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MODIFIED STEROID HORMONES—XXXIX[1]

PREPARATION AND HYDROLYSIS OF STEROIDAL 3-ALKOXY-6-METHYL-3,5,7-TRIENES

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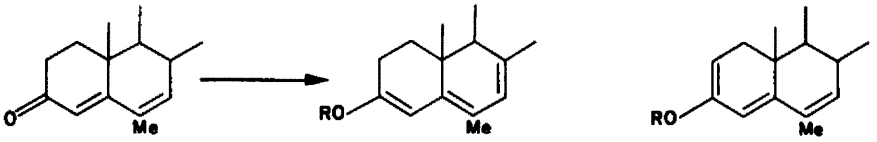
Abstract—Steroidal 3-alkoxy-6-methyl-3,5,7-trienes have been prepared and hydrolysed to the corresponding 6α-methyl-4,7-dien-3-ones.

CONVERSION of Δ^4-3-ketosteroids into suitable 3-enol ether derivatives may result in enhancement of biological activity.[2] The preparation for biological study of 3-enol ethers derived from certain 6-methyl-4,6-diene-3-ketones was therefore undertaken.

Room temperature procedures used for the preparation of 3-enol ethers of Δ^4-3-ketosteroids proved unsatisfactory when applied to 6-methyl-4,6-diene-3-ketones (I). Treatment of 6-methylandrosta-4,6-diene-3,17-dione[3] with triethylorthoformate under



I II III

somewhat more vigorous conditions of enol etherification (Experimental), however, gave in acceptable yield a derivative to which the constitution 3-ethoxy-6-methylandrosta-3,5,7-trien-17-one (II) is assigned on the basis of the UV spectrum, λ_{max} 323 mμ. The alternative formulation, a 3-ethoxy-6-methyl-2,4,6-triene (III), is excluded as such a structure would be expected to show an absorption maximum at a substantially shorter wavelength comparable to that (λ_{max} 300–301 mμ) reported[4] for 6-substituted 3-acetoxy-2,4,6-trienes. The use of trimethyl-orthoformate in place of the triethyl ester employed in the foregoing etherification experiment led to the formation of 6-methyl-3,17,17-trimethoxyandrosta-3,5,7-triene (λ_{max} 320 mμ), the IR spectrum of which significantly lacked the band (ν_{max} 1743 cm^{-1}) associated with a 17-ketone function. Reduction of 3-ethoxy-6-methylandrosta-3,5,7-trien-17-one with sodium borohydride followed by acetylation of the resulting 17β-alcohol afforded 17β-acetoxy-3-ethoxy-6-methylandrosta-3,5,7-triene. The 17β-propionate homologue,

[1] Part XXXVIII, D. Burn, D. N. Kirk and V. Petrow, *Tetrahedron* **21**, (1965).
[2] A. Ercoli and R. Gardi, *J. Amer. Chem. Soc.* **82**, 746 (1960).
[3] B. Ellis, D. N. Kirk, V. Petrow, (Mrs.) B. Waterhouse and D. M. Williamson, *J. Chem. Soc.* 2828 (1960).
[4] B.P. 949, 719.

prepared in like manner and also by an entirely different route (*vide infra*), unexpectedly proved to be very unstable in the solid state.

Enol methyl and ethyl etherification of 17α-acetoxy-6-methylpregna-4,6-diene-3,20-dione[3] gave 17α-acetoxy-3-methoxy-6-methylpregna-3,5,7-trien-20-one and the 3-enol ethyl ether analogue, respectively. The former derivative was readily converted into 17α-acetoxy-3-cyclohexyloxy-6-methylpregna-3,5,7-trien-20-one by ether exchange reaction with cyclohexanol. 17α-acetoxy-3-ethoxy-6-methyl-16-methylenepregna-3,5,7-trien-20-one and 17α-acetoxy-6,16α-dimethyl-3-ethoxypregna-3,5,7-trien-20-one were obtained from the corresponding parent 6-methyl-4,6-diene-3-ketones.[5]

An alternative route to 3-alkoxy-6-methyl-3,5,7-trienes, based upon observations described in Part XXXVI[6] of this series, is exemplified by the following reaction sequence. 17β-Acetoxy-3-ethoxyandrosta-3,5,7-triene, prepared from 6-dehydrotestosterone acetate, was treated in anhydrous ethylene dichloride with the Vilsmeier reagent formed from dimethylformamide and phosgene to give an iminium intermediate (not isolated) which was reduced *in situ* with lithium borohydride. A crystalline borane adduct of 17β-acetoxy-6-dimethylaminomethyl-3-ethoxyandrosta-3,5,7-triene was obtained, which, on treatment in ethanol with Pd—C and cyclohexene, passed into 17β-acetoxy-3-ethoxy-6-methylandrosta-3,5,7-triene (II), identical with a sample prepared from 6-methylandrosta-4,6-diene-3,17-dione (*vide supra*). 6-Dehydrotestosterone propionate was similarly converted into the very unstable 3-ethoxy-6-methyl-17β-propionoxyandrosta-3,5,7-triene (*vide supra*). These results unequivocally establish C-6 as the site of reaction of 3-alkoxy-3,5,7-trienes with the Vilsmeier reagent.

