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Carbon-13 Nuclear Magnetic Resonance Spectra of Hydroxy Steroids

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^{13}C NMR spectra have been obtained and the individual resonances assigned for 31 monohydroxylated androstanes and cholestanes as well as a number of acetoxy derivatives. The chemical shifts are rationalized in terms of α, β, γ, and δ substituent effects. The variation of these effects is discussed in terms of steric interactions of the hydroxyl group. Quantitative correlations are presented relating the α and β substituent effects to the type and number of specific steric interactions of the hydroxyl group. These correlations allow the estimation of substituent shifts of α- and β-carbon atom resonances within 2.0 and 1.0 ppm, respectively. The magnitude of the γ-gauche shift is correlated with 1,3-syn-diaxial OH–CH_3 interactions; furthermore, the possible dependence of the γ-gauche shift upon the presence of a proximate hydrogen atom at the γ carbon is discussed. The downfield δ substituent effect found with OH–C(δ) skew pentane configurations is rationalized in terms of steric deformations to relieve the interaction.

Until very recently the literature data regarding ^{13}C nuclear magnetic resonance spectra of steroids have been of a somewhat fragmentary nature. Therefore we have undertaken a systematic investigation of these compounds by ^{13}C NMR in order to determine (and develop a predictive rationale to describe) the influence of substituents, position, and stereochemistry on their spectra. In the present study we describe the ^{13}C NMR spectra of a series of hydroxy steroids. A previous paper has dealt with the spectra of keto steroids[2] and a study of monounsaturated steroids will be presented in a forthcoming paper.[3] Complete assignments in these series of monofunctional steroids is an absolute prerequisite before attempting the interpretation and eventual prediction of the ^{13}C NMR spectra of polyfunctional steroids, which are frequently of great biological interest. Furthermore, because of the skeletal rigidity which precludes the possible complication of conformational interconversions, hydroxy substituted steroids (such as androstanols and cholestanols) provide an ideal material in which to study the influence of geometrical and stereochemical features upon the substituent effects of the hydroxyl group in cyclic systems. Nearly all possible geometrical environments of the hydroxyl group are represented by the 31 examples in this series, which includes 11 different epimeric pairs.

Experimental Section

The hydroxy steroids (see Table I) included in this study are all known compounds and have been prepared by the following methods: **2** by lithium aluminum hydride reduction,[4] and **4** by reduction with sodium in ethanol[5,6] of cholestan-1-one;[7] **7** by lithium aluminum hydride reduction[8] of cholestan-2-one;[7] **13** by hydroboration–oxidation[9] of Δ^4-cholestene; **15** by Jones oxidation of **13** followed by lithium aluminum hydride reduction;[10] **16** by epoxidation of Δ^4-cholestene[11] followed by lithium aluminum hydride reduction;[12] **17** by reduction with sodium in ethanol[4] of cholestan-6-one[4] and **18** by lithium aluminum hydride reduction[8] of androstan-6-one;[13] **21** by reduction with lithium in ammonia,[15] and **22** by lithium aluminum hydride reduction[8] of androstan-11-one;[14] **23** was prepared analogous to **24** (vide infra) from 12α-acetoxy-5α-spirostane; **26** by hydroboration–oxidation of Δ^{14}-cholestene;[17] **29** by lithium aluminum hydride reduction[8] of androstan-16-one.[9] The following compounds were prepared by previously described methods: **1**,[18] **3**,[18] **19**,[4] **20**,[4] **24**,[16] **27**.[19] An attempt to prepare **3** by reduction of 1-androstanone with K(*sec*-Bu)$_3$BH ("K-selectride", Aldrich)[20] gave only a very small amount (~5%) of the desired product, most of the starting material being recovered unchanged. Compounds **5, 6, 12, 14, 25, 28,** and **30** were generously provided by Dr. Paul V. Demarco.[21]

All the acetoxy steroids were prepared by reaction of the alcohol with acetic anhydride in pyridine, with the exception of 5α-acetoxycholestane, which was made according to the procedure of Plattner et al.[22]

The ^{13}C NMR spectra were recorded at 25.2 MHz using a Varian XL-100-15 system or at 22.6 MHz with a Bruker WH-90 spectrometer, both operating in the Fourier transform mode. Data were accumulated with a maximum of 1.2 Hz per data point. The chemical shifts are relative to internal Me_4Si and are estimated to be accurate to ±0.1 ppm. The probe temperature was ca. 30°.

The spectra were determined as 0.2–0.6 *M* solutions in $CDCl_3$. Variation in sample concentration was found to have a negligible influence (less than 0.1 ppm) on the chemical shift values of all carbons except the carbinyl carbon atom. With increasing sample concentration, within the employed range, this carbon atom became increasingly shielded by up to 0.3 ppm.

The shift reagent experiments were performed with commercial Eu(dpm)$_3$ or Eu(fod)$_3$, which were used without further purification. The ^{13}C spectra were first recorded in the proton noise-decoupling mode in order to measure the exact chemical shifts of all the ^{13}C nuclei present. The degree of substitution of each carbon atom was determined by obtaining a second series of spectra in the single-frequency off-center decoupling mode. Subsequently, a freshly prepared solution of shift reagent in $CDCl_3$ was added in two equal increments to each sample solution and the spectral data in the two modes redetermined. The final molar ratio of reagent to steroid was 0.3. The effects of the addition of the shift reagent on the chemical shift of the ^{13}C nuclei appeared linear in this range.

Results

Chemical shift data for the hydroxy steroids examined are given in Table I along with the values for the parent hydrocarbons, androstane and cholestane. ^{13}C NMR data for

Table I. ^{13}C Chemical Shifts in Hydroxy Steroids[a]

