Some Observations on the Preparation of 2-Hydroxy-steroid 4-En-3-ones

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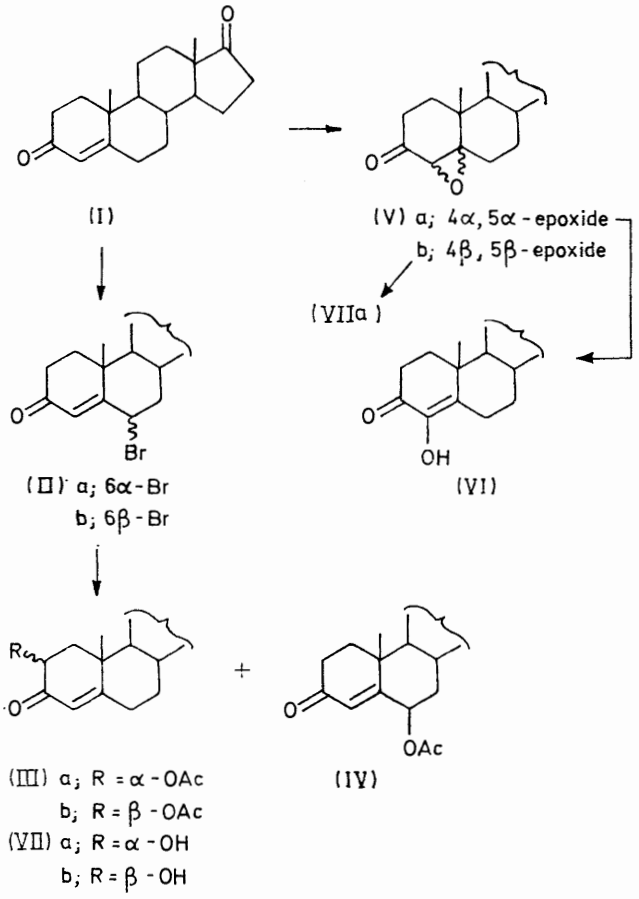
Improved experimental conditions are described for the preparation of 2β,17β- and 2α,17β-dihydroxyestr-4-en-3-one diacetates and 2β-acetoxyandrost-4-ene-3,17-dione. 6β-Acetoxyandrost-4-ene-3,17-dione has been obtained, together with the 2-acetoxy-derivatives, by acetolysis of 6β-bromoandrost-4-ene-3,17-dione. N.m.r. and c.d. data for the 2-hydroxy-compounds and their acetates are interpreted in terms of alternative conformations for ring A.

PUBLISHED procedures for the introduction of 2β- and 2α-hydroxy-substituents into androst-4-ene-3,17-dione (I) and 19-nortestosterone acetate (VIII) have been evaluated; modified experimental conditions gave significant improvements in yields.

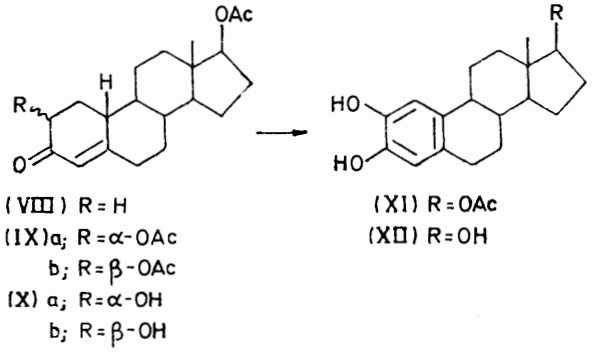
Three methods have been reported for the introduction of 2-hydroxy-substituents into 4-en-3-ones. (i) Direct acetoxylation with lead tetra-acetate gave mixtures of 2β- and 2α-acetoxy-derivatives, in rather low total yield.[1] (ii) Acetolysis of 6β-bromo-4-en-3-ones (with KOAc–HOAc) was reported to give similar mixtures of 2-acet-

[1] (*a*) L. R. Axelrod and P. N. Rao, *Tetrahedron*, 1960, **10**, 144; (*b*) F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 4712; (*c*) G. Rosenkranz, O. Mancera, and F. Sondheimer, *J. Amer. Chem. Soc.* 1955, **77**, 145; (*d*) R. L. Clarke, K. Dobriner, A. Mooradian, and C. M. Martini, *J. Amer. Chem. Soc.*, 1955, **77**, 661.

oxy-derivatives, in proportions (2β : 2α) which varied according to reaction conditions.[2] (iii) Rearrangement of a 4β,5β-epoxy-3-oxo-steroid with aqueous acid provided a route to the 2α-hydroxy-4-en-3-one.[3]