In analogy with the behaviour of 3-alkoxy-3,5-dienes,[7] the iminium intermediate obtained from 3-ethoxy-17β-propionoxyandrosta-3,5,7-triene and the Vilsmeier reagent readily underwent hydrolysis with aqueous methanolic sodium acetate to give 3-ethoxy-6-formyl-17β-propionoxyandrosta-3,5,7-triene (λ_{max} 383 mμ), lithium borohydride reduction of which furnished 3-ethoxy-6-hydroxymethyl-17β-propionoxyandrosta-3,5,7-triene (λ_{max} 320 mμ). Brief treatment of the last compound with warm acetic acid effected hydrolysis of the enol ether system with concomitant dehydration of the 6-hydroxymethyl group to give a crystalline substance with a complex UV absorption spectrum. We hope to report at a later date upon the structure of this product and upon that of an analogous substance prepared in the pregnane series (Experimental).

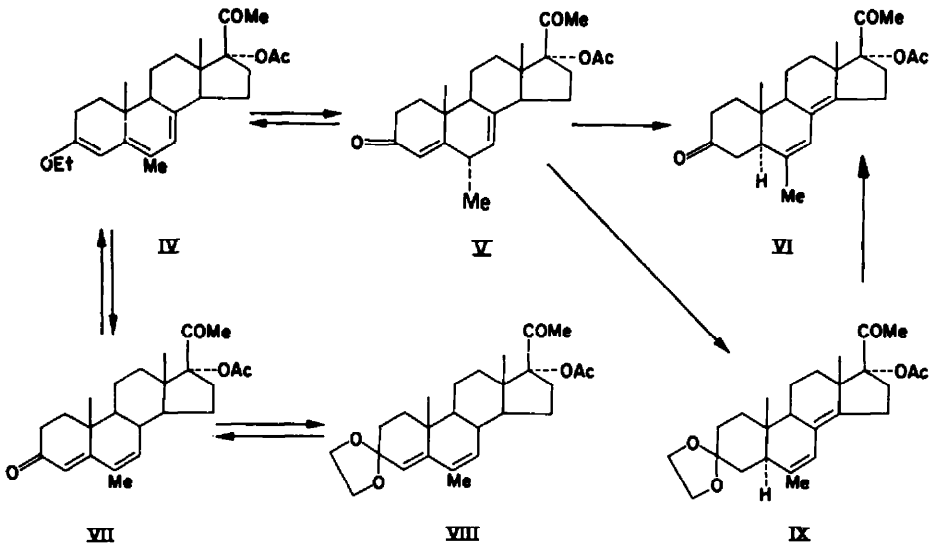
Hydrolysis of 17α-acetoxy-3-ethoxy-6-methylpregna-3,5,7-trien-20-one (IV) with hot aqueous acetic acid gave a mixture from which 17α-acetoxy-6α-methylpregna-4,7-diene-3,20-dione (V) and a compound tentatively regarded as 17α-acetoxy-6-methyl-5α-pregna-6,8(14)-diene-3,20-dione (VI) were isolated in approximately equal amounts. The structure of the first product follows from ultraviolet (λ_{max} 237–8 mμ), infrared (ν_{max} 1674 and 1618 cm^{-1}), and NMR (C_7-H resonance at 4·9τ) spectral data. The IR spectrum of the second compound (VI) failed to show the presence of an αβ-unsaturated ketone grouping, while the UV spectrum revealed a band at

[5] R. P. Graber and M. B. Meyers, *J. Org. Chem.* **26**, 4774 (1961); B. Ellis, (Mrs.) S. P. Hall, V. Petrow and D. M. Williamson, *J. Chem. Soc.* 22, (1962).

[6] D. Burn, G. Cooley, M. T. Davies, A. K. Hiscock, D. N. Kirk, V. Petrow and D. M. Williamson, *Tetrahedron* **21**, 569 (1965).

[7] D. Burn, G. Cooley, M. T. Davies, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, D. N. Kirk, A. P. Leftwick, V. Petrow and D. M. Williamson, *Tetrahedron* **20**, 597 (1964).

λ_{max} 257 (ε = 19,000), pointing to a 6-substituted ergosterol-B_2 type transoid heteroannular diene.[8] The 6α-methyl-4,7-dien-3-one (V) readily passed into its 3,5,7-triene



precursor (IV) in high yield under room temperature enol etherification conditions, in contrast to the behaviour of the isomeric 17α-acetoxy-6-methylpregna-4,6-dien-3,20-dione (VII) which is converted into the same enol ether (IV) only with difficulty. Ketalization of the 6α-methyl-4,7-dien-3-one (V) with ethylene glycol gave a 3-ketal derivative, regarded as (IX) on the basis of its UV spectrum (λ_{max} 256 mμ, ε = 23,480) and its conversion, by deketalization with acetic acid, into the 6,8(14)-dien-3-one (VI), also obtained directly from compound (V) by isomerization with acetic acid–perchloric acid. The behaviour of V on ketalization thus differs from that of 6-desmethyl-4,7-dien-3-ones which pass into 3-ketal-5,7-dienic structures[9] under similar experimental conditions. It is of interest to record that ketalization of the 6-methyl-4,6-dien-3-one (VII) afforded the derivative (VIII), the structure of which follows from its UV spectrum (λ_{max} 242 mμ, ε = 22,840) and its deketalization to the parent ketone (VII). These transformations are analogous to those observed with 4,6-dien-3-ones lacking the 6-methyl group.[10]

Unlike 3-methoxyergosta-3,5,7,22-tetraene which is hydrolysed by methanolic hydrochloric acid to ergosta-4,6,22-trien-3-one (isoergosterone) in high yield,[11] the trienol ether (IV) was converted on prolonged treatment with hot ethanolic hydrochloric acid into a mixture consisting largely of the 6,8(14)-diene (VI) and only a minor proportion of the 4,6-dien-3-one (VII).

