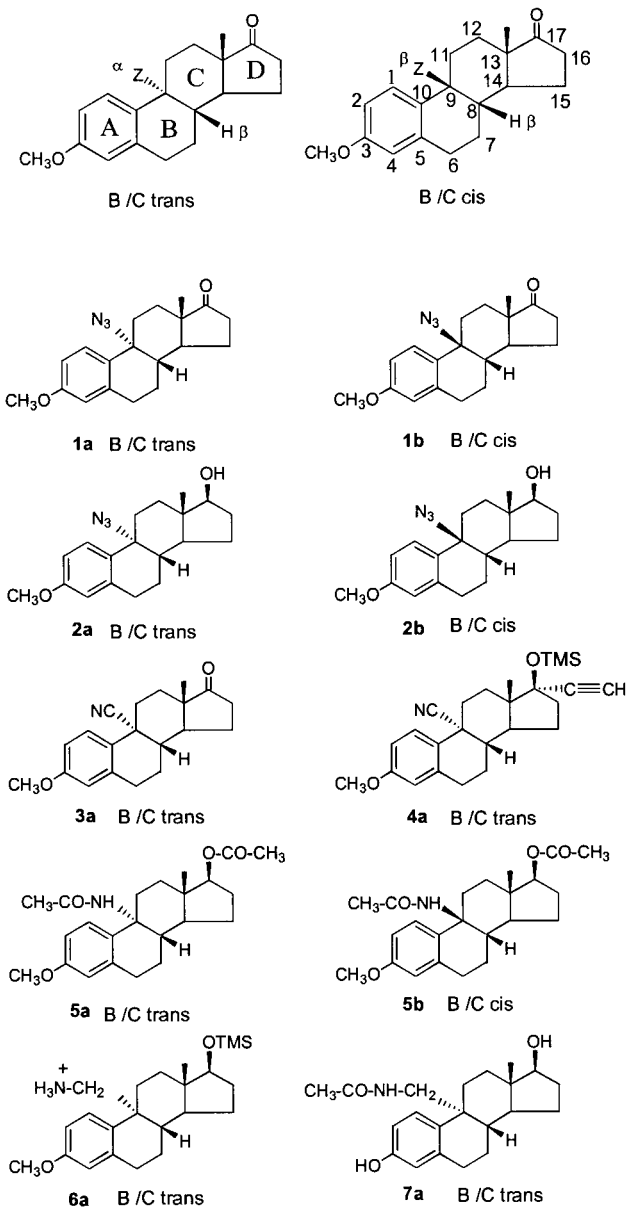
RESULTS AND DISCUSSION

^{1}H spectral assignments were obtained for the 10 compounds from 1D spectra and 2D COSY 45 spectroscopy. Difference NOE experiments involving saturation of the 18β-Me group were used to discriminate the protons situated on the β-face from those on the α-face. The chemical shifts are given in Table 1. The values of the $^{n}J_{(H,H)}$ coupling constants were measured on the ^{1}H 1D spectra and 2D *J*-resolved spectra for the first-order spin systems. In the case of second-order spin systems, the $^{n}J_{(H,H)}$ values were calculated by the usual interactive procedure using the Bruker program PANIC.

The ^{13}C spectra were assigned by use of 2D ^{1}H–^{13}C heteronuclear HETCOR[6] and HMQC experiments.[7] The chemical shifts are given in Table 2.

Determination of the configuration at C-9

The $^{3}J_{(H-H)}$ coupling constants of H-8β are characteristic of the stereochemistry of steroids having natural 9α or



Scheme 1

unnatural 9β configuration and lead to typical multiplet patterns whenever the resonance is non-overlapped. Values are given in Table 3 for 3-methoxy-estra-1,3,5(10)-trien-17-one, (in satisfactory accordance with published data)[8] and for compounds **1a** and **1b**.

A more general way to determine the configuration might be deduced from the variation of chemical shifts observed upon substitution at C-9. The sites of interest are in rings B and C. The effect is evaluated by comparison of each compound with the unsubstituted molecule or at least with a model with the same partial skeleton. In the case of **4a**, which bears a 17α C≡CH group, the comparison must be done with 17α-ethynyl-3-methoxy-1,3,5(10)-estratrien-17β-ol.

