Thermodynamically Controlled Enol Acetylation of Δ^4-3-Oxo-steroids†

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Treatment of steroid ketones with acetic anhydride–hydrobromic acid reagent yields, under thermodynamic control, mixtures of enol acetates. 17β-Hydroxy-2α-phenylandrost-4-en-3-one affords a mixture of 2α-phenylandrosta-3,5-diene-3,17β-diol diacetate and 2-phenylandrosta-2,4-diene-3,17β-diol diacetate in the ratio 3:2. The influence of a 6-methyl group on this reaction is to favour formation of the 3,5-dienol acetate rather than the 2,4-dienol acetate by a free-enrgy difference of 1·44 kcal./mole.

As part of a study of the influence of remote substituents on the enolisation properties of Δ^4-3-oxo-steroids, we have investigated the acid-catalysed enol acetylation of steroid ketones,[2] under conditions of thermodynamic control.[3] Perchloric acid-catalysed enol acetylation is known to effect thermodynamically controlled reactions with saturated oxo-steroids.[4,5] However, under these conditions conjugated ketones are converted into mixtures of *O*- and *C*-acylated products,[1,2] and, furthermore, 2α-alkylated Δ^4-3-oxo-steroids undergo an enone–phenol transformation.[2] Although these reactions were shown to proceed *via* the intermediate $\Delta^{3,5}$- and $\Delta^{2,4}$-dienol acetates, subsequent attack by acetylium ion disturbs the equilibrium between the isomeric enolic forms.

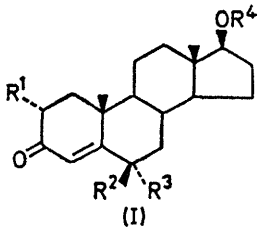
In order to eliminate or minimise the problem of secondary attack by acetylium ion, the use of other acid catalysts was investigated. Equilibrium mixtures of liquid enol acetates have been produced by prolonged heating with isopropenyl acetate and toluene-*p*-sulphonic acid catalyst in sealed tubes.[6] However, enol acetylation of ketones by isopropenyl acetate or acetic anhydride catalysed by toluene-*p*-sulphonic acid or sulphuric acid generally leads to mixtures, the composition

† For a preliminary account of some of this work see P. Toft and A. J. Liston, *Chem. Comm.*, 1970, 111. Part of this work was presented at the joint conference of the Chemical Institute of Canada and the American Chemical Society in Toronto, May 1970.

[1] A. J. Liston and P. Toft, *J. Org. Chem.*, 1968, **33**, 3109.
[2] A. J. Liston and P. Toft, *J. Org. Chem.*, 1969, **34**, 2288.
[3] For a definition see E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 200.
[4] A. J. Liston, *J. Org. Chem.*, 1966, **31**, 2105.
[5] A. J. Liston and M. Howarth, *J. Org. Chem.*, 1967, **32**, 1034.
[6] H. O. House and B. M. Trost, *J. Org. Chem.*, 1965, **30**, 1341.

of which is kinetically controlled.[1-5,7] Satchell[8] has shown that the active species produced in mixtures of sulphuric acid and excess of isopropenyl acetate or acetic anhydride is a mixed anhydride, which then reacts with the ketone. The latter reaction probably reaches equilibrium only slowly in the absence of free acid.

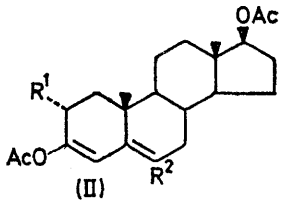
Hydrobromic acid is much stronger than sulphuric acid; its strength approaches that of perchloric acid, as shown by comparison of their ionisation constants in anhydrous acetic acid.[9] Acetic anhydride with hydrobromic acid catalyst has been used for the acetylation of phenols,[10] but has not found use in the enol acetylation of ketones. We have therefore investigated the use of this reagent for the thermodynamically controlled enol acetylation of steroid ketones.



(I)

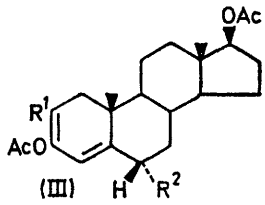
	R^1	R^2	R^3	R^4
a;	Me	Et	H	H
b;	Me	Et	H	Ac
c;	Me	Pr^i	H	H
d;	Me	Pr^i	H	Ac
e;	H	H	Me	H
f;	CHO	H	Me	H
g;	CN	H	H	H
h;	CN	H	H	$CO{\cdot}CF_3$
j;	CN	H	H	Ac
k;	Ph	H	H	H
m;	Ph	H	H	Ac
n;	Ph	H	Me	H
o;	Ph	H	Me	Ac
p;	H	H	H	H
q;	H	H	H	Ac
r;	Me	H	H	H
s;	Me	H	H	Ac

Treatment of 17β-hydroxy-2α-phenylandrost-4-en-3-one[11] (Ik) with isopropenyl acetate–sulphuric acid reagent caused the exclusive formation of 2α-phenylandrosta-3,5-diene-3,17β-diol diacetate (IId), identified by the characteristic u.v. absorption for a heteroannular diene[2,12] and by the n.m.r. spectrum, which shows signals due to the two vinylic protons at C-4 and C-6. However, when either compound (Ik) or (Im) was heated under reflux in benzene with acetic anhydride–hydrobromic acid, a mixture of three products was obtained. G.l.c. analysis indicated that there was no further change after 1 hr., and therefore equilibrium had been established. The products were (Im) (10%), (IId) (54%), and 2-phenylandrosta-2,4-diene-3,17β-diol diacetate (IIIb) (36%), which were isolated by column chromatography. The last compound was identified by its i.r. spectrum, which shows bands for an acetate group and an enol acetate, and its u.v. spectrum ($\lambda_{max.}$ 297 nm.). The u.v. absorption maximum is at longer wavelength than that calculated[12] for a homoannular diene, owing to conjugation with the phenyl group. The structure was confirmed by the n.m.r. spectrum, which had only a one-proton signal in the vinylic region. Conclusive proof that equilibrium had been achieved was obtained by subjecting compounds (IId) and (IIIb) individually to the same reaction conditions. In each case the same ratio of products was observed after 1 hr. Thus, treatment with acetic anhydride–hydrobromic acid leads to thermodynamically controlled enol acetylation.



(II)

	R^1	R^2
a;	Me	Et
b;	Me	Pr^i
c;	CN	H
d;	Ph	H
e;	Ph	Me
f;	H	H
g;	Me	H



(III)

	R^1	R^2
a;	CN	H
b;	Ph	H
c;	Ph	Me

Verification of this observation was obtained when 17β-hydroxy-5β-androstan-3-one was treated with the reagent. After 4 days at 25° the ratio of the products, 5β-androst-3-ene-3,17β-diol diacetate and 5β-androst-2-ene-3,17β-diol diacetate, was 94 : 6, which is the equilibrium ratio observed after treatment with acetic anhydride and perchloric acid catalyst at 25° for 20 hr.[4] The longer reaction time necessary to achieve equilibrium in the former case may reflect the difference in the degree of ionisation of the respective catalysts.

