An Infrared Study of Solvent Effects on the Carbonyl Stretching Bands of Some Androgen Esters

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The solvent effects of chloroform, benzene, and carbon tetrachloride on the carbonyl stretching bands of six 17β-acyloxyandrost-4-en-3-ones (testosterone esters) and 17β-propionyloxy-5α-androstan-3-one (androstanolone propionate) are recorded. In the solute-solvent interactions responsible for the spectral changes, the carbonyl group is considered to be the electron donor and particular attention is directed towards the mode of interaction with benzene and carbon tetrachloride. The changes in a composite band are considered as the integrated modifications of component sub-bands; some of which are resolved and assigned. Also the reasons for the split peak in the conjugated ketone are reviewed.

MUCH of the original work on i.r. studies of steroid esters in solution was performed by Jones and his co-workers, who concerned themselves mainly with formates,¹ acetates,^{1,2} and propionates² in chloroform, carbon tetrachloride, and carbon disulphide. Although these studies recently,³ and a deduction made that the respective solvents were divisible into four categories, characterised by; chlorinated hydrocarbons, aromatics, completely substituted derivatives of methane, and saturated hydrocarbons respectively. Here we report and discuss the

		Solvent effects	on the 17β -ester of	carbonyl absorption	band	
Compd.	Stretching frequency in cyclohexane $(\nu_{max.})$ *	Shift in CHCl ₃ [Δν(CHCl ₃)] * †	Isosbestic points in CHCl ₃ /C ₆ H ₁₂ systems *	Shift in C_6H_6 $[\Delta\nu(C_6H_6)] * \dagger$	Isosbestic points in C ₆ H ₆ /C ₆ H ₁₂ systems *	Shift in CCl_4 $[\Delta \nu(CCl_4)] * \dagger$
(1a) ‡ (1b) ‡ (1c) §	1737 1749 1746	17 24 18	$1733 \\1741 \\1740$	10 9 8	$1735 \\ 1739 \\ 1742$	6 9 7
(1d) (1e)	17431744	18 20	1735 1736	10 10	1741	6 10 6
(1f)	1744	20	1736	10	1739 1741	
(2)	1744	18 ¶	1738	6 10 U	1738 1741	6 9 II

TABLE 1

* cm⁻¹. \dagger Relative to frequency in cyclohexane. \ddagger Concentration of ester 0.04 m; in remainder of solutions, concentration of ester 0.12 m. § Reference 3(a). ¶ Estimated, since ester and ketone bands are partially superimposed. \parallel Where two values are presented for the shift in a given solvent, two peaks of similar intensity occur.

encompassed ester substitution at various sites in the steroid nucleus, they concentrated on the 3- and 17-sites.



The effect on the i.r. spectrum of varying the solvent environment of a 17β -propionate has been considered

¹ R. N. Jones, P. Humphries, F. Herling, and K. Dobriner, J. Amer. Chem. Soc., 1952, 74, 2820. ² R. N. Jones, V. Z. Williams, M. J. Whaler, and K. Dobriner, J. Amer. Chem. Soc., 1948, 70, 2024; R. N. Jones, P. Humphries, and K. Dobriner, *ibid.*, 1950, 72, 956; R. N. Jones and F. Herling, L. Chem. Los 4, 10 (1954), 1054, 10 J. Org. Chem., 1954, 19, 1252.

results obtained in extending this work to the 3-keto- and 17β -ester sites in various esters of 17β -hydroxyandrost-4-en-3-one (testosterone) (Ia--f) and 17β-propionyloxy- 5α -androstan-3-one (androstanolone propionate) (2).

