Carbon-13 nuclear magnetic resonance spectral data of steroidal vicinal ketols and related compounds

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Carbon-13 nuclear magnetic resonance spectra for 31 3β-hydroxy and acetoxy androstane derivatives bearing vicinal oxygenated functions at ring D with and without oxygenated functions at C-6 are reported. Relative substituent effects are discussed. (Steroids **56:**168–172, 1991)

Keywords: steroids; α-ketols, ^{13}C NMR; 16,17-Ketols, ^{13}C NMR spectral data; ^{13}C NMR, substituent-induced chemical shifts

Introduction

Reformatsky reaction of an α-ketol function in steroidal derivatives is an important procedure for the synthesis of complex natural products.[1,2] When the reaction was applied to 16β-acetoxy-17-oxoandrostanes, a rearranged product was obtained[3,4] that was produced by an isomerization reaction.[5] The mechanism of this process has been established by carbon-13 nuclear magnetic resonance (NMR) experiments[6] and mass spectroscopic measurements[7] as an intramolecular 1,2-shift of hydrogen. A similar ^{13}C NMR spectroscopic study was performed on 16α-acetoxy-17-oxo isomers, leading to the proposal of a dissimilar mechanism.[8]

Those experiments allowed us to obtain previously unreported ^{13}C NMR spectroscopic data for several androstane derivatives and to study substituent-induced shifts of 6α-, 16α- and 16β-oxygenated substituents.

Experimental

^{13}C NMR spectra were recorded at 25.2 MHz on a modified Varian XL-100-15 spectrometer operating in the FT mode, using a 620-L100 computer interfaced to a Sykes 7000 dual disk drive. Proton spectra were measured in chloroform-*d* (also acting as internal lock) with tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra were measured for approximately 0.5 M solutions in chloroform-*d* or benzene-d_6/methanol-d_4 (1 : 1) containing TMS (approximately 1%) in 5-mm tubes at about 27 C. Totally proton-decoupled spectra were the result of 10,000 to 15,000 pulses over a spectral width of 5,700 Hz using 45-degree pulses and a pulse repetition rate of 0.71 seconds; they were obtained by irradiation of the ^1H NMR spectrum at a central frequency of 4 ppm, with the irradiation frequency modulated by an external swept-wave modulator. An 8-K data table was used, rendering, after Fourier transformation, spectra with 1.39 Hz per point. Attached proton test (APT) spectra and spectra of quaternary carbons were obtained using known pulse sequences.[9]

Compounds **1** and **2** were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Compound **3** was obtained from **2** by protection of the carbonyl group (ethylene glycol, *p*-toluenesulfonic acid, benzene), hydroboration of the double bond (BH_3.THF, then H_2O_2, NaOH), and deprotection to 17-oxo steroid (AcOH-H_2O).[10] Compounds **7, 8,** and **9** were obtained from **1, 2,** and **3,** respectively, by treatment with *iso*-propenyl acetate-H_2SO_4 as described elsewhere.[11] Compounds **10** and **11** were prepared by epoxydation of the enol acetates **7** and **9,** respectively (*m*-chloroperoxybenzoic acid, CH_2Cl_2, $NaHCO_3$).[11] Compounds **14** and **16** were obtained by $SnCl_4$-catalyzed rearrangement of epoxides **10** and **11,** respectively.[11] Compounds **17** and **18** were prepared by a modified Glazier[12] method ($CuBr_2$, MeOH) starting from **2** and **3,** respectively. Compounds **12** and **13** were obtained by alkaline hydrolysis (NaOH, DMF, H_2O) of bromoketones **17** and **18** according to a known procedure.[13] Compounds **23, 24,** and **25** were obtained by acetoxylation (lead tetraace-

