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OPTICAL ROTATORY DISPERSION SPECTRA OF OXYGEN AND NITROGEN SUBSTITUTED DOUBLE BOND CHROMOPHORES

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Abstract—The ORD measurements of some steroidal ethers, enol acetates, enol lactones, enamines and enol amides have been determined. The ORD curves of enol ethers and enol lactones show a high Cotton effect, while that due to the enol acetate is much smaller. The pronounced Cotton effect in the cyclic enamine and enol amide is derived from the inherent dissymmetry of these chromophores. Comparsion is made between the UV absorption maxima of the compounds studied. It is suggested that some of the Cotton effects observed are due to a transition not observed in the UV spectra.

The recent development in optical instrumentation enables the ORD measurement of substances possessing a chromophore which absorbs in the lower region of the UV spectrum. We reported previously on the ORD of steroids with a single isolated double bond.[1] We now wish to describe the ORD of certain steroids having a double bond substituted with oxygen or nitrogen atoms.

The R—C—OR as well as R—C—NR$_2$ (R = alkyl) chromophores absorb only in the low UV region of the spectrum: the former absorbs much below 190 mμ[2], and the latter between 190–200 mμ.[3] These absorption maxima are associated with the lone pair of electrons on the oxygen or nitrogen atoms, the latter being more readily excited from their ground state to the antibonding σ^* orbital.

When oxygen or nitrogen atoms are linked to a doubly bound carbon atom, the resulting unsaturated chromophores possess a high UV absorption band. The enol ethers absorb at ca. 190 mμ,[4,5] and the enamines at ca. 210–230 mμ,[3] the ε values of the two being between 5000 and 10000. These absorption maxima are bathochromically shifted in respect to those observed in compounds having an isolated double bond unsubstituted with the hetero atom.[4,6] The absorption bands of enol ethers and enamines were assigned to a $\pi \rightarrow \pi^*$ transition as in the corresponding olefins, a resonance effect with the hetero atom being mainly responsible for the red shift.[6]

The ORD curve of the steroidal enol ether[1]; (Fig. 1) shows the high first extremum of a positive Cotton effect ($[\phi]$ +6900°) and has a zero rotation at $\lambda = 223$ mμ. In the non-conjugated dienol ether (II, Fig. 1), the first extremum is more pronounced

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[1] A. Yogev and Y. Mazur, *Chemical Communications* 552 (1965).

[2] A. J. Harrison and D. R. W. Price, *J. Chem. Phys.* **30**, 357 (1959).

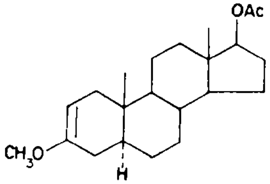
[3] N. J. Leonard and D. Locke, *J. Amer. Chem. Soc.* **77**, 437 (1955).

[4] A. I. Scott, Interpretation of the Ultraviolet Spectra of Natural Products, pp. 15–43. Pergamon Press, London (1964).

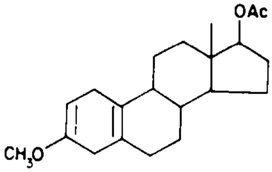
[5] G. Eglinton, E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.* 2873 (1952).

[6] H. H. Jaffe and M. Orchin, *Theory and Application of Ultraviolet Spectroscopy* pp. 173–217. J. Wiley, New York (1962).

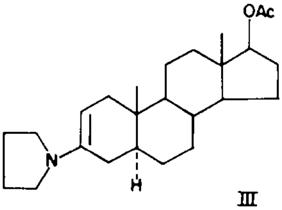
($[\phi]$ +12000°), and the curve is shifted to higher wavelength ($[\phi] = 0°$ at λ 228 mμ). The UV absorption maxima of I and II appear in cyclohexane at λ 192·5 and λ 205 mμ (ε 7800 and 9000) respectively, i.e. at a lower wavelength than the zero rotational values of the ORD curves of these compounds. It may be, therefore, that the transition responsible for the Cotton effect in enol ethers I and II is of a lower energy than that responsible for the absorption maxima in their UV spectra. The absorption band due to the former transition may be weak enough to be covered by a more pronounced lower wavelength band, and therefore is not seen in the UV spectrum. The transition responsible for the Cotton effect may involve the p_y orbital of the lone pair electrons of the oxygen atom,[6] and, therefore, possess a magnetic moment necessary for its rotatory strength.