It has been suggested that the *C*-acylation which occurs during the enol acetylation of Δ^4-3-oxo-steroids by acetic anhydride catalysed by perchloric acid or boron trifluoride proceeds *via* attack of acetylium ion on the intermediate dienol acetates.[1,2,13] The occurrence of participation by acetylium ion and the ion pairs $MeCO^+Br^-$ and $MeCO^+HBr_2^-$ in the acetylation of phenols by acetyl bromide catalysed by hydrobromic acid has been suggested.[10] In the enol acetylation of unsaturated ketones with acetic anhydride–hydrobromic

[7] (*a*) J. Champagne, H. Favre, D. Vocelle, and I. Zbikoswki, *Canad. J. Chem.*, 1964, **42**, 212; (*b*) M. P. Hartshorn and E. R. H. Jones, *J. Chem. Soc.*, 1962, 1312; (*c*) B. Berkoz, E. P. Chavez, and C. Djerassi, *ibid.*, 1962, 1323; (*d*) J. Libman and Y. Mazur, *Tetrahedron*, 1969, **25**, 1699.

[8] (*a*) E. A. Jeffery and D. P. N. Satchell, *J. Chem. Soc.*, 1962, 1876; (*b*) D. P. N. Satchell, *Quart. Rev.*, 1963, **17**, 160.

[9] G. N. Dorofeenko, S. V. Krivun, V. I. Dulenko, and Yu. A. Zhdanov, *Russ. Chem. Rev.*, 1965, **34** 88.

[10] (*a*) J. M. Briody and D. P. N. Satchell, *J. Chem. Soc.*, 1964, 3724; (*b*) J. S. Dereska, U.S.P. 2,752,388/1956 (*Chem. Abs.*, 1957, **51**, 2036).

[11] J. F. Poletto, G. R. Allen, and M. J. Weiss, *J. Medicin. Chem.*, 1967, **10**, 106.

[12] A. I. Scott, 'Interpretation of the Ultraviolet Spectra of Natural Products,' Pergamon, Oxford 1964, p. 45.

[13] M. Gorodetsky, E. Levy, R. D. Youssefyeh, and Y. Mazur, *Tetrahedron*, 1966, **22**, 2039.

acid, no *C*-acylation was observed during the reaction periods studied. Presumably therefore ion pairs such as $MeCO^+Br^-$ and $MeCO^+HBr_2^-$ are involved, with minimum participation by acetylium ion.

Treatment of 2α-phenylandrosta-3,5-diene-3,17β-diol diacetate (IId) with acetic anhydride and toluene-*p*-sulphonic acid as catalyst at 25° did not result in any change after 10 days. However, an equilibrium mixture of (IId), (IIIb), and (Im) was obtained when the mixture was refluxed for 5 days, as compared with 1 hr. necessary with hydrobromic acid as catalyst.

17β-Acetoxy-6α-methyl-2α-phenylandrost-4-en-3-one (Io) was enol acetylated under conditions of kinetic control with isopropenyl acetate catalysed by sulphuric acid. The products were 6-methyl-2α-phenylandrosta-3,5-diene-3,17β-diol diacetate (IIe) and 6α-methyl-2-phenylandrosta-2,4-diene-3,17β-diol diacetate (IIIc) in a 3 : 1 ratio; and were separated on Florisil impregnated with silver nitrate. Compound (IIe) was identified on the basis of its i.r. spectrum, which shows bands for the acetate and enol acetate functions, and the u.v. spectrum, $\lambda_{max.}$ 248 nm. The n.m.r. spectrum has a one-proton signal at δ 6·23 (C-4 H) and a three-proton singlet at δ 1·72 p.p.m. (C:CMe).[14] The 2β-proton gave rise to a double doublet at δ 3·90 p.p.m. due to coupling with the adjacent C-1 axial and equatorial protons. Compound (IIIc) was also identified by its spectra. The n.m.r. spectrum has a one-proton signal at δ 5·45 p.p.m. (C-4 H) and the 6-methyl group now gives rise to a doublet at δ 1·09 p.p.m. due to coupling with the 6 β-proton.

The mixtures of products resulting from the thermodynamically controlled enol acetylation of compound (Io) with acetic anhydride–hydrobromic acid are listed in the Table together with the results obtained from some other steroid ketones.

Equilibrium mixtures (%) from enol acetylation with acetic anhydride–hydrobromic acid reagent

Ketone	⇌ 3,5-Dienol acetate	⇌ 2,4-Dienol acetate
(Im) (10)	(IId) (54)	(IIIb) (36)
(Io) (9)	(IIe) (84)	(IIIc) (7)
(Iq) (12)	(IIf) (88)	
(Ib) (14)	(IIa) (86)	
(Id) (14)	(IIb) (86)	
(Is) (15)	(IIg) (85)	

Kinetically controlled enol acetylation of 2α-cyano-17β-hydroxyandrost-4-en-3-one (Ig) with isopropenyl acetate catalysed by sulphuric acid caused exclusive formation of 2-cyanoandrosta-2,4-diene-3,17β-diol diacetate (IIIa). The same product was obtained on acetylation of compound (Ig) with pyridine–acetic anhydride. Evidently the 2β-hydrogen atom is sufficiently acidic that even this mild reagent can enolise the Δ^4-3-oxo-group. The identification of compound (IIIa) is based on its i.r. spectrum (bands for nitrile, acetate, and enol acetate functions) and u.v. spectrum, $\lambda_{max.}$ 297 nm. The n.m.r. spectrum showed a triplet due to only one proton in the vinylic region, and two three-proton singlets due to the acetate methyl groups. Enol acetylation of compound (Ig) with acetic anhydride catalysed by perchloric acid surprisingly afforded 2α-cyanoandrosta-3,5-diene-3,17β-diol diacetate (IIc) as the sole product, identified on the basis of its i.r. spectrum (nitrile, acetate, and enol acetate bands) and u.v. spectrum, $\lambda_{max.}$ 239 nm., characteristic of 3,5-dienol acetates.[2,12] The n.m.r. spectrum has signals due to two vinylic protons, a doublet at δ 5·89 (C-4 H) and a multiplet at δ 5·56 p.p.m. (C-6 H). There is also a one-proton signal at δ 3·75 p.p.m. (C-2 H), analogous to the corresponding signal (δ 3·58) for 17β-acetoxy-2α-cyanoandrost-4-en-3-one (Ij). Attempted equilibrations of compounds (IIc) and (IIIa) by refluxing with acetic anhydride–hydrobromic acid were unsuccessful. Although each compound was isomerised to a small extent, complete equilibration was not achieved, possibly owing to attack of the electrophilic acetylating species on the nitrogen of the nitrile group to form an ionic product which would not be readily equilibrated with its isomer or with the free ketone (Ij). Prolonged reaction led to decomposition of the nitrile group.