RESULTS AND DISCUSSION

17β-Ester Carbonyl Group.--Relevant data are presented in Table 1. In cyclohexane, the three lower testosterone esters (Ia-c) have significantly different ester carbonyl stretching frequencies from the other members of the series (Id-f), which agrees with the sequence previously observed in simple aliphatic esters.⁴

The presence of isosbestic points ⁵ in the chloroformcyclohexane systems of all of these compounds is in keeping with the formation of a chloroform-ester carbonyl complex (1:1) by hydrogen bonding.³⁶ Thus, the frequency shift of the stretching band in chloroform

³ K. C. James and P. R. Noyce, (a) J. Pharm. Pharmacol., 1970, 22, 1095; (b) Spectrochim. Acta, 1971, 27A, 691. ⁴ H. W. Thompson and P. Torkington, J. Chem. Soc., 1945, 640; E. J. Hartwell, R. E. Richards, and H. W. Thompson,

ibid., 1948, 1436; H. W. Thompson and D. A. Jameson, Spectro-chim. Acta, 1958, **13**, 236.

⁵ M. D. Cohen and E. Fischer, J. Chem. Soc., 1962, 3044.

should be related to the negative charge on the carbonyl oxygen as is borne out by the magnitude of the shifts being in the same order as the Taft's polar substituent constants (σ^*) ⁶ for the ester alkyl groups. The acetate ester is an exception to this trend, and is explicable on the basis of hyperconjugation involving the terminal methyl group of the 17β -side chain. This phenomenon has already been advanced to explain the anomalous hydrolysis of acetates 7 and the hydrogen-bonding propensity of methyl substituted amides.8

In an earlier article,^{3a} we discussed benzene-carbonyl interactions and concluded that a complex of the type recently proposed for acetyl carbonyl groups,⁹ involving π -electrons, is unlikely. Since the frequency shifts of the ester carbonyl group of testosterone propionate (Ic) in substituted aromatic solvents followed the trend of the Hammett substituent constants (σ_p) (Table 2), an interaction between the electron-rich carbonyl group and a peripheral hydrogen of the aromatic ring seems more feasible. Such a hypothesis is corroborated by the proposals for aromatic associations with ethers,¹⁰ and pyridine.¹¹ From our frequency shift data, the strength

TABLE 2

Frequency shifts of carbonyl peaks of 17β-propionyloxyandrost-4-en-3-one in various aromatic solvents and their respective Hammett p-substituent (σ_p) constants

Solvents	Frequency shift of ester C:O group *	Hammett constant	Frequency shift of ketone C:O
Nitrobenzene	14	0.78	10
Chlorobenzene	12	0.23	7
Benzene	8	0.0	5
Toluene	7	-0.12	4

* Shifts are relative to the frequency of the respective carbonyl band in cyclohexane; data from reference 3(a).

of the interaction appears independent of the alkyl side-chain length, although two isosbestic points ⁵ occur with the valerate (Ie) and decanoate (If) esters. Their presence indicates that either steric properties affect complexing or that possibly the interaction is of the cluster type, ^{10a, 12} * which becomes better defined with increasing side-chain length.

Until recently carbon tetrachloride was considered an 'inert' solvent and as such was used as a vehicle for investigating hydrogen-bonded solutes. However, Fletcher¹³ has demonstrated an association between octanol and carbon tetrachloride, in which the solvent acted as an electron donor, confirming earlier speculation.¹⁴ Other work ¹⁵ has indicated a specific attraction between a chlorine atom of carbon tetrachloride and an ether oxygen, in which the chlorinated compound probably acts as an electron acceptor. Moreover, in the other types of carbonyl complexing considered above, the lone pair of electrons on the carbonyl oxygen have been the donor agents, so association by a similar mechanism is probable with carbon tetrachloride. Support for carbon tetrachloride acting as an acceptor is provided by other investigations concerned with both ethylenic ¹⁶ and carbonyl ^{10b} electron-donor systems. Since this solvent is non-polar, interaction is facilitated by a dipole-induced dipole mode and the electrostatic role it adopts is probably dictated by the polar solute.

