Carbon-13 Nuclear Magnetic Resonance Spectra of D-Homoandrostane Derivatives†

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The ^{13}C chemical shift data of a series of ketone, alcohol and ester derivatives of D-homoandrostane are reported. Homologation effects are discussed, as well as substituent effects on the homologated structures.

INTRODUCTION

In spite of the many reports published on the ^{13}C NMR spectroscopy of steroidal structures, there are only few examples on D-homoandrostane derivatives.[3] A systematic study of this type may be useful in the structural elucidation of naturally occurring pentacyclic triterpenes. In the present paper we present the ^{13}C chemical shift data of several oxygenated compounds possessing the perhydrochrysene skeleton.

EXPERIMENTAL

Spectra

The ^{13}C NMR spectra were recorded at 20.1 MHz on a Bruker WP-80-DS spectrometer operating in the Fourier transform mode. The estimated digital resolution is 1.1 Hz (8 K memory for sweep-width of 4504 or 5000 Hz). Spectra were measured as deuteriochloroform solutions, at concentrations of *c.* 0.03–0.1 M, contained in 10 or 5 mm tubes. TMS was used as internal standard. 2000–19 000 pulses, corresponding to a pulse angle of 60° and repetition rate of 2 or 5 s, were employed.

Materials

Most of the compounds were prepared by chemical means, and some by a combination of microbiological and chemical work. The synthetic procedures and structure characterizations, carried out by conventional chemical and spectroscopic methods, have been published elsewhere.[1,2]

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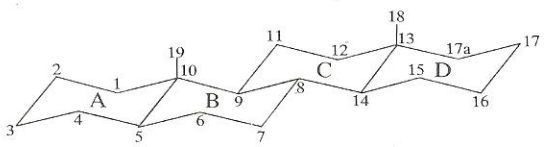
RESULTS AND DISCUSSION

Signal assignments

The shielding data for D-homoandrostane derivatives are listed in Table 1. Substituents are located in each case at the indicated positions, according to the numbering of the parent hydrocarbon.



The assignments for the different carbon atoms of rings A and B were made by comparison with those reported for the equivalent structure in the natural steroid series.[4] The other signals of the D-homo compounds were attributed to C-11 through C-18 of rings C and D, and were assigned by comparing the chemical shifts of D-homo structures varying only in the nature and position of substituents on ring A. C-13, C-14 and C-18 were easily differentiated by their multiplicity patterns in the SFORD spectra. Methylenic or methynic carbons adjacent to a carbonyl group were located by deuterium exchange experiments. The other methylenic carbons were assigned on the basis of the expected chemical shifts estimated by substituent effects observed for similarly situated carbons of ring A, bearing the same group in equivalent positions (e.g. C-1 and C-17a, C-2 and C-17, and so on). The chemical shifts of the ring D methylene groups are also consistent with those reported for the model compounds 1,1,2-trimethylcyclohexane[5] and 2,2-dimethylcyclohexanone, being corrected in the latter case by the effects of a 3-methyl group on cyclohexanone.[6,7]

Homologation effects

Some of the effects due to the expansion of ring D are presented in Table 2. For carbons of ring A, B and C, as well as the angular methyl groups and C-15, these

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Table 1. Carbon-13 chemical shifts of D-homoandrostanes[a]

