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MODIFIED STEROID HORMONES—XXXI[1]

SOME 4,6-DIMETHYL DERIVATIVES

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Abstract—Two routes to 4,6β-dimethyltestosterone have been developed. The reduction of this compound to 4α,6β-dimethyl-17β-hydroxy-5α-androstan-3-one is described. Several 4,6-dimethyl-steroids have been prepared for biological study.

THE recent development by these laboratories of a practical method for the C_4 methylation[2] of steroidal 4-en-3-ones opened the way to a systematic study of 4-methylated hormone types. 4-Methyltestosterone proved to be somewhat less active biologically than the parent hormone, but with an improved anabolic–androgenic index. As we had previously found that 6-methylation[3] likewise enhances the anabolic–androgenic index of testosterone, we turned naturally to the preparation of 4,6-dimethyltestosterone. Biological examination of 4,6β-dimethyl testosterone has revealed an exceptionally favourable index in the "levator ani" assay.

Initial experiments involved the application of the thiomethylation procedure[2] to 6α-methyltestosterone (15; R = ——OH, - - -H), and to 6α-methylandrost-4-ene-3,17-dione (15; R = =O), when the corresponding 4-phenylthiomethyl derivatives (14; R = ——OH, - - -H) and (14; R = =O) were obtained in yields of 40 per cent and 30 per cent respectively. Desulphurization of these derivatives (the former compound as 17β-acetate) with partially deactivated Raney nickel then gave the required 4,6β-dimethyltestosterone acetate (Isomer A) (11; R = ——OAc, - - -H; R′ = O) and 4,6β-dimethylandrost-4-ene-3,17-dione (11; R = R′ = =O)*. Selective reduction of the latter diketone with sodium borohydride afforded the parent 17β-alcohol of Isomer A.

On repeating the preparation of 4,6β-dimethyltestosterone acetate from 6α-methyltestosterone on a larger scale an isomeric compound (Isomer B) was also isolated, in very low yield, and is regarded as 4,6α-dimethyltestosterone (12; R = ——OAc, - - -H) on the basis of (i) spectroscopic data (see following paper) and (ii) its ready conversion *via* the 3-enol acetate (not purified) into the stable 6β-epimer (Isomer A).

It is noteworthy that disappointingly low yields of the 4-thiomethyl derivatives (14; R = ——OH, - - -H) and (14; R = =O) were obtained. This result is not

* The 6-methyl group present in Isomer A has been assigned the "β"-configuration on the basis of spectroscopic evidence presented in Part XXXII (following paper).

[1] Part XXX. *J. Chem. Soc.* (in the press).

[2] D. N. Kirk and V. Petrow, *J. Chem. Soc.* 1091 (1962).

[3] M. Ackroyd, (Mrs) W. J. Adams, B. Ellis, V. Petrow and (Mrs) I. A. Stuart-Webb, *J. Chem. Soc.* 4099 (1957); also H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.* **22**, 99 (1957).

entirely surprising, since examination of Dreiding models reveals a high degree of steric hindrance between the C_6-methyl group and the large incoming group at C_4. We therefore turned to alternative routes for the preparation of 4,6-dimethylated compounds. As 4-methyl steroids were now readily accessible, it seemed that the C_6-methylation of a 4-methyl intermediate might well be preferred. Nearly all the methods available for the 6-methylation of a steroidal 4-en-3-one are based upon a procedure, developed in Part VII,[4] which depends upon the enforced migration of the 4,5-double bond into the 5,6-position consequent upon ketalization of the 3-carbonyl group. Conversion of 4-methyltestosterone acetate (1; R = ——OAc, - - -H; R′ = O) into a 3,3-ethylenedioxy derivative under the specific experimental conditions employed (see Experimental section), however, was *not accompanied by migration of the* 4,5-*double bond.* This conclusion is based upon the observation that the parent 3-ketone (1; R = ——OAc, - - -H; R′ = O) and the ketal (1; R = ——OAc, - - -H; R′ = O·CH_2·CH_2·O) obtained from it have molecular rotations of the same sign and magnitude. Migration of a 4,5-double bond to the 5,6-position, in contrast, is known to result in a very marked laevorotatory change.[5] Further evidence contra-indicating a Δ^5-formulation for the ketal was provided by the N.M.R. spectrum which significantly lacked absorption in the region characteristic of olefinic protons.

We next turned to the preparation of a 4-methylated intermediate having a carbonyl group at C_6, from which it was hoped to obtain the required 4,6-dimethyl-4-en-3-one (11; R = ——OAc, - - -H; R′ = O). 4-Methyltestosterone acetate (1; R = ——OAc, - - -H; R′ = O) was converted by acetic anhydride–toluene-*p*-sulphonic acid into 3,17β-diacetoxy-4-methylandrosta-3,5-diene, which on treatment with monoperphthalic acid gave 17β-acetoxy-6(α + β)-hydroxy-4-methylandrost-4-en-3-one. This mixture of epimeric alcohols was oxidized directly to yield 17β-acetoxy-4-methylandrost-4-ene-3,6-dione (2; R = ——OAc, - - -H; R′ = O). An attempt to prepare the last compound by an alternative method, involving reaction of a 4-ene-3,6-dione with diazomethane[6] (to be followed by pyrolysis of the intermediate pyrazoline), led only to unchanged starting material. 17β-Acetoxy-4-methylandrost-4-ene-3,6-dione (2; R = ——OAc, - - -H; R′ = O) condensed readily with ethylene glycol–toluene-*p*-sulphonic acid to give in excellent yield a *mono*ketal, formulated as 17β-acetoxy-3,3-ethylenedioxy-4-methylandrost-4-en-6-one (2; R = ——OAc, - - -H; R′ = O·CH_2CH_2O) on the basis of the transformations it was subsequently shown to undergo (*vide infra*). Reaction of this 3-ketal-6-one with magnesium methyl iodide followed an abnormal course, however, the major product obtained (after acetylation) being a diacetate lacking a free (tertiary) hydroxyl group (I.R. evidence). The U.V. spectral properties and analysis of this substance are consistent with its formulation as the 3-acetoxy-ethoxy-6-one (3; R = ——OAc, - - -H). The unexpected behaviour of (2; R = ——OAc, - - -H; R′ = O·CH_2·CH_2·O) with the Grignard reagent may be rationalized by the assumption that, under the experimental conditions employed, salt formation via a 6-enolic ion with concomitant fission of one of the C_3-oxygen bonds, takes precedence over addition of the reagent to the 6-carbonyl group. The preparation of the saturated compound (4; R = ——OAc, - - -H; R′ = O), in which such enolisation was

[4] G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.* 4112 (1957).
[5] L. F. Fieser and H. Fieser, *Steroids* p. 178. Reinhold, New York (1959).
[6] L. F. Fieser, *J. Amer. Chem. Soc.* **75**, 4386 (1953).

considered less likely, was next undertaken. We had previously shown[7] that the 6β-hydroxy-4-en-3-one system undergoes rearrangement to a saturated 5α-3,6-dione on treatment with acid. 17β-Acetoxy-6(α + β)-hydroxy-4-methylandrost-4-en-3-one, in contrast, proved completely stable under these experimental conditions, an observation representing a further example of the effect of a 4-methyl substituent upon the reactivity of functional groups in Rings A and B. The required 17-β-acetoxy-4α-methyl-5α-androstane-3,6-dione (4; R = ——OAc, - - -H; R′ = O) was ultimately prepared by reducing the unsaturated diketone (2; R = ——OAc, - - -H; R′ = O) with zinc dust in acetic acid. Two crystalline products were obtained from this reaction, however. The major component was unaffected by H^+ or OH ions and is therefore assigned the more stable 4α-Me, 5α-H structure (4; R = ——OAc, - - -H; R′ = O). The minor component is regarded as the 4β-methyl isomer (5; R = ——OAc, - - -H; R′ = O) as it is converted into the 4α-methyl-3,6-diketone (4; R = ——OAc, - - -H; R′ = O) by treatment with mineral acid or by chromatography on alumina. Subsequent reactions (*vide infra*) established that *only* C_4 is involved in this isomerization. The yield and ease of isolation of the desired diketone (4; R = ——OAc, - - -H; R′ = O) were considerably improved by brief pretreatment of the total reduction product with mineral acid, or by chromatography on unwashed alumina. Hydrogenation of the unsaturated ketone (2; R = ——OAc, - - -H; R′ = O) over Adam's catalyst gave the 4β-methyl-3,6-dione (5; R = ——OAc, - - -H; R′ = O) as the sole isolable product.

