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MODIFIED STEROID HORMONES—L[1]

7-SUBSTITUTED 6-OXO-3α,5α-CYCLOSTEROIDS—2. THE SPECTROSCOPIC PROPERTIES AND STRUCTURE OF 6-OXO-3α,5α-CYCLOSTEROIDS AND THEIR 7-METHYL DERIVATIVES

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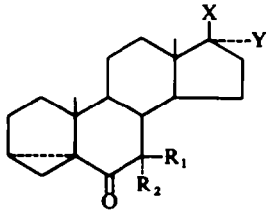
Abstract—The 6-oxo-3α,5α-cyclosteroidal structure is discussed in relation to its UV absorption and rotatory dispersion characteristics. It is noted that the ORD behaviour of these ketones conforms to the conventional Octant Rule, contrary to the observed behaviour of many α-epoxy and -cyclopropyl ketones. Configurational analysis of the C-7 substituents in isomeric 7-methyl-6-oxo-3α,5α-cyclosteroids was effected by ORD on the basis of the Octant Rule. These configurational assignments were fully substantiated by the UV absorption spectra, the IR C=O stretching frequencies and the NMR spectra of these compounds.

THE spectroscopic behaviour of 6-oxo-3α,5α-cyclosteroids is intimately linked with the steric and electronic relationship between the adjacent cyclopropyl and carbonyl functions. In the absence of precise bond-angles and internuclear distances Dreiding models appeared to offer the best available means of portrayal of these molecules, and were used throughout the present work. Whilst it is possible that the representation of the 6-oxo-3α,5α-cyclo- system may not be completely accurate, it is unlikely that the conclusions drawn therefrom in the following discussion will be seriously affected by minor errors in structural representation.



I: $R_1 = R_2 = H$
II: $R_1 = Me$; $R_2 = H$
III: $R_1 = H$; $R_2 = Me$
(a) X = OH; Y = H
(b) X = OAc; Y = H
(c) X = OH; Y = Me
(d) X, Y = O
(e) X = Ac; Y = H
(f) X = Ac; Y = —OAc

Ring B of 6-oxo-3α,5α-cyclosteroids can theoretically assume conformations ranging between the extremes of distorted half-chair (Fig. 1), with carbon atoms

4, 5, 6 and 7 virtually co-planar with the carbonyl oxygen, and an almost undistorted boat conformation, where carbon 3 replaces that at 4 in the co-planarity sequence.

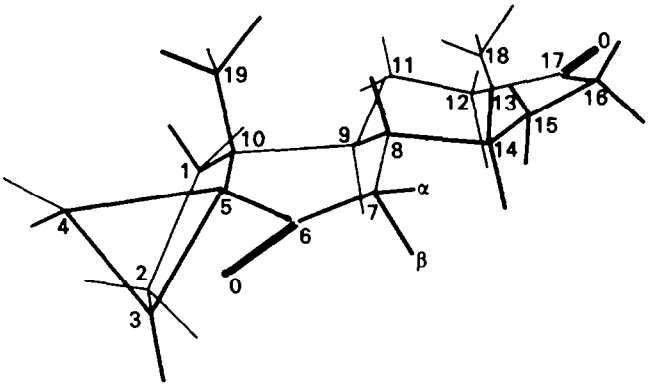


FIG. 1 Dreiding model of 3α,5α-cycloandrostan-6,17-dione (Id), in half-chair ring B conformation, showing the virtually coplanar arrangement of carbon centres 4, 5, 6 and 7 and the 6-oxygen.

The rigidity of the models would appear to preclude the adoption by ring B of appreciably twisted conformations. From measurements on the Dreiding models of these steroids (Ia to f), the following internuclear distances have been estimated:

Nuclei involved	Ring B conformation		(Distances in Å)
	Chair	Boat	
1βH and 19H	2·0	2·0	
4βH and 19H	2·0	1·8	
8βH and 19H	1·9	1·5	
11βH and 19H	1·5	1·7	
8βH and 18H	1·6	1·4	

All other non-bonded interactions are in excess of 2 Å and therefore are of less importance in deciding the relative stabilities of the two extreme conformational forms. On the basis of this dimensional study, the structure possessing ring B in quasi-chair conformation, or in a skew form approximating thereto, is likely to be more stable than that with B in boat form.