The replacement of the enolic hydrogen atom by an acetyl group, which occurs on enol acetylation, should not introduce any significant additional interaction with the remainder of the molecule. The major interaction in ring A occurs between the phenyl group and the lone-pairs of the oxygen atom at C-3, and will be the same in both the enol and the enol acetate. Consequently, the equilibrium ratio of the isomeric dienol acetates reflects the equilibrium ratio of the free dienols (*i.e.* the enolisation properties of the parent ketones), which are present in too small a quantity to be measured directly. For the isomerisation reactions: (IId) ⇌ (IIIb) and (IIe) ⇌ (IIIc), the free-energy differences between the isomeric pairs of dienol acetates can be calculated by use of the relationship $\Delta G^\circ = -RT \ln K$. At 82° the equilibrium ratio (IId) : (IIIb) is 3 : 2, which corresponds to a free-energy difference of 0·29 kcal./mole. Similarly, at the same temperature the equilibrium ratio (IIe) : (IIIc) is 92 : 8, corresponding to a free-energy difference of 1·73 kcal./mole. These two pairs of isomers differ only in the presence or absence of a 6-methyl group. The extra stability of the 3,5-diene structure over the 2,4-diene structure conferred by the introduction of a 6-methyl group can be calculated from the difference between the free-energy differences as 1·44 kcal./mole. Thus, a 6-methyl group favours the enolisation of the Δ^4-3-oxo-group to give the 3,5-dienol by this factor.

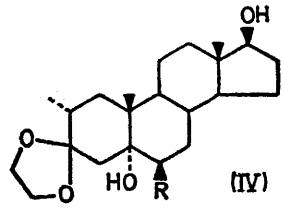
The isomerisation reaction (IId) ⇌ (IIIb) is a convenient system in which to study the effects of remote substituents on the enolisation properties of Δ^4-3-oxo-steroids.

Synthesis.— 6β-Ethyl-17β-hydroxy-2α-methylandrost-4-en-3-one (Ia) and the 6β-isopropyl analogue (Ic) were

[14] N. S. Bhacca and D. H. Williams, 'Applications of N.M.R. Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, (*a*) p. 32; (*b*) p. 99.

synthesised from 5α,6α-epoxy-3,3-ethylenedioxy-2α-methylandrostan-17β-ol.[2] Treatment of the latter with ethylmagnesium bromide afforded the 6β-ethyl-5α-hydroxy-compound (IVa). Acid hydrolysis of the acetal group followed by dehydration with dilute base[15] yielded compound (Ia).

Treatment of 5α,6α-epoxy-3,3-ethylenedioxy-2α-methylandrostan-17β-ol with isopropylmagnesium bromide gave, as the major product, the expected 5α-hydroxy-6β-isopropyl compound (IVb). A second product was compound (IVc), presumably formed by attack at C-6 of a hydride ion transferred from the Grignard reagent. Proof for the structure (IVc) was obtained by deacetalisation followed by dehydration, which gave the known 17β-hydroxy-2α-methylandrost-4-en-3-one (Ir).[2]



(IV)

a; R = Et b; R = Pr^{i} c; R = H

The 2α-phenyl steroids (Ik) and (In) were synthesized by the method of Poletto, Allen, and Weiss.[11]

EXPERIMENTAL

M.p.s were determined with an Electrothermal apparatus by the capillary method and are corrected. Rotations were measured for solutions in chloroform. I.r. spectra were recorded with a Perkin-Elmer model 237B double-beam spectrophotometer. U.v. spectra were determined for solutions in ethanol with a Bausch and Lomb Spectronic 502 recording spectrophotometer. N.m.r. spectra were determined with a Varian A-60 A spectrometer for solutions in deuteriochloroform with tetramethylsilane as internal standard. Hydroxy-proton signals were identified by exchange with deuterium oxide. Mass spectra were determined with a Hitachi–Perkin-Elmer RRU-6D spectrometer. G.l.c. was carried out with a model 810 F and M *chromatograph* equipped with dual flame detectors and a Kipp and Zonen BC1 electronic integrator. The columns were 5% OV-210 (trifluoropropyl silicone) on 60—80 mesh Diatoport S (8 ft. × 4 mm. i.d.); carrier gas helium; flow rate 60 ml./min.; column temperature 230°. Microanalyses were performed by Alfred Bernhardt, Germany.

17β-Hydroxy-2-hydroxymethyleneandrost-4-en-3-one was synthesised by the method of ref. 16. 17β-Hydroxy-2α-phenylandrost-4-en-3-one (Ik) was prepared by the method of ref. 11, and was crystallised from ether–light petroleum ether: m.p. 195—197°, $[\alpha]_D^{28}$ +96° (*c* 1·1) (lit.,[11] m.p. 194—196°, $[\alpha]_D$ +91°).

17β-*Acetoxy*-2α-*phenylandrost*-4-*en*-3-*one* (Im).—17β-Hydroxy-2α-phenylandrost-4-en-3-one (Ik) (118 mg.) was acetylated with acetic anhydride (0·5 ml.) and pyridine (1·0 ml.). The *product* (104 mg.) had m.p. 168—170° (from acetone–hexane), $[\alpha]_D^{28}$ +70·9° (*c* 0·5), $\lambda_{max.}$ 239 nm. (ε 16,700), $\nu_{max.}$ (CCl_4) 1740 and 1245 (OAc), 1680 (C=C–C=O), 1625 (C=C), 1090, and 900 cm.$^{-1}$, δ 0·84 (3H, s, 18-H_3), 1·32 (3H, s, 19-H_3), 2·01 (3H, s, OAc), 3·61 (1H, dd, *J* 12·7 and 5·8 Hz, 2β-H), 4·60 (1H, t, *J* 7·5 Hz, 17-H), 5·82 (1H, d, *J* 1·5 Hz, 4-H), and 7·20 (5H, m, 2-Ph) p.p.m. (Found: C, 80·1; H, 8·45. $C_{27}H_{34}O_3$ requires C, 79·75; H, 8·45%).

17β-*Hydroxy*-6α-*methylandrost*-4-*en*-3-*one* (Ie).—17β-Hydroxy-6α-methylprogesterone (5·0 g.) in ethanol (200 ml.) was treated with sodium borohydride (5·0 g.), and the mixture was stirred at 50° for 1 hr. Then more sodium borohydride (3·5 g.) and sodium hydroxide (15 g.) in water (25 ml.) were added and the solution was refluxed for 3 hr. The ethanol was evaporated off and the product was isolated with dichloromethane to yield the crude trihydroxy-compound (4·3 g.). This was dissolved in ice-cold ethanol (125 ml.) and treated with sodium periodate (5·0 g.) in water (40 ml.). The solution was stirred at room temperature for 4 hr. during which time crystals separated. The ethanol was evaporated off and the product was isolated with dichloromethane to yield crude 3ξ-hydroxy-6α-methylandrost-4-en-17-one (4·1 g.). The latter was dissolved in ethanol (200 ml.) and reduced with sodium borohydride by heating under reflux for 4 hr. to yield crude 3ξ-,17β-dihydroxy-6α-methylandrost-4-ene (4·0 g.). This was taken up in dry chloroform (200 ml.) and shaken for 90 min. with dry freshly precipitated manganese dioxide (27 g.). The inorganic material was filtered off and the filtrate was evaporated. The residue was taken up in benzene and chromatographed on Florisil. Elution with benzene afforded 17β-hydroxy-6α-methylandrost-4-en-3-one (Ie) (3·4 g.), m.p. 156—157° (from aqueous methanol), $[\alpha]_D^{28}$ +94·1° (*c* 1·2) (lit.[15c] m.p. 159—160°, $[\alpha]_D$ +94°).