17β-Acetoxy-4α-methyl-5α-androstane-3,6-dione (4; R = ——OAc, - - -H; R′ = O) readily passed into the 3-monoketal (4; R = ——OAc, - - -H; R′ = O·CH_2·CH_2·O). The last compound reacted normally with magnesium methyl iodide, as anticipated, to give, after acetylation, the tertiary alcohol (7; R = ——OAc, - - -H), which was converted by acid into 17β-acetoxy-4α,6β-dimethyl-6α-hydroxy-5α-androstan-3-one (8; R = ——OAc, - - -H). The same compound was additionally obtained from the 4β-methyl-3-monoketal (5; R = ——OAc, - - -H; R′ = O·CH_2·CH_2·O) by reaction with magnesium methyl iodide, to give the tertiary alcohol (6; R = ——OAc, - - -H), which differed from compound (7; R = ——OAc, - - -H), followed by deketalization (and epimerization of the C_4-methyl group) with acid. This series of transformations confirms C_4 as the site of the isomerism of the diones (4; R = ——OAc, - - -H; R′ = O) and (5; R = ——OAc, - - -H; R′ = O) referred to above, since (a) the 4β-methyl-3-monoketal (5; R = ——OAc, - - -H; R′ = O·CH_2·CH_2·O) was not isomerized by treatment with aqueous alcoholic sodium hydroxide and (b) isomerization at C_5 is not possible in the ketone (8; R = ——OAc, - - -H). The configurations of the C_6-substituents present in the last compound, and hence in the ketals (6; R = ——OAc, - - -H) and (7; R = ——OAc, - - -H), may be inferred from the position in the infrared of the fundamental stretching absorption of the hydroxyl group. The observed frequency of 3615 cm^{-1}, is characteristic of a tertiary *equatorial*[8] hydroxyl group*, and therefore compound (8; R = ——OAc,

* This result is applicable only where O—H . . . X interaction with neighbouring electronegative atoms or π-electron bonds is not possible cf. the 6-hydroxy-6-methyl-3,5-cyclo-steroids discussed by Davies *et al.*[9] For further discussion of these effects, see Davies *et al.*[10] and references cited therein.

[7] B. Ellis and V. Petrow, *J. Chem. Soc.* 1078 (1939).

[8] A. R. H. Cole, (Miss) G. T. A. Müller, D. W. Thornton and R. L. S. Willix, *J. Chem. Soc.* 1218 (1959).

---H) is regarded as the 6α-hydroxy-6β-methyl isomer. Dreiding and Catalin models of this compound and of its C_6 configurational isomer predict that the structure with least steric strain is that in which the hydroxyl group at C_6 is eclipsed with the C_4-methyl group, the residual strain between the C_6-axial and C_{10}-methyl groups being relieved by very slight deformation of the ring B chair. There appears to be no valid reason for invoking possible boat structures for either rings A or B.

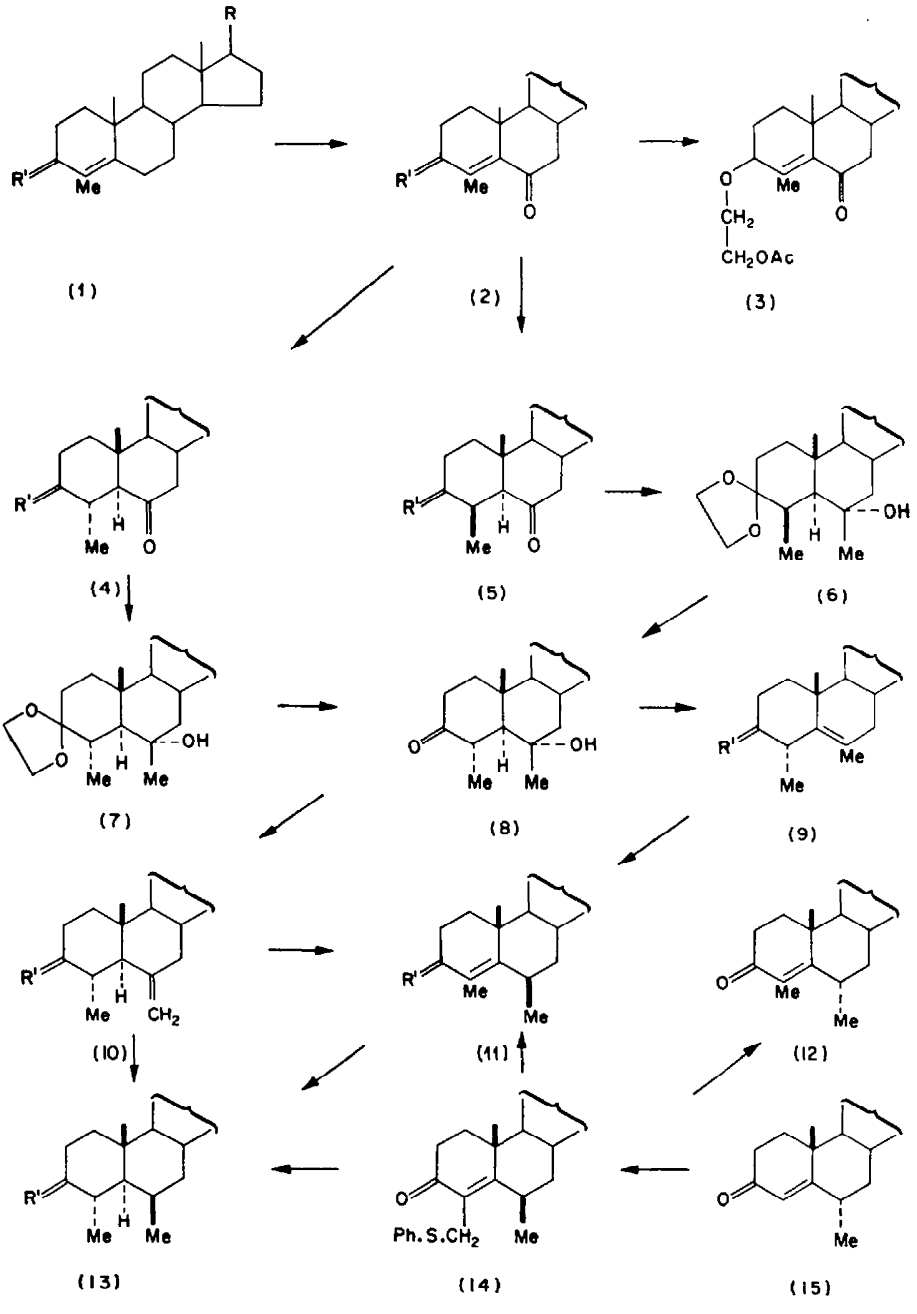
Treatment of the tertiary alcohol (8; R = ——OAc, ---H) with thionyl chloride in pyridine gave an endocyclic olefin which (i) lacked U.V. absorption characteristic of an αβ-unsaturated ketone, and (ii) afforded an N.M.R. spectrum which failed to reveal the presence of an olefinic proton. These observations exclude a 4- or 6-ene structure for the dehydration product and lead to its formulation as 17β-acetoxy-4α,6-dimethylandrost-5-en-3-one (9; R = ——OAc, ---H; R′ = O). When formic acid was used to effect the dehydration, however, the exocyclic 6-methylene isomer (10; R = ——OAc, ---H; R′ = O) (bands in the I.R. spectrum at 1640 and 890 cm^{-1}) was obtained in excellent yield. The isomers (9 and 10; R = ——OAc, ---H; R′ = O) proved to be stable to methanolic sodium hydroxide and to methanolic hydrochloric acid, but were readily isomerized by perchloric acid in acetic acid to give 17β-acetoxy-4,6β-dimethylandrost-4-en-3-one (11; R = ——OAc, ---H; R′ = O), identical with the material previously obtained by C_4-methylation of 6α-methyltestosterone acetate (15; R = ——OAc, ---H).

