Intramolecular Hydrogen Bonding in Hydroxy-keto-steroids

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The i.r. spectra of hydroxy-keto-steroids with an equatorial-hydroxy-group α to the ketone show a band due to hydrogen bonding (OH · · · O type); those with an axial hydroxy-group α or β to the ketone exhibit two absorption bands, due to a free and a bonded hydroxy-group (OH · · · π type). The mode of multiple hydrogen bonding in epimeric pairs of monohydroxy-diketo-steroids and dihydroxy-monoketo-steroids is discussed. Hydrogen bonding in dihydroxy-keto-steroids is more extensive than in monohydroxy-keto-steroids.

INTRAMOLECULAR hydrogen bonding in diols and hydroxy-ketones has been studied extensively by means of i.r. spectroscopy.[1-5] However, there is little information on the hydrogen bonding of polyfunctional compounds such as monohydroxy-diketo-steroids and dihydroxy-monoketo-steroids. This paper deals with the correlation between conformation and intramolecular interaction in polyfunctional steroids as revealed by hydroxy-stretching frequencies in the i.r. spectrum.

RESULTS AND DISCUSSION

The α-*eq*-hydroxy-ketone (2) showed a single band with a large shift of 130 cm^{-1} relative to the free hydroxy-stretching frequency, indicating the presence of an OH · · · O hydrogen bond.† The α-*ax*-hydroxy-ketones (1) and (3) and the β-*ax*-hydroxy-ketone (4) exhibited two bands, one due to a free hydroxy-group and the other shifted 10—20 cm^{-1} due to an OH · · · π interaction, in accord with the data in ref. 4.

Hydroxy- and carbonyl stretching absorptions of hydroxy-keto-steroids

Compd.	$\nu_{max.}$(O–H)/ cm^{-1}	$\varepsilon^{a}_{max.}$ *	$\nu_{max.}$(C=O)/ cm^{-1}	$\varepsilon^{a}_{max.}$ *
(1)	3614	22	1717	509
	3602	70		
(2)	3482	84	1705	603
(3)	3615	20	1721	485
	3603	66		
(4)	3620	12	1721	525
	3610	65		
(5)	3599	54		
(6)	3487	89	1727	656
			1714	754
(7)	3621			
	3599			
(8)	3532	104	1710	601
	3453	144		
(9)	3575	107	1723	710
	3468	100		
(10)	3496	108		
(11)	3498	92		

* Apparent molecular extinction coefficient (l mol^{-1} cm^{-1}).

5-Hydroxy-5α-cholestane-3,6-dione (5), in which the axial hydroxy-group is α to one keto-group and β to the other, showed a slightly shifted band due to the OH · · · π interaction (Figure 1). It is not clear whether the α- or the β-interaction gives rise to the OH · · · π induced shift, since both would exhibit similar hydroxy-absorption. The absence of a free hydroxy-absorption in this compound indicates an increased OH · · · π interaction.

5-Hydroxy-5β-cholestane-3,6-dione (6), whose hydroxy-group is α-*eq* to one keto-group and β-*ax* to the other affords the best opportunity for competition between the OH · · · π interaction and OH · · · O hydrogen bonding [*cf.* (2) and (4)]. The isomer (6) exhibited a band due to an OH · · · O hydrogen bond only (Figure 1) indicating that it has the conformation shown.

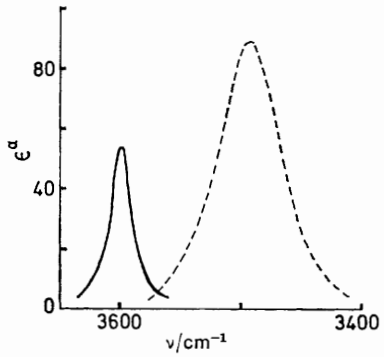

FIGURE 1 The i.r. spectra of 5-hydroxy-5α-cholestan-3,6-dione (5) (full line) and 5-hydroxy-5β-cholestan-3,6-dione (6) (broken line)

3β,5-Dihydroxy-5α-cholestan-6-one (7), which has a *trans*-1,3-diol system and a hydroxy-group α-*ax* to the keto-group, exhibited two hydroxy-bands (Table 1). Since no hydrogen bonding occurs in a *trans*-1,3-diol system (*cf.* *trans*-cyclohexane-1,3-diol [6]) the higher frequency band is due to a free hydroxy-group at C-3 and the lower to an OH · · · π interaction between the C-5-hydroxy- and the carbonyl group. The 5β-isomer (8) with a *cis*-1,3-diaxial diol system and a hydroxy-group α-*eq* to the ketone exhibited a spectrum different from that of the 5α-isomer (7) (Figure 2). The bands

† When the free hydroxy-stretching absorption was not observed, values of 3627 and 3618 cm^{-1} were used for secondary and tertiary hydroxy-groups, respectively, as generally recognized absorption frequencies. OH · · · O Refers to an interaction between the hydroxy-group and the lone-pair electrons of the carbonyl oxygen atom and OH · · · π to that between the hydroxy-group and the π-electrons of the carbonyl group.