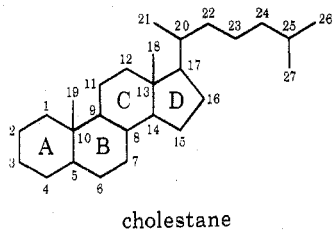
Steroid	1	2	3	4	5	6	7	8	9	10	11	12
Androstane	38.8	22.3	26.9	29.2	47.1	29.2	32.6	36.0	55.1	36.4	20.9	39.0
Cholestane	38.8	22.3	26.9	29.2	47.1	29.2	32.2	35.6	54.9	36.3	20.9	40.2
(1) 1α-Androstanol	71.5	29.0	20.3*	28.6	39.0	29.0	32.2	35.9	47.5	40.2	20.1*	38.8
(2) 1α-Cholestanol	71.5	28.9	20.2	28.5	39.0	28.9	31.8	35.5	47.2	40.1	20.2	39.8
(3) 1β-Androstanol	78.8	33.4	24.7	28.7	46.3	28.9	32.5	36.3	55.4	42.6	24.7	39.3
(4) 1β-Cholestanol	79.0	33.3	24.7	28.7	46.2	28.9	32.2	35.8	55.2	42.5	24.7	40.5
(5) 2α-Androstanol	48.2	68.0	36.3	27.7	46.4	28.2	32.4	35.3	55.0	37.6	21.1	39.0
(6) 2β-Androstanol	45.3	68.1	33.9	23.9	47.4	28.9	32.5	35.4	55.9	36.1	21.0	39.1
(7) 2β-Cholestanol	45.1	67.9	33.9	23.9	47.4	28.8	32.1	35.0	55.6	35.9	21.0	40.2
(8) 3α-Androstanol	32.4	29.1	66.6	36.0	39.2	28.7	32.5	36.0	54.7	36.3	20.9	39.0
(9) 3α-Cholestanol	32.2	29.1	66.5	35.9*	39.1	28.6	32.0	35.5	54.3	36.1	20.8	40.1
(10) 3β-Androstanol	37.1	31.6	71.2	38.3	44.9	28.8	32.5	35.9	54.5	35.6	21.3	38.9
(11) 3β-Cholestanol	37.0	31.5	71.4	38.2	44.9	28.8	32.1	35.5	54.4	35.5	21.3	40.1
(12) 4α-Androstanol	38.1*	20.5	36.4	70.5	54.3	22.8	32.1	35.6	55.1	37.7*	21.0	39.0
(13) 4α-Cholestanol	37.9*	20.4	36.2	70.3	54.0	22.7	31.6	35.1	54.6	37.5*	20.9	40.1
(14) 4β-Androstanol	38.7	17.1	33.9	72.5	50.2	26.1	32.9	36.0	55.9	36.3	20.3	39.0
(15) 4β-Cholestanol	38.6	17.0	33.8	72.4	50.0	26.0	32.4	35.6	55.6	36.2*	20.3	40.0
(16) 5α-Cholestanol	31.6	20.9	20.7	34.4*	73.1	34.6*	26.3	34.9	46.2	39.3	20.9	40.1
(17) 6α-Cholestanol	38.9	21.8	26.2	22.8	53.8	70.0	41.7	34.3	54.2	36.9	20.8	39.9
(18) 6β-Androstanol	40.5	22.2	27.1	26.1	49.8	72.5	40.0	30.7	55.0	36.4	20.7	39.0
(19) 7α-Cholestanol	38.5	22.2	26.8	28.7	39.2	36.8	68.2	39.7	46.4	36.4	20.7	39.7
(20) 7β-Cholestanol	38.7	22.1	26.6	28.7	44.1	38.7	75.2	43.6	53.1	35.7	20.9	40.1
(21) 11α-Androstanol	40.2	22.6	26.7	29.7	47.0	29.7	32.8	35.4	61.2	38.4	69.2	50.5
(22) 11β-Androstanol	38.9	22.0	26.6	28.6	47.8	28.6	32.9	31.7	59.0	36.5	68.6	47.8
(23) 12α-Androstanol	38.8	22.3	26.9	29.2	47.2	29.2	32.4	36.1	48.3	36.1	28.4	72.7
(24) 12β-Androstanol	38.7	22.2	26.8	29.0	47.1	29.0	32.2	34.9	53.9	36.3	29.9	79.7
(25) 15α-Androstanol	38.8	22.2	26.7	29.0	46.9	28.9	32.5	35.5	55.0	36.4	20.7	39.4
(26) 15α-Cholestanol	38.7	22.2	26.8	29.0	46.9	29.0	32.6	35.2	54.7	36.1	20.7	40.6
(27) 15β-Androstanol	38.8	22.3	26.9	29.1	47.4	29.1	31.9	31.9	55.7	36.6	20.8	40.6
(28) 16α-Androstanol	38.8	22.2	26.9	29.1	47.2	29.1	32.5	35.5	55.1	36.4	20.5	39.0
(29) 16β-Androstanol	38.8	22.3	26.9	29.1	47.2	29.1	32.5	35.5	55.0	36.5	20.6	39.3
(30) 17α-Androstanol	38.8	22.2	26.8	29.1	47.0	29.1	32.5	35.8	54.6	36.4	20.3	31.6
(31) 17β-Androstanol	38.8	22.2	26.8	29.1	47.2	29.1	31.8	35.8	55.0	36.4	20.5	36.9

[a] In parts per million relative to Me_4Si. Assignment of chemical shifts for close-lying peaks marked with an asterisk may

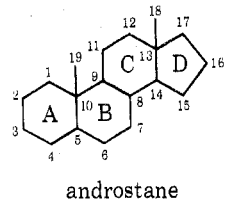
Table II. ^{13}C Chemical Shifts in Acetoxy Steroids[a]

Steroid	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2β-AcO-Cholestane	41.8	70.5	30.8	24.4	46.9	28.7	32.0	35.0	55.3	35.8	20.9	40.1	42.6	56.5
3α-AcO-Cholestane	32.9	26.1	70.0	32.9	40.1	28.3	32.0	35.5	54.3	35.8	20.8	40.1	42.6	56.5
3β-AcO-Androstane	36.9	27.6	73.5	34.1	44.7	28.7	32.4	35.9	54.5	35.6	21.3	38.9	40.8	54.6
5α-AcO-Cholestane	31.7	21.1	21.1	28.3	87.7	28.3	26.7	34.9	46.3	40.3	21.1	40.3	42.8	56.5
6α-AcO-Cholestane	38.8	21.7	26.1	22.8	50.8	73.4	37.8	34.1	54.2	36.2	20.8	40.0	42.7	56.3
6β-AcO-Androstane	40.4	22.0	25.8	26.8	48.7	74.2	36.8	31.3	54.7	36.5	20.7	38.9	40.9	54.4
7α-AcO-Cholestane	38.4	22.1	26.7	28.5	40.0	33.7	71.6	38.4	47.4	36.2	20.7	39.6	42.7	50.6
7β-AcO-Cholestane	38.6	22.1	26.6	28.6	43.7	34.7	77.0	39.5	53.2	35.6	21.0	39.8	43.5	55.4
11α-AcO-Androstane	39.4	22.6	26.5	29.6	46.7	29.6	32.8	35.4	57.0	38.1	71.7	45.5	40.9	53.4
11β-AcO-Androstane	38.9	21.8	26.6	28.6	47.8	28.6	32.8	35.2	57.6	36.2	70.3	43.7	39.8	56.1

[a] In parts per million relative to Me_4Si. [b] Acetoxy methyl group.



cholestane



androstane

a few monohydroxy steroids have been reported in the literature; these are 3β-cholestanol[24] and the epimeric pairs of 3- and 17-androstanols.[23] The chemical shifts for these compounds given in Table I have been redetermined in the present investigation and agree satisfactorily with those previously given. The recently reported ^{13}C NMR spectrum of 14β-androstanol[25] is not included in our discussion, since this compound differs from the hydroxy steroids of the present study by possessing a cis C/D ring junction.

