Synthesis and Carbon-13 Nuclear Magnetic Resonance Studies of Δ^5 and Saturated 4,4-Disubstituted 3-Ketosteroids

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A number of Δ^5-4,4-dialkyl-3-ketosteroids were synthesized by alkylation of steroidal 4-en-3-ones via their enolate anions. Carbon-13 nuclear magnetic resonance spectra of these compounds were measured and assigned. Predicted carbon shifts show fairly good agreement with the observed values in the estrenone series. The deviations for androstenones and cholestenones were interpreted in terms of conformational changes in the steroid skeleton which arise from nonbonded 1,5-interactions (δ effect) between the 19-methyl and the 4,4 substituents. Comparison of the carbon shifts for 4,4-dimethyl-3-ketosteroids with the appropriate Δ^5 derivatives did not indicate any "conformational transmission" in the latter compounds. The observed carbon shift differences for C-14 seem to arise solely from the presence of the 19-methyl group.

The pioneering study of Roberts et al.[1] on the ^{13}C NMR of steroids has led to considerable interest in this area. These studies have been included in a number of excellent reviews.[2-4] Our present study on the ^{13}C NMR of Δ^5 and saturated 4,4-dialkyl-3-ketosteroids was undertaken in order to examine the effects of alkyl substituents on the conformation of rigid steroid systems and as part of a program involved in the synthesis of spiro steroids.[5]

Results and Discussion

The carbon shielding data for compounds **1-20** are collected in Table I. For each compound both noise and off-resonance decoupled spectra were obtained to distinguish the carbon types. Gated decoupled spectra were found to be of little use due to large first- and second-order carbon–hydrogen coupling.[1] Unequivocal assignments of chemical shifts (δ) to various carbons resulted from consolidated application of off-resonance decoupling, Lanthanide shift reagents, deuteration studies, and comparison with the data for the model compounds.

Since our values for C-1 and C-7 in **13** differed from those of Taylor et al.[6] for estr-5(10)-ene-3,17-dione, a shift reagent study on their compound indicated that their assignments for C-1 should be interchanged with C-7 and C-6 with C-12.

The analysis of the ^{13}C NMR data for Δ^5-3-ketosteroids **5a–e** through **8a–e** may be divided into two parts: (a) the effect of a Δ^5 double bond on the steroid skeleton and (b) the additional effect of 4,4-disubstitution, assuming that the theory of additivity for ^{13}C chemical shifts holds true.

The unsubstituted Δ^5-3-keto systems (**5a–8a**) were selected as model compounds. To predict the ^{13}C shifts for these systems the Δ^5 substituent parameters for a steroid[2] were added to the chemical shifts of the appropriate 3-ketosteroids.[2] The previously unavailable data for 17β-hydroxy-5α-estr-3-one (**17a**) and the corresponding 5β epimer **17c** were determined and assigned by comparison with the ^{13}C NMR data for *trans*- and *cis*-bicyclo[4.4.0]-decan-3-ones **16a**[7] and **16b**.

Comparison of carbon shifts for Δ^5-3-ketosteroids **6a–8a** with those for 3-ketosteroids[2] indicates major changes in C-1 through C-10 and C-19. These changes arise mainly due to the conformational difference that results from the introduction of a Δ^5 double bond in a 3-ketosteroid. Dreiding models for compounds **6a–8a** show the A ring to have a flattened or skewed chair conformation and B ring to have a half-chair conformation, whereas in 3-ketosteroids the A and B rings seem to prefer normal chair conformations. This difference is reflected by the poor agreement between the observed and predicted shifts for some of the A and B ring carbons (Tables I and II). Since the substituent parameters used for predicting carbon shifts have been derived from the shift differences between Δ^5-cholestene and cholestane,[2] the differences may also be due to the disregard of certain additional interactions that are characteristic of a Δ^5-3-keto functionality. The ultraviolet studies of β,γ-unsaturated ketones[8] and Δ^5-3-