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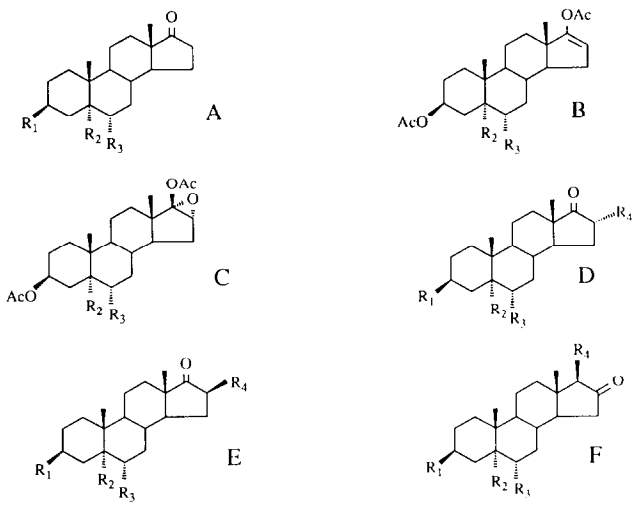

Figure 1 Steroids analyzed by ^{13}C NMR spectroscopy.

tate) of enol acetates **8, 7,** and **9,** respectively.[14] Compounds **20, 21,** and **22** were prepared from **23** following Kincl's procedure.[15] Compound **19** was obtained by catalytic hydrogenation (Pd/C, AcOEt) of compound **20.** Compounds **26, 27,** and **31** were obtained by alkaline rearrangement (KOH, MeOH, benzene) of **24, 23,** and **25,** respectively.[16] Compounds **4, 5, 6, 15, 28, 29,** and **30** were obtained by acetylation (Ac_2O, Py) of compounds **1, 2, 3, 13, 24, 23,** and **25,** respectively. All of the compounds showed, in addition to the ^1H and ^{13}C NMR data, satisfactory infrared and mass spectra.

Table 1 Steroids analyzed by ^{13}C NMR spectroscopy

Compound	Structure	R_1	R_2		R_3	R_4	Solvent
1	A	HO	H		H	—	a
2	A	HO		Δ^5		—	a
3	A	HO	H		OH	—	b
4	A	AcO	H		H	—	c
5	A	AcO		Δ^5		—	c
6	A	AcO	H		AcO	—	c
7	B	—	H		H	—	c
8	B	—		Δ^5		—	c
9	B	—	H		AcO	—	c
10	C	—	H		H	—	c
11	C	—	H		AcO	—	c
12	D	HO	H		H	HO	a
13	D	HO		Δ^5		HO	a
14	D	AcO	H		H	AcO	c
15	D	AcO		Δ^5		AcO	c
16	D	AcO	H		AcO	AcO	c
17	D	HO		Δ^5		Br	c
18	D	HO	H		HO	Br	c
19	E	HO	H		H	HO	a
20	E	HO		Δ^5		HO	a
21	E	AcO		Δ^5		HO	c
22	E	HO		Δ^5		AcO	c
23	E	AcO		Δ^5		AcO	c
24	E	AcO	H		H	AcO	c
25	E	AcO	H		AcO	AcO	c
26	F	HO	H		H	HO	a
27	F	HO		Δ^5		HO	a
28	F	AcO	H		H	AcO	c
29	F	AcO		Δ^5		AcO	c
30	F	AcO	H		AcO	AcO	c
31	F	AcO	H		AcO	AcO	c

a, C_6D_6/CD_3OD (1 : 1); b, $CDCl_3/CD_3OD$ (9 : 1); c, $CDCl_3$.

Results and discussion

The structures of the compounds analyzed are presented in Figure 1 and Table 1, and their ^{13}C NMR chemical shift values are given in Tables 2 through 5. Assignments were done by a combination of APT, single-frequency, off-resonance decoupled spectra (SFORD),[17] single-frequency decoupling (SFD),[18] empiric rules (acetylation shifts),[19] and comparison with literature data.[20–22] Although ^{13}C NMR spectra data for compounds **1, 2, 4,** and **5** have been previously reported, their respective spectra are also presented, for they were recorded in the same solvent as the other steroids. This was done to allow a substituent-induced chemical shift (SCS) study of 6α-, 16α-, and 16β-oxygenated substituents.

Substituent-induced chemical shift for 6-acetoxy group

To obtain SCS for a 6α-acetoxy group, individual resonances of each carbon for different pairs of compounds were compared. The results are indicated in Table 6.