17β-*Hydroxy*-2-*hydroxymethylene*-6α-*methylandrost*-4-*en*-3-*one* (If).—17β-Hydroxy-6α-methylandrost-4-en-3-one (Ie) (3·2 g.) in anhydrous benzene (80 ml.) was treated with ethyl formate (4 ml.) and sodium hydride (50% oil dispersion; 2·8 g.); the slurry was stirred at room temperature under nitrogen overnight. The crude product (3·2 g.) was isolated with ether and used without further purification.

17β-*Acetoxy*-6α-*methyl*-2α-*phenylandrost*-4-*en*-3-*one* (Io). 17β-Hydroxy-2-hydroxymethylene-6α-methylandrost-4-en-3-one (If) (2·2 g.) was added to a solution of potassium (0·25 g.) in dry t-butyl alcohol (50 ml.). Diphenyliodonium chloride (2·2 g.) was added and the stirred suspension was refluxed for 24 hr. The solvent was partially removed, and the mixture was diluted with water, acidified with hydrochloric acid, and extracted with dichloromethane. The extract was washed with sodium hydrogen carbonate solution and brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in methanol (75 ml.) and treated with methanolic N-sodium methoxide (15 ml.), and the solution was refluxed for 1 hr., cooled, neutralised with acetic acid, and partially evaporated. Water was added and the product was isolated with dichloromethane. The product was chromatographed on Florisil with benzene as eluant. The product, 17β-hydroxy-6α-methyl-2α-phenylandrost-4-en-3-one (In) (1·05 g.), failed to crystallise, and was therefore acetylated with acetic anhydride–pyridine to

[15] (*a*) S. Bernstein and R. Littell, *J. Amer. Chem. Soc.*, 1960, **82**, 1235; (*b*) G. Cooley, B. Ellis, D. N. Kirk, and V. Petrow, *J. Chem. Soc.*, 1957, 4112; (*c*) J. A. Campbell, J. C. Babcock, and J. A. Hogg, *J. Amer. Chem. Soc.*, 1958, **80**, 4717.

[16] H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *J. Amer. Chem. Soc.*, 1959, **81**, 427.

yield 17β-*acetoxy*-6α-*methyl*-2α-*phenylandrost*-4-*en*-3-*one* (Io) (0·95 g.), m.p. 205—207° (from acetone–hexane) $[\alpha]_D^{26}$ +51° (*c* 1·0), $\lambda_{max.}$ 240 nm. (ε 14,400), $\nu_{max.}$ (CCl_4) 1740 and 1245 (OAc), 1680 (C=C–C=O), 1618 (C=C), 1040, and 1023 cm.$^{-1}$ (Found: C, 79·9; H, 8·75. $C_{28}H_{36}O_3$ requires C, 79·95; H, 8·65%).

6β-*Ethyl*-3,3-*ethylenedioxy*-2α-*methylandrostane*-5α,17β-*diol* (IVa).—Ethylmagnesium bromide was prepared from ethyl bromide (4·2 ml.) and magnesium turnings (1·3 g.) in anhydrous ether (40 ml.). 5α,6α-Epoxy-3,3-ethylenedioxy-2α-methylandrostan-17β-ol [2] (1·5 g.) in anhydrous tetrahydrofuran (100 ml.) was added, and the mixture was refluxed under nitrogen for 48 hr., cooled, and treated with excess of saturated ammonium chloride solution to quench the reaction. It was then extracted with dichloromethane. The oily product was crystallised from acetone–hexane yielding the *diol* (IVa) (0·97 g.), m.p. 161—162°, $[\alpha]_D^{28}$ +38·1° (*c* 1·4), $\nu_{max.}$ (CCl_4) 3625 and 3525 (OH), and 1095 and 1052 cm.$^{-1}$ (acetal), δ 0·76 (3H, s, 18-H_3), 0·86 (3H, d, *J* 6 Hz, 2-CH_3), 1·01 (3H, s, 19-H_3), 1·42 (1H, s, OH), 3·67 (1H, t, *J* 8 Hz, 17-H), 4·02 (4H, s, 4, acetal H_4), and 4·45 (1H, s, OH) p.p.m. (Found: C, 73·5; H, 10·2. $C_{24}H_{40}O_4$ requires C, 73·4; H, 10·25%).

6β-*Ethyl*-17β-*hydroxy*-2α-*methylandrost*-4-*en*-3-*one* (Ia).—A solution of the acetal (IVa) (450 mg.) in acetic acid (30 ml.) and water (10 ml.) was heated on a steam-bath for 45 min. The product, crude 6β-ethyl-5α,17β-dihydroxy-2α-methylandrostan-3-one, was isolated with ether and then dissolved in 50% aqueous methanolic sodium hydroxide (0·05N; 125 ml.). The solution was stirred at room temperature for 24 hr. Acetic acid (3 ml.) was added and the mixture was evaporated to half its volume. The *product* (216 mg.) was isolated with ether; m.p. 212—214° (from acetone–hexane) $[\alpha]_D^{27}$ +76·2° (*c* 0·8), $\lambda_{max.}$ 242 nm. (ε 13,700), $\nu_{max.}$ ($CHCl_3$) 3620 and 3470 (OH), 1665 (C=C–C=O), 1615 (C=C), 1125, and 880 cm.$^{-1}$, δ 0·82 (3H, s, 18-H_3), 0·88 (3H, t, *J* 6·5 Hz, 6-CH_2·CH_3), 1·12 (3H, d, *J* 6·5 Hz, 2-CH_3), 1·28 (3H, s, 19-H_3), 1·58 (1H, s, OH), 3·72 (1H, t, *J* 8 Hz, 17-H), and 5·74 (1H, s, 4-H) p.p.m. (Found: C, 80·0; H, 10·5. $C_{22}H_{34}O_2$ requires C, 79·95; H, 10·35%).

17β-*Acetoxy*-6β-*ethyl*-2α-*methylandrost*-4-*en*-3-*one* (Ib).—6β-Ethyl-17β-hydroxy-2α-methylandrost-4-en-3-one (Ia) (50 mg.) was acetylated overnight at room temperature with acetic anhydride (1·0 ml.) and pyridine (1·0 ml.). The *product* (26 mg.) had m.p. 193—194° (from acetone–hexane), $[\alpha]_D^{27}$ +52·5° (*c* 0·9), $\lambda_{max.}$ 248 nm. (ε 16,745), $\nu_{max.}$ (CCl_4) 1735 and 1255 (OAc), 1665 (C=C–C=O), and 1610 cm.$^{-1}$ (C=C), δ 0·84 (3H, s, 18-H_3), 1·12 (3H, d, *J* 6 Hz, 2-CH_3), 1·27 (3H, s, 19-H_3), 2·05 (3H, s, 17-OAc), and 5·72 (1H, s, 4-H) p.p.m. (Found: C, 77·4; H, 9·75. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·75%).