Spectral anomalies due to hyperconjugation have been noted previously,¹⁷ so providing a precedent for the high acetate (Ib) frequency observed [cf. Δv (CHCl₃)]. Where two figures are quoted for the ester frequency shift in carbon tetrachloride, this is due to the enhanced intensity of a lower frequency component of the composite ester carbonyl band. Possibly the increasing importance of this sub-band is related to structural changes in the arrangement of the alkyl side-chain as advocated by James and Roberts 18 in their crystallographic studies.

3-Ketone Carbonyl Group .-- Relevant data are presented in Table 3. The two values given for the stretching frequency of the conjugated carbonyl group in the testosterone esters (Ia-f) indicate a splitting of the band. This phenomenon has previously been observed in ketones in the liquid state,19 and in one of the crystalline forms of testosterone; 20 both are attributed to dipolar interaction. Vibrational coupling between the ethylenic and carbonyl groups, in which the characters of the vibrations change from localised stretching modes to in-plane and out-of-plane forms extending throughout the system,²¹ has also been proposed, but neither the ethylenic band of the unsaturated compounds (Ia-f), nor a comparison of the carbonyl bands for compounds (Ic) and (2) support this idea (Figure 1). A more rational suggestion is one involving Fermi resonance as has been forwarded by a number of workers studying the carbonyl doublet of conjugated cycloketo-compounds.²² They

 ¹³ A. N. Fletcher, J. Phys. Chem., 1969, 73, 2217.
¹⁴ R. Heess and H. Kriegsmann, Spectrochim. Acta, 1968, 24A, 2121.

¹⁵ L. A. Beath and A. G. Williamson, J. Chem. Thermodynamics, 1969, **1**, 51.

¹⁶ O. F. Olaj, Makromol. Chem., 1970, 136, 255.

¹⁷ G. B. Bonino and P. Chiorboli, Atti Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat., 1951, 10, 7.

¹⁸ K. C. James and M. Roberts, J. Pharm. Pharmacol., 1968, 20, 709. ¹⁹ A. W. Baker, J. Phys. Chem., 1956, 60, 1660. Stattershim. Acta. 1966, 22, 889

- ²⁰ R. J. Mesley, Spectrochim. Acta, 1966, 22, 889.

^{*} A non-specific ' collision-complex,' in which several solvent molecules become simultaneously orientated towards the carbonyl oxygen forming a quasi-liquid crystalline structure around the carbonyl group.

⁶ R. W. Taft, J. Amer. Chem. Soc., 1953, 75, 4231.

 ⁷ E. A. Halonen, Acta Chem. Scand., 1956, **10**, 485.
⁸ K. V. Ramiah and C. A. I. Chary, Current Sci., 1968, **37**, 130. ⁹ M. A. Freemantle and W. G. Overend, J. Chem. Soc. (B), 1969, 547.

¹⁰ (a) R. D. Bertrand, R. D. Compton, and J. G. Verkade, J. Amer. Chem. Soc., 1970, **92**, 2702; (b) R. P. Rastogi, J. Nath, and R. B. Yadava, Indian J. Chem., 1970, 8, 541. ¹¹ J. N. Murrell and V. M. S. Gil, Trans. Faraday Soc., 1965,

^{61, 4}Ŏ2.

¹² K. M. Baker and R. G. Wilson, J. Chem. Soc. (B), 1970, 236; E. M. Engler and P. Laszlo, J. Amer. Chem. Soc., 1971, **93**, 1317.