In ^{1}H NMR, the effects on protons three bonds away from C-9, mainly due to anisotropy, are expected to depend on the nature of the substituent. The results are given in Table 4. It is well known that a cyano group deshields a proton situated above the triple bond.[9] This deshielding is observed for H-7α, H-12α and H-14α in **3a** and **4a**. The effect of the azido group appears very similar to that of the cyano group despite the fact that for this substituent the C—N bond only is parallel to the axial C—H bonds of interest. H-7α, H-12α and H-14α are deshielded in the 9α-substituted compounds and H-7β in the 9β-substituted compounds.

When an NH—CO—CH_3 group is introduced, the effects on protons three bonds away from C-9 are reduced or even hardly observable, e.g. for H-7α. For this substituent the orientation of the C=O bond is determinant, as shown by the strong deshielding observed for H-11α (1.73 ppm) and even H-1 (0.91 ppm) in **5a** and for H-11β (1.75 ppm) and H-8β (1.67 ppm) in **5b**.

The results are less reliable when one methylene separates the functional group from C-9, as in the case of $CH_2NH_3^+$ and $CH_2NHCOCH_3$.

In ^{13}C NMR, whenever the introduction of a substituent suppresses a 1,3-diaxial interaction between two C—H bonds, shielding is expected for the carbon which bears the remaining proton.[10,11] The results are given in Table 5. As regards C-7, the 9α and 9β substitutions suppress a 1,3-diaxial interaction with H-7α and H-7β, respectively. Thus the shielding observed at C-7 cannot be related to the position of the substituent. Fortunately, the 9α substitution also suppresses 1,3-diaxial interaction at C-12 and C-14 whereas the 9β substitution does not. As expected, C-12 and to a greater extent C-14 are shielded in all the 9α derivatives and slightly deshielded in the 9β derivatives. In this case the nature of the substituent is not an important parameter and thus observation of the signals of C-12 and C-14 provides a more general way to determine the configuration at C-9.

Conformational study

In the solid state, several different forms have been detected for estra-1,3,5(10)-trien-17-one[12] and 3-methoxyestra-1,3,5(10)-trien-17β-ol (forms I, II and III),[13] whereas a single form was observed for 3-methoxyestra-1,3,5(10)-trien-17-one[14] and 9βH-estra-1,3,5(10)-trien-17-one.[15] Great flexibility is therefore expected for estrogens and their derivatives. Molecular mechanics calculations carried out using SYBYL software[16] with the semi-empirical molecular orbital method AM1 give information on the isolated molecules. Calculations were performed on the 9α- and 9β-azido derivatives and on the model compounds. The H—C—C—H dihedral angles might be related through Karplus-type relations to the $^3J_{(H,H)}$ scalar coupling constant. The reason for the choice of this NMR parameter in the present study was to

Table 1. ^{1}H chemical shifts (δ, ppm) for compounds **1a** and **b, 2a** and **b, 3a, 4a, 5a** and **b** and **6a** in C_6D_6 and **7a** in C_6D_6–CD_3OD