Assignment of the α-configuration to the C_6-methyl group in V is based upon the

[8] See L. F. Fieser and M. Fieser, *Steroids* p. 116. Reinhold, New York (1959).
[9] R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.* **17**, 1341 (1952).
[10] G. J. Fonken, *J. Org. Chem.* **26**, 2549 (1961).
[11] D. A. Shepherd, R. A. Donia, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, Jr., J. E. Stafford, R. L. Pederson and A. C. Ott, *J. Amer. Chem. Soc.* **77**, 1212 (1955).

following considerations. Firstly, molecular Dreiding models of the 6ξ-methyl-4,7-diene-3-ketone structure reveal that in order to maintain minimal interaction between the C_{10} and C_{13}-methyl groups, ring B must adopt a conformation in which the C_6 bond directions are almost identical with those in steroidal 4-en-3-ketones lacking the Δ^7 bond. The adoption of this conformation is accompanied by a decrease in strain. These observations lead to the conclusion that the NMR spectrum of such a structure would show the same spin–spin coupling characteristics of the C_4 olefinic proton, allylically coupled to the C_6 protons, as are found in the NMR spectra of 6α- and 6β-methylated-4-en-3-ketones. Thus, for 6α-methyl-4-en-3-ketones, the C_4—H resonance at 4·2τ occurs as a *doublet*, the $C_{4,6\beta}$-proton spin–spin coupling constants lying in the range $J_{4,6} = 2{\cdot}0\ (\pm 0{\cdot}5$ c/s),[12] whereas for 6β-methyl-4-en-3-ketones the $C_{4,6\alpha}$-proton coupling is negligible so that the C_4-proton gives only a singlet absorption band. As the C_4-proton resonance in the NMR spectrum of compound (V) appears at 4·2τ as a *doublet*, $J_{4,6}$ 1·5 c/s (±0·2 c/s), it follows that the C_6-methyl substituent may be assigned the α-configuration. Secondly, steric interaction between the C_6- and C_{10}-methyl groups of 6α-methyl-4-en-3-ketones (lacking the Δ^7 bond) is minimal, resulting in virtually no shift of the C_{10}-methyl proton resonance band at 8·80τ. On the other hand, this type of steric interaction is of sufficient magnitude in 6β-methyl-4-en-3-ketones to lead to a shift of the C_{10}-methyl proton resonance from 8·80τ to 8·73τ.[13] The location in the spectrum of compound (V) of the C_{10}-methyl proton resonance at 8·80τ is entirely consistent with an α-configuration of the C_6-methyl substituent.

Treatment of 6-methyl-3,17,17-trimethoxyandrosta-3,5,7-triene with acetic acid readily furnished 6α-methylandrosta-4,7-diene-3,17-dione. 17α-Acetoxy-3-ethoxy-6,16-dimethylpregna-3,5,7-trien-20-one was similarly transformed into the corresponding 6α-methyl-4,7-dien-3-ketone. These experiments were performed on a relatively small scale which did not permit a satisfactory examination to be made of other products of hydrolysis.

Biological study of V was kindly undertaken by Dr. D. K. Vallance (BDH Biological Dept., Godalming, Surrey) and Dr. G. R. McKinney (Mead Johnson Research Center) and their respective colleagues. Transference of the Δ^6 linkage of megestrol acetate to the Δ^7 position was found to improve the ovulation inhibiting/progestational (Clauberg) index in the rabbit.

EXPERIMENTAL

Optical rotations were determined at concentrations of ca 1% in A.R. $CHCl_3$ containing 0·2% pyridine at laboratory temp, unless otherwise stated. UV spectra refer to solutions in spectro-grade EtOH. IR spectra were determined with a Hilger H800 spectrophotometer fitted with CaF_2 and NaCl prisms for the frequency ranges 4000–1300 and 1350–650 cm^{-1} respectively, the solvents used being as indicated. NMR spectra were determined at 40 Mcs/s. with a Perkin–Elmer permanent magnet spectrometer, employing a crystal calibrated decade field shift. Solutions were in $CDCl_3$ containing tetramethylsilane as internal reference. The spectroscopic determinations were carried out under the direction of Mr. M. T. Davies, B.Sc., F.R.I.C., whom we thank for helpful discussions on their interpretation.

3-Ethoxy-6-methylandrosta-3,5,7-trien-17-one. 6-Methylandrosta-4,6-diene-3,17-dione (6·0 g), in dry benzene (100 ml) was treated with triethylorthoformate (4 ml), EtOH (4 ml) and toluene-*p*-sulphonic acid (200 mg), and the mixture heated under reflux 1½ hr. Pyridine (4 ml) was added, the

[12] D. J. Collins, J. J. Hobbs and S. Sternhell, *Tetrahedron Letters* 197 (1963); also, unpublished observations from these laboratories.