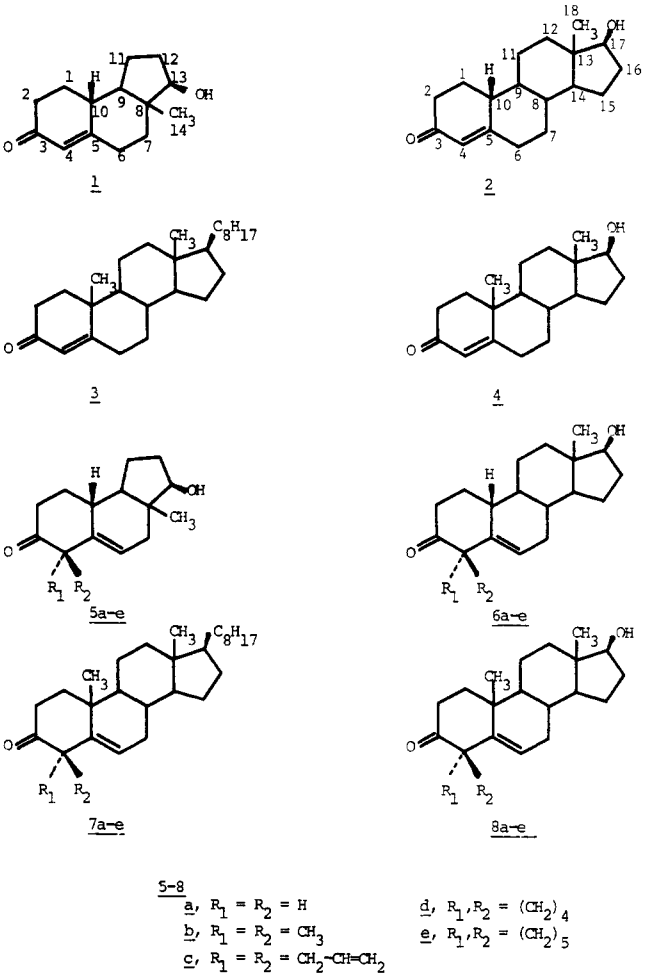

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Table I. ^{13}C NMR Chemical Shifts, δ

compd	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	27.3	36.7	199.6	125.0	166.7	36.0	31.5	43.1	50.7	38.4	23.4	30.3	80.5	10.4		
2	27.0	36.6	198.6	124.8	166.2	35.6	31.3	41.0	49.2	42.9	26.6	37.1	43.4	48.9	23.6	30.7
3	35.7	33.9	198.9	123.6	171.0	32.9	32.1	35.7	53.8	38.6	21.0	39.4	42.4	55.9	24.1	28.1
4	36.1	34.1	198.0	124.2	170.4	32.8	32.2	36.1	54.6	39.0	21.2	37.1	43.2	51.1	23.8	30.7
5a	29.8[a]	40.3	209.7	49.4	134.6	122.4	38.1	42.2	47.3	39.1	23.9	30.2[a]	81.0	10.8		
5b	30.1[a]	37.1	214.2	51.0	144.1	119.4	38.4	41.6	47.8	36.6	24.1	30.2[a]	81.1	10.6		
5c	26.7	39.4	213.0	58.0	139.3	123.1	38.7	41.5	47.5	38.5	24.0	30.5	81.5	11.0		
5d	29.8	38.0	212.6	63.3	142.2	119.6	38.6	41.8	47.9	37.8	24.2	30.5	81.3	10 7		
5e	30.0[a]	37.2	214.8	55.6	143.9	121.0	38.7	41.6	48.4	35.9	24.3	30.5[a]	81.4	10.5		
6a	30.1[a]	40.5	209.4	50.2	135.1	122.5	30.6[a]	36.5	45.2	42.6	27.0	36.5	43.0	50.2	23.1	30.3[a]
6b	30.6[a]	37.3	214.3	51.0	144.3	119.6	31.0	36.0	45.9	39.8	27.0	36.5	42.9	50.3	23.1	30.3[a]
6c	27.8	39.3	213.3	57.8	139.4	122.8	30.7[a]	36.1	45.3	41.7	26.8	36.5	43.0	50.4	23.2	30.4[a]
6d	29.3	38.2	213.1	63.4	142.5	119.6	30.6	36.2	46.0	41.1	27.1	36.5	43.1	50.4	23.2	30.5
6e	29.8	37.4	215.1	55.5	143.8	121.6	30.8	36.1	46.6	36.9	27.2	36.5	43.0	50.3	23.1	30.3
7a	36.9	37.6	209.9	48.3	138.5	122.8	31.8	31.8	49.2	36.9	21.4	39.5	42.4	56.6	24.3	28.2
7b	32.3[a]	33.7	216.0	48.7	149.9	119.9	31.9[a]	31.3	49.1	37.2	21.4	39.6	42.5	56.9	24.2	28.3
7c	31.3[a]	34.9	212.4	57.0[a]	144.3	122.3	31.7[a]	31.3	49.1	36.3	21.4	39.6	42.4	56.8[a]	24.2	28.3
7d	32.9	34.0	214.0	60.7	151.7	119.5	32.0	31.5	49.4	37.3	21.5	39.6	42.5	57.0	24.2	28.3
7e	32.8	35.1	217.0	53.3	151.3	120.4	32.1	31.2	49.3	37.6	21.5	39.6	42.2	56.9	24.2	28.3
8a	36.8[a]	37.5	210.0	48.2	138.6	122.5	31.4[a]	31.6[a]	49.3	36.9[a]	21.0	36.5	42.8	51.2	23.4	30.2
8b	32.1	33.7	216.6	48.7	149.9	119.6	31.3	31.3	49.1	37.1	20.9	36.6	42.8	51.4	23.3	30.5
8c	31.2	34.8	213.6	56.8	144.1	121.9	31.2	31.2	49.0	36.2	20.9	36.5	42.7	51.4	23.3	30.1
8d	32.8	33.9	214.3	60.6	151.7	119.3	31.5	31.5	49.5	37.3	21.1	36.7	42.9	51.7	23.4	30.6
8e	32.7	35.3	216.5	53.4	151.5	120.3	31.7[a]	31.4[a]	49.7	37.7	21.2	36.8	43.0	51.8	23.4	30.8
9	22.6	20.4	65.1		150.6	27.9	26.8	37.8	136.3	105.6	112.9	38.5	41.5	46.7	23.6	30.3
10	26.6	28.6	151.1	106.2	137.2	113.4	31.1	36.8	44.5	42.2	27.3	36.8	43.1	50.9	23.3	30.7
11	25.1	33.6	149.1	105.1	142.0	114.0	32.1	31.5	48.9	35.4[a]	21.3	39.6[a]	42.5	57.2	24.3	28.3
12	25.0	33.5	149.0	104.9	141.9	113.5	31.6[a]	31.5[a]	48.9	35.3	20.8	36.7	42.8	51.6	23.4	30.5
13	27.4	39.0	211.1	44.7	126.4	30.7	25.2	39.2	46.2	131.1	26.5	37.1	43.6	49.8	23.0	30.7
14	27.3	38.8	211.4	45.0	129.3	30.6	25.7	38.1	127.7	136.1	119.3	38.8	41.5	47.0	23.8	30.3[a]
17a	30.0[a]	40.9	211.5	48.4	45.5	33.7	30.4[a]	41.0	47.7	43.5	25.7	36.6	42.9	49.8	23.1	30.1[a]
17b	31.2	37.4	216.4	47.7	52.2	25.8	30.6[a]	40.8[a]	48.9	40.7[a]	25.8	36.7	43.0	50.0	23.2	30.3[a]
17c	27.6	36.3	212.7	42.8	38.5	30.5[a]	25.0[a]	39.8	41.5	38.2	25.5[a]	36.7	43.1	50.0	23.2	30.2[a]
18a	38.6	38.1	211.5	44.6	46.8	28.9	31.3	35.5	54.0	35.8	21.1	36.7	43.0	50.9	23.4	30.5
18b[b]	38.2	34.6	216.9	47.7	55.8[a]	22.5	32.2	35.5	56.1[a]	36.6	20.7	36.8	43.0	51.2	23.4	30.6
19	25.7	36.1	199.0	128.5	159.2	30.8[a]	31.2[a]	40.7	50.0[a]	43.6	26.1	36.6	43.1	49.7[a]	23.2	30.3[a]
20	35.0[a]	33.6	198.8	127.7	163.9	27.6	31.3	35.4[a]	54.4	39.0	20.7	36.5	42.8	50.6	23.3	30.2