No.	Function	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15	C-16	C-17	C-17a	C-18	C-19
1	Δ^4	37.7	19.7	23.8	118.5	145.0	32.7	32.4	36.2	54.8	37.3	20.8	42.3	33.6	50.9	27.4	24.2	21.6	42.3	16.9	19.4
2	3=O	38.5	38.1	212.3	44.7	46.5	29.1	30.8	35.5	54.1	36.1	20.8	42.0	33.6	51.0	27.2	24.1	21.5	42.3	17.0	11.5
3	4=O, 5α-H	37.6	22.7	41.2	213.7	58.9	20.6	29.4	35.1	54.6	42.8	21.1	42.3	33.6	50.9	27.2	24.0	21.5	42.2	17.0	13.9
4	4=O, 5β-H	35.2	20.2	41.5	212.6	56.9	20.2	26.6	36.1	44.2	40.9	20.8	41.9	33.4	50.9	27.4	24.0	21.5	42.3	16.9	23.2
5	3β-OH, Δ^5	37.0	32.0	71.0	42.2	140.5	121.8	31.8	31.8	51.6	37.0	20.3	41.8	33.4	50.4	27.3	24.3	21.7	42.0	16.6	19.4
6	3β-OAc, Δ^5	36.8	27.8	74.0	38.0	139.4	122.7	31.8	31.8	51.5	37.0	20.3	41.7	33.6	50.2	27.3	24.3	21.7	42.0	16.7	19.3
7	4β-OAc, 5β-H	37.8	19.2	32.6	70.8	48.1	21.5	25.4	35.8	36.6	29.8	20.3	42.4	33.7	51.1	27.3	24.2	21.5	42.2	17.0	24.2
8	3,6-Di=O	38.5	37.4	211.0	37.0	57.5	209.3	46.0	38.2	54.0	41.7	21.2	41.1	34.1	51.8	27.1	24.2	21.4	42.1	17.0	12.5
9	3=O, 6α-OH	38.5	37.9	211.7	39.6	52.9	70.4	40.9	34.7	53.6	36.7	20.9	41.9	33.6	50.8	27.2	24.3	21.5	42.2	16.9	12.9
10	3=O, 6β-OH	39.6	37.9	211.4	41.9	51.8	70.8	38.3	30.2	54.3	36.7	20.7	42.2	34.0	50.8	27.2	24.3	21.5	42.2	16.9	13.2
11	3β,6α-Di-OH	37.1	30.6	71.4	32.1	51.0	70.1	40.4	34.6	53.8	36.4	20.5	41.9	33.5	50.7	27.2	24.1	21.4	42.1	16.9	13.5
12	3β,6β-Di-OH	38.5	31.6	71.8	35.4	47.2	72.2	38.8	30.5	54.5	35.7	20.4	42.1	33.2	50.9	27.3	24.2	21.5	42.3	17.0	15.8
13	3,7-Di=O	36.5	37.4	211.0	44.2	48.8	46.6	209.7	49.8	54.9	36.5	21.7	40.7	32.7	43.1	26.7	25.2	21.3	41.5	16.8	11.0
14	3β,7α-Di-OH	36.6	31.4	71.0	37.7	36.8	36.5	66.0	39.6	46.3	35.8	20.3	41.5	33.4	45.1	27.1	23.7	21.5	42.3	16.7	11.4
15	3β,7β-Di-OH	36.6	31.2	71.0	37.7	41.5	38.9	75.5	44.4	54.0	35.1	20.6	41.2	34.3	52.5	29.7	23.7	21.7	42.6	17.4	12.7
16	2,17a-Di=O	53.6	211.4	41.2	27.9	44.5	29.0	31.0	34.6	53.0	40.8	19.7	32.5	48.2	51.4	25.9	23.0	37.1	215.6	16.8	12.5
17	2β,17aβ-Di-OH	45.0	68.0	33.9	23.8	46.8	27.9	32.0	34.5	55.2	36.1	20.2	37.5	39.1	50.1	28.9	23.2	30.0	80.0	11.0	14.8
18	3,16-Di=O	38.5	38.0	211.5	44.5	46.2	28.8	30.4	36.5	53.2	35.9	20.8	41.3	33.2	50.1	40.5	212.0	37.7	40.8	16.3	11.5
19	3,17-Di=O	38.5	38.0	211.8	44.5	46.3	28.8	31.0	35.9	53.6	35.9	20.9	41.3	38.0	49.2	25.8	41.3	211.8	56.7	17.8	11.5
20	3β-OH, 17=O	37.2	31.5	71.2	38.2	44.3	28.7	31.0	35.9	53.6	35.5	20.9	41.2	38.0	49.2	26.0	41.3	211.8	56.7	17.8	12.3