 ²¹ K. Noack and R. N. Jones, *Canad. J. Chem.*, 1961, **39**, 2201.
²² P. Yates and L. L. Williams, *J. Amer. Chem. Soc.*, 1958, **80**, 5896; G. Allen, P. S. Ellington, and G. D. Meakins, *J. Chem. Soc.*, 1960, 1909; H. N. A. Al-Jallo and E. S. Waight, *J. Chem. Soc.*, 1960, 1909; H. N. A. Al-Jallo and E. S. Waight, *J. Chem.* Soc. (B), 1966, 73.

proposed that resonance occurred between the carbonyl stretching fundamental and the first overtone of the outof-plane bending vibration of the conjugated :C·H



FIGURE 1 3-Ketone carbonyl stretching band of (a) 17β -propionyloxy- 5α -androstan-3-one and (b) 17β -propionyloxyandrost-4-en-3-one in cyclohexane solutions; conc. of steroid 0.12M; cell thickness 0.1 mm

group. The point may be taken from the saturated compound (2) which has a whole ketone band, that represents an unconjugated ketone. In benzene, the relatively higher shifts of the ketone carbonyl group in the lower testosterone esters (Ia—c) are particularly interesting since they follow the trend of the ester alkyl group Taft functions. Therefore, it is suggested that an indirect intermolecular carbonyl interaction occurs between the ester carbonyl of one molecule and the ketone carbonyl of another, through the polarised solvent molecules enveloping the ester carbonyl within the cluster complex. This concept is reinforced by a corresponding trend in the shifts for the ester carbonyl and by the interaction being only manifest in benzene, which is the only solvent sufficiently polarisable to form these cluster associations.

From Figure 2 and Table 4 the complexity of carbonyl vibrational bands in polar solvents is abundantly clear. Therefore, the comparison of frequency shifts is meaningful only if the criterion for measuring them is standardised for all solvents. In order to determine which characters have the same aetiology we have attempted to resolve and assign the various components of these bands.

A particularly interesting observation is that a specific vibrational absorption may occur in each of the solvents

	Stret freque cyclob	ching ncy in aexane	Shift in CHCl ₃	Isosbestic points in CHCl ₃ /C ₆ H ₁₂	Shift in C ₆ H ₆	Isosbestic points in C ₆ H ₆ /C ₆ H ₁₂	Shift in CCl ₄
Compd.	$\left[\nu_{\max(a)}\right]^*$	$\left[\nu_{\text{max.(b)}}\right]$ *	$[\Delta \nu (\text{CHCl}_3)] * \dagger$	systems *	$[\Delta\nu(C_6H_6)] * \dagger$	systems *	$[\Delta \nu(\text{CCl}_4)] * \dagger$
(la) ‡	1687	1685	25	$\begin{array}{c} 1683 \\ 1676 \end{array}$	11	1684	7
(1b) ‡	1687	1684	25	$\begin{array}{c} 1682 \\ 1676 \end{array}$	10		8
(1c) §	1688	1684	26	$1682 \\ 1677$	10	1682	8
(1d)	1687	1683	26	$\begin{array}{c} 1683 \\ 1676 \end{array}$	9	1681	8
(1e)	1687	1684	25	$\begin{array}{c} 1682 \\ 1676 \end{array}$	9	1681	8
(1f)	1687	1684	25	$\begin{array}{c} 1682 \\ 1676 \end{array}$	9	1681	8
(2)	1724		14	1722	9	$1723 \\ 1718$	8

TABLE 3

Solvent effects on the 3-ketone carbonyl absorption band

* cm⁻¹. † Relative to high frequency component in cyclohexane. ‡ Concentration of ester 0.04m; in remainder of solutions concentration of ester 0.12m. § Reference 3(a).

The difficulty in measuring shifts from a split peak has been discussed before ²³ and the suggestion made that either the mean or the most prominent peak should represent the frequency of the split band. In our earlier work,³ shifts were measured from the lower component of the doublet, but we have since realised from considering the band modifications in increasingly polar environments that the high frequency contribution is the true carbonyl stretching frequency.

As would be expected, the shifts for each of the testosterone esters (Ia-f) in chloroform and carbon tetrachloride respectively are similar. The markedly lower shift of the 3-ketone group of compound (2) is in keeping at similar frequencies, indicating that the solvents have a common factor which disturbs the carbonyl dipole oscillations. This situation is manifest by the first-order complexed band in both ester and ketone carbonyl dipoles and demonstrates that the association energy for each solvent is of similar magnitude. That carbon tetrachloride forms specific complexes, even in the absence of isosbestic points, is further corroborated by the similarity between the spectral components in this solvent and those in the other solvents.