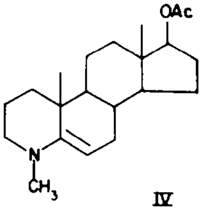
I



II



III



IV

The ORD of a N-substituted Δ^2-steroid, the enamine III and of the cyclic enamine IV were also investigated. The enamine III shows a high absorption band in the UV spectrum at λ_{max} 228 mμ, with ε 8000 (in cyclohexane).[7] The cyclic enamine IV possesses a similar UV spectrum (λ_{max} 221 mμ, ε 8500 in cyclohexane, and λ_{max} 219 mμ, ε 8700 in EtOH). On the other hand only the cyclic enamine IV shows a high Cotton effect (Fig. 2). The shape of this ORD curve indicates that the first Cotton effect is negative, and is then followed by a second positive effect. The remarkable difference in the ORD curves of two the enamines III and IV despite their similar UV spectra may be traced to the differences in steric relation of the p_x orbital of the nitrogen atom, and the π orbital of the double bond. Since free rotation along the C—N bonds in the enamine III is possible, the N—C=C-system becomes planar, and the transition is devoid of a magnetic moment. However, in the enamine IV the nitrogen is fixed in a ring, the relevant orbitals are non-planar (Fig. 3) and the chromophore becomes inherently asymmetric. It is of particular interest to remark that these orbitals in the cyclic enamine IV are twisted in the form of a righthanded helix[8] (Fig. 3). Contrary to expectation, the sign of the first Cotton effect of the ORD curve of enamine IV was found to be negative and not positive.[8] The reason for this deviation from the

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[7] We were unable to determine the UV spectrum of the enamine III in EtOH since it decomposes in this solvent.

For the definition of a helix see S. F. Mason, *Chem & Ind.* 1286 (1964).

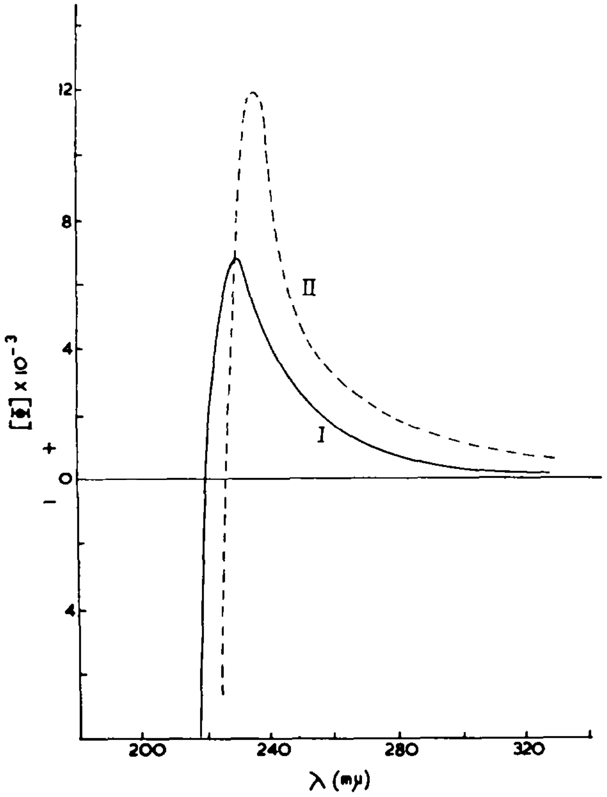
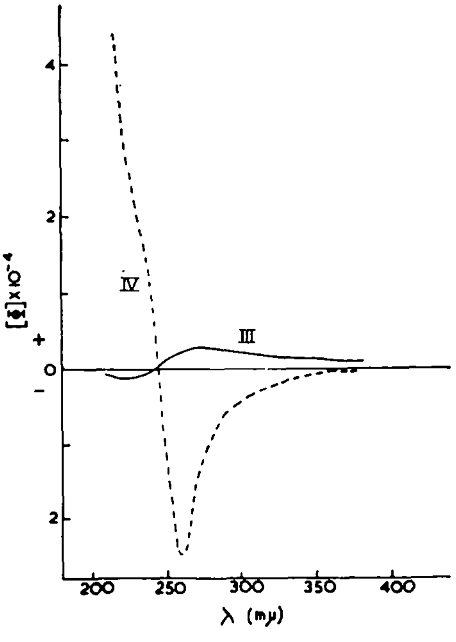


FIG. 1. ORD curves of 2-methoxy-5α-androst-2-en-17β-ol acetate (I), and of 3-methoxy-estra-2,5(10)-dien-17β-ol acetate (II).

