

305. *Hydroxy-steroids. Part I. Doublets in the Hydroxyl Absorption of Monohydric Alcohols.*

By F. DALTON, G. D. MEAKINS, J. H. ROBINSON, and W. ZAHARIA.

The hydroxyl absorptions of a variety of saturated alcohols in dilute solutions have been examined in the fundamental and overtone infrared regions. Most of the alcohols show doublet absorptions, the degree of splitting varying from the presence of a slight shoulder on the main band (*e.g.*, ethanol) to the appearance of two well-separated bands of almost equal intensities (*e.g.*, 5 α -cholestan-5 α -ol). The suggestion¹ that such doublets arise from a conformational effect is supported, and an attempt is made to assign the components to particular vibrations.

RECENT studies with spectrometers of high dispersive power have shown that the O-H stretching bands of many saturated monohydric alcohols are unsymmetrical even when the conditions of examination (the use of dilute solutions in non-polar solvents) preclude intermolecular association, and there is no site for intramolecular bonding of the hydroxyl

group. Studies of the first overtone¹ and fundamental² regions show that the usual effect is the appearance of shoulders on the low-frequency side of the main peaks. This effect was attributed by Piccolini and Winstein¹ to "conformational heterogeneity," but a different explanation, based on Fermi resonance between the hydroxyl fundamental and a combination band arising from lower-frequency vibrations, has also been considered.²

The study of the hydroxyl bands of monohydric alcohols described here was prompted by an examination of the infrared spectra of steroid 3,5- and 4,5-diols,³ which indicated that certain monohydroxy-steroids should exhibit two well-separated O-H stretching bands. This expectation was confirmed by the present work, which is concerned with the influence of a hydroxyl group's environment on the number and positions of its absorption bands. The results are most readily interpreted in terms of the conformational theory and lead to suggestions about the particular conformations responsible for the components of doublet hydroxyl absorption.

EXPERIMENTAL

Materials.—Compounds 1—8, 10, 11, and 26 in Table 1 (which are commercially available or readily prepared from such materials) were dried, distilled, and fractionated to give samples with sharp b. p.s. A solution of 2,3,3-trimethylbutan-2-ol⁴ (no. 12) in ether was dried over sodium and the alcohol fractionated from sodium to give material with b. p. 129—130°: this compound is extremely hygroscopic, rapidly forming a crystalline hydrate on exposure to air. The di-*t*-butyl compound⁵ (no. 9), *cis*-4-butyl-1-methylcyclohexanol⁶ (no. 13), and the *trans*-isomer⁶ (no. 14) were sublimed at 0.1 mm. and then had m. p.s 46—48°, 91—92°, and 67—68°, respectively. Compounds 1—14 and 26 showed single peaks in gas-liquid chromatography.

The steroids (except no. 25) were prepared by published methods which (except for nos. 19 and 20⁷) are referred to in Elsevier's "Encyclopædia of Organic Chemistry," Vol. XIV and Supplements. The m. p. and $[\alpha]_D$ (in chloroform) of specimens dried at 60—100°/0.1 mm. were: no. 15, m. p. 143—144°, $[\alpha]_D$ +24°; no. 16, 184—186°, +23°; no. 17, 174—175°, -19°; no. 18, 208—211°, +5°; no. 19, 139—141°, +51°; no. 20, 136—138°, +45°; no. 21, 113—114°, +53°; no. 22, 99—100°, +11°; no. 23, 80—81°, +39°; no. 24, 104—105°, +25°.

