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DESHIELDING EFFECT ON NEIGHBOURING PROTONS ON THE ESTERIFICATION OF A HYDROXYL GROUP* +

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The deshielding or shielding effect produced on esterifying (1) or methylating (2) a hydroxyl group, on the proton or the protons on the carbon holding the hydroxyl group is well documented. However, work on the effect on neighbouring protons concerns with multiple acetates and thiocompounds in ring A of steroids (3,4) which being a non-rigid end ring, may not also be the best system for the study. We have prepared and determined the PMR spectra of a number of known and new steroid and triterpene alcohols and esters in the rigid ring B of these compounds, which now show that the deshielding effect of the ester carbonyl on the adjacent protons are somewhat different from that reported before. Our results are given in Table 1.

The Table shows that on esterification of an axial tertiary hydroxyl group (5α, here) by a carboxylic acid (acetic or formic), the equatorial protons on the adjacent carbon atoms (C_6 and C_4 here) are shifted downfield by over 1 PPM (8) (I to XIV and XVII, XVIII), i.e. to about the same extent by which the proton on a secondary hydroxylic carbon is deshielded when the hydroxyl is acetylated (1,2). That the presence of an ester carbonyl at C_6 or C_4 is not necessary for this shift, is shown by the same shifts found in the 6β-hydroxylic-5α-acetates (see III & IV, and XI & XII). As the conformation of the acetates of secondary hydroxyl groups in rigid systems is now fairly well established (9), as that in which the carbonyl group, nearly eclipses the secondary hydrogen, Dreiding models show that the distance between the deshielding carbonyl and the secondary hydrogen concerned in such cases (e.g. between the 6β-acetate carbonyl and the 6α-H, or the 6α-acetate carbonyl and the 6β-H) is about 2Å. Since the 4α-H and the 6α-H are equally deshielded by the 5α-ester carbonyl, the latter has to be symmetrically situated between the two protons and be near them. This can only happen if the 5α-ester carbonyl assumes such a conformation that it is parallel to the known conformation of the 6α-ester carbonyl and also points

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+Stereochemical studies by PMR spectroscopy VIII.

TABLE 1

	Compound	Chemical shift of C_6-H, in δ	Downfield shift of the C_6-H on esterification of 5α-OH	Compound reference
I	Cholestane-3β,5α,6β-triol, 3-methyl ether, 6-acetate.	4.62	1.20	5
II	Cholestane-3β,5α,6β-triol, 3-methyl ether 5,6-diacetate	5.83		m.p.108°, $(\alpha)_D$ -53°
III	Cholestane-3β,5α,6β-triol, 3-methyl ether.	3.55	1.20	5
IV	Cholestane-3β,5α,6β-triol, 3-methyl ether 5-acetate.	4.75		m.p.171° $(\alpha)_D$ -11°
V	Cholestane-3β,5α,6β-triol, 3-methyl ether 6-formate.	4.86	1.10	m.p. 152° $(\alpha)_D$ -28°
VI	Cholestane-3β,5α,6β-triol, 3-methyl ether, 5-acetate, 6-formate.	5.96		$(\alpha)_D$ -34°
VII	Cholestane-3β,5α,6β-triol, 3-methyl ether, 5,6-diformate.	5.91	1.05	$(\alpha)_D$ -35°
VIII	Cholestane-3β,5α,6β-triol, 3,6-diacetate.	4.72	1.03	6
IX	Cholestane-3β,5α,6β-triol, 3,5,6-triacetate.	5.75		
X	Cholestane-3β,5α,6β-triol, 6-acetate.	4.75	1.00	6
XI	Cholestane-3β,5α,6β-triol	3.55	1.05	6
XII	Cholestane-3β,5α,6β-triol, 5-acetate.	4.60		
XIII	Cholestane-5α,6β-diol,6-acetate	4.71	1.11	7
XIV	Cholestane-5α,6β-diol,5,6-diacetate.	5.82		
XV	Cholestane-5α,6α-diol,6-acetate	5.00	0.1	7
XVI	Cholestane-5α,6α-diol,5,6-diacetate.	5.10		
		C_4-H in δ		
XVII	Cholestane-4β,5α,diol,4-acetate.	4.75	1.03	7
XVIII	Cholestane-4β,5α,diol 4,5-diacetate.	5.78		

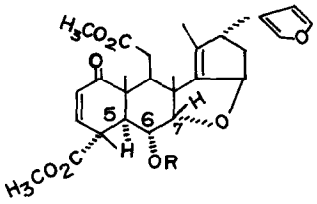
NMR spectra were taken on an A-60 spectrometer at 60 Mc in 10% solution in $CDCl_3$, with TMS as internal standard. All new compounds gave correct analyses.

upwards. That this indeed is the conformation of the 5α-ester carbonyl is confirmed by the solvent shifts in IV, of the 6α-H, $\Delta^{CDCl_3}_{C_6H_6}$ = -0.1 in agreement with its position in front of the carbonyl, and the 5α-acetate methyl $\Delta^{CDCl_3}_{C_6H_6}$ = +0.28, being behind the carbonyl (10,11). It is interesting to note that the distance between the 5α-ester carbonyl and the 4α-H or the 6α-H is also ~ 2Å. These results thus indicate that inductive effect has no significant role in the deshielding of a proton on the carbon holding an aliphatic ester group.

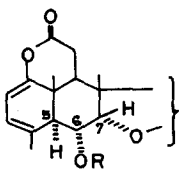
Similar deshielding should be expected for two protons on the two adjacent carbon atoms in the esters of other axial or equatorial tertiary hydroxyl groups, since in those cases, the conformation of the ester carbonyl will be such that it is midway between the two protons. It may also be noted that in the case of esters of primary hydroxyl groups where the deshielding of the two protons concerned is ~ 0.5 PPM only the distance between the carbonyl oxygen and either of the protons, in a similar conformation is ~2.5 Å.

The deshielding effect of an axial ester on an axial proton on the adjacent carbon atom is only about 0.10 (XV & XVI) as would be expected from the conformations.

The effect of esterifying an equatorial hydroxyl group on the axial and equatorial protons on the adjacent carbon atoms is found to be .3 to .45 and 0.02 to 0.05 PPM respectively from the following nimbin derivatives (12).



Nimbin



Pyronimbic acid

		5α-axial H at δ	7β-equatorial H at δ
XIX	Desacetylnimbin (R=H)	3.37	4.01
XX	Nimbin (R=Ac)	3.67	4.03
	Shift on acetylation of 6α-equatorial-OH,	0.30 PPM	0.02 PPM
XXI	'Pyronimbic acid' (R=OH)	2.76	4.15
XXII	Pyronimbic acid acetate (R=Ac)	3.21	4.20
	Shift on acetylation of the 6α-equatorial OH.	0.45 PPM	0.05 PPM

Although the small deshielding effect of 0.02 to 0.05 PPM on the adjacent equatorial proton is reasonable, the large deshielding effect of 0.3 to 0.45 PPM due to the 6α-equatorial ester carbonyl on 5α-axial-H is

not very clear from the known conformation of the carbonyl group.

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