Atom	**1a**	**1b**	**2a**[a]	**2b**	**3a**	**4a**[b]	**5a**	**5b**	**6a**[c]	**7a**
H-1	7.16	7.15	7.25	7.25	7.00	7.10	8.10	7.24	7.73	6.98
H-2	6.69	6.65	6.69	6.70	6.66	6.67	6.75	6.74	7.06	6.77
H-4	6.63	6.62	6.62	6.61	6.54	6.53	6.70	6.66	6.65	6.73
H-6α	2.65	2.43	2.66	2.53	2.61	2.58	2.71	2.62	2.73	2.79
H-6β	2.54	2.44	2.59	2.45	2.47	2.50	2.63	2.47	2.62	2.73
H-7α	1.67	1.37	1.71	1.41	1.75	1.78	1.13	1.46	1.16	1.43
H-7β	1.35	2.18	1.46	2.22	1.44	1.46	1.36	2.00	1.40	1.49
H-8β	1.47	1.79	1.57	1.88	1.31	1.38	1.51	3.50	1.59	1.63
H-11α	2.28	2.41	2.41	2.47	2.22	2.39	3.90	2.17	2.72	2.09
H-11β	1.39	1.77	1.61	1.97	1.28	1.48	1.58	3.48	1.71	1.47
H-12α	1.75	1.09	1.55	0.82	1.95	2.54	1.54	1.11	1.57	1.61
H-12β	1.71	1.59	1.75	1.59	1.80	1.65	1.73	1.73	1.78	1.77
H-14α	1.79	1.27	1.63	1.12	1.81	2.38	1.19	1.25	0.90	1.31
H-15α	1.39	1.29	1.41	1.29	1.33	1.50	1.28	1.35	1.25	1.40
H-15β	0.98	1.00	1.11	1.10	0.90	1.06	1.04	1.26	1.01	1.11
H-16α	1.80	1.49	1.97	1.77	1.67	2.32	2.21	2.02	1.84	1.97
H-16β	2.09	1.97	1.46	1.37	2.01	1.88	1.48	1.51	1.50	1.49
H-17α	–	–	3.63	3.13	–	–	4.79	4.53	3.63	3.71
CH_3-18β	0.49	0.62	0.70	0.81	0.39	0.69	0.68	1.30	0.71	0.72
OCH_3	3.34	3.33	3.35	3.31	3.34	3.34	3.36	3.40	3.50	–
$OSi(CH_3)_3$	–	–	–	–	–	0.32	–	–	0.23	–
CH_2N	–	–	–	–	–	–	–	–	3.30	3.75
									2.86	2.92
CH_3CONH	–	–	–	–	–	–	1.50	1.34	–	1.69
CH_3COO	–	–	–	–	–	–	1.72	1.65	–	–
CH_3CONH	–	–	–	–	–	–	4.84	4.73	–	–

[a] δ OH = 2.08 ppm.
[b] δ C≡CH = 2.29 ppm.
[c] δ NH_3^+ = 8.52 ppm.

Table 2. ^{13}C chemical shifts (δ, ppm) for compounds **1a** and **b, 2a** and **b, 3a, 4a, 5a** and **b** and **6a** in C_6D_6 and **7a** in C_6D_6–CD_3OD

Atom	**1a**	**1b**	**2a**	**2b**	**3a**	**4a**	**5a**	**5b**	**6a**	**7a**
C-1	127.1	128.0	127.1	128.0	127.6	127.7	130.4	128.3	128.8	127.5
C-2	112.3	112.9	112.4	113.0	113.4	113.4	111.4	113.8	112.9	113.2
C-3	160.3	160.2	160.2	160.0	160.2	160.1	159.6	159.9	159.6	156.5
C-4	115.5	115.9	115.5	115.7	115.2	115.2	114.8	115.3	116.0	116.8
C-5	138.8	139.4	139.1	139.8	138.2	138.4	136.9	140.1	138.4	138.5
C-6	29.7	25.6	29.9	26.0	29.3	29.6	28.9	26.1	27.9	28.2
C-7	21.3	20.3	22.1	21.0	23.5	24.3	21.0	20.7	21.4	21.6
C-8	41.8	40.3	42.3	40.8	41.1	42.3	42.3	34.3	41.2	41.1
C-9	66.5	67.1	66.8	67.3	43.9	43.9	56.5	59.7	44.4	44.3
C-10	129.8	125.8	130.4	126.6	129.0	129.6	134.5	130.9	134.1	135.6
C-11	30.3	31.2	30.8	31.7	31.7	32.5	28.9	28.2	29.2	29.2
C-12	28.9	29.5	33.8	34.4	30.1	31.2	34.1	35.1	33.9	33.8
C-13	47.8	47.7	43.8	43.7	47.8	48.8	43.5	43.9	40.2	41.4
C-14	44.1	43.7	44.0	43.6	46.8	45.1	44.4	43.9	44.3	44.9
C-15	21.7	22.2	23.6	23.9	21.7	23.3	23.8	24.5	24.1	24.1
C-16	36.0	35.8	31.3	31.3	35.7	41.1	28.4	28.5	31.7	30.5
C-17	217.4	216.8	81.7	81.2	216.6	81.2	82.8	82.7	82.0	81.9
C-18	13.5	13.8	11.3	11.5	13.6	13.5	12.4	13.1	11.9	11.5
OCH_3	55.2	55.2	55.2	55.1	55.3	55.3	55.2	55.3	55.4	–
C≡N	–	–	–	–	122.0	122.3	–	–	–	–
C≡CH	–	–	–	–	–	87.3	–	–	–	–
C≡*C*H	–	–	–	–	–	76.9	–	–	–	–
$OSi(CH_3)_3$	–	–	–	–	–	2.5	–	–	1.04	–
CH_2N	–	–	–	–	–	–	–	–	41.9	40.8
CH_3CONH	–	–	–	–	–	–	24.8	24.6	–	22.7
CH_3COO	–	–	–	–	–	–	21.1	21.1	–	–
CH_3*C*ONH	–	–	–	–	–	–	168.4	167.9	–	172.4
CH_3*C*OO	–	–	–	–	–	–	170.7	170.5	–	–