Table 2 Chemical shifts (ppm) for compounds **1** through **8**

	Compound							
Carbon	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	37.5	37.7	37.4	36.6	36.9	36.7	36.5	36.9
2	32.1	31.9	31.8	27.3	27.7	27.0	27.4	27.8
3	70.9	71.4	70.7	73.3	73.6	72.3	73.4	73.8
4	38.3	42.5	30.6	33.9	38.1	28.2	(33.5)	38.1
5	45.3	141.6	51.3	44.6	139.8	48.4	44.8	139.9
6	29.0	120.8	68.7	28.2	121.7	71.7	28.4	122.1
7	31.3	31.7	40.0	30.8	31.5	36.4	31.0	30.9
8	35.4	31.8	34.0	35.0	31.5	33.6	34.0	30.0
9	54.9	50.7	54.0	54.3	50.2	53.5	54.7	50.6
10	36.0	37.0	36.4	35.6	36.7	36.6	35.6	36.8
11	20.9	20.7	20.5	20.4	20.3	20.3	20.7	20.4
12	31.6	31.1	31.5	31.5	30.8	31.3	(33.3)	(33.4)
13	48.1	47.8	48.0	47.6	47.4	47.6	44.8	44.7
14	51.7	51.9	51.7	51.3	51.7	50.9	53.9	54.1
15	22.0	22.0	21.8	21.7	21.9	21.6	(28.8)	(29.0)
16	36.0	35.9	35.9	35.7	35.8	35.6	110.9	111.1
17	221.5	220.9	222.1	220.5	220.4	219.9	159.4	159.4
18	13.9	13.5	13.8	13.7	13.5	13.7	15.5	15.4
19	12.4	19.5	13.4	12.2	19.3	13.2	12.2	19.2
CH_3COOR	—	—	—	21.3	21.3	21.1	21.1	21.1
						21.4	21.4	21.4
CH_3*C*OOR	—	—	—	170.2	170.0	170.2[a]	168.4	168.5
							170.2	170.2

Values in parentheses may be interchanged.
[a] Signals with double intensity.

Table 3 Chemical shifts (ppm) for compounds **9** through **17**

	Compound								
Carbon	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
1	36.8	36.5	36.6	37.4	37.8	36.8	36.8	36.6	37.1
2	27.1	27.3	27.0	32.2	32.1	27.3	27.6	27.0	31.5
3	72.9	73.4	72.8	70.7	71.7	73.2	73.5	72.7	71.3
4	28.4	33.9	28.2	38.4	42.6	33.9	38.0	28.3	42.1
5	48.7	44.6	48.4	45.2	141.7	44.5	139.8	48.4	141.0
6	71.9	28.3	71.7	28.9	121.2	28.1	121.4	71.6	120.4
7	36.8	31.2	36.7	(31.6)	32.1	30.4	31.1	36.1	32.2
8	32.3	33.7	32.3	35.3	31.8	34.9	31.4	33.6	30.7
9	(54.2)	54.5	53.9	54.8	51.0	54.2	49.9	53.6	50.0
10	36.9	35.5	36.6	36.0	37.2	35.6	36.6	36.6	36.6
11	20.6	20.5	20.4	20.6	20.7	20.1	19.9	19.9	20.3
12	(33.2)	31.2	31.0	(31.8)	31.8	31.3	30.4	31.1	30.6
13	44.8	42.8	42.8	48.0	48.0	47.5	47.3	47.6	47.5
14	(53.7)	46.2	46.0	48.8	49.5	48.6	48.8	48.4	48.3
15	(28.8)	26.4	26.3	(31.1)	31.1	29.4	29.6	29.5	34.1
16	110.9	59.7	59.5	71.3	71.7	72.3	72.2	72.2	46.2
17	159.2	90.7	90.7	219.3	220.0	213.6	213.5	213.2	213.3
18	15.5	14.6	14.5	14.4	14.2	14.2	13.9	14.2	14.0
19	13.2	12.1	13.2	12.4	19.6	12.1	19.3	13.2	19.4
*C*H$_3$COOR	21.0	21.0	21.0	—	—	20.7	20.8	20.8	—
	21.2	21.3	21.2			21.2	21.3	21.2	
	21.3		21.3					21.3	
CH$_3$*C*OOR	168.3	168.6	168.6	—	—	169.9	170.0	169.9	—
	170.4[a]	170.2	170.2			170.2	170.2	170.3	
			170.5					170.6	

Values in parentheses may be interchanged.
[a] Signals with double intensity.