SCHEME 1



SCHEME 2

Acetoxylation of 19-nortestosterone acetate (VIII) with lead tetra-acetate in acetic acid at reflux temperature was reported to give a maximum total yield of 24% of the mixed (2β + 2α) acetoxy-derivatives.[1a] Our experiments, under a variety of reaction conditions (Table 1), showed that the total yield can be improved to 43% by using a considerable excess (3·5—4 mol. equiv.) of lead tetra-acetate under relatively mild conditions (60—70° in acetic acid, or under reflux in benzene). The reagent was all consumed after the times indicated in Table 1, but additional reagent (total 10 mol. equiv.) reduced the yield. The 2β- (IXb) and 2α-isomers (IXa)

TABLE 1

Direct acetoxylation of 19-nortestosterone acetate (VIII) with lead tetra-acetate in acetic acid

Moles $Pb(OAc)_4$ relative to steroid	Temp. (°C)	Time	Yield (%; isolated)
1·1	100	2 h	2
1·1	90	40 min	3
1·1	70	190 min	5
1·6	90	1 h	13
2·0	80	4·25 h	15
2·0	70	7 h	22
2·0	60	21 h	21
4·0	70	22 h	43
4·0	60	42 h	42
10·0 †	80	15 h	11
1·1 *	Reflux	22 h	27
3·5 *	Reflux	116 h	43

* Solvent benzene. † Reagent not completely consumed.

were readily separated (see Experimental section). Their conversion into 2-hydroxyestradiol 17-monoacetate (XI) according to the published procedure was straightforward, but final removal of the acetate by alkaline hydrolysis to give 2-hydroxyestradiol (XI) was accompanied by considerable destruction of the sensitive material even under oxygen-free conditions. (According to a recent report,[4] acid-catalysed hydrolysis seems less likely to damage the sensitive steroid.)

In attempts to prepare 2β-acetoxyandrost-4-ene-3,17-dione (IIIb) *via* the 6β-bromo-derivative (IIb), some novel features of the reactions were revealed by n.m.r. and g.l.c. analysis. The bromination of steroidal 4-en-3-ones at C-6 with *N*-bromosuccinimide [2] has been assumed [2c] to give only the 6β-bromo-isomer, but n.m.r. examination of the product of bromination of androst-4-ene-3,17-dione in refluxing CCl_4 (dehydrated over $CaCl_2$) showed that the 6β- and 6α-bromo-compounds were formed in a ratio of *ca.* 3 : 1. The isomers could not be separated by chromatography on silica gel, and were decomposed by alumina.[5] Attempted separation by fractional crystallization also failed, except on a single occasion when a small sample of the pure 6α-bromo-compound separated from a solution in acetone–hexane. G.l.c. analysis of the mixed bromination products gave three peaks which were separated by preparative g.l.c. and identified as androst-4-ene-3,17-dione, androsta-1,4-diene-3,17-dione, and androsta-4,6-diene-3,17-dione. These materials must result from thermal decomposition of the 6-bromo-compounds; formation of the 1,4-dienone presumably involves a

[2] (*a*) C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann, and J. Pataki, *J. Amer. Chem. Soc.*, 1950, **72**, 4534; (*b*) P. N. Rao, H. R. Gollberg, and L. R. Axelrod, *J. Org. Chem.*, 1963, **28**, 270; (*c*) D. J. Collins and J. J. Hobbs, *Austral. J. Chem.*, 1963, **16**, 874.

[3] M. Tomoeda, M. Ishizaki, H. Kobayashi, S. Kanatomo, T. Koga, M. Inuzuka, and T. Furuta, *Tetrahedron*, 1965, **21**, 733.

[4] I. Yoshizawa, M. Tamura, and M. Kimura, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1842.

[5] D. J. Collins and J. J. Hobbs, *Austral. J. Chem.*, 1964, **17**, 661.

' 1,6 '-elimination from the enol (XIII), but the reductive step leading to the 4-en-3-one has not been explained. When the bromination was carried out in carbon tetrachloride which had been distilled twice from P_2O_5 the 6β-bromo-compound was obtained in 74% yield, uncontaminated by the 6α-isomer.

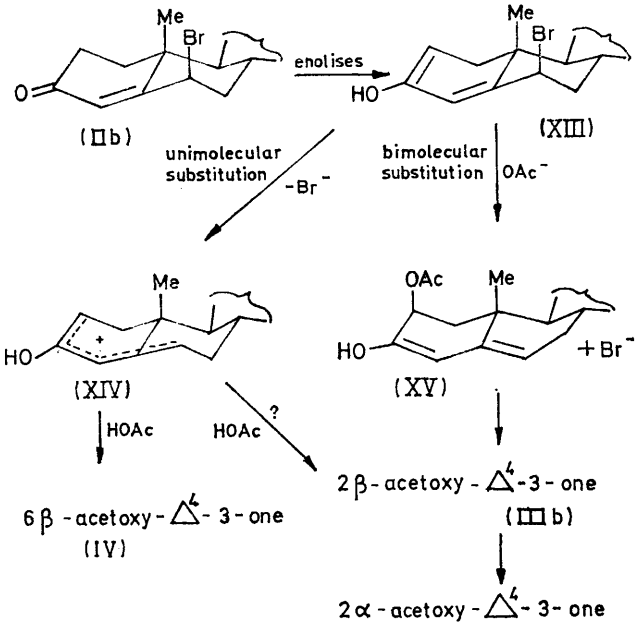
Rao *et al.*[2b] reported the acetolysis of 6β-bromoandrost-4-ene-3,17-dione (IIb) in refluxing acetic acid with a ten-fold excess of potassium acetate, for 12 min; they obtained the 2α- (IIIa) and 2β-acetoxy-compounds (IIIb) in 15—20 and 25—30% yields, respectively. Variation of experimental conditions (Tables 2 and 3),

