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STEROIDAL ANALOGUES OF UNNATURAL CONFIGURATION – IX[1]

NMR SPECTROSCOPY AND CONFORMATIONAL ANALYSIS OF 9β,10α- AND 10α-PREGNANES DERIVED FROM THE CUCURBITACINS

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Abstract – NMR spectra of 78 cucurbitacin derivatives were analysed for evidence of conformational aberrations in the C-ring, and differences were found in the 9β-Me, 9β-H and 9α-H series. Evidence in support of postulated ring deformations was obtained from solvent-dependent and lanthanide shift spectra of selected model substances.

During degradative studies upon the cucurbitacins it became apparent that the unusual substitution patterns and configuration in this series of compounds are sometimes responsible for modified relative stabilities of certain ring junctions,[2,3] and for indeterminate deformation of the skeleton.[3,4] The 4,4,14α-trimethyl grouping exerts an insidious effect upon nuclear reactivity and by inference, also upon stereochemistry. For example, it has been recognised[5] that an inherent strain factor is imposed by the B,C-*cis* ring junction since the 14α-Me group is thereby situated in close proximity to the 10α-proton. This factor is quantitatively similar to that of the 10α-Me group interacting with the 12α- and 14α-protons in lumisterol-derived retrosteroids.[6] Molecular models reveal that while the 9β-configuration is retained, these interactions can only be relieved by deforming the C-ring chair. However, epimerisation at C(9) is also effective since a B,C-*trans* ring junction results in a flattened molecule whose α-face is no longer congested.[3] The former mode of strain relief, *via* C-ring deformation, has been invoked for certain A-nor-cucurbitacin derivatives,[5] while the epimerisation pathway is exemplified by cucurbitacin C derivatives in undergoing retro-aldol loss of the 9β-CH_2OH group.[2] However, it has been shown[2,3] that whereas Δ^5- or 5α,6α-disubstituted products favour 9α-configuration, 5β,6β-disubstituted products exhibit varying degrees of preference for 9β-configuration.

The factors which determine the relative thermodynamic stabilities of epimeric pairs of perhydrophenanthrenes have been intuitively[7] and experimentally[8] demonstrated. These factors are readily adapted to the steroid nucleus,[9] and provide a basis for rationalising stereochemical features of steroids with unnatural configuration. By defining 8β,10α, 13β,14α-stereochemistry, a family of four 5,9-stereoisomers is delineated, and their relative stabilities may be deduced by recourse to the simple empirical rules[7] (Fig 1). The 5β,9α,10α-isomer (B) is constrained to adopt an energy-rich B-ring boat or twist-boat conformation,[8] and is clearly the least stable of the isomers. Their thermodynamic stabilities follow those of the analogous perhydrophenanthrenes *viz*, A > B, A ≫ C, D > C and D ≫ B, since the *trans*-fused D-ring only contributes as a holding group for the C-ring.

It is evident that although the relationships will generally apply, intrusive substitution effects may reverse certain predictions.[10] Examination of molecular models reveals that in the cucurbitacin skeleton the 4,4,14α-trimethyl grouping is unlikely to attenuate the relationships involving the 9α,10α-isomers (A) and (B), but that the axial 4β- and 14α-Me groups in (C) and the latter group in (D) could play a quantitative role in affecting thermodynamic equilibria with related 5- and 9-isomers. A number of such equilibria have been examined or have been deduced from transformations of the cucurbitacins,[2-4] (Fig 2, partial formulae) and it is clear that, with the exception of the 9-isomers of the 5β,6β-epoxy-11-one (f), the preferred isomer can be predicted (Fig 1). A rationalisation of the exceptional case may be sought in the status of the 5-position; it is known[11] that the ring C atoms of oxirans are out of plane with contiguous groups and that their hybridisation is consequently intermediate between the sp^2 and sp^3 states. Whereas the Δ^5-11-one (a) favours 9α-stereochemistry, the 5β,6β-epoxy-11-one (f) under the influence of the sp^3 component at C(5)

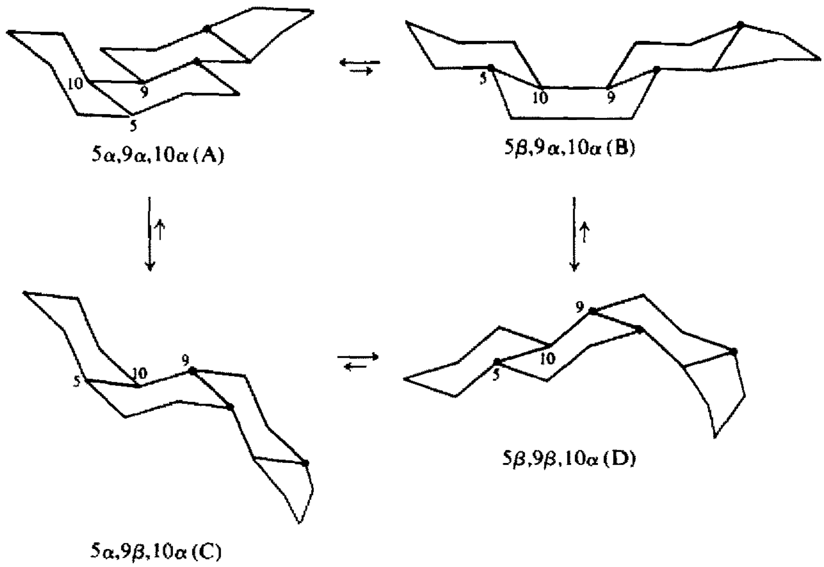


Fig 1. Relative thermodynamic stabilities of 5,9-isomers of 10α-gonane.

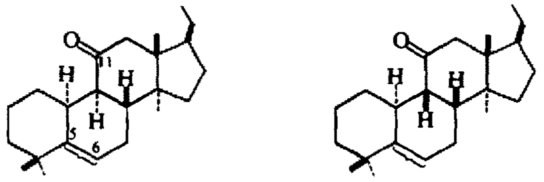
reflects the equilibrium B ⇄ D (Fig 1) favouring the latter, but to a lesser extent than does a B-ring saturated 5β-derivative [*e.g.* (c) Fig 2].