FIG. 2. ORD curves of (3N-pyrrolidyl)-5α-androst-2-en-17β-ol acetate (III), and of 4-methyl-4-aza-androst-5-en-17β-ol acetate (IV).



helicity rule might be due to the mixing of the p_x orbitals on the nitrogen with the neighbouring σ orbitals. This interaction may change the relative direction of the magnetic and electric moments of the relevant transitions.[9] The second Cotton effect, whose onset is seen in the ORD curve of the cyclic enamine IV, is also due to the asymmetry of the absorbing chromophore, since it is absent in the enamine III.

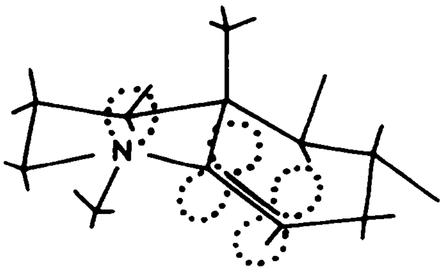
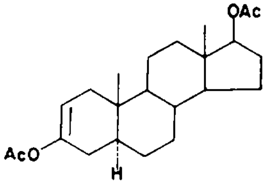


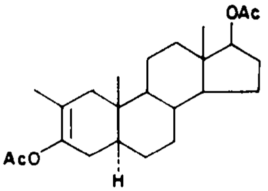
Fig. 3. Conformation of ring A and B of 4-methyl-4-aza-androst-5-en-17β-ol acetate (IV).

The substitution of the double bond with —O—CO— and with —N—CO— chromophores also shifts the UV absorption maxima to higher wavelength, and intensifies their extinction values.

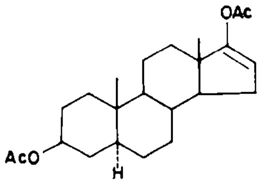
The UV maxima of compounds possessing the —C=C—O—CO— chromophore depends on the geometry of this group. Thus the enol lactones absorb at higher wavelengths than the enol acetates. The steroidal enol acetates V, VI and VII have their UV maxima at below 190 mμ; the "end absorption" values in these enol acetates are higher than those of the corresponding olefins lacking the O-acetyl group.[10]



V



VI



VII

The "transoid" enol lactones VIII, IX and XI have their absorption maxima at ca. 200 mμ (Table 1). The absorption maximum of the "cisoid" enol lactone X lies at an

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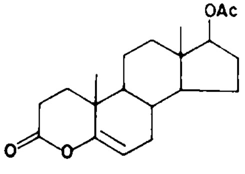
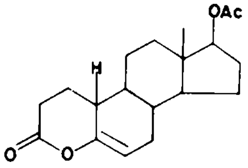
[9] We wish to thank Dr. M. Bixon, Department of Theoretical Chemistry, The Weizmann Institute of Science, for this suggestion.

[10] R. A. Micheli and T. H. Applewhite, *J. Org. Chem.* **27**, 345 (1951); A. Yogev, M. Gorodetsky and Y. Mazur, *J. Amer. Chem. Soc.* **86**, 5208 (1964); the ε values at λ 190 mμ indicated in the Ref. 4 of the latter paper should refer to the end absorptions and not to the absorption maxima.

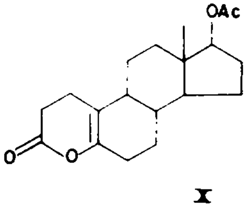
even higher wavelength (λ_{max} 223 mμ) (Table 1). The geometry of the enol lactones enables an extension of the orbital across the whole chromophore,[11] and thus is responsible for a lower energy transition on the UV spectrum. The red shift and decrease in ε values in the "cisoid" enol lactone X as compared to the "transoid" lactones, resembles the similar phenomena in the spectra of the "cisoid" and "transoid" conjugated dienes and α,β-conjugated ketones.[6] This behaviour may be indicative of an extended overlap of the π orbitals in the enol lactones. However such an overlap is less probable in the enol acetates; the most sterically favourable conformation of the latter appears to be the one in which the plane containing the carbonyl group is perpendicular to the plane of the steroidal ring system.[12] It is interesting to remark that a small solvent effect was observed in the spectrum of the enol lactones, the absorption maxima in ethanol being shifted by ca. 1–2 mμ to higher wavelengths, as compared to corresponding maxima in cyclohexane (Table 1). This observation may indicate that the UV absorption of the enol lactones is due to a $\pi \rightarrow \pi^*$ transition.[6]