TABLE 2

Acetolysis of 6β-bromoandrost-4-ene-3,17-dione in anhydrous acetic acid, at 95 °C (a ten-fold excess of anhydrous potassium acetate over steroid was present in each mixture)

Substrate concn.(M)	Time for optimum product formation	6β-OAc-androstenedione (%; g.l.c.)	2β-OAc-androstenedione (%; g.l.c.)	2α-OAc-androstenedione (%; g.l.c.)	Other products (%; g.l.c.)
3×10^{-3}	7 h	28	13	6	Trace
1×10^{-2}	7 h	33	16	10	Trace
3×10^{-2}	7 h	32	25	9	4
8×10^{-2}	7 h	18	35	22	12
0·3	1·5 h	10	29	13	28

with g.l.c. analysis of products, has now shown that *three* acetoxy-derivatives (2α-, 2β-, and 6β-) are formed, in proportions depending upon reaction conditions. seem feasible. It is clear, however, that low concentrations of reactants favour the formation of the 6β-acetate, whereas high concentrations increase the yield of unidentified by-products.



SCHEME 3

Optimum conditions for the preparation of the 2β-acetoxy-derivative appear to be a reaction temperature

TABLE 3

Effects of varying temperature on the acetolysis of 6β-Bromoandrost-4-ene-3,17-dione (conditions otherwise as in Table 2)

Temp. (°C)	Substrate-concn.(M)	Time for optimum product formation	6β-OAc-androstenedione (%, g.l.c.)	2β-OAc-androstenedione (%, g.l.c.)	2α-OAc-androstenedione (%, g.l.c.)	Other products (%; g.l.c.)
Reflux	0·8	20 min	7	13	8	15
95	0·3	1·5 h	10	29	13	28
80	0·4	10 h	14	28	17	32
70	0·4	36 h	13	24	21	30
70	0·2	36 h	15	44	16	17
70	0·1	36 h	16	39	15	12

Reflux temperature caused isomerisation of the 2β- into the 2α-acetoxy-compound, as well as further reactions to give unidentified products, at rates which soon exceeded the rate of acetolysis of the residual bromide. At lower temperatures, isomerisation from the 2β- to the more stable 2α-configuration was relatively slow: optimum conversion into the 2β-acetate resulted, however, when reactions were terminated before the 6β-bromo-compound had been entirely consumed.

Table 2 records typical product compositions (g.l.c.) when the concentrations of the reactants in acetic acid were varied, for reactions at 95°. Table 3 records a selection of results of reactions at different temperatures. Reproducibility was poor, each batch of the unstable 6β-bromo-compound showing its own characteristics despite attempts to obtain material of standard purity. A detailed kinetic investigation of the reaction did not of 70° for 36 h (the reaction is inordinately slow at lower temperatures) and a steroid concentration of *ca.* 0·2 mol l^{-1}, with a ten-fold excess of potassium acetate.

The dependence of product ratio upon concentration (Table 2) seems best explained by simultaneous operation of at least two reaction mechanisms (Scheme 3), both proceeding *via* the enolic structure (XIII). At low concentrations of reactants, a unimolecular ionisation of the bromo-enol leading to a mesomeric cation (XIV) would be relatively favourable. Nucleophilic attack of the solvent acetic acid at the 6β-position of the cation would accord with the usual stereoelectronic preference for ' axial ' attack and results in formation of the stable conjugated 4-en-3-one (4β-attack would lead to the less stable 5-en-3-one). Solvent attack at the 2β-position is also feasible, but is apparently not of great significance. In more concentrated solutions a rate-controlling bi-

molecular substitution would become more favourable, the preferred reaction being nucleophilic substitution of Br^- by 'axial' attack of acetate on the enol at C-2 to give the further enolic structure (XV), which is rapidly converted into the conjugated ketone (IIIb). Product analyses show that 2β-acetoxylation is kinetically favoured over 2α-acetoxylation, although the possibility that a little of the 2α-acetoxy-compound (IIIa) is formed directly cannot be ruled out.