[13] See R. F. Zürcher, *Helv. Chim. Acta* **46**, 2054 (1963).

mixture washed with water, dried, and the solvent evaporated *in vacuo*. Crystallization of the residue from EtOH containing a trace of pyridine gave 3-ethoxy-6-methylandrosta-3,5,7-trien-17-one (2·44 g), prismatic needles, m.p. 125–131°, $[\alpha]_D$ −74°, λ_{max} 323 mμ (ε 18,580), $\nu_{max}^{CCl_4}$ 1743, 1649 and 1618 cm^{-1}. (Found: C, 80·3; H, 9·1. $C_{23}H_{30}O_2$ requires: C, 80·9; H, 9·3%).

6-*Methyl*-3,17,17-*trimethoxyandrosta*-3,5,7-*triene*. 6-Methylandrosta-4,6-diene-3,17-dione (6·0 g) in dry benzene (100 ml) with trimethylorthoformate (4 ml), MeOH (4 ml) and toluene-*p*-sulphonic acid (200 mg) was heated under reflux 2 hr. Pyridine (4 ml) was added and the mixture washed with water, dried, and the solvents removed *in vacuo*. Treatment of the residue with MeOH followed by removal of the solvent *in vacuo* led to crystallization. Purification from acetone containing a trace of pyridine gave 6-methyl-3,17,17-trimethoxyandrosta-3,5,7-triene (2·2 g), golden blades, m.p. 182–187° $[\alpha]_D$ −138°, λ_{max} 320 mμ (ε 19,500), $\nu_{max}^{CCl_4}$ 1649, 1620 and 1392 cm^{-1}. (Found: C, 76·8; H, 9·2. $C_{25}H_{34}O_3$ requires: C, 77·05; H, 9·6%).

17β-*Acetoxy*-3-*ethoxy*-6-*methylandrosta*-3,5,7-*triene*. 3-Ethoxy-6-methylandrosta-3,5,7-trien-17-one (800 mg) in MeOH (160 ml) was treated with $NaBH_4$ (150 mg). After 1 hr at room temp, the mixture was diluted with water and the precipitate purified from aqueous EtOH containing a trace of pyridine to give the 17β-alcohol, needles, m.p. 115–118°, λ_{max}^{EtOH} 322 mμ (ε 18,000), $\nu_{max}^{CCl_4}$ 3624, 1650 and 1618 cm^{-1}. This material (450 mg) in pyridine (2 ml) and acetic anhydride (1 ml) was stored overnight at room temp. The product obtained on pouring the mixture into water was crystallized from EtOH containing pyridine to give 17β-acetoxy-3-ethoxy-6-methylandrosta-3,5,7-triene (320 mg), plates, m.p. 137–142°, $[\alpha]_D$ −134°, λ_{max} 321 mμ (ε 19,120), $\nu_{max}^{CCl_4}$ 1738, 1650 and 1618 cm^{-1}, $\nu_{max}^{CS_2}$ 1383, 1243 and 1041 cm^{-1}. (Found: C, 77·8; H, 8·9. $C_{24}H_{34}O_3$ requires: C, 77·80; H, 9·25%).

3-*Ethoxy*-17β-*propionoxy*-6-*methylandrosta*-3,5,7-*triene*. Prepared in a similar fashion to the foregoing compound, and purified from EtOH containing pyridine, formed pale yellow rods, m.p. 122–129°, $[\alpha]_D$ −143°, $\nu_{max}^{CCl_4}$ 1738, 1648, 1617 and 1181 cm^{-1}, immediately following its isolation. The compound was unstable in the solid state, becoming tacky after storage for 3 days at room temp. The rotation was then $[\alpha]_D$ −44·5°. A satisfactory elemental analysis of this compound could not be obtained.

17α-*Acetoxy*-3-*methoxy*-6-*methylpregna*-3,5,7-*trien*-20-*one*. 17α-Acetoxy-6-methylpregna-4,6-diene-3,20-dione (3·0 g) was enol etherified with trimethylorthoformate to give 17α-acetoxy-3-methoxy-6-methyl-pregna-3,5,7-trien-20-one (1·95 g), golden plates (from MeOH containing a trace of pyridine), m.p. 209–215°, $[\alpha]_D$ −130°, λ_{max} 322 mμ (ε 19,450), $\nu_{max}^{CCl_4}$ 1740, 1720, 1649, 1620 and 1369 cm^{-1}. (Found: C, 75·1; H, 8·7. $C_{25}H_{34}O_4$ requires: C, 75·3; H, 8·6%). The compound remained unchanged on storage for 2½ years at room temp.

17α-*Acetoxy*-3-*ethoxy*-6-*methylpregna*-3,5,7-*trien*-20-*one*. 17α-Acetoxy-6-methylpregna-4,6-diene-3,20-dione (24·0 g) was converted into the corresponding 3-ethoxy-3,5,7-triene, which formed golden-yellow needles (14·1 g) (from EtOH containing a trace of pyridine), m.p. 195-200°, $[\alpha]_D$ −127°, λ_{max} 322·5 mμ (ε 19,060), $\nu_{max}^{CCl_4}$ 1738, 1719, 1648 and 1616 cm^{-1}. (Found: C, 75·6; H, 8·7. $C_{26}H_{36}O_4$ requires: C, 75·7; H, 8·8%). The compound decomposed slowly on storage at room temp, the m.p. falling to 125–150° (dec) after 13 months.