The assignments of the individual chemical shift values to specific carbon atoms presented in Table I were based on our earlier assigned spectra of the parent hydrocarbons,[2] and on the assignment of ApSimon and co-workers for the four 3- and 17-androstanols.[23] In addition, the recently reported assignment of the spectrum of 3β-cholestanol[26] was used. This differs from the original one[24] by reversing the chemical shifts assigned to C-12 and -16 (see also ref 2), and to C-18 and -19. The resonances of carbon atoms five or more bonds removed from the hydroxyl group are in general only slightly shifted relative to the parent hydrocarbons, and the assignments can usually be carried over.

The presence of the hydroxyl group on the ^{13}C chemical shifts in spectra of cyclopentanols and cyclohexanols has been shown[27,28] to result in downfield shifts of 35–50 ppm for α carbons and 2–9 ppm for β carbons, whereas γ carbon atoms are shifted upfield by 1–8 ppm. Our assignments of the resonances of carbon atoms close to the hydroxyl substituent were based on the data quoted above, on shift reagent data, acetylation shifts, and, for those compounds available in sufficient quantity, on off-resonance decoupled spectra. By addition of $Eu(dpm)_3$ or $Eu(fod)_3$ to solutions of the hydroxy steroids (as described in the Experimental

13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
40.8	54.7	25.5	20.5	40.5	17.6	12.3								
42.6	56.7	24.2	28.3	56.4	12.2	12.2	35.9	18.7	36.3	24.0	39.6	28.0	22.5	22.8
40.8	54.5	25.6	20.5	40.5	17.5	12.9								
42.6	56.5*	24.2	28.2	56.3*	12.1	12.9	35.8	18.7	36.2	23.9	39.5	28.0	22.5	22.7
40.2	54.6	25.8	20.4	40.6	17.4	6.7								
42.0	56.5	24.5	28.0	56.5	12.0	6.7	35.8	18.7	36.2	23.9	39.5	28.0	22.6	22.8
40.9	54.6	25.6	20.5	40.5	17.6	13.4								
40.9	54.7	25.5	20.5	40.5	17.7	14.8								
42.7	56.6	24.2	28.3	56.4	12.2	14.7	35.9	18.7	36.3	23.9	39.6	28.1	22.6	22.8
40.9	54.7	25.6	20.6	40.5	17.6	11.2								
42.6	56.5	24.2	28.2	56.2	12.1	11.2	35.8*	18.7	36.2	23.9	39.5	28.0	22.5	22.8
40.8	54.7	25.5	20.5	40.4	17.6	12.4								
42.6	56.5	24.3	28.3	56.3	12.1	12.3	35.8	18.7	36.2	23.9	39.5	28.0	22.6	22.8
40.8	54.7	25.5	20.5	40.5	17.6	13.5								
42.4	56.5	24.2	28.3	56.3	12.1	13.5	35.8	18.7	36.2	23.9	39.5	28.0	22.5	22.7
40.9	54.8	25.6	20.5	40.5	17.6	14.7								
42.6	56.7	24.2	28.2	56.3	12.1	14.7	35.8	18.7	36.1*	23.9	39.5	28.0	22.6	22.8
42.6	56.2	24.1	28.2	56.2	12.2	16.1	35.8	18.7	36.2	23.9	39.5	28.0	22.6	22.8
42.6	56.3	24.2	28.2	56.3	12.1	13.3	35.8	18.7	36.2	23.9	39.5	28.0	22.6	22.8
40.9	54.4	25.5	20.5	40.5	17.6	15.8								
42.7	50.8	23.7	28.3	56.2	11.9	11.2	35.9	18.7	36.3	23.9	39.7	28.1	22.6	22.8
43.6	55.9	27.0	28.7	55.3	12.2	12.3	35.7	18.8	36.2	23.9	39.5	28.0	22.5	22.8
41.2	53.7	25.6	20.6	40.8	18.4	12.8								
39.9	56.4	25.4	20.1	40.8	20.0	15.5								
45.3	46.4	25.2	20.2	33.0	18.7	12.2								
46.3	53.3	25.2	20.7	38.2	11.8	12.2								
41.7	61.9	75.7	32.9	38.3	18.8	12.3								
44.1	64.0	74.0	40.3	53.8	13.4	12.3	35.4	18.5	36.1	23.8	39.5	28.0	22.6	22.8
40.6*	59.6	72.5	34.0	40.4*	20.0	12.3								
41.9	52.3	37.3	71.8	52.2	18.8	12.3								
40.3	54.3	37.3	71.9	51.5	19.1	12.3								
45.3	48.9	24.6	32.5	80.0	17.2	12.3								
43.1	51.3	23.4	30.6	82.1	11.2	12.3								

be reversed.

15	16	17	18	19	20	21	22	23	24	25	26	27	CH_3[b]	CO	Registry no.
24.2	28.2	56.3	12.1	14.0	35.8	18.7	36.2	23.9	39.5	28.0	22.6	22.8	21.5	169.9	1107-37-5
24.2	28.3	56.4	12.1	11.3	35.8	18.7	36.2	23.9	39.5	28.0	22.5	22.8	21.4	170.2	1107-59-1
25.5	20.5	40.5	17.6	12.3									21.3	169.9	1236-13-1
24.1	28.3	56.4	12.3	15.7	35.9	18.8	36.3	23.9	39.6	28.3	22.6	22.9	22.3	169.8	41721-99-7
24.1	28.2	56.3	12.0	13.3	35.8	18.7	36.2	23.9	39.5	28.0	22.6	22.8	21.3	170.2	54657-02-2
25.5	20.5	40.4	17.6	15.2									21.4	170.0	35487-68-4
23.7	28.1	56.2	11.8	11.2	35.9	18.7	36.2	24.0	39.6	28.1	22.6	22.8	21.3	170.1	54676-24-3
25.8	28.6	55.4	12.2	12.2	35.7	18.9	36.2	23.9	39.8	28.0	22.6	22.8	21.8	170.3	54712-41-3
25.5	20.7	40.1	18.1	12.3									22.0	170.4	57031-41-1
25.3	20.1	40.5	19.3	15.1									21.8	169.9	14946-61-3