Table 3. $^3J_{(H,H)}$ coupling constants (Hz) of H-8β in 3-methoxyestra-1,3,5(10)-trien-17-one and compounds **1a** and **b**

$^3J_{(H,H)}$	3-Methoxyestra-1,3,5(10)-trien-17-one	9α group (**1a**)	9β group (**1b**)
$^3J_{(H\text{-}8\beta,H\text{-}9\alpha)}$	11.8	–	–
$^3J_{(H\text{-}8\beta,H\text{-}7\alpha)}$	11.9	12.2	3.3
$^3J_{(H\text{-}8\beta,H\text{-}7\beta)}$	2.6	3.0	3.3
$^3J_{(H\text{-}8\beta,H\text{-}14\alpha)}$	10.6	11.5	12.7

Ring B. In the 9α series, the AM1 calculations suggest for the azido compounds **1a** and **2a** a sofa-type conformation, differing from the 7α/8β half-chair obtained for the model compounds 3-methoxyestra-1,3,5(10)-trien-17-one and 3-methoxyestra-1,3,5(10)-trien-17β-ol. Nevertheless, the experimental values are in best agreement with the 7α/8β half-chair-type conformation for **1a** and **2a** and also for the respective models. The form of **1a** in solution differs slightly from that of 3-methoxyestra-1,3,5(10)-trien-17-one in the solid state.[14] The form of **2a** in solution appears to be very close to the solid-state structure I of 3-methoxyestra-1,3,5(10)-trien-17β-ol.[13] An equilibrium involving structure I and contributions of structure II (more proximate from the chair type) and III (more proximate from the sofa type) cannot be excluded. For **5a**, **6a** and **7a**, which bear a more bulky substituent, the experimental values indicate significant evolution towards the sofa-type conformation.

Table 4. Chemical shift differences $\Delta\delta$ (^{1}H) for protons 7α, 12α, 14α and 7β upon substitution at C_9 ($\Delta\delta = \delta$ in substituted compound $-\delta$ in model compound)

Atom	**1a**[a]	**1b**[b]	**2a**[c]	**2b**[d]	**3a**[a]	**4a**[e]	**5a**[c]	**5b**[d]	**6a**[c]	**7a**[f]
H-7α	+0.56	−0.12	+0.54	−0.21	+0.64	+0.61	−0.04	−0.06	−0.01	+0.32
H-12α	+0.39	−0.23	+0.47	−0.18	+0.59	+0.56	+0.46	+0.22	+0.49	+0.51
H-14α	+0.81	−0.06	+0.77	+0.07	+0.83	+0.66	+0.33	+0.20	+0.04	+0.41
H-7β	−0.29	+0.65	−0.23	+0.70	−0.20	−0.19	−0.33	+0.48	−0.29	−0.16

Model compounds:
[a] 3-methoxyestra-1,3,5(10)-trien-17-one;
[b] 9βH-estra-1,3,5(10)-trien-17-one;
[c] 3-methoxyestra-1,3,5(10)-trien-17β-ol;
[d] 3-acetoxy-9βH-estra-1,3,5(10)-trien-17β-ol;
[e] 17α-ethynyl-3-methoxy-1,3,5(10)-estratrien-17β-ol;
[f] estra-1,3,5(10)-trien-3,17β-diol.