compd	17	18	19	20	21	22	23	24	25	26	27	β1′	α1′	β2′	α2′	3′
1											22.8					
2	81.4	11.4														
3	56.1	12.0	17.4	35.7	18.7	36.1	23.8	39.6	27.9	22.5						
4	81.3	11.3	17.3													
5b												28.7	21.8			
5c												45.8	40.5	135.0	133.5	118.0 (β) 117.1 (α)
5d												39.6	29.5	24.5	24.2	
5e												37.2	31.6	23.3	22.8	26.3
6a	81.4	11.0														
6b	81.4	11.0										28.6	21.7			
6c	81.7	11.0										44.8	39.3	135.1	133.3	117.9 (β) 117.0 (α)
6d	81.6	11.1										39.6	31.0	24.4	24.1	
6e	81.6	11.1										38.9	32.9	23.0	22.7	26.4
7a	56.1	11.9	19.2	35.8	18.7	36.2	23.8	39.7	28.0	22.6	22.8[a]					
7b	56.3	12.0	19.4	35.8	18.8	36.3	24.0	39.9	28.0	22.6	22.8[a]	30.2	27.4			
7c	56.3	12.0	19.3	35.8	18.8	36.2	23.9	39.9	28.0	22.6	22.8[a]	47.5	41.3	135.1	133.7	117.8 (β) 117.2 (α)
7d	56.3	12.0	20.0	35.8	18.8	36.3	24.0	40.0	28.0	22.6	22.8[a]	42.1	38.8	26.8	26.0	
7e	56.3	12.0	19.9	35.8	18.7	36.3	23.9	39.9	28.0	22.6	22.8[a]	39.2	34.9	23.5	23.3	25.9
8a	81.4	11.1	19.2													
8b	81.7	11.0	19.4									30.2	27.3			
8c	81.4	11.1	19.3									47.5	41.1	135.0	133.5	117.9 (β) 117.3 (α)
8d	81.7	11.0	20.0									42.1	38.7	26.8	26.0	
8e	81.8	11.0	20.0									39.1	35.1	23.5	23.3	25.7
9	81.4	11.0														
10	81.9	11.0										65.6		20.6		23.0
11	56.4	12.0	19.1	35.8[a]	18.7	36.3	23.9	39.9[a]	28.1	22.6		65.6		20.9		23.1
12	81.8	11.1	19.1									65.5		20.8		22.9
13	81.7	11.3														
14	81.6	11.3														
17a	81.2	11.1														
17b	81.7	11.1										20.4	22.0			
17c	81.4	11.2														

Table I (*Continued*)

compd	17	18	19	20	21	22	23	24	25	26	27	β1′	α1′	β2′	α2′	3′
18a	81.7	11.2	11.5													
18b[b]	81.7	11.2	14.0									21.7	26.0			
19	81.4	11.2										10.8				
20	81.2	11.1	17.7									11.1				

[a] Assignments can be interchanged. [b] A and B ring carbon assignments match closely to related system in ref 46.