5 α -Ergosta-7,22-dien-5 α -ol (no. 25).—A solution of 5 α -acetoxy-5 α -ergosta-7,22-dien-3 β -ol⁸ (280 mg.; m. p. 158—161°, $[\alpha]_D$ +29°) and toluene-*p*-sulphonyl chloride (300 mg.) in pyridine (5 ml.) was kept at 0° for 2 days. Dilution with water and extraction with ether gave the 3 β -toluene-*p*-sulphonate (310 mg.), m. p. 116—118° (needles from ethyl acetate-methanol), ν_{\max} 1727, 1182, 1171 cm.⁻¹. This material was refluxed for 2 days with lithium aluminium hydride (500 mg.) in ether (100 ml.), the mixture worked up in the usual way, and the product chromatographed on deactivated alumina (20 g.). Elution with light petroleum-benzene (9:1) afforded 5 α -ergosta-7,22-dien-5 α -ol (135 mg.), m. p. 165—166° after crystallisation from acetone and drying at 100°/0.1 mm., $[\alpha]_D$ +4° (*c* 1.0) (Found: C, 84.0; H, 11.7. C₂₈H₄₆O requires C, 84.3; H, 11.6%).

Spectroscopy.—A Unicam S.P. 100 spectrometer (prism-grating monochromator) operated with evacuated optics at a scanning speed of 14 min./100 cm.⁻¹ and a chart scale of 32 cm./100 cm.⁻¹ was used for the fundamental bands. The overtones were recorded on a Cary 14-M spectrometer which was continuously flushed with dry air and operated at scanning speed 2 min./100 cm.⁻¹, chart scale 14 cm./100 cm.⁻¹. Under the conditions used the spectral slit-widths of the spectrometers were less than 5 cm.⁻¹

The alcohols were examined as dilute solutions in carbon tetrachloride (0.007M and path-length 1 cm. for fundamentals; 0.02M and path-length 10 cm. for overtones). In the Tables of results frequencies of maximal absorption (ν_{\max}) and apparent half-intensity band widths ($\Delta\nu_{\frac{1}{2}}$) are in cm.⁻¹ units, and molecular extinction coefficients (ϵ_{\max}) in mole⁻¹ l. cm.⁻¹ units. The ratio of band areas is the area of the stronger band divided by that of the weaker band. The accuracy of the ν_{\max} values for symmetrical bands and the major components of doublets

¹ Piccolini and Winstein, *Tetrahedron Letters*, 1959, No. 13, 4.

² Flynn, Werner, and Graham, *Austral. J. Chem.*, 1959, **12**, 575.

³ Dalton, McDougall, and Meakins, unpublished work.

⁴ Huston and Barratt, *J. Org. Chem.*, 1946, **11**, 661.

⁵ Bartlett and Schneider, *J. Amer. Chem. Soc.*, 1945, **67**, 143.

⁶ Cross and Whitham, *J.*, 1960, 3892.

⁷ Castells, Fletcher, Jones, Meakins, and Swindells, *J.*, 1960, 2785.

is estimated to be ± 2 and ± 4 cm^{-1} for the fundamental and overtone regions, and the values were reproducible to ± 1 and ± 2 cm^{-1} , respectively: with the weaker components of poorly resolved doublets the errors may be larger.

TABLE 1.
Hydroxyl absorption of alcohols.