The carbonyl sub-bands in benzene and carbon tetrachloride are directly comparable, whilst many of those ²³ K. Noack, *Spectrochim. Acta*, 1962, **18**, 697.



FIGURE 2 17 β -Ester carbonyl stretching band of 17 β -propionyloxyandrost-4-en-3-one in benzene under (a) normal resolution and (b) high resolution; conc. of steroid, (a) 0.12M, (b) 0.003M; cell thickness 0.1mm

TABLE 4

(a) List of sub-bands in 17β -ester carbonyl band of 17β -propionyloxyandrost-4-en-3-one in various solvents

Sub-bands in			
Chloroform	Benzene	Carbon tetrachloride	Assignment
1746·6 1743·2 1737·8 ‡	1746·5 1742·7 1738·2 *	1742·6 1738·9 *	Uncomplexed peak Complexed peak of first order
1733·1 1727·6 * 1718·1	1734.7 †	1734·9 ‡	

(b) List of sub-bands in 3-ketone carbonyl band of 17β -propionyloxyandrost-4-en-3-one in various solvents

Sub-bands in					
Chloroform	Benzene	Carbon tetrachloride	Assignment		
1688·3 ‡ 1682·7	1687·2 ‡	1687·5 ‡	Uncomplexed peak Fermi resonance peak		
1678 •0 ‡	1678·9 *	1680·3 *	Complexed peak of first order.		
$1674 \cdot 2$			Complexed peak of second order		
1672.0 ‡ 1665.4 †					

1662·9 * 1652·7 ±

* Main peak. † Peak or shoulder approaching intensity of main peak. ‡ Resolved peak or shoulder of intensity considerably less than main peak. (Concentration of ester 0.003M.)

in chloroform have no counterpart in the other solvents. The reasons for this may be threefold: (a) the chloroform molecules complexed with the carbonyl groups are linearly self-associating with other solvent molecules; ²⁴ (b) higher carbonyl-chloroform complexes (*i.e.* 1:2, 1:3, *etc.*) are being formed; (c) rotational effects. Since these anomalous sub-bands are more numerous in the ketone band, the greater importance of factors (b) and (c) over (a) are in keeping with their more effective influence at this relatively exposed site.

Evidence from high-resolution studies indicates that new vibrational modes arise from discrete energy changes occurring within the dipolar system as a result of specific interactions or given torques acting on it. Continuous shifting of these vibrations occurs through subtle polar variations happening in the solvent environment. Together these two effects are responsible for the spectral shifts experienced in moving from one solvent to another.

EXPERIMENTAL

Testosterone propionate (1c) and decanoate (1f) were gifts from Organon Laboratories Ltd.; purity was checked by m.p. Other esters were prepared from reaction of the steroid alcohol with the appropriate acyl chloride. Products were recrystallised from aqueous methanol and their purity checked by m.p., g.l.c., and i.r. spectroscopy.

I.r. spectra were obtained using a Perkin-Elmer 521 spectrophotometer having a linear scale expansion of 10 and the following dial settings: slit program 10; gain 2.5; attenuator speed 11.0; scan time (gear 2) 1/2; and suppression 8.0. In the higher resolution studies these were modified thus; slit program 6.5; gain 2.9; attenuator speed 8.0; scan time (gear 2) 0; suppression 10.5; intensity scale (0.25-5.0) 2.5.

Concentration of steroid esters used were as follows: compounds (1a,b), 0.04M; compounds (1c—f and 2), 0.12M; in high resolution studies, 0.003M. Other materials and methods are as described in reference (3a).

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²⁴ E. D. Becker, Spectrochim. Acta, 1959, 9, 743.