17α-*Acetoxy*-3-*cyclohexyloxy*-6-*methylpregna*-3,5,7-*trien*-20-*one*. 17α-Acetoxy-3-methoxy-6-methylpregna-3,5,7-trien-20-one (1·34 g) in dry benzene (150 ml) and cyclohexanol (3 ml) was slowly distilled until 60 ml of distillate had been collected. Toluene-*p*-sulphonic acid (20 mg) was then added and the mixture distilled at a slow rate until most of the solvent had been removed. Pyridine (1 ml) was then added and the remaining solvents distilled off under high vac. (0·5 mm press). The dark brown resinous residue was crystallized from MeOH containing a trace of pyridine to give 17α-acetoxy-3-cyclohexyloxy-6-methylpregna-3,5,7-trien-20-one (0·2 g), needles, m.p. 198–207°, $[\alpha]_D$ −102°, λ_{max} 324 mμ (ε 20,440) $\nu_{max}^{CCl_4}$ 1740, 1719, 1649, 1614 and 1369 cm^{-1}. (Found: C, 77·1; H, 8·9. $C_{30}H_{42}O_4$ requires: C, 77·2; H, 9·1%). The compound remained unchanged on storage for 2½ years at room temp.

17α-*Acetoxy*-6-*methyl*-16-*methylenepregna*-4,6-*diene*-3,20-*dione* (with Mr. D. M. Williamson, M.A.). A mixture of 17α-acetoxy-3β-hydroxy-6-methyl-16-methylenepregn-5-en-20-one[14] (2 g), aluminium t-butoxide (2 g) and *p*-benzoquinone (3·3 g) in dry benzene (200 ml) was set aside for 3 days at room temp. The mixture was washed with dil NaOHaq, then with water, dried, and the solvent

[14] D. N. Kirk, V. Petrow and D. M. Williamson, *J. Chem. Soc.* 2821 (1961).

removed. Crystallization of the residue from acetone–hexane gave 17α-acetoxy-6-methyl-16-methylenepregna-4,6-diene-3,20-dione, needles, m.p. 224–226°, $[\alpha]_D$ −127° in $CHCl_3$, λ_{max} 287·5 mμ (log ε = 4·35). (Found: C, 75·6; H, 8·0. $C_{23}H_{32}O_4$ requires: C, 75·7; H, 8·1%).

17α-Acetoxy-3-ethoxy-6-methyl-16-methylenepregna-3,5,7-trien-20-one. The foregoing compound (10 g) was converted into 17α-acetoxy-3-ethoxy-6-methyl-16-methylenepregna-3,5,7-trien-20-one by the method described above. The product formed orange prisms (5·1 g) (from EtOH containing a trace of pyridine), m.p. 194–198°, $[\alpha]_D$ −188°, λ_{max} 324 mμ (ε 18,810), $\nu_{max}^{CCl_4}$ 1746, 1720, 1710, 1649 and 1615 cm^{-1}. (Found: C, 75·7; H, 8·9. $C_{27}H_{36}O_4$ requires: C, 76·4; H, 8·55%).

17α-Acetoxy-6,16α-dimethyl-3-ethoxypregna-3,5,7-trien-20-one. 17α-Acetoxy-6,16α-dimethylpregna-4,6-diene-3,20-dione[5] (6·0 g) was converted into the corresponding 3-ethoxy-3,5,7-triene by the method described above. The product crystallized from EtOH, containing a trace of pyridine, in golden plates (3·4 g), m.p. 202–207°, $[\alpha]_D$ −84°, λ_{max} 323 mμ (ε 19,760), $\nu_{max}^{CCl_4}$ 1744, 1716, 1651 and 1618 cm^{-1}. (Found: C, 75·5; H, 8·95. $C_{27}H_{38}O_4$ requires: C, 76·0; H, 9·0%).

17β-Acetoxy-3-ethoxyandrosta-3,5,7-triene. 6-Dehydrotestosterone acetate (2·4 g) in dry benzene (40 ml), triethylorthoformate (1·6 ml), and EtOH (1·6 ml), was treated with toluene-*p*-sulphonic acid (40 mg), and the mixture heated under reflux for 2 hr. Pyridine (1·6 ml) was added, the mixture was washed with water (40 ml), dried (Na_2SO_4) and evaporated *in vacuo*. The crystalline residue was purified from EtOH containing a trace of pyridine to give 17α-acetoxy-3-ethoxyandrosta-3,5,7-triene (1·33 g) as flat needles, m.p. 145–151°, $[\alpha]_D$ −107·5°, λ_{max} 320 mμ (ε 15,900) and 334 mμ (ε 12,000), $\nu_{max}^{CCl_4}$ 1740, 1643, 1619 and 1377 cm^{-1}. (Found: C, 77·3; H, 9·0. $C_{23}H_{32}O_3$ requires C, 77·5, H, 9·05%).

17β-Acetoxy-6-dimethylaminomethyl-3-ethoxyandrosta-3,5,7-triene borane adduct. 17β-Acetoxy-3-ethoxyandrosta-3,5,7-triene (1·12 g) in ethylene dichloride (5 ml) containing a drop of pyridine was added to a Vilsmeier reagent prepared from dimethylformamide (1·1 ml), ethylene dichloride (4·0 ml) and 10% phosgene solution (7·25 ml).[7] The mixture was stirred for 1 hr and then treated with a solution of $LiBH_4$ (400 mg) in dry tetrahydrofuran (20 ml). The mixture was poured into water and the solution extracted once with ether. Removal of the solvent from the washed and dried extract gave a residue which readily crystallized on trituration with EtOH, giving crude 17β-acetoxy-6-dimethylaminomethyl-3-ethoxyandrosta-3,5,7-triene borane adduct (550 mg). Purification from EtOH (containing a trace of pyridine) gave prisms, m.p. 169–172°, λ_{max} 325 mμ (ε 18,300), (Found: C, 72·3; H, 10·25; N, 3·0. $C_{26}H_{42}O_2NB$ requires: C, 73·05; H, 9·9; N, 3·3%).