The preparation of 2α-hydroxyandrost-4-ene-3,17-dione (VIIa) by hydrolysis of the 4β,5β-epoxy-ketone (Vb) proceeded as described.[3] The 4α,5α-epoxy-ketone (Va) gives mainly 4-hydroxyandrost-4-ene-3,17-dione (VI) under similar conditions.[3]

N.m.r. Spectra (Table 4).—Configurations of the 6-

TABLE 4

60 MHz N.m.r. data (δ values; Me_4Si standard)

Compound	18-H_3	19-H_3	4-H	Other
(I)	0·91	1·21	5·70	
(IIa)	0·91	1·25	6·43	4·85 (m, 6-H)
(IIb)	0·97	1·55	5·93	5·04 (q, 6-H)
(IIIa)	0·92	1·34	5·76	2·14 (2-OAc), 5·43 (q, 2-H)
(IIIb)	0·92	1·23	5·80	2·12 (2-OAc), 5·29 (q, 2-H)
(IV)	0·95	1·31	5·93	2·03 (6-OAc), 5·45 (t, 6-H)
(Va)	0·90	1·10	3·05	
(Vb)	0·90	1·17	2·97	
(VI)	0·92	1·22		6·08 (4-OH)
(VIIa)	0·92	1·32	5·78	3·51 (2-OH), 4·24 (q, 2-H)
(VIIb)	0·93	1·21	5·84	3·46 (2-OH), 4·23 (q, 2-H)
19-Nor-testosterone	0·80		5·81	1·85 (17-OH), 3·66 (t, 71-H)
(VIII)	0·86		5·82	2·03 (17-OAc), 4·63 (t, 17-H)
(IXa)	0·86		5·81	2·01 (17-OAc), 2·13 (2-OAc), 4·59 (t, 17-H), 5·28 (q, 2-H)
(IXb)	0·86		5·81	2·01 (17-OAc), 2·11 (2-OAc), 4·59 (t, 17-H), 5·24 (t, 2-H)
(Xa)	0·84		5·90	2·02 (17-OAc), 3·66 (2-OH), 4·11 (q, 2-H), 4·65 (t, 17-H)
(Xb)	0·83		5·83	2·02 (17-OAc), 3·52 (2-OH), 4·14 (q, 2-H), 4·68 (t, 17-H)
(XI)	0·82		6·58	2·06 (17-OAc), 4·76 (t, 17-H), 6·80 (split, 1-H)
Androsta-4,6-diene-3,17-dione	0·95	1·13	5·69	6·17 (6,7-H)
Testosterone	0·80	1·19	5·71	1·90 (17-OH), 3·65 (t, 17-H)
Testosterone 17β-acetate	0·83	1·18	5·71	2·01 (17-OAc), 4·60 (t, 17-H)
2α-Hydroxy-testosterone diacetate	0·83	1·33	5·73	2·03 (17-OAc), 2·15 2-OAc), 4·60 (t, 17-H), 5·43 (q, 2-H)
2β-Hydroxy-testosterone diacetate	0·83	1·21	5·77	2·03 (17-OAc), 2·13 (2-OAc), 4·58 (t, 17-H), 5·29 (q, 2-H)

bromo-derivatives obtained from the reactions between androstenedione and *N*-bromosuccinimide are based upon their n.m.r. spectra. The 6α-proton in the 6β-bromo-isomer exhibits the reported[6] quartet, implying that distortion of ring B occurs because of van der Waals repulsion between the 6β-Br and the 10β-methyl group. In the absence of distortion a triplet is expected since the torsion angles $\theta_{6\alpha.7\alpha}$ and $\theta_{6\alpha.7\beta}$ would be each *ca.* 60°, making $J_{6\alpha,7\alpha}$ and $J_{6\alpha,7\beta}$ approximately equal. The 6α-proton of 6β-hydroxyandrost-4-ene-3,17-dione acetate (IV) shows as a triplet, distortion being less for the smaller acetate group than for 6β-Br.

An unusual A-ring conformation of 2β-hydroxy-4-en-3-ones and their 2-acetates, in both the 10β-methyl and 19-nor series, has been suggested on the basis of n.m.r.,[7-9] o.r.d., and c.d.[10] spectroscopy, and confirmed by *X*-ray crystallography.[11,12] The coupling constants of the C-2, protons in all the compounds studied, based upon the first-order approximation, are given in Table 5. All the spectra except that of the 2β-acetoxy-19-nor-compound (IXb) show a quartet signal, confirming an abnormal conformation of the 2β-substituted isomers. Dreiding

TABLE 5

Coupling constants (Hz) of 2α- and 2β-protons of 2β- and 2α-RO-Δ^4-3-ones (R = H or Ac) at 60 MHz

