Tetrahedron, 1963, Vol.19, pp. 1771 to 1782. Pergamon Press Ltd. Printed in Northern Ireland

MODIFIED STEROID HORMONES—XXXII

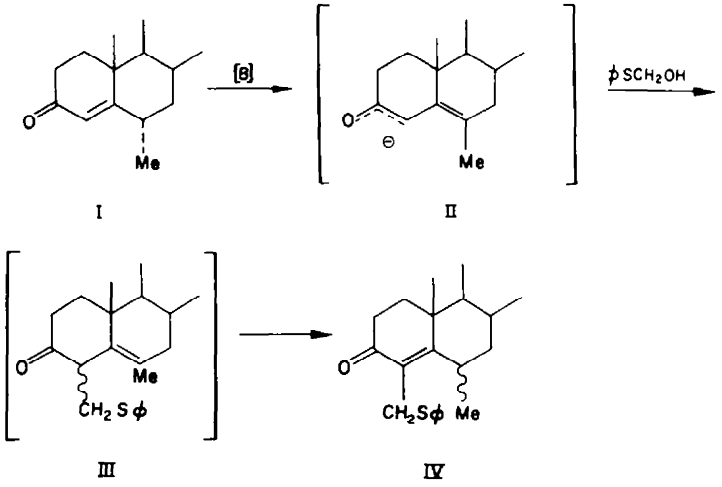
SPECTROSCOPIC ELUCIDATION OF ISOMERISM IN 6-SUBSTITUTED AND 4,6-DISUBSTITUTED-4-EN-3-KETONES

M. T. DAVIES and V. PETROW
The British Drug Houses Ltd., Graham Street, London N.1

(*Received* 29 *April* 1963)

Abstract—The U.V. absorption spectra of steroidal 4-en-3-ketones substituted severally and together at C_4 and C_6 is surveyed and the data employed to differentiate stereoisomers at C_6. The stereochemistry of some 4,6-dimethyl-4-en-3-ketones[1] has been established and the 4,6β-configuration assigned to stable isomers. The optical rotatory dispersion spectra of certain substituted 4-en-3-ketones are discussed.

A METHOD employed in these laboratories[1,2] for introducing a C_4-methyl group into steroidal 6α-methyl-4-en-3-ketones (I) involves the condensation of ketones (I) with formaldehyde and thiophenol in the presence of a basic catalyst to give 6-methyl-4-phenylthiomethyl intermediates (IV), which are then converted by reductive desulphurization into 4,6-dimethyl-4-en-3-ketones. It is probable that formation of the 6-methyl-4-phenylthiomethyl-4-en-3-ketone (IV) proceeds by a reaction of the carbonyl-addition type which includes, *inter alia*, the aldol and Claisen condensations. The first stage of the process may therefore be envisaged as involving the base-catalysed formation of the carbanion (II), followed by its addition to the formaldehyde thiol complex to give III and thence IV as indicated below:



I II III IV

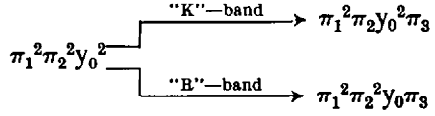
Clearly, the stereochemistry about C_6 of the end-product (IV), and hence the 4,6-dimethyl-4-en-3-ketone derived from it, cannot be taken from that of the starting

[1] Part XXXI—preceding paper.
[2] D. N. Kirk and V. Petrow, *J. Chem. Soc.* 1091 (1962).

material (I), but must be established *de novo*. In addition, more than one conformation of each of the possible 4,6α- and 4,6β-configurational isomers may be anticipated. The present investigation is concerned with a spectroscopic study of relevant steroidal derivatives with the object of elucidating their stereochemistry.

Ultraviolet spectroscopy

The electronic absorption spectra of steroidal-4-en-3-ketones are characterized by two regions of absorption at wavelengths above 200 mμ, the electronic transitions involved being as follows:[3]



The two regions are (1) the K-band, an allowed N → V transition of high intensity (ε max lying between 15,000 and 19,000) which, in the absence of perturbing groups, occurs, regularly and fairly sharply at 240 mμ (ethanol as solvent), and (2) the R-band, which arises from an n → π* "forbidden" transition, and is therefore of low intensity (ε max lies between 10 and 100). It is far more diffuse than the K-band, but in solvents of low polarity is revealed as a number of more or less well resolved features situated between 300 and 400 mμ.

Bird *et al.* have shown[4] that the R-band spectrum of cholest-4-en-3-one undergoes a bathochromic shift by substitution at C_6 of bromine, chlorine, hydroxyl and acetoxyl groupings. Furthermore, the magnitude of shift is determined not only by the nature of the substituent, but also by its orientation, a 6β-(axial) group inducing a considerably greater effect than that occasioned by its 6α-(equatorial) epimer. (See Table 1.) It was suggested that the shift induced by bromine substitution arises, at least in part, from hyperconjugation of the σ-electrons of the C–X band, and possibly by direct involvement of the p-electrons of the bromine atom with the π-orbitals of the conjugated system. It is equally apparent, however, that similar mesomeric effects will operate for substituents other than bromine, and that in general, these will be maximal in cases of axially orientated C_6-X bands. More recently, Ringold and Bowers[5] have correlated the effects of C_6-substitution upon the position of the K-band peak. We have combined their data with that of Bird *et al.* (loc. cit.) and present it in Table 1. Inspection reveals that whereas many of the groups studied induce some degree of shift of the K-band, a 6-methyl substituent, α- or β-, has virtually no effect upon this region of the spectrum. We therefore decided to extend the observations of Bird *et al.* by an investigation of the influence of 6-methyl substitution upon the R-band spectra of 4-en-3-ketosteroids. The results obtained are conveniently discussed under the following sub-headings.

