

¹³C Nuclear Magnetic Resonance Spectra of Some Steroidal Unsaturated Ketones

By **James R. Hanson** * and **Michael Siversns**, School of Molecular Sciences, University of Sussex, Brighton, Sussex BN1 9QJ

The ¹³C n.m.r. spectra of some unsaturated 3- and 7-oxoandrostanes have been assigned. Some transannular shielding effects are noted.

THE steroids provide a rigid framework within which it is possible to identify the conformational and structural effects of various functional groups on carbon-13 chemical shifts. In this context we have examined the ¹³C n.m.r. spectra of a series of steroidal unsaturated ketones. There have been prior studies on a number of steroids¹ including a series of oxo-,² hydroxy-,³ and aromatic⁴ steroids. In the original study¹ tentative assignments were made for some steroidal unsaturated ketones and these have now been confirmed.

The ¹³C n.m.r. spectra were obtained for solutions in deuteriochloroform at 25.15 MHz using a pulsed Fourier transform system with proton noise decoupling. The multiplicity of the resonances in the off-resonance decoupled spectra were used to distinguish between methyl, methylene, methine, and quarternary carbon

atoms. Two series of androstenones with differing degrees of unsaturation based on a 3-carbonyl (1)–(7) and a 7-carbonyl group (8)–(13) were examined. The assignments are tabulated.

The assignment of the resonances in the 3-ketones was based on data for androst-4-ene-3,17-dione (1) in the following manner. The C-18 and C-19 signals appeared as quartets in the off-resonance decoupled spectra and these resonances were distinguished by the effect of changes at C-17 [*cf.* (1) and (2)]. The methylene triplets associated with C-1, C-2, C-6, C-7, C-11, C-12, C-15, and C-16 were distinguished by comparing the changes associated with deuteration and with the introduction of additional unsaturation. Base-catalysed deuteration of androst-4-ene-3,17-dione (1) led to exchange at the enolisable positions to give a [²H₇]-

¹ H. J. Reich, M. Jautelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1969, **91**, 7445.

² H. Eggert and C. Djerassi, *J. Org. Chem.*, 1973, **38**, 3788.

³ J. W. ApSimon, H. Beierbeck, and J. K. Saunders, *Canad. J. Chem.*, 1973, **51**, 3874.

⁴ J. R. Hanson and M. Siversns, *J.C.S. Perkin I*, 1975, 1110.

species, [2,4,6,16-²H₇]androst-4-ene-3,17-dione, in the spectrum of which the resonances at 32.7, 33.7, and 123.9 p.p.m. had collapsed and the two-carbon signal at 35.5

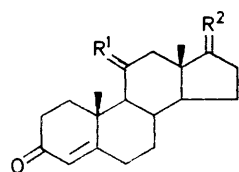
nances were assigned from the effects of introducing additional olefinic and carbonyl groups into the molecule, care was taken in the interpretation of these changes

¹³C N.m.r. spectra of some unsaturated steroids
(in p.p.m. from Me₄Si)

Compd.	Carbon atom																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
(1)	35.5	33.7	198.9	123.9	170.1	32.3	31.1	34.9	53.6	38.4	20.1	30.5	47.3	50.6	21.5	35.5	220.0	13.5	17.2
(2)	35.6	33.8	199.4	123.6	171.0	32.7	31.5	35.0	53.9	38.6	20.6	36.4	42.7	50.4	23.2	30.1	81.0	11.0	17.3
(3)	33.9	33.9	199.2	124.1	162.9	128.7	138.3	37.0	48.7	36.1	20.0	31.3	48.3	50.7	21.4	35.6	219.3	13.7	16.3
(4)	33.9	33.9	199.1	123.7	163.2	128.1	139.9	37.3	48.0	36.5	20.1	36.0	43.4	50.6	23.1	27.4	82.0	12.0	16.3*
(5)	155.2	127.6	186.0	124.0	168.2	32.3	31.2	35.0	52.3	43.4	22.0	32.5	47.6	50.4	21.8	35.5	219.6	13.8	18.7
(6)	34.6	33.6	199.2	124.6	167.8	31.9	30.8	36.2	63.2	38.2	207.4	50.3	50.3	49.6	21.5	35.9	216.7	14.6	17.2
(7)	154.8	127.6	185.9	124.7	165.9	32.1	31.9	35.9	60.6	42.3	207.4	50.3	50.0	49.1	21.6	35.9	216.4	14.7	18.9
(8)	39.0	24.0	26.8	32.7	169.2	124.3	200.8	44.3	45.7	39.2	20.1	30.7	47.8	50.4	21.8	35.5	220.0	13.7	17.4
(9)	39.3	23.4	26.8	32.8	168.9	124.4	201.4	45.0	45.0	39.3	20.4	35.9	43.1	50.2	26.0	27.6	82.0	12.1	17.4*
(10)	37.7	27.2†	71.9	35.7	164.2	126.3	200.8	44.9	44.9	38.3	20.6	35.9	43.0	49.7	25.8	27.4†	81.7	12.0	17.2*
(11)	32.9	23.4	136.6	127.7	161.1	124.1	202.0	46.4	48.8	36.3	20.7	39.3	41.7	49.9	27.7	21.2	38.0	17.4	16.6
(12)	32.8	23.4	136.9	127.6	161.3	123.9	201.5	45.5	45.5	36.3	20.7	36.0	43.4	49.6	26.0	27.6	82.0	12.1	16.6*
(13)	49.2	197.7	143.6	131.3	157.2	129.5	200.7	45.0†	45.3†	39.7	20.6	35.6	43.4	49.2	25.7	27.5	81.7	12.1	19.5*