Section) the peaks in the ^{13}C NMR spectra are shifted linearly downfield with the amount of added shift reagent. The shift changes for the different carbon atoms are reproduced by the pseudocontact shielding expression of McConnell and Robertson,[29] except for those carbons closest to the complexing site, in agreement with previous reports.[23,26,30] Consideration of these shifts alone frequently allows unambiguous signal assignments. Further, by acetylation of the hydroxyl group the resonances of the α and β carbon atoms shift in a predictable manner and allow identification of the corresponding peaks.[24] A secondary α carbon resonance is shifted 1–4 ppm downfield, whereas β carbons are shifted 1–5 ppm upfield; signals of tertiary carbinyl carbons experience much larger downfield α shifts (~11 ppm).[31] The chemical shift data for the acetoxy steroids examined are given in Table II; comparison of the data therein with those in Table I shows the characteristic shifts that take place upon acetylation of the hydroxyl group.

Owing to the difference in the spin-lattice relaxation time of nonmethyl hydrogen bearing carbons (0.2–0.6 sec) and quaternary carbons (4 sec)[26,32] proton noise decoupled spectra obtained under suitable experimental conditions (short pulse repetition time, large pulse width) permit direct identification of the latter as narrow peaks of very low intensity.

A number of ambiguities were resolved by comparing the spectra of corresponding cholestanols and androstanols. Thus the resonances corresponding to the carbon atoms of ring D, as well as to C-12 and C-18, were assigned by considering the shift changes following introduction of the C-17 side chain. Even carbon atoms 8 and 7 are affected by the presence of the side chain, since their resonances are shifted slightly (~0.4 ppm), but consistently, upfield in the cholestanol. The assignment for the carbon atoms of ring A and the C-19 methyl group in compounds **1–15** and **17–20** are corroborated by the hydroxyl substituent effects reported for 10-methyl-*trans*-decalols.[33]

For a few examples the above methods were either not practical or not adequate to allow unequivocal assignments. Comparison with the ^{13}C NMR spectra of further substituted steroids usually resolved the ambiguities. Thus, for the assignment of the spectra of compounds **19, 20, 22,** and

Table III
Hydroxyl Substituent Effects (in ppm)[a]

OH position	α carbon	β carbon[b]	γ carbon[b,c]
1β	40.1	11.0 (2); 6.2 (10)	−2.2 (3) t; −0.9 (5) t; 0.3 (9) g; −5.5 (19) g
1α	32.7	6.6 (2); 3.7 (10)	−6.7 (3) g; −8.1 (5) g; −7.7 (9) g; +0.7 (19) t
2α	45.7	9.4 (1); 9.4 (3)	−1.5 (4) t; 1.2 (10) t
2β	45.7	6.4 (1); 7.0 (3)	−5.3 (4) g; −0.3 (10) g
3β	44.4	9.3 (2); 9.1 (4)	−1.7 (1) t; −2.2 (5) t
3α	39.6	6.8 (2); 6.7 (4)	−6.5 (1) g; −7.9 (5) g
4α	41.2	9.4 (3); 7.1 (5)	−1.8 (2) t; −6.4 (6) g; 1.3 (10) t
4β	43.2	7.0 (3); 3.0 (5)	−5.3 (2) g; −3.1 (6) g; −0.1 (10) g
5α	26.0	5.2 (4); 5.4 (6); 3.0 (10)	−7.2 (1) g; −6.2 (3) g; −5.9 (7) g; −8.7 (9) g; 0.0 (19) t
6α	40.8	6.7 (5); 9.5 (7)	−6.4 (4) g; −1.3 (8) t; 0.6 (10) t
6β	43.3	2.7 (5); 7.4 (7)	−3.1 (4) g; −5.3 (8) g; 0.0 (10) g
7β	43.0	9.5 (6); 8.0 (8)	−3.0 (5) t; −1.8 (9) t; −0.8 (14) g
7α	36.0	7.6 (6); 4.1 (8)	−7.9 (5) g; −8.5 (9) g; −5.9 (14) g
11α	48.3	6.1 (9); 11.5 (12)	−0.6 (8) t; 2.0 (10) g; 0.4 (13) t
11β	47.7	3.9 (9); 8.8 (12)	−4.3 (8) g; 0.1 (10) g; −0.9 (13) g
12β	40.7	9.0 (11); 5.5 (13)	1.2 (9) t; −1.4 (14) t; −2.3 (17) g; −5.8 (18) g
12α	33.7	7.5 (11); 4.5 (13)	−6.8 (9) g; −8.3 (14) g; −7.5 (17) g; 1.1 (18) t
15α	50.0	7.2 (14); 12.4 (16)	−0.5 (8); 1.2 (13); −2.4 (17)
15β	47.0	4.9 (14); 13.5 (16)	−4.1 (8); −0.2 (13); −0.1 (17)
16α	51.3	11.8 (15); 11.7 (17)	1.1 (13); −2.4 (14)
16β	51.4	11.8 (15); 11.0 (17)	−0.5 (13); −0.4 (14)
17α	39.5	12.0 (16); 4.5 (13)	−7.4 (12); −5.8 (14); −0.9 (15); −0.4 (18)
17β	41.6	10.1 (16); 2.3 (13)	−2.1 (12); −3.4 (14); −2.1 (15); −6.4 (18)

[a] The numbers given are the chemical shift differences, $\delta^{ROH} - \delta^{RH}$ for corresponding carbon atoms; a negative sign signifies an upfield shift. [b] Carbon atom number given in parentheses. [c] g and t designate gauche and trans γ interactions.

23, the ^{13}C NMR spectra of the following steroids, not included in the tables, were taken into consideration: 3β-acetoxy-7α- and -7β-cholestanols, 9,12,12-trideuterioandrostane-3β,11β-diol, and 5α-pregnan-12α-ol. As a case in point, in the spectrum of 7β-cholestanol assignment of the C-9 and C-14 and the C-3 and C-15 resonances was not obvious using the above cited methods. Comparison with the spectrum of 3β-acetoxy-7β-cholestanol allows the distinction to be made, since only C-9 and C-3 are expected to shift significantly upon introduction of the C-3 acetoxy group.