a. *Choice of solvent.* R-band transitions are markedly sensitive to differences of solvent polarity which affect both position and resolution of the band features. Thus Bird *et al.*[4] obtained adequate resolution with n-hexane, and noted that polar solvents caused deterioration of resolution. As pure aliphatic hydrocarbons are not ideal

[3] F. A. Matsen, *Electronic Spectra* Chap. V; p. 629 *et seq.* of *Chemical Applications of Spectroscopy* Vol. 9 of *Technique of Organic Chemistry*, (General Editor, A. Weissburger) Interscience (1956).
[4] C. W. Bird, R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.* 3675 (1956).
[5] H. J. Ringold and A. Bowers, *Experientia* **17**, 65 (1961).

TABLE 1. VALUES OF WAVELENGTH SHIFTS IN U.V. BAND COMPONENTS INDUCED BY C_6-SUBSTITUTION IN STEROIDAL-4-EN-3-KETONES, FROM THE COMBINED DATA (Bird[4] *et al.* and of Ringold and Bowers[5])

Substituent	$\Delta\lambda$ (mμ) K-Band		$\Delta\lambda$ (mμ) R-Band	
	α-config.	β-config.	α-config.	β-config.
CH_3	0 to +1	−1 to +1	*	*
F	−4 to −5	−5 to −8	*	*
Cl	−2 to −5	0 to −1	+3	+14
Br	−3 to −4	+3 to +8	+5	+20
I	*	+11 to +13	*	*
OH	0 to −1	−3 to −6	+2	+7
OAc	−5	−4	+2	+10
NO_3	−7 to −9	−6 to −8	*	*

* No data quoted by these authors.

steroid solvents, we searched for possible alternatives and found several, listed in Table 2, that combine adequate power of solvation with sufficient low polarity to permit R-band resolution. Other solvents examined (not listed) of polarity higher than that of ethyl acetate, e.g. ethanol-stabilized chloroform, gave inadequate resolution as well as undesirable "blue shift" characteristic of this transition. Cyclohexane and dioxan were regarded as the solvents of choice, and were employed for the present investigation. Comparative resolutions of the R-band spectrum of cholest-4-en-3-one obtained by their use are shown graphically in Fig. 1.

b. *Effect of* 6α- *and* 6β-*methyl substitution upon the R-band spectra of* 4-*en*-3-*ketones.* Results obtained with a number of substituted and unsubstituted steroidal 4-en-3-ketones are given in Table 3. Inspection of the data reveals that when the R-band spectrum of cholest-4-en-3-one determined in cyclohexane or dioxan (see Table 2), is employed as the standard for comparison (i) 6α- methyl (equatorial) substituents induce a mean shift of less than ± 2 mμ, in contrast to (ii) 6β-methyl (axial) substituents which induce a bathochromic shift of 4·5–6 mμ. The difference between these shifts is of sufficient magnitude to justify the use of R-band spectral data for the determination of orientation of a C_6-methyl substituent, in a 6-methylated-4-en-3-ketone of otherwise unknown stereochemistry.

TABLE 2. SOLVENT DEPENDENCE OF R-BAND WAVELENGTHS OF CHOLEST-4-EN-3-ONE (K-band maximum at 241mμ, in ethanolic solution ε = 16,000). The data for this compound in n-hexane, determined by Bird *et al.*[4] is shown in parentheses and their designation of individual features is also used throughout. Wavelengths refer to absorption maxima unless an inflection (i) is indicated. Insufficient resolution is indicated by *. $\Delta\lambda$ is the mean shift occasioned by the change in solvent from n-hexane to that shown.

Solvent	R-Band component positions (mμ) E	D	C	B	A	$\Delta\lambda$ mμ
n-Hexane	314·5i (314)	324·5 (323·5)	336·5 (336)	350 (349)	366i (367)	—
Cyclohexane	314i	324·5	336·5	350	366i	0
Carbon tetrachloride	*	322	332·5	345i	366i	−2·5
Benzene	*	321	332	344i	363i	−4
Diethyl ether	*	322	333·5	346i	363i	−3
Dioxan	*	320	330	344i	361i	−5
Ethyl acetate	*	320	331	343i	360i	−5·5