Table II. Predicted ^{13}C NMR Chemical Shifts, δ

compd	1	2	3	4	5	6	7	8	9	10	19
5b	29.8	36.9	214.1	53.0	149.0	119.0	38.1	42.2	47.3	35.7	
5d	29.8	37.8	212.5	64.7	147.6	120.2	38.1	42.2	47.3	36.9	
5e	29.8	36.9	214.4	56.5	146.6	117.9	38.1	42.2	47.3	34.6	
6a	31.2	41.2	212.7	52.2			30.1	37.3	43.5	44.8	
6b	30.1	37.1	213.8	53.8	149.5	119.1	30.6	36.5	45.2	39.2	
6d	30.1	38.0	212.2	65.5	148.1	120.3	30.6	36.5	45.2	40.4	
6e	30.1	37.1	214.1	57.3	147.1	118.0	30.6	36.5	45.2	38.1	
7a	39.7	38.4	212.4	48.4			31.4	31.7	49.6	36.9	18.7
7b	36.9	34.2	214.3	51.9	152.9	119.4	31.8	31.8	49.2	33.5	19.2
7d	36.9	35.1	212.7	63.6	151.5	120.6	31.8	31.8	49.2	34.7	19.2
7e	36.9	34.2	214.6	55.4	150.5	118.3	31.8	31.8	49.2	32.4	19.2
8a	39.8	38.4	212.7	48.4			31.0	31.8	49.8	37.1	18.8
8b	36.8	34.1	214.4	52.0	153.0	119.1	31.4	31.6	49.3	33.5	19.3
8d	36.8	35.0	212.8	63.5	151.6	120.3	31.4	31.6	49.3	34.7	19.3
8e	36.8	34.1	214.7	55.3	150.6	118.0	31.4	31.6	49.3	32.4	19.3

ketosteroids[9] show an enhanced extinction coefficient and a red shift of ~20 nm for the long wavelength absorption maximum and point to the presence of some electronic interaction between the carbonyl and the double bond. In other words these interactions may be a contributing factor and partly responsible for the observed anomalies.

The data for 4,4-dialkyl derivatives suggest that 4,4-dialkylation substantially influences only the carbons of A and B rings and, henceforth, the discussion will be confined to C-1 through C-10.

With the knowledge of the carbon shifts for the model compounds **5a–8a** and *gem*-dialkyl and spiro substituent parameters from cyclohexanones,[10] it was possible to predict the shifts for the carbons in the vicinity of the substituent in **5b,d,e–8b,d,e**. These values are summarized in Table II. Examination of the data shows good agreement between the predicted and observed δ values for C-2 and C-7 to C-9 in all four sets of compounds. Chemical shifts for the rest of the carbons of the A and B rings show a difference of varying magnitude from the predicted values. The disagreement appears to be worse in cholestenones **7** and androstenones **8**. Before attempting to explain these differences it is appropriate to point out that the substituent parameters were derived from cyclohexanones. In these compounds the carbons of the cyclohexane ring experience averaged effects from both the substituent carbons due to rapid interconversion of the two chairs. In the case of a steroid, however, the molecule is rigid and such interconversion of the A ring is not possible. This makes the two substituent carbons nonequivalent, thereby causing the substituent effects of a different magnitude.

It is interesting to note that with the exception of sp^2 carbons of the olefin, for tetrahydrobenzohydrindanes **5**[11] and estrenones **6**, only C-4 and C-10 show appreciable disagreement in the predicted and observed δ values. For both of these carbons, overestimation of the substituent effect is observed. For C-5 and C-6, the diversity of the two values is not surprising, since the exact interactions of different groups with the double bond is not known and β and γ substituent parameters used to compute the predicted carbon shifts were for sp^3 hybridized carbons. The nonequivalence of C-4α1′[12] and C-4β1′[12] for the substituent commented above is reflected by the different δ values for the two carbons.

In cholestenones **7b,d,e** and androstenones **8b,d,e**, the deviations from the predicted chemical shift values are much larger, especially for the A ring carbons. Since these compounds, differ from estrenones **5** and **6** by only a 19-methyl group (except for the side chain in cholestenones), it is reasonable to assume that the presence of this group in these compounds is responsible for the observed deviations. Nonbonded interactions between the 19-methyl and 4β-alkyl substituent are known to cause the deformation of the A ring from a normal chair to a skew boat. The evidence in support of such conformational deformation comes from ultraviolet absorption,[9] circular dichroism,[9] optical rotatory dispersion,[9] and proton magnetic resonance studies.[9,13] A recent X-ray analysis of 17β-(iodoacetoxy)-4,4-dimethylandrost-5-en-3-one[14] provides a further proof for the skew boat conformation of the A ring with C-3 and C-10 above the C-1, C-2, C-4, and C-5 plane. In addition, it reveals the conformation of the B ring to be a half-chair which is very similar to the half-chair observed for **7a** and **8a**. This similarity does account for a much closer correlation between the predicted and observed chemical shift values for the ring B carbons than those for the A ring. Due to the lack of data for *gem*-diallyl-substituted cyclohexanones, this group of compounds could not be included in the discussion for 4,4-disubstituted derivatives. However, this substituent follows a similar pattern, i.e., paramagnetic α, β, and δ effect and diamagnetic γ effect.