Steroid	2α-H		2β-H	
	$J_{2\alpha.1\alpha}$	$J_{2\alpha.1\beta}$	$J_{2\beta.1\alpha}$	$J_{2\beta.1\beta}$
2α-Acetates				
2α-OAc-androst-4-ene-3,17-dione (IIIa)			14·0	5·7
2α,17β-$(OAc)_2$-estr-4-en-3-one (IXa)			14·1	5·6
2α-OAc-testosterone 17β-acetate			13·9	5·8
2α-OAc-testosterone 17β-chloroacetate			13·6	5·6
2α-Alcohols				
2α-OH-androst-4-ene-3,17-dione (VIIa)			13·6	5·6
2α-OH,17β-OAc-estr-4-en-3-one (Xa)			13·6	5·2
2β-Acetates				
2β-OAc-androst-4-ene-3,17-dione (IIIb)	5·6	11·8		
2β-17β-$(OAc)_2$-estr-4-en-3-one (IXb)	7·9	7·9		
2β-OAc-testosterone 17β-acetate	5·6	11·7		
2β-OAc-testosterone 17β-chloroacetate	5·4	11·7		
2β-Alcohols				
2β-OH-androst-4-ene-3,17-dione (VIIb)	5·4	14·4		
2β-OH,17β-OAc-estr-4-en-3-one (Xb)	5·4	13·0		

models indicate that there are basically two possible abnormal structures, a 'half-boat' form and an 'inverted chair' form, both illustrated in Newman projection in Figure 1.

The 'half-boat' conformation (in solution) has been proposed by Kuriyama *et al.*[7] for the 2β-acetoxy-4-en-3-ones, but *X*-ray crystallography has shown that crystalline 2β-hydroxytestosterone 2-acetate 17-chloroacetate exists in a perfect inverted chair form.[12] Unless the conformation is significantly different in solution from that

[6] N. S. Bhacca and D. H. Williams, 'Applications of N.m.r. Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, p. 149.
[7] K. Kuriyama, E. Kondo, and K. Tori, *Tetrahedron Letters*, 1963, 1485.
[8] Y. Yamato and H. Kanedo, *Tetrahedron*, 1965, **21**, 2501.
[9] S. Burstein and H. L. Kimball, *Steroids*, 1963, **2**, 1.
[10] S. L. Patashnik, S. Burstein, and H. L. Kimball, *Steroids*, 1963, **2**, 19.
[11] W. L. Duax, C. Eger, S. Pokrywiecki, and Y. Osawa, *J. Medicin. Chem.*, 1971, **14**, 295.
[12] Y. Osawa and J. O. Gardner, *J. Org. Chem.*, 1971, **36**, 3246.

found in the crystal, Kuriyama's allocation of the observed splitting constants (12·0 and 5·4 Hz) to $J_{2\alpha,1\alpha}$ and $J_{2\alpha,1\beta}$, respectively, is in error, and should be reversed. From use of the Karplus [13] equation with the coefficients of Williamson and Johnson [14] the observed J values imply a conformation close to a perfect 'inverted chair', with $\theta_{2\alpha,1\beta}$ *ca.* 160°, $\theta_{2\alpha,1\alpha}$ *ca.* 40°.

The n.m.r. signal of the 2α-proton in the exceptional 19-nor-compound (IXb) is an asymmetric triplet, instead of being a definite quartet. The nearly equal values of $J_{2\alpha,1\alpha}$ and $J_{2\alpha,1\beta}$ are too large for an equatorial proton in a normal half-chair (expected value [15] *ca.* 2·5 Hz). The only alternative conformation which can give

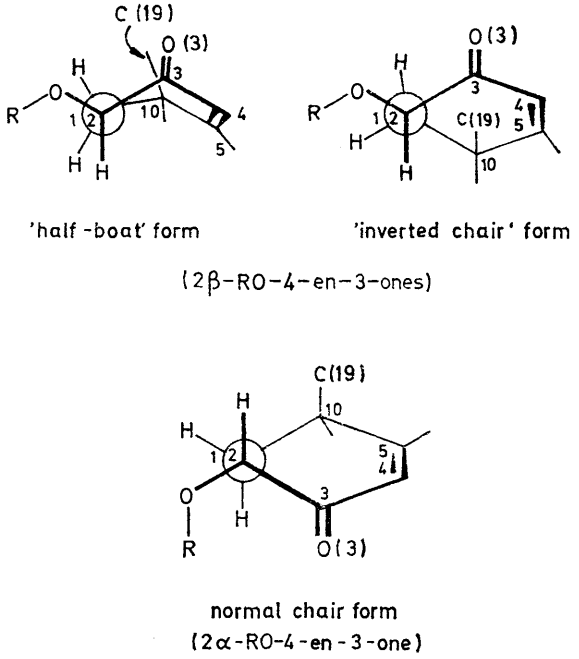


FIGURE 1 The A-ring of 2α- and 2β-RO-4-en-3-ones projected along the C(2)–C(1) bond, showing the basic conformations (R = H or Ac)

J values as large as 8 Hz is close to a 'half-boat'. The Karplus coefficients mentioned above will not provide an exact solution, but suggest torsion angles of the order: $\theta_{2\alpha,1\beta}$ 135—140°; $\theta_{2\alpha,1\alpha}$, 15—20°. Yamato *et al.*[8] reached a similar conclusion, although they report that the 2α-proton in compound (IXb) gave a quartet, $J_{2\alpha,1\alpha}$ 9·3, $J_{2\alpha,1\beta}$ 6·9 Hz.