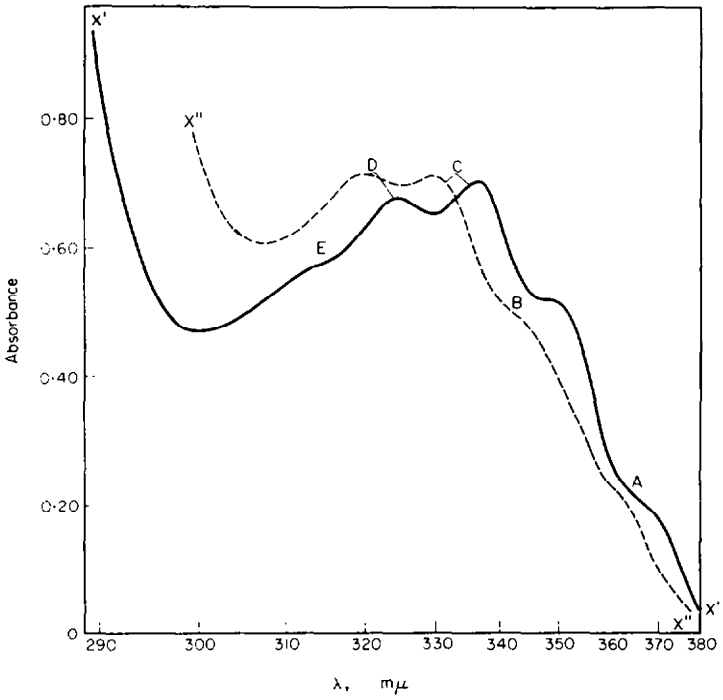


FIG. 1. R-Band spectrum of cholest-4-en-3-one
Curve X′ in cyclohexane.
Curve X″ in dioxan.
c ≈ 0·7 gm/100 ml l = 10 mm.
Band designation after Bird *et al.* (1956).

The shift caused by 6β-methylation must arise from hyperconjugative interaction of the axial substituent with the 4-en-3-ketone system, the average shift of 5 mμ being only slightly less than that induced by an hydroxyl group of the same configuration, notwithstanding the considerable difference of inductive effects of the two groups.

c. *Effect of 4-methyl substitution upon the R-band spectra of 4-en 3-ketones.* Results obtained with three species of 4-methyl-4-en-3-ketones show negligible effect of the 4-substituent upon the position and resolution of the R-band (Table 4). This is also true for 4-bromo- and 4-chlorocholest-4-en-3-one. It is of interest to note, by contrast, that mesomeric interaction of a C_4-X bond (and the p- or higher orbitals of the substituent itself) with the π-electron system can lead to a type of cross-conjugation which is reflected in a large shift of the K-band, characteristic of the substituent.

Cookson and Dandegaonker[6] have postulated that introduction of a methyl group into an αβ-unsaturated ketone system causes a "blue" shift of the R-band spectrum. Assignments of band positions were made by these authors on the basis of the observation that (i) the shape of the absorption envelope is hardly affected by methylation, (ii) band "A" is generally one-quarter to one-third as strong as band "C", and (iii) the separation of bands "A" and "B" is usually greater than that of other pairs of R-band features. It is apparent, however, that their data relating to 2,3-disubstituted-cyclohex-2-enones and given in Table 6 of their paper, cannot be reconciled with the foregoing statements. Our own observations, reported above, reveal that 4-substitution of a steroidal 4-en-3-ketone has no effect opon the number of band features, and that the R-band spectra of the substituted and parent enone are virtually superimposable.

[6] R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.* 1651 (1955).

TABLE 3. THE EFFECT OF 6-METHYLATION UPON THE POSITIONS OF THE R-BAND COMPONENTS OF STEROIDAL 4-EN-3-KETONES. $\Delta\lambda$ is the mean difference between the R-Band components of the compound named, and the corresponding components in the spectrum of cholest-4-en-3-one determined in the same solvent (see Table 2). (*) signifies insufficient resolution for determination of wavelength of feature concerned.

Compound	C_6-Substituent α (eq.)	β (axial)	Solvent	R-band component (mμ) E	D	C	B	A	$\Delta\lambda$ (mμ)
Testosterone	—	—	Cyclohexane	*	326	338	350	367i	+1
	—	—	Dioxan	*	321	330	342i	362i	0
6α-Methyltestosterone[a]	CH_3	—	Cyclohexane	*	324	335	351	365i	0
6β-Methyltestosterone[a]	—	CH_3	Cyclohexane	*	329	341	354	372i	+5·5
17α-Methyltestosterone	—	—	Cyclohexane	*	323	337·5	352	366i	+0·5
6α,17α-Dimethyl-testosterone[a]	CH_3	—	Cyclohexane	*	*	336	350	366i	0
Androst-4-en-3,17-dione	—	—	Cyclohexane	*	*	338	352·5	367i	+2
			Dioxan	*	*	328	343i	361i	−1
6α-Methylandrost-4-en-17-dione[a]	CH_3	—	Cyclohexane	*	*	338	350	368i	−1·5
			Dioxan	*	*	328i	342i	360i	−1·5
6β-Methylandrost-4-en-3,17-dione[a]	—	CH_3	Cyclohexane	*	*	341	356	374i	+6
			Dioxan	*	*	335	348i	366i	+5
Progesterone	—	—	Cyclohexane	*	323	337·5	350	368i	+0·5
6α-Methylprogesterone[b]	CH_3	—	Cyclohexane	*	323	337	350	365i	0
6β-Methylprogesterone[b]	—	CH_3	Cyclohexane	*	327	343	356	372i	+5·5
21-Methylethisterone[c]	—	—	Cyclohexane	*	323·5	337	351	366·5	+0·5
6α,21-Dimethylethisterone[c]	CH_3	—	Cyclohexane	*	324	336	348	367·5	0
6β,21-Dimethylethisterone	—	CH_3	Cyclohexane	*	330	341	354·5	372i	+5·5

[a] H. Ackroyd, W. J. Adams, B. Ellis, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.* 4099 (1957)

[b] D. Burn, B. Ellis, V. Petrow, I. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.* 4092 (1957).