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(11) Compound 1 and its derivatives **5** were considered as des-A-estrenes instead of tetrahydrobenzohydrindanes in this study.[34]
(12) C-4α1′ means the first carbon (1′) of the spiran ring that is attached α to C-4.
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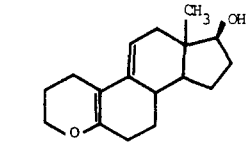
Table III. Physical and Analytical Data

compd[a]	crystalline form	solvent	% yield	mp,[b] °C	molecular formula	mol wt	m/e	calcd C	calcd H	found C	found H
5a	semisolid[c]		70		$C_{14}H_{20}O_2$	220.1473	220.1463				
5b	white needles	hexane	81	119-120	$C_{16}H_{24}O_2$	248	248	77.38	9.74	77.60	9.82
5c	semisolid[c]		58		$C_{20}H_{28}O_2$	300.2089	300.2066				
5d	white needles	hexane	73	103-104	$C_{18}H_{26}O_2$	274	274	78.79	9.55	78.52	9.28
5e	white needles	benzene-hexane	72	148-149	$C_{19}H_{28}O_2$	288	288	79.12	9.78	79.41	9.98
6a	white needles	acetone-hexane	64	105-106	$C_{18}H_{26}O_2$	274.1933	274.1930				
6c	white needles	ether-hexane	46	109-111	$C_{24}H_{34}O_2$	354.2559	354.2395				
6d	white needles	ether-hexane	74	198-201	$C_{22}H_{32}O_2$	328.2402	328.2395				
6e	white needles	benzene-hexane	78	118-119	$C_{23}H_{34}O_2$	342	342	80.64	10.01	80.34	9.81
7c	oil[c]		52		$C_{33}H_{52}O$	464.4018	464.3396				
7e	white needles	ether-hexane	72	174-176	$C_{32}H_{52}O$	452	452	84.88	11.58	84.46	11.36
8c	white needles	acetone-water	68	108-109	$C_{25}H_{36}O_2$	368.2715	368.2729				
8d	colorless needles	benzene-hexane	82	174-175	$C_{23}H_{34}O_2$	342	342	80.64	10.01	80.96	10.04
8e	white crystals	benzene	73	188-191	$C_{24}H_{36}O_2$	356	356	80.85	10.18	80.90	10.32
9	white needles	ether	28	74-76	$C_{17}H_{24}O_2$	260.1776	260.1768				
10	colorless crystals	ether	25	155-156	$C_{21}H_{30}O_2$	314	314	80.21	9.62	80.12	9.75
11	white crystals	hexane	20	138-139	$C_{30}H_{48}O$	424	424	84.84	11.39	84.62	11.56
12	colorless crystals	ether	24	209-211	$C_{22}H_{32}O_2$	328	328	80.44	9.82	80.26	10.07

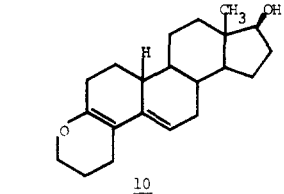
[a] Spectral data consistent with structure. [b] Melting points are uncorrected. [c] Compounds are known to be unstable and they either polymerize or go back to conjugated material.

As commented earlier, the α and β substituent resonances occurred at different magnetic fields due to the rigid geometry of the A ring in a steroid. In estrenones **5** and **6**, the low-field signals were assigned to β or axial substituent carbon(s) and high-field signals to α or equatorial. In cholestenones **7** and androstenones **8**, however, the assignments were reversed. These assignments were based on the α and β-carbon assignments of the 4,4-dimethylestrenone **6b** and 4,4-dimethylandrostenone **8b** via their 4-methyl-d_3 derivatives.[15] In estrenones where ring A prefers a normal chair conformation,[14] Dreiding models show the C-4α1′ carbon is eclipsed with the 3-carbonyl oxygen and almost eclipsed with the vinylic 6-H. The C-4β1′ carbon experiences similar γ interactions from C-2 and C-10 hydrogens. However, the distances involved for the two substituents are of different magnitude. For the equatorial C-4α1′ carbon the distances are a lot closer than the corresponding C-4β1′ axial carbon atom. Since the shielding effect due to γ interactions is a function of the interatomic distance as well as the angle of the two interacting groups,[16] the C-4α1′ experiences greater shielding than C-4β1′ and occurs at higher field. In cholestenones **7** and androstenones **8**, the A ring is not a normal chair but is a skew boat[14] as a consequence of 1,5-interactions (δ effect) between the 19-CH_3 and 4β substituent. Such a conformation of the A ring caused a deshielding of both axial and equatorial groups relative to substituted cyclohexanones.[10] Interestingly, while the C-4α1′ carbon shows a similar paramagnetic shift (8.4 to 12.6 ppm), the C-4β1′ carbon shows a net upfield shift of 1.3 to 4.00 ppm relative to C-4β1′ carbon in estrenones. The paramagnetic shift arising from steric interactions between 1,5-substituents (δ effect) has been reported in the literature.[17,18] However, the systems which were examined had the two substituents in a fixed disposition. In the present study the system is flexible and can achieve a favorable geometry to minimize steric interactions. The above-mentioned paramagnetic shift of the α carbon and diamagnetic shift of the β carbon in **7** and **8** relative to **6** can be explained in terms of Engelhardt's[19] suggestion regarding the origin of steric effects. For the C-4α1′ carbon the more important 1,3-interactions with the 3-keto oxygen and vinylic 6-H in **6** are replaced by less important γ interactions with the C-2 in **7** and **8**, thereby causing a deshielding effect. For the C-4β1′ carbon, however, the situation is reversed. The γ interactions of the C-4β1′ carbon, however, the situation is reversed. The γ interactions of the C-4β1′ are increased due to eclipsing with the 3-keto oxygen and vinylic 6-H in **7** and **8** relative to weaker interaction with C-2 and C-10 in **6**. This in conjunction with the opposite δ effect, if any, is responsible for the shielding.