Circular Dichroism.—In view of recent interest in the low-wavelength c.d. of enones, we examined the c.d. curves for all compounds in the present series over the range 360—200 nm (Figures 2 and 3). Three major features due to the C=C–C=O group are readily apparent in most of the curves: (i) a weak dichroic absorption in the region 320—330 nm (n–π^* transition); (ii) a strong band in the region 240—245 nm (π–π^* transition); and (iii) a further strong band (seen most clearly in the spectra of the 2β-substituted enones) at about 210—220 nm. The curves in Figure 2 also show a band at about 290 nm due to the C(17)=O chromophore (n–π^* transition).

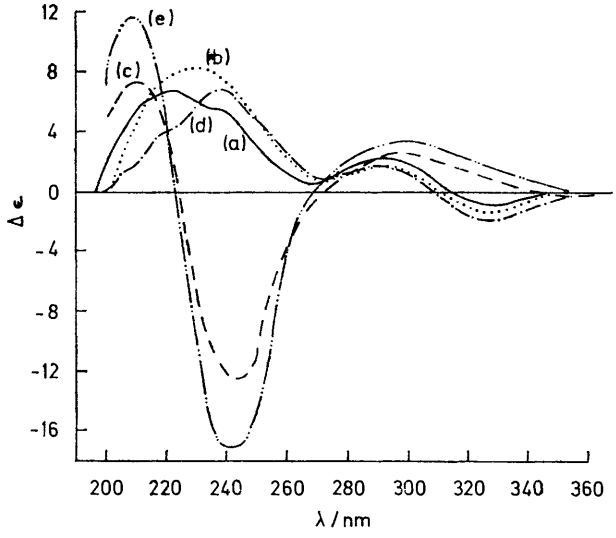


FIGURE 2 C.d. curves for (a) androst-4-ene-3,17-dione (I), (b) 2α-acetoxyandrostenedione (IIIa) and (c) its 2β-isomer (IIIb), and (d) 2α-hydroxyandrostenedione (VIIa) and (e) its 2β-isomer (VIIb)

The signs of the Cotton effects for the 240—245 nm (π–π^*) transition are in good agreement with the original 'helicity rule' put forward by Djerassi *et al.*: [16] the unsubstituted and 2α-substituted enones, with right-handed chirality, have a positive Cotton effect, whereas the 2β-substituted enones, with left-handed chirality due to their abnormal conformation, have an intense negative Cotton effect.

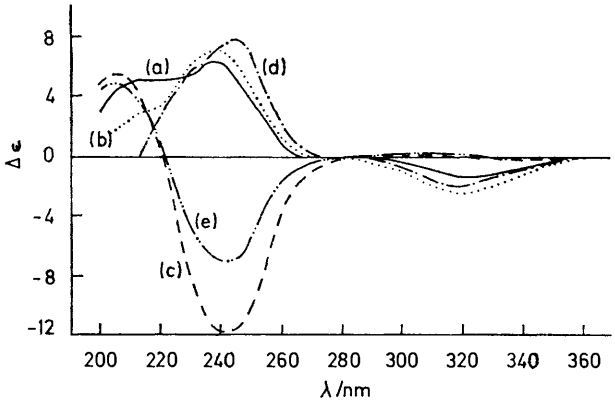


FIGURE 3 C.d. curves for 19-nortestosterone 17β-acetate derivatives: (a) unsubstituted (VIII), (b) 2α-acetoxy (IXa), (c) 2β-acetoxy (IXb), (d) 2α-hydroxy (Xa), (e) 2β-hydroxy (Xb)

An alternative interpretation of the sign associated with the π–π^* transition in terms of the chirality contributions of allylic axial (γ and γ') substituents, has

[13] M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11.
[14] K. L. Williamson and W. S. Johnson, *J. Amer Chem. Soc.*, 1961, **83**, 4623.
[15] D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.*, 1964, **86**, 2742.
[16] C. Djerassi, R. Records, E. Bunnenberg, K. Mislow, and A. Moscowitz, *J. Amer. Chem. Soc.*, 1962, **84**, 870.

recently been suggested by Burgstahler *et al.*[17,18] to explain several apparent exceptions to the helicity rule. In 4-en-3-ones, for example (Figure 4), the observed positive Cotton effect was attributed to the positive contribution from the 10β-Me substituent, overriding the negative contribution from the 6β-H. The α′-substituent (2β-H) was not considered to influence this transition. Burgstahler's interpretation fails to explain the present series of curves, since the C=C bond is influenced by the same γ- and γ′-substituents in both the 2α- and 2β-substituted enones, but the sign of the Cotton effect is reversed in the 2β-series.

