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CONFORMATIONAL DEFORMATION OF RING C IN 14β-ESTRA-1,3,5(10),15-TETRAEN-17-ONES[1]

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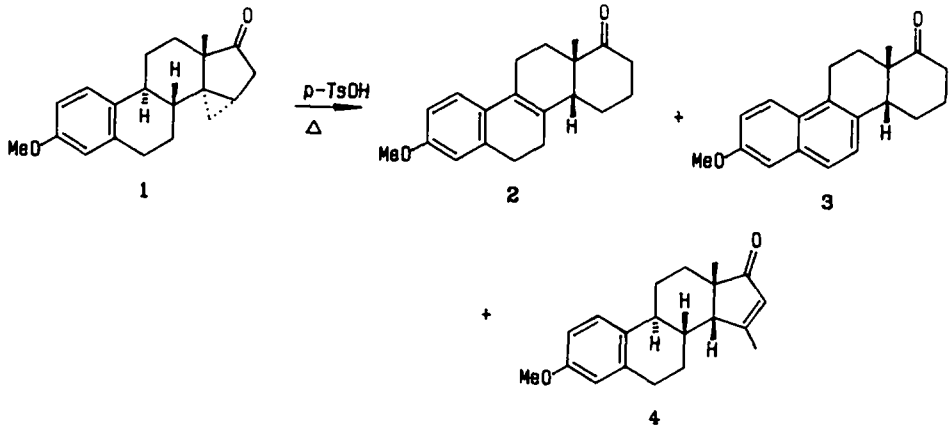
Abstract: High-field n.m.r. analysis of four 3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-ones provides evidence for conformational deformation of ring C to a twist-boat form in solution. These observations are supported by molecular mechanics (MM2) calculations, which predict that the ring C chair and ring C twist-boat conformers have similar steric energies, slightly favouring the latter. An *X*-ray crystal structure determination on 3-methoxy-14-methyl-14β-estra-1,3,5(10),15-tetraen-17-one revealed that ring C does indeed adopt a twist-boat conformation in the solid state.

As part of an ongoing investigation into new synthetic routes to 14-substituted 19-norsteroids,[2] we recently examined the potential of base- and acid-mediated rearrangements of 14,15-methylene 17-ketones for generating products or intermediates which could be used for such purposes.

An exploratory study revealed that, whereas 3-methoxy-14,15α-methylene-estra-1,3,5(10)-trien-17-one (1)[3] was inert to a variety of strong bases, it readily underwent rearrangement in the presence of toluene-*p*-sulphonic acid in refluxing xylene, to give a complex mixture of products. Limited success attended our efforts to purify and characterise all the components, but a major product (40%) was identified as 3-methoxy-15-methyl-14β-estra-1,3,5(10),15-tetraen-17-one (4), accompanied by lesser amounts (*ca* 18%) of an impure product, tentatively identified as 3-methoxy-17a-homo-14β-estra-1,3,5(10),8-tetraen-17a-one (2) contaminated with the inseparable pentaene (3).



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Although our further interest in the synthetic utility of acid-mediated rearrangements of (1) terminated with this finding, the products were characterised as fully as their purity allowed. The 15-methyl compound (4) failed to crystallise, but a 500 MHz n.m.r. spectrum verified the homogeneity of chromatographed material. Furthermore, certain signals provided diagnostic evidence for the assigned structure, in particular, the distinctive coupling between 8β-H and 14β-H (J 5.1 Hz) which, together with an n.O.e enhancement of the 14β-H signal by irradiation of that of 13β-CH_3, verified the assignment of 14β-configuration. Rearrangements of this nature are unexceptional and are supported by analogy.[3,4] The favourable dispersion of the 500 MHz proton n.m.r. spectrum of compound (4) encouraged us to carry out a comprehensive assignment of signals, as part of a programme to map chemical shift and coupling patterns associated with changes in configuration and substitution at C(14).[2,5,6] The results of this analysis (Table 1) revealed that the trends for ring A and ring B proton signals corresponded with expectations based upon our work,[2,5,6] and that of other groups which have studied estrone-based systems.[7-9] However, the signals of protons attached to C(9) - C(12) of compound (4) were markedly different, and suggested that ring C adopts a conformation other than the normally-favoured chair in this case.