Configurational assignments at C(9) in the cucurbitacins have hitherto relied heavily upon CD data. It is well-known[12] that 9β,10α-11-ones display strongly positive Cotton effects, while those of 9α,10α-11-ones unsubstituted at C(9) are weakly positive. Octant projections explain these results qualitatively, but the CD method does not afford detailed information about the stereochemical environment of the chromophore. For example, a general tendency exists for the Cotton effects of 9β-H,10α-H-11-ones to be weaker than those of analogous 9β-Me,10α-H-11-ones.[2,3] Since a 9β-Me group is equatorial to the C-ring in an idealised conformation, it should lie in a nodal plane and thus not be expected to contribute. The CD results merely imply that a ring conformational difference exists between the two skeletal types.

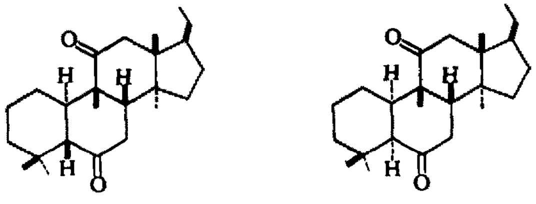
An NMR study of several cucurbitacin derivatives whose preparation has been described in recent publications,[1–4,13,14] was undertaken in order to uncover evidence for conformational differences in the 9β-Me, 9α- and 9β-H series. It was hoped that the influence of alkyl groups and B-ring functionality upon the preferred conformation of the C-ring could thereby be ascertained.

The AB pattern of the 12-H_2 signals in steroids affords much useful information about the C-ring,[15–17] and has been used to deduce conformational changes.[5,18] These data are tabulated (Table 1) (together with Me signals) for 78 cucurbitacin derivatives whose spectra were determined at 100 MHz in $CDCl_3$. Attempts to compile similar data for solvents other than $CDCl_3$ were hampered by solubility problems, but C_6D_6 spectra of certain model substances were also determined (*vide infra*). The subdivisions in Table 1 refer to the skeletal types I–VI.

In many cases the signals for the 12α- and 12β-protons are readily discernable and are mutually



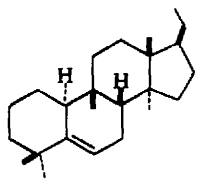
(a) Δ^6	100%	0%*
(b) 5α,6α-$(OH)_2$	100%	0%*
(c) 5β,6β-$(OH)_2$	0%*	100%
(d) 5α-H, 6-Oxo	100%	0%*
(e) 5α,6α-Epoxy	100%	0%*
(f) 5β,6β-Epoxy	45%	55%



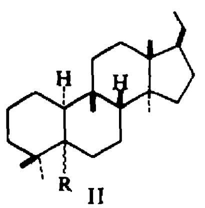
(g)	100%	0%*

*Isomer not detected in crude reaction product.

Fig 2. Isomer distribution of 6- and 11-ketones under base-catalyzed equilibration conditions.



I



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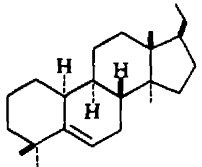

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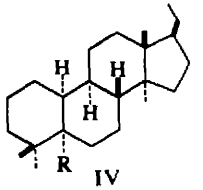

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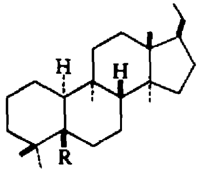
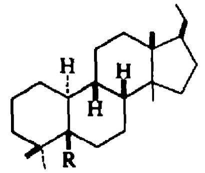


V



VI

separated to an extent which permits first-order analysis. Furthermore, several assignments were facilitated by broadening or splitting (*ca* 0·4–1 Hz) of the axial 12α-H doublet and in the latter event, corresponding splitting of 13β-Me signal. Such assignments were confirmed by double resonance, and the phenomenon is clearly the well-known[19,20] HCCCH coupling between the 12α- and 18-protons. In those cases where the long range coupling was manifested only by broadening of the 12α-H signal, it was not always possible to detect the same effect in the Me signals; this is indicated in Table 1 by the absence of the appropriate superscript. It is evident from molecular models that any C-ring deformation will diminish coplanarity of the participating σ-bonds and so affect the magnitude of long-range coupling.[20]

The results for 9β-Me-Δ^5-compounds (I) reveal that, with few exceptions, a well-defined double doublet or broadened doublet ($J_{12\alpha,12\beta}$ 14–15 Hz and $J_{12\alpha,18}$ *ca* 1 Hz or $w_{1/2}$ *ca* 1·5–2 Hz) is seen for the 12α-proton, while the 12β-proton gives rise to a sharp doublet ($J_{12\beta,12\alpha}$ 14–15 Hz) at higher field. This generalisation also applies to those 9β-Me compounds (II) in which the B-ring is modified by