Clearly neither of these two approaches alone is adequate to cover all known enones. Our own examination of all the available c.d. curves covering this region of the spectrum suggests that in the absence of any dominating influence by either γ- or γ′-substituents the sign of the Cotton effect of the π–π* transition usually conforms to the chirality of the enone system. This is the situation when the total ' γ influence ' consists of a single positive contribution counterbalanced by a single

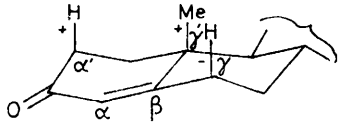


FIGURE 4 Allylic axial chirality contributions in 4-en-3-ones

negative contribution, each from an axial H or Me. However, where there exists an extra positive or negative γ or γ′ contribution, this may dominate the sign of the Cotton effect. A combination of the two rules will account for all five examples quoted by Burgstahler as not obeying the simple helicity rule, and also allows the signs for the present 2-substituted compounds to be dominated by enone helicity.

For the lower wavelength transition at 210—220 nm, Burgstahler noted and tabulated [18] an apparent correlation between the sign of the Cotton effect and the chirality contribution at the carbonyl group by the axial (or pseudoaxial) bond on the α′-carbon atom. It was suggested that a right-handed chirality contribution produces a positively-signed Cotton effect, and a left-handed contribution a negative effect. This rule is apparently inapplicable to the present curves, the sign being positive in all cases, including the 2β-substituted isomers where the α′-axial H(2α) contribution should be negative because of the inverted conformation. This region of the spectrum requires further exploration, which is in progress.[19]

The *n*–π* transition at 330 nm gives a negative curve for the unsubstituted and 2α-substituted enones, as predicted by Snatzke's [20] ' reverse octant ' rule for *transoid* enones. The 2β-substituents cause this transition virtually to disappear (see Figure 3), leaving at most a very weak bisignate curve. This might be expected since the body of the steroid molecule disappears from the negative octant when the conformation of ring A is modified by the 2β-substituent.

[17] A. W. Burgstahler and R. C. Barkhurst, *J. Amer. Chem. Soc.*, 1970, **92**, 7601.
[18] A. W. Burgstahler, R. C. Barkhurst, and J. A. Gawronski, XXIIIrd Int. Congress of Pure and Applied Chemistry, Boston, Mass., July 1971.
[19] R. D. Burnett and D. N. Kirk, in preparation.
[20] G. Snatzke, *Tetrahedron*, 1965, **21**, 413.

EXPERIMENTAL

I.r. spectra were determined for KBr discs, u.v. spectra for solutions in 99·5% ethanol, n.m.r. spectra at 60 MHz for solutions in $CDCl_3$, and c.d. spectra for solutions in methanol and acetonitrile; m.p.s were determined on a Kofler hot-stage apparatus. Analytical g.l.c. was carried out at 240 °C on a 7 ft column of 3·8% QF1 on Diatoport S (80—100 mesh) and preparative g.l.c. on a 7 ft column of 15% QF1 on Anakrom ABS (60—70 mesh). Merck silica gel $HF_{254+366}$ was used for t.l.c., with development by benzene–ethyl acetate (4 : 1 or 7 : 3). Alumina for column chromatography was Spence grade H, deactivated with 5% of aqueous 10% acetic acid.

6β-*Bromoandrost*-4-*ene*-3,17-*dione* (IIb).—Androst-4-ene-3,17-dione (I) (1·0 g), *N*-bromosuccinimide (0·8 g), and benzoyl peroxide (0·05 g), in carbon tetrachloride (250 ml; twice distilled from P_2O_5), were heated for 10 min under reflux in darkness. The solution was then washed with water and sodium hydrogen carbonate solution, and afforded the 6β-bromo-derivative (IIIb) (0·946 g, 74%) as a pale yellow powder (after trituration of the crude product with ether), m.p. 162—164° (decomp.) [lit.,[2a] 175—177° (decomp.)], $\lambda_{max.}$ 246·5 nm (ε 12,150) [lit.,[2a] $\lambda_{max.}$ 240 nm (ε 16,980)]. The longer-wavelength absorption (246·5 nm) is more compatible with the 6β-configuration.[21]