[c] S. P. Barton, D. Burn, G. Cooley, B. Ellis and V. Petrow, *J. Chem. Soc.* 1957 (1959).

d. *Effect of C_6 substitution upon the R-band spectra of 4-substituted-4-en-3-ketones.* In Part IX[7] of this series, bromination of 4-chlorocholest-4-en-3-one was shown to lead to a 6-bromo derivative to which the 6β-bromo-4-chloro structure was assigned on the basis of a shift of +20 mμ in the R-band spectrum. The magnitude of this shift is identical with that observed on passing from cholest-4-en-3-one to its 6β-bromo-derivative (Table 1). The conclusion thus reached on spectral grounds is supported by Catalin models which virtually exclude the 6α-bromo-4-chloro structure as sterically impossible, except in the somewhat improbable ring B boat conformation, a situation discussed below.

During the course of the present investigation, 4-chloro-testosterone propionate was converted by chlorination into a 4,6-dichloro-derivative, the R-band spectrum of which revealed zero shift. In addition, Catalin models of the new compound indicate that an eclipsed 4,6 (equatorial)-dichloro structure is certainly possible, although somewhat strained. Subject to the unlikely ring B conformational alternative mentioned above, the new derivative may be assigned the constitution 4,6α-dichloro testosterone propionate.

[7] D. N. Kirk and V. Petrow, *J. Chem. Soc.* 1334 (1958).

TABLE 4. THE EFFECT OF METHYL AND HALOGENO SUBSTITUTION AT C_4 AND C_6 UPON THE POSITIONS OF K- AND R-BAND FEATURES IN THE U.V. SPECTRA OF STEROIDAL 4-EN-3-ONES. Values of the wavelength shifts refer to the corresponding bands of the absorption spectrum of cholest-4-en-3-one in the same solvents (Table 2) and λ_6^R refers to the effect of 6-substitution upon the R-band of a system already substituted at C_4. * signifies insufficient resolution of the feature.

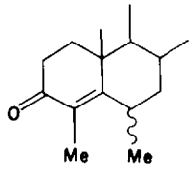
Parent compound	Solvent (for R-band)	Substituents C_4	Substituents $C_6(\alpha)$	Substituents $C_6(\beta)$	K-band position EtOH λ_{max}	K-band position K $\Delta\lambda$	R-band component positions E	D	C	B	A	$\Delta\lambda^R$	$\Delta\lambda_6^R$
					(mμ)	(mμ)	(mμ)						
Testosterone acetate[a]	Cyclohexane	CH_3	—	—	249	+8	*	325	336·5	350	368i	+0·5	
Testosterone acetate (Isomer A)[1]	Cyclohexane	CH_3	—	CH_3	250	+9	*	330	341	355·5	374i	+5·5	+5·0
Testosterone acetate (Isomer B)[1]	Cyclohexane	CH_3	CH_3	—	249	+8	*	327–8	340i	353i	*	+3	+2·5
Androst-4-en-3,17-dione[a]	Cyclohexane	CH_3	—	—	248	+7	*	321	338	350·5	368·5i	+0·5	—
	Dioxan						*	*	329·5	345i	*	0	—
	Cyclohexane	CH_3	—	CH_3	249	+8	*	328·5	342·5	356i	374i	+6	+5·5
	Dioxan						*	*	335	352	371i	+7·5	+7·5
17α-Acetoxy-progesterone[a]	Cyclohexane	CH_3	—	—	248·5	+7·5	*	322·5i	338	349·5i	367i	0	—
17α-Acetoxy-progesterone[1]	Cyclohexane	CH_3	—	CH_3	249	+8	*	331i	*	354i	*	+6	+6
Cholest-4-en-3-one[d]	Cyclohexane	Cl	—	—	255	+14	313	324	337	350i	368i	+0·5	—
Cholest-4-en-3-one[f]	Cyclohexane	Cl	—	Br	266	+25	336	345i	353i	371i	395i	+22	+21·5
Cholest-4-en-3-one[e]	Cyclohexane	Br	—	—	261	+20	313	324·5	338·5	351i	370i	+1	—
Testosterone propionate	Cyclohexane	Cl	Cl	—	258	+17	*	324	336	349i	368i	0	0

[d] D. N. Kirk, D. K. Patel and V. Petrow, *J. Chem. Soc.* 1184 (1956).

[e] D. N. Kirk, D. K. Patel and V. Petrow, *J. Chem. Soc.* 627 (1955).