21	3β-OAc, 17=O, Δ^5	36.9	27.7	73.8	37.3	139.7	122.1	32.0	32.2	49.8	36.9	20.2	40.8	37.3	49.8	25.8	41.3	211.8	56.7	17.6	19.3
22	3,17a-Di=O	38.3	38.0	211.2	44.5	46.0	28.9	31.1	35.5	52.9	35.8	20.3	32.5	48.3	51.4	25.9	23.0	37.1	215.8	16.9	11.5
23	3,17a-Di=O, Δ^1	157.3	127.5	199.2	40.7	43.6	27.4	30.6	35.4	49.1	38.9	20.2	32.4	48.3	51.4	25.7	22.9	37.0	215.3	17.0	12.9
24	3,17a-Di=O, Δ^4	35.5	33.9	198.8	123.6	170.0	32.7	31.4	35.5	53.0	38.7	19.9	32.4	48.0	50.9	25.7	23.1	37.1	215.3	16.8	17.6
25	3,17a-Di=O, $\Delta^{4,16}$	35.5	32.6	199.2	123.9	170.2	32.7	30.6	35.8	53.0	38.7	20.0	33.8	44.5	46.2	26.8	147.5	127.8	204.9	15.8	17.5
26	3,17a-Di=O, 2-Br, Δ^1	157.3	123.3	190.6	40.6	43.5	27.4	30.4	35.2	49.0	42.5	20.3	32.4	48.2	51.3	25.6	22.9	36.9	215.1	17.0	12.7
27	3,17a-Di=O, 2-Br, $\Delta^{1,16}$	157.4	123.4	190.5	40.6	43.5	27.1	29.6	35.5	48.6	42.5	20.4	32.7	44.5	46.6	26.8	147.2	127.4	204.3	15.8	12.6
28	3α-OH, 17a=O	32.0	29.0	66.4	36.3	38.6	28.6	31.4	35.3	53.6	35.8	19.7	32.7	48.5	51.7	26.0	23.0	37.3	216.8	17.0	11.2
29	3β-OH, 17a=O	36.9	31.5	71.3	38.2	44.4	28.7	31.5	35.4	53.6	35.7	20.1	32.7	48.5	51.7	26.0	23.1	37.2	216.6	17.0	12.4
30	3β-OAc, 17a=O	36.5	27.3	73.4	33.8	44.0	28.5	31.3	35.1	53.3	35.6	20.0	32.5	48.2	51.4	25.8	23.0	37.0	215.6	16.9	12.1
31	3β-OTs, 17a=O	36.6	28.4	82.3	35.2	44.3	28.4	31.3	34.9	53.4	35.5	20.1	32.6	48.4	51.6	25.9	23.0	37.2	216.3	17.0	12.1
32	3β-OAc, 17a=O, Δ^5	36.6	27.8	73.8	38.0	139.7	122.1	32.0	32.2	49.3	37.0	19.8	31.8	48.3	51.8	26.0	23.2	37.2	216.0	16.8	19.2
33	3β,17aβ-di-OH	37.4	31.6	71.3	38.2	44.4	28.7	31.6	35.0	54.1	35.7	20.3	36.9	39.0	50.1	28.7	23.2	30.0	79.9	11.0	12.4
34	2,11,17a-Tri=O	52.1	211.2	41.1	27.5	44.5	28.2	31.8	36.6	63.9	40.4	213.1	50.6	51.8	51.4	25.8	23.1	37.9	214.9	17.2	12.4
35	2,17a-Di=O, 11α-OH	58.9	213.4	41.1	29.1	44.6	28.4	31.1	34.8	58.9	41.8	67.5	43.8	48.7	50.5	25.7	23.3	36.7	215.0	17.6	13.2
36	3,7,11-Tri=O	35.5	37.3	209.3	43.8	48.7	46.2	208.3	52.8	64.0	36.0	207.3	57.8	38.2	43.0	26.2	25.2	21.2	41.1	17.3	10.6
37	3,7,17a-Tri=O	36.4	37.3	209.7	44.1	48.5	46.4	209.2	49.3	54.1	36.6	20.9	31.4	47.2	43.2	25.5	24.1	37.3	215.2	17.1	11.0
38	3,11,17-Tri=O	37.3	37.9	211.3	44.0	46.5	28.2	31.9	39.1	64.0	35.2	208.1	57.8	42.8	48.8	25.5	40.7	209.6	55.7	18.4	11.0
39	3,11,17a-Tri=O	37.1	37.9	211.0	44.1	46.4	28.2	31.7	38.7	64.0	35.1	208.2	50.6	51.4	51.4	25.7	22.7	37.0	214.7	17.3	11.0