Discussion

The α Substituent Effect. Several reports have appeared discussing the stereochemical dependence of the shielding of the carbinyl carbon in cyclohexanols.[34-36] Until recently there appeared to be general agreement that the chemical shift of the carbinyl carbon depends markedly on the orientation of the hydroxyl group; i.e., that an axial hydroxyl group shields the α carbon atom more than does the corresponding equatorial substituent. However, in a recent study by Grover and Stothers[33] of the ^{13}C NMR spectra of 10-methyl-*trans*-decalols, this rule was shown to be inapplicable where the hydroxyl group takes part in a syn-diaxial OH–CH_3 interaction. In the present investigation we have attempted to relate in a more general and quantitative way the hydroxyl substituent effect on the α-carbon resonance with the steric relationship between the hydroxyl group and other atoms in the molecule.

To facilitate the following discussion, the hydroxyl substituent effects in steroids are given in Table III, in which the epimeric pairs are grouped together, with the equatorially substituted compound listed first. We have found that the hydroxyl group substituent effect on chemical shift of the carbinyl carbon atom is not primarily dependent on the stereochemistry (i.e., axial or equatorial) of the hydroxyl group. Rather it can be related to the number, n, of γ-gauche carbons possessing hydrogen atoms able to interact with the hydroxyl group, and to the number of skew pentane interactions, p, of the hydroxyl group with carbon atoms. The following relationship reproduced the trend of the substituent effect, Δ_α, on the carbinyl carbon atom except where the hydroxyl group interacts strongly with atoms of ring D.

$$\Delta_\alpha(\text{ppm}) = 45.0 + 3.5p - 3.5n$$

The shifts predicted using this relationship are within 2 ppm of the experimental values, except for the 1β isomers **3** and **4**, discussed below. The constant term, 45.0 ppm, is the substituent effect at a hydroxylated secondary carbon atom free of steric interactions; the corresponding constant will, of course, be different for tertiary hydroxyl groups. The α shift observed in 5α-cholestanol, the only tertiary alcohol included in the present study, suggests that for tertiary alcohols the constant term is 40.0 ppm. The experimental Δ_α for 5β-cholestanol (A/B ring junction cis) was determined to be 29.1 ppm [73.3 (ROH) − 44.2 (RH)[37]], which is within 0.4 ppm of the value calculated using 40.0 ppm as the constant term; however, neither of these two compounds, 5α- and 5β-cholestanol, exhibits a hydroxyl carbon skew pentane interaction, and it has hence not been possible to estimate whether the parameter associated with this interaction holds for tertiary alcohols.

In simpler systems (e.g., cyclohexanols), where skew pentane interactions are absent, the above relationship reduces to the usual generalization that the carbinyl carbon is less shielded in the equatorial epimer than in the axial one. This follows, since the hydroxyl group in the latter usually has a higher number of γ-gauche interactions. Dalling et al.,[38] in their parameter set for calculating the shifts of methyldecalins, found the parameter (V_g) associated with γ-gauche interactions of *neighboring* carbon atoms to be −3.5 ppm; it is noteworthy that this value is the same as the one derived here for examples in which the neighboring carbon atom is replaced by a hydroxyl group. A similar comparison of the value associated with skew pentane interactions is not possible, since this geometrical arrangement was not represented in the decalins reported by Dalling et al.[38]

In cyclohexanols the upfield α shift associated with γ-gauche interactions of the hydroxyl group with proximate hydrogens on γ carbons has been explained[36] as being due to a transmission, through the C–O bond, of this steric interaction to the carbinyl carbon. This interaction also pro-

duces the well-established steric upfield shift at the γ carbon atoms. The downfield α shift associated with a hydroxyl carbon skew pentane interaction could then be the result of geometrical deformations (torsion and valence angle deformation) induced to relieve the severe skew pentane interaction. Thus, in steroids with syn-diaxial hydroxyl–methyl interactions (e.g., 2β-cholestanol) partial relief of this interaction can be obtained by an outward bending of the hydroxyl group. Such a bending will at the same time decrease the gauche interactions of the hydroxyl group with the γ-carbon atoms, and thereby produce at least part of the downfield carbinyl carbon shift. That such deformations do take place is supported by the diminished γ-gauche hydroxyl substituent effects found in steroids with syn-diaxial interactions (see below). Furthermore, bending of the hydroxyl group will in itself influence the chemical shift at the α carbon atom by slightly changing its geometry. In certain cases [e.g., 11α-androstanol (**21**)] downfield carbinyl carbon shifts may also be the result of diminished γ-gauche interactions of the α carbon atom provided the deformations induced to relieve the skew pentane interaction(s) of the hydroxyl group with carbon atoms at the same time relieve these γ-gauche interactions. This interpretation of the observed downfield shifts is supported by noting that the carbinyl carbon resonances of the 1β steroid alcohols **3** and **4** experience a smaller downfield shift than expected. The hydroxylated carbon atom in the 1β isomers does not have a hydrogen able to interact with γ-gauche carbon atoms; undoubtedly the presence of γ-gauche interactions places restrictions on the ways in which relief can be found for the skew pentane interaction. Furthermore, the γ-gauche interaction of the hydroxyl with the C-19 methyl group is apparently not reduced by the hydroxyl C-11 skew pentane configuration, as seen by comparison with ^{13}C NMR data for 1β-10-methyl-*trans*-decalol,[33] where this interaction is absent. The relatively small Δ_α found for 1β steroid alcohols (40.1 ppm) [compared to the calculated Δ_α (45.0 ppm)] is therefore assumed to indicate that the geometrical deformations taking place around the 1β-hydroxyl group to relieve the skew pentane interaction are different from those occurring in, e.g., 11α-androstanol (**21**), due to the absence of γ-gauche interactions of the α carbon atom. In the 7β alcohol (**20**) the interactions in question are comparable to those in the 1β isomers and the experimental Δ_α (43.0 ppm) is also in this case smaller than the calculated value (48.5 ppm). Of course, this may be due partly to the five-membered nature of ring D, making the distance between C-15 and the 7β hydroxyl larger than in a usual skew pentane interaction, and consequently diminishing the requirements for relief.

In order to test the predictive value of the relationship given above the chemical shifts of the carbinyl carbon atoms in various alcohols have been calculated and compared to (experimental) literature values: *cis*- and *trans*-4-*tert*-butylcyclohexanols,[36] the epimeric 1- and 2-*trans*-decalols,[33] the epimeric 1-, 2-, 3-, and 4-10-methyl-*trans*-decalols,[33] cholic acid,[37] litho-, deoxy-, chenodeoxy-, and hyodeoxycholic acid,[37] and lanosterol.[39,40,41] All the calculated shifts are within 2 ppm of the experimental values. The agreement between predicted and experimental values could probably be improved by adding more parameters. However, the chemical shift of the carbinyl carbon atom varies with solvent and concentration, and it would be meaningless to refine the equation to yield an agreement within narrower limits than these variations allow.