It is concluded that the degree of shift of the R-band obtained by C_6-substitution of a 4-substituted-4-en-3-ketone is related to the orientation of the C_6-substituent, and that such interaction as may occur between the two substituents has no significant influence upon this region of the spectrum. As a corollary, it follows that *R-band spectra may be employed to establish the axial or equatorial orientation of a* C_6-*substituent in the presence of a 4-substituent in 4-en-3-ketones.*

e. *R-band spectra of 4·6-dimethyl-4-en-3-ketones.* Theoretical consideration of the stereochemistry of 4,6-dimethyl-4-en-3-ketones (V)

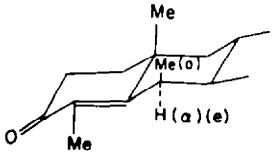


V

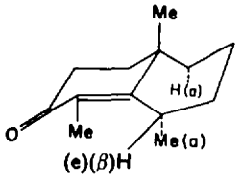
lead to four possible extremities of structure. These are

Va. C_6-α (equatorial)	Ring B in CHAIR conformation
Vb. C_6-β (axial)	Ring B in CHAIR conformation
Vc. C_6-α (axial)	Ring B in BOAT conformation
Vd. C_6-β (equatorial)	Ring B in BOAT conformation.

The 4,6-dimethyl derivatives of 17α-acetoxyprogesterone, androst-4-ene-3,17-dione and testosterone acetate (isomer A)[1], prepared by the route discussed above and listed in Table 4, showed well-resolved R-band spectra, shifted, relative to the spectrum of cholest-4-en-3-one, by +5·5 to 7 mμ. Axial orientations of the 6-methyl groups are thereby indicated. 4,6-dimethyltestosterone acetate (isomer B)[1], obtained as a minor product from a large-scale preparation of isomer A, afforded an R-band spectrum which, by contrast, was poorly resolved, but showed a shift of +3 mμ, indicative of a semi-axial substituent at C_6. Equatorial structures (Va and Vd) are therefore eliminated from discussion, and only axial structures (Vb and Vc) need be considered.



Vb



Vc

Spectral studies of 6β-substituted cholest-4-en-3-ones have revealed[4] that the substituent, irrespective of its bulk, is orientated axially. Ring B is consequently in the "chair" conformation, despite differing degrees of 1,3-diaxial interaction between the substituent and the C_{10}-methyl group. The existence of such interaction, which may be predicted by inspection of molecular models, follows from investigations of O.R.D. spectra (*vide infra*). It is therefore apparent that the energy difference between the two conformational extremes of ring B must be considerable.

Introduction of a symmetrical 4-substituent into a 6-axially substituted 4-en-3-ketone, in either of the possible ring B conformational extremes, would be expected to give rise to an additional steric repulsion. This repulsion between the 4- and 6-substituents, whilst not necessarily of exactly the same magnitude for both conformations (Vb and Vc), would certainly be smaller than the 1,3- and 1,4-diaxial interactions inherent in the chair and boat forms respectively (the latter interaction between the 6-substituent and the 9α-hydrogen atom). It follows, on steric grounds, that the introduction of a substituent at C_4 should hardly affect the conformational situation for 6-axially substituted 4-en-3-ketones.

Consideration of 6(axial)-bromo-, methyl, and chloro-4-en-3-ketones in possible ring B boat conformation suggests that the magnitude of 1,4-diaxial interaction would be least when the C_6-substituent is a chlorine atom. The orientation favoured on steric grounds of the C_6-chlorine atom present in 4,6-dichlorotestosterone propionate would then be α(axial) as opposed to α (equatorial), should, in fact, the ring B boat conformation arise. However, this compound was isolated (*vide supra*) in the *equatorial* form only, and as there is no reason to assume any change in the relative stabilities of the conformational extremes of ring B, the dichloride is accordingly assigned the 4,6α-configuration with ring B in the chair conformation. This molecule is seen to be no more distorted than that of 6β-bromocholest-4-en-3-one.

The U.V. spectroscopic evidence presented herein favours an axial orientation of the 6-methyl group present in the 4,6-dimethyl-4-en-3-ketones examined (except isomer B of the testosterone derivative). It follows that these compounds are best represented by structure (Vb) in which the 6-methyl group is β-orientated and ring B is in chair conformation. The semi-axial character of the 6-methyl bond in 4,6-dimethyltestosterone acetate (isomer B) indicates a high degree of interaction of the 6-methyl group with either the 4-methyl group or the C_9-α-hydrogen atom. This compound is assigned a 4,6α-dimethyl formulation, with ring B adopting a skew conformation, the limiting form of which would be the boat structure (Ve). The ready conversion of this isomer into the more stable 4,6β-dimethyltestosterone acetate (isomer A) has been described.[1]

Optical rotatory dispersion spectra

The ultraviolet O.R.D. spectra of steroidal 4-en-3-ketones arise largely from the interaction of the orbitals involved in the K- and R-band transitions with the electronic asymmetry of their environments. Whereas the localised symmetry of the carbonyl group in saturated ketones has permitted the derivation of a relatively simple octant rule,[8] which is capable of predicting accurately the sign of the Cotton effect associated with the $n \rightarrow \pi^*$ transition, the αβ-unsaturated ketonic chromophore, in contrast, lacks such symmetry, and the signs of the Cotton effects associated with the two transitions are regarded as dependent upon the chirality or sense of twist, of the

4-en-3-ketone system.[8] The existence below 300 m, of strongly positive Cotton effects shown by 4-bromo- and 4-methyl-4-en-3-ketones, and the inversion of this effect shown by 1β-methyl-19-nor progesterone, have been demonstrated by Djerassi *et al.*[9] who employed a spectropolarimeter of advanced design. The inversion shown by the 19-nor compound may be attributed to the change in chirality of the C=C—C=O system occasioned by distortion of ring A resulting from interaction of the 1-methyl group with the 11α-hydrogen atom.