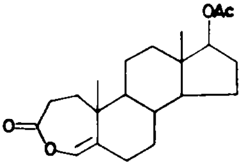
VIII



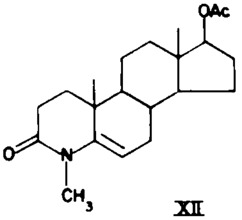
IX



X



XI



XII

The ORD curves of the enol acetates V, VI and VII (Fig. 4) show a first extremum

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[11] The Dreiding models of these enol lactones indicate that a conjugation of the π_x orbitals of the double bond and the carbonyl group, as well as the p_x orbital of the ethereal oxygen is likely to occur. This interaction is even more evident, since the actual conformation of the —CO—O—C=C— chromophore might be planar. Planarity of the —CO—O— group was observed in saturated lactones, cf. Ref 16.

[12] For conformation of ester groups attached to saturated ring systems, cf: A. McL. Mathieson, *Tetrahedron Letters* 4137 (1965).

TABLE 1. UV ABSORPTION MAXIMA OF ENOL LACTONES VIII, IX, X, XI AND OF ENAMINE LACTONE XII

Compound	In cyclohexane λ_{max}	ε	In ethanol λ_{max}	ε	In water λ_{max}	ε
4-Oxa-androst-5-en--3-on-17β-ol acetate VIII	197	7000	198	6500		
4-Oxa-estr-5-en-3-on-17β-ol acetate IX	201	7300	202	8300		
4-Oxa-estr-5(10)-en-3-on-17β-ol acetate X	222	3200	223	3300		
4-Oxa-A-homo-androst-4'-en-3-on-17β-ol acetate XI	202	9300	204	10000		
4-methyl-4-aza-androst-5-en-3-on-17β-ol acetate XII	234	15000	235	13000	236	13500

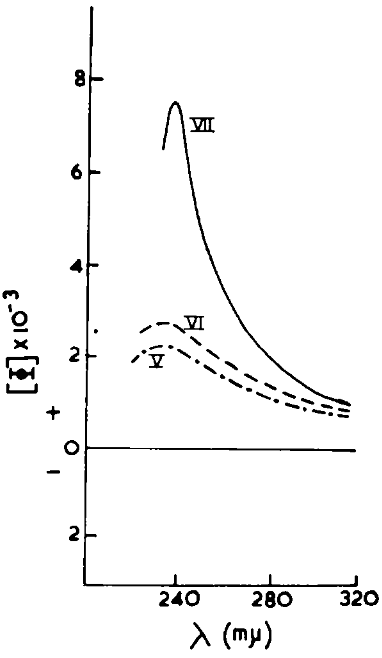

FIG. 4. ORD curves of 5α-androst-2-ene-3,17β-diol diacetate (V), 2-methyl-5α-androst-2-ene-3,17β-diol diacetate (VI), and of 5α-androst-16-ene-3β,17-diol diacetate (VII).