No.	Compound	Fundamental			Ratio of band areas	Overtone			Ratio of band areas
		ν_{max}	ϵ_{max}	$\Delta\nu_{\frac{1}{2}}$		ν_{max}	$10\epsilon_{\text{max}}$	$\Delta\nu_{\frac{1}{2}}$	
1	Methanol	3643	59	20	—	7122	27	37	—
2	Ethanol	3636	40	20	8	7105	17	45	7.5
		3622	8	12		7082	5	22	
3	Pentan-1-ol	3638	43	23	5	7110	17	45	6
		3623	15	14		7086	5	25	
4	2-Methylpropan-1-ol	3640	45	22	7.5	7115	21	45	7
		3624	10	13		7084	6	25	
5	2,2-Dimethylpropan-1-ol	3643	57	24	14	7118	20	42	15
		3629	13	8		7093	3	19	
6	Propan-2-ol	3626	50	17	7.5	7087	23	34	7.5
		3611	8	14		7053	4	27	
7	Butan-2-ol	3628	42	21	6	7089	18	43	6.5
		3609	8	19		7048	4	30	
8	Pentan-3-ol	3630	44	24	5	7096	16	48	5.5
		3603	15	15		7042	4	37	
9	2,2,4,4-Tetramethyl-pentan-3-ol	3651	56	15	3				
		3626	14	20					
10	2-Methylpropan-2-ol	3616	52	16	—	7065	27	30	—
11	2-Methylbutan-2-ol	3618	54	17	—	7073	27	33	—
12	2,3,3-Trimethylbutan-2-ol	3625	50	16	—				
13	<i>cis</i> -1-Methyl-4- <i>t</i> -butyl-cyclohexanol	3611	58	16	—	7057	27	30	—
14	<i>trans</i> -1-Methyl-4- <i>t</i> -butyl-cyclohexanol	3616	50	18	—	7063	21	32	—
15	5 α -Cholestan-3 β -ol	3622	61	20	—				
16	5 α -Cholestan-3 α -ol	3625	69	17	—				
17	5 α -Ergosta-7,22-dien-3 β -ol	3623	60	20	—				
18	5 α -Ergosta-7,22-dien-3 α -ol	3625	70	11	—				
19	5 β -Lumista-7,22-dien-3 β -ol	3627	60	17	—				
20	5 β -Lumista-7,22-dien-3 α -ol	3623	62	19	—				
21	5 α -Cholestan-7 β -ol	3650	40	21	1.1				
		3619	32	24					
22	5 α -Cholestan-7 α -ol	3630	57	16	7				
		3621	12	11					
23	5 β -Cholestan-5 β -ol	3619	55	17	—				
24	5 α -Cholestan-5 α -ol	3629	28	20	1.2	7097	13	35	1.2
		3611	26	18		7057	11	35	
25	5 α -Ergosta-7,22-dien-5 α -ol	3595	40	33	—	7025	18	60	—
		3635	18	24		7105	11	42	
26	2-Phenylethanol	3623	5	14		7081	3	25	
		3606	16	38		7045	8	63	

TABLE 2.
Ratio of band intensities.

5 α -Cholestan-5 α -ol (no. 24)						
Temp.	23°	34°	52°	59°	63°	
$\epsilon_{7097}/\epsilon_{7067}$	1.17	1.16	1.18	1.16	1.20	
Molar concn.	0.0049	0.0073	0.016			
$\epsilon_{3629}/\epsilon_{3611}$ at 23°	1.09	1.08	1.10			
$\epsilon_{3629}/\epsilon_{3611}$ at 23°						1.08
$\epsilon_{2879}/\epsilon_{2866}$ (after exchange with deuterium oxide) at 23°						1.04
2-Phenylethanol (no. 26)						
Temp.	23°	30°	45°	50°	58°	
ϵ_{7106}	1.14	1.15	1.20	1.21	1.22	
ϵ_{7045}	0.78	0.76	0.72	0.71	0.69	
$\epsilon_{7106}/\epsilon_{7045}$	1.45	1.51	1.67	1.70	1.77	

DISCUSSION

Comparison between the present work and previous results obtained under high dispersion can be made with compounds 1—4, 6, 10, 11, 13, and 14 in the fundamental region^{2,6} and with compounds 1, 2, 6—8, and 26 in the overtone region.¹ For the ν_{\max} values of symmetrical bands and the major components of doublets agreement is generally good: as might be expected (see below) there are appreciable discrepancies when the frequencies of the doublets' minor components and the relative band areas are compared.

All the primary and secondary aliphatic alcohols (nos. 2—9) in Table 1 have a shoulder on the low-frequency side of the main hydroxyl absorption. Graphical separation of the

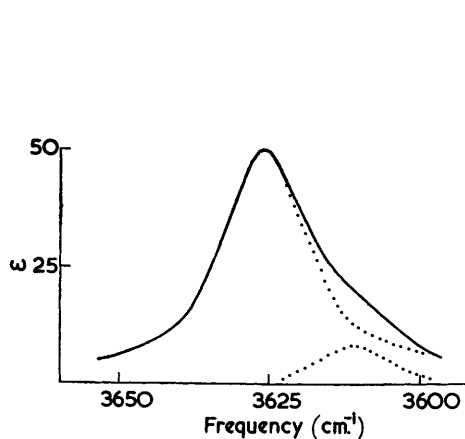


FIG. 1. Propan-2-ol (no. 6).

