Conformational Studies. Part 9.[1] Some Exceptions to the Axial Halogeno-ketone Rule

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Methylation of 6α-methylcholest-4-en-3-one gives 4,4,6-trimethylcholest-5-en-3-one (2; $R^1 = R^2 = H$). The corresponding androst-5-ene (6; $R^1 = Me$, $R^2 = R^3 = H$) was prepared similarly.

4,4-Dimethyl-19-norandrost-5-en-3-one was converted into the ethylene acetal (7) and thence into the (*S*)- and (*R*)-17β-tetrahydropyranyl ethers (8), which were readily separable. The (*S*)-17β-ether was hydroborated to yield the 5α-androstan-6α-ol (9) as the principal product, together with smaller quantities of the isomeric 6β-ol (10). The structures of these alcohols have been defined and the genesis of (10) rationalised.

Reaction of the derived 4,4-dimethyl-6-ketone (12) with methyl-lithium gave 6ξ-hydroxy-4,4,6ξ-trimethyl-19-nor-5α-androstane (13), from which the blocking groups were removed to yield 6ξ,17β-dihydroxy-4,4,6ξ-trimethyl-19-nor-5α-androstan-3-one (14). The ethylene acetal of the (*S*)-17-β-tetrahydropyranyl ether series (8) underwent an analogous series of transformations and gave the same trimethyl ketone (14), which was dehydrated to 17β-hydroxy-4,4,6-trimethyl-19-norandrost-5-en-3-one.

The bromination of these three 4,4,6-trimethyl-5-en-3-ones was investigated. In each case the principal product was the 2α-derivative in which the halogen is axially oriented, and in each case the sign of the o.r.d. curve was at variance with the predictions of the Axial Halogeno-ketone Rule.

BROMINATION [2-6] of 4,4-dimethylcholest-5-en-3-one (1; R = H) gives the 2α-bromo-ketone (1; R = Br) in which the halogen is axially oriented [3-4] in ring A which probably has a boat conformation.[3,4] However, although the contribution of the bromine to the Cotton effect of (1; R = Br) is clearly negative, as predicted by the Axial Halogeno-ketone Rule,[6] the Cotton effect of the bromo-ketone system is still positive,[3,4] and not negative as required by the simple application of the Rule. Since the flexibility of ring A in (1; R = Br) introduces an element of uncertainty it appeared of interest to investigate the chiroptical properties of a similar system, essentially devoid of these mobility problems. The 4,4,6-trimethyl-5-en-3-one steroidal system (2; $R^1 = R^2 = H$) seemed to meet these requirements. The present paper reports our results [7] with the appropriate derivatives in the cholestene, androstene, and 19-norandrostene series.

4,4,6-Trimethylcholest-5-en-2-one was initially obtained from 6α-methylcholest-4-en-3-one,[8] prepared from 6-nitrocholesterol.

Since the nitration method is not applicable in the androstane series an alternative approach was used and applied initially to the cholestane derivative. Thus, 3-methoxycholesta-3,5-diene (3; R = H) was converted by the Vilsmeier process [9] into the 6-formyl derivative (3; R = CHO), which furnished the alcohol (3; R = CH_2OH). Simultaneous demethylation and dehydration of (3; R = CH_2OH) with warm acetic acid gave 6-methylenecholest-4-en-3-one (4), which was reduced over palladium–strontium carbonate to a mixture of 6α- (5) and 6β-methylcholest-4-en-3-one. Treatment with acidic methanol converted the mixture of epimers into 6α-methylcholest-4-en-3-one (5), identical with the product from 6-nitrocholesterol. This was methylated with methyl iodide–potassium t-butoxide to give the 4,4,6-trimethyl-5-en-3-one (2; $R^1 = Me$, $R^2 = R^3 = H$).

Methylation of 6α-methyltestosterone similarly afforded 4,4,6-trimethylandrost-5-en-3-one.

Although methylation of 6α-methyl-19-nortestosterone [10] readily afforded 4,4,6-trimethyl-19-norandrost-5-en-3-one, the comparative inaccessibility of the starting material prompted us to seek an alternative method of synthesis. Thus 4,4-dimethyl-19-norandrost-5-en-3-one was converted into the ethylene acetal (7) and then into the 17β-tetrahydropyran-2-yl ether (8). Unexpectedly, two products were readily isolated from this latter reaction, namely the *R*- and *S*-ethers. To our knowledge there are few reports (see ref. 11) of the isolation of two epimeric tetrahydropyranyl ethers. The absolute stereochemistry of (8), and of cognate ethers, has been determined.[12]

Hydroboration of the *R*-ether [8; (2′*R*)] gave (i) the 5α-androstan-6α-ol (9) as the major product, (ii) the 6β-ol (10), and (iii) the 5α-androstane (11).

The structures of these products were assigned as follows. The hydroboration technique results in *cis*-addition of the elements of water in an anti-Markownikov manner. Thus the major product from the 5-ene (8) would be the 5α-androstan-6α-ol (9). In accord with

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this view, oxidation of (9) gave the 6-ketone (12), which was reduced in high yield to the 5α-androstan-6β-ol (10). Collateral evidence for these structural assignments is provided by (*a*) the ready dehydration of (10) with pyridine–thionyl chloride to the 5-ene (8), (*b*) the failure of the ketone (12) to epimerise at C-5 on treatment with base, (*c*) the reduction of the 6-ketone (12) by the Wolff–Kishner process to (11), which in turn gave 17β-hydroxy-4,4-dimethyl-19-nor-5α-androstan-3-one [13] after removal of the blocking groups, and (*d*) n.m.r. spectral properties (*cf.* ref. 13).

The genesis of the 5α-androstan-6β-ol (10), the minor product from hydroboration, is compatible with *cis*-hydroboration of the 5(6)-double bond, followed by reversal of the process to yield the 6(7)-ene, and then hydroboration of this 6-ene from the β-face of the molecule (*cf.* the similar situation in a parallel case [13]).

Reaction of the 6-ketone (12) with methyl-lithium afforded a homogeneous product (13) of undefined stereochemistry at C-6. Removal of the blocking groups gave 6ξ,17β-dihydroxy-4,4,6ξ-trimethyl-19-nor-5α-androstan-3-one (14).

From the diastereoisomeric (*S*)-tetrahydropyranyl ether [8; (2′*S*)] a similar series of transformations (see Experimental section) gave the same 4,4,6ξ-trimethyl-6ξ,17β-dihydroxy-19-nor-5α-androstan-3-one (14). One minor difference between the behaviour of the *R*- and *S*-series deserves comment. In the latter series, the formation of the 5α-6β-ol as a minor product was replaced by the formation of an isomer, formulated as the 5α-7ξ-ol (15) (*cf.* ref. 13). Oxidation of the alcohol (15) gave a ketone in high yield, indicating that the alcohol was secondary. The ketone was clearly different from the isomeric 6-one (12), and its stability to base together with o.r.d. data (*a* −9° centred at 290 nm) signified that it was not the 5β-isomer of (12) formed by β-face attack of diborane on the alkene (8). These observations are clearly in accord with the formulation of the minor alcohol from the hydroboration of 3,3-ethylenedioxy-17β-[(2*S*)-tetrahydropyran-2-yloxy]-4,4-dimethyl-19-nor-5α-androst-5-ene (8) as the 5α,7ξ-alcohol (15).