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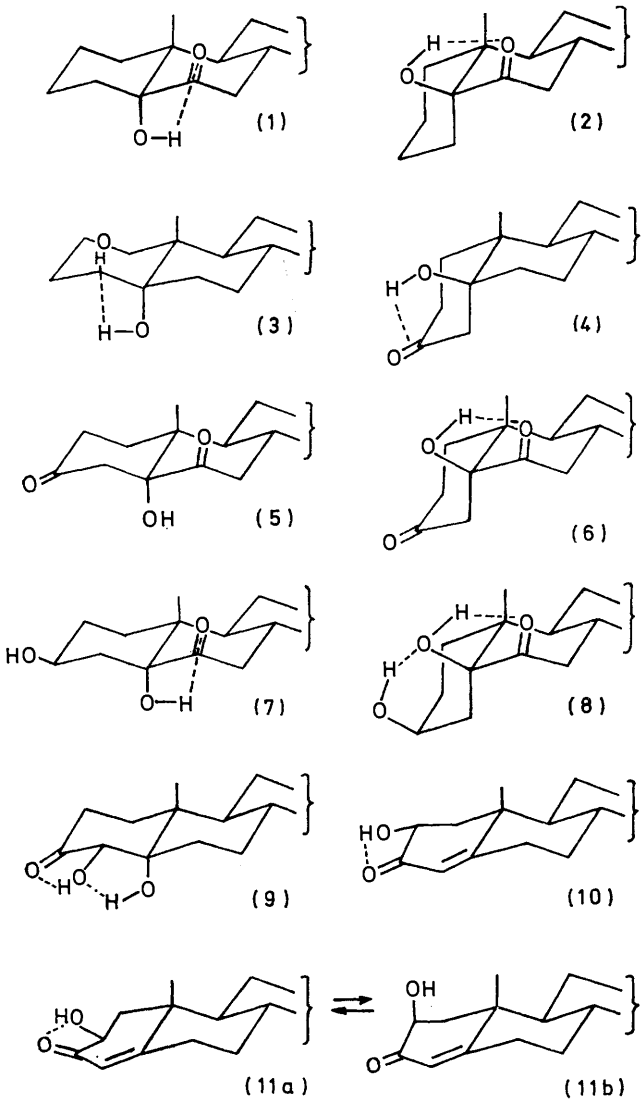
at 3532 and 3453 cm^{-1} are assigned to the OH · · · OH and the OH · · · O hydrogen-bonded hydroxy-absorptions, respectively. The absence of a free hydroxy-band implies intramolecular hydrogen bonding. 4α,5-Dihydroxy-5α-cholestan-3-one (9) also exhibited two peaks (Figure 2). From the Δν values of these bands, the higher frequency band was assigned to the hydrogen-bonded hydroxy-absorption of the *cis*-1,2-diol system and the lower band to the interaction of the α-*eq*-hydroxy- and keto-groups. The Δν values of the OH · · · O band of compounds (8) and (9) were larger than that for 3β,5-dihydroxy-5β-cholestane ($\nu_{max.}$ 3533 cm^{-1} for bonded OH; $\Delta\nu = 87$ cm^{-1}),[2] that for 4α,5-dihydroxy-5α-cholestane ($\nu_{max.}$ 3578 cm^{-1} for bonded OH;



$\Delta\nu = 49$ cm^{-1}),[3] and that for the steroid (2) (Δν *ca.* 130 cm^{-1}). This indicates that hydrogen bonding is enhanced by the electronic effect of the formation of two hydrogen bonds and by the steric effect of the deformation of the carbon skeleton giving the shortest oxygen–oxygen distance. For the compound (8), the formation of the O(3)–O(5) hydrogen bond forces the C-5 hydroxy-hydrogen atom into the most favourable orientation for formation of the O(5)–O(6) hydrogen bond. A similar situation may also occur for compound (9).

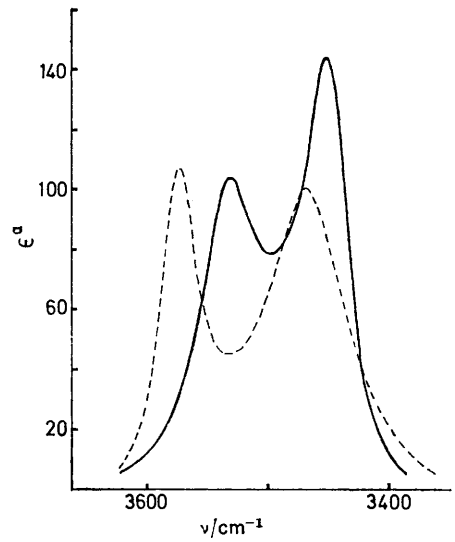


FIGURE 2 The i.r. spectra of 3β,5-dihydroxy-5β-cholestan-6-one (8) (full line) and 4α,5-dihydroxy-5α-cholestan-3-one (9) (broken line)