Reaction of 5α,6α-*Epoxy*-3,3-*ethylenedioxy*-2α-*methylandrostan*-17β-*ol with Isopropylmagnesium Bromide*.—Isopropylmagnesium bromide was prepared from isopropyl bromide (18·0 g.) and ether-washed magnesium turnings (4·3 g.) in anhydrous ether (45 ml.). To this solution was added the acetal (3·0 g.) in anhydrous tetrahydrofuran (200 ml.). The mixture was refluxed under nitrogen for 70 hr., and then worked up in the usual way. The products were taken up in benzene and chromatographed on a column of Florisil (300 g.). Elution with benzene–ether (50 : 1) afforded 3,3-*ethylenedioxy*-6β-*isopropyl*-2α-*methylandrostane*-5α,17β-*diol* (IVb) (1·40 g.), m.p. 192—194° (from acetone–hexane), $[\alpha]_D^{27}$ −58·6° (*c* 0·9), $\nu_{max.}$ (CCl_4) 3625 (OH), 3525 (OH), 1220, 1100 (acetal), 950, and 848 cm.$^{-1}$, δ 0·75 (3H, s, 18-H_3), 0·85 (3H, d, *J* 6 Hz, 2-CH_3), 0·98 (6H, d, *J* 11 Hz, Me_2CH), 1·00 (3H, s, 19-H_3), 1·45 (1H, s, OH), 3·65 (1H, t, *J* 8 Hz, 17-H), and 3·98 (4H, s, acetal H_4) p.p.m. (Found: C, 73·7; H, 10·45. $C_{25}H_{42}O_4$ requires C, 73·85; H, 10·4%).

Further elution with benzene–ether (50 : 1) yielded 3,3-*ethylenedioxy*-2α-*methylandrostane*-5α,17β-*diol* (IVc) (302 mg.), m.p. 219—223° (from acetone–hexane), $[\alpha]_D^{28}$ −15·7° (*c* 0·8), $\nu_{max.}$ (CCl_4) 3625 (OH), 3525 (OH), 1160, 1100 (acetal), and 950 cm.$^{-1}$, δ 0·76 (3H, s, 18-H_3), 0·87 (3H, d, *J* 6·5 Hz, 2-CH_3), 1·01 (3H, s, 19-H_3), 1·45 (1H, s, 17-OH), 3·67 (1H, t, *J* 8 Hz, 17-H), 4·00 (4H, s, acetal H_4), and 4·42 (1H, s, 5-OH) p.p.m. (Found: C, 72·6; H, 9·9. $C_{22}H_{36}O_4$ requires C, 72·5; H, 9·95%).

17β-*Hydroxy*-6β-*isopropyl*-2α-*methylandrost*-4-*en*-3-*one* (Ic).—A solution of 3,3-ethylenedioxy-6β-isopropyl-2α-methylandrostane-5α,17β-diol (IVb) (500 mg.) in acetic acid (30 ml.) and water (10 ml.) was heated on a steam-bath for 45 min., evaporated under reduced pressure, and worked up in the usual way. The residue, crude 5α,17β-dihydroxy-6β-isopropyl-2α-methylandrostan-3-one (450 mg.) was dissolved in 50% aqueous methanolic sodium hydroxide (0·05N; 125 ml.). The solution was stirred at room temperature for 24 hr. Acetic acid (4 ml.) was added, and the mixture was evaporated to half its volume. The product (270 mg.) was isolated with ether; m.p. 220—223° (from acetone–hexane), $[\alpha]_D^{28}$ +106° (*c* 1·1), $\lambda_{max.}$ 243 nm. (ε 12,550), $\nu_{max.}$ ($CHCl_3$) 3675 and 3620 (OH), 1665 (C=C–C=O), 1615 (C=C), 1050, and 955 cm.$^{-1}$, δ 0·82, 0·88, 1·00, 1·05, 1·17, and 1·27 (methyl signals), 1·67 (1H, s, OH), 3·68 (1H, t, *J* 8 Hz, 17-H), and 5·71 (1H, s, 4-H) p.p.m. (Found: C, 80·25; H, 10·4. $C_{23}H_{36}O_2$ requires C, 80·15; H, 10·55%).

17β-*Acetoxy*-6β-*isopropyl*-2α-*methylandrost*-4-*en*-3-*one* (Id).—The ketol (Ic) (50 mg.) was acetylated overnight at room temperature with acetic anhydride (1·0 ml.) and pyridine (1·0 ml.). The *product* (26 mg.) had m.p. 182—183° (from acetone–hexane), $[\alpha]_D^{28}$ +114·5° (*c* 0·9), $\lambda_{max.}$ 248 nm. (ε 17,980), $\nu_{max.}$ (CCl_4) 1735 and 1255 (OAc), 1665 (C=C–C=O), 1615 (C=C), and 1040 cm^{-1}. (Found: C, 75·6; H, 9·4. $C_{27}H_{40}O_4$ requires C, 75·65; H, 9·4%).

Deacetalisation and Dehydration of 3,3-*Ethylenedioxy*-2α-*methylandrostane*-5α,17β-*diol* (IVc). Compound (IVc) (130 mg.) in acetic acid (7·5 ml.) and water (2·5 ml.), was heated on a steam-bath for 45 min. The solution was evaporated, and the product was extracted with ether. A solution of the product, crude 5α,17β-dihydroxy-2α-methylandrostan-3-one (100 mg.), in 50% aqueous methanolic sodium hydroxide (0·05N; 35 ml.) was stirred at room temperature overnight. Acetic acid (1·0 ml.) was added and the mixture was evaporated to half its volume. The product, isolated with ether, yielded 17β-hydroxy-2α-methylandrost-4-en-3-one (Ir) (42 mg.), m.p. 155—156° (from acetone–hexane) (lit.,[2] 155—158°), $[\alpha]_D^{27}$ +109° (*c* 1·0) lit.,[2] $[\alpha]_D^{26}$ +108° (*c* 1·0)}, identical (mixed m.p. and i.r., u.v., and n.m.r. spectra) with authentic material.

2α-*Cyano*-17β-*trifluoroacetoxyandrost*-4-*en*-3-*one* (Ih).—17β-Hydroxy-2-hydroxymethyleneandrost-4-en-3-one (1·2 g.) in anhydrous benzene (50 ml.) was treated with *ON*-bis(trifluoroacetyl)hydroxylamine (2·4 g.).[17] The mixture was refluxed for 2 hr., then evaporated, and the residue was chromatographed on Florisil (200 g.). Elution with benzene–ether (9 : 1) afforded the nitrile (Ih) (0·8 g.),

[17] J. H. Pomeroy and C. A. Graig, *J. Amer. Chem. Soc.*, 1959, **81**, 6340.

m.p. 220—222° (from acetone–hexane), $[\alpha]_D^{26}$ +82° (*c* 1·0) (lit.,[18] m.p. 212—217°, $[\alpha]_D$ +83·3°), δ 0·90 (1H, s, 18-H_3), 1·27 (3H, s, 19-H_3), 3·60 (1H, dd, *J* 14·2 and 4·5 Hz, 2-H), 4·80 (1H, t, *J* 8 Hz, 17-H), and 5·82 (1H, s, 4-H) p.p.m.