[a] Values in ppm from TMS as internal standard.

Table 2. D-Homologation effects on the ^{13}C chemical shifts of androstanes[a]

Carbon	No.[b]	C-17 (→17a) methylene	C-17 (→17a) ketone
7	7	−1.5 (±0.1)	0.4 (±0.3)
8	8	−0.4 (±0.0)	0.4 (±0.2)
9	9	0.0 (±0.1)	−0.9 (±0.3)
11	11	−0.7 (±0.1)	−0.4 (±0.2)
12	12	3.3 (±0.1)	1.1 (±0.1)
13	13	−7.2 (±0.1)	0.7 (±0.2)
14	14	−3.5 (±0.1)	0.2 (±0.1)
15	15	1.7 (±0.1)	4.1 (±0.2)
16	17	1.0 (±0.1)	1.6 (±0.2)
17	17a	2.2 (±0.0)	−4.5 (±0.3)
18	18	−0.6 (±0.0)	3.2 (±0.1)

[a] In ppm, average values from several comparisons of equivalent structures. Negative values correspond to upfield shift from the 5-membered ring D steroid.
[b] The first column corresponds to the numbering of the normal series steroid positions, and the second column to the equivalent carbon in the D-homo series.

effects were evaluated by direct comparison of the chemical shifts of the different carbons in compounds of the 'natural' and D-homo series having the same substituent at equivalent positions. C-16 and C-17 of the 5-membered ring-D steroid were compared with C-17 and C-17a, respectively, of the corresponding expanded structure. This leaves C-16 of the D-homosteroid without a partner in the normal series. As expected, most of the carbon atoms of rings A and B are mainly unaffected by homologation. For the other carbons the shielding effects show variations in sign and/or magnitude, depending upon the nature (CH_2 or CO) of C-17a (see Table 2). Thus, for example, the effect on C-7 changes from −1.5 ppm to 0.4 ppm. The shielding of C-7 due to the expansion of ring D can be explained on the basis of a stronger *gauche* interaction with the methylene at C-15 in the homologated structures. This effect may be compensated by the more complex structural modifications occurring on the carbon skeleton of C-17a-ketones, as inferred by the large deshielding of C-15 and C-17 and the long range shielding effect observed on C-9.

Saturated ketones

The substituent effects due to the introduction of a carbonyl group are shown in Table 3. For ketones at positions 6, 7, 11, 16, 17 and 17a, the shieldings were evaluated principally by comparison of diketones against D-homo-5α-androstan-3-one (**2**) and, when possible, the primary values were confirmed from trisubstituted and disubstituted compounds. Except for the 6- and 16-ketones, the estimated substituent effects are average values of several comparisons.

In some cases, the substitution of a methylene by a carbonyl group causes noticeable chemical shift variations at remote positions; for example, a 7-ketone group shields C-1 (−2.0 ppm), C-12 (−1.2 ppm) and C-17a (−0.7 ppm) but deshields C-16 (1.1 ppm). Conformational changes must be involved in these long range effects. Ring B may adopt a semi-boat conformation in order to minimize the steric interactions of the carbonyl oxygen with C-14 and C-15.

Table 3. Significant carbonyl substituent effects on the ^{13}C chemical shifts of D-homoandrostanes[a]

Ketone at carbon no.	C-6[b]	C-7[c]	C-11[c]	C-16[b]	C-17[c]	C-17a[c]
1		−2.0	−1.2			
2	−0.7	−0.7				
3	−2.0	−1.5	−0.5	−0.8		
4	−7.7	−0.5				
5	11.0	2.4				
6	180.2	17.5	−0.6			
7	15.2	178.9	0.9			
8	2.7	14.0	3.0	1.0		
9		1.0	10.5	−1.1	−0.5	−1.0
10	5.6	0.6			−0.6	
11		0.7	187.2			−0.5
12	−0.9	−1.2	17.0	−0.7	−0.9	−10.0
13	0.5	−1.0	4.5		4.4	14.7
14	0.8	−8.0		−0.9	−1.8	
15		−0.5		13.3	−1.3	−1.2
16		1.1		187.9	17.2	−1.1
17				16.2	190.3	16.0
17a		−0.7	−0.8	−1.5	14.5	174.0
18			0.5	−0.7	0.8	
19	1.0	−0.5	−0.5			

[a] In ppm. Negative values indicate upfield shifts from the unsubstituted compound.
[b] Only one value was available.
[c] Average of more than two values.