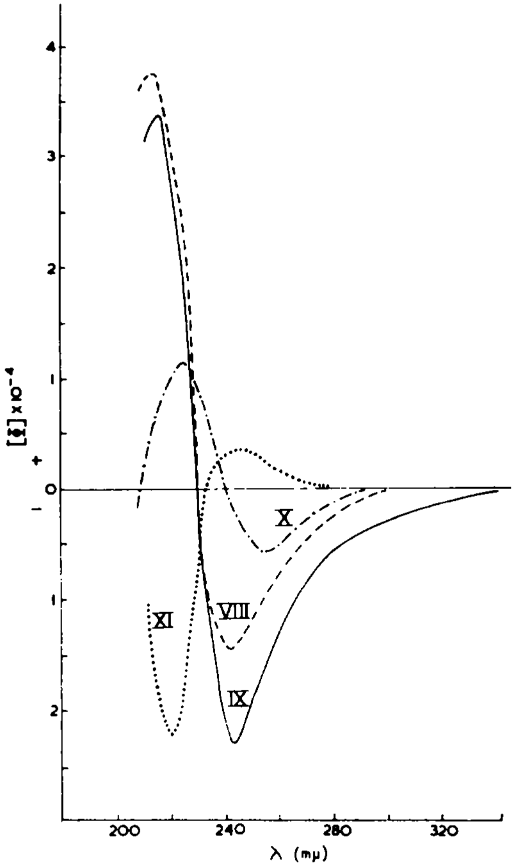

FIG. 5. ORD curves of 4-oxa-androst-5-en-3-on-17β-ol acetate (VIII), 4-oxa-estr-5-en-3-on-17β-ol acetate (IX), 4-oxa-estr-5(10)-en-3-on-17β-ol acetate (X), and of 4-oxa-A-homo-androst-4a-en-3-on-17β-ol acetate (XI).

of a rather small Cotton effect.[13] On the other hand, the ORD curves of the enol lactones VIII, IX, X and XI (Fig. 5) show a pronounced Cotton effect.[14] The wavelengths corresponding to zero rotations in the enol lactones are not the same as their UV maxima, the former appearing at 22–36 mμ longer wavelengths. The Cotton effect of the enol lactones probably also belongs to a transition which is not observed in their UV spectra.[15] The increased values of the second extremum in the ORD curves of the enol lactones (Fig. 5) as compared to the first extremum may be due to a second Cotton effect of an opposite sign.

The Cotton effect of the enol lactones is also more pronounced than the one observed

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[13] Because of the comparatively low values of molecular rotations due to the enol acetate chromophore, the effect of the saturated acetate group in these compounds cannot be disregarded. The effect of 17β-OAc group is to decrease the [ϕ] values, while that of 3β-OAc is to increase them.

[14] For ORD curves of steroidal enol lactones, see also: H. Wolf, *Tetrahedron Letters* 1075 (1965); W. Klyne and P. M. Scopes, cited in: P. Crabbé, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry* pp. 61–63, Holden-Day, San Fracnisco (1965).

[15] The solvent effect in the ORD curves of these enol lactones could not be estimated with certainty.

in the saturated lactones.[16] The transition responsible for the latter was suggested to be due to an n → π^* transition, the n level arising from the combination of the p_y orbitals of both oxygen atoms.[16,17] It is possible that the observed Cotton effect in the enol lactones derives from a transition, involving also the two p_y orbitals of both oxygen atoms, as well as the extended π orbital.

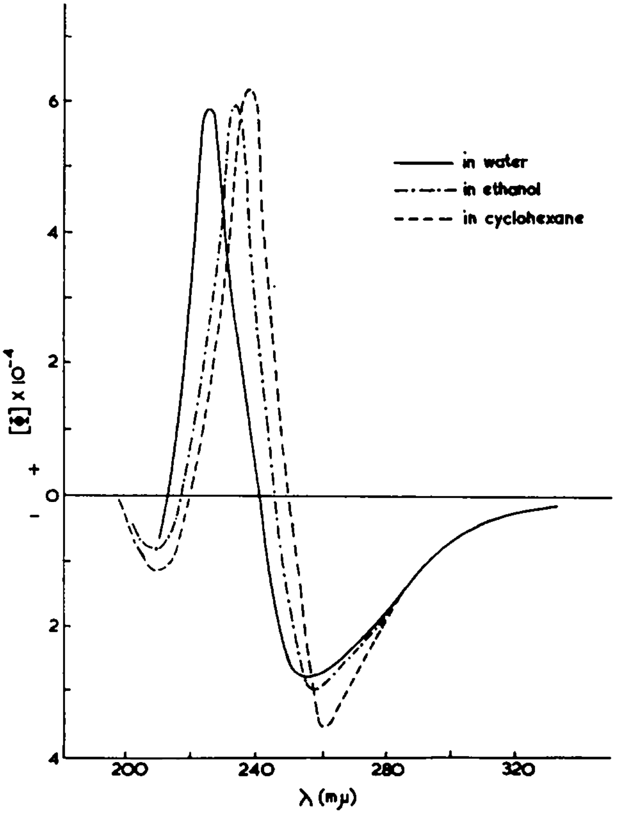

FIG. 6. ORD curve of 4-methyl-4-aza-androst-5-en-3-on-17β-ol acetate (XII) in water, ethanol and cyclohexane.