Table 1. NMR data of cucurbitacin derivatives

	Compound	δ, Me groups	$\delta(J)$, 12α-H	$\delta(J)$, 12β-H
	4,4,14α-Trimethyl-19(10 → 9β)*abeo*-10α-pregn-5-enes (I)			
1	11-One	0·62,^{a} 0·96, 1·0, 1·04, 1·05	2·78 (14^{a})	2·1 (14)
2	2α,3α-epoxy-20β-OH-11-one	0·8, 1·01, 1·07, 1·13, 1·22	2·94 (14^{b})	2·59 (14)
3	2α,3α-epoxy-20α-OH-11-one	0·69, 1·01, 1·06, 1·13, 1·22	2·91 (14^{b})	2·25 (14)
4	$\Delta^{1(10)}$-11-one	0·61,^{b} 0·9, 0·96, 1·04, 1·12	2·68 (13^{b})	2·13 (13)
5	20β-OH-Δ^{2}-11-one	0·82, 1·07, 1·07, 1·09, 1·12	2·92 (14^{b})	2·6 (14)
6	Δ^{2}-11,20-dione	0·64, 1·08, 1·09, 1·12, 1·12	3·11 (14^{b})	2·43 (14)
7	2α,3α-epoxy-11,20-dione	0·73, 1·02, 1·12, 1·15, 1·23	3·15 (14^{a})	2·43 (14)
8	2β-Br-3α-OAc-11,20-dione	0·68,^{b} 0·97, 1·01, 1·06, 1·08	2·94 (15^{b})	2·27 (15)
9	2β-Br-3β-OAc-11,20-dione	0·69,^{b} 1·03, 1·09, 1·09, 1·13	2·94 (14^{b})	2·27 (14)
10	2α-Br-3α-OAc-11,20-dione	0·69,^{b} 1·04, 1·04, 1·1, 1·24	3·0 (15^{b})	2·28 (15)
11	3α,19-(OH)$_2$-11,20-dione	0·73,^{b} 0·92, 1·1, 1·16	*ca* 3·1 (obsc.)	2·44 (14)
12	3α,19-(OAc)$_2$-11,20-dione	0·74,^{b} 0·98, 1·03, 1·09	3·08 (14)^{b}	2·49 (14)
13	3-OMe-$\Delta^{1(10)}$-11,20-dione	0·63,^{b} 1·04, 1·12, 1·18, 1·23	3·04 (13·5^{b})	2·48 (13·5)
14	2,11,20-trione	0·67,^{b} 1·08, 1·13, 1·13, 1·19	3·1 (14^{b})	2·47 (14)
15	3,11,20-trione	0·7,^{a} 1·11, 1·18, 1·27, 1·3	3·19 (14^{a})	2·51 (14)
16	2α-Br-3,11,20-trione	0·67,^{b} 1·08, 1·11, 1·29, 1·39	3·13 (14^{b})	2·5 (14)
17	2β-Br-3,11,20-trione	0·67,^{b} 1·06, 1·11, 1·26, 1·36	3·16 (14^{b})	2·53 (14)
18	17α-Br-3,11,20-trione	0·77, 1·08, 1·23, 1·23, 1·54	3·5 (14^{b})	2·55 (14)
19	1β-Br-2α-OH-3,11,20-trione	0·76, 1·11, 1·14, 1·3, 1·4	3·26 (14^{b})	2·5 (14)
20	2β,16α-(OAc)$_2$-3,11,20-trione	0·72,^{b} 1·1, 1·29, 1·34, 1·34	3·29 (15^{a})	2·51 (15)
21	Δ^{1}-3,11,20-trione	0·7, 0·98, 1·17, 1·18, 1·26	3·17 (14^{b})	2·57 (14)
22	$\Delta^{1(10)}$-3,11,20-trione	0·66,^{b} 0·96, 1·2, 1·22, 1·25	obsc.	2·54 (13)
23	Δ^{16}-3,11,20-trione	0·95, 1·13, 1·13, 1·18, 1·23	3·06^{c}	3·06^{c}
24	2-Br-Δ^{1}-3,11,20-trione	0·7, 1·0, 1·04, 1·21, 1·34	3·16 (14^{b})	2·6 (14)
25	1α,2α-epoxy-3,11,20-trione	0·7, 1·1, 1·16, 1·21, 1·37	3·3 (14^{b})	2·62 (14)
26	2β-OH-Δ^{16}-3,11,20-trione	0·94,^{b} 1·12, 1·13, 1·21, 1·29	3·07^{c}	3·07^{c}
27	2β-OAc-Δ^{16}-3,11,20-trione	0·95,^{b} 1·14, 1·14, 1·26, 1·26	3·1^{c}	3·1^{c}
28	3α-OH-Δ^{16}-3,11,20-trione	0·74, 0·93,^{b} 1·05, 1·21, 1·3	2·88 (15^{b})	3·09 (15)
29	3α-OAc-Δ^{16}-3,11,20-trione	0·91, 0·94,^{b} 1·07, 1·21, 1·24	2·9 (16^{b})	3·12 (16)
30	2-OAc-$\Delta^{1,16}$-3,11,20-trione	0·98,^{b} 1·12, 1·2, 1·27, 1·3	3·0 (15^{b})	3·21 (15)
31	3α,19-(OH)$_2$-Δ^{16}-11,20-dione	0·86, 1·01, 1·1, 1·2	2·98^{c}	2·98^{c}
32	3α,19-(OAc)$_2$-Δ^{16}-11,20-dione	0·93, 1·02, 1·02, 1·1	2·92 (15^{b})	3·12 (15)
33	3α,19-(OH)$_2$-16α,17α-epoxy-11,20-dione	0·9, 0·97,^{a} 1·12, 1·2	3·67 (15^{a})	2·35 (15)

Table 1. (*Continued*)