Cyclic Enol Ethers 9–12. The chemical shift assignments made for 17β-hydroxyestra-5(10)-en-3-one (**13**) were used as a basis for the assignment of 17β-hydroxyestra-5(10),9(11)-dien-3-one (**14**), which itself acted as a model compound for 17β-hydroxy-4-oxaestra-5(10),9(11)-diene (**9**). Due to the expected similarity in the geometry of rings



9



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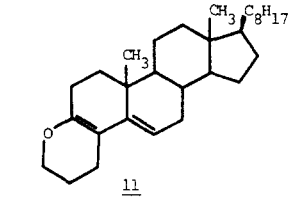

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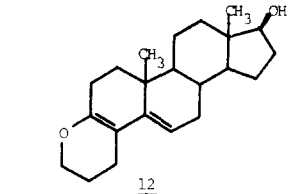

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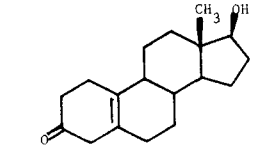
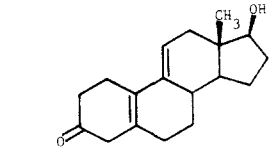


13



14

(15) On the basis of literature precedence[29] the methyl-d_3 group was assigned β in methyl-d_3 **6b** and **17b** and α in methyl-d_3 **8b** and **18b**.
(16) Grant, D. M.; Cheney, B. V. *J. Am. Chem. Soc.* **1967**, *89*, 5315.
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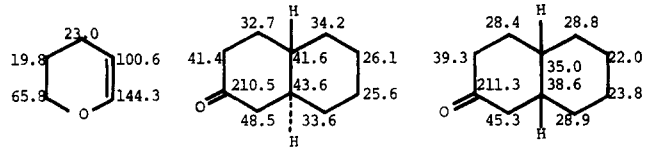
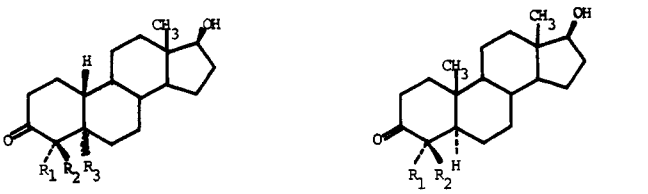
B, C, and D in **13**, **14**, and **9**, the assignment of the sp^3 carbon resonances for these rings was straightforward. The carbons of the A ring and the diene were different due to the conformational differences resulting from the 4-oxa function in **9** and the 4-CH_2 in **14**. In addition, the enolic ether is capable of releasing electrons toward the diene. This delocalization induced the expected diamagnetic shielding for C-10 and C-11. The δ values for C-1 to C-3 were similar in magnitude to those for dihydropyran **15**. The total assignment for the spectra of compounds **10–13** was achieved by comparison with carbon shifts of **9** (for 4-oxa and A rings) and with deconjugated enones **5–8a** (B, C, and D rings).

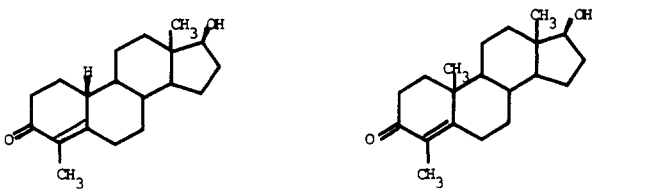
Conformational Transmission. Recent X-ray studies by Ferguson et al.[14] on 4,4-dimethyl-Δ^5-3-ketosteroids **6b** and **8b** and their saturated analogues **17b** and **18b** have



15 16a 16b



17a-c 18a-b



19 20

17-18
a, $R_1 = R_2 = H$, $R_3 = \alpha$-H
b, $R_1 = R_2 = CH_3$, $R_3 = \alpha$-H
c, $R_1 = R_2 = H$, $R_3 = \beta$-H

shown that the presence of a 5,6 double bond in **8b** affects the conformation of the complete steroid molecule and ring A in particular. This deformation of the A ring was transmitted to the D ring where the conformation is distorted away from a half-chair toward a C-13 envelope with C-13 above and C-14 below the C-15 to C-17 plane. We were interested in detecting this conformational transmission[20] by the use of carbon NMR. The comparison of the data for Δ^5-3-ketosteroids **6a** and **6b** with saturated steroids **17a** and **17b** indicated that the presence of a double bond at C-5 caused a diamagnetic shift of 2.0 ± 0.2 ppm for the carbonyl carbon. However, in the case of **8b** relative to **18b**, the expected 2.00-ppm shift difference is only 0.3 ppm and results from a change in the conformation of the A ring in going from the saturated steroid **18b** to Δ^5-steroid **8b**. The carbon shifts for C-11 to C-17 were essentially the same in substituted and unsubstituted saturated and 5,6-unsaturated steroids. There was a definite difference, however, for the C-14 δ value (1.0 ± 0.1 ppm) for estranes compared with androstanes, but this seemed to arise from the presence or absence of the 19-methyl group and not from 19-CH_3–4β substituent interactions. Thus, the use of ^{13}C NMR to observe conformational transmission effects in the D ring proved unsuccessful.