The 5,6-double bond present in compound (9; R = ——OAc, ---H; R′ = O) proved to be resistant to catalytic hydrogenation, but hydrogenation of compounds (10 and 11; R = ——OAc, ---H; R′ = O) over palladium on charcoal, or reduction of (11; R = ——OAc, ---H; R′ = O) with lithium in liquid ammonia (followed by acetylation) gave in high yield a single product formulated as 17β-acetoxy-4α,6β-dimethyl-5α-androstan-3-one (13; R = ——OAc, ---H; R′ = O). The same compound was also obtained by reduction of 17β-acetoxy-6β-methyl-4-phenylthiomethylandrost-4-en-3-one (14; R = ——OAc, ---H) with lithium in liquid ammonia, followed by acetylation of the product. Inspection of Dreiding models of compound (10; R = ——OAc, ---H; R′ = O) reveals that the 4α-methyl group has little influence on the steric environment of the 6-methylene group. It is highly probable, therefore, that hydrogenation will occur from the α-side of the molecule, in accordance with the "rule of the rear", with formation of a 6β-orientated methyl group. The stereochemistry of compound (13; R = ——OAc, ---H; R′ = O) also follows from its preparation from the unsaturated ketone (11; R = ——OAc, ---H; R′ = O) by lithium–liquid ammonia reduction, which procedure is known to yield the more stable 4α-methyl-5α-dihydro types.

The following 4,6-dimethyl compounds were prepared for biological study (see Experimental): 17β-hydroxy-4α,6,17α-trimethylandrost-5-en-3-one, 17α-chlorethynyl-4α,6-dimethyl-17β-hydroxyandrost-5-en-3-one, 17β-hydroxy-4,6β,17α-trimethylandrost-4-en-3-one, 17β-hydroxy-4α,6β,17α-trimethyl-5α-androstan-3-one, 17α-chlorethynyl-4α,6β-dimethyl-17β-hydroxy-5α-androstan-3-one, 17α-acetoxy-4,6β-dimethylpregn-4-ene-3,20-dione and 4,6β-dimethyl-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione.

[9] M. Davis, S. Julia and G. H. R. Summers, *Bull Soc. Chim. Fr.* 742 (1960).

[10] M. T. Davies, (Miss) D. F. Dobson, D. F. Hayman, G. B. Jackman, M. G. Lester, V. Petrow, O. Stephenson and A. A. Webb, *Tetrahedron* **18**, 751 (1962).


R
R'
Me
(1)
O
(2)
O
CH2
CH2OAc
(3)
H
(4)
(5)
OH
(6)
(7)
(8)
(9)
CH2
(10)
(11)
(12)
Ph.S.CH2
(13)
(14)
(15)

EXPERIMENTAL

Optical rotations were determined at concentrations of ca. 1% in A.R. chloroform at laboratory temperature, unless otherwise stated. U.V. spectra refer to solutions in spectro-grade ethanol. I.R. spectra were determined with a Hilger H800 spectrophotometer, fitted with calcium fluoride and sodium chloride prisms for the frequency ranges 4000–1300 and 1350–650 cm^{-1} respectively, the solvents used being as indicated.

4,6β-Dimethyltestosterone acetate (11; R — ——OAc, - - -H; R′ = O)

6α-Methyltestosterone (14 g), thiophenol (10 ml), 40% aqueous formaldehyde (8·5 ml), triethylamine (9·5 ml) and ethanol (25 ml) were heated for 88 hr at ca. 90°. The mixture was poured into water (350 ml) containing potassium hydroxide (6·5 g), and the product isolated with ether. It was chromatographed on alumina (150 g) in benzene–light petroleum (b.p. 40–60°; 2:1), elution with benzene giving crystalline material which was purified from benzene–light petroleum. *17β-Hydroxy-6β-methyl 4-phenylthiomethylandrost-4-en-3-one* (14; R = ——OH, - - -H) separated in needles, m.p. 111–112°, $[\alpha]_D$ −44·8°, λ_{max} 253 mμ (ε 16,390) (Found: C, 77·25; H, 8·35; S, 7·2. $C_{27}H_{36}O_2S$ requires: C, 76·4; H, 8·55; S, 7·55%). This compound (7 g) was treated for 18 hr at room temp with acetic anhydride (15 ml) and pyridine (20 ml). The product obtained by pouring the mixture into water was washed and air-dried. Its solution in acetone (35 ml) was added to a suspension of Raney nickel (50 ml of settled sludge) in acetone (150 ml), which suspension had been heated previously for 1 hr under reflux. The mixture was refluxed for 5 hr, the catalyst was removed by filtration and the solvent removed under red. press. Crystallization of the residue from methanol gave 4,6β-dimethyltestosterone acetate, prisms, m.p. 155–158°, $[\alpha]_D$ +10°, λ_{max} 250 mμ (ε 14,730) (Found: C, 76·8; H, 9·3. $C_{23}H_{34}O_3$ requires: C, 77·05; H, 9·6%).

4,6β-Dimethylandrost-4-ene-3,17-dione (11; R = R′ = O)

A mixture of 6α-methylandrost-4-ene-3,17-dione (15; R = O; 5 g), thiophenol (4 ml), 40% aqueous formaldehyde (3 ml) triethylamine (3 ml) and ethanol (10 ml) was heated for 55 hr at ca. 80°. The mixture was poured into aqueous alkali and the product isolated with ether. It was chromatographed on alumina (175 g) in benzene–light petroleum (b.p. 40–60°) (1:4), elution with benzene giving oils having λ_{max} 252 mμ and consisting essentially of the 4-phenylthiomethyl derivative (14; R = O). These were combined (3·5 g) and added to a suspension of Raney nickel (10 ml of settled sludge) in acetone (125 ml), which suspension had been heated previously for 2 hr under reflux. The mixture was refluxed for 9 hr, and after removal of the catalyst and solvent, the residue was crystallized from acetone–hexane to give 4,6β-dimethylandrost-4-ene-3,17-dione, flakes, m.p. 176–178°, $[\alpha]_D$ +100°, λ_{max} 249 mμ (ε 15,030) (Found: C, 79·9; H, 9·6. $C_{21}H_{30}O_2$ requires: C, 80·2; H, 9·6%).

4,6β-Dimethyltestosterone (11; R = ——OH, - - -H; R′ = O)

A solution of the foregoing dione (0·6 g), sodium hydroxide (1 g) and sodium borohydride (40 mg) in methanol (15 ml) and water (5 ml) was kept overnight at room temp. The deposited solid was collected and crystallized from methanol to give 4,6β-dimethyltestosterone, needles, m.p. 228–229°, $[\alpha]_D$ +14°, λ_{max} 251 mμ (ε 13,890) (Found: C, 80·0; H, 10·0. $C_{21}H_{32}O_2$ requires: C, 79·7; H, 10·2%). Acetylation in pyridine gave the 17β-acetate, m.p. 154–156° (from methanol), not depressed in admixture with a specimen prepared as described above.