UV absorption and rotatory dispersion characteristics of 6-*oxo*-3α,5α-*cyclosteroids.* It has long been established[2,3] that the delocalization of the ring-bonding electrons of the cyclopropyl group extends to include a degree of conjugation with the π-electrons of a carbonyl substituent and that the mesomeric effect is maximal when steric conditions permit relative orientations wherein (a) the planes of the cyclopropyl ring and the π-orbitals of the C=O function are orthogonal to the same third plane and (b) the plane of the C—CO—C grouping bisects the cyclopropyl ring. The effect of this conjugative tendency upon the UV absorption characteristics is well known in the case of the low wavelength transition ($n \rightarrow \sigma^*$) where λ_{max} moves from 188 mμ in the spectrum of acetone to 206 mμ in that of cyclopropylmethyl ketone.[4]

Conjugation will inevitably tend to modify the relative stabilities of the conformational extremes of ring B, discussed above, and it is clear from Fig. 1 that the mesomeric potential energy minimum will be obtained by a skew form of the ring B cyclohexanone, almost midway between the two conformation extrema. The values of λ_{max} of the low wavelength absorption of the 3α,5α-cyclo-6-ketones listed in Table 1, and the observations of Dauben and Berezin[2] upon the absorption of 3α,5α-cyclocholestan-6-one indicate that conjugation occurs in these compounds to a considerable extent.

Very little conjugative effect is noted, however, in the case of the higher wavelength $n \rightarrow \pi^*$ transition, except for slight changes in intensity.[3,4] These observations lead to the suggestion that the $n \rightarrow \pi^*$ transition is hardly affected by the presence of the α-cyclopropyl ring, and that electron transfer effects are here extremely weak, if operative at all. The same observations indicate only a slight possibility that the rotatory power of this transition is subject to ET influences, and predict that the Cotton effect of the keto-group will be affected by an α-cyclopropyl residue in the same manner as by a vicinal unconjugated unsaturated centre, orientated so as to minimise the effective orbital overlap with the p_y- or π-electrons of the CO function.

The magnitude and sign of the Cotton effect of an α-epoxy- or cyclopropyl ketone would then be expected to be predictable by strict application of the original Octant Rule.[5]

It has been shown, however,[6,7] that in many recorded cases an inverted form of the Rule would appear to be followed, even where the $n \rightarrow \pi^*$ absorption characteristics are not appreciably modified by the presence of the 3-membered ring.[3,13]

Use of the UV absorption characteristics is therefore invalid as a guide to the ORD behaviour, and obviously more subtle effects are operative than either simple charge-transfer, or stereochemical disposition, per se.

Djerassi *et al.*[7] have reported ORD data for many α-epoxy- and -cyclopropyl ketones in which there is an apparent inversion of the Octant Rule. Their tables included incomplete data for the two isomeric 6-oxo-3,5-cyclocholestanes, to which they appear to have assigned incorrect octant diagrams.† These authors placed the cyclopropyl ring in the NEAR lower left octant of the CO group (NLL, normally positive). In our view, subject to the model errors referred to above, the whole of the cyclopropyl ring lies in the REAR lower left octant (RLL, normally negative; Fig. 2). Furthermore, the greater part of the steroid skeleton lies in the REAR upper right octant (RUR, negative). It therefore appears certain that the conventional, and not the inverse form of the Octant Rule correctly predicts the strongly negative effects observed in the cases of both 6-oxo-3,5-cyclocholestanes.

In his recent book,[8] Crabbe has suggested that when the cyclopropyl ring is adjacent to the cyclohexanone ring (quoting as example 6-oxo-3α,5α-cyclocholestane) the Cotton effect associated with the carbonyl group is not appreciably affected by the presence of the 3-membered ring. Unfortunately the only information available to him for this compound was the incomplete curve of Djerassi *et al.*[7] ($a = -45!$).‡ In Table 1 data is presented for a number of 6-oxo-3α,5α-cyclosteroids possessing

† This point has been clarified by private communication with Professor W. Klyne, to whom the authors are grateful for helpful discussions.