Table 4 Chemical shifts (ppm) for compounds **18** through **25**

	Compound							
Carbon	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**
1	37.1	37.4	37.8	36.8	37.1	36.8	36.6	36.6
2	32.1	31.6	31.8	27.6	31.4	27.7	27.3	26.9
3	70.8	71.7	71.7	73.5	71.4	73.6	73.2	72.6
4	29.6	38.3	42.6	38.0	42.1	38.1	33.9	28.2
5	51.6	45.6	141.7	139.8	140.9	139.1	44.5	48.3
6	68.8	29.4	121.2	121.5	120.4	121.5	28.1	71.4
7	40.1	31.4	32.4	31.6	31.6	31.6	30.9	36.4
8	33.1	35.5	31.2	30.5	30.7	30.7	34.2	32.7
9	53.6	55.1	51.1	50.3	50.3	50.2	54.4	53.6
10	36.3	36.1	37.3	36.6	36.7	36.8	35.6	36.6
11	20.2	20.8	20.7	20.0	20.1	20.1	20.2	20.0
12	30.8	31.4	31.5	30.9	30.8	30.9	31.7	31.4
13	47.6	47.5	47.2	46.6	46.8	46.8	47.0	46.9
14	47.6	44.8	46.3	45.8	46.2	46.2	45.8	45.4
15	34.0	31.6	31.7	30.6	29.3	29.4	29.2	29.0
16	46.1	75.3	75.2	75.1	74.6	74.6	74.6	74.2
17	212.8	218.2	220.8	220.1	214.3	214.0	214.0	213.5
18	14.2	14.4	14.4	14.6	14.2	14.3	14.5	14.4
19	13.4	12.5	19.6	19.3	19.4	19.4	12.1	13.1
*C*H$_3$COOR	—	—	—	21.3	20.7	20.7	20.6	20.6
						21.4	21.3	21.1
								21.2
CH$_3$*C*OOR	—	—	—	170.3	170.1	170.0	169.8	169.7
						170.2	170.2	170.0
								170.4

From the values of Table 5 it can be established that the carbons significantly affected by the introduction of a 6α-acetoxy group are C-3 to C-10 and C-19, all of which are in the close neighborhood of C-6. The values for the α-effect (approximately 43.4 ppm) are in good agreement with the value proposed by Eggert and coworkers.[21] Carbons in the β-position (C-5 and C-7) are deshielded, although the effect is larger for the latter (5.6 ppm) than for the former (3.8 ppm). C-4, C-8, and C-10 are in the γ-position to C-6. After introduction of a 6α-acetoxy group, C-4 and C-8 are shielded in different magnitude (5.6 and 1.5 ppm, respectively) while C-10 is deshielded (1.1 ppm). The shift for C-19 is in good agreement with the value reported by Grover and Stothers.[22]

Substituent-induced chemical shift for 16α- and 16β-oxygenated groups

As previously, the SCS values for 16α- and 16β-oxygenated substituents were determined by comparison between pairs of compounds, as indicated in Table 6.

From the listed values it can be determined that carbons affected by introduction of an oxygenated substituent at position 16 are C-14 to C-18. If the substituent is β-oriented, C-8 and C-13 also change their respective chemical shift values.

It can be observed that α-effects are larger when the substituent is β-oriented than in the case of the α-epimer (2.3 ppm for the acetates and 3.7 ppm for the alcohols). This fact could be explained by the interaction between 14α-H and 16α-H[23] or by interaction *quasi-syn*-oriented between C-18 and 16β-OR and the interaction *gauche* H-H with C-15.[21]

Carbonyl C-17 groups are shielded by 6.4 ppm for a 16β-acetoxy group and 6.9 ppm for a 16α-acetoxy group. This effect is similar to that produced by other electronegative substituents.[24]

The SCS caused for a hydroxy group is more difficult to understand; in our examples, 16α-OH group shields C-17 in approximately 0.9 to 2.2 ppm while 16β-OH does not produce any significant effect.