There appears to be a relationship between the number and intensity of the shielding interactions produced by the ketonic oxygen on the nearby atoms, and the observed deshielding of the carbon bearing the oxygen atom. Thus in 11-, 16- and 17-ketones, which do not show very intense interactions, the carbonyl carbon is deshielded by between 187 and 190 ppm. In 6-, 7- and 17a-ketones, which present strong γ-*syn* interactions, the deshielding is diminished to a range of *c.* 180–174 ppm; the lowest value is found for the 17a-ketone, which also has the strongest γ-*syn* interaction (with C-12).

The variations in shielding observed for individual carbons of ring A due to the carbonyl at C-2 are similar to those of ring D carbons due to the ketone at C-17. There is only a large difference (of *c.* 3 ppm) in

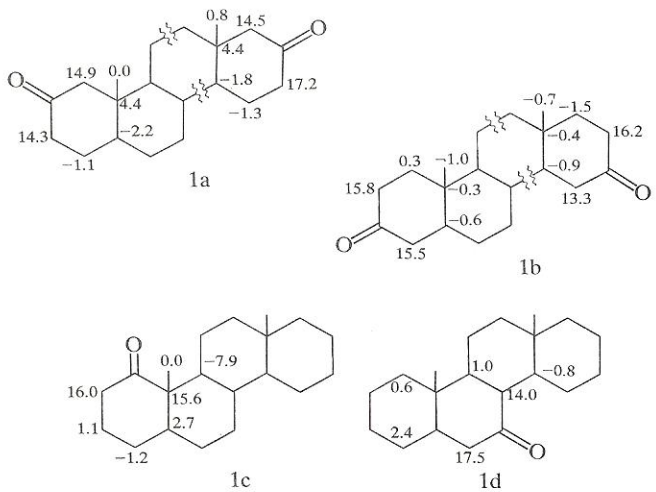

Figure 1. Comparative substituent effects of carbonyl groups located at equivalent positions on the perhydrochrysene skeleton.

one of the β effects [see Fig. 1(a)]. A similar behaviour is found when 3- and 16-ketones are compared, as shown in Fig. 1(b). In the latter case there is also a noticeable difference of *c.* 2 ppm in the γ effects on the methylene carbon atoms. Also, the behaviour of the carbonyl at C-17a does not resemble that of 1- or 4-ketones. The substituent effects of the 'internal' carbonyl at C-7 and C-11 show large differences. The modifications introduced by this group located at position 7 are similar to those due to the 1-ketone [compare Figs 1(c) and (d)].

Enones

The introduction of a double bond α to a carbonyl group shields the ketonic carbon. If the ketone is at the 3-position the shielding is as high as 12.4 ppm, independent of the conjugated unsaturation site, but is only 10.4 ppm when the carbonyl group is located at 17a.

Contrary to the observed effect of the ring A enones on the angular methyl group at C-10, a C-16—C-17 olefinic bond in the 17a-ketones causes a shielding of 1.2 ppm on the angular methyl group at C-13. Although, in both cases, release of the 1,3-diaxial interactions between the axial protons and the methyl carbons results, with the expected deshielding for Δ^1,3- and Δ^4,3-ketones, a decrease of the C-18—C-13 and C-17a—O dihedral angle could reverse the effect in the Δ^{16},17a-ketones.

Alcohols and esters

The chemical shift changes on the neighbouring carbons caused by an hydroxyl group or an ester function are very close to those observed for the steroids of the normal series. The δ-deshielding effects of a 7β-OH on C-15 is similar to that reported for an 11α-hydroxyl group on C-1,[8] reflecting similarities in the geometrical relationships of C-7 to C-11 and C-15 to C-1 in D-homoandrostanes.

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