‡ Amplitude $a = ([\Phi]_1 - [\Phi]_2)/100$, where $[\Phi]_1$ and $[\Phi]_2$ signify the molecular rotations of the first and second features of the Cotton curve, in order of decreasing wavelength.

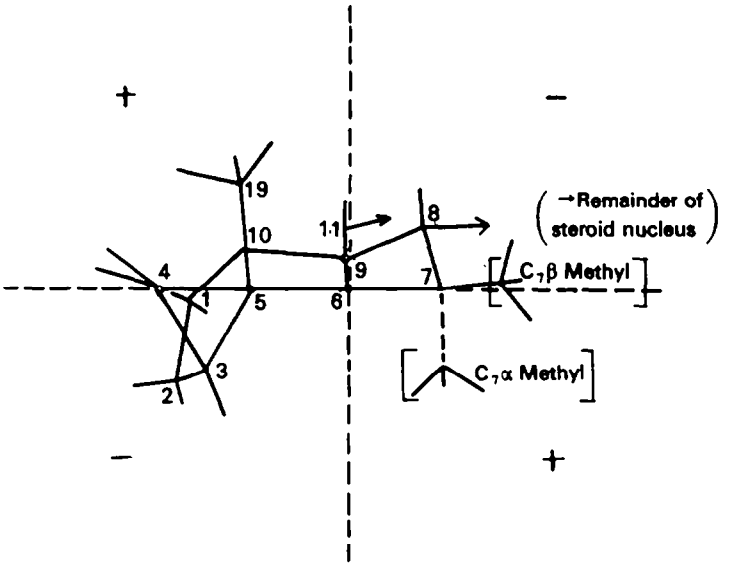


FIG. 2 Octant diagram of rings A and B of a 6-oxo-3α,5α-cyclosteroid and its 7-methyl derivatives (Ring B in quasi-"chair" conformation).

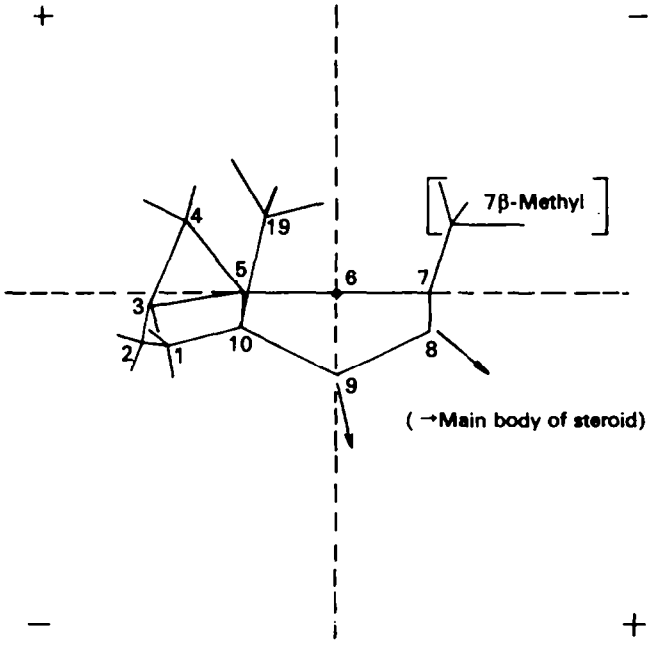


FIG. 3 Octant Diagram of rings A and B of the 6-oxo-stereochemistry of 6-oxo-3α,5α-cyclosteroids, etc. (Ring B in "boat" conformation).