The aqueous layer remaining from the ether extraction was saturated with NaCl, and then again extracted very thoroughly with ether. Removal of the solvent gave a crystalline residue (330 mg) identified as 17β-acetoxy-3-ethoxy-6-methylandrosta-3,5,7-triene (see above) by m.p., mixed m.p., and IR spectrum.

17β-Acetoxy-3-ethoxy-6-methylandrosta-3,5,7-triene. A mixture of 17β-acetoxy-6-dimethylaminomethyl-3-ethoxyandrosta-3,5,7-triene borane adduct (300 mg), EtOH (3 ml), cyclohexene (0·6 ml), and Pd—C (150 mg of 5%), was heated under reflux for 3 hr. The mixture was filtered, and the filtrate evaporated *in vacuo*. The residue was crystallized from ethanol to give the 6-methyl-3,5,7-triene, identical in every respect with an authentic specimen.

3-Ethoxy-17β-propionoxyandrosta-3,5,7-triene. 6-Dehydrotestosterone propionate (5·8 g) in dry benzene (100 ml) was treated with triethylorthoformate (4 ml), EtOH (4 ml) and toluene-*p*-sulphonic acid (40 mg), and the mixture heated under reflux for 3 hr. Pyridine (4 ml) was added, the mixture washed with water, and the dried benzene layer evaporated *in vacuo*. The residue was crystallized from EtOH, containing a trace of pyridine to give 3-ethoxy-17β-propionoxyandrosta-3,5,7-triene[5] (2·5 g) as needles m.p. 156–161°, $[\alpha]_D^{28}$ −200°, λ_{max} 320·5 mμ (ε 19,600), $\nu_{max}^{CCl_4}$ 1736, 1643, 1619, 1384 cm^{-1}. (Found: C, 77·2; H, 9·0. $C_{24}H_{34}O_3$ requires: C, 77·8; H, 9·25%).

6-Dimethylaminomethyl-3-ethoxy-17β-propionoxyandrosta-3,5,7-triene borane adduct. A mixture of dimethylformamide (4·4 ml) and ethylene dichloride (16·0 ml) at 0° was treated dropwise over 15 min with a 10% (w/v) solution of phosgene in ethylene dichloride (29 ml). The mixture was stirred for 15 min and a solution of 3-ethoxy-17β-propionoxyandrosta-3,5,7-triene (4·0 g) in ethylene dichloride (20 ml) containing 1 drop pyridine was then added. The mixture was stirred for 2 hr, then treated with a solution of $LiBH_4$ (0·8 g) in anhydrous tetrahydrofuran (40 ml). The mixture was poured into water and the product isolated with ether. Crystallization from EtOH gave the borane adduct (0·6 g) as needles, m.p. 148–153°, $[\alpha]_D$ −127° (in $CHCl_3$), λ_{max} 323·5 mμ (ε 18,590), $\nu_{max}^{CCl_4}$ 2940, 2365, 1736, 1643, and 1614 cm^{-1}. (Found: C, 72·3; H, 9·8; N, 3·6. $C_{27}H_{44}O_3NB$ requires: C, 73·45; H, 10·05; N, 3·2%).

3-Ethoxy-17β-propionoxy-6-methylandrosta-3,5,7-triene. A mixture of the foregoing borane adduct (2·0 g), EtOH (20 ml), Pd—C (1 g of 5%), and cyclohexene (4 ml), was stirred and heated under reflux for 3 hr. The mixture was filtered and the filtrate concentrated *in vacuo*. The crystalline residue was purified from methylene chloride–MeOH containing pyridine to give the 6-methyl-androsta-3,5,7-triene (0·23 g), m.p. 122–129°, not depressed in admixture with a specimen prepared by the method described above.

3-Ethoxy-6-formyl-17β-propionoxyandrosta-3,5,7-triene. A mixture of dimethylformamide (2·2 ml) and ethylene dichloride (8·0 ml), at 0° was treated dropwise during 15 min with a 10% (w/v) solution of phosgene in ethylene dichloride (14·5 ml). The mixture was stirred for 15 min, then a solution of 3-ethoxy-17β-propionoxyandrosta-3,5,7-triene (2·0 g) in ethylene dichloride (10 ml) containing 1 drop of pyridine was added. The mixture was stirred for 2 hr, then poured into a solution of sodium acetate (3 g) in water (5 ml) and MeOH (20 ml), and stirred a further 10 min. The product was isolated with ether and crystallized from acetone–hexane to give 3-ethoxy-17β-propionoxy-6-formylandrosta-3,5,7-triene (1·75 g) as prisms, m.p. 143–148°, $[\alpha]_D$ −67°, λ_{max} 383 mμ (ε 13,230), $\nu_{max}^{CH_2Cl_2}$ 1729, 1651, 1640 and 1596 cm^{-1}. (Found: C, 75·1; H, 8·7. $C_{25}H_{34}O_4$ requires: C, 75·3; H, 8·6%).