2α-Cyano-17β-hydroxyandrost-4-en-3-one (Ig).—Further elution of the foregoing column with benzene–ether (3 : 1) afforded 2α-cyano-17β-hydroxyandrost-4-en-3-one (Ig) (0·4 g.), m.p. 153—156° (from acetone–hexane), $[\alpha]_D^{28}$ +119° (*c* 1·0) (lit.,[18] m.p. 155—156°, $[\alpha]_D$ +119°). The latter compound was also obtained by hydrolysis of compound (Ih) with aqueous methanolic 0·05N-potassium hydroxide at reflux for 30 min.

Enol Acetylation with Isopropenyl Acetate and Sulphuric Acid.—The steroid (*ca.* 1 g.) in isopropenyl acetate (50 ml.) was treated with sulphuric acid (0·1 ml.), and the mixture was refluxed under nitrogen for 2—4 hr. The reaction was monitored by g.l.c. analysis. The cooled solution was then diluted with ether and washed with sodium hydrogen carbonate solution.

(A) *2α-Phenylandrosta-3,5-diene-3,17β-diol diacetate* (IId). This *compound*, prepared from compound (Ik), had m.p. 156—158° (from aqueous methanol), $[\alpha]_D^{29}$ +37° (*c* 1·0), $\lambda_{max.}$ 239 nm. (ε 25,290), $\nu_{max.}$ (CCl_4) 1755 and 1215 (enol acetate), 1740 and 1245 (OAc), 1135, and 1035 cm.$^{-1}$, δ 0·84 (3H, s, 18-H_3), 1·18 (3H, s, 19-H_3), 1·74 (3H, s, 3-OAc), 2·01 (3H, s, 17-OAc), 3·92 (1H, m, 2-H), 4·60 (1H, t, *J* 7·5 Hz, 17-H), 5·48 (1H, m, 6-H), 5·85 (1H, d, *J* 2·5 Hz, 4-H), and 7·19 (5H, s, 2-Ph) p.p.m. (Found: C, 77·4; H, 7·95. $C_{29}H_{36}O_4$ requires C, 77·65; H, 8·1%).

(B) *6-Methyl-2α-phenylandrosta-3,5-diene-3,17β-diol diacetate* (IIe) *and 6α-methyl-2-phenylandrosta-2,4-diene-3,17β-diol diacetate* (IIIc). These compounds were obtained from 17β-acetoxy-6α-methyl-2α-phenylandrost-4-en-3-one (Io) (800 mg.) in *ca.* 3 : 1 ratio. The mixture was dissolved in benzene and adsorbed on a column of Florisil (100 g.) impregnated with 10% silver nitrate. Elution with benzene afforded the major *product* (IIe) (375 mg.) free from the $\Delta^{2,4}$-isomer, m.p. 186—188° (from acetone–hexane), $[\alpha]_D^{27}$ +13·2° (*c* 1·0), $\lambda_{max.}$ 248 nm. (ε 19,800), $\nu_{max.}$ (KBr) 1755 and 1225 (enol acetate), 1740 and 1248 (acetate), and 920 cm.$^{-1}$, δ 0·83 (3H, s, 18-H_3), 1·16 (3H, s, 19-H_3), 1·72 (3H, s, 6-CH_3), 1·78 (3H, s, 3-OAc), 2·02 (3H, s, 17-OAc), 3·90 (1H, dd, *J* 12 and 5 Hz, 2-H), 4·62 (1H, t, *J* 8 Hz, 17-H), 6·23 (1H, d, *J* 2 Hz, 4-H), and 7·28 (5H, s, 2-Ph) p.p.m. (Found: C, 77·7; H, 8·4. $C_{30}H_{38}O_4$ requires C, 77·9; H, 8·3%).

Further elution with benzene gave the minor *product* (IIIc) (105 mg.), free from the $\Delta^{3,5}$-isomer, m.p. 195—196° (from acetone–hexane), $[\alpha]_D^{27}$ +65° (*c* 0·5), $\lambda_{max.}$ 300 (ε 14,500) and 223 nm. (ε 6950), $\nu_{max.}$ (KBr) 1765 and 1220 (enol acetate), 1740 and 1245 (acetate), and 1040 cm.$^{-1}$, δ 0·83 (3H, s, 18-H_3), 1·09 (3H, d, *J* 6·5 Hz, 6-CH_3), 1·10 (3H, s, 19-H_3) 2·03 (6H, s, 3-OAc and 17-OAc), 2·60 (2H, m, 1-H_2), 4·60 (1H, t, *J* 7·5 Hz, 17-H), 5·45 (1H, d, *J* 2·5 Hz, 4-H), and 7·32 (5H, s, 2-Ph) p.p.m. (Found: C, 77·7; H, 8·35. $C_{30}H_{38}O_4$ requires C, 77·9; H, 8·3%).

Enol Acetylations with Acetic Anhydride and Hydrobromic Acid.—(A) *2α-Phenylandrosta-3,5-diene-3,17β-diol diacetate* (IId) *and 2-phenylandrosta-2,4-diene-3,17β-diol diacetate* (IIIb). 17β-Acetoxy-2α-phenylandrost-4-en-3-one (Im) (1·0 g.) in dry benzene (100 ml.) was treated with acetic anhydride (25 ml.) and hydrobromic acid (45% in acetic acid; 1·0 ml.), and the mixture was refluxed (82°) with stirring for 3 hr. The solution was diluted with ether, washed with saturated aqueous sodium hydrogen carbonate and brine, dried (Na_2SO_4), and evaporated, and the residue was taken up in benzene and adsorbed on a column of Florisil impregnated with 10% silver nitrate. Elution with benzene afforded *compound* (IId) (300 mg.), free from the $\Delta^{2,4}$-isomer, m.p. 156—158° (from aqueous methanol containing a trace of pyridine), $[\alpha]_D^{29}$ +37° (*c* 1·0), identical (mixed m.p. and i.r. spectroscopy) with the sample prepared previously.

Further elution with benzene afforded *compound* (IIIb) (275 mg.), free from the $\Delta^{3,5}$-isomer, m.p. 168—171° (from acetone–hexane), $[\alpha]_D^{29}$ +20·4° (*c* 1·0), $\lambda_{max.}$ 297 (ε 13,390) and 220 nm. (ε 8500), $\nu_{max.}$ (CCl_4) 1760 and 1225 (enol acetate), 1740 and 1245 (acetate), 1370, and 1040 cm.$^{-1}$, δ 0·83 (3H, s, 18-H_3), 1·09 (3H, s, 19-H_3), 2·03 (6H, s, 3-OAc and 17-OAc), 4·62 (1H, t, *J* 8 Hz, 17-H), 5·43 (1H, t, *J* 1·5 Hz, 4-H), and 7·27 (5H, s, 2-Ph) p.p.m. (Found: C, 77·45; H, 7·95. $C_{29}H_{36}O_4$ requires C, 77·65; H, 8·1%).