Dehydration of (14) with toluene-*p*-sulphonic acid–2,4,6-collidine gave 17β-hydroxy-4,4,6-trimethyl-5-en-3-one (6; $R^1 = R^2 = R^3 = H$), identical with that prepared directly from 6α-methyl-19-nortestosterone.

As already adumbrated in this paper, general principles indicate that ring A in (2; $R^1 = R^2 = H$) (and hence in the cognate derivatives of androstane and 19-norandrostane) must exist in a rigid boat conformation with C-3 and C-10 at the stem and stern positions and the C-6 methyl group occupying a more or less completely staggered conformation with respect to the two C-4 methyl groups. This conclusion is in agreement, *inter alia* with (i) the occurrence of the 10-methyl signal of (2; $R^1 = Me$, $R^2 = R^3 = H$) at τ 9.24, owing to this methyl group being in the shielding cone of the C-3 carbonyl group, (ii) reduction of the hindered C-3 carbonyl occurring only under forcing conditions, and then to yield 4,4,6-trimethylcholest-5-en-3β-ol, the configuration of which was defined by the atrolactic acid method,[14] and (iii) the rearrangement of this alcohol under the influence of acids, to yield the less strained, 4,4-dimethyl-6-methylene-5α-cholestan-3β-ol (16; R = CH_2). The constitution of (16; R = CH_2) was defined by ozonolysis of the acetate of (16; R = CH_2) to give 3β-acetoxy-4,4-dimethyl-5α-cholestan-6-one (16; R = O) [*cf.* the similar formation of 17β-acetoxy-4,4-dimethyl-6-methylene-19-nor-5α-androstan-3-one from the alcohol (14) under the influence of toluene-*p*-sulphonic acid].

Bromination of 4,4,6-trimethylcholest-5-en-3-one (2; $R^1 = R^2 = H$) under kinetic or thermodynamically controlled conditions gave the 2α-bromo-derivative (2; $R^1 = H$, $R^2 = Br$) as the major product, in which the halogen is clearly axially oriented ($\nu_{max.}$ 1 706 cm^{-1}; $\lambda_{max.}$ 313 nm), and ring A has a boat conformation (*cf.* ref. 15), with C-3 and C-10 at the stem and stern positions. In the spectra of (2; $R^1 = R^2 = H$) and (2; $R^1 = H$, $R^2 = Br$) the 10-methyl signal occurs at τ 9.24 and 9.25, respectively, the high field position being due to the location of the methyl group in the shielding cone of the C-3 carbonyl group. The minor product of bromination was assigned the 2β-configuration (2; $R^1 = Br$, $R^2 = H$), in which the halogen is equatorially oriented [$\nu_{max.}$ 1 730 cm^{-1}, in contrast to $\nu_{max.}$ 1 704 cm^{-1} for the parent ketone (2; $R^1 = R^2 = H$) and slight hypsochromic shift in the u.v. spectrum from 288 to 286 nm].

Attempts to substantiate these structural assignments (and hence those in the androstene and 19-norandrostene series) by reduction of (2; $R^1 = H$, $R^2 = Br$) and (2; $R^1 = Br$, $R^2 = H$) with sodium borohydride under the usual conditions for bromohydrin formation gave only unchanged starting material. More vigorous conditions, *e.g.* sodium borohydride in benzene–propan-2-ol at 70 °C, gave [from (2; $R^1 = H$, $R^2 = Br$)] a mixture of unchanged bromo-ketone, 4,4,6-trimethylcholest-5-en-3-one, and 4,4,6-trimethylcholest-5-en-3β-ol. This unusual result clearly reflects the rigid boat conformation of ring A in the bromo-ketone since approach of the reagent from the unhindered α-face would necessarily give a very sterically hindered product, irrespective of the precise conformation of ring A, in that product. The 4,4,6-trimethylandrost-5-en-3-one (6; $R^1 = Me$; $R^2 = R^3 = H$) and 4,4,6-trimethyl-19-norandrost-5-en-3-one (6; $R^1 = R^2 = R^3 = H$) also underwent thermodynamic bromination.

Each pair of epimeric bromo-ketones was equilibrated in acetic acid using hydrobromic acid as catalyst. The products were isolated by preparative t.l.c. and the product ratios (Table 1) were determined gravimetrically. The ratio of the two epimers was calculated as a percentage of the total material isolated, on the assumption that manipulative losses would be similar for each epimer. Total recovery was about 90% and the time

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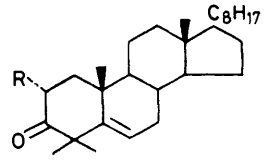
for equilibration (from each epimer) about 7 days. Control experiments established the stability of the epimers on t.l.c.

The 2α-epimer was the more stable in the cholestene and androstene series; the converse was true in the 19-norandrostene group.



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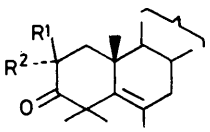

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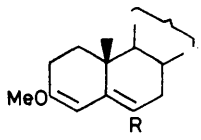

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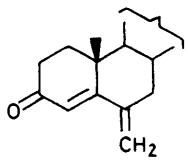

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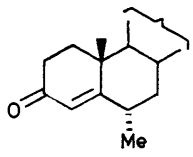

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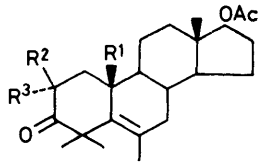

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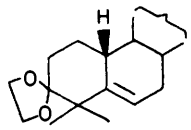

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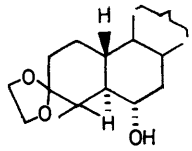

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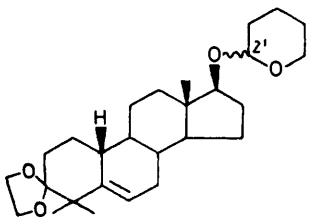

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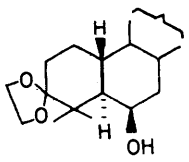

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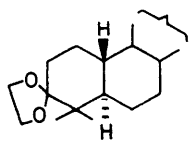

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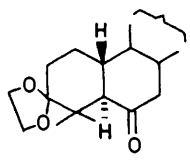

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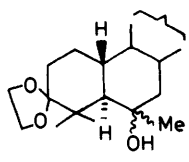

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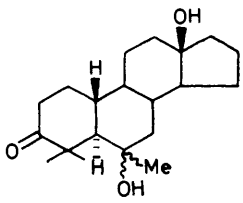

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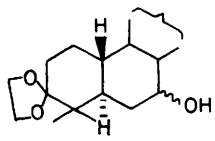

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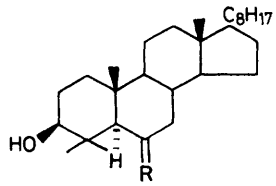

(16)

It is clear in (6; R^1 = Me, R^2 = R^3 = H) and (6; R^1 = R^2 = R^3 = H) that ring A exists in a boat conformation, since in each ketone the non-bonded interactions between the C-4 and C-6 methyl groups are equivalent to those in the cholestene series. Additionally, in the spectrum of (6; R^1 = Me, R^2 = R^3 = H), the 10-methyl signal appears at τ 9.24. In the case of the 2α-bromo-derivatives (6; R^1 = Me, R^2 = H, R^3 = Br) and (6; R^1 = R^2 = H, R^3 = Br) spectroscopic evidence clearly establishes the axial orientation of the halogen. Thus, (6; R^1 = Me, R^2 = H, R^3 = Br) has $\nu_{max.}$ 1 705 cm^{-1} and $\lambda_{max.}$ 316 nm, and (6; R^1 = R^2 = H, R^3 = Br) has $\nu_{max.}$ 1 720 cm^{-1} and $\lambda_{max.}$ 316 nm (*cf.* the corresponding cholestane derivatives).