The β Substituent Effect. The influence of a hydroxyl group on the chemical shift of β carbon atoms varies considerably in magnitude, covering (see Table III) a range from 13.5 to 2.3 ppm. It has previously[33,36] been found that the β carbon atom is more shielded by an axial than by an equatorial hydroxyl group; for the same orientation of this group, the more substituted β carbons show the smaller shifts.[33,42] The origin of the β-substituent effect is not yet understood, but it has been suggested[36] that the difference in β-substituent effects between axial and equatorial hydroxyl groups reflects γ-gauche interactions of the axial hydroxyl group, producing an elongation of the C^β–C^γ bond. Such an elongation should give rise to an upfield shift at the β carbon atom. The upfield β shifts previously associated with branching at the β carbon atom may very well also be a consequence of this interaction, since substitution at the β carbon atom usually leads to more γ-gauche interactions of equatorial as well as axial hydroxyl groups, except when the hydroxyl group and the substituent at the β carbon atom exist in a trans-diaxial relationship. 1α-Cholestanol (**2**) provides an example of the latter, with the hydroxyl and the substituent at the β carbon atom, the C-19 methyl group, trans to each other. The hydroxyl β shift at C-10 (3.7 ppm) is, however, close to the β shifts observed in similar compounds which lack this trans β substituent (e.g., the β shift at C-8 in 7α-cholestanol is 4.1 ppm). In general, we have found that the variation in β shifts in the six-membered rings can be related quantitatively to the number of γ-gauche interactions of the hydroxyl group, except when the latter is involved in a skew pentane arrangement (see below). The hydroxyl β substituent effects, Δ_β, for secondary hydroxyl groups are reproduced by the equation

$$\Delta_\beta(\text{ppm}) = 9.3 - 2.4q$$

where q is the number of γ-gauche interactions of the hydroxyl group with γ carbon atoms connected to the β carbon atom in question. Thus, for 7α-cholestanol, q equals 2 for C-8 and 1 for C-6. Where $q = 0$ the shifts calculated are within 0.3 ppm of the experimental values. With $q = 1$ and 2 the interval becomes larger, ±0.5 and ±0.9 ppm, respectively.

Only one of the steroids studied, 5α-cholestanol (**16**), has a tertiary hydroxyl group. The shifts of the three β carbon atoms in this compound suggest a similar equation for Δ_β in tertiary alcohols, replacing the constant term of 9.3 ppm by 7.7 ppm. This is supported by the experimental Δ_β values found for 5β-cholestanol [$\delta^{ROH} - \delta^{RH}$;[37] 5.8 ppm (C-4); 7.5 ppm (C-6); 7.7 ppm (C-10)], all of which are within 0.5 ppm of the values calculated in this way.

The relationship has in addition been used with success to calculate the expected β shifts in decalols and 10-methyl-*trans*-decalols.[33] Further support for the suggestion that the β shifts may be estimated quantitatively from the number of γ-gauche interactions of the hydroxyl group may be found in the reported[36] ^{13}C NMR data for alkylcyclohexanols. In this group of compounds the β substituent effect of a hydroxyl group is generally smaller than in the steroid series. However, the trend of the β shifts in the cyclohexanols is represented by a similar equation, as for the steroids, using 8.1 ppm as the constant and 2.6 ppm as the q parameter. The reason for the difference in the numerical values of the parameter should probably be sought in the greater flexibility of the monocyclic system and, to a certain extent, in the presence in the cyclohexanol series of interconverting conformers.

The β substituent shifts of the acetoxy group (Table II) can likewise be related quantitatively to the number (q) of γ-gauche interactions of the acetoxy group, but with considerably smaller parameter values: the constant term is found to be 5.3 ppm and the q parameter to be 1.2 ppm. These values apply for secondary acetoxy groups not involved in skew pentane interactions. In the tertiary 5α-acetoxycholestane the effect of the β acetoxy substituent is to

shield C-4 and C-6, and to deshield C-10. These observations indicate a strongly perferred conformation of the 5α-acetoxy group, with the O–CO bond symmetrically situated between C-4 and C-6 and pointing away from C-10.

As mentioned previously, the β shifts of hydroxyl (or acetoxy) groups having a skew pentane interaction with a carbon atom do not follow the relationship discussed above. In most cases one of the experimental Δ_β values agrees with the calcualted Δ_β, while the other is either too small or too large. This lack of correspondence is indeed what should be expected, if the variation in β shift is related to steric interactions of the hydroxyl group, since introduction of skew pentane interactions must cause significantly different deformations of the skeleton than do γ-gauche interactions. Thus, in 1β-androstanol (**3**), where the hydroxyl group has a skew pentane interaction with C-11, an unusually large β effect (11.0 ppm) is found at C-2. The calculated Δ_β value is 9.3 ppm (q = 0). It is conceivable that this compound can relieve the steric interaction by compression of the C^β–C^γ bond and thereby give rise to a greater downfield β shift. A quite similar geometrical arrangement is found in the 11α-hydroxy steroid (**21**), where C-12 also shows a large β hydroxyl substituent effect (11.5 ppm, calculated to be 9.3 ppm).

The β substituent shifts for hydroxyl groups located in ring D vary over a somewhat wider range (2.3–13.5 ppm) than when it is confined to one of the six-membered rings (2.9–11.5 ppm). Although the β shifts of the five-membered ring derivatives do not quantitatively follow a relationship as do the β carbon shifts in the six-membered ring alcohols, they do show similar trends. Average β substituent effects are 12–13 ppm for a hydroxyl group free from steric interactions, and in ring D this value is also reduced in proportion to the number of steric interactions of the hydroxyl group with γ carbons connected to the β carbon concerned.

The γ Substituent Effect. Inspection of Table III reveals a number of general trends for the γ substituent effect of the hydroxyl group. The expected geometrical dependence of this effect allows the separation of these shifts in the six membered rings into γ-gauche shifts, where the hydroxyl and the γ carbon atom are gauche to each other, and the analogously defined γ-trans shifts. Shifts of the latter type are often small; in the present compounds they span a range of +1.3 to −3.0 ppm. Downfield (or zero) shifts are found only at quaternary or methyl γ carbons.