	Compound	δ, Me groups	δ(*J*), 12α-H	δ(*J*), 12β-H
	4,4,14α-Trimethyl-19(10 → 9β)*abeo*-10α-pregn-5-enes (I)			
34	3α,19-(OAc)$_2$-16α,17α-epoxy-11,20-dione	0·98, 0·98, 1·02, 1·2	3·69 (16^{a})	2·42 (16)
35	2β,16α,19-(OAc)$_3$-3,11,20-trione	0·87, 1·32, 1·36, 1·41	3·31 (14^{b})	2·59 (14)
36	2β,19-(OAc)$_2$-Δ^{16}-3,11,20-trione	1·09, 1·14, 1·31, 1·31	3·02 (15^{b})	3·22 (15)
	4,4,14α-Trimethyl-19(10 → 9β)*abeo*-5ξ,10α-pregnanes (II)			
37	5β,6β-epoxy-11-one	0·56,^{a} 0·7, 1·06, 1·08, 1·12	2·76 (14^{a})	2·11 (14)
38	5β,6β-epoxy-20β-OH-Δ^{2}-11-one	0·76, 0·76, 1·1, 1·14, 1·18	2·9 (15^{b})	2·61 (15)
39	2α,3α,5β,6β-diepoxy-20β-OH-11-one	0·75, 0·8, 1·09, 1·15, 1·15	2·91 (15^{b})	2·59 (15)
40	5β,6β-(OH)$_2$-11-one	0·59,^{a} 1·04, 1·04, 1·21, 1·24	2·6 (14^{a})	2·12 (14)
41	5β-OH-6β-OAc-11-one	0·56,^{a} 0·84, 1·0, 1·26, 1·33	2·61 (14^{a})	2·12 (14)
42	6,11-dione(5β-H)	0·61,^{a} 1·02, 1·04, 1·16, 1·28	2·69 (14^{a})	obsc.
43	6,11-dione (5α-H)	0·76,^{b} 1·02, 1·02, 1·26, 1·3	2·53^{c}	2·53^{c}
44	5β-OH-6,11-dione	0·68,^{b} 0·97, 1·11, 1·11, 1·23	2·59 (15^{b})	2·26 (15)
45	Δ$^{5(10)}$-6,11-dione	0·68,^{a} 0·92, 0·92, 1·04, 1·12	2·87 (15^{a})	2·31 (15)
46	3α,19-(OH)$_2$-5β,6β-epoxy-11-20-dione	0·71,^{a} 0·84, 1·03, 1·18	3·07 (14^{a})	2·45 (14)
47	3α,19-(OAc)$_2$-5β,6β-epoxy-11,20-dione	0·7, 0·7, 1·08, 1·17	3·05 (14^{b})	2·49 (14)
48	3α,19-(OAc)$_2$-5β,6β-(OH)$_2$-11,20-dione	0·74,^{b} 1·03, 1·03, 1·31	2·93 (14^{b})	2·53 (14)
49	3α,6β,19-(OAc)$_3$-5β-OH-11,20-dione	0·76,^{b} 0·83, 1·02, 1·41	2·94 (14^{b})	2·56 (14)
50	5β-OH-6β-OAc-3,11,20-trione	0·6,^{b} 1·02, 1·18, 1·27, 1·33	3·02 (14^{b})	2·55 (14)
	4-4,14α-Trimethyl-19-nor-10α-pregn-5-enes (III)			
51	11-one	0·65,^{b} 0·96, 1·01, 1·05	2·24^{c}	2·24^{c}
52	3α-OH-11,20-dione	0·64,^{b} 0·98, 1·04, 1·09	2·71 (16^{b})	2·48 (16)
53	3α-OAc-11,20-dione	0·65,^{b} 1·0, 1·05, 1·07	2·73 (16^{b})	2·5 (16)
54	3α-OH-Δ^{16}-11,20-dione	0·89,^{a} 0·98, 1·08, 1·09	2·59 (17^{a})	3·03 (17)
55	3α-OAc-Δ^{16}-11,20-dione	0·9, 0·99, 1·02, 1·05	2·6 (17^{b})	3·07 (17)
56	3α-OH-16α,17α-epoxy-11,20-dione	0·84,^{a} 0·97, 1·07, 1·16	3·36 (17^{a})	2·36 (17)
57	3α-OAc-16α,17α-epoxy-11,20-dione	0·85,^{a} 0·99, 1·06, 1·18	3·36 (17^{a})	2·38 (17)
58	3α-OAc-16β,17β-epoxy-11,20-dione (17α-Ac)	1·0, 1·05, 1·06, 1·22	2·66 (17^{b})	2·92 (17)
	4,4,14α-Trimethyl-19-nor-5α,10α-pregnanes (IV)			
59	5α,6α-epoxy-11-one	0·59, 0·72, 0·97, 1·06	2·19^{c}	2·19^{c}
60	5α,6β-(OH)$_2$-11-one	0·67, 1·03, 1·03, 1·06	obsc.	obsc.
61	5α,6α-(OH)$_2$-11-one	0·59, 1·04, 1·07, 1·07	2·34 (16^{b})	2·13 (16)
62	5α-OH,6α-OAc-11-one	0·6, 0·85, 1·04, 1·07	2·32 (16^{b})	2·12 (16)
63	5α,6α-(OAc)$_2$-11-one	0·62, 0·97, 1·02, 1·14	2·32 (16^{b})	2·12 (16)
64	5α-Br-6β-OH-11-one	0·66,^{b} 1·08, 1·21, 1·37	2·39 (16^{b})	2·19 (16)
65	5α-OH-6β-Br-11-one	0·69, 1·01, 1·1, 1·1	2·25^{c}	2·25^{c}
66	3α-OH-5α,6α-epoxy-11,20-dione	0·58,^{b} 0·84, 1·02, 1·05	2·7 (16^{b})	2·47 (16)
67	3α-OAc-5α,6α-(OH)$_2$-11,20-dione	0·58,^{b} 1·02, 1·04, 1·1	2·51^{c}	2·51^{c}
68	3α-OAc-5α-Br-6β-OH-11,20-dione	0·6,^{b} 1·12, 1·15, 1·32	2·98 (16^{b})	2·46 (16)
69	3α,6α-(OAc)$_2$-5α-OH-11,20-dione	0·6,^{b} 0·86, 1·07, 1·1	2·7 (16^{b})	2·46 (16)
70	5α,6α-epoxy-3,11,20-trione	0·58, 0·85, 1·07, 1·28	2·72 (16^{b})	2·5 (16)
71	5α-Br-6β-OH-3,11,20-trione	0·66, 1·18, 1·31, 1·44	obsc.	obsc.
	4,4,14α-Trimethyl-19-nor-5β,10α-pregnanes (V)			
72	5β,6β-epoxy-11-one	0·62,^{b} 0·7, 0·89, 1·09	2·17^{c}	2·17^{c}
73	3α-OH-5β,6β-epoxy-11,20-dione	0·63, 0·84, 0·98, 1·04	2·62 (17^{b})	2·43 (17)
74	5β,6β-epoxy-3,11,20-trione	0·64,^{b} 0·86, 1·03, 1·19	2·66 (17^{b})	2·44 (17)
	4,4,14α-Trimethyl-19-nor-5β,9β,10α-pregnanes (VI)			
75	5β,6β-epoxy-11-one	0·72, 0·85, 0·88,^{a} 1·05	2·48 (17^{b})	2·07 (17)
76	3α-OH-5β,6β-epoxy-11,20-dione	0·85, 0·87, 0·93, 1·02	2·83 (17)	2·37 (17)
77	3α,6β-(OAc)$_2$-5β-OH-11,20-dione	0·7, 0·73, 0·98, 1·11	2·76 (17)	2·39 (17)
78	5β,6β-epoxy-3,11,20-trione	0·87, 0·89, 0·98, 1·28	2·84 (17^{b})	2·4 (17)

[a] Clearly defined splitting due to long-range coupling (see text for magnitude).