Furthermore, the chemical shift (τ 9.22) of the 10-methyl group in (6; R^1 = Me, R^2 = H, R^3 = Br) and the identity of the coupling constants for the C-2 protons in (6; R^1 = Me, R^2 = H, R^3 = Br) and [12] in (2; R^1 = H, R^2 = Br) clearly establish the structure and conformation of (6; R^1 = Me, R^2 = H, R^3 = Br). Although similar evidence is not available from the n.m.r. spectrum of the 19-nor-derivative (6; R^1 = R^2 = H, R^3 = Br), it is clear that this compound too must be the 2α-bromo-derivative.

It thus follows that in the three 2α-bromo-ketones (2; R^1 = H, R^2 = Br), (6; R^1 = Me, R^2 = H, R^3 = Br), and (6; R^1 = R^2 = H, R^3 = Br) the halogen is in a negative octant, and that these three ketones should exhibit negative Cotton curves.[6] The data in Table 2, however, clearly show that these bromo-derivatives

exhibit *positive* Cotton effects, albeit of amplitudes less than that of the curve for the parent ketone. These bromo-ketones thus constitute definitive exceptions to the Axial Halogeno-ketone Rule, as originally expressed,[6]

TABLE 1

Equilibration of epimeric bromo-ketones

Equilibrated epimer	Product composition (%) 2α-Epimer	2β-Epimer
Cholestane series		
2α-Epimer (2; R^1 = H, R^2 = Br)	77	23
2β-Epimer (2; R^1 = Br, R^2 = H)	73	27
Androstane series		
2α-Epimer (6; R^1 = Me, R^2 = H, R^3 = Br)	75	25
2β-Epimer (6; R^1 = Me, R^3 = H, R^2 = Br)	75	25
19-Norandrostane series		
2α-Epimer (6; R^1 = R^2 = H, R^3 = Br)	28	72
2β-Epimer (6; R^1 = R^3 = H, R^2 = Br)	31	69

TABLE 2

Cotton-effect amplitudes

Compound	$a \times 10^{-2}$ (°)
(2; R^1 = R^2 = H)	+107
(2; R^2 = Br, R^1 = H)	+84
(6; R^1 = Me, R^2 = R^3 = H)	+107
(6; R^1 = Me, R^2 = H, R^3 = Br)	+89
(6; R^1 = R^2 = R^3 = H)	+83
(6; R^1 = R^2 =H, R^3 = Br)	+61

and applied to 'essentially unstrained cyclohexane rings.'[6] The presently reported deviations are thus not surprising, especially when considered in conjunction with the recognition (see *e.g.* ref. 16), that the chiroptical properties of substituted ketones cannot be satisfactorily correlated on the basis of the Octant (and similar) Rules alone.[16]

EXPERIMENTAL

All rotations were determined for solutions in chloroform, unless otherwise indicated. Light petroleum refers to the fraction of b.p. 40—60 °C.

6α-*Methylcholest-4-en-3-one*.—A 10% w/v solution of phosgene in 1,2-dichloroethane (120 ml) was added to a stirred solution of dimethylformamide (4.8 g) in 1,2-dichloroethane (40 ml) during ½ h at 0 °C. After a further 10 min, a solution of 3-methoxycholesta-3,5-diene (11.8 g) in dichloroethane (30 ml) and pyridine (0.1 ml) was added rapidly. The stirred mixture was allowed to attain room temperature and after 1 h a solution of sodium acetate (9 g) in water (100 ml) and pyridine (40 ml) was added. The mixture was then poured into water (1 l) and the product extracted with ether. Purification from acetone gave *3-methoxycholesta-3,6-diene-6-carbaldehyde* (3; R = CHO) (8.7 g) in needles, m.p. 138°; $[\alpha]_D^{22}$ −118° (*c* 4.45 in $CH_2Cl{\cdot}CH_2Cl$) [Found: C, 81.7; H, 10.6; OMe, 7.4. $C_{28}H_{43}O(OMe)$ requires C, 81.6; H, 10.9; OMe, 7.3%].

Sodium borohydride (0.05 g) was added to a stirred suspension of this formyl derivative (0.2 g) in methanol (80 ml) and the mixture was stirred for 45 min. The clear solution was then diluted with ether (160 ml) to yield *6-hydroxymethyl-3-methoxycholesta-3,5-diene* (3; R = CH_2OH) (0.15 g) which formed needles, m.p. 68—80° (from methanol containing a trace of pyridine) (Found: C, 80.4; H, 11.1. $C_{29}H_{48}O_2$ requires C, 81.3; H, 11.3%).

The crude 6-hydroxymethyl derivative (0.2 g) was dissolved in acetic acid (15 ml) and the solution maintained at 100 °C during 30 min. The product was purified by chromatography from light petroleum on alumina, followed by elution with light petroleum–benzene (19 : 1), to yield *6-methylenecholest-4-en-3-one* (4) (0.14 g) in needles, m.p. 122° (from methanol); $[\alpha]_D^{23}$ +251° (*c* 9.1) (Found: C, 84.1; H, 11.0. $C_{28}H_{44}O$ requires C, 84.8; H, 11.2%).

Hydrogenation of this 6-methylene derivative (1.5 g) dissolved in dioxan (55 ml) containing triethylamine (12 drops) and 2% palladium–strontium carbonate gave 6α-methylcholest-4-en-3-one (0.5 g), which formed needles, m.p. 126° (from methanol containing 1% of hydrochloric acid) (lit.,[8] m.p. 127—128.5°; this material was identical with a specimen prepared from 6-nitrocholesterol [8]).

4,4,6-*Trimethylcholest-5-en-3-one* (2; R^1 = R^2 = H).—A solution of 6α-methylcholest-4-en-3-one (0.4 g) in t-butyl alcohol (10 ml) was added to a solution of potassium (0.25 g) in the same solvent (8 ml). The mixture was refluxed (nitrogen) during 1 h and cooled, and methyl iodide (1.1 ml) was introduced. Potassium iodide commenced to separate immediately. Next day, the product was isolated with ether to yield *4,4,6-trimethylcholest-5-en-3-one* (0.3 g) which formed needles, m.p. 141° (from methanol); $[\alpha]_D^{20}$ −11° (*c* 1.47) (Found: C, 84.6; H, 11.9. $C_{30}H_{50}O$ requires C, 84.4; H, 11.8%).