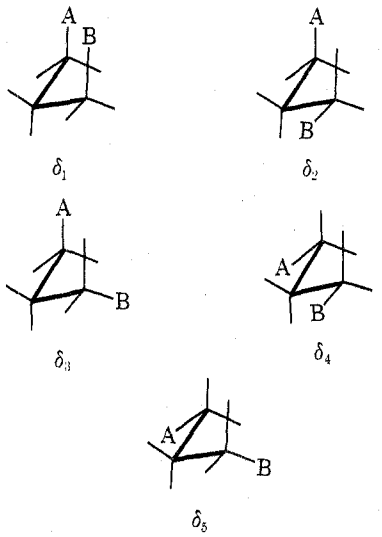
The magnitude of γ-gauche substituent effects depends upon whether the γ carbon atom is secondary or tertiary. Average values are −6.5 ppm for methylene carbons and −7.8 ppm for methine carbon atoms. The larger upfield shifts of methine carbon signals are probably a consequence of the fact that these are bridgehead carbon atoms, which will have less opportunity to escape the gauche interaction than the more flexible methylene carbons. Similar results have also been found for the decalols.[33] Exceptions to this general trend are found where the hydroxyl group is 1,3-syn-diaxial to a methyl group, as in compounds **6, 7, 14, 15, 18,** and **22** (Table I). In each of these the γ-gauche hydroxyl effect is decreased to ∼−4.5 ppm for both methylene and methine γ carbon atoms. It seems reasonable to assume that this reduction of the γ-gauche effect is associated with the deformations that take place to relieve the 1,3-syn-diaxial interaction. Such deformations should cause all of the hydroxyl γ-gauche carbons to become less shielded. This is unlikely with torsional angle deformations alone, which relieve the interaction by flattening of the ring in question, because the puckering transmitted to the next ring would increase the steric interactions of γ-gauche carbons in this ring, in disaccord with the observed shifts. Thus, valence angle deformation of the interacting groups is probably significant, causing the two groups to bend away from each other. Such a bending would at the same time attenuate the γ-gauche substituent effect by diminishing the steric interactions of these γ-carbon atoms with the hydroxyl group.

A relatively large shielding γ effect is observed whenever γ carbon atoms have a gauche arrangement with a substituent.[27,28] This has been explained[43,44] in terms of steric interaction between hydrogen atoms of both the substituent and the observed γ-gauche carbon, resulting in a slight charge polarization in the C(γ)–H bond. However, this theory is not generally applicable, since similar shielding effects are also found when the substituent is without hydrogen atoms.[42,45] Lippmaa et al.[45] have discussed the origin of the γ-gauche substituent shifts and concluded that hydrogen transmitted chemical shift changes at carbon atoms can be disregarded as a possible cause of the γ effect. In the present study, however, upfield γ-gauche shifts have not been observed where the γ-gauche carbon atoms are without hydrogen atoms able to interact with the hydroxyl group. Thus, the resonances of the γ-gauche carbon atoms in 1β-androstanol (**3**), 1β-cholestanol (**4**), and in 7β-cholestanol (**20**) (C-9 and C-14, respectively) are essentially unshifted relative to their parent hydrocarbons. Likewise, C-5 in chenodeoxycholic acid is almost unshifted (+0.4 ppm) compared to C-5 in lithocholic acid.[37] Furthermore, the substituent shifts of quaternary carbon atoms that are γ-gauche to hydroxyl groups are generally within ±1 ppm. Thus, it appears that the presence of an interacting hydrogen atom on the γ-gauche carbon atom is essential for the upfield γ-gauche shift to be observed in the alcohols of the present study.

The γ effect of a hydroxyl group in ring D follows trends similar to those discussed above. It should be noted that the less puckered conformation of this ring, in which a hydroxyl group is never purely axial or equatorial, causes the steric interactions to be less severe than in rings A, B, and C, and γ-gauche shifts are consequently smaller.

The δ-Substituent Effect. In most studies dealing with substituent effects on carbon shieldings attention has been restricted to the α, β, and γ effects, and very few data relating to δ effects have been reported.[33,46] Grover et al.[33] have shown that the methyl carbon is significantly deshielded in compounds with syn-diaxial δ OH–CH_3 interactions. The more rigid systems were found to give rise to the larger shifts. This deshielding δ effect associated with the 1,3-diaxial OH–CH_3 interaction contrasts with the increased shielding caused by the γ-gauche steric effect. Accordingly we have examined about 80 examples of δ effects in the present material in order to elucidate the origin of these shifts. The five different orientations of a hydroxyl group in relation to its δ carbon atom, designated δ_1–δ_5 as in ref 33, are shown in Chart I and the δ_1 hydroxyl substituent effects are given in Table IV. A number of literature values are included for comparison. The data of the table do not support the proposed generalization[33,47] that the more rigid molecules give the larger δ_1 shifts. In fact, the opposite appears to be the case. The δ_1 effect (Table IV) of a 4β hydroxyl group in 10-methyl-*trans*-decalol (**33**) is 3.4 ppm, 1.0 ppm larger than the 2.4 ppm observed in the more rigid 4β steroidal alcohols, in which the buttressing 11β axial hydrogen prevents the angular methyl group from bending away to escape the syn-diaxial OH–CH_3 interaction; such a bending would otherwise partly relieve the steric interaction. In this connection it is remarkable that the 2β and 4β δ_1 shifts in the steroid series (**6, 7** and **14, 15**) are of the same magnitude as the 2β shift in the decalol (**32**), whereas the 4β decalol isomer (**33**), like the 6β-hydroxylated steroid (**18**), exhibits significantly higher shifts (3.4–3.5 ppm). The

Chart I
The Five Different Orientations of a Hydroxyl Group (A or B) in Relation to Its δ Carbon Atom (A or B)



latter two compounds are those without a buttressing axial hydrogen. Thus the trans fusion next to the site of substitution may well make the 4β-10-methyl-*trans*-decalol more resistant to skeletal twist than the 2β isomer, but valence angle deformation of the methyl group can also relieve the strain, and this process is partly hindered in the 2β alcohol by a buttressing hydrogen.

The 11β hydroxy steroid (**22**) is our only example of a hydroxyl group suffering from two syn-diaxial interactions, which makes comparisons with the rest of the material difficult, since the effects of valence bond deformations and conformational transmission in this crowded molecule become hard to assess. It is, however, interesting to note that the two δ_1 interactions of the 11β hydroxyl group give rise to different δ_1 shifts.