Finally, the ORD curve of the unsaturated amide XII was recorded (Fig. 5). This curve shows two distinct Cotton effects, the first being negative and the second positive. In addition, an onset of a third Cotton effect, probably also positive, can be observed in the lower wavelength of the curve. An interesting characteristic of this amide is the effect of the solvent on the position of the ORD spectrum. As seen in Fig. 6, the curve is displaced to the longer wavelengths with decreasing polarity of the solvent. In the UV spectrum however, the amide XII has only one maximum, and the solvent effect, although small, is in the opposite direction (Table 1). This UV maximum may represent two non-separated absorption bands of comparable intensities. The solvent effect observed in the ORD curves of the amide XII may be explained, assuming an influence of the hydrogen bonding of the solvent with the lone pair electrons on

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[16] J. P. Jennings, W. Klyne and P. M. Scopes, *Proceedings of Chem. Soc.* 412 (1964).

[17] G. Snatzke, *J. Chem. Soc.* 5002 (1965).

nitrogen.[6] Since the transitions in systems possessing —N—C═C— chromophores involve promotion of one of these electrons, the increasing polarity of the solvent will tend to increase the energy of the transition.

Comparison of the λ_{max} values in the UV spectrum, and λ values for zero rotation in the ORD curves of the enamine IV and the amide XII shows that in the latter compound, the maxima are shifted to higher wavelengths. This may be due to the extension of the π orbital in the amide XII to include the relevant orbital of the carbonyl group.

The results of these ORD measurements describe only the rotatory power of the chromophores studied. More information may be obtained by CD measurements, and by extension of the investigation to other compounds possessing these chromophores.

EXPERIMENTAL

The ORD measurements were preformed on a JASCO Model ORD/UV-5 instrument of the Japan Spectroscopic Co. Ltd., using cells of 0·1 cm width, unless otherwise stated. The concentrations are given in g/100 cc of solvent.

2-*Methoxy-5α-androst-2-en-17β-ol acetate* (I)[18] (Fig. 1). ORD in cyclohexane: *c*, 0·4; $[\phi]_{300}$ +950°, $[\phi]_{232}$ +6900°, $[\phi]_{223}$ 0°, $[\phi]_{222}$ −2200°.

3-*Methoxy-estra-*2,5(10)*-dien-*17*β-ol acetate* (II)[19] (Fig. 1.) ORD in cyclohexane: *c*, 0·18: $[\phi]_{300}$ +1700°, $[\phi]_{235}$ +12000°, $[\phi]_{228}$ 0°, $[\phi]_{226}$ −4800°.

3(N-*pyrrolidyl*)-5*α-androst-2-en-*17*β-ol acetate* III[20] (Fig. 2). ORD in cyclohexane: *c*, 0·65: $[\phi]_{300}$ +1800°, $[\phi]_{260}$ +3000°, $[\phi]_{242}$ 0°, $[\phi]_{225}$ −3800°, $[\phi]_{210}$ −1200°.

4-*Methyl-4-aza-androst-5-en-*17*β-ol acetate* IV[21] (Fig. 2). ORD in dioxan: *c*, 0·06; $[\phi]_{300}$ −5000°, $[\phi]_{257}$ −24000°, $[\phi]_{241}$ 0°, $[\phi]_{234}$ +15000°, $[\phi]_{212}$ +66000°.

5*α-Androst-2-ene-*3,17*β-diol diacetate* V[22] (Fig. 4). ORD in cyclohexane: *c*, 0·82; $[\phi]_{300}$ +920°, $[\phi]_{235}$ +2400°, $[\phi]_{220}$ +2300°.

2-*Methyl-5α-androst-2-ene-*3,17*β-diol diacetate* VI[23] (Fig. 4). ORD in cyclohexane: *c*, 0·93; $[\phi]_{300}$ +1200°, $[\phi]_{238}$ +2800°, $[\phi]_{230}$ +2500°.