4,4,6-*Trimethylcholest-5-en-3β-ol*.—4,4,6-Trimethylcholest-5-en-3-one (0.5 g) and sodium borohydride (0.5 g) were heated under reflux in propan-2-ol (300 ml) for 5 h. After cooling, acidification with 2N-hydrochloric acid, and dilution with water, the mixture was extracted with ether to give *4,4,6-trimethylcholest-5-en-3β-ol* which separated from ethyl acetate–methanol in small needles (0.4 g), m.p. 155—156°; $[\alpha]_D$ −8.2° (*c* 0.8); $\nu_{max.}(CCl_4)$ 3 630 and 3 036 cm^{-1} (Found: C, 84.4; H, 12.25. $C_{30}H_{52}O$ requires C, 84.0; H, 12.2%).

Atrolactic Acid Synthesis.—A solution of 4,4,6-trimethylcholest-5-en-3β-ol (1.02 g) in benzene–pyridine (3 : 2; 20 ml) was treated with phenylglyoxalyl chloride (0.9 g) in benzene (5 ml) for 24 h at room temperature. After dilution with water, the product was isolated in ether to give a pale yellow oil (1.2 g) which was dissolved in benzene–ether (1 : 1; 15 ml) and added to methylmagnesium iodide in ether (from 0.75 g of magnesium and 2 g of methyl iodide in 20 ml of ether). After 1 h, the mixture was heated under reflux for 1 h and poured onto ice and acetic acid. The product was isolated with ether to give the atrolactate ester (1.1 g) as a yellow oil, shown to be homogeneous by t.l.c. Saponification of this product in benzene (20 ml) with N-potassium hydroxide in ethanol (20 ml) under reflux for 5 h and isolation of the products in the usual way gave 4,4,6-trimethylcholest-5-en-3β-ol, which separated from ethyl acetate–methanol in small needles (0.72 g), m.p. and mixed m.p. 155—156°, and atrolactic acid, $[\alpha]_D$ +6.45° (*c* 5.1 in ethanol).

4,4-*Dimethyl-6-methylene-5α-cholestan-3β-ol*.—4,4,6-Trimethylcholest-5-en-3β-ol (0.37 g) was dissolved in ethanol (220 ml) containing hydrogen chloride (22 g) at room temperature. After 12 h the mixture was cautiously poured into an excess of 2N-sodium hydrogen carbonate and the product isolated in ether. Recrystallised from ether–

[16] M. R. Giddings, E. E. Ernstbrunner, and J. Hudec, *J.C.S. Chem. Comm.*, 1976, 954, 956.

methanol, 4,4-*dimethyl*-6-*methylene*-5α-*cholestan*-3β-*ol* formed needles (0.33 g), m.p. 151—152°, $[\alpha]_D$ +22.2° (*c* 3.1); $\nu_{max.}$ (CCl_4) 3 628, 1 637, and 892 cm^{-1} (Found: C, 83.7; H, 12.0. $C_{30}H_{52}O$ requires C, 84.0; H, 12.2%). Prepared with acetic anhydride–pyridine the *acetate* formed needles (from methanol–ether), m.p. 119—120°; $[\alpha]_D$ +28° (*c* 1.3 in $CHCl_3$), $\nu_{max.}$(CCl_4) 1 720, 1 622, 1 224, and 893 cm^{-1} (Found: C, 81.1; H, 11.5. $C_{32}H_{54}O_2$ requires C, 81.6; H, 11.6%).

Ozonolysis of 4,4-*Dimethyl*-6-*methylene*-5α-*cholestan*-3β-*yl Acetate*.—This compound (0.34 g) in ethyl acetate (75 ml) at −45 °C was treated with a stream of ozone and oxygen until a permanent blue colour was observed. The mixture was then decolourised with a stream of dry oxygen and the resultant solution mixed with a pre-reduced suspension of 5% palladium–barium sulphate (100 mg) in ethyl acetate (5 ml). The mixture was then shaken at 0 °C in hydrogen until the calculated quantity of gas had been absorbed. Isolated in the usual way, an oil (0.32 g) was obtained which was dissolved in light petroleum (b.p. 60—80°)–benzene (3 : 1) and adsorbed on alumina (45 g). Elution with the same solvent gave starting material (43 mg), m.p. and mixed m.p. 119—120°. Further elution with the same solvent mixture gave 3β-acetoxy-4,4-dimethyl-5α-cholestan-6-one (95 mg), which separated from ethyl acetate–methanol in needles, m.p. and mixed m.p. with an authentic sample supplied by Dr. T. G. Halsall, 147—148°; $[\alpha]_D$ +13.7° (*c* 0.99 in $CHCl_3$), $\nu_{max.}$(KBr) 1 746, 1 715, and 1 266 cm^{-1}.

17β-*Acetoxy*-4,4,6-*trimethylandrost*-5-*en*-3-*one* (6; R^1 = Me, R^2 = R^3 = H).—Methylation of a solution of 17β-hydroxy-6α-methylandrost-4-en-3-one (1.8 g) in t-butyl alcohol (115 ml) containing potassium t-butoxide [from potassium (1.1 g)] by addition of methyl iodide (6.6 ml) during 17 h gave a product which was purified by chromatography from benzene on alumina (Spence grade II). Elution with benzene gave a crude product which was further purified by t.l.c. on silica [ethyl acetate–benzene (1 : 19)]. Crystallised from methanol, 17β-*methoxy*-4,4,6-*trimethylandrost*-5-*en*-3-*one* (0.15 g) formed prisms, m.p. 110—111°; $[\alpha]_D^{23}$ −33° (*c* 1.33) [Found: C, 80.2; H, 10.4; OMe, 9.1. $C_{22}H_{33}O$(OMe) requires C, 80.2; H, 10.5; OMe, 9.0%].

Further elution with dichloromethane–benzene (1 : 9) gave 17β-*hydroxy*-4,4,6-*trimethylandrost*-5-*en*-3-*one* (1.2 g) which formed needles, m.p. 214° (from methanol); $[\alpha]_D^{22}$ −36° (*c* 1.33) (Found: C, 80.1; H, 10.5. $C_{22}H_{34}O_2$ requires C, 80.0; H, 10.4%).

The same product was similarly produced by methylation of 17β-hydroxy-6β-methylandrost-4-en-3-one.

Prepared by the pyridine–acetic anhydride method 17β-*acetoxy*-4,4,6-*trimethylandrost*-5-*en*-3-*one* formed needles, m.p. 136° (from aqueous acetone); $[\alpha]_D^{22}$ −15° (*c* 2.23) (Found: C, 77.4; H, 9.6. $C_{24}H_{36}O_3$ requires C, 77.4; H, 9.7%).