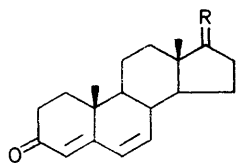
* CH₃·CO·O 21.1—21.2; CH₃·CO·O 170—171 p.p.m. † Assignments may be reversed.

p.p.m. had dropped in relative intensity. These signals were assigned to C-6, C-2, C-16, and C-4 by combining

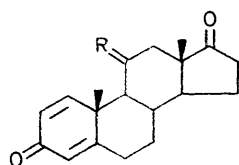


- (1) R¹ = H₂, R² = O
(2) R¹ = H₂, R² =

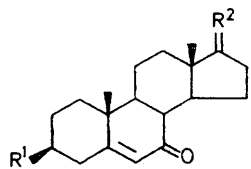
(6) R¹ = R² = O



- (3) R = O
(4) R =

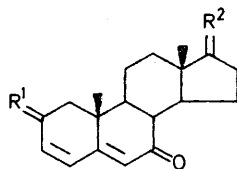


- (5) R = H₂
(7) R = O



- (8) R¹ = H, R² = O
(9) R¹ = H, R² =

(10) R¹ = OAc, R² =



- (11) R¹ = R² = H₂
(12) R¹ = H₂, R² =

(13) R¹ = O, R² =

this evidence with the effects of introducing additional unsaturation into the molecule. Although other reso-

which could affect other carbon resonances. Thus the signals at 31.1 and 32.3 p.p.m. could be assigned to C-7 and C-6 because they were absent in the spectrum of 17β-acetoxyandrost-4,6-dien-3-one (4). Comparison with androsta-4,6-diene-3,17-dione (3) alone was not sufficient as the resonance associated with C-12 in this compound had moved downfield to 31.3 p.p.m. The signals at 35.5 and 33.7 p.p.m. were assigned to C-1 and C-2 because they were absent from the spectrum of androst-1,4-diene-3,17-dione (5). The high-field triplet at 20.1 p.p.m. was assigned to C-11 since this was replaced by a singlet at 207.4 p.p.m. in the 11-ketones (6) and (7). A triplet resonance at 30.5 p.p.m. also showed a downfield shift to 50.3 p.p.m. in the 11-ketones and this was therefore assigned to C-12. The resonances at 21.5 and 35.5 p.p.m., which were assigned to C-15 and C-16, reflected the changes in the oxidation level of C-17 [cf. (1) and (2); (3) and (4)]. In particular the C-16 resonance, which had collapsed in the deuteriated androst-4-ene-3,17-dione, moved downfield from 27.4 p.p.m. in the 17β-acetate to 35.5 p.p.m. in the 17-ketone. The methine doublets associated with C-4, C-8, C-9, and C-14 were readily distinguished by comparing the 11-ketones with the 11-deoxy-steroids. The resonance associated with C-9 (53.6 p.p.m.) showed a large downfield shift to 63.2 p.p.m. in the 11-ketones (6) and (7). The resonance assigned to C-8 showed only a small downfield shift on this change and on the introduction of the 6,7-double bond. The resonance associated with C-14 remained relatively constant, showing a small upfield shift when it lay within the shielding cone of the 11-oxo-group. The singlet resonances were readily assigned. Thus the resonance at 47.3 p.p.m. was assigned to C-13 since it reflected changes in C-17 substitution, and that at 38.1 p.p.m., assigned to C-10, showed a downfield shift on introduction of a C-1 double bond [cf. (1) and (5)]. The assignment of the remaining olefinic and carbonyl resonances was unexceptional. These assignments agree with the tentative assignment made by Reich *et al.*¹ although the actual

positions of the signals differ since the original spectra were determined in dioxan-chloroform and show solvent shifts of the order of 1 p.p.m.