TABLE 1. ORD AND UV ABSORPTION DATA OF 6-OXO-3α,5α-CYCLOSTEROIDS AND THEIR 7-METHYL DERIVATIVES
(Data refer to functional groups in rings A and B only)

Compound	ORD features (MeOH, 0·1 %, 28°)				Cotton amplitudes†			UV features (EtOH)			
	1st extremum		2nd extremum		total observed value	reference compound	6 C=O amplitude	λ_{max} (mμ)	ε	λ_{max} (mμ)	ε
	λ (mμ)	[Φ]	λ (mμ)	[Φ]							
Ia	309	−3120°	258i	+10500°	−136°	—	−136°	210	4380	287	46
IIa	306	−302°	257i	+937°	−21°	—	−21°	213	5290	281	30
	(301i	−250°)									
IIIa	311	−1490°	279	+8190°	−97°	—	−97°	211	4143	289	58
Ib	307	−3050°	256i	+9990°	−130°	—	−130°	210	4560	—	—
IIb	306	−369°									
	(299i)	−348°	254	+1700°	−21°	—	−21°	213	4930	282	31
IIIb	311	−1660°	263	+8360°	−101°	—	−101°	211	4270	289	62
Ic	309	−3650°	260i	+8900°	−126°	—	−126°	—	—	284	45
IIc	307	−817°	303	−800°				213	5060	282	30
Double Cotton effect here leads to further extrema, as											
	299	−846°	265i	+1270°							
					−21°	—	−21° app				
	259	+1320°									
IIIc	311	−1660°	263i	+8360°	−101°	—	−101°	—	—	—	—
Id	320	+4930°	289	−2145°	+71°	+143°[19]	−72°	—	—	—	—
IId	316	+6920°	280	−5680°	+126°	+ +143°	−17°	—	—	—	—
IIId	317	+5880°	286	−650°	+65°	+143°	−78°	—	—	—	—
Ie	307	+4700°	276	+539°	+42°	+178°[20]	−136	—	—	—	—
IIe	307	+7400°	265	−6770°	+98°	+178°	−38	213 mμ	5160	—	—
If	318	+1937°	291	+544°	+14°	+166°[21]	−132	—	—	—	—
IIf	307	+3960°	262	−6620	+106°	+166°	−60	—	—	—	—

† Amplitudes, $a = 10^{-2}[\Phi]_1 - [\Phi]_2$.

In the case of diketones, the amplitudes are quoted for the appropriate reference compounds (containing the corresponding second keto-function, but otherwise possessing simply a 3β-hydroxy or acetoxy, 5α- or 5-enic steroid skeleton). The second Cotton amplitude is subtracted algebraically to obtain nominal amplitudes for the 6-keto function.

NB Compounds IIa, IIb and IIc demonstrate double Cotton effect.

no other keto-groupings within the same molecule, and it is clear that the complete amplitude is probably close to −130. The Cotton effect of 5α-cholestan-6-one has an amplitude of −77,[9] and hence the introduction of the cyclopropyl ring has increased the magnitude of the Cotton effect of the 6-oxo-group by ca 75%.

Use of UV rotatory dispersion and absorption in the configurational analysis of 7-methyl-6-oxo-3α,5α-cyclosteroids

Turning now to the pairs of isomeric 7-methyl-6-oxo-3α,5α-cyclosteroids, the preparation of which was discussed in Part XLIX,[1] we find that compounds to which the general formula II is ascribed herein, were produced directly by catalytic reduction of the corresponding 7-methylene-6-keto-precursors under conditions which may be expected to avoid thermodynamic equilibration.

The isomeric 7-methylated ketones III are produced in turn via the alkali enolates of II, in solution, and are therefore the more stable isomers. Their IR and ORD characteristics support this view (Tables 1 and 2), in that the carbonyl stretching frequencies and Cotton amplitudes of isomers III are in close agreement with those of the corresponding ketones without 7-substituents, whereas II in all cases differs greatly in respect of both features.

It remains to justify the assignment of structures II and III which has been carried out by invoking the use of Dreiding models, discussed above, and the Octant Rule.

In the 7α-methyl-3α,5α-cyclo-6-oxosteroids, where the Me group is axial, and ring B is in chair conformation, the internuclear distances of the 7α-methyl hydrogen atoms and either the 9α- or the 14α-hydrogen atom is 1·7–1·9 Å. In the case of 7β-Me (equatorial when B is in chair conformation) we find the internuclear distances of the 7-Me hydrogens to the 15β and 15α-hydrogen atoms to be 1·2–1·4 and 1·6–1·7 Å respectively. These are the only new purely steric factors to be involved in considering the methylated structures in relation to the ketone with no C-7 substituent.