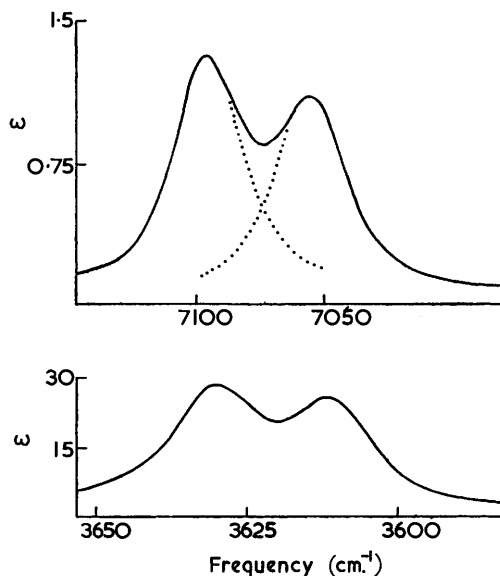


FIG. 2. 5α -Cholestan- 5α -ol (no. 24).

doublets (as illustrated for propan-2-ol, no. 6, in Fig. 1) involves the assumption that the intensity of the minor component is zero at the frequency of maximal absorption of the major peak. This procedure together with the small separation of the components in some cases reduces the significance of the data quoted for the minor components. The hydroxyl bands of the cyclohexanols (nos. 13 and 14) and the 3-hydroxy-steroids (nos. 15—20) appeared to be symmetrical: "graphical separation" showed that there were no significant minor bands. Two of the steroids examined (nos. 21 and 24) each gave two distinct bands of approximately equal intensities (Fig. 2), sufficiently well resolved for measurement of their ν_{\max} and ϵ_{\max} values without graphical separation.

Examination of 5α -cholestan- 5α -ol (Table 2) showed that the doublet's characteristics are not influenced by the concentration of the solution, thus confirming that doublet alcohol absorption is not caused by intermolecular association.¹ In the hope of making a clear distinction between the conformational and Fermi resonance explanations of doublet absorption, the relative intensities of the bands were measured at different temperatures. A marked temperature-dependence would have favoured the conformational theory: the observed absence of any significant variation in the range 25—66° (see Table 2) can be accommodated on either explanation. The effect caused by exchange with deuterium oxide does, however, support the conformational explanation: the bands at 3629 and 3611 cm^{-1} are replaced by new ones at 2679 and 2666 cm^{-1} , the two pairs of bands giving similar intensity ratios. Further evidence against the operation of Fermi

resonance is that the relative intensity of the minor components in Table 1 does not increase as the separation between the components decreases. Indeed, in the case (no. 21) with the highest separation (31 cm^{-1}) the "minor" band is especially prominent.