The *17β-propionate* crystallized from methanol as blades, m.p. 126–128°, $[\alpha]_D$ +8·5°, λ_{max} 250 mμ (ε 13,935) (Found: C, 78·0; H, 9·45. $C_{24}H_{36}O_3$ requires: C, 77·4; H, 9·75%).

4,6α-Dimethyltestosterone acetate (12; R = ——OAc, - - -H)

The residues (12 g) from a large scale 4-phenylthiomethylation of 6α-methyl testosterone (50 g) were acetylated and the product desulphurized with Raney nickel as described above. The gummy product was fractionated from acetone–hexane to give 4,6β-dimethyltestosterone acetate (1 g), m.p. 154–156° and 4,6α-dimethyltestosterone acetate (0·5 g), which crystallized from methanol in rods, m.p. 179–181°, $[\alpha]_D$ +12·8°, λ_{max} 250 mμ (ε 12,730) (Found: C, 77·55; H, 9·65. $C_{23}H_{34}O_3$ requires: C, 77·05; H, 9·6%).

The 4,6α-dimethyl isomer (300 mg) and toluene-*p*-sulphonic acid (150 mg) in acetic anhydride (5 ml) was heated for 35 min at 100°. The product was isolated with ether, and obtained as a gum

showing bands in the infrared at 1752, 1670 and 1640 cm^{-1} characteristic of a 3-acetoxy-3,5-diene system. Saponification with aqueous methanolic potassium carbonate gave 4,6β-dimethyltestosterone, needles (from methanol), m.p. 223–225°, not depressed in admixture with a specimen prepared as described above.

17β-Acetoxy-3,3-ethylenedioxy-4-methylandrost-4-ene (1; R = ——OAc, – – –H; R′ = O.$(CH_2)_2$·O)

A mixture of 4-methyltestosterone acetate {5 g, $[\alpha]_D$ +112°}, ethylene glycol (150 ml) and either anhydrous oxalic acid (0·5 g) or toluene-*p*-sulphonic acid (0·25 g) was slowly distilled at 50°/0·5 mm for 2½ hr. Neutralization of the residual solution with pyridine, and dilution with water afforded a solid which was crystallized from dichloromethane–methanol containing a trace of pyridine to give the 3-*ketal* as needles, m.p. 187–189°, $[\alpha]_D$ +100·2° (Found: C, 74·4; H, 9·2. $C_{24}H_{36}O_4$ requires: C, 74·2; H, 9·35%).

Alkaline hydrolysis gave the *17β-ol* (1; R = ——OH, – – –H; R′ = O.$(CH_2)_2$.O) as needles from aqueous methanol (containing a trace of pyridine), m.p. 196–198°, $[\alpha]_D$ +112° (Found: C, 75·95; H, 9·85. $C_{22}H_{34}O_3$ requires: C, 76·25; H, 9·9%).

17β-Acetoxy-4-methylandrost-4-en-3,6-dione (2; R = ——OAc, – – –H; R′ = O)

A solution of 3,17β-diacetoxy-4-methylandrosta-3,5-diene[11] (36 g) in chloroform (950 ml) was treated with monoperphthalic acid (22 g) in ether (850 ml), and the mixture kept overnight at 0°. The product, consisting of 17β-acetoxy-6(α + β)-hydroxy-4-methylandrost-4-en-3-one was isolated in the usual way, dissolved in acetone (650 ml), and oxidized at room temp with the Jones chromic acid reagent[12] (30 ml). The mixture was poured into water and the resulting solid crystallized from aqueous methanol to give the 3:6-dione as needles, m.p. 211–213°, $[\alpha]_D$ +26·5°, λ_{max} 257 mμ (ε 10,680) (Found: C, 73·95; H, 8·25. $C_{22}H_{30}O_4$ requires: C, 73·7; H, 8·45%).

17β-Acetoxy-3,3-ethylenedioxy-4-methylandrost-4-en-6-one (2; R = ——OAc, – – –H; R′ = O·$(CH_2)_2$·O)

A mixture of the 3,6-dione (2; R = ——OAc, – – –H; R′ = O) (3·5 g), toluene-*p*-sulphonic acid (0·15 g) and ethylene glycol (110 ml) was slowly distilled at 40°/0·2 mm for 2 hr. The residual mixture was poured into aqueous sodium carbonate and the precipitated solid was crystallized from dichloromethane-methanol (containing a trace of pyridine) to give the 3-ketal as needles, m.p. 216–218°, $[\alpha]_D$ +48·9°, λ_{max} 239–241 mμ, (ε 5,580), $\nu_{max}^{CCl_4}$ 1741, 1694 and 1639 cm^{-1}, $\nu_{max}^{CS_2}$ 1243, 1096 and 1035 cm^{-1} (Found: C, 71·2; H, 8·6. $C_{24}H_{34}O_5$ requires: C, 71·6; H, 8·5%).

Action of magnesium methyl iodide on the ketal (2; R = ——OAc, – – –H; R′ = O·$(CH_2)_2$·O). A solution of the ketal (2; R = ——OAc, – – –H; R′ = O·$(CH_2)_2$·O) (5 g) in dry benzene (200 ml) was added to a stirred solution of the Grignard reagent prepared from magnesium (3 g) and iodomethane (9 ml) in dry ether (75 ml). The mixture was refluxed for 2 hr, cooled, and saturated aqueous ammonium chloride (ca. 250 ml) added dropwise. The precipitated solid (A) was collected. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness under red. press. Acetylation of the residue (acetic anhydride–pyridine, 1 hr, 100°) followed by crystallization of the product from aqueous methanol gave the Δ^4-3,6-dione (2; R = ——OAc, – – –H; R′ = O), m.p. 209–211°, not depressed on admixture with an authentic specimen prepared as described above.

The solid (A) was acetylated (acetic anhydride–pyridine overnight at room temp) and the product crystallized from aqueous methanol to give a substance, probably (3; R = ——OAc, – – –H) as needles, m.p. 171–173°, $[\alpha]_D$ +61·1°, λ_{max} 246–7 mμ (ε 5,100), $\nu_{max}^{CCl_4}$ 1744, 1692, 1637 cm^{-1}; $\nu_{max}^{CS_2}$ 1742, 1691, 1240, 1127, 1092, 1037, 1024, 974, 914 cm^{-1} (Found: C, 70·2; H, 8·7. $C_{26}H_{38}O_6$ requires: C, 69·95; H, 8·6%).

Action of mineral acid on 17β-acetoxy-6(α + β)-hydroxy-4-methylandrost-4-en-3-one. The crude mixture of the above hydroxy-ketones (1 g) was heated under reflux in ethanol (70 ml) containing conc hydrochloric acid (0·5 ml). Samples were withdrawn at hourly intervals and their I.R. spectra were determined. After 3 hr the 17-acetoxy grouping had been completely hydrolysed; after 5 hr, the Δ_4-3-ketone moiety was unchanged, and the presence of a saturated ketone could not be detected.

[11] D. N. Kirk, V. Petrow and D. M. Williamson, *J. Chem. Soc.* 3872 (1960).
[12] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946).