Relief of the interaction of the 7α-Me with the C-9 or C-14 hydrogens by skewing of ring B gives rise very quickly to new and severe interactions of the Me hydrogens with the C-15α hydrogen, and any skewing of this nature must be very slight indeed. Whilst the 7α-methyl-C-9–C-14 hydrogen interactions suggest that the 7α-Me destabilizes the 6-oxo-3α,5α-cyclo-system to some extent, it is unlikely to be very strained, and the conformation of ring B in this isomer is almost certainly the same as in the parent ketone, possibly even more rigidly locked into the semi-chair form than in the latter.

In the 7β-Me case, skewing of ring B will effectively reduce the interaction between the Me hydrogen atoms and those at C-15, and will only replace these strains by those involved in changing the ring B conformation to "boat", as already discussed. Whilst the latter effect is destabilizing, a lowering of potential energy is predictable from increased orbital overlap of the ketone and the cyclopropyl ring. The relative magnitudes of these effects is not readily obtained, but it is likely that destabilization will finally result.

If the applications of these conformational changes are considered in relation to rotatory dispersion effects, predicted on the basis of the Octant Rule, we find:

a. In the 7α-Me case, the Me group is placed in the Rear lower right octant (RLR, positive) (Fig. 2). An axial Me group alpha- to a keto-group in a conformationally

rigid 6-membered ring is known to affect the Cotton amplitude by ca 30–40 units,[10] and in this case would serve to reduce the negative Cotton effect of the parent ketone by this amount.

b. In the 7β-Me case, even if ring B be heavily skewed, the slight shift of the semi-equatorial 7-Me group into the Rear upper right octant (RUR, negative; Fig. 3), would be more than outweighed by the effect of moving C-4 into the Rear upper left octant (RUL, positive) and the main portion of the steroid skeleton into the Rear lower right octant (RLR, positive). In view of the involvement of the cyclopropyl ring it is not possible to predict the type of Cotton effect in this case, other than that it should markedly differ from that produced by the 7α-Me isomer.

The observed Cotton effects of these compounds (I, II and III of series a, b and c) are found to have the following average magnitudes:

$$\text{I } a = -131 \text{ units}; \qquad \text{II } a = -21 \text{ units}; \qquad \text{III } a = -100 \text{ units}.$$

It is therefore clear that compounds III give rise to Cotton effects in agreement with prediction (a), whereas those of class II give results far removed from the latter forecast. Accordingly, the formulations of II and III as 7β-methyl- and 7α-methyl-6-oxo-3α,5α-cyclo-steroids are fully justified.

The effect of α-alkylation upon the absorption spectra of saturated cyclohexanones in more or less rigid conformations does not appear to have been the subject of systematic study, and this applies to both the $n \rightarrow \sigma^*$ and $n \rightarrow \pi^*$ transitions. The effect of α′-methylation of α,β-unsaturated cyclohexanones is exemplified by the K-band spectra of 2α-Me (equatorial) and 2,2-dimethyl derivatives of testosterone,[11] λ_{max} at 241 mμ (in 96% ethanol) remaining unchanged with respect to the parent enone. It is therefore highly unlikely that the electronic effect of a 7-Me group upon the low wavelength absorption band of the 6-oxo-3α,5α-cyclo system will be detectable, whatever the configuration of the Me group. In fact, 7β-methylation is observed to give rise to a shift of λ_{max} ($n \rightarrow \sigma^*$) from 210–213 mμ, accompanied by a small but definite increase in band intensity, whereas 7α-methylation has virtually no effect upon the absorption characteristics of this band. This suggests that the conformational change in ring B induced by the introduction of a 7β-Me substituent very slightly increases the degree of conjugation of the cyclopropyl and CO groups.

The effect of 7-methylation upon the $n \rightarrow \pi^*$ transition of the 6-oxo group in these compounds is even less clear and in view of the absence of reliable information from suitable model compounds, no conclusions of any real value can be drawn from our data.