Table 5. Chemical shift differences ($\Delta\delta$ ^{13}C) for carbons C-7 C-12 and C-14 upon substitution at C_9 ($\Delta\delta = \delta$ in substituted compound $-\delta$ in model compound)

Atom	**1a**[a]	**1b**[b]	**2a**[c]	**2b**[d]	**3a**[a]	**4a**[e]	**5a**[c]	**5b**[d]	**6a**[c]	**7a**[f]
C-7	−6.0	−5.2	−6.0	−5.0	−3.8	−3.8	−7.1	−5.3	−6.7	−6.6
C-12	−3.8	+1.0	−3.9	+1.2	−2.6	−2.5	−3.6	+1.9	−3.8	−3.9
C-14	−6.6	+0.9	−6.7	+1.2	−3.9	−5.2	−6.3	+1.5	−6.4	−5.9

Model compounds: see footnote to Table 4.

explore the conformational changes induced by substitution at C-9 in isolated molecules and in solution and to compare the results with the known solid-state structures and to the limit conformation of rings B, C and D.[17] The ^3J values were calculated from the H—C—C—H dihedral angles (θ) by the use of Eqn. (1), which seems particularly well adapted in the case of the steroids:[18]

$$^3J_{(H,H)} = A - B\cos\theta + C\cos 2\theta \qquad (1)$$

with $A = 7$, $B = 1$ and $C = 5$. Relevant data for $^3J_{(H,H)}$ are collected in Table 6 for the 9α compounds and in Table 7 for the 9β compounds.

NOE experiments give information which can be used to eliminate the boat conformation of the six-membered rings but do not allow one to distinguish half-chair- and sofa-type conformations. The results are in agreement with analysis of the J values.

In the 9β series, the AM1 calculations suggest a 7β/8α half-chair-type conformation for the model molecules and a significant evolution towards the sofa-type conformation upon introduction of the azido group. The experimental J values remain in agreement with the 7β/8α half-chair for the model compounds and indicate for **1b** an evolution towards the 8α sofa-type conformation whereas **2b** remains close to the 7β/8α half-chair. The effect of the CH_3CONH group in **5b** is almost identical with that of N_3 in **2b**. Owing to the greater flexibility of compounds with the 9β configuration, the substitution at

Table 6. $^{3}J_{(H,H)}$ coupling constants (Hz) for 3-methoxyestra-1,3,5(10)-trien-17-one, 3-methoxyestra-1,3,5(10)-trien-17β-ol and their 9α derivatives: experimental values, J_E, values calculated for isolated structures (AM1 calculation) J_A or for solid-state structures (x-ray analysis) J_S