In an attempt to identify the structural features responsible for this atypical behaviour, other ring A aromatic steroids were examined, and it was found that the compounds (5) - (7)[2,10,11] also displayed abnormal ring C interproton couplings, similar to those of compound (4) (Table 1). The common structural features are 14β-configuration and the presence of a Δ^{15}-17-ketone group. That these features act in concert to produce the observed effect is evident from the normal spectra which we have recorded for 14β-Δ^{15}- , 14β-17-oxo- , 14α-Δ^{15}-17-oxo- , 14α-Δ^{15}- , and 14α-17-oxo-steroids.[2,5,6,11,12]

TABLE 1 ^{1}H N.m.r. Data[a,b] for 3-Methoxy-14β-estra-1,3,5(10),15-tetraen-17-ones(4) - (7)

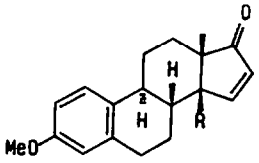
Compound	4	5	6	7	
Proton	Chemical shifts (δ/p.p.m)				
6α-H	2.78	2.79	2.84	2.82	
6β-H	2.82	2.79	2.91	2.83	
7α-H	1.74	1.35	1.69	1.42	
7β-H	2.01	2.17	1.94	2.40	
8β-H	2.07	1.56	1.92	1.88	
9α-H	2.40	2.26	2.25	2.21	
11α-H	2.14	2.27	2.17	2.23	
11β-H	1.43	1.36	1.41	1.42	
12α-H	1.83	1.85	1.79	1.86	
12β-H	1.52	1.56	1.59	1.68	
13β-CH_3	1.10	1.02	1.15	1.10	
14β-H(CH_3)	2.70	(1.19)	2.83	-	
15-H(CH_3)	(2.16)	7.38	7.60	7.37	
16-H	5.95	6.13	6.20	6.26	
Protons	Coupling constants[c] (J/Hz)				
9α,11α	8.3	6.7	6.2	7.5	(3.5)[d]
9α,11β	8.7	10.5	10.0	10.1	(11.5)[d]
11α,11β	-13.6	-12.8	-13.4	-13.0	(-13.0)[d]
11α,12α	6.3	7.5	5.7	6.8	(3.5)[d]
11α,12β	9.3	6.5	7.3	8.2	(3.5)[d]
11β,12α	5.0	6.8	8.0	5.2	(13.5)[d]
11β,12β	6.5	6.0	5.6	7.2	(3.5)[d]
12α,12β	-13.8	-14.0	-14.0	-13.9	(-13.5)[d]
8β,14β	5.1	-	5.7	-	
Other	1.3(14,15^1)	5.9(15,16)	2.4(14,15)	5.9(15,16)	
	1.3(14,16)		2.4(14,16)		
	1.2(15^1,16)		5.9(15,16)		

[a] Data were recorded for $CDCl_3$ solutions at 500 MHz (internal standard $CHCl_3$ δ 7.2400). Assignments were made with the aid of proton-proton correlation spectroscopy (COSY), selective proton-proton spin decoupling, and difference n.O.e. spectroscopy (see Table 2); for these purposes, some spectra were also run in $CDCl_3$ - C_6D_6 mixtures in order to improve dispersion of specific signals. In those cases where stereochemical assignments for 11-H_2 and 12-H_2 could not be made directly by these methods, chemical shift correlations were applied.

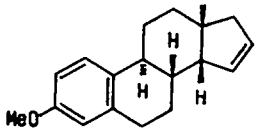
[b] The following signals were recorded for all compounds : δ 3.74 ± 0.01(3H, s, OCH_3), 6.58 ± 0.02(1H, d, *J* 2.8Hz, 4-H), 6.69 ± 0.01(1H, dd, *J* 8.6 and 2.8Hz, 2-H), and 7.04 ± 0.02(1H, d, *J* 8.6Hz, 1-H).