17-Acetoxy-4α-(4; R = ——OAc, - - -H; R′ = O) and 17β-acetoxy-4β-methyl-5α-androstane-3,6-diones (5; R = ——OAc, - - -H; R′ = O)

(a) A mixture of the Δ_4-3,6-dione (2; R = ——OAc, - - -H; R′ = O) (10 g), acetic acid (300 ml) and zinc dust (20 g, not previously activated) was stirred at 100° for ½ hr. The zinc was removed by filtration and the filtrate was poured into a large volume of water. Fractional crystallization of the resulting solid (A), m.p. 175–185° from aqueous acetone gave (i) 17β-acetoxy-4α-methyl-5α-androstane-3,6-dione (6 g) as needles, m.p. 214–216°, $[\alpha]_D$ −39·5° (Found: C, 73·5; H, 8·75. $C_{23}H_{33}O_4$ requires: C, 73·3; H, 8·95%), and (ii) 17β-acetoxy-4β-methyl-5α-androstane-3,6-dione (2 g) as flakes, m.p. 187–189°, $[\alpha]_D$ −26°. (Found: C, 73·25; H, 8·85%).

Brief treatment of the total product (A) with aqueous acetone–dil. hydrochloric acid at room temp followed by crystallization from aqueous acetone gave the 4α-methyl isomer (4; R = ——OAc, - - -H; R′ = O), m.p. 214–216° as the sole product. Passage of the total product (A), in benzene solution, through an alumina column and crystallization of the eluates from aqueous acetone, also gave the 4α-methyl isomer (4; R = ——OAc, - - -H; R′ = O), m.p. 213–216°, as the sole product.

(b) The Δ_4-3,6-dione (2; R = ——OAc, - - -H; R′ = O) (2 g) in dioxan (50 ml) was hydrogenated at normal temp and press over pre-reduced platinum oxide (0·4 g); absorption of hydrogen stopped sharply at 1 mol. The catalyst was removed by filtration and the filtrate was poured into water; crystallization of the solids from aqueous acetone gave the 4β-methyl isomer (5; R = ——OAc, - - -H; R′ = O) (1·3 g), m.p. 186–188°, not depressed in admixture with a specimen prepared by method (a) above.

17β-Acetoxy-3,3-ethylenedioxy-4α-methyl-5α-androstan-6-one (4; R = ——OAc, - - -H; R′ = O·(CH₂)₂·O)

A solution of 4α-methyl-3,6-dione (4; R = ——OAc, - - -H; R′ = O; 2·5 g) and toluene-*p*-sulphonic acid (0·1 g) in ethylene glycol (85 ml) was slowly distilled over 2 hr at 55°/0·5 mm. The residual suspension was cooled, neutrallized with pyridine and the solids (m.p. 208–212°) were collected. Crystallization from aqueous methanol containing a trace of pyridine gave the 3-ketal as needles, m.p. 215–217°, $[\alpha]_D$ −52·2° (Found: C, 71·1; H, 9·0. $C_{24}H_{36}O_5$ requires: C, 71·25; H, 9·0%).

17β-Acetoxy-4α,6β-dimethyl-3,3-ethylenedioxy-5α-androstan-6α-ol (7; R = ——OAc, - - -H)

A mixture of the ketal (4; R = ——OAc, - - -H; R′ = —O·CH₂·CH₂·O—) (5 g) and the Grignard reagent prepared from magnesium (3 g) and iodomethane (9 ml) in dry ether (250 ml) was stirred at room temp for 3 hr. Saturated aqueous ammonium chloride was added, and the product was isolated with ether. A gum was obtained having no carbonyl absorption in the infrared. It was acetylated with acetic anhydride–pyridine for 1 hr at 100°, and the solids obtained on pouring the mixture into water were crystallized from aqueous acetone containing a trace of pyridine. 17β-Acetoxy-4α,6β-dimethyl-3,3-ethylenedioxy-5α-androstan-6α-ol separated as needles, m.p. 174–176°, $[\alpha]_D$ −11·7° (Found: C, 71·2; H, 9·6. $C_{25}H_{40}O_5$ requires: C, 71·4; H, 9·6%).

17β-Acetoxy-3,3-ethylenedioxy-4β-methyl-5α-androstan-6-one (5; R = ——OAc, - - -H; R′ = O·(CH₂)₂·O)

A solution of the 4β-methyl-3,6-dione (5; R = ——OAc, - - -H; R′ = O) (1 g), and toluene-*p*-sulphonic acid (0·04 g) in ethylene glycol (40 ml) was slowly distilled at 55°/0·5 mm for 2 hr. The cooled residual solution was neutrallized with pyridine and the solid obtained on dilution with water was crystallized from aqueous acetone containing a trace of pyridine to give the 3-ketal as needles, m.p. 182–184°, $[\alpha]_D$ −19·1° (Found: C, 71·2; H, 9·0. $C_{24}H_{36}O_5$ requires: C, 71·25; H, 9·0%).

A solution of this ketal (0·5 g) and sodium hydroxide (0·5 g) in water (5 ml) and ethanol (20 ml) was refluxed for 1 hr. The product obtained by pouring the mixture into water was re-acetylated (acetic anhydride–pyridine, 100°, 1 hr) and then crystallized from aqueous acetone containing a trace of pyridine; only the starting material (5; R = ——OAc, - - -H; R′ = O·(CH₂)₂·O) (0·35 g), m.p. 181–183° was obtained.

17β-Acetoxy-4β,6β-dimethyl-3,3-ethylenedioxy-5α-androstan-6α-ol (6; R = ——OAc, - - -H)

A mixture of the ketal (5; R = ——OAc, - - -H; R′ = O·$(CH_2)_2$·O) (1 g) and the Grignard reagent prepared from magnesium (0·7 g) and iodomethane (2·4 ml) in ether (50 ml) and benzene (50 ml) was stirred at room temp for 3 hr. It was poured into saturated aqueous ammonium chloride, and the product was isolated with ether as a gummy solid which showed no carbonyl absorption in the infrared. The material was acetylated (acetic anhydride-pyridine, overnight at room temp), and the solid obtained on pouring the mixture into water was crystallized from aqueous acetone containing a trace of pyridine to give 17β-acetoxy-4β,6β-dimethyl-,33-ethylenedioxy-5α-androstan-6α-ol as needles, m.p. 203–205°, $[\alpha]_D$ −11·7° Found: C, 71·4; H, 9·5. $C_{25}H_{40}O_5$ requires: C, 71·4; H, 9·6%).

17β-Acetoxy-4α,6β-dimethyl-6α-hydroxy-5α-androstan-3-one (R = ——OAc, - - -H)

(a) The 4α-methyl-3-ketal (7; R = ——OAc, - - -H) (2·45 g) in acetone (100 ml) was treated with conc hydrochloric acid (2 ml) in water (10 ml), and the mixture set aside overnight at room temp. The solid obtained on dilution with water was crystallized from aqueous acetone to give the 3-ketone as laths, m.p. 220–222°, $[\alpha]_D$ +9·5°, $\nu_{max}^{CCl_4}$ 3615 [singlet-*tert*-(e)-OH], 1733, 1244 (acetate), 1709 cm^{-1} (3-one), (Found: C, 73·15; H, 9·85. $C_{23}H_{36}O_4$ requires: C, 73·35; H, 9·65%).

(b) The 4β-methyl 3-ketal (6; R = ——OAc, - - -H) (1 g) was treated with dil hydrochloric acid in acetone as described in (a) above; the product, m.p. 219–221°, was identical with that obtained in (a) above.

Alkaline hydrolysis (potassium hydroxide–aqueous ethanol, 1 hr reflux) gave the *17β-ol* (8; R = ——OH, - - -H) needles, (from aqueous acetone) m.p. 236–239°, $[\alpha]_D$ +5·5° (Found: C, 75·15; H, 10·2. $C_{21}H_{34}O_3$ requires: C, 75·4; H, 10·25%).