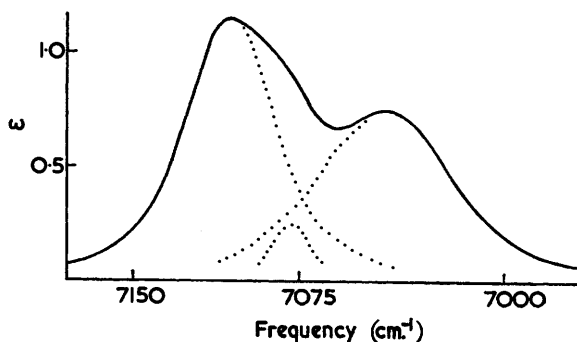
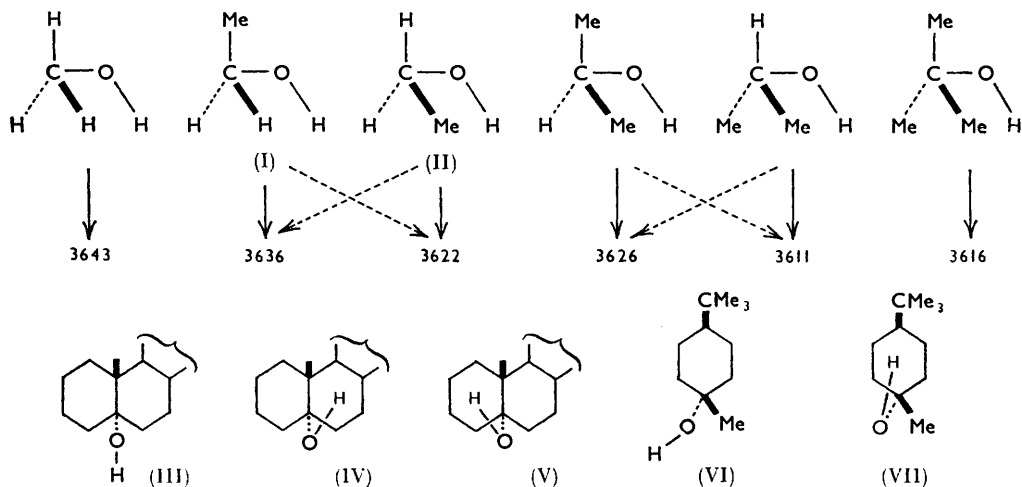


FIG. 3. 2-Phenylethanol (no. 26) at 23°.

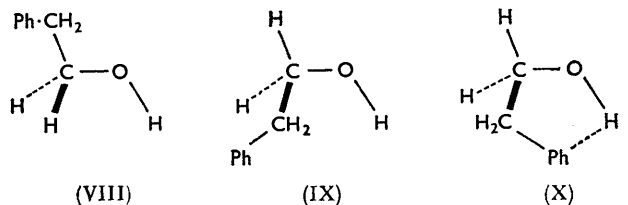
Since the results from the two spectral regions are similar in the cases where both were examined, only the fundamental bands are considered in the development of the conformational theory which follows, and for brevity the cm^{-1} symbol is omitted from the frequency values. Inspection of the data for methyl, ethyl, isopropyl, and t-butyl alcohol



(nos. 1, 2, 6, and 10) shows that the hydroxyl frequency is lowered by introduction of alkyl groups on the carbon atom bearing the hydroxyl group: this decrease must be attributed to steric factors since the inductive effect of alkyl groups would be expected to increase the hydroxyl frequency. There are two possibilities for assigning the components of the hydroxyl absorption of ethyl alcohol to the conformations (I) and (II). [Form (II) represents two equivalent conformations with the methyl group in a skew relationship to the hydrogen atom of the hydroxyl group.] Correlation of the stronger band (3636) with the "skew" form (II), and the weaker band (3622) with the "staggered" form (I) (see dotted lines in formulæ) implies that a staggered methyl group causes the greater decrease in frequency. Assignment of the bands in isopropyl alcohol on this basis (dotted lines) leads to difficulties: it is necessary to assume that skew methyl groups are here causing a marked decrease in frequency. Reversed assignments (full lines) and a reasonable interpretation of the frequency data in Table 1 can be made on the basis of the suppositions (i) that each skew alkyl group causes an appreciable decrease in the hydroxyl

frequency, and (ii) that a staggered alkyl group has a smaller, but distinct, effect whose sign depends on the size of the group.