3,3-*Ethylenedioxy*-17β-[(2R)- *and* (2S)-*tetrahydropyran*-2-*yloxy*]-4,4-*dimethyl*-19-*norandrost*-5-*ene* (8).—A mixture of 17β-hydroxy-4,4-dimethyl-19-norandrost-5-en-3-one (0.5 g), toluene-*p*-sulphonic acid (0.03 g), ethylene glycol (5.5 ml), and benzene (60 ml) was refluxed (nitrogen) using a Dean–Stark apparatus, during 6 h. The semi-crystalline product (0.54 g) was difficult to purify, but was devoid of i.r. absorption at 1 710 cm^{-1} and therefore was used directly for the next operation. A solution of this acetal (1.7 g) in dihydropyran (10 ml) became warm on addition of phosphoryl chloride (2 drops). After 45 min, crystalline material commenced to separate, and after an additional 1½ h a solution of potassium hydroxide (0.9 g) in methanol (26 ml) was added; 5 min later the precipitate (1.1 g) was collected and purified from ethyl acetate containing 0.5% pyridine to yield 3,3-*ethylenedioxy*-17β-[(2R)-*tetrahydropyran*-2-*yloxy*]-4,4-*dimethyl*-19-*norandrost*-5-*ene* (0.9 g) [12] in leaflets, m.p. 210—215°, $[\alpha]_D^{24}$ +54° (*c* 0.84) (Found: C, 75.7; H, 9.7. $C_{27}H_{42}O_4$ requires C, 75.3; H, 9.8%).

The liquor remaining after separation of the crude *R*-isomer was diluted with water and extracted with ether, and the resultant gum purified from methanol containing 0.5% of pyridine to yield the S-*isomer* (0.8 g) [12] in needles, m.p. 143—144°; $[\alpha]_D^{24}$ −80° (*c* 1.16) (Found: C, 75.7; H, 9.7%).

Brown Hydration of the R-*Tetrahydropyranyl Ether* (8).—With nitrogen as carrier, diborane [generated by addition of a solution of sodium borohydride (5 g) in bis-(2-methoxyethyl) ether (180 ml) to boron trifluoride–ether complex (30 ml) in bis-(2-methoxyethyl) ether (30 ml)] was passed, during 1.5 h, into a solution of the *R*-tetrahydropyranyl ether (7.4 g) in tetrahydrofuran (350 ml). After 40 h at room temperature the excess of diborane was decomposed by cautious addition of water. 2N-Sodium hydroxide (150 ml) and hydrogen peroxide (30%; 150 ml) were added to the mixture, which was stirred for 1 h and then poured into water. Extraction with ether followed by chromatography of the product from benzene–light petroleum (1 : 1) on alumina, followed by elution with benzene–light petroleum (7 : 3), gave 3,3-*ethylenedioxy*-17β-[2(R)-*tetrahydropyran*-2-*yloxy*]-4,4-*dimethyl*-19-*norandrostane* (0.15 g) in plates, m.p. 202.5—204.5° (from methanol); $[\alpha]_D^{22}$ +62° (*c* 1.95) (Found: C, 75.0; H, 10.5. $C_{27}H_{44}O_4$ requires C, 75.0; H, 10.3%).

Continued elution with benzene gave 3,3-*ethylenedioxy*-17β-[(2R)-*tetrapyran*-2-*yloxy*]-4,4-*dimethyl*-19-*nor*-5α-*androstan*-6β-*ol*, which formed leaflets (0.9 g), m.p. 213° (from ethyl acetate); $[\alpha]_D^{24}$ +55° (*c* 1.74) (Found: C, 72.1; H, 9.8. $C_{27}H_{44}O_5$ requires C, 72.3; H, 9.9%).

The *acetate* separated from methanol in needles, m.p. 181° (Found: C, 71.0; H, 9.3. $C_{29}H_{46}O_6$ requires C, 71.0; H, 9.5%).

Continued elution with ether–benzene (1 : 3) gave 3,3-*ethylenedioxy*-17β-[(2R)-*tetrahydropyran*-2-*yloxy*]-4,4-*dimethyl*-19-*nor*-5α-*androst*-6α-*ol* (3.2 g) in plates, m.p. 222° (from ethyl acetate); $[\alpha]_D^{24}$ +70° (*c* 1.15) (Found: C, 72.3; H, 9.9. $C_{27}H_{44}O_5$ requires C, 72.3; H, 9.9%).

The *acetate* formed needles, m.p. 199° (from methanol) (Found: C, 70.7; H, 9.2. $C_{29}H_{46}O_6$ requires C, 71.0; H, 9.5%).

Dehydration of the 6β-ol (0.06 g) occurred readily at room temperature when a solution in pyridine (5 ml) containing phosphoryl chloride (0.4 ml) was kept for 18 h, to yield 3,3-ethylenedioxy-17β-[(2*R*)-tetrahydropyran-2-yloxy]-4,4-dimethyl-19-norandrost-5-ene (0.03 g), identical with an authentic specimen.

3,3-*Ethylenedioxy*-17β-[(2R)-*tetrahydropyran*-2-*yloxy*]-4,4-*dimethyl*-19-*nor*-5α-*androstan*-6-*one* (12).—Oxidation of either 3,3-ethylenedioxy-17β-[(2*R*)-tetrahydropyran-2-yloxy]-4,4-dimethyl-19-nor-5α-androstan-6α-ol (3 g) or of the epimeric 6β-ol (3 g) dissolved in pyridine (90 ml) by chromium trioxide (6.1 g) in pyridine (125 ml) during 18 h gave 3,3-*ethylenedioxy*-17β-[(2R)-*tetrahydropyran*-2-*yloxy*]-4,4-*dimethyl*-19-*nor*-5α-*androstan*-6-*one* (2.8 g) in needles, m.p. 202° (from methanol); $[\alpha]_D^{25}$ +50° (*c* 1.37) (Found: C, 72.7; H, 9.5. $C_{27}H_{42}O_5$ requires C, 72.6; H, 9.5%).

Reduction of this 6-one (0.1 g) in methanol (35 ml) by sodium borohydride (0.15 g) during 3 h, followed by chromatography of the product on alumina, gave (*a*) the corresponding 6β-ol [eluted with benzene–light petroleum (4 : 1)] (0.08 g), and (*b*) the 6α-ol (0.01 g) [eluted with ether–benzene (1 : 9)], identical with previously prepared specimens.

Reduction of 3,3-ethylenedioxy-17β-[(2*R*)-tetrahydropyran-2-yloxy]-4,4-dimethyl-19-nor-5α-androstan-6-one (0.1 g) with 99% hydrazine hydrate (0.6 ml) in diethylene glycol (5 ml) by the Wolff–Kishner process gave 3,3-ethylenedioxy-17β-[(2*R*)-tetrahydropyran-2-yloxy]-4,4-dimethyl-19-nor-5α-androstane (0.08 g), identical with the previously prepared specimen.