The Cotton effect between 400 and 300 mμ, the region covering the R-band transition, is complex and of relatively low intensity. Considering the region as a

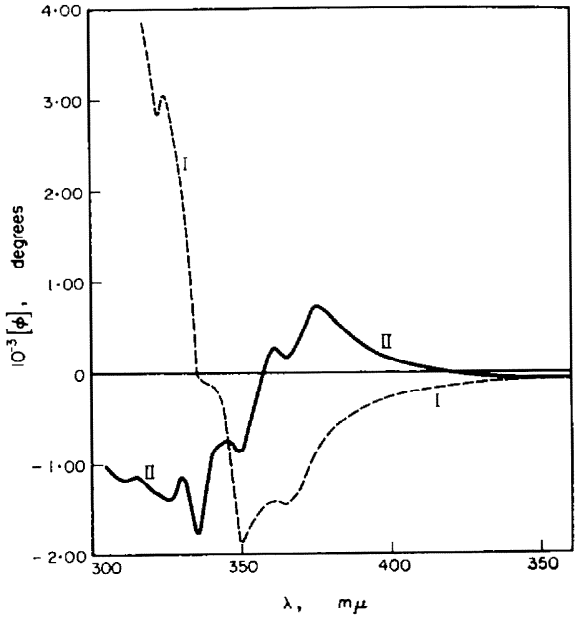


FIG 2. Rotatory disperion curves of:
1. 6α, 21-dimethylethisterone.
11. 6$\alpha\beta$ 21-dimethylethisterone.
(For condition see Experimental section.)

whole and ignoring minor features of the curve (the resolution of which depends markedly upon solvent polarity), the Cotton effect of normal steroidal 4-en-3-ketones is negative, on a positive background leading into the strongly positive effect at wavelengths below 300 mμ (*vide supra*). In general, the curve is little affected by 6α-substitution, or by small 6β-substituents such as a fluorine atom or hydroxyl group. Bulky 6β-substituents such as bromo-, chloro-, and methyl-, in contrast, cause inversion of the Cotton effect throughout, This is demonstrated by the O.R.D. curves of the isomeric 6α- and 6β, 21-dimethylethisterones (Fig. 2). Inversion of the Cotton effect does not occur in the absence of a C_{10}-methyl group.[10] Distortion of the chair conformation

[8] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi *J. Amer. Chem. Soc.* **83**, 4013 (1961).

[9] C. Djerassi, R. Records, E. Bunnenberg, K. Mislow and A. Moscowitz, *J. Amer. Chem. Soc.* **84**, 870 (1962).

[10] R. Villotti, C. Djerassi, and H. J. Ringold, *J. Amer. Chem. Soc.* **81**, 4566 (1959).

of ring B therefore causes a change of chirality of the 4-en-3-ketone system, and inspection of Dreiding models shows that the direction of change is the same as that observed with 1β-methyl-19-nor progesterone. The common factor relating these effects is thus revealed.

The present investigation was restricted to the region covering the R-band transition, in between 400 and 300 mμ, the wavelength region below 280 mμ being in-

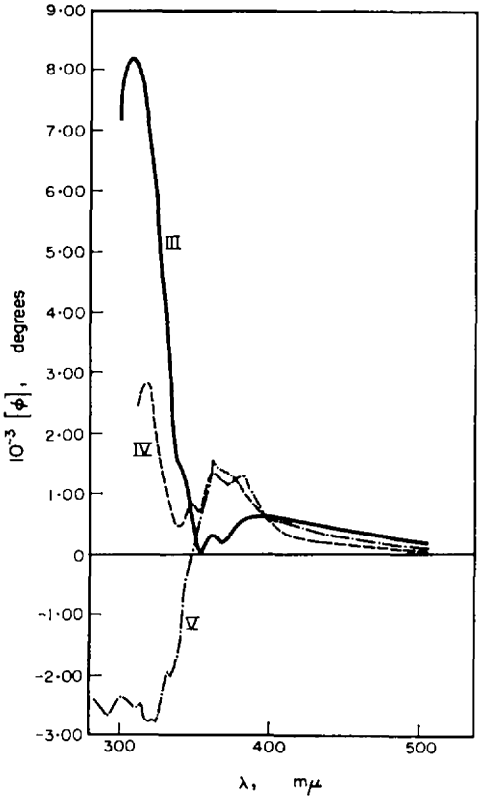


FIG. 3. Rotatory dispersion curves of:
III. 17α-acetoxy-4-methyl-progesterone.
IV. 17α-acetoxy-4,6β-dimethyl-progesterone.
V. 4,6β-dimethyltestosterone acetate.

accessible to us. Substitution at C_4 has been found to have little effect upon the Cotton curve, which only assumes a more positive background. In marked contrast all the 4,6-disubstituted steroids listed in Table 4 give spectra in which the Cotton curves are inverted (see Fig. 3) in a manner similar to that which occurs in passing from testosterone to its corresponding 6β-substituted derivatives.[11] The background curves of the 4,6-dihalogeno-4-en-3-ketones studied are noticeably more negative than those of the corresponding 6β-substituted compounds containing no C_4-substituent (Fig. 4).[12] The significance of this latter effect cannot be explained from our limited data, neither can the shape of the trough near 300 mμ in the curves of the two isomeric

[11] C. Djerassi, A. Halpern, V. Halpern, and B. Riniker, *J. Amer. Chem. Soc.* **80**, 4001 (1958).
[12] C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **80**, 1216 (1958).