On the other hand, C-15 suffers a strong deshielding for acetates (7.5 ppm) and alcohols (9.2 ppm); this value is in agreement with those reported by Eggert and coworkers.[21]

The γ-effect on C-14 differs significantly according to the spatial orientation of the C-16 acetoxy substituent. A shielding effect is observed in both cases, being larger for 16β-isomers (5.5 ppm) than for 16α-analogs (2.7 ppm). This difference could not be produced by the ester function, as alcohols and acetates show similar shift values. These values are in agreement with those reported for steroidal alcohols and decalols.[21,23]

A δ-effect is observed on C-18. The observed values are similar for 16α- or 16β-oriented substituents.

Table 5 Chemical shifts (ppm) for compounds **26** through **31**

	Compound					
Carbon	**26**	**27**	**28**	**29**	**30**	**31**
1	37.3	37.3	36.4	36.6	36.4	36.5
2	31.6	31.8	27.3	27.6	26.9	26.9
3	71.1	71.7	73.3	73.5	72.7	72.7
4	38.3	42.6	33.9	37.9	28.2	28.2
5	(45.2)	141.8	44.5	139.8	48.2	48.3
6	29.0	121.2	28.2	121.3	71.4	71.4
7	32.2	32.1	31.6	31.4	37.0	37.3
8	34.8	31.6	34.4	30.9	32.9	32.9
9	54.8	50.9	54.0	49.7	53.2	53.4
10	36.1	37.3	35.6	36.6	36.6	36.6
11	21.0	21.0	20.3	20.1	20.1	20.3
12	36.9	36.8	(36.3)	36.0	(35.8)	(36.2)
13	42.9	42.6	41.7	41.3	41.6	42.4
14	(45.3)	45.6	45.2	45.4	44.9	44.6
15	36.2	36.3	(36.1)	36.0	(35.9)	(35.3)
16	217.8	217.6	210.7	210.4	210.0	216.3
17	86.6	86.6	85.6	85.4	85.2	86.0
18	11.8	11.7	12.5	12.2	12.3	11.3
19	12.5	19.7	12.2	19.3	13.1	13.2
CH_3COOR	—	—	20.7	20.6	20.6	21.1
			21.4	21.3	21.1	21.3
					21.3	
CH_3COOR	—	—	170.0	170.0	170.0	170.3
			170.4	170.2	170.3	170.5
					170.6	

Values in parentheses may be interchanged.

Table 6 Substituent-induced chemical shift values (ppm) for 6α-, 16α-, and 16β-oxygenated groups

Carbon	6α-OAc	16α-OAc	16α-OH	16β-OAc	16β-OH
1	0.1	0.0	0.0	−0.1	−0.1
2	−0.3	0.0	0.2	0.0	−0.1
3	−0.6	0.1	0.0	0.1	0.2
4	−5.6	0.0	0.1	0.0	0.0
5	3.8	0.0	0.0	−0.3	0.1
6	43.4	−0.2	0.2	−0.2	0.1
7	5.6	−0.4	0.4	0.1	0.4
8	−1.5	−0.1	−0.1	−0.8	−0.8
9	−0.7	−0.1	0.1	0.1	0.3
10	1.1	0.0	0.1	0.0	0.1
11	−0.2	−0.4	−0.2	−0.2	−0.2
12	−0.3	−0.3	0.5	0.1	0.3
13	0.0	−0.1	0.2	−0.6	−0.7
14	−0.3	−2.7	−2.7	−5.5	−5.8
15	−0.1	7.8	9.1	7.5	9.2
16	−0.3	36.5	35.6	38.8	39.3
17	−0.4	−6.9	1.6	−6.4	−0.2
18	−0.1	0.5	0.6	0.8	1.0
19	1.0	0.0	0.1	0.0	0.1

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