Removal of the protecting groups from this acetal followed by acetylation gave 17β-acetoxy-4,4-dimethyl-19-nor-5α-androstan-3-one, identical with a previously prepared specimen.[17]

3,3-*Ethylenedioxy*-17β-[(2R)-*tetrahydropyran*-2-*yloxy*]-4,4,6ξ-*trimethyl*-19-*nor*-5α-*androstan*-6ξ-*ol* (13).—To a stirred suspension of lithium pieces (1.25 g) in ether (20 ml) (in nitrogen), a few drops of a solution of methyl bromide (4.73 ml) in ether (30 ml) were added. Once reaction commenced the remainder of the methyl bromide was added at such a rate as to maintain the mixture at reflux temperature. A solution of 3,3-ethylenedioxy-17β-[(2*R*)-tetrahydropyran-2-yloxy]-4,4-dimethyl-19-nor-5α-androstan-6-one (1.5 g) in benzene (95 ml) was then added, and the mixture was heated under reflux for 4 h. Next day, the product was isolated and purified from benzene–light petroleum to yield 3,3-*ethylenedioxy*-17β-[(2R)-*tetrahydropyran*-2-*yloxy*]-4,4,6ξ-*trimethyl*-19-*nor*-5α-*androstan*-6ξ-*ol* (1.3 g) in needles, m.p. 165—166°; $[\alpha]_D^{25}$ +57° (*c* 1.15) (Found: C, 72.7; H, 10.1. $C_{28}H_{46}O_5$ requires C, 72.7; H, 10.0%).

Prepared by the action of hydrochloric acid (5.0 ml; 2.5N) on the foregoing acetal (1 g) dissolved in acetone (60 ml) and ethanol (60 ml), during 17 h, 6ξ,17β-*dihydroxy*-4,4,6ξ-*trimethyl*-19-*nor*-5α-*androstan*-3-*one* (14) (0.7 g) formed prisms, m.p. 216—217° (from acetone–light petroleum); $[\alpha]_D^{24}$ −42° (*c* 1.66) (Found: C, 75.8; H, 10.1. $C_{21}H_{34}O_3$ requires C, 75.4; H, 10.3%).

Formed by the pyridine–acetic anhydride method, 17β-*acetoxy*-6ξ-*hydroxy*-4,4,6ξ-*trimethyl*-19-*nor*-5α-*androstan*-3-*one* separated from acetone–light petroleum in needles, m.p. 195°; $[\alpha]_D^{25}$ −37° (*c* 1.34) (Found: C, 73.5; H, 9.5. $C_{23}H_{36}O_4$ requires C, 73.4; H, 9.6%).

Brown Hydration of 3,3-*Ethylenedioxy*-17β-[(2S)-*tetrahydropyran*-2-*yloxy*]-4,4-*dimethyl*-19-*norandrost*-5-*ene*.—Hydration of this 5-ene (5 g) by the process used for the corresponding *R*-derivative gave a mixture which was separated by chromatography from benzene–light petroleum (3 : 17) on alumina (Spence activity II). Elution with benzene–light petroleum (3 : 2) gave a mixture (0.1 g) which was discarded: continued elution with benzene gave 3,3-*ethylenedioxy*-17β-[(2S)-*tetrahydropyran*-2-*yloxy*]-4,4-*dimethyl*-19-*nor*-5α-*androstan*-6α-*ol* (3.8 g), which formed needles, m.p. 162° (from methanol followed by light petroleum), $[\alpha]_D^{20}$ −46° (*c* 4.17) (Found: C, 72.6; H, 9.8. $C_{27}H_{44}O_5$ requires C, 72.3; H, 9.9%). The 6α-*acetate* formed needles (from methanol) (Found: C, 71.1; H, 9.5. $C_{29}H_{46}O_6$ requires C, 71.0; H, 9.5%). Continued elution with ether–benzene furnished 3,3-*ethylenedioxy*-17β-[(2S)-*tetrahydropyran*-2-*yloxy*]-4,4-*dimethyl*-19-*nor*-5α-*androstan*-7ξ-*ol* (0.2 g) in needles, m.p. 182° (from methanol); $[\alpha]_D^{22}$ −76° (*c* 2.68) (Found: C, 72.1; H, 10.1. $C_{27}H_{44}O_5$ requires C, 72.3; H, 9.9%).

Oxidation of this 7ξ-alcohol (0.13 g) with the Sarett reagent gave 3,3-*ethylenedioxy*-17β-[(2S)-*tetrahydropyran*-2-*yloxy*]-4,4-*dimethyl*-19-*nor*-5α-*androstan*-7-*one*, which formed needles, m.p. 182° (from methanol); $[\alpha]_D^{25}$ −108° (*c* 1.32) (Found: C, 72.8; H, 9.3. $C_{27}H_{42}O_5$ requires C, 72.6; H, 9.5%).

3,3-*Ethylenedioxy*-17β-[(2S)-*tetrahydropyran*-2-*yloxy*]-4,4-*dimethyl*-19-*nor*-5α-*androstan*-6-*one*.—Oxidation of the corresponding 6α-ol (0.1 g) in pyridine by a solution of chromic oxide (0.2 g) in pyridine (4 ml) gave the *ketone* (12) (0.09 g) in needles, m.p. 152° (from methanol); $[\alpha]_D^{20}$ −67° (*c* 3.98) (Found: C, 72.5; H, 9.3. $C_{27}H_{42}O_5$ requires C, 72.6; H, 9.5%).

Reduction of this ketone (0.12 g) dissolved in methanol by sodium borohydride (0.6 g) during 6 h followed by chromatography from benzene–light petroleum (1 : 3) on alumina [elution with benzene–light petroleum (2 : 1)] gave 3,3-*ethylenedioxy*-17β-[(2S)-*tetrahydropyran*-2-*yloxy*]-4,4-*dimethyl*-19-*nor*-5α-*androstan*-6β-*ol* (0.09 g), which formed needles, m.p. 188° (from light petroleum); $[\alpha]_D^{25}$ −67° (*c* 1.06) (Found: C, 71.8; H, 9.8. $C_{27}H_{44}O_5$ requires C, 72.3; H, 9.9%). The 6β-*acetate* separated from methanol in needles, m.p. 193—195° (Found: C, 71.2; H, 9.4. $C_{29}H_{46}O_6$ requires C, 71.0; H, 9.5%).

Continued elution with benzene gave 3,3-ethylenedioxy-17β-[(2*S*)-tetrahydropyran-2-yloxy]-4,4-dimethyl-19-nor-5α-androstan-6α-ol (0.01 g), identical with a previously prepared specimen.

Reduction of 3,3-ethylenedioxy-17β-[(2*S*)-tetrahydropyran-2-yloxy]-4,4-dimethyl-19-nor-5α-androstan-6-one (0.1 g) by the Wolff–Kishner process gave 3,3-*ethylenedioxy*-17β-[(2S)-*tetrahydropyran*-2-*yloxy*]-4,4-*dimethyl*-19-*nor*-5α-*androstane* (0.08 g) in plates, m.p. 134° (from acetone–methanol); $[\alpha]_D^{25}$ −61° (*c* 1.71) (Found: C, 75.0; H, 10.2. $C_{27}H_{44}O_4$ requires C, 75.0; H, 10.3%). Hydrolysis of this acetal with N-hydrochloric acid gave 17β-hydroxy-4,4-dimethyl-19-nor-5α-androstan-3-one, characterised as the 17β-acetate (identical with an authentic specimen [17]).