17β-Acetoxy-4α,6-dimethylandrost-5-en-3-one (9; R = ——OAc, - - -H; R′ = O)

Purified thionyl chloride (0·3 ml) was added dropwise to a stirred solution of the ketone (8; R = ——OAc, - - -H) (0·5 g) in dry pyridine (5 ml) at 0°. After a further 20 min at 0°, the mixture was poured into water, and the solids were crystallized from aqueous acetone to give unsaturated 3-ketone as flakes, m.p. 152–154°, $[\alpha]_D$ −14° (Found: C, 77·2; H, 9·95. $C_{23}H_{34}O_3$ requires: C, 77·05; H, 9·55%).

Saponification gave the *17β-ol* (9; R = ——OH, - - -H; R′ = O) which crystallized from aqueous acetone as needles, m.p. 161–163°, $[\alpha]_D$ −38° (Found: C, 79·7; H, 10·35. $C_{21}H_{32}O_2$ requires: C, 79·7; H, 10·2%).

17β-Acetoxy-4α-methyl-6-methylene-5α-androstan-3-one (10; R = ——OAc, - - -H; R′ = O)

A solution of the ketone (8; R = ——OAc, - - -H) (0·5 g) in 100% formic acid (12 ml) was maintained at 60° for ½ hr, then poured into dil aqueous sodium carbonate. The precipitated solid was crystallized from aqueous acetone to give the 6-methylene 3-ketone as needles, m.p. 171–173°, $[\alpha]_D$ −50° (Found: C, 76·9; H, 9·7. $C_{23}H_{34}O_3$ requires: C, 77·05; H, 9·55%). The I.R. spectrum (Infracord-nujol) showed bands at 1645 and 890 cm^{-1} indicative of an exocyclic methylene group.

Saponification gave the *17β-ol* (10; R = ——OH, - - -H; R′ = O) which crystallized from aqueous acetone as needles, m.p. 222–224° $[\alpha]_D$ −53° (Found: C, 79·45; H, 10·1. $C_{21}H_{32}O_2$ requires: C, 79·7; H, 10·2%).

17β-Acetoxy-4,6β-dimethylandrost-4-en-3-one (11; R = ——OAc, - - -H; R′ = O)

(a) A solution of the 6-methylene 3-ketone (10; R = ——OAc, - - -H; R′ = O) (0·5 g) in acetic acid (10 ml) and perchloric acid (70%, 0·3 ml) was kept at 100° for 1 hr. The solid obtained on pouring the mixture into aqueous potassium hydroxide was crystallized from aqueous acetone to give 4,6β-dimethyl testosterone acetate as prisms, m.p. 155–158°, $[\alpha]_D$ +10°, identical with a specimen prepared as described above.

(b) A solution of the 5-en-3-one (9; R = ——OAc, - - -H; R′ = O) (0·35 g) in acetic acid (10 ml) and perchloric acid (70%, 0·3 ml) was kept at 100° for 1 hr, to give 4,6β-dimethyl testosterone acetate, m.p. 155–157°, identical with that prepared in (a) above.

17β-Acetoxy-4α,6β-dimethyl-5α-androstan-3-one (13; R = ——OAc, – – –H; R′ = O)

(a) 17β-Acetoxy-4α-methyl-6-methylene-5α-androstan-3-one (10; R = ——OAc, – – –H; R′ = O) (1 g) was hydrogenated in methanol (60 ml) over pre-reduced palladium–charcoal (5%, 0·3 g); absorption of hydrogen was rapid, and stopped sharply at 1 mole. The catalyst was removed by filtration, and the solid obtained by pouring the filtrate into water was crystallized from aqueous acetone to give the saturated 3-ketone as laths, m.p. 167–169°, $[\alpha]_D$ −24°, $\nu_{max}^{CS_2}$ 1738, 1244 (acetate), 1714 cm^{-1} (3-ketone) (Found: C, 76·8; H, 10·05. $C_{23}H_{36}O_3$ requires: C, 76·6; H, 10·05%).

(b) 4,6β-Dimethyltestosterone acetate (0·7 g) was hydrogenated as above. The product, after crystallization from aqueous acetone, had m.p. 158–161° and gave no depression of m.p. in admixture with a specimen prepared by method (a). The I.R. spectrum was identical with that of a specimen prepared by method (a).

(c) A solution of 4,6β-dimethyltestosterone (1·3 g) in dry ether (100 ml) and tetrahydrofuran (40 ml) was added to a solution of lithium (0·65 g) in liquid ammonia (200 ml). After the mixture had been stirred for 45 min solid ammonium chloride was added to destroy excess lithium, and the ammonia was allowed to evaporate. The product, isolated with ether, was crystallized from methanol to give *4α,6β-dimethyl-17β-hydroxy-5α-androstan-3-one* (13; R = ——OH, – – –H; R′ = O) as needles, m.p. 224–225°, $[\alpha]_D$ −25·5° (Found: C, 79·0; H, 10·4. $C_{21}H_{34}O_2$ requires: C, 79·2; H, 10·75%).

Acetylation afforded the 17β-acetate, m.p. 162–165°, not depressed on admixture with a specimen prepared by method (a) above.

The *17β-propionate* (13; R = —O·CO·C_2H_5, – – –H; R′ = O) formed blades from methanol, m.p. 125–128°, $[\alpha]_D$ −23° (Found: C, 77·15; H, 10·15. $C_{24}H_{38}O_3$ requires: C, 76·95; H, 10·25%).

(d) A solution of 17β-acetoxy-6β-methyl-4-phenylthiomethylandrost-4-en-3-one (5 g) in dry tetrahydrofuran (100 ml) was added to a stirred solution of lithium (0·6 g) in liquid ammonia (200 ml). The mixture was stirred for a further 2 min, solid ammonium chloride was added, and the ammonia was allowed to evaporate overnight. The product was isolated with ether, acetylated, and the ester crystallized from aqueous acetone. It had m.p. 162–165°, and was identical with that prepared by method (a) above.

4α,6β-Dimethyl-6α-hydroxy-5α-androstane-3,17-dione (8; R = R′ = O)

4α,6β-Dimethyl-5α-androstane-6α,17β-diol-3-one (8; R = ——OH, – – –H) (1 g) in acetone (75 ml) was oxidized at room temp with the Jones chromic acid reagent[12] (0·5 ml), and the mixture poured into water. Crystallization of the solids from aqueous acetone, gave the 3,17-dione as needles, m.p. 208°, $[\alpha]_D$ +47° (dioxan) (Found: C, 75·5; H, 9·35. $C_{21}H_{32}O_3$ requires C, 75·85; H, 9·7%).

17β-Acetoxy-4α,6-dimethyl-3,3-ethylenedioxyandrost-5-ene (9; R = ——OAc, – – –H; R′ = O·$(CH_2)_2$·O)

A solution of 17β-acetoxy-4α,6-dimethylandrost-5-en-3-one (9; R = ——OAc, – – –H; R′ = O) (7·25 g) and toluene-*p*-sulphonic acid (0·35 g) in ethylene glycol (250 ml) was slowly distilled at 65°/10 mm over 2 hr. The cooled residual mixture was poured into dil. aqueous sodium carbonate and the precipitated solid was crystallized from aqueous acetone containing a trace of pyridine to give the 3-ketal as flakes, m.p. 148–150, $[\alpha]_D$ −30·5° (dioxan) (Found: C, 74·35; H, 9·3. $C_{25}H_{38}O_4$ requires: C, 74·6; H, 9·5%).