[c] Ring B proton-proton coupling constants are omitted from the Table since all are similar (± 1Hz) to those recorded elsewhere for 3-methoxy-14β-estra-1,3,5(10)-trienes (ref. 2).

[d] Average magnitude of proton-proton coupling constants for 14β-methyl steroids having ring C in a chair conformation (ref. 2).



5 R=CH_3
6 R=H
7 R=OH



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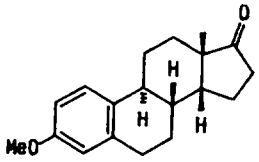

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A comparison of the magnitude of atypical coupling constants in compounds (4) - (7) shows that $J_{11\beta,12\alpha}$ (5 - 8 Hz) is significantly smaller than that of steroids in which ring C is in a chair conformation, whereas $J_{9\alpha,11\alpha}$ (6.2 - 8.3 Hz), $J_{11\alpha,12\alpha}$ (5.7 - 7.5 Hz), $J_{11\alpha,12\beta}$ (6.5 -9.3 Hz), and $J_{11\beta,12\beta}$ (5.6 - 7.2 Hz) are larger. The magnitude of $J_{9\alpha,11\beta}$ (8.7 - 10.5 Hz) is slightly smaller than normal. These ranges exclude the occurrence of the chair conformation of ring C in solution, and are compatible, either with discrete non-chair conformations or with rapid conformational interconversion between energetically similar states. The latter interpretation is supported by difference n.O.e. experiments, in which selected irradiations were performed in an attempt to localise the spatial environment of the protons attached to C(11) and C(12) (Table 2).

Table 2: N.O.e. Enhancements of Ring B and C Proton Signals in (4) - (7)

Compound	Solvent	Irradiated peak	Observed enhancements (difference n.O.e.s)
(4)	$CDCl_3$	13β-Me	8β-H,11β-H,12α-H,12β-H,and 14β-H
(4)	$CDCl_3$	9α-H	7α-H and 12α-H
(5)	$CDCl_3$-C_6D_6 (1:1)	13β-Me	8β-H,11β-H,12α-H, and 14β-Me
(5)	$CDCl_3$-C_6D_6 (1:1)	14β-Me	7β-H,8β-H,15-H, and 13β-Me
(5)	C_6D_6	12α-H	12β-H
(5)	C_6D_6	12β-H	12α-H
(6)	C_6D_6	13β-Me	8β-H,11β-H,12α-H,12β-H, and 14β-H
(7)	$CDCl_3$-C_6D_6 (1:1)	13β-Me	8β-H,12α-H, and 12β-H
(7)	$CDCl_3$-C_6D_6 (1:1)	8β-H	12β-H
(7)	$CDCl_3$-C_6D_6 (1:1)	12α-H	12β-H
(7)	$CDCl_3$-C_6D_6 (1:1)	12β-H	8β-H and 12α-H

Thus, in all four compounds (4) - (7), irradiation of the 13β-CH_3 signal resulted in enhancement of the 12α-H signal as well as that of 12β-H. In addition, mutual enhancements were observed between 8β-H and 12β-H. These results are compatible with a boat or twist-boat conformation of ring C, but not with a chair. On the other hand, irradiation of the 13β-CH_3 signal in compounds (4) -(6) also enhanced that of 11β-H. In one case (4), irradiation of the 9α-H signal resulted in enhancement of the 12α-H signal. These responses indicate a chair-like conformation for ring C. Although some of the foregoing correlations appear to reflect mutual inconsistencies, it is possible that ring C conformations or conformational equilibria differ within the series (4) - (7) and are also influenced differently by solvent interactions. However, attempts to 'freeze out' discrete conformations by recording n.m.r. spectra at -60°C were unsuccessful.