Table IV shows four examples of δ_1 interactions with methylene carbons (**3** and **4**, **20**, **21**, and **34**). A priori, this interaction would be expected to be more severe than the OH–CH_3 interaction, owing to the lesser flexibility of skeletal carbons than methyl groups. The actual δ_1 values are very different; in two situations (**3**, **4**, and **34**) quite large δ_1 shifts (3.8 and 3.2 ppm) are encountered whereas a third (**21**) exhibits the smallest δ_1 shift observed (2.0 ppm). Actually **34** is the one that most easily can reduce its syn-diaxial OH–CH_2 interaction, because the interaction in this case passes over the flexible cis fused A/B ring junction, in contrast to **21**, which has the smallest δ_1 value. Compounds **3**, **4**, and **21** are probably the most rigid cases in the table, owing to the fact that the interacting atoms are situated on each side of two connected trans fusions. Any flattening or puckering in the vicinity of C-1 and/or C-11 that would provide some relief for the interactions will cause concomitant skeletal distortions in the other rings of the steroid molecule. Upon introduction of the 1β hydroxyl group the chemical shifts even of carbon atoms 15 and 18 are affected, presumably as a result of this overall skeletal distortion. 7β-Cholestanol (**20**) represents a special case in this connection, because the five-membered nature of ring D makes the distance from the 7β hydroxyl to the C-15 δ carbon larger than the corresponding distance in, e.g., the 11α-hydroxylated compound. However, the 7β isomer shows the larger δ_1 shift.

With the exception of **3** and **4** it thus appears that when the δ_1 steric interaction can be reduced easily, either by ring flattening or puckering or by valence angle deformation, a large δ_1 value is found, as in **18**, **33**, and **34**. Conversely, the more rigid cases, such as **14**, **15**, and **21**, have smaller δ_1 shifts. This suggests that these differences in molecular flexibility have a bearing on the δ_1 values, and that these shifts reflect the geometrical distortion at the δ carbon atom caused by the relief of the steric interaction, as it is assumed for other long-range effects. That significant distortions do take place is seen from the reduced γ-gauche effects of the hydroxyl group whenever it is syn diaxial to a δ carbon atom, as discussed above. It follows that a small δ_1 shift should result when the distance between neighboring δ_1 nuclei, due to other structural features in the molecule (such as the presence of a double bond), is significantly larger than in a usual syn-diaxial arrangement, since the need for relief of the δ interaction in these cases is less. 15α-Androstanol (**25**) is an example of this, since the distance (measured on Dreiding molecular models) from the 15α hydroxyl to C-7 is considerably larger (~30%) than usual, and this compound shows almost no δ_1 shift at C-7 (0.4 ppm).

Table IV
δ_1 Hydroxyl Substituent Effects (in ppm)[a]

Compd	OH position	δ_1 shift	δ_1 carbon
	5α Steroids		
3, **4**	1β	3.8	C-11
6, **7**	2β	2.5	C-19
14, **15**	4β	2.4	C-19
18	6β	3.5	C-19
20	7β	2.8	C-15
21	11α	2.0	C-1
22	11β	3.2	C-19
22	11β	2.4	C-18
	10-Methyl-*trans*-decalols[b]		
32	2β	2.1	C-10
33	4β	3.4	C-10
	5β Steroid[c]		
34	7α	3.2	C-4

[a] See footnote a, Table III. [b] Taken from ref 33. [c] The δ_1 value given is the C-4 chemical shift difference between chenodeoxycholic acid and lithocholic acid (ref 37).

The difference in δ_1 shifts for the structurally similar compounds **3**, **4**, and **21** may originate from circumstances similar to those that cause the α substituent effect in **3** and **4** (but not in **21**) to deviate from the general pattern.

Without exception the other possible orientations of δ carbons, δ_2–δ_5, give rise to shifts smaller than those found for δ_1 orientations. They span a range of +1.7 to −1.1 ppm, but of the 70 shifts examined only 8 are larger than 1 ppm. Of all the δ shifts nearly half are downfield, among which the δ_1 shifts are only a minor part. For the δ_2 shifts a trend appears, as only those compounds which have an α axial hydroxyl show small (≤0.5 ppm) shielding δ_2 shifts, whereas the remaining δ_2 shifts are deshielding. In compounds with β axial hydroxyl groups, those with a syn-diaxial interaction, the (deshielding) δ_2 effect varies from 0.2 to 1.7 ppm; compounds with equatorial hydroxyl groups all give rise to δ_2 shifts around 1 ppm. The δ_3 and δ_4 type shifts are with a few exceptions very small, while the δ_5 arrangement in general gives rise to larger (~0.8 ppm) upfield shifts.

Studies are now in progress on the ^{13}C NMR spectra of polyfunctional steroids in order to determine to what extent our generalizations of monohydroxylated steroids are usable in such more complicated cases.

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Reactions of α-Ketols and Other 21-Hydroxy Steroids with Phosgene. IV. Formation of 20-Chloro-17,20-cyclic Carbonates from 17α-Hydroxy-20-ones[1]

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Reaction of 17-hydroxy-20-oxopregnenes and the homologous 21-norpregnenes with excess phosgene in methylene chloride–pyridine (condition C) affords chiefly 20β-chloro-17,20α-cyclic carbonates. The epimeric 20α-chloro-17,20β-cyclic carbonates are minor products. Configurational assignments at C-20 were based primarily on optical rotatory properties. Unlike 20ξ-chloro-20,21-cyclic carbonates, the new isomeric chlorocarbonates do not undergo dehydrohalogenation in hot pyridine or acetone–sodium iodide–triethylamine. However, treatment of chlorocarbonates **9a**, **2a**, and **4a** with zinc in acetic acid gave the corresponding $\Delta^{20,21}$-17,20-cyclic carbonates **21**, **22**, and **23** in modest yields. Similar reaction of the C-21-unsubstituted derivatives **7a** and **11a** furnished the corresponding 20β-acetates **26a** and **25a**. Chlorocarbonates of the latter type were converted in refluxing methanol to an epimeric mixture of 20-methoxy-17,20-cyclic carbonates (**27a,b** and **28a,b**). Acid hydrolysis of the 21-acetates **9a** and **10a** gave the respective 21-ols **29a** and **30a** in good yield together with smaller amounts of the 17-*O*-carbomethoxy-21-acetates **31** and **32**. The stability of the 17,20-cyclic carbonate ring to acidic reagents was also illustrated by the oxidation in chromic anhydride–acetic acid of the 21-ol **30a** to the 21-oic acid, obtained as the methyl ester **36a**.

In the second paper of this series[3] we reported that reaction of 17-deoxy-α-ketols in pyridine with excess phosgene at 0° (condition B) affords chiefly an epimeric mixture of 20-chloro-20,21-cyclic carbonates (partial formula a, Scheme I). Unpublished experiments at that time showed that hindered tertiary α-ketols such as cortisone acetate are not affected by these heterogeneous reaction conditions, and can be recovered in nearly quantitative yields.