5*α-Androst-*16*-ene-*3*β*,17*-diol diacetate* VII[24] (Fig. 4). ORD in EtOH: *c*, 0·36; $[\phi]_{300}$ +1250°, $[\phi]_{236}$ +7600°, $[\phi]_{230}$ +7100°.

4-*Oxa-androst-5-en-3-on-*17*β-ol acetate* VIII[25] (Fig. 5). ORD in EtOH: *c*, 0·065; $[\phi]_{280}$ −1500°, $[\phi]_{248}$ −16000°, $[\phi]_{233}$ 0°, $[\phi]_{215}$ +39000°, $[\phi]_{210}$ +37000°.

4-*Oxa-estr-5-en-3-on-*17*β-ol acetate* IX[26] (Fig. 5). ORD in EtOH: *c*, 0·056; $[\phi]_{280}$ −5700°, $[\phi]_{244}$ −22500°, $[\phi]_{230}$ 0°, $[\phi]_{216}$ +34000°, $[\phi]_{212}$ +31000°.

4-*Oxa-estr-*5(10)*-en-3-on-*17*β-ol acetate* X[26] (Fig. 5). ORD in EtOH: *c*, 0·051; $[\phi]_{280}$ −1200°, $[\phi]_{256}$ −5600°, $[\phi]_{241}$ 0°, $[\phi]_{225}$ +11000°, $[\phi]_{200}$ 0°, $[\phi]_{206}$ −1000°.

4-*Oxa-*A*-homo-androst-4′-en-3-on-*17*β-ol acetate* XI[27] (Fig. 5). ORD in EtOH: *c*, 0·05; $[\phi]_{260}$ +1200°, $[\phi]_{245}$ +4000°, $[\phi]_{234}$ 0°, $[\phi]_{220}$ −22000°, $[\phi]_{212}$ −10000°.

4-*Methyl-4-aza-androst-5-en-5-*17*β-ol acetate* XII[21] (Fig. 6). ORD incyclohexane: *c*, 0·0222; $[\phi]_{300}$ −7000°, $[\phi]_{261}$ −38000°, $[\phi]_{249}$ 0°, $[\phi]_{237}$ +62000°, $[\phi]_{221}$ 0°, $[\phi]_{211}$ −12000°, $[\phi]_{198}$ 0°, $[\phi]_{193}$ +4000°; ORD in EtOH; *c*, 0·0328; $[\phi]_{300}$ −6000°, $[\phi]_{258}$ −29000°, $[\phi]_{246}$ 0°, $[\phi]_{232}$ +58000°, $[\phi]_{218}$ 0°, $[\phi]_{209}$ −14000°, $[\phi]_{199}$ −10000°; ORD in water; *c*, 0·0003 in cell of 5 cm width; $[\phi]_{300}$ −6000°, $[\phi]_{258}$ −31000°, $[\phi]_{241}$ 0°, $[\phi]_{225}$ +58000°, $[\phi]_{212}$ 0°, $[\phi]_{210}$ −2500°.

[18] Prepared in this laboratory.

[19] J. A. Campbell and J. C. Babcock, U.S. Patent 2846452. *Chem. Abstr.* **53**, 4352 (1959).

[20] G. I. Fujimoto and R. W. Leeden, *J. Org. Chem.* **29**, 2059 (1964).

[21] Prepared in this laboratory, cf. N. J. Doorenbos and C. L. Huang, *J. Org. Chem.* **26**, 4548 (1961).

[22] R. Villotti, H. J. Ringold and C. Djerassi, *J. Amer. Chem. Soc.* **82**, 5698 (1960).

[23] R. Mauli, H. J. Ringold and C. Djerassi, *J. Amer. Chem. Soc.* **82**, 5494 (1960).

[24] N. S. Leeds, D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.* **76**, 2943 (1954).

[25] G. I. Fujimoto, *J. Amer. Chem. Soc.* **73**, 1856 (1951); H. J. Ringold and G. Rosenkrantz, *J. Org. Chem.* **22**, 602 (1957).

[26] J. A. Hartman, A. J. Tomasewski and A. S. Dreiding, *J. Amer. Chem. Soc.* **78**, 5662 (1956).

[27] Prepared in this laboratory, cf. E. Caspi, Y. W Chang and R. I. Dorfman, *J. Med. Pharm. Chem.* **5**, 714 (1962).