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NMR SPECTRA OF SOME 3,6-DISUBSTITUTED-5α-OXYGENATED CHOLESTANES

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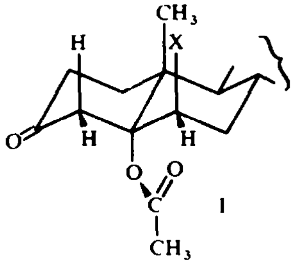
Abstract—The influence of substitituents at C-3, C-6 and C-5α on the chemical shifts of the 3α-, 3β-, 4α-, 4β- and 6α-protons in the cholestane series are described.

DURING chemical studies involving 5α-hydroxy- and 5α-acetoxy-3,6-disubstituted cholestanes we had occasion to examine in some detail the NMR spectra* of these compounds. For many of these compounds, in addition to the protons geminal to substituents at C-3 and C-6, the 4α- and 4β-proton resonances appeared clearly separated from the methylene envelope region of the spectrum. The signals due to the 4α- and 4β-protons were identified by double-irradiation experiments.



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Comparison of chemical shift data for the 6α-proton of the 5α-hydroxy- and 5α-acetoxy- derivatives of 3,6β-substituted cholestanes (Table 1) provides more extensive documentation for the effect[1] of acylation of a 5α-OH group on the chemical shift of a 6α-proton. Similar marked shifts (Table 2) in the 4α-proton resonance were found to occur on acetylation of the 5α-OH group of 6-substituted-3-keto-cholestan-5α-ols. The parallel shifts in the 4α- and 6α-proton resonances found for these latter compounds are consistent with a preferred conformation for the 5α-acetate function in which the CO group is symmetrically located relative to the 4α- and 6α-protons. In contrast to the marked deshielding effect on the 4α- and 6α-proton resonances of a 5α-acetate group, acetylation of a 5α-OH group results in shielding of the 4β-proton resonance (Table 2). Table 2 also reveals the effect on the chemical shift 4α- and 4β-proton resonances of variation of 6β-substituents.

Naryanan *et al.*[1,2] have suggested that the preferred conformation for the 5α-acetate function is that one (I) in which the CO group is eclipsed with the $C^{5\alpha}$-O bond. With the ester group in this orientation the marked deshielding of the 4α- and 6α-

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* Determined at 60 Mc for 10% w/v solutions in $CDCl_3$ with $CHCl_3$ and TMS as internal standards.

protons must arise from a CO oxygen atom-proton proximity effect rather than as a result of the anisotropy of the CO function.[3]

Acetylation of a 5α-OH group of 3β,6-disubstituted-cholestan-5α-ols results in a shift (ca. 0·4 ppm) to higher field of the 3α-proton resonance (Table 3). These values are in accord with the isolated result (0·43 ± 0·05 ppm) for the 3β-acetoxy-5α-hydroxy-6β-acetylthio-5α-cholestane system.[4] The 3β-proton resonance of 3α,6β-disubstituted-cholestan-5α-ols was subject to only minor shifts (0·01–0·07 ppm) to higher field on acetylation of the 5α-OH group.

TABLE 1. CHEMICAL SHIFT OF 6α-H (PPM DOWNFIELD FROM TMS) FOR 3,6-DISUBSTITUTED-5α-OXYGENATED CHOLESTANES

3-Substituent	6-Substituent	6α-H for 5α-Hydroxy-	6α-H for 5α-Acetoxy-	$\delta_{5\alpha\text{-OAc}}-\delta_{5\alpha\text{-OH}}$
C=O	β-OAc	4·72	5·90	+1·18
C=O	β-Cl	3·85	5·20	+1·35
C=O	β-F	4·24	5·50	+1·26
β-OAc	β-OAc	4·75	5·87	+1·12
β-OAc	β-Cl	3·85	5·12	+1·27
β-OAc	β-F	4·23	5·45	+1·22
$-CH_2-$	β-OAc	4·68	5·80	+1·12
α-OH	β-OAc	4·75	5·80	+1·05
α-OAc	β-OAc	4·74	5·78	+1·04
β-Cl	β-OAc	4·72	5·80	+1·08
β-OH	β-Cl	3·85	5·05	+1·20
α-OH	β-OH	3·58	4·65	+1·07