[b] Signal broadened due to long-range coupling (see text for magnitude).

[c] A_2 singlet.

5,6-functionality. In certain cases, accidental shift equivalence or reversed relative chemical shifts of the 12-protons is seen; this is usually associated with the presence of a Δ^{16}-bond and results from selective deshielding of the 12β-proton, which molecular models show to lie close to the nodal plane of the double bond.[21] It is evident that the equivalence of the 12-protons, where a singlet is seen, is anisotropically induced and is not in itself indicative of C-ring flattening as has been suggested in an earlier study[5] upon cucurbitacin derivatives. Other examples of functional group anisotropy are seen in the 17α-Br derivative (**18**) and the 16α,17α-epoxides, (**33**) and (**34**), where the 12α-proton signals suffer large downfield shifts.

Certain exceptions to the median J_{gem} value were observed; two $\Delta^{1(10),5}$-compounds, (**4**) and (**22**), had J_{gem} 13 Hz, and two unrelated compounds, (**29**) and (**34**), had J_{gem} 16 Hz. The significance of the latter deviations is not apparent, but the absence of the 10α-H/14α-Me interaction in **4** and **22** could indicate that their C-ring conformation is close to that of an undeformed cyclohexanone chair,[22] and by implication that the C-ring of compounds exhibiting the 14–15 Hz splitting is slightly deformed. The $\Delta^{5(10)}$-6,11-dione (**45**) represents an inconsistency in this argument since J_{gem} 15 Hz is measured in spite of the absence of the same interaction. This aspect of the problem requires further study.

The presence of clear long-range coupling in all the 9β-Me derivatives (I and II) indicates that the conditions for adequate σ-orbital overlap are fulfilled,[20] and hence that any deformation of the C-ring to alleviate the 10α-H/14α-Me interaction must be very slight. The heavy substitution on the C-ring restricts the possible modes of deformation[23] to that in which the 11-CO group pivots symmetrically in the vertical C(11)/C(14) plane, and in so doing, energetically competitive interactions between 11-CO/1α-H, 9β-Me/8β-H, and ultimately 9β-Me/13β-Me, become significant. The results suggest that these factors suffice to inhibit significant deformation of the C-ring, and that 5,6-substitution does not materially affect the situation.

The 9α-H series of compounds (III and IV) exhibit consistently larger coupling (16–17 Hz) between the 12-protons, and although long-range coupling between the 12α- and 18-protons is evidenced by broadening ($w_{1/2}$ *ca* 1–1·5 Hz), and in a few cases by splitting (J *ca* 0·5 Hz), of the respective signals, it is of a lower order of magnitude than in the 9β-Me series. The similarity in behaviour of the Δ^5-(III) and 5α,6α-disubstituted (IV) compounds indicates that the C-ring conformation is not influenced by B-ring functionality when 5α-configuration is present. The difference in J_{gem} associated with the changes at C(9) can reasonably be ascribed to a change in the C-ring conformation. The larger algebraic magnitude of J_{gem} in the 9α-series (III and IV) may be accommodated by a flattened C-ring in which the dihedral angle (θ) between the π orbital of the 11-CO group and the 12α-proton is decreased, thereby increasing the π-contribution to J_{gem}.[18,24] Furthermore, the dihedral angle defined by 12α-H, C(12), C(13), C(18) will necessarily decrease from 180° and so decrease the magnitude of $J_{12\alpha,18}$.[20] A reason for this deformation is not immediately obvious in view of the known preference for 9α-configuration in the Δ^5- and 5α,6α-disubstituted series (Fig 2). It follows that the α-face interactions in the 9β-series represent an adequate driving force for 9-epimerisation, but that an energetically less demanding interaction occurs in the resultant 9α-products. Examination of molecular models reveals that the only consequential interaction in 9α-H compounds occurs between the 1α-proton and 11-CO group, and that this may indeed be alleviated by partial flattening of the C-ring.

The 5β,6β-epoxy-11-ones, (**72–74**), in the 9α-H series (V) are unique in that their thermodynamic instability suggests the presence of a boat-like B-ring (Fig 1). Nevertheless a similar 11-CO/1α-H interaction is present, and the NMR data (J_{gem} 17 Hz, and slight broadening of the 12α-H and 13β-Me signals) indicate that the conformation of the C-ring is similar to that found in III and IV.

The few 9β-H compounds (VI) available might be expected to display similar spectral behaviour to that of the 9β-Me series (I and II) since the skeletal configurations are identical. However, these compounds, (**75–78**) are remarkably similar to the 9α-H series (III–V) in exhibiting J_{gem} 17 Hz and little or no broadening of the 12α-H and 13β-Me signals. The inescapable conclusion is that the C-ring is deformed at least to the same extent, but this time in order to alleviate the 10α-H/14α-Me interaction. It is suggested that the absence of a potential eclipsing interaction between 9β-Me and 8β-H enables such a deformation to take place.

The postulated ring deformations cannot be examined quantitatively without variable temperature and solvent dependent studies; however the self-consistency of the results in Table 1 provides evidence for the sensitivity of the C-ring to C(9) configuration and substitution. It may also be concluded that the 9β-Me-Δ^5-compounds (I) are "5β-like" (*i.e.* similar to II) in gross conformation, while the 9α-H-Δ^5-compounds (III) are "5α-like" (*i.e.* similar to IV).