3,3-*Ethylenedioxy*-17β-[(2S)-*tetrahydropyran*-2-*yloxy*]-4,4,6ξ-*trimethyl*-19-*nor*-5α-*androstan*-6ξ-*ol*.—Prepared by interaction of the corresponding 6-ketone (3.3 g) with methyl-lithium as for the *R*-analogue, 3,3-*ethylenedioxy*-17β-[(2S)-*tetrahydropyran*-2-*yloxy*]-4,4,6ξ-*trimethyl*-19-*nor*-5α-*androstan*-6ξ-*ol* (13) (3.2 g) separated from methanol in needles, m.p. 202°; $[\alpha]_D^{23}$ −62° (*c* 1.81) (Found: C, 72.4; H, 9.9. $C_{28}H_{46}O_5$ requires C, 72.7; H, 10.0%). Hydrolysis of the alcohol with 2.5N-hydrochloric acid furnished (quantitatively) 6ξ,17β-dihydroxy-4,4,6ξ-trimethyl-19-nor-5α-androstan-3-one (14), identical with that prepared from the *R*-derivative.

Dehydration of 17β-*Acetoxy*-6ξ-*hydroxy*-4,4,6ξ-*trimethyl*-19-*nor*-5α-*androstan*-3-*one*.—(*a*) A solution of this acetate (0.1 g) in acetic acid (4 ml) containing toluene-*p*-sulphonic acid (0.007 g) was refluxed during 15 min. After isolation and purification by t.l.c. 17β-*acetoxy*-4,4-*dimethyl*-6-*methylene*-19-*nor*-5α-*androstan*-3-*one* formed needles, m.p. 149° (from methanol); $[\alpha]_D^{25}$ −36° (*c* 2.92) (Found: C, 77.2; H, 9.5. $C_{23}H_{34}O_3$ requires C, 77.1; H, 9.6%).

(*b*) A solution of 17β-acetoxy-6ξ-hydroxy-4,4,6ξ-trimethyl-19-nor-5α-androstan-3-one (1 g) in 2,4,6-collidine containing toluene-*p*-sulphonic acid (3 g) was refluxed

[17] J. M. Midgley, W. B. Whalley, P. A. Dodson, G. F. Katakar, and B. A. Lodge, *J.C.S. Perkin I*, 1977, 823.

(nitrogen) during 50 h Chromatography on alumina (Spence activity II) from benzene–light petroleum (1 : 4) followed by crystallisation from methanol gave 17β-*acetoxy*-4,4,6-*trimethyl*-19-*norandrost*-5-*en*-3-*one* (0.6 g) in needles, m.p. 140—141°; $[\alpha]_D^{25}$ +27° (*c* 2.23) (Found: C, 77.1; H, 9.5. $C_{23}H_{34}O_3$ requires C, 77.1; H, 9.6%). 17β-Acetoxy-4,4-dimethyl-6-methylene-19-nor-5α-androstan-3-one (0.1 g) was recovered from the residues.

Hydrolysis of 17β-acetoxy-4,4,6-trimethyl-19-norandrost-5-en-3-one with methanolic potassium hydroxide gave (quantitatively) 17β-*hydroxy*-4,4,6-*trimethyl*-19-*norandrost*-5-*en*-3-*one*, which separated from acetone–hexane in needles, m.p. 150°; $[\alpha]_D^{25}$ +43° (*c* 1.37) (Found: C, 79.5; H, 10.3. $C_{21}H_{32}O_2$ requires C, 79.7; H, 10.2%).

Thermodynamically Controlled Bromination of 4,4,6-*Trimethylcholest*-5-*en*-3-*one*.—Brominated in acetic acid as for the androstane series, this ketone (0.65 g) gave (a) 2α-*bromo*-4,4,6-*trimethylcholest*-5-*en*-3-*one* (2; R^1 = H, R^2 = Br) (0.4 g) in needles, m.p. 126—128° (from methanol); $[\alpha]_D^{23}$ −32° (*c* 1.6) (Found: C, 71.2; H, 9.6; Br, 15.6. $C_{30}H_{49}BrO$ requires C, 71.3; H, 9.7; Br, 15.8%); (b) 2,2-*dibromo*-4,4,6-*trimethylcholest*-5-*en*-3-*one* (68 mg), which formed needles, m.p. 119° (from methanol); $[\alpha]_D^{22.5}$ −54° (*c* 0.75) (Found: C, 63.2; H, 8.7; Br, 25.8. $C_{30}H_{48}Br_2O$ requires C, 61.7; H, 8.3; Br, 27.3%); and (c) 2β-*bromo*-4,4,6-*trimethylcholest*-5-*en*-3-*one* (2; R^1 = Br, R^2 = H) (40 mg), which separated from methanol in needles, m.p. 134°; $[\alpha]_D^{23}$ +25° (*c* 0.5) (Found: C, 71.1; H, 9.8; Br, 15.7. $C_{30}H_{49}BrO$ requires C, 71.3; H, 9.7; Br, 15.8%).

Equilibration of 2α- *and* 2β-*Bromo*-4,4,6-*trimethylcholest*-5-*en*-3-*one*.—Treatment of the 2α-bromo-derivative (0.24 g) as for the androstene analogue gave (*a*) starting material (0.12 g) and (*b*) the 2β-epimer (35 mg). Similarly equilibration of the 2β-bromo-compound (50 mg) gave starting material (8 mg) and the 2α-epimer (26 mg).

Reduction of the 2α- and 2β-bromo-epimers and of the 2,2-dibromo-derivative with zinc and acetic acid gave in each case 4,4,6-trimethylcholest-5-en-3-one.

Reduction of 2α-*Bromo*-4,4,6-*trimethylcholest*-5-*en*-3-*one*.—This compound (0.25 g) in benzene–propan-2-ol (2 : 7; 100 ml) and sodium borohydride (0.25 g) were heated together at 70 °C for 3 h. Isolated in the usual way, the product (0.22 g) was subjected to preparative layer chromatography on silica gel GF (Merck) [ether–benzene (1 : 9 v/v) as eluant]. Three principal bands were separated and eluted. Thus obtained, unchanged 2α-bromo-4,4,6-trimethylcholest-5-en-3-one formed needles (18 mg) (from ether–methanol), m.p. and mixed m.p. 128—129°, 4,4,6-trimethylcholest-5-en-3-one formed plates (72 mg) (from ether–methanol), m.p. and mixed m.p. 138—139°, and 4,4,6-trimethylcholest-5-en-3β-ol formed needles (81 mg) (from ethyl acetate–methanol), m.p. and mixed m.p. 155—156°.