(B) *Treatment of 17β-hydroxy-5β-androstan-3-one with hydrobromic acid and acetic anhydride.* 17β-Hydroxy-5β-androstan-3-one was treated with hydrobromic acid and acetic anhydride as in (A) and the solution was stirred at 25°. Samples were withdrawn periodically and examined by g.l.c. The products were 5β-androst-3-ene-3,17β-diol diacetate and 5β-androst-2-ene-3,17β-diol diacetate [4] and after 4 days the equilibrium ratio of 94 : 6 was obtained, identical with the ratio obtained by use of perchloric acid as catalyst.[4] The identity of the g.l.c. peaks was confirmed by enhancement with authentic material.

(C) *Enol acetylation of 17β-hydroxy-2α-methylandrost-4-en-3-one* (Ir). 17β-Hydroxy-2α-methylandrost-4-en-3-one (Ir) (1 g.) was treated with acetic anhydride and hydrobromic acid as in (A). G.l.c. analysis indicated that equilibrium was reached after 4 hr.; the mixture then consisted of 2α-methylandrosta-3,5-diene-3,17β-diol diacetate (IIg) (85%) and 17β-acetoxy-2α-methylandrost-4-en-3-one (Is) (15%). The mixture of products was adsorbed from benzene on a column of Florisil (100 g.). Elution with benzene afforded compound (Is) (85 mg.), m.p. and mixed m.p.[2] 179—180° (from acetone–hexane), i.r. and u.v. spectra identical with those of authentic material.[2] Further elution with benzene–ether (19 : 1) afforded compound (IIg) (770 mg.), m.p. and mixed m.p.[2] 169—171° (from acetone–hexane), i.r. and u.v. spectra identical with those of authentic material.[2]

(D) *Enol acetylation of 2α-cyano-17β-hydroxyandrost-4-en-3-one* (Ig). 2α-Cyano-17β-hydroxyandrost-4-en-3-one (Ig) (1·0 g.) was treated with acetic anhydride (25 ml.) and hydrobromic acid as in (A). G.l.c. analysis indicated that the mixture consisted of two major and one minor component. The mixture was adsorbed from benzene on a column of Florisil (150 g.). Elution with benzene and crystallisation from 1% pyridine–methanol afforded *17β-acetoxy-2α-cyanoandrost-4-en-3-one* (Ij) (422 mg.), m.p. 203—208°, $[\alpha]_D^{26}$ +87° (*c* 1·0), $\lambda_{max.}$ 240 nm. (ε 14,200), $\nu_{max.}$ (KBr) 2230 (CN), 1740 and 1245 (OAc), 1685 (C=C–C=O), 1615 (C=C), and 1038 cm.$^{-1}$, δ 0·85 (3H, s, 18-H_3), 1·27 (3H, s, 19-H_3), 2·05 (3H, s, 17-OAc), 3·58 (1H, dd, *J* 12·5 and 5·5 Hz, 2-H), 4·56 (1H, t, *J* 8 Hz, 17-H), and 5·76 (1H, d, *J* 1·0 Hz, 4-H) p.p.m. (Found: C, 74·2; H, 8·25; N, 4·0. $C_{22}H_{29}NO_3$ requires C, 74·35; H, 8·2; N, 3·95%).

[18] H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, 1961, **26**, 2610.

Further elution with benzene–ether (19 : 1) and crystallisation from 1% pyridine–methanol afforded 2-cyanoandrosta-2,4-diene-3,17β-diol diacetate (IIIa) (357 mg.), identical (mixed m.p., rotation, and i.r. spectrum) with the compound obtained before.

The minor constituent whose g.l.c. retention time corresponded with that of 2α-cyanoandrosta-3,5-diene-3,17β-diol diacetate, was not isolated.

Enol Acetylation with Acetic Anhydride and Perchloric Acid.—(A) *6-Ethyl-2α-methylandrosta-3,5-diene-3,17β-diol diacetate* (IIa). 17β-Hydroxy-6β-ethyl-2α-methylandrost-4-en-3-one (Ia) (300 mg.) in anhydrous benzene (40 ml.) was treated with a solution (6 ml.) prepared from acetic anhydride (50 ml.) and 70% perchloric acid (0·1 ml.). The mixture was stirred at room temperature (25°) for 4 hr., and was then diluted with ether and washed with aqueous sodium hydrogen carbonate and brine. G.l.c. analysis showed that the reaction was complete and that only one product was formed. The ether solution was dried (Na_2SO_4) and evaporated, and the residue (250 mg.) was chromatographed on Florisil. Elution with benzene–hexane (1 : 3) afforded *compound* (IIa) (140 m.g), m.p. 99—100° (from aqueous methanol), $[\alpha]_D^{28}$ −32° (*c* 1·0), $\lambda_{max.}$ 248 nm. (ε 16,750), $\nu_{max.}$ (CCl_4) 1750 and 1215 (enol Ac), 1740 and 1245 (OAc), and 1365 cm.$^{-1}$, δ 0·83 (3H, s, 18-H_3), 1·03 (3H, s, 19-H_3), 2·03 (3H, s, 17-OAc), 2·13 (3H, s, 3-OAc), 4·60 (1H, t, *J* 7 Hz, 17-H), and 5·97 (1H, d, *J* 2 Hz, 4-H) p.p.m. (Found: C, 75·5; H, 9·45. $C_{26}H_{38}O_4$ requires C, 75·3; H, 9·25%).

(B) *6-Isopropyl-2α-methylandrosta-3,5-diene-3,17β-diol diacetate* (IIb). 17β-Hydroxy-6β-isopropyl-2α-methylandrost-4-en-3-one (Ic) (140 mg.) was treated as in (A) with acetic anhydride and perchloric acid. The product, *compound* (IIb) (65 mg.), had m.p. 94—95° (from methanol), $[\alpha]_D^{27}$ −70° (*c* 1·0) $\lambda_{max.}$ 248 nm. (ε 17,900), $\nu_{max.}$ (KBr) 1750 and 1215 (enol Ac), 1735 and 1245 (OAc), and 1090 cm.$^{-1}$, δ 0·83 (3H, s, 18-H_3), 1·03 (3H, s, 19-H_3), 2·03 (3H, s, 17-OAc), 2·14 (3H, s, 3-OAc), 4·60 (1H, t, *J* 8 Hz, 17-H), and 6·08 (1H, d, *J* 2 Hz, 4-H) p.p.m. (Found: C, 75·6; H, 9·4. $C_{27}H_{40}O_4$ requires C, 75·65; H, 9·4%).