Androst-5-ene-7,17-dione (8) was used as a basis for the assignment of the resonances in the 7-ketones. The resonances associated with C-11 to C-19 were readily assigned by comparison with androst-4-ene-3,17-dione(1). They showed the expected variations on altering the substitution at C-17 [*cf.* (8) and (9)]. Deuteration of androst-5-ene-7,17-dione (8) afforded a mixture of predominantly [$^2\text{H}_4$]- and [$^2\text{H}_5$]-species (*m/e* 290 and 291). The ^1H n.m.r. spectrum revealed the incorporation of some deuterium at C-6. In the ^{13}C n.m.r. spectrum triplet resonances at 32.7 and 35.5 p.p.m. had collapsed and these were therefore assigned to C-4 and C-16. The signal at 124.3 p.p.m. had diminished in intensity and this was therefore assigned to C-6. There was also a smaller decrease (12% relative to the adjacent signal at 45.7 p.p.m.) in the doublet at 44.3 p.p.m. (C-8). The remaining ring A triplets were assigned by a comparison of 17 β -acetoxyandrost-5-en-7-one with 3 β ,17 β -diacetoxyandrost-5-en-7-one (10). The resonance at 39.3 p.p.m. was assigned to C-1 since it shows a typical upfield ' γ ' shift on introduction of the acetoxy-group. The resonance at 23.4 p.p.m., on the other hand, was assigned to C-2 since it shows a characteristic downfield shift of 3.8 p.p.m. on introduction of the adjacent acetoxy-group.⁵

When androsta-3,5-dien-7-one (11) was deuteriated ⁶ a [$^2\text{H}_5$]-species (*m/e* 275) was obtained. In the ^1H n.m.r. spectrum, the signal at τ 4.37 (6-H) had disappeared and the two-proton signal at τ 3.89 (3- and 4-H) had collapsed to a single-proton resonance. There was also a loss of intensity equivalent to three protons from a multiplet at τ 8.0. In the ^{13}C n.m.r. spectrum a triplet at 23.4 p.p.m. had 'disappeared' and this was therefore assigned to C-2. In 17 β -acetoxyandrosta-3,5-diene-2,7-dione (13) this signal was replaced by a singlet at 197.7 p.p.m. and the triplet at 39.3 p.p.m. which was assigned to C-1 had moved downfield to 49.2 p.p.m. The doublet at 46.4 p.p.m. in the spectrum of androsta-3,5-dien-7-one was assigned to C-8 since it had 'disappeared' in that of the deuteriated product. This confirmed the assignment in androst-5-ene-7,17-dione. Androsta-3,5-dien-7-one was also deuteriated at C-4 and C-6 enabling these resonances to be distinguished from that of C-3.

⁵ J. T. Clerc, E. Pretsch, and S. Sternhell, ' ^{13}C -Kernresonanzspektroskopie,' Akademische Verlagsgesellschaft, Frankfurt, 1973.

Within these series of compounds, the carbon resonances show some consistent trends. These are revealed by a comparison with the published data ² (also determined in deuteriochloroform) for androstane, and the saturated 3-, 7-, and 17-ketones. Thus a comparison of C-1 and C-2 in the 3-ketones and of C-8 and C-9 in the 7-ketones reveals a shielding in comparison with the saturated ketones of 3–4 p.p.m. on introduction of the transannular double bond. This effect is observed on C-9 and C-10 when a 6,7-double bond is introduced [*cf.* (3) and (4)] and on C-1 and C-10 when a 3,4-double bond is introduced [*cf.* (8), (11), and (12)]. The carbon signals of the unsaturated ketones reveal the expected downfield shift of 3–4 p.p.m. in comparison with the saturated series. However the C-2 signal of 17 β -acetoxyandrost-5-en-7-one (8) remains unchanged on introduction of the additional unsaturation in androsta-3,5-dien-7-one and 17-acetoxyandrosta-3,5-dien-7-one [(11) and (12)]. C-19 is clearly deshielded by the additional unsaturation in rings A and B in comparison with the saturated series. Although there is a slight shielding of C-1 on introduction of a C-11 oxo-group, the effect is nowhere near the same size as that of a C-17 oxo-group on C-12, despite the similar steric relationship of these centres.

EXPERIMENTAL

The ^{13}C n.m.r. spectra were determined with a JEOL PFT-100 Fourier transform spectrometer operating at 25.15 MHz. The spectral width was 250 p.p.m. (8 192 data points and 500–5 000 accumulations). The pulse length was 7 μs (*ca.* 30°) at a pulse interval of 1.0 s. The samples (120–180 mg) were dissolved in deuteriochloroform (0.5 ml) and the solvent deuterium provided the lock signal. Tetramethylsilane was used as an internal standard. The chemical shifts are estimated to be accurate to within ± 0.1 p.p.m.

Deuteration Experiments.—Androst-4-ene-3,17-dione (450 mg) was suspended in methan[^2H]ol (5 ml) and 10% sodium deuterioxide (1.0 ml) was added. The solution was heated under reflux nitrogen for 2 h, then left overnight, and acidified with deuteriochloric acid. The steroid was filtered off, dried, and recrystallized from acetone-light petroleum to give needles, m.p. 172–173° (lit.,⁷ 174°) (*m/e* 293). Androst-5-ene-7,17-dione and androsta-3,5-dien-7-one were deuteriated under similar conditions (*cf.* ref. 6).

[5/786 Received, 28th April, 1975]

⁶ R. Beugelmans, R. H. Shapiro, L. J. Durham, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1964, **86**, 2832.

⁷ L. F. Fieser and M. Fieser, 'Steroids,' Reinhold, New York, 1959, p. 512.