TABLE 2. CHEMICAL SHIFT (PPM) OF 4α-H AND 4β-H FOR 6-SUBSTITUTED-CHOLESTAN-3-ONES

6β-Substituent	4α-H for 5α-Hydroxy-	4α-H for 5α-Acetoxy-	$\delta_{5\alpha\text{-OAc}}-\delta_{5\alpha\text{-OH}}$
H	2·12	3·27	+1·15
OAc	2·04	3·31	+1·27
Cl	2·15	3·38	+1·23
F	2·12	3·33	+1·22

6β-Substituent	4β-H for 5α-Hydroxy-	4β-H for 5α-Acetoxy-	$\delta_{5\alpha\text{-OAc}}-\delta_{5\alpha\text{-OH}}$
H	2·67	2·51	−0·16
OAc	2·88	2·77	−0·11
Cl	3·34	3·14	−0·20
F	3·15	2·98	−0·17

The effect of acetylation of a 5α-OH group on the chemical shifts for the 4α- and 4β-protons is markedly dependent (Table 4) on whether C-6 is tetrahedral or trigonal. The introduction of a ketone function at C-6 into 5α-hydroxy-3-keto-cholestane is accompanied by a shift of the 4α-proton resonance to lower field (0·19 ppm); for 5α-acetoxy-3-keto-cholestane the 4α-proton resonance shifts to *higher* field (0·49 ppm) on the introduction of a 6-ketone function. It is believed that these results for the 4α-proton chemical shift in the 5α-acetoxy compounds reflect a change in conformation of the 5α-acetate group when C-6 is trigonal. This change in conformation may be the consequence of either (or both of) the introduced carbonyl–carbonyl dipolar interaction or the removal in the 6-ketone of the conformational constraint normally exerted on the acetate group by the 6α-proton.

TABLE 3. CHEMICAL SHIFT (PPM) OF 3α-H AND 3β-H FOR 3,6-DISUBSTITUTED-5α-OXYGENATED-CHOLESTANES

3β-Substituent	6-Substituent	3α-H for 5α-Hydroxy-	3α-H for 5α-Acetoxy-	$\delta_{5\alpha\text{-OAc}}-\delta_{5\alpha\text{-OH}}$
OAc	$-CH_2-$	5·18	4·80	−0·38
OAc	β-OAc	5·17	4·75	−0·42
OAc	α-OAc	5·08	4·67	−0·41
OAc	β-Cl	5·12	4·72	−0·40
OAc	β-F	5·12	4·75	−0·37
OH	β-Cl	4·00	3·58	−0·42
OH	$-CH_2-$	4·05	3·70	−0·35

3α-Substituent	6-Substituent	3β-H for 5α-Hydroxy-	3β-H for 5α-Acetoxy	$\delta_{5\alpha\text{-OAc}}-\delta_{5\alpha\text{-OH}}$
OH	β-OAc	4·22	4·20	−0·02
OH	β-OH	4·25	4·18	−0·07
OAc	β-OAc	5·26	5·20	−0·06

TABLE 4. CHEMICAL SHIFT (PPM) OF 4α-H AND 4β-H FOR 3,6-DISUBSTITUTED-5α-OXYGENATED-CHOLESTANES

3-Substituent	5α-Substituent	4α-H for $C^6 = 0$	4α-H for $-C^6H_2-$	$\delta_{CH_2}-\delta_{CO}$
C=O	OH	2·31	2·12	−0·19
C=O	OAc	2·78	3·27	+0·49
β-OAc	OAc	2·39	2·79	+0·40

3-Substituent	5α-Substituent	4β-H for $C^6 = 0$	4β-H for $-C^6H_2-$	$\delta_{CH_2}-\delta_{CO}$
C=O	OH	2·96	2·67	+0·29
C=O	OAc	2·97	2·51	+0·46

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