The experimental conclusions were supported by molecular mechanics (MM2) calculations on compounds (4) -(7). In each case, energy minimisations revealed small differences between the normal conformer having a ring B half-chair, ring C chair and that having a ring B half-chair, ring C twist-boat. However, in all cases the deformed conformers were favoured by a small margin (0.42 -1.3 kcal mol^{-1}). By contrast, the MM2 calculations on 3-methoxy-14β-estra-1,3,5(10),15-tetraene (8) and 3-methoxy-14β-estra-1,3,5(10)-trien-17-one (9) reflected steric energy margins of 1.28 and 4.2 kcal mol^{-1} respectively, favouring undeformed conformers (Table 3).

Table 3: Steric Energies[a] (kcal mol^{-1}) of 3-Methoxy-14β-estra-1,3,5(10)-trienes (4)-(9)

Conformation[b]	(4)	(5)	(6)	(7)	(8)	(9)
HC	14.15	18.17	13.62	16.51	17.55	19.08
BC	17.88	21.14	17.32	19.94	20.41	21.76
HB	13.73	16.87	12.71	15.76	18.83	23.28
BB	18.45	21.61	17.38	20.59	23.40	27.19

[a] Calculated with Allinger's MM2 force field (ref. 13), modified for appropriate management of a phenyl ring (ref. 14).
[b] Conformational descriptors (combinations of H, half-chair; C, chair; B, boat-like) refer sequentially to rings B and C.

The puckering parameters of the compounds (4) - (9) are given in Table 4, and reveal a close correspondence in the predicted conformation of the deformed ring C in the 14β-Δ^{15}-17-ketones (4) - (7); thus, the conformation approximates to a twist-boat having a two-fold axis of symmetry through C(11) and C(14).

Table 4: Calculated Puckering Parameters[a] of Compounds (4) - (9)

		Ring B			Ring C			Ring D	
		Q	θ	ϕ	Q	θ	ϕ	Q	ϕ
(4)	**HB**	**0.520**	**128**	**46**	**0.729**	**85**	**12**	**0.099**	**346**
	HC	0.524	129	41	0.557	15	72	0.220	164
(5)	**HB**	**0.527**	**128**	**43**	**0.733**	**86**	**19**	**0.115**	**346**
	HC	0.543	129	32	0.552	19	95	0.250	164
(6)	**HB**	**0.518**	**129**	**42**	**0.725**	**85**	**16**	**0.098**	**345**
	HC	0.530	129	43	0.548	19	83	0.209	164
(7)	**HB**	**0.520**	**129**	**42**	**0.729**	**85**	**17**	**0.113**	**346**
	HC	0.535	130	33	0.552	18	88	0.236	164
(8)	HB	0.529	128	44	0.739	87	26	0.186	359
	HC	**0.538**	**129**	**35**	**0.560**	**15**	**90**	**0.342**	**176**
(9)	HB	0.525	128	47	0.730	86	20	0.349	45
	HC	**0.542**	**130**	**29**	**0.553**	**10**	**113**	**0.377**	**146**

[a] Puckering parameters are defined conventionally (ref. 15), numbering clockwise from C(5) (ring B), C(8) (ring C), and C(13) (ring D), and are given by Q(Å), θ(°), and ϕ(°)

We ascribe the observed effects in compounds (4) - (7) to conformational transmission induced by flattening of ring D, and the attendant closure of the ring junction torsion angle, $\phi_{17,13,14,15}$, to an extent that cannot be accommodated by a ring C chair. Thus, the MM2 calculations reveal that neither a 17-oxo-group nor a Δ^{15}-bond alone suffice to induce deformation of ring C. The 14β-H-17-ketone (9) displays the largest steric energy margin (4.2 kcal mol^{-1}) favouring the ring C chair, and has a calculated $\phi_{17,13,14,15}$ of 36.2°, whereas the 14β-H-Δ^{15}-compound (8) has an intermediate steric energy margin (1.28 kcal mol^{-1}) and $\phi_{17,13,14,15}$ 32.3°. By contrast, the MM2 calculation for the ring C chair conformer of the 14β-methyl-Δ^{15}-17-ketone (5) gives the smallest $\phi_{17,13,14,15}$ of -23.5° and the largest steric energy margin (4.2 kcal mol^{-1}) favouring the ring C twist-boat.