Dipolar interaction of the 6-oxo group with other keto-groups, in 6-oxo-3α,5α-cyclosteroids. Table 1 includes ORD data for 6-oxo-3α,5α-cyclosteroids which also contain other keto-groups, at either C-17 or C-20, where the possibility arises of interactions between coplanar elements of the electronic dipoles, causing in turn deviations from strict additivity of the individual Cotton effects of the two keto-groups involved. In view also of the distortion of ring B in the 7β-methylated derivatives, as discussed above, it is likely that different interactions will occur in the case of those 6-oxo-3α,5α-cyclosteroids possessing either no C-7 substituents or a 7α-Me substituent, on the one hand, and those with a 7β-Me substituent, on the other. In the 17-keto-substituted case (Id, IId and IIId) this effect is very marked, the dipolar

interaction resulting in a decrease in magnitude of the negative Cotton amplitudes by 50, 4 and 23° respectively.

In the case of steroids with a 17β-acetyl side-chain (I and IIe and f) the effects of the second keto-group upon the Cotton amplitudes of the 6-oxo group are decreases of ca. 2 and 20° (no compounds III were obtainable in these series). These changes are calculated on the basis of deviation from simple additivity of the 6-oxo-3α,5α-cyclo Cotton effect (observed in absence of other keto-groups in the same molecule) and of the Cotton effect of the other keto-component, obtained from the ORD curves of steroids containing the latter group together with a 3β-acetoxy- or hydroxy (5α or 5-ene) system, as the total number of functional groups in the steroid skeleton.

From the results it is probable that the 6-oxo-3α,5α-cyclopropyl system exerts an appreciable dipolar effect at most of the substitution sites in a steroid nucleus.

TABLE 2. C-6-CARBONYL STRETCHING FREQUENCIES (CCl_4 SOLN) AND NMR DATA OF 6-OXO-3α,5α-CYCLOSTEROIDS, AND THEIR 7-METHYL DERIVATIVES.
(Angular Me, C-7 Me- and cyclopropyl proton resonance data only). (Chemical Shifts on Tau scale, referring to TMS as internal standard, in $CDCl_3$).

Compound	ν6 C=O (cm^{-1})	Δν (cm^{-1})	NMR chemical shifts, etc.				
			C-19H	C-18H	C-7Me(H)	(c/s) $J_{7\text{-Me}}$	C-3αH
Ia	1690	—	8·975	9·200	—	—	9·3 (br. s)
IIa	1676	−14	8·943	9·166	8·80	6	*
IIIa	1689	−1	8·989	9·205	8·94	7	9·40 (br. s)
Ib	1691	—	8·980	9·160	—	—	9·28 (br. s)
IIb	1674	−17	8·950	9·125	8·79	6	*
IIIb	1690	−1	8·985	9·155	8·95	7	ca 9·4 (m)
Ic	1689	—	8·915	9·080	—	—	9·50 (br. s)
IIc	1675	−14	8·95	9·07	ca. 8·76	*	*
IIIc	1690	+1	8·980	9·093	8·95	7	ca 9·4 (m)
Id	1693	—	8·943	9·063	—	—	ca 9·3 (m)
IId	1678	−15	8·925	9·045	8·73	6	*
IIId	1690	−3	8·970	9·075	8·89	7	ca 9·4 (m)
Ie	1693	—	8·988	9·320	—	—	*
IIe	1677	−16	8·958	9·300	8·80	6	*
If	1692	—	8·975	9·313	—	—	*
IIf	1678	−14	8·947	9·290	8·79	7	*

* Signifies no identifiable bands.