The 5,6-epoxy-11-ones described here are especially interesting in being simply represented in each of the structural types II, IV, V and VI, by **37**, **59**, **72** and **75**, respectively. These compounds, together with the Δ^5-11-ones, (**1**) and (**51**), representing I and III respectively, formed the subject of a more detailed investigation. The objectives of this study were to corroborate the conclusion based upon the data in Table 1, and to determine the influence of a 5,6-epoxy-group upon equilibration results (Fig 2) and ring conformation.

NMR spectra of the six model substances were determined in C_6D_6 solutions, and the $\Delta^{CDCl_3}_{C_6D_6}$ values[15] of identifiable proton signals were obtained. (Table 2; δ of Me resonances are included for reference purposes, but are not assigned owing to uncertainties in ascertaining the long-range effect of solvent-associated epoxy-groups.[25])

The solvent effect upon the 12-protons differs substantially in the 9β-Me and 9α-H compounds. If it is assumed that the effect of the epoxy-group in **37** is seen as a small positive increment (+0·05) to each of the 12-protons, the same difference factor ($\Delta^{CDCl_3}_{C_6D_6\,12\alpha\text{-H}} - \Delta^{CDCl_3}_{C_6D_6\,12\beta\text{-H}}$) of +0·25 reflects geometric similarity in **1** and **37**. This difference is considerably smaller (+0·12 to +0·14) in **51**, **59** and **72**. The results for **1** and **37** are within the range expected for many steroidal 11-ones,[15] while those of the 9α-H compounds are compatible with a flattened C-ring chair since the 12α-proton is thereby moved closer to the nodal surface at which a sign change occurs,[15,26] thus diminishing the positive increment for $\Delta^{CDCl_3}_{C_6D_6\,12\alpha\text{-H}}$, while the 12β-proton retreats from this surface and acquires a greater positive increment. The 5β,6β-epoxy-11-one (**75**) is remarkable in exhibiting near-equivalence of the $\Delta^{CDCl_3}_{C_6D_6}$ values of the 12α- and 12β-protons, and it is evident that the C-ring adopts a conformation in which these protons are staggered toward the 11-CO group and thus equally influenced by association of that group with C_6D_6.

NMR examination of the model substances under the influence of added $Eu(fod)_3$[27] proved to be highly informative. All of the compounds were examined under identical conditions (Experimental) and the results are summarised in Table 3. Although competing complexation with the alternative sites occurred in **37**, **59**, **72** and **75**, giving rise to non-linear shift/concentration plots, all of the substances underwent highly preferential complexation with the 11-CO group, and linearity was observed to *ca* 0·6–0·7 mol. equiv. of added $Eu(fod)_3$. For the purposes of this study, apparent ΔEu values[28] were obtained by extrapolation from δ at 0·3 mol. equiv. $Eu(fod)_3$, in order to provide a uniform basis for comparison between mono- and bifunctional compounds. It follows that ΔEu values for strongly shifted signals in the 5,6-epoxy-11-ones are higher than experimental values would be, while values for signals of protons in the environment of the epoxy-group may be low. Attempts to separate the two complexing components were foiled by unequal preferences for selective complexation in the different compounds, and the intervention of experimental difficulties prevented the acquisition of reliable ΔEu data at 1 mol. equiv. $Eu(fod)_3$.

The ΔEu values obtained for the 12-protons substantiate the aforegoing conclusions about the C-ring conformation. The 9β-Me compounds (**1** and **37**) show the expected difference in shift rates for α-disposed axial and equatorial protons in a cyclohexanone chair,[29] since ΔEu is measurably greater for 12β-H than for 12α-H. A comparison of ΔEu for the 12α- and 12β-protons in the 9α-H compounds (**51** and **59**) shows a much smaller difference, and although it was not possible to distinguish between the respective signals at higher concentrations of shift reagent, it is assumed that 12β-H is responsible for the slightly higher ΔEu in each case. The 12-protons of **72** and **75** are mutually indistinguishable by this method since their ΔEu values are identical. However, the assignment in **75** was aided by evidence of long-range coupling to the 12α-proton. The solvent-dependent data (Table 2) appear to conflict with ΔEu measurements in **72**, since they imply that the 12α- and 12β-protons are not equivalent. However, it is possible that the non-equivalence is too small to be measurable by the $Eu(fod)_3$ method. Alternatively, the two methods may not be comparable since the geometric requirements for aromatic solvent association[15,30] need not be similar to those of Eu-complexation.[31]

Attempts to define the C-ring geometry more accurately by applying the ψ-contact relationship[32] did not give satisfactory results. This may be ascribed to difficulty in obtaining quantitative data on the competition between functional groups for the complexing agent. The effect of the steric environment of a given functional group upon the stability and geometry of shift reagent complexes is not clear, but it is evident from this work (*e.g.* comparing ΔEu for the 6-protons in **37**, **59**, **72** and **75**) that it does play a role. Further progress on this aspect

Table 2. Comparison of C_6D_6 and $CDCl_3$ spectra of Δ^5- and 5,6-epoxy-11-ones

			$\Delta^{CDCl_3}_{C_6D_6}$			
	Compound	δC_6D_6 (Me groups)	12α-H	12β-H	6-H	13β-Me
1	Δ^5-11-one (9β-Me)	0·5 (d, 1), 0·85, 0·97, 1·07, 1·16	+0·23	−0·02	+0·08	+0·12
37	5β,6β-epoxy-11-one (9β-Me)	0·42 (d, 1), 0·73, 0·78, 0·95, 1·36	+0·28	+0·03	+0·26	+0·14
51	Δ^5-11-one (9α-H)	0·53 (br), 0·66, 1·06, 1·08	+0·17	+0·05	+0·03	+0·12
59	5α,6α-epoxy-11-one (9α-H)	0·46 (d, 0·5), 0·64, 0·73, 1·08	+0·17	+0·05	+0·18	+0·14
72	5β,6β-epoxy-11-one (9α-H)	0·46 (d, 0·5), 0·54, 0·74, 1·02	+0·2	+0·06	+0·25	+0·16
75	5β,6β-epoxy-11-one (9β-H)	0·61, 0·61, 0·76, 0·94	+0·22	+0·19	+0·25	+0·17