The converse interpretation is complementary. Thus, in the MM2 calculations for the ring C twist-boat conformers, the calculated torsion angles ($\phi_{17,13,14,15}$) are: (5) 10.8°; (8) 17.4°; (9) 15.6°; which suggests a trend toward accommodation of ring D puckering in (8) and (9).

In the light of these findings, an *X*-ray crystal structure determination was carried out on 3-methoxy-14-methyl-14β-estra-1,3,5(10),15-tetraen-17-one (5).[2] Details of this investigation are given in the Experimental section, and a perspective drawing of the structure is shown in Figure 1. The puckering parameters derived from this structure determination are *Q* 0.525Å, θ 133.1°, and ϕ 39° for ring B; *Q* 0.749Å, θ 88.1°, and ϕ 26.2° for ring C; and *Q* 0.187Å and θ 352.8° for ring D. These values reveal that the overall conformation of (5) in the solid state approximates to the HB form, and that ring C indeed favours a non-chair conformation. The measured parameters for ring C tend toward the twist form of the twist-boat conformation, whereas the calculations predict a slight tendency toward the boat form. In addition, the measurements reveal that ring C is more puckered than predicted.

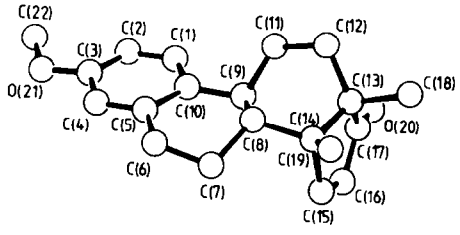

Figure 1 *X*-Ray structure and atom numbering scheme of compound (5)

Nevertheless, the calculated and measured geometries show remarkably good overall agreement, and confirm that the MM2 energy minimisation provides a reliable measure of the conformational preferences in this series of compounds. Although the solid state structure determination does not exclude a dynamic conformational equilibrium in solution, the evidence for such a state is inconclusive, and the experimental data are equally well reconciled with discrete non-chair conformers of (4) - (7).

EXPERIMENTAL

For general directions, see ref. 2

Acid Catalysed Rearrangement of 3-*Methoxy*-14,15α-*methylene*-*estra*-1,3,5(10)-*trien*-17-*one* (1)

A solution of the ketone[3] (1) (190 mg) and toluene-*p*-sulphonic acid (950 mg) in xylene (60 ml) was heated at reflux temperature under nitrogen for 5 h. Work-up with ether and evaporation of the solvent *in vacuo* gave a residue which was chromatographed on silica gel (80 g) with ethyl acetate-benzene (1:49) giving, *inter alia*, 3-methoxy-17a-homo-14β-estra-1,3,5(10),8-tetraen-17a-one (2) (34 mg) [contaminated with a small amount of 3-methoxy-17a-homo-14β-estra-1,3,5(10),6,8-pentaen-17a-one (3)] m.p. 140 - 151°C (from methanol) (Found: M^+, 296.178. $C_{20}H_{24}O_2$ requires M, 296.178); υ_{max} 1695 cm^{-1} (CO); λ_{max} 272 nm (log ε 4.19); δ_H (90 MHz) 1.04 [0.3H, s, 13β-CH_3 of (3)], 1.13 [2.7H, s, 13β-CH_3 of (2)], 3.80 [2,7H, s, OCH_3 of (2)], 3.90 [0.3H, s, OCH_3 of (3)], and 6.6 - 7.2 (3H, m, arom. H); *m/z*(%) 296 [M^+ of (2), 100] and 294 [M^+ of (3), 13], followed by 3-*methoxy*-15-*methyl*-14β-*estra*-1,3,5(10),15-*tetraen*-17-*one* (4) (76 mg) as an oil (Found: M^+, 296.178. $C_{20}H_{24}O_2$ requires M, 296.178); υ_{max} 1680 cm^{-1} (CO); λ_{max} 232 nm (log ε 4.17); *m/z*(%) 296(M^+, 40), 187(100), and 186(40).