3-Ethoxy-6-hydroxymethyl-17β-propionoxyandrosta-3,5,7-triene. The foregoing compound (2·0 g) in dry tetrahydrofuran (15 ml) was treated with $LiBH_4$ (300 mg), and the mixture stirred for 10 min. It was poured into water, and the product isolated with ether. Crystallization from EtOH containing a trace of pyridine gave the 6-hydroxymethyl derivative (0·38 g) as prisms, m.p. 118–124°, $[\alpha]_D$ −103°, λ_{max} 320·5 mμ (ε 17,182), $\nu_{max}^{CH_2Cl_2}$ 1728, 1645 and 1616 cm^{-1}. (Found: C, 74·25; H, 9·2. $C_{25}H_{36}O_4$ requires C, 74·95; H, 9·1%). Hydrolysis with warm aqueous acetic acid gave a substance m.p. 226–229° (dec), $[\alpha]_D$ +65° (in $CHCl_3$), $\nu_{max}^{CH_2Cl_2}$ 1723, 1660 and 1595 cm^{-1}. (Found: C, 77·7; H, 8·5%).

17α-Acetoxy-3-ethoxypregna-3,5,7-trien-20-one. 6-Dehydro-17α-acetoxyprogesterone (1·1 g) was enol etherified with triethylorthoformate as described above to give 17α-acetoxy-3-ethoxypregna-3,5,7-trien-20-one (0·37 g), golden rods, m.p. 214–216°, $[\alpha]_D$ −167·3°, λ_{max} 214–215 mμ (ε 7,388) and 322 mμ (ε 18,590), $\nu_{max}^{CCl_4}$ 1743, 1722, 1645, 1620 and 1372 cm^{-1}. (Found: C, 75·0; H, 8·55. $C_{25}H_{34}O_4$ requires: C, 75·3; H, 8·6%).

17α-Acetoxy-3-ethoxy-6-formylpregna-3,5,7-trien-20-one. To a solution of the Vilsmeier reagent prepared from dimethylformamide (3·2 ml), ethylene dichloride (13·2 ml) and 10% (w/v) phosgene solution (26·6 ml) was added a solution of the foregoing compound (3·4 g) in ethylene dichloride (16 ml). The mixture was stirred at room temp for 1 hr 50 min, and the product isolated in the usual way. 17α-Acetoxy-3-ethoxy-6-formylpregna-3,5,7-trien-20-one (1·85 g) crystallized from EtOH as needles, m.p. 180°, $[\alpha]_D$ −56·7°, λ_{max} 218 mμ (ε 10,960), 272 mμ (ε 10,620) and 383 mμ (ε 12,630), $\nu_{max}^{CCl_4}$ 1742, 1722, 1680, 1663, 1644 and 1601 cm^{-1}. (Found: 73·3; H, 8·2. $C_{26}H_{34}O_5$ requires: C, 73·2; H, 8·0%).

Reduction of this compound with $LiBH_4$ in tetrahydrofuran followed by treatment of the product with warm aqueous acetic acid gave a substance, m.p. 207–210°, $[\alpha]_D$ +69°, $\nu_{max}^{CH_2Cl_2}$ 1732, 1715, 1658 and 1600 cm^{-1}. (Found: C, 71·7; H, 7·7%).

17α-Acetoxy-6α-methylpregna-4,7-diene-3,20-dione (V) *and 17α-acetoxy-6-methyl-5α-pregna-6,8(14)-diene-3,20-dione* (VI). 17α-Acetoxy-3-ethoxy-6-methylpregna-3,5,7-trien-20-one (8·21 g) in acetic acid (300 ml) and water (4 ml) was heated on the steam bath for 10 min and then gradually diluted with water (ca. 500 ml). Heating was continued for 1 hr. The needles, (4·75 g, m.p. 180–190°) deposited on cooling, were filtered off, washed neutral, and dried. The product was chromatographed on alumina (60 g) in benzene. Early fractions, eluted with benzene, were recrystallized from acetone to give 17α-acetoxy-6α-methylpregna-4,7-diene-3,20-dione (1·4 g), cubes, m.p. 240—243°, $[\alpha]_D$ −5·6° (in $CHCl_3$), λ_{max} 237–238 mμ (ε 15,420), $\nu_{max}^{CCl_4}$ 1742, 1719, 1674 and 1618 cm^{-1}. (Found: C, 74·8; H, 8·5. $C_{24}H_{32}O_4$ requires: C, 75·0; H, 8·4%).

The acetone mother liquors were processed to give 17α-acetoxy-6-methyl-5α-pregna-6,8(14)-diene-3,20-dione (1·4 g), m.p. 228–231°, $[\alpha]_D$ +67° (in $CHCl_3$), λ_{max} 257·5 mμ (ε 19,000), $\nu_{max}^{CCl_4}$ 1742, 1716 1369 and 1254 cm^{-1}. (Found: C, 74·45; H, 8·3. $C_{24}H_{32}O_4$ requires C, 75·0; H, 8·4%).

The same compound (VI; 80 mg) was obtained when V (100 mg) in acetic acid (10 ml) was treated with perchloric acid (2 drops of 72%) and the mixture kept for 5 days at room temp. UV spectroscopy revealed that variable amounts of other dienes (of undetermined structure) generally accompanied the formation of VI, irrespective of its method of preparation.