Acetolysis of 6β-*Bromoandrostenedione*.—The steroid (IIb) (1·20 g) and anhydrous potassium acetate (3·24 g) were heated at 66° in anhydrous acetic acid for 27·5 h. Extraction with ether gave a yellow oil (1·15 g) from which three products were isolated by column chromatography on alumina. In order of elution these were (i) (with benzene) 2α-hydroxyandrostenedione 2-acetate (IIIa), plates (from methanol) (110 mg, 9·7%), m.p. 210—212° (lit.,[2b] 210—211·5°); (ii) [with benzene–ether (96 : 4)] 2β-hydroxyandrostenedione 2-acetate (IIIb), needles (from methanol) (95 mg, 8·4%), m.p. 155—157° (lit.,[2b] 156—158°); and (iii) [with benzene–ether (85 : 15)] 6β-hydroxyandrostenedione 6-acetate (IV), cubes (from methanol) (79 mg, 7·0%), unstable in air, m.p. 197—202° (lit.,[22] 202—202·5°), $\lambda_{max.}$ 236 nm (ε 13,630).

4-*Hydroxyandrost*-4-*ene*-3,17-*dione* (VI).—4α,5-Epoxy-5α-androstane-3,17-dione (Va) [23] (150 mg) was heated under reflux in acetone (6 ml) containing aqueous 25% v/v sulphuric acid (0·3 ml) for 3·5 h. Extraction with ether and preparative t.l.c. gave 4-*hydroxyandrostenedione* (VI), needles (from aqueous methanol) (24 mg, 16%), m.p. 199—202°, $\lambda_{max.}$ 278 (ε 11,030); $\nu_{max.}$ 3410, 3380, 1738, 1668, and 1630 cm^{-1} (Found: C, 75·4; H, 8·3. $C_{19}H_{26}O_3$ requires C, 75·5; H, 8·7%).

2α-*Hydroxyandrost*-4-*ene*-3,17-*dione* (VIIa).—4β,5-Epoxy-5β-androstane-3,17-dione (Vb) [23] (300 mg) in acetone (12 ml) containing aqueous 25% v/v sulphuric acid (0·6 ml) was kept at room temperature for 7 days. Extraction with

[21] C. W. Bird, R. C. Cookson, and S. H. Dandegaonker, *J. Chem. Soc.*, 1956, 3675.
[22] K. Tsuda, H. Iizuka, Y. Sato, A. Naito, and M. Kato, *Chem. and Pharm. Bull. (Japan)*, 1961, **9**, 925.
[23] H. B. Henbest and W. R. Jackson, *J. Chem. Soc. (C)*, 1967, 2459.

ether and preparative t.l.c. gave the product (VIIa), plates (from hexane–acetone) (134 mg, 44%), m.p. 158—160° (lit.,[2b] 160—161°).

2α,17β- *and* 2β,17β-*Diacetoxyestr*-4-*en*-3-*one* (IXa and b).—19-Nortestosterone 17β-acetate (VIII) (570 mg) in anhydrous acetic acid (10 ml) was heated at 60° with lead tetra-acetate (3·4 g). After 42 h a starch–iodide test was negative, and the products were extracted into ether. Successive crystallisation from methanol produced (i) (from 3 ml of methanol) 114 mg, m.p. 170—220°, mainly 2α-isomer (g.l.c.); (ii) (from 1 ml of methanol) 97 mg, m.p. 165—180°, mainly 2β-isomer (g.l.c.); and (iii) (from 0·4 ml of methanol) 6 mg, a mixture of isomers. Column chromatography on alumina separated a further 66 mg of mixed isomers from the residues, the 2α-isomer being first eluted (total yield 283 mg, 42%).

Further crystallisation of fraction (i) from methanol then from hexane–acetone gave the 2α-isomer (m.p. 220—230°) contaminated with *ca.* 5% of the 2β-compound, which was not removed by successive crystallisations. A pure sample was obtained by column chromatography and crystallisation from methanol; m.p. 235—240° (lit.,[1a] 235—237°).

Crystallisation of fraction (ii) from methanol gave the pure 2β-isomer (IXb) (19 mg), m.p. 184—186° (lit.,[1a] 185—186°).

17β-*Acetoxy*-2β-*hydroxyestr*-4-*en*-3-*one* (Xb).—Partial hydrolysis of the 2,17-diacetate (IXb) under nitrogen with 1 equiv. of potassium hydroxide in methanol gave the 17β-*monoacetate* (Xb), needles (from aq. methanol) (59%), m.p. 169—176°; $\lambda_{max.}$ 242 nm (ε 14,810); $\nu_{max.}$ 3500, 1732, 1673, 1626, 1237, and 1220 cm^{-1} (Found: C, 72·3; H, 8·1. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·5%).

Similar hydrolysis was used in the preparation of 17β-acetoxy-2α-hydroxyestr-4-en-3-one (Xa), m.p. 150—152° (lit.,[1a] 150—151°) and 2β-hydroxyandrost-4-ene-3,17-dione (VIIa), m.p. 148—150° (lit.,[2b] 144—147°).

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