The direction of a staggered alkyl group is illustrated by the series $R\cdot CH_2\cdot OH$. With $R = Me$ (no. 2) the hydroxyl band is at 3636, a drop of 7 from methyl alcohol. Larger, normal alkyl groups increase the frequency slightly (to 3638 in no. 3 and the longer-chain compounds ²). Successive branching at the α -carbon causes further increases, to 3640 with $R = Me_2CH$ (no. 4) and 3643 with $R = Me_3C$ (no. 5). The effect is also seen in $Me_3C\cdot CMe_2\cdot OH$ (no. 12) which absorbs at higher frequency (3625) than $Me_3C\cdot OH$ (no. 10, 3616). [This treatment is in consonance with the reasonable assumption that in compounds 5 and 12 the favoured conformations have the hydroxyl-hydrogen atom staggered with respect to the bulky t-butyl groups. The di-t-butyl compound (no. 9) has an exceptionally high frequency (3651): it may be that the favoured conformation here is unusual, with a planar arrangement of the H-C-O-H system.]



The data in Table 1 do not suggest any generalisations about the structural features necessary for doublet absorption: of the two cases with the most marked degree of splitting one (5α -cholestan- 7β -ol, no. 21) has a secondary equatorial hydroxyl group while the other (5α -cholestan- 5α -ol) has a tertiary axial group. With 5α -cholestan- 5α -ol the higher-frequency band (3629) can be assigned to the "exo"-form (III) and the second band (3619) to two equivalent "endo"-forms (IV) and (V). Measurement of Dreiding models shows that the distance between the hydroxyl-hydrogen atom and the nearest hydrogen atoms of the steroid skeleton is about 2.3 Å in the *exo*-form (III) and about 2 Å in the *endo*-forms (IV) and (V). *trans*-1-Methyl-4-t-butylcyclohexanol (no. 14), in which the environment of the hydroxyl group appears to be similar to that of the group in 5α -cholestan- 5α -ol, gives only one band. However, in contrast with the steroid, the monocyclic compound has two equivalent *exo*-forms, such as (VI), and one *endo*-form (VII), and the absence of a second hydroxyl band is reasonably attributed to a higher relative proportion of molecules adopting the *exo*-form. The frequency difference between the bands of the *exo*-forms [(III) absorbing at 3629, and (VII) at 3616] arises from the presence of a staggered quaternary carbon centre (C_{10}) in form (III), which (see above) leads to an increase in frequency. Discussion of 5α -cholestan- 7β -ol is deferred until more steroid secondary alcohols have been examined.³

The doublet associated with the 5α -hydroxy-steroid system (no. 24) is markedly changed by introduction of a 7,8-double bond (no. 25). Only one band, shifted to lower frequency (3595), is observed, thus indicating a preferred conformation in which there is intramolecular bonding between the hydroxyl group and the olefinic π -electrons. Similar bonding to the phenyl group is thought to occur in 2-phenylethanol, for which three hydroxyl bands have been reported in the overtone region ¹ but only two in the fundamental range.⁸ Our spectra (see Table 1 and Fig. 3) show two main bands (3635 and 3606) and a shoulder which arises from a minor peak at 3623. While the relative band intensities are not influenced by concentration, the intensity of the 3606 band decreases as the temperature is raised (Table 2). Assignment ^{1,8} of this band to a form involving intramolecular bonding, such as (X), is thus confirmed: the 3635 band arises from the form (VIII) with the benzyl group staggered with respect to the hydroxyl-hydrogen atom, and the 3606

⁸ Schleyer, Wintner, Trifan, and Baeskai, *Tetrahedron Letters*, 1959, No. 14, 1.

absorption from a skew form (IX) in which the phenyl group is directed away from the hydroxyl group. With allyl and benzyl alcohol, both of which exhibit doublet absorption,^{2,9} the lowest frequency is 3619. It seems reasonable that these bands arise from normal conformations which do not involve bonding of the hydroxyl groups.¹¹

A useful relation between the overtone and fundamental hydroxyl frequencies in Table I is: overtone frequency = $2 \times$ fundamental frequency - 165 cm.⁻¹.

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THE DYSON PERRINS LABORATORY, OXFORD.

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⁹ Fox and Martin, *Trans. Faraday Soc.*, 1940, **36**, 897.