Crystal Data of (5)

$C_{20}H_{24}O_2$, M_r = 296.2 g mol^{-1}, orthorhombic space group $P2_12_12_1$, a = 7.7998(6)Å, b = 7.8182(8)Å, c = 26.839(2)Å, V = 1636.7Å^3, Z = 4, D_x = 1.20 g cm^{-1}, μ(Cu) = 5.2 cm^{-1}. A colourless, well-shaped crystal (0.10 x 0.12 x 0.20 mm) was used for data collection.

Data Collection and Processing

The 2052 intensities were measured at room temperature with an Enraf-Nonius CAD4-diffractometer using graphite monochromated Cu-Kα radiation (λ = 1.54184Å). A pure ω-scan was employed, and the ω-angle changed as 0.49 + 0.14 tanθ. The horizontal aperture was fixed to 1.3 mm, the vertical slit to 4 mm. The scan-speed varied between 5.49° min^{-1} and a speed corresponding to a measuring time of 50 s/refl. The unit cell and orientation matrix were determined using 25 reflections in the range 13 - 47° in θ. The stability of the crystal was tested every hour (loss 0.6%), and the orientation (allowed deviation 0.05°) every 200 reflections with three control reflections. Data were corrected for Lorentz and polarisation effects.

Structure Analysis and Refinement

The structure of (5) was solved uneventfully by direct methods[16] and refined[17] anisotropically using a full-matrix method with σ_F^{-2} weights. All hydrogen atoms were placed at calculated positions and refined with a common isotropic thermal parameter (U = 0.101Å^2), riding upon their associated carbon atoms. Final residuals were R = 0.087 and $R\omega$ = 0.052 for 1609 intensities > σ and 209 refined parameters. Final fractional coordinates are given in Table 5. Coordinates of hydrogen atoms, and tables of anisotropic thermal parameters, bond lengths and valence angles, and a complete list of observed and calculated structure factors are available as supplementary material.

Table 5: Fractional Coordinates (x10⁴) and Equivalent Isotropic Thermal Parameters (x10³ Å²) for (5)

	x/a	*y/b*	*z/c*	*U*(eq)
C(1)	-1038(7)	983(7)	-2885(2)	61(3)
C(2)	-296(8)	896(7)	-2415(2)	66(4)
C(3)	-1119(7)	-84(8)	-2051(2)	62(4)
C(4)	-2635(7)	-922(8)	-2152(2)	62(4)
C(5)	-3365(7)	-837(7)	-2628(2)	55(3)
C(6)	-5003(8)	-1818(8)	-2733(2)	69(4)
C(7)	-5993(7)	-1044(8)	-3172(2)	67(4)
C(8)	-4803(7)	-916(7)	-3630(2)	60(3)
C(9)	-3363(6)	363(7)	-3516(2)	55(3)
C(10)	-2563(7)	131(7)	-3000(2)	52(3)
C(11)	-1981(6)	320(8)	-3932(2)	64(4)
C(12)	-2733(7)	-210(9)	-4444(2)	73(4)
C(13)	-4596(8)	368(9)	-4510(2)	67(4)
C(14)	-5823(7)	-417(8)	-4113(2)	65(4)
C(15)	-7004(7)	1071(10)	-4007(2)	66(4)
C(16)	-6466(9)	2585(10)	-4179(2)	72(4)
C(17)	-4848(9)	2315(10)	-4455(2)	79(5)
C(18)	-5135(7)	-55(8)	-5054(2)	88(5)
C(19)	-6833(9)	-1980(8)	-4298(2)	92(5)
O(20)	-3924(7)	3421(7)	-4608(2)	110(4)
O(21)	-513(5)	-287(5)	-1564(1)	73(3)
C(22)	1134(8)	416(9)	-1450(2)	91(5)

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