4,6-dimethyltestosterone acetates. It should be noted that the O.R.D. curves of these isomers are very similar to each other, a fact which suggests that only small changes of identical sign in chirality of the chromophore, and hence of strain in ring B, are involved. Our present O.R.D. results, therefore, are inconclusive and do not permit structure assignments to the two compounds in question. Further investigation in the region below 300 mμ, rendered possible by improved instrumentation, may well provide O.R.D. data enabling an unequivocal decision to be made.

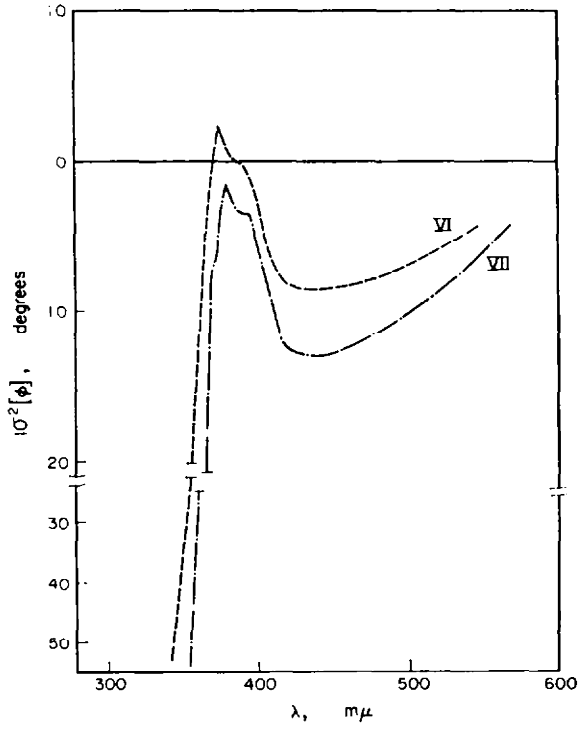


FIG. 4. Rotatory dispersion curves of:
VI. 4,6α-dichlorotestosterone propionate
VII. 4 chloro-6β-bromocholest-4-en-3-one.

EXPERIMENTAL

U.V. spectra: Unicam SP.500 and Beckman DK-2 spectrophotometers were used for the determination of the U.V. spectra, solvents being either "Spectro-grade" or "Analar", whichever was the higher purity obtainable.

O.R.D. spectra: Optical rotatory dispersion measurements were carried out by means of a Bellingham and Stanley "Pepol" spectropolarimeter fitted with a Unicam SP.500 monochromator and 500-watt Xenon arc source.

10 mm path silica cells of low inherent optical polarisation were used for sampling, and AnalaR dioxan was used as solvent throughout.

Optical rotations: Values of $[\alpha]_D$ were determined using chloroform as solvent, except where otherwise stated.

I.R. spectra. I.R. spectra were determined by means of a Hilger H800 spectrophotometer, using calcium fluoride and rocksalt prisms in the appropriate regions. The solvents used were as shown below.

Compounds. Compounds whose U.V. and O.R.D. spectra are described in this paper, and to which references are given, were the analytically pure samples described therein. The physical constants of well-documented compounds used in this work were as follows: (U.V. in ethanol).
Androst-4-en-3,17-dione: m.p. 173–174°; $[\alpha]_D^{20} = +188°$ (*c*, 1·00); $\lambda_{max} = 240$ mμ, $e = 17{,}000$.
Cholest-4-en-3-one: m.p. 79–80°; $[\alpha]_D^{20} = +90°$ (*c*, 1·04); $\lambda_{max} = 241$ mμ. $e = 16{,}500$
Testosterone: m.p. 154–155°; $[\alpha]_D^{20} = +116°$ (*c*, 1·00); $\lambda_{max} = 241$ mμ, $e = 16{,}200$

17α-methyl-testosterone: m.p. 165–167°; $[\alpha]_D^{20} = +81°$ (*c*, 1·02); $\lambda_{max} = 241$ mμ, $e = 16{,}000$.
Progesterone: m.p. 122–123°; $[\alpha]_D^{20} = +198°$ (*c*, 1·00); $\lambda_{max} = 241$ mμ, $e = 16{,}000$.

Optical rotatory dispersion data: The O.R.D. data for the following compounds in the region of 400–280 mμ are reported for the first time. Rotations are in terms of $[\phi]_\lambda^T$, where T lies between 28 and 30°. (*c* in gm/100 ml solution).

6α,21-dimethylethisterone: (Fig. 2, Curve 1). trough 364 mμ (−1625°); peak 358 mμ (−1500°); trough 352 mμ (−2075°); shoulder 340 mμ (−120°); peak 325 mμ (+3130°); trough 322 mμ (+2800°). (*c*, 0·55).