	Limit conformation			3-Methoxyestra-1,3,5(10)-trien-17-one			**1a**		3-Methoxyestra-1,3,5(10)-trien-17β-ol					**2a**		**5a**	**6a**	**7a**
	J	*J*		J_E	J_A	J_S[14]	J_E	J_A	J_E	J_A	J_S I[13]	J_S II[13]	J_S III[13]	J_E	J_A	J_E	J_E	J_E
Ring B	Half-chair 7α/8β	Sofa																
H-6α/H-7α	6.4	8.5		6.2	6.6	6.1	6.8	8.3	6.2	6.6	6.3	5.0	7.9	6.2	8.3	7.8	9.0	8.8
H-6α/H-7β	2.4	2.0		2.2	2.4	2.5	1.5	2.0	2.1	2.5	2.4	3.1	2.0	2.0	2.0	2.8	2.2	2.8
H-6β/H-7α	12.0	10.4		11.9	11.7	12.1	11.8	10.2	11.8	11.6	12.0	12.7	10.7	11.8	10.0	9.5	9.0	9.0
H-6β/H-7β	6.4	8.5		6.9	6.9	6.6	7.1	8.3	6.5	6.9	6.8	5.3	8.3	6.9	8.5	7.7	9.0	9.0
Ring C	Chair																	
H-11α/H-12α	4,6			3.8	5.5	4.7	3.7	5.5	4.2	5.3	4.7	5.0	4.7	3.5	5.3	3.0	3.2	3.4
H-11α/H-12β	3,5			3.2	3.1	3.4	2.9	3.2	2.8	3.2	3.4	3.1	3.4	2.3	3.4	3.4	3.2	3.1
H-11β/H-12α	12,9			12.8	12.4	12.8	12.8	12.4	13.3	12.5	12.8	12.8	12.9	13.4	12.5	13.0	13.0	13.0
H-11β/H-12β	4,6			3.7	5.6	5.0	3.7	5.6	3.8	5.5	5.0	5.0	4.9	3.5	5.5	3.0	4.0	3.6
Ring D	Half-chair 13β/14α	Envelope 14α	Envelope 13β															
H-15α/H-16α	10.6	9.2	11.0	9.0	10.2	9.9	9.1	10.1	9.5	10.6	11.0	10.9	10.9	9.3	10.6	9.5	9.2	9.6
H-15α/H-16β	3.3	2.1	5.0	1.3	2.7	2.5	1.1	2.6	3.4	3.3	4.7	4.2	4.4	3.4	3.3	3.0	3.0	3.3
H-15β/H-16α	7.7	10.0	5.2	8.9	8.3	9.5	9.0	8.3	5.9	7.0	6.0	6.6	6.4	6.0	7.1	6.4	6.0	6.0
H-15β/H-16β	10.4	8.9	11.0	8.9	10.2	9.3	8.8	10.1	12.2	10.6	10.9	10.7	10.8	12.0	10.6	12.0	12.0	12.0

Table 7. $^{3}J_{(H,H)}$ coupling constants (Hz) for 9βH-estra-1,3,5(10)-trien-17-one, 3-acetoxy-9βH-estra-1,3,5(10)-trien-17β-ol and their 9β derivatives: experimental values, J_E, values calculated for isolated structures (AM1 calculation) J_A or for solid-state structures (x-ray analysis) J_S

	Limit conformation		9βH-Estra-1,3,5(10)-trien-17-one			**1b**		3-Acetoxy-9βH-estra-1,3,5(10)-trien-17β-ol		**2b**		**5b**
	J	J	J_E	J_A[a]	J_S[15]	J_E	J_A	J_E	J_A	J_E	J_A	J_E
Ring B	Half-chair 7β/8α	Sofa 8α										
H-6α/H-7α	6.4	8.5	6.9	6.9	6.3	7.6	7.9	6.8	6.9	6.3	7.3	6.3
H-6α/H-7β	12.0	10.4	11.6	11.7	12.3	13.5	10.7	11.6	11.6	13.4	11.3	13.0
H-6β/H-7α	2.4	2.0	3.2	2.4	2.6	1.0	2.1	3.0	2.4	1.4	2.3	1.5
H-6β/H-7β	6.4	8.5	5.8	6.8	5.8	7.0	7.7	5.4	6.8	6.5	7.3	6.4
Ring C	Chair											
H-11α/H-12α	4,6		3.1	4.4	4.7	3.3	4.1	3.6	4.4	3.5	4.3	3.4
H-11α/H-12β	3,5		3.1	4.0	3.4	3.4	4.3	2.8	4.0	3.6	4.1	3.2
H-11β/H-12α	12,9		13.8	12.8	12.8	14.2	12.9	13.9	12.8	14.2	12.8	14.3
H-11β/H-12β	4,6		—	4.9	5.2	3.7	4.6	2.9	4.9	3.8	4.9	3.9
Ring D	Half-chair 13β/14α	Envelope 13β										
H-15α/H-16α	10.6	11.0	8.9	10.1	9.8	8.8	10.1	9.0	10.6	9.3	10.7	9.4
H-15α/H-16β	3.3	5.0	1.1	2.6	2.4	1.2	2.6	3.3	3.3	3.5	3.4	3.6
H-15β/H-16α	7.7	5.2	9.1	8.5	9.5	9.1	8.3	5.6	7.0	6.0	7.0	6.3
H-15β/H-16β	10.4	11.0	9.0	10.1	9.3	9.2	10.2	12.0	10.6	12.2	10.7	12.0