4α,6-Dimethyl-3,3-ethylenedioxyandrost-5-en-17-one (9; R = O; R′ = O·$(CH_2)_2$·O)

A solution of the foregoing ketal (7 g) and sodium hydroxide (2·5 g) in ethanol (250 ml) and water (25 ml) was refluxed for 1 hr. The solid (6·8 g m.p. 156–158°) obtained on pouring the mixture into water was dissolved in pyridine (65 ml), and the solution added at 0° to the complex prepared from chromium trioxide (6·5 g) and pyridine (65 ml). The mixture was left overnight at room temp. and the product isolated with ethyl acetate. It crystallized from aqueous methanol containing a trace of pyridine to give the 17-ketone as flakes, m.p. 165–167°, $[\alpha]_D$ +25° (dioxan) (Found: C, 77·0; H, 9·45. $C_{23}H_{34}O_3$ requires: C, 77·05; H, 9·55%).

17β-Hydroxy-4α,6,17α-trimethylandrost-5-en-3-one (9; R = ——OH, – – –Me; R′ = O)

A solution of the foregoing ketone (1·6 g) in dry benzene (100 ml) was added to the Grignard reagent prepared from magnesium (1·2 g) and iodomethane (4·2 ml) in dry ether (50 ml), and the

mixture was stirred at room temp for 6 hr. Excess reagent was decomposed with saturated aqueous ammonium chloride, and the product, isolated with ether, was treated with 2N hydrochloric acid (5 ml) in acetone (50 ml) overnight at room temp. The solid obtained on pouring the mixture into water was crystallized from aqueous acetone to give 17β-hydroxy-4α,6,17α-trimethylandrost-5-en-3-one as needles, m.p. 171–173°, $[\alpha]_D$ −25° (Found: C, 79·45; H, 10·25. $C_{23}H_{34}O_2$ requires: C, 79·95; H, 10·35%).

17α-Chlorethynyl-4α,6-dimethyl-17β-hydroxyandrost-5-en-3-one (9; R = ——OH, - - -C≡C·Cl; R′ = O)

The ketone (9; R = O; R′ = O·$(CH_2)_2$·O) (1·25 g) in dry tetrahydrofuran (30 ml) was added under nitrogen to a solution of lithium chloracetylide [prepared from lithium (0·4 g), iodomethane (2 ml) and *trans*-dichlorethylene (1·5 ml)]* in dry ether (50 ml), and the mixture was refluxed for 3 hr. Excess reagent was decomposed with saturated aqueous ammonium chloride and the product, isolated with ether, was deketallized with dil. hydrochloric acid in acetone at room temp. Crystallization of the product from aqueous acetone gave 17α-chlorethynyl-4α,6-dimethyl-17β-hydroxyandrost-5-en-3-one as needles, m.p. 202–204°, $[\alpha]_D$ −50°, ν_{max}^{Nujol} (Infracord) 3500, 2230 (C≡C) and 1705 cm^{-1} (Found: C, 73·55; H, 8·15; Cl, 9·45. $C_{23}H_{31}O_2Cl$ requires: C, 73·65; H, 8·35; Cl, 9·45%).

4α-Methyl-6-methylene-5α-androstane-3,17-dione (10: R = R′ = O)

17β-Hydroxy-4α-methyl-6-methylene-5α-androstan-3-one (10; R = ——OH, - - -H; R′ = O) (0·15 g) in acetone (10 ml) was treated at room temp. with the Jones chromic acid reagent (ca. 0·2 ml). The solid obtained on pouring the mixture into water was crystallized from aqueous acetone to give the 3,17-diketone as needles, m.p. 164–166°, $[\alpha]_D$ +47·8° (Found: C, 79·85; H, 9·8. $C_{21}H_{30}O_2$ requires: C, 80·2; H, 9·6%).

17β-Acetoxy-3,3-ethylenedioxy-4α-methyl-6-methylene-5α-androstane (10; R = ——OAc, - - -H; R′ = O·$(CH_2)_2$·O)

A solution of the ketone (10; R = ——OAc, - - -H; R′ = O) (6 g) and toluene-*p*-sulphonic acid (0·25 g) in ethylene glycol (240 ml) was slowly distilled at 70°/8 mm for 1½ hr. The residual mixture was poured into dil aqueous sodium carbonate, and the precipitated solid crystallized from aqueous acetone containing a trace of pyridine to give the 3-ketal as needles, m.p. 209–211°, $[\alpha]_D$ −43·8° (dioxan) (Found: C, 74·35; H, 9·25. $C_{25}H_{38}O_4$ requires: C, 74·6; H, 9·5%).

3,3-Ethylenedioxy-4α-methyl-6-methylene-5α-androstan-17β-ol (10; R = ——OH, - - -H; R′ = O·$(CH_2)_2$·O)

The foregoing 3-ketal (4·5 g) and potassium hydroxide (1·5 g) in ethanol (200 ml) and water (20 ml) was refluxed for 1 hr. Dilution with water, and crystallization of the solids from aqueous acetone containing a trace of pyridine gave the 17β-ol as needles, m.p. 195–197°, $[\alpha]_D$ −48·7° (dioxan) (Found: C, 76·0; H, 10·05. $C_{23}H_{36}O_3$ requires: C, 76·6; H, 10·05%).

3,3-Ethylenedioxy-4α-methyl-6-methylene-5α-androstan-17-one (10; R = O; R′ = O·$(CH_2)_2$·O)

A solution of the foregoing ketal (10; R = ——OH, - - -H; R′ = O·$(CH_2)_2$·O) (11 g) in pyridine (110 ml) was added at 0° to a suspension of the complex prepared from chromium trioxide (11 g) in pyridine (110 ml), and the mixture left overnight at room temp. The product, isolated with ethyl acetate, was crystallized from aqueous acetone containing a trace of pyridine to give the 17-ketone as needles, m.p. 200–202°, $[\alpha]_D$ +11·3° (dioxan) (Found: C, 77·0; H, 9·6. $C_{23}H_{34}O_3$ requires: C, 77·05; H, 9·55%).

4α,17α-Dimethyl-17β-hydroxy-6-methylene-5α-androstan-3-one (10; R = ——OH, - - -Me; R′ = O)

A solution of the foregoing ketone (10; R = O; R′ = O·$(CH_2)_2$·O) (1·6 g) in dry benzene (150 ml) was added to the Grignard reagent prepared from magnesium (1·2 g) and iodomethane (4·2 ml) in dry ether (50 ml). The mixture was stirred for 6 hr at room temp, and the product isolated with ether. It was treated with acetone–dil. hydrochloric acid for 2 hr at room temp and the product

* For experimental details see Part XXIX, *J. Chem. Soc.* 4995 (1962).

crystallized from aqueous acetone to give the 3-ketone as needles, m.p. 182–184°, $[\alpha]_D$ −91·9° (Found: C, 79·9; H, 10·55. $C_{22}H_{34}O_2$ requires C, 79·95; H, 10·35%).

4,6β-Dimethyl-3,3-ethylenedioxy-17β-hydroxyandrost-4-ene (11; R = ——OH, - - -H; R′ = O·$(CH_2)_2$·O)

A solution of 4,6β-dimethyltestosterone (1 g) and toluene-*p*-sulphonic acid (0·05 g) in ethylene glycol (30 ml) was slowly distilled at 80°/20 mm for 2 hr. The solid obtained on pouring the residual mixture into dil. aqueous sodium carbonate was crystallized from aqueous acetone containing a trace of pyridine to give the 3-ketal as needles, m.p. 233–235°, $[\alpha]_D$ +21·8° (dioxan) (Found: C, 76·15; H, 9·8. $C_{23}H_{36}O_3$ requires: C, 76·6; H, 10·05%).