17α-*Acetoxy*-3,3'-*ethylenedioxy*-6-*methyl*-5α-*pregna*-6,8(14)-*dien*-20-*one* (IX). A solution of 17α-acetoxy-6α-methylpregna-4,7-diene-3,20-dione (1·0 g) in toluene (55 ml) and ethylene glycol (8 ml) was slowly distilled to remove traces of water, 15 ml of distillate being collected. Toluene-*p*-sulphonic acid (50 mg) was added, and the mixture heated for 4½ hr under reflux, water being removed continuously with a suitable separator. The mixture was cooled, diluted with benzene, and poured into a 1% $NaHCO_3$ aq (100 ml). The organic phase was washed neutral, dried, and evaporated *in vacuo* after addition of 1 drop pyridine. The residual gum was crystallized by trituration with acetone. Recrystallization from aqueous MeOH gave 17α-acetoxy-3,3'-ethylenedioxy-6-methyl-5α-pregna-6,8(14)-dien-20-one (0·3 g), needles, m.p. 172–173°, $[\alpha]_D$ +7·8°, λ_{max} 256 mμ (ε 23,480), $\nu_{max}^{CCl_4}$ 1739, 1720, 1369 cm^{-1}, $\nu_{max}^{CS_2}$ 1365, 1254, 1100 and 953 cm^{-1}. (Found: C, 72·8; H, 8·4. $C_{26}H_{36}O_5$ requires: C, 72·9; H, 8·5%).

Brief treatment of the ketal with warm aqueous acetic acid gave VI.

17α-*Acetoxy*-3,3'-*ethylenedioxy*-6-*methylpregna*-4,6-*dien*-20-*one* (VIII). A solution of 17α-acetoxy-6-methylpregna-4,6-diene-3,20-dione (2·0 g) in toluene (90 ml) and ethylene glycol (16 ml) was slowly distilled (20 ml distillate collected) to remove traces of water. Toluene-*p*-sulphonic acid (100 mg) was added and the mixture heated under reflux for 4½ hr, water being removed continuously with a suitable separator. When cool, benzene (30 ml) was added and the mixture poured into a 1% $NaHCO_3$ aq (200 ml). The organic phase was washed neutral, dried, and evaporated *in vacuo*. The gummy residue was crystallized by trituration with acetone, and purified from acetone containing a trace of pyridine to give 17α-acetoxy-3,3'-ethylenedioxy-6-methylpregna-4,6-dien-20-one (0·74 g), short rods, m.p. 218–219°, $[\alpha]_D$ +31·2°, λ_{max} 242 mμ (ε 22,840), $\nu_{max}^{CCl_4}$ 1741, 1720 and 1370 cm^{-1}. (Found: C, 73·2; H, 8·4. $C_{26}H_{36}O_5$ requires: C, 72·9; H, 8·5%).

Hydrolysis of the ketal in warm aqueous acetic acid led to almost quantitative regeneration of VII.

Hydrolysis of 17α-*acetoxy*-3-*ethoxy*-6-*methylpregna*-3,5,7-*trien*-20-*one* (IV) *with mineral acid.* The enol methyl ether (1·0 g) in EtOH (100 ml) and water (4·0 ml), was treated with conc. HCl (4·0 ml), and the mixture heated 4 hr under reflux. Dilution with water gave 17α-acetoxy-6-methylpregna-6,8(14)-diene-3,20-dione (800 mg) as needles, m.p. 227–229°. Further dilution of the filtrate with water gave 17α-acetoxy-6-methylpregna-4,6-dien-3,20-dione (40 mg), m.p. 212°, not depressed in admixture with an authentic specimen.

6α-*Methylandrosta*-4,7-*diene*-3,17-*dione*. 6-Methyl-3,17,17-trimethoxyandrosta-3,5,7-triene (1·6 g) in acetic acid (75 ml) and water (3 ml) was heated on the steam bath for 10 min. The solution was then diluted with water during 20 min of further heating. The gummy product, isolated with ether, was chromatographed on alumina (25 g) in benzene. Elution with benzene gave fractions which crystallized upon trituration with MeOH. Recrystallization from MeOH gave 6α-methylandrosta-4,7-diene-3,17-dione (0·25 g) as prismatic needles, m.p. 157–160°, $[\alpha]_D$ +98·3° (in $CHCl_3$), λ_{max} 237·5 mμ (ε 14,800), $\nu_{max}^{CCl_4}$ 1745, 1681, 1620. (Found: C, 80·3; H, 8·8. $C_{20}H_{26}O_2$ requires: C, 80·5; H, 8·8%).

17α-*Acetoxy*-6α,16α-*dimethylpregna*-4,7-*diene*-3,20-*dione*. 17α-Acetoxy-3-ethoxy-6,16α-dimethylpregna-3,5,7-trien-20-one (3·0 g) in acetic acid (100 ml) and water (1·5 ml), was heated on the steam bath for 10 min. Water (200 ml) was then added gradually during 20 min of further heating. The crystalline product deposited on standing, was chromatographed on alumina (60 g) in benzene. Fractions eluted with benzene were crystallized from acetone to give 17α-acetoxy-6α,16α-dimethylpregna-4,7-diene-3,20-dione as cubes (0·5 g), m.p. 172–175°, $[\alpha]_D$ +16·8° (in $CHCl_3$), λ_{max} 238 mμ (ε 14,665), $\nu_{max}^{CCl_4}$ 1745, 1715, 1674, 1620 cm^{-1}. (Found: C, 75·70; H, 8·55. $C_{25}H_{34}O_4$ requires: C, 75·3; H, 8·6%).