[a] 3-Methoxy-9βH-estra-1,3,5(10)-trien-17-one.

C-9 induces noticeable distortions in solution. The difference between **1b** in solution and 9βH-estra-1,3,5(10)-trien-17-one in the solid state[15] is significant. For **2b** and **5b** the dihedral angles are close to 180° for H-6α—C-6—C-7—H-7β and to 90° for H-6β—C-6—C-7—H-7α.

Ring C. The conformation of this ring is always of the chair type. AM1 calculations predict insignificant effects in the α series and moderate effects in the β series upon substitution at C-9. In the solid state, the conformation of this ring remains similar for the 9αH and 9βH models. Distortions are more important in solution, especially for the 3-methoxyestra-1,3,5(10)-trien-17β-ol derivatives.

Ring D. Negligible conformational changes are expected upon substitution at C-9 which is remote from ring D. The main conformational differences originate from the sp^2 or sp^3 hybridization state of C-17. In the first case, **1a, 1b** and their model compounds (17-one), the AM1 calculations suggest an equilibrium between envelope 14α and half-chair 13β/14α while the experimental values are in best agreement with the envelope 14α. In the second case, **2a**, **2b** and their model compounds (17β-ol), the ring is doubtless less rigid and the AM1 calculations suggest a 13β/14α half-chair. The experimental values do not show evolution towards an envelope form but there are significant distortions with respect to the 13β/14α half-chair. It is worth noting that the conformation of **2a** in solution diverges significantly from those of the various solid-state structures of 3-methoxyestra-1,3,5(10)-trien-17β-ol which are similar to an envelope 13β. The preceding results are not modified upon introduction of more bulky substituents, **5a**, **6a**, **7a** and **5b**, whatever the configuration at C-9 is.

CONCLUSION

Chemical shifts changes may be used to assign safely the configuration at C-9 in particular in ^{1}H NMR those due to the anisotropy effect of N_3 or CN and in ^{13}C NMR those due to steric effects of all substituents.

Upon substitution at C-9, the major conformational changes are observed for ring B, which is the more flexible. In the case of a 9α configuration, the bulk of the substituent plays an important role, the removal of steric effects being obtained through evolution from a half-chair towards a sofa-type conformation. This conformation minimizes steric interactions of substituent with H-7α. In the case of a 9β configuration, the effects of the bulk of the substituent are less important. Ring C always holds a chair-type conformation with more significant distortions in the case of 17β-ol derivatives. The substitution has only minor effects on the conformation of ring D remote from C-9.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 500 spectrometer. Data were obtained from solution in benzene-d_6 unless stated otherwise. The ^{1}H δ values in ppm are referenced to internal TMS and the ^{13}C δ values

in ppm to the solvent peak at 128.15 ppm. For second-order systems the $^3J_{(H,H)}$ coupling constants were obtained from simulated spectra using the Bruker program PANIC (Parameter Adjustment in NMR by Iteration Calibration).

Molecular modeling was performed by the use of the MOPAC AM1 program[19] (QCPE program No. 455), included in the SYBYL software. Geometries were fully optimized with the best convergence criterion.

Supplementary material

Dihedral angles θ between HC bonds (AM1 molecular modeling) and $^3J_{(H,H)}$ coupling constants for model molecules (Table 8) and 9-N_3 derivatives (Table 9) are available at the epoc website at http://www.wiley.com/epoc.

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