Conclusion

This study shows that substituent parameters from simpler systems are quite useful in predicting and assigning the carbon resonances.

Secondly, it demonstrates that significant conformational changes, such as those found in the A ring of **7b** and **8b**, caused by steric interactions can be determined by the use of carbon-13 NMR. The results agree with those obtained from X-ray analysis. However, very subtle conformational transmission effects noted by X-ray analysis were not detected by the use of ^{13}C NMR.

Experimental Section

Infrared spectra were measured with a Perkin-Elmer 137 sodium chloride spectrophotometer as KBr pellets. Elemental analyses for all new compounds were performed by Micro-Analysis, Inc., Wilmington, DE, and Galbraith Laboratories, Knoxville, TN. Proton NMR spectra were obtained in $CDCl_3$ solutions with Me_4Si as an internal standard, using a Perkin-Elmer R-32 operating at 90 MHz and a Varian XL-100 spectrometer. Carbon-13 NMR spectra were recorded on a Varian XL-100 instrument operating at 25.2 MHz, using a Nicolet NTCFT 1180 pulse system. Samples were measured in 5-mm tubes as 1.0 M solutions in deuteriochloroform with Me_4Si as internal standard and a Deuterium Pulse lock. All spectra were scanned from 0.0 to 240 ppm. Typical experimental parameters follow: sweep width 6000 Hz, sampling interval 100 μs, delay time 200 μs, pulse width 4 μs (25° flip), data table 16 384 points. Typically, 1024 scans were collected. Mass spectra were taken on an RMH-2 Hitachi-Perkin Elmer mass spectrometer at an ionization energy of 70 eV.

Synthetic Methods. Cholest-4-en-3-one (**3**),[21] 17β-hydroxy-4,4-dimethylestr-5-en-3-one (**6b**),[22] cholest-5-en-3-one (**7a**),[21] 4,4-dimethylcholest-5-en-3-one (**7b**),[23] 4,4-spirocyclopentylcholest-5-en-3-one (**7d**),[24] 17β-hydroxyandrost-5-en-3-one (**8a**),[25] 17β-hydroxy-4,4-dimethylandrost-5-en-3-one (**8b**),[22] $\Delta^{1,9}$-2-octalone,[26] *cis*-β-decalone (**16b**),[27] 17β-hydroxy-5-estran-3-one (**17a**),[30] 17β-hydroxy-4,4-dimethylestran-3-one (**17b**),[28,29] 17β-hydroxy-5β-estran-3-one (**17c**),[30] 17β-hydroxy-4,4-dimethylandrostan-3-one (**18b**),[31] 17β-hydroxy-4-methylestr-4-en-3-one (**19**),[22] and 17β-hydroxy-4-methylandrost-4-en-3-one (**20**)[22] were synthesized by

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methods described in the literature. *anti-trans*-1β-Hydroxy-8β-methyl-4,5-(4-oxo-1,2,3,4-tetrahydrobenzo)hydrindane (1) and 17β-hydroxyestra-5(10)-en-3-one (13) were either gifts or commercially available samples. 17β-Hydroxyestra-5(10),9(11)-dien-3-one (14) was available from another study.[5]

Deconjugated Enones (5a–8a).[29] The conjugated enone (0.2 g) was added to a solution of potassium (0.2 g) in *tert*-butyl alcohol (20 mL) (nitrogen atmosphere) and the mixture allowed to stir at 25 °C for 2 h. The resulting enolate anion was quenched with acetic acid (25 mL, 10%). Careful neutralization with aqueous potassium bicarbonate was followed by extraction with ether. The organic extract was washed with water and dried ($MgSO_4$) to give deconjugated enones. For physical data and analyses see Table III.

4,4-Dialkyl-Δ⁵-enones (5b–e through 8b–e). General Method. Enone (0.005 mol) was added in small portions to a stirred solution of potassium (0.78 g, 0.02 mol) in dry *tert*-butyl alcohol (50 mL) (nitrogen atmosphere). The mixture was refluxed for 15 min and cooled to room temperature. Alkyl halide (0.01 mol) was added and the mixture stirred for 15 min followed by 15 min reflux. Evaporation of *tert*-butyl alcohol under reduced pressure yielded a semisolid residue. This material was dissolved in methylene chloride and washed twice with 100-mL portions of sulfuric acid (5%) followed by water. The organic layer was dried ($MgSO_4$) and evaporated to yield the crystalline dialkyl derivative. The products from the reaction of 1,3-dibromopropane with enones 1–4, however, were viscous oils and were chromatographed on silica gel (100:1 ratio) using ethyl acetate–hexane mixtures as eluents. For the hydroxy derivatives (5, 6, and 8) 20% EtOAc–80% hexane and for cholestenes (7) 10% EtOAc–90% hexane mixtures were found suitable for elution. For physical data and analyses see Table III.