4,6β-Dimethyl-3,3-ethylenedioxyandrost-4-en-17-one (11; R = O; R′ = O·$(CH_2)_2$·O)

A solution of the foregoing 3-ketal (2 g) in pyridine (20 ml) was added at 0° to a suspension of the complex prepared from chromium trioxide (2 g) in pyridine (20 ml), and the mixture was kept overnight at room temp. The product was isolated with ethyl acetate and crystallized from aqueous acetone containing a trace of pyridine to give the 17-ketone as needles, m.p. 139–141°, $[\alpha]_D$ +14·2° (dioxan) (Found: C, 76·75; H, 9·3. $C_{23}H_{34}O_3$ requires: C, 77·05; H, 9·55%).

17β-Hydroxy-4,6β,17α-trimethylandrost-4-en-3-one (11; R = ——OH, - - -Me; R′ = O)

A solution of the foregoing 17-ketone (1·2 g) in dry benzene (50 ml) was added to the Grignard reagent prepared from magnesium (0·8 g) and iodomethane (2·8 ml) in dry ether (75 ml), and the mixture was refluxed for 4½ hr. The product, isolated in the usual way with ether, was treated overnight at room temp with dil. hydrochloric acid-acetone, and crystallized from aqueous acetone to give 17β-hydroxy-4,6β,17α-trimethylandrost-4-en-3-one as needles, m.p. 180–182°, $[\alpha]_D$ −5·25°, λ_{max} 251 mμ (ε 14,940) (Found: C, 80·5; H, 10·7. $C_{22}H_{34}O_2$ requires: C, 79·95; H, 10·35%).

17β-Acetoxy-4α,6β-dimethyl-3,3-ethylenedioxy-5α-androstane (13; R = ——OAc, - - -H; R′ = O·$(CH_2)_2$·O)

A solution of 17β-acetoxy-4α,6β-dimethyl-5α-androstan-3-one (13; R = ——OAc, - - -H; R′ = O) (3·5 g) and toluene-*p*-sulphonic acid (0·2 g) in ethylene glycol (120 ml) was slowly distilled at 65°/10 mm for 2 hr, and the residual mixture poured into dil. aqueous sodium carbonate. The precipitated solid was crystallized from aqueous acetone containing a trace of pyridine to give the 3-ketal as needles, m.p. 209–211°, $[\alpha]_D$ −20° (dioxan) (Found: C, 74·3; H, 9·9. $C_{25}H_{40}O_4$ requires: C, 74·2; H, 9·95%).

4α,6β-Dimethyl-3,3-ethylenedioxy-5α-androstan-17β-ol (13; R = ——OH, - - -H; R′ = O·$(CH_2)_2$·O)

The foregoing acetate (2·2 g) and potassium hydroxide (0·6 g) in water (5 ml) and ethanol (150 ml) was heated for 1 hr under reflux. The product was crystallized from aqueous acetone containing a trace of pyridine to give the 17β-ol as needles, m.p. 205–207°, $[\alpha]_D$ −19·5° (Found: C, 75·8; H, 10·75. $C_{23}H_{38}O_3$ requires: C, 76·2; H, 10·55%).

4α,6β-Dimethyl-3,3-ethylenedioxy-5α-androstan-17-one (13; R = O; R′ = O·$(CH_2)_2$·O)

A solution of 4α,6β-dimethyl-3,3-ethylenedioxy-5α-androstan-17β-ol (1·5 g) in pyridine (15 ml) was added at 0° to a suspension of the complex prepared from chromium trioxide (1·5 g) in pyridine (15 ml), and the mixture was kept overnight at room temp. The product was isolated with ethyl acetate and crystallized from aqueous acetone containing a trace of pyridine to give the 17-ketone as needles, m.p. 188–190°, $[\alpha]_D$ +40·1° (Found: C, 76·35; H, 10·25. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·05%).

17β-Hydroxy-4α,6β,17α-trimethyl-5α-androstan-3-one (13; R = ——OH, - - -Me; R′ = O)

A solution of the foregoing 17-ketone (1·1 g) in dry benzene (50 ml) was added to the Grignard reagent prepared from magnesium (0·8 g) and iodomethane (2·8 ml) in dry ether (50 ml), and the mixture was stirred at room temp. for 7 hr. The product, isolated with ether, was treated with acetone–dil hydrochloric acid for 2 hr at room temp. and the mixture poured into water. Crystallization of the solid from aqueous acetone gave 17β-hydroxy-4α,6β,17α-trimethyl-5α-androstan-3-one

as needles, m.p. 179–181°, $[\alpha]_D$ −43° (Found: C, 79·8; H, 11·2. $C_{22}H_{36}O_2$ requires: C, 79·45; H, 10·9%).

17α-Chlorethynyl-4α,6β-dimethyl-17β-hydroxy-5α-androstan-3-one (13; R = ——OH, - - -C≡C·Cl; R′ = O)

4α,6β-Dimethyl-3,3-ethylenedioxy-5α-androstan-17-one (1·25 g) in dry tetrahydrofuran (25 ml) was added to a solution of lithium chloracetylide [prepared from lithium (0·39 g), iodomethane (2·1 ml) and *trans*-dichlorethylene (1·2 ml)] in dry ether (50 ml), and the mixture was refluxed for 4 hr. The product, isolated with ether, was treated with acetone–dil. hydrochloric acid at room temp for 4 hr and the mixture poured into water. Crystallization of the solid from aqueous acetone gave 17α-chlorethynyl-4α,6β-dimethyl-17β-hydroxy-5α-androstan-3-one as needles, m.p. 167–169°, $[\alpha]_D$ −56°, ν_{max}^{Nujol} (Infracord) 3500, 2240 and 1710 cm^{-1} (Found: C, 73·0; H, 8·65. $C_{23}H_{33}O_2Cl$ requires: C, 73·25; H, 8·8%).

17α-Acetoxy-4,6β-dimethylprogesterone

A mixture of 17α-acetoxy-6α-methylprogesterone[18] (2·65 g), thiophenol (2 ml), 30% formaldehyde (2 ml), triethylamine (2 ml) and ethanol (6 ml) was kept at 100° for 84 hr.

The product, isolated with ether, was chromatographed on alumina (100 g) in benzene. Elution with ether afforded a solid residue which was crystallized from acetone–hexane to give *17α-acetoxy-6β-methyl-4-phenylthiomethylprogesterone* as prisms, m.p. 208–210°, $[\alpha]_D$ −32°, λ_{max} 252 mμ (ε 21,000) (Found: C, 72·9; H, 7·7; S, 6·2. $C_{31}H_{40}O_4S$ requires: C, 73·2; H, 7·95; S, 6·3%).

The above product (2 g) was added to a suspension of partially deactivated Raney nickel (20 ml of settled aqueous suspension) in acetone (100 ml), and the mixture was refluxed for 6 hr. The catalyst was removed by filtration and the residue obtained on evaporation of the filtrate was crystallized from acetone–hexane to give 17α-acetoxy-4,6β-dimethylprogesterone as needles, m.p. 130–137°, $[\alpha]_D$ +5°, λ_{max} 249 mμ (ε 12,975) (Found: C, 74·55; H, 9·2. $C_{25}H_{36}O_4$ requires: C, 74·95; H, 9·05%).

4,6β-Dimethyl-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione (By Mrs. S. M. Waddington-Feather)

16α,17α-Isopropylidenedioxy-6α-methylpregn-4-ene-3,20-dione[14] was 4-phenylthiomethylated by the method described in the foregoing preparation, and the crude crystalline intermediate (m.p. 212–216°) desulphurized with partially deactivated Raney nickel in acetone. The product was purified from acetone–hexane to give the 4,6β-dimethyl derivative needles, m.p. 190°, $[\alpha]_D$ +59° (Found: C, 75·0; H, 9·0. $C_{26}H_{38}O_4$ requires: C, 75·3; H, 9·2%).

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