6β,21-dimethylethisterone: (Fig. 2, Curve II). peak 375 mμ (+730°); trough 365 mμ (+167°); peak 363 mμ (+296)°; trough 349 mμ (−890°); peak 345 mμ (−800°); trough 335 mμ (−1750°); peak 330 mμ (−1160°); trough 325 mμ (−1457°); peak 310 mμ (−360°); trough 305 mμ (−1060°). (*c*, 0·52).

17α-acetoxy-4-methylprogesterone: (Fig. 3, Curve III). peak 385–410 mμ (+560°); trough 368 mμ (+193°); trough 352–5 mμ (+25); shoulder 341–2mμ (+1460°); peak 308 mμ (+8530°). (*c*, 0·91).

17α-acetoxy-4,6β-dimethylprogesterone: (Fig. 3, Curve IV). peak 378 mμ (+1220°); trough 373 mμ (1155°); shoulder 367–70 mμ (+1180°); peak 363 mμ (+1346°); trough 353 mμ (+685°); peak 348 mμ (+857°); trough 337–40 mμ (+449°); peak (? limit of operation of instrument) 315–8 mμ (+2800°). (*c*, 0·94).

4,6β-dimethyltestosterone acetate ("Isomer A"): (Fig. 3, Curve V). peak 382 mμ (+1308°); trough 378 mμ (+1230°); shoulder 373–365 mμ (+1380°); peak 363 mμ (+1538°); trough 335 mμ −2000°); peak 333 mμ (−1850°); trough 323 mμ (−2850°); peak 320 mμ (−2770°); trough 313 mμ (−3000°); peak 308 mμ (−2610°); trough 305 mμ (−2690°); peak 298 mμ (−2536°); trough 292 mμ (−2850°); peak 288 mμ (−2540°); trough 280 mμ (−3460°). (*c*, 0·24).

4,6α-dimethyltestosterone acetate ("Isomer B"): (not illustrated.) peak 372 mμ (+1233°); trough 369 mμ (+1126°); peak 361 mμ (+1233°); shoulder 348 mμ (+430°); shoulder 334 mμ (−592°); trough 328 mμ (−1020°); peak 305 mμ (−860°); trough 295 mμ (−960°). (*c*, 0·67).

4,6α-dichlorotestosterone propionate: (Fig. 4, Curve VI). trough 440–420 mμ (−850 to −860°); shoulder 388 mμ (−16°); peak 375 mμ (+245°). (*c*, 0·78).

4-chloro-6β-bromocholest-4-en-3-one: (Fig. 4, Curve VII). trough at ca. 440 mμ (−1300°); peak 395 mμ (−336°); trough 390 mμ (−365°); peak 380 mμ (−161°); shoulder 372 mμ (−670°). (*c*, 0·59).

The preparation of 6β,21-*dimethylethisterone*

A solution of 6β-methyl-17α-(prop-1′-ynyl)androstan-3β,5α,17β-triol (10 g) and aluminium isopropoxide (10 g) in toluene (350 ml) and methyl ethyl ketone (100 ml) was refluxed fo 3 hr. The solution was washed with dil sulphuric acid and water, and steam-distilled. The product was isolated with ether and chromatographed on alumina (100 g) in benzene. Elution with benzene and benzene-ether (4:1) gave gums (ca 2 g) which crystallized in contact with ether. Crystallization with aqueous methanol gave 6β,21-*dimethylethisterone* as needles, m.p. 177–179°, $[\alpha]_D^{25} = -15°$ (*c*, 0·6) U.V. data given in Table 3, I.R. data as follows: (CS_2 solution), 3618 (hydroxyl), 1678 (4-en-3-one C=O), also bands at 1275, 1233, 1064, 1025, 1002 and 873 cm^{-1}. (Found: C, 81·1; H, 9·5%. $C_{23}H_{32}O_2$ requires: C, 81·1; H, 9·5%).

The preparation of 4,6α-*dichlorotestosterone propionate* (By Dr. D. N. Kirk)

10 g of the methyl enol ether of 4-chlorotestosterone propionate in acetone (500 ml) were mixed with 7 g sodium acetate in water (80 ml). N-chlorosuccinimide (10 g) was dissolved in the mixture and 7 ml glacial acetic acid added dropwise. After 30 min a further 7 ml acetic acid was added, the solution stirred for ½ hr, diluted to 2 litres with water and the solid filtered off and dried. (95 g of mp <140°). Repeated crystallization from acetone–hexane yielded 4,6α-*dichlorotestosterone propionate* m.p. 142–144°. $[\alpha]_D^{25} = 107°$ (*c*, 1·0 in dioxan). U.V. data as Table 4.

I.R. data: (CH_2Cl_2 soln) 1727, 1693, 1573 cm^{-1} (propionate C=O, 4-en-3-one C=O and C=C respectively). (CCl_4 and CS_2 solutions). 1738 (propionate), 1701 (4-en-3-one), 1182 (propionate), also bands at 1433, 1418, 888, 811, 729 and 680 cm.

(Found: C, 64·1; H, 7·53; Cl, 17·45%. $C_{22}H_{30}Cl_2O_3$ requires: C, 63·9; H, 7·3 and Cl, 17·15%).

The authors thank Drs. D. Burn, D. N. Kirk and Professor W. B. Whalley, for useful discussions.