Carbonyl stretching frequencies of 6-oxo-3α,5α-cyclosteroids

The principal feature in the IR spectra of these compounds is the C=O stretching band, which is lowered in frequency relative to that in the spectra of the corresponding 5α,6-oxo-steroids by ca. 24 cm.[12] This bathochromic shift is due, partly at least, to the electronic interactions of the carbonyl and cyclopropyl groups, and is typical of α-cyclopropyl ketones in general.[3,13] Examination of the C=O stretching

frequencies listed in Table 2 shows that only in the case of 7β-methyl-6-oxo-3α,5α-cyclosteroids is this parameter further affected by alpha-methylation ($\Delta^8 = -13$–$-16\ cm^{-1}$), a 7α-Me substituent having a negligible effect. Equatorial alpha-methylation of saturated cyclohexanones, where such a dipole as is possessed by a Me group is likely to exert maximal effect upon the C=O stretching force constant, has been shown in the case of 10-methyl-2-decalone and its 1-Me derivative[14] to cause no change in the C=O frequency^{-1}. Obviously the large effect noted in 7β-methylated-6-oxo-3α,5α-cyclosteroids arises in part from sources other than dipole-dipole interaction, and these must include steric destabilization of ring B and enhanced electronic interactions of the cyclopropyl and carbonyl functions, as evidenced by the parallel change in wavelength of the main UV absorption band.

Proton magnetic resonance spectra of the 6-oxo-3α,5α-cyclosteroids

(a) C-10 *and* C-13 *methyl proton singlets.* By use of the data of Zürcher[15] and others,† together with those of Table 2, the incremental chemical shifts (δ-values measured downfield), induced by formation of a 6-oxo function and a 3α,5α-bond from a standard 5α,14α-steroid skeleton, are found to be as follows:

Function	C-19H	O-18H	(ppm $CDCl_3$ solvent)
6-oxo-3α,5α-cyclo	+0·25	+0·08	
7β-Methyl-6-oxo-3α,5α-cyclo	+0·26	+0·10	
7α-Methyl-6-oxo-3α,5α-cyclo	+0·23	+0·08	

Thus the incremental chemical shift of the C-19 protons in the basic 6-oxo-3α,5α-cyclo system is considerably greater than might at first be expected from studies of 6-oxo-5α-steroids[15] and 3α,5α-cyclo-6-acetates[17] individually. The additional δ-values caused by 7-methylation are too small for serious discussion, but the trend in magnitude of these figures is that predictable on the basis of changing diamagnetic shielding by the CO group, which in the case of 7β-methylation, is tilted even further from the C-10 methyl than in the parent ketone.

(b) C-7-*methyl protons.* In these compounds the 7β-Me protons resonate ca. 0·2 ppm downfield from the position of the 7α-Me proton resonance, the shift being fully consistent with the change of the Me conformation from axial to semi-equatorial in an alpha-methyl cyclohexanone. The resonance in each case is a doublet, J ca. 6–7 c/s, but observation is rendered difficult owing to overlap with the other, tertiary, Me proton signals in the region 8·6–9·1 T.

(c) *Cyclopropyl protons.* Discrete signals attributable to the 3-membered ring protons are observed only in the cases of 7α-methyl-6-oxo-3α,5α-cyclosteroids and their unsubstituted parent ketones. The 6-oxo group in the 7β-methylated ketones causes the signals to move downfield to points below the C-13 Me protons, the signals being just discernable in some cases. The cyclopropyl signal, a multiplet or broad singlet at 40 Mc/s at ca. 9·4 T, is one proton in strength, and probably arises from the C-3 β hydrogen. A signal from this proton would undergo a downfield

† δ C-19H = −0·020 ppm δ C-18H = −0·082 ppm for the 17α-acetoxy-17β-acetyl system ($CDCl_3$ solution).[16]

shift if the conformation of ring B changed to move the CO group over the α-face of the cyclopropyl ring (Fig. 1).

The changes in the NMR spectra of 6-oxo-3α,5α-cyclosteroids caused by 7-methylation, whilst very small in magnitude, are in each case in excellent qualitative agreement with predictions based simply on the known magnetic anisotropy of a saturated CO group,[18] and on the configurational assignment of the C-7 Me substituents, based upon the ORD data. They provide effective further evidence from the validity of these assignments.

EXPERIMENTAL

ORD spectral determinations were carried out by means of a Bellingham Bendix "Polarmatic 62" spectropolarimeter, using "spectro-grade" methanol as solvent. Other details of instrumentation and procedure are as described in Part XLIX of this work.[1]

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