(C) *2α-Cyanoandrosta-3,5-diene-3,17β-diol diacetate* (IIc). 2α-Cyano-17β-hydroxyandrost-4-en-3-one (Ig) (300 mg.) was treated as in (A) with acetic anhydride and perchloric acid, and the mixture was stirred at room temperature for 2 hr. The product, which was isolated with ether, yielded *compound* (IIc) (185 mg.), m.p. 155—158° (from acetone–hexane), $[\alpha]_D^{26}$ +18·8° (*c* 1·0), $\lambda_{max.}$ 239 nm. (ε 16,480), $\nu_{max.}$ (CCl_4) 2235 (CN), 1765 and 1210 (enol acetate), 1735 and 1245 (acetate), and 1190 cm.$^{-1}$, δ 0·84 (3H, s, 18-H_3), 1·04 (3H, s, 19-H_3), 2·05 (3H, s, 17-OAc), 2·22 (3H, s, 3-OAc), 3·75 (1H, m. 2-H), 4·63 (1H, t, *J* 8 Hz, 17-H), 5·56 (1H, m, 6-H), and 5·89 (1H, d, *J* 2·5 Hz, 4-H) p.p.m. (Found: C, 72·35; H, 7·75; N, 3·55. $C_{24}H_{31}NO_4$ requires C, 72·5; H, 7·85; N, 3·5%).

2-Cyanoandrosta-2,4-diene-3,17β-diol Diacetate (IIIa).—(*A*) 2α-Cyano-17β-hydroxyandrost-4-en-3-one (Ig) (100 mg.) was acetylated at room temperature overnight with pyridine (2 ml.) and acetic anhydride (1 ml.). The *product* (IIIa) (78 mg.) isolated with ether, had m.p. 208—210° (from 1% pyridine–methanol), $[\alpha]_D^{26}$ +95·4° (*c* 1·0), $\lambda_{max.}$ 296 nm. (ε 9880), $\nu_{max.}$ (KBr) 2200 (CN), 1778 and 1190 (enol Ac), 1735 and 1245 (Ac), 1655, 1600, and 885 cm.$^{-1}$, δ 0·82 (3H, s, 18-H_3), 1·07 (3H, s, 19-H_3), 2·03 (3H, s, 17-OAc), 2·23 (3H, s, 3-OAc), 2·42 (2H, s, 2-H_2), 4·63 (1H, t, *J* 8 Hz, 17-H), and 5·50 (1H, t, *J* 1·5 Hz, 4-H) p.p.m. (Found: C, 72·8; H, 7·8; N, 3·65. $C_{24}H_{31}NO_4$ requires C, 72·5; H, 7·85; N, 3·5%).

(B) 2α-Cyano-17β-hydroxyandrost-4-en-3-one (Ig) (120 mg.) was treated with isopropenyl acetate and sulphuric acid as before and the mixture was refluxed for 2 hr. The product (IIIa) (87 mg.), crystallised from 1% pyridine–methanol, was identical with the compound obtained in (A).

Equilibrations with Acetic Anhydride–Hydrobromic Acid Reagent.—General reaction conditions. The steroid (10 mg.) in dry benzene (4 ml.) was treated with acetic anhydride (1 ml.) and 45% hydrobromic acid in acetic acid (0·1 ml.), and the mixture was refluxed (82°) with stirring for 24 hr. Samples were analysed periodically on a gas chromatograph fitted with an electronic integrator. Peak identities were confirmed by enhancement with authentic compounds.

(*a*) 17β-Hydroxy-2α-phenylandrost-4-en-3-one (Ik) produced an equilibrium mixture after 1 hr. consisting of 2α-phenylandrosta-3,5-diene-3,17β-diol diacetate (IId) (54%), 2-phenylandrosta-2,4-diene-3,17β-diol diacetate (IIIb) (36%), and 17β-acetoxy-2α-phenylandrost-4-en-3-one (Im) (10%), *i.e.* the ratio of (IId) to (IIIb) is 3 : 2.

(*b*) 2α-Phenylandrosta-3,5-diene-3,17β-diol diacetate (IId) generated the same equilibrium mixture as in (*a*).

(*c*) 2-Phenylandrosta-2,4-diene-3,17β-diol diacetate (IIIb) generated the same equilibrium mixture as in (*a*).

(*d*) 17β-Acetoxy-6α-methyl-2α-phenylandrost-4-en-3-one (Io) produced an equilibrium mixture after 3 hr. consisting of 6-methyl-2α-phenylandrosta-3,5-diene-3,17β-diol diacetate (IIe) (84%), 6α-methyl-2-phenylandrosta-2,4-diene-3,17β-diol diacetate (IIIc) (7%), and 17β-acetoxy-6α-methyl-2α-phenylandrost-4-en-3-one (Io) (9%), *i.e.* the ratio of (IIe) to (IIIc) is 92 : 8.

(*e*) 6-Methyl-2α-phenylandrost-2,4-diene-3,17β-diol diacetate (IIe) generated the same equilibrium mixture as in (*d*).

(*f*) 6α-Methyl-2-phenylandrosta-2,4-diene-3,17β-diol diacetate (IIIc) generated the same equilibrium mixture as in (*d*).

(*g*) Testosterone (Ip) produced an equilibrium mixture after 4 hr. consisting of androsta-3,5-diene-3,17β-diol diacetate (IIf) (88%) and 17β-acetoxyandrost-4-en-3-one (Iq) (12%).

(*h*) 17β-Acetoxy-6β-ethyl-2α-methylandrost-4-en-3-one (Ib) produced an equilibrium mixture after 4 hr. consisting of 6-ethyl-2α-methylandrosta-3,5-diene-3,17β-diol diacetate (IIa) (86%) and (Ib) (14%).

(*i*) 17β-Acetoxy-6β-isopropyl-2α-methylandrost-4-en-3-one (Id) produced an equilibrium mixture after 4 hr. consisting of 6-isopropyl-2α-methylandrosta-3,5-diene-3,17β-diol diacetate (IIb) (86%) and (Id) (14%).

Treatment of 2α-Phenylandrosta-3,5-diene-3,17β-diol Diacetate (IId) *with Toluene-p-sulphonic acid and Acetic Anhydride.—(a) At* 25°. The steroid (12 mg.) in dry benzene (2 ml.) and acetic anhydride (1 ml.) was treated with toluene-*p*-sulphonic acid (50 mg.) and the solution was stirred at 25°. Samples were examined periodically by g.l.c. Only starting material was detected after 10 days at 25°.

(*b*) *At* 85°. 2α-Phenylandrosta-3,5-diene-3,17β-diol diacetate (IId) (36 mg.) in benzene (10 ml.) and acetic anhydride (3 ml.) was treated with toluene-*p*-sulphonic acid (130 mg.) and refluxed (85°) with stirring. Samples were examined periodically by g.l.c., which indicated the following

ratios of (IId) to (IIIb): 85·6 : 14·4 (6 hr.); 73·8 : 26·2 (23 hr.), 64·5: 35·5 (47hr.), 62·3 : 37·7 (4 days), 60·9 : 39·1 (5 days). Peaks were identified by comparisons with authentic material.

Attempted Equilibration of the 2-Cyanoandrosta-2,4- and 3,5-diene-3,17β-diol Diacetates.—A sample of each steroid (10 mg.) was treated with benzene (2 ml.), acetic anhydride (0·5 ml.), and 45% hydrobromic acid in acetic acid (0·2 ml.) and the mixtures were refluxed with stirring. Samples were analysed periodically by gas chromatography. Each compound gave rise to a small quantity of the other isomer (about 10%) but no equilibration occurred even after 3 days at reflux.

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