Table 3. Eu(fod)$_3$ spectral data for Δ^5- and 5,6-epoxy-11-ones

Assignment	δ	$\delta_{0\cdot3}$	ΔEu	Multiplicity and splitting
4,4,14α-Trimethyl-19(10 → 9β)*abeo*-10α-pregn-5-en-11-one (**1**)				
4-Me(β)	0·96	1·35	1·3	s
4-Me(α)	1·05	1·38	1·1	s
9β-Me	1·04	3·7	8·9	s
13β-Me	0·62	2·08	4·9	d, 1
14α-Me	1·0	1·9	3·0	s
1α-H	—	4·6	10·6*	br. d, 12, $w_{1/2}$ 9
6-H	5·55	6·17	2·1	br
7β-H	2·36	3·3	3·1	12-lines, 18, 8, 3, 3
7α-H	—	2·66	2·5*	q, 18, 6
8β-H	—	3·76	6·3*	d, 8
10α-H	*ca* 2·2 (obsc)	4·5	7·7	br. d, 12, $w_{1/2}$ 10
12β-H	2·1	5·44	11·1	d, 14
12α-H	2·78	5·76	9·9	d. d, 14, 1
5,6β-Epoxy-4,4,14α-trimethyl-19(10 → 9β)*abeo*-5β,10α-pregnan-11-one (**37**)				
4-Me(β)	1·06	1·5	1·5	s
4-Me(β)	0·7	1·1	1·3	s
9β-Me	1·12	3·58	8·2	s
13β-Me	0·56	1·84	4·3	d, 1
14α-Me	1·08	1·94	2·9	s
1β-H	—	—	*ca* 4*	br. q, 12, 12, 12
1α-H	—	4·32	9·6*	br. d, 12, $w_{1/2}$ 8
6α-H	3·3	4·2	3·0	d, 5·5
7β-H	2·21	3·2	3·3	q, 16·5, 9
7α-H	—	2·58	3·1*	q, 16·5, 5·5
8β-H	—	3·48	6·0*	d, 9
10α-H	—	4·1	8·3*	q, 12, 3
12β-H	2·11	4·98	9·6	d, 14
12α-H	2·76	5·34	8·6	d. d, 14, 1
4,4,14α-Trimethyl-19-nor-10α-pregn-5-en-11-one (**51**)				
4-Me(β)	1·01	1·3	1·0	s
4-Me(α)	1·05	1·3	0·8	s
13β-Me	0·65	1·79	3·8	br. s
14α-Me	0·95	1·69	2·5	s
1α-H	—	4·74	9·5*	br. d, 10, $w_{1/2}$ 10
6-H	5·39	5·93	1·8	br. d, 5, $w_{1/2}$ 5
7β-H	—	2·46	1·6*	d. t, 16, 5, 5
7α-H	—	2·86	2·4*	q. t, 16, 11, 2, 2
8β-H	—	3·45	4·7*	sext, 11, 11, 5
9α-H	—	5·39	10·9*	q, 11, 5
10α-H	2·88	5·72	9·5	br. d, 12, $w_{1/2}$ 10
12β-H	2·24	5·1	9·5	"s" → d, 17
12α-H	2·24	5·02	9·3	"s" → d, 17
5,6α-Epoxy-4,4,14α-trimethyl-19-nor-5α,10α-pregnan-11-one (**59**)				
4-Me(α)	0·97	1·45	1·6	s
4-Me(β)	1·06	1·52	1·5	s
13β-Me	0·59	1·52	3·1	s
14α-Me	0·72	1·23	1·7	s
1β-H	—	2·6	4*	br. m, (obsc)
1α-H	—	4·15	7·7*	br. d, 12, $w_{1/2}$ 10
6β-H	3·22	4·4	3·9	d, 3·5
7β-H	—	2·48	2·4*	oct, 15, 7, 3·5
7α-H	—	2·82	2·9*	q, 15, 11
8β-H	—	3·42	4·6*	sext, 11, 11, 7
9α-H	—	5·31	9·8*	q, 11, 4
10α-H	2·84	5·72	9·6	sext, 12, 4, 4
12β-H	2·19	4·38	7·3	"s" → d, 16
12α-H	2·19	4·29	7·0	"s" → d, 16
5,6β-Epoxy-4,4,14α-trimethyl-19-nor-5β,10α-pregnan-11-one (**72**)				
4-Me	0·7	1·0	1·0	s
4-Me	1·09	1·31	0·7	s
13β-Me	0·62	1·74	3·7	br. s
14α-Me	0·89	1·61	2·4	s
1β-H	—	2·9	4·3*	br. q, 12, 12, 12, $w_{1/2}$ 8
1α-H	—	4·96	1·04*	br. d, 12, $w_{1/2}$ 8
6α-H	3·39	3·96	1·9	d, 2·5
7β-H	—	*ca* 2·5	*ca* 1·7*	m, (obsc)
7α-H	—	*ca* 2·5	*ca* 1·7*	m, (obsc)
8β-H	—	3·7	5·5*	sext, 11, 11, 3 → q, 8, 8, 8
9α-H	—	5·28	11·3*	q, 11, 7
10α-H	2·88	5·63	9·2	oct, 12, 7, 2
12β-H	2·17	4·95	9·3	"s"
12α-H	2·17	4·95	9·3	"s"
5,6β-Epoxy-4,4,14α-trimethyl-19-nor-5β,9β,10α-pregnan-11-one (**75**)				
4-Me(β)	1·05	1·44	1·3	s
4-Me(α)	0·72	1·18	1·5	s
13β-Me	0·88	1·78	3·0	d, *ca* 0·4
14α-Me	0·85	1·52	2·2	s
1α-H	—	4·98	8·3*	br. m, (obsc)
6α-H	3·21	4·16	3·2	t, 2·5
7β-H	—	—	*ca* 3·2*	oct, 14, 8, 2·5
7α-H	—	—	*ca* 2·3*	oct, 14, 8, 2·5
8β-H	—	3·58	3·9*	q, 8, 8, 8
9β-H	2·33	4·89	8·5	t, 8, 8
10α-H	—	4·17	7·7*	br. d, 12, $w_{1/2}$ 10
12β-H	2·07	4·32	7·5	d, 17
12α-H	2·48	4·75	7·6	br. d, 17