Bromination of 17β-*Hydroxy*-4,4,6-*trimethylandrost*-5-*en*-3-*one*.—(a) *Kinetic*. A portion (3.4 ml) of a solution prepared from bromine (1.76 g), sodium acetate (0.7 g), and acetic acid (50 ml) was added to the ketone (0.2 g) dissolved in part of a solution (12 ml) prepared from acetic acid (100 ml) and acetic acid saturated with hydrogen bromide (0.2 ml), at such a rate that no excess of bromide was present. After dilution with water the product was extracted with ether and the extract washed free from acid. The crude product was acetylated (pyridine–acetic anhydride) chromatographed on silica, from benzene. Elution with the same solvent gave 17β-*acetoxy*-2α-*bromo*-4,4,6-*trimethylandrost*-5-*en*-3-*one* (6; R^1 = R^2 = H, R^3 = Br) (0.07 g) in needles, m.p. 182.5—184.5° (from light petroleum); $[\alpha]_D^{23}$ −63° (*c* 0.017) (Found: C, 63.7; H, 8.0; Br, 16.4. $C_{24}H_{35}BrO_3$ requires C, 63.8; H, 7.8; Br, 17.7%).

(b) *Thermodynamic*. Bromination of 17β-acetoxy-4,4,6-trimethylandrost-5-en-3-one (2.9 g) dissolved in acetic acid (88 ml) containing hydrobromic acid (0.2 ml), by addition of a solution of bromine (0.48 ml) in acetic acid (23.5 ml), occurred during 15 min to yield 17β-acetoxy-2α-bromo-4,4,6-trimethylandrost-5-en-3-one (2.8 g), identical with that described in (a).

Isolated by t.l.c. [on Kieselgel GF_{254} with ether–carbon tetrachloride (1 : 9) as developer] from the methanolic mother liquors remaining after separation of the 2α-bromo-ketone, 17β-*acetoxy*-2,2-*dibromo*-4,4,6-*trimethylandrost*-5-*en*-3-*one* (50 mg) formed needles, m.p. 171—173° (from methanol) (Found: C, 54.8; H, 6.6; Br, 28.9. $C_{24}H_{34}Br_2O_3$ requires C, 54.4; H, 6.4; Br, 30.0%), followed by 17β-*acetoxy*-2β-*bromo*-4,4,6-*trimethylandrost*-5-*en*-3-*one* (6; R^1 = Me, R^3 = H, R^2 = Br) which formed prisms (0.2 g), m.p. 200° (from ethanol); $[\alpha]_D^{20}$ +8° (*c* 0.96) (Found: C, 63.6; H, 7.9; Br, 17.8. $C_{24}H_{35}BrO_3$ requires C, 63.8; H, 7.8: Br 17.7%).

(c) *Using the enol acetate*. A solution of 17β-hydroxy-4,4,6-trimethylandrost-5-en-3-one (0.3 g) in isopropenyl acetate (30 ml) containing toluene-*p*-sulphonic acid (0.06 g) was distilled slowly during 2 h; the residue was then refluxed for 22 h. After isolation in the normal manner, 3,17β-*diacetoxy*-4,4,6-*trimethylandrosta*-2,5-*dien*-3-*one* formed needles (0.23 g), m.p. 137—139° (from methanol); $[\alpha]_D^{22}$ −11° (*c* 2.22) (Found: C, 75.7; H, 9.4. $C_{26}H_{38}O_4$ requires C, 75.3; H, 9.2%).

A solution of bromine (0.09 g) in acetic acid (1.5 ml) was added slowly to a solution of this enol acetate (0.18 g) in acetic acid (9.5 ml) and pyridine (1 ml). Next day, the product was isolated and purified from methanol to yield 17β-acetoxy-2α-bromo-4,4,6-trimethylandrost-5-en-3-one (0.17 g), identical with the samples prepared by methods (a) and (b).

Equilibration of 17β-*Acetoxy*-2α- *and* 17β-*Acetoxy*-2β-*bromo*-4,4,6-*trimethylandrost*-5-*en*-3-*one*.—Acetic acid (1 drop) saturated with hydrogen bromide was added to a solution of 17β-acetoxy-2α-bromo-4,4,6-trimethylandrost-5-en-3-one (0.24 g) in acetic acid (25 ml). After 7 days the mixture was poured into ether and the ethereal extract washed free from acid. Separation of the product by t.l.c. on Kieselgel GF_{254} and elution with ether–carbon tetrachloride (1 : 19) gave (*a*) the 2α-bromo-ketone (0.16 g) and (*b*) the 2β-bromo-epimer (43 mg).

Similar equilibration of the 2β-isomer (0.1 g), which required 14 days, afforded the 2α-isomer (70 mg) and the 2β-isomer (20 mg), identical with authentic specimens.

Reduction of 17β-acetoxy-2α-bromo- or of 17β-acetoxy-2β-bromo-4,4,6-trimethylandrost-5-en-3-one (70 mg) in boiling acetic acid (40 ml) containing zinc dust (2 g) during 20 min gave 17β-acetoxy-4,4,6-trimethylandrost-5-en-3-one (40 mg), identical with an authentic specimen obtained similarly from 17β-acetoxy-2,2-dibromo-4,4,6-trimethylandrost-5-en-3-one.

Thermodynamically Controlled Bromination of 17β-*Acetoxy*-4,4,6-*trimethyl*-19-*norandrost*-5-*en*-3-*one*.—A solution of bromine (0.24 g) in carbon tetrachloride (2.5 ml) was added during 10 min to a stirred solution of 17β-acetoxy-4,4,6-trimethyl-19-norandrost-5-en-3-one (0.5 g) in carbon tetrachloride (20 ml). The mixture was then diluted with water

and extracted with ether. Purification of the product by t.l.c. (Kieselgel GF_{254}) using ether–light petroleum (3 : 17) gave (a) 17β-*acetoxy*-2α-*bromo*-4,4,6-*trimethyl*-19-*norandrost*-5-*en*-3-*one* (6; $R^1 = R^2 = H$, $R^3 = Br$) (0.1 g) in needles, m.p. 159—160° (from methanol); $[\alpha]_D^{25}$ −28° (*c* 1.73) (Found: C, 63.0; H, 7.7; Br, 18.2. $C_{23}H_{33}BrO_3$ requires C, 63.2; H, 7.6; Br, 18.3%), and (b) 17-*acetoxy*-2β-*bromo*-4,4,6-*trimethyl*-19-*norandrost*-5-*en*-3-*one* (6; $R^1 = R^3 = H$, $R^2 = Br$) (0.1 g) in needles, m.p. 150° (from light petroleum); $[\alpha]_D^{25}$ +44° (*c* 0.37) (Found: C, 63.0; H, 7.6; Br, 18.3%).

Equilibrium of 17β-*Acetoxy*-2α- *and* 17β-*Acetoxy*-2β-*bromo*-4,4,6-*trimethyl*-19-*norandrost*-5-*en*-3-*one*.— Prepared as for the androstane analogue the 2α-bromo-19-norandrost-5-ene (50 mg) gave the 2α-bromo-derivative (12 mg) together with the 2β-epimer (31 mg).

Similarly equilibration of 17β-acetoxy-2β-bromo-4,4,6-trimethyl-19-norandrost-5-en-3-one (0.1 g) gave unchanged 2β-derivative (47 mg) together with the 2α-epimer (25 mg).

Reduction of the 2α- and 2β-bromo-ketones with zinc and acetic acid regenerated 17β-acetoxy-4,4,6-trimethyl-19-norandrost-5-en-3-one, in high yield.

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