The epimeric pair of 2-hydroxypregn-4-ene-3,20-diones,[7] (10) and (11), afforded an interesting example of the influence of hydrogen bonding on conformation. The 2α-epimer (10) showed a band due to OH · · · O hydrogen bonding, implying an equatorial orientation of the hydroxy-group in a half-chair conformation. Compound (11) also exhibited an OH · · · O hydrogen-bonded band at almost the same frequency also indicative of an equatorial hydroxy-group. In the energetically favourable half-chair conformation (11b), the hydroxy-group should be axial. However, an unfavourable 1,3-diaxial interaction between the 2-hydroxy- and the 10-methyl groups forces the compound into the half-boat conformation (11a), which is further stabilized by hydrogen bonding between the hydroxy- and the carbonyl groups.

Carbonyl stretching bands were also examined for almost all the compounds. However, the effect of hydrogen bonding on these bands was not clear, as has been previously pointed out.[8]

EXPERIMENTAL

I.r. Spectral Measurements.—The hydroxy- and the carbonyl i.r. spectra were recorded for solutions in dry carbon tetrachloride on a Perkin-Elmer 621 grating spectrometer at a spectral slit width of <2 cm^{-1} at 25°. Sharp and broad peaks were measured with an accuracy of ± 2 and ± 4 cm^{-1}, respectively. The concentrations of samples were 0·005M; sodium chloride cells of 20 mm and 4 mm path

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lengths were used for the measurements of the hydroxy- and the carbonyl stretching frequencies, respectively.

5-Hydroxy-5α-cholestan-6-one (1) *and 5-Hydroxy-5β-cholestan-6-one* (2).—3-Chlorocholest-5-ene was prepared by treating cholesterol with thionyl chloride in pyridine.[9] The chlorocholestene was converted into cholest-5-ene by treatment with metallic sodium in isopentyl alcohol.[10] The cholestene was then hydroxylated with performic acid [11] to give 5,6β-dihydroxy-5α-cholestane (double m.p. 60 and 125°). Oxidation of the diol with *N*-bromosuccinimide afforded 5-hydroxy-5α-cholestan-6-one (1), m.p. 153—154°, $[\alpha]_D^{25}$ +44·5° (*c* 1 in ethanol). 5-Hydroxy-5β-cholestan-6-one (2), m.p. 103—104°, $[\alpha]_D^{25}$ −16·5° (*c* 1 in chloroform),[12] was prepared from the steroid (1) by isomerization with methanolic potassium hydroxide.

5-Hydroxy-5α-cholestan-4-one (3).—4β,5-Dihydroxy-5α-cholestane, prepared from cholest-4-ene by oxidation with performic acid, was further oxidized with *N*-bromosuccinimide to give compound (3), m.p. 158—159°, $[\alpha]_D^{25}$ +37·4° (*c* 1 in chloroform).[13]

5-Hydroxy-5β-cholestan-3-one (4).—Reduction of 4β,5-epoxy-5β-cholestan-3-one with lithium aluminium hydride, followed by oxidation with chromic acid, afforded the ketone (4), m.p. 151—152°, $[\alpha]_D^{25}$ + 63·0° (*c* 2 in $CHCl_3$).[14]

3β,5-Dihydroxy-5α-cholestan-6-one (7) *and 3β,5-Dihydroxy-5β-cholestan-6-one* (8).—Cholesterol was hydroxylated with performic acid [15] to give 3β,5,6β-trihydroxy-5α-cholestane, m.p. 235—238°. Oxidation of the triol with *N*-bromosuccinimide afforded the ketone (7), m.p. 232—233° (decomp.). Isomerization of the ketone (7) with methanolic potassium hydroxide, followed by chromatography, gave the isomer (8), a viscous oil, $[\alpha]_D^{25}$ −5·5° (*c* 2 in $CHCl_3$).[16]

5-Hydroxy-5α-cholestane-3,6-dione (5).—Oxidation of 3β,5,6β-trihydroxy-5α-cholestane with chromic acid in acetic acid afforded the dione (5), m.p. 232—234°, $[\alpha]_D^{25}$ −13·1° (*c* 2 in $CHCl_3$).[17]

5-Hydroxy-5β-cholestane-3,6-dione (6).—Oxidation of compound (8) with chromic acid in acetic acid afforded the dione (6), m.p. 120—121°.[16]

4α,5-Dihydroxy-5α-cholestan-3-one (9).—Cholest-4-en-3-one was hydroxylated with hydrogen peroxide in the presence of osmium tetroxide [13] to give compound (9), m.p. 208—210°, $[\alpha]_D^{25}$ +40·5° (*c* 2 in $CHCl_3$).

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