2,2-Dideuterio Derivatives.[33] Clean sodium (0.10 g) was dissolved in deuteriomethanol (10 mL) (nitrogen atmosphere). When the evolution of deuterium subsided, the 4,4-dialkyl derivative (0.10 g) was added and the mixture heated to boiling. After the addition of deuterium oxide (0.6 mL), heating was continued for an additional 1.5 h. Cooling afforded a crystalline deuterated compound which was washed with water and dried. Certain compounds did not form crystals and in such cases the mixture was evaporated and the residue obtained was extracted with ether. The ether extract was washed with a small amount of deuterium oxide, dried ($MgSO_4$), and evaporated to yield the 2,2-dideuterio compound in quantitative yield.

17β-Hydroxy-4α-trideuteriomethyl-4β-methylandrost-5-en-3-one (8b-d_3)[15] and 17β-Hydroxy-4β-trideuteriomethylestr-5-en-3-one (6b-d_3).[15] The appropriate 4-methyl 4-en-3-one **19** or **20** (0.01 mol) in *tert*-butyl alcohol (25 mL) was added to a solution of potassium (0.078 g, 0.02 mol) in *tert*-butyl alcohol (25 mL). After the mixture was allowed to stir at 25 °C for 30 min methyl-d_3 iodide (0.29 g, 0.02 mol) was added and stirring continued for 24 h. The usual workup (see general method) followed by chromatography on silica gel, using 30% Et_2O–70% hexane, afforded the methyl-d_3 derivatives **6b** and **8b** as colourless needles.

Acknowledgment. We are grateful to Dr. G. Nomine of Roussel-Uclaf for a generous samples of 17β-hydroxy-des-A-estr-9-en-5-one. This investigation was supported by Grant No. HD-09146, awarded by the National Institutes of Child Health and Human Development, and in part by the National Science Foundation through Grant No. CHE 76-05757.

Registry No. **1**, 76249-88-2; **2**, 434-22-0; **3**, 601-57-0; **4**, 58-22-0; **5a**, 76232-80-9; **5b**, 76249-89-3; **5c**, 76232-81-0; **5d**, 76232-82-1; **5e**, 76232-83-2; **6a**, 42028-18-2; **6b**, 31025-33-9; **6b-d_3**, 76232-84-3; **6c**, 76232-85-4; **6d**, 76232-86-5; **6e**, 76232-87-6; **7a**, 601-54-7; **7b**, 2220-42-0; **7c**, 1180-86-5; **7d**, 6916-08-1; **7e**, 76232-88-7; **8a**, 571-25-5; **8b**, 5062-44-2; **8b-d_3**, 76232-89-8; **8c**, 76232-90-1; **8d**, 76232-91-2; **8e**, 76232-92-3; **9**, 76232-93-4; **10**, 76232-94-5; **11**, 76232-95-6; **12**, 76232-96-7; **13**, 1089-78-7; **14**, 5218-51-9; **17a**, 1434-85-1; **17b**, 2059-40-7; **17c**, 19468-31-6; **18a**, 521-18-6; **18b**, 54550-06-0; **19**, 6959-54-2; **20**, 795-83-5.

Analysis of the Proton Nuclear Magnetic Resonance Spectrum of 11β-Hydroxyprogesterone by One- and Two-Dimensional Methods. Some Implications for Steroid and Terpenoid Chemistry

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By use of a recently proposed strategy for the total analysis of the proton NMR spectra of complex natural products, all the chemical shifts and virtually all geminal and vicinal coupling constants have been determined for 11β-hydroxyprogesterone. Two-dimensional *J* spectroscopy at 270 and 400 MHz has been used to resolve 11 virtually first-order multiplets between 1.0 and 2.5 ppm, allowing measurement of most geminal and vicinal coupling constants and some long-range couplings (notably $J_{1\alpha,19}$ and $J_{12\alpha,18}$). Methine protons were resolved and assigned by virtue of their slow spin-lattice relaxation. NOE difference spectroscopy was used to resolve and assign protons on the basis of spatial relationships, particularly between 1,3-diaxial neighbours (and their ring D equivalents). Both steady-state and transient methods of generating enhancements were investigated; the latter appears to be preferable in some circumstances. Decoupling-difference spectroscopy was used to resolve and assign protons by their scalar coupling relationships. Comparison of results for the title compound and the previously analyzed 1-dehydrotestosterone reveals the possibility of using many hitherto inaccessible shift and coupling constant structural correlations in future studies of steroids and related terpenoid substances.

The elucidation of complex natural product structures by using proton NMR spectroscopy has historically been hindered by three problems.

(a) Sensitivity. This has largely been overcome by the Fourier transform technique and, more recently, by the advent of high-field spectrometers.

(b) Resolution of Individual Resonances. High fields clearly help, but even at 400 MHz the spectra of most steroids and terpenoids are complex, containing many overlapping signals in the region above δ 3 and a few re-

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