*Value obtained by linear extrapolation from the Eu(fod)$_3$ concentration at which the signal is first identifiable.

of the study would require appropriate monofunctional model compounds. Nevertheless, the empirical analyses presented in Table 3 afford a wealth of stereochemical information. It was possible by inspection to assign the Me signals, although differentiation between those at C(4) cannot be made with certainty. Crucial ring junction proton signals were identified and assignments were confirmed by double resonance. In each case, the splitting patterns supported the configurational assignments and afforded further information about ring conformations.

The 6α-, 7α-, 7β- and 8β-signals in **37** reveal that the B-ring adopts the preferred half-chair conformation[3] in which the couplings $J_{6\alpha.7\alpha}$ 5·5, $J_{6\alpha.7\beta}$ 0, $J_{7\alpha.7\beta}$ 16·5, $J_{7\alpha,8\beta}$ 0 and $J_{7\beta.8\beta}$ 9 Hz accommodate the approximate dihedral angles, $\phi_{6\alpha.7\alpha} \sim 30°$, $\phi_{6\alpha.7\beta} \sim 90°$, $\phi_{7\alpha,8\beta} \sim 90°$ and $\phi_{7\beta.8\beta} \sim 30°$. The B-ring conformation of **1** is clearly similar. However, the data for the 9β-H compound (**75**) reveal that $J_{6\alpha.7\alpha} \sim J_{6\alpha.7\beta} = 2·5$ Hz, $J_{7\alpha.7\beta}$ 14 and $J_{7\alpha.8\beta} \sim J_{7\beta.8\beta} =$ 8 Hz. This is ascribed to a conformational transmission effect resulting from the C-ring deformation,[3] which imposes a half-boat conformation upon the B-ring ($\phi_{6\alpha,7\alpha} \sim \phi_{6\alpha,7\beta} \sim 30°$, $\phi_{7\beta,8\beta} \sim 20°$ and $\phi_{7\alpha,8\beta} \sim 140°$). This is further evidenced by $J_{8\beta.9\beta}$ 8 Hz which supports the contention that the two protons are nearly eclipsed ($\phi_{8\beta.9\beta} \sim 20°$).

The appropriate signals of **59** show $J_{6\beta.7\beta}$ 3·5, $J_{6\beta.7\alpha} \sim 0$ (very slight broadening), $J_{7\alpha.7\beta}$ 15, $J_{7\alpha.8\beta}$ 11 and $J_{7\beta,8\beta}$ 7 Hz to which the approximate dihedral angles $\phi_{6\beta.7\beta} \sim 30°$, $\phi_{6\beta.7\alpha} \sim 90°$, $\phi_{7\alpha.8\beta} \sim 160°$ and $\phi_{7\beta.8\beta} \sim 40°$ are assigned. This half-chair conformation for the B-ring is clearly very similar in **51** and **59**. Unfortunately much of the information for the 5β,6β-epoxy-11-one (**72**) is lost by the failure of the 7-proton signals to undergo mutual resolution. Clearly the discrete signals are convergent in the concentration range of added Eu(fod)$_3$ since the 8β-H signal did not exhibit first-order behaviour. Consequently the only reliable information on the B-ring is that given by $J_{6\alpha.7\beta}$ 2·5 and $J_{9\alpha.10\alpha}$ 7 Hz, but this does not suffice to draw any conformational conclusions. However, the suggestion that the B-ring adopts a destabilised half-boat confirmation is not precluded by the data.

A further point of interest in the compounds examined here is the high ΔEu for the 1α-protons (Table 3). This is readily explained in the 9α-series (**51**, **59** and **72**) since the 11-CO and 1α-H groups are in close mutual proximity (O$\cdots$H 1·6–1·8 Å) even when the C-ring is deformed. The interatomic distance in **1** and **37** is much greater ($\sim$ 3 Å), and 1α-H is well below the nodal plane defined by the 11-CO π-orbitals. The observation may indicate that the O$\cdots$Eu axis is oriented toward the α-face in these two cases.

The results described here clarify a number of conformational problems encountered in the 9β-Me, 9α- and 9β-H cucurbitacin derivatives, and also demonstrate the power of the lanthanide shift technique in uncovering subtle differences in related compounds. The need for caution in attempting to apply the ψ-contact relationship to defining molecular geometry in bifunctional systems is evident, but the empirical data suffice to support semi-quantitative conclusions. The evidence for deformation in the C-ring, based upon lanthanide shift rates of the 12-protons, is self-consistent, and should make it possible to apply such techniques to other steroidal 11-ones.

EXPERIMENTAL

NMR spectra were recorded for CDCl$_3$ or C$_6$D$_6$ solns at 100 MHz. Shift spectra were determined by the addition of 15 μl aliquots (*ca* 0·01 mmol) of a soln (*ca* 145 μl) of Eu(fod)$_3$ (0·104 g, 0·1 mmol) in CDCl$_3$ (100 μl) to the substrate (0·1 mmol) in CDCl$_3$ (0·35 ml). CDCl$_3$ was filtered through active Al$_2$O$_3$ immediately before use. NMR spectra were recorded after each addition of 0·01 mmol reagent, and the process was repeated until the resolution of spectra deteriorated to the extent of obscuring the desired data. This occurred at *ca* 0·7 mol. equiv. Eu(fod)$_3$ in **1** and **51**, and at *ca* 1·0 mol. equiv. Eu(fod)$_3$ in **37**, **59**, **72** and **75**. Duplicate determinations were carried out for each substance and the data reported in Table 3 were obtained from those spectra which exhibited the closest fit to smooth curves in shift/concentration plots.

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